CAPTIVATE
The Chronic kidney disease Adaptive Platform Trial Investigating Various Agents for Therapeutic Effect

Standard of Care Appendix

Overview of current standard of care treatment for patients with chronic kidney disease

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1 BACKGROUND

1.1 Role of the Standard of Care Appendix

The CAPTIVATE trial is an adaptive platform randomised controlled trial that aims to identify effective therapeutic agents individually and in combination that slow the rate of eGFR decline in patients with chronic kidney disease (CKD) receiving standard of care (SOC). The purpose of this document is to provide guidance around SOC treatment based on the latest international clinical guidelines and to ensure consistency across the study. These recommendations are general in nature and decisions regarding specific treatments should be made by, or in consultation with, the patient's treating doctor. It is also recognised that certain therapeutic agents may not be readily accessible or approved for use in participating countries, which will be addressed in the Country Specific Guidelines (Refer to Section 6). Treatment for those with kidney failure requiring kidney replacement therapy (KRT) such as dialysis or transplantation are outside the scope of this guideline. It is anticipated that as new therapies are discovered and incorporated into therapeutic regimens, and clinical guidelines, the definition of SOC will be updated. The SOC Appendix is a living document which will be reviewed every 6 months and amended as guidelines are updated.

1.2 Definition of chronic kidney disease

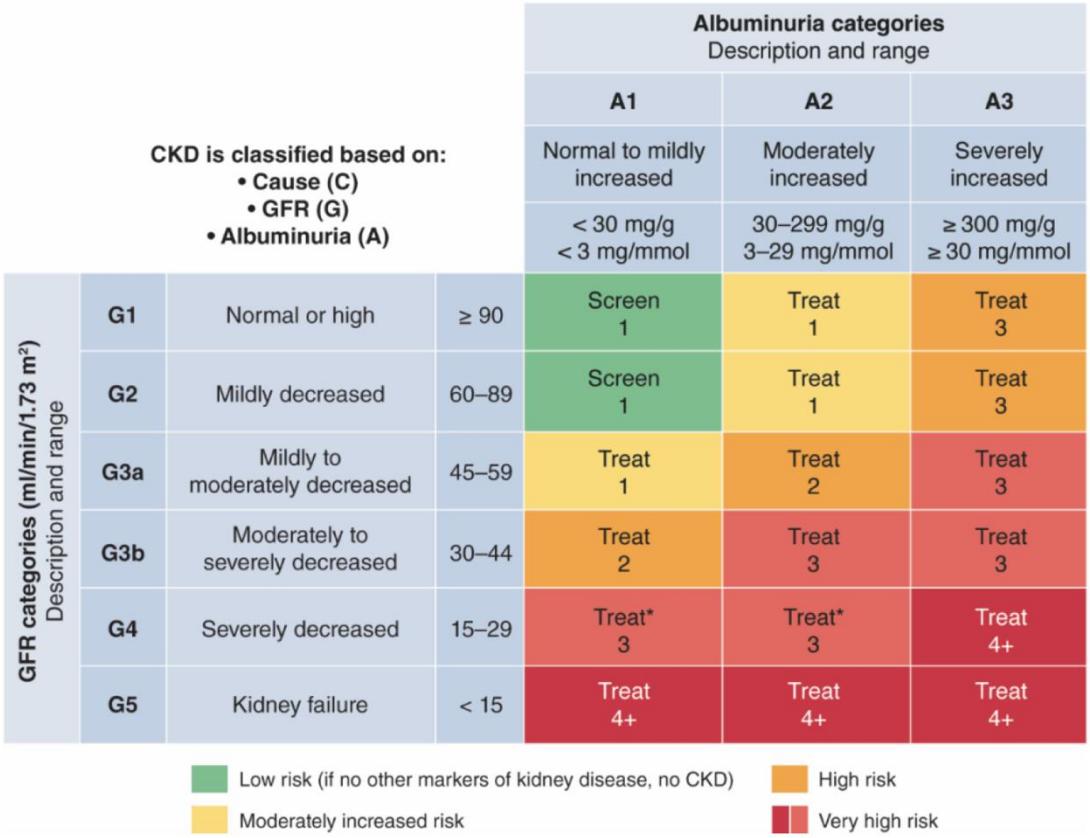
The widely accepted Kidney Disease: Improving Global Outcomes (KDIGO) definition for CKD is "abnormalities of kidney structure or function, present for > 3 months, with implications for health"[1]. CKD is classified based on cause, estimated glomerular filtration rate (eGFR) and degree of albuminuria. Lower eGFR and greater albuminuria correlate with a higher risk of progressive disease and kidney failure (Figure 1).

