Reducing cardiovascular risk in people with chronic kidney disease

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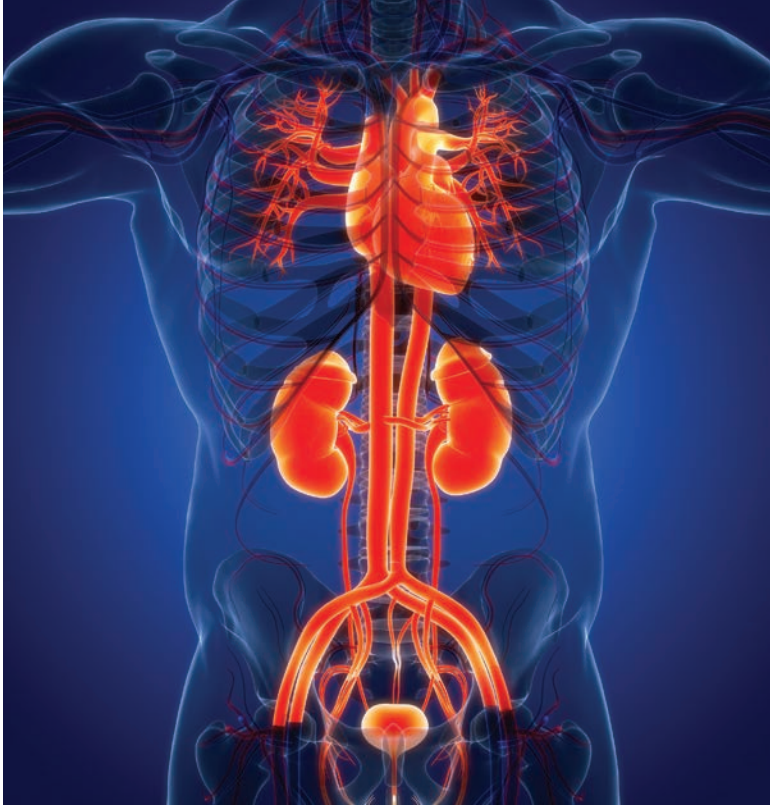

People with chronic kidney disease are at an increased risk of cardiovascular disease. The early recognition of this risk and implementation of effective risk-lowering strategies can be initiated in primary care using a multidisciplinary approach.

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]

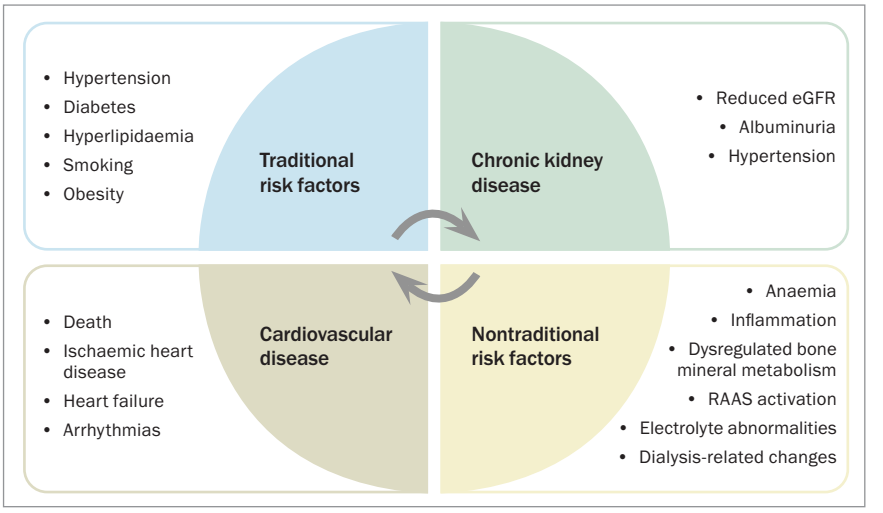


Figure 1. Association between CKD and the risk of developing cardiovascular disease, including shared traditional risk factors and additional nontraditional risk factors specific to CKD.
Abbreviations: CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; RAAS = renin–angiotensin–aldosterone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

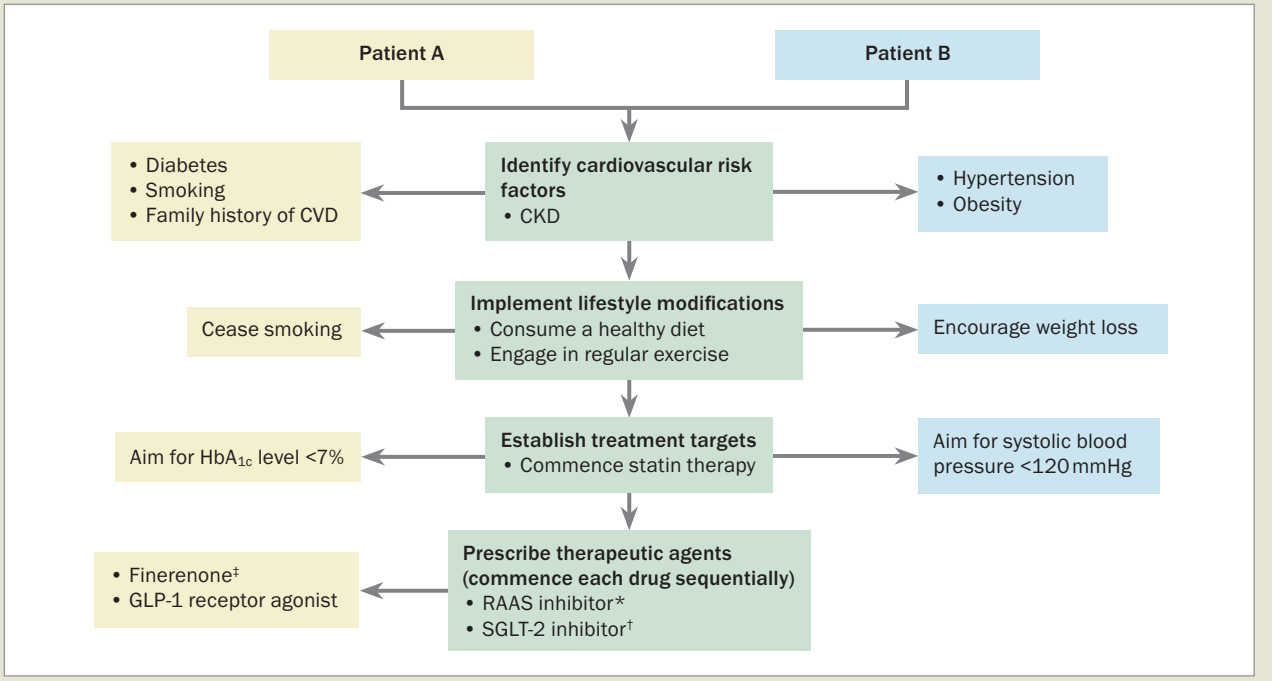
Case presentations

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

References

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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