



Published in final edited form as:

Kidney Int. 2018 February ; 93(2): 325–334. doi:10.1016/j.kint.2017.08.038.

Revisiting RAAS-blockade in CKD with newer potassium binding drugs

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Abstract

Among patients with proteinuric chronic kidney disease (CKD), current guideline recommendations mandate the use of agents blocking the renin-angiotensin-aldosterone-system (RAAS) as first-line antihypertensive therapy on the basis of randomized trials demonstrating that RAAS-inhibitors are superior to other antihypertensive drug classes in showing nephropathy progression to end-stage-renal-disease. However, the opportunities to adequate RAAS-blockade in CKD are often limited and an important impediment is the risk for hyperkalemia, especially when RAAS-inhibitors are used in maximal doses or are combined. Accordingly, a large proportion of patients with proteinuric CKD may not have the anticipated renoprotective benefits, since RAAS-blockers are often discontinued due to incident hyperkalemia or administered at suboptimal doses for fear of developing hyperkalemia. Two newer potassium-binders, patiromer and sodium zirconium cyclosilicate (ZS-9), have been shown to effectively and safely reduce serum potassium levels and maintain long-term normokalemia in CKD patients receiving background therapy with RAAS-inhibitors. Whether these novel potassium-lowering therapies can overcome the barrier of hyperkalemia and enhance the tolerability of RAAS-inhibitor use in proteinuric CKD awaits randomized trials.

Keywords

RAAS-blockade; chronic kidney disease; hyperkalemia; patiromer; sodium zirconium cyclosilicate

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DISCLOSURE

Conflicts of Interest

R.A. has consulted for Abbvie, Amgen, Astra Zeneca, Bayer, Boehringer Ingelheim, Celgene, Daiichi Sankyo Inc, Eli Lilly, Gilead, Glaxosmithkine, Johnson & Johnson, Merck, Novartis, Sandoz, Relypsa, and ZS Pharma. P.I.G. declares no competing interests.

INTRODUCTION

Among patients with proteinuric chronic kidney disease (CKD), guidelines mandate the use of agents blocking the renin-angiotensin-aldosterone-system (RAAS) based on randomized clinical trials (RCTs) demonstrating that these agents are superior to other antihypertensive drug classes in retarding the progression of kidney failure to end-stage-renal-disease (ESRD).¹⁻⁵ Unlike the strong guideline recommendations, the opportunities to provide adequate RAAS-blockade are often limited, due to the risk of inducing hyperkalemia, for example in patients with increased risk, such as those with an estimated-glomerular-filtration-rate (eGFR) <45 ml/min/1.73m², diabetes or heart failure.^{6,7}

In addition to the above, the premature termination of some RCTs evaluating the potential renal benefits of dual RAAS-blockade due to excess risk of hyperkalemia and acute kidney injury (AKI)^{8,9} indicates that in the absence of a more effective treatment of hyperkalemia, the use of RAAS-blockade towards renoprotection in proteinuric CKD may have reached its limit. A 2015 network meta-analysis revives the concept of combined RAAS-blockade as an effective approach to prevent ESRD among patients with diabetic nephropathy.¹⁰ Recent advances in the management of hyperkalemia with the 2015 Food and Drug Administration (FDA) approval of patiromer and the development of sodium zirconium cyclosilicate (ZS-9)^{11,12} that awaits approval offer hope that these novel potassium-binders may reduce the high discontinuation rates of RAAS-blockers and possibly enable their use at higher doses or in combination therapy.

In this article, we provide an overview of the risk of hyperkalemia with the use RAAS-blockers in CKD patients. We also discuss recent RCTs evaluating the efficacy and safety of new potassium-binders in hyperkalemic patients treated with RAAS-blockers and we conclude with an overview of ongoing trials and directions for future research.

OVERVIEW OF HYPERKALEMIA IN CKD PATIENTS TREATED WITH RAAS-BLOCKERS

Among patients with uncomplicated hypertension treated with RAAS-inhibitor monotherapy, the incidence of hyperkalemia is as low as 2%.⁷ Risk factors for hyperkalemia in CKD are as follows: eGFR <45 ml/min/1.73m², baseline sK⁺ ≥ 4.5 mEq/L, older age, co-existence of diabetes or heart failure and RAAS-blockade.^{6,8,9,12,13}

Incidence of hyperkalemia in randomized trials

The clear renoprotective action of angiotensin-converting-enzyme-inhibitors (ACEIs) and/or angiotensin-receptor-blockers (ARBs) demonstrated in phase III trials enrolling patients with proteinuric nephropathy should be balanced against the associated risk of hyperkalemia (Table 1).¹⁴⁻¹⁹ In the Irbesartan Diabetic Nephropathy Trial (IDNT),¹⁸ 1,715 patients with type 2 diabetic nephropathy were randomized to irbesartan (300 mg/day), amlodipine (10 mg/day) or placebo for 2.6 years. The incidence of hyperkalemia (defined as sK⁺ ≥ 6.0 mEq/L) was 18.6% in irbesartan-treated participants versus 6% in placebo-treated participants (P<0.001).¹⁸ In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL),¹⁵ 1,513 patients with overt diabetic nephropathy were

randomized to losartan (50–100 mg/day) or placebo, both administered in addition to conventional antihypertensive therapy. Losartan increased the risk for hyperkalemia versus placebo [Hazard Ratio (HR): 2.0; 95% Confidence Interval (CI): 1.56–2.57].¹⁵ In a post-hoc analysis,²⁰ the incidence of hyperkalemia (defined as $sK \geq 5.5$ mEq/L) over the first 6 months was 10.8% in losartan-treated participants versus 5.1% in placebo-treated participants. Losartan treatment was independent predictor of incident hyperkalemia at 6 months [Odds Ratio (OR): 2.80; 95% CI: 2.00–3.90].²⁰

