Review

Chronic Hyperkalemia in Cardiorenal Patients: Risk Factors, Diagnosis, and New Treatment Options

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Keywords

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Abstract

Chronic hyperkalemia (HK) is a serious medical condition that often manifests in patients with chronic kidney disease (CKD) and heart failure (HF) leading to poor outcomes and necessitating careful management by cardioneurologists. CKD, HF, diabetes, and renin-angiotensin-aldosterone system inhibitors use is known to induce HK. Current therapeutic options are not optimal, as pointed out by a large number of CKD and HF patients with HK. The following review will focus on the main risk factors for developing HK and also aims to provide a guide for a correct diagnosis and present new approaches to therapy.

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Potassium Homeostasis and Definition of Hyperkalemia

Potassium is the most abundant cation in the intracellular fluid, and maintaining the proper distribution of potassium across the cell membrane is critical for normal cell function. Almost all cells possess Na⁺-K⁺-ATPase, which pumps Na⁺ out of the cell and K⁺ into the cell

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Fig. 1. Classification of hyperkalemia.

and leads to a K^+ gradient across the cell membrane ($K^+_{in} > K^+_{out}$) that is partially responsible for maintaining the potential difference across the membrane. The kidney is primarily responsible for maintaining total body K^+ content by matching K^+ intake with K^+ excretion; K^+ levels can also be modified by several normal (i.e., physical activity) and pathological conditions (i.e., metabolic acidosis and chronic kidney disease, CKD), and its renal secretion is particularly influenced by aldosterone increment and the rate of distal delivery of Na^+ and water.

Hyperkalemia (HK) is a serious medical condition that can cause muscle weakness, paralysis, and cardiac arrhythmias and is associated with increased mortality.

Defining hyperkalemia is not easy while values vary from person to person and day to day; the standard normal range of serum potassium is typically considered to be 3.5–5.0 mEq/L [1]. Hypokalemia occurs when serum potassium drops below the normal range, while hyperkalemia is defined as serum potassium levels above the upper limit of normal, typically defined as >5.0 mEq/L [2, 3]. Hyperkalemia may be further classified as mild, moderate, or severe based on the serum potassium level [4] (Fig. 1).

Epidemiology and Risk Factors

CKD, heart failure (HF), diabetes, and renin-angiotensin-aldosterone system inhibitors (RAASi) represent main risk factors for developing a chronic HK (Table 1 shows HK prevalence according to the estimated glomerular filtration rate, eGFR, in several observational studies).

Abnormalities of serum potassium are common in patients with CKD, and HK is a well-recognized complication of CKD with a prevalence rate of 14–20%.

CKD severity, use of medications such as RAASi and diuretics, and dietary potassium intake are major determinants of serum potassium concentration in CKD together with other cardiovascular comorbidities (such as hypertension and HF) and diabetes. Hyperkalemia is strongly associated with increased risks of death, cardiovascular disease, hospitalization, and progression of kidney disease [5].

Patients affected by CKD, HF, diabetes mellitus (DM), and arterial hypertension using RAASi show a 2–3 times higher risk for developing HK.

Among CKD-related HK risk factors, HF is widely represented because of the higher prevalence of CKD among patients hospitalized for HF [6]. Therefore, patients with HF and CKD take large amounts of RAASi and mineralocorticoid receptor antagonists (MRA) contributing to chronic HK.

In HF patients, a strong association between serum potassium and plasma renin is now clearly assessed [7]. Increased levels of plasma renin are mainly due to kidney hypoperfusion inducing potassium excretion by stimulating aldosterone synthesis, while high potassium levels inhibit RAAS [8].

