Cardiovascular protection in chronic kidney disease

Considerations for pre- and post-transplant care

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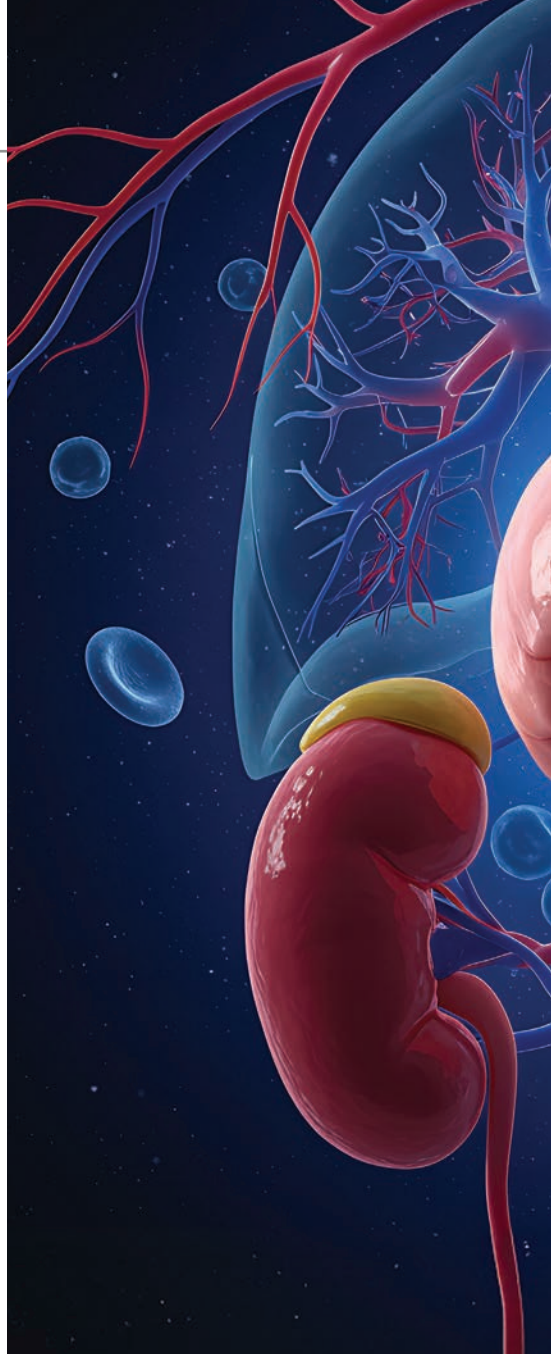
Patients who receive immunosuppression after kidney transplantation or to minimise kidney injury from other systemic immune disorders are at high risk of cardiovascular disease. GPs are likely to care for an increasing number of these patients, whose cardiovascular risk profile needs to be carefully managed.



Patients with chronic kidney disease (CKD) experience a high burden of cardiovascular disease (CVD), such that major adverse cardiovascular events (MACE) constitute the leading cause of mortality in this group.[1] Although this can be partly explained by traditional risk factors, such as diabetes, hypertension and dyslipidaemia, there are nontraditional risk factors, such as anaemia, metabolic bone disease and accumulating uraemic toxins, that are highly relevant to patients with CKD and that further amplify this risk. Both reduced kidney function, manifested as a low glomerular filtration rate (GFR), and albuminuria are independently associated with cardiovascular mortality, and this risk increases with disease progression.[2,3]

Traditional risk factor modification with lipid-lowering therapy, insulin-sensitising agents and antihypertensives provide modest (or no) cardiovascular benefit in patients with CKD,[4-6] although these are valuable in the general population (Table 1).[7-14] Furthermore, patients with CKD have been excluded from more than 80% of clinical studies;[15-18] although this trend has reversed somewhat with the advent of sodium-glucose cotransporter-2 (SGLT-2) inhibitors, nonsteroidal mineralocorticoid receptor antagonists (MRAs) and glucagon-like peptide-1 (GLP-1) receptor agonists.[19-21]

Due to the bidirectional relationship between the heart and kidneys, dysfunction of one organ can contribute to pathological changes in the other – a phenomenon known as cardiorenal syndrome.[22] A burgeoning body of evidence links CKD with CVD, and many online cardiovascular risk prediction tools now incorporate parameters relevant to CKD stage (Table 2).

