Acute and Chronic Cardiovascular Effects of Hyperkalemia: New Insights Into Prevention and Clinical Management

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Hyperkalemia is a common electrolyte disorder associated with life-threatening cardiac arrhythmias and increased mortality. Patients at greatest risk for hyperkalemia include those with diabetes and those with impaired renal function in whom a defect in the excretion of renal potassium may already exist. Hyperkalemia is likely to become more common clinically because angiotensin receptor blockers and angiotensin-converting enzyme inhibitors are increasingly being used in higher doses and are thought to confer cardiovascular and renal protection. Until recently, options for treating hyperkalemia were limited to the use of thiazide and loop diuretics and sodium polystyrene sulfonate. Newer options such as sodium zirconium cyclosilicate will allow for the safe and effective treatment of hyperkalemia while maintaining patients on prescribed renin-angiotensin-aldosterone system inhibitors.

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KEY WORDS

Hyperkalemia • Potassium • Chronic kidney disease • Congestive heart failure • Patiromer • Sodium zirconium cyclosilicate

Potassium is one of the most abundant ions in the body (50-75 mmol/kg body weight) and approximately 98% of potassium is located intracellularly (~ 140 mmol/L).[1] Potassium hemostasis is a very important aspect of electrolyte regulation; hyperkalemia (defined as a serum potassium level > 5 mmol/L) is a common electrolyte disorder associated with life-threatening cardiac arrhythmias and increased mortality.[2-5] This is, in large part, due to the increasing use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in clinical practice as

antihypertensive agents, heart failure treatments, and to decrease cardiovascular events in a large subset of high-risk patients.[6]

The prevalence of hyperkalemia in the general population is unknown and difficult to quantify.[1] However, it is present in up to 10% of hospitalized patients, depending on how hyperkalemia is defined.[7] Patients at greatest risk for hyperkalemia include those with diabetes and those with impaired renal function in whom a defect in the excretion of renal potassium may already exist. The incidence of hyperkalemia with renin-angiotensin-aldosterone system (RAAS) inhibitor monotherapy is low (≤ 2%) in patients without predisposing factors, but increases with dual RAAS inhibitor use (5%) and in patients with risk factors such as chronic kidney disease (CKD), congestive heart failure (CHF), and/or diabetes (5%-10%).[8] And because one third to one half of patients with CHF have CKD, in actual practice a large proportion of patients being treated with these drugs are at increased risk for hyperkalemia.[9]

Predisposing factors for hyperkalemia are numerous. Hyperkalemia may result from impaired potassium distribution between intracellular and extracellular spaces, increased potassium intake, and/or conditions that reduce potassium excretion, including CKD, hypertension, diabetes, and chronic CHF.[4] Additionally, various drugs, including those taken for CKD and CHF, can produce hyperkalemia in up to 88% of hospitalized patients by interfering with normal potassium regulation.[17]

Drug mechanisms leading to hyperkalemia include those that decrease aldosterone synthesis/action (ACE inhibitors, ARBs, heparins, mineralocorticoid receptor antagonists); those that suppress renin release (nonsteroidal anti-inflammatory drugs [NSAIDs], cyclosporine, tacrolimus); those that inhibit sodium-potassium adenosine triphosphatase, including β-blockers and digoxin (as well as digitalis-like remedies); drugs that decrease adrenal steroid synthesis (azole antifungals); antibiotics such as penicillin G, which increase potassium intake into cells (several herbal supplements fall into this category as well, including alfalfa, dandelion, etc); those that impair renal potassium secretion (amiloride, pentamidine, triamterene, trimethoprim); and drugs that shift potassium into the extracellular space (amino acids, aminocaproic acid, succinylcholine).[1,2,8,18,19] The risk of hyperkalemia with the use of the aforementioned drugs increases substantially when the glomerular filtration rate is < 30 mL/min.[6]

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Hyperkalemia is likely to become more common clinically because ARBs and ACE inhibitors are increasingly being used in higher doses, and are known to confer cardiovascular and renal protection.[10-13] They are often prescribed in combination with aldosterone receptor blockers secondary to the evidence that these medications provide incremental and added hard outcomes benefits in patients with CHF.[14,15] These medications have also been shown in combination to slow the progression of CKD.[16]

In normal physiology, potassium is freely filtered by the glomerulus. Most of this filtered potassium is reabsorbed in the proximal tubule and loop of Henle, with only 10% of the filtered load reaching the distal nephron. In addition to this small amount of potassium, which is filtered, potassium is also secreted into urine in the collecting duct. Potassium secretion in this segment is regulated and varies according to physiologic needs. The two most important physiologic determinants of potassium excretion are the serum aldosterone concentration and the delivery of sodium to the distal nephron.[6]

Aldosterone secretion is influenced by potassium concentration in the plasma and the renin-angiotensin system. The juxtaglomerular cells in the afferent arteriole secrete renin when renal perfusion pressure is low (hypovolemia, CHF, cirrhosis). Renin then acts on angiotensinogen to form angiotensin I, which is then converted to angiotensin II by ACE. Angiotensin II stimulates the release of aldosterone from the zona glomerulosa in the adrenal gland. Plasma potassium also has a direct stimulatory effect on aldosterone secretion.[20] The stimulatory effects of angiotensin II and potassium on the release of aldosterone appear to be synergistic because the presence of one factor increases the response to the other.[21] This interaction between potassium and angiotensin II involves the activation of a local intra-adrenal renin-angiotensin system.[22]

The most common method of drug-induced hyperkalemia results from ACE inhibition and ARB use, which impair urinary potassium excretion by interfering with the stimulatory effect of angiotensin II on aldosterone secretion in the adrenal gland. ACE inhibition blocks the formation of angiotensin II, whereas ARBs prevent angiotensin II from binding to its adrenal receptor.

