

# Chronic kidney disease frequently asked questions

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## Introduction

NHS Employers and the General Practitioners Committee (GPC) of the British Medical Association (BMA) have published these frequently asked questions (FAQs) in response to queries received from primary care organisations and practices, in relation to the diagnosis and management of chronic kidney disease (CKD) following its inclusion in the Quality and Outcomes Framework (QOF) in 2006. These FAQs have been updated in July 2011.

## Management of CKD – summary

### 1. I need an overview of CKD management, it seems very complex?

Two factors largely determine the prognosis of CKD: the stage of CKD and the degree of proteinuria (measured quantitatively using albumin-creatinine ratio (ACR)). Complications of CKD become more likely as renal function declines. Declining renal function and increasing proteinuria require more active management and frequently specialist advice from a nephrologist.

Two tables seek to set out the principles of management of CKD. One is for patients with CKD who do not have diabetes and one for people with CKD and diabetes. Areas where primary care management is appropriate (generally early stages of CKD with no or little proteinuria) are marked in green. Areas where primary or secondary care may be appropriate depending on the precise clinical scenario are coloured orange; and areas where specialist management is nearly always required in red.

**Table 1: Managing CKD in a nutshell – for people with CKD but no diabetes**

	eGFR Best over 3/12 period	All CKD general management	ACR <30 mg/mmol	ACR 30 to 69 mg/mmol	ACR ≥ 30 mg/mmol + haematuria	ACR ≥70 mg/mmol
<b>1</b>	>90 + renal damage	<b>All stages lifestyle advice:</b> CVS risk	No CVD no other CKD risk – <b>no action</b>	Use ACE / ARB Control BP >140/90		Manage BP with up to 4 agents – prior to referral
<b>2</b>	60-89 + renal damage	FH Low salt & low K+ diet	CKD risk – – <b>repeat 1 yr</b>	Ideally systolic 120-39		– Send all SCr – Investigate US, Hb, bone
<b>3a</b>	45-59	<b>Obstruction in men</b>	if BP <140/90 no need to change agents	CVD statin + usual 1 <sup>o</sup> prevention		
<b>3b</b>	30-44	Check Hb (<11g/dl)	Check 6/12			
<b>4</b>	15-29	Bone Ca PO4 Bone density	Manage in 1 <sup>o</sup> care if stable / refer if uncertain	<b>Refer:</b> To appropriate specialist – Cardiologist, Urologist, Diabetologist, Renal physician, Palliative care		
<b>5</b>	<15 or renal replacement			Appropriate pre-referral work-up		

Table 2: Managing CKD in a nutshell – for people with CKD and diabetes

	eGFR Best over 3/12 period	All CKD DM patients	ACR ≤ 2.5 Men ≤ 3.5 Women	ACR > 2.5 Men > 3.5 Women
<b>1</b>	>90 + renal damage	<b>All stages lifestyle advice:</b> CVS risk FH	No CVD no other CKD risk – <i>no action</i>	Use ACE / ARB Control BP >130/80
<b>2</b>	60-89 + renal damage	Low salt – low K+ diet <b>Obstruction in men</b>	CKD risk – - <i>repeat 1 yr</i>	Ideally systolic 120-29 Ideally diastolic <80
<b>3a</b>	45-59	Check Hb (<11g/dl) Bone	Control BP	Use ACE / ARB even if no hypertension
<b>3b</b>	30-44	Ca PO4 Bone density	Check 6/12	CVD statin + usual diabetes management
<b>4</b>	15-29		Manage in 1 <sup>o</sup> care if stable / refer if uncertain	
<b>5</b>	<15 or renal replacement	<b>Refer:</b> To appropriate specialist -Cardiologist, Urologist, Diabetologist, Renal physician, Palliative care		

## About eGFR

### 2. What is eGFR?

eGFR (estimated Glomerular Filtration Rate) is a measure of excretory kidney function, as it is a more sensitive indicator of impaired excretory function than serum creatinine alone. Patients can have significant reduction in excretory function even with a serum creatinine in the normal range. It is possible to lose up to 50 per cent of renal function before the creatinine becomes elevated, especially in the elderly.

### 3. Why has eGFR been adopted?

The use of eGFR follows recommendations in the Renal National Service Framework (NSF)<sup>1</sup> which were endorsed by the National Institute of Clinical Excellence (NICE) in their guidelines on the early identification and management of CKD in adults<sup>2</sup>. It is a more sensitive marker of kidney dysfunction than serum creatinine alone and it allows earlier and more accurate identification of patients with CKD. In 2006, the Department of Health (DH) requested that all NHS laboratories routinely report an estimated GFR when a serum creatinine measurement was made<sup>3</sup>. eGFR has a linear relationship to kidney function, whereas serum creatinine concentration increases exponentially as excretory kidney function declines, making changes in serum creatinine concentration much more difficult to interpret.

This is important for two reasons. First, improved recognition of the severity and rate of change of reduced excretory kidney function helps to improve selection of patients who will benefit from referral to a specialist. Secondly, because patients with CKD have a higher risk of cardiovascular disease than those without CKD and have more to gain from risk factor modification, compared with the general population and may benefit from risk factor modification. In addition these patients may require treatment to prevent progression of CKD, in particular exemplary blood pressure control. The use of eGFR facilitates identification of patients with more advanced CKD previously not recognised as such (in particular in relation to the elderly).

### 4. How is eGFR calculated?

Although there are a number of formulae for calculating eGFR, NICE recommend that in adults (18 years and over) eGFR is calculated from the serum creatinine using the simplified modification of diet in renal disease (MDRD)

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<sup>1</sup>NSF for Renal Services (2005). Part Two: Chronic kidney disease, acute renal failure and end of life care:

[www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_4101902](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4101902)

<sup>2</sup> NICE clinical guideline 73 (2008). Early identification and management of chronic kidney disease in adults in primary and secondary care: [www.nice.org.uk/CG73](http://www.nice.org.uk/CG73)

<sup>3</sup> DH (2006). eGFR: Information for laboratories:

[www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT\\_ID=4133024&chk=yfjmy](http://www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4133024&chk=yfjmy)

equation which uses age, sex and ethnicity of the patient. Whenever a request for serum creatinine measurement is made, chemical pathology laboratories are now reporting eGFR automatically alongside any request for creatinine. This is done for all patients whose eGFR is below 60ml/min/1.73m<sup>2</sup>, though the majority (around 80 per cent) report eGFR up to 90ml/min/1.73m<sup>2</sup>. These laboratory generated reports take into account the assay used to measure serum creatinine and for that reason are preferable to calculations using the online calculator.

There are issues (see **Q5**) around standardisation of creatinine assays between different laboratories and laboratories apply appropriate correction factors to allow for this. Thus although online calculators are available via the internet for eGFR<sup>4</sup>, priority should always be given to the laboratory reported eGFR over an eGFR from a one of the available calculators.

The recommended formula for calculating eGFR is the 4-variable (i.e. serum creatinine concentration, age, gender and ethnic origin) isotope dilution mass spectrometry (IDMS) traceable version of the MDRD equation. For those wanting to calculate eGFR for a non-IDMS aligned laboratory there are specific calculators available. The online calculators at [www.mdrd.com](http://www.mdrd.com) have both IDMS-aligned and non-aligned versions.

eGFR  $\geq 60$  ml/min/1.73m<sup>2</sup> should be interpreted with caution as it becomes less accurate as the true GFR increases. For this reason many laboratories have opted to report the numerical value for eGFR only if the eGFR is 60 or under. If the eGFR is over 60 they will simply report it as >60ml/min/1.73m<sup>2</sup>. This is because the MDRD equation was developed in patients with CKD and has been shown to systematically underestimate measured GFR at levels >60ml/min/1.73 m<sup>2</sup>.

The MDRD eGFR will be less reliable in those at the extremes of body size, those with muscle wasting disorders, malnourished individuals, pregnant women, oedematous<sup>5</sup> states (people with swelling due to salt and water retention or a lack of albumin in the blood) and amputees. It has not been validated for use in acute renal failure, nor in certain ethnic populations, for example Asian and Chinese populations.

## **5. Are there inter-laboratory differences in eGFR calculation and reporting?**

Yes. There are different assays for the measurement of serum creatinine concentration in the UK. Therefore, the creatinine in one laboratory is not necessarily equivalent to that in another. However, efforts are ongoing to improve things.