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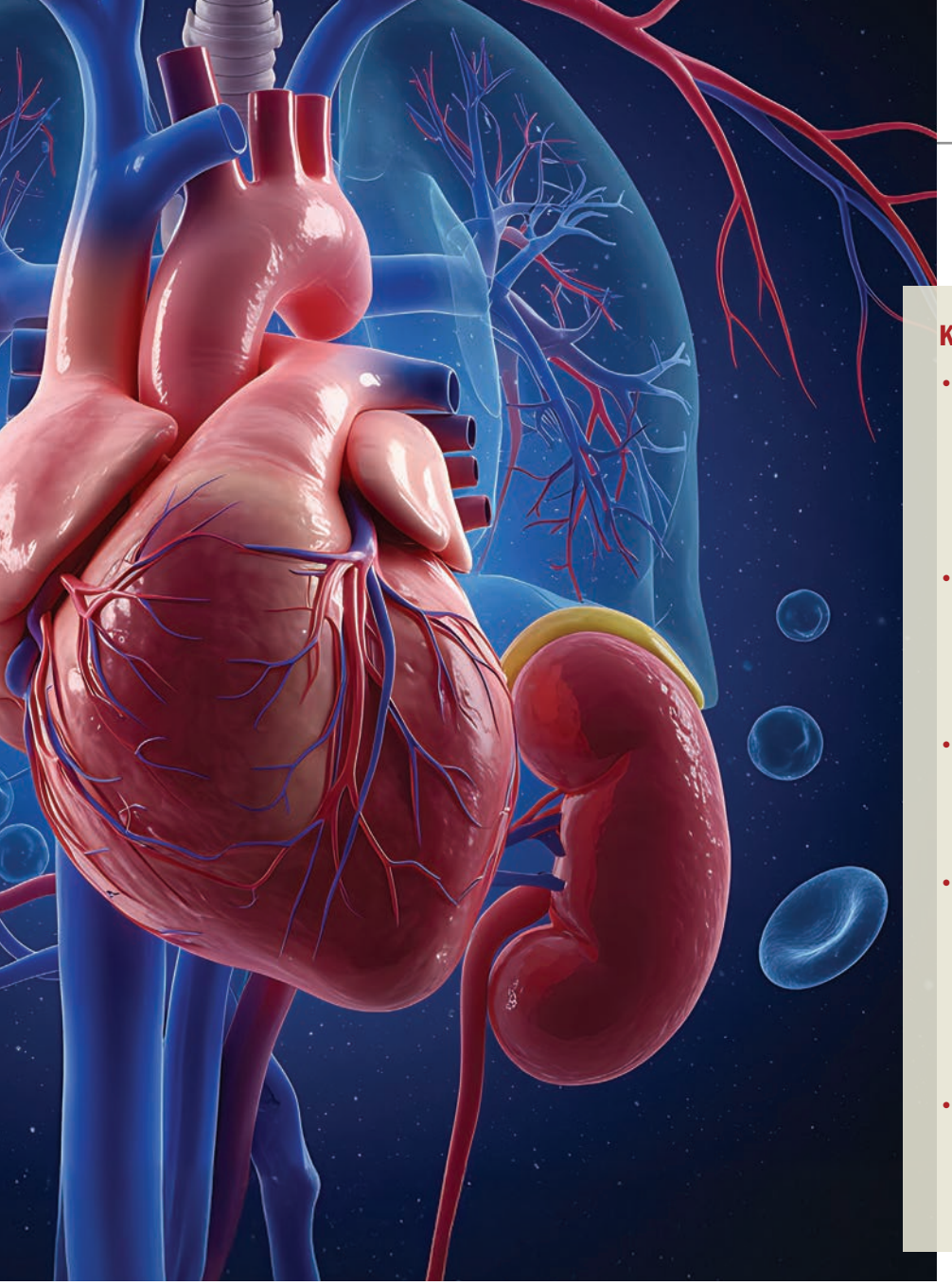

KEY POINTS

- Chronic kidney disease (CKD) and kidney transplantation place patients at the highest risk of cardiovascular disease and major adverse cardiovascular events, independent of traditional risk factors. Immunosuppression compounds this risk by promoting metabolic changes.
- Standard cardiovascular risk factors, such as hypertension, dyslipidaemia and diabetes, should be rigorously managed in patients with CKD or immunosuppression through lifestyle modification and appropriate pharmacological treatment.
- CKD-associated cardiovascular disease is typically driven by medial arterial calcification and left ventricular remodelling, which are poorly captured by standard diagnostic tools.
- The emergence of newer pharmacological agents, such as sodium-glucose cotransporter-2 inhibitors, mineralocorticoid receptor antagonists and glucagon-like peptide-1 receptor agonists, marks a shift towards treatment options that may modify both kidney and cardiovascular disease progression.
- Co-management frameworks that involve cardiology and nephrology can minimise critical gaps in management to address the complex pathophysiology and treatment needs of patients with CKD.

The impact of CKD on CVD is further compounded by the rising incidence of type 2 diabetes, which is now the third most common chronic disease, affecting 1.5 million Australians and contributing to more than one million hospitalisations each year.[23,24] Optimal medical management of diabetes does not provide normal metabolic control, further affecting cardiac and renal function. Diabetes is now the most common cause of CKD and is a comorbidity in more than half of people starting renal replacement therapy (dialysis).[25] Despite advances in surveillance and risk factor modification, CVD is the most prevalent cause of morbidity and mortality in people with diabetes and concomitant CKD.[26]

The combination of diabetes and CKD (so-called cardiovascular–kidney–metabolic health) leads to multimorbidity, further accelerates the burden of CVD and multiplies the risk of MACE (Table 3).[27-29] People with multimorbidity use more health services, require increased contact with primary and tertiary health care, experience more complex hospitalisations and have poorer outcomes than those with single conditions. An improved recognition of poor cardiovascular–kidney–metabolic health and its intersection with socioeconomic disadvantage, including understanding its prevalence and proactive management strategies, is a centrepiece of the American Heart Association and increasingly recognised by Diabetes Australia and Kidney Health Australia.[30-32] The American Heart Association has provided a 10-point recommendation that encompasses risk stratification (Table 4), screening and treatment approaches to facilitate early treatment and interdisciplinary care models.[30]

Chronic kidney disease-specific considerations when investigating cardiovascular disease

There are limited Australian data on differences in coronary artery disease burden in patients with CKD compared with the general population, with international studies estimating a relative risk of five- to 20-fold and a contribution to nearly 50%

