Chronic Kidney Disease in Adults: UK Guidelines for Identification, Management and Referral

CONTENTS

ABBREVIATIONS

AASK	African American Study of Kidney disease and hypertension
ACB	Association of Clinical Biochemists
ACEI	Angiotensin Converting Enzyme Inhibitor
AER	Albumin Excretion Rate
ARAS	Atherosclerotic Renal Artery Stenosis
ARB	Angiotensin Receptor Blocker
ARF	Acute Renal Failure
ASCOT	Anglo-Scandinavian Cardiac Outcomes Study
ASTRAL	Angioplasty and Stent for Renal Artery Lesions
AUA	American Urological Association
BGS	British Geriatrics Society
BMD	Bone Mineral Density
BSA	Body Surface Area
CARDS	Collaborative Atorvastatin Diabetes Study
CARE	Cholesterol and Recurrent Events study
CARI	Caring for Australians with Renal Impairment
CHD	Coronary Heart Disease
CHOIR	Correction of Haemoglobin and Outcomes in Renal Insufficiency
CKD	Chronic Kidney Disease
CREATE	Cardiovascular Risk Reduction by Early Anaemia Treatment with Epoetin
CT	Computed Tomography
CVD	Cardiovascular Disease
DA	Diagnostic Accuracy (see page 8)
DARE	Database of Abstracts of Reviews of Effects
DCCT	Diabetes Control and Complications Trial
EBPG	European Best Practice Guidelines
EDTA	Ethylenediaminetetraacetic acid
EPO	Erythropoietin
ERF	Established Renal Failure
ESA	Erythropoiesis Stimulating Agent
GFR	Glomerular Filtration Rate
HOPE	Heart Outcomes Prevention Evaluation study

HOT	Hypertension Optimal Treatment
HPS	Heart Protection Study
K/DOQI	Kidney Disease Outcomes Quality Initiative
LVH	Left Ventricular Hypertrophy
MDRD	Modification of Diet in Renal Disease
MR	Magnetic Resonance
NHANES	National Health And Nutrition Examination Survey
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NKF	National Kidney Federation
NPfIT	National Programme for Information Technology
NSAID	Non-Steroidal Anti-Inflammatory Drug
NSF	National Service Framework
PCT	Primary Care Trust
PTFE	Polytetrafluoroethylene
PTH	Parathyroid Hormone
RA	Renal Association
RAS	Renin Angiotensin System
RCGP	Royal College of General Practitioners
RCPL	Royal College of Physicians of London
RIFLE	Risk, Injury, Failure, Loss, Endstage
RCT	Randomised Controlled Trial
RRT	Renal Replacement Therapy
SDGHN	Society for District General Hospital Nephrologists
SHARP	Study of Heart and Renal Protection
SIGN	Scottish Intercollegiate Guidelines Network
SLE	Systemic Lupus Erythematosus
UK-HARP	United Kingdom Heart and Renal Protection
UKPDS	UK Prospective Diabetes Study
UTI	Urinary Tract Infection

INTRODUCTION

The need for guidelines on chronic kidney disease

Established renal failure (ERF) is relatively rare, but treatment with dialysis or transplantation is very expensive. The number of patients receiving renal replacement therapy (RRT) in the UK is rising rapidly and is unlikely to reach steady state for another 25 years [1], costing over 2% of the total NHS budget. These figures make any improvement in the cost-effective treatment of early kidney disease highly desirable.

Late referral of patients with ERF requiring RRT to specialist renal services is associated with significant cost and poor clinical outcomes. The great majority of patients starting RRT have progressed from earlier stages of chronic kidney disease (CKD), and most could therefore have been identified and referred earlier. Early CKD is common, however, and referral of all patients with early CKD would completely overwhelm existing specialist services. The great majority of patients with early CKD do not progress to established renal failure, but do have increased risks of cardiovascular disease. Optimal management of the risk factors for cardiovascular disease also reduces the risk of progression from early CKD to ERF. These guidelines were therefore developed to promote the optimal management of patients with CKD within the NHS, including the identification of those who would benefit from referral to specialist services.

Methodology of guideline development

These guidelines were instigated at the suggestion of the Joint Specialty Committee on Renal Disease of the Royal College of Physicians of London (RCPL) and the Renal Association (RA), and were developed jointly with the Royal College of General Practitioners (RCGP), the Association of Clinical Biochemists (ACB), the Society for District General Hospital Nephrologists (SDGHN), the British Geriatrics Society (BGS), the Professional Advisory Council of Diabetes UK, and the National Kidney Federation (NKF). The guidelines were developed in parallel with, but independently from, the consultation process that accompanied the development of advice to Ministers for part 2 of the National Service Framework (NSF) for Renal Services for England. Expenses for attending meetings, and accommodation for meetings, were met by the Department of Health for England. However, the guidelines are intended for use throughout the United Kingdom, as applies to the Renal Association Standards Document [2].

Identification and grading of the evidence

Recommendations were based wherever possible on existing systematic reviews of the relevant literature. We searched the Cochrane Renal Group and the NHS Centre for Reviews and Dissemination DARE (Database of Abstracts of Reviews of Effects) databases for reviews. Where relevant, individual members performed purposive literature searches in their areas of expertise, using Medline, and then narrative synthesis. We have not had the resources to perform systematic quality assessment and grading on

the literature identified. As part of the NSF process, the NHS Centre for Reviews and Dissemination at the University of York undertook searching and narrative synthesis on several topics, and we were given access to the reports; these included screening, kidney stones; weight loss, smoking, and exercise and CKD; influence of lower blood pressure on rate of decline of kidney function; early referral; use of angiotensin converting enzyme inhibitors (ACEI) in those with normal kidney function; risk of progression amongst people with a single kidney; renal function following relief of obstructive nephropathy; nutrition, anaemia, and CKD; and renal bone disease. We have also drawn on existing evidence based guidelines both UK and international, notably those by the National Institute for Clinical Excellence (NICE) on management of Type 1 and Type 2 diabetes mellitus and of hypertension, NSFs for coronary heart disease, diabetes mellitus, older people, cancer and renal services, as well as the Kidney Disease Outcomes Quality Initiative (K/DOQI) series on CKD and the Caring for Australians with Renal Impairment (CARI) guidelines. The guidelines were designed to meet, as far as possible, the criteria suggested by the Appraisal of Guidelines Research and Evaluation Collaboration [3 4].

We recognise that whilst there is significant randomised evidence for many of the interventions used to manage CKD (such as the use of ACEIs in diabetic nephropathy), many of the questions posed by this guidance are about surveillance for, or referral of, kidney disease. These questions have not been addressed by randomised controlled trials. For the specific details of surveillance and referral we have had to rely largely on expert opinion/consensus.

The Renal NSF used the following framework to grade evidence in line with other NSFs:

Level 1: Meta-analyses, systematic reviews of randomised controlled trials, or randomised controlled trials.
Level 2: Systematic reviews of case-control or cohort studies, or case-control or cohort studies.
Level 3: Non-analytic studies, e.g. case reports, case series.
Level 4: Expert opinion (in the absence of any of the above). This includes the views and experiences of people with renal failure and their carers.

NICE subdivides level 1 and 2 into three sub-categories depending on the quality of the studies, a system which is most applicable to treatment interventions; we have not done this. Our recommendations about the diagnosis of kidney disease have largely been based on observational diagnostic accuracy (DA) studies in which the test under consideration is compared with a reference standard. NICE has suggested grading these from 1-4; 1-3 being primary studies or systematic reviews at different levels of quality of such diagnostic accuracy studies, with level 4 being similar to level 4 above. For simplification we have put diagnostic studies into the single overall NSF evidence grading framework above but as level 3 DA to distinguish them from non-analytic intervention studies, and without subdivision by quality.

Many of the recommendations in this document relate to aspects of the organisation, or system, of care, rather than to therapeutic decisions. There are major methodological problems associated with grading levels of evidence for this type of

recommendation, and for this reason many of our recommendations are level 4. **All recommendations made in this document are graded as level 4 evidence unless otherwise stated.**

Membership

The membership of the committee was as follows:

Dr C Tomson (Chair) (RCPL/RA)
Professor R Bilous (Professional Advisory Council, Diabetes UK)
Dr S Blades (RCGP)
Dr R Burden (co-opted, Renal Association)
Dr J Cunningham (co-opted, Renal Association)
Dr J Dennis (RCGP)
Mr D Gilbert (Observer, Department of Health for England)
Dr E Lamb (ACB) (from May 2003)
Dr D Newman (ACB) (until March 2003)
Mr G Nicholas (NKF)
Dr S O'Riordan (BGS)
Dr P Roderick (Public Health observer from External Reference Group for NSF for Renal Services)
Dr P Stevens (SDGHN)
Dr J Vora (Professional Advisory Council, Diabetes UK)

Dr David Newman died in March 2003. He had contributed enormously to British nephrology, with many original research contributions as well as active input into the UK Renal Registry and to this Committee.

Meetings were held on 17th Oct 2002, 17th Dec 2002, 5th Feb 2003, 12th May 2003, 2nd September 2003, 24th March 2004, 21st June 2004, 21st September 2004, 15th November 2004, and 18th March 2005.

Conflicts of interest

Each committee member was asked to record any potential conflicts of interest according to guidance published by the British Medical Journal [5].

Dr Tomson: member of advisory board of Genzyme UK between April 2002 and May 2004. Honoraria from Janssen Cilag, MSD, Bayer, Novartis, Baxter, Amgen, Genzyme, AstraZeneca, Pfizer, Roche. Current member of international steering committee of the Study of Heart and Renal Protection.
Dr Bilous: honoraria and some time member of advisory boards for Takeda, Glaxo Smith Kline, Astra Zeneca, Pfizer, Lilly, Roche, Novo Nordisk and Aventis.
Dr Blades: no conflicts of interest
Dr Burden: honoraria from Astra Zeneca, Fujisawa, Novartis, Novo Nordisk, and Roche
Dr Cunningham: Lecture fees, consultancy fees and research grant support from Amgen and Genzyme; Consultancy fees from Abbott; Lecture fees from Shire.
Dr Dennis: no conflicts of interest
Mr Gilbert (observer): no conflicts of interest
Dr Lamb: no conflicts of interest
Mr Nicholas: no conflicts of interest
Dr O'Riordan: no conflicts of interest
Dr Roderick: honoraria from Glaxo Smith Kline and from meetings sponsored by Orthobiotech and Amgen. Small scale research sponsored by Roche and Pfizer in the past.
Dr Stevens: member of advisory board of Hoffman La Roche from 2002 to date. Honoraria in the past from Ortho Biotech, Bayer, Amgen, Pfizer and Hoffman La Roche. Current research in the field of chronic kidney disease supported by funding from Roche UK.
Dr Vora: honoraria and some time member of advisory boards for Takeda, Glaxo Smith Kline, Astra Zeneca, Lilly, Novonordisk and Aventis

Consultation process

The final draft of the guidelines was circulated electronically to each of the bodies represented (RA, RCPL, RCGP, ACB, BGS, Diabetes UK, NKF) and to the Royal College of Pathologists; the British Hypertension Society; the Renal Information Group; the National Screening Committee; the Departments of Health of England, Northern Ireland, Scotland and Wales; the Scottish Intercollegiate Guidelines Network (SIGN); and the National Coordinating Centre for Chronic Conditions; with the request that they be given as wide a circulation as possible, and inviting comments to be sent direct to the Chairman. Notices drawing attention to the draft guidelines were placed on the websites of the participating organisations. Individuals who commented on earlier drafts and those known to have an interest in referral or management of CKD were also invited to comment directly. A final meeting/teleconference was then held to discuss this feedback and consider revision by consensus. The agreed version was submitted for endorsement by the Joint Specialty Committee on Renal Disease of the RCPL and the RA, and the RCGP.

The need for UK guidelines

Evidence-based guidelines for management of CKD have been developed in other countries, notably the USA [6], Australia [7], and Canada [8]; and European guidelines for haemodialysis include guidance on referral for patients with CKD [9]. Many of these guidelines are directly applicable to the UK. We have, for instance, adapted the North American K/DOQI terminology and classification for CKD, which has many advantages [10]. However, these countries have very different health-care systems. For instance, many Canadian nephrologists provide primary care for chronic dialysis patients [11]. International guidelines are being developed [12], but are not yet available. Because of the unique NHS health care system, with separate primary and secondary care services and a strong gate-keeper role for primary care, we believe that UK guidelines are necessary. It is also highly desirable that guidelines for management of patients with CKD do not conflict with existing UK guidelines (for instance, those issued by NICE, SIGN, and other specialist bodies such as the British Hypertension Society). These guidelines must address two questions:

1. How should people with CKD be identified in the NHS?
2. What is the optimum method of management and referral of patients with CKD?

In addressing the second question, we acknowledge that extra demands on time and resources will be welcomed neither by GPs nor by nephrologists. We have addressed this as much as possible from the patient's perspective, and assumed that patients will not wish to travel further than necessary. What can safely and reliably be done in primary care therefore ought to be done in that setting; any intervention that is better done in a hospital setting should be done there. This has relied on an analysis, based on UK practice, of what interventions and treatments require specialist training, and on when these interventions and treatments are likely to be necessary. We anticipate that the NHS

will develop new ways of working to deliver the best care to patients with CKD, building on existing initiatives for diabetes mellitus and Coronary Heart Disease (CHD).

Implementation

The committee is critically aware of the difficulty in translating guidelines into implementation, particularly when they refer to a condition that is seen by many as relatively rare and that is often thought of as requiring specialist care. We are also aware of the danger of disease-specific guidelines when applied to patients with multiple conditions [13]. Many patients with kidney disease have diabetes, hypertension, or cardiovascular disease. For this reason, these guidelines have been specifically developed to be consistent, wherever possible, with existing UK guidelines on the management of these conditions. Our recommendations are designed to be **integrated** into existing management systems, and in particular into the management of cardiovascular risk and diabetes in the NHS. Full implementation will require

- Measurement of relevant outcomes, such as late referral for dialysis and disparities in access to care.
- Revision of the electronic coding of CKD in the NHS, both in hospital episode statistics and in primary care computer systems.
- Standardisation and simplification of management of CKD.
- Incorporation of markers of quality care of CKD into the Quality and Outcomes Framework and other NHS quality and safety standards.
- Use of the chronic care model [14-16], with particular emphasis on decision support systems.

We have deliberately not addressed the question of which individuals should be responsible for the "care plan" for CKD outlined here. The Department of Health's publication 'National Standards, Local Action' sets out the 2005/2006 to 2007/2008 national priorities for the NHS, including a new national target for the development of personalised care plans for all people with long-term conditions. We anticipate that a variety of models will emerge, including conventional "shared care" between GPs and hospital-based nephrologists; geriatricians, diabetologists, and other secondary care physicians; specialist GPs working within primary care trusts [17 18]; specialist nurses working at General Practice or Primary Care Trust (PCT) level; and computer-based shared care, including prompting systems to trigger clinical actions [19]. It is clear that disease registers and an adequate IT infrastructure will be an essential pre-requisite for delivery of the care plan for CKD. In the longer term, the development of "community nephrologists" with roles similar to community diabetologists [20] may further help to break down unnecessary barriers to the delivery of comprehensive chronic disease management caused by the divide between primary and secondary care.

Implementation of these guidelines will carry cost implications, particularly for the community-based treatment of patients with anaemia, which is not covered by existing funding streams. It is important that the NHS develops a clear strategy for equitable funding of the management of CKD.

It is also clear that there is a pressing need for an educational package for GPs, hospital physicians and surgeons, and community-based nurses, together with clear and concise patient information, on the recognition and management of CKD.

Any system for implementation should be designed to reduce existing ethnic and socioeconomic differences in the burden and consequences of CKD [21-23].

The difference between "targets", "standards" and "intervention thresholds"

These recommendations include numerical values for biological variables – such as haemoglobin concentration, blood pressure, serum calcium, phosphate and parathyroid hormone concentration – that are directly influenced by treatment. In most guidelines published to date, these numerical values represent the desired outcome of treatment. These values are commonly referred to as "targets" or "standards". However, if clinicians use the same values as intervention thresholds (the point at which treatment should be changed), the inevitable outcome is that the results of treatment of a population of patients will be distributed around that numerical value. If the results are normally distributed, this means that half of all patients' values will be above and half below the "target". For instance, if the aim of treatment of anaemia complicating CKD is to ensure that a patient's haemoglobin concentration is above 11 g/dL, increasing the epoetin dosage only when the Hb level falls below 11 g/dL will guarantee that half of all patients so treated will have a Hb below 11 g/dL at any given time. To ensure that nearly all patients being treated for anaemia have a Hb > 11 g/dL at any given time, the treatment strategy should ensure that the mean Hb level should exceed 11 g/dL by 1.34 x the standard deviation of the distribution of Hb values. In clinical practice, this means that clinicians need to recognise the difference between intervention thresholds and targets - a distinction that is not recognised by existing clinical practice guidelines [24 25]. It would be preferable to specify target ranges, with an "ideal" value being in the middle of that range, but no previous guidelines have done this, and only a few of the RCTs whose results inform current practice did so – possibly accounting for the failure of many trials to achieve adequate separation between two groups when these groups are allocated to different "targets", the goals of clinical intervention.

In these recommendations, we have not been able to specify intervention thresholds for each variable, nor a strategy that will result in reliable achievement of the "target" value in the great majority of patients. "Target" values here mean the values that should be achieved in the great majority of patients.

Applicability

These guidelines are intended to apply to adults (aged >18y) of all ages. They are designed primarily for use in General Practice, although they are also applicable to many patients managed jointly with other disciplines, including diabetic medicine, urology, and geriatrics. They do not cover all eventualities, and **nothing in these guidelines should discourage clinicians in any specialty from seeking advice (e.g. by letter, email or telephone conversation)** from a nephrologist about the care of a specific patient. They are designed primarily to improve the care of, and outcome amongst, patients with CKD,

including those who eventually develop ERF and require RRT. We recognise that there might be other reasons for referral to a nephrologist, including acute renal failure (ARF) (see p 30), nephrotic syndrome, unexplained electrolyte or acid-base abnormalities, metabolic disorders, and refractory hypertension without other evidence of kidney disease, and have included limited guidance in some of these areas.

Revision

We hope NICE will develop guidelines for CKD management in future, replacing this document. Failing that, we plan revision in 2009.

RECOMMENDATIONS

Organisation of care

The patient should be placed at the centre of care and kept fully informed of all findings (including laboratory test results) and decisions relating to their kidney disease.

Organisations responsible for contracting for renal services should collect and publish data on the take-on rate for RRT (patients starting RRT per million population) and on the proportion of these referred to specialist renal services within 3 months and 12 months of initiation of RRT.

The NHS and the NPfIT should agree on a coding system for CKD, for use both in Hospital Episode Statistics and in primary care databases, which will allow identification and tracking of all patients with CKD, wherever they currently receive care.

Primary care software packages to categorise kidney function should be revised to allow recording of estimated GFR.

Electronic links should be established between nephrology services and all hospital pathology laboratories that might analyse samples from a service's catchment area, to allow automatic uploading of all measurements of serum creatinine concentration direct to the nephrology service database.

Management of patients with CKD, both in the community and in secondary care, should be integrated with management of that of diabetes, cardiovascular disease and other co-morbidities (when present), and of cardiovascular risk factors.

Identification of patients with chronic kidney disease

Classification of chronic kidney disease

We recommend adoption of a classification of CKD based on that proposed by the US K/DOQI group [6].

This classification is based on estimated GFR, and recognises five stages of kidney disease, as follows:

Stage 1: Normal GFR; GFR >90 mL/min/1.73 m^2 with other evidence of chronic kidney damage*
Stage 2: Mild impairment; GFR 60-89 mL/min/1.73 m^2 with other evidence of chronic kidney damage*
Stage 3: Moderate impairment; GFR 30-59 mL/min/1.73 m^2
Stage 4: Severe impairment: GFR 15-29 mL/min/1.73 m^2
Stage 5: Established renal failure (ERF): GFR < mL/min/1.73 m^2 or on dialysis (For CKD Stage 5 we have adopted the term established renal failure instead of end-stage renal disease or end-stage renal failure, as this is the term used in the National Service Framework for Renal Services).

* The "other evidence of chronic kidney damage" may be one of the following:

- Persistent microalbuminuria
- Persistent proteinuria
- Persistent haematuria (after exclusion of other causes, e.g. urological disease)
- Structural abnormalities of the kidneys demonstrated on ultrasound scanning or other radiological tests, e.g. polycystic kidney disease, reflux nephropathy
- Biopsy-proven chronic glomerulonephritis (most of these patients will have microalbumuria or proteinuria, and/or haematuria)

Patients found to have a GFR of 60-89 mL/min/1.73 m^2 without one of these markers should **not be considered to have CKD** and should not be subjected to further investigation unless there are additional reasons to do so.

Measurement of excretory kidney function

Method for measurement of excretory kidney function

Kidney function in patients with CKD should be assessed by formula-based estimation of GFR, preferably using the 4-variable Modification of Diet in Renal Disease (MDRD) [26] equation[a]: Level of evidence 3 DA

GFR (mL/min/1.73m^2) = 186 x {[serum creatinine (μmol/L)/88.4] $^{-1.154}$} x age (years) $^{-0.203}$

x 0.742 if female and x 1.21 if African American

All clinical biochemistry laboratories should report estimates of GFR alongside measurements of serum creatinine.[b] When estimated GFR exceeds 90 mL/min/1.73 m^2, it should be reported as '>90 mL/min/1.73 m^2'

Laboratories should communicate to their users (possibly using the laboratory report) the following information:

a) that GFR estimates between 60 and 89 mL/min/1.73 m^2 do not indicate CKD unless there is other laboratory/clinical evidence of disease

b) that the estimated GFR should be multiplied by 1.20 for African-Caribbean patients, unless ethnic origin was available to the laboratory and this correction has already been applied.

