Pragmatic diagnostic and therapeutic algorithms to optimize new potassium binder use in cardiorenal disease

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Abstract

Background: Pivotal randomized trials demonstrating efficacy, safety and good tolerance, of two new potassium binders (patiromer and sodium zirconium cyclosilicate) led to their recent approval. A major hurdle to the implementation of these potassium-binders is understanding how to integrate them safely and effectively into the long-term management of cardiovascular and kidney disease patients using renin angiotensin aldosterone system inhibitors (RAASi), the latter being prone to induce hyperkalaemia.

Methods: a multidisciplinary academic panel including nephrologists and cardiologists was convened to develop consensus therapeutic algorithm(s) aimed at optimizing the use of the two novel potassium binders (patiromer and sodium zirconium cyclosilicate) in stable adults who require treatment with RAASi and experience(d) hyperkalaemia in a non-emergent setting.

Results: Two dedicated pragmatic algorithms are proposed. The lowest intervention threshold (i.e. 5.1 mmol/L or greater) was the one used in the patiromer and sodium zirconium cyclosilicate) pivotal trials, both drugs being indicated to treat hyperkalaemia in a non - emergent setting. Acknowledging the heterogeneity across specialty guidelines in hyperkalaemia definition and thresholds to intervene when facing hyperkalaemia, we have been mindful to use soft language i.e. “it is to consider”, not necessarily “to do”.

Conclusions: Providing the clinical community with pragmatic algorithms may help optimize the management of high-risk patients by avoiding the risks of both hyper and hypokalaemia and of suboptimal RAASi therapy

Keywords: potassium binder- patiromer – sodium zirconium cyclosilicate- algorithm- hyperkalaemia

A U-shape relationship has been consistently observed between serum potassium concentration, both hypokalaemia and hyperkalaemia being associated with all-cause mortality, cardiovascular death, and kidney failure in patients with cardiac and/or renal diseases [1]. Hyperkalaemia is common in patients with a low glomerular filtration rate (GFR)[2], whether this is primarily due to renal disease or associated with diabetes, hypertension, heart failure[3],[4] or ageing.

In addition to patient demographics and clinical features, treatment is a key additional determinant of both hypo- and hyperkalaemia. This is an especially vexing issue with agents blocking the renin angiotensin aldosterone system (RAAS), that inherently increase the risk of hyperkalaemia due to their pharmcodynamic potassium-sparing properties, but have substantial benefits on morbidity and mortality. Both cardiology and nephrology guidelines specify target doses that many patients and physicians struggle to achieve[5-7] [8] and failing to achieve target doses is associated with poorer outcomes. Guidelines from the European Society of Cardiology (ESC) recommend that patients with heart failure and a reduced left ventricular ejection fraction (HFrEF) should generally receive four classes of disease-modifying treatment including angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB)/ angiotensin receptor neprilysin inhibitors (ARNi), mineralocorticoid receptor antagonists (MRAs), beta-blockers and SGLT2 inhibitors; all but the latter are associated with an increased risk of hyperkalaemia. For patients with heart failure and preserved ejection fraction (HFpEF), the most recent ESC guidelines point out that despite the lack of evidence for specific disease-modifying therapies, many patients with HFpEF will require similar treatment to patients with HFrEF because they have hypertension, diabetes and/or coronary artery disease[7]. Also, MRAs are recommended for HFpEF in the US[9] and for resistant hypertension in patients with an estimated GFR (eGFR) >45 ml/min/1.73m^2 and serum potassium <4.5 mmol/L[10]. Of note, in patients with proteinuric diabetic kidney disease, the non-steroidal MRA finerenone decreased the progression to end-stage renal disease[11] as well as the primary composite outcome of death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure[12].

While ACEI/ARB are recognized as cardiorenoprotective drugs in chronic kidney and cardiovascular diseases, hyperkalaemia is an inherent risk[13] and a major hurdle that limits optimisation of RAASi use[14], and is a major trigger for their down-titration or discontinuation[15, 16], which are associated with poor outcomes in cardiorenal patients[15, 17].

