Management of chronic kidney disease

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Abstract

Management of chronic kidney disease (CKD) requires a systematic approach including all components of the chronic disease model. Some causes require specific management directed at the underlying cause. For many patients, control of cardiovascular risk factors is the most important intervention, as these also promote progressive loss of kidney function. More intensive control of blood pressure and use of renin–angiotensin axis inhibitors are recommended for patients with diabetes mellitus or significant proteinuria, but excessive blood pressure reduction can be harmful. Reducing the level of proteinuria is an important therapeutic goal. Dietary salt restriction is an important adjunct to drug therapy in preventing fluid retention and reducing cardiovascular burden. Smoking cessation, obesity correction, lipid-lowering treatment and glycaemic control in diabetic patients are also significant. Drug clearance is impaired in CKD, and medication doses often require adjusting in response. Avoiding drugs that are potentially harmful to the kidneys is equally vital. Hypovolaemia and hypotension should be avoided or promptly corrected as they can further damage kidney function. Symptoms are common only in advanced CKD. Patients likely to progress to established renal failure should be referred early enough to allow adequate assessment and preparation for informed decision-making about renal replacement therapy.

Keywords Antihypertensive therapy; chronic disease management; chronic kidney disease; glomerulonephritis; MRCP; progression

Key points

- Chronic kidney disease (CKD) is common and is strongly associated with cardiovascular disease and advanced age
- Most patients with CKD never progress to established renal failure, but they have a significantly increased risk of death from cardiovascular disease
- Control of classical risk factors for atherosclerosis also reduces the risk of progressive kidney disease
- Patients with proteinuria are more likely to develop progressive kidney damage, and they benefit from antihypertensive drug therapy titrated against protein excretion as well as blood pressure; renin–angiotensin axis inhibitors are particularly effective in this situation

Principles of chronic disease management

Chronic kidney disease (CKD) requires a multidisciplinary approach involving specialist teams working alongside primary care physicians. Patients with CKD often have other long-term conditions, such as hypertension, cardiovascular disease, diabetes mellitus and peripheral vascular disease, that require long-term specialist follow-up.

Research into systematic attempts to achieve improvement in the delivery of care for patients with chronic diseases has resulted in development of the 'chronic care model'. Improvement is more likely if each component of the organization of care (self-management, decision support, delivery system design, clinical information systems) is addressed, and unlikely if, for instance, improvement efforts are confined to a hospital-based clinic. Many of the components of the model, including national guidelines on identification, management and referral, are already in place for CKD.

Early stages of CKD are largely asymptomatic, so a balance has to be struck between 'labelling' patients as having 'chronic kidney disease' and ensuring that patients at increased risk of cardiovascular disease or progressive loss of kidney function are identified and offered treatment to reduce these risks.

Diagnosis and classification of CKD

The Kidney Disease: Improving Global Outcomes (KDIGO) guideline 2012[1] and subsequently the National Institute for Health and Care Excellence (NICE) guideline 2014[2] now recommend the use of a new classification of CKD in which the diagnosis and monitoring of CKD involves measuring estimated glomerular filtration rate (eGFR) and proteinuria by albumin:creatinine ratio (ACR).

The KDIGO classification endorses use of the CKD Epidemiology (CKD-EPI) equation to calculate eGFR for creatinine in place of the Modification of Diet in Renal Disease (MDRD) formula; both formulae use age, gender and ethnicity to predict creatinine generation and to derive an estimate of GFR normalized to body surface area, but CKD-EPI is more accurate.

KDIGO currently defines CKD as the presence of kidney damage or reduced kidney function for 3 months or more, irrespective of the cause. A measured eGFR of <60 ml/minute/1.73 m^2 is widely agreed to be the threshold for diagnosing CKD, primarily because of the increased risk of all-cause mortality. For this reason also, a urine ACR of ≥30 mg/g (≥3 mg/mmol) is considered part of the definition of CKD.

In cases where the $eGFR_{creatinine}$ is 45–50 ml/minute/1.73 m^2 for >90 days in the absence of proteinuria (indicated by ACR <3 mg/mmol), KDIGO recommends using eGFR for cystatin C where

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available. This is a more accurate predictor of long-term clinical outcomes in this group. If $eGFR_{cystatin\ C}$ is >60 ml/minute/1.73 m^2, the diagnosis of CKD should not be made. However, the cystatin C assay currently costs considerably more than the creatinine assay, and it will probably take some time before this recommendation is widely adopted.