Table 1. Main observational studies published in the last 5 years on the prevalence of hyperkalemia by eGFR

Study	Setting	Sample size	eGFR, mL/min/1.73 m ²	Hyperkalemia prevalence, % (definition)	Survival by s-K level
Hayes [56]	Renal clinic	1,227	37.0	7.7 (<i>s-K</i> >5.3)	↓ for s-K >5.5
Drawz [57]	Veterans hospital	13,874	46.5	2.5 (<i>s-K</i> ≥5.5)	Not available
Sarafidis [58]	Low-GFR clinic	238	14.5	54.2 (<i>s-K</i> >5.0) 31.5 (<i>s-K</i> ≥5.5) 8.4 (<i>s-K</i> ≥6.0)	Not available
Nakhoul [59]	CKD registry at Cleveland Clinic	36,359	47.0	11.0 (<i>s-K</i> >5.0) 3.3 (<i>s-K</i> >5.5)	↓ for s-K >5.0
Luo [17]	Health care system	55,266	<60	14.9 (<i>s-K</i> 5.0–5.4) 3.9 (<i>s-K</i> 5.5–5.9) 1.1 (<i>s-K</i> ≥6.0)	↓ for s-K >5.0
Chang [60]	Health care system	155,695	<60	5.3, 19.0, 9.4 for <2, 2 to <4, ≥4 s-K test/year (<i>s-K</i> >5.0)	Not available
Betts [61]	Medicare 2014	120,933	<60	9.4 in CKD 3 19.5 in CKD 4 18.5 in CKD 5 52.8 in dialysis (<i>s-K</i> >5.0)	Not available
Núñez [62]	Heart failure	2,164	62.0	5.6 (<i>s-K</i> >5.0)	↓ for s-K >5.0
Collins [63]	US integrated health delivery networks	911,698	with and w/o CKD (eGFR <60)	8.3 in diabetes mellitus 9.1 in heart failure 11.5 in CKD 13.1 combined (<i>s-K</i> ≥5.0)	↓ for s-K ≥5.0

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; s-K, serum potassium.

The above-described pathophysiological pathway could explain why RAASi, MRA, and direct renin inhibitor therapies are significantly associated with HK [9].

HK can be also related to reduced sodium concentration at the distal nephron and/or aldosterone deficiency, and it is worsened by stage 3 or later CKD stages [10].

In healthy subjects, plasma aldosterone levels are inversely related with sodium delivery to the distal nephron, and potassium excretion is not affected by extracellular volume changes [10]. At the same time, HF patients present increased levels of plasma aldosterone leading to increased sodium reabsorption in the proximal nephron and its decreased delivery to the distal nephron with consequent reduced potassium excretion; the final result, often worsened by RAASi-based treatment, is HK development [10, 11].

About 25 million people present signs and symptoms of HF worldwide, and most of them present HK due to the disease itself, comorbidities, and pharmacological management.

Among HF patients, HK can be related to one of the following 2 circumstances:

(a) Comorbidities closely associated with HF: DM, CKD, and hormonal disorders (i.e., Addison's disease and hypoaldosteronism); and

(b) Drug-associated HK (RAASi, MRA, nonsteroidal anti-inflammatory drugs, and diuretics).

HF therapy with RAASi and/or MRA increases the HK risk; HK can occur in about 38% of hospitalized patients on angiotensin-converting enzyme inhibitor (ACEi) treatment, while it can develop in about 10% of RAASi-treated outpatients [12, 13].

Therefore, about 15% of both arms (LCZ696 and enalapril) enrolled patients in the PARADIGM-HF (Prospective Comparison of ARNI with ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial showed HK [14].

Similar evidence was found in RALES (Randomized Aldactone Evaluation Study) trial-enrolled patients; although beneficial effects of spironolactone were demonstrated in the treatment compared to the placebo group, a higher mortality risk was observed with potassium levels > 5.5 mmol/L [15].

Hyperkalemia incidence could increase in patients with HF and impaired renal function, since CKD itself represents an additional risk factor for developing chronic HK.

Referring to the ADHERE (Acute Decompensated Heart Failure National Registry) study, >60% of patients presented kidney disease [16]. CKD patients can develop chronic HK (up to 20%) with a consequent higher incidence of mortality and cardiovascular events often leading to RAASi treatment withdrawal [17].

