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Complications and management of hyperkalemia: implications for the use of the novel cation exchangers zirconium cyclosilicate and patiromer

Hyperkalemia is a serious and common clinical condition associated with increased morbidity and death. The risk of hyperkalemia is increased in patients with chronic kidney disease, diabetes, conditions with impaired distal renal sodium delivery and those on renin–angiotensin–aldosterone system (RAAS) blockade. RAAS blockade has been shown to slow progression of proteinuric kidney disease and reduce mortality in patients with systolic heart failure. Yet delivery of optimum RAAS blockade is frequently limited by development of hyperkalemia. Current treatment for hyperkalemia is suboptimal and few options exist for long-term control of hyperkalemia. In this review article, we explore two new oral nonabsorbable cation exchangers, zirconium cyclosilicate (ZS-9) and patiromer that bind potassium for the treatment of hyperkalemia.

Keywords: chronic kidney disease • heart failure • hyperkalemia • nonabsorbed cation exchangers • patiromer • renin–angiotensin–aldosterone system blockade • sodium zirconium cyclosilicate • diabetes

Lama Noureddine*[,1,2] & Bradley S Dixon[1,3]

[1]Department of Internal Medicine, Carver College of Medicine, University of Iowa, Iowa City, IA 52242, USA

[2] Nephrology Division, University of Iowa School of Medicine, T304 GH, 200 Hawkins Drive, Iowa City, IA 52242–1081, USA

[3]Veterans Administration Medical Center, Iowa City, IA 52246, USA

*Author for correspondence: lama-noureddine@uiowa.edu

Epidemiology of hyperkalemia

Hyperkalemia, defined as a serum potassium (K^+) greater than the upper limit of normal for the lab (generally 5–5.5 mEq/l), is common and has been reported to occur at the statistically expect rate of about 2.5% of the general population [1–2]. In hospitalized patients, the frequency of hyperkalemia (K^+ >5.5 mEq/l) is higher, ranging 2.9–3.5% [3–6]. A serum potassium > 6 mEq/l has been reported to occur in 1.4% of hospital admissions [7] and a serum potassium ≥6.5 mEq/l has been reported to occur in 0.5% of admissions [8].

The incidence and prevalence of hyperkalemia is higher in patients who have impaired renal potassium excretory capacity including those with kidney disease, diabetes, heart failure, those treated with renin–angiotensin–aldosterone system (RAAS) blockade or in patients on potassium-sparing diuretics [9]. A retrospective study by Drawz *et al.* of 13,874 Veterans Affairs (VA) hospital outpatients 65 years of age or older found a prevalence of hyperkalemia (K^+ >5.5 mEq/l) of only 1–2% in patients with a glomerular filtration rate (GFR) of 50–60 ml/min, but 5–9% for patients with a GFR of 15–29.9 ml/min [1]. Similarly, in a large retrospective study of nearly 245,808 hospitalized veterans by Einhorn *et al.*, hyperkalemia (K^+ >5.5 mEq/l) occurred in 3.2% of potassium measurements but the risk was substantially higher in those with chronic kidney disease (CKD) or on RAAS blockade [4]. The adjusted rate of hyperkalemia in patients with CKD but without RAAS blockade was 8.22 versus 1.77 per 100 patient-months in those without CKD. The odds ratio for hyperkalemia rose with more severe CKD and was found to be 2.23 in those with CKD 3, 5.91 for CKD 4 and 11.0 for patients with CKD 5 compared with no CKD [4]. Patients on RAAS blockade and no CKD had an adjusted rate of hyperkalemia of 2.30 per 100 patient-months rising to 7.67 per 100 patient-months in patients with coexisting CKD. The odds ratio of hyperkalemia in patients on RAAS blockade was

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1.41 compared with those not on RAAS blockade [4]. Similarly, in nondiabetic patients with CKD in the AASK trial, hyperkalemia (K^+ ≥5.5 mEq/l) occurred in 1.6% of patients with a GFR over 40 ml/min and in 11.2% with a GFR of 40 ml/min or less [10]. Diabetes is a risk factor for hyperkalemia due to the presence of hyperglycemia, reduced GFR and hyporeninemic hypoaldosteronism [11]. Hyperkalemia (K^+ >5 mEq/l) has been reported in 15% of outpatients with diabetes [12]. Heart failure is also a risk factor for hyperkalemia. A retrospective analysis of the Studies of Left Ventricular Function (SOLVD) trials in which baseline average creatinine was 1.2 ± 0.3 mg/dl and left ventricular ejection fraction was 27 ± 6%, found the incidence of mild hyperkalemia (K^+ ≥5.5 mEq/l) to be 4.2% and severe hyperkalemia (K^+ ≥6 mEq/l) to be 0.8% in the placebo group [13].

Potassium homeostasis

Potassium, by virtue of the activity of plasma membrane Na-K ATPase, is the major intracellular cation (Figure 1) [14,15]. Total body potassium is 50–75 mEq/kg body weight with 98% localized to the intracellular compartment. The intracellular potassium concentration is approximately 150 mEq/l while extracellular potassium is tightly regulated between 3.5 and 5 mEq/l.

Maintenance of potassium homeostasis depends on a balance between intake, transcellular potassium distribution and excretion (Figure 1) [14,15]. The daily intake of potassium on a normal western diet is approximately 80–100 mEq/day, most of which is absorbed in the small intestine. Total extracellular potassium content is only about 60 mEq, which can be consumed in a single large or potassium rich meal. If not buffered, this could lead to a dramatic, potentially life-threatening increase in plasma potassium concentration [16,17]. These acute increases in potassium intake are rapidly buffered by cellular uptake under the control of hormones such as insulin, primarily into liver and muscle to keep serum K^+ concentration stable [16]. Ultimately, the intake of potassium must be balanced by its excretion (Figure 1). If kidney function is normal, the kidney excretes 90–95% of potassium intake while the colon excretes most of the remaining 5–10%.

Acutely, plasma potassium may increase due to massive cell injury (such as the case in rhabdomyolysis), genetic defects in potassium channel proteins or changes in potassium distribution across cell membranes caused by changes in pH, cell tonicity, catecholamines or plasma insulin [15]. However, chronic hyperkalemia is usually a consequence of defective renal potassium handling [9,18]. Renal potassium excretion is determined by distal potassium secretion and the GFR [15,19]. Distal potassium secretion is dependent on the hormone aldosterone, the distal tubular flow rate, and delivery of sodium, bicarbonate and chloride to the distal nephron [20]. Renal dysfunction, alterations in distal water, sodium and anion delivery, genetic defects in renal potassium handling and disorders of the RAAS are all factors which can affect renal potassium excretion and increase plasma potassium concentration.

In the absence of diarrhea or laxative use, fecal potassium excretion is typically low (Figure 1). Most orally ingested potassium is absorbed in the small intestine resulting in a luminal K^+ concentration of about 10 mEq/l, much lower than luminal Na^+ concentration (140 mEq/l) [21]. Due to the low fecal water content, the amount of K^+ excreted in the feces is low. Under normal conditions fecal potassium excretion is 2–20 mEq per day [22]. However, the liquid content of stool is only about 100 ml per day resulting in an elevated colonic K^+ concentration. In fact, the luminal K^+ concentration in the colon is typically 75 mEq/l, where it exceeds luminal sodium (32 mEq/l), calcium or magnesium concentrations, making it the optimal site of action for orally administered K^+ exchange resins [23]. In the setting of hyperkalemia and hyperaldosteronism, enterocytes in the distal colon undergo an adaptive response leading to increased fecal K^+ concentration and excretion (Figure 1) [22]. Colonic potassium excretion increases with severe kidney failure and can reach 20–30 mEq/day. However, this is still not sufficient to maintain potassium balance on a normal diet [22,24].

