Potassium Binders for Hyperkalemia in Chronic Kidney Disease—Diet, Renin-Angiotensin-Aldosterone System Inhibitor Therapy, and Hemodialysis

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Abstract

Hyperkalemia is a potentially life-threatening complication of chronic kidney disease (CKD). The management of CKD requires balancing the benefits of specific treatments, which may exacerbate the potential for hyperkalemia, with the risks of hyperkalemia itself. Renin-angiotensin-aldosterone system (RAAS) inhibitors, which slow CKD progression and improve cardiovascular outcomes, are often discontinued if hyperkalemia develops. Patients with hyperkalemia are frequently advised to restrict dietary potassium (K^+), depriving these patients of many heart-healthy foods. Patients receiving hemodialysis are particularly susceptible to hyperkalemia during long interdialytic intervals, and managing this risk without causing hypokalemia can be challenging. Recently, 2 K^+-binding agents were approved for the treatment of hyperkalemia: sodium zirconium cyclosilicate and patiromer. These agents offer alternatives to sodium polystyrene sulfonate, which is associated with serious gastrointestinal adverse effects. For this review, PubMed was searched for English-language articles published in 2014-2018 using the terms *patiromer*, *sodium zirconium cyclosilicate*, *sodium polystyrene sulfonate*, *hyperkalemia*, *renin-angiotensin-aldosterone*, *diet*, and *dialysis*. In randomized controlled studies of patients with hyperkalemia, sodium zirconium cyclosilicate and patiromer effectively reduced serum K^+ and were generally well tolerated. Furthermore, patients in these studies could maintain RAAS inhibitor therapy and, in some studies, were not required to limit dietary K^+. There may also be a role for these agents in preventing hyperkalemia in patients receiving hemodialysis. Thus, K^+-binding agents may allow patients with CKD at risk for hyperkalemia to optimize RAAS inhibitor therapy, receive benefits of a K^+-rich diet, and experience improved hemodialysis outcomes. Additional long-term studies are necessary to confirm these effects.

Chronic kidney disease (CKD) is a common condition, occurring in 10.4% to 13.4% of individuals worldwide.[1,2] Hyperkalemia, defined as an elevated serum potassium (K^+) concentration (>5.0 or >5.5 mEq/L; to convert values to mmol/L, multiply by 1.0), is a potentially life-threatening complication of CKD[3] that affects an estimated 14% to 20% of all patients with CKD[4]; recent evidence suggests that K^+ fluctuation to either hyperkalemic or hypokalemic levels may be associated with increased mortality or poor cardiovascular (CV) outcomes.[5-8]

Use of renin-angiotensin-aldosterone system (RAAS) inhibitor therapy, a mainstay in the treatment of CKD, can lead to the development of hyperkalemia.[9-12] Other risk factors for hyperkalemia in patients with CKD include advanced renal impairment,[4] comorbidities (eg, diabetes, hypertension, and heart failure [HF]), and a K^+-enriched diet.[3,13-15] The key risk predictors for hyperkalemia development in CKD are an estimated glomerular filtration rate of less than 45 mL/min per 1.73 m^2 and a baseline serum K^+ level of greater than 4.5 mEq/L prior to starting RAAS inhibitor

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ARTICLE HIGHLIGHTS

- Hyperkalemia (serum potassium [K^+] >5.0 or >5.5 mEq/L) is a potentially life-threatening complication of chronic kidney disease (CKD). Risk factors for hyperkalemia in patients with CKD include use of drugs that inhibit the renin-angiotensin-aldosterone system (RAAS); advanced renal impairment; comorbidities such as diabetes, hypertension, and heart failure; and consumption of a K^+-enriched diet.

- Management of hyperkalemia in patients with CKD can be challenging because specific CKD treatments may exacerbate the potential for hyperkalemia. The recent approval of 2 new K^+-binding drugs (sodium zirconium cyclosilicate [formerly ZS-9] and patiromer) provides new options for managing hyperkalemia. These drugs have the potential to ease K^+ dietary restrictions in CKD and attenuate the increase in K^+ during the interdialytic period.

- Potassium-binding drugs reduce serum K^+ levels via ion exchange mechanisms in the gastrointestinal tract. Sodium zirconium cyclosilicate is a nonpolymer compound that exchanges K^+ for sodium and hydrogen ions. In contrast, patiromer is a polymer that exchanges K^+ for calcium ions.

- Sodium zirconium cyclosilicate significantly lowers serum K^+ concentrations 1 hour after administration in patients with hyperkalemia and has been found to maintain serum K^+ in patients with CKD and those receiving RAAS inhibitors for up to 1 year. Sodium zirconium cyclosilicate is associated with dose-related mild to moderate edema that can be managed with dose reductions or with diuretic therapy.

- Patiromer significantly reduces serum K^+ concentrations and facilitates use of RAAS inhibitors in patients with CKD and/or heart failure who either have or are at risk of hyperkalemia. Gastrointestinal adverse effects (constipation, diarrhea, nausea, abdominal discomfort, and flatulence) are the most common adverse effects associated with patiromer.

therapy.[16] Another condition associated with an increased risk of hyperkalemia is type 4 renal tubular acidosis, which often occurs in patients with diabetes and overt nephropathy and may lead to impaired urinary excretion of K^+.[17] Disturbances in K^+ distribution caused by tissue injury, normal anion gap metabolic acidosis, and increased tonicity may also be present in some patients with hyperkalemia.[18]

Hyperkalemia in patients with CKD can be managed by down-titrating or discontinuing RAAS inhibitor therapy or limiting dietary K^+.[9,15,19] These strategies are problematic because they deprive patients with CKD of therapies (Table 1)[10,20-22] and nutrient-rich foods from which they could otherwise benefit.[15,19] Additionally, the relationship between dietary K^+ and serum K^+ is unclear, with studies finding only slight reductions in serum K^+ as a result of limiting dietary K^+.[23-25] Initial management of hyperkalemia may also include the use of loop diuretics, either alone or in combination with thiazide diuretics, which enhance urinary excretion of K^+ by increasing flow and sodium delivery to the distal nephron.[26] However, diuretic therapy is less effective in patients with advanced CKD or end-stage renal disease.[26] In patients receiving hemodialysis, who are at a particularly high risk for hyperkalemia after a long interdialytic interval,[27,28] hyperkalemia is associated with an increased risk of major CV events and mortality.[5,13,28-30] Thus, minimizing the risk of development of hyperkalemia while also properly managing CKD can be challenging.

Until recently, the long-term pharmacological management of hyperkalemia has relied on sodium polystyrene sulfonate (SPS), a resin that exchanges K^+ for sodium in the colon. However, SPS is poorly tolerated and can cause serious gastrointestinal adverse effects,[3,31] which often lead to poor adherence. In a study of approximately 4500 patients initiating therapy with SPS, only 49.8% continued treatment for more than 7 days and less than 10% continued for more than 60 days.[32] Recently, 2 new K^+-binding drugs were approved by the US Food and Drug Administration (FDA) for the treatment of hyperkalemia: sodium zirconium cyclosilicate (SZC; formerly ZS-9), a nonpolymer compound that exchanges K^+ for sodium and hydrogen ions in the gastrointestinal tract,[33] and patiromer, a polymer that exchanges K^+ for calcium ions in the gastrointestinal tract[34]

TABLE 1. Guideline Recommendations for RAAS Inhibitor Therapy for CKD and Common Comorbidities in Adults[a]

Disease	Recommendation	Source
CKD	ARB or ACEi to prevent CKD progression in adults with or without diabetes mellitus who have CKD and UAE >300 mg/d	KDIGO 2012 Clinical Practice Guidelines[10]
	ARB or ACEi to prevent CKD progression in adults with diabetes mellitus who have CKD and UAE 30-300 mg/d	
	ACEi or ARB to improve kidney outcomes in patients with hypertension and CKD	JNC 8 Guidelines[20]
HF	ACEi or ARB to prevent symptomatic HF in patients with reduced EF and a history of MI, and ACEi in patients with reduced EF and no MI	ACCF/AHA 2013 Guidelines[21]
	ACEi to reduce morbidity and mortality in patients with HFrEF (LVEF ≤40%), or an ARB in ACEi-intolerant patients[b]	
	MRA to reduce morbidity and mortality in patients with NYHA class II-IV HF and LVEF ≤35%, and after acute MI in patients with LVEF ≤40% in whom symptoms of HF develop or who have a history of diabetes mellitus	
Diabetes	ACEi or ARB for first-line treatment of hypertension in patients with diabetes mellitus and urinary ACR ≥300 mg/g creatinine or 30-299 mg/g creatinine[c]	ADA 2019 Guidelines[22]

[a]ACCF/AHA = American College of Cardiology Foundation/American Heart Association; ACEi = angiotensin-converting enzyme inhibitor; ACR = albumin to creatinine ratio; ADA = American Diabetes Association; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; CKD = chronic kidney disease; EF = ejection fraction; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; JNC = Joint National Committee; KDIGO = Kidney Disease: Improving Global Outcomes; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; RAAS = renin-angiotensin-aldosterone system; UAE = urinary albumin excretion.

