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Potassium binders for the prevention of hyperkalaemia in heart failure patients: implementation issues and future developments

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New therapeutic options to treat hyperkalaemia, such as potassium binders, have been suggested as potentially beneficial by allowing the maintenance (or increase) of the dose of medications that improve outcomes in several cardiovascular conditions, but which have in common the propensity for raising serum potassium. However, potassium binding drugs have yet to prove their causal association with improvements in patients' prognosis before their widespread use can be recommended. In this review we provided an up-to-dare appraisal on potassium binders, their potential clinical applications and directions for future research.

Introduction

Potassium is the most abundant intracellular cation and is essential for normal cellular function. Derangements of potassium regulation often lead to life-threatening neuromuscular, gastrointestinal, and cardiac abnormalities if left untreated.

New therapeutic options to treat hyperkalaemia, such as potassium binders, have been suggested as potentially beneficial by allowing the maintenance (or increase) of the dose of medications that improve outcomes in several cardiovascular conditions, but which have in common the propensity for raising serum potassium. However, potassium-binding drugs will need to be shown to improve clinical outcomes before their widespread use can be recommended.

This article focuses on implementation issues and future directions for the treatment of hyperkalaemia. We use examples from the heart failure (HF) field which is our area of expertise.

Potassium homeostasis alterations and their association with outcomes

Neuro-hormonal antagonists have driven a remarkable prognostic improvement in patients with heart failure and reduced left ventricular ejection fraction (HF-REF). However, both β-blockers and renin–angiotensin–aldosterone system inhibitors (RAASi) may cause hypotension, and RAASi, in particular, may decrease estimated glomerular filtration rate (eGFR) and increase serum potassium levels. More recently, sacubitril/valsartan has been shown to improve morbidity and mortality compared to enalapril with less frequent hyperkalaemia and eGFR deterioration.[1–3]

The occurrence of hyperkalaemia has been highlighted in several observational studies and, despite the low-grade evidence, hyperkalaemia has become a major concern for clinicians, particularly in association with the use of mineralocorticoid receptor antagonists (MRAs).[4] Consequently,

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MRAs have been persistently under-prescribed and under dosed despite their remarkable improvement in clinical outcomes and Class IA guideline indication for patients with HF-REF.[5-12] Once they are initiated they are often discontinued due to an increase in serum potassium or a decrease in renal function.[13-15] Furthermore once a MRA is administered patients often do not receive guideline-recommended monitoring of serum potassium or renal function. On the other hand, evidence from prospective randomized trials has consistently demonstrated a low rate of hyperkalaemia without any hyperkalaemia-associated fatal events.[10,11,16-19] In the large-scale randomized trials of MRAs in patients with HF including RALES, EPHESUS, EMPHASIS-HF, and TOPCAT, the incidence of hyperkalaemia (serum K^+ >5.5 mmol/L) was low (up to a maximum of 12%), and there has not been, to our knowledge, a single death attributable to hyperkalaemia in a patient randomized to a MRA in these trials, including >7000 patients taking MRAs. Therefore, a discrepancy exists between the evidence from randomized clinical trials and daily clinical practice. Awareness and concern about hyperkalaemia may have been enhanced by the recent introduction of new potassium-binding therapies, putting undue emphasis on the hyperkalaemia 'issue'. Actually, while hyperkalaemia is an important issue, it is possible that an increase in serum potassium contributes to the beneficial mechanism of RAASi, particularly reduced rates of sudden cardiac death associated with the administration of a MRA.[10,16] *Post hoc* analyses of the RALES and EMPHASIS-HF trials show that the outcome benefits of a MRA, compared with placebo, were maintained in patients who developed moderate hyperkalaemia (potassium levels between 5.5 mmol/L and 6.0 mmol/L) during treatment.[20,21] Presumably, once patients manifest potassium levels in this range, many had study drug and/or concomitant RAASi reduced or discontinued, raising the question whether treatment benefit might have been further enhanced if potassium binders had been used, thereby facilitating preservation of RAASi dosing. Whether the use of potassium binders may improve outcome through enabling optimal use of RAASi is still an open question.[22,23] In HF, the association of K^+ with mortality has been described as U-shaped i.e. patients with both low- and high-potassium levels have increased death rates.[24,25] For example, K^+ levels below 4.0 mmol/L are associated with increased death rates with similar risk as K^+ levels above 5.0 mmol/L. Of note, patients with K^+ below 3.0 mmol/L may have higher mortality risk than patients with K^+ above 5.5 mmol/L. U-shaped associations have been described in HF but also in other settings, such as chronic kidney disease (CKD),[26] hypertension,[27] myocardial infarction,[28,29] and in the general population.[30] Despite the narrow nadir of optimal K^+ levels, clinical attitudes towards serum K^+ levels vary widely, with some clinicians becoming concerned when the serum K^+ is <3.5 or >5.5 mmol/L, whereas others become concerned and consider altering cardiovascular drug therapy at a serum K^+ <4.0 or >5.0 mmol/L.[29] Generally, the associations between K^+ levels and clinical outcomes are derived from observational data prone to a number of confounding factors. Reverse causation is one of them, i.e. K^+ alterations arise in consequence of other underlying illnesses or treatments responsible for the outcomes associations (e.g. hyperkalaemia is frequently caused by haemolysis or renal failure—itself associated with RAASi drug discontinuation, whereas hypokalaemia is often caused by diuretics often used to treat patients with severe signs and symptoms of systemic congestion or high blood pressure.