There is **no** need to collect 24 h urine samples to measure creatinine clearance in primary care. Level of evidence 3 DA

Within a renal network, which may or may not be co-terminous with a pathology network, laboratories should provide comparable creatinine results, ideally by the use of identical methodology. This should be audited by internal quality control procedures across the network and satisfactory performance in a national quality assessment scheme. Renal/pathology networks should agree a common approach to the estimation of GFR.

[a] *Until these recommendations are implemented, use of the prediction tables (Appendix 1) will allow estimation of GFR from age, gender, ethnic origin and serum creatinine. These tables give a "best case estimate" of GFR, using the lowest age and creatinine value in each cell for the calculation.*

[b] *As an alternative, software systems used in primary care could be amended to include one of these formulae and generate an estimate of GFR upon receipt of a creatinine result. However, unless this formula was used automatically every time a creatinine result was entered into a primary care system, this strategy would be less likely to ensure widespread use of estimated GFR, and would also not be applicable to measurements of serum creatinine in other settings, such as hospital outpatient clinics.*

Indications for measurement of serum creatinine concentration

Serum creatinine concentration should be measured, allowing calculation of estimated GFR, at initial assessment and then **at least annually** in all adult patients with:

Previously diagnosed CKD, including

- polycystic kidney disease
- reflux nephropathy
- biopsy-proven chronic glomerulonephritis
- persistent proteinuria
- urologically unexplained persistent haematuria

Conditions associated with a high risk of obstructive nephropathy, including

- known or suspected bladder outflow obstruction
- neurogenic bladder caused by spina bifida or spinal cord injury (N.B. calculated GFR may overestimate true GFR in these patients because of decreased muscle mass)
- urinary diversion surgery
- urinary stone disease due to primary hyperoxaluria, cystinuria, Dent's disease, infections (with struvite stones), anatomical abnormalities, or a stone episode rate of > 1/y

Conditions known to be associated with a high risk of silent development of CKD, including

- hypertension
- diabetes mellitus
- heart failure
- atherosclerotic coronary, cerebral, or peripheral vascular disease

Conditions requiring long-term treatment with potentially nephrotoxic drugs, including

- ACEIs and ARBs
- NSAIDs
- Lithium carbonate
- Mesalazine and other 5-aminosalicylic acid drugs
- Calcineurin inhibitors (Cyclosporin, Tacrolimus)

Multisystem diseases that may involve the kidney, including systemic lupus erythematosus (SLE), vasculitis, myeloma, rheumatoid arthritis

A first degree relative with stage 5 CKD

Frequency of measurement of serum creatinine concentration

Kidney function should be measured at least annually in the risk groups outlined above. (ARF must be excluded in all patients with newly detected abnormal kidney function – see page **xxxxx**)

Minimum frequency of measurement of kidney function according to estimated GFR:

Stage 1	GFR >90	annual
Stage 2	GFR 60-89	annual
Stage 3 (known to be stable[a])	GFR 30-59	annual
Stage 3 (newly diagnosed or progressive[b])	GFR 30-59	6-monthly
Stage 4 (known to be stable[a])	GFR 15-29	6-monthly
Stage 4 (newly diagnosed or progressive[b])	GFR 15-29	3-monthly
Stage 5	GFR < 15	3-monthly

[a]: stable kidney function defined as change of GFR of < 2 ml/min/1.73 m^2 over 6 months or more
[b]: progressive kidney damage defined as change of GFR of > 2ml/min/1.73 m^2 over 6 months or more

Kidney function should also be checked during intercurrent illness and peri-operatively in all patients with stage 2-5 CKD.

Interpretation of kidney function measurements in older people

The same criteria should be used for assessment of kidney function in older people as in younger people. "Age-adjusted" reference ranges for GFR are **not** recommended.

Level of evidence: 2

Interpretation of newly diagnosed GFR <60 ml/min/1.73 m^2

Because ARF requires emergency treatment, **all patients with newly detected abnormal kidney function should be assumed to have ARF until proven otherwise,** although the majority will turn out to have CKD.

In patients with newly diagnosed stage 3, 4 or 5 CKD, clinicians should obtain all previous measurements of serum creatinine and estimate GFR from them using the MDRD formula (or tables in Appendix 1) to assess the rate of progression to date.

A blood test showing a GFR < 60 ml/min/1.73 m^2 in a patient who is not **known** to have established CKD with abnormal GFR should prompt:

- Review of medication, particularly recent additions (e.g. diuretics, non-steroidal anti-inflammatory drugs (NSAIDs), any drug capable of causing interstitial nephritis)

- Clinical examination for bladder enlargement
- Urinalysis: haematuria and proteinuria suggest the possibility of glomerulonephritis, which may be rapidly progressive
- Clinical assessment, looking for underlying conditions such as sepsis, heart failure, hypovolaemia
- Repeat measurement of serum creatinine concentration within a maximum of 5 days.

Recognition of Acute Renal Failure (ARF)

Formula-based estimated GFR **should be interpreted with caution** in ARF, because the formulae rely on a stable serum creatinine concentration. Level of evidence 3 DA

ARF is a clinical syndrome characterised by a rapid decline in excretory function occurring over a period of hours or days. ARF should be suspected if there is a >1.5-fold rise in serum creatinine concentration, or a fall in estimated GFR of >25%, or oliguria (defined as urine output <0.5 ml/kg/h), in the context of an acute illness. If baseline serum creatinine concentration or GFR is not known, it should be assumed that baseline GFR was 75 ml/min/1.73 m^2.

All patients with suspected ARF should be referred to a nephrologist

Recognition of acute on chronic kidney disease

A fall in estimated GFR of >25% since the last measurement of kidney function in a patient with CKD should prompt a repeat measurement of kidney function, assessment as for ARF (see preceding section) and referral if the deterioration is confirmed.

Detection of proteinuria

Methods for detection and quantitation of proteinuria

There is no need to perform 24 h urine collections for the quantitation of proteinuria in primary care.
Level of evidence 3 DA

A positive dipstick test (1+ or greater) should result in a urine sample (preferably early morning) being sent to the laboratory for confirmation by measurement of the total protein:creatinine ratio or albumin:creatinine ratio (depending on local practice). Simultaneously, a midstream sample should be sent for culture to exclude urinary tract infection (UTI). Level of evidence 3 DA

Urine protein:creatinine ratios $\geq$45 mg/mmol or albumin:creatinine ratios of $\geq$30 mg/mmol should be considered as positive tests for proteinuria.

Positive tests for proteinuria should be followed by tests to exclude postural proteinuria, by analysis of an early morning urine sample, unless this has already been done.
Level of evidence 3 DA

Patients with two or more positive tests for proteinuria, preferably spaced by 1 to 2 weeks, should be diagnosed as having persistent proteinuria.

Indications for testing for proteinuria

Dipstick urinalysis for protein is indicated –

As part of the initial assessment of patients with

- Newly discovered GFR < 60 ml/min/1.73 m^2
- Newly discovered haematuria
- Newly diagnosed hypertension
- Unexplained oedema
- Suspected heart failure
- Suspected multisystem disease, e.g. SLE, systemic vasculitis
- Diabetes mellitus

As part of the annual monitoring of patients with

- Biopsy-proven glomerulonephritis
- Reflux nephropathy
- Asymptomatic microscopic haematuria
- Asymptomatic proteinuria
- Diabetes mellitus (patients with diabetes mellitus should also have annual testing for albumin:creatinine ratio if the dipstick urinalysis for protein is negative)

Monitoring for proteinuria is also required for patients receiving treatment with gold and penicillamine. Recommendations for frequency of monitoring are given in the British National Formulary: for penicillamine, before starting treatment and then every 1-2 weeks for the first 2 months, monthly thereafter, and in the week after any dose increase. For intramuscular gold, before each intramuscular injection. For oral gold, monthly.

We do not recommend screening of any other groups using dipstick urinalysis

Detection of "microalbuminuria"

Method for detection of microalbuminuria

Urine albumin should be measured using a laboratory method in an early morning (preferred) or random mid-stream urine sample and expressed as an albumin:creatinine ratio. If dipsticks designed to detect urinary albumin are used, positive tests should be followed by laboratory confirmation.
Level of evidence 3 DA

An albumin: creatinine ratio ≥2.5 mg/mmol in a male or ≥3.5 mg/mmol in a female is consistent with microalbuminuria. Patients demonstrating albumin:creatinine ratios above, or equal to, this cut-off should have urine samples sent to the laboratory on two further occasions (ideally within one to three months) for albumin estimation. Patients demonstrating persistently elevated albumin: creatinine ratios in one or both of these further samples have microalbuminuria.

The diagnosis of microalbuminuria cannot be made in the presence of an acute metabolic crisis. As far as is practicable, the best possible metabolic control of diabetes should be achieved before investigating patients for microalbuminuria. Patients should not be screened during intercurrent illness.

There is no need to exclude urinary tract infection before diagnosing microalbuminuria unless the patient has symptoms of urinary tract infection at the time the urine sample is taken.

It is important to consider other causes of increased albumin excretion, especially in the case of type 1 diabetes present for <5 years. In addition to the above caveats, these can include non-diabetic renal disease, menstrual contamination, vaginal discharge, uncontrolled hypertension, heart failure, intercurrent illness and strenuous exercise [27 28].

Indications for testing for microalbuminuria

Patients with diabetes mellitus who have persistent proteinuria (as defined above) do not require testing for microalbuminuria.

All other patients with diabetes mellitus should undergo, as a minimum, annual testing for microalbuminuria.

There is currently no proven role for screening for microalbuminuria in patients who do not have diabetes.

Detection of haematuria

Method for detection of haematuria

Dipstick urinalysis is the test of choice for confirmation of macroscopic haematuria and for detection of microscopic haematuria. Infection, trauma, and menstruation should be excluded before confirmation of haematuria. There is no need in routine clinical practice for confirmation of haematuria by microscopy of a midstream urine sample.
Level of evidence 3DA

Indications for testing for haematuria

Dipstick urinalysis for blood is indicated as part of the initial assessment of patients with

- Newly detected GFR < 60 ml/min/1.73 m^2
- Newly discovered proteinuria
- Suspected multisystem disease with possible renal involvement

"Screening" of unselected populations for haematuria is not recommended.

MANAGEMENT AND REFERRAL OF CKD

Management and referral of CKD: all stages

Methods should be developed that enable the recall, audit and implementation of a care plan for all adult patients with CKD, irrespective of age, that includes:

- Regular measurements of kidney function using serum creatinine concentration and estimated GFR, depending on the severity of kidney impairment (annual in stage 1 and 2 and stage 3 if known to be stable, 6-monthly for newly diagnosed or progressive stage 3).
- Advice on smoking cessation. Level of evidence 2
- Advice on weight loss if obese. Level of evidence 1
- Encouragement to take regular aerobic exercise.
- Advice to limit alcohol intake to no more than 3 units/day (men) or 2 units/day (women).
- Consideration of aspirin treatment for all patients with an estimated 10 year risk of cardiovascular disease of $\geq$ 20%, so long as blood pressure is < 150/90 mm Hg. Level of evidence 2
- Consideration of lipid-lowering drug therapy for all patients (see section below)
- Meticulous control of hypertension if present (see section below).

Referral to a nephrologist is not necessary in most patients with CKD. Indications for referral are given in subsequent sections, and summarised on p **xxxxx**

Lipid-lowering drug therapy in patients with kidney disease

Patients with established macrovascular disease should receive treatment for hyperlipidaemia according to the current Joint British Societies Guidelines [29].

Patients with diabetes and CKD but no established macrovascular disease should be offered lipid-lowering drug treatment according to the current Joint British Societies Guidelines [29], or entry into a trial of such treatment [30]. Level of evidence 2

Patients with CKD who do not have diabetes and who do not have established macrovascular disease should be offered the options of lipid-lowering treatment according to the current Joint British Societies Guidelines [29] if estimated 10 year risk of cardiovascular disease is $\geq$ 20%, OR entry into a trial of such treatment [30].

Antihypertensive therapy in patients with kidney disease

Blood pressure should be measured at least annually in all patients with CKD.

Blood pressure measurement should conform to British Hypertension Society standards [31].

All patients with hypertension should be offered life-style advice, including maintenance of normal body weight (body mass index 20-25 kg/m^2), reduction of dietary sodium intake to < 100 mmol/day, regular aerobic physical exercise, and limitation of alcohol intake to no more than 3 units/day for men and 2 units/day for women.

The threshold for initiation and subsequent adjustment of antihypertensive therapy should be 140/90 mm Hg for patients without proteinuria, and 130/80 for those with urine protein:creatinine ratio > 100 mg/mmol. Level of evidence 2

Antihypertensive therapy should be adjusted to achieve blood pressure < 130/80, or < 125/75 mm Hg for those with urine protein:creatinine ratio > 100 mg/mmol. Level of evidence 2

Many patients will need more than 2 drugs to achieve optimal control. ACEIs should be included in the regimen for all patients with proteinuria (urine protein:creatinine ratio > 100 mg/mmol), diabetic patients with microalbuminuria, and for patients with heart failure; ARBs may be used as alternatives to ACEIs. Level of evidence 1

Patients with refractory hypertension, defined as sustained BP > 150/90 despite combination therapy with drugs from 3 complementary classes, should be referred for specialist evaluation.

Patients with accelerated or malignant phase hypertension should be referred to hospital immediately. Those in whom there is suspicion of underlying kidney disease should be referred to a nephrologist.

Use of ACEIs and/or ARBs in patients with kidney disease and/or heart failure

“Dual blockade” with combinations of ACEIs and ARBs should usually only be initiated under specialist supervision.

Serum creatinine and potassium concentration should be checked prior to starting ACEIs and/or ARBs, within 2 weeks of starting, and within 2 weeks after subsequent increases in dose; during severe intercurrent illness, particularly if there is a risk of hypovolaemia; and at annual intervals thereafter, or more frequently if indicated, according to kidney function. A rise of serum creatinine concentration of >20 % or fall in estimated GFR of > 15% after initiation or dose increase should be followed by further measurements within 2 weeks; if deterioration in kidney function is confirmed, a specialist opinion should be

sought (not necessarily by formal referral) on whether the drug treatment should be stopped or the patient subjected to investigation for renal artery stenosis.

Hyperkalaemia (serum potassium >6.0 mmol/L) should result in stopping of concomitant nephrotoxic drugs (e.g. NSAIDs), reduction or cessation of potassium-retaining diuretics (amiloride, triamterene, spironolactone), and reduction of loop diuretic dosage if there is no sign of congestion. If hyperkalaemia persists, the ACEI or ARB should be stopped.

Management and referral of non-diabetic patients with proteinuria

Proteinuria should be quantified, urine tested for haematuria and GFR estimated.

Non-diabetic patients with early morning urine protein:creatinine ratio >100 mg/mmol (approximately 1 g/24 h or 2+) should be referred to a nephrology service for consideration of kidney biopsy.

Non-diabetic patients with early morning protein:creatinine ratio 45-100 mg/mmol *without haematuria* should be considered to have CKD and entered into a CKD disease management programme, with referral only if other criteria for referral are met.

Patients with both haematuria and proteinuria (protein:creatinine ratio >45 mg/mmol) should be referred to a nephrology service for investigation irrespective of GFR.

Management and referral of patients with diabetes mellitus and microalbuminuria or proteinuria

Patients with type 1 or 2 diabetes mellitus and microalbuminuria or proteinuria should be managed as follows:

- Continued efforts to achieve good glycaemic control (HbA1c 6.5-7.5%). Level of evidence 1
- Prescription of an ACEI (or ARB in the presence of a firm contraindication to ACEI), titrated to full dose, **irrespective of initial blood pressure**, followed by addition of other antihypertensive drugs in combination to reach the blood pressure goal if necessary. Level of evidence 1
- Measurement of urine albumin:creatinine ratio, serum creatinine concentration and estimated GFR at least once a year.
- Referral to a nephrologist as for patients without diabetes.
- Referral to a nephrologist if there is increasing proteinuria without diabetic retinopathy.
- Consideration of dietary protein restriction for patients with type 1 diabetes

- Co-ordination of care between the primary care team and specialist teams (including nephrology, ophthalmology, cardiology, and vascular surgery) at all stages of CKD including stage 5.

There should be a locally defined protocol for the referral of patients with diabetes mellitus and microalbuminuria to a specialist diabetes team.

Management and referral of patients with haematuria

Check for proteinuria and measure serum creatinine concentration in all patients.

- Macroscopic haematuria, with or without proteinuria: fast track urology referral; **refer to nephrology if initial investigations negative or if GFR < 60 mL/min/1.73 m^2.**
- Microscopic haematuria (dipstick **or** laboratory microscopy) without dipstick proteinuria:
  - Age >50 y: refer to urology
  - Age <50 y, or >50 y after exclusion of urological cancer: treat as CKD (includes measurement of serum creatinine concentration and estimated GFR, annual repeat if initially > 60 mL/min/1.73 m^2).
  - All ages: refer to nephrologist if GFR < 60 mL/min/1.73 m^2.
- Microscopic haematuria (dipstick **or** laboratory microscopy) with urine protein:creatinine ratio > 45 mg/mmol: refer to nephrology.

There is no need for laboratory confirmation of dipstick positive haematuria.
Level of evidence 3DA

Kidney biopsy in CKD

Patients with significant proteinuria (urine protein:creatinine > 100 mg/mmol) should be referred for consideration of kidney biopsy. Patients with lower levels of proteinuria (urine protein:creatinine ratio 45-100 mg/mmol) who also have haematuria should also be referred for kidney biopsy. Patients with isolated microscopic haematuria and no or minimal proteinuria do not require kidney biopsy but should be assumed to have CKD.

Investigation for atherosclerotic renal artery stenosis

Patients should be referred for further investigation for atherosclerotic renal artery stenosis (ARAS), with a view to intervention, in the following situations:

- refractory hypertension (inadequate control, defined as BP > 150/90 mm Hg despite 3 antihypertensive agents). Level of evidence 3 DA
- recurrent episodes of pulmonary oedema despite normal left ventricular function on echocardiography (so-called "flash pulmonary oedema", usually associated with hypertension). Level of evidence 3 DA

- rising serum creatinine concentration (rise of >=20% or fall of GFR of >15% over 12 months) with a high clinical suspicion of widespread atherosclerosis. Level of evidence 3 DA
- a rise in serum creatinine concentration of >= 20% or fall of GFR of >15% during the first 2 months after initiation of ACEI or ARB treatment. Level of evidence 3 DA
- unexplained hypokalaemia with hypertension.

Management and referral of stage 3 CKD

All patients with stage 3 CKD should undergo

- Annual measurement of haemoglobin, potassium, calcium and phosphate
- Treatment of anaemia with intravenous iron ± erythropoiesis stimulating agents (ESAs), after exclusion of other causes of anaemia. The threshold Hb concentration for initiation of an ESA should be 11 g/dL, and treatment adjusted to maintain Hb between 11 and 12 g/dL. The patient's functional needs and level of desired physical activity should be taken into account when deciding what level of Hb to aim for. Lower levels of Hb should be accepted if the Hb fails to rise despite adequate iron replacement and a weekly dose of ESA equivalent to 300 iu/kg/week of epoietin alfa or beta. Level of evidence 1
- Measurement of parathyroid hormone (PTH) concentration when stage 3 CKD is first diagnosed.
- Treatment of disorders of calcium, phosphate, or PTH concentrations according to the guidance set out below.
- Renal ultrasonography in patients with lower urinary tract symptoms or refractory hypertension or unexplained progressive fall in GFR.
- Immunisation against influenza and pneumococcus.
- Regular review of all prescribed medication, to ensure appropriate dose adjustments and the avoidance, wherever possible, of nephrotoxic drugs, including NSAIDs.

Whether this disease management programme is undertaken by GPs, nephrologists, specialist nurses, GPs with a specialist interest, or other health-care professionals should be decided locally, and if necessary on a case-by-case basis. Since much of the management of such patients is that of risk factors for cardiovascular disease, and since CKD is a powerful risk marker for cardiovascular disease, we recommend that all patients with CKD be managed in primary care.

There are important options for computerised decision support, including the "virtual nephrologist" model, which requires computerised transfer of information, including laboratory measurements, between the GP surgery, the local laboratory, and the nephrology service; and division of responsibility for acting on such results clearly identified in the care plan.

Renal osteodystrophy: assessment/management in CKD

Antiresorptive treatment (e.g. with bisphosphonates) for suspected or proven reduced bone mineral density should not be commenced in patients with CKD until treatable disorders of calcium, phosphate, PTH and serum 25-hydroxyvitamin D metabolism have been sought and treated.

No measurements of calcium, phosphate, or PTH are required in stage 1 or 2 CKD unless the patient has suspected or proven reduced bone mineral density.

In stage 3 CKD, serum corrected calcium and phosphate should be measured every 12 months. Abnormal values should be confirmed on a repeat fasting sample taken without a tourniquet. Patients with confirmed abnormalities of serum corrected calcium or phosphate should be referred to a nephrologist.