[b]In patients with chronic symptomatic HFrEF NYHA class II or III who are tolerant of an ACEi or ARB, replacement therapy with an ARNI is recommended to further reduce morbidity and mortality.[21]

[c]SI conversion factor: To convert ACR from mg/g creatinine to mg/mmol, multiply by 0.113.

(Table 2).[35-39] Both SZC and patiromer remove bound K^+ via the feces. This article discusses evidence from clinically designed studies and data derived from actual ("real-world") clinical practice patterns regarding the use of K^+-binding agents, with a particular focus on the 3 challenging aspects of CKD management in patients with hyperkalemia: diet, RAAS inhibitor therapy, and hemodialysis.

METHODS

To capture recent literature for review, a search of PubMed was conducted for articles published in English between 2014 and 2018 and included the following terms: *patiromer, sodium zirconium cyclosilicate, sodium polystyrene sulfonate, hyperkalemia, renin-angiotensin-aldosterone, diet,* and *dialysis.* Citation lists of articles identified by the search were also used to identify additional literature. Completed and ongoing trials were searched and verified on ClinicalTrials.gov in December 2018 using the same search terms. The articles in this review were included on the basis of content relevance and quality.

HYPERKALEMIA AND CHALLENGES FOR CKD MANAGEMENT

The risk factors for hyperkalemia in patients with CKD include a K^+-enriched diet, RAAS inhibitor therapy, and interdialytic interval of hemodialysis. The observation that these hyperkalemia risk factors also provide patient benefits poses unique management challenges for clinicians.[15,19,40] This section discusses the clinical implications of addressing the effects of hyperkalemia management on diet, RAAS inhibitor therapy, and hemodialysis and reviews research with new K^+-binding agents that may

Effect on Diet

A K^+-rich diet (primarily achieved by high consumption of fruits and vegetables) can lower blood pressure and may prevent CV events. A diet high in fruits and vegetables is normally recommended in people with normal kidney function as part of a healthy lifestyle.[41,42] However, in patients at risk for hyperkalemia—such as those who have late stages of CKD—high dietary K^+ presents a clinical challenge.[19,42] Dietary K^+ restriction (<3 g/d) is recommended in patients at risk for hyperkalemia but should be individualized because it can lead to patients not receiving the benefits of a heart-healthy diet[43-45] (Table 3).[44,46,47] Appropriate dietary counseling is important in patients with CKD with or at risk of hyperkalemia but can be challenging in clinical practice without dedicated resources.[43] This includes an awareness of K^+-based additives that are often found in processed foods, as well as salt substitutes containing K^+ instead of sodium, which are recommended in patients with hypertension but may increase the risk of hyperkalemia in patients with reduced renal function or in those receiving RAAS inhibitor therapy.[43]

The degree of benefit achieved by reducing dietary K^+ is unclear. In one study of patients undergoing hemodialysis, a diet enriched with fruits and vegetables had a weak correlation ($r=0.14$; $P<.05$) with predialysis serum K^+.[25] In another study of patients receiving hemodialysis, there were no correlations observed between serum K^+ concentrations and dietary K^+ intake ($r=0.06$; $P=.50$) or K^+ density ($r=-0.003$; $P=.97$).[24] In a 24-month prospective controlled trial of patients who have stage 3 or 4 CKD, a K^+-restricted group did have significantly lower serum K^+ concentrations than a control group (4.6 ± 0.5 mEq/L vs 4.8 ± 0.4 mEq/L; $P=.03$) at the end of the study, but this difference was relatively small.[8] In a recent meta-analysis, increased intake of total dietary fiber (including fruits and vegetables) in the general population was associated with reductions in body weight, systolic blood pressure, and cholesterol, as well as reduced mortality, highlighting the potential benefits of a diet enriched in fruits and vegetables.[48] Furthermore, ingestion of a K^+-rich diet is hypothesized to facilitate renal excretion of K^+ in patients with normal renal function by enhancing K^+ transport in the distal convoluted tubule, and thus preventing hyperkalemia development.[49] Taken together, the lost nutritional benefit of a high-K^+ diet, the difficulty in maintaining a K^+-restricted diet, and the modest effects of restricting dietary K^+ can make this aspect of CKD management highly challenging.

A potential use of new K^+ binders is to ease dietary K^+ restrictions in patients with CKD.[19,49-51] In patients with advanced CKD or end-stage renal disease, resuming a plant-based diet may lead to increased fecal excretion of K^+ through increases in stool bulk from dietary fiber.[49] Thus far, studies of SZC and patiromer do not systematically control for diet: some required patients to follow a K^+-restricted diet,[52-54] whereas others did not.[55-58] Furthermore, many of these studies were of short duration. In theory, these K^+-binding agents may allow patients with CKD to be less restrictive in their diet while still minimizing the risk of hyperkalemia.[19] However, future studies are necessary to determine the long-term effects of K^+ binders (eg, on K^+ control, CV events, and mortality) in the context of a high-K^+ (and heart-healthy) diet vs a K^+-restricted diet.

Effect on RAAS Inhibitor Therapy Optimization

The use of RAAS inhibitor therapy, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists (MRAs) is well established in patients with CKD.[15] Treatment with RAAS inhibitors is associated with slowed progression of CKD and improved outcomes in patients with common CKD comorbidities (eg, hypertension, HF, and diabetes).[10,15,20-22]

TABLE 2. Available Potassium-Binding Agents to Treat Hyperkalemia			
Variable	Sodium zirconium cyclosilicate[35,36]	Patiromer[37,38]	Sodium polystyrene sulfonate[39]
Date of FDA approval	May 2018	October 2015	June 1958
Date of EMA approval	March 2018	July 2017	NA
Chemical properties	Nonpolymer; nonabsorbed zirconium silicate	Cross-linked polymer; patiromer sorbitex calcium	Resin/polymer; sodium salt of polystyrene sulfonic acid
Sodium content	80 mg/g	None	∼100 mg/g
Mechanism of action	Preferentially captures K^+ in exchange for hydrogen and sodium	Exchanges calcium for K^+; also binds magnesium	Sodium-K^+ exchange resin/polymer; nonspecifically binds K^+, magnesium, and calcium
Onset of action	1 Hour	7 Hours	Hours to days
Dose	Initial: 10 g TID for up to 48 hours Maintenance: 10 g QD (adjust dose at weekly intervals in 5-g increments to obtain the desired serum K^+ range) Usual maintenance dose: 5 g QoD to 15 g QD	Initial: 8.4 g QD; increase dose as necessary at ≥1-wk intervals in increments of 8.4 g	15 g (4 level teaspoons) 1-4 times daily
Preparation	Combine powder with ≥45 mL (≥3 tablespoons) of water, stir well, and drink immediately	Combine powder with 90 mL of water, stir thoroughly to form a cloudy mixture (powder will not dissolve), and drink immediately	Combine with a small quantity of water, or for greater palatability, syrup; may also give by endogastric tube or as an enema
Administration	Can be taken with or without food	Do not heat or add to heated foods or liquids	Oral suspension or enema
Appearance and texture	Free-flowing, odorless, insoluble white powder for oral suspension	Off-white to light brown powder composed of spherical beads	Cream to light brown finely ground powder
Storage	15°-30°C (59°-86°F)	Refrigerate at 2°-8°C (35°-46°F); if stored at room temperature, use within 3 mo (avoid exposure to temperatures >40°C)	25°C (77°F; excursions to 15°-30°C permitted)
Site of K^+ binding	GI tract	GI tract	GI tract or colon when administered by enema
Adverse effects	Edema (mild to moderate); hypokalemia	Hypomagnesemia; hypokalemia; constipation, diarrhea, nausea, abdominal discomfort, flatulence	Intestinal necrosis; electrolyte disturbances (including hypokalemia); nausea, vomiting, constipation, diarrhea; fluid overload in patients sensitive to high sodium intake; risk of aspiration
Drug interactions	Oral medications that exhibit pH-dependent solubility should be administered ≥2 h before or 2 h after	Take other orally administered drugs ≥3 h before or 3 h after	Take other orally administered drugs ≥3 h before or 3 h after; cation-donating antacids may reduce potassium exchange and increase risk of systemic alkalosis; concomitant use of sorbitol may contribute to risk of intestinal necrosis and is not recommended

EMA = European Medicines Agency; FDA = Food and Drug Administration; GI = gastrointestinal; K^+ = potassium; NA = not applicable (product use predates formation of the EMA); QD = once daily; QoD = every other day; TID = thrice daily.

