

## Chronic kidney disease: the canary in the coal mine

Chronic kidney disease (CKD) is a growing issue in New Zealand. Māori and Pacific peoples are overrepresented in our CKD statistics which is concerning as it is a major driver of cardiovascular disease (CVD), and these groups are already disproportionately affected by risk factors such as diabetes, obesity and hypertension. Early detection of CKD can be achieved via regular testing of at-risk people; this permits timely interventions to lower CVD risk and slow or prevent the rate of kidney function decline.

### KEY PRACTICE POINTS:

- Chronic Kidney Disease (CKD) is defined as defects in kidney structure or function, with negative implications for the patient's health, over a period greater than three months. Damage associated with CKD is generally not reversible, and this condition is associated with a substantial increase in CVD risk.
- Patients can experience a marked reduction in kidney function before symptoms become apparent. Therefore, kidney function testing is recommended to initially identify patients with CKD based on the presence of risk factors, e.g. hypertension, diabetes, Māori/Pacific or South-Indo Asian ethnicity.
- Testing for CKD involves checking serum creatinine (to estimate glomerular filtration rate [eGFR]), urine albumin:creatinine ratio (ACR) and blood pressure every one to two years
- If abnormal eGFR/ACR findings are detected (i.e. eGFR < 60 mL/min/1.73m<sup>2</sup> or ACR ≥ 3 mg/mmol), testing should be repeated over the next three months (see main text for specific recommendations) to confirm impaired kidney function
  - Full classification of CKD is achieved by combining the patient's eGFR grade (G1 – G5), degree of albuminuria (A1 – A3) and the identified underlying cause; this information is used to inform management decisions
- Lifestyle changes are an important first step for all patients to reduce overall CVD risk and optimise CKD management, e.g. weight loss, exercise, reducing salt intake
  - Guidelines vary in their recommendations about protein restriction. A low protein diet is not necessary in most cases, and should only be undertaken with guidance from a nephrologist or dietician with experience in managing patients with CKD.
- Pharmacological management of CKD mostly involves controlling blood pressure and reducing hyperglycaemia (for patients with diabetes)
  - An angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) are the first-line antihypertensives for patients with CKD and a blood pressure target of < 130/80 mmHg is generally appropriate
  - Early introduction of a sodium glucose co-transporter-2 (SGLT-2) inhibitor is now recommended for patients with CKD and diabetes (funded with Special Authority approval) due to its dual kidney- and cardio-protective properties. Evidence suggests that SGLT-2 inhibitors may also benefit patients with CKD without diabetes, but this would require patients to self-fund treatment.
- Regular ongoing monitoring is important to assess the efficacy of treatment and to detect progressive kidney function decline which may require secondary care referral. Patients should also be advised of medicines to temporarily avoid if they develop acute gastrointestinal illness (see main text for details).

## This is a revision of a previously published article.

### What's new for this update:

- A general article revision
- Considerations when interpreting eGFR and ACR results
- A discussion on low protein diets; there is no consistent recommendations in guidelines, they are not considered to be standard practice and are unlikely to be necessary for most patients unless under dietitian or nephrologist supervision
- Update on blood pressure target for patients with CKD; these are now lower than previously recommended but there is still inconsistency between guidelines
- SGLT-2 inhibitors are recommended to be initiated early for patients with diabetes as well as for patients with CKD without diabetes (if they are able to self-fund)

N.B. In January, 2022, the Kidney Disease: Improving Global Outcomes (KDIGO) group announced their intention to evaluate and update the 2012 CKD Guidelines.<sup>1</sup> The article presented here has been written prior to the updated KDIGO guidelines release and will be subsequently reviewed once it is available.

## Chronic kidney disease (CKD) in New Zealand

Chronic kidney disease (CKD) is an umbrella term used to describe any long-term condition that adversely affects kidney structure and function. However, declining kidney function is also a natural part of the ageing process.<sup>2</sup> It is estimated that by the age of 70 years approximately 30% of the population will meet classification criteria for CKD.<sup>3</sup> CKD is generally not reversible, and patients with untreated progressive disease have a substantially high risk of experiencing cardiovascular disease (CVD).<sup>4</sup> As such, early identification and intervention for patients with CKD is essential.

### CKD is a growing problem

The worldwide prevalence of CKD is estimated to be 11 – 13%.<sup>5</sup> While there is no overall prevalence data for CKD in New Zealand, regional estimates are consistent with these figures. An Auckland-based study involving the analysis of health records of over 25,000 patients in 2017 found the total sample prevalence of CKD to be 13%.<sup>6</sup> There was significant variation in rates of CKD between ethnicities; 17.8% of Samoan and 10.4% of Māori patients met the criteria for CKD, compared with 7.1% of non-Pacific/non-Māori patients.<sup>6</sup> An analysis of electronic health records of over 200,000 patients in the Otago-Southland region in 2014 estimated the prevalence of CKD to be 11.8%.<sup>7</sup>

The impact of CKD on New Zealand communities is increasing and the number of people requiring dialysis more

than doubled between 2000 and 2019.<sup>3,8</sup> As of 2020, there were reported to be a total of 3,004 people currently undergoing dialysis in New Zealand, and 2,199 people were living with a successful kidney transplant (187 of which occurred during 2020).<sup>8</sup> Approximately half of all people in New Zealand requiring dialysis have diabetes as a primary cause of their condition and over half are Māori and Pacific peoples.<sup>3,8</sup>

## Defining and classifying CKD

CKD itself is not considered a primary diagnosis. Instead, this term broadly describes any abnormality of kidney function or structure, present for at least three months, which has implications for the patient's health.<sup>9</sup> More specifically, this can involve either:<sup>9,10</sup>

- **Reduced kidney function:** an estimated or measured glomerular filtration rate (eGFR/GFR) < 60 mL/min/1.73m<sup>2</sup> that is present for three or more months with or without evidence of kidney damage; **or**
- **Kidney damage:** evidence of kidney damage with or without decreased eGFR that is present for three or more months. This "evidence" may include one or more of the following abnormalities:
  - Albuminuria (the most commonly assessed marker of kidney damage)
  - Haematuria after exclusion of urological causes
  - Kidney tubular disorders, e.g. renal tubular acidosis, nephrogenic diabetes insipidus, renal potassium wasting
  - Pathologic abnormalities detected by histology or inferred; examples include glomerular conditions (e.g. diabetic nephropathy, autoimmune disease), vascular conditions (e.g. hypertension, atherosclerosis), tubulointerstitial conditions (e.g. urinary tract infections, stones, obstruction), cystic/congenital defects
  - Structural abnormalities detected by imaging, e.g. polycystic kidneys, dysplastic kidneys, renal artery stenosis