Many laboratories can measure PTH in plasma obtained from a blood sample anticoagulated with ethylenediaminetetraacetic acid (EDTA), in which it is stable. This facilitates the submission of samples from primary care to the laboratory without requiring special sample handling precautions.

In stage 3 CKD, plasma or serum PTH should be checked when the diagnosis of CKD stage 3 is first made. If the PTH is < 70 ng/L, no further checking is required unless the patient progresses to stage 4 CKD [a].

If the PTH is > 70 ng/L, serum 25-hydroxyvitamin D should be checked. If the serum 25-hydroxyvitamin D is low (<80 nmol/L, 30 μg/L), therapy should be commenced with ergocalciferol or colecalciferol 800 units/day in a preparation that contains calcium carbonate or calcium lactate but not calcium phosphate; or colecalciferol 10,000 units monthly by intramuscular injection. PTH should then be rechecked after 3 months of replacement therapy. There is no need to repeat the measurement of serum 25-hydroxyvitamin D unless non-adherence or malabsorption is suspected. Vitamin D therapy should be continued long-term unless the clinical situation changes.

If the PTH is > 70 ng/L despite a normal serum 25-hydroxyvitamin D or treatment with ergocalciferol or colecalciferol, the patient should be referred to a nephrologist for specialist advice on management of hyperparathyroidism

[a] *To convert PTH (ng/L) to SI units (pmol/L) multiply by 0.11*

Management and referral of stage 4-5 CKD

Care of **all** patients with stage 4 or 5 CKD should be formally discussed with a nephrologist once this degree of CKD is identified and the appropriate investigations obtained, **even if** it is not anticipated that RRT will be appropriate. Exceptions may include:

- patients in whom stage 4 or 5 CKD supervenes as part of another terminal illness
- patients with stable kidney function in whom all the appropriate investigations and management interventions have been performed and who have an agreed and understood care pathway
- patients in whom further investigation and management is clearly inappropriate

Management of patients with stage 4 or 5 CKD should continue to be shared with the GP and/or with other healthcare professionals, agreed on a case-by-case basis, and a care plan developed. Management should include, in **addition to all interventions listed for stage 3 CKD**:

- 3-monthly measurements of serum creatinine concentration and estimated GFR, haemoglobin, calcium, phosphate, potassium, bicarbonate, and PTH concentrations
- Dietary assessment
- Treatment of anaemia with intravenous iron ± epoietins (as for stage 3 CKD)
- Immunisation against hepatitis B
- Treatment of hyperparathyroidism and phosphate retention
- Correction of acidosis Level of evidence 2
- Counselling and education about the options for treatment, including (when appropriate) home or hospital haemodialysis, peritoneal dialysis, kidney transplantation, and conservative (non-dialytic) management.
- Pre-emptive kidney transplantation wherever possible
- Timely provision of vascular access in all patients for whom haemodialysis is planned Level of evidence 2
- Timely placement of a peritoneal dialysis catheter in patients for whom peritoneal dialysis is planned Level of evidence2
- Agreement in advance for an active conservative/palliative care treatment plan if the patient chooses not to undergo renal replacement therapy; conservative treatment may still include drug treatment of hypertension, anaemia, phosphate retention, hyperparathyroidism and acidosis; palliative care teams may also be involved

Urgency of referral to a nephrology service

All nephrology services should offer 24 h telephone access to qualified advice.

Referrals should be made as follows:

Immediate

- Suspected ARF.
- ARF superimposed on CKD.
- Newly detected ERF (GFR < 15 mL/min/1.73 m^2).
- Accelerated or malignant phase hypertension with suspicion of underlying kidney disease (or if there is no specialist hypertension service available locally).
- Hyperkalaemia, serum potassium >7.0 mmol/L.

Urgent outpatient

- Nephrotic syndrome.
- Newly detected stage 4 (unless known to be stable) or stable stage 5 CKD.
- Multisystem disease (e.g. SLE, systemic vasculitis) with evidence of kidney disease.
- Hyperkalaemia, serum potassium 6.0-7.0 mmol/L (after exclusion of artefactual and treatable causes).

Routine outpatient

- Refractory hypertension (defined as sustained BP >150/90 mm Hg despite combination therapy with 3 drugs from complementary classes).
- Acute deterioration in kidney function (defined as a fall of GFR of >20% or rise of serum creatinine concentration of >30% from baseline) associated with use of ACEIs or ARBs.
- Proteinuria (urine protein >100 mg/mmol) without nephrotic syndrome.
- Proteinuria with haematuria.
- Diabetes with increasing proteinuria but without diabetic retinopathy.
- Stage 3 CKD with haematuria.
- Urologically unexplained macroscopic haematuria (with or without proteinuria).
- Recurrent unexplained pulmonary oedema with clinical suspicion of ARAS.
- Falling GFR (>15% fall over 12 months) with clinical suspicion of ARAS.
- PTH >70 ng/L (7.7 pmol/L) after exclusion or treatment of vitamin D deficiency.
- Stable stage 4 CKD if referred.

GP care +/- "virtual" nephrology support/advice

- Isolated microscopic haematuria (after negative urological evaluation where appropriate).
- Isolated proteinuria with urine protein:creatinine ratio < 100 mg/mmol.

- Known or suspected polycystic kidney disease with GFR > 60 ml/min/1.73 m^2.
- Known reflux nephropathy in stage 1-3 without the above.
- All other stage 1-2 CKD.
- Stable stage 3 or 4 CKD with no other indication for referral.

Information required for referral or letter of advice

The minimum data set for referral of a patient with CKD to a nephrologist should include:

- A tabular list of the dates and results of all previous measurements of serum creatinine concentration (unless or until this can be downloaded automatically to the nephrology service database)
- A full medical history including current drug treatment (and previous drug treatment, if any possibility of drug-associated kidney disease/dysfunction)
- Blood pressure
- The results of dipstick urinalysis plus urine protein:creatinine ratio if there is more than trace proteinuria on dipstick

A policy on whether all patients referred should have an ultrasound scan prior to the appointment should be decided locally

SUPPORTING EVIDENCE

Remit

Recommendations in this document are limited to adults with kidney disease, defined for this purpose as aged > 18y. The issues relating to the care of infants and children with kidney disease are very different to those relating to adults, as is the organisation of services for these patients.

Organisation of care

Patient-centred care

Standard One of the NSF for Renal Services part 1 [32] stated, "All children, young people and adults with chronic kidney disease are to have access to information that enables them with their carers to make informed decisions and encourages partnership in decision-making, with an agreed care plan that supports them in managing their condition to achieve the best possible quality of life." Our recommendation was based on sound evidence that, for patients with long-term chronic conditions, involving patients in their own care results in better health outcomes [33-35].

Variations in take-on rate for RRT

Geographical variations in the incidence rate of RRT – the numbers of new patients taken on to treatment per million population – reflect both variations in the actual incidence of ERF and variations in provision of appropriate treatment. Actual incidence varies with age, ethnic origin, and other risk factors including socioeconomic status. Variations in provision of appropriate treatment are a marker of inequity and must be addressed [36-38].

The importance of early referral

There is a growing literature on the negative effect of "late referral" of patients with advanced impairment of kidney function [39-76]. Observational studies have uniformly shown increased morbidity, hospital stay, and cost of treatment in patients starting long-term dialysis who were referred late (usually defined as within 3 or 4 months of needing dialysis) compared to those referred to a dialysis unit earlier, and three recent studies have reported that late referral to a nephrologist was an independent risk factor for early death on dialysis [72 74 77]. Failure to detect kidney disease and failure of timely referral are common reasons for successful lawsuits in the USA [78].

The Renal Association UK Renal Registry reported that of patients starting RRT in 2002, 30% were referred to a nephrologist less than 3 months before starting RRT, and 20% less than 1 month before starting RRT; patients referred late tended to be older. While patients with diabetic nephropathy were less likely to be referred late compared to patients with other types of CKD, even in this group 23% were referred late [79].

Several factors contribute to increased morbidity amongst late referred patients, including failure to correct anaemia, bone disease, hypertension, and acidosis, together with often being sicker at presentation than those referred earlier, but the dominant factor is lack of sufficient time to prepare the patient for dialysis, particularly if this requires access to the circulation for haemodialysis. It is widely recognised that it may take 6 months or even longer to establish satisfactory vascular access for haemodialysis; during this time the patient is also educated and counselled on the forthcoming need for dialysis, a process which is likely to facilitate an "easy start" when dialysis does commence. Late referred patients are much more likely to start dialysis with a temporary or semi-permanent jugular catheter than with an arteriovenous fistula [46 53 58], and use of such access is associated with a greatly increased morbidity, particularly from infection, and with a higher failure rate requiring re-admission to hospital [63 80]. Late referred patients are less likely to become established on peritoneal dialysis [81] and have no chance of being considered for pre-emptive transplantation.

A recent study in the South West Region, using a case note review including those from referring hospitals and the primary care records, showed that approximately 50% of late referrals were avoidable, the remainder being "unavoidable" – commonly patients presenting in established renal failure having had little or no recent contact with doctors [69].

A common conclusion of many studies is that the problem should be addressed by increased awareness – amongst geriatricians, urologists, diabetologists, general practitioners, and others - of the need for early referral of all patients with CKD. However, there are no nationally agreed guidelines relating to referral of such patients and intended for use by these professional groups. The Renal Association/Royal College of Physicians of London have proposed in their standards document that all patients with a serum creatinine of > 150 μmol/L should be referred to a nephrologist [2], but these guidelines were intended primarily for an audience of nephrologists and have not been published in a peer-reviewed journal. They are available electronically on the RA website [2], but this is a website visited primarily by UK nephrologists; their existence is not mentioned by existing compendia of guidelines (e.g. http://www.eguidelines.co.uk/ or http://rms.nelh.nhs.uk/guidelinesfinder/) or decision support systems (e.g. www.prodigy.nhs.uk), and they are therefore unlikely to reach most of those currently caring for such patients. Similar recommendations have been made by a European Consensus Group [9], the British Hypertension Society [31], a Canadian Consensus Group [8], a US Consensus Group [82], and in the NICE guidelines for management of kidney disease in type 2 diabetes mellitus [83]. All of these referral criteria use serum creatinine concentration, despite the fact that the relationship between this measurement and overall kidney function is highly variable, as discussed below.

The frequency of chronic kidney disease (CKD) in the population

Mild to moderate CKD is very common in unselected populations [21 43 84-95]; some surveys have suggested that as many as 16% of the adult population have some marker of kidney disease [93]. CKD is largely a disease of the elderly; there is also a higher rate of CKD in many ethnic minority groups [23]. Clearly, these figures depend on the precise definition of CKD, but many of these studies used the widely accepted K/DOQI

definition, discussed below. Only a small fraction of these patients are likely ever to develop CKD severe enough to require RRT, but evidence from the UK suggests that many remain untreated for complications of CKD and that non-referral even of advanced CKD is common, particularly amongst the elderly [94]. Recent work suggests that the prevalence of CKD in the UK is very similar to that suggested by the third National Health and Nutrition Examination Survey (NHANES III) in the USA. Data obtained from 112,215 people in 12 GP practices in Greater Manchester, Kent and Surrey indicated that 4.9% of the population had an estimated GFR of less than 60 mL/min/1.73m^2 [96].

We do not believe that it is either possible or practicable for all patients in the UK with CKD to be seen and managed by a consultant nephrologist. There are currently 161 whole time equivalent consultant nephrologists in England for a population of just over 50 million [97]. If 11 % of the UK population have CKD as defined by K/DOQI, as in the USA [92], the average GP Principal's list of 2000 adults would include around 220 patients with CKD. Each nephrologist would have to be responsible for 34,000 patients. To see each of these patients once a year would require each consultant to see 148 outpatients each working day! The great majority of these patients would have mild or moderate CKD, would have no complications that could not be managed perfectly well in primary care, and are not destined ever to reach ERF. However, it is crucially important that patients with progressive CKD are identified and referred to nephrologists in time to avoid the deleterious consequences of late referral. It is also clear that there is a need for increasing numbers of consultant nephrologists in the UK to provide high-quality care to the increasing numbers of patients with CKD who will be recognised if or when UK laboratories move to formula-based estimation of GFR when reporting serum creatinine concentration [98]; demand is also set to increase further due to the effects of increasing rates of type 2 diabetes mellitus, and the ageing of the population (and specially of ethnic minority populations) and improved survival of people with vascular disease.

Information technology requirements

Our recommendations will ensure a uniform approach to the identification and management of CKD across the UK.

Integration of management of CKD with that of cardiovascular disease

CKD may be more important as a risk marker for cardiovascular and cerebrovascular disease than as a predictor of progressive kidney failure [88 99-113]. Markers of CKD are also highly predictive of risk of death, cardiovascular events, and hospitalisation [114], outcome after coronary revascularisation [115-117], survival after myocardial infarction [106 118], and revascularisation for peripheral vascular disease [119]. Proteinuria, including microalbuminuria in non-diabetic patients, is a powerful cardiovascular risk marker even if GFR is normal [120-127].

There is also mounting evidence that established treatable cardiovascular risk factors, including smoking [128-136], hypertension [137-144] and dyslipidaemia [145-147], are also

risk markers for progression of many forms of kidney disease [148 149]. Treatment of these risk factors may therefore be doubly beneficial.

Identification of patients with chronic kidney disease

There are few specific symptoms or signs which draw attention to CKD and as a result people are often unaware that there is something wrong until they are at an advanced stage which is one of the main reasons that they often present late. Another reason for late presentation is lack of familiarity of medical staff with the significance of kidney function test results and the tendency to underestimate the severity of renal disease when relying on serum creatinine; this is one area which should be helped by the adoption of formula-based GFR estimation.

In some people a family history as in polycystic kidney disease draws attention to the need to be tested. Others present with one or other of the classical clinical problems such as nephrotic syndrome or haematuria, but they are a minority. In many instances the kidney disease comes to light as the result of routine monitoring of serum creatinine because of hypertension or diabetes, or from urine testing at well person clinics or for occupational or life insurance purposes, as well as during "routine" investigation of illness. Nevertheless, the opportunity to identify CKD during routine management of hypertension has often been overlooked in the past [54 69]; the majority of patients with stage 3 CKD have hypertension[150].

Classification of CKD using estimated GFR

The reasons for using estimated GFR rather than serum creatinine alone in assessing the severity of impairment of kidney excretory function are set out below and discussed in detail in the K/DOQI guidelines [6]. We are aware that shortcomings of this classification and possible alternative approaches have been discussed [151]. A potential disadvantage of a classification based on GFR is that it downplays the importance of other aspects of CKD, e.g. blood pressure, proteinuria. However, the level of GFR is much better at predicting complications of impaired kidney function than serum creatinine alone.

The common complications of the different stages of kidney disease are set out in Table 1

Stage 1 (GFR > 90 mL/min/1.73 m^2 with other evidence of kidney damage)	Hypertension more frequent than amongst patients without CKD
Stage 2 (GFR 60-89 mL/min/1.73 m^2) with other evidence of kidney damage	Hypertension frequent Mild elevation of parathyroid hormone
Stage 3 (GFR 30-59 mL/min/1.73 m^2)	Hypertension common Decreased calcium absorption Reduced phosphate excretion More marked elevation of parathyroid hormone Altered lipoprotein metabolism Reduced spontaneous protein intake Renal anaemia Left ventricular hypertrophy
Stage 4 (GFR 15-29 mL/min/1.73 m^2)	As above but more pronounced plus - Metabolic acidosis Hyperkalaemia Decreased libido
Stage 5 (GFR 0-14 mL/min/1.73 m^2)	All the above (with greater severity) plus - Salt and water retention causing apparent heart failure Anorexia Vomiting Pruritus (itching without skin disease)

Table 1. Stages of CKD

Measurement of excretory kidney function

Method for assessment of excretory kidney function

Serum creatinine concentration is determined not only by the rate of renal excretion of creatinine but also by the rate of production, which is dependent on muscle mass. Thus serum creatinine may be above the upper limit of normal in patients with normal kidney function but higher than average muscle mass (e.g. young males), but may remain within the reference range despite marked renal impairment in patients with low muscle mass (e.g. older females). Equations that take into account some or all of age, gender, racial origin, and body weight in addition to serum creatinine allow approximate prediction of GFR, have been validated against isotopic measurement [152-157] and improve recognition of CKD [98]. It is recognised that many clinical guidelines, for example those produced by NICE on type 1 and type 2 diabetes and hypertension [83 158-160], recommend assessment of kidney function using serum creatinine. The current guidelines are not in conflict with this, but allow more sensitive recognition of kidney disease using estimated GFR.

Although many formulae have been developed to facilitate estimation of GFR, the most widely used have been those proposed by Cockcroft and Gault [152] and, more recently, the MDRD equations proposed by Levey et al [26 156]. There are relative advantages and disadvantages of these formulae: the Cockcroft and Gault formula was initially validated against creatinine clearance whereas the MDRD formulae were validated against an iothalamate clearance estimate of GFR normalised to body surface area (BSA). The MDRD formulae have been validated in Black-Americans and there is no requirement for patient weight. Conversely, the calculations are more complex than the Cockcroft and Gault equation, requiring power calculations. There is evidence that the two formulae give different estimates of the prevalence of the various stages of CKD [91 92]. Neither of these formulae is completely accurate and their performance compared to gold standard methods of assessment varies depending on the degree of kidney dysfunction. Both formulae were initially validated amongst patients known to have kidney disease, rather than amongst patients with normal kidney function. Recently, two large studies in American [161] and European [162] populations have shown benefits in terms of accuracy and bias of the 4-variable MDRD formula compared to the Cockcroft and Gault formula in patients with CKD; however, both these studies and others [163] have shown significant underestimation of GFR using the 4-variable MDRD formula in patients with higher levels of kidney function. In terms of accuracy and bias there is probably little to choose between the MDRD and Cockcroft and Gault formulae [154 164 165] and there are no strong theoretical grounds for recommending one formula in preference to the other. However, we have chosen to recommend that the 4-variable MDRD formula is used in preference to the Cockcroft and Gault formula. This predominantly reflects the advantage that knowledge of patient weight is not required to enable calculation of GFR and hence implementation is likely to be facilitated. This will ensure a uniform approach across the UK and is consistent with North American recommendations [166].

Neither formula can overcome the methodological problems related to the analysis of serum creatinine, which include significant inter-laboratory differences [157 167 168]. These problems are particularly significant at concentrations within, or just above, the

reference range and can have very significant effects on estimates of GFR at both the individual [161 169] and population level. Although we are aware of international attempts at standardisation, it is likely that these may take several years to materialise and, even then, problems of differential reaction from non-creatinine chromogens may persist. Alternative approaches, for example using isotope dilution mass spectrometry methods, may be feasible in the longer term. In the interim, within a renal network, which may or may not be co-terminous with a pathology network, laboratories should be able to provide comparable creatinine results, ideally by the use of identical methodology. Commutability should be audited by internal quality control procedures within the network and satisfactory performance in a national external quality assessment scheme.

GFR varies with body size, usually expressed as BSA, which can be estimated from height and weight [170]. It has become customary to correct GFR for BSA, typically calculated using the formula proposed by Du Bois and Du Bois [170]. However, there is no good evidence to suggest that estimates of kidney function should be normalised for BSA [155], and this manoeuvre may cause underestimation of GFR in obese subjects [171]. Nevertheless, other guidelines place emphasis on the use of BSA-corrected GFR [7 9]. The MDRD formula gives an estimate of GFR normalised for BSA.

Whether patients whose estimated GFR is 60-89 mL/min/1.73 m^2 but who have no other evidence of CKD should be considered as having CKD simply because of a moderate reduction in GFR is controversial. This question is discussed at length in the K/DOQI guidelines [6]. The inter-laboratory differences in creatinine measurement discussed above have their greatest impact in the near-normal range and lead to great inaccuracies at this level. It is therefore important that laboratory reports emphasise that estimated GFRs between 60 and 89 mL/min/1.73 m^2 are only consistent with CKD in the presence of other laboratory/clinical evidence of renal disease. There is a danger of "labelling" many people who feel completely well as having CKD [151]. However, in particular risk groups there is some evidence that reduced GFR, irrespective of other evidence of CKD, is associated with poorer prognosis compared to completely normal kidney function [113 118 172-175]. Clinicians will have to make individualised decisions in this situation. As a consequence of the poor inter-laboratory performance of creatinine assays at normal or near-normal levels and the lack of validation of the 4-variable MDRD formula at normal levels of GFR, we recommend that when estimated GFR exceeds 90 mL/min/1.73 m^2, it should be reported as '>90 mL/min/1.73 m^2'. It seems reasonable to conclude that, if estimated GFR is >90 mL/min/1.73 m^2, excretory kidney function is probably normal. Changes in serum creatinine, and thus in calculated GFR, are still extremely valuable in tracking changes in kidney function within individuals even when serum creatinine concentration is within the "normal range" [176].

