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Contemporary Treatment of Hyperkalemia

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Abstract
Purpose of Review Hyperkalemia is a common and serious electrolyte abnormality. It can have multiple etiologies but occurs more frequently in the setting of decreased renal function. Although the symptoms of hyperkalemia can be nonspecific and the electrocardiogram can be nondiagnostic, studies show that hyperkalemia increases mortality in- and out-of-hospital settings. Yet advances in treatment have been lacking.
Recent Findings Sodium polystyrene sulfonate (SPS), the sole potassium binder that has been on the market for five decades, has only recently been shown to be effective in a randomized trial in an outpatient setting. Patiromer and ZS-9 are two new oral agents that show promise in treating hyperkalemia effectively. Compared to SPS, these two drugs have more robust data on efficacy and better side effect profiles.
Summary With the advent of new agents, the management of hyperkalemia in both acute and chronic settings has the potential to improve. These drugs will not only provide more options to patients but also decrease morbidity because of fewer side effects.

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Introduction

Hyperkalemia is a common and potentially life-threatening electrolyte disorder in patients with heart failure (HF), chronic kidney disease (CKD), and diabetes mellitus [1, 2]. It has been estimated that up to 10 % of hospitalized patients suffer from hyperkalemia [3]. Although severe hyperkalemia is known to cause arrhythmia and cardiac arrest, mild to moderate hyperkalemia usually causes nonspecific symptoms including nausea, vomiting, abdominal cramps, myalgia, and malaise [4].

Hyperkalemia is more common when the kidney function is impaired. As the glomerular filtration diminishes, the dietary intake exceeds renal clearance and therefore, retention of potassium is common [5]. Additionally, patients with myocardial disease or HF are often treated with renin–angiotensin–aldosterone system inhibitors (RAASI), mineralocorticoid receptor antagonists (MRA), and beta adrenergic antagonists, all of which may cause both acute and chronic hyperkalemia [6, 7]. Despite multiple studies supporting the use of MRA therapy in patients with severe CKD [8, 9], fear of hyperkalemia has limited its use [10, 11]. Similarly, numerous studies have demonstrated that dosing of ACEIs, ARBs, and MRAs are frequently not optimized in patients with HF, often due to concerns about hyperkalemia [12]. Furthermore, the mandate for use of MRAs in HF has been associated with an increased rate of hyperkalemia and hospitalization [13].

Two recent observational studies underscore the importance of management of hyperkalemia. Goyal and colleagues analyzed the Cerner Health Facts database of

38,689 patients with confirmed AMI. Potassium was found to have a U-shaped distribution with in-hospital mortality [14•]. Mean postadmission serum potassium between 3.5 and 4.5 mEq/L resulted in the lowest mortality, while potassium outside this range was associated with a marked increase in death and arrhythmia. Mortality was twice as high for potassium of 4.5 to less than 5.0 mEq/L and even greater for higher potassium levels. Einhorn and colleagues performed a retrospective analysis of 245,808 veterans evaluating the association of hyperkalemia with mortality [15•]. There were 66, 585 hyperkalemic events over a year and that the risk of hyperkalemia was increased with CKD when compared with normal GFR; however, odds of death associated with hyperkalemia was higher in patients with normal GFR compared to those with CKD. They concluded that hyperkalemia increases the odds of mortality within 1 day of its occurrence. These findings highlight the importance of recognizing this metabolic disturbance and correcting it urgently.

Management of chronic hyperkalemia requires a low potassium diet, discontinuation of offending agents, and the use of diuretics. Treatment of acute hyperkalemia includes intravenous (IV) injections of calcium salts to stabilize cardiac membranes, IV sodium bicarbonate, IV infusions of glucose–insulin combinations, and nebulized beta-2 agonists to shift extracellular potassium to the intracellular space, and oral administration of polymer resins that bind potassium leading to its excretion via the gastrointestinal tract, with the ultimate definitive therapy being dialysis [16].

This paper will briefly review the mechanisms of potassium homeostasis and discuss the management of hyperkalemia. Specifically, old, new, and upcoming oral binders to treat hyperkalemia will be discussed and compared. Table 1 shows a comparison of various binders discussed here.