Identification of proteinuria should be by ACR as it is more sensitive for low levels of proteinuria. Protein:creatinine ratio can be used to quantify larger amounts of proteinuria and ensures conditions such as myeloma are not missed. Urinary ACR (UACR) remains the recommended measure of proteinuria in patients with diabetes mellitus.

We recommend that standard notation for CKD stage follows the format 'CKD G3a A2', for instance, indicating a laboratory eGFR of 45–59 ml/minute/1.73 m^2 and UACR of 3–30 mg/mmol. The cause should be stated when known. The eGFR provided by the laboratory should be used wherever possible, as this should include correction factors for the type of creatinine assay used (see Assessment of kidney function in adults in *Medicine* 2019; **47(8):**482–488).

Some patients not defined as having CKD by this classification will have other evidence of chronic kidney damage, such as:

- persistent haematuria (after excluding other causes, such as urological disease)
- structural abnormalities of the kidneys demonstrated on ultrasound scanning or other radiological tests (e.g. polycystic kidney disease, reflux nephropathy)
- biopsy-proven chronic glomerulonephritis (although most of these patients have proteinuria and/or haematuria).

Limitations of eGFR formulae

The CKD-EPI formula is a further modification of the MDRD formula, and was developed to account for inaccuracies of the MDRD formula in estimating GFR, especially at GFR >60 ml/minute/1.73 m^2. However, many limitations remain. Specifically, its use has not been fully validated in elderly individuals, children or pregnant women, acute kidney injury (AKI), extremes of body size or ethnic groups other than white patients and African-American populations.

The limitations of eGFR measurements based on serum creatinine are well known, but it should be noted that there are situations where $eGFR_{cystatin\ C}$ is also inaccurate, including race other than US or European black and white, abnormal thyroid function and use of exogenous corticosteroids.

Management strategies in CKD

When a case of CKD is attributed to a potentially reversible renal insult, treatment targeting this disorder can lead to a degree of reversibility. However, most patients with established CKD of any cause also benefit from non-specific interventions aiming to reduce the rate of disease progression.

Most patients with reduced GFR do not have proteinuria, radiological abnormalities or other markers suggesting a specific underlying cause. In particular, elderly patients with reduced GFR commonly have no proteinuria. There is controversy about the assessment of renal function in the elderly and whether age-related loss of renal excretory function should be considered as chronic disease.

The MDRD/CKD-EPI formulae are not as well validated in elderly people, and any creatinine-based formula that incorporates assumptions about muscle mass at different ages faces the same problems. The apparent high prevalence of CKD in elderly patients may because of:

- the presence of numerous risk factors for CKD, such as a diabetes and hypertension age-associated decline in kidney function that is not explained by other known risk factors
- inaccuracy of creatinine-based estimating equations in the elderly population.

Most CKD in elderly individuals is non-progressive, and research is needed to identify those at risk of developing established renal failure. The *relative* risk of death or end-stage renal disease (ESRD) associated with lower GFR (mostly caused by cardiovascular disease) is much higher in younger people (largely because of fewer competing risks); however, the *absolute* risks, particularly of ESRD, are much higher among older people.

'Chronic kidney disease' is not a diagnosis: attempts should always be made to assign an underlying cause of CKD. Early investigation at the time of presentation for reversible pathology is a crucial part of individualized care. Investigation nearly always includes imaging, and can also include kidney biopsy to look for glomerulonephritis (e.g. in the presence of haematuria, proteinuria or both) or interstitial nephritis (if suspected on clinical grounds, e.g. suspected drug-induced disease).

Reducing the risk of progressive loss of glomerular filtration rate

In addition to specific therapy targeted at the underlying primary disease, recognition of the role of several modifiable secondary factors associated with progressive kidney damage is important clinically, as these can be treated effectively and minimize renal injury. Most of these interventions also reduce the risk of cardiovascular disease (see Cardiovascular complications of chronic kidney disease on pages 585–590 of this issue).

Treatment of systemic hypertension

Hypertension is present in up to 85% of patient with CKD. The two main goals of antihypertensive therapy are modification of cardiovascular disease risk and reduction of risk of progressive GFR decline. Several randomized controlled trials have shown that the risks of cardiovascular events and progressive kidney disease are reduced by blood pressure-lowering treatment. However, studies are still required to compare different intervention thresholds, different blood pressure targets and different strategies for patients with varying degrees of proteinuria, comorbidity and conduit artery compliance or pulse pressure. Two early landmark studies 'targeted' mean arterial pressure rather than systolic or diastolic pressure.

