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A new area for the management of hyperkalaemia with potassium binders: clinical use in nephrology

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Chronic kidney disease (CKD) patients and more so CKD patients treated with renin–angiotensin–aldosterone system inhibitors (RAASi) are prone to experience hyperkalaemia, a condition associated with an increased risk of death. This represents a true dilemma in daily practice since RAASi are the cornerstones of nephroprotective and cardioprotective strategies in CKD patients, as well as in hypertensive patients with or without CKD. The recent availability in the USA and EU of the potassium-binding resin Patiromer, together with sodium zirconium cyclosilicate (SZC), which was more recently approved in the EU and the US, may lead to a paradigm shift both in the treatment of hyperkalaemia and in enabling RAASi maintenance. Whether potassium normalization, potentially combined with a RAASi maintenance strategy, may translate into improved cardiovascular and renal outcomes needs be tested prospectively.

Introduction

There is a current dilemma in the nephrology field with regard to renin–angiotensin–aldosterone system inhibitors (RAASi) use. These drugs, especially angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB), are indeed the cornerstones of nephroprotective strategies, as acknowledged by current guidelines[1–3] and of cardiovascular (CV) protection strategies. RAASi are furthermore one of the five first-line antihypertensive drugs,[4] and one of the compelling components of the triple antihypertensive therapies for managing resistant hypertension, as recommended by international guidelines.[5] However, hypertensive patients with/without chronic kidney disease (CKD) and CKD patients treated with RAASi are more prone to experience hyperkalaemia, a condition associated with an increased risk of death. In the hyperkalaemia setting, current guidelines consistently recommend to not start, to down-titrate or to discontinue RAASi, depending on its severity.[1,3,6–8] The availability in the USA and in the EU of the potassium-binding resin Patiromer,[9] as well as of sodium zirconium cyclosilicate (SZC), now approved in the EU,[10] and in the US (https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/207078s000lbl.pdf) , may lead to a paradigm shift in treating hyperkalaemia and enabling RAASi maintenance.

Position of the problem: the burden of hyperkalaemia in the nephrology setting

Observational data mostly report a U-shape association between serum potassium and death, with hypokalaemia and hyperkalaemia being associated with worse outcomes in various patient populations including general,[11,12] hypertensive,[13] high CV risk,[11] CKD,[11] and acute[14,15] and chronic heart failure[16,17] populations (the latter two conditions associated with CKD in one-third of patients[18]) In a large US health system gathering data from 194 456 outpatients, hyperkalaemia above 5 or 5.5 mmol/L occurred in 10.8% and 2.3% of all patients over a 3-year period. The risk of experiencing hyperkalaemia was logically higher among patients with more frequent potassium measurements and with lower estimated glomerular filtration rate (eGFR).

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Among patients with eGFR <30 mL/min/1.73 m^2 who had ≥4 potassium measurements per year, 62.1% experienced potassium >5 mmol/L and 29.9% experienced potassium >5.5 mmol/L.[19] In an individual-level data meta-analysis of 27 international cohorts (10 general population, 7 high CV risk, and 10 CKD) including 1 217 986 participants followed for a mean of 6.9 years, the prevalence of serum potassium >5.0 mmol/L and serum potassium >5.5 mmol/L was lower in individuals in general population/high CV risk cohorts {3.31% [95% confidence interval (CI) 3.28–3.34%] and 0.49% (95% CI 0.48–0.50%)} comparatively to individuals in the CKD cohorts [17.94% (95% CI 17.58–18.31%) and 4.23% (95% CI 4.03–4.42%)], respectively. The lowest risk of all-cause mortality was observed at serum potassium of 4–4.5 mmol/L. The relative risks associated with hyperkalaemia and hypokalaemia were similar in patients with various levels of kidney (dys)function. Risk relationships were similarly U-shaped for CV mortality and end-stage renal disease.[11] The risk of experiencing hyperkalaemia also increases with lower eGFRs[11,19] and higher microalbuminuria excretion,[11] along with RAASi use.[11,12,19] In a *post hoc* analysis of the Reduction of Endpoints in non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) trial, a randomized, double-blind trial comparing the effects of losartan vs. placebo in addition to conventional antihypertensive medication in patients with Type 2 diabetes and nephropathy, Miao *et al*.[20] showed that increased serum potassium concentrations ≥5.0 mmol/L were associated with an increased risk of doubling serum creatinine or end-stage renal disease, independent of baseline renal function, and other important predictors of renal outcomes. The pathophysiological mechanism whereby increased serum potassium levels affect renal outcomes is however poorly understood. A decrease in renal perfusion (regardless of its cause, including RAASi) and early tubulo-interstitial damage may impair renal potassium excretion, even though renal function is only mildly depressed. This situation may lead to an imbalance in renal potassium/sodium handling that may further damage the tubules, thereby subsequently contributing to a further decline in renal function.[20]

