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# EMCREG-International Multidisciplinary Consensus Panel on Management of Hyperkalemia in Chronic Kidney Disease and Heart Failure

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**Keywords**
Heart failure · Hyperkalemia · Chronic kidney disease

**Abstract**

***Background:*** Hyperkalemia, generally defined as serum potassium levels greater than 5.0 mEq/L, poses significant clinical risks, including cardiac toxicity and muscle weakness. Its prevalence and severity increase in patients with chronic kidney disease (CKD), diabetes mellitus, and heart failure (HF), particularly when compounded by medications like angiotensin converting inhibitors, angiotensin receptor blockers, and potassium sparing diuretics. Hyperkalemia arises from disruptions in potassium regulation involving intake, excretion, and intracellular-extracellular distribution. In CKD and acute kidney injury, these regulatory mechanisms are impaired, leading to heightened risk. The management of chronic hyperkalemia presents a challenge due to the necessity of balancing effective cardiovascular and renal therapies against the risk of elevated potassium levels.

***Summary:*** The emergency department management of acute hyperkalemia focuses on preventing cardiac complications through strategies that stabilize cellular membranes and shift potassium intracellularly. Chronic management often involves dietary interventions and pharmacological treatments. Pharmacological management of acute hyperkalemia includes diuretics, which enhance kaliuresis, and potassium binders such as patiromer and sodium zirconium cyclosilicate, which facilitate fecal excretion of potassium. While diuretics are commonly used, they carry risks of

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volume contraction and renal function deterioration. The newer potassium binders have shown efficacy in lowering chronically elevated potassium levels in CKD and HF patients, offering an alternative to diuretics and other older agents such as sodium polystyrene sulfonate, which has significant adverse effects and limited evidence for chronic use. ***Key Messages:*** We convened a consensus panel to describe the optimal management across multiple clinical settings when caring for patients with hyperkalemia. This consensus emphasizes a multidisciplinary approach to managing hyperkalemia, particularly in patients with cardiovascular kidney metabolic syndrome, to avoid fragmentation of care and ensure comprehensive treatment strategies. The primary goal of this manuscript is to describe strategies to maintain cardiovascular benefits of essential medications while effectively managing potassium levels.

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## Introduction

Hyperkalemia is generally defined as serum potassium levels of greater than 5.0 mEq/L, although the definition varies across guidelines between >4.5 mEq/L and 5.5 mEq/L [1–3]. Hyperkalemia may result in clinical consequences, including cardiac toxicity, muscle weakness, impaired renal acidification, and increased frequency and severity of adverse clinical outcomes. The risk is magnified in the presence of comorbid conditions. In hospitalized patients, longer duration of hyperkalemia is associated with increased risk of in-hospital mortality [4].

Several conditions increase the risk of incident hyperkalemia. Chronic hyperkalemia develops in 5–50% of patients with chronic kidney disease (CKD), and the incidence increases with decreasing kidney function, as well as comorbid conditions including heart failure (HF), past myocardial infarction, advanced age, and diabetes, and is augmented by several medications the indication for which is reduction of CV morbidity and mortality [5]. These include angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB) with or without neprilysin inhibition (ARNI), potassium sparing diuretics mineralocorticoid receptor antagonists (MRAs; e.g., spironolactone, eplerenone), and β-blockers [6–8]. These patients may be taking other medications concomitantly that increase the risk of hyperkalemia, such as non-steroidal anti-inflammatory drugs (NSAIDS), cyclooxygenase-2 (COX-2) inhibitors, certain antibiotics (such as trimethoprim-sulfamethoxazole), and heparin. Several of these drug classes (ACEi, ARB, ARNI, and MRA) are recommended in HF to reduce morbidity and mortality. Clinicians are often challenged to maintain the cardiovascular benefits of these drugs in the context of the hyperkalemia they can cause. Commonly, clinicians choose to discontinue or dose-reduce drugs that are guideline-recommended to lessen the likelihood or the fear of hyperkalemia. Accordingly, the diagnosis and management of chronic hyperkalemia is a common challenge for many practicing clinicians.

It is not uncommon for patients to have concomitant HF, kidney disease, obesity, and diabetes. This combination of comorbid illnesses was recently defined as cardiovascular kidney metabolic syndrome in the American Heart Association presidential advisory report [9]. Patients with cardiovascular kidney metabolic syndrome require a multidisciplinary care approach since their care is at risk of fragmentation by individual specialists. The purpose of this review is to describe the optimal multidisciplinary management approach for patients with chronic hyperkalemia. We have also included a brief overview of acute hyperkalemia management as these patients are at risk of developing this life-threatening condition.

## Methods

A multidisciplinary 2-day meeting was held, bringing together experts from pharmacy, nursing, and physicians from nephrology, cardiology, emergency medicine, and hospitalist medicine to develop our recommendations and manuscript. The event was organized by the Emergency Medicine Cardiac Research and Education Group (EMCREG) – International, which is an organization of experts from the USA, Canada, and across the globe. The goal was to create a document relevant to both community and academic clinicians managing hyperkalemia across different care settings. Before the meeting, each panel member prepared a document and presentation to contribute to the discussions. These materials, along with key clinical trials, were thoroughly reviewed and discussed. Guideline recommendations were a significant factor in shaping our approach. Our recommendations prioritize practical applicability for clinicians working in multidisciplinary settings, where collaboration across specialties is essential for managing hyperkalemia.

## Pathophysiology

Ensuring consistent total body $K^+$ content is essential for maintaining a stable plasma concentration. This equilibrium is upheld by regulating $K^+$ intake and

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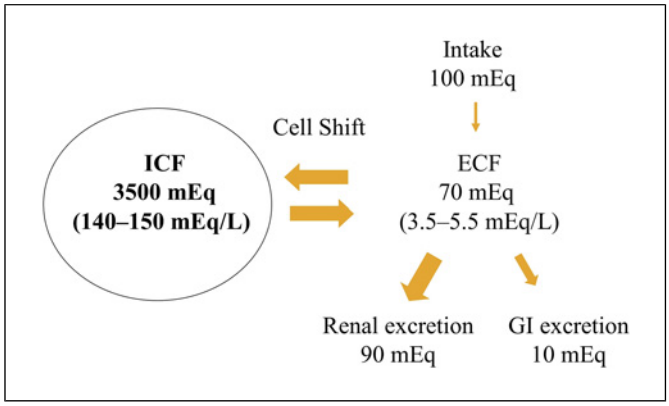


**Fig. 1.** Regulation of $K^+$ homeostasis: consistent total body, extracellular, and intracellular $K^+$ content is critical. The majority of total body $K^+$ is intracellular. The majority of $K^+$ excretion is renal, with a small proportion GI. $K^+$, potassium; mEq, milliequivalent; ECF, extracellular fluid; L, liter; GI, gastrointestinal; ICF, intracellular fluid.

excretion, as well as ensuring proper distribution between the extracellular and intracellular fluid compartments. Notably, only 2% of total body $K^+$ resides in the extracellular fluid, compared to the 98% found within the cells (Fig. 1). $K^+$ is a cation, so this distribution dichotomy establishes the resting voltage of cells, with the cell interior maintaining a negative charge relative to the exterior. Consequently, disruptions in plasma $K^+$ homeostasis can lead to clinical effects in excitable tissues [10].

