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Medicines for chronic kidney disease: A practical guide

Key points:

- For all people with CKD, prescribe an ACE inhibitor or ARB, up-titrated to the maximum tolerated dose.
- Add an SGLT2 inhibitor (dapagliflozin), and blood pressure-lowering, lipid-lowering and glucose-lowering medicines, as determined by clinical factors such as whether the person is meeting a therapeutic target.
- The order in which the above medicines are added is guided by compelling indications such as albuminuria levels, the underlying cause and any comorbidities.
- A person-centred approach to prescribing these medicines includes building your relationship with the patient over the long term and finding ways to help the patient feel they are in control of their health.
- CKD shares many treatment goals and management strategies with CVD and type 2 diabetes. Use a 'whole of person' approach to manage these chronic conditions in conjunction.
- Adjust doses of medicines cleared by the kidneys according to kidney function to reduce risk of adverse effects and avoid nephrotoxic medicines where possible.

A practical guide for medicines for chronic kidney disease

Australian and international guidance is clear on medicines for chronic kidney disease (CKD) that slow CKD progression and reduce cardiovascular (CV) risk.

All people with CKD should first be prescribed an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB).[1,2]

Other medicines can then be added as needed to slow CKD progression and reduce CV risk, including:[1–7]

- sodium–glucose co-transporter-2 (SGLT2) inhibitors (dapagliflozin) as add-on therapy to an ACE inhibitor or ARB
- blood pressure-lowering medicines to treat hypertension
- lipid-lowering medicines for elevated absolute CV risk
- glucose-lowering medicines for elevated glycaemic levels in type 2 diabetes.

This article provides a practical guide on when and how to prescribe the above medicines for people with CKD. It includes an algorithm (see Figure 2) and follows the case study of a patient named Ken.

Pharmacological management for CKD also includes:[1]

- adjusting doses of medicines cleared by the kidneys to reduce adverse effects. See How to manage medicines cleared by the kidneys section below
- avoiding nephrotoxic medicines where possible. See Kidney Health Australia 2020 CKD Management in Primary Care 4th edition handbook for more information.

Case study: Ken

Ken has been newly diagnosed with CKD.

He is a 64-year-old male, married, with two adult-aged children and is a taxi owner/driver. He hasn't smoked for 20 years.

Ken's medical history includes hypertension (at last check it was 145/90 mmHg) and dyslipidaemia, both diagnosed 5 years ago.

His medicines include perindopril erbumine 2 mg daily and atorvastatin 40 mg daily.

See NPS MedicineWise CKD – Integrating kidney health into patient care for how to screen and make a diagnosis of CKD.

What is CKD?

CKD is defined as:[1,8]

- reduced kidney function for ≥ 3 months as demonstrated by:
  - estimated or measured glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2,

and/or

- kidney damage for ≥ 3 months as demonstrated by:
  - albuminuria (elevated urine albumin/creatinine ratio [ACR]), or
  - haematuria after the exclusion of urological causes, or
  - structural abnormalities, such as those found on kidney imaging tests, or
  - pathological abnormalities, such as those found on kidney biopsy.

Management based on risk level

The management for each person with CKD is guided by where that person's estimated GFR (eGFR) and ACR results place them on a colour-coded staging table.[1] See Figure 1.

Ken has an eGFR of 56 mL/min/1.73 m^2, which is Stage 3a CKD.

His urine ACR is 24 mg/mmol, which is *microalbuminuria*.

This places Ken at a high-risk level for progression of CKD and developing cardiovascular disease (CVD).

FIGURE 1: Staging of CKD and colour-coded risk levels that guide clinical action plans for management[a]

		Albuminuria stage		
Kidney function stage	**GFR (mL/min/1.73m²)**	**Normal (urine ACR mg/mmol) Male: < 2.5 Female: < 3.5**	**Microalbuminuria (urine ACR mg/mmol) Male: 2.5–25 Female: 3.5–35**	**Macroalbuminuria (urine ACR mg/mmol) Male: > 25 Female: > 35**
1	≥ 90	Not CKD unless haematuria, structural or pathological abnormalities present		
2	60–89			
3a	45–59			
3b	30–44			
4	15–29			
5	< 15 or on dialysis			

Risk of progressive CKD: low moderate high very high

Source: KHA-CARI Guideline: Early chronic kidney disease: Detection, prevention and management. Johnson DW, Atai E, Chan M, et al. Nephrology 2013;18:340–50. Wiley Online Library.

Clinical action plans for management

The risk levels in the colour-coded CKD staging table correspond to colour-coded clinical action plans presented in the Kidney Health Australia 2020 CKD Management in Primary Care 4th edition handbook.[1] See Table 1 below for an adapted version of these clinical action plans.