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<sup>4</sup> The Renal Association online eGFR calculator: [www.renal.org/eGFRcalc/GFR.pl](http://www.renal.org/eGFRcalc/GFR.pl)

<sup>5</sup> NHS Choices. Definition of oedema:  
[www.nhs.uk/conditions/oedema/Pages/Introduction.aspx](http://www.nhs.uk/conditions/oedema/Pages/Introduction.aspx)

**Technical detail:**

Inter-laboratory variation in the basis of their creatinine estimation causes the significant differences in estimates of GFR. Since 2006, there has been a process to standardise creatinine assays against the gold standard ('IDMS) method through the National External Quality Assurance Scheme (NEQAS) allowing the IDMS traceable version of the MDRD equation to be applied. This version of the MDRD formula has a different constant to that in the eGFR calculators available online. This standardisation enables direct comparison of creatinine and eGFR values between different laboratories. Some laboratories do not yet produce standardised creatinine concentrations; in these cases, assay-specific versions of the MDRD formula (with different slope and intercepts) are applied to local (non-standardised) creatinine values to produce standardised eGFR results. As a result of the complexities, clinicians should therefore always use the lab calculated eGFR ahead of one they might derive in practice using an online calculator.

In many laboratories, a numeric eGFR is reported up to 60ml/min/1.73m<sup>2</sup>; while others report GFR up to 90ml/min/1.73m<sup>2</sup>, with higher readings reported as ≥90ml/min/1.73m<sup>2</sup>. Estimates of eGFR become less accurate as true GFR increases and that there is bias inherent in the MDRD formula such that the MDRD eGFR underestimates the true GFR where the eGFR is at or above 60ml/min/1.73m<sup>2</sup>.

However, changes in renal function in patients even when well preserved renal function can be of importance. NICE recommend that where the eGFR is reported as ≥60ml/min/1.73m<sup>2</sup>, a rise in serum creatinine of greater than 20 per cent should be regarded as clinically significant.

Changes in eGFR within an individual patient are a highly reliable way of tracking changes in kidney function, though there may be some fluctuation between measurements especially if there has been a large protein containing meal pre-test (strictly avoiding a protein heavy meal in the preceding 12-hours) or there has been undue delay in analysing the specimen. Looking at all previous eGFR values or serum creatinine measurements, not just the last two or three, is important to get an idea of trend over time.

**Practical tip:**

Measure serum creatinine, along with proteinuria test (usually ACR as a morning fasting specimen). Many patients with CKD also have other cardiovascular co-morbidities. Cholesterol, renal function tests and ACR can all be collected in the morning – this reduces the chance of large protein containing meals interfering with the result and there are less likely to be delays in analysis.

**6. Why is ethnicity in the eGFR formula?**

African-Caribbean people (and other people of African ancestry) tend to have proportionally greater muscle mass than non-African-Caribbean patients and at any given body size, appear to produce more creatinine. Consequently, a creatinine of, for example, 150 in an African-Caribbean represents better kidney function than the same creatinine value in a non-African-Caribbean patient. The MDRD formulae therefore applies a correction factor of 1.21 for patients of



African-Caribbean ethnicity – in practice this correction factor should also be applied to those of African ethnicity. Generally, the laboratory will not know the ethnicity of the patient. For that reason the eGFR will always be calculated for a non-African-Caribbean patient, with instructions on the report to multiply by 1.21 for an African-Caribbean patient.

As recording of African Caribbean ethnicity is inconsistent it is sensible to apply this correction to all black people. NICE advises that in practice, this correction should also be applied to those of African ethnicity.

The MDRD formula has not been validated in certain ethnic groups (for example, Asian and Chinese populations) and currently there is no adjustment recommended for Asian, Chinese or mixed race populations.

### **7. Will eGFR replace serum creatinine?**

No. Creatinine will continue to be reported, but in adults (18 years and over) it will be supplemented by eGFR.

Changes in serum creatinine concentration within the normal range can be of importance. NICE recommend that where the eGFR is reported as  $\geq 60 \text{ml/min/1.73m}^2$ , a rise in serum creatinine of greater than 20 per cent should be regarded as significant.

### **8. Can eGFR always be relied upon?**

It is essential to remember that eGFR may be less reliable in certain situations (for example, those at the extremes of body size, those with muscle wasting disorders, malnourished individuals, pregnant women, oedematous states and amputees). The MDRD formulae is not suitable for use in children.

Where a highly accurate measure of GFR is required (e.g. during monitoring of chemotherapy and in the evaluation of renal function in potential living donors), a gold standard measure of GFR (insulin,  $^{51}\text{Cr-EDTA}$ ,  $^{125}\text{I-iodohalamate}$  or iohexol) need to be considered, usually in a secondary care setting.

Measurement of creatinine clearance which is cumbersome requiring an accurately collected 24-hour urine collection paired with a blood test is now rarely required.

### **9. What is the normal range for eGFR?**

An eGFR  $>90 \text{ml/min/1.73m}^2$  is considered normal in a young fit adult and many laboratories report numeric values of up to this value. For patients with an eGFR of  $60 \text{ml/min/1.73m}^2$  – see **Q4-7**. However, eGFR frequently declines with age, on average by between 6 -  $9 \text{ml/min/1.73m}^2$  per decade. Around half of females aged 75 years and over and men aged 85 years and over will have an eGFR under  $60 \text{ml/min/1.73m}^2$ . It is generally believed that declining eGFR with increasing age arises in the context of vascular co-morbidities which are common in the elderly, rather than as a consequence of the ageing process per se.

If the eGFR is greater than 60ml/min/1.73m<sup>2</sup>, CKD is only diagnosed if there is other evidence of chronic kidney damage, for example:

- haematuria of renal origin (after exclusion of other causes)
- raised urinary albumin excretion
- biopsy-proven kidney disease
- or structural abnormalities demonstrated on imaging (for instance, polycystic kidney disease).

The finding of an eGFR of 60–89 ml/min/1.73m<sup>2</sup> should not in itself prompt investigations to look for these markers, unless there is an indication of increased risk of CKD (such as diabetes, hypertension or systemic disease).

### 10. What eGFR reading constitutes a diagnosis of CKD?

For a formal diagnosis of stage 3 to stage 5 CKD, two eGFR readings of <60ml/min present on at least two occasions more than three months apart (with no readings of ≥60ml/min/1.73m<sup>2</sup> in between) over a period of at least three months are required. Patients should not be added to the CKD register in response to a single reduced eGFR reading.

### 11. Does eGFR change with age?

Yes. For patients aged 40 years and over a progressive loss of eGFR of up to 1ml/min/year is commonly seen, particularly amongst patients with hypertension or vascular disease. Whether this should be considered 'normal' is controversial.

Although eGFR can decline with increasing age, this in itself should not preclude these patients from receiving care as outlined by NICE. This care which is supported by the QOF indicators, seeks to protect these patients from experiencing preventable cardiovascular complications to which they are more vulnerable. It is not possible to give an age cut off after which CKD should not be diagnosed or hypertension treated. The decision to treat CKD should be made in conjunction with the patient (and where appropriate their carer), taking into account issues such as their general health and quality of life.

Calculating eGFR using the MDRD formula is not valid in children (those under 18 years of age). The Schwartz or Counahan-Barratt formula should be used in this age group. However, should kidney disease be suspected in a child, this would in itself be a reason for referral for specialist care.

There is controversy about the significance of modest change in eGFR in the elderly. An eGFR <60ml/min/1.73m<sup>2</sup> is an independent predictor of mortality in the general population. However, the association of eGFR with mortality is weaker in the elderly than in younger age groups. Research has shown that very modest reductions in eGFR (50 - 59 ml/min/1.73m<sup>2</sup>) were only associated with an increased adjusted risk of death in people below 65 years of age, although an increased risk of death unadjusted for co-morbidities was evident in all age groups. As the risks of mortality in the elderly are high, then even small increases

in relative risk in this age group may be associated with meaningful increases in absolute risk.

There is a major and uncontroversial, increase in the risk of mortality with an eGFR  $<45\text{ml}/\text{min}/1.73\text{m}^2$  in all age groups. The presence of proteinuria dramatically increases the risks of death and cardiovascular events at all levels of eGFR.

## 12. Is eGFR useful in acute renal failure?

No. However, if an unexpected eGFR  $<60\text{ml}/\text{min}/1.73\text{m}^2$  is reported and there are no previous eGFR readings available for comparison it is worth looking at historical serum creatinine or eGFR values. If there has been a sudden rise in serum creatinine or fall in eGFR levels, or there are no historical values available for comparison, then a repeat creatinine and eGFR should be requested urgently (within two weeks) to exclude the possibility of acute kidney injury (AKI) (previously called acute renal failure).

## 13. What are GPs expected to do when they find someone with a low eGFR?

**A.** Exclude AKI. First compare with previous eGFR to see if there has been a significant change in renal function. If there are no previous eGFR values available for comparison, then compare current creatinine with historical creatinine readings to assess stability. If there are no historical eGFR or creatinine readings available for comparison, or if there has been a sudden change in renal function, then consider AKI. The eGFR should be repeated within two weeks and urine dipstick performed (to look for haematuria) and urinary protein quantified (see **Q30**).

If the patient is acutely unwell consider AKI and repeat the test immediately or discuss/ refer for a specialist opinion.

