Appendix A2: Summary of new evidence from surveillance

Investigations for chronic kidney disease

Measuring kidney function

| 182-01 | What is the accuracy of equations to estimate GFR as a measurement of kidney function? |

Recommendations derived from this question

**Creatinine-based estimate of GFR**

1.1.1 Whenever a request for serum creatinine measurement is made, clinical laboratories should report an estimate of glomerular filtration rate (eGFRcreatinine) using a prediction equation (see recommendation 1.1.2) in addition to reporting the serum creatinine result. [2014]

1.1.2 Clinical laboratories should:

- use the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation to estimate GFRcreatinine, using creatinine assays with calibration traceable to standardised reference material
- use creatinine assays that are specific (for example, enzymatic assays) and zero-biased compared with isotope dilution mass spectrometry (IDMS)
- participate in a UK national external quality assessment scheme for creatinine. [new 2014]

For more information about implementing this recommendation, see implementation: getting started.

1.1.3 Apply a correction factor to GFR values estimated using the CKD-EPI creatinine equation for people of African-Caribbean or African family origin (multiply eGFR by 1.159). [new 2014]

**Cystatin C-based estimate of GFR**

1.1.6 Whenever a request for serum cystatin C measurement is made, clinical laboratories should report an estimate of glomerular filtration rate (eGFRcystatinC) using a prediction equation (see recommendation 1.1.7) in addition to reporting the serum cystatin C result. [new 2014]

1.1.7 When an improved assessment of risk is needed (see recommendation 1.1.14), clinical laboratories should use the CKD-EPI cystatin C equation to estimate GFRcystatinC. [new 2014]

1.1.8 Clinical laboratories should use cystatin C assays calibrated to the international standard to measure serum cystatin C for cystatin C-based estimates of GFR. [new 2014]

* 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).
Interpret eGFR\textsubscript{cystatinC} with caution in people with uncontrolled thyroid disease because eGFR\textsubscript{cystatinC} values may be falsely elevated in people with hypothyroidism and reduced in people with hyperthyroidism. [new 2014]

**Reporting and interpreting GFR values**

1.1.10 Clinical laboratories should report GFR either as a whole number if it is 90 ml/min/1.73 m\(^2\) or less, or as 'greater than 90 ml/min/1.73 m\(^2\)' [new 2014]

1.1.11 If GFR is greater than 90 ml/min/1.73 m\(^2\), use an increase in serum creatinine concentration of more than 20% to infer significant reduction in kidney function. [new 2014]

1.1.12 Interpret eGFR values of 60 ml/min/1.73 m\(^2\) or more with caution, bearing in mind that estimates of GFR become less accurate as the true GFR increases. [2014]

1.1.13 Confirm an eGFR result of less than 60 ml/min/1.73 m\(^2\) in a person not previously tested by repeating the test within 2 weeks. Allow for biological and analytical variability of serum creatinine (±5%) when interpreting changes in eGFR. [2008]

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

1.1.14 Consider using eGFR\textsubscript{cystatinC} at initial diagnosis to confirm or rule out CKD in people with:

- an eGFR\textsubscript{creatinine} of 45–59 ml/min/1.73 m\(^2\), sustained for at least 90 days and no proteinuria (albumin:creatinine ratio [ACR] less than 3 mg/mmol) or other marker of kidney disease. [new 2014]

For information about implementing this recommendation, see implementation: getting started.

1.1.15 Do not diagnose CKD in people with:

- an eGFR\textsubscript{creatinine} of 45–59 ml/min/1.73 m\(^2\) and
- an eGFR\textsubscript{cystatinC} of more than 60 ml/min/1.73 m\(^2\) and
- no other marker of kidney disease. [new 2014]

**When highly accurate measures of GFR are required**

1.1.16 Where a highly accurate measure of GFR is required – for example, during monitoring of chemotherapy and in the evaluation of renal function in potential living donors – consider a reference standard measure (inulin, 51Cr-EDTA, 125I-iothalamate or iohexol). [2008]

**Surveillance decision**

This review question should not be updated.

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**4-year surveillance summary**

**Serum cystatin C**

A systematic review\(^1\) (19 studies) found that serum cystatin C (sCysC) was an effective biomarker in the definition of CKD. However, its performance was different in subgroups restricted by clinical settings, race, and sCysC assay.

**Topic expert feedback**

No topic expert feedback was relevant to this evidence.

**Impact statement**

New evidence on serum cystatin C as a biomarker for CKD is consistent with recommendation 1.1.4, but further studies may be needed in specific subgroups to establish its value by clinical setting, race, and sCysC assay.

New evidence is unlikely to change guideline recommendations.
Appendix A2: summary of new evidence from 4-year surveillance of Chronic kidney disease in adults (2014) NICE guideline CG182

182-02 In adults with CKD, what is the biological and analytical variability in eGFR testing and what factors (including fasting) affect it?

1.1.4 In people with extremes of muscle mass – for example, in bodybuilders, people who have had an amputation or people with muscle wasting disorders – interpret eGFRcreatinine with caution. (Reduced muscle mass will lead to overestimation and increased muscle mass to underestimation of the GFR.) [2008]

1.1.5 Advise people not to eat any meat in the 12 hours before having a blood test for eGFRcreatinine. Avoid delaying the despatch of blood samples to ensure that they are received and processed by the laboratory within 12 hours of venepuncture. [2008]

**Surveillance decision**

No new information was identified at any surveillance review.

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182-03 What is the sensitivity and specificity of reagent strips for detecting protein and blood in urine?

**Proteinuria**

1.1.17 Do not use reagent strips to identify proteinuria unless they are capable of specifically measuring albumin at low concentrations and expressing the result as an ACR. [2008]

**Surveillance decision**

No new information was identified at any surveillance review.

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182-04 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?

1.1.18 To detect and identify proteinuria, use urine ACR in preference to protein:creatinine ratio (PCR), because it has greater sensitivity than PCR for low levels of proteinuria. For quantification and monitoring of levels of proteinuria of ACR 70 mg/mmol or more, PCR can be used as an alternative. ACR is the recommended method for people with diabetes. [2008, amended 2014]

1.1.19 For the initial detection of proteinuria, if the ACR is between 3 mg/mmol and 70 mg/mmol, this should be confirmed by a subsequent early morning sample. If the initial ACR is 70 mg/mmol or more, a repeat sample need not be tested. [2008, amended 2014]

1.1.20 Regard a confirmed ACR of 3 mg/mmol or more as clinically important proteinuria. [2008, amended 2014]

1.1.21 Quantify urinary albumin or urinary protein loss as in recommendation 1.1.18 for:

- people with diabetes
• people without diabetes with a GFR of less than 60 ml/min/1.73 m². [2008, amended 2014]

1.1.22 Quantify by laboratory testing the urinary albumin or urinary protein loss of people with a GFR of 60 ml/min/1.73 m² or more if there is a strong suspicion of CKD (see also recommendation 1.1.28). [2008]

**Haematuria**

1.1.23 When testing for the presence of haematuria, use reagent strips rather than urine microscopy.

• Evaluate further if there is a result of 1+ or more.

• Do not use urine microscopy to confirm a positive result. [2008]

**Managing isolated invisible haematuria**

1.1.24 When there is the need to differentiate persistent invisible haematuria in the absence of proteinuria from transient haematuria, regard 2 out of 3 positive reagent strip tests as confirmation of persistent invisible haematuria. [2008]

1.1.25 Persistent invisible haematuria, with or without proteinuria, should prompt investigation for urinary tract malignancy in appropriate age groups. [2008]

1.1.26 Persistent invisible haematuria in the absence of proteinuria should be followed up annually with repeat testing for haematuria (see recommendations 1.1.24 and 1.1.25), proteinuria or albuminuria, GFR and blood pressure monitoring as long as the haematuria persists. [2008]

**Surveillance decision**

No new information was identified at any surveillance review.

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### Markers of Kidney damage

**182-05 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?**

**Recommendations derived from this question**

The same recommendations as in review question 182-01 were derived from this question.

**Surveillance decision**

This review question should be updated.

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### 4-year surveillance summary

**Kidney failure risk equations**

A secondary analysis² (n=595) of a randomised controlled trial (RCT) found that the kidney failure risk equation (KFRE) accurately predicted the progression to kidney failure in European CKD patients, and calibrated slightly more accurately than two simpler models to ascertain the 5-year kidney failure. However, the authors noted that the KFRE is a more complex model which may offset its greater accuracy.

An individual patient data meta-analysis³ (n=721,357) of people with stage 3-5 CKD evaluated the accuracy of kidney failure risk equations, including factors such as age, sex, estimated glomerular filtration rate (eGFR), and calcium and phosphate concentrations. Cohort
specific hazard ratios and overall c-statistics were calculated. The equations originally developed in a Canadian population, also known as the Tangri score, showed high discrimination and adequate calibration when validated in 31 multinational cohorts. However, in some regions the addition of a calibration factor was found to be necessary.

**Serum uric acid**

A systematic review (24 studies n=25,453) found that elevated serum uric acid levels were significantly associated with risk of mortality in patients with CKD. Further RCTs were recommended to determine whether it improves survival to target serum uric acid in patients with CKD.

**p-Cresyl sulfate (PCS) and Indoxyl sulfate (IS)**

A systematic review (11 studies, n=1572) found that elevated levels of PCS and IS were associated with increased mortality in patients with CKD, while PCS, but not IS, was associated with an increased risk of cardiovascular events.

**Topic expert feedback**

Topic expert feedback indicated that the Tangri score is accurate in predicting end stage renal disease (ESRD) with high discrimination. It was considered by the topic expert to have a role in patient decision making and prognostication. A study was cited that is included in the 4-year surveillance summary.

Topic expert feedback further indicated that the equations have the potential to be used in primary and secondary care. In primary care, lower-risk patients could be managed without additional testing or treatment of CKD complications, whereas higher-risk patients could receive more intensive testing and early intervention.

However, the limitations of the model restrict its clinical value, and further evaluation and refinement may be necessary before implementation. For instance, the equations cannot be used currently to predict risk among those with mild impairment in kidney function, because these patients were not included in the model. Additionally the equations only predict risk over 2 or 5 years, which may restrict applicability, because the pattern of decline varies among patients. Topic expert feedback also highlighted that the equations cannot predict the risk of cardiovascular disease or death, and require validation in people with mild kidney disease.