African-Americans have relatively high serum creatinine concentrations compared to GFR-matched Caucasians. Consequently, the 4-variable MDRD equation includes a correction for ethnic origin. Implementation of this recommendation requires that information on ethnic origin is reliably transmitted to the laboratory with the request for creatinine measurement. To aid implementation, an assumption of Caucasian ethnicity could be made at the laboratory, provided that the result is interpreted in relation to ethnic origin. These guidelines make the assumption that the correction factor of 1.21 used in the MDRD equation for African-Americans is equally valid for British African-Caribbeans, but there is no evidence to confirm or refute this. Similarly, there is limited

published evidence on the applicability of the MDRD formula to Indo-Asians or other ethnic groups. In some areas of the UK it may be reasonable for laboratories to assume Caucasian ethnicity due to the low prevalence of other ethnic groups in the population. Further, if laboratories do use the MDRD formula without knowledge of ethnic origin, it is important that they communicate to their users that GFR estimates should be revised upwards by approximately 20% in African-Caribbean patients.

Historically, creatinine clearance has been used as an estimate of GFR. However, they are not equivalent: as kidney function declines, creatinine clearance becomes significantly higher than GFR due to preserved tubular secretion of creatinine, and may be twice true GFR when GFR is severely reduced. Estimation of GFR from 24 h urinary creatinine clearance has been shown to be less reliable than use of a formula-based estimation: this is primarily due to the difficulty of ensuring an accurately timed and complete 24 h urine collection [153]. Collection of 24 h urine samples may still have a role in the assessment of residual kidney function in stage 4 and 5 CKD.

There are alternatives to the use of serum creatinine in the assessment of kidney excretory function that are less dependent on variations in muscle mass. The most promising of these is serum cystatin C concentration. This substance is produced at a constant rate by all nucleated cells and eliminated solely by glomerular filtration. Concentrations become increased at milder degrees of kidney dysfunction than for serum creatinine, and the test may therefore be more useful in the detection of mild to moderate CKD [177-185], including amongst older people [186] and those with spinal injury [187]. However, the use of this test awaits further validation in the routine clinical setting.

Despite these major problems, the use of estimates of GFR will greatly improve the recognition [91 188] and subsequent management of patients with CKD compared with serum creatinine alone. Implementation of this recommendation is likely to lead to a marked increase in the numbers of patients recognised to have CKD. The purpose of these guidelines is to aid management of these patients, many of whom do not necessarily require referral to a nephrologist.

Indications for measurement of serum creatinine concentration

All the following patient groups are at increased risk of developing CKD. Early identification of chronic kidney impairment is important as it can prompt changes in prescribing, greater attention to hypertension control, and introduction of agents to slow progression.

Polycystic kidney disease; reflux nephropathy; biopsy-proven chronic glomerulonephritis; persistent proteinuria; urologically unexplained haematuria.

Regular measurement of kidney function is necessary in patients at risk of progressive kidney disease, because of the adverse effects of late presentation and late referral discussed above and the asymptomatic nature of stages 1-3 of CKD. Each of these diseases is potentially progressive. Progression is often predicted by the presence of proteinuria and hypertension, but not always: proteinuria is uncommon even in progressive polycystic kidney disease. Not surprisingly, abnormal kidney function as

detected by an abnormal serum creatinine concentration is a powerful risk marker for the later development of ERF [189].

Both persistent proteinuria and urologically unexplained haematuria should be treated as markers of CKD. As discussed below, proteinuria is a powerful marker of the presence of CKD and of the risk of progression. The diagnostic approach to haematuria is outlined below (section on CKD management). Asymptomatic microscopic haematuria is common, but kidney biopsy shows glomerular abnormalities in up to 50% of such patients in whom urological disease has been excluded [190]. However, in this situation the results of kidney biopsy do not change management, other than mandating follow-up for the subsequent appearance of markers of progressive kidney damage, which may take years to appear [191]. Because of the risks of kidney biopsy, it is safer to assume that such patients have chronic glomerulonephritis and organise annual follow-up based on that assumption.

Known or suspected bladder outflow obstruction

Bladder outflow obstruction causing high pressure chronic retention is an important cause of acute on chronic kidney failure [192] and of late presentation with ERF [193 194]. This may also occur as a result of recurrent obstruction after a previous transurethral resection of prostate [194]. Research on the long-term outcome of kidney impairment after relief of prostatic bladder outflow obstruction is limited, but there is clear evidence that recovery is often incomplete [195 196]. NICE recommends measurement of serum creatinine concentration as part of the initial assessment of all men with lower urinary tract symptoms suggestive of bladder outflow obstruction, immediate referral of all patients with acute renal failure, and referral of all patients with microscopic haematuria or CKD [197]. In contrast, the American Urological Association (AUA) recently revised its guidance on the management of benign prostatic hypertrophy, stating that measurement of serum creatinine concentration was not necessary [198]. We disagree with this conclusion, because enrolment in the recent trials of finasteride and alpha-blockers (on which the AUA based their recommendations) may have excluded the patients at highest risk of chronic retention – possibly because the symptoms of high pressure chronic retention (typically nocturnal enuresis) are not typical of the lower urinary tract symptoms more commonly associated with bladder outflow obstruction [199 200]. While awaiting further evidence, we therefore recommend an annual measurement of serum creatinine concentration in all patients with lower urinary tract symptoms, whatever treatment they undergo.

Neurogenic bladder

Patients with neurogenic bladder and other causes of abnormal bladder voiding are at high risk of progressive kidney damage [201-209]. This can be prevented by early detection and appropriate management, which may include regular intermittent self-catheterisation and surgical bladder augmentation. Due to muscle atrophy, serum creatinine concentration (and consequently estimated GFR) is a poor marker of kidney function in patients with spinal cord injury. In this situation, the use of alternative markers that are unaffected by muscle mass, such as serum cystatin C, may be of particular benefit [187].

Urinary diversion surgery

Patients who have undergone urinary diversion surgery, either for the management of neurogenic bladder or for malignancy, also have a high risk of

progressive kidney damage, which may go unrecognised unless regular measurements of kidney function are performed [210-222].

Kidney stones

Most patients with kidney stones have a very low risk of developing kidney failure as a result of stone disease or its complications. However, hereditary disorders causing recurrent stone formation, infection-related stones, and stone disease complicating anatomic or functional urinary tract disorders or neurogenic bladder carry a higher risk of kidney failure [223].

Hypertension

For the purposes of these guidelines, hypertension should be defined as in the British Hypertension Society guidelines: a clinic blood pressure of > 140 mm Hg systolic, > 90 mm Hg diastolic, or both [31]. Assessment of kidney function in hypertension is extremely important, as a high proportion of CKD in population studies is found in those with pre-existing hypertension [92]. Hypertension, particularly when severe, may be a primary cause of CKD, but as shown above it is a very common secondary effect of CKD.

Whether all patients with hypertension require annual measurement of kidney function is debated, with significant discrepancies between existing guidance. Many patients with hypertension will require annual creatinine concentration measurements anyway, as a result of treatment with diuretics, ACEIs, or ARBs.

The NSF for CHD [224] recommends measurement of kidney function and urinalysis in the initial assessment of patients with raised blood pressure (p25), and recommends that measurement of kidney function should be repeated annually for all patients on diuretics or ACEIs and every five years in all patients with hypertension (p27). The NICE guidelines on the treatment of hypertension in primary care [158] recommend an annual reassessment of cardiovascular risk, and indicate that cardiovascular risk assessment should include dipstick urinalysis and measurement of serum creatinine concentration as well as lipid profile, implying that all patients on treatment for hypertension should have an annual measurement of serum creatinine concentration. The 4th British Hypertension Society guidelines suggest urinalysis and measurement of serum creatinine concentration as part of the initial assessment of patients with newly diagnosed hypertension, but give no guidance on how frequently these should be repeated once a patient is established on treatment [31]. North American guidelines on hypertension state that "serum potassium and creatinine should be monitored at least 1 to 2 times per year [225]. SIGN guidelines on hypertension in older people suggest an initial measurement of serum creatinine concentration, and suggest annual urinalysis, but not measurement of serum creatinine concentration, for follow-up [226].

Whether essential hypertension *per se* is a risk factor for progressive kidney disease has been questioned. A recent meta-analysis of randomised controlled trials of antihypertensive drug treatment concluded that such treatment had no effect on the incidence of ERF [227]. However, these trials were all too short-term to expect any measurable impact of antihypertensive treatment on the development of ERF, a disease that commonly evolves over 10-20 years or longer. The epidemiological data linking usual blood pressure with subsequent risk of ERF are strong [88 228-232].

The Committee concluded that the safest and simplest advice is that all patients treated for hypertension should have an annual measurement of serum creatinine.

Diabetes mellitus

The NICE inherited guidelines for management of type 2 diabetes mellitus [83] and the NICE national guidelines on the diagnosis and management of type 1 diabetes mellitus [160] both recommend annual measurement of serum creatinine concentration, irrespective of the presence of microalbuminuria or clinical proteinuria. Annual measurement of serum creatinine concentration in patients with diabetes mellitus is a quality indicator in the NHS General Medical Services Contract. The American Diabetes Association Guidelines make no specific recommendations on the frequency of creatinine concentration measurements but imply that these measurements should be performed regularly in all those found to have diabetic nephropathy and that predictive equations should be used to estimate the level of renal function from serum creatinine concentration [233]. The SIGN guidelines on management of diabetes mellitus suggest that "All patients with diabetes mellitus should have their urinary albumin concentration and serum creatinine measured at diagnosis and at regular intervals, usually annually" [27].

Heart failure

The vast majority of patients with heart failure should require annual testing of creatinine concentration as a result of being on ACEIs, ARBs, or diuretics. Even amongst patients with heart failure not on these drugs, kidney dysfunction is very common [234 235]. In a large cohort from the Veterans Administration Hypertension Screening and Treatment Program, congestive cardiac failure was associated with a five-fold increased risk of developing ERF over 15 y of follow-up [236]. This increased risk may be partly due to the frequency of renal vascular disease amongst patients with heart failure [237] and partly due to low arterial pressure leading to pre-renal failure. The NICE guidelines recommend measurement of serum creatinine concentration in the initial diagnostic work-up of patients suspected to have heart failure and at least 6-monthly monitoring of patients with established heart failure, irrespective of treatment [159].

Atherosclerotic coronary, cerebral, or peripheral vascular disease

There is extensive evidence of a high frequency of CKD amongst patients with vascular disease, including coronary disease [112 238-241], cerebrovascular disease [242], and peripheral vascular disease [243-245 246-249]. How much the renal dysfunction is due to impaired blood flow as a direct result of renal artery stenosis and how much to parenchymal disease that develops as a result of intra-renal vascular disease and atheromatous embolism [250-255] is uncertain. Either way, kidney disease is extremely common amongst patients with vascular disease, justifying annual measurement of serum creatinine concentration in this group of patients (if not already indicated as a result of hypertension, heart failure, or diabetes mellitus).

ACEI and ARB use

These drugs confer major prognostic benefit in patients with heart failure and in proteinuric renal disease, including diabetic nephropathy. Rarely, they can precipitate kidney failure by interfering with the autoregulation of renal blood flow in the presence of severe hypovolaemia, hypotension (e.g. severe heart failure), and bilateral renal artery stenosis. They can also promote hyperkalaemia due to their inhibition of aldosterone production. For these reasons, monitoring of kidney function and serum potassium is obligatory if these drugs are prescribed. Neither class of drugs is contraindicated in stage

1, 2 or 3 CKD. Further guidance on monitoring of kidney function during use of these drugs is given below**.** Monitoring of kidney function in patients prescribed these drugs is endorsed by national guidance from the British Hypertension Society [31] and NICE [83 158 159].

Long-term NSAID use

NSAIDs can cause both ARF (by causing acute interstitial nephritis) and CKD (by causing analgesic nephropathy) but can also result in further impairment of kidney function in the presence of pre-existing CKD [256] as well as causing or exacerbating salt and water retention, antagonising the effects of diuretics and antihypertensives. No studies have adequately addressed the risk-benefit ratio of the use of NSAIDs in patients with CKD. Dieppe et al point out that trials of these agents have excluded people with CKD, and that these trials therefore lack external validity. Data from their study of the Medicines Monitoring Unit database and from four previously published studies show that the risk of admission to hospital with renal impairment was increased amongst users of NSAIDs, particularly amongst the elderly [257]. To what extent these admissions could have been prevented by monitoring of kidney function is uncertain, and would depend on whether the excess risk was due to ARF or to progressive worsening of kidney function amongst patients with CKD. The British National Formulary advises that "in patients with renal…. impairment,…. NSAIDs may impair renal function; the dose should be kept **as low as possible** and renal function should be **monitored**." Appendix 2 repeats this advice for "mild renal impairment", defined as a GFR of 20-50 ml/min and advises "avoid if possible" for moderate to severe renal impairment (GFR < 20 ml/min).

Use of the combination of ACEI and NSAID also carries a high risk of kidney failure [258].

Lithium carbonate

Long-term use of lithium carbonate frequently causes nephrogenic diabetes insipidus, but has also been reported to cause progressive CKD, by causing chronic tubulointerstitial nephritis [259-261]. Whether long-term lithium treatment causes progressive CKD in the absence of episodes of lithium intoxication remains controversial. The BNF does not recommend regular monitoring of kidney function but recommends avoidance of lithium in the presence of moderate renal impairment (GFR < 50 ml/min).

Mesalazine and other 5-aminosalicylic acid drugs

Mesalazine can cause CKD by causing interstitial nephritis [262 263]; an analysis of data from the Committee on Safety of Medicines gave an estimate of 11.1 reports per million prescriptions [264]. A recent prospective epidemiological study of 5-aminosalicylic acid nephrotoxicity in the UK suggested an incidence of clinically significant nephrotoxicity of 1 in 4000 treated patients [265]. Improvement of kidney function occurred in 85% of cases in which treatment was withdrawn within 10 months [262].World et al recommended monitoring kidney function monthly for the first 3 months of treatment, then 3-monthly for a further 9 months, then annually [262]. The BNF warns of the risk of interstitial nephritis but does not specifically recommend monitoring of kidney function. Guidelines from the British Society of Gastroenterology recommend monitoring of kidney function only in "patients with pre-existing renal impairment, other potentially nephrotoxic drugs, or comorbid disease" [266].

Calcineurin inhibitors (Cyclosporin, Tacrolimus)

These drugs are increasingly used for indications other than kidney transplantation, including other solid organ transplants, bone marrow and stem cell transplants, and in the treatment of psoriasis, inflammatory bowel disease, and other immunologically mediated conditions, and there is increasing recognition of their potential to cause progressive CKD [267-269].

Systemic disease

Testing kidney function (together with urinalysis – see page **xxxx**) is widely used in primary care and in hospital practice in the initial investigation of systemic illness and in routine monitoring of diseases in which renal problems may develop (eg SLE, systemic vasculitis).

Family history of stage 5 CKD

There is some evidence for a high rate of detection of previously unknown CKD amongst first degree relatives of patients with stage 5 CKD in the USA [270 271]. Part two of the NSF for renal disease recommends surveillance of people with a family history of kidney disease, particularly males of South Asian or African Caribbean origin, citing a study from the USA that targeted first-degree relatives of people with hypertension, diabetes, or CKD and those with a personal history of diabetes mellitus or hypertension; 71.4% had at least one abnormality [272]. However, the yield of screening those with a family history without diabetes or hypertension was not stated. The cost-effectiveness of selective screening for CKD in high risk groups such as those with a family history of CKD and in ethnic minorities urgently requires further research [273]. No published studies address the question of the utility of screening amongst people of South Asian origin. Evidence on the cost-effectiveness of opportunistic or proactive screening for CKD in the UK population is urgently required.

Frequency of monitoring of kidney function

Very little research is available to guide recommendations on the frequency of monitoring of kidney function and its complications [274]. CKD differs from many other conditions requiring regular review (e.g. asthma, diabetes) in that laboratory measurements are required to detect complications, and that symptoms are frequently subtle in the early stages – in which treatment to slow progression or prevent complications are most effective. Regular monitoring of kidney function enables patients with progressive CKD to be identified so that optimum management can be provided and the problems associated with late referral avoided. As the GFR falls increasingly frequent clinical and biochemical assessments are required in order to detect and respond to the increasing number of complications that can arise as summarised on page **xxxxx**.

We know that in unreferred patients with significant CKD (median GFR 28.5 ml/min/1.73m^2) the majority of patients have remarkably stable renal function [94]. 79% of over 1500 patients in whom repeated measurements of renal function were available had stable renal function over a mean follow up period of 31.3 months (decline in eGFR <2 ml/min/1.73 m^2/year). Only 8.3% had a rate of decline of eGFR ≥5 ml/min/1.73 m^2/year, whereas the mortality in the unreferred group was 39.5% over the period of follow up. Similar population-based studies in America [114 175] have also demonstrated that the risk of progression of CKD is outweighed by the risk of death at each stage and at all ages. It is

therefore reasonable to relax the frequency of measurement of GFR in those patients who are appropriately managed and have been demonstrated to have stable renal function after a follow up period of a year or more. In those patients with a rate of decline of eGFR ≥5 ml/min/1.73 m^2/year there may be a requirement for more frequent monitoring than that recommended.

Interpretation of kidney function measurements in older people

Although some studies indicate that GFR declines with age, this is not a reason for using different criteria to categorise kidney function in older people. A fall in GFR is not an inevitable consequence of ageing; if it occurs it indicates kidney pathology and identifies patients at risk of developing ERF. The Baltimore Longitudinal Study on Ageing demonstrated that the decline in GFR with age is largely attributable to hypertension [228-230]. Age-related changes in renal haemodynamics are largely associated with coexistent cardiovascular disease [275-277]; post-mortem studies show that age-related glomerulosclerosis is closely associated with atherosclerosis [278]. These findings suggest that age-related decline in kidney function is not inevitable. The impact of a reduction in GFR on health is independent of age: for instance, a GFR of 10 mL/min/1.73 m^2 is no less likely to cause anorexia, vomiting, anaemia and hyperparathyroidism in an 80-year old than in a 30-year old. In the National Health And Nutrition Examination Survey (NHANES) study in the USA, low GFR was a strong predictor of malnutrition amongst people over 60 y of age [279].

Recognition of acute renal failure

ARF, if severe, may prove rapidly fatal unless managed appropriately. Up to 50% of patients with ARF present direct from the community [192]. Prognosis for recovery of kidney function in some causes of ARF, particularly rapidly progressive glomerulonephritis, is critically dependent on the time delay between initial presentation and diagnosis [280]. It is therefore imperative that these guidelines should not mistakenly be applied to the management or referral of patients who develop ARF in the community, who require immediate referral. A single abnormal measurement of kidney function (e.g. raised serum creatinine concentration) might indicate ARF, ARF superimposed on CKD, or stable CKD. The more impaired the estimated kidney function, the more urgent the situation. Because there is a temporal delay between a change in GFR and the resulting change in serum creatinine concentration [281], neither serum creatinine concentration nor estimated GFR gives an accurate measurement of kidney function at the time the blood test is taken. The severity of ARF can only therefore be judged by the rate of change of serum creatinine concentration over time. The safest assumption is that a patient with a rising serum creatinine concentration (or falling estimated GFR) has a true GFR of zero. However, use of formula-based estimation of GFR may improve recognition of ARF by drawing clinicians' attention to changes in serum creatinine concentration within the "normal range" that might otherwise have been ignored.

An international consensus conference organised by the Acute Dialysis Quality Initiative (ADQI, www.adqi.net) recently proposed the "RIFLE" classification (Risk of renal dysfunction: Injury to the kidney; Failure of kidney function; Loss of kidney function; and End-stage kidney disease) for ARF. ARF is defined using both GFR-based criteria and those based on urine output. "Risk" is defined as a 1.5-fold increase in serum

creatinine concentration, a 25% decrease in GFR, or urine output <0.5 ml/kg/h for 6 h. Injury is defined as a 2-fold increase in serum creatinine concentration, a 50% decrease in GFR, or urine output <0.5 ml/kg/h for 12 h. "Failure" is defined as a 3-fold increase in serum creatinine concentration, a 75% decrease in GFR, or a serum creatinine concentration >350 μmol/L in the setting of an acute increase in serum creatinine concentration of >44 μmol/L [282]. The time course over which these changes in kidney function must occur is not defined, but the classification is designed for use in patients with an acute illness. We recommend adoption of this classification.

Recognition of acute on chronic kidney disease

The purpose of this recommendation is to ensure the prompt recognition, and appropriate treatment, of treatable acute kidney disorders superimposed on CKD. We found no research studies that helped in defining the amount of change of kidney function, or the time course over which a change took place, that identifies patients who benefit from referral and/or further investigation. Ideally, a decision on whether to refer would rest not only on the absolute change in GFR that is observed, but also on the clinical state of the patient (a deterioration during severe intercurrent illness being more likely to reflect an important change in kidney function, for instance) and on the previous rate of loss of GFR, in the case of progressive CKD.

The RIFLE classification suggests that "acute on chronic" kidney disease should be diagnosed when serum creatinine concentration is >350 μmol/L in the setting of an acute increase of serum creatinine of >44 μmol/L [282]. We consider it more logical to continue to use estimated GFR in this setting.