1.3 Recommended approach to chronic kidney disease management

All individuals with CKD should be assessed and managed according to the KDIGO classification system (Figure 1).

Non-pharmacological lifestyle modifications including healthy diet, regular physical activity and smoking cessation are recommended for all people with CKD. Current standard drug therapy includes renin-angiotensin system (RAS) and sodium-glucose co-transporter 2 (SGLT2) inhibitors where appropriate and/or available. Risk assessment for common comorbid conditions including hypertension, type 2 diabetes mellitus and cardiovascular disease should be performed for all individuals and treated accordingly.

Figure 1. KDIGO chronic kidney disease (CKD) heatmap: Approach to staging and management of CKD according to estimated glomerular filtration rate (eGFR) and albuminuria.



The greater intensity of colouring depicts the risk of kidney failure from green to deep red. CKD treatment is recommended in those with mild-moderate decrease in eGFR and/or moderately increased albuminuria indicated by urine albumin to creatinine ratio (uACR). The recommended annual frequency of eGFR and albuminuria monitoring are outlined by the figures in each box (1 to 4+ times per year)[2].

1.4 Monitoring and expected variations in eGFR and albuminuria

The frequency of monitoring of eGFR and albuminuria rises according to the severity of kidney disease ranging between once to 4 times per year (Figure 1). A change in eGFR of >20% and more than doubling of albuminuria on subsequent tests exceeds expected laboratory variability and warrants further evaluation. A reduction in eGFR of > 30% following commencement of haemodynamically active therapeutic agents (e.g., RAS inhibitors, SGLT2 inhibitors) or intensive blood pressure lowering exceeds the expected response and warrants further evaluation.

2 NON-PHARMACOLOGICAL RECOMMENDATIONS

2.1 Dietary recommendations

A healthy and diverse diet is advised for people with CKD. Where available, an accredited nutrition health provider such as a registered dietician should be consulted to provide specific dietary recommendations to meet an individual's specific needs.

2.1.1 Protein intake

- The level of evidence regarding protein intake in CKD is low. Moderate protein restriction to a daily intake of 0.8g/kg/day can be considered in adults with an eGFR <60ml/min/1.73m^2 who do not require KRT.
- Protein restriction is contraindicated in those at risk of undernutrition or with sarcopenia or cachexia.
- Intake of plant-based proteins may be preferred to animal-based protein.

2.1.2 Salt intake

- Suggest a restriction in sodium intake to <2g (<90mmol) per day in adults with CKD. This is equivalent to <5g of sodium chloride (salt) per day.

2.2 Physical activity and weight management

The following advice is general, and recommendations may need to be amended according to the individual's level of frailty, comorbidities, cardiovascular health, exercise tolerance, risk of falls and overall health. Where indicated and available, referrals to health professionals including physiotherapists, dieticians, occupational therapists, and psychologists should be offered. These recommendations are based on the current KDIGO guidelines and are based on limited data.

- Individuals with CKD should be encouraged to undertake regular moderate-intensity physical activity for at least 150 minutes per week if appropriate.
- A healthy weight of a body mass index (BMI) between 20-25kg/m^2 should be maintained.
- Individuals with obesity (BMI ≥30kg/m^2) should be encouraged to lose weight, particularly in those with eGFR ≥20ml/min/1.73m^2.

2.3 Smoking cessation

All individuals with CKD should be advised to cease tobacco products. Referral to smoking cessation programs may be considered.

3 FIRST LINE THERAPEUTIC AGENTS

3.1 Renin-angiotensin system blockade

Several landmark randomized controlled trials (RCT) have shown RAS blockade slows eGFR decline, reduces proteinuria and is protective against kidney failure and adverse cardiovascular outcomes

independent of their blood pressure effect[3-7]. There is a class effect, and the agent of choice should be guided by local practice patterns, clinician preference and availability.

