Original Investigation

Effect of Sodium Zirconium Cyclosilicate on Potassium Lowering for 28 Days Among Outpatients With Hyperkalemia
The HARMONIZE Randomized Clinical Trial

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IMPORTANCE Hyperkalemia is a common electrolyte abnormality that may be difficult to manage because of a lack of effective therapies. Sodium zirconium cyclosilicate is a nonabsorbed cation exchanger that selectively binds potassium in the intestine.

OBJECTIVE To evaluate the efficacy and safety of zirconium cyclosilicate for 28 days in patients with hyperkalemia.

DESIGN, SETTING, AND PARTICIPANTS HARMONIZE was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial evaluating zirconium cyclosilicate in outpatients with hyperkalemia (serum potassium ≥5.1 mEq/L) recruited from 44 sites in the United States, Australia, and South Africa (March-August 2014).

INTERVENTIONS Patients (n = 258) received 10 g of zirconium cyclosilicate 3 times daily in the initial 48-hour open-label phase. Patients (n = 237) achieving normokalemia (3.5-5.0 mEq/L) were then randomized to receive zirconium cyclosilicate, 5 g (n = 45 patients), 10 g (n = 51), or 15 g (n = 56), or placebo (n = 85) daily for 28 days.

MAIN OUTCOMES AND MEASURES The primary end point was mean serum potassium level in each zirconium cyclosilicate group vs placebo during days 8-29 of the randomized phase.

RESULTS In the open-label phase, serum potassium levels declined from 5.6 mEq/L at baseline to 4.5 mEq/L at 48 hours. Median time to normalization was 2.2 hours, with 84% of patients (95% CI, 79%-88%) achieving normokalemia by 24 hours and 98% (95% CI, 96%-99%) by 48 hours. In the randomized phase, serum potassium was significantly lower during days 8-29 with all 3 zirconium cyclosilicate doses vs placebo (4.8 mEq/L [95% CI, 4.6-4.9], 4.5 mEq/L [95% CI, 4.4-4.6], and 4.4 mEq/L [95% CI, 4.3-4.5] for 5 g, 10 g, and 15 g; 5.1 mEq/L [95% CI, 5.0-5.2] for placebo; $P < .001$ for all comparisons). The proportion of patients with mean potassium <5.1 mEq/L during days 8-29 was significantly higher in all zirconium cyclosilicate groups vs placebo (36/45 [80%], 45/50 [90%], and 51/54 [94%] for the 5-g, 10-g, and 15-g groups, vs 38/82 [46%] with placebo; $P < .001$ for each dose vs placebo). Adverse events were comparable between zirconium cyclosilicate and placebo, although edema was more common in the 15-g group (edema incidence: 2/85 [2%], 1/45 [2%], 3/51 [6%], and 8/56 [14%] patients in the placebo, 5-g, 10-g, and 15-g groups). Hypokalemia developed in 5/51 (10%) and 6/56 patients (11%) in the 10-g and 15-g zirconium cyclosilicate groups, vs none in the 5-g or placebo groups.

CONCLUSIONS AND RELEVANCE Among outpatients with hyperkalemia, open-label sodium zirconium cyclosilicate reduced serum potassium to normal levels within 48 hours; compared with placebo, all 3 doses of zirconium cyclosilicate resulted in lower potassium levels and a higher proportion of patients with normal potassium levels for up to 28 days. Further studies are needed to evaluate the efficacy and safety of zirconium cyclosilicate beyond 4 weeks and to assess long-term clinical outcomes.

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Editorial

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Hyperkalemia is a common electrolyte disorder that can cause potentially life-threatening cardiac arrhythmias and is associated with poor prognosis in various patient populations.[1,2] Common comorbidities associated with hyperkalemia, such as chronic kidney disease (CKD), heart failure, and diabetes mellitus, are the same conditions in which renin-angiotensin-aldosterone system (RAAS) inhibitors improve outcomes, leading to their strong endorsement in practice guidelines.[3] However, broader use of RAAS inhibitors, which mechanistically increase potassium levels,[4] accompanied by the parallel increase in the number of individuals with CKD,[5,6] heart failure,[7] and diabetes,[8] have led to higher prevalence of hyperkalemia and an increase in hyperkalemia-related hospitalizations and deaths.[9]

Although effective and safe therapies for acute and chronic management of hyperkalemia are needed, such treatment options are currently lacking in the outpatient setting. Cation exchange resins such as sodium polystyrene sulfonate (SPS) are commonly used, but their effectiveness is uncertain[10] and has not been demonstrated in randomized controlled trials; furthermore, they have been associated with reports of serious intestinal toxicity.[11,12] Other strategies for acute management of hyperkalemia (eg, intravenous insulin and dextrose, intravenous sodium bicarbonate, diuretics, and inhaled β-adrenergic agonists) are impractical in the outpatient setting. Dietary restriction of potassium is associated with variable adherence and limits healthy food options for some patients.[13]

Sodium zirconium cyclosilicate (zirconium cyclosilicate; also known as ZS-9) is a highly selective inorganic cation exchanger designed to entrap potassium in the intestine. In previous studies, zirconium cyclosilicate was well tolerated and effective in lowering potassium within 48 hours of administration.[14,15] This study evaluated the efficacy and safety of zirconium cyclosilicate for 28 days in patients with hyperkalemia.

Methods

The Hyperkalemia Randomized Intervention Multidose ZS-9 Maintenance (HARMONIZE) study was a phase 3, randomized, double-blind, placebo-controlled trial that enrolled ambulatory patients with a potassium level of 5.1 mEq/L or greater. Patients were treated with zirconium cyclosilicate (10 g 3 times daily) in the 48-hour open-label phase; those achieving normokalemia (potassium, 3.5-5.0 mEq/L) were randomized to receive 3 different zirconium cyclosilicate doses or matching placebo for 28 days. The study was conducted in 44 sites from the United States, Australia, and South Africa (March through August 2014). The full study protocol and list of participating sites and investigators can be found in the trial protocol in Supplement 1 and eTable 1 in Supplement 2. The primary aim of the trial was to evaluate the efficacy and safety of 3 zirconium cyclosilicate doses in patients with hyperkalemia for up to 28 days. The study was conducted in accordance with the ICH E6(R1) Guidelines of Good Clinical Practice and the Declaration of Helsinki.

Patient Selection

Full inclusion and exclusion criteria may be found in the trial protocol in Supplement 1. Adult ambulatory patients with a history or laboratory evidence of hyperkalemia were recruited from nephrology, cardiology, and general research sites and screened for participation. To be eligible for enrollment, patients had to have documented hyperkalemia (2 consecutive potassium values, measured 60 minutes apart, both ≥5.1 mEq/L), be able to have repeated blood draws, and provide written informed consent (collected by the principal investigator or designee).

Exclusion criteria were pseudohyperkalemia, dialysis requirement, life expectancy less than 3 months, pregnancy, cardiac arrhythmias requiring immediate treatment, diabetic ketoacidosis, active treatment with sodium polystyrene sulfonate or lactulose, prior participation in another zirconium cyclosilicate trial or treatment with an unapproved drug or device within 30 days of study entry, any severe condition that would affect adherence or place a patient at undue risk, and known hypersensitivity to zirconium cyclosilicate.