The effect of RAAS-blockade on potassium balance among patients with non-diabetic CKD was investigated in the African American Study of Kidney Disease (AASK).¹⁹ In this trial, 1,094 African-Americans with hypertensive nephrosclerosis and macroalbuminuria were randomized to achieve goal mean arterial pressure 102–107 mmHg or ≥ 92 mmHg and to initial therapy with metoprolol (2.5–10 mg/day), ramipril (2.5–10 mg/day) or amlodipine (5–10 mg/day) in a 3×2 factorial design.¹⁹ In a secondary analysis stratified according to the baseline level of eGFR, the incidence of hyperkalemia was 11.2% in the stratum of eGFR ≤ 40 ml/min/1.73m² versus only 1.6% in those with baseline eGFR >40 ml/min/1.73m².²¹ Ramipril treatment was associated with higher risk for hyperkalemia as compared with amlodipine (HR: 7.00; 95% CI: 2.29–21.39) and metoprolol (HR: 2.85; 95% CI: 1.50–5.42).²¹

Dual RAAS-blockade—Phase III trials revealed that the approach of combining an ACEI with an ARB, although potentially beneficial in enhancing the anti-proteinuric effect of monotherapy, aggravates the risk of hyperkalemia and AKI (Table 2). In the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET),¹³ 25,620 patients with high cardiovascular risk profile were randomized to ramipril (10 mg/day), telmisartan (80 mg/day) or their combination for 56 months. The incidence of hyperkalemia (defined as $sK \geq 5.5$ mEq/L) was higher in the combination arm relative to monotherapy (1.29 vs 0.74 hyperkalemic events per 100 patients-months of follow-up, $P < 0.001$).¹³ In the Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE),⁹ 8,561 type 2 diabetic patients with CKD, cardiovascular disease or both were randomized to aliskiren (300 mg/day) or placebo in addition to standard therapy with an ACEI or ARB. This trial was prematurely terminated due to excess risk of hypotension (12.1% vs 8.3%, $P < 0.001$) and hyperkalemia (11.2% vs 7.2%, $P < 0.001$) in the combination group.⁹ The Veteran’s Administration Nephron-Diabetes Trial (VA-NEPHRON-D) was also prematurely stopped owing to safety concerns.⁸ In this trial, 1,448 patients with type 2 diabetic nephropathy already treated with losartan (100 mg/day) were randomized to lisinopril (10–40 mg/day) or placebo. Combination therapy was associated with 70% excess risk for AKI (HR: 1.70; 95% CI: 1.3–2.2) and 2.8-fold higher risk for hyperkalemia (HR: 2.8; 95% CI: 1.8–4.3).⁸ When the VA-NEPHRON-D trial was closed, dual RAAS-blockade showed a strong trend to lowering the risk of ESRD versus monotherapy (HR: 0.66; 95% CI: 0.41–1.07, $P = 0.07$).⁸ This trend suggests a potential emerging signal for renoprotection with combination therapy.²²

The notion that the premature termination of the VA-NEPHRON-D should not be conclusively considered as the end of dual RAAS-blockade is supported by a 2015 network meta-analysis of 157 RCTs incorporating data from 43,256 participants with diabetic kidney

disease.¹⁰ This meta-analysis showed that dual RAAS-blockade was associated with 38% reduced risk for incident ESRD versus placebo (OR: 0.62; 95% CI: 0.43–0.90). Combination therapy increased the risks of hyperkalemia (OR: 2.69; 95% CI: 0.97–7.47) and AKI (OR: 2.69; 95% CI: 0.98–7.38),¹⁰ but the 95% CI of the ORs crossed 1.0.

Add-on therapy with mineralocorticoid-receptor-antagonists (MRAs) may be an alternative approach to enhance the renoprotective action of monotherapy with ACEIs/ARBs. An earlier meta-analysis of 11 RCTs showed that MRA therapy induced an additive reduction in proteinuria [Weighted Mean Difference (WMD): –0.8 g/day; 95% CI: –1.27 to –0.33 g/day]. This anti-proteinuric effect was accompanied by a slower eGFR decline over time that was not significant (WMD: –0.70 ml/min/1.73m²; 95% CI: –4.73 to 3.34 ml/min/1.73m²). However, MRA therapy increased the risk for hyperkalemia (RR: 3.06; 95% CI: 1.26–7.41).²³ A subsequent meta-analysis of 27 RCTs confirmed that MRA therapy offers an additive proteinuria-lowering effect [Standardized Mean Difference (SMD): –0.61; 95% CI: –1.08 to –0.13], but raises the risk of hyperkalemia (RR: 2.0; 95% CI: 1.25–3.20).²⁴ Phase III trials evaluating the effect of add-on MRA therapy on nephropathy progression are unavailable.

A newly-introduced, selective, non-steroidal MRA named finerenone offers promise for similarly effective anti-proteinuric action with established steroidal MRAs, without causing a significant sK elevation.²⁵ The efficacy of finerenone was tested in the Mineralocorticoid Receptor Antagonist Tolerability Study–Diabetic Nephropathy (ARTS-DN) trial,²⁶ in which 821 diabetic patients with high or very high albuminuria already treated with ACEIs/ARBs were randomized to finerenone (1.25–20 mg/day) or placebo. Finerenone improved albuminuria in a dose-dependent manner; the UACR was reduced by 33% and 38% versus baseline in the groups of 15 and 20 mg/day, whereas the incidence of hyperkalemia was as low as 4.1% and 2.6%, respectively.²⁶ However, the slight sK elevation in response to finerenone therapy could, at least partially, be explained by the lower risk of ARTS-DN participants for developing hyperkalemia. Above 60% of study participants had an eGFR >60 ml/min/1.73m² at baseline, whereas patients with sK >4.8 mEq/L at screening visit and those with eGFR <45 ml/min/1.73m² under treatment with a potassium-sparing were excluded.²⁶ Phase III trials with finerenone to demonstrate cardio-renal protection with lower hyperkalemia risk in those with diabetic nephropathy are ongoing and will better clarify the risk for hyperkalemia in relationship to the perceived benefits for the heart and kidney.²⁵