Additionally, these drugs may interfere with the angiotensin II that is generated locally within the adrenal zona glomerulosa.[22]

Clinicians are occasionally confronted with the finding of an elevated serum or plasma potassium level in an otherwise healthy person. Such an abnormality may herald the presence of occult mineralocorticoid deficiency or a defect in renal tubular transport.[23] Alternatively, it may represent pseudohyperkalemia—a condition caused by the release of potassium from formed elements in the blood in patients with severe leukocytosis or thrombocytosis.[24,25] There are not extensive systemic data on pseudohyperkalemia but there are multiple case reports in the literature describing pseudohyperkalemia in various clinical scenarios including repeated fist clenching during venipuncture,[26,27] thrombocytosis,[28] and extreme leukocytosis,[29] to name a few. Pseudohyperkalemia has also been linked to traumatic transport of blood samples in hospital pneumatic tube transport systems.[30-32] Whatever the cause, pseudohyperkalemia should be recognized as a spurious increase of potassium level and should not be treated, as it usually does not have the life-threatening consequences of true hyperkalemia.

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The goal of managing nonemergent hyperkalemia is to prevent the progression to the more life-threatening emergent state and treat the underlying causes of potassium imbalance. Eliminating modifiable causes, including a high potassium intake in foods or with supplements or nonessential medications likely to predispose to hyperkalemia, is a first step (Table 1). A normal amount of potassium in a typical diet of a healthy American is approximately 3500 to 4500 mg/d. A potassium-restricted diet typically includes approximately 2000 mg/d.

TABLE 1

High-potassium Foods

- Apricots
- Artichokes
- Avocados
- Bananas
- Beets
- Brussels sprouts
- Cantaloupe
- Dates
- Greens (beet)
- Nectarines
- Oranges/orange juice
- Parsnips
- Potatoes
- Prunes/prune juice
- Pumpkin
- Spinach
- Sweet potatoes
- Swiss chard
- Tomatoes/tomato juice
- Vegetable juice

Data from Academy of Nutrition and Dietetics.[43]

Carefully reviewing a patient's updated and comprehensive list of all medications and supplements will help to avoid inadvertent use of potassium supplements and removing those medications that can adversely affect potassium balance (Table 2). According to the US Department of Agriculture, herbs including alfalfa, noni, and dandelion, and herbs including chervil, coriander, parsley, tarragon, turmeric, basil, and dill weed are high in potassium.

Until recently, little had changed regarding the treatment of nonemergent hyperkalemia. Approaches to preventing and treating mild hyperkalemia include initiating a low-potassium diet (< 2000 mg/d), and avoiding the use of potassium supplements, NSAIDs and cyclooxygenase-2 inhibitors. Use of RAAS inhibitors, including direct renin inhibitors, ACE inhibitors, ARBs, and mineralocorticoid receptor antagonists, are all associated with an increased risk of hyperkalemia, especially in those most in need of these treatments (those with CKD, heart failure, and diabetes). It is not infrequent that the development of hyperkalemia can interfere with their being utilized for their cardiac and renal protective effects in patients being treated for hypertension and CHF. For treatment of hypertension, ACE inhibitors and ARBs are accorded top-tier recommendations for use in patients with known cardiac and vascular disease and diabetes.[33] In those with heart failure with reduced ejection fraction, blockade of the RAAS has life-saving and quality-of-life (QoL)-enhancing effects and are critical components of national societal guideline recommendations. In an ambulatory practice, ACE inhibitor/ARB therapy contributed to hyperkalemia in up to 10% of patients and has been implicated in hyperkalemia observed in heart failure clinical trials.[34-36]

In the recently reported Prospective Comparison of ARNI with ACE-I to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF)

TABLE 2

Medications That Can Predispose to Hyperkalemia

Medication	Mechanism
Drug-inducing transmembrane potassium movement	
• Nonselective β-blockers	Decrease activity of sodium-potassium adenosine triphosphatase pump and renin release
• Digoxin intoxication	Inhibition of sodium-potassium adenosine triphosphatase pump activity
• Intravenous cationic amino acids	Increase in extracellular potassium shifts
• Mannitol	Hyperosmolality with increase of extracellular potassium shifts
• Suxamethonium	Prolonged depolarization of cell membrane
Drugs that affect aldosterone secretion	
• ACE inhibitors	Blockade of angiotensin II synthesis with decreased aldosterone secretion; impaired delivery of sodium to the distal nephron
• ARBs	Competitive binding to the angiotensin II receptor with decrease of aldosterone synthesis
• Direct renin inhibitors	Inhibition of the conversion of angiotensinogen to angiotensin I with decrease of aldosterone formation
• NSAIDS and COX-2 inhibitors	Decrease of prostaglandin-mediated renin release, renal blood flow, and GFR
• Calcineurin inhibitors	Decrease aldosterone synthesis and sodium-potassium adenosine triphosphatase pump activity
Drugs that cause tubular resistance to the action of aldosterone	
• Aldosterone antagonists	Blockade of mineralocorticoid receptors
• Potassium-sparing diuretics	Blockade of luminal sodium channels
• Trimethoprim, pentamidine	Blockade of luminal sodium channels
Potassium-containing agents	
• Salt substitutes and alternatives	Potassium source
• Penicillin G, stored blood products	Potassium source

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; COX-2, cyclooxygenase 2; NSAID, nonsteroidal anti-inflammatory drug.
Data from Ben Salem C et al.[44]

study that compared the combination of the neprilysin inhibitor sacubitril and the ARB valsartan with enalapril in patients with Class II-IV heart failure with left ventricular dysfunction, hyperkalemia was reported as an adverse event in 12% of patients treated with the combination agent and 14% of patients treated with enalapril during the double-blind period.[37] Preventing and treating hyperkalemia will allow clinicians to maintain important heart failure therapies and therefore have important life-saving and QoL-enhancing implications.