*Normal Potassium Shifts*

To mitigate temporary spikes in plasma $K^+$ levels, which could disrupt cellular voltage, the body employs various physiological mechanisms to shift $K^+$ into cells temporarily while adjustments in excretion occur gradually over a span of several hours. Following a meal, the release of insulin serves not only to regulate glucose levels but also to facilitate the transfer of dietary $K^+$ into cells until the kidneys eliminate the excess K [10].

Catecholamines are important in the physiological regulation of $K^+$ distribution. Elevated interstitial $K^+$ levels prompt vasodilation, promoting increased blood flow to exercising muscles. Through $\beta_2$ receptors, catecholamines enhance the activity of the $Na^+$-$K^+$-ATPase, attenuating the elevation of extracellular $K^+$ levels that would typically arise. In conditions of total body $K^+$ depletion, the accumulation of $K^+$ into the interstitial space is diminished, reducing skeletal muscle blood flow. This scenario contributes to the connection between hypokalemia and rhabdomyolysis [11].

*Renal Handling*

$K^+$ is freely filtered at the glomerulus, followed by extensive reabsorption, primarily in the proximal tubule and ascending limb of Henle. Within the proximal tubule, reabsorption mainly occurs through the paracellular pathway, largely in conjunction with sodium and water reabsorption. In contrast, $K^+$ reabsorption in the thick ascending limb of Henle involves facilitated transport via the apical membrane $Na^+$-$K^+$-$2Cl^-$ cotransporter.

The resorptive aspect of kidney $K^+$ handling operates largely independently of $K^+$ intake. The primary mechanism for maintaining urinary $K^+$ excretion stems from secretion within the aldosterone-sensitive distal nephron (ASDN), encompassing the latter part of the distal convoluted tubule (DCT2), connecting tubule, and collecting duct. Tubular $K^+$ secretion involves two types of apical $K^+$ channels and is driven by a transepithelial voltage oriented negatively in the lumen. This voltage is primarily generated by $Na^+$ reabsorption through channels (ENaC) situated on the apical membrane (Fig. 2). Aldosterone enhances ENaC activity via mineralocorticoid receptors, augmenting both channel quantity and open likelihood [11].

In addition to the mechanisms discussed above, other aspects of $K^+$ homeostasis include the gastric-kidney reflex, which provides an inhibitory effect on the $Na^+$-$Cl^-$ cotransporter and is initiated when $K^+$ enters the stomach. $K^+$ secretion also exhibits a circadian rhythm in which $K^+$ secretion is higher during the day when $K^+$ intake is highest. These mechanisms, which underlie the prodigious capacity of the normal kidney to excrete $K^+$, evolved in response to the diet of prehistoric humans that contained a four-fold higher $K^+$ content. High $K^+$ intake has health benefits, suggesting the evolutionary design of the kidney was to maintain $K^+$ homeostasis in the setting of high $K^+$ intake (Fig. 3) [10].

*Acute Kidney Injury and CKD*

Several distinctive aspects of acute kidney injury (AKI) frequently result in hyperkalemia. In cases where the cause is acute tubular necrosis or tubulointerstitial renal disease, extensive damage to the late distal tubule and collecting duct often leads to direct harm to the cells responsible for $K^+$ secretion. AKI often accompanies significant reductions in the glomerular filtration rate (GFR) (<10 mL/min), which itself becomes a limiting factor for $K^+$ secretion. The rapid decline in kidney function prevents adequate time for normal kidney and extrarenal adaptive mechanisms to develop sufficiently. In patients experiencing more severe injury, as evidenced

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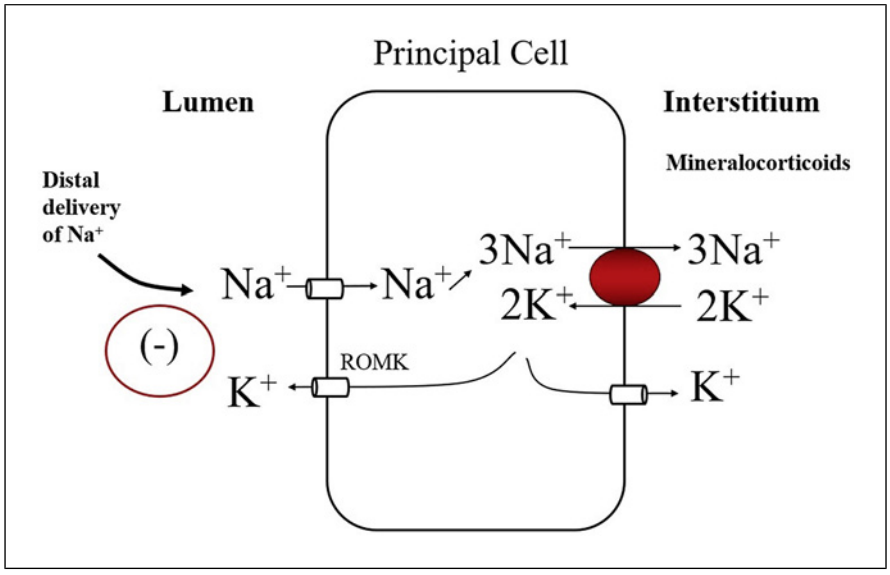


**Fig. 2.** Regulation of $K^+$ secretion: the distal convoluted tubule, connecting tubule, and collecting duct nephrons are largely responsible for urinary $K^+$ excretion. These nephrons are sensitive to aldosterone, a mineralocorticoid hormone. The ROMK is an ATP-dependent $K^+$ channel. $K^+$, potassium; $Na^+$, sodium; ROMK, renal outer medullary potassium channel.

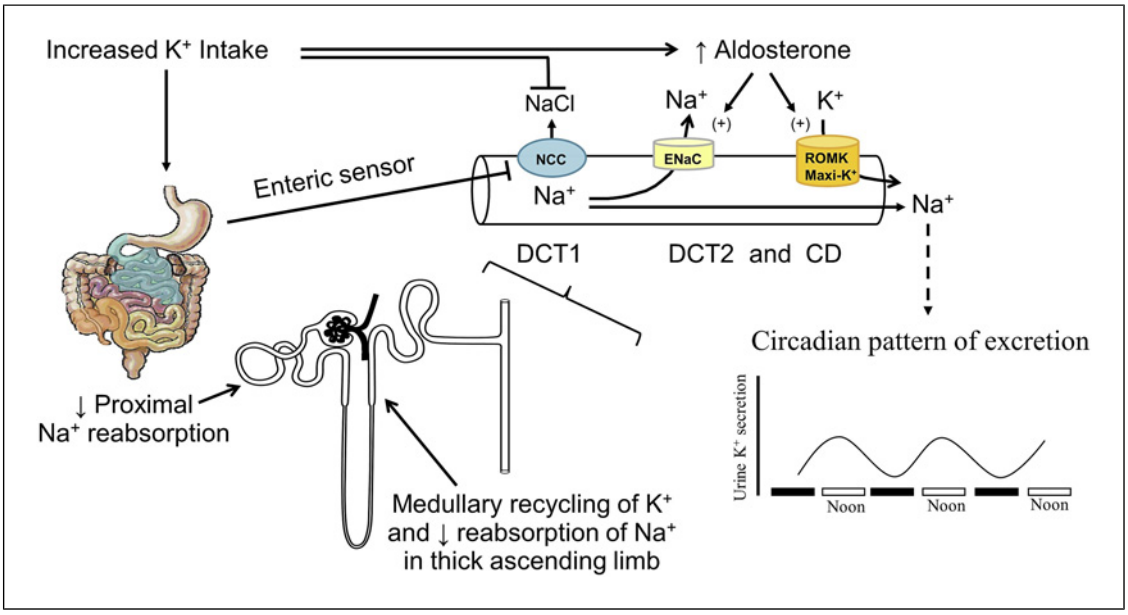


**Fig. 3.** The normal kidney has a prodigious capacity to excrete dietary potassium ($K^+$): $K^+$ homeostasis is regulated by the gastric-kidney reflex, which enhances $K^+$ excretion, and a circadian rhythm, with peak secretion during the day. These mechanisms evolved to handle high-$K^+$ diets, highlighting the kidney's adaptability to maintain $K^+$ balance.

clinically by oliguria or frank anuria, there is a notable decrease in the delivery of salt and water to the distal parts of the nephron, which contributes to reduced $K^+$ secretion. Conversely, in non-oliguric AKI, hyperkalemia tends to be less prevalent due to ample distal delivery of salt and water. Patients with AKI are also more prone to severe acidosis, increased catabolism, and tissue breakdown, all of which contribute to the release of intracellular $K^+$ into the extracellular space. This release of $K^+$, coupled with impaired kidney secretion, frequently results in life-threatening hyperkalemia in AKI patients [10, 11].