Pathophysiology

About 98 % of the total body potassium (K) is intracellular [17, 18], with a 2 % extracellular component maintained within a tight range of 3.5–5.1 mEq/L. [17] Potassium regulation is complicated and is achieved via an interplay of potassium intake, potassium excretion, and transcellular shifts of potassium into and out of cells [19]. The body's regulatory mechanisms can tolerate fluctuations in potassium intake; however, in people with impaired excretion, diet can be crucial in maintaining this balance. The kidneys are responsible for 90 % of excretion under normal physiological conditions [18, 20], while the other 10 % is excreted mostly through the gut, with a very small contribution from sweat. In end-stage renal disease (ESRD), when the kidneys no longer function, the gut upregulates to perform 25 % of the excretion [18].

The renin–angiotensin–aldosterone system (RAAS) is the cornerstone of neurohumoral regulation of potassium, and its main target is the principal cell in the collecting duct of the kidney [19]. Plasma renin increases angiotensin II which in turn acts on the adrenal cortex to secrete aldosterone. Aldosterone acts on the principal cells via MRA receptors to absorb sodium (Na) and excrete potassium. Since this system also regulates blood pressure (via sodium absorption and volume expansion), it is a target of many medications which inadvertently disrupt the potassium homeostasis. Other mechanisms affecting RAAS occur in patients with low renal perfusion, hypovolemia, and a hypertonic state [19].

The ratio of intracellular to extracellular potassium is maintained by the sodium–potassium (Na–K) ATPase pump which uses adenosine triphosphate (ATP) to drive K+ into cells in exchange for sodium. This potassium gradient creates a resting membrane potential which is important for myocytes and neuromuscular cells as it influences cell excitability and electrical conduction. Myocytes are especially sensitive to extracellular potassium levels because they affect the de- and repolarization of cells. The effects of hyperkalemia on myocytes are evident on ECGs in the form of tall or "peaked" T waves, short QT duration, prolonged PR interval, and wide QRS. The "sine wave" pattern is the penultimate state before the rhythm degenerates into ventricular fibrillation. Although the ECG findings are thought to be "typical," there is controversy over the prevalence of these findings and sequence of events, and thus making them unreliable indicators of hyperkalemia [21, 22]. In fact, ECG abnormalities may be absent in up to 50 % of patients with hyperkalemia and a normal ECG has been reported even with potassium levels greater than 8 mEq/L [23] [24].

Sodium Polystyrene Sulfonate (SPS)

Compound

Sodium polystyrene sulfonate is a benzene, diethenyl-, polymer, with an ethenylbenzene, sulfonated, sodium salt [25]. The drug is a light brown finely ground powder with an in vitro exchange capacity of approximately 3.1 mEq of potassium per gram [25]. The sodium content is approximately 100 mg (4.1 mEq) per gram of the drug. It can be administered orally or in an enema form. As the resin passes through the intestine or is retained in the colon after administration by enema, the sodium ions are partially released and are replaced by potassium ions, mostly in the colon. The efficiency of this process is approximately 33

Table 1 Comparison of oral binders

	SPS	Patiromer	ZS-9
Class	Organic polymer	Organic polymer	Inorganic zirconium crystal
Mechanism of action	Cation exchange resin; works in the colon;	Cation exchange resin; works in the colon;	Crystal structure with a micropore to trap potassium; works throughout the GI tract
	Exchanges sodium for potassium	Exchanges calcium for potassium	
Route	PO or PR	PO	PO
Dosing	PO: 15 g, 30 g	8.4, 16.8 and 25.2 g	5 g, 10 g (not FDA approved)
	PR: 30 g, 50 g		
Onset of Action	Delayed onset; hours to days.	7 h	1 h
Safety	GI	GI	GI
	Hypokalemia	Hypokalemia	Hypokalemia
	Drug interaction	Hypomagnesemia	Peripheral edema
	Colonic necrosis	Drug interaction	
Storage	Room temperature; 25 °C	Refrigerator 2–8 °C	Room temperature
Comments	Limited prospective studies	Multiple blinded studies	Multiple blinded studies

SPS sodium polystyrene sulfonate; *ZS*-9 zirconium silicate; *PO* per oral; *PR* per rectum; *GI* gastrointestinal

percent [25]. Even though SPS was first approved in 1958 and in use for more than five decades, it has only been evaluated in two randomized, controlled trials to date. This review will highlight the largest prospective trials on the efficacy of SPS published to date.

