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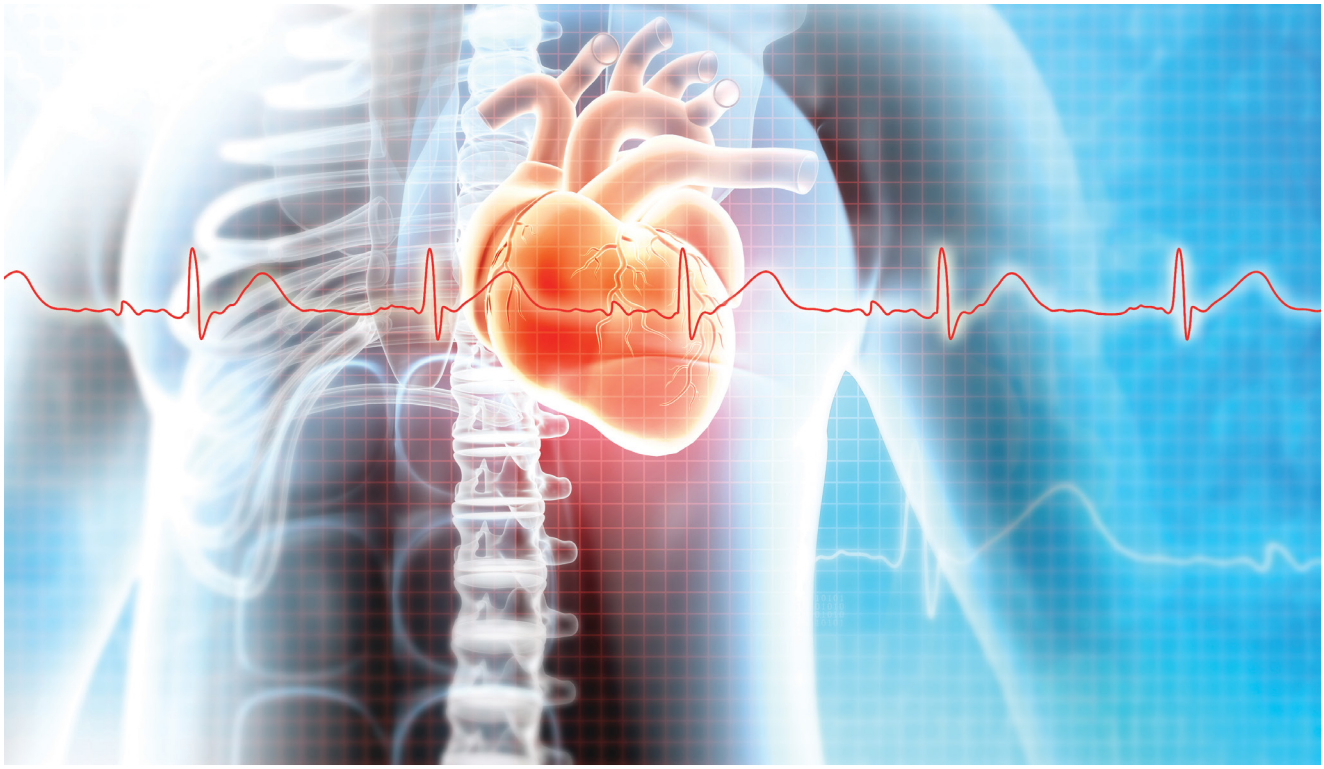
GUIDEBOOK

Enabling RAASi optimisation in heart failure: practical evidence



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RAASi: renin-angiotensin-aldosterone system inhibitors

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Enabling RAASi optimisation in heart failure: practical evidence

Clinical trial data and real-world evidence demonstrate the key role sodium zirconium cyclosilicate can play in correcting hyperkalaemia, particularly for patients with heart failure and chronic kidney disease who require treatment with renin-angiotensin-aldosterone system inhibitors.

Angiotensin-converting enzyme inhibitors (ACEis), angiotensin II receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), and neprilysin inhibitors (ARNIs) are collectively referred to as renin–angiotensin–aldosterone system inhibitors (RAASi). They are foundational therapies for heart failure (HF) and chronic kidney disease (CKD). In patients with heart failure with reduced ejection fraction (HFrEF), these therapies form the cornerstone of disease-modifying treatment, reducing symptoms and lowering the risk of HF-related hospitalisations.[1]

Similarly, RAASi plays a critical role in managing CKD, including patients with hypertension.[2] Current clinical guidelines for HF (European Society of Cardiology 2021) and CKD (KDIGO 2024)[1,2] recommend using the highest tolerated doses of these agents to maximise therapeutic outcomes and improve patient prognosis.

