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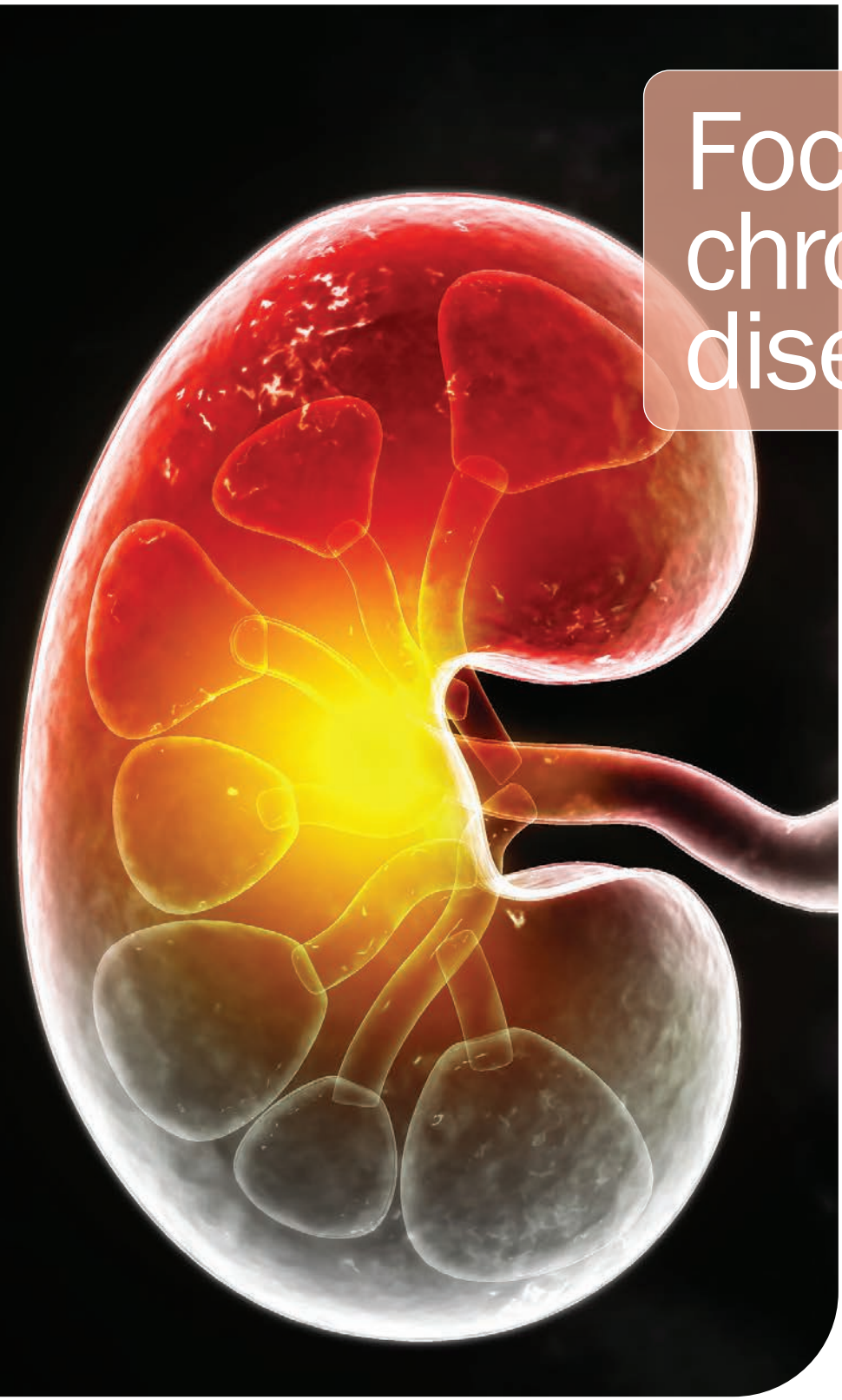

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Focus on chronic kidney disease

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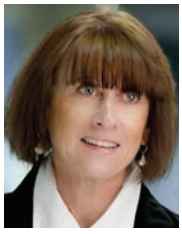
MedicineToday
THE PEER REVIEWED JOURNAL OF CLINICAL PRACTICE

FOREWORD FROM THE COLLECTION EDITOR

Chronic kidney disease (CKD) is a growing global health challenge, driven by the increasing prevalence of diabetes, hypertension, obesity and cardiovascular disease. In Australia, more than two million adults show evidence of CKD, and too many remain undiagnosed until the disease is advanced. Yet, with early recognition and comprehensive, team-based care, its progression can be slowed and its cardiovascular complications reduced.

This *Focus on chronic kidney disease* collection brings together contemporary, practical guidance for clinicians on the front line of detection and management. It underscores the importance of systematic assessment – blood pressure, estimated glomerular filtration rate and urine albumin-to-creatinine ratio – and the need for integrated, multidisciplinary and culturally responsive care that empowers patients and communities alike.

Therapeutic advances now provide the tools to fundamentally alter disease trajectories. The four pillars of therapy – renin–angiotensin system inhibitors, sodium-glucose cotransporter-2 inhibitors, nonsteroidal mineralocorticoid receptor antagonists and glucagon-like peptide-1 receptor agonists – offer proven kidney and cardiovascular protection. When combined with lifestyle measures and patient engagement, these strategies herald a new era in CKD care – one defined by prevention, partnership and possibility.



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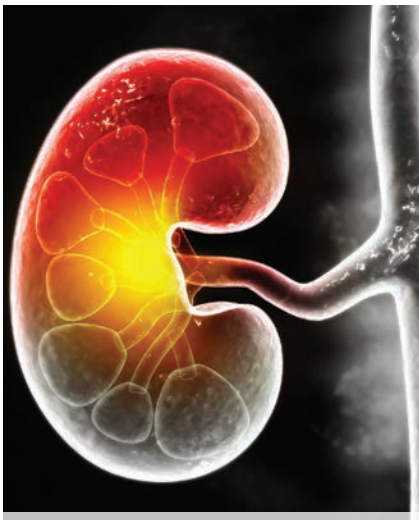

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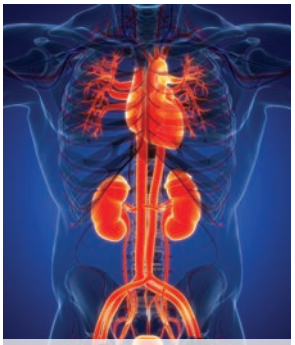

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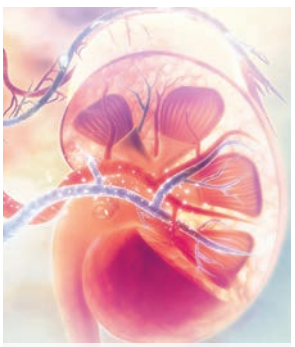

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PEER REVIEWED FEATURE

Chronic kidney disease

Doing simple things well for those most at risk

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The incidence of chronic kidney disease (CKD) is increasing worldwide. A holistic approach to management that includes nonpharmacological and pharmacological strategies to manage risk factors, as well as advocating for patients, particularly those most at risk, can significantly slow the progression of CKD. Input from multidisciplinary team members, including a nephrologist, CKD nurse and allied health professionals, can further reduce the progression of CKD, delay kidney failure and avoid CKD-related mortality.

Chronic kidney disease (CKD) is a global public health emergency, with its incidence increasing in parallel with growing rates of obesity, diabetes, hypertension and cardiovascular disease (CVD).[1] Over 2 million adults in Australia, representing 11% of the adult population, are estimated to have biomedical signs of CKD, and the number of people progressing to kidney failure requiring dialysis (kidney replacement therapy) more than doubled between 2000 and 2021.[2,3] This also comes at a burgeoning cost to public health systems. In 2021, CKD and kidney failure cost the Australian healthcare system $2.38 billion and, internationally, care of people with CKD has threatened to overwhelm the UK's NHS.[2,4,5] Diabetic kidney disease consistently contributes to about 40% of cases

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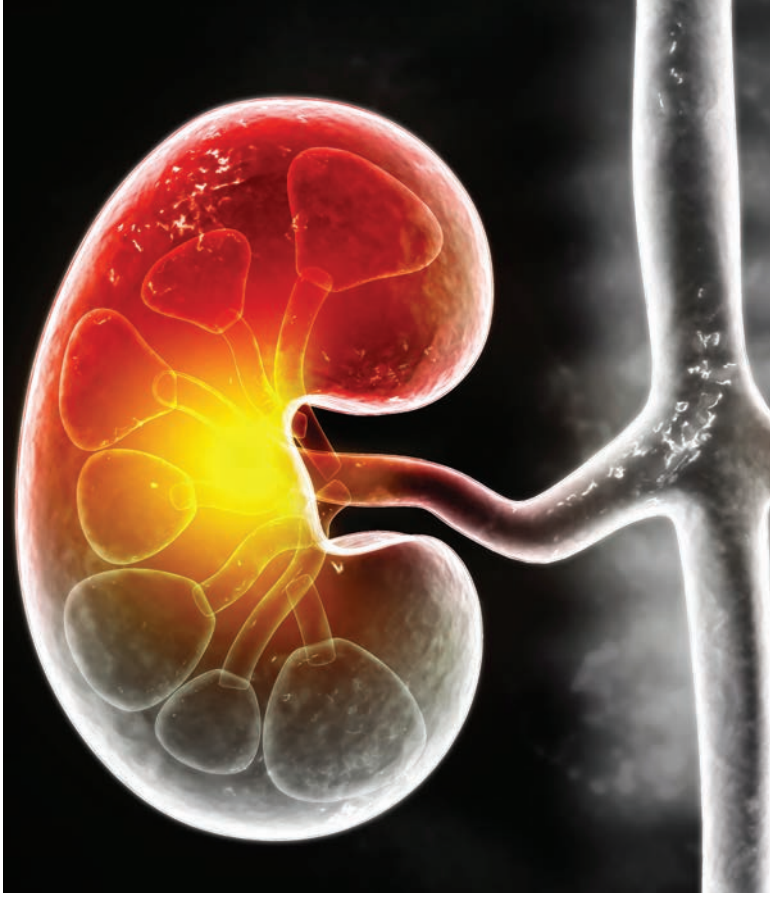

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KEY POINTS

- The incidence of chronic kidney disease (CKD) is increasing in Australia and worldwide, placing a significant burden on the healthcare system and economy.
- A thorough weight history, assessment of volume status and use of three essential tests (blood pressure, estimated glomerular filtration rate and spot urine albumin to creatinine ratio) are imperative to the diagnosis of CKD.
- Aboriginal and Torres Straits Islander people are twice as likely to develop CKD and five times more likely to develop kidney failure requiring dialysis compared with non-Indigenous Australians.
- Nonpharmacological measures, including optimising diet and nutrition, regular exercise and managing mental health, and a culturally responsible approach to care contribute to a patient's overall wellbeing and improved health.
- Risk factors for developing CKD, including diabetes, hypertension, obesity and cardiovascular disease, should be managed aggressively with pharmacotherapy.
- The four pillars of medical management for patients with CKD are renin-angiotensin system inhibitors, sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists and nonsteroidal mineralocorticoid receptor antagonists.

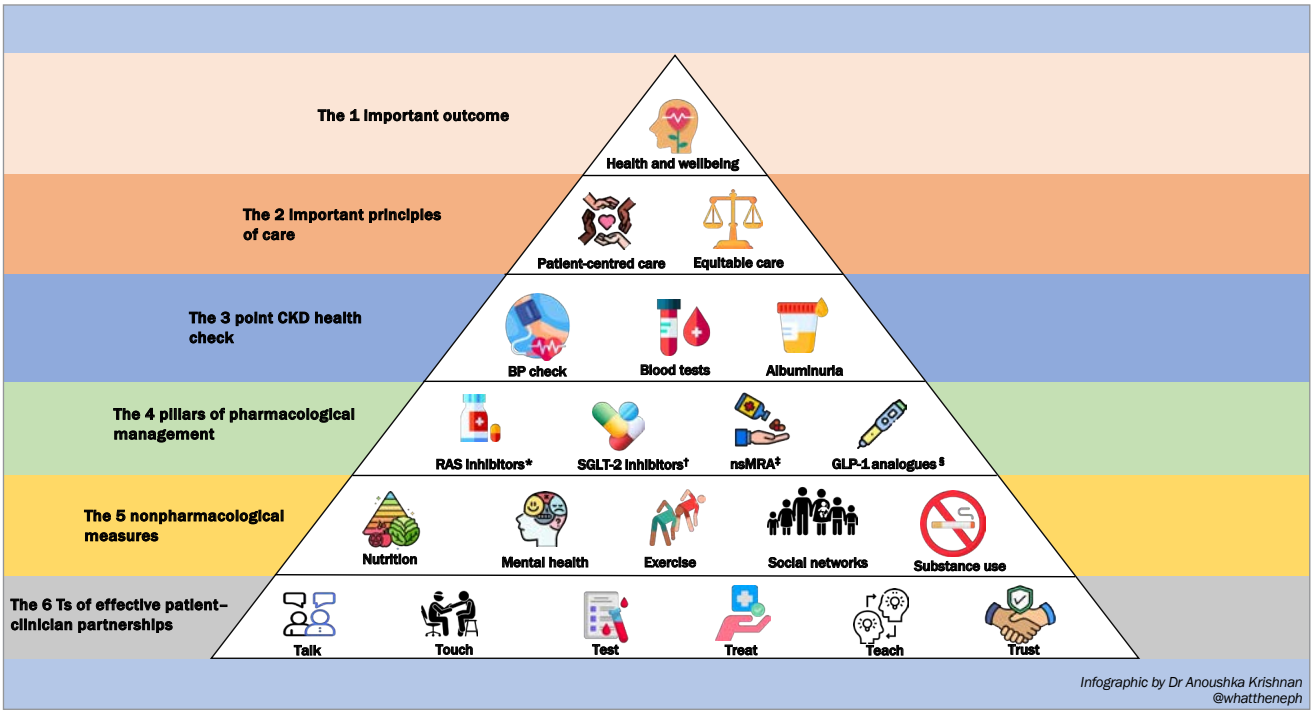

Figure. The chronic kidney disease management pyramid.

Abbreviations: BP = blood pressure; CKD = chronic kidney disease; DKD = diabetic kidney disease; GLP-1 = glucagon-like peptide-1; RAS = renin–angiotensin system; nsMRA = nonsteroidal mineralocorticoid receptor antagonist; SGLT-2 = sodium-glucose cotransporter-2.
* Use to manage all CKD. † Use to manage CKD as per PBS criteria. ‡ Use to manage DKD as per PBS criteria. § Use to manage DKD.

of kidney failure, followed by glomerulonephritis and hypertensive kidney disease.[6] Aboriginal and Torres Strait Islander people are five times more likely to develop kidney failure requiring dialysis (per population size) than non-Indigenous Australians.[2] Although observed in the era before sodium-glucose cotransporter-2 (SGLT-2) inhibitors, nonsteroidal mineralocorticoid receptor antagonists (MRAs) and glucagon-like peptide-1 (GLP-1) receptor agonists, Barr et al. recently reported that cardiac biomarkers, such as troponin and markers of inflammation, are predictive of annual loss in the estimated glomerular filtration rate (eGFR) among Aboriginal and Torres Straits Islander people who had diabetes compared with those without diabetes. They strongly recommended the urgent uptake of interventions to reduce CKD progression in communities living with overlapping cardiovascular disease, diabetes and chronic inflammation.[7]

CKD screening programs in Australia have been simplified to include three essential tests: blood pressure (BP), eGFR and spot urine albumin to creatinine ratio (uACR). Screening is widely promoted through Kidney Health Australia via many medical avenues, but is implemented with only partial success.[8] Home-based screening methods are being developed to improve population screening for CKD;[9] however, translating screening data and a CKD diagnosis into effective CKD therapy poses a further challenge. A recent study showed that pharmacotherapy for CKD management was underprescribed in primary care, with only 4.1% of eligible patients with CKD in Australia prescribed a SGLT-2 inhibitor.[10] Achieving implementation closer to 75% has been estimated to prevent over 3600 cardiorenal events and 1300 kidney failure episodes a year.[11]

At a population level, effective public health policy and resourced strategies can promote kidney health among communities with high CKD risk.[12] The core of public health strategy includes facilitating access to quality nutrition, adequate fitness and physical activity, and providing support to people seeking smoking and alcohol cessation. Effective public health strategies also facilitate access to affordable pharmacological approaches. Recently, several drugs have been developed that show a significant impact on reducing the progression of CKD, both in people with and without diabetes. This article discusses how clinicians can promote conceptually simple actions into highly effective health benefits for patients who are most at risk of kidney disease. The cornerstones of CKD management are summarised in the Figure.

First principles of best care

First principles of best care aim to improve the overall health of people with CKD, particularly at-risk populations. Key aspects of management include providing culturally responsible delivery of kidney care, promoting effective patient–clinician partnerships and delivering targeted care to optimise outcomes. These principles are outlined in Box 1.[13]

1. FIRST PRINCIPLES OF BEST CARE FOR IMPROVING THE HEALTH OF PEOPLE WITH CKD

Provide culturally responsible kidney care for people who need it the most

- Aboriginal and Torres Strait Islander people
- Patients who are vulnerable to accelerated kidney disease

Promote effective patient–clinician partnerships

- Use concepts such as the '6Ts' (talk, touch, test, treat, teach, trust; Figure)[13]

Deliver care to target optimal outcomes

- Improve the global survival of Aboriginal and Torres Strait Islander people
- Close the age gap for the onset of dialysis-requiring kidney failure
- Manage risk factors such as diabetes and hypertension
- Promote the use of new effective medications such as SGLT-2 inhibitors
- Address behaviour modification with regard to diet, exercise and consumption of addictive substances such as cigarettes, e-cigarettes or alcohol

Abbreviations: CKD = chronic kidney disease; SGLT-2 = sodium-glucose cotransporter-2.

Optimise holistic care

Mindset (mental wellness)

Patients' regular practices of healthful living are fundamental to kidney health and preventing related conditions associated with CKD. Over-riding social, financial, pain or mental health issues can be temporary or permanent barriers to healthful practices. These factors may cause elevated cortisol levels (hypercortisolism), resulting in insulin resistance, insomnia, hunger, hypertension, central adiposity and proximal muscle weakness, which contributes to accelerating diabetes, CVD and CKD progression.[14] Online cognitive behavioural therapy modules, such as those provided by This Way Up (https://thiswayup.org.au), may help patients manage poor sleep and anxiety associated with hypercortisolism, and are best prescribed for couples or households rather than isolated individuals, provided they have the technological access and determination to complete the programs.[15]

In the authors' experience, mnemonics can help patients focus attention systematically on their chosen problem area, starting with 'looking after your-SELFF', an acronym for Sleep, Exercise, Love, Foods and Fluids. Improving the quality of caloric intake takes priority over quantity, and includes prioritising a plant-based diet, avoiding ultra-processed foods and optimising water intake.[16] Referral for formal dietetic assessment and individualised advice is a standard of care but, in the authors' experience, broad direction can be quickly given as positive suggestions, for example, 'just eat real food', 'keep foods crunchy and colourful', 'swap salt flavouring to pepper, garlic, lemon and ginger' and 'make your drink a fashion statement traffic light: add mint, strawberry, lemon and orange to plain water for DIY potassium citrate'. Patients keen to avoid similar metabolic issues in their children or grandchildren should be encouraged to avoid smoking and make sure that special treats do not become daily habits.