Furthermore, RAAS inhibition is beneficial in both the early stages of CKD, during which they reduce hypertension, proteinuria, and glomerulosclerosis, and later stages of CKD, during which they help to preserve residual renal function in patients receiving hemodialysis.[59]

Although optimization of RAAS inhibitor therapy is important to achieve the greatest CV and renal benefits obtainable, use of RAAS inhibitors can increase the risk of hyperkalemia in patients with CKD.[3] Among patients with CKD, RAAS inhibitor–associated hyperkalemia has been estimated to occur in 5% to 10% of patients, compared with less than 2% of patients without CKD.[56,60] A common management strategy for hyperkalemia is the down-titration or discontinuation of RAAS inhibitor therapy.[9,61] Accordingly, there is marked inconsistency between guideline recommendations and real-world use of RAAS inhibitors, and the patients who would benefit most from RAAS inhibitor therapy (ie, patients with CKD, HF, or diabetes) are either not receiving it or receiving it in suboptimal doses.[15] In a large retrospective US database analysis, moderate to severe hyperkalemia events resulted in down-titration or discontinuation of RAAS inhibitor therapy in approximately 50% of patients receiving maximal doses and in discontinuation in about 30% of patients receiving submaximal doses.[61] Patients receiving submaximal doses or those who discontinued RAAS inhibitor therapy had worse outcomes, including higher incidence of CV events and more rapid progression of kidney disease and increased mortality compared with patients receiving maximal doses of RAAS inhibitors.[61] These results highlight the challenge faced by clinicians when prescribing RAAS inhibitor therapy in patients with CKD—balancing the risk of hyperkalemia with potential cardiorenal morbidity and mortality benefits.[15]

Given the integral role of RAAS inhibitor therapy in reducing CV risk and slowing the progression of CKD, the use of new K^+ binders to lower serum K^+ and thereby maintain optimal RAAS inhibitor therapy is expected to improve long-term clinical outcomes in patients with CKD.[9,15,51] Although studies evaluating SZC and patiromer included patients receiving RAAS inhibitor therapy and appeared to permit continued use without hyperkalemia,[52,53,55,56,62] the direct effects of these agents on the optimization of RAAS inhibitor dose have not been clearly delineated. Although evidence is emerging on the sustained benefits of K^+ binders,[63] additional studies are necessary to evaluate these effects long term. As described in greater detail later in this article, Zannad et al[51] offer the following potential clinical efficacy end points for investigating K^+ binder and RAAS inhibitor use in CKD: the proportion of patients receiving RAAS inhibitor therapy at follow-up and end points related to improved RAAS inhibitor use (eg, renal or cardiac outcomes).

Effect on Hemodialysis

Maintenance of serum K^+ within the normal range during the intradialytic and interdialytic intervals is a goal of hemodialysis, yet hyperkalemia is common in patients receiving hemodialysis.[40] These patients are at risk of hyperkalemia because K^+ accumulates during the interdialytic period, and alternately, patients are at risk of hypokalemia because K^+ is removed by the dialysis procedure during the intradialytic period. Achieving appropriate dialysate K^+ concentrations is critical because dialysis-induced K^+ lowering may provoke arrhythmias and cardiac death.[40] In addition to the potential mortality risk from hyperkalemia, patients receiving hemodialysis may have an increased risk of mortality due to other factors, such as fluid overload,[64] rapid fluid shifts with high ultrafiltration rates,[65] hemodialysis-associated hypotension,[66] increased muscle sympathetic nerve activity,[67] and acid-base disturbances.[68]

The risk of hyperkalemia may be increased with the thrice-weekly administration of hemodialysis, which includes a long 3-day interdialytic interval (including the weekend) before the first dialysis session of the week.[27,28] A retrospective US database study found that the frequency of

TABLE 3. Dietary Potassium Recommendations[a]

	General dietary K+ recommendations in adults with CKD[44]			
Nutrient	eGFR ≥60 mL/min/1.73 m² with increased CKD risk	eGFR 30 to <60 mL/min/1.73 m²	eGFR <30 mL/min/1.73 m²	Dialysis
K+ (g/d)	4.7	4.7	<3	<3
	Approximate K+ content of selected heart-healthy foods[46,47]			
Food group		Approximate K+ content (serving)[b]		
Grains				
Brown rice, cooked		0.174 g (1 cup)		
Whole-wheat pasta, cooked		0.102 g (1 cup)		
Whole-wheat bread		0.081 g (1 slice)		
Vegetables				
Tomatoes; red, ripe, cooked		0.523 g (1 cup)		
Cooked spinach		0.838 g (1 cup)		
Avocado; raw, California		1.17 g (1 cup, pureed)		
Cooked beet greens		1.31 g (1 cup)		
Fruits and fruit juices				
Bananas		0.422 g (1, medium size)		
Cantaloupe		0.368 g (one-quarter, medium size)		
Orange juice		0.473 g (1 cup)		
Low-fat or fat-free dairy				
Yogurt; plain, nonfat		0.579 g (8 oz)		
1%-2% Milk		0.366 g (1 cup)		
Lean meats, poultry, fish				
Pork loin; roasted		0.371 g (3 oz)		
Chicken; dark or light meat, roasted		0.190-0.200 g (3 oz)		
Cod; Pacific, cooked		0.439 g (3 oz)		

[a]CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; K+ = potassium.
[b]Values listed are an estimation based on the reference source.

hyperkalemia was 2-fold greater the day after the long vs the short interdialytic interval.[28] The long interdialytic interval was associated with greater predialytic risk for sudden cardiac death, with evidence suggesting fluctuations in K+ as a contributor.[69,70] A retrospective analysis of 80 cases of sudden death in patients receiving hemodialysis reported that the risk of sudden death was 3-fold greater 12 hours before hemodialysis after a long interdialytic interval compared with the expected rate of death.[70] In contrast, the risk of sudden death occurring in the 12-hour period prior to initiating dialysis treatment was only 1.7-fold greater than expected. Thus, when clinically feasible, it is recommended that all interdialytic intervals

be 48 hours or less to reduce the risk of hyperkalemia.[28]

Potassium concentration before, during, and after dialysis is of clinical significance. High predialysis serum K+ concentration is a risk factor for sudden death and all-cause mortality.[28,71,72] Use of dialysate with low K+ concentration (<2 mEq/L) has been reported to increase the risk of sudden cardiac death[28,40] and cause adverse electrocardiographic changes during and after hemodialysis.[73,74] Recent data suggest that bradyarrhythmia due to hyperkalemia may cause sudden cardiac death before hemodialysis.[69] Furthermore, rapid prolongation of the QT interval due to a shift in K+ and other electrolytes may be the likely cause

of ventricular arrhythmia and sudden cardiac death after hemodialysis. Additional studies are needed to better understand the effects of serum and dialysate K^+ concentrations on clinical outcomes in patients receiving hemodialysis.

The use of nondialytic measures to improve K^+ homeostasis would decrease the need to expose patients to dialysate with low K^+ concentrations. These measures include, but are not limited to, use of K^+ binders to stabilize K^+ concentrations during the interdialytic period. However, there is a risk of polypharmacy with addition of K^+-binder therapy, particularly in patients undergoing hemodialysis, which is known to increase the risk of hospitalization.[75] Ongoing and planned clinical trials will provide insight into whether a K^+-binding agent can decrease the incidence of predialysis hyperkalemia, lessen the blood to dialysate K^+ gradient, and decrease the rate of decline in serum K^+ concentration during dialysis. If successful, this strategy has the potential to reduce the incidence of arrhythmias and sudden cardiac death during and after dialysis.

The ongoing randomized phase 3 DIAL-IZE study (A Study to Test Whether ZS [Sodium Zirconium Cyclosilicate] Can Reduce the Incidence of Increased Blood Potassium Levels Among Dialyzed Patients; ClinicalTrials.gov Identifier: NCT03303521) is evaluating the efficacy of SZC in maintaining normal serum K^+ concentration after the long interdialytic interval in patients receiving hemodialysis without the need for rescue therapy. Adults receiving hemodialysis thrice weekly for at least 3 months with a predialysis serum K^+ level greater than 5.4 mEq/L after the long interdialytic interval and greater than 5.0 mEq/L after the short interdialytic interval will be evaluated.

The TWOPLUS-HD trial (A Pilot Trial of Twice-weekly Versus Thrice-weekly Hemodialysis in Patients With Incident End-stage Kidney Disease; ClinicalTrials.gov Identifier: NCT03740048) will investigate whether a dialysis-sparing effect may be achieved with the addition of patiromer to a hemodialysis treatment plan. In this randomized pilot study, patients with an indication to initiate hemodialysis will be randomized to thrice-weekly dialysis or twice-weekly dialysis plus pharmacotherapy for 6 weeks followed by thrice-weekly dialysis. The pharmacotherapy for patients randomized to the twice-weekly regimen will consist of a loop diuretic and sodium bicarbonate, and if patients experience hyperkalemia during the first 6 weeks, they will then receive patiromer.