**The Kidney Disease Improving Global Outcomes (KDIGO) criteria** are used to further categorise patients according to their eGFR grade (G1 – G5) and degree of persistent albuminuria (A1 – A3; **Table 1**).<sup>9</sup> This system can provide predictive information on prognosis (see: "Patients with CKD have an increased risk of CVD events"), which can help guide decisions around how intensely to monitor and treat patients. Prognostic assessment according to **Table 1** does not require determination of the underlying cause.<sup>9</sup>

**Full classification of CKD according to KDIGO criteria** can be achieved by combining the patient's eGFR grade and persistent albuminuria category with an identified underlying cause; this

will either be evident when considering the patients history/ co-morbidities, or be determined during the diagnostic work-up following abnormal laboratory findings (see: “Detecting patients with CKD in primary care”).<sup>9,10</sup>

### Patients with CKD have an increased risk of CVD events

Even in the early stages, CKD is a significant risk factor for CVD events and death, and this risk increases further as kidney function declines (**Table 2**). Patients with CKD are 20-times more likely to die as a result of a cardiovascular event than require a kidney transplant or receive dialysis.<sup>10</sup> CVD risk assessment tools can be used in patients with an eGFR  $\geq 30$  mL/min/1.73m<sup>2</sup>; those with CKD and an eGFR  $< 30$  should be assumed to have a five-year CVD risk of  $> 15\%$  (see: [bpac.org.nz/2018/cvd.aspx](http://bpac.org.nz/2018/cvd.aspx)).<sup>11</sup>

The association between CKD and CVD exists in part because two of the largest risk factors for CKD – diabetes and hypertension – are also associated with left ventricular hypertrophy and left ventricular diastolic dysfunction, both of which are predictive of myocardial infarction and stroke.<sup>4</sup> Vascular calcification, dyslipidaemia, inflammation, coagulopathy, altered blood viscosity and endothelial dysfunction have also been suggested as mechanisms for the

increased cardiovascular risk in people with CKD.<sup>4</sup> Patients with established CKD often exhibit characteristic changes in the myocardium, including myocardial fibrosis, collagen deposition and cardiac hypertrophy.<sup>4</sup> Early detection of CKD in groups with an already high CVD-risk, e.g. Māori and Pacific peoples, should therefore be a priority.

### Distinguishing patients with progressive CKD from those with an age-related decline in kidney function

A key clinical challenge associated with CKD is differentiating patients with progressively deteriorating kidney function due to disease from those with uncomplicated, age-related kidney function decline. Age is a variable in the formula for calculating eGFR; in the general population, eGFR therefore declines by approximately 1 mL/min/year, and many older patients will fulfil the criteria for grade G3a CKD (**Table 1**) without having any evidence of active or structural kidney disease.<sup>3</sup>

In general, progressive CKD can be distinguished as being CKD in patients whose eGFR is declining at a rate  $> 5$  mL/min/year.<sup>3</sup> Some regional HealthPathways define progressive CKD in patients with an eGFR  $< 60$  mL/min/1.73m<sup>2</sup> which has decreased  $\geq 15$  mL/min/1.73m<sup>2</sup> within the previous 12 months, or an ACR  $> 250$  mg/mmol (“nephrotic-range” proteinuria).

**Table 1.** Categorisation and prognostic risk\* of patients with CKD according to eGFR (mL/min/1.73 m<sup>2</sup>) and persistent albuminuria category (albumin:creatinine ratio [ACR], mg/mmol). Adapted from KDIGO clinical guidelines, 2012.<sup>9</sup>

			Persistent albuminuria category (based on urine ACR) <sup>†</sup>			
		Description	eGFR range (mL/min/1.73m <sup>2</sup> )	A1 (normal) < 3 mg/mmol	A2 (microalbuminuria) 3 – 30 mg/mmol	A3 (macroalbuminuria) > 30 mg/mmol
eGFR (kidney function) grade	G1	Normal or high	$\geq 90$	Low	Moderate	High
	G2	Mildly decreased	60 – 89	Low	Moderate	High
	G3a	Mildly to moderately decreased	45 – 59	Moderate	High	Very High
	G3b	Moderately to severely decreased	30 – 44	High	Very High	Very High
	G4	Severely decreased	15 – 29	Very High	Very High	Very High
	G5	Kidney failure	< 15 or dialysis	Very High	Very High	Very High

Prognostic risk: Low Moderate High Very High

\* KDIGO guidelines broadly define prognostic risk as relating to “CKD outcomes”.<sup>9</sup> This is a composite of various factors, including those relating to progression (e.g. declining eGFR status, kidney failure), complications (e.g. CVD) and death. Such categorisation is intended to help clinicians triage patients and inform on the intensity of management and monitoring required, as well as the need for nephrologist referral (see **Figure 1** and “Patients requiring a nephrologist referral” for further information). N.B. The specific risk percentage associated with individual outcomes is not given within general risk categories.

† Some guidelines stratify ACR category thresholds by sex (e.g. defining macroalbuminuria as  $> 25$  mg/mmol for males and  $> 35$  mg/mmol for females). However, the KDIGO group contends that this approach creates unnecessary complexity and that other variables may also affect assay precision, e.g. ethnicity, diet, obesity.<sup>9</sup>

**Table 2.** Risk of death due to a cardiovascular cause according to KDIGO criteria relative to a “healthy” person with an eGFR 90 – 105 mL/min/1.73 m<sup>2</sup> and ACR < 1 mg/mmol. N.B. Data derived from a categorical meta-analysis, and the incidence rate of CVD death was 4.5 per 1,000 person-years for the reference cell. Absolute risk can be determined by multiplying a cell’s relative risk by the incidence rate for the reference cell. Adapted from KDIGO clinical guidelines, 2012.<sup>9</sup>