Metabolic and psychological challenges

Supportive weight management

Avoid introducing assumptions or shame in collaborative health planning around weight management. Appreciating the metabolic and psychological challenges faced by many patients with CKD can sometimes be quickly gleaned by taking a five-point weight history of birth, teen post-puberty, maximum adult, minimum adult and current weight – then asking when and why the extreme values occurred, and with what functional impact. Episodes of extreme weight loss and volume depletion (e.g. teenage anorexia nervosa) can leave lasting kidney damage with osteoporosis. Conversely, for patients who are overweight, the dates of onset of painful arthritis, sleep apnoea, high BP, diabetes and stress incontinence are often precipitated by preceding weight gains.

Routine patient assessment

Routine examination of patients with CKD should include a five-point volume assessment, based on height, weight, postural change in BP and pulse rates, determining the extent of oedema and peripheral perfusion by capillary refill (and where possible, visualisation of jugular venous pressure). Total body weight measurement can be an understandably emotive issue and should be explained to patients as comprising the sum total of fluid, fat, muscle and bone weights, with each component having an individualised optimum range that is mostly genetically determined. Most people understand their weight in kg rather than body mass index (BMI). Therefore, using the rule of thumb that an individual's normal body weight (in kg) should roughly correspond to their height (in cm) minus 100 (i.e. a BMI of 25 kg/m^2) allows patients to better estimate their target body weight. Investigations for target organ damage from high BP and diabetes is routine and reimbursed by Medicare.

Glycaemic control

Food accessibility, security, affordability and preparation, nutrition quality, eating frequency and culturally-based eating rituals are important considerations in understanding and supporting a patient's glycaemic control, and a referral to an accredited practicing dietitian may be considered where indicated.[17] Along with self-monitoring of blood glucose levels, made easier with the recent availability of continuous glucose monitoring devices (PBS subsidised for people with type 1 diabetes), the *Kidney Disease Improving Global Outcomes* (KDIGO) guidelines endorse measuring glycated haemoglobin (HbA_{1c}) to monitor glycaemic control, even in individuals with CKD despite limitations associated with concurrent anaemia.[18] HbA_{1c} targets are now individualised, and range from below 6.5% to below 8% in patients with diabetes and CKD.[17] Higher targets are usually reserved for patients with several comorbidities or at increased risk of hypoglycaemia.

Metformin has been a long-standing high-value, low-cost agent for metabolic improvement without weight gain but needs progressive dose reduction as eGFR falls to avoid nausea or diarrhoea, and should be ceased immediately if a patient

is unwell. Dipeptidyl peptidase-4 inhibitors are similarly weight-neutral and have few side effects as eGFR falls. Conversely, sulfonylureas and insulin may cause weight gain and increase the risk of hypoglycaemia, especially in patients with CKD stages 4 and 5. A detailed approach to glycaemic management in the context of CKD has been recently published.[19] Use of SGLT-2 inhibitors and GLP-1 receptor agonists is discussed below.

Management of hypertension

Optimising BP control is crucial to reducing CKD risk. Nonpharmacological measures include dietary salt reduction (<2 g sodium intake or <5 g sodium chloride per day) and regular exercise (at least 150 minutes per week of moderately intense physical activity as tolerated).[20] Weight loss, smoking cessation and reducing alcohol consumption are useful adjunct measures.[9] Current target BP is individualised, with a recommended target of at least 130/80 mmHg or lower if tolerated, with the safety caveat to avoid symptomatic hypotension.[8] Target BP can be safely maintained by home BP monitoring and taking measurements on sitting and standing, taking medications at night rather than morning, ensuring good hydration during hot weather or physical exertion and providing patients the authority to reduce the dose of medications if low BP is consistently symptomatic.

Cardioprotection

Low kidney function and albuminuria are independently additive major cardiac risk factors, with cardiovascular (CV) events the cause of 95% of deaths in people with CKD before reaching kidney failure. Therefore, aggressive cardioprotection is crucial.[21] CKD causes dyslipidaemia (i.e. low HDL-cholesterol and high triglyceride levels) and nephrotic syndrome causes hyperlipidaemia (i.e. raised LDL-cholesterol); therefore, optimising kidney function (by monitoring eGFR) and pursuing antiproteinuric therapies are crucial. Statins do not retard CKD progression or reduce cardiac events in patients who have developed kidney failure; however, they are recommended to reduce CV events in patients with CKD aged under 50 years with just one additional CV risk factor, regardless of lipid level.[22,23] Aspirin is no longer recommended for the primary prevention of CVD in people with CKD because of the increased bleeding risk associated with its use and a lack of proven benefit.[24,25]

Screening

Individuals at risk of developing CKD should undergo a kidney health check every one to two years, incorporating the three essential BP, eGFR and uACR tests promoted by Kidney Health Australia.[8] Aboriginal and Torres Strait Islander peoples are twice as likely to develop CKD than non-Indigenous Australians. Therefore an annual health check from 18 years of age that includes measuring BP, uACR and eGFR is recommended to encourage regular surveillance and promote early detection and management, and is reimbursed under MBS item 715.[26] Recommendations for culturally safe kidney care in First Nations Australians is a nationally recognised and inaugural guideline carefully informed and endorsed by First Nations people, clinicians and peak health organisations, and is a useful resource for clinicians and consumers.[27]

2. PRESCRIBING AND MONITORING TIPS FOR RAS INHIBITORS

- Manage the expected increase in SCr level:
  - reduce or withdraw diuretics
  - choose calcium channel blockers as preferred second-line agents for blood pressure management
  - patients with an acute rise in SCr of >25% should be evaluated for volume depletion (from aggressive diuretic use), concomitant use of NSAIDs and bilateral renal artery stenosis, with the aim to try and continue the RAS blockade after these risk factors have been managed
- Manage hyperkalaemia:
  - limit dietary potassium intake
  - avoid drugs that can impair potassium excretion
  - avoid constipation (ensure adequate fluid intake, exercise, laxatives) and allow for concomitant use of diuretics
  - reduce metabolic acidosis with the use of sodium bicarbonate and concurrent use of potassium binders such as patiromer
- Counsel patients on the value of preparing a sick-day management plan:
  - include temporary cessation of drugs such as RAS inhibitors, diuretics, metformin, sulfonylureas, SGLT-2 inhibitors and NSAIDs
  - Kidney Health Australia provide a patient friendly sick day action plan template (https://assets.kidney.org.au/resources/KHA-Sick-Day-Action-Plan-Consumer-Oct23.pdf)
- Combination ACE inhibitors and angiotensin receptor blockers are not recommended

Abbreviations: RAS = renin-angiotensin system; SCr = serum creatinine; SGLT-2 = sodium-glucose cotransporter-2.

Targeted therapeutics

RAS inhibitors

Renin-angiotensin system (RAS) blockade has stood the test of time in CKD management. Several studies over the past three decades have demonstrated the kidney and cardioprotective benefits and albuminuria-lowering effects of RAS inhibitors.[28-32] They are used as first-line agents in the management of proteinuria and hypertension (with or without diabetes). Typically, changes in BP and serum creatinine (SCr) and serum potassium levels are monitored two weeks after initiation of these agents.[8] A temporary increase in SCr level less than 25% due to the vasodilatory effects on the glomerular outflow is a predictable effect in the first few days, and the agent should be continued. A decline in kidney function of more than 25% is an indication to cease the drug and consider other factors and referral of the patient to a nephrologist. Additionally, RAS blockade inhibits the action of aldosterone, predisposing patients to hyperkalaemia, particularly in patients with advanced CKD. Tips for prescribing and monitoring RAS inhibitors are highlighted in Box 2.

3. PRESCRIBING AND MONITORING TIPS FOR SGLT-2 INHIBITORS

- Perform an accurate volume assessment before prescribing an SGLT-2 inhibitor:
  - estimate jugular venous pressure
  - assess for peripheral oedema and lung auscultation
- Manage the expected rise in SCr level:
  - reduce or withdraw diuretics
  - choose calcium channel blockers as preferred second-line agents for blood pressure management
- Avoid hypovolaemia in euvolaemic patients:
  - consider adding a diuretic or antihypertensive agent
  - do not start these agents until hypovolaemia is corrected
- Manage increased risk of genital mycotic (including *Candida*) infections:
  - educate patients on maintaining meticulous groin hygiene
  - monitor closely for signs of infection
  - consider providing patients with a home mid-stream urine collection pot, a pathology request form and antifungals for prompt presumptive therapy at the time of initial SGLT-2 inhibitor prescription
  - the risk of severe urinary tract infections is not significant compared with other hypoglycaemic agents
- Manage the risk of hypoglycaemia in people with diabetes:
  - consider reducing the dose of medications, such as insulin or sulfonylureas, to reduce the risk of hypoglycaemia
  - the risk is low, especially in individuals without diabetes
- Manage the risk of euglycaemic diabetic ketoacidosis in people with diabetes:
  - consider withdrawal of insulin in those who experience starvation and acute sickness, which are risk factors
- Counsel patients on the value of preparing a sick-day management plan (see Box 2)
- Dapagliflozin and empagliflozin are PBS listed for CKD independent of diabetes status

Abbreviations: CKD = chronic kidney disease; SCr = serum creatinine; SGLT-2 = sodium-glucose cotransporter-2.

SGLT-2 inhibitors

SGLT-2 inhibitors were initially used to treat malaria, and later developed as hypoglycaemic agents. Although their impact on glycaemic control is modest, their efficacy in reducing the progression of CKD and heart failure, irrespective of diabetes status, has been a game changer for patients. SGLT-2 inhibitors are now the second-line agent of choice for managing diabetes (after metformin).[18] More recently, dapagliflozin and empagliflozin showed a 39% and 28% risk reduction in kidney-related outcomes, respectively.[33,34]

Dapagliflozin is PBS listed for patients with CKD independent of diabetes status (eGFR 25 to 75 mL/min/1.73 m^2 and uACR 22.6 to 565 mg/mmol). As of 1 November 2025, the PBS listing of empagliflozin has been updated with extended criteria for patients with CKD independent of diabetes status (eGFR 20 to 90 mL/min/1.73 m^2 and uACR at least 22.6 mg/mmol if their eGFR is between 45 and 90 mL/min/1.73 m^2 inclusive). Patients should be on a stable dose of an ACE inhibitor or an angiotensin II receptor blocker for four weeks (unless medically contraindicated) prior to initiation of these agents. SGLT-2 inhibitors are not approved for use in patients on kidney replacement therapy (dialysis or transplant); however, the A Randomised Controlled Clinical Trial to Assess the Effect of Dapagliflozin on Renal and Cardiovascular Outcomes in Patients With Severe Chronic Kidney Disease (RENAL LIFECYCLE) trial is currently underway to address the efficacy of dapagliflozin in patients with severe CKD (Clinical Trials Identifier: NCT05374291).[35] SGLT-2 inhibitors are also not indicated for those with polycystic kidney disease or acute glomerulonephritis requiring immunosuppression.

SGLT-2 inhibitors are simple to use and have a low side-effect profile. However, as with RAS inhibitors, SGLT-2 inhibitor use can lead to an acute increase in SCr level in the first four weeks of initiation due to glomerular haemodynamic changes. This dip in kidney function is not associated with a greater long-term decline and is, in fact, associated with a rebound and, ultimately, slower progression of CKD.[8] The risk of genital mycotic infections is increased and should be managed with patient education on maintaining meticulous groin hygiene and close monitoring for signs of infection. Euglycaemic diabetic ketoacidosis is also a concerning adverse effect of SGLT-2 inhibitor use, particularly in people with diabetes, and withdrawal of insulin should be considered in those experiencing starvation and acute sickness. Tips for prescribing and monitoring SGLT-2 inhibitors are highlighted in Box 3.

Nonsteroidal MRAs

MRAs such as spironolactone have an established role in the management of heart failure and refractory hypertension (especially in patients with low to normal potassium levels), and also reduce albuminuria.[36-38] However, the side-effect profile, which includes increased risk of hyperkalaemia, acute kidney injury and gynecomastia, can often limit their use. Finerenone is a nonsteroidal MRA that is more selective for mineralocorticoid receptors. It has a lower risk of hyperkalaemia (similar to that of lower-dose spironolactone).

Recent placebo-controlled trials have shown a synergistic effect of finerenone with RAS blockade in reducing the risk of kidney function decline and CV events in patients with type 2 diabetes and albuminuria, but there is a need for electrolyte monitoring as CKD advances.[39,40] The COmbinatioN effect of FInerenone anD EmpagliforiN in participants with chronic kidney disease and type 2 diabetes using a UACR Endpoint (CONFIDENCE) trial assessed the effects of a combination of finerenone with empagliflozin in patients with CKD and type 2 diabetes. Combination therapy resulted in a 29% greater reduction in the urinary ACR than that with finerenone alone and 32% greater than that with empagliflozin alone. After six months, the urine ACR was reduced by 52% with combination therapy and the frequency of hyperkalaemia was lower with combination therapy with no significant adverse effects noted.[41]

Finerenone is listed on the PBS for patients with CKD (eGFR of 25 mL/min/1.73 m^2 or higher and uACR of 22.6 mg/mmol or higher) with type 2 diabetes in combination with RAS blockers and SGLT-2 inhibitors, unless medically contraindicated or intolerant.

4. PRESCRIBING AND MONITORING TIPS FOR NONSTEROIDAL MRAs

- The nonsteroidal MRA finerenone can be added to RAS blockers and SGLT-2 inhibitors for treatment of CKD and type 2 diabetes as per current PBS criteria:
  - eGFR ≥25 mL/min/1.73 m^2 and uACR ≥22.6 mg/mmol
- Monitor serum potassium levels:
  - withhold finerenone if potassium level >5.5 mmol/L
- Manage hyperkalaemia (see Box 2):
  - restart finerenone if potassium level ≤5 mmol/L, but caution is advised in more advanced CKD
- Finerenone is PBS listed for CKD with type 2 diabetes*

Abbreviations: CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; MRA = mineralocorticoid receptor antagonists; RAS = renin-angiotensin system; SCr = serum creatinine; SGLT-2 = sodium-glucose cotransporter-2; uACR = urine albumin-creatinine ratio.

*See full PBS schedule for details (www.pbs.gov.au/pbs).

Tips for prescribing and monitoring nonsteroidal MRAs are highlighted in Box 4.

GLP-1 receptor agonists

GLP-1 receptor agonists stimulate glucose-dependent insulin release from pancreatic beta cells and suppress glucagon release from alpha cells. They are now a well-established third-line treatment for type 2 diabetes (after metformin and SGLT-2 inhibitors).[17] GLP-1 receptor agonists slow gastric emptying, suppress appetite and inhibit unnecessary hepatic gluconeogenesis, thus aiding weight loss, which further improves insulin sensitivity. They have gastrointestinal side effects and increase the risk of hypoglycaemia, although this risk is low.

Even more effective analogues, such as tirzepatide, the first glucose-dependent insulinotropic polypeptide/GLP-1 receptor agonist (or twincretin), and combination semaglutide-cagrilintide, show promise in achieving improved glycaemic control and weight loss.[42,43] Tirzepatide is TGA approved for type 2 diabetes (along with indications for chronic weight management and obstructive sleep apnoea), and semaglutide-cagrilintide is undergoing clinical trials.

Several studies have demonstrated the efficacy of GLP-1 receptor agonists in reducing major cardiovascular events in people with type 2 diabetes and HbA_{1c} below 7%, and in reducing proteinuria, which suggests potential kidney protective benefits.[44-46] The Evaluate Renal Function with Semaglutide Once Weekly (FLOW) trial assessed the impact of semaglutide on kidney function decline in people with diabetic kidney disease. Semaglutide reduced the risk of CKD progression and cardiovascular death (kidney failure, a least 50% reduction in eGFR or death from kidney or cardiovascular causes) by 24%.[47] Semaglutide now has TGA approval for CKD with type 2 diabetes as an adjunct to standard of care to reduce the risk of sustained decline of kidney function and cardiovascular death. Tips for prescribing and monitoring GLP-1 receptor agonists are highlighted in Box 5.

5. PRESCRIBING AND MONITORING TIPS FOR GLP-1 RECEPTOR AGONISTS

- Manage and mitigate gastrointestinal side effects of GLP-1 receptor agonists:
  - start therapy at the lowest dose and up-titrate slowly to the maximal tolerated dose
  - encourage a change in eating patterns from eating out of habit to eating only when hungry and stopping when full
  - aim for slower, smaller, lighter meals
- Manage the (low) risk of hypoglycaemia:
  - consider reducing the dose of sulfonylureas or insulins
- GLP-1 receptor agonists (dulaglutide and semaglutide) are currently PBS listed for type 2 diabetes*
- GLP-1 receptor agonists are not PBS reimbursed if co-prescribed with SGLT-2 inhibitors (or DPP-4 inhibitors or other GLP-1 receptor agonists) for the management of diabetes, but are PBS reimbursed if co-prescribed with SGLT-2 inhibitors for the management of proteinuria

Abbreviations: CKD = chronic kidney disease; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium-glucose cotransporter-2.

*See full PBS schedule for details (www.pbs.gov.au/pbs).

Multidisciplinary team input

This article aims to support clinicians to care for people with CKD or those who may have risk factors for CKD and does not provide exhaustive advice for managing people with kidney failure and advanced comorbid conditions that occur with CKD. Working within a multidisciplinary team that includes (but is not limited to) a nephrologist, a CKD nurse, a psychologist, endocrinologists, cardiologists and allied health professionals can assist GPs in developing individualised care plans and in managing people with complex conditions.

Conclusion

The rising incidence of CKD is a significant public health concern. Addressing this growing problem involves a holistic approach to management that includes implementing nonpharmacological and pharmacological therapies, and input from a multidisciplinary team. Regular screening can help with early diagnosis and management. Optimising holistic care through nonpharmacological measures, including nutritional management and supporting lifestyle changes, is a mainstay for improving patient outcomes. Providing culturally responsible care to vulnerable at-risk populations, specifically Aboriginal and Torres Strait Islander people, is important for ensuring that care is effective, accessible, continuous and sustainable. A growing suite of pharmacological therapies are available for CKD and common comorbidities, and should be used to aggressively manage this disease and its associated risk factors. MT

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A list of references is included in the online version of this article (https://www.medicinetoday.com.au/mt/2025/november/supplements/focus-on-chronic-kidney-disease).

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Chronic kidney disease
Doing simple things well for those most at risk

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Reducing cardiovascular risk in people with chronic kidney disease

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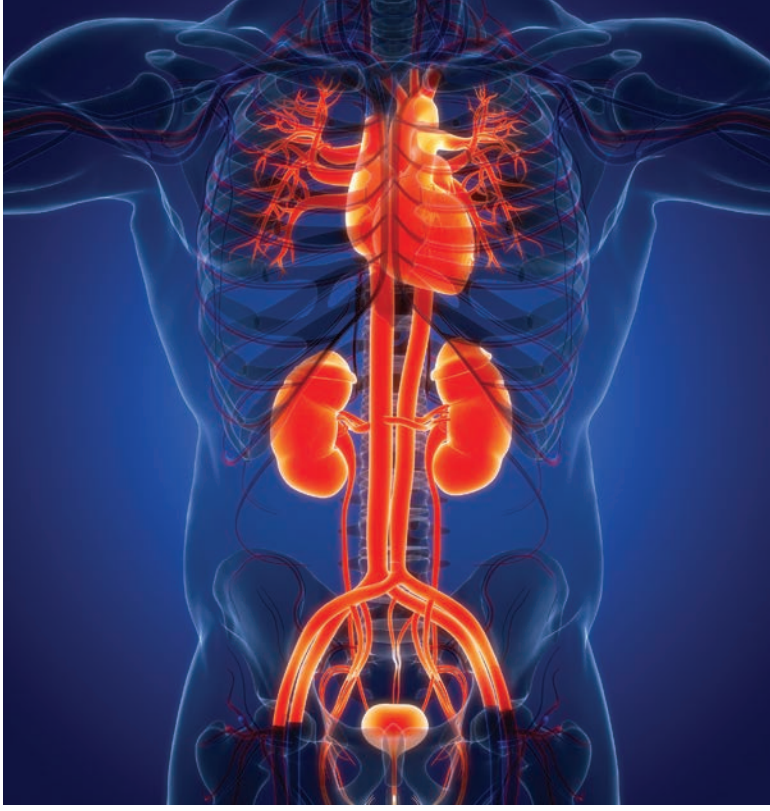

People with chronic kidney disease are at an increased risk of cardiovascular disease. The early recognition of this risk and implementation of effective risk-lowering strategies can be initiated in primary care using a multidisciplinary approach.

