National Clinical Guideline Centre

Chronic kidney disease

Chronic kidney disease (partial update)

Early identification and management of chronic kidney disease in adults in primary and secondary care

Clinical Guideline 182

Methods, evidence and recommendations

July 2014

This guideline was updated and merged with NICE guidelines on managing hyperphosphateamia (CG157) and managing anaemia in CKD (NG8) in 2021. This document preserves evidence reviews and committee discussions for areas of the guideline that were not updated in 2021.

See the chronic kidney disease guideline on the NICE website for the guideline recommendations.

Final version

Commissioned by the National Institute for Health and Care Excellence

Royal College of Physicians
The Royal College of Surgeons of England
RCGP Royal College of General Practitioners
Royal College of Nursing
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Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

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Contents

Guideline update

This guidance is a partial update of NICE clinical guideline 73 (published September 2008) and will replace it.

New and updated recommendations have been included covering the early identification and management of chronic kidney disease in adults in primary and secondary care.

Recommendations are marked to indicate the year of the last evidence review [2008] if the evidence has not been updated since the original guideline, [2008, amended 2014] if the evidence has not been updated since the original guideline, but changes have been made that alter the meaning of the recommendation, [2014] if the evidence has been reviewed but no change has been made to the recommendation and [new 2014] if the evidence has been reviewed and the recommendation has been added or updated. Stakeholders were invited to comment only on the new and updated recommendations in this guideline.

New and updated evidence reviews and recommendations are shaded pink with 'Updated 2014' in the right hand margin.

Appendix O contains recommendations from the 2008 guideline that NICE proposes deleting in the 2014 update. This is because the evidence has been reviewed and the recommendation has been updated or because NICE has updated other relevant guidance and has replaced the original recommendations. Where there are replacement recommendations, details are provided. Where there is no replacement recommendation, an explanation for the proposed deletion is given. Stakeholders were invited to comment on the deleted recommendations as part of the consultation on the 2014 update.

The original NICE guidance and supporting documents are available from http://publications.nice.org.uk/chronic-kidney-disease-cg73/.

Guideline development group members

Guideline development group 2014

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National Clinical Guideline Centre (NCGC) Technical team 2014

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Guideline development group 2008

Name	Role
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The following were invited to attend specific meetings and to advise the GDG:

- Dr Claire Beeson acted as a deputy for Dr Shelagh O'Riordan at a GDG meeting.
- Dr Indranil Dasgupta, Consultant Nephrologist, invited to contribute at a specific meeting as
- an expert representing the Type 2 Diabetes Guideline but was not a full member of the GDG.
- Dr Patrick Fitzgerald acted as a deputy for Dr Ivan Benett at a GDG meeting.
- Dr Neil Iggo, Consultant Nephrologist, acted as a deputy for Dr Lawrence Goldberg at a GDG
- meeting.
- Dr Kanchana Imrapur acted as a deputy for Dr David Stephens at a GDG meeting.
- Dr Marta Lapsley acted as a deputy for Dr Edmund Lamb at a GDG meeting.
- Ms Nicola Thomas acted as a deputy for Ms Natasha McIntyre at a GDG meeting.

Acknowledgments

Acknowledgements 2008

The Guideline Development Group is grateful to the following people for their valuable contributions to the development of this guideline:

- Dr Bernard Higgins, Director, NCC-CC
- Ms Jane Ingham, Assistant Director, NCC-CC
- Ms Susan Tann, Centre Co-ordinator, NCC-CC
- Ms Jill Parnham, Associate Director, NCC-CC
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1 Introduction

1.1 Background

The Renal National Service Framework (NSF)[87], and the subsequent NICE Clinical Practice Guideline for early identification and management of adults with chronic kidney disease (CKD) in primary and secondary care (CG73), served to emphasise the change in focus in renal medicine from treatment of established kidney disease to earlier identification and prevention of kidney disease.

CKD describes abnormal kidney function and/or structure. It is common, frequently unrecognised and often coexists with other conditions (for example, cardiovascular disease and diabetes). Moderate to severe CKD also carries an increased risk of other significant adverse outcomes such acute kidney injury, falls, frailty and mortality. The risk of developing CKD increases with increasing age, and some conditions that coexist with CKD become more severe and increasingly prevalent as kidney dysfunction advances. CKD can progress to end-stage kidney disease (ESKD)in a small but significant percentage of people.

CKD is usually asymptomatic but it is detectable, and tests for detecting CKD are both simple and freely available. There is evidence that treatment can prevent or delay the progression of CKD, reduce or prevent the development of complications and reduce the risk of cardiovascular disease. However, because of a lack of specific symptoms, CKD frequently remains undetected and unrecognised. As a consequence people with CKD are often not diagnosed, or diagnosed late when CKD is at an advanced stage. Late diagnosis is associated with increased morbidity, mortality and healthcare associated costs.

1.2 Definition

CKD is defined as abnormalities of kidney structure or function, present for more than 3 months, with implications for health.[194] The US National Kidney Foundation kidney disease outcomes quality initiative (NKF-KDOQI) introduced a 5 stage classification of CKD in 2002.[288] This classification divided CKD into 5 stages and used the combination of an index of kidney function, glomerular filtration rate (GFR), and markers of kidney damage to define the stages. Stages 3–5 were defined by the finding of a GFR less than 60 ml/min/1.73m^2 with or without markers of kidney damage, on at least two occasions separated by a period of at least 90 days. Stages 1 and 2 required the presence of markers of kidney damage including albuminuria, urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by histology, structural abnormalities detected by imaging and a history of kidney transplantation. On the basis of delineating increased risk of adverse outcome NICE CG 73 suggested 2 key changes to this classification; the sub-division of stage 3 into 3a (GFR 45-59 ml/min/1.73 m^2) and 3b (30-44 ml/min/1.73 m^2), and the addition of the suffix 'P' to denote significant proteinuria at any stage. NICE CG73 defined significant proteinuria as urinary albumin:creatinine ratio (ACR) ≥ 30 mg/mmol, roughly equivalent to a protein:creatinine ratio of ≥50 mg/mmol. More recently the Kidney Disease Improving Global Outcomes (KDIGO) organisation updated the international CKD classification to include the subdivision of GFR categories suggested by NICE CG73 but also included 3 ACR categories (ACR <3, 3-30 and >30 mg/mmol) with each GFR category (Table 1: KDIGO GFR and ACR Categories).

Table 1: KDIGO GFR and ACR Categories

GFR Categories for CKD		
GFR category	**GFR (ml/min/1.73 m^2)**	**Terms**
G1	>90	Normal or high
G2	60-89	Mildly decreased[a]
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney failure
Albuminuria categories in CKD		
ACR category	**ACR (mg/mmol)**	**Terms**
A1	<3	Normal to mildly increased
A2	3-30	Moderately increased[a]
A3	>30	Severely increased[b]

(a) relative to young adult level
(b) Including nephrotic syndrome (ACR usually >220 mg/mmol).

Source: Reprinted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter., Suppl. 2013; 3: 1–150'

1.3 Burden of disease

CKD is increasingly recognised as a public health problem and there is considerable overlap between KD, diabetes and cardiovascular disease, therefore requiring management by multidisciplinary teams. The risk of developing CKD increases with increasing age. In assessing the burden of disease it is therefore important to understand the characteristics of our population. The United Kingdom population is growing and ageing (Figure 1), numbering over 63 million with 54 million people in England alone. In the last 10 years the population has increased by 7 per cent, the median age in 1971 was 34.4 years, that has now increased to 40 years and 16% of the population are aged over 65 years. We have a small ethnic minority population, 5.7% Asian and 2.8% African-Caribean, but that too has grown. National data from primary care registers in the Quality and Outcomes Framework (QOF) suggests that 13.6% of the whole population are hypertensive and data from the 2012 WHO report indicates that 27.7% of men and 19.1% of women over the age of 25 are hypertensive.140 The mean body mass index (BMI) of the population is now 27.5 and 27.1 kg/m2 in men and women respectively and 24.4% of men and 25.2% of women are obese (BMI>30 kg/m2). The QOF data also indicates a prevalence of diabetes mellitus of 5.8%, and suggests a prevalence of 3.4% for coronary heart disease, 1.7% for stroke and 0.7% for heart failure. Despite these figures 25% of men and 23% of women over the age of 15 are smokers.

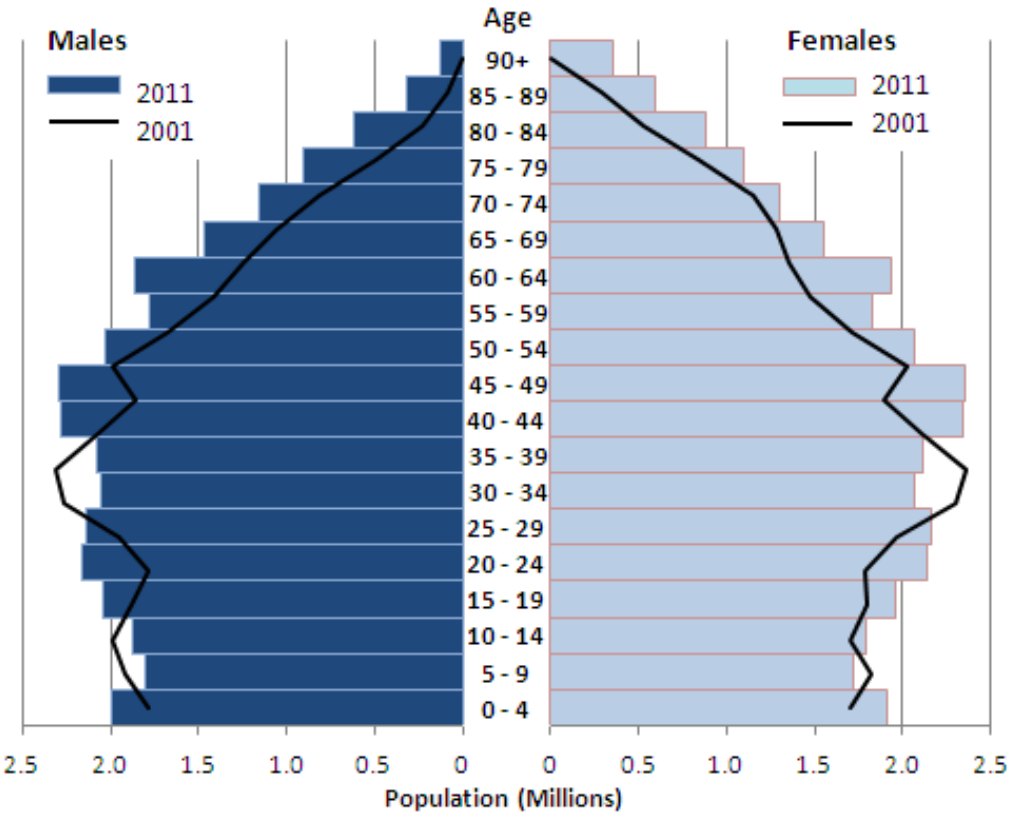
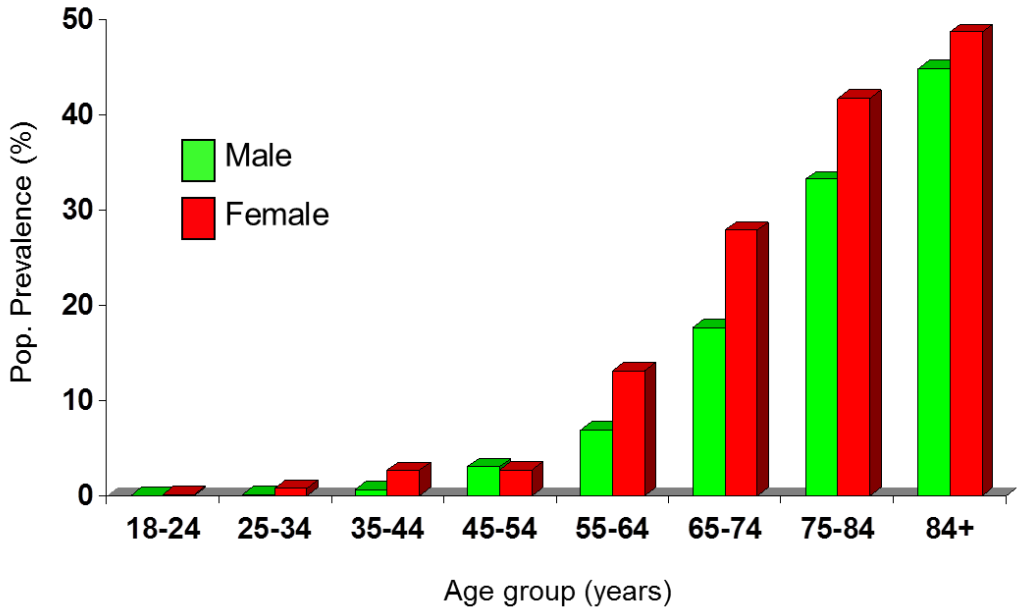

Males
2011
2001
Age
90+
85 - 89
80 - 84
75 - 79
70 - 74
65 - 69
60 - 64
55 - 59
50 - 54
45 - 49
40 - 44
35 - 39
30 - 34
25 - 29
20 - 24
15 - 19
10 - 14
5 - 9
0 - 4
Females
2011
2001
2.5
2.0
1.5
1.0
0.5
0
0
0.5
1.0
1.5
2.0
2.5
Population (Millions)

Figure 2: Adult age-standardised prevalence of CKD stage 3-5 in England



Source of data: Stevens PE, O'Donoghue DJ, de Lusignan S et al. Chronic kidney disease management in the United Kingdom: NEOERICA project results. Kidney International 2007; 72(1):92–99). [387]

Table 2: Health survey for England: adult CKD prevalence

CKD Stage	Male	Female
1	3%	3%
2	6%	3%
3-5	5%	7%
Total	14%	13%

Source: http://www.ic.nhs.uk/statistics-and-data-collections/health-and-lifestyles-related-surveys/health-survey-for-england

Socioeconomic status (SES) is also an important determinant of CKD prevalence. In England the age-sex-adjusted prevalence of a GFR<60 ml/min/1.73 m^2 was associated with lack of qualifications [odds ratio (OR) 2.27 (95% confidence interval 1.40-3.69)], low income [OR 1.50 (1.02-2.21)] and renting tenure [OR 1.36 (1.01-1.84)]. Albuminuria remained associated with several SES measures on full adjustment: low income [OR 1.55 (1.14-2.11)], no vehicle [OR 1.38 (1.05-1.81)], renting [OR 1.31 [1.03-1.67)] and most deprived area-level quintile [OR 1.55 (1.07-2.25)].[111] SES has also been implicated in management and progression of CKD. Another UK study found that SES was inversely associated with both heavy proteinuria on presentation and progression as well as rapid progression of CKD. People living in more deprived areas presenting with CKD were more likely to be at increased risk of poor outcomes.[154]

It has also long been recognised that the prevalence of end-stage kidney disease (ESKD)is higher amongst the black and minority ethnic communities in comparison to Caucasian populations.[351] The predominant reasons for this include the increased prevalence of type 2 diabetes in South Asians and hypertension in African Caribbeans, together with diseases particular to certain communities such as chronic interstitial nephritis in South Asians and focal glomerulosclerosis in African Caribbeans. However, there is a relative lack of knowledge concerning the prevalence of earlier stages of CKD in black and ethnic minority populations in comparison to caucasians. In the United States, CKD

prevalence, defined as a GFR <60 ml/min/1.73 m^2 is higher among white compared with non-white racial/ethnic groups.[405] Higher rates of kidney failure among nonwhite compared with white adults seems to be a function of a higher rate of progression to kidney failure as opposed to increased CKD prevalence.[159] In people with diabetes another study from the USA found that racial/ethnic minorities were more likely to have proteinuric diabetic kidney disease and less likely to have nonproteinuric diabetic kidney disease.[36] A further study in non-diabetic individuals in the USA found that in a multi-racial cohort higher blood pressure, not ethnicity, predicted progression of CKD.[42] Finally, a further study from the USA reported that African Americans experienced a substantially increased risk for developing CKD over 20 years compared with whites. This provides an important contrast to the cross-sectional studies reporting a higher CKD prevalence among whites compared with African Americans. Much of this increased risk was explained by the higher prevalence of albuminuria among African Americans.[266] Clearly future studies are needed to establish exactly whether or not there are racial disparities in both prevalence and progression of CKD.

Late presentation of people with kidney failure increases morbidity, mortality and healthcare associated costs. Since the introduction of national estimated GFR reporting and CKD indicators in the primary care quality and outcomes framework, together with increased public and health professional awareness of CKD, the late presentation of people with advanced kidney disease has improved over successive years but still remains at 19% in the latest UK Renal Registry reports.[123] The total cost of CKD in England in 2009–10 was estimated at £1.44 to £1.45 billion, approximately 1.3% of all NHS spending in that year.[191] More than half of this sum was spent on renal replacement therapy, which was provided for 2% of the CKD population. The economic model estimated that approximately 7000 excess strokes and 12 000 excess myocardial infarcts occurred in the CKD population in 2009–10, relative to an age- and gender-matched population without CKD. The cost of excess strokes and myocardial infarcts was estimated at £174–£178 million. Strategies aimed at earlier identification and (where possible) prevention of progression to end-stage kidney disease (ESKD)are therefore clearly needed.

This clinical guideline seeks to address these issues by updating previous guidance from CG73 where new data have become available, and providing guidance in areas where previously no evidence existed. The new and updated areas include:

- identification and investigation of people who have or are at risk of developing CKD
- classification of CKD and identification of those at risk of complications and progression of CKD
- definition of progression of CKD
- the relationship between acute kidney injury and CKD
- self-management in CKD
- pharmacotherapy in CKD.

2 Development of the guideline

2.1 What is a NICE clinical guideline?

NICE clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of health care. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional.

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- Guideline topic is referred to NICE from the Department of Health.
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Clinical Guideline Centre (NCGC).
- The NCGC establishes a guideline development group.
- A draft guideline is produced after the group assesses the available evidence and makes recommendations.
- There is a consultation on the draft guideline.
- The final guideline is produced.

The NCGC and NICE produce a number of versions of this guideline:

- the full guideline contains all the recommendations, plus details of the methods used and the underpinning evidence
- the NICE guideline lists the recommendations
- the information for the public is written using suitable language for people without specialist medical knowledge
- the NICE pathway links all recommendations and includes links to other relevant guidance.

This version is the full version. The other versions can be downloaded from NICE at www.nice.org.uk

2.2 Remit

NICE received the remit for this guideline from the Department of Health. They commissioned the NCGC to produce the guideline.

This is a partial update of 'Chronic kidney disease' (NICE clinical guideline 73). See section 2.4 for details of which sections will be updated. We will also carry out an editorial review of all recommendations to ensure that they comply with NICE's duties under equalities legislation.

This update is being undertaken as part of the guideline review cycle.

2.3 Who developed this guideline?

A multidisciplinary Guideline Development Group (GDG) comprising professional group members and consumer representatives of the main stakeholders developed this guideline (see section on Guideline Development Group Membership and acknowledgements).

The National Institute for Health and Care Excellence funds the National Clinical Guideline Centre (NCGC) and thus supported the development of this guideline. The GDG was convened by the NCGC and chaired by Paul Stevens in accordance with guidance from the National Institute for Health and Care Excellence (NICE).

The group met every 4-6 weeks during the development of the guideline. At the start of the guideline development process all GDG members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest, which were also recorded (Appendix B).

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B.

Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers, health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost effectiveness analysis where appropriate and drafted the guideline in collaboration with the GDG.

2.4 What this guideline covers

The guideline covers the following populations:

- Adults aged 18 and over.
- Specific consideration will be given to the needs of subgroups:
  - o older people (75 years and older)
  - o black and minority ethnic people (BME) where these differ from the needs of the general population
  - o people at high risk of developing CKD (for example, people with: diabetes, hypertension, cardiovascular disease, or people recovering from acute kidney injury).

The guideline updates the following areas from CG73

- Measurement of kidney function and markers of kidney damage, for example using creatinine-based and cystatin C-based equations.
- Frequency of monitoring.
- Classification of CKD.
- Dietary interventions such as a low protein diet in people with CKD.
- Effectiveness of self-management support systems for people with CKD including relevant information and support.

- The choice of renin-angiotensin-aldosterone system antagonists including aldosterone antagonists in people with CKD.
- Efficacy and safety of antiplatelet and antithrombotic therapy (for example, aspirin, ticagrelor, clopidogrel, dabigatran and warfarin) in people with CKD.
- Uric acid lowering therapy in people with CKD.
- Vitamin D supplementation in the management of renal bone disease in people with CKD.

Areas not in the original guideline that will be included in the update

- The risk of developing CKD after an episode of acute kidney injury.
- The management of acidosis with bicarbonate supplementation in people with CKD.

For further details please refer to the scope in Appendix A and review questions in section 3.1.2.

2.5 What this guideline does not cover

The guideline does not cover:

- People receiving renal replacement therapy (RRT)
- People with acute kidney injury and rapidly progressive glomerulonephritis
- Children and young people under 18 years
- Pregnant women.

No new evidence has been identified to directly change the 2008 recommendations on:

- Investigation of CKD: indications for renal ultrasound.
- Defining progression of CKD and the risk factors associated with progression.
- Blood pressure control: practicalities of treatment with ACE inhibitors/ARBs.
- Managing isolated microscopic haematuria.
- Specific complications of CKD: anaemia.
- Information and support for people and their carers (except for that relating to self-management support systems).

Areas not covered by the original guideline or the update

- The treatment of each of the specific causes of CKD, such as glomerular and tubulointerstitial disease, or nephrotic syndrome.
- Management of pregnancy in women with CKD.
- Management of anaemia in people with CKD.
- Management of acute kidney injury in people with CKD.

2.6 Relationships between the guideline and other NICE guidance

Related NICE Health Technology Appraisals:

Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation. NICE technology appraisal 275 (2013).

Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism. NICE technology appraisal 261 (2012).

Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation. NICE technology appraisal 256 (2012).

Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation. NICE technology appraisal 249 (2012).

Febuxostat for the management of hyperuricaemia in people with gout. NICE technology appraisal 164 (2008).

Cinacalcet hydrochloride for the treatment of secondary hyperparathyroidism in patients with end stage renal disease on maintenance dialysis therapy. NICE technology appraisal 117 (2007).

Guidance on home compared with hospital haemodialysis for patients with end-stage renal failure. NICE technology appraisal 48 (2002).

Related NICE Clinical Guidelines:

Lipid modification. NICE clinical guideline 181 (2014).

Atrial fibrillation. NICE clinical guideline 180 (2014)

Acute kidney injury. NICE clinical guideline 169 (2013).

Anaemia management in people with chronic kidney disease. NICE clinical guideline 114 (2011).

Atrial Fibrillation. NICE clinical guideline 36 (2006)

Chronic heart failure. NICE clinical guideline 108 (2010).

Depression in adults with a chronic physical health problem. NICE clinical guideline 91 (2009).

Hyperphosphataemia in chronic kidney disease. NICE clinical guideline 157 (2013).

Hypertension. NICE clinical guideline 127 (2011).

Medicines adherence. NICE clinical guideline 76 (2009).

Osteoporosis fragility fracture risk. NICE clinical guideline 146. (2012).

Patient experience in adult NHS services. NICE clinical guideline 138 (2012).

Peritoneal dialysis. NICE clinical guideline 125 (2011).

Type 1 diabetes. NICE clinical guideline 15 (2004).

Type 2 diabetes. NICE clinical guideline 66, partially updated by CG87 (2008).

Other related NICE guidance:

Chronic kidney disease. NICE quality standard (2011).

Diabetes in adults. NICE quality standard (2011).

Early identification and management of chronic kidney disease in adults. NICE commissioning guideline 37 (2012).

End of life care for adults. NICE quality standard (2012).

Patient experience in adult NHS services. NICE quality standard (2012).

Related NICE Public Health Guidance:

Brief interventions and referral for smoking cessation. NICE public health guidance 1 (2006).

Prevention of cardiovascular disease. NICE public health guidance 25 (2010).

NICE Related Guidance currently in development:

Anaemia management in people with chronic kidney disease (update). NICE clinical guideline. Publication expected July 2015.

Referal for suspected cancer (update). NICE clinical guideline. Publication expected May 2015

Type 1 diabetes (update). NICE clinical guideline. Publication expected August 2015.

Type 2 diabetes (update). NICE clinical guideline. Publication expected August 2015.

3 Methods

3.1 Methods (2014)

This guidance was developed in accordance with the methods outlined in the NICE Guidelines Manual 2012[285].

3.1.1 Amendments to 2008 text

Text and recommendations from the previous guideline (CG73), that has not been updated has been left unchanged and is not highlighted. For these sections new review questions have not been generated and the evidence has not been searched for. Where amendments have been made to specific recommendations, these are detailed in Appendix O.

3.1.2 Developing the review questions and outcomes

Review questions were developed in a PICO framework (patient, intervention, comparison and outcome) for intervention reviews, and with a framework of population, index tests, comparator test, reference standard and statistical measures for reviews of diagnostic test accuracy. For review questions about prognostic factors the framework used was population, presence of prognostic factor, absence of factor and statistical measures. This was to guide the literature searching process and to facilitate the development of recommendations by the guideline development group (GDG). They were drafted by the NCGC technical team and refined and validated by the GDG. The questions were based on the key clinical areas identified in the scope (Appendix A). Further information on the outcome measures examined follows this section.

Chapter	Review questions	Outcomes
Measurement of kidney function	What is the accuracy of equations to estimate GFR as a measurement of kidney function?	**Critical:** • Accuracy (P30) • Bias • Precision **Important:** • Sensitivity • Specificity • Area under the curve • Net reclassification index
Markers of kidney damage	What is the best combination of measures of kidney function and markers of kidney damage to identify people with CKD who are at increased risk of progression?	• CKD progression: change in eGFR • CKD progression: occurrence of end stage kidney disease (ESRD or ESKD as reported by the study) • Acute Kidney Injury (AKI) • All-cause mortality • Cardiovascular mortality
Classification of CKD	For people with suspected CKD, what is the effect of proteinuria at any given eGFR on adverse outcomes?	**Critical:** • CKD progression: change in eGFR • CKD progression: occurrence of ESRD

Chapter	Review questions	Outcomes
		• All-cause mortality • Cardiovascular mortality • AKI **Important:** • Cardiovascular events • Hospitalisation
Risk factors for adverse outcomes - cause of CKD	For people with CKD, does the presence of; • diabetes • hypertension • glomerular disease, or • acute kidney injury (AKI) have an effect on adverse outcomes at any given category of eGFR and ACR?	**Critical:** • CKD progression: change in eGFR • CKD progression: occurrence of ESRD • All-cause mortality • Cardiovascular mortality • Cardiovascular events **Important:** • Hospitalisation
Frequency of monitoring	How frequently should eGFR, ACR or PCR be monitored in people with CKD?	• CKD progression: change in eGFR • CKD progression: occurrence of ESRD • All-cause mortality • Cardiovascular mortality
Progression/ development of CKD after AKI	What is the risk of developing and/or progression of CKD after an episode of AKI?	• Incident CKD • CKD progression: change in eGFR • CKD progression: occurrence of ESRD
Low protein diet	For people with CKD, are low protein diets a clinically and cost effective method for the management of CKD?	**Critical:** • CKD progression: change in eGFR • CKD progression: occurrence of ESRD • All-cause mortality • Cardiovascular mortality • Health related quality of life **Important:** • Compliance (measured by actual protein intake) • Nutritional status (measured by subjective global assessment) • Nutritional status (measured by change in BMI)
Self-management support systems	For people with CKD, what is the clinical and cost effectiveness of self-management support systems?	**Critical:** • CKD progression: change in eGFR • CKD progression: occurrence of ESRD • All-cause mortality • Cardiovascular mortality • Health related quality of life • Hospitalisation **Important:**

Chapter	Review questions	Outcomes
		• Adherence (to treatments) • Outpatient attendance (including frequency of attendance)
Renin-angiotensin-aldosterone system antagonists in the management of CKD	For people with CKD, what is the clinical and cost effectiveness of renin-angiotensin-aldosterone system antagonists in the management of CKD?	**Critical** • CKD progression: change in eGFR • CKD progression: occurrence of ESRD • All-cause mortality • Cardiovascular mortality • Cardiovascular events • Occurrence of AKI **Important** • Change in proteinuria • Hospitalisation • Health related quality of life
Reducing cardiovascular disease: Antiplatelets and anticoagulants	For people with CKD, what is the clinical and cost effectiveness of oral antiplatelet and anticoagulant therapy in reducing cardiovascular disease?	**Critical:** • Cardiovascular/cerebrovascular events • Major bleeding (as reported by the studies) • All-cause mortality • Cardiovascular mortality **Important:** • CKD progression: change in eGFR • CKD progression: occurrence of ESRD • Minor bleeding (as reported by the studies) • Hospitalisation • Health related quality of life
Asymptomatic hyperuricaemia	For people with CKD and asymptomatic hyperuricaemia, what is the clinical and cost effectiveness of uric acid lowering with allopurinol or febuxostat in the management of CKD?	**Critical:** • CKD progression: change in eGFR • CKD progression: occurrence of ESRD • Cardiovascular events • Reduction in antihypertensive agents • All-cause mortality • Cardiovascular mortality **Important:** • Hospitalisation • Health related quality of life
Vitamin D	For people with GFR 15-60 ml/min/1.73 m^2, what is the clinical and cost-effectiveness of vitamin D supplementation for the management of renal bone disease?	**Critical:** • All-cause mortality • Cardiovascular mortality • Cardiovascular events • Fracture

Chapter	Review questions	Outcomes
		• CKD progression: change in eGFR • CKD progression: occurrence of ESRD • Hypercalcaemia (serum calcium >2.5 mmol/litre) **Important:** • Hospitalisation • Health related quality of life
Oral bicarbonate supplements for the management of CKD	What is the clinical and cost effectiveness of oral bicarbonate supplements in the management of CKD?	**Critical:** • CKD progression: change in eGFR or creatinine clearance • CKD progression: occurrence of ESRD • All-cause mortality • Cardiovascular mortality • Cardiovascular events (including chronic heart failure) • Hypertension (measured by use of antihypertensives) **Important:** • Alkalosis • Nutritional status (measured by subjective global assessment) • Nutritional status (measured by change in BMI) • Hospitalisation • Health related quality of life

3.1.3 Searching for evidence

3.1.3.1 Clinical literature search

Systematic literature searches were undertaken to identify evidence within published literature in order to answer the review questions as per The Guidelines Manual [2012].[285] Clinical databases were searched using relevant medical subject headings, free-text terms and study type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English language. All searches were conducted on the following core databases, MEDLINE, Embase, Cinahl and The Cochrane Library. All searches were updated on 25 November 2013. No papers after this date were considered.

Search strategies were checked by looking at reference lists of relevant key papers, checking search strategies in other systematic reviews and asking the GDG for known studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix F.

During the scoping stage, a search was conducted for guidelines and reports on the websites listed below and on organisations relevant to the topic. Searching for grey literature or unpublished literature was not undertaken. All references sent by stakeholders were considered.

- Guidelines International Network database (www.g-i-n.net)
- National Guideline Clearing House (www.guideline.gov/)

- National Institute for Health and Care Excellence (NICE) (www.nice.org.uk)
- National Institutes of Health Consensus Development Program (consensus.nih.gov/)
- National Library for Health (www.library.nhs.uk/)

3.1.3.2 Health economic literature search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to CKD in the NHS economic evaluation database (NHS EED), the Health Economic Evaluations Database (HEED) and health technology assessment (HTA) databases with no date restrictions. Additionally, the search was run on MEDLINE and Embase, with a specific economic filter, from 2009, to ensure recent publications that had not yet been indexed by these databases were identified. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English language.

The search strategies for health economics are included in Appendix F. All searches were updated on 25 November 2013. No papers published after this date were considered.

3.1.4 Evidence of effectiveness

The Research Fellow:

- Identified potentially relevant studies for each review question from the relevant search results by reviewing titles and abstracts – full papers were then obtained.
- Reviewed full papers against pre-specified inclusion / exclusion criteria to identify studies that addressed the review question in the appropriate population and reported on outcomes of interest (review protocols are included in Appendix C).
- Critically appraised relevant studies using the appropriate checklist as specified in The Guidelines Manual.[285]
- Extracted key information about the study's methods and results into evidence tables (evidence tables are included in Appendix G).
- Generated summaries of the evidence by outcome (included in the relevant chapter write-ups):
  - Randomised studies: meta analysed, where appropriate and reported in GRADE profiles (for clinical studies) – see below for details
  - Diagnostic and prognostic studies: data presented as a range of values in adapted GRADE profiles
  - Qualitative studies: each study summarised in a table where possible, otherwise presented in a narrative.

3.1.4.1 Inclusion/exclusion

See the review protocols in Appendix C for full details.

The following population groups were excluded in all reviews:

- People receiving renal replacement therapy
- People with acute kidney injury and rapidly progressive glomerulonephritis
- Children and young people under 18 years
- Pregnant women.

3.1.4.2 Methods of combining clinical studies

Data synthesis for intervention reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for binary outcomes: all-cause and cardiovascular mortality, CKD progression (occurrence of ESRD), AKI, cardiovascular events, hospitalisation, incident CKD, adherence, major bleeding, minor bleeding, fracture and hypercalcaemia. The continuous outcomes CKD progression (change in eGFR), health related quality of life and nutritional status (measured by subjective global assessment or change in BMI) were analysed using an inverse variance method for pooling weighted mean differences and where the studies had different scales, standardised mean differences were used. For cases where there are no events in either arm, the Peto odds ratio will be calculated instead of the risk ratio as it has been shown to be the least biased and most powerful method of determining effect size for rare events.

Where available, hazard ratios were presented for time-to-event data (e.g. mortality, progression of CKD, occurrence of cardiovascular events). Time-to-event data should not be analysed as the continuous outcome, mean time-to-event (or mean duration of remission) with its standard deviation, because the relevant times are only known for the subset of participants who have had the event. Censored participants who have not had the event are either treated as uncensored - which will underestimate the time to event (bias) – or are excluded, which will again introduce bias, particularly if the censored times are longer than the uncensored times. Survival rates at different time points (treating as dichotomous outcomes) can also lead to bias because of failure to take account of censoring. Dichotomising of time-to-event data is only acceptable when all the participants have been followed up to the particular time point. There is a risk of bias that individual studies may select time points for reporting that maximise the difference between interventions.

The most appropriate way of summarising time-to-event data is to use methods of survival analysis and express the intervention effect as a hazard ratio. Hazard is similar in notion to risk, but is subtly different in that it measures instantaneous risk and may change with time. A hazard ratio is interpreted in a similar way to a risk ratio, because it describes how many times more (or less) likely a participant is to suffer the event at a particular point in time if they receive the experimental rather than the control intervention.

Where studies reported stage of CKD or degree of proteinuria these were considered in the data syntehesis.

Statistical heterogeneity was assessed by considering the chi-squared test for significance at $p<0.1$ or an I-squared inconsistency statistic of >50% to indicate significant heterogeneity. Where significant heterogeneity was present, we carried out predefined subgroup analyses for: age, black and minority ethnic groups, diabetes, hypertension, and cardiovascular disease. Sensitivity analysis based on the quality of studies was also carried out if there were differences, with particular attention paid to allocation concealment, blinding and loss to follow-up (missing data). In cases where there was inadequate allocation concealment, unclear blinding, more than 50% missing data or differential missing data, this was examined in a sensitivity analysis. For the latter, the duration of follow up was also taken into consideration prior to including in a sensitivity analysis.

Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. If no sensitivity analysis was found to completely resolve statistical heterogeneity then a random effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect.

The means and standard deviations of continuous outcomes were required for meta-analysis. However, in cases where standard deviations were not reported, the standard error was calculated if the p-values or 95% confidence intervals were reported and meta-analysis was undertaken with the mean and standard error using the generic inverse variance method in Cochrane Review Manager (RevMan5) software. Where p values were reported as "less than", a conservative approach was undertaken. For example, if p value was reported as "p ≤0.001", the calculations for standard deviations will be based on a p value of 0.001. If these statistical measures were not available then the methods described in section 16.1.3 of the Cochrane Handbook (March 2011) 'Missing standard deviations' were applied as the last resort.

For binary outcomes, absolute event rates were also calculated using the GRADEpro software using event rate in the control arm of the pooled results.

Individual patient data (IPD) meta-analysis

IPD meta-analysis is a specific type of systematic review. Instead of extracting summary data from study reports, the original data for each participant in an included study are sought directly from the researchers responsible for that study. IPD meta-analyses are regarded as gold standard reviews, surpassing systematic reviews of summary data. They are often carried out for time-to-event outcomes, which are themselves analysed by following the course of individual patients over time.

Advantages of IPD meta-analyses are:

- Data from unpublished studies can be included.
- They allow time-to-event analyses and facilitate analysis of studies with long term follow up.
- Data checking is enabled.
- Some aspects of risk of bias are reduced: outcome reporting bias and reasons for missing outcome data can be identified; problems with reporting of risk of bias are largely removed.
- Data can be re-analysed in a consistent way (e.g. reviewers can carry out analyses according to intention-to-treat principles, even if the original trial analyses did not do this).
- Subgroup analyses using IPD are much more straightforward than in conventional aggregate data meta-analyses.

In the latter, it is usually very difficult to extract sufficient compatible data to undertake meaningful subgroup analyses (e.g. data are reported as study level characteristics, such as mean age), and it is especially difficult to characterise individuals by more than one factor at a time. In contrast, IPD permit straightforward categorisation of individuals for subgroup analysis (stratified by study) defined by single or multiple factors.

Analysis is usually carried out in two stages: Each individual study is analysed in the same way, as set out in the meta-analysis protocol or analysis plan. Then summary statistics of each study analysis are combined to provide a pooled estimate of effect in the same way as for a conventional systematic review. This approach maintains the randomisation within individual trials. Combining the patients from all trials into one large cohort first destroys randomisation and is unacceptable. However, regression analysis with trial number as one of the variables is acceptable.

Where IPD studies were identified for a review question, they were included in preference of individual studies (chapters 6.1 and6.3 for classification of CKD and cause of CKD respectively).

Data synthesis for prognostic factor reviews

Odds ratio, relative risks or hazard ratios, with their 95% confidence intervals, from multivariate analyses were extracted from the papers, and standard errors were calculated from the 95%

confidence intervals. The log of the effect size with its standard error was entered into the generic inverse variance technique in the Cochrane Review Manager (RevMan5.1) software. Studies were not combined in a meta-analysis for observational studies. Sensitivity analyses were carried out on the basis of study quality and results were reported as ranges.

Data synthesis for diagnostic test accuracy review

Diagnostic test accuracy was considered in the chapter on the measurement of kidney function (chapter 5.1). The critical outcomes in the review are those used widely in the literature to compare GFR estimating equations: accuracy, bias and precision. Bias describes the difference between estimates of GFR and the measured GFR. This is commonly described as the mean or median bias. Precision is the variability of the estimate of GFR compared to the measured value. The root mean square error (RMSE) of the regression of estimated GFR versus measured GFR is considered to be a direct measure of precision. However, overall interquartile range (IQR) for the differences between estimated GFR and measured GFR, an indirect measure of precision, was more widely reported by studies and so was used in our analysis.

Accuracy is affected by both bias and precision. Accuracy is represented by the P30: the percentage of estimated GFR values lying within 30% of the measured GFR.

The following outcomes were also considered as they are more standard measures of diagnostic accuracy but are less frequently reported in the CKD literature: sensitivity, specificity, and area under the curve. Net reclassification index, a statistic that measures the improvement in prediction performance was also considered important, however it is usually used in the literature to analyse the reclassification between eGFR categories in population studies where only estimated values of GFR (and not measured values) are available.

Data synthesis for qualitative reviews

A qualitative review was considered in the chapter on self-management (chapter 8.6). A customised quality assessment for qualitative studies was undertaken and a narrative summary of the findings is presented.

3.1.4.3 Appraising the quality of evidence by outcomes

The evidence for outcomes from the included RCT and observational studies were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro) developed by the GRADE working group was used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The summary of findings was presented as two separate tables in this guideline. The "Clinical/Economic Study Characteristics" table includes details of the quality assessment while the "Clinical /Economic Summary of Findings" table includes pooled outcome data, where appropriate, an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate the sum of the sample size for continuous outcomes. For binary outcomes such as number of patients with an adverse event, the event rates (n/N: number of patients with events divided by sum of number of patients) are shown with percentages. Reporting or publication bias was only taken into consideration in the quality assessment and included in the Clinical Study Characteristics table if it was apparent.

Each outcome was examined separately for the quality elements listed and defined in Table 3 and each graded using the quality levels listed in Table 4. The main criteria considered in the rating of

these elements are discussed below (see section 3.1.4.4 Grading of Evidence). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome.

The GRADE toolbox is currently designed only for randomised trials and observational studies but we adapted the quality assessment elements and outcome presentation for diagnostic accuracy and prognostic reviews.

Table 3: Description of quality elements in GRADE for intervention studies

Quality element	Description
Limitations	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results.
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect relative to the clinically important threshold.
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

Table 4: Levels of quality elements in GRADE

Level	Description
None	There are no serious issues with the evidence.
Serious	The issues are serious enough to downgrade the outcome evidence by one level.
Very serious	The issues are serious enough to downgrade the outcome evidence by two levels.

Table 5: Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

3.1.4.4 Grading the quality of clinical evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

1. A quality rating was assigned, based on the study design. RCTs start HIGH and observational studies as LOW, uncontrolled case series as LOW or VERY LOW.
2. The rating was then downgraded for the specified criteria: Study limitations, inconsistency, indirectness, imprecision and reporting bias. These criteria are detailed below. Observational studies were upgraded if there was: a large magnitude of effect, dose-response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when

results showed no effect. Each quality element considered to have "serious" or "very serious" risk of bias were rated down -1 or -2 points respectively.

3. The downgraded/upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as HIGH and the overall quality became MODERATE, LOW or VERY LOW if 1, 2 or 3 points were deducted respectively.
4. The reasons or criteria used for downgrading were specified in the footnotes.

The details of criteria used for each of the main quality elements are discussed further in the following sections 3.1.4.5 to 3.1.4.8

3.1.4.5 Study limitations

The main limitations for randomised controlled trials are listed in Table 6.

Table 6: Study limitations of randomised controlled trials

Limitation	Explanation
Allocation concealment	Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (major problem in "pseudo" or "quasi" randomised trials with allocation by day of week, birth date, chart number, etc.).
Lack of blinding	Participant, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated.
Incomplete accounting of patients and outcome events	Loss to follow-up not accounted and failure to adhere to the intention to treat principle when indicated.
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results.
Other limitations	For example: • Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules • Use of unvalidated patient-reported outcomes • Carry-over effects in cross-over trials • Recruitment bias in cluster randomised trials.

3.1.4.6 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect across studies differ widely (i.e. heterogeneity or variability in results), this suggests true differences in underlying treatment effect. When heterogeneity exists (Chi square $p<0.1$ or I- squared inconsistency statistic of >50%), but no plausible explanation can be found, the quality of evidence was downgraded by one or two levels, depending on the extent of uncertainty to the results contributed by the inconsistency in the results. In addition to the I- square and Chi square values, the decision for downgrading was also dependent on factors such as whether the intervention is associated with benefit in all other outcomes or whether the uncertainty about the magnitude of benefit (or harm) of the outcome showing heterogeneity would influence the overall judgment about net benefit or harm (across all outcomes).

If inconsistency could be explained based on pre-specified subgroup analysis, the GDG took this into account and considered whether to make separate recommendations based on the identified explanatory factors, i.e. population and intervention. Where subgroup analysis gives a plausible explanation of heterogeneity, the quality of evidence would not be downgraded.

3.1.4.7 Indirectness

Directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention.

3.1.4.8 Imprecision

The sample size, event rates and the resulting width of confidence intervals were the main criteria considered.

The criteria applied for imprecision are based on the confidence intervals for pooled or the best estimate of effect, outlined in Figure 3. For the purposes of this guideline, the default MIDs of risk ratios of < 0.75 and > 1.25 were used for dichotomous outcomes.

Table 7: Criteria applied to determine precision

Dichotomous outcomes
Confidence interval crosses one default MID and line of no effect: downgrade by −1.
Confidence interval crosses both default MIDs and line of no effect: downgrade by −2.
Continuous outcomes
Hospital duration: MID of mean difference of > 2 days (based on consensus) (downgrade by −1 or −2)
Health-related quality of life (HRQoL) measured using 15D instrument: MID of mean difference of > 0.03 (downgrade by −1 or −2)
Other continuous outcomes: a standard mean difference (SMD) of 0.05 (downgrade by −1 or −2)

Figure 3 considers a positive outcome for the comparison of treatment A versus B. Three decision-making zones can be identified, bounded by the thresholds for clinical importance (MID) for benefit and for harm (the MID for harm for a positive outcome means the threshold at which drug A is less effective than drug B and this difference is clinically important to patients (favours B).

Figure 3: Imprecision illustration

When the confidence interval of the effect estimate is wholly contained in one of the three zones (e.g. clinically important benefit), we are not uncertain about the size and direction of effect

(whether there is a clinically important benefit or the effect is not clinically important or there is a clinically important harm), so there is no imprecision.

When a wide confidence interval lies partly in each of two zones, it is uncertain in which zone the true value of effect estimate lies, and therefore there is uncertainty over which decision to make (based on this outcome alone); the confidence interval is consistent with two decisions and so this is considered to be imprecise in the GRADE analysis and the evidence is downgraded by one ("serious imprecision").

If the confidence interval of the effect estimate crosses into three zones, this is considered to be very imprecise evidence because the confidence interval is consistent with three clinical decisions and there is a considerable lack of confidence in the results. The evidence is therefore downgraded by two in the GRADE analysis ("very serious imprecision").

Implicitly, assessing whether the confidence interval is in, or partially in, a clinically important zone, requires the GDG to estimate an MID or to say whether they would make different decisions for the two confidence limits.

The literature was searched for established MIDs for the selected outcomes in the evidence reviews, but no results were found. In addition, the GDG was asked whether they were aware of any widely accepted MIDs used in the clinical community of Chronic Kidney Disease, but they confirmed an absence of research in the area except for progression of CKD (change in GFR) where the MID was calculated as a change of 30% from the mean (90% of patients will have a measured GFR within 30% of their estimated GFR). The GDG considered it clinically acceptable to use the GRADE default MID values to assess imprecision for all outcomes except those in the measurement of kidney function reviews. These default MID were used for all the outcomes in the interventions evidence reviews.

For the measurement of kidney function review, the GDG agreed that a 5% difference in P30 would be of a magnitude considered clinically important and so this was used as the MID. For bias the minimal important clinical difference was agreed as 5ml/min/1.73 m^2 and for precision a 20% difference.

3.1.4.9 Risk of Bias for prognostic studies

For prognostic review questions, cohort studies were considered as appropriate study designs. As such, a modified GRADE approach was used whereby these studies started from 'high' quality (or 'high' confidence in the effect estimates). The evidence was then downgraded based on a modified framework. The quality of the evidence was assessed using the checklist for prognostic studies.[285] The quality rating (low, high, unclear) was derived by assessing the risk of bias across 6 domains; selection bias, attrition bias, prognostic factor bias, outcome measurement bias, control for confounders and appropriate statistical analysis, with the last 4 domains being assessed per outcome. Reviewers assessed the risk of bias associated with each item and then estimated an overall risk of bias; the overall applicability was also assessed. The quality assessment was summarised and converted into a GRADE-like profile. More details about the quality assessment for prognostic studies are shown below:

1. The study sample represents the population of interest with regard to key characteristics – population, source of sample and inclusion/ exclusion criteria adequately described
2. Loss to follow up is unrelated to key characteristics, sufficient to limit potential bias – reasons for loss to follow up adequately described
3. The prognostic factor of interest is adequately measured in study participants
4. The outcome of interest is adequately measured in study participants
5. Important potential confounders are appropriately accounted for

6. The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of valid results.

IPD meta-analyses

For the IPD meta-analyses included in the classification and cause reviews (chapters 6.1 and 6.3 respectively), quality was assessed per-study using a customised methodology checklist for quality assessment of systematic reviews of prognostic studies adapted from Hayden 2006[138] rather than by using the standard GRADE profile. Where appropriate, this was incorporated into a customised GRADE table (cause of CKD, chapter 6.3). Otherwise, a narrative summary of results is provided in place of the GRADE summary of findings table (classification review, chapter 6.1).

3.1.5 Evidence of cost-effectiveness

Evidence on cost-effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist:

- Undertook a systematic review of the economic literature
- Undertook new cost-effectiveness analysis in priority areas

3.1.5.1 Literature review

The Health Economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts – full papers were then obtained.
- Reviewed full papers against pre-specified inclusion / exclusion criteria to identify relevant studies (see below for details).
- Critically appraised relevant studies using the economic evaluations checklist as specified in The Guidelines Manual Appendix G[285].
- Extracted key information about the study's methods and results into evidence tables (evidence tables are included in Appendix H).
- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter write-ups) – see below for details.

3.1.5.1.1 Inclusion/exclusion

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially applicable as economic evidence.

Studies were excluded if they:

- reported cost per hospital (not per patient), or
- reported average (not incremental) cost effectiveness without disaggregated costs and effects..
- were abstracts, posters, reviews, letters/editorials, foreign language publications or unpublished studies.
- were judged to have an applicability rating of 'not applicable' (this included studies that took the perspective of a non-OECD country).

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly

applicable UK analysis was available other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (The Guidelines Manual, Appendix G[285] and the health economics research protocol in Appendix C.

When no relevant economic analysis was found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the GDG to inform the their decisions. The unit costs reported in the guideline were those presented to the GDG and they were correct at the time recommendations were drafted; they may have changed slightly by the time of publication.

3.1.5.1.2 NICE economic evidence profiles

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates. The economic evidence profile shows, for each economic study, an assessment of applicability and methodological quality, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from The Guidelines Manual, Appendix G[285]. It also shows incremental costs, incremental outcomes (for example, QALYs) and the incremental cost-effectiveness ratio from the primary analysis, as well as information about the assessment of uncertainty in the analysis. See Table 8 for more details.

If a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity[306].

Table 8: Content of NICE economic profile

Item	Description
Study	First author name, reference, date of study publication and country perspective.
Limitations	An assessment of methodological quality of the study*: Minor limitations – the study meets all quality criteria, or the study fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness. Potentially serious limitations – the study fails to meet one or more quality criteria, and this could change the conclusion about cost effectiveness Very serious limitations – the study fails to meet one or more quality criteria and this is very likely to change the conclusions about cost effectiveness. Studies with very serious limitations would usually be excluded from the economic profile table.
Applicability	An assessment of applicability of the study to the clinical guideline, the current NHS situation and NICE decision-making*: Directly applicable – the applicability criteria are met, or one or more criteria are not met but this is not likely to change the conclusions about cost effectiveness. Partially applicable – one or more of the applicability criteria are not met, and this might possibly change the conclusions about cost effectiveness. Not applicable – one or more of the applicability criteria are not met, and this is likely to change the conclusions about cost effectiveness.
Other comments	Particular issues that should be considered when interpreting the study.
Incremental cost	The mean cost associated with one strategy minus the mean cost of a comparator strategy.
Incremental effects	The mean QALYs (or other selected measure of health outcome) associated with one strategy minus the mean QALYs of a comparator strategy.
ICER	Incremental cost-effectiveness ratio: the incremental cost divided by the respective QALYs gained.

Item	Description
Uncertainty	A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data, as appropriate.

**Limitations and applicability were assessed using the economic evaluation checklist from The Guidelines Manual, Appendix G282.*

3.1.5.2 Undertaking new health economic analysis

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the Health Economist in priority areas. Priority areas for new health economic analyses were agreed by the GDG after formation of the review questions and consideration of the available health economic evidence.

Additional data for the analysis was identified as required through additional literature searches undertaken by the Health Economist, and discussion with the GDG. Model structure, inputs and assumptions were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

See Appendices L and M for details of the health economic analyses undertaken for this guideline update.

3.1.5.3 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money[284,285]

In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

a. The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
b. The intervention cost less than £20,000 per quality-adjusted life-year (QALY) gained compared with all other strategies.

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'from evidence to recommendations' section of the relevant chapter with reference to issues regarding the plausibility of the estimate or to the factors set out in the 'Social value judgements: principles for the development of NICE guidance' [284].

When QALYs are not used in the analysis, results are difficult to interpret unless one strategy dominates the others with respect to every relevant health outcome and cost.

3.1.6 Developing recommendations

Over the course of the guideline development process, the GDG was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendix G and H
- Summary of clinical and economic evidence and quality (as presented in chapters 0 to 0)
- Forest plots and summary ROC curves (Appendix I)

- A description of the methods and results of the cost-effectiveness analysis undertaken for the guideline (Appendix L and M)

Recommendations were drafted on the basis of the GDG interpretation of the available evidence, taking into account the balance of benefits, harms and costs. When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on their expert opinion. The considerations for making consensus based recommendations include the balance between potential harms and benefits, economic or implications compared to the benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were done through discussions in the GDG. The GDG may also consider whether the uncertainty is sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation (See section 3.1.6.1 below).

The wording of recommendations was agreed by the GDG and focused on the following factors:

- The actions health professionals need to take.
- The information readers need to know.
- The strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weak recommendations).
- The involvement of patients (and their carers if needed) in decisions on treatment and care.
- Consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions.

The main considerations specific to each recommendation are outlined in the 'Recommendations and link to evidence' sections within each chapter.

3.1.6.1 Research recommendations

When areas were identified for which good evidence was lacking, the guideline development group considered making recommendations for future research. Decisions about inclusion were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility.

3.1.6.2 Validation process

The guidance is subject to a six week public consultation and feedback as part of the quality assurance and peer review the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website.

3.1.6.3 Updating the guideline

A formal review of the need to update a guideline is usually undertaken by NICE after its publication. NICE will conduct a review to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

3.1.6.4 Disclaimer

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

The National Clinical Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

3.1.6.5 Funding

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

3.2 Methods (2008)

3.2.1 Background

The development of this evidence-based clinical guideline draws upon the methods described by the NICE 'Guidelines manual'[282] (see http://www.nice.org.uk) specifically developed by the NCC-CC for each chronic condition guideline. The developers' role and remit is summarised in Table 9.

Table 9: Role and remit of the developers

National Collaborating Centre for Chronic Conditions (NCC-CC)	The NCC-CC was set up in 2001 and is housed within the Royal College of Physicians (RCP). The NCC-CC undertakes commissions received from the National Institute for Health and Care Excellence (NICE). A multiprofessional partners' board inclusive of patient groups and NHS management governs the NCC-CC.
NCC-CC technical team	The technical team met approximately two weeks before each Guideline Development Group (GDG) meeting and comprised the following members: • GDG Chair • GDG Clinical Advisor • Information Scientist • Research Fellow • Health Economist • Project Manager.
Guideline Development Group	The GDG met monthly (January 2007 to February 2008) and comprised a multidisciplinary team of health professionals and people with chronic kidney disease, who were supported by the technical team. The GDG membership details including patient representation and professional groups are detailed in the GDG membership table at the front of this guideline.
Guideline Project Executive (PE)	The PE was involved in overseeing all phases of the guideline. It also reviewed the quality of the guideline and compliance with the DH remit and NICE scope.

	The PE comprised of: • NCC-CC Director • NCC-CC Assistant Director • NCC-CC Manager • NICE Commissioning Manager • Technical Team.
Formal consensus	At the end of the guideline development process the GDG met to review and agree the guideline recommendations.

Members of the GDG declared any interests in accordance with the NICE 'Guidelines manual'.1 A register is given in Appendix Q.4

3.2.2 The process of guideline development

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

7. Developing clinical questions
8. Systematically searching for the evidence
9. Critically appraising the evidence
10. Incorporating health economics evidence
11. Distilling and synthesising the evidence and writing recommendations
12. Grading the evidence statements
13. Agreeing the recommendations
14. Structuring and writing the guideline
15. Updating the guideline.

1. Developing evidence-based questions

The technical team drafted a series of clinical questions that covered the guideline scope. The GDG and Project Executive refined and approved these questions, which are shown in Appendix Q.1.

2. Searching for the evidence

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

Each clinical question dictated the appropriate study design that was prioritised in the search strategy but the strategy was not limited solely to these study types. The research fellow or health economist identified relevant titles and abstracts from the search results for each clinical question and full papers were obtained. Exclusion lists were generated for each question together with the rationale for the exclusion. The exclusion lists were presented to the GDG. See Appendix Q.1 for literature search details.

3. Appraising the evidence

The research fellow or health economist, as appropriate, critically appraised the full papers. In general, no formal contact was made with authors however there were ad hoc occasions when this was required in order to clarify specific details. Critical appraisal checklists were compiled for each

full paper. One research fellow undertook the critical appraisal and data extraction. The evidence was considered carefully by the GDG for accuracy and completeness.

All procedures are fully compliant with the:

- NICE methodology as detailed in the 'Guidelines manual'[282]
- NCC-CC quality assurance document and systematic review chart available at: http://www.rcplondon.ac.uk/college/ceeu/ncccc_index.htm .

4. Health economics evidence

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

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

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

5. Distilling and synthesising the evidence and developing recommendations

The evidence from each full paper was distilled into an evidence table and synthesised into evidence statements before being presented to the GDG. This evidence was then reviewed by the GDG and used as a basis upon which to formulate recommendations. The criteria for grading evidence are shown in Table 10.

Evidence tables have been added to Appendix Q.5

6. Grading the evidence statements

Table 10: Levels of evidence for intervention studies[282]

Level of evidence	Type of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1–	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*.
2++	High-quality systematic reviews of case–control or cohort studies. High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal.
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal.
2–	Case–control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal*.

Level of evidence	Type of evidence
3	Non-analytic studies (for example, case reports, case series).
4	Expert opinion, formal consensus.
*Studies with a level of evidence '–' should not be used as a basis for making a recommendation.	

4 Guideline summary

4.2 Full list of recommendations (2014)

The current recommendations can be found at www.nice.org.uk/guidance/ng203.

4.3 Key research recommendations (2014)

1. Does the provision of educational and supportive interventions to people with chronic kidney disease (CKD) by healthcare professionals increase patients' skills and confidence in managing their conditions and improve clinical outcomes?
2. For people aged over 75 years with CKD, what is the clinical effectiveness of renin–angiotensin–aldosterone system (RAAS) antagonists?
3. For people with CKD at the highest risk of cardiovascular disease, what is the clinical effectiveness of low-dose aspirin compared with placebo for primary prevention of cardiovascular disease?
4. In people with CKD who are at high risk of progression, what is the clinical and cost effectiveness of uric acid lowering agents on the progression of CKD and on mortality?
5. In people with hyperparathyroidism secondary to CKD, does treatment with vitamin D or vitamin D analogues improve patient-related outcomes?

5 Investigating chronic kidney disease

This chapter looks at the investigation of chronic kidney disease:

- The first part of the chapter (sections 5.1. and 5.2) reviews the evidence for the different methods of estimating glomerular filtration rate (GFR) and factors affecting variability of GFR estimation.
- The second part (sections 5.3 and 5.4) reviews the evidence for detecting haematuria and proteinuria, and incorporates the evidence for comparing protein:creatinine and albumin:creatinine ratios. It also reviews the evidence for managing isolated invisible haematuria (section 5.5)
- The third part (section 5.6) reviews evidence for combining tests for the measurement of kidney function with the tests investigating the markers of kidney damage to more accurately identify people at risk of progression and hence facilitate a more clinically relevant classification of chronic kidney disease.

The final part of this chapter (section 5.7) presents all of the recommendations and explains the links between the evidence and recommendations.

The term glomerular filtration rate (GFR) is abbreviated in the following way within the recommendations in this guideline:

- GFR: either a measured or an estimated GFR
- eGFR: estimated GFR (without indicating the method of estimation)
- eGFRcreatinine: an estimation of GFR using serum creatinine
- eGFRcystatinC: an estimation of GFR using cystatin C.

5.1 Measuring kidney function

5.1.1 Introduction

The glomerular filtration rate (GFR) is equal to the sum of the filtration rates in all of the functioning nephrons and is the best index of overall kidney function. Knowledge of GFR is essential for the diagnosis and management of CKD and is a translatable concept. As a normal GFR is approximately 100 ml/min/1.73 m^2, we can explain kidney function to patients and carers in terms of 'a percentage of normal' which may be easier to understand than GFR.

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

At the other end of the accuracy scale lies measurement of serum creatinine, which is a universally available endogenous test of kidney function. Although easy and cheap to measure, creatinine is subject to non-renal and analytical influences which, on its own, make it insufficiently sensitive to detect moderate CKD. Theoretically, measurement of 24-hour urinary creatinine clearance could improve the accuracy of measurement of kidney function. However, this is also subject to the same non-renal and analytical influences compounded by inaccuracies in urine collection and tubular secretion of creatinine, in addition to the inconvenience associated with 24-hour urine collections.

An alternative and more accurate endogenous marker is cystatin C, a 13 kDa cationic protein produced by all nucleated cells. Plasma cystatin C concentrations are chiefly determined by GFR. Development of cystatin C as an index of kidney function was, until recently, limited by the lack of an international standard and readily available assays.

The accuracy of both serum creatinine and cystatin C for detecting reduced kidney function can be improved through use of equations to estimate GFR which correct for some of the more significant non-renal influences. This approach is known to be more sensitive for the detection of CKD than serum creatinine and more accurate than creatinine clearance. Current practice is to estimate GFR from serum creatinine calibrated to the internationally standardised isotope dilution mass spectrometry (IDMS) methodology using the IDMS-related Modification of Diet in Renal Disease (MDRD) equation.

Since the introduction nationally of estimated GFR (eGFR) reporting in April 2006 further eGFR equations have been developed using both serum creatinine and cystatin C, either individually or in combination. The purpose of this question was to compare current practice against these new methods to establish whether or not a different approach offers sufficient advantages to dictate a change in practice. All eGFR units are ml/min/1.73m^2.

5.1.2 Review question: What is the accuracy of equations to estimate GFR as a measurement of kidney function?

This section was partially updated in 2018. See www.nice.org.uk/guidance/NG203/evidence for the 2018 evidence reviews.

For full details see review protocol in Appendix C.

Table 11: Characteristics of review question

Population	Adults (aged 18 and over) with suspected CKD **Subgroups:** • Older people aged over 75 years • Black and minority ethnic groups
Index test	• CKD-EPI (serum creatinine) • Cystatin C estimating equations (cystatin C) • Combined CKD-EPI (serum creatinine + cystatin C)
Comparator test	MDRD
Reference standard	Measured GFR (urinary or plasma clearance of inulin, iohexol, iothalamate, para aminohippurate [PAH], diethylenetriaminepentaacetic acid [DTPA] or ethylenediaminetetraacetic acid [EDTA]).
Outcomes	**Critical:** • Accuracy (P30) • Bias • Precision **Important:** • Sensitivity • Specificity • Area under the (receiver operating characteristic) curve (AUC) • Net reclassification index (NRI)
Study design	Diagnostic studies
Review strategy	• Minimum number of diagnoses 100. • Limit to studies using international standardisation for serum creatinine and cystatin C. • Externally validated equations only.

- Geographical exclusion – studies not relevant to population of England and Wales excluded as equations known to function differently in different populations.
- Medians to be calculated for analysis of outcomes. Due to differences in gold standard mGFRs only studies with more than one equation that meets inclusion criteria will be considered.

5.1.3 Clinical evidence

Fifteen studies were included in the review.[39,163,168,196,201,203,217,257,267,298,366,385,386,391,392] See summary of studies included in the review (Table 12). One further study[401] was identified that met the protocol but did not report any of the critical or important outcomes; therefore the results could not be analysed with the other studies in the review. Further results for Levey et al 2009[217] were identified in an additional study by the same group[386] and Teo et al 2011[391] and Teo et al 2012[392] were by the same group in the same population. Evidence from these are summarised in the clinical GRADE evidence profile below (Table 134). See also the study selection flow in Appendix D.

Of the studies included in the previous guideline (NICE CG73) one study[216] only looked at MDRD and was therefore excluded. The other studies either did not use the international standardisation for serum creatinine, or it was not possible to infer this from the published reports, and so all were excluded from this update.

The serum creatinine and cystatin C calibration and assay details for all studies considered for inclusion in the review were verified by the clinical biochemist member of the GDG to ensure they met international standardisation criteria.

The critical outcomes in this review are those used widely in the literature to compare GFR estimating equations. Bias describes the difference between estimates of GFR and the true value as measured by a reference technique. This is commonly described as the mean or median bias. Precision is the variability of the estimate of GFR compared to the measured value. The root mean square error (RMSE) of the regression of estimated GFR versus measured GFR is considered to be a direct measure of precision. However, overall interquartile range (IQR) for the differences between estimated GFR and measured GFR, an indirect measure of precision, was more widely reported and so was used in our analysis. Accuracy is affected by both bias and precision. Accuracy is represented by the P30: the percentage of estimated GFR values lying within 30% of the measured GFR. The GDG agreed that a 5% difference in P30 would be of a magnitude considered clinically important and so this was used as the minimal important difference (MID). For bias the minimal important clinical difference was agreed as 5 ml/min/1.73m^2 and for precision a 20% difference.

Table 12: Summary of studies included in the review

Study	Index tests	Country and Population	Outcomes	Comments
Bjork et al 2012[39]	• MDRD • CKD-EPI (serum creatinine)	Sweden; non-renal transplant patients aged ≥16 years; patients on dialysis excluded	• Accuracy (P30) • Bias • Precision • Net reclassification index	Equations not validated by subgroups; data set included participants more than once
Iliadis et al 2011[163]	• MDRD • CKD-EPI (serum creatinine)	Greece; Patients with type 2 diabetes; White only; mean age 65	• Accuracy (P30) • Bias • Precision • Sensitivity	Cystatin C not standardised, only sCr equations reviewed

Study	Index tests	Country and Population	Outcomes	Comments
			• Specificity • Area under the curve	
Inker et al 2012[168]	• CKD-EPI (serum creatinine) • CKD-EPI (cystatin C) • CKD-EPI (serum creatinine + cystatin C)	USA; External validation set from 4 studies (NephroTest, Steno, RASS and Lund CKD), excluded renal transplant recipients. 53% diabetic, 3% black, mean age 50.	• Accuracy (P30) • Bias • Precision • Net reclassification index	
Kilbride et al 2013[196]	• 4 variable MDRD • CKD-EPI (serum creatinine) • CKD-EPI (cystatin C) • CKD-EPI (serum creatinine + cystatin C)	UK; People aged 74 years or older; known to the Kidney Care Centre or recruited from the community excluding dialysis	• Accuracy (P30) • Bias • Precision	All European ancestry so no analysis on other ethnicities
Kong et al 2013[201]	• MDRD • CKD-EPI (serum creatinine)	China; people with CKD (70%) and healthy volunteers (30%); mean age 48.	• Accuracy (P30) • Bias • Precision • Sensitivity • Specificity	Chinese population.
Koppe et al 2013[203]	• MDRD • CKD-EPI (serum creatinine)	France; People aged 70 years or older referred to a single centre for inulin clearance for suspected or established renal dysfunction.	• Accuracy (P30) • Bias • Precision	
Levey et al 2009[217] additional subgroup information from Stevens et al 2010[386]	• MDRD • CKD-EPI (serum creatinine)	USA; External validation data set from 16 studies. 28% diabetic, 10% black, mean age 50. 16% kidney donors and 29% kidney transplant recipients	• Accuracy (P30) • Bias • Precision • Net reclassification index For eGFR <60 ml/min/1.73 m^2 only: • Sensitivity • Specificity	Bias for CKD EPI differs between Levey and Stevens studies
Michels et al 2010[257]	• Abbreviated MDRD • CKD-EPI (serum creatinine)	Netherlands; potential kidney donors and adult patients who underwent a GFR measurement for clinical reasons; mGFR ≥15	• Accuracy (P30) • Bias • Precision	178/449 (40%) excluded because no height measurement. Small study (n=271)

Study	Index tests	Country and Population	Outcomes	Comments
		ml/min/1.73 m^2, mean age 44.		
Murata et al 2011[267]	• MDRD • CKD-EPI (serum creatinine)	USA; All patients undergoing iothalamate clearance, mean age 56.	• Accuracy (P30) • Bias (by population subgroups only) For potential kidney donors only: • Sensitivity • Specificity	Too few non-Caucasian people to assess effect of ethnicity
Nyman et al 2011[298]	• MDRD • CKD-EPI (serum creatinine)	Sweden; Patients referred for determination of GFR, 100% Caucasian. Median age 60, 44% female.	• Accuracy (P30) • Bias • Precision • Net reclassification index	
Schaeffner et al 2012[366]	• MDRD • CKD-EPI (serum creatinine) • CKD EPI (cystatin C) • CKD EPI (combined serum creatinine and cystatin C)	Germany; age ≥70 (mean 78.5); White only; German statutory health insurance; living in Berlin; excluded RRT.	• Accuracy (P30) • Bias • Precision NCGC calculated: • Sensitivity • Specificity	BIS 2 excluded as not externally validated equation.
Stevens et al 2008[385]	• MDRD • CKD-EPI (serum creatinine)	France (external validation set); **Total sample:** Mean age 52; 37% female; 53% black; 43% white; 4% other; 13% diabetes. **External validation:** Mean age 59; 29% female; 8% black; 79% white; 13% other; 22% diabetes.	• Accuracy (P30) • Bias • Precision	Racial subgroup analysis used whole data set i.e. not external validation. Cystatin C not standardised, only sCr equtions reviewed
Teo et al 2011[391]	• MDRD • CKD-EPI (serum creatinine)	Singapore; Patients with stable CKD; >21 years; eGFR or mGFR 10-90 ml/min/1.73 m^2; mean age 58; 40.5% Chinese; 32% Malay; 27.5% Indian/ other	• Accuracy (P30) • Bias • Precision • Sensitivity • Specificity	
Teo et al 2012[392]	• CKD-EPI (serum creatinine) • CKD-EPI (cystatin C) • CKD-EPI (serum	Same population as Teo 2011	• Accuracy (P30) • Bias • Precision	Also reports equations with Chinese coefficients.

Study	Index tests	Country and Population	Outcomes	Comments
	creatinine + cystatin C)			

Table 13: Clinical evidence profile: MDRD versus CKD EPI (sCr) versus CKD EPI (Cystatin C) versus CKD EPI (combined)

Quality assessment							Number of people	Effect	Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other		Median [95% CI] and Range	
P30 - MDRD[39,163,196,201,203,217,257,267,298,366,385,391]									
12	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	14174	Median P30[95% CI]: 80% [77-83%] Range of P30: 70-85%	HIGH
P30 – CKD EPI (sCr)[39,163,168,196,201,203,217,257,267,298,366,385,391]									
13	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	15653	Median P30[95% CI]: 83% [80-85%] Range of P30: 72-85%	HIGH
P30 – CKD EPI (cystatin C)[168,196,366,392]									
4	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2315	Median P30[95% CI]: 86% [82-89%] Range of P30: 84-89%	HIGH
P30 – CKD EPI (combined)[168,196,366,392]									
4	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2315	Median P30[95% CI]: 86% [82-90%] Range of P30: 81-92%	HIGH
Bias - MDRD[39,163,196,201,203,217,257,267,298,366,385,391]									
12	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	14174	Median Bias [95% CI]: 1.2 [0.5, 2.1] Range of Bias: -5.5 to 14.6	HIGH
Bias – CKD EPI (sCr)[39,163,168,196,201,203,217,257,267,298,366,385,391]									
13	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	15653	Median Bias [95% CI]: -0.44 [-1.57, 0.69] Range of Bias: -3.7 to 12.3	HIGH
Bias – CKD EPI (cystatin C)[168,196,366,392]									
4	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2315	Median Bias [95% CI]: -2.7 [-3.9 to -1.6] Range of Bias: -3.4 to 8.71	HIGH
Bias – CKD EPI (combined) [168,196,366,392]									

Quality assessment							Number of people	Effect	Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other		Median [95% CI] and Range	
4	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2315	Median Bias [95% CI]: 0.8[-0.4 to 1.9] Range of Bias: -3.9 to 7.66	HIGH
Precision (defined as IQR [mGFR-eGFR])- MDRD[39,163,196,201,217,257,298,366,385,391]									
10	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	9072	Median Precision [95% CI]: 13.8 [12.4-14.9] Range of Precision: 8-23.4	HIGH
Precision – CKD EPI (sCr) [39,163,168,196,201,217,257,298,366,385,391]									
11	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	10191	Median Precision [95% CI]: 13.0 [NR] Range of Precision: 8-20.5	HIGH
Precision – CKD EPI (cystatin C)[168,196,366,392]									
4	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2315	Median Precision [95% CI]: 14.2 [12.5-15.9] Range of Precision: 10.6-16.4	HIGH
Precision – CKD EPI (combined) [168,196,366,392]									
4	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2315	Median Precision [95% CI]: 12.7 [11.5-13.9] Range of Precision: 10.5-13.4	HIGH
Sensitivity at threshold eGFR 60ml/min/1.73m^2 – MDRD[163,217,267,366,391]									
5	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	4875	Median sensitivity [95% CI]: 0.87 [0.80-0.92] Range of sensitivity:0.53-0.95	HIGH
Specificity at threshold eGFR 60ml/min/1.73m^2 – MDRD[163,217,267,366,391]									
5	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	4875	Median specificity [95% CI]: 0.90 [0.86-0.93] Range of specificity:0.78-0.98	HIGH

Quality assessment							Number of people	Effect	Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other		Median [95% CI] and Range	
Sensitivity at threshold eGFR 60ml/min/1.73m^2 – CKD EPI[163,217,267,366,391]									
5	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	4875	Median sensitivity [95% CI]: 0.89 [0.83-0.93] Range of sensitivity:0.50-0.91	HIGH
Specificity at threshold eGFR 60ml/min/1.73m^2 – CKD EPI[163,217,267,366,391]									
5	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	4875	Median specificity [95% CI]:0.88 [0.84-0.92] Range of specificity:0.85-0.98	HIGH
Area under the ROC curve – MDRD [163]									
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	448	AUC at threshold eGFR 60ml/min/1.73m^2 [95% CI]: 0.947 [0.917-0.968]	HIGH
Area under the ROC curve – CKDEPI[163]									
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	448	AUC at threshold eGFR 60ml/min/1.73m^2 [95% CI]: 0.952 [0.924-0.972]	HIGH
Net reclassification index – CKD EPI compared to MDRD									
0	-	-	-	-	-	-	-	-	-

5.1.4 Economic evidence

Published literature

No published economic analyses were found.

New cost-effectiveness analysis

An original cost analyses was conducted for this update. Full details are in Appendix L

The strategies compared were:

- CKD-EPIcreat: In this strategy, no further testing is conducted and the person is diagnosed as having CKD stage 3a.
- CKD-EPIcys: In this strategy, eGFR is re-calculated using serum cystatin C and the CKD-EPIcys equation.
- CKD-EPIcreat-cys: In this strategy, eGFR is re-calculated using serum cystatin C and serum creatinine and the combined CKD-EPI equation.

After reviewing the clinical evidence it was decided that it was unnecessary to consider the MDRD equation since CKD-EPIcreat has both greater precision and less bias and is no more costly to administer.

The population was adults with suspected CKD (CKD-EPIcreat 45-59 and ACR <3), categorised into the following subgroups:

1. 75+ years of age.
2. Under 75 years of age without hypertension.
3. Under 75 years of age with hypertension.

The main outcomes of the model are:

- Proportion of patients falsely diagnosed as having CKD (False positive – FP – eGFR<60 ml/min/1.73 m^2 and mGFR>60 ml/min/1.73 m^2).
- Proportion of patients falsely diagnosed as not having CKD (False Negative – FN – eGFR>60 ml/min/1.73 m^2 and mGFR<60 ml/min/1.73 m^2).
- NHS cost at 1 year.

The model used diagnostic accuracy data from studies in the guideline review[168,196] for 373 patients, unit costs from standard NHS sources and prescribing data from 32,956 patients. Since there was little data for older patients, this was supplemented with unpublished data from the AGES-Reykjavik study[167].

The reagent costs of serum creatinine and serum cystatin testing were assumed to be £0.25 and £2.50 respectively. The average incremental cost of CKD care compared with people not diagnosed with CKD was £51.50 per year for health care visits (and on average £7.00 extra for antihypertensives).

The prevalence of 'true CKD' (mGFR<60 ml/min/1.73 m^2) was lower in the younger cohorts suggesting that the CKD-EPIcreat equation is over-predicting CKD in these people. Sensitivity of the test was similar across the three cohorts but specificity was greater in the younger cohorts particularly in the hypertensive cohort, suggesting that the CKD-EPIcreat equation is over-predicting in younger people much more so than the two cystatin-based equations. Across all three cohorts the combined equation was more sensitive but the cystatin C equation was more specific.

In all three cohorts, the cystatin c equation produced the fewest false positive results, which led to it being the lowest cost strategy (Table 14) – the cost of the test being more than offset by the subsequent reduction in drug and management costs. In the cohort of older patients and the cohort of non-hypertensive patients, it was actually the combined equation that had the most accurate diagnoses since it had fewer false negative results due to its greater sensitivity.

In one sensitivity analysis we extended the time horizon to 5 years, which increased the cost savings associated with CKD-EPI_{cys} compared with CKD-EPI_{creat}. For example in the case of younger patients without hypertension the cost savings per patient tested increased from £14 to £78.

If we add the cost of a follow-up test to try and pick up false negatives after a year then CKD-EPI_{cys} is the lowest cost strategy for younger patients but not for older patients. However, if we increase the timeframe of CKD management costs to 2 or more years then CKD-EPI_{cys} is the strategy with the lowest cost for older patients as well.

If the cystatin C test is ordered after the results of the follow-up test are known then the CKD-EPI_{cys} is the lowest cost strategy but not if there is a follow-up test to try and pick up false negatives after a year. However, again, if we increase the timeframe of CKD management costs to 2 or more years then CKD-EPI_{cys} is the strategy with the lowest cost.

Table 14: Base case results for people with CKD-EPI$_{creat}$ 45-59 and ACR<3 – Probabilistic

	Diagnostic outcomes			Mean costs (£)			
	Correct	False positive	False negative	Diagnosis	Additional drugs	CKD Care	Total
Age75+							
CKD-EPIcreat	80%	20%	0%	0.25		51.50	51.75
CKD-EPIcys	77%	11%	13%	2.75		39.88	42.63
CKD-EPIcreat-cys	80%	12%	7%	2.75		43.60	46.35
Age<75 No hypertension							
CKD-EPIcreat	67%	33%	0%	0.25	0	51.50	51.75
CKD-EPIcys	75%	13%	12%	2.75	0	35.35	38.10
CKD-EPIcreat-cys	81%	17%	3%	2.75	0	41.50	44.25
Age<75 Hypertension							
CKD-EPIcreat	70%	30%	0%	0.25	7.00	51.50	58.75
CKD-EPIcys	79%	7%	14%	2.75	4.43	32.62	39.81
CKD-EPIcreat-cys	79%	11%	11%	2.75	4.93	36.26	43.94

5.1.5 Evidence statements

Clinical

All of the following are based on high quality evidence:

- Over the entire GFR range, the studies did not show an important difference in accuracy of estimating kidney function, defined by P30, between MDRD and CKD-EPI. There was, however a trend towards increased accuracy using cystatin C or combined equations. P30 was slightly better in the subgroup with GFR <60 ml/min/1.73 m^2 compared to a GFR >60 ml/min/1.73 m^2. The CKD-EPI creatinine equation was more accurate than the MDRD in people with a GFR >60 ml/min/1.73 m^2. Only two studies looked at P30 in cystatin C or combined equations for GFR subgroups.
- Five studies[39,196,203,298,366] considered P30 in older people. Two of these[39,298] looked at a pre-specified subgroup of people 80 years and over. The other three studies included only older people: Kilbride et al[196] people aged 74 years and over (median 80 years) and both Koppe et al[203] and Schaeffner et al[366] people aged over 70. In the Kilbride study the P30 of all the CKD-EPI equations was significantly better than that of the MDRD equation in those with GFR greater than 60 ml/min/1.73 m^2. Overall the three studies showed a trend towards CKD-EPI creatinine, cystatin C or combined equations being more accurate than MDRD in this subgroup.
- Overall there was less bias with the CKD-EPI creatinine equation than with MDRD. There was more bias in the GFR>60 ml/min/1.73 m^2 subgroup compared to the GFR<60 ml/min/1.73 m^2. Cystatin C or combined equations showed the least bias in the GFR <60 ml/min/1.73 m^2 group. In the GFR>60 ml/min/1.73 m^2 group there was minimal difference between the performance of the equations. Only two studies reported bias in the older population subgroup. Both showed less bias with cystatin C or combined equations compared to creatinine based equations alone.
- The most precise (defined by interquartile range [mGFR-eGFR]) equation was the combined CKD EPI (serum creatinine and cystatin C) however, overall there was little difference in precision between the equations.
- There was no difference in sensitivity and specificity or area under the curve for CKD EPI creatinine compared to MDRD. These outcomes were not reported for the other equations.
- No data from the studies included were available for net reclassification index for CKD-EPI compared to the MDRD equation.

Economic

- One original comparative cost analysis found that CKD-EPIcys was less costly than CKD-EPIcreatinine and CKD-EPIcreat-cys for diagnosing CKD in people with an initial CKD-EPIcreatinine 45-59, ACR<3mg/mmol and without diabetes (magnitude of cost savings varied according to age group, comorbidity, time horizon and re-testing strategy). This analysis was assessed as partially applicable with minor limitations.

5.1.6 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng203

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

5.2.1 Clinical introduction

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

Biological variation includes random variation and predictable cyclical variation (daily, monthly, seasonal). Within-subject biological variation is the average random fluctuation around a homeostatic set point, expressed mathematically as a coefficient of variation (CV).[343] Large variations in serum creatinine measurements could result in misclassification of people to a particular CKD stage. Factors affecting measured serum creatinine concentration and estimated GFR from prediction equations include ingestion of cooked meat (where the cooking process converts meat creatine to creatinine, which is subsequently absorbed into the bloodstream after ingestion), individual patient fluid status, diurnal variation, and centrifugation of blood samples.

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

The vast majority of creatinine assays in NHS biochemistry laboratories are calibrated to the internationally standardised reference material and reference methodology (isotope dilution mass spectrophotometry (IDMS)). The GFR estimating equations under consideration (IDMS-adjusted MDRD and CKD-EPI equations) are only valid with such methods. This section addresses other sources of bias and variation in creatinine measurement.

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

This section was partially updated in 2018. See www.nice.org.uk/guidance/NG203/evidence for the 2018 evidence reviews.

5.2.2 Methodology

Three case series investigated the biological and analytical variation of serum creatinine measurements in people with CKD[110,151] or with type 1 diabetes.[152]

Two studies examined the effect of delayed centrifugation of outpatient blood samples on the measurement of serum creatinine concentration by the kinetic Jaffe reaction or by enzymatic methods. The effect of delayed centrifugation of blood samples on GFR estimation was determined.[104,373]

Two case series investigated the diurnal variation in serum creatinine measurements in 72 patients with varying degrees of kidney disease[335] and in 9 healthy people.[319]

Two case series evaluated the effect of a cooked meat meal on serum creatinine concentration in healthy subjects and outpatients[331] or in adults with diabetic nephropathy.[329] Two earlier studies examined changes in serum creatinine following ingestion of relatively large portions of cooked meat

(300g) or raw meat (300g) or non-meat meals in six healthy volunteers.[170,250]

5.2.3 Health economics methodology

There were no health economics papers found to review.