Data on race and ethnicity were collected (based on prior literature noting differences in hyperkalemia by race)[16-18] using a 2-question format in which study participants self-reported race/ethnicity information. No monetary compensation was provided for study participation (other than reimbursement of travel expenses for study visits). The study was approved by national regulatory authorities in each country and the institutional review board or local ethics committee for each site.

Study Design

Patients who were deemed eligible by meeting inclusion and exclusion criteria, agreed to participate, and signed informed consent were enrolled in the open-label phase, during which they received 10 g of zirconium cyclosilicate 3 times daily with meals for 48 hours (6 doses total). Zirconium cyclosilicate was administered as an odorless, tasteless white powder mixed with water (240 mL with each dose). No protocol-directed advice on dietary potassium was provided to participants.

Patients who achieved normokalemia at the end of the open-label phase entered the double-blind randomized phase (**Figure 1**). Patients were randomized (4:4:4:7) to once-daily zirconium cyclosilicate (5, 10, or 15 g) or placebo, respectively, for 28 days. If a patient's potassium value was between 3.0 and 3.4 mEq/L at any time during the randomized phase, the dose was reduced from once daily to every other day for the remainder of the study. If a patient developed significant hypokalemia (potassium <3.0 mEq/L) at any time, or severe hyperkalemia (potassium >6.2 mEq/L) or significant arrhythmias (ventricular tachycardia/fibrillation, new atrial fibrillation/flutter, paroxysmal supraventricular tachycardia, second- or third-degree atrioventricular block or significant bradycardia [heart rate <40 beats/min]) during the randomized phase, study drug was discontinued, and the patient was withdrawn from the study and referred to his or her treating physician for the standard of care.

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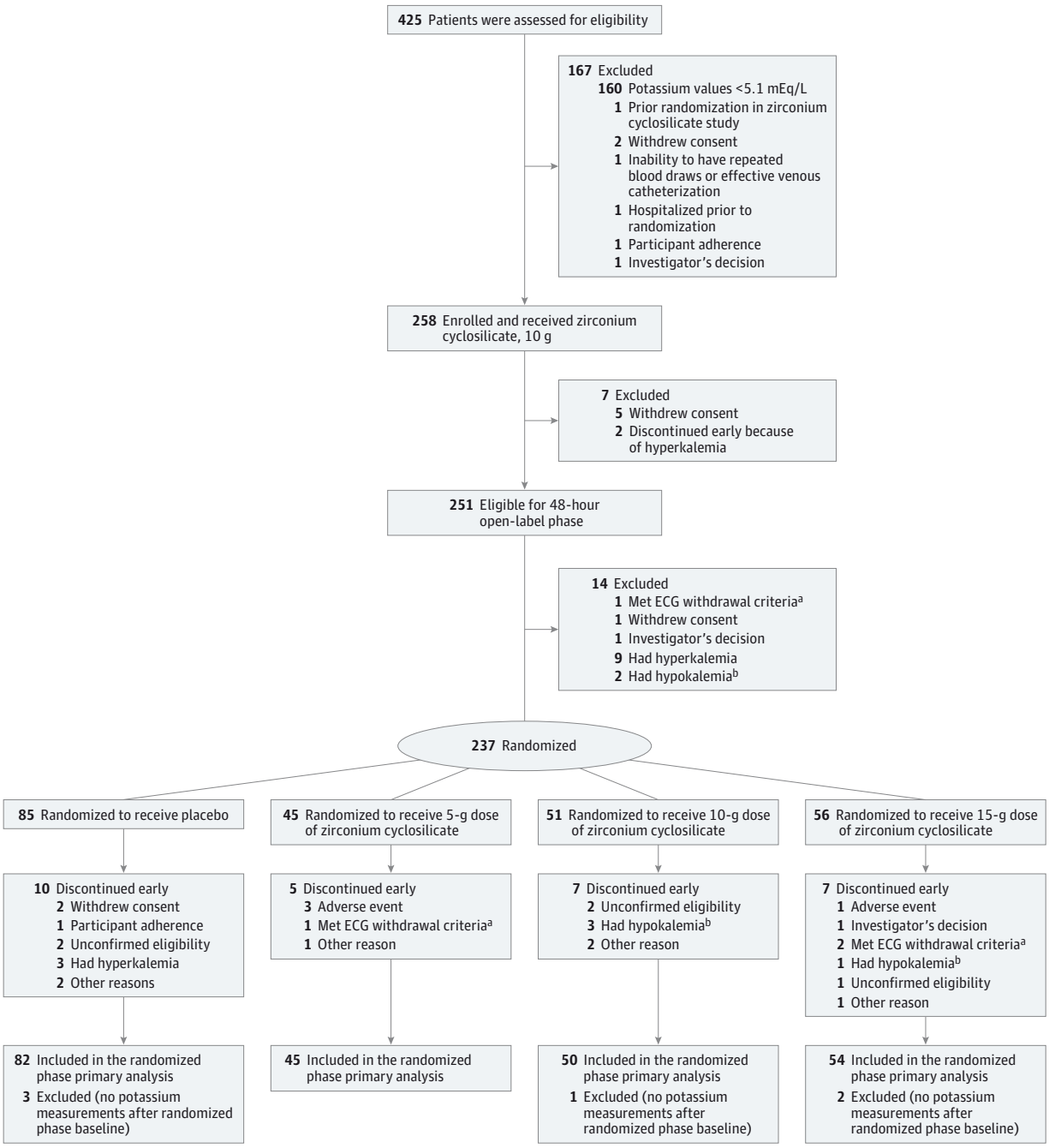
Potassium Measurements

All potassium levels were measured (after an 8-hour fast) in whole blood with a point-of-care device (i-STAT; Abbott Laboratories). All samples were then centrifuged on site and serum sent to a central laboratory (Beckman-Coulter-AU680 chemistry analyzer). Patient eligibility for enrollment and randomization and treatment decisions were based on i-STAT values. Statistical analyses were based on central

Figure 1. Patient Screening and Selection for Open-Label and Randomized Phases of the HARMONIZE Trial



Patients who discontinued study treatment but had at least 1 follow-up serum potassium measurement between days 8-29 were included in the randomized phase intent-to-treat population.

[a] Electrocardiogram (ECG) withdrawal criteria included significant increase in PR interval (>250 milliseconds in the absence of preexisting atrioventricular block), or widening of the QRS complex (>140 milliseconds in the absence of preexisting bundle branch block) or peaked T-wave or an increase in QTc interval >25 milliseconds to more than 500 milliseconds or >25 milliseconds in somebody with a baseline QTc of >500 milliseconds.

[b] According to the study protocol, all clinical decisions to withdraw patients because of a potassium level <3.0 mEq/L were based on i-STAT values; however, in all of these cases, subsequent central laboratory values for serum potassium were ≥3.0 mEq/L.

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laboratory values; if these data were missing, i-STAT values were used (adjusted to reflect the mean difference between i-STAT and laboratory potassium from all available paired samples).