Importance of optimal RAASi dosing

Achieving guideline-directed medical therapy (GDMT) is crucial for the effective management of HF, particularly through optimal medication dosing. The importance of dose optimisation was highlighted in the 2022 STRONG-HF trial, a multinational, open-label, randomised study, which showed that intensive up-titration of HF medications led to better symptom control, improved quality of life, and a reduced risk of 180-day all-cause death or HF readmission compared to usual care.[3]

Despite these proven benefits, studies reveal significant challenges in successfully applying dosage optimisation guidelines. A recent multinational observational cohort study involving 68,172 patients found consistent low up-titration and early discontinuation of GDMT.[4] Across drug classes, only 10–30% of patients reached target doses within a year, and discontinuation rates were as high as 55%. These challenges were particularly pronounced in older adults and patients with CKD, who were more likely to receive suboptimal doses.

Failure to adhere to GDMT has clear consequences for patient outcomes. In a 2015 study by Epstein *et al* involving over 205,000 US patients, mortality rates were 9.8% for stage 3-4 CKD patients and 13.7% for HF patients receiving the maximum RAASi dose. Mortality increased to 20.3% in CKD patients and 27.7% in HF patients when RAASi dosing was suboptimal and rose even further to 22.4% in CKD and 30.1% in HF when RAASi therapy was discontinued.[5] These data indicate submaximal RAASi dosing is almost as detrimental as discontinuation.

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Barriers to the use of GDMT and the risk of suboptimal dosing

Several barriers hinder the implementation of GDMT for HF and CKD, affecting both health systems and individual patient care.[6,7] These barriers include:

- Health system challenges
  - Inadequate clinical resources
  - Limited education for both clinicians and patients
  - Fragmented care delivery models
  - Drug access and costs
  - Clinical inertia in the face of perceived patient stability
- Patient and clinical factors
  - Polypharmacy
  - Multimorbidity
  - Frailty
  - Medication intolerances
  - Hyperkalaemia

Additionally, some patient populations are under-represented in clinical trials, which limits understanding of the specific barriers they face in treatment.

These obstacles are multifaceted and vary depending on healthcare systems and medication intolerances are particularly impactful on the failure to achieve optimal GDMT in both HF and CKD. Hyperkalaemia is an important, but addressable, risk factor for suboptimal treatment in HF and CKD patients, something which can affect the confidence of clinicians in initiating or up-titrating RAASi to achieve GDMT.

Hyperkalaemia: the problem

CKD (from stage 3) is an independent predictor of hyperkalaemia, but RAASi treatment further amplifies this risk. Increased potassium levels beyond the normal range are closely linked with higher mortality in HF and CKD patients.[8] For example, one population-based cohort study demonstrated that 28% of CKD patients experienced hyperkalaemia, with incidence increasing in line with progressive stages of CKD. Risk factors for developing hyperkalaemia included diabetes, HF, and the use of ACEis, potassium supplements, or spironolactone. Hospitalisation rates among CKD patients rose from 34% before hyperkalaemia to 57% afterwards (before–after risk ratio 1.72 (95% CI 1.69–1.74)). Compared to patients without hyperkalaemia, those with elevated potassium had a 2.11-fold higher risk of hospitalisation, over four-times higher risk of intensive care admission, and nearly five-times higher risk of death.[9]

Hyperkalaemia is also an important predictor of failure to achieve GDMT for HF and CKD patients in clinical practice, including RAASi optimisation. For example, Trevisan *et al* found that new users of mineralocorticoid receptor antagonists (MRAs) who developed hyperkalaemia frequently discontinued therapy, with three-quarters of patients failing to reinitiate MRA treatment within the next year.[10] Hyperkalaemia further impacts the optimisation of drug therapy for HF and CKD. A 2023 study by Kanda et al demonstrated that after an episode of hyperkalaemia, 33% of 15,488 US patients and 32% of 6,020 Japanese patients failed to fill a new RAASi prescription. In both cohorts, patients who discontinued or down-titrated RAASi treatment faced a higher risk of cardiorenal complications within six months, compared to those who maintained or increased their dosage.[11]

The incidence of hyperkalaemia arising from the real-world use of RAASi is likely higher than reported in clinical trials.[12] A 2021 systematic review and meta-analysis of adverse events associated with antihypertensive treatment found

> Managing hyperkalaemia is therefore crucial for the effective treatment of heart failure and chronic kidney disease, given its impact on RAASi therapy

that patients were twice as likely to experience hyperkalaemia as an adverse outcome from RAASi.[13] Managing hyperkalaemia is therefore crucial for the effective treatment of HF and CKD, given its impact on the success of RAASi therapy. While dietary measures can help limit potassium intake, they may not fully mitigate the heightened risk of hyperkalaemia in patients with HF and CKD. Potassium binders, agents which bind and remove potassium in the gut, offer clinicians an additional option to manage hyperkalaemia in these high-risk populations.[14]

Sodium zirconium cyclosilicate: an evidence-based potassium-binding agent

Sodium zirconium cyclosilicate (SZC) is a cation exchange resin that is not absorbed in the gut, selectively binds potassium in the gastrointestinal tract and is then excreted via faeces.[15] SZC offers several advantages over polymer resins in selectively binding to, and removing, potassium[16]:

- It binds potassium in the intestine, removing it from circulation, including elimination from ingested food
- Its selectivity ensures that other ions such as magnesium or calcium are not sacrificed in the elimination of potassium
- It has a favourable tolerability due to non-absorption from the gastrointestinal system.