Detection of proteinuria

Methods for detection of proteinuria

Protein excretion displays considerable biological variability, and may be increased by urinary tract infection (UTI), upright posture, exercise, fever, and heart failure as well as by kidney disease. Because standard urine dipsticks rely on estimation of protein concentration, which in turn depends on hydration (i.e. how concentrated the urine sample is), these tests can only give a rough indication of the presence or absence of pathological proteinuria. Typically, a colour matching the 'trace' block on the dipstick corresponds to approximately 150 mg/L of total protein and a colour matching the '1+' block to 300 mg/L. Significant proteinuria is deemed present when the colour change matches any block greater that of the trace block (i.e. >300 mg/L). However, urine of high specific gravity may give a colour change in this range even though protein excretion rate remains normal and, conversely, urinary dilution may mask significant proteinuria. Further, the performance of the dipsticks is operator-dependent and affected by the presence of certain drugs and urinary pH (e.g. infected urine is commonly alkalinised and may give a false-positive reaction for protein). The specificity of urinalysis using protein dipsticks for the detection of proteinuria is approximately 67% [283] and misclassification errors are common. Positive dipstick tests should be confirmed in the laboratory by measuring either the protein:creatinine or albumin:creatinine ratio on an early morning or random urine sample. Measurement of one of these ratios in random

urine samples allows correction for variations in urine concentration [284 285]. This is because creatinine excretion in the urine is relatively constant throughout the 24 h period.

Conventional urine dipsticks, and laboratory measurements of urine protein, measure not just albumin but other proteins also present in urine. Normal urinary protein excretion may be up to 150 mg/24 h, of which albumin comprises up to 30 mg/24 h. The remainder is predominantly tubular secreted proteins such as Tamm Horsfall glycoprotein. Urine proteins excreted in disease include albumin and other protein molecules. The relationship between albumin and total protein excretion is non-linear: typically albumin represents approximately 50% of total urinary protein at 300 mg/L and 70% at 1000 mg/L [286 287]. Whilst the diagnosis of clinical proteinuria in the non-diabetic population has traditionally been based on 'dipstick positivity', in the diabetic population definitions of proteinuria (sometimes termed 'macroalbuminuria') have tended to evolve based upon urinary albumin excretion as a result of the staging system for diabetic nephropathy which has developed around this protein. There is no definitive level of albuminuria to define the cut-off point for proteinuria in the literature. Hence definitions of proteinuria are not always consistent between the diabetic and non-diabetic literature. NICE [83] and and SIGN [27] define proteinuria in diabetes as an albumin concentration in excess of 200 mg/L or >30 mg/mmol creatinine or an excretion rate of >300 mg/24 h (approximating 200 μg/min). The equivalences of these thresholds generally assume an average urinary volume of 1.5 L/24 h and an average creatinine excretion of 10 mmol/24 h. They are broadly in keeping with the international literature: >300 mg/24 h [284], >300 mg/24 h (200 μg/min) or >34 mg/mmol (>300 mg/g) [288]. In the non-diabetic population, proteinuria is typically considered present when total protein exceeds 300 mg/L ('$\geq$1+' on dipstick testing), equivalent to >450 mg/24 h or >45 mg/mmol. North American guidelines have, however, adopted a lower threshold for defining proteinuria of >23 mg/mmol (equivalent to >200 mg/g), based upon the earlier PARADE position statement [284].

Dipstick testing methods are particularly sensitive to albumin (indeed, dipstick tests are unreactive towards some proteins, e.g. monoclonal immunoglobulin light chains, Tamm Horsfall glycoprotein and haemoglobin). Hence, there is an approximate equivalence between the clinical identification of proteinuria in the non-diabetic population using stick testing and its diagnosis in diabetic patients using an albumin:creatinine ratio of $\geq$30 mg/mmol. In the present guidelines, in non-diabetic patients we advocate identification of proteinuria using dipstick testing with confirmation based upon laboratory measurements of either the protein:creatinine or albumin:creatinine ratio, depending on local laboratory practice. Cut-offs of $\geq$45 mg:mmol and $\geq$30 mg/mmol for total protein or albumin respectively are approximately equivalent. In practice, in non diabetic patients in the absence of concomitant haematuria, proteinuria does not act as a trigger for active intervention until the ratio exceeds 100 mg/mmol (approximately 2+ on dipstick testing).

Whilst analytical methods of total protein measurement have changed little in recent years, and remain fairly imprecise especially at low concentrations, albumin is readily measured by quantitative immunoassay methods capable of detecting urine albumin at low concentrations. Proteinuria could be quantitated and monitored by measuring the urinary albumin:creatinine ratio [6 83 286]. However, measurement of urine albumin concentration is more expensive than measurement of urine total protein. Many

of the previous studies of the natural history or treatment of kidney disease stratified patients by urine total protein, rather than by albumin, excretion [120 137 252 289-299] For assessment or follow-up of non-diabetic patients it is therefore more cost-effective to use measurements of urine protein:creatinine ratio rather than albumin:creatinine ratio.

An early morning urine sample is preferred because studies have shown that it correlates best with 24 h protein excretion, and an early morning sample is required for the diagnosis of orthostatic (postural) proteinuria [6]. However, a random urine sample is preferable to no sample at all.

There is no indication for measurement of protein excretion by timed urine collection in routine clinical practice. If required, daily protein excretion (in mg/24 h) can be roughly estimated by multiplying the protein:creatinine ratio (measured in mg/mmol) by a factor of 10 since, although daily excretion of creatinine depends on muscle mass, an average figure of 10 mmol creatinine/day can be assumed [284]. Clearly, the use of this number will lead to overestimation of daily protein excretion amongst patients with low muscle mass and underestimation amongst patients with high muscle mass; in addition, there may be racial variation in creatinine excretion even after adjustment for muscle mass [300].

Conventional advice on investigation of dipstick positive proteinuria is that UTI should be excluded by sending a mid-stream urine sample for culture before further biochemical investigation. This is because UTI can cause urinary alkalinisation, and at pH >8.0 this can cause false positive reactions on dipstick tests; further, proteins released from bacteria and leucocytes can cause protein to be present in bladder urine in the absence of any disorder of glomerular permeability. However, urinalysis for protein has low sensitivity and specificity for diagnosis of UTI, and the introduction of an extra step into the investigation of proteinuria is likely to reduce reliable diagnosis of potentially important kidney disease (particularly because this requires further action on receipt of a "negative" result of urine culture). For this reason, we recommend that samples are sent simultaneously to the biochemistry and microbiology laboratory following the detection of dipstick proteinuria.

Despite these major methodological problems, protein:creatinine ratios measured in an early morning or random urine sample are at least as good a predictor of the rate of loss of GFR in non-diabetic nephropathy as 24 h urine protein estimations [301]. The footnote below helps to explain the relationship between urinary protein (and albumin) concentrations expressed as a ratio to creatinine and other common expressions of their concentration.

The detection of "microalbuminuria" is discussed in the following section.

Footnote: Expressions of urinary protein concentration and their approximate equivalents and clinical correlates.
The following table assumes an average creatinine excretion of 10 mmol/day and an average urine volume of 1.5 L/day. N.B., males and females have different thresholds for the diagnosis of microalbuminuria as a consequence of the lower urinary creatinine excretion in women.

	Dipstick reading	Urine protein: creatinine ratio, mg/mmol (urine protein mg/L)	Urine total protein excretion, mg/24 h (g/24 h)	Urinary albumin: creatinine ratio, mg/mmol	Urinary albumin excretion, μg/min (mg/24 h)
Normal	Negative	< 15 (<100)	<150 (<0.150)	<2.5 (males), <3.5 (females)	<20 (<30)
Microalbuminuria	Negative	< 15 (<100)	<150 (<0.150)	≥2.5-30 (males), ≥3.5-30 (females)	20-200 (30-300)
'Trace' protein	Trace	15-44 (100-299)	150-449 (0.150-0.449)		
Clinical proteinuria ('macroalbuminuria')	1+	45-149 (300-999)	450-1499 (0.450-1.499)	>30	> 200 (>300)
	2+	150-449 (1000-2999)	1500-4499 (1.500-4.499)		
Nephrotic range proteinuria	3+	≥450 (≥3000)	≥4500 (≥4.500)		

Table 2. Classification of proteinuria.

Indications for testing for proteinuria

Proteinuria is an important marker of kidney damage and a potent independent cardiovascular risk marker [105 120 123-127 302-304]. In the K/DOQI classification of CKD, stage 1 and 2 CKD require the presence of a marker of kidney damage other than altered GFR: proteinuria is the most important and frequent of these markers. Proteinuria is therefore important both for the identification of kidney damage and for guiding future treatment and surveillance.

Newly discovered raised creatinine concentration/reduced GFR

Proteinuria is one of the markers of presence of kidney damage that is required for the classification of patients with a GFR in the range 60-89 mL/min/1.73 m^2 as having CKD, as discussed above. Amongst patients whose GFR is < 60 mL/min/1.73 m^2, the presence of proteinuria is of prognostic significance for future progressive kidney damage, and quantitation of proteinuria is necessary to inform a decision about whether or not to refer the patient for specialist assessment (discussed below).

Newly discovered haematuria

The presence of proteinuria is highly predictive of significant glomerular disease amongst patients with haematuria. Although patients with macroscopic haematuria will be referred first for urological evaluation, the presence of proteinuria accompanying macroscopic haematuria greatly increases the probability that the patient will turn out to have glomerular disease, most commonly IgA glomerulonephritis [305].

Hypertension

Urinalysis for proteinuria is recommended as part of the initial assessment of patients with hypertension by the BHS [31], SIGN [226], and NICE [158], because persistent proteinuria may lead to the diagnosis of underlying CKD. We do not recommend annual urinalysis for patients on treatment for hypertension.

Unexplained oedema

The nephrotic syndrome is the combination of peripheral oedema, hypoalbuminaemia, and heavy proteinuria (usually defined as a urine protein excretion of > 3 g/24 h or a spot urine protein:creatinine ratio of > 300 mg/mmol). Lesser degrees of proteinuria can also be associated with retention of salt and water. Management of nephrotic syndrome depends on the underlying cause, diagnosis of which may require kidney biopsy; some cases require steroid, cytotoxic or other immunosuppressive treatment.

Suspected heart failure

NICE guidelines for management of chronic heart failure recommend urinalysis as part of the initial work-up of patients with suspected heart failure, although this is largely to exclude alternative diagnoses [159]. Both heart failure and CKD can cause salt retention, with very similar clinical consequences. Heart failure itself can cause low-grade proteinuria [306], which resolves with diuretic treatment. However, this is probably rare, and proteinuria should not be ascribed to heart failure without further investigation.

Suspected multisystem disease

Urinalysis is widely used both in primary care and in hospital practice and can be very useful in the initial investigation of systemic illness, where a positive protein result should lead to active consideration of rapidly progressive glomerulonephritis [280].

Haematuria and proteinuria are almost universally found in acute glomerulonephritis, both primary and secondary to systemic disease (e.g. vasculitis, systemic lupus erythematosus, cryoglobulinaemia). Proteinuria is the hallmark of renal amyloidosis [307] [308]. Some neoplastic processes also cause paraneoplastic kidney disease, which is also classically associated with proteinuria [309].

Assessment of severity of known kidney disease

Amongst patients with suspected or proven CKD, including reflux nephropathy, and early glomerulonephritis, and those with hypertension, annual urinalysis for proteinuria is accepted as a useful way of identifying patients at risk of progressive kidney disease. Proteinuria is a potent risk marker for progressive kidney disease in non-diabetic kidney disease [254 295 298 299 310 311] and diabetic kidney disease [312]. In a large study of a Japanese population, proteinuria (detected by dipstick) was a far more potent predictor of the later development of ERF than was haematuria [313].

Screening

There is currently no proven role for dipstick urinalysis for urinary protein in screening of unselected populations [314 315]. Whether urinalysis will prove useful in identifying patients at risk of CKD in selected high risk populations, for instance some ethnic minority populations, remains uncertain.

Detection of microalbuminuria

Methods for detection of microalbuminuria

"Microalbuminuria" is a term for the excretion of albumin in the urine in amounts that are abnormal but below the limit of detection of conventional urine dipsticks, and only therefore detected by specific tests for albumin. The term is confusing in that it can mistakenly be taken to mean that there is abnormal excretion of "microalbumin", i.e. a small albumin molecule, whereas in fact the albumin excreted in this condition is exactly the same as in other conditions that cause proteinuria. In "overt diabetic nephropathy" the amount of albumin present in the urine reaches levels that can be detected by conventional urine dipsticks – around 200 to 300 mg/L. The recognition of microalbuminuria in patients with diabetes mellitus allows identification of diabetic nephropathy, and institution of treatment to reduce the risk of progressive kidney damage, at an earlier stage than would be possible with conventional protein dipstick testing. In this clinical situation, the aims of treatment differ according to the presence or absence of microalbuminuria or clinical proteinuria, as described below. This is because there is clear evidence that the detection of early diabetic nephropathy, manifested by microalbuminuria, is responsive to anti-hypertensive therapy, in particular the use of ACEIs or ARBs (see p **xxx**). Whether intensified glycaemic control can reverse proteinuria remains controversial. The recommendations given are consistent with NICE and SIGN recommendations for type 1 and type 2 diabetes [27 83 160].

SIGN guidelines suggest that UTI is excluded as a potential cause of false positive tests for microalbuminuria [27]; NICE make no recommendation [83 160]. A recent prospective study showed that albumin excretion rate (AER) is not affected by asymptomatic UTI [316].

It is controversial whether, in the absence of symptoms suggesting UTI, it is necessary to exclude UTI before sending a sample for measurement of albumin:creatinine ratio.

Point of care testing devices are available that enable accurate measurement and calculation of an albumin:creatinine ratio [317 318]. At the present time, there has been insufficient field and economic evaluation of these devices to recommend that they supplant laboratory-based testing.

Indications for testing for microalbuminuria

These recommendations are consistent with NICE and SIGN recommendations for type 1 and 2 diabetes [27 83 160]. These guidelines do not specify how the clinician should respond to the continued presence, or worsening, of microalbuminuria when this occurs despite optimal treatment: this is discussed below (see p XX).

Although microalbuminuria may act as a cardiovascular risk marker in non-diabetic people [100 122 124-127 150 303 319-323], and may also be a marker of early non-diabetic kidney disease, there is as yet no evidence that identification of such people would have implications for treatment over and above treatment of modifiable cardiovascular risk factors such as hyperlipidaemia, smoking, and hypertension.

During development of these guidelines, the International Society of Nephrology issued a "Call to Action" calling for implementation of recommendations for systematic screening for microalbuminuria, first amongst patients with type 2 diabetes and hypertension and amongst those with increased cardiovascular risk (obesity, smokers, over 50 years of age, family history of heart and kidney disease and/or diabetes and hypertension), and then amongst the general population, with a view to treatment of all patients with microalbuminuriira with ACEI or ARB [324]. Similar recommendations have been made in a recent editorial review [325]. These recommendations were based on the high prevalence of microalbuminuria amongst non-diabetic members of the population, the association between microalbuminuria and cardiovascular risk, and a recently published randomised study demonstrating a trend to reduction in risk of cardiovascular end-points by ACEI treatment (vs placebo) amongst nondiabetic subjects with microalbuminuria [326]. Patients recruited for this study had BP < 160/90 and were not on antihypertensive treatment. A cost-effectiveness analysis, undertaken prior to this study, concluded that screening normotensive non-diabetics was not cost-effective, but might be so if confined to people above 60 years old [315]. At present we do not consider this evidence strong enough to support the call for screening, when assessed using UK criteria [327], but further research is urgently needed.

Detection of haematuria

Methods for detection of haematuria

Although false positive dipstick tests for haematuria have been described, false negative microscopy in the routine microbiology laboratory is also common, due to lysis of red blood cells during transit, particularly in dilute urine. The diagnostic yield of

investigation of patients with dipstick positive haematuria is similar whether or not haematuria is reported on microscopy [305 328-332].

Indications for testing for haematuria

The prognosis for the combination of proteinuria with haematuria is significantly worse than that for proteinuria alone [313]. Detection of haematuria in patients with abnormal GFR or proteinuria aids the identification of those with diseases such as glomerulonephritis (which may be secondary to systemic conditions such as vasculitis or SLE).

The presence of haematuria in a patient with diabetes mellitus and microalbuminuria or proteinuria may be a marker of the presence of non-diabetic kidney disease and is considered by NICE as an indication for referral [83 160].

There is currently no evidence supporting screening of unselected populations for haematuria using dipstick testing [314 315 333 334].

MANAGEMENT AND REFERRAL OF CKD

Treatment of all adults with CKD, irrespective of age

Interventions that slow progressive loss of GFR, such as antihypertensive therapy, are as effective in older people as in younger people. Age itself is not a barrier to acceptance for dialysis treatment, as a good quality of life can be achieved in elderly dialysis patients at reasonable cost [335]; severity of co-morbidity and functional capacity are more important predictors of outcome than age amongst patients starting dialysis [336]. The greatest projected increase in the numbers of patients requiring dialysis will be amongst older people [337]. Older patients are just as likely, if not more likely, to benefit from treatment for renal anaemia. Although the evolution of hyperparathyroidism is a slow process, meaning that patients with early renal bone disease and limited life expectancy may not live long enough to develop significant hyperparathyroidism, many older patients will have had undetected kidney disease for many years; treatment that increases bone density is likely to be of most benefit amongst those at increased risk of falls; and treatment with calcium and vitamin D will also reduce the risk of falls and osteoporotic fractures. Older patients therefore stand to benefit both from interventions designed to prevent progressive deterioration in kidney function and from planning for dialysis treatment. Although dialysis treatment may not be considered suitable for some older patients on the grounds of co-morbidity (e.g. dementia), similar decisions may be equally appropriate in younger patients; in both situations, patients will benefit from active non-dialytic ("conservative") management. We conclude that there should be no upper age barrier to any of the interventions recommended in these guidelines.

Advice to stop smoking

Smoking is a risk factor for progressive kidney disease [128-131 133-135 338]. There is evidence that smoking cessation reduces the rate of loss of kidney function amongst patients with progressive kidney disease [339].

Obesity and exercise

One observational study [340] and one randomised study [341] have documented beneficial effects of weight loss amongst overweight patients with kidney disease. Weight loss results in reduction in blood pressure, and larger reductions are seen amongst patients already taking antihypertensive drug treatment [342]. There is also preliminary evidence that swimming reduces proteinuria amongst patients with CKD [343 344].

Alcohol intake

Excessive alcohol intake is associated with hypertension, and reduction of intake is recommended in the lifestyle advice proposed by the BHS for patients with hypertension [31]. There is also epidemiological evidence linking alcohol intake to the risk of CKD [345].

Rationale: aspirin prophylaxis

Evidence on the role of aspirin in preventing cardiovascular events among patients with CKD is limited. The Antithrombotic Triallists Collaboration performed a meta-analysis of randomised controlled trials of antiplatelet therapy, including data from 14 trials in patients receiving haemodialysis: antiplatelet therapy produced a similar proportional reduction in serious vascular events to that seen in other subgroups [346]. A re-analysis of the Hypertension Optimal Treatment (HOT) study, using Cockcroft and Gault estimated GFR, showed a trend towards benefit from aspirin amongst patients with CKD, but the number of informative patients was small [102]. There is observational evidence that aspirin treatment is under-utilised amongst patients with CKD following myocardial infarction [118], and that outcomes are poorer amongst those who do not receive aspirin compared to those who do [104]. The first UK Heart and Renal Protection (UK-HARP) study randomised 448 patients with CKD to aspirin (100 mg/d) or placebo, and found no difference in the risk of major bleeds, but a 3-fold increase in minor bleeds, in those randomised to aspirin; aspirin had no effect on progression of CKD [347]. However, too few patients have been included in any of these trials to evaluate the risks associated with aspirin use reliably. Thus, although there is level 1 evidence for the use of aspirin in the general population, this evidence is less reliable in CKD.

Our recommendations are based on the British Hypertension Society guidelines for prophylaxis amongst patients with hypertension [31].

Advice on lipid-lowering therapy in CKD

Prevention of cardiovascular events

Almost without exception, randomised controlled trials of the effects of lipid-lowering therapy on cardiovascular disease have excluded patients with most types of kidney disease [348]. There is a high rate of non-coronary cardiac disease (e.g. hypertensive heart failure) in this population [348]. There are few data to guide recommendations on lipid-lowering treatment amongst this population. The only data on the effects of lipid-lowering drug treatment amongst patients with CKD come from *post hoc* subgroup analyses from the Heart Protection Study (HPS) [349], the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) [350], and pooled data from three studies using Pravastatin [351]. Several trials are under way examining the effect of lipid-lowering therapy on cardiovascular outcomes amongst patients with kidney disease [30] and patients on

haemodialysis [352 353]. A study of the effects of Fluvastatin in 2102 kidney transplant recipients has recently been published, with some evidence of benefit although no reduction in the primary endpoint of major adverse cardiac events [354]. The Study of Heart and Renal Protection (SHARP) trial aims to randomise 9000 patients with CKD to lipid-lowering therapy or placebo, excluding only those with definite indications or contraindications to lipid-lowering therapy; patients with established coronary disease will be excluded [30]. Pending the results of those trials, we recommend that patients with CKD and coronary disease should be treated according to existing guidelines [29]. Patients with CKD who do not have evidence of coronary disease should be treated according to their estimated risk, using the Joint British Societies Guidelines, [29], despite the fact that these guidelines specifically exclude CKD from their remit; or entered into an RCT of lipid-lowering therapy.

Progression of CKD

Dyslipidaemia is also a risk factor for progressive kidney disease, both amongst apparently healthy people [145 147 355] and amongst those with known kidney disease [356 357]. A meta-analysis of 11 small trials of lipid-lowering drug therapy amongst patients with kidney disease, mostly proteinuric and with hypercholesterolaemia, showed that such therapy reduced the rate of progression [146]. A substudy of the Cholesterol and Recurrent Events (CARE) study also suggested that pravastatin therapy may slow the decline of kidney function amongst participants with moderate to severe CKD, especially with proteinuria [358]; however, we do not believe that these results can safely be extrapolated to the great majority of patients with CKD in the community without additional evidence. The SHARP study will provide further information on this important question [30].