Potassium was measured at 1, 2, and 4 hours after first dose on day 1, as well as just prior to and 1 hour after first dose on day 2 of the open-label phase. Eligibility for randomization was based on i-STAT potassium level obtained on the morning of study day 3 (after 48 hours of open-label treatment). After randomization, potassium was measured before the dose on days 1, 2, 5, 8, 12, 15, 19, 22, 26, and 29.

Study End Points

The primary end point was the comparison of mean serum potassium levels between placebo and each treatment group (highest to lowest) during days 8 through 29 of the randomized phase. Prespecified secondary efficacy end points for the randomized phase included proportion of patients who were normokalemic at end of study (morning of day 29); absolute and percentage change in serum potassium levels from open-label and randomized phase baselines and proportion of normokalemic patients at measured time intervals; cumulative days patients remained normokalemic between days 8-29 of the randomized phase; time to first recurrence of hyperkalemia (potassium ≥5.1 mEq/L) and time to first return to open-label phase baseline potassium level; mean intrapatient standard deviation in potassium levels between days 8-29 of the randomized phase; and mean change in serum aldosterone and plasma renin between open-label phase baseline and day 29 (US sites only). An additional prespecified analysis compared the proportion of patients with mean potassium level less than 5.1 mEq/L during days 8-29 of the randomized phase between each treatment group and placebo.

Secondary end points for the open-label phase included absolute and percentage change from baseline in serum potassium levels at all measured time intervals after initiation of treatment, proportion of patients who achieved normokalemia by 24 and 48 hours, time to normalization, and exponential rate of change in serum potassium.

Safety and tolerability were assessed throughout the study via ascertainment of adverse events (AEs) and serious adverse events (SAEs), monitoring of serial electrocardiograms, vital signs, body weight, physical examinations, and laboratory assessments (standard hematology and serum chemistry, including serum calcium, magnesium, phosphate, creatinine, blood urea nitrogen, and bicarbonate; urine analysis [including urinary sodium excretion]; and urine culture).

Statistical Analysis

Full details of the statistical analysis may be found in the trial protocol in Supplement 1. A sample size of 232 patients in the randomized phase had 90% power to detect a 0.3-mEq/L mean difference in potassium levels during days 8-29 (assuming a 0.5 participant-level SD) for each dose of zirconium cyclosilicate vs placebo for a 2-sided *t* test with 5.0% type I error.

All patients who received study drug were included in the safety population. The open-label phase intent-to-treat population included all patients in the open-label phase who had at least 1 postbaseline potassium level. The randomized phase modified intent-to-treat population included all patients who had at least 1 postbaseline potassium value on or after day 8 of the randomized phase.

For the primary end point, a log transformation was applied to serum potassium levels to reduce the effect of outliers. A longitudinal generalized estimating equation (GEE) model was used to simultaneously compare each active dose (highest to lowest) vs placebo for the mean day 8-29 values; the model included all serum potassium levels collected at scheduled study visits, baseline covariates for estimated glomerular filtration rate (eGFR), baseline serum potassium, age, sex, and binary indicators for prespecified subgroups (RAAS inhibitors, CKD, heart failure, diabetes mellitus). The longitudinal GEE model uses all available observations in the sequence of data points and a variance-covariance matrix that deals with correlations between consecutive observations to produce population-based estimates of treatment effects without imputing individual patient-specific missing data points. This accounts for missing data.[19]

Additional efficacy end points were evaluated using a logistic regression model (proportion normokalemic at day 29); 2-sample *t* test (absolute and percentage change in potassium levels from open-label and randomized phase baselines at measured time intervals and for changes in aldosterone and renin at day 29); Fisher exact test (proportions of normokalemic patients at measured time intervals and patients with mean day 8-29 potassium <5.1 mEq/L); linear regression model (cumulative days with normokalemia); Kaplan-Meier life table and Wilcoxon-Gehan test (median time to hyperkalemia and return to open-label phase baseline potassium level); and analysis of covariance (mean intrapatient standard deviation).

For the open-label phase efficacy end points, the absolute and percentage change from baseline in potassium at all time points (including 24 and 48 hours) were assessed using 1-sample *t* test to test the null hypotheses that the mean changes from baseline were 0. Kaplan-Meier life table was used to estimate time to normokalemia. Exponential rate of change in serum potassium level was assessed by fitting a straight line through the log of all postbaseline potassium values through 48 hours controlling for age, sex, baseline potassium, baseline eGFR, CKD, diabetes, heart failure, and use of RAAS inhibitors.

Two-sided $P \leq .05$ was considered statistically significant for all end points. All analyses were conducted using SAS version 9.1 (SAS Institute).

Results

In total, 425 patients were assessed for eligibility (Figure 1), and 258 patients were enrolled into the open-label phase. After 48 hours of open-label therapy with zirconium cyclosilicate, 10 g, 3 times daily, 237 patients were randomized to receive either once-daily zirconium cyclosilicate (n = 45 to 5 g, n = 51 to 10 g, n = 56 to 15 g) or matching placebo (n = 85). Six patients (3 in placebo, 1 in 10-g dose, 2 in 15-g dose) did

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Table 1. Baseline Characteristics of Ambulatory Patients With Hyperkalemia Enrolled in HARMONIZE Trial According to the Study Group

	Open-Label Phase (Zirconium Cyclosilicate, 10 g) (n = 258)	Randomized Phase			
		Placebo Group (n = 85)	Zirconium Cyclosilicate Dose Group		
			5 g (n = 45)	10 g (n = 51)	15 g (n = 56)
Age, mean (SD), y	64.0 (12.7)	64.3 (12.1)	61.5 (16.9)	63.8 (10.0)	64.9 (12.9)
Sex, No. (%)					
Male	149 (57.8)	44 (51.8)	27 (60.0)	27 (52.9)	40 (71.4)
Female	109 (42.2)	41 (48.2)	18 (40.0)	24 (47.1)	16 (28.6)
Race, No. (%)					
White	215 (83.3)	73 (85.9)	36 (80.0)	44 (86.3)	46 (82.1)
Black/African American	37 (14.3)	10 (11.8)	8 (17.8)	5 (9.8)	9 (16.1)
Asian	5 (1.9)	3 (3.5)	0	1 (2.0)	1 (1.8)
Other	3 (1.2)	1 (1.2)	1 (2.2)	1 (2.0)	0
Weight, mean (SD), kg	87.9 (22.9)	85.1 (18.6)	89.6 (23.9)	87.4 (25.6)	87.2 (18.6)
Serum potassium, mean (SD), mg/dL	5.6 (0.4)	4.6 (0.4)	4.5 (0.4)	4.4 (0.4)	4.5 (0.4)
Serum potassium, No. (%)					
<5.5 mEq/L	119 (46.1)	43 (50.6)	23 (51.1)	19 (37.3)	24 (42.9)
5.5 to <6.0 mEq/L	100 (38.8)	30 (35.3)	17 (37.8)	23 (45.1)	26 (46.4)
≥6.0 mEq/L	39 (15.1)	12 (14.1)	5 (11.1)	9 (17.6)	6 (10.7)
eGFR,[a] mean (SD), mL/min/1.73 m^2	46.3 (30.5)	48.0 (28.8)	48.0 (30.7)	44.7 (30.7)	44.9 (29.5)
eGFR, No. (%)					
<60 mL/min/1.73 m^2	179 (69.4)	52 (61.2)	31 (68.9)	38 (74.5)	41 (73.2)
≥60 mL/min/1.73 m^2	72 (27.9)	28 (32.9)	12 (26.7)	13 (25.5)	15 (26.8)
Not reported	7 (2.7)	5 (5.9)	2 (4.4)	0	0
Brain natriuretic peptide, mean (SD), pg/mL[b]	125.9 (170)	101.3 (106.5)	174.6 (228.6)	100.6 (143.7)	151.6 (216.8)
Comorbidities, No. (%)					
Chronic kidney disease	169 (65.5)	50 (58.8)	29 (64.4)	36 (70.6)	37 (66.1)
Heart failure	94 (36.4)	26 (30.6)	18 (40.0)	18 (35.3)	25 (44.6)
Diabetes mellitus	170 (65.9)	54 (63.5)	26 (57.8)	38 (74.5)	39 (69.6)
RAASi medication, No. (%)	180 (69.8)	61 (71.8)	33 (73.3)	36 (70.6)	33 (58.9)