In the past, options for treating hyperkalemia that does not correct with conservative measures were limited to the use of diuretics (thiazide and loop diuretics) and the sodium-potassium exchange resin, sodium polystyrene sulfonate. Unfortunately, diuretics can predispose patients to prerenal azotemia and other complications. Sodium polystyrene sulfonate was introduced over 50 years ago as a treatment for hyperkalemia based on very limited data. As it passes along the intestine, sodium ions are released and exchanged for potassium ions. The largest reservoir of potassium is in the large intestine, where most of the sodium-potassium exchange takes place, leading to potassium excretion in the stool. Because of the time needed to transit to the colon, it may take hours to days for a potassium-reducing effect to occur with sodium polystyrene sulfonate (Kayexalate®; Covis Pharmaceuticals, Inc., Cary, NC). By replacing potassium with sodium, sodium polystyrene sulfonate causes a sodium load; therefore, caution is needed when using

in patients with severe CHF, severe hypertension, and edema. Because the cation exchange is not specific to potassium and can lead to inadvertent losses of magnesium and calcium, monitoring electrolyte levels is recommended. The only clinical data supporting the use of sodium polystyrene sulfonate are from one retrospective, uncontrolled analysis.[38] Sodium polystyrene sulfonate is contraindicated in patients with obstructive bowel disease. Cases of colonic necrosis have been reported and are probably related to the large dose of sorbitol associated with its use, leading to a black box warning. Sodium polystyrene sulfonate use is associated with a variety of shortcomings, including the high dose of sorbitol leading to gastrointestinal (GI) intolerance, sodium loading, and the resultant volume overload, making it a poor candidate for the chronic treatment of hyperkalemia.

Patiromer

Patiromer is indicated for the treatment of hyperkalemia and is a recent entrant into the marketplace. It is not to be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action. It is a nonabsorbed, cation exchange polymer that contains a calcium-sorbitol counter-ion. Patiromer increases fecal potassium excretion by binding potassium in the GI tract, leading to greater excretion of potassium, thereby lowering serum levels. Its safety and effectiveness were demonstrated in a series of modest-sized clinical trials (Table 3). The efficacy and safety of patiromer were studied in two key studies, the Two-Part, Single-Blind, Phase 3 Study Evaluating the Efficacy and Safety of Patiromer for the Treatment of Hyperkalemia (OPAL-HK) and Patiromer in the Treatment of Hyperkalemia in Patients With Hypertension and Diabetic Nephropathy (AMETHYST-DN).[39,40]

THE OPAL-HK study was a single-blind randomized trial of 243 hyperkalemic patients with CKD on stable doses of at least one RAAS inhibitor.[39] Subjects with potassium levels of 5.1 to 5.5 mEq/L received a starting daily dose of 8.4 g of patiromer and those with levels of 5.5 to 6.5 mEq/L received 16.8 g of patiromer per day. Dose titrations were designed to maintain potassium levels between 3.8 to 5.1 mEq/L. The primary endpoint was the mean change in serum potassium levels from baseline to week 4, which was −0.65 mEq/L in subjects treated with 8.4 g patiromer per day (total daily dose), −1.23 mEq/L in patients treated with 16.8 g patiromer per day (total daily dose), and −1.01 mEq/L in the overall population.

The largest reservoir of potassium is in the large intestine, where most of the sodium-potassium exchange takes place, leading to potassium excretion in the stool.

The AMETHYST-DN trial was a 52-week open-label trial of 304 hyperkalemic patients with type 2 diabetes and CKD on a RAAS inhibitor.[40] Patients with a baseline serum potassium of > 5.0 to 5.5 mEq/L or baseline serum potassium of > 5.5 to 6.0 mEq/L were randomized to receive one of three starting doses.

Similar to sodium polystyrene sulfonate, patiromer contains sorbitol, but at a much lower exposure. Because patiromer can bind to other orally administered agents, leading to a potential reduction of their bioavailability, a black box warning mandates that other medicines be administered either 6 hours before or after taking patiromer. This 6-hour timeframe may affect compliance in patients taking medications at different times of the day. Use of patiromer should be avoided in patients with severe constipation, bowel obstruction or impaction, including abnormal postoperative bowel motility disorder, as it may be ineffective and may worsen GI conditions.

Because patiromer can also bind to magnesium, leading to increased excretion, and cause hypomagnesemia, magnesium levels should be monitored regularly. The most common adverse reactions of patiromer include constipation, hypomagnesemia, diarrhea, nausea, abdominal discomfort, and flatulence.