5.2.4 Evidence statements

Biological variation of serum creatinine

The intra-individual biological variation of creatinine was significantly higher in people with CKD (n=17, coefficient of variation (CV)=5.3%) than in healthy people (n=24, CV=2.7%, p <0.01).[151]

The CV for serum creatinine for nine people with CKD on all occasions was 61.9%. The average analytical variation for serum creatinine was 0.1% of the total variance. The average intra-individual biological variation of creatinine measurements was 1.1% of the total variance.[110] (Level 3)

The intra-individual biological variation of creatinine measurements was significantly higher in women with insulin-dependent diabetes (n=11, CV=6.53%) than in healthy women (n=14, CV=2.81%, p <0.01). The intra-individual biological variation of creatinine measurements was significantly higher in men with insulin-dependent diabetes (n=16, CV=5.88%) than in healthy men (n=10, CV=2.64%, p <0.01). [152] (Level 3)

Diurnal variation of serum creatinine concentration

In non-fasting healthy participants (n=9) or in non-fasting paralysed participants (n=4), the creatinine concentration increased significantly during the day, peaking at 19:00 (p <0.001). The creatinine concentration then decreased after 19:00 to 7:00 the next morning. In fasting participants (n=9), there was a small but significant decrease in creatinine concentration between 7:00 and 13:00 (p <0.02) and there was no increase in serum creatinine during the rest of the time course.[319] (Level 3)

In people with inulin clearance ≥90 ml/min (n=38), the serum creatinine concentration was significantly greater in the afternoon than in the morning (mean difference 0.087 mg/100 ml [8 µmol/l], p <0.001). By contrast, there was non-significant (NS) difference in serum creatinine concentration between morning and afternoon in people with inulin clearance <90 ml/min (n=34, mean difference 0.035 mg/100 ml [3 µmol/l]).[335] (Level 3)

Effect of cooked meat on serum creatinine concentration and eGFR

Four studies showed that ingestion of a cooked meat meal caused a significant increase in serum creatinine concentration. Following a cooked meat meal (n=6 healthy subjects), the mean serum creatinine concentration significantly increased (86 µmol/l at baseline to 175 µmol/l, 3 hours postprandially, p <0.001). The creatinine concentration then declined and at 10 hours postprandially stabilised, but did not return to baseline. Following a non-meat meal or a raw beef meal, the serum creatinine concentration was relatively unchanged.[170] (Level 3)

Following a cooked meat breakfast (n=6), the mean serum creatinine concentration significantly increased from baseline to 2 to 4 hours postprandially (52% increase, range 36-65%). The creatinine concentration slowly declined and returned to baseline by 12 hours. By contrast, following either a high or low non-meat protein breakfast (control), serum creatinine remained stable.[250] (Level 3)

In 10 people with diabetic nephropathy, the mean serum creatinine concentration significantly increased from baseline (167 µmol/l) to 180 µmol/l in 2 hours (p<0.001) following a cooked meat meal.[329] (Level 3)

Following a cooked meat lunch (n=32 healthy volunteers and outpatients), the median serum creatinine concentration significantly increased from baseline by 18.5 µmol/l 3 to 4 hours

postprandially (p<0.0001). The median eGFR significantly decreased from baseline by 20 ml/min/1.73 m^2 3 to 4 hours postprandially (p<0.0001). Following a meat meal, 11 people changed from a pre-prandial eGFR >59 ml/min/1.73 m^2 to a postprandial eGFR of <60 ml/min/1.73 m^2, erroneously placing them in stage 3 CKD. By contrast, following a vegetarian lunch (n=23), there was a NS change in median serum creatinine concentration; and there was a small but significant increase in eGFR from baseline (preprandial) to 3–4 hours postprandially (3.5 ml/min/1.73 m^2, p=0.006).[331] (Level 3)

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

Two studies showed significant increases in creatinine concentration after a 10- to 24-hour delay in centrifugation of blood samples (kinetic Jaffe method used to assay creatinine). By contrast, the creatinine concentration remained stable, regardless of the delay in centrifugation, when assayed with enzymatic methods.[104,373] From the 24-hour delay experiment (n=113 outpatients), mean creatinine concentration significantly increased from baseline (85 µmol/l) to 24-hour delay (95 µmol/l, 11% increase, p <0.0004).[104] (Level 3)

With a 16 hour delay in centrifugation, 4 out of 7 volunteers with baseline stage 1 CKD had changed to stage 2. After a 36 hour delay in centrifugation, 7 out of 7 volunteers had changed from stage 1 to stage 2 CKD. After a 24-hour delay in centrifugation of samples (n=113 outpatients), mean eGFR significantly decreased from baseline (eGFR 85 ml/min/1.73 m^2) to 24-hour delay (eGFR 75 ml/min/1.73 m^2, 13% decrease, p <0.0001). The CKD staging of 32% of the participants changed after a 24-hour delay in centrifugation of blood samples: 26% went from stage 1 CKD to stage 2, and 6% went from stage 2 to stage 3 CKD.[104] (Level 3)

In 21 patients where the delay in centrifugation of blood samples exceeded 10 hours, the eGFR significantly decreased (p <0.001). This resulted in a change in CKD classification in 4 of these cases.[373] (Level 3)

5.2.5 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng203

5.3 Detection of blood and protein in the urine

5.3.1 Clinical introduction

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

Haematuria is defined as the presence of red blood cells (RBCs) in the urine, either visible (macroscopic haematuria) or invisible and detected by direct microscopy (microscopic haematuria). A reagent strip test to detect blood in urine provides an instant result and is often the method of detection of invisible haematuria in the primary care setting.[54] The reagent strip or 'dipstick' test is commonly considered to be sensitive for the detection of RBCs below the defined (microscopic) 3 RBCs per high power field threshold for invisible haematuria. Dipstick testing of spot urine samples is also used for rapid detection of protein and albumin. However, reagent strips are subject to false positives because of patient dehydration, exercise, infection, and extremely alkaline urine. False negative results occur as a result of excessive hydration and urine proteins other than albumin.

Haematuria can be broadly classified as nephrological or urological in origin. Most forms of intrinsic kidney disease may result in invisible haematuria. Urological causes include tumours, urinary tract

infection, stone disease and bleeding from benign conditions of the urinary tract. Invisible haematuria may also be detected in the absence of any underlying pathology, such as after vigorous exercise.[182] The prevalence of asymptomatic invisible haematuria varies between 0.19% and 21%, depending on age and gender. Screening studies have suggested that the prevalence of asymptomatic invisible haematuria in the UK adult male population is around 2.5%, increasing to 22% in men over the age of 60 years.[49,344]

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

During the 2014 update of the CKD clinical guideline the GDG discussed the terminology used for proteinuria. They agreed that the terminology should be changed from 'protein excretion' to 'protein loss' as protein excretion was not an accurate term (i.e in the physiological sense protein is not 'excreted' from the body). The changes were made throughout the guideline except in situatios where the terminology used in the original guideline was important to retain, for example when it was used in recommendations, or during a call for evidence.

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

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

This section was partially updated in 2018. See www.nice.org.uk/guidance/NG203/evidence for the 2018 evidence reviews.

5.3.2 Methodology

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

ACR and PCR have been shown to correlate with the 24-hour albumin or protein loss rate. Proteinuria is defined as a 24-hour protein loss ≥150 mg/24 h. The term 'microalbuminuria' has been used to define a 24-hour urinary albumin loss of between 30-300 mg/24 h. A 24-hour urinary
albumin loss of >300 mg/24 h has been termed 'macroalbuminuria' and a 24-hour urinary albumin loss of <30 mg/24h as 'normalbuminuria'. In these assays, albumin is measured with

immunonephelometric methods. Protein is measured in turbidimetric or colorimetric assays with a variety of techniques (e.g. Bradford reagents, benzethonium chloride, pyrogallol red-molybdate).

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

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

Four cross-sectional studies compared reagent strips to microscopy of urine sediment to detect haematuria in adults with systemic lupus erythematosus,[58] blunt kidney trauma,[59] urological outpatients,[125] or hospitalised patients.[19] The study by Gleeson et al. was excluded as standard light (and not phase) microscopy was used as the reference test. The study by Chandhoke et al. was excluded as there was little methodological detail on blinding, when the tests were performed, and few population characteristics.

Four cross-sectional studies assessed the diagnostic accuracy of reagent strips to detect albuminuria. Two studies compared reagent strips to ACR in hospitalised patients[334] and in the general population of Takahata, Japan.[202] Two studies compared reagent strips to urinary albumin concentration in 24-hour urine specimens in people with diabetes[122] or in adults with hypertension or diabetes.[72]

Nine cross-sectional studies assessed the diagnostic accuracy of reagent strips to detect proteinuria. Six of these studies compared reagent strips to 24-hour protein in hypertensive pregnant women.[51,145,256,316,364,418] One study compared reagent strips to 24-hour protein in adults with kidney disease.[115] The remaining two studies compared reagent strips to PCR in people with kidney disease[7] or in hospitalised patients.[334]

5.3.3 Health economics methodology

One paper was retrieved.[397] The paper was excluded because the reference standard was quantitative urine culture (QUC).

5.3.4 Evidence statements

Detection of haematuria

Table 15: Diagnostic accuracy of reagent strips to detect blood in urine.

Study	Population	n	Comparison	Cut-off	No of true positives	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
[19]	Hospitalised patients n=100	825 samples	N-Multistix-SG vs. phase-contrast microscopy of un-spun urine	Trace RBC + result	521/825 = 63%	-	-	82% 100 %	-
[58]	Systemic lupus erythematosus	269	Hemastix vs. phase-contrast microscopy of urinary sediment	Trace RBC	63/269 = 24%	98	53	39	99

PPV – Positive predictive value; NPV – Negative predictive value

The sensitivity of reagent strips for detecting trace erythrocytes in urine of adults with lupus (n=269) was high (98%), but the specificity (53%) and positive predictive value (PPV) (39%) were low.[58] In hospitalised patients (n=100, 825 urine samples) the PPV for 'trace' and '+' results on a reagent strip were 82% and 100% respectively.[19] (Level 1b +)

Detection of albuminuria

Table 16: Diagnostic accuracy of reagent strips to detect albuminuria

Study	Population	n	Comparison	Cut-off	No of true positives	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
[334]	Hospitalised patients	310	Multistix PRO vs. ACR	ACR ≤ 80 mg/g creatinine	NR	-	-	84	89
[334]	Kidney disease	113	Multistix PRO vs. ACR	ACR ≤ 80 mg/g creatinine	73/113 = 65%	-	-	86	100
[334]	People with diabetes	80	Multistix PRO vs. ACR	ACR ≤ 80 mg/g creatinine	19/80 = 24%	-	-	83	100
[72]	Hypertensive adults	79	Micraltest II vs. 24-h nephelometry (albumin)	≤ 28.2 mg/l	4/79 = 5%	75	95	43	99
[72]	People with diabetes	166	Micraltest II vs. 24-h nephelometry (albumin)	≤ 30.5 mg/l	71/166 = 42%	83	96	95	88
[202]	General population (Japan)	2321	Multistix vs. ACR	ACR ≤ 30 mg/g creatinine	317/2321 = 14% (ACR 30-300 mg/g)	37[a]	97[a]	71[a]	90[a]
[202]	People with diabetes (Japan)	201	Multistix vs. ACR	ACR ≤ 30 mg/g creatinine	317/2321 = 14% (ACR 30-300 mg/g)	45[a]	98[a]	91[a]	76[a]
[202]	Hypertensive adults (Japan)	1323	Multistix vs. ACR	ACR ≤ 30 mg/g creatinine	317/2321 = 14% (ACR 30-300 mg/g)	37[a]	98[a]	81[a]	86[a]
[122]	People with diabetes	411	Micral-Test II vs. Urinary albumin concentration (radioimmunoassay)	Albumin concentration < 20mg/l	114/411 = 28% (UAC 20-200 mg/l); 47/411 = 11% (UAC > 200 mg/l)	93	93	89	-

(a) Trace proteinuria defined as positive
PPV = Positive predictive value; NPV = Negative predictive value

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

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

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

Detection of proteinuria

Table 17: Diagnostic accuracy of reagent strips to detect proteinuria

Study	Population	n	Comparison	Cut-off	No of true positives	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
[115]	Kidney disease	297	Multistix 10 SG vs. 24-hour protein loss	≤0.150 g/24 h	62%	49	94	-	-
[7]	Kidney disease	332	Multistix 10 SG vs. PCR	PCR ≤1g/g creatinine	125/332 = 38%	100[a]	60[a]	-	-
[7]	Kidney disease	332	Multistix 10 SG vs. PCR	PCR ≤1g/g creatinine	125/332=38%	96[b]	87[b]	-	-
[7]	Kidney disease	332	Multistix 10 SG vs. PCR	PCR ≤3g/g creatinine	51/332=15%	94[c]	83[c]	-	-
[334]	Hospitalised patients	310	Multistix PRO vs. PCR	PCR ≤300 mg/g creatinine	NR	-	-	84	87
[334]	Kidney disease	113	Multistix PRO vs. PCR	PCR ≤300 mg/g creatinine	81/113=72%	-	-	92	93
[334]	People with diabetes	80	Multistix PRO vs. PCR	PCR ≤300 mg/g creatinine	20/80=25%	-	-	83	98
[417]	Hypertensive pregnant women	197	BM-Test-5L vs. 24-h protein loss determined by Benzethonium Chloride assay	≤0.3g/24 h	70%	22	98	97	35
[417]	Hypertensive pregnant women	197	BM-Test-5L vs. 24-h protein lossdetermined by Bradford assay	≤0.3g/24 h	25%	57	97	87	87
[316]	Hypertensive pregnant women	150	Multistix-AMES vs. 24-h urine protein (random dipstick)	≤0.3g/l	84/150=56%	84	61	57	86
			Multistix-AMES vs. 24-h urine protein (aliquot collected at 6-hrs)	≤0.3g/l	84/150=56%	84.5	90.1	84.5	90.0
[51]	Hypertensive	230	Multistix 10SG vs. 24-h urine	≤0.3g/24 h	70/230=30%	-	-	86	38

Study	Population	n	Comparison	Cut-off	No of true positives	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
	pregnant women		protein (Dipstick done before 24-h urine collection)						
			Multistix 10SG vs. 24-h urine protein (Dipstick done after 24-h urine collection)	≤0.3g/24 h	70/230 = 30%	-	-	46	88
[145]	Pregnant women	690 samples	Multistix 10SG vs. 24-h urine protein	≤15 mg/dl	NR	36	97	68	88
[256]	Hypertensive pregnant women	300 samples	Urine dipstick (unspecified) vs. 24-h urine protein	≤0.3g/24 h	NR	67	74	92	34
[364]	Pregnant women	103	Multistix 10SG vs. 24-h urine protein	≤0.3g/l	NR	100	62	24	-

(a) when reagent strip result +1
(b) when reagent strip result +3
(c) when reagent strip result +4
PPV – Positive predictive value; NPV – Negative predictive value

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

In people with kidney disease, a +1 or a +3 result on a reagent strip had high sensitivities to detect a PCR ≥1 g protein/g creatinine (roughly >1 g/day), and the specificity was low.[7] Another study showed that reagent strips had low sensitivity for detecting proteinuria (>0.150 g/24 h).[115] (Level 1b+)

Recommendations
The current recommendations can be found at www.nice.org.uk/guidance/ng203

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

5.4.1 Clinical introduction

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

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

Protein loss displays considerable biological variability, and may be increased by urinary tract infection (UTI), upright posture, exercise, fever, and heart failure as well as by kidney disease. Biological variation of both measures is high, with lower variation generally being reported for an albumin:creatinine ratio (ACR) on an early morning urine (EMU) compared to PCR (e.g. 36% versus 48% respectively). There is a high correlation between total protein and albuminuria at high levels of proteinuria (so-called nephrotic range proteinuria, ACR >220 mg/mmol and PCR >300 mg/mmol) but at low levels correlation is poor. This is because urine protein measurement in the normal range and at low levels is both imprecise and relatively non-specific. Albumin as a proportion of total protein is highly variable at normal and moderately increased levels of proteinuria.[28,95,332,374]

The 2008 NICE Guidelines defined proteinuria as a PCR of ≥50 mg/mmol or an ACR ≥30 mg/mmol but suggest that, in the absence of concomitant haematuria, this should not act as a trigger for active intervention until the PCR exceeds 100 mg/mmol (ACR >70 mg/mmol).[277] .

It has been accepted for many years that total protein measurement is insufficiently sensitive to detect the onset of diabetic nephropathy and that urine albumin must be used for this purpose. This is enshrined in many clinical practice guidelines including those for type 1 and 2 diabetes produced by NICE. There is also evidence that urine albumin is a more sensitive test to enable detection of glomerular disease associated with some other systemic diseases (e.g. SLE, hypertension). The diabetic nephropathy literature and the classification of diabetic nephropathy is based upon urine albumin loss (commonly expressed as an ACR measurement) and the recent Kidney Disease Improving Global Outcomes (KDIGO) classification of CKD is clear in that it requires urine albumin measurement to facilitate diagnosis of stage 1 and 2 CKD, with proteinuria being defined as an ACR $\geq$3 mg/mmol. In other words, the presence of low-level albuminuria ('microalbuminuria') in an individual with a GFR >60 ml/min/1.73 m^2 is indicative of CKD irrespective of whether diabetes mellitus is present or not. There is strong evidence from epidemiological studies linking urinary albumin loss to cardiovascular mortality and kidney disease progression in people with diabetes and to cardiovascular and non-cardiovascular mortality in those without diabetes.[47,68,106,130] Amongst people with diabetes, microalbuminuria is used as a therapeutic target that can be modified by renin-angiotensin-aldosterone system blockade with resulting improvement in clinical outcomes: there is currently a poor evidence base for this strategy in non-diabetic kidney disease.[46]

In the most common types of CKD (i.e. that due to diabetes, hypertension and glomerular disease) and in kidney transplant recipients, albumin is both the most abundant protein in urine and a more sensitive marker of disease. The NKF-KDOQI, NICE 2008 and KDIGO 2012 and CARI 2013 guidelines therefore recommend urinary albumin measurement in preference to total protein when detecting and monitoring proteinuria. Conversely, the Scottish Intercollegiate Guidelines Network recommend PCR.18

There is a need to reconcile these approaches. Increasingly the management of CKD is being undertaken by general practitioners and other non-nephrologists. Also, where the National Vascular Screening Programme identifies people with conditions such as hypertension, diabetes and impaired GFR an ACR will be recommended. Furthermore, the Quality and Outcomes framework now includes

proteinuria in the CKD indicators. There is a need for consistency between detection of proteinuria in diabetes and detection of proteinuria in CKD. The current dual system of proteinuria/albuminuria reporting is at the least confusing and to patients probably unfathomable. Problems remain in defining conversion factors that would enable the proteinuria evidence base to be interpreted on the basis of urine albumin results. This is particularly true at lower levels of protein loss, where the contribution of albumin to total protein is more variable. To attempt to address this, a call for evidence[282] was circulated to registered stakeholder organisations specifically seeking evidence relating to the equivalence of ACR to PCR and to 24-hour urinary protein loss.

Clinical question: What are the benefits in terms of accuracy and cost in measuring albumin:creatinine ratio versus protein:creatinine ratio to quantify proteinuria in adults with CKD?

This section was partially updated in 2018. See www.nice.org.uk/guidance/NG203/evidence for the 2018 evidence reviews.

Call for evidence: What is the equivalence between urinary albumin:creatinine ratios and 24-hour urinary protein excretion and urinary protein:creatinine ratio?

5.4.2 Methodology

There were no studies that directly compared PCR with ACR and provided sensitivity and specificity outcomes. Instead, studies were selected that compared ACR or PCR to the reference standard test, timed overnight or 24-hour urinary albumin (or protein) loss. Studies were excluded if the sample size was small (lower than 100) or if the sulphosalicylic acid test, protein heat coagulation test, or urine electrophoresis were used as the reference test.

Two studies compared PCR in a spot urine sample to timed urinary 24-hour protein loss in diabetic adults[349] or in non-diabetic adults with proteinuria and CKD.[355] These two studies only reported the correlation between the reference standard and PCR. Six studies compared the ACR in a spot urine sample to timed overnight or 24-hour urinary albumin loss in diabetic adults,[57,120,161,246] in a Dutch general population,[118] and in an South Asian general population in Pakistan.[171] Sample sizes in the eight studies ranged from 109 to 2527.

Call for evidence: methodology

Eight studies were received from stakeholders in a call for evidence[282] to address the equivalence of urine albumin with urine total protein. Four of these studies were relevant and admissible under the NICE Guidelines Manual.

In a cross-sectional study of people aged 25 years and older in Australia (AusDiab, n=10596), both urine albumin (rate nephelometry) and urine protein (pyrogallol red molybdate) were measured in random urine samples and the correlation between ACR and PCR was determined. The sensitivity, specificity, positive and negative predictive values of an ACR ≥30 mg/g to detect a PCR ≥200 mg/g were determined. All analyses in this paper were weighted to represent the non-institutionalised Australian population.[22]

Two UK studies compared urinary albumin with total protein from timed 24-hour urine collections. Specifically, the correlation between urinary albumin concentration (mg/l, immunoturbidometric assay) and urinary total protein concentration (mg/l, Ponceau S assay) was assessed in 235 timed 24-hour urine samples.[28] Similarly, the correlation between albumin loss (latex particle enhanced immunoturbidometric assay) and protein loss (biuret, following trichloroacetic acid) was determined from the same timed 24-hour urine samples.[292]

The unpublished manuscript by MacGregor et al. detailed a retrospective analysis of 6761 urine samples. Given that this manuscript was shared with the GDG [of the 2008 chronic kidney disease guideline (CG73)]as unpublished work in progress, there are some methodological limitations. The correlation between ACR (immunoturbidometric assay) and PCR (pyrogallol red or subsequently a benzethonium turbidometric assay) was assessed. The relationships between 24-h protein loss and ACR or PCR were also analysed in a non-randomised subgroup for whom 24-hour protein had been collected (n=1739). Areas under the receiver-operator curves were determined, along with the thresholds of both ACR and PCR to detect 24-hour protein loss >1 g/day or >450 mg/day with sensitivity of 0.95.235,255

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

5.4.3 Health economics methodology

Two studies were retrieved.[61,233] Both were excluded because they were cost analyses and did not consider cost-effectiveness. Given the uncertainty in the clinical evidence below and the cost difference between the tests, a health economic modelling calculation was conducted; details are given below under 'From Evidence To Recommendations' and in full in Appendix Q.

5.4.4 Evidence statements

Correlation of PCR and 24-hour protein loss

In diabetic and non-diabetic populations (n=229 and n=177, respectively), spot morning PCR and 24-hour urinary protein loss rates were log-transformed and a linear regression was fitted, which was highly significant (β=0.948, p <0.0001 in people without diabetes, and β =0.9, significance not stated for people with diabetes).[349,355] However, PCR becomes a less accurate predictor of 24-hour urinary protein loss in the higher values. (Level 1b +)

Correlation of ACR and 24-hour albumin loss

There was a high correlation between first morning urine ACR and overnight albumin loss (r=0.921, p not given, n=261 diabetic adults).[161] Similarly, there was high correlation between overnight albumin loss and first morning ACR (Kendall's τ_b=0.71, p<0.001, n=446), though this study specifically excluded people with clinical proteinuria from the analyses.[120] In a US study of a black people with type 2 diabetes (n=123), there was also a significantly high correlation between ACR and 24-hour albumin loss (r=0.96, p=0.0001). This correlation significantly decreased in adults with normal ACR (<30 µg/mg) (r=0.59, p<0.0001, n=90) as well as in adults with microalbuminuria (ACR 30–300 µg/mg) (r=0.55, p=0.005, n=26).[57] (Level 1b +)

Sensitivity and specificity

Overall, sensitivity and specificity were high for first morning ACR. In the figures given below, sensitivity is the proportion of people with an albumin rate of loss >30µg/min correctly identified by the ACR test. Specificity is the proportion of people with an albumin loss rate <30 µg/min correctly excluded by the ACR test.

At a cut-off value of >3.0 mg/mmol, ACR had a sensitivity of 96.8% and a specificity of 93.9%.[161] The sensitivity 49.0% (95% CI 71.1–56.9) was much lower in a larger healthy population (n=2527), while the specificity was still high 98.7% (95% CI 98.2–99.1).[118] (Level 1b +)

At a cut-off value of >3.5 mg/mmol, overnight ACR had a sensitivity of 88% and a specificity of 99%, p value not given.[120] Another similar study reported 98% sensitivity and 63% specificity, p value not given.[246] (Level 1b + and II+)

At a cut-off of 30 mg/g, ACR had low sensitivity (60% in men and 46% in women) to detect albuminuria (urinary albumin rate of loss ≥30 mg/24 h) in a South Asian population (n=577). The specificity was high (97% in men and 95% in women).[171] (Level 1b +)

Positive and negative predictive values

The positive predictive value (PPV) is the proportion of true positives in the sample and the negative predictive value (NPV) is the proportion of true negatives in the sample. The PPV for ACR was 72% or 68.2%.[120,161] The NPV was 99.5%.[161] (Level 1b +)

In a South Asian population, the PPV for albuminuria in those with high ACR (≥30mg/g) was 72%. The NPV for albuminuria in those with high ACR (≥30mg/g) was 95%.[171] (Level 1b +)

5.4.5 Evidence statements from the 'Call for Evidence'

Correlation of ACR and PCR

MacGregor et al. showed that the relationship between ACR and PCR was non-linear (n=6761). There was poor correlation between ACR and PCR in the range of 10–100 mg/mmol, and this remained the case when the analysis was restricted to subgroups (by gender, primary glomerular disease, diabetic nephropathy, and various bands of eGFR).[235] (Level 1b +)

By contrast, in the AusDiab study, a linear regression of log ACR and log PCR was significant (β = 1.21 (95% CI 1.18 to 1.26), p <0.001, R^2=72.1%, n=10,596 samples). The ratio of urine albumin to total protein significantly increased with increasing degrees of proteinuria from 0.21 for those with PCR of 0-0.20 mg/mg up to 0.73 for people with PCR >0.80 mg/mg. However, there was increased scatter of ACR (below the line of unity) at lower levels of PCR.[22] (Level II +)

Sensitivity and specificity of ACR and PCR

To detect a PCR ≥200 mg/g, the pre-specified threshold of ACR ≥30 mg/g had a sensitivity of 91.7% (95% CI 87.7–94.5%) and a specificity of 95.3% (95% CI 94.9–95.7%).[22] (Level II +)

Positive and negative predictive values of ACR and PCR

To detect a PCR ≥200 mg/g, ACR ≥30 mg/g had a PPV of 32.4% (95% CI 29.0–35.8%) and a NPV of 99.8% (95% CI 99.7–99.9%).[22] Atkins et al. concluded that testing for albuminuria rather than proteinuria was supported. However, among people with known kidney disease, total protein measures may provide better diagnostic/prognostic information (as among people with proteinuria, 9% tested negative for albuminuria). (Level II +)

Correlation of ACR or PCR with 24-hour urinary protein loss

ACR and PCR both correlated well with 24-h urinary protein loss (n=1739, the subgroup in whom 24-hour protein had been successfully collected). ACR had considerable scatter around a urinary protein loss of 300-1000 mg/day.[235] (Level 1b +)

Sensitivity and specificity of ACR or PCR compared with 24-hour protein loss

To predict a 24-h urine protein >1 g/day (n=1739, the subgroup in whom 24-hour protein had been successfully collected), a PCR threshold of 98 mg/mmol was found to give sensitivity of 0.95 with specificity of 0.83. An ACR threshold of 16.5 mg/mmol was found to give the same 0.95 sensitivity, this time with specificity of 0.7. Similarly, to predict a 24-hour urine protein >450 mg/day, a PCR threshold of 45 mg/mmol had the desired sensitivity of 0.95 and specificity of 0.83, whereas the ACR

threshold of 9.5 mg/mmol achieved the same sensitivity with specificity of 0.77. Confidence intervals are not given for these estimates, and it is not possible to construct them from the details available.[235] (Level 1b +)

Correlation of albumin with total protein

The correlation between albumin and total protein (log-log transformed) was high (r=0.924, p<0.001), indicating good agreement between total protein and albumin. Albumin concentration was <100 mg/l and in most cases it was <20 mg/l in samples that tested negative for protein by salicylsulphonic acid precipitation.[28] (Level II +)

Over the range 0–16,800 mg/l protein, the correlation between albumin loss rate and total protein loss rate was high (r=0.93, n=167). Albumin formed 71% of the total protein. For samples with total protein in the range 0–3000 mg/l (n=116), the correlation between albumin loss rate and total protein loss rate (r=0.68) was lower.[292] (Level: II +)

5.4.6 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng203

5.5 Managing isolated invisible haematuria

5.5.1 Clinical Introduction

The presence of red blood cells in urine is termed haematuria. This may be visible to the naked eye (macroscopic) or invisible (microscopic). When haematuria is visible the urine is coloured pink or red. When the urine appears normal to the naked eye but the presence of red blood cells is detected by either reagent strip testing or microscopy, haematuria is termed invisible. The prevalence of asymptomatic invisible haematuria varies between 0.19 and 21%, depending on age and gender. Screening studies have suggested that the prevalence in the UK adult male population is around 2.5 %, increasing to 22 % in males over the age of 60 years.[49,344] The differential diagnosis of invisible haematuria is wide, and includes urinary tract malignancy, urinary tract stones, urinary tract infection, and glomerulonephritis. Causes can be typically divided into urological and nephrological (Table 18).

Table 18: Common causes of haematuria

Urological (surgical disease in the urinary tract)	Nephrological (medical disease of the kidneys)
Stones in the kidney, ureter or bladder	IgA nephropathy
Urinary tract infections (cystitis, urethritis, prostatitis)	Thin membrane nephropathy
Cancer or the kidney, ureter, bladder or prostate	Alport's syndrome
Benign tumours (eg haemangiomas, angiomyolipomas, bladder papillomas)	Glomerulonephritis (other than IgA nephropathy). Usually combined with proteinuria
Trauma	Inherited cystic diseases of the kidney, e.g. polycystic kidney disease, medullary sponge kidney

In the absence of a urological cause, haematuria can be presumed to be coming from the kidneys, most commonly as a result of one of the nephrological diseases listed above. However a firm diagnosis of most of these conditions (except the cystic diseases which are generally diagnosed radiologically) would require a kidney biopsy. This section is concerned with isolated invisible haematuria. This implies that at presentation there is no associated proteinuria, and that the GFR is

normal (or if impaired there is no retrospective evidence of progressive loss of GFR). The challenge therefore is to decide a) how far to investigate the cause, and b) how people with isolated invisible haematuria should be monitored in the long term.

5.5.2 Methodology

Isolated invisible haematuria is defined as ≥2 erythrocytes per high power field in the urine without any other urine abnormalities (absence of infection or proteinuria). The clinical significance of isolated invisible haematuria was assessed with respect to morbidity and progression of CKD (declining GFR, development of proteinuria, progression to ESRD).

One prospective case series assessed kidney functional decline in Japanese men (n=404) with confirmed isolated invisible haematuria (+1 result on a reagent strip and >5 RBC/hpf by microscopy) identified in a mass population screening between 1983 and 1996 in Hitachi, Japan, for a mean follow-up of 6.35 years.[429]

5.5.3 Health economics methodology

There were no health economics papers found to review.

5.5.4 Evidence statements

Development of proteinuria

In a case series, 9% of men with asymptomatic invisible haematuria developed proteinuria (defined as chronic nephritic syndrome) during follow-up.[429] (Level 3)

Impaired kidney function

0.7% of men with asymptomatic haematuria had a deterioration of kidney function (serum creatinine >2.0 mg/dl) during follow-up. The kidney function deterioration rate for asymptomatic haematuria was 3.0% over 10 years.[429] (Level 3)

5.5.5 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng203

5.6 Combining measures of kidney function and markers of kidney damage

5.6.1 Introduction

The widespread adoption of an internationally agreed definition and classification of CKD [KDOQI 2002] [288] has driven a research agenda aimed at improving understanding of the epidemiology of CKD. A longitudinal study of population cohorts has demonstrated that although the majority of people with even severe CKD do not progress to kidney failure, the presence of CKD still confers an increased risk of adverse outcomes including cardiovascular events, acute kidney injury, progression of CKD and mortality. The definition of CKD critically involves the use of thresholds for diagnosis, a glomerular filtration rate (GFR) of less than 60 ml/min/1.73 m^2 and/or urinary albumin:creatinine ratio (ACR) of greater than 3 mg/mmol. GFR and ACR are both continuous variables and the use of

thresholds for diagnosis has generated much debate and controversy in the literature, particularly with respect to age. The GFR range 45-60 ml/min/1.73 m^2 has generated most controversy, especially in people with urine ACR of less than 3 mg/mmol. Similarly the separation of those with eGFR>60 ml/min/1.73 m^2 into separate 60-89 and ≥90 categories also attracts criticism. We know that the risk of adverse outcomes from CKD, including progression of CKD, is substantially increased below a GFR of 45 ml/min/1.73 m^2 regardless of urine ACR, and this drove the subdivision of the original stage 3 CKD into stage 3a and 3b in the 2008 NICE CKD clinical guideline. We know that urine ACR >30 mg/mmol also confers a substantially increased risk of adverse outcome, regardless of GFR, including progression of CKD, highlighted by the recommendation of the addition of the suffix (p) in the NICE guidance. Since the 2008 guidance was published, additional measures of kidney function and markers of kidney damage have been proposed in the literature which may afford better identification of those at risk of progression of CKD, and so may also facilitate an improved, more clinically relevant CKD classification system.

5.6.2 Review question: What is the best combination of measures of kidney function and markers of kidney damage to identify people with CKD who are at increased risk of progression?

This section was partially updated in 2018. See www.nice.org.uk/guidance/NG203/evidence for the 2018 evidence reviews.

For full details see review protocol in Appendix C.

Table 19: PICO characteristics of measures of kidney function and markers of kidney damage review question

Population	Adults (>18yrs) with CKD
Prognostic factor	eGFRcreatinine (MDRD or CKD-EPI) + eGFRcystatin (CKD-EPI) eGFRcreatinine (MDRD or CKD-EPI) + ACR eGFRcystatin (CKD-EPI) + ACR eGFRcreatinine + eGFRcystatin + ACR
Outcomes	• CKD progression: change in eGFR • CKD progression: occurrence of end stage kidney disease (ESRD or ESKD as reported by the study)AKI • All-cause mortality • Cardiovascular mortality.
Covariates	Age, gender, hypertension and diabetes.
Study design	Prospective cohort.

5.6.3 Clinical evidence

Three large prospective cohort studies were included in the review.[324,325,415] These studies looked at combinations of markers for kidney damage (eGFRcreatinine, eGFRcystatin and ACR) and used Cox proportional hazard models to determine their association with specified outcomes (e.g. mortality). These models were adjusted for potential confounders *a priori*. All estimated GFRs were calculated using CKD-EPI equations. A 'positive' result was determined using current clinical CKD cut-offs i.e. an eGFRcreatinine or eGFRcystatin of less than 60 ml/min/1.73 m^2 or an ACR greater than 30 mg/g (approximately 3 mg/mmol). The reference group varied between:

- no CKD (i.e all three markers negative)
- no CKD by eGFR criteria only, and
- CKD by eGFRcreatinine alone.

ESRD was defined in all studies as either dialysis dependence or kidney transplantation. Several other studies look at single marker multivariate models stratified by eGFR, which were excluded as

detailed in Appendix J.

The quality of studies was assessed and presented in an adapted GRADE profile according to criteria stated in the methodology checklist for prognostic studies in the guidelines manual[285]. Evidence from these are summarised in Table 20 and the clinical GRADE evidence profile (Table 21Table 134). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

Summary of included studies

Table 20: Summary of studies included in the review

Study	Population	Markers	Outcomes	Covariates
Peralta 2011[325]	Reasons for Geographic and Racial Differences in Stroke (REGARDS).	eGFRcreatinine + eGFRcystatin, eGFRcreatinine + ACR, eGFRcystatin + ACR, eGFRcreatinine + eGFRcystatin + ACR.	All-cause mortality and ESRD.	Mortality model: age, race, income, educational attainment, hypertension, diabetes, prevalent cardiovascular disease, smoking status and BMI. ESRD: As above plus waist circumference and log albumin-to-creatinine ratio.
Peralta 2011B[324]	Multi-Ethnic Study of Atherosclerosis (MESA) and the Cardiovascular Health Study (CHS).	eGFRcreatinine + eGFRcystatin, eGFRcreatinine + ACR, eGFRcystatin + ACR, eGFRcreatinine + eGFRcystatin + ACR.	MESA: All-cause mortality and cardiovascular disease. CHS: All-cause mortality, cardiovascular disease, heart failure and ESRD.	Adjusted for age, race, gender, diabetes, hypertension, LDL, HDL, CRP, and prevalent CVD for CHS (persons with baseline CVD were excluded for incident CVD analyses).
Waheed 2012[415]	Atherosclerosis Risk in Communities study (ARIC).	eGFRcreatinine + eGFRcystatin, eGFRcreatinine + ACR, eGFRcystatin + ACR, eGFRcreatinine + eGFRcystatin + ACR.	All-cause mortality, coronary heart disease, heart failure, AKI and ESRD.	Adjusted for age, race, sex, and total cholesterol, history of diabetes, hypertension, smoking, BMI, C-reactive protein and eGFR.

Table 21: Clinical evidence profile: Combinations of markers of kidney damage (multivariate analysis)

Quality assessment							No of patients	Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Event	Relative (95% CI)	Absolute		
All-cause mortality: REGARDS eGFRcystatin +ACR[325], referent no CKD											
1	Prospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	105/415	HR 3 (2.42 - 3.72)	-	HIGH	CRITICAL
All-cause mortality: REGARDS eGFRcreatinine + ACR [325] referent CKD by eGFRcreatinine alone											
1	Prospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	27/148	HR 3.3 (2.0 - 5.6)	-	HIGH	CRITICAL
All-cause mortality: REGARDS eGFRcreatinine + eGFRcystatin[325] referent CKD by eGFRcreatinine alone											
1	Prospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	223/1172	HR 3.2 (2.2 - 4.7)	-	HIGH	CRITICAL
All-cause mortality: REGARDS eGFRcreatinine + eGFRcystatin + ACR (eGFRcreatinine <60ml/min/1.73m^2) [325] referent CKD by eGFRcreatinine alone											
1	Prospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	276/883	HR 5.6 (3.9 - 8.2)	-	HIGH	CRITICAL
All-cause mortality: REGARDS eGFRcreatinine + eGFRcystatin[325] referent no CKD by eGFR											
1	Prospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	799/2055	HR 2.1 (1.87 - 2.36)	-	HIGH	CRITICAL
All-cause mortality: ARIC eGFRcreatinine + eGFRcystatin[415] referent no CKD											
1	Prospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	60 IR 32.7[(b)]	HR 1.86 (1.42 - 2.44)	-	HIGH	CRITICAL
All-cause mortality: CHS eGFRcreatinine + eGFRcystatin[324] referent no CKD by eGFR											
1	Prospective cohort	Serious[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	n = 689[(c)]	HR 1.74 (1.57 - 1.92)	-	MODERATE	CRITICAL
All-cause mortality: MESA eGFRcreatinine + eGFRcystatin[324] referent no CKD by eGFR											
1	Prospective cohort	Serious[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	n = 269[(c)]	HR 1.93 (1.27 - 2.93)	-	MODERATE	CRITICAL
All-cause mortality: ARIC eGFRcreatinine + ACR[415] referent no CKD											

Quality assessment							No of patients	Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Event	Relative (95% CI)	Absolute		
1	Prospective cohort	Serious [d]	No serious inconsistency	No serious indirectness	Very serious imprecision[e]	None	6 IR 23.3[b]	HR 1.26 (0.52 - 3.05)	-	VERY LOW	CRITICAL
All-cause mortality: CHS eGFRcreatinine + eGFRcystatin + ACR[324] referent CKD by eGFRcreatinine alone											
1	Prospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	181/200	HR 3.41 (2.54 - 4.58)	-	HIGH	CRITICAL
All-cause mortality: CHS eGFRcreatinine + ACR[324] referent CKD by eGFRcreatinine alone											
1	Prospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision	None	29/39	HR 1.94 (1.23-3.04)	-	HIGH	CRITICAL
All-cause mortality: CHS eGFRcreatinine + eGFRcystatin[324] referent CKD by eGFRcreatinine alone											
1	Prospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	262/380	HR 1.71 (1.30-2.25)	-	HIGH	CRITICAL
All-cause mortality: ARIC eGFRcystatin + ACR[324] referent no CKD											
1	Prospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	29 IR 50.4[b]	HR 2.47 (1.7 - 3.6)	-	HIGH	CRITICAL
All-cause mortality: ARIC eGFRcreatinine + eGFRcystatin + ACR[415] referent no CKD											
1	Prospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	56 IR 70.5[b]	HR 3.69 (2.79 - 4.88)	-	HIGH	CRITICAL
AKI: ARIC eGFRcreatinine + eGFRcystatin[415] referent no CKD											
1	Prospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	32 IR 18.0[b]	HR 3.9 (2.65 - 5.74)	-	HIGH	CRITICAL
AKI: ARIC eGFRcreatinine + ACR[415] referent no CKD											
1	Prospective cohort	Serious [d]	No serious inconsistency	No serious indirectness	Very serious imprecision[e]	None	3 IR 12.2[b]	HR 2.19 (0.7 - 6.88)	-	VERY LOW	CRITICAL
AKI: ARIC eGFRcystatin + ACR[415] referent no CKD											
1	Prospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	13 IR 23.7[b]	HR 3.96 (2.18 - 7.19)	-	HIGH	CRITICAL
AKI: ARIC eGFRcreatinine + eGFRcystatin + ACR[415] referent no CKD											

Quality assessment							No of patients	Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Event**	**Relative (95% CI)**	**Absolute**		
1	Prospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	31 IR 43.5[(b)]	HR 9.78 (6.63 - 14.43)	-	HIGH	CRITICAL
ESRD: CHS eGFRcreatinine + eGFRcystatin[324]											
1	Prospective cohort	Serious[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	n = 689[(c)]	HR 23.82 (12.68 - 44.75)	-	MODERATE	CRITICAL
ESRD: ARIC eGFRcreatinine + eGFRcystatin[415] referent no CKD											
1	Prospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	10 IR 5.5[(b)]	HR 14.57 (6.75 - 31.45)	-	HIGH	CRITICAL
ESRD: REGARDS eGFRcreatinine+ eGFRcystatin[325] referent no CKD by eGFR											
1	Prospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	144/2055	HR 26.1 (14.9-45.7)	-	HIGH	CRITICAL
ESRD: ARIC eGFRcreatinine + ACR[415] referent no CKD											
1	Prospective cohort	Serious limitations[(d)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	2 IR 8.2[(b)]	HR 8.91 (2.06 - 38.51)	-	MODERATE	CRITICAL
ESRD: ARIC eGFRcystatin + ACR[415] referent no CKD											
1	Prospective cohort	Serious limitations[(d)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	5 IR 9.1[(b)]	HR 14.55 (5.38 - 39.33)	-	MODERATE	CRITICAL
ESRD: ARIC eGFRcreatinine + eGFRcystatin + ACR[415] referent no CKD											
1	Prospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	40 IR 60.9[(b)]	HR 125.98 (73.06 - 217.22)	-	HIGH	CRITICAL
Cardiovascular disease: MESA eGFRcreatinine + eGFRcystatin[324] referent no CKD by eGFR											
1	Prospective cohort	Serious[(a)]	No serious inconsistency	No serious indirectness	Serious imprecision[(e)]	None	n = 269[(c)]	HR 1.67 (1.06 - 2.63)	-	LOW	IMPORTANT

Quality assessment							No of patients	Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Event**	**Relative (95% CI)**	**Absolute**		
Cardiovascular disease: CHS eGFRcreatinine + eGFRcystatin[324] referent no CKD by eGFR											
1	Prospective cohort	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	n = 689[c]	HR 1.46 (1.29 - 1.65)	-	MODERATE	IMPORTANT
Coronary heart disease: ARIC eGFRcreatinine + eGFRcystatin[415] referent no CKD											
1	Prospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	42 IR 25.1[b]	HR 1.85 (1.35 - 2.54)	-	HIGH	IMPORTANT
Coronary heart disease: ARIC eGFRcreatinine + ACR[415] referent no CKD											
1	Prospective cohort	Serious [d]	No serious inconsistency	No serious indirectness	Very serious imprecision[e]	None	5 IR 20.3[b]	HR 1.03 (0.38 - 2.78)	-	VERY LOW	IMPORTANT
Coronary heart disease: ARIC eGFRcystatin + ACR[415] referent no CKD											
1	Prospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	Very serious imprecision[e]	None	10 IR 18.3[b]	HR 0.93 (0.49 - 1.75)	-	LOW	IMPORTANT
Coronary heart disease: ARIC eGFRcreatinine + eGFRcystatin + ACR[415] referent no CKD											
1	Prospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	38 IR 55.5[b]	HR 3.01 (2.15 - 4.21)	-	HIGH	IMPORTANT
Heart failure: CHS eGFRcreatinine + eGFRcystatin[324] referent no CKD by eGFR											
1	Prospective cohort	Serious[a]	No serious inconsistency	No serious indirectness	Serious imprecision[e]	None	n = 689[c]	HR 1.43 (1.22 - 1.67)	-	LOW	IMPORTANT
Heart failure: ARIC eGFRcreatinine + eGFRcystatin[415] referent no CKD											
1	Prospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	39 IR 22.3[b]	HR 2 (1.43 - 2.79)	-	HIGH	IMPORTANT
Heart failure: ARIC eGFRcreatinine + ACR[415] referent no CKD											
1	Prospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	11 IR 49.6[b]	HR 4.31 (2.28 - 8.14)	-	HIGH	IMPORTANT
Heart failure: ARIC eGFRcystatin + ACR[415] referent no CKD											
1	Prospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	23	HR 3.25 (2.1 - 5.03)	-	HIGH	IMPORTANT

Quality assessment							No of patients	Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Event**	**Relative (95% CI)**	**Absolute**		
							IR 46.7[(b)]				
Heart failure: ARIC eGFRcreatinine + eGFRcystatin + ACR[415] referent no CKD											
1	Prospective cohort	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	52 IR 79.1[(b)]	HR 6.92 (5.14 - 9.31)	-	HIGH	IMPORTANT

(a) ACR not considered as a separate marker and also not included as a covariate in the multivariable analysis.
(b) Event and incidence rate (IR) reported only. Incidence rates are per 1000 person-years.
(c) Total n reported only.
(d) Event rate is less than 10, likely to be underpowered and therefore there is a risk of bias.
(e) The confidence interval crosses the minimal important difference making the effect size uncertain.

5.6.4 Economic evidence

Published literature

No economic evidence was found.

5.6.5 Evidence statements

Clinical

Evidence from multivariate analysis of large prospective cohort studies[324,325,415] showed for:

Kidney outcomes

ESRD

Two measures/markers for CKD diagnosis

- Diagnosis of CKD with both eGFRcreatinine and eGFRcystatin together conferred an approximately twenty five times increased risk of ESRD in two studies[324,325]. Waheed et al[415] showed up to a 14.5 times increased risk of ESRD with two measures/markers diagnosing CKD (ACR + eGFRcystatin, ACR + eGFRcreatinine, and eGFRcreatinine + eGFRcystatin).

Three markers

- The presence of all three measures/markers was associated with 126 times increased risk of ESRD.[415]

Acute kidney injury

Two markers

- The presence of two measures/markers conferred a 2-4 times increased risk (ACR +eGFRcystatin, ACR + eGFRcreatinine or eGFRcreatinine + eGFRcystatin).[415]

Three markers

- Where all three measures/markers were present the risk of AKI was almost ten-fold increased.[415]

Mortality

Two markers

- The presence of two measures/markers for diagnosis of CKD was associated with a 2-3 times increased risk of all-cause mortality (ACR + eGFRcystatin, ACR + eGFRcreatinine, or eGFRcreatinine + eGFRcystatin). [324,325,415]

Three markers

- When all three measures/markers were present there was a 3.5- 5 times increased risk compared to people without CKD or eGFRcreatinine <60 in isolation.[324,325,415]

Cardiovascular

Cardiovascular or coronary heart disease (compared to people without CKD)

Two measures/markers for diagnosis of CKD

- No increased risk was shown for ACR + eGFRcystatin or ACR + eGFRcreatinine for coronary heart disease, however the number of people in these categories was very low and the uncertainty of true effect therefore greater for these combinations of markers for this particular outcome.[415]
- Diagnosis of CKD with eGFRcreatinine and eGFRcystatin combined was associated with approximately 1.5 times increased risk of cardiovascular disease or coronary heart disease.[324,415]

Three measures/markers

- The presence of all three measures/markers was associated with 3 times the risk compared to people without CKD.[415]

Heart failure

Two measures/markers

- Diagnosis of CKD by eGFRcreatinine and eGFRcystatin together increased risk by 1.5 times and diagnosis by eGFRcreatinine and ACR increased risk 4 times.[415]

Three measures/markers

- The presence of all three markers was associated with an almost 7 times increased risk.[415]

Economic

- No economic evidence was found.

5.6.6 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng203

5.7 Recommendations and link to evidence

5.7.1 Estimation of GFR

Recommendations	The current recommendations can be found at www.nice.org.uk/guidance/ng203

[h] eGFRcreatinine may be less reliable in certain situations (for example, acute kidney injury, pregnancy, oedematous states, muscle wasting disorders, and in people who are malnourished or have had an amputation) and has not been well validated in certain ethnic groups (for example, in people of Asian family origin).

Relative values of different outcomes	The GDG considered that the critical outcomes for decision making were accuracy (defined as P30 - the percentage of estimated GFR values within 30% of the measured GFR), bias and precision. Sensitivity, specificity and area under the (receiver operating characteristic) curve (AUC) were considered as important outcomes. Net reclassification index (NRI) was also considered an important outcome but no data were available in this review for this outcome.
Trade off between clinical benefits and harms	The GDG considered that negatively biased equations at diagnostic thresholds (i.e. GFR 60 ml/min/1.73m^2) would lead to over diagnosis of CKD where eGFR is the sole criterion for diagnosis, with the potential consequences of unnecessary disease-labelling and possible over investigation. Positively biased equations would lead to under diagnosis and lack of recognition of CKD. In people aged over 70 years there was some evidence that eGFR cystatin C was more accurate than the combined eGFR creatinine-cystatin C equation, but this was only from one study.[366] The GDG considered it was important that people were not treated differently according to their age unless there was good evidence to do so. There were limited data concerning age and ethnicity and no data concerning the impact of ethnicity in those over age 75. However, the evidence does show that the CKD EPI creatinine equation correctly identifies more people with GFR <60 ml/min/1.73 m^2 in people over the age of 75 than MDRD. The implications of this are addressed in the classification and markers of kidney damage sections (chapters 6.1 and 5.6).
Economic considerations	No economic evidence was identified. The GDG felt that an original economic analysis was necessary to assess the different measurements of kidney function for the diagnosis of CKD. The CKD EPI creatinine equation is no more costly than the MDRD creatinine equation to implement – both equations are based on age, sex, ethnicity and serum creatinine level. Since it is less biased and more precise than the MDRD equation, it

	is likely to be more cost-effective.
Quality of evidence	All included evidence was from large, high quality studies using international sandardisation for serum creatinine and cystatin C, and using externally validated equations only. The GDG noted that the Teo et al studies[391,392] are in a predominantly Asian population, where the equations are not well validated, however the results were consistent with most other studies. Comparing creatinine-based estimating equations overall CKD-EPI creatinine performed better than the MDRD equation used in current practice. Evidence showed less bias with the CKD-EPI creatinine equation than the MDRD, especially in the group with GFR <60 ml/min/1.73 m^2. The CKD-EPI creatinine equation was more accurate than the MDRD in people with a GFR >60 ml/min/1.73 m^2. The CKD-EPI creatinine equation has a better precision than the MDRD equation, especially above a GFR of 50-60 ml/min/1.73 m^2. The CKD-EPI cystatin C equation is less biased than the MDRD equation and the CKD-EPI combined equation has a better precision than the MDRD. There was also a trend towards increased accuracy using cystatin C or combined equations. The GDG were aware that the P30 of all equations is less with increasing GFR; the evidence affirmed this as P30 was slightly increased in the subgroup with GFR <60 ml/min/1.73 m^2 compared to a GFR >60 ml/min/1.73 m^2 for all equations. However, only 2 studies looked at P30 with cystatin C or combined equations for GFR subgroups. Four studies considered older people as a subgroup, these showed a trend towards CKD-EPI creatinine, cystatin C or combined equations being more accurate than MDRD in this subgroup however as most studies did not report confidence intervals there remains uncertainty as to the true effect. Net reclassification index (NRI) of any of the new equations against current practice (MDRD) was not reported in any of the included studies, however NRI between MDRD versus CKD-EPI has been reported in large population studies reviewed in the health economic analysis.
Other considerations	The use of assays for both creatinine and cystatin C that are traceable to the international standards is not only good laboratory practice but also allows comparability of GFR estimates between different laboratories. Current laboratory practice is to use the IDMS-related MDRD equation to report GFR from serum creatinine. The GDG noted that a stated limitation of the MDRD is that it results in over diagnosis of CKD. However, CKD-EPI in comparison to MDRD is more accurate, and less biased at GFR>60 ml/min/1.73 m^2. Furthermore CKD-EPI has superior performance in those aged 75 years and over. That the GDG were neither the CKD-EPI nor the MDRD Study equation is optimal for all populations and GFR ranges.[97] However, a general practice and public health perspective favoured the CKD-EPI equation as a better predictor of risk of adverse outcome and there is more to gain in absolute terms if people with CKD are correctly identified.[249] Although implementation of CKD-EPI is likely to lead to increased identification of people with GFR<60 ml/min/1.73 m^2 in the population subgroup aged 75 and over it should be noted that in the population as a whole the identified prevalence of CKD (GFR <60 ml/min/1.73 m^2) with CKD-EPI is less than with MDRD i.e. the overall population burden will go down with a switch from MDRD to CKD-EPI. The GDG considered that overall the introduction of CKD-EPI would be beneficial. The GDG agreed that CKD-EPI is a better prediction equation than MDRD for creatinine-based equations. The GDG were aware that other groups (including the Australasian Creatinine Consensus Working Group and the Kidney Disease Improving Global Outcomes CKD guideline development group) have advocated a switch to CKD-EPI from MDRD and felt it was important to reflect current best practice in this guideline. Implementation of the CKD-EPI equation for reporting creatinine-based GFR would obviously require the same coordinated country-wide approach that accompanied the introduction of national eGFR reporting and involve provision of information to

laboratories, health professionals and the public. The information for the public and for primary care would need to consider the potential impact on people previously either side of the GFR diagnostic threshold from the MDRD equation (GFR ranges 45-59 and 60-75 ml/min/1.73 m^2), some of whom will move to above and some to below the diagnostic threshold following implementation. The GDG were aware that online tools are available to enable conversion between the two equations which may be of assistance in the transition phase.

The GDG noted that an advantage of the CKD EPI cystatin C equation is that correction for ethnicity is not required, although the combined CKD-EPI creatinine and cystatin C equation still involves a small ethnicity correction factor (1.08). A disadvantage of all equations other than MDRD is the increased complexity of the actual equations themselves.

It was noted that no major negative clinical issues have been identified and reported using cystatin C. The test has been used since 1993 and is now internationally validated and all laboratories have the facilities to measure cystatin C if required.

One challenge is that the equations assessed perform slightly differently at different levels of measured GFR but there is a requirement for pragmatism as recommending different equations for different levels of expected GFR is untenable.

The GDG agreed that when reporting eGFR using CKD-EPI or cystatin C-based equations values of 90 ml/min/1.73 m^2 and below should be reported as a whole number.

Participation in a national external quality assessment scheme was specifically mentioned as it is not a legal requirement but is recognised as best practice (recommended by Department of Health) and is very important for minimising variation in serum creatinine measurements between laboratories.

The GDG voted recommendation 2 as a key priority for implementation. They agreed that this recommendation would have a high impact on reducing variation in care and outcomes, include actions that are measurable and lead to more efficient use of NHS resources. They highlighted that this would require a change in practice and there may be some training implications for clinical laboratories. They hoped the recommendation would standardise the approach with other westernised countries and improve accuracy of GFR estimation, possibly reducing erroneous over-diagnosis due to MDRD.

5.7.2 Reducing variability in serum creatinine eGFR measurement (from CG73 - evidence not reviewed)

The current recommendations can be found at www.nice.org.uk/guidance/ng203

5.7.2.1 From evidence to recommendation

The GDG noted that although the biochemical assay for creatinine is precise, a number of factors affect serum creatinine concentrations; particularly the person's state of hydration and whether they had recently eaten meat. Serum creatinine concentrations also show diurnal variation. This means that the eGFR derived using the 4-variable MDRD equations will also be affected by these factors.

When making a diagnosis of CKD, assessing the stage of CKD, or monitoring patients for evidence of declining kidney function, it is important that clinicians are aware of the factors that can influence

creatinine concentrations. It was recommended that whenever possible they take steps to minimise the biases that these factors introduce and that they are aware that changes of less than 5% may simply be due to biological and analytical variability.

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

5.7.3 When to use a cystatin C-based estimate of GFR for diagnosis of CKD

Recommendations	The current recommendations can be found at www.nice.org.uk/guidance/ng203
Relative values of different outcomes	In addition to decline in GFR and/or progression to end stage kidney disease, the relationship between the severity of CKD and other known adverse outcomes (AKI, all-cause mortality and cardiovascular mortality) needs to be considered. The GDG were however aware of differences in reporting of cardiovascular outcomes. In Peralta et al[324] cardiovascular disease was defined as myocardial infarction, cardiac arrest, stroke or cardiovascular death. In Waheed et al[415] coronary heart disease was defined as a hospitalised definite or probable MI, fatal CHD or a coronary revascularization procedure. Both studies reported heart failure as a separate outcome.
Trade-off between clinical benefits and harms	The GDG noted that the international definition of CKD uses thresholds of GFR of less than 60 ml/min/1.73 m^2 and urinary ACR greater than 3 mg/mmol. Whilst this is generally accepted it still generates considerable debate, particularly in those with GFR between 45-59 ml/min/1.73 m^2 and no proteinuria (ACR less than 3 mg/mmol) and especially in older people. The GDG were aware that U.S. data indicate that 3.6 % of the whole population have a GFR of 45-59 ml/min/1.73 m^2 and about 40% of these have no proteinuria. [215] Overall the GDG agreed that the evidence showed that the use of all three markers (eGFRcreatinine, ACR and eGFR cystatin C) provides a better prediction of risk; but that for some outcomes there were very few events leading to some uncertainty. AKI as an outcome was only reported in one study[415] and there were wide confidence intervals due to low patient numbers. The GDG debated the evidence for risk of progression of CKD and agreed that more information regarding subgroups and progression of CKD in subgroups was required. However, for end stage kidney disease (defined as dialysis or transplant) the GDG agreed that the evidence demonstrated that use of all three markers were much more predictive of risk.[415] The use of all three markers was also more predictive of all-cause mortality

[i] Markers of kidney disease include albuminuria (ACR more than 3 mg/mmol), urine sediment abnormalities, electrolyte and other abnormalities caused by tubular disorders, abnormalities detected by histology, structural abnormalities detected by imaging and previous kidney transplantation.

	and hence identified those at particular risk. For cardiovascular complications the GDG noted that Peralta et al.[324] did not provide data for all 3 markers. The GDG also found it difficult to interpret the reported outcomes from the ARIC study[415] for coronary heart disease for the combination of eGFR creatinine + ACR and eGFR cystatin C + ACR. There were low event numbers (n=24 and n=63 respectively) and wide confidence intervals rendering comparison with risks from both the eGFR creatinine + eGFR cystatin C combination and the combination of all 3 markers difficult. In relation to heart failure as an outcome the GDG noted that all three markers gave a hazard ratio of almost 7. The GDG debated the clinical interpretation of the evidence and agreed that the addition of eGFR cystatin C to eGFR creatinine and urinary ACR better identifies those at risk but also particularly identifies those at high risk of adverse outcome. The GDG discussed in whom this additional test of kidney function would be predominately useful in. The GDG concluded that identification of those at increased risk of CKD progression and other adverse outcomes would identify those likely to derive the most benefit from treatment and monitoring and hence focus resources where they might achieve the best return. The data reviewed suggested that in people with no proteinuria confirmation of a creatinine-based estimate of GFR 45-59 ml/min/1.73 m^2 with a cystatin C-based eGFR <60 ml/min/1.73 m^2 identified those at greater risk of adverse outcomes related to CKD diagnosis. Conversely, those not confirmed by a cystatin C-based GFR <60 were at no greater risk than people without CKD. The GDG agreed this was important to note as there is concern that there has been over diagnosis of people with CKD who fall within this group, and therefore confirmation of diagnosis with a cystatin C-based eGFR would help address this over-diagnosis. Having reviewed the evidence, the GDG also debated whether there is a continuous relationship between urinary ACR and risk of adverse outcome - starting from normal levels of albuminuria through to the levels of albuminuria seen in people referred to specialist renal units. The GDG agreed that an ACR threshold of 3 mg/mmol was reflective of the data reported by the three studies reviewed. From this the GDG agreed that people with an ACR of greater than 3 mg/mmol should be considered to be at greater risk of cardiovascular disease, mortality and adverse kidney outcomes, regardless of eGFR. The GDG debated whether there was enough evidence to dictate separate recommendations pertaining to older people, in particular those people over 75 with eGFR creatinine and eGFR cystatin C 45-59 ml/min/1.73 m^2 and no proteinuria. The GDG were aware that the 2008 NICE CKD guideline contained a footer to recommendation 23 (R23) 'in people aged >70 years, an eGFR in the range 45-59 ml/min/1.73 m^2, if stable over time and without any other evidence of kidney damage, is unlikely to be associated with CKD-related complications'. Whist the footnote from the previous guideline specifies '70 years of age' the GDG agreed that age should be reconciled to the age specified in the scope (75 years). The GDG further debated whether this was recommendation would inadvertently lead to age-discrimination and if this would deny older people a confirmatory test and the reassurance that other people derive. This also presupposes that healthcare professionals might want to do more about the findings for someone under the age of 75 years than over. The GDG were aware that there might be less impact in older people but agreed that currently there was insufficient information to stratify by age. The GDG were also aware of data from the CKD consortium suggesting that older people with CKD-EPI creatinine 45-59 ml/min/1.73 m^2 and urinary ACR <3 mg/mmol remained at increased risk.[134]
Economic considerations	The reagent cost of a serum cystatin C test is approximately 10 times that of a creatinine test (£2.50 versus. £0.25). An original economic analysis was conducted to compare the cost implications of serum cystatin C testing. The

	costs of tests, visits and antihypertensives were considered. The analysis found that additional eGFR measurement based on serum cystatin C for people with CKD-EPIcreat 45-59 ml/min/1.73 m^2 and ACR<3mg/mmol is **cost saving** and reduces the number of false positives compared to eGFR measurement with serum creatinine alone for all subgroups investigated (older and younger patients, with and without hypertension). However, additional GFR estimation using CKD-EPIcystatin or CKD-EPIcreat-cys will also increase the number of false negatives identified. In all cohorts, the **CKD-EPIcystatin** equation produced the fewest false positive results, which led to it being the lowest cost strategy - the cost of the test being more than offset by the subsequent reduction in drug and management costs. In the cohort of older patients and the cohort of non-hypertensive patients, the CKD-EPIcreat-cys equation had the most accurate diagnoses since it had fewer false negative results due to its greater sensitivity. When the cost was added of a follow-up test to try and pick up false negatives after a year then the CKD-EPIcys equation was still the least costly strategy (although the cost savings are reduced). The GDG considered **false positives** as the outcome of greatest concern because of the risks of medication and the unnecessary anxiety caused by over-diagnosis, which may have broader impacts on patients including life insurance premiums. The GDG assumed that **false negatives** would not experience significant adverse effects as they would mostly be identified in the future according to other symptoms. However, the analysis was assessed as partially applicable since it did not estimate quality-adjusted life-years. The cost savings attributable to cystatin c testing were **sensitive to some of the assumptions** made. For example the addition of the cost of a re-test after 12 months to pick up patients previously given a false negative result meant that there were no net savings. However, even in this scenario when the conservative time horizon of 1 year was increased to 2 years then savings were apparent again. This means that re-testing at 1 year might be considered the optimal strategy. In the absence of re-testing at 1 year, the use of the CKD-$EPI_{creat-cys}$ equation could be considered a reasonable option being the most accurate test and with much of the cost savings of the CKD-EPI_{cys} equation strategy. The analysis cannot definitively conclude which is more cost-effective CKD-$EPI_{creat-cys}$ or CKD-EPI_{cys} since there is a trade-off between accuracy and cost. The guideline's clinical review did not reveal strong evidence for differences in the relative accuracy of the different equations according to ethnicity or the presence of cardiovascular disease or diabetes or a history of acute kidney injury and therefore the findings of this analysis are likely to apply to all these subgroups. The cost savings we observed are only for people without diabetes. For those with **diabetes**, unless stage of CKD has significantly progressed, CKD management is unlikely to add to their NHS costs, since they will already be having regular contact with primary care and regular testing of kidney function. However, the GDG felt that a separate diagnostic testing strategy for patients with diabetes would be confusing and therefore a single recommendation was made for all the comorbidity subgroups.
Quality of evidence	The GDG noted three large (n= 26,000[325], n= 6749[324] and n= 9489[415]) prospective cohort studies that looked at the three markers of interest; creatinine, cystatin C and ACR. The evidence was all of high quality except where limited by low event rates when the outcomes were downgraded from a quality perspective. In particular the outcomes for eGFR creatinine <60 ml/min/1.73 m^2 and ACR >3 from the ARIC study[415] were affected, these were considered to be of very low quality. The GDG acknowledged that small event rates were likely to be from underpowered studies and therefore there was a risk of bias. When discussing the outcomes the GDG were aware of the

	different reference groups used and discussed any impact this may have on any possible recommendations. The GDG noted that for some outcomes from Peralta 2011B[324] for the CHS and MESA studies ACR or proteinuria was not considered as either a separate marker or as a covariate. These outcomes were therefore all downgraded for risk of bias as they only showed a two marker approach with the effect of proteinuria being unknown. All outcomes for people in whom all three markers were positive were of high quality. In addition, the GDGnoted that the data had been adjusted for 6 confounders and it was particularly important to interpret the results with caution when covariate adjustment had been made and low event numbers were reported. The GDG felt that the health economic analysis was based on sound data and plausible assumptions. However, as It would be difficult to estimate the longer-term cost and health impact of the different strategies, since this would depend on the progression of disease in the CKD negative patients (CKD-EPI$_{creat}$ 45-59 ml/min/1.73 m^2 and CKD-EPI$_{creat\ cvs}$ 60+ and ACR<3 mg/mmol) and how that progression is affected by CKD management, which the GDG considered is not known with any precision. It is acknowledged that this was a limitation of the analysis. However, this was not regarded as a major limitation as most false negatives would be subsequently identified before significant progression especially if there is re-testing of CKD-negative patients after 12 months, as in one of the sensitivity analyses performed.
Other considerations	The GDG noted the potential implications of the use of cystatin C in terms of disease 'labelling', either where 'doubt exists in peoples minds' or 'where you are questioning the disease labelling' and for more practical purposes such as health insurance. The GDG were aware of three papers (people with CKD and i) diabetes; ii) hypertension; and iii) different age groups) published by the Chronic Kidney Disease Prognosis Consortium (CKD-PC) – these papers were not reviewed for this question but had a bearing on the discussion. The GDG were aware that these papers provided information about 'GFR category and albuminuria category' and indicated that markers of kidney damage have a greater bearing than diabetes, hypertension or age in terms of outcome. The GDG debated how a cystatin C test would fit into current clinical practice. Currently, a repeat GFR is taken within 90 days to confirm the original result. It is only after this point that a cystatin C test would be undertaken. The recommendation has been drafted to state that the cystatin C test should be consideredwhen the diagnosis is first made on the basis of eGFRcreatinine, which would be after the repeated test. The GDG noted that recommendations regarding use of tests for markers of kidney damage were interrelated with the evidence for other questions (for example classification of CKD, cause of CKD and also the evidence for the risk of developing and/or progression of CKD after an episode of AKI). The GDG voted to have both these recommendations as key priorites for implementation. Recommendation 15 was chosen as the GDG agreed that it will have a high impact on outcomes that are important to patient and set challenging but achievable expectations of health services. The commented that this was not currently routine practice and may be challenging to implement. They highlighted that the recommendation will require the need for cystatin C assays and cystatin C eGFR into laboratory practice and widespread training will be needed. However, a result of implementation it should enable health care resources to be focussed on most needy. Recommendation 16 was chosen as the GDG agreed as they thought it would have a high impact on outcomes that are important to patient, include actions

	that are measurable and lead to more efficient use of NHS resources. They commented that there may be challenges to implementation as it may be viewed as contentious and is a new way of thinking. However, they felt that it provided an improvement in definition (and hopefully understanding of CKD) and would provide reassurance to 25% of current stage 3 CKD patients.

5.7.4 Detecting proteinuria and haematuria (from CG73 - evidence not reviewed)

Proteinuria

The current recommendations can be found at www.nice.org.uk/guidance/ng203

Haematuria

The current recommendations can be found at www.nice.org.uk/guidance/ng203

5.7.4.1 From evidence to recommendations

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

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

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

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

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

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

When considering the use of reagent strips to identify or quantify proteinuria it was again noted that although 24-hour urine collections for urinary protein estimation have been considered to be the

'gold standard' they are subject to inaccuracies due to incomplete collection of all urine voided or inaccurate timing, and the biochemical methods used to quantify the amount of protein present give different results.

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

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

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

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

It is this guideline's purpose to improve early identification and help prevent progression of CKD. Epidemiological study increasingly underlines the importance of even a low level of proteinuria as a strong predictor of adverse outcome. Reagent strips in current clinical practice predominantly detect albumin, not total protein, but are not reliably quantitative. Studies to inform intervention levels of ACR in non-diabetic CKD are not yet available and it is not possible to derive a simple correction factor that allows the precise conversion of ACR values to PRC. However, ACR has far greater sensitivity than PCR for the detection of low levels of proteinuria and thus lends itself to detection and identification of CKD.

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

The GDG noted that an ACR of ≥30 mg/mmol in association with haematuria or an ACR ≥70 mg/mmol in the absence of haematuria were considered indications for referral to nephrology (see section 7.2.4). It was agreed that the finding of levels of ACR <70 mg/mmol, or PCR < 100mg/mmol should be confirmed using an early morning urine sample.

In the update of this guideline, the GDG reviewed the evidence for classification of CKD, specifically looking at the effect of proteinuria at any given eGFR on adverse outcomes. This evidnce demonstrated that adverse outcomes were worse in people with ACR>3 mg/mmol.

The GDG agreed that this evidence was strong enough to recommend that ACR levels of 3mg/mmol or more should be considered as clinically important proteinuria, rather than the range of 3-30mg/mmol being termed 'microalbuminuria' as was the previous convention. A full discussion of this evidence is given in chapter 6.1. The recommendations relating to this have therefore been updated accordingly.

5.7.5 Use of protein:creatinine ratio and albumin:creatinine ratio (from CG73 - evidence not reviewed)

The current recommendations can be found at **www.nice.org.uk/guidance/ng203**

5.7.5.1 From evidence to recommendations

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

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

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

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

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

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

It is not possible to derive a simple correction factor that allows the conversion of ACR values to PCR or 24-hour urinary protein loss rates because the relative amounts of albumin and other proteins will vary depending on the clinical circumstances; however, the GDG produced a table of approximate equivalents that will allow clinicians unfamiliar with ACR values to see the approximate equivalent PCR and 24-hour urinary protein loss rates (Table 22).

Table 22: Urine protein: ACR, PCR and 24-hour protein loss

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

5.7.6 Managing Isolated Haematuria (from CG73 – evidence not reviewed)

The current recommendations can be found at www.nice.org.uk/guidance/ng203

5.7.6.1 From evidence to recommendations

The GDG agreed that by definition isolated invisible haematuria meant that there was no associated proteinuria, the GFR was either normal or stable if below normal, that the kidney was macroscopically normal and that no urological disease was present. Apart from proteinuria there was no evidence that the people included in the study considered had had these other features excluded.

The GDG noted that when renal biopsies are undertaken in people with isolated invisible haematuria, the commonest abnormality identified is IgA nephropathy and that this condition is known to have the propensity to progress to end stage kidney disease. In view of this they recommended that annual follow up should be undertaken.

The GDG agreed that if isolated invisible haematuria had been present and disappeared there was a low or non-existent risk of developing progressive CKD.

6 Classification of CKD

6.1 The influence of GFR, age, gender, ethnicity and proteinuria on patient outcomes [2014]

6.1.1 Introduction

In 2002 the US National Kidney Foundation Kidney Disease Outcomes Quality Initiative published a classification of chronic kidney disease split into five stages defined by glomerular filtration rate (GFR). Although internationally accepted, a classification of CKD based solely on GFR category has been the subject of debate in the intervening years. In 2008 NICE clinical practice guideline CG73 recommended adjusting this classification to sub-divide stage 3 CKD into 3a (GFR 45-59 ml/min/1.73 m^2) and 3b (GFR 30-44 ml/min/1.73 m^2) on the basis of a clear difference in adverse outcomes associated with the 2 different GFR categories. NICE CG73 also recognised the importance of associated proteinuria, recommending the addition of a suffix p for those with significant proteinuria (defined as urinary albumin:creatinine ratio (ACR) >30 mg/mmol), to delineate people at increased risk of adverse outcome. Recent epidemiological studies have focussed on determining the influence of differing levels of proteinuria on outcomes in all categories of GFR. The purpose of this question was to review these new data to determine whether the definition and classification of chronic kidney disease should be further refined.

6.1.2 Review question: For people with suspected CKD, what is the effect of proteinuria at any given eGFR on adverse outcomes?

For full details see review protocol in Appendix C.

Table 23: PICO characteristics of classification review question

Population	Adults (aged 18 and over) with suspected CKD
Prognostic factor	Proteinuria: • ACR <3 mg/mmol (<30mg/g) • ACR 3-29 mg/mmol (30-299mg/g) • ACR >30 mg/mmol (>300mg/g) (or equivalent PCR and reagent strip result
Outcomes	Critical • CKD progression: change in eGFR • CKD progression: occurrence of end stage kidney disease (ESRD or ESKD as reported by the study)All-cause mortality • Cardiovascular mortality • AKI Important • Cardiovascular events • Hospitalisation
Study design	Prospective cohort studies, meta-analysis (retrospective cohort studies if prospective studies not identified)

6.1.3 Clinical evidence

Six individual patient data (IPD) meta-analyses were included in the review.[21,108,117,134,237,408] Evidence from these are summarised below in Table 25, and a narrative summary of results in the evidence

statements. See also the study selection flow chart in Appendix D, forest plots in Appendix I and study evidence tables in Appendix G.

As these studies are all IPD meta-analysis, quality was assessed per-study using a customised methodology checklist for quality assessment of systematic reviews of prognostic studies adapted from Hayden 2006[138] rather than by using the GRADE profile. The study quality rating is given in the final column of Table 25. A narrative summary of results is provided in place of the GRADE summary of findings table.

The included IPD meta-analyses addressed the review question directly and covered all subgroups in the review protocol, therefore individual cohort studies were excluded from this review (Appendix J).

No evidence was identified reporting hospitalisation or cardiovascular events.

The IPD meta-analyses included study populations of people with CKD,[21] populations at high risk of chronic kidney disease,[117,408] those with and without diabetes[108] and those with and without hypertension[237]. Gansevoort et al.[117] also included data from general population cohorts, but data from high risk cohorts was presented separately in the analysis due to important baseline differences between the groups, and only the high risk data are included in this review. Hallan et al.[134] included general population, high risk and CKD cohorts. Although CKD cohorts were separated for analysis of mortality and ESRD, hazard ratios could not be calculated from the data presented. The overall data has therefore been presented as this also separates by eGFR and ACR categories. Although these three studies included populations that could be considered indirect to the review target population (both included data from general population cohorts as well as high risk and CKD cohorts), they were included as they addressed subgroups of interest and provided data on eGFR and proteinuria levels from which CKD status could be derived.

References to the individual cohorts included in each of the meta-analyses are provided in the evidence tables in Appendix G.

All ACR and PCR data in this review are in mg/g as reported in the papers. The equivalent mg/mmol values are given in Table 24 below. Reagent strip category has also been reported from some studies. It is important to note that the evidence does not differentiate ACR category by sex and thus what was previously termed microalbuminuria is equivalent to an ACR of less than 3mg/mmol in both men and women.

Table 24: Unit conversion for albuminuria and proteinuria

Measure	Units	Normal to mildly increased	Moderately increased	Severely increased
ACR	mg/g	<30	30-300	>300
	mg/mmol	<3	3-30	>30
PCR	mg/g	<150	150-500	>500
	mg/mmol	<15	15-50	>50

Summary of included studies

Table 25: Summary of studies included in the review

Study	Population	Proteinuria measures	Outcomes	Length of follow up (range in years)	Covariates	Study quality
Astor et al. 2011[21]	People with CKD (of diverse clinical diagnoses) n = 21,688	ACR (mg/g) PCR (mg/g) Dipstick category*	End stage kidney disease All-cause mortality	2.3-9.5	Age, sex, race, previous cardiovascular disease, smoking status, diabetes mellitus, systolic blood pressure and serum total cholesterol concentration.	High
Fox et al. 2012[108]	General population cohorts, high risk cardiovascular cohorts and people with CKD Total n = 1,024,977 CKD n = 38,612	ACR (mg/g) PCR (mg/g) Dipstick category*	All-cause mortality Cardiovascular mortality End stage kidney disease	2.3-24.9	Age, sex, race (black vs.non-black), smoking, systolic blood pressure, total cholesterol, body-mass index, history of cardiovascular disease, and albuminuria.	High
Gansevoort et al. 2011[117]	People at high risk for CKD Subgroups: Age (< or > 65 years) n = 173,892	ACR (mg/g) Dipstick category*	Progression of CKD (change in eGFR) End stage kidney disease AKI	2.3-21.6	Age, sex, race and cardiovascular risk factors (including cardiovascular disease history, smoking status, diabetes mellitus, systolic blood pressure and serum total cholesterol).	High
Hallan et al. 2012[134]	General population cohorts, high risk cardiovascular cohorts and cohorts of people with CKD. Subgroups:	ACR (mg/g) PCR (mg/g) Dipstick category*	All-cause mortality. End stage kidney disease.	2.3-24.9	Sex, race (black versus non-black) history of cardiovascular disease history, smoking status, diabetes mellitus, systolic blood pressure, serum total cholesterol, BMI, albuminuria and the randomised intervention (for clinical trials).	High

Study	Population	Proteinuria measures	Outcomes	Length of follow up (range in years)	Covariates	Study quality
	Age 18-54, 55-64, 65-74 and ≥75 years. Total n = 2,051 244 CKD n = 38,612					
Mahmoodi et al.2012[237]	General population cohorts, high risk cardiovascular cohorts and people with CKD Total n = 1,127,656 CKD n = 38,160	ACR (mg/g) PCR (mg/g) Dipstick category*	All-cause mortality Cardiovascular mortality End stage kidney disease	2.3-24.9	Age, sex, race (black vs.non-black), history of cardiovascular disease, diabetes, serum total cholesterol, body mass index, smoking and albuminuria.	High
Van der Velde et al. 2011[408]	People at high risk for CKD Subgroups: Age (< or > 65 years) n = 266,975	ACR (mg/g) Dipstick category*	All-cause mortality Cardiovascular mortality	2.3-13.5	Age, sex, race, cardiovascular disease history, smoking status, diabetes mellitus, systolic blood pressure, and serum total cholesterol. For randomised controlled trials, data were also adjusted for treatment arm.	High

Study	Reference group for analysis	
Astor et al. 2011[21]	eGFR 45-74ml/min/1.73 m^2	
	Pooled ACR	**Stratified by ACR / eGFR**
Fox et al. 2012[108]	ACR<30mg/g	eGFR 45-74 ml/min/1.73 m^2, ACR<10mg/g
Gansevoort et al. 2011[117]	N/A	eGFR 60->105 ml/min/1.73 m^2,

Study	Reference group for analysis	
		ACR <10 & 10-29mg/g
Hallan et al. 2012[134]	N/A	eGFR 80ml/min/1.73 m^2 (50ml/min/1.73 m^2 in CKD cohorts)
		ACR<10mg/g (<20mg/g in CKD cohorts)
Mahmoodi et al.2012[237]	ACR<30mg/g	eGFR 45-74 ml/min/1.73 m^2, ACR<10mg/g
Van der Velde et al. 2011[408]	N/A	eGFR 90-104 ml/min/1.73 m^2, A <10mg/g

6.1.4 Economic evidence

Published literature

No relevant economic evaluations were identified

6.1.5 Evidence statements

Clinical

Progression of CKD

- Evidence from one high quality IPD meta-analysis[117] indicates that there is a trend for worse decline in eGFR with increasing ACR. At eGFR of 15-29ml/min/1.73 m^2, only ACR greater than 10mg/g predicts decline in eGFR, although all categories are predictive for eGFR 30-59ml/min/1.73 m^2. At eGFR greater than 90ml/min/1.73 m^2 there is uncertainty as to whether ACR adds any predictive value.
- Evidence from two high quality IPD meta-analyses[21,117] shows that for all eGFR categories ther a trend for increased occurrence of ESRD with increasing PCR and ACR, however for PCR measures, confidence intervals at each stratification of eGFR overlap. The association is cleare with measures of ACR. When stratified by eGFR, ACR significantly predicts increased risk of ESI for eGFR 15-29, 30-44 and 45-59ml/min/1.73 m^2, but the trend declines at higher eGFRs.
- There is no clear difference between those aged over or under 65 years at any eGFR or ACR, except at eGFR 15-29ml/min/1.73 m^2 where increased ACR may be to be more predictive of ES for people aged under 65, although confidence intervals are very wide.[408] However, another IP meta-analysis demonstrated that the association between reduced eGFR and increased risk of progression was decreased with increasing age (greater than 54 years of age), but this was less evident for ACR.[134]
- There is no consistent difference in risk of progression, and confidence intervals are wide for a effect sizes at varying eGFR category or ACR, in people:
  - with or without diabetes,[108]or
  - with or without hypertension.[237]

All-cause mortality

- Evidence from one high quality IPD meta-analysis[21] does not indicate an association with PCR l and incidence of all-cause mortality. Increasing ACR predicts increased all-cause mortality, but differentiation by ACR category is uncertain due to overlapping confidence intervals. When stratified by eGFR[408], the trend decreases as with increasing eGFR category. However, an ACR greater than 30mg/g significantly predicts increased all-cause mortality at all eGFR categories.

- There is no clear difference in risk of all-cause mortality at any category of eGFR or ACR when stratified by either age (over or under 65 years) or presence of diabetes.[108,408] However, another IPD meta-analysis demonstrated that the association between reduced eGFR and increased mortality risk was decreased with increasing age (greater than 54 years of age), but this was less evident for ACR.
- Stratifying by hypertension showed identical results,[237] except for the ACR category 10-29mg/g which appeared to be more predictive of all-cause mortality for people with hypertension, although confidence intervals are very wide. When stratified by eGFR, this difference between populations is no longer apparent.

Cardiovascular mortality

- Evidence from one high quality IPD meta-analysis[408] shows that ACR levels greater than 300mg/g are more predictive of cardiovascular mortality than ACR 10-29 or 30-299mg/g, but all are significant. When stratified by eGFR the trend is indicated at all eGFR levels, but decreases with increasing eGFR.
- There is no clear difference in risk of cardiovascular mortality at any category of eGFR or ACR when stratified by age (over or under 65 years) or presence of diabetes or hypertension.

AKI

- Evidence from one high quality IPD meta-analysis[117] shows that increasing ACR predicts AKI.

Economic

- No relevant economic evaluations were identified.

6.1.6 Recommendations and link to evidence

Recommendations	The current recommendations can be found at www.nice.org.uk/guidance/ng203
Relative values of different outcomes	The GDG considered that the critical outcomes for decision making were CKD progression (measured by change in eGFR and occurrence of end stage kidney disease), all-cause mortality, cardiovascular mortality and acute kidney injury (AKI). Cardiovascular events and hospitalisation were considered as important outcomes, but no information was available in this review for these outcomes.
Trade off between clinical benefits and harms	The GDG considered that in terms of risk of progression, mortality or risk of developing AKI, there was no difference between CKD stages 1 and 2 in the existing classification system. After careful consideration, it was agreed that in view of the risks of changing this classification system in terms of the confusion it may cause to people that had already been diagnosed, and for clinicians, it would be inappropriate to combine these. However, this is reflected in the classification table demonstating the comparable level of risk by the shading.

Economic considerations	Economic evaluations for the classification of CKD were not applicable given the purely clinical nature of this topic. The GDG considered that an accurate and clear classification of CKD is imperative to facilitate appropriate treatment and management of CKD. The inclusion of risk factors that increase the risk of CKD progression and/or associated adverse outcomes within the classification of CKD does not in itself increase the costs of CKD management for a person. Rather, doing so facilitates more appropriate CKD treatment which can help reduce downstream cost and health consequences. Furthermore, the GDG also considered the negative consequences of stress associated with CKD disease labelling and felt it appropriate to ensure patients with insignificant reduction in kidney function (eGFR >90 ml/min/1.73 m^2) did not experience a reduction in their quality of life from a diagnosis of CKD.
Quality of evidence	The evidence reviewed was from 5 large high quality IPD meta-analyses. However, it was noted that all of the data were estimated GFR rather than measured GFR values. In addition, the GDG acknowledged the difficulties of interpreting the evidence for adverse outcomes in people who were 'hyperfiltering' (see glossary) and the inability to distinguish those with spuriously high GFRs as a consequence of abnormally low serum creatinine levels (for example due to severe malnutrition or loss of muscle) from those who were truly hyperfiltering. The GDG considered that itwas unlikely that people with high GFRs who were truly hyperfiltering were older (and therefore those who would most likely have severe malnutrition or muscle loss), and it was more likely that these were younger people.
Other considerations	There was no evidence that the risk differed in people with hypertension or diabetes, or between males and females, and therefore the GDG agreed that separate recommendations for these populations were not indicated. The GDG were aware that the evidence considered reported ACR as mg/g. When discussing the evidence (in this LETR), for reasons of clarity the GDG refer to the mg/mmol equivalent to conform with UK standard units of measurement for ACR (See Table 24). All outcomes were significantly worse in people with ACR>3 mg/mmol (reported in the evidence as 30 mg/g), this held true for those aged both >65 and <65. Similarly in those with ACR<3 mg/mmol all outcomes were significantly worse for those with eGFR<60 ml/min/1.73 m^2, again this was irrespective of age. However, Hallan et al. reported risk of all-cause mortality and end stage kidney disease according to age subgroup. This evidence demonstrated that the risk at any point in time was lower in people aged over 75 than those aged 55-64.[134] The GDG debated the term 'microalbuminuria' in relation to people with diabetes and agreed it was unhelpful to include this term in any classification. The ACR value should be stated specifically to prevent confusion in terminology of what constitutes 'significant proteinuria' and 'microalbuminuria'. Using ACR >3mg/mmol was considered to be more appropriate. The GDG agreed that the data from the CKD prognosis consortia (see classification evidence review, chapter 6.1) indicated that the risk associated with albuminuria rises with increasing albumin creatinine ratio and is evident at levels of ACR below 3mg/mmol. ACR is an independent risk factor for adverse outcomes in people both with and without diabetes mellitus and hypertension. It was noted that a classification incorporating eGFR and ACR categories is rarely used for prescribing, and in this situation GFR category is preferred. The BNF acknowledges that kidney function in adults is reported on the basis of eGFR derived from prediction equations. In the context of drug nephrotoxicity, creatinine clearance is frequently used as a surrogate for GFR. (See recommendation 16) Classification by eGFR and ACR category is more useful in the clinic and for people diagnosed with CKD. The GDG agreed that it was important that people with CKD were made aware that both the eGFR and ACR levels were important, and that this should be highlighted when the classification was explained. The GDG voted to make recommendation 27 a key priority for implementation as

6.2 Who should be tested for CKD

6.2.1 Clinical Introduction

The early identification and treatment of CKD is essential to decrease the risk of cardiovascular disease, progression to ESRD, and mortality. Identification of high-risk groups can help clinicians monitor kidney function and identify people with CKD at an earlier disease stage. Although general population screening may not be cost-effective, targeted screening directed at subgroups of the population who might derive the most benefit from CKD detection was shown to be an effective strategy.[289] A national programme to identify vulnerability to vascular diseases was announced by the Health Secretary in April 2008, following initial results from modelling work carried out by the Department of Health. This work suggested that a vascular check programme would prevent 4000 people a year from developing diabetes and could also detect at least 25,000 cases of diabetes or kidney disease earlier. In those conditions where the prevalence of CKD is high and the risks of preventable complications are increased, testing for CKD is clearly warranted. The KEEP programme identified people with diabetes and hypertension, or people with a first-line relative (parent, grandparent, brother or sister) with diabetes, high blood pressure or kidney disease as being at high risk of CKD. Are there additional high-risk people who should be tested for CKD? The UK CKD guidelines also included those with a high risk of obstructive uropathy, all forms of CVD, multisystem diseases with the potential to involve the kidney such as SLE, and conditions requiring long-term treatment with potentially nephrotoxic drugs.[390] In addressing this question all of these factors were considered, together with other lifestyle factors such as smoking, obesity and alcohol intake.