**B.** If the patient has an eGFR of  $<60\text{ml}/\text{min}$  present on at least two occasions a minimum of three months apart then a diagnosis of stage 3 to stage 5 CKD should be made and the patient added to the CKD register (see **Q10 and Q45**). The patient should be managed according to the principles set out below.

**C.** Check if CKD is progressive. This is defined by NICE as a fall in eGFR  $>5\text{ml}/\text{min}/1.73\text{m}^2$  within a year or a fall in eGFR  $>10\text{ml}/\text{min}/1.73\text{m}^2$  within five years. If it is not clear whether a patient has progressive CKD, a minimum of three readings of eGFR should be taken over a period of at least 90 days.

If the patient has CKD:

- Assess whether the patient has proteinuria (see **Q30**)
- Check the patient's blood pressure. NICE published blood pressure targets for CKD in 2008. These are expressed as ranges. The blood pressure target range is 120-139/ $<90$  mmHg for most patients with CKD. However, if there is higher level proteinuria (ACR  $\geq 70\text{mg}/\text{mmol}$ , equivalent to PCR

≥100mg/mmol) or CKD and diabetes, where a lower target of 120-129/<80 mmHg is recommended. The QOF target has been set at 140/85 mmHg because of the very real difficulty in controlling blood pressure in many of these patients. However, the evidence base supports a target of 120-139/<90 mmHg (or 120-129/<80 mmHg in people with diabetes and/or proteinuria) for the best outcomes.

- In patients with diabetes and microalbuminuria (ACR more than 2.5mg/mmol (men) or more than 3.5mg/mmol (women) ) should be offered treatment with an angiotensin converting enzyme-inhibitor (ACE-I) or angiotensin receptor blockers (ARB) irrespective of the presence of hypertension or CKD stage.
- Non diabetic patients with CKD and hypertensive who have significant proteinuria (ACR ≥30mg/mmol, equivalent to protein-creatinine ratio (PCR) ≥50mg/mmol) should be offered treatment with an ACE-I or ARB and other agents to reduce blood pressure measurements to target.
- In non diabetic patients with CKD there are two proteinuria thresholds to consider:
  - ACR ≥70mg/mmol, equivalent to PCR ≥100mg/mmol, which alters the blood pressure target from 120–139/<90 mmHg to 120 – 129/<80 mmHg
  - ACR ≥30mg/mmol, equivalent to PCR ≥50mg/mmol, which should trigger the use of an ACE-I or ARB as a first line antihypertensive agent.
- It is important to measure potassium and eGFR before starting treatment with an ACE-I or ARB and to repeat this after one to two weeks of therapy and after any increase in dose. ACE-I or ARBs are the best drugs to treat hypertension in proteinuric CKD but they reduce pressure within the kidney (which is often raised in proteinuric CKD) and can cause an initial reduction in eGFR of up to 20 per cent. Greater falls in eGFR might reflect impaired renal perfusion, for instance caused by atherosclerosis and should prompt dose reduction or withdrawal and a specialist referral. Renal function should be measured in any patient on an ACE-I or ARB with a severe intercurrent illness.
- ACE-I and ARBs are often used in non-proteinuric patients to achieve the target blood pressure as part of combination therapy. It is not justified to change patients who have good blood pressure control on other agents and no proteinuria to an ACE-I/ARB just because of CKD stage 3. NICE recommend renal referral where blood pressure is uncontrolled despite the use of four or more anti-hypertensive agents.
- In patients with CKD stage 3B, stage 4 or stage 5 check the patient is not anaemic. Anaemia is generally defined in CKD as Hb<11g/dL (see [Q24](#)).
- Manage other cardiovascular risk by encouraging smokers to stop and consider the use of cholesterol lowering agents and antiplatelet drugs if appropriate.

- Other important measures include:
  1. Ensure there is a quantitative proteinuria test within the last 12 months on the electronic patient record. See **Q29-31** In patients without diabetes, two proteinuria threshold are important:
 

An ACR  $\geq 30$  mg/mmol equivalent to PCR  $\geq 50$ mg/mmol is regarded by NICE as clinically significant proteinuria in patients without diabetes and is the threshold at which ACE-I or ARB treatment is recommended as first line treatment for patients with hypertension and CKD

An ACR  $\geq 70$ mg/mmol, equivalent to PCR  $\geq 100$ mg/mmol defines higher level proteinuria where the blood pressure target is lower at 120–129/<80 mmHg and where ACE-I/ARB treatment is indicated irrespective of presence of hypertension.
  2. In stage 3B and below, check the patient is not anaemic. NICE recommend consideration of investigation and treatment for anaemia where Hb<11g/dL (see **Q24**).
  3. Manage other cardiovascular risk factors by:
    - controlling cholesterol (using the same thresholds and targets as in the general population) encouraging smokers to quit
    - improve control of heart failure and diabetes
    - conduct a medication review for drugs which impair renal function
    - in men, consider whether prostatic disease may be causing outflow problems.

**Further information:**

How CKD is classified (see **Q16**)

How often to re-check creatinine (see **Q37**)

Referral guidance section

**14. Does eGFR vary and what accounts for this variability?**

Yes. The analytical and biological variability of eGFR is estimated to be approximately five per cent. Important sources of variation include:

1. Ingestion of cooked meat. Creatinine is largely a product of protein breakdown and therefore ingestion of high protein meals (largely meat) can change serum creatinine concentration and therefore eGFR. Ingestion of cooked meat may cause a rise in creatinine of 30–40  $\mu$ mol/L or more at four hours, returning to baseline by 12-hours.
2. Change in muscle mass. Loss of muscle mass will result in reduced generation of creatinine and lower eGFR for the same 'actual' renal function. In exceptional cases where muscle mass is greatly reduced expert assistance may be required to interpret eGFR – especially in someone with other vascular disease e.g. a patient with diabetes and amputation.

3. State of hydration.
4. Changes in renal perfusion. This is particularly evident in patients with heart failure in whom small changes in, for example, doses of diuretics and ACE-I, can cause wide fluctuations in eGFR.
5. Intercurrent illness – especially urinary tract infection.
6. Delay in centrifugation of blood samples can cause an increase in creatinine concentration.

## About chronic kidney disease

### 15. What is chronic kidney disease?

CKD has replaced the terms chronic renal failure and renal impairment. It is characterised by one or both of: a reduction in kidney excretory function and the presence of other markers of kidney damage (for example, protein in the urine). The prevalence of CKD increases with age and it is more common in females than in males. The condition is classified into stages of severity on the basis of the eGFR; the less severe stages are extremely common.

**Table 3: Stages of CKD, and the proportion of the population with no creatinine measure and in each stage of CKD (QICKD study data)**

Stage	GFR (ml/min/1.73m <sup>2</sup> )	Percentage of the population (QICKD study data)	Percentage of people >18 years (QICKD study data)	Description
No serum creatinine measure		64.2%	55.5%	We cannot estimate renal function for people who have not had a creatinine measured. However, these are mainly young people and around 75 per cent to 80 per cent of people aged over 60 years have a serum creatinine recorded
1	≥90	23.0%	29.2%	Normal or increased GFR with other evidence of kidney damage is needed to diagnose CKD
2	60 – 89	7.3%	8.3%	Slight decrease in GFR, with other evidence of kidney damage is needed to diagnose CKD (e.g. proteinuria in diabetes)
3A	45 – 59	4.5%	5.8%	Moderate decrease in GFR, with or without other evidence of kidney damage
3B	30 – 44	0.7%	0.9%	
4	15 – 29	0.1%	0.2%	Severe decrease in GFR, with or without other evidence of kidney damage
5	<15	0.0%	0.1%	Established renal failure

**Practical tip to reduce variability:**

Perform eGFR tests under standard conditions where possible, e.g. after an overnight fast but taking water. This can be combined with measurement of fasting lipids and blood glucose in patients with vascular co-morbidities and will usually avoid long delays in the despatch of the blood sample, so it is processed by the laboratory within 12-hours of venepuncture.

Inter-laboratory variation in eGFR has been minimised by the standardisation GFR calculations (see **Q5**).

The stages of CKD are set out in table 3. This table also gives the proportion of the population who do not have a serum creatinine measure in each stage of CKD, as found in the QICKD study.

Patients with CKD can be further 'risk stratified' according to the presence or absence of protein in the urine (proteinuria). Significant proteinuria is associated with an increased risk of renal disease progression towards dialysis, and of cardiovascular disease (CVD). CKD is typically asymptomatic until the more advanced stages of disease.

Most people with CKD have renal function that is relatively stable over time and will never reach dialysis dependence. However all are at risk of CVD. Vascular co-morbidities (for example hypertension, diabetes, peripheral vascular disease and heart failure) are more common in CKD; it is also recognised that reduced eGFR and proteinuria are independent risk factors for CVD. Blood pressure control is effective in reducing cardiovascular risk and slowing progression of CKD.

