



## Chronic kidney disease

Chronic kidney disease (CKD) is a long-term irreversible deterioration in the function of the kidneys, often in patients with diabetes and/or hypertension. It affects approximately 5.5% of adults, with a higher prevalence in older people.<sup>1</sup> CKD can have huge health implications for individual patients, including significantly increased risk of cardiovascular disease (CVD) and an increased vulnerability to acute kidney injury (AKI). A small, but significant, number of cases progress to end-stage renal disease (ESRD) requiring dialysis or kidney transplant, which carries a major personal, social, and economic burden. Historically, CKD was considered to be a condition to be managed primarily by specialists. However, the introduction of laboratory reporting of the estimated glomerular filtration rate (eGFR) alongside serum creatinine values has improved the identification of people with CKD in primary care. When early stage CKD is identified promptly, it is easier to reduce mortality and improve the quality of life, in the most cost-effective way. It is in primary care where there is the greatest opportunity to tackle CKD.

The National CKD Audit was rolled out in England and Wales in 2015. It aimed to provide a comprehensive picture of identification, management, and outcomes of people with CKD. The resulting data, representing 74% of all practices in Wales, show that there are many examples of good practice. However, there is also high variability in the testing of people at high risk of CKD, the accuracy of coding, and the review and management of people with identified CKD.<sup>1</sup>

This bulletin discusses the early identification of patients with CKD in primary care, along with appropriate management to minimise cardiovascular risk, potential complications, and renal morbidity.

### Classification of CKD

CKD is defined as an abnormality of kidney function and/or structure, present for more than three months, with implications for health.<sup>2</sup> This may involve a reduced GFR, increased urinary albumin, or both.<sup>3</sup> The classification of CKD has evolved over time.

### Summary

- CKD can have huge health implications for individual patients, including increased CVD risk, increased vulnerability to AKI, and a small, but significant risk of progressing to ESRD.
- The majority of people with CKD also have hypertension and/or diabetes.
- Not all patients with CKD will progress at the same rate and it is important to be aware of the factors associated with CKD progression.
- Management of CKD aims to minimise cardiovascular risk and to slow the progressive loss of renal function.
- Hypertension is one of the greatest risk factors for the progression of CKD. ACEIs and ARBs have been shown to slow the progression of CKD and delay the need for renal replacement therapy.
- The relationship between AKI and CKD is complex; CKD increases the risk of AKI, and AKI increases the risk of subsequent CKD.
- Medicines use in patients with CKD can be problematic, sometimes requiring dose reduction or a change of medicine.
- Support should be provided to enable people with CKD to self-manage their condition, and to make informed choices about their care.

The current system of classification recommended by the National Institute for Health and Care Excellence (NICE) is adapted from Kidney Disease Improving Global Outcomes (KDIGO)<sup>4</sup> and uses a combination of GFR and albumin:creatinine ratio (ACR) categories (see Figure 1). ACR is an important indicator of cardiovascular risk and progression. The inclusion of the ACR categories reflects the increased risk of adverse outcomes associated with even small levels of albumin in the urine. This increased risk is seen in people both with and without diabetes.<sup>2</sup> A combination of increased ACR and decreased GFR multiplies the risk of adverse outcomes.

### Identifying patients at risk of CKD

The underlying disease processes in CKD are wide-ranging. However, the majority of people with CKD also have hypertension (approximately 75-85%) and/or diabetes (approximately 20%).<sup>3</sup>

As there are often no specific symptoms, particularly in the early stages, CKD is often diagnosed when a marker of renal damage, such as abnormal eGFR, is picked up incidentally, perhaps when monitoring other co-morbidities.

NICE recommends targeted screening for CKD in people with any recognised risk factor/s (see Figure 2). Obesity (without metabolic syndrome), age, gender, or ethnicity should not be used alone, in the absence of other risk factors, as risk markers to test for CKD.<sup>2</sup> Patients prescribed medicines known to be nephrotoxic should have their eGFR monitored at least annually, or more frequently when there are changes to treatment, e.g. dose increases.