TABLE 1. TRADITIONAL AGENTS USED IN CARDIOVASCULAR RISK MODIFICATION

Features	Antihypertensives	Statins	Antiplatelet agents	Glycaemic control
Clinical targets	• Individualised BP target depends on age, aetiology of CKD and comorbidities (typically SBP <120 to 140 mmHg and DBP <75 to 90 mmHg)	• Very high CV risk: LDL-C <1.4 mmol/L – includes patients with ASCVD, diabetes with microvascular complications or severe CKD (eGFR <30 mL/min/1.73 m^2)[7] • High CV risk: LDL-C <1.8 mmol/L – includes patients with diabetes (without microvascular complications) of duration ≥10 years or an additional risk factor, or moderate CKD (eGFR 30–59 mL/min/1.73 m^2)[7] • Moderate CV risk: LDL-C <2.6 mmol/L – includes patients with diabetes of duration <10 years without other risk factors[7]	• Secondary prevention of ischaemic CV events	• Individualised HbA_{1c} target (ranging from <6.5% to <8%), depending on age, comorbidities, hypoglycaemic risk and awareness, severity of CKD, and presence of macrovascular complications
Recommendations for use in patients with CKD	• Beyond RAAS blockade, no additional antihypertensive agents are specifically recommended for use in patients with CKD because of superior efficacy or benefits	• Individuals with stage 1–4 CKD (eGFR >15 mL/min/1.73 m^2) with absolute CV risk of ≥10% should receive statin therapy (with or without ezetimibe) to reduce the risk of CV events and death[8] • ATSI or Maori individuals with CKD and absolute CV risk of ≥5% should receive statin therapy (with or without ezetimibe) to prevent CV events and death[8] • Adults aged ≥50 years with eGFR <60 mL/min/1.73 m^2 but not treated with chronic dialysis or kidney transplantation should receive statin therapy (with or without ezetimibe)[9] • Starting statin therapy is not recommended in patients with kidney failure requiring dialysis, due to uncertain clinical benefit, but can be considered in special circumstances (e.g. very high LDL-C, greater life expectancy) • Statins are recommended for adult kidney transplant recipients[9]	• Recommended for prevention of recurrent ischaemic CV events (i.e. secondary prevention) in individuals with CKD and established ischaemic CV disease[10]	• Individuals with stage 1–3 CKD and diabetes should receive metformin as first-line treatment[11] • Metformin should be dose-reduced with eGFR <45 mL/min/1.73 m^2 and stopped when eGFR <30 mL/min/1.73 m^2 • Sulfonylureas should be used cautiously in patients with severe CKD due to hypoglycaemic risk • DPP-4 inhibitors are safe to use in patients with severe CKD but confer modest antihyperglycaemic benefit
Published evidence for efficacy in patients with CKD	• RAAS blockade (see Table 5)	• Statins reduce all-cause mortality, CV mortality and CV events in individuals with CKD[12,13] • Benefit of statins in individuals receiving dialysis is unclear[12]	• May reduce the risk of myocardial infarction but does not reduce CV or all-cause mortality in individuals with CKD[14]	• No high-quality studies evaluating efficacy of metformin in patients with CKD • Recommendation for use in CKD extrapolated from studies in broader population with type 2 diabetes
Key adverse effects	• Depends on antihypertensive agent used	• Myotoxicity • Liver function derangement	• May increase the risk of major bleeding in individuals with CKD[14]	• Metformin: gastrointestinal intolerances, lactic acidosis • Sulfonylurea: hypoglycaemia

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; ATSI = Aboriginal and/or Torres Strait Islander; BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; DBP = diastolic blood pressure; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; HbA_{1c} = glycated haemoglobin; LDL-C = low-density lipoprotein cholesterol; RAAS = renin–angiotensin–aldosterone system; SBP = systolic blood pressure.

of deaths in those receiving dialysis.[33] Even patients with CKD who had initially normal coronary angiogram results showed an increased risk of acute myocardial infarction,[34] supporting the view of accelerated disease processes and poor outcomes.

The likely molecular basis for this is medial thickening and calcification (rather than just lesions limited to the intimal layer), in addition to the accumulation of uraemic toxins (even in early-stage CKD) that promote inflammation and oxidative stress. Left ventricular hypertrophy is also prevalent due to increased afterload (systolic hypertension), preload (volume expansion) and systemic inflammatory changes that result in fibrosis and cardiac remodelling, similarly portending a poor prognosis.[35,36] Patients with CKD are more likely to present with a cardiac event driven by small vessel disease that presents as unexplained dyspnoea, fatigue or arrhythmia, rather than classic ST-segment electrocardiographic changes.

Echocardiography is a useful initial step to investigate the (potential) burden of left ventricular hypertrophy, subsequent systolic or diastolic dysfunction and risk of sudden death. However, there is a lack of clear guidelines for echocardiographic examination in patients with CKD. Although the Acute Dialysis Quality Initiative working group provided a new classification, it is most relevant to end-stage kidney disease.[37] The clinical vignettes in the Box illustrate how CVD can remain hidden in patients with CKD, as well as the limitations related to noninvasive testing for CVD in these patients.

