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*The National Collaborating Centre  
for Chronic Conditions*

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*Funded to produce guidelines for the NHS by NICE*

# CHRONIC KIDNEY DISEASE

National clinical guideline for early identification and  
management in adults in primary and secondary care

*Published by*



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## National Collaborating Centre for Chronic Conditions

The National Collaborating Centre for Chronic Conditions (NCC-CC) is a collaborative, multiprofessional centre undertaking commissions to develop clinical guidance for the National Health Service (NHS) in England and Wales. The NCC-CC was established in 2001. It is an independent body, housed within the Clinical Standards Department at the Royal College of Physicians of London. The NCC-CC is funded by the National Institute for Health and Clinical Excellence (NICE) to undertake commissions for national clinical guidelines on an annual rolling programme.

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## Chronic kidney disease

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# Preface

Chronic kidney disease (CKD) is of growing importance in the UK. The NHS is increasingly focussing on prevention and on the early detection and treatment of potentially progressive disease, whilst the prevalence of risk factors for CKD, such as diabetes, obesity and hypertension is rising. It is therefore a great pleasure to introduce this timely new guideline on CKD from the National Collaborating Centre for Chronic Conditions (NCC-CC) and the National Institute for Health and Clinical Excellence (NICE).

The recommendations you will read here are the result of a thorough review of the published research. The field of renal medicine has a complex evidence base, and enormous thanks are due to the Guideline Development Group for their hard work and attention to detail, and to the NCC-CC Technical Team who worked enthusiastically alongside them. As for all our guidelines, full evidence tables summarising the clinical evidence base, and full details of the health economic modelling, are available from the Royal College of Physicians' website. Readers involved in research in this field, and those who want to find the full rationale behind a particular recommendation, will find this an invaluable resource.

The Department of Health, in commissioning this guideline, was clear that the focus was to be on early detection and management. This is the area in which the guideline can deliver its greatest potential benefit, through delaying progression of disease and thus reducing the need for dialysis or transplantation. The key priority recommendations singled out in the guideline reflect this emphasis. They present clear criteria for testing for CKD, suspecting progressive CKD, and referring people for specialist assessment, all of which should be useful in primary care. Recommendations are also provided on starting treatment once proteinuria has been assessed.

In common with other guideline topics in chronic conditions, there are some areas in CKD which remain in need of good quality research to inform difficult clinical decisions. The GDG have not shirked from addressing these questions and their expertise informed debates which led to some forward-thinking recommendations, for example those dealing with testing for proteinuria. For many practitioners a change in practice will be required as a result, but great effort has been taken to explain the rationale for this change within the guideline, and to demonstrate that the necessary effort is worthwhile.

As healthcare professionals in primary care take on an increasing role in the management of CKD, it is hoped that this guideline will be a single useful and accessible reference promoting a consistent high quality of care and hence improved quality of life for longer for people with CKD.

**Dr Bernard Higgins MD FRCP**  
Director, National Collaborating Centre for Chronic Conditions



# Acronyms, abbreviations and glossary

## Acronyms and abbreviations

AASK	African American Study of Kidney Diseases and Hypertension
ABLE	A Better Life through Education and Empowerment
ACEI	Angiotensin-converting enzyme inhibitor
ACR	Albumin:creatinine ratio
ACS	Acute coronary syndrome
ADPKD	Autosomal dominant polycystic kidney disease
ALP	Alkaline phosphatase
ARB	Angiotensin receptor blocker
ARIC	Atherosclerosis Risk in Communities
BMD	Bone mineral density
BMI	Body mass index
BNF	British National Formulary
BP	Blood pressure
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CARI	Caring for Australasians with Renal Impairment
CHS	Cardiovascular Health Studies
CRF	Chronic renal failure
CRI	Chronic renal insufficiency
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Events
CI	Confidence interval
CKD	Chronic kidney disease
CrCl	Creatinine clearance
CV	Coefficient of variation
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DMP	Disease management programme
DNCSG	Diabetic Nephropathy Collaborative Study Group
eGFR	Estimated glomerular filtration rate
ESRD	End stage renal disease
GDG	Guideline Development Group
GFR	Glomerular filtration rate
HDL	High-density lipoprotein
ICER	Incremental cost-effectiveness ratio
KEEP	Kidney Early Evaluation Program

HF	Heart failure
HR	Hazard ratio
HYP	Hypertension
IDMS	Isotope dilution mass spectrometry
IDNT	Irbesartan in Diabetic Nephropathy Trial
IgA-GN	Immunoglobulin-A glomerulonephritis
iPTH	Intact parathyroid hormone
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
LDL	Low density lipoprotein
LDL-C	Low density lipoprotein cholesterol
LPD	Low protein diet
LVEF	Left ventricular ejection fraction
MAP	Mean arterial pressure
MDRD	Modification of Diet in Renal Disease
MI	Myocardial infarction
NCC-CC	National Collaborating Centre for Chronic Conditions
NEOERICA	New Opportunities for Early Renal Intervention by Computerised Assessment
NHANES	National Health and Nutrition Examination Surveys
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NKF-KDOQI	National Kidney Foundation Kidney Disease Outcomes Quality Initiative
NNS	Number needed to screen
NNT	Number needed to treat
NS	Non-significant
NSAIDs	Non-steroidal anti-inflammatory drugs
NSF	National service framework
NSTEACS	Non-ST-segment elevation acute coronary syndrome
OR	Odds ratio
PCR	Protein:creatinine ratio
PREVEND	Prevention of Renal and Vascular Endstage Disease
PTH	Parathyroid hormone
pmp	Per million population
QOF	Quality and Outcomes Framework
QALY	Quality-adjusted life year
RBC	Red blood cells
RCT	Randomised controlled trial
REIN RCT	Ramipril Efficacy in Nephropathy RCT
RENAAL	Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan study

ROC	Receiver-operator curve
RR	Relative risk
RRT	Renal replacement therapy
SBP	Systolic blood pressure
SCr	Serum creatinine
SHARP	Study of Heart and Renal Protection
SIGN	Scottish Intercollegiate Guidelines Network
SLT	Systemic lupus erythematosus
STEACS	ST-segment elevation acute coronary syndrome
UKPDS	UK Prospective Diabetes Study
UPD	Usual protein diet
WMD	Weighted mean difference

## Glossary

ACEI	A drug that inhibits ACE (angiotensin-converting enzyme) which is important to the formation of angiotensin II. ACE inhibitors are used for blood pressure control and congestive heart failure.
Adverse events	A harmful, and usually relatively rare, event arising from treatment.
Albuminuria	The presence of albumin in the urine.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline.
Allocation concealment	The process used to prevent advance knowledge of group assignment in an RCT.
Audit	See 'Clinical audit'.
Before and after study	See 'Observational study'.
Bias	The effect that the results of a study are not an accurate reflection of any trends in the wider population. This may result from flaws in the design of a study or in the analysis of results.
Blinding (masking)	A feature of study design to keep the participants, researchers and outcome assessors unaware of the interventions which have been allocated.
Carer (care giver)	Someone other than a health professional who is involved in caring for a person with a medical condition, such as a relative or spouse.
Case-control study	Comparative observational study in which the investigator selects individuals who have experienced an event (for example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.
Clinical audit	A quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change.
Clinician	In this guideline, the term clinician means any health care professional.

<b>Cochrane review</b>	A systematic review of the evidence from randomised controlled trials relating to a particular health problem or healthcare intervention, produced by the Cochrane Collaboration. Available electronically as part of the Cochrane Library.
<b>Cohort study</b>	A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.
<b>Confidence interval (CI)</b>	A range of values which contains the true value for the population with a stated 'confidence' (conventionally 95%). The interval is calculated from sample data, and generally straddles the sample estimate. The 95% confidence value means that if the study, and the method used to calculate the interval, is repeated many times, then 95% of the calculated intervals will actually contain the true value for the whole population.
<b>Cost-effectiveness analysis</b>	An economics study design in which consequences of different interventions are measured using a single outcome, usually in natural units (for example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.
<b>Cost-effectiveness model</b>	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
<b>Cost-utility analysis</b>	A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs).
<b>Diagnostic study</b>	Any research study aimed at evaluating the utility of a diagnostic procedure.
<b>Evidence-based healthcare</b>	The process of systematically finding, appraising, and using research findings as the basis for clinical decisions.
<b>Follow up</b>	An attempt to measure the outcomes of an intervention after the intervention has ended.
<b>Generalisability</b>	The degree to which the results of a study or systematic review can be extrapolated to other circumstances, particularly routine health care situations in the NHS in England and Wales.
<b>Gold standard</b>	See 'Reference standard'.
<b>Guideline development group (GDG)</b>	An independent group set up on behalf of NICE to develop a guideline. They include healthcare professionals and patient and carer representatives.
<b>Hazard ratio (HR)</b>	A statistic to describe the relative risk of complications due to treatment, based on a comparison of event rates.
<b>Haematuria</b>	The presence of blood in the urine; often a symptom of urinary tract disease.

<b>Heterogeneity</b>	In systematic reviews, heterogeneity refers to variability or differences between studies in estimates of effect.
<b>Homogeneity</b>	In a systematic review, homogeneity means there are no or minor variations in the results between individual studies included in a systematic review.
<b>Hyperkalaemia</b>	Abnormally high potassium concentration in the blood, most often due to defective renal excretion, as in kidney disease.
<b>Inclusion criteria</b>	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
<b>Incremental cost</b>	The cost of one alternative less the cost of another.
<b>Incremental cost effectiveness ratio (ICER)</b>	The ratio of the difference in costs between two alternatives to the difference in effectiveness between the same two alternatives.
<b>Level of evidence</b>	A code (e.g. 1++, 1+, 2++) linked to an individual study, indicating where it fits into the NICE hierarchy of evidence and how well it has adhered to recognised research principles.
<b>Macroalbuminuria</b>	Albuminuria characterised by an ACR $\geq 30$ mg/mmol.
<b>Meta-analysis</b>	A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result.
<b>Methodological limitations</b>	Features of the design or reporting of a clinical study, which are known to be associated with risk of bias or lack of validity. Where a study is reported in this guideline as having significant methodological limitations, a recommendation has not been directly derived from it.
<b>Microalbuminuria</b>	Albuminuria characterised by an ACR 2.5–30 mg/mmol in men and 3.5–30 mg/mmol in women.
<b>Multivariate model</b>	A statistical model for analysis of the relationship between two or more predictor (independent) and the outcome (dependent) variable.
<b>National Collaborating Centre for Chronic Conditions (NCC-CC)</b>	A partnership of the Clinical Effectiveness Forum for Allied Health Professions, the NHS Confederation, the NICE Patient & Public Involvement Programme, the Royal College of General Practitioners, the Royal College of Nursing, the Royal College of Physicians of London, the Royal College of Physicians' Patient Involvement Unit, the Royal College of Surgeons of England, and the Royal Pharmaceutical Society of Great Britain. Set up in 2001 to undertake commissions from NICE to develop clinical guidelines for the NHS.
<b>National Health Service (NHS)</b>	This guideline is written for the NHS in England and Wales.
<b>National Institute for Health and Clinical Excellence (NICE)</b>	NICE is the independent organisation responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health.
<b>Negative predictive value</b>	The proportion of people with a negative test result who do not have the disease.

<b>Observational study</b>	Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups, for example cohort studies and case-control studies.
<b>Odds ratio</b>	A measure of treatment effectiveness. The odds of an event happening in the intervention group, divided by the odds of it happening in the control group. The ‘odds’ is the ratio of non-events to events.
<b>Outcome</b>	Measure of the possible results that may stem from exposure to prevention or therapeutic intervention. Outcome measures may be intermediate endpoints or they can be final endpoints.
<b>p values</b>	The probability that an observed difference could have occurred by chance. A p value of less than 0.05 is conventionally considered to be ‘statistically significant’.
<b>Placebo</b>	An inactive and physically indistinguishable substitute for a medication or procedure, used as a comparator in controlled clinical trials.
<b>Positive predictive value (PPV)</b>	The proportion of people with a positive test result who actually have the disease.
<b>Proteinuria</b>	The presence of protein in the urine.
<b>Pure red cell aplasia (PRCA)</b>	Transitory arrest of erythropoiesis.
<b>Quality of life</b>	Refers to the level of comfort, enjoyment, and ability to pursue daily activities.
<b>Quality-adjusted life year (QALY)</b>	A measure of health outcome which assigns to each period of time a weight, ranging from 0 to 1, corresponding to the health-related quality of life during that period, where a weight of 1 corresponds to optimal health, and a weight of 0 corresponds to a health state judged equivalent to death; these are then aggregated across time periods.
<b>Randomisation</b>	Allocation of participants in a study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to reduce sources of bias.
<b>Randomised controlled trial (RCT)</b>	A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.
<b>Reference standard (or gold standard)</b>	An agreed desirable standard, for example a diagnostic test or treatment, against which other interventions can be compared.
<b>Relative risk (RR)</b>	An estimate for the number of times more likely or less likely an event is to happen in one group of people compared with another, based on the incidence of the event in the intervention arm of a study, divided by the incidence in the control arm.
<b>Sample size</b>	The number of participants included in a trial or intervention group.

<b>Sensitivity (of a test)</b>	The proportion of people classified as positive by the gold standard, who are correctly identified by the study test.
<b>Sensitivity analysis</b>	A measure of the extent to which small changes in parameters and variables affect a result calculated from them. In this guideline, sensitivity analysis is used in health economics modelling.
<b>Serum creatinine</b>	An endogenous marker used to estimate kidney function. Creatinine is derived from the muscles of the body and is normally removed from blood by the kidneys. As kidney disease progresses, the level of creatinine in the blood increases.
<b>Single blind study</b>	A study where the investigator is aware of the treatment or intervention the participant is being given, but the participant is unaware.
<b>Specialist</b>	A clinician whose practice is limited to a particular branch of medicine or surgery, especially one who is certified by a higher medical educational organisation.
<b>Specificity (of a test)</b>	The proportion of people classified as negative by the gold standard, who are correctly identified by the study test.
<b>Stakeholder</b>	Any national organisation, including patient and carers' groups, healthcare professionals and commercial companies with an interest in the guideline under development.
<b>Statistical power</b>	In clinical trials, the probability of correctly detecting an underlying difference of a pre-specified size due to the intervention or treatment under consideration. Power is determined by the study design, and in particular, the sample size. Larger sample sizes increase the chance of small effects being correctly detected as statistically significant, though they may not be clinically significant.
<b>Statistical significance</b>	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ( $p < 0.05$ ).
<b>Suffix '(p)'</b>	Used to denote the presence of proteinuria when staging CKD.
<b>Systematic review</b>	Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.
<b>Washout period</b>	The stage in a crossover trial when one treatment is withdrawn before the second treatment is given.
<b>Withdrawal</b>	When a trial participant discontinues the assigned intervention before completion of the study.

# DEVELOPMENT OF THE GUIDELINE



# 1 Introduction

## 1.1 Background

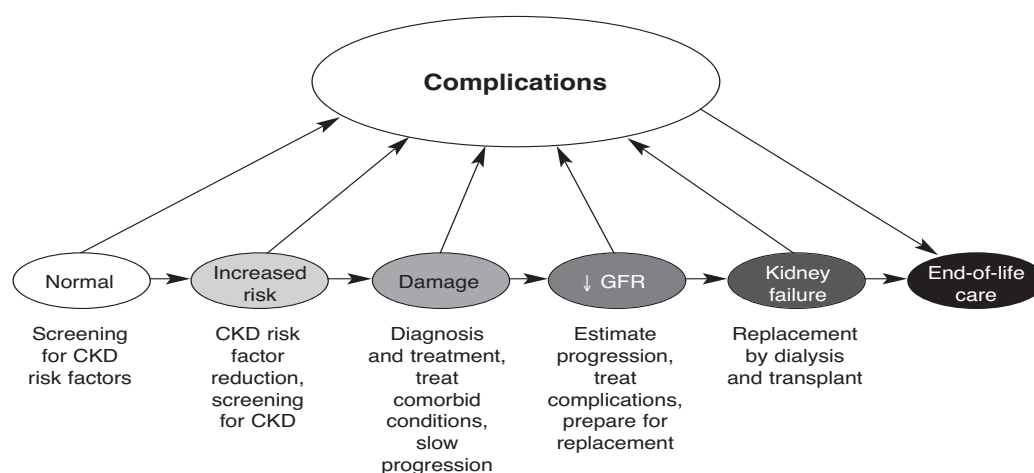
Publication of the second part of the Renal National Service Framework (NSF)<sup>2</sup> served to emphasise the change in focus in renal medicine from treatment of established kidney disease to earlier identification and prevention of kidney disease. Allied to this is the knowledge that late referral of people with advanced kidney disease to nephrology services from both primary and secondary care is still at least as high as 30%, engendering increased mortality and morbidity<sup>3–8</sup> and precluding assessment and preparation of those for whom conservative management is more appropriate.

Over 2% of the total NHS budget is spent on renal replacement therapy (dialysis and transplantation) for those with established renal failure.<sup>9</sup> Strategies aimed at earlier identification and (where possible) prevention of progression to established renal failure are therefore clearly required. Equally importantly, population studies have shown that people with diagnosed chronic kidney disease (CKD) have a far greater likelihood of cardiovascular death than progression to established renal failure.<sup>10–13</sup> Furthermore, the majority of people with CKD are asymptomatic and may not even be aware that they have any form of kidney problem.

The challenge is to:

- identify people with or at risk of developing CKD
- determine who needs intervention to minimise cardiovascular risk and to determine what that intervention should comprise
- determine who will develop progressive kidney disease and/or complications of kidney disease and how they may be identified and managed to reduce/prevent these outcomes
- determine who needs referral for specialist kidney care.

This requires adoption of an overall health approach (Figure 1.1) and an integrated care strategy involving public awareness, professional education, policy influence, and improved care delivery systems all under-pinned by research.



**Figure 1.1 Chronic kidney disease: an overall health approach.** GFR = glomerular filtration rate. (Reprinted by permission from Macmillan Publishers Ltd: *Kidney International*, Levey AS, Atkins R, Coresh J et al. Chronic kidney disease as a global health problem: approaches and initiatives – a position statement from Kidney Disease Improving Global Outcomes. *Kidney International* 2007; 72(3): 247–259.<sup>14</sup> Copyright 2007.)

A key component of the integrated care strategy is development of clinical guidelines which synthesise a scientific understanding of the disease in terms of:

- the disease prevalence
- the ability to identify the disease and the people at risk
- a knowledge of best therapies and strategies
- the ability to deliver effective therapies in the right place at the right time with the right tools.

In March 2006 the Joint Specialty Committee of the Royal College of Physicians of London and the Renal Association, together with representatives from the Royal College of General Practitioners, the Association for Clinical Biochemistry, the Society for District General Hospital Nephrologists, the British Geriatric Society, the Professional Advisory Council of Diabetes UK and the National Kidney Federation produced guidelines for the identification, management and referral of adult people with CKD.<sup>15</sup> Two further national strategies promoting identification of CKD were implemented in April 2006: the automatic reporting of an estimated glomerular filtration rate (eGFR) whenever a serum creatinine measurement is requested of any clinical chemistry laboratory<sup>16</sup> and the introduction of 4 renal domains in the Quality and Outcomes Framework (QOF) subsequently updated in April 2008 (Table 1.1).<sup>17</sup> These national strategies have raised questions that this guideline attempts to answer whilst addressing the challenges detailed above.

**Table 1.1 Quality and Outcomes Framework Guidance Chronic Kidney Disease Indicator Set (updated April 2008)**

<b>Indicator 1</b>	The practice can produce a register of patients aged 18 years and over with CKD (US National Kidney Foundation: Stage 3–5 CKD)
<b>Indicator 2</b>	The percentage of patients on the CKD register whose notes have a record of blood pressure in the previous 15 months
<b>Indicator 3</b>	The percentage of patients on the CKD register in whom the last blood pressure reading, measured in the previous 15 months, is 140/85 mmHg or less
<b>Indicator 5</b>	The percentage of patients on the CKD register with hypertension and proteinuria who are treated with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) (unless a contraindication or side effects are recorded)

## 1.2 Definition

The Renal NSF adopted the US National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) classification of CKD. This classification divides CKD into five stages (Table 1.2) defined by evidence of kidney damage and level of renal function as measured by glomerular filtration rate (GFR). Stages 3–5 may be defined by GFR alone, whilst stages 1 and 2 also require the presence of persistent proteinuria, albuminuria, haematuria or structural abnormalities. Stage 5 CKD may be described as established renal failure (also called end stage renal disease (ESRD)), and is CKD which has progressed so far that renal replacement therapy (regular dialysis treatment or kidney transplantation) may be required to maintain life. Established renal failure is an irreversible, long-term condition. A small number of people with established renal failure may choose conservative management only.

The classification of CKD into 5 stages has been widely adopted but as understanding of the epidemiology of CKD has developed, it has been criticised as not being sufficiently sophisticated for clinical needs. For example, longitudinal population studies have suggested that stage 3 should be subdivided into 3A and 3B. Other studies, underlining the importance of proteinuria/albuminuria as an independent risk factor for adverse outcomes in CKD, suggest the adoption of a '(p)' suffix in the different stages. This evidence and the changes to the classification that the evidence suggests will be considered further in the relevant sections of the guideline.

**Table 1.2 NKF-KDOQI stages of chronic kidney disease**

Stage	Description	GFR (ml/min/1.73m <sup>2</sup> )
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mild reduction in GFR	60–89
3*	Moderate reduction in GFR	30–59
4	Severe reduction in GFR	15–29
5	Kidney failure	<15 (or dialysis)

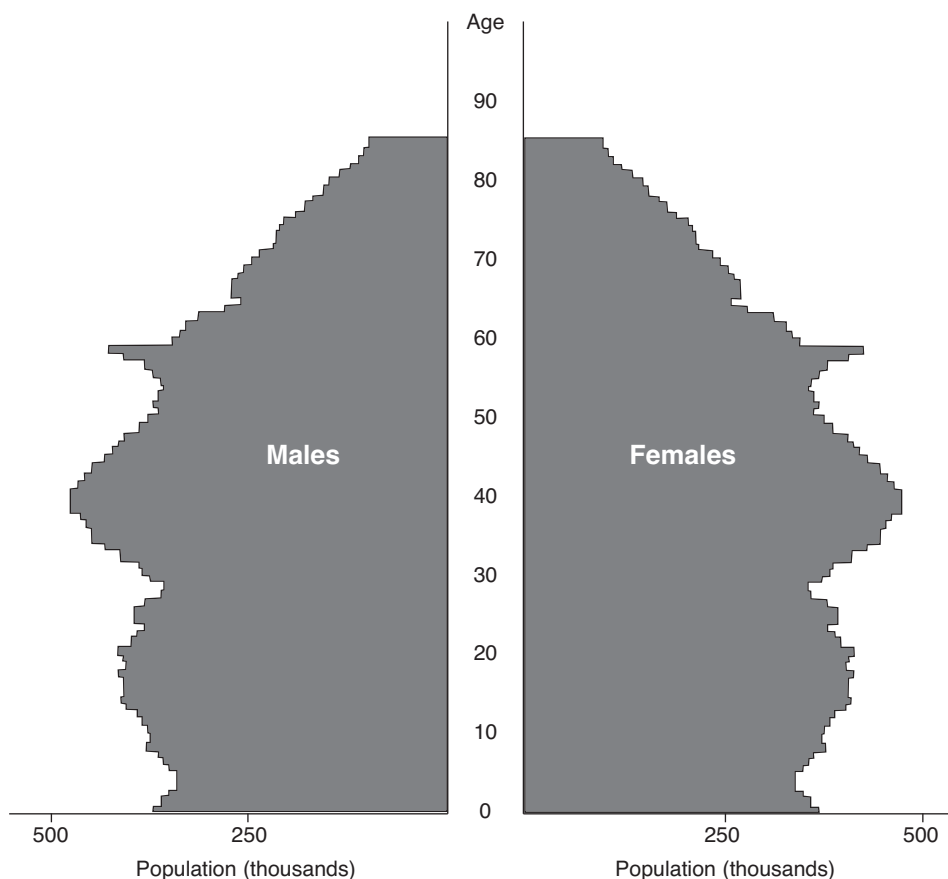
\* This guideline recommends splitting this into 3A and 3B – see section 5.

CKD is defined as either kidney damage (proteinuria, haematuria or anatomical abnormality) or GFR <60 ml/min/1.73m<sup>2</sup> present on at least 2 occasions for ≥3 months.

### 1.3 Burden of disease

CKD is increasingly recognised as a public health problem and is usually characterised by an asymptomatic period, which is potentially detectable. Tests for detecting CKD are both simple and freely available and there is evidence that treatment can prevent or delay progression of CKD, reduce or prevent development of complications, and reduce the risk of cardiovascular disease (CVD). There is considerable overlap between CKD, diabetes and CVD and the risk of developing CKD increases with increasing age. In assessing the burden of disease it is important to understand the characteristics of our population.

The UK is an ageing and growing population. Since 1971 the population has increased by 7.7% and since 2001 by 0.5% per annum such that the UK population in 2005 numbered 60,209,500 people.<sup>18</sup> The mean age of the population in 1971 was 34.4 years and that had increased to 38.8 years with 16% of the population over 65 years of age in 2005 (Figure 1.2). The population is also gaining weight; 67% of men and 58% of women are overweight. The population prevalence of diabetes is 4%; 11.3% of the population are hypertensive; and although smoking rates have decreased, 24% of the population aged over 16 are smokers (25% of men and 23% of women). It is unsurprising that CVD remains prevalent: 3.6% of the population have coronary heart disease, 1.5% cerebrovascular disease, and 0.4% congestive heart failure.

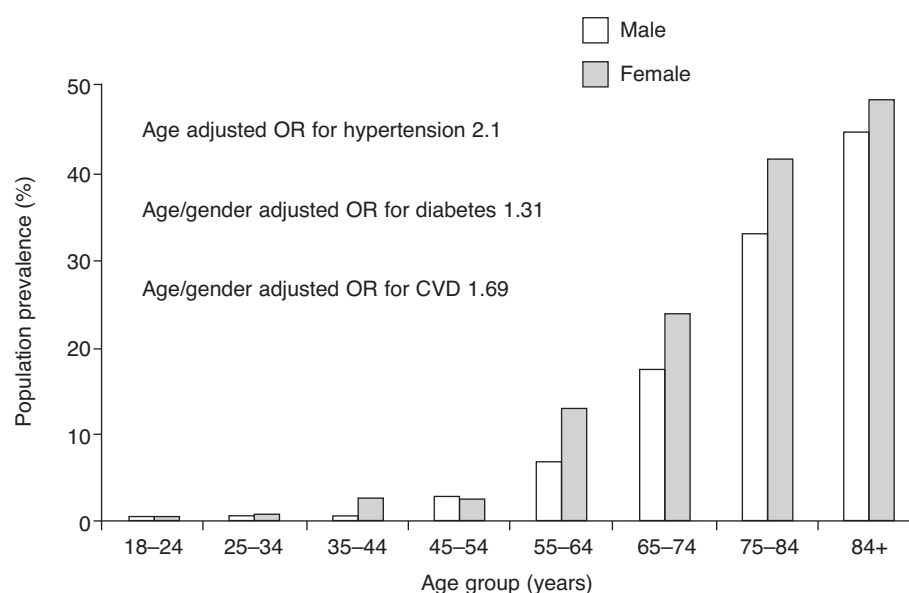


**Figure 1.2 Age and gender distribution of the UK population in 2005.** (Source: Office for National Statistics website: [www.ons.gov.uk](http://www.ons.gov.uk). Crown copyright material is reproduced with the permission of the Controller Office of Public Sector Information (OPSI). Reproduced under the terms of the Click-Use Licence.)

Data from the UK Renal Registry<sup>9</sup> indicate that there were 41,776 adult patients alive on renal replacement therapy (RRT) in the UK at the end of 2005, a prevalence for adults of 694 per million population (pmp). Addition of the 748 children under age 18 on RRT gives a total prevalence of 706 pmp. There was a 5.0% annual increase in the prevalence of people on RRT in the 38 renal units participating in the Registry since 2000. In 2005, the mean percentage of patients referred late (less than 90 days before dialysis initiation) was still 30%, unchanged from the value in 2000.

Whilst the UK Renal Registry provides accurate estimates of numbers of people undergoing RRT, this cannot be seen as a surrogate for the number of people with stage 5 CKD, as the mean GFR of those starting RRT is 7.5 ml/min/1.73 m<sup>2</sup>.

Information relating to the UK population prevalence of stage 3–5 CKD comes from a large primary care study (practice population 162,113) suggesting an age standardised prevalence of stage 3–5 CKD of 8.5% (10.6% in females and 5.8% in males). In these people the age- and gender-adjusted odds ratio (OR) for hypertension was 2.1 (95% CI 2.0–2.2), for diabetes 1.33 (95% CI 1.21–1.41) and for CVD 1.69 (95% CI 1.59–1.79).<sup>19</sup> The prevalence of CKD rose dramatically with age (Figure 1.3).



**Figure 1.3 Adult CKD prevalence in the UK: age-standardised prevalence of stage 3–5  $\approx$  8.5%.** (Reprinted by permission from Macmillan Publishers Ltd: *Kidney International* (Stevens PE, O'Donoghue DJ, de Lusignan S et al. Chronic kidney disease management in the United Kingdom: NEOERICA project results. *Kidney International* 2007; 72(1):92–99).<sup>19</sup> Copyright 2007.)

Although we have very little information about the total burden of CKD in the UK, data from the National Health and Nutrition Examination Surveys (NHANES)<sup>20,21</sup> in the USA not only gives a guide to the likely overall population prevalence, but also suggests that the prevalence is increasing. Comparison of the prevalence of CKD in NHANES 1988–1994 with NHANES 1999–2004 showed an increase in population prevalence from 10.03 to 13.07%.<sup>22</sup> The overall prevalence among men increased from 8.2% to 11.1% and in women from 12.1% to 15.0%. The increased prevalence was partly explained by the increase in a number of CKD risk factors, including an ageing population and an increase in obesity, diagnosed diabetes and hypertension. It is important to note that the NHANES studies included only non-institutionalised people, and the prevalence of CKD in nursing homes is likely to be significantly higher.

UK population studies have demonstrated that the risk of cardiovascular death in people with diagnosed CKD far outweighs the risk of progression. A retrospective cohort study found that only 4% of 1076 individuals progressed to end stage kidney disease over a 5.5 year follow-up period whilst 69% had died at the end of follow-up; the cause of death was cardiovascular in 46% of cases.<sup>10</sup> Similarly, a prospective cohort study of 3240 individuals with a median GFR of 28.5 ml/min/1.73m<sup>2</sup> not known to renal services found that mortality was 39.5% after a median follow-up period of 31.3 months. The cause of death was cardiovascular in 39.7% of cases. Only 8.3% of individuals sustained a decline in GFR greater than 5 ml/min/1.73m<sup>2</sup>/year during the period of follow-up.<sup>11</sup> This remarkable burden of cardiovascular disease in people with CKD, and the relative lack of progression, has been confirmed in a number of observational studies<sup>12,13</sup> and is further illustrated by results from the New Opportunities for Early Renal Intervention by Computerised Assessment (NEOERICA) project where 50% of those with a stage 4 and 5 CKD had coexistent CVD which increased in prevalence as GFR decreased.<sup>19</sup> The magnitude of other comorbidities such as diabetes, hypertension and significant anaemia also increased with more advanced kidney dysfunction (Table 1.3).

**Table 1.3 NEOERICA: Comorbidity stratified by GFR**

<b>GFR</b> (ml/min/1.73m <sup>2</sup> )	<b>&lt;30</b> N=525	<b>30–44</b> N=2475	<b>45–59</b> N=8731	<b>&gt;60</b> N=26531
All CVD (%)	50.7	42.7	27.1	14.8
Diabetes (%)	23.0	16.1	12	9.4
Hypertension (%)	87.8	86.6	71.4	47.1
Haemoglobin (Hb) <11 g/dl (%)	10.0	4.1	2.9	2.7

Adapted and reprinted by permission from Macmillan Publishers Ltd: *Kidney International* (Stevens PE, O'Donoghue DJ, de Lusignan S et al. Chronic kidney disease management in the United Kingdom: NEOERICA project results. *Kidney International* 2007; 72(1):92–99).<sup>19</sup> Copyright 2007.

The study of unreferred CKD by John et al. demonstrated that 85% of those with advanced kidney dysfunction were unknown to renal services.<sup>11</sup> The NEOERICA study serves to underline this but also demonstrates that CKD is still largely unrecognised: only 2.1% of those with a GFR less than 60 ml/min/1.73m<sup>2</sup> had a coded diagnosis of renal disease.

A national programme to identify vulnerability to vascular diseases was announced by the Secretary of State for Health in April 2008 following initial results from modelling work carried out by the Department of Health. This work suggested that a vascular check programme would prevent 4000 people a year from developing diabetes and could also detect at least 25,000 cases of diabetes or kidney disease earlier.

It has long been recognised that the prevalence of established renal failure is higher amongst the black and minority ethnic communities in comparison to Caucasian populations.<sup>23</sup> The predominant reasons for this include the increased prevalence of Type 2 diabetes in South Asians and hypertension in African Caribbeans, together with diseases particular to certain communities such as chronic interstitial nephritis in South Asians and focal glomerulosclerosis in African Caribbeans. However, there is a relative lack of knowledge concerning the prevalence of earlier stages of CKD in black and ethnic minority populations in comparison to Caucasians. In the United States, the racial disparity in the incidence of established renal failure among black compared with white populations is not reflected in the prevalence of less severe degrees of impaired kidney function.<sup>24</sup> Similar findings have been reported from the NHANES III data. It has been suggested that the reasons for this disparity lie with racial differences in the rate of progression to established renal failure. The ABLE projects (A Better Life through Education and Empowerment) in the UK have also demonstrated that kidney disease in South Asians and African Caribbeans may deteriorate more rapidly to established renal failure.<sup>25</sup> In the long term, the ABLE study aims to identify the reasons for this faster deterioration.

## 2 Methodology

### 2.1 Aim

The aim of the National Collaborating Centre for Chronic Conditions (NCC-CC) is to provide a user-friendly, clinical, evidence-based guideline for the National Health Service (NHS) in England and Wales that:

- offers best clinical advice for the early identification and management of CKD in adults in primary and secondary care
- is based on best published clinical and economic evidence, alongside expert consensus
- takes into account patient choice and informed decision-making
- defines the major components of NHS care provision for CKD
- details areas of uncertainty or controversy requiring further research and
- provides a choice of guideline versions for different audiences.

### 2.2 Scope

The guideline was developed in accordance with a scope which detailed the remit of the guideline originating from the Department of Health and specified those aspects of CKD care to be included and excluded.

Prior to the commencement of the guideline development, the scope was subjected to stakeholder consultation in accordance with processes established by the National Institute for Health and Clinical Excellence (NICE).<sup>1</sup> The full scope is shown in Appendix B.

### 2.3 Audience

The guideline is intended for use by the following people or organisations:

- all healthcare professionals
- people with CKD and their carers
- patient support groups
- commissioning organisations and
- service providers.

### 2.4 Involvement of people with CKD

The NCC-CC was keen to ensure the views and preferences of people with CKD and their carers informed all stages of the guideline. This was achieved by:

- having a person with CKD and a carer as patient representatives on the guideline development group

- consulting the Patient and Public Involvement Programme (PPIP) housed within NICE during the pre-development (scoping) and final validation stages of the guideline project and
- the inclusion of patient groups as registered stakeholders for the guideline.

## 2.5 Guideline limitations

Guideline limitations are as follows:

- NICE clinical guidelines usually do not cover issues of service delivery, organisation or provision (unless specified in the remit from the Department of Health).
- NICE is primarily concerned with health services and so recommendations are not provided for social services and the voluntary sector. However, the guideline may address important issues in how NHS clinicians interface with these sectors.
- Generally, the guideline does not cover rare, complex, complicated or unusual conditions.
- It is not possible in the development of a clinical guideline to complete extensive systematic literature review of all pharmacological toxicity. NICE expects the guidelines to be read alongside the summaries of product characteristics.

## 2.6 Other work relevant to the guideline

Related NICE public health guidance comprises:

- 'Brief interventions and referral for smoking cessation in primary care and other settings'.<sup>26</sup>

Related NICE clinical guidelines are:

- 'Anaemia management in chronic kidney disease'<sup>27</sup>
- 'Hypertension: management of hypertension in adults in primary care'<sup>28</sup>
- 'Type 2 diabetes: the management of type 2 diabetes (update)'<sup>29</sup>
- 'Lipid modification: cardiovascular risk assessment: the modification of blood lipids for the primary and secondary prevention of cardiovascular disease'<sup>30</sup>
- 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'.<sup>31</sup>

## 2.7 Background

The development of this evidence-based clinical guideline draws upon the methods described by the NICE 'Guidelines manual'<sup>1</sup> (see <http://www.nice.org.uk>). The developers' role and remit is summarised in Table 2.1.



**Table 2.1 Role and remit of the developers**

<b>National Collaborating Centre for Chronic Conditions (NCC-CC)</b>	The NCC-CC was set up in 2001 and is housed within the Royal College of Physicians (RCP). The NCC-CC undertakes commissions received from the National Institute for Health and Clinical Excellence (NICE). A multiprofessional partners' board inclusive of patient groups and NHS management governs the NCC-CC.
<b>NCC-CC technical team</b>	The technical team met approximately two weeks before each Guideline Development Group (GDG) meeting and comprised the following members: <ul style="list-style-type: none"> <li>• GDG Chair</li> <li>• GDG Clinical Advisor</li> <li>• Information Scientist</li> <li>• Research Fellow</li> <li>• Health Economist</li> <li>• Project Manager.</li> </ul>
<b>Guideline Development Group</b>	The GDG met monthly (January 2007 to February 2008) and comprised a multidisciplinary team of health professionals and people with chronic kidney disease, who were supported by the technical team. The GDG membership details including patient representation and professional groups are detailed in the GDG membership table at the front of this guideline.
<b>Guideline Project Executive (PE)</b>	The PE was involved in overseeing all phases of the guideline. It also reviewed the quality of the guideline and compliance with the DH remit and NICE scope. The PE comprised of: <ul style="list-style-type: none"> <li>• NCC-CC Director</li> <li>• NCC-CC Assistant Director</li> <li>• NCC-CC Manager</li> <li>• NICE Commissioning Manager</li> <li>• Technical Team.</li> </ul>
<b>Formal consensus</b>	At the end of the guideline development process the GDG met to review and agree the guideline recommendations.

Members of the GDG declared any interests in accordance with the NICE 'Guidelines manual'.<sup>1</sup> A register is given in Appendix D, available online at <http://www.rcplondon.ac.uk/pubs/brochure.aspx?e=257>

## 2.8 The process of guideline development

The basic steps in the process of producing a guideline are:

- 1 Developing clinical questions
- 2 Systematically searching for the evidence
- 3 Critically appraising the evidence
- 4 Incorporating health economics evidence
- 5 Distilling and synthesising the evidence and writing recommendations
- 6 Grading the evidence statements
- 7 Agreeing the recommendations
- 8 Structuring and writing the guideline
- 9 Updating the guideline.

### 1 *Developing evidence-based questions*

The technical team drafted a series of clinical questions that covered the guideline scope. The GDG and Project Executive refined and approved these questions, which are shown in Appendix A.

### 2 *Searching for the evidence*

The information scientist developed a search strategy for each question. Key words for the search were identified by the GDG. In addition, the health economist searched for additional papers providing economics evidence or to inform detailed health economics work (for example, modelling). Papers that were published or accepted for publication in peer-reviewed journals were considered as evidence by the GDG. Conference paper abstracts and non-English language papers were excluded from the searches.

Each clinical question dictated the appropriate study design that was prioritised in the search strategy but the strategy was not limited solely to these study types. The research fellow or health economist identified relevant titles and abstracts from the search results for each clinical question and full papers were obtained. Exclusion lists were generated for each question together with the rationale for the exclusion. The exclusion lists were presented to the GDG. See Appendix A for literature search details.

### 3 *Appraising the evidence*

The research fellow or health economist, as appropriate, critically appraised the full papers. In general, no formal contact was made with authors however there were *ad hoc* occasions when this was required in order to clarify specific details. Critical appraisal checklists were compiled for each full paper. One research fellow undertook the critical appraisal and data extraction. The evidence was considered carefully by the GDG for accuracy and completeness.

All procedures are fully compliant with the:

- NICE methodology as detailed in the 'Guidelines manual'<sup>1</sup>
- NCC-CC quality assurance document and systematic review chart available at: [http://www.rcplondon.ac.uk/college/ceeu/nccc\\_index.htm](http://www.rcplondon.ac.uk/college/ceeu/nccc_index.htm).

### 4 *Health economics evidence*

Published economic evaluations were retrieved, assessed and reviewed for every guideline question. Full economic evaluations were included, that is those studies that compare the overall health outcomes of different interventions as well as their cost. Cost analyses and cost-consequence analysis, which do not evaluate overall health gain, were not included. Evaluations conducted in the context of non-OECD countries were also excluded, since costs and care pathways are unlikely to be transferrable to the UK NHS.

Areas for health economics modelling were agreed by the GDG after the formation of the clinical questions. The health economist reviewed the clinical questions to consider the potential application of health economics modelling, and these priorities were agreed with the GDG.

The health economist performed supplemental literature searches to obtain additional data for modelling. Assumptions, data and structures of the models were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

### 5 *Distilling and synthesising the evidence and developing recommendations*

The evidence from each full paper was distilled into an evidence table and synthesised into evidence statements before being presented to the GDG. This evidence was then reviewed by the GDG and used as a basis upon which to formulate recommendations. The criteria for grading evidence are shown in Table 2.2.

Evidence tables are available online at <http://www.rcplondon.ac.uk/pubs/brochure.aspx?e=257>

### 6 *Grading the evidence statements*

Level of evidence	Type of evidence
1++	High-quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias.
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1–	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias.*
2++	High-quality systematic reviews of case-control or cohort studies. High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal.
2–	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal.*
3	Non-analytic studies (for example case reports, case series).
4	Expert opinion, formal consensus.

\*Studies with a level of evidence ‘–’ should not be used as a basis for making a recommendation.

### 7 *Agreeing the recommendations*

The GDG employed formal consensus techniques to:

- ensure that the recommendations reflected the evidence base
- approve recommendations based on lesser evidence or extrapolations from other situations
- reach consensus recommendations where the evidence was inadequate and
- debate areas of disagreement and finalise recommendations.

The GDG also reached agreement on:

- recommendations as key priorities for implementation
- key research recommendations and
- algorithms.

In prioritising key recommendations for implementation, the GDG took into account the following criteria:

- high clinical impact
- high impact on reducing variation in practice
- more efficient use of NHS resources and
- allowing the patient to reach critical points in the care pathway more quickly.

Audit criteria for this guideline will be produced by NICE following publication in order to provide suggestions of areas for audit in line with the key priorities for implementation.

## 8 *Structuring and writing the guideline*

The guideline is divided into sections for ease of reading. For each section the layout is similar and contains:

- *Clinical introduction*: sets a succinct background and describes the current clinical context
- *Methodological introduction*: describes any issues or limitations that were apparent when reading the evidence base
- *Evidence statements*: provides a synthesis of the evidence-base and usually describes what the evidence showed in relation to the outcomes of interest
- *Health economics*: presents, where appropriate, an overview of the cost effectiveness evidence-base, or any economics modelling
- *From evidence to recommendations*: sets out the GDG decision-making rationale, providing a clear and explicit audit trail from the evidence to the evolution of the recommendations
- *Recommendations*: provides stand alone, action-orientated recommendations.
- *Evidence tables*: The evidence tables are not published as part of the full guideline but are available online at <http://www.rcplondon.ac.uk/pubs/brochure.aspx?e=257>. These describe comprehensive details of the primary evidence that was considered during the writing of each section.

## 9 *Writing the guideline*

The first draft version of the guideline was drawn up by the technical team in accordance with the decisions of the GDG, incorporating contributions from individual GDG members in their expert areas and edited for consistency of style and terminology. The guideline was then submitted for a formal public and stakeholder consultation prior to publication. The registered stakeholders for this guideline are detailed on the NICE website, [www.nice.org.uk](http://www.nice.org.uk). Editorial responsibility for the full guideline rests with the GDG.

The different versions of the guideline are shown in Table 2.3.

**Table 2.3 Different versions of the guideline**

<b>Full version</b>	Details the recommendations, the supporting evidence base and the expert considerations of the GDG. Published by the NCC-CC. Available at <a href="http://www.rcplondon.ac.uk/pubs/brochure.aspx?e=257">http://www.rcplondon.ac.uk/pubs/brochure.aspx?e=257</a>
<b>NICE version</b>	Documents the recommendations without any supporting evidence. Available at <a href="http://www.nice.org.uk">http://www.nice.org.uk</a>
<b>'Quick reference guide'</b>	An abridged version. Available at <a href="http://www.nice.org.uk">http://www.nice.org.uk</a>
<b>'Understanding NICE guidance'</b>	A lay version of the guideline recommendations. Available at <a href="http://www.nice.org.uk">http://www.nice.org.uk</a>

### 10 *Updating the guideline*

Literature searches were repeated for all of the evidence-based questions at the end of the GDG development process allowing any relevant papers published up until 8 February 2008 to be considered. Future guideline updates will consider evidence published after this cut-off date.

Two years after publication of the guideline, NICE will ask a National Collaborating Centre to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an early update. If not, the guideline will be considered for update approximately four years after publication.

## 2.9 Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The NCC-CC disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

## 2.10 Funding

The National Collaborating Centre for Chronic Conditions was commissioned by the National Institute for Health and Clinical Excellence to undertake the work on this guideline.

## 3 Key messages of the guideline

### 3.1 Key priorities for implementation

- To detect and identify proteinuria, use urine albumin:creatinine ratio (ACR) in preference, as it has greater sensitivity than protein:creatinine ratio (PCR) for low levels of proteinuria. For quantification and monitoring of proteinuria, PCR can be used as an alternative. ACR is the recommended method for people with diabetes.

Offer ACEI/ARBs to non-diabetic people with CKD and hypertension and ACR  $\geq 30$  mg/mmol (approximately equivalent to PCR  $\geq 50$  mg/mmol, or urinary protein of  $\geq 0.5$  g/day).

Stage 3 CKD should be split into two subcategories defined by:

- GFR 45–59 ml/min/1.73 m<sup>2</sup> (stage 3A)
- GFR 30–44 ml/min/1.73 m<sup>2</sup> (stage 3B).

People with CKD should usually be referred for specialist assessment if any of the following apply:

- stage 4 and 5 CKD (with or without diabetes)
- heavy proteinuria (ACR  $\geq 70$  mg/mmol, approximately equivalent to PCR  $\geq 100$  mg/mmol, or urinary protein excretion  $\geq 1$  g/24 h) unless known to be due to diabetes and already appropriately treated
- proteinuria (ACR  $\geq 30$  mg/mmol, approximately equivalent to PCR  $\geq 50$  mg/mmol, or urinary protein excretion  $\geq 0.5$  g/24 h) together with haematuria
- rapidly declining eGFR ( $>5$  ml/min/1.73m<sup>2</sup> in one year, or  $>10$  ml/min/1.73m<sup>2</sup> within 5 years)
- hypertension that remains poorly controlled despite the use of at least 4 anti-hypertensive drugs at therapeutic doses (see NICE clinical guideline 34, ‘Hypertension: management of hypertension in adults in primary care’)
- a rare or genetic cause of CKD, or the suspicion of one
- suspected renal artery stenosis.

Offer people testing for CKD if they have any of the following risk factors:

- diabetes (types 1 and 2)
- hypertension
- cardiovascular disease (ischaemic heart disease, chronic heart failure, peripheral vascular disease and cerebral vascular disease)
- structural renal tract disease, renal calculi or prostatic hypertrophy
- multisystem diseases with potential kidney involvement, e.g. systemic lupus erythematosus (SLE)
- family history of stage 5 CKD or hereditary kidney disease.

Take the following steps to identify progressive CKD:

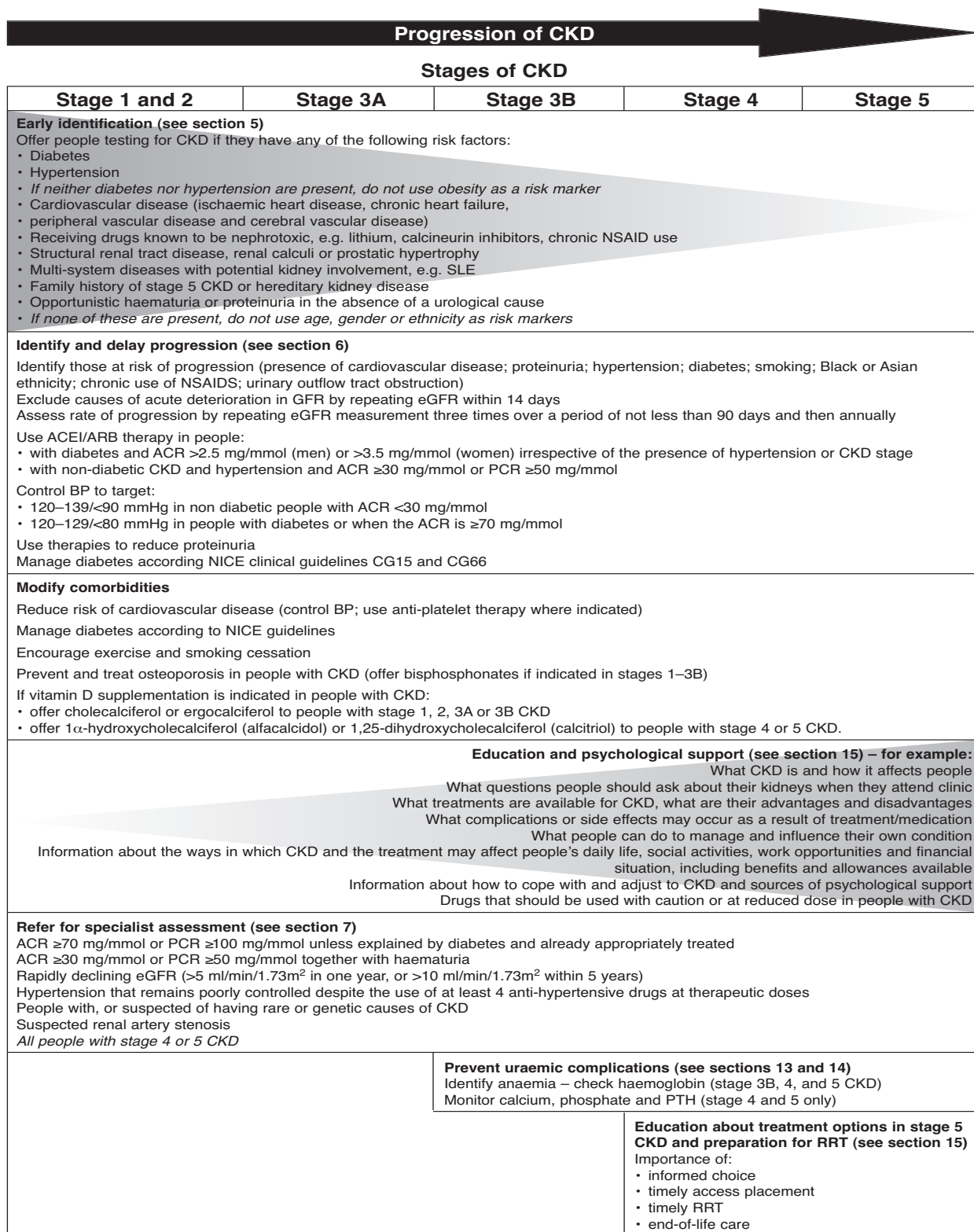
- obtain a minimum of three glomerular filtration rate (GFR) estimations over a period of not less than 90 days
- in people with a new finding of reduced eGFR, repeat the estimated glomerular filtration rate (eGFR) within 2 weeks to exclude causes of acute deterioration of GFR, e.g. acute kidney injury or initiation of angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) therapy

## Chronic kidney disease

- define progression as a decline in eGFR of  $>5$  ml/min/1.73 m<sup>2</sup> within one year, or  $>10$  ml/min/1.73m<sup>2</sup> within 5 years
- focus particularly on those in whom a decline of GFR continuing at the observed rate would lead to the need for renal replacement therapy within their lifetime by extrapolating the current rate of decline.

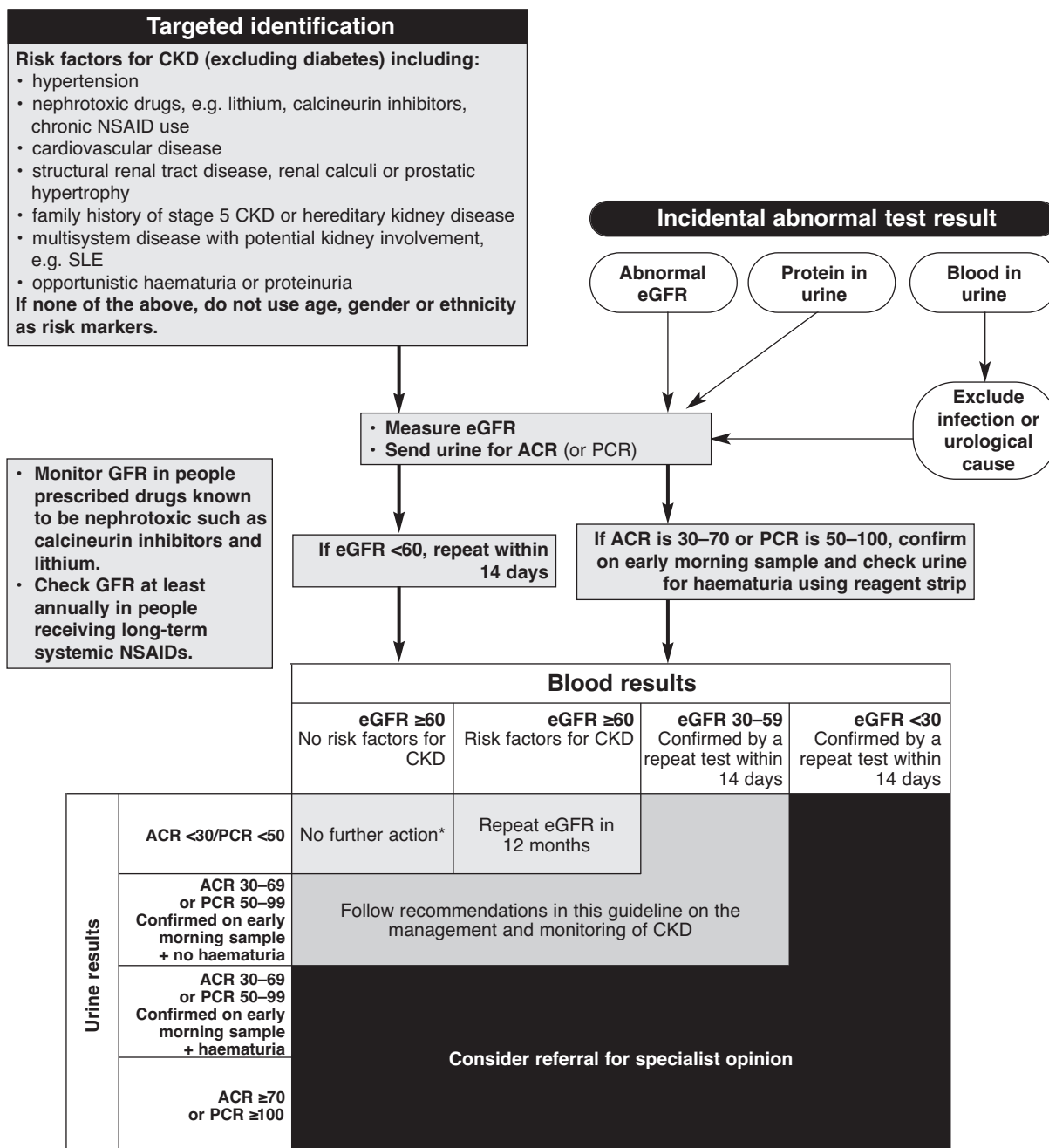
In people with CKD, aim to keep the systolic blood pressure below 140 mmHg (target range 120–139 mmHg) and the diastolic blood pressure below 90 mmHg.

## 3.2 Algorithms

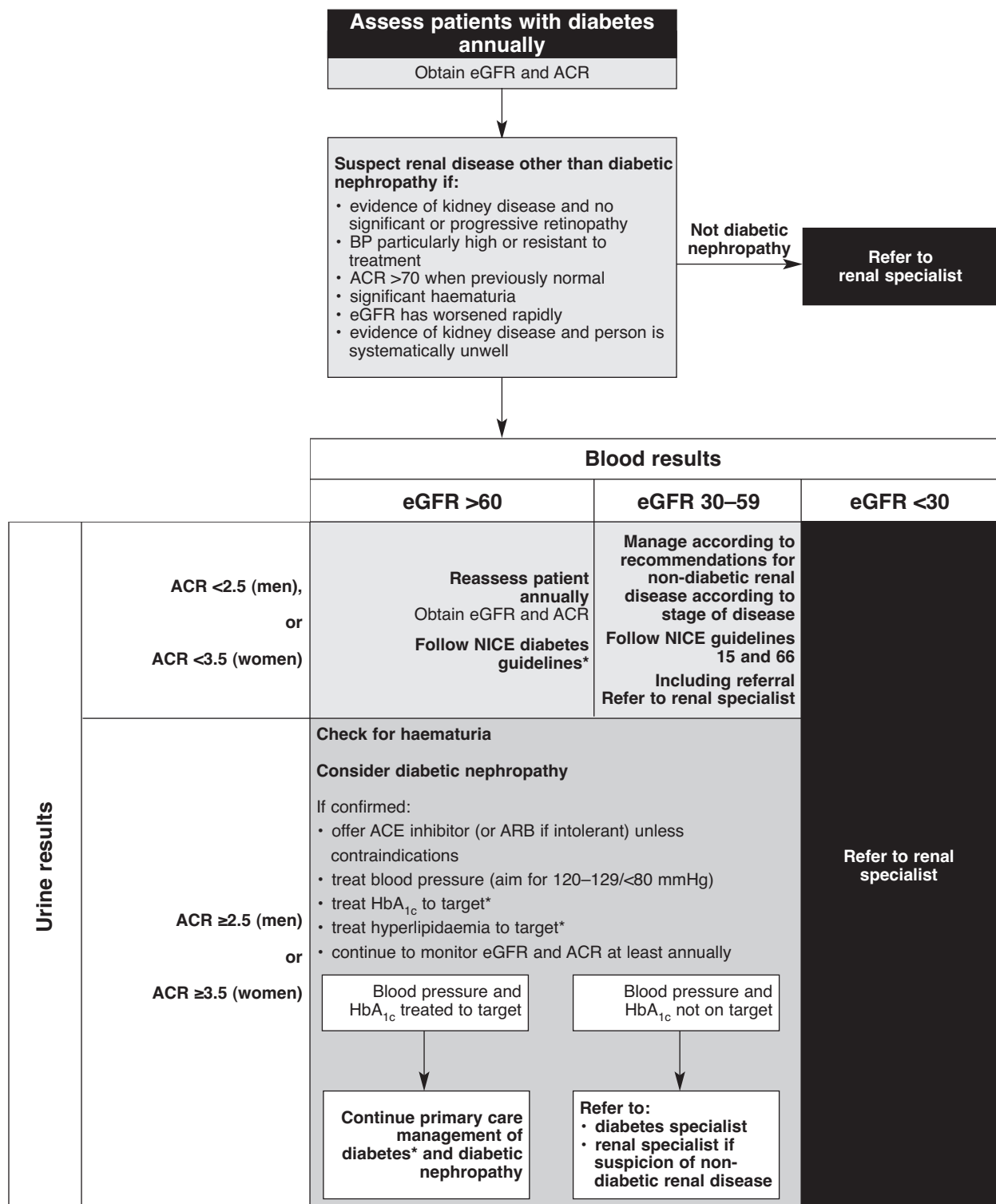


**Figure 3.1 Investigations and interventions at different stages of CKD.** This algorithm should be used as an aide memoire in primary care to trigger various investigations and interventions relevant for people in different stages of CKD. Stages of CKD are shown from left to right and activities appear as horizontal bands, some of which are more relevant to early or late disease, as indicated by their positioning and by the graded shading. BP = blood pressure; NSAID = non-steroidal anti-inflammatory drug; PTH = parathyroid hormone.





**Figure 3.2 Identification, diagnosis and referral of patients with CKD but without diabetes.** eGFR is expressed as ml/min/1.73m<sup>2</sup>. Albumin:creatinine ratio (ACR) and protein:creatinine ratio (PCR) are expressed as mg/mmol.



\*See NICE clinical guidelines on type 1 diabetes (<http://www.nice.org.uk/CG15>) and type 2 diabetes (<http://www.nice.org.uk/CG66>).

**Figure 3.3 Diagnosis and referral of patients with CKD and diabetes.** eGFR is expressed as ml/min/1.73m<sup>2</sup>. Albumin:creatinine ratio (ACR) is expressed as mg/mmol.

# THE GUIDELINE

## 4 Investigation of CKD

### 4.1 Measurement of kidney function

#### 4.1.1 Clinical introduction

The glomerular filtration rate (GFR) is equal to the sum of the filtration rates in all of the functioning nephrons and is the best index of overall kidney function. Knowledge of GFR is essential for the diagnosis and management of CKD and is a translatable concept. Because a normal GFR is roughly 100 ml/min/1.73 m<sup>2</sup>, we can explain kidney function to patients and carers in terms of a percentage of normal – a more easily understandable concept than GFR.

The gold standard methods of estimating GFR require measurement of an ideal filtration marker. These markers should be freely filtered by the glomerulus, should not be bound to plasma proteins, must be excreted unchanged and not be subject to either tubular secretion or absorption. Commonly used markers include inulin, <sup>51</sup>Cr-EDTA, <sup>125</sup>I-iothalamate and iohexol. Gold standard methods of assessing GFR are technically demanding, expensive, time consuming and unsuitable for widespread identification of CKD in the ‘at risk’ population.

At the other end of the accuracy scale lies measurement of serum creatinine, which is a universally available endogenous test of kidney function. Although easy and cheap to measure, creatinine is subject to non-renal and analytical influences which make it insufficiently sensitive to detect moderate CKD on its own. Measurement of 24-hour urinary creatinine clearance improves the accuracy but is also subject to the same non-renal and analytical influences compounded by inaccuracies in urine collection, to say nothing of the inconvenience associated with 24-hour urine collections. An alternative and more accurate endogenous marker is cystatin C, a 13 kDa cationic protein produced by all nucleated cells. Serum cystatin C levels are chiefly determined by GFR. Potential limitations of cystatin C as a marker of GFR include lack of assay standardisation, the requirement for a dedicated analytical system, and increased costs relative to serum creatinine (approximately £3/assay compared to <£0.10/assay).

A further alternative is to measure serum creatinine and estimate GFR using an equation which corrects for some of the more significant non-renal influences. This approach is known to be more sensitive for the detection of CKD than serum creatinine and more accurate than creatinine clearance.

So what have previous guideline groups recommended? The SIGN guidelines<sup>32</sup> recommended use of prediction equations in place of 24-hour creatinine clearance or serum creatinine alone and preferred prediction equations to cystatin C on the grounds of practical and resource considerations. The Modification of Diet in Renal Disease (MDRD) equation was preferred to the Cockcroft-Gault formula. The UK CKD guidelines and the UK consensus conference recommended use of the 4-variable MDRD equation using zero biased creatinine methods.<sup>33,34</sup> Others (KDOQI, CARI and KDIGO)<sup>14,35–37</sup> have recommended that serum creatinine should not be used alone to assess kidney function, that creatinine assays should be traceable to a reference creatinine method, and that an estimated GFR should be reported by laboratories alongside the serum creatinine measurement using the 4-variable MDRD equation.

■ *What is the best diagnostic test to measure renal function in routine clinical practice?*

### 4.1.2 Methodology

Due to the large volume of studies in this area, studies were included if the sample size was greater than 100, gold standard tests were used as the reference test, and bias, accuracy, sensitivity, specificity, positive and negative predictive values, test correlation, or diagnostic accuracy (area under the receiver–operator curve (ROC)) outcomes were reported. For studies comparing the MDRD predictive equation with other equations, the serum creatinine measurements had to be calibrated to the MDRD laboratory reference standard. Two exceptions to the sample size cut-off were the studies that evaluated the GFR equations in older people.<sup>38,39</sup> Publications that reported on the accuracy of tests in dialysis or renal replacement patients were excluded.

Five studies<sup>40–44</sup> that evaluated the accuracy of serum cystatin C were excluded because gold standard tests were not used as the comparator or because creatinine (the MDRD equation) was not calibrated properly to the MDRD laboratory reference values.

Nine studies<sup>38–41,45–49</sup> that evaluated the accuracies of predictive equations in estimating GFR were excluded due to methodological limitations or because the serum creatinine measurements were not calibrated to the MDRD assay as determined by isotope-dilution mass spectrometry.

Five studies<sup>50–54</sup> assessing the accuracies of the MDRD equation and the Cockcroft-Gault equation in predicting the glomerular filtration rate were included. These were conducted in large sample sizes (N=219 to 2095) and were quite heterogeneous in terms of the population studied: older populations, diabetic nephropathy, mild renal impairment, moderate renal impairment, or healthy populations. Differences in performances of the equations may be explained by the different populations in which the equations were derived, and multiple sources of measurement variation when measuring creatinine.

### 4.1.3 Health economics methodology

No health economics papers were found to review.

The estimated reagent costs for some of the tests were presented to the GDG. Cystatin C was the most expensive followed by the creatinine-based technology. However these costs do not take into account all overheads. Furthermore, there are economies of scale if reagents are used in large quantities.

### 4.1.4 Evidence statements

- ▷ Cystatin C concentration versus predictive equations (MDRD or Cockcroft-Gault)

Two cross-sectional studies<sup>40,41</sup> that compared cystatin C to the MDRD and Cockcroft-Gault equations were excluded because the serum creatinine measurements were not calibrated to the MDRD assay.

- ▷ Comparisons of predictive equations for estimating GFR

Five studies compared the performances of the Cockcroft-Gault and the MDRD equations in predicting GFR. The values of several diagnostic parameters are summarised in Table 4.1.

