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Diagnosis and management of chronic kidney disease

A national clinical guideline



2008

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE

- 1⁺⁺ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
- 1⁺ Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
- 1⁻ Meta-analyses, systematic reviews, 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 or bias and a moderate probability that the relationship is causal
- 2⁻ Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
- 3 Non-analytic studies, eg case reports, case series
- 4 Expert opinion

GRADES OF RECOMMENDATION

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

- A** At least one meta-analysis, systematic review, or RCT rated as 1⁺⁺, and directly applicable to the target population; or
A body of evidence consisting principally of studies rated as 1⁺, directly applicable to the target population, and demonstrating overall consistency of results
- B** A body of evidence including studies rated as 2⁺⁺, directly applicable to the target population, and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 1⁺⁺ or 1⁺
- C** A body of evidence including studies rated as 2⁺, directly applicable to the target population and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 2⁺⁺
- D** Evidence level 3 or 4; or
Extrapolated evidence from studies rated as 2⁺

GOOD PRACTICE POINTS

- ☒ Recommended best practice based on the clinical experience of the guideline development group.

NHS Quality Improvement Scotland (NHS QIS) is committed to equality and diversity. This guideline has been assessed for its likely impact on the six equality groups defined by age, disability, gender, race, religion/belief, and sexual orientation.

For the full equality and diversity impact assessment report please see the “published guidelines” section of the SIGN website at www.sign.ac.uk/guidelines/published/numlist.html. The full report in paper form and/or alternative format is available on request from the NHS QIS Equality and Diversity Officer.

Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found on our web site www.sign.ac.uk

Scottish Intercollegiate Guidelines Network

Diagnosis and management of chronic kidney disease

A national clinical guideline



2008

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purpose of implementation in NHSScotland

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1 Introduction

1.1 THE NEED FOR A GUIDELINE

Chronic kidney disease (CKD) is a long term condition caused by damage to both kidneys. There is no single cause and the damage is usually irreversible and can lead to ill health. In some cases dialysis or transplantation may become necessary. It is only relatively recently that the epidemiology of CKD has been studied in detail with the finding that it is more common than previously thought.^{1,2,3} The average prevalence has been reported at 11% in USA and Europe (excluding those on dialysis or with a functioning transplant).⁴ Diabetes mellitus, which is also becoming more common, is one cause of CKD. Chronic kidney disease is seen more frequently in older people and therefore is likely to increase in the population as a whole.²

People with CKD are at higher risk of cardiovascular disease and they should be identified early so that appropriate preventative measures can be taken. In the early stages of CKD people may be unaware that they have any illness and a blood or urine test may be the only way it is discovered. Establishing which conditions predispose to CKD identifies those who should have the necessary blood or urine tests. Early detection of CKD can establish if kidney disease is likely to be progressive allowing appropriate treatment to slow progression.

Previous renal clinical guidelines have focused on patients with end-stage renal disease (ESRD).⁵⁻⁷ End-stage renal disease, also called established renal failure, is chronic kidney disease which has progressed so far that the patient's kidneys no longer function sufficiently and dialysis or transplantation become necessary to maintain life. Given the increased recognition of CKD at earlier stages, the risks of cardiovascular disease and the potential for the disease to progress towards ESRD, guidelines for early identification and management of patients are now a priority.

1.2 REMIT OF THE GUIDELINE

1.2.1 OVERALL OBJECTIVES

This guideline covers three main areas. Firstly, the evidence for the association of specific risk factors with CKD is presented to help identify which individuals are more likely to develop CKD. Secondly, guidance is provided on how to diagnose CKD principally using blood and urine tests. Thirdly, the guideline contains recommendations on how to slow the progression of CKD and how to reduce the risk of cardiovascular disease.

The management of complications of CKD, such as anaemia and bone disease, is also discussed. Evidence for the best psychological and social support for patients and what information they need to take an optimal part in the management of their condition has been identified and incorporated.

The management of patients with ESRD or patients with acute kidney disease is excluded from this guideline. Patients with clinical features suggestive of a primary renal diagnosis, eg glomerulonephritis presenting with nephrotic syndrome, or renal disease secondary to vasculitis presenting with haematuria and proteinuria, should be referred to the renal service. Their specific management is not part of this guideline. The management of complications associated with CKD during pregnancy is a specialised area which is not covered in this guideline. This guideline relates to adult patients only (≥ 18 years).

1.2.2 TARGET USERS OF THE GUIDELINE

This guideline will be of value to all health professionals in primary and secondary care involved in the detection and management of patients with CKD. Specifically it should be of use to:

- patients and their carers
- general practitioners (GPs)
- community and practice nurses
- hospital nurses
- allied healthcare professionals (occupational therapists, dietitians, physiotherapists)
- pharmacists
- nephrologists
- clinical psychologists
- public health specialists
- staff working in other clinical areas including diabetologists, urologists, rheumatologists, cardiologists, vascular surgeons and those working in the care of the elderly
- trainees and medical students.

1.3 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

1.3.1 ADDITIONAL ADVICE TO NHSSCOTLAND FROM NHS QUALITY IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

NHS QIS processes multiple technology appraisals (MTAs) for NHSScotland that have been produced by the National Institute for Health and Clinical Excellence (NICE) in England and Wales.

The Scottish Medicines Consortium (SMC) provides advice to NHS Boards and their Area Drug and Therapeutics Committees about the status of all newly licensed medicines and any major new indications for established products.

SMC advice and NHS QIS validated NICE MTAs relevant to this guideline are summarised in the section implementing the guideline.

2 Risk factors, diagnosis and classification

All patients with evidence of persisting kidney damage, ie for >90 days, are defined as having CKD. Kidney damage refers to any renal pathology that has the potential to cause a reduction in renal functional capacity. This is most usually associated with a reduction in glomerular filtration rate (GFR) but other important functions may be lost without this occurring.

This section covers potential risk factors for the development of CKD (see section 2.1); how kidney damage or excretory function can be measured (see sections 2.2 to 2.4) and a classification system for CKD (see section 2.5). A sample diagnostic pathway is discussed in section 2.6.

2.1 DETECTION OF INDIVIDUALS AT HIGHER RISK OF DEVELOPING CHRONIC KIDNEY DISEASE

Epidemiology reveals an association between a number of clinical characteristics and the development of chronic kidney disease. For many potential risk factors, the supporting evidence is inconclusive, of poor methodological quality or does not clearly establish a causal relationship. Decisions regarding risk factor modification should be taken on an individual basis.

Factors which may be complicated by renal disease, but are not risk factors for its development, such as lithium toxicity or lupus nephritis are not considered here.

2.1.1 DIABETES MELLITUS

Diabetic nephropathy is a renal complication of diabetes mellitus. Diabetes is the commonest cause of ESRD requiring renal replacement therapy.⁸⁻¹⁰ The age-adjusted incidence of all-cause ESRD in men with diabetes is more than 12 times greater than in men without diabetes (199.0 vs 13.7 cases per 100,000 person years; relative risk (RR) 12.7; 95% confidence interval (CI), 10.5 to 15.4).¹¹ This increased incidence was attributable to both diabetic and non-diabetic nephropathy. In 2005, 0.5% of the population with diabetes who were recorded in the National Diabetes Survey were reported to be at ESRD.¹²

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The linkage of diabetes with earlier stages of CKD is more difficult to demonstrate. In one cross-sectional study diabetes was found to be associated with CKD with the relative risk increasing with the severity of CKD.² In the baseline cohort analysis of a large Medicare American study (n=1,091,201 aged >65 years) the presence of diabetes was found to double the risk of developing CKD compared with those without diabetes (odds ratio (OR) 2.04; 95% CI 2.00 to 2.09, p<0.0001).¹⁷

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When followed up over two years, people from this cohort with diabetes, but without known CKD, developed kidney damage at a rate of 0.2 per 100 patient years as compared with 0.04 per 100 patient years for people without diabetes. The progression of disease was also more frequent in patients with CKD and diabetes with 3.4 per 100 patient years requiring dialysis as compared with CKD patients without diabetes who reached this end point at less than half the rate (1.6 per 100 patient years; p<0.0001).

In a community based longitudinal cohort study of patients from the Framingham Offspring Study 2,585 individuals without evidence of CKD were monitored over 12 years. In multivariate analysis those with diabetes at baseline had an increased rate of development of CKD (OR 2.60; 95% CI 1.44 to 4.70) over a 12 year period.¹³

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In contrast to these positive associations a large cross-sectional Australian cohort study (11,247 patients) did not find an association between diabetes and the presence of CKD.¹⁴

3

Within the limitations of cross-sectional cohort methodology and longitudinal cohort data, diabetes is a significant risk factor for CKD and individuals with both diabetes and CKD appear to be more likely to progress to end-stage renal disease.

This supports current recommendations in national guidelines on the surveillance of patients with diabetes for CKD. The optimal surveillance strategy has not been defined.^{15,16}

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D All patients with diabetes should have regular surveillance of renal function.

2.1.2 HYPERTENSION

Four studies have shown that hypertension is a risk factor for CKD.^{2,13,14,17} These were large, retrospective studies with high attrition rates and hence subject to potential selection bias. In a fifth small study (33 patients with hypertension, 30 without hypertension) the demonstrated association between hypertension and CKD did not reach statistical significance.¹⁸

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SIGN guideline 97 on risk estimation and the prevention of cardiovascular disease suggests that cardiovascular risk factors (including a measure of renal function) should be monitored at least annually in individuals who are on antihypertensive or lipid lowering therapy.¹⁹

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Patients who are on antihypertensive or lipid lowering therapy should have renal function assessed at least annually.

2.1.3 SMOKING

A good quality Swedish case control study provides supportive evidence for current or former history of smoking (at five years before survey) as a significant risk factor for CKD in a community based population.²⁰ Odds ratios increased with increasing frequency and duration of smoking. A 'pack year' is calculated by multiplying the number of packs of cigarettes smoked per day by the number of years an individual has smoked. More than 15 pack years of smoking increased the risk of CKD significantly (16-30 pack years: OR 1.32; > 30 pack years: OR 1.52).

2+



Smoking should be considered as a risk factor for the development of chronic kidney disease.

See section 3.8.2 for lifestyle modification advice to reduce cardiovascular risk.

2.1.4 CARDIOVASCULAR DISEASE

One cross-sectional study on an American Medicare population (aged > 65 years) was identified. Patients with atherosclerotic vascular disease were 1.5 times more likely to develop CKD than those without, and patients with congestive cardiac failure were nearly twice as likely to do so.¹⁷ The Medicare population was selective in excluding, for example, certain patients with health insurance. There were also problems of definition and coding since classification was based on diagnostic coding at billing which does not distinguish between CKD stages.

3

2.1.5 AGE

Two retrospective studies, were consistent in showing that age was a significant risk factor; the first examined < 65 year olds compared to > 65 year olds with a resultant odds ratio of 101.5 (95% CI, 61.4 to 162.9) indicating increased risk of renal impairment at an older age.¹⁴ The second showed increasing relative risks in a population > 65 years old, albeit with overlapping confidence intervals.¹⁷

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The Framingham Offspring study established a graded risk associated with age (OR of 2.36 per 10 year age increment; 95% CI 2.00 to 2.78).¹³ There is uncertainty as to whether age associated decline in GFR is pathological and should be afforded the same significance as declining function in other situations.²¹

3

2.1.6 CHRONIC USE OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Two retrospective single cohort studies of physicians²² and nurses,²³ examined non-steroidal anti-inflammatory drug (NSAID) use as a risk factor for developing CKD. Neither found chronic use of aspirin or NSAIDs in prescribed doses to be significant risk factors over a period of 14 and 11 years respectively, although one found use of paracetamol to be so.²³ Selection bias was a significant limitation in both studies, since subjects were not representative of the general population, and small proportions of the original sample populations were included in the final analyses.

3

The use of NSAIDs in patients with established CKD is not addressed in this guideline.

2.1.7 OBESITY AND SOCIOECONOMIC STATUS

One cross-sectional Dutch study on obesity as a risk factor for CKD concluded that BMI (body mass index) had no effect on the prevalence of CKD, although some evidence was presented for a central pattern of fat distribution being associated with CKD compared with a peripheral pattern.²⁴ This retrospectively obtained evidence had limitations, including low response rate.

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An American cohort study concluded that white men and African-American women living in an area of low socioeconomic status had a greater risk of CKD progression than white men and African-American women living in a higher designated area. No similar CKD risk progression was found for white women and African-American men.²⁵ There were methodological limitations in this study and little information on sampling and attrition rates was available.

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A Swedish, community based case control study showed that lower household and individual level socioeconomic status and fewer years of education were significant risk factors for CKD in the Swedish population.²⁶

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C

Low socioeconomic status should be considered as a risk factor for the development of chronic kidney disease.

2.2 DETECTING KIDNEY DAMAGE

Kidney damage may be detected either directly or indirectly. Direct evidence may be found on imaging or on histopathological examination of a renal biopsy. A range of imaging modalities including ultrasound (see section 2.2.3), computed tomography (CT), magnetic resonance imaging (MRI) and isotope scanning can detect a number of structural abnormalities including polycystic kidney disease, reflux nephropathy, chronic pyelonephritis and renovascular disease. Renal biopsy histopathology is most useful in defining underlying glomerular disease such as immunoglobulin A (IgA) nephropathy or focal glomerulosclerosis.

Indirect evidence for kidney damage may be inferred from urinalysis. Glomerular inflammation or abnormal function can lead to leakage of red blood cells or protein into the urine which in turn may be detected as proteinuria or haematuria (see sections 2.2.1 and 2.2.2). Urinary abnormalities may have alternative causes unrelated to kidney dysfunction and there are methodological issues associated with their measurement.

2.2.1 PROTEINURIA

Proteinuria is associated with cardiovascular and renal disease and is a predictor of end organ damage in patients with hypertension. Detection of an increase in protein excretion is known to have both diagnostic and prognostic value in the initial detection and confirmation of renal disease.²⁷

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In evaluating the diagnostic accuracy of tests of proteinuria, measurement of protein (or albumin) excretion in a timed urine collection over 24 hours has been used as a reference standard.²⁸

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Annex 2 explains the relationship between urinary protein (and albumin) concentrations expressed as a ratio to creatinine and other common expressions of their concentration.

Urine dipstick testing

Although urine dipstick testing is widely available, convenient and relatively cheap, evidence for its diagnostic accuracy is limited to studies that have compared dipstick testing with either protein or albumin excretion in a timed urine collection over 24 hours.²⁹⁻³⁶ Pooling the six obstetric studies²⁹⁻³⁴ gives a positive likelihood ratio of 3.48 (95% CI 1.66 to 7.27) and a negative likelihood ratio of 0.6 (95% CI 0.45 to 0.8) for predicting 300 mg/24-hour proteinuria at 1+ or more (likelihood ratios of > 5 or < 0.2 provide good evidence of the diagnostic performance of tests in rule-in and rule-out modes respectively).²⁷

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2⁺

The accuracy of automated analysis is greater than visual analysis of urine dipsticks. In one study, the positive likelihood ratio was 4.27 (95% CI 2.78 to 6.56) and negative likelihood ratio 0.22 (95% CI 0.14 to 0.36) for automated urinalysis compared with 2.27 (95% CI 1.47 to 3.51) and 0.64 (95% CI 0.49 to 0.82) for visual urinalysis.³⁸

2⁺⁺

The existing limited evidence base does not indicate that dipstick testing can reliably be used to diagnose the presence or absence of proteinuria. Automated urinalysis warrants further evaluation.

There is evidence from the Multiple Risk Factor Intervention Trial (MRFIT), that dipstick proteinuria in men predicts long term risk of ESRD.³⁹ In the MRFIT cohort the hazard ratio for ESRD over 25 years for patients with $\geq 1+$ dipstick proteinuria (3.1, 95% CI 1.8 to 5.4) was higher than for an estimated GFR of < 60 ml/min/1.73 m² (2.4, 95% CI 1.5 to 3.8). In addition, dipstick proteinuria identifies individuals at higher cardiovascular risk.⁴⁰⁻⁴²

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A systematic review of the practice of excluding urinary tract infection (UTI) in patients with proteinuria found that symptomatic, but not asymptomatic UTI is commonly associated with proteinuria/albuminuria.⁴³ A threshold above which proteinuria can be definitively attributed to intrinsic renal disease as opposed to a superimposed UTI could not be identified.

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Protein/creatinine ratio

A systematic review comparing measurement of protein/creatinine ratio (PCR) on a random urine sample with 24-hour protein excretion included studies carried out during pregnancy and studies performed in renal and rheumatology outpatient clinics.²⁷ Likelihood ratios < 0.2 were reported in most of the studies, supporting the diagnostic performance of PCR as a test of exclusion. There was a high prevalence of proteinuria in the populations studied, and these findings should be extrapolated with caution to populations with a lower prevalence.

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Protein/creatinine ratio measured in early morning or random urine samples is at least as good as 24-hour urine protein estimation at predicting the rate of loss of GFR in patients with CKD who do not have diabetes.⁴⁴

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Albumin/creatinine ratio

A meta-analysis of ten studies in patients with diabetes compared a random albumin/creatinine ratio (ACR) measurement with albumin excretion rate (AER) from overnight or 24-hour timed samples.⁴⁵ In seven studies ACR was compared with 24-hour albumin excretion. The performance of ACR was expressed as a summary diagnostic odds ratio of 45.8 (95% CI 28.5 to 73.4). The use of ACR could save the inconvenience of collecting a timed urine specimen with only a negligible loss of case detection when compared with AER. The ACR data reported in patients with hypertension are similar.⁴⁶

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Microalbuminuria predicts ESRD in people with diabetes.⁴⁷ Combined estimates of relative risk quoted for microalbuminuria (compared with normoalbuminuria) include an RR of ESRD of 4.8 (95% CI 3.0 to 7.5) in people with type 1 diabetes and 3.6 (95% CI 1.6 to 8.4) in people with type 2 diabetes. Although much of the evidence concerns measures of albuminuria other than ACR, three studies⁴⁸⁻⁵⁰ use this measure. Albumin/creatinine ratio is also a marker of renal insufficiency in non-diabetic subjects,⁵¹ and in the Heart Outcomes Prevention Evaluation (HOPE) cohort (subjects with cardiovascular disease, or diabetes and one or more cardiovascular risk factor), baseline microalbuminuria, as detected by ACR, predicted clinical proteinuria in both diabetic and non-diabetic subjects.⁵²

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In the HOPE cohort and in other studies, microalbuminuria also predicted major cardiovascular events, with an adjusted relative risk of 1.83 (95% CI 1.64 to 2.05) over the period of the study (median 4.5 years). For every 0.4 mg/mmol increase in ACR, the adjusted hazard increased by 5.9%.⁵³⁻⁵⁶

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Summary of evidence and other considerations

Overall, the evidence suggests that urine dipstick testing cannot reliably be used to diagnose the presence or absence of proteinuria although there is evidence that dipstick proteinuria ($\geq 1+$) predicts ESRD and cardiovascular disease. There is no evidence that isolated asymptomatic UTI causes proteinuria/albuminuria. PCR and ACR are accurate rule-out tests in populations with a high probability of proteinuria. PCR and ACR predict subsequent progression of renal disease. ACR has also been shown to predict cardiovascular disease, although similar evidence for PCR was not identified.

The measure of protein excretion that is used in a particular context will be influenced by other considerations. For example, because of its widespread availability, convenience and relatively low cost, urine dipstick testing will often be the initial measure used. Where confirmation is required for diagnostic purposes, the lower cost of PCR should be weighed against the superior accuracy of ACR at low concentrations. The role of microalbuminuria in the detection and management of diabetic nephropathy means that ACR will be preferred in patients with diabetes.

- B** In patients with diabetes, albumin/creatinine ratio may be used to exclude diabetic nephropathy.
- C** Albumin/creatinine ratio is recommended for detecting and monitoring diabetic nephropathy.
- B** In patient groups with a high prevalence of proteinuria without diabetes protein/creatinine ratio may be used to exclude chronic kidney disease.
- D** In patients with established chronic kidney disease and without diabetes, measurement of protein/creatinine ratio may be used to predict risk of progressive disease.
- ☒ Dipstick proteinuria ($\geq 1+$) can be used to identify patients at risk of subsequent end-stage renal disease and cardiovascular disease.
- ☒ Urine dipstick testing cannot be used reliably in isolation to diagnose the presence or absence of proteinuria.

2.2.2 HAEMATURIA

Macroscopic or frank haematuria is often a manifestation of urinary tract malignancy. Exclusion of infection followed by urological investigation is the most appropriate initial step.⁵⁷

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Microscopic haematuria may indicate significant pathology including infection, malignancy and other forms of kidney damage. A single positive dipstick test is not sufficient to indicate pathology as it is a common finding with rates ranging from 1.7% in a UK student population⁵⁸ to 18.1% in a US study of first order relatives of patients with hypertension, diabetes or CKD.⁵⁹ The UK student study showed that repeat analysis was negative in 60% of cases indicating that many patients have transient haematuria.

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Isolated microscopic haematuria is associated with a modest increased risk of progressive kidney disease. A large Australian cross-sectional cohort study found that individuals with isolated haematuria had a greater risk of CKD, defined by $\text{GFR} < 60$ (OR 1.4).¹⁴ A Japanese cohort study involving population screening where patients were followed up over 17 years found that having 2+ haematuria conveyed a relative risk for requiring dialysis of 2.4.⁶⁰ Another Japanese study identified that persisting haematuria carried a 0.7% risk of developing CKD at 10 years in working men.⁶¹ When haematuria and proteinuria were both detected the risk of subsequent CKD rose to 12% over this period.

