



Hyperkalemia: Prevalence, Predictors and Emerging Treatments

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ABSTRACT

It is well established that an elevated potassium level (hyperkalemia) is associated with a risk of adverse events including morbidity, mortality and healthcare system cost. Hyperkalemia is commonly encountered in many chronic conditions including kidney disease, diabetes and heart failure. Furthermore, hyperkalemia may result from the use of renin-angiotensin-aldosterone system inhibitors (RAASi), which are disease-modifying treatments for these conditions. Therefore, balancing the benefits of optimizing treatment with RAASi while miti-

gating hyperkalemia is crucial to ensure patients are optimally treated. In this review, we will briefly discuss the definition, causes, epidemiology and consequences of hyperkalemia. The majority of the review will be focused on management of hyperkalemia in the acute and chronic setting, emphasizing contemporary approaches and evolving data on the relevance of dietary restriction and the use of novel potassium binders.

Keywords: Hyperkalemia; Potassium binder; Patiromer; Sodium zirconium cyclosilicate; Sodium polystyrene sulfonate

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Key Summary Points

Hyperkalemia is associated with morbidity and mortality, and the risks are even higher in individuals with underlying comorbid conditions such as kidney disease, diabetes and heart failure

The management of chronic hyperkalemia requires a multimodal approach. This may include the use of loop or thiazide diuretics, potassium binders, dietary modification, correction of acidosis, or adjusting or stopping medications that lead to hyperkalemia when otherwise clinically indicated

While dietary intake of potassium in those at risk has long been felt to be a cause of hyperkalemia, this paradigm is being challenged, and studies are ongoing to better understand this association

Care should be taken to avoid permanent discontinuation or suboptimal dosing of goal-directed medical therapy that can cause hyperkalemia (i.e., RAASi). When discontinued because of the risk of hyperkalemia, clinicians should look to restart RAASi when safe to do so; newer potassium binders may allow for maintenance or dose up-titration of RAASi when clinically indicated

Limited data exist to support the efficacy and safety of long-term use of older potassium binders. Where available, contemporary potassium binders such as sodium zirconium cyclosilicate and patiromer are efficacious and may be safer and better tolerated. Trials are ongoing to further evaluate the efficacy of these binders in facilitating goal-directed therapy for chronic health conditions

INTRODUCTION

Potassium is an essential cation for cellular function, and serum potassium levels are tightly regulated by the body in a narrow range (typically 3.5–5.0 mmol/l). Hyperkalemia is an issue of clinical importance for patients and providers due, in part, to its long-recognized clinical consequences including cardiac arrhythmias. More recently, the true epidemiologic impact of hyperkalemia has been even better characterized; an elevated potassium level is associated with hospitalization [1, 2], mortality and large increases in healthcare costs on a population level [1, 3]. These consequences are even more profound in patients with underlying pre-existing comorbid conditions [4, 5].

There is a strong association between renin-angiotensin-aldosterone system inhibitors (RAASi), namely, angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs) and mineralocorticoid receptor antagonists (MRAs), and hyperkalemia [6]. RAASi are a key pillar of therapy for kidney disease, diabetes and heart failure. Therefore, discontinuing these agents in response to hyperkalemia compromises care and may in turn lead to morbidity and mortality. How can providers find the right balance to minimize the risks of hyperkalemia while maintaining patients on therapies that optimize their health? In this review, we will discuss the definition, causes, epidemiology and consequences of hyperkalemia. The focus of the review will be on management, providing clinicians and healthcare professionals with practical suggestions around how best to monitor patients, to prevent the development of hyperkalemia and to lower potassium to support the maintenance or implementation of RAASi when clinically indicated. The article is based on previously conducted studies and does not contain any new studies on human participants or animals performed by any of the authors.

DEFINITION/PATHOGENESIS

Hyperkalemia is traditionally defined as a serum potassium level > 5.0 mmol/l. More recently,

stakeholders participating in the Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference suggested the importance of using clinical information to complement the absolute value of serum potassium. In this regard, the classification of acute hyperkalemia (as mild, moderate or severe) should be based both on the absolute serum level and the presence or absence of electrocardiogram (ECG) changes consistent with hyperkalemia [7]. Using such an approach, hyperkalemia may be classified from mild (potassium concentration of 5.0–5.9 mmol/l with no ECG changes) to severe (potassium concentration of 6.0–6.4 mmol/l with ECG changes or ≥ 6.5 mmol/l [7] irrespective of the ECG findings). This classification emphasizes that some patients may experience the consequences of hyperkalemia at lower serum potassium levels, and if symptoms/signs are present, urgent intervention to avoid morbidity and mortality from cardiac arrhythmia is needed [8–10]. Somewhat similar thresholds have been used to define hyperkalemia severity in the chronic setting [11, 12].

Notwithstanding the threshold used to define it, the pathogenesis of hyperkalemia is complex and usually involves reduced potassium excretion, movement of intracellular potassium to the extracellular space or, rarely, excess potassium intake. Chronically, hyperkalemia develops primarily because of reduced urinary potassium excretion. Absorption of potassium does occur in the small intestine (and to a lesser extent, colon), and hyperaldosteronism increases fecal loss of potassium through an exchanger. While the contribution of the bowel to potassium absorption is only minimal [13], anephric patients can become hyperkalemic when intestinal potassium excretion is reduced [14]. In the kidney, potassium is freely filtered by the glomerulus, and approximately 90% is reabsorbed proximally (in the proximal convoluted tubule and ascending loop of Henle) [7]. Potassium is more tightly regulated in aldosterone-sensitive distal nephrons under the influence of several factors (including aldosterone, tubular flow and distal sodium delivery), which enhance the secretion of potassium [7]. Alterations in these factors

(including loss of nephron function due to kidney disease) can result in hyperkalemia.

CAUSES

Acknowledging the complex pathophysiology, one must consider a number of potential causes when assessing patients with hyperkalemia. Rapid potassium shift into the extracellular space can result from some forms of metabolic acidosis, medications, insulin deficiency, rhabdomyolysis and tumor lysis syndrome [9]. Any reduction in kidney function (either acutely or chronically) can lead to impaired potassium excretion. In addition, factors that impair distal urinary flow, distal delivery of sodium or electrogenic sodium reabsorption (i.e., due to aldosterone antagonists, aldosterone deficiency or electrogenic sodium channel blockers) can also lead to hyperkalemia. While these conditions need to be thoroughly evaluated in all patients presenting with acute or chronic hyperkalemia, an important condition that should be ruled out is pseudohyperkalemia, which is a rise in potassium level due to excessive release of potassium. Pseudohyperkalemia can occur during or after blood collection and can be caused by hemolysis (e.g., by a faulty sample collection or fist clenching), leukocytosis or thrombocytosis [9, 15]. While an extensive summary of all causes of hyperkalemia is beyond the scope of this review, a brief summary of common causes (including medications and the location of action) is noted in Table 1.