Efficacy

In 1961, Scherr and colleagues published the largest prospective trial on the use of SPS in the management of hyperkalemia [26]. Thirty-two patients with hyperkalemia from acute or chronic renal failure were enrolled to study the effectiveness of SPS. All patients were started on 20 percent dextrose solution intravenously and a high calorie, low potassium diet at baseline. SPS was administered either orally (20–60 g/day) or rectally (10–40 g/day) for multiple days. Other potassium-lowering interventions were at the discretion of the clinicians. Electrolytes were measured at baseline and at multiple intervals up to 24 h after the last dose of SPS. Twenty-three out of thirty patients had a potassium reduction of at least 0.4 mEq/L, with mean reduction of 1.0 mEq/L in the oral group and 0.8 mEq/L in the rectal group in the first 24 h of treatment. Two patients were treated for a prolonged period with oral SPS three times a week and they achieved satisfactory serum potassium levels per the authors, however, no data were published. Although the study was not blinded or controlled, and the final potassium level was partially influenced by other interventions (insulin and bicarbonate treatment), this study was pivotal in getting SPS reapproved by the FDA in 1962.

More recently, Nasir compared the safety and efficacy of SPS with its calcium counterpart, calcium polystyrene sulfonate (CPS) in patients with CKD and hyperkalemia [27••]. This randomized, controlled trial enrolled 97 CKD patients with K >5.2 mEq/L and treated them with either SPS ($n = 47$) or CPS ($n = 50$) 5 g orally (PO) three times daily (TID) for 3 days. Patients were evaluated for adverse symptoms, weight gain, worsening blood pressure, and effect on electrolytes. At the end of 3 days, mean serum potassium levels went from 5.8 ± 0.6 and 5.8 ± 0.26 mEq/L to 4.3 ± 0.53 and 4.8 ± 0.5 mEq/L in SPS and CPS cohorts, respectively. Nausea ($p = 0.005$), anorexia ($p = 0.013$), and diastolic blood pressure ($p = 0.004$) were significantly higher in the SPS group. The authors concluded that both CPS and SPS were effective in treating hyperkalemia, but CPS had fewer side effects compared to SPS.

Lastly, Lepage and colleagues published the most recent trial on SPS. This was a randomized clinical trial for treatment of mild hyperkalemia in CKD [28••]. Thirty-three patients with CKD and mild hyperkalemia (K of 5.0–5.9 mEq/L) were enrolled in a double-blind randomized trial. Patients were given 30 g of SPS ($n = 16$) or placebo ($n = 17$) once daily for 7 days. Serum potassium was evaluated at the end of 7 days. SPS was found to be superior to placebo in reducing serum potassium (mean difference between groups: 1.04 mEq/L) over 7 days. Electrolyte disturbance and gastrointestinal side effects were higher in the SPS group but the differences were not statistically significant.

Safety

As mentioned above, prospective studies with robust methodology on SPS are limited and thus actual rates of adverse events are estimates at best. For SPS administered with sorbitol, the most common adverse events are nausea, vomiting, diarrhea, abdominal bloating and cramps, anorexia, electrolyte imbalance and hypokalemia, and possibly elevated diastolic blood pressure [25, 27••]. Drug–drug interactions are another concern which recently prompted the FDA to request more studies from the manufacturer. However, a serious adverse event reported in the literature is bowel necrosis and subsequent death. Although this a rare event and actual numbers are not known, a systematic review of the published literature conducted by Harel and colleagues documented 58 cases of bowel necrosis with 33 % mortality associated with SPS use [29•]. In response to this rare but fatal adverse event, the FDA issued a warning against its use [30•].