**16. How is CKD classified?**

CKD is divided into five stages based on eGFR, according to the Kidney Disease Outcomes Quality Initiative (K-DOQI) classification. A minimum of two eGFR values at least three months apart should be used to diagnose and classify CKD – temporary rises in creatinine are common and a diagnosis of progressive CKD should only be based on a sustained decline in renal function. People with an eGFR of 60ml/min/1.73m<sup>2</sup> or over should not be considered to have CKD unless there is other evidence of kidney damage.

In stage 1 and stage 2, other markers of kidney damage are required for a diagnosis of CKD. These markers can either be on imaging (for example, polycystic kidneys) or abnormal urine findings (for example, microalbuminuria, proteinuria or microscopic haematuria).

NICE recommend the addition of the suffix (p) to denote the presence of significant proteinuria (ACR  $\geq$ 30mg/mmol or PCR  $\geq$ 50mg/mmol) (see **Q31**). These patients should be treated with ACE-I/ARB (see **Q26**).



## Stages of Chronic Kidney Disease and complications

### 17. Why has stage 3 been subdivided into stage 3A and stage 3B?

The subdivision of stage 3 into stage 3A (eGFR 45–59 ml/min/1.73m<sup>2</sup>) and stage 3B (eGFR 30–44 ml/min/1.73m<sup>2</sup>) has been adopted in the UK in line with NICE clinical guideline 73. Patients with stage 3B disease are at far higher risk of CVD and end-stage renal disease than those with stage 3A disease and should therefore be regarded as an important target group in primary care.

### 18. What is the expected prevalence of CKD in a practice with a list size of 10,000 patients?

A practice of 10,000 will have around 500 patients with stage 3 to stage 5 CKD, with approximately 15 to 20 of these patients in stage 4 and five to ten of these patients in stage 5. A practice with a higher elderly patient population in a more deprived area are likely to have a higher prevalence. Of the 500 patients with stage 3, 84 per cent (422) will have stage 3A and 16 per cent (68) stage 3B (QICKD trial data)<sup>6</sup>.

About 90 per cent of people with stage 3 to stage 5 will have hypertension, 40 per cent will have vascular disease and 30 per cent will have diabetes. Full details of the current prevalence of stage 3 to stage 5 is recorded on the NHS Health and Social Care Information Centre (NHS IC) website<sup>7</sup>. Patients with CKD are roughly twenty times more likely to die from CVD than progress to end stage renal failure. The all causes mortality rate in CKD is 30 to 60 per cent higher than in the general population.

### 19. What are the most important facts about CKD for primary care clinicians?

- CKD is very common; around five to six per cent of the population have stage 3 to stage 5 disease. It is more common in women than men, though the proportion of men increases as renal function deteriorates.
- Common causes of CKD include diabetes, vascular disease, and in males, obstructive renal disease.
- The majority (greater than 80 per cent) of patients have stable CKD and are at far higher risk from CVD than they are of ever requiring renal replacement therapy. Patients with CKD are roughly 20 times more likely to die from CVD than progress to end stage renal failure. The all causes mortality rate in CKD is 30 to 60 times higher than in the general population. The presence of proteinuria indicates a higher cardiovascular and progressive kidney disease risk.

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<sup>6</sup> de Lusignan S, Gallagher H, Chan T, Thomas N, van Vlymen J, Nation M, Jain N, Tahir A, du Bois E, Crinson I, Hague N, Reid F, Harris K. The QICKD study protocol: a cluster randomised trial to compare quality improvement interventions to lower systolic BP in chronic kidney disease (CKD) in primary care. *Implement Sci.* 2009;4(1):39.

<sup>7</sup> NHS Health and Social Care Information Centre: [www.ic.nhs.uk/nhscomparators](http://www.ic.nhs.uk/nhscomparators)

- NICE define progressive CKD as: a decline in eGFR of  $\geq 5\text{ml/min/1.73m}^2$  within one year based on at least three readings or  $\geq 10\text{ml/min/1.73m}^2$  within five years (see **Q22**).
- The mainstays of management are to:
  - assess stability of disease (by monitoring creatinine, typically every six to 12 months)
  - address cardiovascular risk
  - assess any functional consequences of disease, particularly renal anaemia in those with stage 3B disease and below
  - avoid/reduce exposure to nephrotoxic or potentially nephrotoxic drugs
  - identify patients requiring nephrology referral (see **Q39**).

**Further information:**

The Renal Association: [www.renal.org/JSCRenalDisease/JSCRenalDisease.html](http://www.renal.org/JSCRenalDisease/JSCRenalDisease.html)

SIGN clinical guideline 103 (2008). Diagnosis and management of chronic kidney disease: <http://www.sign.ac.uk/guidelines/fulltext/103/index.html>

Northern Ireland guidelines for management of chronic kidney disease:

<http://www.gain-ni.org/Library/Guidelines/>

<http://www.gain-ni.org/Library/Guidelines/Chronic%20Kidney%20Disease.pdf>

RCGP. Introducing eGFR. Promoting good CKD management. CKD Guidelines Development Committee:

<http://www.renal.org/eGFR/resources/eGFRnatInfoLflt0406.pdf>

BJGP (2006). Chronic kidney disease: a new priority for primary care (straightforward introduction to CKD management in primary care:

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1934049/>

Prescribing in practice (2008). Identification and management of chronic kidney disease (a more detail review of CKD):

<http://www3.interscience.wiley.com/cgi-bin/fulltext/119815475/PDFSTART>

**20. What is the target blood pressure in CKD?**

A target of 120–139/<90mmHg is recommended. A lower threshold of 120–129/<80 mmHg is recommended for:

- patients with CKD and diabetes
- patients with non-diabetic CKD and proteinuria at a level of ACR  $\geq 70\text{mg/mmol}$  or PCR  $\geq 100\text{mg/mmol}$  (see **Q30**) for definitions of proteinuria); note that this is higher than the proteinuria threshold in non-diabetic CKD at which ACEI/ARB are beneficial (see **Q21**).

## 21. How do I manage cardiovascular risk in people with CKD?

Both reduced eGFR and proteinuria are markers of cardiovascular risk which should be documented. The most important aspect of management is blood pressure control.

Other CKD specific aspects of cardiovascular risk management include:

1. appropriate use of ACE-I and ARB (see **Q29**)
2. testing for and treating renal anaemia where appropriate (stage 3B and below)
3. regular recall to reduce and identify progression of CKD
4. lifestyle advice about reducing cardiovascular risk should be given.

Although patients with CKD are at high cardiovascular risk and it is recognised that the Framingham risk assessment tables underestimate cardiovascular risk in CKD, current advice is that the indications for statin therapy in primary prevention and the use of statins and aspirin in secondary prevention, are the same as those in the general population.

## 22. The eGFR seems very variable. How do I assess the stability of CKD?

NICE clinical guideline 73 defines progressive CKD by a fall in eGFR of  $\geq 5\text{ml/min/1.73m}^2$  within one year (based on at least three readings) or a fall of  $\geq 10\text{ml/min/1.73m}^2$  within five years.

These measurements include margins for caution. Modelling the biological and analytical variation of serum creatinine (circa five per cent) using the MDRD equation suggests that to be 95 per cent certain that a change in eGFR is a true change the magnitude of change has to be at least  $12\text{ml/min/1.73m}^2$  when the starting eGFR is greater than 90 ranging down to a change of  $4\text{ml/min/1.73m}^2$  when the starting eGFR is 30 or below.

However, as discussed in **Q5**, there are other important causes of variation in eGFR which should be considered and can cause difficulty. In assessing stability we recommend examining as many eGFR (or serum creatinine) readings over as long a period as possible. You may need to make a professional judgment as to whether you are seeing progressive CKD or normal fluctuation in an individual. If in doubt contact your local renal unit for advice.

NICE recommend that, in assessing progressive CKD, attention is focused upon those in whom continuing decline in eGFR at the observed rate would lead to the need for renal replacement therapy during their natural lifetime.

## 23. What drugs can make CKD worse?

All patients with CKD should have a medication review. The advice of the current issue of the British National Formulary (BNF) should be followed. The priorities for this medication review should be:

- Stop unnecessary medication which may impair renal function. For example, many patients may be on non-steroidal anti-inflammatory drugs (NSAID) which should be discontinued.
- ACE-I and ARB are the best drugs to treat hypertension in proteinuric CKD, although they can sometimes reduce renal perfusion (see **Q26**).
- Renal metabolism and excretion of drugs might be impaired. For example, patients on analgesics, certain beta-blockers (including atenolol), digoxin and allopurinol may all need their dose reducing.
- In patients with diabetes sulphonylureas may accumulate, therefore short acting drugs are preferred. Metformin should only be used under specialist advice when eGFR is below 30mL/min/1.73m<sup>2</sup> (stage 4 and stage 5 CKD). When eGFR is between 30 and 60mL/min/1.73m<sup>2</sup> the risk/benefit ratio of metformin should be assessed on an individual basis.