CLINICAL CONSEQUENCES, IMPACT AND EPIDEMIOLOGY

The incidence and prevalence of hyperkalemia is quite variable because of factors such as the target population and the potassium cut-off used to define it. In a contemporary meta-analysis, the pooled prevalence of hyperkalemia in the inpatient, outpatient, emergency room, intensive care unit and dialysis unit was 6.3% (95% confidence interval 5.8–6.8%) with an incidence of 2.8 cases/100 person years, but much lower in the general, outpatient

Table 1 Select causes of hyperkalemia

Excessive intake^a	Impaired excretion
<i>Food sources high in dietary potassium</i>	<i>Acute kidney injury</i>
Potatoes, squash, bananas and avocados	<i>Chronic kidney injury</i>
Lentils, beans and other legumes	<i>Medications</i>
Fruit juices and soft drinks	Angiotensin-conversion enzyme inhibitors
Meat products	Angiotensin receptor blockers
<i>Sodium chloride substitutes</i>	Angiotensin receptor-neprilysin inhibitors
<i>Potassium supplementation</i>	Direct renin inhibitors
Transcellular shift	Mineralocorticoid-receptor antagonists
<i>Medications</i>	Potassium-sparing diuretics
Betablockers	Nonsteroidal anti-inflammatory drugs
Digoxin	Heparin and derivatives
Succinylcholine	Calcineurin inhibitors
<i>Acidosis</i>	Trimethoprim
<i>Hypoinsulinemia</i>	Pentamidine
<i>Cell lysis</i>	<i>Reduced effective arterial blood volume</i>
Rhabdomyolysis	Heart failure
Tumor lysis syndrome	Cirrhosis
<i>Channelopathies</i>	Renal artery stenosis
	<i>Hypoaldosteronism</i>
	Diabetes
	Primary or secondary adrenal insufficiency
	<i>Tubulopathies</i>

^aUsually not a cause in isolation, rather requires concurrent reduced kidney function

population (prevalence 1.3%, incidence 0.4/100 person years) [16]. Expectedly, the prevalence is influenced by the presence or absence of underlying comorbid conditions. In the same meta-analysis, using a potassium threshold of > 5.0 mmol/l and including only studies with a sample size \geq 1250 participants, Humphrey et al. found that the prevalence was 7.5% in non-dialysis CKD, 8.3% in diabetes, 8.0% in heart failure and 35% in dialysis-dependent CKD [16]. Kidney disease is the single largest predictor of hyperkalemia; in a large meta-analysis by Kovesdy et al., estimated glomerular filtration rate (eGFR) was shown to have a nearly linear relationship with hyperkalemia and those with stage 3 CKD or higher had a nearly threefold increase in moderate to severe hyperkalemia (\geq 5.5 mmol/l) for each 15 ml/min/1.73m² reduction in eGFR [4].

In addition to comorbid conditions, many medications used to treat kidney disease, heart failure and diabetes are also associated with a higher risk of incident and recurrent hyperkalemia although this may simply represent indication bias. In the above-mentioned meta-analysis, among studies with a larger sample size, RAASi use was associated with a 6.2% prevalence of hyperkalemia (using potassium thresholds of > 5.5 mmol/l) whereas prevalence in the outpatient population was 4.2% [16]. Hyperkalemia is also commonly reported in the treatment arm of large, controlled trials evaluating the use of ACEi or ARBs in heart failure and diabetic nephropathy [17–20]. Furthermore, the simultaneous use of two RAASi has been shown to confer an even higher risk of hyperkalemia, which suggests that hyperkalemic risk factors are cumulative [21–23]. Aldosterone antagonists are also associated with hyperkalemia as demonstrated in the Randomized Aldactone Evaluation Study (RALES) and in post-marketing surveillance [24, 25]. Similar increases in serum potassium were found in hypertension and heart failure trials evaluating the use of eplerenone [26–28]. Finally, a post hoc safety analysis of finerenone, a novel, selective nonsteroidal mineralocorticoid receptor antagonist evaluated in two recent clinical trials, also demonstrated a twofold increase in hyperkalemic adverse events, although the risk

of serious hyperkalemia-associated morbidity or mortality was low (potentially due to rigorous routine monitoring and management) [29].

Patients with mild hyperkalemia usually present without signs or symptoms, but at higher levels, hyperkalemia can be associated with life-threatening cardiac dysrhythmias [9]. In most, these arrhythmias occur with potassium elevations > 6.5 mmol/l; however, some patients can develop arrhythmias at lower levels. In contrast, patients with chronic hyperkalemia (e.g., dialysis patients) may remain asymptomatic despite marked elevations in potassium [9, 30, 31]. This is hypothesized to be due to compensatory mechanisms resulting in intracellular potassium storage [11]. In addition to the serum level, the rate of increase also plays a role in determining whether or not a patient will experience symptoms [9]. Other symptoms that can be seen include palpitations, nausea, muscle pain, weakness, paralysis or paresthesia [32, 33]. Chronic hyperkalemia has also been associated with other clinical entities including kidney disease, renal tubular acidosis and peripheral neuropathy [21].

For both the patient and the healthcare system, the burden of hyperkalemia is evident. Patients with hyperkalemia experience a higher frequency of emergency department visits, hospitalizations or even intensive care unit admissions, which in turn amount to a large financial strain [1, 2, 34, 35]. These effects appear to be compounded when hyperkalemia develops in individuals with underlying comorbid conditions [2, 4, 5]. In a large observational study, the predicted risk of all-cause mortality was higher for each 0.5 mmol/l increase in potassium above 4.5 mmol/l. However, the probability of death at each level of potassium was even higher when patients concurrently had diabetes, heart failure or CKD. Specifically, the adjusted all-cause mortality for individuals with hyperkalemia was 7.6-fold higher in those with all three comorbidities and 3.3-, 3.5- and 1.6-fold higher in those with heart failure, chronic kidney disease and diabetes, respectively [5]. While this mortality risk may not all be attributed to hyperkalemia itself, it emphasizes that those with comorbid

conditions may require even closer monitoring in the face of hyperkalemia [8].

A TALE OF TWO RISKS

The morbidity and mortality risk associated with hyperkalemia is well reported, even if hyperkalemia results from the initiation of disease-optimizing treatments. For example, in a post-marketing analysis of the RALES Trial there was a substantial increase in spironolactone prescriptions shortly after publication. Unfortunately, this was accompanied by an increase in hospitalizations for hyperkalemia (from 2.4 to 11.0 per 1000 patient years) and mortality (from 0.3 to 2.0 per 1000 patient years) [24, 25]. Many practitioners choose to decrease or discontinue maximal RAASi when faced with hyperkalemia, and it has been shown that this occurs in as high as 47% of cases after moderate-to-severe hyperkalemic events and in 38% of cases after mild hyperkalemic events [36]. While intuitive, this needs to be balanced with the fact that discontinuation of these medications with proven morbidity and mortality benefits may have downstream consequences. One observational study by Epstein et al. following patients with heart failure, CKD and diabetes in whom RAASi was either decreased or discontinued found a significant increase in cardiorenal morbidity and mortality when compared to those who were maintained on maximal RAASi therapy [36]. In fact, looking strictly at mortality, submaximal dosing or discontinuation of RAASi was associated with a twofold increase in death across the total study population [36]. These findings are echoed by two other observational studies, which found a significantly higher mortality when RAASi were discontinued in the advanced CKD population [37, 38]. In another study of incident hyperkalemia during heart failure hospitalizations, a similar risk of discontinuation was observed. In addition, incident hyperkalemia was more commonly observed in patients using MRAs before admission but was not associated with poor outcomes. In contrast, dose reduction of MRAs during hospitalization was associated with a

73% increase in the adjusted relative mortality hazard in the first 180 days post-admission [39].

HYPERKALEMIA MANAGEMENT

Frequency of Monitoring in the Chronic Setting

As previously mentioned, some patients are at higher risk of developing incident or recurrent hyperkalemia including those with CKD [40], diabetes or heart failure [41] and concomitant use of RAASi [42]. In addition, an initial episode of hyperkalemia (irrespective of the cause) is one of the strongest risk factors for recurrent hyperkalemia [12, 40]. Despite its high prevalence in certain disease states, there is a lack of consensus on how frequently one must monitor serum potassium in the setting of medications that may be associated with hyperkalemia including initiation or up-titration of RAASi or dose reductions in loop or thiazide diuretics (which are in turn associated with a lower risk of incident hyperkalemia) [41]. In these scenarios where patients are identified to be at higher risk, there is a need for more research to guide the frequency of monitoring and need for individualization of care [10, 12]. Generally, comorbidities such as CKD, heart failure and diabetes should prompt more frequent monitoring. Moreover, patients with a history of hyperkalemia should be monitored more closely, especially when increasing doses or reinitiating a previously held RAASi. For patients on RAASi therapy, the serum potassium should be measured prior to the initiation of these medications, within 1–2 weeks of dose initiation and within 1–2 weeks of any dose escalation or discontinuation [10, 43]. While guidelines for monitoring are limited, there are a few suggested approaches that one could consider (Table 2).