Incidence of hyperkalemia in observational studies

The association of RAAS-blockade with hyperkalemia development was explored in a number of observational studies summarized in Table 3. In a cohort of 1,818 outpatients initiating ACEI therapy in a Veterans Affairs Medical Center in USA during 1992–1993, the incidence of hyperkalemia was 11%.²⁷ Over a 1-yearlong follow-up, the re-occurrence of severe hyperkalemia (defined as sK >6 mEq/L) in patients remaining on an ACEI was 10%.²⁷ In a subsequent retrospective analysis of CKD patients starting an ACEI-based therapy during 1998–2006, 2.8% out of 5,171 participants developed hyperkalemia; older age, history of diabetes or heart failure, the use of potassium-sparing diuretics and a high ACEI dose were independent predictors of hyperkalemia.²⁸ In a small interventional study of 46

patients with stage 3–4 CKD and resistant hypertension, add-on MRA therapy was associated with a mean sK elevation of 0.4 mEq/L, with 17.3% of patients manifesting hyperkalemia during follow-up.²⁹

To investigate the incidence of hyperkalemia, Einhorn et al.³⁰ performed a retrospective analysis of electronic records of 245,808 patients cared for over a single year in the Veterans Health Administration in USA. The overall incidence of hyperkalemia during 2005 was 3.2%. RAAS-inhibitor use was associated with 41% increased risk of hyperkalemia (OR: 1.41; 95% CI: 1.37–1.44).³⁰ After multivariate adjustment, the incidence of hyperkalemia among patients treated with RAAS-blockers was higher in those with compared to those without CKD (Incidence rate: 7.67 vs 2.30 events per 100 patients-months of follow-up).³⁰

Mortality hazard associated with hyperkalemia in CKD patients

Observational cohort studies suggest a U-shaped association between sK levels and mortality in CKD patients (Table 4).^{31–33} In a prospective analysis of 820 patients participating in the Renal Research Institute CKD (RRI-CKD) study,³¹ compared with normokalemic patients (i.e., sK 4.0–5.5 mmol/L), those with a time-varying sK < 4 mmol/L (HR: 1.73; 95% CI: 1.02–2.95) as well as those with sK >5.5 mmol/L (HR: 1.57; 95% CI: 0.78–3.20) had increased mortality risk over 2.6 years of follow-up.³¹

A subsequent analysis of 36,359 CKD patients enrolled in an electronic medical record registry during 2005–2009, compared with the reference category of sK 4.0–4.9 mmol/L, a time-varying sK <3.5 mmol/L (HR: 1.95; 95% CI: 1.74–2.18) and a sK >5.5 mmol/L (HR: 1.65; 95% CI: 1.48–1.84) were both associated with excess mortality over a mean follow-up of 2.6 years.³³ In another retrospective analysis of 56,266 patients with stage 3–4 CKD enrolled in an electronic registry of HealthCare Partners in California during 2009–2013,³² hypokalemia defined as sK <3.5 mEq/L [Incidence Rate Ratio (IRR): 3.05; 95% CI: 2.53–3.68] and hyperkalemia defined as sK >6 mEq/L were both associated with increased mortality (IRR: 3.31; 95% CI: 2.52–4.34).³²

The association of sK levels with mortality was explored in a cohort of 2,662,462 US veterans participating in the Racial and Cardiovascular Risk Anomalies in Chronic Kidney Disease (RCAV) Study.³⁴ Using the sK level 4.2 mmol/l as reference standard, both higher and lower sK was associated with higher mortality hazard. This U-shaped pattern was fairly similar in African-Americans and non African-Americans, suggesting that race did not modify the risk relationship of sK with mortality.³⁴

Non-mortal associations of hyperkalemia

Apart from the direct association of hyperkalemia with mortality, hyperkalemia may be associated with physician reluctance to provide adequate RAAS-blockade. In a recent analysis of 194,456 outpatients enrolled in the Geisinger Health System, hyperkalemia (defined as sK >5.5 mEq/L) occurred in 2.3% of study participants over a 3-year-long follow-up.³⁵ The occurrence of a hyperkalemic event resulted in alterations in the antihypertensive regimen in 26.4% of cases. The most commonly recorded medication change was discontinuation and/or dose reduction of RAAS-inhibitors or potassium-sparing diuretics (29.1% and 49.6% of people receiving these medications, respectively).³⁵ In the

aforementioned electronic registry of HeathCare Partners in California, the occurrence of hyperkalemia was associated with a higher likelihood of discontinuing RAAS-blockers regardless of the eGFR level (IRR: 1.70, 2.21, 1.71 and 1.81 for eGFR strata 50–59, 40–49, 30–39 and <30 ml/min/1.73m² respectively, P<0.001 for all strata).³² Whether discontinuing RAAS-blockers alters cardiovascular and renal risk in those prone to hyperkalemia is unknown.

POTASSIUM-BINDERS FOR LONG-TERM MANAGEMENT OF HYPERKALEMIA IN CKD

Sodium polystyrene sulfonate

Sodium polystyrene sulfonate (SPS), a resin that exchanges potassium for sodium in the large intestine, was approved by the FDA in 1958 and has become an important part of hyperkalemia management.^{6,11,12} Given that the FDA approval of drugs before 1962 was not necessarily evidence-based, it is unsurprising that RCTs to prove the efficacy and safety of SPS are absent.³⁶ Earlier uncontrolled interventional studies revealed that the potassium-lowering effect of SPS is associated with the pretreatment sK levels;³⁷ this observation suggests that the major factor determining the efficacy of SPS is the severity of hyperkalemia.