Each clinical action plan includes a set of clinical and laboratory assessments and measures, management goals, and non-pharmacological management and pharmacological management recommendations, including medicines to slow CKD progression and reduce CV risk.[1]

Ken's risk level places him in the orange clinical action plan, which recommends a review of his CKD every 3–6 months.

TABLE 1: Assessment and management for people with CKD based on colour-coded clinical action plans[1]

CKD clinical action plans[c]	eGFR ≥ 60 with microalbuminuria or eGFR 45–59 with normoalbuminuria	eGFR 30–59 with microalbuminuria or eGFR 30–44 with normoalbuminuria	Macroalbuminuria irrespective of eGFR or eGFR < 30 irrespective of albuminuria
Frequency of review	Every 12 months	Every 3–6 months	Every 1–3 months
Clinical assessments	Blood pressure, weight, smoking		
			Oedema
Laboratory assessments[c]	▸ Urine ACR ▸ eGFR ▸ Biochemical profile including EUC ▸ HbA_{1c} (for people with diabetes) ▸ Fasting lipids		
		▸ FBC ▸ Calcium and phosphate ▸ Parathyroid hormone (6–12 monthly if eGFR < 45)	
Other assessments and measures	▸ Assess absolute CV risk[d] ▸ Referral to specialist and/or support services as needed		
		▸ Assess risk of atherosclerotic events and consider treating with an anti-platelet agent ▸ Assess for complications of CKD	
			▸ Proactively discuss support and treatment options as kidney function declines
Non-pharmacological management	▸ Lifestyle modification (SNAP – **S**moking, **N**utrition, **A**lcohol, **P**hysical activity/obesity): • smoking (counselling, NRT or other medicines) • nutrition (< 5 g sodium chloride per day;[4,7] limit foods containing saturated and trans-fats, and sugar; ≤ 6 mmol/L potassium; drink water to satisfy thirst) • alcohol (≤ 2 standard drinks per day) • physical activity (150–300 minutes of moderate-intensity physical activity or 75–150 minutes of vigorous-intensity physical activity per week) • obesity (BMI < 25 kg/m^2; waist circumference < 94 cm in men and < 80 cm in women)		
Pharmacological management	▸ Regardless of underlying causes/comorbidities: • prescribe medicines shown to slow progression of CKD and/or reduce CV risk[4] (see Table 1 of Insert) • avoid nephrotoxic medicines (see Table 3 of Insert) ▸ For specific underlying causes/comorbidities: • blood pressure reduction (maintain < 130/80 mmHg) • lipid-lowering treatment (no target serum cholesterol level recommended) • glycaemic control (HbA_{1c} ≤ 7% or ≤ 53 mmol/mol; fasting BGL 6–8 mmol/L)		
		Reduce doses of medicines that are cleared by the kidneys	

[c] eGFR measures are in mL/min/1.73m^2.
[d] People with moderate or severe CKD (macroalbuminuria or eGFR < 45) are considered to already be at the highest risk of a CV event, and therefore should not be assessed using the absolute CV tool.
ACR = albumin-to-creatinine ratio; BGL = blood glucose level; BMI = body mass index; CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; EUC = electrolytes, urea, creatinine; FBC = full blood count; HbA_{1c} = glycated haemoglobin; NRT = nicotine replacement therapy.

Underlying cause

Ken was diagnosed with hypertension and dyslipidaemia 5 years ago.

Investigations performed as part of Ken's newly diagnosed CKD have determined that the underlying cause of the CKD is hypertension.

See NPS MedicineWise CKD – Integrating kidney health into patient care for the recommended investigations for newly diagnosed CKD.

The appropriate recording of a CKD diagnosis in Ken's patient record includes his eGFR stage, albuminuria level and underlying cause:[1]

Stage 3a CKD with microalbuminuria due to hypertension.

Recommended medicines and reviews for Ken to slow CKD progression and reduce CV risk