Evaluation of left atrium function

The left atrium (LA) is increasingly recognised as a potential marker of cardiovascular disease and adverse outcomes, and both LA size and strain are relevant measurements.[38] Although there is no definitive single marker of LA function, strain (which measures myocardial deformation) and strain rate can be measured using:

- tissue Doppler imaging – where

TABLE 2. CARDIOVASCULAR RISK PREDICTION TOOLS THAT INCORPORATE CKD

Risk calculator	Inclusion of CKD parameters
Australian CVD risk calculator (https://www.cvdcheck.org.au/calculator)	• Considers that a high risk of CVD is conferred by moderate to severe CKD, defined as: – sustained eGFR <45 mL/min/1.73 m^2 – elevated UACR >25 mg/mmol for men and >35 mg/mmol for women
US Pooled Cohort Equation with CKD Patch tool (https://ckdpcrisk.org/ckdpatchpce)	• Provides a broader predictive determination of overall and specific cardiovascular abnormalities by incorporating incremental kidney disease measures: – eGFR – UACR • For example: – a 65-year-old Caucasian woman with borderline untreated hypertension (SBP 140 mmHg), eGFR of 60 mL/min/1.73 m^2, moderately increased albuminuria (UACR 10.1 mg/mmol) and borderline hypercholesterolaemia (cholesterol 5.7 mmol/L) has a 9.6% chance of developing atherosclerotic CVD in the next 10 years – with progression of CKD (eGFR 40 mL/min/1.73 m^2, UACR 56 mg/mmol), this risk increases to 14.5% • These factors are worsened by concomitant diabetes and smoking

Abbreviations: CKD = chronic kidney disease; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; SBP = systolic blood pressure; UACR = urine albumin-to-creatinine ratio.

TABLE 3. RISK OF CARDIOVASCULAR EVENTS IN PEOPLE WITH DIABETES AND CHRONIC KIDNEY DISEASE

Trial	Hazard ratio (95% CI)
***Action to Control Cardiovascular Risk in Diabetes (ACCORD)*[27]**	
• Risk of cardiovascular events in people with diabetes and CKD compared with diabetes alone	2.35 (1.81–3.04)
• All-cause mortality in people with diabetes and CKD compared with diabetes alone	2.36 (1.75–3.13)
***So et al. 2006*[29]**	
• All-cause mortality in people with stage 3 CKD (eGFR 30–59 mL/min/1.73 m^2) and diabetes compared with people with stage 1 CKD (eGFR ≥90 mL/min/1.73 m^2) and diabetes	2.34 (1.16–4.70)
• All-cause mortality in people with stage 4 CKD (eGFR 15–29 mL/min/1.73 m^2) and diabetes compared with people with stage 1 CKD (eGFR ≥90 mL/min/1.73 m^2) and diabetes	9.82 (4.53–21.0)
***Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation Post-Trial Observational Study (ADVANCE-ON)*[28]**	
• Risk of primary outcome (cardiorenal events and mortality) in people with diabetes with an annual substantial decrease in eGFR compared with those with a stable eGFR	1.30 (1.17–1.43)

Abbreviations: CI = confidence interval; CKD = chronic kidney disease; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate.

TABLE 4. DEFINITION AND MANAGEMENT OF CARDIOVASCULAR–KIDNEY–METABOLIC HEALTH STAGES*

Stage	Definition and demographics	Proposed management
Stage 0 – no risk factors	• Normal BMI • Normoglycaemia • Normotension • No proteinuria • No dyslipidaemia • Most often seen in young adults	• Focus on maintenance of cardiovascular health with annual screening
Stage 1 – increased adiposity	• Overweight or obese (BMI ≥25 kg/m^2)† • Waist circumference ≥88 cm in women and ≥102 cm in men† • Fasting BGL ≥5.6–6.9 mmol/L or HbA_{1c} 5.7–6.4% • More common with increasing age and in women with history of gestational diabetes	• Management of weight gain with lifestyle modification: – plant-based and Mediterranean diets – reduced sugar-sweetened beverage intake • Consider use of metformin
Stage 2 – CKD and metabolic syndrome	• Metabolic syndrome (≥3 of the following): – waist circumference ≥88 cm in women and ≥102 cm in men – HDL cholesterol ≤1.3 mmol/L in men and ≤1.0 mmol/L in women – triglycerides ≥1.7 mmol/L – SBP ≥130 mmHg and DBP ≥80 mmHg, with or without use of antihypertensives – fasting BGL ≥5.6 mmol/L	• Lifestyle modifications • Pharmacological intervention: – exploring weight loss options (including bariatric surgery) – statins, with ezetimibe for high-risk individuals, and fibrates if triglycerides ≥5.6 mmol/L – BP control following established guidelines (<130/80 mmHg) – metformin – GLP-1 receptor agonist (not PBS listed for obesity alone in Australia) • If CKD or diabetes present: – prioritise ACE inhibitor or ARB use – consider SGLT-2 inhibitor – consider finerenone
Stage 3 – CKD and metabolic syndrome and subclinical CVD	• Subclinical CVD – minor coronary artery disease (including calcification) diagnosed by CT angiography – HF diagnosed by elevated cardiac biomarkers (N-terminal pro-B-type natriuretic peptide ≥14.8 pmol/L, troponin T ≥0.022 µg/L in men and ≥0.014 µg/L in women, troponin I ≥0.012 µg/L in men and ≥0.01 µg/L in women), or echocardiography • Adiposity or other metabolic risk factors • Risk equivalents include stage 4–5 CKD	• Same as for Stages 0–2 • If coronary artery calcium score >100, consider aspirin use (if concomitant low bleeding risk)
Stage 4 – CKD and metabolic syndrome and clinical CVD	• CVD – coronary artery disease, HF, cerebrovascular accident, peripheral vascular disease or atrial fibrillation • Adiposity or other metabolic risk factors • CKD – Stage 4a: CKD only – Stage 4b: end-stage kidney disease	• Same as for Stages 0–3 with co-ordinated interdisciplinary care • If HF present, avoid DPP-4 inhibitors and thiazolidinediones

Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; BGL = blood glucose level; BMI = body mass index; CKD = chronic kidney disease; CVD = cardiovascular disease; DBP = diastolic blood pressure; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; HbA_{1c} = glycated haemoglobin; HDL = high-density lipoprotein; HF = heart failure; SBP = systolic blood pressure; SGLT-2 = sodium-glucose cotransporter-2.
* Adapted from Ndumele CE, et al. Cardiovascular-kidney-metabolic health: a presidential advisory from the American Heart Association. Circulation 2023; 148: 1606-1635.[30]
† Not accounting for sex- or ethnicity-specific differences in body composition.

offline measurements are taken from colour tissue Doppler images
- two-dimensional speckle tracking echocardiography – which tracks 'speckles' or natural acoustic markers in the two-dimensional ultrasound image
- velocity vector imaging – which combines speckle tracking and endocardial border tracking.