CLINICAL EFFICACY AND SAFETY OF K^+ BINDERS FOR THE TREATMENT OF HYPERKALEMIA IN CKD

Sodium polystyrene sulfonate was approved by the FDA in 1958 for the treatment of hyperkalemia[76]; however, because the FDA did not require significant clinical data for approval prior to 1962, rigorous randomized controlled trial (RCT) efficacy and safety data for SPS in hyperkalemia are lacking.[76,77] In contrast, SZC and patiromer have been evaluated in phase 2 and phase 3 RCTs and have had consistent K^+-lowering efficacy and favorable safety profiles.[52,53,55-58,78] Both agents are approved by the FDA and the European Medicines Agency for the treatment of hyperkalemia. The chemical properties, dosage regimens, and other characteristics of SPS, patiromer, and SZC are shown in Table 2. Sodium zirconium cyclosilicate is a nonpolymer compound that has a rapid onset of action (within 1 hour) when given at 10 g thrice daily for up to 48 hours in the acute setting (Table 2). The typical initial maintenance dose is 10 g once daily titrated to achieve the desired K^+ concentration. The usual maintenance dose ranges from 5 g every other day to 15 g daily.

Patiromer is an insoluble cross-linked polymer, has an onset of action of 7 hours, and is typically given at a dose of 8.4 g once daily (Table 2). When used as maintenance therapy, it is recommended that the dose of patiromer be increased in 8.4-g increments at intervals of 1 week or more.

In the remainder of this section, the results of key clinical studies (registration studies) of SPS, SZC, and patiromer in

patients with hyperkalemia will be described. Apart from one small prospective study in patients receiving hemodialysis,[79] the studies described in this section included predialysis patients with CKD receiving RAAS inhibitor therapy (Tables 4 and 5).[52,53,55-58,78,80] Some study protocols specified K^+-controlled diets or advised restricted diets,[52,53,79] while others had no such dietary restrictions.[55,56,58,78]

Sodium Polystyrene Sulfonate

In a 2015 RCT in which 33 patients with CKD (nondialysis-dependent) and serum K^+ concentrations of 5.0 to 5.9 mEq/L received double-blind treatment with oral sorbitol-free SPS or placebo for 7 days, SPS was superior to placebo in reducing serum K^+ (between-group difference, 1.04 mEq/L; $P<.001$) without a significant difference in gastrointestinal adverse events between the groups.[81] Angiotensin receptor blocker and angiotensin-converting enzyme inhibitor doses remained stable, and patients had received routine counseling to follow a low-K^+ diet and were asked not to modify their diets during the study.[81] However, the small number of patients and short duration of this RCT are not sufficient to support long-term use of SPS in patients with hyperkalemia.[76,77]

Sodium Zirconium Cyclosilicate

Phase 2 and phase 3 studies have investigated the efficacy and safety of SZC for the treatment of hyperkalemia in a wide range of patients, including a high proportion of patients with CKD receiving RAAS inhibitor therapy (Table 4).[55,56,58,78,80] In these studies, patients received doses of SZC ranging from 0.3 to 10 g thrice daily for a short period (ie, 24-72 hours) to normalize serum K^+ concentrations (the correction phase), then continued SZC up to 15 g once daily for a period (ie, ~2 weeks to 12 months) to maintain normokalemia; no dietary restrictions were imposed, and patients were not provided with any protocol-directed dietary advice.[55,56,58,78] More than 50% of patients received RAAS inhibitor therapy in the trials,[55,56,58,78] which was kept at a constant dose in 2 studies.[55,78]

Sodium zirconium cyclosilicate was associated with rapid lowering of serum K^+ concentrations, with significant reductions vs baseline observed 1 hour after the first 10-g dose.[55,56,78] Consistent reductions in serum K^+ with SZC were observed in patients receiving RAAS inhibitor therapy,[55,56,78] as well as in a subgroup of patients with severe hyperkalemia (serum K^+ concentration ≥ 6 mEq/L).[82] Reductions in serum K^+ were maintained with continued daily doses of SZC in 2- to 4-week phase 3 studies,[56,78] including in patients receiving RAAS inhibitor therapy.[56] The long-term efficacy of SZC has been studied for up to 1 year in an open-label study[58] that included patients with CKD and patients receiving RAAS inhibitors.[83,84]

Sodium zirconium cyclosilicate was generally well tolerated in phase 2 and phase 3 trials, with an incidence of gastrointestinal adverse events similar to that of placebo, and a dose-related increase in the incidence of mild to moderate edema in patients during maintenance dosing resolved spontaneously or with diuretic therapy (edema was more common in patients treated with SZC 15 g—the highest dose of SZC in clinical trials).[33,56,85] Hypokalemia that resolved with dose reductions or discontinuation of SZC was also reported in clinical trials.[35]

Ongoing trials are also investigating the effect of SZC in optimizing RAAS inhibitor therapy and in rapid reduction and normalization of serum K^+ in an emergency setting. The PRIORITIZE HF study (Potassium Reduction Initiative to Optimize RAAS Inhibition Therapy With Sodium Zirconium Cyclosilicate in Heart Failure; ClinicalTrials.gov Identifier: NCT03532009) is investigating the optimization of RAAS inhibitor therapy with SZC in patients with HF with reduced ejection fraction (EF; New York Heart Association [NYHA] functional class II-IV disease). The primary objective is to evaluate the efficacy and safety of using SZC to initiate and intensify RAAS inhibitor therapy, including MRAs. The ENERGIZE study (A Study to Evaluate a

Study design	Patient population	Study treatment	Primary efficacy end point results[c]
TABLE 4. Key Clinical Studies of SZC in Patients with Hyperkalemia[a,b]			
Phase 2, 4-d, randomized, double-blind, placebo-controlled, dose-escalating[55]	eGFR 30-60 mL/min/1.73 m^2 and serum K$^+$ 5.0-6.0 mEq/L (n=90); RAASi: n=56	SZC 0.3, 3, or 10 g TID or placebo for 48 h (minimum of 6 doses over 2 d or maximum of 12 doses over 4 d)	Rate of serum K$^+$ decline in first 48 h (SZC 10 g): −0.11±0.46 mEq/L decrease in serum K$^+$ at 1 h vs +0.12±0.36 mEq/L with placebo (P=.04) −0.92±0.52 mEq/L at 38 h vs −0.26±0.4 mEq/L with placebo (P<.001)
Phase 3, 2-wk, randomized, double-blind, placebo-controlled, dose-ranging[78]	Correction phase: serum K$^+$ 5.0-6.5 mEq/L (n=754); CKD: n=463; RAASi: n=502	Correction phase: SZC 1.25, 2.5, 5, or 10 g TID or placebo for 48 h	Correction phase: between-group difference in exponential rate of serum K$^+$ change/h in first 48 h: −0.11% for SZC 1.25 g, −0.16% for SZC 2.5 g, −0.21% for SZC 5 g, and −0.30% for SZC 10 g vs −0.09% for placebo (P<.001 for all except SZC 1.25 g)
	Maintenance phase: serum K$^+$ 3.5-4.9 mEq/L at 48 h of the initial (correction) phase (n=543)	Maintenance phase: SZC dose from initial phase (administered QD) or placebo for 12 d	Maintenance phase: between-group difference in mean serum K$^+$ during 12-d treatment period: SZC 5 g and 10 g were significantly superior to placebo in maintaining normokalemia (P=.008 and P<.001, respectively)[d]
HARMONIZE: phase 3, 4-wk, randomized, double-blind, placebo-controlled[56]	Open-label phase: serum K$^+$ ≥5.1 mEq/L (n=258); CKD: n=169; RAASi: n=180	Open-label phase: SZC 10 g TID for 48 h	NA
	Randomized phase: serum K$^+$ 3.5-5 mEq/L at 48 h of the initial (open-label) phase (n=237); CKD: n=152; RAASi: n=163	Randomized phase: SZC 5, 10, or 15 g QD or placebo for 28 d	Mean serum K$^+$ in each dosing group vs placebo during days 8-29 of the randomized phase: 4.8 mEq/L for SZC 5 g, 4.5 mEq/L for SZC 10 g, and 4.4 mEq/L for SZC 15 g vs 5.1 mEq/L for placebo (P<.001 for all)
Phase 3, 12-mo, open-label, single-arm[58]	Correction phase: serum K$^+$ ≥5.1 mEq/L (n=751)	Correction phase: SZC 10 g TID for 24-72 h	Correction phase: proportion of patients with serum K$^+$ 3.5-5.0 mEq/L: 78%
	Maintenance phase: serum K$^+$ 3.5-5.0 mEq/L (n=746); CKD: n=483; RAASi: n=483	Maintenance phase: SZC titrated to serum K$^+$ 3.5-5.0 mEq/L (maximum 15 g QD, minimum 5 g every other day)	Maintenance phase: proportion of patients with serum K$^+$ ≤5.1 during 3-12 mo: 88%
HARMONIZE-GL: phase 3, 4-wk, randomized, double-blind, placebo-controlled[80]	Correction phase: serum K$^+$ ≥5.1 mEq/L (n=267); CKD: n=209; RAASi: n=205	Correction phase: SZC 10 g TID for 48 h	NA
	Maintenance phase: serum K$^+$ 3.5-5.0 mEq/L (n=248); CKD: n=199; RAASi: n=195	Maintenance (randomized) phase: SZC 5 or 10 g QD or placebo for 28 d	Back-transformed least squares mean serum K$^+$ on days 8-29 of the maintenance phase: 4.81 mEq/L for SZC 5 g and 4.38 mEq/L for SZC 10 g vs 5.32 mEq/L for placebo (P<.001 for both)

[a]CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HARMONIZE = Hyperkalemia Randomized Intervention Multidose ZS-9 Maintenance study; HARMONIZE-GL = HARMONIZE Global; K$^+$ = potassium; NA = not applicable; QD = once daily; RAASi = renin-angiotensin-aldosterone system inhibitor; SZC = sodium zirconium cyclosilicate; TID = thrice daily.