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CKD presents a more complex scenario compared to AKI. Alongside the reduced GFR and subsequent decrease in distal delivery, there are also nephron loss and a diminished count of collecting ducts available for $K^+$ secretion. However, this is counterbalanced by an adaptive process, whereby the remaining nephrons develop an increased ability to excrete $K^+$. In addition, with advancing CKD, a significant proportion of daily $K^+$ excretion occurs via the GI tract. Adaptive increases in kidney and colonic excretion of $K^+$ help prevent hyperkalemia in patients with CKD if the GFR remains >15–20 mL/min. Once the GFR falls below these values, the impact of factors known to adversely affect $K^+$ homeostasis is significantly magnified. The development of hyperkalemia with more modest declines in kidney function are the result of conditions that severely limit distal sodium delivery, decrease mineralocorticoid levels or activity, or cause a distal tubular defect. In clinical practice, hyperkalemia is usually the result of a combination of factors superimposed on kidney dysfunction.

## Acute Management in the Emergency Department

While chronic hyperkalemia can often be managed through outpatient medication adjustments and dietary interventions, acute hyperkalemia may sometimes constitute a medical emergency, especially when accompanied by ECG changes [12]. Hyperkalemia may be present in up to 4.9% of patients presenting to the ED [13, 14]. Although hyperkalemia represents a medical emergency, as many as 32% of hyperkalemic instances are spurious, most often resulting from hemolyzed blood samples [15]. Rechecking serum potassium in patients in whom the sample is hemolyzed is critical.

The primary focus of emergency department (ED) management of hyperkalemia is prevention of cardiac complications of hyperkalemia. Cardiac dysrhythmias associated with hyperkalemia range from bradyarrhythmias and conduction blocks, to ventricular fibrillation and pulseless electrical activity. When patients present to the ED with hyperkalemia, cardiac dysrhythmias are the most important manifestation for emergency physicians to recognize and to prevent the patient's condition from worsening. ECG findings are prognostic of outcome, and include ST segment depression, peaked T waves, and widened QRS [16]. Clinicians need to recognize the ECG changes associated with hyperkalemia as ECG results are typically available before serum potassium levels and can help determine the urgency of treatment.

ED management of hyperkalemia targets stabilization of cardiac cellular membranes by promoting potassium shift from the extracellular to intracellular fluid space, increasing urinary or GI potassium excretion, or even emergent hemodialysis (Table 1). Immediate cellular membrane stabilization can be achieved with calcium salts. Potassium may be temporarily shifted to the intracellular space with insulin (combined with dextrose to avoid hypoglycemia), sodium bicarbonate, or beta-2 adrenergic agonists. In patients who produce urine, loop diuretics will acutely reduce serum potassium levels. Gastrointestinal excretion may occur via oral binders such as patiromer and sodium zirconium cyclosilicate (SZC), although these require a functioning GI tract, and have delayed onset of action, and should not be relied on to emergently reduce potassium in patients with arrhythmias. Of these newer binders, SZC likely provides the more rapid and safest benefit as it binds potassium in the small bowel. Patiromer acts only in the colon, and there are persistent safety concerns (and FDA warnings) about sodium polystyrene sulfonate (SPS) [17]. Lastly, although hemodialysis may be required to reduce serum potassium, initiating hemodialysis in the ED is logistically challenging and time-consuming. However, once hemodialysis is initiated, the serum potassium level can be lowered rapidly [18]. In all patients, re-assessment and frequent monitoring are essential, given the risk of rebound hyperkalemia.

## Approach to Chronic Hyperkalemia

### *Dietary Considerations*

Historically, one common treatment for chronic hyperkalemia is to recommend a restricted intake of foods high in potassium. Early evidence suggested administration of potassium salts, in the form of supplements, may elevate potassium and led to a demonstrated increased risk of cardiac dysrhythmias; however, this clinical effect was small and has not been reproduced in food-based interventions. More specifically, potassium-rich foods, such as many fruits and vegetables, are weakly associated with changes in serum levels. Evidence is accumulating that such dietary restrictions are not effective in reducing hyperkalemia and may in fact be harmful by limiting the intake of important nutrients [19]. While the potassium in whole fruits and vegetables is co-ingested with fiber, limiting absorption, dietary potassium from non-plant sources may be more likely to cause hyperkalemia and restricting intake is a reasonable treatment strategy. Compared to fruits and vegetables, animal-based and processed food products are likely to have higher, albeit minor, impact on levels. In totality, the existing data suggest dietary potassium is less likely to be bioavailable

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**Table 1.** Emergency treatment options for hyperkalemia

| Effect | Agent | Dose | Onset | Duration | Expected effect on serum K |
|---|---|---|---|---|---|
| Stabilize cardiac cell membrane | Calcium gluconate | 10 cc 10% Ca gluconate, IV | 1–2 min | 10–30 min | ECG normalization |
| Redistribution | Insulin | 1 unit per 3–5 g of dextrose | 1 h | Variable | 0.6–1.2 mEq/L |
| | Sodium bicarbonate | 50–100 mEq | 30 min | 2–6 h | Variable |
| | Albuterol | 10–20 mg in 4 mL | 30 min | 2 h | 0.3–0.6 mEq/L |
| Excretion | Furosemide | 40–80 mg IV × 1 | 15 min | 2–3 h | Variable |
| | Hemodialysis | 2–4-h session | Immediate | Variable | >1 mEq/L within 60 min and 2 mEq/L within 180 min |

compared to the potassium salts [20–22]. In response to this evidence, the most recent guidelines acknowledge the lack of evidence that dietary potassium promotes negative clinical outcomes and questions the broad benefit of dietary restrictions. Specifically, the Kidney Disease: Improve Global Outcome (KDIGO) conference recommends promoting consumption of low potassium, plant-based foods when switching from high-potassium foods, as well as promotion of a Mediterranean diet [21].

Since dietary potassium restriction is likely difficult and ineffective on its own, a common approach to deal with hyperkalemia is to remove the medications that are contributing to it, e.g., renin-angiotensin-aldosterone system inhibitors (RAASi) or MRAs, often not considering the potential negative effects of removing guideline therapy. A recent retrospective analysis of a large dataset examined cardiovascular and kidney outcomes in patients whose RAASi were decreased or discontinued in response to hyperkalemia. Compared to patients who were maintained on maximally tolerated RAASi doses, those with decreased or discontinued RAASi had higher rates of all-cause mortality, cardiovascular events, and progression to end-stage renal disease (ESRD) [23]. In light of these findings, it seems reasonable to advocate for preserving RAASi therapy by active management of hyperkalemia with potassium-lowering medications.