In adults, who should be tested for CKD?

This section was partially updated in 2018. See www.nice.org.uk/guidance/NG203/evidence for the 2018 evidence reviews.

6.2.2 Methodology

Three cohort and sixteen observational or cross-sectional studies examined several risk factors for developing CKD. Table 28 summarises the risk factors associated with development of CKD.

Age

The association between developing CKD and age was examined in cross-sectional studies conducted in the UK,[93] Norway,[132,133] USA[70,71] and Australia.[56]

Gender

The association between developing CKD and gender was examined in cross-sectional studies conducted in the UK,[93] Norway,[132] USA[70] and Australia.[56] A longitudinal study examined the association between age and death due to CKD or need for dialysis in an American cohort (n=23,534, 20-year follow-up).[136] This study, while large, was limited by no assessment of kidney disease at baseline, and poor identification of diabetes (assessed by medication use in medical records).

Hypertension

The association between hypertension and risk of developing CKD was examined in one longitudinal study[136] and cross-sectional studies conducted in Norway,[132] USA,[70] and Australia.[56]

Diabetes

The association between diabetes and risk of developing CKD was examined in one longitudinal

study[136] and cross-sectional studies conducted in the UK,[291] Norway,[132] USA[70] and Australia.[56]

Body mass index (BMI) and metabolic syndrome

A cohort study, the Physician's Health Study, followed 11,104 male doctors for 14 years and examined the association of high baseline BMI with developing CKD.[121] A longitudinal study followed 9082 Americans for 13 years and analysed the effect of BMI on the risk of death due to CKD or ESRD.[384]

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

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

A cohort study evaluated the risk of developing CKD in people with metabolic syndrome compared to those without metabolic syndrome (n=10,096, follow-up 9 years, Atherosclerosis Risk in Communities (ARIC) study cohort).[205]

Cardiovascular disease and atherosclerotic risk factors

In a case series study, the development of kidney disease in people with cardiovascular disease (n=1787, mean age 60 years) was compared with people without cardiovascular disease (n=12,039, mean age 57 years, 9.3 years follow-up).[100]

In the ARIC study, n=12,728, 3-year follow-up, USA), the effect of cardiovascular disease risk markers (total cholesterol, high-density lipoprotein (HDL)-2 and HDL-3 cholesterol, LDL cholesterol, apolipoprotein A-1, apolipoprotein-B, Lp(a), triglycerides) on the risk of rising serum creatinine or a ≥25% reduction in estimated creatinine clearance was examined.[265]

Heredity

The prevalence of nephropathy or ESRD in diabetic siblings of people with diabetic nephropathy was compared with diabetic siblings of people without diabetic nephropathy.[44,369]

The incidence of a family history of ESRD among 28,111 ESRD patients initiating renal replacement therapy during 1994,[112] or during 1995 and 2003[381] was examined. A family history of ESRD was considered present if an incident ESRD patient reported having either a first-degree (parent, child, sibling) or second-degree (grandparent, aunt, uncle, grandchild, or half-sibling) relative with ESRD.

Ethnicity

The incidence of microalbuminuria was compared between European, South Asian, and African-Caribbean people (n=2965) in the UK. This cohort study was excluded as 27% of the cohort did not have albumin loss rate measurements and there were significant differences between those whose data were included and those whose data were not. The study mainly assessed the relationship between microalbuminuria and coronary heart disease, rather than ethnicity and the development of CKD.[396]

One case series study (UK Prospective Diabetes Study (UKPDS) 74)[340] investigated the associations of ethnicity with the development of microalbuminuria, macroalbuminuria, and CrCl ≤60 ml/min/1.73 m^2 in adults with newly diagnosed type 2 diabetes (n=5032, 15 years median follow-up). This study should be interpreted with caution as the multivariate analysis was restricted to n=2167, a loss of half of the study participants.

In the NHANES III study, prevalence of severe or moderate CKD was compared between non-Hispanic black people (n=4163) and non-Hispanic white people (n=6635).[70]

Smoking

One case series study (UKPDS 74)[340] investigated the associations of smoking with the development of microalbuminuria or CrCl ≤60 ml/min/1.73 m^2 in adults with newly diagnosed type 2 diabetes (n=5032, 15 years median follow-up). Two US longitudinal studies examined the association between smoking and death due to CKD or development of ESRD.[136,384]

Alcohol consumption

A longitudinal study followed 9082 Americans for 13 years and analysed the effect of alcohol consumption on the risk of death due to CKD or ESRD.[384]

Physical inactivity

A longitudinal study followed 9082 Americans for 13 years and analysed the effect of physical inactivity on the risk of death due to CKD or ESRD.[384]

Socioeconomic deprivation

The association between developing CKD and socioeconomic deprivation (measured with a Townsend score) was examined in a UK cross-sectional study.[93]

6.2.3 Health economics methodology

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

The first study was a simulation study in a Canadian setting.[193] It compared screening for microalbuminuria with screening for hypertension and macroproteinuria in patients with insulin-dependent diabetes.

The second study[45] evaluated annual screening of the US population aged 50–75 from a societal perspective using a Markov model.

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

Since none of these studies were from an NHS perspective, we made our own decision analysis to evaluate the cost-effectiveness of different case-finding strategies (see Appendix Q.3).

6.2.4 Evidence statements

Age as a risk factor for developing CKD

Four cross-sectional studies showed that older people (over 65 years of age) had a greater risk of an eGFR <60 ml/min/1.73 m^2 than younger people.[56,70,93,132] Analysis of a Norwegian cross-sectional study showed that screening people with diabetes or hypertension or people over 55 years of age identified 93% of cases with stage 3-5 CKD (number needed to screen (NNS) 8.7, 95% CI 8.5–9.0).[133] (Level 3)

Gender as a risk factor for developing CKD

There was NS difference between men and women for prevalence of CKD.[70] (Level 3)

Two studies showed that women had a lower risk of CKD than men.[93,136] (Level 3)

However, an Australian study (AusDiab) and a Norwegian study (HUNT II) showed that women had a higher risk of CKD than men.[56,132] (Level 3)

Hypertension as a risk factor for developing CKD

Four studies showed that people with hypertension had a significantly higher risk of developing CKD than normotensive people.[56,70,132,136] (Level 3)

Diabetes as a risk factor for developing CKD

An Australian cross-sectional study showed that people with diabetes had NS risk of kidney impairment compared with people without diabetes.[56] (Level 3)

By contrast, NHANES III,[70] HUNT II,[132] a UK cross-sectional study[291] and a longitudinal study[136] all showed that diabetes was associated with a significantly increased risk for CKD. (Level 3)

In the paper by New et al, only 33% of people with diabetes with moderate CKD had serum creatinine values >120 µmol/l (upper limit of normal), indicating that measuring serum creatinine level alone failed to identify stage 3 CKD. Also, 63% of people with diabetes and eGFR <60 ml/min/1.73 m^2 had normoalbuminuria, indicating that microalbuminuria testing was insensitive and used alone was not sufficient for screening for CKD.[291] (Level 3)

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

The risk of developing CKD (GFR <60 ml/min/1.73 m^2) increased with increasing BMI (p=0.007). Compared to men who remained within 5% of their baseline BMI (n=5670), men who had a >10% increase in BMI (n=1669) had a significantly increased risk of CKD (OR 1.24, 95% CI 1.03–1.50).[121] (Level 2+)

By contrast, the NHANES II follow-up study showed NS risk for a CKD-related death or ESRD at any level of BMI.[384] (Level 3)

Metabolic syndrome was significantly associated with an increased risk of developing CKD. As the number of traits increased, there was a significant stepwise increase in risk of developing CKD. Those with 5 criteria had an OR of 2.45 (95% CI 1.32–4.54) for developing CKD compared to those with none.[205] (Level 2+)

Cardiovascular disease and atherosclerotic risk factors associated with CKD

People with baseline CVD (n=1787) had a significantly increased risk of either a rise in serum creatinine of ≥0.4 mg/dl or a eGFR decrease of ≥15 ml/min/1.73 m^2 compared with people without baseline CVD (n=12,039).[100] (Level 3)

High triglycerides were associated with a significantly increased risk of a rise in creatinine ≥0.4 mg/dl from baseline. High HDL or HDL-2 cholesterol levels were associated with a significantly decreased risk of a rise in creatinine ≥0.4 mg/dl.[265] (Level 3)

Heredity as a risk factor for developing CKD

Diabetic siblings of people with diabetic nephropathy had a significantly increased risk of incipient or overt nephropathy compared to diabetic siblings of people without nephropathy (OR 4.9, 95% CI 1.3–

19.1).[44] Seaquist et al. reported a higher prevalence of nephropathy in the siblings of diabetics with nephropathy compared with siblings without nephropathy (83% versus 17%, p<0.001). ESRD was higher in the siblings of diabetics with nephropathy (41%) compared to siblings of diabetics without nephropathy (0%).[369] (Level 3)

In two case series, a family history of ESRD was reported by 20% of people with incident ESRD.[112,381] Factors independently associated with a family history of ESRD were race, hypertension, diabetes, glomerulonephritis, BMI, and smoking. Overweight people with ESRD (n=6584, BMI 25.0–29.9 kg/m^2) had a 17% greater odds of reporting a family of ESRD compared with normal weight people with ESRD (n=9037, BMI 18.5–24.9 kg/m^2, adjusted OR 1.17, 95% CI 1.08–1.26, p <0.001). Obese people with ESRD (n=3624, BMI 30–34.9 kg/m^2) had a 25% greater odds of reporting a family of ESRD compared with normal weight people with ESRD (n=9037, BMI 18.5–24.9 kg/m^2) (adjusted OR 1.25, 95% CI 1.14–1.37, p <0.001). Black people with ESRD (n=13,645) were significantly more likely to report a family history of ESRD than white people with ESRD (n=10,127) (adjusted OR 2.38, 95% CI 2.21–2.55, p <0.001). People with ESRD and a history of hypertension (n=19,987) were significantly more likely to report a family history of ESRD than people with ESRD and no history of hypertension (n=3835) (adjusted OR 1.12, 95% CI 1.02–1.23, p <0.001).[381] (Level 3)

Ethnicity as a risk factor for developing CKD

In the NHANES III study, non-Hispanic black people (n=4163) were significantly less likely to have moderate CKD compared to non-Hispanic white people (n=6635). There was NS difference in prevalence of severe CKD in non-Hispanic black or white people.[70] (Level 3)

In multivariate analysis of adults with newly diagnosed type 2 diabetes (n=2167) in the UKPDS, African-Caribbeans had NS risk of developing microalbuminuria, macroalbuminuria or CrCl ≤60 ml/min/1.73 m^2 compared with Caucasians. Indian Asians had a significantly increased risk of developing microalbuminuria, macroalbuminuria or a creatinine clearance ≤60 ml/min/1.73 m^2 compared with Caucasians.[340] (Level 3)

Smoking as a risk factor for developing CKD

Three studies showed that smokers had a significantly higher risk for CKD than non-smokers.[136,340,384] (Level 3)

Alcohol consumption as a risk factor for developing CKD

Alcohol consumption was NS associated with a risk of ESRD or a CKD-related death.[384] (Level 3)

Physical Inactivity as a risk factor for developing CKD

People with low physical activity had a significantly higher risk of ESRD or a CKD-related death than people who had high physical activity. People with moderate physical activity have NS risk of CKD compared to people who had high physical activity (adjusted RR 1.2, 95% CI 0.7 to 2.0).[384] (Level 3)

Socioeconomic deprivation as a risk factor for developing CKD

People who were least deprived (Townsend score =1) had a significantly lower risk of CKD compared to the overall population, whereas people who were most deprived (Townsend score =5) had a significantly higher risk of CKD compared to the overall population.[93] (Level 3)

Table 28: Risk factors for developing CKD

Reference	Population	n	Definition of CKD	Risk factor for developing CKD
[205]	ARIC cohort,	10 096	eGFR < 60	**Metabolic syndrome**: elevated triglycerides

Reference	Population	n	Definition of CKD	Risk factor for developing CKD
	USA		ml/min/1.73 m^2	OR 1.34 (1.12-1.59); abdominal obesity 1.18 (1.00-1.40); low LDL 1.27 (1.08-1.49); hypertension 1.99 (1.69-2.35); impaired fasting glucose 1.11 (0.87-1.40)
[265]	ARIC cohort, USA	12 728	Rise in serum creatinine of ≥ 0.4 mg/dl ≥ 25% reduction in estimated creatinine clearance (Cockroft-Gault)	**Atherosclerotic risk markers**: comparison is lowest quartile Highest quartile of triglycerides (> 156 mg/dl) RR 1.65 (1.1 to 2.5), p=0.01 Highest quartile of HDL cholesterol (> 64 mg/dl) RR 0.47 (0.3 to 0.8), p<0.02 Highest quartile of HDL-2 cholesterol (> 20 mg/dl) RR 0.57 (0.4 to 0.9, p<0.02) The RR of a rise in creatinine ≥ 0.4 mg/dl from baseline was NS for Lp (a), HDL-3 cholesterol, and apolipoprotein A. For each three-fold higher triglycerides, the RR of developing a ≥ 25% reduction in estimated creatinine clearance was 1.51 (95% CI 1.2 to 2.0), p=0.003
[100]	ARIC + CHS, USA	13826	Rise in serum creatinine of ≥ 0.4 mg/dl	**Cardiovascular disease**: comparison is people without baseline CVD (n=12039) People with baseline CVD (n=1787) had a significantly increased risk of developing CKD (adjusted OR 1.75, 95% CI 1.32 to 2.32, p<0.001).
			GFR decrease of ≥ 15 ml/min/1.73 m^2	**Cardiovascular disease**: comparison is people without baseline CVD (n=12039) People with baseline CVD had an increased risk of developing CKD (adjusted OR 1.54, 95% CI 1.26 to 1.89, p<0.001).
[121]	Physician's Health Study cohort, USA	11104	GFR < 60 ml/min/1.73 m^2	**Body mass index**: compared to BMI < 22.7 kg/m^2 BMI > 26.6 kg/m^2 (n=2220) OR 1.26 (1.03 to 1.54) BMI 25.1-26.6 kg/m^2 (n=2250) OR 1.32 (1.09 to 1.61) NS risk when BMI 22.7-25.0.
[384]	Follow-up of NHANES II, USA	9082	CKD-related death or ESRD	**Body mass index**: comparison is normal BMI (18.5-24 kg/m^2) NS risk when BMI < 18.5 kg/m^2, 25-29 kg/m^2, 30-34 kg/m^2 or > 35 kg/m^2). **Physical inactivity**: comparison is high physical activity Low physical activity RR 2.2 (1.2 to 4.1). Moderate physical activity: NS risk.

Reference	Population	n	Definition of CKD	Risk factor for developing CKD
[93]	Cross-sectional Southampton and South-west Hampshire, UK	404541	Serum creatinine value > 1.7 mg/dl or >150 µmol/l persisting for six months or more	**Smoking**: compared to non-smokers Smokers (> 20 cigarettes/day) RR 2.6 (1.4 to 4.7). Smokers (1-20 cigarettes/day) have NS risk Former smokers have NS risk. **Alcohol consumption**: compared to non-drinkers NS risk for daily drinkers or weekly drinkers or people who seldom drank. The incidence of CKD was 1701 pmp, 95% CI 1613 to 1793 pmp). For people < 80 years old, the incidence was 1071 pmp (95% CI 1001 to 1147). **Age**: The incidence of CKD increased with increasing age. 74% of CKD cases were identified in people ≥ 70 years old. **Gender**: The male:female rate ratio was 1.6 (95% CI 1.4 to 1.8). The preponderance of men with CKD was significant in all ages > 40 years of age. **Socioeconomic deprivation**: compared with overall population Least deprived directly standardised rate ratio 0.80 (95% CI 0.69 to 0.93) Most deprived directly standardised rate ratio 1.17, 95% CI 1.02 to 1.33).
[291]	Cross-sectional; Surrey, Kent, greater Manchester area, UK	162113	GFR < 60 ml/min/1.73 m^2	The prevalence of diabetes was 3.1% (5072/162,113). **Diabetes**: 31.3% of people with diabetes had stage 3-5 CKD (GFR < 60 ml/min/1.73 m^2) compared to 6.9% of people without diabetes (p<0.001). The higher prevalence of diabetes-associated CKD was seen at all stages of CKD.
[56]	Cross-sectional, Australia	11247	GFR < 60 ml/min/1.73 m^2	The prevalence of stage 1 CKD in Australia was 0.9%, stage 2 was 2.0%, stage 3 was 10.9%, stage 4 was 0.3%, stage 5 was 0.003%. **Age**: compared with people < 65 People ≥ 65 years OR 101.5 (61.4-162.9, p<0.001). **Gender**: females OR 1.3 (1.0-1.7), p=0.012. **Diabetes**: compared to people without diabetes

Reference	Population	n	Definition of CKD	Risk factor for developing CKD
				People with diabetes had NS risk: OR 0.9 (0.7-1.1, p=0.308). **Hypertension**: compared to normotensive people People with hypertension: OR 1.4 (1.2-1.6, p<0.001).
[70]	Cross-sectional NHANES III, USA	15600	GFR 60-89 ml/min/1.73 m^2 Moderate CKD (GFR 30-59 ml/min/1.73 m^2) Severe CKD (GFR 15-29 ml/min/1.73 m^2)	The prevalence of stage 1 CKD in the USA was 3.3%, stage 2 was 3.0%, stage 3 was 4.3%, stage 4 was 0.2%, stage 5 was 0.2%. The overall prevalence of CKD in USA was 11%. **Age**: 48% of people > 70 years of age (n=2965) had mild CKD (GFR 60-89 ml/min/1.73 m^2) and 25% had moderate to severe CKD (GFR < 60 ml/min/1.73 m^2). **Gender**: NS difference in prevalence between males and females. **Hypertension**: 17.5% of hypertensive people taking antihypertensive agents (n=2553) and 7.9% of hypertensive people not taking medication (2340) had moderate CKD (GFR 30-59 ml/min/1.73 m^2) compared to 1.5% of non-hypertensive people (n=10,707). **Diabetes**: 40% of people with diabetes had mild CKD (GFR 60-89 ml/min/1.73 m^2) whereas 31% of people without diabetes had mild CKD (GFR 60-89 ml/min/1.73 m^2). 14% of people with diabetes had moderate CKD (GFR 30-59 ml/min/1.73 m^2) whereas 3.7% of people without diabetes had moderate CKD (GFR 30-59 ml/min/1.73 m^2). **Ethnicity**: compared to non-Hispanic white people Non-Hispanic black people (n=4163) were significantly less likely to have moderate CKD (GFR 30-59 ml/min/1.73 m^2) adjusted OR 0.56 (0.44 to 0.71). There was NS difference in prevalence of severe CKD (GFR 15-29 ml/min/1.73 m^2) in non-Hispanic black or white people (adjusted OR 1.10, 95% CI 0.51 to 2.37).
[132]	Cross-sectional, Norway HUNT II	65181	GFR < 60 ml/min/1.73 m^2	The prevalence of GFR 60-89 ml/min/1.73 m^2 was 38.6%. The prevalence of moderate CKD (GFR 30-59 ml/min/1.73 m^2) was 4.5% and severe CKD (GFR 15-29 ml/min/1.73

Reference	Population	n	Definition of CKD	Risk factor for developing CKD
				m^2) was 0.2%. **Age**: The prevalence of GFR < 60 ml/min/1.73 m^2 was 50-100 times greater in people > 70 years old compared to people 20-39 years old. **Gender**: Women age-adjusted OR 1.5 (1.4-1.6). **Hypertension**: compared with normotensives Hypertension age-adjusted OR 1.5 (1.3-1.6). **Diabetes**: compared with people with no diabetes Diabetes age-adjusted OR 1.5 (1.3-1.7).
[136]	Case series, CLUE study	23 534	Need for dialysis or death certificate notification of kidney disease.	**Gender**: compared to men Women: adjusted HR 0.6 (95% CI 0.4 to 0.8). **Hypertension**: compared with SBP < 120 mm Hg or DBP < 80 mm Hg Stage 2 hypertension (160-179 mmHg systolic or 100-109 mmHg diastolic) (adjusted HR 5.7, 95% CI 1.7-18.9) Stage 3 or 4 hypertension (≥ 180 mmHg systolic or ≥ 110 mmHg diastolic) (adjusted HR 8.8, 95% CI 2.6-30.3). **Diabetes**: compared with no diabetes (identified by medication use) Diabetes: adjusted HR 7.5 (95% CI 4.8-11.7). **Smoking**: compared with non current smokers Current smokers: adjusted HR 2.6 (95% CI 1.8 to 3.7).
[340]	Case series, type 2 diabetics, UKPDS	2167	Development of microalbuminuria (UAC 50-299 mg/l)	**Ethnicity**: compared with Caucasians African Caribbeans: NS (HR 1.21, 95% CI 0.89-1.65, p=0.22) Indian Asians: HR 2.02 (95% CI 1.59-2.60), p<0.0001. **Smoking**: compared with non-smokers Smokers: HR 1.20 (95% CI 1.01-1.42), p=0.036.
			Development of macroalbuminuria (UAC ≥ 300 mg/l)	**Ethnicity**: compared with Caucasians African Caribbeans: NS (HR 1.05, 95% CI 0.59-1.86, p=0.87) Indian Asians: HR 2.07 (95% CI 1.36-3.15, p=0.00066).

Reference	Population	n	Definition of CKD	Risk factor for developing CKD
			CrCl ≤ 60 ml/min/1.73 m^2	**Ethnicity**: compared with Caucasians African Caribbeans: NS (HR 1.26 (95% CI 0.91-1.76, p=0.17) Indian Asians: HR 1.93 (95% CI 1.38-2.72), p=0.00015. **Smoking**: compared with non-smokers Smokers: HR 1.25 (95% CI 1.03-1.52), p=0.022.

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

6.2.5 Health economics evidence statements

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

The first published study[193] found that screening for microalbuminuria cost an extra Can$27,000 (£14,000) per QALY gained compared with screening for hypertension and macroproteinuria in patients with insulin-dependent diabetes. However, they found the model to be highly uncertain and said that further evidence is required.

The second published study[45] found that for people with neither hypertension nor diabetes, the incremental cost-effectiveness ratio (ICER)for screening at age 50 versus no screening was unfavourable at $283,000 (£189,000) per QALY gained; screening at age 60 was more favourable at $53,372 (£34,000) per QALY gained. For people with hypertension the ICER was highly favourable at $18,621 (£12,000) per QALY gained. The authors concluded that early detection of urine protein to slow progression of CKD is not cost-effective unless selectively directed toward high-risk groups (older people and people with hypertension) or conducted at an infrequent interval of 10 years.

The third study[157] found that screening (50–69 years) for proteinuria cost Aus$3577 (£1600) per QALY gained.

Original modelling: non-diabetic hypertensive

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

Original modelling: non-diabetic, non-hypertensive

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

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

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

- Effectiveness of high-dose ACE inhibitor. Reduction in all-cause mortality is not proven (except for diabetic population).

- The model assumes that without these case-finding tests patients will not be picked up until they require RRT. If in reality patients are picked up sooner, then the benefits of case-finding are reduced.
- Compliance with medication might be less than observed in trials and hence the effectiveness of screening might be less.
- Most hypertensive patients are already on low dose ACE inhibitor. The difference in effects between high and low dose ACE inhibitor is not clear but the effectiveness of screening might be over-estimated for such patients.
- In the base case analysis, ACR is assumed to be 100% sensitive and 100% specific. Even in the sensitivity analysis, the model doesn't measure the health impact or long-term costs of false positives.

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

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

Comparisons between the guideline model and the published studies

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

Two previous studies have evaluated the cost-effectiveness of CKD testing in the general population. The first (US) study[45] found that, similar to our model, testing for proteinuria in non-diabetic non-hypertensive people was not cost-effective around the ages 50–60 but did become cost-effective at older ages.

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

- We have modelled a period of ESRD where patients do not receive RRT. This may not be incorporated in to the other models. Therefore they may have estimated higher cost savings.
- CVD costs savings may have been modelled more explicitly in the published models.
- The prevalence of proteinuria might be different to the figures used.
- The other models may be attributing the same clinical effect to patients with GFR above 60 ml/min/1.73 m^2 as they do with patients with GFR below 60 ml/min/1.73 m^2. In our model, we do not include long-term costs or health gain for patients with proteinuria but GFR >60 ml/min/1.73 m^2.

6.2.6 From evidence to recommendations

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

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

The evidence principally assessed demographic and behavioural risk factors for CKD but in addition it was recognised that diabetes and cardiovascular disease, particularly ischaemic heart disease, chronic heart failure, peripheral vascular disease and cerebrovascular disease are all risk factors for

CKD. The GDG noted that the increased prevalence of CKD seen in the NHANES studies (1988–1994 compared with 1999–2004) was associated with an increased prevalence of diagnosed diabetes and hypertension.

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

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

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

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

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

The 2014 GDG voted that recommendation 31 shoud be a key priority for implementation as the recommendation was likely to have a high impact on outcomes that are important to patients and include actions that are measurable. They felt that this recommendation could be a key target for primary care and could be collected within CKD National Audit.

6.2.7 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng203

6.3 Acute kidney injury, diabetes, glomerular disease and hypertension as risk factors for CKD

6.3.1 Introduction

The 2 major causes of CKD are diabetes and hypertension and the prevalence of CKD in the population rises with age. In many people with CKD the cause is uncertain and both diabetes and/or hypertension may co-exist with CKD together with the primary cause. There is a complex relationship between hypertension and kidney disease, hypertension may develop as a complication of CKD accelerate progression. In UK renal registry data[123] diabetes remains the biggest documented cause of end stage kidney failure (Table 29).

Table 29: Primary renal diagnosis by UK country in the 2012 incident renal replacement therapy cohort

Country	Uncertain aetiology	Diabetes	Glomerulo-nephritis	Hyper-tension	Other	Polycystic kidney disease	Pyelo-nephritis	Renal vascular disease
England	15.7	25.3	13.7	7.9	18.1	6.7	6.7	5.9
N Ireland	16.0	22.7	13.3	9.4	17.1	4.4	11.1	6.1

Scotland	15.2	28.5	16.4	4.2	15.4	7.5	6.7	6.0
Wales	18.7	27.3	14.8	4.5	15.3	6.1	3.9	9.5
UK	15.9	25.6	14.0	7.4	17.7	6.7	6.6	6.1

Source/Note: Modified from NHS renal registry: From Gilga J, Raoa A, Fogarty D. UK Renal Registry 16th Annual Report: Chapter 1 UK Renal Replacement Therapy Incidence in 2012: National and Centre-specific Analyses. Available from: http://www.renalreg.com/Reports/2013.html

Other causes of CKD in addition to diabetes and hypertension include glomerulonephritis; inherited diseases, such as polycystic kidney disease; congenital malformations of the urinary tract; systemic disease affecting the body's immune system such as SLE and systemic vasculitis; urinary tract obstruction; repeated upper urinary tract infection; and kidney damage from certain nephrotoxic drugs such as lithium and cyclosporine.

The classification of CKD proposed by the Kidney Disease Outcome Quality Initiative (KDOQI) in 2002 was modified in NICE Clinical Guideline 73 to reflect the improved understanding of CKD gained through epidemiological research. The modifications included splitting stage 3 CKD into 3a (45-59 ml/min/1.73 m^2) and 3b (30-44 ml/min/1.73 m^2) and recognising the importance of proteinuria at all categories of CKD by the addition of the suffix p in people with urine albumin to creatinine ratios of greater than 30 mg/mmol. Most recently the Kidney Disease Improving Global Outcomes guideline recommended classifying CKD by cause, GFR category and albuminuria category (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group).[194] Data from a succession of meta-analyses have highlighted that the risks of adverse outcomes associated with CKD at all categories of GFR are influenced by albuminuria category, and vice versa.[21,64,117] Adverse outcomes associated with CKD include increased cardiovascular events leading to increased morbidity and mortality, acute kidney injury (AKI), infection, cognitive impairment, impaired physical function and progression of kidney disease.[222] The risk for any adverse outcome increases with lower GFR and is increased by co-existent proteinuria. Not all people with CKD progress and there is still controversy surrounding 'over

diagnosis' of some populations with CKD, particularly people with an isolated finding of a GFR between 45-59 ml/min/1.73 m^2 and with urine albumin creatinine ratio (ACR)<3 mg/mmol.

Specialist centres usually categorise newly presenting CKD by kidney function (GFR), proteinuria (urine ACR) and by cause. Despite this we still have large knowledge gaps to fill; we do not fully understand how some people come to have CKD, why some people with stable low levels of GFR do not progress despite their low level of GFR and what the precise role of episodes of AKI is in the development and progression of CKD. The purpose of these related questions was to examine whether the underlying cause of CKD has an effect on adverse outcomes.

This review question has been split into four sections to cover the 4 causes that the GDG were particularly interested in; a) diabetes, b) hypertension, c) AKI and d) glomerular disease.

6.3.2 Review question: For people with CKD, does the presence of diabetes have an effect on adverse outcomes at any given category of eGFR and ACR?

For full details see review protocol in Appendix C.

Table 30: PICO characteristics of diabetes as a risk factor review question

Population	Adults with CKD
Presence of prognostic factor	CKD and diabetes
Absence of prognostic factor	CKD and no known diabetes (or history of)
Outcomes	**Critical:** • CKD progression:change in eGFR • CKD progression: occurrence of end stage kidney disease (ESRD or ESKD as reported by the study) • All-cause mortality • Cardiovascular mortality • Cardiovascular events **Important:** • Hospitalisation
Study design	• IPD meta-analysis • Prospective cohort studies (retrospective if no cohort studies identified) • Cross sectional studies

6.3.3 Clinical evidence

When the review for the classification of CKD was carried out, an individual patient data (IPD) meta-analysis was identified for people with diabetes,[108] which was a subgroup of that review question. The study is also relevant to this review question. However, the data presented in the study and the classification review does not directly inform this review question, and therefore the authors were contacted to obtain analysis of the CKD cohorts to compare those with and without diabetes.

The study included general population cohorts as well as high risk and CKD cohorts, and it cannot be determined whether diabetes was the direct cause of CKD. However, the study provided data on eGFR and proteinuria levels as required by the review protocol and is included because it is from a large data set and is likely to inform the review question.

As this was an IPD meta-analysis, quality was assessed per-study using a customised methodology checklist for quality assessment of systematic reviews of prognostic studies adapted from Hayden

2006[138] this has been incorporated into a GRADE profile, Table 32. See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

Table 31: Summary of included study

Study	Population	Proteinuria measures	Outcomes	Length of follow up (range in years)	Covariates	Study quality
Fox et al. 2012[108]	General population cohorts, high risk cardiovascular cohorts and people with CKD	ACR (mg/g) PCR (mg/g) Dipstick category*	All-cause mortality Cardiovascular mortality End stage kidney disease	2.3-24.9	Age, sex, race (black vs.non-black), smoking, systolic blood pressure, total cholesterol, body-mass index, history of cardiovascular disease, and albuminuria.	High

Table 32: Clinical evidence profile: Diabetes versus no diabetes

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	With diabetes	Without diabetes	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality(follow up range 2.3-24.9 years)[108]												
1	Randomised trials (a)	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	0%	HR 1.42 (1.34 to 1.51)	- (b)	HIGH	CRITICAL
Cardiovascular mortality(follow up range 2.3-24.9 years)[108]												
1	Randomised trials (a)	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	0%	HR 1.43 (1.31 to 1.57)	- (b)	HIGH	CRITICAL
Progression of CKD (ESRD) (follow up range 2.3-24.9 years)[108]												
1	Randomised trials (a)	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious (c)	None	-	0%	HR 1.76 (1.03 to 3.02)	- (b)	MODERATE	CRITICAL

(a) IPD meta-analysis
(b) Absolute event rate cannot be calculated raw data not available.
(c) The confidence interval crosses one minimally important difference making the effect size uncertain.

6.3.4 Review question: For people with CKD, does the presence of hypertension have an effect on adverse outcomes at any given category of eGFR and ACR?

For full details see review protocol in Appendix C.

Table 33: PICO characteristics of hypertension as a risk factor review question

Population	Adults with CKD
Presence of prognostic factor	CKD and hypertension
Absence of prognostic factor	CKD and no known hypertension (or history of)
Outcomes	**Critical:** • CKD progression:change in eGFR • CKD progression: occurrence of end stage kidney disease (ESRD or ESKD as reported by the study) • All-cause mortality • Cardiovascular mortality • Cardiovascular events **Important:** • Hospitalisation
Study design	• IPD meta-analysis • Prospective cohort studies (retrospective if no cohort studies identified) • Cross sectional studies

6.3.5 Clinical evidence

When the review for the classification of CKD was carried out, an IPD meta-analysis was identified for people with hypertension,[237] which was a subgroup of that review question. This study was also relevant to this review question. However, the data presented in the study and the classification review does not directly inform this review question, and therefore the authors were contacted to obtain analysis of the CKD cohorts to compare those with and without hypertension.

The study included general population cohorts as well as high risk and CKD cohorts, and it cannot be determined whether hypertension was the direct cause of CKD. However, the study provided data on eGFR and proteinuria levels as required by the review protocol and is in a large data set and is likely to inform the review question and is therefore included.

As this was an IPD meta-analysis, quality was assessed per-study using a customised methodology checklist for quality assessment of systematic reviews of prognostic studies adapted from Hayden 2006[138] this has been incorporated into a GRADE profile, Table 35. See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

Study	Population	Proteinuria measures	Outcomes	Length of follow up (range in years)	Covariates	Study quality
Mahmoodi et al.2012[237]	General population cohorts, high risk cardiovascular cohorts and people with CKD	ACR (mg/g) PCR (mg/g) Dipstick category*	All-cause mortality Cardiovascular mortality End stage kidney disease	2.3-24.9	Age, sex, race (black vs. non-black), history of cardiovascular disease, diabetes, serum total cholesterol, body mass index, smoking and albuminuria.	High

Table 35: Clinical evidence profile: Hypertension versus no hypertension

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	With hypertension	Without hypertension	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality - eGFR <30 (follow up range 2.3-24.9 years)[237]												
1	Randomised trials (a)	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious (b)	None	-	0%	HR 0.72 (0.53 to 0.98)	- (c)	MODERATE	CRITICAL
All-cause mortality - eGFR 31-45(follow up range 2.3-24.9 years)[237]												
1	Randomised trials (a)	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	0%	HR 0.94 (0.84 to 1.05)	- (c)	HIGH	CRITICAL
All-cause mortality - eGFR 46-60(follow up range 2.3-24.9 years)[237]												
1	Randomised trials (a)	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	0%	HR 1.08 (0.99 to 1.18)	- (c)	HIGH	CRITICAL
Cardiovascular mortality - eGFR <30(follow up range 2.3-24.9 years)[237]												
1	Randomised trials (a)	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious (b)	None	-	-	HR 0.78 (0.51 to 1.19)	- (c)	MODERATE	CRITICAL
Cardiovascular mortality - eGFR 31-45(follow up range 2.3-24.9 years)[237]												
1	Randomised trials (a)	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	0%	HR 1.1 (0.94 to 1.29)	- (c)	HIGH	CRITICAL
Cardiovascular mortality - eGFR 46-60(follow up range 2.3-24.9 years)[237]												
1	Randomised	No	No serious	No serious	Serious (b)	None	-	0%	HR 1.22	- (c)	MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**With hypertension**	**Without hypertension**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
	trials (a)	serious risk of bias	inconsistency	indirectness					(1.02 to 1.46)			
Progression of CKD (ESRD) eGFR<60(follow up range 2.3-24.9 years)[237]												
1	Randomised trials (a)	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious (b)	None	-	0%	HR 1.25 (0.8 to 1.97)	- (c)	MODERATE	CRITICAL

(a) IPD meta-analysis.
(b) The confidence interval crosses one minimally important difference making the effect size uncertain.
(c) Absolute event rate could not be calculated as raw data were not provided.
NB all GFR measrements are in ml/min/1.73 $m^{2.}$.

6.3.6 Review question: For people with CKD, does the presence of glomerular disease have an effect on adverse outcomes at any given category of eGFR and ACR?

For full details see review protocol in Appendix C.

Table 36: PICO characteristics of glomerular disease as a risk factor review question

Population	Adults with CKD
Presence of prognostic factor	CKD and glomerular disease (to include: proliferative glomerulonephritis, membranous glomerulonephritis, minimal-change nephropathy, IgA nephropathy, Focal glomerulosclerosis, nephrotic syndrome, focal segmental).
Absence of prognostic factor	CKD and no glomerular disease
Outcomes	**Critical:** • CKD progression:change in eGFR • CKD progression: occurrence of end stage kidney disease (ESRD or ESKD as reported by the study) • All-cause mortality • Cardiovascular mortality • Cardiovascular events **Important:** • Hospitalisation
Study design	• IPD meta-analysis • Prospective cohort studies (retrospective if no cohort studies identified) • Cross sectional studies

6.3.7 Clinical evidence

We searched for cohort studies of people with CKD and glomerular disease compared to those without glomerular disease.

No studies were identified that were directly relevant to the review question comparing people with glomerular disease compared to those without. Three retrospective cohorts were identified that included people with different glomerular diseases and compared how each affected progression.[63,213,261] These have been included as indirect evidence which is informative to the review question.

Evidence from these are summarised in the clinical GRADE evidence profile below (Table 134). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

Summary of included studies

Table 37: Summary of studies included in the review

Study	Comparison	Cohort	Outcomes	Comments
Chou et al. 2012[63]	• Minimal change disease • Focal and segmental glomerulosclerosis • IgA nephropathy • Membranous	Retrospective cohort of adults (aged 18 or over) undergoing biopsy for nephrotic syndrome, unexplained kidney	• All-cause mortality • Dialysis	Hazard ratio calculated with Minimal change disease as 'control' group for analysis.

Study	Comparison	Cohort	Outcomes	Comments
	nephropathy	failure, or persistent urinary abnormalities. Median follow-up 5.9 years.		
Lee et al. 2013[213]	• Minimal change disease • Focal and segmental glomerulosclerosis • Membranous nephropathy • IgA nephropathy • Membranoproliferative glomerular nephropathy	Retrospective cohort of people aged over 15 undergoing percutaneous native kidney biopsy with primary glomerular nephropathy. Follow-up: median 7.5 years.	• End stage kidney disease • All-cause mortality	Hazard ratio calculated with Minimal change disease as 'control' group for analysis.
Moranne et al.2008[261]	• Focal and segmental glomerulosclerosis • Membranous nephropathy • IgA nephropathy	Retrospective cohort of white adults aged over 18 diagnosed with primary focal and segmental glomerulosclerosis, membranous nephropathy or IgA nephropathy. Follow-up: Mean 7 years.	• End stage kidney disease	Hazard ratio calculated with IgA nephropathy as 'control' group for analysis.

Table 38: Clinical evidence profile: Glomerular diseases compared to IgA nephropathy (IgAN)

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Membranous nephropathy or FSGS**	**IgAN**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
End stage kidney disease - Membranous nephropathy versus IgAN (follow-up mean 7 years)[261]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious (a)	Serious (b)	None	114/129 (88.4%)	232/283 (82%)	HR 2.6 (0.3 to 22.53)	169 more per 1000 (from 418 fewer to 180 more)	LOW	CRITICAL
End stage kidney disease - Focal segmental glomerulosclerosis (FSGS) versus IgAN follow-up mean 7 years)[261]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious (a)	No serious imprecision	None	86/124 (69.4%)	232/283 (82%)	HR 7 (2 to 24.5)	180 more per 1000 (from 148 more to 180 more)	MODERATE	CRITICAL

(a) Different types of glomerular disease compared to IgA nephropathy rather than those without glomerular disease.
(b) Confidence interval crosses the MID in both directions making the effect size very uncertain.

Table 39: Clinical evidence profile: Glomerular diseases compared to minimal change disease

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Membranous nephropathy, IgAN, FSGS Membranoproliferative glomerulosclerosis	Minimal change disease	Relative (95% CI)	Absolute	Quality	Importance
Dialysis / end stage kidney disease - Membranous nephropathy (follow-up median 6.7 years)[63,213]												
2	Observational studies	Serious (a)	No serious inconsistency	Serious (b)	No serious imprecision (c)	None	-	0%	HR 3.39 (1.62 to 7.07)	(d)	VERY LOW	CRITICAL
Dialysis / end stage kidney disease - IgA nephropathy (follow-up median 6.9 years)[63,213]												
2	Observational studies	Serious (a)	No serious inconsistency	Serious (b)	No serious imprecision	None	-	0%	HR 3.48 (2.38 to 5.09)	(d)	LOW	CRITICAL
Dialysis / end stage kidney disease - Focal segmental glomerulosclerosis (follow-up median 6.9 years)[63,213]												
2	Observational studies	Serious (a)	No serious inconsistency	Serious (b)	No serious imprecision	None	-	0%	HR 5 (3.26 to 7.65)	(d)	LOW	CRITICAL
Dialysis / end stage kidney disease - Membranoproliferative glomerulosclerosis (follow-up median 7.5 years) [213]												
1	Observational studies	Serious (a)	No serious inconsistency	Serious (b)	No serious imprecision	None	-	0%	HR 34.65 (9.54 to 125.85)	(e)	LOW	CRITICAL
Mortality - Membranous nephropathy (follow-up median 6.9 years)[63,213]												
2	Observational studies	Serious (a)	No serious inconsistency	Serious (b)	No serious imprecision	None	69/442 (15.6%)	15/296 (5.1%)	HR 1.73 (1.25 to 2.41)	35 more per 1000 (from 12 more to 67 more)	LOW	CRITICAL
Mortality - IgA nephropathy (follow-up median 6.9 years)[63,213]												
2	Observational studies	Serious (a)	No serious inconsistency	Serious (b)	No serious imprecision	None	50/1139 (4.4%)	15/296 (5.1%)	HR 1.08 (0.97 to	4 more per 1000	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Membranous nephropathy, IgAN, FSGS Membranoproliferative glomerulosclerosis**	**Minimal change disease**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
									1.21)	(from 1 fewer to 10 more)		
Mortality - Focal segmental glomerulosclerosis (follow-up median 6.9 years)[63,213]												
2	Observational studies	Serious (a)	No serious inconsistency	Serious (b)	Serious (c)	None	53/383 (13.8%)	15/296 (5.1%)	HR 1.65 (1.18 to 2.3)	32 more per 1000 (from 9 more to 62 more)	VERY LOW	CRITICAL
Mortality - Membranoproliferative glomerulosclerosis (follow-up median 7.5 years)[213]												
1	Observational studies	Serious (a)	No serious inconsistency	Serious (b)	Serious (c)	None	11/47 (23.4%)	11/187 (5.9%)	HR 1.8 (0.97 to 3.34)	45 more per 1000 (from 2 fewer to 124 more)	VERY LOW	CRITICAL

(a) Hazard ratios calculated from Kaplan Meier plots and are therefore unadjusted.
(b) Different types of glomerular disease compared to minimal change disease rather than those without glomerular disease.
(c) The confidence interval crosses one MID making the effect size uncertain.
(d) Number of events not reported by one study therefore absolute event rate could not be calculated.
(e) Number of events not reported therefore absolute event rate could not be calculated.

6.3.8 Review question: For people with CKD, does the presence of AKI have an effect on adverse outcomes at any given category of eGFR and ACR?

For full details see review protocol in Appendix C.

Table 40: PICO characteristics of AKI as a risk factor review question

Population	Adults with CKD
Presence of prognostic factor	CKD and AKI
Absence of prognostic factor	CKD and no known AKI (or history of)
Outcomes	**Critical:** • CKD progression:change in eGFR • CKD progression: occurrence of end stage kidney disease (ESRD or ESKD as reported by the study) • All-cause mortality • Cardiovascular mortality • Cardiovascular events **Important:** • Hospitalisation
Study design	• IPD meta-analysis • Prospective cohort studies (retrospective if no cohort studies identified) • Cross sectional studies

6.3.9 Clinical evidence

We searched for cohort studies of people with CKD and AKI compared to those without AKI.

Four studies were identified that included people with AKI .

Evidence from these are summarised in the clinical GRADE evidence profile below (Table 134). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

Summary of included studies

The included studies had different comparator groups. Only one study stratified results by eGFR level.[315] Details have been summarised in Table 37 below. One study was identified that included a cohort of people with CKD and assessed probability of all-cause mortality and dialysis,[209] however results for this analyses were only reported on Kaplan Meier curves without the full data to calculate hazard ratios and therefore could not be analysed.

Table 41: Summary of studies included in the review

Study	Comparison	Cohort	Outcomes	Comments
Amdur et al. 2009[12]	People with: • acute kidney failure • acute tubular necrosis • chronic kidney disease	Retrospective analysis of a database of people with a primary diagnosis of acute kidney failure, acute tubular necrosis or pneumonia or myocardial infarction.	• Progression to CKD stage 4. • All-cause mortality.	Control group was not defined.

Study	Comparison	Cohort	Outcomes	Comments
	and a control group*.	Follow-up: Up to 5 years.		
LaFrance et al. 2010[209]	• People with CKD and AKI • People with CKD and no AKI	Retrospective cohort of people with CKD (people referred to nephrologists or on dialysis therapy) followed up for at least 6 months and had at least 3 eGFR values.	• All-cause mortality • Dialysis	All participants registered with CKD – study determines how many had AKI. Data for those with AKI versus those without only presented in Kaplan Meier plots without number at risk – could not be extracted.
Pannu et al. 2011[315]	People with: • CKD • AKI stage 1 • AKI stage 2 • AKI stage 3	Retrospective cohort of people aged 18 and older hospitalised with at least 1 serum creatinine measurement during hospitalisation and 1 outpatient measurement within 6 months preceding admission. AKI defined during the index hospitalisation. Follow-up: 2 years.	• All-cause mortality (in hospital) • Mortality or ESRD	Some participants had pre-existing CKD. Stratified by stage of AKI and eGFR level.
Wu et al. 2011[427]	People with no prior CKD: • Without AKI* • With AKI RIFLE-R • With AKI RIFLE-I • With AKI RIFLE-F. People with prior CKD: • Without AKI • With AKI.	Retrospective cohort of people admitted to surgical ICU after major surgery during 2002-2008. Follow-up: Median 4.76 years.	• Long term mortality • Long-term dialysis	AKI defined by RIFLE criteria – risk, injury and failure.

** Not included in analysis.*

Table 42: Clinical evidence profile: Acute tubular necrosis, acute kidney failure or CKD versus control

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Acute tubular necrosis or acute kidney failure	Control	Relative (95% CI)	Absolute	Quality	Importance
Progression to CKD stage 4 - Acute tubular necrosis (ATN) (follow-up 1-5 years)[12]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	69/345 (20%)	2100/62850 (3.3%)	HR 6.64 (3.75 to 11.76)	169 more per 1000 (from 86 more to 296 more)	HIGH	CRITICAL
Progression to CKD stage 4 - Acute renal failure (ARF) (follow-up 1-5 years)[12]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	663/5021 (13.2%)	2100/62850 (3.3%)	HR 4.03 (3.49 to 4.65)	95 more per 1000 (from 78 more to 113 more)	HIGH	CRITICAL
Progression to CKD stage 4 - CKD (follow-up 1-5 years)[12]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	9263/37562 (24.7%)	2100/62850 (3.3%)	HR 6.5 (6.26 to 6.75)	165 more per 1000 (from 158 more to 172 more)	HIGH	CRITICAL
All-cause mortality - Acute tubular necrosis (ATN) (follow-up 1-5 years)[12]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious (b)	None	127/345 (36.8%)	24622/62850 (39.2%)	HR 1.1 (0.93 to 1.3)	30 more per 1000 (from 22 fewer to 84 more)	MODERATE	CRITICAL
All-cause mortality - Acute renal failure (ARF) (follow-up 1-5 years)[12]												
1	Observational	No	No serious	No serious	No serious	None	1958/5021	24622/62850	HR 1.12	35 more per	HIGH	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Acute tubular necrosis or acute kidney failure**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
	studies	serious risk of bias	inconsistency	indirectness	imprecision		(39%)	(39.2%)	(1.07 to 1.17)	1000 (from 21 more to 49 more)		
All-cause mortality - CKD (follow-up 1-5 years)[12]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	23544/44076 (53.4%)	24622/62850 (39.2%)	HR 1.2 (1.18 to 1.22)	58 more per 1000 (from 52 more to 63 more)	HIGH	CRITICAL

(a) The confidence interval crosses one MID making the effect size uncertain.

Table 43: Clinical evidence profile: Stages of AKI stratified by eGFR level compared to no AKI eGFR>60

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Stage of AKI**	**No AKI eGFR >60**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
In-hospital mortality - eGFR >60 AKI stage 1 (follow-up up to 2 years)[315]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	270/1935 (14%)	823/26357 (3.1%)	HR 2.99 (2.59 to 3.45)	59 more per 1000 (from 48 more to 72 more)	HIGH	CRITICAL
In-hospital mortality - eGFR >60 AKI stage 2 (follow-up up to 2 years)[315]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	143/388 (36.9%)	823/26357 (3.1%)	HR 8.28 (6.92 to 9.91)	200 more per 1000 (from 166 more to 239 more)	HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Stage of AKI**	**No AKI eGFR >60**	**Relative (95% CI)**	**Absolute**		
In-hospital mortality - eGFR >60 AKI stage 3 (follow-up up to 2 years)[315]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	131/264 (49.6%)	823/26357 (3.1%)	HR 10.62 (8.78 to 12.85)	255 more per 1000 (from 212 more to 304 more)	HIGH	CRITICAL
In-hospital mortality - eGFR 45-59 no AKI (follow-up up to 2 years)[315]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	294/5377 (5.5%)	823/26357 (3.1%)	HR 1.02 (0.94 to 1.11)	1 more per 1000 (from 2 fewer to 3 more)	HIGH	CRITICAL
In-hospital mortality - eGFR 45-59 AKI stage 1 (follow-up up to 2 years)[315]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	234/1358 (17.2%)	823/26357 (3.1%)	HR 2.92 (2.52 to 3.38)	57 more per 1000 (from 46 more to 70 more)	HIGH	CRITICAL
In-hospital mortality - eGFR 45-59 AKI stage 2 (follow-up up to 2 years)[315]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	85/182 (46.7%)	823/26357 (3.1%)	HR 7.53 (5.98 to 9.48)	181 more per 1000 (from 142 more to 229 more)	HIGH	CRITICAL
In-hospital mortality - eGFR 45-59 AKI stage 3 (follow-up up to 2 years)[315]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	85/182 (46.7%)	823/26357 (3.1%)	HR 8.01 (6.12 to 10.48)	193 more per 1000 (from 145 more to 252 more)	HIGH	CRITICAL
In-hospital mortality - eGFR 30-44 no AKI (follow-up up to 2 years)[315]												
1	Observational	No	No serious	No serious	No serious	None	182/2616	823/26357	HR 1.07	2 more per	HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Stage of AKI**	**No AKI eGFR >60**	**Relative (95% CI)**	**Absolute**		
	studies	serious risk of bias	inconsistency	indirectness	imprecision		(7%)	(3.1%)	(0.90 to 1.27)	1000 (from 3 fewer to 8 more)		
In-hospital mortality - eGFR 30-44 AKI stage 1 (follow-up up to 2 years)[315]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	289/1580 (18.3%)	823/26357 (3.1%)	HR 2.89 (2.50 to 3.34)	56 more per 1000 (from 45 more to 69 more)	HIGH	CRITICAL
In-hospital mortality - eGFR 30-44 AKI stage 2 (follow-up up to 2 years)[315]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	88/171 (51.5%)	823/26357 (3.1%)	HR 7.46 (5.95 to 9.35)	180 more per 1000 (from 141 more to 225 more)	HIGH	CRITICAL
In-hospital mortality - eGFR 30-44 AKI stage 3 (follow-up up to 2 years)[315]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	88/171 (51.5%)	823/26357 (3.1%)	HR 8.35 (6.20 to 11.25)	201 more per 1000 (from 147 more to 269 more)	HIGH	CRITICAL
In-hospital mortality - eGFR <30 no AKI (follow-up up to 2 years)[315]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	97/802 (12.1%)	823/26357 (3.1%)	HR 1.67 (1.34 to 2.08)	20 more per 1000 (from 10 more to 33 more)	HIGH	CRITICAL
In-hospital mortality - eGFR <30 AKI stage 1 (follow-up up to 2 years)[315]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	276/1394 (19.8%)	823/26357 (3.1%)	HR 2.93 (2.52 to 3.41)	58 more per 1000 (from 46 more to 71 more)	HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Stage of AKI**	**No AKI eGFR >60**	**Relative (95% CI)**	**Absolute**		
In-hospital mortality - eGFR <30 AKI stage 2 (follow-up up to 2 years)[315]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	44/108 (40.7%)	823/26357 (3.1%)	HR 6.74 94.96 to 9.16)	161 more per 1000 (from 114 more to 221 more)	HIGH	CRITICAL
In-hospital mortality - eGFR <30 AKI stage 3 (follow-up up to 2 years)[315]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	44/108 (40.7%)	823/26357 (3.1%)	HR 4.71 (3.61 to 6.15)	108 more per 1000 (from 77 more to 146 more)	HIGH	CRITICAL
Mortality or ESRD - eGFR >60 AKI stage 1 (follow-up up to 2 years)[315]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious (a)	Serious (b)	None	495/1665 (29.7%)	4791/25534 (18.8%)	HR 1.26 (1.15 to 1.38)	43 more per 1000 (from 25 more to 62 more)	LOW	CRITICAL
Mortality or ESRD - eGFR >60 AKI stage 2 (follow-up up to 2 years)[315]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious (a)	No serious imprecision	None	91/245 (37.1%)	4791/25534 (18.8%)	HR 2.08 (1.69 to 2.56)	163 more per 1000 (from 109 more to 225 more)	MODERATE	CRITICAL
Mortality or ESRD - eGFR >60 AKI stage 3 (follow-up up to 2 years)[315]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious (a)	No serious imprecision	None	41/133 (30.8%)	4791/25534 (18.8%)	HR 1.48 (1.09 to 2.01)	77 more per 1000 (from 15 more to 154 more)	MODERATE	CRITICAL
Mortality or ESRD - eGFR 45-59 no AKI (follow-up up to 2 years)[315]												
1	Observational	No	No serious	Serious (a)	No serious	None	1532/508	4791/25534	HR 0.97	15 fewer	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Stage of AKI**	**No AKI eGFR >60**	**Relative (95% CI)**	**Absolute**		
	studies	serious risk of bias	inconsistency		imprecision		3 (30.1%)	(18.8%)	(0.91 to 1.03)	per 1000 (from 15 fewer to 5 more)		
Mortality or ESRD - eGFR 45-59 AKI stage 1 (follow-up up to 2 years)[315]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious (a)	Serious (b)	None	453/1124 (40.3%)	4791/25534 (18.8%)	HR 1.31 (1.18 to 1.45)	51 more per 1000 (from 30 more to 73 more)	LOW	CRITICAL
Mortality or ESRD - eGFR 45-59 AKI stage 2 (follow-up up to 2 years)[315]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious (a)	Serious (b)	None	46/97 (47.4%)	4791/25534 (18.8%)	HR 1.53 (1.14 to 2.05)	85 more per 1000 (from 23 more to 159 more)	LOW	CRITICAL
Mortality or ESRD - eGFR 45-59 AKI stage 3 (follow-up up to 2 years)[315]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious (a)	No serious imprecision (b)	None	23/46 (50%)	4791/25534 (18.8%)	HR 1.34 (0.89 to 2.02)	55 more per 1000 (from 19 fewer to 155 more)	LOW	CRITICAL
Mortality or ESRD - eGFR 30-44 no AKI (follow-up up to 2 years)[315]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious (a)	No serious imprecision	None	1011/2434 (41.5%)	4791/25534 (18.8%)	HR 1.06 (0.99 to 1.13)	10 more per 1000 (from 2 fewer to 22 more)	MODERATE	CRITICAL
Mortality or ESRD - eGFR 30-44 AKI stage 1 (follow-up up to 2 years)[315]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious (a)	Serious (b)	None	572/1291 (44.3%)	4791/25534 (18.8%)	HR 1.24 (1.13 to 1.36)	40 more per 1000 (from 22 more to 59 more)	LOW	CRITICAL
Mortality or ESRD - eGFR 30-44 AKI stage 2 (follow-up up to 2 years)[315]												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Stage of AKI**	**No AKI eGFR >60**	**Relative (95% CI)**	**Absolute**		
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious (a)	No serious imprecision	None	54/83 (65.1%)	4791/25534 (18.8%)	HR 1.99 (1.52 to 2.61)	151 more per 1000 (from 83 more to 231 more)	MODERATE	CRITICAL
Mortality or ESRD - eGFR 30-44 AKI stage 3 (follow-up up to 2 years)[315]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious (a)	No serious imprecision	None	26/46 (56.5%)	4791/25534 (18.8%)	HR 2.74 (1.86 to 4.04)	246 more per 1000 (from 133 more to 380 more)	MODERATE	CRITICAL
Mortality or ESRD - eGFR <30 no AKI (follow-up up to 2 years)[315]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious (a)	No serious imprecision	None	378/705 (53.6%)	4791/25534 (18.8%)	HR 1.67 (1.34 to 2.08)	106 more per 1000 (from 55 more to 163 more)	MODERATE	CRITICAL
Mortality or ESRD - eGFR <30 AKI stage 1 (follow-up up to 2 years)[315]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious (a)	No serious imprecision	None	676/1118 (60.5%)	4791/25534 (18.8%)	HR 1.75 (1.60 to 1.91)	117 more per 1000 (from 95 more to 140 more)	MODERATE	CRITICAL
Mortality or ESRD - eGFR <30 AKI stage 2 (follow-up up to 2 years)[315]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious (a)	No serious imprecision	None	43/64 (67.2%)	4791/25534 (18.8%)	HR 3.40 (2.51 to 4.61)	319 more per 1000 (from 219 more to 429 more)	MODERATE	CRITICAL
Mortality or ESRD - eGFR <30 AKI stage 3 (follow-up up to 2 years)[315]												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Stage of AKI**	**No AKI eGFR >60**	**Relative (95% CI)**	**Absolute**		
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious (a)	No serious imprecision	None	148/214 (69.2%)	4791/25534 (18.8%)	HR 4.04 (3.43 to 4.77)	380 more per 1000 (from 322 more to 441 more)	MODERATE	CRITICAL

(a) Composite outcome of mortality and end stage kidney disease.
(b) The confidence interval crosses one MID making the effect size uncertain.
NB All GFR measrements are in ml/min/1.73 m^2.

Table 44: Clinical evidence profile: AKI in people without CKD versus no prior CKD or AKI

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**With AKI**	**No prior CKD / AKI**	**Relative (95% CI)**	**Absolute**		
Long-term dialysis - AKI All RIFLE stages (follow-up median 4.76 years)[427]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	79/4158 (1.9%)	13/4724 (0.28%)	HR 2.09 (0.97 to 4.5)	3 more per 1000 (from 0 fewer to 10 more)	HIGH	CRITICAL
Long-term mortality - AKI All RIFLE stages (follow-up median 4.76 years)[427]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1384/4158 (33.3%)	676/4724 (14.3%)	HR 1.62 (1.45 to 1.81)	78 more per 1000 (from 58 more to 101 more)	HIGH	CRITICAL

Table 45: Clinical evidence profile: Prior CKD with or without AKI versus no prior CKD or AKI

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	With prior CKD with or without AKI	No prior CKD/AKI	Relative (95% CI)	Absolute	Quality	Importance
Long-term dialysis - Non-AKI (follow-up median 4.76 years)[427]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	21/116 (18.1%)	13/4724 (0.28%)	HR 52 (25.6 to 105.63)	131 more per 1000 (from 65 more to 250 more)	HIGH	CRITICAL
Long-term dialysis - AKI (follow-up median 4.76 years)[427]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	69/235 (29.4%)	13/4724 (0.28%)	HR 122.9 (66.8 to 226.11)	285 more per 1000 (from 165 more to 461 more)	HIGH	CRITICAL
Long-term mortality - Non-AKI (follow-up median 4.76 years)[427]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	45/116 (38.8%)	676/4724 (14.3%)	HR 2.62 (1.92 to 3.58)	190 more per 1000 (from 113 more to 282 more)	HIGH	CRITICAL
Long-term mortality - AKI (follow-up median 4.76 years)[427]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	111/235 (47.2%)	676/4724 (14.3%)	HR 3.58 (2.91 to 4.4)	282 more per 1000 (from 219 more to 350 more)	HIGH	CRITICAL

6.3.10 Economic evidence

Published literature

This is solely a clinical question where economic studies were not relevant. No relevant economic evaluations looking at the cause of CKD were identified.

New cost-effectiveness analysis

New analysis was not prioritised for this area.

6.3.11 Evidence statements

Clinical

Diabetes

- One IPD meta-analysis reported high quality evidence demonstrating that people with CKD and diabetes are at greater risk of mortality, and also suggested they are at increased risk of progression to end stage kidney disease (moderate quality evidence) than people without diabetes.

Hypertension

- Evidence from one IPD meta-analysis suggested that there is no clear difference in people with CKD irrespective of presence of hypertension in terms of risk of mortality or progression of CKD.

Glomerular disease

- One retrospective cohort study reported low quality evidence suggesting that membranous nephropathy may be associated with an increased risk of end stage kidney disease than IgA nephropathy, and moderate quality evidence showing that focal segmental glomerulosclerosis was associated with an increased risk.
- Two retrospective cohort studies reported very low and low quality evidence that membranous nephropathy, IgA nephropathy, focal segmental glomerulosclerosis and membranoproliferative glomerulosclerosis were all associated with an increased risk of long term dialysis compared to minimal change disease. Membranoproliferative glomerulosclerosis had the greatest increased risk. Membranous nephropathy, focal segmental glomerulosclerosis and membranoproliferative glomerulosclerosis were also associated with increased risk of all-cause mortality.

AKI

- Evidence from one retrospective cohort study suggested that acute tubular necrosis, acute renal failure and CKD all have increased risks of progression to CKD stage 4 compared to a 'control' group. The high quality evidence indicated that this risk may be greatest in people with acute tubular necrosis, however for all-cause mortality, the risk was only increased in people with acute renal failure and those with CKD.
- One retrospective cohort study showed that at any level of eGFR , the risk of in-hospital mortality (high quality evidence), or composite outcome of end stage kidney disease or all-cause mortality (after hospital discharge – moderate to low quality evidence) was greater in people who had an episode of AKI compared to those who had no previous AKI (or history of). In general, the risk increased with increased stage of AKI.

- One retrospective cohort study reported high quality evidence that AKI defined as RIBLE risk, injury or failure, all had an increased risk of long term dialysis or mortality compared to people without AKI or CKD and compared to those who already had CKD.

Economic

- No relevant economic evaluations were identified.

6.3.12 Recommendations and link to evidence

Recommendations	The current recommendations can be found at www.nice.org.uk/guidance/ng203
Relative values of different outcomes	The GDG agreed that progression of CKD (measured by change in eGFR and occurrence of end stage kidney disease), mortality (all-cause and cardiovascular) and cardiovascular events were critical to decision making. Hospitalisation was also considered as important. However, no information was available for cardiovascular events or hospitalisation.
Trade off between clinical benefits and harms	**Diabetes** There was evidence from an IPD meta-analysis that people with CKD and diabetes are at increased risk of mortality compared to those without diabetes irrespective of eGFR. The effect on progression of CKD was suggestive of an increased risk in people with diabetes, but the association was less clear. **Hypertension** Evidence from an IPD meta-analysis did not suggest that hypertension was consistently associated with an increased risk of adverse events. This evidence suggested that people with eGFR less than 30 ml/min/1.73 m^2 had a greater risk of all-cause mortality than those without. The GDG considered that this was most likely due to reverse causality. This is because people with advanced CKD are also at greater risk of heart failure and relative hypotension, and thus greater risk of all-cause mortality. For other outcomes and eGFR ranges, there was no clear difference between those with and without hypertension. **Glomerular disease** The only available evidence for glomerular disease compared progression in different histological types of primary glomerulonephritis. Evidence suggested that membranous nephropathy, IgA nephropathy and focal segmental glomerulosclerosis and membranoproliferative glomerulosclerosis were all associated with a sequentially increased risk of end stage kidney disease or dialysis than minimal change disease (membranoproliferative glomerulonephritis carried the greatest risk). Focal segmental glomerulosclerosis was associated with a greater risk of end stage kidney disease than IgA nephropathy. However, the increased risk of all-cause mortality was only greater in membranous nephropathy, focal segmental glomerulosclerosis and membranoproliferative glomerulonephritis. The GDG agreed a recommendation could not be based on this evidence alone, although it did suggest that type of glomerular disease could influence CKD progression. **AKI** The objective of this review was to determine whether adverse outcomes are different in people with CKD and AKI (or history of AKI) compared to those without AKI. However, there was overlap with another question to determine whether an episode of AKI affects progression of CKD. The evidence reviewed included a mixture

	of comparisons. One compared two types of AKI, CKD and a control group,[12] one compared people with CKD to different stages of AKI[315] and another compared people with and without prior CKD with or without AKI.[427] The study which most directly met the review question, did not present sufficient data for analyses.[209] However, the included studies did indicate that AKI increases risk of CKD progression, at all levels of eGFR. The GDG discussed that current practice was to treat people who recover from AKI as normal and not at increased risk of CKD, but evidence from this review suggests that this is not the case. In light of this evidence the GDG agreed that recommendation R25 from CG73 should include AKI in the list of risk factors that indicate testing for CKD be considered when the other AKI review was considered. The GDG also agreed that it was important to draft a recommendation to highlight that cause of CKD should be investigated following diagnosis. This was particularly important with a view to identifying possible treatable causes of CKD.
Economic considerations	There were no economic evaluations looking at the cause of CKD. The GDG judged that raising awareness of conditions which increase the risk of CKD may require an additional time in patient consultations with health care professionals. This was considered worthwhile as more stringent management and treatment of people with conditions that increase the risk of CKD could aid in the reduction of the development and progression of CKD. In doing so, the long term cost and health outcome consequences could be kept minimal.
Quality of evidence	The GDG considered it important to note that none of the included studies were able to determine whether the underlying condition was the cause of CKD or a comorbid condition. However, the review question was framed to include these studies as it was deemed unlikely to find any evidence with clear causality. These studies were therefore all included as informative to the review question. **Diabetes and hypertension** The evidence for both diabetes and hypertension was from high quality meta-analyses. The data presented in the studies did not directly compare the groups of interest (with versus without diabetes / hypertension) and therefore the authors were contacted to provide the hazard ratios and confidence intervals for these comparisons, separated by eGFR. All of this evidence was moderate or high quality, with moderate level evidence due to imprecision of the effect size. **Glomerular disease** No evidence was identified that compared people with glomerular disease to those without. Studies were identified that assessed progression in different forms of glomerular disease. Although this did not directly answer the review question, the GDG agreed it was useful to inform the different rates of progression according to glomerular disease. All evidence was however or very low quality. The reference group in the comparisons was minimal change disease for two of the three included studies[63,214] and IgA nephropathy for the third.[261] It was noted that minimal change disease only causes proteinuria, not progressive kidney disease and is often used as the control arm in such studies. **AKI** All evidence reviewed was of very low quality from retrospective cohort studies. It was highlighted that this review overlaps with that in chapter 7.4 which looks at the risk of developing and/or progression of CKD after an episode of AKI.
Other considerations	The GDG agreed that when investigating the cause of CKD, it was important that why this was being done, and the implications different causes may have, were explained in discussion with the patient. The GDG were aware that little information is available to assist healthcare professionals in 'breaking the news' to patients and implementation tools to guide health care professionals on how to do this would be

	beneficial. The GDG agreed that a recommendation should be made to determine a plan with the patient to identify the cause enabling identification of potentially reversible causes of CKD. This recommendation was partially based on the evidence reviewed, however, as this was very low quality, and not directly relevant to the review question in many cases, GDG consensus opinion informed the recommendation. The GDG agreed that glomerular disease was a cause if CKD that was potentially reversible, which was indicted by the review. They also considered that other causes that were not reviewed were important to state (urinary tract obstruction, nephrotoxic drugs). This was based on consensus opinion. The recommendation from CG73 stating risk factors for development of CKD was amended to include AKI (recommendation 31, see chapter 6.2).

6.4 Indications for renal ultrasound in the evaluation of CKD

6.4.1 Clinical introduction

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

- determining the presence, size and shape of kidneys and assessing cortical thickness prior to renal biopsy
- identifying obstructive uropathy
- assessing renal scarring
- identifying polycystic kidney disease.[53]

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

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

6.4.2 Methodology

Due to the difficulty in searching this question, the results of a broad literature search were reviewed for systematic reviews on criteria for referral for renal ultrasound in a CKD population. No studies were identified. An algorithm was provided by a GDG member, who had conducted an (unpublished) retrospective analysis of people with CKD undergoing ultrasound scans. The algorithm served as a starting point to guide discussions and enabled the GDG to formulate consensus recommendations.

6.4.3 Health economics methodology

There were no health economics papers found to review.

6.4.4 Evidence statements

There were no clinical papers found to review.

6.4.5 From evidence to recommendation

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

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

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

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

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

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

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

6.4.6 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng203

7 Progression of chronic kidney disease [2014]

7.1 Frequency of monitoring

7.1.1 Introduction

Part 2 of The Renal National Service Framework detailed two key quality requirements; Prevention and early detection of CKD, and Minimising the progression and consequences of CKD. Underpinning these quality requirements was the subsequent introduction of automated GFR reporting and renal indicators in the primary care quality and outcomes framework. These indicators required primary care to produce a register of people with GFR <60 ml/min/1.73 m^2 and to record measures of proteinuria in people on the CKD register. The latter recognises the importance of proteinuria as a predictor of progression of CKD. However, definition of what constitutes progression of CKD has proved difficult. Traditionally progression of CKD was viewed as being linear, although at a variable rate depending on the underlying cause. However, longitudinal whole population studies have shown that a significant proportion of people with CKD do not progress to end stage kidney disease. Furthermore, studies also suggest that when progression occurs it is frequently non-linear, in turn making identification of those at risk from progression problematic. Identifying which people with CKD are at high risk for adverse outcomes is a crucial issue, particularly with respect to the definition of progression of CKD. Rate of change in kidney function based on pooled measures of eGFR across several years is known to predict outcome but guidance concerning how frequently kidney function should be measured, and whether or not this frequency should vary depending on GFR category has

to date been opinion based only (Table 46).

Table 46: Table on frequency of monitoring from CG73

Measurement of eGFR: how often?[a]		
Annually in all at-risk groups.		
During intercurrent illness and peri-operatively in all patients with CKD.		
Exact frequency should depend on the clinical situation. The frequency of testing may be reduced where eGFR levels remain very stable but will need to be increased if there is rapid progression.		
Stage	eGFR range (ml/min/1.73 m^2)	Typical testing frequency
1 and 2	≥60 + other evidence of kidney disease	12 monthly
3a and 3b	30-59	6 monthly
4	15-29	3 monthly
5	<15	6 weekly

(a) The information in this table is based on GDG consensus and not on evidence.

The purpose of this question was to determine how frequently the key measures of CKD, GFR and proteinuria, should be monitored in people with CKD.

7.1.2 Review question: How frequently should eGFR, ACR or PCR be monitored in people with CKD?

This section was partially updated in 2018. See www.nice.org.uk/guidance/NG203/evidence for the 2018 evidence reviews.

For full details see review protocol in Appendix C. In the review a threshold of 25% change in eGFR and cut-offs of 3 and 30mg/mmol for ACR were used to mark significant change at various time points.

Table 47: PICO characteristics of frequency of monitoring review question

Population	Adults (aged 18 and over) with CKD
Prognostic factor	• eGFR measure • ACR measure • PCR measure
Outcomes	• CKD progression: change in eGFR • CKD progression: occurrence of end stage kidney disease (ESRD or ESKD as reported by the study) • All-cause mortality • Cardiovascular mortality
Study design	Prospective cohort studies (or retrospective if no prospective available) Cross sectional studies

7.1.3 Clinical evidence

The evidence review is concerned with the prognosis of people who have a change in eGFR or albuminuria parameters, specifically, how quickly that change occurs and therefore how frequently people should be monitored. The prognostic (or predictive) factor is the change from baseline at particular time point, or the absolute value at two or more time points, in eGFR, ACR or PCR. The review question aims to determine whether these factors are predictive of progression of CKD or mortality, and if so, over what timescale.

Eleven retrospective cohort studies were identified.[13,29,82,147,220,232,244,326,402,403,410] Details have been summarised in Table 48 below. Meta-analysis was not carried out due to differences in reference groups for hazard ratios and covariates included in the multivariate analyses. One study[29] looked specifically at ethnicity. An additional UK study[94] was identified in people with diabetes and CKD including people of South Asian, African or African Caribbean family origin. However the data from this study could not be analysed because only final and change values for eGFR were reported with no standard deviations, standard errors or confidence intervals.

Only two studies[402,403] assessed the data in a way that looked at significant change at a particular time point, in this case monitoring at 1 year and therefore is considered the highest quality evidence. These studies defined change in eGFR as:

- 'certain drop' - drop in CKD category with ≥25% decrease in eGFR;
- 'uncertain drop'- (drop in CKD category with <25% decrease in eGFR;
- 'stable' - no change in CKD category;
- 'uncertain rise' - rise in CKD category with <25% rise in eGFR, and
- 'certain rise' (rise in CKD category with ≥25% increase in eGFR).

In other studies Kaplan Meier curves, if reported, were used to give information about outcomes at different time points to help assess if there was a time point at which this would be significant.

The forest plots in Appendix I are split into those presenting risk of progression, assessed by hazard ratios (appendix I.5.1), and those showing probability of progression in the groups of interest versus a reference group at varying time points, assessed by odds ratios (appendix I.5.2). The latter group of forest plots were used to show patterns of progression as additional information for the GDG and therefore a GRADE profile was not done for these outcomes.

Table 48: Summary of studies included in the review

Study	Comparison	Cohort	Outcomes	Comments
Amin et al. 2013[13]	• Adults with diabetes and	Retrospective	• .All-cause mortality	Results

Study	Comparison	Cohort	Outcomes	Comments
Country: USA	eGFR <105 ml/min/1.73 m^2 or ACR >30mg/g • Adults with diabetes and eGFR ≥105 ml/min/1.73 m^2 or ACR <30mg/g	n=42,761 Follow up: Median 4 years	• Progression to ESRD	stratified by eGFR and ACR separately.
Barbour et al. 2010[29] Country: Canada	• Oriental Asian or South Asian adults with CKD referred to nephrology • Caucasian adults with CKD referred to nephrology	Retrospective n=3444 Follow up: 2-8 years	• All-cause mortality	
de Goeij et al. 2012[82] Country: The Netherlands	• Adults with CKD 4-5 on predialysis care with proteinuria • Adults with CKD 4-5 on predialysis care with no proteinuria	Retrospective n=413 Follow up: Median 11.6 months	• Progression to RRT	
Hoefield et al. 2010[147] Country: UK	• Adults with CKD 3-5 not on dialysis therapy with eGFR <45 ml/min/1.73 m^2 • Adults with CKD 3-5 not on dialysis therapy with eGFR 45-59 ml/min/1.73 m^2	Retrospective n=1325 Follow up: Median 26 months	• All-cause mortality • Progression to RRT	
Levin et al. 2008[220] Country: Canada	• Adults with eGFR <25 ml/min/1.73 m^2 referred to nephrology and on dialysis therapy • Adults with eGFR 25-29 ml/min/1.73 m^2 referred to nephrology and on dialysis therapy	Retrospective n=4231 Follow up: median 31 months	• Mortality before RRT • Progression to RRT	Results stratified by eGFR level.
Lorenzo et al. 2010[232] Country: Spain (Canary Islands)	• Adults with CKD (eGFR <50 ml/min/1.73 m^2) and diabetes • Adults with CKD (eGFR <50 ml/min/1.73 m^2) and no diabetes	Retrospective n=407 Follow up: Mean 30 months	• Dialysis free survival	Analysis restricted to 333 people who had >3 serum creatinine tests.
Marks et al. 2013[244] Country: UK	• Adults with CKD stage 4 • Adults with CKD stage 3 • Adults with CKD stage 3 and 4 with ACR ≥30 • Adults with CKD stage 3 and 4 with ACR ≥3 • Adults with CKD stage 3 and 4 with normoalbuminuria	Retrospective n=3322 Follow up: 6 years	• Progression (sustained drop of eGFR by 15 or to 10ml/min/1.73 m2) • Progression (sustained 25% reduction in eGFR and CKD stage change) • Progression to RRT	
Perkins et al.	• Adults with eGFR 15-59	Retrospective	• All-cause mortality	CKD-EPI serum

Study	Comparison	Cohort	Outcomes	Comments
2011[326] Country: USA	ml/min/1.73 m^2 predialysis with declining or increasing eGFR • Adults with eGFR 15-59 ml/min/1.73 m^2 predialysis with stable eGFR	n=15,465 Follow up: Median 3.4 years		creatinine equation.
Turin et al. 2012[402,403] Country: Canada	• Adults with certain or uncertain drop or rise in eGFR during 1 year accrual period • Adults with stable eGFR during 1 year accrual period	Retrospective n=598,397 Follow up: median 3.5 years (minimum 1 year)	• All-cause mortality • Progression to ESRD	Results stratified by baseline eGFR. No data on ethnicity available. CKD-EPI serum creatinine equation.
Van Pottelbergh et al. 2012[410] Country: Belgium	Adults with ≥4 serum creatinine measurements: • aged 80+ years • aged 65-79 years • aged 50-64 years (reference group)	n=24,682 Follow up: mean 7.8 years	• Progression to ESRD	Results stratified by baseline eGFR. Excluded eGFR <15.

Table 49: Clinical evidence profile: Frequency of monitoring eGFR, ACR or PCR in people with CKD by change in serum creatinine and eGFR subgroups

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	New Comparison	Control	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality - Certain drop; baseline eGFR ≥90[402]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	660/7080 (9.3%)	5829/210520 (2.8%)	HR 1.64 (1.51 to 1.78)	17 more per 1000 (from 14 more to 21 more)	HIGH	CRITICAL
All-cause mortality - Certain drop; baseline eGFR 60-89[402]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2197/8001 (27.5%)	15751/204702 (7.7%)	HR 1.85 (1.76 to 1.94)	61 more per 1000 (from 54 more to 67 more)	HIGH	CRITICAL
All-cause mortality - Certain drop; baseline eGFR 45-59[402]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1159/2734 (42.4%)	5171/26694 (19.4%)	HR 1.82 (1.71 to 1.94)	130 more per 1000 (from 114 more to 148 more)	HIGH	CRITICAL
All-cause mortality - Certain drop; baseline eGFR 30-44[402]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	783/1414 (55.4%)	3790/11111 (34.1%)	HR 2.06 (1.90 to 2.23)	235 more per 1000 (from 206 more to 264 more)	HIGH	CRITICAL
All-cause mortality - Certain drop; baseline eGFR 15-29[402]												
1	Observational studies	No serious risk of	No serious inconsistency	No serious indirectness	No serious imprecision	None	227/362 (62.7%)	1786/3543 (50.4%)	HR 2.07 (1.79 to 2.39)	262 more per 1000 (from 211	HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	New Comparison	Control	Relative (95% CI)	Absolute		
		bias								more to 309 more)		
All-cause mortality - Uncertain drop; baseline eGFR ≥90[402]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1770/42989 (4.1%)	5829/210520 (2.8%)	HR 0.72 (0.68 to 0.76)	8 fewer per 1000 (from 7 fewer to 9 fewer)	HIGH	CRITICAL
All-cause mortality - Uncertain drop; baseline eGFR 60-89[402]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2199/14954 (14.7%)	15751/204702 (7.7%)	HR 0.99 (0.96 to 1.02)	1 fewer per 1000 (from 3 fewer to 1 more)	HIGH	CRITICAL
All-cause mortality - Uncertain drop; baseline eGFR 45-59[402]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1409/4858 (29%)	5171/26694 (19.4%)	HR 1.22 (1.15 to 1.29)	37 more per 1000 (from 26 more to 49 more)	HIGH	CRITICAL
All-cause mortality - Uncertain drop; baseline eGFR 30-44[402]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	500/1138 (43.9%)	3790/11111 (34.1%)	HR 1.24 (1.13 to 1.36)	63 more per 1000 (from 35 more to 92 more)	HIGH	CRITICAL
All-cause mortality - Uncertain drop; baseline eGFR 15-29[402]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	74/128 (57.8%)	1786/3543 (50.4%)	HR 1.64 (1.29 to 2.08)	179 more per 1000 (from 91 more to	HIGH	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	New Comparison	Control	Relative (95% CI)	Absolute	Quality	Importance
										263 more)		
All-cause mortality - Uncertain rise; baseline eGFR 60-89[402]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1570/32161 (4.9%)	15751/204702 (7.7%)	HR 1.81 (1.72 to 1.90)	58 more per 1000 (from 52 more to 64 more)	HIGH	CRITICAL
All-cause mortality - Uncertain rise; baseline eGFR 45-59[402]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1444/9583 (15.1%)	5171/26694 (19.4%)	HR 0.98 (0.93 to 1.03)	3 fewer per 1000 (from 12 fewer to 5 more)	HIGH	CRITICAL
All-cause mortality - Uncertain rise; baseline eGFR 30-44[402]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	761/2739 (27.8%)	3790/11111 (34.1%)	HR 0.84 (0.78 to 0.90)	45 fewer per 1000 (from 28 fewer to 63 fewer)	HIGH	CRITICAL
All-cause mortality - Uncertain rise; baseline eGFR 15-29[402]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	241/515 (46.8%)	1786/3543 (50.4%)	HR 0.85 (0.74 to 0.98)	55 fewer per 1000 (from 7 fewer to 99 fewer)	HIGH	CRITICAL
All-cause mortality - Certain rise; baseline eGFR 60-89[402]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	768/9935 (7.7%)	15751/204702 (7.7%)	HR 4.29 (3.97 to 4.64)	214 more per 1000 (from 195 more to 233 more)	HIGH	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**New Comparison**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
All-cause mortality - Certain rise; baseline eGFR 45-59[402]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1542/7120 (21.7%)	5171/26 694 (19.4%)	HR 1.55 (1.46 to 1.65)	90 more per 1000 (from 76 more to 105 more)	HIGH	CRITICAL
All-cause mortality - Certain rise; baseline eGFR 30-44[402]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1200/3682 (32.6%)	3790/11 111 (34.1%)	HR 1.21 (1.13 to 1.30)	55 more per 1000 (from 35 more to 78 more)	HIGH	CRITICAL
All-cause mortality - Certain rise; baseline eGFR 15-29[402]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	648/1434 (45.2%)	1786/35 43 (50.4%)	HR 0.93 (0.85 to 1.02)	25 fewer per 1000 (from 55 fewer to 7 more)	HIGH	CRITICAL
ESRD -Certain drop; baseline eGFR ≥90[403]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	47/7080 (0.66%)	137/210 520 (0.07%)	HR 4.49 (3.12 to 6.46)	2 more per 1000 (from 1 more to 4 more)	HIGH	CRITICAL
ESRD -Certain drop; baseline eGFR 60-89[403]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	97/8001 (1.2%)	190/204 702 (0.09%)	HR 5.20 (3.94 to 6.86)	4 more per 1000 (from 3 more to 5 more)	HIGH	CRITICAL
ESRD -Certain drop; baseline eGFR 45-59[403]												
1	Observational	No	No serious	No serious	No serious	None	98/2734	96/2669	HR 5.57	16 more	HIGH	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**New Comparison**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
	studies	serious risk of bias	inconsistency	indirectness	imprecision		(3.6%)	4 (0.36%)	(4.11 to 7.55)	per 1000 (from 11 more to 23 more)		
ESRD -Certain drop; baseline eGFR 30-44[403]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	137/1414 (9.7%)	179/11111 (1.6%)	HR 4.02 (3.18 to 5.08)	47 more per 1000 (from 34 more to 63 more)	HIGH	CRITICAL
ESRD -Certain drop; baseline eGFR 15-29[403]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	155/362 (42.8%)	459/3543 (13%)	HR 4.85 (4.01 to 5.87)	360 more per 1000 (from 297 more to 428 more)	HIGH	CRITICAL
ESRD - Uncertain drop; baseline eGFR ≥90[403]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious(a)	None	31/42989 (0.07%)	137/210520 (0.07%)	HR 1.08 (0.72 to 1.62)	0 more per 1000 (from 0 fewer to 0 more)	LOW	CRITICAL
ESRD - Uncertain drop; baseline eGFR 60-89[403]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	38/14954 (0.25%)	190/204702 (0.09%)	HR 1.96 (1.38 to 2.78)	1 more per 1000 (from 0 more to 2 more)	HIGH	CRITICAL
ESRD - Uncertain drop; baseline eGFR 45-59[403]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	47/4858 (0.97%)	96/26694 (0.36%)	HR 1.86 (1.31 to 2.64)	3 more per 1000 (from 1 more to 6 more)	HIGH	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**New Comparison**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
ESRD - Uncertain drop; baseline eGFR 30-44[403]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	65/1138 (5.7%)	179/11111 (1.6%)	HR 2.31 (1.73 to 3.08)	21 more per 1000 (from 12 more to 33 more)	HIGH	CRITICAL
ESRD - Uncertain drop; baseline eGFR 15-29[403]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	55/128 (43%)	459/3543 (13%)	HR 2.93 (2.20 to 3.90)	204 more per 1000 (from 134 more to 288 more)	HIGH	CRITICAL
ESRD - Uncertain rise; baseline eGFR 60-89[403]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	12/32161 (0.04%)	190/204702 (0.09%)	HR 0.38 (0.21 to 0.69)	1 fewer per 1000 (from 0 fewer to 1 fewer)	HIGH	CRITICAL
ESRD - Uncertain rise; baseline eGFR 45-59[403]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious(b)	None	19/9583 (0.2%)	96/266694 (0.36%)	HR 0.65 (0.39 to 1.08)	1 fewer per 1000 (from 2 fewer to 0 more)	MODERATE	CRITICAL
ESRD - Uncertain rise; baseline eGFR 30-44[403]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	17/2739 (0.62%)	179/11111 (1.6%)	HR 0.42 (0.26 to 0.68)	9 fewer per 1000 (from 5 fewer to 12 fewer)	HIGH	CRITICAL
ESRD - Uncertain rise; baseline eGFR 15-29[403]												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**New Comparison**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	14/515 (2.7%)	459/3543 (13%)	HR 0.25 (0.15 to 0.42)	95 fewer per 1000 (from 73 fewer to 109 fewer)	HIGH	CRITICAL
ESRD - Certain rise; baseline eGFR 60-89[403]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious(b)	None	9/9935 (0.09%)	190/204702 (0.09%)	HR 0.63 (0.32 to 1.24)	0 fewer per 1000 (from 1 fewer to 0 more)	MODERATE	CRITICAL
ESRD - Certain rise; baseline eGFR 45-59[403]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious(b)	None	17/7120 (0.24%)	96/26694 (0.36%)	HR 0.58 (0.34 to 0.99)	2 fewer per 1000 (from 0 fewer to 2 fewer)	MODERATE	CRITICAL
ESRD - Certain rise; baseline eGFR 30-44[403]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	22/3682 (0.6%)	179/11111 (1.6%)	HR 0.35 (0.23 to 0.53)	10 fewer per 1000 (from 8 fewer to 12 fewer)	HIGH	CRITICAL
ESRD - Certain rise; baseline eGFR 15-29[403]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	25/1434 (1.7%)	459/3543 (13%)	HR 0.18 (0.12 to 0.27)	105 fewer per 1000 (from 93 fewer to 113 fewer)	HIGH	CRITICAL

(a) 95% confidence intervals cross both minimally important differences making the effect uncertain.
(b) 95% confidence interval crosses one minimally important difference making the effect uncertain.