Management of Acute Hyperkalemia

At a serum potassium threshold of > 5.5 mmol/l, potassium can disrupt cellular conduction in musculoskeletal and cardiac tissue [5].

Table 2 Suggested frequency of monitoring serum potassium after initiating RAASi

Guideline	Recommendation
KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease [129]	Monitor serum potassium within 2–4 weeks of initiation or titration of a RAASi. In those at high risk of hyperkalemia, monitoring should start within 1 week
European Society of Cardiology 2016 Guidelines for the diagnosis and treatment of acute and chronic heart failure [130]	Monitor serum potassium 1–2 weeks after initiation and 1–2 weeks after final dose titration
ACCF/AHA 2013 Guideline for the management of heart failure [131]	Monitor serum potassium within 1–2 weeks for ACEi or ARB and within 2–3 days and again 7 days after initiation for MRA
KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease [132]	Monitor serum potassium within 1 week of initiating or increasing the dose
NICE 2021 Chronic kidney disease: assessment and management [133]	Monitor serum potassium 1–2 weeks after initiation and 1–2 weeks after each dose increase

Treatment of acute hyperkalemia depends on a number of factors including absolute potassium value, chronicity, concomitant co-morbidity and the presence of hyperkalemia related end organ injury. Most guidelines agree that emergent treatment is warranted for potassium values > 6 mmol/l or > 5.5 mmol/l in the setting of ECG changes, oligoanuria, critical illness or a rapidly rising potassium level [7]. Goals of treatment include reversing conduction

abnormalities, shifting potassium intracellularly, promoting potassium elimination and removing contributing factors. Patients with acute hyperkalemia should be examined for otherwise unexplained muscle weakness/paralysis, and an electrocardiogram should be completed to assess for hyperkalemia-related conduction abnormalities. If conduction abnormalities are present, intravenous calcium should be administered to stabilize the myocellular membrane. Calcium chloride and calcium gluconate are two common formulations of intravenous calcium but they should not be used interchangeably. Calcium chloride contains three-fold more elemental calcium than calcium gluconate for a given concentration and should be administered only through central venous access as it carries a higher risk of tissue necrosis should extravasation occur. Calcium gluconate can be given through a peripheral intravenous if needed but may still lead to tissue necrosis with extravasation. Regardless of which calcium formulation is used, ECGs should be repeated after administration to ensure resolution of cardiac conduction abnormalities. Additional doses of calcium may be required given its relatively short duration of effect.

Potassium shifting can rapidly lower serum levels through the movement of potassium from the extracellular to intracellular space. Insulin is the most commonly used shifting agent given its rapid onset, ease of administration and evidence-based effect [44]. Regular insulin is given through the intravenous route, typically as a 10-unit bolus, following administration of 25–50 g of dextrose (50–100 ml of dextrose 50%). The onset of effect occurs within 30–60 min and can last up to 6 h. Serum glucose levels should be trended for up to 6 h after administration of insulin since hypoglycemic episodes have been reported in 13–17% of such treatments [45, 46]. Serum potassium levels should be monitored as repeat insulin doses may be required for refractory hyperkalemia if serum potassium levels remain equal to or greater than the pre-shift value. Beta-2 adrenergic agonist can also be used to shift serum potassium [44, 47]. However, they should be used as an adjunct to intravenous insulin to

maximize their potassium-lowering effect. Finally, the ability of sodium bicarbonate to lower potassium (acutely) is minimal and should only be considered as an adjunct to the aforementioned therapies in the setting of a concurrent metabolic acidosis [48].

Endogenous routes of potassium removal primarily involve the gastrointestinal tract and renal excretion. Gastrointestinal excretion can be promoted through the use of potassium-binding resins although the onset of effect is typically delayed; thus, current evidence does not support the use of potassium binders as a treatment for acute hyperkalemia to rapidly lower the potassium level [49]. Renal excretion involves the use of intravenous crystalloid solutions in the setting of hypovolemia and diuretics in the setting of hypervolemia. Eliminating potassium through these mechanisms should be considered sub-acute treatment as time to peak effect is hours. Most episodes of acute hyperkalemia can successfully be treated using a combination of potassium shifting and elimination; however, in situations where hyperkalemia persists despite optimal medical management, hemodialysis should be considered for potassium removal. Most commonly this occurs when hyperkalemia is accompanied by significant and persistent renal impairment.

A final consideration for treating acute hyperkalemia is to ensure exogenous potassium intake is reduced and contributory medications are temporarily discontinued. Exogenous sources of potassium include dietary intake, oral supplements and intravenous fluid additives. Medications related to hyperkalemia include, but are not limited to, renin angiotensin aldosterone system inhibitors, NSAIDs and trimethoprim. Although there is little guiding evidence, treatment algorithms for acute hyperkalemia focused on minimizing harm do exist. We recently proposed such an algorithm to better guide clinicians on how best to manage acute hyperkalemia in the inpatient setting (Fig. 1).

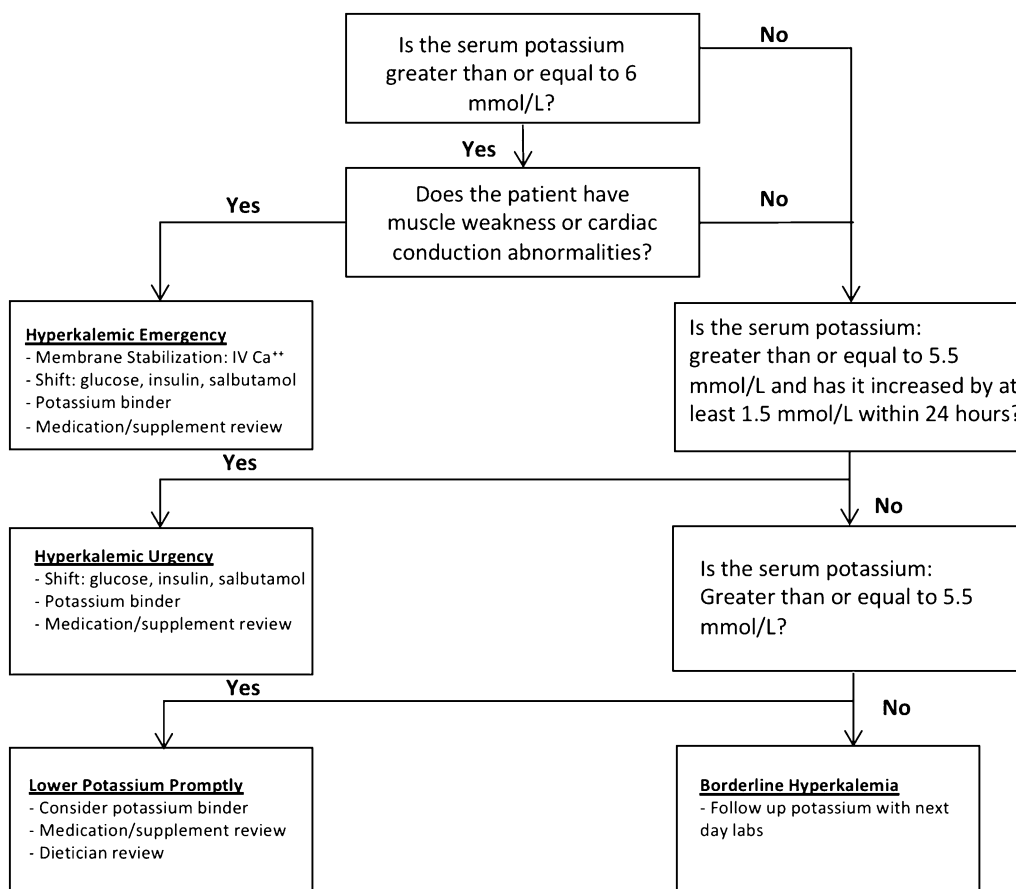


Fig. 1 Acute hyperkalemia management in the in-patient setting. *IV Ca⁺⁺* Intravenous calcium

Management of Outpatient Hyperkalemia

Chronic management of hyperkalemia is focused on prevention of adverse hyperkalemic episodes (including those that are recurrent) by attempting to normalize potassium homeostasis [50]. Standard chronic management of hyperkalemia involves removal and/or management of contributors to hyperkalemia, increasing movement of potassium into cells and excretion. To address contributors to hyperkalemia, one must counsel on potassium-restricted diets (appreciating that data supporting this approach is lacking), carefully review any concomitant medications that cause hyperkalemia, potentially dose adjust RAASi (acknowledging that there are risks to doing so) and optimize the management of comorbid conditions, such as CKD and heart failure. To enhance intracellular movement of potassium, oral formulations

of sodium bicarbonate can be used, while increasing potassium excretion involves the use of loop or thiazide diuretics and/or potassium binders.