Hyperkalemia & mortality

Hyperkalemia, even after correcting for other comorbidities, is an independent risk factor for hospitalization, cardiovascular mortality and all-cause mortality [25–28]. Interestingly, in the study by McMahon *et al.*, the association between hyperkalemia and mortality was no longer significant if the plasma potassium decreased by ≥1 mEq/l within 48 h of admission to the critical care unit [27].

Hyperkalemia can have lethal effects on the heart by causing arrhythmias and asystole that lead to sudden death [29,30]. The ratio of potassium across cell membranes is the major determinant of resting membrane potential [14]. Efflux of potassium, the major intracellular cation, down its concentration gradient from inside to outside the cell generates a negative intracellular transmembrane potential gradient. The ratio of potassium concentration across the cell membrane at equilibrium establishes the magnitude of the resting membrane potential that sets the baseline activity of all other voltage-sensitive cellular processes. Extracel-

lular potassium concentration is thus a critical determinant of the resting cell membrane potential and must be maintained within tight limits between 3.5 and 5 mEq/l. Disorders of potassium homeostasis that alter extracellular potassium concentration will affect voltage-dependent physiological processes in many tissues, but its effects on the heart, including cardiac conduction and excitability resulting in cardiac arrhythmias, asystole and death are most feared [31,32].

Electrocardiographic manifestations of hyperkalemia may include peaked T-waves, first-degree atrioventricular block, diminished P-wave amplitude and sinus arrest, while higher levels of hyperkalemia (particularly over 9 mEq/l) may be associated with bundle branch block, intraventricular conduction defect, ventricular tachycardia, fibrillation and asystole [30,32]. However, the correlation between electrocardiogram (EKG) changes and serum potassium is poor and 50% of people with plasma potassium above 6.5 mEq/l may lack any EKG changes [33].

Hyperkalemia & renin–angiotensin–aldosterone system blockade

Drugs that impair potassium excretion or transcellular distribution are a common risk factor for hyperkalemia, particularly in patients with underlying kidney disease, diabetes or heart failure [34]. Drugs have been reported to be a factor in 61% of cases of life-threatening hyperkalemia (K^+ >6.5 mEq/l) [35]. RAAS blockers, including mineralocorticoid receptor antagonists and potassium supplements were the most common drugs associated with severe hyperkalemia [36].

RAAS blockade is recommended to slow the progression of diabetic [37–39] and nondiabetic proteinuric kidney disease [40–42], prolong survival and reduce rehospitalization in patients with systolic heart failure and reduce mortality after myocardial infarction associated with left ventricular dysfunction [43]. These cardioprotective effects are augmented with higher dosing of RAAS blockers [44]. However these are also the groups at increased risk for developing hyperkalemia [19,44–45]. RAAS blockade is reportedly underutilized or underdosed in the recommended populations [46–48]. Hyperkalemia is one factor (though not necessarily the most common factor [49]) limiting use of RAAS blockade [45]. Initiation of RAAS blockade with either an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) has been reported to raise serum potassium by 0.21 ± 0.02 mEq/l when measured within 54.7 ± 43 days after starting therapy in an unselected ambulatory population [45,50]. However, the rise in serum potassium was dependent on renal function, with hyperkalemia (K^+≥5.5 mEq/l) developing in only 1.1% of patients with CKD stage 2, 3.1% of patients with CKD stage 3 and 13.7% of patients with CKD stage 4 [50]. Hyperkalemia of any degree has been reported to occur at a rate of 10% within a year of initiating RAAS blockade and in approximately 1% of diabetic patients this is severe (K^+>6 mEq/l) [19,45,51]. Hyperkalemia of any degree has also been reported in 10% of hospitalized patients with 10–39% of those being attributed to RAAS blockade [2,52–54]. The association between RAAS blockade and hyperkalemia has been reported to be higher in instances of life-threatening hyperkalemia [35].

Mineralocorticoid receptor antagonists (MRAs) when added to recommended therapy (including an ACE inhibitor or ARB and beta blocker) improved survival and reduced the hospitalization rate for patients with chronic systolic heart failure [55,56]. MRAs also lower blood pressure in patients with apparent treatment-resistant hypertension and lower proteinuria in patients with proteinuric kidney disease on RAAS blockade [57,58]. While the incidence of hyperkalemia was low in the RALES trial, after publication of the RALES trial the rate of prescriptions for spironolactone spiked by a factor of five, along with a threefold increase in the rate of hyperkalemia-associated hospital admissions and in-hospital mortality [59]. The incidence of hyperkalemia in patients with heart failure on MRA has been reported to be up to 12% [56,60]. Combined treatment with MRA and other RAAS inhibitors is frequently seen in cases of hospitalizations for severe life-threatening hyperkalemia [36]. Close monitoring is important to prevent such severe hyperkalemia. Observational studies have shown that the time period from initiation of one or more of such drugs and the onset of hyperkalemia is approximately 1 week [61]. However, many patients lack close follow-up of their serum potassium levels, placing them at risk of developing hyperkalemia that goes unnoticed [62]. When used properly, the side effects of hyperkalemia and acute renal failure did not eliminate the survival advantage of using MRA for heart failure [44,63–64].

Management of hyperkalemia

Acute management

Acute hyperkalemia is treated in the hospital setting with medications that lead to stabilization of cardiac conduction abnormalities such as intravenous calcium, and pharmacological agents that lead to the temporary K^+ shifting from extracellular into intracellular compartments, such as nebulized β2-adrenergic agonists, intravenous sodium bicarbonate and insulin [65,66]. These drugs are impractical to use in the outpatient setting and do not cause elimination of excess K^+ from the body [67,68]. Removal of excess K^+ from the body

