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In pursuit of balance: renin–angiotensin–aldosterone system inhibitors and hyperkalaemia treatment

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Hyperkalaemia is a life-threatening condition leading to significant morbidity and mortality. It is common in heart failure (HF) patients due to the disease itself, which often co-exists with chronic kidney disease and diabetes mellitus, the fluctuations in renal function, and the use of some drugs [i.e. renin–angiotensin–aldosterone system (RAAS) inhibitors]. In particular, hyperkalaemia opposes to their administration or up-titration, thus impacting on mortality. New K^+ binders, namely, patiromer and sodium zirconium cyclosilicate, are an intriguing option to manage hyperkalaemia in HF patients, both to reduce its fatal effects and to let clinicians up-titrate RAAS inhibitors. Even if their real impact on strong outcomes is still to be determined, we hereby provide an overview of hyperkalaemia in HF and its current management. New trials are welcome to fill the gap in knowledge.

Hyperkalaemia and heart failure

Hyperkalaemia (HK) is a life-threatening condition associated with significant morbidity and mortality. It is commonly defined as serum potassium >5 mEq/L, and usually it is classified into mild (K^+ 5.1–5.4 mEq/L), moderate (5.5–6.0 mEq/L), and severe (>6.0 mEq/L).[1]

HK is commonly found in heart failure (HF) patients partly because of neurohormonal activation and partly due to the frequent co-presence of chronic kidney disease (CKD) and diabetes, the fluctuations in renal function, and the use of some drugs.[2–4] About one-fourth of patients with HF have HK,[5,6] reaching one-half in those with both HF and CKD.[5] Importantly, HK impacts the prognosis determining abnormal excitability in muscular and cardiac cells, conduction disorders, and risk of malignant arrhythmias.[7] The mortality is even higher in the presence of HK-linked comorbidities, namely CKD, diabetes, and HF.[8]

Two out of four pillars of treatment of HF with reduced ejection fraction (HFrEF), namely ACE inhibitors (ACEis) or angiotensin receptor blockers (ARBs) with or without neprilysin inhibitor (ARNi), and mineralocorticoid receptor antagonists (MRAs), especially the latter, directly cause HK.[9–12] The more, HK opposes to their use or uptitration.[13,14] In the QUALIFY international prospective observational longitudinal survey assessing physicians' adherence to guideline-recommended medications for the treatment of chronic HFrEF, a large proportion of patients (69.3%) were treated with MRAs. Of those who were not taking them, contraindications were reported in 18.9% and intolerance in 14.9%, mostly due to renal dysfunction or hyperkalaemia.[13] A study by Trevisan *et al.* investigated the 1-year incidence and clinical HK predictors and quantified drug prescription changes after an episode of HK in 13 726 Swedish patients initiating MRA therapy during 2007–2010. 18.5% of patients experienced at least one detected HK. Of them, 47% discontinued MRA and 10% reduced the prescribed dose after the event. Discontinuation rates were higher after moderate/severe HK and within 3 months from MRA initiation. When MRA was discontinued, most patients (76%) were not reintroduced to MRA therapy during the subsequent year. Participants with CKD carried the highest risk of MRA discontinuation.[14]

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However, the European Society of Cardiology (ESC) guidelines recommend the administration of the highest tolerated dose for renin–angiotensin–aldosterone (RAAS) inhibitors, in order to improve morbidity and mortality, but also a tight control of serum potassium levels in HF patients.[15] Notably, both the pro-arrhythmic effect of HK and the suboptimal use of such drugs are associated with increased mortality in HFrEF patients.[7,16-18]

Regarding the prognostic impact of HK, recent data from 9222 patients in the ESC-HFA-EORP Heart Failure Long-Term Registry confirmed the relationship between HK and mortality. However, adjusting for the discontinuation of RAAS inhibitors, HK was no longer associated with long-term mortality.[19] Accordingly, a cohort study from the Swedish Heart Failure Registry demonstrated that HK impacts the prognosis only at short-term, namely 30 days, by means of arrhythmic risk and metabolic derangements.[20] Consequently, HK impacts short-term mortality directly,[20] and long-term prognosis indirectly as a marker of risk for RAAS inhibitors discontinuation rather than a risk factor for worse outcomes.[19]