A rise in potassium level represents a frequent cause for RAASi dose reduction or discontinuation—actions that may deprive patients of therapy proven to improve clinical outcomes.[7,21] Although optimal dosing of MRAs for outcome benefit has not been explored, for other RAASi antagonists the clinical benefit has been shown to be dose-dependent, despite an increased risk of hyperkalaemia.[31,32] For these reasons, management of the adverse effects of RAASi, without discontinuing or reducing the dose of the therapeutic agent, may represent an attractive goal. Thus, the recent availability of safe and tolerable oral potassium binders may change the approach to managing hyperkalaemia and RAASi usage.[22,33] However, without a clear demonstration of outcome improvement with these agents their widespread use cannot be recommended. More research and education about hyperkalaemia may help increase awareness about this issue and promote better clinical practice. This should include: (i) identifying patients at risk of hyperkalaemia, (ii) preventing hyperkalaemia with available 'life-style' changes, including dietary changes, (iii) monitoring serum potassium as per international guidelines, and (iv) treating emerging rise of potassium with dose adjustments of drugs likely to increase serum potassium, and/or using potassium binders. One should use good clinical judgement to mitigate an increase in serum potassium levels before adding another drug to the polypharmacy of a HF patient. Finally, education should be more generally applied to potassium haemostasis. Hypokalaemia is also an often-overlooked cause of iatrogenic mortality among patients with cardiovascular conditions. Focus on hyperkalaemia should not shift the attention to only 'one side of the coin'.

Potassium binders

The majority of potassium is renally excreted, but ≈5–10% is secreted in the colon. Two new agents, patiromer and sodium zirconium cyclosilicate (SZC), were developed for the treatment of hyperkalaemia. These agents may offer advantages over existing approaches to hyperkalaemia treatment (e.g. kayexylate). Both patiromer and SZC act to remove potassium by exchanging cations (calcium and sodium for patiromer and SZC, respectively) for potassium in the gastrointestinal tract, binding potassium, and increasing its faecal excretion.[34]

Patiromer clinical trials

The PEARL-HF study (Evaluation of RLY5016 in Heart Failure Patients) was a multicentre, randomized, double-blind, placebo-controlled parallel-group study to evaluate the effects of patiromer in 120 patients with HF.[35] All patients had either an eGFR of <60 mL/min or a documented history of RAASi discontinuation because of hyperkalaemia within 6 months. Spironolactone 25 mg/day was

initiated in all patients. At 28 days, serum potassium was significantly lower in the patiromer group compared with placebo and fewer patients randomized to patiromer experienced serum potassium >5.5 mEq/L (7% vs. 25%; $P = 0.015$). However, more patiromer-treated patients had serum potassium <3.5 mEq/L (6% vs. 0%; $P = 0.094$) and hypomagnesaemia (<1.8 mg/dL) was reported in 24% of the patiromer patients and 2% of the placebo patients ($P = 0.001$). Overall, patiromer was well tolerated.