Sodium Zirconium Cyclosilicate (ZS-9)

Sodium zirconium cyclosilicate is a highly selective cation exchanger that entraps potassium in the intestinal tract in exchange for sodium and hydrogen that is pending US Food and Drug Administration approval. Cyclosilicate is not a polymer, as is the case with sodium polystyrene sulfate and patiromer, nor is it delivered with sorbitol; it is a crystal that is highly selective, capturing only potassium and ammonium ions. It was engineered to have a high-capacity, highly selective crystalline lattice that entraps potassium cations over other divalent cations such as calcium or magnesium. A result of sodium zirconium cyclosilicate binding the ammonium ion is a net loss of acid, blood urea nitrogen, and elevation of serum bicarbonate levels, which may be favorable in patients with CKD who often have a relative metabolic acidosis. A robust clinical trial program has evaluated the safety and efficacy of

TABLE 3

Clinical Studies Using Patiromer Sorbitex Calcium to Reduce Serum Potassium Levels

Study	Clinical Trial	Study Design	Participants	Endpoints	Baseline	Patiromer Therapy vs Placebo Reduction of K (< 96 h)	Patiromer Therapy vs Placebo Reduction of K (> 96 h)
Data on file; Relypsa, Inc., Redwood City, CA	RLY5016-101	Phase 1 prospective randomized double-blind, placebo-controlled trial	Healthy volunteers n = 33 (25/8)[a]	Safety and tolerability, urinary and fecal patiromer excretion		No change	Significant dose-dependent increase in fecal potassium excretion and decrease in urinary potassium excretion at doses of 15-60 g/d compared with placebo
Data on file; Relypsa, Inc., Redwood City, CA	RLY5016-102	Phase 1 open-label trial	n = 12 (12/0)[a]	Pharmacologic activity/ safety		Not placebo controlled	Significant increase in fecal potassium excretion and a concomitant decrease in urinary potassium excretion across the QD/BID/TID dosing regimen
Data on file; Relypsa, Inc., Redwood City, CA	RLY5016-103	Phase 1 onset-of-action trial	Pts with CKD and hyperkalemia n = 15 (15/0)[a]	Time to onset of potassium-lowering action		Not placebo controlled	First statistically significant change at 7 h Mean K did not normalize by 48 h
Data on file; Relypsa, Inc., Redwood City, CA	RLY5016-201	Phase 2a proof-of-concept trial	Patients with hyperkalemia receiving hemodialysis n = 6 (6/0)[a]	Efficacy/safety of a fixed dose of patiromer	K mEq/L ≥ 5.5	Not placebo controlled	Pharmacologic action in reducing serum potassium levels and well-tolerated
Pitt B et al	RLY5016-202 PEARL-HF (NCT 00868439)	Phase 2 prevention trial (a prospective randomized, double-blind, placebo-controlled trial)	Patients with HF receiving a RAAS inhibitor (ACE inhibitors, β-blockers, ARBs) or Spiro (25-50 mg/d) therapy n = 105 (56/49)[a]	Efficacy/safety in preventing hyperkalemia	K 4.7 mEq/L for patiromer and placebo	15 g/d patiromer (n = 55) or placebo (n = 49), BID for 4 wk; patiromer → reduction in K at 24 and 72 h; placebo → increase in K at 24 and 72 h	15 g/d patiromer or placebo, BID for 4 wk: Patiromer → K −0.225 mEq/L relative to baseline at d 28 Placebo → K +0.23 mEq/L relative to baseline at d 28 Patients with HF were able to increase dose of Spiro compared with patients on placebo

Tamargo J et al, Bushinsky DA et al	RLY5016-204 (NCT 01130597)	Phase 2 prevention trial (an open-label single-arm trial)	HF patients with CKD treated with a RAAS inhibitor (ACE inhibitors, ARBs, β-blockers), n = 63 (63/0)[a]	Efficacy/safety of a titration regimen in preventing hyperkalemia	AU	AU	At the end of 8 wk, 91% of patients → 3.5–5.5 mEq/L; 84% of patients → 4.0–5.1 mEq/L
Tamargo J et al	RLY5016-205 AMETHYST-DN) (NCT 01371747)	Phase 2b treatment trial (an open-label, randomized, dose-ranging trial)	Hypertension patients with diabetic nephropathy treated with ACE inhibitors and/or ARBs, with or without Spiro, n = 306 (306/0)[a]	Efficacy/safety in treating hyperkalemia, determination of starting dose, and long-term safety in chronic treatment	AU	AU	The primary outcomes were the changes in K from baseline to the end of the study, but results were not published
Weir MR et al	OPAL-HK RLY5016-301 OPAL-HK (NCT 01810939)	A 2-part phase 3 trial: Part A (a single-blind phase); Part B (a placebo-controlled, randomized, withdrawal phase)	Patients with hyperkalemia, CKD, HF receiving RAAS inhibitor therapy Part A: 243 (243/0)[a] Part B: 107 (55/52)[a]	Part A: efficacy/safety of patiromer, Part B: effect of withdrawing patiromer on control of serum potassium levels, to assess whether chronic treatment with patiromer prevents recurrence of hyperkalemia, to provide placebo-controlled safety data		Hyperkalemia (K 5.1− < 5.5 and 5.5 − < 6.5 mEq/L	Part A: initial treatment phase (n = 237) 4.2 g and 8.2 g patiromer for patients with K 5.1 − < 5.5 mEq/L BID for 4 wk; 8.2 g patiromer for patients with K 5.5 − < 6.5 mEq/L BID for 4 wk; patiromer → K −1.01 mEq/L from baseline to week 4; K −0.65 mEq/L for mild hyperkalemia, K −1.23 mEq/L for moderate-severe hyperkalemia. Part B: randomized withdrawal phase (n = 107) Continue patiromer (8 wk) → K 0 mEq/L 8 wk-placebo → K 0.72 mEq/L In subgroup analyses, patients from EE sites had greater mean reductions in K (−1.15 vs 0.75 mEq/L; $P < .001$) and a greater percentage achieved normokalemia during the treatment phase than patients from EU and US sites; in the withdrawal phase, the difference in median change from baseline in K was greater in the EU and US patients than EE patients (1.39 vs 0.52 mEq/L)

[a]Information abstracted from multiple sources.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AU, awaiting update; BID, twice daily; CKD chronic kidney disease; EE, Eastern Europe; EU, European Union; HF, heart failure; K, potassium; QD, daily; RAAS, renin-angiotensin-aldosterone system; Spiro, spironolactone; TID, three times daily; US, United States.

