Hyperkalemia in Heart Failure

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ABSTRACT

Disorders of potassium homeostasis can potentiate the already elevated risk of arrhythmia in heart failure. Heart failure patients have a high prevalence of chronic kidney disease, which further heightens the risk of hyperkalemia, especially when renin-angiotensin-aldosterone system inhibitors are used. Acute treatment for hyperkalemia may not be tolerated in the long term. Recent data for patiromer and sodium zirconium cyclosilicate, used to treat and prevent high serum potassium levels on a more chronic basis, have sparked interest in the treatment of hyperkalemia, as well as the potential use of renin-angiotensin-aldosterone system inhibitors in patients who were previously unable to take these drugs or tolerated only low doses. This review discusses the epidemiology, pathophysiology, and outcomes of hyperkalemia in heart failure; provides an overview of traditional and novel ways to approach management of hyperkalemia; and discusses the need for further research to optimally treat heart failure. (J Am Coll Cardiol 2016;68:1575–89) © 2016 by the American College of Cardiology Foundation.

Hyperkalemia can be life threatening because of the associated risk for arrhythmias and conduction system abnormalities (1,2). Generally, a serum potassium level higher than 5.0 mmol/l is defined as hyperkalemia (1). Among patients hospitalized for any cause, the prevalence of hyperkalemia has been estimated at 1% to 10% (3). Patients with chronic kidney disease (CKD), heart failure (HF), and diabetes mellitus and those using renin-angiotensin-aldosterone system inhibitors (RAASi) are at 2 to 3 times higher risk for hyperkalemia (4–6). In hospitalized patients admitted with worsening HF, despite aggressive diuresis, increases in serum potassium levels are observed (7). With growing numbers of CKD and HF patients taking RAASI and mineralocorticoid receptor antagonists (MRAs), hyperkalemia has become a more common concern. Angiotensin-converting enzyme inhibitors (ACEI), angiotensin-receptor blockers (ARBs), and MRAs have proven benefit in patients who are also

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at high risk for hyperkalemia (8). Even more challenging is the fact that many patients have several of these comorbidities simultaneously and are attempting to use 1 or more RAASi together. Thus, many patients in need for these therapies are unable to tolerate them, or if these medicines are prescribed, they are prescribed at less than optimal dosages. RAASI discontinuation for hyperkalemia represents an undesirable clinical compromise. Importantly, many clinical trials have excluded patients with advanced CKD and those with or at risk for hyperkalemia, leaving a critical evidence gap in pharmacotherapy for these high-risk patients.

**POTASSIUM HOMEOSTASIS**

Under normal circumstances, the kidneys are responsible for excreting 90% of the potassium that is consumed daily (9). Most of the potassium is freely filtered by the glomerulus and is absorbed in the proximal tubule and loop of Henle, and only 10% reaches the distal tubule (10,11). Principal cells in the renal collecting duct are responsible for secreting excess potassium from the circulation into the tubular lumen and excreting it in the urine. Luminal membrane potassium channels that respond to the electrochemical gradient for potassium generated by membrane potassium channels that respond to the electrochemical gradient for potassium generated by the basolateral membrane sodium-potassium adenosine triphosphatase (Na+/K+-ATPase) and a luminal membrane sodium channel accomplish this secretion. In states of potassium depletion, potassium secretion by the principal cells is inhibited, and the luminal membrane hydrogen-potassium adenosine triphosphatase (H+/K+-ATPase) is activated in the intercalated cells to reabsorb the potassium (Figure 1) (12). Secretion of potassium by the collecting duct is regulated by the serum aldosterone and sodium concentration in the distal tubule (11). Aldosterone is regulated by the renin-angiotensin-aldosterone system (RAAS) and by serum potassium levels (13). In HF, when the renal perfusion pressure falls, juxtaglomerular cells secrete renin, which converts angiotensinogen to angiotensin II, in conjunction with angiotensin-converting enzyme (ACE) (14). Angiotensin II acts on zona glomerulosa of the adrenal glands and stimulates aldosterone secretion. High serum potassium is also a stimulator of aldosterone, which lowers serum potassium by stimulating potassium excretion from distal tubule (13,15).

Increased potassium intake increases kaliuresis, and it is postulated that potassium receptors also reside in gastrointestinal tract, enterohepatic circulation, and liver (12). A role for the pituitary gland in potassium homeostasis has been shown in rats where renal potassium excretion was impaired post-hypophysectomy (16,17). In human subjects, hourly increased renal and gastrointestinal potassium excretion after 35 mmol of oral potassium persisted following aldosterone blockade, suggesting a gastrointestinal-renal kaliuretic signaling axis that is independent of the changes in serum potassium concentration and aldosterone (18).