Concerning diabetes, the incidence of HK is higher in diabetic patients than in the general population [10, 18]. Redistribution of potassium from the intracellular to the extracellular compartment (shift HK) can induce HK with no net total body K⁺ increase, as far as in acidosis (for each 0.1 fall in pH, potassium increases by approximately 0.4 mmol/L), insulin deficiency, hypertonicity, cell lysis (rhabdomyolysis), and drugs (e.g., β -blockers). Reduced glomerular filtration of K⁺ (due to acute kidney injury and CKD) and many drugs that interfere with K⁺ excretion are associated with HK (ACEi, angiotensin II receptor blockers, renin inhibitors, β -blockers, and potassium-sparing diuretics) [10, 18]. Nevertheless, the most common causal factor of chronic HK in diabetics is the reduced tubular secretion of K⁺ due to the syndrome of hyporeninemic hypoaldosteronism, characterized by mild-to-moderate renal insufficiency, and patients typically present with asymptomatic HK [19]. The development of overt HK is most common in patients with other risk factors that further impair the efficiency of potassium excretion, such as renal insufficiency, volume depletion, or the use of medications that interfere with potassium handling (see above).

Worsening renal function and HK may occur in patients on SGLT-2 inhibitor therapy (such as canagliflozin or dapagliflozin), especially in patients predisposed to HK due to impaired renal function, medication, or other medical conditions [20, 21]. Hyporeninemic hypoaldosteronism is more frequently observed in diabetic and elderly patients as well as in those with chronic renal impairment. Moreover, elderly patients may have decreased renal function even without significant elevations in serum creatinine levels (<1.2 mg/dL). Consequently, diabetics (especially the elderly) on medications known to interfere with K⁺ homeostasis are at increased risk for HK, and close K⁺ monitoring is fully requested [22, 23].

Therefore, type 1 DM patients can also develop HK due to concurrent adrenal insufficiency in the setting of the autoimmune polyglandular syndrome [24].

Finally, a major issue for developing chronic HK is represented by RAAS-inhibiting drugs that are so crucial in treatment of diabetes and CKD-related hypertension as far as HF.

An “1B” recommendation KDIGO (Kidney Disease: Improving Global Outcomes) guideline states RAASi therapy in CKD proteinuric hypertensive patients (urine albumin excretion >300 mg/24 h or proteinuria >500 mg/24 h) based on nephroprotective properties since it was revealed that the risk of end-stage renal disease falls by 24% for each 30% reduction in albuminuria levels [25, 26]. At the same time, a post hoc analysis of the LIFE (Losartan Intervention for Endpoint Reduction in Hypertension) trial showed that cardiorenal protection is strictly related to proteinuria reduction [27]. Actual guidelines suggest a level of 0.5 g/24 h as a major goal of antiproteinuric therapy [25] although this is not an easy achievement due

to RAASi side effects: acute kidney injury episodes (<2% of treated patients) and, especially, HK (ranging from 5 to 40%) often accountable for RAASi treatment withdrawal [28].

Risk Factors for Chronic HK

- Potassium intake – salt substitutes and other dietary sources
- CKD (eGFR <30 mL/min/1.73 m²) or end-stage renal disease
- Drugs – e.g., NSAIDs, RAASi
- Cardiac failure – reduced renal perfusion
- DM – hyperglycemia, diabetic ketoacidosis
- Coronary artery and peripheral vascular diseases
- Advanced age – decreased plasma renin activity, decreased aldosterone levels

Diagnosis of HK

Potassium is the most abundant intracellular cation (100–150 mmol/L) and is critical in many physiological functions. Absorption of potassium from the gastrointestinal tract is rapid and usually complete. Depending on diet, the normal daily intake can vary. Common potassium-rich foods include fruits, potatoes, beans, and grains; in contrast, high-fat diets usually contain low amounts of potassium.

Pseudo-HK (a falsely high potassium), caused by poor phlebotomy technique, hemolysis, laboratory processing, thrombocytosis, and leukocytosis, can lead to inappropriate intervention [29]. The serum potassium rises with and falls after exercise [30].

Potassium is released from platelets during clotting, raising the serum but not plasma potassium in patients with thrombocytosis. To exclude pseudo-HK, plasma potassium (obtained from a heparinized sample) or whole blood potassium should be measured if platelet counts exceed 500,000 [29].