Figure 2. Risk factors for CKD<sup>2,5</sup>

- diabetes
- hypertension
- cardiovascular disease
- history of acute kidney injury
- structural renal tract disease, recurrent renal calculi, or prostatic hypertrophy
- disease that causes multisystem damage e.g. systemic lupus erythematosus
- family history of ESRD
- persistent haematuria
- history of nephrotoxic medicine use, e.g. NSAIDs, calcineurin inhibitors, and lithium

For other high-risk groups the frequency of monitoring (eGFR and ACR) should be agreed with the patient. The suggested frequencies in Figure 1 should be tailored to individual patients according to underlying causes, co-morbidities, medication, intercurrent illness, and past patterns of eGFR and ACR.<sup>2</sup>

Figure 1. Classification of CKD and recommended frequency of monitoring of GFR (number of times per year, by GFR and ACR category) for people with, or at risk of, CKD.<sup>2</sup>

		ACR categories (mg/mmol), description and range			Increasing risk ↓
		A1 < 3 Normal to mildly increased	A2 3 - 30 Moderately increased	A3 > 30 Severely increased	
GFR categories (ml/min/1.73m <sup>2</sup> ), description and range	G1 ≥ 90 Normal and high	≤ 1 <sup>†</sup>	1	≥ 1	Increasing risk ↓
	G2 60 - 89 Mild reduction related to normal range for a young adult	≤ 1 <sup>†</sup>	1	≥ 1	
	G3a 45 - 59 Mild to moderate reduction	1	1	2	
	G3b 30 - 44 Moderate to severe reduction	≤ 2	2	≥ 2	
	G4 15 - 29 Severe reduction	2	2	3	
	G5 < 15 Kidney failure	4	≥ 4	≥ 4	
Increasing risk →					

<sup>†</sup> Not CKD in the absence of markers of kidney damage (see Figure 3).

## Testing for CKD

### 1. Measure serum creatinine (for laboratory to calculate eGFR)

An eGFR  $< 60\text{ml}/\text{min}/1.73\text{m}^2$  observed for the first time in a patient should be checked within two weeks, particularly to rule out AKI and a rapid decline in renal function, which would require prompt attention.<sup>6</sup> If the eGFR remains  $< 60\text{ml}/\text{min}/1.73\text{m}^2$  with no evidence of acute deterioration, repeat within three months.<sup>5</sup>

When measuring eGFR, the patient should be advised not to eat any meat for 12 hours beforehand. Laboratories calculate eGFR using a formula based on serum creatinine, age, and gender. The eGFR is an estimate of an adjusted GFR (not the person's actual GFR), standardised for average body size. Average body size equates to a body surface area of  $1.73\text{m}^2$ , and so the eGFR is reported as  $\text{ml}/\text{min}/1.73\text{m}^2$ . The eGFR should be interpreted with caution if the person has extremes of muscle mass, or in people who are pregnant, oedematous, or malnourished, or where renal function is changing rapidly.<sup>5</sup> Trimethoprim is a competitive inhibitor of creatinine secretion and therefore has the potential to raise serum creatinine independently of actual GFR, with no true change in overall kidney function.<sup>7</sup> It may be prudent to avoid testing for CKD while a patient is taking trimethoprim, or to re-test when the course has been completed.

Figure 3. CKD is diagnosed by one of the following persisting after 90 days:<sup>2,5</sup>

- markers of kidney disease
  - abnormality of renal function on imaging/histology
  - abnormal urinary sediment
  - electrolyte or other abnormalities due to tubular disorders
  - history of kidney transplantation
  - albuminuria (ACR  $> 3\text{mg}/\text{mmol}$ )
- eGFR  $< 60\text{ml}/\text{min}/1.73\text{m}^2$

### 2. Take an early morning urine sample to measure urinary ACR

A morning urine sample is more reliable, because a false positive, due to orthostatic proteinuria, which is not clinically significant, is less likely.<sup>5</sup> An abnormal ACR of between 3 to  $70\text{mg}/\text{mmol}$  should be repeated within three months;  $70\text{mg}/\text{mmol}$  or more is considered to be significant proteinuria and requires referral to a nephrologist.