**HYPERKALEMIA IN PATIENTS WITH HF: ROLE OF RENAL DISEASE AND THERAPY**

Approximately 26 million people globally have HF (19). These patients, by virtue of their disease, comorbidities, and medical therapy, are at risk for hyperkalemia. Hyperkalemia can be classified into 2 types:

1. Inherent hyperkalemia: includes hormonal disorders (e.g., Addison’s disease, hyporeninemic hypoaldosteronism), diabetes mellitus, CKD, and diseases with cell membrane instability that can cause intracellular and extracellular potassium shifts (20,21); and
2. Treatment-related hyperkalemia: medications (e.g., RAASi, MRA, nonsteroidal anti-inflammatory drugs, diuretic agents, heparin).

In addition, excess dietary intake of foods high in potassium or sodium supplements containing high potassium content can cause hyperkalemia (22-24) (Figures 2 and 3). MRAs or RAASI increase the risk of hyperkalemia (25). As the use of RAASI has increased, especially in higher doses and in combination (26-29), hyperkalemia has become more common. The use of ACEi is attributed to the development of hyperkalemia in 10% to 38% of hospitalized patients (3,30), whereas hyperkalemia develops in up to 10% of the outpatient population within 1 year of prescribing RAASI (31). Patients with impaired renal function and those with diabetes are at higher risk of hyperkalemia (11). In the PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure) trial, despite renal function, potassium-based eligibility criteria, and a run-in period, approximately 15% of patients in both the LCZ696 and the enalapril arms developed hyperkalemia (32). In a recent HF study (n = 19,194), 11.3% of patients had hyperkalemia over a mean follow-up of 3.9 ± 3.2 years, yielding an incidence of 2.90/100 person-years (95% confidence interval [CI]: 2.78 to 3.02) (33). Similarly, in RALES (Randomized Aldactone Evaluation Study), although the beneficial effect of...
spironolactone continued in the treatment group versus placebo, despite higher potassium levels in the treatment group (4.54 ± 0.49 mmol/l vs. 4.28 ± 0.50 mmol/l, respectively; p < 0.001), a higher mortality risk was observed when potassium levels increased to more than 5.5 mmol/l in the spironolactone group (34). The beneficial effect of spironolactone compared with placebo was maintained at all levels of hyper- or hypokalemia, showing a U-shaped relationship between potassium levels and mortality, with higher mortality rates in patients randomized to placebo at all potassium levels (p < 0.0001) (34). The use of spironolactone increased after the RALES trial; however, the hospitalizations attributed to hyperkalemia also increased to 11 of 1,000 patients in 2001 compared with 2.4 of 1,000 patients in 1994 (p < 0.001) (8). Additionally, the rate of in-hospital hyperkalemia–associated death in HF patients increased from 0.10 of 1,000 patients in 1994 to 0.39 of 1,000 patients in 2001 (p < 0.001) (8). These data underscore both the importance of hyperkalemia when augmenting RAASi and the need for careful monitoring of electrolytes.

Hyperkalemia risk is increased with concomitant CKD in HF patients. In 105,388 HF patients enrolled in the ADHERE (Acute Decompensated Heart Failure National Registry) study, more than 60% of patients had kidney disease (35). In patients with CKD, the prevalence of hyperkalemia can be up to 20% and is
associated with the risk of mortality and major adverse cardiovascular events and discontinuation of RAASi (36). The use of RAASi in patients with cardiovascular diseases, including myocardial infarction, HF, diabetes, and CKD, can reduce adverse long-term consequences (37). However, most trials excluded patients with moderate or severe CKD, which is common in HF, especially at advanced stages (37).

The use of effective and safe potassium binders now provides an opportunity to assess RAASi in such patients. In the meantime, several steps can be taken to attempt RAASi therapy in such patients. First, potassium supplements or salt substitutes containing potassium should be stopped or used judiciously under supervision. It may be preferable to use lower doses of both RAASi and MRAs rather than higher doses of one and not to use the other class of drugs altogether. Higher doses of ACEi and ARBs are associated with better outcomes in HF with reduced ejection fraction (38,39). However, this benefit is modest, and lower doses were better tolerated. Thus, lower doses of RAASi are better than avoiding these drugs. In case of worsening renal function, the risk of hyperkalemia and the rate of decline in renal function should be assessed. There are no specific guidelines, but generally, ACEi or ARB doses may be reduced or stopped, either temporarily or permanently, with

![FIGURE 2 Hyperkalemia in Heart Failure Patients Increases as Renal Function Declines](image)

Impaired renal function increases the risk of hyperkalemia in both the patients taking placebo and the MRA-treated patients. Modified with permission from Go et al. (23). eGFR = estimated glomerular filtration rate; MRA = mineralocorticoid receptor antagonist; WRF = worsening renal function.

![FIGURE 3 Prevalence of Heart Failure and Diabetes Mellitus in Relation to Chronic Kidney Disease](image)

Prevalence of heart failure and diabetes mellitus may increase the risk of hyperkalemia on the basis of disease and concomitant therapies. Modified with permission from Go et al. (23). eGFR = estimated glomerular filtration rate.
estimated glomerular filtration rate (eGFR) <15 to 30 ml/min, whereas they can be used in dialysis patients with careful monitoring. Currently, MRAs are contraindicated in patients with eGFR <30 ml/min. In hospitalized patients receiving intravenous diuretic agents who have rapid changes in renal function with or without hypotension, holding or lowering RAASi is common. However, this decision should be individualized, and currently, evidence for what to do in such a situation is not available.