Lipid-lowering treatment for patients with diabetes mellitus

Patients with diabetes mellitus are at greatly increased risk of vascular disease, and it is now frequently suggested that patients with diabetes mellitus should be considered as "coronary equivalents" when assessing their cardiovascular risk [31]. The HPS and the Collaborative Atorvastatin Diabetes Study (CARDS) studies provided further evidence for the beneficial effects of lipid-lowering drug treatment amongst patients with diabetes mellitus [359 360]. However, relatively few patients with CKD were included in these studies, which both had exclusion criteria based on serum creatinine concentration. Although patients with diabetes mellitus and CKD might be perceived to be at higher risk than patients with diabetes mellitus and normal kidney function, they are also more complex, have more competing risks, and more likely to be receiving multiple drug treatments for other conditions. The results of the "4D" (Die Deutsche Diabetes Dialyse) Study were presented at the American Society of Nephrology meeting in October 2004; lipid-lowering treatment was not associated with a significant reduction of major vascular events compared to placebo. Full publication of these results is awaited. We recommend that patients with diabetes mellitus and CKD who have no additional risk factors should be considered for entry into SHARP; patients thought to be at higher risk should be offered lipid-lowering drug therapy.

Blood pressure management

Treating patients with CKD and hypertension with antihypertensive drugs has two aims: reduction of the risk of cardiovascular disease, and reduction of the risk of progressive loss of kidney function. Extensive guidance on the assessment and treatment of hypertension has been published by the BHS [31]; we have tried to make our recommendations consistent with the BHS guidelines, with the exception of enhancements such as use of estimated GFR in place of serum creatinine for assessment of excretory kidney function and the provision of more detailed advice on management of hypertensive patients with CKD. However, it proved impossible fully to reconcile all existing sources of national guidance, largely due to poor definition of the intervention thresholds and optimal blood pressure goals in some guidelines, as illustrated in Table 3

	Intervention threshold BP	Optimal/target/goal BP
BHS nondiabetic	>160, >90; between 140-159 SBP and 90-99 DBP depends on overall CVS risk assessment	<140, <85
BHS diabetic		<130, <80
y disease	>140, >90	<130, <80 (<125, <75 "may produce additional benefit with proteinuria > 1 g/24h")
ıtial hypertension	>160, >90 or >140, >90 with estimated 10y CVD risk >20%	<140, <90
NICE type 1 diabetes, uncomplicated	>135, >85	<130, <80
NICE type 1 diabetes, with abnormal AER or another feature of the metabolic syndrome (defined by waist circumference, HDL-cholesterol, triglycerides, or BP > 135/80	>130, >80	<130, <80
NICE type 2 diabetes, normal AER	Not given*	<140, <80
NICE type 2 diabetes, microalbuminuria	Not given*	<135, <75
ɛtes	Not given*	<140, <80

Table 3. Intervention thresholds and optimal blood pressure goals recommended by BHS [31], NICE [83 160] and SIGN [27] for patients with and without kidney disease and/or diabetes. *: these guidelines appear to imply that the intervention threshold is the same as the target blood pressure.

Salt intake

This recommendation is consistent with BHS recommendations for patients with hypertension [31]. In addition, there is evidence that salt restriction amplifies the protective effect of ACEI in patients with proteinuria [361 362]; that high sodium intake increases albumin excretion, particularly amongst overweight subjects [363] and amplifies the effect of arterial pressure on albumin excretion [364 365]. There is also some observational evidence that loss of GFR amongst patients with CKD is correlated with dietary sodium intake [366], although this finding may have been confounded by effects of protein intake.

Reduction of cardiovascular risk

Most of the evidence that blood pressure reduction is associated with a reduction in the subsequent risk of cardiovascular disease comes from studies amongst patients with "essential" hypertension, although it is likely that many patients with early CKD were included in these studies. In addition, there is recent evidence that ACEIs and ARBs reduce cardiovascular risk amongst patients with kidney disease [367 368].

Reduction of progressive kidney damage

There is unequivocal evidence that antihypertensive treatment reduces the rate of progression of diabetic and non-diabetic kidney disease [141 294 369-376]. The Heart Outcomes Prevention Evaluation (HOPE) study also showed that Ramipril reduced the risk of the development of proteinuria amongst patients at high cardiovascular risk [321].

The evidence supporting a lower blood pressure "target" amongst patients with proteinuria is discussed below (p**xxx).** Amongst patients with non-proteinuric kidney disease, there is less evidence that a lower blood pressure target confers additional benefit. In the African American Study of Kidney Disease (AASK) trial, 1094 African-Americans with hypertensive nephrosclerosis were randomised to a mean arterial pressure goal of 102-107 mm Hg or <92 mm Hg and to initial treatment with metoprolol, ramipril, or amlodipine. No difference in the rate of decline of GFR was noted between the two blood pressure groups; however, progression was slower in those assigned to ramipril, suggesting that ACEI treatment may confer protection, independent of blood pressure, against progression even in the absence of significant proteinuria [377].

Drugs that inhibit the renin-angiotensin axis are of proven value in reducing the risk of progressive kidney failure in proteinuric non-diabetic kidney disease [141 294 370 378] and in diabetic nephropathy [321 369 371-375 379], reducing mortality in heart failure [159], and also in reducing mortality amongst patients with vascular disease or diabetes mellitus with normal left ventricular function [367]. Existing guidance is that ACEI treatment should be offered to all patients with LV dysfunction, all diabetic patients with microalbuminuria, and all diabetic patients with a history of vascular disease even without heart failure [83 224].

NICE guidelines recommend that primary care clinicians "consider the need for specialist investigation of patients with unusual signs and symptoms, where a secondary cause of hypertension is suspected, or in patients whose hypertension is resistant to drug treatment" and recommend immediate referral of patients with accelerated hypertension [158]. SIGN guidelines give similar advice [226].

Monitoring kidney function during treatment with ACEI or ARB

Many clinicians are concerned that ACEI or ARB treatment might be contraindicated in the presence of CKD or might cause kidney damage. The BHS guidelines advise that ACEI and ARB be used with caution and under specialist advice in the presence of "renal impairment" [31] and the BNF and NICE [158] both advise that they be initiated under specialist supervision in patients with plasma creatinine concentration above 150 μmol/L. Both sources state that the drugs are contraindicated in the presence of renovascular disease. These concerns result in many patients being denied this treatment with these drugs [380 381]. However, there is also extensive evidence that these drugs may be uniquely effective in reducing the progression of some types of CKD, as well as in reducing mortality and morbidity in patients with heart failure.

There is undoubtedly a risk that these drugs will precipitate acute renal failure as a result of unrecognised bilateral critical renal vascular disease [382-385], by interrupting the intrarenal production of angiotensin II that normally maintains GFR in the presence of reduced renal perfusion. Failure to monitor kidney function during treatment with ACEI/ARBs for heart failure is common and may result in avoidable late referral of patients with severe CKD [386]. **However**, the great majority of patients with hypertension, ischaemic heart disease, or heart failure **benefit** from treatment with ACEIs. Unrecognised ARAS is extremely common amongst patients with vascular disease [237 238 240-242 246-249 362 387-389], so it is likely that many patients included in the trials that demonstrated survival advantage resulting from ACEI treatment had ARAS. Even amongst patients with known renal vascular disease, use of an ACEI is associated with an improved prognosis [311].

Even in the absence of ARAS, antihypertensive drugs can cause reduction in GFR, by reducing renal perfusion; this is particularly likely in the presence of kidney disease, affecting autoregulation of renal blood flow. ACEI and ARBs are more likely to reduce GFR, and to reduce albuminuria, because of their effects on the pressure gradient within the renal circulation, whereas dihydropyridine calcium channel blockers have opposite effects [390 391]. Some researchers have reported that an initial ACEI-induced reduction of GFR even predicts long-term stability of kidney function [384 392-394].

Existing guidelines on ACEI/ARB use in CKD suggest that a rise in serum creatinine concentration of up to 30% should be accepted [385 393]. These guidelines rely on an analysis of the results of randomised controlled clinical trials of antihypertensive therapy in patients with CKD: most trials demonstrated an acute fall in GFR or rise in serum creatinine concentration. An inverse correlation was found between the initial fall in GFR and the subsequent rate of decline. The rise in serum creatinine concentration seen in these studies was up to 30% from baseline over the first two months [384]. Assuming a simple reciprocal relationship between GFR and serum creatinine, this equates arithmetically to a 22% fall in GFR. However, the trials in this analysis are unlikely to have included many patients at high risk of ARAS, and the results of this analysis cannot therefore be safely extrapolated to an unselected population of patients with CKD, many of whom will have non-proteinuric CKD and some of whom may have haemodynamically significant ARAS. Amongst 108 patients at high risk of ARAS, the effect of ACEI (with or without subsequent addition of diuretics to achieve blood pressure reduction) was compared with the results of renal angiography. In this study a

rise of serum creatinine concentration of >20% during ACEI treatment was 100% sensitive in the prediction of severe bilateral ARAS, with a specificity of 70% [395].

Whether the presence of proteinuria could be used to help discriminate between patients likely to benefit from ACEI/ARB-induced reduction in GFR and those likely to be harmed deserves further study. Many of the patients included in the analysis of Bakris et al [384] are likely to have had proteinuria. No data are given on protein excretion in the patients studied by Van de Ven et al [395], but it is likely that many of these patients had negligible proteinuria.

The summary of product characteristics for ACEIs and ARBs all state that kidney function should be measured prior to prescription and "regularly" thereafter. NICE guidelines on management of hypertension in primary care state, "a significant rise in serum creatinine when starting ACEI may indicate renovascular hypertension" (p10).

NICE heart failure guidelines state that ACEI and ARB may be contraindicated in the presence of renal dysfunction, defined there as creatinine > 200 μmol/L, and that such patients require specialist assessment. They also state that an increase in serum creatinine concentration of up to **50%** above baseline, or to 200 μmol/L, whichever is the smaller, is acceptable during treatment of heart failure with ACEIs [159]. This guidance is based on a European Consensus document [396], but no evidence is cited to support the figures of >50% and 200 μmol/L. None of the major trials of ACEI or ARB in the treatment of heart failure have reported in detail on changes in kidney function.

A further difficulty is that the evidence summarised above is based on changes in serum creatinine concentration, rather than on estimated GFR. The theoretical reciprocal relationship between serum creatinine concentration and GFR means that a rise in serum creatinine concentration of 20% is equivalent to a fall in GFR of 17%, and a rise of 30% equivalent to a fall of 22%. However, as GFR falls, tubular secretion of creatinine distorts this reciprocal relationship, so that a given rise in serum creatinine concentration will lead to underestimation of the fall in GFR. For these reasons we have decided to err on the side of safety and recommend discussion with a specialist of all patients whose serum creatinine concentration rises by 30% or whose estimated GFR falls by 20% as an apparent consequence of ACEI/ARB use.

ACEI/ARBs can also cause hyperkalaemia due to their inhibition of aldosterone production. This is a particular risk amongst patients with stage 3 or greater CKD and amongst those also prescribed other drugs that interfere with renal potassium handling, including NSAIDs and spironolactone. A recent report drew attention to a marked increase in rate of admission for hyperkalaemia and death associated with hyperkalaemia since the publication of the "RALES" study that demonstrated benefit from spironolactone in heart failure, and concluded that this was due to treatment with larger doses, and in a wider variety of clinical situations, than had been the case in the original trial [397]. This report adds emphasis to the need for regular monitoring of serum potassium concentration during treatment with drugs that affect potassium homeostasis.

Hyperkalaemia is the most frequent life-threatening complication of CKD; severe hyperkalaemia (e.g. greater than 8 mmol/L) can cause cardiac arrest and death with very few warning symptoms. In stage 4-5 CKD, hyperkalaemia becomes increasingly common as GFR declines, and may be an indication for starting RRT. Some types of CKD, particularly diabetic nephropathy and interstitial nephritis, can be associated with suppression of renin and aldosterone release, causing hyperkalaemia disproportionate to

the reduction in GFR. Drug treatment with ACEIs and ARBs can contribute to hyperkalaemia, which can also be exacerbated by treatment with spironolactone (indicated in the treatment of heart failure), beta-blockers, and NSAIDs. Severe effective hypovolaemia, which may complicate the treatment of heart failure with high dose diuretics, may also cause hyperkalaemia in the presence of CKD – although in the presence of volume overload, diuretic treatment may be a logical **treatment** for hyperkalaemia. For these reasons, working out the cause and appropriate treatment of hyperkalaemia can be difficult, and a good reason for referral to a nephrologist.

Management of non-diabetic patients with proteinuria

Proteinuria is a potent risk marker for progressive kidney dysfunction in non-diabetic kidney disease [295 298 299 301 398]. Reduction of protein excretion by antihypertensive drug treatment, dietary modification, or both, results in reduction in the risk of progressive kidney failure, and is therefore an important therapeutic target [140 289 399]. In proteinuric kidney disease, there is also good evidence that ACEIs and ARBs reduce proteinuria more than other antihypertensive drugs with equivalent effects on blood pressure, and that treatment-induced reduction of proteinuria reduces the risk of subsequent progression of kidney disease [376 378].

Treatment with ACEIs and/or ARBs can slow the progression of non-diabetic nephropathy [141 369 370]. The justification for lower blood pressure targets in patients with proteinuric kidney disease stems from a *post* hoc analysis of the MDRD study, in which allocation to a lower blood pressure target (mean arterial pressure 92 mm Hg) resulted in greater protection against progressive kidney disease than allocation to conventional blood pressure target (mean arterial blood pressure 107 mm Hg) only amongst patients with baseline protein excretion greater than 1 g/day [137 296]. However, in this study it is difficult to distinguish the effects of blood pressure lowering from the selective use of ACEIs in the lower blood pressure group. A long-term follow-up of participants in the MDRD study showed that, on an intention to treat analysis, the adjusted hazard ratio of kidney failure was 0.68 (95% CI 0.57-0.82) in those allocated to the low target blood pressure compared to those allocated to the conventional blood pressure target; in this analysis, there was no interaction with baseline proteinuria [400]. In a meta-analysis of 11 trials including 1860 non-diabetic patients, an achieved systolic blood pressure of between 110 and 129 mm Hg was associated with the lowest risk of progressive kidney dysfunction amongst patients with baseline protein excretion greater than 1 g/day; systolic blood pressure lower than 110 mm Hg was associated with a higher risk of disease progression [294]. The REIN-2 study, reported recently, randomised 338 non-diabetic patients with proteinuria (defined as > 1 g/24h) on background antihypertensive treatment with Ramipril, to conventional blood pressure control, defined as a diastolic blood pressure < 90 mm Hg, or to treatment with felodipine adjusted to achieve a blood pressure of < 130/80 mm Hg [401]. Over a median follow-up of 19 months, no difference in the rate of progression to ERF was detected. However, the mean separation in blood pressure between the two groups was only about 3.0 mm Hg over the course of the study.

BHS guidelines suggest a lower target blood pressure (125/75 instead of 130/80) amongst patients with proteinuria > 1 g/day [31].

Management of diabetic patients with proteinuria or microalbuminuria

Diabetic nephropathy management has been the subject of guidelines produced by SIGN [27] and NICE [83 160] in the last few years. Although there have been some recent publications in the field of type 2 diabetic nephropathy [372-374], much of this guidance remains up-to-date.

The introduction of a staging system for CKD based on estimated GFR risks causing confusion with the classification of diabetic nephropathy, which has classically been based on AER. To complicate matters further, the histological changes of diabetic nephropathy correlate poorly either with GFR or with albumin excretion. Table 4 attempts to clarify the situation.

		Estimated glomerular filtration rate (ml/min/1.73 m^2)				
AER		>90	60-89	30-59	15-29	<15
	normal	Normal	Normal unless other evidence of CKD*	CKD stage 3**	CKD stage 4**	CKD stage 5**
	30-300 mg/24h	CKD stage 1	CKD stage 2	CKD stage 3	CKD stage 4	CKD stage 5
	>300 mg/24h	CKD stage 1	CKD stage 2	CKD stage 3	CKD stage 4	CKD stage 5

*other evidence might include persistent microscopic haematuria, structural abnormalities (e.g. polycystic kidneys, reflux nephropathy), or biopsy-proven abnormalities. Kidney biopsy in these patients might show histological evidence of diabetic kidney disease but there is no current evidence to suggest that these patients should be treated differently.

**reduction in GFR in patients with diabetes but no microalbuminuria is well described both in type 1 and type 2 diabetes mellitus [150]; kidney biopsy in such patients often shows histological evidence of diabetic kidney disease [402].

The presence of retinopathy in type 2 diabetic patients with albuminuria usually predicts the presence of histological evidence of diabetic nephropathy; the absence of retinopathy does not exclude diabetic nephropathy. Non-diabetic CKD is present in < 15% of type 2 patients with albuminuria and no retinopathy and few of these individuals have a disease process the management of which would be altered by knowledge of the biopsy results [403].

Hypertension may both precede and result from diabetic nephropathy and other kidney diseases. ACEI or ARB treatment should be instituted for all patients with diabetes and microalbuminuria or clinical proteinuria irrespective of blood pressure. BP should be reduced below 130/80 in all patients with diabetes [27 31 83 160] (N.B. the NICE guidelines for type 2 diabetes [83] give an optimal BP of <135/75 rather than <130/80)

Only three treatments have been shown to have an impact on the development and progression of diabetic nephropathy: glycaemic control, blood pressure control, and dietary protein restriction.

Glycaemic control

Both the Diabetes Control and Complications Trial (DCCT) [404] and the United Kingdom Prospective Diabetes Study (UKPDS) [405] confirmed that improved glycaemic control in type 1 and type 2 diabetes mellitus can prevent the development of microalbuminuria. Moreover the UKPDS showed that the number of patients doubling their serum creatinine concentration was reduced in the intensively treated group. However the number of patients was small and these data need to be confirmed. Apart from this the impact of glycaemic control on rate of change of GFR is still not proven. However patients with worse glycaemia tend to progress more rapidly [406].

The evidence of a benefit of intensive glycaemic control on the progression from microalbuminuria to overt nephropathy is controversial. There are no consistent studies showing benefit in this regard. However glycaemic control is still important for the progression of other complications such as retinopathy in these patients.

Antihypertensive therapy

Classic studies of Parving established anti-hypertensive therapy with diuretics, beta-blockers and hydralazine as effective agents in the reduction in the rate of loss of GFR in type 1 patients with overt nephropathy [407]. Since then there have been numerous studies confirming the benefit of anti-hypertensive therapy in both type 1 and type 2 patients with nephropathy and an increasing awareness that ACEIs and ARBs may confer additional protection.

There are now many studies establishing the superiority of ACEIs and ARBs in the prevention of progression from microalbuminuria to overt nephropathy in type 1 [379] and type 2 diabetic patients [374]. As a result, drugs that block the renin angiotensin system are indicated in microalbuminuric patients irrespective of blood pressure. The evidence for effectiveness in slowing GFR decline is less secure. There is preliminary evidence that ACEIs and ARBs can retard the development of microalbuminuria amongst patients with type 2 diabetes [408], and this treatment may prove cost-effective [409]; whether these findings indicate that all patients with type 2 diabetes should be so treated requires further analysis. In a recent meta-analysis of studies of ACEIs and ARBs in diabetic nephropathy, ACEIs, but not ARBs, were found to confer a survival benefit [410].

For overt clinical nephropathy, ACEI/ARBs are probably superior to other anti-hypertensive treatments in slowing the rate of deterioration of kidney function [369] although the key objective is to lower blood pressure to target [31 373].

Target blood pressure levels can be difficult to achieve. The current Joint Society guidelines suggest an overall target for diabetic patients of 140/80 mm Hg. For those with microalbuminuria or proteinuria the target is 130/80 mm Hg. It is suggested that those with total proteinuria >1g/day the target should be 125/75 mm Hg [31].

Recent observations have shown that the greater the reduction in albumin excretion after intensification of antihypertensive treatment in diabetic nephropathy, the less kidney function declines over follow-up [411]; similarly, reduction in albumin excretion is associated with reduced cardiovascular risk [304]. These observations have led to

suggestions that antihypertensive treatment should be titrated not against blood pressure but also against albumin excretion, aiming for complete normalisation. Several trials have tested combinations of ACEI and ARBs ("dual renin-angiotensin blockade") in diabetic nephropathy, demonstrating superior efficacy in reduction of albumin excretion compared to full-dose monotherapy [412-415]. However, this strategy has not been specifically tested in randomised controlled trials (RCTs) amongst diabetic patients, and full suppression of the renin-angiotensin axis outside the discipline of an RCT might carry increased risks – of ARF complicating hypovolaemia, and of hyperkalaemia, for example. The committee therefore recommended that patients with worsening albuminuria should be referred to a specialist, and that combination blockade should be initiated by a specialist.

