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GPs should be vigilant for accelerated progression of CKD

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Abstract

Chronic kidney disease (CKD) is a potentially progressive condition resulting in a decline in renal function secondary to a range of causes. An individual is considered to have CKD if abnormalities of kidney function or structure have been present for more than three months. Despite being common, CKD often remains undiagnosed partly because of lack of symptoms until late in the disease process. Late detection of CKD, and hence lack of effective management, increases the risk of progression to end-stage renal disease which often requires renal replacement therapy such as dialysis or transplantation. Furthermore, delayed diagnosis of CKD is associated with increased morbidity and mortality. Derangement in serum creatinine and eGFR will alert a clinician to a patient with potential CKD. However, creatinine and eGFR are imperfect measurements of kidney function and should be interpreted in the context of the individual patient. All patients with CKD should have the following parameters checked at the earliest opportunity: blood pressure; full blood profile, glucose and lipid profile; dipstick urinalysis; and urinary albumin:creatinine ratio. Patients with CKD should be provided with information and education tailored to the severity of their CKD and risk of progression. Timely referral for specialist nephrology input when required is key. The decision to refer to nephrology should take account of the patient's wishes and their comorbidities.

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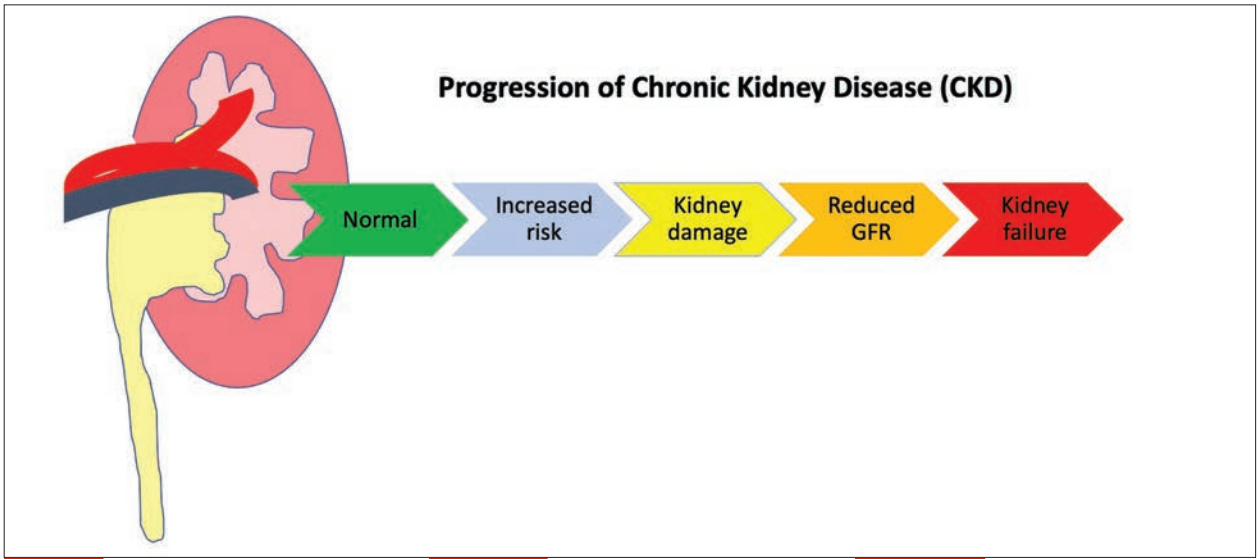


FIGURE 1
Progression of chronic kidney disease

How should patients be assessed?

CHRONIC KIDNEY DISEASE (CKD) IS A POTENTIALLY PROGRESSIVE CONDITION RESULTING IN A DECLINE IN renal function secondary to a range of causes. An individual is considered to have CKD if abnormalities of kidney function or structure have been present for more than three months.

The definition of CKD includes all individuals with markers of kidney damage or those with an estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73m^2 on at least two occasions 90 days apart (with or without markers of kidney damage).