NB All GFR measurements are in ml/min/1.73 m^2.

Table 50: Clinical evidence profile: Frequency of monitoring eGFR, ACR or PCR in people with CKD

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	New Comparison	Control	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality - overall - Reference stable eGFR; median follow up 3.4[326] to 3.5[402] years												
2	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	20094/161037 (12.5%)	32706/452825 (7.2%)	HR 1.91 (1.85 to 1.97)	61 more per 1000 (from 57 more to 65 more)	HIGH	CRITICAL
All-cause mortality - Amin - Baseline eGFR 90-104 (Reference eGFR ≥105; median follow up 4 years)[13]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	Serious(a)	None	-	-	HR 0.84 (0.66 to 1.07)	-(b)	LOW	CRITICAL
All-cause mortality - Amin - Baseline eGFR 75-89 (Reference eGFR ≥105; median follow up 4 years)[13]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	Serious(a)	None	-	-	HR 0.88 (0.7 to 1.11)	-(b)	LOW	CRITICAL
All-cause mortality - Amin - Baseline eGFR 60-74 (Reference eGFR ≥105; median follow up 4 years)[13]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	Serious(a)	None	-	-	HR 0.92 (0.73 to 1.16)	-(b)	LOW	CRITICAL
All-cause mortality - Amin - Baseline eGFR 45-59 (Reference eGFR ≥105; median follow up 4 years)[13]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	Serious(a)	None	-	-	HR 1.23 (0.97 to 1.56)	-(b)	LOW	CRITICAL
All-cause mortality - Amin - Baseline eGFR 30-44 (Reference eGFR ≥105; median follow up 4 years)[13]												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**New Comparison**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	Serious(a)	None	-	-	HR 1.4 (1.09 to 1.8)	-(b)	LOW	CRITICAL
All-cause mortality - Amin - Baseline eGFR <30 (Reference eGFR ≥105; median follow up 4 years)[13]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	No serious imprecision	None	-	-	HR 1.74 (1.31 to 2.31)	-(b)	MODERATE	CRITICAL
All-cause mortality - Hoefield - Baseline eGFR 30-44 (Reference eGFR 45-59; median follow up 26 months)[147]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	Serious(a)	None	-	-	HR 1.65 (0.98 to 2.78)	-(c)	LOW	CRITICAL
All-cause mortality - Hoefield - Baseline eGFR 15-29 (Reference eGFR 45-59; median follow up 26 months)[147]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	No serious imprecision	None	-	-	HR 2.38 (1.43 to 3.96)	-(c)	MODERATE	CRITICAL
All-cause mortality - Hoefield - Baseline eGFR <15 (Reference eGFR 45-59; median follow up 26 months)[147]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	No serious imprecision	None	-	-	Not estimable	-(c)	MODERATE	CRITICAL
All-cause mortality - Levin - Baseline eGFR 15-24 (Reference eGFR 25-29; median follow up 31 months)[220]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	Serious(a)	None	210/1905 (11%)	168/1679 (10%)	HR 1.25 (1.03 to 1.52)	23 more per 1000 (from 3 more to 48 more)	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	New Comparison	Control	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality - Levin - Baseline eGFR <15 (Reference eGFR 25-29; median follow up 31 months)[220]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	No serious imprecision	None	116/647 (17.9%)	168/1679 (10%)	HR 2.56 (1.87 to 3.5)	136 more per 1000 (from 79 more to 209 more)	MODERATE	CRITICAL
All-cause mortality - proteinuria subgroups - ACR 3-30 (Reference ACR <3; median follow up 4 years)[13]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	No serious imprecision	None	-	-	HR 1.79 (1.62 to 1.98)	-(b)	MODERATE	CRITICAL
All-cause mortality - proteinuria subgroups - ACR >30 (Reference ACR <3; median follow up 4 years)[13]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	No serious imprecision	None	-	-	HR 3.16 (2.7 to 3.7)	-(b)	MODERATE	CRITICAL
Progression of CKD - Reference stable eGFR; median follow up 3.5 years[403]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	534/19591 (2.7%)	1061/447570 (0.24%)	HR 5.11 (4.56 to 5.73)	10 more per 1000 (from 8 more to 11 more)	HIGH	CRITICAL
Progression (sustained drop of eGFR by 15 or to 10ml/min/1.73 m²) - CKD Stage 4 (Reference CKD Stage 3) (follow-up 6 years)[244]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	No serious imprecision	None	114/1044 (10.9%)	361/2289 (15.8%)	HR 0.96 (0.78 to 1.18)	6 fewer per 1000 (from 32 fewer to 26 more)	MODERATE	CRITICAL
Progression (sustained drop of eGFR by 15 or to 10ml/min/1.73m²) – ACR ≥2.5mg/mmol for men or ≥3.5mg/mmol for women (Reference normoalbuminuria)(follow-up 6 years)[244]												
1	Observational	No serious	No serious	Serious(d)	Serious(a)	None	28/178	55/498	HR 1.7 (1.07 to	70 more per 1000	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**New Comparison**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
	studies	risk of bias	inconsistency				(15.7%)	(11%)	2.7)	(from 7 more to 160 more)		
Progression (sustained drop of eGFR by 15 or to 10ml/min/1.73m²) – ACR ≥30mg/mmol (Reference normoalbuminuria) (follow-up 6 years)[244]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	No serious imprecision	None	80/273 (29.3%)	55/498 (11%)	HR 3.14 (2.21 to 4.46)	197 more per 1000 (from 117 more to 296 more)	MODERATE	CRITICAL
Progression (sustained 25% reduction in eGFR and CKD stage change) - CKD Stage 4 (Reference CKD Stage 3) (follow-up 6 years)[244]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	No serious imprecision	None	70/1044 (6.7%)	362/2289 (15.8%)	HR 0.47 (0.36 to 0.61)	80 fewer per 1000 (from 58 fewer to 98 fewer)	MODERATE	CRITICAL
Progression (sustained 25% reduction in eGFR and CKD stage change) – ACR ≥2.5mg/mmmol for men or ≥3.5mg/mmol for women (Reference normoalbuminuria) (follow-up 6 years)[244]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	Serious(a)	None	-	-	HR 1.51 (0.95 to 2.4)	-(e)	LOW	CRITICAL
Progression (sustained 25% reduction in eGFR and CKD stage change) – ACR ≥30mg/mmol (Reference normoalbuminuria) (follow-up 6 years)[244]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	No serious imprecision	None	-	-	HR 3.59 (2.54 to 5.07)	-(e)	MODERATE	CRITICAL
Progression of CKD - ESRD - Amin - Baseline eGFR 90-104 (Reference eGFR ≥105; median follow up 4 years)[13]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	Serious(a)	None	-	-	HR 1.51 (0.77 to 2.96)	-(b)	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**New Comparison**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Progression of CKD - ESRD - Amin - Baseline eGFR 75-89 (Reference eGFR ≥105; median follow up 4 years)[13]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	Serious(a)	None	-	-	HR 1.83 (0.97 to 3.45)	-(b)	LOW	CRITICAL
Progression of CKD - ESRD - Amin - Baseline eGFR 60-74 (Reference eGFR ≥105; median follow up 4 years)[13]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	No serious imprecision	None	-	-	HR 2.86 (1.54 to 5.31)	-(b)	MODERATE	CRITICAL
Progression of CKD - ESRD - Amin - Baseline eGFR 45-59 (Reference eGFR ≥105; median follow up 4 years)[13]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	No serious imprecision	None	-	-	HR 5.93 (3.25 to 10.82)	-(b)	MODERATE	CRITICAL
Progression of CKD - ESRD - Amin - Baseline eGFR 30-44 (Reference eGFR ≥105; median follow up 4 years)[13]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	No serious imprecision	None	-	-	HR 18.48 (10.27 to 33.25)	-(b)	MODERATE	CRITICAL
Progression of CKD - ESRD - Amin - Baseline eGFR <30 (Reference eGFR ≥105; median follow up 4 years)[13]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	No serious imprecision	None	-	-	HR 84.2 (46.57 to 152.25)	-(b)	MODERATE	CRITICAL
Progression to RRT - CKD Stage 4 (Reference CKD Stage 3) (follow-up 6 years)[244]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	No serious imprecision	None	81/1044 (7.8%)	43/2289 (1.9%)	HR 5.6 (3.84 to 8.17)	82 more per 1000 (from 51 more to	MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**New Comparison**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
										125 more)		
Progression to RRT – ACR ≥2.5mg/mmmol for men or ≥3.5mg/mmol for women (Reference normoalbuminuria) (follow-up 6 years)[244]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	Serious(a)	None	-	-	HR 2.07 (0.82 to 5.23)	-(e)	LOW	CRITICAL
Progression to RRT – ACR ≥30mg/mmol (Reference normoalbuminuria) (follow-up 6 years)[244]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	No serious imprecision	None	-	-	HR 5.31 (2.86 to 9.86)	-(e)	MODERATE	CRITICAL
Progression of CKD - RRT - Hoefield - Baseline eGFR 30-44 (Reference eGFR 45-59; median follow up 26 months)[147]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	Serious(a)	None	-	-	HR 1.88 (0.62 to 5.7)	-(c)	LOW	CRITICAL
Progression of CKD - RRT - Hoefield - Baseline eGFR 15-29 (Reference eGFR 45-59; median follow up 26 months)[147]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	No serious imprecision	None	-	-	HR 5.54 (1.96 to 15.66)	-(c)	MODERATE	CRITICAL
Progression of CKD - RRT - Hoefield - Baseline eGFR <15 (Reference eGFR 45-59; median follow up 26 months)[147]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	No serious imprecision	None	-	-	HR 18.82 (6.45 to 54.92)	-(c)	MODERATE	CRITICAL
Progression of CKD - RRT - Levin - Baseline eGFR 15-24 (Reference eGFR 25-29; median follow up 31 months)[220]												
1	Observational studies	No serious risk of	No serious inconsistency	Serious(d)	No serious imprecision	None	667/1905 (35%)	302/1679 (18%)	HR 1.94 (1.73 to 2.18)	139 more per 1000 (from 111	MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	New Comparison	Control	Relative (95% CI)	Absolute	Quality	Importance
		bias								more to 171 more)		
Progression of CKD - RRT - Levin - Baseline eGFR <15 (Reference eGFR 25-29; median follow up 31 months)[220]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	No serious imprecision	None	408/647 (63.1%)	302/1679 (18%)	HR 7.52 (6.32 to 8.95)	595 more per 1000 (from 535 more to 651 more)	MODERATE	CRITICAL
Progression of CKD - proteinuria subgroups - ACR 3-30 (Reference ACR <3; median follow up 4 years)[13]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	No serious imprecision	None	-	-	HR 6.44 (4.81 to 8.62)	-(b)	MODERATE	CRITICAL
Progression of CKD - proteinuria subgroups - ACR >30 (Reference ACR <3; median follow up 4 years)[13]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	No serious imprecision	None	-	-	HR 15.11 (10.9 to 20.95)	-(b)	MODERATE	CRITICAL
Progression of CKD - proteinuria (UPE) - UPE >0.3 to ≤1.0g/24h (Reference no proteinuria; median follow up 11.6 months)[82]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	No serious imprecision	None	72/88 (81.8%)	27/45 (60%)	HR 1.7 (1.05 to 2.75)	189 more per 1000 (from 18 more to 320 more)	MODERATE	CRITICAL
Progression of CKD - proteinuria (UPE) - UPE >1.0 to ≤3.0g/24h (Reference no proteinuria; median follow up 11.6 months)[82]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	No serious imprecision	None	109/132 (82.6%)	27/45 (60%)	HR 1.87 (1.17 to 2.99)	220 more per 1000 (from 58 more to 335 more)	MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	New Comparison	Control	Relative (95% CI)	Absolute	Quality	Importance
Progression of CKD - proteinuria (UPE) - UPE >3.0 to ≤6.0g/24h (Reference no proteinuria; median follow up 11.6 months)[82]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	No serious imprecision	None	92/101 (91.1%)	27/45 (60%)	HR 2.62 (1.59 to 4.32)	309 more per 1000 (from 167 more to 381 more)	MODERATE	CRITICAL
Progression of CKD - proteinuria (UPE) - UPE >6.0g/24h (Reference no proteinuria; median follow up 11.6 months)[82]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	No serious imprecision	None	44/47 (93.6%)	27/45 (60%)	HR 2.52 (1.45 to 4.38)	301 more per 1000 (from 135 more to 382 more)	MODERATE	CRITICAL
Progression of CKD - ESRD; Age 65-79, Baseline eGFR >60 (referent group age 50-64) (follow-up mean 7.8 years)[410]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	No serious imprecision	None	25/6277 (0.4%)	23/12833 (0.18%)	HR 2.49 (2.41 to 2.57)	3 more per 1000 (from 3 more to 3 more)	MODERATE	CRITICAL
Progression of CKD -ESRD; Age 65-79, Baseline eGFR 45-60 (referent group age 50-64) (follow-up mean 7.8 years)[410]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	No serious imprecision	None	27/2002 (1.3%)	5/1185 (0.42%)	HR 2.78 (2.61 to 2.96)	7 more per 1000 (from 7 more to 8 more)	MODERATE	CRITICAL
Progression of CKD - ESRD; Age 65-79, Baseline eGFR 30-45 (referent group age 50-64) (follow-up mean 7.8 years)[410]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	Serious(a)	None	30/401 (7.5%)	12/109 (11%)	HR 0.7 (0.62 to 0.79)	32 fewer per 1000 (from 22 fewer to 40 fewer)	LOW	CRITICAL
Progression of CKD - ESRD; Age 65-79, Baseline eGFR 15-30 (referent group age 50-64) (follow-up mean 7.8 years)[410]												
1	Observational	No serious	No serious	Serious(d)	Serious(a)	None	24/63	21/33	HR 0.58 (0.41 to	193 fewer per 1000	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**New Comparison**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
	studies	risk of bias	inconsistency				(38.1%)	(63.6%)	0.82)	(from 73 fewer to 297 fewer)		
Progression of CKD - ESRD; Age 80+, Baseline eGFR >60 (referent group age 50-64) (follow-up mean 7.8 years)[410]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	No serious imprecision	None	6/821 (0.73%)	23/12833 (0.18%)	HR 4.43 (4.03 to 4.87)	6 more per 1000 (from 5 more to 7 more)	MODERATE	CRITICAL
Progression of CKD - ESRD; Age 80+, Baseline eGFR 45-60 (referent group age 50-64) (follow-up mean 7.8 years)[410]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	No serious imprecision	None	7/562 (1.2%)	5/1185 (0.42%)	HR 2.55 (2.15 to 3.02)	7 more per 1000 (from 5 more to 8 more)	MODERATE	CRITICAL
Progression of CKD - ESRD; AGe 80+, Baseline eGFR 30-45 (referent group age 50-64) (follow-up mean 7.8 years)[410]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	No serious imprecision	None	18/330 (5.5%)	12/109 (11%)	HR 0.52 (0.43 to 0.63)	51 fewer per 1000 (from 39 fewer to 61 fewer)	MODERATE	CRITICAL
Progression of CKD - ESRD; Age 80+, Baseline eGFR 15-30 (referent group age 50-64) (follow-up mean 7.8 years)[410]												
1	Observational studies	No serious risk of bias	No serious inconsistency	Serious(d)	No serious imprecision	None	13/66 (19.7%)	21/33 (63.6%)	HR 0.3 (0.23 to 0.39)	375 fewer per 1000 (from 310 fewer to 429 fewer)	MODERATE	CRITICAL

(a) 95% confidence interval crosses one minimally important difference making the effect uncertain.
(b) Unable to calculate absolute effect as only incidence per 1,000 person years reported.
(c) Unable to calculate absolute effect as number of events for mortality or RRT not reported.
(d) Study does not look at significant change after monitoring at a particular time point.
(e) Unable to calculate absolute effect as only rate per 100 person years reported.
NB All GFR measurements are in ml/min/1.73 m^2.

7.1.4 Economic evidence

Published literature

No relevant economic evaluations comparing the frequency of monitoring were identified.

7.1.5 Evidence statements

Clinical

Mortality

- High quality evidence from one study[402] showed an increased risk of mortality for people with a certain drop in eGFR at one year for all baseline eGFR categories compared to those whose eGFR remained stable. This was also true for a certain rise in eGFR for those with a baseline eGFR 45-8 ml/min/1.73 m^2.
- There was a two-fold increase in mortality with a drop in eGFR compared to those with a stable eGFR.[326,402]
- Other studies showed an increasing risk of mortality with lower baseline eGFR and with higher baseline ACR.[13,147,220]

Progression of CKD

- Moderate to high quality evidence from one study[403] showed a 4-5 times increased risk ESRD (by one-year change in kidney function) for people with a certain drop in eGFR at one year for all baseline eGFR categories compared to those whose eGFR remained stable. An uncertain drop in eGFR also conferred a 2-3 times increased risk of ESRD. Any rise in eGFR was protective against progression to ESRD at all baseline eGFR levels.
- Other studies showed an increasing risk of ESRD with lower baseline eGFR and with higher baseline ACR.[13,82,147,220]
- One study provided moderate to low quality evidence that increasing proteinuria was associated with an increased risk of progression defined by either a sustained drop in eGFR by 15 or to 10ml/min/1.73 m^2 or defined as a sustained 25% reduction in eGFR and CKD stage change.[244] The same study found a 5 times increased risk of progression to RRT with CKD stage 4 compared to stage 3 and with ACR >30 compared to no proteinuria.
- There was an increased risk, over a period of 7.8 years, of ESRD in older people (aged 65-79 and over 80 years) with baseline eGFR 45-60 or >60 ml/min/1.73 m^2 compared to people aged 50-64 ml/min/1.73 m^2 in the same eGFR categories. The opposite was true with lower baseline eGFR values.

Economic

- No relevant economic evaluations were identified.

7.1.6

Recommendations	The current recommendations can be found at www.nice.org.uk/guidance/ng203
Relative values of different outcomes	The GDG agreed that progression of CKD (measured by change in eGFR) and mortality (All-cause and CVD) were equally important outcomes for decision making to determine the frequency of monitoring of eGFR.
Trade off between clinical benefits and harms	It was highlighted that both a 25% increase in eGFR and a 25% decrease in eGFR were associated with an increased mortality risk. Although this was surprising, it was considered important to highlight. However, the same was not true for the risk of ESRD, where only a decrease in eGFR was associated with an increased risk, as would have been expected. The GDG noted that although previously people have made the assumption that progression of CKD is linear, data have recently been published indicating that CKD progression is non-linear,[226,301] and this is important to take into account when determining monitoring frequencies. It is also possible that kidney function and eGFR can often remain stable. (See chapter 7.2 for recommendations on progression). It was considered that the factors which matter most to the person with CKD are: • How often do they need to be checked in order to know whether there is something wrong, and whether something should be done about it? • Whether things are changing and whether their management needs to change and the consequence of that? For clinicians it may also include: • How many measurements are needed to know whether a change has been significant? • What is the variability of the measurement and the error of that measurement? • When is a change a true change? • Does the change matter? The GDG considered that knowing whether a change mattered was important to ensure that people were not over-treated, and whether or not a change was a true change. The answers to the above would also be important in informing patients of their prognosis. The GDG noted that although a general guide on frequency of monitoring could be provided, it should be tailored to the individual. For people with a history of erratic kidney function it may be necessary to monitor more frequently. Whereas, someone who has been stable for a long period of time may require less frequent monitoring. Some people are happy to have regular monitoring, however others find it an inconvenience, for example due to having to take time off work. The GDG recognised that there was an important trade-off between what is seen at a population level, i.e. that people are at a greater risk of adverse outcomes when their eGFR drops below 45ml/min/1.73 m^2, and the preferences and individual needs of the person with CKD. Comorbidities and intercurrent illness would also indicate whether additional monitoring was necessary.

	Patients with heart failure are particularly sensitive to alterations in renal perfusion. The effective arterial blood volume tends to be reduced in these patients, and even minor manipulations in renin-angiotensin blocking drugs or diuretics may result in significant changes in eGFR. Additional monitoring after such changes should therefore be considered
Economic considerations	Monitoring of CKD can be resource intensive both to the patient and the NHS. There was no economic evidence identified and the GDG wanted to reduce any unnecessary monitoring of kidney function. The GDG felt that periodic monitoring of kidney function could increase immediate costs of CKD management but was appropriate given the potential to reduce long term costs and negative health outcomes due to CKD progression and associated adverse events. The GDG considered that the frequency of monitoring should be determined by the stability of kidney function and the level of ACR. In light of clinical evidence, the GDG considered that the increased cost of more frequent monitoring for people with a high level of ACR was likely to be a good use of NHS resources given a patient's high risk of negative health consequences associated with CKD. The GDG also noted that some patients would have relatively stable kidney function. The GDG felt these patients would not benefit from frequent monitoring of CKD and hence recommended that monitoring should be kept to a minimum in such cases. The frequency of monitoring suggested in Table 51 represents less frequent monitoring than advocated in CG73 and therefore is likely to improve the efficiency of care for CKD patients. For example most patients at GFR 30-59 ml/min/1.73 m^2 annual monitoring is recommended (not 6 monthly) and for many patients eGFR ≥60 ml/min/1.73 m^2 can be seen less than annually.
Quality of evidence	The GDG noted that there was a lack of literature that directly answered the review question. It was also acknowledged that it would be very difficult to conduct a study to address this. Only one study identified for this review directly met the review question. [402] However, outcomes were only reported after monitoring at one time point (one year). This does not provide the GDG with information about whether testing should be every 3 months in someone with an eGFR of 25 ml/min/1.73 m^2, or every 6 months in someone with eGFR of 40 ml/min/1.73 m^2 for example. As this did not inform the review question, additional data was extracted from studies which reported progression of CKD over time. Although this was indirect evidence outcomes were predominately from high to moderate quality evidence. Covariates had been included in the analyses in the majority of cases. The recommendation was made largely based on consensus, using the available evidence to help inform the decisions made. The probability of ESRD at varying time points by eGFR category versus reference group (eGFR ≥105 ml/min/1.73 m^2) reported by Amin et al[13] indicated that only at eGFR levels <29 ml/min/1.73 m^2 was the risk significantly increased at all measured time points. At eGFRs of 30-34 ml/min/1.73 m^2 the increased risk was approaching significance at 12 months and was significant after 18 months. The GDG agreed that this was useful to inform rates of progression of CKD in people with diabetes. The evidence showed that at any GFR category, outcomes were worse at increasing ACR categories. For eGFR <30 ml/min/1.73 m^2 with proteinuria, the GDG agreed that people are at great risk of needing renal replacement therapy and hence should be seen more frequently. There was evidence from one UK, retrospective cohort study[94] in people with diabetes and CKD that compared to white (British, Irish or other white) ethnicity there was an increased rate of kidney function decline in people with an African/African Caribbean or South Asian family origin with proteinuria and in people of a South Asian family origin with no proteinuria. However the data

	from this study could not be analysed because only final and change values for eGFR were reported with no standard deviations, standard errors or confidence intervals.
Other considerations	Underlying individual causes of CKD, intercurrent illness and changes in drug therapy may all have an impact on progression of CKD but the evidence presented does not enable further deliberation and conclusion to determine different monitoring strategies. Similarly although the annualised rate of eGFR progression (mean ± SD, median [IQR] and range) in a study of patients with diabetes and CKD showed that Black African/Caribbeans with proteinuria were most likely to have progression of CKD , followed by South Asians and then Caucasians, the data presented did not enable determination of different monitoring strategies (Dressler et al.). The recommendation of a guide to frequency of monitoring relates to eGFR. The GDG agreed it was unnecessary for ACR to be monitored every time eGFR was measured. Exceptions may be when evaluating response to a treatment strategy targeted at reduction in proteinuria. For example, the dose of ACE inhibitor or ARB may need to be increased if the required reduction in proteinuria has not been achieved. The GDG agreed that monitoring could be done by, for example, a nurse or a pharmacist as well as a doctor. The GDG voted to have recommendation 37 as a key priority for recommendation. They felt that it would a have a high impact on outcomes that are important to patient and on reducing variation in care. They felt that the actions were measurable and it would set challenging but achievable expectations of health services. The recommendation focuses on key infrastructural and clinical requirements for high-quality care. They wished to highlight that as this is a change in practice, educational and implementation support would be required.

7.2 Defining progression [2014]

7.2.1 Clinical introduction

The Renal NSF adopted the US National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) classification of CKD.[288] Whilst the beauty of this classification was its simplicity, this was also its weakness. The clinical features and course of CKD are dependent on a number of factors including the underlying cause, severity and associated conditions of the underlying cause.

NICE Clinical Guideline 73 updated the NKF-KDOQI classification to subdivide the GFR category 30-59 ml/min/1.73 m^2 into 2 separate categories (45-59 and 30-44 ml/min/1.73 m^2) and also recommended introduction of the suffix '(p)' in parenthesis to underline the importance of proteinuria/albuminuria as an independent risk factor for adverse outcomes. In this update of NICE CG73 the classification has been further updated to reflect new data with respect to urinary albumin:creatinine ratio as a predictor of adverse outcome. We have recommended a combination of GFR and ACR categories (as described in Table 27 of Chapter 6.1) to classify CKD which recognises that both increasing levels of ACR and decreasing levels of GFR are associated with increased risk, and that ACR and GFR are risk multipliers in combination.

We further recommend that the approach to CKD should not be determined solely by age and that both GFR and ACR categories should be used to assess and discuss the person's risk of adverse outcomes (for example, progression of CKD) – see Chapter 6.1

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

Although this question was not updated as part of this guideline, the frequency of monitoring chapter (section 7.1) is concerned with the prognosis of people who have a change in eGFR or albuminuria parameters, specifically, how quickly that change occurs. The frequency of monitoring chapter and the progression chapter are therefore inextricably linked and the GDG agreed the evidence reviewed in the frequency of monitoring chapter was important enough to justify changes to the original recommendations in this section. The changes made to the original recommendations are explained at the end of the 'from evidence to recommendations' section below (7.2.5).

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

This section was updated and replaced in 2018. See www.nice.org.uk/guidance/NG203/evidence for the 2018 evidence reviews.

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7.3 Risk factors associated with progression of CKD (2008)

7.3.1 Clinical introduction

In the literature, progression of kidney disease has been variously defined as doubling of serum creatinine, declining GFR or creatinine clearance, increasing proteinuria/albuminuria, and progression to renal replacement therapy (RRT, dialysis or kidney transplantation) or end stage

kidney disease. The list of possible factors associated with progression does not consider how differences in access to healthcare and poverty may influence the initiation and progression of CKD. Specifically, neither early life influences governing foetal development and low birth weight nor childhood factors contributing to the emergence of hypertension and diabetes are considered here.[79,211,234]

Whilst it is clear that CKD is common, and recently published studies suggest that its prevalence is increasing,[71] it is also clear that many people with diagnosed CKD do not progress.[180,189] Importantly, their risk of cardiovascular disease is massively increased compared to the general population. In those that do progress, the subsequent mortality and morbidity risks rise exponentially, as do the associated healthcare costs. A reduced GFR is also associated with a wide range of complications such as hypertension, anaemia, renal bone disease, malnutrition, neuropathy and reduced quality of life. It is therefore important to clarify exactly what factors are associated with CKD progression, and which are remediable or potentially modifiable, in order to intervene at the earliest possible stage and improve the associated adverse outcomes.

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

7.3.2 Methodological introduction

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

In a pooled analysis of the ARIC Study and Cardiovascular Health Studies (CHS), kidney function decline (serum creatinine increase ≥0.4 mg/dl or a GFR decrease ≥15 ml/min/1.73 m^2) in people with cardiovascular disease (n=1787, mean age 60 years) was compared with people without cardiovascular disease (n=12,039, mean age 57 years, 9.3 years follow-up).[100]

A Swedish case series investigated the effect of BMI on progression to RRT in people with stage 4 and 5 CKD (n=920, mean follow-up 2 years).[101]

The effect of smoking on kidney functional decline was examined in two diabetic cohort studies and two case-control studies. A diabetic cohort of smokers (n=44, mean age 47 years, 86% had baseline proteinuria > 0.15 g/d) were followed for 5.1 years (median) and changes in proteinuria and GFR (20% decline) were compared with non-smokers (n=141, mean age 54 years, 72% had baseline proteinuria >0.15 g/d).[308] In a Danish cohort of people with type 1 diabetes and persistent albuminuria >300 mg/24 h, changes in GFR during a median follow-up of 7 years were compared between smokers (n=176), non-smokers (n=94) and ex-smokers (n=31).[155] In a case-control study, men with autosomal dominant polycystic kidney disease (ADPKD) or immunoglobulin-A glomerulonephritis (IgA-GN) who had progressed to ESRD were matched with controls with ADPKD or IgA-GN who had not progressed to ESRD. Progression to ESRD was compared between males who smoked for 0–5 pack-years (n=73), 5–15 pack years (n=28), or >15 pack years (n=43).[309] In a Spanish case control study, cases (people who had progressed to ESRD, n=520) were age-, sex- and hospital-matched with controls (hospital patients who had not progressed to ESRD, n=982) and the effects of smoking compared with non-smoking on progression to ESRD were analysed.[162]

An English cross-sectional study of renal units examined rates of acceptance to RRT in Caucasians compared with Asians or blacks (n =5901).[351] A London, UK case series investigated doubling of serum creatinine and the rate of serum creatinine increase in Caucasian (n=24), Indo-Asian (n=10), and African-Caribbean (n=11) people with type 2 diabetes and nephropathy.[96] A case series of US Medicare beneficiaries over 65 years old examined progression to ESRD in black (n=94,511) compared with white people (n=1,163,868) in the presence of diabetes, hypertension or neither comorbid condition. It was difficult to determine whether these participants had CKD at baseline[428]

Four studies assessed the effect of chronic NSAID use on progression of kidney disease. One small, open-label RCT compared changes in creatinine clearance and adverse events with chronic use of ibuprofen, piroxicam, or sulindac in adults aged over 65 years with (CrCl <70 ml/min, n=15) or without renal insufficiency (CrCl > 70 ml/min, n=14) [268]. In two Spanish case control studies, cases (people who had progressed to ESRD, n=520) were age-, sex- and hospital-matched with controls (hospital patients who had not progressed to ESRD, n=982) and the effects of chronic use of salicylates, pyrazolones and non-aspirin NSAIDs on progression to ESRD were analysed.[162,262] In a Swedish case-control study, cases (patients with ‘chronic kidney failure’, n=926) were age and sex matched to controls (n=998) and the risk of chronic kidney failure (serum creatinine >3.4 mg/dl in men or >2.8 mg/dl in women) in regular or sporadic users of aspirin was compared with non-users.[105]

Table 53(page 195) summarises risk factors for progression of CKD.

7.3.3 Health economics methodology

There were no health economics papers found to review.

7.3.4 Evidence statements

Effect of cardiovascular disease on progression of CKD

People with baseline cardiovascular disease had a significantly increased risk of a decline in kidney function compared with people without CVD at baseline.[100] (Level 3)

Effect of obesity on progression of CKD

In a Swedish case series, BMI was NS associated with risk of kidney disease progression.[101] (Level 3)

Effect of smoking on progression of CKD

In a cohort study of adults with diabetic nephropathy, smokers had significantly increased odds of a 20% decline in GFR compared with non-smokers. This relationship persisted after adjustment for diabetes type or control, retinopathy, age, BMI, ACE inhibitor use, BP, proteinuria. Proteinuria increased in both smokers and non-smokers, but there were NS differences between the two groups.[308] (Level 2+)

In a cohort of adults with type 1 diabetic nephropathy, there were NS differences in annual GFR decline between smokers, non-smokers, and ex-smokers.[155] (Level 2+)

Two case control studies showed that smoking was significantly associated with progression to ESRD. When ACE inhibitor use was taken into account, the association between smoking and progression to ESRD was NS.[162,309] (Level 2+)

Effect of ethnicity on progression of CKD

In a cross-sectional analysis, Asian people (RR 5.5, 95% confidence interval (CI) 4.7–7.2) and black people (RR 6.5, 95% CI 5.1–8.3) had significantly higher rates of RRT compared with Caucasians due to diabetic kidney disease. Asian people (RR 2.2, 95% CI 1.2–4.1) and black people (RR 3.2, 95% CI 1.4–7.2) had significantly higher rates of RRT compared with Caucasians due to hypertension.[351] (Level 3)

In people with type 2 diabetes and nephropathy, 100% of Indo-Asian people (n=10) experienced a doubling of serum creatinine compared with 45% of African-Caribbean people (n=11) and 50% of Caucasians (n=24) (p=0.025) during follow-up. The mean rise in serum creatinine in Indo-Asian people was significantly greater than in African-Caribbean or Caucasians.[96] (Level 3)

In a US case series, black people with baseline diabetes (n=25,049) were 2.4 times more likely (CI not given) to develop ESRD than Caucasians with baseline diabetes (n=175,313). Compared with white people with baseline hypertension (n=426,300), black people with baseline hypertension (n=51,016) were 2.5 times more likely (CI not given) to develop ESRD. Compared with white people with neither baseline hypertension nor diabetes (n=4,651,490), black people with neither hypertension nor diabetes at baseline (n=34,916) were 3.5 times more likely (CI not given) to develop ESRD.[428] (Level 3)

Effect of chronic use of NSAIDs on progression of CKD

In people with creatinine clearance <70 ml/min, there were NS changes in creatinine clearance from baseline after 1 month of ibuprofen. However, 1 month treatment of piroxicam or sulindac was associated with a significant decrease in creatinine clearance.[268] (Level 1+)

In two case-control studies, users of salicylates had a significantly increased risk of ESRD compared with nonusers. Users of pyrazolones had NS risk of ESRD compared with nonusers. Users of non-aspirin NSAIDs had NS risk of ESRD compared with nonusers.[162,262] (Level 2+)

In a case-control study, an average intake >500 g/year of aspirin significantly increased the risk of chronic kidney failure (adjusted OR 3.3, 95% CI 1.4–8.0). Sub-analysis showed regular use of aspirin compared with non-use of aspirin was significantly associated with increased risk of chronic kidney failure in people with diabetic nephropathy, glomerulonephritis, nephrosclerosis, or hereditary kidney disease.[105] (Level 2+)

Table 53: Summary of risk factors for progression of CKD with associated odds ratios (OR) or relative risks (RR). 95% confidence levels in parentheses

Reference	Study	Risk factor	Population	n	Outcome	Effect size

Reference	Study	Risk factor	Population	n	Outcome	Effect size
[100]	Case series	Cardiovascular disease (CVD)	No baseline CVD	12039	Serum creatinine increase of 0.4 mg/dl	Reference group
			Baseline CVD	1787	Serum creatinine increase of 0.4 mg/dl	OR 1.70 (1.36-2.13), p<0.001
			No baseline CVD	12039	GFR decrease of 15 ml/min/1.73 m^2	Reference group
			Baseline CVD	1787	GFR decrease of 15 ml/min/1.73 m^2	OR 1.28 (1.13-1.46), p<0.001
[101]	Case series	Obesity	CKD + BMI 20.1-25 kg/m^2	377	Requirement for RRT	Reference group
			CKD + BMI ≤ 20 kg/m^2	77	Requirement for RRT	RR 1.26 (0.95-1.67)
			CKD + BMI 25.1-30 kg/m^2	314	Requirement for RRT	RR 0.79 (0.67-0.94)
			CKD + BMI >30 kg/m^2	26	Requirement for RRT	RR 0.86 (0.68-1.07)
[308]	Cohort	Smoking	Non-smokers + diabetic nephropathy	141	20% decline in GFR	Reference group
			Smokers + diabetic nephropathy	44	20% decline in GFR	OR 2.52 (1.06-5.99), p <0.01
			Non-smokers + diabetic nephropathy	141	Changes in proteinuria	Reference group 0.47 baseline to 0.54 g/24 h
			Smokers + diabetic nephropathy	44	Changes in proteinuria	0.36 baseline to 0.44 g/24 h NS compared to non-smokers
[155]	Cohort	Smoking	Non-smokers + type 1 diabetic nephropathy	94	GFR Decline	mean decline 4.4 ml/min/year
			Ex-smokers + type 1 diabetic nephropathy	31	GFR Decline	mean decline 3.4 ml/min/year
			Smokers + type 1 diabetic nephropathy	176	GFR Decline	mean decline 4.0 ml/min/year NS differences between groups
[309]	Case control (ADPKD and IgA-GN with ESRD matched	Smoking	Men smoking 0-5 pack-years	Cases =26 controls =47	ESRD	Reference group
			Men smoking 5-15 pack-years	cases =17 controls =11	ESRD	OR 3.5 (1.3-9.6), p=0.017
			Men smoking	Cases =29	ESRD	OR 5.8 (2.0-17),

Reference	Study	Risk factor	Population	n	Outcome	Effect size
	to non-ESRD controls)		>15 pack-years	controls =14		p=0.001
			Men smoking 0-5 pack-years and no ACE inhibitor	No ACE inhibitor use: cases = 54 controls = 42	ESRD	Reference group
			Men smoking > 5 pack-years and no ACE inhibitor		ESRD	OR 10.1 (2.3-45), p=0.002
			Men smoking 0-5 pack-years and received ACE inhibitor	ACE inhibitor use: cases=18 controls = 30	ESRD	Reference group
			Men smoking > 5 pack-years and received ACE inhibitor		ESRD	1.4 (0.3-7.1), p=0.65
[162]	Case control (patients with ESRD matched to non-ESRD controls)	Smoking	Non-smokers	Not stated	ESRD	Reference group
			Smokers	Cases=320 controls = 577	ESRD	OR 1.54 (1.14-2.07)
[351]	Cross-sectional	Ethnicity	Caucasian men	3063	Acceptance to RRT	Reference group
			Asian men	262	Acceptance to RRT	RR 3.1 (2.7-3.5)
			Black men	161	Acceptance to RRT	RR 3.0 (2.6-3.5)
			Caucasian women	1871	Acceptance to RRT	Reference group
			Asian women	178	Acceptance to RRT	RR 3.9 (3.3-4.5)
			Black women	111	Acceptance to RRT	RR 3.4 (2.8-4.1)
[96]	Case series	Ethnicity	Indo-Asian people with type 2 diabetes and nephropathy	10	Doubling of serum creatinine	100%
			Caucasians with type 2 diabetes and nephropathy	24	Doubling of serum creatinine	50%, p=0.025
			African-Caribbean people with type 2 diabetes and nephropathy	11	Doubling of serum creatinine	45%, p=0.025
			Indo-Asian	10	Rate of serum	5.36

Reference	Study	Risk factor	Population	n	Outcome	Effect size
			people with type 2 diabetes and nephropathy		creatinine increase	µmol/l/month
			Caucasians with type 2 diabetes and nephropathy	24	Rate of serum creatinine increase	2.22 µmol/l/month, p=0.031
			African-Caribbean people with type 2 diabetes and nephropathy	11	Rate of serum creatinine increase	3.14 µmol/l/month, p=0.031
[428]	Case series	Ethnicity	White men with baseline hypertension	Not stated	ESRD	Reference group
			Black men with baseline hypertension	Not stated	ESRD	HR 2.12 (1.90-2.36)
			White men with baseline diabetes	Not stated	ESRD	Reference group
			Black men with baseline diabetes	Not stated	ESRD	HR 2.05 (1.87-2.25)
			White men no hypertension, no diabetes	Not stated	ESRD	Reference group
			Black men no hypertension, no diabetes	Not stated	ESRD	HR 3.27 (2.55-4.19)
[268]	RCT	Chronic NSAID use	1 month of ibuprofen in people with CrCl <70 ml/min	15	Change in creatinine clearance from baseline	1.00 ml/min vs. 1.00 ml/min, 0% change, NS
			1 month of piroxicam in people with CrCl <70 ml/min	15	Change in creatinine clearance from baseline	1.12 ml/s vs. 1.00 ml/s, 12% decrease, p=0.022
			1 month of sulindac in people with CrCl <70 ml/min	15	Change in creatinine clearance from baseline	1.10 ml/s vs. 0.98 ml/s, 11% decrease, p=0.022
[262]	Case control (patients with ESRD	Chronic NSAID use	Non-users of salicylates	Not stated	ESRD	Reference group
			Users of salicylates	Cases =23 Controls =21	ESRD	OR 2.54 (1.24-5.20)

Reference	Study	Risk factor	Population	n	Outcome	Effect size
	matched to non-ESRD controls)		Non-users of pyrazolones	Not stated	ESRD	Reference group
			Users of pyrazolones	Cases =15 Controls =13	ESRD	OR 2.16 (0.87-5.32)
[162]	Case control (patients with ESRD matched to non-ESRD controls)	Chronic NSAID use	Non-users of aspirin	Not stated	ESRD	Reference group
			Users of Aspirin	Cases =81 Controls =94	ESRD	OR 1.56 (1.05-2.30)
			Non-users of pyrazolones	Not stated	ESRD	Reference group
			Users of pyrazolones	Cases =34 Controls =51	ESRD	OR 1.03 (0.60-1.76) NS
			Non-users of non-aspirin NSAIDs	Not stated	ESRD	Reference group
			Users of non-aspirin NSAIDs	Cases =37 Controls =51	ESRD	OR 0.94 (0.57-1.56) NS
[105]	Case control (patients with CRF matched with non-CRF controls)	Chronic NSAID use	Non-users of aspirin	Cases =224 Controls =363	Chronic renal failure (serum creatinine > 3.4 mg/dl, men or > 2.8 mg/dl, women)	Reference group
			Sporadic users of aspirin	Cases =459 Controls =496	Chronic renal failure (serum creatinine > 3.4 mg/dl, men or > 2.8 mg/dl, women)	OR 1.5 (1.2-1.8)
			Regular users of aspirin	Cases =213 Controls =141	Chronic renal failure (serum creatinine > 3.4 mg/dl, men or > 2.8 mg/dl, women)	OR 2.5 (1.9-3.3)

CRF = chronic renal failure.

7.3.5 From evidence to recommendations

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

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

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

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

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

Despite the lack of evidence for urinary outflow tract obstruction for progression of CKD, the GDG consensus was that obstruction to outflow would lead to progression of CKD if it was not treated. Therefore it was agreed that untreated urinary outflow tract obstruction should be considered as a risk factor.

One further risk factor, acute kidney injury (AKI), was considered in the guideline update and the evidence is presented in section 7.4. This evidence review in this section showed an increased risk of progression of CKD with AKI. The GDG agreed that AKI should be added to the list of risk factors for progression of CKD in the recommendation below.

7.3.6 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng203

Risk factors associated with progression of CKD (2014) – Acute kidney injury

Introduction

Acute kidney injury (AKI) is a Department of Health priority, highlighted by the NCEPOD report 'Adding insult to injury' and reflected in recently published NICE clinical guidance 169 'Acute kidney injury: Prevention, detection and management of acute kidney injury up to the point of renal replacement therapy'.[276] Traditionally it was believed that the vast majority of people surviving an episode of AKI made a full recovery with no long term consequences. Although CKD has been known to be a risk factor for development of AKI for decades it is only more recent epidemiological study, using internationally accepted definitions of AKI, that has brought about the realisation that AKI is a common clinical problem with significant immediate and long term implications for health. These include both progression of pre-existing CKD and development of new CKD. The purpose of this question was to explore this risk relationship.

[J] This recommendation has been updated. However, only acute kidney injury was included in the evidence review. The other bullet points were not reviewed for this update and so we will not be able to accept comments on these.

7.4.2 Review question: What is the risk of developing and/or progression of CKD after an episode of AKI?

For full details see review protocol in Appendix C.

Table 54: PICO characteristics of CKD after AKI review question

Population	Adults (aged 18 and over) Subgroups: People aged over 75 years
Presence of prognostic factor	Prior episode of acute kidney injury
Absence of prognostic factor	No history of acute kidney injury
Outcomes	• Incident CKD • CKD progression:change in eGFR • CKD progression: occurrence of end stage kidney disease (ESRD or ESKD as reported by the study)
Study design	• Prospective cohort studies • Cross sectional studies

7.4.3 Clinical evidence

We searched for cohort studies of people with a history AKI compared to those without a history AKI.

Eleven studies were identified. Five studies included results for people with de-novo CKD (eGFR <60 ml/min/1.73 m^2) after an episode of AKI[12,169,175,183,416] and five studies that looked at progression in people with prior CKD after an episode of AKI .[12,160,169,175,209] Five studies only gave results for a mixed population of people with and without CKD at baseline.[174,230,293,393,416] Two studies[169,293] looked specifically at outcomes in older people.

The quality of studies was assessed and presented in an adapted GRADE profile according to criteria stated in the methodology checklist for prognostic studies in the guidelines manual. Evidence from these are summarised in the clinical GRADE evidence profile below (Table 56). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

Summary of included studies

The included studies had different comparator groups. Only 2 studies stratified results by eGFR level,[175,393] and two studies by severity of AKI.[174,293] Details have been summarised in Table 55 below.

Table 55: Summary of studies included in the review

Study	Comparison	Cohort	Outcomes	Comments
Amdur et al. 2009[12]	People with: • acute renal failure (ARF)	Retrospective analysis of a	• Progression to CKD stage 4.	Control group:

Study	Comparison	Cohort	Outcomes	Comments
Country: USA	• acute tubular necrosis (ATN) • chronic kidney disease with either ARF or ATN • control group.	database of people with a primary diagnosis of acute renal failure, acute tubular necrosis or pneumonia or myocardial infarction. n=113,272 Follow-up: Up to 5 years.	.	people with acute admission for MI or pneumonia with no ATN or ARF. Veterans population
Hsu et al. 2009[160] Country: USA	• People with CKD and dialysis-requiring acute renal failure who did not develop ESRD within 30 days of discharge • People with CKD and no dialysis-requiring acute renal failure who did not develop ESRD within 30 days of discharge.	Retrospective analysis of a database; people who had ≥1 outpatient eGFR <45 ml/min/1.73 m^2 and hospitalisation. n=39,805 Follow-up: 6 months.	• ESRD (RRT)	
Ishani et al. 2009[169] Country: USA	People ≥67 years: • with AKI (34% had CKD) • with no AKI (11% had CKD)	Retrospective analysis of a 5% random sample of Medicare database n=233,803 Follow-up: 2 years	• ESRD (enrolment in the ESRD program)	
James et al. 2010[175] Country: Canada	• People with AKI • People without AKI	Retrospective analysis of a database; people with ≥1 outpatient serum creatinine and proteinuria. n=920,985 Follow-up: median 35 months	• ESRD (RRT) or doubling of serum creatinine (composite outcome)	Results stratified by baseline eGFR and proteinuria categories.
James et al. 2011[174] Country: Canada	People undergoing coronary angiography: • People with mild AKI • People with moderate/severe AKI • People with no AKI	Retrospective analysis of a database; people with ≥1 serum creatinine 6 months prior to angiography and another 7 days after. n=14,782 Follow-up: median 19.7	• ESRD (RRT)	

Study	Comparison	Cohort	Outcomes	Comments
		months.		
Jones et al. 2012[183] Country: USA	• People with AKI • People without AKI	Retrospective analysis of a database; people with ≥1 hospitalisation with serum creatinine at least 90 days prior to admission and another at least 1 year after. n=3809 Follow-up: median 2.5 years.	• Incident CKD stage 3 (eGFR <60 ml/min/1.73 m^2)	
LaFrance et al. 2010[209] Country: Canada	• People with CKD and AKI • People with CKD and no AKI	Retrospective cohort of people with CKD (people referred to nephrologists or on dialysis therapy). n=6862 Follow up: at least 6 months and had at least 3 eGFR values.	• ESRD (Dialysis)	Data for those with AKI versus those without only presented in Kaplan Meier plots without number at risk – could not be extracted.
Lo et al. 2009[230] Country: USA	• People with dialysis-requiring acute renal failure who did not develop ESRD within 30 days of discharge • People with no dialysis-requiring acute renal failure who did not develop ESRD within 30 days of discharge	Retrospective cohort of people with eGFR ≥45 ml/min/1.73 m^2. n=3773 Follow up: 10,344 person years (over the 8 year study period)	• Progressive CKD (Stage 4 or higher defined as eGFR ≤30 ml/min/1.73 m^2 or ESRD)	Each patient matched to 10 controls.
Newsome et al. 2008[293] Country: USA	People ≥65 years with acute MI and: • Increase in serum creatinine during admission • No increase or decrease in serum creatinine during admission	Retrospective cohort of people ≥65 years with acute MI. n=87,094 Follow-up: median 4.1 years	• ESRD (identified via US Renal Data System)	Results for quartiles of increase in serum creatinine.
Thakar et al. 2011[393] Country: USA	People with diabetes and eGFR >30 ml/min/1.73 m^2: • with AKI • with no AKI	Retrospective cohort of people with diabetes and eGFR >30 ml/min/1.73 m^2. n=3679 Folow up: Mean	• Stage 4 CKD (eGFR <30 ml/min/1.73 m^2)	Veterans population

Study	Comparison	Cohort	Outcomes	Comments
		61.2 months		
Wald et al. 2009[416] Country: Canada	• People with dialysis-requiring AKI who did not develop ESRD within 30 days of discharge • People with no dialysis-requiring AKI who did not develop ESRD within 30 days of discharge	Retrospective cohort of people admitted to acute care hospital. 25% CKD in previous 5 years	• Chronic dialysis beginning .30 days after discharge and lasting ≥90 days	

Table 56: Clinical evidence profile: AKI versus no AKI for risk of CKD

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AKI	No AKI	Relative (95% CI)	Absolute		
Risk of progression to CKD stage 3 (follow-up median 2.5 years)[183]												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	108/719 (15%)	97/3090 (3.1%)	HR 3.82 (2.81 to 5.19)	83 more per 1000 (from 54 more to 121 more)	MODERATE	CRITICAL
Risk of progression to CKD stage 4 or ESRD (composite) (follow-up 10344 patient-years)[230]												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	47.9 per 100 person-years	1.7 per 100 person-years	HR 28.1 (21.1 to 37.43)	-[b]	MODERATE	CRITICAL
Risk of ESRD or doubling of serum creatinine - Baseline eGFR 60ml/ min/1.73m^2 ; proteinuria normal (follow-up median 35 months)[175]												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	122/1992 (6.1%)	618/752166 (0.08%)	HR 30 (24 to 37)	24 more per 1000 (from 19 more to 29 more) [c]	MODERATE	CRITICAL
Risk of ESRD or doubling of serum creatinine - Baseline eGFR 60ml/ min/1.73 m^2; proteinuria mild (follow-up median 35 months)[175]												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	35/560 (6.3%)	618/752166 (0.08%)	HR 39 (29 to 52)	31 more per 1000 (from 23 more to 41 more) [c]	MODERATE	CRITICAL
Risk of ESRD or doubling of serum creatinine - Baseline eGFR 60ml/ min/1.73 m^2; proteinuria heavy (follow-up median 35 months)[175]												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	22/182 (12.1%)	618/752166 (0.08%)	HR 107 (77 to 150)	83 more per 1000 (from 61 more to 115 more) [c]	MODERATE	CRITICAL
Risk of ESRD or doubling of serum creatinine - Baseline eGFR 45-59.9ml/ min/1.73 m^2; proteinuria normal (follow-up median 35 months)[175]												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	54/1082 (5%)	618/752166 (0.08%)	HR 21 (16 to 27)	16 more per 1000 (from 12 more to 21 more) [c]	MODERATE	CRITICAL
Risk of ESRD or doubling of serum creatinine - Baseline eGFR 45-59.9ml/ min/1.73 m^2; proteinuria mild (follow-up median 35 months)[175]												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	27/376	618/752166	HR 23 (16 to	18 more per 1000	MODERATE	CRITICAL

							(7.2%)	(0.08%)	32)	(from 12 more to 25 more) [c]		
Risk of ESRD or doubling of serum creatinine - Baseline eGFR 45-59.9ml/ min/1.73 m²; proteinuria heavy (follow-up median 35 months)[175]												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	31/198 (15.7%)	618/752166 (0.08%)	HR 87 (62 to 122)	68 more per 1000 (from 49 more to 95 more) [c]	MODERATE	CRITICAL
Risk of ESRD or doubling of serum creatinine - Baseline eGFR 30-44.9ml/ min/1.73 m²; proteinuria normal (follow-up median 35 months)[175]												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	46/795 (5.8%)	618/752166 (0.08%)	HR 24 (18 to 32)	19 more per 1000 (from 14 more to 25 more) [c]	MODERATE	CRITICAL
Risk of ESRD or doubling of serum creatinine - Baseline eGFR 30-44.9ml/ min/1.73 m²; proteinuria mild (follow-up median 35 months)[175]												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	32/369 (8.7%)	618/752166 (0.08%)	HR 33 (24 to 45)	26 more per 1000 (from 19 more to 35 more) [c]	MODERATE	CRITICAL
Risk of ESRD or doubling of serum creatinine - Baseline eGFR 30-44.9ml/ min/1.73 m²; proteinuria heavy (follow-up median 35 months)[175]												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	47/263 (17.9%)	618/752166 (0.08%)	HR 80 (58 to 110)	63 more per 1000 (from 46 more to 86 more) [c]	MODERATE	CRITICAL
Risk of ESRD or doubling of serum creatinine - Baseline eGFR 15-29.9ml/ min/1.73 m²; proteinuria normal (follow-up median 35 months)[175]												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	27/299 (9%)	618/752166 (0.08%)	HR 50 (12 to 20)	39 more per 1000 (from 9 more to 15 more) [c]	MODERATE	CRITICAL
Risk of ESRD or doubling of serum creatinine - Baseline eGFR 15-29.9ml/ min/1.73 m² ; proteinuria mild (follow-up median 35 months)[175]												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	33/204 (16.2%)	618/752166 (0.08%)	HR 76 (54 to 108)	60 more per 1000 (from 43 more to 84 more) [c]	MODERATE	CRITICAL
Risk of ESRD or doubling of serum creatinine - Baseline eGFR 15-29.9ml/ min/1.73 m²; proteinuria heavy (follow-up median 35 months)[175]												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	64/201 (31.8%)	618/752166 (0.08%)	HR 230 (165 to 320)	171 more per 1000 (from 126 more to 230 more) [c]	MODERATE	CRITICAL
Risk of ESRD in people with no prior CKD - All patients (follow-up median 3 years)[416]												

1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	127/2710 (4.7%)	41/9914 (0.41%)	HR 15.54 (9.65 to 25.02)	58 more per 1000 (from 35 more to 94 more)	MODERATE	CRITICAL
Risk of ESRD in people with no prior CKD - Older people (follow-up 2 years)[169]												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	116/4730 (2.5%)	418/200953 (0.21%)	HR 13 (10.6 to 15.94)	25 more per 1000 (from 20 more to 31 more)	MODERATE	CRITICAL
Risk of ESRD in mixed population (CKD and no CKD) at baseline - All patients (all AKI) (follow-up median 3 years)[416]												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	322/3769 (8.5%)	403/13598 (3%)	HR 3.23 (2.7 to 3.86)	63 more per 1000 (from 48 more to 80 more)	MODERATE	CRITICAL
Risk of ESRD in mixed population (CKD and no CKD) at baseline - All patients undergoing coronary angiography (mild AKI) (follow-up median 19.7 months)[174]												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	25/1610 (1.6%)	29/21864 (0.13%)	HR 4.15 (2.32 to 7.42)	4 more per 1000 (from 2 more to 8 more)	MODERATE	CRITICAL
Risk of ESRD in mixed population (CKD and no CKD) at baseline - All patients undergoing coronary angiography (moderate to severe AKI) (follow-up median 19.7 months)[174]												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	39/339 (11.5%)	29/21864 (0.13%)	HR 11.74 (6.38 to 21.6)	14 more per 1000 (from 7 more to 27 more)	MODERATE	CRITICAL
Risk of ESRD in mixed population (CKD and no CKD) at baseline - Older people (all AKI) (follow-up 2 years)[169]												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	312/7197 (4.3%)	929/226606 (0.41%)	HR 6.74 (5.9 to 7.7)	23 more per 1000 (from 20 more to 27 more)	MODERATE	CRITICAL

(a) Retrospective cohort study.
(b) Event rate reported per 100 patient-years therefore absolute effect not calculated in GRADE.
(c) Reference group: no AKI, normal proteinuria and eGFR ≥60.

Table 57: Clinical evidence profile: Acute tubular necrosis or acute renal failure for risk of CKD in people with and without CKD

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Acute tubular necrosis or acute renal failure	Control	Relative (95% CI)	Absolute		
De novo CKD stage 4 - Acute tubular necrosis (ATN) (follow-up 1-5 years)[12]												
1	Observational studies	Serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision	None	69/345 (20%)	2100/62850 (3.3%)	HR 6.64 (3.75 to 11.76)	169 more per 1000 (from 86 more to 296 more)	MODERATE	CRITICAL
De novo CKD stage 4 - Acute renal failure (ARF) (follow-up 1-5 years)[12]												
1	Observational studies	Serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision	None	663/5021 (13.2%)	2100/62850 (3.3%)	HR 4.03 (3.49 to 4.65)	95 more per 1000 (from 78 more to 113 more)	MODERATE	CRITICAL
Progression to CKD stage 4 - CKD with ARF or ATN (follow-up 1-5 years)[12]												
1	Observational studies	Serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision	None	9263/37562 (24.7%)	2100/62850 (3.3%)	HR 6.5 (6.26 to 6.75)	165 more per 1000 (from 158 more to 172 more)	MODERATE	CRITICAL

(a) Retrospective cohort study.

Table 58: Clinical evidence profile: AKI versus no AKI in people with previous CKD

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	CKD with AKI	CKD with no AKI	Relative (95% CI)	Absolute		
ESRD - All patients (reference group CKD with no AKI) (follow-up 6 months)[160]												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	27/213 (12.7%)	590/34721 (1.7%)	HR 1.47 (0.95-2.27)	8 more per 1000 (from 1 fewer to 21 more)	LOW	CRITICAL

ESRD - All patients (reference group CKD with no AKI) (follow-up 4 years)[209]												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	711/3079 (23.1%)	533/3783 (14.1%)	HR 2.33 (2.07-2.62)	157 more per 1000 (from 129 more to 186 more)	MODERATE	CRITICAL
ESRD - Older people (reference group no CKD or AKI) (follow-up 2 years)[169]												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	196/2467 (7.9%)	418/200953 (0.21%)	HR 41.2 (34.6 to 49.06)	80 more per 1000 (from 67 more to 95 more)	MODERATE	CRITICAL

(a) Retrospective cohort study.
(b) 95% confidence interval crosses one default minimally important difference (MID) .

Table 59: Clinical evidence profile: AKI versus no AKI in people with diabetes

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Diabetes with AKI**	**Diabetes with no AKI**	**Relative (95% CI)**	**Absolute**		
Risk of progression to CKD stage 4 - All patients (follow-up mean 61.2 months)[393]												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	124/530 (23.4%)	134/1292 (10.4%)	HR 2.02 (1.78 to 2.29)	95 more per 1000 (from 73 more to 118 more)	MODERATE	CRITICAL
Risk of progression to CKD stage 4 - Baseline eGFR <60 (follow-up mean 61.2 months)[393]												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	NR	NR	HR 1.61 (1.28 to 2.02)	-	MODERATE	CRITICAL
Risk of progression to CKD stage 4 - Baseline eGFR 60-90 (follow-up mean 61.2 months)[393]												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	NR	NR	HR 2.33 (1.93 to 2.81)	-	MODERATE	CRITICAL
Risk of progression to CKD stage 4 - Baseline eGFR >90 (follow-up mean 61.2 months)[393]												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	NR	NR	HR 2.27 (1.69 to 3.05)	-	MODERATE	CRITICAL

(a) Retrospective cohort study.
NR=not reported

Table 60: Clinical evidence profile: Small rises in serum creatinine versus decrease or no change in serum creatinine in older people during hospitalisation for acute myocardial infarction

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Small rises in serum creatinine	Decrease or no change in serum creatinine	Relative (95% CI)	Absolute		
ESRD - Serum creatinine increase 0.1mg/dL (follow-up median 4.1 years)[293]												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	NR	NR	HR 1.45 (1.2 to 1.75)	-[c]	LOW	CRITICAL
ESRD - Serum creatinine increase 0.2 mg/dL (follow-up median 4.1 years)[293]												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	NR	NR	HR 1.97 (1.6 to 2.43)	-[c]	MODERATE	CRITICAL
ESRD - Serum creatinine increase 0.3-0.5mg/dL (follow-up median 4.1 years)[293]												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	NR	NR	HR 2.36 (2 to 2.78)	-[c]	MODERATE	CRITICAL
ESRD - Serum creatinine increase 0.6-3.0mg/dL (follow-up median 4.1 years)[293]												
1	Observational studies	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	NR	NR	HR 3.26 (2.73 to 3.89)	-[c]	MODERATE	CRITICAL

(a) 1 95% confidence intervals calculated from lower 95% confidence interval read from graph and upper 95% confidence interval calculated by NCGC using RevMan 5.2, asymmetrical confidence intervals shown in graph. For the one group reported in the text only the lower 95% interval agrees with that shown in the graph.
(b) 95% confidence interval crosses one minimally important difference making the true effect uncertain.
(c) Only incidence rate per 1000 person years reported, therefore unable to calculate absolute risk.
NR=not reported

7.4.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

7.4.5 Evidence statements

Clinical

All of the following are based on moderate quality evidence unless otherwise stated:

- All the included studies showed an increased risk of incident CKD or progression of CKD with AKI.
- One study[183] considered people whose serum creatinine had returned to baseline after the episode of AKI. They found an almost four times increased risk of incident CKD stage 3 compared to people without AKI.
- A single study[175] looked at the risk of CKD progression (defined as ESRD or doubling of serum creatinine) stratified by baseline eGFR and proteinuria category and found an increased risk with a baseline eGFR of 15-29.9ml/min/1/73m^2 and an increasing risk with proteinuria category with heavy proteinuria (2+ on urine dipstick) more than doubling the risk of CKD progression compared to mild proteinuria (trace or 1+ on urine dipstick) in people with the same baseline eGFR.
- In people with diabetes there was twice the risk of progression to CKD stage 4 over a mean follow up of 61 months for people with AKI compared to no AKI.[393] The risk was found to be slightly greater in those with relatively preserved renal function (baseline eGFR >60 ml/min/1.73 m^2) compared to those with a baseline eGFR <60 ml/min/1.73 m^2.
- One study[169] showed an increased risk of ESRD with older age (mean age 80 years) in people with CKD who have an episode of AKI. The risk of ESRD in older people without pre-existing CKD who have an episode of AKI was similar to that of a younger population.[416]
- Low to moderate evidence from one study[293] showed that in older people (mean age 77 years) hospitalised for acute myocardial infarction those with small rises of serum creatinine were at 1.5-2 times the risk of ESRD compared to those with no rise or a decrease in serum creatinine.

Economic

- No relevant economic evaluations were identified.

7.4.6 Recommendations and link to evidence

Recommendations	The current recommendations can be found at www.nice.org.uk/guidance/ng203
Relative values of different outcomes	The GDG agreed that the critical outcomes for decision making were incident CKD or progression of CKD (measured by change in GFR or ESRD).
Trade-off between clinical benefits and harms	The evidence showed an increased risk of incident CKD or progression of CKD with AKI. The GDG wanted to highlight that this increased risk remained even in people who make a complete recovery from their episode of AKI. The GDG considered that knowing this group were at elevated risk of developing CKD, the trade-off between additional monitoring of people who had made a complete recovery was outweighed by the potential to identify development of CKD at an earlier stage.

	The GDG discussed that the evidence considered was in people who were hospitalised, either with community or hospital acquired AKI. The risk of incident CKD or progression of CKD would very likely be the same for those with AKI in the community although to date there are no published data. Whilst the whole spectrum of AKI from small increases in serum creatinine through to AKI requiring acute renal replacement therapy were included in the studies the GDG acknowledged that there are inconsistencies in how AKI is defined and coded. Nevertheless even small rises in serum creatinine were associated with increased risk of adverse outcome. In people with diabetes and AKI, there was twice the risk of progression to CKD stage 4 over a mean follow up of 61 months compared to no AKI.[393] The risk was found to be slightly greater in those with relatively preserved renal function (baseline eGFR >60 ml/min/1.73 m^2) compared to those with a baseline eGFR <60 ml/min/1.73 m^2. The GDG agreed that, whilst AKI is still a risk factor for incident CKD or progression of CKD, the effects in this group were less due to diabetes itself being a risk factor. A large population study stratified by GFR and proteinuria category found an increased risk of progression of CKD following an episode of AKI with increasing severity of proteinuria.[175]
Economic considerations	No economic evidence was identified. It is expected that monitoring these patients will be cost-effective given that they are at increased risk of developing CKD.
Quality of evidence	The evidence was of moderate quality engendered by risk of bias due to study design (retrospective cohort studies). For occurrence of ESRD, reported in one study with a 6 month follow up, the evidence was low quality due to serious imprecision, probably due to the low event rate associated with such a short follow up period.[160] Another study[293] in older people (mean age 77 years) hospitalised for acute myocardial infarction demonstrated that small rises of serum creatinine were associated with 1.5-2 times the risk of ESRD compared to those with no rise or a decrease in serum creatinine.
Other considerations	People making a complete recovery from their AKI episode who had no prior evidence of CKD had a significantly increased incidence of subsequent new onset CKD compared to people without AKI at a median of 2.5 years follow-up.[183] The GDG therefore considered that even people making a complete recovery to a normal baseline level of kidney function should be followed up for a period of 2-3 years after an episode of AKI. It is important that the risk of subsequent development of CKD following an episode of AKI is communicated to both the person at risk and their carers. Those people with prior CKD who experience an episode of AKI are at increased risk of progression of their CKD and this risk depends on both their GFR and ACR category. The subsequent monitoring following an episode of AKI should be dictated by their baseline GFR and ACR category (Table 51). The GFG voted to make recommendation 44 a key priority for implementation as it has a high impact on outcomes that are important to patient, has a high impact on reducing variation in care and outcomes and includes actions that are measurable. They GDG commented that this will be a change in practice and so educational support will be needed.

8 Information and education

8.1 Information, education and support for people with CKD and their carers

8.1.1 Clinical introduction

People accessing NHS services need to be provided with education to allow them to understand their condition and treatment and to be involved in decisions about their care. Current NHS policy recognises the need to develop patient-led services[86] and that education is of benefit to those with long term conditions, giving them skills and knowledge and ensuring they can be actively involved in planning their own care.[88]

This idea has been actively promoted within renal services, with the Renal National Service Framework Standard 1 stating that people with CKD should 'have access to information that enables them and their carers to make informed decisions and encourages partnership in decision-making'.[85]

This policy reflects the desire of people with CKD themselves to have information and education. A study by Ormandy et al.[307] concluded that people with CKD have identifiable information needs which change at different times as their condition progresses.

Information has typically been provided in the form of verbal information received face to face from health professionals in a clinical setting, or by way of written information such as leaflets provided at clinical appointments. Other ways of providing information include audio-visual methods such as CDs, videos and DVDs. Coulter et al.[73] have identified that 'where information leaflets are to be used in support of patients' involvement in treatment decisions, they must contain relevant, research-based data in a form that is acceptable and useful to patients'. In addition, such information should be based on the needs of those who will use the information and they should be involved in developing and testing the information.

However, although information is necessary to achieve informed decision-making, it is not always sufficient on its own, even where it is of good quality. Studies show that the context in which the information is given and providing support for the decision-making process are also important.[32] Therefore education programmes are being developed to ensure that people with CKD can not only access appropriate information but learn how to use it to make decisions about their own care.

What information, education, and support are needed for CKD patients and their carers to understand and cope with the diagnosis, treatment and outcome of CKD?

8.1.2 Methodology

There were no studies that examined the impact of education, information, or support on people with early (stage 1–3) CKD. There were no studies that investigated support systems for carers of people with CKD. Most educational intervention studies were conducted in people with advanced stage CKD prior to initiation of dialysis. The outcomes of interest were quality of life, compliance with medication, and preparation for ESRD therapy (timely creation for access for dialysis, hepatitis vaccinations, emotional issues surrounding initiation of dialysis, and choice of dialysis modality).

One open label RCT assessed the intent to start home-care dialysis in people with eGFR <30 ml/min/1.73 m^2 randomised to standard education (n=35, education on kidney disease, dietary instruction, and different dialysis modalities) or to a 2 phase education + standard care intervention

(n=35, booklets and videos discussing advantages/disadvantages of self-care dialysis, followed by a group discussion of self-care dialysis with a nephrologist and predialysis nurse).[243]

One retrospective Japanese cohort study assessed planned initiation of renal replacement therapy (RRT) and choice of dialysis modality in people initiating dialysis who had received predialysis education (n=70: lectures on chronic renal failure, treatment, daily-life instructions, explanations of different dialysis modalities and dietary therapy) compared with people who did not receive predialysis education (n=106; standard dialysis information was provided by the attending physician if requested by the patient).[165]

An American retrospective cohort study assessed timing of vascular access in people exposed to the Healthy Start Clinic education program (n=61: consisting of lectures, handbooks, and slide presentations on chronic renal failure, treatment, explanations of dialysis modalities and dietary therapy) compared with patients who did not receive the Healthy Start Clinic education program (n= 86: conventional care with dialysis modality information, CKD video, meeting with a social worker in hospital).[228]

A Canadian cohort study examined dialysis modality choice and urgent dialysis initiation in people taking a predialysis clinic education program (n=37) compared with people receiving standard care (n=39). The clinic education program consisted of discussions with a nurse educator, physician, social worker, and nutritionist about renal function, blood pressure, bone disease, and diet therapy over multiple visits.[221]

A potential source of bias in all the cohort studies may be the voluntary participation in the education group, such that these participants may have already been more concerned about their health, acted to enhance their health, and thus be better prepared for dialysis initiation compared with participants who did not receive education.

The effect of pre-dialysis education in adults with CKD is summarised in Table 61 at the end of the evidence statements.

8.1.3 Health economics methodology

There were no health economics papers found to review.

8.1.4 Evidence statements

Planned initiation of dialysis

Two cohort studies showed that significantly more people in the predialysis education group had a planned initiation of RRT compared with those who did not receive education.[165,221] (Level 2+)

Choice of dialysis modality

In an RCT, significantly more people in the education + standard care group intended to start self-care dialysis compared with the standard care group.[243] (Level 1+)

One cohort study showed NS differences between education and standard care groups for choice of haemodialysis.[165] (Level 2+)

Two cohort studies showed NS differences between education versus standard care for choice of peritoneal dialysis.[165,221] (Level 2+)

Use of catheter for dialysis

One cohort study showed that significantly fewer people in the predialysis education group used a double-lumen catheter for haemodialysis compared with those who did not receive education.[165] (Level 2+)

Another cohort study showed that significantly fewer people in the predialysis education program initiated dialysis with a temporary catheter compared with people who did not participate in the education program.[228] (Level 2+)

Permanent vascular access before initiation of dialysis

Significantly more people in the predialysis education program had arteriovenous fistulas placed before initiation of dialysis compared with people who did not participate in the education program.[228] (Level 2+)

Permanent vascular access used for dialysis initiation

Significantly more people in the education program initiated dialysis with an arteriovenous fistula compared with people who did not participate in the program. Significantly fewer people in the predialysis education program initiated dialysis with a graft compared with people who did not participate in the education program.[228] (Level 2+)

Table 61: Effect of predialysis education in adults with CKD

Reference	Population	Intervention	Comparison	Outcome	Size effect
165	People initiating dialysis	Educational intervention n=70	No educational intervention n=106	Planned initiation of dialysis	Education: ≅ 65% No education: ≅ 35% p=0.001
221	People initiating dialysis	Clinic-based education n=37	Standard care n=39	Urgent dialysis start	Clinic education: 13% Standard care: 35% p<0.05
243	eGFR < 30 ml/min/1.73 m^2	Standard care + 2 phase educational intervention n=28	Standard care n=34	Intent to start home-care dialysis	Education + standard care: 82.1% Standard care: 50% p=0.015
165	People initiating dialysis	Educational intervention n=70	No educational intervention n=106	Choice of haemodialysis Choice of peritoneal dialysis	Education: 90% No education: 95% NS Education: 10% No education: 5% in NS
221	People initiating dialysis	Clinic-based education n=37	Standard care n=39	Choice of peritoneal dialysis	Education: 53% Standard care: 42% NS
228	Creatinine >4.0 mg/dl, creatinine clearance <20 ml/min,	Healthy Start program educational intervention	No Healthy Start educational intervention	Permanent Vascular Access before Initiation of	HS education: 77%, No HS education: 36% p <0.001

Reference	Population	Intervention	Comparison	Outcome	Size effect
	albuminuria, or microalbuminuria initiating haemodialysis	n=61	n=86	Dialysis Arteriovenous fistulas placed before dialysis initiation	HS education: 74%, No HS education: 38% p <0.05
				Permanent Vascular Access used for Initiation of Dialysis	HS education: 49% No HS education: 23% p <0.01
				Arteriovenous fistulas used to initiate dialysis	HS education: 70%, No HS education: 30% p <0.01
				Grafts used to initiate dialysis	HS education: 30%, No HS education: 70% p <0.01
[165]	People initiating dialysis	Educational intervention n=70	No educational intervention n=106	Use of double-lumen catheter to initiate dialysis	Education: 5% No education: 25%, p <0.0003
[228]	Creatinine >4.0 mg/dl, creatinine clearance <20 ml/min, albuminuria, or microalbuminuria initiating haemodialysis	Healthy Start Program educational intervention n=61	No Healthy Start educational intervention n=86	Use of a temporary catheter to initiate dialysis	HS Education : 51% No HS education: 77% p <0.001

8.1.5 From evidence to recommendations

Most studies had been carried out in people with stage 5 CKD around the time they were starting renal replacement therapy; however, they were asked what information they needed at an early stage of their disease. The evidence suggested topics that should be covered but the detailed content of education packages would vary depending on the individual.

People at different stages of CKD required different information, and, for example, people with stable stage 3a or 3b CKD did not need detailed information about dialysis. However, it was agreed that it was important that people were given information about their prognosis and that they should be aware of options for dialysis access prior to having to make a decision about this.

The GDG agreed that it was not sufficient for people simply to be given information about CKD and its treatment. This information had to form part of a programme that educated them about the disease. It was agreed that it was important that after the education programme, people's understanding should be assessed. It was also agreed that programmes should be run by clinicians who have sufficient knowledge to be able to answer people's questions.

Older people do not always learn easily from information given on paper and some people may need psychological support to help them cope with the consequences of the information that they have been given.

A summary of research findings by Ormandy et al.[307] identified key information needs of people in renal units in the UK. The GDG used these to guide making recommendations.

We have not found evidence of cost-effectiveness. We do not believe this recommendation will have a big cost impact for the NHS since this is part of the existing National Service Framework and such programmes are already widespread.

8.1.6 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng203

8.2 Available tools to aid identification and maximise effectiveness of treatment and management of CKD

8.2.1 Clinical introduction

CKD is common, usually asymptomatic, often unrecognised and as a result subject to deficiencies in appropriate management and late referral of people with advanced disease to specialist services. A

number of tools have recently been introduced to help identify people with CKD and aid early intervention and appropriate management to reduce/prevent complications and progression of CKD.

In March 2006 guidelines for the identification, management and referral of adult patients with chronic kidney disease were published by the Royal College of Physicians of London on behalf of a number of collaborating agencies.[354]

In April 2006 a Department of Health initiative led to the automatic reporting of an isotope dilution mass spectrometry (IDMS) traceable estimated GFR using the Modification of Diet in Renal Disease Study Equation (MDRD) whenever a serum creatinine is requested through any clinical chemistry laboratory.[89]

In April 2004 the new General Services (GMS) contract was introduced in the UK, and part of this change included the national Quality and Outcomes Framework (QOF). Participation by practices in the QOF is voluntary, but participation rates are high possibly because there is a financial incentive to do this. In March 2006, four renal domains were included for the first time in the QOF. These indicators focused on creating a register of people with chronic kidney disease with an eGFR <60 ml/min/1.73 m^2 (stage 3–5 CKD), measuring blood pressure, achieving a target blood pressure and prescription of drugs blocking the rennin–angiotensin system (ACE inhibitors or ARBs).

These national tools have increased referral of people with CKD to their local specialist and in turn have resulted in a number of local initiatives aimed at providing a structured delivery of care for people with kidney disease in partnership with primary care. This section was aimed at identifying whether any of these tools had yet improved the identification and management of adults with CKD.

8.2.2 Methodology

The literature was reviewed to assess the utility of computerised tools (decision support systems and information technologies) to aid primary care workers in identifying people with CKD and in offering the most appropriate and timely treatments. Outcomes of interest were appropriate investigations and follow-up, referral, medicines management, and achieving clinical targets.

The New Opportunities for Early Renal Intervention by Computerised Assessment (NEOERICA) project used computer searching to extract a retrospective dataset of all patients with a valid serum creatinine measurement from 17 primary care practices in the UK (n=38,262 with valid serum creatinine measures).[387] The aim of this study was to ascertain if computerised medical records contain sufficient information to estimate the prevalence of CKD, its comorbidities, as well as medication usage and BP targets achieved. Manual searching of medical records from 1 practice (n=492 with stages 3-5 CKD identified by computer searching) was used to test the validity of computer searching to estimate the prevalence of CKD.[15] In both of these retrospective observational studies, ethnicity was unreliably reported, and the CKD prevalence estimation was limited to only stages 3 to 5 due to poor recording of proteinuria and haematuria in the medical records. Serum creatinine measurements were calibrated to the original MDRD study in Stevens et al., but not in Anandarajah et al.

Two publications from the Optimal Renal Care UK (ORC UK) study assessed the utility of a disease management programme (DMP) that was guideline- and algorithm-based to identify, manage, and appropriately refer people with CKD.[341,342]

In a case series study, a clinical tool to identify people at risk of rapid progression of kidney disease (≥25% decline in mean eGFR over 2 years) was developed in adults ≥66 years (mean age 76.1 years, n=6789) and validated in a second cohort of older adults (n=3395). Medications dispensed prior to the index creatinine measurements were used to determine disease categories, which were considered in a stepwise logistic regression analysis. Risk scores were calculated for each subject and then categorised into risk classes (I to V).[141] Albuminuria was not included in the model and disease

categories assigned based on medication may misclassify and underestimate true prevalence of a certain disease.

Another study investigated the ability of the Framingham prediction equation to predict 5 year and 10 year risk of cardiac events (myocardial infarction and fatal coronary heart disease) in people with CKD from the pooled ARIC and CHS studies (n=934).[419]

8.2.3 Health economics methodology

There were no health economics papers found to review.

8.2.4 Evidence statements

Computer searching of medical records

Identifying people with CKD

In the NEOERICA validation study, computer searching of medical records from one UK practice identified 492 people with stage 3–5 CKD (adjusted prevalence of stage 3-5 CKD was 5.1%). Only 36/492 (7.3%) of people identified as having CKD were known to renal services or had a renal diagnosis on their records. Manual checking of medical records identified only 4 additional cases of CKD missed by the computer search.[15] (Level 3)

In the large NEOERICA study (n=38,262 with valid serum creatinine measures, 17 UK practices), computer searching identified 11,731(30.7%) people with an eGFR <60 ml/min/1.73 m^2. Only 242 (2.1%) of these were coded as a renal diagnosis in the records. The recording of a renal diagnosis improved as renal function declined.[387] (Level 3)

Achieving clinical targets

The NEOERICA study showed that blood pressure targets were not achieved in most instances: only 63/461 (13.7%) of people with hypertension and eGFR < 30 ml/min/1.73 m^2 achieved BP <130/80 mmHg. Only 571/6235 (9.2%) people with hypertension and eGFR 45–59 ml/min/1.73 m^2 achieved BP <130/80 mmHg. Only 270/1313 (20%) of people with diabetes, hypertension, and eGFR <60 ml/min/1.73 m^2 achieved target BP <130/80 mmHg.[387] (Level 3)

Disease management programmes

Achieving clinical targets

The percentage of total cholesterol measurements in target range increased significantly after 9 months of the DMP (64.5% in target at baseline to 75% in target after 9 months, p=0.001). In people with stage 3–5 CKD without diabetes and a PCR <100, the percentage of systolic blood pressure measurements in target range increased significantly after 9 months of the DMP (37.1% in target at baseline to 53.2% in target after 9 months, p=0.001).[341] (Level 3)

There were NS improvements in HDL cholesterol, LDL cholesterol, or triglyceride levels after 9 months on the DMP. In people with stage 3–5 CKD, with diabetes or a PCR >100, there was NS differences in blood pressure measurements in target range at baseline compared to 9 months on the DMP.[341] (Level 3)

Preservation of renal function

The median fall in eGFR was significantly less after 12 months on the DMP (–0.32 ml/min/1.73 m^2) compared with 9 months preceding the DMP (–3.69 ml/min/1.73 m^2, p <0.001). This was also true for

people with eGFR fall ≥5 ml/min/1.73 m^2 (≥9.90 ml/min/1.73 m^2 prior to DMP versus ≥1.70 ml/min/1.73 m^2 after the DMP, p<0.001).[341] (Level 3)

Impact of eGFR reporting on nephrology referrals

Following initiation of a disease management programme (DMP), the number of referrals rose 2.7 times compared to the number of referrals prior to DMP commencement. After introduction of a referral assessment service, the referral rate decreased rapidly and by 6 months, an average of five new CKD stage 4 or 5 patients were being referred (0.16% incidence). This referral rate was within the capacity of local nephrology services.[342] (Level 3)

Risk tool for predicting rapid progression of kidney dysfunction (≥ 25% decline in mean eGFR between the two study periods)

Multivariate analysis showed that age >75 years old, cardiac disease, diabetes, gout, and anti-emetic drug use were significantly associated with rapid progression of kidney dysfunction. In both the derivation (n=6789) and validation cohorts (n=3395), people in the Class V risk index had triple the risk of rapid kidney disease progression compared with people in the Class I risk index. The c-statistic for the model was 0.59, indicating a modest ability to discriminate between people with and without risk of rapid kidney disease progression.[141] (Level 3)

Utility of the Framingham equation to predict cardiac events in people with CKD

The Framingham prediction equation had poor discrimination (the ability to separate those who had cardiac events from those who did not) in the CKD cohort. The Framingham equation correctly identified men with CKD who would develop a cardiac event within 10 years only 60% of the time, compared with 69% of the time in the non-CKD male cohort and 73% in the original Framingham cohort. In women with CKD, discrimination was 73% for 10-year cardiac events compared with 76% in the original Framingham cohort.[419] (Level 3)

The Framingham equation under-predicted cardiac events when men with CKD were stratified into quintiles of Framingham Risk. The 5-year calibration for men was poor (chi-square 33.4, p <0.001) and the 10-year calibration was also poor (chi-square 71.3, p <0.001). The Framingham equation under-predicted cardiac events in women with CKD and had poor 5- and 10-year calibration. Recalibrated models performed better, although prediction remained poor in men with CKD. In women with CKD, re-calibration showed NS difference in predicted and observed cardiac events in 5- and 10-year probability models.[419] (Level 3)

8.2.5 From evidence to recommendations

The GDG noted that the NEOERICA study had been carried out prior to the introduction of GFR reporting and prior to the inclusion of renal outcomes in the QOF. It was also prior to the introduction of appropriate Read Codes and the renal NSF. All of these factors may have subsequently improved the identification of CKD in primary care populations. Nevertheless the GDG agreed that it was still possible that people with an abnormal GFR or proteinuria were not classified as having CKD. As this information is usually recorded on practice computer databases it appears that it would be quite simple to devise programmes to identify these people.