These guidelines suggest referral once GFR falls below 30 mL/min/1.73 m^2, i.e. stage 4 CKD, unless other criteria are met first. This criterion for referral stands in contrast to NICE guidance, which for both type1 and type 2 diabetes suggests referral when the serum creatinine is above 150 μmol/L [83 160]. However, the committee feel that staging of CKD by estimated GFR is far superior to staging using serum creatinine concentration alone. A serum creatinine concentration of 150 μmol/L would predict, using the MDRD equation, a GFR of 67 mL/min/1.73 m^2 in a 20-year old black man, and a GFR of 31 mL/min/1.73 m^2 in a white woman aged 80y. Whether a GFR of 30 mL/min/1.73 m^2 is early enough to plan for RRT in a patient with diabetic nephropathy, a disease that can be more rapidly progressive than other kidney diseases is open to question, particularly given the widespread belief that patients with diabetes benefit from institution of RRT at a higher GFR than non-diabetic patients. However, we believe that the other referral criteria listed, including rising albumin excretion and inadequate blood pressure control, will ensure timely referral of those destined to reach stage 5 CKD.

Dietary protein restriction

The effects of dietary protein restriction are controversial. A meta-analysis in 1996 concluded that this intervention reduces proteinuria and slows the rate of the progression by reducing the rate of decline of GFR [416]. A later meta-analysis concluded that effects were less in RCTs than in non-RCT studies, that the effect was relatively greater in patients with diabetes, and that the magnitude of the effect was relatively weak. A Cochrane review, last updated in 1997 and not confined to RCTs, concluded that reducing protein intake does appear to slow progression of nephropathy in type 1 diabetes, but identified several unanswered questions: the level of protein restriction that should be used, whether compliance could be expected in routine care, and whether improvement in intermediate outcomes (e.g. creatinine clearance) would translate into improved clinical outcomes [417]. Since those reports an RCT confined to patients with type 2 diabetes and nephropathy has reported negative effects [418], but an RCT in type 1 patients suggested a reduction in mortality [419].

Co-ordination of care

Diabetic nephropathy should be managed in the expectation that other complications co-exist, including diabetic retinopathy, autonomic retinopathy, ischaemic heart disease, peripheral vascular disease, and diabetic foot problems. Structured care for diabetic patients with stage 5 CKD has been shown to improve outcomes, including a reduced risk of amputation and of hospitalisation and an improved quality of life [420].

Management of patients with haematuria

The differential diagnosis of haematuria is wide, and includes urinary tract malignancy, urinary tract stones, urinary tract infection, and glomerulonephritis. Haematuria can be the first presenting feature of kidney and bladder cancer, as well as some other serious urological diseases, although the yield from investigation of asymptomatic microscopic haematuria is very small, and the benefit of earlier detection of such tumours, compared to limiting investigation to patients with macroscopic haematuria, is uncertain [305 421]. Urinary tract malignancy is extremely rare under the age of 30 and rare under the age of 50. Current evidence does not support the use of urinalysis as a screening tool for urological malignancy [333 334]. Current NHS guidance on cancer referral suggests that macroscopic haematuria in adults, and microscopic haematuria in adults over 50 years, should result in urgent referral [422] and this guidance is reproduced in draft NICE guidelines [423]. At present this guidance does not include specific recommendations on the appropriate referral of patients with haematuria who also have proteinuria.

Asymptomatic microscopic haematuria is commonly due to minor glomerular abnormality, for instance thin basement membrane nephropathy or mild IgA nephropathy. Although a proportion of patients with IgA nephropathy develop progressive CKD, this is always accompanied by the development of hypertension and proteinuria. The great discrepancy between the frequency with which haematuria is found in the general population – around 4% [93 313 424] - (and with which IgA deposits are found at necropsy of patients with no known history of kidney disease or in deceased organ donors – up to 10% [425-428]) - and the frequency of ERF in the population is additional evidence that the great majority of patients with isolated microscopic haematuria are not destined to progress to ERF [305 313]. However, up to 50% of patients with urologically unexplained asymptomatic isolated haematuria have a defined glomerular disorder if subjected to kidney biopsy [190]; a small proportion of such patients will develop proteinuria or hypertension on prolonged follow-up [429].

Further guidance on the management of patients with asymptomatic microscopic haematuria is expected from an ongoing NHS R&D Health Technology Assessment funded systematic review.

Referral for kidney biopsy

The role of kidney biopsy in aiding management of unexplained ARF, nephrotic syndrome, and renal involvement in multisystem disease is well established. A number of studies have examined the impact of kidney biopsy on management [429-437]. Conditions diagnosed on biopsy that led to a change in management for patients presenting with CKD were rare. Paone et al concluded that biopsy only influenced management in the presence of significant proteinuria [431]. Turner et al reported that patients with less than 3 g/day proteinuria were less likely to have their management changed as a result of kidney biopsy – a change was made in 20% - but did not analyse lower degrees of proteinuria separately [433]. Cohen et al reported 3 changes in therapeutic decisions based on the biopsy result amongst 13 patients with CKD; in each case the change in management was to "withhold corticosteroids" [434]. Farrington et al concluded that the impact of biopsy on management was almost wholly confined to patients with interstitial nephritis and rapidly progressive glomerulonephritis but did not specifically analyse the impact of biopsy

result according to mode of presentation [435]. Richards et al reported that the result of kidney biopsy altered management in 58/128 (45%) of cases of chronic renal failure: these cases included 5 patients with myeloma and 27 who received steroid and cytotoxic treatment; treatment was withheld or reduced as a result of the biopsy in 15 [436].

The role of kidney biopsy in diabetic patients with proteinuria and no retinopathy remains unclear. Most unselected series have suggested that around 10% of these patients will turn out to have non-diabetic glomerulopathies but few diagnoses are amenable to specific therapies [403].

The published studies on the yield of kidney biopsy in older people [438-442] have all concluded that the diagnostic yield is no lower than in younger patients, with a wide range of pathologies including primary glomerulonephritis, renal involvement in systemic vasculitis, interstitial nephritis, and amyloidosis. However, the biopsies in these series were performed in highly selected patients, most commonly for accepted indications such as nephrotic syndrome and acute or sub-acute renal failure. In the series of Preston et al, 57 had chronic renal failure, including 6 patients with crescentic glomerulonephritis, considered to be potentially reversible [438].

The patients included in these reports are highly unlikely to be representative of the great majority of older patients with CKD, most of whom have negative urinalysis or low-grade proteinuria only [150]. It seems likely that the commonest histological finding in such patients would be nephrosclerosis – a lesion for which there is no specific treatment other than control of cardiovascular risk factors. However, there is clearly a pressing need for more research into the pathological processes underlying CKD in the elderly, and on how frequently kidney biopsy might lead to a change of management in this population.

Referral for suspected atherosclerotic renal artery stenosis

The suggestion that atherosclerotic renal artery stenosis (ARAS) is an important cause of kidney failure, refractory hypertension, and ACEI-induced deterioration in kidney function, and that patients with ARAS may benefit from revascularisation (usually with angioplasty and stent placement), combined with the fact that in the UK nephrologists are the "gate-keepers" for computed tomography (CT), magnetic resonance (MR), and direct renal angiography (the most common diagnostic methods), mean that guidance is required on which patients should be referred for these investigations.

Clinical prediction of ARAS

Numerous angiographic series have shown that atherosclerotic renal vascular disease (ARAS) is common amongst patients with carotid disease [242], coronary disease [238 240 241 362 387] or peripheral vascular disease [246-249 388 389] and amongst patients with heart failure [237] and aortic aneurysm [443]. The severity of ARAS amongst patients with coronary disease is a strong independent predictor of mortality [239]. So-called "flash pulmonary oedema", a syndrome of left ventricular failure usually with severe hypertension and with normal left ventricular function on echocardiography, is also highly suggestive of ARAS [444-448]. It is therefore easy to predict that a significant proportion of patients with atherosclerotic vascular disease and CKD will have ARAS, if subjected to angiography. In an analysis of 477 patients at high pre-test clinical probability of ARAS, a prediction rule based on age, sex, presence of atherosclerotic disease elsewhere, recent onset hypertension, smoking history, body mass index, presence of an abdominal bruit, serum creatinine concentration and serum cholesterol concentration was developed, and was

highly predictive of ARAS on angiography [449]. The same group later reported that 20% of patients with drug-resistant hypertension (defined as a diastolic BP > 95 mm Hg despite 2-drug antihypertensive therapy amongst patients referred on suspicion of secondary hypertension or because of refractory hypertension) were found to have ARAS on angiography [450]. The relevance of these findings to routine clinical practice amongst unselected patients with hypertension is unclear, as poor blood pressure control despite two-drug therapy is very common, and because the benefits of revascularisation amongst patients so identified are uncertain.

Natural history of ARAS

ARAS may progress to complete renal artery occlusion [246 247 451-453]; bilateral renal artery occlusion is invariably associated with ERF. Several authors have shown a high rate of undiagnosed ARAS amongst patients requiring dialysis, and suggested that earlier diagnosis and treatment of ARAS might have prevented kidney failure in some of these patients [243 454]. In those patients with ARAS who start RRT survival is relatively poor, the mean survival in one study being 27 months, with only 20% surviving 5 years [454]. Most patients with ARAS die from cardiovascular disease without reaching stage 5 kidney disease [455].

Correlation between ARAS and kidney function

The presence of atherosclerotic disease in the renal arteries by angiography does not prove that this is the cause of ERF [456-458]. Mounting evidence [250-255] suggests that in the great majority of such patients the renal impairment is due to parenchymal disease – atherosclerotic disease of intrarenal arteries and arterioles, often associated with glomerular abnormalities and proteinuria – and in such patients, no improvement in kidney function should be expected as a result of revascularisation.

Deterioration of kidney function during ACEI/ARB treatment

Advice on use of ACEI/ARBs in CKD is given above. Patients with a >30% rise in serum creatinine concentration after initiation or dose increase of an ACEI/ARB, particularly if not proteinuric, may have ARAS, and should be discussed with or referred to a nephrologist.

Which patients are likely to benefit from intervention?

Angioplasty with stenting has superseded surgical correction of renal artery lesions in most instances. There is general agreement (albeit not based on randomised controlled trials) that it is indicated in patients with "flash" pulmonary oedema and should be considered seriously in those with refractory, severe hypertension. Although ERF due to renal artery stenosis is potentially preventable, irreversible parenchymal disease due to hypertension, diabetes mellitus, or atheroembolism may be the main reason for impaired function rather than the stenosis itself. Various methods have been suggested for predicting the response to intervention but none is universally accepted [459]. The improvement in blood pressure control after angioplasty, with or without stent placement, is much less impressive in ARAS than in fibromuscular dysplasia [460], although angioplasty and stent placement was more likely to improve blood pressure control if kidney function was normal [461 462]. In a single centre, prospective observational study, stenting appeared to arrest deterioration in those with a rise in serum creatinine concentration of more than 20% over the previous 12 months, but had no beneficial effect on kidney function in those with stable renal function [463]. Another study found a modest increase in GFR after revascularization only amongst those patients with initially

abnormal GFR [461]. Two meta-analyses concluded that there was very little evidence of benefit that revascularisation reduces the rate of progression towards renal failure [464 465].

In many clinical situations there is insufficient evidence to indicate whether the benefits would outweigh the risks of stenting. For this reason a randomised controlled trial (ASTRAL – Angioplasty and Stent for Renal Artery Lesions) has been designed (**http://www.astral.bham.ac.uk/**). Nevertheless there will be individual patients in whom intervention will appear to be worthwhile. Factors to be taken into account include local facilities and expertise, coexistent disease, degree of renal impairment and rate of progression and estimated survival on dialysis.

Conclusions

There is an urgent need for further research to identify patients who will benefit from investigation with a view to revascularization for ARAS. Renal physicians are likely to best placed to be up to date with the relevant research. The recommendations for referral will require modification once the results of the ASTRAL trial and others have been published.

Frequency of measurements of creatinine concentration, potassium, phosphate, and haemoglobin concentrations in stage 3 CKD

These recommendations are based on practical considerations rather than RCT evidence. To our knowledge there are no studies that have specifically studied the optimal timing of repeat measurements. For patients with completely stable CKD, it may be that 6-monthly measurements add little value other than peace of mind. Our recommendations are based on accepted UK practice and are similar to those in the K/DOQI guidelines [6].

Management of anaemia in patients with CKD

The importance of anaemia in CKD has been increasingly recognised since the introduction of erythropoietin therapy in the 1980s but until recent years studies were largely confined to anaemia in dialysis-dependent patients, and guidelines for the management of anaemia in non-dialysis dependent patients are largely based on data from these studies. Care must therefore be taken in the interpretation and implementation of the available recommendations.

Definition of anaemia

The Kidney Disease Outcomes Quality Initiative guidelines of the National Kidney Foundation (NKF K/DOQI) define anaemia in CKD as a haemoglobin concentration of less than 11 g/dL in pre-menopausal females and pre-pubertal patients, and less than 12 g/dL in adult males and post-menopausal females. The Revised European Best Practice Guidelines (EBPG) [466] define anaemia as a Hb concentration 2 SD below the population mean, i.e. <11.5 g/dL in adult female patients, < 13.5 g/dL in adult male patients, and <12.0 g/dL in adult male patients aged > 70y. The Renal Association Standards recommend evaluation of anaemia "when Hb < 12 g/dL (adult males and post-menopausal females), < 11 g/dL (pre-menopausal females)"; and that "anaemia may be considered the result of uraemia if the glomerular filtration rate (GFR) is < 30 mL/min (< 45 mL/min in diabetics) and no other cause, e.g. blood loss, folate or B12 deficiency, is identified [2].

Prevalence of anaemia in CKD

Data from a Canadian cohort show that anaemia is present in around 25% of patients with CKD whose GFR is >50 mL/min/1.73 m^2, 44% between 35-49 mL/min/1.73 m^2, 51% between 25-34 mL/min/1.73 m^2, and 87% below 25 mL/min/1.73 m^2 [467]. Data from the third NHANES study suggest that the decline in Hb level starts at a GFR of 70 mL/min/1.73 m^2 in men and 50 mL/min/1.73 m^2 in women [468]. The prevalence of renal anaemia increased from 1 percent at an estimated GFR of 60 mL/min/1.73 m^2, to 9 and 33 percent at estimated GFRs of 30 and 15 mL/min/1.73 m^2 respectively. A report from the Kidney Early Evaluation Program showed that anaemia is particularly common amongst patients with diabetes and CKD: 22.2% of diabetic participants with stage 3 CKD were anaemic compared to 7.9% of non-diabetics with stage 3 CKD [469].

In the UK, two studies afford information on the prevalence of anaemia in CKD. In one study of patients with significant CKD (defined by a median GFR of 28.5 mL/min/1.73 m^2) not yet referred to nephrology services, the prevalence of significant anaemia (Hb < 11 g/dL) was 1295 adults per million population [94]. Another study suggested that 3.8% of those with stage 3-5 CKD would require treatment for anaemia according to the K/DOQI and EBPG haemoglobin threshold value of < 11 g/dL, equivalent to 1862 per million population [96].

Consequences of anaemia

Untreated anaemia has a number of adverse consequences both for the individual patient and for the healthcare system ranging from effects on quality of life, cognitive function and libido through to increased mortality and morbidity with its associated economic burden. Of paramount importance is the strong association between anaemia and cardiovascular disease (CVD). One of the earliest manifestations of heart disease in CKD is left ventricular hypertrophy (LVH) [467]. Anaemia has both direct and indirect effects on left ventricular function and growth. Age, hypertension, and Hb level are independent predictors for the presence of LVH. In the Canadian multicentre cohort study of patients with early kidney disease (mean GFR 36.8 mL/min/1.73 m^2) a fall in haemoglobin of 0.5 g/dL over 12 months' observation was associated with an odds ratio of 1.32 for increase in left ventricular growth; an increase in systolic blood pressure of 5 mm Hg conferred an odds ratio of 1.11 [467]. A number of other studies have shown that anaemia predicts increased left ventricular mass, left ventricular dilatation, heart failure and death, and that anaemia is associated with increased hospitalisation rates and increased mortality.

Analysis of patients in the Studies Of Left Ventricular Dysfunction trial found that anaemia and CKD were independent risk factors for mortality amongst patients with heart failure due to left ventricular dysfunction [470]. Other retrospective studies of patients with CKD and heart failure have also demonstrated that Hb level is independently associated with increased subsequent risk of death [471-475]. In the UK there are 6,000 deaths per year due to heart failure associated with CHD and the annual mortality for those with heart failure ranges from 10 to >50% depending on severity. Standard 11 of the NSF for CHD dictates that treatments most likely to relieve symptoms and reduce the risk of death in patients with heart failure should be offered [224]. Anaemia is also a potent risk marker for poor outcome amongst patients with acute myocardial infarction [476].

Management of renal anaemia associated with CKD

Anaemia in CKD is due to relative deficiency of erythropoietin (EPO), but measurements of EPO levels are seldom necessary in the management of renal anaemia. It is important to exclude other treatable causes of anaemia [466]. Treatment of renal anaemia should not be started until other causes of anaemia – for instance, iron deficiency, folate or B12 deficiency, haemolysis – have been excluded, with further investigation of the underlying cause (e.g. of iron deficiency) according to standard medical practice. Treatment with intravenous iron may, by itself, correct anaemia amongst some patients with CKD [477].

There are several commercially available ESAs: epoetin alfa, epoetin beta, and darbepoetin alfa. Adequate iron stores are necessary to permit an optimal response to ESA treatment; reduced transferrin saturation is independently associated with anaemia in the NHANES III dataset [478] and also in unselected patients with diabetes mellitus [479]. Options for assessment of iron stores include serum ferritin, transferrin saturation, and percentage hypochromia (a measurement of the percentage of hypochromic red cells, which can be generated by some automated cell counting machines) [466]. Ensuring adequate iron stores for response to EPO often requires intravenous iron replacement.

Most of the data on treatment of renal anaemia come from studies in patients already established on dialysis. A recent meta-analysis concluded that such treatment "provides important clinical and quality-of-life benefits while substantially reducing hospitalisations and transfusions" [480]. However, an extensive meta-analysis [481] concluded that the benefits of higher Hb targets (14 g/dL versus <10 g/dL) did not outweigh the risks of hypertension, vascular access thrombosis and mortality. These conclusions were largely derived from the US normalisation of haematocrit trial [482], which was confined to haemodialysis patients with severe cardiovascular disease. This trial was terminated because the mortality in patients randomised to normalisation of Hb ($\geq$ 13 g/dL) was greater than in the group randomised to standard Hb levels ($\cong$ 11 g/dL). However, this did not achieve significance and in post hoc analysis of both groups a high level of Hb was correlated with lower mortality. An earlier meta-analysis confined to pre-dialysis patients concluded that there was insufficient data to draw firm conclusions about the benefits of normalisation of Hb [483]. In uncontrolled and controlled studies of correction of anaemia with intravenous iron and EPO in patients with resistant heart failure and CKD, improvements in cardiac function, reduced hospitalisation and reduction in the rate of progression of kidney failure have been reported [484-488].

Recently published randomised controlled trials in the treatment of anaemia have yielded conflicting results. The effects of early and late intervention with epoetin alfa on left ventricular mass among patients with stage 3-4 CKD were recently reported in a study from Australia [489]. Patients in the GFR range 15-50 mL/min/1.73 m^2 with haemoglobin levels between 11-12 g/dL (female) and 11-13 g/dL (male) were monitored for 2 years or to start of dialysis and randomised to either treatment to maintain haemoglobin levels of 12-13 g/dL (Group A), or to treatment to maintain haemoglobin levels of 9-10 g/dL (Group B). There were 75 patients in group A, 74 of whom received epoetin alpha, and 80 patients in group B, only 8 of whom received epoetin alpha. After 2 years haemoglobin levels in group B had fallen from a mean of 11.2±0.8 to 10.8±1.3 g/dL, in group A mean haemoglobin level rose slightly from 11.2±0.9 to 12.1±1.4 g/dL. There was no significant difference in change in left ventricular mass index between the 2

groups (group A = 2.5±20 g/m^2 versus group B 4.5±20 g/m^2) and no difference in decline in renal function (group A 8±9 mL/min/1.73 m^2 versus group B 6±8 mL/min/1.73 m^2). There was no difference in blood pressure and prevalence of diabetes between the 2 groups, and no difference in use of ACEI/AII receptor blockers. One criticism of this study was that the 2 year mean haemoglobin level did not differ substantially and values were maintained at the lower limit of the target range for group A patients. Those who did achieve target levels in group A had a change in left ventricular mass index consistent with the findings of previous studies identifying anaemia as an independent predictor of LVH. Contrasting results on progression of renal failure were found in a randomised controlled trial of treating anaemia early in non-diabetic renal failure patients that demonstrated a highly significant reduction in progression of renal failure in the early treatment arm [490]. Patients with serum creatinine levels of 177-530 μmol/L and haemoglobin levels of 9-11.6 g/dL were randomised to either immediate treatment with subcutaneous erythropoeitin alpha aiming for a haemoglobin level of ≥13 g/dL, or to deferred treatment when haemoglobin fell to below 9 g/dL. An interesting feature of this study was that patients were not allowed either ACE inhibitors or AII receptor blockers for the duration of the study. At the start of the study mean haemoglobin (early treatment 10.1±0.5 g/dL, deferred treatment 10.1±0.6 g/dL) and (Cockcroft and Gault) creatinine clearance (early treatment 25.7±9.1 mL/min, deferred treatment 22.3±6.0 mL/min) did not differ significantly between the 2 groups. After 12 months haemoglobin had risen to 12.9±0.4 g/dL in the early treatment arm and fallen to 10.3±1.0 g/dL in the deferred treatment arm and there was a highly significant difference in mean creatinine clearance between the 2 groups (early treatment arm 21.9±9.4 mL/min vs. 16.1±6.3 mL/min in the deferred treatment arm, $p<0.001$).