Many existing guidelines are therefore based on post hoc analyses of randomized controlled trials and observational studies, and of 'translation' of mean arterial pressures into systolic and diastolic pressures. As a result, there has been considerable variation between the guidelines and audit measures currently used in the UK. We suggest following the NICE recommendations (Figure 1).[2]

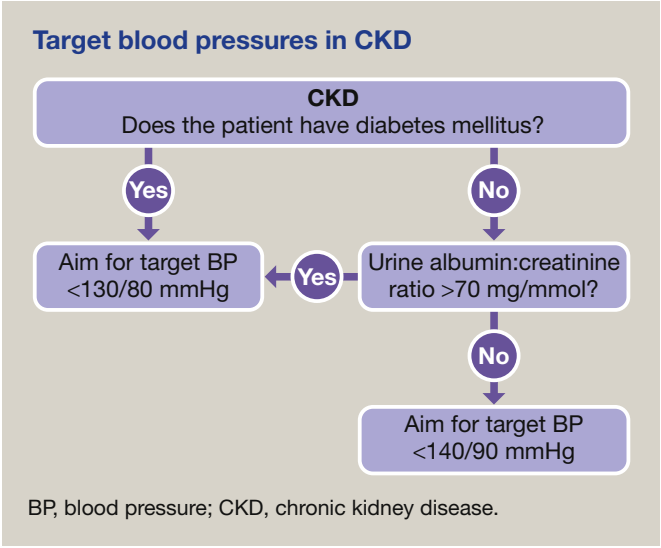

Figure 1

According to NICE guidance, the threshold clinic blood pressure for intervention is 140/90 mmHg for patients with CKD, but this is lowered to 130/80 mmHg for patients with CKD and either diabetes or severe proteinuria (defined as UACR >70 mg/mmol). NICE hypertension guidelines now include the standardized use of ambulatory or home blood pressure monitoring in the general population[3]; the above targets should be 10/5 mmHg lower if home or ambulatory readings are being used (i.e. 130/85 mmHg for non-proteinuric CKD, 120/75 mmHg for proteinuric CKD). Reduction of proteinuria is an additional therapeutic goal; dietary salt restriction amplifies the antiproteinuric effect of antihypertensive therapy.

Since the publication of the NICE guidelines, two major trials have tested the hypothesis that more 'aggressive' blood pressure lowering, to a target systolic pressure of <120 mmHg, would provide additional benefit. ACCORD was performed in patients with type 2 diabetes, and SPRINT in patients at high cardiovascular risk without diabetes.

ACCORD found no significant reduction in the primary endpoint (non-fatal myocardial infarction, non-fatal stroke, death from cardiovascular causes), although there was a reduction in risk of stroke. Adverse events were more common with intensive treatment, although this finding was driven largely by more frequent declines in kidney function (e.g. to eGFR <30 ml/minute/1.73 m^2) with intensive treatment; whether these changes were caused by progressive kidney disease or altered renal haemodynamics is uncertain. The risk of development of macroalbuminuria was reduced with intensive treatment.

SPRINT randomized non-diabetic patients with a high cardiovascular risk to a target systolic blood pressure <140 mmHg (standard therapy) or <120 mmHg (intensive therapy). There were fewer fatal and non-fatal cardiovascular events with intensive treatment. Subsequent reports from SPRINT have demonstrated similar benefits for intensive treatment among frail elderly individuals. Patients with early CKD appear also to benefit from intensive blood pressure reduction, although there was a slightly higher rate of decline of GFR over time, the significance of which requires longer follow-up.

NICE guidelines are currently being revised in the light of the findings of these and other recent studies: there is wide variation in the blood pressure targets set by other national and international guideline groups for patients with CKD. Meta-analysis demonstrates consistent benefit from intensive blood pressure reduction, with the greatest benefit seen among patients with pre-existing vascular disease, diabetes or kidney disease (see Xie X, Atkins E et al. in Further reading). However, it seems obvious that there must be a point at which further reduction in blood pressure will cause harm, as a result of reduced perfusion of vital organs, but for most patients that point has not yet been defined; it could well be a systolic blood pressure well below 120 mmHg.

For each individual patient, the possible benefits of more intensive treatment must be balanced against the pill burden and risk of adverse effects. This is particularly important in patients with multiple co-morbidities, in whom the benefits of intensive treatment are less certain. This decision should be shared with the patient, taking into account the patient's attitude to risk and medication.