The introduction of a disease management programme tailored to people with CKD resulted in significant improvements in blood pressure and lipid control. A significant reduction in progression of CKD also followed the introduction of the disease management programme.

The GDG were surprised that the tool for predicting rapid decline in kidney function did not include known factors such as hypertension and proteinuria in the score whilst anti-emetic use was. It was agreed that the anti-emetic use was probably a marker of the presence of an acute illness which may have affected GFR.

The GDG agreed that separate tools for the identification of patients with CKD and the identification of people with CKD at risk of progressing would be useful.

8.2.6 Recommendations

There are no recommendations.

8.3 Lifestyle modification

This section was titled 'Self-management' in the 2008 NICE guideline (CG73). However, due to a new evidence review on self-management (section Self-management8.6) this section was renamed to
'Lifestyle modification' for the update.

8.3.1 Clinical introduction

The increased prevalence of CKD has been linked to lifestyle-related factors such as hypertension and diabetic nephropathy (see NICE Clinical Guideline 127 'Management of hypertension in adults in
primary care'; NICE Clinical Guideline 66 'Management of Type 2 diabetes'; NICE Clinical Guideline 15 'Diagnosis and management of Type 1 diabetes in children, young people and adults'; and NICE
Clinical Guideline 43 'Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children').[278-281] Smoking has been associated with more severe proteinuria and progression of kidney disease. In rat models of CKD, exercise training has been shown to be renoprotective.[200] The association between obesity, smoking, physical activity and CKD therefore may be important. Equally there may be insufficient adjustment of potential confounders. Obesity leads to CKD through diabetes and hypertension but is it an independent

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

8.3.2 Methodology

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

One RCT examined changes in GFR, muscle strength, and total body potassium over 3 months in people aged over 50 years old with CKD on a low protein diet randomised to resistance training (n=14) or sham training (n=12).[55] Another RCT examined nondiabetic people with CKD (median GFR 25 ml/min/1.73 m^2) randomised to exercise training (n=15, 18 months follow-up, bicycle ergometer, running, swimming, and walking) or a control group (n=15, 20 months follow-up, mostly sedentary lifestyle).[98]

A non-randomised controlled trial compared water-based aerobic activity (n=17) to control (sedentary lifestyle, n=9, 3-month follow-up) for changes in GFR, cystatin C, and proteinuria in people with CKD.[321] This study was excluded because of small sample size and methodological limitations.

One RCT[260] and two before-and-after observational studies[361,377] investigated the effect of weight loss on kidney disease progression in obese, mostly diabetic populations. The Morales et al. RCT compared a low-calorie diet (n=20, 5-months follow-up, reduction of 500 kcal, consisting of 25–30% fat and 55–65% carbohydrate, and protein content adjusted to 1.0–1.2 g/kg/day) with a usual diet

(n=10) in people with diabetic or nondiabetic nephropathy.[260] The before and after study of Saiki et al. investigated changes in BMI, creatinine clearance, and proteinuria before and after one month of a low calorie formula diet (740 or 970 kcal/day or 11–19 kcal/kg) in 22 obese, hospitalised adults with diabetic nephropathy.[361] The before and after study of Solerte et al. compared changes in BMI, proteinuria, and kidney function decline before and after 12 months of a low calorie diet (1410 kcal/day consisting of 170 g carbohydrate, 58 g protein, 49 g fat) in 24 obese people with diabetic nephropathy.[377]

The effect of alcohol consumption on the risk of ESRD was examined in a case control study in which alcohol consumption was compared between cases (people with new ESRD, n=716) and age-match controls (general population, n=361).[327] This study was rejected as several aspects of a robust case-control study were ignored (exclusion criteria, comparison between participants and non-participants, differentiation between cases and controls).

The effect of smoking on kidney functional decline was examined in two diabetic cohort studies and two case-control studies. A German diabetic cohort of smokers (n=44, mean age 47 years, 86% had baseline proteinuria >0.15 g/d) were followed for 5.1 years (median) and changes in proteinuria and GFR (20% decline) were compared with non-smokers (n=141, mean age 54 years, 72% had baseline proteinuria >0.15 g/d).[308] In a Danish cohort of people with type 1 diabetes and persistent albuminuria >300 mg/24 h (n=301), changes in GFR during a median follow-up of 7 years were compared between smokers (n=176), non-smokers (n=94) and ex-smokers (n=31).[155] In a case-control study, men with ADPKD or IgA-GN who had progressed to ESRD were matched with controls with ADPKD or IgA-GN who had not progressed to ESRD. Progression to ESRD was compared between males who smoked for 0–5 pack-years (n=73), for 5–15 pack years (n=28), and for >15 pack years (n=43).[309] In a Spanish case control study, cases (people who had progressed to ESRD, n=520) were age, sex, hospital matched with controls (hospital patients who had not progressed to ESRD, n=982) and the effects of smoking compared with non-smoking on progression to ESRD were analysed.[162]

The effect of lifestyle changes on the progression of CKD is summarised in Table 62 at the end of the evidence statements.

8.3.3 Health economics methodology

No health economics papers were found to review.

8.3.4 Evidence statements

Exercise training: change in GFR

Median GFR decreased in both control and exercise groups but there were NS differences between groups.[98] (Level 1 +)

GFR increased in people with resistance training + low protein diet, whereas GFR decreased in the sham training + low protein diet group (p=0.048 between groups).[55] (Level 1 +)

Exercise training: change in total body potassium

Total body potassium increased in the resistance training + low protein diet, whereas it decreased in the sham training + low protein diet (p=0.014 between groups).[55] (Level 1+)

Exercise training: adverse events

In one RCT, 3/15 people in the exercise group and 2/15 people in the control group started dialysis. One person in the control group died, and 1 person in the control group withdrew after 10 months

for personal reasons. No exercise adverse events or injuries were reported in either the resistance training or sham training group.[55] (Level 1+)

Weight loss: change in creatinine clearance (CrCl)

One RCT showed that there were NS changes in CrCl after 5 months of a low calorie diet. However, CrCl significantly decreased in the usual diet group, but there were NS changes between groups.[260] (Level 1 +)

One before and after study showed that there was NS change in CrCl after four weeks of a low calorie formula diet.[361] (Level 3)

One before and after study showed that CrCl significantly increased after 12 months of a low calorie diet.[377] (Level 3)

Weight loss: change in serum creatinine

One RCT showed that there were NS changes in serum creatinine after 5 months of a low calorie diet, whereas creatinine significantly increased with a usual diet.[260] (Level: 1 +)

Two before and after studies showed that serum creatinine significantly decreased after 1 or 12 months of a low calorie diet.[361,377] (Level 3)

Weight loss: change in protein loss

One RCT showed that urinary protein loss significantly decreased after 5 months of a low calorie diet, whereas there was a NS change in proteinuria in the usual diet group ($p < 0.05$ between groups). Weight loss was significantly correlated with a decrease in protein loss ($r=0.62$, $p < 0.01$), but not blood pressure or creatinine clearance.[260] (Level: 1 +)

Urinary protein significantly decreased after 4 weeks of a low calorie-formula diet. Weight loss was significantly correlated with a decrease in serum creatinine ($r=0.621$, $p=0.0021$) and with a decrease in protein loss ($r=0.487$, $p=0.0215$).[361] (Level 3)

Urinary protein loss significantly decreased by 51% after 12 months of a low calorie diet, $p<0.01$. Urinary albumin loss significantly decreased by 31% after 12 months of a low calorie diet, $p<0.01$. Weight loss was NS correlated with a decrease in UPE or UAE.[377] (Level 3)

Smoking cessation

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

Effect of smoking on GFR decline

In a cohort study, GFR remained stable during follow-up in non-smokers but decreased significantly in smokers. Smokers had a significantly increased odds of a 20% decline in GFR compared to non-smokers (OR 2.52, 95% CI 1.06–5.99, $p < 0.01$). This relationship persisted after adjustment for diabetes type or control, retinopathy, age, BMI, ACE inhibitor use, BP, proteinuria (F-ratio=65.9, $p < 0.0001$).[308] (Level 2+)

In a diabetic cohort with nephropathy, GFR declined in non-smokers, ex-smokers, and smokers, with NS differences between groups.[155] (Level 2+)

Effect of smoking on proteinuria

In a cohort study, proteinuria increased in smokers and non-smokers, with NS differences between the two groups.[308] (Level 2+)

Effect of smoking on progression to ESRD

In a case control study, men who smoked 5–15 pack years or >15 pack years had a significantly increased risk of ESRD than men who smoked for 0–5 pack years.[309] (Level 2+)

Another case control study showed that smokers had a significantly increased risk of ESRD compared with non-smokers.[162] (Level 2+)

Table 62: The effect of lifestyle changes on progression of CKD

Reference	Population	Duration (months)	Intervention	Comparison	Outcome	Size effect
[98]	Nondiabetic people (median GFR 25 ml/min/1.73 m^2, range 10-43 ml/min/1.73 m^2)	18	Exercise training n=15	Control (sedentary lifestyle) n=15	Change in GFR (ml/min/month)	Exercise: 0.27 Control -0.28 NS between groups
[55]	CKD (creatinine 133-442 µmol/l or 1.5-5.0 mg/dl)	3	Resistance training + low protein diet n=14	Sham training + low protein diet n=12	Change in GFR (ml/min/1.73m^2)	Resistance training: + 1.18 ml/min/1.73m^2 Sham training: -1.62 ml/min/1.73m^2 P=0.048 between groups.
[55]	CKD (creatinine 133-442 µmol/l or 1.5-5.0 mg/dl)	3	Resistance training + low protein diet n=12	Sham training + low protein diet n=11	Change in total body potassium (%)	Resistance training: +4% Sham training: -6% p=0.014 between groups
[260]	People with diabetic or nondiabetic nephropathy and BM1 > 27 kg/m^2	5	Low calorie diet n=20	Usual diet n=10	Changes in creatinine clearance (ml/min/1.73 m^2)	Low calorie diet: NS Usual diet: 61.8 → 56, p<0.05 NS between groups
[361]	Diabetic people with proteinuria (urinary	1	After low calorie formula	Before low calorie formula diet	Changes in creatinine clearance	0.68 → 0.77, NS

Reference	Population	Duration (months)	Intervention	Comparison	Outcome	Size effect
	albumin > 300 mg/day), diabetic retinopathy, BMI > 25 kg/m^2		diet n=22	n=22	(ml/s/1.73 m^2)	
377	Obese diabetic people with nephropathy (urinary protein loss > 500 mg/day) and diabetic retinopathy	12	After low calorie diet n=24	Before low calorie diet n=24	Changes in creatinine clearance (ml/s/1.73 m^2)	80 → 90, p<0.01
260	People with diabetic or nondiabetic nephropathy and BM1 > 27 kg/m^2	5	Low calorie diet n=20	Usual diet n=10	Changes in serum creatinine (mg/dl)	Low calorie diet: NS Usual diet: 1.6 →1.8 , p<0.05 NS between groups
361	Diabetic people with proteinuria (urinary albumin >300 mg/day), diabetic retinopathy, BMI >25 kg/m^2	1	After low calorie formula diet n=22	Before low calorie formula diet n=22	Changes in serum creatinine (µmol/l)	172.4 →130.8, p<0.0001
377	Obese diabetic people with nephropathy (urinary protein loss >500 mg/day) and diabetic retinopathy	12	After low calorie diet n=24	Before low calorie diet n=24	Changes in serum creatinine (µmol/l)	145.2 →101.2, p <0.001
260	Obese (BMI >27 kg/m^2) people with diabetic or nondiabetic nephropathy	5	Low calorie diet n=20	Usual diet n=10	Changes in protein loss (g/24 h)	Low calorie diet: 2.8 → 1.9 (-31%), p<0.05 Usual diet: 3 →3.5, NS p <0.05 between groups
361	Diabetic people with proteinuria (urinary albumin >300 mg/day), diabetic retinopathy, BMI >25 kg/m^2	1	After low calorie formula diet n=22	Before low calorie formula diet n=22	Changes in protein loss (g/24 h)	3.27 → 1.50, p <0.0001

Reference	Population	Duration (months)	Intervention	Comparison	Outcome	Size effect
[377]	Obese diabetic people with nephropathy (urinary protein loss >500 mg/day) and diabetic retinopathy.	12	After low calorie diet n=24	Before low calorie diet n=24	Changes in protein loss (%)	- 51%, p <0.01
[260]	People with diabetic or nondiabetic nephropathy and BMI >27 kg/m^2	5	Low calorie diet n=20	Usual diet n=10	Changes in BMI (kg/m^2)	Low calorie diet: 33 →31.6, p <0.01 Usual diet: 34.3 → 35, p <0.05 p <0.05 between groups
[361]	Diabetic people with proteinuria (urinary albumin > 300 mg/day), diabetic retinopathy, BMI > 25 kg/m^2	1	After low calorie formula diet n=22	Before low calorie formula diet n=22	Changes in BMI (kg/m^2)	30.4 →28.2, p <0.0001
[377]	Obese diabetic people with nephropathy (urinary protein loss >500 mg/day) and diabetic retinopathy.	12	After low calorie diet n=24	Before low calorie diet n=24	Changes in BMI (kg/m^2)	33.5 →26.2, p <0.001
[308]	Diabetic patients	60	Smokers n= 44	Non-smokers =141	Change in GFR (ml/min)	Non-smokers: 107 → 106, NS Smokers: 95 → 83, p <0.001
[155]	People with type 1 diabetes and nephropathy (persistent albuminuria >300 mg/24 h), presence of diabetic	84	Smokers n = 176 Ex-smokers n=31	Non-smokers n = 94	Change in GFR (ml/min/year)	Non-smokers: - 4.4 Ex-smokers: - 3.4 Smokers: - 4.0 NS between groups

Reference	Population	Duration (months)	Intervention	Comparison	Outcome	Size effect
	retinopathy					
[308]	Diabetic patients	60	Smokers n= 44	Non-smokers=141	Change in proteinuria (g/24 h)	Non-smokers: 0.47 → 0.54 Smokers : 0.36 → 0.44 NS between groups.
[309]	Case patients: ESRD Control patients: failure to progress to ESRD matched according to AKPKD or IgA-GN, gender, region of residence, and age at kidney death	N/A	5-15 pack-years n cases = 17 n controls = 11 >15 pack years n cases=29 n controls = 14	0-5 pack-years n cases = 26 n controls = 47	Progression to ESRD	5-15 pack years: unadjusted OR 3.5 (95% CI 1.3-9.6), p=0.017]. >15 pack years: unadjusted OR 5.8 (95% CI 2.0-17), p=0.001]
[162]	Cases: people with ESRD Controls: randomly selected from hospital admission lists	N/A	Smokers n=320 cases n=557 controls	Non-smokers n not stated	Progression to ESRD	OR 1.54 (95% CI 1.14-2.07)

8.3.5 From evidence to recommendations

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

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

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

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

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

8.3.6 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng203

8.4 Dietary intervention and renal outcomes (2008)

8.4.1 Clinical Introduction

Diet is considered one of the cornerstones in the treatment of CKD. Kidney function is essential for eliminating waste material from digested food and the body. As kidney function worsens, it may be necessary to alter a person's diet to reduce the problems resulting from the accumulation of waste products.[411] Dietary habits may be influenced by patient preference, lifestyle and cultural factors but dietary recommendations depend on the stage of disease, biochemistry, normal dietary intake, co-morbidities and nutritional status.[197] Dietary advice may include information about energy, protein, sodium, phosphate, potassium and fluid. [197] The overall aim is to prevent malnutrition, hyperkalaemia, hyperphosphataemia, and obesity and to aid the treatment of hypertension and (as CKD advances) alleviate uraemic symptoms. All of this must occur in the context of any other dietary modification a person might be following, such as a diabetic diet, to ensure a balanced healthy diet to meet individual nutritional requirements. [197]

Malnutrition is both a cause and consequence of ill health; it is defined as a state in which deficiency of nutrients such as energy, vitamins and minerals causes measurable adverse effects on body composition, function or clinical outcome.[322] It is very common in people with CKD[322] and can increase a person's vulnerability to disease and infections.[5] In people with CKD, one of the causes of malnutrition is loss of appetite secondary to uraemia.[197] Inadequate calorie intake lead to the breakdown of muscle to provide energy; this is a sign of malnutrition. As kidney failure progresses, people tend to eat less, and poor nutrition can become a major problem.[197]

Hyperphosphataemia becomes a significant problem in CKD stages 4 and 5.[41] Hyperphosphataemia has also been implicated as a risk factor for progression of CKD.[367,413] Dysregulation of calcium and phosphate can eventually result in renal bone disease if they are not controlled.[41] Dietary restrictions may not adequately control phosphate in severe kidney failure and phosphate binders, taken with food to prevent intestinal absorption of phosphate, are often prescribed (although it should be noted that certain phosphate binders are only licensed for use in patients on dialysis).[192,371] Hyperkalaemia is also a problem in people with advanced kidney failure particularly those taking renin angiotensin-aldosterone system antagonists.

Hyperkalaemia is also a problem in people with advanced kidney failure.[210] Dietary potassium should not be restricted routinely, only in those with raised serum levels, as potassium containing foods are required for a healthy balanced diet and restrictions need to be carefully monitored.[197]

Dietary protein restriction in the management of people with CKD has been debated since the first descriptions of delayed progression of kidney failure associated with severe dietary protein restriction in 1964.[124] The question about the clinical and cost effectiveness of low protein diets is reviewed in section 0. The details of the low protein evidence review from 2008 NICE CKD guideline (CG73)[277] have been removed and can be found in Appendix P

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

8.4.2 Methodology

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

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

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

8.4.3 Health economics methodology

There were no health economics papers found to review.

8.4.4 From evidence to recommendations

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

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

8.4.5 Recommendations

- The current recommendations can be found at www.nice.org.uk/guidance/ng203

8.5 Low protein diets [2014]

8.5.1 Introduction

The place of dietary protein restriction in the management of people with CKD has been debated since the first descriptions of delayed progression of kidney failure associated with severe dietary protein restriction in 1964.[124] The rationale for dietary protein restriction is that excess protein leads to the accumulation of metabolic waste products that may suppress the appetite and stimulate muscle protein wasting. The role of protein restriction in slowing progression of CKD is controversial. Advanced CKD is associated with a protein wasting syndrome directly correlated with morbidity and mortality. Insufficient protein intake may lead to loss of lean body mass, and malnutrition, especially in older people.

The NICE clinical guideline for the management of hyperphosphataemia[287] in patients with stage 4 or 5 CKD notes that the risks and disadvantages of a protein-restricted diet, with or without keto- and amino-acid supplementation, were greater than the benefit of the observed phosphate reduction. The hyperphosphatemia guideline GDG did not feel that the evidence they reviewed was sufficient to recommend restricting protein intake below minimum recommended nutrient intake levels, the accepted standards used for protein intake in adults. The hyperphosphatemia guideline made no recommendations about a protein restricted diet for the management of hyperphosphatemia in adults with advanced CKD.

Current dietary protein intake recommendations for healthy adults suggest an intake of at least 0.8 g/kg/day[290] whereas for people with CKD stages 1-4 the recommended intake is 0.6-0.75 g/kg/day.[3] This question therefore sought to determine the risk:benefit ratio of a dietary protein intake of 0.6-0.8 g/kg body weight per day on progression of chronic kidney disease and nutritional status

8.5.2 Review question: Are low protein diets a clinically and cost effective method for the management of CKD?

For full details see review protocol in Appendix C.

Table 63: PICO characteristics of low protein diets review question

Population	Adults (aged 18 and over) with CKD Subgroups: • Older people (≥75 years) • People with diabetes
Intervention/s	Low protein diet (0.6 - 0.8g/kg)
Comparison/s	Higher protein diet (greater than 0.8g/kg, free or unrestricted diet)
Outcomes	Critical: • CKD progression: change in eGFR • CKD progression: occurrence of end stage kidney disease, all-cause mortality • Cardiovascular mortality • Health related quality of life Important: • Compliance (measured by actual protein intake) • Nutritional status (measured by subjective global assessment) • Nutritional status (measured by change in BMI)
Study design	RCT or Systematic Review

8.5.3 Clinical evidence

We searched for randomised trials comparing the effectiveness of a low protein diet versus a higher protein diet for the management of CKD.

Studies were included if the actual protein intake matched the intervention and comparison and not only if the values in the studies' protocols matched the review protocol. The minimum duration of studies was 12 months.

The GDG decided not to consider protein restriction diets at levels lower than 0.6g/kg body weight/day as below this there was concern about the risks of protein malnutrition. The GDG also noted that studies investigating dietary protein restriction less than this usually give amino acid or keto-acid supplements to the low protein diet group, and that compliance is poor.

Two Cochrane reviews were identified for low protein diets in the management of CKD. One evaluated the effectiveness of low protein diet in patients with diabetic nephropathy but it was not relevant to the review protocol as it included "before and after" trials (within patient control) and some of the included studies had a duration of less than 12 months[346]. The other Cochrane review was in patients with CKD but no diabetes; it included studies where diets containing less than 0.6g/kg body weight/day of protein were used.[107] The actual protein restriction achieved was checked in these studies and all relevant studies from these Cochrane reviews were included in this review.

Ten studies were included in the review.[50,66,67,199,231,253,254,424,430] Two additional studies gave longer-term outcomes.[65,218]Evidence from these are summarised in Table 2 and the clinical GRADE evidence

profile below (Table 134). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

GFR measurements were analysed with the units reported in the study (except where values were given per second in which case this was calculated as per minute). No heterogeneity was identified in the meta-analysis.

Summary of included studies

Table 64: Summary of studies included in the review

Study	Intervention / comparison	Population	Outcomes reported	Comments
Brouhard et al. 1990[50]	Low protein diet (0.6g/kg body weight/day achieved not reported) Higher protein diet (1.0g/kg body weight /day achieved not reported) Duration 12 months	Insulin dependent diabetes mellitus and diabetic nephropathy n=15	Critical: • Progression of CKD (measured by occurrence of end stage kidney disease) • Progression of CKD (measured by change in mGFR) • Mortality (all-cause and cardiovascular)	• Baseline differences in eGFR • Small study size. • Compliance was assessed at 3 months. Method of assessment not reported. One patient requested to have normal diet reinstated.
Cianciaruso et al. 2008 (long term follow up Cianciaruso et al. 2009)[65,66]	Low protein diet (target 0.55, achieved 0.71g/kg body weight /day). Also given a multivitamin and mineral tablet. Higher protein diet (target 0.8, achieved 0.86g/kg body weight /day) Dietary sodium was restricted in all patients. Duration 48 months (18 months + 30 months)	Adults with basal eGFR ≤30 ml/min/1.73 m^2. 12% had diabetes. n=423	Critical: • Progression of CKD (measured by occurrence of end stage kidney disease) • Progression of CKD (measured by change in eGFR [MDRD6]) • Mortality (all-cause and cardiovascular) Important: • Compliance (measured by actual protein intake)	Median 30 months (Q1-Q3 21-39 months), reasons not reported.
Ciarambino et al 2012[67]	Low protein diet 0.7g/kg/day 7 days a week Low protein diet 0.7g/kg/day 6 days a week and normal protein diet on the 7th day Duration 30 months	Adults with Type 2 diabetes and chronic kidney disease stage 3 or 4 n=38	Critical: • Health related quality of life Important: • Nutritional status (measured by change in BMI)	

Study	Intervention / comparison	Population	Outcomes reported	Comments
Klahr et al. 1994 (MDRD) (long term follow up Levey et al. 2006A)[199,218]	Low protein diet (target 0.58, achieved 0.77g/kg body weight /day) Higher protein diet (target 1.3, achieved 1.11g/kg body weight /day) Also blood pressure control with ACE inhibitor ± diuretic for both groups. Duration 11 years (2 years + 9 years)	Non diabetic adults with GFR 25-55 ml/min/1.73 $m^{2.}$ n=585	Critical: • Progression of CKD (measured by occurrence of end stage kidney disease) • Progression of CKD (measured by change in mGFR) • Mortality (all-cause and cardiovascular) Important: • Compliance (measured by actual protein intake)	Change in mGFR – reported ml/min/3 years, likely to be transformed data. Unable to meta-analyse, long term follow up did not report GFR.
Locatelli et al. 1991[231]	Low protein diet (target 0.6g/kg body weight /day, achieved 0.73-0.8g/kg body weight /day) Higher protein diet (target 1g/kg body weight /day, compliance "good") Both groups also had calcium carbonate supplements and restricted phosphate intake. Hypertension controlled but ACE inhibitor and minoxidil were avoided as much as possible. Duration 2 years	Non diabetic adults with CrCl <60 n=456	Critical: • Mortality (all-cause and cardiovascular)	Reported change in CrCl not GFR and no SD or 95% CI reported.
Meloni et al. 2002[253]	Low protein diet (target 0.6, achieved 0.68g/kg body weight /day) Higher protein diet (free protein , mean 1.39g/kg body weight /day) Duration 12 months	Insulin dependent diabetes mellitus and diabetic nephropathy and hypertension treated with ACE inhibitor and calcium blocker n=69	Critical: • Progression of CKD (measured by change in mGFR) Important: • Compliance (measured by actual protein intake)	
Meloni et al. 2004[254]	Low protein diet (target 0.6, achieved 0.67g/kg body weight /day) Higher protein diet (free protein , mean 1.54g/kg body weight /day)	Adults with CKD. Only non diabetic subgroup met our protocol. n=89 in subgroup	Critical: • Progression of CKD (measured by change in mGFR) Important:	

Study	Intervention / comparison	Population	Outcomes reported	Comments
	Duration 12 months		• Compliance (measured by actual protein intake) • Nutritional status (measured by change in BMI)	
Rosman et al. 1989[352]	Low protein diet (target 0.6, achieved not reported) Higher protein diet (usual diet, achieved not reported) Duration 48 months	Adults with CKD, total number of people with diabetes unclear but <15%. n= 151	Critical: • Progression of CKD (measured by occurrence of end stage kidney disease) • Mortality (all-cause and cardiovascular)	• People from the control group were protein restricted if their serum urea exceeded 25 mmol/l • CrCl not GFR used and only median values reported
Williams et al. 1991[424]	Low protein diet (target 0.6, achieved 0.69g/kg body weight /day) Higher protein diet (target ≥0.8, achieved 1.14g/kg body weight /day) Duration (mean) 19 months	Adults with CKD, 12% with diabetic nephropathy. n=65	Critical: • Progression of CKD (measured by occurrence of end stage kidney disease) • Mortality (all-cause and cardiovascular) Important: • Compliance (measured by actual protein intake)	• Low protein group had lower urinary creatinine loss at baseline (10.2 versus 11.7) but no difference in serum creatinine
Zeller et al. 1991[430]	Low protein diet (target 0.6, achieved 0.72g/kg body weight /day) Higher protein diet (target ≥1.0, achieved 1.08g/kg body weight /day) Duration (mean) 35 months	Adults with Type 1 diabetes (onset before the age of 30) and diabetic nephropathy. n=35	Critical: • Progression of CKD (measured by change in mGFR) Important: • Compliance (measured by actual protein intake)	

Table 65: Clinical evidence profile: Low protein versus higher protein diets for the management of CKD

Quality assessment							No of patients/ percentage with event		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Low protein diet	Higher protein diet	Relative (95% CI)	Absolute	Quality	Importance
Progression of CKD (measured by end stage renal disease requiring RRT) (HR) - 48 months (follow-up mean 32)[65,66]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (a)	n=423	19%	21.9%	HR 0.98 (0.64 to 1.51)	4 fewer per 1000 (from 73 fewer to 93 more)	LOW	CRITICAL
Progression of CKD (measured by end stage renal disease requiring RRT) (HR) - 11 years[199,218]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious (b)	n=585	52.9%	58.8%	HR 0.89 (0.71 to 1.12)	42 fewer per 1000 (from 121 fewer to 42 more)	MODERATE	CRITICAL
Progression of CKD (measured by end stage renal disease requiring RRT) - 24 months[424]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (a)	n=65	1/31 (3.2%)	3.5%	RR 0.94 (0.06 to 14.27)	2 fewer per 1000 (from 33 fewer to 464 more)	LOW	CRITICAL
Progression of CKD (measured by end stage renal disease requiring RRT) - 48 months[352]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (a)	n=151	7/74 (9.5%)	3.9%	RR 2.43 (0.65 to 9.04)	56 more per 1000 (from 14 fewer to 314 more)	LOW	CRITICAL
Progression of CKD (measured by change in mGFR) - 12 months (final values, ml/min/1.73m^2) (measured with: Radioisotope chromium 51-EDTA cleaRance)[137]												
1	Randomised trials	No serious	No serious inconsistency	No serious indirectness	Serious (b)	n=89	44	45	-	MD 3.5 higher	MODERATE	CRITICAL

Quality assessment							No of patients/ percentage with event		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Low protein diet	Higher protein diet	Relative (95% CI)	Absolute		
		risk of bias								(2.18 to 4.82 higher)		
Progression of CKD (measured by change in mGFR) - 12 months (ml/min/year) (measured with: Radioisotope chromium 51-EDTA cleaRance)[253]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious (b)	n=69	35	34	-	MD 0.11 higher (0.71 lower to 0.93 higher)	MODERATE	CRITICAL
Progression of CKD (measured by change in mGFR) - 12 months (ml/min/month) (measured with: Radioisotope chromium inulin clearance)[50]												
1	Randomised trials	Serious (c)	No serious inconsistency	No serious indirectness	Very serious (a)	n=15	8	7	-	MD 0.4 higher (0.09 to 0.71 higher)	VERY LOW	CRITICAL
Progression of CKD (measured by change in mGFR) - 30-36 months (ml/min/month) (measured with: Iothalamate clearance)[430]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	n=35	20	15	-	MD 0.81 higher (0.64 to 0.98 higher)	HIGH	CRITICAL
Progression of CKD (measured by change in eGFR) - 48 months (ml/min/month) (measured with: 6 variable MDRD study equation)[65,66]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	n=392	200	192	-	MD 0.01 lower (0.1 lower to 0.08 higher)	HIGH	CRITICAL
Mortality (all-cause and cardiovascular) (HR) - 48 months (follow-up mean 32 months)[65,66]												

Quality assessment							No of patients/ percentage with event		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Low protein diet	Higher protein diet	Relative (95% CI)	Absolute	Quality	Importance
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (a)	n=423	11%	13%	HR 1.04 (0.59 to 1.83)	5 more per 1000 (from 51 fewer to 95 more)	LOW	CRITICAL
Mortality (all-cause and cardiovascular) - 24 months[231,424]												
2	Randomised trials	Serious (d)	No serious inconsistency	No serious indirectness	Very serious (a)	n=521	3/261 (1.1%)	2.4%	RR 0.73 (0.16 to 3.21)	6 fewer per 1000 (from 20 fewer to 53 more)	VERY LOW	CRITICAL
Mortality (all-cause and cardiovascular) - 48 months[352]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (a)	n=151	4/74 (5.4%)	9.1%	RR 0.59 (0.18 to 1.95)	37 fewer per 1000 (from 75 fewer to 86 more)	LOW	CRITICAL
Mortality (all-cause and cardiovascular) - 11 years[199,218]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious (a)	n=585	63/291 (21.6%)	22.4%	RR 0.96 (0.71 to 1.31)	9 fewer per 1000 (from 65 fewer to 69 more)	LOW	CRITICAL
Health related quality of life (SF-36) (follow-up 30 months; range of scores: 0-100; better indicated by higher values)[67]												
1	Randomised trials	Serious (e)	No serious inconsistency	No serious indirectness	No serious imprecision	None	19	19	-	MD 11.84 lower (12.14 to 11.55 lower)	MODERATE	CRITICAL

Quality assessment							No of patients/ percentage with event		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Low protein diet	Higher protein diet	Relative (95% CI)	Absolute		
Health related quality of life (SF-36) - SF-36 MCS (follow-up 30 months; range of scores: 0-100; better indicated by higher values)[67]												
1	Randomised trials	Serious (e)	No serious inconsistency	No serious indirectness	No serious imprecision	None	19	19	-	MD 12.2 lower (12.55 to 11.85 lower)	MODERATE	CRITICAL
Health related quality of life (SF-36) - SF-36 PCS (follow-up 30 months; range of scores: 0-100; better indicated by higher values)[67]												
1	Randomised trials	Serious (e)	No serious inconsistency	No serious indirectness	No serious imprecision	None	19	19	-	MD 11 lower (11.54 to 10.46 lower)	MODERATE	CRITICAL
Compliance (measured by actual protein intake) - 12-18 months[66,253,254]												
3	Randomised trials	No serious risk of bias	serious	No serious indirectness	No serious imprecision	n=581	291	290	-	MD 0.17 lower (0.19 to 0.15 lower)	MODERATE	IMPORTANT
Compliance (measured by actual protein intake) - 18-24 months[424]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	n=60	31	29	-	MD 0.45 lower (0.56 to 0.34 lower)	HIGH	IMPORTANT
Compliance (measured by actual protein intake) – 24-36 months[199,352]												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	n=613	306	307	-	MD 0.34 lower (0.36 to 0.32	HIGH	IMPORTANT

Quality assessment							No of patients/ percentage with event		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Low protein diet	Higher protein diet	Relative (95% CI)	Absolute		
										lower)		
Nutritional status (measured by change in BMI) - 12 months[254]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious (b)	n=89	44	45	-	MD 1.2 lower (2.51 lower to 0.11 higher)	MODERATE	IMPORTANT
Nutritional status (measured by change in BMI) - 30 months[67]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	19	19	-	MD 0.5 higher (0.15 to 0.85 higher)	HIGH	IMPORTANT

a The confidence interval crosses the minimum important difference in both directions, making the effect size very uncertain.
b The confidence interval crosses the minimum important difference in one direction, making the effect size uncertain.
c Baseline difference in mGFR between the groups: low protein group 80 (+/- 24) ml/min/1.73m^2 versus higher protein group 72 (+/-40) ml/min/1.73m^2. Direction of bias would favour low protein diet group. Small study n=15.
d Baseline characteristics not reported for one study[231] and comparable for limited number of factors (Urinary creatinine clearance differed at baseline between groups) in the other study.[424]
e Study not blinded; subjective outcome[67]

8.5.4 Economic evidence

Published literature

No relevant economic evaluations were identified

New cost-effectiveness analysis

New analysis was not prioritised for this area.

8.5.5 Evidence statements

Clinical

- For CKD progression measured by ESRD requiring RRT at 24 months[424], 48 months[65] or 11 years[218] low to moderate quality evidence suggested there was no clinical difference between low protein diets and higher protein diets. One study[352] did show a potential benefit of low protein diets at 48 months, however this was low quality evidence and there was still some uncertainty regarding the effectiveness of low protein diets.
- For CKD progression measured by change in GFR there was no clinically important difference between people on a low protein diet compared to those on a higher protein diet over a range of 12-48 months. The quality of the evidence was high to very low.[50,65,137,253,430]
- Low to very low quality evidence suggested that there may be advantages for low protein diets over higher protein diets for reducing cardiovascular and all-cause mortality at 24-48 months however the uncertainty of these effects was too large to make clear conclusions about clinical benefit.[65,231,352,424] No clinically important difference was seen for cardiovascular or all-cause mortality at 11 years, although again there was a large amount of uncertainty and the evidence was of low quality.[218]
- For older people with type 2 diabetes health related quality of life measured by SF-36 at 30 months favoured a low-protein diet (0.7g/kg/day) 6 days a week with one day of normal protein intake compared to 7 days a week of 0.7g/kg protein per day (considered a lower protein diet).[67]
- Moderate to high quality evidence showed that in all studies people were compliant with the diet they were randomised to at 12-36 months.[66,199,253,254,352,424] However, for nutritional status measured by change in BMI at 12 or 30 months moderate quality evidence suggested that there may be no clinical difference between low protein diets and higher protein diets.[67,254]
- There were no studies that reported nutritional status measured by subjective global assessment.

Economic

- No relevant economic evaluations were identified.

8.5.6 Recommendations and link to evidence

Recommendation	The current recommendations can be found at www.nice.org.uk/guidance/ng203
Relative values of different outcomes	The GDG considered that the critical outcomes for this question were progression of CKD measured by occurrence of end stage renal disease requiring renal replacement therapy (RRT) or change in GFR; mortality and health related quality of life. The important outcomes were compliance (measured by actual protein intake) and nutritional status measured by change in BMI or subjective global assessment.
Trade-off between clinical benefits and	The original CKD guideline looked at what dietary interventions were associated with improved renal outcomes in adults with CKD. At the time there was limited evidence

harms

pertaining to protein restriction and no evidence about optimal protein intake.

In light of this the GDG decided to ask a focused question about the clinical and cost effectiveness of low protein diets and ten studies were reviewed [50,66,67,199,231,253,254,352,424,430].

The intention of this review was to exclude very low protein diets, as the GDG were concerned about the risks of malnutrition. In the Modification of Diet in Renal Diseases study, in 255 patients with more advanced CKD (GFR 13-24 ml/min/1.73 m^2), a very-low-protein diet (0.28 g/kg/day) with a keto acid-amino acid supplement did not result in significantly slower decline in GFR compared with a low-protein diet (0.58 g/kg/day). However, longer term follow-up of these patients suggested that assignment to the very low protein diet was associated with greater mortality. It was also noted that many of the studies which have looked at very low protein diets prescribed adjunctive keto acid and/or amino acid analogues and this was considered a specialist intervention in selected people. The GDG acknowledged that very low protein diets could potentially be beneficial for people with CKD choosing not to have dialysis, but this was outside of the scope for this review.

The review did not show a consistent clinical difference between low protein diets and higher protein diets. The GDG considered that the protein levels included in this review could be considered as 'moderate' levels of protein, rather than 'low' or 'very low', but that if more extreme levels of protein restriction reduced progression of CKD, there would be a trade off at the expense of protein calorie malnutrition.

GFR was reported differently across trials as final values[137] and as change values in ml/min/month[50,430], ml/min/year[253] and ml/min/3 years[218]. Two studies[50,430] reported creatinine clearance and not GFR. Four[50,137,253,430] of the five studies reporting GFR used a reliable way of measuring GFR such as iothalamate clearance; one study[65] reported eGFR using the MDRD equation. The GDG had concerns regarding the study by Meloni et al. 2004[137] as this compared a low protein diet (target 0.6, achieved 0.67g/kg body weight /day) with a free protein diet (mean actual protein intake 1.54g/kg body weight /day). The GDG felt that this level of protein was higher than would be expected on a free protein diet and levels this high could be deleterious. They believed this could explain why people on the low protein diet performed so well in terms of kidney progression measured by mGFR compared to the control group in this study.

In one small (n=35) study,[430] a low protein diet was found to be clinically effective when compared to a higher protein diet at reducing progression of CKD measured by change in mGFR ml/min/month at 35 months. However this was countered by another, larger (n=392) study[65,66] that showed no clinical difference between low protein diets and higher protein diets at reducing progression of CKD measured by change in eGFR ml/min/month at 48 months. The evidence for this outcome was high quality from both studies. The evidence from other studies reporting CKD progression (of very low to moderate quality) did not support the use of low protein diets.

Different levels of protein restriction were used in the studies and there were differences in the range between low and higher protein intake in individual studies (over the eight RCTs this varied from 0.15-0.87g/kg body weight /day difference between the groups). Overall there was good compliance at 12-36 months,[66,199,253,254,352,424] however, health related quality of life measured by SF-36 at 30 months favoured a low protein diet 6 days a week compared to 7 days a week.[67]

Most studies did not report nutritional status. Moderate quality evidence from two studies reporting change in BMI at 12 or 30 months suggested that there was no

	clinical difference between low protein diets and higher protein diets.[67,254] No studies reported nutritional status measured by subjective global assessment.
Economic considerations	There was no cost effectiveness evidence. Given the uncertainty about the effectiveness and potential harm associated with these diets, it must be concluded that their cost-effectiveness is also questionable.
Quality of evidence	Ten RCTs were identified ranging from high to very low quality evidence. The studies were predominately conducted in USA and Italy with one study conducted in the UK. Studies are now fairly old – publication dates ranged from 1989 to 2009 (one study was published 23 years ago and since then diets and the foods available have changed. No studies reported participant blinding, however as all the outcomes except for the SF-36 were objectively collected this did not affect the quality of the evidence.
Other considerations	The GDG acknowledged that compliance with low protein diets can be poor and therefore these diets are most successful in more motivated people. In the current review, studies were included on actual level of protein intake, so compliance was good in all the included studies. All studies except one [50] used urinary excretion of urea to assess compliance either throughout the study or to establish reliability of patient diaries and/or dietician interviews. The GDG also considered that these diets are most appropriate in people with uraemic symptoms. In most studies included in the review, regular dietician support was provided and it is unknown if such good compliance can be achieved without this additional support. The GDG noted that there could be a difference between studies comparing a 'usual protein diet', 'high protein diet' and 'free protein diets'; across the studies in this review all three of these comparisons were used. It was noted that eight of the included studies were in people aged less than 75 years of age. One study[65] reported a mean age of 61 ± 18, however the actual number of people aged 75 and over was not reported. One study[67] particularly looked at the long term effects of low protein diet on quality of life in older people with Type 2 diabetes (mean age 71 years, people under 65 excluded).The GDG agreed that there was no need for different considerations for people over the age of 75 as this age group was believed to generally have a protein intake at or below 0.8g/kg body weight/day. The GDG acknowledged that an individual's need for dietary advice and intervention would vary according to many factors including their age, GFR, the presence of proteinuria and the cause of CKD amongst other factors. The GDG noted that the evidence indicated that a high protein intake is potentially harmful for CKD patients, but this aspect was not part of the review protocol. The GDG agreed that the current evidence available did not support the use of low protein diets for all people with CKD in order to reduce their risk of progression. There was limited evidence and further longer duration trials for specific populations would be useful to inform future management of CKD patients. The CKD GDG noted that the NICE hyperphosphataemia Clinical Guideline (CG157)[287] made specific recommendations regarding low and very low protein diets for people with CKD and hyperphosphataemia. The hyperphosphataemia guideline focused upon people with stage 4 or 5 CKD who were not on dialysis and were interested to know; i) whether the dietary management of phosphate was effective compared to placebo or other treatments and ii) in managing serum phosphate and its associated outcomes which dietary methods are most effective? The review looked at interventions that were based on varying degrees of restriction in the intake of

	phosphate and/or protein, with or without supplementation with keto and amino acids. The evidence was assessed as very low quality and the hyperphosphataemia guideline GDG did not feel that the evidence they reviewed was sufficient to recommend restricting protein intake below minimum recommended nutrient intake levels, the accepted standards used for protein intake in adults.

8.6 Self-management

Introduction

8.6.1 Self-management of CKD can be defined as involving the individual with CKD in a working partnership with their families/carers and health professionals with the goal of empowering and preparing them to manage their health care and help them live with their CKD. Whatever delivery system is designed to achieve this goal needs to assure provision of effective, efficient clinical care and self-management support. The composition and interactions of the working partnership need to be described and the CKD care provided has to be consistent with scientific data and patient choice (no decision about me without me). There must be no failure in delivery of best care. Successful self-management will also require clinical information systems that are reliable, capture the right data and are fit for purpose.

The degree to which self-management is achievable will depend on patient preference and a variety of other factors such as language barriers and patient age, gender, and education level. Disease-specific factors such as co-morbidities and cognitive and functional impairment are additional barriers to achieving successful self-management.

Patients will need to know their condition and the various treatment options and have a care plan that details the activities they need to engage in to protect and promote their health. They will need to know how CKD is monitored and how to recognise and manage important complications. They will also need to know how to manage the impact of CKD on their physical functioning, emotions and interpersonal relationships. The overall aim is to have informed people actively participating in their CKD care leading to maintained health, and prevention or amelioration of progression of CKD and its complications. That in turn should also achieve reductions in unplanned health service utilisation.

The key question is whether or not chronic disease self-management is effective for CKD. The purpose of these two related questions was to define the important components of CKD self-management, describe existing systems or models of CKD self-management, and determine the clinical and cost effectiveness of CKD self-management.

Review question: For people with CKD, what is the clinical and cost effectiveness of self-management support systems?

8.6.2 For full details see review protocol in Appendix C.

A summary of the protocol is presented in Table 66.

Table 66: PICO characteristics of self-management review question

Population	Adults (aged 18 and over) with CKD **Subgroups:** • Older people (≥75 years) • People with diabetes • BME groups
Intervention/s	Self-management support systems, e.g. renal patient view (internet based system)

Comparison/s	Usual care
Outcomes	**Critical:** • CKD progression: change in eGFR • CKD progression: occurrence of end stage kidney disease (ESRD or ESKD as reported by the study) • All-cause mortality • Cardiovascular mortality • Health related quality of life • Hospitalisation **Important:** • Adherence (to treatments) • Outpatient attendance (including frequency of attendance)
Study design	• Randomised controlled trials (RCTs), if no RCTs consider observational studies / qualitative reviews / surveys / abstracts

8.6.3 Clinical evidence

A search was conducted for all study types investigating the effectiveness of self-management compared to usual care. In addition to the abstract list from medical databases, the websites of registered stakeholder organisations were searched. In the first instance RCTs were selected but since only three trials were identified other evidence was also considered. Three RCTs (two papers on one study)[31,60,153,422] and one qualitative study[264] were reviewed. A variety of interventions was used and the main characteristics are outlined in Table 67. Evidence from the RCTs are summarised in the clinical GRADE evidence profile below (Table 134) and evidence from the qualitative study is presented in section 8.6.3.2. See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

8.6.3.1 Summary of included studies

RCTs

Table 67: Summary of studies included in the review

Study	Intervention/comparison	Population	Outcomes	Comments
Barrett 2011[31]; Hopkins 2011[153]	Nurse-coordinated care focusing on risk factor modification n=238 The nurse followed medical protocols and worked in close collaboration with a nephrologist. Plus usual care. Defined as care delivered by a family doctor providing assessments and treatments for their parents as they saw fit. The family doctors could consult specialists or involve allied health personnel if necessary.	Patients with elevated serum creatinine levels identified by community laboratories, and their family physicians were then asked to consider referring the patient to the study. Inclusion criteria: Aged 40 to 75 years and had documented CKD with an estimated GFR (eGFR) between 25 and 60	• Progression of CKD • Dialysis • Mortality (all-cause) • Mortality (cardiovascular) • Health-related quality of life • Hospitalisation • Outpatient attendance	Self-management: Delivering care took 12 minutes of nephrologist time and 187 minutes of nursing time per working day

Study	Intervention/comparison	Population	Outcomes	Comments
	Additional clinical care delivered by a study nurse and nephrologist guided by protocols aimed at achieving the pre-specified targets but focused on the needs of the individual. Most intervention-group patients were seen for additional interim study visits to address identified clinical issues. There was emphasis on patient self-management and working collaboratively Usual care (as described above) n=236	ml/min/1.73 m^2		
Chen 2011[60]	Self-management Provision of information, reinforced learning incentives and encouraged self-care and maintenance of the therapeutic regimen. Support came from a multidisciplinary force of management nurses, dieticians, peers and volunteers. The program included the provision of health information, patient education, telephone-based support and the aid of a support group. The health information and education comprised an integrated course involving individualised lectures on renal health, nutrition, lifestyle, nephrotoxin avoidance, dietary principles and pharmacological regimens. The lectures were delivered by the case-management nurse, according to guidelines in a standardised instruction booklet. Program included telephone-based support, support groups and dietary counselling n=27 No self-management No details	Incidental pre-dialysis CKD (stages III-V) Inclusion criteria: aged 18-80 years with the ability to communicate verbally and orally in Taiwanese and Mandarin	• Progression of CKD • Mortality • Hospitalisation	n=6 refused to participate

Study	Intervention/comparison	Population	Outcomes	Comments
	n=27			
Williams 2012 [422]	Self-monitoring of blood pressure Individualised medication review 20 min Digital Versatile Disc (DVD) Fortnightly motivational interviewing follow-up telephone contact for 12 weeks to support blood pressure control and optimal medication self-management Delivered by an intervention nurse with renal specialist and doctoral qualifications trained in motivational interviewing n=39 Usual care Blood pressure control was the most important aspect of standard care and care was dependent on the patients' individual circumstances and morbidity n=41	People age ≥ 18 years of age who comprehended English, who were mentally competent, who had Type 1 or Type 2 diabetes and CKD estimated by a Modified Diet in Renal Disease eGFR > 15 (≤ 60 ml/min/1.73m²) or diabetic kidney disease (microalbumin/creatinine rations > 2.0 mg/mmol for men, > 3.5 mg/mmol for women), a systolic hypertension ≥ 130 mmHg treated with prescribed hypertensive medication	• Adherence to treatments	n=1389 assessed for eligibility
Mukoro 2012 - Renal patient view[264]	Secure internet based system that enables kidney patients to view their live test results online and obtain information about their kidney disease. The system was designed specifically for patients to use and is available at 43 of 52 kidneys units in England with over 17 000 registered users. NHS Kidney Care supported the further improvement of Renal Patient View (RPV) by commissioning the development of enhanced interactive capabilities, including online discussion forum, and tools to help patients add data such as blood pressure, glucose and weight readings to their records Patient surveys: 9 kidney units 257 responses from 507 invitations	The majority of respondents were patients (89%). Two-thirds of respondents have had a form of renal replacement therapy (RRT), including kidney transplantation (45%), haemodialysis (13%) and peritoneal dialysis (8%). Nearly all participants who were not RRT patients reported having functioning kidneys, although 3% were in conservative care pathway. Over 70% of respondents indicated that they were well-informed	• Narrative review	

Study	Intervention/comparison	Population	Outcomes	Comments
	Staff survey: 10 kidney units n=108 respondents	about their kidney disease and engaged in decisions about their care.		

Study	Population	Methods	Limitations
RPV[264]	Patient surveys: 9 kidney units 257 responses from 507 invitations Staff survey: 10 kidney units n=108 respondents The majority of respondents were patients (89%). Two-thirds of respondents have had a form of renal replacement therapy (RRT), including kidney transplantation (45%), haemodialysis (13%) and peritoneal dialysis (8%). Nearly all participants who were not RRT patients reported having functioning kidneys, although 3% were in conservative care pathway. Over 70% of respondents indicated that they were well-informed about their kidney disease and engaged in decisions about their care.	Online patient and staff survey; patient and staff interviews. Grounded theory principles used to analyse the interview data.	None – clear data collection and analysis. Good validity (for example context clearly described, reliable methods).

Table 69: Clinical evidence profile: Self-management support systems versus usual care

Quality assessment							Summary of Findings					
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self-management (n) Mean (SD) or Event rate	Usual care (n) Mean (SD) or Event rate	Relative (95% CI)	Absolute effect / Mean Difference or other measures of effect size (95% CI)	Quality	Importance
Progression of CKD (eGFR) (follow-up 12 months; better indicated by higher values)[60]												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	27	27	-	MD 13.39 higher (4.64 to 22.14 higher)	LOW	CRITICAL
Progression of CKD (follow-up 24 months; better indicated by higher values)[31]												
1	Randomised trials	Very serious[c]	No serious inconsistency	No serious indirectness	Very serious[d]	None	n=310 in total	n=310 in total	-	Repeated measures adjusted p=0.009 in favour of self-management, difference in marginal mean 1.4 ml/min/1.73 m^2 (95%CI 0.36 to 2.5). Increase in eGFR at months 4 and 8 with similar rate of decline thereafter.	VERY LOW	CRITICAL
Dialysis (follow-up 24 months)[31]												
1	Randomised trials	Very serious[c]	No serious inconsistency	No serious indirectness	Very serious[d]	None	2/238 (0.84%)	0.4%	RR 1.98 (0.18 to	4 more per 1000 (from 3 fewer to 83	VERY LOW	CRITICAL

Quality assessment							Summary of Findings					
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self-management (n) Mean (SD) or Event rate	Usual care (n) Mean (SD) or Event rate	Relative (95% CI)	Absolute effect / Mean Difference or other measures of effect size (95% CI)	Quality	Importance
									21.72)	more)		
Health-related quality of life (Health Utility Index) (follow-up 24 months; better indicated by higher values)[153]												
1	Randomised trials	Very serious[c]	No serious inconsistency	No serious indirectness	N/A[e]	None	238	236	-	Self-management +0.024 Usual care -0.021 p=0.01 in favour of self-management. Minimally important difference 0.05	LOW	CRITICAL
Mortality all-cause (follow-up 12-24 months)[31,60]												
2	Randomised trials	Very serious[f]	No serious inconsistency	No serious indirectness	Very serious[d]	None	7/265 (2.6%)	1.1%	RR 2.13 (0.6 to 7.5)	26 more per 1000 (from 9 fewer to 149 more)	VERY LOW	CRITICAL
Mortality cardiovascular (follow-up 24 months)[31]												
1	Randomised trials	Very serious[c]	No serious inconsistency	No serious indirectness	Very serious[d]	None	2/238 (0.84%)	0.9%	RR 0.99 (0.14 to 6.98)	0 fewer per 1000 (from 8 fewer to 54 more)	VERY LOW	CRITICAL
Hospitalisation all-cause (follow-up 12 months)[60]												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	5/27 (18.5%)	44.4%	RR 0.42 (0.17 to 1.02)	258 fewer per 1000 (from 369 fewer to 9 more)	LOW	CRITICAL

Quality assessment							Summary of Findings					
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self-management (n) Mean (SD) or Event rate	Usual care (n) Mean (SD) or Event rate	Relative (95% CI)	Absolute effect / Mean Difference or other measures of effect size (95% CI)	Quality	Importance
Hospitalisation (annualised resource use per patient year) (follow-up 24 months; better indicated by lower values)[153]												
1	Randomised trials	Very serious[c]	No serious inconsistency	No serious indirectness	N/A[e]	None	238	236	-	Self-management 0.47 Usual care 0.58 p=0.03 in favour of self-management	LOW	CRITICAL
Adherence to treatments[422]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[d]	None	24/36 (66.7%)	64.1%	RR 1.04 (0.75 to 1.45)	26 more per 1000 (from 160 fewer to 288 more)	LOW	IMPORTANT
Outpatient attendance (annualised resource use per patient year) (follow-up 24 months; better indicated by lower values)[153]												
1	Randomised trials	Very serious[c]	No serious inconsistency	No serious indirectness	N/A[e]	None	238	236	-	Self-management 4.34 Usual care 4.25 p=0.58	LOW	IMPORTANT

a Unclear allocation concealment
b The 95%CI crosses the minimally important difference (MID) for either benefit or harm
c Unclear randomisation and unblinded
d The 95%CI crosses the MID for benefit and harm
e Imprecision could not be assessed, no variance reported
f 2/2 unclear allocation concealment 1/2 unblinded

8.6.3.2 Renal patient view[264] summary of evidence

Qualitative report

The most frequently visited section of RPV was results followed by patient information.

39% of patients had entered a blood pressure reading. 11% had not entered any reading. Most people reported using RPV when they were expecting results, when a test result worried them or after a visit to the hospital/GP.

Survey findings

Patients

Using RPV…(strong agree or agree) (top five reasons reported here)

- Makes me feel more in control of my medical care 88%
- Gives me better understanding of my renal disease 89%
- Helps me communicate better with my doctor 79%
- Helps me to be more involved in decisions about my care 75%
- Reassures me about my treatment 77%

Opinions and perceived benefits of using the forum (top five benefits of using the forum reported only)

n=103 patients

Strong agree or agree

- The forum is a good place for learning from others (61%)
- The forum has helped me to learn about symptom(s) I experienced (45%)
- The forum is helping me cope better with problems in my life (32%)
- The forum is a good place of social support (48%)
- The forum has helped me to find ways of reducing treatment side effects (27%)

Staff

- 69% of respondents were nurses and 19% were Doctors.
- 87% of respondents said their patients used RPV
- 76% respondents said they discussed RPV some of the time or more often
- 97% of respondents were either quite or very supportive of their patients using RPV

Positive statement where >80% of respondents strongly agreed or agreed:

- Helps my patients to be more involved in decisions about their care
- Helps my patients to be more engaged in their care planning
- Gives my patients a better understanding of their kidney disease
- Users are more informed about their kidney disease

30% of respondents strongly agreed or agreed that users misunderstand information they access in RPV

15% strongly agreed or agreed that RPV makes more patients more anxious about their kidney disease

12% strongly agreed or agreed that is has resulted in an overall increase in my workload

Qualitative themes

Patients

Patient interest and involvement

Patients using RPV are very involved in their own care and are keen on knowing the status of their kidney function. RPV is a useful tool that allows them to monitor trends over time.

Some professionals noted that not all patients want to be involved with their care and are not willing to use RPV.

Patient understanding of issues around their kidney health

Using RPV makes people more aware of their results and the relevance of the tests carried out at the hospital. RPV users understood how changes in lifestyle could impact on their health and that being able to see their results enables them to make adjustments to their lifestyle, especially their diet, where necessary.

Patient empowerment

RPV enhances patients' awareness and ability to self-care. Users of RPV were less reliant on professionals to make decisions and manage aspects of their care

Providing reassurance

Early access to results helped to remove uncertainties and unnecessary worry especially when they are feeling unwell or after a recent blood test. Using RPV gave them "piece of mind" and a sense of reassurance that, in the events of unexpected or declining results, they could react quickly to get help and abate any potential problems

Preparedness for consultations with healthcare team

RPV made users better prepared for consultations or meetings with a health professional.

Patient-staff communication

RPV users tend to instigate communication with their health professionals when they had concerns about their results

Patient satisfaction and patient experience

Patients felt their experience with the hospital and their care had improved since they started using RPV. For some patients, knowledge gained by their usage of RPV makes them feel "respected" by healthcare professionals.

Effect of using RPV on staff

Quality of practice and patient safety

Instances when an abnormal test results was acted on quicker than it would have been had they not been on RPV

Demands on staff time

Patient demand on staff time had been reduced as a result of using RPV. Professionals' time is better utilised because they are already aware of their own results prior to consultations

8.6.4 Economic evidence

Published literature

One study was included with the relevant comparison.[153] This is summarised in the economic evidence profile below (Table 70). See also the study selection flow chart in Appendix E and study evidence tables in Appendix H.

Another study that met the inclusion criteria was selectively excluded due to it being only partially applicable and having very serious limitations. It was a Taiwanese costing study. – see the list of excluded studies in Appendix K.

Table 70: Economic evidence profile: Self-management and support interventions versus usual care

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Hopkins 2011 (Canadian CUA)	Partially applicable*	Potentially serious limitations**	Compares a goal setting and risk target intervention with usual care for people with CKD stage 3-4.	- £614	0.046 QALYs	Intervention is dominant over usual care	The result was robust to changes in assumptions

**The study was conducted in a Canadian setting and therefore costs and resource use could be different to the UK NHS. The quality of life weights used the HUI-3, not the EQ-5D.*
***In guideline review of clinical effectiveness, it was noted that the trial was unblinded and the randomisation method was unclear.*

The single analysis from Hopkins2011 appears to show, that the use of more focussed and intense therapy, with involvement of a nurse specialist and /or a nephrologist, saves money and increases health benefits. The analysis was from a Canadian study and was only done over two years, but it did show the intervention to be dominant over standard care at CKD stages 3 and 4. This means that more intense therapy with patients at risk of CKD could be cost effective, although it was based on a trial which was rated as being at high risk of bias in the review of clinical effectiveness.

8.6.5 Evidence statements

Clinical

- Low and very low quality evidence from 2 RCTs suggested that self-management programmes (Nurse-coordinated care focussing on risk factor modification or programmes focussing on provision of information, reinforced learning incentives and encouraging self-care and maintenance of the therapeutic regimen delivered by a multidisciplinary team) do not reduce progression of CKD measured by change in GFR or progression to dialysis, and this may be lower in the groups who did not participate in self-management programmes. However, there was a lot of uncertainty in the effect.
- Very low quality evidence from 2 RCTs suggested that there may be an increase in all-cause mortality in the groups that participated in self-management programmes, and no difference in cardiovascular mortality. However, the event rates were low and there was uncertainty in the effect.
- Low quality evidence from 1 RCT indicated that hospitalisation was reduced by self-management programmes focussing on provision of information, reinforced learning incentives and encouraging self-care and maintenance of the therapeutic regimen delivered by a multidisciplinary team when compared to no self-management programme.
- An RCT of a programme of self-monitoring of blood pressure and individualised medication review did not demonstrate a difference in terms of adherence to treatment (low quality evidence).

Summary of evidence from renal patient view is provided in the narrative summary in section 8.6.3.2

Economic

- One cost–utility analysis found that in people with CKD stage 3 or 4, a nurse-led goal setting and risk target intervention was dominant (less costly and more effective) compared to usual care. This analysis was assessed as partially applicable with potentially serious limitations.

8.6.6 Recommendations and link to evidence

Research recommendation	• **Does the provision of educational and supportive interventions to people with chronic kidney disease (CKD) by healthcare professionals increase patients' skills and confidence in managing their conditions and improve clinical outcomes?**
Relative values of different outcomes	The GDG agreed that progression of CKD, (measured by change in eGFR and occurrence of end stage renal disease), mortality, health-related quality of life and hospitalisation were all outcomes that were critical to decision making. However, no outcome information was identified for hospitalisation or health related quality of life. Adherence to treatments and outpatient attendance (including frequency of attendance) were also thought to be important outcomes to consider. The GDG were also interested in whether data were available for the following subgroups: • Older people (75 years and older). • People with diabetes. • BME groups. The GDG noted that no evidence was found for the question regarding what information and support is required for people using self-support systems.
Trade-off between clinical benefits and harms	The GDG noted that the recommendations in the original CKD guideline were about information and lifestyle (for example exercise, diet and smoking cessation) rather than self-management or self-management systems. Any new recommendations would be an addition to and not a substitute for the earlier recommendations. Although there is potential to harm with uninformed self-care, the GDG agreed that self-care should be encouraged. The evidence reviewed in this chapter was limited and only two randomised controlled studies of short duration and a qualitative survey from a stakeholder organisation website were found of relevance to the question. Based upon the 2 RCTs, one Taiwanese60 and one Australian,422 there is little evidence in a CKD population that self-management demonstrates positive outcomes. The studies were both small with n=54 and n=80 respectively. The Chen study was undertaken in a Taiwanese population (n=54) and the GDG noted that the outcomes may not be applicable to all populations. Furthermore, baseline characteristics were different in the two study groups in particular with regard to eGFR; in the self-management group eGFR was 27 versus 23 ml/min/1.73 m2 in the standard care group. The primary end points of CKD progression and number of hospitalisations both favoured the self-management group. The GDG felt that it was difficult to assess CKD progression in a year in such a small trial particularly as the GDG were aware of a general population study of un-referred CKD180 in whom the participants' median eGFR was 28 ml/min/1.73 m2 (in over 3,000 people) and only 8% of these people had a decline in eGFR of more than 5vml/min/year over a three year follow-up period. In the light of this, the GDG agreed that the Chen study population appeared to be highly selected. Williams et al.422 found no difference between self-management and usual care groups in relation to treatment adherence. The self-management element included individualised medication reviews (for people with known hypertension, diabetes and CKD), a DVD and motivational interviewing with follow-up telephone contact compared to standard care. The GDG agreed it

was not possible to distinguish between people being intentionally non-adherent to their medicines (i.e. due to concerns relating to side effects); or non-intentionally non-adherent (i.e. due to forgetting to take their medicines).

The GDG also reviewed qualitative findings from a survey report about Renal Patient View (RPV).[264] RPV is a secure internet based system that enables people with kidney disease who are attending specialist renal clinics to review their current information on-line, including diagnoses, blood results and prescribed medicines, and to view letters written about them. Within RPV there are also links to web-based information sources concerning medicines and diagnoses enabling patients to obtain a wealth of information about their kidney disease. The GDG agreed that the survey provided rich qualitative information (9 UK kidney units with 257 respondents). Respondents reported that RPV increased their control of their medical care, gave them a better understanding of their kidney disease, enabled better communication with their doctor, made them feel more involved in decisions about their care, and reassured them about their treatment. In addition the RPV forum enabled learning from others. The GDG noted that, where available, RPV can be accessed by all people with chronic kidney disease whether they are receiving dialysis, have a functioning transplant or are not receiving renal replacement therapy.

The GDG noted that a potential limitation with RPV is that its use is restricted to patients under the care of a renal department in secondary care. The system is currently unavailable for patients in primary care. RPV is currently funded locally by renal units, although access is not universal. The GDG also acknowledged a further limitation in that people with CKD may have multiple co-morbidities and present to other specialities but the information held on RPV is unavailable to other healthcare areas unless shared by the individual themselves.

The GDG agreed that the qualitative evidence derived from the RPV survey was overwhelmingly positive and a recommendation for self-management could be made based upon this. Elements of self-management that the GDG thought were important included: access to a multidisciplinary team for support; the opportunity for telephone or face to face contact; and availability of training packages and information for people with CKD, their carers and health professionals. The GDG agreed that primary care should encourage people with CKD to adopt these elements of self-management until such a time when an RPV-like system is available to all.

The GDG were aware of the NICE guideline for Patient experience in adult NHS services (CG138) and agreed that recommendations within this guideline relate to aspects of self-management.[275]

Despite the limited RCT evidence, the GDG agreed that self-management systems should be recommended and unanimously agreed that the concept of self-care should be actively encouraged.

In addition to making recommendations, the GDG debated the need for future research recommendations and agreed that there was value in better defining which aspects of self-management improve patient care in people with CKD. They also agreed that self-management systems should be tailored to the stage of CKD. The GDG agreed that further research was required to establish how self-management can be encouraged for Asian, black and minority ethnic groups, those with multi-morbidity and the hard to reach groups including

	those with poor health literacy, cognitive impairment and low socio-economic status, and this was noted within the research recommendation. Full details of which are in Appendix N. The GDG acknowledged the recently completed Kidney Research UK project in early CKD (ENABLE) and were also aware of an on-going RCT on self-management in primary care in England (BRinging Information and Guided Help Together (BRIGHT) in people with stage 3 chronic kidney disease).[40]
Economic considerations	A Canadian cost utility analysis from 2009 (Hopkins 2011)[153] in people with stage 3 CKD showed that a self-management support system was dominant (less costly and greater QALY gain) over usual care. The GDG considered that the health benefit from self-management support systems could outweigh the additional costs associated with this intervention. Although this study was rated as partially applicable (due to setting and utility measure) and with potentially serious limitations (due to issues with randomisation and blinding).
Quality of evidence	Two randomised controlled trials were of low quality, small sample sizes and had short follow-up periods. The GDG agreed that there was a lack of high-quality RCT evidence and a clear definition of 'self-management'. The GDG agreed that the concepts of self-management and information provision overlap. The RPV survey had good validity with a clear data collection and analysis underpinning it and the GDG were able to make recommendations based upon this.
Other considerations	The GDG patient representatives described their experience of self-management and their views concurred with the findings of the RPV survey. They described that Renal Patient View (RPV) has enabled them *'to manage blood results and learn from these blood results'*. Previously they were required to *'phone in for their results and this could be a frustrating experience with concerns about blocking the phone line and taking up nursing time. With RPV, blood results are usually available within 24hrs and hence provide an up-to-date result that can be compared with previous results enabling people to easily see trends in their result. The patient can share results with family members, or carers which helps those caring for the patient to understand why alterations may be needed in diet, or if they can give added support with adherence to medication e.g. phosphate binders. RPV can also assist people to prepare in advance for consultations with health care professionals. They have time to think of questions that may ordinarily be forgotten in a clinic appointment, for example, the subtleties of some of the immuno suppressants or the impact of taking calcium or steroids*'. In addition the patient representatives described RPV as '*having the benefit of providing a description of the range for their results and if blood results are falling outside of this range what the patient should be looking at. RPV also has the opportunity for the patient to record their blood pressure results. The system also acts as a hub of credible information links for example the local Kidney Patients Association'*. It was acknowledged that the potential limitations of the system are that it does depend upon someone being motivated (as does anything pertaining to self-management) and having access to a ready source of fairly instant information could make some people overly anxious. However the GDG patient representatives agreed '*that RPV bought massive benefits to people with chronic kidney disease*'. They described feeling '*more empowered* to *ask questions and have conversations about care with the consultant and that, partnerships in care are important*'. RPV is partly self-management but linked with involvement, for example self-monitoring of ciclosporin levels enabling dose adjustment accordingly. The patient representatives confirmed that currently this happens to a limited

	extent as some people with CKD determine when they take their erythropoiesis stimulating agent (ESA) based upon their haemoglobin level. In addition, one patient representative highlighted the development of an 'app' to help patients manage their appointments and key aspects of treatment including medicines management. In addition, the GDG noted that self-management is often poorly defined and described in the literature. The GDG debated the difference between information provision and self-management and agreed that it is difficult to tease out the essential success elements within a self-management package of care. They debated self-management across other chronic conditions such as asthma, COPD, type I and type II diabetes, atrial fibrillation, psoriasis and agreed that it was often difficult to pin-point factors of success. The GDG noted the Health Foundation report published in 2011 pertaining to self-management across a whole spectrum of chronic conditions.[394] Importantly, the GDG were aware that CKD is under recognised in primary care and that some people with CKD are not notified of their diagnosis. In the Health Survey of England the prevalence of doctor diagnosed CKD was only 1.5%, far lower than that expected or that recorded in the Quality and Outcomes Framework data.[139] A further study found that 41% of participants (n=1741) were unaware of their CKD diagnosis, after multiple adjustment age remained a significant predictor of CKD diagnosis awareness (those aged <75 years were more likely to be aware of their diagnosis).[251] Knowing the diagnosis is a prerequisite for being able to self-manage. The issue of disclosure is a significant one in CKD. In contrast to other common chronic diseases, CKD is rarely clinically manifested at the stages when management may have the greatest impact on prognosis. Disclosure and patient awareness may therefore impact on outcomes.

9 Referral criteria

9.1 Indications for referral to specialist care

9.1.1 Clinical introduction

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

The area that has deservedly received the most attention is planning for renal replacement therapy. There is abundant literature detailing the negative effect of late referral of patients with advanced CKD. Late referral leads to increased morbidity and mortality, increased length of hospital stay, and increased costs.[184,185,223,269,336,370] Several factors contribute to the adverse outcomes associated with late referral, including untreated anaemia, bone disease, hypertension and acidosis. The dominant factor though is insufficient time to prepare the patient for dialysis, particularly the establishment of permanent vascular access for haemodialysis.

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

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

What are the criteria for referral to specialist care?

This section was partially updated in 2018. See www.nice.org.uk/guidance/NG203/evidence for the 2018 evidence reviews.

9.1.2 Methodology

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

9.1.3 Health economics methodology

There were no health economics papers found to review.

9.1.4 Evidence statements

There are no evidence statements.

9.1.5 From evidence to recommendation

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

The GDG consensus was that the principles guiding referral should be: early identification of people

likely to require renal replacement therapy, the need for additional input to the management of CKD,

e.g. for uncontrolled hypertension, the need for specialist advice about rare or genetic causes of CKD and the need to access specialist investigations such as magnetic resonance angiography.

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

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

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

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

9.1.6 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng203

Pharmacotherapy

Blood pressure control in people with CKD

9.2 Optimal blood pressure ranges

9.2.1 Clinical introduction

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

General aspects of blood pressure management will not be covered in this guideline but for advice relating to measuring blood pressure and lifestyle interventions to reduce blood pressure please see NICE clinical guideline 127 ('Hypertension: management of hypertension in adults in primary care').

The UK CKD guidelines[354] recommended that the threshold for initiation and subsequent adjustment of antihypertensive therapy should be 140/90 mmHg for patients without proteinuria, and 130/80 mmHg for those with a PCR >100 mg/mmol. Antihypertensive therapy should be adjusted to achieve blood pressure <130/80, or <125/75 mmHg for those with a PCR >100 mg/mmol. The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines[288] recommend achieving blood pressure <130/80 mmHg and the SIGN guidelines[368] recommend a target maximum systolic blood pressure of 130 mmHg in those with 1 g/day of proteinuria. CARI guidelines are more proscriptive, recommending a target blood pressure of <125/75 mmHg in those with proteinuria >1 g/day but acknowledging that the precise goal below 130/80 mmHg is not clear. The British Hypertension Society guidelines define optimal blood pressure control in people with kidney disease as <130/80 mmHg and suggest reducing blood pressure to <125/75 mmHg in those with proteinuria ≥1 g/24 h.[282,423]

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

This section was updated and replaced in 2018. See www.nice.org.uk/guidance/NG203/evidence for the 2018 evidence reviews.

9.3 Choice of antihypertensive agent [2014]

9.3.1 Introduction

Existing clinical practice guidelines recommend that treatment with angiotensin converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs) is indicated in the following population groups:

1. diabetes and urine ACR of 3 mg/mmol or more
2. hypertension and urine ACR of 30 mg/mmol or more
3. urine ACR of 70 mg/mmol or more
4. resistant hypertension (where treatment with 3 or more drugs is required)
5. step 1 treatment for hypertension in those aged less than55 years
6. step 2 treatment for hypertension in those aged over 55 years (ARB preferred to ACE for black people of African or Caribbean family origin)
7. following acute myocardial infarction
8. chronic heart failure.

Diabetes, hypertension and cardiovascular disease are all more common in people with CKD and those with hypertension frequently require treatment with multiple agents. NICE also recommends considering treatment with low dose spironolactone (25 mg once daily) in people with resistant hypertension if the blood potassium level is 4.5 mmol/l or lower, recommending caution in people with impaired GFR.[274] Expected benefits from treatment with ACE inhibitor and ARB in those population groups where such treatment is recommended include reduction of all-cause and cardiovascular mortality, reduction in proteinuria and reduction in progression of CKD.

However, the majority of people with CKD will not progress to end stage kidney disease and are predominantly managed by primary care. Treatment with ACE inhibitors and ARBs in people with

CKD and hypertension has been incorporated into the clinical domain of the primary care Quality and Outcomes Framework (QOF) since 2006. Incentivised prescription of ACE inhibitors and ARBs is also included in 3 other areas of the QOF - diabetes, heart failure and myocardial infarction. Following such initiatives there has been a steady increase in prescription of renin-angiotensin-aldosterone system (RAAS) antagonists which appears to have now plateaued. Nevertheless in England during 2012 prescriptions for ACE inhibitors, ARBs and direct renin inhibitors accounted for 6.0% of all prescription items.[294] Not all of these prescriptions will be for the indications discussed and this widespread use of RAAS antagonists has raised questions about possible harm without additional benefit, particularly in older people.[300] The most important of these is acute kidney injury (AKI) but there are also concerns regarding increased falls (especially in older people) and hyperkalaemia, particularly in those prescribed combinations of RAAS antagonists with or without other drugs known to increase the risk of hyperkalaemia.

The purpose of this question was to examine the clinical and cost effectiveness of RAAS antagonists in the management of CKD, considering the different classes of RAAS antagonists either alone or in combination.

9.3.2 Review question: For people with CKD, what is the clinical and cost effectiveness of renin-angiotensin-aldosterone system antagonists in the management of CKD?

For full details see review protocol in Appendix C.

Table 74: PICO characteristics of renin-angiotensin-aldosterone system antagonists review question

Population	Adults (aged 18 and over) with CKD
Intervention/s	• ACE inhibitors • Angiotensin-II receptor blockers • Aldosterone antagonists: spironolactone, eplerenone • Direct renin inhibitors: Aliskiren
Comparison/s	• Placebo • All compared to each other
Outcomes	**Critical** • Progression of CKD (measured by change in eGFR) • Progression of CKD (measured by occurrence of end stage kidney disease (ESRD or ESKD as reported by the study)) • Mortality (all-cause and cardiovascular) • Cardiovascular events • Occurrence of AKI **Important** • Change in proteinuria • Hospitalisation • Health related quality of life
Study design	RCTs

Analysis

Due to the large amount of data, studies with fewer than 30 participants were excluded from the review as better quality data were available. This decision was made after the protocol was initially written, and agreed by the GDG as an appropriate amendedment, whilst still including the most informative studies.

9.3.3 Clinical evidence

We searched for randomised trials comparing the effectiveness of ACE inhibitors (ACE inhibitor: captopril, cilazopril, enalapril, fosinopril, imidapril, lisonpril, perindopril, ramipril, trandolapril), angiotensin-II receptor blockers (ARB: azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan); aldosterone antagonists (spironolactone, eplerenone) or direct renin inhibitors (aliskiren), or any combination of these drugs, compared with placebo or with each other, for people with chronic kidney disease.

Forty-seven studies (a total of 51 papers) were included in the review.[2,4,9,10,14,17,20,25,30,34,37,43,48,78,102,113,116,164,179,186,188,207,208,212,224,225,227,238,240,241,245,248,263,270-272,302,317,318,323,338,358,372,379,398,400,404,407,412] Evidence from these is summarised, by comparison in, the clinical GRADE evidence profiles in sections 9.3.3.1-9.3.3.9. See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

Where evidence for hazard ratios were available, these have been calculated in preference to risk ratios, however, if the study only presented the results as a dichotomous outcome, the risk ratio has been calculated and presented in addition to the hazard ratios (see methodology chapter, section 3.1.4.2).

The majority of these studies were in people with diabetes and proteinuria, or diabetic nephropathy. Evidence from non-diabetic populations is labelled separately in the forest plots, and analysed as a separate subgroup where appropriate (if heterogeneity is present).

Change in proteinuria was presented in a variety of ways in the studies. Where available, data were extracted for final values or change from baseline in urinary protein (or albumin) loss, or rate of loss. When no other data were available, percentage change has been reported.

No evidence was identified for eplerenone.

All drug doses are recorded in the summary tables below. The GDG noted within the LETR section of this chapter when they had concerns about the use of non-standard or when sub-therapeutic drug dosages are being used as a comparator drug.

9.3.3.1 ACE inhibitors versus placebo

Evidence reported below includes captopril, enalapril, fosinopril, lisinopril, ramipril, perindopril and trandolapril pooled for analysis compared to placebo.[2,9,10,20,78,179,208,212,224,240,245,263,272,302,323,337,358,379,400,412] Two further studies were identified, but no means or standard deviations were presented, so data could not be analysed.[4,43]

Two studies included mixed populations with and without diabetes.[240,379] Only 2 were in a non-diabetic CKD population.[20,358] A summary of included studies is given in Table 75.

No data were identified for occurrence of AKI or health related quality of life measures.

Table 75: Summary of studies included in the review

Study	Intervention /comparison	Population (Mean blood pressure at baseline in mmHg)	Age (years)	Length of follow-up	Comments
Ahmad et al. 1997[9]	Enalapril (10mg) vs. placebo	Type II diabetes with microalbuminuria. Normotensive (BP = 132/81).	43-55 (mean 49.6)	5 years	Single blind
Ahmad et al. 2003[10]	Enalapril (10mg) vs. placebo	Type I diabetes and microalbuminuria. Normotensive (BP = 131/81).	< 40	5 years	Double blind
Asselbergs et al. 2004[20]	Fosinopril (20mg) vs. placebo	Persistent microalbuminuria. Normotensive (BP <160/100 mmHg and no use of antihypertensive)	Mean 51	4 years	Study is a 2x2 factorial design also including simvastatin vs. placebo (results not included here). 2.55% had diabetes mellitus.
Gisen et al. 1997[1]	Ramipril (1.25mg) vs. placebo	Proteinuric non-diabetic nephropathy. Normotensive or hypertensive (BP = 149/92).	Mean 49	3 years	Stratum 2 of the Ramipril Efficacy in Nephropathy (REIN) study. Baseline proteinuria ≥3g/24h. (See Ruggenenti 1999).
Crepaldi et al. 1998[78]	Lisinopril (10mg) vs. placebo	Type I diabetes with incipient nephropathy. Normotensive (BP = 129/83).	18-65 (mean 37.5)	3 years.	Double blind.
Jerums et al. 2004[179]	Perindopril (8mg) vs. placebo	Type II diabetes and microalbuminuria. Normotensive (BP = 137/81).	15-65 (mean 51.5)	6 years.	Single blind (investigator blinded).
Laffel et al. 1995[208]	Captopril (50mg 2x/day) vs. placebo	Type I diabetes and diabetic nephropathy (with microalbuminuria). Normotensive, BP <140/90 (baseline not given).	14-57 (mean 32.7)	2 years.	Double blind.
Lebovitz et al. 1994[212]	Enalapril (starting dose 5mg titrated up – final dose not provided) vs. placebo	Type II diabetes. GFR 30-100 ml/min/1.73 m^2.	Not stated	3 years.	Double blind. Post-hoc analysis.

Study	Intervention /comparison	Population (Mean blood pressure at baseline in mmHg)	Age (years)	Length of follow-up	Comments
		Hypertensive, diastolic BP >90mmHg or on therapy for hypertension (baseline not given).			
Lewis et al. 1993[224]	Captopril (25mg 3x/day) vs. placebo	Diabetic nephropathy (type I diabetes). Regardless of blood-pressure status (BP = 139/86).	18-49 (mean 34.5)	3 years.	Double blind.
Mann et al. 2001[240]	Ramipril vs. placebo (dose not stated).	Vascular disease or diabetes plus another cardiovascular risk factor with microalbuminuria. (BP = 140/79)	> 55 (mean 68)	Unclear.	Double blind. Post hoc analysis in people with renal insufficiency: serum creatinine concentration of at least 124 µmol/l.
Marre et al. 2004[245]	Ramipril (1.25mg) vs. placebo	Type II diabetes and raised loss of urinary albumin (≥20mg/l). (BP = 145/82).	> 50 (mean 65)	6 years.	Double blind.
Muirhead et al. 1999[263]	Captopril (25mg 3x/day) vs. placebo	Type II diabetes and microalbuminuria. Mixed normotensive and hypertensive (BP = 136/83).	> 18 (mean 56)	1 year.	Double blind.
Nankervis et al. 1998[272]	Perindopril (4mg) vs. placebo	Diabetes (type I or II) and microalbuminuria. Mixed normotensive and hypertensive (BP = 141/83).	18-65 (mean 46)	3 years.	Double blind.
O'Hare et al. 2000[302]	Ramipril 1.25 or 5mg vs. placebo (NB 1.25mg data not reported as this is a sub-therapeutic dose)	Type I diabetes with microalbuminuria. Normotensive (BP = 132/76).	Mean 40	2 years.	Double blind.
Penno et al. 1998[323]	Lisinopril vs. placebo (dose not stated)	Type I diabetes – normoalbuminuria (85%) or microalbuminuria (15%). (BP = 122/80)	20-59	2 years.	Double blind. Post-hoc analysis of EUCLID study.[1,1]
Ravid et al. 1993[337]	Enalapril (10mg) vs. placebo	Type II diabetes and microalbuminuria. Normotensive, <140/90 (baseline not given).	< 50 (mean 44)	5 years.	Double blind.
Ruggenenti et al. 1999[358]	Ramipril (1.25mg starting dose, titrated up in 2.5 or	Proteinuric non-diabetic nephropathy.	Mean 49	6 years.	Stratum 1 of the Ramipril Efficacy in Nephropathy

Study	Intervention /comparison	Population (Mean blood pressure at baseline in mmHg)	Age (years)	Length of follow-up	Comments
	5mg capsules every two weeks until blood pressure below 90mmHg – final mean dose not given) vs. placebo	Normotensive or hypertensive. (BP = 143/89).			(REIN) study. Baseline proteinuria 1-2.9g/24h. (See Gisen 1997).
Solomon et al. 2006[379]	Trandolapril (4mg) vs. placebo	Chronic stable coronary disease and baseline serum creatinine / GFR measurement. (BP = 135/77)	Mean 69	5 years.	Double blind. Post-hoc analysis of PEACE trial. [399]
Tong et al. 2006[400]	Fosinopril (20mg) vs. placebo	Type II diabetes with moderate renal insufficiency. (BP = 160/82)	< 75 (mean 66)	2 years.	Double blind. Chinese population.
Viberti et al. 1994[412]	Captopril (50mg) vs. placebo.	Type I diabetes and microalbuminuria. Normotensive (BP = 124/77).	18-55 (mean 31.5)	2 years.	Double blind.