Conversely, diuretics that increase urinary potassium excretion may cause hypokalaemia. Thiazide (-like) diuretics are one of the cornerstones of treatment for hypertension[10].

Loop diuretics are essential for the management of symptoms and signs of congestion in patients with heart failure[18, 19] and for the management of end-stage kidney disease[8].

For ethical reasons related to the established pro-arrhythmogenic risks associated with hypo- and hyper-kalaemia, strategies of potassium normalization vs. permissive hypo or hyperkalaemia cannot be studied in a randomized fashion. Several observational studies, however, strongly suggest that potassium level normalization is associated with better outcomes in various initially hypokalaemic or hyperkalaemic patient populations [20-22]. A patient-level simulation model designed to characterise the natural history of CKD supports the notion that maintaining normokalaemia enables optimal RAASi therapy and improves long-term health and economic outcomes in CKD patients[23]. Guidelines universally emphasize the importance of close monitoring of kidney function and electrolytes and adjusting doses of RAASi accordingly but such monitoring remains suboptimal in patients receiving RAASi[24-26].

The recent availability of safe and well tolerated agents that bind potassium in the gastro-intestinal tract is a major advance in the chronic management of hyperkalaemia, thereby potentially enabling RAASi optimization[3], as already demonstrated in randomized clinical trials for patiromer[27-29]. Both drugs displayed a sustainable effect ascertained by uncontrolled 52-week open label studies [30-32] led in initially hyperkalemic patients. Importantly, a consistent rebound in serum potassium was observed following the study

drug discontinuation. This underlines the need of a chronic administration in such patients, prone to recurrent hyperkalemia.

Patiromer and sodium zirconium cyclosilicate (SZC), both act to remove potassium by exchanging other cations (calcium for patiromer, sodium and hydrogen for SZC) for potassium in the gastrointestinal tract, thus increasing its faecal excretion and lowering serum potassium concentrations. Preventing or managing hyperkalaemia in this way, reduces the need for down-titration or cessation of RAASi as acknowledged by the latest guidelines [5-7, 33]. Furthermore, the KDIGO guidelines endorse new potassium binders for the treatment of hyperkalaemia in patients with CKD[5, 6] . The latest ESC HF guidelines state that "administration of the K lowering agents, patiromer or sodium zirconium cyclosilicate, may allow renin-angiotensin-aldosterone system (RAAS) inhibitor initiation or uptitration in a larger proportion of patients".[7] It is noteworthy that, while RAASi maintenance is associated with better cardiovascular outcomes in observational studies, evidence of a cardiovascular and renal protection due to a RAASi enablement through K lowering agents is awaited from large, long-term randomized trials.

A major hurdle to implementation of potassium-binders is understanding how to integrate them safely and effectively into long-term management protocols for cardiovascular and renal disease. Until now, treatment for hyperkalaemia has focussed on the management of acute episodes and typically involved down-titration or discontinuation of RAASi therapy. Moreover, existing recommendations included in package inserts from manufacturers need to be considered, which often give detailed information about how to handle RAASi-therapy in case of a current, imminent or past hyperkalaemia.

To address these challenges, a multidisciplinary academic panel including nephrologists and cardiologists was convened to develop a consensus therapeutic algorithm aimed at optimizing the use of two novel potassium binders (Patiromer and SZC) in stable adults who require treatment with RAASi and experience(d) hyperkalaemia. (**Tables 1-2**)

Importantly, the lowest intervention threshold we selected (i.e. 5.1 mmol/L or greater) was the one used in the patiromer (ClinicalTrials.gov number, NCT01810939) [29] and SZC

clinicaltrials.gov Identifier: NCT02088073) [34] pivotal trials, which led to their approval, with both of them being indicated to treat hyperkalaemia in a non -emergent setting. Acknowledging the heterogeneity across specialty guidelines in hyperkalaemia definition and related to thresholds to intervene in front of hyperkalaemia, we have been mindful to use soft language i.e. “it is to consider”, not necessarily “to do”. Furthermore, the anticipated patient adherence to a suitable biological monitoring needs to be taken into account. For instance, the decision on whether to decrease RAASi or add a potassium binder at a specific potassium concentration threshold is obviously left to the medical judgement, and may depend on how far away the patient lives or whether he/she has easy access to a healthcare provider.