Role of Dietary Restriction

It has been suggested that increased dietary intake of potassium contributes to hyperkalemia, and it may be an important consideration in people with risk factors such as kidney disease [51, 52]. Therefore, patients at risk of hyperkalemia are often recommended to adhere to a potassium restricted diet [53]. The 2004 Kidney Disease Outcomes Quality Initiatives (KDOQI) guidelines [54] recommended limiting potassium to approximately 51–102 mEq/day (2–4 g/day), while the more recent KDIGO 2012 Clinical Practice Guideline [55] recommended that individuals with CKD should receive expert dietary advice on potassium intake.

While it seems intuitive that patients should be counseled on a potassium-restricted diet to help mitigate hyperkalemia, the evidence surrounding potassium restriction is limited, and opinions towards the need for tight dietary restriction have shifted. Dietary liberalization of potassium in someone at risk of hyperkalemia is not universally associated with hyperkalemia or death [56]. In fact, in a prospective observational study, lower dietary potassium intake was associated with higher mortality risk in hemodialysis [57], although this may represent bias (i.e., lower consumption of potassium may be a marker of inadequate nutrition which in turn is associated with a higher mortality risk). While excessive intake of dietary potassium may be associated with hyperkalemia in some situations, there has been recent evidence suggesting that a diet rich in potassium may actually improve blood pressure and lower the risk of cardiovascular disease and stroke [52, 58]. With the introduction of new potassium-binding agents, studies are planned to evaluate whether dietary liberalization of potassium intake (in CKD) may be feasible [59]. In addition to the potential benefits of potassium liberalization, implementation and adherence to potassium-restricted diets is technically challenging and may be overly restrictive and costly. Furthermore, potassium-restricted diets may lead to the exclusion of foods that are otherwise beneficial for health [60]. For example, the Mediterranean diet, which largely focuses on healthy fats, whole grains and plant-based foods, has been associated with reduced cardiovascular disease but is typically associated with a higher potassium intake [61]. The Mediterranean diet may also be associated with a slowing of kidney function decline and improved survival among CKD patients [62]. Plant-based diets in general have shown promising outcomes in CKD [63], and more recent trials evaluating the feasibility of plant-based diets that are high in alkali (which may minimize extracellular shifting of potassium) and strategies to avoid potassium restriction will be important in ascertaining the true risk/benefit ratio of a potassium restricted diet [64]. A recent review emphasized other benefits of plant-based diets that may help with potassium

removal including increased fibre content to improve gastrointestinal motility [65]. In addition, it has been shown that the bioavailability of potassium in whole fruits is lower than that of fruit juices. Therefore, a plant-based diet containing whole fruits may lead to relatively less potassium absorption compared with one made of predominantly fruit juice [66]. Finally, some studies have pointed out the importance of potassium kinetics in this conversation; dietary potassium intake does not necessarily associate with plasma potassium concentration [60]. Once again, individualization appears to be the best approach. A recent review highlighted the approach of personalized meal planning and nutritional counseling to account for the fact that some patients experience transient elevations in potassium and post-prandial hyperkalemia [60]. Current literature is limited, and there is a need for more studies, specifically clinical trials, addressing the question of potassium-restricted diets and outcomes.

Metabolic Acidosis

Patients with reduced kidney function are at risk of developing persistent metabolic acidosis, defined as serum bicarbonate < 20–22 mEq/l. Metabolic acidosis causes hyperkalemia through potassium and hydrogen ion exchange. In turn, hyperkalemia can lead to metabolic acidosis through impacts on renal ammonia levels [67]. This cycle leads to deleterious effects which may be treated with therapies such as sodium bicarbonate or sodium citrate [67]. While beneficial in kidney disease for slowing the loss of kidney function, correction of acidosis with oral bicarbonate may require high pill burden and requires careful candidate selection [68]. Furthermore, in patients with heart failure, sodium bicarbonate may precipitate extracellular fluid overload. Most of these patients were excluded from clinical trials of sodium bicarbonate for metabolic acidosis in CKD. Finally, it has been shown that a persistently high bicarbonate level may be associated with death and heart failure events in those with pre-existing kidney disease [69].

In addition to potential risks, the impact on potassium achieved through correcting acidosis

with oral sodium bicarbonate may be small. A recent trial [70] that evaluated sodium bicarbonate (0.4 mEq per kg of ideal body weight per day) versus placebo in patients with later stage CKD demonstrated a decrease in serum potassium levels by only 0.1 mEq/l for treated patients, although the risk of a patient having a level > 5.0 mEq/l was lower in treated patients (OR 0.35, 95% CI 0.17–0.74). Nevertheless, other studies have shown that correcting acidosis leads to a lowering of serum potassium, albeit to varying degrees [71, 72]. Thus, in the absence of side effects, and if there may be other benefits that are valued, correction of acidosis may be a therapeutic option.

Medication review

Drug-induced hyperkalemia is considered to account for a large proportion of hyperkalemia [73], and beyond RAASi, many medications may contribute [74, 75]. Therefore, it is critical to conduct a review of a patient's medications, carefully weighing the risks and benefits and evaluating alternatives where possible.

Loop and Thiazide Diuretics

Diuretics are frequently used in the acute management of hyperkalemia to facilitate potassium excretion. However, they can also be used in the chronic management, especially when already part of the routine care of a patient (for example, heart failure or CKD with fluid overload). The most frequently used diuretics for patients at risk of hyperkalemia are loop and thiazide diuretics as they both cause a relative net lowering in serum potassium [76]. Thiazide diuretics are not recognized as having the same degree of potassium lowering as loop diuretics because of their site of action (namely the distal convoluted tubule at which only a small proportion of filtered sodium is absorbed). However, in a recent trial of chlorthalidone to treat hypertension in patients with stage 4 chronic kidney disease, hypokalemia occurred in 10% versus 0% of those randomized to chlorthalidone [77]. In observational studies, there has been an association between use of non-potassium sparing diuretics and lower potassium levels (on a population level) [41].

While diuretics may be effective at lowering potassium, their efficacy depends on renal function and duration of action as they need to reach the loop of Henle or the distal convoluted tubule to exert their effect, and this may be limited in the setting of reduced GFR [68]. Furthermore, they do have important side effects to consider including volume contraction, worsening of renal function and an association with gout and diabetes (specifically thiazide diuretics) [3].

Sodium Glucose Cotransporter 2 Inhibitors (SGLT2i)

Mechanistically, SGLT2i result in increased tubular flow and overall improved kidney function, so they may protect against hyperkalemia [78]. In the recent FIDELIO-DKD trial, participants in the treatment group who concurrently used SGLT2i had lower serum potassium values; this suggests that SGLT2i may have an independent potassium lowering ability [78]. More recently, two meta-analyses of trials evaluating SGLT2i in patients with diabetes mellitus type 2 or CKD found that SGLT2i reduced the risk of serious hyperkalemia [79, 80]. While yet to be explored in a trial with lower potassium as a primary outcome, these drugs may prove to be another tool for the clinician to modestly reduce hyperkalemic events in patients with diabetes, CKD (noting that most studies enrolled patients with an eGFR cutoff of ≥ 20 –30 ml/min/1.73 m²) [81, 82] or heart failure, especially when otherwise clinically indicated.