Markers of kidney damage include: albuminuria (ACR > 3 mg/mmol), haematuria (of presumed or confirmed renal origin), electrolyte abnormalities due to tubular disorders, renal histological abnormalities, structural abnormalities detected by imaging (e.g. polycystic kidneys, reflux nephropathy) or a history of kidney transplantation.

CKD is predicted to be the fifth leading cause of death globally by 2040.[1] Currently, 10% of adults have some form of CKD, resulting annually in 1.2 million deaths and 28 million lost years of life worldwide.[2] The prevalence of CKD (eGFR < 60ml/min/1.73m^2) in England is estimated to be between 5.2 and 7.7%[3]

Despite being common, CKD often remains undiagnosed partly because of lack of symptoms until late in the disease process. One UK study found that 18.2% of individuals aged over 60 had CKD, but 44% of this population were undiagnosed.[4] Late detection of CKD, and hence lack of effective management, increases the risk of progression to end-stage renal disease (ESRD) which often requires renal replacement therapy such as dialysis or transplantation. Furthermore, delayed diagnosis of CKD is associated with increased morbidity and mortality.[5]

NICE published updated guidelines on the assessment and management of CKD (NG203) in August 2021.[6]

What are the risk factors for progression?

RISK FACTORS

CKD has a wide range of causes including diabetes, hypertension, renovascular disease, urological disorders, and hereditary conditions and can occur following acute kidney injury (AKI). In older patient populations, CKD may be caused by a combination of associated conditions such as hypertension and atherosclerotic vascular disease.

When should patients be referred?

NICE recommends testing for the presence of CKD in certain adult patient groups at increased risk by using eGFR and/or urinary albumin: creatinine ratio (ACR) to quantify proteinuria, see table 1, p12.

NICE recommends that patients who have experienced an episode of AKI should have annual checks of eGFR and urinary ACR for at least three years post AKI, even if their eGFR has returned to baseline.

INVESTIGATIONS

Serum creatinine and eGFR

Derangement in serum creatinine and eGFR will alert a clinician to a patient with potential CKD. Initially, it is important to differentiate AKI from established CKD or a new AKI in the setting of CKD. Reviewing previous creatinine and eGFR results is helpful or, if not available, repeat sampling within two weeks is recommended to assess whether kidney function is stable or is continuing to decline.

Creatinine and eGFR are, however, imperfect measurements of kidney function and should be interpreted in the context of the individual patient. For example, eGFR is not a reliable measurement of renal function during »

Table 1

Recommendations for monitoring patients at risk of developing CKD[6]

Patient group	Monitoring for CKD
Adults who take medications known to affect renal function such as calcineurin inhibitors (tacrolimus) or chronic use of NSAIDs	● Monitor eGFR at least annually
Adults with the following conditions: ● Diabetes ● Hypertension ● Previous episode of AKI ● Cardiovascular disease ● Structural renal tract disease (including renal stone and prostatic hypertrophy) ● Gout ● Incidental haematuria or proteinuria ● Family history of end-stage renal disease or hereditary renal disease ● Multisystem disease with potential kidney involvement (such as systemic lupus erythematosus)	● Offer eGFR testing and urinary ACR (see table 3)

an episode of AKI or during pregnancy. As serum creatinine is a breakdown product of creatinine and phosphocreatine in muscle, caution is needed interpreting results in patients at the extremes of muscle mass. For example, individuals with significant muscle wasting or limb amputees may have their eGFR overestimated, while body builders with high muscle mass may have their eGFR underestimated.

The updated NICE guidance recommends omitting ethnicity in calculating eGFR.[6] There is no evidence to support its use and including ethnicity in the eGFR calculation risks delaying appropriate referral and treatment. NICE has recommended further research to establish how best to estimate GFR in non-Caucasian patients.

