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Challenges in Treating Cardiovascular Disease: Restricting Sodium and Managing Hyperkalemia

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Abstract

High sodium intake, whether via diet or drugs, augments cardiorenal risk. Regardless of its source, high sodium intake can both lead to hypertension and reduce the efficacy of renin-angiotensin-aldosterone system inhibitors, which are currently guideline-recommended treatments for hypertension, chronic kidney disease, and heart failure. Reducing sodium intake is therefore recommended to reduce the risk of adverse cardiorenal outcomes. An inverse relationship exists between sodium and potassium, with foods high in sodium being lower in potassium. Diets high in potassium have been associated with reducing hypertension and heart failure; however, optimal renin-angiotensin-aldosterone system inhibitor dosing is often limited by hyperkalemia, which can lead to life-threatening cardiac arrhythmias and increased mortality. Potassium binders are effective at reducing potassium levels. Although some use sodium as the potassium exchange ion, thus increasing sodium intake, a new potassium binder uses another exchange ion and therefore does not increase sodium intake. When treatment options require agents that may precipitate hyperkalemia, particularly in patients at high cardiorenal risk, drugs that do not add to the sodium load may be preferred. A literature search was conducted using PubMed; search terms included *potassium, sodium, hyperkalemia, potassium binders,* and the literature search focused on manuscripts published more recently since 2000.

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High sodium intake is associated with adverse cardiorenal outcomes, including oxidative stress, arteriolar damage, interstitial fibrosis, glomerular hyalinization, glomerular fibrosis, increased glomerular hydrostatic pressure in the kidneys, and ventricular hypertrophy, myocardial fibrosis, and diastolic dysfunction in the heart.[1] To reduce cardiovascular risk, the US Department of Agriculture dietary guidelines emphasize reducing sodium intake to less than 2.3 g/d as part of a healthy eating pattern.[2] For patients with prehypertension and hypertension, the US Department of Agriculture guidelines recommend targeting 1.5 g/d to achieve blood pressure (BP) reductions. Similarly, treatment guidelines for patients with hypertension, chronic kidney disease (CKD), and heart failure (HF) recommend reducing dietary sodium intake to less than 2.0 g/d to less than 2.4 g/d.[3-5] The American Heart Association (AHA) recommends an even more stringent target of less than 1.5 g/d.[1]

Diets low in sodium are often rich in potassium, which may also contribute to clinical benefits inasmuch as increased dietary potassium reduces BP and lowers risk of stroke and renal calculus disease.[6-8] Conversely, underconsumption of potassium, particularly when combined with high sodium intake, has been associated with a variety of chronic disorders, including hypertension, diabetes, obesity, and renal calculi.[8] However, in patients with impaired renal function, potassium-enriched diets and renin-angiotensin-aldosterone system (RAAS) inhibitors can cause hyperkalemia, which in turn is associated with adverse outcomes.[8-11] The benefits associated with low-sodium diets have come into question because recent data indicate an adverse effect on cardiovascular risk.[12-14] Despite paradoxical data, the benefits of low-sodium diets remain a primary intervention for improving cardiorenal outcomes.[15]

In this article, we review the impact of high sodium intake on cardiorenal outcomes and its impact on RAAS inhibitor activity. We then describe the catch-22 that patients with CKD often face while balancing the risks

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of hyperkalemia with the benefits of RAAS inhibition. Recognizing that diet may not be the only important sodium source, we describe how drugs containing sodium may contribute to adverse outcomes and how available potassium binders, and those in development, treat hyperkalemia but differ as sources of sodium, which may be an important consideration when prescribing these agents.

COMPLIANCE WITH LOW-SODIUM DIETS

Data from the National Health and Nutrition Examination Survey 2009-2010 revealed that most Americans exceed dietary sodium recommendations, with 52% reporting sodium intake exceeding 3 g/d and 15% exceeding 5 g/d.[16] Even patients with CKD have higher than recommended sodium intake. Using 24-hour urinary sodium excretion data from more than 10,000 patients with CKD and renal transplant recipients, sodium intake averaged 3.8 g/d,[17] almost double the recommended level of less than 2.0 g/d for patients with CKD in the Kidney Disease: Improving Global Outcomes guidelines[4] and substantially above the 1.5 g/d limit recommended for adults by the AHA.[1] Importantly, however, 24-hour urinary sodium excretion may not fully reflect daily sodium intake in light of recent data indicating that sodium stores are important in maintaining sodium balance.[18] These sodium stores may fluctuate independently of sodium intake or body weight, exhibit weekly to monthly rhythms, and are larger in hypertensive compared with normotensive individuals. Functionally, sodium stores may reflect differences in hemodynamic responses between salt-sensitive and salt-resistant individuals.[19] Additionally, it has been suggested that sodium stores may be mobilized to regulate a hypertonic interface in the skin that may serve a protective barrier function.[18]

Given the prevalence of sodium in our food choices, fewer than half of patients prescribed dietary sodium restriction successfully follow the recommendations.[20] Numerous reasons contribute to patients' failure to follow a low-sodium diet, including more expensive and limited food choices, perceived loss of taste without added salt, inherent difficulty when eating at restaurants or places away from home, family or friends who do not follow the same diet, and lack of adequate dietary instructions.[20] Patients with additional comorbidities, such as diabetes, may experience confusion when asked to follow more than one type of diet.

