

Practical guide to RAASi* optimisation in individuals with cardiorenal disease

Two key aims:

1

The optimisation of RAASi therapies for cardiorenal protection

2

The prevention and management of hyperkalaemia

RAASi therapy optimisation describes prescription of RAASi therapy at either:
The highest licensed dose for the indication **or** the maximal tolerated dose

RAASi therapy optimisation is essential in cardiorenal disease to provide cardiorenal protection

- ✓ International evidence-based guidelines, for both chronic kidney disease (CKD) and heart failure (HF), recommend treatment with RAASi therapy at target or maximum tolerated doses to achieve the **best clinical outcomes**¹⁻³
- ✓ In individuals with CKD, RAASi therapies have been evidenced to lower blood pressure and proteinuria, slow the decline of estimated glomerular filtration rate (eGFR) and reduce the risk of end stage kidney disease, cardiovascular (CV) morbidity and all-cause mortality^{4,5}
- ✓ In individuals with HF, RAASi therapies have demonstrated a reduction in CV morbidity and mortality⁶

RAASi therapy optimisation and hyperkalaemia

- ✓ RAASi therapy, in addition to underlying cardiorenal disease, confers an increased risk of hyperkalaemia due to reduced urinary potassium excretion^{7,8}
- ✓ **Hyperkalaemia is a predictable, recurrent and manageable risk in individuals on RAASi therapy – requiring a pre-emptive, proactive and long-term approach**
- ✓ Hyperkalaemia is often managed via the down-titration or discontinuation of RAASi therapy
- ✓ Down-titration or discontinuation of RAASi therapy is associated with increased morbidity and mortality in individuals with cardiorenal disease⁹⁻¹²
- ✓ There are alternative potassium lowering strategies and therapies available which can facilitate the continuation and optimisation of RAASi therapy. See '**Potassium lowering strategies and therapies**'
- ✓ **International evidence-based guidelines, for both CKD and HF, emphasise the importance of proactively managing hyperkalaemia to facilitate RAASi therapy optimisation; recommending the use of alternative potassium lowering strategies and therapies, before RAASi therapy down-titration or discontinuation, where clinically appropriate**¹⁻³

How to optimise RAASi therapy in practice

All individuals prior to starting RAASi therapy require thorough assessment:

- ✓ Blood pressure
- ✓ Fluid status
- ✓ Renal function including serum potassium
(CAUTION in starting ACEi/ARB and do not start MRA if potassium >5.0 mmol/L¹³ – consider 'Potassium lowering therapies and strategies' to reduce potassium – seek specialist advice if needed)
- ✓ Concurrent medications
- ✓ Review of risk factors for hyperkalaemia:
 - o Serum potassium
 - o Potassium elevating drugs**
 - o Diet
 - o Poor glycaemic control
 - o Constipation

Monitoring after optimisation

Once RAASi therapy dose is established, monitor as per '**Long-term monitoring advice sheet for individuals with cardiorenal disease on RAASi therapy with hyperkalaemia**'

All individuals must be monitored following initiation and each titration of RAASi therapy dose:

- ✓ Clinical status
- ✓ Renal function:
 - o For ACEi/ARB measure 1–2 weeks after initiation and every dose titration¹³
 - o For MRA measure 1 week after initiation and every dose titration, then monthly for 3 months, then 3-monthly for first year and 4-monthly thereafter¹³
 - o **For individuals initiating or titrating haemodynamically active therapies, e.g. RAASi, some eGFR reduction can be expected.¹ If serum creatinine rises by >30%, or eGFR falls >25%, this exceeds expected variability and warrants further assessment¹⁴**
- ✓ Serum potassium – If hyperkalaemia occurs please see '**Practical guide to the definition and management of acute hyperkalaemia in individuals with cardiorenal disease on RAASi therapy**'

*Renin Angiotensin Aldosterone System inhibitor therapy (ACE inhibitors, angiotensin II receptor blockers, angiotensin receptor/neprilysin inhibitor, mineralocorticoid receptor antagonists)

Potassium lowering strategies and therapies:

1. Address correctable causes of hyperkalaemia:

- ✓ **Adjust potassium elevating drugs**¹³** – Prioritise those that can be swapped/withheld with least adverse consequences. **Down-titrate/discontinue RAASi therapy as a last resort¹** – see 'RAASi therapy in the context of hyperkalaemia'
- ✓ **Modify diet** – Advise a healthy, diverse diet with higher consumption of plant-based foods than animal-based foods and low consumption of ultra processed foods.¹ If potassium remains >5.5 mmol/L once non-dietary factors are addressed, refer to specialist dietician¹³
- ✓ **Correct metabolic acidosis¹³** – Metabolic acidosis increases the risk of hyperkalaemia
- ✓ **Optimise glycaemic control¹³** – Poorly controlled diabetes increases the risk of hyperkalaemia
- ✓ **Avoid/address constipation¹³** – Constipation increases the risk of hyperkalaemia

2. Consider potassium lowering medications (acutely or longer term):

- ✓ **Diuretics** – Can increase potassium excretion
- ✓ **Bicarbonate** – Consider adding oral sodium bicarbonate if serum bicarbonate <22 mmol/L
- ✓ **Potassium binders** – Remove potassium from the body via the gastrointestinal tract¹³

3. Prevent recurrence of hyperkalaemia:

- ✓ Recurrence of hyperkalaemia should be anticipated and steps taken to avoid it¹³
- ✓ Careful prescribing of potassium elevating drugs – use only where clearly indicated, with particular care if combinations are required, e.g. ACEi/ARB/ARNi + MRA for heart failure (HF)¹³
- ✓ Regular review of correctable causes and consideration of the need for potassium lowering medications (as above)¹³
- ✓ Regular monitoring of bloods (potassium and renal function) and review should occur at the frequency appropriate for the disease state and the individual, e.g. 1–4 times per year for chronic kidney disease (CKD)¹ and HF², with additional monitoring during intercurrent illness (especially dehydrating illness), titration of medications that affect potassium levels or renal function, or change in the underlying cardiorenal condition
- ✓ Education of individuals with cardiorenal disease