Causes of pseudo-HK are summarized in Table 2.

Although chronic HK is strictly associated with a renal function decline, we cannot provide an ultimate HK definition in CKD patients, and no actual guidelines clearly indicate how many blood tests have to be performed before diagnosing chronic HK. Current KDIGO guidelines suggest serum potassium measurement within 1 week of starting RAASi therapy or dose uptitration in subjects with reduced renal function, while NICE (National Institute for Health and Care Excellence) guidelines recommend serum potassium testing in CKD patients administered RAASi before starting therapy and between 1 and 2 weeks thereafter as well as after each dose increase to stress the importance of potassium level monitoring during treatment [25, 31].

Large proportions of many observational studies have evaluated the prevalence of chronic HK in CKD patients on the basis of a single sampling [32–34], whereas recent randomized controlled trials performed serum potassium laboratory tests at least twice in order to stratify patients to enroll for HK treatment [35–37].

A recent study that evaluated hypertensive patients undergoing various antihypertensive medications, including CKD ones, showed that the proportion of subjects with HK increased as eGFR worsened and the number of laboratory serum (s)-K assessment increased. About 54% of CKD patients with eGFR ranging from 30 to 44 mL/min/1.73 m² BSA having >4 laboratory testings per year had serum potassium >5 mEq/L and 22% >5.5 mEq/L over a 3-year observation period [38]. In this study, further subgrouping was made according to the frequency of HK that helped to identify subjects with transient, intermittent, or persistent HK. Interestingly, the prevalence of HK of all these clinical forms progressively increased with increasing number of laboratory samplings per year. Furthermore, HK risk significantly increased with lower eGFR, and the use of RAASi, especially ACEi. In the Renal Research

Fig. 2. ECG changes according to kalemia levels.

Table 2. Determinants of pseudohyperkalemia

Cause	Explanation
Mechanical factors	Tourniquet applied for prolonged periods, fist clenching, traumatic venipuncture or probing, vigorous mixing, or excessive centrifugal force of specimens
Chemical factors	Ethanol-containing antiseptics
Temperature	Specimens exposed to low (2–8°C) or above room temperature can result in potassium leakage
Time	Delayed processing can result in potassium leakage
Patient factors/diseases	Fear of venipuncture/crying and associated hyperventilation (even for a few minutes) is associated with acute respiratory alkalosis and significant hyperkalemia; thrombocytosis and chronic lymphocytic leukemia can result in increased potassium levels
Miscellaneous	False plasma reference ranges or mislabeling, contaminants such as potassium-containing intravenous fluids

Institute CKD Study cohort [39], an average of 6 serum potassium values was performed during a 2.6-year follow-up period in CKD patients in order to identify subjects with hypokalemia ($s\text{-K} \leq 4 \text{ mEq/L}$), normokalemia ($4\text{--}5.5 \text{ mEq/L}$), and HK ($s\text{-K} \geq 5.5 \text{ mEq/L}$).

Last, despite generally being tested at least twice a year, CKD patients are not necessarily aware of their potassium levels, and this finding points to the need of informing them about the opportunity of monitoring serum potassium and the importance of this approach for safety reasons [31, 40].

Chronic HK can also be diagnosed by performing a 12-lead electrocardiographic (ECG) test since HK has depolarizing effects on the heart that are manifested by changes in the electrocardiogram (Fig. 2). The progressive changes in HK are classically listed as:

- (a) peaked T waves that are tall, narrow, and symmetrical and can occasionally be confused with the hyperacute T-wave change associated with an ST-segment elevation in myocardial infarction; however, in the latter condition, the T waves tend to be more broad based and asymmetric in shape;
- (b) ST-segment depression;
- (c) widening of the PR and QRS interval; and
- (d) loss of the P wave, a sine-wave pattern [41].