	ACR < 1	ACR 1 – 2.9	ACR 3 – 29	ACR ≥ 30
eGFR > 105	0.9	1.3	2.3	2.1
eGFR 90 – 105	Reference value	1.5	1.7	3.7
eGFR 75 – 90	1.0	1.3	1.6	3.7
eGFR 60 – 75	1.1	1.4	2.0	4.1
eGFR 45 – 60	1.5	2.2	2.8	4.3
eGFR 30 – 45	2.2	2.7	3.4	5.2
eGFR 15 – 30*	14.0	7.9	4.8	8.1

\* In general, increasing ACR correlates with a higher risk of cardiovascular mortality (and other prognostic outcomes, e.g. kidney failure, all-cause mortality). However, in patients with a very low eGFR (e.g. < 30 mL/min/1.73m<sup>2</sup>) the opposite association is observed in this Table. This is likely to be because the analysis was based on general-population cohorts and therefore not sufficiently powered to report accurate estimates for the relatively small number of patients with severe eGFR grading.<sup>9</sup> The confidence intervals for such eGFR categories (at any given ACR) are therefore substantially wider than for higher eGFR categories and overlap.

## Detecting patients with CKD in primary care

People with CKD are generally asymptomatic in the early stages and in some cases, kidney function can reduce by up to 90% before symptoms develop.<sup>10</sup> Therefore, to increase the detection of CKD in primary care, a risk-based approach to investigation is recommended (**Figure 1**).<sup>3,10</sup>

To investigate for CKD, request:

- **Serum creatinine**, which automatically generates an eGFR from the laboratory.

The eGFR reported from New Zealand laboratories is usually calculated with the CKD-EPI algorithm as this is now the recommended equation and considered most accurate. N.B. The Cockcroft-Gault equation may be used to guide dose adjustments for certain medicines, e.g. metformin (see: “Glycaemic control”).

- **Urine ACR**, to determine albuminuria status; if a first void urine specimen, when the urine is most concentrated, is not possible a random urine sample can be used

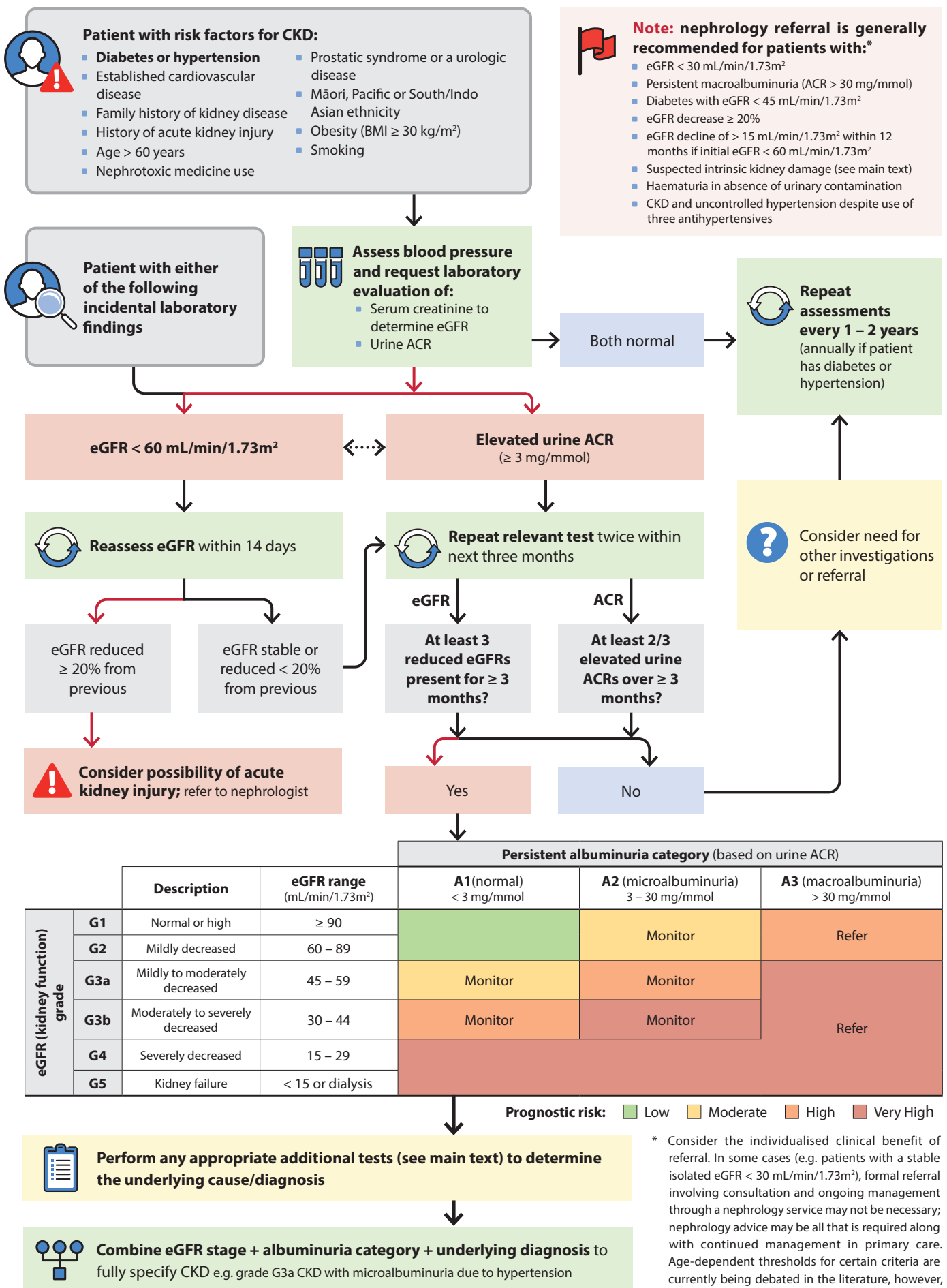
**Albumin:creatinine ratio is preferable to protein:creatinine ratio in most cases.** ACR is considered to be a more sensitive and specific measure of changes in glomerular permeability than the total urinary protein:creatinine ratio. Evaluation of the protein:creatinine ratio may

be appropriate when non-albumin proteinuria is suspected (e.g. in patients with disorders of tubular function or myeloma).