[b]SI conversion factors: To convert potassium values to mmol/L, multiply by 1.0.

[c]Safety was also assessed. In clinical studies, edema (generally mild to moderate in severity) was the most commonly reported adverse reaction with SZC. SZC should not be used in patients with severe constipation, bowel obstruction, or impaction, including bowel motility disorders that occur postoperatively; it may be ineffective or worsen gastrointestinal conditions.[35]

[d]Maintenance phase efficacy was a secondary end point in this study.[78]

Potassium Normalization Treatment Regimen Including Sodium Zirconium Cyclosilicate [ZS] Among Patients With S-K $\geq$5.8; ClinicalTrials.gov Identifier: NCT03337477) is investigating the effect of SZC added to a K^+-normalization treatment regimen in patients with serum K^+ concentrations of 5.8 mEq/L or greater. The primary outcome is mean absolute change in serum K^+ concentration from baseline until 4 hours after the start of dosing with SZC added to insulin and glucose vs that with placebo added to insulin and glucose.

Patiromer

The efficacy and safety of patiromer in patients with CKD and/or HF receiving RAAS inhibitor therapy was established in several key clinical studies (registration studies) that are described in Table 5.[52,53,57] Patients either had hyperkalemia (counseled to follow a low-K^+ diet)[52,53] or were at risk for development of hyperkalemia (eg, had CKD, HF, history of hyperkalemia leading to discontinuation of RAAS inhibitors).[57] In these studies, patiromer significantly reduced serum K^+ concentrations[52,53,57] and facilitated continuation and up-titration of RAAS inhibitor therapy.[53,57] In the 4-week PEARL-HF study (Evaluation of Patiromer in Heart Failure Patients; Clinical-Trials.gov Identifier: NCT00868439), significantly more patients treated with patiromer were able to increase their spironolactone dose from 25 to 50 mg/d vs those receiving placebo (91% vs 74%; P=.019) without experiencing hyperkalemia.[57] All patients in this trial had NYHA class I to III HF (mean EF, 40%-41%); 11 patients (15%) had HF with preserved EF ($\geq$50%).[57] In the 12-week OPAL-HK (A Two-Part, Single-Blind, Phase 3 Study Evaluating the Efficacy and Safety of Patiromer for the Treatment of Hyperkalemia; Clinical-Trials.gov Identifier: NCT01810939) study, 94% of patients in the patiromer group were able to continue RAAS inhibitor therapy, whereas discontinuation of RAAS inhibitors was required in 56% of patients receiving placebo because of recurrence of hyperkalemia.[53] Approximately 42% of patients (102 of 243) in this trial had NYHA class I to III HF (EF not reported).[53] In prespecified subgroup analyses, 100% of patiromer recipients with HF and 100% of patiromer recipients aged 65 years or older continued RAAS inhibitor therapy while maintaining K^+ control.[62,86] A post hoc analysis of OPAL-HK found that the efficacy and safety of patiromer were not compromised by background diuretic therapy, which is often required in patients with CKD.[87] In the AMETHYST-DN study (Patiromer in the Treatment of Hyperkalemia in Patients With Hypertension and Diabetic Nephropathy; ClinicalTrials.gov Identifier: NCT01371747), serum K^+ concentrations were reduced with patiromer through week 4 of treatment, and K^+ was maintained in a normal range over 52 weeks.[52] Approximately 35% of patients (105 of 304) in this trial had NYHA class I to II HF (EF not reported).[52] Reductions in serum K^+ in patients with HF (despite maintenance of RAAS inhibitor therapy) were consistent with those observed in patients without HF at week 4.[63] More recently, a patiromer dose-titration strategy to prevent hyperkalemia was evaluated in patients with NYHA class II to III HF (mean EF, 39%; $\sim$8% of patients [5 of 63] had an EF >50%).[88] Starting at a dose of 16.8 g/d, rather than the 25.2-g/d fixed-dose strategy used in the PEARL-HF study, was found to be potentially beneficial.[88] A small phase 2 study of patiromer in patients with hyperkalemia receiving hemodialysis has also been conducted.[79] In this study, patients were placed on a K^+-controlled diet for the entire study period (both pretreatment and treatment phases) and had reduced serum K^+ concentrations with patiromer treatment vs the pretreatment phase. Overall, patiromer has been generally well tolerated among patients in clinical trials, with the most common adverse events being gastrointestinal disorders.[89]

Ongoing trials of patiromer are investigating effects in patients with CKD and resistant hypertension and in patients receiving dialysis, including children. The AMBER trial (Spironolactone With Patiromer in the

TABLE 5. Key Clinical Studies of Patiromer in Patients with Hyperkalemia[a,b]

Study: design	Patient population	Study treatment	Primary efficacy end point results[c]
PEARL-HF: phase 2, 4-wk, double-blind, placebo-controlled, randomized[57]	HF, an indication to start MRA therapy, serum K^+ 4.3-5.1 mEq/L, and either (1) eGFR <60 mL/min/1.73 m^2 and ≥1 HF therapy (RAASi or β-blocker) or (2) hyperkalemia resulting in RAASi or β-blocker discontinuation in the past 6 mo (n=120)	Patiromer 15 g BID or placebo (plus spironolactone 25 mg/d, titrated to 50 mg/d at week 2 if serum K^+ >3.5 to ≤5.1 mEq/L)	Mean change in serum K^+ from baseline to week 4: patiromer −0.22 mEq/L vs placebo +0.23 mEq/L (P<.001)
AMETHYST-DN: phase 2, 52-wk, open-label, randomized, dose-ranging[52]	Type 2 diabetes, eGFR 15 to <60 mL/min/1.73 m^2, serum K^+ >5.0 to <6.0 mEq/L, and RAASi therapy (n=306)	Patiromer 4.2, 8.4, or 12.6 g BID for serum K^+ >5.0 to <6.0 mEq/L; patiromer 8.4, 12.6, or 16.8 g BID for serum K^+ >5.5 to <6.0 mEq/L	Mean change in serum K^+ from baseline to week 4: Mild hyperkalemia: −0.35 to −0.55 mEq/L (P<.001 vs baseline for all dose groups) Moderate hyperkalemia: −0.87 to −0.92 mEq/L (P<.001 vs baseline for all dose groups)
OPAL-HK: phase 3, 4-wk, single-group, single-blind initial treatment phase plus an 8-wk placebo-controlled, single-blind, randomized withdrawal phase[53]	Initial treatment phase: eGFR 15 to <60 mL/min/1.73 m^2, serum K^+ 5.1 to <6.5 mEq/L, and stable dose of ≥1 RAASi for ≥28 d (n=243)	Treatment phase: patiromer 4.2 g BID for serum K^+ 5.1 to <5.5 mEq/L; patiromer 8.4 g BID for serum K^+ 5.5 to <6.5 mEq/L	Treatment phase (mean change in serum K^+ from baseline to week 4): −1.01 mEq/L (P<.001 vs baseline)
	Withdrawal phase: serum K^+ ≥5.5 mEq/L at initial treatment baseline, serum K^+ 3.8 to <5.1 mEq/L at end of initial treatment while receiving patiromer, and RAASi therapy (n=107)	Withdrawal phase: patiromer at previous week 4 dose or placebo	Withdrawal phase (difference for patiromer vs placebo in median change in serum K^+ at week 4 or earliest visit at which serum K^+ was <3.8 mEq/L or ≥5.5 mEq/L): patiromer 0 mEq/L vs placebo +0.72 mEq/L (P<.001)

[a]AMETHYST-DN = Patiromer in the Treatment of Hyperkalemia in Patients With Hypertension and Diabetic Nephropathy; BID = twice daily; eGFR = estimated glomerular filtration rate; HF = heart failure; K^+ = potassium; MRA = mineralocorticoid receptor antagonist; OPAL-HK = A Two-Part, Single-Blind, Phase 3 Study Evaluating the Efficacy and Safety of Patiromer for the Treatment of Hyperkalemia; PEARL-HF = Evaluation of Patiromer in Heart Failure Patients; RAASi = renin-angiotensin-aldosterone system inhibitor.

[b]SI conversion factors: To convert potassium values to mmol/L, multiply by 1.0.