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Although the risk of developing progressive CKD in patients with isolated microscopic haematuria is low, renal or urinary pathology is often present. The Japanese study followed 165 patients with persisting haematuria and 13 of 17 patients who underwent renal biopsy had IgA nephropathy.⁶¹ A similar rate of IgA disease was detected in a UK biopsy study.⁶²

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Isolated microscopic haematuria may be present in other glomerulonephritic conditions including systemic vasculitis. This is most often seen in the context of acute renal disease.

A health technology assessment examining the most effective method to evaluate haematuria concluded that there were insufficient data to derive an evidence based algorithm for the evaluation of haematuria.⁶³ A strategy based on expert opinion was reviewed in the context of international guidelines.⁶⁴⁻⁶⁶ The assessment recommended that after the exclusion of infection, isolated microscopic haematuria should be evaluated to exclude malignancy of the urinary tract, with more urgent assessment required in those over 50 years of age. If coexistent

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proteinuria and abnormal serum creatinine were detected then a medical/renal evaluation was recommended.⁶³ 2++
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D Patients with persisting isolated microscopic haematuria should be initially evaluated for urinary tract infection and malignancy.

2.2.3 RENAL TRACT ULTRASOUND

Ultrasound is the optimal first line test for imaging the renal tract in patients with CKD and identifies obstructive uropathy, renal size and symmetry, renal scarring and polycystic disease.⁶⁷ 4

Large studies of ultrasound screening in asymptomatic members of the general population have been carried out in Japanese adults,⁶⁸ in older American adults⁶⁹ and in older German adults.⁷⁰ They demonstrated an incidence of obstructive uropathy of between 0.13-0.34% of the population. The German study found renal calculi in 2.14% and renal asymmetry in 0.40%. Additional minor findings were found in 13%. 3

No evidence was identified on the usefulness of renal ultrasound alone in the diagnosis of CKD.

☒ Ultrasound is the imaging modality of choice in the evaluation of patients with suspected chronic kidney disease.

2.3 MEASURING RENAL FUNCTION

2.3.1 DEFINING GLOMERULAR FILTRATION RATE

The glomerular filtration rate is defined as the volume of plasma which is filtered by the glomeruli per unit time and is usually measured by estimating the rate of clearance of a substance from the plasma. Glomerular filtration rate varies with body size and conventionally is corrected to a body surface area (BSA) of 1.73 m², the average BSA of a population of young men and women studied in the mid-1920s.⁷¹

2.3.2 CREATININE

Historically, measurement of creatinine or urea in serum or plasma has been used to assess kidney function. Both are convenient but insensitive (GFR has to halve before a significant rise in serum creatinine becomes apparent). In addition, serum concentrations of creatinine are affected by various analytical interferences, and depend critically on muscle mass, for example, a serum creatinine concentration of 130 micromol/l might be normal in one individual but require further investigation in another.

Other factors which affect creatinine concentrations include age, sex, ethnicity, body habitus and diet.⁷²⁻⁷³ Diet may have a rapid and transient effect on creatinine concentration⁷⁴⁻⁷⁶ and there is evidence that consumption of cooked meat, in particular, may affect CKD categorisation based on estimated glomerular filtration rate (eGFR).⁷⁷ 3
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One study has reported that the delay in separating serum from venous blood samples may affect some creatinine measurements, and result in CKD misclassification.⁷⁸ Leaving clotted blood unseparated increased creatinine concentration significantly after 16 hours (p<0.001). By 48 hours creatinine concentrations had increased above the baseline measurement (samples separated after 30 minutes) on average by 29% (range 21–63%). The CKD staging of 32% of patients in the study changed as a result of delaying sample separation for 24 hours. 3

☒ Depending on the creatinine method used, staging of chronic kidney disease should not be based on blood samples which have been separated 16 hours or more after collection.

Simultaneous measurement of urinary excretion of creatinine by means of a timed urine collection allows estimation of creatinine clearance. This is more sensitive than serum creatinine in detecting reduced GFR but is inconvenient for patients and imprecise.⁷⁹ 3

2.3.3 PREDICTION EQUATIONS

Prediction equations improve the inverse correlation between serum creatinine and GFR by taking into account confounding variables such as age, sex, ethnic origin and body weight. The formula developed by Cockcroft and Gault to estimate creatinine clearance,⁸⁰ and the four-variable formula derived from the Modification of Diet in Renal Disease (MDRD) study to estimate GFR,⁸¹ are the most widely used of these prediction equations. The Cockcroft-Gault formula incorporates age, sex and weight in addition to creatinine, while the four-variable MDRD formula incorporates age, sex, and ethnicity, but not weight.

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2.3.4 CYSTATIN C

Serum concentrations of the low molecular weight protein cystatin C correlate inversely with GFR. The concentration of cystatin C is independent of weight and height, muscle mass, adult age or sex and is largely unaffected by intake of meat or non-meat-containing meals.⁷⁷ Cystatin C has become a candidate marker for GFR assessment.

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2.3.5 OTHER MARKERS

Various other markers have been used to estimate clearance, including inulin, iothexol and radioisotopic markers such as ⁵¹Cr-ethylenediaminetetraacetic acid (EDTA), ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA) and ¹²⁵I-iothalamate. Measurement of any of these markers is too costly and labour intensive to be widely applied. For the purposes of evaluating methods of GFR assessment, inulin clearance is widely regarded as the most accurate (gold standard) estimate of GFR,⁸² whilst the radioisotopic methods listed above are accepted as validated reference standards.^{83,84}

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2.4 COMPARING RENAL FUNCTION TESTS

Forty one hospital based studies were identified that compared measures of renal function with a gold standard (inulin clearance) or validated reference standard (in most cases ⁵¹Cr-EDTA clearance). The appropriateness of generalising from hospital based evidence to all patients at risk of CKD is not clear. In addition, the accuracy of prediction equations may be influenced by the methods used to measure creatinine, further limiting the conclusions that can be drawn from some of the studies cited.

2.4.1 PREDICTION EQUATIONS

Comparison with other methods

Prediction equations are consistently more accurate than serum creatinine in the assessment of GFR.⁸⁵⁻⁹⁷ An estimated GFR of less than 60 ml/min/1.73 m² is associated with an increased risk of the major adverse outcomes of CKD (impaired kidney function, progression to kidney failure and premature death from cardiovascular disease).^{98-101,125} Prediction equations perform as well as or better than 24-hour urine creatinine clearance in all but one study (see section 2.4.4).¹⁰² Only two studies out of thirteen suggest that cystatin C is superior to prediction equations (specifically Cockcroft-Gault);^{92,93} most studies show comparable performance.

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Comparison of different prediction equations

Studies comparing the four-variable (also known as simplified) MDRD with Cockcroft-Gault give inconsistent results, though a majority indicate either comparable performance or superiority of MDRD over Cockcroft-Gault.^{88-90,92,102-111} These studies include the largest by far (> 2,000 patients), in which comparison was made across a range of subgroups defined according to age, sex, true GFR, and BMI.¹⁰⁶ This study concluded that the MDRD formula provided more reliable estimations of kidney function than the CG formula.

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Only three out of 14 studies^{91,112,113} suggest that Cockcroft-Gault is better. In these studies, the poorer performance of MDRD may reflect the older age of the patients, or the high GFRs of the subjects studied (MDRD is less accurate and precise in estimating normal renal function).¹⁰⁶

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The performance of Cockcroft-Gault and simplified MDRD equations is differentially affected by true GFR, age, sex, BMI and creatinine methodology, and these factors may explain some of the inconsistent findings.

In general, both MDRD and Cockcroft-Gault perform better at low GFR, probably reflecting the populations in which they were developed. The MDRD equation is preferred by most laboratories estimating GFR.

Limitations of prediction equations

The MDRD equation is widely used to estimate GFR in order to facilitate the detection of CKD. Although MDRD is superior to serum creatinine in the assessment of GFR (see section 2.4.2), there are several problems with this approach.

The MDRD equation is not completely accurate, and the extent of its inaccuracy varies between different patient groups. Even in the MDRD study population (patients with CKD) which was used to validate the equation, 9% of GFR estimates were 30% or more outwith the isotope-measured values.⁸¹ Estimates of GFR are even less accurate in populations with higher GFR (≥ 60 ml/min/1.73 m²).¹⁰⁶ The tendency of MDRD to underestimate true GFR in this range results in a significant risk of false positive diagnosis of CKD. This makes it difficult to interpret estimated GFR values of ≥ 60 ml/min/1.73 m².

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The best approach may be to report a specific value only if the estimated GFR is < 60 ml/min/1.73 m². In patients with a reported eGFR of ≥ 60 ml/min/1.73 m², serum creatinine can still be used to assess trends in renal function.

In addition, the MDRD equation is only validated for use in Caucasian and African-American populations. Validation studies in other ethnic groups are underway. Groups in which the equation has not been fully validated include older patients, pregnant women, patients with serious comorbid conditions, and patients with extremes of body size, muscle mass, or nutritional status. Application of the equation to these patient groups may lead to errors in GFR estimation.¹¹⁴

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Finally, estimates of GFR obtained by creatinine methods that are biased compared to the creatinine assay used in the original MDRD study can be substantially different. In one example, reanalysis of data after standardisation of one creatinine assay to the MDRD assay changed a pre-standardisation mean positive bias for the MDRD equation of 6.4 ml/min/1.73 m² compared with ⁵¹Cr-EDTA⁹¹ to no significant bias.¹¹⁵

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If accuracy is an overriding consideration (eg for potential kidney donors or administration of drugs that are excreted by, or toxic to, the kidneys), a more accurate method of measurement, such as one of the validated reference methods listed in section 2.3.5 is required.

2.4.2 SERUM CREATININE

Serum creatinine is less sensitive than prediction equations^{85-89,92-97,104,116} and 24-hour urine creatinine clearance^{87,104} in detecting reduced GFR.

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The literature comparing cystatin C with serum creatinine is inconclusive (see section 2.4.3).

2.4.3 CYSTATIN C

In half of the studies identified, cystatin C was more sensitive than serum creatinine in detecting reduced GFR.^{87,90,93,94,97,103,117-119} In the remaining half, studies did not demonstrate superiority of either measure.^{85,86,88,89,92,95,96,116,120} Two studies^{93,94} out of twelve^{85-89,92-97,116} suggest that cystatin C is superior to Cockcroft-Gault; most of the rest show comparable performance with prediction equations.

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Differences between populations studied with respect to true GFR, age and sex may explain some of the inconsistencies observed.

2.4.4 24-HOUR URINARY CREATININE CLEARANCE

In most studies this method performs less well than prediction equations or cystatin C, ^{85-87,91, 102,104, 121} although two studies found little difference. ^{88,89} One study found it to be superior to prediction equations in assessing GFR in normoalbuminuric type 1 diabetic patients and healthy controls;¹¹³ this may reflect the high GFR of the study population and the carefully controlled study conditions.

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2.4.5 SUMMARY

Prediction equations are more accurate than serum creatinine or 24-hour urine creatinine clearance in the assessment of GFR. 24-hour urine creatinine clearance is inconvenient and imprecise, and offers no advantages over prediction equations in most patients. The literature comparing cystatin C with serum creatinine is inconclusive. Prediction equations are at least as good in the detection of reduced GFR as cystatin C.

Drug dosing

Virtually all published recommendations for dose adjustment in patients with reduced renal function, including the British National Formulary (BNF),¹²² and manufacturers' summaries of product characteristics¹²³ are based on creatinine clearance estimated by the Cockcroft-Gault formula. There is no evidence that this estimate can be used interchangeably with the four variable MDRD formula. The current practice of using the Cockcroft-Gault formula for drug dosing should be continued until such evidence is forthcoming.¹²⁴

C Where an assessment of glomerular filtration rate is required prediction equations should be used in preference to 24-hour urine creatinine clearance or serum creatinine alone.

☒ Laboratories should only report a numerical value at estimated glomerular filtration rates of less than 60 ml/min/1.73 m².

☒ Where accuracy is an overriding consideration, clearance should be measured using a validated standard.

☒ Staging of chronic kidney disease (see section 2.5.1) should not be based on samples collected after consumption of meals containing cooked meat. Confirmatory samples should be taken in the fasting state.

☒ Alterations in drug dosing in patients with reduced renal function should be made on the basis of creatinine clearance as estimated by the Cockcroft-Gault formula.

2.5 CLASSIFICATION OF CHRONIC KIDNEY DISEASE

A widely adopted classification of chronic kidney disease was developed by the American National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI tm).^{125,126} Minor revisions have been made by the Kidney Disease Improving Global Outcomes (KDIGO) organisation, and by a UK Consensus Conference.¹²⁸

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The original intention of the KDOQI group was to develop both a severity classification system for patients with established CKD and diagnostic criteria for CKD. The system suggested that CKD could be diagnosed solely on the basis of GFR < 60 ml/min/1.73 m². As single aberrant results are relatively common the abnormality should be present for at least three months.

As GFR may decline with age GFR in the very elderly may already be at this diagnostic threshold. As this might reflect the high incidence of kidney disease in older individuals no age or sex adjustment was made to the GFR thresholds. This aspect of the diagnostic criteria has been extensively used in many subsequent epidemiological studies that have tried to estimate the prevalence of CKD.² In most cases a single creatinine blood result combined with GFR prediction equations have been used. These studies reported a high prevalence of CKD in the elderly. It has since been suggested that a modestly reduced GFR in an older person may not have the same clinical significance as an identical finding in a younger person.^{21,129}

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The guideline development group suggests that the KDOQI classification system is used only after the patient has been clinically evaluated, when it is useful for staging the severity of disease, any likely associated complications and to identify those that are most likely to progress.

- ☒ The KDOQI classification system should only be used to stage patients with a diagnosis of chronic kidney disease.

2.5.1 STAGES OF DISEASE

In 2002, KDOQI proposed that CKD be stratified into five stages of disease based on the normalised GFR. The cut-offs between stages were arbitrary but have clinical correlates. For example, compared with people who do not have CKD, patients with stage 1 CKD are more likely to have hypertension and the incidence of hypertension increases progressively as the stage advances.¹²⁵

At stage 5, the suffix D indicates that the patient is on dialysis, and at stages 1-5 the suffix T indicates that the patient has a functioning kidney transplant.¹²⁷

The UK Consensus Conference recommended dividing stage 3 into two parts. Population studies had suggested that stage 3 CKD encompassed a large spectrum of patients most of whom were asymptomatic. Complications of renal disease are far more common amongst those with a GFR below 45 and this was set as the threshold for stage 3B. It was felt that these individuals were likely to require increased monitoring and treatment.

The suffix p indicates significant proteinuria (> 1 g per day – approximately equivalent to a protein/creatinine ratio of 100 mg/mmol). This group are at a high risk of deterioration of renal function and warrant thorough investigation and intensive management.^{2,128}

The modified classification system is shown in Table 1.

Table 1: Stratification of chronic kidney disease

Stage	Description	GFR (ml/min/1.73 m ²)
1*	Kidney damage with normal or raised GFR	≥ 90
2*	Kidney damage with mild decrease in GFR	60-89
3A	Moderately lowered GFR	45-59
3B		30-44
4	Severely lowered GFR	15-29
5	Kidney failure (end-stage renal disease)	< 15

Notes: *in order to diagnose stages 1 and 2 CKD, additional evidence of kidney damage must be present, eg proteinuria.

If proteinuria (> 1 g per day or > 100 mg/mmol) is present the suffix p should be added.

Patients on dialysis are classified as stage 5D.

The suffix T indicates patients with a functioning renal transplant (can be stages 1-5).

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2.6 CLINICAL EVALUATION AND REFERRAL

No evidence was identified on how to incorporate individual markers of kidney damage or estimation of GFR into a framework for evaluating patients as part of the diagnostic pathway. The guideline development group has developed an algorithm that can be used to evaluate patients and plan services related to the identification of CKD (see *Figure 1*).

2.6.1 ALGORITHM FOR SCREENING, ASSESSMENT AND DIAGNOSIS OF PATIENTS WITH CHRONIC KIDNEY DISEASE

Individuals with CKD are identified in many different circumstances, eg a surveillance programmes within a diabetic clinic, as part of the evaluation of a patient with a known risk factor for CKD or as an incidental finding during a routine health medical examination (see *Figure 1A*).

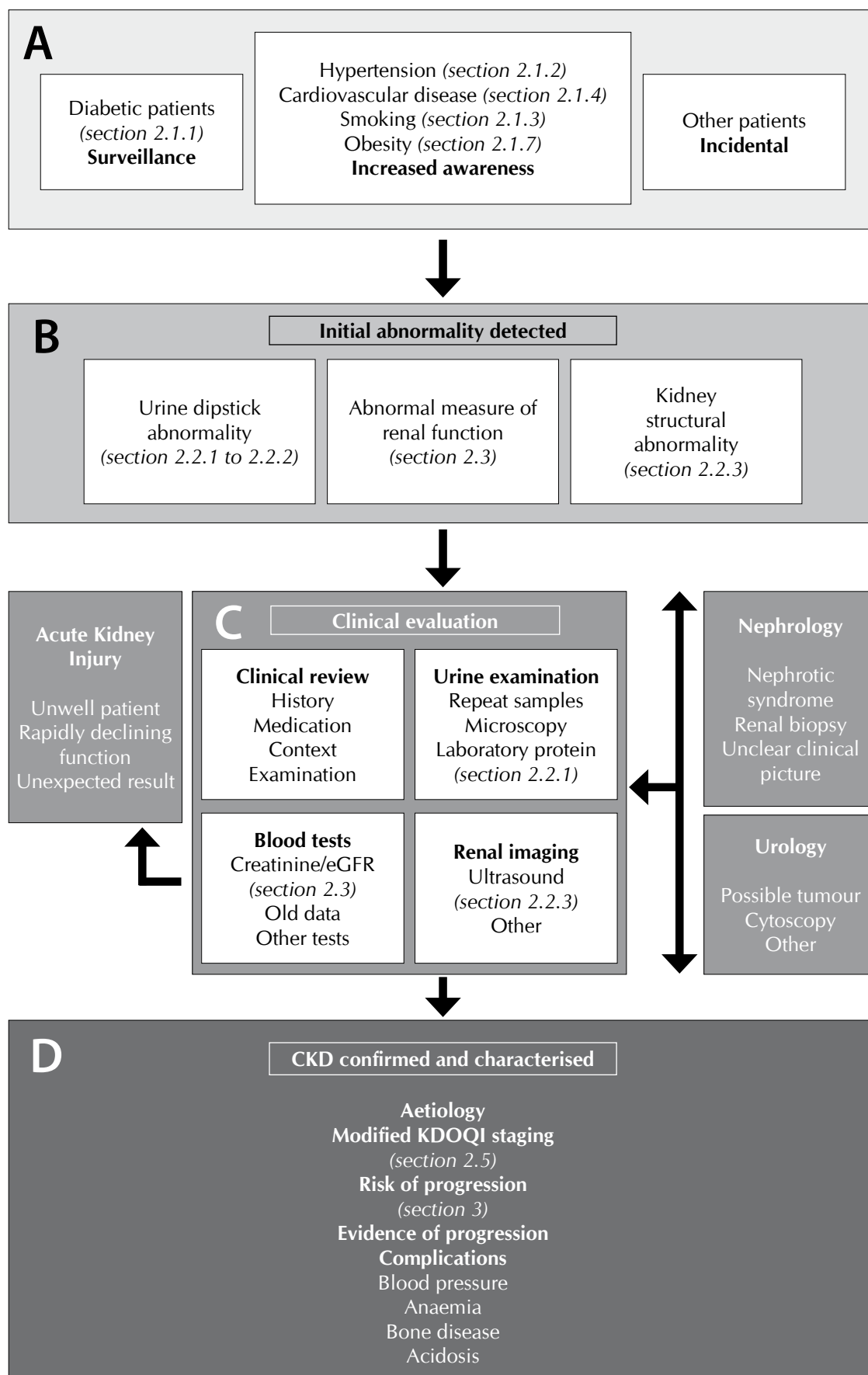
A single marker is a common point of entry for an individual into the pathway of CKD evaluation. Even if there is direct evidence of kidney pathology, for example an ultrasound demonstrating kidneys with multiple cysts, further clinical evaluation will be needed to make a firm diagnosis and a functional assessment will be required to plan future care (see *Figure 1B*).

Clinical evaluation should include history taking, examination and confirmation of initial observations. All patients should have urine sent for protein quantification and a renal tract ultrasound if there are relevant symptoms (see *Figure 1C*).

The exclusion of acute or 'acute on chronic' renal disease is of key importance. If this is the first time an abnormal creatinine has been detected, or the patient is unwell it is reasonable to assume that this could be acute kidney injury. An urgent repeat blood test will usually confirm if there is a rapidly progressive decline in kidney function which requires specialist referral.

The outcome of this evaluation should establish whether there is clear evidence of CKD. Once this is established a profile can be constructed describing the likely aetiology, the KDOQI staging of the disease (see *section 2.5.1*) and an indication of any documented disease progression or an assessment of the risk of future progression (see *Figure 1D*).

Figure 1: Example algorithm for screening, assessment and diagnosis of patients with chronic kidney disease



3 Treatment

This section examines the evidence for the effectiveness of interventions in slowing the rate of progression of CKD or reducing cardiovascular risk. Some interventions have additive effects. Blood pressure will affect proteinuria and a reduction in both is often achieved by agents that may have an independent effect on GFR. Much of the evidence for the assessment of the effects of blood pressure or proteinuria reduction are sub-analyses of studies designed to assess the effect of a specific drug intervention and it is important to determine that the effect seen is drug-independent. Similarly, studies suggesting a specific drug effect on CKD progression must account for changes in blood pressure and proteinuria achieved in the treatment group compared to the control group.