ARTICLE HIGHLIGHTS

- Many drugs contain sodium, including some used to treat hyperkalemia, and therefore have the potential to substantially increase sodium levels and influence outcomes.
- Low-sodium diets and renin-angiotensin-aldosterone system inhibitor therapy are recommended for patients with hypertension, chronic kidney disease, and heart failure to improve cardiorenal outcomes.
- High sodium intake reduces the efficacy of renin-angiotensin-aldosterone system inhibitor therapy, and continued treatment with these agents at recommended doses is often limited by the development of hyperkalemia.
- Both dietary and medication-based sodium intake should be considered when treating hyperkalemia.
- Unlike potassium binders that use sodium as the exchange ion for potassium, a new potassium binder that uses another ion for exchange does not increase sodium intake.

EFFECTS OF EXCESS DIETARY SODIUM INTAKE ON OUTCOMES

Excess dietary sodium worsens hypertension, CKD, and HF. The LowSALT CKD study, a double-blind, placebo-controlled, randomized crossover study, evaluated sodium restriction in 20 patients with hypertension and stage 3 to 4 CKD.[21] Patients received individualized counseling on following a low-sodium diet and were then randomized to high or low sodium intake for 2-week periods (1380-1840 mg/d plus either 2760 mg/d or placebo tablet; to convert to mmol, divide by 23). Compared with the high sodium intake period, 24-hour systolic BP (SBP)/diastolic BP (DBP) was significantly reduced by a mean of 9.7/3.9 mm Hg with low sodium intake ($P \leq .01$). Proteinuria and albuminuria were also significantly reduced with low sodium intake ($P \leq .01$).

In the Trials of Hypertension Prevention I and II, 3126 individuals with prehypertension (defined as DBP of 80-89 mm Hg and SBP/DBP of <140/83-89 mm Hg, respectively) were randomized to a sodium reduction

intervention (comprehensive education or counseling) or control for 18 or 36 to 48 months.[22,23] Both studies found that sodium restriction was associated with reduced BP in normal weight and overweight participants. On long-term follow-up for 10 to 15 years after these trials, sodium reduction was associated with a 25% decrease in risk of a major cardiovascular event vs controls (relative risk, 0.75; 95% CI, 0.57-0.99; *P*=.044).[22] Evaluations more than 20 years after these trials indicated further benefit of low sodium intake on mortality. Although the results revealed a nonsignificant 15% risk reduction in mortality with sodium reduction (hazard ratio [HR], 0.85; 95% CI, 0.66-1.09; *P*=.19), a direct linear association between average sodium intake (as measured by 24-hour urinary sodium excretion) and mortality was observed (HR, 0.75, 0.95, 1.00 [reference], and 1.07 [*P*=.30 for trend] for <2300, 2300 to <3600, 3600 to <4800, and ≥4800 mg/24 h, respectively). For every added 1000 mg/24 h, the risk of premature death increased by 12% (HR 1.12; 95% CI, 1.00-1.26; *P*=.05). Additionally, the absence of a J-shaped or nonlinear relationship lends credence to continuous sodium reduction in this patient population.

In patients with CKD, high sodium intake has been associated with worsening proteinuria, progression to end-stage renal disease (ESRD), and adverse cardiovascular outcomes. The Ramipril Efficacy in Nephropathy (REIN) and REIN-2 studies evaluated the efficacy of the angiotensin-converting enzyme (ACE) inhibitor ramipril in patients with CKD who had persistent proteinuria. A post hoc analysis was conducted on 500 patients without diabetes who received ramipril, 5 mg/d, to evaluate the association of sodium intake with progression to ESRD.[24] Serial measurements of 24-hour urinary sodium/creatinine excretion were used to define patients with low (<100 mEq/g), medium (100 to <200 mEq/g), and high (≥200 mEq/g) sodium intake. After follow-up of more than 4.25 years, the incidence of ESRD was 6.1, 7.9, and 18.2 per 100 patient-years in patients with low, medium, and high sodium intake, respectively. On multivariate analysis, each 100-mEq/g increase in urinary sodium/creatinine excretion was associated with a 1.67-fold higher risk of ESRD (*P*=.025), or after adjusting for baseline proteinuria, with a 1.37-fold higher risk (*P*=.20).

High sodium intake, measured by higher urinary sodium excretion, was recently reported to be associated with increased risk of cardiovascular disease in a prospective cohort study of 3757 patients with CKD.[25] During a median follow-up of 6.8 years, the cumulative incidence of the composite end point (HF, myocardial infarction [MI], or stroke) was significantly higher among patients in the highest (≥4548 mg/24 h) vs lowest (<2894 mg/24 h) quartiles of urinary sodium excretion (29.8% vs 18.4%; HR, 1.36; 95% CI, 1.09-1.70; *P*=.007). This relationship was also evident for the individual outcomes of HF (23.2% vs 13.3%; *P*=.03), MI (10.9% vs 7.8%), and stroke (6.4% vs 2.7%; *P*=.02).

In patients with HF, the reduction in effective intravascular volume triggers a neurohumoral cascade in an effort to maintain hemodynamic stability.[26] This cascade reduces glomerular filtration rate (GFR) and increases sodium reabsorption in the proximal tubules and sodium and water reabsorption in the collecting tubules. Key neurohumoral mediators include norepinephrine, angiotensin II, aldosterone, and vasopressin, with endothelium-derived factors such as nitric oxide and prostaglandins also thought to be important. Collectively, the neurohumoral cascade limits sodium and water excretion, thereby promoting edema. Although natriuretic peptides are released to counter these effects, resistance to these agents ultimately develops.