The current guidelines RAS inhibition in individuals with CKD include[2]:

- Recommended for those with:
  - CKD (G1-G4) with severely increased albuminuria (A3) without diabetes
  - CKD (G1-G4) with moderate-severely increased albuminuria (A2-A3) with diabetes
- Recommend considering for specific indications:
  - CKD (G1-G4) with normal-mildly increased albuminuria (A1) and heart failure with reduced ejection fraction
  - CKD (G1-G4) with normal-mildly increased albuminuria (A1) and hypertension
- Suggest in those with:
  - CKD (G1-G4) with moderately increased albuminuria (A2) without diabetes

Table 1. Examples of common renin-angiotensin system inhibitors and their usual daily dose range and frequency[8].

Angiotensin-converting Enzyme Inhibitor (ACEi)			**Angiotensin 2 Receptor Blocker (ARB)**		
Drug name	**Daily Dose Range (mg/day)**	**Frequency (per day)**	**Drug name**	**Daily Dose Range (mg/day)**	**Frequency (per day)**
Captopril	25-100	2	Candesartan	8-32	1
Enalapril	5-40	1-2	Irbesartan	150-300	1
Fosinopril	10-40	1	Losartan	25-100	1-2
Perindopril	4-8	1	Olmesartan	20-40	1
Quinapril	10-80	1	Telmisartan	20-80	1
Ramipril	2.5-10	1	Valsartan	80-320	1-2

Practical considerations

- Avoid dual RAS inhibitor therapy with any combination of ACEi or ARB.
- Target the maximum labelled dose of RAS inhibitor therapy if tolerated.
- Review blood pressure, serum potassium and serum creatinine within 2-4 weeks of drug initiation or dose adjustment.
- Dose reduction or drug discontinuation may need to be considered if:
  - The serum potassium is >5.5mmol/L despite medical management of hyperkalaemia.
  - A reduction in eGFR of ≥30% is seen within 4 weeks of treatment with no alternate cause identified.
  - Symptomatic hypotension occurs.
- Where possible and appropriate, RAS inhibition should be continued or re-initiated as soon as possible.

3.2 Sodium-glucose co-transporter 2 inhibitors

Meta-analyses of several large RCTs have shown that SGLT2 inhibitors reduce the risk of kidney failure in those with CKD and albuminuria and reduce the risk of acute kidney injury and cardiac events including hospitalisation for heart failure, cardiovascular death and myocardial infarction regardless of kidney function or diabetes status[9,10].

The current recommended indications for SGLT2 inhibitors in individuals with CKD with an eGFR ≥20ml/min/1.73m^2 include[2]:

- Moderate-severe albuminuria (uACR ≥200mg/g or 20mg/mmol)
- Type 2 diabetes mellitus with or without albuminuria
- Heart failure with or without albuminuria

It is suggested that SGLT2 inhibitor therapy also be considered in individuals with CKD with:

- eGFR 20-45ml/min/1.73m^2 with uACR <200mg/g

There are country-level variations in the availability and funding of these agents. SGLT2i may therefore not be widely accessible as SOC in certain countries (Section 6).

Table 2. Examples of sodium-glucose co-transporter 2 inhibitors and recommended dosage[11].

Drug name	Maximum daily labelled dose
Dapagliflozin	10mg daily
Empagliflozin	25mg daily
Canagliflozin	300mg daily

Practical considerations

- Consider withholding SGLT2 inhibitor pre-operatively, during critical illness or where a prolonged period of fasting is anticipated.
- SGLT2 inhibitors may lower the risk of hyperkalaemia including when prescribed concurrently with medications that increase serum potassium (e.g. ACE inhibitors, ARBs and mineralocorticoid receptor antagonists)[12]. Therefore, when ceased or withheld, consider monitoring serum potassium where appropriate.
- A reversible rise in serum creatinine by <30% may be seen and should not prompt drug cessation for this reason.

4 TARGETED THERAPIES

4.1 Hypertension

Hypertension is one of the leading causes in CKD and individuals with CKD are also more likely to develop hypertension compared with the average population. Adults with hypertension and CKD are generally recommended to be treated to target a systolic blood pressure of <120mmHg where appropriate. Blood pressure targets should be individualised based on age, comorbid disease including cardiovascular disease, risk of falls, frailty, and life-expectancy. Less intensive therapy may also be required in individuals with symptomatic postural hypotension.

4.2 Type 2 Diabetes Mellitus

Diabetes is also one of the leading causes of CKD. As described above, both RAS inhibitors and SGLT2 inhibitors are indicated in diabetic kidney disease where tolerated. Additional pharmacological management considerations are outlined in Table 3.