According to the Health Care Cost and Utilization Project database, in 2011, the estimated total annual charges for Medicare admissions with hyperkalemia as the primary diagnosis were $697 million, the average Medicare length of stay was 2 to 3 days with mean charges of $24,085 per day, and one-third of the patients were discharged to another short-term hospital or home health care (40).

**CURRENT MANAGEMENT OF HYPERKALEMIA**

The treatment of hyperkalemia depends on the severity and cause (Table 1).

**EMERGENT MANAGEMENT.** In patients with electrocardiographic changes and/or potassium levels >7.0 mmol/l, intravenous calcium is administered to prevent arrhythmia (41). To rapidly lower potassium levels, insulin and beta-2 adrenoreceptor agonists are used to redistribute potassium from the extracellular to the intracellular space; however, this is a temporary measure (11).

**INTERMEDIATE MANAGEMENT.** Dialysis can be used in patients with poor kidney function or in those who are unresponsive to other treatments. In patients with CKD and metabolic acidosis, sodium bicarbonate therapy is an effective strategy to minimize increases in the potassium concentration (42). Loop diuretic agents are effective in excretion of potassium by the delivery of sodium in the collecting duct (11).

**MAINTENANCE.** In addition to dietary potassium intake restriction, lowering the dose of drugs that impair potassium excretion or administering them every other day or totally discontinuing them is often needed (11). This should include a review of all dietary and herbal supplements and salt substitutes as well. Potassium-binding resins can also be used; however, until recently, the only approved ion-exchange resin was sodium polystyrene sulfonate, which was not well tolerated and may cause colonic necrosis and intestinal injury (43).

Patiromer has recently become available for use, expanding the armamentarium of therapies available for the management of these patients. However, chronic therapy targeting prevention of hyperkalemia and subsequent optimization of RAASi needs further studies.

**PATHOPHYSIOLOGY OF HYPERKALEMIA IN HF**

A close association exists between serum potassium and plasma renin concentration in HF (44). Renin elevation due to renal hypoperfusion in HF causes the excretion of potassium by stimulating the synthesis of aldosterone, whereas high potassium concentrations can directly inhibit the RAAS (45). ACEi block the stimulatory effect of angiotensin II on aldosterone secretion, whereas ARBs prevent angiotensin II from binding to its adrenal receptors (45). In addition, these drugs may interfere with angiotensin I produced locally within the adrenal glands (14). RAASi, such as ACEi, ARBs, MRAs, and direct renin inhibitors, are associated with an increased risk of hyperkalemia, particularly when administered in combination (46).

This risk is increased in patients with stage 3 or higher CKD; hence, dual RAAS blockade is of concern in this scenario (47). Hyperkalemia can also develop secondary to decreased sodium delivery to the distal nephron, aldosterone deficiency, and abnormal functioning of the cortical collecting tubule (11). These abnormalities can result from the effects of other drugs or from underlying diseases.

In normal circumstances, the serum aldosterone concentration varies inversely with delivery of sodium to the distal nephron, so that potassium excretion remains independent of changes in extracellular fluid volume (9–11). However, in HF, increased aldosterone causes increased absorption of sodium in proximal tubules, resulting in its decreased delivery to the distal nephrons, which in turn, results in decreased potassium excretion. The use of RAASi in the presence of tubulointerstitial renal disease increases the risk of hyperkalemia by

<table>
<thead>
<tr>
<th>Severity</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Emergent</td>
<td>Calcium gluconate, Insulin, Beta-adrenoreceptor agonists</td>
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<tr>
<td>Intermediate</td>
<td>Dialysis, Loop diuretic agents, Thiazide diuretic agents, Sodium bicarbonate in patients with metabolic acidosis.</td>
</tr>
<tr>
<td>Maintenance</td>
<td>Review of medication list and dietary supplements, Reduce dose of renin-angiotensin-converting enzyme inhibitors, Stop offending medications, Potassium-binding resins</td>
</tr>
</tbody>
</table>
Many of the diseases that affect tubular function also impair the release of renin and result in hypoaldosteronism and impaired tubular function (11).

NEW TREATMENTS FOR HYPERKALEMIA

Sodium polystyrene sulfonate has significant limitations for chronic use and has not been evaluated in large randomized trials (48–50). Its use in HF is limited, as it may worsen edema by exchanging sodium for potassium ions (51). In addition, it is poorly tolerated as it may worsen edema by exchanging sodium for potassium ions (51). In addition, it is poorly tolerated as it may worsen edema by exchanging sodium for potassium ions (51). In addition, it is poorly tolerated as it may worsen edema by exchanging sodium for potassium ions (51). In addition, it is poorly tolerated as it may worsen edema by exchanging sodium for potassium ions (51). In addition, it is poorly tolerated as it may worsen edema by exchanging sodium for potassium ions (51). In addition, it is poorly tolerated as it may worsen edema by exchanging sodium for potassium ions (51).