✗ **Sick day guidance** – A temporary pause of RAASi therapy, diuretics, metformin and sodium-glucose co-transporter-2 inhibitors during acute dehydrating illness may decrease the risk of acute kidney injury and hyperkalaemia. However, the evidence base for this is weak and there is potential for harm if these medications are not re-instated. **Sick day guidance should be based on an individual risk assessment and there must be a clear plan to re-instate any paused medications.**^{1,13}

**Potassium elevating drugs¹³

- RAASi (ACE inhibitors, angiotensin II receptor blockers, mineralocorticoid receptor antagonists)
- Potassium supplements
- Potassium-sparing diuretics
- Trimethoprim/co-trimoxazole
- Non-steroidal anti-inflammatory drugs
- Non-selective beta-blockers
- Antifungals
- Digoxin
- Salt substitutes
- Herbal medicines (e.g. alfalfa, dandelion)

RAASi therapy in the context of hyperkalaemia:

- Hyperkalaemia associated with RAASi use can often be managed by measures to reduce potassium other than down-titration or discontinuation of RAASi therapy¹
- Down-titration or discontinuation of RAASi therapies is associated with adverse clinical outcomes in CKD and HF⁹⁻¹²
- Only down-titrate or discontinue RAASi as a last resort; if hyperkalaemia is uncontrolled despite '**Potassium lowering strategies and therapies**', or symptomatic hypotension or serum potassium >6.5 mmol/L (until normokalaemia achieved)¹
- Re-initiate and re-optimize RAASi therapies that are down-titrated or discontinued once normokalaemia is achieved wherever possible – utilise appropriate '**Potassium lowering therapies and strategies**'
- If hyperkalaemia is preventing RAASi optimisation, seek specialist advice
- N.B. If RAASi therapies are discontinued, also discontinue potassium lowering therapies as appropriate

References:

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int.* 2024 Apr;105(4S):S117–S314.
2. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. *European Heart Journal.* 2021;42(36):3599–726.
3. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation.* 2022;145(18):e895–1032.
4. Jafar TH. Angiotensin-Converting Enzyme Inhibitors and Progression of Nondiabetic Renal Disease. *Annals of Internal Medicine.* 2001;135(2):73–87.
5. Xie X, Liu Y, Perkovic V, Li X, Ninomiya T, Hou W, et al. Renin-Angiotensin System Inhibitors and Kidney and Cardiovascular Outcomes in Patients With CKD: A Bayesian Network Meta-analysis of Randomized Clinical Trials. *American Journal of Kidney Diseases.* 2016;67(5):728–41.
6. Werner C, Baumhäkel M, Teo KK, Schmieder R, Mann J, Unger T, et al. RAS Blockade with ARB and ACE Inhibitors: Current Perspective on Rationale and Patient Selection. *Clinical Research in Cardiology.* 2008;97(7):418–31.
7. Sarnowski A, Gama RM, Dawson A, Mason H, Banerjee D. Hyperkalemia in Chronic Kidney Disease: Links, Risks and Management. *International Journal of Nephrology and Renovascular Disease.* 2022;15:215–28.
8. Hundemer G, Sood M. Hyperkalemia with RAAS Inhibition: Mechanism, Clinical Significance, and Management. *Pharmacological Research.* 2021;172:105835.
9. Kanda E, Rastogi A, Murohara T, Lesén E, Agiro A, Arnold M, et al. Clinical Impact of Suboptimal RAASi Therapy Following an Episode of Hyperkalemia. *BMC Nephrology.* 2023;24(1):18.
10. Epstein M, Reaven NL, Funk SE, McGaughey KJ, Oestreicher N, Knispel J. Evaluation of the Treatment Gap Between Clinical Guidelines and the Utilization of Renin-Angiotensin-Aldosterone System Inhibitors. *The American Journal of Managed Care.* 2015;21(11 Suppl):S212–20.
11. Linde C, Bakhal A, Furuland H, Evans M, McEwan P, Ayoubkhani D, et al. Real-World Associations of Renin-Angiotensin-Aldosterone System Inhibitor Dose, Hyperkalemia, and Adverse Clinical Outcomes in a Cohort of Patients With New-Onset Chronic Kidney Disease or Heart Failure in the United Kingdom. *Journal of the American Heart Association.* 2019;8(22):e012655.
12. Leon SJ, Whitlock R, Rigatto C, Komenda P, Bohm C, Sucha E, et al. Hyperkalemia-Related Discontinuation of Renin-Angiotensin-Aldosterone System Inhibitors and Clinical Outcomes in CKD: A Population-Based Cohort Study. *American Journal of Kidney Diseases.* 2022;80(2):164–73.e1.
13. Alfonzo A, Harrison A, Baines R, Chu A, Mann S, MacRury M. Clinical Practice Guidelines: Treatment of Acute Hyperkalemia in Adults. UKKA. 2023. Available from: https://ukkidney.org/sites/renal.org/files/FINAL%20VERSION%20-%20UKKA%20CLINICAL%20PRACTICE%20GUIDELINE%20-%20MANAGEMENT%20OF%20HYPERKALAEMIA%20IN%20ADULTS%20-%2020191223_0.pdf
14. NICE. Chronic Kidney Disease: Assessment and Management. NICE [Internet]. www.nice.org.uk. 2021. Available from: <https://www.nice.org.uk/guidance/ng203>