Current international CKD guidelines recommend using RAASi in order to achieve nephroprotection, since they enable preserving kidney function and delay the progression to ESRD in CKD.[2] Indeed, these agents are able to slow the progression of kidney disease,[2,3] and to reduce proteinuria.[1,3] Their use is valuable in CKD and indicated in proteinuria,[1,2] with known beneficial effects in diabetic nephropathy.[1] Better renal outcomes have furthermore been observed with higher RAASi doses.[21,22] Proteinuria can be lowered by dual renin angiotensin aldosterone blockade with ACEi and ARBs or with direct renin inhibitors to a greater extent than monotherapy.[23] While this combination may potentially preserve renal function in patients with diabetes and CKD to some extent, according to a network meta-analysis,[24] this combination also increases the risk of hyperkalaemia, hypotension, and acute renal failure.[23] Therefore, dual RAS blockade is discouraged by both NICE and ESH guidelines as well as the European Medicines Agency.[4,25] RAASi are more effective at reducing kidney function decline than other blood pressure lowering drugs.[3]

However, the use of RAASi drugs is inherently associated with a risk of hyperkalaemia owing to their pharmacological properties, leading to aldosterone inhibition. Should hyperkalaemia arise, it is advised by current nephrology and cardiology guidelines to not initiate, to down-titrate or to discontinue RAASi, according to its severity.[1,3,6–8] In the aforementioned US health system, the most common medication changes were discontinuation/dose reduction of RAASi. For instance, compared with a control with a potassium measurement <5 mmol/L, a patient with a serum potassium >5.5 mmol/L had a 3.7-fold (95% CI 3.3–4.3) odds of ACEi/ARB discontinuation within the next 60 days.[19]

The approach to and treatment of patients with chronic hyperkalaemia is however currently undergoing significant change. Until recently, recommendations for patients with chronic hyperkalaemia have been to: (i) place them on a low potassium diet; (ii) eliminate potassium supplements and drugs that compromise renal function, such as non-steroidal anti-inflammatory drugs; (iii) initiate treatment with a non-potassium sparing diuretic, if indicated, or increase the dose if already on a diuretic, and (iv) reduce the dose or discontinue RAASi.[26]

However, reducing the dose of the RAASi or discontinuing the latter could place the patient with heart failure and reduced ejection fraction at increased risk of death, since major clinical trials have demonstrated a reduction in CV mortality and total death with RAASi treatment, leading to a Class I indication in major European and United States guidelines.[7,8] In a large US database including more than 20 000 heart failure patients, nearly 60% who discontinued RAASi after an hyperkalaemic episode experienced an adverse outcome or mortality compared with 52% of patients on submaximum RAASi doses and 44% of patients on maximum doses (all comparisons $P < 0.05$). Heart failure patients on submaximum dose or who discontinued RAASi died twice as frequently as patients on maximum dose. Over 50% of the 43 388 patients with CKD Stages 3 to 4 who discontinued RAAS inhibitors experienced an adverse outcome or died compared with 47.4% of patients on submaximum doses and 42.6% of patients on maximum doses (all comparisons $P < 0.05$). Mortality was also recorded in 9.8% of patients with CKD Stages 3 to 4 on maximum RAASi doses compared with 20.3% of patients on submaximum doses and 22.4% of patients who discontinued therapy after an hyperkalaemic event.[27]