Other investigations

All patients identified as having CKD should have the following parameters checked at the earliest opportunity.

- Blood pressure
- Full blood profile, glucose and lipid profile
- Dipstick urinalysis
- Urinary ACR

Ultrasound imaging should be offered to all adults with CKD as outlined in box 1, above right. Patients with suspected hereditary conditions, such as polycystic kidney disease, should be counselled about the implications of an abnormal result before imaging is requested.

Assessing for albuminuria or proteinuria in CKD is important. Proteinuria predicts those patients at highest risk of progressive CKD and is associated with increased risk of cardiovascular mortality.

NICE does not recommend the use of reagent strips in measuring proteinuria in patients with CKD. Urinary ACR, rather than urinary protein: creatinine ratio (PCR), should be the first-line investigation for proteinuria as it is more sensitive for detecting low levels of proteinuria.

Urinary ACR results are interpreted as follows:

- < 3 mg/mmol – normal
- 3-70 mg/mmol – should be repeated with an early morning sample in the first instance but may represent early proteinuria
- ≥ 70 mg/mmol equates to proteinuria (no need for repeat testing)

At high levels of proteinuria (ACR ≥ 70 mg/mmol) PCR testing may be used as an alternative.

HAEMATURIA

Asymptomatic invisible haematuria is a common finding on urinalysis. The cause is often urological such as renal stones, urological malignancy, urinary tract infection or hyperplasia/infection of the bladder or prostate.

In young people haematuria is often transient and of little consequence. NICE recommends regarding two/three reagent strips positive for haematuria as persistent invisible haematuria.

Box 1

Indications for ultrasound scanning of renal tracts[6]

- Accelerated progression of CKD
- Visible or persistent invisible haematuria
- Symptoms of urinary tract obstruction
- Family history of polycystic kidney disease and aged 20 years or older
- GFR < 30 ml/min/1.73m²

The UK Kidney Association recommends testing patients with persistent invisible haematuria for eGFR and proteinuria. It recommends the following management:[7]

- Age ≥ 40 years; usually refer to urology. If renal impairment and/or proteinuria consider simultaneous referral to nephrology
- Age < 40 or ≥ 40 years with negative urological investigations; if no proteinuria **and** eGFR ≥ 60 ml/min/1.73m² manage as CKD stage G1/G2. Otherwise, refer to nephrology

Note that previous guidance from the British Association of Urological Surgeons on haematuria has been withdrawn since the publication of NICE guideline *NG12. Suspected cancer: recognition and referral*.[8]

CKD STAGING

CKD is classified based on GFR and ACR with the GFR categories G1-G5 similar to previous GFR thresholds for CKD stages 1-5. ACR is categorised as A1-A3 according to the levels of proteinuria. A1-A3 are added to CKD classification to highlight the risks that proteinuria is associated with progression to ESRD and cardiovascular disease, see figure 2, opposite. The GFR and ACR categories are listed in table 2, below.

Table 2

CKD staging

GFR category	GFR (ml/min/1.73m²)
G1	≥ 90
G2	60-89
G3a	45-59
G3b	44-30
G4	15-29
G5	< 15
ACR category	**ACR (mg/mmol)**
A1	< 3
A2	3-30
A3	> 30

PROGNOSIS

Risk factors associated with progression of CKD include:

- Cardiovascular disease
- Proteinuria
- Previous episode of AKI
- Hypertension
- Diabetes
- Smoking
- African, African-Caribbean or Asian ethnicity
- Chronic use of NSAIDs
- Untreated urinary outflow obstruction

MONITORING

Most patients with CKD can be successfully managed in primary care. Fortunately, CKD is not progressive in many cases and care should be taken not to alarm patients unduly who are at lower risk of progressing to ESRD. Agreement should be made with the patient about the frequency of eGFR and ACR monitoring. The minimum suggested monitoring from NICE based on CKD staging annually is outlined in table 3, below right.