How to traditionally manage hyperkalaemia

A deep anamnesis about diet, use of supplements, salt substitutes, and concomitant medications that may contribute to HK is mandatory in every HF patient. In addition, a potassium-poor diet (<2.4 g/day) is generally recommended in patients with CKD.[21] However, dietary K^+ restriction is difficult to achieve and can deny CKD patients the beneficial effects of K^+ rich diets,[22,23] hampers the quality of life[24] and is consistently associated with poor general well-being and psychological stress.[25-28] In patients advised for sodium restriction, attention should be paid on the use of salt substitutes including K^+. Moreover, also drugs that might cause acute kidney injury (e.g. NSAIDs) are not recommended.

In CKD patients, HF management guidelines recommend caution with the use of RAAS inhibitors, particularly focusing on low dose initiation and slower titration,[15,29] due to the risk of HK. The same can be said for patients with diabetic nephropathy[30] and CKD patients with hypertension and albuminuria.[31]

The treatment of HK, either acute or chronic, consists of four different mechanisms:[1]

(1) excretion of K^+ into the intracellular space stimulating the Na^+/K^+-ATPase by means of iv or inhaled β_2-agonists, iv insulin, or iv sodium bicarbonate if metabolic acidosis is also present;
(2) cardiac membrane stabilization to avoid arrhythmias, using iv calcium gluconate or hypertonic saline;
(3) renal K^+ elimination with loop diuretics or through urine alkalinization with sodium bicarbonate; haemodialysis when rapid removal of K^+ from blood is required;
(4) faecal K^+ elimination, using resins or new K^+ binders.

Sodium polystyrene sulphonate (SPS) and calcium polystyrene sulphonate are commonly available cation exchange resins, which remove K^+ via the gastrointestinal tract. However, despite being acutely useful, they are poorly tolerated, and their magnitude of action is unpredictable. More importantly, they have not been tested in adequately powered randomized trials to assess long-term safety, tolerability, and efficacy.[32,33] In addition, SPS can determine volume expansion due to its K^+ exchange for sodium. Finally, some reports suggested a causative association between these resins and colonic necrosis.[34-36]

Notably, two new drugs have been recently developed to treat HK: patiromer and sodium zirconium cyclosilicate (ZS-9). Below their characteristics are reported and a practical approach to their use in everyday clinical practice is provided. *Table 1* summarizes the key messages.

Patiromer

Patiromer (Veltassa®) is a spherical, non-resorbed, metal-free, cross-linked fluoroacrylate polymer.[37] It increases K^+ faecal excretion in a dose-dependent way by exchanging it with calcium in the gastrointestinal tract. In the evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (PEARL-HF) trial, the administration of patiromer vs. placebo for 4 weeks to patients with HF and a history of HK resulting in discontinuation of a RAAS inhibitor or CKD significantly reduced the occurrence of HK (7.3% vs. 24.5%, *P* 0.015) and favoured a higher proportion of patients receiving the target dose of spironolactone (91% vs. 74%, *P* 0.019).[38] On the other hand, beyond stipsis or diarrhoea, patiromer caused a higher risk of hypokalaemia (6% vs. 0%)

Table 1 Comparison between potassium binders

	Patiromer	ZS-9
Temperature to be kept	2–8 °C	Environment
Taste	Tasteless	Tasteless
Water solution	85 mL	45 mL
Administration with food	Not influenced	Recommended
Administration with drugs	3 h apart	2 h apart from drugs with pH-dependent solubility
Acute dose	Not applicable	10 g thrice a day for maximum of 72 h
Chronic dose	Starting dose: 8.4 g per day Maximum dose: 25.2 g per day	Maintaining dose: 5 g per day Maximum dose: 10 g per day
Onset of action	4–7 h	1 h
Typical side effects	Hypomagnesaemia, constipation, diarrhoea	Oedema/hypervolaemia, constipation, diarrhoea
Inpatients	Yes	No

and hypomagnesaemia (24% vs. 2%), but severe adverse events have been not reported.