Abbreviations: eGFR, estimated glomerular filtration rate; RAASi, renin-angiotensin-aldosterone system inhibitor.

[a] Calculated from the Modification of Diet in Renal Disease Study equation.

[b] US sites only; brain natriuretic peptide values shown represent open-label baseline.

not have follow-up potassium measurements between days 8-29 and were not included in the randomized phase modified intent-to-treat analyses.

Baseline characteristics are listed in **Table 1**. Mean age was 64 years, 58% were men, and 83% were white. Eighty percent of patients were enrolled in the United States, 8% in Australia, and 12% in South Africa (eTable 1 in Supplement 2). Substantial proportions of patients had CKD (169/258 [66%]), heart failure (94 [36%]), and diabetes (170 [66%]) and were treated with RAAS inhibitors (180 [70%]). Mean baseline serum potassium was 5.6 mEq/L, 100 patients (39%) had moderate hyperkalemia (potassium 5.5 to <6.0 mEq/L), 39 patients (15%) had severe hyperkalemia (potassium ≥6.0 mEq/L), and mean eGFR was 46 mL/min/1.73 m^2 (Table 1). Overall, 6.2% of potassium values were missing during randomized phase. Higher proportions of patients taking zirconium cyclosilicate had heart failure, CKD, eGFR less than 60 mL/min/1.73 m^2, and diabetes, and brain natriuretic peptide levels were higher in the 5-g and 15-g dose groups, compared with placebo (Table 1).

Efficacy

Open-Label 48-Hour Phase

Zirconium cyclosilicate significantly reduced serum potassium during the initial 48 hours vs baseline (**Figure 2**A). A significant change in potassium (−0.2 mEq/L; 95% CI, −0.3 to −0.2) was noted 1 hour after the first 10-g dose compared with baseline ($P < .001$). At 2 and 4 hours after the first dose, mean change in potassium was −0.4 mEq/L (95% CI, −0.5 to −0.4) and −0.5 mEq/L (95% CI, −0.6 to −0.5), respectively ($P < .001$ for both time points). Absolute change in serum potassium was −0.7 mEq/L (95% CI, −0.7 to −0.6; −12%) at 24 hours and −1.1 mEq/L (95% CI, −1.1 to −1.0; −19%) at 48 hours ($P < .001$ for both time points). Patients with higher baseline potassium experienced greater magnitude of potassium reduction (Figure 2B). Serum potassium was within the normal range in 84% of patients (95% CI, 79% to 88%) by 24 hours and in 98% (95% CI, 96% to 99%) by 48 hours. Median time to potassium normalization was 2.2 hours (interquartile range, 1.0 to 22.3). The effect of zirconium cyclosilicate was consistent across all prespecified

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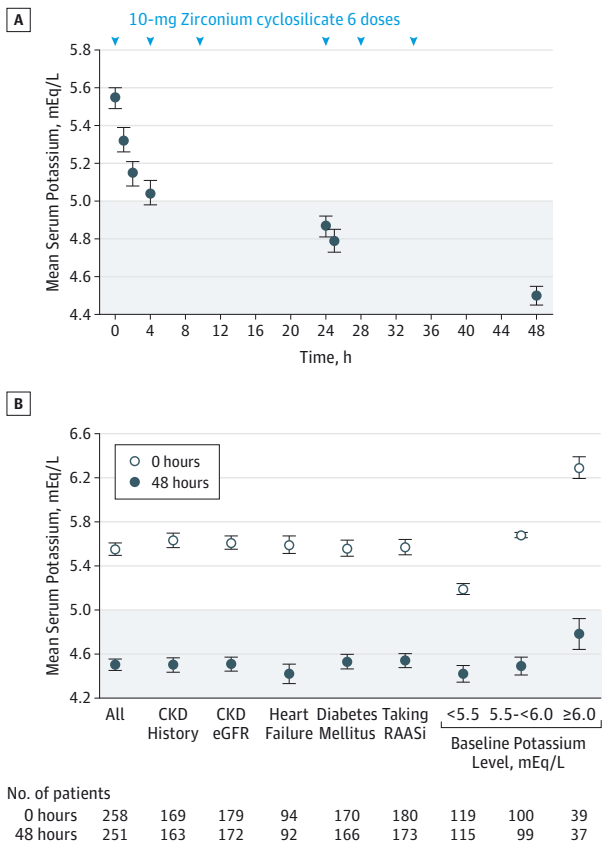
Figure 2. Serum Potassium Levels During the Open-Label Phase (48 Hours)



A, Mean serum potassium levels over time in patients treated during the open-label phase with zirconium cyclosilicate, 10 g, 3 times daily for 48 hours. B, Mean serum potassium levels at 0 and 48 hours across prespecified subgroups of chronic kidney disease (CKD) (by patient history and by estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2), heart failure, diabetes mellitus, concomitant renin-angiotensin-aldosterone system inhibitor (RAASi) use, and baseline potassium levels. Error bars indicate 95% confidence intervals; shaded region, normal potassium range.

subgroups and all ranges of hyperkalemia at baseline (Figure 2B). Mean exponential rate of change in potassium at 48 hours was −0.3% per hour (95% CI, −0.4% to −0.3% per hour).

Randomized 28-Day Phase

Mean serum potassium during days 8-29 was significantly reduced in all zirconium cyclosilicate groups vs placebo, with numerically lower potassium achieved with higher doses (4.8 mEq/L [95% CI, 4.6-4.9], 4.5 mEq/L [95% CI, 4.4-4.6], and 4.4 mEq/L [95% CI, 4.3-4.5] for 5-g, 10-g, and 15-g doses, respectively; 5.1 mEq/L [95% CI, 5.0-5.2] for placebo; $P < .001$ for each zirconium cyclosilicate dose vs placebo comparison (**Figure 3**A and **Table 2**). This effect was consistent throughout the randomized phase (Figure 3B). The greater degree of potassium lowering with zirconium cyclosilicate compared with placebo was consistent across all prespecified subgroups (eFigure in the Supplement).