LA strain correlates with diastolic dysfunction.[39] LA enlargement is well documented in end-stage kidney disease, as it likely correlates with left ventricular hypertrophy and archetypal risk factors (hypertension and diabetes). CKD itself may affect LA function (particularly strain patterns) and precedes changes in size. This is postulated to occur through mechanisms such as volume expansion due to activation of the renin–angiotensin–aldosterone system (RAAS), reduced vascular compliance due to endothelial dysfunction and medial calcification, chronic inflammation and oxidative stress, and accumulation of uraemic toxins. LA reservoir strain has been shown to independently predict cardiovascular death and MACE in people with CKD, as well as progression to end-stage kidney disease, independent of established clinical risk factors.[40,41]

Accordingly, routine evaluation of LA function presents an opportunity to improve cardiovascular risk stratification in patients with CKD. However, limitations – such as lack of widespread availability and analytical expertise in such evaluation, and a lack of clinical studies showing that targeting the proposed pathways which promote LA dysfunction mitigates MACE – need to be overcome for this analysis to become embedded in routine clinical practice.

Challenges in screening for coronary artery disease

Screening for coronary artery disease in patients with CKD remains challenging and is typically performed in partnership with nephrologists and cardiologists. Available noninvasive investigations include dobutamine stress echocardiography, myocardial perfusion scintigraphy and coronary CT angiography.

In patients with CKD, dobutamine stress echocardiography has shown widely variable sensitivity (44 to 96%) and specificity (60 to 100%), with an overall diagnostic odds ratio (the odds of a positive test in those with disease relative to the odds of a positive test in those without) of 29.98.[42] Myocardial perfusion scintigraphy performed even less robustly (sensitivity of 29 to 100% and specificity of 31 to 88%, diagnostic odds ratio of 6.69). These data suggest moderate diagnostic accuracy, which precludes using either of these tests as a general screening tool. Further, balanced triple vessel disease, submaximal heart rate during testing and subjective interpretation of results also contribute to reduced specificity.

Coronary CT angiography is less useful in patients with CKD than in the general population, as extensive coronary artery calcification does not always correlate with significant stenosis and may lead to gross overestimation of luminal stenosis.[43] However, coronary CT angiography, particularly when combined with myocardial perfusion scintigraphy, was found to be useful in ruling out obstructive coronary artery disease and was recommended for potential kidney transplant recipients.[44] A recent small meta-analysis found lower sensitivity in patients with CKD compared with the general population.[45]

Invasive coronary angiography

In patients with CKD presenting with non-ST-elevation acute coronary syndrome, early use of invasive coronary angiography significantly reduced the risk of rehospitalisation but did not substantially reduce risk of death or re-infarction rates.[46] The International Study of Comparative Health Effectiveness With Medical and Invasive Approaches-Chronic Kidney Disease (ISCHEMIA-CKD) trial found that an initial invasive strategy (angiography with or without revascularisation) did not reduce the risk of death or nonfatal myocardial infarction compared with medical therapy

CLINICAL VIGNETTES: TWO CASES OF SILENT CVD IN PATIENTS WITH CKD

Case 1. Potential crisis averted

A 31-year-old woman with a more than 20-year history of type 1 diabetes progressed to stage 5 CKD on a background of pre-eclampsia two years earlier, when she gave birth at 31 weeks' gestation. She was treated postpartum with enalapril and atorvastatin. There was no evidence of other macro- or microvascular diabetic complications, and adequate cardiovascular function was confirmed by routine echocardiography, which showed low-normal systolic function and LVEF of 50%. Repeat echocardiography nine months later, just before living-donor kidney transplantation, showed moderately reduced systolic function, LVEF of 35%, diffuse hypokinesis and grade 3 diastolic dysfunction. Coronary angiography showed 70% stenosis in the left anterior descending artery, which was successfully stented. Further imaging after six months showed recovery of LVEF, but the diastolic dysfunction remained. The patient proceeded to have a successful living related-donor kidney transplant without any evidence of a cardiac event.

Case 2. Crisis not averted

A 67-year-old man with end-stage kidney disease secondary to type 2 diabetes and hypertension had been maintained on peritoneal dialysis for five years without any complications or hospitalisations. There was no evidence of any cardiovascular disease on routine testing (electrocardiography, echocardiography and sestamibi scan). He was taking olmesartan, linagliptin and metoprolol. One day after deceased-donor kidney transplantation, he developed a new left bundle branch block and rise in troponin level, consistent with an acute coronary syndrome. Anticoagulation led to a large retroperitoneal bleed, requiring a relook laparotomy for evacuation. Once stabilised, urgent coronary angiography showed 30% left main coronary artery, 70% left anterior descending artery and 60% ostial left circumflex artery disease. Despite maximal medical treatment, repeated episodes of acute pulmonary oedema led to coronary artery bypass grafting, which was performed two months after transplantation.