Other factors can be considered in tailoring the management of individual patients. Enhanced monitoring may be required with recent AKI, high-risk comorbidities (diabetes, hypertension or heart failure), or changes in treatment such as introduction or dose changes of renin-angiotensin-aldosterone system (RAAS) antagonists or diuretics. Reduced monitoring may be appropriate in patients who have opted for conservative care.

It is vital to detect accelerated progression of CKD, this may be a catalyst for referral to specialist nephrology services because of the risk of progression to ESRD. NICE defines accelerated progression of CKD as:

- Sustained decrease in GFR of 25% or more and a change in GFR category within 12 months **or**
- Sustained decrease in GFR of 15 ml/min/1.73m^2 per year

MANAGEMENT

Patients with CKD should be provided with information and education tailored to the severity of their CKD and personal risk of progression.

Patients should be given appropriate support and have access to their own data (test results, correspondence regarding their diagnosis and management plan) to enable them to self-manage aspects of their condition.

Maintaining a healthy weight, smoking cessation, dietary salt reduction, good glycaemic control and exercise all help to minimise CKD progression and also help reduce morbidity and mortality associated with comorbid conditions e.g. cardiovascular disease.

Statin therapy for primary prevention and antiplatelet therapy for secondary prevention of cardiovascular disease should be considered.

Patients can be advised how to lower their risk of AKI particularly with regard to medications and sick day rules. They should avoid NSAIDs and trimethoprim containing antibiotics and also be advised that medications such as diuretics and RAAS antagonists should be temporarily withheld when at risk of dehydration (for example during vomiting and diarrhoeal illness.) Diuretics and RAAS antagonists can be restarted 2-3 days after recovery from acute illness.

Blood pressure

In patients with CKD, blood pressure (BP) should be targeted to a clinic »

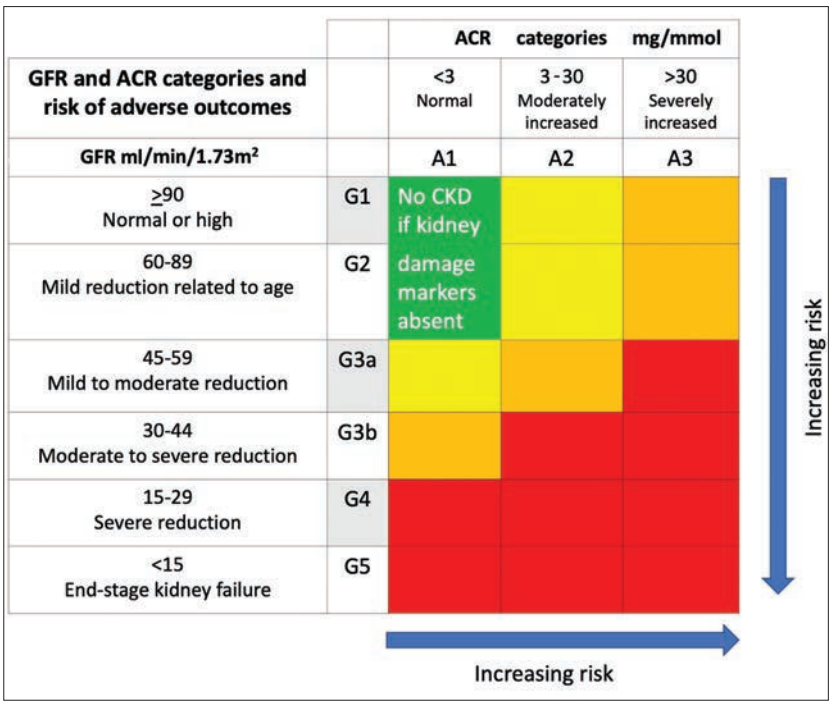


FIGURE 2
GFR and ACR categories and risk of adverse outcomes

Table 3

Minimum monitoring recommendations for CKD patients per year[6]