Investigation should occur every one to two years in most patients with risk factors for CKD, e.g. hypertension, diabetes, people of Māori, Pacific or South/Indo Asian ethnicity (see **Figure 1** for a full list of risk factors). A blood pressure measurement should also be included to contextualise these markers of kidney health with respect to the patient’s overall CVD risk.<sup>3,10</sup> These appointments can be an opportune time to emphasise lifestyle changes which may reduce the likelihood of CKD developing in people with risk factors (see: “Lifestyle management of CKD”). If patients have established diabetes or hypertension, investigation for CKD should take place at least annually.<sup>10</sup> Population screening for CKD in isolation is not recommended.

### CKD symptoms and signs

The presence of symptoms or signs generally indicates more advanced CKD but these are often non-specific. Patients with grade 3 CKD may be asymptomatic, or report nocturia, mild malaise or anorexia.<sup>10</sup> If present, symptoms and signs of grade 4 and 5 CKD are usually more overt, including nausea, pruritus, restless legs and dyspnoea.<sup>10</sup> Features resulting from diminished kidney function may also become apparent in advanced disease, e.g. oedema. Cognitive impairment is




**Figure 1.** Algorithm for the initial detection and diagnosis of patients with CKD. Adapted from Kidney Health Australia.<sup>10</sup>

also more common in patients with CKD than the general population, which can range in severity from mild cognitive dysfunction to dementia.<sup>12</sup>

## Evaluating kidney test results

**Decreased eGFR.** If a patient is found to have an eGFR < 60 mL/min/1.73 m<sup>2</sup>, serum creatinine should be measured again within 14 days as small variations in eGFR are possible and measurements in isolation are not always indicative of kidney disease progression.<sup>13</sup> If the reduced eGFR is confirmed, and it is stable or decreased < 20% from the previous result, eGFR should be re-tested at least twice over the next three months (**Figure 1**).<sup>10</sup> Patients with an eGFR < 45 mL/min/1.73 m<sup>2</sup> are at higher risk of significant cardiovascular and kidney consequences, e.g. end stage kidney disease or heart failure, regardless of their age.<sup>10</sup> N.B. Serum creatinine results within normal parameters does not exclude the possibility of CKD; kidney function decreases of > 50% can occur before serum creatinine values exceed the upper limit of normal.<sup>10</sup>

 **Practice point:** a reduction of ≥ 20% in eGFR from baseline is considered clinically significant and may indicate acute kidney injury (see: “Preventing acute kidney injury in patients with CKD”); nephrologist referral is required.<sup>10</sup>

**Increased ACR.** If ACR is elevated, it should usually be repeated twice within three months to confirm results (**Figure 1**).<sup>10</sup> Albuminuria is classified according to the criteria in **Table 1**.

## Considerations when interpreting eGFR/ACR results

There are numerous factors that can influence eGFR and ACR results other than CKD. These factors should always be considered, particularly for patients with borderline or isolated abnormalities. This includes:<sup>10, 14</sup>

eGFR*	
<b>Overestimation,</b> i.e. true GFR likely to be lower	<ul style="list-style-type: none"> <li>Reduced skeletal muscle mass decreases serum creatinine, e.g. anorexia nervosa, paraplegics, amputees</li> <li>Meat is the main exogenous source of creatinine (particularly red meat); people who follow vegan/vegetarian diets have lower serum levels</li> <li>Liver disease may reduce hepatic creatinine production</li> </ul>
<b>Underestimation,</b> i.e. true GFR likely to be higher	<ul style="list-style-type: none"> <li>High red meat diets and creatine supplementation</li> <li>Increased muscle mass</li> <li>Medicines that limit creatinine excretion, e.g. fenofibrate or trimethoprim</li> <li>Pregnancy</li> <li>Age &lt; 18 years</li> </ul>

## ACR

<b>Overestimation</b>	<ul style="list-style-type: none"> <li>Urinary tract infection</li> <li>Acute fever</li> <li>Menstruation</li> <li>Heart failure</li> <li>Intense exercise within 24 hours before sample</li> <li>Medicines, e.g. non-steroidal anti-inflammatory drugs (NSAIDs)</li> </ul>
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\* The eGFR reported from New Zealand laboratories is usually calculated with the CKD-EPI algorithm; this is considered a more accurate estimate of true GFR compared with other equations, e.g. MDRD, Cockcroft-Gault.<sup>14</sup> N.B. The Cockcroft-Gault equation may still be used to guide dose adjustments for certain medicines, e.g. metformin (see: “Glycaemic control”).

## Other tests to request when confirming CKD

Following confirmation of consistently decreased eGFR and/or increased urine ACR over a three-month period, additional tests should be requested to investigate and confirm the underlying cause (if not immediately apparent due to existing co-morbidities/history).

This may include:<sup>9, 10</sup>

- Kidney ultrasound
- Full blood count and CRP testing
- Glucose, lipids and HbA<sub>1c</sub>
- Serum electrolytes
- Dipstick urine test to detect haematuria or pyuria; if positive, request urine microscopy, e.g. to detect dysmorphic red cells, red cell casts or crystals
- Other tests according to patient-specific risk factors and clinical suspicion

## Patients requiring a nephrologist referral

Decisions to refer patients with CKD to secondary care should be made on a case-by-case basis.<sup>10</sup> A lower threshold for referral is usually appropriate for younger patients, and for Māori and Pacific peoples.<sup>10</sup>

Nephrology referral is generally recommended for patients with:<sup>3, 10</sup>

- eGFR < 30 mL/min/1.73 m<sup>2</sup>
- Persistent macroalbuminuria (ACR ≥ 30 mg/mmol)
- Diabetes and an eGFR < 45 mL/min/1.73 m<sup>2</sup>
- Suspected acute kidney injury, e.g. eGFR decrease ≥ 20% between measurements
- Suspected progressive CKD, e.g. eGFR decline of > 15 mL/min/1.73m<sup>2</sup> within 12 months if initial eGFR < 60 mL/min/1.73m<sup>2</sup>
- Suspected intrinsic kidney disease, e.g. acute glomerulonephritis may be suspected in unwell patients

who are dehydrated, with rapidly rising creatinine, increasing oedema and blood pressure, proteinuria and haematuria

- Haematuria in the absence of urinary contamination, e.g. bacteriuria
- Resistant hypertension and/or significant issues with blood glucose and/or multiple vascular complications