Table 76: Clinical evidence profile: ACE inhibitor versus placebo

Quality assessment							No of patients / mean score		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ACE inhibitor	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Progression of CKD (change in eGFR) (follow-up median 3 years; assessed with: change in eGFR)												
1[224]	Randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	25/207 (12.1%)	21.3%	HR 0.7 (0.54 to 0.91)	59 fewer per 1000 (from 17 fewer to 92 fewer)	HIGH	CRITICAL
Progression of CKD (measured by change in eGFR): (follow-up mean 3.8 years; measured with: change from baseline or final measured GFR (ml/min/1.73 m²); better indicated by higher values)												
4[9,10,212,272]	Randomised trials	Very serious (a, b)	No serious inconsistency	No serious indirectness	No serious imprecision	None	145	133	-	MD 0.35 higher (0.04 lower to 0.73 higher)	LOW	CRITICAL
Progression of CKD (measured by occurrence of end stage renal disease):ESRD - time to event (follow-up mean 4.5 years)												
2[2,358]	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	26/177 (14.7%)	26.9%	HR 0.47 (0.31 to 0.73)	132 fewer per 1000 (from 65 fewer to 176 fewer)	HIGH	CRITICAL
Progression of CKD (measured by occurrence of end stage renal disease):ESRD (doubling creatinine or dialysis or transplantation) (follow-up mean 3.7 years)												
3[224,245,400]	Randomised trials	Very serious (b, c, k)	No serious inconsistency	No serious indirectness	Serious (f)	None	28/2666 (1.1%)	15.5%	RR 0.61 (0.39 to 0.95)	60 fewer per 1000 (from 8 fewer to 95 fewer)	VERY LOW	CRITICAL
All-cause mortality (assessed with: time to event)												
1[240]	Randomised trial	Serious (d)	No serious inconsistency	No serious indirectness	No serious imprecision	None	68/509 (13.4%)	22.5%	HR 0.59 (0.42 to 0.83)	85 fewer per 1000 (from 34 fewer to 123 fewer)	MODERATE	CRITICAL
All-cause mortality (follow-up mean 4.6 years)												
5[2,224,245,358,379]	Randomised trials	Very serious (b,	No serious inconsistency	No serious indirectness	No serious imprecision	None	644/6981 (9.2%)	7.5%	RR 0.96 (0.86 to	3 fewer per 1000 (from 10	LOW	CRITICAL

Quality assessment							No of patients / mean score		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ACE inhibitor	Placebo	Relative (95% CI)	Absolute		
		e, k)							1.06)	fewer to 4 more)		
Cardiovascular mortality (assessed with: time to event)												
1[240]	Randomised trial	Serious (d)	No serious inconsistency	No serious indirectness	No serious imprecision	None	43/509 (8.4%)	14.6%	HR 0.59 (0.39 to 0.89)	57 fewer per 1000 (from 15 fewer to 86 fewer)	MODERATE	CRITICAL
Cardiovascular mortality (follow-up mean 5.5 years)												
2[20,245,379]	Randomised trials	Very serious (b, d, k)	No serious inconsistency	No serious indirectness	No serious imprecision	None	292/7027 (4.2%)	5.4%	RR 1.01 (0.86 to 1.18)	1 more per 1000 (from 8 fewer to 10 more)	LOW	CRITICAL
Cardiovascular events (assessed with: time to event)												
1[240]	Randomised trial	Serious (d)	No serious inconsistency	No serious indirectness	Serious (f)	None	189/509 (37.1%)	45%	HR 0.87 (0.7 to 1.09)	44 fewer per 1000 (from 108 fewer to 29 more)	LOW	CRITICAL
Cardiovascular events (follow-up mean 4.25 years)												
4[2,245,302,358]	Randomised trials	Serious (b, k)	No serious inconsistency	No serious indirectness	No serious imprecision	None	220/7539 (2.9%)	236/7628 (3.1%)	RR 0.94 (0.79 to 1.13)	2 fewer per 1000 (from 6 fewer to 4 more)	MODERATE	CRITICAL
Change in proteinuria (follow-up mean 2 years; assessed with: progression to clinical proteinuria - time to event)												
1[208]	Randomised trial	Serious (g)	No serious inconsistency	No serious indirectness	No serious imprecision	None	4/67 (6%)	18.6%	HR 0.3 (0.1 to 0.9)	126 fewer per 1000 (from 17 fewer to 166 fewer)	MODERATE	IMPORTANT
Change in proteinuria (follow-up mean 4.25 years; assessed with: progression to clinical proteinuria)												
8[9,10,179,263,302,323,]	Randomised trials	Very serious (b,	No serious inconsistency	No serious indirectness	No serious imprecision	None	44/444 (9.9%)	27.3%	RR 0.39 (0.28 to	167 fewer per 1000 (from 126	LOW	IMPORTANT

Quality assessment							No of patients / mean score		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**ACE inhibitor**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
[338,358,412]		h)							0.54)	fewer to 197 fewer)		
Change in proteinuria (follow-up mean 4.2 years; measured with: Albumin loss rate (final values/24hrs); better indicated by lower values)												
5[9,10,212,272,338]	Randomised trials	Serious (i)	No serious inconsistency	No serious indirectness	No serious imprecision	None	175	157	-	SMD 0.91 lower (1.2 to 0.62 lower)	MODERATE	IMPORTANT
Change in proteinuria (follow-up mean 3.25 years; assessed with: Regression to normoalbuminuria)												
4[78,179,302,323]	Randomised trials	No serious risk of bias (j)	No serious inconsistency	No serious indirectness	Serious (f)	None	33/126 (26.2%)	4.4%	RR 1.79 (1.08 to 2.97)	35 more per 1000 (from 4 more to 87 more)	MODERATE	IMPORTANT
Hospitalisation (for heart failure) (assessed with: Time to event)												
1[240]	Randomised trial	Serious (d)	No serious inconsistency	No serious indirectness	Serious (f)	None	21/509 (4.1%)	8.1%	HR 0.56 (0.3 to 1.05)	35 fewer per 1000 (from 56 fewer to 4 more)	LOW	IMPORTANT
Hospitalisation for non-fatal myocardial infarction, heart failure, peripheral vascular disease or cerebrovascular accident.												
1[20]	Randomised trial	Very serious(b, g)	No serious inconsistency	No serious indirectness	Serious (f)	none	14/431 (3.2%)	5.8%	RR 0.56 (0.3 to 1.07)	26 fewer per 1000 (from 41 fewer to 4 more)	VERY LOW	IMPORTANT

(a) Three studies had unclear randomisation methods and allocation concealment. Rate of missing data differed between groups in one study.
(b) Data not analysed as time to event: incorrect analysis.
(c) Two studies had unclear allocation concealment.
(d) Post-hoc subgroup analysis. Allocation concealment unclear.
(e) Two studies had unclear allocation concealment.In one study urinary protein excretion was higher in the placebo group. Another was a post-hoc analysis of previously published data.
(f) Confidence interval crosses one MID making the effect size uncertain.
(g) Unclear allocation concealment.
(h) Four studies had unclear randomisation and allocation concealment. One study is a post-hoc analysis of previously published data.
(i) Four studies had unclear allocation concealment. One study is a post-hoc analysis of previously published data.
(j) One out of four studies was a post-hoc analysis of previously published data. No other risks of bias.
One study used a sub therapeutic dose of ACE inhibitor.

9.3.3.2 ARB versus placebo

Evidence reported below includes irbesartan, losartan, olmesartan, telmisartan and valsartan pooled for analysis compared to placebo.[14,33,48,164,225,227,238,241,317,372,398]

The majority of studies were in people with type II diabetes. Of the remaining studies, 1 was in people with IgA nephropathy[227] 1 in a non-diabetic CKD population,[372] 1 people with heart failure[14] and 2 were a mixed population of people with CKD with either diabetes or cardiovascular disease (these 2 studies are in the same population, with the latter being a post-hoc analysis of the data).[241,398] A summary of included studies is provided in Table 77.

No data were identified for hospitalisation or health related quality of life measures.

Table 77: Summary of studies included in the review

Study	Intervention / comparison	Population (Mean blood pressure at baseline in mmHg)	Age (years)	Length of follow-up	Comments
Anand et al. 2009[14]	Valsartan (160mg BID) vs. placebo	Stable symptomatic heart failure. Systolic BP<90mmHg (BP = 127/78).	Mean 65.5	2 years.	Data separated by presence of proteinuria and/or CKD (pre-specified).
Berl et al. 2005[33]	Irbesartan (300mg) vs. placebo	Type II diabetes and overt nephropathy. BP > 135/85 (160/87)	30-70 mean 63.8)	4.5 years.	Double blind.
Brenner et al. 2001[48]	Losartan (50-100mg) vs. placebo	Type II diabetes and nephropathy. (BP = 152/82).	31-70 (mean 60)	3.5 years.	Double blind.
Imai et al. 2011[164]	Olmesartan (10-40mg) vs. placebo	Type II diabetes and overt nephropathy. (BP = 141/77)	30-70 (mean 59)	4.5 years.	Double blind. Chinese and Japanese population.
Lewis et al. 2001[225]	Irbesartan (300mg) vs. placebo	Type II diabetes and nephropathy. Hypertensive (BP = 159/87).	30-70 (mean 63.8)	4.5 years.	Double blind.
Li et al. 2006[227]	Valsartan (160mg) vs. placebo	IgA nephropathy. Irrespective of blood pressure status (BP = 137/82).	> 18 (mean 40.5)	2 years.	Double blind. Chinese population.
Makino et al. 2008[238]	Telmisartan (40 or 80mg) vs. placebo	Type II diabetes and incipient nephropathy. Normotensive (BP = 131/75) and hypertensive (BP = 140/79).	30-74 (mean 61.7)	1 year.	Double blind. Japanese population. Post-hoc analysis stratified by blood pressure status.

Study	Intervention / comparison	Population (Mean blood pressure at baseline in mmHg)	Age (years)	Length of follow-up	Comments
Mann et al. 2009[241]	Telmisartan (80mg) vs. placebo	Cardiovascular disease or diabetes. Intolerant to ACE inhibitors. (BP = 141/82).	> 55 (mean 68)	4.5 years.	Double blind. Pre-specified post-hoc analysis.
Parving et al. 2001[317]	Irbesartan (150mg or 300mg) vs. placebo	Type II diabetes and microalbuminuria. Hypertensive (BP = 153/90).	30-70 (mean 58)	2 years.	Double blind.
Shen et al. 2012 [372]	Losartan (50mg) vs. placebo	Non-diabetic CKD. Normotensive (BP = 124/82).	18-70 (mean 49.8)	1 year.	States open label, although treatment assigned in sealed envelopes
Tobe et al. 2011 [398]	Telmisartan (80mg) vs. placebo	Cardiovascular disease or diabetes. Intolerant to ACE inhibitors. (BP = 143/81)	> 55 (mean 69.5)	4.5 years.	Double blind. Post-hoc analysis.

Table 78: Clinical evidence profile: ARB versus placebo

Quality assessment							No of patients / mean score		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ARB	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Progression of CKD (measured by change in GFR) (follow-up mean 3.5 years; assessed with: time to event)												
1[48]	Randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious (a)	None	-	21.3%	HR 0.77 (0.62 to 0.96)	45 fewer per 1000 (from 8 fewer to 75 fewer)	MODERATE	CRITICAL
Progression of CKD (measured by change in eGFR): (follow-up mean 1.5 years; measured with: final eGFR (ml/min/1.73 m²); better indicated by higher values)												
2[227,372]	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	166	169	-	MD 5.09 higher (3.14 to 7.04 higher)	HIGH	CRITICAL
Progression of CKD (measured by occurrence of ESRD) - IgA nephropathy (follow-up mean 2 years; assessed with: time to event)												
1[227]	Randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious [(a)	None	-	26.9%	HR 0.2 (0.02 to 2)	208 fewer per 1000 (from 263 fewer to 197 more)	MODERATE	CRITICAL
Progression of CKD (measured by occurrence of ESRD) - CKD with diabetes (follow-up mean 4.2 years; assessed with: time to event)												
3[48,164,225]	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious (b)	None	-	26.9%	HR 0.8 (0.68 to 0.93)	47 fewer per 1000 (from 16 fewer to 77 fewer)	MODERATE	CRITICAL
Progression of CKD (measured by occurrence of ESRD) - CKD with diabetes or cardiovascular disease (follow-up mean 4.5 years; assessed with: time to event)												
1[241]	Randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious (a)	None	-	26.9%	HR 1.29 (0.87 to 1.91)	63 more per 1000 (from 30 fewer to 181 more)	MODERATE	CRITICAL
All-cause mortality (follow-up mean 3.66 years; assessed with: time to event)												

Quality assessment							No of patients / mean score		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**ARB**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
3[14,164,225]	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	22.5%	HR 0.96 (0.83 to 1.11)	8 fewer per 1000 (from 34 fewer to 21 more)	HIGH	CRITICAL
All-cause mortality (follow-up mean 4 years)												
2[48,398]	Randomised trials	Very serious (c)	No serious inconsistency	No serious indirectness	No serious imprecision	None	291/1477 (19.7%)	18.4%	RR 1.07 (0.92 to 1.24)	13 more per 1000 (from 15 fewer to 44 more)	LOW	CRITICAL
Cardiovascular mortality (follow-up mean 4.5 years; assessed with: time to event)												
2[34,164]	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious (a)	None	-	14.6%	HR 1.17 (0.8 to 1.73)	23 more per 1000 (from 27 fewer to 93 more)	MODERATE	CRITICAL
Cardiovascular mortality (follow-up mean 4.5 years)												
1[398]	Randomised trial	Very serious (d)	No serious inconsistency	No serious indirectness	Serious (a)	None	88/729 (12.1%)	11.1%	RR 1.09 (0.82 to 1.45)	10 more per 1000 (from 20 fewer to 50 more)	VERY LOW	CRITICAL
Cardiovascular events (follow-up mean 4.5 years; assessed with: occurrence of myocardial infarction, revascularisation, cerebrovascular accident, congestive heart failure or stroke.)												
3[34,164,225]	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious (a)	None	-	45%	HR 0.77 (0.64 to 0.94)	81 fewer per 1000 (from 20 fewer to 132 fewer)	MODERATE	CRITICAL
Cardiovascular events (follow-up mean 3.3 years)												
3[48,164,317]	Randomised trials	Serious (e)	No serious inconsistency	No serious indirectness	Serious (a)	None	140/1224 (11.4%)	16.7%	RR 0.67 (0.55 to 0.82)	55 fewer per 1000 (from 30 fewer to 75 fewer)	LOW	CRITICAL
Acute kidney injury (follow-up mean 4.5 years)												

Quality assessment							No of patients / mean score		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**ARB**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1[164]	Randomised trial	Serious (f)	No serious inconsistency	No serious indirectness	Very serious (g)	None	1/282 (0.35%)	0.4%	RR 1.01 (0.06 to 16.02)	0 more per 1000 (from 4 fewer to 60 more)	VERY LOW	CRITICAL
Change in proteinuria (follow-up mean 2.5 years; assessed with: progression to clinical proteinuria, macroalbuminuria or overt nephropathy)												
3[238,241,317]	Randomised trials	Very serious (b)	No serious inconsistency	No serious indirectness	No serious imprecision	None	110/1271 (8.7%)	25.6%	RR 0.42 (0.34 to 0.52)	148 fewer per 1000 (from 123 fewer to 169 fewer)	LOW	IMPORTANT
Change in proteinuria: general - non-diabetic CKD (follow-up mean 1.5 years; measured with: Final proteinuria; better indicated by lower values)												
2[227,372]	Randomised trials	No serious risk of bias	Serious (h)	No serious indirectness	Serious (a)	None	166	169	-	SMD 0.92 lower (1.73 to 0.11 lower)	LOW	IMPORTANT
Change in proteinuria: normotensive - with diabetes (follow-up mean 1 years; measured with: final proteinuria; better indicated by lower values)												
1[238]	Randomised trial	Serious (i)	No serious inconsistency	No serious indirectness	Serious (a)	None	117	120	-	SMD 0.68 lower (0.95 to 0.42 lower)	LOW	IMPORTANT
Change in proteinuria: hypertensive - with diabetes (follow-up mean 1 years; measured with: final proteinuria; better indicated by lower values)												
1[238]	Randomised trial	Serious (i)	No serious inconsistency	No serious indirectness	Serious (a)	None	109	108	-	SMD 0.61 lower (0.88 to 0.33 lower)	LOW	IMPORTANT
Change in proteinuria: (follow-up mean 4.5 years; measured with: change from baseline proteinuria (g/24hr); better indicated by lower values)												
1[224]	Randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious (a)	None	574	565	-	MD 0.8 lower (1.18 to 0.42 lower)	MODERATE	IMPORTANT
Change in proteinuria: < 2 years non-diabetic CKD (follow-up mean 1 years; assessed with: regression to normoalbuminuria)												
1[372]	Randomised trial	No serious	No serious inconsistency	No serious indirectness	No serious imprecision	None	16/112 (14.3%)	0%	RR 33.58 (2.04 to	-	HIGH	IMPORTANT

Quality assessment							No of patients / mean score		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**ARB**	**Placebo**	**Relative (95% CI)**	**Absolute**		
		risk of bias			(j)				553.1)			
Change in proteinuria: < 2 years with diabetes (follow-up mean 1 years; assessed with: regression to normoalbuminuria (random effects))												
1[238]	Randomised trial	Serious (i)	No serious inconsistency	No serious indirectness	No serious imprecision (k)	None	19/109 (17.4%)	1.9%	RR 9.43 (2.25 to 39.49)	160 more per 1000 (from 24 more to 731 more)	MODERATE	IMPORTANT
Change in proteinuria: 2 years with diabetes (follow-up mean 1 years; assessed with: regression to normoalbuminuria)												
1[317]	Randomised trial	Serious (l)	No serious inconsistency	No serious indirectness	Serious (a)	None	113/389 (29%)	20.9%	RR 1.39 (1.02 to 1.9)	82 more per 1000 (from 4 more to 188 more)	LOW	IMPORTANT

(a) Confidence interval crosses one MID making the effect size uncertain.
(b) No explanation was provided
(c) Data not analysed as time to event, incorrect analysis. One study was a post-hoc analysis of previously published data.
(d) Data not analysed as time to event, incorrect analysis. Post-hoc analysis of previously published data.
(e) Data not analysed as time to event, incorrect analysis. One study had unclear randomisation and allocation concealment.
(f) Data not analysed as time to event, incorrect analysis.
(g) Confidence interval crosses both MIDs making the effect size very uncertain.
(h) Heterogeneity unexplained by subgroup analysis.
(i) Post-hoc analysis of previously published data. Unclear randomisation and allocation concealment.
(j) Very wide confidence intervals due to zero events in control arm.
(k) Very wide confidence intervals due to low event rate in control arm.
(l) Unclear randomisation and allocation concealment.

9.3.3.3 Spironolactone versus placebo

One study was included that compared spironolactone with placebo in people with CKD and type II diabetes. Both groups had been receiving an ACE inhibitor or an ARB for at least a year.[407]

No data were identified for progression of CKD (measured by change in eGFR or ESRD), cardiovascular mortality, cardiovascular events, occurrence of AKI, hospitalisation or health related quality of life.

Study	Intervention/ comparison	Population (Mean blood pressure at baseline in mmHg)	Age (years)	Length of follow-up	Comments
Van den Meiracker et al. 2006[407]	Spirinolactone (50mg) vs. placebo	Type II diabetes with microalbuminuria. Long term use of ACE inhibitor or ARB. (BP = 150/80).	20 – 80 (mean = 55)	1 year	Double blind.

Table 80: Clinical evidence profile: Spirinolactone versus placebo

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Spironolactone**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
All-cause mortality (follow-up mean 1 years)												
1[407]	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Very serious (b)	None	0/24 (0%)	7.1%	RR 0.23 (0.01 to 4.61)	55 fewer per 1000 (from 70 fewer to 256 more)	VERY LOW	CRITICAL

(a) Baseline eGFR lower in placebo group (mean 64 vs. 87ml/min/1.73m2, p=0.02) and creatinine higher (103 vs. 78 micromol/L, p=0.007).
(b) Confidence intervals cross both MIDs making the effect size very uncertain. NB zero event rate in intervention arm.

9.3.3.4 ACE inhibitor versus ARB

Evidence below includes comparison of enalapril with losartan,[404,425] captopril with valsartan,[263] lisinopril with irbesartan,[102] enalapril with telmisartan[30] and one study that compared perindopril, trandolapril, candesartan and losartan.[248] One study compared ramipril with valsartan,[37] and another compared enalapril with losartan,[207] but data could not be analysed as no standard deviations were reported. One further study compared enalapril with telmisartan, but only presented data graphically, so it could not be analysed.[270]

All studies were in people with type II diabetes with the exception of 1 which was in people with IgA nephropathy.[425]

No data were identified for occurrence of AKI, hospitalisation or health related quality of life measures.

Table 81: Summary of studies included in the review

Study	Intervention/ comparison	Population (Mean blood pressure at baseline in mmHg)	Age (years)	Length of follow-up	Comments
Barnett et al. 2004[30]	Enalapril 20mg vs. telmisartan 80mg	Type II diabetes and early nephropathy. Mild to moderate hypertension (BP = 152/86).	35-80 (mean 60.6)	5 years	Double blind.
Fernandez et al. 2013[102]	Lisinopril 40mg vs. irbesartan 600mg	Type II diabetic nephropathy. Hypertensive, but BP<180/95 (BP = 153/81).	> 35 (mean 66.5)	Median of 32 months	Open label
Matsuda et al. 2003[248]	Perindopril 2mg/day, trandolapril 0.5mg/day, candesartan 4mg/day and losartan 25mg/day (starting doses titrated to achieve a systemic blood pressure of <135/85mmHg, final doses not given). All versus each other.	Chronic kidney disease. Hypertension (BP = 153/92).	Mean 52.5	1.8 years	Blinding unclear.
Muirhead et al. 1999[263]	Captopril 25mg 3x/day vs. valsartan 80 or 160mg/day.	Type II diabetes and microalbuminuria. Normotensive and hypertensive (BP = 136/83).	> 18 (mean 56)	1 year	Double blind.
Tutuncu et al. 2001[404]	Enaplapril 5mg vs. losartan 50mg.	Type II diabetes with microalbuminuria. Normotensive. (BP = 117/77).	Mean 55.7	1 year	Blinding unclear.
Woo et al. 2009[425]	Losartan 100 or 200 mg/day vs. enalapril 10 or 20mg/day	IgA nephritis. (BP = 133/85).	Mean 33	6 years	Open label

Table 82: Clinical evidence profile: ACE inhibitor versus ARB

Randomised							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ACE inhibitor	ARB	Relative (95% CI)	Absolute	Quality	Importance
Progression of CKD (measured by change in eGFR): Losartan 100mg (follow-up mean 6 years; measured with: Final eGFR (ml/min/1.73 m²) ; better indicated by higher values)												
1[425]	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision	None	101	86	-	MD 1.56 higher (6.37 lower to 9.49 higher)	MODERATE	CRITICAL
Progression of CKD (measured by change in eGFR): Final eGFR (ml/min) - >48 months Losartan 200mg (follow-up mean 6 years; measured with: Final eGFR (ml/min/1.73 m²) ; better indicated by higher values)												
1[425]	Randomised trials	Serious (a,b)	No serious inconsistency	No serious indirectness	Serious (c)	None	101	126	-	MD 17.34 lower (25.07 to 9.61 lower)	LOW	CRITICAL
Progression of CKD (measured by occurrence of end stage renal disease): ESRD (follow-up mean 4.3 years)												
2[102,425]	Randomised trials	Very serious (b,d,e)	No serious inconsistency	No serious indirectness	Serious (c)	None	62/237 (26.2%)	17.9%	RR 1.64 (1.14 to 2.36)	115 more per 1000 (from 25 more to 243 more)	VERY LOW	CRITICAL
All-cause mortality (follow-up mean 3.8 years)												
2[30,102]	Randomised trials	Serious (f)	No serious inconsistency	No serious indirectness	Very serious (g)	None	8/165 (4.8%)	4.3%	RR 1.03 (0.38 to 2.77)	1 more per 1000 (from 27 fewer to 76 more)	VERY LOW	CRITICAL
Cardiovascular mortality (follow-up mean 5 years)												
1[30]	Randomised trials	Serious (e)	No serious inconsistency	No serious indirectness	Very serious (g)	None	2/130 (1.5%)	2.5%	RR 0.62 (0.1 to 3.62)	9 fewer per 1000 (from 23 fewer to 65 more)	VERY LOW	CRITICAL

Randomised							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ACE inhibitor	ARB	Relative (95% CI)	Absolute	Quality	Importance
Cardiovascular events (follow-up mean 5 years; assessed with: Including heart failure, myocardial infarction or stroke.)												
1[30]	Randomised trials	Serious (e)	No serious inconsistency	No serious indirectness	Serious (c)	None	19/130 (14.6%)	20%	RR 0.73 (0.42 to 1.26)	54 fewer per 1000 (from 116 fewer to 52 more)	LOW	CRITICAL
Change in proteinuria: Progression to macroalbuminuria (follow-up mean 1 years)												
1[263]	Randomised trials	Very serious (h)	No serious inconsistency	No serious indirectness	Very serious (i)	None	1/62 (1.6%)	3.5%	RR 0.47 (0.03 to 7.22)	19 fewer per 1000 (from 34 fewer to 218 more)	VERY LOW	IMPORTANT
Change in proteinuria: urinary protein (subgrouped by dose) - High dose ARB (Losartan 200mg) (follow-up mean 6 years; better indicated by lower values)												
1[425]	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (c)	None	101	126	-	SMD 0.57 higher (0.3 to 0.84 higher)	LOW	IMPORTANT
Change in proteinuria: urinary protein (subgrouped by dose) - Standard dose ARB (Losartan 100mg) (follow-up mean 6 years; better indicated by lower values)												
1[425]	Randomised trials	Serious (a,b)	No serious inconsistency	No serious indirectness	No serious imprecision	None	101	86	-	SMD 0.11 higher (0.18 lower to 0.4 higher)	MODERATE	IMPORTANT
Change in proteinuria: urinary protein (pooled doses) - CKD and type II diabetes (follow-up mean 1 years; measured with: Change from baseline; better indicated by lower values)												
2[102,404]	Randomised trials	Very serious (j)	No serious inconsistency	No serious indirectness	Serious (c)	None	47	40	-	SMD 0.55 lower (0.98 to 0.12 lower)	VERY LOW	IMPORTANT
Change in proteinuria: urinary protein (pooled doses) - IgA nephropathyPooled (follow-up mean 6 years; better indicated by lower values)												
1[425]	Randomised trials	Serious (a)	Serious (k)	No serious indirectness	Serious (c)	None	80	106	-	SMD 0.35 higher (0.05 to 0.64 higher)	VERY LOW	IMPORTANT

Randomised							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ACE inhibitor	ARB	Relative (95% CI)	Absolute	Quality	Importance
Change in proteinuria: urinary protein subgrouped by drug - IgA nephropathy (Losartan 200mg vs. enalapril 10mg) (follow-up mean 6 years; better indicated by lower values)												
1[425]	Randomised trials	Serious (l)	No serious inconsistency	No serious indirectness	Serious (c)	None	40	63	-	SMD 0.56 higher (0.16 to 0.97 higher)	LOW	IMPORTANT
Change in proteinuria: urinary protein subgrouped by drug - IgA nephropathy (Losartan 100mg vs. enalapril 10mg) (follow-up mean 6 years; measured with: Final value g/day; better indicated by lower values)												
1[425]	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (c)	None	40	43	-	SMD 0.1 higher (0.33 lower to 0.54 higher)	LOW	IMPORTANT
Change in proteinuria: urinary protein subgrouped by drug - Type II diabetes (Losartan 50mg vs. enalapril 5mg) (follow-up mean 1 years; measured with: Final value (mg/day); better indicated by lower values)												
1[404]	Randomised trials	Very serious (h)	No serious inconsistency	No serious indirectness	Serious (c)	None	12	12	-	SMD 0.28 lower (1.09 lower to 0.52 higher)	VERY LOW	IMPORTANT
Change in proteinuria: urinary protein subgrouped by drug - Type II diabetes (Irbesartan 600mg vs. lisiNopril 40mg) (measured with: Change from baseline (g/g); better indicated by lower values)												
1[102]	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	35	28	-	SMD 0.66 lower (1.17 to 0.15 lower)	HIGH	IMPORTANT
Change in proteinuria (follow-up mean 1 years; assessed with: Regression to normoalbuminuria)												
1[263]	Randomised trials	Very serious (h)	No serious inconsistency	No serious indirectness	Serious (c)	None	10/12 (83.3%)	66.7%	RR 1.25 (0.78 to 2.01)	167 more per 1000 (from 147 fewer to 674 more)	VERY LOW	IMPORTANT

(a) Allocation concealment was unclear - open label study, 10mg dose of enalapril sub therapeutic.

(b) 10mg dose of enalapril sub therapeutic.
(c) Confidence interval crosses one MID making the effect size uncertain.
(d) Allocation concealment unclear - both open label studies.
(e) Data not analysed as time to event, incorrect analysis.
(f) Data not analysed as time to event, incorrect analysis. Allocation was unclear in one open label study.
(g) Confidence interval crosses both MIDs making the effect size very uncertain.
(h) Randomisation and allocation concealment unclear, ACE inhibitor is at a sub therapeutic dose.
(i) Confidence interval crosses the MID in both directions making the effect size very uncertain. NB, low event rate in both arms.
(j) In one study, randomisation and allocation concealment unclear and a sub therapeutic dose of enalapril was used.
(k) Heterogeneity unexplained by subgroup analysis.
(l) Allocation concealment unclear, open label study.

9.3.3.5 ACE inhibitor plus ARB versus ACE inhibitor

Evidence reported below includes comparisons of lisinopril plus irbesartan with lisinopril alone,[102] enalapril plus losartan with enalapril alone,[404] and mixed ACE inhibitors plus candesartan with ACE inhibitors.[186] One study compared ramipril plus valsartan with ramipril alone, but the data could not be analysed as standard deviations were not reported.[37]

Data were from people with CKD and type II diabetes, with the exception of 1 study which was in non-diabetic CKD.[186]

No data were identified for cardiovascular mortality, cardiovascular events, occurrence of AKI, hospitalisation or health related quality of life measures.

Table 83: Summary of studies included in the review

Study	Intervention / comparison	Population (Mean blood pressure at baseline in mmHg)	Age (years)	Length of follow-up	Comments
Fernandez et al. 2013[102]	Lisinopril (20mg) plus irbesartan (300mg) vs. Lisinopril 40mg	Type II diabetes and diabetic nephropathy (stage 2 or 3 CKD). Hypertensive, but BP<180/95 (BP = 153/81).	> 35 (mean 66.5)	Median 32 months	Double blind.
Kanno et al. 2006[186]	Candesartan (2-12mg) added to existing ACE inhibitor treatment. The main ACE inhibitors used benezapril (2.5-10mg) or trandolapril (2-4mg)	Kidney dysfunction. Hypertensive, systolic BP of >130 and <180mHg, diastolic BP >80 and <120mmHg (baseline BP not given).	Mean 60.1	3 years	Open label. People were already on an ACE inhibitor prior to starting the study. ARB was added to this. Control group carried on their usual treatment. Japanese population.
Tutuncu et al. 2001[404]	Enalapril (5mg) plus losartan (50mg) vs. enalapril 5mg	Type II diabetes with microalbuminuria. Normotensive. (BP = 117/77).	Mean 57.5	1 year	Blinding unclear.

Table 84: Clinical evidence profile: ACE inhibitor plus ARB versus ACE inhibitor

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ACE inhibitor + ARB	ACE inhibitor	Relative (95% CI)	Absolute	Quality	Importance
Progression of CKD (measured by occurrence of ESRD) (follow-up mean 2.8 years)												
2[102,186]	Randomised trials	Very serious (a,b)	No serious inconsistency	No serious indirectness	Very serious (c)	None	12/115 (10.4%)	10.8%	RR 0.87 (0.38 to 2)	14 fewer per 1000 (from 67 fewer to 108 more)	VERY LOW	CRITICAL
All-cause mortality (follow-up median 32 months)												
1[102]	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Very serious (c)	None	6/70 (8.6%)	5.7%	RR 1.5 (0.32 to 7.05)	28 more per 1000 (from 39 fewer to 345 more)	VERY LOW	CRITICAL
Change in proteinuria: CKD and type II diabetes (follow-up mean 1.8 years; measured with: Final urinary albumin loss rate (mg/day or g/g) ; better indicated by lower values)												
2[102,404]	Randomised trials	Serious (d)	No serious inconsistency	No serious indirectness	No serious imprecision	None	80	47	-	SMD 0.83 higher (0.45 to 1.21 higher)	MODERATE	IMPORTANT
Change in proteinuria: Non-diabetic CKD (follow-up mean 3 years; measured with: Final urinary albumin loss rate (g/day) ; better indicated by lower values)												
1[186]	Randomised trials	Very serious (e)	No serious inconsistency	No serious indirectness	No serious imprecision	None	45	45	-	SMD 3.96 lower (4.69 to 3.24 lower)	LOW	IMPORTANT
Change in proteinuria (follow-up mean 1 years; assessed with: Regression to normoalbuminuria)												
1[404]	Randomised trials	Very serious (f)	No serious inconsistency	No serious indirectness	Very serious (c)	None	7/10 (70%)	83.3%	RR 0.84 (0.52 to 1.36)	133 fewer per 1000 (from 400 fewer to 300 more)	VERY LOW	IMPORTANT

(a) One study was open label, details of which ACE inhibitors used not provided, all participants remained on ACE inhibitor they had been using prior to the study.
(b)Data not analysed as time to event, incorrect analysis.
(c) The confidence interval crosses both MIDs making the effect size very uncertain.
(d) Randomisation and allocation concealment was unclear in one study and the doses of enalapril were sub therapeutic.
(e) Open label study, details of which ACE inhibitors used not provided, all participants remained on ACE inhibitor they had been using prior tothe study
(f) Randomisation and allocation concealment was unclear and the doses of enalapril were sub therapeutic.

9.3.3.6 ACE inhibitor plus ARB versus ARB

Evidence reported below includes comparisons of lisinopril plus irbesartan with irbesartan alone,[102] enalapril plus losartan with losartan alone[404] and lisinopril plus losartan versus losartan alone.[113] All of these were in populations with CKD and type II diabetes. One study compared ramipril plus valsartan with valsartan alone, but the data could not be analysed as standard deviations were not reported.[37]

No data were identified for cardiovascular mortality, occurrence of AKI, hospitalisation or health related quality of life measures.

Study	Intervention/ comparison	Population (Mean blood pressure at baseline in mmHg)	Age (years)	Length of follow-up	Comments
Fernandez et al. 2013[102]	Lisinopril (20mg) plus irbesartan (300mg) vs. irbesartan 600mg	Type II diabetes and diabetic nephropathy (stage 2 or 3 CKD). Hypertensive, but BP<180/95 (BP = 153/81).	> 35 (mean 66.5)	Median 32 months	Double blind.
Fried et al 2013[113]	Losartan 50-100mg/day + lisinopril 10-40mg/day vs. Losartan 50-100mg/day	Type II diabetes and diabetic nephropathy (GFR of 30.0 to 89.9 ml per minute per 1.73 m^2 of body-surface area; urinary albumin to creatinine ratio ≥300mg/g) Mean BP 137/73 on multiple medications.	Mean 64.6	Median 2.2 years	Double blind.
Tutuncu et al. 2001[404]	Enalapril (5mg) plus losartan (50mg) vs. enalapril 5mg	Type II diabetes with microalbuminuria. Normotensive. (BP = 117/77).	Mean 57.5	1 year	Blinding unclear.

Table 86: Clinical evidence profile: ACE inhibitor plus ARB versus ARB

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	ACE inhibitor + ARB	ARB	Relative (95% CI)	Absolute	Quality	Importance
Progression of CKD (measured by occurrence of end stage renal disease): ESRD (dialysis or transplant) (follow-up 26-32 months)												
2[102,113]	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision	None	37/794 (4.7%)	11.9%	RR 0.65 (0.43 to 1)	42 fewer per 1000 (from 68 fewer to 0 more)	MODERATE	CRITICAL
All-cause mortality (follow-up 26 to 32 months)												
2[102,113]	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision	None	69/794 (8.7%)	5.9%	RR 1.08 (0.77 to 1.51)	5 more per 1000 (from 14 fewer to 30 more)	MODERATE	CRITICAL
Change in proteinuria: Final urinary albumin loss rate (mg/day) (follow-up mean 1.8 years; better indicated by lower values)												
2[102,404]	Randomised trials	Serious (b)	No serious inconsistency	No serious indirectness	No serious imprecision	None	80	40	-	SMD 0.05 higher (0.34 lower to 0.44 higher)	MODERATE	IMPORTANT
MI, heart failure or stroke (follow-up median 2.2 years)												
1[113]	Randomised trials	Serious (c)	No serious inconsistency	No serious indirectness	No serious imprecision	None	134/724 (18.5%)	18.8%	RR 0.99 (0.79 to 1.22)	2 fewer per 1000 (from 39 fewer to 41 more)	MODERATE	CRITICAL
Regression to normoalbuminuria (follow-up 1 years)												
1[404]	Randomised trials	very serious (d)	No serious inconsistency	No serious indirectness	Very serious (e)	None	7/10 (70%)	66.7%	RR 1.05 (0.59 to 1.86)	33 more per 1000 (from 273 fewer to 574 more)	VERY LOW	IMPORTANT
Acute kidney injury (follow-up median 2.2 years)												
1[113]	Randomised trials	Serious (c)	No serious inconsistency	No serious indirectness	No serious imprecision	None	130/724 (18%)	11.1%	RR 1.62 (1.25 to 2.1)	69 more per 1000 (from 28 more to 122 more)	MODERATE	CRITICAL

(a) Data not analysed as time to event, incorrect analysis
(b) One study had unclear randomisation and allocation concealment and the doses of enalapril were sub therapeutic
(c) Unclear randomisation and allocation concealment

(d) Unclear randomisation and allocation concealment and the doses of enalapril were sub therapeutic
(e) The confidence interval crosses the MID in both directions making the effect size very uncertain.

9.3.3.7 ACE inhibitors versus ACE inhibitors

Evidence below includes one study comparing perindopril and trandolapril,[248] and one comparing imidapril and captopril.[188] However, the latter study did not present standard deviations, therefore this data could not be included in the meta-analysis.[188]

Matsuda et al. was in people with non-diabetic CKD.[248]

No data were identified for progression of CKD, mortality, cardiovascular events, occurrence of AKI, hospitalisation or health related quality of life measures.

Table 87: Summary of studies included in the review

Study	Intervention/ comparison	Population (Mean blood pressure at baseline in mmHg)	Age (years)	Length of follow-up	Comments
Matsuda et al. 2003[248]	Perindopril (2mg) vs. trandolopril (0.5mg) (starting doses titrated to achieve a systemic blood pressure of <135/85mmHg, final doses not given).	Proteinuria (due to glomerulonephritis, membranous nephropathy or focal segmental glomerulosclerosis). Non-diabetic. Hypertensive (BP = 153/92).	Mean 52.5	96 weeks	Blinding unclear.

Table 88: Clinical evidence profile: Perindopril versus trandolopril

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Perindopril versus trandolapril	Control	Relative (95% CI)	Absolute	Quality	Importance
Change in proteinuria (follow-up mean 96 weeks; measured with: Percentage change in proteinuria; better indicated by higher values)												
1[248]	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Very serious (b)	None	15	15	-	MD 7 lower (26.39 lower to 12.39 higher)	VERY LOW	IMPORTANT

(a) Randomisation and allocation concealment unclear.
(b) The confidence interval crosses both MIDs making the effect size very uncertain.

9.3.3.8 ARB versus ARB

Evidence below includes one study comparing; losartan with telmisartan,[25] telmisartan with valsartan[116] and candesartan with losartan.[248] One study[17] contained 3 ARBs in head to head comparisons; candesartan, losartan, telmisartan. Matsuda only presented data on percentage change in proteinuria, as this was the only data available for a non-diabetic population, it has been included.[248] One study compared candesartan and olmesartan and reported change in proteinuria, but the data could not be analysed as it was only presented graphically.[271]

The studies were in people with CKD and type II diabetes with the exception of Matsuda et al. which was in people with non-diabetic CKD.[248]

No evidence was identified for occurrence of AKI or quality of life measures. Data for hospitalisation all related to cardiovascular events, and therefore are included under this outcome.

Table 89: Summary of studies included in the review

Study	Intervention/comparison	Population (Mean blood pressure at baseline in mmHg)	Age (years)	Length of follow-up	Comments
Arai et al. 2008[17]	Telmisartan (48mg), valsartan (116mg), candesartan (10.2mg) or losartan (71.3mg) (mean doses at study completion).	Type II diabetes and early nephropathy (stage 2). Hypertensive (175/86).	Mean 73.5	1 year	Blinding unclear.
Bakris et al. 2008[25]	Telmisartan (80mg) vs. losartan (100mg)	Type II diabetes with overt nephropathy. Hypertensive. (143/80)	21-80 (mean 60.25)	1 year	Double blind.
Galle et al. 2008[116]	Telmisartan (40mg titrated to 80mg at 2 weeks) vs. valsartan (80mg titrated to 160mg at 2 weeks)	Type II diabetes and overt nephropathy. Hypertensive (148/82).	30-80 (mean 61.2)	1 year	Double blind
Matsuda et al. 2003[248]	Losartan (25mg) vs. candesartan (4mg) (starting doses titrated to achieve a systemic blood pressure of <135/85mmHg, final doses not given).	Proteinuria (due to glomerulonephritis, membranous nephropathy or focal segmental glomerulosclerosis). Non-diabetic. Hypertensive (BP = 153/92).	Mean 52.5	96 weeks	Blinding unclear.

Table 90: Clinical evidence profile: Telmisartan versus valsartan

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Telmisartan	Valsartan	Relative (95% CI)	Absolute	Quality	Importance
Progression of CKD (measured by change in eGFR) (follow-up mean 1 years; measured with: Final eGFR (ml/min/1.73 m^2); better indicated by higher values)												
1[116]	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Very serious (b)	None	428	429	-	MD 0.7 lower (3.71 lower to 2.31 higher)	VERY LOW	CRITICAL
Progression of CKD (measured by occurrence of end stage renal disease): ESRD (follow-up mean 1 years)												
1[116]	Randomised trials	Very serious (a, c)	No serious inconsistency	No serious indirectness	No serious imprecision	None	7/428 (1.6%)	1.9%	RR 0.88 (0.32 to 2.4)	2 fewer per 1000 (from 13 fewer to 27 more)	LOW	CRITICAL
All-cause mortality												
1[116]	Randomised trials	Very serious (a, c)	No serious inconsistency	No serious indirectness	Very serious (b)	None	15/428 (3.5%)	1.9%	RR 1.88 (0.81 to 4.39)	17 more per 1000 (from 4 fewer to 64 more)	VERY LOW	CRITICAL
Cardiovascular mortality (follow-up mean 1 years)												
1[116]	Randomised trials	Very serious (a, c)	No serious inconsistency	No serious indirectness	Very serious (b)	None	8/428 (1.9%)	1.4%	RR 1.34 (0.47 to 3.82)	5 more per 1000 (from 7 fewer to 39 more)	VERY LOW	CRITICAL
Cardiovascular events (follow-up mean 1 years; assessed with: Including myocardial infarction, stroke, first hospitalisation for coronary or peripheral revascularisation, heart failure or unstable angina)												
1[116]	Randomised trials	Very serious (a, c)	No serious inconsistency	No serious indirectness	Very serious (b)	None	31/428 (7.2%)	7.9%	RR 0.91 (0.57 to 1.46)	7 fewer per 1000 (from 34 fewer to 36 more)	VERY LOW	CRITICAL
Change in proteinuria (follow-up mean 1 years; measured with: Final urinary albumin loss (mg/d); better indicated by lower values)												
1[17]	Randomised trials	Serious (d)	No serious inconsistency	No serious indirectness	Serious (e)	None	20	20	-	MD 8.8 lower (25.78 lower	LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Telmisartan	Valsartan	Relative (95% CI)	Absolute	Quality	Importance
										to 8.18 higher)		

(*(b) Doses of study drugs not equivalent.*
(c) The confidence interval crosses the MID in both directions making the effect size very uncertain.
(d) Data not analysed as time to event, incorrect analysis.
(e) Randomisation and allocation concealment unclear.

Table 91: Clinical evidence profile: Losartan versus telmisartan

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Losartan	Telmisartan	Relative (95% CI)	Absolute	Quality	Importance
Progression of CKD (measured by change in eGFR) (follow-up mean 1 years; measured with: Change in eGFR (ml/min/1.73 m²); better indicated by lower values)												
1[25]	Randomised trials	Very serious (a, d)	No serious inconsistency	No serious indirectness	No serious imprecision	None	441	419	-	MD 0.01 lower (0.16 lower to 0.14 higher)	LOW	CRITICAL
All-cause mortality (follow-up mean 1 years)												
1[25]	Randomised trials	Very serious (a, b, d)	No serious inconsistency	No serious indirectness	No serious imprecision	None	13/441 (2.9%)	0.5%	RR 6.18 (1.4 to 27.2)	26 more per 1000 (from 2 more to 131 more)	LOW	CRITICAL
Cardiovascular morbidity or mortality (follow-up mean 1 years)												
1[25]	Randomised trials	Very serious (a, b, d)	No serious inconsistency	No serious indirectness	Serious (c)	None	37/441 (8.4%)	5%	RR 1.67 (1 to 2.81)	33 more per 1000 (from 0 more to 90 more)	VERY LOW	CRITICAL
Change in proteinuria (follow-up mean 1 years; measured with: Final urinary albumin loss (mg/d); better indicated by lower values)												
1[17]	Randomised	Serious	No serious	No serious	Serious (c)	None	20	20	-	MD 17 higher	LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Losartan	Telmisartan	Relative (95% CI)	Absolute	Quality	Importance
	trials	(a)	inconsistency	indirectness						(1.21 lower to 35.21 higher)		

(a) Unclear randomisation and allocation concealment.
(b) Data not analysed as time to event, incorrect analysis.
(c) The confidence interval crosses one MID making the effect size uncertain.
(d) Doses of study drugs not equivalent.

Table 92: Clinical evidence profile: Losartan versus valsartan

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Losartan	Valsartan	Relative (95% CI)	Absolute	Quality	Importance
Change in proteinuria (follow-up mean 1 years; measured with: Final urinary albumin loss (mg/d); better indicated by lower values)												
1[17]	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (b)	None	20	20	-	MD 8.2 higher (10.18 lower to 26.58 higher)	LOW	IMPORTANT

(a) Randomisation and allocation concealment was unclear.
(b) The confidence interval crosses one MID making the effect size uncertain.

Table 93: Clinical evidence profile: Candesartan versus telmisartan

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Candesartan	Telmisartan	Relative (95% CI)	Absolute	Quality	Importance
Change in proteinuria (follow-up mean 1 years; measured with: Final urinary albumin loss (mg/d); better indicated by lower values)												
1[17]	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision	None	20	20	-	MD 24 higher (5.15 to 42.85 higher)	MODERATE	IMPORTANT

(a) Randomisation and allocation concealment was unclear.

Table 94: Clinical evidence profile: Candesartan versus losartan

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Candesartan	Losartan	Relative (95% CI)	Absolute	Quality	Importance
Change in proteinuria (follow-up mean 1 years; measured with: Final urinary albumin loss (mg/d); better indicated by lower values)												
1[17]	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (b)	None	20	20	-	MD 7 higher (13.12 lower to 27.12 higher)	LOW	IMPORTANT
Change in proteinuria (follow-up mean 96 weeks; measured with: Percentage change; range of scores: 0-100; better indicated by lower values)												
1[248]	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (b)	None	17	15	-	MD 13 lower (25.5 lower to 0.45 higher)	LOW	IMPORTANT

(a) Randomisation and allocation concealment was unclear.
(b) The confidence interval crosses one MID making the effect size uncertain.

Table 95: Clinical evidence profile: Candesartan versus valsartan

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Candesartan	Valsartan	Relative (95% CI)	Absolute	Quality	Importance
Change in proteinuria (follow-up mean 1 years; measured with: Final urinary albumin loss (mg/d); better indicated by lower values)												
1[17]	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (b)	None	20	20	-	MD 15.2 higher (3.82 lower to 34.22 higher)	LOW	IMPORTANT

(a) Randomisation and allocation concealment was unclear.
(b) The confidence interval crosses one MID making the effect size uncertain.

9.3.3.9

Direct renin inhibitor versus placebo

Evidence below includes one study comparing; aliskiren with placebo as an adjunct to either an ACE inhibitor or an ARB in people with type II diabetes.[318] Ninety eight% of the population had CKD. It is important to note that this trial was stopped prematurely after the second interim efficacy analysis as it was deemed that the excess risk of adverse events in the aliskiren group was not offset by a reduction in major cardiovascular and renal events.

Study	Intervention/ comparison	Population (Mean blood pressure at baseline in mmHg)	Age (years)	Length of follow-up	Comments
Parving et al. 2012[318]	Aliskiren 300mg once daily (150mg for first 4 weeks). Placebo	Aged ≥35 years. Type II diabetes and evidence of microalbuminuria, macroalbuminuria or cardiovascular disease. 94.5% diagnosed with hypertension (baseline blood pressure 137/74 in both groups). 98% had CKD. 84.1% had proteinuria (baseline ACR 206mg/g in aliskiren group and 208mg/g in placebo group).	Aliskiren: mean 64.6±9.6 Placebo: Mean 64.4±9.9	Median 32.9 months NB. Trial stopped prematurely.	All participants were receiving either an ACE inhibitor or ARB as standard treatment. Trial stopped prematurely due to primary end point occurring in 18.3% of aliskiren group compared to 17.1% in the placebo group.

Table 97: Clinical evidence profile: Direct renin inhibitor (aliskerin) versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Aliskiren	Placebo	Relative (95% CI)	Absolute		
All-cause mortality (follow-up median 32.9 months)[318]												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision	None	376/4274 (8.8%)	358/4287 (8.4%)	HR 1.06 (0.92 to 1.22)	5 more per 1000 (from 6 fewer to 17 more)	MODERATE	CRITICAL
Cardiovascular mortality (follow-up median 32.9 months)[318]												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (b)	None	246/4274 (5.8%)	15/4287 (0.35%)	HR 1.16 (0.96 to 1.4)	1 more per 1000 (from 0 fewer to 1 more)	LOW	CRITICAL
Cardiovascular events (follow-up median 32.9 months; assessed with: Cardiac arrest with resuscitation)[318]												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (b)	None	19/4274 (0.44%)	8/4287 (0.19%)	HR 2.4 (1.05 to 5.49)	3 more per 1000 (from 0 more to 8 more)	LOW	CRITICAL
Cardiovascular events (follow-up median 32.9 months; assessed with: Myocardial infarction (fatal or non-fatal))[318]												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (b)	None	147/4274 (3.4%)	142/4287 (3.3%)	HR 1.04 (0.83 to 1.3)	1 more per 1000 (from 6 fewer to 10 more)	LOW	CRITICAL
Cardiovascular events (follow-up median 32.9 months; assessed with: Stroke (fatal or non-fatal))[318]												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (b)	None	147/4274 (3.4%)	122/4287 (2.8%)	HR 1.22 (0.96 to 1.55)	6 more per 1000 (from 1	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Aliskiren	Placebo	Relative (95% CI)	Absolute	Quality	Importance
										fewer to 15 more)		
Hospitalisation (unplanned, for heart failure) (follow-up median 32.9 months)[318]												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision	None	205/4274 (4.8%)	219/4287 (5.1%)	HR 0.97 (0.8 to 1.18)	1 fewer per 1000 (from 10 fewer to 9 more)	MODERATE	IMPORTANT
ESRD, death attributable to kidney failure, or loss of kidney function (follow-up median 32.9 months)[318]												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (b)	None	121/4274 (2.8%)	113/4287 (2.6%)	HR 1.08 (0.84 to 1.39)	2 more per 1000 (from 4 fewer to 10 more)	LOW	CRITICAL
Doubling of baseline serum creatinine (follow-up median 32.9 months)[318]												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision	None	210/4274 (4.9%)	217/4287 (5.1%)	HR 0.97 (0.8 to 1.18)	1 fewer per 1000 (from 10 fewer to 9 more)	MODERATE	CRITICAL

(a) All participants already taking an ACE inhibitor or ARB (unable to separate data according to concomitant treatment).
(b) The confidence interval crosses one MID making the effect size uncertain.

9.3.4 Economic evidence

Published literature (CG73)

Eight studies were included with a relevant comparison.(Hendry 1997[143], Hogan2002[148], Palmer2004[310], Ruggenenti2001[356], Schadlich2001[365], vanHout1997[409], Vora2005 [414]) from CG73. These are summarised in the economic evidence profiles below (Table 98 and Table 99). See also the study selection flow chart in Appendix E and study evidence tables in Appendix H.

Twelve studies from CG73 that met the inclusion criteria were selectively excluded due to the availability of more applicable evidence [Burgess2004[52], Coyle2004[75], Coyle2007[74], Garrattini1997[119], Herman2003[144], Palmer2003[313], Palmer2006[311], Rodby1996[348], Rodby 2003[347],Souchet2003[380], Szucs2004[389],Stafylas2007[383]] or to methodological limitations. These are listed in Appendix K, with reasons for exclusion given.

Published literature (this update)

Three studies were included with a relevant comparisons [Adarkwah 2013[6], Delea 2009A[84], Palmer2007[312]]. These are summarised in the evidence profile table below (Table 98, Table 99 and Table 100). See also the study selection flow chart in Appendix E and study evidence tables in Appendix H.

One study met the inclusion criteria but was selectively excluded due to the availability of more applicable evidence[83]. Excluded studies are listed in Appendix K, with reasons for exclusion given.

Table 98: Economic evidence profile: ACE inhibitor versus placebo

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Adarkwah 2013, Netherlands [6] Non diabetic proteinuric patients with hypertension and advanced renal disease	Partially applicable(a)	Minor limitations	ACE inhibitor- Benezapril 10 mg twice a day.	-£29,073	1.79 QALYs	Benezapril was the dominant strategy.	Base case results remained robust to univariate sensitivity analyses on key model parameters and discount rate.
Hendry 1997, UK. [143] People with insulin diabetes and nephropathy	Partially applicable (b)	Minor limitations	Captopril 25mg 3 daily	-£953	0.195 life-years	Captopril was the dominant strategy.	If a risk reduction of only 18% is assumed (compared with the trial result of 50%) the cost per life-year saved is £1360.
Hogan 2002, USA. [148] People with chronic renal insufficiency	Partially applicable (c)	Minor limitations	Benazepril. Dose and quantity NR.	£-8,479	0.092 QALYs	Benazepril was the dominant strategy	Results favouring the benazepril therapy arm were found in sensitivity analyses of changes in key model parameters.
Ruggenenti 2001, Italy.[357] People with non-diabetic chronic nephropathy	Partially applicable (d)	Minor limitations.	Ramipril versus placebo, dose not reported.	GFR decline model: £-10,408 Events based model £-14,964	GFR decline model 1.2 life-years Events based model 1.4 life-years	Results from both models showed Ramipril was the dominant strategy.	A sensitivity analysis was done to compute the best case and worst case results for costs, mortality rate, and discount rate. Conclusions about CE were not affected.
Schadlich 2001, Germany. [365]	Partially applicable (e)	Minor limitations (f)	Ramipril (target =5mg/d)	£-57,442	0.212 patient-years of chronic dialysis avoided	Ramipril was the dominant strategy	Cost of chronic dialysis had the greatest impact on cost savings associated with ramipril. In 95%

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
People with non-diabetic nephropathy and hypertension					over 3 years		of simulations ramipril was cost saving.
Van Hout 1997, Netherlands, Switzerland and Germany.[409] People with chronic renal insufficiency	Partially applicable (g)	Minor limitations.	Benazepril.	£-£17,983	0.32 life-years. 18.1% surviving without ESRD at 10 years	Benezepril was the dominant strategy.	Varying the costs of ESRD, the preventive therapy and other important parameters used in the model showed that the conclusion of a combination of additional effectiveness and cost savings is extremely robust.

(a) Netherlands setting. Discount rates – 4% for costs and 1% for health effects
(b) Costs and benefits discounted at 6%, health effects not expressed in QALYs
(c) USA setting
(d) Italy setting. Health effects not expressed in QALYs.
(e) Germany setting. Health effects not expressed in QALYs. Costs and benefits discounted at 5%.
(f) Time horizon = 3 years only.
(g) Setting is Netherlands, Switzerland and Germany. Value of health effects not expressed in QALYs.
Abbreviations: CEA = cost-effectiveness analysis; CI = 95% confidence interval; CRI = chronic renal insufficiency; GFR= glomerular filtration rate; ESRD= end-stage renal disease; ICER = incremental cost-effectiveness ratio; IDDM=insulin dependent diabetes mellitus; NIDDM= non-IDDM; NR = not reported; psa = probabilistic sensitivity analysis; PYCDA=patient-year of chronic dialysis avoided; QALY=quality-adjusted life year.

Table 99: Economic evidence profile: angiotensin II receptor antagonist versus conventional therapy

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Palmer 2004, UK. [310] People with type 2 diabetes, hypertension and proteinuria.	Partially applicable. (a)	Minor limitations	1: Irbesartan 300mg/d 2: Amlodipine 10mg/d 3: Conventional antihypertensive therapy	1-2= £-6,533 1-3 = £-3,758	Life years (1-2): 0.08 (1-3): 0.23	Irbesartan dominates	One-way sensitivity analysis showed that the annual costs of dialysis in the UK would have to fall below £3,000 before irbesartan would no longer be cost saving compared to standard antihypertensives alone.
Palmer 2007, UK. [312] People with type 2 diabetes, hypertension and proteinuria.	Partially applicable. (b)	Minor limitations	1: Early (24-hr UAE 20-199µg/min) irbesartan 300mg/d 2: Late (UAE 1100mg/24hr) Irbesartan 300mg/d 3: Conventional antihypertensive therapy	1-2 = £-2310 2-3 = £-1491	Life years (1-2): 0.81 (2-3): 0.02	Irbesartan dominates	One-way sensitivity analysis using the confidence limits for progression rates found that early irbesartan remained dominant
Vora 2005, UK. [414] People with Type 2 diabetes and proteinuria	Partially applicable (c)	Minor limitations	losartan vs. conventional antihypertensive therapy	£-6,622 (CI: 2,653 to 10,591)	0.44 life-years (CI 0.16 to 0.71)	Losartan dominates	Losartan treatment was cost saving in all scenarios, even if the cost of renal replacement therapy was reduced by 50%.

(a) Costs discounted at 5%, benefits at 1.5%. Health effects not expressed as QALYs.
(b) Health effects not expressed as QALYs.
(c) Health effects not expressed as QALYs.
Abbreviations: CI = 95% confidence interval; ESRD= end-stage renal disease; ICER = incremental cost-effectiveness ratio; NR = not reported; QALY=quality-adjusted life year.

Table 100: Economic evidence profile: Direct Renin Inhibitor & angiotensin II receptor antagonist versus angiotensin II receptor antagonist

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Delea 2009A [84] People with type 2 diabetes, hypertension, and renal disease	Partially applicable. (a)	Potentially serious limitations (b)	Losartan 100 mg/d and optimal antihypertensive therapy Aliskerin 300 mg/d plus losartan 100 mg/d and optimal antihypertensive treatment	£1888	0.0967 QALYs	£19 500 per QALY gained	Aliskiren not cost effective when: - risk reduction of progression from early overt nephropathy to advanced overt nephropathy is low, - cost of aliskiren is over £913 - the time frame is 10 years, - the treatment starting age is 70 (c)

(a) US setting means that costs are less applicable to the UK NHS.
(b) The study does not reflects the risks and effectiveness seen in the ALTITUDE study
(c) Baseline results robust to changes in all other parameters. In the probabilistic analysis, the cost effectiveness of aliskiren ranged from dominated to dominant, reflecting uncertainty around the probabilities of progression of renal disease derived from AVOID

9.3.5 Evidence statements

Clinical

9.3.5.1 ACE inhibitors versus placebo

- In terms of progression of CKD in people with diabetic CKD, measured by change in eGFR, high quality evidence from one study showed that ACE inhibitors are more clinically effective at slowing progression when this was assessed as a hazard ratio. Four studies showed no clear difference between the two when this was assessed by mean difference, however this was low quality evidence.
- When progression of CKD is reported as occurrence of end stage kidney disease, high quality evidence from two studies in people with non-diabetic CKD showed that ACE inhibitors are more clinically effective than placebo in reducing the occurrence of end stage kidney disease when assessed as a hazard ratio. Very low quality evidence form three studies in people with diabetic CKD suggested that ACE inhibitors may be more effective than placebo, but there was some uncertainty in this effect.
- In people with CKD with and without diabetes, one study reported moderate quality evidence that ACE inhibitors are more clinically effective than placebo in reducing all-cause mortality when assessed as a hazard ratio. Five studies showed no clear difference between the two when this was assessed as relative risk, however this was low quality evidence.
- In terms of cardiovascular mortality in people with CKD with or without diabetes, one study showed that ACE inhibitors are more clinically effective than placebo in reducing cardiovascular mortality with moderate quality evidence assessed as a hazard ratio. Three studies showed there is no difference between the two when assessed as a risk ratio, however this was low quality evidence.
- No clear difference in occurrence of cardiovascular events was observed in the studies reviewed (low quality evidence from 1 study assessed as a hazard ratio, and moderate quality evidence from 4 studies assessed by relative risk) in people with CKD with or without diabetes. Considering the type of event (for example, stroke, myocardial infarction or revascularisation) or length of follow-up did not alter this finding.
- In terms of change in proteinuria, moderate and low quality evidence suggested that ACE inhibitors are more effective than placebo in preventing an increase in proteinuria, demonstrated by 1 study in people with diabetic CKD assessed by a hazard ratio (moderate quality), 8 studies in people with or without diabetes assessing progression to clinical proteinuria by relative risk (low quality), 5 studies reporting change in albumin loss rate in people with diabetic CKD (moderate quality) and 4 studies in people with diabetic CKD reporting regression to normoalbuminuria (moderate quality).
- Two studies suggested that ACE inhibitors were more effective than placebo at reducing hospitalisation in people with CKD with or without diabetes (low and very low quality evidence).
- No evidence was available for occurrence of AKI or health related quality of life.

9.3.5.2 ARBs versus placebo

- Three studies showed that ARBs are more effective than placebo in reducing progression of CKD in terms of change in eGFR in people with CKD with or without diabetes when assessed by hazard ratio or mean difference (moderate and high quality evidence).
- When progression is assessed by occurrence of end stage kidney disease, one study in people with IgA nephropathy and three in people with diabetic CKD suggested that ARBs are more effective than placebo. However one study in people with CKD and diabetes or cardiovascular

disease suggested that ARBs may be no more effective than placebo (all moderate quality evidence).

- There appears to be no benefit of ARBs over placebo in reducing all-cause mortality when assessed by hazard ratio (3 studies, high quality), or by relative risk (2 studies, low quality), or cardiovascular mortality assessed by hazard ratio (2 studies, moderate quality) or relative risk (1 study, very low quality) in people with CKD with or without diabetes.
- There is evidence from 3 studies to suggest that ARBs may be more effective than placebo in reducing occurrence of cardiovascular events in people with CKD and diabetes (3 studies assessed as a hazard ratio, moderate quality and 3 assessed as relative risk, low quality). The overall effect did not differ according to type of cardiac event.
- In terms of occurrence of acute kidney injury, one study in people with CKD and diabetes suggested that there is no appreciable benefit or harm of ARBs over placebo, however there was considerable uncertainty in this effect (very low quality evidence).
- Studies show that ARBs are more effective than placebo in reducing increase in proteinuria when assessed by progression to clinical proteinuria, macroalbuminuria or overt nephropathy (3 studies, low quality evidence) or change in baseline proteinuria (4 studies, 3 low and 1 moderate quality evidence) in people with CKD with or without diabetes, irrespective of whether or not they are hypertensive. When assessed in terms of regression to normoalbuminuria, 2 studies suggest that up to 2 years, ARBs are more effective than placebo in people with CKD with or without diabetes (high and moderate quality evidence), at 2 years, 1 study in people with diabetic CKD suggests there may be more uncertainty in the effect (low quality evidence).
- No evidence was available for hospitalisation or health related quality of life.

9.3.5.3 Spirinolactone versus placebo

- One study reported very low quality evidence suggesting that spirinolactone may be more effective than placebo in reducing all-cause mortality in people with CKD and diabetes, but there was considerable uncertainty about this effect.

9.3.5.4 ACE inhibitor versus ARB

- One study in people with IgA nephropathy showed that there is no difference between ACE inhibitors and ARBs in reducing progression of CKD measured by change in eGFR when a standard dose ARB is used (moderate quality evidence), but high dose ARB is more effective than an ACE inhibitor (low quality evidence).
- When progression is measured in terms of occurrence of end stage kidney disease, 2 studies suggest that ARBs are more effective than ACE inhibitors in people with CKD and diabetes or IgA nephropathy, but it was noted that 1 of these studies used a high dose ARB. When standard doses are used the difference between the treatments is uncertain (very low quality evidence).
- Two studies suggested that there is no difference between ACE inhibitors and ARBs in people with diabetic CKD in terms of occurrence of all-cause mortality and one study suggested that ACE inhibitors were more effective than ARBs in reducing occurrence of cardiovascular mortality, however there was considerable uncertainty in both of these effects and the evidence was very low quality.
- One study showed no difference between ACE inhibitors and ARBs in terms of occurrence of cardiovascular events, irrespective of type of event (low quality evidence).
- The difference in change in proteinuria differed according to means of assessment and whether equivalent doses were assessed. One study reported very low quality evidence that suggested ACE inhibitors were more effective than ARBs in terms of reducing progression to macroalbuminuria, even with a dose of ACE inhibitor that would be considered sub therapeutic, although there was considerable uncertainty in the effect. In people with IgA nephropathy, one study suggested ARBs were more effective in terms of change from baseline proteinuria levels,

but when standard doses were used, it was unclear if this was a meaningful difference (moderate quality). Two studies suggested that ACE inhibitors were more effective in people with CKD and type II diabetes (very low quality), but 1 study suggested that ARBs may be more effective in people with IgA nephropathy, although this was very low quality evidence in which not all doses were equivalent. Only 1 study compared equivalent doses, which showed that ACE inhibitors are more effective than placebo in people with type II diabetes (high quality evidence).

- No evidence was available for occurrence of AKI, hospitalisation or health related quality of life.

9.3.5.5 ACE inhibitor plus ARB versus ACE inhibitor

- Two studies suggested that there is no difference in reducing occurrence of end stage kidney disease between combinations of ACE inhibitors and ARBs compared to ACE inhibitors alone in diabetic or non-diabetic CKD (very low quality evidence).
- One study suggested that ACE inhibitors may be more effective than a combination in reducing all-cause mortality although there was a lot of uncertainty in the effect and this was very low quality evidence.
- In terms of change in proteinuria, the effect appeared to differ according to whether the population was diabetic or non-diabetic CKD. Two studies suggested that there was no meaningful difference between combination treatments or ACE inhibitors alone in people with CKD and type II diabetes assessing change from baseline proteinuria levels or regression to normoalbuminuria (moderate and very low quality evidence), however one study showed that the combination of ACE inhibitors and ARBs is more effective in people with non-diabetic CKD, however this was low quality evidence from a study in which the ACE inhibitor used was unknown.
- No evidence was available for change in eGFR, cardiovascular mortality, cardiovascular events, occurrence of AKI, hospitalisation or health related quality of life.

9.3.5.6 ACE inhibitor plus ARB versus ARB

- Studies suggest that there may be no difference between a combination of ACE inhibitor and ARB when compared to an ARB alone in people with CKD and type II diabetes in terms of change in proteinuria (2 studies, moderate quality evidence) or regression to normoalbuminuria (one study, very low quality evidence). However occurrence of end stage kidney disease appeared to be lower in the combination of treatments, but there was some uncertainty (2 studies, moderate quality evidence).
- Evidence indicated that there was no difference between ARBs alone and a combination of treatments in reducing all-cause mortality (2 studies, moderate quality evidence) or occurrence of cardiovascular events in people with CKD and diabetes (1 study, moderate quality evidence).
- Occurrence of acute kidney injury was lower in the group receiving an ARB alone compared to combination of treatments in people with CKD and type II diabetes (1 study, moderate quality evidence).
- No evidence was available for change in eGFR, cardiovascular mortality, hospitalisation or health related quality of life.

9.3.5.7 ACE inhibitors versus ACE inhibitors

- One study suggested that there was no difference between perindopril and trandolapril in terms of percentage change in proteinuria in people with non-diabetic CKD (very low quality evidence).
- No evidence was available for change in eGFR, occurrence of end stage kidney disease, mortality, cardiovascular events, occurrence of AKI, hospitalisation or health related quality of life.

9.3.5.8 ARBs versus ARBs

Telmisartan versus valsartan

- One study suggested that there was no difference between telmisartan and valsartan in terms of reducing progression of CKD measured by either change in eGFR or occurrence of end stage kidney disease (very low and low quality evidence with considerable uncertainty) in people with CKD and type II diabetes.
- One study suggested that valsartan was more effective than telmisartan in reducing all-cause and cardiovascular mortality in people with CKD and type II diabetes although the evidence was very low quality.
- In terms of occurrence of cardiovascular events, one study showed no difference between telmisartan and valsartan in people with CKD and type II diabetes, irrespective of the type of event (very low quality evidence).
- Evidence from one study suggested that telmisartan may be more effective than valsartan in reducing albumin loss rate in people with CKD and type II diabetes (low quality with considerable uncertainty in the effect).
- No evidence was available for occurrence of AKI, hospitalisation or health related quality of life.

Losartan versus telmisartan

- One study suggested that in people with CKD and type II diabetes there was no difference between losartan and telmisartan in reducing change in eGFR (low quality evidence).
- Low quality evidence from one study showed that telmisartan was more effective than losartan at reducing all-cause mortality, and suggested it may be more effective in reducing cardiovascular morbidity or mortality in people with CKD and type II diabetes.
- Telmisartan was also suggested to be more effective than losartan at reducing urinary albumin loss in people with CKD and diabetes (low quality evidence).
- No evidence was available for occurrence of end stage kidney disease, AKI, hospitalisation or health related quality of life.

Losartan versus valsartan

- One study in people with CKD and type II diabetes suggested that valsartan may be more effective than losartan at reducing urinary albumin loss (low quality).
- No evidence was available for change in eGFR, occurrence of end stage kidney disease, mortality, cardiovascular events, occurrence of AKI, hospitalisation or health related quality of life.

Candesartan versus telmisartan

- One study in people with CKD and type II diabetes showed that telmisartan is more effective than candesartan at reducing urinary albumin loss (moderate quality).
- No evidence was available for change in eGFR, occurrence of end stage kidney disease, mortality, cardiovascular events, occurrence of AKI, hospitalisation or health related quality of life.

Candesartan versus losartan

- In terms of change in proteinuria, one study suggested losartan may be more effective than candesartan at reducing albumin loss rate in people with CKD and type II diabetes (low quality evidence with some uncertainty in the effect), however, another suggested that candesartan may be more effective in people with non-diabetic CKD in reducing the percentage change in proteinuria from baseline (low quality evidence).

- No evidence was available for change in eGFR, occurrence of end stage kidney disease, mortality, cardiovascular events, occurrence of AKI, hospitalisation or health related quality of life.

Candesartan versus valsartan

- One study suggested that valsartan may be more effective than candesartan in reducing albumin loss rate in people with CKD and type II diabetes, however this was low quality evidence with considerable uncertainty in the effect.
- No evidence was available for change in eGFR, occurrence of end stage kidney disease, mortality, cardiovascular events, occurrence of AKI, hospitalisation or health related quality of life.

9.3.5.9 Direct renin inhibitor (aliskiren) versus placebo

- One study suggested that there is no difference between 300mg aliskiren or placebo on a background of ACE inhibitor or ARB in terms of mortality, myocardial infarction, stroke, unplanned hospitalisation for heart failure, occurrence of ESRD or kidney failure or doubling of baseline serum creatinine in people with type II diabetes with albuminuria, from moderate to low quality evidence. There was low quality evidence to suggest that aliskiren may be associated with an increased risk of cardiac arrest (with resuscitation) in this population when compared to placebo.

Economic

- One cost-effectiveness analysis found that captopril was dominant (less costly and more effective) compared to placebo for management of people with diabetes and proteinuria. This analysis was assessed as partially applicable with minor limitations.
- One cost-utility analysis found that ramipril was dominant (less costly and more effective) compared to placebo for people with hypertension and proteinuria. This analysis was assessed as partially applicable with minor limitations.
- One cost-utility analysis found that ramipril was dominant (less costly and more effective) compared to placebo for people with proteinuria. This analysis was assessed as partially applicable with minor limitations.
- One cost-utility analysis and one cost-effectiveness analysis found that benazepril was dominant (less costly and more effective) compared to placebo for people with proteinuria. These analyses were assessed as partially applicable with minor limitations.
- One cost-utility analysis found that benazepril was dominant (less costly and more effective) compared to placebo for people with hypertension and proteinuria. This analysis was assessed as partially applicable with minor limitations.
- One cost–effectiveness analysis found that losartan was dominant (less costly and more effective) compared to conventional antihypertensive treatment for people with diabetes and proteinuria. This analysis was assessed as partially applicable with minor limitations.
- One cost–effectiveness analysis found that irbesartan was dominant (less costly and more effective) compared to amlodipine and standard antihypertensive treatment for people with diabetes and proteinuria. This analysis was assessed as partially applicable but with potentially serious limitations.
- One cost–effectiveness analysis found that early irbesartan was dominant (less costly and more effective) compared to late irbesartan for people with diabetes and proteinuria. This analysis was assessed as partially applicable with minor limitations.
- One cost–utility analysis found that aliskerin plus losartan plus conventional antihypertensive therapy was cost effective compared to losartan and antihypertensive therapy in people with diabetes, hypertension and proteinuria (ICER: £19,500). This study was assessed as partially applicable with potentially serious limitations.

9.3.6 Recommendations and link to evidence

Recommendations	The current recommendations can be found at www.nice.org.uk/guidance/ng203
Research Recommendations	• **For people aged over 75 years with CKD, what is the clinical effectiveness of renin–angiotensin–aldosterone system (RAAS) antagonists?**
Relative values of different outcomes	For this review, progression of CKD measured by change in eGFR or occurrence of end stage kidney disease, mortality (all-cause or cardiovascular), cardiovascular events and occurrence of AKI were all considered as critical outcomes for decision making. Change in proteinuria, hospitalisation and health related quality of life were considered as important outcomes. However, no data was available for health related quality of life.
Trade off between clinical benefits and harms	The GDG discussed that the relative risks of mortality with ACE inhibitors versus placebo do not always indicate a benefit. However, the hazard ratios do show a benefit for ACE inhibitors and ARBs over placebo. Hazard ratios are a more robust measure of time-to-event data for outcomes in which the time of the event is important. The evidence for the hazard ratios is of better quality than that for those outcomes assessed as relative risks. The GDG noted that the majority of the studies did not include people aged over 75 years. However, those studies that included older people did not demonstrate a difference in effect from those seen in younger populations.[242] The GDG debated the potential risks and benefits of renin angiotensin aldosterone system (RAAS) antagonists in the over 75 age group. The GDG consensus was that indiscriminate use of RAAS antagonists may result in harm and concerns were expressed (based on clinical experience) that the risks of AKI could be higher in older people with multiple comorbidities. Only 1 study[164] reported occurrence of AKI in people with CKD and diabetes (ARB versus placebo) and demonstrated no effect. There was limited evidence in the over 75 age group and on this basis the GDG agreed RAAS antagonists should be used with caution in this population, and that clinical expertise

[m] The evidence to support these criteria is limited in people aged over 70 years.

	would have to guide the decision as there was no evidence to suggest that this age group should be treated differently. It was agreed a footnote would be added to the recommendation to highlight the limited evidence base in older people. The NICE hypertension guideline[274] stratifies treatment to age and recommends ACE inhibitors and ARBs as step 1 treatment for those aged under 55 years, with calcium channel blockers or thiazide type diuretics recommended for people with hypertension aged over 55 years. It was noted that this was based on the hypertension guideline health economic analysis, and the lack of clinical evidence of effectiveness for calcium channel blockers or thiazide type diuretics in a younger population. There was no evidence for a difference in effect of ACE inhibitors or ARBs in different age groups in the review and therefore it was agreed that a separate recommendation stratified by age would not be made for people with CKD. This review has not considered the side effects that may be associated with ACE inhibitors or ARBs including hyperkalaemia and AKI. It was noted that falls may be increased in older populations, but again evidence for this was not available from this review. Experience from people with CKD on the GDG suggests that reduction in proteinuria and slowed progression of CKD are the most important factors when considering response to treatment. It is acknowledged that the side effects can be unpleasant and the benefits are not always clear to patients initially. It is important that the benefits of medications to control blood pressure and reduce progression of CKD are clearly explained to patients. All people who have indications for ACE inhibitors or ARBs are at higher risk of AKI therefore these drugs should be temporarily stopped during an acute illness that increased the risk of AKI (for example, diarrhoea, vomiting and other conditions leading to dehydration or shock). Having reviewed the evidence, the GDG agreed that: • Overall limited evidence was available since the publication of the last CKD guideline and no evidence was found that countered the original recommendations. However, ACE inhibitors and ARBs appeared to be equally effective, and as many ARBs will soon be generic, there would be no significant cost difference. The GDG agreed there was therefore no reason to discriminate between the two as a first line agent. • There is limited evidence available specifically in the over 75 year age group. In older people, RAAS antagonists should be used with caution, but with the same guidance as younger age groups. • Evidence for spironolactone was still limited and no recommendation could be made. • Evidence for aliskerin in combination with an ACE inhibitor or ARB showed an increased risk of hyperkalaemia and hypotension and demonstrated no additional clinical benefit. However it was noted that the BNF says not to use aliskerin in combination with an ACE or an ARB and therefore no recommendation was needed. • Overall no real improvement in effect could be seen for combination therapy with an ACE inhibitor and an ARB. Many of the combination studies did not use maximum dose of one agent before combining with another. The GDG noted that on this occasion there is evidence, but evidence of no benefit and agreed to continue with the original recommendation – that there is no evidence to use combination therapy.
Economic	**Intra-class comparisons**

considerations	There was no economic evidence that compared ACE inhibitor versus ACE inhibitor or ARB versus ARB. The GDG concluded that there was a class effect for ACEs and ARBs and that within each drug class, drugs with greater acquisition costs were unlikely to confer additional clinical benefits compared to those with lower acquisition costs. The GDG observed some difference in the occurrence of end-stage-kidney disease, cardiovascular morbidity, and change in proteinuria from low quality clinical evidence and were wary of recommending one class of drug over the other based on this evidence. Instead, the GDG felt the drug with the lowest acquisition cost in each drug class should be the prescription choice. Furthermore, the GDG acknowledged that the current price differentiations between ACE inhibitors and ARB drug classes are likely to diminish as ARBs come off patent in the near future and found it sufficient to recommend first line therapy as the drug with the lowest acquisition cost for this subgroup. **Combination therapy** There was one economic evaluation comparing combination therapy (Renin Inhibitor plus ARB) versus ARB alone which found combination therapy cost effective (£19,500 per QALY). But, the GDG noted that this study has potentially serious limitations in light of conflicting clinical evidence of harms and benefits associated with combination therapy observed in the ALTITUDE study and Fernandez et al 2013. Hence the GDG have not recommended combination therapy. **Monotherapy** Nine economic evaluations comparing ACE inhibitor (6 studies) or ARB (3 studies)[310,312,414] versus placebo found treatment to be not just cost-effective but cost saving in: • people with diabetes and proteinuria [143,310,312,414] • people with hypertension and proteinuria[6,365] • other people with proteinuria [148,356,409]. These studies had minor limitations and were partially applicable due to not estimating QALYs and in some cases not being in a UK setting. The GDG were uncertain about the appropriateness of RAAS therapy for older people. The GDG made a research recommendation to determine the effectiveness of RAAS antagonists in the population of people with CKD aged over 75 as there is a clinical suspicion that older people have a high incidence of adverse effects from using RAAS antagonists and older people are frequently not recruited to clinical trials. Appendix N contains further details of the research recommendation.
Quality of evidence	The evidence for this review varied from high to very low quality. See methodology section (3.1.4.2) for explanation of quality rating for Hazard ratios. For the comparison of ACE inhibitor versus ARB there was high and moderate quality evidence available to inform recommendations. However, for some of the comparisons (spirinolactone versus placebo and head to head ACE inhibitor comparison) the only available evidence was of very low quality. The GDG noted that many studies, with the exception of those in the ARB versus placebo comparisons, compared drugs at doses that are considered sub therapeutic, and would not be expected to be of benefit. Most studies of combinations of ACE inhibitors and ARBs do not use a therapeutic dose of one drug before combining with another. This represents a limitation in the evidence for these comparisons. Some of the studies comparing ARBs to each other in head to head comparisons compared a therapeutic dose of one drug to a sub therapeutic dose of the other. The evidence from these trials is therefore of lower quality. In some of the other trials,

final achieved doses were not provided, so it is unclear if the doses compared were

	equivalent. The GDG did not believe there was any evidence to suggest that combinations of ACE inhibitors and ARBs provide additional benefit to one drug. The GDG noted that some of the studies were in people with CKD who were normotensive. These people were given antihypertensive treatment for the potential reno-protective effects. In addition, some inclusion criteria did not specify parameters around blood pressure but it was noted that many of the study participants were hypertensive. The GDG debated whether these two groups (hypertensive and normotensives) could be considered together but noted that there were few outcomes which demonstrated heterogeneity when studies were pooled. The GDG debated whether a mixed treatment comparison would be beneficial or was possible, comparing all the ACE inhibitors and ARBs with one another (this would have fed into the health economic analysis). However, when exploring his possibility, it was identified that the outcome with the greatest number of interventions included, which was also deemed clinically important (occurrence of end stage kidney disease) did not have enough treatments included to form a complete loop for a network. A further confounding factor would be whether these were diabetic or non diabetic populations or people with or without hypertension or proteinuria which the GDG were concerned may not be appropriate to compare in a mixed treatment comparison. The evidence reviewed did not demonstrate significant differences within class for ACE inhibitors or ARBs and the GDG agreed that a class effect could be assumed and the lack of a network meta-analysis would not negatively impact on this review or recommendation.
Other considerations	In the present review, there wasn't evidence for difference in effect at different levels of proteinuria as there was no unexplained heterogeneity. The majority of evidence was from populations with proteinuria, although some did not report this. The GDG therefore agreed that the original guideline recommendation considerations for proteinuria should remain. It was noted that in primary care, the majority of patients with CKD will have no proteinuria. The GDG noted that for people with non-diabetic CKD and no proteinuria, the NICE hypertension guidelines should be followed.[274]

9.4 Practicalities of treatment with ACE inhibitors/ARBs in people with CKD

9.4.1 Clinical introduction

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

Physicians may be reluctant to prescribe ACE inhibitor/ARBs in people with reduced GFR, hyperkalaemia, and non-critical renal artery stenosis. A rise in serum creatinine concentration and fall in GFR should be expected following introduction of treatment with ACE inhibitor/ARBs and

hyperkalaemia is a known complication of treatment.[26,339] The incidence of hyperkalaemia with ACE inhibitor/ARB treatment is low in those with normal kidney function but obviously increases as GFR falls. However, changes in serum creatinine and potassium concentrations to lesser or greater degrees variably influence physicians in their approach to continuing treatment. What one physician perceives as an intolerable fall in GFR or rise in potassium may not be interpreted as such by another. Furthermore, changes in GFR and potassium during treatment with ACE inhibitor/ARBs may be significantly influenced by a person's volume status, degree of sodium depletion, and concurrent medications. Many people 'intolerant' of ACE inhibitor/ARB treatment may be successfully treated once these factors have been addressed. Educating the healthcare community about these relative contraindications, and clearly stating what parameters should be monitored, how often these parameters should be monitored, and what levels are acceptable, could significantly affect outcomes in many people who might otherwise not be treated with ACE inhibitor/ARBs (and also help avoid unwanted complications).

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

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

9.4.2 Methodology

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

One systematic review (12 studies, n=1102 randomised to ACE inhibitors, mean follow-up 3.2 years)[26] examined the changes in serum creatinine and potassium in people with >25% loss of kidney function upon commencement of ACE inhibitors. The authors presented an algorithm for monitoring serum creatinine and potassium levels in people commencing ACE inhibitors.

9.4.3 Health economics methodology

No health economics papers were found to review.

9.4.4 Evidence statements

Serum creatinine levels

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

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

There was limited data on the benefit of ACE inhibitors in advanced disease (GFR <30 ml/min/1.73 m^2). (Level 1+)

Serum potassium levels

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

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

9.4.5 From evidence to recommendation

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

There was little evidence to guide the formulation of recommendations.

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

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

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

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

9.4.6 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng203

10 Reducing cardiovascular disease

Clinical guideline 73 reviewed the evidence for lipid-lowering therapy in people with CKD. However, during the scoping for the update of this guideline, it was agreed that the partial update of NICE clinical guideline 67 for lipid modification (CG67: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease), which also updates the NICE technology appraisal 'Statins for the prevention of cardiovascular events' (TA 94, 2007) would include CKD as a subgroup and would update the evidence for this section

10.1 Statin therapy and reduction in proteinuria

10.1.1 Clinical introduction

Animal models of hyperlipidaemia produced by cholesterol-rich diets promote progression of kidney disease. Epidemiological studies suggest that dyslipidemia is a risk factor for CKD initiation, and that lipid lowering may slow disease progression. Elevated cholesterol and triglyceride levels are associated with a more rapid decline in kidney function. Possible mechanisms include accelerated atherosclerosis of arteries within the kidney and damaging effects of lipids on mesangial cells. Hyperlipidaemia may activate mesangial cells (which have low-density lipoprotein (LDL) receptors), leading to stimulation of mesangial cell proliferation and to increased production of macrophage chemotactic factors, accumulation of extracellular matrix, and reactive oxygen species. Studies in animal models show that reducing lipid levels with a drug such as lovastatin slows the rate of progressive injury.[299,303,304] Furthermore, the beneficial effect of lipid lowering may be additive to that of lowering the blood pressure in at least some models of chronic kidney disease (see section 0). Treatment may reduce kidney injury by decreasing albuminuria and reducing mesangial matrix accumulation and mesangial hypercellularity.