People with chronic kidney disease are at significantly increased risk of cardiovascular events. In a pooled analysis of four large community based, longitudinal studies, CKD (GFR between 15-60 ml/min/1.73 m²) was associated with a 20% increased risk of cardiovascular events and death. Cardiovascular risk was particularly high in black individuals (75% increase), compared with whites (13%).¹⁰⁰ Patients with ESRD have a very high prevalence of cardiovascular disease.

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Outwith the context of CKD, the benefits of lipid lowering therapy, antihypertensive and antiplatelet therapy in terms of cardiovascular disease risk reduction have been demonstrated consistently in large randomised controlled trials.¹⁹

Patients with CKD are often prescribed medications for comorbid conditions, such as diabetes. All drug dosages should be adjusted for kidney function, where appropriate. Drugs with potentially adverse effects on kidney function or complications of decreased kidney function should be discontinued if possible.¹⁰¹ Information on drug dosage alteration is available in The Renal Drug Handbook, 2nd Edition.¹²⁴ Information on whether drugs are contraindicated in CKD is available in the current British National Formulary (BNF)¹²² and summary of product characteristics (SPC).¹²³

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3.1 LOWERING BLOOD PRESSURE

High blood pressure is very common in CKD and represents a major target for intervention to prevent progression.¹²⁵ There is a strong epidemiological relationship between blood pressure and cardiovascular disease and meta-analyses of randomised controlled trials (RCTs) in the general population have demonstrated that the benefits of antihypertensive therapy are primarily a consequence of the level of blood pressure control attained rather than the specific agents used.¹³² Multiple antihypertensive agents are routinely required in the management of blood pressure in patients with CKD.

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3.1.1 REDUCING THE PROGRESSION OF CHRONIC KIDNEY DISEASE

Analysis of blood pressure (BP) effects on renal outcomes in trials of antihypertensive therapy underlines the importance of blood pressure reduction in delaying the progression of CKD.¹³³⁻¹³⁸ In a meta-analysis of 20 RCTs including over 50,000 patients with CKD the risk of ESRD reduced with each tertile of BP control, independent of the agent used. The group with the highest tertile of BP reduction (-6.9 mmHg (-9.1 to -4.8) had a relative risk of ESRD of 0.74 (0.59 to 0.92).¹³⁸

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A systolic BP of > 130 mmHg is significantly associated with CKD progression in non-diabetic patients with proteinuria of > 1 g/day. This meta-analysis identified the optimal systolic BP as 110-129 mmHg.¹³⁶ This study suggested that for patients with proteinuria, systolic BPs of < 110 mmHg may be associated with a more rapid decline in GFR.

1⁺⁺

A meta-analysis of 55 RCTs in CKD patients (n = 5,714) demonstrates a clear association between reduction in BP and reduction in albuminuria.¹³⁸ The effect of blood pressure on proteinuria is greater in patients with higher baseline levels of urinary protein excretion.¹³³

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1⁺

A Blood pressure should be controlled to slow the deterioration of glomerular filtration rate and reduce proteinuria. Patients with ≥ 1 g/day of proteinuria (approximately equivalent to a protein/creatinine ratio of 100 mg/mmol) should have a target maximum systolic blood pressure of 130 mmHg.

3.2 REDUCING PROTEINURIA

3.2.1 REDUCING THE PROGRESSION OF CHRONIC KIDNEY DISEASE

Proteinuria is associated with progression of CKD and has been linked to cardiovascular risk.¹³⁹ It can be modified by blood pressure reduction. Some antihypertensive drugs may have an antiproteinuric effect in addition to their antihypertensive effects.

One meta-analysis and five post hoc analyses of RCTs assessed the relationship between proteinuria and the progression of CKD, measured by change in GFR, doubling of serum creatinine or progression to ESRD. The analyses include patients with diabetic and non-diabetic renal disease, all with proteinuria. A higher baseline proteinuria was shown to be predictive of CKD progression and a reduction in proteinuria reduced the relative risk of CKD progression.^{133,137,140-143}

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For example, a baseline urinary protein excretion (UPE) of < 1.1 g/day confers a 7.7% risk of ESRD at three years. For baseline UPE of 2 to 4 g/day; this risk rises to 22.9% and at > 8 g/day, the risk of ESRD is 64.9%.¹³⁷

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In a meta-analysis of 11 RCTs in patients with non-diabetic CKD (1,860 patients), a 1 g/day reduction in UPE was associated with an 80% reduction in the risk of CKD progression/ESRD (RR 0.20; 95% CI 0.13 to 0.32).¹³³ In patients with type 2 diabetes, for each halving of the degree of proteinuria in the first year of follow up, the risk of ESRD at three years was reduced by 56% (hazard ratio HR = 0.44; 95% CI 0.40 to 0.49).¹³⁷

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Any reduction in proteinuria in patients with CKD will lower the relative risk of disease progression, although patients with higher degrees of proteinuria will benefit more. There should be no lower target as the greater the reduction from baseline urinary protein excretion, the greater the effect on slowing the rate of loss of GFR.^{133,137,143}

A Patients with chronic kidney disease and proteinuria should be treated to reduce proteinuria.

3.3 ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS

Angiotensin converting enzyme inhibitors (ACE inhibitors) and angiotensin II receptor blockers (ARBs) confer both cardioprotective and renoprotective effects. ACE inhibitors and ARBs preferentially dilate the efferent renal arteriole reducing intraglomerular hypertension and reducing proteinuria independent of systemic blood pressure effects.

3.3.1 REDUCING THE PROGRESSION OF CHRONIC KIDNEY DISEASE

Twelve meta-analyses have examined the effects of ACE inhibitors and ARBs in diabetic and non-diabetic patients with CKD on urinary protein excretion and CKD progression.^{134-136,138,144-151}

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Microalbuminuria in diabetes mellitus

Twenty five to forty per cent of patients with diabetes develop diabetic nephropathy.^{152,153} Microalbuminuria identifies the population at risk of progressive diabetic nephropathy. Having two out of three urine samples positive for microalbuminuria (30-300 mg /day albumin) is viewed as incipient diabetic nephropathy.¹⁶

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Prevention or regression of albuminuria is a key target in the treatment of early diabetic kidney disease.

ACE inhibitors can prevent the development of diabetic nephropathy (microalbuminuria)¹⁴⁹ and are able to regress microalbuminuria to no albuminuria.^{134,144} ACE inhibitors can also reduce the rate of progression of microalbuminuria to macroalbuminuria^{134,144,145} and reduce albuminuria.^{138,146} ARBs can reduce the rate of progression of microalbuminuria to macroalbuminuria and regress microalbuminuria to no albuminuria¹⁴⁴ and can reduce albuminuria.¹³⁸

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In three meta-analyses, the beneficial effects of ACE inhibitors on albuminuria could not be fully explained by reduction of blood pressure.^{134,138,149} In the other meta-analyses, the independence of effect of ACE inhibitors on AER from effect on BP could not be established either because of lack of data or the analyses not achieving statistical significance.¹⁴⁴⁻¹⁴⁶

Prevention of microalbuminuria

One meta-analysis of 16 trials (7,603 patients) demonstrated that ACE inhibitors prevent the development of diabetic kidney disease in patients with no microalbuminuria (albumin excretion <30 mg/day) at baseline.¹⁴⁹ This effect appears to be present in patients with or without hypertension, patients with type 1 or type 2 diabetes, and patients with or without normal GFR.

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Regression of microalbuminuria to no albuminuria in diabetes mellitus

ACE inhibitors and ARBs can cause microalbuminuria to regress to no albuminuria in diabetes mellitus.^{134,144} A meta-analysis of 36 RCTs (1,888 patients) demonstrated that ACE inhibitors increased the likelihood of regression from microalbuminuria to no albuminuria (RR 3.42; 95% CI 1.95 to 5.99) in patients with type 1 or 2 diabetes, both normotensive and with pre-existing hypertension. In patients with type 2 diabetes with hypertension, ARBs also increased the likelihood of regression from microalbuminuria to no albuminuria (RR 1.42; 95% CI 1.05 to 1.93), although this analysis did not correct for the BP lowering effects of these drugs.¹⁴⁴ A smaller meta-analysis of 12 RCTs (689 patients) demonstrated an odds ratio for regression to no albuminuria of 3.07 (95% CI 2.15 to 4.44) for patients treated with ACE inhibitors; an effect attenuated but not abolished by adjusting for blood pressure, suggesting a specific antiproteinuric effect of these drugs.¹³⁴

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Progression of microalbuminuria to macroalbuminuria in diabetes mellitus

There is a reduction in the rate of progression of microalbuminuria to macroalbuminuria in patients with diabetes treated with ACE inhibitors or ARBs.^{134,144,145} A meta-analysis in patients with type 1 or type 2 diabetes in primary care demonstrated that ACE inhibitors (36 RCTs, 2,010 patients) reduced the rate of progression of micro to macroalbuminuria by 45%, and ARBs (four RCTs, 761 patients, type 2 diabetes only) by 51% regardless of the presence or absence of baseline hypertension, diabetes type, or duration of treatment (ACE inhibitors: RR 0.55; 95% CI 0.28 to 0.71, ARBs: RR 0.49; 95% CI 0.32 to 1.05). ACE inhibitors and ARBs were not significantly different in their effects on progression of microalbuminuria. The analysis did not correct for BP effects of these drugs.¹⁴⁴

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A meta-analysis of 12 RCTs in normotensive patients with type 1 diabetes (689 patients) demonstrated that the reduction in progression of micro to macroalbuminuria (OR for progression 0.38; 95% CI 0.25 to 0.57) with ACE inhibitors was attenuated when blood pressure effects were adjusted for but not abolished suggesting a BP independent effect of ACE inhibitors on microalbuminuria.¹³⁴

ACE inhibitors and ARBs reduce albuminuria in patients with diabetes¹⁴⁶ and reduce proteinuria ranging from microalbuminuria to overt proteinuria (7.2 to 3,000 g/day albuminuria). All the RCTs included had an active control arm in respect of BP. No difference in blood pressure was noted between the treatment groups to explain the reduction in albumin excretion rate.¹³⁸

A Patients with chronic kidney disease and type 1 diabetes with microalbuminuria should be treated with an angiotensin converting enzyme inhibitor irrespective of blood pressure.

A Patients with chronic kidney disease and type 2 diabetes with microalbuminuria should be treated with an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker irrespective of blood pressure.

Proteinuria reduction in non-diabetic patients with CKD

Three meta-analyses in non-diabetic patients with CKD show a reduction in overt proteinuria with ACE inhibitors or ARBs.^{135,138,147} In a meta-analysis of eight RCTs (142 patients) in patients with polycystic kidney disease and proteinuria, ACE inhibitors reduced proteinuria significantly after correction for baseline and subsequent changes in BP. The reduction was greater at higher baseline proteinuria levels.¹⁴⁷

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A Angiotensin converting enzyme inhibitors and angiotensin receptor blockers are the agents of choice to reduce proteinuria in patients without diabetes but who have chronic kidney disease and proteinuria.

Rate of progression of CKD in patients with and without diabetes

There is conflicting evidence regarding the role of ACE inhibitors and ARBs in reducing the rate of progression of CKD.^{135,136,145,148}

In a meta-analysis of 7 RCTs including 1,389 patients with established proteinuria, ACE inhibitors reduced the risk of CKD progression or the numbers reaching ESRD by 40% (RR 0.60; 95% CI 0.49 to 0.73).¹⁴⁵ In a meta-analysis of 10 RCTs in 1,594 patients without diabetes, ACE inhibitors reduced the risk of ESRD by 30% (RR 0.70; 95% CI 0.51 to 0.97).¹⁴⁸ Neither of these analyses could separate the effect of ACE inhibitors on CKD progression from their effect on BP. In a meta-analysis of 11 RCTs in 1,860 patients with non-diabetic kidney disease, ACE inhibitors reduced the risk of ESRD or doubling of serum creatinine after adjusting for baseline and follow up BP and proteinuria (RR of ESRD in ACE inhibitor group 0.69; 95% CI 0.51 to 0.94, doubling of serum creatinine /ESRD combined 0.70; 95% CI 0.55 to 0.88).

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Further analysis of this cohort of patients has demonstrated that there was no additional benefit of ACE inhibitors over other blood pressure treatments for patients with a baseline urinary protein excretion of <0.5 g/day.¹⁵⁴

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Conflicting results were reported in three meta-analyses.^{138,144,147}

In one meta-analysis (142 patients) whilst a significant reduction in proteinuria was demonstrated in patients with autosomal dominant polycystic kidney disease (ADPKD) treated with ACE inhibitors, only a trend to slowing CKD progression was seen, which was greater in patients with higher baseline proteinuria levels.¹⁴⁷ The mechanism underlying cyst formation is not affected by blood pressure.

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In a meta-analysis of 36 RCTs in patients with type 1 or 2 diabetic nephropathy in primary care, the point estimate for developing ESRD or the doubling of serum creatinine was less in patients who were prescribed ACE inhibitors but not statistically significant (all cause mortality RR 0.64; 95% CI 0.40 to 1.03; doubling of serum creatinine RR 0.60; 0.35 to 1.05). This included the micro-HOPE study accounting for over half the patients in the analysis and which recruited patients with a high cardiovascular risk and mortality but relatively low renal risk. This study alone produced opposite findings to the others in the meta-analysis (ie favoured placebo/no treatment), but, because of its size, accounted for 29% of the weighting of the overall result. Angiotensin receptor blockers did significantly reduce the risk of an adverse renal outcome in patients with type 2 diabetes (ESRD: RR 0.78; 95% CI 0.67 to 0.91; doubling of serum creatinine: RR 0.79; 95% CI 0.67 to 0.93).¹⁴⁴

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A meta-analysis of 13 RCTs in 37,089 patients did demonstrate a reduction in the risk of ESRD in patients on ACE inhibitors or ARBs (RR 0.87) although no benefit was demonstrated in the diabetic sub-population. Blood pressure was not different between the ACE inhibitor/ARB and comparison group. The analysis included 33,357 patients in the ALLHAT trial, where the 24,303 patients in the control group assigned thiazides had an approximately 2 mmHg lower systolic BP at the end of the study, which could have attenuated any benefits of ACE inhibitors. This individual study heavily weighted the overall outcome of the analysis in a direction contrary to the other RCTs analysed. In the 11 RCTs (3,376 patients) with doubling of serum creatinine as a renal outcome, a non-significant reduction in risk was observed in patients on ACE inhibitors/ARBs (RR 0.71; 95% CI 0.49 to 1.04) with no benefit in the diabetic sub-population. The meta-analysis did not assess the effects of ACE inhibitors or ARBs individually.¹³⁸

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Combination treatment with ACE inhibitors and ARBs

Two meta-analyses have looked at the effect of adding ARB treatment to ACE inhibitors in patients with CKD.^{150,151} These show that combination treatment reduces proteinuria more than ACE inhibitors alone in both patients with diabetic and non-diabetic kidney disease. The role of blood pressure reduction in this effect is not clear.¹⁵¹ The use of sub-maximal doses of the drugs limited the validity of conclusions.¹⁵⁰ Only one study in these meta-analyses studied the ability of the combination to slow CKD progression and suggested that the combination was better.¹⁵⁰ In one meta-analysis hyperkalaemia was increased overall by a small but significant amount (0.11 mmol/l, 95% CI 0.05 to 0.17 mmol/l).¹⁵¹ In the other meta-analysis, clinically significant hyperkalaemia occurred in only 19 out of 434 patients, suggesting this is a safe combination, if monitored.¹⁵⁰

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More data are required to determine the effect of combination therapy on disease progression before it will be possible to make a recommendation on this treatment.

A

Angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers should be used as agents of choice in patients (with or without diabetes) with chronic kidney disease and proteinuria (≥ 0.5 g/day, approximately equivalent to a protein/creatinine ratio of 50 mg/mmol) in order to reduce the rate of progression of chronic kidney disease.

3.3.2 REDUCING THE RISK OF CARDIOVASCULAR DISEASE

There are limited data on the specific impact of antihypertensive therapy on cardiovascular outcomes in people with CKD. In a systematic review of 50 randomised trials of ACE inhibitor and/or ARB therapy in people with diabetic nephropathy, neither agent was associated with a significant overall reduction in mortality. A subgroup analysis of studies using full-dose ACE inhibitor therapy compared with studies using half or less than half of the maximum dose showed that full dose therapy was associated with a 22% reduction in all-cause mortality.¹⁵⁵ This finding was confirmed by another RCT which showed that an ACE inhibitor reduced all-cause mortality by 21% in people with diabetic nephropathy, independently of the modest effect on blood pressure reduction while ARBs had no effect on mortality.¹⁵⁶

In the Anglo Scandinavian Cardiac Outcomes Trial (ASCOT), a blood pressure regimen incorporating amlodipine and perindopril was associated with fewer cardiovascular events in patients with CKD, than a regimen incorporating atenolol and bendroflumethiazide.¹⁵⁷

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In the Survival and Ventricular Enlargement trial (SAVE), CKD was associated with an increased risk of cardiovascular events after myocardial infarction, particularly when GFR was < 45 ml/min/1.73 m². Subjects randomised to captopril post-myocardial infarction had a reduced risk of cardiovascular events, compared with placebo, irrespective of baseline renal function. Patients with CKD accrued greater absolute benefit with 12.4 cardiovascular events prevented per 100 subjects with CKD, compared with 5.5 events per 100 subjects without CKD.¹⁵⁸

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3.3.3 ADVERSE EFFECTS OF RENIN ANGIOTENSIN SYSTEM BLOCKADE

Hyperkalaemia (> 5.5 mmol/l) is a recognised consequence of ACE inhibitor and ARB therapy and can occur independently at various stages of CKD.

Renin angiotensin system blockade can cause a decline in GFR in the context of low renal perfusion. Low renal perfusion can occur acutely, eg volume depletion, or chronically, eg renovascular disease or low cardiac output states (severe heart failure or outflow tract obstruction).

It is not always necessary to discontinue ACE inhibitor/ARB therapy if GFR declines following initiation or dose increase, providing the fall in GFR is less than 20% and renal function stabilises. Similarly, modest, stable hyperkalaemia may be preferable to discontinuing a useful treatment.



Potassium and renal function should be checked after commencing and changing the dose of angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers.

3.4 NON-DIHYDROPYRIDINE CALCIUM CHANNEL BLOCKERS

3.4.1 REDUCING THE PROGRESSION OF CHRONIC KIDNEY DISEASE

One meta-analysis in patients with hypertension and proteinuria concluded that non-dihydropyridine calcium channel blockers (CCBs), but not other CCBs, reduce proteinuria.¹⁵⁹ Although BP changes were the same, the independence of effect on proteinuria from that of BP reduction was not statistically significant. An effect on disease progression could not be assessed.

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Non-dihydropyridine calcium channel blockers should be considered in patients with chronic kidney disease and proteinuria who are intolerant of angiotensin converting enzyme inhibitors or angiotensin receptor blockers.

3.5 LIPID LOWERING

There are no published large scale RCTs of the effect of lipid-lowering therapy on cardiovascular disease or renal outcomes, specifically in people with stage 1-3 CKD. Data are available from subgroup analyses of the major statin trials and one RCT of fibrate therapy. The Study of Heart and Renal Protection (SHARP) is currently recruiting 9,000 patients with CKD (6,000 pre-dialysis patients and 3,000 undergoing dialysis) and will examine the effects of therapy with simvastatin and ezetimibe (a cholesterol absorption inhibitor) on cardiovascular and renal outcomes.¹⁶⁰

3.5.1 REDUCING THE PROGRESSION OF CHRONIC KIDNEY DISEASE

Dyslipidaemia may contribute to progression of renal disease by intrarenal atherosclerosis or direct toxicity to renal cells.^{161,162} The use of statins (HMG-CoA reductase inhibitors) to reduce serum cholesterol may slow the progression of CKD. Statins may have a renoprotective effect that is not dependent on lipid lowering,¹⁶³ and appear to have an additional anti-inflammatory effect.¹⁶⁴

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4

Four systematic reviews of the use of statins in slowing the progression of CKD were found. Two were of low methodological quality.^{165,166}

1-

In a study investigating the rate of kidney function loss in patients with stages 1-3 CKD, pravastatin reduced the rate of decline in renal function by 34% in patients with stage 3 CKD (0.22 ml/min per 1.73 m²/year, p=0.002).¹⁶⁷

1+

In a meta-analysis including 39,704 patients from 27 studies,¹⁶⁸ statins reduced the rate of decline of GFR by 1.22 ml/min/yr (95% CI 0.44 to 2.00 ml/min/yr). This benefit was only 0.22 ml/min/yr when the analysis was restricted to well performed trials, and the only subgroup in which the effect of statins on GFR proved to be significant was patients with cardiovascular disease.

1++

Two meta-analyses examined reduction in proteinuria with statin treatment. One demonstrated a non-significant favourable change¹⁶⁸ while the second demonstrated a significant reduction in microalbuminuria of 48% (95% CI 71% to 25%) and proteinuria of 47% (95% CI 67% to 26%). The effect was greatest with higher degrees of proteinuria.¹⁶⁹

1++

3.5.2 REDUCING THE RISK OF CARDIOVASCULAR DISEASE

In the population without CKD, therapy with statins reduces the five year incidence of major coronary events, coronary revascularisation and stroke by about 20% for every mmol/l reduction in low density lipoprotein (LDL) cholesterol. This is largely irrespective of initial lipid profile, but absolute risk reduction relates to baseline absolute risk and the reduction in LDL cholesterol achieved.^{170,171}

1++

Consideration for statin therapy is also indicated for individuals aged over 40 years whose 10-year cardiovascular risk is calculated to be $\geq 20\%$.¹⁹ Current cardiovascular risk assessment tools, such as the Joint British Societies CVD risk prediction chart⁷² do not include CKD in their risk prediction algorithm and so underestimate cardiovascular risk in people with CKD (see *SIGN guideline 97 on risk estimation and the prevention of cardiovascular disease*).¹⁹ The majority of older adults with stage 3 CKD should be considered as having a 10-year cardiovascular risk in excess of 20%.¹⁹ Individuals with stage 1 and 2 CKD may cross this threshold if they have other risk factors for cardiovascular disease.