Whether alternative hyperkalaemia mitigation strategies (potassium diet restriction, potassium binders, bicarbonates, non-potassium sparing diuretics) may enable achieving better clinical and kidney outcomes has yet to be tested in dedicated randomized trials. Interestingly, we recently conducted a hospital-based, prospective, multicentre cohort study, the French NephroTest study, comprised of 2084 adult CKD patients Stages 1–5, the latter of whom were non-dialysed. These patients received optimized nephrologist care with a reinforced follow-up, providing nephrologists with a large set of blood and urine tests to assess each patient's metabolic complications and CV risk at yearly intervals. Laboratory findings reported all relevant abnormal values, such as plasma potassium <3.5 or >5.0 mmol/L, together with a reminder of current

recommended targets, to guide treatment adjustment. Results revealed that low plasma potassium (<4 mmol/L) was relatively common, whereas hypokalaemia (<3.5 mmol/L) and high plasma potassium were uncommon. Neither high nor low plasma potassium, at baseline or during follow-up, was found associated with all-cause or CV mortality in this population. A key finding from this selected patient cohort was the apparent lack of excess mortality observed in the absence of reduction of ACEi or ARB use over time, while 74.4% of the patients were treated with ACEi or ARB at baseline. Although no causality could be ascertained in this observational setting, we noted that the nephrologists were not reluctant to prescribe drugs that might favor higher potassium. Strikingly, low plasma and high plasma potassium were corrected in a substantial number of patients between the first and second NephroTest work-up performed at a 1-year interval: overall, between the two visits, half of the patients remained in the normokalaemic subgroup, while 39.9% of those with low plasma potassium and 54.1% of those with high plasma potassium at baseline had normal plasma potassium at the second visit. Management was indeed responsive to test results, as shown by the increased prescription of ARBs in patients with low baseline plasma potassium, and the increased prescription of potassium-binding resins and bicarbonate in those with high baseline plasma potassium.[28,29]

The management of hyperkalaemia in the chronic hemodialysis setting (i.e. CKD Stage 5D) appears to be even more challenging since, in a recent study, we reported hyperkalaemia to be highly prevalent and recurrent in a French regional registry despite the widespread and dynamic prescription of low-potassium dialysis baths and potassium-binders [sodium or calcium polystyrene sulfonate (SPS or CPS)], thereby highlighting the need for more effective potassium mitigating strategies.[30]

A new era for hyperkalaemia management with the advent of new potassium binders, and future directions/indications?

Sodium or calcium polystyrene sulfonate (SPS or CPS) are cation exchange resins that remove potassium via the gastrointestinal tract. These compounds were approved decades ago at a time when the concept of evidence-based medicine was not yet invented, i.e. in the absence of adequately-designed randomized controlled trials. SPS has long been prescribed to reduce serum potassium, although its tolerability is poor, having been associated with colonic necrosis, while its onset of action and degree of potassium lowering is unpredictable.[31,32] Furthermore, in patients with volume overload, the use of SPS may be associated with volume expansion and the development of manifest heart failure since SPS exchanges potassium for sodium.[33] A recent randomized, double-blind, placebo-controlled trial in 33 outpatients with CKD and mild hyperkalaemia (5.0–5.9 mEq/L) reported that 30 g SPS administered orally once daily for 7 days reduced serum potassium significantly more than placebo (−1.04 mEq/L, 95% CI −1.37 to −0.71), although the proportion of patients achieving normokalaemia at the end of treatment was not significantly different between treatment groups (73% SPS vs. 38% placebo, $P = 0.07$).[34,35]

In contrast, two new potassium binders have been developed under the latest standards of drug development and have been recently approved: Patiromer (FDA approved in 2015, EMA approved in July 2017[9]) and sodium zirconium cyclosilicate (SZC) (EMA approved April 2018[10] and FDA approved May 2018[36]). Patiromer exchanges potassium for calcium while SZC exchanges potassium for sodium. Patiromer and SZC appear to be effective in lowering serum potassium in patients with hyperkalaemia, as demonstrated by relatively short-term (maximum 1 month) published and peer-reviewed studies for SZC, and up to 12 months for Patiromer. Patiromer and SZC appear to offer tolerability advantages over SPS, although direct comparative clinical studies have not been performed. Both SZC and Patiromer are free flowing powders that do not swell appreciably in the gastrointestinal tract.[35,37–39] Mild to moderate constipation has been reported in 1–11% of patients enrolled in the pivotal clinical trials.[35,40–43] No cases of colonic necrosis have been reported in clinical trials conducted to date. Other adverse effects include hypokalaemia (5–10%, depending on drug and dose) and hypomagnesaemia (3–7%, depending on Patiromer dose).[31,35] Patiromer has also been associated with mild constipation,[41] while SZC has been associated with an increased incidence of oedema.[35,42] The comorbidities of the patients enrolled in the Patiromer and SZC Phase II–III trials