Patiromer, is a nonabsorbed polymer designed to bind potassium in the gastrointestinal tract and reduce serum potassium levels, which was recently approved by the U.S. Food and Drug Administration (FDA) (56).

STRUCTURE AND MECHANISM OF ACTION.

Patiromer (Figure 4) is synthesized as a 100-μm bead with optimized flow and viscosity properties and is made in a high-yield 2-step process with polymerization followed by hydrolysis (57). Patiromer predominantly uses calcium as the exchange cation, instead of sodium (57). Patiromer is administered as once daily with food and promotes ionization of the polymeric potassium-binding moiety under pH conditions present along the extent of the gastrointestinal tract, predominantly in the colon (43). As a result of this structure, patiromer exchanges monovalent (sodium ion [Na⁺]) and divalent (calcium ion [Ca²⁺] and magnesium ion [Mg²⁺]) cations through the length of the gastrointestinal tract and preferentially binds potassium in the colon, where the concentration of this cation is substantially higher than that of Na⁺, Ca²⁺, or Mg²⁺ (58). The net effect is a reduction in serum potassium under hypokalemic conditions.

<table>
<thead>
<tr>
<th>Table 2: Comparison of Sodium Polystyrene Sulfonate, Patiromersorbitex Calcium (RLYS016), and Sodium Zirconium Cyclosilicate (ZS-9)</th>
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<tr>
<td><strong>Characteristic</strong></td>
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<tr>
<td>FDA approval</td>
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<tr>
<td>Structure</td>
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<tr>
<td>Mechanism of action</td>
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<td>Administration</td>
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<td>Storage temperature</td>
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<td>Efficacy</td>
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<td>Normokalemia maintained</td>
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<td>Safety</td>
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**AE = adverse events; Ca²⁺ = calcium ion; CKD = chronic kidney disease; FDA = Food and Drug Administration; GI = gastrointestinal; K⁺ = potassium ion; Mg²⁺ = magnesium ion; Na⁺ = sodium ion; QTc = QT interval corrected for heart rate.**

**Patiromer.** Patiromer, is a nonabsorbed polymer designed to bind potassium in the gastrointestinal tract and reduce serum potassium levels, which was recently approved by the U.S. Food and Drug Administration (FDA) (56).
conditions in the colon, where increased potassium secretion through big potassium channels represents an adaptive response to elevated serum potassium (59). Hypomagnesemia is reported in clinical trials of patiromer; however, there were no significant neuromuscular or cardiac abnormalities noted with treatment (56, 60–62).

**CLINICAL TRIALS WITH PATIROMER (RLY5016).** Patiromer has been evaluated in 3 clinical trials (Table 3).

**Efficacy.** OPAL-HK (Study Evaluating the Efficacy and Safety of Patiromer for the Treatment of Hyperkalemia) included 237 CKD patients with potassium levels of 5.1 to 6.4 mmol/l, who were taking RAASi (60). There were 2 phases: a 4-week phase in which patients received patiromer 4.2 g or 8.4 g twice a day, followed by an 8-week randomized withdrawal phase, in which patients were randomly assigned to continue the initial dose or were switched to placebo. Seventy-six percent of patients achieved normal potassium levels in 4 weeks. During the withdrawal phase, the hyperkalemia incidence was 15% in the treatment arm and 60% in the placebo group. The AMETHYST-DN (Patiromer in the Treatment of Hyperkalemia in Patients With Hypertension and Diabetic Nephropathy) study (61) was a multicenter, open-label, dose-ranging, randomized trial with a total of 306 patients with diabetes mellitus, CKD (eGFR: 15 to <60 ml/min/1.73 m²), and serum potassium level >5.0 mmol/l. All patients received RAASi before and during study treatment. Treatment with patiromer in both the mild and the moderate

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**CENTRAL ILLUSTRATION**

**NEW TREATMENTS FOR HYPERKALEMIA:** Patiromer (RLY5016) and Sodium zirconium cyclosilicate (ZS-9)

<table>
<thead>
<tr>
<th>Positive effects:</th>
<th>Side Effects:</th>
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<tbody>
<tr>
<td>• Normalizes and maintains potassium levels</td>
<td>• Drug-drug interactions</td>
</tr>
<tr>
<td>• Efficacy in heart failure</td>
<td>• Edema (at high doses of ZS-9)</td>
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<tr>
<td>• Reduces aldosterone levels and blood pressure</td>
<td>• Constipation, diarrhea, flatulence, nausea</td>
</tr>
<tr>
<td></td>
<td>• Hypomagnesemia</td>
</tr>
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<td></td>
<td>• Hypokalemia</td>
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</table>

**Evidence gaps:**

• *Prevention* of hyperkalemia

• Limitation of RAASi optimization due to hypotension or worsening renal function

• Safety and efficacy of RAASi optimization in patients excluded from previous trials

• Safety and efficacy of RAASi use at higher doses than used in previous trials


This figure shows the advantages, concerns, and clinical scenarios that have been tested and those that need to be addressed with patiromer and sodium zirconium cyclosilicate for the treatment of hyperkalemia in heart failure population. RAASi = renin-angiotensin aldosterone system.
Hyperkalemia in HF