[c]Safety was also assessed. Patiromer may bind to magnesium ions in the colon, which can lead to hypomagnesemia. In clinical studies, 5.3% of patients treated with patiromer experienced hypomagnesemia as an adverse event. Patiromer should not be used in patients with severe constipation, bowel obstruction or impaction, including bowel motility disorders that occur postoperatively; it may be ineffective or worsen gastrointestinal conditions.[37]

Treatment of Resistant Hypertension in Chronic Kidney Disease; ClinicalTrials.gov Identifier: NCT03071263) is investigating the concomitant use of patiromer and spironolactone in patients with resistant hypertension and CKD to determine whether this strategy prevents hyperkalemia and allows for long-term use of spironolactone for the management of hypertension.[90] The primary end point of the AMBER study is the proportion of patients continuing to take spironolactone at week 12. Secondary end points include changes in blood pressure and albuminuria (a marker of CV and renal outcomes). As noted previously, the TWOPLUS-HD trial will investigate whether a dialysis-sparing effect may be achieved with the addition of patiromer to a hemodialysis treatment plan. Patients initiating hemodialysis will be randomized to thrice-weekly dialysis or twice-weekly dialysis plus pharmacotherapy for 6 weeks followed by thrice-weekly dialysis. Patients randomized to receive pharmacotherapy who have

development of hyperkalemia during the first 6 weeks will receive patiromer. Patient recruitment is currently under way for the EMERALD study (Pharmacodynamic & Safety of Patiromer in Children & Adolescents [2-<18 Yrs] With Chronic Kidney Disease and Hyperkalemia; ClinicalTrials.gov Identifier: NCT03087058), which is designed to evaluate the efficacy and safety of patiromer in children (aged 2 to <18 years) with CKD and hyperkalemia. As part of this study, the effect of different patiromer doses on the change in serum K^+ concentrations from baseline to day 14 in this patient population will be explored.

Real-World Experience With K^+ Binders

Multiple recent real-world evidence studies (ie, prospective or retrospective database analyses) support the burden of hyperkalemia,[6,7,91-100] and actual-use data on the agents used to treat hyperkalemia are accruing.[101,102] Available real-world data indicate that SPS is associated with a high incidence of severe gastrointestinal adverse events, including reports of colonic necrosis and gastrointestinal injury, particularly when combined with sorbitol and in patients with CKD.[31,76,101,102] In retrospective observational analyses of low-dose sorbitol-free SPS use in 26 patients with CKD and 14 patients with CKD as well as heart disease, significant and sustained reductions in serum K^+ were observed without significant safety concerns, with continued/optimal RAAS inhibitor therapy in those with CKD and heart disease (3 of 14 patients did not reach the target dose of RAAS inhibitor therapy).[103,104] This real-world experience adds to the minimal RCT evidence available for SPS.[104] Retrospective observational studies have begun to examine patiromer in patients receiving hemodialysis,[89] including a study of early adopters of patiromer in US dialysis centers.[105] A recent retrospective analysis of 527 patients undergoing hemodialysis who received patiromer for hyperkalemia found that treatment with patiromer was associated with a mean reduction in serum K^+ of 0.5 mEq/L.[106] In this study, the proportion of patients with severe hyperkalemia (serum K^+ ≥6.0 mEq/L) decreased from 64% at baseline to 23% after initiation of patiromer.[106] However, long-term real-world experience is needed to confirm the safety of patiromer and SZC if used as maintenance therapy.[76,89]

CONCLUSION

Sodium zirconium cyclosilicate and patiromer have been found to be effective and tolerable in clinical trials and are viable alternatives to SPS for the management of hyperkalemia in patients with CKD. These agents also offer improved taste, texture, and appearance compared with SPS. Both SZC and patiromer effectively lower serum K^+ concentrations in patients with CKD with hyperkalemia. Sodium zirconium cyclosilicate has a rapid onset of action (1 hour) that makes it well suited to restore normokalemia in outpatients with severe hyperkalemia (K^+ ≥6.0 mEq/L). Clinical data suggest that SZC and patiromer can maintain serum K^+ concentrations without limits on RAAS inhibitors, including MRAs, or dietary restrictions in some patients, although additional studies are needed. Furthermore, use of SZC and patiromer to limit predialysis hyperkalemia may be useful in lowering the blood to dialysate K^+ gradient and may decrease the rate and extent of the decrease in serum K^+ concentration during dialysis. If successful, this strategy has the potential to reduce the incidence of arrhythmias and sudden cardiac death in patients receiving dialysis. Clinical studies are either ongoing or being planned to confirm these hypotheses.

ACKNOWLEDGMENTS

REFERENCES

1. Hill NR, Fatoba ST, Oke JL, et al. Global prevalence of chronic kidney disease - a systematic review and meta-analysis. *PLoS One*. 2016;11(7):e0158765.
2. Mills KT, Xu Y, Zhang W, et al. A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. *Kidney Int*. 2015;88(5):950-957.
3. Palmer BF, Clegg DJ. Treatment of abnormalities of potassium homeostasis in CKD. *Adv Chronic Kidney Dis*. 2017;24(5):319-324.
4. Gilligan S, Raphael KL. Hyperkalemia and hypokalemia in CKD: prevalence, risk factors, and clinical outcomes. *Adv Chronic Kidney Dis*. 2017;24(5):315-318.
5. Luo J, Brunelli SM, Jensen DE, Yang A. Association between serum potassium and outcomes in patients with reduced kidney function. *Clin J Am Soc Nephrol*. 2016;11(1):90-100.
6. Thomsen RW, Nicolaisen SK, Hasvold P, et al. Elevated potassium levels in patients with chronic kidney disease: occurrence, risk factors and clinical outcomes—a Danish population-based cohort study. *Nephrol Dial Transplant*. 2018;33(9):1610-1620.
7. Gasparini A, Evans M, Barany P, et al. Plasma potassium ranges associated with mortality across stages of chronic kidney disease: the Stockholm CREAtinine Measurements (SCREAM) project [published online ahead of print August 6, 2018]. *Nephrol Dial Transplant*, https://doi.org/10.1093/ndt/gfy249.
8. Cheungpasitporn W, Thongprayoon C, Kittanamongkolchai W, Sakhuja A, Mao MA, Erickson SB. Impact of admission serum potassium on mortality in patients with chronic kidney disease and cardiovascular disease. *QJM*. 2017;110(11):713-719.
9. Chang AR, Sang Y, Leddy J, et al. Antihypertensive medications and the prevalence of hyperkalemia in a large health system. *Hypertension*. 2016;67(6):1181-1188.
10. Kidney Disease: Improving Global Outcomes. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*. 2013; 3(1):1-150.
11. Xie X, Liu Y, Perkovic V, et al. Renin-angiotensin system inhibitors and kidney and cardiovascular outcomes in patients with CKD: a Bayesian network meta-analysis of randomized clinical trials. *Am J Kidney Dis*. 2016;67(5):728-741.
12. Hu JR, Coresh J. The public health dimension of chronic kidney disease: what we have learnt over the past decade. *Nephrol Dial Transplant*. 2017;32(suppl 2):ii113-ii120.
13. Collins AJ, Pitt B, Reaven N, et al. Association of serum potassium with all-cause mortality in patients with and without heart failure, chronic kidney disease, and/or diabetes. *Am J Nephrol*. 2017;46(3):213-221.
14. 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.
15. Epstein M. Hyperkalemia constitutes a constraint for implementing renin-angiotensin-aldosterone inhibition: the widening gap between mandated treatment guidelines and the real-world clinical arena. *Kidney Int Suppl (2011)*. 2016; 6(1):20-28.
16. Lazich I, Bakris GL. Prediction and management of hyperkalemia across the spectrum of chronic kidney disease. *Semin Nephrol*. 2014;34(3):333-339.
17. Palmer BF, Clegg DJ. Electrolyte and acid-base disturbances in patients with diabetes mellitus. *N Engl J Med*. 2015;373(6): 548-559.
18. Palmer BF, Clegg DJ. Physiology and pathophysiology of potassium homeostasis. *Adv Physiol Educ*. 2016;40(4):480-490.
19. Palmer BF, Clegg DJ. Achieving the benefits of a high-potassium, paleolithic diet, without the toxicity. *Mayo Clin Proc*. 2016;91(4):496-508.
20. James PA, Oparil S, Carter BL, et al. 2014 Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8) [published correction appears in *JAMA*. 2014;311(17):1809]. *JAMA*. 2014;311:507-520.
21. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;136(6):e137-e161.
22. American Diabetes Association. 10. Cardiovascular disease and risk management: *Standards of Medical Care in Diabetes—2019*. *Diabetes Care*. 2019;42(suppl 1):S103-S123.
23. Clegg DJ, Hill Gallant KM. Plant-based diets in CKD. *Clin J Am Soc Nephrol*. 2019;14(1):141-143.
24. St-Jules DE, Goldfarb DS, Sevick MA. Nutrient non-equivalence: does restricting high-potassium plant foods help to prevent hyperkalemia in hemodialysis patients [published correction appears in *J Ren Nutr*. 2016;26(6):416]? *J Ren Nutr*. 2016;26(5):282-287
25. Noori N, Kalantar-Zadeh K, Kovesdy CP, et al. Dietary potassium intake and mortality in long-term hemodialysis patients. *Am J Kidney Dis*. 2010;56(2):338-347.
26. Kovesdy CP. Management of hyperkalaemia in chronic kidney disease. *Nat Rev Nephrol*. 2014;10(11):653-662.
27. Georgianos PI, Sarafidis PA, Sinha AD, Agarwal R. Adverse effects of conventional thrice-weekly hemodialysis: is it time to avoid 3-day interdialytic intervals? *Am J Nephrol*. 2015;41(4-5): 400-408.
28. Yusuf AA, Hu Y, Singh B, Menoyo JA, Wetmore JB. Serum potassium levels and mortality in hemodialysis patients: a retrospective cohort study. *Am J Nephrol*. 2016;44(3):179-186.
29. Karaboyas A, Zee J, Brunelli SM, et al. Dialysate potassium, serum potassium, mortality, and arrhythmia events in hemodialysis: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis*. 2017;69(2):266-277.
30. Nakhoul GN, Huang H, Arrigain S, et al. Serum potassium, end-stage renal disease and mortality in chronic kidney disease. *Am J Nephrol*. 2015;41(6):456-463.
31. 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.
32. Betts K, Woolley JM, Chu L, Mu F, Tang W, Wu E. Real-world treatment discontinuation of sodium polystyrene sulfonate. *J Am Soc Nephrol*. 2016;27(abstract edition). Abstract FR-PO786.
33. Hoy SM. Sodium zirconium cyclosilicate: a review in hyperkalaemia [published correction appears in *Drugs*. 2019;79(5): 591]. *Drugs*. 2018;78(15):1605-1613.