Patiromer

Compound

Patiromer is a nonabsorbed, oral potassium binder [31]. The chemical compound consists of calcium, hydrolyzed divinylbenzene-Me 2-fluoro-2-propenoate-1,7-octadiene polymer sorbitol complexes and is available as an off-white to light brown powder [32]. It binds potassium in exchange for calcium, which is a part of the polymer. The site of action of patiromer is in the colon, where potassium concentration is the highest [32] and under physiologic conditions, 1 g of patiromer can bind to more than 8 mEq of potassium [32]. The sorbitol content in patiromer is between 2 and 4 g and it helps to improve its stability [32, 33••] by slowing degradation and formation of the calcium fluoride complexes. Radiolabeled studies have shown that patiromer is minimally absorbed from the gastrointestinal tract. Lastly, patiromer does not require laxative administration, making it amenable for chronic use [31].

Efficacy

Patiromer has been studied in approximately 700 patients, of whom 306 have been followed for more than a year. In phase I trials, patiromer established its safety and efficacy in patients with CKD on RAAS inhibitors. These trials also showed that patiromer can significantly lower serum potassium within 7 h of its first dose [34]. Moreover, 90 % of patients achieved a target K of $\leq$5 mEq/L within 48 h of treatment. Furthermore, treatment discontinuation caused a rise in serum potassium level by 0.27 mEq/L, which was observed about 3 days after the last dose [34]. These initial results led to 3 pivotal phase II and III studies which are discussed below.

The PEARL-HF trial was a phase II double-blinded, placebo-controlled study, whose focus was on heart failure patients with an indication to start spironolactone [35••]. Patients had to have either a history of discontinuing treatment with RAASI or beta blockers due to hyperkalemia, or have a history of chronic kidney disease with glomerular filtration rate (GFR) <60 mL/min to be enrolled. Eligible patients were randomized to either placebo ($n = 49$) or 30 g/day of patiromer ($n = 56$) for 4 weeks. Both groups were started on 25 mg/day of spironolactone. At day 15, the spironolactone dose was increased to 50 mg/day if the potassium level was between 3.5 and 5.1 mEq/L. The primary end point was the mean difference in potassium levels from baseline to day 28. Secondary end points were the proportion of patients who had a serum K level >5.5 mEq/L and patients in whom the spironolactone dose was increased to 50 mg/day. Eighty-eight patients completed the study. Patiromer was able to significantly lower potassium levels compared to placebo (−0.45 mEq/L, $p < 0.001$). The incidence of hyperkalemia (K >5.5 mEq/L) was lower in patients on patiromer than those on placebo (7.3 vs. 24.5 %; $p = 0.015$). Patiromer also enabled more patients to be on 50 mg of spironolactone compared to the placebo group (91 vs 74 %; $p = 0.019$).

The OPAL-HK was a 12-week phase III study, evaluating the efficacy and safety of patiromer in patients with CKD on RAASI with hyperkalemia (serum K 5.1–6.5 mEq/L) [33••]. Eligible patients had stage 3 or 4 CKD with potassium levels between 5.1 and 6.5 mEq/L and were being treated with a stable dose of RAASI for a duration of 28 days or more. Two hundred forty-three patients entered the initial treatment phase and received patiromer based on their potassium level; 4.2 g twice daily for a baseline potassium of 5.1–5.5 mEq/L or 8.4 g twice daily for a baseline potassium of 5.5–6.5 mEq/L. The primary end point for the treatment phase was the mean change in potassium level from baseline to week 4. The secondary end point was the proportion of subjects who had reached the target potassium range of 3.8–5.1 at week 4. Patients who had a serum potassium level $\geq$5.5 mEq/L at baseline or a potassium level between 3.8–5.1 mEq/L at the end of the initial treatment phase were eligible for the 8 week randomized withdrawal phase. One hundred and seven patients were randomized to either continue patiromer or change to receiving placebo. For the randomized withdrawal phase, the primary end point was the difference between the two groups in serum potassium levels at the start of the phase to end of week 4 or to the first time K <3.8 or $\geq$5.5 mEq/L. In the initial treatment phase, the

mean change in serum potassium level was -1.01 ± 0.03/L ($p < 0.001$) and 76 % of patients reached a target potassium level of 3.8–5.1 mEq/L by week 4. In the withdrawal phase, 15 % of patients in the patiromer group and 60 % of patients in the placebo group had recurrence of hyperkalemia ($p < 0.001$) at the end of 8 weeks. Lastly, more patients on patiromer (94 vs. 44 %) could tolerate RAASI at the end of the randomization phase compared to those on placebo.