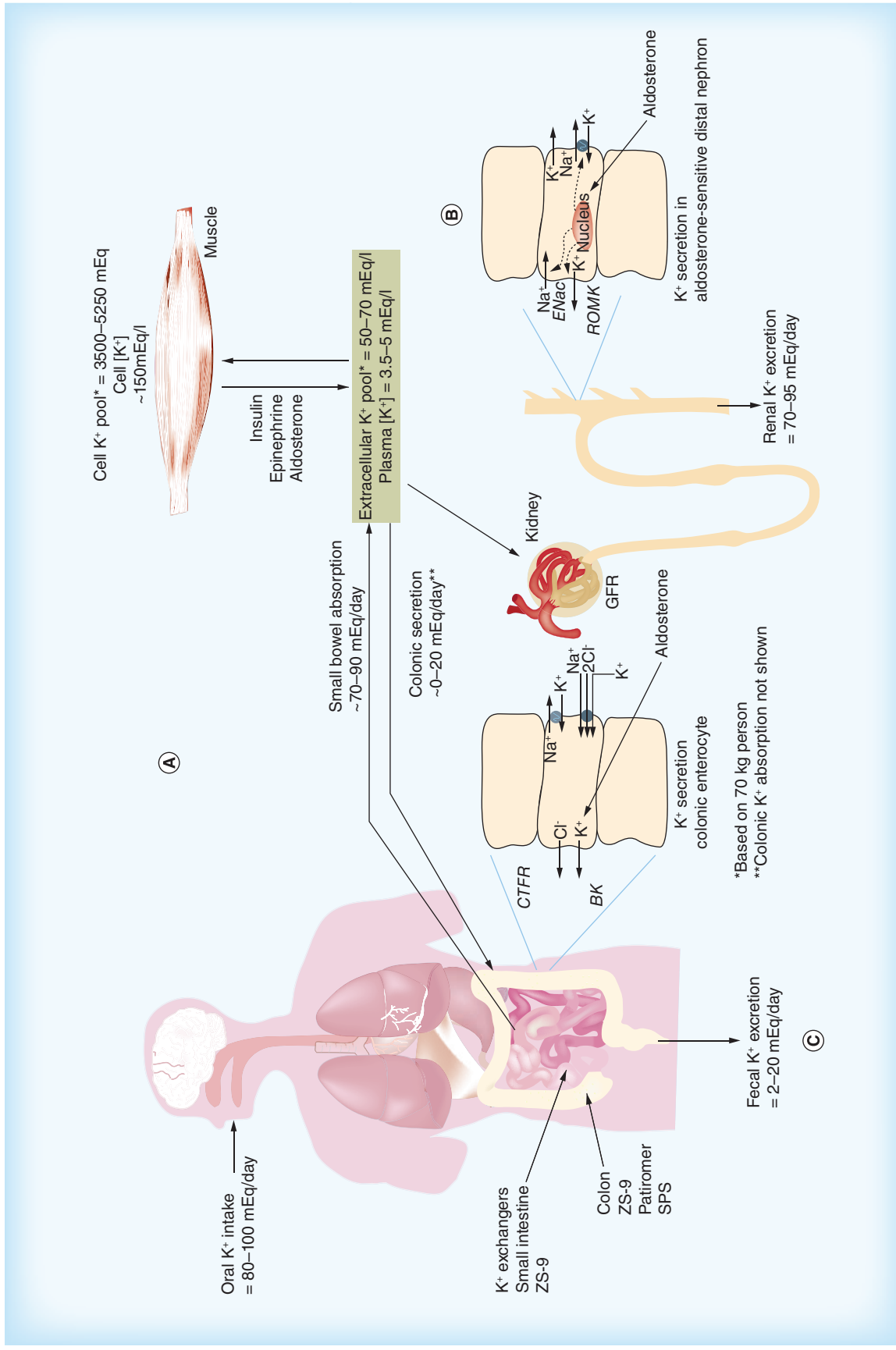
Cell K+ pool* = 3500–5250 mEq
Cell [K+] ~150mEq/l
Muscle
Insulin
Epinephrine
Aldosterone
Extracellular K+ pool* = 50–70 mEq/l
Plasma [K+] = 3.5–5 mEq/l
Small bowel absorption ~70–90 mEq/day
Colonic secretion ~0–20 mEq/day**
Kidney
GFR
Aldosterone
Renal K+ excretion = 70–95 mEq/day
Oral K+ intake = 80–100 mEq/day
K+ exchangers Small intestine ZS-9
Colon ZS-9 Patiromer SPS
Fecal K+ excretion = 2–20 mEq/day
CTFR
BK
K+ secretion colonic enterocyte
Na+
ENac
ROMK
Nucleus
K+ secretion in aldosterone-sensitive distal nephron
*Based on 70 kg person
**Colonic K+ absorption not shown
A
B
C

Figure 1. Mechanism of potassium handling by the kidney and gut after ingestion of a K^+ rich diet and site of action of the novel K^+ exchangers ZS-9 and patiromer (see facing page). **(A)** Total body K^+ is 50–75 mEq/kg body weight or 3500–5250 mEq in a 70 kg person. About 98% is in the intracellular K^+ pool and 2% (~50–70 mEq) is extracellular. The intracellular K^+ concentration is ~150 mEq/l. Extracellular K^+ concentration (plasma K^+) is tightly controlled between 3.5 and 5 mEq/l. The average daily oral intake of K^+ is ~80–100 mEq. Approximately 70–90 mEq of this is absorbed in the small intestine. In a patient with normal renal function, the kidney maintains K^+ homeostasis by excreting 90–95% of total daily K^+ intake (~70–95 mEq/day). Since renal potassium excretion takes several hours, rapid increases in extracellular K^+ such as after a meal are initially buffered by transcellular shifts into the liver and skeletal muscle. This process, referred to as internal potassium balance, is regulated by insulin, aldosterone and catecholamines such as epinephrine. **(B)** K^+ secretion in ASDN: the kidney is responsible for the majority of K^+ excretion (70–95 mEq excreted daily). Renal K^+ excretion is determined by K^+ secretion in the ASDN and the GFR. The major determinants of K^+ secretion in the ASDN are the distal tubular delivery of Na+, water and nonresorbable anions Cl- and HCO3-, and aldosterone. Aldosterone promotes K^+ secretion by stimulating the activity of the Na+-K+-ATPase pump, enhancing K^+ secretion through the apical membrane ROMK channel and stimulating Na^+ reabsorption through the apical ENaC. Na^+ absorption increases lumen electronegativity and enhances K^+ secretion through ROMK. If renal K^+ handling is decreased, hyperkalemia ensues and fecal K^+ excretion is increased via adaptation of colonic enterocytes (see below). **(C)** K^+ secretion in distal colonic enterocyte: the remaining 5–10% of K^+ intake is excreted in the colon (accounting for 2–20 mEq of total daily K^+ ingested). Normally the proximal colon is the site of action of the majority of net K^+ secretion (although the exact mechanism is still unknown) while net K^+ absorption (not shown) occurs in the distal colon. Colonic adaptation to hyperkalemia leading to increased potassium secretion occurs in the distal colon and involves the aldosterone-sensitive BK channel located in the apical membrane of the distal colonic enterocyte (Figure). K^+ entry occurs via Na-K ATPase and the basolaterally localized NKCC1. Chloride which enters via NKCCl exits via the apical CTFR chloride (Cl^-) channel. Potassium exit via the basolateral K^+ channel leads to hyperpolarization of this membrane driving Cl- secretion through the CTFR channel. During renal impairment fecal K^+ excretion is upregulated and may reach 20–30 mEq/day. Orally administered K^+ exchange resins such as SPS and the newer agents patiromer and ZS-9 act in the colon to increase fecal K^+ excretion. ZS-9 is thought to also bind K^+ in the upper GI tract.
ASDN: Aldosterone-sensitive distal nephron; CTFR: Cystic fibrosis transmembrane conductance regulator; ENaC: Epithelial sodium channel; GFR: Glomerular filtration rate; SPS: Sodium polystyrene sulfonate.

necessitates the use of diuretics, exchange resins or even performing dialysis in extreme cases of hyperkalemia.

Chronic management

The current management strategies used to treat chronic hyperkalemia include dietary restriction of K^+ intake, discontinuation of medications that impair renal K^+ excretion (such as nonsteroidal anti-inflammatory drugs or RAAS inhibitors), treating concurrent acidosis with oral sodium bicarbonate, and promoting K^+ excretion either by increasing sodium and water delivery to the distal nephron (via the use of loop diuretics), administration of exogenous mineralocorticoid (i.e., fludrocortisone) or via excretion of excess K^+ through the gut with the use of the oral sodium-potassium exchange resin sodium polystyrene sulfonate (SPS) [14–15,19,69]. However, current treatments are far from optimal.

Dietary K^+ restriction

High dietary K^+ is associated with increased mortality risk in end stage renal disease patients [70]. However, restricting K^+ in the diet of hyperkalemic patients usually results in dietary nonadherence, inefficient control of total body K^+ excess and limits healthy food choices associated with beneficial cardiovascular and renal outcomes. For instance, higher dietary potassium intake is associated with improvement in metabolic acidosis, slowing of progression of CKD, decreased risk of stroke in the general population and decreased blood pressure in hypertensive patients [71,72].