Topic expert feedback also highlighted the ongoing eGFR-C study as having potential relevance to the guideline recommendations, although this study does not have an estimated publication date.

**Impact statement**

**Kidney failure risk equations**

NICE guideline CG182 does not include recommendations for the use of risk equations in assessing risk of progression for people already diagnosed with CKD. New evidence and topic expert feedback supports the use of the Tangri risk equation in predicting ESRD in CKD patients, and has a potential impact on recommendations 1.2.1-1.2.4 and Table 1, to review the advice for determining the risk of progression and adverse outcomes.

Further studies may be required on the KFRE to establish a definite impact on the guideline recommendations. The new evidence based on RCT data from one study, which indicates the higher accuracy but greater complexity of the KFRE, may require further studies to validate its use in predicting CKD progression to kidney failure.

**Prognostic biomarkers**

Further studies may be needed on the following prognostic biomarkers for CKD progression, for which new evidence is inconclusive, particularly in specific subgroups, to establish an impact on the guideline:

- serum cystatin C
- serum uric acid
- p-Cresyl sulfate
- indoxyl sulfate

The ongoing eGFR-C study will be monitored for publication and the impact of its results will be considered at a future surveillance review point.

**New evidence identified that may change current recommendations.**
Classification of CKD

182-06 For people with suspected CKD, what is the effect of proteinuria at any given eGFR on adverse outcomes?

Recommendations derived from this question

1.2.1 Classify CKD using a combination of GFR and ACR categories (as described in table 1). Be aware that:

- increased ACR is associated with increased risk of adverse outcomes
- decreased GFR is associated with increased risk of adverse outcomes
- increased ACR and decreased GFR in combination multiply the risk of adverse outcomes.

[new 2014]

For information about implementing this recommendation, see implementation: getting started.

Table 1 Classification of chronic kidney disease using GFR and ACR categories
<table>
<thead>
<tr>
<th>GFR categories (ml/min/1.73 m²)</th>
<th>ACR categories (mg/mmol), description and range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;3 Normal to mildly increased</td>
</tr>
<tr>
<td>≥90 Normal and high</td>
<td>A1</td>
</tr>
<tr>
<td>60–89 Mild reduction related to normal range for a young adult</td>
<td>G1</td>
</tr>
<tr>
<td>45–59 Mild–moderate reduction</td>
<td>G2</td>
</tr>
<tr>
<td>30–44 Moderate–severe reduction</td>
<td>G3a</td>
</tr>
<tr>
<td>15–29 Severe reduction</td>
<td>G3b</td>
</tr>
<tr>
<td>&lt;15 Kidney failure</td>
<td>G4</td>
</tr>
</tbody>
</table>

1 Consider using eGFRcystatinC for people with CKD G3aA1 (see recommendations 1.1.14 and 1.1.15)

Abbreviations: ACR, albumin:creatinine ratio; CKD, chronic kidney disease; GFR, glomerular filtration rate


1.2.2 Do not determine management of CKD solely by age. [new 2014]
1.2.4 Use the person’s GFR and ACR categories (see table 1) to indicate their risk of adverse outcomes (for example, CKD progression, acute kidney injury, all-cause mortality and cardiovascular events) and discuss this with them. [new 2014]

**Surveillance decision**
This review question should be updated.

Appendix A2: summary of new evidence from 4-year surveillance of Chronic kidney disease in adults: assessment and management (2014) NICE guideline CG182
4-year surveillance summary
A systematic review (40 studies, n=318,898) found that male sex and substantial proteinuria were significant risk factors for the progression from late stage CKD to ESRD, and diabetes played a minor role for the outcome of ESRD among patients with later stages of CKD. Substantial proteinuria was not defined in the abstract, however, which limits the strength of the findings.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The new systematic review evidence indicating that substantial proteinuria is a significant risk factor for progression from late stage CKD to ESRD is consistent with guideline recommendations 1.2.1 and 1.2.4 for the classification and risk of adverse outcomes of CKD. These advise using the person's GFR and ACR categories in table 1 to indicate their risk of adverse outcomes. However, the new evidence did not define substantial proteinuria in the abstract, which limits any potential assessment against the categories in table 1.

New evidence and topic expert feedback highlighted in question 182-05 supports the use of the Tangri risk equation in predicting ESRD in CKD patients, and has a potential impact on recommendations 1.2.1-1.2.4 and Table 1, to review the advice for determining the risk of progression and adverse outcomes.

New evidence identified that may change current recommendations.

182-07 In adults, who should be tested for CKD?

Recommendations derived from this question

1.1.27 Monitor GFR at least annually in people prescribed drugs known to be nephrotoxic, such as calcineurin inhibitors (for example, cyclosporin or tacrolimus), lithium and non-steroidal anti-inflammatory drugs (NSAIDs). [2008, amended 2014]

1.1.28 Offer testing for CKD using eGFRcreatinine and ACR to people with any of the following risk factors:

- diabetes
- hypertension
- acute kidney injury (see recommendation 1.3.9)
- cardiovascular disease (ischaemic heart disease, chronic heart failure, peripheral vascular disease or cerebral vascular disease)
- structural renal tract disease, recurrent renal calculi or prostatic hypertrophy
- multisystem diseases with potential kidney involvement – for example, systemic lupus erythematosus
- family history of end-stage kidney disease (GFR category G5) or hereditary kidney disease
- opportunistic detection of haematuria. [new 2014]

1.1.29 Do not use age, gender or ethnicity as risk markers to test people for CKD. In the absence of metabolic syndrome, diabetes or hypertension, do not use obesity alone as a risk marker to test people for CKD. [2008, amended 2014]
Appendix A

2: summary of new evidence from 4-year surveillance of Chronic kidney disease in adults: assessment and management (2014) NICE guideline CG182

**Surveillance decision**

This review question should not be updated.

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**4-year surveillance summary**

*Elevated serum uric acid and hyperuricemia*

A systematic review\(^7\) (13 studies, n=190,718) found a significant positive association between elevated serum uric acid levels and new-onset CKD at follow-up. Hyperuricemia was found to be an independent predictor for the development of newly diagnosed CKD in non-CKD patients.

*Socioeconomic status*

A systematic review\(^8\) (35 studies, n=3,632,531 participants, 832,948 CKD cases) found that low socioeconomic status (SES) was associated with low eGFR, high albuminuria and renal failure, irrespective of how SES was measured. Variations in the strength of associations were related to the level of covariate adjustment for low eGFR and high albuminuria.

*Cardiovascular and cerebrovascular risk*

A systematic review\(^9\) (16 studies, n=315,321) found that prehypertension and hypertension, were independent predictors of decreased GFR in the general population, with the effect being more pronounced in the elderly. However, it should be noted that the authors did not report the proportion of participants with CKD.

A systematic review\(^10\) (7 studies n=261,264) found that compared with the optimal blood pressure values, prehypertension showed an increased risk of CKD. Gender and ethnic differences were exhibited in this association, however, and the findings may not be applicable to the UK population.

*Diabetes and prediabetes*

A systematic review\(^11\) (9 studies, n=185,452) found that, after adjustment for established risk factors, prediabetes was modestly associated with an increase in chronic kidney disease risk.

**Topic expert feedback**

Topic expert feedback highlighted new data\(^12\) on risk prediction using eGFR and ACR from the CKD Prognosis Consortium but indicated that this is unlikely to change guideline recommendations.

Additional topic expert feedback stated that whilst it is recognised that SES is associated with an increased risk of CKD (as per most vascular diseases) it is a relatively small association and does not warrant formally testing purely on the basis of SES. The feedback also stated there are several factors on the causal pathway for SES and CKD which are indicated for testing, such as type 2 diabetes and hypertension, as listed in guideline recommendation 1.1.28.

Topic expert feedback indicated that that the association between uric acid and new onset CKD may not be causal, and that uric acid is not widely measured in practice. It was felt that intervention studies to lower uric acid in CKD patients, as recommended in research recommendation 3.4, remain the main research priority.

**Impact statement**

*Elevated serum uric acid and hyperuricemia*

The new systematic review evidence indicates the predictive value of elevated serum uric acid levels and hyperuricemia as risk factors for the development of newly diagnosed CKD. However, topic expert feedback indicated that the association may not be causal, and that uric acid is not widely measured in practice. Intervention studies to lower uric acid in CKD patients are recommended in research recommendation 3.4.

The new evidence is therefore unlikely to impact on recommendation 1.1.28.

*Socioeconomic status*

In the development of the guideline, the guideline committee did not consider the evidence about lower socioeconomic status strong enough to recommend that people in this groups should be tested for CKD.

The new systematic review evidence indicates that low SES may be an independent risk factor for CKD symptoms but is unlikely to impact on recommendation 1.1.28. This is because topic expert feedback indicates that SES in isolation does not warrant testing, and that there are several other recommended risk factors on the causal pathway for SES and CKD which are indicated for testing, such as type 2 diabetes and hypertension.
Cardiovascular and cerebrovascular risk

The new systematic review and RCT evidence relating to CKD and cardiovascular risk factors is consistent with recommendation 1.1.28 which lists cardiovascular disease as one of several risk factors to trigger testing.

Prediabetes

The new systematic review evidence indicating that prediabetes may be a risk factor for chronic kidney disease is broadly consistent with recommendation 1.1.28, which lists diabetes as a risk factor. Further research may be needed to establish prediabetes, as distinct from diabetes, as a definite risk factor warranting testing for CKD.

New evidence is unlikely to impact on the guideline.

182-08 For people with CKD, does the presence of diabetes have an effect on adverse outcomes at any given category of eGFR and ACR?

Investigating the cause of CKD and determining the risk of adverse outcomes

Recommendations derived from this question

1.2.3 Agree a plan to establish the cause of CKD during an informed discussion with the person with CKD, particularly if the cause may be treatable (for example, urinary tract obstruction, nephrotoxic drugs or glomerular disease). [new 2014]

Surveillance decision

No new information was identified at any surveillance review.

182-09 For people with CKD, does the presence of hypertension have an effect on adverse outcomes at any given category of eGFR and ACR?