Potassium Binders

Evidence of Efficacy 1. Older potassium binders

Although sodium polystyrene sulfonate (SPS) has been FDA approved since the late 1950s, trials addressing its efficacy as a serum potassium-reducing agent only became available in 2015 [83, 84]. In a single-center double-blind RCT comprising 33 patients with CKD, the use of SPS for an average duration of 6.9 days was associated with a greater serum potassium reduction than placebo (difference of -1.04 mEq/l; $P < 0.001$) [84]. Despite this, the difference in the proportion of patients

achieving normal serum potassium levels was not statistically significant ($P = 0.07$) [84]. In this trial, SPS dosing was fixed at 30 g orally daily. However, SPS is suggested to have a dose-dependent potassium-lowering property and can potentially be titrated to achieve normokalemia with doses reaching up to 60 g orally daily [85]. While SPS is effective, there are two main concerns with its widespread use. The first is related to the risk of gastrointestinal complications. In one study, severe gastrointestinal adverse events requiring emergency department visit or hospitalization among SPS users had an incidence rate of 22.97 per 1000 person-years versus 11.01 per 1000 person-years among non-users. However, the risk of colonic necrosis was not as high in another study of inpatients that identified an incidence of 0.14% among SPS users versus 0.07% among non-users (relative risk of 2.10, 95% CI 0.68–6.48) [86, 87]. It was previously thought that these events were related to SPS preparations containing sorbitol, but systematic reviews have shown similar gastrointestinal events in SPS without sorbitol [88]. The second concern is related to the sodium content. One study has shown that the use of SPS has been associated with edema and greater interdialytic weight gain [89]. Calcium polystyrene sulfonate (CPS) is a sodium-free alternative to SPS. Two trials have found no statistical difference in serum potassium reduction between SPS and CPS, and another has shown that CPS significantly decreases serum potassium when compared to placebo in participants undergoing hemodialysis [90–92]. While CPS may spare patients from a high sodium load, there is a concern that calcium, the ion replacing sodium in SPS, may increase vascular calcification [91]. While hypercalcemia as a result of CPS has been reported in one case series, none of the aforementioned trials have demonstrated an increase in serum calcium levels with its use [90–93]. Notably though, CPS has been linked to gastrointestinal ischemia in some case reports and case series [94–96]. Despite these concerns and risks, anecdotally, SPS or CPS has been used to lower potassium in the short term (i.e., over a few days) and long term (as chronic potassium lowering therapies in those with a tendency to hyperkalemia),

especially in settings where kidney replacement therapies are not immediately available or as a bridge to maintain potassium while kidneys recover from acute kidney injury. In addition, novel potassium binders are not readily available in many countries. Nonetheless, considering the potential for risk and lack of robust studies demonstrating benefit, chronic use of SPS or CPS to support RAASi initiation or up titration is generally not advised and newer potassium binders (if available) are usually recommended instead [12, 97].

2. New potassium binders

Patiromer and sodium zirconium cyclosilicate (SZC) are newer potassium binders with different mechanisms and adverse events compared with SPS (Table 3) although no randomized trials have compared SPS to patiromer or SZC. These two agents have only recently been approved for use in Canada. Both agents have evidence supporting their dose-dependent potassium-lowering activity in various populations, specifically in those with CKD, diabetes, hypertension and taking RAASi [98–104]. Both agents also have safety data from trials lasting up to 1 year and are generally well tolerated [103, 105–107]. A summary of recent major trials evaluating the efficacy of these agents is noted in Table 4.

Patiromer was found to be effective when compared to placebo in the OPAL-HK trial [99]. In this trial, 76% of the 237 hyperkalemic participants (with a serum potassium at a day 3 scheduled visit) who were started on patiromer achieved normokalemia after 4 weeks. At the end of the 4th week, mean serum potassium values had decreased by 1.0 mmol/l from a mean baseline of 5.6 mmol/l. Of those who achieved normokalemia, 107 were then randomized to either maintenance with patiromer or placebo. Overall, 60% of the patients in the placebo group versus 15% in the patiromer group had at least one potassium of ≥ 5.5 after 8 weeks of follow-up, and the median change in potassium was 0.72 mmol/l in the placebo group versus 0 in the patiromer group [99]. As for SZC, the HARMONIZE trial [108] was similarly constructed with a 2-day open-label phase with a 28-day randomized phase. Of the participants in the first phase, 98% achieved

Table 3 Current potassium binders and mechanism of action

	Sodium polystyrene sulfonate [134]	Patiromer sorbitex calcium [135]	Sodium zirconium cyclosilicate [136]
Approval date	USA:1958, CA: 1961	USA: 2015; EU: 2017; CA: 2018	EU, USA: 2018; CA: 2019
Structure	Cation-exchange polymer	Cation-exchange polymer	Non-polymer micropore structure
K ⁺ -binding specificity	Binds K ⁺ , Ca ²⁺ and Mg ²⁺	Exchanges Ca ²⁺ for K ⁺ , binds Mg ²⁺	Preferentially captures K ⁺ in exchange for H ⁺ and Na ⁺
Location	Colon	Colon	GI tract
Sodium content	100 mg per 1 g (1500 mg/15 g dose)	None	80 mg per 1 g (400 mg/5 g dose)
Sorbitol content	14 g sorbitol per 15 g dose (suspension only)	4 g sorbitol per 8.4 g	None
Onset	Variable ^t	4–7 h	1 h
Indications [10, 12]	Treatment of hyperkalemia	Treatment of hyperkalemia in adults (egfr ≥ 15 ml/min/1.73m ²)	Treatment of hyperkalemia in adults
Adverse effects [10, 12]	GI stenosis, intestinal ischemia, ischemic colitis, rectal hemorrhage, GI necrosis, intestinal perforation with fatal outcomes, hypomagnesemia, hypokalemia, hypocalcemia	Mild to moderate GI effects, hypomagnesemia, hypokalemia	Mild to moderate GI effects, edema, hypokalemia
Drug interactions	Administer at least 3 h before or 3 h after other oral medications. Gastroparesis may require 6 h	Administer at least 3 h before or 3 h after other oral medications	Administer at least 2 h before or 2 h after gastric pH-dependent oral medications
Precautions	May worsen edema, Bp and weight gain. Avoid sorbitol containing preparation because of cases of fatal GI injuries	Serum magnesium at least 1 month after treatment initiation. Calcium supplementation not recommended. Avoid use if severe constipation, bowel obstruction or impaction	During correction of HK, QT prolongation can be observed due to decline in serum potassium. Avoid use if severe constipation, bowel obstruction or impaction
Dosing	15 g 1–4 times daily (oral) 30–50 g 1–2 times (rectal)	8.4 g daily (max 25.2 g) (oral)	10 g TID for up to 48 h (Correction, oral) 5 g daily or Q 2 days (max. 10 g) (MD, oral) 5 g non-dialysis days (max 15 g) (chronic HD, oral)

Table 3 continued

	Sodium polystyrene sulfonate [134]	Patiromer sorbitex calcium [135]	Sodium zirconium cyclosilicate [136]
Administration	Powder for suspension, mix 3–4 ml water per gram (15 g = 60 ml)	Powder for suspension, mix with 90 ml water. Do not heat or add to heated foods	Powder for suspension, mix with 45 ml water (45 ml)
Powder	454 g jar	8.4/16.8/25.2 g sachets	5/10 g sachets
Cost ^{tt}	\$29.42 (generic), \$91.20 (brand) per jar	\$14.10 (all strengths)	\$13.56 per 5 g

t not listed in product monograph, *tt* actual acquisition cost, *HK* hyperkalemia, *HD* hemodialysis, *GI* gastrointestinal, *CKD* chronic kidney diseases, *Bp* blood pressure, *MD* maintenance

normokalemia after 48 h. The baseline mean serum potassium was 5.6 mmol/l, and the absolute reduction was –1.1 mmol/l at 48 h. Two hundred thirty-seven participants were then randomized to placebo or SZC at doses of 5 g, 10 g and 15 g per day. The mean baseline serum potassium values were 4.6 mmol/l, 4.5 mmol/l, 4.4 mmol/l and 4.5 mmol/l, respectively, and the mean serum potassium values from day 8 to 29 were 5.1 mmol/l, 4.8 mmol/l, 4.5 mmol/l and 4.4 mmol/l, respectively ($P < 0.01$) [108].