SZC is a potassium binding agent which, in two separate multicentre phase 3 clinical trials, has demonstrated efficacy and safety in normalising serum potassium.

HARMONIZE was a phase 3, multicentre, randomised, double-blind, placebo-controlled trial evaluating SZC in outpatients with hyperkalaemia. Patients received 10 g SZC three-times daily in the initial 48-hour open-label phase, followed by a maintenance phase of varying drug doses, or placebo, daily for 28 days. SZC significantly lowered serum potassium within the first 48 hours compared to baseline, and during the follow-up phase, all SZC dosing groups maintained lower mean serum potassium levels compared to placebo.[17]

Another multicentre, double-blind, phase 3 trial confirmed the potassium-lowering effects of SZC compared to placebo, with the most clinically applicable effects noted for the 5 g and 10 g doses.[18] A pooled analysis of both of these trials confirmed the effectiveness of SZC in reducing serum potassium levels, as rapidly as one hour post-administration, with a concomitant favourable safety profile.[19] The majority of patients in both of these trials had HF, CKD or diabetes mellitus and/or were prescribed RAASi.

Two additional studies extended the evaluation of SZC's efficacy and safety over longer periods. An 11-month open-label extension of the HARMONIZE trial showed that 79% of patients maintained normokalaemia with once-daily SZC dosing, and the drug was generally well tolerated. RAASi dosing either remained stable or increased in 90.3% of patients, with only 3.6% discontinuing RAASi. Increases in serum potassium concentrations were noted after discontinuation of SZC.[20]

Another longer (12-month) prospective, international, multicentre, open label, single-arm, phase 3 trial assessed SZC-associated correction of hyperkalaemia over 24–72 hours, maintenance of normokalaemia over 12 months, and adverse events. Of 751 entering the initial correction phase of the trial (746 continued to the maintenance phase) most participants had multiple comorbidities, required concomitant RAASi therapy, and over 50% had a history of hyperkalaemia. Initial, short-term three times daily SZC dosing restored normokalaemia in >99% of outpatients within 24–72 hours; maintenance, once daily, individualised dosing with SZC provided maintenance of normokalaemia for almost 9 out of every 10 participants at 12 months. Seventy-four per cent of participants maintained their RAASi doses, while 13% had their RAASi doses increased. Observed adverse events did not lead to an interruption of SZC treatment.[21]

Licensed use of SZC (LOKELMA®)

LOKELMA® (sodium zirconium cyclosilicate; the licensed SZC product in the UK and Europe) is an orally administered potassium binder indicated for the treatment of hyperkalaemia in adults. It is typically prescribed in two phases: an initial correction phase to restore normokalaemia, followed by a maintenance phase to sustain normokalaemia.

Correction phase: The recommended starting dose of LOKELMA is 10 g, administered three times a day orally as a suspension in water. When normokalaemia is achieved, the maintenance regimen should be followed. Typically, normokalaemia is achieved with 24 to 48 hours.

Maintenance phase: A starting dose of 5 g once daily is recommended, with possible titration up to 10 g once daily, or down to 5 g once every other day, as needed, to maintain a normal potassium level. No more than 10 g once daily should be used for maintenance therapy. Serum potassium levels should be monitored regularly during treatment. Dosage adjustments are not required for patients with renal impairment (except for dialysis), hepatic impairment, or for elderly patients. **Refer to the LOKELMA Summary of product characteristics for further details regarding dosage, special populations, adverse reactions, interactions, warnings and precautions, contraindications, and monitoring requirements.**

Safety information

Common adverse events include hypokalaemia, gastrointestinal disorders (constipation, >

> Findings from clinical trials and real-world evaluations of SZC are optimally positioned to inform local clinical guidelines, streamlining management of patients with cardiac and renal diseases

Abbreviations
- ACEis: angiotensin-converting enzyme inhibitors
- ARBs: angiotensin II receptor blockers
- ARNIs: neprilysin inhibitors
- CKD: chronic kidney disease (stage 3-4)
- GDMT: guideline-directed medical therapy
- HF: heart failure
- HFrEF: heart failure with reduced ejection fraction
- MRAs: mineralocorticoid receptor antagonists
- NT-proBNP: N-terminal proB-type natriuretic peptide
- RAASi: renin–angiotensin–aldosterone system inhibitors
- SZC: sodium zirconium cyclosilicate

nausea, diarrhoea, abdominal pain/distention and vomiting), oedema, and hypersensitivity reactions (rash and pruritis). Adverse reactions are mild to moderate and generally resolve during treatment.[22]

LOKELMA® is not absorbed or metabolised by the body and does not meaningfully bind to other medicinal products, so there are limited effects on other medicinal products and other drugs' effects on its action. It should be administered at least two hours before or after oral medications with clinically meaningful gastric pH-dependent bioavailability.[22]

In cases of severe hypokalaemia, treatment should be discontinued. Intestinal perforation has been reported with potassium binders so specific attention should be paid to any signs of intestinal perforation. Its high sodium content must be considered for patients on a low-salt diet.[22]