Excess dietary sodium intake worsens HF, as illustrated by a prospective study in 123 patients with stable systolic HF (left ventricular ejection fraction <35%) receiving optimal medical therapy.[27] Estimates of dietary sodium intake were obtained from two 3-day food records taken 6 to 12 weeks apart. Patients were divided into groups on the basis of the tertile of sodium intake, with mean values of 1.4, 2.4, and 3.8 g/d in the low, medium, and high tertiles, respectively. The primary outcome was the development of acute decompensated HF (ADHF). During a median follow-up of 3.0 years, cumulative ADHF rates were 12%, 15%, and 46% in the low, middle, and high sodium intake groups,

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respectively (*P*=.001). On multivariate analysis, sodium intake of 2.8 g/d or more was the only independent predictor of ADHF (HR, 2.55; 95% CI, 1.61-4.04; *P*<.001); it was also predictive of all-cause hospitalization (HR, 1.39; 95% CI, 1.06-1.83; *P*=.018) and mortality (HR, 3.54; 95% CI, 1.46-8.62; *P*=.005).

If high sodium intake worsens HF outcomes, then sodium restriction would be expected to be beneficial. However, outcomes data with sodium restriction in HF appear inconsistent. In one 12-week, prospective, multicenter study, 97 stable patients who had New York Heart Association (NYHA) classes II through IV HF, documented left ventricular dysfunction, and a history of fluid retention and were receiving optimal medical therapy (including furosemide) were randomized to individualized sodium and water restriction or to a nurse-led HF clinic.[28] The primary end point was a composite variable consisting of NYHA class, hospitalization, weight, peripheral edema, quality of life, thirst, and diuretic dose. After 12 weeks, more patients allocated to sodium and water restriction than in the control group improved on the composite end point (51% vs 16%; *P*<.001), largely reflecting improvements in NYHA class and leg edema. Similarly, sodium and water restriction (2.0-2.4 g/d and 1.5 L/d, respectively) was associated with significant reductions in edema frequency (37% vs 7%; *P*=.008) and fatigue (59% vs 26%; *P*=.012) compared with controls in a 6-month observational study of 65 patients with HF with either reduced or preserved ejection fraction.[29]

Conversely, contrasting findings were reported in a post hoc analysis from the multihospital Heart Failure Adherence and Retention Trial, in which 833 patients with classes II/III HF with either reduced or preserved ejection fraction were classified as sodium restricted (intake <2.5 g/d) or unrestricted (≥2.5 g/d).[13] During a median follow-up of 3.0 years, sodium restriction was associated with a trend for a higher rate of the primary end point of death or HF hospitalization (42.8% vs 35.0%; *P*=.054) and a significantly higher rate of HF hospitalization (30.3% vs 22.5%; *P*=.033). In the propensity-matched cohort, sodium restriction was associated with a significantly higher risk of death or HF hospitalization compared with the unrestricted group (42.3% vs 26.2%; HR, 1.85; 95% CI, 1.21-2.84; *P*=.004), largely reflecting an increase in hospitalization rate. Interestingly, an exploratory analysis suggested that the association between sodium restriction and increased adverse outcomes was due to patients who were not receiving an ACE inhibitor or angiotensin receptor blocker (ARB).

DRUGS CONTAINING SODIUM MAY ADVERSELY AFFECT CARDIORENAL DISORDERS

The impact of nondietary sodium intake on hospital length of stay (LOS) was evaluated in a retrospective study of 182 consecutive patients admitted to a cardiac intensive care unit for acute exacerbation of HF.[30] The mean nondietary sodium load was 4 g/d, predominantly from intravenous administration of 0.9% or 0.45% sodium chloride, and was unrelated to patient age, sex, HF type, or presence of comorbidities. However, daily sodium administration was directly related to the hospital LOS, with an average sodium load of 1.2 g/d corresponding to hospital stays of up to 5 days and an average sodium load of 2.6 g/d correlating with stays of up to 10 days. Daily sodium load was the only predictor of hospital LOS in the multivariate analysis (*P*<.001).

Patients taking sodium-containing drug formulations have a higher incidence of cardiovascular events compared with those taking nonsodium formulations of the same drugs. In a population-based, nested, case-control study that used the UK Clinical Practice Research Datalink, 24 different sodium-containing drug formulations were compared with 116 different non−sodium-containing formulations of the same drugs.[31] The analysis included 1.29 million patients followed up for a mean of 7.23 years. A total of 61,072 cardiovascular events were recorded and matched with the same number of controls. For the primary end point of nonfatal MI, nonfatal stroke, or cardiovascular death, the adjusted odds ratio for exposure to sodium-containing drugs compared with the other formulations was 1.16 (95% CI, 1.12-1.21). A significant dose-related linear trend for cardiovascular events was observed based on sodium exposure (*P*<.01), with adjusted odds ratios of 1.10 (95% CI, 0.99-1.22), 1.33 (95% CI,

1.20-1.48), and 1.31 (95% CI, 1.18-1.45) for the lowest (≤7120 mmol sodium), middle (7121-30,285 mmol sodium), and highest (>30,285 mmol sodium) tertiles, respectively, and the impact was particularly evident on the risk of stroke and hypertension.