Recommendations derived from this question

1.2.3 Agree a plan to establish the cause of CKD during an informed discussion with the person with CKD, particularly if the cause may be treatable (for example, urinary tract obstruction, nephrotoxic drugs or glomerular disease). [new 2014]

Surveillance decision

No new information was identified at any surveillance review.
For people with CKD, does the presence of glomerular disease have an effect on adverse outcomes at any given category of eGFR and ACR?

Recommendations derived from this question
1.2.3 Agree a plan to establish the cause of CKD during an informed discussion with the person with CKD, particularly if the cause may be treatable (for example, urinary tract obstruction, nephrotoxic drugs or glomerular disease). [new 2014]

Surveillance decision
No new information was identified at any surveillance review.

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

Recommendations derived from this question
1.2.3 Agree a plan to establish the cause of CKD during an informed discussion with the person with CKD, particularly if the cause may be treatable (for example, urinary tract obstruction, nephrotoxic drugs or glomerular disease). [new 2014]

Surveillance decision
No new information was identified at any surveillance review.

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

Recommendations derived from this question (no questions made in guideline)

Indications for renal ultrasound

1.2.5 Offer a renal ultrasound scan to all people with CKD who:
   - have accelerated progression of CKD (see recommendation 1.3.3)
   - have visible or persistent invisible haematuria
   - have symptoms of urinary tract obstruction
   - have a family history of polycystic kidney disease and are aged over 20 years
   - have a GFR of less than 30 ml/min/1.73m2 (GFR category G4 or G5)
   - are considered by a nephrologist to require a renal biopsy. [2008, amended 2014]

1.2.6 Advise people with a family history of inherited kidney disease about the implications of an abnormal result before a renal ultrasound scan is arranged for them. [2008]
Surveillance decision
No new information was identified at any surveillance review.

Frequency of Monitoring

| 182-013 | How frequently should eGFR, ACR or PCR be monitored in people with CKD? |

Recommendations derived from this question

1.3.1 Agree the frequency of monitoring (eGFRcreatinine and ACR) with the person with, or at risk of, CKD; bear in mind that CKD is not progressive in many people. [new 2014]

1.3.2 Use table 2 to guide the frequency of GFR monitoring for people with, or at risk of, CKD, but tailor it to the person according to:

- the underlying cause of CKD
- past patterns of eGFR and ACR (but be aware that CKD progression is often non-linear)
- comorbidities, especially heart failure
- changes to their treatment (such as renin–angiotensin–aldosterone system [RAAS] antagonists, NSAIDs and diuretics)
- intercurrent illness
- whether they have chosen conservative management of CKD. [new 2014]
### Surveillance decision

No new information was identified at any surveillance review.

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Appendix A2: summary of new evidence from 4-year surveillance of Chronic kidney disease in adults: assessment and management (2014) NICE guideline CG182
Defining progression

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

Recommendations derived from this question

1.3.3 Define accelerated progression of CKD as:
- a sustained decrease in GFR of 25% or more and a change in GFR category within 12 months or
- a sustained decrease in GFR of 15 ml/min/1.73m² per year. [new 2014]

1.3.4 Take the following steps to identify the rate of progression of CKD:
- Obtain a minimum of 3 GFR estimations over a period of not less than 90 days.
- In people with a new finding of reduced GFR, repeat the GFR within 2 weeks to exclude causes of acute deterioration of GFR – for example, acute kidney injury or starting renin–angiotensin system antagonist therapy. [2008, amended 2014]

1.3.5 Be aware that people with CKD are at increased risk of progression to end-stage kidney disease if they have either of the following:
- a sustained decrease in GFR of 25% or more over 12 months or
- a sustained decrease in GFR of 15 ml/min/1.73m² or more over 12 months. [2008, amended 2014]

1.3.6 When assessing CKD progression, extrapolate the current rate of decline of
- GFR and take this into account when planning intervention strategies,
- particularly if it suggests that the person might need renal replacement therapy in their lifetime. [2008, amended 2014]

Surveillance decision

This review question should be updated.

4-year surveillance summary

Decline in estimated GFR

An individual patient data meta-analysis\(^\text{13}\) (n=1.7 million) examined the association of decline in estimated GFR with subsequent progression to ESRD with implications for using lesser declines in estimated GFR as potential alternative end points for CKD progression. Results showed that smaller declines in estimated GFR occurred more commonly and were strongly and consistently associated with the risk of ESRD and mortality, supporting consideration of lesser declines in estimated GFR (such as a 30% reduction over 2 years) as an alternative end point for CKD progression. The results are based on a default of 2 year follow-up but sensitivity analysis was conducted at 1 and 3 years. The hazard ratios for lesser declines were significant for 1, 2 and 3 years for ESRD and all-cause mortality.

Topic expert feedback

Topic expert feedback indicated that the standard annual review in clinical practice fits with recommended 1 year follow up, as distinct
from a 2 or 3 year follow up. However, additional topic expert feedback highlighted that CKD is a long-term condition, and that definitions of progression that are easy to apply in practice over a longer time period are needed.

The finding that a 30% change over 2 years is associated with a 5-fold increase in risk of ESRD was considered by topic experts to be very significant. It was considered that this has the potential to capture patients at high risk of ESRD who are likely to benefit from earlier referral and will not be highlighted as such currently.

Further expert feedback highlighted a limitation of the guideline, which risks missing patients who decline by successive increments just below the currently recommended annual threshold. These patients could benefit from specialist review. A review of the current description of accelerated progression, which uses comparison of annual blood tests rather than trends over longer periods, was also suggested.

Additional topic expert feedback indicated that:

- The rate of decline should be 30% over 2 years to a threshold of less than 60 ml/min/1.73m², as distinct from 100 to 70 ml/min/1.73m², as even the CKD Epidemiology Collaboration (CKD-EPI) creatine equation has considerable imprecision above a GFR of 60 ml/min/1.73m².
- The smaller the rate of decline that is set to define progression the higher the sensitivity and the lower the specificity. The imprecision arises from the non-linear nature of CKD progression and the impact of related events, such as acute kidney injury.
- A rate of decline over a longer period may also affect other health parameters aside from CKD progression, such as cardiovascular complications and morbidity. It was suggested that incorporating a revised rate of decline into the guideline could complement the use of the Tangri score (see question 182-05).

**Impact statement**

The new evidence, based on a very large data set, highlights the potential value of smaller declines to indicate CKD progression over 1, 2 and 3 years. This is partly consistent with recommendation 1.3.5, which defines increased risk of progression to ESRD as a sustained decrease in GFR of 25% or more over 12 months. The evidence reviewed for CG182 showed that a sustained drop in eGFR of 25% or a sustained drop of 15 ml/min/1.73 m² over the period of a year was associated with an increased risk of mortality and progression to end stage kidney disease. There was more uncertainty of risk of progression with smaller declines in eGFR and over longer periods.

The new evidence and topic expert feedback indicates a potential impact on the recommendation, to consider definitions of progression over a longer time period that are easy to apply in practice.

**New evidence identified that may change current recommendations.**

### Risk factors associated with CKD progression

| 182-015 | 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? |

**Recommendations derived from this question**

1.3.7 Work with people who have any of the following risk factors for CKD progression to optimise their health:

Appendix A2: summary of new evidence from 4-year surveillance of Chronic kidney disease in adults: assessment and management (2014) NICE guideline CG182
- cardiovascular disease
- proteinuria
- acute kidney injury
- hypertension
- diabetes
- smoking
- African, African-Caribbean or Asian family origin
- chronic use of NSAIDs
- untreated urinary outflow tract obstruction. [new 2014]

1.3.8 In people with CKD the chronic use of NSAIDs may be associated with progression and acute use is associated with a reversible decrease in GFR. Exercise caution when treating people with CKD with NSAIDs over prolonged periods of time. Monitor the effects on GFR, particularly in people with a low baseline GFR and/or in the presence of other risks for progression. [2008]

**Surveillance decision**

This review question should not be updated.

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**4-year surveillance summary**

**Cardiovascular disease and stroke**

A systematic review\(^4\) (83 studies, 63 cohort studies n=2,085,225 participants, and 20 RCTs n=168,516) found that there was an inverse linear relationship between GFR and risk of stroke, with the risk increasing linearly and additively with declining GFR and increasing albuminuria.

An IPD meta-analysis\(^12\) (n=637,315) assessed the addition of creatinine-based eGFR and albuminuria to traditional risk factors for prediction of cardiovascular risk in CKD patients. Results indicated that the simultaneous assessment of eGFR and ACR could facilitate improved classification of cardiovascular risk.

Two systematic reviews\(^15,16\) (98 studies and 23 studies) of patients with CKD, both with and without suspected acute coronary syndrome, found that elevated troponin levels were associated with worse prognosis. However, the diagnostic utility was limited by varying estimates of sensitivity and specificity.

A post hoc analysis of an RCT\(^17\) (n=237) of CKD patients found that high eGFR variability was significantly associated with the primary end point of first event of ESRD, as well as hypertension, high proteinuria, low baseline eGFR and steep eGFR slope.

A systematic review\(^18\) (26 studies, n=1,986,850) found that decreased baseline eGFR was independently associated with increased future myocardial infarction, and the risk increased with advanced renal insufficiency.

A systematic review\(^19\) (19 studies) found that the presence of CKD in patients with atrial fibrillation was associated with an almost 50% increased thromboembolic risk, which was decreased with appropriate antithrombotic therapy. Further prospective studies were recommended by the authors to better evaluate anticoagulation in patients with severe CKD.

**Topic expert feedback**

No topic expert feedback was relevant to this evidence.

**Impact statement**

The new evidence on cardiovascular risk factors for the progression of CKD is consistent with recommendation 1.3.7, to work with people who have cardiovascular disease to optimise their health.
**Acute kidney injury and CKD**

**182-016** What is the risk of developing and/or progression of CKD after an episode of AKI?

**Recommendations derived from this question**

1.3.9 Monitor people for the development or progression of CKD for at least 2–3 years after acute kidney injury, even if serum creatinine has returned to baseline. [new 2014]

1.3.10 Advise people who have had acute kidney injury that they are at increased risk of CKD developing or progressing. [new 2014]

**Surveillance decision**

No new information was identified at any surveillance review.

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**Information and education**

**182-017** 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?

**Recommendations derived from this question**

1.4.1 Offer people with CKD education and information tailored to the severity and cause of CKD, the associated complications and the risk of progression. [2008]

1.4.2 When developing information or education programmes, involve people with CKD in their development from the outset. The following topics are suggested.