We also acknowledge that “old generation” potassium binders (i.e. sodium or calcium polystyrene sulfonate) are still widely used worldwide to treat hyperkalaemia, with however substantial heteogeneity across countries[35, 36]. We did not consider to develop therapeutic algorithms for these “old generation” potassium binders” approved decades ago, at a time when adequately-designed randomized controlled trials were not required to ascertain efficacy and safety[3]. So far, no randomized data may indeed support their chronic use to manage hyperkalaemia nor a RAASi enabling effect, while in the short term, these compounds have poor tolerability, unstable onset of action, and unpredictable magnitude of potassium lowering[3]. Importantly, real-world observational data provided conflicting results, some suggesting that sodium polystyrene sulfonate may induce colonic necrosis[37, 38], while others did not[39, 40]. It may further induce fluid overload[41], owing to the sodium-potassium exchange[3].

Providing the clinical community with pragmatic algorithms may help optimize the management of high-risk patients by avoiding the risks of both hypo- and hyperkalaemia and suboptimal RAASi therapy.

Table 1: Diagnostic and therapeutic algorithm with patiromer

Table 2: Diagnostic and therapeutic algorithm with sodium zirconium cyclosilicate

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Table 1

Stable adults with chronic hyperkalaemia ± requirement for RAASi
Patiromer should not replace emergency treatment for acute life-threatening hyperkalaemia

***Individualise recommended actions according to the clinical situation**

Serum K+ (mmol/L) *(confirmed by two consecutive valid samples)*		Action*	Additional actions, if clinically required:*	Monitoring†
Severe hyperkalaemia	≥6.0	• Initiate[a,b] patiromer at 8.4 g once daily, or • Up-titrate[b,c] patiromer if started at ≥7-day intervals by 8.4 g once daily, to a maximum dose of 25.2 g daily, until serum K+ <5.1 mmol/L	• Suspend RAASi and re-assess serum K+ levels after 3–7 days[d]	• After initiating or changing patiromer dose, measure serum K+ and creatinine within 3–7 days† and repeat after 1 week. If target K+ value is achieved, measure serum K+ at 1 month, then every 3 months • Monitor serum Mg for at least 1 month after initiating patiromer.' Consider Mg supplementation in patients who develop low serum Mg levels (0.58 mmol/L) • Any time that a change in electrolyte or volume status is suspected, eg due to gastrointestinal problems, re-measure serum K+ and creatinine and repeat the above monitoring sequence as per standard clinical practice and applicable guideline recommendations ***'Monitoring frequency should be individualised based on the clinical situation. Some clinical scenarios may require a change in the frequency of monitoring; refer to applicable guidelines for recommendations.*** • Maintain RAASi if started, but re-assess serum K+ levels after 3–7 days:[d] – If K+ levels are still high and patiromer is on maximum dose, consider RAASi down-titration[d] – If K+ levels <5.1 mmol/L, consider up-titration of RAASi if not on guideline-recommended target dose[d]
Moderate hyperkalaemia	5.6–5.9			
Mild hyperkalaemia	5.1–5.5	• Consider initiation[a] of patiromer at 8.4 g once daily, or • Maintain / up-titrate[c] patiromer if started at ≥7-day intervals by 8.4 g once daily, to a maximum dose of 25.2 g daily, until serum K+ <5.1 mmol/L	• Initiate / maintain RAASi at guideline-recommended target dose and re-assess serum K+ levels after 7 days[d] • Consider up-titration of RAASi to guideline-recommended target dose[d] depending on the clinical situation and if patiromer has been started[a]	
Normokalaemia	4.1–5.0	• If started on patiromer, maintain dose	• Initiate / maintain / up-titrate RAASi to guideline-recommended target dose and re-assess serum K+ levels after 7 days[d]	
Mild hypokalaemia	3.5–4.0	• Stop patiromer[a] if on lowest dose, or • Down-titrate[c] patiromer at ≥7-day intervals by 8.4 g once daily		
Hypokalaemia	<3.5	• If on patiromer, stop treatment[b,a]		