Table 3. Pharmacologic comparison of potassium-lowering agents

Pharmacologic property	Sodium polystyrene sulfonate (SPS)	Patiromer calcium sorbitex	Sodium zirconium cyclosilicate
Brand name	Kayexalate	Veltassa	Lokelma
Mechanism of action	Binds potassium in the GI tract and facilitates excretion in the feces	Binds potassium in the GI tract and facilitates excretion in the feces	Binds potassium in the GI tract and facilitates excretion in the feces
Selectivity for potassium ion	Nonselective; also binds calcium and magnesium	Selective; also binds magnesium	Highly selective; 9 times the potassium-binding capacity compared to SPS; also binds ammonium
Sodium content	1,500 mg sodium per 15-g dose	No sodium content	Approximately 1,000 mg sodium per 10-g dose
Sorbitol content	20 g sorbitol per 15-g dose	4 g sorbitol per 8.4-g dose	No sorbitol content
Onset of effect	Variable; 2–6 h	7–48 h	1–6 h
Duration of effect	Variable; 6–24 h	12–24 h	Unclear; appears to be 4–12 h based on trial data
Dosing	15 g p.o. 1–4 times/day	8.4 g p.o. once daily with a meal titrated to 25.2 g/day based on response	10 g p.o. thrice daily with meals for chronic treatment (not approved); based on trial data
Preparation(s)/administration	Liquid or powder for suspension; mix with water (3–4 mL/g drug) and administer within 24 h	Powder for suspension; mix with water (90 mL) and administer immediately; store in refrigerator (36–46°F or 2–8°C); use within 3 months upon removal from refrigerator	White, tasteless powder for suspension; mix vigorously with water (240 mL) and administer immediately
FDA, US Food and Drug Administration; GI, gastrointestinal; p.o., per os (by mouth).			

The plasma potassium concentration often correlates poorly with cardiac manifestations; in a retrospective review, only 16 of 90 cases met strict criteria for ECG changes reflective of HK (defined as new peaked and symmetric T waves that resolved on follow-up). In 13 of these cases, the electrocardiogram was interpreted as showing no T-wave changes even when read by a cardiologist [41]. In addition, ECG criteria for HK were noted in only 1 of 14 patients who manifested arrhythmias or cardiac arrest attributed to increased plasma potassium concentration. Therefore, the use of ECG can help to risk stratify patients with severe HK for short-term adverse events [42].

Diagnosis of Chronic HK

- Although single s-K testing can identify patients at risk for chronic HK, testing at least 2 times per year seems to be a wise approach to properly identify chronic HK.
- Assessment of s-K in CKD patients is strongly recommended before starting RAASi therapy, 1–2 weeks thereafter, and at each dose uptitration.
- ECG is considered a main diagnostic tool for HK diagnosis; however, this is true in only 40–50% of chronic HK patients.

Treatment Options

Chronic HK management is mainly based on RAASi therapy downtritation or withdrawal according to current available guidelines and potassium binders.

Table 3 summarize pharmacological properties of potassium-lowering drugs.

RAASi Therapy Modulation

Evidence-based medicine and current clinical practice suggest that RAAS inhibition represents a cornerstone for both cardioprotection in HF patients and renoprotection in diabetic patients (especially those with associated hypertension) [43, 44]. However, RAAS inhibition could be difficult in patients with CKD due to the risk of progression towards end-stage renal disease and/or HK development.

NICE guidelines do not recommend to start RAASi therapy in CKD patients with basal potassium levels >5 mEq/L but to withdraw it for patients with potassium levels increasing to 6 mEq/L [31]; this is particularly true when an MRA is added to the therapeutic schedule leading to discontinuation rates up to 25–50% [17].

The drawback of RAASi therapy reduction or discontinuation is that high-risk patients (as HF and diabetic ones) miss the best treatment option available, and it is closely related to the growing incidence of major cardiovascular events and mortality [45].

It is possible to avoid HK by adding alkali to correct metabolic acidosis, prescribing a low potassium diet and encouraging diuretic therapy paying attention to consequent hypovolemia and potential worsening of underlying kidney disease [46].

Sodium Polystyrene Sulfonate

Sodium polystyrene sulfonate (SPS) has represented and actually still represents primary care for controlling potassium levels in CKD and HF patients, but only 1 randomized controlled trial has been conducted [47]. As observed in daily clinical practice, the most common adverse events experienced were nausea, vomiting, and constipation.