#### 24. Can Metformin be used in patients with CKD?

Metformin is a useful drug for treating diabetes and can be safely used in early CKD. However, specialist advice is needed if eGFR is <30mL/min/1.73m<sup>2</sup> (stage 4 and stage 5 CKD). The concerns with metformin are:

1. it is excreted via the kidneys
2. accumulation has been associated with lactic acidosis.

However, trials and reviews show that metformin is safe and improves outcomes<sup>8</sup>; it is argued by some that the lactic acidosis risk with metformin has possibly been overstated and more commonly attributable to intercurrent infection than to accumulation of metformin<sup>9</sup>.

In practical terms, it is reasonable for GPs to use metformin in patients with stage 3 disease who have an eGFR >30ml/min/1.73m<sup>2</sup>. However, dosage reduction and specialist involvement should be considered as renal function declines towards this level through normal diabetes shared care arrangements.

Practitioners should be more cautious about increasing metformin doses as renal function declines. The risks of lactic acidosis in people with eGFR <30ml/min/1.73m<sup>2</sup> are said to be related to the age of the patient and the dose of metformin: the higher the dose and the older the patient, the greater the risk.

The Summary of Product Characteristics, which was agreed before the use of eGFR, states that Metformin should not be used if the serum creatinine concentration is >150 µmol/L. Practitioners should exercise clinical judgement and monitor eGFR.

<sup>8</sup> Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med.* 2008 Oct;359(15):1577–89.

<sup>9</sup> Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus: systematic review and meta-analysis. *Arch Intern Med.* 2003;163(21):2594–602

## 25. When should ACE-I and ARBs be used OR not used in CKD?

ACE-I and ARBs should be first line drugs for hypertension in patients with proteinuric CKD. They are indicated in three broad settings in CKD:

- patients with hypertension and non-diabetic CKD who have significant proteinuria (ACR  $\geq 30$ mg/mmol or PCR  $\geq 50$ mg/mmol)
- patients with non-diabetic CKD and higher levels of proteinuria (ACR  $\geq 70$ mg/mmol or PCR  $\geq 100$ mg/mmol) regardless of level of blood pressure
- patients with diabetes and microalbuminuria (ACR  $\geq 2.5$ mg/mmol in men or  $\geq 3.5$ mg/mmol in women) regardless of level of blood pressure.

ACE-I and ARBs can cause a decline in GFR and can increase serum potassium. eGFR and potassium measurements should be repeated one to two weeks after initiation of therapy and after dose increases.

- ACE-I/ARB therapy should not normally commence if the pre-treatment serum potassium concentration is significantly above the normal reference range (typically  $>5.0$ mmol/l). Factors known to promote hyperkalaemia should be looked for.
- ACE-I/ARB therapy should be ceased if the serum potassium concentration rises to above 6.0mmol/l. Ensure other drugs known to promote hyperkalaemia have been discontinued.
- If the eGFR falls by 25 per cent or more (or creatinine increase by greater than or equal to 30 per cent) then the ACE-I/ARB therapy should be ceased immediately and referral to a specialist should be considered to exclude renal artery stenosis. However, it is important to consider other causes of a deterioration in renal function such as volume depletion, intercurrent illness or concurrent medication (e.g. non-steroidal anti-inflammatory drugs (NSAIDs)).
- A small decline in eGFR is a predictable effect of these drugs and there is no need to modify the dose as long as the decline in eGFR is less than 25 per cent. However, follow-up blood tests to ensure the decline is not progressive are essential.

### **Summary of NICE clinical guideline 73 in relation to when ACE-I/ARB should be used:**

- Some small decline in eGFR is expected as part of the effect of these drugs on renal perfusion.
- NICE recommends that following the introduction, or dose increase of ACE-I /ARB, no modification of the dose is required if either the GFR decrease from pre-treatment baseline is less than 25 per cent or the plasma creatinine increase from baseline is less than 30 per cent. If there is a fall in eGFR or rise in plasma creatinine after starting or increasing the dose of ACE-I /ARB, but it is less than 25 per cent (eGFR) or 30 per cent (serum

creatinine) of baseline, the test should be repeated in a further one to two weeks.

- If the decline is greater than 25 per cent or progressive then discontinuation and specialist advice may be appropriate. This can be seen with, for example, hypovolaemia and with renal artery stenosis. It is therefore important to check electrolytes two weeks after starting, after increasing dose and during any intercurrent illness likely to cause hypovolaemia (including acute sepsis).

ACE-I/ARB are often used in non-proteinuric patients to achieve the target blood pressure as part of combination therapy. It is not justified to change patients who have good blood pressure control on other agents to an ACE-I or an ARB just because of non-proteinuric CKD stage 3.

## 26. What are the practicalities of using ACE-I and ARB in CKD?

- ACE-I or ARBs are the best drugs to treat hypertension in proteinuric CKD although they can sometimes reduce renal perfusion. These agents are often used in non-proteinuric patients to achieve the target blood pressure as part of combination therapy. It is not appropriate to change patients who have good blood pressure control on other agents and no proteinuria to an ACE-I/ARB just because of CKD stage 3.

### **Summary of NICE clinical guideline 73 in relation the practicalities of using ACE-I/ARB:**

- Check eGFR and potassium before starting ACEI/ARBs therapy. ACE-I/ARBs should generally not be started where  $K^+ > 5 \text{ mmol/L}$  (potassium). Repeat these measurements between one and two weeks after commencing ACEI/ARB therapy and after each dose increase.
- ACE-I/ARBs should generally be stopped where  $K^+ > 6 \text{ mmol/L}$  and other drugs promoting hyperkalaemia have been discontinued. Concurrent prescription of drugs known to promote hyperkalaemia is not a contraindication to the use of ACEI/ARBs but more frequent monitoring of serum potassium concentration is required.

The eGFR is likely to decrease on commencing ACE-I/ARBs. Following the introduction or dose increase of ACE-I/ARBs, the dose should not be modified if either the GFR decrease from pre-treatment baseline is less than 25 per cent or the plasma creatinine increase from baseline is less than 30 per cent.

- If there is a fall in eGFR or rise in plasma creatinine after starting or increasing the dose of ACEI/ARBs, but it is less than 25 per cent (eGFR) or 30 per cent (serum creatinine) of baseline, the test should be repeated in a further one to two weeks. The ACE-I/ARB dose should not be modified if the change in eGFR less than 25 per cent or change in plasma creatinine is less than 30 per cent.
- However, if the eGFR change is greater than or equal to 25 per cent or change in plasma creatinine is greater than or equal to 30 per cent:

1. investigate other causes of a deterioration in renal function such as volume depletion or concurrent medication (e.g. NSAIDS)
2. if no other cause for the deterioration in renal function is found, cease the ACE-I/ARB therapy or reduce the dose to a previously tolerated lower dose and add an alternative antihypertensive medication if required.

## **27. What attitude does the insurance industry take to CKD?**

A risk assessment will be carried out for life, critical illness and income protection policies. Those patients at highest risk (for example, those who are young or have more advanced disease) are likely to be asked to pay increased premiums or excluded from cover if the risk is thought to be too high. However, although the absolute risk of cardiovascular disease is higher in older people with stage 3 CKD, the increased risk relative to their peers without CKD may not be high enough to warrant higher premiums.

There is little formal risk assessment with travel insurance policies. Pre-existing or associated medical conditions are generally excluded. If comprehensive cover is required then patients should be advised to shop around to ensure they have an appropriate level of cover. Specialist insurers do offer travel policies for the elderly or those with pre-existing conditions, but there is no guarantee that cover will be complete.

## Testing for proteinuria and investigation of people with CKD

### 28. Who should have their urine tested for protein?

Everyone who is known to have CKD should have proteinuria measured annually using a quantitative test (ACR or, if ACR is not available, PCR). Patients with diabetes, who are having annual urinary ACR tests as part of their screening for complications process, don't need to be additionally checked.

People at risk of CKD (particularly those with hypertension and vascular disease) should have a one-off quantitative proteinuria test. This does not need to be repeated on an ongoing basis unless there is significant proteinuria (ACR  $\geq 30$ mg/mmol or PCR  $\geq 50$ mg/mmol). See **Q31** for (the lower) values to be used for patients with diabetes.

Testing of proteinuria is also indicated in other circumstances, for example, oedema or systemic disease.

ACR or PCR is best measured using an early morning urine specimen. This is essential when a random urine sample ACR is 30 to 70 mg/mmol to avoid mislabelling people. Reporting of tests can be complicated as the record does not include whether the sample was taken fasted, thereby making interpretation difficult when looking back at test results<sup>10</sup>.