34. Epstein M, Pitt B. Recent advances in pharmacological treatments of hyperkalemia: focus on patiromer. *Expert Opin Pharmacother*. 2016;17(10):1435-1448.

35. *Lokelma [prescribing information]*. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2018.

36. *Lokelma [summary of product characteristics]*. Södertälje Sweden: AstraZeneca AB; 2018.

37. *Veltassa [prescribing information]*. Redwood City, CA: Relypsa, Inc; 2018.

38. *Veltassa [summary of product characteristics]*. Paris, France: Vifor Fresenius Medical Care Renal Pharma; 2018.

39. *Kayexalate [prescribing information]*. St. Michael, Barbados: Concordia Pharmaceuticals Inc; 2017.

40. Pun PH, Middleton JP. Dialysate potassium, dialysate magnesium, and hemodialysis risk. *J Am Soc Nephrol*. 2017;28(12): 3441-3451.

41. 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.

42. Kovesdy CP, Appel LJ, Grams ME, et al. Potassium Homeostasis in Health and Disease: a scientific workshop cosponsored by the National Kidney Foundation and the American Society of Hypertension. *Am J Kidney Dis*. 2017;70(6):844-858.

43. Cupisti A, Kovesdy CP, D'Alessandro C, Kalantar-Zadeh K. Dietary approach to recurrent or chronic hyperkalaemia in patients with decreased kidney function. *Nutrients*. 2018; 10(3):261.

44. Kalantar-Zadeh K, Fouque D. Nutritional management of chronic kidney disease. *N Engl J Med*. 2017;377(18): 1765-1776.

45. Rastogi A, Arman F, Alipourfetrati S. New agents in treatment of hyperkalemia: an opportunity to optimize use of RAAS inhibitors for blood pressure control and organ protection in patients with chronic kidney disease. *Curr Hypertens Rep*. 2016;18(7):55.

46. US Department of Health and Human Services; US Department of Agriculture. Appendix B: Food sources of selected nutrients. In: *Dietary Guidelines for Americans, 2005*. 6th ed. Washington, DC: US Government Printing Office; 2005.

47. US Department of Agriculture. USDA Food Composition Databases. https://ndb.nal.usda.gov/ndb/. Accessed March 10, 2019.

48. Reynolds A, Mann J, Cummings J, Winter N, Mete E, Te Morenga L. Carbohydrate quality and human health: a series of systematic reviews and meta-analyses [published correction appears in *Lancet*. 2019;393(10170):406]. *Lancet*. 2019; 393(10170):434-445.

49. Palmer BF, Clegg DJ. Cardiovascular benefits of a diet enriched in fruits and vegetables. *Am J Nephrol*. 2019;49(6):435-437.

50. Kovesdy CP. Updates in hyperkalemia: outcomes and therapeutic strategies. *Rev Endocr Metab Disord*. 2017;18(1):41-47.

51. Zannad F, Rossignol P, Stough WG, et al. New approaches to hyperkalemia in patients with indications for renin angiotensin aldosterone inhibitors: considerations for trial design and regulatory approval. *Int J Cardiol*. 2016;216:46-51.

52. Bakris GL, Pitt B, Weir MR, et al; AMETHYST-DN Investigators. Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease: the AMETHYST-DN randomized clinical trial [published correction appears in *JAMA*. 2015;314(7):731]. *JAMA*. 2015;314(2): 151-161.

53. Weir MR, Bakris GL, Bushinsky DA, et al; OPAL-HK Investigators. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med*. 2015; 372(3):211-221.

54. Bushinsky DA, Williams GH, Pitt B, et al. Patiromer induces rapid and sustained potassium lowering in patients with chronic kidney disease and hyperkalemia. *Kidney Int*. 2015; 88(6):1427-1433.

55. Ash SR, Singh B, Lavin PT, Stavros F, Rasmussen HS. A phase 2 study on the treatment of hyperkalemia in patients with chronic kidney disease suggests that the selective potassium trap, ZS-9, is safe and efficient. *Kidney Int*. 2015;88(2):404-411.

56. Kosiborod M, Rasmussen HS, Lavin P, et al. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial [published correction appears in *JAMA*. 2015;313(5):526]. *JAMA*. 2014;312(21):2223-2233.

57. Pitt B, Anker SD, Bushinsky DA, Kitzman DW, Zannad F, Huang IZ; PEARL-HF Investigators. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. *Eur Heart J*. 2011; 32(7):820-828.

58. Spinowitz BS, Fishbane S, Pergola PE, et al; ZS-005 Study Investigators. Sodium zirconium cyclosilicate among individuals with hyperkalemia: a 12-month phase 3 study. *Clin J Am Soc Nephrol*. 2019;14(6):798-809.

59. Zhang F, Liu H, Liu D, et al. Effects of RAAS inhibitors in patients with kidney disease. *Curr Hypertens Rep*. 2017;19(9):72.

60. Dunn JD, Benton WW, Orozco-Torrentera E, Adamson RT. The burden of hyperkalemia in patients with cardiovascular and renal disease. *Am J Manag Care*. 2015;21(15, suppl): s307-s315.

61. Epstein M, Reaven NL, Funk SE, McGaughey KJ, Oestreicher N, Knispel J. Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. *Am J Manag Care*. 2015;21(11, suppl):S212-S220.

62. Weir MR, Bushinsky DA, Benton WW, et al. Effect of patiromer on hyperkalemia recurrence in older chronic kidney disease patients taking RAAS inhibitors. *Am J Med*. 2018; 131(5):555-564.e3.

63. Pitt B, Bakris GL, Weir MR, et al. Long-term effects of patiromer for hyperkalaemia treatment in patients with mild heart failure and diabetic nephropathy on angiotensin-converting enzymes/angiotensin receptor blockers: results from AMETHYST-DN. *ESC Heart Fail*. 2018;5(4):592-602.

64. Siriopol D, Siriopol M, Stuard S, et al. An analysis of the impact of fluid overload and fluid depletion for all-cause and cardiovascular mortality [published online ahead of print January 8, 2019]. *Nephrol Dial Transplant*, https://doi.org/10.1093/ndt/gfy396.

65. Flythe JE, Kimmel SE, Brunelli SM. Rapid fluid removal during dialysis is associated with cardiovascular morbidity and mortality. *Kidney Int*. 2011;79(2):250-257.

66. Shoji T, Tsubakihara Y, Fujii M, Imai E. Hemodialysis-associated hypotension as an independent risk factor for two-year mortality in hemodialysis patients. *Kidney Int*. 2004; 66(3):1212-1220.

67. Kaur J, Young BE, Fadel PJ. Sympathetic overactivity in chronic kidney disease: consequences and mechanisms. *Int J Mol Sci*. 2017;18(8):1682.

68. Qian Q. Acid-base alterations in ESRD and effects of hemodialysis. *Semin Dial*. 2018;31(3):226-235.

69. Joki N, Tokumoto M, Takahashi N, Nishimura M. Current perspectives on sudden cardiac death in hemodialysis patients. *Contrib Nephrol*. 2018;196:5-12.

70. Bleyer AJ, Hartman J, Brannon PC, Reeves-Daniel A, Satko SG, Russell G. Characteristics of sudden death in hemodialysis patients. *Kidney Int*. 2006;69(12):2268-2273.