INFLUENCE OF SODIUM INTAKE ON RAAS INHIBITOR ACTIVITY

Renin-angiotensin-aldosterone system inhibitors are vital drugs in the management of CKD and HF, as well as in hypertension for patients with specific comorbidities such as diabetes.[5,32-36] However, high dietary sodium intake diminishes the efficacy of RAAS inhibitors. For example, in the aforementioned post hoc analysis of the REIN and REIN-2 trials, the benefit of ACE inhibition in reducing proteinuria was blunted by high sodium intake, with a significant trend observed for less proteinuria reduction with increasing sodium intake.[24] Additionally, the antiproteinuric effect of the RAAS inhibitors was lost by the end of the observation period in the high sodium intake group but sustained in the low and medium sodium intake groups. These observations were independent of BP changes. Comparable results were reported in a post hoc analysis of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) and Irbesartan Diabetic Nephropathy Trial (IDNT) studies in patients with diabetic nephropathy.[37] Compared with non–RAAS inhibitor–based antihypertensive therapy, the treatment benefit of ARBs on renal and cardiovascular event rates was greater among patients with lower vs higher sodium intake (estimated from 24-hour urinary sodium to creatinine ratio: $P<.001$ for renal events; $P=.021$ for cardiovascular events).

RAAS INHIBITORS AND RISK OF HYPERKALEMIA

Besides sodium, another cation that critically affects cardiorenal function is potassium. An inverse relationship exists between sodium and potassium, such that foods high in sodium tend to be low in potassium. Dietary guidelines recommend diets high in potassium and low in sodium to realize BP and cardiorenal benefits.[2] Although RAAS inhibitors are efficacious in improving BP control, they can increase serum potassium levels, which can have negative consequences.

Hyperkalemia is typically defined as a serum potassium concentration of more than 5.0 or more than 5.5 mEq/L (to convert to mmol/L, multiply by 1.0), with the upper limit of normal varying across guidelines and publications.[5,32-34,38,39] Hyperkalemia is relatively uncommon in individuals with normal renal function, but the incidence ranges from 5% to 50% in patients with renal insufficiency or CKD, increasing as renal function declines.[40] In patients who are not receiving RAAS inhibitors, 2 key factors predicting risk of development of hyperkalemia are an estimated GFR of less than 45 mL/min per 1.73 m^2 and a serum potassium concentration of more than 4.5 mEq/L.[41] Hyperkalemia is also common in older individuals, in patients with diabetes mellitus, hypertension, HF, or other cardiovascular comorbidities, and in those taking multiple medications, including RAAS inhibitors.[40-42] Risk of hyperkalemia is markedly increased when patients are prescribed multiple RAAS inhibitors with any combination of ACE inhibitor, ARB, renin inhibitor, or aldosterone receptor antagonist.[41] Importantly, hyperkalemia can lead to cardiac arrhythmias and increased mortality.[43-46] The relationship between serum potassium and mortality is U-shaped, with mortality increasing at low and high serum potassium levels. This relationship has been reported in a variety of cardiorenal populations, including patients with hypertension,[47] CKD,[44] and ESRD.[45]

The relationship between hyperkalemia and renal function is illustrated by results from a large, retrospective Veterans Health Administration study.[38] The incidence of hyperkalemia (potassium level ≥5.5 mEq/L) was 8.9% in a control cohort (defined in the study by a GFR of ≥60 mL/min per 1.73 m^2) and increased to 20.7%, 42.1%, and 56.7% in patients with stages 3, 4, and 5 CKD, respectively.[38] Compared with the control cohort, the odds of hyperkalemia in patients with stages 3, 4, and 5 CKD were 2.24, 5.91, and 11.0, respectively. Notably, a hyperkalemic event increased the risk of death within 1 day across all groups, even those without CKD.[38] Comparable results were obtained from the Humedica database in an analysis of 1.7 million persons with serum

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TABLE. Guideline Recommendations on the Use of RAAS Inhibitors[a,b]

Guideline	Recommendations
JNC 8[36]	• Initial or add-on antihypertensive treatment of adults with CKD should include an ACE inhibitor or ARB to improve kidney outcomes; this recommendation applies to all patients with CKD who have hypertension regardless of race/ethnicity or diabetes status • ACE inhibitors and ARBs are recommended as one of several options for initial antihypertensive treatment in the general nonblack population and also as an option for add-on therapy when the initial agents do not achieve BP targets
ADA[35]	• A regimen including an ACE inhibitor or ARB (but not both) should be used in patients with diabetes and hypertension; multidrug therapy is generally required to achieve BP targets • Serum potassium and serum creatinine levels and eGFR should be monitored if an ACE inhibitor or ARB is used
KDIGO[4]	• An ARB or ACE inhibitor is recommended for diabetic adults with CKD who have urine albumin excretion of 30-300 mg/d and for all adults with CKD who have urine albumin excretion >300 mg/d • An ARB or ACE inhibitor is suggested for children with CKD in whom BP-lowering therapy is indicated, irrespective of the level of proteinuria
ACCF/AHA[32,33]	• All patients with HF should be treated with an ACE inhibitor (or ARB or ARNI) and a β-blocker to reduce morbidity and mortality • An aldosterone antagonist should be added for patients with NYHA classes II-IV disease who have LVEF ≤35% provided eGFR is >30 mL/min and serum potassium level is <5.0 mEq/L; careful monitoring of serum potassium level, renal function, and diuretic dosing is necessary • Other medications should be added in specific situations, including a loop diuretic in patients with NYHA classes II-IV disease with volume overload, hydralazine and nitrate in persistently symptomatic African American patients with NYHA classes III-IV disease, and ivabradine to reduce hospitalizations for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF ≤35%) who are receiving guideline directed therapy