Whether early anaemia treatment prevents development of LVH, reduces cardiovascular mortality and morbidity, delays progression of CKD and reduces stroke and heart failure related hospitalisations, is clearly still open to question. There are currently 3 large studies seeking to answer these questions. The Correction of Haemoglobin and Outcomes in Renal Insufficiency (CHOIR) study seeks to randomise 2000 patients aged >18 years with GFR 15-50 mL/min and Hb <11 g/dL at enrollment to a Hb level as close to 13.5 g/dL as possible or to as close to 11.3 g/dL as possible [491]. The CREATE trial (Cardiovascular risk reduction by Early Anaemia Treatment with Epoetin beta) has randomised 600 predialysis patients (creatinine clearance 15-35 mL/min) with Hb levels of 11-12.5 g/dL to either immediate treatment (target Hb levels 13-15 g/dL) or delayed treatment (target Hb levels 10.5-11.5 g/dL once Hb falls to < 10.5 g/dL) [492]. The TREAT (Trial to Reduce cardiovascular Events with Aranesp Therapy study will randomise 4000 patients with CKD and type 2 diabetes mellitus to darbepoetin, adjusted to achieve a Hb of 13 g/dL, or placebo unless Hb falls below 9 g/dL, with 4 year follow-up [493]. The results of these trials should help to determine the optimal management of predialysis renal anaemia.

NICE will be publishing guidelines for the management of anaemia associated with CKD and it seems likely that they will be making similar recommendations to the EBPG and KDOQI about haemoglobin thresholds and the ranges of Hb level to be achieved. EBPG recommend that ESAs should be given to all patients with CKD with Hb levels consistently below 11 g/dL where all other causes of anaemia have been excluded.

Management of disorders of calcium, phosphate and parathyroid hormone in patients with CKD

These metabolic disturbances are common in CKD, and not only cause significant bone disease but also contribute to cardiovascular disease. In addition, treatment that may benefit the skeleton may contribute further to cardiovascular disease, making the choice of treatment complex.

Parathyroid hormone, calcium and phosphate.

Elevations in plasma PTH concentration (secondary hyperparathyroidism) are seen early, are common when estimated GFR is < 60 mL/min/1.73 m^2 , and clearly precede the onset of hyperphosphataemia [494-501]. Elevated PTH is the most sensitive marker for disordered bone and mineral metabolism in early CKD. Elevation of PTH in the CKD 3 and 4 populations predicts the development of more severe hyperparathyroid disease, which in turn is clearly associated with increased skeletal and cardiovascular morbidity and mortality.

Parathyroid stimulation in CKD arises from any combination of decreased calcium, increased phosphate and decreased calcitriol concentration. This stimulation results in:

1. Increased parathyroid hormone synthesis per cell.
2. Increased cell proliferation rate leading to parathyroid hyperplasia..

The first of these is reversible by correction of hyperphosphataemia (dietary phosphate restriction and oral phosphate binders), and reprovision of deficient calcitriol. Hyperplasia, on the other hand, is largely irreversible and its development frequently sets the stage for progressive disease, ultimately requiring parathyroidectomy. Prevention of these processes is important and, although robust clinical data are lacking, logic, observational data and experimental evidence suggest that early intervention is appropriate.

Treatment guidelines on the management of renal osteodystrophy from the Renal Association [2], US National Kidney Foundation [502] and European Best Practice Guidelines [9] are aimed at attainment of target PTH, calcium and phosphate concentrations. These guidelines also recommend PTH as the marker of choice for the early detection of renal osteodystrophy in patients with CKD. There is a good association between the prevailing concentration of PTH and the underlying state of the bone [503]. The K/DOQI targets for PTH reflect this [502], with very high PTH predicting hyperparathyroid bone disease, moderately elevated PTH within the K/DOQI target predicting normal bone turnover, and PTH below target predicting low turnover adynamic bone disease. The PTH targets for advanced CKD (stage 4 and 5) are above typical laboratory normal ranges. Both extremes of PTH are associated with an increased risk of cardiovascular disease in patients with CKD stage 5 [504].

Fragments of PTH accumulate in CKD [505-507] and these are detected by many commercial so-called “intact” PTH assays. However, the overall prevalence of secondary hyperparathyroidism in the CKD population appears to be similar even when more specific PTH assays are used which do not detect these fragments [508]. This feature of the commonly used commercial PTH assays has no impact on the diagnosis of disordered bone metabolism in stage 3 CKD, but becomes relevant in stage 4 and 5 CKD. Because of lack of consensus on management of this complex disorder, these guidelines suggest

that treatment of disordered bone metabolism in CKD 4 and 5 is initiated by nephrologists.

Phosphate retention is an important contributor to hyperparathyroidism, and a powerful predictor of mortality risk amongst patients on haemodialysis [509 510], possibly because it promotes vascular calcification [511-513]. Phosphate binders, taken with meals to reduce phosphate absorption, is the mainstay of treatment; dietary restriction of high phosphate foods also has a limited role. The optimal choice of phosphate binder in CKD has not been defined. Until recently, calcium-containing phosphate binders were the mainstay of treatment, but in haemodialysis patients, studies have shown that overuse of these drugs may contribute further to vascular calcification, at least when compared to sevelamer hydrochloride, a non-calcium phosphate binder that also reduces LDL cholesterol [514]. Sevelamer is currently only licensed for use in patients receiving haemodialysis. The complexity of treatment of phosphate retention, and the lack of evidence on which to base guidelines in CKD, led us to recommend that all such treatment be initiated and supervised by nephrologists, although there is clearly room for shared care of patients with CKD being treated with phosphate binders.

Our recommendations for measurement of PTH in all patients with stage 3 CKD will have significant cost implications. The evidence-base demonstrating improved outcomes in patients with stage 3 CKD as a consequence of better evaluation and treatment of renal osteodystrophy is limited, although in a recent cohort study in the USA of patients starting RRT, it was found that measurement of PTH and use of vitamin D analogues or calcium-containing phosphate binders was markedly less amongst patients who had not been managed by a nephrologist prior to ERF compared to those who had. These interventions were associated with a reduced 1-year mortality, independent of early vs. late referral [515]. The frequency of measurement of PTH set out above is to be seen as a minimum and is somewhat lower than that recommended in comparable guidelines from other countries (K/DOQI, EBPG). It is anticipated that these recommendations will be revised as new evidence emerges.

PTH assays

Clotted blood samples sent for PTH assay need to be kept on ice and separated rapidly. However, PTH is stable in blood samples anticoagulated with EDTA [516].

Vitamin D Deficiency

Vitamin D deficiency, with low plasma 25-hydroxyvitamin D concentration, is common in all stages of CKD [517]. It is a risk factor for more severe hyperparathyroidism in CKD and in elderly populations (in which the prevalence of CKD is substantial), low 25-hydroxyvitamin D predisposes to low bone mineral density (BMD) and fracture [518 519]. Conversely, supplementation with colecalciferol/ergocalciferol reduces hip fracture and falls [520 521].

A single measurement of 25-hydroxyvitaminD in any CKD stage 3 patient with elevated PTH will identify those in whom vitamin D deficiency dictates a need for supplementation. There is no evidence that stage 5 patients respond usefully to native vitamin D supplementation

Bone Density and Bone Histology

Reduced hip bone mass is a powerful predictor of mortality amongst dialysis patients [522]. Abnormalities of bone histology are common amongst patients with CKD in the pre-dialysis phase [499 523-526] although most of the patients included in these studies

probably had stage 4-5 CKD. A cross-sectional study in 113 patients with renal disease and 89 matched controls showed evidence of reduced bone density and increased bone turnover early in the course of CKD, when GFR was less than 70 mL/min [527]. Risk factors for having significant bone disease when starting dialysis include female sex, tubulointerstitial disease, long duration of uraemia (i.e. extended periods in CKD stage 3 and 4), and youth [523]. Others have found no independent correlation between estimated GFR and bone mineral density in a large population sample [528].

Reduced bone mineral density in association with CKD is likely to be secondary to the CKD and thus to form a component of the prevailing renal osteodystrophy. Low BMD is part of the renal osteodystrophy data set and in CKD does not constitute a diagnosis in its own right [529]. Any therapy designed for osteoporosis (eg bisphosphonates) should be on a background of optimised management of the underlying renal osteodystrophy. In most cases it will take place in specialist centres.

Indications for bone density measurement (usually by Dual Energy X-ray Absorptiometry – DEXA), are similar to those in the non-renal population - history of low trauma fracture or presence of risk fractures for fracture

Use of renal ultrasound in investigation of CKD

Ultrasound scanning gives information on renal size and echogenicity and also allows detection of hydronephrosis, a feature of obstructive nephropathy. Occasionally, other abnormalities are detected. We found no population-based studies of the diagnostic yield of ultrasound scanning in unselected patients with CKD. Ultrasound is an integral part of the assessment of patients with ARF, and of those with progressive kidney disease and those in whom kidney biopsy may be indicated. In these situations, the main role of ultrasound is to aid a decision about whether kidney biopsy is indicated.

Immunisation in patients with CKD

The recommendations for influenza and pneumococcal immunisation here are consistent with those from the Department of Health, which recommend immunisation for “chronic renal disease, including nephrotic syndrome, chronic renal failure, and renal transplantation”; chronic renal failure is not further defined. [530 531]. However, the evidence that patients with CKD as defined here (or even patients with stage 4-5 CKD) are at increased risk of complications from these diseases is extremely limited. Immunisation against hepatitis B is part of the preparation of patients being considered for RRT, largely because of the high potential for spread of hepatitis B on haemodialysis units, and is also Department of Health policy [532 533].

Recommendations for regular review of drug treatment and avoidance of NSAIDs

Many drugs are cleared by renal excretion, and the clearance of these drugs is therefore reduced in the presence of reduced kidney function. This can lead to drug accumulation with enhanced toxicity. In some instances, particularly in the use of aminoglycosides (e.g. gentamicin), this requires major dosage adjustments according to kidney function. Other drugs may be completely contraindicated in the presence of impaired kidney function. Several studies have identified a high frequency of failure to adjust doses for reduced GFR, particularly amongst elderly people [534-537 538-540].

Unfortunately, the current British National Formulary [541] uses a different classification of kidney function to the one adopted here. It recommends measurement of kidney function either by measurement of creatinine clearance using a 24 h urine collection or by serum creatinine, stating "The serum creatinine concentration is sometimes used instead as a measure of renal function but is only a rough guide even when corrected for age, weight, and sex. Nomograms are available for making this correction and should be used where accuracy is important." However, it gives no reference to these nomograms, nor to any of the commonly used formulae for estimation of GFR. It recommends division of renal impairment into 3 grades, according to creatinine clearance: mild (GFR 20-50 mL/min, serum creatinine 300-300 μmol/L), moderate (creatinine clearance 10-20 mL/min, serum creatinine 300-700 μmol/L) and severe (GFR < 10 mL/min, serum creatinine >700 μmol/L). However, product literature may not correspond with this grading. Most product information sheets give advice on drug dosage adjustment based on creatinine clearance, without "normalisation" for body surface area: normalisation would clearly be inappropriate in this instance, as it would lead to prescription of higher doses for smaller patients. Whether the differences between the Cockcroft and Gault formula (which predicts non-normalised creatinine clearance) and the MDRD formula (which predicts normalised GFR) would result in clinically important differences in drug doses in stage 3 CKD is uncertain. Pending definitive guidance, we recommend use of either formula to identify patients with CKD for whom dosage adjustments may be appropriate, followed by individualised decisions on drug doses based on the best available source of evidence.

NSAIDS may cause kidney damage in a number of ways, including idiosyncratic reactions that include ARF, interstitial nephritis, and nephrotic syndrome. Long-term use may increase the risk of analgesic nephropathy. They also cause a predictable reduction in GFR, which is also seen with cyclo-oxygenase 2 (COX-2) inhibitors [256]. The benefits of these drugs must therefore be weighed carefully against the possible deleterious effects on kidney function in each patient with CKD in whom their use is considered.

Recommendations for stage 4-5 CKD, including dietary assessment, correction of acidosis, counselling and education, pre-emptive transplantation, vascular and peritoneal access, and palliative care

All of these recommendations are consistent with those in the Part 1 of the NSF for Renal Services [32]. We have not repeated the evidence for these interventions here.

Referral criteria

Many patients with microalbuminuria, proteinuria, haematuria, or mild to moderate CKD are not destined to develop progressive CKD but may be at increased risk of cardiovascular disease. Those who **are** at risk of progressive CKD can be identified, without the need to travel to a hospital, by the detection of proteinuria or hypertension [284 295 299].

Patients should not be expected to travel to hospital for tests that can just as easily be done in primary care. A perceived need to ensure long-term follow-up (for instance in patients with suspected chronic glomerulonephritis) is **not** an adequate reason for long-term hospital follow-up; rather, such patients should be entered into a disease

management programme and care plan that allows reliable identification and recall of such patients within primary care.

Certain aspects of clinical management of patients with CKD will require the patient to be seen in a hospital setting. These include

- renal biopsy
- renal angiography (including CT and MR angiography)
- counselling and education about renal replacement therapy
- construction of arteriovenous fistulae or polytetrafluoroethylene (PTFE) grafts for haemodialysis

Urgency of referral

Ideally, no patient should be kept waiting for a specialist opinion, and if the system is in steady state (rate of referrals = rate of patients being seen) there is no good reason why immediate access should not be offered in all clinical situations warranting referral. However, where waiting lists for outpatient consultations occur, referrals should be prioritised according to clinical urgency. We identified no research studies addressing this question. The recommendations for immediate referral are all situations in which delay in institution of treatment, which might include urgent dialysis, might cause harm or death. The recommendations for urgent referral are all situations in which, without prompt treatment, further clinical deterioration is possible. The recommendations for routine referral include all other clinical situations covered in this guideline document. As stated earlier, nothing in these guidelines should deter any clinician from seeking advice about a given patient, whatever the precise clinical situation.

Appendix 1. Prediction of GFR from age and serum creatinine

White men	Age						
Creatinine	**20**	**30**	**40**	**50**	**60**	**70**	**80**
70	>90	>90	>90	>90	>90	>90	>90
80	>90	>90	>90	>90	>90	88	86
90	>90	>90	86	82	79	77	75
100	88	81	76	73	70	68	66
110	79	72	68	65	63	61	59
120	71	66	62	59	57	55	54
130	65	60	56	54	52	50	49
140	60	55	52	49	48	46	45
150	55	51	48	46	44	43	42
160	51	47	44	42	41	40	39
170	48	44	41	40	38	37	36
180	45	41	39	37	36	35	34
190	42	39	36	35	34	32	32
200	39	36	34	33	32	31	30
210	37	34	32	31	30	29	28
220	35	33	31	29	28	27	27
230	34	31	29	28	27	26	25
240	32	29	28	27	26	25	24
250	31	28	27	25	24	24	23
260	29	27	25	24	23	23	22
270	28	26	24	23	22	22	21
280	27	25	23	22	21	21	20
290	26	24	22	21	21	20	19
300	25	23	21	21	20	19	19
310	24	22	21	20	19	18	18
320	23	21	20	19	18	18	17
330	22	20	19	18	18	17	17
340	21	20	19	18	17	17	16
350	21	19	18	17	17	16	16
360	20	18	17	17	16	16	15
370	19	18	17	16	16	15	15
380	19	17	16	16	15	15	14
390	18	17	16	15	15	14	14
400	18	16	15	15	14	14	13
410	17	16	15	14	14	13	13
420	17	15	15	14	13	13	13
430	16	15	14	14	13	13	12
440	16	15	14	13	13	12	12
450	15	14	13	13	12	12	12
460	15	14	13	13	12	12	11
470	15	14	13	12	12	11	11
480	14	13	12	12	11	11	11

White Women

Creatinine	20	30	40	50	60	70	80
40	>90	>90	>90	>90	>90	>90	>90
50	>90	>90	>90	>90	>90	>90	>90
60	>90	>90	>90	>90	>90	>90	89
70	>90	>90	85	82	79	76	74
80	84	78	73	70	67	65	64
90	74	68	64	61	59	57	56
100	65	60	57	54	52	51	49
110	58	54	51	48	47	45	44
120	53	49	46	44	42	41	40
130	48	44	42	40	39	37	36
140	44	41	38	37	35	34	33
150	41	38	35	34	33	32	31
160	38	35	33	31	30	29	29
170	35	33	31	29	28	27	27
180	33	30	29	27	26	26	25
190	31	29	27	26	25	24	23
200	29	27	25	24	23	23	22
210	28	25	24	23	22	21	21
220	26	24	23	22	21	20	20
230	25	23	22	21	20	19	19
240	24	22	21	20	19	18	18
250	23	21	20	19	18	18	17
260	22	20	19	18	17	17	16
270	21	19	18	17	17	16	16
280	20	18	17	16	16	15	15
290	19	18	17	16	15	15	14
300	18	17	16	15	15	14	14
310	18	16	15	15	14	14	13
320	17	16	15	14	14	13	13
330	16	15	14	14	13	13	12
340	16	15	14	13	13	12	12
350	15	14	13	13	12	12	12
360	15	14	13	12	12	12	11
370	14	13	13	12	12	11	11

Black Men	Age						
Creatinine	**20**	**30**	**40**	**50**	**60**	**70**	**80**
90	>90	>90	>90	>90	>90	>90	>90
100	>90	>90	>90	88	85	82	80
110	>90	88	83	79	76	74	72
120	86	79	75	71	69	67	65
130	79	72	68	65	63	61	59
140	72	66	63	60	58	56	54
150	67	61	58	55	53	52	50
160	62	57	54	51	49	48	47
170	58	53	50	48	46	45	43
180	54	50	47	45	43	42	41
190	51	47	44	42	41	39	38
200	48	44	41	40	38	37	36
210	45	42	39	37	36	35	34
220	43	39	37	36	34	33	32
230	41	37	35	34	33	32	31
240	39	36	34	32	31	30	29
250	37	34	32	31	30	29	28
260	35	32	31	29	28	27	27
270	34	31	29	28	27	26	25
280	32	30	28	27	26	25	24
290	31	29	27	26	25	24	23
300	30	28	26	25	24	23	23
310	29	27	25	24	23	22	22
320	28	26	24	23	22	22	21
330	27	25	23	22	21	21	20
340	26	24	22	21	21	20	20
350	25	23	22	21	20	19	19
360	24	22	21	20	19	19	18
370	23	22	20	19	19	18	18
380	23	21	20	19	18	18	17
390	22	20	19	18	18	17	17
400	21	20	19	18	17	17	16
410	21	19	18	17	17	16	16
420	20	19	18	17	16	16	15
430	20	18	17	16	16	15	15
440	19	18	17	16	15	15	15
450	19	17	16	16	15	15	14
460	18	17	16	15	15	14	14
470	18	16	15	15	14	14	13
480	17	16	15	14	14	13	13
490	17	16	15	14	14	13	13
500	17	15	14	14	13	13	13
510	16	15	14	13	13	13	12
520	16	15	14	13	13	12	12
530	16	14	13	13	12	12	12
540	15	14	13	13	12	12	11
550	15	14	13	12	12	12	11
560	15	13	13	12	12	11	11
570	14	13	12	12	11	11	11

Black Women **Creatinine**	**20**	**30**	**40**	**50**	**60**	**70**	**80**
70	>90	>90	>90	>90	>90	>90	90
80	>90	>90	89	85	82	79	77
90	89	82	77	74	71	69	67
100	79	73	68	65	63	61	60
110	71	65	61	59	57	55	53
120	64	59	56	53	51	50	48
130	58	54	51	48	47	45	44
140	53	49	46	44	43	41	40
150	49	45	43	41	40	38	37
160	46	42	40	38	37	36	35
170	43	39	37	35	34	33	32
180	40	37	35	33	32	31	30
190	38	35	33	31	30	29	28
200	35	33	31	29	28	27	27
210	33	31	29	28	27	26	25
220	32	29	28	26	25	25	24
230	30	28	26	25	24	23	23
240	29	26	25	24	23	22	22
250	27	25	24	23	22	21	21
260	26	24	23	22	21	20	20
270	25	23	22	21	20	19	19
280	24	22	21	20	19	19	18
290	23	21	20	19	18	18	17
300	22	20	19	18	18	17	17
310	21	20	19	18	17	17	16
320	21	19	18	17	16	16	16
330	20	18	17	17	16	15	15
340	19	18	17	16	15	15	14
350	19	17	16	15	15	14	14
360	18	17	16	15	14	14	14
370	17	16	15	14	14	14	13
380	17	16	15	14	14	13	13
390	16	15	14	14	13	13	12
400	16	15	14	13	13	12	12
410	15	14	13	13	12	12	12
420	15	14	13	12	12	12	11
430	15	13	13	12	12	11	11
440	14	13	12	12	11	11	11

Appendix 1. Tables for estimation of GFR using 4-variable MDRD formula. Adapted from tables developed by the British Columbia Renal Agency, Guidelines Protocols and Advisory Committee, Ministry of Health Chronic Disease Management Group, and Kidney Foundation British Columbia Branch, British Columbia, Canada, with permission.

Stage 1	Stage 2	Stage 3	Stage 4	Stage 5

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