## The Management of Chronic Hyperkalemia: Pharmacology Consideration

A comprehensive plan to evaluate and treat chronic hyperkalemia should include a medication review as several classes of therapies can be implicated through various mechanisms (Table 2) [24]. In disease states like HF and early CKD, the use of agents like RAASi and MRAs have profound effects on mortality, morbidity, and patient quality of life, and it is critical to initiate and maintain these agents [25]. Medications that can provoke hyperkalemia that do not have an indication in HF or CKD should be avoided where possible and minimized when they are required.

A critical pillar of chronic hyperkalemia management is to stabilize potassium levels via removal. The two main classes of medications for this pillar are diuretics and potassium binders; however, there are also data that sodium glucose cotransporter-2 (SGLT2) inhibitors can be utilized for potassium stabilization [26].

### *Loop and Thiazide Diuretics*

To improve or reverse hyperkalemia, kaliuresis can be enhanced with use of diuretics. Loop and thiazide diuretics are often one of the early choices in the management paradigm of chronic hyperkalemia in patients with HF and CKD given their role in fluid overload in these disease states. Likewise, these diuretics should be avoided in patients who are volume depleted. The thiazide diuretics reduce potassium concentration via inhibition of the sodium-chloride symporter at the distal convoluted tubule of the nephron and stimulation of aldosterone. The loop diuretics block the sodium-potassium-chloride transporter at the Loop of Henle [27]. Loop diuretics can be used across the spectrum of CKD and are also effective at reducing serum potassium. There have been no specific randomized-controlled trials looking at the use of either class of diuretics in the management of hyperkalemia. The efficacy of each class of diuretic to reduce potassium levels is dependent on the mechanism, renal function and duration of action, with loop diuretics providing a more robust potassium wasting

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**Table 2.** Mechanisms and associated medications that cause hyperkalemia

| Mechanism | Medication class |
|---|---|
| Inhibition of potassium uptake | Beta-blocking agents, more pronounced with non-selective beta-blockers<br>Verapamil |
| Reduced aldosterone production | Non-steroidal anti-inflammatory agents (e.g., ibuprofen, naproxen)<br>Calcineurin inhibitors (e.g., cyclosporine, tacrolimus)<br>Renin-angiotensin-aldosterone system (RAAS) inhibitors (e.g., angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], direct renin inhibitors, mineralocorticoid receptor antagonists [MRA])<br>Chronic heparin therapy |
| Aldosterone resistance via inhibition of the epithelial sodium/potassium channel | Potassium sparing diuretics (e.g., amiloride and triamterene)<br>Trimethoprim<br>Pentamidine |
| Increased potassium supply | Potassium salts<br>Penicillin G |

effect [17]. While diuretics are effective to some degree, they also can be limited due to important, and common, side effects such as volume contraction, worsening renal function with over diuresis, and gout [27].

*Potassium Binders*

In general, potassium binders are non-absorbed and consist of a counterion that is exchanged for $K^+$, leading to excretion of bound $K^+$ in the feces. However, each agent has differences in formulations, pharmacology, and supporting data (Tables 3, 4). Historically, sodium polystyrene sulfonate (SPS) has been available for the clinical management of hyperkalemia; however, SPS has a lack of randomized evidence for chronic hyperkalemia and poor patient tolerability (Table 3). Furthermore, SPS also carries a black box warning from the Food and Drug Administration related to the risk of intestinal necrosis, pronounced risk of gastrointestinal adverse events such as nausea, diarrhea and vomiting, as well as a risk of edema with its sodium content which brings into question the risk/benefit ratio for chronic use [28]. SPS is delivered by sorbitol, hence adding volume to patients who may already be volume overloaded.

Given these limitations, advancements in the development of potassium binders have been made with the introduction of patiromer and SZC (Tables 3, 4). Both products are currently approved in the USA and European Union and have evidence demonstrating a dose-dependent response, in terms of potassium-lowering, among those with CKD, diabetes, hypertension, HF, and those taking RAASi (Table 4). SZC is a sodium-based, potassium-selective cation exchanger that is primarily active in the GI tract [44]. SZC is orally administered through a correction phase (10 g three times a day) followed by a maintenance dose (starting dose of 5 g). Patiromer is a sodium-free insoluble polymer that binds potassium in the colon as an exchange ion with fecal excretion [45]. Patiromer is given once a day at a starting dose of 8.4 g and may be increased or decreased by 8.4 g to reach target potassium levels (up to a maximum dose of 25.2 g daily). These agents have numerous clinical trials data demonstrating the ability to initiate or maintain RAASi in the populations who require those therapies. The ongoing REALIZE-K and OPRA-HF trials, both related to optimizing RAASi in HF, will provide additional evidence for their use [46, 47].

In contrast to SPS, patiromer and SZC, have data showing long-term control of hyperkalemia, including in patients with CKD who are also receiving RAASi [32, 36]. Hyperkalemia commonly recurs in patients with CKD on RAASi, so episodic treatment exposes patients to repeated risk, while long-term therapy with potassium binders, leads to sustained control. Best practice for hyperkalemia now includes binder therapy to preserve RAASi use in the setting of hyperkalemia. These two agents are generally well tolerated with mild gastrointestinal side effect and risk of hypokalemia and hypomagnesemia, which should be monitored during treatment. As such, patiromer and SZC, should be the preferred potassium binders for the management of chronic hyperkalemia and/or used to maintain RAASi in CKD and/or HF. In fact, clinical guidance in both disease states support the use of these agents in order to optimize RAAS inhibition. [41–43] The RAASi optimization toolkit, which was developed by the

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**Table 3.** Characteristics of currently available potassium binding agents (FDA package inserts)

| | Sodium polystyrene sulfonate | Patiromer | Sodium zirconium cyclosilicate |
|---|---|---|---|
| Approval date | 1958 | USA: 2015<br>European Union: 2017 | USA: 2015<br>European Union: 2017 |
| Mechanism of actions | $K^+$ binding in exchange for $Na^+$ in GI tract; increased fecal excretion | $K^+$ binding in exchange for $Ca^{2+}$ in GI tract; increased fecal excretion | $K^+$ binding in exchange for $H^+$ and $Na^+$ in GI tract; increased fecal excretion |
| Site of action | Colon | Colon | Small and large intestines |
| Selectivity for $K^+$ | Non-selective (also binds $Ca^{2+}$ and $Mg^{2+}$) | Non-selective (also binds $Na^+$ and $Mg^{2+}$) | Highly selective (also binds $NH^{4+}$) |
| Onset of action | Variable, several hours | 7 h | 1 h |
| Sodium content | 1,500 mg per 15 g dose | None | 400 mg per 5 g dose |
| Calcium content | None | 1.6 g per 8.4 g dose | None |
| Sorbitol content | 20,000 mg per 15 g dose | 400 mg per 8.4 g dose | None |
| Dosing | 15 g, 1–4 times orally 30–50 g, 1–2 times rectally | 8.4 g oral daily, titrate up to 16.8 g or 25.2 g daily | 10 g three times daily orally for initial correction (for ≤48 h), then 5 g every other day to 15 mg daily for maintenance |
| Serious adverse events | Intestinal necrosis | None reported | None reported |
| Common adverse events | Constipation, diarrhea, nausea, vomiting, gastric irritation, hypomagnesemia, hypokalemia, hypocalcemia systemic alkalosis | Abdominal discomfort, constipation, diarrhea, nausea, flatulence, hypomagnesemia | Constipation, diarrhea, nausea, vomiting, mild to moderate edema |
| Drug interactions | Administer at 3 h before or 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 |

GI, gastrointestinal tract; $Ca^{2+}$, calcium; $Mg^{2+}$, magnesium; $Na^+$, sodium; $NH^{4+}$, ammonium; $K^+$, potassium.