TABLE 4

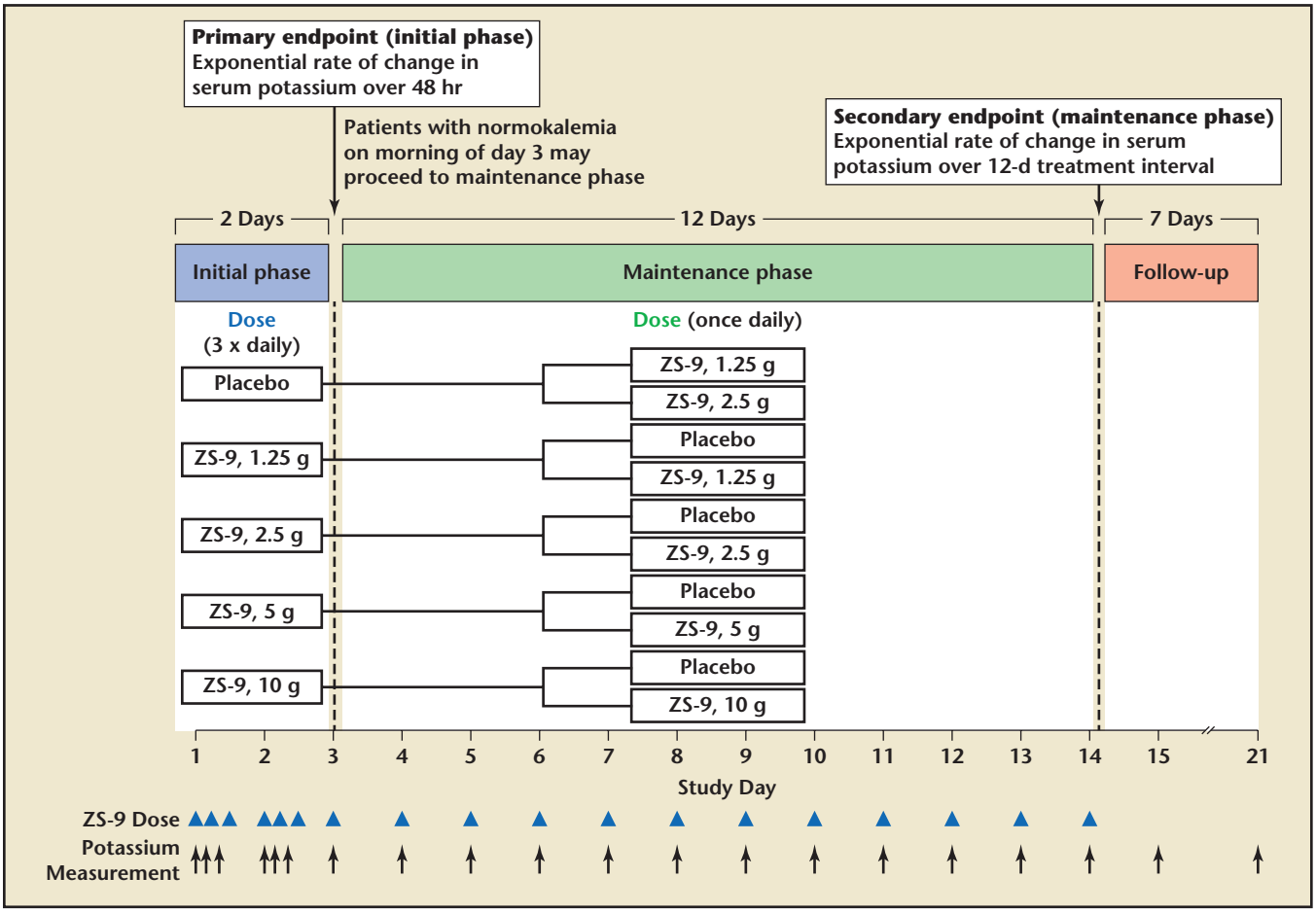
Clinical Studies Using Sodium Zirconium Cyclosilicate (ZS-9) to Reduce Serum Potassium Levels