Diuretics

Diuretics increase distal sodium delivery and are a mainstay in the treatment of hyperkalemia associated with total body sodium overload [19]. However, diuretics may be associated with complications that limit their use including hypotension, a decrease in glomerular filtration rate, loss of magnesium and calcium, and metabolic alkalosis [73]. Moreover, diuretics may be counterproductive for cardiovascular and renal outcomes by stimulating RAAS activity [74]. Importantly, adequate sodium and water intake and renal perfusion are needed for diuretics to remain effective at increasing renal potassium excretion [20]. Diuretics may be ineffective in treating hyperkalemia in patients with severe renal failure or severe intravascular volume depletion associated with distributive edema.

Mineralocorticoid agonists

Treatment with exogenous mineralocorticoids can lower serum potassium [75]. However, this often occurs at the expense of hypertension and volume overload. Moreover, many of the conditions associated with hyperkalemia are associated with RAAS activation and treatment with additional mineralocorticoids may be counterproductive for optimal cardiovascular and renal outcomes. In practice, exogenous mineralocorti-

coid treatment is rarely used for treatment of chronic hyperkalemia.

Dialysis

Dialysis is effective at removing potassium both acutely and chronically in patients with a severely reduced GFR. However, dialysis can cause rapid and intermittent shifts in serum potassium that may provoke cardiac arrhythmias [76] and is not an optimal approach to treat hyperkalemia for patients who do not have severe renal failure.

Oral cation exchangers

The organic polymer polystyrene sulfonate is the only currently available oral cation exchanger therapy for hyperkalemia [77,78]. It is an insoluble powder available in either a sodium (e.g., Kayexalate) or calcium (e.g., Calcium Resonium) form, but the latter is not available in the USA. It works by binding K^+ in the colon in exchange for its counter ion thereby increasing fecal K^+ loss [79]. Each gram of SPS contains 4 mEq of Na^+ and can bind approximately 1–2 mEq of K^+ *in vitro* [79]. The amount of K^+ bound by SPS depends on the fecal concentration of Na^+ and K^+, with the most favorable conditions (low Na^+ and high K^+ concentration) occurring in the colon [80]. Clinically, fecal K^+ excretion is reported to be 10 mEq per 30 g of resin [78]. SPS is relatively nonselective for K^+ binding such that other cations, such as ammonium or calcium, can compete with K^+ for binding to the resin [81].

SPS was approved by the US FDA in 1958 when it was the only available therapy for life-threatening hyperkalemia [78,81]. SPS has never undergone rigorous testing in a double-blind placebo-controlled trial, and there are questions regarding its efficacy and safety [77,82]. While the effect of SPS is not rapid enough for acute life-threatening hyperkalemia, clinical experience and published studies suggest it can lower serum potassium over the course of a day and maintain acceptable potassium levels in patients with chronic hyperkalemia [78,83]. In 1961, sorbitol, an osmotic cathartic, was mixed with SPS to hasten delivery of the resin to the active site in the colon and to prevent SPS-induced fecal impaction [84]. This led to controversy as to how much sorbitol alone contributes to the fecal excretion of potassium [78,79]. However, studies have suggested that SPS without sorbitol can be effective to treat chronic hyperkalemia [83].

Though widely prescribed for hyperkalemia, the use of SPS is limited due to side effects. It is unpalatable to many patients, causes constipation, nausea and other gastrointestinal effects, can lead to sodium retention associated with edema and hypertension, binds other drugs and may be associated with multiple electrolyte disorders including hypernatremia, hypokalemia, metabolic alkalosis and hypomagnesemia [83,85–86]. Most notably, its gastrointestinal toxicity, particularly reports of fatal bowel necrosis, led the FDA in 2009 to advise against the concomitant use of SPS mixed with hypertonic sorbitol [77–78,87–91]. This serious complication however, appears to be rare. A recent retrospective cohort study of over 123,000 inpatients found SPS to have been prescribed in 2194 patients. The rate of colonic necrosis was 0.14% (95% CI: 0.03–0.40%) in those who received SPS within the preceding 30 days and 0.07% (95% CI: 0.05–0.08%) in those who had not, with a relative risk of 2.10 that was not statistically significant (95% CI: 0.68–6.48; p = 0.2) [92]. Hence, SPS-induced colonic necrosis is an apparently rare but potentially catastrophic side effect of treatment with SPS. Clearly, a palatable, rapid and safe therapy proven to be effective for the acute and chronic treatment of hyperkalemia is lacking, and there is a strong necessity for new therapeutic options.

Novel selective cation exchangers

Recently, two novel cation exchangers, patiromer (previously called RLY5016) and zirconium cyclosilicate (ZS-9) have been under investigation for the treatment of hyperkalemia, and have shown promise in published Phase III randomized controlled trials (Tables 1 & 2).

ZS-9

ZS-9 is an insoluble crystalline lattice structure that selectively traps potassium in exchange for sodium and hydrogen (Table 1). It is currently formulated as a tasteless, odorless powder or tablet that does not require the additional use of a cathartic and does not need refrigeration or special handling. In clinical trials it has been administered in 240 ml of water with a meal [93]. *In vitro* studies have shown that the potassium binding capacity of ZS-9 is nine-times higher by weight and is 125-times more selective for K^+ over Ca^{++} or Mg^{++} than that of SPS [95]. Its high selectivity may allow ZS-9 to work faster by binding K^+ in the small intestine (where K^+ concentration is lower) as well as the colon. ZS-9 is prepared with a balance of both sodium (Na^+) and hydronium (H^+) counter ions. It is hypothesized that the hydronium sites are actually responsible for the majority of potassium binding, thus exchanging H^+ for K^+, whereas most Na^+ remains bound to ZS-9 in a less exchangeable site. However, the exact mechanism of how this exchange with K^+ occurs and the exchange ratio with other counter ions remains unconfirmed [95]. By analogy with SPS, drug–drug interactions may include interference with absorption of calcium-, magnesium-, aluminum- or lithium-containing products and possibly other agents such as levothyroxine and digoxin.

Table 1. Comparison of chemical and physical properties of cation exchangers.

Cation exchanger	Chemical properties	Sorbitol content	Site of action	Counter-ion bound	Selectivity for K^+ compared with divalent cations (in fold)	K^+ exchange capacity (mEq K^+/g exchanger)	Dose
Sodium polystyrene sulfate (SPS, Kayexelate®)	Organic polymer resin	20 g in each 15 g SPS	Colon	Sodium	0.2–0.3	0.3	Daily q.i.d.
Zirconium cyclosilicate (ZS-9)	Inorganic crystal lattice structure	None	Small intestine and colon	Sodium and hydrogen	25†	2.7	Daily
Patiromer (RLY5016)	Organic polymer resin and sorbitol complex	2 g in each 4.2 g of patiromer	Colon	Calcium	Unknown	2× SPS	b.i.d.

†ZS-9 selectivity for K^+ over calcium and magnesium is 125-times greater than sodium polystyrene sulfonate.
b.i.d.: Two-times a day; SPS: Sodium polystyrene sulfonate; q.i.d.: Four-times a day; ZS-9: Zirconium cyclosilicate.