### 3. Dip the urine for haematuria

If urine dipstick shows 1+ or more of blood, a mid-stream urine sample should be used to exclude urinary tract infection (UTI).

Patients with persistent haematuria (two out of three dipsticks show 1+ or more of blood) and no UTI, should be referred to a specialist (if in the appropriate age group) to exclude urological cancer.<sup>2,8</sup> Abnormal tests should be repeated after 90 days to confirm persistence and fulfil the CKD diagnostic criteria (see Figure 3).

For people with a borderline diagnosis of CKD (e.g. those with eGFR of  $45\text{--}59\text{ml}/\text{min}/1.73\text{m}^2$  for at least 90 days with no proteinuria or other marker of kidney disease), advice should be sought from a nephrologist.

## Progression of CKD

Once CKD is diagnosed, not all patients will progress at the same rate. However, in those who do progress, the subsequent mortality and morbidity risks rise exponentially, as do the associated healthcare costs.<sup>2</sup> It is therefore important to be aware of the factors associated with CKD progression, in order to identify patients at risk, intervene at the earliest possible stage, and improve the associated adverse outcomes. Several factors associated with progression of CKD have been identified (see Figure 4).

Figure 4. Risk factors for CKD progression<sup>2,5</sup>

- cardiovascular disease
- proteinuria
- acute kidney injury
- hypertension
- diabetes
- smoking
- African, African-Caribbean or Asian family origin
- chronic use of NSAIDs
- untreated urinary outflow obstruction

When assessing the rate of progression, the eGFR should be repeated a minimum of three times over a period of at least 90 days. An **accelerated** progression of CKD is indicated by:

- Sustained decrease in eGFR of  $\geq 25\%$  and a change in GFR category within a year, or
- Sustained decrease in eGFR of  $15\text{ml}/\text{min}/1.73\text{m}^2$  per year.

However, when deciding whether any decline in renal function is significant, the person's baseline eGFR should be considered along with the lifetime likelihood, if they continued the same rate of decline, that they would eventually reach an eGFR level that would require renal replacement therapy.<sup>5</sup> For example, a rate of decline of  $3\text{ml}/\text{min}/1.73\text{m}^2$  per year would be of greater concern in a person of 40 years of age with a baseline eGFR of  $30\text{ml}/\text{min}/1.73\text{m}^2$  than in a person of 70 years of age with a baseline eGFR of  $60\text{ml}/\text{min}/1.73\text{m}^2$ .<sup>5</sup>

## Referral to specialist care

Although many patients with CKD can be treated in primary care, certain groups should normally be referred for specialist assessment (see Figure 5). An individual's wishes and co-morbidities should be taken into account when considering referral.<sup>2</sup>

Figure 5. Who should be referred?<sup>2,5</sup>

- GFR < 30ml/min/1.73m<sup>2</sup> (GFR category G4 or G5), with or without diabetes
- ACR ≥ 70mg/mmol, unless known to be caused by diabetes and already appropriately treated
- ACR ≥ 30mg/mmol (ACR category A3), together with haematuria
- sustained decrease in GFR of ≥ 25%, and a change in GFR category or sustained decrease in GFR of ≥ 15ml/min/1.73m<sup>2</sup> within 12 months
- hypertension that remains poorly controlled despite the use of at least four antihypertensives at therapeutic doses
- known or suspected rare or genetic causes of CKD
- suspected renal artery stenosis
- complications of CKD such as renal anaemia (haemoglobin < 110g/L) or renal bone disease (e.g. abnormal serum calcium, phosphate, or parathyroid hormone).

On a practical note, if a patient is thought to require a renal ultrasound scan, a request at the time of referral or beforehand can reduce potential treatment delay.

## Management of CKD

People with CKD are five to 10 times more likely to die prematurely than they are to progress to ESRD requiring dialysis. This increased risk of death rises exponentially as kidney function worsens and is largely attributable to CVD.<sup>9</sup> Therefore, the overall aims in the management of CKD are to minimise cardiovascular risk and to slow the progressive loss of renal function.