The AMETHYST-DN (RLY5016 in the Treatment of Hyperkalaemia in Patients With Hypertension and Diabetic Nephropathy) trial[36] was a multicentre, randomized, open-label, dose-ranging study, randomizing 304 patients with type 2 diabetes mellitus and CKD (eGFR 15 to <60 mL/min/1.73 m^2) who developed hyperkalaemia in the setting of RAASi optimization to either patiromer or 'control'. Serum potassium fell with patiromer treatment and rose after patiromer discontinuation. Serum potassium <3.5 mEq/L occurred in 17 patients (5.6%). Hypomagnesaemia (7.2%), and constipation (4.6%) were the most commonly reported treatment-related adverse events.

The OPAL-HK (Study Evaluating the Efficacy and Safety of Patiromer for the Treatment of Hyperkalaemia),[23] examined the effects of patiromer on serum potassium levels of 102 patients with CKD (eGFR 15 to <60 mL/min/1.73 m^2) and serum potassium of 5.1 to <6.5 mmol/L. In this study, patiromer treatment decreased serum potassium levels and reduced hyperkalaemia recurrence compared with placebo. Hypokalaemia (serum potassium of <3.8 mmol/L) was observed in 5% and 2% of the patiromer and placebo groups, respectively. Hypomagnesaemia occurred in 8 (3%) patiromer patients during the initial treatment phase.

Sodium zirconium cyclosilicate clinical trials

The sodium zirconium cyclosilicate in hyperkalaemia[37] randomized 753 patients with serum potassium between 5.0 and 6.5 mmol/L to either SZC or placebo for 48 h. No specific requirements for eGFR (excluding dialysis) or RAASi use were specified. The decrease in serum potassium was greater with SZC compared with placebo. Adverse events were rare and similar between SZC and placebo.

The HARMONIZE (Hyperkalaemia Randomized Intervention Multidose SZC Maintenance) trial[22] studied the effects of SZC on serum potassium levels in 95 HF patients with baseline K^+ ≥5.1 mmol/L. Among these, 93% achieved the target potassium level of 3.5–5 mmol/L within 48 h of receiving open-label SZC without adjusting RAASi doses. Oedema was reported in 2.4% of the placebo group and up to 14.3% with 15 g SZC dosing. Serum potassium of <3.5 mmol/L was observed in 10% of patients in the SZC 10 g group and 11% of patients in the SZC 15 g group vs. no cases in the 5 g or placebo groups. No clinically significant changes in serum magnesium, phosphate, or bicarbonate were observed.

Taken together, these studies demonstrate that both patiromer and SZC are effective for reducing hyperkalaemia. However, both agents increase the rates of hypokalaemia and patiromer increased rates of hypomagnesaemia, and SZC, in particular, is associated with increased oedema in patients with HF.

Potassium binders for the prevention of hyperkalaemia in heart failure patients: the equipoise

The benefit of potassium-binding agents in controlling hyperkalaemia in patients' at risk, needs to be substantiated with further studies determining whether administration of potassium-binding agents will allow maximizing the use of RAASi in patients at risk of hyperkalaemia, and consequently improving clinical outcomes. The current state of equipoise may be summarized as follows:

- In daily practice, physicians may be less permissive to hyperkalaemia due to concern about its consequences.
- Yet, monitoring of serum potassium in daily practice, including in hyperkalaemia risk situations, is suboptimal and below guideline recommendations.
- Inertia is the likely main driver of suboptimal monitoring of serum potassium.
- Inertia is also one reason for lack of optimal monitoring, because time and resource consuming, HF drug-dose adjustments, including drug re-initiation or re-up titration after drug discontinuation or down titration, in response to rise in potassium.
- An increase in serum creatinine after initiation of a MRA may be due to reversible haemodynamic factors rather than renal injury.
- Down-titration of RAASi in response to hyperkalaemia and or an increase in serum creatinine may be unnecessarily conservative for many patients, provided that potassium levels and kidney function are carefully monitored.[38]
- Potassium-binding agents may enable using life-saving RAASi at target doses.
- Potassium-binding agents may enable optimal use of life-saving RAASi and therefore may improve clinical outcomes.