The efficacy of ZS-9 for the treatment of hyperkalemia was recently tested in the HARMONIZE trial [93]. This was a Phase III multicenter randomized double-blind placebo-controlled trial examining the short-term effect of ZS-9 on potassium lowering among outpatients with hyperkalemia defined as a serum K^+ of at least 5.1 mEq/l. The trial enrolled 258 patients who were initially given 10 g of ZS-9 in 240 ml of water t.i.d. for 48 h (open label phase). Patients who achieved normokalemia (serum K^+ 3.5–5 mEq /l) were then enrolled in the maintenance phase where they were randomized in a 4:4:4:7 allocation to receive either 5, 10 or 15g of ZS-9, or placebo daily for 28 days. The primary outcome was the mean serum K^+ level in each group compared with placebo during day 8–29 of the study. The secondary outcomes were the safety of the drug and the efficacy of the three different daily doses of ZS-9 for 28 days in achieving and maintaining normokalemia. The mean age of the patients enrolled was 64 years and mean baseline serum K^+ was 5.6 mEq/l. These patients had significant co-morbidities for the development of hyperkalemia: 66% had CKD, 36% had congestive heart failure, 66% were diabetic and 70% were taking RAAS inhibitors. Key exclusion criteria are listed in Table 2. The results of the open-label phase demonstrated that the mean serum K^+ significantly declined from baseline by 0.2 mEq/l (95% CI: 0.2–0.3 mEq/l) in 1 h, 0.4 mEq/l (95% CI: 0.4–0.5 mEq/l) in 2 h, 0.5 mEq/l (95% CI: 0.5–0.6 mEq/l) in 4 h, 0.7 mEq/l (95% CI: 0.6–0.7 mEq/l) in 24 h and 1.1 mEq/l (95% CI: 1.0–1.1 mEq/l) in 48 h. About 80 and 98% of patients achieved normokalemia in 24 and 48 h, respectively. In the randomized treatment phase, ZS-9 resulted in statistically significant lower potassium levels (4.8, 4.5 and 4.4 mEq/l in the 5, 10 and 15 g groups, respectively) compared with placebo (5.1 mEq/l). However, the absolute between-group differences in mean serum K^+ were modest (-0.3, -0.6, -0.7 mEq/l in 5, 10 and 15 g groups, respectively) compared with placebo.

The most significant adverse effects in the HARMONIZE study was edema and hypokalemia, both of which occurred more in the highest two ZS-9 dose groups. The authors suggest that edema was more frequent in the 15 g dosing group due to a higher percentage of patients with baseline heart failure, higher B-type natriuretic peptide (BNP) and lower estimated GFR compared with placebo. There were no changes in blood pressure, heart rate, body weight and no dose dependent increase in urinary sodium excretion between the groups. One speculation as to why edema occurred in a dose-dependent manner in this study is that at higher ZS-9 doses, a small amount of bound sodium may be absorbed and retained in salt-sensitive patients [96]. In addition, ZS-9 was provided with 240 ml of water with each dose and this could contribute to volume overload in patients who are on a fluid restricted diet. Hypokalemia developed in 10% of ZS-9 patients taking the 10 g dose and 11% taking the 15 g dose. All cases were mild (3–3.4 mEq/l) and without clinically significant adverse events. One patient taking the 10 g dose of ZS-9 died on day 18 of treatment. However, this death was thought to be unrelated to the study drug. The authors concluded that ZS-9 was safe and very well tolerated and could potentially be used for the treatment of outpatients with mild hyperkalemia in the acute setting.

In a separate, short-term, double-blind, Phase III trial, Packham and colleagues randomized 753 patients with hyperkalemia (serum K^+ between 5 and 6.4 mEq/l) to receive 1.25, 2.5, 5 or 10 g of ZS-9 or placebo t.i.d. for 48 h [94]. Patients who had normalized their serum K^+

Table 2. Summary of clinical trials on the use of cation exchangers for hyperkalemia.

Agent	Study	Study design	Patient population	Exclusion criteria	Serum K+ level (mEq/l; % pts)	Number of subjects (n)	Oral dose	Duration of therapy	Ref.
ZS-9	HARMONIZE	Open-label initial treatment phase	66% CKD, 36% CHF, 66% DM, 70% on RAAS blocker	Pseudohyperkalemia, need for dialysis, pregnancy, life expectancy <3 months, diabetic ketoacidosis, cardiac arrhythmias requiring prompt treatment, active use of SPS or lactulose, xifaxan, phosphate binders, known hypersensitivity to ZS-9, HIV positive, participation in any other ZS-9 trial within 30 days of entry into the trial, any condition-limiting adherence or confers unwarranted medical risk	≥5.1, <5.5 (46%), 5.5–<6 (39%), ≥6 (15%)	258	10 g t.i.d.	48 h	[93]
		Phase III randomized double-blind placebo-controlled (maintenance phase)	Same as above	Same as above		237 of the open-label subjects who achieved normokalemia	5 g, 10 g, 15 g or placebo daily	28 days	[93]
	Sodium Zirconium Cyclosilicate in Hyperkalemia	Initial treatment phase	60% CKD, 40% CHF, 60% DM, 63–70% on RAAS blocker	Similar to HARMONIZE trial	5–5.3 (60%) 5.4–5.5 (14%) 5.6–6.5 (26%)	753	1.25, 2.5, 5, 10 g or placebo t.i.d.	48 h	[94]
		Phase III randomized double-blind placebo-controlled (maintenance phase)	Same as above	Same as above	Normal K after initial phase	542 of the treatment phase subjects who achieved normokalemia	Same daily dose of ZS-9 or matched placebo dose	14 days (day 3–14)	[99]

CHF: Congestive heart failure; CKD: Chronic kidney disease; DM: Diabetes mellitus; GI: Gastrointestinal; RAAS: Renin–angiotensin–aldosterone system; SPS: Sodium polystyrene sulfonate; TIA: Transient ischemic attack; t.i.d.: Three-times a daily; ZS-9: Zirconium cyclosilicate.

Table 2. Summary of clinical trials on the use of cation exchangers for hyperkalemia (cont.).

Agent	Study	Study design	Patient population	Exclusion criteria	Serum K+ level (mEq/l; % pts)	Number of subjects (n)	Oral dose	Duration of therapy	Ref.
Patiromer	OPAL-HK	Initial treatment phase	100% CKD, 45% CHF, 60% DM, 30% MI, 100% on RAAS blocker	EKG changes related to elevated potassium or need for urgent intervention, severe GI disorders, unstable cardiac arrhythmias, recent cardiac surgery or transplantation, acute coronary syndrome, or TIA within 2 months, acute heart failure treatment within the past 3 months or NYHA class IV, acute kidney injury within 3 months, SBP >180 mmHg or <110 mmHg, DBP >110 mmHg or <60 mmHg, DM1 or emergency treatment of DM2, BMI ≥40 kg/m^2, serum magnesium <1.4 mg/dl, numerous medications, numerous additional exclusions (see protocol)	5.1 to <6.5 Mean baseline = 5.6 ± 0.5	243	4.2 or 8.4 g b.i.d.	4 weeks	[99]
		Phase III single-blind placebo-controlled withdrawal phase	Same as above	Same as above plus: baseline serum K <5.5 mEq/l, serum K <3.8 or ≥5.1 mEq/l at end of 4 week initial phase	Normal K after initial phase	107 of the initial treatment phase subjects who achieved normokalemia	Same total daily dose of patiromer or matched placebo dose	8 weeks	

CHF: Congestive heart failure; CKD: Chronic kidney disease; DM: Diabetes mellitus; GI: Gastrointestinal; RAAS: Renin–angiotensin–aldosterone system; SPS: Sodium polystyrene sulfonate; TIA: Transient ischemic attack; t.i.d.: Three-times a daily; ZS-9: Zirconium cyclosilicate.