- What is CKD and how does it affect people?
- What questions should people ask about their kidneys?
- What treatments are available for CKD, what are their advantages and disadvantages and what complications or side effects may occur as a result of treatment/medication?
- What can people do to manage and influence their own condition?
- In what ways could CKD and its treatment affect people’s daily life, social activities, work opportunities and financial situation, including benefits and allowances available?
- How can people cope with and adjust to CKD and what sources of psychological support are available?
• When appropriate, offer information about renal replacement therapy (such as the frequency and length of time of dialysis treatment sessions or exchanges and preemptive transplantation) and the preparation required (such as having a fistula or peritoneal catheter).

• Conservative management and when it may be considered. [2008]

1.4.3 Offer people with CKD high-quality information or education programmes as appropriate to the severity of their condition to allow time for them to fully understand and make informed choices about their treatment. [2008]

1.4.4 Healthcare professionals providing information and education programmes should ensure they have specialist knowledge about CKD and the necessary skills to facilitate learning. [2008]

1.4.5 Healthcare professionals working with people with CKD should take account of the psychological aspects of coping with the condition and offer access to appropriate support – for example, support groups, counselling or a specialist nurse. [2008]

**Surveillance decision**

This review question should not be updated.

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**4-year surveillance summary**

**Educational interventions**

An RCT\(^2\) (n=436) found that an intervention to provide tailored information and telephone-guided access to community support was associated with modest but significant improvements in health related quality of life and better maintenance of blood pressure control for patients with stage 3 CKD compared with usual care. The authors recommended further research to identify the mechanisms of action of the intervention.

A systematic review\(^2\) (26 studies, n=5403) evaluated educational interventions for primary and secondary prevention of CKD. Characteristics of effective interventions included:

- teaching sessions that were interactive
- workshops/practical skills
- integrated negotiated goal setting
- groups of patients, their families, and a multidisciplinary team.
- frequent (weekly or monthly) participant and educator encounters.

**Patient and caregiver perspectives**

A systematic review\(^2\) (26 studies, n=711) aimed to describe patients’ and caregivers’ perspectives on conservative treatment and end-of-life care in CKD. Five themes were identified: invasive suffering (bodily deterioration, loss of freedom and independence, unyielding fatigue and pain, resignation, treatment burden and harm, financial strain, personal vulnerability (imminence of death, misunderstanding and judgment, autonomy and dignity, medical abandonment, trust and safety), relational responsibility (being a burden, demonstrating loyalty, protecting others from grief), negotiating existential tensions (accepting natural course of life, disrupted aging, worthlessness, living on borrowed time, respecting sanctity of life, life satisfaction, preserving self-identity), and preparedness (decisional clarity, informational power, spirituality and hope).

**Topic expert feedback**

No topic expert feedback was relevant to this evidence.

**Impact statement**

**Educational interventions**

The new evidence on educational interventions and patient and caregiver perspectives is consistent with recommendations 1.4.1-14.5, including the involvement of patients, provision of high quality programmes as appropriate to the severity of the condition, and taking account of psychological aspects of coping.

New evidence is unlikely to impact on the guideline.

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Appendix A2: summary of new evidence from 4-year surveillance of Chronic kidney disease in adults: assessment and management (2014) NICE guideline CG182
**182-018**  
Available tools to aid identification and maximise effectiveness of treatment and management of CKD

**Recommendations derived from this question**

There were no recommendations derived from this question.

**Surveillance decision**

No new information was identified at any surveillance review.

**4-year surveillance summary**

A systematic review (7 studies, n=271) found that progressive resistance training induced skeletal muscle hypertrophy and increased muscular strength and health related quality of life outcomes in adults with CKD. An RCT (n=119) found that a 12-week/24-session renal rehabilitation exercise program improved physical capacity and quality of life in patients with CKD stages 3 and 4. Longer follow-up is needed to determine if these findings will translate into decreased mortality rates.

A systematic review (11 studies) found insufficient evidence to evaluate the effect of negative energy balance interventions, including dietary restriction and exercise, on mortality in diabetic patients with advanced CKD. However, these interventions had beneficial effects on glycaemic control, BMI and body composition, functional status and quality of life, and no harmful effects were observed.

An RCT (n=2379) found that a behaviour modification intervention for CKD patients resulted in significantly lower discontinuous clinical visits, significantly higher referral and co-treatment rates from GPs and nephrologists. This consequently led to the slowing of CKD progression, especially in patients with proteinuric Stage 3 CKD. The intervention resulted in significantly lower discontinuous clinical visits, significantly higher referral and co-treatment rates from GPs and nephrologists. This consequently led to the slowing of CKD progression, especially in patients with proteinuric Stage 3 CKD. The intervention

**182-019**  
In adults with CKD, do improving lifestyle habits slow the progression of CKD?

**Recommendations derived from this question**

**Lifestyle advice**

1.4.6 Encourage people with CKD to take exercise, achieve a healthy weight and stop smoking. [2008]

**Surveillance decision**

This review question should not be updated.
included an educational component for dietary and lifestyle modification and a CKD status letter, attempting to prevent withdrawal from treatment.

**Topic expert feedback**
No topic expert feedback was relevant to this evidence.

**Impact statement**
The new systematic review and RCT evidence on exercise and negative energy balance interventions is consistent with recommendation 1.4.6 to encourage people with CKD to take exercise and achieve a healthy weight.

New evidence is unlikely to impact on the guideline.

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### 182-020 What dietary interventions are associated with improved renal outcomes in adults with CKD?

#### Recommendations derived from this question

**Dietary interventions**

1.4.7 Offer dietary advice about potassium, phosphate, calorie and salt intake appropriate to the severity of CKD. [2008, amended 2014]

1.4.8 Where dietary intervention is agreed this should occur within the context of education, detailed dietary assessment and supervision to ensure malnutrition is prevented. [2008]

#### Surveillance decision

This review question should not be updated.

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### 4-year surveillance summary

**Dietary fibre**

A systematic review of 27 (14 studies, n=143) found that dietary fibre supplementation significantly reduced serum urea and creatinine levels in CKD patients. Larger, longer duration and higher-quality clinical trials measuring a greater variety of uremic toxins in CKD were recommended by the authors.

**Soy protein**

A systematic review of 28 (12 studies, n=280) found that intake of soy protein containing isoflavones significantly decreased serum creatinine, serum phosphorus, C-reactive protein (CRP) and proteinura in predialysis patients with CKD, while no significant change was found in creatinine clearance and glomerular filtration rate. Soy protein intake also maintained the nutritional status in dialysis patients, though no significant change in CRP, blood urea nitrogen, and serum phosphorus was detected. Future large, long-term RCTs were recommended to verify the results.

A systematic review of 29 (9 studies, n=197) found that soy protein consumption had a protective effect on serum creatinine and serum phosphorus concentrations in predialysis CKD patients. It also significantly reduced serum triglyceride but not total cholesterol.

**Vitamin D**

A systematic review of 30 Li (7 studies, n=731) found that active vitamin D reduced the incidence of cardiovascular events and induced a reduction in proteinuria in pre-dialysis CKD patients. Results also showed an increased

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Appendix A2: summary of new evidence from 4-year surveillance of Chronic kidney disease in adults: assessment and management (2014) NICE guideline CG182
probability of hypercalcemia after paricalcitol therapy.

**Calcium enrichment and low protein intake**
A systematic review (9 studies n=634) found limited low quality evidence to indicate that dietary interventions (calcium-enriched bread or low phosphorus/protein intake) may positively affect CKD-mineral and bone disorders by increasing serum calcium, decreasing serum phosphorus, the calcium x phosphate product and fibroblast growth factor 23.

**Salt restriction**
A systematic review (8 studies, n=258) found insufficient evidence to determine long-term effects of salt restriction in people with CKD, in terms of mortality and progression to end-stage kidney disease. Salt reduction in people with CKD reduced blood pressure considerably and consistently reduced proteinuria.

**Vitamin B and its derivatives**
A systematic review (9 studies, n=1354) found insufficient evidence to support the use of vitamin B therapy alone or in combination with folic acid for delaying progression of diabetic kidney disease. Thiamine was found to be beneficial for reduction in albuminuria in a single study, but further studies were recommended to establish conclusive evidence on this and other vitamin B preparations used alone or in combination.

An ancillary study to an RCT (n=328) of hyperlipidemic patients with CKD, extended release niacin alone, but not in combination with the selective prostaglandin D2 receptor subtype 1 inhibitor laropiprant, lowered Fibroblast growth factor 23 and parathyroid hormone concentrations.

**Dietary restriction**
A systematic review (11 studies) found insufficient evidence to evaluate the effect of negative energy balance interventions, including dietary restriction and exercise, on mortality in diabetic patients with advanced CKD. However, these interventions had beneficial effects on glycaemic control, body mass index and body composition, functional status and quality of life, and no harmful effects were observed.

A secondary analysis (n=3088) of an RCT analysed whether diet quality and adherence to dietary guidelines using the modified Alternate Healthy Eating Index (mAHEI) score was associated with CKD incidence or progression after 5.5 years. Participants in the healthiest tertile of the mAHEI score had a decreased risk of incidence or progression of CKD and death compared with participants in the least healthy tertile.

**Folic acid**
A sub-study of an RCT (n=15104, CKD n=1671) found that enalapril-folic acid therapy, compared with enalapril alone, significantly delayed the progression of CKD among patients with mild-to-moderate CKD and hypertension. However, the study was conducted in Chinese patients only, which limits its potential impact in the UK.

**Topic expert feedback**
No topic expert feedback was relevant to this evidence.

**Impact statement**
The new evidence relating to dietary restriction, adherence to dietary guidelines and salt intake is consistent with recommendations 1.4.7 and 1.4.8.

Further research may be needed on the benefits of the following dietary interventions, for which new evidence is inconclusive, to establish an impact on the guideline recommendations:
- dietary soy protein
- calcium enriched foods
- vitamin B and its derivatives, including niacin and thiamine
- dietary fibre
- vitamin D
- folic acid in combination with enalapril

New evidence is unlikely to impact on the guideline.
For people with CKD, are low protein diets a clinically and cost effective method for the management of CKD?