Table 4.1 Summary of predictive equations to estimate renal function

Study	Evidence level	N	Bias (ml/min/1.73m <sup>2</sup> )	Sensitivity (%)	Specificity (%)	Accuracy (P30)	Test correlation with gold standard
52	1b +	2095 (CKD + kidney donors)	MDRD −0.99 ml/min/1.73 m <sup>2</sup> , p=0.001 CG 1.94 ml/min/1.73 m <sup>2</sup> , p<0.0001 Bias was greater for MDRD equation (−6.2 ml/min/1.73 m <sup>2</sup> ) than the Cockcroft-Gault equation (−0.3 ml/min/1.73 m <sup>2</sup> ) in patients with a measured GFR >90 ml/min/1.73 m <sup>2</sup> . The MDRD equation was less biased than the Cockcroft-Gault equation in patients with stage 3, 4, or 5 CKD. The MDRD equation was significantly less biased than the Cockcroft-Gault equation when patients were analysed by age (above or below 65 years) and gender (p<0.0001).	MDRD (78.9%) , CG (67.6%) in stage 4 CKD MDRD (64.8%) CG (43%) in stage 5 CKD	Both MDRD and Cockcroft-Gault equations had similar specificities across the 5 stages of CKD (approx. 90%).	MDRD 92% CG 88% in people with GFR >60 ml/min/1.73 m <sup>2</sup> . People with GFR <60 ml/min/1.73 m <sup>2</sup> (82% MDRD versus 69% Cockcroft-Gault).	MDRD (r=0.910) Cockcroft-Gault (r=0.894)
51	1b +	219 (CKD + non-CKD)	MDRD 2275 arbitrary units vs CG 630 arbitrary units	NR	NR	MDRD 62% vs CG 48.8%, p<0.01	NR
53	II +	1286 (type 1 diabetes)	MDRD − 22 vs CG −6	NR	NR	When GFR >120 MDRD 97% CG 87%, p<0.001. When GFR <120 MDRD 82% CG 92%, p<0.001	NR
54	1b +	1628 (CKD)	MDRD 0.2 vs CG −7.3 When GFR >90 MDRD −3.0 vs CG −21.8	MDRD 97 vs CG 85, p<0.001	MDRD 70 vs CG 88, p<0.001	MDRD 90% (95% CI 89–91) vs CG 60% (95% CI 58–62)	NR
50	1b +	828 (CKD) 457 (kidney donors)	MDRD −0.5 vs CG 3.5, p<0.001	NR	NR	MDRD 71% CG 60%, p<0.001	CKD group: MDRD (r=0.90) and CG (r=0.89). Kidney donor control group: MDRD (r=0.36) CG (r=0.41)

NR = not reported.

▷ Test correlation

Regression analysis was used to determine the correlation between GFR measured by the gold standard test and GFR calculated using the MDRD or Cockcroft-Gault predictive equations. Two studies<sup>50,52</sup> showed that both the MDRD and Cockcroft-Gault equations correlated highly with the measured GFR in people with CKD, often with no statistical difference between the correlation coefficients for the MDRD and Cockcroft-Gault equations. Both MDRD and Cockcroft-Gault equations correlated poorly with the gold standard test in renal donors.<sup>50</sup> (Level 1b +)

▷ Bias

In diabetic populations<sup>53</sup> and in CKD populations,<sup>50,51</sup> the MDRD equation often underestimated the measured GFR. The Cockcroft-Gault equation often overestimated the GFR. (Level 1b +)

In CKD populations, the MDRD equation was superior to the Cockcroft-Gault equation in terms of bias.<sup>50,52,54</sup> The MDRD equation slightly underestimated the measured GFR, while the Cockcroft-Gault equation significantly overestimated the GFR ( $-0.5$  vs.  $3.5$  ml/min/ $1.73$  m<sup>2</sup>,  $p < 0.001$ ). The MDRD equation was also significantly less biased than the Cockcroft-Gault equation in the nondiabetic CKD (N=579) subgroup, the diabetic CKD (N=249) subgroup, and in people with a measured GFR  $< 30$  ml/min/ $1.73$  m<sup>2</sup> (N=546) ( $p < 0.001$  in each group). (Level 1b +)

The MDRD and Cockcroft-Gault equations were significantly more biased in people with GFR  $> 60$  ml/min/ $1.73$  m<sup>2</sup> (N=117). The MDRD equation underestimated the measured GFR, while the Cockcroft-Gault equation significantly overestimated the GFR ( $-3.5$  vs.  $7.9$  ml/min/ $1.73$  m<sup>2</sup>,  $p < 0.001$ ). In the kidney donor control group (N=459), the Cockcroft-Gault equation was superior to the MDRD equation in terms of bias ( $1.9$  vs.  $-9.0$  ml/min/ $1.73$  m<sup>2</sup>,  $p < 0.001$ ).<sup>50</sup> (Level 1b+)

▷ Sensitivity and specificity

Two studies<sup>52,54</sup> reported sensitivity and specificity outcomes for the MDRD and Cockcroft-Gault equations. The MDRD had higher sensitivity than the Cockcroft-Gault equation. Specificity was similar for the two predictive equations. (Level 1b+)

▷ Accuracy (P30)

Five studies<sup>50-54</sup> reported the percentage of estimated GFR values falling within 30% of the GFR values measured by the gold standard test. Generally, the MDRD equation was more accurate than the Cockcroft-Gault equation. (Level 1b+)

▷ Area under the ROC

Area under the ROC values is a measure of the overall diagnostic accuracy or power of a test. The MDRD equation had significantly higher diagnostic accuracy (AUC=0.961) than the Cockcroft-Gault equation (AUC=0.942,  $p < 0.01$ ).<sup>54</sup> (Level 1b+)

### 4.1.5 From evidence to recommendations

The evidence suggests that in general the 4-variable MDRD performs better than the Cockcroft-Gault equation. However, in older people and in people with GFR greater than 60ml/min/1.73 m<sup>2</sup> the MDRD is subject to bias and can underestimate GFR.

The GDG noted that serum creatinine is correlated with muscle mass and therefore estimation of GFR using prediction equations in people with extremes of muscle mass is subject to inaccuracy. In those with increased muscle mass GFR will be under estimated and in those with reduced muscle mass GFR will be over estimated.

Gold standard measures of GFR are time consuming and expensive to perform but where a highly accurate measurement of GFR is required, for example in assessment of kidney donors or for accurate calculation of dosing of potentially toxic chemotherapy, the evidence suggests that GFR estimated from prediction equations is insufficiently accurate.

The GDG agreed that significant changes in GFR are equally important in those individuals with GFR greater than 60 ml/min/1.73 m<sup>2</sup>. Where laboratories do not report levels of GFR greater than 60 ml/min/1.73 m<sup>2</sup> the GDG considered that a rise in serum creatinine of greater than 20% should be considered significant.

Although the original MDRD equation included a correction factor for the American black population, there are no correction factors for other populations and in routine use the derived GFR is not corrected for any ethnicity other than African-Caribbean.

Although most laboratories would be capable of measuring cystatin C concentrations there is no evidence to suggest that it was more useful than using the MDRD, with the caveat that existing evidence comparing cystatin C and the MDRD failed to appropriately calibrate serum creatinine measurements to the method of the MDRD laboratory. Cystatin C measurement is also currently more expensive.

### 4.1.6 RECOMMENDATIONS

- R1 Whenever a request for serum creatinine measurement is made, clinical laboratories should report an estimate of GFR (eGFR) using a prediction equation (see recommendation R2) in addition to reporting the serum creatinine result.\*
- R2 Use the isotope dilution mass spectrometry (IDMS)-traceable simplified MDRD equation to estimate GFR, using creatinine assays with calibration traceable to a standardised reference material. Ideally use creatinine assays that are specific and zero-biased compared to IDMS (e.g. enzymatic assays). When non-specific assays are used (e.g. Jaffe assays), employ appropriate assay-specific adjustment factors to minimise between-laboratory variation (e.g. those provided by national external quality assessment schemes).
- R3 Where indicated, apply a correction factor for ethnicity to reported GFR values (multiply eGFR by 1.21 for African-Caribbean ethnicity).\*\*
- R4 Interpret reported values of eGFR  $\geq 60$  ml/min/1.73m<sup>2</sup> with caution, bearing in mind that estimates of GFR become less accurate as the true GFR increases.

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\* eGFR may be less reliable in certain situations (for example, acute renal failure, pregnancy, oedematous states, muscle wasting disorders, amputees and malnourished people) and has not been well validated in certain ethnic groups (for example, Asians and Chinese).

\*\* In practice this correction factor should also be applied to those of African ethnicity.



- R5 Where eGFR is simply reported as  $\geq 60$  ml/min/1.73m<sup>2</sup>, use a rise in serum creatinine concentration of >20% to infer significant reduction in renal function.
- R6 Where a highly accurate measure of GFR is required (e.g. during monitoring of chemotherapy and in the evaluation of renal function in potential living donors), consider a gold standard measure (inulin, <sup>51</sup>Cr-EDTA, <sup>125</sup>I-iothalamate or iohexol).
- R7 In cases where there are extremes of muscle mass (e.g. body builders, amputees, muscle wasting disorders) interpret the eGFR with caution. (Reduced muscle mass will lead to over-estimation and increased muscle mass to under-estimation).

## 4.2 Factors affecting the biological and analytical variability of GFR estimated from measurement of serum creatinine

### 4.2.1 Clinical introduction

The measurement of serum creatinine to estimate GFR with predictive equations is subject to biological and analytical variation.

Biological variation includes random variation and predictable cyclical variation (daily, monthly, seasonal). Within-subject biological variation is the average random fluctuation around a homeostatic set point, expressed mathematically as a coefficient of variation (CV).<sup>55</sup> Large variations in serum creatinine measurements could result in misclassification of people to a particular CKD stage. Factors affecting measured serum creatinine concentration and estimated GFR from prediction equations include ingestion of cooked meat (where the cooking process converts meat creatine to creatinine, which is subsequently absorbed into the bloodstream after ingestion), individual patient fluid status, diurnal variation, and centrifugation of blood samples.

Plasma creatinine measurements also vary depending on the method/analyser used and there is inter-laboratory variation which changes with creatinine concentration. There is no (single) standard method used across England. Method precision at higher levels of creatinine has less variability and thus has marginal impact on the interpretation of eGFR from prediction equations. However, in the critical diagnostic range there is concern that inter-method/laboratory variation may impact on the diagnostic utility of eGFR. This is probably at creatinine concentrations of less than 180  $\mu$ mol/l. If creatinine levels are overestimated because of method bias/variability this will result in a reduced eGFR (false positives) and misclassification of CKD. This will lead to increased referral rates and inappropriate labelling of patients as having CKD. If creatinine levels are underestimated, the reverse will happen (false negatives).

Since April 2006, creatinine assays in chemistry laboratories in England have been calibrated to the gold standard reference method of isotope dilution mass spectrophotometry (IDMS) through the National External Quality Assurance Scheme. This has enabled reporting of an IDMS-related MDRD derived eGFR to minimise interlaboratory variation in GFR results. This section addresses other sources of bias and variation in creatinine measurement.

- *In adults with CKD, what is the biological and analytical variability in eGFR testing and what factors (including fasting) affect it?*

### 4.2.2 Methodology

Three case series investigated the biological and analytical variation of serum creatinine measurements in people with CKD<sup>56,57</sup> or with type 1 diabetes.<sup>58</sup>

Two studies examined the effect of delayed centrifugation of outpatient blood samples on the measurement of serum creatinine concentration by the kinetic Jaffe reaction or by enzymatic methods. The effect of delayed centrifugation of blood samples on GFR estimation was determined.<sup>59,60</sup>

Two case series investigated the diurnal variation in serum creatinine measurements in 72 patients with varying degrees of renal disease<sup>61</sup> and in 9 healthy people.<sup>62</sup>

Two case series evaluated the effect of a cooked meat meal on serum creatinine concentration in healthy subjects and outpatients<sup>63</sup> or in adults with diabetic nephropathy.<sup>64</sup> Two earlier studies examined changes in serum creatinine following ingestion of relatively large portions of cooked meat (300g) or raw meat (300g) or non-meat meals in six healthy volunteers.<sup>65,66</sup>

### 4.2.3 Health economics methodology

There were no health economics papers found to review.

### 4.2.4 Evidence statements

#### ▷ Biological variation of serum creatinine

The intra-individual biological variation of creatinine measurements was significantly higher in people with CKD (N=17, coefficient of variation (CV)=5.3%) than in healthy people (N=24, CV=2.7%,  $p<0.01$ ).<sup>57</sup>

The CV for serum creatinine for nine people with CKD on all occasions was 61.9%. The average analytical variation for serum creatinine was 0.1% of the total variance. The average intra-individual biological variation of creatinine measurements was 1.1% of the total variance.<sup>56</sup> (Level 3)

The intra-individual biological variation of creatinine measurements was significantly higher in women with type 1 diabetes (N=11, CV=6.53%) than in healthy women (N=14, CV=2.81%,  $p<0.01$ ). The intra-individual biological variation of creatinine measurements was significantly higher in men with type 1 diabetes (N=16, CV=5.88%) than in healthy men (N=10, CV=2.64%,  $p<0.01$ ).<sup>58</sup> (Level 3)

#### ▷ Diurnal variation of serum creatinine concentration

In non-fasting healthy participants (N=9) or in non-fasting paralysed participants (N=4), the creatinine concentration increased significantly during the day, peaking at 19:00 ( $p<0.001$ ). The creatinine concentration then decreased after 19:00 to 7:00 the next morning. In fasting participants (N=9), there was a small but significant decrease in creatinine concentration between 7:00 and 13:00 ( $p<0.02$ ) and there was no increase in serum creatinine during the rest of the time course.<sup>62</sup> (Level 3)

In people with inulin clearance  $\geq 90$  ml/min (N=38), the serum creatinine concentration was significantly greater in the afternoon than in the morning (mean difference 0.087 mg/100 ml,  $p<0.001$ ). By contrast, there was non-significant (NS) difference in serum creatinine concentration between morning and afternoon in people with inulin clearance  $< 90$  ml/min (N=34, mean difference 0.035 mg/100 ml).<sup>61</sup> (Level 3)

#### ▷ Effect of cooked meat on serum creatinine concentration and eGFR

Four studies showed that ingestion of a cooked meat meal caused a significant increase in serum creatinine concentration. Following a cooked meat meal (N=6 healthy subjects), the mean serum

creatinine concentration significantly increased (86  $\mu\text{mol/l}$  at baseline to 175  $\mu\text{mol/l}$  3 hours postprandially,  $p < 0.001$ ). The creatinine levels then declined and at 10 hours postprandially, the levels stabilised, but did not return to baseline levels. Following a non-meat meal or a raw beef meal, the serum creatinine concentration was relatively unchanged.<sup>65</sup> (Level 3)

Following a cooked meat breakfast ( $N=6$ ), the mean serum creatinine concentration significantly increased from baseline to 2 to 4 hours postprandially (52% increase, range 36–65%). The creatinine levels slowly declined and returned to baseline by 12 hours. By contrast, following either a high or low non-meat protein breakfast (control), serum creatinine remained stable.<sup>66</sup> (Level 3)

In 10 people with diabetic nephropathy, the mean serum creatinine concentration significantly increased from baseline (167  $\mu\text{mol/l}$ ) to 180  $\mu\text{mol/l}$  in 2 hours ( $p < 0.001$ ) following a cooked meat meal.<sup>64</sup> (Level 3)

Following a cooked meat lunch ( $N=32$  healthy volunteers and outpatients), the median serum creatinine concentration significantly increased from baseline by 18.5  $\mu\text{mol/l}$  3 to 4 hours postprandially ( $p < 0.0001$ ). The median eGFR significantly decreased from baseline by 20  $\text{ml/min}/1.73 \text{ m}^2$  3 to 4 hours postprandially ( $p < 0.0001$ ). Following a meat meal, 11 people changed from a pre-prandial eGFR  $> 59 \text{ ml/min}/1.73 \text{ m}^2$  to a postprandial eGFR of  $< 60 \text{ ml/min}/1.73 \text{ m}^2$ , erroneously placing them in stage 3 CKD. By contrast, following a vegetarian lunch ( $N=23$ ), there was a NS change in median serum creatinine concentration; and there was a small but significant increase in eGFR from baseline (preprandial) to 3–4 hours postprandially (3.5  $\text{ml/min}/1.73 \text{ m}^2$ ,  $p=0.006$ ).<sup>63</sup> (Level 3)

▷ Effect of delays in centrifugation of blood samples on serum creatinine concentration and eGFR

Two studies showed significant increases in creatinine concentration after a 10- to 24-hour delay in centrifugation of blood samples (kinetic Jaffe method used to assay creatinine). By contrast, the creatinine concentration remained stable, regardless of the delay in centrifugation, when assayed with enzymatic methods.<sup>59,60</sup> From the 24-hour delay experiment ( $N=113$  outpatients), mean creatinine concentration significantly increased from baseline (85  $\mu\text{mol/l}$ ) to 24-hour delay (95  $\mu\text{mol/l}$ , 11% increase,  $p < 0.0004$ ).<sup>60</sup> (Level 3)

With a 16 hour delay in centrifugation, 4 out of 7 volunteers with baseline stage 1 CKD had changed to stage 2. After a 36 hour delay in centrifugation, 7 out of 7 volunteers had changed from stage 1 to stage 2 CKD. After a 24-hour delay in centrifugation of samples ( $N=113$  outpatients), mean eGFR significantly decreased from baseline (eGFR 85  $\text{ml/min}/1.73 \text{ m}^2$ ) to 24-hour delay (eGFR 75  $\text{ml/min}/1.73 \text{ m}^2$ , 13% decrease,  $p < 0.0001$ ). The CKD staging of 32% of the participants changed after a 24-hour delay in centrifugation of blood samples: 26% went from stage 1 CKD to stage 2, and 6% went from stage 2 to stage 3 CKD.<sup>60</sup> (Level 3)

In 21 patients where the delay in centrifugation of blood samples exceeded 10 hours, the eGFR significantly decreased ( $p < 0.001$ ). This resulted in a change in CKD classification in 4 of these cases.<sup>59</sup> (Level 3)

#### 4.2.5 From evidence to recommendation

The GDG noted that although the biochemical assay for creatinine is precise, a number of factors affect serum creatinine levels, particularly the person's state of hydration and whether they had

recently eaten meat. Serum creatinine concentrations also show diurnal variation. This means that the eGFR derived using the 4-variable MDRD equation will also be affected by these factors.

When making a diagnosis of CKD, assessing the stage of CKD, or monitoring patients for evidence of declining kidney function, it is important that clinicians are aware of the factors that can influence creatinine concentrations. It was recommended that whenever possible they take steps to minimise the biases that these factors introduce and that they are aware that changes of less than 5% may simply be due to biological and analytical variability.

Whilst a simple solution to the variability introduced by eating meat would be to recommend an overnight fast before having a blood sample taken, it was agreed that this was unnecessarily restrictive.

#### 4.2.6 RECOMMENDATIONS

- R8** Advise people not to eat any meat in the 12 hours before having a blood test for GFR estimation. Avoid delaying the despatch of blood samples to ensure that they are received and processed by the laboratory within 12 hours of venepuncture.
- R9** An eGFR result below 60 ml/min/1.73 m<sup>2</sup> in a person not previously tested should be confirmed by repeating the test within 2 weeks. Make an allowance for biological and analytical variability of serum creatinine ( $\pm 5\%$ ) when interpreting changes in eGFR.

##### Measurement of eGFR: how often?<sup>a</sup>

Annually in all at-risk groups.

During intercurrent illness and peri-operatively in all patients with CKD.

Exact frequency should depend on the clinical situation. The frequency of testing may be reduced where eGFR levels remain very stable but will need to be increased if there is rapid progression.

Stage	eGFR range (ml/min/1.73m <sup>2</sup> )	Typical testing frequency
1 and 2	$\geq 60$ + other evidence of kidney disease	12 monthly
3A and 3B	30–59	6 monthly
4	15–29	3 monthly
5	<15	6 weekly

<sup>a</sup> The information in this table is based on GDG consensus and not on evidence.

### 4.3 Detection of blood and protein in the urine

#### 4.3.1 Clinical introduction

The persistent presence of protein (proteinuria), albumin (albuminuria), or red blood cells (haematuria) in urine is evidence of kidney damage. Diagnostic tests that can rapidly detect the presence of protein or red blood cells in urine with high specificity and sensitivity are integral to the early detection and management of CKD.

Haematuria is defined as the presence of red blood cells (RBCs) in the urine, either visible (macroscopic haematuria) or invisible and detected by direct microscopy (microscopic haematuria). A reagent strip test to detect blood in urine provides an instant result and is often the method of detection of invisible haematuria in the primary care setting.<sup>67</sup> The reagent strip

or 'dipstick' test is commonly considered to be sensitive for the detection of RBCs below the defined (microscopic) 3 RBCs per high power field threshold for invisible haematuria. Dipstick testing of spot urine samples is also used for rapid detection of protein and albumin. However, reagent strips are subject to false positives because of patient dehydration, exercise, infection, and extremely alkaline urine. False negative results occur as a result of excessive hydration and urine proteins other than albumin.

Haematuria can be broadly classified as nephrological or urological in origin. Most forms of intrinsic kidney disease may result in invisible haematuria. Urological causes include tumours, urinary tract infection, stone disease and bleeding from benign conditions of the urinary tract. Invisible haematuria may also be detected in the absence of any underlying pathology, such as after vigorous exercise.<sup>68</sup> The prevalence of asymptomatic invisible haematuria varies between 0.19% and 21%, depending on age and gender. Screening studies have suggested that the prevalence of asymptomatic invisible haematuria in the UK adult male population is around 2.5%, increasing to 22% in men over the age of 60 years.<sup>69,70</sup>

Detection of 'clinical' proteinuria at the point of care using dipsticks is usually defined by a colour change of '+' or greater on the relevant pad on the strip device. This is thought to equate to approximately 300 mg/l of total protein or an excretion rate of 450 mg/24 h. Reagent strip devices for proteinuria detection have been in clinical use for approximately 50 years but they have significant limitations. They rely on estimation of protein concentration which is dependent on urine flow rate. Concentrated urine may yield a colour change in the positive range even though protein excretion rate remains normal. Conversely, dilute urine may mask significant proteinuria. Also, the performance of the dipsticks is operator-dependent and affected by the presence of certain drugs and urinary pH. Finally, although purporting to measure total protein, most protein strips are predominantly sensitive to albumin.

The purpose of this section was therefore to evaluate the efficacy of reagent strip tests to detect haematuria and proteinuria/albuminuria and determine their diagnostic accuracy.

- *What is the sensitivity and specificity of reagent strips for detecting protein and blood in urine?*

### 4.3.2 Methodology

Much of the published research that aims to detect or quantify protein or albumin in urine uses 24-hour urinary protein or albumin excretion as a 'gold standard'. However there are important reservations to be borne in mind regarding this technique. The 24-hour timed urine sample is subject to inaccurate sample collection, low patient compliance, expense, and time requirement, making this test difficult to implement as a routine test in a primary care setting. Other ways of detecting proteinuria are the protein:creatinine ratio (PCR) or albumin:creatinine ratio (ACR) in a spot urine sample. But, as has been discussed in the clinical introductions, it is not yet established whether proteinuria or albuminuria best predicts progression of CKD in people who do not have diabetes. It is therefore not necessarily helpful to know that a more practical measurement such as protein:creatinine ratio correlates with 24-hour protein. Another caution required in interpreting the evidence base is that albumin is one component of the protein detected, and although the proportion varies between individuals, particularly at low levels of proteinuria, it is not surprising to find protein measurements correlating reasonably with albumin measurements. Finally, a certain amount of the agreement between ACR and PCR will be attributable to the creatinine measurement for each individual, which is the denominator of each ratio.

ACR and PCR have been shown to correlate with the 24-hour albumin or protein excretion rate. Proteinuria is defined as a 24-hour protein excretion rate  $\geq 150$  mg/24 h. Microalbuminuria is

defined as a 24-hour albumin excretion rate of 30–300 mg/24 h. Macroalbuminuria is defined as a 24-hour albumin excretion rate of >300 mg/24 h. In these assays, albumin is measured with immunonephelometric methods. Protein is measured in turbidometric assays with Bradford reagents, benzethonium chloride, or pyrogallol red-molybdate.

Phase-contrast microscopy of fresh urinary sediment is the gold standard test to identify haematuria (defined as  $\geq 5$  red blood cells/high power field).

Studies were included if the sample size was  $N > 100$ . Studies were excluded if the sulfosalicylic acid test, protein heat coagulation test, urine electrophoresis, or standard light microscopy was used as a gold standard test.

Four cross-sectional studies compared reagent strips to microscopy of urine sediment to detect haematuria in adults with systemic lupus erythematosus,<sup>71</sup> blunt renal trauma,<sup>72</sup> urological outpatients,<sup>73</sup> or hospitalised patients.<sup>74</sup> The study by Gleeson et al. was excluded as standard light (and not phase) microscopy was used as the reference test. The study by Chandhoke et al. was excluded as there was little methodological detail on blinding, when the tests were performed, and few population characteristics.

Four cross-sectional studies assessed the diagnostic accuracy of reagent strips to detect albuminuria. Two studies compared reagent strips to ACR in hospitalised patients<sup>75</sup> and in the general population of Takahata, Japan.<sup>76</sup> Two studies compared reagent strips to urinary albumin concentration in 24-hour urine specimens in people with diabetes<sup>77</sup> or in adults with hypertension or diabetes.<sup>78</sup>

Nine cross-sectional studies assessed the diagnostic accuracy of reagent strips to detect proteinuria. Six of these studies compared reagent strips to 24-hour protein in hypertensive pregnant women.<sup>79–84</sup> One study compared reagent strips to 24-hour protein in adults with renal disease.<sup>85</sup> The remaining two studies compared reagent strips to PCR in people with renal disease<sup>86</sup> or in hospitalised patients.<sup>75</sup>

### 4.3.3 Health economics methodology

One paper was retrieved.<sup>87</sup> The paper was excluded because the reference standard was quantitative urine culture (QUC).

### 4.3.4 Evidence statements

- ▷ Detection of haematuria

**Table 4.2 Diagnostic accuracy of reagent strips to detect blood in urine**

Study	Population	N	Comparison	Cut-off	Number of true positives	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
74	Hospitalised patients N=100	825 samples	N-Multistix-SG vs phase-contrast microscopy of un-spun urine	Trace RBC + result	521/825 = 63%	–	–	82%	–
71	Systemic lupus erythematosus	269	Hemastix vs phase-contrast microscopy of urinary sediment	Trace RBC	63/269 = 24%	98	53	39	99

The sensitivity of reagent strips for detecting trace erythrocytes in urine of adults with lupus (N=269) was high (98%), but the specificity (53%) and PPV (39%) were low.<sup>71</sup> In hospitalised patients (N=100, 825 urine samples) the PPV for 'trace' and '+' results on a reagent strip were 82% and 100% respectively.<sup>74</sup> (Level 1b +)

▷ Detection of albuminuria

**Table 4.3 Diagnostic accuracy of reagent strips to detect albuminuria**

Study	Population	N	Comparison	Cut-off	Number of true positives	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
<sup>75</sup>	Hospitalised patients	310	Multistix PRO vs ACR	ACR $\leq$ 80 mg/g creatinine	NR	–	–	84	89
<sup>75</sup>	Kidney disease	113	Multistix PRO vs ACR	ACR $\leq$ 80 mg/g creatinine	73/113 = 65%	–	–	86	100
<sup>75</sup>	People with diabetes	80	Multistix PRO vs ACR	ACR $\leq$ 80 mg/g creatinine	19/80 = 24%	–	–	83	100
<sup>78</sup>	Hypertensive adults	79	Micraltest II vs 24-h nephelometry (albumin)	$\leq$ 28.2 mg/L	4/79 = 5%	75	95	43	99
<sup>78</sup>	People with diabetes	166	Micraltest II vs 24-h nephelometry (albumin)	$\leq$ 30.5 mg/L	71/166 = 42%	83	96	95	88
<sup>76</sup>	General population (Japan)	2321	Multistix vs ACR	ACR $\leq$ 30 mg/g creatinine	317/2321 = 14% (ACR 30–300 mg/g)	37 (trace proteinuria defined as +)	97 (trace proteinuria defined as +)	71 (trace proteinuria defined as +)	90 (trace proteinuria defined as +)
<sup>76</sup>	People with diabetes (Japan)	201	Multistix vs ACR	ACR $\leq$ 30 mg/g creatinine	317/2321 = 14% (ACR 30–300 mg/g)	45 (trace proteinuria defined as +)	98 (trace proteinuria defined as +)	91 (trace proteinuria defined as +)	76 (trace proteinuria defined as +)
<sup>76</sup>	Hypertensive adults (Japan)	1323	Multistix vs ACR	ACR $\leq$ 30 mg/g creatinine	317/2321 = 14% (ACR 30–300 mg/g)	37 (trace proteinuria defined as +)	98 (trace proteinuria defined as +)	81 (trace proteinuria defined as +)	86 (trace proteinuria defined as +)
<sup>77</sup>	People with diabetes	411	Micral-Test II vs Urinary albumin concentration (radioimmunoassay)	Albumin concentration <20 mg/l	114/411 = 28% (UAC 20–200 mg/l); 47/411 = 11% (UAC >200 mg/l)	93	93	89	–



Overall, the sensitivity of reagent strips for detecting albuminuria was low. The specificity of reagent strips for detecting albuminuria was high, ranging from 93–98%. (Level 1b+)

Overall, the positive predictive values of the reagent strips for detecting albuminuria were low, ranging from 71–91%. (Level 1b+)

The negative predictive value of reagent strips varied according to the cut-off value used to define albuminuria. (Level 1b+)

▷ Detection of proteinuria

**Table 4.4 Diagnostic accuracy of reagent strips to detect proteinuria**

Study	Population	N	Comparison	Cut-off	Number of true positives	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
85	Kidney disease	297	Multistix 10 SG vs 24-hour protein excretion	$\leq 0.150$ g/24 h	62%	49	94	–	–
86	Kidney disease	332	Multistix 10 SG vs PCR	PCR $\leq 1$ g/g creatinine	125/332 = 38%	100 (when reagent strip result +1)	60 (when reagent strip result +1)	–	–
86	Kidney disease	332	Multistix 10 SG vs PCR	PCR $\leq 1$ g/g creatinine	125/332 = 38%	96 (when reagent strip result +3)	87 (when reagent strip result +3)	–	–
86	Kidney disease	332	Multistix 10 SG vs PCR	PCR $\leq 3$ g/g creatinine	51/332 = 15%	94 (when reagent strip result +4)	83 (when reagent strip result +4)	–	–
75	Hospitalised patients	310	Multistix PRO vs PCR	PCR $\leq 300$ mg/g creatinine	NR	–	–	84	87
75	Kidney disease	113	Multistix PRO vs PCR	PCR $\leq 300$ mg/g creatinine	81/113 = 72%	–	–	92	93
75	People with diabetes	80	Multistix PRO vs PCR	PCR $\leq 300$ mg/g creatinine	20/80 = 25%	–	–	83	98
88	Hypertensive pregnant women	197	BM-Test-5L vs 24-h protein excretion determined by Benzethonium Chloride assay	$\leq 0.3$ g/24 h	70%	22	98	97	35

*continued*



Table 4.4 Diagnostic accuracy of reagent strips to detect proteinuria – *continued*

Study	Population	N	Comparison	Cut-off	Number of true positives	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
88	Hypertensive pregnant women	197	BM-Test-5L vs 24-h protein excretion determined by Bradford assay	≤0.3g/24 h	25%	57	97	87	87
83	Hypertensive pregnant women	150	Multistix-AMES vs 24-h urine protein (random dipstick)	≤0.3g/l	84/150 = 56%	84	61	57	86
			Multistix-AMES vs 24-h urine protein (aliquot collected at 6 hrs)	≤0.3g/l	84/150 = 56%	84.5	90.1	84.5	90.0
80	Hypertensive pregnant women	230	Multistix 10SG vs 24-h urine protein (Dipstick done before 24-h urine collection)	≤0.3g/24 h	70/230 = 30%	–	–	86	38
			Multistix 10SG vs 24-h urine protein (Dipstick done after 24-h urine collection)	≤0.3g/24 h	70/230 = 30%	–	–	46	88
81	Pregnant women	690 samples	Multistix 10SG vs 24-h urine protein	≤15 mg/dl	NR	36	97	68	88
82	Hypertensive pregnant women	300 samples	Urine dipstick (unspecified) vs 24-h urine protein	≤0.3g/24 h	NR	67	74	92	34
84	Pregnant women	103	Multistix 10SG vs 24-h urine protein	≤0.3g/l	NR	100	62	24	–

Studies in pregnant women showed that reagent strips had low sensitivity and variable specificity for detecting proteinuria. The positive and negative predictive values also varied greatly. (Level 1b +)

In people with kidney disease, a +1 or a +3 result on a reagent strip had high sensitivities to detect a PCR ≥1 g protein/g creatinine (roughly >1 g/day), and the specificity was low.<sup>86</sup> Another study showed that reagent strips had low sensitivity for detecting proteinuria (>0.150 g/24 h).<sup>85</sup> (Level 1b +)

### 4.3.5 From evidence to recommendations

It was noted that reagent strips have been used to identify and quantify the presence of albumin, total protein and red blood cells in a urine sample. Some reagent strips identify the presence of both haematuria and proteinuria.

There was no evidence to suggest one type of reagent strip performed better than the others. It was noted that the reagent strips used to detect proteinuria in routine clinical practice are predominantly sensitive to albumin not to total protein.

When considering the evidence concerning haematuria the GDG were aware that in many circumstances haematuria is a feature of urological disease rather than CKD.

Unless performed using phase contrast microscopy on a sample that has been received promptly, laboratory assessment of haematuria is less accurate than reagent strip testing because of cell lysis during transport to the laboratory and inaccuracies in quantifying the red blood cells present.

There is no consensus about whether a 'trace' or one '+' should be considered positive when testing for haematuria using reagent strips. The GDG recommended that the presence of one '+' should be considered positive.

When considering nephrological causes of haematuria it was noted that most clinicians would need evidence of concurrent proteinuria (ACR >30 mg/mmol) and/or evidence of deterioration in GFR before recommending renal biopsy.

When considering the use of reagent strips to identify or quantify proteinuria it was again noted that although 24-hour urine collections for urinary protein estimation have been considered to be the 'gold standard' they are subject to inaccuracies due to incomplete collection of all urine voided or inaccurate timing, and the biochemical methods used to quantify the amount of protein present give different results.

There is no evidence about the frequency with which testing for proteinuria should subsequently be repeated.

It was noted that the timing of the urine sample was important to get a meaningful result. A morning sample is best as the urine is most concentrated and thus the concentration of protein will be highest and more likely to be detected. It was recognised, however, that stipulating that testing should only be undertaken on morning samples would cause practical difficulties for service organisation and might inhibit opportunistic testing.

The GDG noted that use of reagent strip tests for identification of significant proteinuria was dependent on urine concentration, rendering them unreliable for both detection of small amounts of proteinuria and for accurately quantifying the degree of proteinuria.

ACR is the test of choice to identify proteinuria in people with diabetes and is already widely used in practice. Albumin is the predominant component of proteinuria in glomerular disease, however the non-diabetic CKD literature reviewed in this guideline is based on 24-hour urinary protein excretion.

It is this guideline's purpose to improve early identification and help prevent progression of CKD. Epidemiological study increasingly underlines the importance of even a low level of proteinuria as a strong predictor of adverse outcome. Reagent strips in current clinical practice

predominantly detect albumin, not total protein, but are not reliably quantitative. Studies to inform intervention levels of ACR in non-diabetic CKD are not yet available and it is not possible to derive a simple correction factor that allows the precise conversion of ACR values to PCR. However, ACR has far greater sensitivity than PCR for the detection of low levels of proteinuria and thus lends itself to detection and identification of CKD.

When the clinical and cost-effectiveness evidence is all taken into account, considerable uncertainty remains about the choice of ACR or PCR. Clinical opinion was divided among stakeholder organisations and within the GDG, but given the considerations above, the GDG made a consensus recommendation that ACR should be the test of choice to identify proteinuria and possible chronic kidney disease. The GDG however also noted that there will often be good clinical reasons for subsequently using PCR to quantify and monitor significant levels of proteinuria.

The GDG noted that an ACR of  $\geq 30$  mg/mmol, or PCR  $\geq 50$  mg/mmol in association with haematuria or an ACR  $\geq 70$  mg/mmol, or PCR  $\geq 100$  mg/mmol in the absence of haematuria were considered indications for referral to nephrology (see section 6.1.4). It was agreed that the finding of levels of ACR  $< 70$  mg/mmol, or PCR  $< 100$  mg/mmol should be confirmed using an early morning urine sample.

#### 4.3.6 RECOMMENDATIONS

▷ Haematuria

- R10 When testing for the presence of haematuria, use reagent strips rather than urine microscopy.
- Evaluate further if there is a result of 1+ or more.
  - Do not use urine microscopy to confirm a positive result.

▷ Proteinuria

- R11 Do not use reagent strips to identify proteinuria unless they are capable of specifically measuring albumin at low concentrations and expressing the result as an ACR .
- R12 To detect and identify proteinuria, use urine albumin:creatinine ratio (ACR) in preference, as it has greater sensitivity than protein:creatinine ratio (PCR) for low levels of proteinuria. For quantification and monitoring of proteinuria, PCR can be used as an alternative. ACR is the recommended method for people with diabetes.
- R13 For the initial detection of proteinuria, if the ACR is 30 mg/mmol or more (this is approximately equivalent to PCR 50 mg/mmol or more, or a urinary protein excretion 0.5 g/24 h or more) and less than 70 mg/mmol (approximately equivalent to PCR less than 100 mg/mmol, or urinary protein excretion less than 1 g/24 h) this should be confirmed by a subsequent early morning sample. If the initial ACR is 70 mg/mmol or more, or the PCR 100 mg/mmol or more, a repeat sample need not be tested.

## 4.4 Urinary albumin:creatinine and protein:creatinine ratios, and their relationship to 24-hour urinary protein

### 4.4.1 Clinical introduction

Proteinuria is a cardinal sign of kidney disease. Measurement of total protein in urine is a traditional, inexpensive and well established test for kidney injury. A vast body of nephrological literature is predicated on 24-hour urinary total protein. Significant proteinuria is an independent risk factor for both progression of CKD and cardiovascular disease. Monitoring of urinary proteinuria is both part of the routine evaluation of those at risk of CKD and is an important method of assessing progression and response to therapy.

Proteins normally excreted in the urine include albumin, low molecular weight immunoglobulin (filtered plasma proteins), and secreted tubular proteins. There is no consistent definition of proteinuria. The upper limit of normal is approximately 150 mg/24 h, equivalent to a protein:creatinine ratio (PCR) of 15 mg/mmol (given an average daily urine creatinine excretion of 10 mmol), but the cut off for abnormal varies from laboratory to laboratory. By contrast, urinary albumin measurement provides a quantitative, relatively standardised measurement of excretion of the single most important protein in most nephropathies. The normal mean value for urine albumin is 10 mg/day, microalbuminuria is defined as 30–300 mg/day or an albumin:creatinine ratio (ACR) of >2.5 mg/mmol in men and >3.5 mg/mmol in women. Macroalbuminuria is a urinary albumin greater than 300 mg/day (ACR >30 mg/mmol).

Proteinuria displays considerable biological variability, and may be increased by urinary tract infection (UTI), upright posture, exercise, fever, and heart failure as well as by kidney disease. Biological variation of both measures is high, with lower variation generally being reported for an albumin:creatinine ratio (ACR) on an early morning urine (EMU) compared to PCR (e.g. 36% versus 48% respectively). There is a high correlation between total protein and albuminuria at high levels of protein excretion (so-called nephrotic range proteinuria, PCR >300 mg/mmol) but at low levels correlation is poor. This is because urine protein measurement in the normal range and at low levels is both imprecise and relatively non-specific. Albumin as a proportion of total protein is highly variable at normal and moderately increased levels of proteinuria.<sup>89–92</sup>

The UK CKD Guidelines have defined proteinuria as a PCR of  $\geq 45$  mg/mmol or an ACR  $\geq 30$  mg/mmol but suggest that, in the absence of concomitant haematuria, this should not act as a trigger for active intervention until the PCR exceeds 100 mg/mmol (ACR >70 mg/mmol).<sup>33</sup> KDOQI guidelines define proteinuria as a PCR >23 mg/mmol (200 mg/g). The Welsh Renal NSF has defined proteinuria as a PCR of  $\geq 100$  mg/mmol, approximately equivalent to an excretion rate of 1000 mg/24 h.

It has been accepted for many years that total protein measurement is insufficiently sensitive to detect the onset of diabetic nephropathy and that urine albumin must be used for this purpose. This is enshrined in many clinical practice guidelines including those for type 1 and 2 diabetes produced by NICE. There is also evidence that urine albumin is a more sensitive test to enable detection of glomerular disease associated with some other systemic diseases (e.g. SLE, hypertension). The diabetic nephropathy literature and the classification of diabetic nephropathy is based upon urine albumin excretion (commonly expressed as an ACR measurement) and the

recent Kidney Disease Improving Global Outcomes (KDIGO) classification of CKD is clear in that it requires urine albumin measurement to facilitate diagnosis of stage 1 and 2 CKD. In other words, the presence of low-level albuminuria ('microalbuminuria') in an individual with a glomerular filtration rate (GFR)  $\geq 60$  ml/min/1.73 m<sup>2</sup> is indicative of CKD irrespective of whether diabetes mellitus is present or not. There is strong evidence from epidemiological studies linking urinary albumin excretion to cardiovascular mortality and kidney disease progression in people with diabetes and to cardiovascular and non-cardiovascular mortality in those without diabetes.<sup>93–96</sup> Amongst people with diabetes, microalbuminuria is used as a therapeutic target that can be modified by renin-angiotensin-aldosterone system blockade with resulting improvement in clinical outcomes; there is currently a poor evidence base for this strategy in non-diabetic kidney disease.<sup>97</sup>

In the most common types of CKD (i.e. that due to diabetes, hypertension and glomerular disease) and in kidney transplant recipients, albumin is both the most abundant protein in urine and a more sensitive marker of disease. The NKF-KDOQI guidelines therefore recommend urinary albumin measurement in preference to total protein when detecting and monitoring proteinuria. Conversely, the UK CKD guidelines and CARI guidelines have recommended urine PCR for non-diabetic kidney disease, with ACR being reserved for patients with diabetes.<sup>33</sup> The Welsh Renal NSF has adopted a similar position and this was endorsed by the UK consensus conference statement and by the Scottish Intercollegiate Guidelines Network.<sup>34</sup>

There is a need to reconcile these approaches. Increasingly the management of CKD is being undertaken by general practitioners and other non-nephrologists. Also, where the National Vascular Screening Programme identifies people with conditions such as hypertension, diabetes and impaired GFR an ACR will be recommended. Furthermore, the Quality and Outcomes framework now includes proteinuria in the CKD indicators. There is a need for consistency between detection of proteinuria in diabetes and detection of proteinuria in CKD. The current dual system of proteinuria/albuminuria reporting is at the least confusing and to patients probably unfathomable. Problems remain in defining conversion factors that would enable the proteinuria evidence base to be interpreted on the basis of urine albumin results. This is particularly true at lower levels of protein excretion, where the contribution of albumin to total protein is more variable. To attempt to address this, a call for evidence<sup>1</sup> was circulated to registered stakeholder organisations specifically seeking evidence relating to the equivalence of ACR to PCR and to 24-hour urinary protein excretion.

- *Clinical question: What are the benefits in terms of accuracy and cost in measuring albumin:creatinine ratio versus protein:creatinine ratio to quantify proteinuria in adults with CKD?*
- *Call for evidence: What is the equivalence between urinary albumin:creatinine ratios and 24-hour urinary protein excretion and urinary protein:creatinine ratio?*

#### 4.4.2 Methodology

There were no studies that directly compared protein:creatinine ratio (PCR) with albumin:creatinine ratio (ACR) and provided sensitivity and specificity outcomes. Instead, studies were selected that compared ACR or PCR to the reference standard test, timed overnight

or 24-hour urinary albumin (or protein) excretion. Studies were excluded if the sample size was small (lower than 100) or if the sulfosalicylic acid test, protein heat coagulation test, or urine electrophoresis were used as the reference test.

Two studies compared PCR in a spot urine sample to timed urinary 24-hour protein excretion in diabetic adults<sup>98</sup> or in non-diabetic adults with proteinuria and CKD.<sup>99</sup> These two studies only reported the correlation between the reference standard and PCR. Six studies compared the ACR in a spot urine sample to timed overnight or 24-hour urinary albumin excretion in diabetic adults,<sup>100–103</sup> in a Dutch general population,<sup>104</sup> and in a South Asian general population in Pakistan.<sup>105</sup> Sample sizes in the eight studies ranged from 109 to 2527.

#### ▷ Call for evidence

Eight studies were received from stakeholders in a call for evidence<sup>1</sup> to address the equivalence of urine albumin with urine total protein. Four of these studies were relevant and admissible under the NICE Guidelines Manual.

In a cross-sectional study of people aged 25 years and older in Australia (AusDiab, N=10596), both urine albumin (rate nephelometry) and urine protein (pyrogallol red molybdate) were measured in random urine samples and the correlation between ACR and PCR was determined. The sensitivity, specificity, positive and negative predictive values of an ACR  $\geq 30$  mg/g to detect a PCR  $\geq 0.20$  mg/mg were determined. All analyses in this paper were weighted to represent the non-institutionalised Australian population.<sup>106</sup>

Two UK studies compared urinary albumin with total protein from timed 24-hour urine collections. Specifically, the correlation between urinary albumin concentration (mg/l, immunoturbidometric assay) and urinary total protein concentration (mg/l, Ponceau S assay) was assessed in 235 timed 24-hour urine samples.<sup>90</sup> Similarly, the correlation between albumin excretion rate (latex particle enhanced immunoturbidometric assay) and protein excretion rate (biuret, following trichloroacetic acid) was determined from the same timed 24-hour urine samples.<sup>107</sup>

The unpublished manuscript by MacGregor et al. detailed a retrospective analysis of 6761 urine samples. Given that this manuscript was shared with the GDG as unpublished work in progress, there are some methodological limitations. The correlation between ACR (immunoturbidometric assay) and PCR (pyrogallol red or subsequently a benzethonium turbidometric assay) was assessed. The relationships between 24-h protein excretion and ACR or PCR were also analysed in a non-randomised subgroup for whom 24-hour protein had been collected (N=1739). Areas under the receiver-operator curves were determined, along with the thresholds of both ACR and PCR to detect a 24-hour protein excretion rate  $>1$  g/day or  $>450$  mg/day with sensitivity of 0.95.<sup>108</sup>

All the studies were limited by the inability to assess whether adequate blinding had occurred.

### 4.4.3 Health economics methodology

Two studies were retrieved.<sup>109,110</sup> Both were excluded because they were cost analyses and did not consider cost-effectiveness. Given the uncertainty in the clinical evidence below and the cost difference between the tests, a health economic modelling calculation was conducted; details are given below under 'From Evidence To Recommendations' and in full in Appendix C.

#### 4.4.4 Evidence statements

##### ▷ Correlation of PCR and 24-hour urinary protein

In diabetic and non-diabetic populations (N=229 and N=177, respectively), spot morning PCR and 24-hour urinary protein excretion rates were log-transformed and a linear regression was fitted, which was highly significant ( $\beta=0.948$ ,  $p<0.0001$  in people without diabetes, and  $\beta=0.9$ , significance not stated for people with diabetes).<sup>98,99</sup> However, PCR becomes a less accurate predictor of 24-hour urinary protein excretion in the higher values. (Level 1b +)

##### ▷ Correlation of ACR and 24-hour urinary albumin

There was a high correlation between first morning urine ACR and overnight albumin excretion rate ( $r=0.921$ ,  $p$  not given,  $N=261$  diabetic adults).<sup>101</sup> Similarly, there was high correlation between overnight albumin excretion rate and first morning ACR (Kendall's  $\tau_b=0.71$ ,  $p<0.001$ ,  $N=446$ ), though this study specifically excluded people with clinical proteinuria from the analyses.<sup>100</sup> In a US study of a black people with type 2 diabetes ( $N=123$ ), there was also a significantly high correlation between ACR and 24-hour albumin excretion rate ( $r=0.96$ ,  $p=0.0001$ ). This correlation significantly decreased in adults with normal ACR ( $<30 \mu\text{g}/\text{mg}$ ) ( $r=0.59$ ,  $p<0.0001$ ,  $N=90$ ) as well as in adults with microalbuminuria (ACR  $30\text{--}300 \mu\text{g}/\text{mg}$ ) ( $r=0.55$ ,  $p=0.005$ ,  $N=26$ ).<sup>103</sup> (Level 1b +)

##### ▷ Sensitivity and specificity

Overall, sensitivity and specificity were high for first morning ACR. In the figures given below, sensitivity is the proportion of people with an albumin excretion rate  $>30 \mu\text{g}/\text{min}$  correctly identified by the ACR test. Specificity is the proportion of people with an albumin excretion rate  $<30 \mu\text{g}/\text{min}$  correctly excluded by the ACR test.

At a cut-off value of  $>3.0 \text{ mg}/\text{mmol}$ , ACR had a sensitivity of 96.8% and a specificity of 93.9%.<sup>101</sup> The sensitivity 49.0% (95% CI 71.1–56.9) was much lower in a larger healthy population ( $N=2527$ ), while the specificity was still high 98.7% (95% CI 98.2–99.1).<sup>104</sup> (Level 1b +)

At a cut-off value of  $>3.5 \text{ mg}/\text{mmol}$ , overnight ACR had a sensitivity of 88% and a specificity of 99%,  $p$  value not given.<sup>100</sup> Another similar study reported 98% sensitivity and 63% specificity,  $p$  value not given.<sup>102</sup> (Level 1b + and II +)

At a cut-off of  $30 \text{ mg}/\text{g}$ , ACR had low sensitivity (60% in men and 46% in women) to detect albuminuria (urinary albumin excretion rate  $\geq 30 \text{ mg}/24 \text{ h}$ ) in a South Asian population ( $N=577$ ). The specificity was high (97% in men and 95% in women).<sup>105</sup> (Level 1b +)

##### ▷ Positive and negative predictive values

The positive predictive value (PPV) is the proportion of true positives in the sample and the negative predictive value (NPV) is the proportion of true negatives in the sample. The PPV for ACR was 72% or 68.2%.<sup>100,101</sup> The NPV was 99.5%.<sup>101</sup> (Level 1b +)

In a South Asian population, the PPV for albuminuria in those with high ACR ( $\geq 30 \text{ mg}/\text{g}$ ) was 72%. The NPV for albuminuria in those with high ACR ( $\geq 30 \text{ mg}/\text{g}$ ) was 95%.<sup>105</sup> (Level 1b +)



#### 4.4.5 Evidence statements from the ‘Call for Evidence’

##### ▷ Correlation of ACR and PCR

MacGregor et al. showed that the relationship between ACR and PCR was non-linear (N=6761). There was poor correlation between ACR and PCR in the range of 10–100 mg/mmol, and this remained the case when the analysis was restricted to subgroups (by gender, primary glomerular disease, diabetic nephropathy, and various bands of eGFR).<sup>108</sup> (Level 1b +)

By contrast, in the AusDiab study, a linear regression of log ACR and log PCR was significant ( $\beta=1.21$  (95% CI 1.18 to 1.26),  $p<0.001$ ,  $R^2=72.1\%$ , N=10,596 samples). The ratio of urine albumin to total protein significantly increased with increasing degrees of proteinuria from 0.21 for those with PCR of 0–0.20 mg/mg up to 0.73 for people with PCR >0.80 mg/mg. However, there was increased scatter of ACR (below the line of unity) at lower levels of PCR.<sup>106</sup> (Level II +)

##### ▷ Sensitivity and specificity of ACR and PCR

To detect a PCR  $\geq 0.20$  mg/mg, the pre-specified threshold of ACR  $\geq 30$  mg/g had a sensitivity of 91.7% (95% CI 87.7–94.5%) and a specificity of 95.3% (95% CI 94.9–95.7%).<sup>106</sup> (Level II +)

##### ▷ Positive and negative predictive values of ACR and PCR

To detect a PCR  $\geq 0.20$  mg/mg, ACR  $\geq 30$  mg/g had a PPV of 32.4% (95% CI 29.0–35.8%) and a NPV of 99.8% (95% CI 99.7–99.9%).<sup>106</sup> Atkins et al. concluded that testing for albuminuria rather than proteinuria was supported. However, among people with known renal disease, total protein measures may provide better diagnostic/prognostic information (as among people with proteinuria, 9% tested negative for albuminuria). (Level II +)

##### ▷ Correlation of ACR or PCR with 24-hour urinary protein

ACR and PCR both correlated well with 24-hour urinary protein (N=1739, the subgroup in whom 24-hour protein had been successfully collected). ACR had considerable scatter around a urinary protein of 300–1000 mg/day.<sup>108</sup> (Level 1b +)

##### ▷ Sensitivity and specificity of ACR or PCR compared with 24-hour protein excretion

To predict a 24-hour urine protein >1 g/day (N=1739, the subgroup in whom 24-hour protein had been successfully collected), a PCR threshold of 98 mg/mmol was found to give sensitivity of 0.95 with specificity of 0.83. An ACR threshold of 16.5 mg/mmol was found to give the same 0.95 sensitivity, this time with specificity of 0.7. Similarly, to predict a 24-hour urine protein >450 mg/day, a PCR threshold of 45 mg/mmol had the desired sensitivity of 0.95 and specificity of 0.83, whereas the ACR threshold of 9.5 mg/mmol achieved the same sensitivity with specificity of 0.77. Confidence intervals are not given for these estimates, and it is not possible to construct them from the details available.<sup>108</sup> (Level 1b +)



▷ Correlation of albumin with total protein

The correlation between albumin and total protein (log-log transformed) was high ( $r=0.924$ ,  $p<0.001$ ), indicating good agreement between total protein and albumin. Albumin concentration was  $<100$  mg/l and in most cases it was  $<20$  mg/l in samples that tested negative for protein by salicylsulphonic acid precipitation.<sup>90</sup> (Level II +)

Over the range 0–16,800mg/l protein, the correlation between albumin excretion rate (AER) and total protein excretion rate (TPER) was high ( $r=0.93$ ,  $N=167$ ). Albumin formed 71% of the total protein. For samples with total protein in the range 0–3000 mg/l ( $N=116$ ), the correlation between AER and TPER ( $r=0.68$ ) was lower.<sup>107</sup> (Level II +)

#### 4.4.6 From evidence to recommendations

Although 24-hour urine collections for protein and albumin are often used in diagnostic studies as the 'gold standard', 24-hour collections are subject to inaccuracies due to incomplete collection of all urine voided or inaccurate timing and the biochemical methods used to quantify the amount of protein present will give different results. Further, the objective of these tests in clinical practice is to detect people with CKD at increased risk of progression, and it is not yet established whether either one of proteinuria or albuminuria is superior to the other in this regard.

The evidence reviewed for the measurement of protein, albumin, PCR and ACR came from different disease groups, and in some cases different ethnic groups. The GDG noted that the influence of either disease or ethnicity on actual measurement was questionable.

ACR and PCR overcome inaccuracies related to timing of collection and incomplete urine collection but measure different proteins.

For the identification of proteinuria in routine clinical practise a single test has been recommended.

The amount of albuminuria was considered the most relevant measurement and has the advantage that the amount of albumin can be accurately measured if an immunologic assay is used.

The cost-effectiveness analysis (Appendix C) showed that ACR (performed in a hospital laboratory) was more cost-effective than the use of protein or albumin reagent strips. In a sensitivity analysis, we found that ACR has to be only very slightly more accurate than PCR for ACR to be cost-effective across a range of plausible cost differentials.

It is not possible to derive a simple correction factor that allows the conversion of ACR values to PCR or 24-hour urinary protein excretion rates because the relative amounts of albumin and other proteins will vary depending on the clinical circumstances; however, the GDG produced a table of approximate equivalents that will allow clinicians unfamiliar with ACR values to see the approximate equivalent PCR and 24-hour urinary protein excretion rates (Table 4.5).

**Table 4.5 Urine protein: ACR, PCR and 24-hour protein excretion**

Albumin:creatinine ratio	Protein:creatinine ratio	24-hour urinary protein excretion (g/day)
30 mg/mmol	Approx. equivalent to 50 mg/mmol	Approx. equivalent to 0.5 g/day
70 mg/mmol	Approx. equivalent to 100 mg/mmol	Approx. equivalent to 1 g/day

#### 4.4.7 RECOMMENDATIONS

- R14** In people without diabetes consider clinically significant proteinuria to be present when the ACR is 30 mg/mmol or more (this is approximately equivalent to PCR 50 mg/mmol or more, or a urinary protein excretion 0.5 g/24 h or more).
- R15** In people with diabetes consider microalbuminuria (ACR more than 2.5 mg/mmol in men and ACR more than 3.5 mg/mmol in women) to be clinically significant.
- R16** All people with diabetes, and people without diabetes with a GFR less than 60 ml/min/1.73 m<sup>2</sup>, should have their urinary albumin/protein excretion quantified. The first abnormal result should be confirmed on an early morning sample (if not previously obtained).
- R17** Quantify by laboratory testing the urinary albumin/protein excretion of people with an eGFR 60 ml/min/1.73 m<sup>2</sup> or more if there is a strong suspicion of CKD (see also 4.2.7).

### 4.5 Indications for renal ultrasound in the evaluation of CKD

#### 4.5.1 Clinical introduction

Ultrasound is the first-line imaging study for evaluating people with previously undiagnosed kidney disease. It helps the clinician separate end stage kidney disease from potentially reversible acute kidney injury or earlier stages of CKD by:

- determining the presence, size and shape of kidneys and assessing cortical thickness prior to renal biopsy
- identifying obstructive uropathy
- assessing renal scarring
- identifying polycystic kidney disease.<sup>111</sup>

Although ultrasound is the optimal imaging modality for CKD, it is not known what proportion of those with CKD will benefit from ultrasound imaging.

- *What are the indications for renal ultrasound in adults with CKD?*

#### 4.5.2 Methodology

Due to the difficulty in searching this question, the results of a broad literature search were reviewed for systematic reviews on criteria for referral for renal ultrasound in a CKD population. No studies were identified. An algorithm was provided by a GDG member, who

had conducted an (unpublished) retrospective analysis of people with CKD undergoing ultrasound scans. The algorithm served as a starting point to guide discussions and enabled the GDG to formulate consensus recommendations.

#### 4.5.3 Health economics methodology

There were no health economics papers found to review.

#### 4.5.4 Evidence statements

There were no clinical papers found to review.

#### 4.5.5 From evidence to recommendation

There was no evidence on which to base recommendations about when a renal ultrasound scan should be performed in people with CKD.

The recommendations about the use of renal ultrasound scanning are based on knowledge of the information that an ultrasound scan provides.

Renal ultrasound can be used to confirm that people have two kidneys, to measure the size of the kidneys and to show structural abnormalities in the kidney such as polycystic kidneys. Ultrasound scans can also be used to identify the presence of renal tract obstruction.

Ultrasound may identify renal size discrepancy but where diagnosis or exclusion of renovascular disease is indicated additional imaging such as CT angiography or magnetic resonance renal angiography will be required (newer generation MR scanners may afford imaging of vessels without exposure to gadolinium and the attendant risks of nephrogenic systemic fibrosis).

A renal ultrasound scan is always necessary before undertaking a renal biopsy.

Ultrasound scanning cannot exclude the diagnosis of autosomal dominant polycystic kidney disease in people under the age of 20 and is therefore of limited use in people under this age with a family history of this condition.

The GDG agreed that before undertaking a renal ultrasound scan in people at risk of kidney disease on the basis of a family history of inherited kidney disease, it was important that people were fully informed of the implications of an abnormal scan result. This should encompass counselling about the benefits of early identification of kidney disease but should also outline the social consequences of a diagnosis, including its effect on life insurance. Where indicated help to cope with the psychological consequences of a diagnosis should be offered.

#### 4.5.6 RECOMMENDATIONS

R18 Offer a renal ultrasound to all people with CKD who:

- have progressive CKD (eGFR decline  $>5$  ml/min/1.73 m<sup>2</sup> within one year or  $>10$  ml/min/1.73 m<sup>2</sup> within 5 years)
- have visible or persistent invisible haematuria

- have symptoms of urinary tract obstruction
- have a family history of polycystic kidney disease and are aged over 20
- have stage 4 or 5 CKD
- are considered by a nephrologist to require a renal biopsy.

**R19** Advise people with a family history of inherited kidney disease about the implications of an abnormal result before a renal ultrasound scan is arranged for them.

## 5 Classification and early identification

### 5.1 The influence of GFR, age, gender, ethnicity and proteinuria on patient outcomes

#### 5.1.1 Clinical introduction

If we cannot prevent CKD then we want to minimise the associated adverse outcomes. To do this we need to know:

- what the adverse outcomes are
- at what level of GFR we should be alert to adverse outcomes *and*
- the impact of associated factors such as age, gender and presence or absence of proteinuria at any given level of GFR.

Large population studies have clearly suggested that the risk of death, hospitalisation and cardiovascular events rises exponentially at levels of GFR below 60 ml/min/1.73 m<sup>2</sup>.<sup>13</sup> Other complications associated with reduced GFR, such as the increased potential for dose-related drug toxicity, are less obvious but equally important.

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) stratified chronic kidney disease into five stages according to glomerular filtration rate and the presence of kidney damage:

- *Stage 1:* GFR >90 ml/min/1.73 m<sup>2</sup> with other evidence of kidney damage (persistent microalbuminuria, persistent proteinuria, persistent haematuria, structural abnormalities of the kidneys demonstrated on ultrasound scanning or other radiological tests, or biopsy-proven chronic glomerulonephritis)
- *Stage 2:* GFR 60–89 ml/min/1.73 m<sup>2</sup> with other evidence of kidney damage
- *Stage 3:* GFR 30–59 ml/min/1.73 m<sup>2</sup>
- *Stage 4:* GFR 15–29 ml/min/1.73 m<sup>2</sup>
- *Stage 5:* GFR <15 ml/min/1.73 m<sup>2</sup>.

CKD is common and its prevalence increases markedly with age, with a female predominance. However, the CKD classification is neither staged according to age and gender, nor according to level of proteinuria. All patients, regardless of age, gender and proteinuria or albuminuria are considered to have at least moderately severe CKD when their GFR is <60 ml/min/1.73 m<sup>2</sup>. However, we have some evidence that GFR reduces as a consequence of ageing,<sup>112</sup> although the exact level of reduction is still a subject of debate, and reduced GFR is very common in certain older populations.<sup>113</sup> It has been suggested that the rate of progression of CKD in black and minority ethnic groups may be higher than in Caucasians.<sup>24</sup> The ABLE projects in the UK have also suggested that kidney disease in people of South Asian and African-Caribbean ethnicity may deteriorate more rapidly to established renal failure<sup>25</sup>. Long term, the ABLE study aims to identify the reasons for this faster deterioration.

The degree of proteinuria is a significant risk factor both for progression of CKD and for cardiovascular disease.<sup>114–117</sup> We therefore need a better understanding of the prognostic significance of different levels of GFR, and of what other factors should be considered. Intuitively

a ‘one size fits all’ approach to clinical decision making throughout the population is unlikely to be appropriate. This has already been recognised by the CARI (Caring for Australasians with Renal Impairment) guidelines which recommend that the suffix ‘(p)’ should be applied to the corresponding CKD stage for all patients with proteinuria  $\geq 1$  g/day. The recently published SIGN (Scottish Intercollegiate Guidelines Network) guideline also makes the same recommendation, as did the UK consensus conference on early CKD which also recommended sub-classifying CKD stage 3 into 2 groups: 3A which defines a lower risk group with GFR 45–59 ml/min/1.73 m<sup>2</sup>, and 3B which defines a higher risk group with GFR 30–44 ml/min/1.73 m<sup>2</sup>.<sup>34</sup>

- *At what level of GFR are patient outcomes significantly affected? Does this change with age? Gender? Ethnicity? Presence or absence of proteinuria?*

### 5.1.2 Methodology

Twenty-two longitudinal studies assessed the risks of all-cause mortality, cardiovascular disease, hospitalisation, renal disease progression, and the quality of life of adults with decreasing eGFR levels. Baseline characteristics were significantly different between groups with lower eGFR compared with higher eGFR. People with low eGFR were almost always older, more likely to be female, and had higher prevalence of diabetes and cardiovascular diseases. While statistical analyses in these studies have been adjusted for confounding variables such as age, gender, race, and several comorbidities, it is difficult to identify all variables which could potentially affect the size of the risk. These unknown variables make it impossible to assign cause and effect, and the confidence intervals were sometimes so wide that the associations with eGFR could be spurious.

Eight cohort studies examined the association between different eGFR levels and several outcomes of interest in populations with concomitant cardiovascular disease; specifically high-risk hypertension,<sup>118</sup> acute myocardial infarction,<sup>119,120</sup> heart failure,<sup>121</sup> acute coronary syndrome,<sup>122</sup> coronary disease,<sup>123</sup> coronary artery disease<sup>124</sup> and peripheral arterial disease.<sup>125</sup> These studies ranged in sample size from 1015 to 31,897 and length of follow-up ranged from 1 to 6 years. The mean age of people with higher eGFR (typically  $>60$  ml/min/1.73 m<sup>2</sup>) ranged from 57 to 72 years, while the mean age range of those with lower eGFR (typically  $<60$  ml/min/1.73 m<sup>2</sup>) ranged from 62 to 83 years. The study by Beddhu et al. was excluded due to missing patient baseline data, and lack of inclusion and exclusion criteria.

A very large US cohort study (N=1,120,295, follow-up 2.8 years, age range 47–71) examined age-adjusted risk of mortality, cardiovascular events, and hospitalisation in people with stage 3, 4, or 5 CKD compared to people with GFR  $>60$  ml/min/1.73 m<sup>2</sup>.<sup>13</sup> In another US cohort study, participants with CKD were age- and sex-matched with people without CKD (N=19,945 pairs, follow-up 4.5 years) and the risk of all-cause mortality was examined.<sup>126</sup> The KEEP study assessed mortality and cardiovascular disease (N=37,153, median follow-up 16 months) in a self-selected population of people with diabetes, hypertension, or a family history of kidney disease, hypertension, or diabetes.<sup>127</sup> Participants in the ARIC cohort (N=14,280) were assessed for incidence of peripheral arterial disease as a function of eGFR.<sup>128</sup>

A UK cohort study (N=3249 unreferral, 2.6 years follow-up, mean age 82 years) examined the mortality outcomes of people who had not been referred to renal services with stage 4 or 5 CKD compared to eGFR 30–42 ml/min/1.73 m<sup>2</sup>.<sup>11</sup>

Three cohort studies in diabetic adults examined the association of eGFR with renal disease progression and cardiovascular outcomes.<sup>129–131</sup> A UK study of people identified from a

diabetes register (N=3288, median follow-up 10.5 years) assessed all-cause mortality and mortality due to circulatory disease, ischaemic heart disease, or cerebrovascular disease in this population stratified by eGFR.<sup>131</sup> The Patel et al. study (N=12,570, follow-up 3 years, range of groups' mean ages 64–72) reported mortality rates and kidney disease progression rates at different eGFR levels in a predominantly male diabetic cohort. This study was rejected as there was little statistical analysis of the results; only mortality rates were presented.