Study	Clinical Trial	Study Design	Participants	Endpoints	Baseline	ZS-9 Therapy vs Placebo and Reduction of K (< 96 h)	ZS-9 Therapy vs Placebo and Reduction of K (> 96 h)
Ash SR et al, Singh B	Phase II trial ZS002 (NCT 014930248)	Prospective, randomized, double-blind, placebo-controlled study	Patients with hyperkalemia (K 5-6 mEq/L), eGFR (30-60 mL/min/1.73 m^2), CKD, on RAAS inhibitor therapy (n = 90)	Rate of change in serum potassium from baseline over 48 h	K 5-6 mEq/L	ZS-9: 0.3, 3, or 10 g. TID for ≥ 2 d; at 3 and 10 g, ZS-9 produced a rapid decrease in K over the first 48 h; at 10 g, mean rate of decline in K was −0.68 mEq/L and the maximum K was −0.92 mEq/L	None
Packham DK et al	First phase III trial ZS003 (NCT 01737697)	Two-part, multicenter, randomized, double-blind, placebo-controlled trial	Patients with hyperkalemia, regardless of etiology (CKD, DM, HF) on RAAS inhibitor therapy (n = 753)	Primary: rate of change in serum potassium from baseline to 48 h Secondary: rate of change in serum potassium from 48 h to day 14	Acute phase: K 5.3 mEq/L Extended phase: ZS-9 10 g (n = 30), K 4.5 mEq/L placebo (n = 30), K 4.5 mEq/L	48-h induction phase (K^+: 3.5-5.0 mEq/L) ZS-9: 1.25 g (n = 154) → K 5.1 mEq/L (−0.30) ZS-9: 2.5 g (n = 141) → K 4.9 mEq/L (−0.46) ZS-9: 5 g (n = 157) → K 4.8 mEq/L (−0.54) ZS-9: 10 g (n = 143) → K 4.6 mEq/L (−0.73) Placebo (n = 158) → K 5.0 mEq/L (−0.25) TID for 48 h	12-d maintenance phase ZS-9: 5 g (n = 64) → K 4.7 mEq/L ZS-9: 10 g (n = 63) → K 4.5 mEq/L Placebo (n = 129) → K 5.0 mEq/L
Kosiborod M et al, El-Shahaway	Ongoing phase III trial ZS004 (NCT 02088073)	HARMONIZE trial: multicenter, randomized, double-blind, placebo-controlled trial	Patients with hyperkalemia, regardless of etiology (CKD, DM, CHF) on RAAS inhibitor therapy (n = 258)	Primary: comparison of mean potassium from day 8 to day 28 Secondary: proportion of patients normokalemic during induction phase and during 28-d maintenance period	K 5.6 mEq/L	Open-label induction phase ZS-9: 10 g (n = 237) → K 4.5 mEq/L (normal K3.5-5.0 mEq/L) TID for 48 h	Double-blind randomized withdrawal phase (mean K < 5.18 mEq/L) QD for 28 d ZS-9: 5 g (n = 45) → K 4.8 mEq/L ZS-9: 10 g (n = 51) → K 4.5 mEq/L ZS-9: 15 g (n = 56) → K 4.4 mEq/L Placebo (n = 85) → K 5.1 mEq/L 12-mo extension ZS-9: 10 g/d
Tamargo J et al	Planned phase III trial ZS005 (NCT 02163499)	Open-label safety exposure study	Patients with hyperkalemia (> 5.0 mEq/L) regardless of etiology (n = 600)	Primary: long-term safety and tolerability Secondary: proportion of patients normokalemic during induction phase and during 12-mo period	> 5.0 mEq/L	48- to 72-h open-label acute phase ZS-9: 10 g, TID for 48-72 h	12-mo maintenance phase ZS-9: 10 g, QD during 1 y (5-g dose titration if needed)

ZS-9 (ZS Pharma, Inc., Coppell, TX).

CHF, congestive heart failure; CKD chronic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; DM, diabetes; HARMONIZE, Hyperkalemia Randomized Intervention Multi-dose ZS-9 Maintenance; HF, heart failure; QD, daily; RAAS, renin-angiotensin aldosterone system; TID, three times daily.

Figure 1. Study design for the ZS003 trial. Patients whose serum potassium level decreased to 3.5 to 4.9 mEq/L at 48 hours during the initial phase of the study were randomly assigned to receive either their original sodium zirconium cyclosilicate dose or placebo once daily before breakfast on days 3 to 15 (maintenance phase). Patients assigned to the placebo group in the initial phase were randomly assigned to receive either 1.25 g or 2.5 g of sodium zirconium cyclosilicate in the maintenance phase. ZS-9, sodium zirconium cyclosilicate (ZS Pharma, Coppell, TX). Reprinted with permission from McCullough PA et al. *Rev Cardiovasc Med.* 2015;16:140-155.



sodium zirconium cyclosilicate in treating hyperkalemia in a number of clinical scenarios (Table 4).

The clinical trial program for sodium zirconium cyclosilicate includes ZS003, the multicenter, two-phase, multidose, prospective, randomized, double-blind placebo-controlled study of 753 patients with mild to moderate hyperkalemia (potassium levels of 5.0-6.5 mEq/L), including patients with CKD, heart failure, and diabetes who are on ACE inhibitors, ARBs, or mineralocorticoid antagonists. Treatment included four different doses of sodium zirconium cyclosilicate (1.25 g, 2.5 g, 5 g, and 10 g) or placebo given three times daily for the initial 48-hour acute phase (Figure 1).[41] Patients who became normokalemic at 48 hours were then randomly assigned on day 3 to receive either sodium zirconium cyclosilicate or placebo once daily for the next 12 days followed by a 7-day follow-up phase.

The primary endpoint was the rate of change of potassium from baseline throughout the 48-hour acute phase. At 48 hours the mean reductions for the four doses tested was 0.46 mEq/L in the 2.5-g group, 0.54 mEq/L in the 5.0-g group, and 0.73 mEq/L in the 10-g group (Figure 2). At 1 hour following the first 10-g dose, a potassium level reduction of 0.11 mEq/L was observed. The more rapid reduction of potassium levels observed with sodium zirconium cyclosilicate than with other agents indicates that the potassium-binding effect starts higher in the GI tract, perhaps in the stomach or small bowel.