Chronic kidney disease (CKD) affects over 10% of the global population and is unequivocally associated with increased risks of cardiovascular disease (CVD) and cardiovascular mortality.[1-4] Specifically, a reduced estimated glomerular filtration rate (eGFR) and the presence of albuminuria or proteinuria portend greater cardiovascular events independent of one another and in addition to other potential confounding factors, such as the presence of diabetes and hypertension.[1,5] Compared with individuals with normal kidney function, the risk of cardiovascular death is twice and three times as high in those with eGFR 30 to 59 mL/min/1.73 m^2 and 15 to 29 mL/min/1.73 m^2, respectively. CVD is the main cause of death in people with kidney failure requiring kidney replacement therapy (maintenance dialysis or kidney transplantation).[6,7]

KEY POINTS

- Chronic kidney disease (CKD) is associated with an increased risk of cardiovascular disease (CVD) and CVD-related death independent of other traditional risk factors.
- Individuals with moderate-to-severe CKD have an estimated five-year CVD risk of at least 10%, placing them in the highest risk category.
- GPs play a key role in the multidisciplinary care required to reduce cardiovascular risk in individuals with CKD, which includes lifestyle modifications, the management of traditional risk factors (e.g. hypertension, diabetes mellitus, hyperlipidaemia) and preventing progressive CKD.
- First-line pharmacotherapy includes renin–angiotensin–aldosterone system (RAAS) inhibitors and sodium-glucose cotransporter-2 (SGLT-2) inhibitors.
- Adjunct therapy for diabetic kidney disease includes nonsteroidal mineralocorticoid receptor antagonists and glucagon-like peptide-1 receptor agonists.
- If medications such as RAAS inhibitors, SGLT-2 inhibitors and mineralocorticoid receptor antagonists have been ceased in patients with CKD consider recommencing as soon as appropriate to maximise their long-term cardioprotective effects.

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The strong association between CKD and CVD, alongside prevalent shared comorbidities, highlights the importance of adopting a multidisciplinary approach to cardiovascular risk reduction. GPs play a pivotal role in fostering patient engagement and facilitating effective care co-ordination. Individuals with early stages of CKD do not require specialist involvement and usually present in primary care settings; thus, understanding the risk of CVD and implementing long-term risk-reducing treatments remain crucial. As more efficacious therapeutic

options become available to curb cardiovascular events and delay CKD progression, it becomes increasingly important to ensure they are used appropriately. This article summarises the underlying mechanisms linking CVD and CKD, discusses screening for CVD in people with CKD and outlines lifestyle modifications and pharmacological interventions aimed at mitigating CVD risk in those with CKD. Additionally, two clinical vignettes illustrate the practical application of these strategies in real-world scenarios.

Risk factors for cardiovascular disease in chronic kidney disease

CKD is associated with a range of CVD subtypes resulting in outcomes such as ischaemic heart disease, heart failure, arrhythmias, sudden cardiac death, peripheral vascular disease, cerebrovascular disease and venous thrombosis.[8,9] This spectrum reflects the number of underlying mechanisms contributing to CVD in people with CKD, which include shared traditional risk factors such as hypertension and diabetes (the two leading causes of CKD), as well as nontraditional factors unique to patients with CKD, such as those listed below and illustrated in Figure 1.

- **Anaemia:** this is a significant complication of CKD that can lead to adverse cardiovascular outcomes (e.g. heart failure).
- **Inflammation:** CKD can induce inflammation, reflected by elevated levels of inflammatory markers (e.g. ferritin, C-reactive protein, interleukin-6, tumour necrosis factor), which is associated with cardiac remodelling and fibrosis, cardiomyopathy, left ventricular hypertrophy and diastolic dysfunction.
- **Dysregulation in bone mineral metabolism:** elevated levels of fibroblast growth factor 23 (seen even in early stages of CKD), parathyroid hormone and phosphate levels, along with 1,25-dihydroxyvitamin D deficiency, drive vascular calcification and increase arterial stiffness and potentially the risk of cardiac fibrosis and heart failure.
- **Overactivation of the renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system:** this contributes to hypertension, vasoconstriction and an increased risk of CVD.
- **Electrolyte abnormalities:** hyperkalaemia is particularly prevalent in advanced CKD and can lead to an increased risk of cardiac arrhythmias.
- **Dyslipidaemia:** patients with CKD typically exhibit hypertriglyceridaemia and low levels of HDL cholesterol, with increased atherogenic qualities of these lipids.
- **Dialysis-related shifts:** patients with kidney failure receiving chronic haemodialysis are at particular risk of sudden cardiac death, precipitated by intradialytic hypotension, hypoxaemia and rapid electrolyte and volume shifts.[8,10,11]

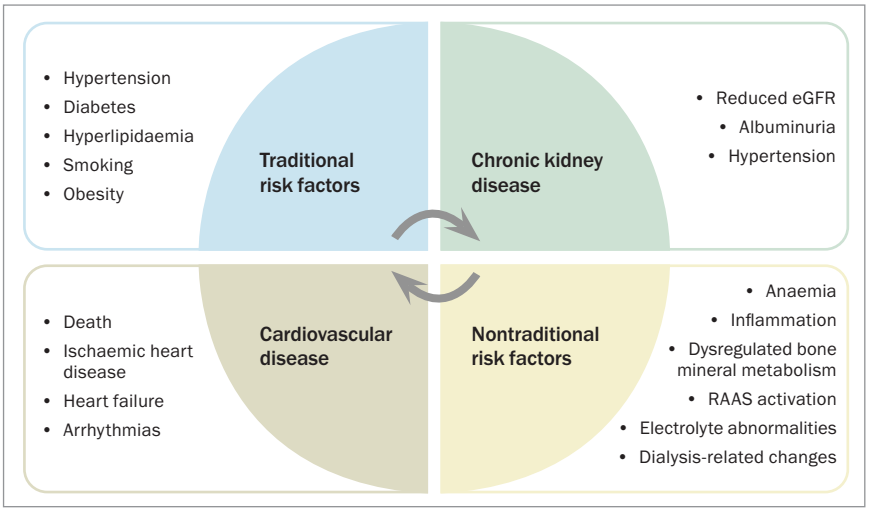


Figure 1. Association between CKD and the risk of developing cardiovascular disease, including shared traditional risk factors and additional nontraditional risk factors specific to CKD.
Abbreviations: CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; RAAS = renin–angiotensin–aldosterone system.

Assessment of cardiovascular risk in chronic kidney disease

Screening

There are insufficient data to support routine screening for coronary artery disease in asymptomatic patients with CKD, as no evidence suggests it improves cardiovascular outcomes or alters management.[9,12] This is further emphasised by the results of the International Study of Comparative Health Effectiveness With Medical and Invasive Approaches-Chronic Kidney Disease (ISCHEMIA-CKD), which found no difference in a composite outcome of death or nonfatal myocardial infarction in patients with advanced CKD (eGFR <30 mL/min/1.73 m^2) and moderate-to-severe ischaemia on stress testing randomised to medical therapy compared with invasive coronary revascularisation.[13] Therefore, CVD risk assessment and appropriate risk factor modification in all patients with CKD are recommended in the first instance.

Risk assessment of cardiovascular disease

Most cardiovascular risk prediction calculators do not consider the eGFR or presence of albuminuria and, thus, largely

TABLE. CVD RISK STRATIFICATION IN CHRONIC KIDNEY DISEASE[14]

eGFR (mL/min/1.73 m^2)	uACR (mg/mmol)	Recommendation
≥60	Men: <2.5 Women: <3.5	Assess CVD risk using validated CVD risk prediction tools
45 to <60	Men: 2.5 to 25 Women: 3.5 to 35	CVD risk may be underestimated when using standard prediction tools; consider reclassifying to a higher risk category
<45	Men: >25 Women: >35	Do not use CVD risk prediction tools; manage as high risk for CVD

Abbreviations: CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; uACR = urine albumin-to-creatinine ratio.
Adapted from: Commonwealth of Australia as represented by the Department of Health and Aged Care. Australian guideline for assessing and managing cardiovascular disease risk; 2023.[14]

underestimate CVD risk in patients with CKD. These calculators are not validated for use in people with advanced CKD or kidney failure requiring dialysis or transplantation.[5,9] As such, current Australian guidelines recommend individuals with an eGFR less than 45 mL/min/1.73 m^2 or macroalbuminuria (urine albumin-to-creatinine ratio [uACR] >25 mg/mmol in men and >35 mg/mmol in women) be regarded as at high CVD risk with a five-year risk of 10% or greater (Table).[14]

Approach to reducing cardiovascular risk in chronic kidney disease

The management approach to reducing cardiovascular risk in patients with CKD should include a multidisciplinary team to address lifestyle modifications and common traditional risk factors, such as hypertension, hyperlipidaemia and diabetes, and consider additional pharmacological therapies where appropriate. As CKD itself is a significant cardiovascular risk factor, efforts to prevent kidney disease progression by reducing albuminuria and slowing the rate of eGFR decline should also be prioritised in mitigating CVD risk. It must be recognised that in an increasingly comorbid and older population, the treatment targets and recommendations are general in nature. A holistic, patient-centred approach is advised, taking into consideration factors such as tolerability, safety and polypharmacy.

Lifestyle modifications

Clear and effective communication of an individual's cardiovascular risk, along with behavioural strategies and continual patient engagement, are essential for the successful implementation of lifestyle modifications. There are limited data regarding lifestyle modifications aimed at reducing cardiovascular risk specifically in CKD populations, so these guidelines are largely extrapolated from studies conducted in general populations and expert opinions. Some recommended lifestyle modifications are listed in Box 1.

Diet

A well-balanced diet with increased fruit and vegetable intake and limited intake of processed meats, refined carbohydrates and sweetened beverages is recommended.[15-17] Dietary interventions, such as consuming a Mediterranean diet, increasing plant-based intake and restricting carbohydrate intake, appear to lower blood pressure and are associated with improved kidney function.[18] Salt restriction in patients with CKD has been shown to significantly lower blood pressure and albuminuria, as well as increase the efficacy of RAAS inhibitors.[19] Therefore, a sodium intake of less than 2 g/day is recommended.

Exercise

Regular exercise in adults with CKD reduces albuminuria, increases aerobic capacity, lowers blood pressure and improves quality of life.[20,21] Moderate-intensity physical activity is recommended for 30 minutes, five times per week, or 150 minutes per week; however, this should be tailored to the individual patient's tolerance and cardiovascular fitness levels.[22,23]

1. RECOMMENDED LIFESTYLE MODIFICATIONS TO REDUCE CARDIOVASCULAR RISK IN ADULTS WITH CHRONIC KIDNEY DISEASE

Diet
- Consume a well-balanced diet
- Increase fruit and vegetable intake
- Consume a combination of whole grains, fibre, legumes, plant-based proteins, unsaturated fats and nuts in diet
- Limit intake of processed meats, refined carbohydrates and sweetened beverages
- Aim for a sodium intake <2 g/day
- Conduct dietitian review in patients with advanced kidney disease and patients on dialysis

Exercise
- Engage in moderate-intensity physical activity for 30 minutes, five times per week, or 150 minutes per week
- Tailor to the patient's overall health and cardiovascular fitness level

Smoking
- Cease smoking and tobacco products

Obesity
- Consider losing weight if body mass index >25 kg/m^2

Smoking cessation

Chronic smoking is associated with an increased risk of irreversible proteinuria independent of the daily or cumulative number of cigarettes smoked, and an increased risk of kidney failure in CKD.[24,25] On this basis, along with robust evidence indicating that smoking cessation is associated with a reduction in cardiovascular risk in the general population, the cessation of smoking and tobacco products is recommended in patients with CKD.[22]

Obesity

Obesity is associated with an increased risk of CKD and CVD. People with a body mass index greater than 25 kg/m^2 should

be encouraged to lose weight, taking into consideration their other medical comorbidities, overall health and physical activity levels.[23]

Management of traditional risk factors

The treatment targets of traditional risk factor management are outlined in Box 2.

Blood pressure control

The lowering of blood pressure in patients with hypertension significantly reduces the risk of CVD and mortality in patients with CKD; however, optimal treatment targets remain contentious.[26-28] Current international CKD guidelines suggest aiming for a systolic blood pressure less than 120 mmHg, but to consider a more liberal approach depending on the patient's overall health, frailty and risk of postural hypotension and falls.[29] Other guidelines, including the *Kidney Health Australia CKD Management in Primary Care* handbook, recommend higher targets of blood pressure (<130/80 mmHg).[17] These guidelines do not apply to patients on dialysis, in whom ideal blood pressure targets are even more unclear.

Glycaemic control

Type 2 diabetes is a significant shared risk factor of CKD and CVD. Australian guidelines recommend a glycated haemoglobin (HbA_{1c}) target of 7.0% or less in patients with CKD.[9] Tight glycaemic control has not been shown to reduce the risk of kidney failure or cardiovascular death in CKD, although it may help reduce microalbuminuria and nonfatal myocardial infarction.[30] The safety of tight glycaemic control has also not been confirmed in CKD, particularly in frail patients with comorbidities. International guidelines have more recently recommended individualised treatment parameters, with HbA_{1c} targets ranging from less than 6.5% to less than 8.0% to balance the risk of hypoglycaemia and long-term benefits of glycaemic control depending on the patient.[15] Of note, HbA_{1c} measurements can be unreliable in people with advanced CKD or end-stage kidney disease because of anaemia and anaemia treatments including erythropoietin-stimulating agents, iron replacement and blood transfusions.[15] Specific medications, such as sodium-glucose cotransporter-2 (SGLT-2) inhibitors, nonsteroidal mineralocorticoid receptor antagonists (MRAs) and glucagon-like peptide-1 (GLP-1) receptor agonists, may reduce the risk of cardiovascular events and slow CKD progression in type 2 diabetes.

Lipid management

The Study of Heart and Renal Protection (SHARP) trial clearly demonstrated that primary prevention with simvastatin plus ezetimibe reduced the risk of major atherosclerotic events in patients with CKD compared with placebo.[31] The cardiovascular effects of statin therapy do not appear to extend to patients on dialysis, despite significantly lowering LDL cholesterol levels, and the benefits in terms of major vascular events and mortality diminish as the eGFR declines.[32,33] Specific LDL treatment targets for these populations have not been defined.

Statin-based therapy is currently recommended in adults with CKD:

- aged 50 years and older not treated with chronic dialysis or kidney transplantation
  - in those with an eGFR less than 60 mL/min/1.73 m^2, a statin or statin plus ezetimibe combination should be considered
- younger than 50 years of age at high risk of CVD, defined as having one or more of the following:
  - known coronary disease
  - diabetes mellitus
  - prior ischaemic stroke
  - estimated 10-year risk of coronary death or myocardial infarction greater than 10%.[23,34]

Pharmacotherapy

The landscape of available therapies to reduce cardiovascular risk and slow the rate of eGFR decline in CKD is evolving, with the relatively recent development of drugs including SGLT-2 inhibitors, MRAs and GLP-1 receptor agonists.

Aspirin

Overall, aspirin has been shown to reduce the risk of myocardial infarction in people with CKD when used for both primary and secondary prevention, while also increasing the risk of bleeding.[35] When studied for primary prevention alone, the risk of bleeding from aspirin appeared to outweigh the potential cardiovascular benefits of treatment.[36] Therefore, aspirin is only recommended for the secondary prevention of recurrent ischaemic cardiovascular events in people with CKD and established coronary artery disease.

Renin–angiotensin–aldosterone system inhibitors

RAAS blockade slows the rate of eGFR decline, lowers proteinuria and reduces the risk of kidney failure and cardiovascular events independent of its blood

2. RISK FACTOR MANAGEMENT TARGETS TO REDUCE CARDIOVASCULAR RISK IN ADULTS WITH CHRONIC KIDNEY DISEASE

Hypertension
- Systolic blood pressure <120 mmHg
- Consider a higher blood pressure target of <130/80 mmHg, or higher depending on the risk of hypotension and falls and patient's overall health

Type 2 diabetes
- HbA_{1c} level ≤7.0%
- Consider HbA_{1c} target levels ranging from <6.5% to <8.0%, depending on the patient's overall health and risk of hypoglycaemia

Hyperlipidaemia
- Commence statin therapy if:
  - age ≥50 years and not on dialysis
  - age <50 years, at high risk of cardiovascular disease and not on dialysis
- No specific recommended LDL cholesterol targets

Abbreviations: BMI = body mass index; HbA_{1c} = glycated haemoglobin.

3. PBS INDICATIONS FOR DAPAGLIFLOZIN AND EMPAGLIFLOZIN IN PATIENTS WITH CKD, TYPE 2 DIABETES OR CHRONIC HEART FAILURE*

CKD

Empagliflozin

- The patient must have a diagnosis of CKD present for at least 3 months AND
- eGFR 20 to 90 mL/min/1.73 m^2 prior to treatment initiation AND
- uACR ≥22.6 mg/mmol if eGFR is between 45 and 90 mL/min/1.73 m^2 AND
- Not be receiving treatment with another SGLT-2 inhibitor AND
- Be stabilised on a RAAS inhibitor for at least four weeks unless medically contraindicated, before starting combination therapy with this drug

Dapagliflozin

- The patient must have a diagnosis of CKD present for at least 3 months AND
- eGFR 25 to 75 mL/min/1.73 m^2 prior to treatment initiation AND
- uACR 22.6 to 565 mg/mmol AND
- Not be receiving treatment with another SGLT-2 inhibitor AND
- Be stabilised on a RAAS inhibitor for at least four weeks unless medically contraindicated, before starting combination therapy with this drug

For both empagliflozin and dapagliflozin, the patient must discontinue treatment prior to initiating kidney replacement therapy (dialysis or transplant). Patients with polycystic kidney disease, lupus nephritis, ANCA-associated vasculitis, current/recent cytotoxic or immunosuppressive therapy for kidney disease or with an organ transplant are ineligible for treatment with this drug

Type 2 diabetes

- Treatment must be used in combination with metformin unless contraindicated or intolerant AND
- The patient must be in a high-risk population defined as
  - having cardiovascular disease OR
  - being at high risk of a cardiovascular event OR
  - identifying as Aboriginal or Torres Strait Islander
- In all other populations, the treatment must be used in combination with at least one of metformin, a sulfonylurea or insulin, and have inadequate glycaemic control in response to at least one of these agents
- The patient must not be undergoing concomitant PBS-subsidised treatment with a GLP-1 receptor agonist or another SGLT-2 inhibitor

Chronic heart failure

- The patient must be symptomatic (New York Heart Association classes II, III or IV) independent of LVEF AND
- If LVEF is ≤40%, the treatment must be add-on therapy to optimal standard chronic heart failure treatment, including a beta-blocker and RAAS inhibition or angiotensin receptor with neprilysin inhibitor combination therapy unless contraindicated or intolerant
- If LVEF is >40%, there must be structural changes on echocardiography expected to cause diastolic dysfunction AND at least one of:
  - diastolic dysfunction with high filling pressure
  - hospitalisation for heart failure in the past 12 months
  - requirement for intravenous diuretic therapy in the past 12 months
  - elevated N-terminal pro brain natriuretic peptide AND
- The patient must not be receiving treatment with another SGLT-2 inhibitor

Abbreviations: ANCA = antineutrophil cytoplasmic antibody; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; GLP-1 = glucagon-like peptide-1; HbA_{1c} = glycated haemoglobin; LVEF = left ventricular ejection fraction; RAAS = renin–angiotensin–aldosterone system; SGLT-2 = sodium-glucose cotransporter-2; uACR = urine albumin-to-creatinine ratio.