International Society of Nephrology with input from American Society for Preventative Cardiology, Heart Failure Association of the European Society of Cardiology, Kidney Disease Improving Global Outcomes, and the Renal Physicians Association provides valuable input regarding RASSi optimization. This toolkit also includes recommendations for clinicians to consider the initiation and continuation of potassium binders to facilitate RAASi therapy. Ideally, once a patient has started taking a potassium binder, clinicians should recommend continuation, if at all possible, with dose adjustments as necessary (Table 5). Clinicians should emphasize to patients that continuation may reduce the risk of rebound hyperkalemia. Although periodic treatment may be less ideal for maintaining a steady and predictable potassium level, clinicians should be aware that some patients may wish not to continue their potassium binder long-term for many reasons such as cost, willingness, or polypharmacy. In cases where patients need to restart their binder, they should restart at a low dose, reserving the lowest dose for those patients who are normokalemic ($K^+$ of 4.1–5.0) [48]. Additional recommendations regarding the dose of each of these agents and the dose to restart the agents, if necessary, can be found in Table 5.

*Acidosis Management*

Patients with CKD develop acidosis because of diminished ability to excrete dietary acid load. Administration of exogenous alkali can be used to treat acute and chronic hyperkalemia by shifting potassium into the

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**Table 4.** Clinical studies with potassium binding agents

| Study, design, follow-up duration | Population | Treatment arms | Primary outcome |
|---|---|---|---|
| *Sodium polystyrene sulfonate (SPS)* | | | |
| Phase 4, double-blind, randomized, placebo-controlled, 7 days. Rossignol 2022 [29] | Outpatients with chronic kidney disease and mild hyperkalemia ($K^+$ = 5.0–5.9); $n$ = 33 | SPS 30 g or placebo oral daily | Mean change in serum $K^+$:<br>−1.25 mmol/L with SPS<br>−0.21 mmol/L with placebo<br>Mean difference (95% CI) versus placebo: −1.04 mmol/L (−1.37 to 0.71 mmol/L); $p < 0.01$ |
| *Patiromer* | | | |
| Phase 4, randomized, open-label, single-blind, 10 h. Rafique 2020 [30] | Emergency department patients with end-stage renal disease and serum $K^+$ ≥6.0; $n$ = 43 | Single dose of patiromer 25.2 g + standard of care or standard of care alone | Adjusted mean serum $K^+$ at 6 h:<br>5.81 mmol/L with patiromer<br>6.32 mmol/L with standard of care; $p = 0.155$<br>Adjusted mean serum $K^+$ at 2 h:<br>5.90 mmol/L with patiromer<br>6.51 mmol/L with standard of care; $p = 0.009$ |
| PEARL-HF; phase 2, randomized, double-blind, placebo-controlled, 28 days. Pitt et al. [31] (2013) | Patients with chronic HF with (a) history of hyperkalemia leading to RAAS inhibitor and/or beta-blocker withdrawal or (b) CKD; $n$ = 105 | Patiromer 15 g or placebo twice daily (both groups got spironolactone 25 mg/d added if able) | Least square mean difference of patiromer versus placebo −0.45 mmol/L; $p < 0.001$ |
| AMETHYST-DN; phase 2, randomized, open-label, 28 days. Bakris et al. [32] (2015) | Outpatients with diabetic kidney disease and mild or moderate hyperkalemia; $n$ = 306 | Mild hyperkalemia: patiromer 4 g twice daily<br>Patiromer 8.4 g twice daily<br>Patiromer 12.6 g twice daily<br>Moderate hyperkalemia:<br>Patiromer 8.4 g twice daily<br>Patiromer 12.6 mg twice daily<br>Patiromer 16.8 g twice daily | Mild hyperkalemia:<br>Least square mean changes in serum $K^+$:<br>−0.35 mmol/L with 4.2 g<br>−0.51 mmol/L with 8.4 g<br>−0.55 mmol/L with 12.6 g<br>Moderate hyperkalemia:<br>Least square mean changes in serum $K^+$:<br>−0.87 mmol/L with 8.4 g<br>−0.97 mmol/L with 12.6 g<br>−0.92 mmol/L with 16.8 g |
| AMBER, phase 2, randomized, double-blind, placebo-controlled, 12 weeks Agarwal et al. [33] (2019) | Patients with CKD, $K^+$ 4.3–5.1 mmol/L, and resistant hypertension, $n$ = 295 | Patiromer 8.4 g or placebo daily (both groups had open-label spironolactone added if able) | Patients remaining on spironolactone:<br>Patiromer versus placebo, 19.5% difference, $p < 0.001$<br>More patients in placebo versus patiromer with serum $K^+$ ≥5.5 mmol/L, $p < 0.001$ |
| OPAL-HK; phase 3, 2 stages: (a) treatment, single group, single-blind (4 week) and (b) withdrawal, randomized, single-blind, placebo-controlled (8 week). Weir et al. [34] (2015) | Patients with CKD on RAAS inhibitor therapy with mild or moderate-to-severe hyperkalemia, $n$ = 237 | Treatment stage: patiromer 4.2 g (mild hyperkalemia) or 8.4 g (moderate to severe) twice daily Withdrawal stage: patiromer (at same dosage) or placebo | Treatment stage:<br>Mean change in serum $K^+$ at week 4<br>Overall: −1.01 mmol/L ($p < 0.001$ versus baseline)<br>Mild hyperkalemia: −0.65 mol/L<br>Moderate-to-severe hyperkalemia: −1.23 mmol/L<br>Withdrawal stage: |

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**Table 4** (continued)