Recommendations derived from this question

Low protein diets

1.4.9 Do not offer low-protein diets (dietary protein intake less than 0.6–0.8 g/kg/day) to people with CKD.

Surveillance decision

This review question should not be updated.

4-year surveillance summary

A secondary analysis of an open label RCT\( ^{37} \) (n=227) found that in patients with CKD the baseline value of estimated urine albumin excretion was positively correlated with both the estimated urine urea nitrogen or protein intake. The authors did not quantify the protein intake in the abstract, however, which limits any potential impact of this study.

An RCT\( ^{38} \) found that a ketoanalogue-supplemented vegetarian very low protein diet was more effective than a conventional low protein diet in slowing the progression of CKD, measured by dialysis initiation or >50% reduction in initial eGFR. However, the sample size of the trial was not reported in the abstract.

A systematic review\( ^{39} \) (7 studies) found that restricted protein diet supplemented with keto analogues, compared with normal diet, significantly prevented the deterioration of eGFR, hyperparathyroidism, hypertension and hyperphosphatemia in patients with CKD, without resulting in malnutrition. However, the sample sizes of included studies were not reported in the abstract.

A systematic review\( ^{40} \) (15 studies, n=1965) found that protein diet restriction compared with normal diet, measured by change in mean GFR over at least 1 year, slowed CKD progression in non-diabetic and in type 1 diabetic patients, but not in type 2 diabetic patients. However, the mean pooled protein intake in the experimental arm was 0.83 g/kg/day which is higher than the 0.6-0.8 g/kg/day low intake range stipulated in the CG182 review protocol.

An RCT\( ^{41} \) (n=108) found that a low protein diet supplemented with keto acid, compared with normal protein diet, was both nutritionally safe and beneficial, providing nephroprotective effects for patients with early-stage CKD and steroid-resistant proteinuria. However, there were no differences in nutritional status, renal function, hemoglobin, or blood pressure between the two groups. It was also unclear from the abstract how the outcomes had been measured, which limits the potential impact of the study.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

In the development of CG182 the guideline committee agreed that the evidence available, from 10 RCTs, 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 were considered important to inform future management of CKD patients. New systematic review evidence indicates that protein diet restriction may slow CKD progression in non-diabetic and in type 1 diabetic patients, but not in type 2 diabetic patients. However, the experimental low protein groups in the included studies had an actual mean pooled protein intake higher than the
range defined in CG182. The new evidence is therefore unlikely to impact on recommendation 1.4.9, which advises against offering low protein diets to all people with CKD.

The new RCT evidence on low protein diet supplemented with keto acid did not demonstrate any effect on renal function or nutritional status or other outcomes considered in the guideline, and is therefore unlikely to impact on recommendation 1.4.9.

New evidence is unlikely to impact on the guideline.

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182-022 For people with CKD, what is the clinical and cost effectiveness of self-management support systems?

Recommendations derived from this question

Self-management

1.4.10 Ensure that systems are in place to:
- inform people with CKD of their diagnosis
- enable people with CKD to share in decision-making about their care
- support self-management (this includes providing information about blood pressure, smoking cessation, exercise, diet and medicines) and enable people to make informed choices. [new 2014]

1.4.11 Give people access to their medical data (including diagnosis, comorbidities, test results, treatments and correspondence) through information systems, such as Renal PatientView, to encourage and help them to self-manage their CKD. [new 2014]

Surveillance decision

This review question should not be updated.

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4-year surveillance summary

Multidisciplinary care

A systematic review\(^2\) (3 studies) found that multidisciplinary care (MDC) was associated with a statistically significant improvement of glycated haemoglobin as compared with standard usual care for patients with diabetic kidney disease.

An RCT\(^3\) (n=451) found that an interprofessional team using telehealth was a feasible care delivery strategy and was non-inferior to usual care for health outcomes in patients with CKD.

An RCT\(^4\) (n=164) found that a shared care model between GP, nurse practitioner and nephrologist is beneficial in reducing systolic blood pressure in patients with CKD in primary care.

A systematic review\(^5\) (18 studies n=8853) found that MDC compared with non-MDC in patients with CKD was associated with lower risk of all-cause mortality, a lower risk of starting dialysis and lower risk of temporal catheterisation for dialysis. MDC was not associated with a higher chance of choosing peritoneal dialysis or a lower chance of hospitalisation for dialysis. Further research was recommended to determine the optimal composition of the MDC team.

Appendix A2: summary of new evidence from 4-year surveillance of Chronic kidney disease in adults: assessment and management (2014) NICE guideline CG182
**Topic expert feedback**
No topic expert feedback was relevant to this evidence.

**Impact statement**
The new systematic review evidence indicating the potential benefits of multidisciplinary care is consistent with guideline recommendation 1.4.10 to ensure systems are in place to enable people with CKD to share in decision making about their care, and to support self-management and make informed choices about their care.

New evidence is unlikely to impact on the guideline.

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**Referral criteria**

182-023 What are the criteria for referral to specialist care?

**Recommendations derived from this question**

1.5.1 Take into account the individual's wishes and comorbidities when considering referral. [2008]
1.5.2 People with CKD in the following groups should normally be referred for specialist assessment:

- GFR less than 30 ml/min/1.73 m2 (GFR category G4 or G5), with or without diabetes
- ACR 70 mg/mmol or more, unless known to be caused by diabetes and already appropriately treated
- ACR 30 mg/mmol or more (ACR category A3), together with haematuria
- sustained decrease in GFR of 25% or more, and a change in GFR category or sustained decrease in GFR of 15 ml/min/1.73 m2 or more within 12 months
- hypertension that remains poorly controlled despite the use of at least 4 antihypertensive drugs at therapeutic doses (see also Hypertension [NICE guideline CG127]) known or suspected rare or genetic causes of CKD
- suspected renal artery stenosis. [2008, amended 2014]

1.5.3 Consider discussing management issues with a specialist by letter, email or telephone in cases where it may not be necessary for the person with CKD to be seen by the specialist. [2008]
1.5.4 Once a referral has been made and a plan jointly agreed (between the person with CKD or their carer and the healthcare professional), it may be possible for routine follow-up to take place at the patient's GP surgery rather than in a specialist clinic. If this is the case, criteria for future referral or repeated referral should be specified. [2008]
1.5.5 People with CKD and renal outflow obstruction should normally be referred to urological services, unless urgent medical intervention is required – for example, for the treatment of hyperkalaemia, severe uraemia, acidosis or fluid overload. [2008]

**Surveillance decision**
This review question should not be updated.

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Appendix A2: summary of new evidence from 4-year surveillance of Chronic kidney disease in adults: assessment and management (2014) NICE guideline CG182
4-year surveillance summary

**Early referral**

A systematic review (40 cohort studies, n=63,887) found that early referral to a nephrologist for patients with CKD reduced mortality and hospitalisation, improved uptake of peritoneal dialysis and resulted in earlier placement of arteriovenous fistulae. Differences in mortality and hospitalisation data between the two groups were not explained by differences in prevalence of comorbid disease or serum phosphate. However, early referral was associated with better preparation and placement of dialysis access. Early referral was defined as more than one to six months, and late referral less than one to six months prior to starting dialysis.

**Topic expert feedback**

Topic expert feedback indicated that the new systematic review evidence is consistent with the guideline recommendations and reinforces current knowledge that early referral in ESKD is associated with improved outcomes on RRT. It was considered unlikely to impact on the recommendations.

**Impact statement**

The new systematic review evidence supporting early referral to specialist care is consistent with the guideline recommendations 1.5.2-1.5.5. Although these do not advise specific timing of referral, the guideline committee consensus was that one of the principles guiding referral should be early identification of people likely to require renal replacement therapy. The new evidence supports this consensus.

New evidence is unlikely to impact on the guideline.
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?

Recommendations derived from this question (no questions made in guideline)

1.6.1 In people with CKD aim to keep the systolic blood pressure below 140 mmHg (target range 120–139 mmHg) and the diastolic blood pressure below 90 mmHg.[3] [2008]

1.6.2 In people with CKD and diabetes, and also in people with an ACR of 70 mg/ mmol or more, aim to keep the systolic blood pressure below 130 mmHg (target range 120–129 mmHg) and the diastolic blood pressure below 80 mmHg†. [2008]

Surveillance decision
This review question should not be updated.

4-year surveillance summary
An RCT47 (n=2199) found that: A one-time pharmacist based intervention did not improve blood pressure control in patients with CKD, but did improve guideline adherence, and the number of antihypertensive medications prescribed to subjects with poorly controlled blood pressure. Blood pressure control was measured in patients with poorly controlled hypertension at baseline.

An RCT48 (n=9361) found that among patients at high risk for cardiovascular events but without diabetes, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause, although significantly higher rates of some adverse events were observed in the intensive-treatment group, including hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure.

A systematic review49 (19 studies, n=44,989) assessed the efficacy and safety of intensive blood pressure-lowering strategies in high risk patients, versus less intensive strategies. Intensive blood pressure-lowering treatment achieved relative risk reductions for major cardiovascular events, myocardial infarction, stroke, albuminuria, and retinopathy progression. However, more intensive treatment had no clear effects on heart failure, cardiovascular death, total mortality, or end-stage kidney disease. The number of included studies covering the CKD population was not reported in the abstract.

Topic expert feedback
Topic expert feedback indicated the potential relevance of an RCT48, but that the impact may be limited by whether the results are generalisable to all people with CKD. The study is summarised in the 4-year surveillance summary. Topic expert feedback also indicated that a systematic review50 should be considered for its potential impact but that its impact may be limited by the small number of studies relevant to CKD. The study is included in the 4-year surveillance summary.

Additional topic expert feedback indicated that the new RCT and systematic review evidence

† The GDG searched for and appraised evidence on blood pressure control, and did not set out to establish definitive safe ranges of blood pressure in CKD. The evidence presented in the full guideline does not therefore include safety of low blood pressure, but some such evidence does exist. The GDG set out a range of blood pressure targets, given in these recommendations, which in their clinical experience will inform good practice in CKD.

Appendix A2: summary of new evidence from 4-year surveillance of Chronic kidney disease in adults: assessment and management (2014) NICE guideline CG182
Impact statement
The new systematic review and RCT evidence indicating the potential value of intensive blood pressure control in patients at high risk of cardiovascular events may require further evidence, specifically covering the CKD population, to establish a definite impact on the guideline recommendations 1.6.1 and 1.6.2.