In a 2015 RCT, 33 outpatients with CKD and mild hyperkalemia (sK: 5–5.9 mEq/L) were randomly assigned to SPS (30 g orally once daily) or placebo for 7 days.³⁸ SPS was superior to placebo in reducing sK (between-group difference: –1.04 mEq/L; 95% CI: –1.37 to –0.71, P<0.001), without significant increase in the incidence of hypernatremia and gastrointestinal side-effects.³⁸ Owing to the short duration of therapy, this trial cannot support the safety of SPS for long-term hyperkalemia management. The current clinical experience suggests that the long-term use of SPS is associated with volume overload, hypernatremia, diarrhea and gastrointestinal intolerance.^{6,11,12}

Importantly, in 2009, the FDA released a black box warning for SPS on the basis of accumulated data showing a high incidence of colonic necrosis attributable to this compound.^{39–41} A 2013 meta-analysis of adverse gastrointestinal adverse effects of SPS identified 30 reports encompassing 58 patients.³⁹ Colon was the most frequent site of injury in 76% of the cases, transmural necrosis the most common pathology (62%) and the gastrointestinal injury was associated with a mortality rate of 33%.³⁹ This potentially life-threatening complication is a serious safety concern, particularly when SPS is combined with sorbitol, but can also occur without sorbitol. The authors of the meta-analysis identified as risk factors for gastrointestinal injury with SPS use as kidney disease, transplantation, and a post-operative state.³⁹

Newer potassium-blindners

Two newer potassium-bindingers, patiromer and ZS-9, have been evaluated in phase II and III RCTs, showing excellent potassium-lowering efficacy, highly predictable dose-response relationship and favorable side-effect profile.^{6,11,12} Patiromer is an FDA-approved, organic, non-absorbed, sodium-free, potassium-binding polymer that exchanges potassium for

calcium in the gastrointestinal track (Figure 1).^{42–44} ZS-9 is a non-absorbed, insoluble, inorganic crystal, which selectively entraps potassium in the gastrointestinal tract in exchange for sodium and hydrogen (Figure 2).^{42,43,45} Similarities and differences between older and newer potassium-binders in their pharmacological characteristics and side-effect profile are provided in Table 5. The results of phase II and III RCTs evaluating efficacy and safety of patiomer and ZS-9 is summarized in Table 6 and discussed further below.

Studies with Patiomer—In the Evaluation of RLY5016 in Heart Failure Patients (PEARL-HF) trial,⁴⁶ 105 patients with heart failure and a history of hyperkalemia resulting in discontinuation of RAAS-inhibitors and/or β -blockers within the 6 previous months or CKD were randomized to double-blind patiomer (30 g/day) or placebo for 4 weeks. Study participants were also administered spironolactone, initiated at 25 mg/day, a dose that was up-titrated to 50 mg/day at Day 15, if sK was <5.1 mEq/L. Compared with placebo, patiomer significantly lowered sK levels during follow-up, with a between-group difference of -0.45 mEq/L ($P<0.001$); the incidence of hyperkalemia was lower (7.3% vs 24.5%, $P=0.015$) and the proportion of patients on spironolactone 50 mg/day was higher (91% vs 74%, $P=0.019$) in patiomer-treated participants.⁴⁶ Side effects were mainly gastrointestinal (patiomer group 21% vs placebo group 6%). The rate of drug discontinuation was identical in both study arms (7% vs 6%).⁴⁶ The most important finding of the PEARL-HF trial was that patiomer enabled the administration of spironolactone in a larger proportion of patients having the indication of MRA therapy, despite their propensity for hyperkalemia.

In the two-part, single-blind, phase 3 study evaluating the efficacy and safety of patiomer for the treatment of hyperkalemia (OPAL-HK) trial,⁴⁷ 243 hyperkalemic patients with stage 3–4 CKD already treated with RAAS-blockers entered an initial 4-week, single-blind treatment phase, during which patiomer was administered at an initial dose of 4.2 g or 8.4 g twice daily. Participants with baseline sK 5.5–6.5 mmol/L, in whom sK was lowered at a level ranging from 3.8 to 5.1 mmol/l at the end of this phase, entered a subsequent 8-week, randomized, placebo-controlled withdrawal phase. In this part of the trial, patients were randomized to continue patiomer at the same dose as their week 4 dose in the initial phase or switched over to placebo.⁴⁷ In the initial phase, a significant reduction of 1.01 ± 0.03 mmol/l in sK was noted. In the randomized withdrawal phase, a significant elevation of 0.72 mmol/l in sK was noted with placebo, whereas sK remained unchanged in those randomized to continue patiomer. The proportion of patients with recurrent hyperkalemia during the withdrawal phase was 4-fold higher with placebo than with patiomer (60% vs 15%, $P<0.001$). The most commonly reported adverse event was mild-to-moderate constipation.⁴⁷

Treatment of hyperkalemia in patients with hypertension and diabetic nephropathy (AMETHYST-DN) was a phase II, multi-centre, open-label, randomized, dose-ranging trial aiming to evaluate the long-term potassium-lowering efficacy and safety of patiomer in hyperkalemic patients with diabetic nephropathy already treated with RAAS-blockers.⁴⁸ Study participants were classified into mild or moderate hyperkalemia strata according to the level of baseline sK and were randomized to different starting doses of patiomer (mild stratum: 4.2, 8.4 or 12.6 g twice daily; moderate stratum: 8.4, 12.6 or 16.8 g twice daily). Study investigators were allowed to up-titrate these doses aiming to maintain sK <5 mEq/L during follow-up.⁴⁸ Between the baseline and week 4, significant reductions of -0.47 ± 0.04

mEq/L and -0.92 ± 0.08 mEq/L in sK were noted in both mild and moderate hyperkalemia strata. During the maintenance phase (Week 4 – Week 52), significant reductions in sK levels were evident at each monthly follow-up visit in patients with mild and moderate hyperkalemia. Hypomagnesaemia (defined as serum magnesium <1.8 mg/dl), which was the most commonly reported adverse event, occurred in 7.2% of participants; hypokalemia (defined as sK <3.5 mEq/L) occurred in 5.6% of patients.⁴⁸ These electrolyte disturbances were not associated with higher incidence of cardiac arrhythmias during follow-up.