	ACR category A1 < 3 mg/mmol	ACR category A2 3-30 mg/mmol	ACR category A3 > 30 mg/mmol
GFR category G1 ≥ 90 ml/min/1.73m^2	0 to 1 times a year	once a year	1 or more times a year
GFR category G2 60-89 ml/min/1.73m^2	0 to 1 times a year	once a year	1 or more times a year
GFR category G3a 45-59 ml/min/1.73m^2	once a year	once a year	2 times a year
GFR category G3b 30-44 ml/min/1.73m^2	1 to 2 times a year	2 times a year	2 or more times a year
GFR category G4 15-29 ml/min/1.73m^2	2 times a year	2 times a year	3 times a year
GFR category G5 < 15 ml/min/1.73m^2	4 times a year	4 or more times a year	4 or more times a year

key points

SELECTED BY

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Chronic kidney disease (CKD) is a potentially progressive condition resulting in a decline in renal function secondary to a range of causes. An individual is considered to have CKD if abnormalities of kidney function or structure have been present for more than three months. Despite being common, CKD often remains undiagnosed partly because of lack of symptoms until late in the disease process. Late detection of CKD, and hence lack of effective management, increases the risk of progression to end-stage renal disease (ESRD) which often requires renal replacement therapy such as dialysis or transplantation. Furthermore, delayed diagnosis of CKD is associated with increased morbidity and mortality.

Derangement in serum creatinine and eGFR will alert a clinician to a patient with potential CKD. However, creatinine and eGFR are imperfect measurements of kidney function and should be interpreted in the context of the individual patient. For example, eGFR is not a reliable measurement of renal function during an episode of AKI or during pregnancy. As serum creatinine is a breakdown product of creatinine and phosphocreatine in muscle, caution is needed interpreting results in patients at the extremes of muscle mass. For example, individuals with significant muscle wasting or limb amputees may have their eGFR overestimated, while body builders with high muscle mass may have their eGFR underestimated.

All patients identified as having CKD should have the following parameters checked at the earliest opportunity: blood pressure; full blood profile, glucose and lipid profile; dipstick urinalysis; and urinary albumin:creatinine ratio (ACR).

CKD is classified based on GFR and ACR with the GFR categories G1-G5 similar to previous GFR thresholds for CKD stages 1-5. ACR is categorised as A1-A3 according to the levels of proteinuria. A1-A3 are added to CKD classification to highlight the risks that proteinuria is associated with progression to ESRD and CVD.

Patients with CKD should be provided with information and education tailored to the severity of their CKD and personal risk of progression. Patients should be given appropriate support and have access to their own data (test results, correspondence regarding their diagnosis and management plan) to enable them to self-manage aspects of their condition. Maintaining a healthy weight, smoking cessation, dietary salt reduction, good glycaemic control and exercise all help to minimise CKD progression and also help reduce morbidity and mortality associated with comorbid conditions e.g. CVD.

Timely referral for specialist nephrology input when required is key. The decision to refer to nephrology should take account of the patient's wishes and their comorbidities. Often patients do not require regular hospital review and agreement on management can be reached through liaison between primary care and nephrology.

systolic pressure below 140 mmHg (target range 120-139 mmHg) and clinic diastolic pressure below 90 mmHg even if multiple agents are required. If patients with CKD have an ACR > 70 mg/mmol then the BP target should be for a clinic systolic pressure less than 130 mmHg (target range 120-129 mmHg) and diastolic pressure less than 80 mmHg. ACE inhibitors (ACEi) or angiotensin receptor blockers (ARB) are first-line agents.

Caution is needed when reducing BP in elderly individuals with widespread vascular disease as kidney perfusion may be compromised by the fall in BP leading to AKI. Serum creatinine, eGFR and potassium should be monitored 7-10 days after commencement or dose change of ACEi/ARB.