Quality of life outcomes such as cognitive impairment, frailty, and disability were assessed in postmenopausal women<sup>124</sup> or in older populations with varying levels of serum creatinine<sup>132</sup> or eGFR.<sup>133</sup>

The effect of proteinuria or no proteinuria at a particular eGFR on the risk of ESRD was assessed in a Japanese population study (N=95,255, follow-up 7 years).<sup>134</sup> The So et al. study investigated the effect of proteinuria on patient outcomes within several GFR ranges in a Chinese diabetic cohort (N=4421, follow-up 3.3 years, mean ages in higher versus lower eGFR ranges 57 and 69 years).

The effects of age and gender on mortality and kidney disease progression were examined in people with stage 3 CKD in a Norwegian population study (N=3027, median observation time 3.7 years, median age 75 years).<sup>135</sup> In a predominantly male cohort study (N=8,218,817, mean follow-up 3.17 years), people were stratified by age within decreasing ranges of eGFR and the effect of age on mortality was examined.<sup>136</sup> In another analysis of this cohort (N=209,622, follow-up 4 years), people were stratified by eGFR and the risk of death or progression to ESRD was assessed with increasing age.<sup>137</sup>

There were no studies that assessed cardiovascular and renal outcomes as a function of race within different levels of renal function.

Table 5.1 summarises the association of GFR and mortality, cardiovascular risk, and renal disease progression in adults with varying severity of CKD.

### 5.1.3 Health economics methodology

There were no health economics papers to review.

### 5.1.4 Evidence statements

#### ▷ All-cause mortality

Three studies showed that the risk of all-cause mortality rose sharply in people with eGFR <45 ml/min/1.73m<sup>2</sup>.<sup>13,119,121</sup> Every 10 ml/min/1.73 m<sup>2</sup> decrease in GFR from 75 ml/min/1.73 m<sup>2</sup> was associated with a significantly higher risk of all-cause mortality (adjusted HR 1.09, 95% CI 1.06–1.14, p<0.001).<sup>121</sup> (Level 2+)

#### ▷ Cardiovascular mortality

Three studies showed that risk of cardiovascular mortality increased with declining renal function.<sup>119,121,131</sup> The risk of circulatory disease mortality, ischaemic heart disease mortality, and cerebrovascular disease mortality all significantly increased with decreasing renal function.<sup>131</sup> (Level 2+)

▷ Cardiovascular events

Three studies showed NS risk of cardiovascular events in people with GFR 60–89 ml/min/1.73 m<sup>2</sup> compared with eGFR >90 ml/min/1.73 m<sup>2</sup>.<sup>119,127,130</sup> The risk of cardiovascular events significantly increased at eGFR <60 ml/min/1.73 m<sup>2</sup>.<sup>118,119,127,128</sup> The risk of cardiovascular events rose sharply in people with eGFR <45 ml/min/1.73m<sup>2</sup>.<sup>13</sup> (Level 2+)

▷ Frailty

People with chronic renal insufficiency (CRI) (N=648) had a significantly increased risk of frailty (adjusted odds ratio (OR) 1.76, 95% CI 1.28–2.41, p not stated) compared to people without CRI. The prevalence of frailty increased with decreasing GFR (p for trend <0.001) and was particularly high in those with GFR <40 ml/min/1.73 m<sup>2</sup>. Black ethnicity and female gender were associated with increased likelihood of frailty.<sup>132</sup> (Level 3)

▷ Disability

There was NS risk of disability for people with CRI compared to people without CRI. Black race and female gender were associated with increased likelihood of disability.<sup>132</sup> (Level 3)

▷ Cognitive impairment (3MS score <80)

The risk of cognitive impairment was significantly greater for people with eGFR 45–59 ml/min/1.73 m<sup>2</sup> (adjusted OR 1.32, 95% CI 1.03–1.69) or eGFR <45 ml/min/1.73 m<sup>2</sup> (adjusted OR 2.43, 95% CI 1.38–4.29, compared to people with GFR >60 ml/min/1.73 m<sup>2</sup>).<sup>133</sup> (Level 2+)

In postmenopausal women under 80 years old with established coronary artery disease, the risk of cognitive impairment was significantly higher at eGFR <30 ml/min/1.73 m<sup>2</sup> compared to women with eGFR >60ml/min/1.73 m<sup>2</sup> (adjusted OR 5.01, 95% CI 1.27–19.7). There was NS risk of cognitive impairment at eGFR 45–49 or 30–44 ml/min/1.73 m<sup>2</sup>. A decline in eGFR of 10 ml/min/1.73m<sup>2</sup>/year was associated with an increased risk of cognitive impairment (adjusted OR 1.27, 95% CI 1.01–1.59).<sup>124</sup> (Level 3)

▷ Effect of age on all-cause mortality

When participants with various levels of CKD were age- and sex-matched with people without CKD (N=19,945 pairs, follow-up 4.5 years), the relative risk (RR) of mortality in people aged 60, 75 or 90 was relatively stable until eGFR decreased to 55 ml/min/1.73 m<sup>2</sup> when the risk of mortality increased in all three age groups (<60, 75 or 90 years). The risk of mortality was highest in those <60 years old. At eGFR <30 ml/min/1.73 m<sup>2</sup>, the mortality risk increased sharply. Again the risk was highest in those <60 years of age.<sup>126</sup> (Level 2+)

The risk of all-cause mortality at a certain eGFR decreased as age increased. An eGFR of 50–59ml/min/1.73 m<sup>2</sup> was still associated with an increased risk of death among all age groups under 65 years.<sup>136</sup> (Level 3)

However, in a Norwegian cohort of people with stage 3 CKD stratified by age (≤69 years, 70–79 years, >79 years) each 10-year increment of age was associated with a significantly increased risk of all-cause mortality (HR 2.28, 95% CI 2.11–2.46, p<0.0001).<sup>135</sup> The risk of death increased with increasing age within each stratum of baseline eGFR.<sup>137</sup> (Level 3)



▷ Effect of age on renal failure

In people with stage 3 CKD, each 10-year increment of age was associated with a significantly decreased risk of renal failure (HR 0.75, 95% CI 0.63–0.89,  $p=0.0009$ ).<sup>135</sup> The risk of ESRD decreased with increasing age within each stratum of baseline eGFR.<sup>137</sup> (Level 3)

▷ Effect of age on GFR decline

Each 10-year increment in age was associated with a decline in GFR ( $-0.38$  ml/min/  $1.73$  m<sup>2</sup>/year, 95% CI  $-0.51$  to  $-0.26$ ,  $p<0.0001$ ).<sup>135</sup> (Level 3)

▷ Effect of gender on all-cause mortality

In people with CKD and acute coronary syndromes, men had a significantly increased risk of all-cause mortality compared to women HR 1.185, 95% CI 1.116–1.259,  $p$  not stated.<sup>122</sup> (Level 2+)

Women with stage 3 CKD had a significantly reduced risk of all-cause mortality compared with men with stage 3 CKD (HR 0.55, 95% CI 0.48–0.62,  $p<0.0001$ ).<sup>135</sup> (Level 3)

Unreferred women had a decreased risk of all-cause mortality compared to unreferred men (HR 0.73, 95% CI 0.65–0.82,  $p<0.001$ ).<sup>11</sup> (Level 3)

Compared to males, females had a decreased risk of in-hospital death (adjusted OR 0.7, 95% CI 0.5–1.5,  $p=0.012$ ).<sup>120</sup> (Level 2+)

▷ Effect of gender on renal failure

Women with stage 3 CKD had a significantly reduced risk of renal failure compared with men with stage 3 CKD (HR 0.35, 95% CI 0.21–0.59,  $p<0.0001$ ).<sup>135</sup> (Level 3)

▷ Effect of gender on GFR decline

The decline in eGFR in men with stage 3 CKD was greater ( $-1.39$  ml/min/ $1.73$  m<sup>2</sup>/year) than in women ( $-0.88$  ml/min/ $1.73$  m<sup>2</sup>/year). Female gender was associated with an increased change in eGFR compared to men ( $+0.50$  ml/min/ $1.73$  m<sup>2</sup>/year, 95% CI 0.20–0.81,  $p=0.001$ ).<sup>135</sup> (Level 3)

▷ Effect of proteinuria on all-cause mortality

The risk of death increased as eGFR decreased and proteinuria was present. In an age- and sex-matched cohort, the matched risk ratio was 2.09 (95% CI 1.71–2.55) for people with proteinuria and eGFR 60–89 ml/min/ $1.73$  m<sup>2</sup>. For people with proteinuria and eGFR 30–59 ml/min/ $1.73$  m<sup>2</sup>, the matched risk ratio was 2.73, 95% CI 2.23–3.35. For people with proteinuria and eGFR 15–29 ml/min/ $1.73$  m<sup>2</sup>, the matched risk ratio was 6.96 (95% CI 4.63–10.46).<sup>126</sup> (Level 2+)

▷ Effect of proteinuria on cardiovascular events (ischemic heart disease, stroke, congestive heart failure, revascularisation procedures)

At a given eGFR, the presence of proteinuria significantly increased the risk of cardiovascular events.<sup>127,130</sup> When eGFR was  $\geq 90$  ml/min/ $1.73$  m<sup>2</sup>, those with albuminuria had a significantly increased risk of cardiovascular events than those without albuminuria (HR 1.85, 95% CI

1.07–3.18, p=0.03). Similarly, people with GFR 60–89 ml/min/1.73 m<sup>2</sup> with albuminuria had a significantly increased risk of cardiovascular events than those without albuminuria (HR 1.89, 95% CI 1.13–3.16, p=0.016).<sup>130</sup> (Level 2+ and 3)

▷ Effect of proteinuria on ESRD

In a Japanese cohort study, proteinuria significantly increased the risk of ESRD (HR 4.19, 95% CI 3.76–4.68, p<0.0001). For people with proteinuria and creatinine clearance (CrCl) 64.0–79.3 ml/min (N=727), the 7-year cumulative incidence of ESRD per 1000 subjects was 8.3, whereas it was only 0.04 in those without proteinuria (N=22,420). For people with proteinuria and CrCl 50.2–63.0 ml/min (N=807), the 7-year cumulative incidence of ESRD per 1000 subjects was 13.6, whereas it was only 0.7 in those without proteinuria (N=22,232). For people with proteinuria and CrCl <50.2 ml/min (N=1198), the 7-year cumulative incidence of ESRD per 1000 subjects was 86.8, whereas it was only 1.2 in those without proteinuria (N=21,878).<sup>134</sup> (Level 2+)

**Table 5.1 Association of adverse outcomes with declining GFR**

Reference	Population	Reference GFR (ml/min/ 1.73 m <sup>2</sup> )	GFR 89–75 (95% CI)	GFR 74.9–60 (95% CI)	GFR 59–45 (95% CI)	GFR 45–30 (95% CI)	GFR 29–15 (95% CI)	GFR <15 (95% CI)
<b>Outcome: risk of all-cause mortality</b>								
125	Men with peripheral vascular disease (N=5787)	≥60	–	–	1.32 (1.13, 1.53)		2.97 (2.39, 3.69)	
121	Heart failure (N=2680)	>90	NS	NS	1.50 (1.12, 2.00), p=0.006	1.91 (1.42, 2.58), p<0.001		
122	Acute coronary syndrome (N=5549)	>80	0.889 (0.795, 0.994) – decreased risk		1.060 (1.008, 1.115)		1.225 (1.175, 1.292)	
119	Acute MI and LVEF ≤40% (N=2183)	≥75	–	NS	NS	1.81 (1.32, 2.48)		
130	Type 2 diabetes (N=4421)	≥90	NS		2.34 (1.16, 4.70)		9.82 (4.53, – 21.0)	
13	Kaiser Permanente cohort (N= 1120295)	≥60	–	–	1.2 (1.1, 1.2)	1.8 (1.7–1.9)	3.2 (3.1–3.4)	5.9 (5.4–6.5)
126	Kaiser Permanente cohort (N=19945 sex, age matched pairs)	60–89	–	–	Matched RR 1.311 (1.142, 1.505), p<0.0001		Matched RR 3.335 (2.272, 4.896), p<0.0001	

*continued*

Table 5.1 Association of adverse outcomes with declining GFR – *continued*

Reference	Population	Reference GFR (ml/min/ 1.73 m <sup>2</sup> )	GFR 89–75 (95% CI)	GFR 74.9–60 (95% CI)	GFR 59–45 (95% CI)	GFR 45–30 (95% CI)	GFR 29–15 (95% CI)	GFR <15 (95% CI)
11	People unreferred to renal services (N=3822)	30–42.8	–	–	–	–	1.41 (1.25, 1.60), p<0.001	3.12 (2.53, 3.83), p<0.001
127	Adults with diabetes, hypertension, or family history of diabetes, hypertension, or kidney disease (N=37153)	≥90	NS		NS		NS	
131	Adults with type 1 + type 2 diabetes (N=3288)	≥90	1.28 (1.02, 1.60)		2.58 (2.05, 3.25)		6.42 (4.25, 9.71)	
<b>Outcome: risk of cardiovascular mortality</b>								
121	Heart failure (N=2680)	> 90	NS	NS	1.54 (1.22, 1.94), p<0.001	1.86 (1.47, 2.36, p<0.001)		
119	Acute MI and LVEF ≤40% (N=2183)	≥75	–	NS	NS	1.96 (1.39, 2.76)		
<b>Outcome: risk of cardiovascular events</b>								
118	Hypertension + high risk for CVD (N=31897, ALL-HAT)	≥90	1.08 (1.01, 1.15), p=0.027		1.35 (1.24, 1.46), p<0.001			
119	Acute MI and LVEF ≤40% (N=2183)	≥75	–	Recurrent MI: NS heart failure: NS	Recurrent MI: 1.42 (1.03, 1.96) heart failure: NS	Recurrent MI: NS Heart failure: NS		
130	Type 2 diabetes (N=4421)	≥90	NS		NS		3.23 (1.74, – 5.99)	
13	Kaiser Permanente cohort (N=1120295)	≥60	–	–	1.4 (1.4–1.5)	2.0 (1.9–2.1)	2.8 (2.6–2.9)	3.4 (3.1–3.8)

*continued*

**Table 5.1 Association of adverse outcomes with declining GFR – continued**

Reference	Population	Reference GFR (ml/min/ 1.73 m <sup>2</sup> )	GFR 89–75 (95% CI)	GFR 74.9–60 (95% CI)	GFR 59–45 (95% CI)	GFR 45–30 (95% CI)	GFR 29–15 (95% CI)	GFR <15 (95% CI)
127	Adults with diabetes, hypertension, or family history of diabetes, hypertension, or kidney disease (N=37153)	≥90	NS		1.37 (1.13, 1.67), p=0.001		NS	
<b>Outcome: risk of hospitalisation</b>								
13	Kaiser Permanente cohort (N=1120295)	≥60	–	–	1.1 (1.1–1.1)	1.5 (1.5–1.5)	2.1 (2.0–2.2)	3.1 (3.1–3.3)
<b>Outcome: risk of ESRD</b>								
118	Hypertension + high risk for CVD (N=31897, ALL-HAT)	≥90	2.90 (1.90, 4.67), p<0.001		20.33 (12.74, 32.42), p<0.001			
130	Type 2 diabetes (N=4421)	≥90	NS		3.34 (2.06, 5.42)		27.3 (15.6, 47.8)	–
<b>Outcome: risk of peripheral arterial disease</b>								
128	ARIC cohort (N=14280)	≥90	NS		1.58 (1.14, 2.17)			–

Shaded boxes indicate studies spanning different GFR ranges.

ALL-HAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ARIC = Atherosclerosis Risk in Communities; LVEF = left ventricular ejection; MI = myocardial infarction.

### 5.1.5 From evidence to recommendations

There has been debate about the implications of having a reduced GFR and, in particular, whether a stable GFR that does not change over time is associated with adverse health outcomes.

Not all studies stratified patients according to whether or not they had diabetes and this may affect estimates of the risk of death.

The evidence suggested that if the GFR is less than 60 ml/min/1.73 m<sup>2</sup>, then there is an increased risk of mortality which is seen in all age groups.

There was limited evidence about outcomes in older people. However, given that they are at increased absolute risk of mortality and cardiovascular events it was agreed that even small increases in relative risk in older people are of significance.

The GDG considered that the evidence suggested that the risk of mortality and cardiovascular events increased considerably when the GFR was less than 45 ml/min/1.73 m<sup>2</sup>. This led to the proposal to adopt the sub-division of stage 3 CKD into stages 3A and 3B, defined by an eGFR 45–59 ml/min/1.73 m<sup>2</sup> and 30–44 ml/min/1.73m<sup>2</sup> respectively.

The GDG noted that although it has been suggested that the rate of progression of CKD in black and ethnic minority groups may be higher than in Caucasians, as yet there is no published evidence to support this.

It was noted that the presence of proteinuria was associated with a doubling of CVD risk and mortality at all levels of GFR. This led to the proposal to adopt the suffix '(p)' notation to denote the presence of proteinuria when staging CKD. Evidence from longitudinal population studies and from meta-analysis of progression risk and level of proteinuria suggested that an ACR  $\geq 30$  mg/mmol should be used as a marker of the increased risk (roughly equivalent to a PCR  $\geq 50$  mg/mmol or proteinuria values  $\geq 0.5$  g/day).

The GDG agreed not to recommend age-related decision points for eGFR. However, it seemed clear that in people aged  $>70$  years, an eGFR in the range 45–59 ml/min/1.73m<sup>2</sup>, if stable over time and without any other evidence of kidney damage is unlikely to be associated with CKD-related complications.

### 5.1.6 RECOMMENDATIONS

- R20** Use the suffix '(p)' to denote the presence of proteinuria when staging CKD.
- R21** For the purposes of this classification define proteinuria as urinary albumin:creatinine ratio (ACR)  $\geq 30$  mg/mmol or PCR  $\geq 50$  mg/mmol (approximately equivalent to urinary protein excretion  $\geq 0.5$  g/24 hours)
- R22** Stage 3 CKD should be split into two subcategories defined by:
- GFR 45–59 ml/min/1.73m<sup>2</sup> (stage 3A) *and*
  - GFR 30–44 ml/min/1.73m<sup>2</sup> (stage 3B)
- R23** At any given stage of CKD, management should not be influenced solely by age.\*

Stages of chronic kidney disease (updated)		
Stage <sup>a</sup>	GFR (ml/min/1.73 m <sup>2</sup> )	Description
1	$\geq 90$	Normal or increased GFR, with other evidence of kidney damage
2	60–89	Slight decrease in GFR, with other evidence of kidney damage
3A	45–59	Moderate decrease in GFR, with or without other evidence of kidney damage
3B	30–44	
4	15–29	Severe decrease in GFR, with or without other evidence of kidney damage
5	$<15$	Established renal failure

<sup>a</sup> Use the suffix (p) to denote the presence of proteinuria when staging CKD (recommendation R20).

\* In people aged  $>70$  years, an eGFR in the range 45–59 ml/min/1.73m<sup>2</sup>, if stable over time and without any other evidence of kidney damage, is unlikely to be associated with CKD-related complications.

## 5.2 Who should be tested for CKD?

### 5.2.1 Clinical Introduction

The early identification and treatment of CKD is essential to decrease the risk of cardiovascular disease, progression to ESRD, and mortality. Identification of high-risk groups can help clinicians monitor renal function and identify people with CKD at an earlier disease stage. Although general population screening may not be cost-effective, targeted screening directed at subgroups of the population who might derive the most benefit from CKD detection was shown to be an effective strategy.<sup>138</sup> A national programme to identify vulnerability to vascular diseases was announced by the Health Secretary in April 2008, following initial results from modelling work carried out by the Department of Health. This work suggested that a vascular check programme would prevent 4000 people a year from developing diabetes and could also detect at least 25,000 cases of diabetes or kidney disease earlier. In those conditions where the prevalence of CKD is high and the risks of preventable complications are increased, testing for CKD is clearly warranted. The KEEP programme identified people with diabetes and hypertension, or people with a first-line relative (parent, grandparent, brother or sister) with diabetes, high blood pressure or kidney disease as being at high risk of CKD. Are there additional high-risk people who should be tested for CKD? The UK CKD guidelines also included those with a high risk of obstructive uropathy, all forms of CVD, multisystem diseases with the potential to involve the kidney such as SLE, and conditions requiring long-term treatment with potentially nephrotoxic drugs.<sup>33</sup> In addressing this question all of these factors were considered, together with other lifestyle factors such as smoking, obesity and alcohol intake.

- *In adults, who should be tested for CKD?*

### 5.2.2 Methodology

Three cohort and sixteen observational or cross-sectional studies examined several risk factors for developing CKD. Table 5.2 summarises the risk factors associated with development of CKD.

#### ▷ Age

The association between developing CKD and age was examined in cross-sectional studies conducted in the UK,<sup>10</sup> Norway,<sup>139,140</sup> USA<sup>20,22</sup> and Australia.<sup>141</sup>

#### ▷ Gender

The association between developing CKD and gender was examined in cross-sectional studies conducted in the UK,<sup>10</sup> Norway,<sup>140</sup> USA<sup>20</sup> and Australia.<sup>141</sup> A longitudinal study examined the association between age and death due to CKD or need for dialysis in an American cohort (N=23,534, 20-year follow-up).<sup>142</sup> This study, while large, was limited by no assessment of renal disease at baseline, and poor identification of diabetes (assessed by medication use in medical records).

#### ▷ Hypertension

The association between hypertension and risk of developing CKD was examined in one longitudinal study<sup>142</sup> and cross-sectional studies conducted in Norway,<sup>140</sup> USA,<sup>20</sup> and Australia.<sup>141</sup>

▷ Diabetes

The association between diabetes and risk of developing CKD was examined in one longitudinal study<sup>142</sup> and cross-sectional studies conducted in the UK,<sup>143</sup> Norway,<sup>140</sup> USA<sup>20</sup> and Australia.<sup>141</sup>

▷ Body mass index (BMI) and metabolic syndrome

A cohort study, the Physician's Health Study, followed 11,104 male doctors for 14 years and examined the association of high baseline BMI with developing CKD.<sup>144</sup> A longitudinal study followed 9082 Americans for 13 years and analysed the effect of BMI on the risk of death due to CKD or ESRD.<sup>145</sup>

Metabolic syndrome is defined as possessing three or more of the following:

- waist measurement >88 cm for women or >102 cm for men
- triglycerides  $\geq 150$  mg/dl
- HDL (high-density lipoprotein) cholesterol <50 mg/dl for women or <40 mg/dl for men
- BP  $\geq 130/\geq 85$  mmHg or the use of BP medications
- fasting glucose  $\geq 110$  mg/dl.

A cohort study evaluated the risk of developing CKD in people with metabolic syndrome compared to those without metabolic syndrome (N=10,096, follow-up 9 years, Atherosclerosis Risk in Communities (ARIC) study cohort).<sup>146</sup>

▷ Cardiovascular disease and atherosclerotic risk factors

In a case series study, the development of kidney disease in people with cardiovascular disease (N=1787, mean age 60 years) was compared with people without cardiovascular disease (N=12,039, mean age 57 years, 9.3 years follow-up).<sup>147</sup>

In the ARIC study, N=12,728, 3-year follow-up, USA), the effect of cardiovascular disease risk markers (total cholesterol, high-density lipoprotein (HDL)-2 and HDL-3 cholesterol, LDL cholesterol, apolipoprotein A-1, apolipoprotein-B, Lp(a), triglycerides) on the risk of rising serum creatinine or a  $\geq 25\%$  reduction in estimated creatinine clearance was examined.<sup>148</sup>

▷ Heredity

The prevalence of nephropathy or ESRD in diabetic siblings of people with diabetic nephropathy was compared with diabetic siblings of people without diabetic nephropathy.<sup>149,150</sup>

The incidence of a family history of ESRD among 28,111 ESRD patients initiating renal replacement therapy during 1994,<sup>151</sup> or during 1995 and 2003<sup>152</sup> was examined. A family history of ESRD was considered present if an incident ESRD patient reported having either a first-degree (parent, child, sibling) or second-degree (grandparent, aunt, uncle, grandchild, or half-sibling) relative with ESRD.

▷ Ethnicity

The incidence of microalbuminuria was compared between European, South Asian, and African-Caribbean people (N=2965) in the UK. This cohort study was excluded as 27% of the cohort did not have albumin excretion rate measurements and there were significant differences between those whose data were included and those whose data were not. The study mainly assessed the relationship between microalbuminuria and coronary heart disease, rather than ethnicity and the development of CKD.<sup>153</sup>

One case series study (UK Prospective Diabetes Study (UKPDS) 74)<sup>154</sup> investigated the associations of ethnicity with the development of microalbuminuria, macroalbuminuria, and CrCl  $\leq 60$  ml/min/1.73 m<sup>2</sup> in adults with newly diagnosed type 2 diabetes (N=5032, 15 years median follow-up). This study should be interpreted with caution as the multivariate analysis was restricted to N=2167, a loss of half of the study participants.

In the NHANES III study, prevalence of severe or moderate CKD was compared between non-Hispanic black people (N=4163) and non-Hispanic white people (N=6635).<sup>20</sup>

▷ Smoking

One case series (UKPDS 74)<sup>154</sup> investigated the associations of smoking with the development of microalbuminuria or CrCl  $\leq 60$  ml/min/1.73 m<sup>2</sup> in adults with newly diagnosed type 2 diabetes (N=5032, 15 years median follow-up). Two US longitudinal studies examined the association between smoking and death due to CKD or development of ESRD.<sup>142,145</sup>

▷ Alcohol consumption

A longitudinal study followed 9082 Americans for 13 years and analysed the effect of alcohol consumption on the risk of death due to CKD or ESRD.<sup>145</sup>

▷ Physical inactivity

A longitudinal study followed 9082 Americans for 13 years and analysed the effect of physical inactivity on the risk of death due to CKD or ESRD.<sup>145</sup>

▷ Socioeconomic deprivation

The association between developing CKD and socioeconomic deprivation (measured with a Townsend score) was examined in a UK cross-sectional study.<sup>10</sup>

### 5.2.3 Health economics methodology

Three cost-effectiveness analyses were retrieved. Each was based on a model and each measured health gain in terms of quality-adjusted life-years (QALYs). All three studies attributed the health gain to prescribing of ACE inhibitors or ARBs after diagnosis of proteinuria.

The first study was a simulation study in a Canadian setting.<sup>155</sup> It compared screening for microalbuminuria with screening for hypertension and macroproteinuria in patients with insulin-dependent diabetes.

The second study<sup>156</sup> evaluated annual screening of the US population aged 50–75 from a societal perspective using a Markov model.

The third study<sup>157</sup> evaluated screening for proteinuria in the Australian population aged 50–69 using a decision analysis with Markov chains.

Since none of these studies were from an NHS perspective, we performed our own decision analysis to evaluate the cost-effectiveness of different case-finding strategies (see Appendix C).



### 5.2.4 Evidence statements

▷ Age as a risk factor for developing CKD

Four cross-sectional studies showed that older people (over 65 years of age) had a greater risk of an eGFR <60 ml/min/1.73 m<sup>2</sup> than younger people.<sup>10,20,140,141</sup> Analysis of a Norwegian cross-sectional study showed that screening people with diabetes or hypertension or people over 55 years of age identified 93% of cases with stage 3-5 CKD (number needed to screen (NNS) 8.7, 95% CI 8.5–9.0).<sup>139</sup> (Level 3)

▷ Gender as a risk factor for developing CKD

There was NS difference between men and women for prevalence of CKD.<sup>20</sup> (Level 3)

Two studies showed that women had a lower risk of CKD than men.<sup>10,142</sup> (Level 3)

However, an Australian study (AusDiab) and a Norwegian study (HUNT II) showed that women had a higher risk of CKD than men.<sup>140,141</sup> (Level 3)

▷ Hypertension as a risk factor for developing CKD

Four studies showed that people with hypertension had a significantly higher risk of developing CKD than normotensive people.<sup>20,140–142</sup> (Level 3)

▷ Diabetes as a risk factor for developing CKD

An Australian cross-sectional study showed that people with diabetes had NS risk of renal impairment compared with people without diabetes.<sup>141</sup> (Level 3)

By contrast, NHANES III,<sup>20</sup> HUNT II,<sup>140</sup> a UK cross-sectional study<sup>143</sup> and a longitudinal study<sup>142</sup> all showed that diabetes was associated with a significantly increased risk for CKD. (Level 3)

In the paper by New et al., only 33% of people with diabetes with moderate CKD had serum creatinine values >120 µmol/l (upper limit of normal), indicating that measuring serum creatinine level alone failed to identify stage 3 CKD. Also, 63% of people with diabetes and eGFR <60 ml/min/1.73 m<sup>2</sup> had normoalbuminuria, indicating that microalbuminuria testing was insensitive and used alone was not sufficient for screening for CKD.<sup>143</sup> (Level 3)

▷ Body mass index or metabolic syndrome as risk factors for developing CKD

The risk of developing CKD (GFR <60 ml/min/1.73 m<sup>2</sup>) increased with increasing BMI (p=0.007). Compared to men who remained within 5% of their baseline BMI (N=5670), men who had a >10% increase in BMI (N=1669) had a significantly increased risk of CKD (OR 1.24, 95% CI 1.03–1.50).<sup>144</sup> (Level 2+)

By contrast, the NHANES II follow-up study showed NS risk for a CKD-related death or ESRD at any level of BMI.<sup>145</sup> (Level 3)

Metabolic syndrome was significantly associated with an increased risk of developing CKD. As the number of traits increased, there was a significant stepwise increase in risk of developing CKD. Those with 5 criteria had an OR of 2.45 (95% CI 1.32–4.54) for developing CKD compared to those with none.<sup>146</sup> (Level 2+)

▷ Cardiovascular disease and atherosclerotic risk factors associated with CKD

People with baseline CVD (N=1787) had a significantly increased risk of either a rise in serum creatinine of  $\geq 0.4$  mg/dl or a eGFR decrease of  $\geq 15$  ml/min/1.73 m<sup>2</sup> compared with people without baseline CVD (N=12,039).<sup>147</sup> (Level 3)

High triglycerides were associated with a significantly increased risk of a rise in creatinine  $\geq 0.4$  mg/dl from baseline. High HDL or HDL-2 cholesterol levels were associated with a significantly decreased risk of a rise in creatinine  $\geq 0.4$  mg/dl.<sup>148</sup> (Level 3)

▷ Heredity as a risk factor for developing CKD

Diabetic siblings of people with diabetic nephropathy had a significantly increased risk of incipient or overt nephropathy compared to diabetic siblings of people without nephropathy (OR 4.9, 95% CI 1.3–19.1).<sup>149</sup> Seaquist et al. reported a higher prevalence of nephropathy in the siblings of diabetics with nephropathy compared with siblings without nephropathy (83% vs. 17%,  $p < 0.001$ ). ESRD was higher in the siblings of diabetics with nephropathy (41%) compared to siblings of diabetics without nephropathy (0%).<sup>150</sup> (Level 3)

In two case series, a family history of ESRD was reported by 20% of people with incident ESRD.<sup>151,152</sup> Factors independently associated with a family history of ESRD were race, hypertension, diabetes, glomerulonephritis, BMI, and smoking. Overweight people with ESRD (N=6584, BMI 25.0–29.9 kg/m<sup>2</sup>) had a 17% greater odds of reporting a family of ESRD compared with normal weight people with ESRD (N=9037, BMI 18.5–24.9 kg/m<sup>2</sup>, adjusted OR 1.17, 95% CI 1.08–1.26,  $p < 0.001$ ). Obese people with ESRD (N=3624, BMI 30–34.9 kg/m<sup>2</sup>) had a 25% greater odds of reporting a family of ESRD compared with normal weight people with ESRD (N=9037, BMI 18.5–24.9 kg/m<sup>2</sup>) (adjusted OR 1.25, 95% CI 1.14–1.37,  $p < 0.001$ ). Black people with ESRD (N=13,645) were significantly more likely to report a family history of ESRD than white people with ESRD (N=10,127) (adjusted OR 2.38, 95% CI 2.21–2.55,  $p < 0.001$ ). People with ESRD and a history of hypertension (N=19,987) were significantly more likely to report a family history of ESRD than people with ESRD and no history of hypertension (N=3835) (adjusted OR 1.12, 95% CI 1.02–1.23,  $p < 0.001$ ).<sup>152</sup> (Level 3)

▷ Ethnicity as a risk factor for developing CKD

In the NHANES III study, non-Hispanic black people (N=4163) were significantly less likely to have moderate CKD compared to non-Hispanic white people (N=6635). There was NS difference in prevalence of severe CKD in non-Hispanic black or white people.<sup>20</sup> (Level 3)

In multivariate analysis of adults with newly diagnosed type 2 diabetes (N=2167) in the UKPDS, African-Caribbeans had NS risk of developing microalbuminuria, macroalbuminuria or CrCl  $\leq 60$  ml/min/1.73 m<sup>2</sup> compared with Caucasians. Indian Asians had a significantly increased risk of developing microalbuminuria, macroalbuminuria or a creatinine clearance  $\leq 60$  ml/min/1.73 m<sup>2</sup> compared with Caucasians.<sup>154</sup> (Level 3)

▷ Smoking as a risk factor for developing CKD

Three studies showed that smokers had a significantly higher risk for CKD than non-smokers.<sup>142,145,154</sup> (Level 3)

- ▷ Alcohol consumption as a risk factor for developing CKD  
Alcohol consumption was NS associated with a risk of ESRD or a CKD-related death.<sup>145</sup> (Level 3)
  
- ▷ Physical inactivity as a risk factor for developing CKD  
People with low physical activity had a significantly higher risk of ESRD or a CKD-related death than people who had high physical activity. People with moderate physical activity have NS risk of CKD compared to people who had high physical activity (adjusted RR 1.2, 95% CI 0.7 to 2.0).<sup>145</sup> (Level 3)
  
- ▷ Socioeconomic deprivation as a risk factor for developing CKD  
People who were least deprived (Townsend score =1) had a significantly lower risk of CKD compared to the overall population, whereas people who were most deprived (Townsend score =5) had a significantly higher risk of CKD compared to the overall population.<sup>10</sup> (Level 3)

Table 5.2 Risk factors for developing CKD

Reference	Population	N	Definition of CKD	Risk factor for developing CKD
146	ARIC cohort, USA	10,096	eGFR < 60 ml/min/1.73m <sup>2</sup>	<b>Metabolic syndrome:</b> elevated triglycerides OR 1.34 (1.12–1.59); abdominal obesity 1.18 (1.00–1.40); low LDL 1.27 (1.08–1.49); hypertension 1.99 (1.69–2.35); impaired fasting glucose 1.11 (0.87–1.40)
148	ARIC cohort, USA	12,728	Rise in serum creatinine of ≥0.4 mg/dl ≥25% reduction in estimated creatinine clearance (Cockcroft-Gault)	<b>Atherosclerotic risk markers:</b> comparison is lowest quartile Highest quartile of triglycerides (>156 mg/dl) RR 1.65 (1.1–2.5), p=0.01 Highest quartile of HDL cholesterol (>64 mg/dl) RR 0.47 (0.3–0.8), p<0.02 Highest quartile of HDL-2 cholesterol (>20 mg/dl) RR 0.57 (0.4–0.9, p<0.02) The RR of a rise in creatinine ≥0.4 mg/dl from baseline was NS for Lp (a), HDL-3 cholesterol, and apolipoprotein A. For each three-fold higher triglycerides, the RR of developing a ≥25% reduction in estimated creatinine clearance was 1.51 (95% CI 1.2 to 2.0), p=0.003
147	ARIC + CHS, USA	13,826	Rise in serum creatinine of ≥0.4 mg/dl	<b>Cardiovascular disease:</b> comparison is people without baseline CVD (N=12039) People with baseline CVD (N=1787) had a significantly increased risk of developing CKD (adjusted OR 1.75, 95% CI 1.32 to 2.32, p<0.001).
			GFR decrease of ≥15 ml/min/1.73 m <sup>2</sup>	<b>Cardiovascular disease:</b> comparison is people without baseline CVD (N=12039) People with baseline CVD had an increased risk of developing CKD (adjusted OR 1.54, 95% CI 1.26 to 1.89, p<0.001).

continued

Table 5.2 Risk factors for developing CKD – *continued*

Reference	Population	N	Definition of CKD	Risk factor for developing CKD
144	Physician's Health Study cohort, USA	11,104	GFR < 60 ml/min/1.73m <sup>2</sup>	<p><b>Body mass index:</b> compared to BMI &lt;22.7 kg/m<sup>2</sup></p> <p>BMI &gt;26.6 kg/m<sup>2</sup> (N=2220) OR 1.26 (1.03 to 1.54)</p> <p>BMI 25.1–26.6 kg/m<sup>2</sup> (N=2250) OR 1.32 (1.09 to 1.61)</p> <p>NS risk when BMI 22.7–25.0</p>
145	Follow-up of NHANES II, USA	9,082	CKD-related death or ESRD	<p><b>Body mass index:</b> comparison is normal BMI (18.5–24 kg/m<sup>2</sup>)</p> <p>NS risk when BMI &lt;18.5 kg/m<sup>2</sup>, 25–29 kg/m<sup>2</sup>, 30–34 kg/m<sup>2</sup> or &gt;35 kg/m<sup>2</sup>.</p> <p><b>Physical inactivity:</b> comparison is high physical activity</p> <p>Low physical activity RR 2.2 (1.2 to 4.1).</p> <p>Moderate physical activity: NS risk</p> <p><b>Smoking:</b> compared to non-smokers</p> <p>Smokers (&gt;20 cigarettes/day) RR 2.6 (1.4 to 4.7).</p> <p>Smokers (1–20 cigarettes/day) have NS risk</p> <p>Former smokers have NS risk</p> <p><b>Alcohol consumption:</b> compared to non-drinkers</p> <p>NS risk for daily drinkers or weekly drinkers or people who seldom drank</p>
10	Cross-sectional Southampton and South-west Hampshire, UK	404,541	Serum creatinine value >1.7 mg/dl or >150 µmol/l persisting for six months or more	<p>The incidence of CKD was 1701 pmp, 95% CI 1613 to 1793 pmp). For people &lt;80 years old, the incidence was 1071 pmp (95% CI 1001 to 1147).</p> <p><b>Age:</b> The incidence of CKD increased with increasing age. 74% of CKD cases were identified in people ≥70 years old.</p> <p><b>Gender:</b> The man:woman rate ratio was 1.6 (95% CI 1.4 to 1.8). The preponderance of men with CKD was significant in all ages &gt;40 years of age.</p> <p><b>Socioeconomic deprivation:</b> compared with overall population</p> <p>Least deprived directly standardised rate ratio 0.80 (95% CI 0.69 to 0.93)</p> <p>Most deprived directly standardised rate ratio 1.17, 95% CI 1.02 to 1.33)</p>
143	Cross-sectional; Surrey, Kent, greater Manchester area, UK	162,113	GFR <60 ml/min/1.73m <sup>2</sup>	<p>The prevalence of diabetes was 3.1% (5072/162,113).</p> <p><b>Diabetes:</b> 31.3% of people with diabetes had stage 3–5 CKD (GFR &lt;60 ml/min/1.73 m<sup>2</sup>) compared to 6.9% of people without diabetes (p&lt;0.001). The higher prevalence of diabetes-associated CKD was seen at all stages of CKD.</p>

*continued*

Table 5.2 Risk factors for developing CKD – *continued*

Reference	Population	N	Definition of CKD	Risk factor for developing CKD
141	Cross-sectional, Australia	11,247	GFR <60 ml/min/1.73m <sup>2</sup>	<p>The prevalence of stage 1 CKD in Australia was 0.9%, stage 2 was 2.0%, stage 3 was 10.9%, stage 4 was 0.3%, stage 5 was 0.003%.</p> <p><b>Age:</b> compared with people &lt;65 People ≥65 years OR 101.5 (61.4–162.9, p&lt;0.001)</p> <p><b>Gender:</b> females OR 1.3 (1.0–1.7), p=0.012</p> <p><b>Diabetes:</b> compared to people without diabetes People with diabetes had NS risk: OR 0.9 (0.7–1.1, p=0.308)</p> <p><b>Hypertension:</b> compared to normotensive people People with hypertension: OR 1.4 (1.2–1.6, p&lt;0.001)</p>
20	Cross-sectional NHANES III, USA	15,600	GFR 60–89 ml/min/1.73m <sup>2</sup> Moderate CKD (GFR 30–59 ml/min/1.73m <sup>2</sup> ) Severe CKD (GFR 15–29 ml/min/1.73m <sup>2</sup> )	<p>The prevalence of stage 1 CKD in the USA was 3.3%, stage 2 was 3.0%, stage 3 was 4.3%, stage 4 was 0.2%, stage 5 was 0.2%. The overall prevalence of CKD in USA was 11%.</p> <p><b>Age:</b> 48% of people &gt;70 years of age (N=2965) had mild CKD (GFR 60–89 ml/min/1.73m<sup>2</sup>) and 25% had moderate to severe CKD (GFR &lt;60 ml/min/1.73m<sup>2</sup>).</p> <p><b>Gender:</b> NS difference in prevalence between males and females</p> <p><b>Hypertension:</b> 17.5% of hypertensive people taking antihypertensive agents (N=2553) and 7.9% of hypertensive people not taking medication (2340) had moderate CKD (GFR 30–59 ml/min/1.73m<sup>2</sup>) compared to 1.5% of non-hypertensive people (N=10,707).</p> <p><b>Diabetes:</b> 40% of people with diabetes had mild CKD (GFR 60–89 ml/min/1.73m<sup>2</sup>) whereas 31% of people without diabetes had mild CKD (GFR 60–89 ml/min/1.73m<sup>2</sup>). 14% of people with diabetes had moderate CKD (GFR 30–59 ml/min/1.73m<sup>2</sup>) whereas 3.7% of people without diabetes had moderate CKD (GFR 30–59 ml/min/1.73m<sup>2</sup>).</p> <p><b>Ethnicity:</b> compared to non-Hispanic white people, non-Hispanic black people (N=4163) were significantly less likely to have moderate CKD (GFR 30–59 ml/min/1.73m<sup>2</sup>) adjusted OR 0.56 (0.44 to 0.71). There was NS difference in prevalence of severe CKD (GFR 15–29 ml/min/1.73m<sup>2</sup>) in non-Hispanic black or white people (adjusted OR 1.10, 95% CI 0.51 to 2.37).</p>

*continued*

Table 5.2 Risk factors for developing CKD – *continued*

Reference	Population	N	Definition of CKD	Risk factor for developing CKD
140	Cross-sectional, Norway HUNT II	65,181	GFR <60 ml/min/1.73m <sup>2</sup>	<p>The prevalence of GFR 60–89 ml/min/1.73m<sup>2</sup> was 38.6%. The prevalence of moderate CKD (GFR 30–59 ml/min/1.73m<sup>2</sup>) was 4.5% and severe CKD (GFR 15–29 ml/min/1.73m<sup>2</sup>) was 0.2%.</p> <p><b>Age:</b> The prevalence of GFR &lt;60 ml/min/1.73m<sup>2</sup> was 50–100 times greater in people &gt;70 years old compared to people 20–39 years old.</p> <p><b>Gender:</b> Women age-adjusted OR 1.5 (1.4–1.6).</p> <p><b>Hypertension:</b> compared with normotensives Hypertension age-adjusted OR 1.5 (1.3–1.6).</p> <p><b>Diabetes:</b> compared with people with no diabetes Diabetes age-adjusted OR 1.5 (1.3–1.7).</p>
142	Case series, CLUE study	23,534	Need for dialysis or death certificate notification of kidney disease.	<p><b>Gender:</b> compared to men Women: adjusted HR 0.6 (95% CI 0.4 to 0.8)</p> <p><b>Hypertension:</b> compared with SBP &lt;120 mm Hg or DBP &lt;80 mm Hg Stage 2 hypertension (160–179 mmHg systolic or 100–109 mmHg diastolic) (adjusted HR 5.7, 95% CI 1.7–18.9) Stage 3 or 4 hypertension (≥180 mmHg systolic or ≥110 mmHg diastolic) (adjusted HR 8.8, 95% CI 2.6–30.3)</p> <p><b>Diabetes:</b> compared with no diabetes (identified by medication use) Diabetes: adjusted HR 7.5 (95% CI 4.8–11.7)</p> <p><b>Smoking:</b> compared with non current smokers Current smokers: adjusted HR 2.6 (95% CI 1.8 to 3.7)</p>
154	Case series, type 2 diabetics, UKPDS	2,167	Development of microalbuminuria (UAC 50–299 mg/l)	<p><b>Ethnicity:</b> compared with Caucasians African Caribbeans: NS (HR 1.21, 95% CI 0.89–1.65, p=0.22) Indian Asians: HR 2.02 (95% CI 1.59–2.60), p&lt;0.0001</p> <p><b>Smoking:</b> compared with non-smokers Smokers: HR 1.20 (95% CI 1.01–1.42), p=0.036</p>
			Development of macroalbuminuria (UAC ≥300 mg/l)	<p><b>Ethnicity:</b> compared with Caucasians African Caribbeans: NS (HR 1.05, 95% CI 0.59–1.86, p=0.87) Indian Asians: HR 2.07 (95% CI 1.36–3.15, p=0.00066).</p>
			CrCl ≤60 ml/min/1.73 m <sup>2</sup>	<p><b>Ethnicity:</b> compared with Caucasians African Caribbeans: NS (HR 1.26 (95% CI 0.91–1.76, p=0.17) Indian Asians: HR 1.93 (95% CI 1.38–2.72), p=0.00015</p> <p><b>Smoking:</b> compared with non-smokers Smokers: HR 1.25 (95% CI 1.03–1.52), p=0.022</p>

DBP = diastolic blood pressure; Lp = lipoprotein; SBPB = systolic blood pressure; UAC = urinary albumin concentration

### 5.2.5 Health economics evidence statements

There were three published studies. We converted costs to UK pounds using purchasing power parities for the study year, without inflating.

The first published study<sup>155</sup> found that screening for microalbuminuria cost an extra Can\$27,000 (£14,000) per QALY gained compared with screening for hypertension and macroproteinuria in patients with insulin-dependent diabetes. However, they found the model to be highly uncertain and said that further evidence is required.

The second published study<sup>156</sup> found that for people with neither hypertension nor diabetes, the incremental cost-effectiveness ratio for screening at age 50 versus no screening was unfavourable at \$283,000 (£189,000) per QALY gained; screening at age 60 was more favourable at \$53,372 (£34,000) per QALY gained. For people with hypertension the ICER was highly favourable at \$18,621 (£12,000) per QALY gained. The authors concluded that early detection of urine protein to slow progression of CKD is not cost-effective unless selectively directed toward high-risk groups (older people and people with hypertension) or conducted at an infrequent interval of 10 years.

The third study<sup>157</sup> found that screening (50–69 years) for proteinuria cost Aus\$3577 (£1600) per QALY gained.

#### ▷ Original modelling: non-diabetic hypertensive

The base case analysis showed that one-off testing of hypertensive adults at various ages is highly cost-effective. The initial use of ACR is more cost-effective than ACR after a positive reagent strip test. ACR is likely to be more cost-effective than PCR as long as it is sensitive enough to pick up 1% more cases than the PCR test. The results were not sensitive to any individual model parameter. Although the results were not sensitive to the individual treatment effect of ACEI on progression or the effect of ACEI on mortality, when both parameters were covaried, testing was not always cost-effective.

#### ▷ Original modelling: non-diabetic, non-hypertensive

The base case analysis showed that testing of non-hypertensive, non-diabetic adults at ages 55–79 is not cost-effective. However, at age 80, testing appeared to be cost-effective.

There were a number of limitations to the model, some of which might bias slightly in favour of testing; others might bias against testing.

#### *Limitations that might potentially bias in favour of testing*

- Effectiveness of high-dose ACEI. Reduction in all-cause mortality is not proven (except for diabetic population).
- The model assumes that without these case-finding tests patients will not be picked up until they require RRT. If in reality patients are picked up sooner, then the benefits of case-finding are reduced.
- Compliance with medication might be less than observed in trials and hence the effectiveness of screening might be less.



- Most hypertensive patients are already on low dose ACEI. The difference in effects between high and low dose ACEI is not clear but the effectiveness of screening might be over-estimated for such patients.
- In the base case analysis, ACR is assumed to be 100% sensitive and 100% specific. Even in the sensitivity analysis, the model doesn't measure the health impact or long-term costs of false positives.

*Limitations that might potentially bias in favour of **no testing***

- Benefits of early diagnosis other than from ACEI/ARB treatment are not captured by the model.

▷ Comparisons between the guideline model and the published studies

To our knowledge, no economic evaluations have evaluated CKD testing in hypertensive people.

Two previous studies have evaluated the cost-effectiveness of CKD testing in the general population. The first (US) study<sup>156</sup> found that, similar to our model, testing for proteinuria in non-diabetic non-hypertensive people was not cost-effective around the ages 50–60 but did become cost-effective at older ages.

However, the second (Australian) study<sup>157</sup> found that, testing for proteinuria in the general population age 50–69 was cost-effective at Aus\$3600 per QALY gained. The reason for this difference in results is difficult to determine, given that the cost and outcome results have not been broken down in these studies and not all the methods and data are explicitly reported. The effectiveness of treatment in the Australian model was derived in the same way as our model, so this cannot explain this difference. Possible explanations are as follows:

- We have modelled a period of ESRD where patients do not receive RRT. This may not be incorporated in to the other models. Therefore they may have estimated higher cost savings.
- CVD costs savings may have been modelled more explicitly in the published models.
- The prevalence of proteinuria might be different to the figures used.
- The other models may be attributing the same clinical effect to patients with GFR above 60 as they do with patients with GFR below 60. In our model, we do not include long-term costs or health gain for patients with proteinuria but GFR >60.

## 5.2.6 From evidence to recommendations

When considering this evidence the GDG was particularly concerned with facilitating the early identification of people with CKD so that they may benefit from treatment to prevent worsening kidney function.

The GDG considered that multisystem diseases with the potential to involve the kidney, such as SLE, were clearly risk factors for CKD.

The evidence principally assessed demographic and behavioural risk factors for CKD but in addition it was recognised that diabetes and cardiovascular disease, particularly ischaemic heart



disease, chronic heart failure, peripheral vascular disease and cerebrovascular disease are all risk factors for CKD. The GDG noted that the increased prevalence of CKD seen in the NHANES studies (1988–1994 compared with 1999–2004) was associated with an increased prevalence of diagnosed diabetes and hypertension.

The cost-effectiveness evidence suggests that testing for CKD in high-risk groups (such as those with hypertension or diabetes) is highly cost-effective. However, for over 55s without additional risk factors, the prevalence of CKD with proteinuria was too low for testing to be cost-effective.

Although specific evidence for drug-induced nephrotoxicity was not considered, the GDG noted that both acute and chronic use of drugs known to be potentially nephrotoxic can lead to CKD. The use of certain agents such as lithium and calcineurin inhibitors should be monitored and the GDG considered that long-term chronic use of NSAIDs should prompt an annual GFR check. Further information can be obtained in the BNF.

The GDG did not consider the evidence about smoking, alcohol intake, abnormal lipids, obesity (in the absence of metabolic syndrome), lower socioeconomic status and ethnicity strong enough to recommend that people in these groups should be tested for CKD.

There was uncertainty regarding the significance of a family history of CKD but the GDG recommended that people with a family history of stage 5 CKD or hereditary kidney disease should be considered at risk of having CKD.

GDG consensus was that those with structural renal tract disease, multiple and recurrent renal calculi and urinary outflow tract obstruction should be considered at risk of having CKD. The GDG also recommended that people found incidentally to have haematuria or proteinuria on opportunistic medical testing should be considered at risk of having CKD.

### 5.2.7 RECOMMENDATIONS

- R24** Monitor glomerular filtration rate (GFR) in people prescribed drugs known to be nephrotoxic, such as calcineurin inhibitors and lithium. Check GFR at least annually in people receiving long-term systemic non-steroidal anti-inflammatory drug (NSAID) treatment.
- R25** Offer people testing for CKD if they have any of the following risk factors:
- diabetes
  - hypertension
  - cardiovascular disease (ischaemic heart disease, chronic heart failure, peripheral vascular disease and cerebral vascular disease)
  - structural renal tract disease, renal calculi or prostatic hypertrophy
  - multisystem diseases with potential kidney involvement, e.g. systemic lupus erythematosus (SLE)
  - family history of stage 5 CKD or hereditary kidney disease
  - opportunistic detection of haematuria or proteinuria.
- R26** In the absence of the above risk factors, do not use age, gender, or ethnicity as risk markers to test people for CKD. In the absence of metabolic syndrome, diabetes or hypertension, do not use obesity alone as a risk marker to test people for CKD.

## 6 Defining progression of CKD and the risk factors associated with progression

### 6.1 Defining progression

#### 6.1.1 Clinical introduction

The Renal NSF adopted the US National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) classification of CKD.<sup>35</sup> Whilst the beauty of this classification is its simplicity, this is also its weakness. The clinical features and course of CKD are dependent on a number of factors including the underlying cause, severity and associated conditions of the underlying cause.

Although the classification of CKD into 5 stages has been widely adopted, it has been criticised as not being sufficiently sophisticated for clinical needs. The existing classification is neither staged according to age, nor according to level of proteinuria. All patients, regardless of age, gender and proteinuria/albuminuria are considered to have at least moderately severe CKD when their GFR is  $<60$  ml/min/1.73 m<sup>2</sup>. This guideline recommends that stage 3 should be subdivided into 3A and 3B, and that the suffix '(p)' in parenthesis be adopted in the different stages to underline the importance of proteinuria/albuminuria as an independent risk factor for adverse outcomes (Table 6.1).

**Table 6.1 Modifications to existing stages of chronic kidney disease**

Stage	Description	GFR (ml/min/1.73m <sup>2</sup> )	Proteinuria
1	Kidney damage with normal or increased GFR	$\geq 90$	
2	Kidney damage with mild reduction in GFR	60–89	
3A	Moderate reduction in GFR	45–59	Use '(p)' to denote when significant proteinuria is present (ACR $\geq 30$ mg/mmol)
3B		30–44	
4	Severe reduction in GFR	15–29	
5	Kidney failure	$<15$ (or dialysis)	

CKD is defined as either kidney damage (proteinuria, haematuria or anatomical abnormality) or GFR  $<60$  ml/min/1.73 m<sup>2</sup> present on at least 2 occasions for  $\geq 90$  days.

A further criticism of the existing classification of CKD has been the suggestion that loss of GFR is a feature of ageing and that many people classified as stage 3 CKD are merely exhibiting a normal ageing process. The effects of normal ageing on renal function are controversial. Data from some studies suggest that the decline in GFR with increasing age may be largely attributable to comorbidities such as hypertension and heart failure. Loss of renal function may not, therefore, be an inevitable consequence of ageing.<sup>158–160</sup> This was supported by studies demonstrating no or very little decline in GFR in the older population with longitudinal follow-up.<sup>161</sup>

The focus of defining progression of CKD in this section was to consider what constitutes progression in terms of rate of decline of GFR in order to provide clear guidance to clinicians. However, controversy over what constitutes normality in the group with the highest prevalence of CKD makes defining what constitutes progression even more difficult. Consideration must also be given to the inherent biological and analytical variation associated with estimation of GFR from serum creatinine measurements.

- *In people with CKD, what constitutes a clinically significant decline in eGFR?*

### 6.1.2 Methodology

Decline in eGFR in the Prevention of Renal and Vascular Endstage Disease (PREVEND) cohort (N=8592) was compared with the eGFR decline in people with macroalbuminuria ( $\geq 300$  mg/24 h, N=134) or impaired renal function (lowest 5% of the cohort in terms of CrCl or MDRD eGFR, N=103). The power of this study was undermined by a high drop-out rate in the macroalbuminuria, impaired renal function, and haematuria groups, although the authors noted that the baseline characteristics of those who were lost to follow-up were NS different from subjects who completed follow-up.<sup>162</sup>

Two cross-sectional studies examined GFR decline in 'healthy' kidney donors with increasing age. GFR was measured by iothalamate clearance in 365 potential living kidney donors<sup>163</sup> or by inulin clearance in 141 healthy subjects who had a nephrectomy.<sup>164</sup> The main limitation of the Rule et al. study<sup>163</sup> was that 71% of the kidney donors were related to recipients, therefore the donors may have had a greater prevalence of subclinical renal disease. This was evident in the lower GFR values in apparently healthy people (mean GFR=111 ml/min/1.73 m<sup>2</sup> in healthy twenty-year olds). As this was a retrospective analysis of medical records, there was no detail on how often GFR was measured. The Slack et al. study<sup>164</sup> did not address whether the donors were relatives of the kidney recipients and there was no data from people >67 years of age.

The cross-sectional Biomedical Nijmegen Study measured eGFR (MDRD) in apparently healthy men and women (N=3732) and in men and women with comorbid conditions (N=2365). Limitations of this study included:

- a questionnaire, rather than a clinical examination, was used to assess the health of participants
- GFR was estimated with the MDRD equation and creatinine was measured only once
- the GFR decline was inferred from cross-sectional data, rather than from a longitudinal follow-up.<sup>165</sup>

A cross-sectional study examined inulin clearance in healthy younger subjects (N=24, mean age 26 years) compared with healthy older people (N=29, mean age 68 years), hypertensive older people (N=25, mean age 70 years) or older people with heart failure (N=14, mean age 69 years). The younger and older healthy subjects were matched for body weight. This study was limited by the small sample size and it did not address rate of GFR decline.<sup>159</sup>

Two observational studies from the Baltimore Longitudinal Study of Aging examined creatinine clearance over time (1958–1981) in a male cohort aged 22–97 years. In the first study,<sup>166</sup> the decline in creatinine clearance with increasing age was assessed in healthy males (N=548). In a follow-up study,<sup>158</sup> the decline in creatinine clearance over time in healthy males (N=254) was compared with creatinine clearance decline in men with renal/urinary tract disease (N=118) or

with hypertensive/oedematous disorders (N = 74). The effect of increasing blood pressure on creatinine clearance was also examined.

An observational study (N=10,184, mean age 76 years, 2 years follow-up) examined GFR decline over time in older (>66 years old) males and females stratified by GFR. The decline in GFR in diabetics was compared with non-diabetics.<sup>161</sup>

Table 6.2 (p xx) summarises the decline in GFR in different populations.

### 6.1.3 Health economics methodology

There were no health economics papers found to review.

### 6.1.4 Evidence statements

#### ▷ Renal functional decline in healthy adults

Two cross-sectional studies of healthy kidney donors showed that GFR declined with increasing age and this was a steady decline as age increased. Regression analysis of GFR normalised to body surface area was significant for age ( $p < 0.001$ ), but not sex ( $p = 0.826$ ).<sup>163,164</sup> (Level 3)

In the Longitudinal Study of Aging male cohort, creatinine clearance was stable in healthy men <35 years old, but then declined steadily in healthy men age 35–60 years. After age 60, creatinine clearance declined steeply.<sup>158,166</sup> (Level 3)

Mean inulin clearance was significantly lower in older healthy people compared with young healthy people.<sup>159</sup> (Level 3)

In the Nijmegen Biomedical cross-sectional study, a GFR  $< 60$  ml/min/1.73 m<sup>2</sup> was within the normal reference range for non-diseased men >55 years old and non-diseased women >40 years old (5<sup>th</sup> percentile).<sup>165</sup> (Level 3)

#### ▷ Renal function decline in adults with renal disease

For men with renal disease or urinary tract disease, there was NS difference in the decline in creatinine clearance compared with healthy.<sup>158</sup> (Level 3)

In the PREVEND cohort study, the decline in GFR was significantly greater in people with macroalbuminuria compared with the general population ( $-7.2$  vs.  $-2.3$  ml/min/1.73 m<sup>2</sup>,  $p < 0.01$ ) Interestingly, the decline in GFR was significantly less in those with impaired renal function compared with the general population ( $-0.2$  vs.  $-2.3$  ml/min/1.73 m<sup>2</sup>,  $p < 0.01$ ). This data suggests that macroalbuminuria is a better predictor of GFR decline than low baseline GFR.<sup>162</sup> (Level 2+)

#### ▷ Renal function decline in adults with hypertension

There was NS difference in the decline in creatinine clearance in men taking antihypertensive drugs compared with healthy men. Renal function decreased more rapidly as mean arterial pressure (MAP) increased.<sup>158</sup> (Level 3)

Mean inulin clearance was significantly lower in older hypertensive people compared with young healthy people. Mean GFR was NS different between older healthy and older hypertensive people.<sup>159</sup> (Level 3)

▷ Renal function decline in adults with diabetes

In adults >66 years of age (N=10,184), the rate of GFR decline was greater in people with diabetic CKD compared with people nondiabetic CKD. Few participants in this older cohort experienced a rapid progression of CKD (decline in GFR >15 ml/min/1.73 m<sup>2</sup>/year): 14% of mild, 13% of moderate, and 9% of severe CKD subjects.<sup>161</sup> (Level 3)

▷ GFR in adults with heart failure

Mean GFR (inulin clearance) was significantly lower in older people with heart failure (92 ml/min/1.73 m<sup>2</sup>, N=14, mean age 69 years) compared with young healthy people (121 ml/min/1.73 m<sup>2</sup>, N=24, mean age 26 years, p <0.05). Mean GFR (inulin clearance) was significantly lower in older people with heart failure (92 ml/min/1.73 m<sup>2</sup>, N=14, mean age 69 years) compared with older healthy (103 ml/min/1.73 m<sup>2</sup>, N=29, mean age 68 years) or older hypertensive (103 ml/min/1.73 m<sup>2</sup>, N=25, mean age 70 years) people (p<0.05).<sup>159</sup> (Level 3)

**Table 6.2 Decline in renal function in various populations**

Reference	Population	N	GFR decline
163	Female healthy kidney donors	205	0.71 ml/min/year
163	Male healthy kidney donors	160	0.46 ml/min/year
163	Healthy kidney donors	365	0.49 ml/min/1.73m <sup>2</sup> /year
164	Healthy kidney donors	141	0.4 ml/min/year
166	Healthy males (cross-sectional)	548	0.80 ml/min/1.73 m <sup>2</sup> /year (CrCl)
166	Healthy males (longitudinal)	293	0.90 ml/min/1.73 m <sup>2</sup> /year. (CrCl)
165	Healthy people (cross-sectional)	3,732	0.4 ml/min/year
158	Healthy + renal/urinary tract disease + hypertensive males (cross-sectional)	446	0.87 ml/min/year (CrCl)
158	Healthy males (longitudinal)	254	0.75 ml/min/year (CrCl)
158	Males with renal/urinary tract disease (longitudinal)	118	1.10 ml/min/year (CrCl)
158	Males with hypertension (longitudinal)	74	0.92 ml/min/year (CrCl)
162	Total population (PREVEND cohort)	6,894	2.3 ml/min/1.73m <sup>2</sup> (after 4.2 years)
162	Adults with macroalbuminuria (PREVEND cohort)	86	7.2 ml/min/1.73m <sup>2</sup> (after 4.2 years)
162	Adults with impaired renal function (5% lowest CrCl/MDRD GFR, PREVEND cohort)	68	0.2 ml/min/1.73m <sup>2</sup> (after 4.2 years)
161	Older males with diabetes	Not stated	2.7 ml/min/1.73 m <sup>2</sup> /year
161	Older males without diabetes	Not stated	1.4 ml/min/1.73 m <sup>2</sup> /year
161	Older females with diabetes	Not stated	2.1 ml/min/1.73 m <sup>2</sup> /year
161	Older females without diabetes	Not stated	0.8 ml/min/1.73 m <sup>2</sup> /year

### 6.1.5 From evidence to recommendations

The GDG agreed that the evidence regarding the relationship between adverse outcomes and levels of GFR should be used as the basis of defining CKD but noted that the management and prognosis in people with a reduced but stable GFR may be quite different to that in people with a progressive decline in GFR. Hence the consideration of the evidence centered on a review of whether there is a decline in GFR and whether the decline was always the result of kidney disease or whether there was a 'natural' decline as a function of ageing and if so what level of decline should be considered normal.

The longitudinal studies contained mixed populations in that not all participants were followed up for the full duration of the study.

The lower kidney function described in one study of older people may be due to unrecognised kidney disease. However, there appears to be a small 'natural' age related decline in kidney function. Nevertheless it was recommended that the interpretation of GFR measurements should not normally be affected by the age of the person and that a low value should prompt the same response regardless of age.

The GDG agreed that a decline in GFR of more than 2 ml/min/1.73 m<sup>2</sup> per year was more than could be accounted for by ageing alone.

The GDG recommended that, when interpreting the rate of decline of eGFR, it was also necessary to consider the baseline level of kidney function and the likelihood that kidney function would reach a level where renal replacement therapy would be needed if the rate of decline was maintained. For example, a rate of decline of 3 ml/min/1.73 m<sup>2</sup> per year would be of greater concern in a person with a baseline eGFR of 30 ml/min/1.73 m<sup>2</sup> aged 40 than in a person aged 70 with a baseline eGFR of 60 ml/min/1.73 m<sup>2</sup>.

When assessing the rate of decline in eGFR, the GDG agreed that a minimum of 3 measurements in not less than 90 days was required (depending on the initial level of eGFR). If a large and unexplained fall in GFR was observed, more frequent monitoring would be needed. Changes in GFR must be interpreted in light of the evidence on biological and assay variability in serum creatinine measurements, which is estimated at 5%. A calculation based on this would suggest that a decline in eGFR of 10 ml/min/1.73m<sup>2</sup> per year would carry a 95% probability of significance. However, given that a decline in eGFR of more than 2 ml/min/1.73 m<sup>2</sup> per year was more than could be accounted for by ageing alone the GDG agreed to define progression as either a decline in eGFR of >5 ml/min/1.73m<sup>2</sup> within 1 year or a decline of >10 ml/min/1.73m<sup>2</sup> within 5 years.