Consider discussing patients with a nephrologist if there is any uncertainty regarding referral. As CKD progresses, changes in bone mineral metabolism and calcium and phosphate metabolism develop.<sup>10</sup> Anaemia will often occur in patients with severely reduced kidney function due to a reduction in kidney synthesis of erythropoietin.<sup>10</sup> Complications of advanced CKD will be managed by a kidney team, e.g. acidosis, metabolic bone disease, anaemia, malnutrition, infection risk and acute kidney injury.<sup>3</sup>

## Managing patients with CKD in primary care


The majority of patients with stable CKD can be fully managed in primary care, particularly if they have stable grade G3 CKD or are aged over 75 years with early and stable grade G4 CKD.<sup>3</sup> Given that CKD rarely occurs in isolation, patients often have other co-morbidities which may share common management strategies and priorities.<sup>10</sup>

The key aspects of CKD management in primary care are:<sup>9,10</sup>

1. Lifestyle changes to optimise CKD management and the associated CVD risk

2. Preventing or slowing CKD progression, primarily through pharmacological management of blood pressure and hyperglycaemia (if the patient has diabetes)

Software-based decision support, audit and patient recall systems are an important part of best practice in the management of CKD.<sup>3</sup>

 If you do not have an integrated CKD decision support installed in your patient management system (PMS), contact BPAC Clinical Solutions ([bpacsolutions.co.nz/contact/](https://bpacsolutions.co.nz/contact/)) for information about their CKD module.

Complementary community-based care strategies involving nurse-lead teams have been shown to improve short-term outcomes in patients with moderate CKD who are at high-risk of progressing to kidney failure (see: “The utility of nurse-led management programmes: the DEFEND trial”).<sup>3,19</sup>

In rare cases, a reversible cause of CKD may be present in patients with a recent diagnosis or be the driver of acute deterioration in those with established disease. If corrected, this may lead to recovery of kidney function. Examples include hypovolaemia, sepsis, urinary tract obstruction and nephrotoxic medicine use, e.g. NSAIDs.<sup>9,10</sup> For further information, see: “Preventing acute kidney injury in patients with CKD”.

## CKD is a prominent risk factor for gout

Declining kidney function limits urate clearance, resulting in increased serum levels; once this passes the saturation point, monosodium urate crystal deposition can occur in joints, resulting in gout symptoms for some patients.<sup>15</sup> Up to 70% of patients with gout have an eGFR < 60 mL/min/1.73 m<sup>2</sup>, and gout further increases the CVD risk in patients with CKD.<sup>16</sup> As with CKD, the prevalence of gout increases with age and rates are significantly higher for Māori and Pacific peoples.<sup>15</sup>

Urate lowering treatment is indicated in patients with **symptomatic hyperuricaemia** and grade ≥ G3 CKD (i.e. eGFR < 60 mL/min/1.73m<sup>2</sup>) – kidney dysfunction alone is not an indication for urate lowering treatment in the absence of a gout flare.<sup>17,18</sup>

Monitoring kidney function in patients with CKD and gout is particularly important as many of the medicines used to treat gout are potentially nephrotoxic, and initial dosing decisions are made according to the patient’s eGFR status.<sup>16</sup> For example, patients with CKD who are receiving urate lowering treatment require a lower starting dose of allopurinol, and more gradual dose escalation.<sup>15</sup>

For further information on the medicines, dosing decisions and monitoring considerations involved in gout management, see:

- [bpac.org.nz/2021/gout-part1.aspx](https://bpac.org.nz/2021/gout-part1.aspx)
- [bpac.org.nz/2021/gout-part2.aspx](https://bpac.org.nz/2021/gout-part2.aspx)


## Lifestyle management of CKD

Lifestyle modifications are important for all patients with CKD as they can help to slow the rate of kidney function decline and reduce the patient's overall CVD risk.<sup>10,20</sup> These changes can also be recommended to people who have risk factors for CKD but do not yet have evidence of impairment, as part of a general kidney health discussion.

Key examples of lifestyle changes and their benefits include:<sup>10,20</sup>



**Weight loss.** Reducing BMI to at least  $\leq 30$  kg/m<sup>2</sup> with an ideal target of  $\leq 25$  kg/m<sup>2</sup>. Weight reduction of 5.1 kg decreases systolic blood pressure by approximately 4.4 mmHg. Central obesity is an important risk factor, and a waist circumference for males of  $< 94$  cm and for females  $< 88$  cm should be targeted.

 For further information on weight loss, see: **"Weight loss: the options and the evidence"**



**Exercise.** Performing 150 – 300 minutes/week of moderate intensity physical activity or 75 – 150 minutes/week of vigorous intensity physical exercise is estimated to reduce systolic blood pressure by 3 – 5 mmHg. Strength/resistance training is advised on at least two days per week, e.g. lifting weights, using a resistance band, stair climbing.




**Nutrition.** Patients with CKD should be advised to eat a balanced diet which emphasises intake of fruits, vegetables, nuts, low-fat dairy products, whole grains and fish, e.g. the **DASH diet**. In addition, the diet should include the following features:

- Reduce sodium intake to no more than 2.3 g per day ( $\leq 6$  g/day total salt); this change alone can help achieve a decrease in systolic blood pressure of 4 – 7 mmHg. Advise patients to avoid adding salt during cooking or at the table, and to select salt reduced packaged food products, where possible.
- Avoid trans fats and minimise intake of processed meats, refined carbohydrates and sweetened beverages
- Drink water to satisfy thirst but avoid overconsumption
- High protein diets and creatine supplements should be avoided in patients with CKD. The suitability of protein restriction continues to be debated in the literature (see: "The jury remains out on low protein diets") and is not routinely recommended.



**Reducing alcohol consumption.** All patients with CKD should be advised to have at least two alcohol-free days per week, and ideally only have one or two standard drinks on the days they consume alcohol.

 For further information on alcohol, see [bpac.org.nz/2018/alcohol.aspx](http://bpac.org.nz/2018/alcohol.aspx)



**Smoking cessation.** Smoking is an important modifiable risk factor for CKD progression and encouraging cessation should be a priority, if relevant. The few studies that have been conducted on the effects of smoking cessation in patients with CKD have found that albuminuria decreases significantly and the progression of diabetic neuropathy slowed.<sup>21,22</sup>

Achieving these recommendations may be difficult for some patients, and despite evidence for their efficacy in clinical trials, there is variable success in the real-world setting.<sup>20</sup>

Poor communication and planning has been highlighted as a barrier to Māori engaging with interventions to promote kidney health.<sup>23</sup> Consideration must be given to whether lifestyle advice is culturally appropriate and tailored to their priorities.<sup>23</sup> For example, nutritional changes may be difficult for individuals to adopt when the sharing of food has significant importance in engaging with their whānau. Inclusion of family members in the planning process is one strategy to create an environment that promotes long-term adherence.