Real world evidence for LOKELMA®

A retrospective analysis involving 44 patients with HFrEF assessed the effectiveness of SZC in enabling the optimisation of RAASi therapy over 24 months.[23] Prescribing SZC enabled a higher number of patients to take RAASi therapy, with a higher number on guideline-recommended doses across the following drug classes:

- ACEi/ARB/ARNI
  - All patients were prescribed therapy after, compared to 89% before, LOKELMA®
  - 100% were placed on guideline-recommended doses after, compared to 50% before LOKELMA®
- MRA
  - 93% of patients were prescribed therapy after, compared to 52% before, LOKELMA®
  - After LOKELMA®, 50% of patients were prescribed guideline-recommended versus 50% before LOKELMA®

Additionally, prescribing SZC to this cohort also enabled a higher number of patients (64% vs 32%) to be prescribed guideline-directed 'Four Pillar Therapy'. Similar to clinical trial results, SZC was well tolerated and supported RAASi optimisation. Enabling RAASi and controlling potassium levels in this patient cohort resulted in improvements in:

- Mean left ventricular ejection fraction (from 29% to 36%)
- NT-proBNP levels (from 3458 ng/L to 2055 ng/L)
- Hospitalisation rate for hyperkalaemia (from 14% to 7%)
- Hospitalisation rate for HF (from 30% to 11%).

Furthermore, a survival rate of 91% was observed over the 24-month observation period.[23]

A more recent multicentre, observational cohort study compared the likelihood of maintained (stabilised or up-titrated) RAASi therapy at six months following a hyperkalaemia episode among patients with CKD and/or HF treated with SZC for at least 120 days relative to those receiving no K+ binder treatment. Across three countries (USA, Japan and Spain), the study compared a propensity-matched cohort of 1397 patients prescribed SZC versus 4900 patients not prescribed a potassium binder. The primary outcome was the proportion of patients who maintained RAASi therapy at 180 days. Meta-analysed across countries, the odds ratio of maintained RAASi therapy in the SZC cohort versus no potassium binder cohort was 2.56 (95% confidence interval 1.92–3.41; $p < 0.0001$).[24]

In routine clinical practice across three countries, patients treated with SZC were substantially more likely to maintain guideline-concordant RAASi therapy at six months following hyperkalaemia relative to patients with no K+ binder treatment.

Translation of clinical evidence to clinical guidelines

Real-world evidence, coupled with clinical trial results for the safety and efficacy of LOKELMA®, has been translated to international clinical guidelines for managing HF and CKD. Both the ESC[1] and KDIGO[2] international clinical guidelines acknowledge the barrier of hyperkalaemia in achieving optimal RAASi dosing in the HF and CKD populations, respectively. These guidelines also provide more specific information on the place of potassium binders in managing hyperkalaemia as a strategy to achieve optimal RAASi dosing for these patient populations while avoiding RAASi discontinuation.

Findings from clinical trials and real-world evaluations of SZC are also optimally positioned to inform local clinical guidelines, streamlining the management of patients with cardiac and renal diseases. For example, at the Princess of Wales Hospital, Bridgend (NHS Wales), data from SZC studies, practical prescribing information, monitoring protocols, and guideline-directed RAASi up-titration have been fully integrated into a comprehensive set of clinician guidelines. These guidelines are also available to primary care clinicians, enhancing integrated care for patients with HF and CKD.

Conclusion

SZC has emerged as a crucial tool in the management of hyperkalaemia, particularly for patients with HF and CKD who require RAASi therapy. Both clinical trial data and real-world evidence demonstrate the efficacy and safety of SZC in correcting and maintaining normokalaemia, thereby enabling the continued use of RAASi. By preventing hyperkalaemia-induced interruptions to GDMT, SZC can be considered as a support to improve clinical outcomes, including better left ventricular ejection fraction, reduced hospitalisations, and enhanced survival rates.

This study had a small sample size of 44

patients, which reduces the statistical power and may not be sufficient to be representative of the broader HFrEF population. All results require cautious interpretation. The selection of patients treated with SZC was also at the discretion of the prescribing physicians, which could potentially introduce bias.

Integration of these findings into clinical practice guidelines is essential to ensure that both hospital and primary care clinicians can effectively manage hyperkalaemia as a barrier to achieving optimal HF and CKD management.

SZC represents a meaningful advancement in hyperkalaemia treatment, offering tangible benefits to patient care in both controlled and real-world settings.

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References

1 McDonagh TA et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2021;42(36):3599–726.

2 Stevens PE et al. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int 2024;105(4):S117–S314.

3 Mebazaa A et al. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial. Lancet 2022;400(10367):1938–52.

4 Savarese G et al. Heart failure drug titration, discontinuation, mortality and heart failure hospitalization risk: a multinational observational study (US, UK and Sweden). Eur J Heart Fail 2021;23(9):1499–511.