Studies with ZS-9—In a multi-centre, double-blind, phase III trial, 753 hyperkalemic patients with heart failure, CKD or diabetes were randomized to ZS-9 (at a dose of 1.25g, 2.5g, 5g or 10g) or placebo 3 times a day for 48 hours.⁴⁹ Patients reaching normokalemia at 48 hours had randomized withdrawal of the drug: ZS-9 or placebo once daily. The aim of this study was to investigate the efficacy of ZS-9 in maintaining normokalemia until Day 15. Significant dose-dependent reductions in sK levels were noted between the baseline and the evaluation at 48 hours (0.46 mmol/L in the 2.5g group, 0.54 mmol/L in the 5g group and 0.73 mmol/L in the 10g group, relative to a mean reduction of 0.25 mmol/L with placebo, $P < 0.001$ for all comparisons).⁴⁹ In the randomized withdrawal phase, ZS-9 was superior to placebo in maintaining normokalemia at Days 3 and 15; episodes of recurrent hyperkalemia were observed in patients assigned to placebo who had been treated with ZS-9 at doses of 5g and 10g during the initial phase of the trial.⁴⁹ The incidence of adverse events was not different between the active-treatment and placebo groups (initial phase: 12.9% vs 10.8%; maintenance phase: 25.1% vs 24.5%, respectively), with diarrhea being the most commonly reported complication.⁴⁹

In The Hyperkalemia Randomized Intervention Multidose ZS-9 Maintenance (HARMONIZE) study,⁵⁰ 258 hyperkalemic patients with CKD, heart failure or diabetes received ZS-9 at a dose of 10g 3 times daily for 48 hours in an initial open-label, non-randomized phase. Subsequently, those patients achieving normokalemia were randomized to double-blind ZS-9 (at doses of 5g, 10g, or 15g once daily) or placebo for 28 days. In the initial open-label phase, a mean reduction of -1.1 mEq/L (95% CI: -1.1 to -1.0 mEq/L, $P < 0.001$) in sK was noted from baseline to 48 hours; the proportion of patients achieving normokalemia at 48 hours was 98%. In the randomized phase, ZS-9 reduced sK during days 8–29 in a dose-dependent manner (differences relative to placebo: -0.3 , -0.6 and -0.7 mEq/L for 5g, 10g and 15g doses of ZS-9, respectively, $P < 0.001$ for all comparisons). The proportion of patients maintaining normokalemia was significantly higher in the active-treatment groups versus placebo.⁵⁰ Therapy with ZS-9 was well-tolerated and the incidence of adverse events was comparable between the active-treatment and placebo groups. ZS-9 increased the incidence of edema in a dose-dependent manner (2%, 6%, and 14% for 5g, 10g, and 15g ZS-9 doses vs 2% with placebo), but edema occurrence had no impact on the drug tolerability.⁵⁰ Since ZS-9 contains sodium, the release and absorption of sodium in the intestine is the most likely mechanistic explanation for the dose-dependent edema occurrence. The clinical importance of ZS-9-inducible sodium retention, particularly in susceptible patients with heart failure or CKD, remains to be elucidated in ongoing trials.

PERSPECTIVES

Currently available RCTs have demonstrated that newer potassium-lowering therapies can effectively and safely correct hyperkalemia and maintain normokalemia in patients receiving background treatment with RAAS-blockers.^{46–51} It has to be noted, however, that the long-term (i.e., >12 months) efficacy and safety of newer potassium-binders remains to be ascertained. Even with increased numbers in modern day RCTs of potassium binders, the power to identify with confidence rare events such as colonic necrosis is limited. Thus, real-world experience will be needed to establish the longer term safety of the newer agents. The low cost and the accumulated clinical experience with SPS should compel us to conduct additional RCTs to determine the role of SPS in the long-term management of hyperkalemia and explore its comparative effectiveness and safety with newer potassium-binders.

The next step is to evaluate whether newer potassium-binders may overcome the barrier of hyperkalemia and enable the administration of ACEIs/ARBs at higher doses or in combination in patients with anticipated benefits from such a therapeutic approach (i.e., patients with proteinuric nephropathy, patients with heart failure and reduced left ventricular ejection fraction). A step in this direction is the trial of spironolactone with.^{52,53} This ongoing phase II trial is planning to recruit 290 CKD patients with resistant hypertension and sK 4.3–5.1 mEq/L. Eligible patients will be randomized to spironolactone plus blinded patiromer or spironolactone plus blinded placebo and the primary endpoint is the between-group difference in the proportion of patients remaining on spironolactone after 12 weeks of therapy.⁵² The use of new potassium-binders towards cardiovascular and renal risk reduction with combined RAAS-blockade therapy will require phase III trials.