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Agent	Study	Study design	Patient population	Exclusion criteria	Serum K+ level (mEq/l; % pts)	Number of subjects (n)	Oral dose	Duration of therapy	Ref.
	PEARL-HF	Phase III randomized double-blind placebo-controlled trial	100% CHF on spironolactone, 41% history of discontinuation of RAASi due to hyperkalemia, 50% CKD	Severe GI disorders, Major GI surgery, bowel obstruction or swallowing disorders, significant primary valvular disease, known obstructive or restrictive cadiomyopathy, uncontrolled or unstable arrhythmia, episode of unstable angina within 3 months prior to baseline, acute coronary syndrome, transient ischemic attack, QTc ≥.500 ms, recent or anticipated cardiac surgery or intervention, kidney transplantation or need for transplantation, dialysis or anticipated need for dialysis during the study, Sustained SBP >170 or <90 mmHg, elevated liver enzymes, any condition that has the potential to interfere with study compliance or jeopardize the safety of the patient	4.3–5.1 at screening	104	30 g/day patiromer or placebo	4 weeks	[103]

CHF: Congestive heart failure; CKD: Chronic kidney disease; DM: Diabetes mellitus; GI: Gastrointestinal; RAAS: Renin–angiotensin–aldosterone system; SPS: Sodium polystyrene sulfonate; TIA: Transient ischemic attack; t.i.d.: Three-times a daily; ZS-9: Zirconium cyclosilicate.

Table 2. Summary of clinical trials on the use of cation exchangers for hyperkalemia (cont.).

Agent	Study	Study design	Patient population	Exclusion criteria	Serum K+ level (mEq/l; % pts)	Number of subjects (n)	Oral dose	Duration of therapy	Ref.
	AMETHYST-DN	Ongoing Phase II randomized open-label dose ranging study	CKD diabetic nephropathy RAAS blocker with or without spironolactone	Type 1 diabetes mellitus, hemoglobin A1c > 12%, emergency treatment for T2DM within the last 3 months, diabetic gastroparesis, nondiabetic chronic kidney disease, history of bowel obstruction, swallowing disorders, severe GI disorders or major GI, NYHA class III or IV heart failure, BMI ≥ 40 kg/m^2, unstable angina, acute coronary syndrome, cardiac arrest or clinically significant ventricular arrhythmias, TIA or stroke, use of any intravenous cardiac medication within 2 months, prior kidney transplant, or anticipated need for transplant during study participation, active cancer or history of cancer in the past 2 years except for nonmelanocytic skin cancer, history of alcoholism or drug/chemical abuse within 1 year, abnormal liver enzymes, treatment with loop and thiazide diuretics or other antihypertensive medications for <28 days, use of polymer-based drugs, lithium, potassium sparing drugs, use of any investigational product within 30 days, inability to comply with the protocol, any medical condition that decreases study compliance or jeopardizes patient safety	>5 to <6 at randomization Mean baseline = 5.3 ± 0.4	306	4.2, 8.4 or 12.6 g b.i.d. depending on level of hyperkalemia (mild if 5 to <5.5 mEq/l, moderate if 5.5 to <6 mEq/l)	52 weeks	[104]

CHF: Congestive heart failure; CKD: Chronic kidney disease; DM: Diabetes mellitus; GI: Gastrointestinal; RAAS: Renin–angiotensin–aldosterone system; SPS: Sodium polystyrene sulfonate; TIA: Transient ischemic attack; t.i.d.: Three-times a daily; ZS-9: Zirconium cyclosilicate.

to 3.5–4.9 mEq/l on ZS-9 during the initial 48-h treatment phase were then randomized to receive either the same dose of ZS-9 or a matched placebo daily on days 3–14 during a follow-up maintenance phase. Patients who were assigned to placebo in the initial treatment phase were randomly assigned to receive either 1.25 or 2.5 g of ZS-9 during the maintenance phase. Dose adjustments to maintain serum K^+ within the normal range were not allowed in this study. The primary end point was the exponential rate of change in mean serum K^+ level at the end of the initial treatment phase (48 h). There were no significant differences in the baseline characteristics of the patients. About 60% of patients had CKD, 40% had heart failure, 60% had diabetes mellitus and roughly 63–70% of patients were taking a RAAS inhibitor. At 48 h, the mean serum K^+ level had decreased from 5.3 mEq/l at baseline to 4.9, 4.8 and 4.6 mEq/l in the 2.5, 5 and 10 g ZS-9 groups, respectively compared with 5.1 mEq/l in the placebo and 1.25 g groups. The mean reduction in serum K^+ from baseline at 48 h was 0.5, 0.5 and 0.7 mEq/l for the 2.5, 5 and 10 g groups, respectively, compared with a 0.3 mEq/l reduction in the placebo and 1.25 g groups. At 48 h, 99% of the 10 g group patients and 94% of the 5 g group patients achieved normokalemia that persisted throughout the maintenance phase (4.7 and 4.5 mEq/l, respectively for the 5 and 10 g groups, compared with serum K^+ levels of greater than 5mEq/l in the placebo group). Recurrence of hyperkalemia occurred when patients whose potassium was controlled on ZS-9 in the initial treatment phase were randomized to placebo in the maintenance phase or within 7 days after stopping the 10 mg dose of ZS-9 at the end of the maintenance phase (15 days).

Overall, ZS-9 was well tolerated [94]. The reduction in serum K^+ level after ZS-9 was greater in patients with higher baseline serum K^+ concentrations. The rate of occurrence of adverse events was similar in all groups and was not dose-dependent (12.9% for ZS-9 groups combined and 10.8% for the placebo group, respectively in the initial phase, and 25.1 and 24.5%, respectively in the maintenance phase). The most common adverse effect was diarrhea, which occurred at equal rates between the ZS-9- and placebo-treated patients (1.7% for ZS-9 vs 2.2% for placebo). There were two cases of mild hypokalemia (serum K^+ level <3–3.5 mEq/l) reported in the ZS-9 group that were transient and resolved without treatment. Edema was not reported to occur and weight and blood pressure did not change during treatment with ZS-9 [94]. As with the HARMONIZE trial, this was a short-term trial in patients with modestly elevated serum K^+.

In a recent letter to the editor, authors of both the ZS-9 trials combined their analyses of the short-term changes in serum K^+ (within the first 4 h) of receiving an initial 10 g dose of ZS-9 in a subpopulation of patients with severe hyperkalemia (defined as serum K^+ 6.1–7.2 mEq/l) [97]. At baseline, the mean serum K^+ was 6.3 mEq/l. After a single 10 g dose of ZS-9, mean serum K^+ declined by 0.4 mEq/l (95% CI: 0.2–0.5 mEq/l) at 1 h, 0.6 mEq/l (95% CI: 0.4–0.8 mEq/l) at 2 h and 0.7 mEq/l (95% CI: 0.6–0.9 mEq/l) at 4 h. The median time to a serum K^+ level <6 and 5.5 mEq/l was 1.07 and 4 h, respectively. No cases of hypokalemia or adverse side effects were reported during the first 48 h of ZS-9 therapy. Taken together, these results showed that ZS-9 was safe and efficacious in reducing serum K^+ levels in severe hyperkalemia (serum K^+ > 6 mEq/l) as early as 1 h after administration.

Uncertainties in the use of ZS-9 remain [96]. First, due to the short duration of the two trials, the long-term effects and tolerability of the drug are not known. Also, the long-term clinical implication of edema at higher doses of ZS-9 used in the HARMONIZE trial is unclear and if confirmed, could be a potential concern, especially in advanced CKD and heart failure patients. Will the 240 ml of water administered with each dose in the clinical trials be a problem for patients on a fluid restricted diet? Whether or not using ZS-9 will allow increased use and optimized dosing of RAAS blockers to improve cardiovascular and renal outcomes without increasing hospitalizations or mortality from hyperkalemia or hypokalemia is unknown. In addition, hospitalized patients, patients with severe hyperkalemia and patients with end-stage renal disease undergoing dialysis were excluded from these studies. Further studies will be needed to test the use of this drug in these high-risk populations. Also, the cost–benefit of this therapy compared with current management remains to be determined [98].