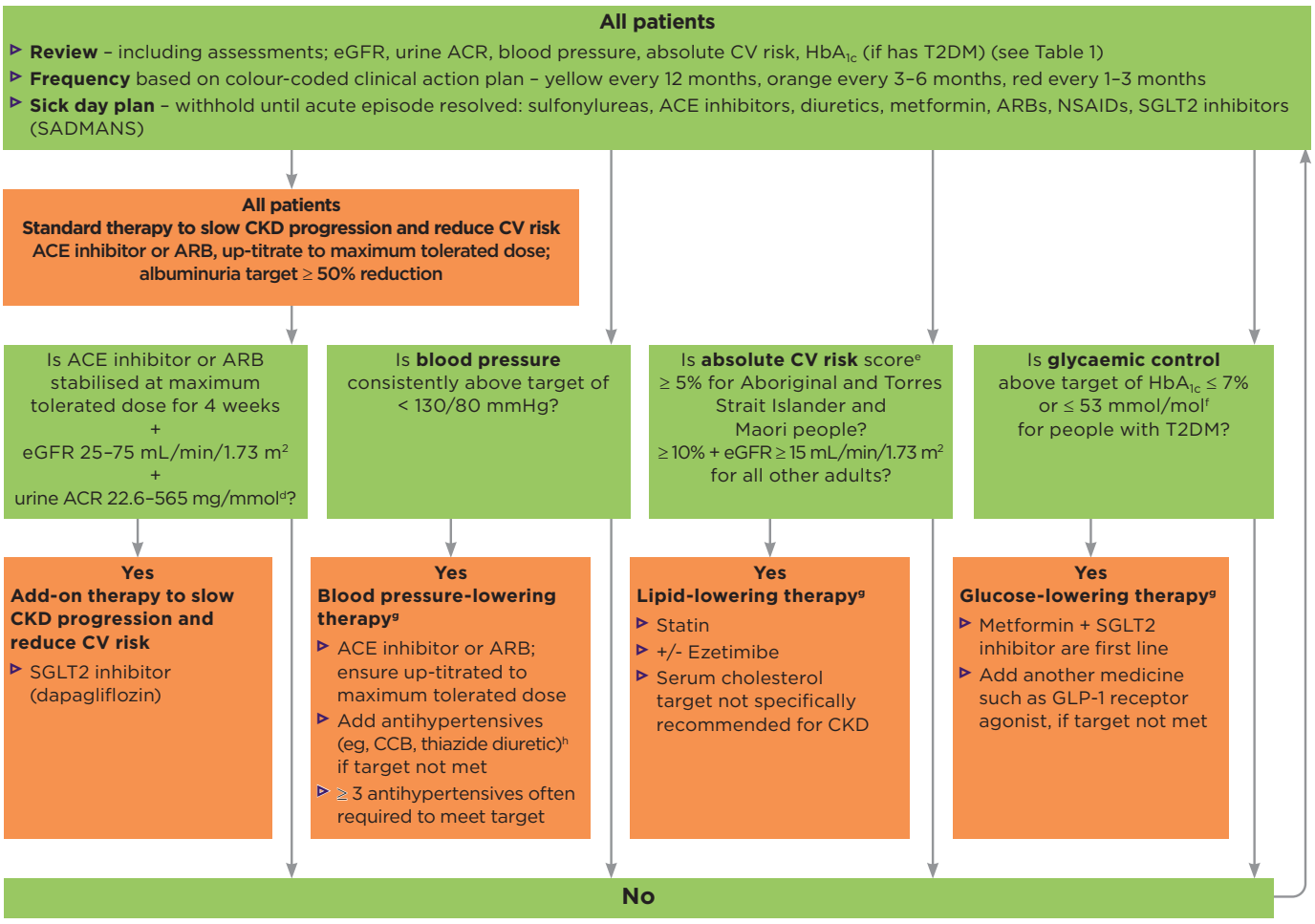
An algorithm based on the Australian and international guidance presents the recommended medicines that slow CKD progression and reduce CV risk for people with CKD. See Figure 2 on following page.

The medicines and reviews recommended for Ken based on this algorithm are as follows:

- An ACE inhibitor or ARB; standard therapy for all people with CKD.
- Blood pressure-lowering therapy to treat hypertension, the underlying cause of his CKD.
- Review the need for add-on therapy to an ACE inhibitor or ARB, with an SGLT2 inhibitor (dapagliflozin).
- Review Ken's current lipid-lowering therapy for his dyslipidaemia, including an assessment of his absolute CV risk and eGFR level.

Algorithm for medicines that slow CKD progression and reduce CV risk for people with CKD[1-7,11,12]

FIGURE 2: Algorithm for medicines that slow CKD progression and reduce CV risk for people with CKD



[d] PBS criteria for dapagliflozin for CKDt;
[e] Moderate or severe CKD (eGFR < 45 mL/min/1.73 m² or persistent ACR > 25 mg/mmol [males] or > 35 mg/mmol [females]) already considered highest risk of CV event (> 15% probability in 5 years);
[f] Cut off level needs individualising according to patient circumstances;
[g] Therapy for underlying cause/comorbidity to slow CKD progression and reduce CV risk;
[h] Antihypertensive choice depends on patient preferences, comorbidities, eGFR and cost.