Table 3. Pharmacological management of individuals with type 2 diabetes mellitus and chronic kidney disease

Drug class	Indication
Nonsteroidal mineralocorticoid receptor antagonists (e.g., finerenone)[1]	eGFR >25ml/min/1.73m^2, normal serum potassium and albuminuria (uACR >30mg/g) despite maximum tolerated RAS inhibitor
Glucagon-like peptide receptor agonist (e.g., semaglutide)	Suboptimal glycaemic control despite metformin and SGLT2 inhibitor or contraindications to those medications

[1] *Note: Steroidal MRAs (e.g., spironolactone, eplerenone) are indicated in heart failure, hyperaldosteronism, or refractory hypertension, and should not be used in conjunction with a nonsteroidal MRA. They also have a higher risk of causing hyperkalaemia than nonsteroidal agents. The decision on which agent to use should be made by the treating physician.*

4.3 Cardiovascular disease

Individuals with CKD are at an increased risk of cardiovascular disease. Generally, the treatment principles for those with an increased risk of atherosclerotic cardiovascular disease are the same regardless of CKD status. The specific recommendations for statin therapy in individuals with CKD include those:

- Age ≥50 years and eGFR <60ml/min/1.73m^2 not requiring chronic dialysis or kidney transplantation
- Age ≥50 years and eGFR ≥60ml/min/1.73m^2
- Age 18-49 not requiring chronic dialysis or kidney transplantation AND
    - Confirmed coronary heart disease
    - Diabetes mellitus
    - History of ischaemic stroke
    - Estimated 10-year cardiovascular risk of >10%

In individuals with CKD and established ischaemic cardiovascular disease, antiplatelet therapy with low-dose oral aspirin is recommended for secondary prevention.

5 COMPLICATIONS OF CKD

5.1 Hyperkalaemia

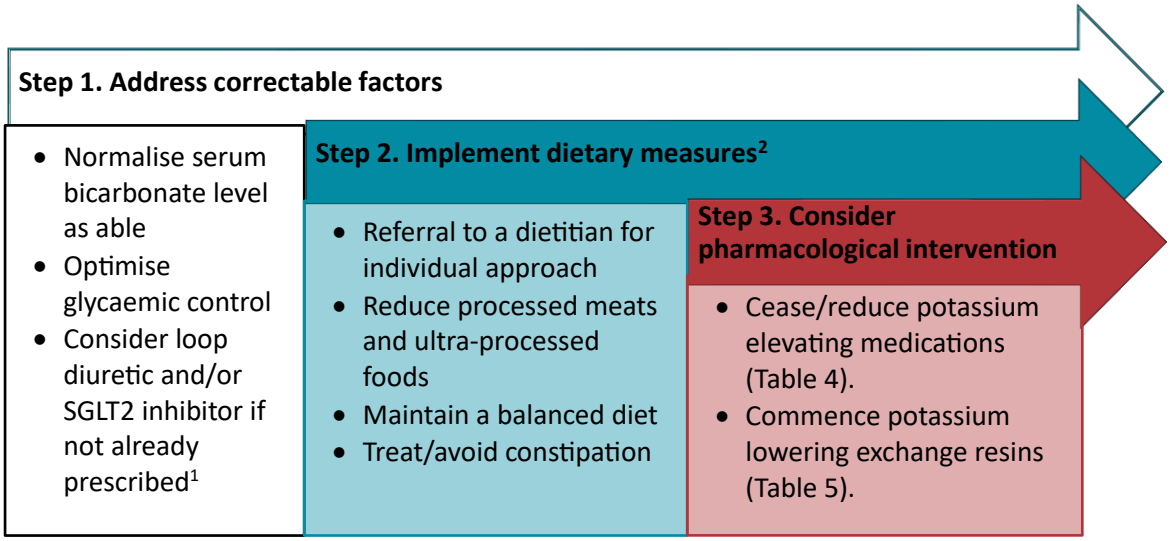
Potassium regulation is predominantly managed by the kidneys and is therefore at risk of disruption in CKD. Normal serum potassium levels are vital for cell membrane electrophysiology. Abnormal levels can lead to dangerous cardiac conduction abnormalities. The risk of hyperkalaemia rises as

eGFR decreases, compounded by therapeutic agents commonly used in CKD (e.g., RAS inhibitors, MRAs) that also increase serum potassium.