* Refer to the PBS website for full details.

pressure-lowering effects.[37-40] RAAS inhibition with ACE inhibitors and angiotensin receptor blockers has been the cornerstone of CKD treatment for many years. Discontinuation of RAAS inhibitors in patients with CKD is associated with elevated risks of all-cause mortality and cardiovascular events; thus, these agents should be continued if safe and feasible, or promptly recommenced after any period of discontinuation, such as during acute illness or episodes of acute kidney injury.[41]

RAAS inhibitors are recommended for the following patients with CKD:

- patients requiring first-line treatment for hypertension
- patients with type 2 diabetes and uACR greater than 3 mg/mmol
- patients without type 2 diabetes and uACR greater than 30 mg/mmol
- consider in patients with uACR between 3 and 30 mg/mmol.[15,29,42]

Sodium-glucose cotransporter-2 inhibitors

The cardio- and renoprotective class effects of SGLT-2 inhibitors demonstrated in studies (e.g. the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation [CREDENCE], Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease [DAPA-CKD] and Study of Heart and Kidney Protection with Empagliflozin [EMPA-KIDNEY] trials) conducted in patients with CKD with and without diabetes are overwhelmingly positive.[43-46] SGLT-2 inhibitors have been shown to lower albuminuria and reduce the risk of kidney failure, acute kidney disease and cardiovascular events, including cardiovascular death and hospitalisation for heart failure. In a meta-analysis including the three aforementioned randomised controlled trials, SGLT-2 inhibitors were associated with a 13% risk reduction in major adverse cardiovascular events (MACE, a composite of cardiovascular death, myocardial infarction or stroke) and a 20% reduction in cardiovascular death compared with placebo among individuals with CKD.[47]

The benefits and safety of SGLT-2 inhibitors across the spectrum of CKD are increasingly recognised, as reflected by the recent expansion of PBS-listed indications for empagliflozin to align with the latest international guideline recommendations, as summarised in Box 3.[23]

Finerenone

Finerenone is a selective, nonsteroidal MRA that has been shown to reduce the risk of kidney failure and cardiovascular events in patients with type 2 diabetes and CKD in the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic

Kidney Disease (FIDELIO-DKD) and Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trials.[48-50] A class effect has not been confirmed with other selective and nonselective MRAs. The ongoing Finerenone Non-Diabetic Chronic Kidney Disease (FIND-CKD) and Chronic Kidney Disease Adaptive Platform Trial Investigating Various Agents for Therapeutic Effect (CAPTIVATE) trials will provide insights into whether these kidney and cardiovascular benefits also extend to people with CKD without diabetes.[51,52]

4. CLINICAL VIGNETTES: TWO CASES OF EARLY CKD AND HIGH CVD RISK

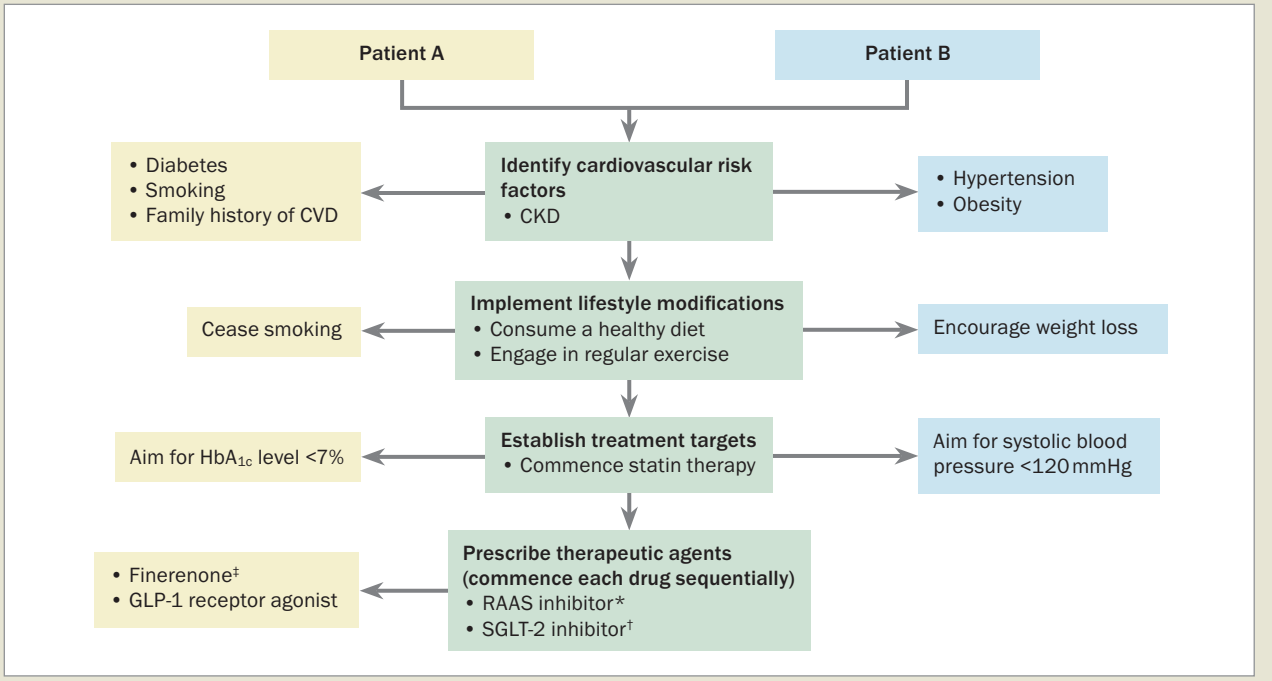
Case presentations

Patient A is a 53-year-old woman with a background of type 2 diabetes for which she has been on single-agent metformin for 10 years. She is a current smoker and has a strong family history of CVD and CKD. She has come to see you for an annual medical check up. Her BMI is 22 kg/m^2 and blood pressure is 121/73 mmHg. You arrange for her to undergo routine blood and urine tests, which show a serum creatinine level of 92 micromol/L, eGFR of 64 mL/min/1.73 m^2, HbA_{1c} level of 7.8% and uACR of 53 mg/mmol.

Patient B is a 64-year-old man with hypertension diagnosed 15 years prior. He has come to see you for the first time to renew his prescription for amlodipine. You perform a comprehensive medical check up. His BMI is 32 kg/m^2 and blood pressure is 162/95 mmHg. Investigation findings show a serum creatinine level of 99 micromol/L, eGFR of 74 mL/min/1.73 m^2 and uACR of 32 mg/mmol.

Management approaches

Both patients present with early CKD and a high risk of CVD. In individuals with a new diagnosis of CKD, it is important to repeat blood and urine tests to monitor the trend in kidney function and confirm persistent albuminuria, and consider renal tract imaging for potential structural abnormalities. At this stage, both patients could continue to be appropriately monitored in the primary care setting unless there are signs of disease progression or abnormal findings such as sustained microscopic haematuria to prompt nephrology referral.[23] The management of cardiovascular risk factors (i.e. optimal glycaemic control in Patient A and blood pressure lowering plus weight loss in Patient B) should be prioritised. The onset of any signs or symptoms of CVD would warrant cardiology referral, keeping in mind that both patients, particularly Patient A (being female and having diabetes), could present with atypical symptoms. Additional specific strategies to reduce cardiovascular risk are outlined below in the Flowchart.



Flowchart. Strategies to reduce cardiovascular risk in Patient A and Patient B.[23] Suggested treatment algorithm to reduce the risk of CVD in two patients with CKD. Strategies specific for Patient A are in yellow. Strategies specific for Patient B are in blue. Strategies applicable to both patients are in green.

Abbreviations: BMI = body mass index; CKD = chronic kidney disease; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; GLP-1 = glucagon-like peptide-1; HbA_{1c} = glycated haemoglobin; RAAS = renin–angiotensin–aldosterone system; SGLT-2 = sodium-glucose cotransporter-2; uACR = urine albumin-to-creatinine ratio.

* Practice point: Check blood pressure, serum potassium level, creatinine level and eGFR 2 to 4 weeks after initiation and dose increase. Uptitrate to maximal tolerated dose.
† Practice point: No additional monitoring outside of standard of care is required.
‡ Practice point: Check serum potassium level, creatinine level and eGFR 4 weeks after initiation and dose increase. As Patient A is normotensive, confirm blood pressure will tolerate additional agents.

Finerenone is currently PBS listed for patients who have CKD with type 2 diabetes, plus all the following:

- absence of known significant nondiabetic renal disease
- eGFR 25 mL/min/1.73 m^2 or greater
- uACR of 22.6 mg/mmol or greater
- stabilised on a RAAS inhibitor for at least four weeks unless medically contraindicated, before starting combination therapy with this drug
- treatment must be in combination with an SGLT-2 inhibitor unless medically contraindicated or intolerant
- must not be receiving treatment with another selective nonsteroidal MRA, renin inhibitor or potassium-sparing diuretic
- must not have established heart failure with reduced ejection fraction with an indication for MRA treatment.

Refer to the PBS website for full details.

GLP-1 receptor agonists

GLP-1 receptor agonists reduce the risk of major cardiovascular events in patients with type 2 diabetes, including in those with an eGFR less than 60 mL/min/1.73 m^2.[53] More recently, the findings from the Evaluate Renal Function with Semaglutide Once Weekly (FLOW) trial, specifically studying the effects of semaglutide on renal and cardiovascular outcomes in patients with type 2 diabetes and CKD, have been published.[54] Adults with type 2 diabetes, an HbA_{1c} level of 10% or less and CKD with albuminuria and who were established on maximal tolerated RAAS blockade were included in the study, regardless of treatment with other concomitant glucose-lowering agents. The study found that semaglutide lowered the risk of the primary outcome (a composite of kidney failure, 50% reduction in the eGFR or death from kidney-related or cardiovascular causes) by 24% and major cardiovascular events by 16% compared with placebo over a median follow-up period of 3.4 years.

Long-acting GLP-1 receptor agonists are currently recommended as an additional glucose-lowering agent in patients with CKD and type 2 diabetes who are yet to achieve their individualised glycaemic targets despite use of metformin and SGLT-2 inhibitor therapy, or in those who are unable to use these drugs.[15] However, based on the results of the FLOW trial, the indications for use in CKD may broaden in the future.

Practical prescribing considerations

Considering the acute effects of treatment, it is generally recommended to commence each drug sequentially after establishing a period of stability for at least four weeks. RAAS inhibitors, SGLT-2 inhibitors and finerenone can induce haemodynamic changes resulting in a reversible decline in eGFR, referred to as the 'eGFR dip', which typically occurs within the first four weeks of treatment.[55] If the reduction in the eGFR exceeds 30% or continues to decline beyond the initial dip following drug commencement, alternative causes should be considered. All these agents also exhibit blood pressure-lowering effects, which should be monitored. Another safety concern with RAAS inhibitor and finerenone use is hyperkalaemia, particularly in advanced kidney disease (eGFR <30 mL/min/1.73 m^2); therefore, serum potassium levels should be monitored following drug initiation and dose escalation in line with the Australian Medicines Handbook guidelines. Notably, concurrent therapy with SGLT-2 inhibitors may lower the risk of hyperkalaemia associated with finerenone.[56] These potential adverse effects are likely to be heightened in the setting of acute illness and hypovolaemic states, and therefore may require additional monitoring or drug suspension during these periods.

Despite potential safety concerns, clinicians should be encouraged to implement combination therapy and avoid unnecessary or prolonged discontinuation of these efficacious therapies unless clinically indicated. Indeed, the role of combination therapy in CKD for both kidney and cardiovascular benefits is increasingly recognised. Analyses of large trial data suggest additive benefits of SGLT-2 inhibitors, nonsteroidal MRAs and GLP-1 receptor agonists in reducing the risk of MACE in patients with type 2 diabetes and kidney disease.[57] Recently, the COmbinatioN effect of FInerenone anD EmpagliflozIN in participants with chronic kidney disease and type 2 diabetes using a UACR Endpoint (CONFIDENCE) trial demonstrated that combination finerenone and empagliflozin therapy commenced simultaneously produced additive reductions in albuminuria from baseline compared with either agent alone, with comparable safety profiles regarding symptomatic hypotension and hyperkalaemia. Although the observed acute eGFR dip was greater in participants receiving combination therapy, this stabilised by day 30 and was reversible upon drug discontinuation.[58] These findings are encouraging, and the CAPTIVATE trial is anticipated to provide further insights into the efficacy and safety of combination therapy in CKD including its effects on cardiovascular outcomes.[52]

Two clinical vignettes are presented in Box 4, with management approaches outlined in the Flowchart.[23]

Conclusion

Patients with CKD face a heightened risk of CVD, significantly worsening their health outcomes. Combatting this risk requires a multidisciplinary approach, leveraging various existing and emerging therapies. However, the long-term benefits of some strategies may be limited in advanced CKD. Therefore, early CKD diagnosis, risk assessment and prompt management initiated in primary care are crucial. MT

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A list of references is included in the online version of this article (https://www.medicinetoday.com.au/mt/2025/november/supplements/focus-on-chronic-kidney-disease).

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Reducing cardiovascular risk in people with chronic kidney disease

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PEER REVIEWED FEATURE

Preventing diabetic kidney disease progression

A 2025 update

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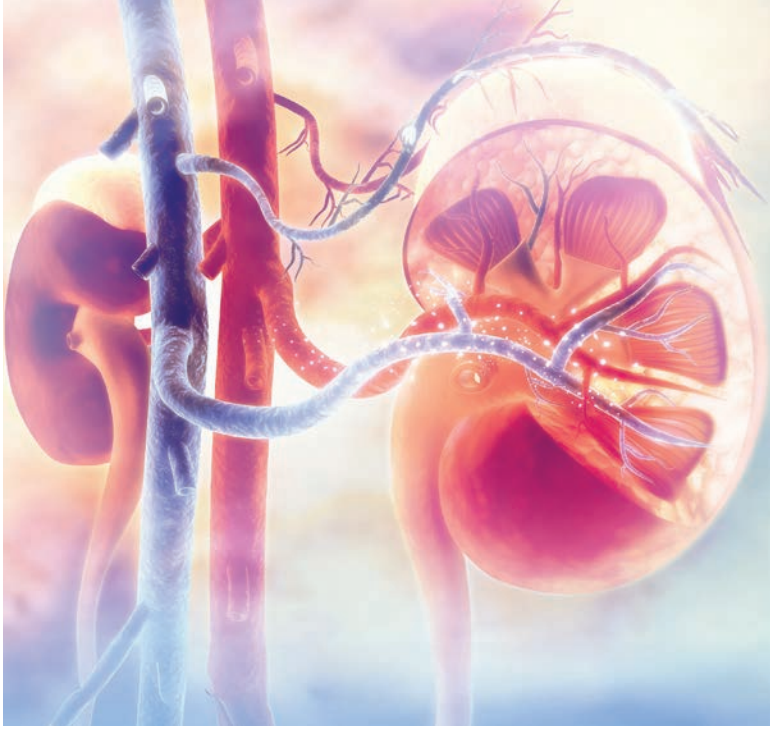
It is important to implement treatments to delay and prevent diabetic kidney disease progression by aiming for tight metabolic and blood pressure control and simultaneously addressing cardiovascular risk factors aggressively. Using pharmacological agents with cardiovascular and kidney benefits, including renin–angiotensin system inhibitors and sodium-glucose cotransporter-2 inhibitors, is paramount. Glucagon-like peptide-1 receptor agonists and finerenone have also been shown to have cardio-kidney protective properties.

KEY POINTS

- In patients with type 2 diabetes, screen for diabetic kidney disease (DKD) by measuring the albumin-to-creatinine ratio (ACR) in an early-morning spot urine sample and measuring the serum creatinine level to calculate the estimated glomerular filtration rate (eGFR).
- A diagnosis of DKD should be made if repeat testing confirms an elevated ACR (greater than 2.5 mg/mmol in men or greater than 3.5 mg/mmol in women) or an eGFR less than 60 mL/min/1.73 m^2.
- Delay the progression of DKD by aiming for glycaemic (general HbA_{1c} target: less than 53 mmol/mol) and blood pressure (general target: less than 130/80 mmHg) control.
- Use single-agent renin–angiotensin system inhibitors at maximally tolerated doses and, when appropriate, sodium-glucose cotransporter-2 inhibitors and finerenone to slow the progression of DKD.
- Semaglutide has also recently been shown to slow kidney function loss.
- Treat cardiovascular risk factors aggressively in patients with DKD.



The incidence of diabetes is increasing worldwide, secondary to the marked increase in the incidence of type 2 diabetes. Diabetes is also an established and major risk factor for the development and progression of chronic kidney disease (CKD). As a result, diabetes is now the leading cause of end-stage kidney disease in Western countries. Traditionally, diabetic kidney disease (DKD) has been referred to as 'diabetic nephropathy', but this is a term that should be reserved for people with progressive albuminuria. There is now growing appreciation that kidney impairment can develop in people with diabetes in the absence of increasing albuminuria and in the presence of other nondiabetes-related causes of CKD. Therefore, the term DKD is now preferred to describe CKD in people with diabetes.[1]

DKD occurs in 25 to 40% of people with type 1 or type 2 diabetes who also have risk factors, including hyperglycaemia, hypertension, a history or current habit of smoking, poor plasma lipid control and a genetic predisposition.[2] People who have DKD have increased rates of morbidity and mortality, mainly

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TABLE 1. MANAGEMENT STRATEGIES FOR CKD IN PEOPLE WITH DIABETES ACCORDING TO ALBUMIN LEVEL AND eGFR[5]

Albumin level (mg/mmol)	Recommended management and number of clinical visits per year by eGFR (mL/min/1.73 m²)*					
	≥90 (normal to high)	60 to 89 (mild reduction)	45 to 59 (mild to moderate reduction)	30 to 44 (moderate to severe reduction)	15 to 29 (severe reduction)	<15 (kidney failure)
<3 (normal to mild increase)	Screen 1		Treat 1	Treat 2	Treat and refer 3	Treat and refer ≥4
3 to 29 (moderate increase)	Treat 1		Treat 2	Treat and refer 3		Treat and refer ≥4
≥30 (severe increase)	Treat and refer 3				Treat and refer ≥4	

Abbreviations: CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.
* The number in each cell is a a guide to the recommended frequency of clinical visits (number of times per year).

because of the high risk of cardiovascular (CV) events.[3,4] In parallel, kidney failure also predisposes to poorer glycaemic control (both hyper- and hypoglycaemia) because of an altered kidney physiology, which disrupts normal glucose and insulin metabolism. Therefore, in people with diabetes, the early identification of DKD and implementation of effective treatments are imperative to minimise the progression of CKD and its associated comorbidities.

However, the good news is that novel effective treatments to help prevent the progression of DKD in people with type 2 diabetes have been developed over the past decade. Ample evidence indicates that optimising metabolic health and using renin–angiotensin system (RAS) inhibitors and sodium-glucose cotransporter-2 (SGLT-2) inhibitors can delay the progression of DKD. The mineralocorticoid receptor antagonist finerenone and the glucagon-like peptide-1 receptor agonists are also emerging as effective therapies for slowing loss of kidney function in people with type 2 diabetes. This article focuses primarily on DKD management in people with type 2 diabetes. It was originally written in November 2023 for *Medicine Today* but has been updated in November 2025 to include information on new type 2 diabetes and CKD trial results and new indications for DKD protective medications.