Adoption of a lower blood pressure target makes it more important than ever to ensure that blood pressure is measured in a standardized manner. SPRINT, for instance, used three measurements taken using an automated oscillometric machine, mostly without an observer present, and all trials of antihypertensive treatment have used a standardized blood pressure measurement. Such measurements nearly always give lower readings than 'casual' measurements taken in the clinic that ignore requirements to avoid caffeine in the 30 minutes before measurement, rest quietly for several minutes before measurement, avoid conversation during measurement, and use at least two measurements a few minutes apart. *Adjustment of drug therapy according to unstandardized clinic measurements is poor practice and should be avoided.*

The use of blood pressure monitoring in outpatient clinics can lead to misinterpretation of blood pressure control in the outpatient setting and inappropriate increases in drug therapy. In the event of a single blood pressure reading >130/85 mmHg, ambulatory/home reading should be sought to rule out the 'white-coat' phenomenon before initiation or adjustment of therapy.

Given that arterial blood pressure is just one of several risk factors for cardiovascular and kidney disease, it would be more logical to adopt a 'risk-based' approach rather than one based on separate thresholds. Using this approach, more intensive treatment to reduce blood pressure (and other risk factors) would be recommended for patients at higher risk. The transition to a risk-based approach is under way in many national and international guideline groups; it is likely to result in more coherent guidelines that will allow patients and their physicians to use the evidence base to come to shared decisions on which treatments to use. Such an approach is likely also to improve adherence to treatment.

Choice of antihypertensive agents

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) offer significant renal protection in addition to that attributable to lowered blood pressure. They should be used as first-line agents in all individuals with diabetes mellitus (with or without evidence of albuminuria), in non-diabetic kidney disease with proteinuria (random UACR

>100 mg/mmol) and in those with heart failure. In patients with diabetes, ACEIs also reduce the all-cause mortality and incidence of cardiac events, whereas ARBs do not appear to have this effect (see Xie X, Liu Y et al. in Further reading). ACEIs should therefore be offered as first-line agents for renal protection in patients with diabetes. The role of ACEIs and ARBs in preventing progression of non-diabetic kidney disease with less severe proteinuria is not as well established; although there is good evidence that these drugs reduce albumin excretion, benefits in terms of 'hard' clinical outcomes have not been established.

Many patients need more than one agent to achieve target blood pressure goals. Non-dihydropyridine calcium channel blockers, such as verapamil and diltiazem, have additional antiproteinuric effects and are preferred to dihydropyridine agents, such as amlodipine and nifedipine, which can increase proteinuria. Many patients with CKD are volume-overloaded and can benefit from concomitant diuretic therapy, preferably with a loop diuretic. Thiazide diuretics, such as indapamide, are less effective at GFRs <30 ml/minute/1.73 m^2. The PATHWAY-2 trial demonstrated that spironolactone was a superior add-on agent (compared with bisoprolol or doxazosin) for patients with resistant hypertension (i.e. blood pressure >150/90 mmHg despite three classes of antihypertensive agent), but excluded patients with an eGFR <45 ml/minute/1.73 m^2.[4] In more advanced CKD, the benefits of aldosterone antagonism are less certain, and the risks of hyperkalaemia higher.

Previously, there was a suggestion that combination therapy with ACEIs and ARBs offered a synergistic benefit in patients with CKD and proteinuria. However, any potential benefits are outweighed by an increased risk of hyperkalaemia, hypotension and AKI, and current advice (from the Medicine and Healthcare products Regulatory Authority) is that combination therapy should be avoided.

Monitoring during ACEI/ARB treatment: in patients commencing ACEIs or ARBs, serum creatinine and potassium should be checked within 2 weeks of initiating therapy and after every increment in dosage. If the serum creatinine rises >30% or GFR falls >25% from baseline, alternative causes of deterioration in renal function should be investigated, the dosage reduced to that previously tolerated or the agent withdrawn, and an alternative antihypertensive agent deployed. However, a rise in creatinine of even 10% after initiation of treatment is associated with increased risk of adverse outcomes and identifies a high-risk group of patients. A significant fall in kidney function during ACEI/ARB inhibition can indicate haemodynamically significant renal artery narrowing, but the selection of patients who will benefit from revascularization remains problematic (see Renovascular disease in *Medicine* 2019; **47(8):**526–532).