This appendix provides a general recommendation for the management of non-emergent hyperkalaemia based on international guidelines (Figure 2). This may be referred to throughout the study period as a participant's risk of hyperkalaemia may change depending on the study intervention or their clinical status. At each treatment step, it is recommended that the serum potassium is rechecked, and the participant's treating physician is consulted.

Please refer to your local guidelines for the normal reference range for serum potassium as this may be variable dependent on the laboratory. The management of moderate-severe hyperkalaemia is outside the scope of this document. Moderate-severe hyperkalaemia is typically defined as a serum potassium of ≥6.0mmol/L.

Figure 2. Stepwise approach to the management of non-emergent hyperkalaemia.



[1] SGLT2 inhibitors have been shown to lower serum potassium levels including when used in conjunction with RAS inhibitors and MRAs.

[2] Refer to the International Society of Nephrology RAS inhibition toolkit online for additional guidance around dietary measures available at https://www.theisn.org/initiatives/toolkits/raasi-toolkit/#1684867542809-330edb79-52b4.

Table 4. Examples of medications associated with hyperkalaemia

Category	Examples
Potassium supplements	Slow K, Span K, Chlorvescent
Potassium-sparing diuretics	Amiloride, triamterene
RAS inhibitors	ACE inhibitors Angiotensin receptor blockers
MRAs	Nonsteroidal MRAs Steroidal MRAs
Other	Angiotensin receptor-neprilysin inhibitors Beta blockers (e.g., metoprolol, atenolol) Calcineurin inhibitors (e.g., cyclosporine, tacrolimus)

	Digoxin Heparin NSAIDs and COX2 antagonists (e.g., ibuprofen, naproxen, diclofenac)[$] Pentamidine Trimethoprim

[$] The Australian Medicines Handbook advises that the use of NSAIDs or COX2 antagonists should be reviewed for concomitant use with RAS inhibitors especially in the context of deteriorating renal function.

Table 5. Potassium exchange resins

Drug	Mechanism of Action	Onset	Dose	Adverse Effects*
Polystyrene sulfonate Resins	Sodium or calcium ions are exchanged for potassium ions in the GIT, which are then excreted faecally.	Several hours	Oral: Commence at 15g daily, up to maximum four times daily Rectal: 30g once daily	GIT: Constipation, faecal impaction, diarrhoea, nausea, vomiting, anorexia Electrolyte disturbances: Hypokalaemia, hypomagnesaemia, hypernatraemia, hypo/hypercalcaemia Rare/severe: Ischaemic colitis, GIT obstruction, ulceration, perforation or necrosis
Patiromer	Cation exchange polymer that binds potassium ions in the GIT lumen which are then excreted faecally.	4-7 hours	Commence at 8.4g once daily, up to maximum 25.2g daily	GIT: Constipation, diarrhoea, pain, flatulence, nausea, vomiting Electrolyte disturbances: Hypokalaemia, hypomagnesaemia
Sodium zirconium cyclosilicate	Binds potassium ions in exchange for hydrogen and sodium cations in the GIT, which are then excreted faecally.	4 hours	Commence at 10g up to a maximum three times daily for 48 hours, then maintenance of maximum 10g once daily.	Oedema Hypokalaemia

The dose and duration of potassium exchange resin administration should be as low and as short as possible. Cease when no longer required. Patiromer and zirconium are not currently available in India or New Zealand.
** Patiromer and sodium zirconium cyclosilicate have not been studied in patients with severe constipation, a history of bowel obstruction, major gastrointestinal surgery or post-operative bowel motility disorders.*
Abbreviations: GIT, gastrointestinal tract

6 COUNTRY SPECIFIC GUIDELINES

Country	Difference from International SOC Guidelines (Including Public Funding Criteria)
Australia	Nil
India	Nil
Italy	Nil
New Zealand	Empagliflozin is currently the only funded SGLT2i under the following authority criteria: Type 2 diabetes with an HbA1c > 53 mmol/mol despite at least 3 months of regular use of at least one blood-glucose lowering agent, AND not on a funded GLP1RA AND any of the following: • Urinary albumin:creatinine ratio > 3 mg/mmol and/or eGFR < 60 mL/min OR • Known cardiovascular disease (any ischaemic heart disease, cerebrovascular event, peripheral vascular disease, congestive heart failure or familial hypercholesterolaemia) OR • 5-year cardiovascular disease risk > 15% OR • A high lifetime cardiovascular risk due to onset of diabetes in childhood or as a young adult OR • Māori or Pacific ethnicity Finerenone is currently not funded for any indication.

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