[a] Prior to initiating patiromer, consider:
1. Eliminating K+ supplements, non-steroidal anti-inflammatory drugs and decreasing K+ rich foods (where possible)
2. Evaluating: lab parameters (eg eGFR), adherence to therapy (especially in cases of polypharmacy) / ability to understand treatment, main disease diagnosis and comorbidities, age / life expectancy / frailty, history of previous hyperkalaemia, concomitant medication use and dose (or intention to start), other possible reasons for hyperkalaemia (eg metabolic acidosis)

[b] Manage serum K+ as per standard clinical practice and applicable guideline recommendations for the immediate management of acute hyperkalaemia or hypokalaemia.

[c] Prior to patiromer dose adjustment, check if diuretic dose has changed as serum K+ levels could be affected.
[d] Refer to applicable guideline recommendations for RAASi use (the term RAASi includes: angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, angiotensin receptor neprilysin inhibitors, mineralocorticoid-receptor antagonists). Assess volume status and consider adding/adapting diuretic dose.

[a] When discontinuing patiromer, serum K+ levels may rise, especially if RAASi treatment is continued. Patients should be instructed not to discontinue patiromer without consulting their physicians. Serum K+ may increase as early as 2 days after the last patiromer dose.

Note ' Hypomagnesaemia was reported in 5.3% of patients treated with patiromer in the clinical trial programme; all reports were mild–moderate, with no patient developing a serum Mg level <0.4 mmol/L.

Refer to the patiromer Summary of product characteristics/ US Product information for full prescribing information. *eGFR, estimated glomerular filtration rate; K+, potassium; Mg, magnesium; RAASi, renin angiotensin aldosterone system inhibitor.*

Table 2

Stable adults with chronic hyperkalaemia ± requirement for RAASi
SZC should not replace emergency treatment for acute life-threatening hyperkalaemia