4

Patients with mild to moderate CKD should, in theory, accrue greater absolute benefit from statin therapy, because of their higher absolute risk. In contrast, observational studies among dialysis patients have reported a negative association between total cholesterol and mortality.¹⁷³ RCTs of statin therapy in patients with advanced CKD (ie haemodialysis or post-transplant patients) showed no overall benefit on cardiovascular outcomes.^{174,175} There are also concerns about the potential toxicity of long term statin therapy in people with CKD.

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3

Pravastatin (40 mg daily) reduced cardiovascular outcomes by 23% in a meta-analysis of three RCTs including 4,491 patients with moderate CKD (mean GFR 55 ± 8 ml/min).¹⁶⁷ Over 70% had coronary heart disease at baseline, but the relative risk reduction was the same in people with or without coronary disease. The overall risk reduction was comparable with patients who had normal kidney function, but the absolute benefit accrued by the CKD patients was greater because of their higher baseline risk.

1++

In another study, atorvastatin (10 mg daily) reduced cardiovascular events by 40% in patients with CKD (serum creatinine up to 200 micromol/l) over five years.¹⁷⁶ All patients in the primary study had hypertension, at least three other cardiovascular risk factors and a total cholesterol < 6.5 mmol/l. Gemfibrozil (1,200 mg daily) reduced cardiovascular events by 27% in patients with mild to moderate CKD (GFR 30-75 ml/min/1.73 m²), low high density lipoprotein (HDL) cholesterol concentrations and a prior history of cardiovascular disease.¹⁷⁷ There was no overall difference in adverse events between the gemfibrozil and placebo arms, but gemfibrozil was associated with an increased risk of sustained increase in serum creatinine compared with placebo (5.9% vs 2.8%).

1+

B Statin therapy should be considered in all patients with stage 1-3 chronic kidney disease, with a predicted 10-year cardiovascular risk $\geq 20\%$.

3.6 ANTIPLATELET THERAPY

3.6.1 REDUCING THE RISK OF CARDIOVASCULAR DISEASE

Aspirin (or other antiplatelet therapy) reduces cardiovascular events by 25% in patients at increased cardiovascular risk in the general population.¹⁷⁸ Aspirin is indicated both for patients with established cardiovascular disease and, as primary prevention, in individuals at high estimated risk of cardiovascular disease.¹⁷² There are no data from large scale RCTs specifically in patients with stage 1-3 CKD. In the UK-HARP-1 study, aspirin therapy was associated with a threefold increased risk of minor, although not major bleeding in a heterogeneous group of patients with advanced CKD (242 pre-dialysis patients with serum creatinine ≥ 150 micromol/l; 73 patients on dialysis and 133 post-transplant patients).¹⁷⁹ The substantial benefit of aspirin therapy in terms of cardiovascular disease risk reduction must be weighed against the risk of potential adverse effects.

1++

B Low-dose antiplatelet therapy should be considered in all patients with stage 1-3 chronic kidney disease, whose estimated 10-year cardiovascular risk is $\geq 20\%$.

3.7 DIETARY MODIFICATION

3.7.1 REDUCING THE PROGRESSION OF CHRONIC KIDNEY DISEASE

Protein restriction

Stages 1-3 chronic kidney disease

Four small RCTs (n = 69-131) conducted in patients with stages 2-3 CKD and diabetes (type 1 and type 2) did not demonstrate a beneficial effect of protein restriction (0.6-0.8 g/kg) on delaying disease progression.¹⁸⁰⁻¹⁸³ These studies followed up patients for one to four years.

1++

One small RCT (n = 89) in non-diabetic patients with stage 3 CKD conducted over 12 months demonstrated a positive effect of protein restriction (0.6 g/kg/day) on progression (p < 0.01). Compliance in the restricted group was suboptimal, the protein intake in the control group was 2.3 times higher than in the restricted group (0.67 g vs 1.54 g) and a significant decline in energy intake coupled with a deterioration (body weight and BMI) were seen in the protein restricted group (p < 0.05).¹⁸³

1++

Stage 4 chronic kidney disease

For non-diabetic and diabetic patients with stage 4 CKD two systematic reviews and one meta-analysis suggest that, in comparison to other treatments, there is, at most, a modest benefit associated with restricting protein leading to a delay in CKD progression (0.53 ml/min/year; 95% CI 0.08 to 0.98 ml/min/year).¹⁸⁴⁻¹⁸⁶

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1-

There are many limitations to these studies; they include stage 5 CKD patients; the original studies are heterogeneous in nature (CKD diagnosis, duration of intervention, varying levels of protein restrictions), few studies used GFR as an outcome; several studies specifically excluded patients receiving ACE inhibitors; compliance with protein restriction was suboptimal; the effect of restriction on nutritional status was largely ignored, smaller studies reported greater effects and funnel plots indicate a publication bias in favour of protein restricted diets.

In clinical practice any benefits of protein restriction have to be offset against the potential detrimental effects on nutritional status; the difficulties of patient compliance, potential effects on quality of life and the costs associated with implementation and monitoring.

It is not possible to deduce an optimal protein level from the available evidence. High protein intakes are associated with high phosphate intakes as foods that contain protein also tend to contain phosphate.¹⁸³ It would appear prudent to avoid high protein intakes in stage 4 CKD patients when hyperphosphatemia is prevalent¹⁶² and this should be done under the guidance of an appropriately qualified dietitian.

A Dietary protein restrictions (<0.8 g/kg/day) are not recommended in patients with early stages of chronic kidney disease (stages 1-3).

☒ In stage 4 chronic kidney disease patients high protein intake (>1.0 g/kg) is not recommended.

Phosphate restriction

No evidence was identified to show that phosphate restriction affects the progression of CKD.

Sodium restriction

One small cohort study of poor methodological quality was identified, which suggested a slower progression of CKD with salt restriction, but the groups within the study had different baseline characteristics and diagnoses, including interstitial nephritis, which may be salt losing.¹⁸⁷

2-

One systematic review looked for the evidence linking dietary salt intake and progression of chronic kidney disease.¹⁸⁸ The available evidence consists of small scale studies of short duration and poor quality. There is a suggestion that dietary salt consumption directly links to albuminuria but no consistent evidence regarding the effect of dietary sodium intake on progression of kidney disease.

2++

3.7.2 REDUCING THE RISK OF CARDIOVASCULAR DISEASE

The evidence for the role of sodium in reducing the risk of cardiovascular disease has been reviewed in detail within the KDOQI clinical practice guidelines on hypertension and antihypertensive agents in CKD.¹⁸⁹

4

In the Dietary Approaches to Stop Hypertension (DASH) - Sodium Trial, adoption of the DASH diet (which emphasises fruits, vegetables, low-fat dairy products and includes wholegrains, poultry, fish, and nuts; contains only small amounts of red meats, sweets, and sugar-containing beverages) lowered blood pressure at all sodium levels compared with a typical American diet.¹⁹⁰ In addition, blood pressure was lowered in consumers of a DASH diet or a typical American diet by reducing the sodium intake from 3.2 g/day to 2.4 g/day, the currently recommended upper limit in the USA. An even greater blood pressure reduction (ie a larger reduction per mmol sodium) was achieved with consumption of either diet at a level of sodium of 1.5 g/day. The DASH-Sodium Trial has demonstrated the short term efficacy and safety of this diet in adults with high normal blood pressure and hypertension, but did not include adults with hypertension and CKD.

1+

Due to the potential for increased potassium and phosphate levels, patients with CKD may not be able to adhere to the DASH diet, although the principle of sodium reduction remains valid.

B For patients with stage 1-4 chronic kidney disease and hypertension a reduction in sodium (<2.4 g/day or <100 mmol/day which is equivalent to <6 g of salt) is recommended as part of a comprehensive strategy to lower blood pressure and reduce cardiovascular risk.

☒ Salt substitutes that contain high amounts of potassium salts should not be used in patients with chronic kidney disease.

3.7.3 HYPERKALAEMIA

Hyperkalaemia (> 5.5 mmol/l) can occur independently at various stages of CKD (see section 3.3.3). In the absence of other recognised medical causes the patient's diet should be investigated for sources of potassium.

☒ In the absence of other recognised medical causes patients with chronic kidney disease and consistently raised serum potassium levels should be managed with the involvement of an appropriately qualified dietitian.

3.8 LIFESTYLE MODIFICATION

3.8.1 REDUCING THE PROGRESSION OF CHRONIC KIDNEY DISEASE

No evidence was identified that weight reduction or exercise affect the progression of CKD.

In observational studies, smoking is associated with increasing proteinuria and a faster progression of renal insufficiency in patients with established renal disease, suggesting cessation would be of benefit¹⁹¹⁻¹⁹⁴ although this finding is not universal.¹⁹⁵

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Only one prospective study was identified which has looked at the effect of stopping smoking on the rate of decline of renal function.¹⁹⁶ Forty five patients with established chronic kidney disease who smoked were matched with 45 non-smoking controls. Sixteen patients with CKD were persuaded to stop smoking over 24 months. At baseline, progression of renal failure was twice as high in smokers compared with non-smokers. Compared to patients who gave up during the study or who had never smoked, patients continuing to smoke had a faster decline in renal function. In those who stopped smoking the rate of decline in renal function slowed from 1.2 ± 0.3 to 0.7 ± 0.1 ml/min/month, similar to their matched controls.

3

3.8.2 REDUCING THE RISK OF CARDIOVASCULAR DISEASE

There are no good quality data on the benefits of smoking cessation on cardiovascular events in people with CKD, but epidemiological data associate smoking with increased cardiovascular risk in the general population.^{197,198}

2++

- ☒ People with chronic kidney disease who smoke should be advised to stop and referred to an NHS smoking cessation service if they are motivated to quit.

There are no good quality data on the benefits of weight reduction on cardiovascular events in people with CKD, but epidemiological data associate increased central abdominal obesity with increased cardiovascular risk.¹⁹⁹

4

- ☒ People with chronic kidney disease with a waist circumference ≥ 94 cm in men or ≥ 80 cm in women should be considered for weight management with the involvement of an appropriately qualified dietitian.

There are no good quality data on the benefits of regular exercise on cardiovascular events in people with CKD, but epidemiological data associate regular exercise with reduced cardiovascular risk in the general population.^{200,201}

2++

- ☒ People with chronic kidney disease should be encouraged to take regular exercise.

3.9 OTHER INTERVENTIONS

3.9.1 FISH OILS

There is conflicting evidence about how fish oils affect the progression of CKD. In one meta-analysis some studies indicate a negative effect on the progression of CKD, one showed a positive effect and one demonstrated no effect.²⁰² Another study showed that fish oils did not delay the progression of CKD in IgA nephropathy.²⁰³ There is insufficient evidence to support the use of fish oils to delay the progression of CKD stages 1-4.

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3.9.2 SUPPLEMENTS AND HERBAL MEDICINES

No evidence was identified to support the use of vitamin supplements, herbal remedies, Chinese medicines or homeopathic preparations as means of slowing the progression of chronic kidney disease.

Case studies reported the occurrence of nephrotoxic effects of some Chinese and Ayurvedic medicines.²⁰⁴⁻²⁰⁷

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- ☒ Patients with chronic kidney disease who express an intent to use alternative or complementary therapies should be made aware of the lack of evidence to support their use and be warned of the possible nephrotoxic effects of some Chinese and Ayurvedic medicines.

3.10 TREATMENTS TO IMPROVE QUALITY OF LIFE

3.10.1 EXERCISE THERAPY

Limited evidence exists on the effects of exercise on functional status and quality of life (QoL) in patients with CKD.

In a small cohort study in patients with stage 4 CKD who followed an exercise programme for 12 weeks, exercise had a positive impact on functional status and mobility, but there was no perceived improvement in QoL.²⁰⁸

2+

A randomised controlled trial in a small group of patients with stage 4 CKD reported increased type I and II muscle-fibre cross-sectional area in patients who performed resistance training (mean \pm standard deviation of $24\% \pm 31\%$, and $22\% \pm 29\%$, respectively), compared with those who did not. Improvement in muscle strength was significantly greater with resistance training ($32\% \pm 14\%$) than without ($-13\% \pm 20\%$) ($p < 0.001$).²⁰⁹ Resistance training exercise appears to be a safe and effective countermeasure to the negative effects of protein restriction. The findings may not be applicable to patients with chronic renal insufficiency who are not on low protein diets.

1+

If CKD progresses, functional status and QoL may decline. Early education about the benefits of exercise in CKD patients may be of benefit. All members of the multidisciplinary team can provide patients with advice related to the benefits of remaining active and of exercise.

- ☒ If patients experience a reduction in exercise capacity which impacts on their daily life, they should have access to an appropriately qualified physiotherapist.

3.10.2 PSYCHOSOCIAL MANAGEMENT

Quality of life

One single-cohort study evaluated the effects of attendance at pre-dialysis clinics on quality of life following initiation of dialysis.²¹⁰ Patients who were actively managed prior to the initiation of dialysis experienced improved quality of life following initiation of dialysis. Observational studies identified significantly compromised quality of life in CKD patients and at initiation of dialysis, highlighting the importance of acknowledging, assessing and managing such issues in the CKD population.²¹¹⁻²¹³

3

Psychosocial difficulties

Observational studies identified significant levels of depression, the presence of major life stressors and psychosocial adjustment difficulties in the CKD population.²¹⁴⁻²¹⁶ Self expression (eg psychological therapy) is important in the process of psychosocial adjustment to the stressors associated with diagnosis, symptoms and treatments related to CKD.²¹⁷ One qualitative study of relatively poor methodological quality indicated patient satisfaction with, and benefits of, a CKD counselling service.²¹⁸ An observational study identified the role certain personality variables (ie low conscientiousness and high neuroticism) may play in the prediction of mortality in patients with CKD.²¹⁹

3

The general psychosocial needs of the pre-dialysis population remain relatively poorly understood.

- ☒ Quality of life and psychosocial stressors should be routinely assessed and actively managed psychologically, where indicated.

Patient education

Psychoeducation refers to a package of information and educational elements relating to a disease process and its treatment, aimed at improving patient understanding, awareness and management of the condition and its psychological correlates. Such packages may comprise personalised health related information, supportive telephone calls, adaptive coping strategies and the development of informed decision making.

In one RCT, a pre-dialysis psychoeducational intervention delivered to patients with CKD was found to significantly extend time to dialysis ($p < 0.001$) when compared with usual treatment.²²⁰

1++

A cohort study reported that an enhanced pre-dialysis patient education programme significantly extended time to dialysis ($p < 0.05$) when compared to standard education procedures.²²¹

2++

Another cohort study reported the impact of a pre-dialysis patient education programme, which comprised group based education sessions covering information on renal disease and its management.²²² After initiation of dialysis, those who received the package scored higher on subscales of the Health Index ($p < 0.001$ to $p < 0.05$) and scored lower on the Sickness Impact Profile ($p < 0.01$ to $p < 0.05$) and the State-Trait Anxiety Inventory ($p < 0.01$).

2++

A further cohort study on the effect of a pre-dialysis psychoeducational intervention on long term disease related knowledge in patients with CKD found that a package of individually delivered information on kidney disease and management led to significantly improved disease-related knowledge ($p < 0.002$) as measured by the Kidney Disease Questionnaire.²²³

2+

While these studies did not specifically refer to participants' GFR or CKD stage, patients included were generally in the advanced stages of CKD and it is acknowledged that the majority of patients with CKD will not require renal replacement therapy.

B The delivery of a psychologically informed, pre-dialysis psychoeducation programme is recommended for all patients with progressive chronic kidney disease at any stage who will eventually require renal replacement therapy.

3.10.3 OCCUPATIONAL THERAPY

The underlying causes of renal disease, eg diabetes, vascular disease or comorbid medical conditions, often cause patients to experience difficulties in their occupational roles. Although there is no specific evidence to support the role of occupational therapy in the care of the patient with CKD, there is evidence that skilled occupational therapy advice should be available to those experiencing limitations in function.^{224,225}

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☒ All patients with chronic kidney disease who have problems with the activities of daily living should have access to an occupational therapist.

3.10.4 ERYTHROPOIESIS STIMULATING AGENTS IN THE MANAGEMENT OF ANAEMIA

As CKD progresses the kidney produces less erythropoietin and patients can become anaemic. It is estimated that 9% of men and women in stage 3 and 33% of men and 67% of women in stage 4 have a haemoglobin level below the normal range (≥ 120 g/l for men and ≥ 110 g/l for women).²²⁶

In a systematic review of 15 studies which focused on the treatment of the anaemia of CKD in pre-dialysis patients there was a significant improvement in quality of life on treatment with erythropoietin.²²⁷ This review included a meta-analysis of three small studies which showed no effect of treatment of anaemia on mortality (RR 0.60, 95% CI 0.13 to 2.88).

1+

A systematic review of nine studies examined the relationship between target haemoglobin levels and mortality in patients with anaemia and CKD, including patients on dialysis.²²⁸ The risk of all cause mortality was significantly higher in the higher (120 to 160 g/l) haemoglobin target group than in the lower (90 to 120 g/l) haemoglobin target group (RR 1.17, 95% CI 1.01 to 1.35; $p = 0.031$) although this effect was dominated by one large study of dialysis patients with known cardiac disease. A subgroup analysis which included only pre-dialysis patients showed no significant difference in mortality between the low and high haemoglobin target groups (RR 1.33, 95% CI 0.98 to 1.81; $p = 0.067$). The relative risk of poorly controlled BP was also greater in the higher haemoglobin target group (RR 1.27, 95% CI 1.08 to 1.50; $p = 0.004$).

1++

In 2007 the European Medicines Agency (EMA) revised the summary of product characteristics for epoetins to highlight the potential risk of raising haemoglobin levels in patients with anaemia associated with cancer or CKD. Trials of patients with anaemia associated with cancer have shown a small unexplained excess mortality relating to treatment with epoetins.²²⁹ EMA recommends that epoetins should be used in the treatment of anaemia only if associated with symptoms, and has stipulated a uniform target haemoglobin range for all epoetins of 100 g/l to 120 g/l with a warning not to exceed a concentration of 120 g/l.

4

A Erythropoiesis stimulating agents should be considered in all patients with anaemia of chronic kidney disease to improve their quality of life.

☒ In patients with chronic kidney disease treated with erythropoiesis stimulating agents the haemoglobin should normally be kept between 100 g/l and 120 g/l.

There may be circumstances where the use of erythropoiesis stimulating agents (ESAs) is inappropriate. There is more information on this and other aspects of the management of anaemia in the NICE guideline on Anaemia Management in Chronic Kidney Disease.²³⁰ 4

3.10.5 PREVENTING MALNUTRITION

Observational studies suggest that undernutrition exists in patients with stage 3 CKD although it predominantly occurs in patients with stage 4-5 CKD. Nutritional status deteriorates as GFR declines.²³¹⁻²³³ 2+
3

One study found a relationship between undernutrition and morbidity²³³ (likelihood of hospital admission $p < 0.001$). None of the studies identified examined the impact of undernutrition on the quality of life, mortality and functional status of CKD patients. 2+

There is evidence from cohort studies that obesity, and in particular central obesity, affects cardiovascular risk (see section 3.8.2).

D **Nutritional status** (*height, weight, body mass index, percentage weight loss*) **should be monitored in all patients with chronic kidney disease at stage 3 or higher.**

☒ Patients exhibiting signs of malnutrition (*body mass index $< 20 \text{ kg/m}^2$ or $> 30 \text{ kg/m}^2$ or unintentional weight loss of $> 10\%$ in six months*) should be referred to an appropriately qualified dietitian.

3.11 MANAGING RENAL BONE DISEASE

3.11.1 INTRODUCTION

As GFR falls phosphate is usually retained, hydroxylation to activate vitamin D is impaired and hyperparathyroidism develops. Parathyroid hormone (PTH) acts on the bone to increase resorption.

Only 38% of patients starting renal replacement therapy (RRT) have a normal bone biopsy.²³⁵ 27% of patients have bone pathology often related to hyperparathyroidism. 12% have osteomalacia and 23% adynamic bone disease (characterised by excess osteoid, fewer osteoblasts and osteoclasts and possibly related to oversuppression of PTH). 3

Patients with CKD may also have reduced bone mineral density or osteoporosis.^{236,237}

The consequences of bone disease include bone pain and deformity, fractures or microfractures, myalgia and weakness, and tendon rupture. Eventually, (usually in stage 5 CKD) soft tissue calcification occurs in association with prolonged phosphate retention and increased calcium-phosphorus product. This can involve the lungs (with features of impaired lung function or fibrosis and features of right heart failure), the heart (valvular calcification, heart failure, arrhythmias and coronary artery calcification) and soft tissues and vessels (with painful subcutaneous calcification, conjunctival calcification, keratopathy, peripheral vascular insufficiency, itch and skin ulcers). Elevated levels of PTH and serum phosphorus have been associated with an increased risk of mortality, possibly through soft tissue calcification.

3.11.2 INTERVENTIONS

No RCTs were identified to suggest that clinically relevant outcomes (bone pain, fracture rates, painful soft tissue calcification) are influenced by interventions in patients with CKD stages 1-4.