Studies evaluating the use of binders with RAASi Appreciating the benefits of maintaining patients on RAASi while avoiding the morbidity and mortality of hyperkalemia, there have been a number of studies evaluating combination therapy with RAASi and novel potassium binders. The four largest trials studying patiromer, (AMETHYST-DN [105], AMBER [100], DIAMOND [104] and the aforementioned OPAL-HK [99]) were designed to exclusively include participants who were taking a RAASi. The first, AMETHYST-DN, was an open-label trial of 306 patients evaluating the long-term use of patiromer in those with diabetes and CKD taking one or more RAASi agent. Mean serum potassium values at baseline were 5.3 mmol/l, and the mean reduction from baseline after initiation of patiromer was between 0.35 and 0.97 mmol/l (depending on the dose of patiromer and baseline hyperkalemia severity). AMETHYST-DN showed a

significant reduction in baseline serum potassium at every monthly time point with serum potassium values within the target range in 83.1% to 92.7% of those with mild hyperkalemia (> 5.0 – 5.5 mmol/l) at baseline and 77.4–95.1% of those with moderate hyperkalemia (> 5.5 – 6.0 mmol/l) at baseline [105].

In the ZS-002 trial, 90 participants with CKD and hyperkalemia were randomized to placebo or to SZC at doses of 0.3 g, 3 g or 10 g three times daily. Two days later, serum potassium in the 10 g RAASi subgroup ($n = 20$) had dropped by 1.1 mmol/l from a baseline of 5.1 mmol/l ($P < 0.001$) [102]. In the larger, open-label trial, ZS-005, hyperkalemic individuals (mean baseline serum potassium 5.6 mmol/l) were subject to a treatment phase followed by a maintenance phase (baseline serum potassium 4.8 mmol/l). Fourteen percent of the 263 RAASi-naïve participants who were hyperkalemic at baseline were able to, over a 12-month period, initiate RAASi therapy after starting SZC. As for the 483 participants who were already on RAASi therapy, 74% maintained their dose [103].

Studies evaluating the use of binders with potassium sparing diuretics The use of patiromer as an enabler for potassium-sparing diuretics has been studied in three large trials. In the AMBER trial (which sought to evaluate the efficacy of patiromer as an enabler for K-sparing diuretics in those with resistant hypertension) [100], use of patiromer allowed for 86% of participants taking an ACEi or an

Table 4 Studies evaluating the efficacy of potassium binders in the management of hyperkalemia

Trial	Agent and dose	Design	Population (% of representation if > 50%)	Duration	Conclusion
Sodium polystyrene sulfonate/calcium polystyrene sulfonate					
Lepage et al. (2015) [84]	SPS 30 g daily	Randomized, placebo controlled, single center, double blind	$N = 33$, eGFR ≤ 60 (100%), RAASi (70%), DM (73%), HTN (88%), hyperkalemic and non-hyperkalemic	Mean: 6.9 days	Reduced serum K by a difference of 1.04 mmol/l compared to placebo (95% CI - 1.37 to - 0.71) [84]
Nayakama et al. (2018) [91]	CPS 5 g TID, SPS 5 g TID	Randomized, single center, open label, crossover study	$N = 20$ eGFR ≤ 60 (100%), RAASi (55%), hyperkalemic	4 weeks per period	Mean serum K reduction was not statistically different between CPS and SPS (1.25 and 1.48, respectively; $P = 0.51$) [91]
Nasir et al. (2014) [90]	CPS 5 g TID, SPS 5 g TID	RCT, single center, single blind	$N = 97$ DM (65%), HF (96%), hyperkalemic	3 days	Mean serum K reduction was not significantly different between CPS and SPS [90]
Wang et al. (2018) [92]	CPS 5 g TID	Randomized, placebo-controlled, crossover study	$N = 58$ mHD (100%), hyperkalemic	3 weeks per period	Hyperkalemia-related ECG findings were less frequent in the CPS group compared to the control group (13.8% vs 31.03%; $P < 0.001$) [92]
Patiromer sorbitex calcium					
OPAL-HK (2015) [99]	Patiromer 4.2–8.4 g BID	Multicenter phase 1: single group, single arm; phase 2: randomized, single blind, placebo controlled withdrawal phase	Phase 1: $N = 243$ Phase 2: $N = 107$ eGFR ≤ 60 (91%), RAASi (100%), DM (57%), HTN (97%), hyperkalemic	Phase 1: 4 weeks Phase 2: 8 weeks	Mean serum K reduction in phase 1 was -1.01 mmol/l ($P < 0.001$). Between-group difference in potassium during the withdrawal phase was 0.72 mmol/l (95% CI 0.46–0.99, $P < 0.001$). Sixty percent of the placebo group compared with 15% of the patiromer group had a serum K reading ≥ 5.5 mmol/l [99]

Table 4 continued

Trial	Agent and dose	Design	Population (% of representation if > 50%)	Duration	Conclusion
PEARL-HF (2011) [137]	Patiromer 15 g BID	RCT, multicenter, double blind	$N = 104$ eGFR ≤ 60 (55%), RAASi (90%), K-sparing (100%), HF (100%), non-hyperkalemic	4 weeks	Patiromer reduced serum K to a greater degree than placebo with a between-group difference of -0.45 mmol/l ($P < 0.001$) and allowed for increased dose of spironolactone (50 mg/day) in 91% versus 74% of placebo ($P < 0.019$) [137]
AMETHYST-DN (2015) [105]	Patiromer 4.2–16.8 g bid	Randomized dose-ranging clinical trial, multicenter, open label	$N = 306$ eGFR < 60 (88%), DM (100%), non-hyperkalemic	8-week treatment phase, up to 44-week maintenance phase	A significant reduction in serum potassium from baseline was observed at the 4- and 8-week marks (from 0.35 to 0.97 mmol/l at 4 weeks; $P < 0.001$). These were maintained at each monthly time point up to week 52 ($P < 0.001$) [105]
AMBER (2019) [100]	Patiromer 8.4 g od	RCT, multicenter, double blind	$N = 295$ eGFR < 60 (100%), RAASi (100%), K-sparing (100%), HTN (100%), non-hyperkalemic	12 weeks	A higher proportion of patients receiving patiromer remained on spironolactone by week 12 (between-group difference 19.5%, $P < 0.0001$) [100]. The difference remained significant for those with eGFR 25 to < 30 ($n = 66$; $P < 0.02$), but not heart failure ($n = 132$; $P = 0.05$) [138, 139]; 34 patients in the placebo arm discontinued due to hyperkalemia compared to 10 on patiromer [100]

Table 4 continued

Trial	Agent and dose	Design	Population (% of representation if > 50%)	Duration	Conclusion
REDUCE (2019) [112]	Patiromer 25.2 g once	RCT, single center, single blind	$N = 30$ eGFR ≤ 60 (100%), hyperkalemic	4 to 6 h	In the acute setting, there was no statistically significant reduction in serum K between the patiromer and placebo at the 6-h mark [112]
DIAMOND (2022) [104]	Patiromer	Multicenter Phase 1: open label, run in Phase 2: Randomized triple blind placebo controlled withdrawal phase	Phase 1: $N = 1195$ Phase 2: $N = 878$ RAASi (100%), MRA (100%), HTN (91%), HF (100%), hyperkalemic	Phase 1: up to 12 weeks Phase 2: 13 to 43 weeks (median: 27 weeks)	Serum K was 0.10 mmol/l higher in the placebo group ($P < 0.001$). Serum K > 5.5 mmol/l and discontinuation or dose reduction of MRA was less frequent in the patiromer group (HR of 0.63 and 0.62, with $P = 0.006$ for both) [104]
Sodium zirconium cyclosilicate					
ZS-002 (2015) [102]	SZC 0.3 g or 3 g or 10 g TID	RCT, multicenter, double blind	$N = 90$ eGFR ≤ 60 (100%), RAASi (62%), DM (56%), hyperkalemic	6 days	SZC 10 g TID reduced serum K after 48 h compared to placebo in both ITT and RAASi subgroups (by 0.92 mmol/l and 1.05 mmol/l, respectively; $P < 0.001$). A significant reduction was seen as early as 1 h after SZC 10 g ($- 0.11$ mmol/l; $P < 0.04$) [102]