SPS is typically used in hospitals and less frequently in the outpatient setting due to low tolerability [47] since in 2009 the US Food and Drug Administration posted a warning because of reported cases of colonic necrosis, bleeding, ischemic colitis, and perforation related to SPS therapy [48]. Based on clinical reports, SPS therapy is not suitable for chronic HK therapy, and new potassium binders are needed.

Patiromer

Patiromer is an organic, unabsorbable potassium-binding polymer. It is formulated with calcium as the exchange ion and sorbitol to improve stability, rather than promote movement through the gastrointestinal tract, as is the case with SPS [49]. Fecal excretion of potassium bound to patiromer facilitates a reduction in serum potassium concentration in a dose-dependent manner. Recommended dosing is 8.4 g once daily, titrated to 25.2 g/day based on response. Clinical trials have utilized a twice-daily dosing regimen (Table 4), but a phase I trial showed that fecal potassium excretion was similar between 8.4 g thrice daily, 12.6 g twice daily, and 25.2 g daily [49]. Several clinical trials have investigated patiromer potassium-binding properties. The PEARL-HF trial was designed to assess the safety, efficacy, and tolerability of patiromer in 105 HF patients with either CKD (eGFR <60 mL/min) or a history of HK [31, 50]. The subset of CKD patients had a mean potassium reduction of −0.14 mEq/L in the patiromer group from baseline to week 4 compared to an increase of 0.38 mEq/L in the placebo group, similar to the overall population.

The AMETHYST-DN study was designed to determine the safety, efficacy, and optimal dosing of patiromer in 306 outpatients with HK and CKD (Table 3) [51]. After a 4-week run-in

Table 4. Summary of patiromer clinical studies for the treatment of hyperkalemia

Study design	Patient population	Primary end point(s)	Study treatment and duration	Major findings
PEARL-HF: phase II, prospective, randomized, double-blind, placebo-controlled, parallel-group clinical trial	Patients with heart failure and a potassium concentration of 4.3–5.1 mEq/L ($n = 105$) with an indication to start aldosterone antagonist therapy	Mean change in potassium concentration from baseline to the end of the study (day 28)	Patiromer 15 g p.o. twice daily or placebo for 4 weeks	Baseline potassium 4.69 mEq/L; least-square mean reduction of -0.22 mEq/L with patiromer; increase of 0.23 mEq/L with placebo (mean difference -0.45 mEq/L, $p < 0.001$)
AMETHYST-DN: phase II, prospective, randomized, open-label, dose-ranging clinical trial	Outpatients with hyperkalemia (>5 mEq/L), type 2 diabetes mellitus, and CKD (eGFR 15–59 mL/min/1.73 m ²) receiving an ACEi, ARB, or both ($n = 306$)	Mean change in potassium concentration from baseline to week 4 or prior to dose titration	Patiromer 4.2, 8.4, or 12.6 g p.o. twice daily for 52 weeks for mild hyperkalemia (5.1–5.5 mEq/L); patiromer 8.4, 12.6, or 16.8 g p.o. twice daily for 52 weeks for moderate hyperkalemia (5.6–5.9 mEq/L)	Mild hyperkalemia: least-square mean reduction of -0.35 mEq/L (95% CI -0.48 to -0.22) for 4.2-g group, -0.51 mEq/L (95% CI -0.64 to -0.38) for 8.4-g group, and -0.55 mEq/L (95% CI -0.68 to -0.42) for 12.6-g group ($p < 0.001$ for each group) Moderate hyperkalemia: least-square mean reduction of -0.87 mEq/L (95% CI -1.14 to -0.60) for 8.4-g group, -0.97 mEq/L (95% CI -1.23 to -0.7) for 12.6-g group, and -0.92 mEq/L (95% CI -1.17 to -0.67) for 16.8-g group ($p < 0.001$ for each group)
OPAL-HK: phase III prospective clinical trial with a single group, single-blind initial treatment phase and a randomized, single-blind, placebo-controlled withdrawal phase	Initial 4-week phase: patients with stage 3 or 4 CKD (eGFR 15–59 mL/min/1.73 m ²) and a potassium concentration of 5.1–6.4 mEq/L stabilized on an RAASi ($n = 243$)	Initial phase: mean change in potassium concentration from baseline to week 4	Initial phase: patiromer 4.2 g p.o. for mild hyperkalemia (5.1–5.4 mEq/L) or 8.4 g p.o. for moderate-to-severe hyperkalemia (5.5–6.4 mEq/L) twice daily for 4 weeks	Initial phase: reduction in potassium concentration of -1.01 ± 0.03 mEq/L (95% CI -1.07 to -0.95) ($p < 0.001$)
	Randomized withdrawal 8-week phase: patients with a potassium concentration of 3.8–5 mEq/L at the end of the initial phase who had potassium ≥ 5.5 mEq/L at baseline ($n = 107$)	Randomized phase: between-group difference in the median change in potassium concentration over the first 4 weeks or to the earliest visit when potassium was <3.8 or ≥ 5.5 mEq/L	Randomized phase: continued patiromer at same dose as at week 4 or switched to placebo for 8 weeks	Randomized phase: median change in potassium concentration was an increase of 0.72 mEq/L for placebo and no change (median 0 mEq/L) for patiromer; between-group difference of -0.72 mEq/L (95% CI -0.99 to -0.46) ($p < 0.001$)
Phase I, prospective, open-label, single-arm clinical trial	Patients with CKD (eGFR 15–89 mL/min/1.73 m ²) and hyperkalemia (5.5–6.4 mEq/L) stabilized on an RAASi ($n = 25$)	Change in potassium concentration from baseline over 48 h; time of onset when mean change in potassium concentration was significant ($p < 0.05$)	Patiromer 8.4 g p.o. twice daily with meals for 2 days	Baseline potassium 5.93 mEq/L; change in potassium concentration 7 h after the final dose (-0.21 mEq/L; 95% CI -0.35 to -0.07) ($p = 0.004$); mean potassium concentration decreased to 5.41 mEq/L by 20 h after the first dose ($p < 0.001$)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; p.o., per os (by mouth); RAASi renin-angiotensin-aldosterone system inhibitor.