There is no evidence to suggest that osteoporosis should be treated differently in patients with CKD stages 3 or 4 from the remainder of the population (see SIGN guideline 71 on the management of osteoporosis).²³⁸ 4

If the underlying condition responsible for CKD is treated by systemic corticosteroids, general guidelines for prophylaxis against osteoporosis should be considered.²³⁸ At CKD stage 4 the evidence supporting the use of antiresorptive agents for osteoporosis is limited although some bisphosphonates are often used safely in these patients. A post hoc analysis in osteoporotic women identified that 5 mg of risedronate daily reduced the radiological vertebral fracture rate in a substantial proportion of patients who started the studies with a reduced creatinine clearance.²³⁹ There was no excess toxicity in the patients with CKD.

4

Biochemical data have shown that dietary phosphate restriction in compliant patients reduces PTH levels. Conventional treatments include phosphate binders and/or vitamin D analogues.²³⁵ Bone biopsy follow up has shown that alfacalcidol has a preventive action.²⁴⁰ Excessive suppression of PTH levels to normal or near normal PTH values has been associated with an increased risk of adynamic bone disease.²⁴¹

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☒ In patients with stages 3 or 4 chronic kidney disease, serum calcium, phosphate, and alkaline phosphatase levels should be measured when rechecking serum creatinine or eGFR.

☒ General guidelines for the management of osteoporosis should be applied to patients with chronic kidney disease.

3.12 MANAGING METABOLIC ACIDOSIS

Metabolic acidosis (manifested by a low venous bicarbonate) becomes increasingly prevalent with deteriorating renal function below an eGFR of 30 ml/min/1.73 m² (19.1% of patients with stage 4 CKD). A small minority of patients may have a metabolic acidosis at a higher level of renal function (2.1% of patients with stage 3 CKD, 1.3 to 1.6% of patients with stages 1 and 2 CKD). Generally the metabolic acidosis of uraemia is mild to moderate in severity. Serum bicarbonate < 12 mmol/l should raise suspicion of an alternate cause.²⁴²

3

Metabolic acidosis is associated with increased protein catabolism, decreased protein synthesis²⁴³ and worsening bone demineralisation.²⁴⁴ Metabolic acidosis may accelerate the progression of renal failure.

4

Metabolic acidosis may be treated with oral alkali, most commonly, sodium bicarbonate. The typical dose range is 500 mg to 1 g three or four times daily. These drugs can correct metabolic acidosis and markers of bone demineralisation and protein degradation.^{246,247} Potential harms include sodium loading, with possible resultant hypertension and fluid overload, and calcium loading possibly contributing to extra-osseous calcification.

3

A placebo-controlled RCT of 40 patients with CKD followed for three months in India, demonstrated that oral sodium bicarbonate can correct metabolic acidosis.²⁴⁸

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In one uncontrolled, non-randomised study of 18 patients, treatment for six months with 4.5 g/day of sodium bicarbonate corrected venous bicarbonate and increased serum albumin and pre-albumin. This was interpreted to be due to improved nutritional status, but no other markers of nutritional status improved.²⁴⁹

3

It is not possible to make any evidence based recommendation on the treatment of metabolic acidosis.

4 Provision of information

4.1 SAMPLE INFORMATION LEAFLET

An example information leaflet for patients with chronic kidney disease is given below. Healthcare professionals may wish to adapt this for use in their own departments, remembering to insert relevant local details.

What do my kidneys do?

Your kidneys are very important and do several jobs for your body. All the blood in your body is filtered through your kidneys which pull out any extra fluid. The extra fluid becomes urine. Any waste that has been produced either by muscle use or from digestion of your food is removed from your body in the urine. The kidneys also help to:

- maintain your blood pressure;
- maintain the right level of chemicals in your body (for example, sodium, potassium, chloride and bicarbonate). This allows your heart and muscles to function properly;
- produce a form of vitamin D which your body uses to maintain healthy bones; and
- produce a substance called erythropoietin which tells your bone marrow when to make more red blood cells.

When the kidneys are not able to filter the blood properly for at least a few months, doctors call this chronic kidney disease (CKD).

Am I at risk of having chronic kidney disease (CKD)?

You may be more likely to develop CKD if you:

- have high blood pressure (hypertension);
- have vascular disease (eg angina, stroke, peripheral vascular disease);
- are diabetic;
- are over 65; or
- smoke.

There are many causes of kidney disease, including inherited conditions.

How does my doctor know I have CKD?

There are several tests that your doctor may do to check how well your kidneys are functioning. Your doctor may check your urine for any signs of blood or protein or take a blood test to check the level of creatinine (a chemical which is a breakdown product of muscle activity) in your blood.

The results of the creatinine test are used to work out your estimated Glomerular Filtration Rate (eGFR). This tells your doctor how well your blood is being filtered through your kidneys. Your doctor may also send you to have an X-ray or ultrasound scan of your kidneys.

Will my kidneys fail?

Most patients with CKD respond well to treatment and continue to live normal lives. A small percentage of patients will remain unable to filter their blood and will need dialysis or a kidney transplant. It is important to control your blood pressure since high blood pressure can make CKD worse and can lead to problems with your vascular system and your heart which in turn can reduce kidney function.

Will I get better?

Having a chronic disease means that it won't go away. However, there are treatments available to try to keep it from getting worse and there are things that you can do to control the effects of your CKD.

What are the treatments?

Regular check ups are very important to check your kidney function and your blood pressure. You will probably be given medication for your blood pressure and may need medication to lower your cholesterol. However, every patient will be different and your treatment will depend on how well your kidneys are working and any other medical problems you may have.

What can I do to help myself?

Living a healthy lifestyle is the most important thing that you can do to reduce the risk of your CKD getting worse. You should:

- reduce your salt intake;
- eat a diet that includes fruits, vegetables, low fat dairy products, whole grains, poultry, fish and is lower in red meats and sugar;
- take regular exercise; and
- stop smoking.

Be sure to take the medications that your doctor prescribes for you. If you have any questions or problems with your treatment, make sure you talk these over with your doctor as alternatives which suit you better may be available.

If you want to take any over-the-counter medications or any alternative or herbal medicines, be sure to check with your doctor or with the pharmacist first because some of these may be harmful to your kidneys.

4.2 SOURCES OF FURTHER INFORMATION

British Kidney Patients Association

BKPA, Bordon, Hants, GU35 9JZ
Telephone: 01420 472021/2
www.britishkidney-pa.co.uk

The British Kidney Patients Association supports the material and physical needs of patients with renal disease and their relatives and lobbies for more and improved facilities and increased governmental funding into the management of kidney disorders.

Kidney Patient Guide

www.kidneypatientguide.org.uk

An online guide, for patients and carers, to many aspects of kidney disease including physical aspects of the disease and information about treatments.

Kidney Research UK

King Chambers, Priestgate, Peterborough, PE1 1FG
Telephone: 0845 070 7601
www.nkrf.org.uk

Kidney Research UK funds research that focuses on the prevention, treatment and management of kidney disease. Kidney Research UK also dedicates its work to improving patient care and raising awareness of kidney disease.

National Kidney Federation

Helpline: 0845 601 02 09
www.kidney.org.uk

The National Kidney Federation is run by kidney patients for kidney patients. Its aim is to promote the best renal medical practice and treatment, the health of persons suffering from kidney disease or renal failure, and to support the related needs of those relatives and friends who care for kidney patients.

Renalinfo

www.renalinfo.com

Renalinfo is a website for individuals affected by kidney failure. The website provides definitions, symptoms, causes, and treatments of kidney failure.

Renal PatientView

www.renalpatientview.org

Renal PatientView provides online information about renal patients' diagnosis, treatment, and their latest test results. Patients can share this information with anyone they want, and view it from anywhere in the world.

Royal Infirmary of Edinburgh Renal Unit

Renal Medicine, Royal Infirmary, Little France, Edinburgh, EH16 4SA
Telephone: 0131 242 1233
www.edren.org

EdRenINFO is a source of information about kidney diseases for patients and non-specialist doctors developed by staff at the renal unit of Edinburgh Royal Infirmary. It includes a large number of pages describing causes, tests and treatments for different kidney disorders.

5 Implementing the guideline

This section provides advice on the resource implications associated with implementing the key clinical recommendations, and advice on audit as a tool to aid implementation.

Implementation of national clinical guidelines is the responsibility of each NHS Board and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

5.1 RESOURCE IMPLICATIONS OF KEY RECOMMENDATIONS

This section is based on discussions with the guideline development group regarding current resource use in Scotland and the likely impact of implementing the recommendations made in the guideline. Where current practice will not change as a result of the recommendations it is unlikely there will be resource implications.

5.1.1 MANAGEMENT OF ANAEMIA

The group has identified one recommendation that will have significant resource implications for NHSScotland.

A Erythropoiesis stimulating agents should be considered in all patients with anaemia of chronic kidney disease to improve their quality of life.

The National Institute for Health and Clinical Excellence has developed a budgetary impact model for its guideline on anaemia management in people with chronic kidney disease.²⁵⁰ This model provides estimates of the prevalence of anaemia by stage of CKD in people who are not on dialysis, which may be extrapolated to Scotland as shown in Table 2.

Table 2: Breakdown of prevalence of anaemia by stage of CKD in the Scottish population

Scotland population	Prevalence of CKD stage 3–5 with haemoglobin < 11 g/dl	Total number with condition
Stage 3	0.19%	9,722
Stage 4	0.02%	1,023
Stage 5	0.01%	512
Total (5,117,000)	0.22%	11,257

No national data are available on the prescription of ESAs to patients with anaemia associated with CKD. Regional data collated by NICE for prescription of ESAs in a population of 3.5 million patients in England have been used to calculate estimates of prescribing practice as shown in Table 3.²⁵⁰

Table 3: Prescribing of ESAs by stage of CKD from sample population of 3.5 million patients

Stage of CKD	Estimated prevalence of anaemia of CKD (%)	Estimated prevalence of anaemia of CKD by stage	Number currently receiving ESAs	Percentage receiving ESAs (%)
3	0.19	6,650	54	0.8
4	0.02	700	215	30.7
5	0.01	350	184	52.6

Expert opinion has suggested a range of population estimates of patients who are likely to benefit from ESA therapy.²⁵⁰ This assumption defines those patients with anaemia who will receive improvements in quality of life on prescription of ESAs (see Table 4).

Table 4: Estimated numbers of people who would benefit from ESA treatment by stage of CKD

Stage of CKD	Estimated minimum % to benefit from ESA treatment	Estimated maximum % to benefit from ESA treatment	Mid-point (%)
3	5	10	7.5
4	35	55	45
5	65	80	72.5

Applying the estimates of current national and optimum prescribing behaviour to the prevalence data gives the total current and projected prescription of ESAs in Scotland as shown in Table 5.

Table 5: Estimated increases in number of people receiving ESAs in Scotland

Stage of CKD	Prevalence of anaemia in CKD	Estimated current prescribing of ESAs (%)	Estimated current number receiving ESAs	Proposed prescribing of ESAs (%)	Proposed number to receive ESAs
3	9,722	0.8	78	7.5	729
4	1,023	30.7	314	45	460
5	512	52.6	269	72.5	371
Total	11,257		661		1,560

It is assumed that treating the entire patient group is unlikely. Identifying everyone with anaemia of CKD poses a significant challenge, and a number may have significant comorbidities that may preclude treatment with ESAs. The figure used as an estimate of uptake of this recommendation is 90% (1,404 patients).

In 2007 the Scottish Medicines Consortium issued advice on epoetin delta (Dynepo®) which accepted it for use within NHSScotland for the treatment of anaemia in patients with chronic renal failure. It may be used in patients on dialysis and in patients not on dialysis. In the advice, the price per patient per week was estimated as £45 for 50 IU/kg subcutaneous injection twice weekly in a 70 kg patient, assuming one dose per pre-filled syringe. This results in an annual cost of £2,340 per patient.

Applying the NICE assumptions and the SMC costs to the Scottish population suggests that there are currently 11,257 people in stages 3-5 with haemoglobin of less than 11 g/dl. This would result in a possible additional cost to NHSScotland of £2.1 million per annum (see Table 6).

Table 6: Estimated increases in costs associated with increased prescribing of ESAs in Scotland

Estimated current prescribing costs ESAs (£000s)	Proposed prescribing costs ESAs (£000s)	Proposed increase in ESA prescribing costs (£000s)
1,547	3,650	2,103

5.1.2 OTHER RESOURCE IMPLICATIONS

Two further recommendations in sections 2.2 (detection of kidney damage) and 3.10.2 (delivery of a psychoeducation programme) may also have resource implications, depending on local practice with respect to laboratory urine testing and availability of appropriately trained staff to develop and deliver such education.

5.2 AUDITING CURRENT PRACTICE

A first step in implementing a clinical practice guideline is to gain an understanding of current clinical practice. Audit tools designed around guideline recommendations can assist in this process. Audit tools should be comprehensive but not time consuming to use. Successful implementation and audit of guideline recommendations requires good communication between staff and multidisciplinary team working.

The guideline development group has identified the following as key points to audit to assist with the implementation of this guideline:

- the proportion of patients with diabetes who have regular surveillance of renal function
- the proportion of people who smoke who are motivated to quit and are offered support to achieve this
- the proportion of patients who have an assessment of proteinuria and haematuria
- the proportion of patients with ≥ 1 g/day of proteinuria with a maximum systolic blood pressure of ≤ 130 mmHg
- the proportion of patients with chronic kidney disease and type 1 diabetes with microalbuminuria who are treated with an angiotensin converting enzyme inhibitor
- the proportion of patients with chronic kidney disease and type 2 diabetes with microalbuminuria who are treated with an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker
- the proportion of patients with chronic kidney disease and proteinuria (≥ 0.5 g/day) who are treated with angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers
- the proportion of patients with stage 1-3 chronic kidney disease, with a predicted 10-year cardiovascular risk $\geq 20\%$ who are treated by a statin
- the proportion of patients with stage 1-3 chronic kidney disease, with a predicted 10-year cardiovascular risk $\geq 20\%$ who are treated by a low dose antiplatelet agent
- the proportion of patients on renal replacement therapy who received a psychologically informed, pre-dialysis psychoeducation programme
- the proportion of patients with chronic kidney disease at stage 3 or higher whose nutritional status (height, weight, body mass index, percentage weight loss) is monitored.

5.3 ADVICE TO NHSSCOTLAND FROM THE SCOTTISH MEDICINES CONSORTIUM

The Scottish Medicines Consortium has issued advice on epoetin delta (November 2007). They advise that epoetin delta (Dynepo®) is accepted for use within NHS Scotland for the treatment of anaemia in patients with chronic renal failure. It may be used in patients on dialysis and in patients not on dialysis (www.scottishmedicines.org.uk).

Clinical studies have demonstrated epoetin delta's efficacy and safety profile in correcting and maintaining haemoglobin levels for up to a year in predialysis, haemodialysis and peritoneal dialysis patients, when administered via both the subcutaneous and intravenous routes.

6 The evidence base

6.1 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using a search strategy devised by a SIGN Information Officer. Databases searched include Medline, Embase, Cinahl, PsycINFO and The Cochrane Library. For most searches the year range covered was 2000-2006, but some went back to 1995. Internet searches were carried out on various websites including the New Zealand Guidelines Programme, NELH Guidelines Finder, and the US National Guideline Clearinghouse. The Medline version of the main search strategies can be found on the SIGN website, in the section covering supplementary guideline material. The main searches were supplemented by material identified by individual members of the development group.

The National Institute for Health and Clinical Excellence kindly made copies of certain evidence tables available from their guideline Anaemia Management in Chronic Kidney Disease²³⁰ to inform section 3.10.4 of this guideline.

6.1.1 LITERATURE SEARCH FOR PATIENT ISSUES

At the start of the guideline development process, a SIGN Information Officer conducted a literature search for qualitative and quantitative studies that addressed patient issues relevant to chronic kidney disease. The search was run in Medline, Embase, CINAHL and PsycINFO, and the results were summarised and presented to the guideline development group.

Most of the literature focused on dialysis and transplantation. However, some of the themes identified could be extrapolated to the predialysis stage, the main ones being 'information needs', 'adherence to diet regimens' and 'emotional impact'. A copy of the Medline version of the patient search strategy is available on the SIGN website.

6.2 RECOMMENDATIONS FOR RESEARCH

The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline (see *annex 1*). The following areas for further research have been identified:

- the effects of exercise on quality of life in patients with CKD
- the association between diabetes and the development of CKD
- establishing the threshold for pathological changes in GFR in the elderly
- the utility of ACE inhibitors for primary prevention of diabetic nephropathy, particularly in normotensive patients with diabetes
- the effects of weight reduction on cardiovascular events in people with CKD
- the effects of exercise on cardiovascular events in people with CKD
- the value of measuring calcium, phosphate and alkaline phosphatase to monitor progression of CKD and the most effective measurement technique
- which minimally invasive markers best reflect the development of the different types of renal bone disease
- the mechanisms for osteoporosis in patients with CKD
- whether treating bone abnormalities or abnormalities in calcium, phosphate and alkaline phosphatase affects progression of CKD
- whether the use of phosphate binders, vitamin D analogues, calcimimetics or other therapies can influence clinically important outcomes for patients with stage 3/4 CKD
- establish unmet psychosocial needs of the pre-dialysis population.

6.3 REVIEW AND UPDATING

This guideline was issued in 2008 and will be considered for review in three years. Any updates to the guideline in the interim period will be noted on the SIGN website: **www.sign.ac.uk**

7 Development of the guideline

7.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of NHS Quality Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising clinicians using a standard methodology based on a systematic review of the evidence. The views and interests of NHS Quality Improvement Scotland as the funding body have not influenced any aspect of guideline development, including the final recommendations. Further details about SIGN and the guideline development methodology are contained in “SIGN 50: A Guideline Developer’s Handbook”, available at www.sign.ac.uk

7.2 THE GUIDELINE DEVELOPMENT GROUP

Professor Alison MacLeod (Chair)	Consultant Nephrologist, Aberdeen Royal Infirmary
Dr Tariq Ali	Research Associate, Aberdeen Royal Infirmary
Dr Gordon Allan	General Practitioner, Methil
Mrs Jane Bryce	Scottish Patients Advisory Group, Kidney Research UK
Mrs Hazel Elliott	Dietitian, Edinburgh Royal Infirmary
Dr Nicholas Fluck	Consultant Nephrologist, Aberdeen Royal Infirmary
Dr Jane Goddard	Consultant Nephrologist, Edinburgh Royal Infirmary
Dr John Hunter	Consultant Physician and Rheumatologist, Gartnavel General Hospital, Glasgow
Mrs Joanna Kelly	Information Officer, SIGN
Dr Mark MacGregor	Consultant Nephrologist, Crosshouse Hospital, Kilmarnock
Ms Shonaid McCabe	Clinical Specialist in Occupational Therapy, Monklands Hospital, Airdrie
Dr Michael J Murphy	Senior Lecturer in Biochemical Medicine, University of Dundee
Dr Moray Nairn	Programme Manager, SIGN
Ms Maureen Perry	Clinical Nurse Specialist, Renal Unit, Ninewells Hospital, Dundee
Dr Maria K Rossi	Consultant in Public Health, NHS Grampian
Dr Diana Johnston	General Practitioner, Dundee
Ms Shelagh Salter	Physiotherapist, Edinburgh Royal Infirmary
Ms Sara Smith	Undergraduate Programme Leader – Dietetics, Queen Margaret University, Edinburgh
Dr Casey Stewart	Clinical Director - Acute Medicine, Edinburgh Royal Infirmary
Dr Mark Strachan	Consultant Physician, Western General Hospital
Ms Morag Whittle	Renal Pharmacist, Glasgow Royal Infirmary
Dr Matt Wild	Consultant Clinical Psychologist, Glasgow Royal Infirmary

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest and further details of these are available on request from the SIGN Executive.

Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive.

7.2.1 PATIENT INVOLVEMENT

In addition to the identification of relevant patient issues from a broad literature search (see section 6.1.1), SIGN involves patients and carers throughout the guideline development process in several ways. SIGN recruits a minimum of two patient representatives to guideline development groups by inviting nominations from the relevant “umbrella”, national and/or local patient focused organisations in Scotland. Where organisations are unable to nominate, patient representatives are sought via other means, eg from consultation with health board public involvement staff.

Further patient and public participation in guideline development was achieved by involving patients, carers and voluntary organisation representatives at the National Open Meeting (see section 7.4.1). Patient representatives were invited to take part in the peer review stage of the guideline and specific guidance for lay reviewers was circulated. Members of the SIGN patient network were also invited to comment on the draft guideline section on provision of information.

7.3 ACKNOWLEDGEMENTS

SIGN would like to offer special acknowledgement to Mr George Stenhouse, lay representative, who sadly died during the development of this guideline.

SIGN is grateful to the following former members of the guideline development group who have contributed to the development of this guideline.

Ms Katie Ronald	<i>formerly Public Affairs Manager (Scotland), National Kidney Research Fund</i>
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7.4 CONSULTATION AND PEER REVIEW

7.4.1 NATIONAL OPEN MEETING

A national open meeting is the main consultative phase of SIGN guideline development, at which the guideline development group presents its draft recommendations for the first time. The national open meeting for this guideline was held on 22 June 2006 and was attended by 144 representatives of all the key specialties relevant to the guideline. The draft guideline was also available on the SIGN website for a limited period at this stage to allow those unable to attend the meeting to contribute to the development of the guideline.

7.4.2 SPECIALIST REVIEW

This guideline was sent in draft form to the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. The guideline group addresses every comment made by an external reviewer, and must justify any disagreement with the reviewers' comments. SIGN is very grateful to all of these experts for their contribution to the guideline.