5 Epstein M et al. Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. Am J Manag Care 2015;21(11 Suppl):S212–20.

6 Nee R et al. Overcoming barriers to implementing new guideline-directed therapies for chronic kidney disease. Nephrol Dial Transplant 2023;38(3):532–41.

7 Shahid I et al. Bridging gaps and optimizing implementation of guideline-directed medical therapy for heart failure. Prog Cardiovasc Dis 2024;82:61–9.

8 Collins AJ et al. Association of Serum Potassium with All-Cause Mortality in Patients with and without Heart Failure, Chronic Kidney Disease, and/or Diabetes. Am J Nephrol 2017;46(3):213–21.

9 Thomsen RW et al. Elevated potassium levels in patients with chronic kidney disease: occurrence, risk factors and clinical outcomes – a Danish population-based cohort study. Nephrol Dial Transplant 2018;33(9):1610–20.

10 Trevisan M et al. Incidence, predictors and clinical management of hyperkalaemia in new users of mineralocorticoid receptor antagonists. Eur J Heart Fail 2018;20(8):1217–26

11 Kanda E et al. Clinical impact of suboptimal RAASi therapy following an episode of hyperkalemia. BMC Nephrology 2023;24(1):18.

12 Fonseca C et al. Hyperkalemia and management of renin-angiotensin-aldosterone system inhibitors in chronic heart failure with reduced ejection fraction: A systematic review. Rev Port Cardiol (Engl Ed) 2020;39(9):517–41.

13 Albasri A et al. Association between antihypertensive treatment and adverse events: systematic review and meta-analysis. BMJ 2021;372:n189.

14 Pitt B, Bakris GL. New potassium binders for the treatment of hyperkalemia: current data and opportunities for the future. Hypertension 2015;66(4):731–8.

15 Linder KE, Krawczynski MA, Laskey D. Sodium Zirconium Cyclosilicate (ZS-9): A Novel Agent for the Treatment of Hyperkalemia. Pharmacotherapy 2016;36(8):923–33.

16 Yang A et al. In vitro ion exchange capacity and selectivity of ZS-9, a novel, selective cation trap for the treatment of hyperkalemia. AJKD 2014;63(5).

17 Kosiborod M et al. Effect of Sodium Zirconium Cyclosilicate on Potassium Lowering for 28 Days Among Outpatients With Hyperkalemia: The HARMONIZE Randomized Clinical Trial. JAMA 2014;312(21):2223–33.

18 Packham DK et al. Sodium zirconium cyclosilicate in hyperkalemia. N Engl J Med 2015;372(3):222–31.

19 Amin AN et al. Efficacy and safety of sodium zirconium cyclosilicate in patients with baseline serum potassium level ≥ 5.5 mmol/L: pooled analysis from two phase 3 trials. BMC Nephrol 2019;20(1):440.

20 Roger S et al. Efficacy and Safety of Sodium Zirconium Cyclosilicate for Treatment of Hyperkalemia: An 11-Month Open-Label Extension of HARMONIZE. Am J Nephrol 2019;50(6):473–80.

21 Spinowitz BS et al. Sodium Zirconium Cyclosilicate among Individuals with Hyperkalemia: A 12-Month Phase 3 Study. Clin J Am Soc Nephrol 2019;14(6):798–809.

22 European Medicines Agency. Lokelma Summary of Product Characteristics 2024 [updated 11/01/24]. www.ema.europa.eu/en/documents/product-information/lokelma-epar-product-information_en.pdf (accessed November 2024).

23 Williams R et al. Sodium Zirconium Cyclosilicate for Renin–Angiotensin–Aldosterone System Inhibitor Optimization in Patients with Heart Failure with Reduced Ejection Fraction: A Retrospective Analysis. Cardiol Ther 2024;Nov 1; doi.org/10.1007/s40119-024-00388-z.

24 Rastogi A et al. Maintained renin-angiotensin-aldosterone system inhibitor therapy with sodium zirconium cyclosilicate following a hyperkalaemia episode: a multicountry cohort study. Clin Kidney J 2024;17(5):sfae083.

At the coalface: personal insights into the management of hyperkalaemia

Aaron Wong

Rhys Williams

Hospital Healthcare Europe *spoke with consultant cardiologist Aaron Wong and specialist clinical pharmacist in cardiology Rhys Williams, who shared their first-hand insights on the complexities of hyperkalaemia management, the role of potassium binders, and how real-world evidence on the management of hyperkalaemia with these drugs supports better patient care.*

One of the major concerns clinicians face when managing heart failure (HF) and chronic kidney disease (CKD) patients is the risk of hyperkalaemia, especially when using renin–angiotensin–aldosterone system inhibitors (RAASi). As Dr Wong explains, 'As healthcare professionals, when we see hyperkalaemia, we immediately worry about heart rhythm problems. Elevated potassium levels are associated with an increased risk of fatal arrhythmias, such as ventricular tachycardia or fibrillation, which contributes to clinician hesitation in prescribing or optimising RAASi.'

Hyperkalaemia is prevalent in patients with certain risk factors, making it a predictable complication in many cases. 'The risk increases with age, progressive CKD, and the presence of diabetes,' he says. 'Patients with both HF and CKD are already at a higher risk, and when RAASi therapy is introduced, the risk of hyperkalaemia rises further.'