Efficacy in HF. A subgroup analysis of the OPAL-HK trial studied the effects of patiromer in HF patients (63). Of the 102 patients in the first 4 weeks, 76% achieved a serum potassium level of 3.8 mmol/l to 5.0 mmol/l. In the second withdrawal phase, hyperkalemia occurred in 52% (n = 22) of patients taking placebo and 8% (n = 27) of those taking patiromer (p < 0.001). The PEARL-HF (Evaluation of Patiromer in Heart Failure Patients) trial studied patiromer in patients with chronic HF (56). Patients either had eGFR <60 ml/min or a history of hyperkalemia resulting in discontinuation of a RAASI. A total of 155 patients were started on 25 mg/day of spironolactone and were randomized to double-blind treatment with 30 g/day of patiromer or placebo for 4 weeks. At 4 weeks, the patiromer treatment group had lowered potassium levels (7.3% vs. 24.5%, respectively; p = 0.015) and was more likely to have spironolactone increased to 50 mg/day (91% vs. 74%, respectively; p = 0.019).

Safety and tolerability. The most common side effect in the initial phase of the OPAL-HK trial was constipation (11%), followed by diarrhea (8%), hypomagnesemia (8%), and hypokalemia (3%). Magnesium replacement therapy was initiated in 4% of subjects during the initial phase. In the withdrawal phase, constipation, diarrhea, and nausea (4% each) were the most common gastrointestinal events reported with patiromer, whereas these events occurred in none of the patients with placebo (63). In the PEARL-HF trial, the most common adverse events were gastrointestinal complaints (12%, n = 21: flatulence, diarrhea, constipation, or vomiting) (56).

Hypokalemia is an important concern in HF (64). When used as preventive measure for hyperkalemia, patiromer in PEARL-HF resulted in hypokalemia (<3.5 mmol/l) in 6% of patients versus 0% of placebo patients (p = 0.094) (56). In addition, hypomagnesemia (<1.8 mg/dl) was observed in 24% of the patients in the treatment group versus 2.1% in the placebo group. Adverse events resulting in patient withdrawal were similar in both groups (56).

**DRUG-DRUG INTERACTION WITH PATIROMER.** Initial in vitro study data showed patiromer binding of >30% in 14 of 28 drugs tested, including 30% to 50% binding to clopidogrel, furosemide, metformin, warfarin, metoprolol, verapamil, and lithium, whereas there was >50% binding to amlodipine, cinacalcet, ciprofloxacin, levothryoxine, quinidine, thiamine, and trimethoprim (65). In addition, a 30% reduction was seen in the availability of valsartan and rosiglitazone in preclinical coadministration studies in rats (56). Of 14 drugs tested initially for drug-drug interactions, 12 were tested in healthy volunteers (phase 1) in randomized, open-label studies, using a 3-way crossover design, according to FDA recommendations. The results released by the manufacturer showed no clinically meaningful reduction in absorption and no impact on peak concentration (Cmax) of lithium, trimethoprim, verapamil, and warfarin. There was also no clinically meaningful reduction in absorption, although there was some reduction in Cmax of amlodipine, cinacalcet, clopidogrel, furosemide, and metoprolol and reduced absorption and Cmax of ciprofloxacin, levothryoxine, and metformin. Quinidine and thiamine were not tested (66). Meanwhile, the manufacturer, on the basis of in vitro studies, recommends taking these medications at least 6 h before or 6 h after patiromer, whereas the data from in vivo studies are being reviewed by the FDA (67).

**SODIUM ZIRCONIUM CYCLOSILICATE**

Sodium zirconium cyclosilicate (ZS-9) is an inorganic, orally administered potassium-binding compound that has recently been investigated in phase II and III clinical trials.
**TABLE 3** Clinical Trials With Patiromer