The AMETHYST-DN was a 52-week phase II study evaluating the long-term safety and efficacy of patiromer in patients with hyperkalemia and diabetic nephropathy [36]. This multicenter, randomized dose titration study was designed to evaluate the optimal starting and maintenance doses of patiromer. All patients were on ACE inhibitor or ARB with or without spironolactone. The study consisted of a 4-week run-in phase where antihypertensive medications were optimized; an 8-week treatment phase where patients were divided into mild and moderate-hyperkalemia groups and treated with various doses of patiromer; and finally, a 44-week maintenance phase where patiromer was titrated to prevent hyperkalemia. The primary endpoint was mean change in serum potassium from baseline to week 4 of the treatment phase. The secondary end point was the mean change in serum potassium levels through 52 weeks. Subjects who developed hyperkalemia (due to optimization of hypertension medications) during the run-in phase or presented with hyperkalemia (due to current regimen) were enrolled in the dose titration treatment phase. Three hundred six subjects were divided into mild and moderate-hyperkalemia groups and given various doses of patiromer. The dose was further titrated to maintain a potassium level of $\leq$5 mEq/L. The primary endpoints of mean reduction of potassium from baseline to week 4 in the mild-hyperkalemia cohort were 0.35, 0.51, and 0.55 mEq/L for 4.2, 8.4, and 12.6 g patiromer groups, respectively. Mean reduction values in the moderate-hyperkalemia cohort were 0.87, 0.97, and 0.92 mEq/L in the 8.4, 12.6, and 16.8 g patiromer groups, respectively. The change in mean potassium level was significant in all groups. A total of 238 patients entered the 44-week maintenance phase. Up to 92 % in the mild-hyperkalemia group and 95 % in the moderate-hyperkalemia group remained within the target range of potassium (K: 3.8–5.0 mEq/L) throughout the 52 weeks of treatment.

Safety

Patiromer is generally well tolerated both acutely and on a long-term basis [37]. However, an AE rate of up to 54 % has been reported in the PEARL-HF study [35••]. Common adverse symptoms are related to the gastrointestinal system with constipation being the most common event which occurred in 11 % of patients in the OPAL-HK study. Hypokalemia was another common adverse event, reported in all three studies, and worst in the PEARL-HF study at 6 %. However, this might be easily corrected with dose adjustment [33••]. A serum magnesium $\leq$1.2 mEq/dL was reported in up to 4.3 % of subjects in the AMETHYST-DM study and up to 24 % had a serum magnesium $\leq$1.8 mEq/dL. Since hypomagnesemia can potentiate cardiac arrhythmias, electrolyte monitoring while on patiromer therapy should be considered. Other adverse events from worsening CKD to death were reported in various trials but none were thought be related to patiromer according to the authors of the respective studies. Lastly, animal data show that patiromer may interact with positively charged drugs and reduce their absorption and bioavailability by 30 % [32, 31].

Zirconium Cyclosilicate (ZS-9)

Compound

ZS-9 is an insoluble, inorganic compound, with a high selectivity for potassium and ammonium ions [38]. Its specificity for potassium is attributed to its crystal structure, with a micropore diameter of $\sim$3Å, roughly equivalent to the size of a potassium ion [38]. It has the empirical formula Na2ZrSi3O9 · nH20, and the crystal structure of its pore has an asymmetrical 7-member ring, which traps and stabilizes potassium [38]. ZS-9 is an odorless, white crystalline powder and is neither absorbed, nor metabolized [38]. In in vitro studies simulating the small and large intestines, ZS-9 bound to potassium ions within the first 5 min, and reached a steady state within the first 100 min. It has an affinity for potassium 25 times greater than that for calcium or magnesium, with a potassium exchange capacity of 3.5 mEq/g [38, 39].

Clinical Efficacy

ZS-9 has been studied in more than 1000 ambulatory patients with the longest trial being 4 weeks in duration. Moreover, a 1-year trial with 500 patients is near completion although no safety or efficacy data are available yet.