Mr Rob Bradley	<i>Lead Pharmacist for Nephrology and Transplantation, University Hospital of Wales, Cardiff and Vale NHS Trust</i>
Dr Rodney Burnham	<i>Registrar, Joint Specialty Committee for Renal Medicine, Royal College of Physicians, London</i>
Professor Gary Eknoyan	<i>Professor of Medicine, Baylor College of Medicine, Houston, USA</i>
Dr Ian Gunn	<i>Consultant Biochemist, Wishaw General Hospital</i>

Ms Gill Hartley	<i>Senior Pharmacist, University Hospitals of Leicester NHS Trust</i>
Dr David Jenkins	<i>Consultant Nephrologist, Queen Margaret Hospital, Dunfermline</i>
Dr Edmund Lamb	<i>Consultant Clinical Scientist and Head of Department, Clinical Biochemistry, Kent and Canterbury Hospital</i>
Miss Elizabeth Lamerton	<i>Senior Clinical Pharmacist, Hope Hospital, Salford</i>
Dr Adeera Levin	<i>Director, British Columbia Provincial Renal Agency, Canada</i>
Miss Fiona Manson	<i>Senior Dietitian, Raigmore Hospital, Inverness</i>
Dr Janet McCarlie	<i>Clinical Lead, North Ayrshire Community Health Partnership, Ayrshire Central Hospital</i>
Dr Robert K Peel	<i>Consultant Renal Physician, Head of Service, Raigmore Hospital, Inverness</i>
Mr Euan Reid	<i>Senior Pharmacist, Renal Services, Queen Margaret Hospital, Dunfermline</i>
Dr Paul Roderick	<i>Epidemiologist, Southampton General Hospital</i>
Dr Stuart Rodger	<i>Consultant Nephrologist, Western Infirmary, Glasgow</i>
Ms Ann Ross	<i>Lead Allied Healthcare Professional, Emergency Care and Medical Specialties, Western Infirmary, Glasgow</i>
Dr John Sharp	<i>Clinical Psychologist, Liaison Psychiatry Service, Western Infirmary, Glasgow</i>
Dr Bryan Whittingham	<i>General Practitioner, Cupar</i>
Dr Chris Winearls	<i>Clinical Director, Oxford Kidney Unit, Oxford Radcliffe Hospitals NHS Trust</i>

7.4.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline was reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments were addressed adequately and that any risk of bias in the guideline development process as a whole was minimised. The editorial group for this guideline was as follows:

Dr Keith Brown	<i>Chair of SIGN; Co-Editor</i>
Professor Hillary Capell	<i>Member of SIGN Council</i>
Dr Hugh Gilmour	<i>Member of SIGN Council</i>
Mrs Fiona McMillan	<i>Member of SIGN Council</i>
Dr Safia Qureshi	<i>SIGN Programme Director; Co-Editor</i>
Dr Sara Twaddle	<i>Director of SIGN; Co-Editor</i>

Abbreviations

ACE	angiotensin converting enzyme
ACR	albumin/creatinine ratio
ADPKD	autosomal dominant polycystic kidney disease
AER	albumin excretion rate
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ARB	angiotensin II receptor blocker
ASCOT	Anglo Scandinavian Cardiac Outcomes Trial
BMI	body mass index
BNF	British National Formulary
BP	blood pressure
BSA	body surface area
CCB	calcium channel blockers
CI	confidence interval
CKD	chronic kidney disease
CT	computed tomography
CVD	cardiovascular disease
DASH	Dietary Approaches to Stop Hypertension trial
DTPA	Tc-diethylenetriaminepentaacetic acid
EDTA	Cr-ethylenediaminetetraacetic acid
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ESRD	end-stage renal disease
ESA	erythropoiesis stimulating agent
GFR	glomerular filtration rate
GP	general practitioner
HDL	high density lipoprotein cholesterol
HMG-CoA	3-hydroxy-3-methyl-glutaryl-CoA
HOPE	Heart Outcomes Prevention Evaluation trial
HR	hazard ratio
IgA	immunoglobulin A
KDIGO	Kidney Disease Improving Global Outcomes
LDL	low density lipoprotein
MDRD	Modification of Diet in Renal Disease study
MDT	multidisciplinary team
MRFIT	Multiple Risk Factor Intervention Trial
MRI	magnetic resonance imaging

MTA	multiple technology appraisal
NHSQIS	NHS Quality Improvement Scotland
NICE	National Institute for Health and Clinical Excellence
NKF KDOQI	National Kidney Foundation Kidney Disease Outcomes Quality Initiative
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio
PCR	protein/creatinine ratio
PKD	polycystic kidney disease
PTH	parathyroid hormone
QoL	quality of life
RCT	randomised controlled trial
RR	relative risk
RRT	renal replacement therapy
SAVE	Survival and Ventricular Enlargement trial
SHARP	Study of Heart and Renal Protection trial
SIGN	Scottish Intercollegiate Guidelines Network
SLE	systemic lupus erythematosus
SMC	Scottish Medicines Consortium
SPC	summary of product characteristics
UK-HARP-1	first United Kingdom Heart and Renal Protection study
UPE	urinary protein excretion
UTI	urinary tract infection

Annex 1

Key questions used to develop the guideline

SCREENING / IDENTIFICATION

- 1 What is the evidence that members of the following groups are more likely to develop CKD than unaffected members of the general population?
 - a. diabetes (type 1 and 2)
 - b. hypertension
 - c. cardiovascular disease
 - d. urinary tract obstruction/urinary tract stones/UTI/structural renal tract abnormalities/urinary reflux
 - e. rheumatic diseases
 - f. connective tissue disease [Systemic lupus erythematosus (SLE), scleroderma]
 - g. spinal injuries
 - h. chronic use of NSAIDs
 - i. elderly
 - j. smokers
 - k. obese
 - l. socially deprived
- 2 In patients with diagnosed CKD, or at risk of CKD, which of the following is the most accurate and practical method of assessing GFR:
 - a. prediction equations [Cockcroft-Gault; (4-variable abbreviated) MDRD (or Levey) equation]
 - b. serum cystatin C
 - c. serum creatinine
 - d. 24-hour urine creatinine clearance
- 3 What is the most accurate way to detect significant proteinuria?
 - a. timed urine protein collection
 - b. spot urine for protein-creatinine ratio
 - c. spot urine for albumin-creatinine ratio
- 4 In patients with a reduced GFR (<90 ml/min/1.73 m²), does a renal ultrasound significantly increase the probability of identifying obstruction, PKD, renal scarring and renal asymmetry? Are there subgroups in whom ultrasound is more or less effective?
- 5 What is the evidence that microscopic haematuria can be used to predict CKD?

TREATMENT

- 6 What is the evidence that treatment of renal anaemia (with human recombinant erythropoietin) improves mortality and morbidity in CKD patients?
- 7 What is the evidence that the following interventions are effective in slowing the progression of CKD (as measured in terms of GFR?) and which is more effective:
 - a. BP control
 - b. ACE inhibitors, angiotensin-II receptor antagonists, calcium channel blockers
 - c. dietary interventions (sodium, phosphate and protein restriction; weight reduction)
 - d. fish oils
 - e. statins (anti-lipid agents)
 - f. proteinuria

- 8 What evidence is there that malnutrition (including obesity) has a negative impact on morbidity, QoL and functional status in CKD patients; and what is the threshold for dietary intervention? (all interventions apart from protein and potassium restriction; and interventions associated with bone disease).
- 9 What interventions reduce the risk of cardiovascular disease in CKD patients:
 - a. statins (anti-lipid agents)
 - b. aspirin
 - c. weight reduction
 - d. smoking cessation
 - e. exercise
 - f. blood pressure reduction
- 10 Do any of the following increase/slow the progression of CKD (as measured in terms of GFR)?
 - a. vitamin and nutritional supplements (including creatine supplements)
 - b. homeopathic medicines
 - c. chinese medicine
 - d. herbal remedies
- 11 What is the evidence that early treatment (patients who are not on renal replacement therapy) of hyperparathyroidism reduces complications associated with renal bone disease (osteomalacia, osteoporosis, fractures, bone pain, vascular calcification, mobility function scores) in CKD patients?
 - a. phosphate restricted diet
 - b. phosphate-binders
 - c. calcium and vitamin D
 - d. vitamin D analogues
 - e. calcimimetics
 - f. exercise therapy
- 12 What is the evidence that treatment of metabolic acidosis (with bicarbonates) in patients with CKD improves quality of life, reduce mortality and morbidity?
- 13 What is the evidence that exercise therapy is effective in improving the quality of life in patients with CKD?
- 14 What is the evidence that the frequency with which excretory renal function is monitored has an effect in detecting deterioration in function?

REFERRAL/MODELS OF CARE

- 15 Is there evidence that treatment in a nephrology/specialist renal unit improves survival, time to dialysis, BP, urine protein and GFR (as compared to other settings)?
- 16 What is the evidence that intervention from the following MDT/allied healthcare professionals influences QoL, patient satisfaction and functional status in patients with CKD?
 - a) occupational therapy
 - b) dietetics
 - c) physiotherapy
 - d) psychological and social support

Annex 2

Expressions of urinary protein concentration and their approximate equivalents and clinical correlates

	Dipstick reading	Urine protein: creatinine ratio, mg/mmol (PCR)	Urine total protein excretion, g/24 hour	Urinary albumin: creatinine ratio, mg/mmol (ACR)	Urinary albumin excretion, micrograms/min (mg/24 hour)
Normal	Negative	< 15	< 0.150	< 2.5 (males) < 3.5 (females)	< 20 (< 30)
Microalbuminuria "Trace" protein	Negative	< 15	< 0.150	≥ 2.5 to 30 (males)	20-200 (30-300)
	Trace	15-44	0.150-0.449	≥ 3.5 to 30 (females)	
Clinical proteinuria (macroalbuminuria)	1 +	45-149	0.450-1.499	> 30	> 200 (> 300)
	2 +	150-449	1.50-4.49		
Nephrotic range proteinuria	3 +	≥ 450	≥ 4.50		

Values in this table are based on an assumed average creatinine excretion of 10 mmol/day and an average urine volume of 1.5 l/day.

NB males and females have different thresholds for the diagnosis of microalbuminuria as a consequence of the lower urinary creatinine excretion in women.

There is no single value for the accurate conversion between ACR to PCR, however, at low levels of proteinuria (< 1 g/day), a rough conversion is that doubling the ACR gives the PCR. At proteinuria excretion rates of > 1 g/day, the relationship is more accurately represented by $1.3 \times \text{ACR} = \text{PCR}$.

Adapted from: Joint Specialty Committee on Renal Medicine of the Royal College of Physicians and the Renal Association, and the Royal College of General Practitioners. Chronic kidney disease in adults: UK guidelines for identification, management and referral. London: Royal College of Physicians; 2006. [cited 28 April 2008].

Available from URL www.renal.org/CKDguide/full/CKDprintedfullguide.pdf

References

- 1 John R, Webb M, Young A, Stevens PE. Unreferred chronic kidney disease: a longitudinal study. *Am J Kidney Dis* 2004;43(5):825-35.
- 2 Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 2003;41(1):1-12.
- 3 de Lusignan S, Chan T, Stevens P, O'Donoghue D, Hague N, Dzregah B, et al. Identifying patients with chronic kidney disease from general practice computer records. *Fam Pract* 2005;22(3):234-41.
- 4 Hallan SI, Coresh J, Astor BC, Asberg A, Powe NR, Romundstad S, et al. International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. *J Am Soc Nephrol* 2006;17(8):2275-84.
- 5 Renal Association. Treatment of adults and children with renal failure: standards and audit measures. 3rd ed. London: Royal College of Physicians of London and the Renal Association; 2002. [cited 3 Jan 2008]. Available from url: <http://www.renal.org/Standards/standards.html>
- 6 K/DOQI Workgroup. (2005). K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. *Am J Kidney Dis* 2005;45(4 Suppl 3):S1-153.
- 7 Caring for Australasians with Renal Impairment. Selection of patients for automated peritoneal dialysis versus continuous ambulatory peritoneal dialysis. Westmead, NSW: CARI; 2004. [cited 4 Jan 2008]. Available from url: http://www.cari.org.au/Selection_of_patients_for%20_APD.pdf
- 8 The Renal Association. UK Renal Registry Report 2005. Bristol: UK Renal Registry; 2005. [cited 3 Jan 2008]. Available from url: <http://www.renalreg.com/reports/renal-registry-reports/2005>
- 9 U.S. Renal Data System. USRDS 2002 Annual Data Report: Atlas of End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2002. [cited 3 Jan 2008]. Available from url: http://www.usrds.org/atlas_2002.htm
- 10 The Renal Association. UK Renal Registry Report 2006. Bristol: UK Renal Registry; 2006. [cited 3 Jan 2008]. Available from url: <http://www.renalreg.com/reports/renal-registry-reports/2006>
- 11 Brancati FL, Whelton PK, Randall BL, Neaton JD, Stamler J, Klag MJ. Risk of end-stage renal disease in diabetes mellitus: a prospective cohort study of men screened for MRFIT. Multiple Risk Factor Intervention Trial. *Jama* 1997;278(23):2069-74.
- 12 Scottish Executive Health Department. Scottish Diabetes Survey 2005. Edinburgh: Scottish Executive Health Department; 2007. [cited 3 Jan 2008]. Available from url: <http://www.diabetesinscotland.org/diabetes/MaintainPages/pdfFiles/SDS2005.pdf>
- 13 Fox CS, Larson MG, Leip EP, Culleton B, Wilson PW, Levy D. Predictors of new-onset kidney disease in a community-based population. *JAMA* 2004;291(7):844-50.
- 14 Chadban SJ, Briganti EM, Kerr PG, Dunstan DW, Welborn TA, Zimmet PZ, et al. Prevalence of kidney damage in Australian adults: The AusDiab kidney study. *J Am Soc Nephrol* 2003;14(7 Suppl 2).
- 15 National Institute for Health and Clinical Excellence (NICE). Management of type 2 diabetes: Renal disease - prevention and early management. London: NICE; 2002. (NICE Inherited Guideline F). [cited 3 Jan 2008] Available from url: <http://www.nice.org.uk/guidance/page.redirect?o=27924>
- 16 Scottish Intercollegiate Guidelines Network (SIGN). Management of Diabetes. Edinburgh: SIGN; 2001. (SIGN publication no. 55). [cited 20 Dec 2007]. Available from url: <http://www.sign.ac.uk>
- 17 Foley RN, Murray AM, Li S, Herzog CA, McBean AM, Eggers PW, et al. Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. *J Am Soc Nephrol* 2005;16(2):489-95.
- 18 Fesler P, Ribstein J, du Cailar G, Mimran A. Determinants of cardiorenal damage progression in normotensive and never-treated hypertensive subjects. *Kidney Int* 2005;67(5):1974-9.
- 19 Scottish Intercollegiate Guidelines Network (SIGN). Risk estimation and the prevention of cardiovascular disease. Edinburgh: SIGN; 2007. (SIGN publication no. 97). [cited 20 Dec 2007]. Available from url: <http://www.sign.ac.uk>
- 20 Ejerblad E, Forel CM, Lindblad P, Fryzek J, Dickman PW, Elinder CG, et al. Association between smoking and chronic renal failure in a nationwide population-based case-control study. *J Am Soc Nephrol* 2004;15(8):2178-85.
- 21 O'Hare AM, Bertenthal D, Covinsky KE, Landefeld CS, Sen S, Mehta K, et al. Mortality risk stratification in chronic kidney disease: one size for all ages? *J Am Soc Nephrol* 2006;17(3):846-53.
- 22 Kurth T, Glynn RJ, Walker AM, Rexrode KM, Buring JE, Stampfer MJ, et al. Analgesic use and change in kidney function in apparently healthy men. *Am J Kidney Dis* 2003;42(2):234-44.
- 23 Curhan GC, Knight EL, Rosner B, Hankinson SE, Stampfer MJ. Lifetime nonnarcotic analgesic use and decline in renal function in women. *Arch Intern Med* 2004;164(14):1519-24.
- 24 Pinto-Sietsma SJ, Navis G, Janssen WM, de Zeeuw D, Gans RO, de Jong PE. A central body fat distribution is related to renal function impairment, even in lean subjects. *Am J Kidney Dis* 2003;41(4):733-41.
- 25 Merkin SS, Coresh J, Roux AV, Taylor HA, Powe NR. Area socioeconomic status and progressive CKD: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Kidney Dis* 2005;46(2):203-13.
- 26 Forel CM, Ejerblad E, Fryzek JP, Lambe M, Lindblad P, Nyren O, et al. Socio-economic status and chronic renal failure: a population-based case-control study in Sweden. *Nephrol Dial Transplant* 2003;18(1):82-8.
- 27 Price CP, Newall RG, Boyd JC. Use of protein: Creatinine ratio measurements on random urine samples for prediction of significant proteinuria: A systematic review. *Clin Chem* 2005;51(9):1577-86.
- 28 Newman DJ, Pugia MJ, Lott JA, Wallace JF, Hiar AM. Urinary protein and albumin excretion corrected by creatinine and specific gravity. *Clin Chim Acta* 2000;294(1-2):139-55.
- 29 Meyer NL, Mercer BM, Friedman SA, Sibai BM. Urinary dipstick protein: a poor predictor of absent or severe proteinuria. *Am J Obstet Gynecol* 1994;170(1 Pt 1):137-41.
- 30 Brown MA, Buddle ML. Inadequacy of dipstick proteinuria in hypertensive pregnancy. *Aust N Z J Obstet Gynaecol* 1995;35(4):366-9.
- 31 Higby K, Suiter CR, Siler-Khodr T. A comparison between two screening methods for detection of microproteinuria. *Am J Obstet Gynecol* 1995;173(4):1111-4.
- 32 Saudan PJ, Brown MA, Farrell T, Shaw L. Improved methods of assessing proteinuria in hypertensive pregnancy. *Br J Obstet Gynaecol* 1997;104(10):1159-64.
- 33 Paruk F, Moodley J, Daya PK, Meineke K. Screening for proteinuria in hypertensive disorders of pregnancy. *J Obstet Gynaecol* 1997;17(6):528-30.
- 34 Waugh J, Bell SC, Kilby M, Lambert P, Shennan A, Halligan A. Effect of concentration and biochemical assay on the accuracy of urine dipsticks in hypertensive pregnancies. *Hypertens Pregnancy* 2001;20(2):205-17.
- 35 Khan DA, Ahmad TM, Qureshi AH, Halim A, Ahmad M, Afzal S. Assessment of proteinuria by using protein: Creatinine index in random urine sample. *J Pak Med Assoc* 2005;55(10):428-31.
- 36 Pfaf T, Franz U, Herfeld F, Lun A, Armbruster F, Hoehner B. Rapid immunochromatographic strip test for the detection of albuminuria and brief literature review on albuminuria screening. *Eur J Med Res* 2006;11(1):3-6.
- 37 Waugh JJ, Clark TJ, Divakaran TG, Khan KS, Kilby MD. Accuracy of urinalysis dipstick techniques in predicting significant proteinuria in pregnancy. *Obstet Gynecol* 2004;103(4):769-77.
- 38 Waugh JJS, Bell SC, Kilby MD, Blackwell CN, Seed P, Shennan AH, et al. Optimal bedside urinalysis for the detection of proteinuria in hypertensive pregnancy: A study of diagnostic accuracy. *Br J Obstet Gynaecol* 2005;112(4):412-7.
- 39 Ishani A, Grandits GA, Grimm RH, Svendsen KH, Collins AJ, Prineas RJ, et al. Association of single measurements of dipstick proteinuria, estimated glomerular filtration rate, and hematocrit with 25-year incidence of end-stage renal disease in the multiple risk factor intervention trial. *J Am Soc Nephrol* 2006;17(5):1444-52.
- 40 Kannel WB, Stampfer MJ, Castelli WP, Verter J. The prognostic significance of proteinuria: the Framingham study. *Am Heart J* 1984;108(5):1347-52.
- 41 Muntner P, He J, Hamm L, Loria C, Whelton PK. Renal insufficiency and subsequent death resulting from cardiovascular disease in the United States. *J Am Soc Nephrol* 2002;13(3):745-53.
- 42 Tonelli M, Jose P, Curhan G, Sacks F, Braunwald E, Pfeffer M. Proteinuria, impaired kidney function, and adverse outcomes in people with coronary disease: analysis of a previously conducted randomised trial. *Br Med J* 2006;332(7555):1426.
- 43 Carter JL, Tomson CRV, Stevens PE, Lamb EJ. Does urinary tract infection cause proteinuria or microalbuminuria? A systematic review. *Nephrol Dial Transplant* 2006;21(11):3031-7.
- 44 Ruggerenti P, Gaspari F, Perna A, Remuzzi G. 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. *Br Med J* 1998;316(7130):504-9.
- 45 Ewald B, Attia J. Which test to detect microalbuminuria in diabetic patients? A systematic review. *Aust Fam Physician* 2004;33(7):565-7.
- 46 Derhaschnig U, Kittler H, Woisetschlager C, Bur A, Herkner H, Hirschl MM. Microalbumin measurement alone or calculation of the albumin/creatinine ratio for the screening of hypertension patients? *Nephrol Dial Transplant* 2002;17(1):81-5.
- 47 Newman DJ, Mattock MB, Dawnay ABS, Kerry S, McGuire A, Yakoob M, et al. Systematic review on urine albumin testing for early detection of diabetic complications. *Health Technol Assess.* 2005;9(30). [cited 20 Dec 2007]. Available from url: <http://www.nchta.org/fullmono/mon930.pdf>