The recently published Patiromer for the Management of Hyperkalaemia in Subjects Receiving RAASi Medications for the Treatment of Heart Failure (DIAMOND; NCT03888066) trial enrolled 1195 HF patients with or without CKD aiming at demonstrating if the use of patiromer enables to treat them with the target dose of RAAS inhibitors and if this is associated with better outcomes. On the recommendation of the independent study Executive Committee and due to COVID-19 impact on recruitment, the primary endpoint has been changed in June 2021 to investigate the role of patiromer in controlling serum K^+, preventing HK and maintaining RAAS inhibitors use in HF patients. After a run-in phase with patiromer and optimization of the RAAS inhibitors therapy (i.e. $\geq$ 50% recommended dose of ACEi/ARBs/ARNi, and 50 mg of spironolactone or eplerenone), 878 (84.6%) patients were able to be optimized to guideline-recommended RAAS inhibitors therapy and were randomized to patiromer or placebo. In addition, in these patients the use of patiromer led to a difference in mean change of K^+ levels of −0.10 mEq/L. Risk of K^+ >5.5 mEq/L (HR 0.63; 95%CI 0.45–0.87; $P=0.006$), reduction of MRA dose (HR 0.62; 95%CI 0.45–0.87; $P=0.006$), and total adjusted HK events/100 person-years (77.7 vs. 118.2; HR 0.66; 95%CI 0.53–0.81; $P<0.001$) were lower with patiromer. Moreover, patiromer was well tolerated and did not cause safety concerns.[39] So far, only patiromer has data cited in the most recent ESC guidelines to support RAAS inhibitor use or uptitration.[15] In addition, the effect of patiromer on MRA inhibitors optimization is supported by a recent meta-analysis.[40]

Patiromer is a powder for tasteless oral suspension. It should be kept in the fridge at 2–8°C and diluted in 80 mL of water. The starting dose is 8.4 g once a day, which can be increased to 25.2 g/day. Due to its mechanism of action, patiromer may increase serum calcium levels, which should be periodically screened, particularly in CKD patients. The TOURMALINE trial demonstrated that patiromer equally reduces serum K^+ levels when assumed either with or without food.[41] Importantly, patiromer can bind to other drugs preventing their absorption in the gastrointestinal tract, so it should be assumed at least 3 h apart from other oral drugs. Although patiromer should not replace emergency treatment for life-threatening hyperkalaemia, due to its onset of action of about 4–7 h after administration, however, a recent publication evaluating 881 patients admitted in the emergency room due to HK showed that patiromer was effective in lowering or reversing non-life-threatening hyperkalaemia.[42] Regarding special populations, there is limited experience with patiromer use in patients with stage 5 CKD and in patients receiving dialysis treatment. However, a phase 4 study is ongoing in haemodialysis patients aimed at exploring the role of patiromer in hyperkalaemia prevention in end-stage kidney disease (PEARL-HD; NCT03781089). In addition, it is preferable to avoid it during pregnancy.

Sodium zirconium cyclosilicate (ZS-9)

ZS-9 (Lokelma®) is a non-absorbed, non-polymeric inorganic powder with a uniform microporous structure.[43] Also ZS-9 increases faecal excretion of K^+ in a dose-dependent way by exchanging it in the gut with other cations, namely sodium and hydrogen. In the Hyperkalaemia Randomized Intervention Multidose ZS-9 Maintenance (HARMONIZE) trial, 93% of HF patients with HK receiving 48-hour open-label ZS-9 reached the target level of K^+ (3.5–5.0 mEq/L) within the same time span and without modifying the RAAS inhibitors doses.[44] In particular, the mean time to reach normokalaemia was 2 h, so ZS-9 is faster than patiromer. In the maintaining phase, a greater proportion of patients had normal K^+ levels (83%, 89%, and 92% with 5, 10, and 15 g, respectively) than placebo (40%, $P<0.001$).[44] Besides stipsis and diarrhoea, the main adverse event was oedema, typically at the higher doses of ZS-9.[45] No severe side effects were reported.