A routine of measuring ACR on early morning samples may reduce the need for repeat tests. If the ACR is  $\geq 70$ mg/mmol (PCR  $\geq 100$ mg/mmol) or there is microscopic haematuria and ACR  $\geq 30$ mg/mmol (PCR  $\geq 50$ mg/mmol) renal referral is indicated. In asymptomatic individuals there is no evidence that urinary tract infection causes proteinuria; consequently there is no need to send the urine samples of asymptomatic individuals for microscopy and culture<sup>11</sup>.

### 29. How should I measure proteinuria?

NICE recommend that reagent strips should not be used to detect and identify proteinuria, unless they are capable of specifically measuring albumin at low concentrations and expressing the result as an ACR. 24-hour urine collections for protein are similarly unnecessary.

Two quantitative tests to measure proteinuria from a random urine sample are available, ACR and the total PCR, ideally (but not essentially) testing an early morning sample.

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<sup>10</sup> de Lusignan S. Flagging fasting plasma glucose specimens: time to routinely label the context in which pathology specimens are recorded. *Inform Prim Care*. 2009;17(2):63–4.

<sup>11</sup> Carter JL. Tomson CR. Stevens PE. Lamb EJ. Does urinary tract infection cause proteinuria or microalbuminuria? A systematic review. *Nephrology Dialysis Transplantation*. 21(11):3031–7, 2006



NICE recommend that the ACR should be used for the early detection of proteinuria as it has higher sensitivity than the PCR. PCR is an alternative for monitoring proteinuria, particularly where ACR is not available. ACR remains the preferred test for patients with diabetes.

The units for ACR and PCR in the UK are mg (of urine protein) per mmol (of urine creatinine). As a rough estimate the PCR value in mg/mmol divided by 100 approximates to the total daily 24-hour protein excretion in g/day. For example, if PCR = 100mg/mmol, then total daily protein excretion = 100 divided by 100 = 1 g/day.

The ACR is the preferred measure of proteinuria and recommended by NICE. There are proteins other than albumin in urine so the PCR will always be greater than the ACR.

ACR is already in use to diagnose (and monitor) microalbuminuria, the first stage of diabetic nephropathy, and there is logic that a single test can be used to monitor the progression of CKD.

### 30. What is the normal range for ACR (and PCR)?

Urine protein excretion is most simply categorised either: normal or microalbuminuria, or significant proteinuria.

Microalbuminuria can only be assessed using an ACR test. Microalbuminuria is defined as an ACR of  $\geq 2.5$ mg/mmol in males and an ACR of  $\geq 3.5$ mg/mol in females. Microalbuminuria is of great significance in diabetes as an indicator of early diabetic nephropathy and of the need to prescribe ACE-I/ARBs (see **Q26**).

Microalbuminuria is also a marker of kidney damage (in diabetics and non-diabetics) and the demonstration of microalbuminuria is sufficient for a diagnosis of stage 1 or stage 2 where the eGFR is  $>60$ ml/min/1.73m<sup>2</sup> (see **Q16**).

However, in non diabetic CKD the presence of microalbuminuria as such does not require specific therapy (ACE-I/ARB), nor does it justify the use of the suffix (p) in the CKD staging (see **Q16**).

In non-diabetic CKD, clinically significant proteinuria is defined by an ACR  $\geq 30$ mg/mmol or a PCR of  $\geq 50$ mg/mmol. It is these patients to whom the suffix (p) should be added to their staging, and who should receive ACE-I/ARB for non-diabetic CKD. Patients with higher levels of proteinuria benefit from tighter BP control (target 120–129/<80 mmHg) and ACE-I/ARBs regardless of level of blood pressure.

**Table 4: Quantitative proteinuria tests and their approximate equivalents**

ACR mg/ mmol	PCR mg/ mmol	24-hour protein equivalent (g/day)	Significance in non diabetic CKD
30	50	0.5	Clinically significant proteinuria. Initiate ACE-I/ARBs if hypertension present. Target BP 120-139/<90 mmHg. Consider nephrology referral if microscopic haematuria also present
70	100	1	Add suffix (p) to staging. Require ACE-I/ARBs regardless of level of blood pressure. Target BP 120 - 129/<80 mmHg. Consider nephrology referral.

**31. When and how should I test for haematuria?**

When testing for haematuria use reagent strips rather than urine microscopy. It is not necessary to confirm the presence of haematuria using urine microscopy.

In CKD the urine should be tested for blood with a reagent strip if there is significant proteinuria on quantitative testing, e.g. ACR  $\geq 30$  mg/mmol or PCR  $\geq 50$ mg/mmol. In diabetic CKD, the urine should be tested for blood if microalbuminuria is present.

A result of 1+ should be regarded as significant and requires further investigation (see NICE clinical guideline 73, haematuria).

The demonstration of microscopic haematuria with clinically significant proteinuria is an indication for nephrology referral. Persistent non-visible haematuria (with or without proteinuria) should also always prompt investigation for urological disease of urinary tract malignancy in those aged 40 years and over<sup>12</sup>.

**32. When should I test for anaemia in CKD?**

The haemoglobin should be checked in patients with stage 3B, stage 4 and stage 5 to identify anaemia (Hb <11.0 g/dl<sup>13</sup>). NICE recommend that investigation and management of anaemia in patients with CKD should be considered if their Hb level falls to 11 g/dl or less (or 10.5 g/dl or less if younger than two years of age) or, they develop symptoms attributable to anaemia (such as tiredness, shortness of breath, lethargy and palpitations).

Anaemia is common in CKD and more prevalent as renal function declines (table 5).

<sup>12</sup> Kelly JD, Fawcett DP, Goldberg LC. Assessment and management of non-visible haematuria in primary care. *BMJ*. 2009 Jan 16;338:a3021.

<sup>13</sup> NICE clinical guideline 39 (2006). Anaemia management in people with chronic kidney disease: <http://guidance.nice.org.uk/CG39>

**Table 5: Prevalence of anaemia in patients with CKD**

	Population With eGFR & Hb recorded	Hb (g/dl)		Patients with Anaemia (Hb<11g/dl)	
		Mean	Standard deviation	N	%
Mildly impaired renal function	35,669	14.1	1.4	489	1.6%
Stage 3A	6,956	13.6	1.4	223	3.5%
Stage 3B	1,140	12.8	1.6	127	12.0%
Stage 4	184	11.9	1.7	39	22.7%
Stage 5	32	11.5	1.9	10	37.0%

When considering if the anaemia is renal origin, practitioners should always consider whether there are any symptoms to suggest causes other than CKD. Other causes should be sought if there are: suggestive symptoms; a micro- or macrocytic picture; if the anaemia is disproportionate to the level of kidney function (anaemia is mild outside stage 5 disease); or if there is a falling haemoglobin concentration with stable eGFR.

### 33. How is renal anaemia treated?

Patients with renal anaemia are treated with iron (frequently parenteral iron) and erythropoiesis stimulating agents (ESA)/erythropoietin (EPO). Advice should be sought from your local renal unit; how the service might be configured can be found in the IV iron in the community document from the Anaemia Nurse Specialist Association (ANSA)<sup>14</sup>.

### 34. Do I need to measure calcium, phosphate and parathyroid hormone in CKD?

There is no need to measure calcium, phosphate or parathyroid hormone (PTH) in patients with stage 1 to stage 3B CKD. They should be measured in stage 4 and stage 5 CKD. The frequency of testing depends on individual clinical circumstances and generally specialist advice should be sought from your local renal unit.

### 35. Do all CKD patients need a renal ultrasound?

No. Ultrasound should be reserved for those with progressive disease, advanced (stage 4 or stage 5) disease, visible or persistent non-visible haematuria, those

<sup>14</sup> Anaemia Nurse Specialist Association (2009). A guide to the administration of intravenous iron for people with anaemia of chronic kidney disease in a non acute hospital setting: [www.anaemianurse.org/docs/CKD\\_Book\\_A4\\_Final\\_090408.pdf](http://www.anaemianurse.org/docs/CKD_Book_A4_Final_090408.pdf)

with a family history of polycystic kidney disease who are aged 20 years and over, or those with a palpable bladder/lower urinary tract symptoms.

Practices should refer to local care pathways prior to making a referral for a renal ultrasound (see [Q42](#)).

### 36. Who should be tested for CKD?

eGFR should be measured annually in patients with the following risk factors:

- hypertension
- diabetes mellitus
- CVD (ischaemic heart disease, cerebrovascular disease, peripheral vascular disease, heart failure)
- patients receiving potentially nephrotoxic drugs (e.g. NSAIDs, lithium, ciclosporin)
- structural renal tract disease, (prostatic hypertrophy, renal calculi)
- people with a family history of stage 5 CKD
- people with a genetic risk of kidney disease
- multisystem disease with potential kidney involvement (e.g. systemic lupus erythematosus)
- patients with opportunistic detection of haematuria or proteinuria.

All patients at risk of CKD should have a urine dipstick to detect haematuria and quantitative estimation of urinary protein (ACR or PCR).