Another important area of investigation is the efficacy and safety of new potassium-binders in hemodialysis patients. This patient population is highly susceptible to hyperkalemia, particularly during the long interdialytic interval.⁵⁴ A small study showed that treatment with patiromer over 7 days reduced sK levels and enhanced fecal potassium excretion as compared with the pre-treatment 7-day period in 6 hyperkalemic hemodialysis patients;⁵⁵ these promising results enable the design of phase II trials aiming to evaluate the maintenance of normokalemia over a longer period.⁵⁶

Acknowledgments

Sources of support

R.A. is supported by NIH 5 R01 HL126903-02 and a grant from VA Merit Review 5I01CX000829-04.

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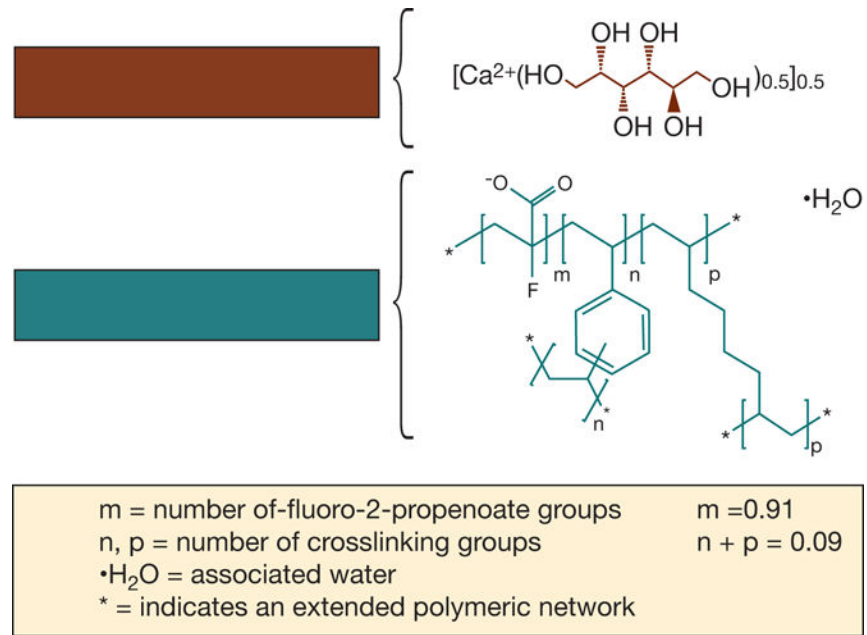


Figure 1. Chemical structure of patiomer and the calcium-sorbitol counter ion
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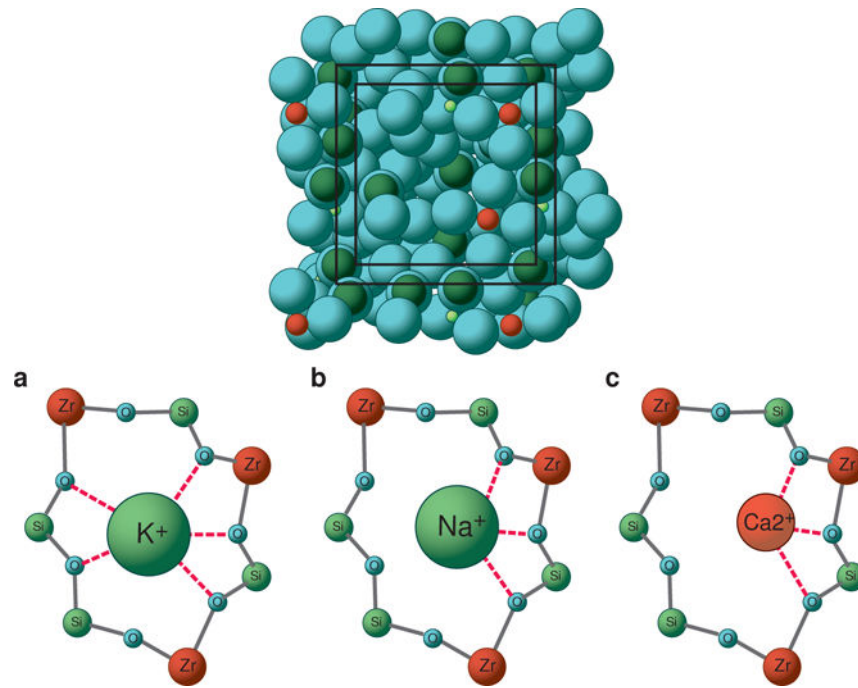


Figure 2. Structure of Sodium zirconium cyclosilicate

Pore detail with potassium ion (A), sodium ion (B), and calcium ion (C). Blue sphere indicates oxygen atoms; green spheres, silicon atoms; and red spheres, zirconium atoms. Reprinted from Stavros et al.⁴⁵ with permission of the publisher. Copyright: © 2014 Stavros et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Table 1
Major randomized controlled trials evaluating the effect of RAAS-blockade on renal outcomes and the associated risk of hyperkalemia among patients with proteinuric CKD