There is insufficient evidence to support the use of a one-time pharmacist intervention to improve blood pressure control in people with CKD.

1.6.1 and 1.6.2

For people with CKD, what is the clinical and cost effectiveness of renin-angiotensin-aldosterone system antagonists in the management of CKD?

Recommendations derived from this question

1.6.3 Offer a low-cost renin–angiotensin system antagonist to people with CKD and:
- diabetes and an ACR of 3 mg/mmol or more (ACR category A2 or A3)
- hypertension and an ACR of 30 mg/mmol or more (ACR category A3)
- an ACR of 70 mg/mmol or more (irrespective of hypertension or cardiovascular disease)‡.

1.6.4 Do not offer a combination of renin–angiotensin system antagonists to people with CKD. [new 2014]

1.6.5 Follow the treatment recommendations in Hypertension (NICE guideline CG127) for people with CKD, hypertension and an ACR of less than 30 mg/mmol (ACR categories A1 and A2), if they do not have diabetes. [new 2014]

1.6.6 To improve concordance, inform people who are prescribed renin–angiotensin system antagonists about the importance of:
- achieving the optimal tolerated dose of renin–angiotensin system antagonists and
- monitoring eGFR and serum potassium in achieving this safely. [2008]

1.6.7 In people with CKD, measure serum potassium concentrations and estimate the GFR before starting renin–angiotensin system antagonists. Repeat these measurements between 1 and 2 weeks after starting renin–angiotensin system antagonists and after each dose increase. [2008]

1.6.8 Do not routinely offer a renin–angiotensin system antagonist to people with CKD if their pretreatment serum potassium concentration is greater than 5.0 mmol/litre. [2008, amended 2014]

‡ The evidence to support these criteria is limited in people aged over 70 years.

Appendix A2: summary of new evidence from 4-year surveillance of Chronic kidney disease in adults: assessment and management (2014) NICE guideline CG182
1.6.9  When hyperkalaemia precludes use of renin–angiotensin system antagonists, assessment, investigation and treatment of other factors known to promote hyperkalaemia should be undertaken and the serum potassium concentration rechecked. [2008]

1.6.10  Concurrent prescription of drugs known to promote hyperkalaemia is not a contraindication to the use of renin–angiotensin system antagonists, but be aware that more frequent monitoring of serum potassium concentration may be required. [2008]

1.6.11  Stop renin–angiotensin system antagonists if the serum potassium concentration increases to 6.0 mmol/litre or more and other drugs known to promote hyperkalaemia have been discontinued. [2008]

1.6.12  Following the introduction or dose increase of renin–angiotensin system antagonists, do not modify the dose if either the GFR decrease from pretreatment baseline is less than 25% or the serum creatinine increase from baseline is less than 30%. [2008]

1.6.13  If there is a decrease in eGFR or increase in serum creatinine after starting or increasing the dose of renin–angiotensin system antagonists, but it is less than 25% (eGFR) or 30% (serum creatinine) of baseline, repeat the test in 1–2 weeks. Do not modify the renin–angiotensin system antagonist dose if the change in eGFR is less than 25% or the change in serum creatinine is less than 30%. [2008]

1.6.14  If the eGFR change is 25% or more, or the change in serum creatinine is 30% or more:

- investigate other causes of a deterioration in renal function, such as volume depletion or concurrent medication (for example, NSAIDs)
- if no other cause for the deterioration in renal function is found, stop the renin–angiotensin system antagonist or reduce the dose to a previously tolerated lower dose, and add an alternative antihypertensive medication if required. [2008]

**Surveillance decision**

This question should not be updated.

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**4-year surveillance summary**

**Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs)**

A network meta-analysis\(^{51}\) (157 studies \(n=43,256\)) of patients with diabetes and CKD compared orally administered blood pressure-lowering drugs. Primary outcomes were all-cause mortality and end-stage kidney disease. Secondary safety and cardiovascular outcomes were also explored. No drug regimen was more effective than placebo for reducing all-cause mortality. However, compared with placebo, end-stage renal disease was significantly less likely after combined treatment with an ARB and an ACEI and after ARB monotherapy. No regimen significantly increased hyperkalaemia or acute kidney injury, although combined ACE inhibitor and ARB treatment had the lowest rank among all interventions because of borderline increases in estimated risks of these harms.

A systematic review\(^{52}\) (10 studies) found that the use of ACEIs or ARBs in patients with nondialysis-dependent CKD was associated with improved survival. However the sample sizes of included studies were not reported in the abstract.

A systematic review of reviews\(^{53}\) (8 meta-analyses including 2177 to 61,264 patients)
found that in patients with diabetes and kidney disease, ACEIs or ARBs were consistently protective for the development of ESRD. Use of ACEIs additionally reduced deaths but increased the risk for cough. Use of ARBs increased the risk for hyperkalaemia without additional benefit of death protection. No data were reported on combination therapy.

A network meta-analysis\(^5\) (119 RCTs n = 64,768) found that use of ACEIs or ARBs in people with CKD reduced the risk for kidney failure and cardiovascular events. ACE inhibitors also reduced the risk for all-cause mortality and were superior to ARBs for kidney failure, cardiovascular death, and all-cause mortality in patients with CKD.

A systematic review\(^4\) (7 studies, n=1277) found that taking at least one blood pressure-lowering medication at bedtime was not shown to reduce total death or cardiovascular death but was shown to reduce total events and major cardiovascular events in both RCTs and non-RCTs. Compared with a morning dosing regimen, taking antihypertensive drug in the evening significantly lowered night time systolic blood pressure and diastolic blood pressure. More studies were recommended by the authors to verify the findings, based on the small size and non-randomised design of some included studies.

An RCT\(^5\) (n=140) found that combination therapy of valsartan with amlodipine significantly lowered the albuminuria in chronic kidney disease and reduced the progression of disease as compared to Valsartan alone therapy. However, data were not reported on adverse effects, change in GFR or other critical outcomes relevant to the review protocol in the abstract, which limits any potential impact of the study.

A secondary analysis\(^6\) (n=8561) of the ALTITUDE RCT, which was included in CG182 evidence review, found that aliskiren showed no beneficial effect on renal outcomes in the overall population of patients with type 2 diabetes and chronic kidney disease or cardiovascular disease, or in various subgroups. It did delay progression to microalbuminuria and macroalbuminuria, and improved regression to microalbuminuria and normoalbuminuria. However, the data for the CKD subgroup was not reported in the abstract.

**Calcium channel blockers**

A systematic review\(^7\) (7 RCTs n=628 patients) found that for patients with hypertension and CKD, ACEI and ARB in combination with calcium channel blockers had no additional renoprotective benefit beyond that which could be achieved with ACEI or ARB monotherapy.

A further systematic review\(^8\) (Zhao H) (8 trials, n=25,647) found that calcium channel blockers did not increase all-cause mortality incidence in patients with CKD though they displayed weaker renoprotective effects, compared to ACEIs or ARBs therapy.

**Mineralocorticoid receptor antagonists (MRAs)**

Two systematic reviews examined MRAs in treating CKD. The first\(^9\) (12 studies, n=1003) found that in patients with CKD MRAs improved all-cause mortality, and major cardiovascular events with no incidence of severe hyperkalemia. However, due to small sample sizes and variable quality of included studies, the authors recommended further larger studies to verify the findings.

The second systematic review\(^10\) (29 trials n=1581) found the use of mineralocorticoid receptor MRAs was associated with an increased serum potassium and higher risk ratio of hyperkalaemia. Data on long-term cardiovascular outcomes and mortality were not available in any of the trials.

An RCT\(^11\) (n=823) found that in patients with diabetes and CKD, the addition of the MRA finerenone compared with placebo to existing ARB and an ACE inhibitor treatment resulted in a dose-dependent reduction in UACR. The primary outcome, the placebo-corrected mean ratio of the UACR at day 90 relative to baseline, was reduced in the finerenone group. Further research was recommended by the authors to compare finerenone with other comparator drugs.

**Topic expert feedback**

Topic expert feedback highlighted the ongoing STOPACE trial as potentially relevant. The trial has completed with an intention to publish date in 2020.

**Impact statement**

ACEI and ARB

The collective new systematic review evidence supports CG182 recommendation 1.6.3, which advises the use of a low cost renin–angiotensin
system antagonist to people with CKD. There is inconclusive evidence on the safety of combination treatment, which is consistent with the advice against this in recommendation 1.6.4.

The new systematic review evidence suggesting potential benefits of taking an antihypertensive drug in the evening was based on small trials with variable quality, and is therefore unlikely to impact on CG182 recommendations.

The ongoing STOPACE trial will be monitored for publication and considered in a future surveillance review.

Calcium channel blockers

The new systematic review evidence on calcium channel blockers is consistent with CG182 recommendations, which do not advise their combined use with renin–angiotensin system antagonists to people with CKD.

Mineralocorticoid receptor antagonists (MRAs)

The new systematic review evidence on the use of MRAs in patients with CKD is inconclusive and is therefore unlikely to impact on CG182.

New evidence is unlikely to impact on the guideline.

Statin therapy and reduction in proteinuria

**182-026** In adults with CKD and proteinuria, do statins decrease proteinuria and decrease the risk of progression of CKD compared with other treatments or placebo?

**Recommendations derived from this question (no questions made in guideline)**

1.6.15 Follow the recommendations in Lipid modification (NICE guideline CG181) for the use of statins in CKD. [new 2014]]

**Surveillance decision**

This question should not be updated.

**4-year surveillance summary**

7 Systematic reviews62-68 and 8 RCTs69-76 were identified relating to statins for patients with CKD. However, guidance on statins can be found in CG181: Cardiovascular disease: risk assessment and reduction, including lipid modification (July 2014), which updated and replaced CG67: Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease (May 2008). CG182 cross referred to CG67, as the extant guideline at the time of publication. The cardiovascular disease prevention NICE pathway now incorporates CG181, and is included in the chronic kidney disease NICE pathway. The new information will be considered when CG181 undergoes its next surveillance review.

**Topic expert feedback**

No topic expert feedback was relevant to this evidence.

**Impact statement**

The new evidence on statins is not directly relevant to CG182 recommendations, and is more relevant to the guideline on...
New evidence is unlikely to impact on the guideline.