The Kidney Disease Improving Clinical Outcomes (KDIGO) 2021 updated guideline and other international bodies now recommend a systolic BP target < 120 mmHg for patients with CKD.[9] This is largely based on evidence from the SPRINT study (Systolic Blood Pressure Intervention Trial) which showed a significant reduction in cardiovascular events with tighter BP control without a significant increase in adverse outcomes (with the exception of AKI where there was an increased risk).[10] Whether this, along with the increasing use of ambulatory/home BP measurements[11] leads to changes in UK hypertension guidance remains to be seen.

Proteinuria

ACEi/ARB therapy should be offered to patients with CKD to reduce proteinuria. Treatment should be commenced and titrated to maximum tolerated dose in patients with CKD **and**:

- Diabetes with ACR ≥ 3 mg/mmol
- Hypertension with ACR > 30 mg/mmol
- ACR ≥ 70 mg/mmol

SGLT2 inhibitors are increasingly being used in individuals with diabetes, CKD and proteinuria following the impressive results in CREDENCE[12] and DAPA-CKD[13] trials that demonstrated their ability to reduce eGFR decline and slow progression to ESRD. NICE guidance on the management of type 2 diabetes[14] in adults was updated in 2021 stating that:

For patients with diabetic nephropathy on maximum tolerated ACEi/ARB therapy **and**:

- ACR 3-30 mg/mmol – addition of an SGLT2 inhibitor should be considered
- ACR > 30 mg/mmol – addition of an SGLT2 inhibitor should be offered

It is likely that the role of SGLT2 inhibitors will expand to treatment for proteinuria in other conditions that cause CKD with additional trials, such as EMPA-KIDNEY, due to publish results in the near future. This is a large double-blind placebo-controlled trial of empagliflozin involving more than 6,000 patients with CKD. This trial will help to establish if empagliflozin reduces the rate of CKD progression, all-cause mortality and cardiovascular mortality in individuals with CKD. (www.empakidney.org)

REFERRAL

Appropriate and timely referral for specialist nephrology input when required is key. The decision to refer to nephrology should always take into account the individual patient's wishes and their comorbidities.

Often patients do not require regular hospital review and agreement on management can be reached through liaison between primary care and nephrology.

Referral of adults with CKD to the nephrology service should be considered if they have the following:

- Five-year risk > 5% of needing renal replacement therapy, measured using the 4-variable Kidney Failure Risk Equation. (See Useful information box, p15)
- ACR > 70 mg/mmol or more, unless known to be caused by diabetes and already appropriately treated
- ACR > 30 mg/mmol (ACR category A3), together with haematuria
- Sustained decrease in eGFR > 25% or more and a change in eGFR category within 12 months
- Sustained decrease in eGFR > 15 ml/min/1.73m^2 or more per year
- Hypertension that remains poorly controlled (above the patient's individual target) despite the use of at least four antihypertensive medications at therapeutic doses (see also NICE guideline on hypertension in adults)[15]
- Known or suspected rare or genetic causes of CKD
- Suspected renal artery stenosis

Patients with CKD and renal outflow obstruction should be referred to urological services, unless urgent treatment is needed.

CONCLUSION

Despite being common, CKD is often under recognised leading to late diagnosis and increased risk of progression to ESRD with associated higher mortality. An individual's risk of progressive CKD is assessed by measuring eGFR and ACR.

Effective monitoring and early

management of CKD in primary care can reduce rapid progression to ESRD and ensure timely referral to nephrology if required.

Competing interests: None

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We welcome your feedback

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Useful information

UK Kidney Association eCKD Guide
A quick online support for the diagnosis and management of CKD
https://ukkidney.org/health-professionals/information-resources/uk-eckd-guide

Kidney Failure Risk Equation
An online support tool for patients and healthcare professionals that explains CKD stages, causes of CKD and has an individual risk calculator
https://kidneyfailurerisk.com

Edinburgh Renal Unit
Articles on kidney disease for both healthcare professionals and patients
https://edren.org/ren/edren-info