RAASi therapy is being refined

In the PARADIGM-HF trial,[2] sacubitril/valsartan (an angiotensin receptor blocker combined with a neprilysin inhibitor), when used concomitantly with an MRA, resulted in lower hyperkalaemia rates when compared to the concomitant use of enalapril and an MRA. This lower risk of hyperkalaemia was also observed among participants who were not treated with an MRA at baseline but who were initiated on MRA therapy during the course of the study.[2] These data from the PARADIGM-HF trial suggest that the substitution of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) for sacubitril/valsartan may enhance the potassium safety and tolerability of MRAs in suitable HF-REF patients by moderating the risk of serious hyperkalaemia. Therefore, future studies of potassium binders might be needed specifically within the context of use of HF medications, including sacubitril/valsartan.

Several new non-steroidal MRAs are being developed. The one that has undergone the most extensive clinical evaluation is finerenone.[39] Finerenone is tightly bound to

Table 1 Spironolactone dose adjustment proposal

Serum K^+ (mmol/L)	Dose adjustment
	Baseline: eGFR $\geq$50 mL/min/1.73 m^2 → spironolactone dose = 25 mg/day eGFR 30–49 mL/min/1.73 m^2 → spironolactone dose = 25 mg every other day
<4.5	Increase dose: If spironolactone dose = 25 mg/day → increase to 50 mg/day If spironolactone dose = 25 mg every other day → increase to 25 mg/day
4.5–5.4	No adjustment recommended
5.5–5.9	Decrease dose: If spironolactone dose = 50 mg/day → decrease to 25 mg/day If spironolactone dose = 25 mg/day → decrease to 25 mg very other day If spironolactone dose = 25 mg every other day → stop treatment
$\geq$6.0	Stop treatment and reintroduce when serum K^+ $\leq$4.5 mmol/L Stop treatment at any case if eGFR $\leq$30 mL/min/1.73 m^2 and reintroduce upon clinical decision

and highly specific for the MRA. In the ARTS trial,[40] finerenone was compared to spironolactone in patients with HF-REF and CKD. The incidence of hyperkalaemia was less frequent with finerenone compared with spironolactone (5.3% vs. 12.7%, $P = 0.048$). In the ARTS-HF study,[41] finerenone was compared to eplerenone in patients with chronic HF-REF plus CKD and/or diabetes mellitus. A potassium level increase to $\geq$5.6 mmol/L at any time point occurred in 4.3% of patients without differences between finerenone and eplerenone. Finerenone is currently under evaluation in patients with diabetic nephropathy (FIDELIO trial: NCT02540993) and in patients with renal disease at increased risk for cardiovascular events (FIGARO trial: NCT02545049). These patients are also at increased risk of hyperkalaemia. It has to be seen whether finerenone will be 'potassium-safe' and whether potassium binders might be useful in this context of use. Unfortunately, finerenone is not currently being developed for HF.

How to manage the risk of hyperkalaemia?

Most often, hyperkalaemia is predictable, manageable, and reversible. Risk factors for hyperkalaemia are well documented and include: advanced stages of CKD (frequency up to 40–50%),[30] chronic HF (frequency up to 30%),[21] diabetes mellitus (frequency up to 17%),[42] resistant hypertension with add-on MRA therapy (frequency 8–17%),[43] advanced age,[44] and drugs that interfere with renal potassium excretion (especially when used concomitantly).[44] In all these conditions, more frequent serum potassium monitoring is advisable, patient education about potassium diet is important, and in case of recurrent episodes of hyperkalaemia the use of potassium binders may be useful in maintaining normokalaemia and optimal RAASi therapy. Monitoring of serum potassium is often overlooked, even in high-risk situations and after an episode of hyperkalaemia.[15] International guidelines suggest that serum potassium should be tested within 120 days before initiation of a RAASi, during the early post-initiation period (Days 1 through 10), and during the extended post-initiation period (Days 11 through 90), typically every 4 months.[45] This cycle of monitoring should be repeated at each new RAASi initiation, re-initiation or dose adjustment, and after any change in electrolyte status.

How to manage hyperkalaemia?