[a]ACE = angiotensin-converting enzyme; ACCF/AHA = American College of Cardiology Foundation/American Heart Association; ADA = American Diabetes Association; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; BP = blood pressure; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; JNC 8 = Eighth Joint National Committee; KDIGO = Kidney Disease: Improving Global Outcomes; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.
[b]SI conversion factors: To convert the potassium value to mmol/L, multiply by 1.0.

potassium measurements on 2 dates during the period from 2008 to 2012.[48] The prevalence of hyperkalemia (serum potassium level of ≥5.1 mEq/L) during the study period was 8.5% for a control population consisting of individuals without CKD stages 2 to 5, HF, diabetes, or ESRD compared with 22.8%, 32.7%, 46.9%, 56.5%, and 68.7% in patients with CKD stages 3A, 3B, 4, and 5 and ESRD, respectively.[48]

Current guidelines for CKD, HF, and hypertension recommend treatment with RAAS inhibitors (Table).[5,32-36] However, hyperkalemia often limits their use, leading to dose modifications or discontinuations (Figure 1). For example, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative guidelines advocate use of ACE inhibitors and ARBs at moderate to high doses, consistent with clinical trials documenting their efficacy.[34] In most patients, drugs can be continued if the GFR decline from baseline over 4 months is less than 30% and serum potassium level remains at 5.5 mEq/L or lower. However, if hyperkalemia develops, the dose of the ACE inhibitor or ARB should be reduced by 50%, and serum potassium levels should be reassessed every 5 to 7 days. If the serum potassium level does not return to baseline within 2 to 4 weeks, the ACE inhibitor or ARB should be discontinued, and the patient should be switched to an alternative medication. The National Institute for Health and Clinical

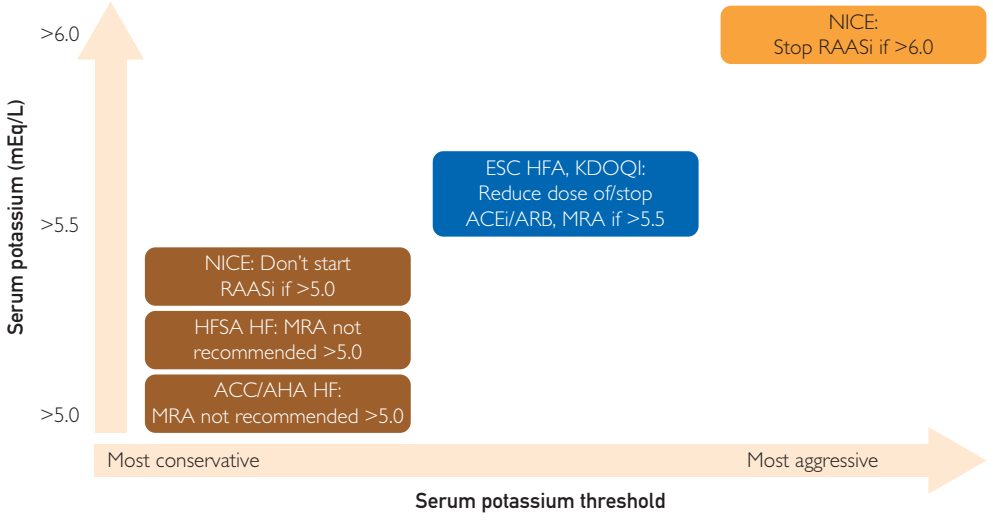

FIGURE 1. Serum potassium threshold before changes in renin-angiotensin-aldosterone system inhibitor (RAASi) guidelines recommendation. (Kidney Disease: Improving Global Outcomes guidelines do not provide recommendations.) ACC/AHA = American College of Cardiology/American Heart Association; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ESC HFA = European Society of Cardiology Heart Failure Association; HF = heart failure; HFSA = Heart Failure Society of America; KDOQI = Kidney Disease Outcomes Quality Initiative; MRA = mineralocorticoid receptor antagonist; NICE = National Institute for Health and Care Excellence.

Excellence guidelines recognize that RAAS inhibitors should not be initiated in patients whose baseline serum potassium level is greater than 5 mEq/L and should be discontinued if the serum potassium level increases to 6.0 mEq/L or higher and other drugs known to cause hyperkalemia have been stopped.[39] Additionally, if GFR decreases by 25% or more or the serum creatinine concentration increases by 30% or more due to impaired autoregulatory capacity of the kidney and after other causes of deterioration in renal function have been excluded, then the RAAS inhibitor should be stopped or the dose reduced to a tolerated level.[49]

Most patients with CKD stage 3 to 4, HF, or diabetes mellitus are not receiving maximum doses of RAAS inhibitors. In a retrospective analysis of a large US claims database, only 22% of patients with at least one of these conditions received an RAAS inhibitor at the labeled dose, whereas 62% were receiving a lower than recommended dose and 15% had discontinued the medication.[50] In patients receiving the labeled doses, the drug was down-titrated or discontinued in 38% of cases when the serum potassium level was 5.1 to 5.4 mEq/L and in 47% of cases when the serum potassium level was 5.5 mEq/L or higher. Notably, adverse cardiorenal outcomes increased with RAAS inhibitor dose reduction or discontinuation, particularly in the cohorts with CKD and HF.[50] Therefore, optimizing the therapeutic dosage of RAAS inhibitors is encouraged albeit difficult to achieve because of hyperkalemia. To provide therapies to maximize RAAS inhibitor dosing while maintaining potassium levels within normal limits, new medications have been developed.