In the phase 3, multicenter, double-blind, placebo-controlled Hyperkalemia Randomized Intervention Multidose ZS-9 Maintenance (HARMONIZE) trial, 258 ambulatory outpatients with a potassium concentration $>$ 5.1 mEq/L at baseline received 10 g of sodium zirconium cyclosilicate three times daily during an initial 48-hour open-label phase.[42] Patients achieving normokalemia (3.5-5.0 mEq/L) were then randomized to one of three daily doses of sodium zirconium cyclosilicate

Figure 2. Extended-use sodium zirconium cyclosilicate (ZS-9), 10 g three times daily by mouth versus placebo in those who initially achieved normokalemia and were followed for 21 days. ZS-9, sodium zirconium cyclosilicate (ZS Pharma, Coppell, TX). Reprinted with permission from McCullough PA et al. *Rev Cardiovasc Med.* 2015;16:140-155. © 2015 MedReviews®, LLC. All rights reserved.

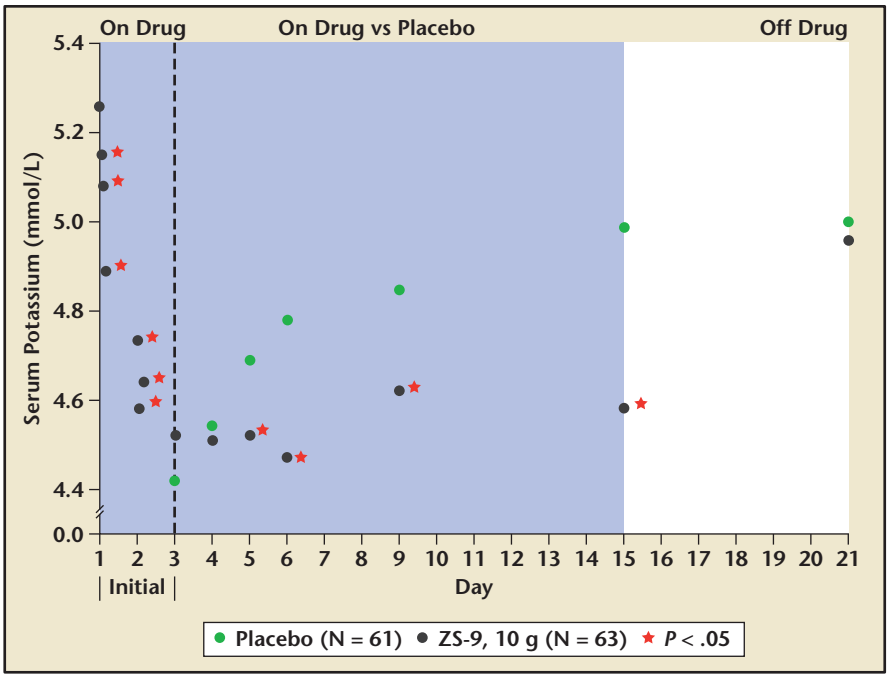
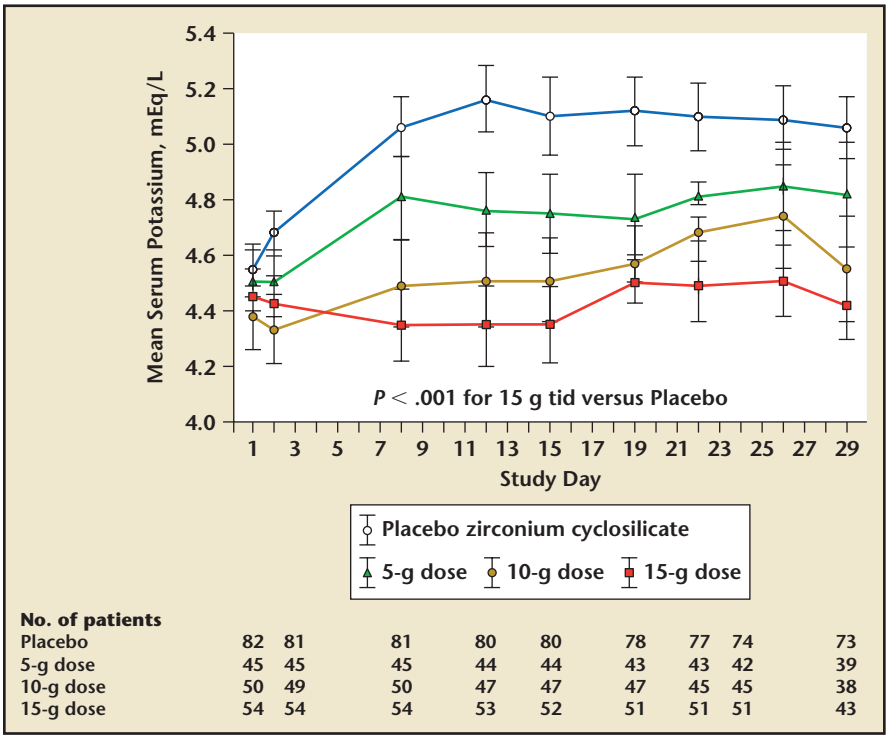


Figure 3. Results from the HARMONIZE trial with serial potassium concentrations over time. HARMONIZE, Hyperkalemia Randomized Intervention Multidose ZS-9 Maintenance; tid, three times daily. ZS-9, sodium zirconium cyclosilicate (ZS Pharma, Coppell, TX). Reprinted with permission from McCullough PA et al. *Rev Cardiovasc Med.* 2015;16:140-155. © 2015 MedReviews®, LLC. All rights reserved.