Corresponding between-group differences for mean serum potassium level during days 8-29 of the randomized phase were −0.3 mEq/L (95% CI, −0.3 to −0.3), −0.6 mEq/L (95% CI, −0.5 to −0.6), and −0.7 mEq/L (95% CI, −0.7 to −0.7) for 5-g, 10-g, and 15-g doses, respectively, vs placebo. The proportion of patients who had normal potassium levels at the end of the randomized phase was significantly higher in each of the 3 zirconium cyclosilicate groups compared with placebo and was numerically greater with higher doses (71%, 76%, and 85% for 5-g, 10-g, and 15-g groups, respectively, vs 48% with placebo; $P = .01$ for 5-g, $P = .002$ for 10-g, $P < .001$ for 15-g dose of zirconium cyclosilicate vs placebo). Similarly, the proportion of patients with mean potassium less than 5.1 mEq/L during randomized phase days 8-29 was significantly higher in all zirconium cyclosilicate groups vs placebo and was numerically higher with higher doses (80%, 90%, and 94% for 5-g, 10-g, and 15-g groups, respectively, vs 46% with placebo; $P < .001$ for each dose vs placebo). Other secondary efficacy end points are presented in Table 2, and all demonstrated superiority for all 3 doses of zirconium cyclosilicate compared with placebo (with the exception of mean intrapatient standard deviation in serum potassium levels, which was higher in the 10-g group vs placebo, and plasma renin, which was lower in the 10-g group vs placebo).

Safety

The most common AEs are listed in **Table 3**. Edema occurred in 2 of 85 patients (2%), 1 of 45 patients (2%), 3 of 51 patients (6%), and 8 of 56 patients (14%) in the placebo, 5-g, 10-g, and 15-g groups, respectively. Seven of 14 patients who developed edema (1/1 in 5-g group, 3/3 in 10-g group, 3/8 in 15-g group) did not require any changes in therapy; 13 of 14 patients who developed edema completed the study. Gastrointestinal AEs were reported in 12 patients (14%) taking placebo vs 3 patients (7%), 1 patient (2%), and 5 patients (9%) in the 5-g, 10-g, and 15-g groups. No drug-related serious AEs were reported (Table 3). Treatment-related AEs were recorded in 8% of placebo patients vs 8% of zirconium cyclosilicate patients (eTable 2 in Supplement 2). One death (10-g zirconium cyclosilicate group), of a patient with stage 5 CKD, diabetes, hypertension, and known cardiovascular disease that was due to myocardial infarction, occurred on randomized phase day 18 and was deemed not related to study drug.

Hypokalemia (defined as potassium level <3.5 mEq/L) developed in 5 of 51 patients (10%) and 6 of 56 patients (11%) receiving 10 g and 15 g of zirconium cyclosilicate vs no patients in the 5-g or placebo groups. All cases of hypokalemia were mild (3.0-3.4 mEq/L) and resolved after the dose of study drug was reduced. No clinically significant changes in vital signs or other electrolytes (including sodium, calcium, and magnesium) were observed. Specifically, there were no significant changes in blood pressure, heart rate, or body weight at any dose level. No dose-dependent increase in urinary sodium excretion was noted. No clinically significant arrhythmias occurred in any of the zirconium cyclosilicate groups or placebo.

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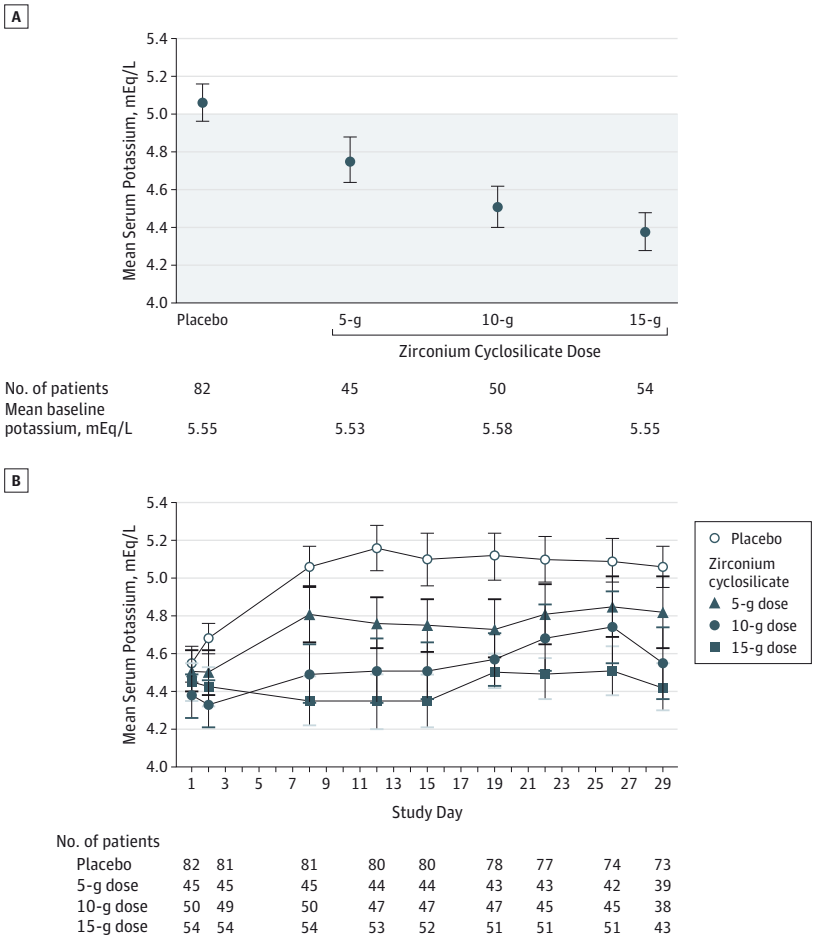
Figure 3. Serum Potassium Levels During the Randomized Phase (Days 8-29) According to Study Group



A, Primary end point: mean serum potassium over days 8-29 of the randomized phase in the placebo and 5-g, 10-g, and 15-g doses of zirconium cyclosilicate. B, Serum potassium levels during the randomized phase: patients received placebo or zirconium cyclosilicate, 5 g, 10 g, or 15 g, once daily for 28 days. Error bars indicate 95% confidence interval; shaded region, normal potassium range.

Discussion

The HARMONIZE randomized trial was designed to evaluate the efficacy and safety of zirconium cyclosilicate for up to 4 weeks in patients with hyperkalemia, a common and potentially serious electrolyte abnormality.[20-22] Our findings demonstrate that zirconium cyclosilicate was effective both in rapidly lowering potassium to normal range and maintaining normal potassium levels for up to 4 weeks in patients with various degrees of hyperkalemia. The potassium-lowering effect of zirconium cyclosilicate was consistent across all patient subgroups and observed immediately (after 1 hour of the first dose), and normokalemia was achieved in 84% of the patients within 24 hours and 98% within 48 hours of treatment initiation. Compared with placebo, all 3 doses of zirconium cyclosilicate resulted in significantly higher proportions of patients with normal potassium levels for up to 28 days. These outcomes occurred with a tolerability profile that was comparable with that of placebo.