In adults with CKD and proteinuria, do statins decrease proteinuria and decrease the risk of progression of CKD compared with other treatments or placebo?

10.1.2 Methodology

There were no trials of statins versus other antilipemic agents such as fibrates or fish oils. No trials addressed clinically relevant markers of kidney progression such as doubling of serum creatinine or time to ESRD.

Three meta-analyses assessed the efficacy of statins compared to placebo in decreasing the risk of kidney disease progression in adults with CKD.

The meta-analysis by Douglas et al. (15 RCTs, n=1384, mean follow-up 6 months)[92] investigated the effect of statins on changes in proteinuria. Study heterogeneity was mostly avoided by stratifying the data by baseline levels of proteinuria. The limitations with this meta-analysis were that the individual studies were few, small and methodologically limited.

The meta-analysis by Sandhu et al. (27 RCTs, n=39704, mean follow-up 1 year)[362] measured the effect of statins compared to control on the rate of change of GFR and on changes in proteinuria in populations with diabetic or hypertensive kidney disease or in people with glomerulonephritis. While this meta-analysis included the studies in the Douglas et al. meta-analysis, the between-study heterogeneity was very high. The pooled analysis of changes in proteinuria or albuminuria was particularly marred by significant heterogeneity. However, the analysis of changes in GFR was an important outcome, and was not reported in the Douglas et al. 2006 meta-analysis.

A systematic review assessed cardiovascular outcomes, changes in GFR and 24-hour proteinuria in people with CKD randomised to statins or placebo/no treatment (50 studies, n=30,144, follow-up ranged from 2–60 months).[388] Subgroup analysis was performed in people with pre-dialysis CKD (26 studies), people undergoing dialysis (11 studies) and kidney transplant recipients (17 studies).

The effects of statins versus placebo on kidney disease progression in adults with varying severity and different causes of CKD are summarised in Table 101, at the end of the evidence statements.

10.1.3 Health economics methodology

There were no health economics papers found to review.

10.1.4 Evidence statements

Statins versus placebo

Refer to Table 101 for a summary of studies comparing statins with placebo.

Changes in GFR

Overall, statins did not significantly slow decline in GFR. There was significant heterogeneity in the meta-analyses for this outcome.[362,388] (Level 1+)

Change in proteinuria

Statins significantly reduced proteinuria compared to placebo in people with CKD and baseline proteinuria 30–299 mg/day.[92] (Level 1++)

Statins significantly reduced proteinuria compared with placebo; however there was significant heterogeneity in this analysis.[388] (Level 1++)

By contrast, the meta-analysis of Sandhu et al. showed NS effect of statins on proteinuria. However, there was significant between-study heterogeneity in this analysis. (Level 1+)

Table 101: Effect of statins versus placebo on changes in GFR and proteinuria in adults with CKD

Study	CKD population	Change in GFR	Change in proteinuria
362	Glomerulonephritis (n=222, 7 studies)	NS*	
	Hypertensive CKD (n=212, 4 studies),	NS*	NS*
	Diabetic CKD (n=122, 6 studies)	NS	
92	Baseline proteinuria 30-299 mg/day (n=181, 6 studies)	-	WMD -48% (95% CI -71 to -25)
	Baseline proteinuria > 300 mg/day (n=275, 6 studies)	-	WMD -47% (95% CI -67 to -26)**
388	Pre-dialysis (CKD stages 1-4) (n=548, 11 studies)	NS *	-
	Pre-dialysis (CKD stages 1-4) (n=311, 6 studies)	-	WMD -0.73 g/24 h (95% CI -0.95 to -0.52)**

** Significant heterogeneity in this analysis.*

10.1.5 From evidence to recommendations

The evidence considered shows that people prescribed statins for secondary prevention of cardiovascular events may accrue additional benefits from statin therapy.

The GDG noted that the data assessing the impact of statins on proteinuria were derived largely from studies involving patients with (or at high risk of) overt cardiovascular disease. The Strippoli meta-analysis showed that in people with CKD not on dialysis statins significantly reduced all-cause mortality, cardiovascular mortality, non-fatal cardiovascular events and 24-hour urinary proteinuria. However there was significant heterogeneity in the 24-hour urinary protein analysis. There was no significant benefit from statin therapy on change in GFR but that analysis was also subject to significant heterogeneity.

There was therefore insufficient evidence to support a role for statin therapy on either reduction of proteinuria or progression of CKD. This is noted in a footnote to the statins recommendations in the following section.

10.2 Lipid lowering in people with CKD [2014]

The evidence for this section is now reviewed in the partial update of NICE clinical guideline 67 for lipid modification (CG67: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease). The introductory paragraph in section 10.1 has further information. Evidence reviewed in the previous guideline can be found in the deleted content appendix (Appendix P). The recommendation below was developed as a reference to the Lipid modification guideline (CG181).

10.2.1 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng203

10.3 Oral antiplatelets and anticoagulants [2014]

10.3.1 Introduction

Treatment with anti-platelet and anticoagulant therapy is used to prevent cardiovascular and cerebrovascular events. People with CKD are at higher risk for major events following coronary revascularisation and CKD is associated with increased rates of cardiovascular disease and may increase the risk of stroke. CKD and atrial fibrillation (AF) frequently coexist. Observational studies show that AF is three times as frequent in patients with stage 3 CKD compared to those without and that CKD is an independent predictor of stroke.[378] However, impaired kidney function is also associated with a bleeding risk that increases with severity of CKD. Treatment with warfarin in people with CKD has also been implicated in progression of CKD. Conversely, impairment of kidney function is reported to be associated with poorer response to antiplatelet therapy.

The values and preferences of people with CKD in terms of the risk:benefit ratio of antiplatelet and anticoagulation therapy are not well-understood but it is unlikely that many people would accept the risk for major bleeding without evidence of clear benefit. Extrapolation of findings from trials in people without CKD may not be indicated and in the last decade the antiplatelet and anticoagulation armamentarium has considerably widened.

The purpose of this question is therefore to consider the clinical and cost effectiveness of oral antiplatelet and anticoagulant therapy in people with CKD.

10.3.2 Review question: For people with CKD, what is the clinical and cost effectiveness of oral antiplatelet and anticoagulant therapy in reducing cardiovascular disease?

For full details see review protocol in Appendix C.

Table 102: PICO characteristics of oral antiplatelet and anticoagulant therapy review question

Population	Adults (aged 18 and over) with CKD **Subgroups:** • Older people (≥75 years) • People with cardiovascular disease
Intervention/s	**Antiplatelet agents** • Aspirin • Ticagrelor • Clopidogrel • Prasugrel **Oral anticoagulants** • Dabigatran • Apixaban • Rivaroxaban • Warfarin
Comparison/s	• Placebo • All compared to each other
Outcomes	**Critical:** • Cardiovascular/Cerebrovascular events • Major bleeding (as reported by the studies) • Mortality (all-cause and cardiovascular) **Important:** • Progression of CKD (measured by change in eGFR and occurrence of end stage kidney disease (ESRD or ESKD as reported by the study)) • Minor bleeding (as reported by the studies) • Hospitalisation • Health related quality of life
Study design	RCTs only
Analysis	See review protocol in Appendix C for details.

10.3.3 Clinical evidence

We searched for randomised trials on the clinical and cost effectiveness of oral antiplatelet and anticoagulant therapy in reducing cardiovascular disease in people with CKD.

No direct evidence was found. There were no trials designed and powered to look at these drugs specifically in people with CKD. Twelve publications were included in the review which had subgroup analyses of people with CKD within larger studies in indirect populations.[8,11,35,80,99,109,146,149,177,178,190,252] The majority of these were post-hoc analyses, however, 4 were pre-specified.[8,109,149]

The indirect populations that these subgroup analyses were taken from include people with; deep vein thrombosis or pulmonary embolism, elective or planned PCI, cardiovascular disease, atrial fibrillation, ST-segment elevation myocardial infarction (STEMI), non-STEMI and hypertension.

The characteristics of these studies are summarised in table Table 103. Evidence is summarised in the clinical GRADE evidence profile below (**Error! Reference source not found.** to Table 114). See also

the study selection flow chart in Appendix D, forest plots in Appendix I, clinical evidence tables in Appendix G and exclusion list in Appendix J.

Table 103: Summary of studies included in the review

Study	Intervention/comparison	Population	Outcomes	Comments
Agnelli 2013 (AMPLIFY-EXT)[8]	• Apixaban 2.5mg • Apixaban 5mg • Placebo	• Symptomatic deep-vein thrombosis or pulmonary embolism. • 6-12 months prior treatment with standard anticoagulant or apixaban, enoxaparin and warfarin. • Mean age not stated.	• All-cause mortality • Cardiovascular/ cerebrovascular events • Major bleeding.	• Renal impairment (mild andsevere or moderate renal impairment) subgroup analysis (**pre-specified**).
Alexander 2011[11]	• Apixaban 5mg twice daily. • Placebo.	• Patients with recent ACS and ≥2 risk factors for recurrent ischaemic events. • Median 67 (IQR 58-74) years.	• Cardiovascular death, myocardial infarction or ischaemic stroke • TIMI major bleeding.	• A priori subgroups: mild or moderate/ severe renal impairment (not defined). • Most participants had ACE inhibitor,beta-blocker and statin.
Best 2008 (CREDO)[35]	• Clopidogrel 300mg 3-24 hours before PCI, and 75mg daily for 1 year after procedure • Placebo	• Elective PCI planned or considered likely. • Creatinine clearance <60ml/min. • Mean age 73.5 (8.1) years.	• Composite of death, myocardial infarction or stroke • Major bleeding • Minor bleeding. *NB only relative risks reported and confidence intervals reported.	• Mild to moderately reduced renal function post-hoc analysis (unclear whether pre-specified). • Aspirin 325mg/day for 1st 28 days then 81-325mg daily for 1 year given to all participants.
Dasgupta 2009 (CHARISMA)[80]	• Clopidogrel 75mg/day • Placebo	• Clinically evidenced cardiovascular disease (CVD) or multiple atherothrombotic risk factors for CVD. • Mean age 63 years (SD not specified).	• All-cause mortality • Cardiovascular mortality • Cardiovascular/ cerebrovascular events • Hospitalisation • Major bleeding	• Diabetic nephropathy (diabetes and microalbuminuria, albumin ≥30µg/ml) post-hoc subgroup analysis (not pre-specified).

Study	Intervention/comparison	Population	Outcomes	Comments
			• Minor bleeding.	• Aspirin 75-162mg/day given to all participants.
Eikelboom 2012 (AVERROES)[99]	• Apixaban 5mg twice daily. • Aspirin 81-324mg daily.	• Permanent or paroxysmal atrial fibrillation and at least 1 additional risk factor for stroke.	• All-cause mortality • Cardiovascular/ cerebrovascular events • Major bleeding.	• Stage 3 CKD (eGFR 30-59 ml/min/1.73m^2) post-hoc subgroup analysis.
Fox 2011 (ROCKET-AF) [109]	• Rivaroxaban 15mg/day. • Warfarin. Dose adjusted to target INR 2.0 to 3.0. Median time in therapeutic range for warfarin was 57.7 (42.2-69.9 25th/75th percentiles)	• ECG documented non-valvular atrial fibrillation and at moderate to high risk of stroke. • Median age 79.	• Cardiovascular/ cerebrovascular events • Major bleeding.	• eGFR 30-49ml/min/1.73 m^2 post-hoc subgroup analysis (**pre-specified**).
Hijazi 2014 (RE-LY)[146]	• Diabigatran 110mg twice daily. • Dabigatran 150mg twice daily. • Warfarin. Dose adjusted to target INR 2.0 to 3.0.	• People with atrial fibrillation and at least one additional risk factor for stroke. • Mean age 71.	• All-cause mortality • Cardiovascular/ cerebrovascular events • Major bleeding.	• **Pre-specified** subgroup analysis with renal impairment eGFR ≥80, 50-80 or 30-50ml/min/1.73 m^2.
Hohnloser 2012 (ARISTOTLE)[149]	• Apixaban 5mg twice daily or 2.5mg twice daily (results combined) • Warfarin 2mg tables adjusted to target INR of 2.0 to 3.0.	• Atrial fibrillation or flutter at enrolment. • Mean age not stated.	• All-cause mortality • Cardiovascular/ cerebrovascular events • Major bleeding.	• **Pre-specified** subgroup analysis with eGFR ≤50 ml/min/1.73m^2.
James 2010 (PLATO)[177] *Trial design reported in James 2009[176]	• Ticagrelor. Loading dose 180mg then 90mg twice daily. (n=1619) • Clopidogrel. If no clopidogrel in last 5 days: 300mg loading dose then 75mg daily; if previousclopidogrel: 75mg daily.	• Hospitalised for potential ST-segment elevation or non-ST-segment elevationmyocardial infarction; onset in previous 24 hours. • Median age 74, IQR 68 to 79.	• All-cause mortality • Cardiovascular/ cerebrovascular events Major bleeding.	• Post-hoc subgroup analysis of eGFR < 60 ml/min/1.73m^2 defined by MDRD (unclear if pre-specified). • All participants were allowed aspirin 75-

Study	Intervention/comparison	Population	Outcomes	Comments
				100mg daily, but up to 325mg was allowed for 6 months after stent placement.
Jardine 2010 (HOT)[178]	• Aspirin 75mg/day. • Placebo.	• People with hypertension (diastolic blood pressure 100-115mmHg). • Age 50-80 years (mean 61.3).	• All-cause mortality • Cardiovascular mortality • Cardiovascular/ cerebrovascular events • Major bleeding • Minor bleeding.	• eGFR< 60 ml/min/1.73 m^2 post hoc subgroup analysis (not pre-specified). • All participants had antihypertensive treatment.
Keltai 2007 (CURE)[190]	• Clopidogrel. Loading dose 300mg then 75mg daily for 3-12 months. (n=2044) • Placebo.	• Non-ST-segment elevationmyocardial infarction; hospitalised within 24 hours of symptoms. • Mean age 69.6 (9.9) years.	• All-cause mortality • Cardiovascular mortality • Major bleeding • Minor bleeding. * NB only relative risks reported and confidence intervals reported.	• Post-hoc subgroup analysis of eGFR <64ml/min/1.73 m^2 (unclear if pre-specified). • All participants received aspirin 75-325mg daily.
Mega 2012[252]	• Rivaroxaban 2.5mg twice daily • Placebo	• Patients with ACS and creatinine clearance < 50ml/min. • Mean age 62 (9) years.	• Cardiovascular death, myocardial infarction or stroke.	• A priori subgroups: eGFR < 50ml/min/1.73 m^2. • Most patients on aspirin, thienopyridine, beta-blocker and statin.

Data from Best et al. and Keltai.et al. could not be included in the forest plots or GRADE tables as insufficient data was presented, therefore this has been presented in a summary table with the relevant GRADE evidence profile below (see Table 106).

Table 104: Clinical evidence profile: Aspirin (75mg/day) versus placebo

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Aspirin	Placebo	Relative (95% CI)	Absolute	Quality	Importance
All-cause mortality at 3.8 years - eGFR 45-59 (follow-up mean 3.8 years)[178]												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Very serious (b)	None	47/1527 (3.1%)	54/1556 (3.5%)	HR 0.89 (0.6 to 1.32)	4 fewer per 1000 (from 14 fewer to 11 more)	VERY LOW	CRITICAL
All-cause mortality - eGFR <45 (follow-up mean 3.8 years)[178]												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (b)	None	15/264 (5.7%)	30/272 (11%)	HR 0.51 (0.27 to 0.96)	52 fewer per 1000 (from 4 fewer to 79 fewer)	LOW	CRITICAL
Cardiovascular mortality - eGFR 45-59 (follow-up mean 3.8 years)[178]												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Very serious (b)	None	27/1527 (1.8%)	30/1556 (1.9%)	HR 0.92 (0.54 to 1.57)	2 fewer per 1000 (from 9 fewer to 11 more)	VERY LOW	CRITICAL
Cardiovascular mortality - eGFR <45 (follow-up mean 3.8 years)[178]												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (c)	None	6/264 (2.3%)	17/272 (6.3%)	HR 0.36 (0.14 to 0.93)	40 fewer per 1000 (from 4 fewer to 54 fewer)	LOW	CRITICAL
Cardiovascular/cerebrovascular events - eGFR 45-59 (follow-up mean 3.8 years; assessed with: Major cardiovascular disease)[178]												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (c)	None	65/1527 (4.3%)	78/1556 (5%)	HR 0.85 (0.61 to 1.18)	7 fewer per 1000 (from 19 fewer to 9 more)	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Aspirin**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Cardiovascular/cerebrovascular events - eGFR <45 (follow-up mean 3.8 years; assessed with: Major cardiovascular disease)[178]												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision	None	11/264 (4.2%)	32/272 (11.8%)	HR 0.85 (0.73 to 0.99)	17 fewer per 1000 (from 1 fewer to 30 fewer)	MODERATE	CRITICAL
Cardiovascular/cerebrovascular events - eGFR 45-59 (follow-up mean 3.8 years; assessed with: Myocardial infarction)[178]												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (c)	None	27/1527 (1.8%)	43/1556 (2.8%)	HR 0.64 (0.39 to 1.05)	10 fewer per 1000 (from 17 fewer to 1 more)	LOW	CRITICAL
Cardiovascular/cerebrovascular events - eGFR <45 (follow-up mean 3.8 years; assessed with: Myocardial infarction)[178]												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (c)	None	5/264 (1.9%)	16/272 (5.9%)	HR 0.31 (0.11 to 0.87)	40 fewer per 1000 (from 7 fewer to 52 fewer)	LOW	CRITICAL
Cardiovascular/cerebrovascular events - eGFR 45-59 (follow-up mean 3.8 years; assessed with: Stroke)[178]												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Very serious (b)	None	36/1527 (2.4%)	36/1556 (2.3%)	HR 1.02 (0.64 to 1.63)	0 more per 1000 (from 8 fewer to 14 more)	VERY LOW	CRITICAL
Cardiovascular/cerebrovascular events - eGFR <45 (follow-up mean 3.8 years; assessed with: Stroke)[178]												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (c)	None	3/264 (1.1%)	14/272 (5.1%)	HR 0.31 (0.11 to 0.87)	35 fewer per 1000 (from 7 fewer to 46 fewer)	LOW	CRITICAL
Major bleeding - eGFR 45-59 (follow-up mean 3.8 years; assessed with: Fatal, life-threatening, disabling or requiring hospital admission)[178]												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Aspirin**	**Placebo**	**Relative (95% CI)**	**Absolute**		
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (c)	None	NR	NR	HR 1.07 (0.74 to 1.55)	(e)	LOW	CRITICAL
Major bleeding - eGFR <45 (follow-up mean 3.8 years; assessed with: Fatal, life-threatening, disabling or requiring hospital admission)[178]												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision	None	NR	NR	HR 1.61 (1.21 to 2.14)	(e)	MODERATE	CRITICAL
Minor bleeding - eGFR 45-59 (follow-up mean 3.8 years)[178]												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision	None	NR	NR	HR 2.25 (1.22 to 4.15)	(e)	MODERATE	IMPORTANT
Minor bleeding - eGFR <45 (follow-up mean 3.8 years)[178]												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Very serious (c)	None	NR	NR	HR 2.7 (0.5 to 14.58)	(e)	VERY LOW	IMPORTANT

a) Post-hoc analysis of subgroups with CKD. Not pre-specified.
b) The confidence interval crosses both MIDs making the effect size very uncertain.
c) The confidence interval crosses one MID making the effect size uncertain.
e) Absolute event rate could not be calculated as number of events was not reported.
NR = not reported.
NB All GFR measurements are in ml/min/1.73 m^2.

Table 105: Clinical evidence profile: Clopidogrel (75mg daily) versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Clopidogrel**	**Placebo**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up median 28 months)[190]												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Clopidogrel**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (a)	No serious imprecision	None	73/1006 (7.3%)	45/1003 (4.5%)	HR 1.6 (1.1 to 2.33)	26 more per 1000 (from 4 more to 57 more)	LOW	CRITICAL
Cardiovascular mortality (follow-up median 28 months)[190]												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	No serious imprecision	None	51/1006 (5.1%)	31/1003 (3.1%)	HR 1.7 (1.1 to 2.63)	21 more per 1000 (from 3 more to 48 more)	LOW	CRITICAL
Cardiovascular/cerebrovascular events - Non-fatal stroke (follow-up median 28 months)[190]												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	Very serious (c)	None	20/1006 (2%)	22/1003 (2.2%)	HR 0.9 (0.5 to 1.62)	2 fewer per 1000 (from 11 fewer to 13 more)	VERY LOW	CRITICAL
Cardiovascular/cerebrovascular events - Non-fatal myocardial infarction (follow-up median 28 months)[190]												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	Very serious (c)	None	22/1006 (2.2%)	29/1003 (2.9%)	HR 0.8 (0.4 to 1.6)	6 fewer per 1000 (from 17 fewer to 17 more)	VERY LOW	CRITICAL
Hospitalisation (follow-up median 28 months)[190]												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	Serious (d)	None	97/1006 (9.6%)	104/1003 (10.4%)	HR 0.9 (0.7 to 1.16)	10 fewer per 1000 (from 30 fewer to 16 more)	VERY LOW	IMPORTANT
Major bleeding (follow-up median 28 months; assessed with: GUSTO severe bleeding)[190]												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	Serious (c)	None	26/1006 (2.6%)	15/1003 (1.5%)	HR 1.8 (0.9 to 3.6)	12 more per 1000 (from 1 fewer to 38 more)	VERY LOW	CRITICAL
Minor bleeding (follow-up median 28 months; assessed with: GUSTO moderate bleeding)[190]												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Clopidogrel	Placebo	Relative (95% CI)	Absolute		
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	Very serious (c)	None	28/1006 (2.8%)	24/1003 (2.4%)	HR 1.2 (0.7 to 2.06)	5 more per 1000 (from 7 fewer to 25 more)	VERY LOW	IMPORTANT

(a) Post-hoc subgroup analysis of people with diabetic nephropathy, not pre-specified.
(b) From an overall population with clinically evidenced cardiovascular disease or multiple atherothrombotic risk factors for cardiovascular disease.
(c) Confidence interval crosses both MIDs making the effect size very uncertain.
(d) Confidence interval crosses one MID therefore the effect size is uncertain.

Table 106: Clinical evidence profile: Clopidogrel (75mg) versus placebo – data unable to combine in meta-analysis

Study	Follow-up	Outcome measure	Effect size (95% confidence interval)
Best 2008[35]	1 year	Composite of mortality, myocardial infarction or stroke	HR 1.41 (0.81, 2.45)
		Major bleeding (modified TIMI criteria)	RR 1.124 (0.511, 2.476)
		Minor bleeding (modified TIMI criteria)	RR 0.546 (0.250, 1.189)
Keltai 2007[190]	1 year	All-cause mortality	RR 0.95 (0.78, 1.16)
		Cardiovascular mortality	RR 0.95 (0.77, 1.17)
		Life threatening bleeding	RR 0.89 (0.60, 1.31)
		Major bleeding	1.37 (0.89, 2.12)
		Minor bleeding	1.50 (1.21, 1.86)

Insufficient data provided to calculate standard deviations, therefore data could not be included in the meta-analysis.

Table 107: Clinical evidence profile: Ticagrelor (90mg twice daily) versus clopidogrel (75mg daily)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ticagrelor	Clopidogrel	Relative (95% CI)	Absolute		

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other conside rations**	**Ticagrelor**	**Clopidogrel**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up mean 1 years)[177]												
1	Randomise d trials	Very serious (a, b)	No serious inconsistency	Serious (c)	Serious (d)	None	109/1619 (6.7%)	173/1618 (10.7%)	HR 0.64 (0.5 to 0.82)	37 fewer per 1000 (from 18 fewer to 52 fewer)	VERY LOW	CRITICAL
Cardiovascular mortality, myocardial infarction or stroke (follow-up mean 1 years)[177]												
1	Randomise d trials	Very serious (a, b)	No serious inconsistency	Serious (c)	Serious (d)	None	189/1619 (11.7%)	268/1618 (16.6%)	HR 0.71 (0.59 to 0.85)	45 fewer per 1000 (from 23 fewer to 64 fewer)	VERY LOW	CRITICAL
Major bleeding (follow-up mean 1 years; assessed with: PLATO defined)[177]												
1	Randomise d trials	Very serious (a,b)	No serious inconsistency	Serious (c)	Serious (d)	None	161/1619 (9.9%)	158/1619 (9.8%)	HR 1.08 (0.87 to 1.34)	7 more per 1000 (from 12 fewer to 31 more)	VERY LOW	CRITICAL

(a) Post-hoc analysis of people with creatine clearance <60ml/min. Unclear if pre-specified.
(b) Total n per treatment group for subgroup not stated, assumed 50/50 of total n by NCGC.
(c) From overall population of people hospitalised for ST-segment elevation acute coronary syndrome or non ST-segment elevation acute coronary syndrome.
(d) Confidence interval crosses one MID making the effect size uncertain.

Table 108: Clinical evidence profile: Apixaban (2.5mg) versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Apixaban 2.5mg**	**Placebo**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (or symptomatic recurrent venous thromboembolism). (follow-up mean 1 years)[8]												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Apixaban 2.5mg**	**Placebo**	**Relative (95% CI)**	**Absolute**		
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious (a)	No serious imprecision	None	12/222 (5.4%)	33/240 (13.8%)	RR 0.39 (0.2 to 0.73)	84 fewer per 1000 (from 37 fewer to 110 fewer)	MODERATE	CRITICAL
Cardiovascular/cerebrovascular events (follow-up mean 1 years; assessed with: VTE or death due to VTE)[8]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious (a)	No serious imprecision	None	7/222 (3.2%)	27/240 (11.3%)	RR 0.28 (0.12 to 0.63)	81 fewer per 1000 (from 42 fewer to 99 fewer)	MODERATE	CRITICAL
Major bleeding or clinically relevant non-major bleeding (follow-up mean 1 years)[8]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious (a)	Serious (b)	None	11/222 (5%)	5/239 (2.1%)	RR 2.31 (0.82 to 6.5)	27 more per 1000 (from 4 fewer to 115 more)	LOW	CRITICAL

(a) From an overall population with symptomatic deep vein thrombosis or pulmonary embolism.
(b) The confidence interval crosses one MID making the effect size uncertain.

Table 109: Clinical evidence profile: Apixaban (5mg) versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Apixaban 5mg**	**Placebo**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (or symptomatic recurrent venous thromboembolism). (follow-up mean 1 years)[8]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious (a)	No serious imprecision	None	8/212 (3.8%)	33/240 (13.8%)	RR 0.28 (0.13 to 0.58)	99 fewer per 1000 (from 58 fewer to 120 fewer)	MODERATE	CRITICAL
Cardiovascular/cerebrovascular events (follow-up mean 1 years; assessed with: VTE or death due to VTE)[8]												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Apixaban 5mg**	**Placebo**	**Relative (95% CI)**	**Absolute**		
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious (a)	No serious imprecision	None	5/212 (2.4%)	28/240 (11.7%)	RR 0.22 (0.09 to 0.54)	91 fewer per 1000 (from 54 fewer to 106 fewer)	MODERATE	CRITICAL
Major bleeding or clinically relevant non-major bleeding (follow-up mean 1 years)[8]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious (a)	Serious (b)	None	13/211 (6.2%)	5/239 (2.1%)	RR 2.9 (1.06 to 7.95)	40 more per 1000 (from 1 more to 145 more)	LOW	CRITICAL

(a) From an overall population with symptomatic deep vein thrombosis or pulmonary embolism.
(b) The confidence interval crosses one MID making the effect size uncertain.

Table 110: Clinical evidence profile: Apixaban 5mg (twice daily) versus placebo for CKD

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Apixaban 5mg**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Cardiovascular mortality, MI, ischaemic stroke - Mild renal impairment (follow-up 241 days)[11]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious (a)	Serious (b)	None	NR	NR	RR 1.04 (0.79 to 1.37)	(d)	LOW	CRITICAL
Cardiovascular mortality, MI, ischaemic stroke - Moderate or severe renal impairment (follow-up 241 days)[11]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious (a)	Very serious (c)	None	NR	NR	RR 0.94 (0.69 to 1.29)	(d)	VERY LOW	CRITICAL
TIMI major bleeding - Mild renal impairment (follow-up 241 days)[11]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious (a)	Very serious (c)	None	NR	NR	RR 1.3 (0.57 to 2.96)	(d)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Apixaban 5mg	Placebo	Relative (95% CI)	Absolute		
TIMI major bleeding - Moderate or severe renal impairment (follow-up 241 days)[11]												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious (a)	No serious imprecision	None	NR	NR	RR 4.94 (1.42 to 17.22)	(d)	MODERATE	CRITICAL

(a) ACS patients; renal impairment subgroup (pre-specified)
(b) The confidence interval crosses one MID making the effect size uncertain.
(c) The confidence interval crosses both MIDs making the effect size very uncertain.
(d) Absolute event rate could not be calculated as numbers of events per treatment arm were not provided.

Table 111: Clinical evidence profile: Apixaban (2.5 or 5mg twice daily) versus warfarin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Apixaban 2.5 or 5mg	Warfarin	Relative (95% CI)	Absolute		
All-cause mortality (follow-up median 1.8 years)[149]												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	Serious (c)	None	152/1422 (10.7%)	191/1422 (13.4%)	HR 0.78 (0.63 to 0.97)	28 fewer per 1000 (from 4 fewer to 47 fewer)	VERY LOW	CRITICAL
Cardiovascular/cerebrovascular events (follow-up median 1.8 years; assessed with: Stroke or systemic embolism)[149]												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	Serious (c)	None	33/1422 (2.3%)	53/1422 (3.7%)	HR 0.61 (0.39 to 0.95)	14 fewer per 1000 (from 2 fewer to 23 fewer)	VERY LOW	CRITICAL
Major bleeding - Median follow-up 1.8 years (follow-up median 1.8 years)[149]												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Apixaban 2.5 or 5mg**	**Warfarin**	**Relative (95% CI)**	**Absolute**		
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	No serious imprecision	None	73/1422 (5.1%)	143/1422 (10.1%)	HR 0.48 (0.37 to 0.62)	51 fewer per 1000 (from 37 fewer to 62 fewer)	LOW	CRITICAL

(a) Baseline details not provided for treatment groups in subgroup analysis, including n per treatment group.
(b) From an overall population with atrial fibrillation or flutter at enrolment.
(c) The confidence interval crosses one MID making the effect size uncertain.

Table 112: Clinical evidence profile: Apixaban (5mg twice daily) versus aspirin (81-324mg daily)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Apixaban 5mg twice a day**	**Aspirin**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up mean 1.1 years)[99]												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	Serious (c)	None	59/857 (6.9%)	66/840 (7.9%)	HR 0.86 (0.61 to 1.21)	11 fewer per 1000 (from 30 fewer to 16 more)	VERY LOW	CRITICAL
Cardiovascular/cerebrovascular events (follow-up mean 1.1 years; assessed with: Stroke or systemic embolism)[99]												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	No serious imprecision	None	17/857 (2%)	51/840 (6.1%)	HR 0.32 (0.18 to 0.57)	41 fewer per 1000 (from 26 fewer to 50 fewer)	LOW	CRITICAL
Major bleeding (follow-up mean 1.1 years; assessed with: Major haemorrhage)[99]												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Apixaban 5mg twice a day**	**Aspirin**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	Very serious (d)	None	24/857 (2.8%)	20/840 (2.4%)	HR 1.2 (0.65 to 2.22)	5 more per 1000 (from 8 fewer to 28 more)	VERY LOW	CRITICAL

(a) Post hoc analysis of stage 3 CKD. Not pre-specified.
(b) From an overall population with permanent or paroxysmal atrial fibrillation and at least one additional risk factor for stroke.
(c) The confidence interval crosses one MID making the effect size uncertain.
(d) The confidence interval crosses both MIDs making the effect size very uncertain.

Table 113: Clinical evidence profile: Rivaroxaban (15mg) versus warfarin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rivaroxaban	Warfarin	Relative (95% CI)	Absolute		
Cardiovascular/cerebrovascular events (follow-up median 1.9 years; assessed with: Haemorrhagic stroke)[109]												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	Serious (c)	None	-	-	HR 0.56 (0.21 to 1.49)	-	VERY LOW	CRITICAL
Cardiovascula/cerebrovascular r events (follow-up median 1.9 years; assessed with: Ischaemic stroke)[109]												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	Serious (c)	None	-	-	HR 1.11 (0.71 to 1.74)	-	VERY LOW	CRITICAL
Cardiovascular/cerebrovascular events (follow-up median 1.9 years; assessed with: Undetermined stroke)[109]												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	Very serious (d)	None	-	-	HR 0.51 (0.05 to 5.2)	-	VERY LOW	CRITICAL
Major bleeding (follow-up median 1.9 years; assessed with: Intracranial haemorrhage)[109]												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	Serious (c)	None	-	-	HR 0.81 (0.41 to 1.6)	-	VERY LOW	CRITICAL
Major bleeding (follow-up median 1.9 years; assessed with: Haemoglobin drop, transfusion, clinical organ and fatal bleeding)[109]												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	No serious imprecision	None	-	-	HR 0.95 (0.72 to 1.25)	-	LOW	CRITICAL

(a) Number of events not provided for calculation of absolute event rate.
(b) From an overall population of people with ECG documented non-valvular atrial fibrillation and at moderate to high risk of stroke.
(c) The confidence interval crosses one MID making the effect size uncertain.
(d) The confidence interval crosses both MIDs making the effect size very uncertain.

Table 114: Clinical evidence profile: Rivaroxaban versus placebo for CKD

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Rivaroxaban	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Cardiovascular mortality, MI or stroke (follow-up 13.1 months)[252]												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	Serious (c)	None	80/686 (11.7%)	49/368 (13.3%)	HR 0.88 (0.62 to 1.25)	15 fewer per 1000 (from 48 fewer to 30 more)	VERY LOW	CRITICAL

(a) Randomisation and allocation concealment unclear
(b) ACS patients; renal impairment subgroup (pre-specified)
(c) The confidence interval crosses one MID making the effect size uncertain.

Table 115: Clinical evidence profile: Dabigatran 110mg twice daily versus warfarin

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Dabigatran 110mg BID	Warfarin	Relative (95% CI)	Absolute	Quality	Importance
Cardiovascular events - eGFR >80ml/min/1.73m² (follow-up median 2 years; assessed with: Stroke or systemic embolism)												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	Very serious (c)	None	28/1284 (2.2%)	32/1300 (2.5%)	HR 0.87 (0.53 to 1.43)	3 fewer per 1000 (from 11 fewer to 10 more)	VERY LOW	CRITICAL
Cardiovascular events - eGFR 50-80ml/min/1.73m² (follow-up median 2 years; assessed with: Stroke or systemic embolism)												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	No serious imprecision	None	116/3547 (3.3%)	124/3574 (3.5%)	HR 0.94 (0.73 to 1.21)	2 fewer per 1000 (from 9 fewer to 7 more)	LOW	CRITICAL
Cardiovascular events – eGFR 30-50ml/min/1.73m² (follow-up median 2 years)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Dabigatran 110mg BID	Warfarin	Relative (95% CI)	Absolute	Quality	Importance
1	Rand omised trials	Serious (a)	No serious inconsistency	Serious (b)	Serious (d)	None	37/1126 (3.3%)	45/1091 (4.1%)	HR 0.78 (0.51 to 1.19)	9 fewer per 1000 (from 20 fewer to 8 more)	VERY LOW	CRITICAL
All cause mortality eGFR >80ml/min/1.73m² (follow-up median 2 years)												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	Serious (d)	None	71/1284 (5.5%)	86/1300 (6.6%)	HR 0.82 (0.6 to 1.12)	12 fewer per 1000 (from 26 fewer to 8 more)	VERY LOW	CRITICAL
All cause mortality – eGFR 50-80ml/min/1.73m² (follow-up median 2 years)												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	No serious imprecision	None	233/3547 (6.6%)	229/3576 (6.4%)	HR 0.88 (0.74 to 1.05)	7 fewer per 1000 (from 16 fewer to 3 more)	LOW	CRITICAL
All cause mortality – eGFR 30-50ml/min/1.73m² (follow-up median 2 years)												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	No serious imprecision	None	136/1126 (12.1%)	133/1091 (12.2%)	HR 0.97 (0.77 to 1.22)	3 fewer per 1000 (from 27 fewer to 25 more)	LOW	CRITICAL
Major bleeding - eGFR >80ml/min/1.73m² (follow-up median 2 years)												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	No serious imprecision	None	32/1284 (2.5%)	77/1300 (5.9%)	HR 0.41 (0.27 to 0.62)	35 fewer per 1000 (from 22 fewer to 43 fewer)	LOW	CRITICAL
Major bleeding – eGFR 50-80ml/min/1.73m² (follow-up median 2 years)												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	Serious (d)	None	196/3547 (5.5%)	238/3574 (6.7%)	HR 0.82 (0.68 to 0.99)	12 fewer per 1000 (from 1 fewer to 21	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Dabigatran 110mg BID	Warfarin	Relative (95% CI)	Absolute	Quality	Importance
										fewer)		
Major bleeding - eGFR 30-50ml/min/1.73m² (follow-up median 2 years)												
1	Randomised trials	Serious (a)	no serious inconsistency	Serious (b)	Very serious (c)	None	111/1126 (9.9%)	135/1157 (11.7%)	HR 1.02 (0.78 to 1.33)	2 more per 1000 (from 24 fewer to 35 more)	VERY LOW	CRITICAL

(a) Baseline details not provided for treatment groups in subgroup analysis, including n per treatment group.
(b) From an overall population with atrial fibrillation and at least one additional risk factor for stroke.
(c) The confidence interval crosses the MID in both directions making the effect size very uncertain.
(d) The confidence interval crosses one MID making the effect size uncertain.

Table 116: Clinical evidence profile: Dabigatran 150mg twice daily versus warfarin

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Dabigatran 150mg BID	Warfarin	Relative (95% CI)	Absolute	Quality	Importance
Cardiovascular/cerebrovascular events - eGFR >80ml/min/1.73m² (follow-up median 2 years; assessed with: Stroke or systemic embolism) [146]												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	Serious (c)	None	21/1296 (1.6%)	32/1300 (2.5%)	HR 0.65 (0.37 to 1.14)	9 fewer per 1000 (from 15 fewer to 3 more)	VERY LOW	CRITICAL
Cardiovascular/cerebrovascular events – eGFR 50-80ml/min/1.73m² (follow-up median 2 years; assessed with: Stroke or systemic embolism) [146]												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	Serious (c)	None	86/3576 (2.4%)	124/3574 (3.5%)	HR 0.69 (0.52 to 0.92)	11 fewer per 1000 (from 3 fewer to 17 fewer)	VERY LOW	CRITICAL
Cardiovascular/cerebrovascular events - eGFR 30-50ml/min/1.73m² (follow-up median 2 years; assessed with: Stroke or systemic embolism)[146]												
1	Randomised	Serious	No serious	Serious (b)	Serious (c)	None	27/1157	45/1091	HR 0.55	18 fewer	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Dabigatran 150mg BID	Warfarin	Relative (95% CI)	Absolute	Quality	Importance
	trials	(a)	inconsistency				(2.3%)	(4.1%)	(0.34 to 0.89)	per 1000 (from 4 fewer to 27 fewer)		
All cause mortality - eGFR >80ml/min/1.73m² (follow-up median 2 years)[146]												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	Serious (c)	None	61/1296 (4.7%)	229/3576 (6.4%)	HR 0.7 (0.5 to 0.98)	19 fewer per 1000 (from 1 fewer to 31 fewer)	VERY LOW	CRITICAL
All cause mortality - eGFR 50-80ml/min/1.73m² (follow-up median 2 years)[146]												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	Serious (c)	None	229/3576 (6.4%)	265/3574 (7.4%)	HR 0.85 (0.71 to 1.02)	11 fewer per 1000 (from 21 fewer to 1 more)	VERY LOW	CRITICAL
All cause mortality - eGFR 30-50ml/min/1.73m² (follow-up median 2 years)[146]												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	Serious (c)	None	148/1157 (12.8%)	133/1091 (12.2%)	HR 1.03 (0.82 to 1.29)	3 more per 1000 (from 21 fewer to 32 more)	VERY LOW	CRITICAL
Major bleeding - eGFR >80ml/min/1.73m² (follow-up median 2 years)[146]												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	Serious (c)	None	46/1296 (3.5%)	77/1300 (5.9%)	HR 0.59 (0.41 to 0.85)	24 fewer per 1000 (from 9 fewer to 35 fewer)	VERY LOW	CRITICAL
Major bleeding - eGFR 50-80ml/min/1.73m² (follow-up median 2 years)[146]												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	No serious imprecision	None	217/3576 (6.1%)	238/3574 (6.7%)	HR 0.9 (0.75 to 1.08)	6 fewer per 1000 (from 16 fewer to	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Dabigatran 150mg BID**	**Warfarin**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
										5 more)		
Major bleeding - eGFR 30-50ml/min /1.73m^2 (follow-up median 2 years)[146]												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	Serious (c)	None	135/1157 (11.7%)	105/1091 (9.6%)	HR 1.22 (0.95 to 1.57)	20 more per 1000 (from 5 fewer to 51 more)	VERY LOW	CRITICAL

(a) Baseline details not provided for treatment groups in subgroup analysis, including n per treatment group.
(b) From an overall population with atrial fibrillation and at least one additional risk factor for stroke.
(c) The confidence interval crosses one MID making the effect size uncertain.

10.3.4 Economic evidence

Published literature

No relevant economic evaluations comparing antiplatelets and anticoagulants were identified.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs were derived from the BNF 65, Electronic National Drug Tariff 2013 and the Apixaban NICE Technology Appraisal (TA275)[286]. These are provided below in Table 117 to aid consideration of cost effectiveness. The GDG considered that additional monitoring costs were applicable to warfarin only. New Oral Anticoagulants require annual measurement of kidney function which will already be administered to patients with CKD.

Table 117 Annual Costs of Antiplatelet and Anticoagulant Treatment

Drug Name	Dose(mg)		Unit cost per pack	Tablets per pack	Cost per day	Annual Drug Cost	Annual Monitoring Costs (TA 275)	Total Annual Cost
	Dose (mg)	Frequency per Day						
Antiplatelets (in order of cost)								
Aspirin	75	1	£0.82	28	£0.03	£11		£11
Clopidogrel	75	1	£1.83	28	£0.07	£24		£24
Prasugrel	10	1	£47.56	28	£1.70	£620		£620
Ticagrelor	90	2	£54.60	56	£1.95	£641		£641
Oral anticoagulants (in order of cost)								
Warfarin	5	1	£0.99	28	£0.04	£13	£248	£261
Warfarin	1	2	£0.90	28	£0.06	£23	£248	£271
Rivaroxaban	15	1	£58.80	28	£2.10	£767		£767
Dabigatran	110	2	£65.90	60	£2.20	£802		£802
Apixaban	2.5	2	£65.90	60	£2.20	£802		£802

Note: The costs per day reported here were correct at the time recommendations were drafted; prices may have changed slightly by the time of publication.

If there is no difference in the clinical benefit provided by antiplatelet and anticoagulants, then the drug type with the lowest acquisition cost can be recommended.

However, if drug types lend to different risks of adverse events, then the GDG should consider whether more expensive drug types can help reduce the occurrence of adverse events (major bleeding, stroke or systemic embolism) and associated downstream health costs.

Original model

An original cost-utility analysis was conducted to compare anticoagulants for people with CKD and non-valvular atrial fibrillation. There was only clear evidence of survival benefit for two comparisons: apixaban compared to warfarin or aspirin. The analysis was therefore based on the results of the eGFR CKD-EPI$_{creat}$<50 ml/min/1.73 m^2 subgroup of the ARISTOTLE trial[149] and the eGFR<50 ml/min/1.73 m^2 subgroup of the AVERROES[99]. Dabigatran was considered using RE-LY trial results[146] but only in a sensitivity analysis because of the lack of evidence of a survival benefit. Rivaroxaban was not included because of the general lack of evidence of effectiveness.

Utility estimates from CG173 were used along withunit costs from Apixaban NICE Technology Appraisal (TA275)[286] and the NICE CKD clinical guideline (CG73)[277]. Full details of this analysis can be found in Appendix M.

Compared with warfarin there was a gain of 0.6 QALYs associated with apixaban (Table 118). The incremental costs of apixaban were augmented by the cost of CKD care in additional months of life and only partially offset by the avoidance of INR monitoring and reduced events. The cost per QALY gained was £9,748 versus warfarin and £14,637 versus aspirin, indicating that apixaban is cost-effective for patients with CKD and non-valvular atrial fibrillation. At a threshold of £20,000 per QALY gained, apixaban was cost-effective compared with warfarin in 95% of simulations and compared with aspirin in 66%.

In the most conservative analysis, apixaban was slightly over the £20,000 per QALY threshold. In all other analyses, apixaban was cost-effective compared with warfarin.

For dabigatran 110mg the reduction in stroke/systemic embolism and very small gain in survival was not cost effective even at a threshold of £30,000 per QALY (it cost £43,700 per QALY gained). For dabigatran 150mg the very small increase in mortality and the increase in major bleeding meant that there were actually QALYs lost compared with warfarin.

The analysis was assessed to have direct applicability and only minor limitations.

Table 118: Base case results – costs and cost-effectiveness (probabilistic)

	Apixaban	Warfarin	Aspirin	Apixaban vs warfarin	Apixiban vs aspirin
Mean health outcomes (undiscounted)					
Major bleeding	0.27	0.48	0.22	-0.21	0.05
Stroke or systemic embolism	0.11	0.15	0.33	-0.04	-0.22
Life years	8.23	7.07	7.49	1.16	0.74
Mean health outcomes (discounted)					
Major bleeding	0.22	0.41	0.19	-0.18	0.04
Stroke or systemic embolism	0.09	0.13	0.28	-0.04	-0.19
Life years	6.83	6.00	6.30	0.84	0.54
QALYs	***4.97***	***4.35***	***4.53***	***0.62***	***0.44***
Mean costs (£, discounted)					
Drugs	5,481	263	161	5,218	5,320
Anticoagulation clinic	-	1,491	-	- 1,491	-
Annual CKD care	22,436	19,695	20,674	2,741	1,761
Major bleeding	336	609	282	- 273	53
Strokeor systemic embolism	363	521	1,124	- 159	- 762
Total	***28,615***	***22,580***	***22,242***	***6,035***	***6,373***
Cost per QALY gained (£, discounted)				***9,748***	***14,637***

10.3.5 Evidence statements

Clinical

Aspirin versus placebo

- Low and moderate quality evidence from a post-hoc subgroup analyses from one RCT in people with hypertension showed that in people with an eGFR <45ml/min/1.73 m^2aspirin reduced the risk of all-cause and cardiovascular mortality, myocardial infarction and stroke compared to placebo. Moderate quality evidence from the same study also showed that risk of major bleeding was greater in this population for those receiving aspirin compared to placebo. This was not true for people with an eGFR ≥45ml/min/1.73 m^2.

Clopidogrel versus placebo

- Low and very low quality evidence from a post-hoc subgroup analysis of people with diabetic nephropathy from one RCT in people with cardiovascular disease or multiple risk factors for cardiovascular disease showed that people treated with 75mg of clopidogrel had an increased risk of all-cause and cardiovascular mortality and major bleeding, compared with those that received placebo. No difference was observed in terms of cardiovascular events, hospitalisation or minor bleeding.

Ticagrelor versus clopidogrel

- Very low quality evidence from a post-hoc subgroup analysis of people with eGFR <60ml/min/1.73 m^2, from an overall RCT of people hospitalised for ST-segment elevation or non-ST segment elevation myocardial infarction, showed that people who were treated with 90mg ticagrelor twice daily had a lower risk of all-cause mortality and cardiovascular mortality, myocardial infarction or stroke, than people treated with 75mg clopidogrel. There was no difference in terms of major bleeding.

Apixaban versus placebo

- Moderate quality evidence showed apixaban at doses of 2.5 or 5mg to be more effective than placebo at reducing the risk of all-cause mortality and venous thromboembolism or death due to venous thromboembolism in people with mild, moderate or severe renal impairment who also had symptomatic deep vein thrombosis or pulmonary embolism. However, in people with recent acute coronary syndrome and at least 2 risk factors for recurrent ischaemic events, low and very low quality evidence suggested there was no difference between placebo and apixaban in people with renal impairment.
- Low quality evidence suggested that there was a greater risk of major bleeding or clinically relevant non-major bleeding at both doses of apixaban compared to placebo in people with symptomatic deep vein thrombosis or pulmonary embolism, and major bleeding in people with acute recent coronary syndrome and moderate or severe renal impairment.

Apixaban versus warfarin

- Apixaban at doses of 2.5 or 5mg twice daily also appears to be more effective than warfarin at reducing the risk of all-cause mortality, stroke and systemic embolism and major bleeding or clinically relevant non-major bleeding in people with an eGFR 15-50 ml/min/1.73 m^2 and atrial fibrillation or flutter. This was suggested by low and very low quality evidence.

Apixaban versus aspirin

- Very low quality evidence suggested that there is no difference between 5mg apixaban twice daily and aspirin (at varying doses) in people with stage 3 CKD and permanent or paroxysmal atrial

fibrillation and at least one additional risk factor for stroke, in reducing the risk of all-cause mortality or major bleeding, however low quality evidence showed that apixaban was more effective than aspirin at reducing the risk of stroke or systemic embolism in this population.

Rivaroxaban versus placebo

- Very low qualit y evidence demonstrated no difference in efficacy between rivaroxaban (2.5mg) and placebo in terms of reducing cardiovascular mortality, myocardial infarction or stroke in people with acute coronary syndrome and eGFR less than 50ml/min/1.73 m^2.

Rivaroxaban versus warfarin

- In people with ECG documented non-valvular atrial fibrillation who were at moderate to high risk or stroke and had an eGFR of 30-49 ml/min/1.73 m^2, very low and low quality evidence suggested that there was no clinically effective difference between 15mg rivaroxaban and warfarin in terms of reducing risk of ischemic stroke or haemoglobin drop, transfusion, clinical organ or fatal bleeding. The evidence suggested that rivaroxaban may be more effective in terms of reducing haemorrhagic stroke, undetermined stroke and intracranial haemorrhage, but there was uncertainty in the magnitude and direction of this effect.

Dabigatran versus warfarin

- In people with atrial fibrillation and at least one additional risk factor for stroke, low and very low quality evidence showed no difference between dabigatran 100 or 150 mg twice daily and warfarin in terms of reducing mortality at eGFR of 30-80 ml/min/1.73 m^2 or occurrence of major bleeding at doses of 110mg and eGFR of 30-50 ml/min/1.73 m^2 or 150mg at eGFR of 50-80 ml/min/1.73 m^2.
- The evidence suggested that dabigatran 150 mg twice daily was more effective than warfarin in reducing mortality in people without renal impairment (eGFR >80 ml/min/1.73 m^2), but at 110 mg twice daily there was more uncertainty about the effect.Low and very low quality evidence showed that dabigatran 110 and 150 mg twice daily was more effective than warafarin at reducing occurrence of major bleeding, and suggested that 150mg twice daily was more effective that warfarin in terms of reducing occurrence stroke and systemic embolism at all levels of renal impairment, but there was uncertainty about the magnitude of these effects. Very low quality evidence suggested that dabigatran 150mg twice daily was less effective than was less effective than warfarin in people with eGFR of 30-50 ml/min/1.73 m^2.

Economic

- An original cost–utility analysis found that apixaban was cost effective compared to warfarin for treating patients with non-valvular atrial fibrillation and eGFR 25-50 ml/min/1.73 m^2 (ICER: £9,700 per QALY gained). This analysis was assessed as directly applicable with minor limitations.
- An original cost–utility analysis found that apixaban was cost effective compared to aspirin for treating patients with non-valvular atrial fibrillation and eGFR 25-50 ml/min/1.73 m^2 (ICER: £14,600 per QALY gained). This analysis was assessed as directly applicable with minor limitations.
- An original cost–utility analysis found that dabigatran 110mg was not cost-effective compared to warfarin for treating patients with non-valvular atrial fibrillation and eGFR 25-50 ml/min/1.73 m^2 (ICER: £43,700 per QALY gained). This analysis was assessed as directly applicable with minor limitations.
- An original cost–utility analysis found that dabigatran 150mg was dominated by warfarin (i.e. dabigatran was less effective and more costly) for treating patients with non-valvular atrial fibrillation and eGFR 25-50 ml/min/1.73 m^2. This analysis was assessed as directly applicable with minor limitations.

10.3.6 Recommendations and link to evidence

Recommendations	The current recommendations can be found at www.nice.org.uk/guidance/ng203
Research Recommendations	• **For people with CKD at the highest risk of cardiovascular disease, what is the clinical effectiveness of low-dose aspirin compared with placebo for primary prevention of cardiovascular disease?**
Relative values of different outcomes	The GDG considered that cardiovascular or cerebrovascular events, major bleeding (as reported by the studies) and mortality (all-cause and cardiovascular) were all critical to decision making. Progression of CKD (measured by change in eGFR and occurrence of end stage kidney disease), minor bleeding (as reported by the studies), hospitalisation and health related quality of life were considered as important outcomes to consider. However, no outcome data was identified for progression of CKD, health related quality of life, and only one study reported hospitalisation.[190]
Trade off between clinical benefits and harms	**Antiplatelets** The original 2008 CKD guideline made a positive recommendation to offer antiplatelet drugs for secondary prevention of cardiovascular disease. The GDG agreed that the recommendation should still stand, based on the updated evidence reviewed, however, it was amended to reflect that there was an increased risk of bleeding in general (not just minor bleeding as previously state) and that this could occur with single antiplatelet agents. The GDG considered that the data reported from the subgroup analysis of people with an eGFR <60ml/min/1.73 m^2 from the HOT trial in an overall population of 50-70 year olds with hypertension (Jardine et al.)[178] suggested that although the bleeding risk with aspirin is increased in people with an eGFR <45 ml/min/1.73 m^2, the increased cardiovascular risk of this group of people means that the benefits of aspirin demonstrated in the study in terms of reduced risk of mortality and cardiovascular events, outweigh the risks. The GDG carefully considered this evidence, as it could be suggested of a possible primary prevention option for a high risk group. However, this was from a post-hoc subgroup analysis which was not powered to detect changes in this group, and the evidence was not strong enough to base a recommendation on, but a research recommendation for the use of aspirin for primary prevention of cardiovascular disease has been made, see Appendix N for further information. All studies of clopidogrel that were included in this review had aspirin as background therapy in both treatment arms.[35,80,190] These were in populations with NSTEMI, atherosclerotic disease (or multiple risk factors for atherosclerotic disease) and those undergoing elective PCI for symptomatic coronary artery disease. None of the evidence reported favoured clopidogrel. The GDG were aware that people with CKD may be resistant to clopidogrel[16] which could explain why the results of the

	subgroup analyses differ from the overall trial results. The GDG agreed that no recommendation should be made rather than recommending against giving clopidogrel in people with CKD as the evidence was from a limited number of subgroup analyses, not powered to detect differences in this population. The evidence for ticagrelor compared to clopidogrel did show some benefit for mortality and cardiovascular events for ticagrelor over clopidogrel,[177] however, the GDG agreed that this was not sufficient evidence to recommend that people with CKD should be treated any differently. It was noted that the people at higher risk had an increased absolute benefit. **Oral anticoagulants** The available evidence was for warfarin, dabigatran, apixaban and rivaroxaban. One study compared rivaroxaban with warfarin in a subgroup of people with creatine clearance of 30-49 ml/min/1.73 m^2, and another compared rivaroaxaban with placebo in people with acute coronary syndrome. Neither demonstrated a difference between the treatments.[99,252] However, the ARISTOTLE trial of apixaban compared with warfarin suggested that apixaban was beneficial compared to warfarin.[149] The trial demonstrated superiority of apixaban over warfarin in people with CKD as a pre-specified subgroup. In patients with atrial fibrillation kidney impairment was associated with increased risk of cardiovascular events and bleeding. When compared with warfarin, apixaban treatment reduced the rate of stroke, death, and major bleeding, regardless of kidney function. People with impaired kidney function, GFR between 25-50 ml/min/1.73 m^2, seemed to have the greatest reduction in major bleeding with apixaban. In all patients the confidence intervals of the two groups effect sizes overlapped and there was significant evidence of heterogeneity based on treatment effect by eGFR category (P=0.03), but the balance between benefit and risk clearly favoured apixaban in those with GFR 25-30 ml/min/1.73 m^2. The RELY trial compared dabigatran with warfarin in a similar population and also reported results in people with kidney impairment as a pre-specified subgroup analysis. Dabigatran did appear to reduce the rate of stroke and systemic embolism compared to warfarin at doses of 150 mg twice daily, but there was no consistent benefit at 110mg twice daily. However, at 150 mg twice daily, in the group with GFR between 30-50 ml/min, warfarin was superior to dabigatran in reducing major bleeding. The GDG agreed that as the safety benefits in terms of reduction in major bleeding in the most renal impaired group demonstrated with apixaban were not replicated with dabigatran, that there was not sufficient evidence to recommend that dabigatran should be used in preference to warfarin in this group. The GDG were also aware that advice in the BNF is for doses of 150 mg of dabigatran not to be used inpeople aged over 80 years. The GDG considered that there was sufficient evidence to highlight that in people with CKD, apixaban should be considered in preference to warfarin in people with non-valvular atrial fibrillation.
Economic considerations	**Antiplatelets** No published economic evaluations were identified that focused on a CKD population. The annual cost of aspirin and clopidiogrel is small. These will be outweighed by the cost of treating bleeding and potential cost savings from averting cardiovascular events. The cost of ticagrelor and prasugrel are considerably greater. The GDG judged that although increased bleeding might be greater for CKD patients than for other patients, the benefits of aspirin therapy in terms of reduced cardiovascular events are likely to outweigh the risks and costs.

The GDG were concerned with the uncertainty around health outcomes associated with ticagrelor and clopidogrel and felt it most appropriate to make no specific recommendation about these drugs.

Oral anticoagulants

No published economic evaluations were identified that focused on a CKD population.

Even though the novel oral anticoagulants do not require regular blood testing their cost is still greater than the use of warfarin. Based on the eGFR<50 ml/min/1.73 m^2 subgroup of the ARISTOTLE trial, The clinical review found apixaban favourable over warfarin in all three critical health outcomes: all-cause mortality; stroke or systemic embolism; and major bleeding. Furthermore there are likely to be less drug interactions with the novel anticoagulants than with warfarin and they are more convenient for patients since they require less monitoring.

An original cost-utility analysis was conducted for apixaban compared to warfarin and aspirin on the basis of the $_{eGFR}$subgroup of the ARISTOTLE and AVERROES trials. In the base case apixaban was found to cost £9,700 per QALY gained compared with warfarin for people with non-valvular atrial fibrillation and CKD. In the most conservative analysis, apixaban was slightly over the £20,000 per QALY threshold (at £20,800 compared with warfarin and £22,600 compared with aspirin). This was based on a lower estimate of treatment effect, higher estimate of CKD treatment cost, lower estimate of cardiovascular treatment cost and lower estimate of utility. However, there are additional reasons to think that this is a conservative estimate (i.e. biased against apixaban):

- The disutility associated with a cardiovascular event were assumed to only last for one year
- There was no disutility attributed to major bleeding
- Only short-term costs of cardiovascular and bleeding events were included
- There was assumed to be no disutility associated with attending anticoagulation clinics (and no cost to the patient).

Had these limitations been explicitly addressed then apixaban would be more cost-effective.

We assumed complete compliance with each treatment. Although this is clearly a gross simplification it does not necessarily undermine the results, since patients that drop out are likely to receive less benefit but also incur less treatment cost. Models that allow for switching are often difficult to interpret because it is unclear what is driving the overall result (the initial treatment or the second-line or third-line treatment).

This model compared apixaban with both warfarin and aspirin and found apixaban to be cost-effective. However, it is possible that, for some patient subgroups at least, none are effective or cost-effective. Consideration should be given to an individual patient's cardiovascular and bleeding risk.

Dabigatran was considered using RE-LY trial results in a sensitivity analysis. Due to the lack of evidence of a survival benefit, dabigatran 110mg was not cost-effective for these patients (£43,700 per QALY gained). And at a dose of 150mg the QALYs were slightly reduced compared with warfarin.

The manufacturer's model in NICE Technology Appraisal TA275[286] assessed the cost-

	effectiveness of apixaban compared with warfarin in a broader non-valvular atrial fibrillation population. Both models used results from the ARISTOTLE trial but in this model we have used a CKD subgroup from the trial. The TA275 model was a more sophisticated analysis in that it modelled different CV and bleeding events separately and estimated results probabilistically but it arrived at a similar result: £11,000 per QALY gained (versus £9,700). It would not have been possible to replicate the methods of the TA exactly since some of the data have been kept confidential. The TA model had a similar baseline life expectancy but the LY gain was much bigger in the base case of this model (0.15 versus 0.84) because the relative treatment effect was greater in the CKD subgroup. The incremental costs were also larger in our model (£1,795 versus £6,035) since we included the cost of CKD care in extra months of life and we were somewhat conservative with regard to cost savings from events averted. The TA model estimated a lowerincremental cost-effectiveness ratio for apixaban versus aspirin compared to this analysis (£2,900 versus £14,600). This was because the mortality treatment effect was smaller in the CKD subgroup and as noted above we have been more conservative in our assumptions about care in extra years of life and cost savings associated with treatment averted.
Quality of evidence	**Antiplatelets** All of the evidence for antiplatelet agents included in this review was from post-hoc subgroup analyses, and studies were not powered to detect changes in these subgroups. Although the GDG agreed that there was some evidence for benefit of aspirin in people with lower levels of eGFR, it was noted that this was based on post-hoc analysis in a study which wasn't powered to detect differences according to kidney function, and only a very small percentage (2.9%) of the overall trial population had an eGFR <45 ml/min/1.73 m^2.[178]The GDG discussed that this could be a result of fluctuation in treatment effects, and were also aware that age is a major factor for cardiovascular risk. Jardineet al. reported that in people with an eGFR <45 ml/min/1.73 m^2 the mean age was 68 in people with eGFR >60 ml/min/1.73 m^2 the mean age was 60, so there was a possibility that the effect may be due to age rather than eGFR. It was noted that the study reported that the interaction of eGFR level was significant (P=0.02) adding strength to this being a true effect, however it was agreed more research was required to determine the true effect. The GDG have developed a research recommendation to this effect, see Appendix N for further details. No evidence was identified for prasugrel in people with CKD. For clopidogrel, there were three studies comparing clopidogrel with placebo,[35,80,190] and one comparing clopidogrel with ticagrelor.[177] The GDG agreed that from the review, there was no evidence to recommend clopidogrel to people with CKD, only evidence of harm as all-cause mortality, cardiovascular mortality and major bleeding had lower risks in the placebo group compared to the group treated with clopidogrel.[80] The GDG noted that in Keltai et al. (CURE trial) the population were all high risk NSTEMI patients, and therefore would be given clopidogrel, however in Dasgupta et al. (CHARISMA trial) the population are low risk (people with cardiovascular disease or multiple risk factors for cardiovascular disease), and therefore probably wouldn't be given clopidogrel in clinical practice. It was agreed that evidence therefore could not be extrapolated from this trial. The GDG discussed that the evidence from James et al. suggests ticagrelor is potentially better than clopidogrel for older people with CKD, but this was very low quality evidence from a subgroup analysis in which the baseline details of the subgroup treatment groups were not provided.

	Oral anticoagulants Although one study demonstrated benefits of apixaban versus placebo,[8] the GDG highlighted that everyone included in the trial had had 6 months of treatment before entering the trial, and it was therefore looking at whether changing treatment to apixaban after 6 months usual treatment for VTE, conferred any additional benefit. Another study in people with recent acute coronary syndrome and at least 2 risk factors for recurrent ischaemic events demonstrated no consistent benefit of apixaban over placebo, and an increased bleeding risk. The GDG agreed a recommendation could not be made based on this evidence. The evidence demonstrating benefit of dabigatran and apixaban compared to warfarin in people with CKD and atrial fibrillation, was of low and very low quality, however they were both from pre-specified subgroup analysis. The quality rating of the evidence was based on the lack of baseline details for the subgroup analysis, and the indirect population that the analyses were taken from. However, all evidence included in this review was from indirect populations originally. Evidence reviewed for rivaroxaban versus warfarin was from very low quality evidence in which absolute event rates could not be calculated as the number of events per treatment arm were not reported by the study.[109] There was uncertainty due to imprecision in all effect sizes, except for the outcome of major bleeding assessed by haemoglobin drop, transfusion, clinical organ and fatal bleeding. The GDG agreed that no recommendation could be made based on this evidence.
Other considerations	**Antiplatelets** The GDG noted that in the general population, aspirin would only be used for primary prevention of cardiovascular disease in high risk groups. However, evidence reviewed by the GDG in this guideline has identified that at eGFRs of <45ml/min/1.73 m^2 people are at high risk of cardiovascular events. It was also noted that measures of cardiovascular risk that are used in clinical practice do not adequately address chronic kidney disease. Therefore it was useful for healthcare professionals, especially those in primary care, to have a guide as to what eGFR level indicates an increased risk. The GDG agreed this would be useful to inform a future research recommendation for primary prevention of cardiovascular disease in people with chronic kidney disease. See Appendix N for further information about this research recommendation. The GDG agreed the original recommendation for secondary prevention(recommendation 1.8.21) from CG73 should remain although 'minor' should be deleted from the comment on bleeding risk, as evidence indicated that major bleeding risk was also increased in people with CKD. The GDG agreed there was no evidence to do anything differently for people with CKD and STEMI, other than to be aware of their bleeding risks, as is currently done in clinical practice. **Oral anticoagulants** The GDG acknowledged that TA 275 recommends that apixaban is recommended as an option for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation with 1 or more risk factors. Although the TA is partially based on the ARISTOTLE trial, of which the Hohnloser study is a subgroup analysis,[149] the TA does not make any recommendations specific to people with CKD, and therefore it was agreed that a recommendation for the use of apixaban in preference with warfarin in people with CKD could be made in this guideline, and did not directly conflict with the TA.

	The GDG were aware that the ARISTOTLE trial excluded people with eGFR <25. However, there were a very small percentage of people with agreed that for consistency with ranges usually reported, and kidney disease classification, the recommendation should state 30-50 ml/min/1.73m^2.

11 Asymptomatic hyperuricaemia [2014]

11.1 Asymptoamtic hyperuricaemia in CKD

11.1.1 Introduction

Uric acid is a product of purine metabolism. After glomerular filtration uric acid is both reabsorbed and excreted in the proximal tubule. Hyperuricaemia may result from either increased production or decreased excretion of uric acid. Increased production may occur through enzyme defects, increased purine turnover (myeloproliferative disorders and certain forms of cancer), or from increased consumption in diet. In patients with kidney disease there is decreased urinary uric acid excretion. Whether this gives rise to hyperuricaemia depends on the degree of gastrointestinal excretory compensation but population studies indicate a rise in serum uric acid concentration as GFR decreases.

There is a relationship between serum uric acid concentration and development and progression of CKD, and it has been suggested that lowering serum uric acid levels in individuals with CKD and asymptomatic hyperuricaemia may be beneficial. There is theoretical evidence to support the role for uric acid as both an initiator of CKD, and a factor involved in its progression. It has been proposed that an elevated uric acid may have a role in initiating hypertension, arteriolosclerosis, kidney disease, insulin resistance, and hypertriglyceridaemia. Once renal microvascular disease develops, the kidney will drive hypertension; once obesity develops fat-laden adipocytes will contribute to insulin resistance, and once kidney disease develops the kidney will also drive progression.

Allopurinol decreases serum uric acid levels by inhibiting the enzyme xanthine oxidase. Experimental rat models have suggested that allopurinol treatment can prevent hyperuricaemia-induced functional and structural injury of the kidney. In animal models of established kidney diseases, correction of the hyperuricemic state can significantly improve blood pressure control, decrease proteinuria, and decrease the amount of glomerulosclerosis, tubulointerstitial fibrosis, and vasculopathy. Febuxostat is a selective xanthine oxidase inhibitor and has also been shown to prevent progression of kidney disease in animal models.

11.1.2 Review question: What is the clinical and cost effectiveness of uric acid lowering with allopurinol or febuxostat in the management of CKD?

For full details see review protocol in Appendix C.

Table 119: PICO characteristics of uric acid lowering with allopurinol or febuxostat review question

Population	Adults with CKD and asymptomatic hyperuricaemia **Subgroups:** Older people (≥75 years)
Intervention/s	Allopurinol, febuxostat
Comparison/s	Each other, placebo, (usual care)
Outcomes	**Critical:** • Progression of CKD (GFR final values or end stage renal disease requiring RRT) • Cardiovascular events • Reduction in antihypertensive agents • Mortality (all-cause and cardiovascular) **Important:** • Hospitalisation

	• Health related quality of life
Study design	RCTs

11.1.3 Clinical evidence

We searched for randomised trials comparing the effectiveness of allopurinol or febuxostat versus each other, placebo or usual care for the management of CKD for people with CKD and asymptomatic hyperuricaemia.

One NICE technology appraisal (TA164) on febuxostat was identified,[283] however this was excluded as the population studied was people with gout, not asymptomatic hyperuricaemia and there were no specific recommendations for people with CKD. No other relevant studies of febuxostat were identified.

Three randomised trials on the use of allopurinol were included in the review.[126,187,375] Evidence from these is summarised in the clinical GRADE evidence profile below (Table 121). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

All were small studies conducted in single centres, only one[187] was from the United Kingdom. The dose of oral allopurinol used varied from 100mg once a day up to 300mg once a day. The population also differed slightly between studies (see Table 120). The aim of these studies was to assess whether allopurinol is effective in the management of CKD for people who have asymptomatic hyperuricaemia. One study[187] was described as a double blind placebo control trial but the methods were not described clearly and it is uncertain if outcome assessors were blinded. The other two studies[126,375] both compared allopurinol to "usual treatment". No further details on usual therapy or treatment provided were given for either of these studies.

Change in eGFR, as a measure of kidney progression was reported as final values in two studies,[126,375] and change from baseline in the third study.[187]

Summary of included studies

Table 120: Summary of studies included in the review

Study	Intervention / comparison	Population	Outcomes	Comments
GOICOECHEA et al 2010 (Spain)[126]	Allopurinol 100mg once a day Route: oral Compared with usual care	People with "moderate CKD" not already on allopurinol	Critical: • Progression of CKD (eGFR [MDRD4] and RRT) • Cardiovascular events • Mortality (all-cause) Important: • Hospitalisation	Small study, single centre. Only outcome assessors blinded. No placebo. Figures reported in study baseline characteristics for number and percentage inconsistent and inaccurate.
KAO et al 2011 (United Kingdom)[187]	Allopurinol 300mg once a day Route: oral Compared with	People with stage 3 CKD and left ventricular hypertrophy	Critical: • Progression of CKD (eGFR [method not reported]) • Reduction in antihypertensive agents	**Conflict of interest:** University of Dundee and last author submitted a patent on the use of xanthine oxidase inhibitors (including allopurinol) to

Study	Intervention / comparison	Population	Outcomes	Comments
	placebo		• Mortality (all-cause) Important:	treat anginal chest pain. **Limitations:** 14/67 (21%) did not complete study, no imputation. Methods including patient selection and method of randomisation not clearly described Unclear if outcome assessors blinded. Baseline differences in diastolic blood pressure and diabetic nephropathy. Small, single centre study in limited population.
SIU et al 2006 (China)[375]	Allopurinol 100-300mg once a day Route: oral Compared with usual treatment	People with "mild to moderate CKD" and asymptomatic hyperuricaemia not already on allopurinol	Critical: • Progression of CKD (RRT) • Reduction in antihypertensive agents • Mortality (all-cause)	Small study, single centre. No blinding or placebo. Unclear denominator used in baseline characteristics. Originally excluded from CG73.

Table 121: Clinical evidence profile: Allopurinol versus usual care

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Allopurinol	Placebo or usual care	Relative (95% CI)	Absolute	Quality	Importance
Renal progression - eGFR (final values) - 100mg (follow-up 12 months; Better indicated by higher values)[126]												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision	None	57	56	-	MD 5.5 higher (0.59 to 10.51 higher)	LOW	CRITICAL
Renal progression - eGFR (change values) - 300mg (follow-up 9 months; Better indicated by higher values)[126,187]												
1	Randomised trials	Very serious (a),(b)	No serious inconsistency	No serious indirectness	No serious imprecision	None	67	53	-	MD 0 higher (3.35 lower to 3.35 higher)	LOW	CRITICAL
Renal progression - eGFR (final values) 100mg (follow-up mean 24 months; Better indicated by higher values)[126]												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	No serious imprecision	None	57	56	-	MD 6.3 higher (1.6 to 11 higher)	LOW	CRITICAL
Renal progression - end stage renal disease needing RRT[126,375]												
2	Randomised trials	Very serious (a),(b)	No serious inconsistency	No serious indirectness	Very serious (d)	None	2/82 (2.4%)	2.8%	RR 1.01 (0.15 to 6.98)	0 more per 1000 (from 24 fewer to 167 more)	VERY LOW	CRITICAL
All-cause mortality[126,187,375]												
3	Randomised trials	Very serious (a),(b)	No serious inconsistency	No serious indirectness	Very serious (d)	None	0/114 (0%)	2.9%	Peto Odds Ratio 0.14 (0.01 to 1.32)	25 fewer per 1000 (from 29 fewer to 9 more)	VERY LOW	CRITICAL
Cardiovascular events[126]												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Allopurinol**	**Placebo or usual care**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1	Randomised trials	Serious (b)	No serious inconsistency	No serious indirectness	Serious (c)	None	7/57 (12.3%)	26.8%	RR 0.46 (0.2 to 1.04)	145 fewer per 1000 (from 214 fewer to 11 more)	LOW	CRITICAL
Antihypertensive agents stopped[187,375]												
2	Randomised trials	Very serious (a),(b)	No serious inconsistency	No serious indirectness	Very serious (d)	None	6/50 (12%)	6.5%	RR 1.85 (0.5 to 6.87)	55 more per 1000 (from 32 fewer to 382 more)	VERY LOW	CRITICAL
Antihypertensive agents commenced[187,375]												
2	Randomised trials	Very serious (a),(b)	No serious inconsistency	No serious indirectness	Very serious (d)	None	3/50 (6%)	12.3%	RR 0.46 (0.12 to 1.75)	66 fewer per 1000 (from 108 fewer to 92 more)	VERY LOW	CRITICAL
Hospitalisation[126]												
1	Randomised trials	Serious (a)	No serious inconsistency	No serious indirectness	Serious (c)	None	12/57 (21.1%)	39.3%	RR 0.54 (0.29 to 0.98)	181 fewer per 1000 (from 8 fewer to 279 fewer)	LOW	IMPORTANT

a "Usual care" was not clearly described. Small, single centre, open labelled study.
b 14/67 (21%) did not complete study, no imputation. Methods including patient selection and method of randomisation not clearly described. "Double blinded" not described. Unclear if outcome assessors blinded. Baseline differences in diastolic blood pressure and diabetic nephropathy.
c The confidence interval crosses the minimum important difference in one direction.
d The confidence interval crosses the minimum important difference in both directions.

11.1.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

11.1.5 Evidence statements

Clinical

- For CKD progression measured by change in eGFR low quality evidence suggested that at doses of 100mg per day, allopurinol may be more effective than placebo in preventing decline in eGFR, however at doeses of 300mg low quality evidence suggested no difference, and there appeared to be no difference in occurrence of ESRD requiring RRT from very low quality evidence.[126,187,375]
- Very low quality evidence suggested that allopurinol is potentially more clinically effective when compared to placebo or usual care at reducing all-cause mortality, cardiovascular events and hospitalisation at 9-24 months; however the uncertainty of these effects was too large to make clear conclusions about clinical benefit.[126,187,375]
- Allopurinol is potentially more clinically effective when compared to placebo or usual care at improving the number of people stopping antihypertensive agents at 9-12 months and at reducing the number of people commencing use of antihypertensive agents at 9-12 months but again the uncertainty of these effects was too large to make clear conclusions about clinical benefit and the evidence was of very low quality.[187,375]
- There were no studies that reported health related quality of life as an outcome measure.

Economic

- No relevant economic evaluations were identified.

11.1.6 Recommendations and link to evidence

Recommendations	The current recommendations can be found at www.nice.org.uk/guidance/ng203
Research recommendation	• **In people with CKD who are at high risk of progression, what is the clinical and cost effectiveness of uric acid lowering agents on the progression of CKD and on mortality?**
Relative values of different outcomes	The GDG agreed that the outcomes that were critical to decision making were: progression of CKD (measured by change in eGFR and occurrence of end stage kidney disease), cardiovascular events, hypertension (measured by use of antihypertensives) and all-cause and cardiovascular mortality. Hospitalisation, occurrence of serious adverse events and health related quality of life were considered as important to decision making. However, no studies reported health related quality of life.
Trade-off between clinical benefits and harms	The original CKD guideline (2008) included a chapter on asymptomatic hyperuricaemia in people with CKD. At the time only one RCT[375] was found which was subsequently excluded due to methodological limitations. This study has been included in the updated review, but the methodological limitations remained a concern to the GDG. Since the publication of the original guideline only three randomised trials were found on the use of allopurinol relevant to the question asked and were included in this review.[126,187,375]

	The GDG noted that all were small studies conducted in single centres and only one[187] was from the United Kingdom. The dose of oral allopurinol used varied from 100mg once a day up to 300mg once a day. The population also differed slightly between studies. No relevant studies of the clinical effectiveness of febuxostat in uric acid lowering were identified as this is a newer agent. Due to the limited amount and low quality of the evidence reviewed the GDG considered that the evidence precluded assessment of the clinical benefit or harm of allopurinol. There may be potential benefits that could be gained by uric acid lowering therapy, but the current evidence base did not allow sufficient assessment.
Economic considerations	No cost effectiveness evidence was identified for this review. As such, there is no basis for the assessing the cost effectiveness of uric acid lowering therapy for improving outcomes in people with CKD.
Quality of evidence	All of the evidence (3 trials in total) was of low or very low quality with serious or very serious risks of bias or imprecision in the effect estimates. The trials were underpowered to estimate effect size and were all of too short a duration to properly assess cardiovascular outcomes. The GDG found that the evidence indicated potentially positive effects on reducing progression of CKD from using allopurinol. For 2 year progression, allopurinol was favoured, however there was a lot of uncertainty in this effect as the confidence interval crossed the MID. There was particular concern about the SIU2006[375] study which included very few patients, did not measure eGFR, had no placebo and no blinding. The GDG therefore agreed that there was a lack of good quality evidence on the effectiveness of uric acid lowering therapy in the management of CKD and that they were unable to make a clinical recommendation in this area. However, the GDG agreed that this area warranted further research, and formed a research recommendation to determine the effectiveness of uric acid lowering therapies in people with CKD and who are at high risk of progression. See appendix N for further details of the proposed research recommendation.
Other considerations	The evidence from up to two year outcomes indicated a trend showing some benefit of uric acid lowering therapy, but the three included trials were studies with a follow-up period of only 9-24 months. A follow-up period of 3-5 years would be preferred.

Other complications of chronic kidney disease

12 Bone Metabolism and Osteoporosis

12.1 Monitoring of calcium, phosphate, vitamin D and parathyroid hormone levels in people with CKD

12.1.1 Clinical introduction

Alterations in the control mechanisms for calcium and phosphate homeostasis occur early in the course of CKD and progress as kidney function decreases. Changes that occur include abnormalities of calcium, phosphate, parathyroid hormone (PTH), and vitamin D metabolism; together with abnormalities of bone turnover, mineralisation, volume, linear growth, and strength; plus vascular or soft tissue calcification.[247] A wide variety of disturbances of bone metabolism may occur in the setting of CKD necessitating an understanding of the changes that occur in order to design a treatment strategy. However, an in-depth discussion of metabolic bone disease in CKD is beyond the scope of this guideline. This section is focussed on the changes that occur early in the course of CKD. The aim is to prevent metabolic bone disease by maintaining the blood levels of calcium and phosphate as close to normal as possible, and preventing the development of established hyperparathyroidism and parathyroid hyperplasia.

Central to the prevention of these disturbances is an ability to intervene early, recognising that bone disease in people with kidney disease is often asymptomatic, and symptoms appear only late in its course, long after the opportunity for early intervention has passed. Whilst bone biopsy may be the gold standard for assessment of metabolic bone disease it is neither widely available nor widely used. Biochemical assessment is the mainstay of diagnosis and treatment. In addition to measurements of calcium and phosphate it is essential to obtain a direct index of parathyroid activity by measurement of PTH. Under certain circumstances measurement of vitamin D may also be necessary. When should these parameters be measured and at what frequency should they be repeated?

12.1.2 Methodology

Serum calcium, phosphate, intact parathyroid hormone (iPTH), and vitamin D levels were assessed in adults with various stages of CKD in five cross-sectional studies and one observational study.

Two reports from the cross-sectional US NHANES III study (n=14,679) examined changes in serum calcium and phosphate[158] and 25-hydroxyvitamin D[62] by level of kidney function. Hsu et al. also reported the prevalence of hyperphosphataemia.

A cross-sectional study compared levels of serum calcium, phosphate, iPTH, and vitamin D amongst stage 3, 4, and 5 CKD. The prevalence of vitamin D deficiency, hyperphosphataemia, and hypocalcaemia was examined in people with stages 3 and 4 CKD.[206]

A cross-sectional analysis of CKD patients (n=1836) was performed to ascertain levels of serum calcium, phosphate, iPTH, 1,25-dihydroxyvitamin D, and 25-hydroxyvitamin D within each stage of CKD.[77]

A cross-sectional analysis at baseline of the Study for the Evaluation of Early Kidney disease participants (SEEK, n=1814, mean age 70 years)[219] examined serum calcium, phosphate, iPTH, 1,25-dihydroxyvitamin D, and 25-hydroxyvitamin D within decreasing deciles of eGFR. This study also reported the prevalence of abnormal calcium, phosphate, iPTH, and vitamin D with decreasing eGFR.

All of these studies were limited by the use of one serum creatinine measurement to estimate kidney function.

GFR was measured by 99Tc-DTPA clearance in one small observational study and levels of serum calcium, phosphate, iPTH, 1,25-dihydroxyvitamin D, and 25-hydroxyvitamin D in people with mild CRF (n=27) or moderate CRF (n=12) were compared with healthy people (n=12).[382]

Calcium, phosphate, iPTH, and vitamin D levels with decreasing renal function are summarised in

Table 122 at the end of the evidence statements.

12.1.3 Health economics methodology

There were no health economics papers found to review.

12.1.4 Evidence statements

Serum calcium

Five studies showed that serum calcium levels decreased only in advanced kidney disease. Two of these studies reported the prevalence of hypocalcaemia in a CKD population.

Of people with GFR <20 ml/min/1.73 m^2, 15% had abnormal Ca levels (Ca <2.1 mmol/l).[219] (Level 3)

43% of people with stage 3 CKD and 71% of people with stage 4 CKD had serum Ca <2.37 mmol/l.[206] (Level 3)

Two studies showed that people with stage 4 CKD had significantly lower serum calcium than people with stage 3 CKD.[77,206] (Level 3)

People with moderate CRF (GFR 20-39 ml/min/1.73 m^2) had significantly lower Ca levels than people with mild CRF (GFR 40-90 ml/min/1.73 m^2).[382] (Level 3)

Compared to men with CrCl > 80 ml/min, men with CrCl < 20 ml/min had a significant decrease in ionised serum Ca.[158] (Level 3)

Serum phosphate

Five studies showed that serum phosphate levels increased with advanced kidney disease. Three of these studies showed that abnormal phosphate levels were highly prevalent when eGFR was <20 ml/min/1.73 m^2.

Of people with eGFR 20–29 ml/min/1.73 m^2, 15% had abnormal phosphorus levels (P >1.49 mmol/l). Of people with GFR < 20 ml/min/1.73 m^2, 40% had abnormal phosphorus levels.[219] (Level 3)

The prevalence of hyperphosphataemia (serum P >1.45 mmol/l) increased with declining CrCl: 7% of people with CrCl 20–30 ml/min/1.73 m^2, and 30% of people with CrCl <20 ml/min/1.73 m^2 had hyperphosphataemia.[158] (Level 3)

3% of people with stage 3 CKD and 22% of people with stage 4 CKD had serum P >1.52 mmol/l.[206] (Level 3)

Two studies showed that people with stage 4 CKD had significantly higher serum phosphate levels than people with stage 3 CKD.[77,206] (Level 3)

People with stage 5 CKD had significantly higher serum phosphate than people with stage 4 CKD.[77] (Level 3)

Serum intact parathyroid hormone (iPTH)

Four studies showed that iPTH increased in early stages of CKD. One of these studies reported the prevalence of hyperparathyroidism in the CKD population.

Levin et al. showed hyperparathyroidism (iPTH >65 ng/ml) was prevalent in approximately 20%, 30%, 40%, 55%, and 70% of people with eGFR 69–60, 59–50, 49–40, 39–30, and 29–20 ml/min/1.73 m^2, respectively.[382] The increase in iPTH above reference values began at GFR <60 ml/min/1.73 m^2. People with mild CRF (GFR 40–90 ml/min/1.73 m^2) had significantly higher levels of iPTH than healthy people. People with moderate CRF (GFR 20–39 ml/min/1.73 m^2) had significantly higher iPTH levels than people with mild CRF. (Level 3)

Craver et al. showed that serum iPTH increased across all stages of CKD. (Level 3)

Serum 1,25-dihydroxyvitamin D

Four studies reported decreases in 1,25-dihydroxyvitamin D in early stages of CKD.