ACE = angiotensin-converting enzyme; ACR = albumin-to-creatinine ratio; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; GLP-1 = glucagon-like peptide-1; ; HbA_{1c} = glycated haemoglobin; NSAIDs = non-steroidal anti-inflammatory drugs; PBS = Pharmaceutical Benefits Scheme; SGLT2 = sodium-glucose co-transporter 2; T2DM = type 2 diabetes mellitus

Before going into more detail about the recommended medicines and reviews for Ken to slow CKD progression and reduce CV risk, it can be helpful to address some guiding principles and issues.

Integrating CKD management into patient care

CKD rarely occurs in isolation. Of the estimated one in 10 adults with probable CKD in Australia, 35% have CVD and CKD, 6% have type 2 diabetes and CKD, and 11% have all three.[1,13]

CKD shares many treatment goals and management strategies with CVD and type 2 diabetes. Taking a 'whole of person' approach and managing these chronic conditions in conjunction with one another can lead to improved patient outcomes.[1]

"There is an overlap between CKD, cardiovascular disease and diabetes with regards to management.

We as GPs are already doing much of what is needed for CKD in our management of these other conditions. You don't need to do much more to manage CKD."

Dr Tim Senior, GP at Tharawal Aboriginal Corporation, clinical senior lecturer at the University of Western Sydney Medical School and CKD expert in general practice

A GP's strategy to support confidence

"Prescribing medicines that slow CKD progression and reduce cardiovascular risk for people with newly diagnosed CKD can be done over several consultations. In most cases there is ample time to optimise a patient's management.

"This enables me to start with the medicines I'm confident prescribing. For many GPs this will be an ACE inhibitor or an ARB. For medicines I'm less familiar with, I develop a list of priorities about doses that need to be changed or medicines started.

"I know I have time to upskill or refresh my knowledge when required before the next appointment by reading the guidance or contacting my local hospital renal service or a private nephrologist. So when the patient comes back, I can be confident with prescribing them."

Dr Caitlin Sum, Adelaide GP and member of the Kidney Health Australia Primary Care Educational Advisory committee.

Person-centred approach to medicines for CKD

"The main task with person-centred care is to spark interest and help people with CKD be motivated to get involved in their care from the start.

"This involves finding ways to give the person a feeling they have some control over their health, rather than the health professional trying to control their health.

"CKD has its challenges, particularly because it is usually asymptomatic. I find using the colour-coded staging table can be helpful. I explain that taking their medicines and making lifestyle changes can reduce their ACR number, which means they're slowing the progression of disease. You can use reducing their blood pressure number as a motivator in the same way."

Graeme Turner, nurse practitioner in the Northern NSW Local Health District and co-author of the 2013 KHA-CARI Guideline: Early chronic kidney disease: Detection, prevention and management

How to decide what order to prescribe medicines?

All people with CKD should first be prescribed an ACE inhibitor or ARB, up-titrated to the maximum dose.

What is the next step? What guidance should GPs follow to decide the order of medicines?

"My approach is to first pick the low-hanging fruit. I look at what the patient is already taking and prioritise a dose that needs up-titrating. Then I prioritise treating the underlying cause and any comorbidities.

"Patients often need to take multiple medicines, so you need to have their agreement to come back over a number of appointments to monitor them and see what works. You don't have to do everything at once, your focus is on the long term and building your relationship with the patient."

Dr Caitlin Sum

Compelling indications that guide prioritisation

"Compelling indications guide my decisions about which medicines to prescribe. The most compelling are usually targeting the albuminuria level, because it is just such a significant factor for cardiovascular risk, but I still target… hypertension and diabetes and comorbidities like dyslipidaemia and obesity with support from GPs, and for me I will of course also focus on the underlying cause of the CKD if it's not hypertension or diabetes.

"For people with high albuminuria levels, my priority is to up-titrate the ACE inhibitor or ARB to maximum tolerated dose, then I add on a SGLT2 inhibitor.

"For lower albuminuria levels I'll increase the ACE inhibitor or ARB dose once, but then look at increasing another medicine they're already taking or start a new medicine for their existing hypertension or diabetes and lastly focus on a specific underlying cause. Then I'll go back to up-titrating the ACE inhibitor or ARB."

Professor Ivor Katz, nephrologist at St George Hospital in Sydney and member of the Kidney Health Australia Primary Care Educational Advisory committee.