Reduction of intraglomerular hypertension

Proteinuric CKD (including diabetic nephropathy) is typically characterized by intraglomerular hypertension, caused by alterations in regulation of vascular tone in the afferent and efferent glomerular arterioles, permitting greater transmission of systemic pressure to the glomerulus. This increase in intraglomerular pressure is thought to be a major cause of progressive glomerular damage. Although reduction of systemic blood pressure helps to limit damage, some antihypertensive drugs (including ACEIs, ARBs and non-dihydropyridine calcium channel blockers) directly reduce intraglomerular pressure by selective vasodilatation of the efferent arterioles, whereas others (including dihydropyridine calcium channel blockers) can increase intraglomerular pressure and worsen proteinuria.

Inhibition of renal fibrosis

ACEIs and ARBs can have additional beneficial effects in progressive CKD by inhibiting the actions of angiotensin II on glomerular permeability and tubulo-interstitial fibrosis. Several targets for anti-fibrotic agents have been validated in cellular and animal studies, but progress in translating these results to clinical practice has been disappointing. Nevertheless, drugs targeting biochemical pathways causing fibrosis are possible future therapeutic agents.

Bardoxolone methyl, an activator of the Nrf2 pathway that reduces oxidative stress and was postulated to have a role in slowing progression of CKD, was not found to be of benefit among patients with diabetes mellitus and CKD stage G4 in a recent randomized controlled trial. The study was terminated early because of an increased incidence of cardiovascular events in the treatment group.

Maintenance of fluid balance

Patients with an eGFR <15 ml/minute/1.73 m^2 (stage G5) lose the homeostatic mechanisms responsible for sodium and fluid balance. Even those with mild to moderate CKD struggle to respond to rapid shifts in sodium intake and are prone to fluid overload. A combination of dietary sodium restriction and diuretic therapy, usually with loop diuretics, helps to alleviate the symptoms of congestion and can also reduce progression of CKD by lowering glomerular pressure.

Smoking cessation

Population-based studies have shown an association between tobacco smoking and increased incidence of CKD. Although there is no direct evidence that smoking causes an increased risk of progression of CKD, both smoking and CKD are strongly associated with increased risk of cardiovascular disease. Smoking cessation should form part of a multifaceted approach to reduce this risk.

Correction of obesity

In addition to the beneficial effects of weight loss on blood pressure and the potential to ameliorate or reverse type 2 diabetes, weight loss has been shown to ameliorate obesity-induced glomerular hyperfiltration, and decrease proteinuria in patients with chronic proteinuric nephropathies.

Glycaemic control

The optimal HbA_{1c} target for patients with diabetes and CKD continues to be debated. The DCCT, ACCORD and UKPDS trials provided evidence that improved glycaemic control prevents the development of albuminuria as well as other microvascular complications in patients with type 1 and type 2 diabetes mellitus; long-term follow-up suggests that improved glycaemic control might have long-term beneficial effects on macrovascular disease as well.

However, a meta-analysis of seven trials comparing intensive (target glycated haemoglobim (HbA_{1c}) <47 mmol/mol (<6.5%))

versus standard glycaemic control failed to show any benefit in terms of hard renal endpoints (doubling of creatinine concentration, ESRD and death from renal disease) (See Coca SG et al. in Further reading). Intensive control is also associated with an increased risk of hypoglycaemia, which is associated with an increased risk of death. We advise that clinicians individualize therapy after discussion with patients, taking into account life expectancy and overall cardiovascular and renal risk, usually aiming for a target HbA_{1c} <58 mmol/mol (<7.5%).

Sodium glucose co-transporter 2 (SGLT-2) inhibitors (canagliflozin, dapagliflozin, empagliflozin) are a new class of glucose-lowering drug that have been shown to reduce both the risk of cardiovascular disease and the rate of progression of diabetic kidney disease. They work by inhibiting sodium–glucose reabsorption in the proximal tubule, causing glycosuria and natriuresis. Their renoprotective effects are likely to be caused by a reduction in systemic blood pressure together with a further reduction in intraglomerular pressure, rather than by improved glycaemic control. The product licenses for each drug currently advise avoiding initiation if eGFR is <60 ml/minute/1.73 m^2, and cessation if eGFR drops to <45 ml/minute/1.73 m^2. The EMPA-KIDNEY study will determine whether SGLT-2 inhibition with empagliflozin can reduce the risk of cardiorenal outcomes in a broad range of non-diabetic people with CKD.[5]

Treatment of dyslipidaemia

Dyslipidaemia is a risk marker for progressive kidney injury and a risk factor for cardiovascular disease. There is high-quality evidence that lipid-lowering treatment using statins reduces cardiovascular events in patients with CKD, although the relative risk reduction becomes smaller as eGFR declines. Statins reduce atherosclerotic events but not non-atherosclerotic cardiovascular events, such as sudden cardiac death and haemorrhagic stroke – events that are particularly common in patients with established renal failure. Despite the association between dyslipidaemia and progressive kidney disease, there is only limited evidence that statins reduce proteinuria or progression of CKD (see Su X et al. in Further reading).