A proactive not reactive approach

Dr Wong suggests a proactive approach in identifying patients at risk. 'In the past, we were reactive, waiting for hyperkalaemia to occur before pausing or discontinuing RAASi therapy,' he says. However, now there is a growing awareness that clinicians must anticipate hyperkalaemia and manage it pre-emptively. 'We need to reassess patients before starting RAASi and plan for hyperkalaemia management.'

Multidisciplinary management and patient education are key

The importance of multidisciplinary care in managing these complex cases is stressed by Mr Williams. He points out that HF and CKD patients, often with multiple comorbidities, require coordinated care between primary and secondary services to ensure optimal treatment and monitoring. 'In an integrated health system like ours at Cwm Taf Morgannwg, collaboration between general practitioners, specialists and pharmacists is key,' he says, emphasising the need for seamless transitions between care providers.

Education and discussion to allow the patient to fully understand the benefits their medications will provide is vital. 'We need to break the stereotype of patients thinking that prescribing more pills is just a way of making more money – it's not about the quantity of the medicines taken but being on the right medicines at the right time for the right condition.'

'Patient-focused medicine and making them key stakeholders in their own health is the aim.'

'So, I'll often explain to patients that I am merely just a vessel for giving them information so they can make an informed choice about what they want best for them. I will advocate four-pillar therapy as much as possible. If potassium binders are a tool to help achieve that, then I will also recommend that as well.'

The importance of guideline-directed RAASi

RAASi therapies are the cornerstone of guideline-directed medical therapy for HF and CKD,[1,2] but their full potential is only realised when they are optimised to the highest tolerable dose. Achieving this balance, while mitigating the risks of hyperkalaemia, remains one of the key challenges for clinicians.

Dr Wong explains: 'The data shows us the association between RAASi dosing and patient outcomes: low dose, less benefit; higher dose, higher benefits for appropriate patients. We also see from registry data that, for those who have a dose reduction, it can be as bad as discontinuation. This reminds us of the importance of not just putting patients with HF on RAASi therapy, but trying to optimise it to the maximal tolerable dose for that particular patient is very important.'

Enabling RAASi retention and optimisation

LOKELMA® (sodium zirconium cyclosilicate; SZC) has emerged as an effective potassium binder that enables clinicians to continue RAASi therapy without the risk of hyperkalaemia disrupting treatment. According to Dr Wong, 'The focus should be on optimising RAASi, and LOKELMA® helps to remove the barrier of hyperkalaemia.'

Mr Williams echoes this sentiment, noting that potassium binders allow clinicians to push for

higher doses of RAASi for appropriate patients, thus improving patient outcomes. 'We've seen that binders are very well tolerated, and from what we've observed in practice, it's effective in keeping potassium levels in check, allowing patients to remain on their vital therapies,' he says. Real-world evidence from their patient population supports these claims.

Providing the bridge between clinical trials and everyday practice

While randomised controlled trials provide the gold standard for assessing drug efficacy and safety, real-world evidence plays a crucial role in demonstrating how therapies perform in broader, more diverse patient populations. As Dr Wong highlights, 'Our real-world evidence isn't about the binders themselves –we know pharmacologically that they work. The focus is on optimising RAASi and seeing the downstream effects in terms of patient outcomes.'

Dr Wong and Mr Williams recently conducted a retrospective analysis involving 44 HF patients with reduced ejection fraction (mean value 29%) to assess the effectiveness of LOKELMA® in enabling RAASi optimisation over 24 months.[3] This was a comorbid cohort of patients with:

- New York Heart Association class II-III HF (84%)
- CKD stage 3b or 4 (59%)
- Diabetes (38%)
- Ischaemic heart disease (55%)

Prescribing LOKELMA® modified several disease markers in these patients, enabled a higher number of patients to take RAASi and supported prescribers to optimise RAASi dosing.[3]

Furthermore, a survival rate of 91% was observed over the 24-month observation period for this patient cohort.[3]

Elaborating further on this study, Dr Wong explained: 'The key focus of this study was optimising RAASi and using potassium binders to achieve that. We know from clinical trial evidence that maximising RAASi dosing improves outcomes for these patients. Importantly, that is what we also observed in our study. The patients in this study were a bit more complex; some of them developed cardiorenal syndrome and had a particular problem with hyperkalaemia. Biomarkers in these patients improved, as did hospitalisation rates through optimising RAASi.'

Mr Williams further emphasised the importance of establishing this real-world evidence to complement clinical trial findings.

'It's nice to have these real-world evaluations that back up the clinical trial data. If we look at the HARMONIZE trial, the focus is on maintaining serum potassium. That's great; that is what we want the binders to do, but again, the focus is on RAASi, and we know from previous clinical trials that the greatest benefits are seen at optimal RAASi doses. So, the real-world evidence shows that we can get more patients into therapy with a greater mean average dosing as well. Not only do we see more patients on the drugs, but we also see them at optimal doses of the drugs and the long-term outcomes with improvements in disease markers.'