Non-pharmacological management

The medicines described below should always be prescribed together with non-pharmacological management.[1]

Non-pharmacological management, which includes lifestyle modifications for key risk factors including smoking, nutrition, alcohol, physical activity and obesity, is first-line management for all people with CKD.[1]

It can have positive effects on CKD outcomes and slow CKD progression, and should be included in the development of a person-centred management plan for the patient.[1]

ACE inhibitor (or ARB) – standard therapy to slow CKD progression and reduce CV risk

The first step recommended for Ken is to up-titrate the currently prescribed low dose of ACE inhibitor, perindopril erbumine 2 mg daily, to maximum tolerated dose to:[1]

- reduce his albuminuria levels, and
- treat his hypertension (see Blood pressure-lowering therapy section for more details).

Target

The recommended therapeutic target for albuminuria is ≥ 50% reduction.[1,12] This recommendation is based on expert opinion and trial evidence of relative risk reduction in kidney failure and CV events due to reduction in albuminuria.

The target maximum dose for perindopril erbumine is 8 mg daily.[7] Start and target maximum doses for ACE inhibitors and ARBs for people with CKD are found in the KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease (see Page S33, Figure 3).

Guidance

"The dose increase for up-titration of an ACE inhibitor or ARB should be done every 4 to 6 weeks. Because it can take time for the albuminuria to decrease, I measure the ACR around three times a year for most patients."

Professor Ivor Katz

When starting an ACE inhibitor or ARB, or at each dose increase:[1]

- monitor eGFR, potassium and blood pressure
- a reversible reduction in eGFR is expected at initiation
- continue if eGFR reduction < 25%
- decline in eGFR > 25% requires assessment to determine if cessation and/or referral to a nephrologist is required.

ACE inhibitors and ARBs should be temporarily stopped during periods of illness or when dehydrated. They should be recommenced when the acute episode has resolved.[1,11]

Evidence

A 2016 Bayesian network meta-analysis of 119 randomised controlled trials (RCTs) of people with CKD (n = 64,748) found that ACE inhibitors or ARBs compared to placebo reduced the risk for kidney failure by 39% and 30% respectively, major cardiovascular events by 18% and 24% respectively, and for ACE inhibitors alone the reduction in all-cause mortality was 28%.[14]

A 2015 meta-regression analysis of 14 RCTs for people with CKD receiving an ACE inhibitor or ARB found for each 30% reduction of albuminuria, there was a 32% reduction in kidney failure.[15]

Blood pressure-lowering therapy

Up-titrating the ACE inhibitor to the maximum tolerated dose is expected, in addition to reducing albuminuria, to decrease Ken's blood pressure. It was 145/90 mmHg at the last check.

If Ken's blood pressure remains above target, further blood pressure-lowering medicines may need to be added. Often, three or more blood pressure-lowering medicines are needed for most people with CKD to adequately meet the blood pressure target.[1]

Target

The target blood pressure for people with CKD is consistently < 130/80 mmHg.[1]

This target is supported by a 2019 meta-analysis comparing groups of people with CKD: an intensive target group (average systolic blood pressure [SBP] 125) and a standard target group (average SBP 137). It found a 21% reduction in all-cause mortality and an 18% reduction in composite CV events (myocardial infarction, stroke, CV death, heart failure, non-myocardial infarction coronary event, hospitalisation) for the intensive target group.[16]

"The blood pressure target is important, but it can be difficult to reach. I'm okay if I don't reach it, after trying to add on the maximum antihypertensive medications possible. The main thing is to get some decrease. Even small declines in mean arterial pressure will improve outcomes. That will still have a great impact on reducing the risk of CKD progression and cardiovascular risk."

Professor Ivor Katz

Guidance

The KDIGO 2021 Clinical practice guideline for the management of blood pressure in chronic kidney disease and Kidney Health Australia 2020 CKD Management in Primary Care 4th edition handbook recommend:[1,6]

1. starting with an ACE inhibitor or ARB up-titrated to maximum tolerated dose
2. adding a calcium channel blocker and/or thiazide diuretic
3. adding a beta blocker, mineralocorticoid receptor antagonist (MRA) or other blood pressure-lowering medicines as appropriate for compelling indications.

Thiazide diuretic should be temporarily stopped during periods of illness or when dehydrated. It can be recommenced when the acute episode has resolved.[1,11]

"It takes at least four weeks until any reduction in blood pressure is found.

"It can be difficult to know how many anti-hypertensives to add. But people with CKD will need more antihypertensive medications as their renal function declines. I try get as close to the target as possible without having too many side effects. I like to get the patient supporting and understanding the plan and I want to try to avoid side effects so they take their tablets.

"Once the optimal dose is found for each drug separately, then I will move onto a combination drug to reduce the pill burden. I explain this to them up front so they are not too overwhelmed with so many medications."