Other pharmacological treatments

Many water-soluble drugs are cleared by the kidney; they accumulate in CKD as a result of impaired excretion. For drugs with a high therapeutic index, reduced excretion is seldom a problem in stage CKD stage G3, but it can become important in stages G4 and G5.

When using an estimate of GFR to decide on drug dosage adjustments in patients at the extremes of body size, it is also important to remember that the CKD-EPI formula gives a normalized estimate of GFR (i.e. what the GFR would be if the

Frequency of mon itoring (number of times per year) by glomerular filtration rate and albumin:creatinine ratio category		Albumin:creatinine ratio (ACR) categories (mg/mmol), description and range		
		<3 Normal to mildly increased ACR A1	**3–30 Moderately increased ACR A2**	**>30 Severely increased ACR A3**
Glomerular filtration rate (GFR) categories (ml/minute/1.73m2), description and range				
>90 Normal and high GFR	G1	<1	1	>1
60–89 Mild reduction in GFR related to normal range for a young adult	G2	<1	1	>1
45–59 Mild-moderate reduction in GFR	G3a	1	1	2
30–44 Moderate-severe reduction in GFR	G3b	<2	2	>2
15–29 Severe reduction in GFR	G4	2	2	3
<15 Kidney failure	G5	4	4	>4

Adapted from KDIGO guideline 2012[1]. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl. 2013; 3: 1–150.

Table 1

patient had a 'normal' body surface area of 1.73 m^2; this is the best overall measure of the adequacy of renal excretory function, because metabolic rate, and thus the need for excretion of waste products, varies with body size). Actual GFR (which determines drug clearance) can be significantly lower than normalized GFR in small patients; the converse is true in large patients. Formula-based estimates of GFR should not, therefore, be used to adjust the dose of renally excreted drugs with a low therapeutic index. Nephrotoxic drugs are more likely to cause a clinically important reduction in GFR if GFR is already significantly reduced.

Metformin: the use of metformin presents particular problems, given the frequency with which CKD is found among people with type 2 diabetes. Metformin can cause type 2 lactic acidosis, and the risk of this very rare complication is probably greater if the drug accumulates as a result of reduced GFR. The Summary of Product Characteristics suggests that the drug should be avoided in patients whose serum creatinine concentration is >150 micromol/litre; this corresponds to an eGFR of 67 ml/minute/1.73 m^2 in a young black man, but 33 ml/minute/1.73 m^2 in an elderly white woman. This illustrates the dangers of using serum creatinine concentration as the basis for drug dosage adjustment.

The incidence of lactic acidosis in individuals with an eGFR of 30–60 ml/minute/1.73 m^2 is very low, and current opinion is that patients with an eGFR >30 ml/minute/1.73 m^2 can safely be given low-dose metformin This is also the current advice from the British National Formulary. Use of very low doses below this cut-off is likely to be safe (and would be safer still if assays for plasma metformin were available to guide treatment), but patients opting for this treatment in preference to other drugs should be informed that this is against current guidance.

Avoiding haemodynamic insults

The 'classical' model of progressive, proteinuric CKD (of which diabetic nephropathy is the exemplar) does not fully explain the epidemiology of CKD; in particular, it is inconsistent with the frequency of stable stage G3 and G4 CKD. The existence of so many patients with stable but significant kidney damage suggests an alternative model in which kidney function deteriorates as a result of a series of stepwise 'hits' caused by episodes of nephrotoxicity, renal hypoperfusion or atheromatous embolism. Clinical management of patients with CKD should include precautions to minimize the risk of such insults.

ACEIs and ARBs significantly reduce the autoregulation of renal blood flow during episodes of hypovolaemia, so their use may increase the risk of AKI during intercurrent illness. Many nephrologists now provide 'sick-day' rules advising patients to interrupt treatment with these drugs for the duration of any illness. Whether such advice reduces the incidence or severity of AKI is uncertain, and some patients are reluctant to resume therapy after recovery. It is logical to stop all blood pressure-lowering therapy during hypotension complicated by AKI, and to stop diuretics during episodes of hypovolaemia. However, patients for whom such drugs are indicated long-term – particularly those with heart failure – must be advised to re-start treatment as soon as possible after recovery.