### 37. How often does eGFR need to be monitored in people with CKD?

**Table 6: Measurement of eGFR: how often?**

Stage	eGFR range (ml/min/1.73 m <sup>2</sup> )	Typical testing frequency
1 and 2 (not part of the QOF)	≥60 + other evidence of kidney disease	12 monthly
3A and 3B	30–59	6 monthly
4	15–29	3 monthly**
5	<15	6 weekly

See also NICE clinical guideline 73.

\*\*Where stage 4 disease is clearly non-progressive (in authors' experience often elderly people) in asymptomatic patients with less than two years stable eGFR/creatinine, six month review is adequate.

## Referral in CKD

### 38. How should referral policy be developed locally?

It is expected that all primary care organisations bring together stakeholders representing patients, renal specialists, and primary care to develop a care pathway for the management of CKD.

### 39. Which patients should be referred for a renal opinion?

Please refer to the NICE CKD clinical guideline 73.

Referral is indicated in the following situations:

- AKI - the discovery of an abnormal eGFR should prompt a review of historical eGFR and where eGFR is not available creatinine measurements.
- All those with stage 4 and stage 5 disease should have their care plan formally discussed with a specialist. It may be possible in some cases for assessment and follow up to take place at the practice. However, guidance for monitoring and future referral or re-referral should be made explicit.
- Higher levels of proteinuria (ACR  $\geq 70\text{mg}/\text{mmol}$  or PCR  $\geq 100\text{mg}/\text{mmol}$ ) unless known to be due to diabetes and already appropriately treated.
- Persistent invisible (microscopic) haematuria and proteinuria (ACR  $\geq 30\text{mg}/\text{mmol}$  or PCR  $\geq 50\text{mg}/\text{mmol}$ ).
- Progressive CKD. NICE defines progressive CKD by a fall in eGFR of  $\geq 5\text{ml}/\text{min}/1.73\text{m}^2$  within one year (based on at least three readings) or a fall of  $\geq 10\text{ml}/\text{min}/1.73\text{m}^2$  within five years.
- Hypertension which remains poorly controlled despite the use of at least four antihypertensive drugs at therapeutic doses.
- Renal anaemia (Hb  $< 11\text{g}/\text{dl}$  and thought to be due to CKD).
- Patients who present with a rare or genetic cause of renal disease (e.g. Adult Polycystic Kidney Disease – APKD).
- Suspected renal artery stenosis.

In certain circumstances referral to another specialist would be appropriate initially. For example, elderly people with complex multiple problems may benefit from initial assessment by a geriatrician. Persistent non-visible haematuria (with or without proteinuria) should also always prompt the urological exclusion of urinary tract disease in those aged 40 years and over. Once malignancy and other urological pathology are excluded, these patients can have their CKD managed by their GP in the usual way.

Where practices are experiencing difficulties accessing specialist renal advice then they should discuss this with the person responsible for commissioning the service.

Patients with newly diagnosed stage 4 CKD should normally be discussed with a renal specialist. Patients who are frail and stable in stage 4 or stage 5 and thought to be in the last year of life or who choose conservative management of their CKD (no dialysis) should be recorded as needing support and palliative care without referral. Such patients are eligible for inclusion on the Gold Standards Framework (GSF).

Approximately 15 to 20 per cent of patients approaching end stage renal disease (ESRD) will choose conservative kidney care (i.e. a non interventional, no dialysis option). This choice should only be made after careful informed discussion and be the result of shared decision making between the patient, their carers and relevant professionals. This decision should be made with healthcare professionals familiar with all the dialysis modality options. Patients in these circumstances may still benefit from treatment of renal anaemia and other complications of CKD and need careful medicines management. On average patients who choose conservative kidney care live about two years.

**Further information:**

NHS National End of Life Care programme (2009). End of life care in advanced kidney disease:

[www.endoflifecareforadults.nhs.uk/publications/eolcadvancedkidneydisease](http://www.endoflifecareforadults.nhs.uk/publications/eolcadvancedkidneydisease)

**40. Who needs urgent referral?**

Patients with newly diagnosed stage 5 CKD should be referred urgently unless it is part of a known terminal illness or they are stable with a known management plan.

Urgent referral is required for AKI (previous termed acute renal failure), malignant hypertension, hyperkalaemia ( $K^+ >7\text{mmol/L}$ ), severe uraemia, fluid overload, and nephrotic syndrome.

**41. What information is required in a referral to a nephrologist?**

- list of dates and results of previous serum creatinine measurements to assess stability, (many practice computerised medical record systems allow a list to be created of previous creatinine measures and then printed off or pasted into a referral letter)
- serum potassium
- haemoglobin
- past medical and full drug history
- blood pressure
- ACR or PCR values
- urinalysis results
- renal ultrasound, if it has been performed (see **Q35**)
- if diabetic: HbA1c-IFCC results and evidence of other diabetic complications

- history of prostate disease in males.

Practices should also refer to any local guidance as to the information required to support referral.

#### **42. When is it reasonable NOT to refer someone to the renal unit?**

Patients' wishes and co-morbidities should be taken into account when considering referral. It may not always be appropriate to refer patients who are frail and stable in stage 4 or stage 5 and thought to be in the last year of life. However, it is essential that the management plan is agreed and documented to avoid confusion and inappropriate referral in the future. These patients may still benefit from treatment of their renal anaemia.

#### **43. How should I provide end of life care (EoLC) in CKD**

GPs may be involved in EoLC in CKD. Most important is that time should be set aside for adequate discussion and exploring our patients wishes. Patients receiving EoLC in CKD should be placed on the cause for palliative care register or identified using other appropriate flags. Anaemia control may be important to reduce symptoms in EoLC in CKD.

## QOF issues, computer reporting and exception reporting

### 44. Why is CKD included in the Quality and Outcomes Framework (QOF)?

There is evidence that the management of the CVD risk factors of patients with CKD is not always optimal. Patients with CKD can readily be identified if pathology labs estimate GFR when they measure creatinine. There is strong evidence that good blood pressure control in patients with CKD alters their outcome. Therefore, blood pressure control became one of the QOF targets from 1 April 2006.

The QOF has been remarkably successful in raising awareness of and improving the management of CKD.

### 45. When should I add someone to the CKD disease register?

The QOF CKD disease register is for patients with stage 3 to stage 5 CKD, e.g. the three more serious of the five stages of CKD, an eGFR  $<60\text{ml/min}/1.73\text{m}^2$ . Therefore, for the purposes of QOF, patients coded as stage 1 or stage 2, will be excluded from the QOF register.

Most practice systems do not automatically add people with a low eGFR to the disease register. This is because to diagnose CKD an eGFR of  $<60\text{ml/min}$  must be present on at least two occasions more than three months apart (without an intermediate reading  $\geq 60\text{ml/min}/1.73\text{m}^2$ ) (see **Q10**). If the criteria for diagnosing CKD are met but the two eGFR readings are in different stages of disease, then the class of CKD is determined by the higher (the least serious) reading.

Having determined the patient has CKD you next need to go on and 'code' the diagnosis. Most of the UK currently uses "5-Byte" Read codes (see **Q47**).

### 45. What code should I use for CKD?

The codes for CKD with and without proteinuria are set out in the 1Z... part of the Read code hierarchy. For which codes to use see the table below. For a more detailed discussion about the layout of the codes and where this code sits in the hierarchy please see the next question.

Please only use the 'with proteinuria' codes where a quantitative proteinuria test confirms proteinuria is present at clinically significant levels (e.g. ACR  $\geq 30\text{mg}/\text{mmol}$  or PCR  $\geq 50\text{mg}/\text{mmol}$  – see **Q29**). Do not base decisions about a diagnosis of proteinuria on urinary dipstick tests.

Please only use the codes in the table and migrate people coded as stage 3 to either stage 3A or stage 3B.