Screening for diabetic kidney disease

Early-stage DKD is usually a silent disease, with minimal clinical manifestations until the patient has progressed to an advanced stage of kidney disease. Therefore, it is essential to screen for markers of kidney disease in people with diabetes as part of routine clinical care (Table 1).[5]

A spot urine sample should be collected annually to measure the albumin-to-creatinine ratio (ACR). A diagnosis of DKD should only be made if repeat testing confirms an elevation in this ratio (greater than 2.5 mg/mmol in men or greater than 3.5 mg/mmol in women). The urine ACR fluctuates by 30 to 40% on the basis of several factors, such as the presence of a fever, dehydration, vigorous physical activity or urinary tract infection. Therefore, if an abnormal ACR is found, perform one to two more tests over the subsequent three months to ensure persistent albuminuria.

Serum creatinine levels should be measured to calculate the estimated glomerular filtration rate (eGFR). A persistent eGFR less than 60 mL/min/1.73 m² indicates possible DKD, even in the absence of albuminuria if nondiabetes-related causes of CKD are excluded.

In patients with type 2 diabetes, the timing of onset is often difficult to determine; therefore, screening should begin at the time of diagnosis. In patients with type 1 diabetes, the general approach is to start screening for DKD five years after diagnosis.[6] However, earlier screening is suggested in people with poor metabolic control or other risk factors.

Screening for nondiabetic kidney disease

Careful consideration should be given to nondiabetic causes of CKD, particularly in patients with rapidly increasing albuminuria or decreasing eGFR. Factors that should alert clinicians to possible nondiabetic aetiologies include an absence of retinopathy, duration of diabetes less than five years, acute kidney injury pattern of kidney dysfunction rather than gradual progression, presence of haematuria, other systemic disease or nephrotic syndrome (albuminuria greater than 3 g/day, low serum albumin level, oedema and symptoms such as frothy urine). The absence of retinopathy and a short duration of diabetes are the strongest predictors that kidney disease is not diabetes-related, although DKD may still occur in some people without retinopathy.

A rapidly decreasing eGFR or rapidly increasing albuminuria should prompt referral of the patient to a nephrologist. A general cut-off of the eGFR of less than 30 mL/min/1.73 m² can also be used as a guide for referral, but ideally, the severity

TABLE 2. EFFECTS TO CONSIDER WHEN SELECTING GLUCOSE-LOWERING AGENTS IN PEOPLE WITH DIABETIC KIDNEY DISEASE[5]

Glucose-lowering agent	Glucose-lowering effect	Effect on risk of other conditions				Effect on body weight
		CKD progression	Atherosclerotic CVD	Heart failure	Hypoglycaemia	
Metformin	High	None	Reduction*	Reduction*	Reduction	None
SGLT-2 inhibitors	Intermediate	Reduction	Reduction	Reduction	Reduction	Reduction
GLP-1 receptor agonists	High	Reduction*	Reduction	Reduction*	Reduction	Reduction
DPP-4 inhibitors	Intermediate	None	None	Increase*	Reduction	None
Insulin	Very high	None	None	None	Increase	Increase
Sulfonylureas	High	None	None	None	Increase	Increase
Thiazolidinediones	High	None	Reduction*	Increase	Reduction	Increase
α-Glucosidase inhibitors	Intermediate	None	None	None	Reduction	None

Abbreviations: CKD = chronic kidney disease; CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium-glucose cotransporter-2.
* Potential effect.

of albuminuria should also be taken into account, which may warrant the involvement of a nephrologist before arriving at this eGFR cut-off.[5] Referral of the patient to a nephrologist is important, as complications such as volume overload, anaemia, electrolyte imbalances and CKD-related mineral and bone disorders can become prominent management issues when the eGFR declines to below the cut-off. Timely initiation of iron replacement, epoetin and phosphatebinding treatments are important considerations. Furthermore, early preparation for pre-emptive kidney or possible combined kidney and pancreas transplantation for type 1 diabetes is beneficial, as is early preparation for kidney replacement therapy.

Preventing the progression of diabetic kidney disease

Multimorbidity is common in people with DKD and, therefore, there is an increasing emphasis on comprehensive, holistic medical care to improve overall patient outcomes.[5] This approach incorporates treatment directed to optimise lifestyle factors, targeted pharmacological therapy to preserve end-organ function and additional therapies to address risk factors such as glycaemia, hypertension and dyslipidaemia.

Management of lifestyle factors

The latest guidelines from the American Diabetes Association and Kidney Disease Improving Global Outcomes (KDIGO) highlight the role of patient education in nutritional management from dietitians for optimal diabetes management. The recommendation is for patients to consume balanced diets high in vegetables, fruits and whole grains but low in refined carbohydrates and sugar-containing sweetened beverages.[7,8]

Although there is some evidence that low protein diets can slow the progression of DKD, this approach is rarely used in clinical practice. People with advanced-stage kidney disease on maintenance dialysis are advised to have a higher protein intake, considering that this population is often malnourished or in a catabolic state. Moderate to intense physical activity for more than 150 min/week and the avoidance of sedentary activity is also recommended.[7,8] Tobacco should not be consumed by any person with diabetes. Alcohol consumption should be limited.[6]

Glycaemia management

Intensive glycaemic management (glycated haemoglobin [HbA_{1c}] less than 53 mmol/mol) delays the development and progression of albuminuria and slows the rate of eGFR decline and progression to end-stage kidney disease. Early initiation of metformin treatment plus an SGLT-2 inhibitor is recommended in most people with type 2 diabetes, followed by the addition of glucose-lowering agents as needed to achieve individualised glycaemic targets (Table 2).[5] Dose adjustment and medication choice based on the eGFR (Table 3) is important to take into consideration.[5]

Diabetes technologies, including continuous glucose monitors, are increasingly becoming a part of routine clinical management, particularly for type 1 diabetes, for which they are subsidised under the National Diabetes Services Scheme. Continuous glucose monitoring (CGM) technology is a powerful tool to identify and correct glycaemic derangements, prevent hypoglycaemia, direct medication management and guide medical nutritional therapy and physical activity recommendations. CGM technology with and without insulin pump therapy is an emerging attractive approach to help insulin-treated people with DKD optimise their glycaemic control.

Recommendations from the Joint British Diabetes Societies suggest the use of continuous glucose monitors, where

TABLE 3. DOSE ADJUSTMENTS OF GLUCOSE-LOWERING AGENTS IN PEOPLE WITH A LOW eGFR[5]

Glucose-lowering agent	eGFR (mL/min/1.73 m²)		
	30 to 44	15 to 29	<15
Insulin	Start and titrate with caution to avoid hypoglycaemia		
Metformin	Reduce dose to 1000 mg/day	Do not use	
SGLT-2 inhibitors			
Dapagliflozin	Use 10 mg daily if eGFR is 25 to 44 mL/min/1.73 m²	Do not start if eGFR <25 mL/min/1.73 m²; if using, may continue 10 mg daily if tolerated until dialysis	
Empagliflozin	Use 10 mg daily; do not start for glycaemic control if eGFR is <30 mL/min/1.73 m² or for heart failure if eGFR is <20 mL/min/1.73 m²		Do not start if eGFR <20 mL/min/1.73 m²; if using, may continue 10 mg daily if tolerated until dialysis
GLP-1 receptor agonists			
Dulaglutide	No dose adjustment required		Limited experience, use with caution
Liraglutide	No dose adjustment required		Limited experience, use with caution
Semaglutide	No dose adjustment required		Limited experience, use with caution
DPP-4 inhibitors			
Alogliptin	Use maximum 12.5 mg daily (for eGFR 30 to 50 mL/min/1.73 m²)	Use maximum 6.25 mg daily	
Linagliptin	No dose adjustment required		
Saxagliptin	Use maximum 2.5 mg daily		Not recommended
Sitagliptin	Use maximum 50 mg daily	Use maximum 25 mg daily	
Sulfonylureas (second generation)			
Gliclazide	Start at 30 mg daily with caution	Do not use	
Glimepiride	Start at 1 mg daily with caution; titrate slowly to avoid hypoglycaemia	Contraindicated	
Glipizide	Start at 2.5 mg daily with caution; titrate slowly to avoid hypoglycaemia		Contraindicated
Glibenclamide	Do not use		
Thiazolidinediones			
Pioglitazone	No dose adjustment required		Not recommended in patients on dialysis
α-Glucosidase inhibitors			
Acarbose	No dose adjustment required	Do not use	

Abbreviations: DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium-glucose cotransporter-2.

available, in patients on dialysis as the best way to monitor glucose control (Figure).[9,10] When CGM technology can be used, there is an emphasis on looking at the time in range, with the range defined as 3.9 to 10.0 mmol/L, rather than using an HbA_{1c} target. The target time in range is greater than 70% for most people with diabetes. This should be achieved while minimising the time in range for hypoglycaemia, aiming for less than 4% in a range of less than 3.9 mmol/L.[9] At the time of writing, there are no specific CGM targets for people with DKD.

Blood pressure management

A crucial goal for the prevention of CKD progression, cardiovascular disease

(CVD) and heart failure is managing blood pressure. For people with diabetes, hypertension and a high risk of atherosclerotic CVD (10-year risk greater than 15%), a blood pressure target of less than 130/80 mmHg is suggested. Previously, for those with diabetes, hypertension and a low risk of atherosclerotic CVD (10-year risk less than 15%), a blood pressure target of less than 140/90 mmHg was the recommendation.[8] The general blood pressure target for people with diabetes has now been revised to 130/80 mmHg by the American Diabetes Association, and the systolic blood pressure target recommended by KDIGO for patients with CKD not on dialysis is less than 120 mmHg.[11] Therefore, lowering systolic blood pressure levels to less than 130 mmHg in most people with DKD and to less than 120 mmHg in high-risk patients may be a reasonable approach. The blood pressure targets should be individualised and account for possible adverse outcomes, such as postural hypotension, which is particularly relevant in people with concurrent autonomic neuropathy.

RAS inhibitors are the preferred initial pharmacological antihypertensive agents. It is important that these medications are titrated to maximally tolerated approved doses. They have been shown to decrease the risk of CKD, as well as slowing the progression to end-stage kidney disease in people with a reduced eGFR and macroalbuminuria. Calcium channel blockers are suggested as a second-line agent, followed by a diuretic as a third-line antihypertensive agent. General advice to patients to reduce salt intake by substituting with nonsalt-containing food flavourings (e.g. pepper, garlic, lemon and ginger) are also helpful lifestyle measures to lower blood pressure.

Finerenone, a nonsteroidal mineralocorticoid receptor agonist, has impressive benefits in the setting of DKD; however, its blood pressure-lowering effect appears less than those of spironolactone and eplerenone (both steroidal mineralocorticoid receptor antagonists).

Management of lipid levels

Lipid-lowering agents, particularly statins, are the cornerstone of both primary and secondary prevention of atherosclerotic CVD, which has a markedly high risk of developing in people with DKD. There are no specific lipid targets for patients with diabetes and CKD, but it is recommended to initiate statin therapy in most of these patients who are not on dialysis.[12,13] By virtue of having both diabetes and CKD, this population is considered to be at high risk for CVD. Therefore, the following targets are recommended:[14]

- LDL-cholesterol less than 2.0 mmol/L (or less than 1.8 mmol/L if CVD is established)
- HDL-cholesterol greater than 1.0 mmol/L
- triglycerides less than 2.0 mmol/L.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (no adjustment for CKD but safety data with very advanced CKD are lacking) and inclisirin (no dose adjustment for CKD but not recommended for very advanced CKD) can also lower LDL-cholesterol levels and improve CV outcomes when added to statin therapy for secondary prevention.[15,16] Some evidence indicates that fenofibrate, which is effective in treating hypertriglyceridaemia, attenuates albuminuria and eGFR decline in type 2 diabetes.[17]

Recent advances in pharmacological treatments

Sodium-glucose cotransporter-2 inhibitors

An SGLT-2 inhibitor is recommended in most people with type 2 diabetes and CKD, given the strong evidence that SGLT-2 inhibitors reduce CKD progression, heart failure and the risk of atherosclerotic CVD in people with type 2 diabetes and CKD. These effects are independent of HbA_{1c} levels or the need for additional glucose lowering.[5,18]

The SGLT-2 inhibitors available in Australia are dapagliflozin and empagliflozin. These are not recommended for use

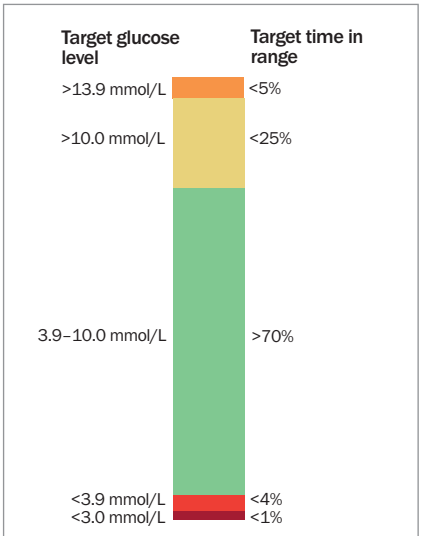

Figure. Continuous glucose monitoring-based targets for nonfrail people with diabetes.[9]

in patients with an eGFR less than 20 mL/min/1.73 m^2 (empagliflozin) or less than 25 mL/min/1.73 m^2 (dapagliflozin). Although SGLT-2 inhibitors maintain their renoprotective effects at low eGFRs, their glucose-lowering effects are significantly impaired. People with low eGFRs may therefore require the addition of other glucose-lowering therapies.

Both empagliflozin and dapagliflozin are PBS listed for proteinuric CKD, independent of diabetes status. However, from 1 November 2025 the PBS listing for empagliflozin has been expanded for use in patients with an eGFR of 20 to 90 mL/min/1.73 m^2. Patients must still have a urinary ACR of at least 22.6 mg/mmol if their eGFR is between 45 and 90 mL/min/1.73 m^2; but for patients with an eGFR between 20 and less than 45 mL/min/1.73 m^2, empagliflozin is PBS subsidised regardless of albuminuria status (see Box 1 for the PBS criteria for empagliflozin and dapagliflozin for the indication of CKD). It is expected that dapagliflozin will obtain a similar PBS listing for CKD in the near future.

Both dapagliflozin and empagliflozin are TGA approved as an adjunct to standard care for the treatment of symptomatic heart failure, irrespective of

1. PBS INDICATIONS FOR DAPAGLIFLOZIN AND EMPAGLIFLOZIN IN PATIENTS WITH CKD*

Empagliflozin

- The patient must have a diagnosis of CKD present for at least 3 months AND
- eGFR 20 to 90 mL/min/1.73 m^2 prior to treatment initiation† AND
- uACR ≥22.6 mg/mmol if eGFR is between 45 and 90 mL/min/1.73 m^2† AND
- Not be receiving treatment with another SGLT-2 inhibitor AND
- Be stabilised on a RAAS inhibitor for at least four weeks unless medically contraindicated, before starting combination therapy with this drug

Dapagliflozin

- The patient must have a diagnosis of CKD present for at least 3 months AND
- eGFR 25 to 75 mL/min/1.73 m^2 prior to treatment initiation AND
- uACR 22.6 to 565 mg/mmol AND
- Not be receiving treatment with another SGLT-2 inhibitor AND
- Be stabilised on a RAAS inhibitor for at least four weeks unless medically contraindicated, before starting combination therapy with this drug

For both empagliflozin and dapagliflozin, the patient must discontinue treatment prior to initiating kidney replacement therapy (dialysis or transplant). Patients with polycystic kidney disease, lupus nephritis, ANCA-associated vasculitis, current/recent cytotoxic or immunosuppressive therapy for kidney disease or with an organ transplant are ineligible for treatment with this drug

* Refer to the PBS website for full details.
† The implication is that for patients with CKD with an eGFR between 20 and less than 45 mL/min/1.73 m^2, there is PBS indication for empagliflozin regardless of albuminuria status.

Abbreviations: ANCA = antineutrophil cytoplasmic antibody; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; RAAS = renin–angiotensin–aldosterone system; SGLT-2 = sodium-glucose cotransporter-2; uACR = urine albumin-to-creatinine ratio.

ejection fraction or diabetes status. Both are PBS listed for symptomatic chronic heart failure with reduced ejection fraction (HFrEF, with left ventricular ejection fraction 40% or less) or with preserved ejection fraction. Refer to the PBS schedule and TGA website for full details.

Importantly, despite the evidence for use of SGLT-2 inhibitors for DKD treatment, they should not be used in patients with type 1 diabetes because of the risk of euglycaemic diabetic ketoacidosis. SGLT-2 inhibitors can be associated with diabetic ketoacidosis in patients with type 2 diabetes, particularly during times of fasting or illness. Therefore, guidelines have been developed to address appropriate SGLT-2 inhibitor withdrawal for these cases.[19]

Glucagon-like peptide-1 receptor agonists

Many of the large-scale CV outcome trials of glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes have included kidney disease outcomes as secondary outcomes. These studies have indicated a reduction in albuminuria or lower risk of new or worsening nephropathy and slowing of the expected eGFR decline.[20-22] Although a reduction in the progression to end-stage kidney disease is yet to be definitively demonstrated, evidence for this class of medication having cardio-kidney protective effects in people with type 2 diabetes is accumulating.

A trial of the effect of the GLP-1 receptor agonist semaglutide on the progression of CKD in people with type 2 diabetes and CKD has recently been published. The Evaluate Renal Function with Semaglutide Once Weekly (FLOW) trial showed that semaglutide (1 mg administered once weekly by subcutaneous injection) significantly reduced the primary composite outcome – kidney failure (defined as a persistent eGFR <15 mL/min/1.73 m^2 or initiation of chronic kidney replacement therapy), a sustained 50% reduction or more in eGFR, or death from kidney or CV causes – by 24% compared with placebo.[23] Given the above findings, semaglutide now has TGA approval for CKD and type 2 diabetes as an adjunct to standard of care to reduce the risk of sustained decline of kidney function and CV death.

In people with type 2 diabetes and advanced-stage CKD whose body mass index exceeds the limits required for kidney transplantation, the use of GLP-1 receptor agonists has been suggested to aid with weight loss. This may then facilitate eligibility for transplantation.

Furthermore, the TGA-approved dual glucose-dependent insulinotropic polypeptide/GLP-1 receptor agonist tirzepatide has some evidence of kidney benefit, based on a post-hoc analysis of the Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4) trial findings.[24] Dedicated kidney outcome trials of tirzepatide are warranted.

Nonsteroidal mineralocorticoid receptor antagonist

Finerenone has recently been investigated in people with DKD (defined as an ACR of at least 3 mg/mmol and eGFR of 25 to 75 mL/min/1.73 m^2) who were treated with RAS inhibitors. This medication was shown to reduce the risk of CKD progression and kidney failure, as well as dialysis initiation, in the FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease) trial, which involved participants with type 2 diabetes who had albuminuria and advanced CKD.[25] Furthermore, FIGARO-DKD (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease), which involved participants with stage 2 to 4 CKD and moderately elevated albuminuria or stage 1 or 2 CKD and severely increased albuminuria, showed a reduction in CV morbidity, most prominently through a reduction in heart failure-related hospitalisations, with finerenone therapy.[26]

A pooled analysis of the findings of these two trials further showed the safety and efficacy of finerenone in a large cohort of patients with type 2 diabetes and CKD to reduce important kidney and CV outcomes.[27] Hyperkalaemia was an adverse effect in a small proportion of

participants; regular monitoring of potassium levels is recommended when using this medication.