<table>
<thead>
<tr>
<th>Trial, First Author, Year (Ref. #)</th>
<th>Type</th>
<th>Number of Patients</th>
<th>Intervention</th>
<th>Endpoints</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPAL-HK Weir et al., 2015 (60)</td>
<td>RCT</td>
<td>237 CKD patients on RAASi with hyperkalemia (K⁺ 5.1–6.5 mmol/l)</td>
<td>Phase 1: 4-week initial treatment with 4.2 or 8.4 g twice daily Phase 2: 8-week randomized withdrawal phase. Patients who had decreased K⁺ to 3.8–5.1 mmol/l, received treatment vs. placebo</td>
<td>Change in median K⁺ levels in first 4 weeks of each phase</td>
<td>The mean K⁺ level at baseline was 5.6 ± 0.5 mmol/l (5.3 ± 0.6 mmol in patients with mild hyperkalemia and 5.7 ± 0.4 mmol in those with moderate-to-severe hyperkalemia). At 4 weeks, mean ± SE change in K⁺ from baseline was 1.01 ± 0.03 mmol/l (95% CI: 1.07 to −0.95; p = 0.001). The change in patients with mild hyperkalemia was −0.65 ± 0.05 mmol/l (95% CI: −0.74 to −0.55), and the change in those with moderate-to-severe hyperkalemia was −1.23 ± 0.04 mmol/l (95% CI: −1.31 to −1.16). In the withdrawal phase at week 8, 60% of patients in the placebo group had recurrence of hyperkalemia (K⁺ &gt; 5.5 mmol/l) vs. 15% in the treatment group (p &lt; 0.001). At the end of phase 2, 55% of HF patients on placebo and 100% of treatment group patients were receiving RAASi.</td>
</tr>
<tr>
<td>OPAL-HK (Substudy) Pitt et al., 2015 (63)</td>
<td>RCT</td>
<td>102 patients with CKD and HF</td>
<td>Phase 1: 4-week treatment with 4.2 or 8.4 g twice daily Phase 2: 8-week withdrawal phase in patients with K⁺ to 3.8–5.1 mmol/l, received treatment vs. placebo</td>
<td>Change in median K⁺ levels in first 4 weeks of each phase</td>
<td>Phase 1 at 4 weeks: the mean SE change in serum K⁺ from baseline was −1.06 ± 0.05 mmol/l (95% CI: −1.16 to −0.95; p &lt; 0.001). In withdrawal phase at week 8, 52% of patients in the placebo group had a recurrence of hyperkalemia (K⁺ &gt; 5.5 mmol/l) vs. 8% in the treatment group (p &lt; 0.001). At the end of phase 2, 55% of HF patients on placebo and 100% of treatment group patients were receiving RAASi</td>
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<tr>
<td>PEARL-HF Pitt et al., 2011 (56)</td>
<td>RCT</td>
<td>105 HF patients on standard therapy and spironolactone</td>
<td>Patient randomized to 3 g/day of treatment vs. placebo for 4 weeks</td>
<td>Change in median K⁺ levels at 4 weeks</td>
<td>Treatment group normalized K⁺ in 24% (12 of 49 patients) vs. 7% (4 of 55 patients) in placebo (p = 0.015). 91% in the treatment group were able to reach the target dosage of spironolactone (50 mg/day at 4 weeks, increased from 25 mg/day). A greater number of patients in the treatment group were able to have their spironolactone dose increased vs. the placebo group (91% vs. 74%; p = 0.039).</td>
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<tr>
<td>AMETHYST-DN Baliris et al., 2015 (61)</td>
<td>RCT</td>
<td>306 diabetic patients on RAASI with K⁺ &gt;5.0 mmol/l</td>
<td>Varying patiromer twice-daily dosing in: 1. Mild hyperkalemia group, dose of 4.2, 8.4, or 12.6 g 2. Moderate hyperkalemia group, dose of 8.4, 12.6, or 16.8 g Dose titrated to keep K⁺ &lt;5.0 mmol/l</td>
<td>Change in median K⁺ levels at 4 weeks or before dose titration. Adverse events up to 52 weeks</td>
<td>1. Mild hyperkalemia group: K⁺ at 4 weeks was 0.35 (95% CI: 0.22–0.48) mmol/l for the 4.2-g twice-daily starting-dosage group, 0.51 (95% CI: 0.38–0.64) mmol/l for the 8.4-g twice-daily starting-dosage group, and 0.55 (95% CI: 0.42–0.68) mmol/l for the 12.6-g twice-daily starting-dosage group. 2. Moderate hyperkalemia group: K⁺ reduction at 4 weeks was 0.87 (95% CI: 0.60–1.14) mmol/l for the 8.4-g twice-daily starting-dosage group, 0.97 (95% CI: 0.70–1.23) mmol/l for the 12.6-g twice-daily starting-dosage group, and 0.92 (95% CI: 0.67–1.17) mmol/l for the 16.8-g twice-daily starting-dosage group (p &lt; 0.001 for all groups). This effect was maintained through week 52, where mean daily patiromer dosages were similar to those at week 4 through week 8 (19.4 g/day vs. 27.2 g/day) in patients with mild vs. moderate hyperkalemia, respectively. Adverse events: hypomagnesemia (8.6%), mild to moderate constipation, and hypokalemia (&lt;3.5 mmol/l) occurred in 5.6% of patients.</td>
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**STRUCTURE AND MECHANISM OF ACTION.** ZS-9 is administered as a once-daily dose, and its physiological ion channels filter ions on the basis of their differing diameters. ZS-9 has a structure that mimics physiological potassium channels and selectively captures potassium cations. This is accomplished by the use of a selectivity filter (62). In order to pass through the channel, an ion must shed its hydration...
sphere and only then can it interact with the carbonyl oxygens in the channel. Both sodium and potassium are of the size that would fit in the ZS-9 structure ring, but after shedding their hydration shells, only K\(^+\) has a size sufficient to fit into the ZS-9 pore size (68) (Figure 5).