### 6.1.6 RECOMMENDATIONS

R27 Take the following steps to identify progressive CKD:

- Obtain a minimum of three glomerular filtration rate (GFR) estimations over a period of not less than 90 days.
- In people with a new finding of reduced eGFR, repeat the estimated glomerular filtration rate (eGFR) within 2 weeks to exclude causes of acute deterioration of GFR, e.g. acute kidney injury or initiation of ACEI/ARB therapy

- Define progression as a decline in eGFR of  $>5$  ml/min/1.73 m<sup>2</sup> within one year, or  $>10$  ml/min/1.73 m<sup>2</sup> within 5 years
- Focus particularly on those in whom a decline of GFR continuing at the observed rate would lead to the need for renal replacement therapy within their lifetime by extrapolating the current rate of decline.

## 6.2 Risk factors associated with progression of CKD

### 6.2.1 Clinical introduction

In the literature, progression of kidney disease has been variously defined as doubling of serum creatinine, declining GFR or creatinine clearance, increasing proteinuria/albuminuria, and progression to renal replacement therapy (RRT, dialysis or kidney transplantation) or end stage renal disease. The list of possible factors associated with progression does not consider how differences in access to healthcare and poverty may influence the initiation and progression of CKD. Specifically, neither early life influences governing foetal development and low birth weight nor childhood factors contributing to the emergence of hypertension and diabetes are considered here.<sup>167–169</sup>

Whilst it is clear that CKD is common, and recently published studies suggest that its prevalence is increasing,<sup>22</sup> it is also clear that many people with diagnosed CKD do not progress.<sup>11,12</sup> Importantly, their risk of cardiovascular disease is massively increased compared to the general population. In those that do progress, the subsequent mortality and morbidity risks rise exponentially, as do the associated healthcare costs. A reduced GFR is also associated with a wide range of complications such as hypertension, anaemia, renal bone disease, malnutrition, neuropathy and reduced quality of life. It is therefore important to clarify exactly what factors are associated with CKD progression, and which are remediable or potentially modifiable, in order to intervene at the earliest possible stage and improve the associated adverse outcomes.

- *What factors are associated with progression of CKD: (a) cardiovascular disease; (b) acute kidney injury; (c) obesity; (d) smoking; (e) urinary tract obstruction; (f) ethnicity; (g) chronic use of NSAIDs?*

### 6.2.2 Methodological introduction

Hypertension, diabetes mellitus, and proteinuria/albuminuria are well-established factors that promote progression of CKD. The literature was reviewed to examine additional promoters of renal disease progression: cardiovascular disease, acute kidney injury, obesity, smoking, urinary tract obstruction, ethnicity, and chronic use of non-steroidal anti-inflammatory drugs (NSAIDs). There were no studies examining acute kidney injury or urinary tract obstruction on progression of CKD.

In a pooled analysis of the ARIC Study and Cardiovascular Health Studies (CHS), kidney function decline (serum creatinine increase  $\geq 0.4$  mg/dl or a GFR decrease  $\geq 15$  ml/min/1.73 m<sup>2</sup>) in people with cardiovascular disease (N=1787, mean age 60 years) was compared with people without cardiovascular disease (N=12,039, mean age 57 years, 9.3 years follow-up).<sup>147</sup>



A Swedish case series investigated the effect of BMI on progression to RRT in people with stage 4 and 5 CKD (N=920, mean follow-up 2 years).<sup>170</sup>

The effect of smoking on renal functional decline was examined in two diabetic cohort studies and two case-control studies. A diabetic cohort of smokers (N=44, mean age 47 years, 86% had baseline proteinuria >0.15 g/day) were followed for 5.1 years (median) and changes in proteinuria and GFR (20% decline) were compared with non-smokers (N=141, mean age 54 years, 72% had baseline proteinuria >0.15 g/day).<sup>171</sup> In a Danish cohort of people with type 1 diabetes and persistent albuminuria >300 mg/24 h, changes in GFR during a median follow-up of 7 years were compared between smokers (N=176), non-smokers (N=94) and ex-smokers (N=31).<sup>172</sup> In a case-control study, men with autosomal dominant polycystic kidney disease (ADPKD) or immunoglobulin-A glomerulonephritis (IgA-GN) who had progressed to ESRD were matched with controls with ADPKD or IgA-GN who had not progressed to ESRD. Progression to ESRD was compared between males who smoked for 0–5 pack-years (N=73), 5–15 pack years (N=28), or >15 pack years (N=43).<sup>173</sup> In a Spanish case control study, cases (people who had progressed to ESRD, N=520) were age-, sex- and hospital-matched with controls (hospital patients who had not progressed to ESRD, N=982) and the effects of smoking compared with non-smoking on progression to ESRD were analysed.<sup>174</sup>

An English cross-sectional study of renal units examined rates of acceptance to RRT in Caucasians compared with Asians or blacks (N=5901).<sup>23</sup> A London, UK case series investigated doubling of serum creatinine and the rate of serum creatinine increase in Caucasian (N=24), Indo-Asian (N=10), and African-Caribbean (N=11) people with type 2 diabetes and nephropathy.<sup>175</sup> A case series of US Medicare beneficiaries over 65 years old examined progression to ESRD in black (N=94,511) compared with white people (N=1,163,868) in the presence of diabetes, hypertension or neither comorbid condition. It was difficult to determine whether these participants had CKD at baseline.<sup>176</sup>

Four studies assessed the effect of chronic NSAID use on progression of renal disease. One small, open-label RCT compared changes in creatinine clearance and adverse events with chronic use of ibuprofen, piroxicam, or sulindac in adults aged over 65 years with (CrCl <70 ml/min, N=15) or without renal insufficiency (CrCl >70 ml/min, N=14).<sup>177</sup> In two Spanish case control studies, cases (people who had progressed to ESRD, N=520) were age-, sex- and hospital-matched with controls (hospital patients who had not progressed to ESRD, N=982) and the effects of chronic use of salicylates, pyrazolones and non-aspirin NSAIDs on progression to ESRD were analysed.<sup>174,178</sup> In a Swedish case-control study, cases (patients with 'chronic renal failure', N=926) were age and sex matched to controls (N=998) and the risk of chronic renal failure (serum creatinine >3.4 mg/dl in men or >2.8 mg/dl in women) in regular or sporadic users of aspirin was compared with non-users.<sup>179</sup>

Table 6.3 (page 81) summarises risk factors for progression of CKD.

### 6.2.3 Health economics methodology

There were no health economics papers found to review.



## 6.2.4 Evidence statements

- ▷ Effect of cardiovascular disease on progression of CKD

People with baseline cardiovascular disease had a significantly increased risk of a decline in renal function compared with people without CVD at baseline.<sup>147</sup> (Level 3)

- ▷ Effect of obesity on progression of CKD

In a Swedish case series, BMI was NS associated with risk of renal disease progression.<sup>170</sup> (Level 3)

- ▷ Effect of smoking on progression of CKD

In a cohort study of adults with diabetic nephropathy, smokers had significantly increased odds of a 20% decline in GFR compared with non-smokers. This relationship persisted after adjustment for diabetes type or control, retinopathy, age, BMI, ACEI use, BP, proteinuria. Proteinuria increased in both smokers and non-smokers, but there were NS differences between the two groups.<sup>171</sup> (Level 2+)

In a cohort of adults with type 1 diabetic nephropathy, there were NS differences in annual GFR decline between smokers, non-smokers, and ex-smokers.<sup>172</sup> (Level 2+)

Two case control studies showed that smoking was significantly associated with progression to ESRD. When ACEI use was taken into account, the association between smoking and progression to ESRD was NS.<sup>173,174</sup> (Level 2+)

- ▷ Effect of ethnicity on progression of CKD

In a cross-sectional analysis, Asian people (RR 5.5, 95% CI 4.7–7.2) and black people (RR 6.5, 95% CI 5.1–8.3) had significantly higher rates of RRT compared with Caucasians due to diabetic renal disease. Asian people (RR 2.2, 95% CI 1.2–4.1) and black people (RR 3.2, 95% CI 1.4–7.2) had significantly higher rates of RRT compared with Caucasians due to hypertension.<sup>23</sup> (Level 3)

In people with type 2 diabetes and nephropathy, 100% of Indo-Asian people (N=10) experienced a doubling of serum creatinine compared with 45% of African-Caribbean people (N=11) and 50% of Caucasians (N=24) (p=0.025) during follow-up. The mean rise in serum creatinine in Indo-Asian people was significantly greater than in African-Caribbean or Caucasians.<sup>175</sup> (Level 3)

In a US case series, black people with baseline diabetes (N=25,049) were 2.4 times more likely (CI not given) to develop ESRD than Caucasians with baseline diabetes (N=175,313). Compared with white people with baseline hypertension (N=426,300), black people with baseline hypertension (N=51,016) were 2.5 times more likely (CI not given) to develop ESRD. Compared with white people with neither baseline hypertension nor diabetes (N=4,651,490), black people with neither hypertension nor diabetes at baseline (N=34,916) were 3.5 times more likely (CI not given) to develop ESRD.<sup>176</sup> (Level 3)

- ▷ Effect of chronic use of NSAIDs on progression of CKD

In people with creatinine clearance <70 ml/min, there were NS changes in creatinine clearance from baseline after 1 month of ibuprofen. However, 1 month treatment of piroxicam or sulindac was associated with a significant decrease in creatinine clearance.<sup>177</sup> (Level 1+)

In two case-control studies, users of salicylates had a significantly increased risk of ESRD compared with nonusers. Users of pyrazolones had NS risk of ESRD compared with nonusers. Users of non-aspirin NSAIDs had NS risk of ESRD compared with nonusers.<sup>174,178</sup> (Level 2+)

In a case-control study, an average intake >500 g/year of aspirin significantly increased the risk of chronic renal failure (adjusted OR 3.3, 95% CI 1.4–8.0). Sub-analysis showed regular use of aspirin compared with non-use of aspirin was significantly associated with increased risk of chronic renal failure in people with diabetic nephropathy, glomerulonephritis, nephrosclerosis, or hereditary renal disease.<sup>179</sup> (Level 2+)

**Table 6.3 Summary of risk factors for progression of CKD with associated odds ratios (OR) or relative risks (RR). 95% confidence levels in parentheses**

Reference	Study	Risk factor	Population	N	Outcome	Effect size
147	Case series	<i>Cardiovascular disease (CVD)</i>	No baseline CVD	12039	Serum creatinine increase of 0.4 mg/dl	Reference group
			Baseline CVD	1787	Serum creatinine increase of 0.4 mg/dl	OR 1.70 (1.36–2.13), p<0.001
			No baseline CVD	12039	GFR decrease of 15 ml/min/1.73 m <sup>2</sup>	Reference group
			Baseline CVD	1787	GFR decrease of 15 ml/min/1.73 m <sup>2</sup>	OR 1.28 (1.13–1.46), p<0.001
170	Case series	Obesity	CKD + BMI 20.1–25 kg/m <sup>2</sup>	377	Requirement for RRT	Reference group
			CKD + BMI ≤20 kg/m <sup>2</sup>	77	Requirement for RRT	RR 1.26 (0.95–1.67)
			CKD + BMI 25.1–30 kg/m <sup>2</sup>	314	Requirement for RRT	RR 0.79 (0.67–0.94)
			CKD + BMI >30 kg/m <sup>2</sup>	26	Requirement for RRT	RR 0.86 (0.68–1.07)
171	Cohort	Smoking	Non-smokers + diabetic nephropathy	141	20% decline in GFR	Reference group
			Smokers + diabetic nephropathy	44	20% decline in GFR	OR 2.52 (1.06–5.99), p<0.01
			Non-smokers + diabetic nephropathy	141	Changes in proteinuria	Reference group 0.47 baseline to 0.54 g/24 h
			Smokers + diabetic nephropathy	44	Changes in proteinuria	0.36 baseline to 0.44 g/24 h NS compared to non-smokers

*continued*

**Table 6.3 Summary of risk factors for progression of CKD with associated odds ratios (OR) or relative risks (RR). 95% confidence levels in parentheses – *continued***

Reference	Study	Risk factor	Population	N	Outcome	Effect size
172	Cohort	Smoking	Non-smokers + type 1 diabetic nephropathy	94	GFR Decline	mean decline 4.4 ml/min/year
			Ex-smokers + type 1 diabetic nephropathy	31	GFR Decline	mean decline 3.4 ml/min/year
			Smokers + type 1 diabetic nephropathy	176	GFR Decline	mean decline 4.0 ml/min/year NS differences between groups
173	Case control (ADPKD and IgA-GN with ESRD matched to non-ESRD controls)	Smoking	Men smoking 0–5 pack-years	Cases=26 Controls=47	ESRD	Reference group
			Men smoking 5–15 pack-years	Cases=17 Controls=11	ESRD	OR 3.5 (1.3–9.6), p=0.017
			Men smoking >15 pack-years	Cases=29 Controls=14	ESRD	OR 5.8 (2.0–17), p=0.001
			Men smoking 0–5 pack-years and no ACEI	No ACEI use: cases=54 controls=42	ESRD	Reference group
			Men smoking >5 pack-years and no ACEI		ESRD	OR 10.1 (2.3–45), p=0.002
			Men smoking 0–5 pack-years and received ACEI	ACEI use: cases=18 controls = 30	ESRD	Reference group
			Men smoking >5 pack-years and received ACEI		ESRD	1.4 (0.3–7.1), p=0.65
174	Case control (patients with ESRD matched to non-ESRD controls)	Smoking	Non-smokers	Not stated	ESRD	Reference group
			Smokers	Cases=320 Controls=577	ESRD	OR 1.54 (1.14–2.07)
23	Cross-sectional	Ethnicity	Caucasian men	3063	Acceptance to RRT	Reference group
			Asian men	262	Acceptance to RRT	RR 3.1 (2.7–3.5)
			Black men	161	Acceptance to RRT	RR 3.0 (2.6–3.5)
			Caucasian women	1871	Acceptance to RRT	Reference group
			Asian women	178	Acceptance to RRT	RR 3.9 (3.3–4.5)
			Black women	111	Acceptance to RRT	RR 3.4 (2.8–4.1)

*continued*

**Table 6.3 Summary of risk factors for progression of CKD with associated odds ratios (OR) or relative risks (RR). 95% confidence levels in parentheses – *continued***

Reference	Study	Risk factor	Population	N	Outcome	Effect size
175	Case series	Ethnicity	Indo-Asian people with type 2 diabetes and nephropathy	10	Doubling of serum creatinine	100%
			Caucasians with type 2 diabetes and nephropathy	24	Doubling of serum creatinine	50%, p=0.025
			African-Caribbean people with type 2 diabetes and nephropathy	11	Doubling of serum creatinine	45%, p=0.025
			Indo-Asian people with type 2 diabetes and nephropathy	10	Rate of serum creatinine increase	5.36 $\mu\text{mol/l/month}$
			Caucasians with type 2 diabetes and nephropathy	24	Rate of serum creatinine increase	2.22 $\mu\text{mol/l/month}$ , p=0.031
			African-Caribbean people with type 2 diabetes and nephropathy	11	Rate of serum creatinine increase	3.14 $\mu\text{mol/l/month}$ , p=0.031
176	Case series	Ethnicity	White men with baseline hypertension	Not stated	ESRD	Reference group
			Black men with baseline hypertension	Not stated	ESRD	HR 2.12 (1.90–2.36)
			White men with baseline diabetes	Not stated	ESRD	Reference group
			Black men with baseline diabetes	Not stated	ESRD	HR 2.05 (1.87–2.25)
			White men, no hypertension, no diabetes	Not stated	ESRD	Reference group
			Black men, no hypertension, no diabetes	Not stated	ESRD	HR 3.27 (2.55–4.19)

*continued*

**Table 6.3 Summary of risk factors for progression of CKD with associated odds ratios (OR) or relative risks (RR). 95% confidence levels in parentheses – *continued***

Reference	Study	Risk factor	Population	N	Outcome	Effect size
177	RCT	Chronic NSAID use	1 month of ibuprofen in people with CrCl <70 ml/min	15	Change in creatinine clearance from baseline	1.00 ml/min vs. 1.00 ml/min, 0% change, NS
			1 month of piroxicam in people with CrCl <70 ml/min	15	Change in creatinine clearance from baseline	1.12 ml/s vs. 1.00 ml/s, 12% decrease, p=0.022
			1 month of sulindac in people with CrCl <70 ml/min	15	Change in creatinine clearance from baseline	1.10 ml/s vs. 0.98 ml/s, 11% decrease, p=0.022
178	Case control (patients with ESRD matched to non-ESRD controls)	Chronic NSAID use	Non-users of salicylates	Not stated	ESRD	Reference group
			Users of salicylates	Cases=23 Controls=21	ESRD	OR 2.54 (1.24–5.20)
			Non-users of pyrazolones	Not stated	ESRD	Reference group
			Users of pyrazolones	Cases=15 Controls=13	ESRD	OR 2.16 (0.87–5.32)
174	Case control (patients with ESRD matched to non-ESRD controls)	Chronic NSAID use	Non-users of aspirin	Not stated	ESRD	Reference group
			Users of Aspirin	Cases=81 Controls=94	ESRD	OR 1.56 (1.05–2.30)
			Non-users of pyrazolones	Not stated	ESRD	Reference group
			Users of pyrazolones	Cases=34 Controls=51	ESRD	OR 1.03 (0.60–1.76) NS
			Non-users of non-aspirin NSAIDs	Not stated	ESRD	Reference group
			Users of non-aspirin NSAIDs	Cases=37 Controls=51	ESRD	OR 0.94 (0.57–1.56) NS
179	Case control (patients with CRF matched with non-CRF controls)	Chronic NSAID use	Non-users of aspirin	Cases=224 Controls=363	Chronic renal failure (serum creatinine >3.4 mg/dl, men or >2.8 mg/dl, women)	Reference group
			Sporadic users of aspirin	Cases=459 Controls=496	Chronic renal failure (serum creatinine >3.4 mg/dl, men or >2.8 mg/dl, women)	OR 1.5 (1.2–1.8)
			Regular users of aspirin	Cases=213 Controls=141	Chronic renal failure (serum creatinine >3.4 mg/dl, men or >2.8 mg/dl, women)	OR 2.5 (1.9–3.3)

CRF = chronic renal failure, as defined in the study.

### 6.2.5 From evidence to recommendations

The GDG accepted that there was extensive clinical evidence that hypertension, diabetes and the presence of proteinuria are well recognised risk factors for progression of CKD.

The GDG also accepted that nephrotoxic drugs may affect progression. Of particular concern are the possible acute and chronic effects of NSAIDs which are available without prescription. Acute use of NSAIDs can lead to an acute and usually reversible fall in GFR but chronic use at therapeutic doses could be associated with progression of CKD. The GDG considered that the Murray et al. study examining the effects of chronic use of NSAIDs had follow-up too short to allow meaningful conclusions to be drawn. It was recommended that if chronic use of NSAIDs was considered clinically necessary the effect on GFR should be monitored and the drugs should be stopped if there is evidence of progressive CKD.

The evidence about possible adverse effects of aspirin was felt to be confounded by the use of aspirin in patients with cardiovascular disease which is a known risk factor for progression of CKD.

The evidence on the effects of smoking and ethnicity on the risk of progression was not conclusive but was sufficiently suggestive to merit highlighting within a recommendation.

The evidence on the effects of obesity on the risk of progression was unconvincing and did not require highlighting within a recommendation.

Despite the lack of evidence for urinary outflow tract obstruction for progression of CKD, the GDG consensus was that obstruction to outflow would lead to progression of CKD. Therefore it was agreed that urinary outflow tract obstruction should be considered as a risk factor.

### 6.2.6 RECOMMENDATIONS

**R28** Work with people who have risk factors for progression of CKD to optimise their health.

These risk factors are:

- cardiovascular disease
- proteinuria
- hypertension
- diabetes
- smoking
- black or Asian ethnicity
- chronic use of non-steroidal anti-inflammatory drugs (NSAIDs)
- urinary outflow tract obstruction.

**R29** In people with CKD the chronic use of NSAIDs may be associated with progression and acute use is associated with a reversible fall in glomerular filtration rate (GFR). Exercise caution when treating people with CKD with NSAIDs over prolonged periods of time. Monitor the effects on GFR, particularly in people with a low baseline GFR and/or in the presence of other risks for progression.

## 7 Referral criteria

### 7.1 Indications for referral to specialist care

#### 7.1.1 Clinical introduction

What do nephrologists do for patients with CKD? The answer to this predominantly lies in 3 main areas: diagnosis and treatment of treatable kidney disease, identification and control of risk factors for progression of CKD and planning for renal replacement therapy in patients progressing to end stage renal disease.

The area that has deservedly received the most attention is planning for renal replacement therapy. There is abundant literature detailing the negative effect of late referral of patients with advanced CKD. Late referral leads to increased morbidity and mortality, increased length of hospital stay, and increased costs.<sup>5-7,180-182</sup> Several factors contribute to the adverse outcomes associated with late referral, including untreated anaemia, bone disease, hypertension and acidosis. The dominant factor though is insufficient time to prepare the patient for dialysis, particularly the establishment of permanent vascular access for haemodialysis.

A CKD management programme encompasses blood pressure control and reduction of proteinuria, treatment of hyperlipidaemia, smoking cessation and dietary advice, treatment of anaemia, treatment of acidosis and metabolic bone disease, and just as importantly, the provision of timely and understandable information and education.

The converse question though is how much of what nephrologists do could be done just as safely and effectively in primary care, and how much of an overlap is there between nephrology, diabetes, cardiology and the care of older people?

- *What are the criteria for referral to specialist care?*

#### 7.1.2 Methodology

Due to the difficulty in searching this question, the results of a broad literature search were reviewed for systematic reviews on criteria for referral to specialist care in a CKD population. Seven papers were identified and all were excluded as they were narrative reviews or guidelines.

#### 7.1.3 Health economics methodology

There were no health economics papers found to review.

#### 7.1.4 Evidence statements

There are no evidence statements.

#### 7.1.5 From evidence to recommendation

The GDG noted that there was no evidence to guide recommendations on who should be referred. The GDG considered the recommendations in other guidelines on who should be referred and also considered the aims and benefits of referral from their own professional standpoint.

The GDG consensus was that the principles guiding referral should be: early identification of people likely to require renal replacement therapy, the need for additional input to the management of CKD, e.g. for uncontrolled hypertension, the need for specialist advice about rare or genetic causes of CKD and the need to access specialist investigations such as magnetic resonance angiography.

The GDG noted that section 5 and section 6 of the guideline had reviewed evidence relating to level of eGFR, proteinuria and risk factors for CKD and progression of CKD. From this evidence a consensus was reached regarding appropriate referral criteria in these areas.

The GDG agreed that all people with a rapidly declining GFR and those with stage 4 and 5 CKD (with or without diabetes) should be referred, as well as those with heavy proteinuria unless this was already known to be due to diabetes and was being appropriately treated.

The GDG agreed that specialist care can be provided by GPs, specialist nurses, renal nurses, geriatricians, diabetologists, cardiologists and nephrologists and that referral did not necessarily mean that the individual had to attend an out-patient clinic. In some situations advice could be obtained by correspondence. Furthermore, once an individual had been seen in a specialist clinic and a management plan agreed, it may be possible for their future care to be carried out by the referring clinician rather than the specialist.

The GDG recommended that if people with lower urinary tract symptoms required referral, this should initially be to urological services.

### 7.1.6 RECOMMENDATIONS

- R30 People with CKD in the following groups should normally be referred for specialist assessment:
- stage 4 and 5 CKD (with or without diabetes)
  - heavy proteinuria (ACR  $\geq 70$  mg/mmol, approximately equivalent to PCR  $\geq 100$  mg/mmol, or urinary protein excretion  $\geq 1$ g/24 hours) unless known to be due to diabetes and already appropriately treated
  - proteinuria (ACR  $\geq 30$  mg/mmol, approximately equivalent to PCR  $\geq 50$  mg/mmol, or urinary protein excretion  $\geq 0.5$  g/24 hours) together with haematuria
  - rapidly declining eGFR ( $>5$  ml/min/1.73 m<sup>2</sup> in one year, or  $>10$  ml/min/1.73 m<sup>2</sup> within 5 years)
  - hypertension that remains poorly controlled despite the use of at least 4 antihypertensive drugs at therapeutic doses (see NICE clinical guideline 34, 'Hypertension: management of hypertension in adults in primary care')
  - people with, or suspected of having rare or genetic causes of CKD
  - suspected renal artery stenosis.
- R31 Consider discussing management issues with a specialist by letter, email or telephone in cases where it may not be necessary for the person with CKD to be seen by the specialist.
- R32 Once a referral has been made and a plan jointly agreed, it may be possible for routine follow-up to take place at the patient's GP surgery rather than in a specialist clinic. If this is the case, criteria for future referral or re-referral should be specified.
- R33 Take into account the individual's wishes and comorbidities when considering referral.
- R34 People with CKD and renal outflow obstruction should be referred to urological services, unless urgent medical intervention is required, e.g. for treatment of hyperkalaemia, severe uraemia, acidosis or fluid overload.



## 8 Self management

### 8.1 Modification of lifestyle

#### 8.1.1 Clinical introduction

The increased prevalence of CKD has been linked to lifestyle-related factors such as hypertension and diabetic nephropathy (see NICE Clinical Guideline 34 'Management of hypertension in adults in primary care'; NICE Clinical Guideline 66 'Management of Type 2 diabetes'; NICE Clinical Guideline 15 'Diagnosis and management of Type 1 diabetes in children, young people and adults'; and NICE Clinical Guideline 43 'Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children').<sup>28,29,183,184</sup> Smoking has been associated with more severe proteinuria and progression of renal failure. In rat models of CKD, exercise training has been shown to be renoprotective.<sup>185</sup> The association between obesity, smoking, physical activity and CKD therefore may be important. Equally, there may be insufficient adjustment of potential confounders. Obesity leads to CKD through diabetes and hypertension but is it an independent risk factor for CKD? Similarly, although it is suggested that smoking and physical inactivity contribute to progression of CKD, is this a direct or indirect effect, and is there a relationship to gender?<sup>186</sup>

- *In adults with CKD, do improving lifestyle habits slow the progression of CKD?*

#### 8.1.2 Methodology

Modification of lifestyle habits (smoking cessation, exercise, moderate alcohol consumption, and weight loss in obese people) was reviewed to determine if these changes would slow the progression of CKD. There were very few lifestyle intervention studies. There were no smoking cessation studies in a CKD population. All of these studies were limited by small sample sizes. Observational studies that assessed the association of smoking, obesity, alcohol consumption, or exercise with progression of CKD were therefore included.

One RCT examined changes in GFR, muscle strength, and total body potassium over 3 months in people aged over 50 years old with CKD on a low protein diet randomised to resistance training (N=14) or sham training (N=12).<sup>187</sup> Another RCT examined nondiabetic people with CKD (median GFR 25 ml/min/1.73 m<sup>2</sup>) randomised to exercise training (N=15, 18 months follow-up, bicycle ergometer, running, swimming, and walking) or a control group (N=15, 20 months follow-up, mostly sedentary lifestyle).<sup>188</sup>

A non-randomised controlled trial compared water-based aerobic activity (N=17) to control (sedentary lifestyle, N=9, 3-month follow-up) for changes in GFR, cystatin C, and proteinuria in people with CKD.<sup>189</sup> This study was excluded because of small sample size and methodological limitations.

One RCT<sup>190</sup> and two before-and-after observational studies<sup>191,192</sup> investigated the effect of weight loss on renal disease progression in obese, mostly diabetic populations. The Morales et al. RCT compared a low-calorie diet (N=20, 5-months follow-up, reduction of 500 kcal, consisting

of 25–30% fat and 55–65% carbohydrate, and protein content adjusted to 1.0–1.2 g/kg/day) with a usual diet (N=10) in people with diabetic or nondiabetic nephropathy.<sup>190</sup> The before and after study of Saiki et al. investigated changes in BMI, creatinine clearance, and proteinuria before and after one month of a low calorie formula diet (740 or 970 kcal/day or 11–19 kcal/kg) in 22 obese, hospitalised adults with diabetic nephropathy.<sup>191</sup> The before and after study of Solerte et al. compared changes in BMI, proteinuria, and renal function decline before and after 12 months of a low calorie diet (1410 kcal/day consisting of 170 g carbohydrate, 58 g protein, 49 g fat) in 24 obese people with diabetic nephropathy.<sup>192</sup>

The effect of alcohol consumption on the risk of ESRD was examined in a case control study in which alcohol consumption was compared between cases (people with new ESRD, N=716) and age-match controls (general population, N=361).<sup>193</sup> This study was rejected as several aspects of a robust case-control study were ignored (exclusion criteria, comparison between participants and non-participants, differentiation between cases and controls).

The effect of smoking on renal functional decline was examined in two diabetic cohort studies and two case-control studies. A German diabetic cohort of smokers (N=44, mean age 47 years, 86% had baseline proteinuria >0.15 g/day) were followed for 5.1 years (median) and changes in proteinuria and GFR (20% decline) were compared with non-smokers (N=141, mean age 54 years, 72% had baseline proteinuria >0.15 g/day).<sup>171</sup> In a Danish cohort of people with type 1 diabetes and persistent albuminuria >300 mg/24 h (N=301), changes in GFR during a median follow-up of 7 years were compared between smokers (N=176), non-smokers (N=94) and ex-smokers (N=31).<sup>172</sup> In a case-control study, men with ADPKD or IgA-GN who had progressed to ESRD were matched with controls with ADPKD or IgA-GN who had not progressed to ESRD. Progression to ESRD was compared between males who smoked for 0–5 pack-years (N=73), for 5–15 pack years (N=28), and for >15 pack years (N=43).<sup>173</sup> In a Spanish case control study, cases (people who had progressed to ESRD, N=520) were age, sex, hospital matched with controls (hospital patients who had not progressed to ESRD, N=982) and the effects of smoking compared with non-smoking on progression to ESRD were analysed.<sup>174</sup>

The effect of lifestyle changes on the progression of CKD is summarised in Table 8.1 at the end of the evidence statements.

### 8.1.3 Health economics methodology

No health economics papers were found to review.

### 8.1.4 Evidence statements

#### ▷ Exercise training: change in GFR

Median GFR decreased in both control and exercise groups but there were NS differences between groups.<sup>188</sup> (Level 1 +)

GFR increased in people with resistance training + low protein diet, whereas GFR decreased in the sham training + low protein diet group (p=0.048 between groups).<sup>187</sup> (Level 1 +)

#### ▷ Exercise training: change in total body potassium

Total body potassium increased in the resistance training + low protein diet, whereas it decreased in the sham training + low protein diet (p=0.014 between groups).<sup>187</sup> (Level 1+)

▷ Exercise training: adverse events

In one RCT, 3/15 people in the exercise group and 2/15 people in the control group started dialysis. One person in the control group died, and 1 person in the control group withdrew after 10 months for personal reasons. No exercise adverse events or injuries were reported in either the resistance training or sham training group.<sup>187</sup> (Level 1+)

▷ Weight loss: change in creatinine clearance (CrCl)

One RCT showed that there were NS changes in CrCl after 5 months of a low calorie diet. However, CrCl significantly decreased in the usual diet group, but there were NS changes between groups.<sup>190</sup> (Level 1 +)

One before and after study showed that there was NS change in CrCl after four weeks of a low calorie formula diet.<sup>191</sup> (Level 3)

One before and after study showed that CrCl significantly increased after 12 months of a low calorie diet.<sup>192</sup> (Level 3)

▷ Weight loss: change in serum creatinine

One RCT showed that there were NS changes in serum creatinine after 5 months of a low calorie diet, whereas creatinine significantly increased with a usual diet.<sup>190</sup> (Level 1 +)

Two before and after studies showed that serum creatinine significantly decreased after 1 or 12 months of a low calorie diet.<sup>191,192</sup> (Level 3)

▷ Weight loss: change in protein excretion

One RCT showed that urinary protein excretion significantly decreased after 5 months of a low calorie diet, whereas there was a NS change in proteinuria in the usual diet group ( $p < 0.05$  between groups). Weight loss was significantly correlated with a decrease in protein excretion ( $r = 0.62$ ,  $p < 0.01$ ), but not blood pressure or creatinine clearance.<sup>190</sup> (Level 1 +)

Urinary protein significantly decreased after 4 weeks of a low calorie-formula diet. Weight loss was significantly correlated with a decrease in serum creatinine ( $r = 0.621$ ,  $p = 0.0021$ ) and with a decrease in protein excretion ( $r = 0.487$ ,  $p = 0.0215$ ).<sup>191</sup> (Level 3)

Urinary protein excretion significantly decreased by 51% after 12 months of a low calorie diet,  $p < 0.01$ . Urinary albumin excretion significantly decreased by 31% after 12 months of a low calorie diet,  $p < 0.01$ . Weight loss was NS correlated with a decrease in UPE or UAE.<sup>192</sup> (Level 3)

▷ Smoking cessation

There were no studies that examined the impact of smoking cessation on renal function in people with CKD.

▷ Effect of smoking on GFR decline

In a cohort study, GFR remained stable during follow-up in non-smokers but decreased significantly in smokers. Smokers had a significantly increased odds of a 20% decline in GFR

compared to non-smokers (OR 2.52, 95% CI 1.06–5.99,  $p < 0.01$ ). This relationship persisted after adjustment for diabetes type or control, retinopathy, age, BMI, ACEI use, BP, proteinuria (F-ratio=65.9,  $p < 0.0001$ ).<sup>171</sup> (Level 2+)

In a diabetic cohort with nephropathy, GFR declined in non-smokers, ex-smokers, and smokers, with NS differences between groups.<sup>172</sup> (Level 2+)

▷ Effect of smoking on proteinuria

In a cohort study, proteinuria increased in smokers and non-smokers, with NS differences between the two groups.<sup>171</sup> (Level 2+)

▷ Effect of smoking on progression to ESRD

In a case control study, men who smoked 5–15 pack years or >15 pack years had a significantly increased risk of ESRD than men who smoked for 0–5 pack years.<sup>173</sup> (Level 2+)

Another case control study showed that smokers had a significantly increased risk of ESRD compared with non-smokers.<sup>174</sup> (Level 2+)

**Table 8.1 The effect of lifestyle changes on progression of CKD**

Reference	Population	Duration (months)	Intervention	Comparison	Outcome	Size effect
188	Nondiabetic people (median GFR 25 ml/min/1.73m <sup>2</sup> , range 10–43 ml/min/1.73m <sup>2</sup> )	18	Exercise training N=15	Control (sedentary lifestyle) N=15	Change in GFR (ml/min/month)	Exercise: 0.27 Control –0.28 NS between groups
187	CKD (creatinine 133–442 µmol/l or 1.5–5.0 mg/dl)	3	Resistance training + low protein diet N=14	Sham training + low protein diet N=12	Change in GFR (ml/min/1.73m <sup>2</sup> )	Resistance training: +1.18 ml/min/1.73m <sup>2</sup> Sham training: –1.62 ml/min/1.73m <sup>2</sup> p=0.048 between groups.
187	CKD (creatinine 133–442 µmol/l or 1.5–5.0 mg/dl)	3	Resistance training + low protein diet N=12	Sham training + low protein diet N=11	Change in total body potassium (%)	Resistance training: +4% Sham training: –6% p=0.014 between groups
190	People with diabetic or nondiabetic nephropathy and BM1 >27 kg/m <sup>2</sup>	5	Low calorie diet N=20	Usual diet N=10	Changes in creatinine clearance (ml/min/1.73 m <sup>2</sup> )	Low calorie diet: NS Usual diet: 61.8 → 56, p<0.05 NS between groups

*continued*

**Table 8.1 The effect of lifestyle changes on progression of CKD – continued**

Reference	Population	Duration (months)	Intervention	Comparison	Outcome	Size effect
191	Diabetic people with proteinuria (urinary albumin >300 mg/day), diabetic retinopathy, BMI >25 kg/m <sup>2</sup>	1	After low calorie formula diet N=22	Before low calorie formula diet N=22	Changes in creatinine clearance (ml/s/1.73 m <sup>2</sup> )	0.68 → 0.77, NS
192	Obese diabetic people with nephropathy (urinary protein excretion >500 mg/day) and diabetic retinopathy	12	After low calorie diet N=24	Before low calorie diet N=24	Changes in creatinine clearance (ml/s/1.73 m <sup>2</sup> )	80 → 90, p<0.01
190	People with diabetic or nondiabetic nephropathy and BMI >27 kg/m <sup>2</sup>	5	Low calorie diet N=20	Usual diet N=10	Changes in serum creatinine (mg/dl)	Low calorie diet: NS Usual diet: 1.6 → 1.8, p<0.05 NS between groups
191	Diabetic people with proteinuria (urinary albumin >300 mg/day), diabetic retinopathy, BMI >25 kg/m <sup>2</sup>	1	After low calorie formula diet N=22	Before low calorie formula diet N=22	Changes in serum creatinine (µmol/l)	172.4 → 130.8, p<0.0001
192	Obese diabetic people with nephropathy (urinary protein excretion >500 mg/day) and diabetic retinopathy	12	After low calorie diet N=24	Before low calorie diet N=24	Changes in serum creatinine (µmol/l)	145.2 → 101.2, p<0.001
190	Obese (BMI >27 kg/m <sup>2</sup> ) people with diabetic or nondiabetic nephropathy	5	Low calorie diet N=20	Usual diet N=10	Changes in protein excretion (g/24 h)	Low calorie diet: 2.8 → 1.9 (-31%), p<0.05 Usual diet: 3 → 3.5, NS p <0.05 between groups
191	Diabetic people with proteinuria (urinary albumin >300 mg/day), diabetic retinopathy, BMI >25 kg/m <sup>2</sup>	1	After low calorie formula diet N=22	Before low calorie formula diet N=22	Changes in protein excretion (g/24 h)	3.27 → 1.50, p<0.0001
192	Obese diabetic people with nephropathy (urinary protein excretion >500 mg/day) and diabetic retinopathy.	12	After low calorie diet N=24	Before low calorie diet N=24	Changes in protein excretion (%)	-51%, p <0.01

*continued*

**Table 8.1 The effect of lifestyle changes on progression of CKD – continued**

Reference	Population	Duration (months)	Intervention	Comparison	Outcome	Size effect
190	People with diabetic or nondiabetic nephropathy and BMI >27 kg/m <sup>2</sup>	5	Low calorie diet N=20	Usual diet N=10	Changes in BMI (kg/m <sup>2</sup> )	Low calorie diet: 33 → 31.6, p<0.01 Usual diet: 34.3 → 35, p<0.05 p<0.05 between groups
191	Diabetic people with proteinuria (urinary albumin >300 mg/day), diabetic retinopathy, BMI >25 kg/m <sup>2</sup>	1	After low calorie formula diet N=22	Before low calorie formula diet N=22	Changes in BMI (kg/m <sup>2</sup> )	30.4 → 28.2, p<0.0001
192	Obese diabetic people with nephropathy (urinary protein excretion >500 mg/day) and diabetic retinopathy.	12	After low calorie diet N=24	Before low calorie diet N=24	Changes in BMI (kg/m <sup>2</sup> )	33.5 → 26.2, p<0.001
171	Diabetic patients	60	Smokers N=44	Non-smokers =141	Change in GFR (ml/min)	Non-smokers: 107 → 106, NS Smokers: 95 → 83, p<0.001
172	People with type 1 diabetes and nephropathy (persistent albuminuria >300 mg/24 h), presence of diabetic retinopathy	84	Smokers N=176 Ex-smokers N=31	Non-smokers N=94	Change in GFR (ml/min/year)	Non-smokers: -4.4 Ex-smokers: -3.4 Smokers: -4.0 NS between groups
171	Diabetic patients	60	Smokers N= 44	Non-smokers=141	Change in proteinuria (g/24 h)	Non-smokers: 0.47 → 0.54 Smokers: 0.36 → 0.44 NS between groups.
173	Case patients: ESRD Control patients: failure to progress to ESRD matched according to AKPKD or IgA-GN, gender, region of residence, and age at renal death	N/A	5–15 pack-years N cases = 17 N controls = 11 >15 pack years N cases=29 N controls = 14	0–5 pack-years N cases = 26 N controls = 47	Progression to ESRD	5–15 pack years: unadjusted OR 3.5 (95% CI 1.3–9.6), p=0.017. >15 pack years: unadjusted OR 5.8 (95% CI 2.0–17), p=0.001

*continued*

**Table 8.1 The effect of lifestyle changes on progression of CKD – *continued***

Reference	Population	Duration (months)	Intervention	Comparison	Outcome	Size effect
174	Cases: people with ESRD Controls: randomly selected from hospital admission lists		N/A	Smokers N=320 cases N=557 controls	Non-smokers N not stated	Progression to ESRD OR 1.54 (95% CI 1.14–2.07)

### 8.1.5 From evidence to recommendations

The GDG recognised that weight control, healthy eating, taking regular exercise and not smoking are of benefit in everyone and particularly important in people with cardiovascular disease.

There was no evidence about whether people with CKD who smoke are at further increased risk of developing cardiovascular disease compared to people without CKD.

There was no evidence about specific adverse effects of alcohol consumption in people with CKD

The GDG agreed that there was no evidence that weight control, healthy eating, taking regular exercise and not smoking had additional benefits in people with CKD. Nevertheless because of the increased risk of cardiovascular disease in people with CKD the GDG recommended that people with CKD should be encouraged to take exercise, control their weight and stop smoking.

The GDG agreed that further studies are needed to examine the effect of weight reduction in people with CKD who have an elevated BMI.

### 8.1.6 RECOMMENDATIONS

R35 Encourage people with CKD to take exercise, achieve a healthy weight and stop smoking.

## 8.2 Dietary intervention and renal outcomes

### 8.2.1 Clinical Introduction

Diet is considered one of the cornerstones in the treatment of CKD. Kidney function is essential for eliminating waste material from digested food and the body. As kidney function worsens, it may be necessary to alter a person's diet to reduce the problems resulting from the accumulation of waste products.<sup>194</sup> Dietary habits may be influenced by patient preference, lifestyle and cultural factors but dietary recommendations depend on the stage of disease, biochemistry, normal dietary intake, comorbidities and nutritional status.<sup>195</sup> Dietary advice may include information about energy, protein, sodium, phosphate, potassium and fluid.<sup>195</sup> The overall aim is to prevent malnutrition, hyperkalaemia, hyperphosphataemia, and obesity and to aid the treatment of hypertension and (as CKD advances) alleviate uraemic symptoms. All of this must occur in the context of any other dietary restriction a person might be following, such as a diabetic diet, to ensure a balanced healthy diet to meet individual nutritional requirements.<sup>195</sup>

A real concern with respect to dietary protein restriction in people with CKD is the spontaneous reduction in dietary protein intake with declining GFR. Spontaneous dietary protein intakes were observed to fall from 1.1 g/kg/day for patients with creatinine clearances >50 ml/min to 0.85 g/kg/day at 25–50 ml/min, 0.70 g/kg/day at 10–25 ml/min and 0.54 g/kg/day at <10 ml/min.<sup>196</sup> Malnutrition is both a cause and consequence of ill health; it is defined as a state in which deficiency of nutrients such as energy, vitamins and minerals causes measurable adverse effects on body composition, function or clinical outcome.<sup>197</sup> It is very common in people with CKD<sup>197</sup> and can increase a person's vulnerability to disease and infections.<sup>198</sup> In people with CKD, one of the causes of malnutrition is loss of appetite secondary to uraemia.<sup>195</sup> Too few calories lead to the breakdown of muscle to provide energy; this is a sign of malnutrition. As kidney failure progresses, people tend to eat less, and poor nutrition can become a major problem.<sup>195</sup>

The use of protein restricted diets for people with CKD has remained a controversial issue.<sup>199</sup> In the 1960s people were often following the Giovanetti Diet, containing 20 g high biological value protein to cover the essential amino acid requirements, but as dialysis became available its use has declined.<sup>200</sup> In the 1980s there was a renewed interest in low protein, high energy diets as partially nephrectomised rats showed that protein restriction delayed the progression of renal disease. This led in 1985 to the National Institute of Health (NIH) in the USA commissioning a large multi-centre study – the Modification of Diet in Renal Disease (MDRD) study<sup>199</sup> – to investigate the effect of protein restriction on the progression of kidney disease. Although the results of this trial did not support severely protein restricted diets, the findings focussed on improvement in blood pressure control and the prevention of complications due to uraemia and malnutrition and dietary phosphorus restriction to prevent renal bone disease.<sup>201</sup>

Hyperphosphataemia becomes a significant problem in CKD stages 4 and 5.<sup>202</sup> Hyperphosphataemia has also been implicated as a risk factor for progression of CKD.<sup>203,204</sup> Dysregulation of calcium and phosphate can eventually result in renal bone disease if they are not controlled.<sup>202</sup> Dietary restrictions alone are rarely enough to control phosphate in severe renal failure and phosphate binders, taken with food to prevent intestinal absorption of phosphate, are often prescribed (although it should be noted that certain phosphate binders are only licensed for use in patients on dialysis).<sup>205,206</sup>

Hyperkalaemia is also a problem in people with advanced renal failure.<sup>207</sup> Dietary potassium should not be restricted routinely, only in those with raised serum levels, as potassium containing foods are required for a healthy balanced diet and restrictions need to be carefully monitored.<sup>195</sup>

- *What dietary interventions are associated with improved renal outcomes in adults with CKD?*

### 8.2.2 Methodology

The utility of low protein, low phosphate, low sodium, or low potassium diets in delaying progression of renal disease was reviewed in diabetic and nondiabetic populations with CKD. Non-randomised trials were excluded, as were any studies in which compliance with the randomised diet was poor. Meta-analyses that combined trials in diabetic and nondiabetic renal disease populations were excluded. The outcomes of interest were decline in GFR or creatinine clearance, increasing proteinuria, progression to end stage renal disease (dialysis or renal



transplantation), and markers of malnutrition (serum albumin or pre-albumin, mid arm circumference, tricep skinfolds, mid-arm muscle circumference, Subjective Global Assessment, or Malnutrition Universal Screen Tool).

There were no studies that compared low sodium, low potassium, or low phosphate diets to control diets in pre-dialysis CKD populations.

The Pedrini et al. systematic review compared a low protein diet (LPD) with a usual diet (5 RCTs, N=1413, protein intake in the LPD group ranged from 0.4 to 0.6 g/kg/day, follow-up range 18–36 months) in people with nondiabetic moderate CKD (all participants analysed had a GFR <55 ml/min).<sup>208</sup>

The Foque et al. systematic review was an update on the Pedrini et al. analysis and it compared LPD with a usual diet (8 RCTs, N=1524, protein intake in the LPD group ranged from 0.3–0.6 g/kg/day, follow-up range 12–24 months) in people with nondiabetic CKD (5/8 studies were conducted in people with stage 4–5 CKD).<sup>209</sup>

The Roberston et al. systematic review compared LPD (0.3–0.8 g/kg/day protein intake) with a usual diet (protein intake 1–2 g/kg/day) in people with type 1 diabetic nephropathy (8 studies, N=322) or type 2 diabetic nephropathy (1 study, N=263). The mean follow-up ranged from 4.5 months to 4 years.<sup>210</sup>

Most of the trial pooled in these meta-analyses were conducted in people with stage 4–5 CKD. The effect of LPD compared with a usual protein diet on renal disease progression in adults with diabetic or nondiabetic nephropathy is summarised in Table 8.2, at the end of the evidence statements.

### 8.2.3 Health economics methodology

There were no health economics papers found to review.

### 8.2.4 Evidence statements

- ▷ Renoprotective effects of low protein diets (LPDs) compared with usual protein diets (UPDs) in nondiabetic nephropathy

Protein intake was significantly lower in the LPD group compared with UPD, but compliance was a problem as few achieved the target protein level in the LPD group.<sup>208,209</sup>

- ▷ Low protein diets: risk of ESRD or death

There was a significant reduction in the occurrence of death or ESRD in people with nondiabetic renal disease on a LPD compared with those on a UPD.<sup>208,209</sup> Sensitivity analysis showed that stricter LPD (0.3 to 0.6 g/kg/day) significantly reduced the risk of death or ESRD compared with a UPD, whereas there was NS difference in risk when the protein restriction was moderate (0.6 g/kg/day).<sup>209</sup> (Level 1+)

- ▷ Low protein diets: changes in GFR, creatinine clearance, or serum creatinine

There was no meta-analysis for this outcome. A beneficial effect on GFR change with a LPD was seen in 1 RCT<sup>211</sup> and a possible beneficial effect was seen in the MDRD study.<sup>201</sup> One RCT

showed NS differences in creatinine clearance between LPD and UPD.<sup>212</sup> One RCT showed NS differences between LPD and UPD for serum creatinine increases,<sup>213</sup> whereas another RCT<sup>214</sup> showed a beneficial effect of a LPD on serum creatinine changes. (Level 1+)

▷ Low protein diets: change in mid-arm circumference

This outcome was not assessed in either systematic review. Extraction of data from one included trial showed that there were NS differences between UPD group (N=32) and LPD group (N=33) for changes in mid-arm circumference.<sup>212</sup> (Level 1+)

▷ Renoprotective effects of low protein diets compared with usual protein diets in diabetic nephropathy

The intended protein intake in the LPD group ranged from 0.3–0.8 g/kg/day, however compliance was low as the actual protein intake ranged from 0.6–1.1 g/kg/day.<sup>210</sup>

▷ Low protein diets: risk of ESRD or death

The risk of ESRD or death (adjusted for baseline cardiovascular disease) was significantly lower in people with type 1 diabetes and nephropathy randomised to LPD compared with UPD (1 study, N=82).<sup>210</sup> (Level 1+)

▷ Change in GFR

In people with type 1 diabetes and nephropathy, there was NS improvement in GFR in those randomised to a LPD compared with UPD (7 RCTs, N=222). There was significant heterogeneity ( $I^2=62%$ ,  $p=0.01$ ). In people with type 2 diabetes and nephropathy, there was a NS improvement in GFR in the LPD group compared with the UPD (1 RCT, N=160). Another RCT in people with type 2 diabetes and nephropathy (N=37) showed a similar decline in GFR in the LPD compared with the UPD group. In one RCT in which people with type 1 and type 2 diabetes and nephropathy were combined (N=80), there were NS differences in GFR decline between those randomised to LPD compared with a UPD.<sup>210</sup> (Level 1+)

▷ Quality of life

No study assessed this outcome.

▷ Nutritional status

Nine studies assessed nutritional status, but only 1 study found evidence of malnutrition as serum pre-albumin and albumin significantly decreased in the LPD group compared with the UPD group.<sup>210</sup> Four studies showed NS differences between LPD or UPD groups for serum albumin.<sup>215–218</sup> (Level 1+)

▷ Changes in mid-arm circumference

This outcome was not assessed in the Robertson et al. meta-analysis. Extraction of data from a trial included in the meta-analysis showed that there were NS differences between LPD group

(N=41) and UPD (N=41) for changes in mid arm circumference in people with type 1 diabetes and nephropathy.<sup>216</sup> (Level 1+)

**Table 8.2 Effect of a low protein diet (LPD) compared with a usual protein diet (UPD) on renal disease progression in adults with diabetic or nondiabetic nephropathy (95% confidence intervals)**

Reference	Population	Outcome	LPD vs. UPD
208	Nondiabetic CKD: 5 RCTs, N=1413 of LPD	ESRD or death	RR 0.67 (0.50–0.89), p=0.007 in favour of LPD
209	Nondiabetic CKD: 8 RCTs, N=1524	ESRD or death	RR 0.69 (0.56–0.86), p=0.0007 in favour of LPD
209	Nondiabetic CKD: 3 RCTs, N=1116	ESRD or death	RR 0.76 (0.54–1.05), p=0.1 NS LPD (0.6 g/kg/day) vs. UPD
209	Nondiabetic CKD: 5 RCTs, N=408	ESRD or death	RR 0.65 (0.49–0.86), p=0.002 LPD (0.3–0.6 g/kg/day) vs. UPD
208	Nondiabetic CKD: 2 RCTs, N=649	GFR change	Beneficial/possibly beneficial effect
208	Nondiabetic CKD: 1 RCT, N=65	Changes in creatinine clearance	NS
208	Nondiabetic CKD: 2 RCTs, N=704	Changes in serum creatinine	1 RCT=NS 1 RCT=benefit
210	Type 1 diabetic nephropathy: 1 RCT, N=82	ESRD or death	RR 0.23 (0.07–0.72), p=0.01 (adjusted for baseline CVD) in favour of LPD
210	Type 1 diabetic nephropathy: 7 RCTs, N=222	GFR change	WMD +0.14 ml/min/month (–0.06 to +0.34) NS Heterogeneity (p=0.01)
210	Type 2 diabetic nephropathy: 2 RCTs, N=197	GFR change	LPD: –0.4 ml/min/month UPD: –0.3 ml/min/month (NS, 1 RCT, N=160) LPD: –0.51 ml/min/month UPD: –0.52 ml/min/month (NS, 1 RCT, N=37)
210	Type 1 + type 2 diabetic nephropathy: 1 RCT, N=80	GFR change	LPD: –0.48 ml/min/month UPD: –0.50 ml/min/month NS

WMD = weighted mean difference.

## 8.2.5 From evidence to recommendations

The GDG noted that the utility of low protein, low phosphate, low sodium, or low potassium diets had been reviewed in diabetic and nondiabetic populations with CKD.

The GDG recognised the importance of dietary advice in the management of hyperkalaemia, hyperphosphataemia and salt and water intake for people with advanced CKD. The GDG agreed that people with advanced CKD and hyperkalaemia, hyperphosphataemia or salt/water overload therefore need advice from an appropriately trained professional. In this context, advanced CKD will usually be people in stage 4 and 5 and generally those with an eGFR <20 ml/min/1.73m<sup>2</sup> (see section 13.1).

It was noted that dietary protein intake often declines as people get older and that this is likely to occur in people with CKD.

It was noted that apart from the risks of malnutrition, low protein diets are usually unpalatable and are time consuming to adhere to as all portions must be weighed. These aspects are likely to affect the quality of life of people with CKD and therefore any recommendations about dietary restriction must have a sound evidence base.

The GDG also noted that adequate iron in the diet is important in CKD and restricting protein intake may adversely influence iron intake.

The GDG agreed that the studies combined in the meta-analysis by Pedrini et al. were too heterogeneous in terms of the severity of the underlying CKD for the analysis and conclusions to be appropriate. It was also noted that some of the studies were carried out at a time when the pharmacological management, particularly the use of ACE inhibitors, was likely to be different. The individual studies were examined and the GDG agreed that there was limited evidence that there may be a benefit of protein restriction in patients with stage 4 and 5 CKD, but the evidence did not point to an optimal protein intake.

#### **8.2.6 RECOMMENDATIONS**

- R36 Where the clinician in discussion with the patient has decided that dietary intervention to influence progression of CKD is indicated, an appropriately trained professional should discuss the risks and benefits of dietary protein restriction, with particular reference to slowing down the progression of disease versus protein-calorie malnutrition.
- R37 Where dietary intervention is agreed this should occur within the context of education, detailed dietary assessment and supervision to ensure malnutrition is prevented.
- R38 Offer dietary advice to people with progressive CKD concerning potassium, phosphate, protein, calorie and salt intake when indicated.

## 9 Blood pressure control

### 9.1 Blood pressure control in people with CKD

#### 9.1.1 Clinical introduction

There is strong evidence that lowering blood pressure reduces cardiovascular risk and progression of CKD. The optimal treatment target remains poorly defined and considerable confusion has occurred because there is a lack of conformity between recommended treatment targets in different disease guidelines and in the Quality and Outcomes Framework. The objective of this section was both to consider the evidence and to rationalise treatment targets with those recommended by the NICE guidelines for management of type 2 diabetes and hypertension.

General aspects of blood pressure management will not be covered in this guideline but for advice relating to measuring blood pressure and lifestyle interventions to reduce blood pressure please see NICE clinical guideline 34 ('Hypertension: management of hypertension in adults in primary care'). Although the hypertension guideline did not recommend home monitoring recent data shows that self-measurement leads to less medication use than clinic blood pressure measurement without leading to significant differences in outpatient values of blood pressure.<sup>219</sup>

The UK CKD guidelines<sup>15</sup> recommended that the threshold for initiation and subsequent adjustment of antihypertensive therapy should be 140/90 mmHg for patients without proteinuria, and 130/80 mmHg for those with a PCR >100 mg/mmol. Antihypertensive therapy should be adjusted to achieve blood pressure <130/80, or <125/75 mmHg for those with a PCR >100 mg/mmol. The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines<sup>35</sup> recommend achieving blood pressure <130/80 mmHg and the SIGN guidelines<sup>32</sup> recommend a target maximum systolic blood pressure of 130 mmHg in those with 1 g/day of proteinuria. CARI guidelines are more proscriptive, recommending a target blood pressure of <125/75 mmHg in those with proteinuria >1 g/day but acknowledging that the precise goal below 130/80 mmHg is not clear. The British Hypertension Society guidelines define optimal blood pressure control in people with kidney disease as <130/80 mmHg and suggest reducing blood pressure to <125/75 mmHg in those with proteinuria  $\geq 1$  g/24 h.<sup>1,220</sup>

- *In adults with proteinuric/nonproteinuric CKD, what are the optimal blood pressure ranges for slowing kidney disease progression, and for reducing cardiovascular disease risk and mortality?*

#### 9.1.2 Methodology

One meta-analysis, three randomised controlled trials, four case series studies, and five post-hoc analyses of RCTs, examined the effects of 'intense' versus 'usual' blood pressure control on renal and cardiovascular outcomes in people with diabetic or nondiabetic kidney disease. All post-hoc analyses of RCTs were downgraded to level two evidence.<sup>1</sup> The long-term follow-up study of the MDRD trial<sup>221</sup> was rejected because blood pressure measurements were not recorded during the follow-up period and participants were not advised to maintain their originally randomised diet and antihypertensive regimens.

The effects of blood pressure control on cardiovascular and renal outcomes in people with CKD are summarised in Tables 9.2 and 9.3 at the end of the evidence statements.

### 9.1.3 Health economics methodology

No health economics papers were found to review.

### 9.1.4 Evidence statements

#### ▷ Cardiovascular outcomes

The African American Study of Kidney Disease and Hypertension (AASK) RCT (N=1094, follow-up 4 years),<sup>222</sup> compared the effect of intense (MAP  $\leq 92$  mmHg) versus usual (MAP 102–107 mmHg) blood pressure control on cardiovascular outcomes in African-American adults with proteinuric, hypertensive nondiabetic kidney disease.

A case series (N=860, follow-up 10 years) investigated the association of systolic blood pressures  $< 133$  mmHg and mortality in a cohort of men (mean age  $68 \pm 10$  years) with stages 3 to 5 CKD.<sup>223</sup> Another case series (N=1549, mean follow-up 8.8 years) examined the effect of SBP  $< 120$  mmHg on stroke in elderly people (mean age  $70.2 \pm 10.3$  years) with stages 3 and 4 CKD.<sup>224</sup> This study lacked data on baseline proteinuria.

Two post-hoc analyses of the Irbesartan in Diabetic Nephropathy Trial (IDNT) RCT (N=1590, median follow-up 2.9 years)<sup>225,226</sup> suggested that systolic blood pressures  $< 120$  mmHg were associated with poor cardiovascular outcomes and increased all-cause mortality in proteinuric diabetic kidney disease. Diastolic blood pressure was not significantly associated with all-cause mortality, cardiovascular mortality, or congestive heart failure.<sup>225</sup> These results should be interpreted with caution as the number of participants with systolic blood pressure  $< 120$  mmHg was small (N=53).

#### ▷ All-cause mortality

In the AASK trial, people assigned to usual versus intense blood pressure control had NS difference in the risk for all-cause mortality.<sup>222</sup> (Level 1+)

People with diabetic nephropathy and overt proteinuria with an achieved SBP  $\leq 120$  mmHg (N=53) had a significantly greater risk of all-cause mortality compared to people with an achieved SBP  $> 120$  mmHg (N=1537).<sup>225,226</sup> (Level 2+)

In US veterans with stage 3–5 CKD, men with SBP 134–154 mmHg (N=238) had a significantly decreased risk for all-cause mortality compared with men who had SBP  $< 133$  mmHg (N=217).<sup>223</sup> Mortality was highest in men with DBP  $< 64$  mmHg and lowest in men with DBP  $> 86$  mmHg. (Level 3)

There was a significant reduction in the risk for all-cause mortality for men with DBP  $> 86$  mmHg (N=200) compared with DBP  $< 65$  mmHg (N=233).<sup>223</sup> (Level 2 + and 3)

#### ▷ Cardiovascular mortality

In the AASK trial, people assigned to usual versus intense blood pressure control had NS difference in the risk for cardiovascular mortality.<sup>222</sup> (Level 1+)

In people with diabetic nephropathy and overt proteinuria, the risk of cardiovascular mortality decreased as achieved SBP decreased from >170 mmHg to 120–130 mmHg. There was a significantly higher risk of cardiovascular mortality for people with an achieved SBP <120 mmHg compared with SBP >120 mmHg.<sup>225</sup> (Level 2+)

▷ Congestive heart failure

In people with diabetic nephropathy and overt proteinuria the risk for congestive heart failure decreased as achieved SBP decreased from >170 mmHg to 120–130 mmHg. People with an achieved SBP ≤120 mmHg had a significantly greater risk of congestive heart failure compared to people with an achieved SBP >120 mmHg.<sup>225</sup> (Level 2 +)

▷ Myocardial infarction

People with diabetic nephropathy and overt proteinuria and an achieved SBP ≤120 mmHg had NS difference in risk of MI compared to people with an achieved SBP >120 mmHg.<sup>225</sup> (Level 2 +)

The risk for MI was significantly higher in people with DBP <70 mmHg (no numerical data provided) compared to the reference DBP 70–80 mmHg. (Level 2 +)

The risk for MI was significantly lower in people with DBP >85 mmHg (no numerical data provided) compared to the reference DBP 70–80 mmHg.<sup>225</sup> (Level 2 +)

▷ Stroke

People with diabetic nephropathy and overt proteinuria and an achieved SBP ≤120 mmHg had NS difference in risk of stroke compared to people with an achieved SBP >120 mmHg.<sup>225</sup> (Level 2 +)

In contrast, a case series of people with stage 3 to 4 CKD (no proteinuria data provided) showed a SBP <120 mmHg (N=209) significantly increased the risk for stroke compared with a SBP 120–129 mmHg (N=173).<sup>224</sup> (Level 3)

▷ Renal outcomes

One meta-analysis of eleven randomised controlled trials (N=1860, mean follow-up 2.2 years) evaluated the effect of increasing systolic blood pressures and proteinuria on the progression of kidney disease in predominantly nondiabetic proteinuric CKD populations.<sup>227</sup>

The effects of intense versus usual blood pressure control on renal outcomes in adults with proteinuric, nondiabetic kidney disease were analysed in three randomised controlled trials: the MDRD RCT (N=840, mean follow-up 2.2 years),<sup>201</sup> the REIN-2 RCT (N=338, median follow-up 1.6 years)<sup>228</sup> and the AASK RCT (N=1094, follow-up 4 years).<sup>222</sup> Table 9.1 details the blood pressure goals of each RCT.

**Table 9.1 Blood pressure goals of three RCTs**

RCT	Intense blood pressure control	Usual blood pressure control
MDRD	MAP $\leq$ 92 mmHg for people 18–60 years or $\leq$ 98 mmHg for people 61 and older	MAP $\leq$ 107 mmHg for people 18–60 years or $\leq$ 113 mmHg for people 61 and older
REIN-2	SBP <130 mmHg, DBP <80 mmHg	DBP <90 mmHg, irrespective of SBP
AASK	MAP $\leq$ 92 mmHg	MAP 102–107 mmHg

Two post-hoc analyses of RCTs conducted in proteinuric diabetic populations investigated the impact of blood pressure control on renal outcomes: the IDNT (N=1590, mean follow-up 2.9 years)<sup>226</sup> and the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan study (RENAAL) (N=1513, median follow-up 3.4 years).<sup>229</sup>

In a type 1 diabetic kidney disease cohort (N=301, follow-up 7 years, mean age 36 years) participants who achieved regression (GFR decline <1 ml/min/year) or remission (decrease in albuminuria <200  $\mu$ g/min sustained for at least one year) of renal disease were compared with participants who failed to achieve regression or remission in terms of levels of blood pressure control, albuminuria, and GFR decline.<sup>230</sup>

The Leiden 85-Plus case series (N=550, age range 85–90 years, follow-up 5 years, no proteinuria data) assessed the effect of blood pressure on the decline in creatinine clearance over time in an elderly cohort.<sup>231</sup>

▷ Decline in GFR or creatinine clearance

In the AASK, REIN-2, and MDRD trials, there were no significant differences in GFR decline between intense and usual control. (Level 1 +)

In subgroup analysis of people in the MDRD trial with baseline urinary protein <1 g/day (N=420) or 1–3 g/day (N=63), there was NS difference in GFR decline between intense and usual control after 3 years. For people with baseline urinary protein excretion >3 g/day (N=32), there was a benefit of intense control (GFR decline 5.5 ml/min/year) on declining GFR compared with usual control (GFR decline 8 ml/min/year) (no p value given).<sup>201</sup> (Level 1 +)

In patients with baseline proteinuria of 0.25–3.0 g/day, the association of higher blood pressure with faster GFR decline was apparent at 98 mmHg MAP. In patients with baseline proteinuria >3.0 g/day, the association of higher blood pressure with faster GFR decline was apparent at 92 mmHg MAP.<sup>232</sup> (Level 2 +)

In the Leiden 85-Plus elderly cohort, the decline in creatinine clearance was significantly faster in people with DBP <70 mmHg than in people with DBP 70–89 mmHg.<sup>231</sup> (Level 3)

▷ Combined renal endpoint: doubling of serum creatinine, ESRD, or death

In post-hoc analysis of the RENAAL trial, people with achieved SBP <130 mmHg (N=278) had a significantly lower risk of reaching the combined renal endpoint compared to people with achieved SBP 140–159 mmHg (N=522). There was NS risk for the combined renal endpoint



between people with achieved SBP 130–139 mmHg (N=401) compared to people with achieved SBP <130 mmHg (N=278).<sup>229</sup> (Level 2 +)

There was NS difference in risk for the combined renal endpoint at achieved DBP 70–89 mmHg compared with achieved DBP <70 mmHg. People with an achieved DBP <70 mmHg (N=365) had a significantly lower risk of reaching the combined renal endpoint compared with those with an achieved DBP of 90–99 mmHg (N=152).<sup>229</sup> (Level 2+)

▷ Progression to ESRD or death

In the MDRD trial, there was NS difference in risk of death or ESRD for intense versus usual MAP control. (Level 1+)

In post-hoc analysis of the RENAAL trial, there was NS risk for ESRD or death at achieved DBP 70–89 mmHg compared to achieved DBP <70 mmHg. People with an achieved DBP of 90–99 mmHg (N=144) had a significantly higher risk of reaching ESRD or death compared to people with achieved DBP <70 mmHg (N=377).<sup>229</sup> (Level 2+)

There was NS difference in risk for ESRD or death at achieved SBP 130–139 mmHg (N=392) compared with achieved SBP <130 mmHg (N=286). People with achieved SBP 140–159 mmHg (N=518) had a significantly higher risk of reaching ESRD or death compared with people with achieved SBP <130 mmHg (N=286).<sup>229</sup> (Level 2+)

▷ Progression to ESRD

In the AASK and REIN-2 trials, there was NS risk for ESRD between intense or usual control. (Level 1+)

In post-hoc analysis of the RENAAL trial, there was NS difference in risk for reaching ESRD for people with achieved SBP 130–139 mmHg (N=392) compared with people with achieved SBP <130 mmHg (N=286). Achieved SBP 140–159 mmHg (N=518) was associated with a significantly higher risk of reaching ESRD compared with achieved SBP <130 mmHg (N=286). (Level 2 +)

There was NS difference in risk for ESRD at achieved DBP 70–89 mmHg compared with achieved DBP <70 mmHg. Achieved DBP of 90–99 mmHg (N=144) was associated with a significantly higher risk of reaching ESRD compared to achieved DBP <70 mmHg (N=377).<sup>229</sup> (Level 2 +)

▷ Kidney disease progression: doubling of serum creatinine or initiation of dialysis

In a meta-analysis of eleven RCTs conducted in people with nondiabetic kidney disease, there was NS risk for renal disease progression when urine protein excretion was less than 1 g/day at any level of blood pressure. For people with urine protein excretion  $\geq 1$  g/day, there was NS risk for renal disease progression when SBP was 120–129 mmHg compared with SBP 110–119 mmHg. For people with urine protein excretion  $\geq 1$  g/day, there was a significantly increased risk for renal disease progression when SBP was 130–139 mmHg (RR 4.5, no CI given) compared with SBP 110–119 mmHg.<sup>227</sup> (Level 1+)

▷ Proteinuria

In the AASK trial, proteinuria was significantly decreased by 17% in the intense control group, whereas proteinuria increased by 7% in the usual control group (p<0.001). (Level 1+)

In the REIN-2 trial, there was NS difference in proteinuria between those with intensive (N=167) BP control compared to those with conventional (N=168) BP control. (Level 1+)

In post-hoc analysis of the MDRD trial,<sup>232</sup> assignment to intense control significantly decreased proteinuria during follow-up compared to usual control. This was seen in people with baseline proteinuria >0.25 g/day. (Level 2+)

▷ Remission

Remission was defined as a decrease in albuminuria <200 µg/min in at least two out of three consecutive 24-hour urine collections that was sustained for at least one year during follow-up, with a decrease of at least 30% from pre-remission levels.