Study	Patient characteristics	N	Intervention	Follow-up	Effect on renal outcomes		Associated hyperkalemia risk			Ref	
					DScr	ESRD	Definition	Incidence in RAAS group	Incidence in control group		Comparison
Collaborate study group trial	Type 1 DM with overt nephropathy	409	Captopril (25 mg thrice daily) vs placebo	3 yrs	↓	↓	sK 6.0 mEq/L	1.4%	0%	non-significant	17
RENAAL	Type 2 DM with overt nephropathy	1,513	Losartan (50–100 mg/day) vs placebo	3.4 yrs	↓	↓	sK 5.5 mEq/L	24.2%	12.3%	HR:2.0; 95% CI: 1.56–2.57)	15
IDNT	Type 2 DM with overt nephropathy	1,715	Irbesartan (300 mg/d) vs Amlodipine (10 mg/d) vs placebo	2.6 yrs	↓	↓	sK 6.0 mEq/L	18.6%	6%	P<0.001 vs placebo	18
REIN-2	Non-diabetic, proteinuric CKD	352	Ramipril (5 mg/d) vs placebo	1.25 yrs	↓	↓	NR	NR	NR	NR	14
AASK	African-Americans with hypertensive nephrosclerosis	1,094	Ramipril (2.5–10 mg/d) vs metoprolol (50–200 mg/d) vs amlodipine (5–10 mg/d)	3–6.1 yrs	↓	↓	5.5 sK mEq/L	2.45 events per 100 patients-months	1.33 events per 100 patient-months	ACEI vs CCB; HR= 7.0; 95% CI:2.29–21.39; ACEI vs BB; HR= 2.85; 95% CI: 1.50–5.42.	19
Benazepril for advanced renal insufficiency	Advanced-stage, non-diabetic, proteinuric CKD	224	Benazepril (20 mg/d) vs placebo	3.4 yrs	↓	↓	sK 6.0 mEq/L	5.4%	4.5%	non-significant	16

Abbreviations: DM= diabetes mellitus; CV= cardiovascular; CKD= chronic kidney disease; ACEI= angiotensin-converting-enzyme-inhibitor; ARB= angiotensin-receptor-blocker; DScr= doubling of serum creatinine; ESRD= end-stage-renal-disease; RENAAL= Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; IDNT= Irbesartan Diabetic Nephropathy Trial; REIN-2= Ramipril-Efficacy-In-Nephropathy-2; AASK= African American Study of Kidney Disease

↓ indicates significant reduction versus control group

Major randomized controlled trials evaluating the effect of dual RAAS-blockade on renal outcomes and the associated risk of hyperkalemia.

Table 2

Study	Patient characteristics	N	Intervention	Follow-up	Effect on renal outcomes		Associated hyperkalemia risk				Ref
					DScr	ESRD	Definition	Incidence in dual RAAS group	Incidence in mono-therapy	Comparison	
ONTARGET	Established CV disease or high risk DM	26620	Ramipril (10 mg/d) vs telmisartan (80 mg/d) vs their combination	4.6 yrs	↑	↑	sK 5.5 mEq/L	1.29 events per 100 patient-years	0.74 events per 100 patient-years	P<0.001 vs monotherapy	13
ALTITUDE	Type 2 DM, CKD, CV disease or both	8651	Aliskiren (300 mg/d) vs placebo on top of background therapy with ACEI or ARB	2.7 yrs	No difference	No difference	sK 6.0 mEq/L	11.2%	7.2%	P<0.001 vs monotherapy	9
VA-NEPHRON-D	Type DM with overt nephropathy	1448	Lisinopril (10–40 mg/d) vs placebo on top of background therapy with losartan (100 mg/d)	2.2 yrs	No difference	No difference	sK 6.0 mmol/L	6.3 events per 100 patient-years	2.6 events per 100 patient-years	HR:2.80; 95% CI: 1.80–4.30, P<0.001 vs monotherapy	8

Abbreviations: DM= diabetes mellitus; CV= cardiovascular; CKD= chronic kidney disease; ACEI= angiotensin-converting-enzyme-inhibitor; ARB= angiotensin-receptor-blocker; DScr= doubling of serum creatinine; ESRD= end-stage-renal-disease; ONTARGET= Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial; ALTITUDE= Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints; VA-NEPHRON-D= Veteran’s Administration Nephron-Diabetes Trial;

Table 3

Reported in observational or non-randomized interventional studies incidence of hyperkalemia in CKD patients under treatment with RAAS-blockers

Patient characteristics	n	Year	Design	Follow-up	Definition of hyperkalemia	Reported incidence rate	Ref
CKD outpatients initiating an ACEI at a VA medical centre	1,818	1998	Observational cohort study	12 mo	>5.1 mmol/l	11%	27
Patients with resistant hypertension and stage 2-3 CKD who received spironolactone added to pre-existing BP-lowering therapies	46	2009	Single-arm, interventional study	1.5 mo	>5.5 mmol/L	17.3%	29
National US sample of veterans treated with ACEIs/ARBs during the fiscal year 2005	245,808 (70,873 with stage 3-4 CKD)	2009	Observational cohort study	12 mo	5.5 mEq/L	13.7% in CKD patients treated with ACEIs/ARBs	30
CKD outpatients initiating an ACEI-based antihypertensive regimen	5,171	2010	Observational cohort study	3 mo	>5.5 mmol/L	2.8%	28
Outpatients enrolled in the Geisinger Health System	194,456	2016	Registry study	3 yrs	>5.5 mmol/L	2.3%	31

Abbreviations: AASK= African American Study of Kidney Disease; ACEI= angiotensin-converting-enzyme-inhibitor; ARB= angiotensin-receptor-blocker; BP= blood pressure; CKD= chronic kidney disease;

Table 4 Observational cohort studies evaluating the association of serum potassium with all-cause mortality in patients with non-dialysis CKD

Patient characteristics	n	Year	Follow-up	Pattern of the association	Details	Ref
Stage 3–4 CKD patients participating in the Renal Research Institute CKD Study	820	2010	2.6 yrs	U-shaped	Time-varying SK of 4 mmol/L (HR: 1.73; 95% CI: 1.02–2.95) as well as time-varying SK >5.5 mmol/L were both associated with increased risk of ACM (HR: 1.57; 95% CI: 0.78–3.20)	31
CKD patients enrolled in an electronic medical record registry	36,359	2015	2.6 yrs	U-shaped	Time-varying SK <3.5 mmol/L (HR: 1.95; 95% CI: 1.74–2.18) and SK >5.5 mmol/L were both associated with ACM (HR: 1.65; 95% CI: 1.48–1.84)	32
Stage 3–4 CKD patients enrolled in an electronic registry of HealthCare Partners in California	55,266	2016	2.76 yrs	U-shaped	SK <3.5 mEq/L (IRR: 3.05; 95% CI: 2.53–3.68) and SK >6 mEq/L were both associated with ACM (IRR: 3.31; 95% CI: 2.52–4.34).	33
US veterans participating in the Racial and Cardiovascular Risk Anomalies in Chronic Kidney Disease (RCAV) study.	2,662,462	2017	5.9 yrs	U-Shaped	Compared to serum potassium level of 4.2 mmol/l, both higher and lower serum potassium levels were associated with higher risk of ACM regardless of the African-American race.	34