| Study, design, follow-up duration | Population | Treatment arms | Primary outcome |
|---|---|---|---|
| | | | Mean change in $K^+$ at week 4<br>0 mmol/L with patiromer versus 0.72 mmol/L with placebo, $p <$ 0.001 |
| DIAMOND, phase 3, multicenter, double-blind, randomized withdrawal placebo-controlled, study, 27 weeks. Butler et al. [35] (2022) | Adult patients with NYHA II–IV HF and LFEF ≤40% with hyperkalemia ($K^+$ >5.0 mmol/L) while receiving RAAS inhibitors or normokalemia but dose reduction or discontinuation of RAAS inhibitors due to hyperkalemia | Patiromer titrated up to a maximum of three 8.4 g pack/day | Mean change in serum potassium: −0.10 mmol/L, $p < 0.001$)<br>In terms of secondary, more patients in patiromer were able to maintain MRA dose, had less hyperkalemic events |
| *Sodium zirconium cyclosilicate (SZC)* | | | |
| Phase 3, 2-stage, randomized, double-blind, placebo-controlled, 14 day. Spinowitz et al. [36] (2019) | Patients with hyperkalemia, $n = 754$ | Correction phase:<br>SZC 1.25, 2.5, 5, or 10 g or placebo three times daily for 48 h<br>Maintenance phase:<br>SZC (same dose) or placebo daily ($K^+$ 3.5–4.9) for 14 days | Correction phase:<br>Exponential rate of change in mean serum $K^+$ at 48 h:<br>−0.11% with 1.25 g<br>−0.16% with 2.5 g<br>−0.21% with 5 g<br>−0.30% with 10 g<br>−0.09% with placebo; $p < 0.001$ for 3 highest doses<br>Maintenance phase:<br>Exponential rate of change in mean serum $K^+$:<br>+0.14% per hour with SZC 10 g versus +1.04% per hour with placebo; $p < 0.01$<br>+0.09% per hours with SZC 5 g versus 0.47% per hour with placebo; $p < 0.008$ |
| HARMONIZE, phase 3, 2-stage, randomized, double-blind, placebo-controlled, 28 days. Kosiborod et al. [37] (2014) | Outpatients with hyperkalemia; $n = 258$ | Initial phase (open-label):<br>SZC 10 g three times daily for 48 h<br>Maintenance phase (double-blind):<br>SZC 5, 10, or 15 g or placebo daily for 28 days | Initial phase:<br>Mean change in serum $K^+$ over 48 h: −1.1 mmol/L; $p < 0.001$ versus baseline<br>Maintenance phase:<br>Mean serum $K^+$ during day 8–29:<br>4.8 mmol/L with 5 g<br>4.5 mmol/L with 10 g<br>4.4 mmol/L with 15 g<br>5.1 mmol/L with placebo; $p < 0.001$ with each dose |
| HARMONIZE-Global; phase 3, randomized, double-blind, placebo-controlled, 28 days. Zannad et al. [38] (2020) | Outpatients with hyperkalemia; $n = 267$ | Correction phase (open-label): SZC 10 g three times daily for 48 h<br>Maintenance phase (double-blind): MSZC 5 or 10 g or placebo daily for 28 days | Correction phase:<br>Mean change in serum $K^+$ over 48 h: −1.28 mmol/L; $p < 0.001$ versus baseline<br>Maintenance phase:<br>Mean serum $K^+$ during days 8–29:<br>4.8 mmol/L with 5 g<br>4.4 mmol/L with 10 g<br>5.3 mmol/L with placebo; $p < 0.001$ at each dose |

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**Table 4** (continued)

| Study, design, follow-up duration | Population | Treatment arms | Primary outcome |
|---|---|---|---|
| ZS-005; phase 3, stage, open-label, 12 months. Spinowitz et al. [36] (2019) | Outpatients with hyperkalemia, $n$ = 751 | Correction phase: SZC 10 g three times daily for 24–72 h Maintenance phase: SZC 5 g daily | Correction phase: 78% of patients had serum $K^+$ 3.5–5.0 at 72 h Maintenance phase: 88% had serum $K^+$ <5.1 mmol/L over 3–12 months |
| DIALIZE, phase 3b, randomized, double-blind, placebo-controlled, 4 weeks. Fishbane et al. [39] (2019) | Patients with end-stage renal disease on hemodialysis with hyperkalemia, $n$ = 196 | SZC 5, 10, or 15 g or placebo daily on non-dialysis days for 4 weeks | Maintenance of pre-dialysis serum $K^+$ 4.0–5.0 mmol/L during ≥3 of 4 hemodialysis sessions after long interdialytic interval without rescue therapy: 41% with SZC 1% with placebo, $p < 0.001$ |
| PRIORITIZE-HF, international, parallel-group, randomized, double-blind, placebo-controlled, 12 weeks. Tardif et al. [40] (2023) | Adult patients with symptomatic HFrEF ≤40% NYHA II–IV, on GDMT, with hyperkalemia, $n$ = 182 (trial stopped early due to COVID-19) | SZC 5 g or placebo daily | Proportion of patients in the following categories: (a) any RAAS inhibitor at less than target dose, (b) any RAAS inhibitor at target dose no MRA, (c) MRA at less than target dose, (d) MRA at target dose; no difference in any group, $p$ = 0.43. Numerically higher number of patients on target MRA (56.4% versus 47.0%) |

Patiromer and SZC, based on available evidence, should be the preferred potassium binders for the management of chronic hyperkalemia and/or used to maintain RAAS inhibitors in CKD and/or HF. In fact, clinical guidance in both disease states support the use of these agents in order to optimized RAAS inhibition [41–43]. Recommendations regarding the role of each of these agents within in the context of managing and preventing hyperkalemia in CKD and HF encompassing the roles the two potassium, with the aim of preserving RAAS inhibitors, binders can be found in Table 2. Note: 1 mEq/L = 1 mmol/L. CI, confidence interval; CKD, chronic kidney disease; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoids receptor antagonist; RAAS, renin-angiotensin-aldosterone system.

intracellular compartment [6]. While supplemental bicarbonate was previously recommended to halt progression of CKD, this recommendation is no longer supported. Nevertheless, continued use of bicarbonate is a cost-effective therapy in patients with CKD, metabolic acidosis, and chronic hyperkalemia.

*SGLT2is*

Finally, SGLT2i are now part of the standard of care in patients across the spectrum of CKD and HF. In patients with diabetes, HF, or proteinuria, they are recommended to be administered along with RAASi. Finally, SGLT2i have a mild diuretic action and are commonly administered along with RAASi in patients with CKD and DM due to their overlapping benefits in these populations [50, 51]. Coadministration of SGLT2i along with RAASi, in particular with non-steroidal MRAs [52–55], reduces incidence of hyperkalemia [50]. Therefore, encouraging implementation of the standard of care for CKD can reduce hyperkalemia by exposing more patients to the beneficial combined effects of SGLT2i and RAASi.

In summary, hyperkalemia is commonly encountered in patients with CKD and HF. Beneficial medications including RAASi and MRA can exacerbate hyperkalemia. Mitigation of chronic hyperkalemia includes the use of diuretics, alkali in patients with metabolic acidosis, and potassium binders. Restriction of whole plant foods that are high in potassium may lead to excessive restriction on fiber and micronutrients which are important for overall health, though limiting potassium from ultra processed foods remains a reasonable approach. Finally, reduction

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**Table 5.** Potassium binders management algorithm in stable adults with chronic hyperkalemia

| | |
|---|---|
| General management | Prior to initiating potassium binder or potassium binder dose change, consider<br>– Eliminating potassium supplements<br>– Medication review and drugs that cause hyperkalemia and de-prescribe those not required<br>– Appropriate dietary changes<br>– Check if diuretic dose has changed as $K^+$ could be affected<br>Evaluate the following<br>– Main disease diagnosis/co-morbidities/life expectancy/fragility<br>– Laboratory parameters (e.g., eGFR)<br>– Other possible reasons for hyperkalemia (e.g., metabolic acidosis)<br>– Concomitant medication indication and dose (or intent to start)<br>– Adherence to therapy/ability to understand treatment<br>– History of hyperkalemic events |