An additional uncertainty is the mechanism of the early reduction in serum potassium within 1–2 h after oral administration of ZS-9. The low pH in the stomach and low K^+ concentration in the small intestine limits the capacity of most oral cation exchangers to bind K^+ before reaching the colon, which generally takes 6–8 h. However, ZS-9 has a higher affinity for K^+ than the other available oral cation exchangers [95]. In addition, given the small pool of extracellular potassium (e.g., 84 mEq in a 70 kg person with a serum potassium of 6.0 mEq/l) a reduction of 5.6 mEq could explain the observed drop of 0.4 mEq/l in serum K^+ within 1 h of administration if no transcellular release of K^+ from the intracellular compartment occurred. With a binding capacity of ZS-9 for K^+ of 2.6 mEq/g it would only require 22% of the total binding capacity of a 10 g dose of ZS-9 to achieve this level of K^+ reduction. Other explanations proposed for the acute

drop in serum K^+ include the administration of ZS-9 with meals that might increase insulin release and promote intracellular potassium uptake and binding of H^+ by ZS-9 in the stomach promoting systemic alkalosis that might promote intracellular uptake of potassium. This latter mechanism seems unlikely if the primary exchangeable cation in ZS-9 is the hydronium ion.

Patiromer

Patiromer is an oral, insoluble, nonabsorbable organic (poly-α-fluoroacrylic acid-based) polymer resin that binds potassium in exchange for calcium. It does not require coadministration with a laxative and is reportedly more palatable than SPS. Patiromer is a dry, odorless, tasteless powder that has a low viscosity, consisting of small (100 µm) uniform free-flowing beads that swell up minimally when suspended in small amounts of water (Table 1). In clinical trials it has been administered in 40 ml of water with a meal [99]. Published data on physiochemical properties of patiromer are sparse. Based on the Relypsa patent application, it has approximately twice the *in vitro* potassium-binding capacity of SPS (Kayexalate). Compared with ZS-9, it appears that patiromer has a lower affinity and less selectivity for K^+. It works primarily to bind K^+ in the colon where the K^+ concentration is higher, thus leading to increased fecal K^+ excretion. By analogy with SPS, drug–drug interactions may include interference with absorption of calcium-, magnesium-, aluminum- or lithium-containing products and possibly other agents such as levothyroxine and digoxin.

Patiromer in chronic kidney disease

The short-term safety and efficacy of patiromer in patients with hyperkalemia (defined as K^+ of 5.1–6.4 mEq/l) and CKD who were on a RAAS inhibitor was examined in a recent Phase III, single-blind, multicenter prospective trial (OPAL-HK) [99]. Exclusion criteria are listed in Table 2. The study had two phases: in the initial treatment phase, 243 patients received patiromer at a dose of 4.2 or 8.4 g b.i.d. for 4 weeks. The primary end point was the mean change in serum K^+ from baseline to week 4. The initial dose was titrated to achieve normokalemia defined as a serum K^+ of 3.8–5 mEq/l. There was a gradual decline in serum K^+ over 4 weeks. For all patients combined, there was a mean drop in serum K^+ of 0.44 ± 0.03 mEq/l after 3 days of patiromer. After 4 weeks, the mean decrease in serum potassium was 1.01 mEq/l for all patients. At the end of the initial phase, 76% of patients achieved normokalemia. In the following placebo-controlled withdrawal phase, 107 of these patients who achieved normokalemia on patiromer were randomized to receive either patiromer at the same dose as they had received during the initial treatment phase or a placebo for an additional 8 weeks. The median increase in serum K^+ over the first 4 weeks was 0.72 mEq/l for the placebo group, and zero for the patiromer group. The primary end point, the between-group difference in the median change in serum K^+ over the first 4 weeks was -0.72 mEq/l, favoring the patiromer group over placebo. Hyperkalemia recurrence (serum K^+ level ≥5.5 mEq/l) occurred in 60% of patients who were switched to placebo and only 15% of patients who continued on patiromer. Discontinuation of the RAAS inhibitor occurred in 56% of placebo patients and only 6% of patiromer group patients.

Serious adverse events including atrial fibrillation, endocarditis, Escherichia coli bacteremia, urinary tract infection, chronic renal failure and mesenteric vessel thrombosis were thought to be unrelated to the study drug. The most common adverse side effect was constipation, which occurred in 11% of patients in the initial treatment phase and 4% of patients taking patiromer in the randomized withdrawal phase. The incidence of hypokalemia, defined as a serum K^+ < 3.5 mEq/l, was 3% in the initial phase, and after randomization was 5% in the patiromer group and 2% in the placebo group during the withdrawal phase. Hypomagnesemia (defined as magnesium level < 1.4 mEq/l) occurred in 3% of patients in the initial phase, consistent with the lower selectivity of patiromer for potassium over divalent cations (Table 3). In summary, in hyperkalemic patients with CKD, patiromer was associated with a gradual reduction in elevated serum K^+ levels from baseline after 4 weeks. Normokalemia was maintained more effectively than placebo, and there was less discontinuation of RAAS blockers reported in the patiromer group.

The efficacy of patiromer in reducing serum potassium levels within the first 24–48 h was not reported in this study. However, in a recent preliminary study of 25 patients with CKD on at least one RAAS inhibitor and a serum potassium of 5.5 to 6.4 mEq/l, there was a drop of 0.75 mEq/l in serum K^+ within 48 h of treatment with patiromer after a total of four doses of 8.4 g/dose (twice a day dosing for 2 days), and about 40% of patients achieved normokalemia. Reduction in mean serum K^+ occurred 4 h after the first dose, with a significant reduction occurring 7 h after the first dose and throughout the 48-h study [100]. In a separate preliminary study, patiromer was reported to be effective in reducing K^+ levels in people with CKD stages 4 or 5 who tended to have more severe hyperkalemia [99].

Patiromer in heart failure

Patiromer has also been studied for the prevention of hyperkalemia in patients with heart failure [103]. This

Table 3. Outcomes and adverse events of clinical trials on the use of cation exchangers for hyperkalemia.

Agent	Study	Onset of action	Normokalemia achieved	Time to normalization of serum K+	Adverse events (%)†	Serious adverse events (%)‡	Ref.
ZS-9	HARMONIZE	1 h	80% by 24 h 98% by 48 h	4–24 h, median 2.2 h	Constipation (1.8 vs 7.1%) Edema (14.3 vs 2.4%) Hypokalemia (10.7 vs 0%)	None	[93]
ZS-9	Sodium Zirconium Cyclosilicate in Hyperkalemia	1 h	99% by 48 h	Normokalemia maintained during 12 days of maintenance therapy	Diarrhea (1.8 vs 2.2%) Hypokalemia in 1.8% (2.5 g) and 1.6% (10 g) vs 0%	1 placebo group patient with gastroenteritis	[94]
Patiromer	OPAL-HK	7 h	76% by 4 weeks	Mean 1 week	Constipation (4 vs 0%) Diarrhea (4 vs 0%) Hypokalemia (5 vs 2%) Hypomagnesemia (3% in initial phase)	None	[99]
Patiromer	PEARL-HF	1 day	98% by day 3	3 days	Hypokalemia (6 vs 0%) Hypomagnesemia (24 vs 2%) GI disturbance (flatulence, diarrhea, constipation, vomiting in 21 vs 0%)	None	[103]
Patiromer	AMETHYST-DN	Not reported	77–95% by weeks 12–52	48 h	Constipation (6%) Hypomagnesemia (4%)	Not reported	[104]

†Adverse events (%) of 15 g dose drug versus placebo.
‡Serious adverse events deemed to be related to the study drug.
ZS-9: Zirconium cyclosilicate.