When asked what their patients say about taking LOKELMA®, Mr Williams says: 'I think it's very well tolerated from what we've seen in real-world practice. I'm struggling to think of a patient we discontinued because of tolerability issues. Patients are generally quite happy to try it, and if it keeps them on RAASi or reduces their symptom burden, then it's a win.' >

	Before prescribing LOKELMA®	After prescribing LOKELMA®
Disease markers		
LVEF (%)	29	36
NT-proBNP (ng/L)	3458	2055
Hospitalisation for hyperkalaemia (%)	14	7
Hospitalisation for HF (%)	30	11
RAASi dosing and optimisation		
Any dose of ACEi/ARB/ARNI (%)	89	100
Guideline-recommended dose of ACEi/ARB/ARNI (%)	50	100
Any dose of MRA (%)	52	93
Optimised dose of MRA (%)	50	50
Proportion prescribed quadruple therapy (%)	32	64

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, neprilysin inhibitor; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, B-type natriuretic peptide; RAASi: renin–angiotensin–aldosterone system inhibitor

This study had a small sample size of 44 patients, which reduces the statistical power and may not be sufficient to be representative of the broader HFrEF population. All results require cautious interpretation. The selection of patients treated with SZC was also at the discretion of the prescribing physicians, which could potentially introduce bias.

References
1 McDonagh T et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42(36):3599–726.
2 KDIGO. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int 2024;105(4S):S117–314.
3 Williams R et al. Sodium Zirconium Cyclosilicate for Renin–Angiotensin–Aldosterone System Inhibitor Optimization in Patients with Heart Failure with Reduced Ejection Fraction: A Retrospective Analysis. Cardiol Ther 2024;Nov 1; doi.org/10.1007/s40119-024-00388-z.

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Implementing evidence-based practice

Dr Wong highlights the importance of healthcare professionals implementing evidence-based practice. 'We share information with our colleagues and patients about clinical trial results and real-world evidence, and we also share information about how to implement the recommendations in practice. Importantly, we also share how our patients feel about any new therapy or approach to care.'

'I think we, as healthcare professionals, do have different types of personalities. Some people are very quick to embrace new ideas and new practices, and some are more skeptical. So it's important that we keep sharing our findings with our secondary and primary care colleagues, and hopefully, at some point, they will realise their potential [of the potassium binders].'

Within Cwm Taf Morgannwg University Trust, where Dr Wong and Mr Williams practise, LOKELMA® has been incorporated into integrated clinical guidelines for initiating and maintaining guideline-directed HF therapy. Mr Williams highlights the proactive approach in designing this guideline: 'Looking to the future, we might see general practitioners prescribing these drugs long term as maintenance therapy, once they have been optimised.

Managing more stable patients in primary care allows us to see the new, more acute patients and optimise them. The protocol is also quite comprehensive, not only looking at dosing strategies for LOKELMA® but also for RAASi maintenance and optimisation.'

Conclusion

As Dr Wong concludes, 'At the end of the day, as healthcare professionals, our most rewarding experience is seeing the patient live well and live long.'

RAASi therapy remains the cornerstone treatment for managing HF and CKD. While prescribing RAASi is crucial, optimising the dose through up-titration is equally important to ensure maximum benefit for patients. Achieving the highest tolerable dose has been shown to improve clinical outcomes, including reducing hospitalisations and improving cardiac function.

However, clinicians often perceive hyperkalaemia as a significant barrier to prescribing or up-titrating RAASi, given the risks of elevated potassium levels. This concern can lead to suboptimal dosing or even discontinuation of these life-saving therapies.

LOKELMA® (sodium zirconium cyclosilicate) offers a solution to this challenge by effectively managing hyperkalaemia, thus allowing clinicians to continue optimising RAASi therapy. Real-world evidence supports the effectiveness and tolerability of LOKELMA® in maintaining normokalaemia, enabling clinicians to up-titrate RAASi and improve outcomes for patients with HF and CKD. By overcoming the barrier of hyperkalaemia, LOKELMA® plays a key role in supporting guideline-directed medical therapy and enhancing patient care.

The interviewees

Aaron Wong MD is a consultant cardiologist and general physician at the Princess of Wales Hospital, Cwm Taf Morgannwg University Health Board and an honorary lecturer at the University of Cardiff, UK.

Rhys Williams MPharm PGDip MRPharmS is a specialist clinical pharmacist (cardiology) at Cwm Taf Morgannwg University Health Board, UK.

The opinions expressed in this interview are those of the participating healthcare professionals and reflect their individual perspectives based on clinical practice and experience. These views do not represent the opinions or recommendations of any institution, organisation, or company.

PRESCRIBING INFORMATION

LOKELMA® (sodium zirconium cyclosilicate) 5g & 10g POWDER FOR ORAL SUSPENSION

Consult Summary of Product Characteristics before prescribing.

Indication: Lokelma is indicated for treatment of hyperkalaemia in adults.