23% of people with CRF were below the reference range of serum 1,25-dihydroxyvitamin D at GFR < 60 ml/min/1.73 m^2. People with mild CKD (GFR 40–90 ml/min/1.73 m^2) had significantly lower levels of 1,25-dihydroxyvitamin D compared with healthy people.[382] (Level 3)

Deficiency of 1,25-dihydroxyvitamin D (< 22 pg/ml) was seen as GFR decreased to approximately 45 ml/min/1.73 m^2. The prevalence of 1,25-dihydroxyvitamin D deficiency was approximately 15%, 15%, 20%, 30%, 45%, 50%, and 65% in people with eGFR 70–79, 60–69, 50–59, 40–49, 30–39, 20–29, and <20 ml/min/1.73 m^2, respectively.[219] (Level 3)

Two studies showed that people with stage 4 CKD had significantly lower serum 1,25-dihydroxyvitamin D levels compared with people with stage 3 CKD.[77,206] (Level 3)

Serum 25-hydroxyvitamin D

Two studies showed NS differences in serum 25-hydroxyvitamin D with worsening kidney function.[77,382] (Level 3)

There was NS difference in serum 25-hydroxyvitamin D for people with GFR 30–59 ml/min/1.73 m^2 compared with people with GFR ≥ 90 ml/min/1.73 m^2. Compared with people with GFR ≥90 ml/min/1.73 m^2, people with GFR 15–29 ml/min/1.73 m^2 had significantly lower serum 25-hydroxyvitamin D.[62] (Level 3)

Multiple regression analysis showed NS relationship between eGFR and serum 25-hydroxyvitamin D (p=0.8932). The prevalence of deficiency in serum 25-hydroxyvitamin D (< 15 ng/ml) remained stable until GFR <30 ml/min/1.73 m^2, when the prevalence of serum 25-hydroxyvitamin D deficiency increased. The prevalence of serum 25-hydroxyvitamin D deficiency was approximately 15%, 20%, and 25% in people with eGFR 39–30, 29–20, and <20 ml/min/1.73 m^2, respectively.[219] (Level 3)

57% of people with stage 3 CKD and 58% of people with stage 4 CKD had serum 25-hydroxyvitamin D insufficiency (10–30 ng/ml). 14% of people with stage 3 CKD and 26% of people with stage 4 CKD had serum 25-hydroxyvitamin D deficiency (<10 ng/ml).[206] (Level 3)

Table 122: Summary of serum calcium, phosphate, iPTH, 1,25-dihydroxyvitamin D, and 25-hydroxyvitamin D levels according to level of renal function (95% CI)

Reference	n	Serum parameter	CKD stage 3a (GFR 59-45 ml/min/1.73 m^2)	CKD stage 3b (GFR 44-30 ml/min/1.73 m^2)	CKD stage 4 GFR (29-15 ml/min/1.73 m^2)	CKD stage 5 (GFR < 15 ml/min/1.73 m^2)
[77]	1836	Mean Ca	2.39 mmol/l; n=856		2.34 mmol/l; n=354, p<0.05	
[206]	201	Mean Ca	2.37 mmol/l; n=65		2.30 mmol/l, n=113, p not stated but significant	2.25 mmol/l, n=22, p not stated but significant
[382]	51	Mean Ca	2.31 mmol/l; GFR 40-90 ml/min/1.73m^2, n=27	2.24 mmol/l ; GFR 20-39 ml/min/1.73m^2, n=12, p<0.05		
[158]	14,722	Change Ca			-0.03 mmol/l (95% CI -0.05 to -0.01 mmol/l), p=0.002 ; CrCl <20 ml/min, n=20 vs. CrCl >80 ml/min, n=4347	
[219]	1814	% Abnormal Ca (Ca <2.1 mmol/l)			< 10 %, GFR 20-29 ml/min n=204	15%, GFR < 20 ml/min, n=93
[206]	201	% Abnormal Ca (Ca <2.37 mmol/l)	43%, n=65		71%, n=113	
[382]	51	Mean phosphate	1.0 mmol/l ;GFR 40-90 ml/min/1.73 m^2, n=27	1.2 mmol/l; GFR 20-39 ml/min/1.73m^2, n=12, p <0.05		
[77]	1836	Mean phosphate	1.16 mmol/l; n=856		1.27 mmol/l, n=354, p <0.05 vs. stage 3	1.58 mmol/l, n=111, p <0.05 vs. stage4
[206]	201	Mean phosphate	1.13 mmol/l, n=65		1.32 mmol/l, n=113, p not stated but significant	1.42 mmol/, n=22, p not stated but significant
[206]	201	% Hyperphosphataemia (P > 1.52 mmol/l)	3%, n=65		22%, n=113	
[219]	1814	% Hyperphosphataemia (P> 1.49 mmol/l)			15%, GFR 20-29 ml/min, n=204	40%, GFR < 20 ml/min, n=93
[158]	14722	% Hyperphosphataemia (P> 1.45 mmol/l)		3% (95% CI 1-6%), CrCl 30-40 ml/min, n=614	7% (95% CI 1-12%), CrCl 20-30 ml/min, n=224	30% (95% CI 0-62%), CrCl <20 ml/min , n=47

Reference	n	Serum parameter	CKD stage 3a (GFR 59-45 ml/min/1.73 m^2)	CKD stage 3b (GFR 44-30 ml/min/1.73 m^2)	CKD stage 4 GFR (29-15 ml/min/1.73 m^2)	CKD stage 5 (GFR < 15 ml/min/1.73 m^2)
[382]	51	Mean iPTH	57.5 pg/ml, GFR 40-90 ml/min/1.73 m^2, n=27 vs. 25.4 pg/ml, healthy people, n=12, p <0.05	139 pg/ml, GFR 20-39 ml/min/1.73 m^2, n=12, p <0.05		
[77]	1836	Mean iPTH	8.96 pmol/l, n=856 vs. 5.97 pmol/l , stage 2, n=341, p <0.05		16.47 pmol/l, n=354, p <0.05	24.29 pmol/l , n=111, p <0.05
[206]	201	Mean iPTH	114 pg/ml, n=65		235 pg/ml, n=113, p not stated but significant	310 pg/ml, n=22, p not stated but significant
[219]	1814	% Hyperparathyroidism (iPTH >65 ng/ml)	30%, GFR 50-59, n= 396	55%, GFR 30-39, n=358	70%, GFR 20-29, n=204	85%, GFR < 20, n=93
[382]	51	Mean 1,25-dihydroxyvitamin D	42.1 pg/ml , GFR 40-90 ml/min/1.73 m^2, n=27 vs. 54.6 pg/ml healthy people, n=12, p <0.05	39.2 pg/ml, GFR 20-39 ml/min/1.73 m^2, n=12 vs. 54.6 pg/ml healthy people, n=12, p <0.05		
[77]	1836	Mean 1,25-dihydroxyvitamin D	25.7 pg/ml, n=221 vs. 33.9 pg/ml stage 2, n=87, p<0.05		16.8 pg/ml, n=156, p <0.05 vs. stage 3	13.2 pg/ml, n=43, p <0.05 vs. stage 4
[206]	201	Mean 1,25-dihydroxyvitamin D	79.6 pmol/l , n=63		62.3 pmol/l, n=108, p not stated but significant	54.3 pmol/l, n=20, p not stated but significant
[219]	1814	% 1,25-dihydroxyvitamin D deficiency (< 22 pg/ml)	20%, GFR 50-59, n= 396	45%, GFR 30-39, n=358	50%, GFR 20-29, n=204	65%, GFR <20, n=93
[62]	14679	Mean 25-hydroxyvitamin D	75.8 nmol/l, n= 854 vs. 73.3 nmol/l, GFR ≥ 90 ml/min/1.73m^2, n= 9687, NS		61.1 nmol/l, n=44 vs. 73.3 nmol/l, GFR ≥90 ml/min/1.73 m^2, n=9687, p=0.0002	
[77]	1836	Mean 25-hydroxyvitamin D	29.6 ng/ml, n=43		26.2 ng/ml, n=115, NS	23.4 ng/ml, n=35, NS

Reference	n	Serum parameter	CKD stage 3a (GFR 59-45 ml/min/1.73 m^2)	CKD stage 3b (GFR 44-30 ml/min/1.73 m^2)	CKD stage 4 GFR (29-15 ml/min/1.73 m^2)	CKD stage 5 (GFR < 15 ml/min/1.73 m^2)
[382]	51	Mean 25-hydroxyvitamin D	63.3 nmol/lGFR 40-90 ml/min/1.73 m^2, n=27	47.1 nmol/l, GFR 20-39 ml/min/1.73 m^2, n=12, NS		
[219]	1814	% 25-hydroxyvitamin D deficiency (< 15 ng/ml)		15%, GFR 30-39, n=358	20%, GFR 20-29, n=204	25%, GFR <20, n=93
[206]	201	% 25-hydroxyvitamin D insufficiency (10-30 ng/ml).	57%, n=65		58%, n=113	
[206]	201	% 25-hydroxyvitamin D deficiency (< 15 ng/ml)	14%, n=65		26%, n=113	

12.1.5 From evidence to recommendations

The GDG noted that in many of the studies the results were not broken down by stage of CKD or level of GFR.

Although there were statistically significant differences in mean calcium concentrations at different levels of GFR these were unlikely to be clinically significant differences. On the basis of the evidence the GDG agreed that there was no need to routinely measure serum calcium concentrations in people with stage 1, 2 and 3a CKD and that it was not usually necessary to measure it in people with stage 3b CKD.

The GDG noted that although there were statistically significant differences in mean phosphate concentrations at different levels of GFR these values were all within the normal range. Serum phosphate concentrations generally fell within the normal range unless the GFR level was below 20 ml/min/1.73 $m^{2.}$ On the basis of the evidence the GDG agreed that there was no need to routinely measure serum phosphate concentrations in people with stage 1, 2 and 3a CKD and that it was not usually necessary to measure it in people with stage 3b CKD.

The prevalence of hyperparathyroidism in people with a reduced GFR was higher than in healthy individuals; however, the significance of modestly elevated PTH concentrations was thought unclear and there was no consensus on whether people with concentrations elevated to this extent benefit from treatment. On the basis of the evidence the GDG agreed that there was no requirement to routinely measure serum PTH concentrations in people with stage 1, 2 and 3a CKD and that it was not usually necessary to measure it in people with stage 3b CKD in absence of specific indications. Specific indications to measure serum PTH would include unexplained hypercalcaemia and symptoms suggestive of hyperparathyroidism.

The prevalence of abnormally low vitamin D concentrations increased once the GFR fell below 45 ml/min/1.73m^2;[219] however, there was no information in this study on the prevalence of low vitamin D concentrations in the general population.

Most laboratories do not measure 1,25 dihydroxyvitamin D concentrations.

On the basis of the evidence the GDG agreed that there was no need to routinely measure serum vitamin D concentrations in people with stage 1, 2 and 3a CKD and that it was not usually necessary to measure it in people with stage 3b CKD except where there are specific indications such as unexplained hypocalcaemia or symptoms suggestive of vitamin D deficiency.

Because of the increased prevalence of abnormal serum calcium, phosphate, PTH and vitamin D concentrations in people with stage 4 and 5 CKD and the fact that these people may require treatment for renal bone disease it was recommended that calcium, phosphate and PTH concentrations should be measured in people with stage 4 and 5 CKD.

There was no evidence to guide a recommendation about how frequently the calcium, phosphate, PTH and vitamin D concentrations should be measured in people with stage 4 and 5 CKD and the GDG agreed that this would be determined by the clinical circumstances.

12.1.6 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng203

12.2 Risks and benefits of bisphosphonates for preventing osteoporosis in adults with CKD

12.2.1 Clinical introduction

Osteoporosis is caused by the cumulative effect of bone resorption in excess of bone formation. Bisphosphonates inhibit bone resorption with relatively few side effects and are widely used for the prevention and treatment of osteoporosis. Osteoporosis can also develop in people with CKD and ESRD for many reasons beyond age-related bone loss and postmenopausal bone loss. People with CKD are far more likely than the general population to have conditions putting them at risk of osteoporosis and are much more likely to be prescribed medication promoting development of osteoporosis. The diagnosis of osteoporosis in people with advanced CKD is not as straightforward as it is in people with postmenopausal osteoporosis. Neither fragility fractures nor the World Health Organization bone mineral density criteria can be used to diagnose osteoporosis in this population since all forms of renal bone disease may fracture or have low 'T scores'. The diagnosis of osteoporosis in people with CKD must be done by first excluding the other forms of renal osteodystrophy.[258]

Bisphosphonates are poorly absorbed orally (1–5% of an oral dose), and absorption is best when the drug is given on an empty stomach. Approximately 80% of the absorbed bisphosphonate is usually cleared by the kidney, the remaining 20% being taken up by bone. Relative bone uptake is increased in conditions of high bone turnover, with less of the drug being excreted by the kidneys. The plasma half-life is approximately one hour, while the bisphosphonate may persist in bone for the lifetime of the patient.

Product data sheets do not recommend bisphosphonates for people with stage 4 or 5 CKD. What is the evidence for this and what is the evidence for the routine use of bisphosphonates in the prevention and treatment of osteoporosis in people with CKD?

12.2.2 Methodology

There were very few papers that examined the effect of bisphosphonates on bone mineral density (BMD) and fracture outcomes in a CKD population.

One open-label RCT was excluded due to limitations in randomisation.[114]

One RCT (n=38, 1 year follow-up) investigated the effects of risedronate with and without vitamin D in people with CKD (mean eGFR 78 ml/min/1.73 m^2) with high dose corticosteroid-induced bone loss.[195] Corticosteroids are frequently used in the treatment of kidney disease and even at low doses may cause osteoporosis and bone fractures. Limitations of this study include the small sample size, although there was no loss to follow-up.

A meta-analysis of data from nine phase III trials (n=9883, 2 years follow-up, mean age 75 years) investigated the effects of risedronate in osteoporotic women with varying levels of kidney function.[259] Although this was not a systematic review and included only phase III trials, due to lack of other evidence, this paper was included. 91% of the pooled cases had some degree of kidney impairment and the analyses were conducted in categories of patients with mild (CrCl 50–80 ml/min), moderate (CrCl 30–50 ml/min) or severe (CrCl <30 ml/min) kidney dysfunction.

A post-hoc analysis of the Fracture Intervention Trial (FIT, n=6458, 3 year follow-up, mean age 68 years)[173] investigated the effects of alendronate on BMD and fracture in osteoporotic women with moderate/normal kidney function (eGFR ≥45 ml/min/1.73 m^2, n=5877) or severe renal dysfunction (eGFR <45 ml/min/1.73 m^2, n=581).

The safety and efficacy of bisphosphonates in preventing osteoporosis in people with CKD are summarised in

Table 123, at the end of the evidence statements.

12.2.3 Health economics methodology

There were no health economics papers found to review.

12.2.4 Evidence statements

Risedronate

Change in BMD

Combination therapy of risedronate (2.5 mg/day) and vitamin D together resulted in a significant increase in BMD, whereas BMD significantly decreased in the vitamin D alone group. There was a NS decline in BMD in the risedronate group. The difference between BMD changes in the risedronate and vitamin D combination therapy group and the vitamin D alone group were statistically significant.[195] (Level 1+)

The mean percent increase from baseline to endpoint in BMD at the lumbar spine, femoral neck and trochanter was significantly greater in the risedronate (5 mg/day) arm than in the placebo arm in all mild, moderate and severe renal impairment subgroups, with the exception of the femoral neck in the severe renal impairment subgroup.[259] (Level 1+)

Fractures

In one RCT, no fractures occurred over 1 year of follow-up.[195] (Level 1+)

The incidence of new vertebral fractures was significantly lower in the risedronate (5 mg/day) group than placebo groups within mild, moderate and severe renal impairment subgroups.[259] Within the risedronate treatment group, the incidence of new vertebral fractures was similar across renal impairment subgroups (p=0.124). Within the placebo group, new vertebral fractures increased significantly with increasing severity of renal impairment (p<0.001). (Level 1+)

Adverse events

There were no adverse events in any of the treatment arms in the Kikuchi et al. RCT. (Level 1+)

The incidence of overall, urinary and renal function related adverse events were similar between risedronate (5 mg/day) and placebo groups in the subgroups of patients with severe, moderate and mild renal impairment.[259] (Level 1+)

Alendronate

Change in BMD

Alendronate increased BMD at the total hip, femoral neck and spine to a greater extent in postmenopausal women with eGFR <45 ml/min/1.73 m^2, than in women with eGFR ≥45 ml/min/1.73 m^2. There was a significant interaction between renal function and the increase in total hip BMD (p=0.04). Among women with osteoporosis (n=3214), alendronate produced a greater increase in BMD at the hip and femoral neck in the group with eGFR <45 ml/min/1.73 m^2 than women with eGFR ≥45 ml/min/1.73 m^2. However at the spine the increase in BMD was greater in women with eGFR ≥45 ml/min/1.73 m^2. There was no significant interaction between renal function and increase in BMD.[173] (Level 1+)

Fractures

Overall, alendronate significantly reduced the risk of clinical fractures (OR 0.8, 95% CI 0.7–0.9) and spine factures (OR 0.54, 95% CI 0.37–0.87) compared with placebo. The risk reduction was significant in women with eGFR ≥45 ml/min/1.73 m^2 for both clinical and spine fractures, but NS in women with eGFR <45 ml/min/1.73 m^2. (Level 1+)

Women with a reduced eGFR <45 ml/min/1.73 m^2 had an increased risk of any clinical fracture (OR 1.3, 95% CI 1.0–1.6) and of spine fractures (OR 2.5, 95% CI 1.6–3.9) compared with women with an eGFR ≥45 ml/min/1.73 m^2.[173] (Level 1+)

Adverse events

There was no difference for adverse events among women with reduced renal function compared with women without reduced renal function (p=0.189).[173] (Level 1+)

Table 123: Summary of the safety and efficacy of bisphosphonates in preventing osteoporosis in people with CKD (95% confidence intervals)

Reference	Population	Treatment groups	Outcomes	Size effect
[195]	People with glomerulonephritis + high-dose corticosteroid	n=12 risedronate n=15 alfacalcidol n=11 risedronate + alfacalcidol	Change in BMD	Risedronate: NS change from baseline Alfacalcidol: -5.6% from baseline ($p<0.05$); $p=0.001$ vs. R+A Risedronate + alfacalcidol: +2% from baseline ($p<0.05$)
			Fractures	No fractures occurred in any trial arm.
			Adverse events	No adverse events in any trial arm.
[259]. Pooled analysis of 9 phase III RCTs	Osteoporotic women GFR < 30 ml/min/1.73 m^2	n=301 risedronate n=271 placebo	All adverse events	RR 0.96 (0.91-1.02) NS
			Urinary and renal function adverse events	RR 0.93 (0.67-1.30) NS
			Specific renal function adverse events	RR 0.80 (0.31-2.04) NS
	Osteoporotic women GFR 30-50 ml/min/1.73 m^2	n=2034 risedronate n=2037 placebo	All adverse events	RR 1.02 (0.99-1.04) NS
			Urinary and renal function adverse events	RR 1.00 (0.88-1.14) NS
			Specific renal function adverse events	RR 0.88 (0.53-1.45) NS
	Osteoporotic women GFR 50-80 ml/min/1.73 m^2	n=2161 risedronate n=2192 placebo	All adverse events	RR 1.01 (0.99-1.02) NS
			Urinary and renal function adverse events	RR 0.63 (0.37-1.07) NS
			Specific renal function adverse events	RR 0.96 (0.85-1.09) NS
	Osteoporotic	n=301	Change in	Placebo: -1.37% vs. risedronate: +4.23%,

Reference	Population	Treatment groups	Outcomes	Size effect
	women GFR <30 ml/min/1.73 m^2	risedronate n=271 placebo	BMD	p<0.001
	Osteoporotic women GFR 30-50 ml/min/1.73 m^2	n=2034 risedronate n=2037 placebo	Change in BMD	Placebo: -0.47% vs. risedronate: +4.33; p<0.001
	Osteoporotic women GFR 50-80 ml/min/1.73 m^2	n=2161 risedronate n=2192 placebo	Change in BMD	Placebo: -0.14% vs. risedronate +3.96%; p<0.001
	Osteoporotic women GFR <30 ml/min/1.73 m^2	n=232	Incidence of new vertebral fractures	Placebo approx. 27% vs. risedronate approx. 14%, p=0.021 EC estimated from Fig. 2
	Osteoporotic women GFR 30-50 ml/min/1.73 m^2	n=2426	Incidence of new vertebral fractures	Placebo approx. 19% vs. risedronate approx. 13%, p<0.001
	Osteoporotic women GFR 50-80 ml/min/1.73 m^2	n=3086	Incidence of new vertebral fractures	Placebo approx. 16% vs. risedronate approx. 12%, p=0.001
[173]	Postmenopausal women GFR <45 ml/min/1.73 m^2 (n=581)	Alendronate n=not stated Placebo n=not stated	Change BMD, total hip Change BMD, femoral neck Change BMD, spine	+ 5.6% (4.8-6.5) + 5.0% (4.0-5.9) + 6.7% (5.7-7.8)
	Postmenopausal women GFR ≥45 ml/min/1.73 m^2 (n=5877)	Alendronate n= not stated Placebo n=not stated	Change BMD, total hip Change BMD, femoral neck	+ 4.8% (4.6-5.0) + 4.5% (4.2-4.8)

Reference	Population	Treatment groups	Outcomes	Size effect
			Change BMD, spine	+ 6.6% (6.3-6.9)
	Postmenopausal women GFR <45 ml/min/1.73 m^2 (n=581)	Alendronate n=not stated Placebo n=not stated	Clinical Fractures	OR 0.78 (0.51-1.2) NS
			Spine fractures	OR 0.72 (0.31-1.7) NS
	Postmenopausal women GFR ≥45 ml/min/1.73 m^2 (n=5877)	Alendronate n= not stated Placebo n=not stated	Clinical Fractures	OR 0.81 (0.70-0.94)
			Spine fractures	OR 0.50 (0.32-0.76)
	Postmenopausal women GFR <45 ml/min/1.73 m^2 (n=581)	Alendronate n= not stated Placebo n=not stated	GI Adverse Events	4.5%
			Cerebrovascular Adverse Events	2.2%
			Cardiovascular Adverse Events	2.6%
			Death	1.6%
			Renal Adverse Events	2.1%
	Postmenopausal women GFR ≥45 ml/min/1.73 m^2 (n=5877)	Alendronate n= not stated Placebo n=not stated	GI Adverse Events	5.2% NS compared to GFR <45 ml/min/1.73 m^2 group
			Cerebrovascular Adverse Events	2.2% NS
			Cardiovascular Adverse Events	3.2% NS
			Death	1.9% NS
			Renal Adverse Events	2.3% NS

12.2.5 From evidence to recommendations

The GDG concluded that from the studies presented there was no evidence of an increased risk of drug related adverse events in people with CKD. Bisphosphonates appeared to have benefits on bone mineral density in people with CKD.

The studies did not include people with a GFR <30 ml/min/1.73 m^2 and therefore there is no evidence about either the effectiveness or the safety of bisphosphonates in this group.

Guidelines on the management of osteoporosis do not make recommendations that relate to people with CKD.

The dose of bisphosphonate may need adjusting according to the GFR and clinicians should refer to the drugs' Summary of Product Characteristics (SPC) for guidance on this.

12.2.6 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng203

12.3 Vitamin D supplements in the management of CKD-mineral and bone disorders [2014]

12.3.1 Introduction

Changes in bone mineral metabolism and alterations in calcium and phosphate homeostasis occur early in the course of CKD and progress as kidney function declines (Table 131). Abnormalities of circulating hormone concentrations related to CKD-mineral and bone disorders (CKD-MBD) include parathyroid hormone (PTH), 25-hydroxyvitamin D (25(OH)D), 1,25-dihydroxyvitamin D (1,25(OH)2D), fibroblast growth factor-23 (FGF-23), and growth hormone. At the tissue level there is down regulation of vitamin D receptors and resistance to the actions of PTH. The prevalence of hyperparathyroidism increases from 5.5% in those with a GFR>90 ml/min/1.73 m^2 to 23%, 44% and 73% in people with GFRs 45-59, 30-44 and <30 ml/min/1.73 m^2 respectively. 25-Hydroxyvitamin D deficiency is twice as prevalent in those with a GFR <30 ml/min/1.73 m^2 compared to those with normal GFR.[166,219] Decreased bone mass and changes in bone microarchitecture occur and progress early in CKD such that patients with CKD are at increased risk of bone fracture. A major contributor to the risk of fracture is the increased falls risk associated with CKD-MBD.

The term 'vitamin D' includes vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). The active forms of vitamin D result from a cascade of metabolic steps beginning with cutaneous ultraviolet-dependent generation of vitamin D2 and D3. These molecules are then hydroxylated to 25-hydroxyvitamin-D3 or -D2 in the liver before further 1a-hydroxylation in the kidney to the active forms: 1,25 dihydroxyvitamin-D3 (usually called calcitriol) and 1,25dihydroxyvitamin-D2. For simplicity, they are described collectively as 1,25 dihydroxyvitamin-D, but calcitriol (often called 'active vitamin D') is by far the most important molecule with regard to calcium/phosphate homeostasis and CKD-MBD. The definition of vitamin D deficiency varies but most experts define a healthy concentration of vitamin D as a 25-(OH)D concentration > 75 nmol/l (> 30 ug/l). Vitamin D insufficiency is defined as a 25-(OH) D concentration of 25-75 nmol/l (20 to 30 ug/l) and Vitamin D deficiency as a 25-(OH) D <25 nmol/l (<20 ug/l).[38,150,239,395] The Department of Health (England) define 'low status' as a plasma concentration of 25-(OH) D below 25 nmol/l (<10 ug/l).[90]

The recommended daily dietary allowance for vitamin D when sun exposure is minimal is 15-20ug. To treat vitamin D deficiency either ergocalciferol (D2) or cholecalciferol (D3) can be prescribed as

supplements. The activated forms of vitamin D, alfacalcidol and calcitriol are also available for this purpose. These have the potential advantage of being independent of renal hydroxylation which might be affected by CKD. Not all people with CKD are vitamin D deficient and there are also racial differences in the parameters of bone mineral metabolism. People of Afro-Caribbean origin with CKD have been found to have significantly lower 25(OH)D but similar 1,25(OH)2D levels compared with other ethnicities. Even following adjustment for age, gender, eGFR, BMI, and diabetes, Afro-Caribbeans have significantly lower 25(OH)D and higher PTH levels than Caucasians.[127,128]

In CKD, vitamin D supplementation has the potential to restore muscle and bone strength and to suppress PTH over-production. However, vitamin D analogues can also cause hypercalcaemia and vascular calcification. The latter may contribute to cardiovascular risk.

12.3.2 Review question: For people with GFR 15-60 ml/min/1.73 m^2, what is the clinical and cost-effectiveness of vitamin D supplementation for the management of renal bone disease?

For full details see review protocol in Appendix C.

Table 124: PICO characteristics of vitamin D review question

Population	Adults with CKD and GFR 15-60 ml/min/1.73 m^2 **Subgroups:** • Older people (≥75 years) • Black and minority ethnic groups • People with secondary hyperparathyroidism
Intervention/s	• Ergocalciferol (Vitamin D2) • Alfacalcidol (1 alpha hydroxycholecalciferol) • Calcitriol (1,25 dihidroxycholecalciferol) • Cholecalciferol (Vitamin D3) • Dihydrotachysterol • Paracalcitrol • Doexercalciferol
Comparison/s	Placebo / each other.
Outcomes	**Critical:** • Mortality (all-cause and cardiovascular) • Cardiovascular events • Fracture • Progression of CKD (change in eGFR) • Hypercalcaemia (serum calcium >2.5 mmol/litre) **Important:** • Hospitalisation • Health related quality of life
Study design	RCTs

12.3.3 Clinical evidence

We searched for randomised trials comparing the effectiveness of vitamin D with placebo, or other vitamin D supplements for renal bone disease in people with chronic kidney disease.

One Cochrane review was identified[314], but this was excluded as it included studies with a paediatric population and follow up less than 6 months.

Eight RCTs were included in this review[23,69,76,135,295,320,333,345]. Evidence was found for the following preparations calcitrol (1,25 hydroxylated), doexercalciferol, paracalcitol (1,25 hydroxylated), alfacalcidol (1α hydroxylated) and calcitriol (1,25 hydroxylated). No evidence was found for ergocalciferol, or cholecalciferol. Evidence from these studies is presented in the summary of included studies table (Table 125) and clinical GRADE evidence profile (Table 2) below. See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

Table 125: Summary of studies included in the review

Study	Intervention/comparison	Population	Outcomes
Baker 1989[23]	**Vitamin D:** Calcitriol. 0.25 to 0.5 µg daily (n=8) Duration: 12 months Concurrent medication: All patients received D_3. One patient received thyroxine replacement **Placebo** (n=8)	eGFR 20 to 60 ml/min/1.73 m^2. 7/13 had elevated concentrations of parathyroid hormone.	Critical: • Cardiovascular events • Progression of CKD • Hypercalcaemia
Coburn 2004[69]	**Vitamin D:** Doexercalciferol. 2 capsules (0.5 µg each) daily before breakfast; increased by 1 capsule per day at monthly intervals if required Maximum dose 10 capsules/day (5microg). Duration 24 weeks. Concurrent medication/care: Only calcium-based phosphate binders were administered (n=27) **Placebo** (n=28)	CKD stage 3 or 4 and secondary hyperparathyroidism Age 18-85 years; serum creatinine 1.8-5.0mg/dL (159-442 µmol/l) for men or 1.6-4.0mg/dL (141-353 µmol/l) for women; plasma iPTH >85pg/ml. (8.5 pmol/l)	Critical: • Progression of CKD • Hypercalcaemia
Coyne 2006[76]	**Vitamin D** Paracalcitol. Titrated Duration 24 weeks. Concurrent medication/care: Patients on phosphate binder therapy were to maintain a stable regimen (brand and doses) throughout treatment. (n=107) **Placebo** (n=113)	CKD stages 3 and 4 and secondary hyperparathyroidism. Diagnosed with CKD for longer than 2 months, and had not been on active vitamin D therapy in the previous 4 weeks. eGFR 15-60 ml/min/1.73 m^2 who were not expected to begin dialysis therapy for at least 6 months. People who had been administered a phosphate binder were to have been on a stable regimen for at least 4 weeks before the screening visit. Patients who had two consecutive iPTH levels that averaged 150 pg/ml (15 pmol/l) or greater (all values must have been ≥ 120 pg/ml (12 pmol/l), two consecutive calcium levels	Critical: • Mortality • Progression of CKD • Hypercalcaemia

Study	Intervention/comparison	Population	Outcomes
		below 8.0 and 10.0 (mg/dL) and two consecutive phosphorus levels of 5.2 mg/dL or less were eligible to enter the treatment phase.	
Hamdy 1995[135]	**Vitamin D**: Alfacalcidol 0.25 µg titrated to a maximum of 1 µg Duration: 2 yrs Concurrent medication: Calcium supplements allowed. Phosphate binding drugs allowed when required (n=89) **Placebo** (n=87)	eGFR 15-50 ml/min/1.73 m^2 with no evidence of renal bone disease. Elevated para thyroid hormone 50/72	Critical: • Hypercalcaemia • Progression of CKD
Nordal 1988[295]	**Vitamin D:** Calcitriol 0.25 µg increased to 0.5 µg daily Duration 8 mths Concurrent medication: Al-containing phosphate binders used (n=15) **Placebo** (n=15)	Serum creatinine 180µmol/l and stable renal function for the previous 4 mths	Critical: • Hypercalcaemia
Patel 2011[320]	**Vitamin D**: Doexercalciferol. 2 capsules (1µg) daily; titrations of 1 capsule daily at 2-week intervals Duration 24 weeks. Concurrent medication/care: Patients advised to maintain constant dietary intake of calcium and phosphorus, and current dose of phosphate binder during study (n=12) **Placebo** (n=12)	CKD stage 3 or 4; serum 25(OH)D 30ng/ml or more; iPTH >110 (11 pmol/l) and <450pg/ml (45 pmol/l) for stage 3 and >150 (15 pmol/l) and <450 (45 pmol/l) for stage 4	Critical: • Hypercalcaemia
Przedlacki 1995[333]	**Vitamin D:** Calcitriol 0.25 µg/daily. Low phosphorus and calcium diet Duration: One year Concurrent medication: Some on calcium carbonate or aluminium-containing phosphate binders (n=13) **Placebo** (n=13)	GFR equal or below 51.2 ml/min/1.73 m^2 and age below 70 years	Critical: • Cardiovascular events • Hypercalcaemia
Ritz 1995[345]	**Vitamin D:** Calcitriol 0.125 µg per day	Serum creatinine above 1.4 mg/dl (124 µmol/l) and below	Critical:

Study	Intervention/comparison	Population	Outcomes
	Duration: One year Concurrent medication: Calcium carbonate if required (n=24 **Placebo** (n=21)	6.5 mg/dl (575 µmol/l). 1,84 iPTH levels above the normal range i.e. 6 pmol/l on three separate occasions	• Hypercalcaemia

Table 126: Clinical evidence profile: Vitamin D versus placebo

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D	Control	Relative (95% CI)	Absolute	Quality	Importance
Mortality (follow-up 6-24 months) [76,135]												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[(a)]	None	6/196 (3.1%)	2/200 (1%)	RR 3.03 (0.62 to 14.89)	20 more per 1000 (from 4 fewer to 139 more)	LOW	CRITICAL
Progression of CKD (GFR) (follow-up 6-24 months; better indicated by higher values)[69,76]												
2	Randomised trials	Serious [(b)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	104	113	-	MD 0.8 lower (3.34 lower to 1.75 higher)	MODERATE	CRITICAL
Progression of CKD (eGFR ml/min/1.73 m^2) (follow-up 12-24 months; better indicated by higher values)[24,135]												
2	Randomised trials	Serious [(c)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	96	93	-	MD 2.16 lower (from 6.40 lower to 2.08 more)	MODERATE	CRITICAL
Hypercalcaemia (follow-up 6-24 months)[69,76,135,295,320,333,345]												
7	Randomised trials	Serious [(d)]	No serious inconsistency	No serious indirectness	No serious imprecision	None	31/293 (10.8%)	5/294 (1.7%)	RR 4.63 (2.10 to 10.19)	57 more per 1000 (from 15 more to 153 more)	MODERATE	CRITICAL
Cardiovascular events (follow-up 12 months)[23,333]												
2	Randomised trials	Serious [(c)]	no serious inconsistency	No serious indirectness	Very serious[(a)]	None	0/21 (0%)	2/21 (9.5%) Myocard	Peto OR 0.14 (0.01 to	100 fewer per 1000 (from 270	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Vitamin D**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
								ial infarctio n x 2	2.16)	fewer to 80 more)		
Fracture (follow-up 12 months)[333]												
1	Randomise d trials	Serious [(c)]	No serious inconsistency	No serious indirectness	Serious[(e)]	None	0/13 (0%)	1/12 (8.3%)	Peto OR 0.12 (0 to 6.29)	80 fewer per 1000 (from 230 fewer to 120 more)	LOW	CRITICAL

(a) The confidence interval crosses the minimally important difference in both directions.
(b) 17-23% missing data.
(c) Unclear allocation concealment and randomisation.
(d) > 50% weighted mean unclear allocation concealment and randomisation.
(e) The confidence intervals crosses the MID in one direction.

12.3.4 Economic evidence

Published literature

One study with a relevant comparison was included [297]. This is summarised in the economic evidence profile below (Table 128). See also the study selection flow chart in Appendix E and study evidence table in Appendix H.

One study[296] that met the inclusion criteria was selectively excluded because it had a less applicable setting than the included study (see Appendix K).

Unit costs

Table 127 presents typical drug costs for treating/preventing vitamin D deficiency for those drugs for which there was clinical evidence (see above). The associated monitoring of serum calcium and phosphate concentrations that is recommended for people receiving these treatments is low with the reagent cost less than £0.10 per test

Table 127: Unit costs for drug treatment/prevention of vitamin D deficiency

			Dose per day	Cost per day	Cost per Year	Source of unit cost
Alfacalcidol	Capsule	Non-proprietary	1µg	£0.42	£ 151.84	Drug Tariff December 2013
Calcitriol	Capsule	Rocaltrol	0.5µg	£ 0.32	£ 117.71	BNF66
Colecalciferol	Capsule	Fultium-d3	20ng	£0.12	£ 43.80	Drug Tariff December 2013
Ergocalciferol	Tablet	Non-proprietary	20ng	£0.17	£ 61.32	BNF66
Paracalcitrol	Capsule	Zemplar	2µg	£4.96	£1811.64	BNF66

Note: The costs per day reported here were correct at the time recommendations were drafted; prices may have changed slightly by the time of publication.

Table 128: Economic evidence profile: Paricalcitol versus s Alfacalcidol

Study	Applicability	Limitations	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Nuijten 2010[297] CKD patients with secondary hyper-parathyroidism	Directly Applicable	Potentially serious limitations*	£3,224	0.465 QALYs	£6933 per QALY gained	Results were sensitive to prevalence of proteinuria.

** Treatment effects are not derived from randomised evidence and therefore there is a high risk of bias. Dosage and duration of medication was not reported; thus, uncertain whether the dosage and duration is similar to UK current practice.*

12.3.5 Evidence statements

Clinical

- There was a possible increase in mortality with vitamin D supplementation compared to placebo,[76,135], however the quality of the evidence was low and the uncertainty of these effects was too large to make clear conclusions about clinical harm.
- For progression of CKD moderate quality evidence showed a small reduction in change in GFR or creatinine clearance with vitamin D supplementation compared to placebo,[24,69,76,135] however this was unlikely to be clinically significant in terms of CKD progression.
- From moderate quality evidence there was an increase in hypercalcaemia with vitamin D supplementation compared to placebo.[69,76,135,295,320,333,345]
- There was a possible reduction of cardiovascular events or fracture at 12 months with vitamin D supplementation compared to placebo,[23,333] however due to very low patient numbers and event rates the uncertainty of these effects was too large to make clear conclusions about clinical benefit.
- There were no studies that reported health related quality of life or hospitalisation as an outcome measure.

Economic

- One cost–utility analysis found that paricalcitol was cost effective compared to alfacalcidol for patients with CKD and secondary hyper-parathyroidism (ICER: £6933 per QALY gained). This analysis was assessed as directly applicable with potentially serious limitations.

12.3.6 Recommendations and link to evidence

Recommendations	The current recommendations can be found at www.nice.org.uk/guidance/ng203
Research recommendation	• **In people with hyperparathyroidism secondary to CKD, does treatment with vitamin D or vitamin D analogues improve patient-related outcomes?**
Relative values of different outcomes	The GDG considered that the critical outcomes for decision making were CKD progression (measured by change in eGFR), all-cause mortality, cardiovascular mortality, cardiovascular events, fractures and hypercalcaemia. Health related quality of life and hospitalisations were considered as important outcomes. Whilst the GDG agreed that falls, fractures, bone pain, health related quality of life and hospitalisations were all outcomes of relevance there was no evidence found for

	these in the review.
Trade-off between clinical benefits and harms	Only two studies reported mortality[76,135] and only two studies reported CKD progression.[69,76] The GDG agreed that the evidence does not show clinical effectiveness for vitamin D supplements over and above treatment of vitamin D deficiency with either cholecalciferol or ergocalciferol. There is insufficient and inconclusive evidence to support the routine use of nutritional or active vitamin D supplements for the management of renal bone disease in people with CKD (GFR 15-60 ml/min/1.73 m^2). There is moderate evidence of harm, in the form of hypercalcaemia, in people treated with active Vitamin D.
Economic considerations	There were no published economic evaluations comparing vitamin D and placebo. One study was identified comparing two different types of vitamin D supplementation for patients with CKD and hyper-parathyroidism. However, this was not based on randomised evidence and therefore has a high risk of bias. This was not considered strong enough to influence the recommendations. There was no economic evidence to inform the value of vitamin D supplementation. The cost of vitamin D supplementation is relatively low at £0.12-£0.42 per day for the recommended supplements.
Quality of evidence	Two studies[69,320] were identified in addition to six relevant RCTs from the original guideline.[23,76,135,295,333,345] The GDG noted that the evidence was of moderate to low quality mainly due to imprecision, missing data, as well as unclear allocation, concealment and randomisation processes. Publication dates range from 1988 (over twenty five years old) through to 2011. Some of the studies have a small patient population[23,69,295,320,345] and many of the included studies are in people with secondary hyperparathyroidism.[23,69,76,135] Overall the GDG considered that the follow-up periods in the reviewed studies were too short to show any long-term effects, only Hamdy et al followed up to two years.[135]
Other considerations	The GDG discussed the supplements which were included in the review. Cholecalciferol and ergocaliferol are standard Vitamin D replacements but before they become active they are biochemically modified in the body. Normally these compounds are first modified in the liver with the addition of a hydroxyl group in the 25 position; they are then modified in the kidney with the addition of a further hydroxyl group to become 1:25 dihydroxycholecalciferol, the active form of vitamin D. People with kidney disease become less able to add the 1 alpha hydroxyl group and will only be able to 25-hydroxylate Vitamin D, they will therefore have relative Vitamin D deficiency despite being 25-hydroxycholecalciferol replete. Hence the choice of supplement was of either 1 alpha hydroxycholecalciferol or 1:25 dihydroxycholecalciferol which therefore bypasses the kidney step in the activation of Vitamin D The GDG discussed the definition of vitamin D deficiency as many different definitions are used, they agreed the following as a guide: deficiency <50nmols, insufficiency 50-75nmols. The studies reviewed all look at activated vitamin D, whereas the GDG noted that non-activated forms are most frequently prescribed in UK practice. Furthermore, calcium and vitamin D are normally prescribed together. As most people with CKD and vitamin D deficiency are managed in primary care the GDG agreed that there was a requirement to consider when calcium, vitamin D and parathyroid hormone need to be measured. Although parathyroid hormone and serum phosphate concentrations begin to rise early in the evolution of CKD (see Table 131 in section 14.1.1, their routine measurement in people with GFR greater than 30 ml/min/1.73 m^2 is not recommended (see section 12.1). The GDG acknowledged that current guidance is to give calcium plus vitamin D to older people in nursing homes, but not to measure their vitamin D. The exact indication for vitamin D therapy may be unclear as there may be other indications than CKD-MBD

	such as people with osteoporosis and increased fracture risk. The GDG acknowledged that observational studies (not reviewed) show benefit of vitamin D supplement, but this was not confirmed by the reviewed and higher level RCT evidence. The consensus opinion of the GDG was that in the absence of hypercalcaemia, vitamin D supplements may be of value where there are clear indications. These include vitamin D deficiency, symptoms attributable to CKD-MBD (such as bone pain, joint pain, proximal limb girdle muscle weakness) and moderately severe secondary hyperparathyroidism (PTH >60pmol/l and rising) after correction of hypocalcaemia. In the GDG's discussions of the wording of a recommendation the term 'do not give' was considered too strong wording, so 'do not routinely offer' was agreed. The GDG agreed that the recommendation from CG73 relating to monitoring serum calcium and phosphate concentrations in people receiving alfacalcidol or calcitriol supplements was still relevant. No new evidence had been reviewed on this recommendation. The GDG acknowledged recommendations on the use of vitamin D in other clinical guidelines and the BNF. The GDG highlighted the lack of evidence for Vitamin D supplementation for people with CKD (GFR 15-60 ml/min/1.73 m^2) who are vitamin D deficient and who have secondary hyperthyroidism. They agreed to make a research recommendation to investigate the use of Vitamin D or vitamin D analogues to improve patient related outcomes in this group. Further information about the research recommendation can be found in Appendix N.

13 Anaemia

This section was updated and replaced in 2018. See www.nice.org.uk/guidance/NG203/evidence for the 2018 evidence reviews.

14 Oral bicarbonate supplements [2014]

14.1 Oral bicarbonate supplements in the management of metabolic acidosis in people with CKD

14.1.1 Introduction

Chronic metabolic acidosis is associated with increased protein catabolism, CKD-mineral and bone disorders, muscle wasting, chronic inflammation, impaired glucose homeostasis, impaired cardiac function, progression of CKD and increased mortality. The normal range of serum bicarbonate is 22-29mmol/l. The prevalence of metabolic acidosis, defined as a serum bicarbonate less than 21mmol/l, increases significantly as GFR declines below 45 ml/min/1.73 m^2 (Table 131). Treatment of acidosis by bicarbonate supplementation represents an attractive simple form of therapy. This idea is not new and was first mooted by Richard Bright in 1827, who postulated that oral sodium bicarbonate may protect the kidney and delay disease progression. However, it is still unclear if bicarbonate supplementation confers overall benefit. It has the potential to slow progression of CKD and improve nutritional status, but the concomitant sodium load might worsen blood pressure control and heart failure, thus adversely affecting outcome.

The chapter covers the use of oral bicarbonate supplements only, detailed advice on the management of metabolic acidosis is beyond the scope of this guideline.

Table 131: Prevalence of CKD Complications by GFR Category (modified from KDIGO CKD 2012)[91,166,194,219,387]

Complication	GFR Category (ml/min/1.73m²)					Reference
	≥90	60-89	45-59	30-44	<30	
Haemoglobin ≤110g/l	4.5	2.8	5.3	17.1	35.7	1[91]
Hypertension	47.1		71.4	86.6	87.8	2[387]
25(OH) D <15 µg/l (<37nmol/l)	14.1	9.1	10.7	27.2		3[219]
Serum bicarbonate <21 mmol/l	11.2	8.4	9.4	18.1	31.5	4[166]
Serum phosphate >1.5 mmol/l	7.2	7.4	9.2	9.3	23.0	4[166]
Serum albumin <35 g/l	1.0	1.3	2.8	9.0	7.5	4[166]
Parathyroid hormone >7.6 pmol/l	5.5	9.4	23.0	44.0	72.5	4[166]

Source: Reprinted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter., Suppl. 2013; 3: 1–150'

14.1.2 Review question: What is the clinical and cost effectiveness of oral bicarbonate supplements in the management of CKD?

For full details see review protocol in Appendix C.

Table 132: PICO characteristics of oral bicarbonate supplements review question

Population	Adults (aged 18 and over) with CKD **Subgroups:** Older people (≥75 years)

Intervention/s	Oral bicarbonate supplements
Comparison/s	Placebo or usual care
Outcomes	**Critical:** • Progression of CKD (measured by change in eGFR or creatinine clearance) • Progression of CKD (measured by occurrence of end stage kidney disease (ESRD or ESKD as reported by the study)) • All-cause mortality • Cardiovascular mortality • Hypertension (measured by use of antihypertensives) • Cardiovascular events (including chronic heart failure) **Important:** • Alkalosis • Nutritional status (measured by subjective global assessment) • Nutritional status (measured by change in BMI) • Hospitalisation • Health related quality of life
Study design	RCT or Systematic review Minimum duration of study 6 months
Analysis	See review protocol in Appendix C for details.

14.1.3 Clinical evidence

One Cochrane review was identified for oral bicarbonate supplements in the management of CKD.[350] It only found evidence in patients with end stage kidney disease on RRT (outside of the remit of the CKD scope) and so was excluded in this review.

Two randomised controlled trials were included in the review.[81,236] Evidence from these are summarised in the clinical GRADE evidence profile below (Table 134). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

Table 133: Summary of studies included in the review

Study	Intervention/ comparison	Population	Outcomes	Comments
de Brito-Ashurst et al. 2009[81]	Sodium bicarbonate. 600mg orally three times a day increased as necessary to maintain bicarbonate level ≥23 mmol/l. Mean 1.82 ± 0.8g/day Comparison: Standard care Duration: 2 years Note: 500mg is equivalent to 6mEq	Adults with stage 4-5 CKD (creatinine clearance 15-30ml/min/1.73 m^2); plasma bicarbonate <20 and >16mmol/l. n=134	Critical: Progression of CKD (measured by change in creatinine clearance) Progression of CKD (measured by occurrence of end stage kidney disease requiring RRT) Hypertension (measured by use of antihypertensives) Cardiovascular events (including chronic heart failure) Important: Hospitalisation	Dropouts: 17 people in control group due to rapid decline and reached ESRD between 6-12 months. No SD reported for creatinine clearance and 95% CI not symmetrical - unable to analyse. Alkalosis reported as bicarbonate levels in figure

Study	Intervention/ comparison	Population	Outcomes	Comments
				only – unable to extract values for analysis. Unclear method of randomisation and allocation concealment
Mahajan et al. 2010[236]	Sucrose + sodium bicarbonate tablets, each 10mEq. Dose 0.5mEq/kg lean body weight daily. Prescribed tablets to nearest half tablet (for example weight 70kg, dose 3.5 tablets). Comparison: Placebo Duration: 5 years Note: 500mg is equivalent to 6mEq	Adults with CKD (eGFR 60-90ml/min/1.73 m^2 by MDRD) n=80	Critical: Progression of CKD (measured by change in eGFR) Important: Alkalosis (venous total carbon dioxide) Note: this is equivalent to venous bicarbonate, normal reference range 24-32mmol/l)	Indirect population (63% Black American, 22% Hispanic). 349 people were consented, matched for age, eGFR, albuminuria and ethnicity into 3 groups of 40 each (3rd arm sodium chloride) Inadequate randomisation and allocation concealment

Table 134: Clinical evidence profile: Oral bicarbonate supplements versus placebo or usual care

Quality assessment							No of patients/ Mean (SD)		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Oral bicarbonate supplements	Placebo or usual care	Relative (95% CI)	Absolute	Quality	Importance
Progression of CKD (measured by change in eGFR) - eGFR (MDRD) at 5 years (better indicated by higher values)[236]												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	No serious imprecision	None	67.6 (4.9) n=37	64.0 (6.1) n=34	-	MD 3.6 higher (1.01 to 6.19 higher)	LOW	CRITICAL
Progression of CKD (measured by change in eGFR or creatinine clearance) - eGFR (CKD-EPI cystatin C) at 5 years (better indicated by higher values)[236]												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	No serious imprecision	None	66.4 (4.9) n=37	60.8 (6.3) n=34	-	MD 5.6 higher (2.96 to 8.24 higher)	LOW	CRITICAL
Progression of CKD (measured by end stage kidney disease)[81]												
1	Randomised trials	Serious (e)	No serious inconsistency	No serious indirectness	No serious imprecision	None	4/62 (6.5%)	32.8%	RR 0.2 (0.07 to 0.54)	262 fewer per 1000 (from 151 fewer to 305 fewer)	MODERATE	CRITICAL
Mortality (all-cause and cardiovascular) - not reported												
0	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Hypertension (measured by use of antihypertensives) - Worsening hypertension requiring increase in therapy at 2 years[81]												
1	Randomised trials	Serious (d,e)	No serious inconsistency	No serious indirectness	Serious (f)	None	41/67 (61.2%)	47.8%	RR 1.28 (0.94 to 1.76)	134 more per 1000 (from 29 fewer to 363 more)	LOW	CRITICAL
Cardiovascular events (including chronic heart failure) - Worsening oedema requiring increase in loop diuretics at 2 years[81]												
1	Randomised trials	Serious (d,e)	No serious inconsistency	No serious indirectness	Serious (f)	None	26/67 (38.8%)	29.9%	RR 1.3 (0.81 to	90 more per 1000 (from	LOW	CRITICAL

Quality assessment							No of patients/ Mean (SD)		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Oral bicarbonate supplements**	**Placebo or usual care**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
									2.09)	57 fewer to 326 more)		
Alkalosis - Venous total carbon dioxide (mM) at 5 years[236]												
1	Randomised trials	Serious (a)	No serious inconsistency	Serious (b)	Serious (f)	None	26.4(0.6) n=37	26.1(0.8) n=34	-	MD 0.3 higher (0.03 lower to 0.63 higher)	VERY LOW	IMPORTANT
Hospitalisation - Hospitalisation for congestive heart failure at 2 years[81]												
1	Randomised trials	Serious (d)	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/67 (0%)	0%	-	-	MODERATE	IMPORTANT

(a) Inadequate randomisation and allocation concealment. 349 people consented then matched according to age, eGFR, albuminuria and ethnicity into groups of 40 (3 arm trial, 120 people in total). Within each triplet group the person with the lowest identifying number was placebo, next highest sodium chloride and highest sodium bicarbonate.

(b) 63% population Black American and 23% Hispanic.

(c) Allocation concealment unclear. Missing data 5/67 (7.5%) of bicarbonate group, no reason reported. No missing data from control group, although 17 people in control group had rapid decline and reached ESRD (CrCl <10ml/min) between 6 and 12 months.

(d) Only percentages reported in study, assume ITT but other outcomes have missing data so unclear. Allocation concealment unclear.

(e) Unclear from methods if there was set guidance for treatment of hypertension or oedema.

(f) The confidence interval crosses the minimum important difference in one direction.

14.1.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

Unit costs

Table 135: Unit costs for oral bicarbonate supplements

			Dose per day	Cost per day	Cost per Year	Source of unit cost
Sodium bicarbonate	Capsule	Non-proprietary	1.8g	£ 0.21	£76.65	Drug Tariff December 2013

Note: The cost per day reported here was correct at the time recommendations were drafted; prices may have changed slightly by the time of publication.

14.1.5 Evidence statements

Clinical

- For CKD progression measured by change in eGFR (estimated by MDRD or CKD-EPI cystatin C equations) at 5years[236] low quality evidence suggested a possible small clinical benefit for bicarbonate compared to placebo. For ESRD requiring RRT at 2 years,[81] moderate quality evidence showed a clinical benefit for bicarbonate compared to placebo or standard care.
- Low quality evidence suggested that bicarbonate is potentially less clinically effective when compared to standard care at reducing hypertension (measured by use of antihypertensives) or oedema (measured by use of loop diuretics) at 2 years; however the uncertainty of these effects was too large to make clear conclusions about clinical harm.[81]
- No clinical difference was found for bicarbonate compared to placebo or standard care for alkalosis at 5 years[236] or hospitalisation for congestive heart failure at 2 years.[81]
- There were no studies that reported mortality, nutritional status (measured by subjective global assessment or change in BMI), or health related quality of life as an outcome measure.

Economic

- No relevant economic evaluations were identified.

14.1.6 Recommendations and link to evidence

Recommendations	The current recommendations can be found at www.nice.org.uk/guidance/ng203
Relative values of different outcomes	The GDG agreed that progression of CKD (measured by change in eGFR and end stage kidney disease requiring RRT), all-cause and cardiovascular mortality, hypertension (measured by use of antihypertensives) and cardiovascular events (including heart failure) were all critical to decision making. Alkalosis, nutrition status (measured by subjective global assessment and body mass index), hospitalisation and health related quality of life were considered as important.

	However, there were no studies identified that reported mortality, health related quality of life or nutritional status.
Trade-off between clinical benefits and harms	The management of acidosis with bicarbonate supplementation in people with CKD was not covered by the original 2008 CKD guideline. During the review for update process, undertaken in December 2011, oral bicarbonate interventions were raised as a relevant topic for consideration and hence included in the scope of the update guideline as a new area for review. Two trials were included in the review, one American (Mahajan et al) and one from the UK (de Brito-Ashurst) both of relatively recent publication (2009-10). The de Brito-Ashurst et al. 2009[81] study was in adults with stage 4-5 CKD over 2 years duration with n=134 people and the outcomes reported were progression of CKD, hypertension, cardiovascular events and hospitalisation. The Mahajan et al. 2010[236] study was over 5 years duration with n=80 people with stage 2 CKD but only reported outcomes of progression of CKD. The GDG noted that these studies included two very different populations; one group of people with CKD stage 2, proteinuria and hypertensive nephropathy (Mahajan et al. 2010[236]) and another group of people with CKD stage 4-5 (but people with poorly controlled blood pressure (>150/90mmHg) were excluded) (de Brito-Ashurst et al. 2009[81]). The GDG agreed that these were very different groups of patients and that the study results could not be pooled because of this. Furthermore, in the Mahajan et al study metabolic acidosis was not present, unsurprising given that the prevalence of acidosis only rises at GFR levels <45 mL/min/1.73m^2 (Table 129). In relation to the outcomes reported the GDG noted that: Progression of CKD - eGFR Both eGFR outcomes (MDRD and CKD-EPI cystatin C) were low quality. The changes in eGFR for MDRD were too small (less than 10%) to be clinically important, although for the CKD-EPI cystin C equation there was possibly a small clinical benefit to bicarbonate use compared to placebo.[236] Progression of CKD – ESRD requiring RRT Moderate quality evidence showed potential benefits in slowing progression of CKD in patients with moderately severe CKD, measured by renal replacement therapy requirement. The absolute difference was 262 fewer cases in the bicarbonate group per 1000 with a range of 151 to 305 fewer and a number needed to treat of 4. Cardiovascular events and Hypertension The only “cardiovascular event” reported was oedema (in one study, de Brito-Ashurst et al. 2009[81]), which was used as a surrogate for heart failure. The GDG questioned the validity of this assumption, although oedema is a sign of chronic heart failure oedema per se is not diagnostic of heart failure and is not normally considered a cardiovascular outcome. The consensus was that there was no valid evidence for any adverse cardiovascular events as a result of bicarbonate therapy. For hypertension there was a possible increase in antihypertensive therapy at 2 years in the people receiving bicarbonate compared to standard care, however there was uncertainty about clinical harm, allocation concealment was unclear and it was unclear from the methods if there was a protocol for treatment of hypertension.[81] Overall the GDG agreed that there was a lack of

	data to make a judgement concerning evidence of harm from the intervention.
Economic considerations	There were no published health economic evaluations. The GDG considered sodium bicarbonate supplementation for people with CKD stages 4 & 5 to be relatively cheap (about £0.21 per day - Table 135) and thought the potential longer term amelioration of progression of CKD could make this intervention cost effective. At that price it need only bring about a health gain equivalent to 0.004 QALYs per year for it to be considered cost-effective at a threshold of £20,000 per QALY gained.
Quality of evidence	The outcome measures were predominately judged to be of either low or very low quality. This was mainly because allocation concealment was unclear and or missing data was apparent. Only progression of CKD measured by end stage kidney disease requiring renal replacement therapy and hospitalisations were assessed as being of moderate quality. The GDG noted though that there were no events reported for hospitalisations in either arm of the study.[81] de Brito-Ashurst et al[81]reported change in CrCl at 2 years (mean 1.88ml/min in the bicarbonate group versus 5.93ml/min in control group). It did not, however, report standard deviations or standard errors, and the 95% confidence intervals were not symmetrical so further analysis was not possible. ANOVA detected a difference of 4.05ml/min/1.73 m^2 (95% confidence intervals 2.95-5.13; P<0.0001) between the two groups after adjustment for age and gender.
Other considerations	The GDG considered a possible research recommendation for people with CKD at high risk of progression, but noted that there is a large HTA trial of bicarbonate supplementation currently recruiting (population aged 65 years and over with stage 4-5 CKD and serum bicarbonate <22 mmol/l). The primary outcomes are physical function, quality of life, and bone and blood vessel health. The GDG were aware that nutritional status is usually assessed using a panel of measurements as there is no single ideal nutritional marker. The search protocol for this question was limited to subjective global assessment and body mass index as outcomes of nutritional status. The GDG noted that the studies included in this review also reported additional measurements of nutritional status and that these would be consistent with the recommendation made. The GDG debated the common misconception that bicarbonate levels are hard to measure in primary care. For more accurate values it is advised that blood should not be allowed to have contact with air as delays in processing of the sample would then lead to falsely low results. This is simply avoided by ensuring that blood is collected into a sealed bottle (for example a standard vacutainer) where it is reported that bicarbonate remains stable in whole blood for 24 hours at 25 degrees centigrade.[305]

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16 Acronyms and abbreviations [2014]

AASK trial	African American Study Of Kidney Diseases And Hypertension
ABLE	A Better Life through Education and Empowerment
ACE inhibitor	Angiotensin-converting enzyme inhibitor
ACR	Albumin:creatinine ratio
ACS	Acute coronary syndrome
ADPKD	Autosomal dominant polycystic kidney disease
AKI	Acute kidney injury
ALP	Alkaline phosphatase
AMPLIFY-EXT	Apixaban for Extended Treatment of Venous Thromboembolism
ARB	Angiotensin receptor blocker
ARIC	Atherosclerosis Risk in Communities
ARISTOTLE	Apixaban for Reduction In STroke and Other ThromboembоLic Events (in Atrial Fibrillation)
AUC	Area under the curve
AVERROES	Apixaban Versus Acetylsalicylic Acid to Prevent Stroke (in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment)
BMD	Bone mineral density
BMI	Body mass index
BNF	British National Formulary
BP	Blood pressure
CAD	Coronary artery disease
CARI	Caring for Australasians with Renal Impairment
CHS	Cardiovascular Health Studies
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CKD-MBD	CKD mineral and bone disorders
CKD-PC	Chronic Kidney Disease Prognosis Consortium
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance
CrCl	Creatinine clearance
CREDO	Clopidogrel for the Reduction of Events During Observation
CRF	Chronic renal failure
CRI	Chronic renal insufficiency
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Events
CV	Coefficient of variation
CVD	Cardiovascular disease
CysC	Cystatin C
DBP	Diastolic blood pressure
DMP	Disease management programme
DNCSG	Diabetic Nephropathy Collaborative Study Group
eGFR	Estimated glomerular filtration rate
ESKD	End-stage kidney disease

ESRD	End-stage renal disease
FN	False negative
FP	False positive
GDG	Guideline Development Group
GFR	Glomerular filtration rate
GUSTO (bleeding criteria)	Global Use of Strategies to Open Occluded Arteries
HDL	High-density lipoprotein
HF	Heart failure
HOT study	*Hypertension Optimal Treatment study*
HR	Hazard ratio
HYP	Hypertension
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IDMS	Isotope dilution mass spectrometry
IDNT	Irbesartan in Diabetic Nephropathy Trial
IgA-GN	Immunoglobulin-A glomerulonephritis
IPD	Individual patient data
iPTH	Intact parathyroid hormone
IQR	Interquartile range
IR	Incidence rate
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
KEEP	Kidney Early Evaluation Program
LDL	Low density lipoprotein
LDL-C	Low density lipoprotein cholesterol
LPD	Low protein diet
LVEF	Left ventricular ejection fraction
MAP	Mean arterial pressure
MDRD	Modification of Diet in Renal Disease
mGFR	Measured glomerular filtration rate
MI	Myocardial infarction
MID	Minimal important difference
NCC-CC	National Collaborating Centre for Chronic Conditions
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
NCGC	National Clinical Guideline Centre
NEOERICA	New Opportunities for Early Renal Intervention by Computerised Assessment
NHANES	National Health and Nutrition Examination Surveys
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NKF-KDOQI	National Kidney Foundation Kidney Disease Outcomes Quality Initiative
NNS	Number needed to screen
NNT	Number needed to treat
NOAC	New oral anticoagulants

NPV	Negative predictive value
NRI	Net reclassification index
NS	Non-significant
NSAIDs	Non-steroidal anti-inflammatory drugs
NSF	National service framework
NSTEACS	Non-ST-segment elevation acute coronary syndrome
OR	Odds ratio
P30	Percentage of estimated GFR values lying within 30% of the measured GFR
PCI	Percutaneous coronary intervention
PCR	Protein:creatinine ratio
PICO	Framework incorporating patients, interventions, comparisons and outcomes
PLATO	Platelet Inhibition and Patient Outcomes
PPV	Positive predictive value
PTH	Parathyroid hormone
pmp	Per million population
PREVEND	Prevention of Renal and Vascular Endstage Disease
QOF	Quality and Outcomes Framework
QALY	Quality-adjusted life year
RAAS	Renin-angiotensin-aldosterone system
RAS	Renin- angiotensin system antagonists
RBC	Red blood cells
RCT	Randomised controlled trial
REIN RCT	Ramipril Efficacy in Nephropathy RCT
RENAAL	Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan study
RIFLE	Risk Injury, Failure, Loss, End stage renal disease
RPV	Renal Patient View
ROC	Receiver-operator curve
ROCKET-AF	Rivaroxaban Once daily Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation
RR	Relative risk
RRT	Renal replacement therapy
SBP	Systolic blood pressure
SCr	Serum creatinine
SHARP	Study of Heart and Renal Protection
SIGN	Scottish Intercollegiate Guidelines Network
SLE	Systemic lupus erythematosus
STEACS	ST-segment elevation acute coronary syndrome
STEMI	ST-segment elevation myocardial infarction
TIMI (bleeding criteria)	Thrombolysis In Myocardial Infarction
TN	True negative
TP	True positive
UKPDS	UK Prospective Diabetes Study
VTE	Venous thromboembolism
WMD	Weighted mean difference

17 Glossary [2014]

17.1 Methodology specific

Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Adverse events	A harmful, and usually relatively rare, event arising from treatment.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in an RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Applicability	How well the results of a study or NICE evidence review can answer a clinical question or be applied to the population being considered.
Arm (of a clinical study)	Subsection of individuals within a study who receive one particular intervention, for example placebo arm.
Association	Statistical relationship between two or more events, characteristics or other variables. The relationship may or may not be causal.
Audit	See 'Clinical audit'.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Before-and-after study	A study that investigates the effects of an intervention by measuring particular characteristics of a population both before and after taking the intervention, and assessing any change that occurs.
Bias	Influences on a study that can make the results look better or worse than they really are. (Bias can even make it look as if a treatment works when it does not.) Bias can occur by chance, deliberately or as a result of systematic errors in the design and execution of a study. It can also occur at different stages in the research process, for example, during the collection, analysis, interpretation, publication or review of research data. For examples see selection bias, performance bias, information bias, confounding factor, and publication bias. (See also guideline specific definition of bias).
Blinding	A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The purpose of 'blinding' or 'masking' is to protect against bias. A single-blinded study is one in which patients do not know which study group they are in (for example whether they are taking the experimental drug or a placebo). A double-blinded study is one in which neither patients nor the researchers/doctors know which study group the patients are in. A triple blind study is one in which neither the patients, clinicians or the people carrying out the statistical analysis know which treatment patients received.
Carer (caregiver)	Someone who looks after family, partners or friends in need of help because they are ill, frail or have a disability.
Case–control study	A study to find out the cause(s) of a disease or condition. This is done by comparing a group of patients who have the disease or condition (cases) with a group of people who do not have it (controls) but who are otherwise as similar as possible (in characteristics thought to be unrelated to the causes of the disease or condition).
Case series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison

	(control) group of patients.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical audit	A quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change.
Clinical effectiveness	How well a specific test or treatment works when used in the 'real world' (for example, when used by a doctor with a patient at home), rather than in a carefully controlled clinical trial. Trials that assess clinical effectiveness are sometimes called management trials. Clinical effectiveness is not the same as efficacy.
Cochrane Review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).
Cohort study	A study with two or more groups of people - cohorts - with similar characteristics. One group receives a treatment, is exposed to a risk factor or has a particular symptom and the other group does not. The study follows their progress over time and records what happens. See also observational study.
Comorbidity	A disease or condition that someone has in addition to the health problem being studied or treated.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Concordance	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.
Confidence interval (CI)	A range of values for an unknown population parameter with a stated ‘confidence’ (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The ‘confidence’ value means that if the method used to calculate the interval is repeated many times, then that proportion of intervals will actually contain the true value.
Confounding factor	A factor that will distort the observed association between the disease and exposure under study if not controlled for in the study design.
Consensus methods	Techniques used to reach agreement on a particular issue. Consensus methods may be used to develop NICE guidance if there is not enough good quality research evidence to give a clear answer to a question. Formal consensus methods include Delphi and nominal group techniques.
Control group	A group of people in a study who do not receive the treatment or test being studied. Instead, they may receive the standard treatment (sometimes called 'usual care') or a dummy treatment (placebo). The results for the control group are compared with those for a group receiving the treatment being tested.
Cost–benefit analysis (CBA)	Cost-benefit analysis is one of the tools used to carry out an economic evaluation. The costs and benefits are measured using the same monetary units (for example, pounds sterling) to see whether the benefits exceed the costs.
Cost–consequences analysis (CCA)	Cost-consequence analysis is one of the tools used to carry out an economic evaluation. This compares the costs (such as treatment and hospital care)

	and the consequences (such as health outcomes) of a test or treatment with a suitable alternative. Unlike cost-benefit analysis or cost-effectiveness analysis, it does not attempt to summarise outcomes in a single measure (like the quality-adjusted life year) or in financial terms. Instead, outcomes are shown in their natural units (some of which may be monetary) and it is left to decision-makers to determine whether, overall, the treatment is worth carrying out.
Cost-effectiveness analysis (CEA)	Cost-effectiveness analysis is one of the tools used to carry out an economic evaluation. The benefits are expressed in non-monetary terms related to health, such as symptom-free days, heart attacks avoided, deaths avoided or life years gained (that is, the number of years by which life is extended as a result of the intervention).
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Cost–utility analysis (CUA)	Cost-utility analysis is one of the tools used to carry out an economic evaluation. The benefits are assessed in terms of both quality and duration of life, and expressed as quality-adjusted life years (QALYs). See also utility.
Credible Interval	The Bayesian equivalent of a confidence interval.
Decision analysis	An explicit quantitative approach to decision-making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Diagnostic study	Any research study aimed at evaluating the utility of a diagnostic procedure.
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Dominance	A health economics term. When comparing tests or treatments, an option that is both less effective and costs more is said to be 'dominated' by the alternative.
Drop-out	A participant who withdraws from a trial before the end.
Economic evaluation	An economic evaluation is used to assess the cost effectiveness of healthcare interventions (that is, to compare the costs and benefits of a healthcare intervention to assess whether it is worth doing). The aim of an economic evaluation is to maximise the level of benefits - health effects - relative to the resources available. It should be used to inform and support the decision-making process; it is not supposed to replace the judgement of healthcare professionals. There are several types of economic evaluation: cost-benefit analysis, cost-consequence analysis, cost-effectiveness analysis, cost-minimisation analysis and cost-utility analysis. They use similar methods to define and evaluate costs, but differ in the way they estimate the benefits of a particular drug, programme or intervention.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	A measure that shows the magnitude of the outcome in one group compared with that in a control group. For example, if the absolute risk reduction is shown to be 5% and it is the outcome of interest, the effect size is 5%.
Effectiveness	How beneficial a test or treatment is under usual or everyday conditions, compared with doing nothing or opting for another type of care.
Efficacy	How beneficial a test, treatment or public health intervention is under ideal conditions (for example, in a laboratory), compared with doing nothing or

	opting for another type of care.
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (for example, infection, diet) and interventions.
EQ-5D (EuroQol 5 dimensions)	A standardised instrument used to measure health-related quality of life. It provides a single index value for health status.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals or patients).
Evidence-based healthcare	The process of systematically finding, appraising, and using research findings as the basis for clinical decisions.
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Extended dominance	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore more cost effective and should be preferred, other things remaining equal.
Extrapolation	An assumption that the results of studies of a specific population will also hold true for another population with similar characteristics.
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Generalisability	The extent to which the results of a study hold true for groups that did not participate in the research. See also external validity.
Gold standard	A method, procedure or measurement that is widely accepted as being the best available to test for or treat a disease.
GRADE, GRADE Profile	A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.
Guideline development group (GDG)	An independent group set up on behalf of NICE to develop a guideline. They include healthcare professionals and patient and carer representatives.
Harms	Adverse effects of an intervention.
Hazard ratio (HR)	A statistic to describe the relative risk of complications due to treatment, based on a comparison of event rates.
Health economics	Study or analysis of the cost of using and distributing healthcare resources.
Health-related quality of life (HRQoL)	A measure of the effects of an illness to see how it affects someone's day-to-day life.
Heterogeneity	The term is used in meta-analyses and systematic reviews to describe when the results of a test or treatment (or estimates of its effect) differ significantly in different studies.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with

	different interventions.
Incremental cost	The extra cost linked to using one test or treatment rather than another. Or the additional cost of doing a test or providing a treatment more frequently.
Incremental cost-effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.
Incremental net benefit (INB)	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 x QALYs gained) – Incremental cost.
Indirectness	The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome).
Individual patient data (IPD) meta-analysis	A specific type of systematic review. Rather than extracting data from study publications, the original research data are sought directly from the researchers responsible for each study. These data can then be re-analysed centrally and combined, if appropriate, in meta-analyses. IPD reviews offer benefits related to the quality of data and the type of analyses that can be done. For this reason they are considered to be a 'gold standard' of systematic review.
Intention to treat analysis (ITT)	An assessment of the people taking part in a clinical trial, based on the group they were initially (and randomly) allocated to. This is regardless of whether or not they dropped out, fully complied with the treatment or switched to an alternative treatment.
Intervention	In medical terms this could be a drug treatment, surgical procedure, diagnostic or psychological therapy. Examples of public health interventions could include action to help someone to be physically active or to eat a more healthy diet.
Length of stay	The total number of days a participant stays in hospital.
Level of evidence	A code (e.g. 1++, 1+, 2++) linked to an individual study, indicating where it fits into the NICE hierarchy of evidence and how well it has adhered to recognised research principles.
Licence	See 'Product licence'.
Life years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Likelihood ratio	The likelihood ratio combines information about the sensitivity and specificity. It tells you how much a positive or negative result changes the likelihood that a patient would have the disease. The likelihood ratio of a positive test result (LR+) is sensitivity divided by (1 minus specificity).
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Meta-analysis	A method often used in systematic reviews. Results from several studies of the same test or treatment are combined to estimate the overall effect of the treatment.
Methodological limitations	Features of the design or reporting of a clinical study, which are known to be associated with risk of bias or lack of validity.
Minimal important difference (MID)	The smallest difference in score in the outcome of interest which patients perceive as beneficial and which would mandate, in the absence of troubling side effects and excessive cost, a change in the patient's management.
Multivariate model	A statistical model for analysis of the relationship between two or more predictor (independent) variables and the outcome (dependent) variable.

National Collaborating Centre for Chronic Conditions (NCC-CC)	A partnership of the Clinical Effectiveness Forum for Allied Health Professions, the NHS Confederation, the NICE Patient & Public Involvement Programme, the Royal College of General Practitioners, the Royal College of Nursing, the Royal College of Physicians of London, the Royal College of Physicians' Patient Involvement Unit, the Royal College of Surgeons of England, and the Royal Pharmaceutical Society of Great Britain. Set up in 2001 to undertake commissions from NICE to develop clinical guidelines for the NHS. The NCC-CC was combined with 3 other National Collaborating Centres in 2009 to create the National Clinical Guidelines Centre (NCGC).
National Clinical Guidelines Centre	The National Clinical Guideline Centre (NCGC) is a multi-disciplinary health services research team funded by the National Institute for Health and Care Excellence (NICE) to produce evidence based clinical practice guidelines on behalf of NICE.
Negative predictive value (NPV)	In screening or diagnostic tests: A measure of the usefulness of a screening or diagnostic test. It is the proportion of those with a negative test result who do not have the disease, and can be interpreted as the probability that a negative test result is correct. It is calculated as follows: NPV = TN/TN+FN
Number needed to treat (NNT)	The average number of patients who need to be treated to get a positive outcome. The closer the NNT is to one, the better the treatment.
Observational study	Individuals or groups are observed or certain factors are measured. No attempt is made to affect the outcome. Changes or differences in one characteristic (for example, whether or not people received a specific treatment or intervention) are studied without intervening. There is a greater risk of selection bias than in experimental studies.
Odds ratio	Odds are a way to represent how likely it is that something will happen (the probability). An odds ratio compares the probability of something in one group with the probability of the same thing in another. An odds ratio of 1 between two groups would show that the probability of the event is the same for both. An odds ratio greater than 1 means the event is more likely in the first group. An odds ratio less than 1 means that the event is less likely in the first group. See also confidence interval, relative risk.
Opportunity cost	The loss of other health care programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Outcome	The impact that anintervention has on a person, group or population. Researchers should decide what outcomes to measure before a study begins.
p-value	The p value is a statistical measure that indicates whether or not an effect is statistically significant. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance) it is considered that there probably is a real difference between treatments.
Placebo	A fake (or dummy) treatment given to participants in the control group of a clinical trial. It is indistinguishable from the actual treatment (which is given to participants in the experimental group). The aim is to determine what effect the experimental treatment has had - over and above any placebo effect caused because someone has received (or thinks they have received) care or attention.
Positive pre dictive value (PPV)	In screening or diagnostic tests: A measure of the usefulness of a screening or diagnostic test. It is the proportion of those with a positive test result who have the disease, and can be interpreted as the probability that a

	positive test result is correct. It is calculated as follows: PPV = TP/TP+FP
Power (statistical)	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Primary care	Healthcare delivered outside hospitals. It includes a range of services provided by GPs, nurses, health visitors, midwives and other healthcare professionals.
Primary outcome	The outcome of greatest importance, usually the one in a study that the power calculation is based on.
Product licence	An authorisation from the MHRA to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Prospective study	A research study in which the health or other characteristic of participants is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
Publication bias	Publication bias occurs when researchers publish the results of studies showing that a treatment works well and don't publish those showing it did not have any effect. This type of bias can be assessed by a funnel plot.
Quality of life	See 'Health-related quality of life'.
Quality-adjusted life year (QALY)	A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYS are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality of life score (on a zero to one scale). It is often measured in terms of the person's ability to perform the activities of daily life, freedom from pain and mental disturbance.
Randomisation	Assigning participants in a research study to different groups without taking any similarities or differences between them into account. Each individual (or each group in the case of cluster randomisation) has the same chance of receiving each intervention.
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to two (or more) groups to test a specific drug or treatment. One group (the experimental group) receives the treatment being tested, the other (the comparison or control group) receives an alternative treatment, a placebo or no treatment at all. The groups are followed up to see how effective the experimental treatment was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
Receiver operated characteristic (ROC) curve	A graphical method of assessing the accuracy of a diagnostic test. Sensitivity is plotted against 1 minus specificity. A perfect test will have a positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Relative risk (RR)	The ratio of the risk of disease or death among those exposed to certain conditions compared with the risk for those who are not exposed to the same conditions. If both groups face the same level of risk, the relative risk is 1. If the first

	group had a relative risk of 2, subjects in that group would be twice as likely to have the event happen. Relative risk is sometimes referred to as risk ratio.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Review question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Sample size	The number of participants included in a trial or intervention group.
Secondary outcome	An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.
Selection bias	Selection bias occurs if: a) The characteristics of the people selected for a study differ from the wider population from which they have been drawn, or b) There are differences between groups of participants in a study in terms of how likely they are to get better.
Sensitivity	How well a test detects the thing it is testing for. If a diagnostic test for a disease has high sensitivity, it is likely to pick up all cases of the disease in people who have it (that is, give a 'true positive' result). But if a test is too sensitive it will sometimes also give a positive result in people who don't have the disease (that is, give a 'false positive'). See related term 'Sensitivity'.
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study. Multi-way simple sensitivity analysis (scenario analysis): two or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example, Monte Carlo simulation).
Significance (statistical)	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p<0.05$).
Specificity	The proportion of true negatives that are correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases correctly diagnosed as non-cases. See related term 'Sensitivity'.
Stakeholder	An organisation with an interest in a topic that NICE is developing a clinical guideline or piece of public health guidance on. Organisations that register as stakeholders can comment on the draft scope and the draft guidance.
Systematic review	A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. It may include a meta-analysis.

Time horizon	The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.
Univariate	Analysis which separately explores each variable in a data set.
Utility	In health economics, a 'utility' is the measure of the preference or value that an individual or society places upon a particular health state. It is generally a number between zero (representing death) and one (perfect health). The most widely used measure of benefit in cost-utility analysis is the quality-adjusted life year, but other measures include disability-adjusted life years (DALYs) and healthy year equivalents (HYEs).
Withdrawal	When a trial participant discontinues the assigned intervention before completion of the study.

17.2 Guideline specific

Accuracy (Measurement of renal function)	See P30
Angiotensin converting enzyme (ACE) inhibitor	A drug that inhibits angiotensin-converting enzyme (ACE) which is important to the formation of angiotensin II. ACE inhibitors are used for blood pressure control and congestive heart failure.
Acute kidney injury (AKI)	Previously known as acute renal failure. This is wide spectrum of injury to the kidneys (not just failure) and is characterised by rapid loss of renal function.
Albuminuria	The presence of albumin in the urine.
Angiotensin receptor blocker (ARB)	A drug that blocks the activation of angiotensin II AT1 receptors which causes vasodilation, reduces secretion of vasopressin, and reduces production and secretion of aldosterone. ARBs are used for blood pressure control and congestive heart failure.
Antiplatelet	Drugs that decrease platelet aggregation and inhibit thrombus formation. These include aspirin, ticagrelor, clopidogrel and prasugrel. See also oral anticoagulants.
Bias (Measurement of kidney function)	The difference between estimates of GFR and the true value as measured by a reference technique. This is commonly described as the mean or median bias.
Chronic kidney disease	Abnormalities of kidney function and/or structure, present for more than three months, with implications for health.
CKD-mineral and bone disorders	A spectrum of disorders of mineral metabolism that occur in CKD and progress as kidney function decreases. It includes abnormalities of calcium, phosphorus, parathyroid hormone (PTH), and vitamin D metabolism which affect s bone modeling and remodeling and can result in vascular and soft tissue calcification.
Cystatin C	An endogenous marker used to estimate kidney function. Cystatin C is a low molecular weight protein produced by all nucleated cells and is normally removed from blood by the kidneys. As kidney disease progresses, the level of cystatin C in the blood increases.
Direct renin inhibitor	A drug that directly inhibits renin which is important to the formation of angiotensin I, the first and rate-limiting step of the renin-angiotensin-aldosterone system (RAAS). Direct renin inhibitors are licensed for the management of hypertension. Combination treatment with an ACE or ARB is not recommended.[181]
Glomerular disease	Includes membranous nephropathy, IgA nephropathy and focal segmental glomerulosclerosis and membranoproliferative glomerulosclerosis.
GUSTO bleeding criteria	The Global Use of Strategies to Open Occluded Arteries (GUSTO) definition of bleeding, used to identify significant bleeding: **Severe or life-threatening** • Intracerebral haemorrhage. • Resulting in substantial hemodynamic compromise requiring treatment. **Moderate** • Requiring blood transfusion but not resulting in hemodynamic compromise. **Mild** • Bleeding that does not meet above criteria.
Haematuria	The presence of blood in the urine; often a symptom of urinary tract disease.
Hyperfiltering	An elevation in the glomerular filtration rate.

Hyperkalaemia	Abnormally high potassium concentration in the blood, most often due to defective renal excretion, as in kidney disease.
Hyperparathyroidism	Over-activity of the parathyroid gland resulting in excess production of parathyroid hormone. (See CKD-MBD).
Hyperuricaemia	Abnormally high uric acid concentration in the blood resulting from either increased production or decreased excretion of uric acid.
Net reclassification index	A statistic that measures the improvement in prediction performance gained by assessing the relative rates of appropriate and inappropriate reclassification (with positive value indicating improvement).
Oral anticoagulants	Drugs that effect the clotting cascade to prevent the formation of fibrin and therefore inhibit thrombus formation. These include warfarin, dabigatran, apixaban and rivaroxaban. See also antiplatelets.
P30	The percentage of estimated GFR values lying within 30% of the measured GFR, used to evaluate accuracy.
Precision	The variability of the estimate of GFR compared to the measured value. Usually reported as wither the root mean square error (RMSE) of the regression of estimated GFR versus measured GFR or as the interquartile range (IQR) for the differences between estimated GFR and measured GFR.
Proteinuria	The presence of protein in the urine.
Renal Patient View	A secure internet based system that enables people with kidney disease who are attending specialist renal clinics to review their current information on-line, including diagnoses, blood results and prescribed medicines, and to view letters written about them. Within Renal Patient View there are also links to web-based information sources concerning medicines and diagnoses enabling patients to obtain a wealth of information about their kidney disease.
Renal replacement therapy (RRT)	Renal replacement therapy is a term used to encompass life-supporting treatments for severe AKI or end stage chronic kidney disease. It includes: haemodialysis, haemofiltration, peritoneal dialysis and renal transplantation.
Renin-angiotensin system antagonsists (RAS)	A drug that blocks or inhibits the renin angiotensin system including ACE inhibitors, angiotensin receptor blockers and direct renin inhibitors. This group of drugs does not include aldosterone antagonists.
Renin-angiotensin-aldosterone system antagonsists (RAAS)	A drug that blocks or inhibits the renin angiotensin-aldosterone system including ACE inhibitors, angiotensin receptor blockers, direct renin inhibitors and aldosterone antagonists.
RIFLE Classification	The Acute Dialysis Quality Initiative formulated the Risk, Injury, Failure, Loss, and End-stage Kidney (RIFLE) classification. RIFLE defines three grades of increasing severity of acute kidney injury– risk (class R), injury (class I) and failure (class F)–and two outcome classes (loss and end-stage kidney disease).
Serum creatinine	An endogenous marker used to estimate kidney function. Creatinine is derived from the muscles of the body and is normally removed from blood by the kidneys. As kidney disease progresses, the level of creatinine in the blood increases.
Suffix '(p)'	Used to denote the presence of proteinuria when staging CKD.
TIMI bleeding criteria	The Thrombolysis in Myocardial Infarction (TIMI) definition of bleeding, used to identify significant bleeding: **Major** • Any intracranial bleeding (excluding microhemorrhages <10 mm evident only on gradient-echo MRI). • Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dl.

	Fatal bleeding (bleeding that directly results in death within 7 days). **Minor** Clinically overt (including imaging), resulting in hemoglobin drop of 3 to <5 g/dl.