Professor Ivor Katz

SGLT2 inhibitor (dapagliflozin) – add-on therapy to slow CKD progression and reduce CV risk

The next step for Ken is to start dapagliflozin as add-on therapy to the ACE inhibitor that has been up-titrated to the maximum tolerated dose. The aim of the therapy is to slow CKD progression and reduce CV risk.[4,5]

Ken qualifies for dapagliflozin for CKD based on the PBS listing criteria, which include that the patient:[4]

- is stabilised at maximum tolerated dose for 4 weeks on an ACE inhibitor or ARB
- has an eGFR 25–75 mL/min/1.73 m^2
- has a urine ACR 22.6–565 mg/mmol.

Guidance

The recommended dose of dapagliflozin for people with CKD is 10 mg taken once daily, with or without food. No dose adjustments are required for reduced kidney function, mild–moderate hepatic impairment or based on age.[17,18]

See the NPS MedicineWise RADAR article Dapagliflozin (Forxiga) for heart failure with reduced ejection fraction (LVEF ≤ 40%) 'Safety' section for detailed information about contraindications, precautions and adverse effects.

Evidence

The key evidence supporting this recommendation is the 2020 DAPA-CKD trial of people with CKD, with or without type 2 diabetes (n = 4304).[5]

It found a 39% reduction with dapagliflozin in comparison to placebo (9.2% with dapagliflozin vs 14.5% with placebo) for the primary composite outcome of worsening kidney function (eGFR decline ≥ 50%) or onset of kidney failure (dialysis, kidney transplant or GFR < 15 mL/min/1.73 m^2) or death due to kidney disease or CVD.[5]

For more details see the NPS MedicineWise RADAR article Dapagliflozin for chronic kidney disease.

Lipid-lowering therapy

While all the above medicines have been up-titrated or added on, Ken has continued taking atorvastatin 40 mg daily for his dyslipidaemia. Ken's dose of atorvastatin was increased from 20 mg to 40 mg daily 2 years ago.

The next step for Ken, as part of the orange clinical action plan, is to calculate his absolute CV risk score (see Australian absolute cardiovascular disease risk calculator). If Ken had moderate or severe CKD (eGFR < 45 mL/min/1.73 m^2 or persistent ACR > 25 mg/mmol (or > 35 mg/mmol for females) he would already be considered high risk of a CV event (> 15% probability in 5 years) and not require this assessment.[1]

Ken's absolute CV risk score is 16%, based on total cholesterol 5.6 mmol/L and high-density lipoprotein 0.9 mmol/L.

The CARI Guidelines 2022 Management of cholesterol-lowering therapy in people with chronic kidney disease recommend a statin with or without ezetimibe for:[3]

- adults with CKD (eGFR ≥ 15 mL/min/1.73 m^2) and absolute CV risk ≥ 10%
- Aboriginal and Torres Strait Islander peoples and Māori with CKD (reduced GFR and/or albuminuria/proteinuria) and absolute CV risk ≥ 5%.

Ken meets this guideline recommendation for lipid-lowering therapy and also the PBS criteria to add ezetimibe 10 mg daily to atorvastatin, based on his eGFR being 56 mL/min/1.73 m^2 and having an absolute CV risk score of 16%.[19,20] He can take the two medicines as a combination product[21] to reduce pill burden.

Target

No target serum cholesterol level is recommended for people with CKD[1] due to a lack of evidence of benefit from titration of statin or ezetimibe to a specific low-density lipoprotein (LDL)-cholesterol target.[3,22]

"It's not recommended to aim for a particular lipid target solely because the patient has CKD. A target is only recommended for other reasons such as secondary prevention of CVD."

Dr Caitlin Sum

Evidence

A 2014 Cochrane review of 50 studies of people with CKD (n = 45,285) found that statins consistently lowered the death rate and major CV events by 20% in people with CKD not requiring dialysis.[23]

The best available evidence for statin with ezetimibe for people with CKD comes from a single RCT, the SHARP trial (n = 9270), which found a 17% proportional reduction in major atherosclerotic events.[24]

The CARI Guidelines 2022 Management of cholesterol-lowering therapy in people with chronic kidney disease state that the effect of statin therapy with or without ezetimibe on CKD progression remains largely unknown.[23]

Guidance

The CARI Guidelines 2022 Management of cholesterol-lowering therapy in people with chronic kidney disease recommend that people with CKD should be:[3,22]

- provided with information about the effects of statin therapy, with or without ezetimibe, for preventing CV events and death
- started on a low-dose statin because higher doses may result in an increased risk of adverse events.

"You can find that you are chasing your tail with lipid-lowering drugs aiming for a target, where you are likely to not have more benefit with higher dose but rather just more side effects.