Table 4 continued

Trial	Agent and dose	Design	Population (% of representation if > 50%)	Duration	Conclusion
ZS-003 (2015) [101]	SZC 1.25 g, 2.5 g, 5 g or 10 g TID	Phase 1: Multicenter, double-blind correction phase; phase 2: randomized controlled, multicenter, double blind maintenance phase	Phase 1: $N = 753$ Phase 2: $N = 543$ eGFR ≤ 60 (74.5%), RAASi (67%), DM (60%), hyperkalemic	Phase 1: 48 h Phase 2: 12 days	In the correction phase, SZC reduced serum K by 0.30% per hour while placebo reduced serum K by 0.09% per hour ($P < 0.001$). During the maintenance phase, the SZC 5 g and 10 g significantly decreased mean serum K at days 9 and 15 (5.11 mmol/l vs 4.62 mmol/l and 5.11 mmol/l vs 4.60 mmol/l, respectively; $P < 0.001$ for both) but not at day 21 (5.14 mmol/l vs 4.96 mmol/l, $P = 0.221$). There were no significant between-group changes in arrhythmias [101]
HARMONIZE (2014) [108]	Phase 1: SZC 10 g TID; phase 2: SZC 5 g, 10 g, or 15 g TID	Phase 1: multicenter, open label correction phase; phase 2: randomized-controlled, multicenter, double-blind maintenance phase	Phase 1: $N = 251$ Phase 2: $N = 237$ eGFR ≤ 60 (69%), RAASi (72%), DM (68%), hyperkalemic	Phase 1: 48 h Phase 2: 28 days	By the end of phase 1, mean reduction in serum K was -1.1 mmol/l ($P < 0.001$). In phase 2, normal serum K levels were obtained more often in the SZC arms (71%, $P = 0.01$; 76%, $P = 0.002$; 85%, $P < 0.001$; for 5 g, 10 g and 15 g, respectively) [108] The difference remained significant in the HF subgroup [140]
HARMONIZE-OLE (2019) [106]	SZC 2.5 to 15 g daily	Multicenter, open-label, single-arm maintenance phase extension	$N = 121$ eGFR ≤ 60 (74%), RAASi (69%), DM (67%), hyperkalemic	≥ 11 months	Mean serum K ≤ 5.1 mmol/l was achieved by 76.6 to 87.5% of participants, and mean serum K < 5.5 mmol/l was obtained by all participants [106]

Table 4 continued

Trial	Agent and dose	Design	Population (% of representation if > 50%)	Duration	Conclusion
ZS-005 (2019) [103]	Phase 1: SZC 10 g TID; Phase 2: SZC 7.2 g daily (mean dose)	Phase 1: multicenter, open label correction phase; phase 2: multicenter, open label, maintenance phase	Phase 1: $N = 751$ Phase 2: $N = 746$ eGFR ≤ 60 (73%), RAASi (64%), DM (63%), HTN (82%), hyperkalemic	Phase 1: 24–72 h Phase 2: up to 12 months	At completion of the correction phase, 78% of patient had a normal serum K. During the maintenance phase, 74% of participants maintained their RAASi dose [103]
Kashihara et al. (2018) [107]	SZC 5 g or 10 g TID	RCT, multicenter, double blind	$N = 103$ eGFR ≤ 60 (97%), RAASi (78%), DM (60%)	48 h	At 48 h, the proportion of patients with normal serum K was higher in the SZC 5 g and 10 g arms versus placebo (85.3% and 91.7% vs 15.2%, respectively; $P < 0.0001$) [107]
Kashihara et al. (2020) [141]	Phase 1: SZC 10 g TID; phase 2: SZC 2.5, 5, 10 or 15 g daily	Multicenter, open label, single arm correction and maintenance phase	$N = 150$ eGFR ≤ 60 (93%), RAASi (71%), DM (58%), hyperkalemic	Phase 1: 1–3 days Phase 2: 1 year	99% of the patients in the correction phase had normal serum K after 72 h. $\geq 65.5\%$ of patients were normokalemic throughout [141]
DIALIZE (2019) [110]	SZC 5–15 g daily	RCT, multicenter, double blind	$N = 196$ mHD (100%), predialysis hyperkalemia	8 weeks	A greater number of participants in the SZC arm had pre-dialysis serum K levels between 4 and 5 mmol/l in at least 3/4 long interdialytic intervals without requiring rescue therapy versus placebo (41.2% vs 1.0%; $P < 0.001$). Rescue therapy for hyperkalemia was similar in both arms [110]
ENERGIZE (2020) [113]	SZC 10 g up to 3 times	RCT, multicenter, double blind	$N = 70$ Emergency room, hyperkalemic	10 h	No statistically significant reduction in serum K between SZC and placebo at 10 h [113]

SPS sodium polystyrene sulfonate, eGFR estimated glomerular filtration rate (ml/min), RAASi renin angiotensin aldosterone system inhibitor, DM diabetes mellitus, K potassium, HTN hypertension, CPS calcium polystyrene sulfonate, RCT randomized controlled trial, mHD maintenance hemodialysis, TID three times per day, HF heart failure, BID twice per day, SZC sodium zirconium cyclosilicate

ARB to remain on spironolactone without a hyperkalemic event compared to 66% in the placebo arm for the duration of the 12-week trial [100]. In one of the first patiromer trials, PEARL-HF, after starting spironolactone, serum potassium values increased by a mean of 0.23 mmol/l in the placebo group and decreased by 0.22 mmol/l in the patiromer group. In the patiromer group, spironolactone doses could be increased from 25 mg daily to 50 mg daily without hyperkalemic event in 91% of participants with heart failure compared to 74% in the placebo arm [98, 137]. The recently published DIAMOND study revealed similar findings in the heart failure population. Patiromer was shown to reduce the occurrence of hyperkalemia (> 5.5 mmol/l) and MRA dose reductions by slightly more than one third over a median follow-up period of 27 weeks [104].

Although SZC has had fewer trials evaluating its use specifically in populations taking potassium-sparing diuretics, it appears the use of SZC for optimizing RAASi is intended for future study [109].

Other clinical scenarios In maintenance hemodialysis patients, 51.5% of participants in the SZC arm of the DIALIZE study had predialysis serum potassium levels between 3.5 and 5.5 mmol/l in at least four long interdialytic intervals compared with only 5.1% of those in the placebo arm [110]. Despite this, comparable proportions of patients in both groups required potassium-lowering rescue therapies (2.1% and 5.1% in the SZC and placebo groups, respectively) [110]. A small study suggested that patiromer may decrease serum potassium levels in hemodialysis patients, but these findings were limited by a sample size of six and the absence of a placebo arm [111]. Finally, both patiromer and SZC have had trials evaluating their use in the emergency department for the acute treatment of hyperkalemia; while potentially beneficial in a short-term setting (the patiromer group had a significant mean reduction of serum K by 0.52 mmol/l compared to 0.17 mmol/l with placebo at the 2-h time point and the SZC group had a 0.72 mmol/l reduction compared to 0.36 mmol/l in the placebo group), neither showed a significant reduction in serum

potassium values at their study primary endpoints of 6 h and 4 h for patiromer and SZC, respectively [112, 113].

Side Effects As with SPS, SZC is a sodium-based potassium binder and thus has the potential of causing peripheral edema. Two studies found that edema was reported by participants in a dose-dependent fashion and became more significant at SZC doses > 10 g/day [103, 108]. Patiromer is not a sodium-based binder and therefore not believed to be associated with this same side effect. However, patiromer is less specific regarding its affinity and also binds magnesium. Serum magnesium levels were significantly lower in one study; however, the mean magnesium levels for both arms remained within normal range, and there were no clinically significant arrhythmias associated with hypomagnesemia [98].