Finerenone is TGA approved to delay progressive decline of kidney function and to reduce the risk of CV mortality and morbidity in adults with CKD (with albuminuria) associated with type 2 diabetes, in addition to standard of care. It is listed on the PBS for patients who fulfil the following criteria:

- an eGFR of 25 mL/min/1.73 m^2 or greater
- an ACR of 22.6 mg/mmol or greater
- must be on a stable dose of either an ACE inhibitor or ARB
- must not have established HFrEF
- must be on an SGLT-2 inhibitor unless medically contraindicated or intolerant (refer to the full PBS clinical criteria at: www.pbs.gov.au/pbs/home).

Combination therapy

Some evidence suggests that combination therapy with SGLT-2 inhibitors and mineralocorticoid receptor antagonists in patients with type 2 diabetes and CKD reduces the risk of CV events and the mineralocorticoid receptor antagonist-associated risk of hyperkalaemia without a significant interaction between the two drugs.[28] However, dedicated trials involving both SGLT-2 inhibitors and mineralocorticoid receptor antagonists are required to demonstrate the true benefits of combining these two classes of medications. The recently published COmbinatioN effect of FInerenone anD EmpagliflozIN in participants with chronic kidney disease and type 2 diabetes using a UACR Endpoint (CONFIDENCE) trial has shown that in people with type 2 diabetes and CKD (with albuminuria) the combination of finerenone and empagliflozin led to a greater reduction in albuminuria than either treatment alone.[29]

Of note, even before the introduction of the newer classes of medications, multifactorial, target-driven therapies addressing glycaemic, blood pressure and lipid control that incorporated RAS blockade, the use of statins and attention to lifestyle factors significantly reduced the progression to end-stage kidney disease by about 50% in people with type 2 diabetes, hypertension and microalbuminuria.[30]

Sick day management

GPs can play an important role in reinforcing the principles of sick day management, especially those related to medication use, in people with DKD. The acronym 'SAD MANS' is a useful mnemonic to remember medications that may have reduced clearance and an increased risk of adverse effects in people with CKD (Box 2). Some medications need dose adjustments or withdrawing, especially in the setting of acute illness that can result in dehydration and acute kidney failure.

Most guidelines support the use of metformin in people with an eGFR of 30 mL/min/1.73 m^2 or greater (although not at maximum recommended doses) and that there is a growing appreciation of temporarily withholding SGLT-2 inhibitors when patients are unwell or need to fast for a prolonged period of time to prevent the development of euglycaemic diabetic ketoacidosis.

Conclusion

Screening people with diabetes for early markers of DKD and initiating measures to slow the progression of kidney disease are part of routine clinical practice. In addition, it is necessary to measure, assess and manage CV risk factors aggressively. Attention to glycaemic, blood pressure and lipid control, as well as improving lifestyle factors (e.g. consuming a healthy diet, avoiding weight gain and undertaking regular physical activity) remain the cornerstone of management in people with DKD. The use of RAS inhibitors, SGLT-2 inhibitors and novel agents, such as finerenone, have also been shown to slow the progression of DKD to end-stage kidney disease and provide CV protection. There is emerging evidence for GLP-1 receptor agonists as renoprotective agents, but their role in slowing progression to end-stage kidney disease is yet to be established. Consideration of sick day management, patient education, the adjustment of glucose-lowering medications as the eGFR declines and screening for other microvascular diabetes-related complications (e.g. retinopathy and foot disease), together with a timely referral to a nephrology service, are important considerations in the optimal care of people with DKD. MT

2. SICK DAY MEDICATION LIST FOR PEOPLE WITH TYPE 2 DIABETES AND KIDNEY DISEASE ('SAD MANS')

- **S** – Sulfonylureas
- **A** – ACE inhibitors
- **D** – Diuretics
- **M** – Metformin
- **A** – Angiotensin receptor blockers
- **N** – NSAIDs
- **S** – Sodium-glucose cotransporter-2 inhibitors

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A list of references is included in the online version of this article (https://www.medicinetoday.com.au/mt/2025/november/supplements/focus-on-chronic-kidney-disease).

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Preventing diabetic kidney disease progression

An update

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Diabetic kidney disease

The four pillars of therapy

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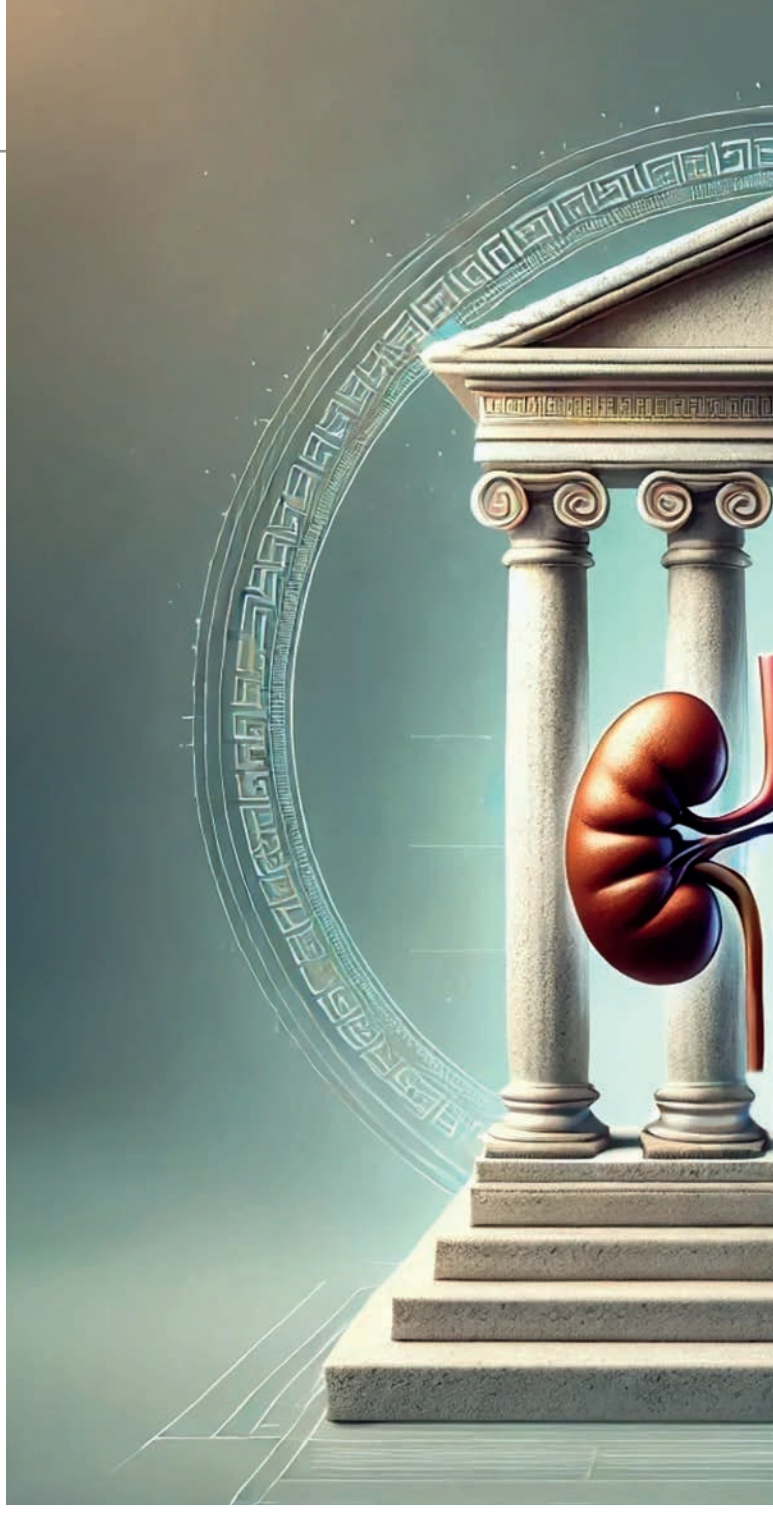
Diabetic kidney disease is a leading cause of end-stage kidney disease and premature death worldwide. Modern management combines lifestyle changes with four key treatments: ACE inhibitors or angiotensin receptor blockers, sodium-glucose cotransporter-2 inhibitors, nonsteroidal mineralocorticoid receptor antagonists and glucagon-like peptide-1 receptor agonists. Early use of these therapies can significantly improve long-term kidney and heart health.



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Over the past two decades, the prevalence of type 2 diabetes in Australia has doubled, affecting at least 1.5 million people in Australia.[1] Diabetic kidney disease (DKD) is a common complication of diabetes, affecting an estimated 330,000 people with diabetes in Australia, and is associated with higher rates of hospitalisation and mortality and significantly poorer health-related quality of life.[2,3] Many people with type 2 diabetes are unaware of their kidney disease, in part because of low rates of testing for albuminuria.[4] Early screening for kidney disease, including the detection of albuminuria, is therefore crucial to stratify a patient's cardiovascular and kidney risk, personalise risk prediction and facilitate the uptake of proven therapies to improve cardiorenal outcomes.

Kidney failure requiring dialysis or transplantation is associated with a substantially increased morbidity and mortality.[5] DKD remains the leading cause of kidney failure in Australia, responsible for about 40% of cases of kidney failure.[6] Moreover,

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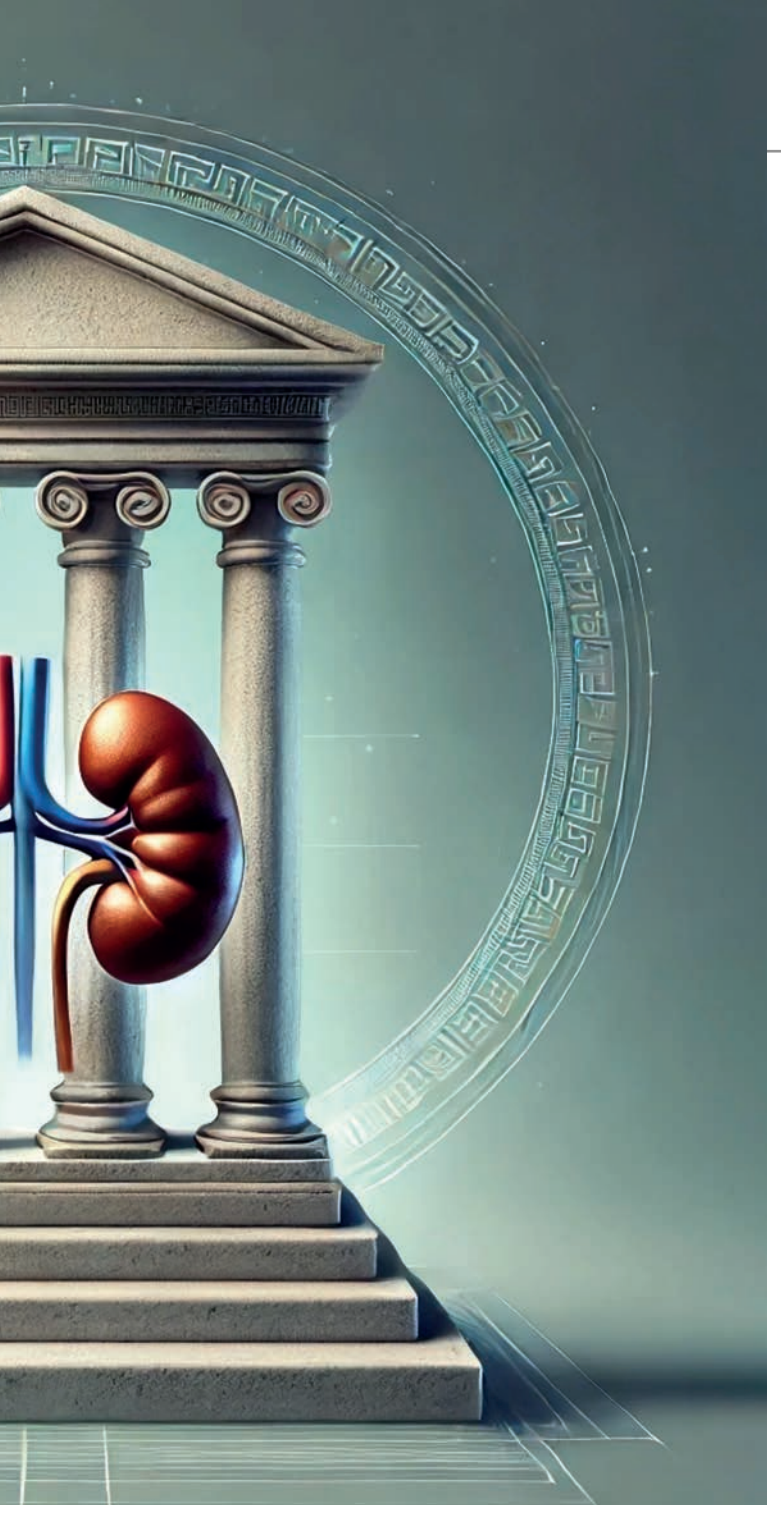

KEY POINTS

- The management of diabetic kidney disease (DKD) secondary to type 2 diabetes now centres on four pillars of treatment: renin-angiotensin system blockade (with ACE inhibitors or angiotensin receptor blockers), sodium-glucose cotransporter-2 inhibitors, nonsteroidal mineralocorticoid receptor antagonists and glucagon-like peptide-1 receptor agonists.
- These pillars have a wide range of cardiorenal benefits, reducing the risk of progression of kidney disease, cardiovascular events and death.
- Initiating these therapies is dependent on the detection of DKD, by screening for reduced estimated glomerular filtration rate and albuminuria, which both independently predict the risk of cardiovascular disease as well as the risk of chronic kidney disease progression.
- These pillars of therapy have different mechanisms of action, addressing the abnormalities in haemodynamics (glomerular hyperfiltration), metabolism, inflammation and fibrosis that characterise the development and progression of DKD.
- Emerging evidence suggests that using the four pillars of therapy in combination can be safe and confer substantial additive benefits. Sodium-glucose cotransporter-2 inhibitors can ameliorate the risk of hyperkalaemia caused by ACE inhibitors and angiotensin receptor blockers.
- Strategies in routine clinical practice can match the intensity of combination therapy to a patient's overall cardiovascular-kidney-metabolic risk profile.

chronic kidney disease (CKD) itself is associated with 33% of all cardiovascular deaths in Australia, reflecting the multidirectional relationship between kidney and cardiovascular disease.[7,8] Preventing cardiovascular events is a critical aspect of managing CKD, as most deaths in patients with CKD are caused by cardiovascular disease before the patients reach kidney failure.

The landscape of DKD treatment has dramatically changed in the past 10 years. There are now four proven therapies that can reduce the risk of kidney disease progression in people with type 2 diabetes:

- renin–angiotensin–aldosterone system (RAAS) blockade, with either ACE inhibitors or angiotensin receptor blockers (ARBs)
- sodium-glucose cotransporter-2 (SGLT-2) inhibitors
- nonsteroidal mineralocorticoid receptor antagonists (MRAs)
- glucagon-like peptide-1 (GLP-1) receptor agonists.

Individuals at high risk of disease progression may benefit from an accelerated initiation of multiple therapies within a compressed timeframe, rather than a stepwise sequential approach. Emerging evidence suggests that the pillars of DKD therapy confer additive benefits and can be used in combination safely, with targeted education and appropriate sick day medication guidance. Evidence for these therapies is currently limited to type 2 diabetes, although trials in patients with type 1 diabetes are underway.

This article focuses on the mechanisms of action and evidence for these four 'pillars' of DKD therapy, how to stratify and personalise cardiorenal risk in patients with DKD and practical recommendations for the potential use of these therapies in combination safely.

eGFR categories (mL/min/1.73 m²)	Albuminuria level		
	Normal to mildly increased (<3 mg/mmol)	Moderately increased (3–30 mg/mmol)	Severely increased (>30 mg/mmol)
Normal or high (>90*)	Monitor	Treat	Treat and refer†
Mildly decreased (60–89)	Monitor	Treat	Treat and refer†
Mildly to moderately decreased (45–59)	Treat	Treat	Treat and refer
Moderately to severely decreased (30–44)	Treat	Treat and refer	Treat and refer
Severely decreased (15–29)	Treat and refer	Treat and refer	Treat and refer
Kidney failure (<15)	Treat and refer	Treat and refer	Treat and refer

Figure 1. CKD staging by eGFR and albumin level. The colours represent the risk of CKD progression, morbidity and mortality. Green indicates low risk; monitor with at least an annual kidney health check, including a blood test for kidney function, urine albumin-creatinine ratio and blood pressure check. Yellow indicates moderately increased risk; treat with lifestyle changes and implementation of the four pillars of therapy. Orange and red indicate high and very high risk, respectively; treat with lifestyle changes and implementation of the pillars of therapy, in addition to referral of the patient to a nephrology service.

Abbreviations: CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.

* Note that patients with an eGFR greater than 90 mL/min/1.73 m² may also be at higher risk because of glomerular hyperfiltration in diabetic kidney disease.

† PBS-listed CKD indications for empagliflozin include adults with an eGFR between 20 and 90 mL/min/1.73 m². Those with an eGFR between 45 and 90 mL/min/1.73 m² should also have a urine albumin-creatinine ratio of 22.6 mg/mmol or greater. PBS-listed CKD indications for dapagliflozin include adults with an eGFR between 25 and 75 mL/min/1.73 m² and a urine albumin-creatinine ratio between 22.6 and 565 mg/mmol. If patients do not meet the PBS criteria for the CKD indication, they may have alternative indications (e.g. cardiac- or diabetes-related) for other pillars of therapy.

Adapted from de Boer IH et al. Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). Diabetes Care 2022. Available online at: https://kdigo.org/wp-content/uploads/2018/03/ADA-KDIGO-Consensus-Report-Diabetes-CKD-Diabetes-Care-2022.pdf (accessed October 2025).

Pathophysiology of diabetic kidney disease

The development of DKD shares many risk factors with established cardiovascular disease, including obesity, hypertension, and dyslipidaemia.[9] Glomerulopathy tends to be an early feature of DKD, characterised by hyperfiltration and activation of pro-inflammatory and fibrotic pathways. This in turn leads to albuminuria and subsequently potentiates a cascade of progressive fibrosis. Yet heterogeneity is seen on a cellular level: up to half of patients with DKD have been found to exhibit classic diabetic glomerulopathy, although many others have been found to demonstrate severe tubulointerstitial or arteriolar or vascular changes in the presence of mild glomerular lesions.[10] This heterogeneity underscores the need for multiple therapeutic agents with different mechanisms of action to reduce the decline of kidney function.

Screening and risk stratification

CKD is diagnosed as either a persistent reduction in estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m² or evidence of kidney damage (including albuminuria) over at least three months.[11] Detection of CKD is the first step towards initiating appropriate treatment. Screening for CKD with an annual measurement of kidney function (serum creatinine level and eGFR) and at least one urinary albumin-creatinine ratio (UACR) measurement to assess for the presence of albuminuria is recommended for all patients with diabetes.[12] Measurement of the UACR is a readily accessible, non-invasive screening test that is available for the detection of CKD and remains underused in clinical practice.[4] Causes of CKD other than DKD should also be considered, although this is beyond the scope of this article. Further guidance can be found in the *Chronic Kidney Disease Handbook*, available online at: https://assets.kidney.org.au/resources/KHA-CKD-Handbook-5th-Ed-July2024.pdf.

CKD is itself a risk multiplier for cardiovascular disease, with reduced eGFR and albuminuria both independently associated with cardiovascular morbidity and mortality.[13] Since 2012, Kidney Disease Improving Global Outcomes (KDIGO) CKD staging has rephrased what has been known as 'normo-, micro- and macroalbuminuria' to 'mildly, moderately and severely increased albuminuria', respectively, in recognition that albuminuria of any level carries an increased risk of cardiovascular disease (Figure 1). Accordingly, the presence of albuminuria is incorporated in the updated Australian Cardiovascular Disease Risk Calculator (https://www.cvdcheck.org.au/calculator).[14] It reclassifies people with moderate-to-severe CKD (patients with an eGFR of less than 45 mL/min/1.73 m²) as at high risk for cardiovascular disease, irrespective of other risk factors.