Abbreviations: ACM= all-cause mortality; CKD= chronic kidney disease; CI= confidence interval; HR= hazard ratio; IRR= incidence rate ratio; SK= serum potassium;

Table 5

Similarities and differences among sodium polystyrene sulfonate, patiromer and sodium zirconium cycosilicate in pharmacological characteristics and side-effect profile.

Characteristic	SPS	Patiromer	ZS-9
FDA approval	Yes (1958)	Yes (2015)	Pending
Chemical structure	Non-absorbed, organic, sodium-containing resin	Non-absorbed, organic, sodium-free polymer	Non-absorbed, insoluble, inorganic, sodium-containing crystalline silicate
Mechanism of action	Nonspecific cation binding in exchange for sodium	Nonspecific cation binding in exchange for calcium	Selective potassium binding in exchange for sodium and hydrogen
Administration	Oral or rectal	Oral	Oral
Formulation	Suspension in sorbitol or dissolvable powder	Oral suspension	Oral suspension
Location of action	Colon	Distal colon predominantly	Entire intestinal track
Onset of action	1–2 hours	7 hours	1 hour
Dosing	<ul style="list-style-type: none"> • 15–60 g/day orally • 30–50 g/day rectally 	8.4 – 25.2 g daily	5–10 g daily, depending on FDA recommendations
Drug interactions	<ul style="list-style-type: none"> • Cation donating agents may interfere with the potassium-lowering efficacy of SPS. • Intestinal obstruction when aluminum hydroxide was combined with SPS. • Possible decreased absorption of co-administered lithium and thyroxin. • Co-administration with non-absorbable cation-donating antacids and laxatives was associated with systemic alkalosis. 	<ul style="list-style-type: none"> • Reduced systemic exposure of coadministered ciprofloxacin, metformin, and levothyroxine.⁵⁷ • No interaction when patiromer and these drugs were taken 3 hours apart.⁵⁷ 	<ul style="list-style-type: none"> • No significant drug-drug interactions involving ZS-9 in currently available clinical studies
Commonly reported adverse reactions	<ul style="list-style-type: none"> • GI disorders (i.e., constipation, nausea, vomiting, diarrhea) • Hyponatremia • Hypokalemia • Metabolic alkalosis • Volume overload 	<ul style="list-style-type: none"> • GI disorders (i.e., constipation, nausea, vomiting, diarrhea, flatulence) • Hypokalemia • Hypomagnesemia 	<ul style="list-style-type: none"> • GI disorders (i.e., constipation, nausea, vomiting, diarrhea) • Hypokalemia • Edema
Serious adverse events	Colonic necrosis	None	None

Abbreviations: FDA; Food and Drug Administration; GI= gastrointestinal; sK= serum potassium; SPS= sodium polystyrene sulfonate; ZS-9= sodium zirconium cycosilicate;

Randomized controlled trials evaluating the efficacy and safety of newer potassium-binding resins in hyperkalemic patients already treated with RAAS-blockers

Table 6

Patient characteristics	n	Year	Design	Intervention	Follow-up	Effect on SK	Major adverse events	Ref
Studies with Patiromer								
Outpatients with HF and a history of hyperkalemia or CKD receiving standard therapy and add-on spironolactone	105	2011	Double-blind RCT	Patiromer (30g/day) vs placebo	4 wks	↓	GI disorders (flatulence, diarrhea, constipation and vomiting) were more frequent in the patiromer than in the placebo group (21% vs 6%, respectively)	46
Hyperkalemic outpatients with CKD already treated with RAAS-blockers	107	2014	Randomized, placebo-controlled withdrawal	Patiromer (4.2gr or 8.4gr twice a day) vs placebo	8 wks	↓	Constipation was the most frequently reported adverse event (incidence rate: 11%)	47
Hyperkalemic outpatients with CKD already treated with RAAS-blockers	306	2015	Open-Label, dose-ranging RCT	Patiromer (mild hyperkalemia stratum: 4.2, 8.4 or 12.6 gr twice daily; moderate hyperkalemia stratum: 8.4 or 12.6 gr twice daily) versus placebo	52 wks	↓	Hypomagnesemia, constipation and diarrhea had an overall incidence of 8.6%, 6.3% and 5.6%, respectively	48
Studies with ZS-9								
Hyperkalemic outpatients with HF, CKD or diabetes	237	2014	Double-blind RCT	ZS-9 (5, 10 or 15 gr daily) vs placebo	4 wks	↓	Dose-dependent increase in the incidence of edema	49
Hyperkalemic outpatients with HF, CKD or diabetes	753	2015	Double-blind RCT	ZS-9 (1.25, 2.5, 5, or 10 gr daily) vs placebo	2 wks	↓	GI disorders, mainly diarrhea, were the most commonly reported drug-related complications	50

Abbreviations: CKD= chronic kidney disease; GI= gastro-intestinal; HF= heart failure; RAAS= renin-angiotensin-aldosterone-system; RCT= randomized controlled trial; SK= serum potassium; ZS-9= sodium zirconium cyclosilicate;