Pharmacotherapy: Oral antplatelets and anticoagulants

182-027 For people with CKD, what is the clinical and cost effectiveness of oral antplatelet and anticoagulant therapy in reducing cardiovascular disease?

Recommendations derived from this question

1.6.16 Offer antplatelet drugs to people with CKD for the secondary prevention of cardiovascular disease, but be aware of the increased risk of bleeding. [new 2014]

1.6.17 Consider apixaban in preference to warfarin in people with a confirmed eGFR of 30–50 ml/min/1.73 m2 and non-valvular atrial fibrillation who have 1 or more of the following risk factors:

- prior stroke or transient ischaemic attack
- age 75 years or older
- hypertension
- diabetes mellitus
- symptomatic heart failure. [new 2014]

Surveillance decision

This question should not be updated.

4-year surveillance summary

Novel oral anticoagulants

A systematic review77 (8 studies) found that in patients with CKD the use of novel oral anticoagulants (NOACs) (rivaroxaban, dabigatran, apixaban) compared to vitamin K antagonists resulted in no significant difference in stroke or systemic thromboembolism (n=9693), recurrent thromboembolism or thromboembolism-related death (n=891).

A systematic review78 (10 trials n=40693) found that compared with other anticoagulants in patients with mild renal insufficiency there was significantly less major or clinically relevant non-major bleeding and stroke or systemic embolism with novel oral anticoagulants (NOACs).

A systematic review79 (12 studies, n=unreported) found that in patients with atrial fibrillation and non end stage CKD, there was no significant increase in the incidence of major bleeding outcomes in warfarin use compared with placebo/antplatelet drugs. NOACs reduced the risk of major bleeding by 19% compared to warfarin and further data-exploration indicated that the risk did not increase as renal function deteriorated during the renal status of mild to moderate impairment.

A systematic review80 (6 studies n=40,145) found that the risk of bleeding with apixaban in patients with mild renal impairment was significantly less than with conventional anticoagulants. In patients with moderate to severe renal impairment, the risk of bleeding was found to be similar.
Pentoxifylline
A systematic review (12 trials n=613) found that pentoxifylline, an oral peripheral vasodilator derived from methylxanthine, significantly decreased proteinuria compared to placebo or no-treatment groups in CKD patients, but the decrease was not significant compared to captopril treatment. The decrease of glomerular filtration rate was significantly less in the pentoxifylline group than in the controls. There was no significant difference in serum creatinine, diastolic blood pressure and adverse events. There were no cardiovascular outcomes were reported in the abstract, however.

Aspirin
A systematic review (3 studies, n=4468) found no clear benefit of aspirin for the primary prevention of cardiovascular events in CKD and no statistically significant reduction in mortality. Major bleeding events were significantly increased with aspirin.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
NOACs
The new systematic review evidence supports the use of NOACs, particularly apixaban, in patients with mild renal impairment. This is consistent with recommendation 1.6.17, which advises apixaban over warfarin in patients with a confirmed eGFR of 30–50 ml/min/1.73 m2 and non-valvular atrial fibrillation who have 1 or more of specific risk factors. In the evidence review for CG182, the guideline committee found apixaban to be more clinically and cost-effective than warfarin, based on the health economic modelling and on the ARISTOTLE trial.

Pentoxifylline
Further research may be needed to confirm the potential benefits of pentoxifylline, specifically on cardiovascular outcomes, before a definite impact on the guideline recommendations can be established.

Aspirin
The identified evidence does not support the universal use or avoidance of aspirin for primary prevention of cardiovascular events in CKD. It is unlikely to impact on recommendation 1.6.16, which recommends antiplatelet drugs to people with CKD for the secondary prevention of cardiovascular disease, but not for primary prevention.

New evidence is unlikely to impact on the guideline.

Asymptomatic hyperuricaemia

182-028 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?

Recommendations derived from this question
No recommendations were derived from this question, but a research recommendation was made (See research recommendation RR04).

Surveillance decision
This question should not be updated.

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**Allopurinol**

A systematic review\(^2\) (8 studies, n=476) assessed the effects of uric acid-lowering therapy with allopurinol on renal outcomes in CKD, compared with placebo or no treatment. In the majority of studies there was no significant difference in change in glomerular filtration rate from baseline between the allopurinol and control arms. Allopurinol had no effect on proteinuria and blood pressure. Data for effects of allopurinol therapy on progression to end-stage kidney disease and death were insufficient. Allopurinol had uncertain effects on the risks of adverse events.

A systematic review\(^3\) (4 RCTs and 21 observational studies) found limited evidence that allopurinol reduced CKD progression and cardiovascular events. Adverse events attributable to allopurinol were rarely observed. Additional RCT and observational evidence comparing allopurinol with usual care was recommended to confirm the findings. The comparator interventions were not reported in the abstract.

A systematic review\(^4\) (19 RCTs n=992) assessed the benefits and risks of treatments that lower urate in patients with stages 3-5 CKD, compared with inactive control. Pooled estimates for eGFR was in favour of allopurinol and this was consistent with results for serum creatinine. Statistically significant reductions in serum uric acid, systolic and diastolic blood pressure were found, favouring allopurinol. However, there were insufficient data on adverse events, incidence of ESRD and cardiovascular disease for analysis and further RCTs were recommended.

A post hoc analysis of an RCT\(^5\) (n=113) found that in patients with CKD, long-term treatment with allopurinol over 5 years, compared with standard treatment, resulted in significantly fewer renal and cardiovascular events than with control.

A systematic review\(^6\) (7 RCTs n=451) found that uric-acid-lowering therapy with allopurinol compared to control delayed the increase of serum creatinine and blood urea nitrogen as well as the decrease of glomerular filtration rate, decreased systolic blood pressure and reduced the risk of renal disease progression. However, there was no statistically significant difference in 24-h urinary protein quantity and diastolic blood pressure. The control intervention was not reported in the abstract.

**Topiroxostat**

An RCT\(^7\) (n=123) found that topiroxostat 160 mg, compared with placebo, effectively reduced the serum urate level in the hyperuricemic stage 3 CKD patients with or without gout.

**Topic expert feedback**

No topic expert feedback was relevant to this evidence.

**Impact statement**

**Allopurinol**

The new systematic review and RCT evidence on allopurinol is inconsistent in terms its potential benefits in lowering uric acid and further research may be needed to establish definitive evidence on its benefits and risks of adverse effects. It was also unclear from the abstracts of included studies whether they covered asymptomatic hyperuricaemia, which further limited the relevance to the review question.

**Topiroxostat**

In addition to the single small RCT conducted in Japan, further evidence may be needed to establish the benefits of topiroxostat in lowering uric acid, which is not licensed for use in the UK.

New evidence is unlikely to impact on the guideline.
Other complications

| 182-029 | Monitoring of calcium, phosphate, vitamin D and parathyroid hormone levels in people with CKD |

**Recommendations derived from this question (no questions made in guideline)**

1.7.1 Do not routinely measure calcium, phosphate, parathyroid hormone (PTH) and vitamin D levels in people with a GFR of 30 ml/min/1.73 m² or more (GFR category G1, G2 or G3). [2008]

1.7.2 Measure serum calcium, phosphate and PTH concentrations in people with a GFR of less than 30 ml/min/1.73 m² (GFR category G4 or G5). Determine the subsequent frequency of testing by the measured values and the clinical circumstances. Where doubt exists, seek specialist opinion. [2008]

1.7.3 Offer bisphosphonates if indicated for the prevention and treatment of osteoporosis in people with a GFR of 30 ml/min/1.73 m² or more (GFR category G1, G2 or G3). [2008]

**Surveillance decision**

This question should not be updated.

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**4-year surveillance summary**

A systematic review\(^1\) (10 studies, n=734) found that, compared with active non-selective vitamin D receptor activators, paricalcitol showed no significant difference in both parathyroid hormone (PTH) reduction and the proportion of CKD patients with secondary hyperparathyroidism who achieved the target reduction of PTH. In addition, no statistical differences were found in terms of serum calcium, episodes of hypercalcemia, serum phosphorus, calcium x phosphorus products, and bone metabolism index. Further trials were recommended by the authors to verify the findings. The GFR levels were not reported in the abstract.

A systematic review\(^2\) (12 studies n=25,546) found an independent association between serum phosphorus level and kidney failure and mortality among non-dialysis-dependent patients with CKD. Large-scale RCTs were recommended to target disordered phosphorus homeostasis in CKD.

**Topic expert feedback**

No topic expert feedback was relevant to this evidence.

**Impact statement**

Due to inconclusive evidence, further research may be needed on paricalcitol and on targeted phosphorus homeostasis therapy to establish a definite impact on the guideline recommendations.

**New evidence is unlikely to impact on the guideline.**

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**Recommendations derived from this question**

Detailed advice on the management of CKD–mineral and bone disorders is beyond the scope of this guideline. If uncertain, seek advice from your local renal service.

1.7.4 Do not routinely offer vitamin D supplementation to manage or prevent CKD–mineral and bone disorders. [new 2014]

1.7.5 Offer colecalciferol or ergocalciferol to treat vitamin D deficiency in people with CKD and vitamin D deficiency. [new 2014]

1.7.6 If vitamin D deficiency has been corrected and symptoms of CKD–mineral and bone disorders persist, offer alfacalcidol (1-alpha-hydroxycholecalciferol) or calcitriol (1-25-dihydroxycholecalciferol) to people with a GFR of less than 30 ml/min/1.73 m2 (GFR category G4 or G5). [new 2014]

1.7.7 Monitor serum calcium and phosphate concentrations in people receiving alfacalcidol or calcitriol supplements. [2014]

**Surveillance decision**

This question should not be updated.

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**4-year surveillance summary**

An RCT\(^9\) (n=120) found that daily (2000 IU/D) and monthly (40,000 IU/month) vitamin D3 supplementation for six months in adults with diabetes and CKD was safe, and resulted in equivalent adherence and improvements in overall vitamin D status, but only modest changes in markers of bone health and quality of life.

A systematic review\(^9\) (13 studies) found no significant treatment effect of oral vitamin D on all-cause mortality, cardiovascular mortality or serious adverse cardiovascular events in patients with CKD, compared with placebo. Larger trials were recommended with clinical primary outcomes related to vitamin D supplementation.