Because of the increase in the common comorbid risk factors for developing hyperkalemia, such as CKD, heart failure, diabetes, aging population, and broader use of RAAS inhibitors, the prevalence of hyperkalemia and related hospitalizations has been increasing.[3,4,23] Because hyperkalemia is associated with serious cardiac arrhythmias, conduction system abnormalities, and increased mortality, strategies for lowering potassium are often necessary to minimize potential harm to patients. Treatments commonly used for severe hyperkalemia in the hospital—such as intravenous calcium, insulin, sodium bicarbonate, and inhaled β-adrenergic agonists—do not eliminate excess potassium and are typically not feasible in the outpatient setting.[24-27] Dietary interventions that limit potassium intake[13,28] are met with nonadherence and can limit healthier food options. Withdrawal of RAAS and mineralocorticoid receptor antagonists is also potentially problematic because these agents improve survival in several at-risk patient populations, such as those with heart failure and CKD (particularly when accompanied by proteinuria).[29,30]

Although polymeric exchange resins (SPS) are commonly used for treatment of hyperkalemia, their effectiveness is uncertain, as they have not been evaluated in randomized trials.[31-33] Furthermore, numerous reports of serious, even fatal gastrointestinal complications associated with SPS coadministration with 70% sorbitol (leading to the US Food and Drug Administration recommendations to avoid its use in 2009[34])

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Table 2. Randomized Phase End Points

	Placebo Group (n = 82)	Zirconium Cyclosilicate Dose Group					
		5 g (n = 45)	*P* Value	10 g (n = 50)	*P* Value	15 g (n = 54)	*P* Value
Primary End Point							
Potassium, days 8-29, mean (95% CI), mEq/L[a]	5.1 (5.0 to 5.2)	4.8 (4.6 to 4.9)	<.001	4.5 (4.4 to 4.6)	<.001	4.4 (4.3 to 4.5)	<.001
Secondary End Points							
Proportion of normokalemic patients, No./Total No. (%)							
At day 15[b]	35/80 (43.8)	31/44 (70.5)	.005	40/47 (85.1)	<.001	43/52 (82.7)	<.001
At day 29 (ITT)[b,c]	39/82 (47.6)	32/45 (71.1)	.01	38/50 (76.0)	.002	45/54 (85.2)	<.001
Change in potassium from open-label phase baseline[d]							
Day 15 No. of patients	80	44		47		52	
Mean (95% CI), mEq/L	−0.5 (−0.6 to −0.3)	−0.8 (−0.9 to −0.6)	.008	−1.1 (−1.3 to −0.9)	<.001	−1.2 (−1.4 to −1.0)	<.001
% (95% CI)	−8.3 (−10.7 to −5.9)	−13.7 (−16.3 to −11.2)	.004	−19.3 (−22.5 to −16.1)	<.001	−21.2 (−24.1 to −18.2)	<.001
Day 29 (ITT) No. of patients	82	45		50		54	
Mean (95% CI), mEq/L	−0.4 (−0.6 to −0.3)	−0.8 (−0.9 to −0.6)	.001	−1.1 (−1.3 to −0.9)	<.001	−1.2 (−1.4 to −1.0)	<.001
% (95% CI)	−7.7 (−9.6 to −5.7)	−13.9 (−16.7 to −11.0)	<.001	−19.3 (−23.3 to −15.3)	<.001	−21.1 (−24.1 to −18.0)	<.001
Change in potassium from RP baseline[d]							
Day 15 No. of patients	80	44		47		52	
Mean (95% CI), mEq/L	0.5 (0.4 to 0.7)	0.3 (0.1 to 0.4)	.02	0.1 (−0.1 to 0.3)	<.001	−0.1 (−0.3 to 0.1)	<.001
% (95% CI)	12.5 (9.0 to 16.0)	6.0 (2.3 to 9.7)	.02	2.9 (−0.8 to 6.7)	<.001	−1.9 (−5.3 to 1.5)	<.001
Day 29 (ITT) No. of patients	82	45		50		54	
Mean (95% CI), mEq/L	0.6 (0.4 to 0.7)	0.3 (0.1 to 0.5)	.007	0.1 (−0.1 to 0.3)	<.001	−0.1 (−0.3 to 0.1)	<.001
% (95% CI)	13.0 (10.1 to 15.9)	6.1 (1.8 to 10.5)	.008	3.0 (−2.0 to 8.1)	.001	−1.4 (−5.2 to 2.3)	<.001
Days with normokalemia, days 8-29, mean No./Total No. (95% CI)[e]	7.4/22 (5.6 to 9.1)	13.4/22 (11.1 to 15.6)	<.001	13.9/22 (11.6 to 16.1)	<.001	16.8/22 (14.9 to 18.7)	<.001
Time to first hyperkalemic measure, median, d[f]	7	14	.002	28	<.001	NR	<.001
Time to first return to open-label phase baseline, median, d[f]	19	29	.006	NR	<.001	NR	<.001
Intraparticipant potassium SD during RP[g]							
No. of patients	82	45		50		54	
Mean (95% CI), mEq/L	0.06 (0.06 to 0.07)	0.06 (0.06 to 0.07)	.96	0.08 (0.07 to 0.09)	.008	0.07 (0.06 to 0.08)	.34
Proportion of patients with mean potassium <5.1 mEq/L, days 8-29 (ITT), No./Total No. (%)[b]	38/82 (46.3)	36/45 80.0)	<.001	45/50 (90.0)	<.001	51/54 (94.4)	<.001
Change in serum aldosterone[c,h]							
Day 29 (ITT) No. of patients	59	30		32		33	
Mean (95% CI), ng/dL	−0.8 (−2.1 to 0.5)	−4.8 (−7.8 to −1.9)	.01	−6.1 (−10.1 to −2.1)	.01	−3.7 (−5.8 to −1.6)	.02
Change in plasma renin[c,h]							
Day 29 (ITT) No. of patients	57	29		31		30	
Mean (95% CI), ng/mL/h	3.0 (−0.5 to 6.5)	0.8 (−2.2 to 3.7)	.33	−2.3 (−5.5 to 1.0)	.03	−0.32 (−4.2 to 3.5)	.23

Abbreviations: ITT, intent-to-treat population; NR, not reached; RP, randomized phase.

[a] Generalized estimating equation model for zirconium cyclosilicate dose vs placebo.

[b] Fisher exact test for zirconium cyclosilicate dose vs placebo.

[c] Logistic regression.

[d] 2-Sample *t* test for zirconium cyclosilicate dose vs placebo.

[e] Linear regression. Normokalemic days counted only if both the beginning and end assessments for that time interval displayed normal serum potassium values.

[f] Wilcoxon-Gehan test for zirconium cyclosilicate dose vs placebo.

[g] Analysis-of-covariance test for zirconium cyclosilicate dose vs placebo.

[h] US sites only; differences reported are between the open-label phase baseline and randomized phase day 29.