The efficacy of ZS-9 was first demonstrated in a double-blind, placebo-controlled, randomized, phase II study evaluating its safety and efficacy in patients with moderate CKD and hyperkalemia (serum potassium 5.0–6.0/L) [39]. Ninety patients were randomized to escalating doses of ZS-9 or placebo for 2 days. ZS-9 significantly reduced serum potassium from baseline compared to placebo at 38 h (0.92 mEq/L with a 10-g dose ZS-9 versus 0.26 mEq/L with placebo; $P < 0.001$). The results of this study led to 2 pivotal phase 3 studies that are discussed below.

The first phase III study was a multicenter, randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of ZS-9 in patients with hyperkalemia [40••]. Seven hundred fifty-three patients with a mean serum potassium of 5.3/L were randomized to 1 of 4 doses of ZS-9 (1.25, 2.5, 5, or 10 g) or placebo TID for 2 days (acute phase).This was followed by a maintenance phase of 12 days, during which patients who achieved a normal serum potassium (3.5–4.9 mEq/L) at the end of the acute phase were randomly assigned to either continue the same dose of ZS-9 once daily (QD) or were switched to placebo QD. Patients on placebo during the acute phase were randomly assigned to receive either 1.25 or 2.5 g ZS-9 QD. The primary endpoint for the acute phase was mean change in serum potassium at 48 h, while for the maintenance phase the primary outcome was the between-group difference in the mean serum potassium level. There was a dose-dependent reduction in serum potassium from baseline to 48 h, with absolute mean reductions of 0.73 and 0.53 mEq/L in the 10 and 5 g dose groups, respectively ($P < 0.001$), as compared to 0.25/L in the placebo group. During the maintenance phase, patients who remained on 10 and 5 g ZS-9 were significantly better in maintaining normokalemia than those on placebo [40••]. Lastly, the reduction of the serum potassium with 10 g ZS-9 was rapid when compared with placebo (0.30 % in ZS-9 and 0.09 % per hour in placebo; $p < 0.001$).

HARMONIZE was the second phase III trial: a multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of ZS-9 in patients with hyperkalemia (serum potassium $\geq$5.1 mEq/L) treated for 4 weeks [41••]. Patients were first treated with 10 g of ZS-9 TID for 48 h (acute open label phase). Patients achieving a normal potassium (3.5–5.0/L) were then randomized to 1 of 3 ZS-9 doses (5, 10, or 15 g) QD, or placebo QD, for 28 days in the maintenance phase. The primary endpoint was the difference in mean serum potassium in each ZS-9 dose group versus placebo during days 8–29 of the maintenance phase. Secondary endpoints included the proportion of patients achieving and maintaining a normal serum potassium level in the acute and maintenance phases respectively. Overall, 258 patients enrolled in the acute phase, and 237 patients were randomized into the maintenance phase. In the acute phase, potassium level declined from 5.6 to 4.5 mEq/L after 48 h of ZS-9 treatment. Significant reductions in potassium were observed within 1 h of ZS-9 administration, with 84 % of patients achieving normokalemia at 24 h and 98 % at 48 h. Potassium levels were significantly lower with all three ZS-9 doses compared with placebo in the maintenance phase (4.8, 4.5, and 4.4 mEq/L for ZS-9 5, 10, and 15 g doses, respectively, vs. 5.1 mEq/L for placebo; $p \leq 0.0001$). Greater proportions of patients in all three ZS-9 groups maintained normokalemia versus placebo (71, 76, and 85 % for 5, 10, and 15 g of ZS-9, respectively, vs. 48 % with placebo; $P = 0.015$ for 5 g, $p = 0.002$ for 10 g, $p < 0.001$ for 15 g dose of ZS-9 vs. placebo).

A subgroup analysis of these data focusing on patients ($n = 94$) with chronic heart failure, most of whom (69 %) were on RAASI at baseline, was performed. Baseline mean serum potassium was 5.6 mEq/L (95 % confidence interval [CI], 5.5–5.7), and normalized to 4.4 mEq/L (95 % CI, 4.3–4.5) after 48 h of ZS 9 treatment. Despite patients being on RAASI, those treated with ZS-9 maintained a lower serum potassium than patients on placebo ($P < 0.01$) and were more likely to maintain normokalaemia than the placebo group during the follow-up period ($P < 0.01$) [42].