Patients with CKD should be considered as being in the highest risk group for CVD. Although published evidence on **statin** use in CVD has largely excluded people with CKD, there is no evidence to suggest that the effectiveness of statin therapy would be different for people with CKD compared to other populations. NICE recommends all people with CKD should be offered **atorvastatin** 20mg for primary or secondary prevention of CVD. The dose should be increased if > 40% reduction in non-HDL cholesterol is not achieved. A renal specialist should be consulted if higher doses are required for patients with a eGFR < 30ml/min/1.73m<sup>2</sup>.<sup>2</sup>

**Antiplatelet** treatment is not routinely needed for the primary prevention of CVD in patients with CKD. However, when prescribing antiplatelet treatment for secondary prevention,<sup>2</sup> be aware that patients with CKD, paradoxically, have both thrombotic and bleeding tendencies. An increased risk of bleeding becomes more prevalent as severity of CKD increases.<sup>5</sup>

**Hypertension** is one of the greatest risk factors for the progression of CKD, regardless of aetiology. There is good evidence that reducing blood pressure reduces cardiovascular risk and renal progression.<sup>2</sup>

Figure 6. Blood pressure (BP) targets in CKD<sup>2</sup>

	Target BP
People with CKD	< 140/90mmHg
People with CKD and diabetes or with ACR ≥ 70 mg/mmol	< 130/80mmHg

**ACE inhibitors and angiotensin II receptor blockers (ARBs)** have been shown in clinical trials to slow the progression of CKD and delay the need for renal replacement therapy in both diabetic and non-diabetic patients.<sup>7</sup> However, the beneficial effects of ACE inhibitors and ARBs appear to be more closely related to the presence or absence of proteinuria rather than blood pressure control.<sup>5</sup> Therefore, one of these agents should be offered first-line to people with CKD and:

- diabetes and an ACR ≥ 3mg/mmol
- hypertension and an ACR ≥ 30mg/mmol
- an ACR ≥ 70mg/mmol (irrespective of hypertension or CVD)<sup>2</sup>

The treatment of hypertension in people with CKD and an ACR < 30mg/mmol, but no diabetes, should be guided by the NICE Hypertension guideline (CG127). Before initiating treatment with an ACE inhibitor or ARB, eGFR and serum potassium concentration should be measured as a baseline and then measured one to two weeks after starting, and after each dose increase. The dose should be titrated to the maximum tolerated. These medicines should not be used if the pre-treatment serum potassium is > 5.0 mmol/L.<sup>2</sup> ACE inhibitors and ARBs cause a reversible reduction in glomerular blood flow and the eGFR often falls when treatment is initiated.<sup>6</sup> This is not usually an indication of increased damage, and providing the decrease in eGFR is < 25% of baseline, no dose adjustment is necessary, but the test should be repeated in one to two weeks. If the eGFR change is ≥ 25% or the change in serum creatinine is ≥ 30%, if no other cause of renal deterioration can be found, the ACE inhibitor or ARB should be stopped or reduced to a previously tolerated dose, and alternative antihypertensive medication added if required.<sup>2</sup>

If the eGFR fails to recover fully, or if the hypertension is difficult to manage in this context, consider referring to a nephrologist.

It was previously thought that combination therapy of an ACE inhibitor with an ARB to completely block the renin-angiotensin system would delay progression of CKD. However, currently available evidence suggests that the risks of hyperkalaemia and AKI outweigh the benefits in most patients with CKD, and this combination is not recommended.<sup>2</sup>

Patients may require multiple medicines to control their blood pressure and other classes of antihypertensive medicines can be combined with ACE inhibitors or ARBs if target blood pressure is not achieved. Choice of antihypertensive should be based on cardiovascular indications and co-morbidities. Patients with hypertension that remains poorly controlled, despite the use of at least four antihypertensive medicines at therapeutic doses, should be referred to a specialist.<sup>2</sup>