Observational evidence suggests that episodes of AKI are associated with increased risk of later CKD, and NICE guidelines now recommend monitoring of renal function for a 2–3-year

Approach to common symptoms in chronic kidney disease

Symptom	Cause	Intervention
Nocturia	Reduced ability to produce concentrated urine	No specific treatment available. If the patient is taking diuretics, ensure that these are taken in divided doses in the morning and late afternoon. Fluid overload and systemic hypertension may also contribute to nocturia, and should be fully corrected
Pruritus	Dry skin; histamine release; phosphate accumulation may also play a role	Skin hydration; antihistamines; treatment of hyperphosphataemia. Correction of anaemia is also of benefit
Restless legs syndrome	Uncertain	Exclude iron deficiency. Drug treatment with antiparkinsonian drugs, gabapentin, codeine, or clonazepam may help individual patients (all unlicensed indications)
Loss of appetite, nausea, and vomiting	Uncertain – accumulation of uraemic metabolites	Renal replacement therapy (RRT). If an active decision has been made not to embark on RRT, anti-emetics may be used
Neuropathy	Uncertain – accumulation of uraemic metabolites	Beware attributing clinically evident neuropathy to chronic kidney disease (CKD), particularly in stage 1–4; consider alternative causes. Although patients with advanced CKD often have subclinical evidence of impaired peripheral nerve function, this is seldom severe

Table 2

Glomerular filtration rate and albumin:creatinine ratio categories and level of increased risk of adverse outcomes		Albumin:creatinine ratio (ACR) categories (mg/mmol), description and range		
		<3 Normal to mildly increased ACR A1	**3–30 Moderately increased ACR A2**	**>30 Severely increased ACR A3**
Glomerular filtration rate (GFR) categories (ml/minute/1.73m^2), description and range				
>90 Normal and high GFR	G1	No chronic kidney disease in the absence of markers of kidney damage	Moderate	High
60–89 Mild reduction in GFR related to normal range for a young adult	G2		Moderate	High
45–59 Mild-moderate reduction in GFR	G3a	Moderate	High	Very high
30–44 Moderate-severe reduction in GFR	G3b	High	Very high	Very high
15–29 Severe reduction in GFR	G4	Very high	Very high	Very high
<15 Kidney failure	G5	Very high	Very high	Very high

Adapted from KDIGO guideline 2012[1]. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl. 2013; 3: 1–150.

Table 3

period after an episode of AKI, even if serum creatinine has returned to baseline.[2]

Managing the symptoms and complications of CKD: management of bone disease and anaemia are covered elsewhere (see Renal bone disease, pp 580–584 and Anaemia and chronic kidney disease, pp 591–595 of this issue).

Treatment of gout in CKD: gout is common in CKD and often undertreated because of advice to reduce the dose of allopurinol as GFR declines: it is often impossible to achieve the target urate concentration of <300 micromol/litre with a low dose. The advice is driven by concern that full-dose allopurinol causes severe cutaneous adverse reactions. Although initiation of full-dose allopurinol in patients with reduced GFR appears to increase the risk of these severe reactions, there is now some evidence that initiation at a low dose with subsequent stepwise upwards titration of the dose allows effective control of hyperuricaemia (greatly reducing the risk of acute attacks and tophaceous gout) without any risk of severe reactions (see Stamp LK et al. in Further reading). Whether febuxostat has advantages over allopurinol titrated in this way remains uncertain.

The HLA B-5801 allele, common in people of Han Chinese or Korean descent, confers a greatly increased risk of hypersensitivity to allopurinol. Patients from these backgrounds should therefore be screened for this allele before commencing therapy.

Treatment of acidosis

There is increasing evidence that correction of uraemic acidosis with oral alkali therapy slows the rate of progression of renal failure and improves muscle and bone strength. Supplementation with oral sodium bicarbonate (typically 1.5–3.0 g/day) to correct serum bicarbonate concentration is reasonable and does not

result in oedema or hypertension. Further large studies are in progress. Increased intake of base-producing fruits and vegetables has been proposed as an alternative to pharmaceutical therapy; the major disadvantage of this approach is the risk of hyperkalaemia.

An approach to the management of common 'uraemic' symptoms is outlined in Table 2.

Follow-up and preparation for renal replacement therapy: patients with CKD should be offered life-long follow-up to ensure optimal management as described above and to monitor changes in kidney function. KDIGO and NICE now recommend a follow-up frequency based on the risk of adverse outcomes, using the new staging system described earlier.