Dietary management

Restriction of dietary potassium to <2.4 g/day is recommended in patients with stage 3 (eGFR <60 mL/min/1.73 m^2) or higher CKD.[46] However, specific guideline-directed advice is lacking on dietary potassium intake for other patient groups at risk of hyperkalaemia. In patients with HF in whom sodium restriction is frequently advised, the use of salt substitutes including potassium chloride may expose these patients to the risk of hyperkalaemia, especially if they have concomitant CKD or diabetes mellitus. Although patients are often educated to avoid commonly recognized high-potassium foods, many high-potassium foods may remain unrecognized by patients and healthcare providers. Patients at risk for hyperkalaemia should receive comprehensive dietary potassium education and if necessary consultation with a dietician.

Dose adjustments

The management of hyperkalaemia may require a short-term cessation of potassium-retaining agents and/or RAASi, but this should be minimized and RAASi should be carefully reintroduced as soon as possible while monitoring potassium levels.[8,9]

One suggested approach is to reduce ACEi/ARB dose by 50% and recheck the serum potassium in 5–7 days until it has returned to baseline. If serum potassium does not return to baseline in ~2–4 weeks, discontinue the ACEi/ARB. If the patient is taking some combination of an ACEi or ARB and a MRA, discontinue one of the agents and recheck the potassium within 5–7 days.[44]

In the case of the MRA spironolactone a detailed algorithm for dose adjustment is provided in *Table 1*.

Future developments and potential clinical applications

The FDA and EMA approved Patiromer and SZC for the treatment of chronic hyperkalaemia in patients receiving RAASi, with the 'wide' indication of 'treatment of hyperkalaemia'.

Physicians will have to figure out how they may take advantage of these agents. Certainly, because of these are safer compared to the 'older' potassium binders, physicians may feel more comfortable using Patiromer or SZC to mitigate transient increases in serum potassium in patients receiving RAASi therapy. Further clinical experience will be required, and future studies may help understand when best to use these medications, i.e. at what level of serum potassium they should be initiated and whether or not they should be initiated before or after adjusting the doses of RAASi. The optimal duration of treatment in clinical practice will also need to be better described, i.e. should the K^+ binder be discontinued after resolution of hyperkalaemia or continued with the aim of preventing a recurrence of hyperkalaemia in high-risk patients? Importantly, Patiromer and SZC are not interchangeable. They have important pharmacokinetic and safety profile differences. Ideally, a head-to-head comparison should help physicians determine the best conditions to use Patiromer and SZC, respectively. Cost and reimbursement are other factors which will influence the clinical use of Patiromer and SZC. Cost-effectiveness studies are required including a comparison to the currently used potassium binder resins (calcium polystyrene sulfonate and sodium polystyrene sulfonate).

The benefit of more aggressive use of RAASi with higher doses might also be investigated if facilitated with concomitant use of potassium binders.

A potential use of the new potassium-lowering agents would be to allow new indications, such as the use of MRAs in patients with an eGFR $\leq$30 mL/min/1.73 m^2 in whom they are currently contraindicated due to the fear of inducing hyperkalaemia and further renal dysfunction. Another potential use of the new potassium-lowering agents in association with a MRA could be in patients with ESRD on renal dialysis who are at a high risk for HF and sudden cardiac death.

The long-term risks and benefits of strategies using potassium-lowering agents should be thoroughly tested in adequately powered outcome trials.[29,47]

Conflict of interest: F.Z. has received consultant/scientific advisory board fees from Actelion, Astrazeneca, Amgen, Bayer, Boehringer, Boston Scientific, CEVA, CVRx, EDDH, GE Healthcare, Janssen, Novartis, Pfizer, Quantum Genomics, Relypsa, Resmed, Stealth peptide, Takeda, and ZS Pharma. He is CardioRenal co-founder. J.P.F. has no conflicts of interest to declare. B.P. is a consultant to Bayer, Astra Zeneca, Sanofi, Stealth peptides, Relypsa/Vifor*, Sarfez*, KBP Biosciences*, Tricida*, and Sc Pharmaceuticals*. He has patent—site-specific delivery of eplerenone to the myocardium—US Patent # 9931412 (* denotes stock options).

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