**Table 7: Table of recommended Read Codes (Significant proteinuria levels are for people without diabetes)**

Rubric	Code	Notes	Use
Codes which do not specify whether there is proteinuria – <i>only use early in diagnosis before carrying out ACR test</i>			
CKD stage 1	1Z10.	Note break in sequence as originally just one CKD3 code	Use a CKD code without specifying proteinuria at the stage you have at least two readings less than three months apart
CKD stage 2	1Z11.		
CKD stage 3A	1Z15.		
CKD stage 3B	1Z16.		
CKD stage 4	1Z13.		
CKD stage 5	1Z14.		
Codes to use when there is no significant proteinuria <i>ACR &lt; 30 mg/mol (or PCR &lt; 50 mg/mmol) in people without diabetes</i>			
CKD stage 1 no proteinuria	1Z18.	Note sequence is alternate alphanumeric as the intermediary value is with proteinuria. There are two sequence breaks one for just stage 3 (do not use) and one for no I in the letter sequence	Use a CKD and no proteinuria code for people without clinically significant proteinuria (ACR test is <30mg/mmol or PCR <50mg/mmol)
CKD stage 2 no proteinuria	1Z1A.		
CKD stage 3A no proteinuria	1Z1E.		
CKD stage 3B no proteinuria	1Z1G.		
CKD stage 4 no proteinuria	1Z1J.		
CKD stage 5 no proteinuria	1Z1L.		
Codes to use where a person with CKD has proteinuria <i>ACR ≥ 30 mg/mmol or PCR ≥ 50 mg/mmol</i>			
CKD stage 1 with proteinuria	1Z17.	Note break in sequence as originally just one CKD3 code	Use a CKD and proteinuria code where there is a quantitative lab confirmation of clinically significant proteinuria (ACR test is ≥30mg/mmol or PCR >50mg/mmol)
CKD stage 2 with proteinuria	1Z19.		
CKD stage 3A with proteinuria	1Z1D.		
CKD stage 3B with proteinuria	1Z1F.		
CKD stage 4 with proteinuria	1Z1H.		
CKD stage 5 with proteinuria	1Z1K.		

**47. Why do people think that CKD has the wrong type of hierarchy in the wrong section of the Read code/terminology?**

There has been a surprising amount of correspondence about this issue and the points raised are good ones, and probably like many things were these codes to be reset out they would not be done in this way. The codes clinicians need are all there and the detail is set out in the question above.

However, for those who are interested in informatics and coding there are three basic problems:

- The codes do not sit where you would expect within the 'genitourinary disease' chapter. In this chapter K04 is the code for 'acute renal failure' and K05 is for 'chronic renal failure', with K050 for 'end stage renal failure.' Here or as part of K06 (renal failure unspecified) or its child code K060 (renal impairment) is the sort of place you expect to find CKD. Not in Chapter 1 the 'symptoms' chapter.
- The hierarchy would be better if the 'with proteinuria' or without proteinuria' were child codes of the same parent.
- Placing stages 3Aa and stage 3Bb 'on the end' of one part of the hierarchy and in the middle of another can be confusing.

However, Read can be unclear in other areas. For example: the H3 (COPD) and H33 (Asthma) have a wholly inappropriate parent-child relationship<sup>15</sup>; and the limitations in our ability to record data and investigations in osteoporosis<sup>16</sup> are even more problematic. Although not set out in the easiest order to follow, we can code everything we need to.

To discuss or debate the above outlined issues in further detail, please write to Simon de Lusignan at Informatics in Primary Care<sup>17</sup>.

#### **48. Who could/should be exception reported?**

The usual categories of exception codes apply: 'patient unsuitable' and 'informed dissent'. There may be few situations where these apply other than in terminal illness where renal function may fail and there is no benefit to the patient in attempting to manage their renal impairment.

People who are intolerant to ACE-I and ARB are effectively exception reported as they are removed from the target population. The maximum tolerated dose of antihypertensive code has the same effect.

In the absence of proteinuria it is unnecessary to use ACE-I/ARBs if blood pressure control is satisfactory.

The proportion of patients needed to be treated to achieve the target payment has been set so that there should be a very limited need to exception report.

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<sup>15</sup> Faulconer ER, de Lusignan S. An eight-step method for assessing diagnostic data quality in practice. COPD as an exemplar. *Inform Prim Care*. 2004;12(4):243–54.

<sup>16</sup> de Lusignan S, Chan T, Wood O, Hague N, Valentin T, Van Vlymen J. Quality and variability of osteoporosis data in general practice computer records: implications for disease registers. *Public Health*. 2005;119(9):771–80.

<sup>17</sup> Simon de Lusignan at Informatics in Primary Care. [EditorIPC@googlemail.com](mailto:EditorIPC@googlemail.com)

#### 49. What should GPs record in their computer system?

Recording of all creatinine measures, cardiovascular risk factors (blood pressure, cholesterol and smoking habit) and evidence of renal damage, including the presence of proteinuria, are all important. Haemoglobin should be measured and recorded as some patients with CKD become anaemic. A family history of CKD should also be recorded.

Negative results, particularly negative urine proteinuria tests and renal tract imaging results, will help with more sophisticated sorting of patients at a later date.

Diagnosis codes are not assigned automatically in many computer systems. So whilst eGFR results may be incorporated into records once pathology results are filed these patients may not be assigned a diagnostic code. You should not assign a diagnostic code based on a single eGFR reading as strictly at least two eGFR readings a minimum of three months apart are required for a diagnosis of CKD to be made. The class of CKD is based on the best (e.g. highest) eGFR reading during this period.

Sometimes when there is only one eGFR reading there are many more historic creatinine readings. If there are a series of similar serum creatinine values which are similar to the current result it may be reasonable to assign a class of CKD.

Finally, the stage of CKD should only be qualified as with or without proteinuria when proper quantitative measures (e.g. ACR or PCR) have been made and NICE threshold values exceeded (see **Q30**).

#### 49. How do I get more information?

As a practice or locality consider talking to the nephrologist or unit that covers your geographical patch. Many produce local guidance and most are happy to come and talk/meet with local practice or locality groups. Also consider asking your local GP tutor to include management of CKD in your postgraduate programme and update courses.

##### **Further information:**

NICE clinical guideline 73.

The Renal Association. A comprehensive set of resources to help manage CKD, including links to calculators and guidelines: [www.renal.org](http://www.renal.org)

#### 50. Is any patient information available?

Patients may find the comprehensive information available from NICE helpful: [www.nice.org.uk/Guidance/CG73/](http://www.nice.org.uk/Guidance/CG73/)

A patient information leaflet can be downloaded from: [www.renal.org/eGFR/resources/PatientCKDinf/an2007.pdf](http://www.renal.org/eGFR/resources/PatientCKDinf/an2007.pdf)

Many of the computerised medical record systems contain embedded links to patient information sheets.

## Annex 1

This question no longer applies to UK practices as eGFR is generally available, however it is possible that this document may be used internationally where this question may still be relevant therefore it has been inserted as an annex to the updated FAQs.

### What should practices do if they do not have access to eGFR?

All practices should have access to eGFR. In the rare circumstances in which they don't, practices should use one of the available calculators. Two suggested strategies (which can be used alone or in combination) are:

- Calculate eGFR for each serum creatinine result that comes into the practice. This can be done using an online calculator available at: [www.renal.org](http://www.renal.org)
- Export age, gender and creatinine from your GP computer system into a spreadsheet which will run the calculation for you. This can be downloaded from <http://www.clininf.eu/gfr/> (N.B. You must 'enable macros' if asked to do so when you download this; full instructions are available via a tab at the bottom of the spreadsheet). Once in the spreadsheet the data can be sorted by stage of CKD. We would recommend that you flag patients for a blood pressure review at their next visit.

Some of the software manufacturers have developed options which allow eGFR to be estimated for the whole practice population. Practices should contact their computer system supplier about this. However, do remember that there are inter-laboratory differences in creatinine assays (see **Q4-7** How is eGFR calculated) and that where the in-house calculated eGFR differs from the laboratory eGFR, priority should be given to the laboratory result.

There is no easy way of defining a serum creatinine cut-off level as an alternative to using eGFR. This is because creatinine is a relatively poor measure of renal function – it is possible to lose up to 50 per cent of renal excretory function before the serum creatinine concentration rises above the upper limit of normal.

## Annex 2

### Glossary of terms

Abbreviation	Definition
ACE-I	Angiotensin Converting Enzyme - Inhibitor
ACR	Albumin-Creatinine Ratio
AKI	Acute Kidney Injury
ANSA	Anaemia Nurse Specialist Association
APKD	Adult Polycystic Kidney Disease
ARB	Angiotensin Receptor Blockers
BJGP	British Journal of General Practice
BMA	British Medical Association
BNF	British National Formulary
CKD	Chronic Kindey Disease
CVD	Cardiovascular Disease
DH	Department of health
eGFR	estimated Glomerular Filtration Rate
EoLC	End of Life Care
EPO	Erythropoietin
ESA	Erythropoiesis Stimulating Agents
ESRD	End Stage Renal Disease
GFR	Glomerular Filtration Rate
GPC	General Practitioners Committee
GSF	Gold Standards Framework
IDMS	Isotope Dilution Mass Spectrometry
K-DOQI	Kidney Disease Outcomes Quality Initiative

MDRD	Modification of Diet in Renal Disease
NEQAS	National External Quality Assurance Scheme
NHHS IC	NHS Health and Social Care Information Centre
NHS	National Health Service
NICE	National Institute of Clinical Excellence
NSAID	Non-steroidal anti-inflammatory drugs
NSF	National Service Framework
PCR	Protein-Creatinine Ratio
QICKD	Quality Improvement Online Data Dictionary
QOF	Quality and Outcomes Framework
RCGP	Royal College of General Practitioners
SIGN	Scottish Intercollegiate Guidelines Network

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