### The jury remains out on low-protein diets


One of the most extensively studied dietary interventions for CKD is protein restriction, however, investigations have yielded mixed results over time. This approach is proposed to reduce progressive glomerular injury by reducing glomerular hyperfiltration.<sup>20</sup> Several guidelines still recommend patients with CKD should maintain a normal daily intake of protein, i.e. 0.8 g/kg/day, and that low protein diets should be avoided as insufficient dietary protein can lead to malnutrition, particularly in older patients.<sup>10,13</sup>

The 2020 Kidney Disease Outcomes Quality Initiative (KDOQI) clinical guideline for nutrition in CKD recommended that, under close supervision, stable patients with grades G3 – 5 CKD (without diabetes and not on dialysis) consume 0.55 – 0.6 g/kg/day of protein to prevent hyperfiltration and kidney disease progression.<sup>24</sup> This equates to 48 g of protein per day for an 80 kg person, e.g. approximately 170 g of fillet steak, 150 g chicken breast or 190 g of canned tuna.<sup>25</sup> However,



other food sources also contribute to total protein intake and these should be factored in when reviewing options, e.g. soy protein sources, grains, nuts and pulses.<sup>25</sup> Vegetable-derived proteins may induce lower levels of glomerular hyperfiltration than animal-derived protein, and can be more suitable in certain situations, e.g. patients with hyperphosphataemia.<sup>20</sup>

**Recommendation of a low protein diet is not considered standard practice in New Zealand for the treatment of patients with CKD.** If it is being considered, it should ideally be under the guidance of a dietitian or nephrologist. Excessive protein restriction (e.g. 0.3 – 0.4 g/kg/day) in particular is not recommended unless under dietitian/nephrologist supervision – complementary ketoacid analogue supplementation may be required.<sup>24</sup>

 For further information on the nutritional content of foods, see: [nutritionfoundation.org.nz/nutrition-facts/nutrients/protein/](https://nutritionfoundation.org.nz/nutrition-facts/nutrients/protein/)

## Pharmacological treatment in patients with CKD

All patients with a new diagnosis of CKD should have their current medicines reviewed for potential nephrotoxicity, and consider whether dose adjustments, switching or discontinuation is required. Key examples include NSAIDs and certain antibiotics (e.g. aminoglycosides and penicillins).<sup>9</sup> Also consider any use of over-the-counter NSAIDs or other nephrotoxic substances, as well as complementary or alternative medicines. Decisions around nephrotoxic medicine use can sometimes be challenging in the setting of CKD; while they may contribute to further deteriorating kidney function, some are essential to the management of other pre-existing conditions. If there is uncertainty, seek secondary care advice.

There are several traditional Rongoā Māori treatments for kidney and urinary complaints. These include Kawakawa (Māori Pepper Tree), Karamu (Coprosma), Manuka (Red tea tree) and Kanuka (White tea tree). While patients should generally be supported in the use of traditional healing remedies when there is no evidence for harm, advise stopping use if there is suspicion of nephrotoxicity or possible interactions between the active ingredient and other conventional medicines being taken.

## Blood pressure management

Pharmacological treatment of blood pressure is a cornerstone of CKD management, both to prevent or slow the rate of disease progression and to bolster the effects lifestyle changes have on reducing overall CVD risk.

**Overall blood pressure objective.** There is variation between guidelines regarding the recommended blood pressure target for patients with CKD:

- Guidelines from the International Society of Hypertension and American College of Cardiology (ACC)/ American Heart Association (AHA) recommend a target systolic blood pressure of < 130/80 mmHg<sup>26,27</sup>; NICE guidelines also recommend this target for patients with CKD and albuminuria<sup>13</sup>
- KDIGO 2021 guidelines on blood pressure management in CKD recommend that for patients not undergoing dialysis, a more assertive systolic blood pressure target of < 120 mmHg is appropriate (N.B. diastolic target not specified);<sup>28</sup> they also place an emphasis on using **standardised methods for clinic blood pressure measurements**, and note that out-of-office measurements (with at-home or ambulatory monitoring) should be considered as a complementary strategy wherever possible

Evidence supporting systolic blood pressure targets of < 120 mmHg is more limited and, if being considered, is most likely to benefit patients with CKD and multiple additional CVD risk factors or those with proteinuric CKD. More lenient blood pressure targets (e.g. < 140/90 mmHg) may be more appropriate for some patient groups, e.g. frail patients or those with a high burden of co-morbidities.

### First-line treatment: ACE or ARB.

Either an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB) should be used first-line for controlling blood pressure in patients with CKD.<sup>10,28</sup> ARBs are often preferred due to the comparable efficacy and lower risk of adverse effects. ACE inhibitors and ARBs also have an antiproteinuric effect, which is most pronounced in patients on a low sodium diet.<sup>28</sup> Following initiation, patients should be monitored\* for acute reductions in serum creatinine and hyperkalaemia (see: “Stopping an ACE inhibitor or ARB due to hyperkalaemia in a patient with CKD should be a last resort”) – ideally within one to two weeks in the first instance, then less frequently once the target blood pressure is achieved.<sup>10,28</sup> If following initiation serum creatinine reduces by ≥ 30% or eGFR decreases ≥ 25% from baseline, consider a dose decrease or discontinuation and investigate possible non-pharmacological causes, e.g. a rapid deterioration may indicate possible renal artery stenosis.<sup>28</sup>

\* Other laboratory investigations such as renin, aldosterone and angiotensin testing are not routinely required and would most likely be arranged in secondary care, or after discussion with a nephrologist

Concurrent use of an ACE inhibitor and ARB is not recommended in clinical guidelines,<sup>28</sup> however, there is some evidence that dual ACE inhibitor/ARB treatment is effective

for preventing end-stage kidney disease.<sup>29</sup> This combination should generally not be used unless under the guidance of a nephrologist.