71. Kovesdy CP, Regidor DL, Mehrotra R, et al. Serum and dialysate potassium concentrations and survival in hemodialysis patients. *Clin J Am Soc Nephrol*. 2007;2(5):999-1007.

72. Genovesi S, Valsecchi MG, Rossi E, et al. Sudden death and associated factors in a historical cohort of chronic haemodialysis patients. *Nephrol Dial Transplant*. 2009;24(8):2529-2536.

73. Santoro A, Mancini E, London G, et al. Patients with complex arrhythmias during and after haemodialysis suffer from different regimens of potassium removal. *Nephrol Dial Transplant*. 2008;23(4):1415-1421.

74. Buemi M, Aloisi E, Coppolino G, et al. The effect of two different protocols of potassium haemodiafiltration on QT dispersion. *Nephrol Dial Transplant*. 2005;20(6):1148-1154.

75. Flythe JE, Katsanos SL, Hu Y, Kshirsagar AV, Falk RJ, Moore CR. Predictors of 30-day hospital readmission among maintenance hemodialysis patients: a hospital's perspective. *Clin J Am Soc Nephrol*. 2016;11(6):1005-1014.

76. Georgianos PI, Agarwal R. Revisiting RAAS blockade in CKD with newer potassium-binding drugs. *Kidney Int*. 2018;93(2): 325-334.

77. Beccari MV, Meaney CJ. Clinical utility of patiromer, sodium zirconium cyclosilicate, and sodium polystyrene sulfonate for the treatment of hyperkalemia: an evidence-based review [published correction appears in *Core Evid*. 2019;14:1]. *Core Evid*. 2017;12:11-24.

78. Packham DK, Rasmussen HS, Lavin PT, et al. Sodium zirconium cyclosilicate in hyperkalemia. *N Engl J Med*. 2015; 372(3):222-231.

79. Bushinsky DA, Rossignol P, Spiegel DM, et al. Patiromer decreases serum potassium and phosphate levels in patients on hemodialysis. *Am J Nephrol*. 2016;44(5):404-410.

80. Zannad F, Hsu B-G, Maeda Y, et al. Sodium zirconium cyclosilicate for hyperkalemia: results of the randomized, placebo-controlled, multi-dose HARMONIZE-GLOBAL study. Poster presented at: ASN Kidney Week; October 25, 2018; San Diego, CA. Abstract TH-PO1158.

81. Lepage L, Dufour AC, Doiron J, et al. Randomized clinical trial of sodium polystyrene sulfonate for the treatment of mild hyperkalemia in CKD. *Clin J Am Soc Nephrol*. 2015;10(12): 2136-2142.

82. Kosiborod M, Peacock WF, Packham DK. Sodium zirconium cyclosilicate for urgent therapy of severe hyperkalemia [letter]. *N Engl J Med*. 2015;372(16):1577-1578.

83. McCullough P, Pergola P, Fishbane S, et al. Efficacy and safety of sodium zirconium cyclosilicate to treat hyperkalemia among patients taking renin-angiotensin-aldosterone system inhibitors in a 12-month, open-label, phase 3 study: a post hoc subgroup analysis. *Circulation*. 2017;136(suppl 1). Abstract 16610.

84. Roger S, Lavin P, Lerma E, et al. Safety and efficacy of sodium zirconium cyclosilicate for long-term treatment of hyperkalaemia in patients with chronic kidney disease: results from an open-label, phase 3 study. *Nephrol Dial Transplant*. 2018; 33(suppl 1):i72. Abstract FP071.

85. Anker SD, Kosiborod M, Zannad F, et al. Maintenance of serum potassium with sodium zirconium cyclosilicate (ZS-9) in heart failure patients: results from a phase 3 randomized, double-blind, placebo-controlled trial. *Eur J Heart Fail*. 2015; 17(10):1050-1056.

86. Pitt B, Bakris GL, Bushinsky DA, et al. Effect of patiromer on reducing serum potassium and preventing recurrent hyperkalaemia in patients with heart failure and chronic kidney disease on RAAS inhibitors. *Eur J Heart Fail*. 2015;17(10):1057-1065.

87. Weir MR, Mayo MR, Garza D, et al. Effectiveness of patiromer in the treatment of hyperkalemia in chronic kidney disease patients with hypertension on diuretics. *J Hypertens*. 2017; 35(suppl 1):S57-S63.

88. Pitt B, Bushinsky DA, Kitzman DW, et al; Patiromer-204 Investigators. Evaluation of an individualized dose titration regimen of patiromer to prevent hyperkalaemia in patients with heart failure and chronic kidney disease. *ESC Heart Fail*. 2018;5(3): 257-266.

89. Pitt B, Garza D. The tolerability and safety profile of patiromer: a novel polymer-based potassium binder for the treatment of hyperkalemia [published correction appears in *Expert Opin Drug Saf*. 2018;17(5):xi]. *Expert Opin Drug Saf*. 2018;17(5):525-535.

90. Agarwal R, Rossignol P, Garza D, et al. Patiromer to enable spironolactone use in the treatment of patients with resistant hypertension and chronic kidney disease: rationale and design of the AMBER study. *Am J Nephrol*. 2018;48(3): 172-180.

91. Fitch K, Woolley JM, Engel T, Blumen H. The clinical and economic burden of hyperkalemia on Medicare and commercial payers. *Am Health Drug Benefits*. 2017;10(4):202-210.

92. Bandak G, Sang Y, Gasparini A, et al. Hyperkalemia after initiating renin-angiotensin system blockade: the Stockholm Creatinine Measurements (SCREAM) project. *J Am Heart Assoc*. 2017;6(7):e005428.

93. Nilsson E, Gasparini A, Ärnlöv J, et al. Incidence and determinants of hyperkalemia and hypokalemia in a large healthcare system. *Int J Cardiol*. 2017;245:277-284.

94. Betts KA, Woolley JM, Mu F, Xiang C, Tang W, Wu EQ. The cost of hyperkalemia in the United States. *Kidney Int Rep*. 2017;3(2):385-393.

95. Trevisan M, de Deco P, Xu H, et al. Incidence, predictors and clinical management of hyperkalaemia in new users of mineralocorticoid receptor antagonists [published correction appears in *Eur J Heart Fail*. 2019;21(4):540]. *Eur J Heart Fail*. 2018;20(8):1217-1226.

96. Thomsen RW, Nicolaisen SK, Hasvold P, et al. Elevated potassium levels in patients with congestive heart failure: occurrence, risk factors, and clinical outcomes; a Danish population-based cohort study. *J Am Heart Assoc*. 2018; 7(11):e008912.

97. Betts KA, Woolley JM, Mu F, McDonald E, Tang W, Wu EQ. The prevalence of hyperkalemia in the United States. *Curr Med Res Opin*. 2018;34(6):971-978.

98. Karaboyas A, Xu H, Morgenstern H, et al. DOPPS data suggest a possible survival benefit of renin angiotensin-aldosterone system inhibitors and other antihypertensive medications for hemodialysis patients. *Kidney Int*. 2018;94(3): 589-598.

99. Furuland H, McEwan P, Evans M, et al. Serum potassium as a predictor of adverse clinical outcomes in patients with chronic kidney disease: new risk equations using the UK Clinical Practice Research Datalink. *BMC Nephrol*. 2018;19(1):211.

100. Hughes-Austin JM, Rifkin DE, Beben T, et al. The relation of serum potassium concentration with cardiovascular events and mortality in community-living individuals. *Clin J Am Soc Nephrol*. 2017;12(2):245-252.

101. Hagan AE, Farrington CA, Wall GC, Belz MM. Sodium polystyrene sulfonate for the treatment of acute hyperkalemia: a retrospective study. *Clin Nephrol*. 2016;85(1):38-43.

102. Hunt TV, DeMott JM, Ackerbauer KA, Whittier WL, Peksa GD. Single-dose sodium polystyrene sulfonate for hyperkalemia in chronic kidney disease or end-stage renal disease. *Clin Kidney J*. 2018;12(3):408-413.

103. Chernin G, Gal-Oz A, Ben-Assa E, et al. Secondary prevention of hyperkalemia with sodium polystyrene sulfonate in cardiac and kidney patients on renin-angiotensin-aldosterone system inhibition therapy. *Clin Cardiol*. 2012;35(1):32-36.

104. Georgianos PI, Liampas I, Kyriakou A, et al. Evaluation of the tolerability and efficacy of sodium polystyrene sulfonate for long-term management of hyperkalemia in patients with chronic kidney disease. *Int Urol Nephrol*. 2017;49(12): 2217-2221.

105. Chatoth DK, Spiegel DM, Weir MR, et al. Outcomes in ESRD patients on hemodialysis taking patiromer for hyperkalemia. Presented at: ASN Kidney Week; November 2, 2017; New Orleans, LA. Abstract TH-PO779.

106. Kovesdy CP, Rowan CG, Conrad A, et al. Real-world evaluation of patiromer for the treatment of hyperkalemia in hemodialysis patients. *Kidney Int Rep*. 2018;4(2):301-309.