HYPERKALEMIA TREATMENT AS A POTENTIAL SOURCE OF ADDED SODIUM INTAKE

The US Food and Drug Administration (FDA) has approved 2 potassium binders for the treatment of hyperkalemia—sodium polystyrene sulfonate (Kayexalate [SPS]) and patiromer (Veltassa).[51,52] Another agent, sodium zirconium cyclosilicate (ZS-9), is under regulatory review (Figure 2). Whereas patiromer uses calcium as the exchange ion

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for potassium, both SPS and ZS-9 use sodium (and ZS-9 also uses hydrogen) as their exchange ion for potassium and thereby have the potential to increase daily sodium intake.

Sodium Polystyrene Sulfonate

Sodium polystyrene sulfonate was approved in 1958, before the FDA requirement that manufacturers prove that their products are efficacious before they are approved for use.[56] Sodium polystyrene sulfonate uses sodium as the exchange ion and contains 9.4% sodium by weight (4.1 mEq/g or 94.3 mg/g).[51] An average daily dose of 15 to 60 g of SPS corresponds to approximately 1.4 to 5.7 g/d of sodium intake. With an exchange capacity of 33% in vivo, this intake corresponds to 0.47 to 1.89 g/d of sodium available for absorption. In product labeling, caution is advised when SPS is administered to patients who cannot tolerate even a small increase in sodium loads (ie, those with severe HF, severe hypertension, or marked edema).[51] Sodium polystyrene sulfonate was often administered with sorbitol, an osmotic laxative, to prevent fecal impaction and speed drug delivery to its site of action in the colon; however, the FDA issued a warning against this practice because of concerns about colonic necrosis.[56]

Sodium polystyrene sulfonate has also been associated with interdialytic weight gain (IDWG) in patients undergoing hemodialysis. In an analysis from the Dialysis Outcomes and Practice Patterns Study (DOPPS), predialysis and postdialysis weights were analyzed in patients receiving SPS. The study evaluated 11,409 patients undergoing hemodialysis at 288 facilities in Belgium, Canada, France, and Italy (countries with >5% SPS use) to identify patients using SPS and evaluate its impact on IDWG and electrolyte concentrations.[57] Sodium polystyrene sulfonate was prescribed to 2296 patients (20%). Patients receiving SPS had higher IDWG and higher serum sodium and phosphorus levels and tended to have lower serum potassium concentrations than those who did not receive SPS.

Sodium Zirconium Cyclosilicate

The experimental agent ZS-9 uses sodium and hydrogen as the exchange ions for potassium.[53] The sodium content of ZS-9 is 3.5 mEq/g or approximately 80 mg/g, corresponding to approximately 8% by weight. The average daily dose evaluated in clinical trials was 5 to 15 g given 3 times per day for 48 hours and then 10 g once daily for maintenance, which corresponds to an added sodium intake of 2.4 g/d with a 10-g dose 3 times per day and 0.8 g/d with the maintenance dose. Limited information is available concerning the in vivo exchange capacity of ZS-9. However, the standard 10-g dose of ZS-9 is likely to contribute substantially to the daily sodium load. For example, 0.8 g/d of added sodium represents 40% of the sodium intake recommended for patients with CKD in the Kidney Disease: Improving Global Outcomes guidelines[4] and 53% of that recommended by the AHA.[1] To put these values into perspective, the original Alka-Seltzer tablet formulation contains aspirin, sodium hydrogen carbonate, and citric acid, with a total sodium content of 567 mg. Therefore, the recommended 2-tablet dosage adds 1.1 g of sodium. Other formulations may contain somewhat lower amounts of sodium but still add significantly to daily sodium intake.[58] Additionally, injectable penicillin-based antibiotics, such as piperacillin sodium and ticarcillin disodium, contain 0.77 g/d and 2.7 g/d of added sodium, respectively, similar to the values for once daily and 3 times per day regimens of ZS-9.[59]

The randomized, controlled phase 3 Hyperkalemia Randomized Intervention Multidose ZS-9 Maintenance (HARMONIZE) trial evaluated the safety and efficacy of ZS-9 in outpatients with hyperkalemia (serum potassium level ≥5.1 mEq/L).[60] A total of 258 patients received ZS-9 at 10 g 3 times a day during an initial 48-hour, open-label phase. The 237 patients achieving normokalemia (serum potassium level of 3.5-5.0 mEq/L) were randomized to maintenance with ZS-9 at doses of 5, 10, or 15 g once daily or placebo for 28 days. During the initial open-label phase, mean serum potassium levels decreased from 5.6 mEq/L at baseline to 4.5 mEq/L at 48 hours, with a median time to normalization of serum potassium of 2.2 hours. During maintenance, serum potassium levels remained significantly lower in all ZS-9 groups compared with the placebo group ($P<.001$). The early onset of action with ZS-9 is notable and has been observed consistently across