Table 1 Baseline comorbidities across Patiromer Phase II-III trials

Number of patients with the following comorbidities or treatment	Trial 201[44] Haemodialysis subjects ($n = 6$)	Trial 202[37,45] PEARL-HF ($n = 104$)	Trial 204[46] CKD with HF ($n = 63$)	Trial 205[40] AMETHYST-DN ($n = 304$)	Trial 301[41] OPAL-HK ($n = 243$)
DT2 (%)	?	33 (32%)	27 (43%)	304 (100%)	139 (57%)
HF (%)	?	100 (100%)	63 (100%)	106 (35%)	102 (42%)
HTN (%)	4 (67%)	?	59 (94%)	304 (100%)	236 (97%)
CKD (%)	6 (100%)	57 (55%)	63 (100%)	304 (100%)	243 (100%)
Any RAASi	3 (50%)	102 (98%)	63 (100%)	304 (100%)	243 (100%)
Dual RAAS blockade	?	?	1 (1.6%)	?	41 (17%)

CKD, chronic kidney disease; DT2, diabetes Type 2; HF, heart failure; HTN, hypertension; RAASi, renin angiotensin aldosterone system inhibitor.

Table 2 Baseline comorbidities or treatment across SZC Phase II-III trials

Number of patients with the following comorbidities or treatment	ZS-002[47] ($n=90$)	ZS-003[43] ($n=753$)	HARMONIZE, or ZS-004[42] ($n=258$)
DT2 (%)	50 (56%)	451 (59.9%)	170 (66%)
HF (%)	?	300 (39.8%)	94 (36%)
HTN (%)	?	?	?
CKD (%)	90 (100%)	561 (74.5%)	169 (66%)
Any RAASi	56 (62%)	502 (66.7%)	180 (70%)
Dual RAAS blockade	10 (11%)	?	?

CKD, chronic kidney disease; DT2, diabetes Type 2; HF, heart failure; HTN, hypertension; RAASi, renin angiotensin aldosterone system inhibitor.

are summarized in *Tables 1 and 2*, respectively.[40-47] As expected, a substantial proportion of the enrolled patients were CKD patients (including CKD Stage 5D hemodialysis patients for Patiromer[44]) with a high prevalence of Type 2 diabetes, approximately 96% with hypertension in the Patiromer studies when documented (data not reported with SZC), thereby perfectly matching the clinical patient patterns typically encountered by nephrologists. Of note, more than 99% of patients enrolled in the Patiromer development studies were initially treated with a RAASi (approximately 70% for SZC studies). Exploratory analyses performed in the Patiromer Phase III trial showed that 32 patients (62%) in the placebo group comparatively to 9 (16%) in the Patiromer group required an intervention to manage a recurrence of hyperkalaemia; at the end of the randomized withdrawal phase, 44% in the placebo group compared to 94% in the Patiromer group were still receiving RAASi.[41] Interestingly, in the PEARL-HF Phase II trial conducted in heart failure patients with either CKD or a history of hyperkalaemia resulting in discontinuation of a RAASi and/or beta-adrenergic blocking agent, Patiromer use vs. Placebo led to a lower incidence of hyperkalaemia (7.3% Patiromer vs. 24.5% placebo, $P=0.015$) and to a higher proportion of patients on spironolactone 50 mg/day (91% Patiromer vs. 74% placebo, $P=0.019$). In patients with CKD ($n=66$), the incidence of hyperkalaemia was 6.7% with Patiromer vs. 38.5% with placebo ($P=0.041$). In the resistant hypertension and CKD setting, i.e. a population particularly prone to dismal outcomes,[5] the ongoing randomized, double-blind, placebo-controlled AMBER study of Patiromer for the enablement of spironolactone use as the fourth antihypertensive drug for blood pressure control in patients with resistant hypertension and CKD (eGFR 25 to $\leq$45 mL/min/1.73 m^2) aims to determine whether Patiromer treatment, used concomitantly with spironolactone, will result in a more persistent use of the mineralocorticoid receptor antagonist spironolactone through prevention of hyperkalaemia and lead to improved blood pressure control[48]. More broadly, whether a strategy of RAASi maintenance whilst using new potassium binders in CKD patients presenting hyperkalaemia or RAASi uptitration in patients with hypokalaemia may ultimately translate into better cardiorenal outcomes warrants dedicated clinical trials (*Figure 1*, reprinted from Pitt and Rossignol[49]) Of utmost importance is the necessity of potassium and