"Many current CKD guidelines including KDIGO don't recommend regular lipid testing but simply starting and keeping patients on highest tolerable dose. Based on the SHARP study [see above] I'm happy with simvastatin 20 mg and ezetimibe 10 mg daily. The exception may be if the patient has severe coronary heart disease and a lot of coronary events, which may need to be treated with a higher-dose statin."

Professor Ivor Katz

Glucose-lowering therapy

Ken doesn't have type 2 diabetes. But if he did, the KDIGO 2020 clinical practical guidelines on management of diabetes in CKD recommend the following medicines:[7]

- Start as first-line therapy both metformin and an SGLT2 inhibitor, preferably one with documented kidney or CV benefits.
- If the therapeutic target is not met, add another blood glucose-lowering medicine such as a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist that has documented CV benefits.

Target

The target for people with CKD and type 2 diabetes is $HbA_{1c} \leq 7\%$ or ≤ 53 mmol/mol.[1]

Guidance

Sulfonylureas are not recommended first-line treatments for people with CKD because they increase endogenous insulin production, which can lead to an increased half-life of metabolites and prolonged hypoglycaemia.[8]

People with CKD already treated with sulfonylureas may need to add an SGLT2 inhibitor if additional glucose lowering is recommended, and to receive benefits of slow progression of CKD and reduced risk of CVD independent of glucose-lowering effect. If an SGLT2 inhibitor is added, the sulfonylurea dose may need to be stopped or reduced to avoid the risk of hypoglycaemia.[7]

Some people with CKD and type 2 diabetes and an eGFR ≥ 30 mL/min/1.73 m^2 may not achieve the glycaemic target with a combination of non-pharmacological management, metformin, and an SGLT2 inhibitor. Others may not be able to take these medicines due to intolerances or other restrictions, such as for people with eGFR < 30 mL/min/1.73 m^2.[7]

Other medicines are likely to be needed in these situations. GLP-1 receptor agonists are generally preferred because of their demonstrated CV benefits, particularly among patients with established atherosclerotic CVD, and possible kidney benefits.[7]

Kidney impairment may require dosing adjustment or selection of an alternative medicine if a specific one is not recommended.[25] See Table 2 below for guidance on selected glucose-lowering medicines.

Metformin, SGLT2 inhibitors and sulfonylureas should be temporarily stopped during periods of illness or when dehydrated. They should be recommenced when the acute episode has resolved.[1,11]

TABLE 2 Guidance for selected glucose-lowering medicines for people with CKD and reduced kidney function[26,27]

CLASS/MEDICINE		REDUCED KIDNEY FUNCTION GUIDANCE (GFR units = mL/minute)
metformin[28] ●		Reduce maximum dose for people with stable kidney function: ▶ GFR 60–90: 2 g daily ▶ GFR 30–60: 1 g daily ▶ GFR 15–30: 500 mg daily and monitor kidney function closely ▶ GFR < 15: not recommended
SGLT2 inhibitors ○	**dapagliflozin**[17,18]	▶ GFR < 25: starting treatment is not recommended ▶ GFR decreases to < 25: continuing treatment is acceptable
	empagliflozin[29]	▶ GFR < 30: not recommended
	ertugliflozin[30]	▶ GFR < 30: not recommended ▶ GFR < 45: starting treatment is not recommended
GLP-1 receptor agonists	**dulaglutide**[31] ●	▶ GFR < 15: not recommended
	semaglutide[32] ○	▶ GFR < 15: not recommended
	liraglutide[33] ●	▶ Renal impairment: may increase risk of gastrointestinal adverse effects ▶ GFR < 30: not recommended
	exenatide[34] ●	▶ GFR 30–50: proceed conservatively with dose increase from 5 micrograms to 10 micrograms ▶ GFR < 30: not recommended
Dipeptidyl peptidase-4 inhibitors	**alogliptin**[35] ●	▶ GFR 30–50: 12.5 mg once daily. ▶ GFR < 30: 6.25 mg once daily
	linagliptin[36]	▶ Dose adjustment is not required with kidney impairment
	saxagliptin[37] ○	▶ GFR < 45: 2.5 mg once daily
	vildagliptin[38] ●	▶ GFR < 60: 50 mg once daily
Sulfonylureas[39] ●	**glibenclamide** **gliclazide** **glimepiride** **glipizide**	▶ Dosage reduction may be required in severe renal impairment (GFR < 30) because of increased risk of hypoglycaemia ▶ glipizide or gliclazide are preferred if concerned about hypoglycaemia

● GFR calculated using creatinine clearance (CrCl) in the approved product information / Australian Medicines Handbook

○ GFR calculated using eGFR in the approved product information / Australian Medicines Handbook