ZS-9 is not absorbed in the gastrointestinal tract and is available as insoluble, free-floating, odorless, tasteless, white crystalline powder. It is an inorganic compound, unlike sodium polystyrene sulfonate, and specifically traps monovalent (potassium and ammonium) over divalent cations (like Ca\(^{2+}\) or Mg\(^{2+}\)). Because it is not systemically absorbed, the risk of systemic toxicity is low (69–71). The potassium exchange capacity of ZS-9 was studied using a simulated gastrointestinal tract medium with various concentrations of ZS-9 doses and medium pH (68). It was observed that in the simulated gastric fluid (pH \(\sim 1.2\)), there is an initial drop in potassium concentration, which reverses soon afterward. In the small intestine (pH \(\sim 4.5\)), there is an immediate uptake of potassium, followed by a small release, with equilibrium reached in approximately 20 min. In the large intestine (pH 6.8), there is a rapid uptake of potassium during the first 10 min, followed by continued but slower uptake over the next hour with no further increase thereafter. It was also observed that the binding capacity of ZS-9 increased proportionately with increasing concentration >0.5 to 50 mg/ml. These results led to the conclusion that, in environments mimicking the human gastrointestinal tract and in the presence of ZS-9, potassium equilibrium was reached relatively quickly (<20 min) (68). Mg\(^{2+}\) after shedding its water coat has a diameter of 1.44 Å (72). This diameter is energetically unfavorable for Mg\(^{2+}\) to interact with the oxygen bonds in the ZS-9 structural ring (68).

**CLINICAL TRIALS WITH ZS-9.** Sodium zirconium cyclosilicate has been evaluated in 4 clinical trials (Table 4).

**Efficacy.** The effect of ZS-9 over 14 days, including at the 48-h acute phase was demonstrated in the ZS-003 trial (71). Overall, 753 patients with potassium levels between 5.0 and 6.4 mmol/l were given various doses of ZS-9, and the exponential rate of change in serum potassium levels at 48 h was measured. A dose-related reduction in potassium levels was observed. A similar short-term phase II study by Ash et al. (70), using lower various doses of ZS-9 provided favorable results with significant reductions in potassium levels, even at lower doses, with only mild constipation reported (70).

The HARMONIZE (Hyperkalemia Randomized Intervention Multi-Dose ZS-9 Maintenance Another) trial (69) enrolled ambulatory patients with hyperkalemia (>5.1 mmol/l). In the first 48 h, the patients (n = 258) received 10 g of ZS-9 3 times a day, which resulted in lowering of potassium levels from 5.6 mmol/l to 4.5 mmol/l. The median time to normalization was 2.2 h. At 24 h, 84% of patients were normokalemic, and by 48 h, 98% were normokalemic. This was followed by the maintenance phase, in which patients who achieved normokalemia were randomized to receive ZS-9, 5 g (n = 45), 10 g (n = 51), or 15 g (n = 56), or placebo (n = 85) daily for 28 days.

**FIGURE 5 ZS-9 Pore Detail**

The ZS-9 pore is shown with a potassium ion (A), a sodium ion (B), and a calcium ion (C). The specificity for potassium is likely due to the size and binding sites of the pores. Adapted with permission from Stavros et al. (68). Abbreviations as in Figures 1 and 4.
Maintenance of normokalemia was observed with once-daily doses of ZS-9 at 5, 10, and 15 g, with serum potassium levels of 4.8, 4.5, and 4.4 mmol/l, respectively, versus placebo (5.1 mmol/l). It was also demonstrated that patients with higher baseline potassium levels experienced greater absolute reductions.

**Efficacy in HF.** The effect of ZS-9 on the subgroup population of HF patients (n = 94) from the HARMONIZE trial showed that all 3 doses of ZS-9 were effective in lowering and maintaining normal potassium levels, including those taking RAASi therapy with similar safety profiles (73) (Table 4).
**Safety and tolerability.** In the ZS-003 trial, the rates of adverse events were similar to those in the ZS-9 group (12.9%) and the placebo groups (10.8%), with diarrhea being the most common complication in both groups (1.7% in ZS-9 vs. 2.2% in placebo). In HARMONIZE, adverse events occurred in 53%, 29%, and 44% of patients receiving ZS-9 doses of 5, 10, and 15 g, respectively, compared with 32% in patients who received placebo. Edema was more common in the 15-g group. Gastrointestinal side effects were similar to those in the placebo group (14% placebo vs. 7%, 2%, and 9% for the 5-, 10-, and 15-g groups, respectively) (70).

**EFFECT ON ALDOSTERONE**

Renal hypoperfusion in HF activates the RAAS, which increases norepinephrine and angiotensin II, causing vasoconstriction and release of aldosterone through alpha-adrenergic and angiotensin II type 1 receptors (74). RAAS stimulation contributes to salt and water retention, renal potassium excretion, and activation of the sympathetic nervous system (75). RAASi inhibit aldosterone, resulting in decreased potassium excretion (11,76). Weir et al. (77) analyzed the effect of patiromer on serum aldosterone levels in patients with CKD in the OPAL-HK trial. A reduction in plasma aldosterone levels and in the urine aldosterone-to-creatinine ratio at 4 and 8 weeks of patiromer use was observed. Similarly, a reduction in systolic (SBP) and diastolic (DBP) blood pressure and in the urinary albumin to creatinine ratio was also observed. Data from HARMONIZE showed a 30% reduction in serum aldosterone with ZS9 after 28 days of treatment. It is important to study the clinical relevance of this finding.