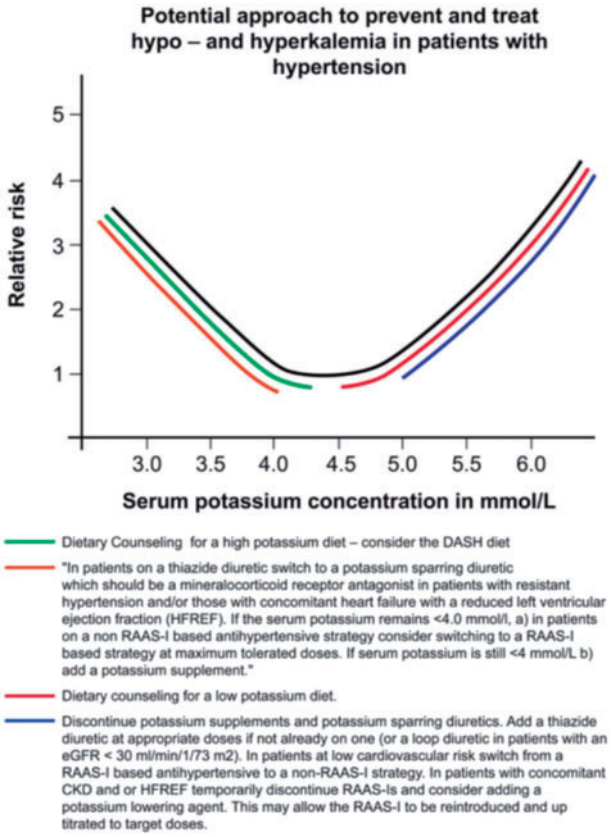

Figure 1 Potential hypokalaemia and hyperkalaemia treatment patterns. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; RAAS-I, renin-angiotensin-aldosterone system inhibitor. Reprinted from Pitt and Rossignol.[49]

creatinine monitoring, given the increased risk of death in patients with CKD and in hypertensive patients with/without CKD, both with mild hypo- and hyperkalaemia. One might also reconsider current recommendations for the monitoring of serum potassium. There are guideline recommendations for the frequency of potassium monitoring in patients with heart failure administered a RAASi[8] as well as suggestions regarding the frequency of potassium monitoring in patients with hyperkalaemia receiving a potassium-lowering agent. These suggestions are based on

the experience gained in initiating these new agents in pivotal clinical trials,[33] which led to a low prevalence of incident hypokalaemia overall and especially in the trials with Patiromer, while reports by the European Medicines Agency highlighted hypokalaemia (and oedema) side effects associated with SZC use 'which may affect up to 1 in 10 people'[10] vs. side-effects associated with Patiromer use, including the digestive system (constipation, diarrhea, abdominal pain and wind) and low blood magnesium, 'which may affect more than one in 100 people'[9]) However, data in the US and the EU suggest that these monitoring recommendations are often not followed and that many patients do not undergo any monitoring of their serum potassium or renal function after initiation of a RAASi.[50,51] In view of the known risk factors for both hypo- and hyperkalaemia, a more frequent monitoring of serum potassium and renal function should be considered in those patients with the aforementioned risk factors. However, the cost effectiveness and efficacy of any new potassium monitoring strategy will inexorably require further evaluation.[52]

Conclusion

In conclusion, the new potassium binders obviously meet medical needs and open new avenues for the management of hyperkalaemia in the nephrology field. Furthermore, potassium binders may enable RAASi optimization, as already shown with Patiromer.[41,45] However, whether this strategy, along with potassium normalization, may translate into improved CV and renal outcomes needs be tested prospectively.[32]

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