Presentation: 5g or 10g powder for oral suspension. Each sachet contains 5g or 10g sodium zirconium cyclosilicate.

Dosage and Administration: **Correction phase:** Recommended starting dose is 10g, administered orally, three times a day as a suspension in water. When normokalaemia is achieved the maintenance regimen should be followed. Typically, normokalaemia is achieved within 24 to 48 hours. If patient is still hyperkalaemic after 48 hours of treatment the same regimen can be continued for an additional 24 hours. If normokalaemia not achieved after 72 hours of treatment, other treatment options should be considered. **Maintenance phase:** Establish the minimal effective dose to prevent recurrence of hyperkalaemia. Recommended starting dose of 5g once daily, with possible titration up to 10g once daily, or down to 5g once every other day, as needed, to maintain normal potassium level. No more than 10g once daily should be used for maintenance therapy. Monitor serum potassium levels regularly during treatment. **Missed dose:** If a dose is missed the patient should take the next usual dose at their normal time. **Renal impairment:** No dosage adjustment required for patients who are not on chronic haemodialysis. For patients on dialysis Lokelma should only be dosed on non-dialysis days. The recommended starting dose is 5g once daily. To establish normokalaemia (4.0-5.0 mmol/L), the dose may be titrated up or down weekly based on the pre-dialysis serum potassium value after the long inter-dialytic interval (LIDI). The dose could be adjusted at intervals of one week in increments of 5gup to 15g once daily on non-dialysis days. It is recommended to monitor serum potassium weekly while the dose is adjusted; once normokalaemia is established, potassium should be monitored regularly (e.g. monthly, or more frequently based on clinical judgement including changes in dietary potassium or medication affecting serum potassium. **Hepatic impairment:** No changes from the normal doses are required for patients with hepatic impairment. **Elderly population:** No special dose and administration guidelines are recommended for this population. **Paediatric population:** Safety and efficacy has not been established in children and adolescents (<18 years). **Method of administration**: The entire contents of the sachet(s) should be emptied in a drinking glass containing approximately 45ml of water and stirred well. The tasteless liquid should be drunk while still cloudy. The powder will not dissolve. If the powder settles, the liquid should be stirred again and taken. If needed, rinse the glass with more water to ensure that all of the content is taken. The suspension can be taken with or without food.

Contraindications: Hypersensitivity to the active substance.

Warnings and Precautions: **Serum potassium levels:** Monitor serum potassium levels when clinically indicated, including after changes are made to medicinal products that affect the serum potassium concentration (e.g. renin-angiotensin-aldosterone system (RAAS) inhibitors or diuretics) and after Lokelma dose is titrated. Monitoring frequency will depend upon a variety of factors including other medicinal products, progression of chronic kidney disease and dietary potassium intake. **Hypokalaemia:** Hypokalaemia may be observed. To prevent moderate to severe hypokalaemia dose titration (maintenance posology) may be required. Discontinue and re-evaluate treatment in patients with severe hypokalaemia. **QT Prolongation:** During correction phase, a lengthening of QT interval can be observed as the physiologic result of decline in serum potassium concentration. **Risk of interaction with X rays:** Sodium zirconium cyclosilicate may be opaque to X-rays, keep in mind if patient has abdominal X-ray. **Intestinal perforation:** Risk of intestinal perforation unknown. Special attention to be paid as intestinal perforation has been reported with potassium binders including Lokelma. **Sodium content:** Lokelma is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

Drug Interactions: No expected effects of other medicines on sodium zirconium cyclosilicate as it is not absorbed or metabolised by the body. Sodium zirconium cyclosilicate can transiently increase gastric pH and can lead to changes in solubility where co-administered medicinal product haspH-dependent stability and therefore should be administered at least 2 hours before or 2 hours after oral medicinal products with clinically meaningful gastric pH dependent bioavailability (e.g. azole antifungals, a number of anti-HIV agents, and tyrosine kinase inhibitors). Sodium zirconium cyclosilicate can be co-administered without spacing of dosing times with oral medicinal products that do not exhibit pH-dependent bioavailability. Tacrolimus should be taken at least 2 hours before or after Lokelma.

Pregnancy and Lactation: Preferable to avoid use during pregnancy. Can be used duringbreast-feeding.

Ability to Drive and Use Machines: Lokelma has no or negligible influence on the ability to drive and use machines.

Undesirable Events: Consult SmPC for full list of side effects. Common: Hypokalaemia, constipation, oedema related events (including fluid retention, generalised oedema, hypervolaemia, localised oedema, oedema, oedema peripheral, peripheral swelling).

Legal Category: POM.

Marketing Authorisation Numbers: PLGB 17901/0332, PLGB 17901/0331.

Presentation & Basic NHS Cost: 5g x 30 pack: £156; 10g x 3 pack: £31.20; 10g x 30 pack: £312.

Business Responsible for Sale and Supply / Further Information: AstraZeneca UK Ltd., 2 Pancras Square, 8th Floor, London, N1C 4AG, UK.

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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to AstraZeneca by visiting https://contactazmedical.astrazeneca.com or by calling 0800 783 0033.


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