- 48 Watts GF, Harris R, Shaw KM. The determinants of early nephropathy in insulin-dependent diabetes mellitus: a prospective study based on the urinary excretion of albumin. *Q J Med* 1991;79(288):365-78.
- 49 Nelson RG, Bennett PH, Beck GJ, Tan M, Knowler WC, Mitch WE, et al. Development and progression of renal disease in Pima Indians with non-insulin-dependent diabetes mellitus. Diabetic Renal Disease Study Group. *N Engl J Med* 1996;335(22):1636-42.
- 50 Chan JC, Cheung CK, Cheung MY, Swaminathan R, Critchley JA, Cockram CS. Abnormal albuminuria as a predictor of mortality and renal impairment in Chinese patients with NIDDM. *Diabetes Care* 1995;18(7):1013-6.
- 51 Garg AX, Kiberd BA, Clark WF, Haynes RB, Clase CM. Albuminuria and renal insufficiency prevalence guides population screening: results from the NHANES III. *Kidney Int* 2002;61(6):2165-75.
- 52 Mann JF, Yi QL, Gerstein HC. Albuminuria as a predictor of cardiovascular and renal outcomes in people with known atherosclerotic cardiovascular disease. *Kidney Int Suppl* 2004(92):S59-62.
- 53 Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *Jama* 2001;286(4):421-6.
- 54 Borch-Johnsen K, Feldt-Rasmussen B, Strandgaard S, Schroll M, Jensen JS. Urinary albumin excretion. An independent predictor of ischemic heart disease. *Arterioscler Thromb Vasc Biol* 1999;19(8):1992-7.
- 55 Romundstad S, Holmen J, Kvenild K, Hallan H, Ellekjaer H. Microalbuminuria and all-cause mortality in 2,089 apparently healthy individuals: a 4.4-year follow-up study. The Nord-Trøndelag Health Study (HUNT), Norway. *Am J Kidney Dis* 2003;42(3):466-73.
- 56 Yuyun MF, Khaw KT, Luben R, Welch A, Bingham S, Day NE, et al. Microalbuminuria independently predicts all-cause and cardiovascular mortality in a British population: The European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) population study. *Int J Epidemiol* 2004;33(1):189-98.
- 57 National Institute for Health and Clinical Excellence (NICE). Referral for suspected cancer. London: NICE: 2005. (NICE Guideline CG27) [cited 8 May 2007]. Available from url: <http://www.nice.org.uk/nicemedia/pdf/cg027niceguideline.pdf>
- 58 Topham PS, Jethwa A, Watkins M, Rees Y, Feehally J. The value of urine screening in a young adult population. *Fam Pract* 2004;21(1):18-21.
- 59 Brown WW, Peters RM, Ohmit SE, Keane WF, Collins A, Chen SC, et al. Early detection of kidney disease in community settings: the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis* 2003;42(1):22-35.
- 60 Iseki K, Ikemiya Y, Iseki C, Takishita S. Proteinuria and the risk of developing end-stage renal disease. *Kidney Int* 2003;63(4):1468-74.
- 61 Yamagata K, Takahashi H, Tomida C, Yamagata Y, Koyama A. 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.
- 62 Eardley KS, Ferreira MA, Howie AJ, Gosling P, Lipkin GW. Urinary albumin excretion: a predictor of glomerular findings in adults with microscopic haematuria. *QJM* 2004;97(5):297-301.
- 63 Rodgers M, Nixon J, Hempel S, Aho T, Kelly J, Neal D, et al. Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation. *Health Technol Assess*. 2006;10(18). [cited 20 Dec 2007]. Available from url: <http://www.ncchta.org/fullmono/mon1018.pdf>
- 64 Grossfeld GD, Litwin MS, Wolf JS, Hricak H, Shuler CL, Agerter DC, et al. Evaluation of asymptomatic microscopic hematuria in adults: the American Urological Association best practice policy—part I: definition, detection, prevalence, and etiology. *Urology* 2001;57(4):599-603.
- 65 Grossfeld GD, Litwin MS, Wolf JS, Jr., Hricak H, Shuler CL, Agerter DC, et al. Evaluation of asymptomatic microscopic hematuria in adults: the American Urological Association best practice policy—part II: patient evaluation, cytology, voided markers, imaging, cystoscopy, nephrology evaluation, and follow-up. *Urology* 2001;57(4):604-10.
- 66 Newhouse JH, Amis ES, Jr., Bigongiari LR, Bluth EI, Bush WH, Jr., Choyke PL, et al. Radiologic investigation of patients with hematuria. American College of Radiology. ACR Appropriateness Criteria. *Radiology* 2000;215 Suppl:687-91.
- 67 Bush WH, Jr., Choyke PL, Bluth EI, Casalino DD, Francis IR, Jafri SZH, et al. ACR Appropriateness Criteria: Renal Failure. Reston, VA: American College of Radiology; 2005. [cited 3 Jan 2008]. Available from url: <http://acsearch.acr.org/VariantsList.aspx?topicid=30683>
- 68 Mizuma Y, Watanabe Y, Ozasa K, Hayashi K, Kawai K. Validity of sonographic screening for the detection of abdominal cancers. *J Clin Ultrasound* 2002;30(7):408-15.
- 69 Malaeb BS, Martin DJ, Littooy FN, Lotan Y, Waters WB, Flanigan RC, et al. The utility of screening renal ultrasonography: identifying renal cell carcinoma in an elderly asymptomatic population. *BJU Int* 2005;95(7):977-81.
- 70 Filipas D, Spix C, Schulz-Lampel D, Michaelis J, Hohenfellner R, Roth S, et al. Screening for renal cell carcinoma using ultrasonography: a feasibility study. *BJU Int* 2003;91(7):595-9.
- 71 McIntosh JF, Moller E, Van Slyke DD. Studies of Urea Excretion. III: The Influence of Body Size on Urea Output. *J Clin Invest* 1928;6(3):467-83.
- 72 James GD, Sealey JE, Alderman M, Ljungerman S, Mueller FB, Pecker MS, et al. A longitudinal study of urinary creatinine and creatinine clearance in normal subjects. Race, sex, and age differences. *Am J Hypertens* 1988;1(2):124-31.
- 73 Heymsfield SB, Arteaga C, McManus C, Smith J, Moffitt S. Measurement of muscle mass in humans: validity of the 24-hour urinary creatinine method. *Am J Clin Nutr* 1983;37(3):478-94.
- 74 Jacobsen FK, Christensen CK, Mogensen CE, Andreassen F, Heilskov NS. Pronounced increase in serum creatinine concentration after eating cooked meat. *Br Med J* 1979;1(6170):1049-50.
- 75 Mayersohn M, Conrad KA, Achari R. The influence of a cooked meat meal on creatinine plasma concentration and creatinine clearance. *Br J Clin Pharmacol* 1983;15(2):227-30.
- 76 Bosch JP, Saccaggi A, Lauer A, Ronco C, Belledonne M, Glabman S. Renal functional reserve in humans. Effect of protein intake on glomerular filtration rate. *Am J Med* 1983;75(6):943-50.
- 77 Preiss DJ, Godber IM, Lamb EJ, Dalton RN, Gunn IR. The influence of a cooked-meat meal on estimated glomerular filtration rate. *Ann Clin Biochem* 2007;44(Pt 1):35-42.
- 78 Ford L, Berg J. Delay in separating blood samples affects creatinine measurement using the Roche kinetic Jaffe method. *Ann Clin Biochem*. 2008;45(Pt 1):83-7.
- 79 Brochner-Mortensen J, Rodbro P. Selection of routine method for determination of glomerular filtration rate in adult patients. *Scand J Clin Lab Invest* 1976;36(1):35-43.
- 80 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16(1):31-41.
- 81 Levey AS, Greene T, Kusek J, Beck G. A simplified equation to predict glomerular filtration rate from serum creatinine. *J Am Soc Nephrol* 2000;11:155A.
- 82 Smith, HW. The Kidney. New York, NY: Oxford University Press, Inc; 1951. p.47-55.
- 83 Chantler C, Garnett ES, Parsons V, Veall N. Glomerular filtration rate measurement in man by the single injection methods using ⁵¹Cr-EDTA. *Clin Sci* 1969;37(1):169-80.
- 84 Perrone RD, Steinman TI, Beck GJ, Skibinski CI, Royal HD, Lawlor M, et al. Utility of radioisotopic filtration markers in chronic renal insufficiency: simultaneous comparison of ¹²⁵I-iothalamate, ¹⁶⁹Yb-DTPA, ^{99m}Tc-DTPA, and inulin. The Modification of Diet in Renal Disease Study. *Am J Kidney Dis* 1990;16(3):224-35.
- 85 Burkhardt H, Bojarsky G, Gretz N, Gladisch R. Creatinine clearance, Cockcroft-Gault formula and cystatin C: estimators of true glomerular filtration rate in the elderly? *Gerontology* 2002;48(3):140-6.
- 86 Oddo C, Morange S, Portugal H, Berland Y, Dussol B. Cystatin C is not more sensitive than creatinine for detecting early renal impairment in patients with diabetes. *Am J Kidney Dis* 2001;38(2):310-6.
- 87 O'Riordan SE, Webb MC, Stowe HJ, Simpson DE, Kandarpa M, Coakley AJ, et al. Cystatin C improves the detection of mild renal dysfunction in older patients. *Ann Clin Biochem* 2003;40(Pt 6):648-55.
- 88 Van Den Noortgate NJ, Janssens WH, Delanghe JR, Afschrift MB, Lameire NH. Serum cystatin C concentration compared with other markers of glomerular filtration rate in the old old. *J Am Geriatr Soc* 2002;50(7):1278-82.
- 89 Daniel JP, Chantrel F, Offner M, Moulin B, Hannedouche T. Comparison of cystatin C, creatinine and creatinine clearance vs. GFR for detection of renal failure in renal transplant patients. *Ren Fail* 2004;26(3):253-7.
- 90 Schuck O, Gottfriedova H, Maly J, Jabor A, Stollva M, Bruzkova I, et al. Glomerular filtration rate assessment in individuals after orthotopic liver transplantation based on serum cystatin C levels. *Liver Transpl* 2002;8(7):594-9.
- 91 Lamb EJ, Webb MC, Simpson DE, Coakley AJ, Newman DJ, O'Riordan SE. Estimation of glomerular filtration rate in older patients with chronic renal insufficiency: is the modification of diet in renal disease formula an improvement? *J Am Geriatr Soc* 2003;51(7):1012-7.
- 92 Harmoinen A, Lehtimäki T, Korpela M, Turjanmaa V, Saha H. Diagnostic accuracies of plasma creatinine, cystatin C, and glomerular filtration rate calculated by the Cockcroft-Gault and Levey (MDRD) formulas. *Clin Chem* 2003;49(7):1223-5.
- 93 Mussap M, Dalla Vestra M, Fioretto P, Saller A, Varagnolo M, Nosadini R, et al. Cystatin C is a more sensitive marker than creatinine for the estimation of GFR in type 2 diabetic patients. *Kidney Int* 2002;61(4):1453-61.
- 94 Hojs R, Bevc S, Antolinc B, Gorenjak M, Puklavc L. Serum cystatin C as an endogenous marker of renal function in the elderly. *Int J Clin Pharmacol Res* 2004;24(2-3):49-54.
- 95 Burkhardt H, Bojarsky G, Gladisch R. Diagnostic efficiency of cystatin C and serum creatinine as markers of reduced glomerular filtration rate in the elderly. *Clin Chem Lab Med* 2002;40(11):1135-8.
- 96 Chantrel F, Agin A, Offner M, Koehl C, Moulin B, Hannedouche T. Comparison of cystatin C versus creatinine for detection of mild renal failure. *Clin Nephrol* 2000;54(5):374-81.
- 97 Perlemoine C, Beauvieux MC, Rigalleau V, Baillet L, Barthes N, Derache P, et al. Interest of cystatin C in screening diabetic patients for early impairment of renal function. *Metabolism* 2003;52(10):1258-64.

- 98 Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Hypertension* 2003;42(5):1050-65.
- 99 Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;351(13):1296-305.
- 100 Weiner DE, Tighiouart H, Amin MG, Stark PC, MacLeod B, Griffith JL, et al. Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. *J Am Soc Nephrol* 2004;15(5):1307-15.
- 101 Coresh J, Astor B, Sarnak MJ. Evidence for increased cardiovascular disease risk in patients with chronic kidney disease. *Curr Opin Nephrol Hypertens* 2004;13(1):73-81.
- 102 Mariat C, Alamartine E, Barthelemy JC, De Filippis JP, Thibaudin D, Berthouix P, et al. Assessing renal graft function in clinical trials: can tests predicting glomerular filtration rate substitute for a reference method? *Kidney Int* 2004;65(1):289-97.
- 103 Nitta K, Hayashi T, Uchida K, Honda K, Tsukada M, Sekine S, et al. Serum cystatin C concentration as a marker of glomerular filtration rate in patients with various renal diseases. *Intern Med* 2002;41(11):931-5.
- 104 Burkhardt H, Hahn T, Gretz N, Gladisch R. Bedside estimation of the glomerular filtration rate in hospitalized elderly patients. *Nephron Clin Pract* 2005;101(1):c1-8.
- 105 Kingdon EJ, Knight CJ, Dustan K, Irwin AG, Thomas M, Powis SH, et al. Calculated glomerular filtration rate is a useful screening tool to identify scleroderma patients with renal impairment. *Rheumatology (Oxford)* 2003;42(1):26-33.
- 106 Froissart M, Rossert J, Jacquot C, Paillard M, Houillier P. Predictive performance of the modification of diet in renal disease and Cockcroft-Gault equations for estimating renal function. *J Am Soc Nephrol* 2005;16(3):763-73.
- 107 Hallan S, Asberg A, Lindberg M, Johnsen H. Validation of the Modification of Diet in Renal Disease formula for estimating GFR with special emphasis on calibration of the serum creatinine assay. *Am J Kidney Dis* 2004;44(1):84-93.
- 108 Lamb EJ, Wood J, Stowe HJ, O'Riordan SE, Webb MC, Dalton RN. Susceptibility of glomerular filtration rate estimations to variations in creatinine methodology: a study in older patients. *Ann Clin Biochem* 2005;42(Pt 1):11-8.
- 109 Cirillo M, Anastasio P, De Santo NG. Relationship of gender, age, and body mass index to errors in predicted kidney function. *Nephrol Dial Transplant* 2005;20(9):1791-8.
- 110 Rigalleau V, Lasseur C, Perlemoine C, Barthe N, Raffaitin C, Liu 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):838-43.
- 111 Saracino A, Morrone LF, Suriano V, Niccoli-Asabella A, Ramunni A, Fanelli M, et al. A simple method for correcting overestimated glomerular filtration rate in obese subjects evaluated by the Cockcroft and Gault formula: a comparison with ⁵¹Cr EDTA clearance. *Clin Nephrol* 2004;62(2):97-103.
- 112 Pierrat A, Gravier E, Saunders C, Caira MV, Ait-Djafer Z, Legras B, et al. Predicting GFR in children and adults: a comparison of the Cockcroft-Gault, Schwartz, and modification of diet in renal disease formulas. *Kidney Int* 2003;64(4):1425-36.
- 113 Vervoort G, Willems HL, Wetzels JF. Assessment of glomerular filtration rate in healthy subjects and normoalbuminuric diabetic patients: validity of a new (MDRD) prediction equation. *Nephrol Dial Transplant* 2002;17(11):1909-13.
- 114 Myers GL, Miller WG, Coresh J, Fleming J, Greenberg N, Greene T, et al. Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. *Clin Chem* 2006;52(1):5-18.
- 115 Lamb EJ, Webb MC, O'Riordan SE. Using the modification of diet in renal disease (MDRD) and Cockcroft and Gault equations to estimate glomerular filtration rate (GFR) in older people. *Age Ageing* 2007;36(6):689-92.
- 116 Schuck O, Teplan V, Sibova J, Stollova M. Predicting the glomerular filtration rate from serum creatinine, serum cystatin C and the Cockcroft and Gault formula with regard to drug dosage adjustment. *Int J Clin Pharmacol Ther* 2004;42(2):93-7.
- 117 Thomassen SA, Johannessen IL, Erlandsen EJ, Abrahamsen J, Randers E. Serum cystatin C as a marker of the renal function in patients with spinal cord injury. *Spinal Cord* 2002;40(10):524-8.
- 118 Fliser D, Ritz E. Serum cystatin C concentration as a marker of renal dysfunction in the elderly. *Am J Kidney Dis* 2001;37(1):79-83.
- 119 Christensson AG, Grubb AO, Nilsson JA, Norrgren K, Sterner G, Sundkvist G. Serum cystatin C advantageous compared with serum creatinine in the detection of mild but not severe diabetic nephropathy. *J Intern Med* 2004;256(6):510-8.
- 120 Schuck O, Teplan V, Jabor A, Stollova M, Skibova J. Glomerular filtration rate estimation in patients with advanced chronic renal insufficiency based on serum cystatin C levels. *Nephron Clin Pract* 2003;93(4):c146-51.
- 121 Schuck O, Teplan V, Mareckova O, Skibova J, Stollova M. Estimation of glomerular filtration rate based on the modification of diet in renal disease equation in patients with chronic renal failure. *Kidney Blood Press Res* 2005;28(2):63-7.
- 122 Joint Formulary Committee. *British National Formulary*. 54th ed. London: BMJ Publishing Group and Royal Pharmaceutical Society of Great Britain; 2007.
- 123 Electronic Medicines Compendium. [cited 3 Jan 2008]. Available at url: <http://emc.medicines.org.uk>
- 124 Ashley C, Currie A, editors. *The Renal Drug Handbook*, 2nd ed. Oxon: Radcliffe Publishing Ltd; 2003.
- 125 National Kidney Foundation. *K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification*. *Am J Kidney Dis* 2002;39(2 Suppl 1):S1-266.
- 126 Clase CM, Garg AX, Kiberd BA. Classifying kidney problems: can we avoid framing risks as diseases? *Br Med J* 2004;329(7471):912-5.
- 127 Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2005;67(6):2089-100.
- 128 Archibald G, Bartlett W, Brown A, Christie B, Elliott A, Griffith K, et al. UK consensus conference on early chronic kidney disease. Edinburgh: Royal College of Physicians; 2007. [cited 3 Jan 2008]. Available from url: <http://www.rcpe.ac.uk/education/standards/consensus/UK-Consensus-Conference-on-Early-Chronic-Kidney-Disease-Feb-2007.pdf>
- 129 Raymond NT, Zehnder D, Smith SC, Stinson JA, Lehnert H, Higgins RM. Elevated relative mortality risk with mild-to-moderate chronic kidney disease decreases with age. *Nephrol Dial Transplant* 2007;22(11):3214-20.
- 130 Levey AS, Beto JA, Coronado BE, Eknoyan G, Foley RN, Kasiske BL, et al. Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease. *Am J Kidney Dis* 1998;32(5):853-906.
- 131 Kappel J, Calissi P. Nephrology: 3. Safe drug prescribing for patients with renal insufficiency. *CMAJ* 2002;166(4):473-7.
- 132 Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, et al. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004-BHS IV. *J Hum Hypertens* 2004;18(3):139-85.
- 133 Jafar TH, Stark PC, Schmid CH, Landa M, Maschio G, Marcantoni C, et al. Proteinuria as a modifiable risk factor for the progression of non-diabetic renal disease. *Kidney Int* 2001;60(3):131-40.
- 134 ACE inhibitors in Diabetic Nephropathy Trialist group. Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. *Ann Intern Med* 2001;134(5):370-9.
- 135 Jafar TH, Schmid CH, Landa M, Giatras I, Toto R, Remuzzi G, et al. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. *Ann Intern Med* 2001;135(2):73-87.
- 136 Jafar TH, Stark PC, Schmid CH, Landa M, Maschio G, de Jong PE, et al. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. *Ann Intern Med* 2003;139(4):244-52.
- 137 Atkins RC, Briganti EM, Lewis JB, Hunsicker LG, Braden G, Champion de Crespigny PJ, et al. Proteinuria reduction and progression to renal failure in patients with type 2 diabetes mellitus and overt nephropathy. *Am J Kidney Dis* 2005;45(2):281-7.
- 138 Casas JP, Chua W, Loukogeorgakis S, Vallance P, Smeeth L, Hingorani AD, 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):2026-33.
- 139 Tonelli M, Jose P, Curhan G, Sacks F, Braunwald E, Pfeffer M. Proteinuria, impaired kidney function, and adverse outcomes in people with coronary disease: analysis of a previously conducted randomised trial. *Br Med J* 2006;332(7555):1426.
- 140 Donadio JV, Bergstralh EJ, Grande JP, Rademacher DM. Proteinuria patterns and their association with subsequent end-stage renal disease in IgA nephropathy. *Nephrol Dial Transplant* 2002;17(7):1197-203.
- 141 Ruggenenti P, Perna A, Remuzzi G. Retarding progression of chronic renal disease: the neglected issue of residual proteinuria. *Kidney Int* 2003;63(6):2254-61.
- 142 de Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S, et al. Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL. *Kidney Int* 2004;65(6):2309-20.
- 143 Lea J, Greene T, Hebert L, Lipkowitz M, Massry S, Middleton J, 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. *Arch Intern Med* 2005;165(8):947-53.