GFR units = mL/minute; CKD = chronic kidney disease; GLP-1 = glucagon-like peptide-1; SGLT2 = sodium-glucose co-transporter 2

Evidence

There is a strong body of evidence that supports the recommendation for glucose-lowering medicines to stop CKD progression and reduce CV risk for people with CKD and type 2 diabetes. For example, SGLT2 inhibitors have been found to decrease the risk of kidney failure by 35%[7,40] and GLP-1 receptor agonists reduce the risk of CV death by 12% in people with type 2 diabetes.[7,41]

How to manage medicines cleared by the kidneys

Pharmacological management for CKD also includes adjusting doses of medicines cleared by the kidneys to reduce adverse effects.[1]

Dose reduction or cessation of medicines cleared by the kidneys is generally required once eGFR is < 60 mL/minute/1.73 m^2.[8] The product information for each medicine, and prescribing resources such as the Australian Medicines Handbook (AMH), provide guidance if the medicine's dosage needs adjusting and by how much.

GFR can be assessed using serum creatinine-based formulae.[42]

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) is the recommended formula to determine GFR. It provides an eGFR by incorporating age and sex, and is automatically presented on pathology referral forms when creatinine is requested.[42]

eGFR via the CKD-EPI is the preferred method in Australia for calculating kidney function in clinical practice and has been shown to have greater accuracy and precision compared to other formulae.[1]

The Cockcroft-Gault formula estimates creatinine clearance (CrCl) and incorporates age, sex and body weight.[42] CrCl may be presented in drug dosing resources such as the AMH to reflect what was used in the available trial evidence.[25]

eGFR should not be used for calculating doses for medicines for patients at extremes of body weight unless it is first corrected to the actual GFR for that patient.[43] For these patients the eGFR calculation is:[1]

$$\textbf{CKD-EPI eGFR result in mL/min/1.73m}^2 \times \frac{\textbf{Individual's body surface area (BSA)*}}{\textbf{173}} = \textbf{eGFR result in mL/min}$$

* BSA = 0.007184 × Weight in $kg^{0.425}$ × Height in $cm^{0.725}$ (Du Bois formula)

Careful estimation of GFR and subsequent dosage modification is particularly pertinent for medicines with a narrow therapeutic index (eg aminoglycosides). Therapeutic drug monitoring, if available, should be used to individualise dosing.[44]

A Home Medicines Review can be a useful service to provide support for GPs and people with CKD with medicines cleared by the kidneys.[8]

Conclusion

All people with CKD should first be prescribed an ACE inhibitor or ARB that is up-titrated to the maximum tolerated dose. Other medicines should be added as needed, including blood pressure-lowering, lipid-lowering and blood-glucose lowering medicines, and SGLT2 inhibitors (dapagliflozin), to slow CKD progression and reduce CV risk.

Australian and international recommendations and expert guidance for the medicines described in this article can help to:

- decide on the order of medicines to be prescribed
- understand therapeutic targets
- know what to monitor
- understand how to up-titrate dosages.

Useful resources

For health professionals

- Kidney Health Australia 2020 CKD Management in Primary Care handbook 4th edition
- KDIGO 2021 Clinical practice guideline for the management of blood pressure in chronic kidney disease
- KDIGO 2020 Clinical practice guideline for diabetes management in chronic kidney disease
- CARI 2022 Guidelines Management of cholesterol-lowering therapy in people with chronic kidney disease
- RACGP National guide to a preventive health assessment for Aboriginal and Torres Strait Islander people. Chapter 13: Chronic kidney disease prevention and management
- NPS MedicineWise Chronic kidney disease: clinical resources and tools for more guidelines, medicine management strategies and resources
- Veterans'MATES 2019 Topic 56: Medicines and your kidneys

For your patients

- NPS MedicineWise: Fact sheet How healthy are my kidneys and how do I stay well?
- NPS MedicineWise: Patient action plan My Kidney Health Plan
- NPS MedicineWise Card stack: How do I know if my kidneys are healthy and why is it important?
- Kidney Health Australia has developed patient resources Books, publications and fact sheets to help manage your patients with kidney disease.
- My Kidneys My Health (handbook) Available as a free hardcopy handbook and as a free mobile smart phone app
- How to look after your kidneys (fact sheet)
- All about chronic kidney disease (fact sheet).
- Make the Link: Chronic Kidney Disease, Diabetes and Cardiovascular Disease (fact sheet).
- This video from Kidney Health Australia explains what your kidneys do and how to keep your kidneys healthy
- Resources for Aboriginal and Torres Strait Islander peoples

Kidney Health® Australia

NACCHO National Aboriginal Community Controlled Health Organisation

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