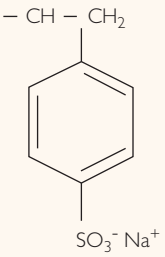
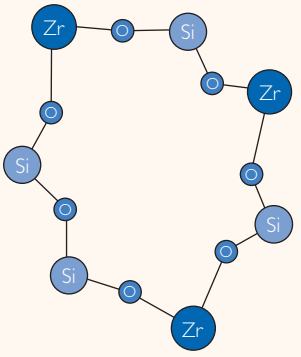
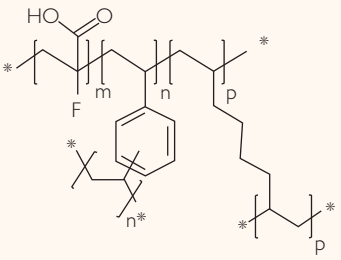
	SPS	ZS-9	Patiromer
Structure			
	Benzene, diethenyl-polymer with a benzene-sulfonated sodium salt	Octahedrally oxygen-coordinated zirconium atoms and tetrahedrally oxygen-coordinated silicon atoms creating a microporous cubic structure with an average opening of 3 Å	2-propenoic acid, 2-fluoro-, polymer with diethenylbenzene and 1,7-octadiene
Status	FDA approved for the treatment of hyperkalemia	Under regulatory review	FDA approved for treatment of hyperkalemia
Exchange ion for potassium	Sodium	Sodium and hydrogen	Calcium
Recommended dose	15 g QD to QID	5-15 g TID for 48 h; then 10 g QD†	8.4 g QD; dose can be titrated at ≥1-wk intervals in 8.4-g increments to a maximum of 25.2 g QD

FIGURE 2. Comparison of potassium binders.[51-55] *Indicates an extended polymeric network. †Dose used in phase 3 HARMONIZE (Hyperkalemia Randomized Intervention Multidose ZS-9 Maintenance) trial. m = number of 2-fluoro-2-propenoic acid groups (m=91%); n, p = number of cross-linking groups (n + p=9%); QD = once daily; QID = 4 times per day; SPS = sodium polystyrene sulfonate; TID = 3 times per day; ZS-9 = sodium zirconium cyclosilicate.

clinical studies, although it was not the primary efficacy end point.[54,60] Moreover, there is no evidence that ZS-9 binds to calcium or magnesium and therefore should not have potential for causing hypocalcemia or hypomagnesemia.[60]

Adverse event rates, including events in the gastrointestinal tract, were generally comparable between ZS-9 and placebo.[54,60] In the HARMONIZE trial, the overall incidence of adverse events was 53.3%, 29.4%, and 44.6% in patients receiving 5, 10, or 15 g of ZS-9, respectively, compared with 31.8% for those receiving placebo.[60] However, edema and hypokalemia (serum potassium level <3.5 mEq/L) occurred more frequently with the 10-g and 15-g doses than with placebo, with most cases of edema reported in patients with HF.[61] In comparison, evidence of increased edema was not seen in another phase 3 study in which ZS-9 was administered at doses ranging from 1.25 to 10 g 3 times per day during the first 48 hours and then once daily during maintenance for 12 days.[54]

Patiromer

Patiromer differs from SPS and ZS-9 in that calcium, rather than sodium, is exchanged for potassium.[52,55] Patiromer is a free-flowing powder of small, spherical beads (~100 μm in diameter). The patiromer polymer anion itself is not systemically absorbed, based on animal studies. Of note, these studies were performed with [^{14}C]-RLY5016, which is the

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polymer anion with calcium counterion, and not the calcium-sorbitol counterion in the currently available formulation.[55] The sorbitol in patiromer serves as a stabilizing agent to extend room temperature shelf-life, not to induce an osmotic diarrhea as was the case with sorbitol added to SPS. Further, the amount of sorbitol in patiromer (~4 g of sorbitol in the 8.4 g once daily dose of patiromer) is approximately 5- to 10-fold lower than that commonly administered in a dose of SPS. Patiromer works by binding potassium in the gastrointestinal lumen, thereby reducing luminal concentrations of free potassium available for absorption and increasing fecal potassium excretion, resulting in a reduction in serum potassium levels.

The effect of patiromer on urinary ion excretion, which reflects gastrointestinal ion absorption, was evaluated in healthy volunteers in 2 studies: a dose-finding study and a crossover dose-frequency study.[62] Patiromer use resulted in dose-dependent decreases in urinary potassium, magnesium, and sodium levels and increases in calcium excretion (each $P<.01$). The reduction in urinary sodium excretion suggests that patiromer also binds some sodium in the gastrointestinal tract.[62] Patiromer use at 25.2 g daily led to an increase in urinary calcium of 73 mg/d and a decrease in urinary phosphate of 64 mg/d. These data suggest that only a small fraction of calcium released from patiromer is available for absorption and that some of it potentially binds to intestinal phosphate. Nevertheless, physicians should be aware of the potential for increased calcium absorption, particularly when treating patients at risk of calcification whose calcium intake must be tightly controlled.