In a cohort of type 1 diabetic patients with nephropathy (N=301), more people with a lower follow-up MAP achieved remission. Stratified by MAP: MAP 93 mmHg (58% remission), MAP 99 mmHg (33% remission), MAP 103 mmHg (25% remission), MAP 107 mmHg (20% remission), MAP 113 mmHg (17% remission).<sup>230</sup> (Level 3)

▷ Regression (a rate of decline in GFR ≤1 ml/min/year during the observation period).

In a cohort of type 1 diabetic patients with nephropathy (N=301), more people with a lower follow-up MAP achieved regression. Stratified by MAP: MAP 93 mmHg (42% regression), MAP 99 mmHg (32% regression), MAP 103 mmHg (11% regression), MAP 107 mmHg (20% regression), MAP 113 mmHg (17% regression). The adjusted odds ratio for regression associated with a 10 mmHg decline in MAP was 2.14 (95% CI 1.33 to 3.44, p<0.001).<sup>230</sup> (Level 3)

**Table 9.2 Cardiovascular and renal outcomes according to SBP or MAP control in adults with either diabetic or nondiabetic CKD stratified by baseline urinary protein excretion rate (95% confidence interval)**

Outcome	Nondiabetic CKD		Diabetic CKD	
	<1 g/day proteinuria	>1 g/day proteinuria	<1 g/day proteinuria	>1 g/day proteinuria
<b>All-cause mortality</b>	NS difference intense vs. usual MAP control (AASK)	–	HR 0.62 (0.45–0.85), p=0.003 SBP 134–154 mmHg vs. ≤133 mmHg (US vet)	RR 3.05 (1.80–5.17), p<0.0001 SBP ≤120 mmHg vs. SBP >120 mmHg (IDNT*)
<b>Cardiovascular mortality</b>	NS difference intense vs. usual MAP control (AASK)	–	–	RR 4.06 (2.11–7.80), p<0.0001 SBP ≤120 mmHg vs. SBP >120 mmHg (IDNT*)
<b>Congestive heart failure</b>	–	–	–	RR 1.80 (1.17–2.86), p=0.008 SBP ≤120 mmHg vs. SBP >120 mmHg (IDNT*)

*continued*

**Table 9.2 Cardiovascular and renal outcomes according to SBP or MAP control in adults with either diabetic or nondiabetic CKD stratified by baseline urinary protein excretion rate (95% confidence interval) – *continued***

Outcome	Nondiabetic CKD		Diabetic CKD	
	<1 g/day proteinuria	>1 g/day proteinuria	<1 g/day proteinuria	>1 g/day proteinuria
<b>Myocardial infarction</b>	–	–	–	NS $\leq 120$ vs. $>120$ (IDNT*)
<b>Stroke</b>	HR 2.26 (1.16–4.41) SBP $<120$ mmHg vs. SBP 120–129 mmHg (ARIC + CHS CKD cohort, 18% diabetic, no proteinuria data)	–	–	NS $\leq 120$ vs. $>120$ (IDNT*)
<b>Decline in GFR or creatinine clearance</b>	NS difference intense vs. usual MAP control (MDRD) NS difference intense vs. usual MAP control (AASK) SBP not predictive (Leiden 85-Plus; 16% diabetic, no proteinuria data)	Intense MAP control (GFR decline 5.5 ml/min/year) vs. usual MAP control (GFR decline 8 ml/min/year) (no p value) (MDRD) NS difference intense vs. usual MAP control (REIN-2)	–	–
<b>Doubling serum creatinine, ESRD, or death</b>	–	–	–	NS risk SBP 130–139 mmHg vs. SBP $<130$ mmHg HR 1.49 (1.18–1.90), $p=0.001$ SBP 140–159 mmHg vs. SBP $<130$ mmHg (RENAAL*)
<b>ESRD or death</b>	NS risk intense vs. usual MAP control (MDRD-GFR 13–24 ml/min/1.73 m <sup>2</sup> )	–	–	NS difference in risk SBP 130–139 mmHg vs. SBP $<130$ mmHg HR 1.33 (1.02–1.72), $p=0.03$ SBP 140–159 mmHg vs. SBP $<130$ mmHg vs. (RENAAL*)
<b>ESRD</b>	NS risk intense vs. usual MAP control (AASK)	NS risk intense vs. usual MAP control (REIN-2)	–	NS risk SBP 130–139 mmHg vs. SBP $<130$ mmHg HR 1.52 (1.07–2.15), $p=0.02$ SBP 140–159 mmHg vs. SBP $<130$ mmHg (RENAAL*)
<b>Doubling serum creatinine or ESRD</b>	NS risk SBP $<110$ to $>160$ mmHg (Jafar meta-analysis)	NS risk SBP 120–129 vs. 110–119 mmHg RR 4.5, no CI given SBP 130–139 mmHg vs. 110–119 mmHg (Jafar meta-analysis)	–	–

*continued*

**Table 9.2 Cardiovascular and renal outcomes according to SBP or MAP control in adults with either diabetic or nondiabetic CKD stratified by baseline urinary protein excretion rate (95% confidence interval) – *continued***

Outcome	Nondiabetic CKD		Diabetic CKD	
	<1 g/day proteinuria	>1 g/day proteinuria	<1 g/day proteinuria	>1 g/day proteinuria
<b>Proteinuria</b>	↓ Proteinuria intense MAP control (AASK) ↓ Proteinuria intense MAP control (MDRD*)	NS difference intense vs. usual MAP control (REIN-2) ↓ Proteinuria intense MAP control (MDRD*)	–	–

\*Post-hoc analysis.

**Table 9.3 Cardiovascular and renal outcomes according to DBP control in adults with either diabetic or nondiabetic CKD stratified by baseline urinary protein excretion rate**

Outcome	Nondiabetic CKD		Diabetic CKD	
	<1 g/day proteinuria	>1 g/day proteinuria	<1 g/day proteinuria	>1 g/day proteinuria
<b>All-cause mortality</b>	–	–	HR 0.6 (0.4–0.9, p=0.005). DBP >86 mmHg vs. DBP <65 mmHg (US vet)	DBP not predictive (IDNT*)
<b>Cardiovascular mortality</b>	–	–	–	DBP not predictive (IDNT*)
<b>Congestive heart failure</b>	–	–	–	DBP not predictive (IDNT*)
<b>Myocardial infarction</b>	–	–	–	↑ Risk DBP <70 mmHg vs. DBP 70–80 mmHg. ↓ Risk DBP >85 mmHg vs. DBP 70–80 mmHg. (IDNT*)
<b>Stroke</b>	–	–	–	RR 0.65 (0.48–0.88), p=0.005  10 mmHg lower achieved DBP vs. 85 mmHg DBP) (IDNT*)
<b>Decline in GFR or creatinine clearance</b>	DBP <70 mmHg (CrCl decline –1.63 ml/min) vs. DBP 70–79 mmHg (–1.21 ml/min, p=0.01) or DBP 80–89 mmHg (–1.26 ml/min, p=0.03). NS difference in CrCl decline for DBP <70 mmHg vs. DBP ≥90 mmHg. (Leiden 85-Plus; 16% diabetic, no proteinuria data)	–	–	–

*continued*

**Table 9.3 Cardiovascular and renal outcomes according to DBP control in adults with either diabetic or nondiabetic CKD stratified by baseline urinary protein excretion rate – *continued***

Outcome	Nondiabetic CKD		Diabetic CKD	
	<1 g/day proteinuria	>1 g/day proteinuria	<1 g/day proteinuria	>1 g/day proteinuria
<b>Doubling serum creatinine, ESRD, or death</b>	–	–	–	NS risk DBP 70–89 mmHg vs. DBP <70 mmHg. HR 1.72 (1.32–2.23), $p < 0.001$ DBP 90–99 mmHg vs. DBP <70 mmHg (RENAAL*)
<b>ESRD or death</b>	–	–	–	NS risk DBP 70–89 mmHg vs. DBP <70 mmHg. HR 1.55 (1.16–2.08), $p = 0.003$ DBP 90–99 mmHg vs. DBP <70 mmHg (RENAAL*)
<b>ESRD</b>	–	–	–	NS risk DBP 70–89 mmHg vs. DBP <70 mmHg. HR 1.67 (1.15–2.44), $p = 0.008$ DBP 90–99 mmHg vs. DBP <70 mmHg (RENAAL*)
<b>Doubling serum creatinine or ESRD</b>	DBP not predictive (Jafar meta-analysis)	DBP not predictive (Jafar meta-analysis)	–	–

\*Post-hoc analysis.

### 9.1.5 From evidence to recommendations

The evidence considered has come from a mixture of meta-analysis, RCTs, longitudinal cohort studies and post-hoc analysis of RCTs.

Evidence relating to lifestyle advice (such as salt restriction) in blood pressure control can be found in the NICE clinical guideline 34 on hypertension.<sup>28</sup>

The GDG noted that there may be confounding effects of blood pressure control and adverse outcomes such that adverse outcomes seen with lower blood pressure levels may have been subject to reverse causality.

The evidence presented suggests that there are optimal ranges, with increased risk of adverse outcomes both above and below the optimal range, for both systolic and diastolic blood pressure. In practice, when treatment is given to maintain the systolic blood pressure in the optimal range, this results in the diastolic blood pressure falling below its optimal range. Recommendations were therefore made for a systolic range and a diastolic threshold.

The evidence suggests that the optimal blood pressure range is not influenced by age and the studies considered have included people aged up to 80.

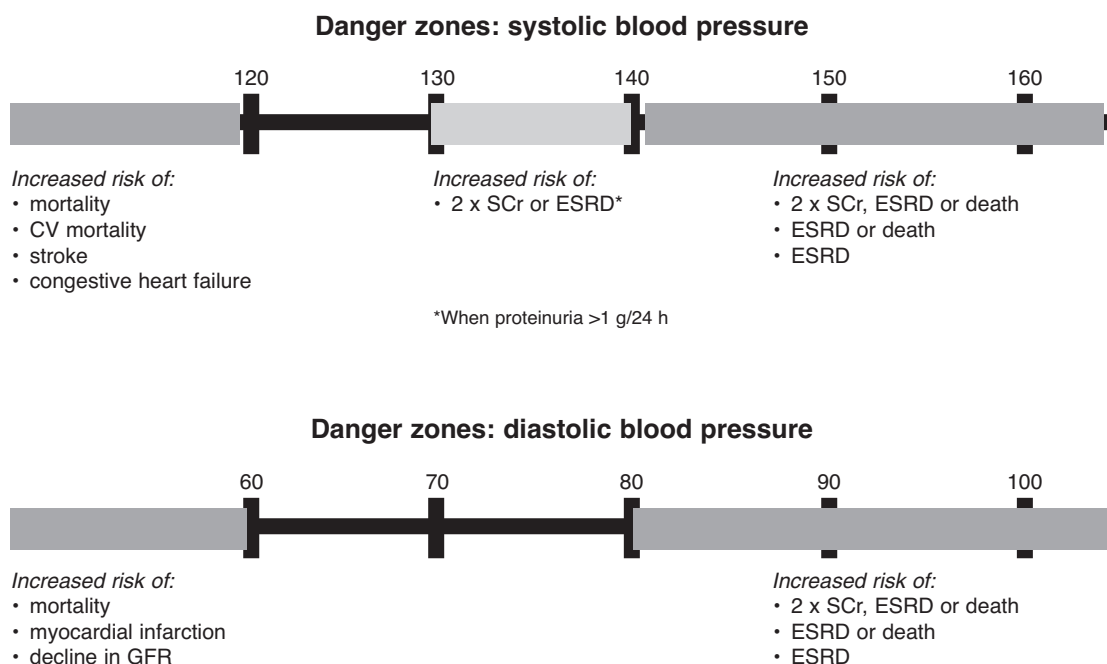
In people with CKD without diabetes, there is some evidence to suggest lower blood pressure targets in those with a threshold level of proteinuria equivalent to an ACR of  $\geq 70$  mg/mmol, or PCR  $\geq 100$  mg/mmol (approximately equivalent to urinary protein excretion of  $\geq 1$  g/day).

In order to be consistent with the available evidence on ACEI/ARB therapy a threshold level of proteinuria at which ACEI/ARBs should also be recommended for blood pressure control in people without diabetes was set at an ACR of  $\geq 30$ mg/mmol, or PCR  $\geq 50$  mg/mmol (approximately equivalent to a urinary protein excretion of 0.5 g/day).

### 9.1.6 RECOMMENDATIONS

- R39** In people with CKD aim to keep the systolic blood pressure below 140 mmHg (target range 120–139 mmHg) and the diastolic blood pressure below 90 mmHg.
- R40** In people with diabetes and CKD or when the ACR is  $\geq 70$  mg/mmol, or PCR  $\geq 100$  mg/mmol (approximately equivalent to PCR  $\geq 100$  mg/mmol, or urinary protein excretion  $\geq 1.0$  g/24 h) aim to keep the systolic blood pressure below 130 mmHg (target range 120–129 mmHg) and the diastolic blood pressure below 80 mmHg.

The diagrams in Figure 9.1 are not included in the above recommendations but illustrate the BP values that are associated with adverse outcomes.



**Figure 9.1 Blood pressure values associated with adverse outcomes.**

## 9.2 Choice of anti-hypertensive agents for blood pressure control in people with CKD

### 9.2.1 Clinical introduction

In general, different classes of anti-hypertensives reduce blood pressure to a similar degree, and a number of trials of anti-hypertensive therapy have shown that reduction of blood pressure reduces the risk of end stage kidney disease and of cardiovascular disease regardless of the class of agent employed.<sup>220,233–236</sup> NICE recommends that for people newly diagnosed with hypertension, those younger than 55 years should be started on an ACE inhibitor or ARB, and those either over 55 years or of black ethnicity should be started on either a calcium-channel blocker or thiazide-type diuretic.<sup>28</sup> Where blood pressure remains uncontrolled additional classes of anti-hypertensives such as alpha-blockers and beta-blockers are recommended. Hypertension is extremely common in people with CKD and the mean number of antihypertensive agents prescribed is associated with the stage of CKD, increasing as GFR falls.<sup>19</sup>

Existing guidelines are quite clear that certain anti-hypertensive agents have specific benefits in patients with additional comorbidities and it is well known that ACEI/ARBs have additional benefits over and above blood pressure control in people with diabetes. The UK CKD guidelines<sup>15</sup> recommend that ACEI/ARBs should be used as first line therapy only for people with diabetic kidney disease and for those with proteinuria (urine PCR >100 mg/mmol) and this was endorsed by the UK consensus conference. Although the evidence is less clear in non-diabetic kidney disease with lesser degrees of proteinuria the Quality and Outcomes Framework requires the use of ACEI/ARBs in people with stage 3–5 CKD hypertension and proteinuria. The CARI guidelines<sup>36</sup> recommend that regimens including ACEI/ARBs are more effective in slowing progression of non-diabetic CKD, and that combination of ACEIs and ARBs slow progression more effectively than either single agent. They also conclude that ACEI/ARBs are more effective than beta-blockers and dihydropyridine calcium channel blockers, and that beta-blockers may be more effective than dihydropyridine calcium channel blockers.

- *What are the most appropriate antihypertensive drugs to reduce the risk of progression of CKD and to decrease mortality in adults with CKD?*

### 9.2.2 Methodology

Six systematic reviews<sup>237–242</sup> and ten RCTs<sup>118,222,243–250</sup> compared the use of ACE inhibitors and/or ARBs with placebo or other antihypertensive agents (alpha or beta blockers, calcium channel blockers, thiazide diuretics). Most trials used non-ACEI or non-ARB antihypertensive agents in both arms to achieve blood pressure control and to ascertain if ACEI or ARBs provided renoprotective effects beyond blood pressure control.

The sample sizes in these studies ranged from N=180 to 39485 and the duration of the trials ranged from 6 months to 6 years. The mean age of study participants was under sixty years of age, with the exception of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study,<sup>118</sup> in which the mean age was 67 or 70 in each treatment arm. The studies were also quite heterogeneous in terms of the population studied – diabetic nephropathy or nondiabetic CKD.

Two studies<sup>243,246</sup> were excluded as important features such as the number of people in each trial arm, intention to treat analysis, baseline characteristics, or statistical power estimations were not provided. The study by Marin et al.<sup>245</sup> was excluded as it was not blinded and was underpowered for the mortality outcome. A systematic review of ten RCTs<sup>241</sup> comparing combination therapy ACEI + ARB versus monotherapy (ACEI or ARB) in adults with diabetic nephropathy was excluded because the quality of each included trial was not assessed; the primary outcome (proteinuria change) had significant heterogeneity and there was no heterogeneity analysis for sub-group analyses. Studies included in the meta-analysis were only 8–12 weeks long. There was wide variation in the dosage of ACEI and ARB, and few studies titrated to the maximum tolerated dose.

### 9.2.3 Health economics methodology

Seven papers<sup>251–257</sup> were included that evaluated ACEI (Table 9.4) and a further 10 papers<sup>258,258–266</sup> evaluated ARBs (Table 9.5), all based on randomised controlled trials. Two more studies<sup>267,268</sup> evaluated ACEI or ARB treatment based on meta-analysis of RCTs.

Most papers evaluated the drugs in the context of diabetic nephropathy.

Of the papers appraised, only 3 were UK-based. Studies which are not UK-based may not be easily transferable to a UK setting. However, the UK studies reached similar conclusions to the North American and European studies.

**Table 9.4 Summary of economic evaluations of ACE inhibitors to treat CKD**

Study and country	ACEI	Authors	Time horizon (years)	Discount rate (% p.a.)	
				Costs	Effects
<b>DNCSG (diabetes)</b>					
	<i>Captopril</i>				
UK		251	4	6	6
Italy		252	10	5	5
US		253	Lifetime	5	5
<b>REIN (non-diabetes)</b>					
	<i>Ramipril</i>				
US		254	Lifetime	5	5
Germany		255	3	5	5
<b>AIPRI (various)</b>					
	<i>Benazepril</i>				
Netherlands		256	10	5	5
US		257	7	5	5



Table 9.5 Summary of economic evaluations of ARB to treat CKD

Study and country	ARB	Authors	Time horizon (years)	Discount rate (% p.a.)	
				Costs	Effects
<b>IDNT (diabetes)</b>					
	<i>Irbesartan</i>				
UK		258	10	6	1.5
US		259	3, 10 and 25	3	3
Switzerland		260	25	5	5
Canadian		261	25	3	3
Belgium and France		258	Lifetime	3	3
<b>RENAAL (diabetes)</b>					
	<i>Losartan</i>				
UK		262	Lifetime	3.5	3.5
US		263	3.5	3.5	NM
Switzerland		264	3.5	NM	NM
Canadian		265	4	NM	NM
France		266	5	NM	NM

NM = not modelled.

### 9.2.4 Evidence statements

- ▷ Renoprotective effects of ACE inhibitors or ARBs compared with placebo/no treatment

One systematic review<sup>237</sup> investigated the renoprotective effects of ACE inhibitors or ARBs compared to placebo or no treatment in adults with diabetic kidney disease.

Another systematic review (49 RCT, N=6181, trial durations 1–12 months) assessed changes in proteinuria in people with renal disease of various causes randomised to ARBs versus placebo, calcium channel blockers, or ACE inhibitors. It also assessed combination therapy (ACEI + ARB) versus ACEI or ARB monotherapy.<sup>242</sup> In the combination therapy comparisons, few trials titrated the ACEI and ARB dosage to the maximum tolerated doses.

The Ramipril Efficacy in Nephropathy (REIN) RCT compared an ACE inhibitor (ramipril) with placebo in non-diabetic adults with CKD (N=352) stratified by baseline proteinuria: stratum one covered 1–2.9 g/24 h<sup>248</sup> and stratum two  $\geq 3$  g/24 h.<sup>247</sup> Both trial arms received non-ACEI antihypertensive agents to control blood pressure.

- ▷ Risk of ESRD

There was a significant reduction in the risk of ESRD with ACEI (10 studies, N=6819, RR 0.60, 95% CI 0.39–0.93) or ARB (3 studies, N=3251, RR 0.78, 95% CI 0.67–0.91) compared with placebo or no treatment.<sup>237</sup> (Level 1++)

In adults with non-diabetic CKD and baseline proteinuria 1–2.9 g/24 h, ramipril (ACE inhibitor) significantly reduced the risk of progression to ESRD by 56% compared to placebo.<sup>248</sup> For adults with baseline proteinuria  $\geq 3$  g/24 h, ramipril significantly reduced the risk of ESRD or doubling of serum creatinine (18/78 ramipril versus 40/88 placebo,  $p=0.04$ ). A higher baseline urinary protein excretion rate was associated with a higher risk of reaching the combined endpoint in the placebo group, but not in the ramipril group.<sup>247</sup> (Level 1+)

▷ Doubling of serum creatinine

There was NS reduction of the risk of doubling of serum creatinine for ACEI compared to placebo or no treatment.<sup>237</sup> (Level 1++)

There was a significant reduction in the risk of the doubling of serum creatinine with ARB compared with placebo/no treatment (3 studies,  $N=3251$ , RR 0.79, 95% CI 0.67–0.93).<sup>237</sup> (Level 1++)

▷ Progression from micro- to macroalbuminuria

ACEI (17 studies,  $N=2036$ , RR 0.45, 95% CI 0.29–0.69) or ARB (3 studies,  $N=761$ , RR 0.49, 95% CI 0.32–0.75) significantly reduced the risk of progression from micro- to macroalbuminuria compared with placebo. There was NS reduction in progression from micro- to macroalbuminuria for ACEI vs. ARB (1 study,  $N=41$ ).<sup>237</sup> (Level 1++)

In the REIN study, ramipril significantly reduced the risk of progression to overt proteinuria by 52% compared to placebo.<sup>248</sup> (Level 1+)

▷ Regression to normoalbuminuria

ACEI (16 studies,  $N=1910$ , RR 3.06, 95% CI 1.76–5.35) or ARB (2 studies,  $N=670$ , RR 1.42, 95% CI 1.05–1.93) significantly increased regression from micro- to normoalbuminuria compared with placebo or no treatment. There was NS difference in regression to normoalbuminuria for ACEI compared with ARB.<sup>237</sup> (Level 1++)

▷ Changes in proteinuria

In adults with baseline proteinuria 1–2.9 g/24 h, median proteinuria increased from baseline by 15% in the placebo group and decreased by 13% in the ramipril group ( $p=0.003$ ).<sup>248</sup> In adults with baseline proteinuria rate  $\geq 3$  g/24 h, proteinuria decreased from baseline by 35% and 55% at month 3 and month 36, respectively ( $p=0.002$ ), while proteinuria did not change in the placebo arm.<sup>247</sup> (Level 1+)

ARBs significantly decreased proteinuria compared with placebo (6 RCTs,  $N=2994$ , 5–12 month follow-up, ratio of means 0.66 (96% CI 0.63–0.69) or CCBs.<sup>242</sup> (Level 1+)

▷ Change in GFR

In adults with baseline proteinuria 1–2.9 g/24 h, there was NS difference in the mean GFR decline per month in the ramipril versus the placebo group.<sup>248</sup> In those with baseline proteinuria

$\geq 3$  g/24 h, the mean GFR decline was significantly slower in the ramipril group than the placebo group (0.53 vs. 0.88 ml/min per month,  $p=0.03$ ).<sup>247</sup> (Level 1+)

▷ Renoprotective effects of ACE inhibitors or ARBs compared to other antihypertensive agents

One meta-analysis<sup>238</sup> compared ACE inhibitors or ARBs against other antihypertensive drugs in adults with CKD. Trials of ACE inhibitors were not separated from trials of ARBs, thus confounding factors such as differences in drug tolerability could not be separated. Even with these caveats, this meta-analysis was interesting as it provided sensitivity analyses in diabetic and non-diabetic populations. (Level 1+)

One RCT conducted in hypertensive diabetic adults with CKD compared an ACE inhibitor with a calcium channel blocker.<sup>244</sup> One RCT conducted in hypertensive nondiabetic populations with CKD compared an ACE inhibitor with a beta blocker.<sup>222</sup> One RCT compared an ACE inhibitor with a thiazide diuretic conducted in a mixed diabetic/nondiabetic population with CKD.<sup>118</sup> (Level 1+)

▷ Risk of ESRD

In the meta-analysis, ACEI or ARB use was associated with a significant reduction in the occurrence of ESRD compared with other antihypertensive drugs (13 trials (N=37,089, RR 0.87, 95% CI 0.75–0.99,  $p=0.04$ ). When trials in diabetic and nondiabetic populations were separated from each other, there was NS difference between ACEI or ARB compared with other antihypertensive drugs<sup>238</sup>. (Level 1+)

In a nondiabetic population, there was no significant difference between ramipril and metoprolol in risk reduction for ESRD alone.<sup>222</sup> (Level 1+)

▷ Doubling of serum creatinine

There was NS reduction in the risk of doubling serum creatinine with ACEI or ARBs compared with other antihypertensive drugs (11 trials, N=3376).<sup>238</sup> (Level 1+)

▷ Progression from micro- to macroalbuminuria

In a hypertensive diabetic population with microalbuminuria, there was NS difference in progression to macroalbuminuria between people treated with ramipril (ACEI) versus lercanidipine (calcium channel blocker).<sup>244</sup> (Level 1+)

▷ Regression to normoalbuminuria

There was NS difference in regression to normoalbuminuria between people treated with ramipril (ACEI) versus lercanidipine (calcium channel blocker).<sup>244</sup> (Level 1+)

▷ Changes in proteinuria

ACEI or ARBs showed a small reduction in albuminuria compared with other antihypertensive treatments (44 trials, N=5266, mean difference  $-15.73$ , 95% CI  $-24.72$  to  $-6.74$ ,  $p=0.001$ ). However, there was significant interstudy heterogeneity ( $p<0.0001$ ) and small study bias

( $p=0.001$ ).<sup>238</sup> In participants with diabetic CKD, a small reduction in albuminuria was noted for ACEI or ARBs compared with other antihypertensive treatments (34 trials,  $N=4772$ , mean difference  $-12.68$ , 95% CI  $-21.68$  to  $-2.74$ ). In studies only including people without diabetes, ACEI or ARBs were associated with a significant reduction in albuminuria compared with other antihypertensive agents (8 trials,  $N=414$  mean difference  $-32.30$ , 95% CI  $-49.18$  to  $-15.42$ ).<sup>238</sup> (Level 1+)

In a hypertensive diabetic population with microalbuminuria ( $N=180$ ), there was NS difference between albuminuria in people treated with ramipril (ACEI) versus lercanidipine (calcium channel blocker).<sup>244</sup> (Level 1+)

ARBs significantly decreased proteinuria compared with calcium channel blockers (5 RCTs,  $N=1432$ , 5–12 month follow-up, ratio of means 0.62 (95% CI 0.55–0.70).<sup>242</sup> (Level 1+)

ACEI + ARB combination therapy significantly decreased proteinuria compared with ARB monotherapy (7 RCTs,  $N=362$ , ratio of means 0.75, 95% CI 0.61–0.92).<sup>242</sup> (Level 1+)

There was NS effect on proteinuria of ACEI versus ARB.<sup>242</sup> (Level 1+)

▷ Change in GFR

ACEI or ARBs had NS effect on GFR decline compared with other antihypertensive treatments.<sup>238</sup> (Level 1+)

By contrast, in a black nondiabetic hypertensive population, the mean GFR decline was significantly slower in the ramipril group (ACEI) than the metoprolol group (beta blocker) ( $1.81$  vs.  $2.42$  ml/min / $1.73$  m<sup>2</sup>,  $p=0.007$ ).<sup>222</sup> (Level 1+)

▷ Cardiovascular protection by ACE inhibitors or ARBs compared to placebo or no treatment: all-cause mortality

There was NS decrease in the risk of all-cause mortality with ACEI or ARB or combination ACEI + ARB compared with placebo/no treatment. In a subgroup analysis of studies which used ACEI at the maximum tolerable dose compared with placebo/no treatment, there was a significant decrease in the risk of all-cause mortality (5 studies,  $N=2034$ , RR 0.78, 95% CI 0.61–0.98).<sup>237</sup> (Level 1++)

In the REIN study, there was NS difference between ramipril and placebo for all-cause mortality. However, the study was underpowered for this outcome.<sup>247</sup> (Level 1+)

▷ Nonfatal MI and fatal coronary heart disease

There was no significant difference between ramipril and placebo for non-fatal cardiovascular events.<sup>247</sup> (Level 1+)

▷ Cardiovascular protection by ACE inhibitors or ARBs compared to other antihypertensive agents: all-cause mortality

There was NS difference between ramipril (ACEI) and metoprolol (beta blocker) for all-cause mortality.<sup>222</sup> (Level 1+)

▷ Nonfatal MI and fatal coronary heart disease

There was NS difference in the risk for MI or CHD between lisinopril (ACEI) or chlorthalidone (thiazide diuretic) for people with mild or moderate/severe renal impairment.<sup>118</sup> (Level 1+)

There was NS difference between ramipril (ACEI) and metoprolol (beta blocker) for cardiovascular events or cardiovascular mortality.<sup>222</sup> (Level 1+)

▷ Combined CVD: composite of nonfatal MI, fatal CHD, coronary revascularisation, hospitalised angina, stroke, fatal/hospitalised/treated non-hospitalised heart failure, peripheral arterial disease

People with mild (OR 1.09, 95% CI 1.02–1.17,  $p=0.015$ ,  $N=13,259$ ) or moderate/severe renal impairment (OR 1.12, 95% CI 1.01–1.25,  $p=0.038$ ,  $N=4146$ ) receiving lisinopril (ACEI) had a significantly increased chance of combined CVD than those receiving chlorthalidone (thiazide diuretic).<sup>118</sup> (Level 1+)

▷ Stroke

There was NS difference in the risk for stroke between lisinopril or chlorthalidone for those with mild or moderate/severe renal impairment.<sup>118</sup> (Level 1+)

▷ Heart failure

People with moderate/severe renal impairment receiving lisinopril had significantly increased odds of heart failure compared with those receiving chlorthalidone (OR 1.29, 95% CI 1.06–1.58,  $p=0.011$ ).<sup>118</sup> (Level 1+)

▷ Adverse events with ACE inhibitors or ARBs compared to placebo or no treatment: cough

ACEI use was associated with a significant increase in the risk of cough compared to placebo (10 studies,  $N=7087$ , RR 3.17, 95% CI 2.29–4.38). ARB or combination ACEI + ARB use were NS associated with cough compared with placebo.<sup>237</sup> (Level 1++)

▷ Hyperkalaemia

There was NS difference in the risk of hyperkalaemia for ACEI versus placebo/no treatment. There was a significant increase in the risk of hyperkalaemia with ARB compared with placebo (2 studies,  $N=2287$ , RR 5.41, 95% CI 1.87–15.65).<sup>237</sup> (Level 1+)

▷ Adverse events from ACE inhibitors or ARBs compared to other antihypertensive agents: cough

The proportion of patients reporting cough was significantly higher in those receiving ramipril (ACEI) than metoprolol (beta blocker) (54.9% vs. 41.5 %,  $p<0.05$ ).<sup>222</sup> (Level 1+)

▷ Hyperkalaemia

There was no hyperkalaemia in people treated with ramipril (ACEI) versus lercanidipine (calcium channel blocker).<sup>244</sup> (Level 1+)

There was no significant difference in hyperkalaemia incidence between ramipril and metoprolol.<sup>222</sup> (Level 1+)

▷ Reno-protective effects of ACEI or ARBs in non-diabetic patients with proteinuria of <1 g/day

There were two meta-analyses that used a database of patient-level data from 9 published and 2 unpublished RCTs comparing an ACEI with either placebo or active controls in people without diabetes.<sup>239,240</sup> In this database 40% of the included patients had proteinuria of <500 mg/day and 60% had a proteinuria of ≥500 mg/day.<sup>240</sup>

Three papers on one RCT (AASK trial) compared an ACEI with either a beta-blocker or a calcium channel blocker, in a population of African-American non-diabetic adults with CKD.<sup>222,249,250</sup> One third of the patients included in this trial had a baseline PCR >0.22 (a value corresponding approximately to the threshold of 300 mg/day for clinically significant proteinuria) and the remaining two thirds had a PCR of ≤0.22.<sup>250</sup>

▷ Risk of ESRD

The unadjusted relative risk of developing ESRD was in favour of the ACEI group, becoming significantly less than 1 at a baseline proteinuria of >1.0 g/day. For people with baseline proteinuria of <0.5 g/day, the relative risk of ESRD was 1.01 (95% CI 0.44–2.32), and 0.66 (95% CI 0.28–1.56) for patients with baseline proteinuria of 0.5–1.0 g/day.<sup>239</sup> (Level 1+)

There was significant interaction between baseline urine protein and ACEI therapy (interaction  $p=0.003$ ). The Kent et al. meta-analysis did not find any additional benefit of ACEI therapy among patients with proteinuria <500 mg/day, even amongst those at high risk for progression to ESRD. In people with urinary protein ≥500 mg/day, a substantial treatment effect was seen across all risk groups.<sup>240</sup> (Level 1+)

From the results of the AASK trial, the reduction in risk for developing the clinical outcomes of ESRD or a halving of GFR was 38% (95% CI 13–56%) for the ACEI vs. the calcium-channel blocker comparison group and among participants with a PCR >0.22, the reduction in risk of developing the clinical outcomes was 48% (95% CI 20–66%,  $p=0.003$ ).<sup>250</sup> Another analysis of these trial data found that the baseline level of proteinuria was an independent predictor of change in GFR and the risk of developing ESRD.<sup>249</sup> The risk of developing ESRD was found to be similar in all treatment groups: ACEI, calcium channel blocker and beta-blocker, although the magnitude of the change in GFR at 6 months was greater in the calcium channel blocker treatment group than the ACEI or beta-blocker treatment groups. (Level 1+)

▷ Proteinuria

One RCT<sup>250</sup> found a significantly greater reduction in proteinuria in the ACEI treated group compared with the control calcium channel blocker group both above and below a baseline PCR of 0.22. Among those with PCR <0.22, the rate at which participants developed PCR ≥0.22

was 56% (95% CI 37–69%) lower for the ACEI group than for the calcium-channel blocker group.<sup>250</sup> (Level 1+)

One of the meta-analyses found a significantly greater mean decrease in proteinuria in the ACEI group than in the control group of 0.46 g/day (95% CI 0.33–0.59 g/day).<sup>239</sup> (Level 1+)

#### ▷ Change in GFR

The analyses of the AASK trial all found the baseline proteinuria level to be a strong predictor of GFR decline, with higher baseline proteinuria levels associated with significantly greater declines in GFR.<sup>222,249,250</sup> The Agodoa et al. study reported a significantly greater GFR decline over three years in the ACEI treated group compared with the calcium channel blocker group in patients who had a baseline PCR of  $\leq 0.22$ . By contrast, the GFR decline was significantly slower in the ACEI group than the calcium channel blocker group in people who had a baseline PCR  $> 0.22$  (corresponding to proteinuria of  $> 300$  mg/day,  $p=0.006$ ). (Level 1+)

A second paper found that baseline proteinuria did not influence the comparison of ACEI to beta-blocker with respect to GFR change.<sup>222</sup> (Level 1+)

### 9.2.5 Health economics evidence statements

#### ▷ ACE inhibitors

Economic evaluations based on the DNCSG study have looked at the costs and effects in several healthcare settings:

- In the US, Rodby et al.<sup>253</sup> estimated an absolute direct cost saving of \$32,550 and indirect savings of \$84,390 per patient with type 1 diabetes over a lifetime; year of costing not stated. For type 2 diabetes, the direct cost savings totalled \$9900 per patient and \$45,730 for indirect costs. For type 1 diabetes patients, the estimated increase in life years was 0.2 over a 5 year period and 2.15 over a 31 year period with the use of captopril therapy compared with the placebo. The savings in dialysis years were 0.18 over 5 years and 0.72 over 31 years. For type 2 diabetes patients, the estimated average increase in life years over 12 years was 1.04, and 0.29 dialysis years.
- In Italy, Garattini et al.<sup>252</sup> used a 10-year horizon, calculated direct costs savings of L8,450,965 per patient (total direct cost savings of 28%, 1993 values). Captopril was also more effective than placebo by resulting 20.01 discounted dialysis-years avoided (DYA) per 100 patients.
- In the UK, Hendry et al.<sup>251</sup> estimated that discounted cost savings associated with ACE inhibitor treatment over 4 years for a cohort of 1000 patients would total £0.95 million (year of costing not stated). Life years saved over 4 years for a cohort of 1000 patients treated with an ACE inhibitor was estimated to be 195.

Economic evaluations based on the REIN study:

- In the US, Ruggenti et al.<sup>254</sup> estimated the difference in overall per year costs between ramipril and the control group was  $-\$2422$  in the GFR model and  $-\$4203$  in the events model. Both models constructed by the authors also predicted a reduced and delayed progression to ESRD and a prolonged patient survival in the ramipril group.



- In Germany, Schadlich et al.<sup>255</sup> estimated incremental cost-effectiveness ratios (ICERs) for ramipril of approximately –DM76,700 for 1 year, –DM80,660 for 2 years and –DM81,900 for 3 years.

Economic evaluations based on the AIPRI study:

- In the Netherlands, van Hout et al.<sup>256</sup> projected an overall savings of US\$4200 per patient over the 3-year period and when a 10-year time span was applied, similar results were shown with approximately US\$28,000 cost saving per patient comparing benazepril and placebo. It was also estimated that 51.2% of placebo patients and 63.3% of patients treated with benazepril would never require dialysis at any point.
- In the US, Hogan et al.<sup>257</sup> over 7 years of analysis, showed that patients randomised to antihypertensive treatment with concomitant benazepril therapy incurred on average lower medical costs than patients prescribed antihypertensive treatment without benazepril by US\$12,991 (1999 values) and obtained an additional 0.091 QALYs.

#### ▷ ARBs

Economic evaluations based on the IDNT study have looked at the costs and effects in several healthcare settings:

- Data for ESRD projections have been published for Belgium and France but not for the UK, USA or Canada. As the transition probabilities from the states progressing to ESRD were taken from the IDNT rather than country-specific data, the model produced the same projections for all countries. Over a 10-year time span the mean time to onset of ESRD was 8.23 years for irbesartan, 6.82 years for amlodipine and 6.88 years for the control. The mean cumulative incidence of ESRD over the 10-year time span was 45% for control, 49% for amlodipine and 36% for irbesartan. Although the UK and the USA (and Canada) were simulated using the same model and transition probabilities, it could be expected that the results might be the same for these countries.
- In summary, life expectancy was improved in the irbesartan group compared to amlodipine and control groups in all the papers reviewed. However, in the UK study by Palmer et al.<sup>258</sup> life expectancy projections were reported only in relative terms, comparing irbesartan to amlodipine and control. Treatment with irbesartan was projected to extend life further than that with either amlodipine or control.
- For cost analysis, irbesartan resulted in cost savings very early, usually within 2–3 years of treatment for all settings. In the UK, cost savings due to avoided or delayed ESRD were evident after 3 years compared to the amlodipine group and after 4 years compared to the control group.
- Based on the published evidences from various studies, it appears that irbesartan has a valuable role in reducing the huge clinical and economic burden associated with ESRD in patients with type 2 diabetes, hypertension and overt nephropathy.

Economic evaluations based on the RENAAL study have looked at the costs and effects in several healthcare settings. Treatment with losartan was associated with a reduced number of ESRD days by an average of 46.9 days per patient compared to the placebo and a net saving of:

- C\$6,554 in Canada<sup>265</sup>
- US\$7,058 in the USA<sup>263</sup>
- €5835 in France,<sup>266</sup>
- CHF6511 in Switzerland.<sup>264</sup>



Also, the UK study projected £6622 net savings and the mean number of life years saved were 0.44 years.<sup>262</sup>

An economic evaluation based on the IDNT and IRMA-2 study has looked at the costs and effects in the Canadian healthcare setting.<sup>267</sup> Treatment with irbesartan (early and late initiation of treatment) was compared to conventional care of people with hypertension and type 2 diabetes. The early irbesartan strategy was dominant over both the late irbesartan and conventional antihypertensive therapy strategies. Initiating irbesartan therapy during advanced overt nephropathy was dominant over conventional antihypertensive therapy. Late irbesartan treatment resulted in a mean of 0.16 life years gained and \$14,300 cost savings compared with conventional antihypertensive therapy. When irbesartan treatment is initiated early, there is a mean of 0.45 life-years gained per patient and a cost saving of \$54,100 compared with starting irbesartan treatment later. The early irbesartan strategy was found to be cost-saving by year 5 compared with conventional treatment strategy and year 6 compared with the late irbesartan treatment strategy.

These economic evaluations using different time horizons suggest ARBs versus conventional therapy is cost saving for type 2 diabetes nephropathy patients, mainly because of the high costs of dialysis and transplantation.

An economic evaluation based on a meta-analysis of randomised studies investigated the effects of ACEI/ARB therapy on the incidence of ESRD in patients with diabetic nephropathy in both a Greek and a US healthcare setting<sup>268</sup>. ACEI or ARB therapy was compared with alternative treatment regimens that did not include these drugs. For patients receiving ACEI or ARBs, the net cost saving was more than \$2000 per patient in both settings, but these results were not statistically significant and there was heterogeneity between trials. The study demonstrates that treating patients with diabetic nephropathy with agents that block the renin-angiotensin system as part of the treatment regimen is cost effective, resulting in a 23% reduction in the incidence of ESRD and in net cost savings for the insurance system organisations.

#### ▷ Conclusion

All of the economic evaluations found that these drugs confer both health gains and net cost savings compared with conventional (non-ACE inhibitor) therapy, ie they are dominant therapies.

### 9.2.6 From evidence to recommendations

When considering the evidence, the GDG noted that many of the studies combine people with types 1 and 2 diabetes and very few of the studies include older people. The GDG also noted that certain studies such as AASK were in defined populations and extrapolation of findings into the UK population should be viewed with caution.

When considering the evidence about the effects of ACEI/ARBs, the GDG noted that the beneficial effects appeared to be more closely related to the presence or absence of proteinuria rather than blood pressure control.

In order to confidently detect changes in the rate of decline of GFR the GDG agreed that studies must be of duration  $\geq 3$  years.

The GDG agreed that the evidence of benefit of ACEI/ARBs in people with diabetes and micro- or macroalbuminuria was strong.

RCTs and meta-analyses of RCTs that have analysed cardiovascular outcomes in patients with CKD/proteinuria treated with renin-angiotensin blockade have shown significant reduction in cardiovascular outcomes in both diabetic nephropathy and nondiabetic nephropathy. Benefits in terms of reduction in proteinuria and reduction in progression of CKD have also been shown. Renin-angiotensin blockade confers benefit in reducing adverse cardiovascular events in patients with proteinuria when compared with control therapy; a similar benefit is seen in reducing the risk for heart failure in diabetic nephropathy and total cardiovascular outcomes in nondiabetic nephropathy patients. These results might suggest that renin-angiotensin system blockade may be more beneficial in CKD patients with proteinuria.

On the basis of the evidence, the GDG agreed that the threshold level of proteinuria at which ACEI/ARBs should be recommended in people without diabetes or hypertension was an ACR  $\geq 70$  mg/mmol or PCR  $\geq 100$  mg/mmol (approximately equivalent to urinary protein excretion of  $\geq 1$  g/day). The threshold level of proteinuria at which ACEI/ARBs should be recommended in people without diabetes with hypertension was an ACR of  $\geq 30$  mg/mmol or PCR  $\geq 50$  mg/mmol (approximately equivalent to urinary protein excretion of  $\geq 0.5$  g/day).

It is possible that ACEI/ARB therapy in people with CKD without diabetes and with lower levels of proteinuria may also be beneficial but there is no evidence in this group at present. The GDG agreed that clinical trials examining the effects in these people were needed as a matter of urgency.

The GDG agreed that there was no evidence to suggest an advantage of one particular ACE inhibitor over and above another or of ARB over and above an ACE inhibitor. There was also no evidence to suggest increased effectiveness of combining an ACE inhibitor with an ARB over and above the maximum recommended dose of each individual drug. However, the health economic evidence suggested increased cost-effectiveness for ACEIs versus ARBs, indicating an ACE inhibitor should first be prescribed, switching across to an ARB if the ACEI is not tolerated due to non-renal side effects.

## 9.2.7 RECOMMENDATIONS

- R41 When implementing blockade of the renin-angiotensin system, start treatment with an ACE inhibitor first then move to an ARB if the ACE inhibitor is not tolerated.
- R42 Offer ACE inhibitors/ARBs to people with diabetes and ACR more than 2.5 mg/mmol (men) or more than 3.5 mg/mmol (women) irrespective of the presence of hypertension or CKD stage.
- R43 Offer ACE inhibitors/ARBs to non-diabetic people with CKD and hypertension and ACR 30 mg/mmol or more (approximately equivalent to PCR 50 mg/mmol or more, or urinary protein excretion of 0.5 g/24 h or more).
- R44 Offer ACE inhibitors/ARBs to non-diabetic people with CKD and ACR 70 mg/mmol or more (approximately equivalent to PCR 100 mg/mmol or more, or urinary protein excretion 1 g/24 h or more), irrespective of the presence of hypertension or cardiovascular disease.
- R45 Offer non-diabetic people with CKD and hypertension and ACR less than 30 mg/mmol (approximately equivalent to PCR less than 50 mg/mmol, or urinary protein excretion less than 0.5 g/24 h) a choice of antihypertensive treatment according to the NICE guidance on hypertension (NICE clinical guideline 34) to prevent or ameliorate progression of CKD.

- R46 When using ACE inhibitors/ARBs, titrate them to the maximum tolerated therapeutic dose before adding a second-line agent.\*
- R47 To improve concordance, inform people who are prescribed ACE inhibitors or ARB therapy about the importance of:
- achieving the optimal tolerated dose of ACE inhibitor/ARB, and
  - monitoring eGFR and serum potassium in achieving this safely.

## 9.3 Practicalities of treatment with ACEI/ARBs in people with CKD

### 9.3.1 Clinical introduction

Reviews conducted across disease areas and countries suggest that 30–50% of prescribed medication is not taken as recommended. Adverse effects, poor instructions and poor communication between healthcare professional and patient all contribute, particularly where the tablet burden is high as is frequently the case in people with CKD. Nevertheless, the benefits of ACEI/ARBs in prevention of progression of CKD in people with diabetes and proteinuric kidney disease are clear, as are their benefits to people with heart failure and reduced left ventricular function. Whilst rare complications such as anaphylaxis and angioedema are absolute contraindications to ACEI/ARB therapy, and symptomatic hypotension and severe aortic stenosis may also preclude their use, some contraindications may be more perceived than real.

Physicians may be reluctant to prescribe ACEI/ARBs in people with reduced GFR, hyperkalaemia, and non-critical renal artery stenosis. A rise in serum creatinine concentration and fall in GFR should be expected following introduction of treatment with ACEI/ARBs and hyperkalaemia is a known complication of treatment.<sup>269,270</sup> The incidence of hyperkalaemia with ACEI/ARB treatment is low in those with normal renal function but obviously increases as GFR falls. However, changes in serum creatinine and potassium concentrations to lesser or greater degrees variably influence physicians in their approach to continuing treatment. What one physician perceives as an intolerable fall in GFR or rise in potassium may not be interpreted as such by another. Furthermore, changes in GFR and potassium during treatment with ACEI/ARBs may be significantly influenced by a person's volume status, degree of sodium depletion, and concurrent medications. Many people 'intolerant' of ACEI/ARB treatment may be successfully treated once these factors have been addressed. Educating the healthcare community about these relative contraindications, and clearly stating what parameters should be monitored, how often these parameters should be monitored, and what levels are acceptable, could significantly affect outcomes in many people who might otherwise not be treated with ACEI/ARBs (and also help avoid unwanted complications).

Concordance with agreed treatment plans is of obvious importance and the overall medication burden faced by some patients is a consideration taken into account as part of good medical practice.

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\* There is insufficient evidence to recommend the routine use of spironolactone in addition to ACE inhibitor and ARB therapy to prevent or ameliorate progression of CKD.

- *In adults with CKD upon commencing an ACE inhibitor or ARB, what parameters of renal function should be monitored and how often? (What action threshold should be used for stopping treatments with an ACE inhibitor/ARB)?*

### 9.3.2 Methodology

There were several studies that showed that serum creatinine and potassium levels increase upon treatment with ACE inhibitors, however, analysis of the clinical impact of these changes (for example, occurrence of acute renal failure) was lacking, and thus, did not address the question.

One systematic review (12 studies, N=1102 randomised to ACE inhibitors, mean follow-up 3.2 years)<sup>269</sup> examined the changes in serum creatinine and potassium in people with >25% loss of renal function upon commencement of ACE inhibitors. The authors presented an algorithm for monitoring serum creatinine and potassium levels in people commencing ACE inhibitors.

### 9.3.3 Health economics methodology

No health economics papers were found to review.

### 9.3.4 Evidence statements

#### ▷ Serum creatinine levels

Initiation of ACE inhibitor or ARB is associated with a  $\leq 30\%$  increase in serum creatinine levels above baseline. This increase will occur within the first 2 weeks of treatment and usually stabilises within 2 to 4 weeks. In 11 studies (N not given), the GFR decline was slower at the end of the study than after initiation of ACEI therapy. (Level 1+)

In 2 long-term studies in diabetic CKD populations, (N=65) initiation of ACE inhibitor treatment resulted in a 3–9% reduction in GFR from baseline. After 6 years of therapy, the GFR returned to levels not significantly different from baseline within 1 month of stopping ACE inhibitor treatment. (Level 1+)

There were limited data on the benefit of ACE inhibitors in advanced disease (GFR <30 ml/min). (Level 1+)

#### ▷ Serum potassium levels

In people with diabetic or nondiabetic renal disease (serum creatinine levels 133–265  $\mu\text{mol/l}$ ), serum potassium levels increased by 0.4 to 0.6 mmol/l during ACE inhibitor or ARB treatment. Approximately 1 to 1.7% developed hyperkalaemia >6 mmol/l. (Level 1+)

The authors of this systematic review do not advise discontinuation of ACEI unless serum creatinine levels rise above 30% over baseline during the first 2 months after commencement of ACEI therapy or serum potassium levels >5.6 mmol/l develop.

### 9.3.5 From evidence to recommendation

This is an important topic where a balance must be struck between ensuring that people receive optimal therapy with ACEI/ARBs but do not suffer adverse effects from using these drugs. The two main concerns about using ACEI/ARBs are the development of hyperkalaemia and worsening of underlying kidney function, usually as a result of their use in people with undiagnosed renovascular disease.

There was little evidence to guide the formulation of recommendations.

From a practical point of view it was noted that delays in transporting blood samples from a GP surgery to the laboratory can make potassium readings artificially high and could lead to unnecessary dose reductions or cessation of ACEI/ARB therapy.

The GDG agreed that ACEI/ARBs should not normally be started if the pre-treatment serum potassium concentration is significantly above the normal reference range, particularly by non-specialists. This will vary from laboratory to laboratory but the upper limit is typically 5.0 mmol/l.

The GDG recommended that if the serum potassium rises above 6.0 mmol/l after starting ACEI/ARB therapy or after increasing the dose other drugs known to cause hyperkalaemia should be stopped if possible. If this is not possible or if the person is not receiving other drugs, the ACEI/ARB should be stopped.

The GDG noted that the Bakris study suggested that there was often a small increment in baseline serum creatinine level of up to 30%, equivalent to a stepwise reduction in eGFR of up to 25%, on starting ACEI/ARB therapy but recommended that as long as the change does not exceed this there was no need to stop the ACEI/ARB. If there was a sustained increment in serum creatinine of more than 30%, or a reduction of more than 25% in eGFR, the GDG recommended that the ACEI/ARB dose should be halved and that additional anti-hypertensive drugs should be added if needed to maintain blood pressure control.

### 9.3.6 RECOMMENDATIONS

- R48 In people with CKD, measure serum potassium concentrations and estimate the GFR before starting ACEI/ARB therapy. Repeat these measurements between 1 and 2 weeks after starting ACEI/ARB therapy and after each dose increase.
- R49 ACEI/ARB therapy should not normally be started if the pre-treatment serum potassium concentration is significantly above the normal reference range (typically >5.0 mmol/l).
- R50 When hyperkalaemia precludes use of ACEI/ARBs, assessment, investigation and treatment of other factors known to promote hyperkalaemia should be undertaken and the serum potassium concentration re-checked .
- R51 Concurrent prescription of drugs known to promote hyperkalaemia is not a contraindication to the use of ACEI/ARBs but be aware that more frequent monitoring of serum potassium concentration may be required.
- R52 Stop ACEI/ARB therapy if the serum potassium concentration rises to above 6.0 mmol/l and other drugs known to promote hyperkalaemia have been discontinued.

- R53 Following the introduction or dose increase of ACEI/ARB, do not modify the dose if either the GFR decrease from pre-treatment baseline is <25% or the plasma creatinine increase from baseline is <30%.
- R54 If there is a fall in eGFR or rise in plasma creatinine after starting or increasing the dose of ACEI/ARB, but it is less than 25% (eGFR) or 30% (serum creatinine) of baseline, the test should be repeated in a further 1–2 weeks. Do not modify the ACE/ARB dose if the change in eGFR <25% or change in plasma creatinine is <30%.
- R55 If the eGFR change is  $\geq 25\%$  or change in plasma creatinine is  $\geq 30\%$ :
- investigate other causes of a deterioration in renal function such as volume depletion or concurrent medication (e.g. non-steroidal anti-inflammatory drugs (NSAIDS))
  - if no other cause for the deterioration in renal function is found, stop the ACEI/ARB therapy or reduce the dose to a previously tolerated lower dose, and add an alternative antihypertensive medication if required.

## 9.4 Considerations of age in prescription of ACEI/ARB therapy

### 9.4.1 Clinical introduction

Although there is much clinical evidence to support the use of ACE inhibitors and ARBs to delay progression of chronic kidney disease, few studies include older people with CKD in the study population. The older population are also more prone to reduced volume status and sodium depletion, have greater comorbidity and are more likely to be taking concurrent medications making them potentially more susceptible to the adverse effects of ACEI/ARBs. Indeed, there is a perception that ACEI or ARB treatment puts the older person at greater risk for adverse events such as acute kidney failure/injury, hypotension, falls, and reduced quality of life. Few studies have described the progression of CKD in older community based individuals, and none have confirmed the widely held belief that low GFR is associated with a rapid progression of kidney dysfunction in older people.<sup>161,271</sup> Should we reconsider the role of renin-angiotensin system blockade to prevent progression of CKD in the context of the older population in which the burden of overt proteinuric nephropathies is believed to be lower than in other populations?

Is there a greater potential risk of further deterioration of renal function because of the high prevalence of renal stenotic atherosclerotic lesions and very frequent concomitant use of diuretics and nonsteroidal anti-inflammatory drugs?

### 9.4.2 Methodology

An open-label RCT conducted in Japanese adults with nondiabetic, hypertensive renal disease (N=141, age range 60–75 years, mean age 67, mean follow-up 3.1 years) compared the effect of an ARB (candesartan) with conventional antihypertensive treatment on cardiovascular events in those with and without a previous history of cardiovascular disease.<sup>272</sup> This small, open-label RCT was terminated after 3 years, due to the increasing prevalence of ARBs as physicians were switching from conventional treatment to ARBs.

One post-hoc analysis of the RENAAL trial (N=1513, mean follow-up 3.4 years) examined the effect of increasing age on the efficacy and safety of losartan versus placebo (conventional antihypertensive treatment).<sup>273</sup> The trial participants had type 2 diabetes with nephropathy and were stratified by age:  $\leq 57$  years (N=505), age  $>57$  to 65 years (N=587), and age  $>65$  years (N=421). Although this study lacked the statistical power necessary to assess efficacy of losartan treatment in each of the three increasing age ranges, it did analyse the interaction between age and losartan treatment for the outcomes of death, hyperkalaemia, and adverse events such as acute renal failure. The oldest participant in the study was 74 years old, and thus this study lacks data on very elderly people.

A retrospective cohort analysis of people  $>65$  years of age was conducted to investigate whether receiving an ACE inhibitor at hospital discharge following an acute myocardial infarction increased one year survival rates in people with poor renal function (serum creatinine  $>3$  g/dl, N=1582) compared with people with better renal function (serum creatinine  $\leq 3$  mg/dl, N=19,320).<sup>274</sup> This study was limited by lacking data on protein excretion rate and the use of serum creatinine alone as an indicator of renal function.

### 9.4.3 Health economics methodology

No health economics papers were found to review.

### 9.4.4 Evidence statements

#### ▷ All-cause mortality

The treatment effect of losartan on risk of death in a population with diabetic nephropathy did not significantly differ by age ( $p=0.695$  adjusted for treatment group, region, proteinuria, albumin, creatinine, haemoglobin). In all three age groups (people  $\leq 57$  years, age  $>57$  to 65 years, or  $>65$  years) there was NS difference in risk of death between losartan and placebo.<sup>273</sup> (Level 2+)

In a nondiabetic Japanese population with renal disease (N=141), no deaths occurred in the people without a past history of cardiovascular disease (treated with candesartan or conventional therapy).

- Four deaths occurred in the group with a past history of CVD treated with candesartan.
- Four deaths occurred in the group with a past history of CVD treated with conventional therapy (p value not stated).<sup>272</sup> (Level 1+)

#### ▷ Stroke

In people with nondiabetic, hypertensive renal disease, with or without a previous history of CVD, there was NS difference between candesartan and conventional treatment for the incidence of stroke.<sup>272</sup> (Level 1+)

#### ▷ Myocardial infarction (MI)

In people with nondiabetic, hypertensive renal disease, with or without a previous history of CVD, there was NS difference between candesartan and conventional treatment for the incidence of MI.<sup>272</sup> (Level 1+)



▷ Congestive heart failure

In people with nondiabetic, hypertensive renal disease and a previous history of CVD, candesartan treatment (4/33) significantly decreased the incidence of congestive heart failure compared with conventional treatment (13/38,  $p < 0.05$ ). In people without a previous history of CVD, there was NS difference between candesartan and conventional treatment for the incidence of congestive heart failure.<sup>272</sup> (Level 1+)

▷ One-year survival following acute MI

The receipt of an ACE inhibitor at hospital discharge was associated with a 37% increase in 1-year survival for patients with poor renal function (serum creatinine  $> 3$  mg/dl,  $N = 1582$ , mean age 72, HR 0.63, 95% CI 0.48–0.84,  $p$  value not stated). The receipt of an ACE inhibitor at hospital discharge was associated with a 16% increase in 1-year survival for patients with better renal function (serum creatinine  $\leq 3$  mg/dl,  $N = 19,320$ , mean age 75, HR 0.84, 95% CI 0.77–0.92,  $p$  value not stated).<sup>274</sup> (Level 2+)

▷ Adverse events (acute renal failure or ESRD)

Older patients were no more susceptible to experiencing adverse events from losartan than younger people. In all three age groups (people  $\leq 57$  years, age 57–65 years, or  $> 65$  years) there was NS difference in incidence of adverse events between losartan or placebo.<sup>273</sup> (Level 2+)

▷ Hyperkalaemia

Losartan was associated with a greater rate of hyperkalaemia. This effect was present in all age ranges. Thus, increasing age did not significantly increase the risk of hyperkalaemia from losartan.<sup>273</sup> (Level 2+)

#### 9.4.5 From evidence to recommendations

It was noted that in the observational studies those with better renal function were more likely to receive ACEI/ARBs (60% versus only 30% in those with poor renal function) and this has the potential to bias the interpretation of these studies.

None of the people in the studies were over 75 years of age. Thus there is a lack of evidence for changes in the risk/benefit of ACEI/ARB therapy in people over this age; however, the GDG felt that in the absence of evidence of harm people above this age should not be denied the benefits of ACEI/ARB therapy.

#### 9.4.6 RECOMMENDATION

- R56 Where indicated, the use of ACEI/ARBs should not be influenced by a person's age as there is no evidence that their appropriate use in older people is associated with a greater risk of adverse effects.



## 9.5 The role of aldosterone antagonism in people with CKD

### 9.5.1 Clinical introduction

Aldosterone is thought to contribute to progressive renal disease. Studies in experimental rat models showed that aldosterone may contribute to the progression of kidney disease and antagonists of aldosterone may reduce proteinuria and retard the progression of kidney disease independently of effects on blood pressure.<sup>275,276</sup> Plasma aldosterone level was shown to correlate with the rate of progression of kidney disease and the increase in rate of kidney disease progression caused by high protein intake was attributable in part to aldosterone.<sup>277–279</sup> Although ACEI/ARBs inhibit the renin-angiotensin system, they do not efficiently decrease plasma aldosterone. Haemodynamic and humoral actions of aldosterone have important clinical implications for the pathogenesis of progressive renal disease and consequently may influence future antihypertensive strategies. Although ACEI/ARBs are effective in preventing disease progression, there may be additional benefit from concurrent aldosterone-receptor blockade.<sup>280</sup> To date there has been limited research into the use of spironolactone, an aldosterone receptor antagonist, to reduce aldosterone escape during treatment with ACEI/ARBs in adults with CKD.

- *In adults with proteinuric or non-proteinuric CKD, does treatment with (a) spironolactone alone, (b) combinations of spironolactone and ACE inhibitors, (c) combinations of spironolactone and ARBs, or (d) combinations of spironolactone and ACE inhibitors and ARBs decrease mortality and reduce the risk of progression of CKD compared with placebo or other antihypertensive agents?*

### 9.5.2 Methodological introduction

There were no studies in a CKD population that compared spironolactone with alpha- or beta-blockers, calcium channel blockers, or diuretics. There were no studies that investigated spironolactone in adults with non-proteinuric CKD.

Three double-blind RCTs examined the effects of spironolactone in addition to treatment with ACE inhibitors and/or ARBs in adults with diabetic nephropathy<sup>281,282</sup> and in a mixed population of diabetic and nondiabetic nephropathy.<sup>283</sup> One open label randomised study compared the addition of spironolactone to conventional ACEI and ARB therapy with conventional therapy alone in nondiabetic adults with proteinuric CKD.<sup>284</sup> One study that compared spironolactone with cilazapril (ACEI) in a diabetic population with proteinuric nephropathy was excluded because it lacked intention-to-treat analysis, and concealment and blinding were not stated.<sup>285</sup>

The results of these studies should be viewed with caution as the sample sizes were small (N=21–165) and duration of these trials (2 months–1 year) was short. None of the studies reported cardiovascular outcomes, mortality, or progression to ESRD.

### 9.5.3 Health economics methodology

No health economics papers were found to review.

### 9.5.4 Evidence statements

▷ Renoprotective effects of spironolactone: reduction in proteinuria or albuminuria

In two RCTs conducted in diabetic adults with nephropathy concomitantly treated with ACE inhibitors or ARBs, spironolactone significantly reduced albuminuria compared with placebo.<sup>281,282</sup> (Level 1+)

In a nondiabetic CKD population, addition of spironolactone to ACEI or ARB therapy resulted in a significant reduction in proteinuria. The reduction in proteinuria was significantly greater in people with GFR <60 ml/min/1.73 m<sup>2</sup> than in people with GFR >60 ml/min /1.73 m<sup>2</sup>. By contrast, proteinuria did not change from baseline in people treated with ACEI or ARB therapy alone.<sup>284</sup> (Level 1+)

In an RCT conducted in a mixed diabetic/nondiabetic mixed CKD population, the reduction in 24-hour proteinuria was significantly greater in either the ramipril + spironolactone group or in the ramipril + irbesartan + spironolactone group, compared to the ramipril group. Compared with the ramipril + irbesartan group, there was a greater reduction in 24-hour proteinuria in the ramipril + irbesartan + spironolactone group. There was NS difference in proteinuria reduction between ramipril + spironolactone group and ramipril + irbesartan + spironolactone groups. The spironolactone-induced decrease in proteinuria was similar regardless of presence of diabetes.<sup>283</sup> (Level 1+)

▷ Change in GFR

In three studies,<sup>281,283,284</sup> there was no significant difference in GFR decline in patients receiving spironolactone with ACEI or ARB therapy compared to the control (placebo or no treatment). (Level 1+)

By contrast, van den Meiracker et al. reported that spironolactone significantly decreased the eGFR compared to placebo. (Level 1+)

▷ Toxicity of spironolactone: hyperkalaemia

Treatment with spironolactone in addition to ACEI and ARB therapy seemed to be associated with a higher incidence of hyperkalaemia, although these studies were probably too underpowered to detect a significant difference between treatment groups.