| Serum ($K^+$) level (in mmol/L) [confirmed by two consecutive samples] | Potassium binder | |
|---|---|---|
| | patiromer | sodium zirconium cyclosilicate (SZC) |
| | action | |
| Severe hyperkalemia ($K^+ \geq 6$) | • Severe hyperkalemia represents a medical emergency, even in stable patients with a history of chronic hyperkalemia<br>• Patients should have an ECG performed, and treatment initiated from Table 1 | |
| Moderate hyperkalemia ($K^+$ = 5.6–5.9) | • Initiate patiromer at 8.4 g once daily, ***OR***<br>• Up titrate patiromer if started at ≥7-day intervals by 8.4 g once daily, to a maximum dose of 25.2 g daily, until serum $K^+$ <5.1<br>• Maintain RAAS inhibitor if started, but re-assess serum $K^+$ levels after 3–7 days, assess volume status and consider adding/ adjusting diuretic dose<br>– If $K^+$ levels are still high and patiromer is on maximum dose, consider RAAS inhibitor down titration<br>– If $K^+$ <5.1, consider up-titration of RAAS inhibitor if not on guideline-recommended target dose | • Initiate SCZ at 10 g thrice daily for 24, 48, or 72 h (i.e., until normokalemia), then proceed to maintenance phase, starting with 5 g/ day, max 10 g–15 g/day ***OR***<br>• Up titrate SZC, if started, by 5 g once daily, to a maximum dose of 10–15 g/daily, until serum $K^+$ <5.1, or down titrating to 5 g every other day, depending on $K^+$ level<br>• Maintain RAAS inhibitor if started, but re-assess serum $K^+$ levels after 3–7 days, assess volume status and consider adding/ adjusting diuretic dose<br>– If $K^+$ levels are still high and SZC is on maximum dose, consider RAAS inhibitor down titration<br>– If $K^+$ <5.1, consider up-titration of RAAS inhibitor if not on guideline-recommended target dose |
| Mild hyperkalemia ($K^+$ = 5.1–5.5) | • Consider initiation of patiromer at 8.4 g once daily, OR<br>• Maintain/up-titrate patiromer if started at >7-day intervals by 8.4 g once daily, to a maximum dose of 25.2 g daily, until serum $K^+$ <5.1<br>• Initiate/maintain RAAS inhibitor at guideline-recommended target dose, asses volume status and consider adding/ adjusting diuretic dose, and re-assess serum $K^+$ level after 7 days, after OR<br>• Consider up-titration of RAAS inhibitor to guideline-recommended target dose depending on clinical situation | • Consider initiation of SZC at 10 g thrice daily for 24, 48, or 72 h (i.e., until normokalemia), then proceed to the maintenance phase, starting with 5 g/day, then up-titrating to maximum 10–15 g/day, or down titrating to 5 g every other day, depending on $K^+$ level, ***OR***<br>• Maintain/up-titrate SZC, if started, to a maximum dose of 10 g daily, until serum $K^+$ <5.1<br>• Initiate/maintain RAAS inhibitor at guideline-recommended target dose, asses volume status and consider adding/ adjusting diuretic dose, and re-assess serum $K^+$ level after 7 days, after ***OR***<br>• Consider up-titration of RAAS inhibitor to guideline-recommended target dose depending on clinical situation |

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**Table 5** (continued)

| Serum ($K^+$) level (in mmol/L) [confirmed by two consecutive samples] | Potassium binder | |
|---|---|---|
| | patiromer | sodium zirconium cyclosilicate (SZC) |
| | action | |
| Normokalemia ($K^+$ = 4.1–5.0) | • If started on patiromer, maintain dose<br>• Initiate/maintain/up-titrate RAAS inhibitor to guideline-recommended target dose, assess volume status and consider adding/adjusting diuretics, and re-assess $K^+$ levels after 7 days | • If started on SZC, maintain dose<br>• Initiate/maintain/up-titrate RAAS inhibitor to guideline-recommended target dose, assess volume status and consider adding/adjusting diuretics, and re-assess $K^+$ levels after 3–7 days |
| Mild hypokalemia ($K^+$ = 3.5–4.0) | • Stop patiromer if on lowest dose, **OR**<br>• Down-titrate patiromer at ≥7-day intervals by 8.4 g daily | • Stop SZC if on lowest (5 g every other day) dose ***OR***<br>• Down-titrate SZC at ≥7-day intervals by 5 g daily |
| Hypokalemia ($K^+$ <3.5) | • If on patiromer, stop treatment | • Stop temporarily until $K^+$ is above 3.5 (or 4.0 if being conservative) then restart at lower dose. Stop if patient was already on 5 g every other day |
| Mrnitoring recommendations | • Monitoring frequency should be individualized based on the clinical situation. Some clinical scenarios may require a change in the frequency of monitoring; refer to applicable guidelines for recommendations; below are general recommendations<br>• After initiating or changing potassium binder dose, measure serum $K^+$ and creatinine within 3–7 days and repeat and repeat after 1 week. If target $K^+$ value is achieved, measure serum $K^+$ at 1 month, then every 3 months<br>• Anytime that a change in electrolyte or volume status is suspected, e.g., due to gastrointestinal problems, re-measure serum $K^+$ and creatinine and repeat above monitoring sequence as per standard clinical practice and applicable guideline recommendations<br>• ***Patiromer specific recommendation:*** Monitor serum magnesium for at least 1 month after initiating. Consider magnesium supplementation in patients who develop low serum magnesium levels (0.58 mmol/L)<br>• ***SZC specific recommendation:*** SZC mechanism of action involves potassium exchange for sodium (or hydrogen) in the gastrointestinal tract, monitor for edema during SZC therapy particularly in patients prescribed a SZC dose higher than 10 g daily | |

RAAS, renin-angiotensin-aldosterone system; SZC, sodium zirconium cyclosilicate. Adapted from Rossignol et al. [49].

or discontinuation of RAASi therapy due to hyperkalemia has been associated with adverse outcomes. Rather than stopping these medications, use the above listed measures as well as the potassium binders patiromer and SZC to preserve RAASi protections in the CKD and HF populations.

### Members of a Medical Team Who Interact with the Patient

Hyperkalemia is managed routinely by a broad medical team. Numerous members of the care team assist in the short- and long-term care needs of patients with hyperkalemia, including nursing, emergency physicians, primary care physicians, hospitalists, cardiologists, nephrologists, and pharmacists (Fig. 4). Depending on the patient's needs, input from dieticians, physical therapists, occupational therapists, social workers, and case management may also be valuable. It is critical, particularly during transitions of care from one setting to another, such as an inpatient admission to hospital discharge, that members of the care team communicate well with one another. Implementing guideline-directed medical therapy (GDMT) can be particularly challenging as it requires individualized interventions and the use of multiple medications that need to be titrated quickly and safely, all while ensuring the treatment remains affordable for the patient. For example, some

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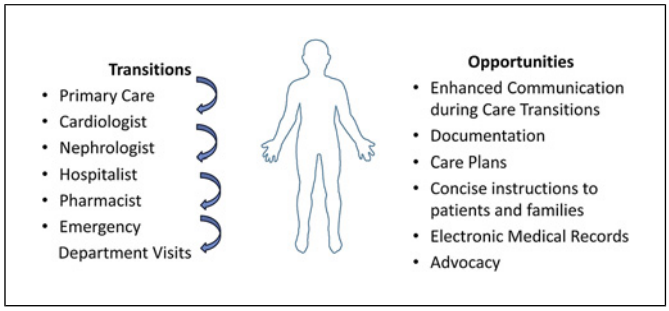


**Fig. 4.** The patient journey through many care transitions: management of hyperkalemia involves a multidisciplinary care team, particularly during transitions of care, including physicians, nurses, pharmacists, and specialists such as cardiologists and nephrologists. Additional support from dieticians, therapists, and social workers may be integrated based on patient needs.

patients may benefit from synergistic drug effects (e.g., kaliuresis from SGLT2i with MRAs), or other tailored therapies based on the patient's individual characteristics. Follow-up and laboratory testing, along with the continuation and adjustments of binder dosage and schedule, are essential for optimal patient care. For this reason, communication and insight from multiple members of the team is valuable for patient care.