### Acute kidney injury

AKI is a clinical syndrome with a spectrum of severity from minor changes in kidney function to acute failure requiring renal replacement therapy.<sup>10</sup> It is characterised by an acute deterioration in renal function and defined as a rapid (over hours or days) rise in creatinine, fall in eGFR, or fall in urine output.<sup>11</sup> Older patients with chronic conditions such as CKD, diabetes, heart failure, and cancer are at increased risk of AKI.<sup>11,12</sup> Most cases occur in conjunction with co-existing acute illness, as a result of infection, hypovolaemia, hypotension (e.g. during periods of vomiting, diarrhoea, or blood loss), or medication effects. These causes, often combined, account for up to 80% of cases, on a background of increased risk.<sup>13</sup>

AKI is associated with extremely poor outcomes, e.g. very high mortality rates (>20%), increased length of hospital stay, and incomplete recovery of kidney function (many patients will be left with CKD). AKI and CKD are complex interconnected syndromes; CKD increases the risk of AKI and an episode of AKI increases the likelihood of subsequent development of CKD. Although AKI is common in hospitalised patients, it is not just a secondary care problem. Primary care practitioners have an important role in prevention, early detection and management, and post-AKI care.<sup>13</sup>

It has been estimated that up to 30% of AKI cases may be medicine-related, with NSAIDs, diuretics, and ACE inhibitors/ARBs the main culprits.<sup>14</sup> Although patients taking ACE inhibitors/ARBs or diuretics should have their renal function regularly monitored,

AKI typically develops over the course of days. Therefore, it is key for practitioners to be aware of the risk of AKI, to measure serum creatinine in patients at increased risk (such as those with CKD) presenting with an acute illness, and to modify treatment during high-risk periods if possible.

The implementation of 'sick day rules' for patients at high risk of AKI has been widely advocated. This involves anticipatory advice to patients to discontinue certain medicines (such as ACE inhibitors, ARBs, NSAIDs, diuretics, metformin, and sulfonylureas) should they experience periods of acute illness, such as diarrhoea or vomiting.

The 'Think Kidneys' programme prefers the term 'sick day guidance' to 'sick day rules' as the latter term suggests a dogmatic approach to management instead of providing individualised advice. While there is weak evidence that provision of such advice reduces net harm, it is possible that there are potential harms, particularly when the patients have not been clinically assessed, or where it is unclear at what level of illness the medicines should be stopped. Potential harms include patients not re-starting their treatment upon recovery, or stopping their treatments during even minor illness, decompensated heart failure occurring when ACE inhibitors/ARBs and diuretics are stopped, and diabetes control adversely affected by cessation of glucose-lowering treatment.<sup>15</sup> The 'Think Kidneys' programme recommends that practitioners should discuss the possible causes of AKI with patients and carers, including the need to maintain fluid balance during episodes of acute illness. It advises that it is reasonable to provide sick day guidance on temporary cessation of medicines, assessment of illness severity, and when to seek professional help for patients considered to be at higher risk of AKI based on an individual risk assessment.<sup>15</sup>

The management of AKI is dependent on aetiology and severity. Initial management generally includes clinical assessment of volume status, appropriate fluid resuscitation, and medication review.<sup>16</sup> The risk for developing CKD after AKI is long-term and increases with increasing severity of AKI.<sup>16</sup> It is important to ensure appropriate follow-up and patient education. Patients should be monitored for the development or progression of CKD for at least two to three years after AKI, even if serum creatinine has returned to baseline.<sup>2</sup> A plan to carefully re-introduce or re-titrate necessary medicines that were withheld during the acute illness should be discussed with the patient together with the risk of recurrent AKI, and the potential causative role of dehydrating illnesses and certain medicines, such as NSAIDs, which are available without prescription.

## Prescribing for patients with CKD

The use of medicines in patients with reduced renal function can be problematic for several reasons:

- Reduced renal excretion of a medicine or its metabolites may cause toxicity
- Sensitivity to some medicines is increased even if elimination is not impaired
- Many adverse effects are tolerated poorly by patients with renal impairment
- Some medicines are not effective when renal function is reduced.