Four people receiving spironolactone + conventional therapy and two people receiving conventional therapy alone developed hyperkalaemia (no p value stated).<sup>284</sup> (Level 1+)

Three patients receiving spironolactone developed hyperkalaemia.<sup>283</sup> (Level 1+)

One patient treated with spironolactone was excluded from the study due to hyperkalaemia.<sup>281</sup> (Level 1+)

Despite decreasing the dose of spironolactone from 50–25 mg/d, five patients treated with spironolactone were excluded from the study due to hyperkalaemia compared to only one patient in the placebo group (no p value stated).<sup>282</sup> (Level 1+)

### 9.5.5 From evidence to recommendation

The GDG noted that all the evidence on this topic comes from short duration trials that are small and underpowered. Very few of the trials reported on relevant outcomes such as cardiovascular events and none reported on progression of CKD.

Because of the limitations of trial design and their duration, the GDG agreed that a recommendation about the use of spironolactone should not be made based on the evidence regarding effects on proteinuria. Reference is made in a footnote to the recommendations on ACE inhibitors/ARBs.

The GDG noted that hyperkalaemia was more common in people treated with spironolactone.

# 10 Reducing cardiovascular disease

## 10.1 Statin therapy and reduction in proteinuria

### 10.1.1 Clinical introduction

Animal models of hyperlipidaemia produced by cholesterol-rich diets promote progression of renal disease. Epidemiological studies suggest that dyslipidemia is a risk factor for CKD initiation, and that lipid lowering may slow disease progression. Elevated cholesterol and triglyceride levels are associated with a more rapid decline in kidney function. Possible mechanisms include accelerated atherosclerosis of arteries within the kidney and damaging effects of lipids on mesangial cells. Hyperlipidaemia may activate mesangial cells (which have low-density lipoprotein (LDL) receptors), leading to stimulation of mesangial cell proliferation and to increased production of macrophage chemotactic factors, accumulation of extracellular matrix, and reactive oxygen species. Studies in animal models show that reducing lipid levels with a drug such as lovastatin slows the rate of progressive injury.<sup>286–288</sup> Furthermore, the beneficial effect of lipid lowering may be additive to that of lowering the blood pressure in at least some models of chronic renal disease (see section 9). Treatment may reduce renal injury by decreasing albuminuria and reducing mesangial matrix accumulation and mesangial hypercellularity.

- *In adults with CKD and proteinuria, do statins decrease proteinuria and decrease the risk of progression of CKD compared with other treatments or placebo?*

### 10.1.2 Methodology

There were no trials of statins versus other antilipemic agents such as fibrates or fish oils. No trials addressed clinically relevant markers of renal progression such as doubling of serum creatinine or time to ESRD.

Three meta-analyses assessed the efficacy of statins compared to placebo in decreasing the risk of renal disease progression in adults with CKD.

The meta-analysis by Douglas et al. (15 RCTs, N=1384, mean follow-up 6 months)<sup>289</sup> investigated the effect of statins on changes in proteinuria. Study heterogeneity was mostly avoided by stratifying the data by baseline levels of proteinuria. The limitations with this meta-analysis were that the individual studies were few, small and methodologically limited.

The meta-analysis by Sandhu et al. (27 RCTs, N=39704, mean follow-up 1 year)<sup>290</sup> measured the effect of statins compared to control on the rate of change of GFR and on changes in proteinuria in populations with diabetic or hypertensive renal disease or in people with glomerulonephritis. While this meta-analysis included the studies in the Douglas et al. meta-analysis, the between-study heterogeneity was very high. The pooled analysis of changes in proteinuria or albuminuria was particularly marred by significant heterogeneity. However, the analysis of changes in GFR was an important outcome, and was not reported in the Douglas et al. 2006 meta-analysis.

A systematic review assessed cardiovascular outcomes, changes in GFR and 24-hour proteinuria in people with CKD randomised to statins or placebo/no treatment (50 studies, N=30,144,

follow-up ranged from 2–60 months).<sup>291</sup> Subgroup analysis was performed in people with pre-dialysis CKD (26 studies), people undergoing dialysis (11 studies) and renal transplant recipients (17 studies).

The effects of statins versus placebo on renal disease progression in adults with varying severity and different causes of CKD are summarised in Table 10.1, at the end of the evidence statements.

### 10.1.3 Health economics methodology

There were no health economics papers found to review.

### 10.1.4 Evidence statements

#### ▷ Statins versus placebo

Refer to Table 10.1 for a summary of studies comparing statins with placebo.

#### ▷ Changes in GFR

Overall, statins did not significantly slow decline in GFR. There was significant heterogeneity in the meta-analyses for this outcome.<sup>290,291</sup> (Level 1+)

#### ▷ Change in proteinuria

Statins significantly reduced proteinuria compared to placebo in people with CKD and baseline proteinuria 30–299 mg/day.<sup>289</sup> (Level 1++)

Statins significantly reduced proteinuria compared with placebo; however there was significant heterogeneity in this analysis.<sup>291</sup> (Level 1++)

By contrast, the meta-analysis of Sandhu et al. showed NS effect of statins on proteinuria. However, there was significant between-study heterogeneity in this analysis. (Level 1+)

**Table 10.1 Effect of statins versus placebo on changes in GFR and proteinuria in adults with CKD**

Study	CKD population	Change in GFR	Change in proteinuria
290	Glomerulonephritis (N=222, 7 studies)	NS*	
	Hypertensive CKD (N=212, 4 studies),	NS*	NS*
	Diabetic CKD (N=122, 6 studies)	NS	
289	Baseline proteinuria 30–299 mg/day (N=181, 6 studies)	–	WMD –48% (95% CI –71 to –25)
	Baseline proteinuria > 300 mg/day (N=275, 6 studies)	–	WMD –47% (95% CI –67 to –26)*
291	Pre-dialysis (CKD stages 1–4) (N=548, 11 studies)	NS *	–
	Pre-dialysis (CKD stages 1–4) (N=311, 6 studies)	–	WMD –0.73 g/24 h (95% CI –0.95 to –0.52)*

\*Significant heterogeneity in this analysis.

### 10.1.5 From evidence to recommendations

The evidence considered shows that people prescribed statins for secondary prevention of cardiovascular events may accrue additional benefits from statin therapy.

The GDG noted that the data assessing the impact of statins on proteinuria were derived largely from studies involving patients with (or at high risk of) overt cardiovascular disease. The Strippoli meta-analysis showed that in people with CKD not on dialysis statins significantly reduced all-cause mortality, cardiovascular mortality, non-fatal cardiovascular events and 24-hour proteinuria. However there was significant heterogeneity in the 24-hour urinary protein analysis. There was no significant benefit from statin therapy on change in GFR but that analysis was also subject to significant heterogeneity.

There was therefore insufficient evidence to support a role for statin therapy on either reduction of proteinuria or progression of CKD. This is noted in a footnote to the statins recommendations in the following section.

## 10.2 Lipid lowering in people with CKD

### 10.2.1 Clinical introduction

The benefits of lipid-lowering therapy in people with pre-existing cardiovascular disease are clear and very well described.<sup>292–294</sup> Although people with CKD are at increased risk of CVD and might reasonably be expected also to benefit from the effects of lipid lowering therapy, the published randomised controlled trials have largely excluded people with most types of kidney disease. Furthermore, the expected positive association between blood cholesterol levels and cardiovascular outcomes were not observed in studies conducted in people receiving haemodialysis.<sup>295</sup> Studies in animal models suggest that treatment of dyslipidaemia should have beneficial effects on progression of CKD.<sup>296–298</sup> A systematic review pooling the literature from all human studies that were conducted before 2000 (n=404 participants) suggested that similar benefits might accrue in humans. The studies included evaluated multiple classes of medications, including statins, fibric acid derivatives, and probucol.<sup>299</sup>

The spectrum of dyslipidaemia in CKD is distinct from the general population and varies with stage of CKD and presence of diabetes and/or nephrotic syndrome. Plasma triglycerides start to increase early in CKD and show the highest concentrations in nephrotic syndrome and people receiving dialysis. HDL-cholesterol concentrations are generally reduced compared with people without CKD and the distribution of subfractions is different, leading to impairment in reverse cholesterol transport and promoting atherosclerosis. Although elevated plasma LDL-cholesterol is a feature of nephrotic syndrome, it is not typical of advanced CKD but, like HDL-cholesterol, there are qualitative changes in the LDL subfractions with an increase in those that are highly atherogenic. Lipoprotein (a), a risk factor for CVD in the general population is also influenced by CKD. Levels rise early in CKD and are mostly influenced by the degree of proteinuria. The hallmarks of uraemic dyslipidaemia are hypertriglyceridaemia, increased remnant lipoproteins, reduced HDL-cholesterol, increased atherogenic sub-types of LDL-cholesterol, increased lipoprotein (a) and increased apolipoprotein A-IV.<sup>300</sup>

The optimal targets for plasma lipids in people with CKD are not yet known. Statins are effective at lowering total and low-density lipoprotein (LDL)-cholesterol and fibrates reduce plasma triglyceride concentrations and raise HDL-cholesterol. Nicotinic acid appears most suited to the dyslipidaemia of CKD because it raises HDL-cholesterol, lowers lipoprotein (a), reduces triglycerides and shifts the LDL-cholesterol fraction to less atherogenic particles. SIGN guidelines recommend treatment with statins for people with stage 1–3 CKD and a predicted 10 year cardiovascular risk of  $\geq 20\%$ , irrespective of baseline lipid parameters. The CARI guidelines suggest that statins may retard progression of renal failure but make no specific recommendation. The UK CKD guidelines recommend that people with CKD and coronary disease should be treated according to existing guidelines and those who do not have evidence of coronary disease should be treated according to their estimated risk, using the Joint British Societies Guidelines (recognising that these guidelines specifically exclude CKD from their remit).

- *In adults with CKD and dyslipidaemia, do lipid lowering agents (statins, fibrates, fish oils) decrease cardiovascular disease risk and all cause mortality compared with placebo or each other?*

## 10.2.2 Methodology

Hydroxymethyl glutaryl CoA reductase inhibitors (statins), fibric acid derivatives (fibrates), and omega-3 fatty acids (fish oils) are antilipemic therapies that may reduce the risk of cardiovascular disease by decreasing triglyceride or LDL cholesterol levels and increasing HDL cholesterol levels. There were very few trials of antilipemic therapies in non-dialysis CKD populations. There were no head-to-head studies of the three antilipemic therapies in adults with CKD. There were no studies that examined the efficacy of omega-3 fatty acids to reduce the risk of cardiovascular disease in adults with CKD.

A post-hoc analysis of the Veterans' Affairs High-Density Lipoprotein Intervention RCT (VA-HIT: N=1046, follow-up 5.3 years),<sup>301</sup> compared a fibrate (gemfibrozil) to placebo for cardiovascular outcomes in men with a history of coronary heart disease and creatinine clearance  $< 75$  ml/min. This study is limited by a lack of baseline proteinuria data, all the participants were men and the population did not include people with severe renal disease. Creatinine clearance overestimates GFR and it is likely that the participants identified as having chronic renal insufficiency could have had lower renal function than estimated. Also, the creatinine concentrations were not standardised between centres or calibrated against a reference standard.

A systematic review assessed cardiovascular outcomes, changes in GFR and 24-hour proteinuria in people with CKD randomised to statins or placebo/no treatment (50 studies, N=30,144, follow-up ranged from 2–60 months).<sup>291</sup> Subgroup analysis was performed in people with pre-dialysis CKD (26 studies), people undergoing dialysis (11 studies) and renal transplant recipients (17 studies).

A post-hoc analysis of the Scandinavian Simvastatin Survival RCT (4S: N=2314, follow-up 5.5 years, mean age 60 years) compared cardiovascular outcomes in people with coronary heart disease, raised cholesterol, and GFR  $< 60$  ml/min/1.73 m<sup>2</sup> randomised to placebo or simvastatin. This study lacked proteinuria data and cause of CKD. Estimated, rather than measured, GFR was used to assess renal function.<sup>302</sup>

### 10.2.3 Health economics methodology

There were no health economics papers found to review.

### 10.2.4 Evidence statements

- ▷ Fibrates versus placebo: Primary endpoint: nonfatal MI or death from coronary disease (including fatal MI, sudden death, death during a coronary intervention, death from other coronary causes)

In men with CrCl  $\leq$ 75 ml/min (N=1046), gemfibrozil significantly reduced the risk of nonfatal MI or death from coronary disease compared to treatment with placebo (adjusted HR 0.74, 95% CI 0.56–0.96,  $p=0.02$ , NNT =16).<sup>301</sup> (Level 1+)

- ▷ Secondary endpoints: major cardiovascular events (fatal coronary disease, nonfatal MI, or stroke)

In men with CrCl  $\leq$ 75 ml/min (N=1046), gemfibrozil significantly reduced the risk of major cardiovascular events compared with placebo (adjusted HR 0.75, 95% CI 0.59–0.96,  $p=0.02$ ).<sup>301</sup> (Level 1+)

There was NS difference between placebo and gemfibrozil<sup>301</sup> for risk of:

- non-fatal myocardial infarction
- all-cause mortality
- stroke
- adverse events: myositis. (Level 1+)

- ▷ Adverse events: creatinine  $>0.5$  mg/dl higher from baseline

The incidence of sustained elevations in serum creatinine ( $>0.5$  mg/dl higher from baseline) was significantly higher among gemfibrozil recipients compared with placebo (5.9% vs. 2.8%,  $p=0.02$ ).<sup>301</sup> (Level 1+)

- ▷ Adverse events: rhabdomyolysis

There were no cases of rhabdomyolysis in either the placebo or gemfibrozil group.<sup>301</sup> (Level 1+)

- ▷ Statins versus placebo

Refer to Table 10.2 for a summary of the efficacy of statins versus placebo in people with CKD.

Compared with placebo, statins significantly reduced the risk of:

- all-cause mortality<sup>291,302</sup> (Level 1+)
- cardiovascular mortality<sup>291</sup> (Level 1++)
- non-fatal cardiovascular events<sup>291</sup> (Level 1++)
- major coronary events (coronary mortality, non-fatal acute MI, resuscitated cardiac arrest, definite silent MI).<sup>302</sup> (Level 1+)



There were NS differences between statins and placebo for stroke.<sup>302</sup> (Level 1+)

▷ Adverse events

Rates of discontinuation of study drug therapy because of adverse events were similar in simvastatin and placebo groups.<sup>302</sup> (Level 1+)

**Table 10.2 Effect of statins versus placebo on cardiovascular outcomes in adults with CKD**

Study	Population	Outcome	N total participants	Effect size	Heterogeneity (% I <sup>2</sup> )
291	Pre-dialysis CKD (Stage 1–4)	All cause mortality	18,781	RR 0.81 (95% CI 0.74 to 0.89), p<0.001, mostly driven by Pravastatin Pooling Project	0 NS
302	GFR <75 ml/min/1.73 m <sup>2</sup> with coronary heart disease, raised low-density lipoprotein cholesterol (LDL-C)	All cause mortality	2,314	HR 0.69 (95% CI 0.54–0.89)	Not applicable
302	GFR <60 ml/min/1.73m <sup>2</sup> with coronary heart disease, raised LDL-C	All cause mortality	508	HR 1.232 (1.024–1.117) [sic] NS [sic]	Not applicable
291	Pre-dialysis CKD (stage 1–4)	Cardiovascular mortality	18,085	RR 0.80 (95% CI 0.70 to 0.90), p<0.001, mostly driven by Pravastatin Pooling Project	0 NS
291	Pre-dialysis CKD (stage 1–4)	Non-fatal cardiovascular events	19,363	HR 0.851 (0.921–1.128) [sic] NS	30.7 NS
302	GFR <60 ml/min/1.73 m <sup>2</sup> with coronary heart disease, raised LDL-C	Major coronary events	508	HR 0.65 (95% CI 0.46–0.92)	Not applicable
302	GFR <75 ml/min/1.73 m <sup>2</sup> with coronary heart disease, raised LDL-C	Major coronary events	2,314	HR 0.67 (95% CI 0.56–0.79)	Not applicable

### 10.2.5 From evidence to recommendations

The main reason for examining the evidence in this area was the anecdotal observation that in people on dialysis, statins do not appear to offer the benefits seen in other groups. This may be due to the fact that there is reduced long-term survival in this particular group of people and that this may mask any beneficial effect of statins.

The GDG discussed whether CKD itself should be considered a risk factor for cardiovascular disease and should influence the use of statins as primary preventative therapy. In the absence of evidence that CKD is a causal risk factor for cardiovascular disease it was decided that the GDG should recommend that the use of statins for primary prevention of cardiovascular disease should be determined using existing risk tables bearing in mind the fact that a different

table should be used for people with diabetes.<sup>29</sup> It was further recommended that studies are needed to assess the effect of CKD on cardiovascular risk.

On the basis of the evidence of effect in secondary prevention of cardiovascular disease the GDG recommended that lipid lowering therapy should be prescribed in people who have experienced a cardiovascular event. The evidence showed that there was benefit from statins in all people not just those with elevated lipid concentrations.

The lack of statistically significant differences observed in subgroup analyses may be due to the small numbers of people in these groups and the consequent lack of statistical power.

The GDG noted that there is a large international multicentre trial in progress which addresses the effects of lipid lowering with simvastatin and ezetimibe on outcomes in people with CKD without established coronary heart disease.

The GDG concluded that there was no evidence that statins had detrimental effects on kidney function in people with CKD, but it was noted that there appeared to be an increase in creatinine concentrations in people prescribed fibrates.

## 10.2.6 RECOMMENDATIONS

- R57 The use of statin therapy for the primary prevention\* of CVD in people with CKD should not differ from its use in people without CKD and should be based on existing risk tables for people with and without diabetes. It should be understood that the Framingham risk tables significantly underestimate risk in people with CKD.†
- R58 Offer statins to people with CKD for the secondary prevention of CVD irrespective of baseline lipid values

## 10.3 Antiplatelet therapy and anticoagulation in people with CKD

### 10.3.1 Clinical introduction

People with CKD paradoxically have both thrombotic and bleeding tendencies. Bleeding symptoms are usually mild, correlate best with prolonged bleeding times, and tend to become more prevalent with increasing severity of CKD.<sup>303–305</sup> Factors involved include anaemia, platelet defects, abnormal function of von Willebrand factor, uraemic toxins and endothelial factors, such as increased production of nitric oxide.<sup>306–309</sup> The greater risk of thrombotic events has been attributed to higher levels of procoagulant activity in people with CKD. Described abnormalities include increased levels of thrombin concurrent with high levels of fibrinogen, and elevated levels of factors VII and VIII.

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\* There is insufficient evidence to support the routine use of statins to prevent or ameliorate progression of CKD.

† The use of statins for the primary prevention of CVD in people with CKD should be informed by the Study of Heart and Renal Protection (SHARP) reported in: Baigent C, Landry M. Study of heart and renal protection. *Kidney International* (2003); 63: S207–S210.

CKD is an independent risk factor for the development of generalised atherosclerosis and coronary artery disease, and is associated with a worse prognosis following cardiovascular events. People with CKD have a higher risk of morbidity and death related to cardiovascular disease than of progression to end stage renal failure. Large clinical trials in the general population have demonstrated that antiplatelet agents reduce the risk of cardiovascular events, and may improve patency rates following revascularisation therapy. What evidence is there that the benefits of antiplatelet therapy in people with CKD outweigh the potential risks of bleeding complications?

### 10.3.2 Methodology

There were very few studies conducted in populations with non-ESRD CKD that assessed the safety and efficacy of antiplatelet agents (aspirin, clopidogrel, dipyridole, glycoprotein IIb/IIIa inhibitors). There were no studies that investigated anticoagulants (warfarin) to prevent mortality and cardiovascular events in people with CKD.

One post hoc analysis of the double blind Clopidogrel in Unstable Angina to Prevent Recurrent Events RCT (CURE, N=12,253, mean follow-up 9 months) compared clopidogrel with placebo in patients with various levels of renal dysfunction and non-ST-segment elevation acute coronary syndrome (NSTEMI). Both trial arms received aspirin (75–325 mg/day).<sup>310</sup>

Three cohort studies investigated the effect of prescription of aspirin compared with non-prescription of aspirin on mortality in people with CKD and heart failure (HF) and coronary artery disease (CAD) (N=6427, 1 year follow-up)<sup>311</sup> or in people with acute MI and CKD (N=1342, 9.8 months follow-up)<sup>312</sup> or in people with ACS and CKD (N=5549, 2 year follow-up).<sup>122</sup>

One cohort study investigated the effect of non-prescription of any antiplatelet agent (aspirin, clopidogrel, dipyridole, or ticlopidine) on mortality within 6 months of hospital discharge in men with CKD undergoing coronary artery bypass grafting (CABG) (N=19,411).<sup>313</sup>

Renal function assessment was limited to one measurement of serum creatinine upon hospital admission in all of the cohort studies. The cohort studies are also limited by lack of data on treatment adherence.

The effect of antiplatelet agents on mortality, cardiovascular events, and adverse events in people with CKD and various baseline cardiovascular comorbidities is summarised in Table 10.2, at the end of the evidence statements.

### 10.3.3 Health economics methodology

There were no health economics papers found to review.

### 10.3.4 Evidence statements

- ▷ All-cause mortality: clopidogrel versus placebo

In people with NSTEMI and either GFR <64 ml/min or GFR 64–81.2 ml/min, there was NS difference in mortality for clopidogrel compared with placebo (both groups received aspirin).<sup>310</sup> (Level 1+)

▷ Aspirin versus non-prescription of aspirin

Two cohort studies of people discharged from hospital following acute MI<sup>312</sup> or ACS<sup>122</sup> showed that aspirin use was NS associated with death in people with mild (GFR 60–80 ml/min/1.73m<sup>2</sup>) or moderate (GFR 30–59 ml/min/1.73m<sup>2</sup>) CKD. In people with ACS and GFR <30 ml/min/1.73m<sup>2</sup>, aspirin use was associated with a significantly increased risk of death.<sup>122</sup> In people with acute MI and GFR 15–29 ml/min, aspirin significantly reduced mortality.<sup>312</sup> (Level 2+)

In another cohort with renal disease, HF, and CAD, use of aspirin significantly reduced 1-year mortality in people with CrCl 30–59 ml/min compared with non-use of aspirin. The risk of death was NS different between people with CrCl <30 ml/min + HF + CAD for aspirin compared with non-use of aspirin.<sup>311</sup> (Level 2+)

▷ Non-prescription of antiplatelet drugs (aspirin, clopidogrel, dipyridamole, or ticlopidine)

Non-prescription of antiplatelet agents was associated with significantly increased odds of mortality in men with GFR <60 ml/min + CABG.<sup>313</sup> (Level 2+)

▷ Cardiovascular death: clopidogrel versus placebo

In people with NSTEMACS and GFR <64 ml/min or GFR 64–81.2 ml/min, there was NS difference in cardiovascular mortality for clopidogrel compared with placebo.<sup>310</sup> (Level 1+)

▷ Cardiovascular death, non-fatal MI, or stroke: clopidogrel versus placebo

Clopidogrel significantly decreased the risk of cardiovascular death, non-fatal MI, or stroke in people with GFR 64–81.2 ml/min + NSTEMACS. Clopidogrel did NS reduce this outcome in people with GFR <64 ml/min.<sup>310</sup> (Level 1+)

▷ Bleeding: clopidogrel versus placebo

In people with NSTEMACS and GFR <64 ml/min or GFR 64–81.2 ml/min, there was NS risk of either life-threatening or major bleeding for clopidogrel compared with placebo. However, clopidogrel use was associated with a significantly increased risk of minor bleeds.<sup>310</sup> (Level 1+)

**Table 10.3 The effect of antiplatelet agents on mortality, cardiovascular events, and adverse events in people with CKD and various cardiovascular comorbidities (95% CI)**

Reference	Comparison	Population	N	Outcome	Effect size
310	Clopidogrel vs. placebo (aspirin in both arms)	GFR <64 ml/min + NSTEMACS	4,087	All-cause mortality	RR 0.95 (0.78–1.16) NS
310	Clopidogrel vs. placebo (aspirin in both arms)	GFR 64–81.2 ml/min + NSTEMACS	4,075	All-cause mortality	RR 0.91 (0.68–1.21) NS
122	Aspirin use at hospital discharge	GFR <30 ml/min/1.73m <sup>2</sup> + ACS	306	All-cause mortality	HR 1.232 (1.024–1.117), p not stated
122	Aspirin use at hospital discharge	GFR 30–59 ml/min/1.73m <sup>2</sup> + ACS	1,795	All-cause mortality	HR 1.029 (0.988–1.081) NS

*continued*

**Table 10.3 The effect of antiplatelet agents on mortality, cardiovascular events, and adverse events in people with CKD and various cardiovascular comorbidities (95% CI) – continued**

Reference	Comparison	Population	N	Outcome	Effect size
122	Aspirin use at hospital discharge	GFR 60–80 ml/min/ 1.73m <sup>2</sup> + ACS	2,018	All-cause mortality	HR 0.851 (0.921–1.128) NS
312	Aspirin versus no cardioprotective agents* at hospital discharge	GFR 15–29 ml/min/ 1.73m <sup>2</sup> + MI	70	All-cause mortality	HR 0.21 (0.08–0.53), p not stated
312	Aspirin versus no cardioprotective agents* at hospital discharge	GFR 30–59 ml/min/ 1.73m <sup>2</sup> + MI	412	All-cause mortality	HR 0.65 (0.37–1.12) NS
312	Aspirin versus no cardioprotective agents* at hospital discharge	GFR 60–89 ml/min/ 1.73m <sup>2</sup> + MI	612	All-cause mortality	HR 0.97 (0.50–1.86) NS
311	Aspirin versus no aspirin at hospital discharge	CrCl < 30 ml/min + HF + CAD	466	1 year All-cause mortality	HR 0.84 (0.64–1.11) NS
311	Aspirin versus no aspirin at hospital discharge	CrCl 30–59 ml/min + HF + CAD	2,047	1 year All-cause mortality	HR 0.81 (0.67–0.98), p not given
313	Non-prescription of antiplatelet drugs** within 6 months of hospital discharge	GFR <60 ml/min + CABG	3,260	All-cause mortality within 6 months of hospital discharge	OR 1.90 (1.23–2.94), p=0.004
310	Clopidogrel vs. placebo (aspirin in both arms)	GFR <64 ml/min + NSTEACS	4,087	Cardiovascular death, non-fatal MI, or stroke	RR 0.89 (0.76–1.05) NS
310	Clopidogrel vs. placebo (aspirin in both arms)	GFR 64–81.2 ml/min + NSTEACS	4,075	Cardiovascular death, non-fatal MI, or stroke	RR 0.68 (0.56–0.84) p<0.05
310	Clopidogrel vs. placebo (aspirin in both arms)	GFR <64 ml/min + NSTEACS	4,087	Cardiovascular death	RR 0.95 (0.77–1.17) NS
310	Clopidogrel vs. placebo (aspirin in both arms)	GFR 64–81.2 ml/min + NSTEACS	4,075	Cardiovascular death	RR 0.85 (0.63–1.16) NS
310	Clopidogrel vs. placebo (aspirin in both arms)	GFR <64 ml/min + NSTEACS	4,087	Life-threatening bleed	RR 0.89 (0.60–1.31) NS
310	Clopidogrel vs. placebo (aspirin in both arms)	GFR 64–81.2 ml/min + NSTEACS	4,075	Life-threatening bleed	RR 1.23 (0.78–1.93) NS
310	Clopidogrel vs. placebo (aspirin in both arms)	GFR <64 ml/min + NSTEACS	4,087	Major bleed	RR 1.37 (0.89–2.12) NS
310	Clopidogrel vs. placebo (aspirin in both arms)	GFR 64–81.2 ml/min + NSTEACS	4,075	Major bleed	RR 1.78 (0.95–3.34) NS
310	Clopidogrel vs. placebo (aspirin in both arms)	GFR <64 ml/min + NSTEACS	4,087	Minor bleed	RR 1.50 (1.21–1.86), p<0.05
310	Clopidogrel vs. placebo (aspirin in both arms)	GFR 64–81.2 ml/min + NSTEACS	4,075	Minor Bleed	RR 1.61 (1.27–2.06), p <0.05

\*Cardioprotective agent = aspirin, beta-blocker, or ACEI.  
\*\*Antiplatelet agents = aspirin, clopidogrel, dipyridamole or ticlopidine.

### 10.3.5 From evidence to recommendations

Interpretation of the results of observational studies of the impact of aspirin may be confounded by the indications for aspirin prescription. The study participants had varying levels of kidney function and follow up was relatively short.

Use of aspirin was associated with a reduction in mortality in people with a GFR below 60 ml/min/1.73 m<sup>2</sup> who had had a myocardial infarction.

The GDG agreed that there was no reason to believe that antiplatelet drugs were less effective for secondary prevention of cardiovascular events in people with CKD.

People with CKD are at increased risk of bleeding and this risk is increased by the use of one or more antiplatelet drugs. The evidence does not show a significant increase in the incidence of major bleeding but there is an increased risk of minor bleeding.

### 10.3.6 RECOMMENDATION

- R59** Offer antiplatelet drugs to people with CKD for the secondary prevention of CVD. CKD is not a contraindication to the use of low dose aspirin but clinicians should be aware of the increased risk of minor bleeding in people with CKD given multiple antiplatelet drugs.

# 11 Asymptomatic hyperuricaemia

## 11.1 Asymptomatic hyperuricaemia in people with CKD

### 11.1.1 Clinical introduction

Uric acid is a product of purine metabolism. After glomerular filtration, uric acid is both reabsorbed and excreted in the proximal tubule. Hyperuricaemia may result from either increased production or decreased excretion of uric acid. Increased production may occur through enzyme defects, increased purine turnover (myeloproliferative disorders and certain forms of cancer), or from increased consumption in diet. In patients with renal disease there is decreased urinary uric acid excretion. Whether this gives rise to hyperuricaemia depends on the degree of gastrointestinal excretory compensation.<sup>314</sup> It has been shown that increasing levels of uric acid are associated with significantly increased hazard ratios for CKD, but the associations with progressive CKD are less strong.<sup>315,316</sup>

There is theoretical evidence to support the role for uric acid as both an initiator of CKD, and a factor involved in its progression. It has been proposed that an elevated uric acid may have a role in initiating hypertension, arteriolosclerosis, kidney disease, insulin resistance, and hypertriglyceridaemia. Once renal microvascular disease develops, the kidney will drive hypertension; once obesity develops fat-laden adipocytes will contribute to insulin resistance, and once kidney disease develops the kidney will also drive progression.<sup>317</sup>

Allopurinol decreases serum uric acid levels by inhibiting the enzyme xanthine oxidase. Experimental rat models have suggested that allopurinol treatment can prevent hyperuricaemia-induced functional and structural injury of the kidney. In animal models of established renal diseases, correction of the hyperuricemic state can significantly improve blood pressure control, decrease proteinuria, and decrease the amount of glomerulosclerosis, tubulointerstitial fibrosis, and vasculopathy.<sup>318–320</sup>

- *Does lowering uric acid with (a) allopurinol, (b) uricosuric agents (probenecid, sulfapyrazone), (c) rasburicase (urate oxidase), decrease morbidity and mortality in adults with CKD and hyperuricaemia?*

### 11.1.2 Methodology

In non-CKD populations, treatment of hyperuricaemia is only indicated if the patient has symptomatic arthritis. The literature was reviewed to determine if treatment with allopurinol, probenecid, sulfapyrazone, or rasburicase decreases progression of CKD and mortality in people with CKD and hyperuricaemia. There was little evidence in this area. There were no studies assessing rasburicase, probenecid, or sulfapyrazone in people with pre-dialysis CKD.

Only one open label RCT<sup>321</sup> compared 12 months of allopurinol treatment (100–200 mg/day dose, N=25) with usual treatment (N=26) in adults (mean age 48 years) with CKD and hyperuricaemia. Both trial arms received lipid lowering and antihypertensive agents throughout the study. This study was excluded as it had several methodological limitations. It was a small study, open-labelled, did not present intention to treat analysis, and did not provide

statistical power calculations. There was little information on what treatments the 'usual treatment' group received. It may be also be difficult to extrapolate the findings from this study to a UK population as it was conducted in a Chinese population.

### **11.1.3 Health economics methodology**

There were no health economics papers found to review.

### **11.1.4 Evidence statements**

There are no evidence statements.

### **11.1.5 From evidence to recommendation**

The GDG agreed that there was no evidence to support treatment of asymptomatic hyperuricaemia in people with CKD.

### **11.1.6 RECOMMENDATION**

**R60** There is insufficient evidence to recommend the routine use of drugs to lower uric acid in people with CKD who have asymptomatic hyperuricaemia.



# 12 Managing isolated invisible haematuria

## 12.1 Isolated invisible (microscopic) haematuria

### 12.1.1 Clinical Introduction

The presence of red blood cells in urine is termed haematuria. This may be visible to the naked eye (macroscopic) or invisible (microscopic). When haematuria is visible the urine is coloured pink or red. When the urine appears normal to the naked eye but the presence of red blood cells is detected by either reagent strip testing or microscopy, haematuria is termed invisible. The prevalence of asymptomatic invisible haematuria varies between 0.19 and 21%, depending on age and gender. Screening studies have suggested that the prevalence in the UK adult male population is around 2.5 %, increasing to 22 % in males over the age of 60 years.<sup>69,70</sup> The differential diagnosis of invisible haematuria is wide, and includes urinary tract malignancy, urinary tract stones, urinary tract infection, and glomerulonephritis. Causes can be typically divided into urological and nephrological (see Table 12.1).

**Table 12.1 Common causes of haematuria**

<b>Urological (surgical disease in the urinary tract)</b>	<b>Nephrological (medical disease of the kidneys)</b>
Stones in the kidney, ureter or bladder	IgA nephropathy
Urinary tract infections (cystitis, urethritis, prostatitis)	Thin membrane nephropathy
Cancer of the kidney, ureter, bladder or prostate	Alport's syndrome
Benign tumours (eg haemangiomas, angiomyolipomas, bladder papillomas)	Glomerulonephritis (other than IgA nephropathy). Usually combined with proteinuria
Trauma	Inherited cystic diseases of the kidney, e.g. polycystic kidney disease, medullary sponge kidney

In the absence of a urological cause, haematuria can be presumed to be coming from the kidneys, most commonly as a result of one of the nephrological diseases listed above. However a firm diagnosis of most of these conditions (except the cystic diseases which are generally diagnosed radiologically) would require a kidney biopsy. This section is concerned with isolated invisible haematuria. This implies that at presentation there is no associated proteinuria, and that the GFR is normal (or if impaired there is no retrospective evidence of progressive loss of GFR). The challenge therefore is to decide a) how far to investigate the cause, and b) how people with isolated invisible haematuria should be monitored in the long term.

### 12.1.2 Methodology

Isolated invisible haematuria is defined as  $\geq 3$  erythrocytes per high power field in the urine without any other urine abnormalities (absence of infection or proteinuria). The clinical significance of isolated invisible haematuria was assessed with respect to morbidity and progression of CKD (declining GFR, development of proteinuria, progression to ESRD).

One prospective case series assessed renal functional decline in Japanese men (N=404) with confirmed isolated invisible haematuria (+1 result on a reagent strip and >5 RBC/hpf by microscopy) identified in a mass population screening between 1983 and 1996 in Hitachi, Japan, for a mean follow-up of 6.35 years.<sup>322</sup>

### 12.1.3 Health economics methodology

There were no health economics papers found to review.

### 12.1.4 Evidence statements

▷ Development of proteinuria

In a case series, 9% of men with asymptomatic invisible haematuria developed proteinuria (defined as chronic nephritic syndrome) during follow-up.<sup>322</sup> (Level 3)

▷ Impaired renal function

0.7% of men with asymptomatic haematuria had a deterioration of renal function (serum creatinine >2.0 mg/dl) during follow-up. The renal function deterioration rate for asymptomatic haematuria was 3.0% over 10 years.<sup>322</sup> (Level 3)

### 12.1.5 From evidence to recommendations

The GDG agreed that by definition isolated invisible haematuria meant that there was no associated proteinuria, the GFR was either normal or stable if below normal, that the kidney was macroscopically normal and that no urological disease was present. Apart from proteinuria there was no evidence that the people included in the study considered had had these other features excluded.

The GDG noted that when renal biopsies are undertaken in people with isolated invisible haematuria, the commonest abnormality identified is IgA nephropathy and that this condition is known to have the propensity to progress to end stage renal disease. In view of this they recommended that annual follow up should be undertaken.

The GDG agreed that if isolated invisible haematuria had been present and disappeared there was a low or non-existent risk of developing progressive CKD.

### 12.1.6 Recommendations

- R61 When there is the need to differentiate persistent invisible haematuria in the absence of proteinuria from transient haematuria, regard two out of three positive reagent strip tests as confirmation of persistent invisible haematuria.
- R62 Persistent invisible haematuria, with or without proteinuria, should prompt investigation for urinary tract malignancy in appropriate age groups.
- R63 Persistent invisible haematuria in the absence of proteinuria should be followed up annually with repeat testing for haematuria, proteinuria/albuminuria, glomerular filtration rate (GFR) and blood pressure monitoring as long as the haematuria persists.

## 13 Specific complications of CKD – renal bone disease

### 13.1 Monitoring of calcium, phosphate, vitamin D and parathyroid hormone levels in people with CKD

#### 13.1.1 Clinical introduction

Alterations in the control mechanisms for calcium and phosphate homeostasis occur early in the course of CKD and progress as kidney function decreases. Changes that occur include abnormalities of calcium, phosphate, parathyroid hormone (PTH), and vitamin D metabolism; together with abnormalities of bone turnover, mineralisation, volume, linear growth, and strength; plus vascular or soft tissue calcification.<sup>323</sup> A wide variety of disturbances of bone metabolism may occur in the setting of CKD necessitating an understanding of the changes that occur in order to design a treatment strategy. However, an in-depth discussion of metabolic bone disease in CKD is beyond the scope of this guideline. This section is focussed on the changes that occur early in the course of CKD. The aim is to prevent metabolic bone disease by maintaining the blood levels of calcium and phosphate as close to normal as possible, and preventing the development of established hyperparathyroidism and parathyroid hyperplasia.

Central to the prevention of these disturbances is an ability to intervene early, recognising that bone disease in people with kidney disease is often asymptomatic, and symptoms appear only late in its course, long after the opportunity for early intervention has passed. Whilst bone biopsy may be the gold standard for assessment of metabolic bone disease it is neither widely available nor widely used. Biochemical assessment is the mainstay of diagnosis and treatment. In addition to measurements of calcium and phosphate it is essential to obtain a direct index of parathyroid activity by measurement of PTH. Under certain circumstances measurement of vitamin D may also be necessary. When should these parameters be measured and at what frequency should they be repeated?

#### 13.1.2 Methodology

Serum calcium, phosphate, intact parathyroid hormone (iPTH), and vitamin D levels were assessed in adults with various stages of CKD in five cross-sectional studies and one observational study.

Two reports from the cross-sectional US NHANES III study (N=14,679) examined changes in serum calcium and phosphate<sup>324</sup> and 25-hydroxyvitamin D<sup>325</sup> by level of renal function. Hsu et al. also reported the prevalence of hyperphosphataemia.

A cross-sectional study compared levels of serum calcium, phosphate, iPTH, and vitamin D amongst stage 3, 4, and 5 CKD. The prevalence of vitamin D deficiency, hyperphosphataemia, and hypocalcaemia was examined in people with stages 3 and 4 CKD.<sup>326</sup>

A cross-sectional analysis of CKD patients (N=1836) was performed to ascertain levels of serum calcium, phosphate, iPTH, 1,25-dihydroxyvitamin D, and 25-hydroxyvitamin D within each stage of CKD.<sup>327</sup>

A cross-sectional analysis at baseline of the Study for the Evaluation of Early Kidney disease participants (SEEK, N=1814, mean age 70 years)<sup>328</sup> examined serum calcium, phosphate, iPTH, 1,25-dihydroxyvitamin D, and 25-hydroxyvitamin D within decreasing deciles of eGFR. This study also reported the prevalence of abnormal calcium, phosphate, iPTH, and vitamin D with decreasing eGFR.

All of these studies were limited by the use of one serum creatinine measurement to estimate renal function.

GFR was measured by <sup>99</sup>Tc-DTPA clearance in one small observational study and levels of serum calcium, phosphate, iPTH, 1,25-dihydroxyvitamin D, and 25-hydroxyvitamin D in people with 'mild CRF' (N=27) or 'moderate CRF' (N=12) were compared with healthy people (N=12).<sup>329</sup>

Calcium, phosphate, iPTH, and vitamin D levels with decreasing renal function are summarised in Table 13.1 at the end of the evidence statements.

### 13.1.3 Health economics methodology

There were no health economics papers found to review.

### 13.1.4 Evidence statements

#### ▷ Serum calcium

Five studies showed that serum calcium levels decreased only in advanced renal disease. Two of these studies reported the prevalence of hypocalcaemia in a CKD population.

Of people with GFR <20 ml/min, 15% had abnormal Ca levels (Ca <2.1 mmol/l).<sup>328</sup> (Level 3)

43% of people with stage 3 CKD and 71% of people with stage 4 CKD had serum Ca <2.37 mmol/l.<sup>326</sup> (Level 3)

Two studies showed that people with stage 4 CKD had significantly lower serum calcium than people with stage 3 CKD.<sup>326,327</sup> (Level 3)

People with moderate CRF (GFR 20–39 ml/min/1.73m<sup>2</sup>) had significantly lower Ca levels than people with mild CRF (GFR 40–90 ml/min/1.73m<sup>2</sup>).<sup>329</sup> (Level 3)

Compared to men with CrCl >80 ml/min, men with CrCl <20 ml/min had a significant decrease in ionised serum Ca.<sup>324</sup> (Level 3)

#### ▷ Serum phosphate

Five studies showed that serum phosphate levels increased with advanced renal disease. Three of these studies showed that abnormal phosphate levels were highly prevalent when eGFR was <20 ml/min.

Of people with eGFR 20–29 ml/min, 15% had abnormal phosphorus levels (P >1.49 mmol/l). Of people with GFR <20 ml/min, 40% had abnormal phosphorus levels.<sup>328</sup> (Level 3)

The prevalence of hyperphosphataemia (serum P >1.45 mmol/l) increased with declining CrCl: 7% of people with CrCl 20–30 ml/min, and 30% of people with CrCl <20 ml/min had hyperphosphataemia.<sup>324</sup> (Level 3)

3% of people with stage 3 CKD and 22% of people with stage 4 CKD had serum P >1.52 mmol/l.<sup>326</sup> (Level 3)

Two studies showed that people with stage 4 CKD had significantly higher serum phosphate levels than people with stage 3 CKD.<sup>326,327</sup> (Level 3)

People with stage 5 CKD had significantly higher serum phosphate than people with stage 4 CKD.<sup>327</sup> (Level 3)

▷ Serum intact parathyroid hormone (iPTH)

Four studies showed that iPTH increased in early stages of CKD. One of these studies reported the prevalence of hyperparathyroidism in the CKD population.

Levin et al. showed hyperparathyroidism (iPTH >65 ng/ml) was prevalent in approximately 20%, 30%, 40%, 55%, and 70% of people with eGFR 69–60, 59–50, 49–40, 39–30, and 29–20 ml/min/1.73 m<sup>2</sup>, respectively.<sup>329</sup> The increase in iPTH above reference values began at GFR <60 ml/min/1.73 m<sup>2</sup>. People with mild CRF (GFR 40–90 ml/min/1.73 m<sup>2</sup>) had significantly higher levels of iPTH than healthy people. People with moderate CRF (GFR 20–39 ml/min/1.73 m<sup>2</sup>) had significantly higher iPTH levels than people with mild CRF. (Level 3)

Craver et al. showed that serum iPTH increased across all stages of CKD. (Level 3)

▷ Serum 1,25-dihydroxyvitamin D

Four studies reported decreases in 1,25-dihydroxyvitamin D in early stages of CKD.

23% of people with CRF were below the reference range of serum 1,25-dihydroxyvitamin D at GFR <60 ml/min/1.73m<sup>2</sup>. People with mild CKD (GFR 40–90 ml/min/1.73m<sup>2</sup>) had significantly lower levels of 1,25-dihydroxyvitamin D compared with healthy people.<sup>329</sup> (Level 3)

Deficiency of 1,25-dihydroxyvitamin D (<22 pg/ml) was seen as GFR decreased to approximately 45 ml/min/1.73 m<sup>2</sup>. The prevalence of 1,25-dihydroxyvitamin D deficiency was approximately 15%, 15%, 20%, 30%, 45%, 50%, and 65% in people with eGFR 70–79, 60–69, 50–59, 40–49, 30–39, 20–29, and <20 ml/min/1.73 m<sup>2</sup>, respectively.<sup>328</sup> (Level 3)

Two studies showed that people with stage 4 CKD had significantly lower serum 1,25-dihydroxyvitamin D levels compared with people with stage 3 CKD.<sup>326,327</sup> (Level 3)

▷ Serum 25-hydroxyvitamin D

Two studies showed NS differences in serum 25-hydroxyvitamin D with worsening renal function.<sup>327,329</sup> (Level 3)

There was NS difference in serum 25-hydroxyvitamin D for people with GFR 30–59 ml/min/1.73 m<sup>2</sup> compared with people with GFR ≥90 ml/min/1.73m<sup>2</sup>. Compared with people with GFR ≥90 ml/min/1.73 m<sup>2</sup>, people with GFR 15–29 ml/min/1.73 m<sup>2</sup> had significantly lower serum 25-hydroxyvitamin D.<sup>325</sup> (Level 3)

Multiple regression analysis showed NS relationship between eGFR and serum 25-hydroxyvitamin D (p=0.8932). The prevalence of deficiency in serum 25-hydroxyvitamin D (<15 ng/ml)

remained stable until GFR <30 ml/min/1.73 m<sup>2</sup>, when the prevalence of serum 25-hydroxyvitamin D deficiency increased. The prevalence of serum 25-hydroxyvitamin D deficiency was approximately 15%, 20%, and 25% in people with eGFR 39–30, 29–20, and <20 ml/min/1.73 m<sup>2</sup>, respectively.<sup>328</sup> (Level 3)

57% of people with stage 3 CKD and 58% of people with stage 4 CKD had serum 25-hydroxyvitamin D insufficiency (10–30 ng/ml). 14% of people with stage 3 CKD and 26% of people with stage 4 CKD had serum 25-hydroxyvitamin D deficiency (<10 ng/ml).<sup>326</sup> (Level 3)

**Table 13.1 Summary of serum calcium, phosphate, iPTH, 1,25-dihydroxyvitamin D, and 25-hydroxyvitamin D levels according to level of renal function (95% CI)**

Reference	N	Serum parameter	CKD stage 3a (GFR 59–45 ml/min/ 1.73m <sup>2</sup> )	CKD stage 3b (GFR 44–30 ml/min/ 1.73m <sup>2</sup> )	CKD stage 4 GFR (29–15 ml/min/ 1.73m <sup>2</sup> )	CKD stage 5 (GFR <15 ml/min/ 1.73m <sup>2</sup> )
327	1,836	Mean Ca	2.39 mmol/l; N=856		2.34 mmol/l; N=354, p<0.05	
326	201	Mean Ca	2.37 mmol/l; N=65		2.30 mmol/l, N=113, p not stated but significant	2.25 mmol/l, N=22, p not stated but significant
329	51	Mean Ca	2.31 mmol/l; GFR 40–90 ml/min/ 1.73m <sup>2</sup> , N=27	2.24 mmol/l; GFR 20–39 ml/min/ 1.73m <sup>2</sup> , N=12, p<0.05		
324	14,722	Change Ca			–0.03 mmol/l (95% CI –0.05 to –0.01 mmol/l), p=0.002; CrCl <20 ml/min, N=20 vs. CrCl >80 ml/min, N=4347	
328	1,814	% Abnormal Ca (Ca <2.1 mmol/l)			<10%, GFR 20–29 ml/min N=204	15%, GFR <20 ml/min, N=93
326	201	% Abnormal Ca (Ca <2.37 mmol/l)	43%, N=65		71%, N=113	
329	51	Mean phosphate	1.0 mmol/l; GFR 40–90 ml/min/ 1.73 m <sup>2</sup> , N=27	1.2 mmol/l; GFR 20–39 ml/min/ 1.73m <sup>2</sup> , N=12, p<0.05		
327	1,836	Mean phosphate	1.16 mmol/l; N=856		1.27 mmol/l, N=354, p<0.05 vs. stage 3	1.58 mmol/l, N=111, p<0.05 vs. stage 4
326	201	Mean phosphate	1.13 mmol/l, N=65		1.32 mmol/l, N=113, p not stated but significant	1.42 mmol/l, N=22, p not stated but significant
326	201	% Hyper- phosphataemia (P >1.52 mmol/l)	3%, N=65		22%, N=113	

*continued*

**Table 13.1 Summary of serum calcium, phosphate, iPTH, 1,25-dihydroxyvitamin D, and 25-hydroxyvitamin D levels according to level of renal function (95% CI) – *continued***

Reference	N	Serum parameter	CKD stage 3a (GFR 59–45 ml/min/ 1.73m <sup>2</sup> )	CKD stage 3b (GFR 44–30 ml/min/ 1.73m <sup>2</sup> )	CKD stage 4 GFR (29–15 ml/min/ 1.73m <sup>2</sup> )	CKD stage 5 (GFR <15 ml/min/ 1.73m <sup>2</sup> )
328	1,814	% Hyper-phosphataemia (P >1.49 mmol/l)			15%, GFR 20–29 ml/min, N=204	40%, GFR <20 ml/min, N=93
324	14,722	% Hyper-phosphataemia (P >1.45 mmol/l)		3% (95% CI 1–6%), CrCl 30–40 ml/min, N=614	7% (95% CI 1–12%), CrCl 20–30 ml/min, N=224	30% (95% CI 0–62%), CrCl <20 ml/min, N=47
329	51	Mean iPTH	57.5 pg/ml, GFR 40–90 ml/min/1.73 m <sup>2</sup> , N=27 vs. 25.4 pg/ml, healthy people, N=12, p<0.05	139 pg/ml, GFR 20–39 ml/min/1.73 m <sup>2</sup> , N=12, p<0.05		
327	1,836	Mean iPTH	8.96 pmol/l, N=856 vs. 5.97 pmol/l, stage 2, N=341, p<0.05		16.47 pmol/l, N=354, p<0.05	24.29 pmol/l, N=111, p<0.05
326	201	Mean iPTH	114 pg/ml, N=65		235 pg/ml, N=113, p not stated but significant	310 pg/ml, N=22, p not stated but significant
328	1,814	% Hyper-parathyroidism (iPTH >65 ng/ml)	30%, GFR 50–59, N= 396	55%, GFR 30–39, N=358	70%, GFR 20–29, N=204	85%, GFR <20, N=93
329	51	Mean 1,25-dihydroxyvitamin D	42.1 pg/ml, GFR 40–90 ml/min/1.73 m <sup>2</sup> , N=27 vs. 54.6 pg/ml healthy people, N=12, p<0.05	39.2 pg/ml, GFR 20–39 ml/min/1.73 m <sup>2</sup> , N=12 vs. 54.6 pg/ml healthy people, N=12, p<0.05		
327	1,836	Mean 1,25-dihydroxyvitamin D	25.7 pg/ml, N=221 vs 33.9 pg/ml stage 2, N=87, p<0.05		16.8 pg/ml, N=156, p<0.05 vs. stage 3	13.2 pg/ml, N=43, p<0.05 vs. stage 4
326	201	Mean 1,25-dihydroxyvitamin D	79.6 pmol/l , N=63		62.3 pmol/l, N=108, p not stated but significant	54.3 pmol/l, N=20, p not stated but significant
328	1,814	% 1,25-dihydroxyvitamin D deficiency (<22 pg/ml)	20%, GFR 50–59, N= 396	45%, GFR 30–39, N=358	50%, GFR 20–29, N=204	65%, GFR <20, N=93

*continued*

**Table 13.1 Summary of serum calcium, phosphate, iPTH, 1,25-dihydroxyvitamin D, and 25-hydroxyvitamin D levels according to level of renal function (95% CI) – continued**

Reference	N	Serum parameter	CKD stage 3a (GFR 59–45 ml/min/ 1.73m <sup>2</sup> )	CKD stage 3b (GFR 44–30 ml/min/ 1.73m <sup>2</sup> )	CKD stage 4 GFR (29–15 ml/min/ 1.73m <sup>2</sup> )	CKD stage 5 (GFR <15 ml/min/ 1.73m <sup>2</sup> )
325	14,679	Mean 25-hydroxyvitamin D	75.8 nmol/l, N= 854 vs. 73.3 nmol/l, GFR ≥90 ml/min/1.73m <sup>2</sup> , N= 9687, NS		61.1 nmol/l, N=44 vs. 73.3 nmol/l, GFR ≥90 ml/min/1.73 m <sup>2</sup> , N=9687, p=0.0002	
327	1,836	Mean 25-hydroxyvitamin D	29.6 ng/ml, N=43		26.2 ng/ml, N=115, NS	23.4 ng/ml, N=35, NS
329	51	Mean 25-hydroxyvitamin D	63.3 nmol/IGFR 40–90 ml/min/1.73 m <sup>2</sup> , N=27	47.1 nmol/l, GFR 20–39 ml/min/1.73 m <sup>2</sup> , N=12, NS		
328	1,814	% 25-hydroxyvitamin D deficiency (<15 ng/ml)	15%, GFR 30–39, N=358		20%, GFR 20–29, N=204	25%, GFR <20, N=93
326	201	% 25-hydroxyvitamin D insufficiency (10–30 ng/ml).	57%, N=65		58%, N=113	
326	201	% 25-hydroxyvitamin D deficiency (<15 ng/ml)	14%, N=65		26%, N=113	

### 13.1.5 From evidence to recommendations

The GDG noted that in many of the studies the results were not broken down by stage of CKD or level of GFR.

Although there were statistically significant differences in mean calcium concentrations at different levels of GFR these were unlikely to be clinically significant differences. On the basis of the evidence the GDG agreed that there was no need to routinely measure serum calcium concentrations in people with stage 1, 2 and 3A CKD and that it was not usually necessary to measure it in people with stage 3B CKD.

The GDG noted that although there were statistically significant differences in mean phosphate concentrations at different levels of GFR these values were all within the normal range. Serum phosphate concentrations generally fell within the normal range unless the GFR level was below 20 ml/min/1.73 m<sup>2</sup>. On the basis of the evidence the GDG agreed that there was no need to routinely measure serum phosphate concentrations in people with stage 1, 2 and 3A CKD and that it was not usually necessary to measure it in people with stage 3B CKD.

The prevalence of hyperparathyroidism in people with a reduced GFR was higher than in healthy individuals; however, the significance of modestly elevated PTH concentrations was thought unclear and there was no consensus on whether people with concentrations elevated to this extent



benefit from treatment. On the basis of the evidence the GDG agreed that there was no requirement to routinely measure serum PTH concentrations in people with stage 1, 2 and 3A CKD and that it was not usually necessary to measure it in people with stage 3B CKD in the absence of specific indications. Specific indications to measure serum PTH would include unexplained hypercalcaemia and symptoms suggestive of hyperparathyroidism.

The prevalence of abnormally low vitamin D concentrations increased once the GFR fell below 45 ml/min/1.73 m<sup>2</sup>;<sup>328</sup> however, there was no information in this study on the prevalence of low vitamin D concentrations in the general population.

Most laboratories do not measure 1,25 dihydroxyvitamin D concentrations.

On the basis of the evidence the GDG agreed that there was no need to routinely measure serum vitamin D concentrations in people with stage 1, 2 and 3A CKD and that it was not usually necessary to measure it in people with stage 3B CKD except where there are specific indications such as unexplained hypocalcaemia or symptoms suggestive of vitamin D deficiency.

Because of the increased prevalence of abnormal serum calcium, phosphate, PTH and vitamin D concentrations in people with stage 4 and 5 CKD and the fact that these people may require treatment for renal bone disease it was recommended that calcium, phosphate and PTH concentrations should be measured in people with stage 4 and 5 CKD.

There was no evidence to guide a recommendation about how frequently the calcium, phosphate, PTH and vitamin D concentrations should be measured in people with stage 4 and 5 CKD and the GDG agreed that this would be determined by the clinical circumstances.

### 13.1.6 RECOMMENDATIONS

- R64 The routine measurement of calcium, phosphate, parathyroid hormone (PTH) and vitamin D levels in people with stage 1, 2, 3A or 3B CKD is not recommended.
- R65 Measure serum calcium, phosphate and PTH concentrations in people with stage 4 or 5 CKD (glomerular filtration rate (GFR) <30 ml/min/1.73 m<sup>2</sup>). Determine the subsequent frequency of testing by the measured values and the clinical circumstances. Where doubt exists seek specialist opinion.

## 13.2 Risks and benefits of bisphosphonates for preventing osteoporosis in adults with CKD

### 13.2.1 Clinical introduction

Osteoporosis is caused by the cumulative effect of bone resorption in excess of bone formation. Bisphosphonates inhibit bone resorption with relatively few side effects and are widely used for the prevention and treatment of osteoporosis. Osteoporosis can also develop in people with CKD and ESRD for many reasons beyond age-related bone loss and postmenopausal bone loss. People with CKD are far more likely than the general population to have conditions putting them at risk of osteoporosis and are much more likely to be prescribed medication promoting development of osteoporosis. The diagnosis of osteoporosis in people with advanced CKD is

not as straightforward as it is in people with postmenopausal osteoporosis. Neither fragility fractures nor the World Health Organization bone mineral density criteria can be used to diagnose osteoporosis in this population since all forms of renal bone disease may fracture or have low 'T scores'. The diagnosis of osteoporosis in people with CKD must be done by first excluding the other forms of renal osteodystrophy.<sup>330</sup>

Bisphosphonates are poorly absorbed orally (1–5% of an oral dose), and absorption is best when the drug is given on an empty stomach. Approximately 80% of the absorbed bisphosphonate is usually cleared by the kidney, the remaining 20% being taken up by bone. Relative bone uptake is increased in conditions of high bone turnover, with less of the drug being excreted by the kidneys. The plasma half-life is approximately one hour, while the bisphosphonate may persist in bone for the lifetime of the patient.

Product data sheets do not recommend bisphosphonates for people with stage 4 or 5 CKD. What is the evidence for this and what is the evidence for the routine use of bisphosphonates in the prevention and treatment of osteoporosis in people with CKD?

### 13.2.2 Methodology

There were very few papers that examined the effect of bisphosphonates on bone mineral density (BMD) and fracture outcomes in a CKD population.

One open-label RCT was excluded due to limitations in randomisation.<sup>331</sup>

One RCT (N=38, 1 year follow-up) investigated the effects of risedronate with and without vitamin D in people with CKD (mean eGFR 78 ml/min) with high dose corticosteroid-induced bone loss.<sup>332</sup> Corticosteroids are frequently used in the treatment of kidney disease and even at low doses may cause osteoporosis and bone fractures. Limitations of this study include the small sample size, although there was no loss to follow-up.

A meta-analysis of data from nine phase III trials (N=9883, 2 years follow-up, mean age 75 years) investigated the effects of risedronate in osteoporotic women with varying levels of renal function.<sup>333</sup> Although this was not a systematic review and included only phase III trials, due to lack of other evidence, this paper was included. 91% of the pooled cases had some degree of renal impairment and the analyses were conducted in categories of patients with mild (CrCl 50–80 ml/min), moderate (CrCl 30–50 ml/min) or severe (CrCl <30 ml/min) renal dysfunction.

A post-hoc analysis of the Fracture Intervention Trial (FIT, N=6458, 3 year follow-up, mean age 68 years)<sup>334</sup> investigated the effects of alendronate on BMD and fracture in osteoporotic women with moderate/normal renal function (eGFR  $\geq$ 45 ml/min, N=5877) or severe renal dysfunction (eGFR <45 ml/min, N=581).

The safety and efficacy of bisphosphonates in preventing osteoporosis in people with CKD are summarised in Table 13.2, at the end of the evidence statements.

### 13.2.3 Health economics methodology

There were no health economics papers found to review.

### 13.2.4 Evidence statements

#### ▷ Risedronate

##### *Change in BMD*

Combination therapy of risedronate (2.5 mg/day) and vitamin D together resulted in a significant increase in BMD, whereas BMD significantly decreased in the vitamin D alone group. There was a NS decline in BMD in the risedronate group. The difference between BMD changes in the risedronate and vitamin D combination therapy group and the vitamin D alone group were statistically significant.<sup>332</sup> (Level 1+)

The mean percent increase from baseline to endpoint in BMD at the lumbar spine, femoral neck and trochanter was significantly greater in the risedronate (5 mg/day) arm than in the placebo arm in all mild, moderate and severe renal impairment subgroups, with the exception of the femoral neck in the severe renal impairment subgroup.<sup>333</sup> (Level 1+)

##### *Fractures*

In one RCT, no fractures occurred over 1 year of follow-up.<sup>332</sup> (Level 1+)

The incidence of new vertebral fractures was significantly lower in the risedronate (5 mg/day) group than placebo groups within mild, moderate and severe renal impairment subgroups.<sup>333</sup> Within the risedronate treatment group, the incidence of new vertebral fractures was similar across renal impairment subgroups ( $p=0.124$ ). Within the placebo group, new vertebral fractures increased significantly with increasing severity of renal impairment ( $p<0.001$ ). (Level 1+)

##### *Adverse events*

There were no adverse events in any of the treatment arms in the Kikuchi et al. RCT. (Level 1+)

The incidence of overall, urinary and renal function related adverse events were similar between risedronate (5 mg/day) and placebo groups in the subgroups of patients with severe, moderate and mild renal impairment.<sup>333</sup> (Level 1+)

#### ▷ Alendronate

##### *Change in BMD*

Alendronate increased BMD at the total hip, femoral neck and spine to a greater extent in postmenopausal women with eGFR <45 ml/min, than in women with eGFR  $\geq$ 45 ml/min. There was a significant interaction between renal function and the increase in total hip BMD ( $p=0.04$ ). Among women with osteoporosis (N=3214), alendronate produced a greater increase in BMD at the hip and femoral neck in the group with eGFR <45 ml/min than women with eGFR  $\geq$ 45 ml/min. However at the spine the increase in BMD was greater in women with eGFR  $\geq$ 45 ml/min. There was no significant interaction between renal function and increase in BMD.<sup>334</sup> (Level 1+)

*Fractures*

Overall, alendronate significantly reduced the risk of clinical fractures (OR 0.8, 95% CI 0.7–0.9) and spine fractures (OR 0.54, 95% CI 0.37–0.87) compared with placebo. The risk reduction was significant in women with eGFR  $\geq$ 45 ml/min for both clinical and spine fractures, but NS in women with eGFR <45 ml/min. (Level 1+)

Women with a reduced eGFR <45 ml/min had an increased risk of any clinical fracture (OR 1.3, 95% CI 1.0–1.6) and of spine fractures (OR 2.5, 95% CI 1.6–3.9) compared with women with an eGFR  $\geq$ 45 ml/min.<sup>334</sup> (Level 1+)

*Adverse events*

There was no difference for adverse events among women with reduced renal function compared with women without reduced renal function (p=0.189).<sup>334</sup> (Level 1+)

**Table 13.2 Summary of the safety and efficacy of bisphosphonates in preventing osteoporosis in people with CKD (95% confidence intervals)**

Reference	Population	Treatment groups	Outcomes	Size effect
332	People with glomerulonephritis + high-dose corticosteroid	N=12 risedronate	Change in BMD	Risedronate: NS change from baseline Alfacalcidol: -5.6% from baseline (p<0.05); p=0.001 vs. R+A Risedronate + alfacalcidol: +2% from baseline (p<0.05)
		N=15 alfacalcidol		
		N=11 risedronate + alfacalcidol	Fractures	No fractures occurred in any trial arm.
			Adverse events	No adverse events in any trial arm.
333	Osteoporotic women GFR < 30 ml/min	N=301 risedronate	All adverse events	RR 0.96 (0.91–1.02) NS
		N=271 placebo	Urinary and renal function adverse events	RR 0.93 (0.67–1.30) NS
			Specific renal function adverse events	RR 0.80 (0.31–2.04) NS
	Osteoporotic women GFR 30–50 ml/min	N=2034 risedronate	All adverse events	RR 1.02 (0.99–1.04) NS
		N=2037 placebo	Urinary and renal function adverse events	RR 1.00 (0.88–1.14) NS
			Specific renal function adverse events	RR 0.88 (0.53–1.45) NS
Osteoporotic women GFR 50–80 ml/min	N=2161 risedronate	All adverse events	RR 1.01 (0.99–1.02) NS	
	N=2192 placebo	Urinary and renal function adverse events	RR 0.63 (0.37–1.07) NS	
		Specific renal function adverse events	RR 0.96 (0.85–1.09) NS	

*continued*

**Table 13.2 Summary of the safety and efficacy of bisphosphonates in preventing osteoporosis in people with CKD (95% confidence intervals) – continued**

Reference	Population	Treatment groups	Outcomes	Size effect
	Osteoporotic women GFR <30 ml/min	N=301 risedronate  N=271 placebo	Change in BMD	Placebo: –1.37% vs. risedronate: +4.23%, p<0.001
	Osteoporotic women GFR 30–50 ml/min	N=2034 risedronate  N=2037 placebo	Change in BMD	Placebo: –0.47% vs. risedronate: +4.33; p<0.001
	Osteoporotic women GFR 50–80 ml/min	N=2161 risedronate  N=2192 placebo	Change in BMD	Placebo: –0.14% vs. risedronate +3.96%; p<0.001
	Osteoporotic women GFR <30 ml/min	N=232	Incidence of new vertebral fractures	Placebo approx. 27% vs. risedronate approx. 14%, p=0.021 (estimated from figure in paper)
	Osteoporotic women GFR 30–50 ml/min	N=2426	Incidence of new vertebral fractures	Placebo approx. 19% vs. risedronate approx. 13%, p<0.001
	Osteoporotic women GFR 50–80 ml/min	N=3086	Incidence of new vertebral fractures	Placebo approx. 16% vs. risedronate approx. 12%, p=0.001
334	Postmenopausal women GFR <45 ml/min (N=581)	Alendronate N=not stated  Placebo N=not stated	Change BMD, total hip  Change BMD, femoral neck  Change BMD, spine	+ 5.6% (4.8–6.5)  + 5.0% (4.0–5.9)  + 6.7% (5.7–7.8)
	Postmenopausal women GFR ≥45 ml/min (N=5877)	Alendronate N= not stated  Placebo N=not stated	Change BMD, total hip  Change BMD, femoral neck  Change BMD, spine	+ 4.8% (4.6–5.0)  + 4.5% (4.2–4.8)  + 6.6% (6.3–6.9)
	Postmenopausal women GFR <45 ml/min (N=581)	Alendronate N=not stated  Placebo N=not stated	Clinical fractures  Spine fractures	OR 0.78 (0.51–1.2) NS  OR 0.72 (0.31–1.7) NS
	Postmenopausal women GFR ≥45 ml/min (N=5877)	Alendronate N= not stated  Placebo N=not stated	Clinical fractures  Spine fractures	OR 0.81 (0.70–0.94)  OR 0.50 (0.32–0.76)

*continued*

**Table 13.2 Summary of the safety and efficacy of bisphosphonates in preventing osteoporosis in people with CKD (95% confidence intervals) – *continued***

Reference	Population	Treatment groups	Outcomes	Size effect
	Postmenopausal women GFR <45 ml/min (N=581)	Alendronate N= not stated	GI adverse events	4.5%
			Cerebrovascular adverse events	2.2%
		Placebo N=not stated	Cardiovascular adverse events	2.6%
			Death	1.6%
			Renal adverse events	2.1%
	Postmenopausal women GFR ≥45 ml/min (N=5877)	Alendronate N= not stated	GI adverse events	5.2% NS compared to GFR <45 ml/min group
			Cerebrovascular adverse events	2.2% NS
		Placebo N=not stated	Cardiovascular adverse events	3.2% NS
			Death	1.9% NS
			Renal adverse events	2.3% NS

### 13.2.5 From evidence to recommendations

The GDG concluded that from the studies presented there was no evidence of an increased risk of drug related adverse events in people with CKD. Bisphosphonates appeared to have benefits on bone mineral density in people with CKD.