(5 g, 10 g, or 15 g) or placebo for 28 days. Potassium was significantly reduced by 0.2 mEq/L at 1 hour following the first 10-g dose from baseline, with reductions at 2 and 4 hours after the first dose of 0.4 mEQ/L and 0.5 mEq/L, respectively. At 24 and 48 hours postdose, reductions of potassium were 0.7 mEQ/L and 1.1 mEq/L, respectively. Median time to normokalemia was 2.2 hours. The primary endpoint was a comparison of mean serum potassium levels among the different doses and placebo. Patients receiving 5 g, 10 g, or 15 g of sodium zirconium cyclosilicate were maintained at 4.8, 4.5, and 4.4 mEq/L versus 5.1 mEq/L for placebo patients (Figure 3). Of importance was that the potassium-lowering effect and maintenance of normokalemia occurred in patients with CKD, heart failure, and diabetes without the need to remove them from their RAAS inhibitor treatment. There was no difference from placebo in GI adverse events, with no observed increase in body weight, blood pressure, or urinary excretion. There was an increase in the incidence of edema at the 10- and 15-g doses. A comparison of the mechanism of action, efficacy, and safety of sodium zirconium cyclosilicate and patiromer are provided in Table 5.

Conclusions

Hyperkalemia is a common problem observed in both the acute care and chronic ambulatory care settings by primary care practitioners, cardiologists, nephrologists, and endocrinologists. It is especially seen among patients with diabetes, heart failure, and CKD who are treated with the renal and cardioprotective RAAS inhibitors. Until recently, the treatment of hyperkalemia was limited to discontinuation of these important and

TABLE 5

Comparison of Sodium Zirconium Cyclosilicate and Patiromer Sorbitex Calcium

		Sodium Zirconium Cyclosilicate	Patiromer Sorbitex Calcium
Mechanism and Administration	Mechanism of action	Inorganic crystal → selective potassium trap	Organic polymer → nonspecific binding of cations
	Site potassium binding	Entire GI tract	Colon
	Administration	Once daily	Twice daily
	Daily drug total (g)	5-10	21-35
	Volume expansion	None	Swelling (H_2O absorbed)
	Storage	Room temperature	2-8°C
Efficacy	Time of Onset (h)	1	7
	@ 4 h [baseline potassium > 5.5 (mEq/L)]	−0.51	−0.14
	Median time to normalization (h)	2.2	> 48 (estimated 1 wk)
	Response rate	98% at 24 h	76% at 1 mo
	Potassium level maintained (mEq/L)	4.5 (5-10 g QD)	4.6 (17.5 g BID)
Safety	GI adverse event rate		
	Open-label phase	3.5%	19%
	Randomized phase	6% vs 14% for placebo	13% vs 6% for placebo
	Sorbitol	None	10 g for every 21 g of polymer
	Calcium	No impact	~ 4 g calcium load but small amounts absorbed, may bind PO_4
	Magnesium	No hypomagnesia	24% with Mg^{2+} < 1.8 mg/dL
	Fluoride	No impact	Increased serum fluoride
	Bicarbonate	↑ 2.3 mEq/L in 15 d	No significant changes
	Blood urea nitrogen	↓ Potentially due to binding of ammonium	No significant changes
	Drug-drug interaction	None	Valsartan and rosiglitazone
	Sodium absorption	None	None

BID, twice daily; GI, gastrointestinal; QD, daily; TID, three times per day.

potentially life-saving RAAS inhibitors and, in worse cases, the use of sodium polystyrene sulfonate with its associated high incidence of adverse reactions. Newer options will allow for effective treatment of hyperkalemia while maintaining patients on prescribed RAAS inhibitors. The introduction of patiromer to the marketplace provides one new option to treat hyperkalemia that appears to be better tolerated then sodium polystyrene sulfonate, but it has a black box warning not to be given within 6 hours of other medications. The anticipated introduction of ZS-9 to the marketplace will provide another new option for treating hyperkalemia. It appears to be well tolerated, with a more rapid onset of action; with its high

specificity for potassium the timing of its use is not limited by concomitant medication. The introduction of these new options for treating hyperkalemia is expected to lead to treatment at the time of diagnosis by cardiologists. ■

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MAIN POINTS

- Hyperkalemia (defined as a serum potassium level > 5 mmol/L) is a common electrolyte disorder associated with life-threatening cardiac arrhythmias and increased mortality. It is likely to become more common clinically because angiotensin receptor blockers and angiotensin-converting enzyme inhibitors are increasingly being used in higher doses.
- Patients at greatest risk for hyperkalemia include those with diabetes and those with impaired renal function in whom a defect in the excretion of renal potassium may already exist.
- Sodium polystyrene sulfonate use is associated with a variety of shortcomings, including the high dose of sorbitol leading to gastrointestinal intolerance, sodium loading, and the resultant volume overload, making it a poor candidate for the chronic treatment of hyperkalemia.
- Patiromer, a recent entrant into the marketplace, is indicated for the treatment of hyperkalemia. Its safety and effectiveness were demonstrated in a series of modest-sized clinical trials.
- Sodium zirconium cyclosilicate is a highly selective cation exchanger that entraps potassium in the intestinal tract in exchange for sodium and hydrogen; US Food and Drug Administration approval is pending.

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