Abbreviations: CKD = chronic kidney disease; CVD = cardiovascular disease; LVEF = left ventricular ejection fraction.

alone, and this mirrored findings in people with normal renal function.[47,48]

Furthermore, as CKD progresses, the risks (and potential consequences) of angiography increase. These risks include major and minor bleeding, restenosis and death after percutaneous coronary intervention, and risk of acute kidney injury secondary to contrast exposure, which occurs at a higher rate than in the general population.[49,50]

Cardiovascular implications of immunosuppression in patients with chronic kidney disease

Kidney transplantation, when compared with alternative renal replacement therapies (dialysis), offers the best cardiovascular and long-term survival outcomes, highlighting the beneficial effects of ameliorating non-traditional cardiovascular risk factors through a functioning renal allograft and 'normalising' GFR.[51,52] However, a significant and sustained improvement in renal function is only possible through strict adherence to lifelong immunosuppression to prevent allograft rejection. Paradoxically, the very immunosuppression that is directly responsible for achieving improved renal function is associated with adverse cardiometabolic effects that concurrently increase a patient's cardiovascular risk and expedite development of CVD. This complex balance is highly relevant for kidney transplant recipients, who still experience a higher risk of CVD than the general population and in whom this remains the leading cause of mortality.[52-54]

Kidney transplant recipients are not the only patients with CKD who require immunomodulation as standard of care. Systemic immune disorders – a consequence of autoimmunity, haematological malignancy or mutations in complement genes – can manifest primarily as glomerular disease, requiring immunosuppression to effectively minimise kidney injury.

Although antiproliferative agents (e.g. mycophenolate mofetil and azathioprine) are not considered to exacerbate cardiovascular risk, pivotal immunosuppressive agents, such as calcineurin inhibitors (CNIs) and corticosteroids, as well as mammalian target of rapamycin inhibitors (mTORIs) that are designated for use in certain circumstances, are strongly associated with increased cardiovascular risk. The key pathophysiological mechanisms for this increased cardiovascular risk are summarised below.

Diabetes

New-onset diabetes after transplant (NODAT), which affects about 25% of kidney transplant recipients, is a consequential complication of transplantation, leading to an increased risk of CVD, graft failure and infections, and decreased patient survival.[55-57] Immunosuppressive therapy significantly contributes to the development of NODAT, with a dose-dependent relationship explaining why most cases of NODAT are diagnosed in the first three months after transplantation.[56]

Corticosteroids exert diabetogenic effects, including impairing pancreatic beta islet cell secretory function and glucose sensitivity, promoting insulin resistance in peripheral tissues by directly interfering with components of the insulin signalling cascade, and increasing hepatic gluconeogenesis.[57,58] CNIs also impair pancreatic beta islet cell growth and function and reduce adipocyte expression of glucose transporter type 4 receptors, which hinder insulin secretion and promote peripheral insulin resistance, respectively.[57,59,60] Further, CNIs are directly toxic to pancreatic beta islet cells, with increased beta cell vacuolisation seen in patients with higher CNI trough levels.[57] Notably, tacrolimus has been linked with a higher risk of NODAT than cyclosporin. Finally, mTORIs exert toxic effects on pancreatic beta islet cells and impair insulin-mediated suppression of hepatic glucose production.[54]

Hypertension

Hypertension is highly prevalent in kidney transplant recipients, constituting a leading cause of allograft dysfunction and incident CVD.[52] Standard immunosuppressive therapies, such as CNIs and corticosteroids, are key drivers of post-transplant hypertension. Corticosteroids promote hypertension primarily through their modulation of vascular smooth muscle tone, which increases peripheral vascular resistance, with renal sodium retention also thought to play a role.[54] CNIs increase blood pressure through multiple mechanisms, including sympathetic nervous system activation, afferent arteriolar vasoconstriction, activation of the RAAS, oxidative stress, and, in the long term, their contribution towards chronic allograft nephropathy.[52-54]

Dyslipidaemia

Immunosuppressive agents also contribute to the development of dyslipidaemia after transplantation. CNIs, particularly cyclosporin, interfere with low-density lipoprotein (LDL) cholesterol binding, leading to reduced LDL clearance.[54] Corticosteroids promote dyslipidaemia through multiple mechanisms, including increased hepatic synthesis of very-low-density lipoprotein (VLDL) cholesterol, increased conversion of VLDL to LDL cholesterol, increased activity of 3-hydroxy-3-methylglutaryl coenzyme A (which drives cholesterol synthesis) and impaired triglyceride clearance through reduced lipoprotein lipase activity. mTORIs are strongly linked with dyslipidaemia through reduced lipoprotein lipase activity, hepatic overproduction of lipoprotein and increased secretion of VLDL cholesterol.[54] Transition from a CNI to an mTORI, typically done to avoid CNI toxicities, is associated with a two- to threefold increase in the risk of dyslipidaemia.[61]

Management considerations

Immunosuppression

Recognition of the significant cardiovascular sequelae of immunosuppression has inspired attempts to implement CNI-free or corticosteroid-free regimens; however, these have been unsuccessful owing to an unacceptable risk of acute allograft rejection.[62] Consideration of a patient's individualised cardiovascular risk when selecting and reviewing an immunosuppression