The 'pillars' of therapy for diabetic kidney disease

Despite conventional treatment for DKD that is focused on glycaemic and blood pressure control with RAAS inhibition, high-risk patients with DKD and increased albuminuria may still lose kidney function at up to 5 mL/min/1.73m² per year.[15,16] Even with the addition of SGLT-2 inhibitor therapy, the residual risk of kidney function decline remains high (at 2 to 3 mL/min/1.73 m² per year) in people with severely increased albuminuria.[17] This underscores the need for additional therapies to further reduce the rate of kidney function decline to be able to achieve one that is similar to normal healthy ageing (about 1 mL/min/1.73 m² per year). Combination therapy with multiple agents offers the opportunity to address the haemodynamic, inflammatory and metabolic abnormalities that characterise the development and progression of DKD (Figure 2).

Pillar 1: Renin–angiotensin–aldosterone system blockade

The evidence for RAAS blockade in DKD treatment has been established for over 30 years. Captopril was first shown to reduce DKD progression in patients with insulin-dependent diabetes in 1993.[18] Two landmark trials followed, establishing RAAS blockade as the standard of care for preventing DKD. The effects of ACE inhibitors and ARBs on DKD are independent of their blood pressure lowering effects and are achieved by reducing intraglomerular pressure (which can lead to mesangial cell proliferation, activation of proinflammatory responses, fibrosis and albuminuria).[19,20]

Beyond their role in DKD, ACE inhibitors and ARBs continue to be part of the mainstay of treatment for cardiovascular disease, including hypertension and heart failure.

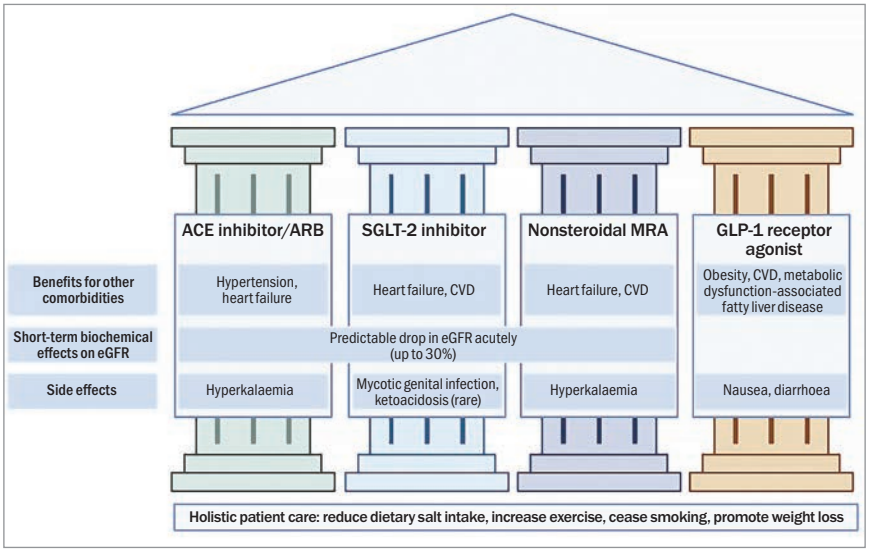

Figure 2. The four 'pillars' of therapy for diabetic kidney disease secondary to type 2 diabetes. The short-term biochemical effects on the eGFR differ from the long-term kidney protective effects in reducing eGFR decline.
Abbreviations: ARB = angiotensin receptor blocker; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; GLP-1 = glucagon-like peptide-1; MRA = mineralocorticoid receptor antagonist; SGLT-2 = sodium-glucose cotransporter-2.

Practical tips for the initiation and maintenance of RAAS inhibition

- When initiated, ACE inhibitors and ARBs can cause a reduction in glomerular blood flow, thereby leading to an acute decline in eGFR of up to 30%. In this context, these kidney-protective agents should be continued, provided the acute reduction in eGFR is less than 30%.
- The risk of hyperkalaemia should be recognised if ACE inhibitors or ARBs are initiated in patients with serum potassium levels at the upper limit of the normal range, which can be managed effectively with dietary and medical interventions.
- RAAS inhibition should ideally be uptitrated to the maximum tolerated dose, balanced with the risk of side effects (e.g. hypotension and electrolyte abnormalities, such as hyperkalaemia), and recommenced following episodes of recovered acute kidney injury.
- Using ACE inhibitor and ARB therapies in combination should be avoided because of the increased risk of acute kidney injury and hyperkalaemia.

Pillar 2: Sodium-glucose cotransporter-2 inhibitors

Originally developed as glucose-lowering agents, SGLT-2 inhibitors have also demonstrated cardiac and kidney protective effects, even in people without diabetes. By inhibiting sodium and glucose reuptake in the proximal tubule, SGLT-2 inhibitors increase distal sodium delivery, thereby restoring tubuloglomerular feedback. This leads to afferent arteriolar vasoconstriction and a reduction in intraglomerular pressure, manifesting clinically as an acute 'dip' in eGFR. This mechanism parallels and is complementary to that of RAAS blockade, which also reduces intraglomerular pressure. SGLT-2 inhibitors also modestly lower blood pressure (comparable to the introduction of a thiazide diuretic), reduce albuminuria and induce modest weight loss.[21-24]

Three landmark kidney outcome trials have established SGLT-2 inhibitors as foundational therapy for CKD, alongside RAAS blockade. In patients with type 2 diabetes and CKD, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) first established that canagliflozin could reduce the risk of end-stage kidney disease, progressive CKD or death from cardiovascular kidney causes by about 30%.[16] The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial then demonstrated that dapagliflozin reduced the risk of decline in eGFR, end-stage kidney disease or death because of cardiovascular or kidney causes in patients with CKD, irrespective of diabetes.[25] Further, the Study of Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY) trial confirmed that empagliflozin also reduced the risk of progressive CKD or cardiovascular death by 28% in a broad population of patients with CKD with or without diabetes.[26]

SGLT-2 inhibitors have been found to reduce the risk of cardiovascular events, particularly heart failure, irrespective of the presence of established atherosclerotic cardiovascular disease, diabetes or the level of kidney function, solidifying their clinical benefits in improving cardiorenal outcomes as a class of treatment.[27] They are broadly approved in Australia for the treatment of not only diabetes and CKD, but also heart failure, irrespective of ejection fraction or diabetes.

Practical tips for the initiation and maintenance of SGLT-2 inhibition

- Empagliflozin is indicated in adults with CKD over a broad range of eGFR (20 to 90 mL/min/1.73 m^2). However, those with an eGFR of 45 to 90 mL/min/1.73 m^2 must also have a UACR 200 mg/g or greater (≥22.6 mg/mmol per PBS criteria). Dapagliflozin's indication is limited to adults with proteinuric CKD (eGFR 25 to 75 mL/min/1.73 m^2) and UACR 200 to 5000 mg/g (22.6 to 565 mg/mmol per PBS criteria). Dapagliflozin and empagliflozin should not be initiated if the starting eGFR is less than 25 mL/min/1.73 m^2 or 20 mL/min/1.73 m^2, respectively.
- Similar to ACE inhibitors and ARBs, SGLT-2 inhibitors can cause a predictable acute and reversible reduction in a patient's eGFR because of changes in glomerular haemodynamics. Clinicians may expect up to a 30% short-term decrease in eGFR but should stay the course by continuing therapy to derive long-term benefits. For example, patients with an eGFR of 60 mL/min/1.73 m^2 would need to reduce their eGFR by 18 mL/min/1.73 m^2 to reach the 30% decline threshold.
- As the eGFR declines to below 45 mL/min/1.73 m^2, the glucose-lowering effects of SGLT-2 inhibitors are modest and other glucose-lowering medications may need to be introduced. However, the kidney and cardiovascular benefits of SGLT-2 inhibitors are still maintained at lower eGFRs, at least to a starting eGFR of 20 mL/min/1.73m^2.
- SGLT-2 inhibition in combination with other therapies is not only safe but can enhance adherence to other therapies. They reduce the risk of serious hyperkalaemia and acute kidney injury, which can help maintain the use of RAAS inhibition and nonsteroidal MRAs.[28]
- Potential adverse effects from SGLT-2 inhibitors include genital mycotic infection as well as euglycemic diabetic ketoacidosis; therefore, patients with diabetes must be cautioned to temporarily cease SGLT-2 inhibitors during periods of illness, dehydration or fasting.
- Despite their use in a broad range of conditions, SGLT-2 inhibitors are not approved for use in patients with type 1 diabetes (because of the potential risk of ketoacidosis), and they are currently considered off-label for patients receiving immunosuppression for kidney disease (e.g. lupus nephritis, vasculitis and patients with an organ transplant). Their benefits and potential harms have not yet been studied in autosomal dominant polycystic kidney disease.

Pillar 3: Nonsteroidal MRAs

Despite maximally tolerated ACE or ARB therapy and SGLT-2 inhibition, people with DKD are still at heightened cardiorenal risk, related to elevated aldosterone activity.[29] Increased mineralocorticoid receptor activation by aldosterone activates downstream proinflammatory and profibrotic pathways within the kidneys, contributing to DKD progression.[30]

Steroidal MRAs (e.g. spironolactone and eplerenone) can decrease albuminuria; however, data on clinical outcomes are limited and the risk of hyperkalaemia has hindered their widespread use. In comparison, nonsteroidal MRAs have greater selectivity for the mineralocorticoid receptor, cause less hyperkalaemia and gynaecomastia, have more balanced distribution in cardiac and kidney tissue, and may have more pronounced anti-inflammatory or antifibrotic effects.[31]

Two companion trials, Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) and Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD), have collectively studied the impact of finerenone on clinical outcomes in almost 13,000 patients with DKD.[32,33] Like the SGLT-2 inhibitor trials, all participants were taking the maximum tolerated or labelled dose of RAAS blockade. In the pooled Combined FIDELIO-DKD and FIGARO-DKD Trial Programme Analysis (FIDELITY), finerenone reduced the risk of CKD progression (a 57% or greater reduction in eGFR, kidney failure or death due to kidney failure) by 23% and reduced the risk of major adverse cardiovascular events by 14%.[34] These effects were observed irrespective of SGLT-2 inhibitor use.[35]

Practical tips for the initiation and maintenance of nonsteroidal MRAs

- The current PBS criteria for finerenone include patients with CKD and type 2 diabetes, residual albuminuria (UACR ≥22.6 mg/mmol) and an eGFR 25 mL/min/1.73 m^2 or greater despite treatment with RAAS blockade, and an SGLT-2 inhibitor unless medically contraindicated or intolerant.
- The main adverse effect of finerenone is hyperkalaemia, but the absolute risk is low. Finerenone can be commenced in patients with a baseline serum potassium level of up to 5.0 mmol/L, with routine monitoring of potassium.
- Like RAAS or SGLT-2 inhibitors, finerenone can cause a predictable drop in eGFR, which typically recovers and stabilises.
- Finerenone should not be used in combination with steroidal MRAs, including spironolactone or eplerenone.

Pillar 4: GLP-1 receptor agonists

GLP-1 is an incretin that is produced following a meal, which acts to stimulate insulin release and inhibit glucagon release. GLP-1 receptor agonists were developed as potent glucose-lowering agents but have also been shown to lead to substantial weight loss and reduce cardiorenal outcomes.[36]

The recently published Evaluate Renal Function with Semaglutide Once Weekly (FLOW) trial was the first to examine the long-term kidney protective effects of a GLP-1 receptor agonist in patients with DKD. Semaglutide reduced the risk of CKD progression or cardiovascular death (kidney failure, at least 50% reduction in eGFR, or death from kidney or cardiovascular causes) by 24%.[37] Outcomes from large cardiovascular outcome trials have also shown that GLP-1 receptor agonists significantly reduce major adverse cardiovascular events in patients with type 2 diabetes by 14%.[38]

Furthermore, there is emerging evidence from the Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) trial that semaglutide reduces the risk of cardiovascular events and may improve CKD outcomes in overweight and obese patients without diabetes.[39] A post-hoc analysis of the SELECT trial also suggested that semaglutide might reduce the risk of adverse kidney outcomes (death from kidney disease, initiation of renal replacement therapy, onset of eGFR <15 mL/min/1.73 m^2, persistent reduction in eGFR of greater than 50% or onset of macroalbuminuria) by 22%, driven largely by reductions in albuminuria.[40] Recently, semaglutide was also shown to substantially reduce albuminuria in patients who are overweight or obese in the setting of nondiabetic CKD.[41]

These cardiorenal protective benefits appear to be only partially mediated by reductions in body weight, blood pressure and HbA_{1c}, suggesting there are potentially vascular- and kidney-specific mechanisms underlying their clinical benefits.[42] The mechanism of action of GLP-1 receptor agonists is also entirely distinct to that of SGLT-2 inhibitors and nonsteroidal MRAs, indicating that there are likely to be additive benefits to their use in combination. Indeed, a prespecified analysis of the FLOW trial and meta-analyses showed that the benefits of GLP-1 receptor agonists in patients with type 2 diabetes and CKD were consistent, irrespective of SGLT-2 inhibitor use, and vice versa.[43-45]

Practical tips for the initiation and maintenance of GLP-1 receptor agonists

- The GLP-1 receptor agonists semaglutide and dulaglutide are currently PBS listed for use in patients with type 2 diabetes in combination with at least one of: metformin, a sulfonylurea and/or insulin. Patients must also not have achieved a clinically meaningful glycaemic response with an SGLT-2 inhibitor, or have a contraindication to, or intolerance requiring treatment discontinuation of an SGLT-2 inhibitor.
- At present, unlike SGLT-2 inhibitor therapy or finerenone, there is no PBS-listed CKD indication for a GLP-1 receptor agonist. However, the TGA has recently approved semaglutide for reducing the risk of kidney function decline in adults with type 2 diabetes and CKD.
- In Australia, GLP-1 receptor agonists can be used in combination with SGLT-2 inhibitors if the SGLT-2 inhibitor is used for a PBS-listed indication outside of diabetes (i.e. CKD or heart failure). GLP-1 receptor agonists are not currently PBS listed for indications outside of type 2 diabetes.
- The most common adverse effects with GLP-1 receptor agonists are gastrointestinal, including nausea and diarrhoea, and patients should have their dose initiated and uptitrated slowly with appropriate counselling to increase the likelihood of treatment persistence.

Implementation of the four pillars

Co-prescribing therapies

Given the availability of several cardiorenoprotective drugs, the next question to address is whether using them in combination is safe and confers additional benefits. Emerging evidence from pooled analyses of trial subgroups including individuals on combinations of therapies have shown that the benefit of SGLT-2 inhibitors was consistent in patients with or without GLP-1 receptor agonist therapy, and vice versa.[43-45] This suggests that the benefits of these pillars of therapies, which have different mechanisms of action, are additive. A further analysis showed that if individuals were using all four pillars of therapies, then this approach may delay progression of CKD by 5.5 years compared with conventional care (i.e. addressing risk factors and RAAS inhibition).[46]

There may also be important safety advantages with combination therapy as SGLT-2 inhibitors can ameliorate increases in serum potassium levels caused by RAAS inhibition or nonsteroidal MRAs.[28] In the multicentre, double-blind CONFIDENCE trial, patients with CKD and type 2 diabetes who started finerenone and empagliflozin together experienced a greater reduction in UACR compared with either drug alone, confirming the additive benefits of combination therapy. Importantly, this approach did not lead to unexpected adverse effects; symptomatic hypotension, acute kidney injury and hyperkalaemia requiring treatment discontinuation were uncommon.[47] Further data from ongoing trials will help to substantiate the benefits and safety of combination therapy. We envisage that additional evidence regarding the implementation of these pillars of therapy will be forthcoming in future studies.

Matching the intensity of treatment to a patient's risk

It is important to select the right drugs for the right patient at the right time. To tailor the implementation of therapy for DKD, clinicians should build a profile of each patient's cardiovascular and kidney risk. There are multiple proposed approaches to implementing the four pillars of DKD therapy. The KDIGO guidelines for diabetes management in CKD describes first-line treatment that comprises RAAS inhibition and SGLT-2 inhibitors, with the

addition of a nonsteroidal MRA for patients with residual albuminuria (in line with current PBS prescribing criteria) and GLP-1 receptor agonists for additional glycaemic and cardiovascular benefits.

There is emerging evidence that selected patients with the highest cardiovascular–kidney–metabolic risk should have accelerated implementation of these therapies, whereas low- or moderate-risk individuals need not be on all four pillars of therapies.[48,49] This method of implementation has drawn parallels with the pillars of guideline-directed medical therapy for heart failure. Indeed, treating one condition can delay or prevent the onset of the other. Early referral to a nephrologist should be considered as part of a multidisciplinary team approach, particularly for high-risk individuals with severely increased albuminuria (UACR of ≥30 mg/mmol) regardless of the level of their eGFR, as they may gain greater absolute benefits from early combination therapy.

Patients with advanced CKD who have been commenced on SGLT-2 inhibitors, nonsteroidal MRAs and/or GLP-1 receptor agonists should continue these medications to maintain their kidney protective benefits until they reach dialysis.

Beyond initiating medication, educating patients regarding appropriate use of medications is of utmost importance. Sick day medication guidance should be provided (such as the Sick Day Action Plan from Kidney Health Australia, available online at https://assets.kidney.org.au/resources/KHA-How-To-Sick-Day-Action-Plan-FINAL.pdf), so that patients with diabetes are aware to temporarily withhold SGLT-2 inhibitors when unwell or not eating or drinking normally.[50]

Lastly, addressing lifestyle factors, such as smoking cessation, promoting weight loss and dietary salt reduction, remains the foundation of holistic patient-centred care. Implementing these strategies alongside medications with targeted education can give patients a greater sense of agency.

Conclusion

DKD is a common and clinically important complication of type 2 diabetes that portends increased dual risk of cardiovascular disease and kidney failure. Since the advent of RAAS blockade, the landscape of DKD treatment has changed dramatically with additional therapies: SGLT-2 inhibitors, nonsteroidal MRAs and GLP-1 receptor agonists. Together, these form four pillars of current DKD management in conjunction with comprehensive lifestyle modification. These therapies offer the opportunity to address the multiple distinct pathways of injury that underlie the development and progression of DKD. Primary care plays a pivotal role in ensuring early detection, stratifying risk of future cardiorenal complications, initiating treatments to match this risk and preventing serious long-term complications in patients with DKD. MT

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A list of references is included in the online version of this article (https://www.medicinetoday.com.au/mt/2025/november/supplements/focus-on-chronic-kidney-disease.

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Diabetic kidney disease

A new era in therapeutic management

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Diabetes is associated with chronic kidney disease (CKD) and is the major cause of renal failure in Australia. New therapies are emerging to reduce the adverse cardiovascular outcomes and progression of CKD in type 2 diabetes. These therapies, including renin–angiotensin system inhibitors, sodium-glucose cotransporter-2 inhibitors, the nonsteroidal mineralocorticoid receptor antagonist finerenone and glucagon-like peptide-1 receptor agonists, should be considered for all patients with type 2 diabetes for renoprotection.

In 2021, about one in 20 individuals in Australia had diagnosed diabetes mellitus.[1] Diabetes contributes significantly to the burden of chronic kidney disease (CKD) and is the leading cause of kidney failure.[2] It is also a major risk factor for major atherosclerotic cardiovascular events (MACE) and death, which are significantly amplified in the presence of CKD. Novel therapies are now available to manage diabetic kidney disease (DKD) which slow the progression of CKD and reduce MACE. This article discusses current therapies for managing CKD in patients with type 2 diabetes and when they should be prescribed.