phase where RAASI therapy was initiated and/or titrated, patiomer doses were adjusted to maintain target potassium levels of 4–5 mEq/L. All patients continued to receive RAASI treatment throughout the study duration. The least-square mean reduction in potassium from baseline to week 4 ranged from –0.35 to –0.97 mEq/L in a dose-dependent manner. In a 44-week maintenance phase ($n = 262$), the proportion of patients with normal potassium (3.8–5 mEq/L) at each visit through week 52 was 83.1–92.7% in the mild-HK group and 77.4–95.1% in the moderate-HK group. Common adverse effects experienced by patients in this study were constipation (6.3) and diarrhea (5.6%) [35]. Additionally, hypokalemia occurred in 5.6% and hypomagnesemia in 8.6% of the patients on patiomer. No study provided information on aldosterone plasma concentration after patiomer therapy. Interestingly, in patients with chronic HF, the administration of the polymeric potassium binder allowed up-titration to the maximal spironolactone dose, suggesting that a change in plasma aldosterone disposal could ensue as an effect of therapy [49].

Worsening CKD (9.2%) and hypertension (7.9%) were observed, but they were strictly related to the natural disease history. The OPAL-HK phase III trial evaluated the efficacy and safety of patiomer in 243 CKD patients with HK (Table 4). At week 8 of the randomized withdrawal phase, the recurrence of HK (potassium >5.0 mEq/L) was observed in 43% of patients on patiomer compared to 91% on placebo ($p < 0.001$); 94% of patients on patiomer were able to continue RAASI therapy by the end of the randomized phase compared to 44% of placebo patients. The most common adverse effects of patiomer during the initial treatment phase were constipation (11%), diarrhea (3%), nausea (3%), and hypomagnesemia (3%). Hypokalemia occurred in 3% of patients [51, 52]. Based on the consistent results of these 4 studies, patiomer appears to play a significant role as maintenance treatment for HK and in initiating, maintaining, and titrating RAASI therapy in patients with CKD and/or HF.