In the Two-Part, Single-Blind, Phase 3 Study Evaluating the Efficacy and Safety of Patiromer for the Treatment of Hyperkalemia (OPAL-HK) conducted in patients with stage 3 or 4 CKD in whom hyperkalemia developed while they were receiving RAAS inhibitors, patiromer reduced serum potassium levels by a mean of 0.65 mEq/L in patients with mild hyperkalemia (5.1 to <5.5 mEq/L) and 1.23 mEq/L in those with moderate to severe hyperkalemia (5.5 to <6.5 mEq/L) during the initial 4-week treatment phase.[63] Overall, 76% of patients achieved target serum potassium levels at week 4, and by the end of the withdrawal phase, 94% of patients in the patiromer group, compared with 44% of those in the placebo group, were still receiving RAAS inhibitor therapy. Patiromer was generally well tolerated, with the most common adverse event being mild to moderate constipation. Hypokalemia was reported in 3%, usually occurring transiently after dosage adjustment.[63]

The long-term safety and efficacy of patiromer was documented in an open-label, randomized trial conducted in outpatients with type 2 diabetes and CKD with serum potassium levels greater than 5.0 mEq/L.[64] All patients received an ACE inhibitor, ARB, or both before and during patiromer treatment. Over the course of 52 weeks, patiromer provided statistically significant mean decreases in serum potassium levels in patients with mild (serum potassium level >5.0-5.5 mEq/L) or moderate (serum potassium level >5.5 to <6.0 mEq/L) hyperkalemia.

Patiromer binds to magnesium in the colon and therefore may reduce magnesium uptake. In clinical trials, hypomagnesemia was reported as an adverse event in 5.3% of patiromer-treated patients.[52,62-64] The incidence of mild hypomagnesemia ranged from 4.3% (defined by serum magnesium level <1.2 mg/dL [to convert to mmol/L, divide by 18]) to 24% (serum magnesium level <1.8 mg/dL). However, there were no reports of severe hypomagnesemia in any of the clinical trials, and no patient discontinued patiromer because of hypomagnesemia. Magnesium replacement therapy was needed in 4% of patients.[52] Patiromer has a delayed onset of action with significant reductions in serum potassium level at 7 hours, as documented in a clinical study of inpatients with prespecified serum potassium levels consuming low-potassium diets in which measurements commenced at hour 4.[65] Accordingly, patiromer should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action.[52]

Potassium is involved in a negative feedback loop with aldosterone. The adrenal zona glomerulosa cells are very sensitive to serum potassium levels: increases in serum potassium stimulate aldosterone, which then

increases renal potassium loss and vice versa.[66] In addition, dietary sodium restriction and potassium loading influence aldosterone levels by increasing the activity of aldosterone synthase and thereby the degree of conversion of corticosterone into aldosterone.[66]

The effect of patiromer on serum aldosterone and BP was explored in the prespecified exploratory analysis of the OPAL-HK study.[67] During the initial treatment phase, mean serum aldosterone (−1.99 ng/dL; $P<.001$) and SBP/DBP (−5.6/−3.8 mm Hg; $P<.001$) levels decreased in parallel with the decrease in serum potassium concentration. During the withdrawal phase, the decreases in aldosterone and SBP/DBP levels were sustained with continued patiromer therapy but not with placebo. Patiromer did not significantly affect plasma renin activity in either phase. Thus, patiromer reduces serum potassium and aldosterone levels independently of plasma renin activity in patients with CKD and hyperkalemia receiving RAAS inhibitor therapy.

CONCLUSION

Sodium intake plays a role in progression of cardiorenal disorders, including hypertension, CKD, and HF. Current guidelines recommend reduced sodium intake for each of these conditions. However, compliance with low-sodium diets is difficult, and consumption of dietary sodium remains too high. Many drugs also contain sodium, which may have the potential to adversely affect cardiorenal outcomes. Renin-angiotensin-aldosterone system inhibitors are recommended in patients with hypertension, CKD, and HF, but high sodium intake reduces their efficacy. Renin-angiotensin-aldosterone system inhibitor therapy is often limited by hyperkalemia, which can lead to life-threatening cardiac arrhythmias and increased mortality. Several potassium binders are available for treating hyperkalemia. Both patiromer and ZS-9 appear to be effective and more tolerable than SPS, although there have been no head-to-head trials to date. Optimizing RAAS inhibitor therapy to achieve cardiorenal benefits is the clinician's therapeutic goal when practicing evidence-based medicine. Providing patients with agents that can liberalize the diet will enhance well-being and patient adherence while simultaneously reducing cardiorenal risk. With new opportunities to treat hyperkalemia, controlling serum potassium levels without exacerbating sodium intake may afford clinicians new options to enhance patient outcomes.

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Abbreviations and Acronyms: **ACE** = angiotensin-converting enzyme; **ADHF** = acute decompensated heart failure; **AHA** = American Heart Association; **ARB** = angiotensin receptor blocker; **BP** = blood pressure; **CKD** = chronic kidney disease; **DBP** = diastolic BP; **ESRD** = end-stage renal disease; **FDA** = Food and Drug Administration; **GFR** = glomerular filtration rate; **HF** = heart failure; **HR** = hazard ratio; **IDWG** = interdialytic weight gain; **LOS** = length of stay; **MI** = myocardial infarction; **NYHA** = New York Heart Association; **RAAS** = renin-angiotensin-aldosterone system; **REIN** = Ramipril Efficacy in Nephropathy; **SBP** = systolic BP; **SPS** = sodium polystyrene sulfonate; **ZS-9** = sodium zirconium cyclosilicate

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