randomized double-blind placebo-controlled 4-week trial evaluated the efficacy and safety of patiromer in 104 heart failure patients treated with spironolactone who had a prior history of either discontinuation of RAAS blockers or β-adrenergic blockers due to hyperkalemia, or had CKD stage 3 or 4. Patients were randomized to receive 30 g/day of oral patiromer or matched placebo. Spironolactone was given to both groups at 25 mg/day and increased to 50 mg/day if serum K^+ was less than or equal to 5.1 mEq/l. There was a statistically significant difference in serum K^+ noted between the two groups starting on day 3 of the trial. At 4 weeks, the serum K^+ levels decreased by 0.22 mEq/l in the patiromer group while the serum K^+ levels increased in the placebo group by 0.22 mEq/l, for a between-group difference of -0.45 mEq/l favoring patiromer over placebo. There was a lower incidence of hyperkalemia in the patiromer group (7%) compared with the placebo group (25%), and a greater percentage of patients in the patiromer group that were able to take the higher dose of spironolactone (50 mg/day) compared with placebo (91 vs 74%, respectively). However, hypokalemia occurred in 6% of the patients taking patiromer and none of the patients on placebo. Hypomagnesemia, defined as a serum magnesium level of <1.8 mg/dl, occurred with greater incidence in the patients on patiromer (24%) compared with only 2% in those on placebo [103]. Gastrointestinal side effects, mild-moderate in severity, were more frequent in the patiromer group (21%) compared with placebo (6%). The drug discontinuation rates were similar in both groups (6% patiromer and 7% placebo). Interestingly, in the subgroup of patients with CKD, the between-group difference in serum K^+ levels was -0.52 mEq/l and the incidence of hyperkalemia even lower in those randomized to patiromer (7 vs 39% with placebo), suggesting that the drug is effective in high-risk patients with renal dysfunction [101]. Long-term, randomized controlled trials will be needed to assess whether patiromer can increase the use of optimum doses of RAAS inhibitors and improve outcomes in patients with heart failure.

Patiromer in diabetic nephropathy

AMETHYST-DN was a multicenter, randomized open-label Phase II dose ranging study sponsored by Relypsa that evaluated the efficacy and safety of patiromer in the treatment of hyperkalemia in patients with hypertension and diabetic nephropathy receiving an ACE inhibitor and/or ARB, with or without spironolactone over 52 weeks [104]. A total of 306 patients with CKD and diabetic nephropathy who were all taking RAAS inhibitors were randomized into one of three patiromer dose groups (4.2, 8.4 or 12.6 g twice a day) if the baseline hyperkalemia was mild (serum K^+ >5.0 to 5.5 mEq/l) or one of three patiromer dose groups (8.4 g, 12.6 g, or 16.8 g twice a day) if hyperkalemia was moderate (K^+ >5.5 to <6.0 mEq/l). Patiromer doses were adjusted to maintain serum K^+ levels normal. There was a statistically significant reduction in serum K^+ as early as 48 h in both mild and moderate hyperkalemia groups, and this reduction was sustained throughout the entire 52-week study period. Hypomagnesemia (7.2%), constipation (6.3%) and hypokalemia (5.6%) were notable treatment-related side effects. Approximately 77–95% of patients with both mild and moderate hyperkalemia had serum K^+ levels maintained in the normal range (between 3.8 and 5 mEq/l) during the entire 44-week maintenance phase. Stopping patiromer after 52 weeks lead to a rapid rise in serum K^+. Interestingly, renal function was reported to have remained stable throughout the 52-week study period in this population of patients that would be expected to experience a decline in GFR. This may have important implications in patients that have not tolerated RAAS blockade due to adverse effects of hyperkalemia.

Further studies are needed to better establish the rapidity of the potassium-lowering effect of patiromer in treating acute hyperkalemia. The rate of lowering of serum potassium appears to be faster for ZS-9 compared with patiromer, which may be related to the ability of ZS-9 to bind potassium in the small and large intestine. However, a direct comparison in a randomized, blinded trial would be needed to establish whether there is a difference in the rate of potassium lowering between the different oral agents. Moreover, the optimal rate of lowering of potassium in acute hyperkalemia has not been established. Development of hypomagnesemia may be a concern with patiromer in selected patient populations (e.g., congestive heart failure), compared with ZS-9 and the effect of this remains to be determined. As for ZS-9, the long-term tolerability of patiromer is not known and further study is needed to determine if long-term use of patiromer can maintain optimum RAAS blockade and improve morbidity and mortality outcomes in this patient population. Hospitalized patients, patients with severe hyperkalemia (serum K^+ >6.5 mEq/l) and hemodialysis patients were excluded from these studies. Therefore, the effects of patiromer on these patient populations that are at significant risk of developing fatal hyperkalemia will need to be considered in future studies [102]. The cost–benefit ratio of using patiromer over standard therapy was not addressed in any study. Neither ZS-9 nor patiromer are currently FDA approved for the treatment of hyperkalemia.

Conclusion

Hyperkalemia is a common clinical problem, particularly in patients with impaired renal potassium excretion including those with CKD, diabetic nephropathy, congestive heart failure and treated with RAAS inhibitors. It is important to diagnose and treat hyperkalemia to prevent cardiac arrhythmias and possibly death. Currently available therapies, particularly for management of chronic hyperkalemia are suboptimal and limit the delivery of effective RAAS blockade to high-risk target populations such as those with proteinuric kidney disease and heart failure. Recently developed novel oral, nonabsorbed potassium exchange therapies including ZS-9 and patiromer have shown great promise in clinical trials in treating and controlling hyperkalemia. Many questions remain regarding their use, but none more pressing than whether these new agents will allow safe delivery of optimized doses of RAAS blockade to the target populations and whether this will further improve outcomes in these high-risk patients.

Future perspective

We anticipate that if approved by the FDA for use, the new oral cation exchangers will allow increased utilization of RAAS blockade in patients with hyperkalemia and may improve dietary choices, quality of life and possibly morbidity and mortality in these high-risk populations compared with current therapy. The acute therapy of hyperkalemia in conscious patients with a functional GI tract that lack urgent (i.e., EKG) indications for potassium reduction will change, most likely utilizing oral ZS-9 to rapidly lower serum potassium instead of insulin plus glucose. Acute dialysis for the sole indication of hyperkalemia will likely be eliminated. There will still be a need to use intravenous calcium along with insulin plus glucose for management of hyperkalemia in patients with urgent EKG changes. Current intravenous therapies will still be needed for hyperkalemia in unconscious patients and those without a functional GI tract. Use of ZS-9 may be preferred in patients at higher risk of hypomagnesemia while patiromer might be more useful for patients who cannot tolerate larger fluid loads used for ZS-9 (240 vs 40 ml per dose for patiromer, although this may change in future formulations of ZS-9). Management of hyperkalemia in the dialysis population will also likely change

as potassium binders may be used to improve nutrition choices and stabilize intermittent fluctuations in serum potassium that come with dialysis. Future studies will be needed to determine if there are fluid and electrolyte or acid base changes or drug–drug interactions or long-term tolerability or outcomes that might favor patiromer or ZS-9 for certain populations or indications.

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Executive summary

- Hyperkalemia, a common medical problem with high morbidity and mortality, is a major obstacle for optimized treatment with renin–angiotensin–aldosterone system blockade for chronic kidney disease, diabetic nephropathy and congestive heart failure.
- Current therapeutic strategies to decrease potassium levels are usually temporizing measures that lack efficacy, tolerability and sustainability.
- Zirconium cyclosilicate and patiromer are two novel orally administered potassium exchangers that have been shown to be efficacious and safe in the short-term treatment of hyperkalemia for up to 28 days in published Phase III randomized placebo-controlled trials.
- Further studies are needed to ensure the long-term efficacy, safety and tolerability of these new cation exchangers and to determine their impact to optimize renin–angiotensin–aldosterone system blockade and improve cardiovascular and renal outcomes.

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