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Table 3. Adverse Events Occurring in 5% or More of Patients in Any Group and All Serious Adverse Events

	No. (%)				
	Open-Label Phase (Zirconium Cyclosilicate, 10 g) (n = 258)	Randomized Phase			
		Placebo Group (n = 85)	Zirconium Cyclosilicate Dose Group		
			5 g (n = 45)	10 g (n = 51)	15 g (n = 56)
Adverse Events					
Any event	20 (7.8)	27 (31.8)	24 (53.3)	15 (29.4)	25 (44.6)
Blood and lymphatic system disorders					
Anemia	0	0	0	0	3 (5.4)
Gastrointestinal disorders					
Constipation	2 (0.8)	6 (7.1)	0	1 (2.0)	1 (1.8)
General disorders and administration site conditions					
Edema[a]	0	2 (2.4)	1 (2.2)	3 (5.9)	8 (14.3)
Metabolism and nutrition disorders					
Hypokalemia (all)	0	0	0	5 (9.8)	6 (10.7)
Hypokalemia (reported as adverse event)	0	0	0	0	1 (1.8)
Infections and infestations					
Nasopharyngitis	0	1 (1.2)	0	0	3 (5.4)
Upper respiratory tract infection	1 (0.4)	1 (1.2)	3 (6.7)	1 (2.0)	1 (1.8)
Serious Adverse Events[b]					
Any event	0	0	5 (11.1)	2 (3.9)	3 (5.4)
Cardiac disorders					
Cardiac failure, congestive	0	0	1 (2.2)	0	0
Myocardial infarction	0	0	0	1 (2.0)	0
Gastrointestinal disorders					
Small intestinal obstruction	0	0	1 (2.2)	0	0
General disorders and administration site conditions					
Generalized edema	0	0	0	0	1 (1.8)
Hepatobiliary disorders					
Hepatotoxicity	0	0	1 (2.2)	0	0
Cellulitis	0	0	0	1 (2.0)	0
Pneumonia	0	0	1 (2.2)	0	1 (1.8)
Psychiatric disorders					
Confusional state	0	0	1 (2.2)	0	0
Respiratory, thoracic, and mediastinal disorders					
Dyspnea	0	0	0	0	1 (1.8)

[a] Including generalized and peripheral edema.

[b] None of the serious adverse events were deemed by the investigator to be related to study treatment. An adverse event was considered serious if it was life threatening or resulted in death, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

and other SPS preparations have led to calls to significantly limit their clinical use.[11,12,35-37] Moreover, the poor gastrointestinal tolerability of polymer exchange resins makes these agents generally unsuitable for chronic use. Therefore, there is a substantial need for novel, effective, and safe treatment strategies in patients with hyperkalemia.

Zirconium cyclosilicate is unique in its potassium-lowering mechanism, which offers several potential benefits compared with currently available treatments. One advantage over polymer resins is that the crystal structure of zirconium cyclosilicate selectively entraps potassium in the intestinal tract, thereby limiting potassium's enteric recirculation.[38] In addition, zirconium cyclosilicate is substantially (ie, >125 times) more selective for potassium than organic polymer exchange resins that also bind calcium and magnesium and hence can cause hypocalcemia and hypomagnesemia.[38] Zirconium cyclosilicate binds potassium throughout the gastrointestinal tract, including potassium in food, which may explain its rapid onset of action. Zirconium cyclosilicate is insoluble, does not expand on contact with water, and is not systemically absorbed, which may explain its tolerability.[38]

In this study, we observed a favorable safety and tolerability profile for zirconium cyclosilicate, with no major treatment-related SAEs. Treatment-related AEs, including gastrointestinal AEs, were comparable across the groups. Edema was observed more frequently with 15-g zirconium cyclosilicate dose than with the other doses or with placebo; however, this difference might be explained by significantly higher baseline rates of heart failure and eGFR less than 60 mL/min/1.73 m^2 and higher baseline levels of brain natriuretic peptide among

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patients randomized to receive the 15-g dose compared with placebo. There was a numerically higher rate of hypokalemia with higher zirconium cyclosilicate doses, which is expected given its mechanism of action; all episodes of hypokalemia were mild and were corrected with protocol-directed dose adjustments. Nevertheless, monitoring for hypokalemia and appropriate dose optimization should be incorporated with higher doses of zirconium cyclosilicate.

This study should be interpreted in the context of several potential limitations. First, some patient groups that may benefit from potassium-lowering treatments, such as those receiving dialysis, were not included. However, a substantial proportion of patients in the study (36%) had severe CKD (stages 4 and 5). Second, because this study focused on the effects of zirconium cyclosilicate for up to 4 weeks in the outpatient setting, hospitalized patients and those with life-threatening arrhythmias were also excluded. The effectiveness and safety of zirconium cyclosilicate in these patient groups will need to be demonstrated in future studies. Third, the randomized study duration was 28 days, and clinical outcomes other than potassium levels were not assessed. Whether better control of chronic hyperkalemia will improve long-term patient outcomes, such as survival and quality of life, remains to be established.

Conclusions

Among ambulatory patients with hyperkalemia, open-label administration of sodium zirconium cyclosilicate reduced serum potassium levels to the normal range within 48 hours, and in the randomized phase, compared with placebo, administration of all 3 doses of zirconium cyclosilicate resulted in lower potassium levels and a higher proportion of patients with normal potassium levels for up to 28 days. Further studies are needed to evaluate the efficacy and safety of zirconium cyclosilicate beyond 4 weeks and to assess long-term clinical outcomes.

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Study concept and design: Kosiborod, Rasmussen, Lavin.
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REFERENCES

1. Khanagavi J, Gupta T, Aronow WS, et al. Hyperkalemia among hospitalized patients and association between duration of hyperkalemia and outcomes. *Arch Med Sci*. 2014;10(2):251-257.

2. An JN, Lee JP, Jeon HJ, et al. Severe hyperkalemia requiring hospitalization: predictors of mortality. *Crit Care*. 2012;16(6):R225.

3. Jain N, Kotla S, Little BB, et al. Predictors of hyperkalemia and death in patients with cardiac and renal disease. *Am J Cardiol*. 2012;109(10):1510-1513.

4. Navaneethan SD, Nigwekar SU, Sehgal AR, Strippoli GF. Aldosterone antagonists for preventing the progression of chronic kidney disease: a systematic review and meta-analysis. *Clin J Am Soc Nephrol*. 2009;4(3):542-551.

5. Ahn SY, Ryu J, Baek SH, et al. Incident chronic kidney disease and newly developed complications related to renal dysfunction in an elderly population during 5 years: a community-based elderly population cohort study. *PLoS One*. 2013;8(12):e84467.

6. Palmer BF, Fenves AZ. Optimizing blood pressure control in patients with chronic kidney disease. *Proc (Bayl Univ Med Cent)*. 2010;23(3):239-245.

7. Vardeny O, Claggett B, Anand I, et al; Randomized Aldactone Evaluation Study (RALES) Investigators. Incidence, predictors, and outcomes related to hypo- and hyperkalemia in patients with severe heart failure treated with a mineralocorticoid receptor antagonist. *Circ Heart Fail*. 2014;7(4):573-579.