Upcoming Trials 1. Novel potassium binders

While the new potassium binders have robust data supporting their potassium-lowering ability, the major limitation has been a lack of data on the impact of novel potassium binders on hard outcomes including death or hospitalization. In fact, out of all the placebo-controlled trials reported above, only three deaths and three hospitalizations were reported [114]. It is hoped that newer trials will help to better address this limitation. The recently published DIAMOND trial evaluating patiromer-enabled optimization of RAASi therapy was initially designed with cardiovascular death or cardiovascular hospitalization as primary outcomes. Unfortunately, due to logistic challenges associated with the COVID-19 pandemic, the primary outcome was changed to the difference in serum potassium compared to baseline [115]. Specific to SZC, DIALIZE-Outcome, an upcoming placebo-controlled trial, is currently recruiting participants on maintenance hemodialysis to evaluate whether SZC decreases the risk of sudden cardiac death, strokes and arrhythmia-related hospitalizations [115]. It will be the first trial evaluating mortality and patient-centered outcomes with the use of the novel potassium binders. In addition to hard outcomes, evaluating the role of novel binders

in optimization of therapy is another area of focus. In this regard, the LIFT study is aimed at evaluating the effect of SZC on facilitating up titration of both RAASi and MRA while maintaining normokalemia in participants with heart failure [117].

In addition to future studies evaluating the role of binders on different outcomes, upcoming trials for both drugs are looking at broader populations including pediatric patients and participants on calcineurin inhibitors for dose selection and safety studies [118–122]. Both drugs will also be studied as enablers for potassium-liberalized diets [59, 123]. Trials evaluating patiromer use in end-stage kidney disease are currently recruiting as are others looking at use of SZC after hyperkalemia hospitalization and in participants who have undergone a parathyroidectomy [124–126]. It is hoped that the results from these studies may support the use of novel potassium-binding agents more broadly.

2. Thiazide-like Diuretics

While not typically used for the purposes of treating hyperkalemia, the CLICK trial published in 2021 that evaluated the use of thiazide-like diuretics in CKD demonstrated a higher incidence of hypokalemic events compared to placebo (10% vs 0%) [77]. The SPICE-PILOT trial, another study by Agarwal, is currently recruiting participants to assess whether chlorthalidone's hypokalemic properties will enable higher doses of spironolactone to be used in participants with resistant hypertension [127].

3. Dietary intake of potassium and safety

The extent to which dietary potassium plays a role in serum potassium levels remains to be fully understood. One upcoming trial, DK-LIB, a randomized-crossover study, will randomize participants with CKD to either restricted (< 2000 mg) or liberalized (3500 mg) potassium diets and follow changes in serum potassium [128]. This is one of only few trials exploring this question. This study may provide the groundwork for the upcoming studies involving the use of new potassium binders to enable liberalized dietary potassium diets.

Putting It All Together—a Management Approach for Chronic Hyperkalemia in the Setting of RAASi Use

How might one incorporate the principles of diagnosis, monitoring and therapy into clinical practice—especially when treating a patient with RAASi? Generally speaking, RAASi should not be initiated unless the serum potassium is ≤ 5.0 mmol/l. For those already receiving a RAASi, drawing on existing recommendations, we propose a simple approach that may be helpful to consider when faced with an individual with hyperkalemia (Fig. 2). Such an approach considers the risks and benefits of treating hyperkalemia, balanced with the potential risks of discontinuing disease-modifying therapy. This approach also considers the use of novel medications (i.e., potassium binders), recognizing that these therapies may not be available in all countries. The principles of this approach includes the following:

1. Recognize the potential morbidity and mortality associated with hyperkalemia, especially for those with pre-existing risk factors.
2. Be aware of conditions that place patients at a higher risk of developing hyperkalemia
3. Classify hyperkalemia into risk thresholds to be better prepared for the potential consequences and to help guide when to intervene with therapy.
4. Monitor patients who are at risk with serial blood work, especially those who are initiating or up-titrating RAASi.
5. Address reversible causes of hyperkalemia (medications, dietary, correcting metabolic acidosis, non-potassium sparing diuretics when accompanied by volume overload) in all patients with hyperkalemia.
6. Consider the use of novel potassium binders (if available, affordable, and tolerated) in eligible patients if hyperkalemia is moderate to severe; especially in those individuals who are candidates for initiation of a RAASi or who have not yet reached target dose.
7. If hyperkalemia is moderate to severe, discontinue RAASi, but look to re-trialing them

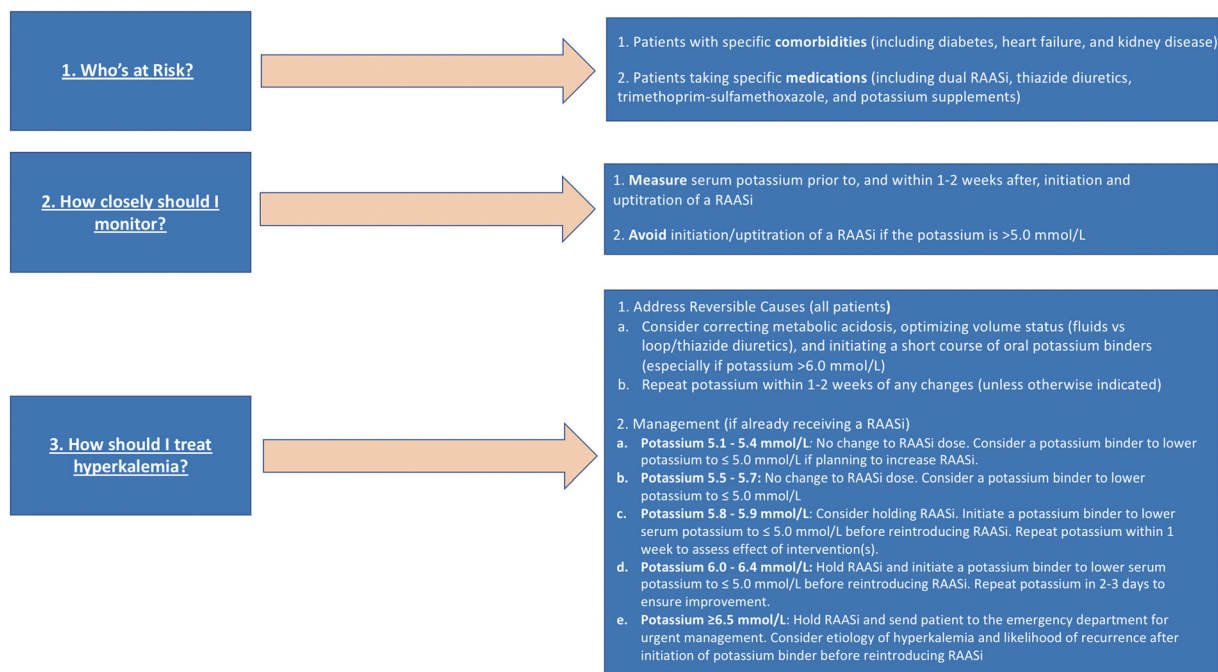


Fig. 2 Treatment approach to hyperkalemia in the setting of renin angiotensin aldosterone system inhibitors (RAASi)

when clinically indicated and the potassium improves to safe range.

CONCLUSION

Hyperkalemia places patients at risk of morbidity and mortality. The principles of management include identifying those at risk, close monitoring and instituting therapy to lower potassium into a safe range while trying to ensure disease-modifying treatments that cause hyperkalemia (i.e., RAASi) can be safely utilized. While there is much to be learned, a number of future studies will help to better understand the consequences of hyperkalemia and how best to treat patients using evidence-based approaches.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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DATA AVAILABILITY

This narrative review utilized publically available data that has already been published and can be accessed through the reference list.

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