Safety and Tolerability

Overall, adverse event (AE) rates among ZS-9 treatment groups and placebo have been similar. In the early dose escalating study, when ZS-9 was administered TID for 48 h to correct hyperkalemia, AEs were reported in 12.9 % compared with 10.8 % of patients on placebo. In the 12-day maintenance phase, AEs were reported in 25.1 and 24.5 % of ZS-9 and placebo patients, respectively. Gastrointestinal side effects were uncommon across treatment arms, occurring in less than 5 % of patients receiving ZS-9, with diarrhea as the most commonly reported event (1.8 % with ZS-9 vs. 2.5 % with placebo during the acute phase; 1.7 vs. 2.2 %, during the maintenance phase) [40••]. The HARMONIZE study also had low rates of AEs, with the exception of edema and hypokalemia for patients receiving ZS-9 at the highest dose [41••]. Although the incidence of edema was dose dependent, 14 % reported extremity edema in the 15 g ZS-9 group compared to 2 % in the placebo group. Mild hypokalemia occurred in 10 and 11 % of patients in the 10 and 15 g dose groups, and was easily corrected with protocol-directed dose adjustments [41••]. Lastly, there were no statistically significant differences between groups in serum calcium, magnesium, or sodium levels in either of the phase III studies.

Conclusion

Hyperkalemia is a common electrolyte abnormality in patients with CKD, HF, and DM and is reported in up to 10 % of hospitalized patients [3]. Recent studies have suggested that hyperkalemia might be an independent predictor of mortality in in- and out-of-hospital patients [15•, 14•]. Since the symptoms of hyperkalemia are non-specific [4] and the ECG is often unreliable and nondiagnostic [43, 44], hyperkalemia may be regarded as a "silent killer" [45]. Moreover, the rising prevalence of HF, DM,

and CKD and the increasing use of RAAS inhibitors and MRAs have increased the incidence of hyperkalemia [46] [5, 6], and have made the need for therapeutic options more urgent. Although SPS has been around for more than five decades, robust efficacy data are lacking, and the potential for serious bowel injury is concerning [47, 29•]. Clearly, there is an unmet need for better and safer treatment options for acute and chronic hyperkalemia.

Patiromer, commercially available since January of 2016, is a new and promising drug for the treatment of chronic hyperkalemia. Patiromer is an organic polymer and of the same class as SPS; however, efficacy data are much more robust demonstrating effectiveness within 7 h of administration [32]. Patiromer has been tested in patients with CKD, HF, and DM who are predisposed to hyperkalemia, and its use helped up-titrate RAASI and MRA while maintaining potassium in the normal range. Long-term use of patiromer, up to 1 year, has been well tolerated with mild GI complaints; however, hypomagnesemia and drug–drug interactions (reducing efficacy of other drugs when ingested concomitantly) have been noted as concerning side effects.

ZS-9, awaiting FDA approval, is another promising drug for the treatment of acute and chronic hyperkalemia. ZS-9 is an inorganic sodium zirconium crystal and belongs to a novel class of potassium-binding agents. It has been shown to significantly reduce potassium within 1 h of administration. Although the longest published trial is 4 weeks in duration, with a 52-week study in progress, its effectiveness in treating hyperkalemia is remarkable. Likewise, the adverse event rates were similar to placebo, except for leg edema noted in patients receiving the maximal dose of the drug.

Both of the new drugs are promising treatments for hyperkalemia in acute and chronic settings with few side effects and a good efficacy profile. Although more studies will definitely help strengthen the data and show effectiveness in acute settings, what is evident is that these drugs are superior to SPS and have the potential to transform hyperkalemia treatment. Together, these two drugs might be able to decrease morbidity, reduce emergency department visits, lower the need for emergency dialysis and hospitalization rates, and ultimately decrease mortality and health care costs.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Rafique reports that he is a consultant for ZS Pharma and received a grant from Relypsa, Inc. Dr. Singer reports that he is a consultant for ZS Pharma.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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- • Of importance
- •• Of importance

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