TABLE 5. AGENTS THAT DELAY PROGRESSION OF CKD

Features	RAAS blockade	SGLT-2 inhibitors	Nonsteroidal MRAs	GLP-1 receptor agonists
Mechanism of renoprotective benefit (proven or putative)	• Systemic vasodilatation and inhibition of aldosterone secretion achieves antihypertensive effect[68] • Reduction in intraglomerular pressure through efferent arteriolar vasodilatation[68] • Mitigation of podocyte injury[69] • Inhibition of mesangial cell proliferation[68] • Decreased oxidative stress[70]	• Increased sodium delivery to distal tubule enables afferent arteriolar vasoconstriction through tubuloglomerular feedback mechanism, resulting in reduced intraglomerular pressure[71,72] • Decreased glucose-mediated toxicity to proximal convoluted tubular cells[72] • Modest antihypertensive effect through natriuresis[71,72] • Modest improvements in weight and HbA_{1c}[71,72] • Decreased oxidative stress[71]	• Inhibition of aldosterone-mediated proinflammatory and profibrotic pathways[73,74] • Decreased podocyte injury and effacement[73] • Modest antihypertensive effect[73,74]	• Unclear; postulated to be related to antioxidant and anti-inflammatory properties[75] • Improved glycaemic control through stimulation of pancreatic beta cells to synthesise and secrete insulin[76] • Weight loss primarily mediated through stimulation of POMC/CART-expressing arcuate nucleus neurons (to promote satiety) and inhibition of neuropeptide Y and agouti-related peptide (to reduce appetite)[77]
Published evidence for efficacy in patients with CKD	• Reduction in proteinuria[78] • Reduction in CV risk (including risk of composite outcome of CV mortality, hospitalisation for HF and all-cause mortality) for people with CKD[79] • Slowing of CKD progression[78,80] • Reduction in risk of progression to kidney failure[78,80,81]	• Reduction in risk of composite outcome of CKD progression, onset of kidney failure and risk of death from renal or CV causes[19,82,83] • Reduction in all-cause mortality[82] • Reduction in proteinuria[84]	• Reduction in risk of composite outcome of CV death, nonfatal myocardial infarction, nonfatal stroke and hospitalisation for HF[20,85] • Reduction in risk of composite outcome of CKD progression, onset of kidney failure and death from renal causes[20] • Reduction in proteinuria[86]	• Reduction in risk of composite outcome of CV death, nonfatal myocardial infarction and nonfatal stroke[87-90] • Reduction in risk of composite outcome of development of proteinuria, CKD progression, onset of kidney failure and death from renal causes[91] • Reduction in all-cause mortality[91]
PBS prescribing criteria	• No restrictions	• Empagliflozin and dapagliflozin (both PBS subsidised): eGFR 25–75 mL/min/1.73 m^2 and UACR 22.6–565 mg/mmol • Expanded criteria for dapagliflozin: approved for use in any patient with type 2 diabetes with either known CVD or high risk of CV event (at least 10% over 5 years) or ATSI heritage (enables access for patients with type 2 diabetes with early CKD)	• Finerenone (only PBS subsidised MRA): DKD plus eGFR >25 mL/min/1.73 m^2 plus UACR >22.6 mg/mmol • Must not have established HF with reduced ejection fraction with indication for steroidal MRA use	• Type 2 diabetes, in combination with at least one of metformin, a sulfonylurea or insulin, but without clinically meaningful glycaemic response • SGLT-2 inhibitor coprescription is allowable under PBS if the SGLT-2 inhibitor is prescribed for a separate indication (e.g. CKD, HF)
Approved for use in patients without DKD?	• Yes	• Yes	• No	• No

Abbreviations: ATSI = Aboriginal and/or Torres Strait Islander; CART = cocaine- and amphetamine-regulated transcript; CKD = chronic kidney disease; CV = cardiovascular; DKD = diabetic kidney disease; eGFR = estimated glomerular filtration rate; GLP-1 = glucagon-like peptide-1; HbA_{1c} = glycated haemoglobin; HF = heart failure; MRA = mineralocorticoid receptor antagonist; POMC = pro-opiomelanocortin; RAAS = renin–angiotensin–aldosterone system; SGLT-2 = sodium-glucose cotransporter-2; UACR = urine albumin-to-creatinine ratio.

TABLE 5. AGENTS THAT DELAY PROGRESSION OF CKD *continued*

Features	RAAS blockade	SGLT-2 inhibitors	Nonsteroidal MRAs	GLP-1 receptor agonists
When to start this medication	• Considered a first-line agent for hypertension • Patients with hypertension and CKD stage G1–G4 with moderate to severely increased albuminuria[92] • Low dose of RAAS blockade can be considered in normotensive patients with stage G1–G4 CKD with moderate to severely increased albuminuria, as tolerated, to enable antiproteinuric benefits[11,93] • RAAS blockade can be considered in patients with stage G1–G4 CKD without albuminuria, to enable CV and mortality risk reduction	• Patients with type 2 diabetes: eGFR >25 mL/min/1.73 m^2 • Patients without diabetes: eGFR 25–75 mL/min/1.73 m^2 • Do not start when eGFR <25 mL/min/1.73 m^2 but can continue when eGFR falls below 25 mL/min/1.73 m^2 due to CKD progression; discontinue once renal replacement therapy is started	• Patients with eGFR >25 mL/min/1.73 m^2; typically as adjunct to RAAS blockade and SGLT-2 inhibition in patients with DKD with persistent proteinuria	• Patients with type 2 diabetes and CKD who have not achieved individualised glycaemic target with metformin and SGLT-2 inhibitor, or unable to tolerate one or both of these agents[11] • Limited data for use in patients with stage 5 CKD or kidney failure requiring renal replacement therapy; caution should be exercised in these groups
Key adverse effects	• Hyperkalaemia	• Euglycaemic ketoacidosis • Genital mycotic infections • Volume depletion	• Hyperkalaemia	• Dose-dependent gastrointestinal intolerances (nausea, vomiting, diarrhoea) • Injection site reactions
Practice points	• Check biochemistry 1–2 weeks after starting to assess for hyperkalaemia • Anticipate rise in serum creatinine level up to 30% from baseline on initiation; typically stabilises within 2 months with long-term renal function preservation	• Advise patients to withhold perioperatively and during acute illness to reduce risk of ketoacidosis • Counsel on increased risk of genital mycotic infections; no strong evidence suggesting increased risk of urinary tract infection • Anticipate rise in serum creatinine level up to 30% from baseline on initiation; typically stabilises within 2–4 months, with long-term preservation of renal function • Consider dose reduction of insulin and/or sulfonylurea to reduce risk of hypoglycaemia • Not approved for use in kidney transplant recipients • Not approved for use in patients with type 1 diabetes	• Check biochemistry 1–2 weeks after starting to assess for hyperkalaemia • Not recommended to start until hyperkalaemia is well controlled (trials recruited patients with serum potassium levels consistently <4.8 mmol/L) • Reduce dose or suspend therapy if hyperkalaemia occurs	• Consider reducing dose of insulin and/or sulfonylurea therapy to reduce risk of hypoglycaemia • Gradual dose uptitration (where multiple doses exist; e.g. semaglutide) is recommended to improve gastrointestinal tolerability • Contraindicated in patients with a history of acute pancreatitis, medullary thyroid cancer or with multiple endocrine neoplasia 2
Safety during pregnancy	• RAAS blockade contraindicated in pregnancy • Contraception advised	• No data, avoid use • Contraception advised	• No data, avoid use • Contraception advised	• Limited data, avoid use • Contraception advised