The studies did not include prevention of osteoporosis in people with a GFR <30 ml/min/1.73 m<sup>2</sup> and therefore there is no evidence about either the effectiveness or the safety of bisphosphonates in this group.

Guidelines on the management of osteoporosis do not make recommendations that relate to people with CKD.

The dose of bisphosphonate may need adjusting according to the GFR and clinicians should refer to the drugs' Summary of Product Characteristics (SPC) for guidance on this.

### 13.2.6 RECOMMENDATIONS

- R66** Offer bisphosphonates if indicated for the prevention and treatment of osteoporosis in people with stage 1, 2, 3A or 3B CKD.

## 13.3 Vitamin D supplementation in people with CKD

### 13.3.1 Clinical introduction

Vitamin D is normally either ingested or synthesised in the skin under the influence of sunlight. It is then hydroxylated in the liver to form 25-hydroxyvitamin D (calcidiol) and then hydroxylated

in the kidney to 1,25-dihydroxyvitamin D (calcitriol), which is the most active form. Vitamin D deficiency can therefore occur as a result of decreased intake or absorption, reduced sun exposure, increased hepatic catabolism, or decreased endogenous synthesis (via 25-hydroxylation in the liver and subsequent 1-hydroxylation in the kidney). Active vitamin D has a variety of actions on calcium, phosphate, and bone metabolism. By increasing intestinal calcium and phosphate reabsorption and increasing the effect of parathyroid hormone (PTH) on bone, in health vitamin D has the net effect of increasing the serum calcium and phosphate concentrations. Vitamin D deficiency or resistance interferes with these processes, sometimes causing hypocalcaemia and hypophosphataemia. Since hypocalcaemia stimulates the release of PTH, however, the development of hypocalcaemia is often masked. The secondary hyperparathyroidism, via its actions on bone and the kidney, partially corrects the hypocalcaemia but enhances urinary phosphate excretion, thereby contributing to the development of hypophosphataemia. In people with CKD the kidney component of this loop is increasingly compromised as CKD advances.

As renal function declines, the hydroxylating activity of renal 1 $\alpha$ -hydroxylase on 25-hydroxyvitamin D<sub>3</sub> also decreases, resulting in decreased production of active vitamin D (1,25-dihydroxyvitamin D<sub>3</sub>) and decreased intestinal absorption of calcium. The decrease in calcium and active vitamin D<sub>3</sub> alleviates the repression of parathyroid hormone (PTH) production, resulting in hyperproliferation of parathyroid cells. High PTH levels cause an increase in bone remodelling, leading to high bone-turnover (osteitis fibrosa), loss of bone density and structure. This excess bone remodelling liberates calcium and phosphorus from bone, resulting in hypercalcaemia and hyperphosphataemia and increasing the risk for vascular calcification.

Vitamin D supplementation in people with CKD should therefore be driven by the underlying metabolic abnormality. This in turn will depend on the stage of CKD but is complicated by the fact that in the population with the highest prevalence of CKD, the older population, vitamin D deficiency is common. Cutaneous vitamin D production and vitamin D stores decline with age coupled with the fact that intake is often low in older subjects. Furthermore, even in those with adequate vitamin D intake, achlorhydria, which is common in older people, limits vitamin D absorption. Nutritional forms of vitamin D include ergocalciferol and cholecalciferol; active forms of vitamin D include alfacalcidol, calcitriol and paricalcitol. Elderly patients are likely to be vitamin D deficient from diet, lack of sunlight and poor absorption for which they will need nutritional vitamin D. However as CKD progresses (particularly in stages 4 and 5), renal function is impaired to such a degree that active vitamin D may also be required.

- *What type of vitamin D supplementation, if any, should be used in adults with CKD?*

### 13.3.2 Methodology

Eight RCTs and one case series investigated the safety and efficacy of various natural and synthetic vitamin D metabolites to treat secondary hyperparathyroidism and to prevent bone loss in people with pre-dialysis CKD. Outcomes of interest included adverse events, fractures, changes in serum calcium, phosphorus, PTH, osteocalcin, alkaline phosphatase, GFR, and bone mineral density. All of these studies are limited by small sample sizes (N=25–220), and very few presented intention to treat analyses. There were no studies of acceptable methodological quality that compared different vitamin D metabolites head-to-head.

Four RCTs<sup>335–338</sup> compared calcitriol supplementation to placebo in people with CKD. Two of these RCTs titrated the dose of calcitriol from 0.25 µg/day up to 0.5 µg/day.<sup>335,336</sup> In the RCT of Przedlacki et al., treatment with calcitriol (0.25 µg/day, N=13, 12 months follow-up) was compared with placebo (N=12) in people with eGFR <51.2 ml/min. In the RCT of Ritz et al., a low dose of calcitriol (0.125 µg/day, N=28, follow-up 1 year) was compared with placebo (N=24) in people with nondiabetic CKD and abnormal iPTH levels (iPTH >6 pmol/l on 3 separate occasions). The Baker et al. study (N=13, follow-up 12 months) was excluded due to small sample size, high dropout rate, and lack of baseline data comparison between the two trial arms.

One RCT compared 6 months of treatment with calcitriol (N=8, 1 µg/day) or calcidiol (N=9, 4000 IU/day) in people with chronic renal failure.<sup>339</sup> This study was rejected because there was no indication of blinding, concealment, intention to treat, and statistical power to detect differences between the two groups.

Two RCTs investigated the effects of treatment with alfacalcidol (1- $\alpha$ -hydroxycholecalciferol) compared to placebo in people with mild to moderate CKD (creatinine clearance 10–60 ml/min).<sup>340,341</sup> The Hamdy et al. RCT (N=89 alfacalcidol and N=87 placebo, 24 months follow-up) titrated the dose of alfacalcidol from 0.25 to 1 µg/day. Most of the participants had abnormal bone histology at baseline (NS difference between the trial arms). The smaller RCT of Rix et al. (N=36, 18 months follow-up) titrated alfacalcidol from 0.25 to 0.75 µg/day.

A pooled analysis of 3 RCTs with identical inclusion/exclusion criteria and different dosing regimens (3 times weekly or once daily) compared paricalcitol (N=107, 6 months follow-up, mean dose was 1.3 to 1.4 µg/day) with placebo (N=113) in people with CKD and hyperparathyroidism (iPTH  $\geq$ 150 pg/ml). Although this study was not a systematic review, it was included as an RCT (albeit pooled) due to lack of studies of non-dialysis CKD populations.<sup>342</sup>

One retrospective case series examined changes in serum calcium, phosphate, iPTH, and adverse events before and after 6 months' treatment with ergocalciferol (vitamin D<sub>2</sub>) in men with stage 3 CKD and plasma iPTH >70 ng/l (N=44) or stage 4 CKD and plasma iPTH >110 ng/l (N=22).<sup>343</sup>

### 13.3.3 Health economics methodology

There were no health economics papers found to review.

### 13.3.4 Evidence statements

▷ Calcitriol versus placebo

Refer to Table 13.3 for summary of studies.

#### *Serum calcium*

One RCT showed that serum calcium significantly increased with calcitriol (0.25 titrated to 0.5 µg/day) compared with placebo.<sup>336</sup> (Level 1+)

Two RCTs showed NS changes in mean serum calcium in people taking calcitriol (0.25 µg/day steady or 0.125 µg/day) or placebo.<sup>337,338</sup> (Level 1 +)



*Serum phosphorus*

Three RCTs showed that mean serum phosphate did NS change in either the placebo or calcitrol groups.<sup>336-338</sup> (Level 1 +)

*Serum parathyroid hormone (PTH)*

Two RCTs showed that iPTH significantly decreased in people receiving calcitrol, whereas in the placebo groups, iPTH levels either increased significantly<sup>336</sup> or did not significantly change.<sup>337</sup> (Level 1 +)

One RCT showed that iPTH decreased from baseline in the calcitrol group whereas iPTH increased from baseline in those taking placebo ( $p < 0.05$  between placebo and calcitrol groups).<sup>338</sup> (Level 1 +)

*Serum alkaline phosphatase (ALP)*

Two RCTs showed that serum ALP decreased significantly in people taking calcitrol, whereas there were NS changes in ALP in people taking placebo.<sup>336,337</sup> (Level 1 +)

*Serum osteocalcin*

One RCT showed that mean serum osteocalcin significantly decreased in the calcitrol group, whereas osteocalcin significantly increased in the placebo group.<sup>337</sup> (Level 1 +)

*Change in eGFR or creatinine clearance*

Two RCTs showed that creatinine clearance or GFR significantly decreased in both the calcitrol and the placebo groups, but there were NS differences between the groups.<sup>336,337</sup> (Level 1)

*Bone mineral density (BMD)*

BMD of the lumbar spine (L2–L4), femoral neck, and trochanter significantly increased in the calcitrol group. By contrast BMD of the lumbar spine (L2–L4), femoral neck, and trochanter significantly decreased in the placebo group ( $p < 0.01$  between groups).<sup>337</sup> (Level 1+)

*Indices of bone formation, remodelling and structure*

There were NS changes in bone volume in placebo or calcitrol groups.<sup>336</sup> (Level 1+)

Indices of bone formation, remodelling and structure (osteoid volume, osteoid thickness, osteoid surface, eroded surface, osteoclast surface, bone formation rate, mineralisation surface, and mineral apposition rate, singly labelled trabecular surfaces) significantly decreased in the calcitrol group, whereas there were NS changes in the placebo group.<sup>336</sup> (Level 1+)

There were NS changes in doubly labelled trabecular surfaces in calcitrol or placebo groups. (Level 1+)

*Adverse events*

Hypercalcaemia (>2.6 mmol/l) was observed in 2/13 people receiving calcitriol and 0/12 receiving placebo. Hyperionised calcaemia (blood ionised Ca >1.29 mmol/l) occurred in 5/13 on calcitriol and 3/12 in the placebo group.<sup>337</sup>

There was no hypercalcaemia (>2.7 mmol/l on three consecutive occasions) in either calcitriol (0.125 µg/day) or placebo groups.<sup>338</sup>

There was no hyperphosphataemia (>2.2 mmol/l on 3 consecutive occasions) in either calcitriol (0.125 µg/day) or placebo groups.<sup>338</sup>

Hyperphosphataemia (P >1.5 mmol/l) occurred in 3/12 placebo and 10/13 randomised to calcitriol (NS between groups).<sup>337</sup> (Level 1+)

**Table 13.3 Summary of studies comparing calcitriol with placebo**

Study	Population	Duration (months)	Calcitriol (N)	Placebo (N)	Outcome	Size effect
336	Creatinine >180 µmol/l and stable renal function	8	14	14	Change iPTH (µg/l)	Calcitriol 1.33 → 0.98 (-26%), p<0.01  Placebo 0.94 → 1.37, (+46%), p<0.01
337	GFR <51.2 ml/min	12	13	12	Change iPTH (ng/l)	Calcitriol 150 → 105.8 (-29%), p<0.05  Placebo 122.6 → 151.4, (+23%) p NS
338	Creatinine >1.4 mg/dl and <6.5 mg/dl and iPTH >6 pmol/l	12	28	24	Change iPTH (pmol/l)	Calcitriol 16.2 → 18.2, p not given  Placebo 14.0 → 27.8  p<0.05 between treatments
337	GFR <51.2 ml/min	12	13	12	Change Osteocalcin (µmol/l)	Calcitriol 26.3 → 20.0 (-24%), p<0.05  Placebo 24.6 → 28.3 (+15%) p<0.05
336	Creatinine >180 µmol/l and stable renal function	8	14	14	Change Serum alkaline phosphatase (U/l)	Calcitriol: 201 → 155 (-23%), p<0.05  Placebo: 209 → 200 (-4%) NS.  p<0.05 for between groups

*continued*

Table 13.3 Summary of studies comparing calcitriol with placebo – *continued*

Study	Population	Duration (months)	Calcitriol (N)	Placebo (N)	Outcome	Size effect
337	GFR <51.2 ml/min,	12	13	12	Change Serum alkaline phosphatase (U/l)	Calcitriol: 165.0 → 143, p<0.05). Placebo: NS
336	Creatinine >180 µmol/l and stable renal function	8	15	15	Change in CrCl	Calcitriol: -5ml/min (approx.), p<0.01 Placebo: -5ml/min (approx.), p<0.01 NS between groups
337	GFR <51.2 ml/min	12	13	12	Change in GFR	Calcitriol: 21.5 ml/min → 18.7 ml/min, p<0.05) Placebo: 31.3 ml/min → 26.3 ml/min, p<0.05 NS between treatments.
337	GFR <51.2 ml/min	12	13	12	Change Bone Mineral Density (g/cm <sup>2</sup> )	Calcitriol lumbar spine: 1.111 → 1.133, p<0.001 Placebo lumbar spine: 1.214 → 1.201, p<0.05 p<0.01 between groups Calcitriol femoral neck 0.806 → 0.832, p<0.001. Placebo femoral neck 0.860 → 0.845, p<0.05 p<0.001 between groups. Calcitriol: Ward's triangle NS Placebo: Ward's triangle 0.720 → 0.702, p<0.05 Calcitriol: trochanter 0.708 → 0.724, p<0.05 Placebo: trochanter 0.800 → 0.783, p<0.05

*continued*

Table 13.3 Summary of studies comparing calcitriol with placebo – *continued*

Study	Population	Duration (months)	Calcitriol (N)	Placebo (N)	Outcome	Size effect
336	Creatinine > 180 µmol/l	8	14	14	Change Bone volume	NS change placebo or calcitriol.
					Change Osteoid volume	Calcitriol: 5% → 3%, p<0.01 Placebo: 8% → 6%, NS p<0.01 between groups
					Change Osteoid thickness (µm)	Calcitriol: 9.6 → 6.1, p<0.01) placebo: 9.0 → 10, NS
					Change Osteoid surface	Calcitriol decreased, p<0.05 Placebo: NS change p<0.01 between groups
					Change Eroded surface	Calcitriol decreased, p<0.05 Placebo: NS change p<0.05 between groups
					Change Osteoclast surface	Calcitriol decreased, p<0.01 Placebo: NS change p<0.01 between groups
					Change Bone formation rate	Calcitriol: decreased, p<0.01 Placebo: NS change p<0.05 between groups
					Change Mineral apposition rate (µm/day)	Calcitriol: 0.53 → 0.44, p<0.05. Placebo: 0.55 → 0.50, NS

▷ Alfacalcidol (1 $\alpha$ -hydroxycholecalciferol) versus placebo

Refer to Table 13.4 at the end of the evidence statements for a summary of studies.

*Serum calcium*

Two RCTs showed that mean serum calcium increased significantly in people taking alfacalcidol, while there were NS changes in calcium in people taking placebo, p<0.001 between groups.<sup>340,341</sup> (Level 1 +)

*Serum phosphorus*

Two RCTs showed that there were NS changes in serum P in the alfacalcidol or placebo groups.<sup>340,341</sup> (Level 1+)

*Serum parathyroid hormone (PTH)*

The RCT of Hamdy et al. showed a NS decrease in iPTH with alfacalcidol treatment and a significant increase in iPTH in the placebo group. At 24 months, iPTH returned to baseline levels in those with alfacalcidol treatment. (Level 1+)

The RCT of Rix et al. showed a significant decrease in iPTH with treatment with alfacalcidol, whereas there were NS changes in iPTH in the placebo group,  $p < 0.05$  between groups. (Level 1+)

*Serum alkaline phosphatase (ALP)*

Bone-specific ALP significantly decreased in the alfacalcidol group, whereas there was NS change in ALP in the placebo group.<sup>341</sup> (Level 1+)

*Serum osteocalcin*

Osteocalcin significantly decreased in the alfacalcidol group, whereas there was NS change in osteocalcin in the placebo group. At the end of the study only 1 person in the alfacalcidol group had osteocalcin levels above the reference range (4.2–31.4 ng/ml), whereas 6 people in the placebo group had osteocalcin levels exceeding reference ranges.<sup>341</sup> (Level 1+)

*Change in creatinine clearance*

Two RCTs showed that CrCl decreased significantly in both placebo and alfacalcidol groups, but there were NS differences between treatments.<sup>340,341</sup> (Level 1+)

*Bone mineral density (BMD)*

There was a significant difference for BMD of the spine in the alfacalcidol versus placebo group (4.2%,  $p < 0.05$ ).<sup>341</sup> (Level 1+)

There was a significant difference for BMD of the femoral neck in the alfacalcidol versus placebo group (4.9%,  $p < 0.05$ ).<sup>341</sup> (Level 1+)

There were NS changes in total body BMD or forearm BMD in the placebo or the alfacalcidol groups.<sup>341</sup> (Level 1+)

*Indices of bone formation, remodelling and structure*

In people with histological bone abnormalities at baseline (N=100), there were NS differences in bone volume in the placebo (N=45) or alfacalcidol (N=55). (Level 1+)

Osteomalacia improved in people taking alfacalcidol as the number of osteoid lamellae decreased whereas the number of osteoid lamellae increased in the placebo group,  $p = 0.002$  between groups. (Level 1+)

The proportion of people with bone abnormalities at the beginning of the study was similar between the placebo (73%) and alfacalcidol (76%) groups. After 24 months treatment, 54% of people taking alfacalcidol and 82% on placebo had bone abnormalities (no p given). (Level 1+)

Fibrosis significantly decreased in people taking alfacalcidol, while fibrosis increased in the placebo group,  $p=0.0002$  between groups. (Level 1+)

Osteoid volume, osteoid surface, osteoblast surface, and osteoclast surface all decreased significantly in the alfacalcidol group, whereas there were NS changes in any of these parameters in the placebo group,  $p<0.05$  between groups for each outcome. (Level 1+)

There were NS differences in mineral apposition rate between placebo or alfacalcidol groups. (Level 1+)

Bone formation rate decreased significantly in alfacalcidol group, but there was NS change in placebo and NS difference between groups. (Level 1+)

Bone resorption decreased in people taking alfacalcidol compared with placebo. The eroded bone surface significantly decreased in the alfacalcidol group while it increased in the placebo group,  $p=0.04$  between groups. Also, alfacalcidol was associated with a significant decrease of active eroded surface compared with placebo,  $p=0.0006$  between groups.<sup>340</sup> (Level 1+)

#### Adverse events

Mild hypercalcaemia ( $>2.63$  mmol/l on 2 occasions) was seen in 10/89 patients receiving alfacalcidol and 3/87 patients receiving placebo ( $p=0.09$ , NS). Severe hypercalcaemia ( $>3.00$  mmol/l on 1 occasion) was observed in 4 people taking alfacalcidol and 0 people on placebo.<sup>340</sup> (Level 1+)

Hypercalcaemia occurred in 1/18 people on alfacalcidol.<sup>341</sup> (Level 1+)

Mild GI disturbances were reported in 6/89 people on alfacalcidol and 1/87 on placebo.<sup>340</sup> (Level 1+)

Pseudogout was reported by 2/89 people on alfacalcidol.<sup>340,340</sup> (Level 1+)

**Table 13.4 Summary of studies comparing alfacalcidol with placebo**

Study	Population	Duration (months)	Alfacalcidol (N)	Placebo (N)	Outcome	Size effect
340	CrCl 15–50 ml/min, 75% had bone abnormalities	24	89	87	Change iPTH (pmol/l)	Alfacalcidol: -1.6 pmol/l, NS Placebo +7.3 pmol/l, $p<0.001$
341	CrCl 10–60 ml/min and Ca $<1.35$ mmol/l and P $<2.0$ mmol/l.	18	16	15	Change iPTH (%)	Alfacalcidol: -47%, $p<0.05$ Placebo NS $p<0.05$ between groups

*continued*

Table 13.4 Summary of studies comparing alfacalcidol with placebo – *continued*

Study	Population	Duration (months)	Alfacalcidol (N)	Placebo (N)	Outcome	Size effect
341	CrCl 10–60 ml/min and Ca <1.35 mmol/l and P <2.0 mmol/l.	18	16	15	Change osteocalcin (%)	Alfacalcidol: –24%, p<0.05 Placebo: +25%, NS p<0.05 between groups
341	CrCl 10–60 ml/min and Ca <1.35 mmol/l and P <2.0 mmol/l.	18	16	15	Change bone-specific alkaline phosphatase (%)	Alfacalcidol: –48% p<0.05 Placebo: NS
340	CrCl 15–50 ml/min, 75% had bone abnormalities	24	89	87	Change in CrCl	Alfacalcidol: –5.7ml/min Placebo: –4.0 ml/min NS between treatments
341	CrCl 10–60 ml/min and Ca <1.35 mmol/l and P <2.0 mmol/l.	18	16	15	Change in CrCl	Decreased significantly in both placebo and alfacalcidol groups NS between treatments.
341	CrCl 10–60 ml/min and Ca <1.35 mmol/l and P <2.0 mmol/l.	18	16	15	Change Bone Mineral Density	Alfacalcidol spine: +2.9% NS Placebo spine: –1.1% change, NS Alfacalcidol versus placebo group (4.2%, p<0.05). Alfacalcidol femoral neck : +1.5%, NS placebo femoral neck: –1.5%, NS Alfacalcidol versus placebo group (4.9%, p<0.05). NS changes in total body BMD in the placebo or the alfacalcidol NS changes in forearm BMD in the placebo or the alfacalcidol groups

*continued*

**Table 13.4 Summary of studies comparing alfacalcidol with placebo – *continued***

Study	Population	Duration (months)	Alfacalcidol (N)	Placebo (N)	Outcome	Size effect
340	CrCl 15–50 ml/min, 75% had bone abnormalities	24	55	45	Change Bone volume	Alfacalcidol: 1.22 Placebo: 1.09  p=0.75 between groups
		24	55	45	Change Osteoid volume	Alfacalcidol: –0.30, p<0.01 Placebo: 0.09, NS  p=0.005 between groups
		24	55	45	Change Osteoid surface	Alfacalcidol: –6.85, p<0.01 Placebo: +1.35, NS  p=0.008 between groups
		24	55	45	Change Eroded surface	Alfacalcidol: –3.76 Placebo: +0.45  p=0.04 between groups
		24	55	45	Change Osteoclast surface	Alfacalcidol: –0.30, NS NS placebo: +0.17  p=0.002 between groups
		24	55	45	Change Bone formation rate	Alfacalcidol: –4.66, p<0.05 Placebo: +0.51  p=0.15 NS between groups
		24	55	45	Change Mineral apposition rate (µm/day)	NS changes in alfacalcidol or placebo and NS between groups (p=0.34)

## ▷ Paricalcitol versus placebo

Refer to Table 13.5 for a summary of studies.

*Serum calcium*

Mean serum calcium increased slightly in people taking paricalcitol, while there were small decreases in serum calcium in the placebo group, NS between groups.<sup>342</sup> (Level 1+)

*Serum phosphorus*

There were NS changes in serum phosphate in the paricalcitol or placebo groups.<sup>342</sup> (Level 1 +)

*Serum parathyroid hormone (PTH)*

Serum iPTH decreased significantly from baseline to 6 months treatment with paricalcitol, whereas iPTH increased in the placebo group (p<0.001 between groups).<sup>342</sup> (Level 1+)



*Serum alkaline phosphatase (ALP)*

Bone-specific ALP significantly decreased from baseline to 6 months in the paricalcitol group, compared with a smaller decrease in bone ALP in the placebo group,  $p < 0.001$  between groups.<sup>342</sup> (Level 1+)

*Serum osteocalcin*

Serum osteocalcin significantly decreased in the paricalcitol group, compared with an increase in osteocalcin in the placebo group ( $p < 0.001$  between groups).<sup>342</sup> (Level 1+)

*Change in GFR*

After 6 months, eGFR decreased in both placebo and paricalcitol groups, but there were NS differences between treatments.<sup>342</sup> (Level 1+)

*Two consecutive reductions in iPTH  $\geq 30\%$  from baseline*

Significantly more people taking paricalcitol achieved 2 consecutive  $\geq 30\%$  decreases in serum iPTH from baseline compared with people taking placebo ( $p < 0.001$  between groups). Significantly more people taking paricalcitol achieved iPTH  $< 110$  ng/l compared with those on placebo.<sup>342</sup> (Level 1+)

*Four consecutive reductions in iPTH  $\geq 30\%$  from baseline*

Significantly more people taking paricalcitol achieved 4 consecutive  $\geq 30\%$  decreases in serum iPTH from baseline compared with the placebo group ( $p < 0.001$  between groups).<sup>342</sup> (Level 1+)

*Urinary deoxypryidinoline*

There were NS differences between paricalcitol or placebo groups for changes in urinary deoxypryidinoline.<sup>342</sup> (Level 1+)

*Urinary pyridinoline*

Urinary pyridinoline decreased significantly in the paricalcitol group, compared with an increase in the placebo group ( $p = 0.006$  between groups).<sup>342</sup> (Level 1+)

*Adverse events*

Hypercalcaemia (2 consecutive Ca  $> 2.62$  mmol/l) occurred in 2 people on paricalcitol and no people on placebo (NS).

Hyperphosphataemia (2 consecutive PO<sub>4</sub>  $> 1.78$  mmol/l) occurred in 11 people on paricalcitol and 13 people on placebo (NS).<sup>342</sup> (Level 1+)

**Table 13.5 Summary of studies comparing paricalcitol with placebo**

Study	Population	Duration (months)	Paricalcitol (N)	Placebo (N)	Outcome	Size effect
342	3 pooled RCTs: CKD, iPTH $\geq$ 150 pg/ml, Ca 1.99–2.40 mmol/l and PO <sub>4</sub> $\leq$ 1.68 mmol/l.	6	101	108	Change iPTH (%)	Paricalcitol: –45.2% (max) Placebo: +13.9% (max) p<0.001 between groups
			101	108	2 consecutive decreases $\geq$ 30% of iPTH	Paricalcitol: 91% Placebo: 13% p<0.001 between groups
			100	104	Change osteocalcin, ng/ml	Paricalcitol: –21.6 ng/ml Placebo: +10.7 ng/ml p<0.001 between groups
			101	107	Change Bone-specific alkaline phosphatase ( $\mu$ g/l)	Paricalcitol: –7.89 $\mu$ g/l Placebo: –1.44 $\mu$ g/l, p<0.001 between groups
			82	93	Change in GFR:	Paricalcitol: –2.52 ml/min/ 1.73 m <sup>2</sup> , (–10.4%) Placebo: –1.57 ml/min/ 1.73 m <sup>2</sup> (–6.95%) NS between treatments.

- ▷ Before versus after treatment with ergocalciferol (vitamin D2)

#### *Serum calcium*

Mean serum calcium did NS change after 6 months treatment with ergocalciferol in the whole group (N=66), stage 3 CKD alone (N=44) or stage 4 CKD alone (N=22).<sup>343</sup> (Level 3)

#### *Serum phosphate*

Mean serum phosphate did NS change after 6 months treatment with ergocalciferol in the whole group, stage 3 CKD alone or stage 4 CKD alone.<sup>343</sup> (Level 3)

#### *Serum parathyroid hormone (PTH)*

In those with stage 3 CKD (N=44), iPTH significantly decreased after 6 months of ergocalciferol treatment (–22%, p<0.005). In the stage 4 CKD group (N=22) there was NS change in iPTH.<sup>343</sup> (Level 3)

#### *Adverse events*

There were no cases of hypercalcaemia or hyperphosphataemia before or after ergocalciferol.<sup>343</sup> (Level 3)

### 13.3.5 From evidence to recommendations

The classification in the BNF<sup>344</sup> of the forms of vitamin D available as pharmacological supplementation can be confusing. Both preparations containing ergocalciferol (vitamin D<sub>2</sub>) and cholecalciferol (vitamin D<sub>3</sub>) are listed under the heading ‘ergocalciferol’.

Tablets of ergocalciferol combined with calcium are the cheapest form of vitamin D, but preparations of cholecalciferol combined with calcium are also cheaper than alfacalcidol and calcitriol. The GDG observed that cholecalciferol is the most commonly prescribed form used to treat simple vitamin D deficiency in primary care.

The GDG noted that the costs of 1- $\alpha$ -hydroxyvitamin D (alfacalcidol) and 1,25-dihydroxyvitamin D (calcitriol) are very similar.

There is no evidence as to whether one form of vitamin D is more effective than another as all the studies were comparisons with placebo and there were no trials that looked at 25-hydroxyvitamin D.

The GDG noted that all forms of vitamin D will suppress PTH secretion.

It was agreed that given the similar prevalence of vitamin D deficiency in people with stage 1, 2, 3A and 3B CKD it was most likely that the deficiency was related to poor dietary intake or limited sunlight exposure. Renal hydroxylation was likely to be normal in these people. They therefore recommended that ergocalciferol or cholecalciferol should be the first treatment used to treat vitamin D deficiency in these people.

Because of reduced renal hydroxylation in people with stage 4 and 5 CKD the GDG recommended that when vitamin D supplementation was necessary in these people, it should be with the 1- $\alpha$ -hydroxylated or 1,25-dihydroxylated forms.

Although no statistically significant increase in the overall frequency of hypercalcaemia was observed in people with CKD given vitamin D, severe hypercalcaemia occurred in 4 people on calcitriol versus 0 people in the placebo group in one study of calcitriol. The GDG also noted that the BNF suggests that ‘all people receiving pharmacological doses of vitamin D should have the plasma calcium concentration checked at intervals (initially weekly) and whenever nausea or vomiting are present’. The GDG recommended that further research should be undertaken on the occurrence of hypercalcaemia in people with CKD treated with different vitamin D preparations.

### 13.3.6 RECOMMENDATIONS

- R67** When vitamin D supplementation is indicated in people with CKD, offer:
- cholecalciferol or ergocalciferol to people with stage 1, 2, 3A or 3B CKD
  - 1- $\alpha$ -hydroxycholecalciferol (alfacalcidol) or 1,25-dihydroxycholecalciferol (calcitriol) to people with stage 4 or 5 CKD.
- R68** Monitor serum calcium and phosphate concentrations in people receiving 1- $\alpha$ -hydroxycholecalciferol or 1,25-dihydroxycholecalciferol supplementation.\*

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\* Detailed advice concerning management of bone and mineral disorders in CKD is beyond the scope of this guideline. Where uncertainty exists seek advice from your local renal service.

# 14 Specific complications of CKD – anaemia

## 14.1 Anaemia identification in people with CKD

### 14.1.1 Clinical introduction

We know from epidemiological data that the prevalence of anaemia increases as GFR declines (Table 14.1); we also know that anaemia develops relatively early during the course of CKD.

**Table 14.1 Prevalence of anaemia from NHANES III**

Stage of CKD	eGFR (ml/min/1.73 m <sup>2</sup> )	Median Hb in men (g/dl)	Median Hb in women (g/dl)	Prevalence of anaemia*
2	60	14.9	13.5	1%
3	30	13.8	12.2	9%
4	15	12.0	10.3	33%

\*Hb <12.0 g/dl in men, Hb <11.0 g/dl in women.  
 (Reprinted from *American Journal of Kidney Diseases*, copyright 2003, with permission from Elsevier: Coresh J, Astor BC, Greene T et al. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third national health and nutrition examination survey. *American Journal of Kidney Diseases* 2003; 41(1):1–12.)<sup>20</sup>

NICE clinical guideline 39 ('Anaemia management in people with CKD')<sup>27</sup> recommended that management of anaemia should be considered in people with anaemia of CKD when their haemoglobin (Hb) level is less than or equal to 11 g/dl. The guideline was written for people with a GFR <60 ml/min/1.73 m<sup>2</sup> already known to have a haemoglobin level ≤11 g/dl but gave no recommendations about testing for anaemia.

In the UK we know that from primary care data, 85% of patients who have had a serum creatinine measurement have also had their haemoglobin level measured.<sup>19</sup> This study demonstrated that the prevalence of anaemia rises sharply from CKD stage 3B onwards (Table 14.2), suggesting the importance of testing for anaemia at levels of GFR <45 ml/min/1.73 m<sup>2</sup>.

**Table 14.2 Anaemia identification in CKD: prevalence of Hb <11 g/dl in the general population**

GFR stratum	<30 ml/min/1.73 m <sup>2</sup>	30–44 ml/min/1.73 m <sup>2</sup>	45–59 ml/min/1.73 m <sup>2</sup>	≥60 ml/min/1.73 m <sup>2</sup>
Hb tested, N (%)	439 (83.6)	2057 (83.1)	7308 (83.7)	22581 (85.1)
Hb <11 g/dl, N (%)	44 (10)	84 (4.1)	213 (2.9)	611(2.7)

Adapted and reproduced by permission from Macmillan Publishers Ltd: *Kidney International* (Stevens PE, O'Donoghue DJ, de Lusignan S et al. Chronic kidney disease management in the United Kingdom: NEOERICA project results. *Kidney International* 2007; 72(1):92–99).<sup>19</sup> Copyright 2007.

### 14.1.2 RECOMMENDATION

- R69** If not already measured, check the haemoglobin level in people with stage 3B, 4 and 5 CKD to identify anaemia (Hb <11.0 g/dl – see NICE clinical guideline 39: ‘Anaemia management in people with chronic kidney disease’). Determine the subsequent frequency of testing by the measured value and the clinical circumstances.

# 15 Information needs

## 15.1 Information, education and support for people with CKD and their carers

### 15.1.1 Clinical introduction

People accessing NHS services need to be provided with education to allow them to understand their condition and treatment and to be involved in decisions about their care. Current NHS policy recognises the need to develop patient-led services<sup>345</sup> and that education is of benefit to those with long term conditions, giving them skills and knowledge and ensuring they can be actively involved in planning their own care.<sup>346</sup>

This idea has been actively promoted within renal services, with the Renal National Service Framework Standard 1 stating that people with CKD should 'have access to information that enables them and their carers to make informed decisions and encourages partnership in decision-making'.<sup>347</sup>

This policy reflects the desire of people with CKD themselves to have information and education. A study by Ormandy et al.<sup>348</sup> concluded that people with CKD have identifiable information needs which change at different times as their condition progresses.

Information has typically been provided in the form of verbal information received face to face from health professionals in a clinical setting, or by way of written information such as leaflets provided at clinical appointments. Other ways of providing information include audio-visual methods such as CDs, videos and DVDs. Coulter et al.<sup>349</sup> have identified that 'where information leaflets are to be used in support of patients' involvement in treatment decisions, they must contain relevant, research-based data in a form that is acceptable and useful to patients'. In addition, such information should be based on the needs of those who will use the information and they should be involved in developing and testing the information.

However, although information is necessary to achieve informed decision-making, it is not always sufficient on its own, even where it is of good quality. Studies show that the context in which the information is given and providing support for the decision-making process are also important.<sup>350</sup> Therefore education programmes are being developed to ensure that people with CKD can not only access appropriate information but learn how to use it to make decisions about their own care.

- *What information, education, and support are needed for CKD patients and their carers to understand and cope with the diagnosis, treatment and outcome of CKD?*

### 15.1.2 Methodology

There were no studies that examined the impact of education, information, or support on people with early (stage 1–3) CKD. There were no studies that investigated support systems for carers of people with CKD. Most educational intervention studies were conducted in people

with advanced stage CKD prior to initiation of dialysis. The outcomes of interest were quality of life, compliance with medication, and preparation for ESRD therapy (timely creation for access for dialysis, hepatitis vaccinations, emotional issues surrounding initiation of dialysis, and choice of dialysis modality).

One open label RCT assessed the intent to start home-care dialysis in people with eGFR <30 ml/min/1.73 m<sup>2</sup> randomised to standard education (N=35, education on kidney disease, dietary instruction, and different dialysis modalities) or to a 2 phase education + standard care intervention (N=35, booklets and videos discussing advantages/disadvantages of self-care dialysis, followed by a group discussion of self-care dialysis with a nephrologist and predialysis nurse).<sup>351</sup>

One retrospective Japanese cohort study assessed planned initiation of renal replacement therapy (RRT) and choice of dialysis modality in people initiating dialysis who had received predialysis education (N=70: lectures on chronic renal failure, treatment, daily-life instructions, explanations of different dialysis modalities and dietary therapy) compared with people who did not receive predialysis education (N=106: standard dialysis information was provided by the attending physician if requested by the patient).<sup>352</sup>

An American retrospective cohort study assessed timing of vascular access in people exposed to the Healthy Start Clinic education program (N=61: consisting of lectures, handbooks, and slide presentations on chronic renal failure, treatment, explanations of dialysis modalities and dietary therapy) compared with patients who did not receive the Healthy Start Clinic education program (N=86: conventional care with dialysis modality information, CKD video, meeting with a social worker in hospital).<sup>353</sup>

A Canadian cohort study examined dialysis modality choice and urgent dialysis initiation in people taking a predialysis clinic education program (N=37), compared with people receiving standard care (N=39). The clinic education program consisted of discussions with a nurse educator, physician, social worker, and nutritionist about renal function, blood pressure, bone disease, and diet therapy over multiple visits.<sup>354</sup>

A potential source of bias in all the cohort studies may be the voluntary participation in the education group, such that these participants may have already been more concerned about their health, acted to enhance their health, and thus be better prepared for dialysis initiation compared with participants who did not receive education.

The effect of predialysis education in adults with CKD is summarised in Table 15.1 at the end of the evidence statements.

### 15.1.3 Health economics methodology

There were no health economics papers found to review.

### 15.1.4 Evidence statements

#### ▷ Planned initiation of dialysis

Two cohort studies showed that significantly more people in the predialysis education group had a planned initiation of RRT compared with those who did not receive education.<sup>352,354</sup> (Level 2+)

▷ Choice of dialysis modality

In an RCT, significantly more people in the education + standard care group intended to start self-care dialysis compared with the standard care group.<sup>351</sup> (Level 1+)

One cohort study showed NS differences between education and standard care groups for choice of haemodialysis.<sup>352</sup> (Level 2+)

Two cohort studies showed NS differences between education versus standard care for choice of peritoneal dialysis.<sup>352,354</sup> (Level 2+)

▷ Use of catheter for dialysis

One cohort study showed that significantly fewer people in the predialysis education group used a double-lumen catheter for haemodialysis compared with those who did not receive education.<sup>352</sup> (Level 2+)

Another cohort study showed that significantly fewer people in the predialysis education program initiated dialysis with a temporary catheter compared with people who did not participate in the education program.<sup>353</sup> (Level 2+)

▷ Permanent vascular access before initiation of dialysis

Significantly more people in the predialysis education program had arteriovenous fistulas placed before initiation of dialysis compared with people who did not participate in the education program.<sup>353</sup> (Level 2+)

▷ Permanent vascular access used for dialysis initiation

Significantly more people in the education program initiated dialysis with an arteriovenous fistula compared with people who did not participate in the program. Significantly fewer people in the predialysis education program initiated dialysis with a graft compared with people who did not participate in the education program.<sup>353</sup> (Level 2+)

**Table 15.1 Effect of predialysis education in adults with CKD**

Reference	Population	Intervention	Comparison	Outcome	Size effect
352	People initiating dialysis	Educational intervention N=70	No educational intervention N=106	Planned initiation of dialysis	Education: ≈65% No education: ≈35% p=0.001
354	People initiating dialysis	Clinic-based education N=37	Standard care N=39	Urgent dialysis start	Clinic education: 13% Standard care: 35% p<0.05
351	eGFR < 30 ml/min/ 1.73 m <sup>2</sup>	Standard care + 2 phase educational intervention N=28	Standard care N=34	Intent to start home-care dialysis	Education + standard care: 82.1% Standard care: 50% p=0.015

*continued*



**Table 15.1** Effect of predialysis education in adults with CKD – *continued*

Reference	Population	Intervention	Comparison	Outcome	Size effect
352	People initiating dialysis	Educational intervention N=70	No educational intervention N=106	Choice of haemodialysis	Education: 90% No education: 95% NS
				Choice of peritoneal dialysis	Education: 10% No education: 5% in NS
354	People initiating dialysis	Clinic-based education N=37	Standard care N=39	Choice of peritoneal dialysis	Education: 53% Standard care: 42% NS
353	Creatinine >4.0 mg/dl, creatinine clearance <20 ml/min, albuminuria, or microalbuminuria initiating haemodialysis	Healthy Start program educational intervention N=61	No Healthy Start educational intervention N=86	Permanent Vascular Access before Initiation of Dialysis	HS education: 77%, No HS education: 36% p<0.001
				Arteriovenous fistulas placed before dialysis initiation	HS education: 74%, No HS education: 38% p<0.05
				Permanent Vascular Access used for Initiation of Dialysis	HS education: 49% No HS education: 23% p<0.01
				Arteriovenous fistulas used to initiate dialysis	HS education: 70%, No HS education: 30% p<0.01
				Grafts used to initiate dialysis	HS education: 30%, No HS education: 70% p<0.01
352	People initiating dialysis	Educational intervention N=70	No educational intervention N=106	Use of double-lumen catheter to initiate dialysis	Education: 5% No education: 25%, p<0.0003
353	Creatinine >4.0 mg/dl, creatinine clearance <20 ml/min, albuminuria, or microalbuminuria initiating haemodialysis	Healthy Start Program educational intervention N=61	No Healthy Start educational intervention N=86	Use of a temporary catheter to initiate dialysis	HS Education: 51% No HS education: 77% p<0.001

### 15.1.5 From evidence to recommendations

Most studies had been carried out in people with stage 5 CKD around the time they were starting renal replacement therapy; however, they were asked what information they needed at an early stage of their disease. The evidence suggested topics that should be covered but the detailed content of education packages would vary depending on the individual.

People at different stages of CKD required different information, and, for example, people with stable stage 3A or 3B CKD did not need detailed information about dialysis. However, it was

agreed that it was important that people were given information about their prognosis and that they should be aware of options for dialysis access prior to having to make a decision about this.

The GDG agreed that it was not sufficient for people simply to be given information about CKD and its treatment. This information had to form part of a programme that educated them about the disease. It was agreed that it was important that after the education programme, people's understanding should be assessed. It was also agreed that programmes should be run by clinicians who have sufficient knowledge to be able to answer people's questions.

Older people do not always learn easily from information given on paper and some people may need psychological support to help them cope with the consequences of the information that they have been given.

A summary of research findings by Ormandy et al.<sup>348</sup> identified key information needs of people in renal units in the UK. The GDG used these to guide making recommendations.

We have not found evidence of cost-effectiveness. We do not believe this recommendation will have a big cost impact for the NHS since this is part of the existing National Service Framework and such programmes are already widespread.

### 15.1.6 RECOMMENDATIONS

- R70** Offer people with CKD education and information tailored to the stage and cause of CKD, the associated complications and the risk of progression.
- R71** When developing information or education programmes, involve people with CKD in their development from the outset. The following topics are suggested:
- What is CKD and how does it affect people?
  - What questions should people ask about their kidneys when they attend clinic?
  - What treatments are available for CKD, what are their advantages and disadvantages and what complications or side effects may occur as a result of treatment/medication?
  - What can people do to manage and influence their own condition?
  - In what ways could CKD and its treatment affect people's daily life, social activities, work opportunities and financial situation, including benefits and allowances available?
  - How can people cope with and adjust to CKD and what sources of psychological support are available.
  - When appropriate, offer information about renal replacement therapy (such as the frequency and length of time of dialysis treatment sessions or exchanges and pre-emptive transplantation), and the preparation required (such as having a fistula or peritoneal catheter).
  - Conservative management may be considered where appropriate.
- R72** Offer people with CKD high quality information or education programmes at appropriate stages of their condition to allow time for them to fully understand and make informed choices about their treatment
- R73** Healthcare professionals providing information and education programmes should ensure they have specialist knowledge about CKD and the necessary skills to facilitate learning.
- R74** Healthcare professionals working with people with CKD should take account of the psychological aspects of coping with the condition and offer access to appropriate support (for example, support groups, counselling or a specialist nurse).

## 15.2 Available tools to aid identification and maximise effectiveness of treatment and management of CKD

### 15.2.1 Clinical introduction

CKD is common, usually asymptomatic, often unrecognised and as a result subject to deficiencies in appropriate management and late referral of people with advanced disease to specialist services. A number of tools have recently been introduced to help identify people with CKD and aid early intervention and appropriate management to reduce/prevent complications and progression of CKD.

In March 2006 guidelines for the identification, management and referral of adult patients with chronic kidney disease were published by the Royal College of Physicians of London on behalf of a number of collaborating agencies.<sup>15</sup>

In April 2006 a Department of Health initiative led to the automatic reporting of an isotope dilution mass spectrometry (IDMS) traceable estimated GFR using the Modification of Diet in Renal Disease Study Equation (MDRD) whenever a serum creatinine is requested through any clinical chemistry laboratory.<sup>16</sup>

In April 2004 the new General Services (GMS) contract was introduced in the UK, and part of this change included the national Quality and Outcomes Framework (QOF). Participation by practices in the QOF is voluntary, but participation rates are high possibly because there is a financial incentive to do this. In March 2006, four renal domains were included for the first time in the QOF. These indicators focused on creating a register of people with chronic kidney disease with an eGFR  $<60$  ml/min/1.73 m<sup>2</sup> (stage 3–5 CKD), measuring blood pressure, achieving a target blood pressure and prescription of drugs blocking the renin–angiotensin system (ACE inhibitors or ARBs).

These national tools have increased referral of people with CKD to their local specialist and in turn have resulted in a number of local initiatives aimed at providing a structured delivery of care for people with kidney disease in partnership with primary care. This section was aimed at identifying whether any of these tools had yet improved the identification and management of adults with CKD.

### 15.2.2 Methodology

The literature was reviewed to assess the utility of computerised tools (decision support systems and information technologies) to aid primary care workers in identifying people with CKD and in offering the most appropriate and timely treatments. Outcomes of interest were appropriate investigations and follow-up, referral, medicines management, and achieving clinical targets.

The New Opportunities for Early Renal Intervention by Computerised Assessment (NEOERICA) project used computer searching to extract a retrospective dataset of all patients with a valid serum creatinine measurement from 17 primary care practices in the UK (N=38,262 with valid serum creatinine measures).<sup>19</sup> The aim of this study was to ascertain if computerised medical records contain sufficient information to estimate the prevalence of CKD, its comorbidities, as well as medication usage and BP targets achieved. Manual searching

of medical records from 1 practice (N=492 with stages 3–5 CKD identified by computer searching) was used to test the validity of computer searching to estimate the prevalence of CKD.<sup>355</sup> In both of these retrospective observational studies, ethnicity was unreliably reported, and the CKD prevalence estimation was limited to only stages 3 to 5 due to poor recording of proteinuria and haematuria in the medical records. Serum creatinine measurements were calibrated to the original MDRD study in Stevens et al., but not in Anandarajah et al.

Two publications from the Optimal Renal Care UK (ORC UK) study assessed the utility of a disease management programme (DMP) that was guideline- and algorithm-based to identify, manage, and appropriately refer people with CKD.<sup>356,357</sup>

In a case series study, a clinical tool to identify people at risk of rapid progression of kidney disease ( $\geq 25\%$  decline in mean eGFR over 2 years) was developed in adults  $\geq 66$  years (mean age 76.1 years, N=6789) and validated in a second cohort of older adults (N=3395). Medications dispensed prior to the index creatinine measurements were used to determine disease categories, which were considered in a stepwise logistic regression analysis. Risk scores were calculated for each subject and then categorised into risk classes (I to V).<sup>358</sup> Albuminuria was not included in the model and disease categories assigned based on medication may misclassify and underestimate true prevalence of a certain disease.

Another study investigated the ability of the Framingham prediction equation to predict 5 year and 10 year risk of cardiac events (myocardial infarction and fatal coronary heart disease) in people with CKD from the pooled ARIC and CHS studies (N=934).<sup>359</sup>

### 15.2.3 Health economics methodology

There were no health economics papers found to review.

### 15.2.4 Evidence statements

- ▷ Computer searching of medical records

#### *Identifying people with CKD*

In the NEOERICA validation study, computer searching of medical records from one UK practice identified 492 people with stage 3–5 CKD (adjusted prevalence of stage 3–5 CKD was 5.1%). Only 36/492 (7.3%) of people identified as having CKD were known to renal services or had a renal diagnosis on their records. Manual checking of medical records identified only 4 additional cases of CKD missed by the computer search.<sup>355</sup> (Level 3)

In the large NEOERICA study (N=38,262 with valid serum creatinine measures, 17 UK practices), computer searching identified 11,731 (30.7%) people with an eGFR  $< 60$  ml/min/1.73 m<sup>2</sup>. Only 242 (2.1%) of these were coded as a renal diagnosis in the records. The recording of a renal diagnosis improved as renal function declined.<sup>19</sup> (Level 3)

#### *Achieving clinical targets*

The NEOERICA study showed that blood pressure targets were not achieved in most instances: only 63/461 (13.7%) of people with hypertension and eGFR  $< 30$  ml/min/1.73 m<sup>2</sup> achieved BP

<130/80 mmHg. Only 571/6235 (9.2%) people with hypertension and eGFR 45–59 ml/min/1.73 m<sup>2</sup> achieved BP <130/80 mmHg. Only 270/1313 (20%) of people with diabetes, hypertension, and eGFR <60 ml/min/1.73 m<sup>2</sup> achieved target BP <130/80 mmHg.<sup>19</sup> (Level 3)

▷ Disease management programmes

*Achieving clinical targets*

The percentage of total cholesterol measurements in target range increased significantly after 9 months of the DMP (64.5% in target at baseline to 75% in target after 9 months,  $p=0.001$ ). In people with stage 3–5 CKD without diabetes and a PCR <100, the percentage of systolic blood pressure measurements in target range increased significantly after 9 months of the DMP (37.1% in target at baseline to 53.2% in target after 9 months,  $p=0.001$ ).<sup>357</sup> (Level 3)

There were NS improvements in HDL cholesterol, LDL cholesterol, or triglyceride levels after 9 months on the DMP. In people with stage 3–5 CKD, with diabetes or a PCR >100, there were NS differences in blood pressure measurements in target range at baseline compared to after 9 months on the DMP.<sup>357</sup> (Level 3)

*Preservation of renal function*

The median fall in eGFR was significantly less after 12 months on the DMP ( $\geq 0.32$  ml/min/1.73 m<sup>2</sup>) compared with 9 months preceding the DMP ( $\geq 3.69$  ml/min/1.73 m<sup>2</sup>,  $p < 0.001$ ). This was also true for people with eGFR fall  $\geq 5$  ml/min/1.73 m<sup>2</sup> ( $\geq 9.90$  ml/min/1.73 m<sup>2</sup> prior to DMP versus  $\geq 1.70$  ml/min/1.73 m<sup>2</sup> after the DMP,  $p < 0.001$ ).<sup>357</sup> (Level 3)

*Impact of eGFR reporting on nephrology referrals*

Following initiation of a disease management programme (DMP), the number of referrals rose 2.7 times compared to the number of referrals prior to DMP commencement. After introduction of a referral assessment service, the referral rate decreased rapidly and by 6 months, an average of five new CKD stage 4 or 5 patients were being referred (0.16% incidence). This referral rate was within the capacity of local nephrology services.<sup>356</sup> (Level 3)

*Risk tool for predicting rapid progression of kidney dysfunction ( $\geq 25\%$  decline in mean eGFR between the two study periods)*

Multivariate analysis showed that age >75 years old, cardiac disease, diabetes, gout, and anti-emetic drug use were significantly associated with rapid progression of kidney dysfunction. In both the derivation (N=6789) and validation cohorts (N=3395), people in the Class V risk index had triple the risk of rapid renal disease progression compared with people in the Class I risk index. The c-statistic for the model was 0.59, indicating a modest ability to discriminate between people with and without risk of rapid renal disease progression.<sup>358</sup> (Level 3)

*Utility of the Framingham equation to predict cardiac events in people with CKD*

The Framingham prediction equation had poor discrimination (the ability to separate those who had cardiac events from those who did not) in the CKD cohort. The Framingham equation correctly identified men with CKD who would develop a cardiac event within 10 years only

60% of the time, compared with 69% of the time in the non-CKD male cohort and 73% in the original Framingham cohort. In women with CKD, discrimination was 73% for 10-year cardiac events compared with 76% in the original Framingham cohort.<sup>359</sup> (Level 3)

The Framingham equation under-predicted cardiac events when men with CKD were stratified into quintiles of Framingham Risk. The 5-year calibration for men was poor (chi-square 33.4,  $p < 0.001$ ) and the 10-year calibration was also poor (chi-square 71.3,  $p < 0.001$ ). The Framingham equation under-predicted cardiac events in women with CKD and had poor 5- and 10-year calibration. Recalibrated models performed better, although prediction remained poor in men with CKD. In women with CKD, re-calibration showed NS difference in predicted and observed cardiac events in 5- and 10-year probability models.<sup>359</sup> (Level 3)

### 15.2.5 From evidence to recommendations

The GDG noted that the NEOERICA study had been carried out prior to the introduction of GFR reporting and prior to the inclusion of renal outcomes in the QOF. It was also prior to the introduction of appropriate Read Codes and the renal NSF. All of these factors may have subsequently improved the identification of CKD in primary care populations. Nevertheless the GDG agreed that it was still possible that people with an abnormal GFR or proteinuria were not classified as having CKD. As this information is usually recorded on practice computer databases it appears that it would be quite simple to devise programmes to identify these people.

The introduction of a disease management programme tailored to people with CKD resulted in significant improvements in blood pressure and lipid control. A significant reduction in progression of CKD also followed the introduction of the disease management programme.

The GDG were surprised that the tool for predicting rapid decline in kidney function did not include known factors such as hypertension and proteinuria in the score whilst anti-emetic use was. It was agreed that the anti-emetic use was probably a marker of the presence of an acute illness which may have affected GFR.

The GDG agreed that separate tools for the identification of people with CKD and the identification of people with CKD at risk of progressing would be useful.

### 15.2.6 RECOMMENDATIONS

There are no recommendations.

# References

- 1 National Institute for Health and Clinical Excellence. *Guidelines Manual*. UK: London: National Institute for Health and Clinical Excellence, 2007.
- 2 Department of Health. *National Service Framework for Renal Services – Part Two: Chronic kidney disease, acute renal failure and end of life care*. London: UK: Department of Health, 2005.
- 3 Arora P, Obrador GT, Ruthazer R et al. Prevalence, predictors, and consequences of late nephrology referral at a tertiary care center. *Journal of the American Society of Nephrology*. 1999; 10(6):1281–1286.
- 4 Innes A, Rowe PA, Burden RP et al. Early deaths on renal replacement therapy: the need for early nephrological referral. *Nephrology Dialysis and Transplantation*. 1992; 7(6):467–471.
- 5 Jungers P, Zingraff J, Albouze G et al. Late referral to maintenance dialysis: detrimental consequences. *Nephrology Dialysis and Transplantation*. 1993; 8(10):1089–1093.
- 6 Ratcliffe PJ, Phillips RE, Oliver DO. Late referral for maintenance dialysis. *British Medical Journal Clinical Research Ed*. 1984; 288(6415):441–443.
- 7 Sesso R, Belasco AG. Late diagnosis of chronic renal failure and mortality on maintenance dialysis. *Nephrology Dialysis and Transplantation*. 1996; 11(12):2417–2420.
- 8 Lameire N, Van BW. The pattern of referral of patients with end-stage renal disease to the nephrologist—a European survey. *Nephrology Dialysis and Transplantation*. 1999; 14 Suppl 6:16–23, 1999:16–23.
- 9 Ansell D, Feest T, Hodsman A, and Rao, R. *UK Renal Registry, The Renal Association, The Ninth Annual Report*. Bristol, UK: UK Renal Registry, 2006.
- 10 Drey N, Roderick P, Mullee M et al. A population-based study of the incidence and outcomes of diagnosed chronic kidney disease. *American Journal of Kidney Diseases*. 2003; 42(4):677–684.
- 11 John R, Webb M, Young A et al. Unreferred chronic kidney disease: a longitudinal study. *American Journal of Kidney Diseases*. 2004; 43(5):825–835.
- 12 Keith DS, Nichols GA, Gullion CM et al. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Archives of Internal Medicine*. 2004; 164(6): 659–663.
- 13 Go AS, Chertow GM, Fan D et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *New England Journal of Medicine*. 2004; 351(13):1296–1305 +1370.
- 14 Levey AS, Atkins R, Coresh J et al. Chronic kidney disease as a global public health problem: approaches and initiatives – a position statement from Kidney Disease Improving Global Outcomes. *Kidney International*. 2007; 72(3):247–259.
- 15 Royal College of Physicians. *Chronic kidney diseases in adults: UK guidelines for identification, management and referral*. London: RCP, 2006.
- 16 Department of Health. *Estimated Glomerular Filtration Rate (eGFR)*. London: DH, 2007.
- 17 *Quality and Outcomes Framework (QOF)*. Available from: Department of Health. Last accessed on: Feb. 28, 2008.
- 18 Office for National Statistics. *Office for National Statistics population and Vital Statistics, England And Wales*. 3-12-2007. <http://www.statistics.gov.uk/>
- 19 Stevens PE, O’Donoghue DJ, de Lusignan S et al. Chronic kidney disease management in the United Kingdom: NEOERICA project results. *Kidney International*. 2007; 72(1):92–99.
- 20 Coresh J, Astor BC, Greene T et al. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *American Journal of Kidney Diseases*. 2003; 41(1):1–12.
- 21 Centers for Disease Control and Prevention. *National Health and Nutrition Examination Survey*. Available from: Centers for Disease Control and Prevention. Last accessed on: Feb. 28, 2008.
- 22 Coresh J, Selvin E, Stevens LA et al. Prevalence of chronic kidney disease in the United States. *JAMA : the Journal of the American Medical Association*. 2007; 298(17):2038–2047.



- 23 Roderick PJ, Raleigh VS, Hallam L et al. The need and demand for renal replacement therapy in ethnic minorities in England. *Journal of Epidemiology and Community Health*. 1996; 50(3):334–339.
- 24 McClellan W, Warnock DG, McClure L et al. Racial differences in the prevalence of chronic kidney disease among participants in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Cohort Study. *Journal of the American Society of Nephrology*. 2006; 17(6):1710–1715.
- 25 Kidney Research UK. *Summaries of the ABLE Projects*. Available from: Kidney Research UK. Last accessed on: June 19, 2006.
- 26 National Institute for Health and Clinical Excellence. *Brief interventions and referral for smoking cessation in primary care and other settings*. (PHI001). London: UK: National Institute for Health and Clinical Excellence, 2006.
- 27 National Institute for Health and Clinical Excellence. *Anaemia management in people with chronic kidney disease (CKD)*. (CG39). London: UK: National Institute for Health and Clinical Excellence, 2006.
- 28 National Institute for Health and Clinical Excellence. *Hypertension: management of hypertension in adults in primary care*. (CG34). London: UK: National Institute for Health and Clinical Excellence, 2006.
- 29 National Institute for Health and Clinical Excellence. *Type 2 diabetes: the management of type 2 diabetes (update)*. (CG 66). London: UK: National Institute for Health and Clinical Excellence, 2008.
- 30 National Institute for Health and Clinical Excellence. *Cardiovascular risk assessment: the modification of blood lipids for the primary and secondary prevention of cardiovascular disease*. 2008. <http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11628>
- 31 National Institute for Health and Clinical Excellence. *Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk*. 2008. London: UK, National Institute for Health and Clinical Excellence.
- 32 Scottish Intercollegiate Guidelines Network. *Chronic Kidney Disease*. Edinburgh: SIGN, 2008.
- 33 Taal, M. *UK Renal Association Clinical Practice Guidelines*. The Renal Association, London, 2007.
- 34 Archibald G, Bartlett W, Brown A, Christie B, Elliott A. UK Consensus Conference on Early Chronic Kidney Disease. 2008.
- 35 National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *American Journal of Kidney Diseases*. 2002; 39(2:Suppl 1):S1–S266.
- 36 Caring for Australasians with Renal Impairment (CARI) Steering Committee. Proteinuria—CARI guidelines. *Australian Family Physician*. 2005; 34(11):942–943.
- 37 *Kidney Disease: improving global outcomes (KDIGO)*. Available from: Kidney Disease: Improving Global Outcomes (KDIGO). Last accessed on: Feb. 28, 2008.
- 38 Burkhardt H, Hahn T, Gretz N et al. Bedside estimation of the glomerular filtration rate in hospitalized elderly patients. *Nephron Clinical Practice*. 2005; 101(1):c1–c8.
- 39 Lamb EJ, Webb MC, Simpson DE et al. Estimation of glomerular filtration rate in older patients with chronic renal insufficiency: is the modification of diet in renal disease formula an improvement? *Journal of the American Geriatrics Society*. 2003; 51(7):1012–1017.
- 40 Harmoinen A, Lehtimäki T, Korpela M et al. Diagnostic accuracies of plasma creatinine, cystatin C, and glomerular filtration rate calculated by the Cockcroft-Gault and Levey (MDRD) formulas. *Clinical Chemistry*. 2003; 49(7):1223–1225.
- 41 Hojs R, Bevc S, Ekart R et al. Serum cystatin C as an endogenous marker of renal function in patients with mild to moderate impairment of kidney function. *Nephrology Dialysis and Transplantation*. 2006; 21(7):1855–1862.
- 42 Bicik Z, Bahcebasi T, Kulaksizoglu S et al. The efficacy of cystatin C assay in the prediction of glomerular filtration rate. Is it a more reliable marker for renal failure? *Clinical Chemistry & Laboratory Medicine*. 2005; 43(8):855–861.
- 43 Hayashi T, Nitta K, Uchida K et al. Clinical assessment of serum cystatin C as a marker of glomerular filtration rate in patients with various renal diseases. *Clinical & Experimental Nephrology*. 2000; 4(2): 133–136.



- 44 Christensson AG, Grubb AO, Nilsson JA et al. Serum cystatin C advantageous compared with serum creatinine in the detection of mild but not severe diabetic nephropathy. *Journal of Internal Medicine*. 2004; 256(6):510–518.
- 45 Mahajan S, Mukhiya GK, Singh R et al. Assessing glomerular filtration rate in healthy Indian adults: a comparison of various prediction equations. *Journal of Nephrology*. 2005; 18(3):257–261.
- 46 Rigalleau V, Lasseur C, Perlemoine C et al. Estimation of glomerular filtration rate in diabetic subjects: Cockcroft formula or modification of diet in renal disease study equation? *Diabetes Care*. 2005;28(4): 838–843.
- 47 Rigalleau V, Lasseur C, Perlemoine C et al. A simplified Cockcroft-Gault formula to improve the prediction of the glomerular filtration rate in diabetic patients. *Diabetes & Metabolism*. 2006; 32(1):56–62.
- 48 Bostom AG, Kronenberg F, Ritz E. Predictive performance of renal function equations for patients with chronic kidney disease and normal serum creatinine levels. *Journal of the American Society of Nephrology*. 2002; 13(8):2140–2144.
- 49 Spinler SA, Nawarskas JJ, Boyce EG et al. Predictive performance of ten equations for estimating creatinine clearance in cardiac patients. Iohexol Cooperative Study Group. *Annals of Pharmacotherapy*. 1998; 32(12): 1275–1283.
- 50 Poggio ED, Wang X, Greene T et al. Performance of the modification of diet in renal disease and Cockcroft-Gault equations in the estimation of GFR in health and in chronic kidney disease. *Journal of the American Society of Nephrology*. 2005; 16(2):459–466.
- 51 Hallan S, Asberg A, Lindberg M et al. Validation of the modification of diet in renal disease formula for estimating GFR with special emphasis on calibration of the serum creatinine assay. *American Journal of Kidney Diseases*. 2004; 44(1):84–93.
- 52 Froissart M, Rossert J, Jacquot C et al. Predictive performance of the modification of diet in renal disease and Cockcroft-Gault equations for estimating renal function. *Journal of the American Society of Nephrology*. 2005; 16(3):763–773.
- 53 Ibrahim H, Mondress M, Tello A et al. An alternative formula to the Cockcroft-Gault and the modification of diet in renal diseases formulas in predicting GFR in individuals with type 1 diabetes. *Journal of the American Society of Nephrology*. 2005; 16(4):1051–1060.
- 54 Levey AS, Coresh J, Greene T et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Annals of Internal Medicine*. 2006; 145(4):247–254.
- 55 Ricos C, Iglesias N, Garcia-Lario JV et al. Within-subject biological variation in disease: collated data and clinical consequences. *Annals of Clinical Biochemistry*. 2007; 44(Pt 4):343–352.
- 56 Fraser CG, Williams P. Short-term biological variation of plasma analytes in renal disease. *Clinical Chemistry*. 1983; 29(3):508–510.
- 57 Holzel WG. Intra-individual variation of some analytes in serum of patients with chronic renal failure. *Clinical Chemistry*. 1987; 33(5):670–673.
- 58 Holzel WG. Intra-individual variation of some analytes in serum of patients with insulin-dependent diabetes mellitus. *Clinical Chemistry*. 1987; 33(1):57–61.
- 59 Shepherd J, Warner M, Kilpatrick E. Stability of creatinine with delayed separation of whole blood and implications for eGFR. *Annals of Clinical Biochemistry*. 2007; 44(4):384–387.
- 60 Ford L, Berg J. Delay in separating blood samples affects creatinine measurement using the Roche kinetic Jaffe method. *Annals of Clinical Biochemistry*. 2008; 45(1):83–87.
- 61 Rapoport A, Husdan H. Endogenous creatinine clearance and serum creatinine in the clinical assessment of kidney function. *Canadian Medical Association Journal*. 1968; 99(9):149–156.
- 62 Pasternack A, Kuhlback B. Diurnal variations of serum and urine creatine and creatinine. *Scandinavian Journal of Clinical & Laboratory Investigation*. 1971; 27(1):1–7.
- 63 Preiss DJ, Godber IM, Lamb EJ et al. The influence of a cooked-meat meal on estimated glomerular filtration rate. *Annals of Clinical Biochemistry*. 2007; 44(Pt 1):35–42.