8. St Peter WL, Odum LE, Whaley-Connell AT. To RAS or not to RAS? the evidence for and cautions with renin-angiotensin system inhibition in patients with diabetic kidney disease. *Pharmacotherapy*. 2013;33(5):496-514.

9. Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med*. 2004;351(6):543-551.

10. Sterns RH, Rojas M, Bernstein P, Chennupati S. Ion-exchange resins for the treatment of hyperkalemia: are they safe and effective? *J Am Soc Nephrol*. 2010;21(5):733-735.

11. Harel Z, Harel S, Shah PS, Wald R, Perl J, Bell CM. Gastrointestinal adverse events with sodium polystyrene sulfonate (Kayexalate) use: a systematic review. *Am J Med*. 2013;126(3):264.e9-264.e24.

12. Yuan CM, Nee R, Little DJ, Abbott KC. Incidence of sodium polystyrene sulfonate-associated colonic necrosis. *Am J Med*. 2013;126(9):e13.

13. Aaron KJ, Sanders PW. Role of dietary salt and potassium intake in cardiovascular health and disease: a review of the evidence. *Mayo Clin Proc*. 2013;88(9):987-995.

14. Ash S, Singh B, Lavin P, Stavros F, Rasmussen H. Safety and efficacy of ZS-9, a novel selective cation trap, for treatment of hyperkalemia in CKD patients [abstract]. *J Am Soc Nephrol*. 2013;24:2B.

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15. El Shahawy M, Rasmussen H, Lavin P, Yang A, Packham D. Acute-phase efficacy in a phase 3 multicenter, randomised, double-blind, placebo-controlled trial of ZS-9 for hyperkalaemia. Poster presented at 51st European Renal Association and European Dialysis and Transplant Association Congress 2014. http://www.postersessiononline.eu/pr/aula_poster.asp?congreso=796093165. Accessed October 24, 2014.

16. Weinberg JM, Appel LJ, Bakris G, et al; African American Study of Hypertension and Kidney Disease Collaborative Research Group. Risk of hyperkalemia in nondiabetic patients with chronic kidney disease receiving antihypertensive therapy. *Arch Intern Med*. 2009;169(17):1587-1594.

17. Rossignol P, Dobre D, McMurray JJ, et al. Incidence, determinants, and prognostic significance of hyperkalemia and worsening renal function in patients with heart failure receiving the mineralocorticoid receptor antagonist eplerenone or placebo in addition to optimal medical therapy: results from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF). *Circ Heart Fail*. 2014;7(1):51-58.

18. Vardeny O, Cavallari LH, Claggett B, et al; Randomized Aldactone Evaluation Study (RALES) Investigators. Race influences the safety and efficacy of spironolactone in severe heart failure. *Circ Heart Fail*. 2013;6(5):970-976.

19. Burton P, Gurrin L, Sly P. Extending the simple linear regression model to account for correlated responses: an introduction to generalized estimating equations and multi-level mixed modelling. *Stat Med*. 1998;17(11):1261-1291.

20. Einhorn LM, Zhan M, Hsu VD, et al. The frequency of hyperkalemia and its significance in chronic kidney disease. *Arch Intern Med*. 2009;169(12):1156-1162.

21. McMahon GM, Mendu ML, Gibbons FK, Christopher KB. Association between hyperkalemia at critical care initiation and mortality. *Intensive Care Med*. 2012;38(11):1834-1842.

22. Goyal A, Spertus JA, Gosch K, et al. Serum potassium levels and mortality in acute myocardial infarction. *JAMA*. 2012;307(2):157-164.

23. Svensson M, Gustafsson F, Galatius S, Hildebrandt PR, Atar D. How prevalent is hyperkalemia and renal dysfunction during treatment with spironolactone in patients with congestive heart failure? *J Card Fail*. 2004;10(4):297-303.

24. Fordjour KN, Walton T, Doran JJ. Management of hyperkalemia in hospitalized patients. *Am J Med Sci*. 2014;347(2):93-100.

25. Łoniewski I, Wesson DE. Bicarbonate therapy for prevention of chronic kidney disease progression. *Kidney Int*. 2014;85(3):529-535.

26. Blumberg A, Weidmann P, Ferrari P. Effect of prolonged bicarbonate administration on plasma potassium in terminal renal failure. *Kidney Int*. 1992;41(2):369-374.

27. Abramowitz MK, Melamed ML, Bauer C, Raff AC, Hostetter TH. Effects of oral sodium bicarbonate in patients with CKD. *Clin J Am Soc Nephrol*. 2013;8(5):714-720.

28. Goraya N, Wesson DE. Dietary management of chronic kidney disease: protein restriction and beyond. *Curr Opin Nephrol Hypertens*. 2012;21(6):635-640.

29. Kuijvenhoven MA, Haak EA, Gombert-Handoko KB, Crul M. Evaluation of the concurrent use of potassium-influencing drugs as risk factors for the development of hyperkalemia. *Int J Clin Pharm*. 2013;35(6):1099-1104.

30. Cohn JN. Reducing cardiovascular risk by blockade of the renin-angiotensin-aldosterone system. *Adv Ther*. 2007;24(6):1290-1304.

31. Kessler C, Ng J, Valdez K, Xie H, Geiger B. The use of sodium polystyrene sulfonate in the inpatient management of hyperkalemia. *J Hosp Med*. 2011;6(3):136-140.

32. Scherr L, Ogden DA, Mead AW, Spritz N, Rubin AL. Management of hyperkalemia with a cation-exchange resin. *N Engl J Med*. 1961;264:115-119.

33. Flinn RB, Merrill JP, Welzant WR. Treatment of the oliguric patient with a new sodium-exchange resin and sorbitol; a preliminary report. *N Engl J Med*. 1961;264:111-115.

34. Watson M, Abbott KC, Yuan CM. Damned if you do, damned if you don't: potassium binding resins in hyperkalemia. *Clin J Am Soc Nephrol*. 2010;5(10):1723-1726.

35. Watson MA, Baker TP, Nguyen A, et al. Association of prescription of oral sodium polystyrene sulfonate with sorbitol in an inpatient setting with colonic necrosis: a retrospective cohort study. *Am J Kidney Dis*. 2012;60(3):409-416.

36. Tongyoo A, Sriussadaporn E, Limpavitayaporn P, Mingmalairak C. Acute intestinal obstruction due to Kalimate, a potassium-lowering agent: a case report and literature review. *J Med Assoc Thai*. 2013;96(12):1617-1620.

37. Castillo-Cejas MD, De-Torres-Ramírez I, Alonso-Cotoner C. Colonic necrosis due to calcium polystyrene sulfonate (Kalimate) not suspended in sorbitol. *Rev Esp Enferm Dig*. 2013;105(4):232-234.

38. Yang A, Leon A, Nuttall M, Low J, Rasmussen H. In vitro ion exchange capacity and selectivity of ZS-9, a novel, selective cation trap for the treatment of hyperkalemia. *Am J Kidney Dis*. 2014;63(5):B115.

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