**Escalating antihypertensive treatment: CCB is often the next step.**

KDIGO guidelines recommend titrating the ACE inhibitor/ARB dose to the maximum (approved) tolerated level in most patients with CKD to optimise their antiproteinuric effect.\*<sup>28</sup> This differs somewhat to the approach for managing uncomplicated hypertension in international guidelines, where there is increasing emphasis on the early use of low-dose dual antihypertensive treatment (i.e. avoiding early high dose monotherapy).

Ultimately, many patients with CKD will eventually require multiple medicines to achieve blood pressure targets and this need increases as a patient’s eGFR declines.<sup>10</sup> There is little evidence to identify the optimal combination of antihypertensives for patients with CKD. In those requiring treatment escalation, adding a calcium channel blocker (CCB) is a suitable next step.<sup>28</sup> The efficacy of thiazide diuretics reduces with worsening kidney impairment; loop diuretics may instead be beneficial, if required, particularly in patients with an eGFR < 30 mL/min/1.73m<sup>2</sup>. A beta-blocker may be considered as another option for combination treatment, particularly if indicated for CVD co-morbidities (especially in patients with diastolic dysfunction).<sup>28</sup>

\* While the KDIGO guidelines do not specifically recommend against this titration strategy in patients with advanced CKD (e.g. eGFR < 30 mL/min/1.73m<sup>2</sup>), they note that there is not yet sufficient RCT evidence to guide use (most studies exclude such patients). Management decisions for patients with advanced CKD should ideally be made under nephrologist guidance. If antihypertensive treatment is being initiated while awaiting referral, a lower initial dose may be required depending on the ACE inhibitor/ARB used (see the corresponding New Zealand Formulary monograph for further information).

**Stopping an ACE inhibitor or ARB due to hyperkalaemia in a patient with CKD should be a last resort**

Up to 10% of patients with CKD treated with ACE inhibitors/ARBs in primary care develop hyperkalaemia and increases in serum potassium of approximately 0.5 mmol/L are common.<sup>10, 28, 30</sup> In a long-term CKD management setting, serum potassium levels up to 6.0 mmol/L are acceptable.

Before lowering the dose or stopping use altogether, clinicians should consider other options to reduce serum potassium in patients with CKD if the increase is < 30% from the baseline value, including:<sup>28</sup>

- Reduce dietary potassium intake
- Stop or switch out beta-blocker if the patient is taking one (if it will not compromise management of any

co-morbidities), as these increase serum potassium levels more significantly than ACE inhibitors/ARBs

- Consider stopping/switching any other medicines and supplements that impair kidney function or reduce potassium excretion if hyperkalaemia is an issue
- Consider diuretics to increase potassium excretion by the kidneys (e.g. frusemide), particularly if the patient has resistant hypertension or volume overload
- Oral sodium bicarbonate can be used if the patient has metabolic acidosis

**Glycaemic control**

One in two primary care patients with diabetes meet the criteria for CKD.<sup>10</sup> Glycaemic control is essential in patients with these co-morbidities to prevent or delay the progression of microvascular complications (e.g. diabetic neuropathy) and reduce overall CVD risk.<sup>30</sup>

**Glycaemic target.** A HbA<sub>1c</sub> target of < 53 mmol/mol is generally appropriate for patients with CKD and diabetes, but more lenient targets can be considered depending on individual circumstances, e.g. older patients living alone, or those with multiple other co-morbidities or a limited life expectancy.<sup>10</sup> Given that hypoglycaemia becomes more common as eGFR decreases, less intensive glycaemic control may be appropriate in patients with advanced grade G4 and grade G5 CKD.<sup>3, 10</sup>

**Treatment strategy.** The initial approach to glycaemic control in patients with CKD and diabetes is lifestyle changes plus metformin.<sup>30</sup> The maximum dose of metformin in patients with CKD will depend on their kidney function (**Table 3**).<sup>31, 32</sup>

**Table 3.** The maximum dose of metformin based on the patient’s kidney function.<sup>31, 32</sup>

Patient eGFR (mL/min/1.73m <sup>2</sup> )*	Maximum recommended metformin dose
≥ 60	2 g daily
30 – 59	1 g daily
15 – 29	0.5 g daily
< 15	Contraindicated

\* While in many cases eGFR will be sufficient to estimate kidney function in patients taking metformin, the NZF recommends using the Cockcroft-Gault equation for a more accurate calculation of creatinine clearance, which may be particularly useful in people with more severe renal impairment.<sup>32</sup> A calculator is available here: [www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation](http://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation).

**Escalating glycaemic control with a SGLT-2 inhibitor.** If metformin is insufficient for controlling HbA<sub>1c</sub>, use of a sodium glucose co-transporter-2 (SGLT-2) inhibitor is recommended

as this has dual kidney- and cardio-protective effects.<sup>30</sup> Empagliflozin is the only SGLT-2 inhibitor currently available in New Zealand; while KDIGO guidance states that a SGLT-2 inhibitor should be initiated concurrently with metformin in most patients,<sup>30</sup> the Special Authority criteria for empagliflozin requires that patients with diabetes and CKD have “an HbA<sub>1c</sub> level > 53 mmol/mol despite the regular use of at least one blood-glucose lowering agent (e.g. metformin, vildagliptin or insulin) for at least three months”.

**SGLT-2 inhibitors may also be beneficial in non-diabetic patients with CKD.** There is evidence that patients with proteinuric CKD without diabetes still benefit from SGLT-2 inhibitor use.<sup>33</sup> However, under the current Special Authority criteria this would involve patients having to self-fund treatment. This option should be discussed with patients, so they have the opportunity to consider it depending on their individual circumstances, as appropriate.

**Additional glucose lowering treatments.** If further management is required, the addition of a glucagon-like peptide-1 (GLP-1) receptor agonist can be considered as the next step in management,<sup>30</sup> however, dual SGLT-2 inhibitor/GLP-1 receptor agonist treatment is not currently funded in New Zealand. Alternatives include vildagliptin, pioglitazone (unless the patient has heart failure), a sulfonylurea or insulin.

