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.

MedicineToday 2025; 26(11 Suppl): 29-32
First published in MedicineToday 2024; 25(1-2): 47-51
Updated November 2025

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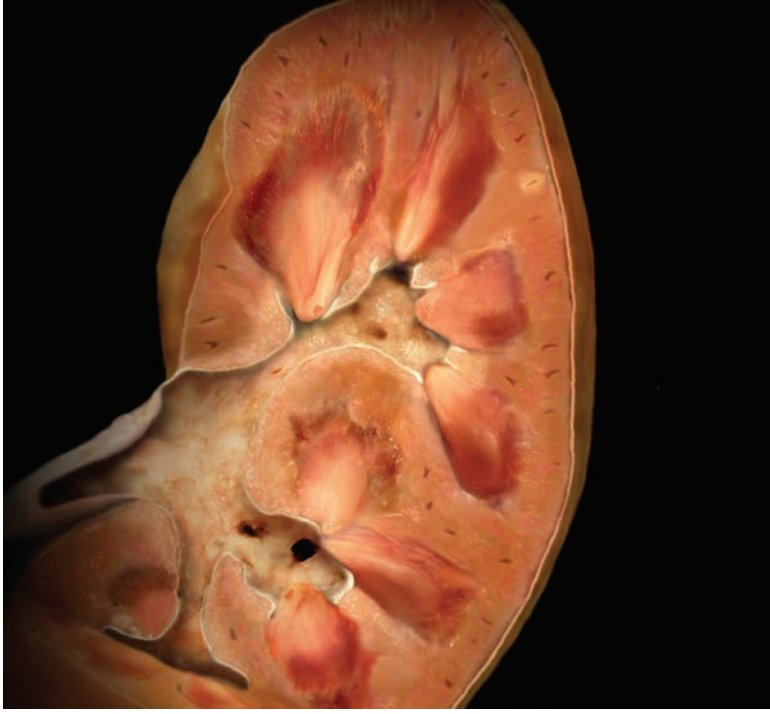

KEY POINTS

- 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

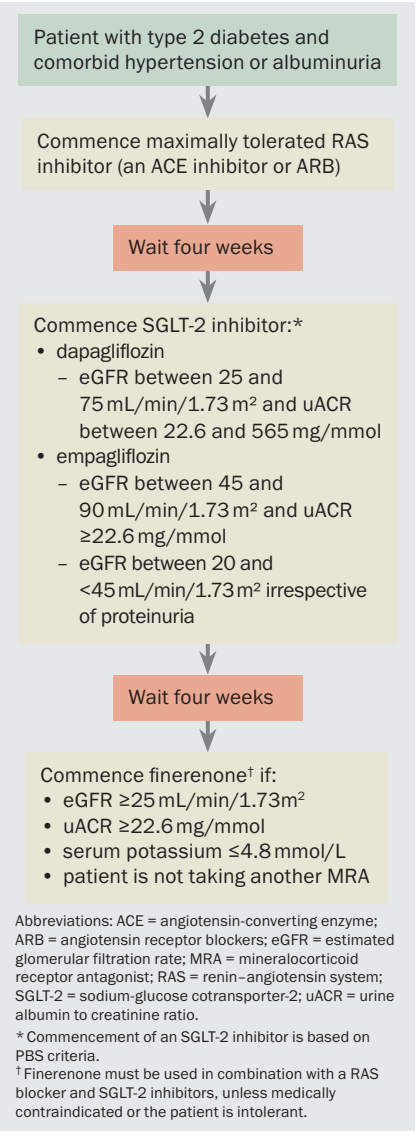

Figure. An approach to renoprotective treatment for patients with type 2 diabetes and chronic kidney disease.

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.

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).

COMPETING INTERESTS: Dr Kolovos has received fees for lectures from AstraZeneca and Boehringer Ingelheim. Professor Pollock has received fees for consultation and lectures from AstraZeneca, Bayer and Boehringer Ingelheim; and support for attending meetings from AstraZeneca and Boehringer Ingelheim.

MedicineToday 2025; 26(11 Suppl): 29-32
First published in MedicineToday 2024; 25(1-2): 47-51
Updated November 20255

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