Abbreviations: ATSI = Aboriginal and/or Torres Strait Islander; CART = cocaine- and amphetamine-regulated transcript; CKD = chronic kidney disease; CV = cardiovascular; DKD = diabetic kidney disease; eGFR = estimated glomerular filtration rate; GLP-1 = glucagon-like peptide-1; HbA_{1c} = glycated haemoglobin; HF = heart failure; MRA = mineralocorticoid receptor antagonist; POMC = pro-opiomelanocortin; RAAS = renin–angiotensin–aldosterone system; SGLT-2 = sodium-glucose cotransporter-2; UACR = urine albumin-to-creatinine ratio.

regimen and appropriately reducing the doses of immunosuppression – particularly CNIs and corticosteroids – in patients considered to have a lower risk of rejection are important ways in which clinicians can identify, and reduce, iatrogenic cardiovascular risk.

Modification of traditional cardiovascular risk factors

Aggressive modification of traditional cardiovascular risk factors in patients with CKD, and particularly kidney transplant recipients, requires greater attention (Table 1).[63] Almost one-third of kidney transplant recipients do not meet the blood pressure target of less than 130/80 mmHg, and one-fifth have borderline or elevated LDL cholesterol levels.[64]

With respect to hypertension management, dihydropyridine calcium channel blockers have been identified as a preferred antihypertensive due to their attenuation of CNI-induced vasoconstriction.[52] Calcium channel blockers have shown greater preservation of renal function when compared with placebo, as well as RAAS blockade.[65]

Additionally, initiation of statin therapy to treat elevated LDL cholesterol levels has been shown to be beneficial in kidney transplant recipients, with a randomised controlled trial finding that moderate- to high-dose fluvastatin achieved a 38% reduction in risk of cardiovascular mortality and a 32% reduction in risk of non-fatal myocardial infarction, despite not significantly reducing the risk of MACE.[66] However, caution must be exercised when coadministering statins with CNIs because of the risk of increased systemic statin exposure and possible myotoxicity from the competitive inhibitory effect of cyclosporin on cytochrome P450 3A4, impairing statin catabolism.[67]

Pharmacotherapy to slow progression of chronic kidney disease

Newer pharmacotherapeutic agents – SGLT-2 inhibitors, GLP-1 receptor agonists and MRAs (finerenone) – have all been shown to play a central role in slowing the progression of CKD (Table 5).[68-94] These agents complement the pre-existing treatment rationale of using RAAS blockers, but patients remain at higher risk of disease progression and MACE, suggesting that the therapeutic ceiling has not yet been reached. The nephroprotective effects of these agents (irrespective of diabetes status) reflect haemodynamic, metabolic and anti-inflammatory changes that have been poorly characterised in human studies but robustly supported by many clinical trials and meta-analyses.[68-91] Treatment strategies must be tailored to a patient's CKD stage, comorbidities and risk of adverse events (e.g. persistent deterioration in eGFR or hyperkalaemia).

Conclusion

The benefits and cardiovascular side effect profile of immunosuppression after kidney transplantation pose a complex clinical dilemma. Clinicians are tasked with striking a balance between avoiding under-immunosuppression – to successfully prevent allograft rejection, preserve renal function and ultimately reduce a patient's cardiovascular and mortality risk – while avoiding over-immunosuppression and its anticipated cardiovascular sequelae. To improve cardiovascular outcomes for kidney transplant recipients and other patients who require immunosuppression for preservation of native kidney function, frequent evaluation of the immunosuppression regimen, with individualised modification of immunosuppression dosing where appropriate, should complement traditional cardiovascular risk reduction measures. A focus on cardiovascular–kidney–metabolic health, with increasing clinician and consumer awareness, multidisciplinary care, appropriate screening and pharmacological intervention, is an important consideration for integration into clinical care. MT

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A list of references is included in the online version of this article (www.medicinetoday.com.au).

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Cardiovascular protection in chronic kidney disease

Considerations for pre- and post-transplant care

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