 For further information on:

- The management of diabetes, see: [bpac.org.nz/2021/diabetes-management.aspx](https://www.bpac.org.nz/2021/diabetes-management.aspx)
- SGLT-2 inhibitors and GLP-1 receptor antagonists, see: [bpac.org.nz/2021/diabetes.aspx](https://www.bpac.org.nz/2021/diabetes.aspx)

### Additional medicines to consider

**Lipid management.** Dyslipidaemia is common among patients with CKD, particularly high triglyceride and low HDL-C levels.<sup>34</sup> Given the high risk of CVD associated with CKD, the benefits of statin treatment (starting with atorvastatin) should be discussed with patients.<sup>10, 34</sup> Addition of ezetimibe (Special Authority approval required) can be considered for patients whose LDL-C remains > 2 mmol/L despite the maximal tolerated statin dose.<sup>10, 34</sup>

**Antiplatelet treatment.** In general, long-term aspirin use should be considered for secondary prevention in patients with CKD and established CVD.<sup>9, 30</sup> Dual antiplatelet treatment (e.g. aspirin + clopidogrel) may be considered for patients with acute coronary syndrome or after percutaneous coronary intervention.<sup>30</sup> Aspirin may also be considered for primary prevention in patients with a high risk of atherosclerotic events unless there is an increased bleeding risk.<sup>9, 10</sup>

## Preventing acute kidney injury in patients with CKD

People with CKD have an increased risk of developing acute kidney injury.<sup>10</sup> Medicines are a common cause and those with acute illness (e.g. a gastrointestinal illness, sepsis and respiratory or urinary tract infection causing hypovolaemia) are at significant risk.

In people with CKD, some medicines should be used with caution. For example, the “triple whammy” of NSAIDs, ACE inhibitors (or ARBs) and diuretics can potentiate acute kidney injury by interfering with homeostatic mechanisms needed to preserve kidney perfusion during acute illness.<sup>10</sup> Adequate fluid intake and electrolyte maintenance are important in people with CKD who are acutely unwell.

The **Mnemonic: SAD MANS** can be used as a reminder of medicines which should be withheld in people with CKD during an acute illness:<sup>10</sup>

- Sulfonylureas
- ACE-inhibitors
- Diuretics
- Metformin
- ARBs
- NSAIDs
- SGLT-2 inhibitors

Use of essential medicines (e.g. ACE inhibitors, ARBs, metformin and SGLT-2 inhibitors) should then recommence once the patient recovers from the acute illness.

### Patients with CKD undergoing medical procedures.


People with CKD are also at an increased risk of developing acute kidney injury when they undergo procedures involving radiocontrast material and it may be necessary to temporarily withdraw potentially nephrotoxic medicines.<sup>10</sup> The use of metformin is contraindicated in patients undergoing procedures involving iodine-containing X-ray contrast media due to the small risk of lactic acidosis (particularly in elderly patients), e.g. when investigating cancers.<sup>35</sup>

## Monitoring patients with established CKD

Patients with established CKD should have their eGFR and albuminuria assessed at least annually.<sup>10</sup> **Table 4** provides a recommended monitoring schedule for patients with established CKD according to severity. Patients with progressive grade G3 – 4 CKD have a much greater risk of developing kidney failure and require intensive management with weekly or fortnightly review of risk factor management until their condition is stable.<sup>3</sup>

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**Table 4.** Monitoring and investigation schedule for patients with CKD.<sup>10</sup>

CKD parameters	Frequency of review	Clinical assessment	Laboratory investigations
<ul style="list-style-type: none"> <li>■ eGFR <math>\geq</math> 60 mL/min/1.73m<sup>2</sup> with microalbuminuria; <b>or</b></li> <li>■ eGFR 45 – 59 mL/min/1.73m<sup>2</sup> with normoalbuminuria</li> </ul>	Annually; less frequent review may be appropriate if patient's eGFR is stable and risk factors are well controlled	<ul style="list-style-type: none"> <li>■ Blood pressure</li> <li>■ Weight</li> <li>■ Medicine use; avoid nephrotoxic options and adjust doses to levels appropriate for level of kidney function</li> </ul>	Serum creatinine (eGFR), urine ACR, serum electrolytes, urea, HbA <sub>1c</sub> for patients with diabetes, lipids
<ul style="list-style-type: none"> <li>■ eGFR 30 – 59 mL/min/1.73m<sup>2</sup> with microalbuminuria; <b>or</b></li> <li>■ eGFR 30 – 44 mL/min/1.73m<sup>2</sup> with normoalbuminuria</li> </ul>	Every 3 to 6 months		Serum creatinine (eGFR), urine ACR, serum electrolytes, urea, HbA <sub>1c</sub> for patients with diabetes, lipids
<ul style="list-style-type: none"> <li>■ Macroalbuminuria irrespective of eGFR status; <b>or</b></li> <li>■ eGFR &lt; 30 mL/min/1.73m<sup>2</sup> irrespective of albuminuria status</li> </ul>	Every 1 to 3 months	<ul style="list-style-type: none"> <li>■ In addition to the above: checking for features of advanced CKD, e.g. oedema</li> </ul>	<p>In addition to the above: plasma bicarbonate</p> <p>Investigations will likely be determined in conjunction with a nephrologist</p>

## The utility of nurse-led management programmes for CKD: the DEFEND trial

General practice can help support improved outcomes for patients at high risk of progressing to kidney failure through relatively simple complementary nurse-led interventions involving the use of healthcare assistants.

The **DE**lay **F**uture **E**nd-stage **N**ephropathy due to **D**iabetes (DEFEND) trial involved 65 Māori and Pacific patients aged 47 – 75 years with type 2 diabetes, moderate CKD and hypertension, living in Auckland.<sup>36</sup> Patients received either routine medical care and follow-up or nurse-led, community based, monthly assessments and monitoring delivered by healthcare assistants.<sup>36</sup> This study found that community care resulted in clinically significant decreases in systolic blood pressure and proteinuria as well as delayed progression of left ventricular hypertrophy and diastolic dysfunction.<sup>36</sup> The success of the programme

was attributed to Māori and Pacific healthcare assistants providing culturally appropriate care, the more frequent follow-up and prompting of patients to take medicines, and reduced costs to patients because of home visits.<sup>36</sup>

After the intervention ended in 11 – 21 months, patients reverted back to routine medical care. In a 2015 follow-up study, the initial short-term improvements in systolic blood pressure and proteinuria for the intervention cohort did not result in long-term reductions in mortality and end-stage kidney disease rates compared with the usual care group.<sup>37</sup> These findings indicate that such community-based interventions may need to be initiated earlier and maintained throughout care to have a more meaningful impact for people with CKD.<sup>37</sup>

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