Twelve drugs were tested for potential pharmacological interactions with patiomer; 9 of these (amlodipine, cinacalcet, clopidogrel, furosemide, lithium, metoprolol, trimethoprim, verapamil, and warfarin) showed no interaction, while for the remaining 3 (ciprofloxacin, levothyroxine, and metformin) a 3-h separation between dosing with patiomer was sufficient to avoid an interaction as suggested by the guidelines of the European Medicines Agency [53].

Sodium Zirconium Cyclosilicate (ZS-9)

ZS-9 is an inorganic, unabsorbable polymer of zirconium silicate [54]. It is believed that the ion channels formed by the atomic structure of ZS-9 mimic those of endogenous potassium channels. When the sodium (or hydrogen) ion dissociates from ZS-9, a negative charge and pore size of 3 Å make potassium (2.98 Å) the ideal cation for trapping [55]. ZS-9 possesses 9 times the potassium-binding capacity of SPS in vitro [54].

A phase II clinical trial was designed to determine the safety, efficacy, and optimal dosing of ZS-9 in 90 patients with HK and stage 3 CKD. A potassium reduction >1.0 mEq/L occurred in 41.7% of patients on the 10-g dose compared to 3.4% on placebo by hour 38 of the study. The 3- and 10-g groups experienced a greater rate of potassium concentration reduction over 48 h compared to placebo. In 66 patients receiving RAASI therapy, the 10-g dose produced a mean reduction of -0.12 ± 0.50 mEq/L by 1 h compared to a mean increase of 0.19 ± 0.31 mEq/L with placebo ($p < 0.03$). The most common adverse effects were nausea, vomiting, and urinary tract infection, with each occurring in 5% (3 of 60) of ZS-9 patients [55].

The HARMONIZE phase III trial evaluated the efficacy and safety of ZS-9 for 28 days in HK outpatients. In the open-label phase, 10-g ZS-9 thrice daily produced a mean reduction in potassium from baseline of –0.4 mEq/L by 2 h ($p < 0.001$) for both comparisons. Patients on RAASI therapy achieved a mean potassium reduction of –1.02 mEq/L by hour 48, which was similar to the overall study population. Normal potassium concentration (3.5–5 mEq/L) was

achieved by 84% of patients within 24 h and 98% within 48 h. At least 1 adverse event was observed in 7.8% of patients on ZS-9. Hypokalemia occurred in 7.2% (11 of 152) of patients receiving ZS-9, but hypomagnesemia was not observed [35]. ZS-9 was recently approved (May 2018) by the FDA for HK treatment in adult subjects with the recommended 10-g starting dose administered 3 times a day for up to 48 h. For maintenance treatment, the recommended dose is 10 g once daily, adjusting dose at 1-week intervals as needed (by 5 g daily) to obtain the desired serum potassium target range (<https://www.drugs.com/history/lokelma.html>).

Therapy of Chronic HK

- RAASi therapy modulation
- SPS
- Patiromer
- ZS-9

Conclusions

Chronic HK is a major concern in CKD, HF, and diabetic patients, especially under RAASi therapy. The current management of chronic HK does not provide whole control of potassium levels during a long period of treatment. RAASi therapy withdrawal limits the patients in managing their underlying diseases, and patiromer and ZS-9 are significant advancements for the treatment of chronic HK. These drugs have enhanced specificity for potassium together with an improved safety profile compared to SPS. Based on the currently available evidence, patiromer seems to be the preferred agent for the treatment of chronic HK, whereas ZS-9 may have a role in the treatment of acute HK. Further comparative trials among patiromer, ZS-9, and SPS would provide essential evidence and should be considered in the future for better HK management.

Ultimate Key Points

- Hyperkalemia is a major issue in CKD patients
- Main risk factors are also represented by HF and diabetes
- RAASi therapy could be accountable for chronic HK
- New treatment options (patiromer and zirconium silicate) should be considered to avoid RAASi therapy withdrawal

Statement of Ethics

The paper is in accord to ethical principles.

Disclosure Statement

All Authors have nothing to disclose.

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