An RCT\(^9\) (n=204) found that The 25-hydroxyvitamin D levels of CKD patients receiving ergocalciferol increased significantly and significantly more than those receiving calcitriol. Maintenance target levels of serum calcium, phosphorus, and intact parathyroid hormone as the primary outcome measure did not show significant difference in frequencies between two groups.

A systematic review\(^9\) (31 studies, n=2621) found that patients receiving vitamin D receptor activators (VDRAs) had lower eGFR and elevated serum creatinine in sensitivity analysis excluding studies with dropout rate more than 30%. However, subgroup analysis of the 5 studies that did not use serum creatinine-based measures did not indicate lower GFR in the VDRAs group. Compared with control groups, there was no difference in all-cause mortality, cardiovascular disease, and severe adverse events for the VDRAs groups.

**Topic expert feedback**

No topic expert feedback was relevant to this evidence.

**Impact statement**

The new systematic review and RCT evidence does not support the routine use of vitamin D supplementation or VDRAs to manage or prevent CKD–mineral and bone disorders. This is consistent with recommendation 1.7.4, which...
advises against the routine use of vitamin D supplements.

New RCT evidence supporting the use of ergocalciferol is consistent with recommendation 1.7.5, which includes this as one of the recommended drugs to treat vitamin D deficiency in people with CKD.

New evidence is unlikely to impact on the guideline.

### 182-031 Anaemia identification in people with CKD

**Recommendations derived from this question (no questions made in guideline)**

1.7.8 If not already measured, check the haemoglobin level in people with a GFR of less than 45 ml/min/1.73 m² (GFR category G3b, G4 or G5) to identify anaemia (haemoglobin less than 110 g/litre [11.0 g/dl], see Anaemia management in people with chronic kidney disease [NICE guideline CG114]). Determine the subsequent frequency of testing by the measured value and the clinical circumstances. [2008]

**Survey decision**

This question should be updated.

### 4-year surveillance summary

No relevant evidence was identified.

**Topic expert feedback**

In developing the related guideline NG8: Chronic kidney disease: managing anaemia (2015) (July 2014), the guideline committee discussed the previous 2006 recommendation for the trigger threshold of the eGFR for investigation of anaemia being due to CKD. Currently this is recommended to be below 60ml/min in NG8, although the rationale for this was both consensus based and was considered contradictory in the old LETR tables.

Although no new evidence was assessed in the development of NG8, the guideline committee considered that a threshold below 60ml/min was too high, did not reflect current practice and was out of date. The preferred threshold was agreed by the group to be less than 30ml/min in current clinical practice today. However, the original recommendation was not changed because no new evidence was reviewed at the time of developing NG8.

**Impact statement**

There is a potential impact on recommendation 1.7.8 if the threshold for investigation into whether anaemia is due to CKD is revised in the related guideline NG8: Chronic kidney disease: managing anaemia (2015) (July 2014). This guideline replaced NICE guideline CG114: Anaemia management in people with chronic kidney disease, which is currently cross referenced in CG182 recommendation 1.7.8.

New evidence identified that may change current recommendations.
What is the clinical and cost effectiveness of oral bicarbonate supplements in the management of CKD?

**Recommendations derived from this question**

Detailed advice on the management of metabolic acidosis is beyond the scope of this guideline. If uncertain, seek advice from your local renal service.

1.7.9 Consider oral sodium bicarbonate supplementation for people with both:

- a GFR less than 30 ml/min/1.73 m² (GFR category G4 or G5) and
- a serum bicarbonate concentration of less than 20 mmol/litre. [new 2014]

**Surveillance decision**

No new information was identified at any surveillance review. The ongoing study BiCARB study will be monitored for publication and considered at the next surveillance review.

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### NQ – 01  Treatment for mild hyperkalaemia

This question was not addressed by the guideline. New evidence has subsequently been identified and considered for possible addition to the guideline as a new question.

**Surveillance decision**

This question should not be added.

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### 4-year surveillance summary

**Patiromer**

In an RCT\(^97\) (n=306) among patients with hyperkalaemia and diabetic kidney disease, patiromer starting doses of 4.2 to 16.8 g twice daily resulted in statistically significant decreases in serum potassium level after 4 weeks of treatment, lasting through 52 weeks. A secondary analysis of an RCT\(^98\) (n=243) found that in patients with CKD and heart failure who were hyperkalaemic and receiving RAAS inhibitors, patiromer was well tolerated, decreased serum K(+), and, compared with placebo, reduced recurrent hyperkalaemia.

**Sodium zirconium cyclosilicate**

A multicentre RCT\(^100\) (n=753) investigated whether sodium zirconium cyclosilicate (ZS-9), a novel selective cation exchanger, could lower serum potassium levels in patients with mild-to-moderate constipation was the most common adverse event.

An RCT\(^99\) (n=237) found that in patients with CKD who were receiving RAAS inhibitors and who had hyperkalaemia, patiromer treatment was associated with a decrease in serum potassium levels and, as compared with placebo, a reduction in the recurrence of hyperkalaemia.

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hyperkalaemia. The findings showed that patients with hyperkalaemia who received ZS-9, as compared with those who received placebo, had a significant reduction in potassium levels at 48 hours, with normokalaemia maintained during 12 days of maintenance therapy. An RCT\textsuperscript{101} (n=495) found that among outpatients with hyperkalaemia, open-label sodium zirconium cyclosilicate reduced serum potassium to normal levels within 48 hours; compared with placebo, all 3 doses of zirconium cyclosilicate resulted in lower potassium levels and a higher proportion of patients with normal potassium levels for up to 28 days. However, it should be noted that the proportion of patients with CKD was not reported in the abstract, and the authors recommended further research to evaluate the efficacy and safety of zirconium cyclosilicate beyond 4 weeks and to assess long-term clinical outcomes.

**Topic expert feedback**
Topic expert feedback highlighted that uncertainty remains over the management of mild hyperkalaemia in the outpatient setting in CKD, which is extremely common. The topic expert feedback indicated that this area should be incorporated into the guideline. Pharmacotherapy for hyperkalaemia was highlighted as being the subject of several recent studies, which are summarised in the 4-year surveillance summary.

Additional stakeholder feedback from external communications advocated the inclusion of hyperkalaemia in the guideline, but no studies were cited. Additional topic expert feedback confirmed that both patiromer and sodium zirconium cyclosilicate are not licensed in the UK for any indication.

**Impact statement**

**Patiromer**
New RCT evidence indicates that patiromer may be effective in CKD patients with hyperkalaemia and either heart disease or diabetes, although further studies may be required to verify its clinical and cost effectiveness.

**Sodium zirconium cyclosilicate**
New RCT evidence indicates that sodium zirconium cyclosilicate may be effective in CKD patients with hyperkalaemia, although further studies may be required to verify its clinical and cost effectiveness, particularly for long term clinical outcomes. Patiromer and sodium zirconium cyclosilicate are not licensed in the UK for any indication. No new evidence was identified in the surveillance review on licensed interventions, and therefore there is unlikely to be any impact on CG182.

New evidence is unlikely to impact on the guideline.

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**NQ – 02 Complementary therapies**

This question was not addressed by the guideline. New evidence has subsequently been identified and considered for possible addition to the guideline as a new question.

**Surveillance decision**
This question should not be added.

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Manual acupressure
A systematic review (24 studies n=1787) found very low quality of evidence of the short-term effects of manual acupressure as an adjuvant intervention for fatigue, depression, sleep disturbance and uraemic pruritus in CKD patients undergoing regular haemodialysis.

Shen shauning
A systematic review (20 studies n=1606) found that shen shauning capsule treatment significantly reduced serum creatinine and blood urea nitrogen, and increased haemoglobin in patients with CKD. However, the authors highlighted the low quality of the evidence and recommended further research.

Oral adsorbents
A systematic review (15 studies, n=1590) investigated the benefits and harms of oral adsorbents for preventing or delaying the progression of CKD. There was no evidence on the primary outcomes of incidence of, and time to, ESRD, and all-cause mortality. There was only limited quality evidence that AST-120, Ai Xi Te and Niaoduqing granules had positive effects on delaying the decline of kidney function. There were no serious adverse events for any of the interventions in patients with CKD.

An RCT (n=2035) did not find any significant benefit of adding orally administered spherical carbon adsorbent AST-120 to standard therapy in patients with moderate to severe CKD.

Cordyceps
A systematic review (22 studies n=1746) found that cordyceps preparation, a traditional Chinese herbal medicine, when used in treating patients with CKD as an adjuvant therapy to conventional medicine decreased serum creatinine, increased creatine clearance, and reduced proteinuria. However, all studies had either a high or unclear risk of bias, and the authors advised caution in interpreting the results.

Astragalus
A systematic review (22 studies n=1323) found that the Chinese herbal medicine astragalus reduced proteinuria and increased haemoglobin and serum albumin in CKD patients. However, the authors acknowledged that the findings were based on low methodological quality and poor reporting in included studies.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
There is insufficient evidence to support the use of the following interventions for CKD patients, due to inconclusive and low quality evidence, and further research may be needed to establish any impact on the guideline:

- manual acupressure
- shen shauning
- oral adsorbents
- cordyceps
- astragalus.

New evidence is unlikely to impact on the guideline.
Research recommendations

RR – 01 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?

New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the evidence is insufficient to impact on the recommendations.

Surveillance decision
This research recommendation will be considered again at the next surveillance point.

RR – 02 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?

New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the evidence is insufficient to impact on the recommendations.

Surveillance decision
This research recommendation will be considered again at the next surveillance point.

RR – 03 For people aged over 75 years with CKD, what is the clinical effectiveness of renin–angiotensin–aldosterone system (RAAS) antagonists?

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision
This research recommendation will be considered again at the next surveillance point.

RR – 04 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?

New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the evidence is insufficient to impact on the recommendations.

Surveillance decision
This research recommendation will be considered again at the next surveillance point.

RR – 05 In people with hyperparathyroidism secondary to CKD, does treatment with vitamin D or vitamin D analogues improve patient-related outcomes?

New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the evidence is insufficient to impact on the recommendations.

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**Surveillance decision**

This research recommendation will be considered again at the next surveillance point.
References


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46. Smart NA, Dieberg G, Ladhani M et al. (2014) Early referral to specialist nephrology services for preventing the progression to end-stage kidney disease. The Cochrane database of systematic reviews 6:CD007333.

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