- 64 Pinto JR, Bending JJ, Dodds RA et al. Effect of low protein diet on the renal response to meat ingestion in diabetic nephropathy. *European Journal of Clinical Investigation*. 1991; 21(2):175–183.
- 65 Jacobsen FK, Christensen CK, Mogensen CE et al. Postprandial serum creatinine increase in normal subjects after eating cooked meat. *Proceedings of the European Dialysis & Transplant Association*. 1979; 16:506–512.
- 66 Mayersohn M, Conrad KA, Achari R. The influence of a cooked meat meal on creatinine plasma concentration and creatinine clearance. *British Journal of Clinical Pharmacology*. 1983; 15(2):227–230.
- 67 Cameron JS. Common clinical presentations and symptoms in renal disease. *Oxford Textbook of Medicine*. In: Weatherall DJ, Ledingham JGG, Warrell DA (eds), Oxford: UK: Oxford University Press, 1996: 3144–3191.
- 68 Jones GR, Newhouse IJ, Jakobi JM et al. The incidence of hematuria in middle distance track running. *Canadian Journal of Applied Physiology*. 2001; 26(4):336–349.
- 69 Ritchie CD, Bevan EA, Collier SJ. Importance of occult haematuria found at screening. *British Medical Journal*. 1986; 292(6521):681–683.
- 70 Britton JP, Dowell AC, Whelan P. Dipstick haematuria and bladder cancer in men over 60: results of a community study. *British Medical Journal*. 1989; 299(6706):1010–1012.
- 71 Chan RWY, Chow KM, Tam LS et al. Can the urine dipstick test reduce the need for microscopy for assessment of systemic lupus erythematosus disease activity? *Journal of Rheumatology*. 2005; 32(5): 828–831.
- 72 Chandhoke PS, McAninch JW. Detection and significance of microscopic hematuria in patients with blunt renal trauma. *Journal of Urology*. 1988; 140(1):16–18.
- 73 Gleeson MJ, Connolly J, Grainger R et al. Comparison of reagent strip (dipstick) and microscopic haematuria in urological out-patients. *British Journal of Urology*. 1993; 72(5:Pt 1):594–596.
- 74 Arm JP, Peile EB, Rainford DJ et al. Significance of dipstick haematuria. 1. Correlation with microscopy of the urine. *British Journal of Urology*. 1986; 58(2):211–217.
- 75 Pugia MJ, Wallace JF, Lott JA et al. Albuminuria and proteinuria in hospitalized patients as measured by quantitative and dipstick methods. *Journal of Clinical Laboratory Analysis*. 2001; 15(5):295–300.
- 76 Konta T, Hao Z, Takasaki S et al. Clinical utility of trace proteinuria for microalbuminuria screening in the general population. *Clinical & Experimental Nephrology*. 2007; 11(1):51–55.
- 77 Gilbert RE, Akdeniz A, Jerums G. Detection of microalbuminuria in diabetic patients by urinary dipstick. *Diabetes Research & Clinical Practice*. 1997; 35(1):57–60.
- 78 CortesSanabria L, MartinezRamirez HR, Hernandez JL et al. Utility of the dipstick micraltest II in the screening of microalbuminuria of diabetes mellitus type 2 and essential hypertension. *Revista de Investigacion Clinica*. 2006; 58(3):190–197.
- 79 Waugh JJ, Bell SC, Kilby MD et al. Optimal bedside urinalysis for the detection of proteinuria in hypertensive pregnancy: a study of diagnostic accuracy. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2005; 112(4):412–417.
- 80 Brown MA, Buddle ML. Inadequacy of dipstick proteinuria in hypertensive pregnancy. *Australian & New Zealand Journal of Obstetrics & Gynaecology*. 1995; 35(4):366–369.
- 81 Higby K, Suiter CR, Siler KT. A comparison between two screening methods for detection of microproteinuria. *American Journal of Obstetrics & Gynecology*. 1995; 173(4):1111–1114.
- 82 Meyer NL, Mercer BM, Friedman SA et al. Urinary dipstick protein: a poor predictor of absent or severe proteinuria. *American Journal of Obstetrics & Gynecology*. 1994; 170(1:Pt 1):137–141.
- 83 Paruk F, Moodley J, Daya PK et al. Screening for proteinuria in hypertensive disorders of pregnancy. *Journal of Obstetrics & Gynaecology*. 1997; 17(6):528–530.
- 84 Saudan PJ, Brown MA, Farrell T et al. Improved methods of assessing proteinuria in hypertensive pregnancy. *British Journal of Obstetrics & Gynaecology*. 1997; 104(10):1159–1164.
- 85 Gai M, Motta D, Giunti S et al. Comparison between 24-h proteinuria, urinary protein/creatinine ratio and dipstick test in patients with nephropathy: Patterns of proteinuria in dipstick-negative patients. *Scandinavian Journal of Clinical & Laboratory Investigation*. 2006; 66(4):299–308.

- 86 Agarwal R, Panesar A, Lewis RR. Dipstick proteinuria: Can it guide hypertension management? *American Journal of Kidney Diseases*. 2002; 39(6):1190–1195.
- 87 Tissot E, Woronoff-Lemsi MC, Cornette C et al. Cost-effectiveness of urinary dipsticks to screen asymptomatic catheter-associated urinary infections in an intensive care unit. *Intensive Care Med*. 2001; 27(12):1842–1847.
- 88 Waugh J, Bell SC, Kilby M et al. Effect of concentration and biochemical assay on the accuracy of urine dipsticks in hypertensive pregnancies. *Hypertension in Pregnancy*. 2001; 20(2):205–217.
- 89 Dube J, Girouard J, Leclerc P et al. Problems with the estimation of urine protein by automated assays. *Clinical Biochemistry*. 2005; 38(5):479–485.
- 90 Ballantyne FC, Gibbons J, O'Reilly DS. Urine albumin should replace total protein for the assessment of glomerular proteinuria. *Annals of Clinical Biochemistry*. 1993; 30(Pt 1):101–103.
- 91 Shihabi ZK, Konen JC, O'Connor ML. Albuminuria vs urinary total protein for detecting chronic renal disorders. *Clinical Chemistry*. 1991; 37(5):621–624.
- 92 Price CP, Newall RG, Boyd JC. Use of protein:creatinine ratio measurements on random urine samples for prediction of significant proteinuria: a systematic review. *Clinical Chemistry*. 2005; 51(9):1577–1586.
- 93 Foster MC, Hwang SJ, Larson MG et al. Cross-classification of microalbuminuria and reduced glomerular filtration rate: associations between cardiovascular disease risk factors and clinical outcomes. *Arch Intern Med*. 2007; 167(13):1386–1392.
- 94 Hallan S, Astor B, Romundstad S et al. Association of kidney function and albuminuria with cardiovascular mortality in older vs younger individuals: The HUNT II Study. *Arch Intern Med*. 2007; 167(22):2490–2496.
- 95 Cirillo M, Lanti MP, Menotti A et al. Definition of kidney dysfunction as a cardiovascular risk factor: use of urinary albumin excretion and estimated glomerular filtration rate. *Arch Intern Med*. 2008; 168(6): 617–624.
- 96 Brantsma AH, Bakker SJ, de ZD et al. Extended prognostic value of urinary albumin excretion for cardiovascular events. *Journal of the American Society of Nephrology*. 2008; advance e-publication.
- 97 Brantsma AH, Aththobari J, Bakker SJ et al. What predicts progression and regression of urinary albumin excretion in the nondiabetic population? *Journal of the American Society of Nephrology*. 2007; 18(2): 637–645.
- 98 Rodby RA, Rohde RD, Sharon Z et al. The urine protein to creatinine ratio as a predictor of 24-hour urine protein excretion in type 1 diabetic patients with nephropathy. The Collaborative Study Group. *American Journal of Kidney Diseases*. 1995; 26(6):904–909.
- 99 Ruggenenti P, Gaspari F, Perna A et al. Cross sectional longitudinal study of spot morning urine protein: Creatinine ratio, 24 hour urine protein excretion rate, glomerular filtration rate, and end stage renal failure in chronic renal disease in patients without diabetes. *British Medical Journal*. 1998; 316(7130):504–509.
- 100 Gatling W, Knight C, Mullee MA et al. Microalbuminuria in diabetes: A population study of the prevalence and an assessment of three screening tests. *Diabetic Medicine*. 1988; 5(4):343–347.
- 101 Hutchison AS, O'Reilly DSJ, MacCuish AC. Albumin excretion rate, albumin concentration, and albumin/creatinine ratio compared for screening diabetics for slight albuminuria. *Clinical Chemistry*. 1988; 34(10):2019–2021.
- 102 Marshall SM. Screening for microalbuminuria: Which measurement? *Diabetic Medicine*. 1991; 8(8): 706–711.
- 103 Chaiken RL, Khawaja R, Bard M et al. Utility of untimed urinary albumin measurements in assessing albuminuria in black NIDDM subjects. *Diabetes Care*. 1997; 20(5):709–713.
- 104 Gansevoort RT, Verhave JC, Hillege HL et al. The validity of screening based on spot morning urine samples to detect subjects with microalbuminuria in the general population. *Kidney International – Supplement*. 2005; 67(94):S28–S35.
- 105 Jafar TH, Chaturvedi N, Hatcher J et al. Use of albumin creatinine ratio and urine albumin concentration as a screening test for albuminuria in an Indo-Asian population.[see comment]. *Nephrology Dialysis and Transplantation*. 2007; 22(8):2194–2200.

- 106 Atkins RC, Briganti EM, Zimmet PZ et al. Association between albuminuria and proteinuria in the general population: the AusDiab Study. *Nephrology Dialysis and Transplantation*. 2003; 18(10):2170–2174.
- 107 Newman DJ, Thakkar H, Medcalf EA et al. Use of urine albumin measurement as a replacement for total protein. *Clinical Nephrology*. 1995; 43(2):104–109.
- 108 MacGregor MS, Traynor JP, O'Reilly DSJ et al. *Assessing proteinuria in chronic kidney disease: protein–creatinine ratio versus albumin–creatinine ratio*. 2007, personal correspondence.
- 109 Lum G. How effective are screening tests for microalbuminuria in random urine specimens? *Annals of Clinical & Laboratory Science*. 2000; 30(4):406–411.
- 110 Chitalia VC, Kothari J, Wells EJ et al. Cost-benefit analysis and prediction of 24-hour proteinuria from the spot urine protein–creatinine ratio. *Clinical Nephrology*. 2001; 55(6):436–447.
- 111 Bush WH, Choyke BL, Bluth RI, Casalino DD. *Renal failure*. National Guidelines Clearing House, 2005. [www.guideline.gov](http://www.guideline.gov)
- 112 Lindeman RD, Tobin J, Shock NW. Longitudinal studies on the rate of decline in renal function with age. *Journal of the American Geriatrics Society*. 1985; 33(4):278–285.
- 113 Garg AX, Papaioannou A, Ferko N et al. Estimating the prevalence of renal insufficiency in seniors requiring long-term care. *Kidney International*. 2004; 65(2):649–653.
- 114 Iseki K, Ikemiya Y, Iseki C et al. Proteinuria and the risk of developing end-stage renal disease. *Kidney International*. 2003; 63(4):1468–1474.
- 115 Klausen K, Borch JK, Feldt RB et al. Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. *Circulation*. 2004; 110(1):32–35.
- 116 Hillege HL, Fidler V, Diercks GF et al. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation*. 2002; 106(14):1777–1782.
- 117 Arnlov J, Evans JC, Meigs JB et al. Low-grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and nondiabetic individuals: the Framingham Heart Study. *Circulation*. 2005; 112(7):969–975.
- 118 Rahman M, Pressel S, Davis BR et al. Cardiovascular outcomes in high-risk hypertensive patients stratified by baseline glomerular filtration rate.[see comment][summary for patients in *Ann Intern Med*. 2006 Feb 7; 144(3):133; PMID: 16461958]. *Annals of Internal Medicine*. 2006; 144(3):172–180.
- 119 Tokmakova MP, Skali H, Kenchaiah S et al. Chronic kidney disease, cardiovascular risk, and response to angiotensin-converting enzyme inhibition after myocardial infarction: the Survival And Ventricular Enlargement (SAVE) study. *Circulation*. 2004; 110(24):3667–3673.
- 120 Wright RS, Reeder GS, Herzog CA et al. Acute myocardial infarction and renal dysfunction: a high-risk combination. *Annals of Internal Medicine*. 2002; 137(7):563–570.
- 121 Hillege HL, Nitsch D, Pfeffer MA et al. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. *Circulation*. 2006; 113(5):671–678.
- 122 Keough RMT, Kiberd BA, Dipchand CS et al. Outcomes of acute coronary syndrome in a large Canadian cohort: impact of chronic renal insufficiency, cardiac interventions, and anemia. *American Journal of Kidney Diseases*. 2005; 46(5):845–855.
- 123 Beddhu S, Allen BK, Cheung AK et al. Impact of renal failure on the risk of myocardial infarction and death. *Kidney International*. 2002; 62(5):1776–1783.
- 124 Kurella M, Yaffe K, Shlipak MG et al. Chronic kidney disease and cognitive impairment in menopausal women. *American Journal of Kidney Diseases*. 2005; 45(1):66–76.
- 125 O'Hare AM, Bertenthal D, Shlipak MG et al. Impact of renal insufficiency on mortality in advanced lower extremity peripheral arterial disease. *Journal of the American Society of Nephrology*. 2005; 16(2):514–519.
- 126 Gullion CM, Keith DS, Nichols GA et al. Impact of comorbidities on mortality in managed care patients with CKD. *American Journal of Kidney Diseases*. 2006; 48(2):212–220.
- 127 McCullough PA, Jurkovitz CT, Pergola PE et al. Independent components of chronic kidney disease as a cardiovascular risk state: results from the Kidney Early Evaluation Program (KEEP). *Arch Internal Medicine*. 2007; 167(11):1122–1129.

- 128 Wattanakit K, Folsom AR, Selvin E et al. Kidney function and risk of peripheral arterial disease: Results from the Atherosclerosis Risk in Communities (ARIC) study. *Journal of the American Society of Nephrology*. 2007; 18(2):629–636.
- 129 Patel UD, Young EW, Ojo AO et al. CKD progression and mortality among older patients with diabetes. *American Journal of Kidney Diseases*. 2005; 46(3):406–414.
- 130 So WY, Kong AP, Ma RC et al. Glomerular filtration rate, cardiorenal end points, and all-cause mortality in type 2 diabetic patients. *Diabetes Care*. 2006; 29(9):2046–2052.
- 131 Nag S, Bilous R, Kelly W et al. All-cause and cardiovascular mortality in diabetic subjects increases significantly with reduced estimated glomerular filtration rate (eGFR): 10 years' data from the South Tees Diabetes Mortality study. *Diabetic Medicine*. 2007; 24(1):10–17.
- 132 Shlipak MG, Stehman BC, Fried LF et al. The presence of frailty in elderly persons with chronic renal insufficiency. *American Journal of Kidney Diseases*. 2004; 43(5):861–867.
- 133 Kurella M, Chertow GM, Fried LF et al. Chronic kidney disease and cognitive impairment in the elderly: the health, aging, and body composition study. *Journal of the American Society of Nephrology*. 2005; 16(7):2127–2133.
- 134 Iseki K, Kinjo K, Iseki C et al. Relationship between predicted creatinine clearance and proteinuria and the risk of developing ESRD in Okinawa, Japan. *American Journal of Kidney Diseases*. 2004; 44(5):806–814.
- 135 Eriksen BO, Ingebretsen OC. The progression of chronic kidney disease: A 10-year population-based study of the effects of gender and age. *Kidney International*. 2006; 69(2):375–382.
- 136 O'Hare AM, Bertenthal D, Covinsky KE et al. Mortality risk stratification in chronic kidney disease: one size for all ages? *Journal of the American Society of Nephrology*. 2006; 17(3):846–853.
- 137 O'Hare AM, Choi AI, Bertenthal D et al. Age affects outcomes in chronic kidney disease. *Journal of the American Society of Nephrology*. 2007; 18(10):2758–2765.
- 138 National Kidney Foundation. *Kidney early evaluation program (KEEP)*. Available from: National Kidney Foundation, [www.kidney.org.uk](http://www.kidney.org.uk). Last accessed on: Feb. 27, 2008.
- 139 Hallan SI, Dahl K, Oien CM et al. Screening strategies for chronic kidney disease in the general population: follow-up of cross sectional health survey.[see comment]. *British Medical Journal*. 2006; 333(7577):1030–1031.
- 140 Hallan SI, Coresh J, Astor BC et al. International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. *Journal of the American Society of Nephrology*. 2006; 17(8):2275–2284.
- 141 Chadban SJ, Briganti EM, Kerr PG et al. Prevalence of kidney damage in Australian adults: The AusDiab kidney study. *Journal of the American Society of Nephrology*. 2003; 14(7:Suppl 2):S131–S138.
- 142 Haroun MK, Jaar BG, Hoffman SC et al. Risk factors for chronic kidney disease: a prospective study of 23,534 men and women in Washington County, Maryland. *Journal of the American Society of Nephrology*. 2003; 14(11):2934–2941.
- 143 New JP, Middleton RJ, Klebe B et al. Assessing the prevalence, monitoring and management of chronic kidney disease in patients with diabetes compared with those without diabetes in general practice. *Diabetic Medicine*. 2007; 24(4):364–369.
- 144 Gelber RP, Kurth T, Kausz AT et al. Association between body mass index and CKD in apparently healthy men. *American Journal of Kidney Diseases*. 2005; 46(5):871–880.
- 145 Stengel B, Tarver CM, Powe NR et al. Lifestyle factors, obesity and the risk of chronic kidney disease. *Epidemiology*. 2003; 14(4):479–487.
- 146 Kurella M, Lo JC, Chertow GM. Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults. *Journal of the American Society of Nephrology*. 2005; 16(7):2134–2140.
- 147 Elsayed EF, Tighiouart H, Griffith J et al. Cardiovascular disease and subsequent kidney disease. *Archives of Internal Medicine*. 2007; 167(11):1130–1136.
- 148 Muntner P, Coresh J, Smith JC et al. Plasma lipids and risk of developing renal dysfunction: the atherosclerosis risk in communities study. *Kidney International*. 2000; 58(1):293–301.
- 149 Borch-Johnsen K, Norgaard K, Hommel E et al. Is diabetic nephropathy an inherited complication? *Kidney International*. 1992; 41(4):719–722.



- 150 Seaquist ER, Goetz FC, Rich S et al. Familial clustering of diabetic kidney disease. Evidence for genetic susceptibility to diabetic nephropathy. *New England Journal of Medicine*. 1989; 320(18):1161–1165.
- 151 Freedman BI, Soucie JM, McClellan WM. Family history of end-stage renal disease among incident dialysis patients. *Journal of the American Society of Nephrology*. 1997; 8(12):1942–1945.
- 152 Speckman RA, McClellan WM, Volkova NV et al. Obesity is associated with family history of ESRD in incident dialysis patients. *American Journal of Kidney Diseases*. 2006; 48(1):50–58.
- 153 Tillin T, Forouhi N, McKeigue P et al. Microalbuminuria and coronary heart disease risk in an ethnically diverse UK population: A prospective cohort study. *Journal of the American Society of Nephrology*. 2005; 16(12):3702–3710.
- 154 Retnakaran R, Cull CA, Thorne KI et al. Risk factors for renal dysfunction in type 2 diabetes: U.K. Prospective Diabetes Study 74. *Diabetes*. 2006; 55(6):1832–1839.
- 155 Kiberd BA, Jindal KK. Screening to prevent renal failure in insulin dependent diabetic patients: an economic evaluation. *British Medical Journal*. 1995; 311(7020):1595–1599.
- 156 Boulware LE, Jaar BG, Tarver CM et al. Screening for proteinuria in US adults: a cost-effectiveness analysis. [see comment]. *JAMA : the Journal of the American Medical Association*. 2003; 290(23):3101–3114.
- 157 Howard K, White S, Chadban S et al. *The cost-effectiveness of early detection and intervention to prevent the progression of chronic kidney disease in Australia*. Melbourne: Australia: Kidney Health Australia, 2006.
- 158 Lindeman RD, Tobin JD, Shock NW. Association between blood pressure and the rate of decline in renal function with age. *Kidney International*. 1984; 26(6):861–868.
- 159 Fliser D, Franek E, Joest M et al. Renal function in the elderly: impact of hypertension and cardiac function. *Kidney International*. 1997; 51(4):1196–1204.
- 160 Lindeman RD. Is the decline in renal function with normal aging inevitable? *Geriatric Nephrology & Urology*. 1998; 8(1):7–9.
- 161 Hemmelgarn BR, Zhang J, Manns BJ et al. Progression of kidney dysfunction in the community-dwelling elderly. *Kidney International*. 2006; 69(12):2155–2161.
- 162 Halbesma N, Kuiken DS, Brantsma AH et al. Macroalbuminuria is a better risk marker than low estimated GFR to identify individuals at risk for accelerated GFR loss in population screening. *Journal of the American Society of Nephrology*. 2006; 17(9):2582–2590.
- 163 Rule AD, Gussak HM, Pond GR et al. Measured and estimated GFR in healthy potential kidney donors. *American Journal of Kidney Diseases*. 2004; 43(1):112–119.
- 164 Slack TK, Wilson DM. Normal renal function: CIN and CPAH in healthy donors before and after nephrectomy. *Mayo Clinic Proceedings*. 1976; 51(5):296–300.
- 165 Wetzels JF, Kiemeny LA, Swinkels DW et al. Age- and gender-specific reference values of estimated GFR in Caucasians: the Nijmegen Biomedical Study. *Kidney International*. 2007; 72(5):632–637.
- 166 Rowe JW, Andres R, Tobin JD et al. The effect of age on creatinine clearance in men: a cross-sectional and longitudinal study. *Journal of Gerontology*. 1976; 31(2):155–163.
- 167 Luyckx VA, Brenner BM. Low birth weight, nephron number, and kidney disease. *Kidney International – Supplement*. 2005;(97):S68–S77.
- 168 Cruickshank JK, Mzayek F, Liu L et al. Origins of the ‘black/white’ difference in blood pressure: roles of birth weight, postnatal growth, early blood pressure, and adolescent body size: the Bogalusa heart study. *Circulation*. 2005; 111(15):1932–1937.
- 169 Law CM, Shiell AW, Newsome CA et al. Fetal, infant, and childhood growth and adult blood pressure: a longitudinal study from birth to 22 years of age. *Circulation*. 2002; 105(9):1088–1092.
- 170 Evans M, Fryzek JP, Elinder CG et al. The natural history of chronic renal failure: results from an unselected, population-based, inception cohort in Sweden. *American Journal of Kidney Diseases*. 2005; 46(5):863–870.
- 171 Orth SR, Schroeder T, Ritz E et al. Effects of smoking on renal function in patients with type 1 and type 2 diabetes mellitus. *Nephrology Dialysis and Transplantation*. 2005; 20(11):2414–2419.
- 172 Hovind P, Rossing P, Tarnow L et al. Smoking and progression of diabetic nephropathy in type 1 diabetes. *Diabetes Care*. 2003; 26(3):911–916.

- 173 Orth SR, Stockmann A, Conrads C et al. Smoking as a risk factor for end-stage renal failure in men with primary renal disease. *Kidney International*. 1998; 54(3):926–931.
- 174 Ibanez L, Morlans M, Vidal X et al. Case-control study of regular analgesic and nonsteroidal anti-inflammatory use and end-stage renal disease. *Kidney International*. 2005; 67(6):2393–2398.
- 175 Earle KK, Porter KA, Ostberg J et al. Variation in the progression of diabetic nephropathy according to racial origin. *Nephrology Dialysis and Transplantation*. 2001; 16(2):286–290.
- 176 Xue JL, Eggers PW, Agodoa LY et al. Longitudinal study of racial and ethnic differences in developing end-stage renal disease among aged medicare beneficiaries. *Journal of the American Society of Nephrology*. 2007; 18(4):1299–1306.
- 177 Murray MD, Black PK, Kuzmik DD et al. Acute and chronic effects of nonsteroidal antiinflammatory drugs on glomerular filtration rate in elderly patients. *American Journal of the Medical Sciences*. 1995; 310(5):188–197.
- 178 Morlans M, Laporte JR, Vidal X et al. End-stage renal disease and non-narcotic analgesics: A case-control study. *British Journal of Clinical Pharmacology*. 1990; 30(5):717–723.
- 179 Fored CM, Ejerblad E, Lindblad P et al. Acetaminophen, aspirin, and chronic renal failure. *New England Journal of Medicine*. 2001; 345(25):1801–1808.
- 180 Myers GL, Miller WG, Coresh J et al. Recommendations for improving serum creatinine measurement: A report from the Laboratory Working Group of the National Kidney Disease Education Program. *Clinical Chemistry*. 2006; 52(1):5–18.
- 181 Jungers P, Joly D, Nguyen KT et al. Continued late referral of patients with chronic kidney disease. Causes, consequences, and approaches to improvement. *Presse Medicale*. 2006; 35(1:Pt 1):t–22.
- 182 Levinsky NG. Specialist evaluation in chronic kidney disease: too little, too late. *Annals of Internal Medicine*. 2002; 137(6):542–543.
- 183 National Institute for Health and Clinical Excellence. *Diagnosis and management of type 1 diabetes in children, young people and adults*. (CG15). London: UK: National Institute for Health and Clinical Excellence, 2004.
- 184 National Institute for Health and Clinical Excellence. *Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children*. (CG43). London: UK: National Institute for Health and Clinical Excellence, 2006.
- 185 Kohzuki M, Kamimoto M, Wu XM et al. Renal protective effects of chronic exercise and antihypertensive therapy in hypertensive rats with chronic renal failure. *Journal of Hypertension*. 2001; 19(10):1877–1882.
- 186 Hallan S, de MR, Carlsen S et al. Obesity, smoking, and physical inactivity as risk factors for CKD: are men more vulnerable? *American Journal of Kidney Diseases*. 2006; 47(3):396–405.
- 187 Castaneda C, Gordon PL, Uhlin KL et al. Resistance training to counteract the catabolism of a low-protein diet in patients with chronic renal insufficiency. A randomized, controlled trial. *Annals of Internal Medicine*. 2001; 135(11):965–976.
- 188 Eidemak I, Haaber AB, Feldt RB et al. Exercise training and the progression of chronic renal failure. *Nephron*. 1997; 75(1):36–40.
- 189 Pechter U, Ots M, Mesikepp S et al. Beneficial effects of water-based exercise in patients with chronic kidney disease. *International Journal of Rehabilitation Research*. 2003; 26(2):153–156.
- 190 Morales E, Valero MA, Leon M et al. Beneficial effects of weight loss in overweight patients with chronic proteinuric nephropathies. *American Journal of Kidney Diseases*. 2003; 41(2):319–327.
- 191 Saiki A, Nagayama D, Ohhira M et al. Effect of weight loss using formula diet on renal function in obese patients with diabetic nephropathy. *International Journal of Obesity*. 2005; 29(9):1115–1120.
- 192 Solerte SB, Fioravanti M, Schifino N et al. Effects of diet-therapy on urinary protein excretion albuminuria and renal haemodynamic function in obese diabetic patients with overt nephropathy. *International Journal of Obesity*. 1989; 13(2):203–211.
- 193 Perneger TV, Whelton PK, Puddey IB et al. Risk of end-stage renal disease associated with alcohol consumption. *American Journal of Epidemiology*. 1999; 150(12):1275–1281.

- 194 Varella L, Utermohlen V. Nutritional support for the patient with renal failure. *Critical Care Nursing Clinics of North America*. 1993; 5(1):79–96.
- 195 Klahr S, Buerkert J, Purkerson ML. Role of dietary factors in the progression of chronic renal disease. *Kidney International*. 1983; 24(5):579–587.
- 196 Ikkizler TA, Greene JH, Wingard RL et al. Spontaneous dietary protein intake during progression of chronic renal failure. *Journal of the American Society of Nephrology*. 1995; 6(5):1386–1391.
- 197 Pecoits FR, Lindholm B, Stenvinkel P. The malnutrition, inflammation, and atherosclerosis (MIA) syndrome — the heart of the matter. *Nephrology Dialysis and Transplantation*. 2002; 17(Suppl 11):28–31.
- 198 British Association for Parenteral and Enteral Nutrition. *Malnutrition Universal Screening Tool (“MUST”)*. BAPEN [www.bapen.org.uk/must\\_tool.html](http://www.bapen.org.uk/must_tool.html), 2003.
- 199 Levey AS, Greene T, Beck GJ et al. Dietary protein restriction and the progression of chronic renal disease: What have all of the results of the MDRD study shown? *Journal of the American Society of Nephrology*. 1999; 10(11):2426–2439.
- 200 Giovanetti S, Maggiore Q. A low nitrogen diet with proteins of high biological value for severe chronic uremia. *Lancet*. 1964; 1:1000–1003.
- 201 Klahr S, Levey AS, Beck GJ et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. *New England Journal of Medicine*. 1994; 330(13):877–884.
- 202 Block GA, Hulbert-Shearon TE, Levin NW et al. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: A national study. *American Journal of Kidney Diseases*. 1998; 31(4); 607–617.
- 203 Schwarz S, Trivedi BK, Kalantar-Zadeh K et al. Association of disorders in mineral metabolism with progression of chronic kidney disease. *Clinical Journal of the American Society of Nephrology*. 2006; 1(4):825–831.
- 204 Voormolen N, Noordzij M, Grootendorst DC et al. High plasma phosphate as a risk factor for decline in renal function and mortality in pre-dialysis patients. *Nephrology Dialysis and Transplantation*. 2007; 22(10):2909–2916.
- 205 Kestenbaum B. Phosphate metabolism in the setting of chronic kidney disease: significance and recommendations for treatment. *Seminars in Dialysis*. 2007; 20(4):286–294.
- 206 Sheikh MS, Maguire, JA et al. Reduction of dietary phosphorus absorption by phosphorus binders. A theoretical, in vitro, and in vivo study. *Journal of Clinical Investigation*. 1989; 83(1):66–73.
- 207 Lancaster KJ. Dietary treatment of blood pressure in kidney disease. *Advances in Chronic Kidney Disease*. 2004; 11(2):217–221.
- 208 Pedrini MT, Levey AS, Lau J et al. The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases: a meta-analysis. *Annals of Internal Medicine*. 1996; 124(7):627–632.
- 209 Fouque D, Laville M, Boissel JP. Low protein diets for chronic kidney disease in non diabetic adults. *Cochrane Database of Systematic Reviews*. 2006;(2):CD001892.
- 210 Robertson L, Waugh N, Robertson A. Protein restriction for diabetic renal disease. *Cochrane Database of Systematic Reviews*. 2007;(4):CD002181.
- 211 Ihle BU, Becker GJ, Whitworth JA et al. The effect of protein restriction on the progression of renal insufficiency. *New England Journal of Medicine*. 1989; 321(26):1773–1777.
- 212 Williams PS, Stevens ME, Fass G et al. Failure of dietary protein and phosphate restriction to retard the rate of progression of chronic renal failure: a prospective, randomized, controlled trial. *QJM: monthly journal of the Association of Physicians*. 1991; 81(1):837–855.
- 213 Locatelli F, Alberti D, Graziani G et al. Prospective, randomised, multicentre trial of effect of protein restriction on progression of chronic renal insufficiency. Northern Italian Cooperative Study Group. *Lancet*. 1991; 337(8753):1299–1304.
- 214 Rosman JBLK, Brandl M, Peris-Becht TPM et al. Protein-restricted diets in chronic renal failure: a four year follow-up shows limited indications. *Kidney International – Supplement*. 1989; 27(36):S96–S102.
- 215 Meloni C, Tatangelo P, Cipriani S et al. Adequate protein dietary restriction in diabetic and nondiabetic patients with chronic renal failure. *Journal of Renal Nutrition*. 2004; 14(4):208–213.



- 216 Hansen HP, Tauber LE, Jensen BR et al. Effect of dietary protein restriction on prognosis in patients with diabetic nephropathy. *Kidney International*. 2002; 62(1):220–228.
- 217 Dullaart RP, Beusekamp BJ, Meijer S et al. Long-term effects of protein-restricted diet on albuminuria and renal function in IDDM patients without clinical nephropathy and hypertension. *Diabetes Care*. 1993; 16(2):483–492.
- 218 Raal FJ, Kalk WJ, Lawson M et al. Effect of moderate dietary protein restriction on the progression of overt diabetic nephropathy: a 6-mo prospective study. *American Journal of Clinical Nutrition*. 1994; 60(4): 579–585.
- 219 Verberk WJ, Kroon AA, Lenders JW et al. Self-measurement of blood pressure at home reduces the need for antihypertensive drugs: a randomized, controlled trial. *Hypertension*. 2007; 50(6):1019–1025.
- 220 Williams B, Poulter NR, Brown MJ et al. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004-BHS IV. *Journal of Human Hypertension*. 2004; 18(3):139–185.
- 221 Sarnak MJ, Greene T, Wang X et al. The effect of a lower target blood pressure on the progression of kidney disease: long-term follow-up of the modification of diet in renal disease study. *Annals of Internal Medicine*. 2005; 142(5):342–351.
- 222 Wright JT, Jr., Bakris G, Greene T et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA : the Journal of the American Medical Association*. 2002; 288(19):2421–2431.
- 223 Kovesdy CP, Trivedi BK, Kalantar ZK et al. Association of low blood pressure with increased mortality in patients with moderate to severe chronic kidney disease. *Nephrology Dialysis and Transplantation*. 2006; 21(5):1257–1262.
- 224 Weiner DE, Tighiouart H, Levey AS et al. Lowest systolic blood pressure is associated with stroke in stages 3 to 4 chronic kidney disease. *Journal of the American Society of Nephrology*. 2007; 18(3):960–966.
- 225 Berl T, Hunsicker LG, Lewis JB et al. Impact of achieved blood pressure on cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial. *Journal of the American Society of Nephrology*. 2005; 16(7): 2170–2179.
- 226 Pohl MA, Blumenthal S, Cordonnier DJ et al. Independent and additive impact of blood pressure control and angiotensin II receptor blockade on renal outcomes in the irbesartan diabetic nephropathy trial: clinical implications and limitations. *Journal of the American Society of Nephrology*. 2005; 16(10): 3027–3037.
- 227 Jafar TH, Stark PC, Schmid CH et al. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. *Annals of Internal Medicine*. 2003; 139(4):244–252.
- 228 Ruggenenti P, Perna A, Loriga G et al. Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. *Lancet*. 2005; 365(9463):939–946.
- 229 Bakris GL, Weir MR, Shanifar S et al. Effects of blood pressure level on progression of diabetic nephropathy: results from the RENAAL study. *Archives of Internal Medicine*. 2003; 163(13):1555–1565.
- 230 Hovind P, Rossing P, Tarnow L et al. Remission and regression in the nephropathy of type 1 diabetes when blood pressure is controlled aggressively. *Kidney International*. 2001; 60(1):277–283.
- 231 van Bommel T., Woittiez K, Blauw GJ et al. Prospective study of the effect of blood pressure on renal function in old age: the Leiden 85-Plus Study. *Journal of the American Society of Nephrology*. 2006; 17(9): 2561–2566.
- 232 Peterson JC, Adler S, Burkart JM et al. Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease Study. *Annals of Internal Medicine*. 1995; 123(10): 754–762.
- 233 Perneger TV, Nieto FJ, Whelton PK et al. A prospective study of blood pressure and serum creatinine. Results from the ‘Clue’ Study and the ARIC Study. *JAMA : the Journal of the American Medical Association*. 1993; 269(4):488–493.

- 234 Rosansky SJ, Hoover DR, King L et al. The association of blood pressure levels and change in renal function in hypertensive and nonhypertensive subjects. *Archives of Internal Medicine*. 1990; 150(10): 2073–2076.
- 235 Shulman NB, Ford CE, Hall WD et al. Prognostic value of serum creatinine and effect of treatment of hypertension on renal function. Results from the hypertension detection and follow-up program. The Hypertension Detection and Follow-up Program Cooperative Group. *Hypertension*. 1989; 13(5:Suppl): Suppl–93.
- 236 Walker WG, Neaton JD, Cutler JA et al. Renal function change in hypertensive members of the Multiple Risk Factor Intervention Trial. Racial and treatment effects. The MRFIT Research Group. *JAMA: the Journal of the American Medical Association*. 1992; 268(21):3085–3091.
- 237 Strippoli GFM, Bonifati C, Craig M et al. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. *Cochrane Database of Systematic Reviews*. 2006;(4):CD006257.
- 238 Casas JP, Chua W, Loukogeorgakis S et al. Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. *Lancet*. 2005; 366(9502): 2026–2033.
- 239 Jafar TH, Schmid CH, Landa M et al. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. *Annals of Internal Medicine*. 2001; 135(2): 73–87.
- 240 Kent DM, Jafar TH, Hayward RA et al. Progression risk, urinary protein excretion, and treatment effects of Angiotensin-converting enzyme inhibitors in nondiabetic kidney disease. *Journal of the American Society of Nephrology*. 2007; 18(6):1959–1965.
- 241 Jennings DL, Kalus JS, Coleman CI et al. Combination therapy with an ACE inhibitor and an angiotensin receptor blocker for diabetic nephropathy: a meta-analysis. *Diabetic Medicine*. 2007; 24(5):486–493.
- 242 Kunz R, Friedrich C, Wolbers M et al. Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. *Annals of Internal Medicine*. 2008; 148(1):30–48.
- 243 Perkovic V, Ninomiya T, Arima H et al. Chronic kidney disease, cardiovascular events, and the effects of perindopril-based blood pressure lowering: data from the PROGRESS study. *Journal of the American Society of Nephrology*. 2007; 18(10):2766–2772.
- 244 Dalla VM, Pozza G, Mosca A et al. Effect of lercanidipine compared with ramipril on albumin excretion rate in hypertensive Type 2 diabetic patients with microalbuminuria: DIAL study (diabete, ipertensione, albuminuria, lercanidipina). *Diabetes, Nutrition & Metabolism – Clinical & Experimental*. 2004; 17(5): 259–266.
- 245 Marin R, Ruilope LM, Aljama P et al. A random comparison of fosinopril and nifedipine GITS in patients with primary renal disease. *Journal of Hypertension*. 2001; 19(10):1871–1876.
- 246 Ruggenti P, Perna A, Benini R et al. Effects of dihydropyridine calcium channel blockers, angiotensin-converting enzyme inhibition, and blood pressure control on chronic, nondiabetic nephropathies. Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN). *Journal of the American Society of Nephrology*. 1998; 9(11):2096–2101.
- 247 Anon. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). *Lancet*. 1997; 349(9069):1857–1863.
- 248 Ruggenti P, Perna A, Gherardi G et al. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet*. 1999; 354(9176):359–364.
- 249 Lea J, Greene T, Hebert L et al. The relationship between magnitude of proteinuria reduction and risk of end-stage renal disease: results of the African American study of kidney disease and hypertension. *Archives of Internal Medicine*. 2005; 165(8):947–953.
- 250 Agodoa LY, Appel L, Bakris GL et al. Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial.[see comment]. *JAMA : the Journal of the American Medical Association*. 2001; 285(21):2719–2728.

- 251 Hendry BM, Viberti GC, Hummel S et al. Modelling and costing the consequences of using an ACE inhibitor to slow the progression of renal failure in type I diabetic patients. *QJM : monthly journal of the Association of Physicians*. 1997; 90(4):277–282.
- 252 Garattini L, Brunetti M, Salvioni F et al. Economic evaluation of ACE inhibitor treatment of nephropathy in patients with insulin-dependent diabetes mellitus in Italy. *Pharmacoeconomics*. 1997; 12(1):67–75.
- 253 Rodby RA, Firth LM, Lewis EJ. An economic analysis of captopril in the treatment of diabetic nephropathy. The Collaborative Study Group. *Diabetes Care*. 1996; 19(10):1051–1061.
- 254 Ruggenti P, Pagano E, Tammuzo L et al. Ramipril prolongs life and is cost effective in chronic proteinuric nephropathies. *Kidney International*. 2001; 59(1):286–294.
- 255 Schadlich PK, Brecht JG, Brunetti M et al. Cost effectiveness of ramipril in patients with non-diabetic nephropathy and hypertension: economic evaluation of Ramipril Efficacy in Nephropathy (REIN) Study for Germany from the perspective of statutory health insurance. *Pharmacoeconomics*. 2001; 19(5):497–512.
- 256 van Hout BA, Simeon GP, McDonnell J et al. Economic evaluation of benazepril in chronic renal insufficiency. *Kidney International – Supplement*. 1997; 63:S159–S162.
- 257 Hogan TJ, Elliott WJ, Seto AH et al. Antihypertensive treatment with and without benazepril in patients with chronic renal insufficiency: a US economic evaluation. *Pharmacoeconomics*. 2002; 20(1):37–47.
- 258 Palmer AJ, Annemans L, Roze S et al. An economic evaluation of the Irbesartan in Diabetic Nephropathy Trial (IDNT) in a UK setting. *Journal of Human Hypertension*. 2004; 18(10):733–738.
- 259 Rodby RA, Chiou CF, Borenstein J et al. The cost-effectiveness of irbesartan in the treatment of hypertensive patients with type 2 diabetic nephropathy. *Clinical Therapeutics*. 2003; 25(7):2102–2119.
- 260 Palmer AJ, Roze S, Valentine WJ et al. Health economic implications of irbesartan plus conventional antihypertensive medications versus conventional blood pressure control alone in patients with type 2 diabetes, hypertension, and renal disease in Switzerland. *Swiss Medical Weekly*. 2006; 136(21–22):346–352.
- 261 Coyle D, Rodby RA. Economic evaluation of the use of irbesartan and amlodipine in the treatment of diabetic nephropathy in patients with hypertension in Canada. *Canadian Journal of Cardiology*. 2004; 20(1):71–79.
- 262 Vora J, Carides G, Robinson P. Effects of losartan-based therapy on the incidence of end-stage renal disease and associated costs in type 2 diabetes mellitus: A retrospective cost-effectiveness analysis in the United Kingdom. *Current Therapeutic Research, Clinical & Experimental*. 2005; 66(6):475–485.
- 263 Herman WH, Shahinfar S, Carides GW et al. Losartan reduces the costs associated with diabetic end-stage renal disease: the RENAAL study economic evaluation. *Diabetes Care*. 2003; 26(3):683–687.
- 264 Szucs TD, Sandoz MS, Keusch GW. The cost-effectiveness of losartan in type 2 diabetics with nephropathy in Switzerland—an analysis of the RENAAL study. *Swiss Medical Weekly*. 2004; 134(31–32):440–447.
- 265 Burgess ED, Carides GW, Gerth WC et al. Losartan reduces the costs associated with nephropathy and end-stage renal disease from type 2 diabetes: Economic evaluation of the RENAAL study from a Canadian perspective. *Canadian Journal of Cardiology*. 2004; 20(6):613–618.
- 266 Souchet T, Durand Z, I, Hannedouche T et al. An economic evaluation of Losartan therapy in type 2 diabetic patients with nephropathy: an analysis of the RENAAL study adapted to France. *Diabetes & Metabolism*. 2003; 29(1):29–35.
- 267 Coyle D, Rodby R, Soroka S et al. Cost-effectiveness of irbesartan 300 mg given early versus late in patients with hypertension and a history of type 2 diabetes and renal disease: a Canadian perspective. *Clinical Therapeutics*. 2007; 29(7):1508–1523.
- 268 Stafylas PC, Sarafidis PA, Grekas DM et al. A cost-effectiveness analysis of Angiotensin-converting enzyme inhibitors and Angiotensin receptor blockers in diabetic nephropathy. *Journal of Clinical Hypertension*. 2007; 9(10):751–759.
- 269 Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? *Archives of Internal Medicine*. 2000; 160(5):685–693.
- 270 Reardon LC, Macpherson DS. Hyperkalemia in outpatients using angiotensin-converting enzyme inhibitors. How much should we worry? *Archives of Internal Medicine*. 1998; 158(1):26–32.

- 271 Bleyer AJ, Shemanski LR, Burke GL et al. Tobacco, hypertension, and vascular disease: risk factors for renal functional decline in an older population. *Kidney International*. 2000; 57(5):2072–2079.
- 272 Nakamura T, Kanno Y, Takenaka T et al. An angiotensin receptor blocker reduces the risk of congestive heart failure in elderly hypertensive patients with renal insufficiency. *Hypertension Research – Clinical & Experimental*. 2005; 28(5):415–423.
- 273 Winkelmayer WC, Zhang Z, Shahinfar S et al. Efficacy and safety of angiotensin II receptor blockade in elderly patients with diabetes. *Diabetes Care*. 2006; 29(10):2210–2217.
- 274 Frances CD, Noguchi H, Massie BM et al. Are we inhibited? Renal insufficiency should not preclude the use of ACE inhibitors for patients with myocardial infarction and depressed left ventricular function. *Archives of Internal Medicine*. 2000; 160(17):2645–2650.
- 275 Rocha R, Chander PN, Khanna K et al. Mineralocorticoid blockade reduces vascular injury in stroke-prone hypertensive rats. *Hypertension*. 1998; 31(1:Pt 2):t–8.
- 276 Rocha R, Chander PN, Zuckerman A et al. Role of aldosterone in renal vascular injury in stroke-prone hypertensive rats. *Hypertension*. 1999; 33(1:Pt 2):t–7.
- 277 Hene RJ, Boer P, Koomans HA et al. Plasma aldosterone concentrations in chronic renal disease. *Kidney International*. 1982; 21(1):98–101.
- 278 Walker WG. Hypertension-related renal injury: a major contributor to end-stage renal disease. *American Journal of Kidney Diseases*. 1993; 22(1):164–173.
- 279 Rosenberg ME, Salahudeen AK, Hostetter TH. Dietary protein and the renin-angiotensin system in chronic renal allograft rejection. *Kidney International – Supplement*. 1995; 52:S102–S106.
- 280 Epstein M. Aldosterone as a mediator of progressive renal disease: pathogenetic and clinical implications. *American Journal of Kidney Diseases*. 2001; 37(4):677–688.
- 281 Rossing K, Schjoedt KJ, Smidt UM et al. Beneficial effects of adding spironolactone to recommended antihypertensive treatment in diabetic nephropathy: a randomized, double-masked, cross-over study. *Diabetes Care*. 2005; 28(9):2106–2112.
- 282 van den Meiracker AH, Baggen RG, Pauli S et al. Spironolactone in type 2 diabetic nephropathy: Effects on proteinuria, blood pressure and renal function. *Journal of Hypertension*. 2006; 24(11):2285–2292.
- 283 Chrysostomou A, Pedagogos E, MacGregor L et al. Double-blind, placebo-controlled study on the effect of the aldosterone receptor antagonist apironolactone in patients who have persistent proteinuria and are on long-term angiotensin-converting enzyme inhibitor therapy, with or without an angiotensin II receptor blocker. *Clin J Am Soc Nephrol*. 2006; 1(2):256–262.
- 284 Bianchi S, Bigazzi R, Campese VM. Long-term effects of spironolactone on proteinuria and kidney function in patients with chronic kidney disease. *Kidney International*. 2006; 70(12):2116–2123.
- 285 Rachmani R, Slavachevsky I, Amit M et al. The effect of spironolactone, cilazapril and their combination on albuminuria in patients with hypertension and diabetic nephropathy is independent of blood pressure reduction: a randomized controlled study. *Diabetic Medicine*. 2004; 21(5):471–475.
- 286 Oda H, Keane WF. Recent advances in statins and the kidney. *Kidney International – Supplement*. 1999; 71: S2–5, 1999 Jul.:S2–S5.
- 287 Oda H, Keane WF. Lipids in progression of renal disease. *Kidney International – Supplement*. 1997; 62: S36–8, 1997 Nov.:S36–S38.
- 288 O'Donnell MP, Kasiske BL, Kim Y et al. Lovastatin inhibits proliferation of rat mesangial cells. *Journal of Clinical Investigation*. 1993; 91:83–87.
- 289 Douglas K, O'Malley PG, Jackson JL. Meta-analysis: the effect of statins on albuminuria (Provisional record). *Annals of Internal Medicine*. 2006; 145(2):117–124.
- 290 Sandhu S, Wiebe N, Fried LF et al. Statins for improving renal outcomes: a meta-analysis. *Journal of the American Society of Nephrology*. 2006; 17(7):2006–2016.
- 291 Strippoli GF, Navaneethan SD, Johnson DW et al. Effects of statins in patients with chronic kidney disease: meta-analysis and meta-regression of randomised controlled trials. *British Medical Journal*. 2008; 336(7645):645–651.

- 292 Anon. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994; 344(8934):1383–1389.
- 293 Cheung BM, Lauder IJ, Lau CP et al. Meta-analysis of large randomized controlled trials to evaluate the impact of statins on cardiovascular outcomes. *British Journal of Clinical Pharmacology*. 2004; 57(5): 640–651.
- 294 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002; 360(9326):7–22.
- 295 Wanner C, Krane V, Marz W et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *New England Journal of Medicine*. 2005; 353(3):238–248.
- 296 Kasiske BL, O'Donnell MP, Garvis WJ et al. Pharmacologic treatment of hyperlipidemia reduces glomerular injury in rat 5/6 nephrectomy model of chronic renal failure. *Circulation Research*. 1988; 62(2):367–374.
- 297 Kasiske BL, O'Donnell MP, Cleary MP et al. Treatment of hyperlipidemia reduces glomerular injury in obese Zucker rats. *Kidney International*. 1988; 33(3):667–672.
- 298 O'Donnell MP, Kasiske BL, Kim Y et al. Lovastatin retards the progression of established glomerular disease in obese Zucker rats. *American Journal of Kidney Diseases*. 1993; 22(1):83–89.
- 299 Fried LF, Orchard TJ, Kasiske BL. Effect of lipid reduction on the progression of renal disease: a meta-analysis. *Kidney International*. 2001; 59(1):260–269.
- 300 Kwan BC, Kronenberg F, Beddhu S et al. Lipoprotein metabolism and lipid management in chronic kidney disease. *Journal of the American Society of Nephrology*. 2007; 18(4):1246–1261.
- 301 Tonelli M, Collins D, Robins S et al. Gemfibrozil for secondary prevention of cardiovascular events in mild to moderate chronic renal insufficiency. *Kidney International*. 2004; 66(3):1123–1130.
- 302 Chonchol M, Cook T, Kjekshus J et al. Simvastatin for secondary prevention of all-cause mortality and major coronary events in patients with mild chronic renal insufficiency. *American Journal of Kidney Diseases*. 49(3); 373–382.
- 303 Rabelink TJ, Zwavinga JJ, Koomans HA et al. Thrombosis and hemostasis in renal disease. *Kidney International*. 1994; 46(2):287–296.
- 304 Steiner RW, Coggins C, Carvalho AC. Bleeding time in uremia: a useful test to assess clinical bleeding. *American Journal of Hematology*. 1979; 7(2):107–117.
- 305 Gordge MP, Neild GH. Platelet function in uraemia. *Platelets*. 1991; 2(115)
- 306 Mezzano D, Tagle R, Panes O et al. Hemostatic disorder of uremia: the platelet defect, main determinant of the prolonged bleeding time, is correlated with indices of activation of coagulation and fibrinolysis. *Thrombosis & Haemostasis*. 1996; 76(3):312–321.
- 307 Remuzzi G, Perico N, Zoja C et al. Role of endothelium-derived nitric oxide in the bleeding tendency of uremia. *Journal of Clinical Investigation*. 1990; 86(5):1768–1771.
- 308 Gordge MP, Faint RW, Rylance PB et al. Platelet function and the bleeding time in progressive renal failure. *Thrombosis and Haemostasis*. 1988; 60(1):83–87.
- 309 Escolar G, Cases A, Bastida E et al. Uremic platelets have a functional defect affecting the interaction of von Willebrand factor with glycoprotein IIb–IIIa. *Blood*. 1990; 76(7):1336–1340.
- 310 Keltai M, Tonelli M, Mann JFE et al. Renal function and outcomes in acute coronary syndrome: Impact of clopidogrel. *European Journal of Cardiovascular Prevention & Rehabilitation*. 2007; 14(2):312–318.
- 311 Ezekowitz J, McAlister FA, Humphries KH et al. The association among renal insufficiency, pharmacotherapy, and outcomes in 6,427 patients with heart failure and coronary artery disease. *Journal of the American College of Cardiology*. 2004; 44(8):1587–1592.
- 312 Krause MW, Massing M, Kshirsagar A et al. Combination therapy improves survival after acute myocardial infarction in the elderly with chronic kidney disease. *Renal Failure*. 2004; 26(6):715–725.
- 313 Gibney EM, Casebeer AW, Schooley LM et al. Cardiovascular medication use after coronary bypass surgery in patients with renal dysfunction: A National Veterans Administration study. *Kidney International*. 2005; 68(2):826–832.



- 314 Vaziri ND, Freel RW, Hatch M. Effect of chronic experimental renal insufficiency on urate metabolism. *Journal of the American Society of Nephrology*. 1995; 6(4):1313–1317.
- 315 Foley RN, Wang C, Ishani A et al. NHANES III: influence of race on GFR thresholds and detection of metabolic abnormalities. *Journal of the American Society of Nephrology*. 2007; 18(9):2575–2582.
- 316 Chonchol M, Shlipak MG, Katz R et al. Relationship of uric acid with progression of kidney disease. *American Journal of Kidney Diseases*. 2007; 50(2):239–247.
- 317 Nakagawa T, Kang DH, Feig D et al. Unearthing uric acid: An ancient factor with recently found significance in renal and cardiovascular disease. *Kidney International*. 2006; 69(10):1722–1725.
- 318 Sanchez-Lozada LG, Tapia E, Santamaria J et al. Mild hyperuricemia induces vasoconstriction and maintains glomerular hypertension in normal and remnant kidney rats. *Kidney International*. 2005; 67(1):237–247.
- 319 Nakagawa T, Mazzali M, Kang DH et al. Hyperuricemia causes glomerular hypertrophy in the rat. *American Journal of Nephrology* 2003; 23(1):2–7.
- 320 Johnson RJ, Kang DH, Feig D et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? *Hypertension*. 2003; 41(6):1183–1190.
- 321 Siu YP, Leung KT, Tong MK et al. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. *American Journal of Kidney Diseases*. 2006; 47(1):51–59.
- 322 Yamagata K, Takahashi H, Tomida C et al. Prognosis of asymptomatic hematuria and/or proteinuria in men. High prevalence of IgA nephropathy among proteinuric patients found in mass screening. *Nephron*. 2002; 91(1):34–42.
- 323 Martin KJ, Gonzalez EA. Metabolic bone disease in chronic kidney disease. *Journal of the American Society of Nephrology*. 2007; 18(3):875–885.
- 324 Hsu CY, Chertow GM. Elevations of serum phosphorus and potassium in mild to moderate chronic renal insufficiency. *Nephrology Dialysis and Transplantation*. 2002; 17(8):1419–1425.
- 325 Chonchol M, Scragg R. 25-Hydroxyvitamin D, insulin resistance, and kidney function in the Third National Health and Nutrition Examination Survey. *Kidney International*. 2007; 71(2):134–139.
- 326 LaClair RE, Hellman RN, Karp SL et al. Prevalence of calcidiol deficiency in CKD: a cross-sectional study across latitudes in the United States. *American Journal of Kidney Diseases*. 2005; 45(6):1026–1033.
- 327 Craver L, Marco MP, Martinez I et al. Mineral metabolism parameters throughout chronic kidney disease stages 1–5 – Achievement of K/DOQI target ranges. *Nephrology Dialysis and Transplantation*. 2007; 22(4):1171–1176.
- 328 Levin A, Bakris GL, Molitch M et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. *Kidney International*. 2007; 71(1):31–38.
- 329 St John A., Thomas MB, Davies CP et al. Determinants of intact parathyroid hormone and free 1,25-dihydroxyvitamin D levels in mild and moderate renal failure. *Nephron*. 1992; 61(4):422–427.
- 330 Miller PD. Treatment of osteoporosis in chronic kidney disease and end-stage renal disease. *Current Osteoporosis Reports*. 2005; 3(1):5–12.
- 331 Fujii N, Hamano T, Mikami S et al. Risedronate, an effective treatment for glucocorticoid-induced bone loss in CKD patients with or without concomitant active vitamin D (PRIUS-CKD). *Nephrology Dialysis and Transplantation*. 2007; 22(6):1601–1607.
- 332 Kikuchi Y, Imakiire T, Yamada M et al. Effect of risedronate on high-dose corticosteroid-induced bone loss in patients with glomerular disease. *Nephrology Dialysis and Transplantation*. 2007; 22(6):1593–1600.
- 333 Miller PD, Roux C, Boonen S et al. Safety and efficacy of risedronate in patients with age-related reduced renal function as estimated by the Cockcroft and Gault method: a pooled analysis of nine clinical trials. *Journal of Bone & Mineral Research*. 2005; 20(12):2105–2115.
- 334 Jamal SA, Bauer DC, Ensrud KE et al. Alendronate treatment in women with normal to severely impaired renal function: an analysis of the fracture intervention trial. *Journal of Bone & Mineral Research*. 2007; 22(4):503–508.

- 335 Baker LR, Abrams L, Roe CJ et al. 1,25(OH)2D3 administration in moderate renal failure: a prospective double-blind trial. *Kidney International*. 1989; 35(2):661–669.
- 336 Nordal KP, Dahl E. Low dose calcitriol versus placebo in patients with predialysis chronic renal failure. *Journal of Clinical Endocrinology & Metabolism*. 1988; 67(5):929–936.
- 337 Przedlacki J, Manelius J, Huttunen K. Bone mineral density evaluated by dual-energy X-ray absorptiometry after one-year treatment with calcitriol started in the predialysis phase of chronic renal failure. *Nephron*. 1995; 69(4):433–437.
- 338 Ritz E, Kuster S, Schmidt-Gayk H et al. Low-dose calcitriol prevents the rise in 1,84 iPTH without affecting serum calcium and phosphate in patients with moderate renal failure (prospective placebo-controlled multicentre trial). *Nephrology Dialysis and Transplantation*. 1995; 10(12):2228–2234.
- 339 Christiansen C, Rodbro P, Christensen MS et al. Deterioration of renal function during treatment of chronic renal failure with 1,25-dihydroxycholecalciferol. *Lancet*. 1978; 2(8092:Pt 1):700–703.
- 340 Hamdy NA, Kanis JA, Beneton MN et al. Effect of alfacalcidol on natural course of renal bone disease in mild to moderate renal failure. *British Medical Journal*. 1995; 310(6976):358–363.
- 341 Rix M, Eskildsen P, Olgaard K. Effect of 18 months of treatment with alfacalcidol on bone in patients with mild to moderate chronic renal failure. *Nephrology Dialysis and Transplantation*. 2004; 19(4):870–876.
- 342 Coyne D, Acharya M, Qiu P et al. Paricalcitol capsule for the treatment of secondary hyperparathyroidism in stages 3 and 4 CKD. *American Journal of Kidney Diseases*. 2006; 47(2):263–276.
- 343 Al-Aly Z, Quazi RA, Gonzalez EA et al. Changes in Serum 25-Hydroxyvitamin D and Plasma Intact PTH Levels Following Treatment With Ergocalciferol in Patients With CKD. *American Journal of Kidney Diseases*. 2007; 50(1):59–68.
- 344 *British National Formulary* (57). 2008. UK: BMJ Publishing Group Ltd and RPS Publishing. <http://www.bnf.org/bnf/>
- 345 Department of Health. *Creating a patient-led NHS-delivering the NHS improvement plan*. London: UK: Department of Health, 2005.
- 346 Department of Health. *Supporting People with Long Term Conditions. An NHS and Social Care Model to support local innovation and integration*. London: UK: Department of Health, 2005.
- 347 Department of Health. *National Service Framework for Renal Services – Part One: dialysis and Transplantation*. London: UK: Department of Health, 2004.
- 348 Ormandy P, Hulme CT, Caress AL, et al. *Executive Summary: Identifying chronic kidney disease patients' priorities and preferences for information topics*. Salford: UK: Institute for Health and Social Care Research Report, University of Salford, 2007.
- 349 Coulter A, Entwistle V, Gilbert D. Sharing decisions with patients: is the information good enough? *British Medical Journal*. 1999; 318(7179):318–322.
- 350 Bekker H, Thornton JG, Airey CM et al. Informed decision making: an annotated bibliography and systematic review. *Health Technology Assessment*. 1999; 3(1):1–156.
- 351 Manns BJ, Taub K, Vanderstraeten C et al. The impact of education on chronic kidney disease patients' plans to initiate dialysis with self-care dialysis: a randomized trial. *Kidney International*. 2005; 68(4):1777–1783.
- 352 Inaguma D, Tatematsu M, Shinjo H et al. Effect of an educational program on the predialysis period for patients with chronic renal failure. *Clinical & Experimental Nephrology*. 2006; 10(4):274–278.
- 353 Lindberg JS, Husserl FE, Ross JL et al. Impact of multidisciplinary, early renal education on vascular access placement. *Nephrology News & Issues*. 2005; 19(3):35–36.
- 354 Levin A, Lewis M, Mortiboy P et al. Multidisciplinary predialysis programs: quantification and limitations of their impact on patient outcomes in two Canadian settings. *American Journal of Kidney Diseases*. 1997; 29(4):533–540.
- 355 Anandarajah S, Tai T, de Lusignan S et al. The validity of searching routinely collected general practice computer data to identify patients with chronic kidney disease (CKD): a manual review of 500 medical records. *Nephrology Dialysis and Transplantation*. 2005; 20(10):2089–2096.

- 356 Richards N, Harris K, Whitfield M et al. The impact of population-based identification of chronic kidney disease using estimated glomerular filtration rate (eGFR) reporting. *Nephrology Dialysis and Transplantation*. 2008; 23(2): 556–561.
- 357 Richards N, Harris K, Whitfield M et al. Primary care-based disease management of chronic disease (CKD), based on estimated glomerular filtration rate (eGFR) reporting, improves patient outcomes. *Nephrology Dialysis and Transplantation*. 2008; 23(2): 549–555.
- 358 Hemmelgarn BR, Culeton BF, Ghali WA. Derivation and validation of a clinical index for prediction of rapid progression of kidney dysfunction. *QJM: monthly journal of the Association of Physicians*. 2007; 100(2):87–92.
- 359 Weiner DE, Tighiouart H, Elsayed EF et al. The Framingham predictive instrument in chronic kidney disease. *Journal of the American College of Cardiology*. 2007; 50(3):217–224.
- 360 Garg AX, Bryce AK, Williams FC et al. Albuminuria and renal insufficiency prevalence guides population screening: Results from the NHANES III. *Kidney International*. 2002; 61(6):2165.
- 361 Iseki K, Ikemiya Y, Kinjo K et al. Prevalence of high fasting plasma glucose and risk of developing end-stage renal disease in screened subjects in Okinawa, Japan. *Clinical & Experimental Nephrology*. 2004; 8(3):250–256.
- 362 Whitfield M, Holmes M. *Final report to Optimal Renal Care UK Ltd. A cost and clinical effectiveness evaluation of a “disease management programme” for chronic kidney disease (CKD)*. Sheffield: Sheffield School of Health and Related Research, 2007.
- 363 Government Actuary’s Department. *Interim life tables*. 2007. [http://www.gad.gov.uk/Demography\\_Data/Life\\_Tables/Interim\\_life\\_tables.asp](http://www.gad.gov.uk/Demography_Data/Life_Tables/Interim_life_tables.asp)
- 364 Curtis, L. *Unit Costs of Health and Social Care*. Canterbury: UK: Personal Social Services Research Unit, 2007.
- 365 Department of Health. *NHS reference Costs 2005 – 2006*. UK: Department of Health, 2006.
- 366 Fretheim A, Oxman AD. International variation in prescribing antihypertensive drugs: its extent and possible explanations. *BMC Health Services Research*. 2005; 5(1):21.
- 367 Klebe B, Irving J, Stevens PE et al. The cost of implementing UK guidelines for the management of chronic kidney disease. *Nephrology Dialysis and Transplantation*. 2007; 22(9):2504–2512.
- 368 The Information Centre for Health and Social Care. *HESonline*. 2007. UK: The Information Centre for Health and Social Care. [www.hesonline.nhs.uk](http://www.hesonline.nhs.uk)
- 369 Palmer AJ, Valentine WJ, Ray JA. Irbesartan treatment of patients with type 2 diabetes, hypertension and renal disease: a UK health economics analysis. *International Journal of Clinical Practice*. 2007; 61(10):1626–1633.
- 370 UK Transplant. *Cost effectiveness of transplantation*:[1–87] Available from: UK Transplant. Last accessed on: 27 Feb, 2008.
- 371 Baboolal K, McEwan P, Sondhi S et al. The cost of renal dialysis in a UK setting—a multicentre study. *Nephrology Dialysis and Transplantation*. 2008; 23(6): 1982–1989.
- 372 de Wit GA, Merkus MP, Krediet RT et al. Health profiles and health preferences of dialysis patients. *Nephrology Dialysis and Transplantation*. 2002; 17(1):86–92.