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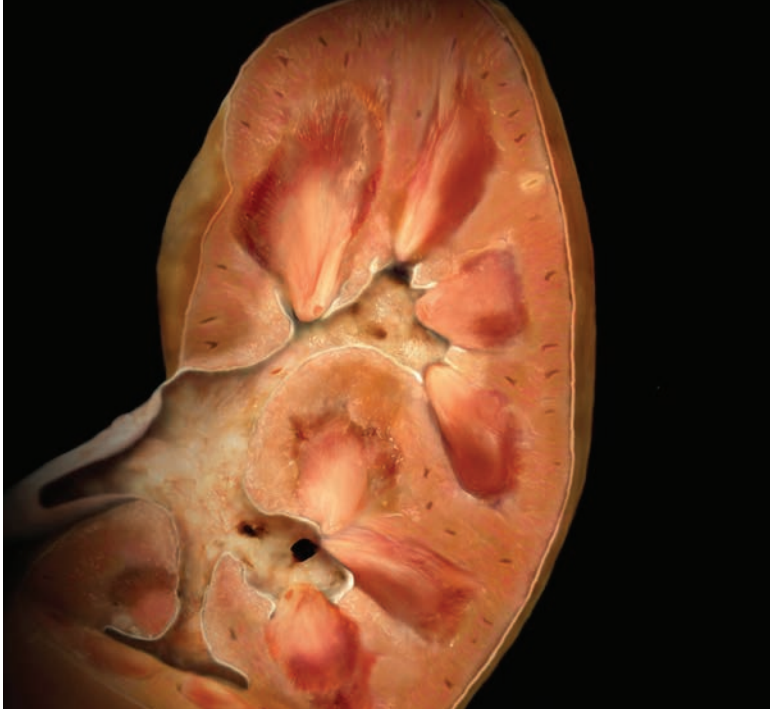

KEY POINTS

- Directed therapies for diabetic kidney disease (DKD) can lower chronic kidney disease progression and cardiovascular events.
- All patients with DKD and proteinuria should be on an ACE inhibitor or angiotensin receptor blockers (ARB) at the maximally tolerated dose.
- Sodium-glucose cotransporter-2 (SGLT-2) inhibitors should be considered for all patients with type 2 diabetes requiring glycaemic control or to further reduce proteinuria after ACE inhibitor or ARB therapy.
- Finerenone should be prescribed if there is persistent proteinuria despite use of an ACE inhibitor or ARB and SGLT-2 inhibitor therapy.
- Glucagon-like peptide-1 receptor agonists should be considered after SGLT-2 inhibitor therapy given its cardiovascular benefits and role in slowing kidney function decline
- If there is intolerability of treatment, patients should be referred for specialist input.

ACE inhibitors and ARBs

ACE inhibitors and angiotensin receptor blockers (ARBs) are the cornerstone of treatment for DKD. They have a profound effect on lowering proteinuria by lowering systemic blood pressure while having a direct action on the kidney microcirculation and reducing glomerular hypertension and hyperfiltration. This has a marked effect on lowering the rate of CKD progression, demonstrated over 20 years ago in the RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) trial and IDNT (Irbesartan Diabetic Nephropathy Trial).[3,4]

All patients with diabetes (including those with type 1 diabetes) and hypertension or albuminuria should be considered for ACE inhibitor or ARB therapy. In patients who are normotensive, an ACE inhibitor or ARB should be started at a low dose and progressively uptitrated to avoid precipitating symptomatic hypotension. There is a direct correlation with dosing and the degree of proteinuria reduction. All patients should be on

1. BENEFITS OF SGLT-2 INHIBITORS IN PATIENTS WITH TYPE 2 DIABETES AND KIDNEY DISEASE

- Decreased rates of progression of chronic kidney disease
- Decreased rates of hospitalisations from heart failure
- Reduced cardiovascular death when cardiovascular disease is established
- Reduced cardiovascular outcomes
- Decreased rates of acute kidney injury
- Improved blood pressure control
- Improved management of hyperkalaemia

the maximally tolerated dose. These medications act in a class effect with no single ACE inhibitor or ARB being more efficacious.

The dose should be titrated at four-week intervals.[5] This is the typical time to see the peak effect on blood pressure and elevations in serum creatinine and potassium levels. A rise in creatinine level up to 30% from baseline is an anticipated finding with drug initiation or dose modification and is due to the reduction in intraglomerular pressure; however, this does not warrant withdrawal of the medication. Studies have shown that this initial drop in glomerular filtration rate (GFR) stabilises within two months and leads to long-term preservation of kidney function.[5]

Patients should be monitored for the presence of hyperkalaemia. A serum potassium level above 5.5 mmol/L should prompt a clinical review to consider the possibility of concurrent culprit medications or excessive dietary potassium intake, but not necessarily precipitate a reduction or cessation of the renin–angiotensin–aldosterone system blocker. The use of potassium binders should be considered if the serum potassium is above 6 mmol/l to facilitate ongoing treatment. ACE inhibitors and ARBs are contraindicated in pregnancy; therefore, women of reproductive age who are taking these medications should be advised to use appropriate contraception. These drugs should be discontinued in patients planning pregnancy or if an unexpected pregnancy is confirmed.

SGLT-2 inhibitors

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are a class of drug that promotes glucose excretion in the urine by inhibiting its reabsorption in the proximal tubule. Initially designed to improve glycaemic control, they have revolutionised treatment of CKD and have conclusively been shown to reduce the rate of CKD progression and MACE.[6] This benefit is irrespective of weight loss, blood pressure reduction or improvement in glycaemic index associated with these drugs.

The nephroprotective benefits of SGLT-2 inhibitors are attributed to multiple factors but, primarily, to a reduction in intraglomerular hypertension. Ordinarily, sodium is reabsorbed alongside glucose in the proximal tubule. Inhibiting the reabsorption of glucose leads to sodium wasting. This increased sodium excretion is detected by the macula densa, which acts to minimise further salt wasting by causing afferent arteriole vasoconstriction. This has the effect of lowering intraglomerular pressures and reducing single nephron GFR and subsequent proteinuria. Additional mechanisms acting outside of the kidney account for the impressive cardiovascular benefits associated with these drugs.

SGLT-2 inhibitors offer numerous benefits to patients with type 2 diabetes and kidney disease (Box 1). They should be prescribed for all eligible patients with type 2 diabetes with or without metformin, given the significant cardiovascular benefits associated with their use.[7,8] PBS indications have enabled its prescription either as an add-on for glycaemic control or as initial therapy in patients considered at high cardiovascular risk. Prescribers should refer to The Australian Absolute Cardiovascular Disease Risk Calculator (see: www.cvdcheck.org.au) for assisting in establishing risk.

The available SGLT-2 inhibitors in Australia are empagliflozin and dapagliflozin. A third SGLT-2 inhibitor, ertugliflozin, was deleted from the Australian market in mid-2023. Both empagliflozin and dapagliflozin are indicated for proteinuric CKD, independent of diabetic status.

The benefits of these drugs are likely class related. However, a key consideration in prescription is differing PBS criteria. Both can be commenced with an initiating estimated GFR (eGFR) of more than 25 mL/min/1.73 m^2 and an accompanying urine albumin to creatinine ratio between 22.6 and 565 mg/mmol. However, from 1 November 2025, empagliflozin's PBS listing has been expanded for use in patients with an eGFR of 20 to 90 mL/min/1.73 m^2. For patients with an eGFR of 45 to 90 mL/min/1.73 m^2, PBS subsidy still requires a urine albumin to creatinine ratio of at least 22.6 mg/mmol, but for those with an eGFR of 20 to less than 45 mL/min/1.73 m^2, empagliflozin is PBS subsidised irrespective of proteinuria. This represents empagliflozin's broader renal indication.

Both empagliflozin and dapagliflozin have proven cardiovascular benefit in heart failure with preserved ejection (HFpEF, with left ventricular ejection fraction >40%) and heart failure with reduced ejection fraction (HFrEF with left ventricular ejection fraction <40%).[9-12] Both are listed on the PBS for these indications.

Once commenced for CKD, the SGLT-2 inhibitor should be continued until kidney replacement therapy (i.e. dialysis or transplantation) occurs. SGLT-2 inhibitors are largely well tolerated. Notable adverse effects include a higher association with genital mycotic infections and urinary tract infections. These can be managed with education regarding good hygiene practices and the use of topical antifungal agents. Initial studies suggested a higher incidence of lower limb amputation; however, this has not been a consistent finding within a meta-analysis.[13] SGLT-2 inhibitor monotherapy is associated with a low risk of hypoglycaemia, as glycosuria is minimised when serum glucose levels normalise. However, the risk increases with the addition of therapies, notably sulfonylureas and insulin, which are associated with hypoglycaemia. If appropriately considering an SGLT-2 inhibitor for cardiovascular or renal protection for a patient with well-controlled blood glucose levels, a dose reduction of their existing therapies should be considered.

All patients prescribed an SGLT-2

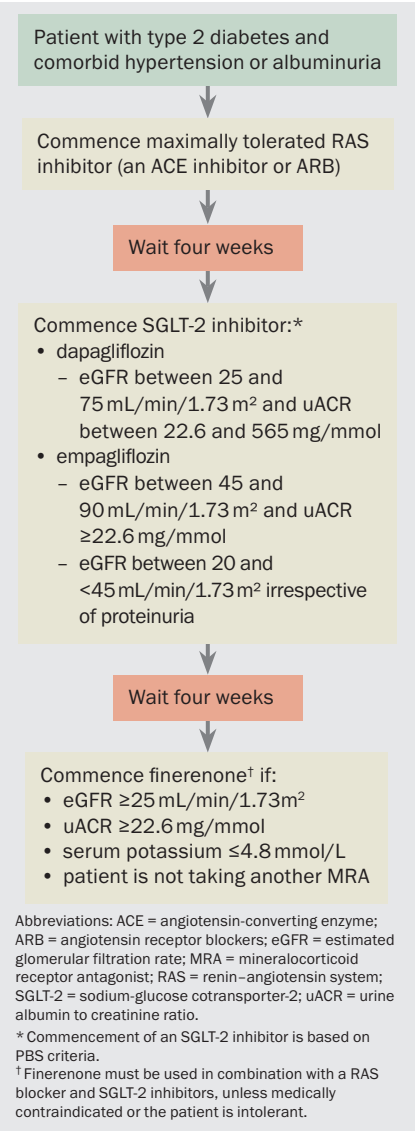

Figure. An approach to renoprotective treatment for patients with type 2 diabetes and chronic kidney disease.

inhibitor should be cautioned on the possibility of euglycaemic ketoacidosis, a rare complication that may occur if patients are fasting or have an intercurrent illness. The drug should be withheld for at least two days before surgery or during periods of acute illness. For patients taking concurrent diuretics, it may be appropriate to reduce the dose of these medications given the diuretic effect associated with SGLT-2 inhibitors and the risk of precipitating hypovolaemia.

Given the safety of these drugs has not been established for type 1 diabetes and their association with euglycaemic ketoacidosis, they should be avoided in this population.

An increase in serum creatinine level of up to 30% is an expected finding and should not lead to drug withdrawal.[5] This phenomenon is a result of reducing intraglomerular hypertension and is reversible if the medication is ceased.

Given the significant benefits associated with these medications, adverse side effects that lead to drug discontinuation warrant the consideration of a specialist consultation before withdrawal of treatment.

2. DOSING OF FINERENONE

eGFR 25 to <60 mL/min/1.73 m²
- Start at 10 mg once daily
- Consider dose escalation to 20 mg daily after one month if the serum potassium level is ≤4.8 mmol/L and the eGFR is stable

eGFR ≥60 mL/min/1.73 m²
- Start at 20 mg daily

3. MANAGING HYPERKALAEMIA ASSOCIATED WITH FINERENONE USE[5]

Serum potassium level ≤4.8 mmol/L
- Initiate finerenone
  - 10 mg daily if eGFR between 25 and <60 mL/min/1.73 m²
  - 20 mg daily if eGFR ≥60 mL/min/1.73 m²
- Monitor serum potassium one month after initiation and then every four months
- Increase dose to 20 mg daily if the patient is on 10 mg daily
- Restart 10 mg daily for patients withheld from treatment because of hyperkalaemia and serum potassium level ≤5.0 mmol/L

Serum potassium level 4.9 to 5.5 mmol/L
- Continue finerenone 10 or 20 mg daily
- Monitor serum potassium level every four months

Serum potassium level >5.5 mmol/L
- Withhold finerenone
- Consider adjustments to diet or concomitant medications to mitigate hyperkalaemia
- Recheck serum potassium level
- Consider reinitiation if potassium level falls to ≤5.0 mmol/L

Nonsteroidal MRAs

Finerenone, an oral nonsteroidal mineralocorticoid receptor antagonist (MRA), is indicated for patients with DKD. Unlike spironolactone, which is a steroidal MRA, finerenone more selectively inhibits the mineralocorticoid receptor and has limited antiandrogenic and oestrogenic effects. Overactivation of the mineralocorticoid receptor has been implicated in the progression of CKD and cardiovascular disease through the promotion of inflammation and fibrosis. Downregulation of the mineralocorticoid receptor has also been shown to lower proteinuria, a strong predictor for progression of CKD.

Finerenone is the most recently PBS-listed therapy for DKD that reduces progression of CKD and cardiovascular events.[14] Notably, this landmark study did not require patients to be prescribed an SGLT-2 inhibitor, now considered standard of care for patients with type 2 diabetes and DKD. However, subsequent studies have demonstrated that coprescription of finererone with empagliflozin lead to a greater reduction in proteinuria.[15]

Notable PBS criteria for prescribing finerenone include concurrent therapy with a renin-angiotensin system (RAS) inhibitor (an ACE inhibitor or ARB) for at least four weeks, followed by combination therapy with an SGLT-2 inhibitor (unless contraindicated or the patient is intolerant) and the avoidance of coadministration of other MRAs such as spironolactone. If the urine albumin to creatinine ratio remains above 22.6 mg/mmol despite these therapies, finerenone can be prescribed. Finerenone should not be commenced in patients with a serum potassium level above 5.0 mmol/L and should be avoided in women who are pregnant or planning pregnancy as well as in those who are breastfeeding due to a lack of safety data. An approach to renoprotective treatment for patients with type 2 diabetes and CKD, including prescription requirements for finerenone, are outlined in the Figure.[5]

The dosing of finerenone is dependent on renal function (Box 2). Patients with an eGFR between 25 and less than 60 mL/min/1.73 m² should be started on 10 mg finerenone daily and the dose uptitrated. For those with an eGFR

4. PRACTICE POINTS

- Monitor patient closely for hyperkalaemia with use of an ACE inhibitor or angiotensin receptor blocker (ARB) and finerenone. The potassium binder patiromer can be used to manage hyperkalaemia and allow drug continuation.
- Withhold sodium-glucose cotransporter-2 (SGLT-2) inhibitors for at least two days if fasting or during periods of acute illness.
- Continue SGLT-2 inhibitors until the initiation of renal replacement therapy (dialysis or renal transplant).
- Anticipate a rise in creatinine level up to 25% with use of ACE inhibitor or ARB therapy, SGLT-2 inhibitors and finerenone.

60 mL/min/1.73 m^2 or higher, treatment should start at 20 mg daily. Finerenone is contraindicated in people with an eGFR below 25 mL/min/1.73 m^2.

Following commencement, patients should be monitored for hyperkalaemia (Box 3). This should initially occur at one month and subsequently every four months. A dose reduction is required for patients with serum potassium levels between 4.9 and 5.5 mmol/L and it should be withheld for those with a potassium level above 5.5 mmol/L. Similar to other medications known to be protective in CKD, finerenone can cause a slight elevation in the serum creatinine level on commencement. A rise in the serum creatinine level above 25% should lead to consultation with a nephrologist.

The most common side effect associated with finerenone is hyperkalaemia. Most incidents of hyperkalaemia can be managed with treatment pauses of 72 hours, given its short drug half-life, or the use of oral potassium binders. In particular, patiromer is PBS listed for patients with stage 3 and 4 CKD with confirmed hyperkalaemia (serum potassium level above 6 mmol/L). See PBS website for full details (www.pbs.gov.au). The use of potassium binders may facilitate the use of finerenone in selected patients. Unlike other MRAs, finerenone does not significantly impact blood pressure and, given its nonsteroidal nature, is not associated with gynaecomastia.

GLP-1 receptor agonists

Glucagon-like peptide-1 (GLP-1) receptor agonists are used to improve glycaemic control in people with type 2 diabetes. GLP-1 is a hormone secreted from the intestine after the ingestion of glucose. It acts on the pancreas to stimulate the glucose-dependent release of insulin and inhibit glucagon release. This has the net effect of improving glycaemic index. It additionally acts to delay gastric emptying, reducing appetite and leading to weight loss.

The role of GLP-1 receptor agonists in the management of type 2 diabetes has been established, with compelling evidence showing marked cardiovascular benefits associated with treatment. A 2021 systemic review of eight trials demonstrated that GLP-1 receptor agonists use was associated with a reduction in cardiovascular death, stroke, myocardial infarction, hospitalisation for heart failure and all-cause mortality in patients with type 2 diabetes.[16] Although benefits were seen in DKD, the trials were not selected to assess benefits in CKD.

However, the recent Evaluate Renal Function with Semaglutide Once Weekly (FLOW) study primarily assessed for a kidney outcome and demonstrated a reduction in the progression of CKD and MACE. The study included patients with type 2 diabetes who had an eGFR between 50 and 75 mL/min/1.73 m^2 and urine albumin to creatinine ratio above 33 and below 565 mg/mmol, or an eGFR between 25 and 50 mL/min/1.73 m^2 and urine albumin to creatinine ratio above 11.3 and below 565 mg/mmol. Overwhelming efficacy led to the trial being stopped early.[17]

The major adverse effects associated with GLP-1 receptor agonists use are nausea and vomiting. These can be minimised by starting on the lowest dose with progressive uptitration as required for improved glycaemic control.

The TGA has approved semaglutide for reducing the risk of kidney function decline in adults with type 2 diabetes and chronic kidney disease. However, the PBS has not yet listed it for this specific use, meaning it is not subsidised for CKD treatment. At present, the PBS indication for a GLP-1 receptor agonist (dulaglutide and semaglutide) is restricted to a glycaemic control indication. Notably, the current indication excludes patients that are receiving concomitant PBS-subsidised SGLT-2 inhibitor. This is unfortunate given the clear cardiovascular and renal benefits associated with each treatment.

Diabetic kidney disease in 2025

In the past decade, treatment options and accessibility of guideline-directed medical therapy (GDMT) for DKD has expanded rapidly. These agents act through distinct and complementary pathways, making early and layered initiation of GDMT a priority for all patients. We urge clinicians to avoid therapeutic inertia and consider prompt initiation of GDMT, as the impact on renal and cardiovascular outcomes is substantial. Although current guidelines suggest a one-month interval between prescriptions, concurrent initiation is likely to become routine practice.

Conclusion

DKD is the leading cause of renal failure in Australia and a significant risk factor for cardiovascular disease. Until recent years, treatment options for managing this disease were limited. Current therapies represent an exciting opportunity to not only minimise the rate of CKD progression, but also reduce cardiovascular events. All patients with diabetes should be screened for DKD and, where possible, should be considered candidates for therapy. Specialist input should always be sought if there are any concerns with drug tolerability. Practice points for managing DKD are summarised in Box 4.

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A list of references is included in the online version of this article (https://www.medicinetoday.com.au/mt/2025/november/supplements/focus-on-chronic-kidney-disease).

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