Similarly to the DIAMOND trial, the Potassium Reduction Initiative to Optimize RAAS Inhibition Therapy With Sodium Zirconium Cyclosilicate in Heart Failure (PRIORITIZE-HF; NCT03532009) trial, has enrolled 182 patients to evaluate whether ZS-9 may favour target-dose RAAS inhibitors uptitration after 3 months in HF patients. The study was prematurely stopped due to the COVID-19 pandemic and failed to reach the primary endpoint.[46] As a consequence, and differently from patiromer, no conclusive data are still available about RAAS inhibitors maximization using ZS-9.[40]

ZS-9 was tested in hyperkaliaemic patients showing promising results in the short,[47] medium[44,48] and long-term[49,50] regardless of CKD stage.

ZS-9 is a powder for colourless and odourless oral suspension to be diluted in 45 mL of water. Differently from patiromer, it can be kept outside the fridge. Moreover, ZS-9 can be taken with or without food. ZS-9 can temporarily increase the gastric pH, thus altering the absorption of drugs with pH-dependent solubility; consequently it should be assumed 2 h apart from them (e.g. antifungal azoles, tyrosine-kinase inhibitors, antiretrovirals).[51,52] Its onset of action is faster (1 h), so that ZS-9 can be used both for acute hyperkalaemia (at the dose of 10 g thrice a day for a maximum of 72 h) and for chronic one (at the maintaining dose of 5 g per day to maximum 10 g per day). However, no study about ZS-9 has enrolled inpatients.

Potassium binders in clinical practice

Traditionally, when HK occurs, some consensus papers exist about how and when to reduce or stop RAAS inhibitors.[1,15,53] In general, they should be reduced when K^+ is >5.5 mEq/L and stopped (for the shortest time possible) when >6.0 mEq/L, thus affecting both cardiovascular and renoprotection. In addition, ACEi can be changed to ARNi, which is demonstrated to carry a lower risk of HK.[54] However, the availability of the new potassium binders may change the clinical practice. An expert consensus document by the Working Group on Cardiovascular Pharmacotherapy of the ESC suggests to use new K^+ binders in case of chronic or recurrent HK in patients taking RAAS inhibitors and to uptitrate them consensually.[1] When K^+ is between 5.0 and 6.5 mEq/L new K^+ binders should be initiated and then RAAS inhibitors uptitrated.[1] Only when K^+ rises above 6.5 mEq/L RAAS inhibitors should be reduced or discontinued and new K^+ binders started.[1]

Two practical and detailed algorithms to use new K^+ binders have been provided by Rossignol *et al.* also considering the timing for K^+ evaluation, up/downtitration for both RAAS inhibitors and K^+ binders, side effects, and caveats.[55]

New K^+ binders are an intriguing option to manage HK in HF patients, both to reduce its fatal effects and to let clinicians uptitrate RAAS inhibition. Even if their real impact on strong outcomes is still to be determined, we suggest to consider their use in routine clinical practice in order to gain the correct confidence and provide an additive tool to HF patients' well-being. Therapeutic inertia is the leading cause preventing clinicians from adding new drugs to poly-treated patients. Indeed, it is obvious and well-accepted to administer a protein pump inhibitor to those taking antithrombotic drugs in order to prevent their unwanted side effects and to favour their life-saving actions.[56] Accordingly, clinicians should also consider K^+ binders to let HF patients receive prognostically relevant and disease-modifying drugs such as RAAS inhibitors, avoiding HK. New trials are welcome to fill the gap in knowledge.

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Data availability

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