The great majority of patients with CKD stage G3 do not progress to ESRD and, even among CKD stage G4 patients, death from cardiovascular disease is more frequent than progression to ESRD. However, patients who require renal replacement therapy have increased morbidity and reduced survival if they present late in their illness. (28) It is essential that those who are at risk of developing ESRD are identified early and referred to secondary care. NICE[2] recommends referral to a consultant nephrologist for patients with:

- GFR <30 ml/minute/1.73 m^2, with or without diabetes mellitus (advice may be appropriate only if this is a stable or isolated finding)
- UACR ≥70 mg/mmol, unless known to result from diabetes mellitus and already appropriately treated
- proteinuria (UACR ≥30 mg/mmol) if accompanied by haematuria
- a sustained decrease in GFR of >25% and a change in GFR category, or a sustained decrease of 15 ml/minute/1.73 m^2 or more in 12 months
- hypertension that remains poorly controlled despite the use of at least four antihypertensive drugs at therapeutic dosage
- rare or genetic causes of CKD, or suspected of having these
- suspected renal artery stenosis. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 51-year-old man presented for review of newly diagnosed hypertension and diabetes mellitus. He had started a programme of lifestyle modification for his diabetes mellitus but had not started antihypertensive therapy.

On clinical examination, his blood pressure (measured according to guidelines, including 5 min' rest before two measurements) was 148/92mmHg, and body mass index 33 kg/m^2. The remainder of the examination was unremarkable. Urine dipstick testing was negative for blood, but 1+ for protein.

Investigations

- 24-Hour ambulatory blood pressure monitoring showed a mean daytime blood pressure of 139/88 mmHg
- Potassium 4.2 mmol/litre (3.5–4.9)
- Creatinine 133 micromol/litre (60–110)
- Estimated glomerular filtration rate 52 ml/minute/1.73 m^2 (<60)
- Spot urine albumin:creatinine ratio 50 mg/mmol (<2.5)

Which of the following is the most appropriate first-line management plan for this patient's blood pressure?

A. A thiazide-like diuretic
B. An angiotensin-converting enzyme (ACE) inhibitor
C. A dihydropyridine calcium channel blocker
D. No medical treatment required
E. A combination of an ACE inhibitor and angiotensin receptor blocker

Question 2

A 63-year-old woman presented with a decline in her renal function over 6 months. She also had type 2 diabetes mellitus, atrial fibrillation and hypertension. She had a 30 pack–year smoking history. Medications included aspirin, metformin, gliclazide, losartan, indapamide and warfarin.

On clinical examination, there was mild peripheral oedema. Her heart rate was 93 beats/minute and irregular, and blood pressure 153/86mmHg. The chest was clear. She weighed 96 kg (BMI 32 kg/m^2).

Investigations

- Creatinine 216 micromol/litre (60–110) (183 6 months previously)
- Estimated glomerular filtration rate 22 ml/minute/1.73m^2 (>60)
- HbA_{1c} 74 mmol/mol (20–42); 8.9% (4.0–6.0)
- Spot urine albumin:creatinine ratio 120 mg/mmol (<3.5)

Which single intervention has the greatest evidence base for reducing this patient's risk of developing end-stage renal failure?

A. Stopping smoking
B. Stopping metformin
C. Lowering blood pressure
D. Improving glycaemic control
E. Losing weight

Question 3

A 28-year-old white male presented with systolic hypertension confirmed by ambulatory blood pressure monitoring. He had chronic kidney disease (CKD) secondary to reflux nephropathy. He had a history of recurring urinary tract infections but was asymptomatic at that time. Results of urine dipstick were normal. Ten days previously, the creatinine concentration had been 126 micromol/litre (60–110) (estimated glomerular filtration rate 62 ml/minute/1.73 m^2 (>60)) and he had been advised to take lisinopril 2.5 mg daily, which he was tolerating well.

On clinical examination, there was no peripheral oedema. His temperature was 37.0°C, and blood pressure was 136/85 mmHg. Cardiovascular examination was normal.

Investigations

- Sodium 142 mmol/litre (137–144)
- Potassium 3.8 mmol/litre (3.5–4.9)
- Creatinine 145 micromol/litre (60–110)
- eGFR 53 ml/minute/1.73 m^2 (>60)

Spot urine albumin/creatinine ratio 1.5 mg/mmol

What is the most appropriate next step in his management?

A. Discontinue the lisinopril
B. Increase the dose of lisinopril
C. Continue on current treatment
D. Refer for imaging of the renal vasculature
E. Switch his lisinopril for a dihydropyridine calcium channel blocker