**EFFECT ON BLOOD PRESSURE**

Treating hyperkalemia with patiromer, in addition to maintenance of RAASI therapy, may improve blood pressure control. A subgroup analysis from the AMETHYST-DN trial in a cohort of 79 of 306 patients with diabetic kidney disease and resistant hypertension (defined as systolic blood pressure [SBP] >140 mm Hg in 4 or more classes of antihypertensive drugs), who were treated with patiromer for hyperkalemia and continued with RAASI therapy, showed decreases in SBP and diastolic blood pressure (DBP) of $-18 \pm 17$ mm Hg and $-9.0 \pm 13$ mm Hg, respectively, at the end of 52 weeks of therapy (78). The interim analysis of the 711 patients enrolled in an ongoing ZS-9 study (ZS005) to evaluate the long-term (52-week) efficacy and safety of ZS-9 showed hypertension in 7% (48 of 684) patients (79). More prospective data are needed to further explore the effect of patiromer on blood pressure.

**CHRONIC USE FOR PREVENTION OF HYPERKALEMIA**

The treatment of acute hyperkalemia is well recognized. It is equally important to develop treatments for chronic use by both previously hyperkalemic patients and those who are at risk of developing hyperkalemia. The utility of this approach will require long-term data for the safety of these compounds, as well as the efficacy of such an approach to optimize RAASI use. This will require both clinical outcomes and quality-of-life data comparing patients’ willingness to continue the therapy versus using other approaches, such as dietary potassium restrictions in patients who are already on a low-carbohydrate and low-salt diet. Also, in case of noncompliance and abrupt discontinuation of therapy by patients, the risk of rebound hyperkalemia in patients optimized to RAASI therapy in HF needs to be studied.

**ONGOING TRIALS FOR PATIROMER AND ZS-9**

The TOURMALINE (Patiromer With or Without Food for the Treatment of Hyperkalemia) study is an ongoing trial to determine patiromer’s efficacy and safety when used once daily with or without food, focusing more on African American and Hispanic patients (NCT02694744) (80). ZS-9 has an ongoing trial (ZS-005) to evaluate the safety and efficacy of 10 g 3 times a day for 24 to 72 h, followed by a long-term maintenance phase once daily for up to 12 months (NCT02163499) (81).

**FUTURE DIRECTION**

According to HF guidelines, MRAs should not be used in patients with eGFR <30 ml/min or serum potassium levels >5.0 mmol/l (5,6). This leads to the exclusion of a significant group of HF patients (18% to 40%) with reduced ejection fraction who are not prescribed MRAs (82,83). Similarly, the use of ACEi or ARBs is seen only in 55% to 63% of patients with CKD (82,83) with reduced ejection fraction who are not prescribed MRAs (82,83). This leads to the exclusion of a significant group of HF patients (18% to 40%) with reduced ejection fraction who are not prescribed MRAs (82,83). Similarly, the use of ACEi or ARBs is seen only in 55% to 63% of patients with CKD (82,83). It is evident that there is a need for better therapies for hyperkalemia. The promising initial results shown by patiromer and ZS-9 may have a favorable impact on this paradigm. Although both compounds have demonstrated positive short- and longer-term
efficacy and tolerability, the long-term optimization of RAASi with the use of potassium binders needs to be evaluated. In addition, further data for their safety also need to be considered. This will also provide the opportunity to study those groups of patients who were excluded from clinical trials due to hyperkalemia. Although subgroup analysis of HF patients supported the ability of these agents to continue RAASi use in HF, further studies of up-titration to optimal dosing of RAASi in HF are needed. On the basis of these evidence gaps, there are 3 proposed areas for future research, as follows:

1. Prevention of hyperkalemia and the ability to optimize RAASi. We don’t know if it is possible, even if hyperkalemia is prevented, as patients may still be intolerant on the basis of hypotension or worsening renal function.

2. Broadening the use of RAASi to patients with eGFR <30 ml/min, who have generally been excluded from previous trials. These patients may benefit more from RAASi due to their higher risk, but it is not known. Additionally, in this high-risk group, the efficacy of novel binders may be different.

3. Assessing higher doses of RAASi than previously used, for example, a high dose in the setting of acute HF.

No trials are ongoing to assess the highlighted gaps in evidence in order to optimize long-term management of HF patients. It also needs to be determined whether these evidence gaps would require large-scale morbidity and mortality trials or whether only short-term safety and tolerability trials would suffice by implicitly accepting the fact that if the newer potassium-lowering agents reduced hyperkalemia, then use of RAASi would improve outcomes in populations where they have not been tested specifically.

**REFERENCES**


83. Maggioni AP, Anker SD, Dahlström U, et al., Heart Failure Association of the ESC (HFA). Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail 2013;15:1173–84.


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