[a]Individualise recommended actions according to the clinical situation

Serum K+ (mmol/L) *(confirmed by two consecutive valid samples)*		Action[a]	Additional actions, if clinically required:[a]	Monitoring[f]
Severe hyperkalaemia	**≥6.0**	• Initiate[a,b] SZC at 10g thrice daily for 24, 48 or 72 h (i.e. until normokalaemia), then proceed to the maintenance phase, starting with 5 g/day, max 10 (EU SMPC)-15 (USPI) g/day • or • Up-titrate[a,c] SZC , if started, by 5 g once daily, to a maximum dose of 10 (EU SMPC) -15 (USPI) g daily, until serum K+ <5.1 mmol/L, or down-titrating to 5g every other day, depending on potassium levels.	• Suspend RAASi and re-assess serum K+ levels after 3–7 days[d]	• After initiating[f] or changing SZC dose, measure serum K+ and creatinine within 3–7 days[f] and repeat after 1 week. If target K+ value is achieved, measure serum K+ at 1 month, then every 3 months • Any time that a change in electrolyte or volume status[f] is suspected, eg due to gastrointestinal problems, re-measure serum K+ and creatinine and repeat the above monitoring sequence as per standard clinical practice and applicable guideline recommendations • **as SZC mechanism of action involves potassium exchange for sodium (or hydrogen) in the GI tract , monitor edema during SZC therapy particularly in patients prescribed a SZC dose higher than 10 g daily[e].** ***[f]Monitoring frequency should be individualised based on the clinical situation. Some clinical scenarios may require a change in the frequency of monitoring; refer to applicable guidelines for recommendations.***
Moderate hyperkalaemia	**5.6–5.9**		• Maintain RAASi if started, but re-assess serum K+ levels after 3–7 days[d] – If K+ levels are still high and SZC is on maximum dose, consider RAASi down-titration[d] – If K+ levels <5.1 mmol/L, consider up-titration of RAASi if not on guideline-recommended target dose[d]	
Mild hyperkalaemia	**5.1–5.5**	• Consider initiation[a] of SZC at 10 g thrice daily for 24, 48, or 72 h (i.e. until normokalaemia), then proceed to the maintenance phase, starting with 5 g/day, then uptitrating to max 10 (EU SMPC) -15 (USPI) g/day, or down-titrating to 5g every other day, depending on potassium levels. • or • Maintain / up-titrate[a,c] SZC, if started, to a maximum dose of 10 g daily, until serum K+ <5.1 mmol/L	• Initiate / maintain RAASi at guideline-recommended target dose and re-assess serum K+ levels after 7 days[d] • Consider up-titration of RAASi to guideline-recommended target dose[d] depending on the clinical situation and if SZC has been started[a]	
Normokalaemia	**4.1–5.0**	• If started on SZC, maintain dose	• Initiate / maintain / up-titrate RAASi to guideline-recommended target dose and re-assess serum K+ levels after 3-7 days[d]	
Mild hypokalaemia	**3.5–4.0**	• Stop SZC[a] if on lowest (5g everyother day) dose, or • Down-titrate[a,c] SZC at ≥7-day intervals by 5 g once daily		
Hypokalaemia	**<3.5**	• Stop temporarily until K is above 3.5 (or 4.0 if you want to be conservative) then restart at lower dose. Stop if patient was already on 5g every other day.[b,e]		

[a]Prior to initiating SZC, consider:

1. Eliminating K+ supplements, non-steroidal anti-inflammatory drugs and decreasing K+ rich foods (where possible)
2. Evaluating: lab parameters (eg eGFR), adherence to therapy (especially in cases of polypharmacy) / ability to understand treatment, main disease diagnosis and comorbidities, age / life expectancy / frailty, history of previous hyperkalaemia, concomitant medication use and dose (or intention to start), other possible reasons for hyperkalaemia (eg metabolic acidosis
3. Typically, normokalaemia is achieved within 24 to 48 hours. If patients are still hyperkalaemic after 48 hours of treatment, the same regimen can be continued for an additional 24 hours. If normokalaemia is not achieved after 72 hours of treatment, other treatment approaches should be considered.

[b]Manage serum K+ as per standard clinical practice and applicable guideline recommendations for the immediate management of acute hyperkalaemia or hypokalaemia.

[c]Prior to SZC dose adjustment, check if diuretic dose has changed as serum K+ levels could be affected.
[d]Refer to applicable guideline recommendations for RAASi use (the term RAASi includes: angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, angiotensin receptor neprilysin inhibitors, mineralocorticoid-receptor antagonists). Assess volume status and consider adding/adapting diuretic dose.

[e]When discontinuing SZC, serum K+ levels may rise, especially if RAASi treatment is continued. Patients should be instructed not to discontinue SZC without consulting their physicians. Serum K+ may increase within 7 days after the last SZC dose.

Note [f]In the clinical development program, the most commonly reported adverse reactions were hypokalaemia (4.1%) and oedema related events (5.7%). Each 5 g dose of SZC contains approximately 400 mg of sodium. Oedema was only noted with doses above 10 grams daily.
[a]Refer to the SZC SmPC (Summary of product characteristics)/USPI US Product Information for full prescribing information. *eGFR, estimated glomerular filtration rate; K+, potassium; RAASi, renin angiotensin aldosterone system inhibitor.*