- 144 Strippoli GFM, Bonifati C, Craig M, Navaneethan SD, Craig JC. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease (Cochrane Review). In: The Cochrane Library, Issue 4, 2006. London: John Wiley & Sons Ltd.
- 145 Kshirsagar AV, Joy MS, Hogan SL, Falk RJ, Colindres RE. Effect of ACE inhibitors in diabetic and nondiabetic chronic renal disease: a systematic overview of randomized placebo-controlled trials. *Am J Kidney Dis* 2000;35(4):695-707.
- 146 Hamilton RA, Kane MP, Demers J. Angiotensin-converting enzyme inhibitors and type 2 diabetic nephropathy: a meta-analysis. *Pharmacotherapy* 2003;23(7):909-15.
- 147 Jafar TH, Stark PC, Schmid CH, Strandgaard S, Kamper AL, Maschio G, et al. The effect of angiotensin-converting-enzyme inhibitors on progression of advanced polycystic kidney disease. *Kidney Int* 2005;67(1):265-71.
- 148 Giatras I, Lau J, Levey AS, Zucchelli PC, Kamper AL, Strandgaard S, et al. Effect of angiotensin-converting enzyme inhibitors on the progression of nondiabetic renal disease: A meta-analysis of randomized trials. *Ann Intern Med* 1997;127(5):337-45.
- 149 Strippoli GFM, Craig M, Craig JC. Anti-hypertensive agents for preventing diabetic kidney disease (Cochrane Review). In: The Cochrane Library, Issue4, 2006. London: John Wiley & Sons Ltd.
- 150 Doultou TWR, He FJ, MacGregor GA. Systematic review of combined angiotensin-converting enzyme inhibition and angiotensin receptor blockade in hypertension. *Hypertension* 2005;45(5):880-6.
- 151 MacKinnon M, Shurraw S, Akbari A, Knoll GA, Jaffey J, Clark HD. Combination therapy with an angiotensin receptor blocker and an ACE inhibitor in proteinuric renal disease: a systematic review of the efficacy and safety data. *Am J Kidney Dis* 2006;48(1):8-20.
- 152 Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney Int* 2003;63(1):225-32.
- 153 Retnakaran R, Cull CA, Thorne KI, Adler AI, Holman RR. Risk factors for renal dysfunction in type 2 diabetes: U.K. Prospective Diabetes Study 74. *Diabetes* 2006;55(6):1832-9.
- 154 Kent DM, Jafar TH, Hayward RA, Tighiouart H, Landa M, de Jong P, et al. Progression risk, urinary protein excretion, and treatment effects of angiotensin-converting enzyme inhibitors in nondiabetic kidney disease. *J Am Soc Nephrol* 2007;18(6):1959-65.
- 155 Strippoli GFM, Craig M, Deeks JJ, Schena FP, Craig JC. Effects of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists on mortality and renal outcomes in diabetic nephropathy: Systematic review. *Br Med J* 2004;329(7470):828-31.
- 156 Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet* 2000;355(9200):253-9.
- 157 Dahlöf B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005;366(9489):895-906.
- 158 Tokmakova MP, Skali H, Kenchaiah S, Braunwald E, Rouleau JL, Packer M, 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):3667-73.
- 159 Bakris GL, Weir MR, Secic M, Campbell B, Weis-McNulty A. Differential effects of calcium antagonist subclasses on markers of nephropathy progression. *Kidney Int* 2004;65(6):1991-2002.
- 160 Baigent C, Landry M. Study of Heart and Renal Protection (SHARP). *Kidney Int Suppl* 2003(84):S207-10.
- 161 Keane WF. The role of lipids in renal disease: future challenges. *Kidney Int Suppl* 2000;75:S27-31.
- 162 Kasiske BL, O'Donnell MP, Kim Y, Keane WF. Treatment of hyperlipidemia in chronic progressive renal disease. *Curr Opin Nephrol Hypertens* 1993;2(4):602-8.
- 163 Massy ZA, Guijarro C, O'Donnell MP, Kasiske BL, Keane WF. Lipids, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, and progression of renal failure. *Adv Nephrol Necker Hosp* 1997;27:39-56.
- 164 Ridker PM, Rifai N, Clearfield M, Downs JR, Weis SE, Miles JS, et al. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med* 2001;344(26):1959-65.
- 165 Maisch NM, Pezzillo KK. HMG-CoA reductase inhibitors for the prevention of nephropathy. *Ann Pharmacother* 2004;38(2):342-5.
- 166 Fried LF, Orchard TJ, Kasiske BL. Effect of lipid reduction on the progression of renal disease: a meta-analysis. *Kidney Int* 2001;59(1):260-9.
- 167 Tonelli M, Isles C, Craven T, Tonkin A, Pfeffer MA, Shepherd J, et al. Effect of pravastatin on rate of kidney function loss in people with or at risk for coronary disease. *Circulation* 2005;112(2):171-8.
- 168 Sandhu S, Wiebe N, Fried LF, Tonelli M. Statins for improving renal outcomes: a meta-analysis. *J Am Soc Nephrol* 2006;17(7):2006-16.
- 169 Douglas K, O'Malley PG, Jackson JL. Meta-analysis: the effect of statins on albuminuria. *Ann Intern Med* 2006;145(2):117-24.
- 170 LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA* 1999;282(24):2340-6.
- 171 Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;366(9493):1267-78.
- 172 JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* 2005;91 Suppl 5:v1-52.
- 173 Liu Y, Coresh J, Eustace JA, Longenecker JC, Jaar B, Fink NE, et al. Association between cholesterol level and mortality in dialysis patients: role of inflammation and malnutrition. *JAMA* 2004;291(4):451-9.
- 174 Holdaas H, Fellstrom B, Jardine AG, Holme I, Nyberg G, Fauchald P, et al. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. *Lancet* 2003;361(9374):2024-31.
- 175 Wanner C, Krane V, Marz W, Olschewski M, Mann JF, Ruf G, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005;353(3):238-48.
- 176 Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Drugs* 2004;64 Suppl 2:43-60.
- 177 Tonelli M, Collins D, Robins S, Bloomfield H, Curhan GC, Veterans' Affairs High-Density Lipoprotein Intervention Trial I. Gemfibrozil for secondary prevention of cardiovascular events in mild to moderate chronic renal insufficiency. *Kidney Int* 2004;66(3):1123-30.
- 178 Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *Br Med J* 2002;324(7329):71-86.
- 179 Baigent C, Landray M, Leaper C, Altmann P, Armitage J, Baxter A, et al. First United Kingdom Heart and Renal Protection (UK-HARP-I) study: biochemical efficacy and safety of simvastatin and safety of low-dose aspirin in chronic kidney disease. *Am J Kidney Dis* 2005;45(3):473-84.
- 180 Hansen HP, Tauber-Lassen E, Jensen BR, Parving HH. Effect of dietary protein restriction on prognosis in patients with diabetic nephropathy. *Kidney Int* 2002;62(1):220-8.
- 181 Pijls LTJ, de Vries H, van Eijk J, Donker AJM. Protein restriction, glomerular filtration rate and albuminuria in patients with type 2 diabetes mellitus: A randomized trial. *Eur J Clin Nutr* 2002;56(12):1200-7.
- 182 Meloni C, Morosetti M, Suraci C, Pennafina MG, Tozzo C, Taccone-Gallucci M, et al. Severe dietary protein restriction in overt diabetic nephropathy: benefits or risks? *J Ren Nutr* 2002;12(2):96-101.
- 183 Meloni C, Tatangelo P, Cipriani S, Rossi V, Suraci C, Tozzo C, et al. Adequate protein dietary restriction in diabetic and nondiabetic patients with chronic renal failure. *J Ren Nutr* 2004;14(4):208-13.
- 184 Fouque D, Laville M, Boissel JP. Low protein diets for chronic renal failure in non diabetic adults (Cochrane Review). In: The Cochrane Library, Issue 1, 2005. London: John Wiley & Sons Ltd.
- 185 Kasiske BL, Lakatua JDA, Ma JZ, Louis TA. A meta-analysis of the effects of dietary protein restriction on the rate of decline in renal function. *Am J Kidney Dis* 1998;31(6):954-61.
- 186 Robertson L, Waugh N, Robertson A. Protein restriction for diabetic renal disease (Cochrane Review). In: The Cochrane Library, Issue 4, 2007. London: John Wiley & Sons Ltd.
- 187 Cianciaruso B, Bellizzi V, Minutolo R, Tavera A, Capuano A, Conte G, et al. Salt intake and renal outcome in patients with progressive renal disease. *Miner Electrolyte Metab* 1998;24(4):296-301.
- 188 Jones-Burton C, Mishra SI, Fink JC, Brown J, Gossa W, Bakris GL, et al. An in-depth review of the evidence linking dietary salt intake and progression of chronic kidney disease. *Am J Nephrol* 2006;26(3):268-75.
- 189 Kidney Disease Outcomes Quality Initiative. K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis* 2004;43(5 Suppl 1):S1-290.
- 190 Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med* 2001;344(1):3-10.
- 191 Orth SR, Schroeder T, Ritz E, Ferrari P. Effects of smoking on renal function in patients with type 1 and type 2 diabetes mellitus. *Nephrol Dial Transplant* 2005;20(11):2414-9.

- 192 Chuahirun T, Wesson DE. Cigarette smoking predicts faster progression of type 2 established diabetic nephropathy despite ACE inhibition. *Am J Kidney Dis* 2002;39(2):376-82.
- 193 Chuahirun T, Khanna A, Kimball K, Wesson DE. Cigarette smoking and increased urine albumin excretion are interrelated predictors of nephropathy progression in type 2 diabetes. *Am J Kidney Dis* 2003;41(1):13-21.
- 194 Warmoth L, Regalado MM, Simoni J, Harrist RB, Wesson DE. Cigarette smoking enhances increased urine albumin excretion as a risk factor for glomerular filtration rate decline in primary hypertension. *Am J Med Sci* 2005;330(3):111-9.
- 195 Hovind P, Rossing P, Tarnow L, Parving HH. Smoking and progression of diabetic nephropathy in type 1 diabetes. *Diabetes Care* 2003;26(3):911-6.
- 196 Schiff H, Lang SM, Fischer R. Stopping smoking slows accelerated progression of renal failure in primary renal disease. *J Nephrol* 2002;15(3):270-4.
- 197 Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 Years' observations on male British doctors. *Br Med J* 2004;328(7455):1519-28.
- 198 Law MR, Morris JK, Wald NJ. Environmental tobacco smoke exposure and ischaemic heart disease: an evaluation of the evidence. *Br Med J* 1997;315(7114):973-80.
- 199 Ritchie SA, Connell JM. The link between abdominal obesity, metabolic syndrome and cardiovascular disease. *Nutr Metab Cardiovasc Dis* 2007;17(4):319-26.
- 200 Altieri A, Tavani A, Gallus S, La Vecchia C. Occupational and leisure time physical activity and the risk of nonfatal acute myocardial infarction in Italy. *Ann Epidemiol* 2004;14(7):461-6.
- 201 Tanasescu M, Leitzmann MF, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Exercise type and intensity in relation to coronary heart disease in men. *JAMA* 2002;288(16):1994-2000.
- 202 MacLean CH, Mojica WA, Morton SC, Pencharz J, Hasenfeld Garland R, Tu W, et al. Effects of Omega-3 Fatty Acids on Lipids and Glycemic Control in Type II Diabetes and the Metabolic Syndrome and on Inflammatory Bowel Disease, Rheumatoid Arthritis, Renal Disease, Systemic Lupus Erythematosus, and Osteoporosis. Rockville, MD: Agency for Healthcare Research and Quality; 2004. (AHRQ Publication No. 04-E012-2). [cited 4 Jan 2008]. Available from url: <http://www.ahrq.gov/downloads/pub/evidence/pdf/o3lipid/o3lipid.pdf>
- 203 Strippoli GF, Manno C, Schena FP. An "evidence-based" survey of therapeutic options for IgA nephropathy: assessment and criticism. *Am J Kidney Dis* 2003;41(6):1129-39.
- 204 Luyckx VA, Steenkamp V, Stewart MJ. Acute renal failure associated with the use of traditional folk remedies in South Africa. *Ren Fail* 2005;27(1):35-43.
- 205 Martinez MC, Nortier J, Vereerstraeten P, Vanherweghem JL. Progression rate of Chinese herb nephropathy: impact of Aristolochia fangchi ingested dose. *Nephrol Dial Transplant* 2002;17(3):408-12.
- 206 Mason RG, Donaldson D. Chinese herbal nephropathy and urothelial malignancy. *J R Soc Health* 2002;122(4):266-7.
- 207 Saper RB, Kales SN, Paquin J, Burns MJ, Eisenberg DM, Davis RB, et al. Heavy metal content of ayurvedic herbal medicine products. *JAMA* 2004;292(23):2868-73.
- 208 Heiwe S, Tollback A, Clyne N. Twelve weeks of exercise training increases muscle function and walking capacity in elderly predialysis patients and healthy subjects. *Nephron* 2001;88(1):48-56.
- 209 Castaneda C, Gordon PL, Uhlin KL, Levey AS, Kehayias JJ, Dwyer JT, et al. Resistance training to counteract the catabolism of a low-protein diet in patients with chronic renal insufficiency. A randomized, controlled trial. *Ann Intern Med* 2001;135(11):965-76.
- 210 White CA, Pilkey RM, Lam M, Holland DC. Pre-dialysis clinic attendance improves quality of life among hemodialysis patients. *BMC Nephrol* 2002;3:3.
- 211 Chow FYF, Briganti EM, Kerr PG, Chadban SJ, Zimmet PZ, Atkins RC. Health-related quality of life in Australian adults with renal insufficiency: a population-based study. *Am J Kidney Dis* 2003;41(3):596-604.
- 212 Frank A, Auslander GK, Weissgarten J. Quality of life of patients with end-stage renal disease at various stages of the illness. *Soc Work Health Care* 2003;38(2):1-27.
- 213 Walters BAJ, Hays RD, Spritzer KL, Fridman M, Carter WB. Health-related quality of life, depressive symptoms, anemia, and malnutrition at hemodialysis initiation. *Am J Kidney Dis* 2002;40(6):1185-94.
- 214 Harwood L, Locking-Cusolito H, Spittal J, Wilson B, White S. Preparing for hemodialysis: patient stressors and responses. *Nephrol Nurs J* 2005;32(3):295-303.
- 215 Hedayati SS, Jiang W, O'Connor CM, Kuchibhatla M, Krishnan KR, Cuffe MS, et al. The association between depression and chronic kidney disease and mortality among patients hospitalized with congestive heart failure. *Am J Kidney Dis* 2004;44(2):207-15.
- 216 Watnick S, Kirwin P, Mahnensmith R, Concato J. The prevalence and treatment of depression among patients starting dialysis. *Am J Kidney Dis* 2003;41(1):105-10.
- 217 King N, Carroll C, Newton P, Dorman T. "You can't cure it so you have to endure it": The experience of adaptation to diabetic renal disease. *Qual Health Res* 2002;12(3):329-46.
- 218 Kelly M, Tibbles R. Counselling should be offered to people with end-stage renal failure. *EDNA ERCA J* 2004;30(1):31-3.
- 219 Christensen AJ, Ehlers SL, Wiebe JS, Moran PJ, Raichle K, Femeyhough K, et al. Patient personality and mortality: a 4-year prospective examination of chronic renal insufficiency. *Health Psychol* 2002;21(4):315-20.
- 220 Devins GM, Mendelssohn DC, Barre PE, Binik YM. Predialysis psychoeducational intervention and coping styles influence time to dialysis in chronic kidney disease. *Am J Kidney Dis* 2003;42(4):693-703.
- 221 Binik YM, Devins GM, Barre PE, Guttman RD, Hollomby DJ, Mandin H, et al. Live and learn: patient education delays the need to initiate renal replacement therapy in end-stage renal disease. *J Nerv Ment Dis* 1993;181(6):371-6.
- 222 Klang B, Bjorvell H, Berglund J, Sundstedt C, Clyne N. Predialysis patient education: effects on functioning and well-being in uraemic patients. *J Adv Nurs* 1998;28(1):36-44.
- 223 Devins GM, Hollomby DJ, Barre PE, Mandin H, Taub K, Paul LC, et al. Long-term knowledge retention following predialysis psychoeducational intervention. *Nephron* 2000;86(2):129-34.
- 224 Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke (Cochrane Review). In: The Cochrane Library, Issue 4, 2007. Oxford: Update Software.
- 225 British Renal Society. The Renal Team: A multi-professional renal workforce plan for adults and children with renal disease. Recommendations of the National Renal Workforce Planning Group 2002. Surrey: British Renal Society; 2002. [cited 4 Jan 2008]. Available from url: http://www.britishrenal.org/workfpg/WFP_Renal_Book.pdf
- 226 Astor BC, Muntner P, Levin A, Eustace JA, Coresh J. Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988-1994). *Arch Intern Med* 2002;162(12):1401-8.
- 227 Cody J, Daly C, Campbell M, Donaldson C, Khan I, Rabindranath K, et al. Recombinant human erythropoietin for chronic renal failure anaemia in pre-dialysis patients. (Cochrane Review). In: The Cochrane Library, Issue 3, 2005. Chichester, UK: John Wiley & Sons, Ltd.
- 228 Phrommintikul A, Haas SJ, Elsik M, Krum H. Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis. *Lancet* 2007;369(9559):381-8.
- 229 European Medicines Agency. Public Statement: Epoetins and the risk of tumour growth progression and thromboembolic events in cancer patients and cardiovascular risks in patients with chronic kidney disease. London: EMEA; 2007. [cited 4 Jan 2008]. Available from url: <http://www.emea.europa.eu/pdfs/human/press/pus/49618807en.pdf>
- 230 National Institute for Health and Clinical Excellence. Anaemia management in chronic kidney disease. London: NICE; 2006. (NICE Guideline CG39). [cited 4 Jan 2008]. Available from url: <http://www.nice.org.uk/guidance/index.jsp?action=byID&o=10992>
- 231 Kopple JD, Greene T, Chumlea WC, Hollinger D, Maroni BJ, Merrill D, et al. Relationship between nutritional status and the glomerular filtration rate: results from the MDRD study. *Kidney Int* 2000;57(4):1688-703.
- 232 Carvalho KT, Silva MI, Bregman R. Nutritional profile of patients with chronic renal failure. *J Ren Nutr* 2004;14(2):97-100.
- 233 Lawson JA, Lazarus R, Kelly JJ. Prevalence and prognostic significance of malnutrition in chronic renal insufficiency. *J Ren Nutr* 2001;11(1):16-22.
- 234 National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 2003;42(4 Suppl 3):S1-201.
- 235 Spasovski GB, Bervoets AR, Behets GJ, Ivanovski N, Sikole A, Dams G, et al. Spectrum of renal bone disease in end-stage renal failure patients not yet on dialysis. *Nephrol Dial Transplant* 2003;18(6):1159-66.
- 236 Hsu CY, Cummings SR, McCulloch CE, Chertow GM. Bone mineral density is not diminished by mild to moderate chronic renal insufficiency. *Kidney Int* 2002;61(5):1814-20.
- 237 Lobao R, Carvalho AB, Cuppari L, Ventura R, Lazaretti-Castro M, Jorgetti V, et al. High prevalence of low bone mineral density in pre-dialysis chronic kidney disease patients: bone histomorphometric analysis. *Clin Nephrol* 2004;62(6):432-9.
- 238 Scottish Intercollegiate Guidelines Network (SIGN). Management of Osteoporosis. Edinburgh: SIGN; 2003. (SIGN publication no. 71). [cited 20 Dec 2007]. Available from url: <http://www.sign.ac.uk>
- 239 Miller PD, Roux C, Boonen S, Barton IP, Dunlap LE, Burgio DE. 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. *J Bone Miner Res* 2005;20(12):2105-15.
- 240 Llach F, Massry SG. On the mechanism of secondary hyperparathyroidism in moderate renal insufficiency. *J Clin Endocrinol Metab* 1985;61(4):601-6.
- 241 Hamdy NA, Kanis JA, Beneton MN, Brown CB, Juttmann JR, Jordans

- JG, et al. Effect of alfacalcidol on natural course of renal bone disease in mild to moderate renal failure. *Br Med J* 1995;310(6976):358-63.
- 242 Eustace JA, Astor B, Muntner PM, Ikizler TA, Coresh J. Prevalence of acidosis and inflammation and their association with low serum albumin in chronic kidney disease. *Kidney Int* 2004;65(3):1031-40.
- 243 Kopple JD, Kalantar-Zadeh K, Mehrotra R. Risks of chronic metabolic acidosis in patients with chronic kidney disease. *Kidney Int Suppl* 2005(95):S21-7.
- 244 Bushinsky DA. The contribution of acidosis to renal osteodystrophy. *Kidney Int* 1995;47(6):1816-32.
- 245 Kraut JA, Kurtz I. Metabolic acidosis of CKD: diagnosis, clinical characteristics, and treatment. *Am J Kidney Dis* 2005;45(6):978-93.
- 246 Jenkins D, Burton PR, Bennett SE, Baker F, Walls J. The metabolic consequences of the correction of acidosis in uraemia. *Nephrol Dial Transplant* 1989;4(2):92-5.
- 247 Reaich D, Channon SM, Scrimgeour CM, Daley SE, Wilkinson R, Goodship TH. Correction of acidosis in humans with CRF decreases protein degradation and amino acid oxidation. *Am J Physiol* 1993;265(2 Pt 1):E230-5.
- 248 Mathur RP, Dash SC, Gupta N, Prakash S, Saxena S, Bhowmik D. Effects of correction of metabolic acidosis on blood urea and bone metabolism in patients with mild to moderate chronic kidney disease: a prospective randomized single blind controlled trial. *Ren Fail* 2006;28(1):1-5.
- 249 Verove C, Maisonneuve N, El Azouzi A, Boldron A, Azar R. Effect of the correction of metabolic acidosis on nutritional status in elderly patients with chronic renal failure. *J Ren Nutr* 2002;12(4):224-8.
- 250 National Institute for Health and Clinical Excellence. Anaemia management in chronic kidney disease: Costing report. London: NICE; 2006. (NICE Guideline No. CG39). Available from url: http://www.nice.org.uk/nicemedia/pdf/word/CG39_Anaemia_management_in_CKD_Costing_report.doc

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