Many of these problems can be avoided by reducing the dose or by using a different medicine.<sup>17</sup> Although few medications truly have a direct toxic effect on the kidneys, the term “nephrotoxic” is widely used to describe medicines that have the potential to impair renal function if used under certain circumstances, such as where a patient has a degree of CKD in conjunction with hypovolaemia and acute illness.<sup>18</sup> Potentially nephrotoxic medication should, if possible, be avoided in patients with CKD. The consequences of nephrotoxicity are likely to be more serious when renal reserve is already reduced.

### Figure 7. Potentially nephrotoxic medicines

- NSAIDs
- calcineurin inhibitors e.g. ciclosporin, tacrolimus
- lithium salts
- diuretics
- certain antibiotics
- radiographic contrast agents
- ACE inhibitors\*
- ARBs\*

*\*Although ACE inhibitors or ARBs are recommended in many patients with CKD, their use in combination with a diuretic and an NSAID can result in AKI, especially in volume-depleted patients.*

Information concerning the prescribing of individual medicines in renal impairment can be found in the summary of product characteristics (SPC), the British National Formulary (BNF), or via your local medicines information centre ([www.wmic.wales.nhs.uk](http://www.wmic.wales.nhs.uk)).

Published information on the effects of renal impairment on drug elimination is usually stated in terms of creatinine clearance (based on the Cockcroft and Gault formula) as a surrogate for GFR. However, the information on dosage adjustment in renal impairment for most medicines in the BNF is expressed in terms of eGFR, rather than creatinine clearance.

Although the two measures of renal function are not interchangeable, the BNF advises that in practice, for most medicines and for most patients (over 18 years) of average build and height, eGFR (MDRD formula) can be used to determine dosage adjustments. For potentially toxic medicines with a narrow therapeutic index, creatinine clearance should be used in addition to plasma drug concentration and clinical response.

In patients at both extremes of weight, the absolute GFR or creatinine clearance (calculated from the Cockcroft and Gault formula) should be used to adjust dosages.<sup>17</sup>

## Self management

Support should be provided to enable people with CKD to self-manage their condition, and to make informed choices about their care.<sup>2</sup>

This includes offering advice and information about:

- blood pressure management
- regular exercise and healthy body weight
- smoking cessation and alcohol limits
- healthy diet (do not offer low-protein diets)
- the relationship of CKD with co-existing conditions, e.g. diabetes
- the importance of keeping vaccinations up-to-date, e.g. influenza and pneumococcal
- medicines, including those that should be avoided, e.g. over-the-counter NSAIDs.<sup>2,5,19</sup>

Healthcare professionals may not always inform people that they have CKD. This could be due to concerns over the validity of the diagnosis and a desire not to induce unnecessary anxiety or ‘medicalise’ the ageing process.<sup>19</sup> Older people, in whom reduced kidney function is common, may find the use of the words ‘chronic’ and ‘disease’ distressing unless a sensitive explanation is offered.<sup>19</sup>

As well as enabling self-management, there is a patient safety element to a disclosure of the diagnosis; patients need to know they have CKD to be aware of their increased risk of AKI.<sup>19</sup> In many patients, CKD is of greater significance as a risk factor than a disease process (depending on many factors including disease stage, rate of progression, and primary disease). It is important that these aspects are discussed with patients.

Helpful advice for people with kidney disease is available from kidney charities such as

- Kidney Research UK ([www.kidneyresearchuk.org](http://www.kidneyresearchuk.org))
- National Kidney Federation ([www.kidney.org.uk](http://www.kidney.org.uk))
- Kidney Care UK ([www.kidneycareuk.org](http://www.kidneycareuk.org)).
- Kidney Wales ([www.kidneywales.cymru](http://www.kidneywales.cymru))

Summaries of Product Characteristics (SPCs) should be consulted for full prescribing information.  
References available at [www.wemerec.org](http://www.wemerec.org)

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