In the outpatient setting, patients being treated with GDMT for HF with reduced EF may be taking multiple medications that increase serum potassium [56]. The outpatient management of hyperkalemia may entail collaboration between a primary care physician, nephrologist, cardiologist, and/or other specialists, and begins by evaluating both the physiological and environmental exposures that may be contributing to hyperkalemia [6]. A hospitalization may be an ideal time to initiate $K^+$ binding therapy which can be continued in the outpatient setting. Give many clinicians can manager hyperkalemia, healthcare providers may benefit from up-to-date electronic or paper visual reminders-algorithms, guidelines, decision support systems and other cues to action.

*Physicians*

Numerous physician specialists such as hospitalists, nephrologists, and cardiologists play a substantial role in the management of patients admitted to the hospital with acute exacerbations of HF or CKD, who may also experience hyperkalemia. When patients taking RAASi therapy are hospitalized for other reasons, it is important to maintain these medications unless it is absolutely necessary to discontinue them. Effective communication at the time of discharge is important since care may become fragmented by hospitalizations. Clinicians are at risk of continuing the medication changes that a previous provider has made. As such, if RAASi therapy is stopped, episodes of hyperkalemia occur, or RAASi dosages are changed, communicating with a patient's primary care physician and other specialists is important. While hospitalized, it is important for consulting specialists to include in their documentation what changes in laboratory testing might be expected by dosage changes, and what additional inpatient and outpatient testing may be necessary. Lastly, in the context of busy clinical practices, having checks and balances within the healthcare system are important. For example, pharmacists may query why a medication is being stopped or a dosage unnecessarily changed.

*Advance Practice Providers and Nursing Impact on the Management Hyperkalemia*

In today's healthcare systems and in private practices, many adults with cardiovascular diseases (hypertension, MI/ischemia, HF, or cardiomyopathies) are being cared for by physicians who work collaboratively with advance practice providers (APP) including clinical nurse specialists, nurse practitioners and physician's assistants. In addition, during acute care, the primary caregivers providing patient education are clinical nurses who work on medical-surgical and cardiovascular units where patients receive care before hospital discharge. Nurses and APPs should educate patients about a weak benefit of low potassium diets on serum potassium in CKD [57], the lack of value of withholding dietary fruits and vegetables [58], not using potassium-based seasoning as an alternative to sodium-based products [59], and the established benefits of continuing or reintroducing RAASi therapies. Nurses can use communication technologies and techniques (for example, shared decision making) to individualize and optimize treatment plans. Nursing care delivery can have a major impact on the management of chronic hyperkalemia, but only if nurses, including APPs, understand the issues surrounding hyperkalemia, and are knowledgeable and comfortable teaching patients and families about chronic hyperkalemia treatment plans.

Since many patients with cardiovascular diseases are older, have diabetes and other comorbidities and receive RAASi treatments as part of guideline-recommended care, it is important for clinical nurses and APPs to understand the need for careful monitoring of potassium and to take necessary steps when chronic hyperkalemia

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is present. Clinical nurses and APPs should maintain *secondary prevention* RAASi therapies as they are considered first-line therapies in atherosclerotic cardiovascular disease [5], and heart failure with reduced ejection fraction (HFrEF), mildly reduced EF [41], and HF with preserved EF [41, 60].

*The Pharmacist's Role in Hyperkalemia Management*

Pharmacists play an important role in the medication process in both CKD and HF patients, including the management of a patient's individual pharmacotherapy regimens, quality improvement initiatives, patient education, and guidelines development [61]. Pharmacists are key at performing an accurate medication history and reconciliation, adherence assessment, identifying drug-drug interactions via polypharmacy, and monitoring laboratory values and symptoms in patients with a diagnosis of chronic hyperkalemia. As a part of the multidisciplinary team, pharmacists work collaboratively to assure patients are titrated on GDMT start potassium binders if indicated, and monitor patients for adjustment [61]. Lastly, pharmacists can help navigate financial and adherence barriers patients encounter with their drug regimens.

The success of pharmacists managing chronic hyperkalemia was demonstrated in a case-controlled study of HF patients with or at risk of hyperkalemia in Latin America [62]. Patients were followed over the study period of 1 year to determine which had recurrence or developed hyperkalemia. The investigators looked to see who received a pharmacist-based multidimensional intervention (PBMI) which included (1) medication regimen review (2) patient interview including adherence factors (3) development of a medication plan and (4) education including a drug interaction chart. The authors of the study determined those who developed hyperkalemia, new or recurrence, were less likely to have received the PBMI (Odds Ratio 0.57; 95% confidence interval 0.43–0.80). The investigators concluded a PBMI is a practical approach to prevent hyperkalemia in HF patients. Further implementation studies must promote pharmacists' engagement in management of chronic hyperkalemia. Current clinical guidelines support and encourage team-based care, including pharmacists, in the management of these patients related to GDMT.

*Barriers to Management of Chronic Hyperkalemia in HF*

Chronic hyperkalemia is a common complication in patients with HF, which may limit use of GDMT and can lead to serious consequences [63–65]. The management of chronic hyperkalemia in patients with HF is challenging, with many barriers (Fig. 5) [66]. The use of RAASis are components of GDMT in HFrEF, and may also be considered for patients with HF with mildly reduced or preserved EF [41]. However, these agents can also lead to hyperkalemia or exacerbate hyperkalemia. The potential risk of hyperkalemia in patients with HF is further increased in those with frequently encountered comorbidities such as diabetes and CKD [66]. The presence of hyperkalemia often leads to the down titration and discontinuation of RAASi therapy [41, 65, 67]. Further, perceived concerns regarding hyperkalemia risk may lead to these otherwise indicated, life-enhancing HF therapies to not be initiated [67, 68].

Previously the only available treatment option for hyperkalemia using $K^+$ binding agents was SPS. However, this agent has several limitations such as poor tolerability, gastrointestinal side effects, drug interactions, and safety concerns [66]. In recent years, patiromer and SZC have been FDA approved for the management of hyperkalemia, including for patients with HF [35, 40]. These drugs provide therapeutic options for management of patients predisposed to developing hyperkalemia and their use may allow for further optimization of GDMT. Patiromer and SZC have both been shown to reduce the frequency of hyperkalemia in patients with HF predisposed to developing recurrent hyperkalemia. These agents can potentially reduce the rates in which renin RAASi needs to be discontinued [35, 40]. With patiromer and SZC there is the potential for drug interactions, hypokalemia, hypomagnesemia, and gastrointestinal side effects [63, 64]. With SZC in particular, a perceived barrier may be volume overload in patients with HF, given its sodium content (Table 3). Edema in patients utilizing SZC is generally mild to moderate, and more common with the highest doses (15 g). Increased edema secondary to SZC may require additional monitoring, adjustment of dietary sodium, or an increase in diuretic dose if needed [69]. In recent clinical trials intermediate term treatment with these agents in HF patients appeared to be safe and generally well tolerated [35, 40]. Further research is needed to determine the long-term safety and efficacy of these drugs. Potential barriers include out of pocket costs, access, prior authorizations, and formulary restrictions.

Clinicians managing patients with HF with or at risk for hyperkalemia must ensure close monitoring of the patient's HF condition, volume status, laboratory test results, new medications, and procedures [41, 66]. This is challenging, as clinicians often have a limited amount of time with a patient. In these settings, the importance of team care as described above cannot be overemphasized. Timely, accurate communication, education, and comprehensive coordination of care with the patient, caregivers, multidisciplinary team members, and various specialists is essential. Therapeutic inertia often leads to

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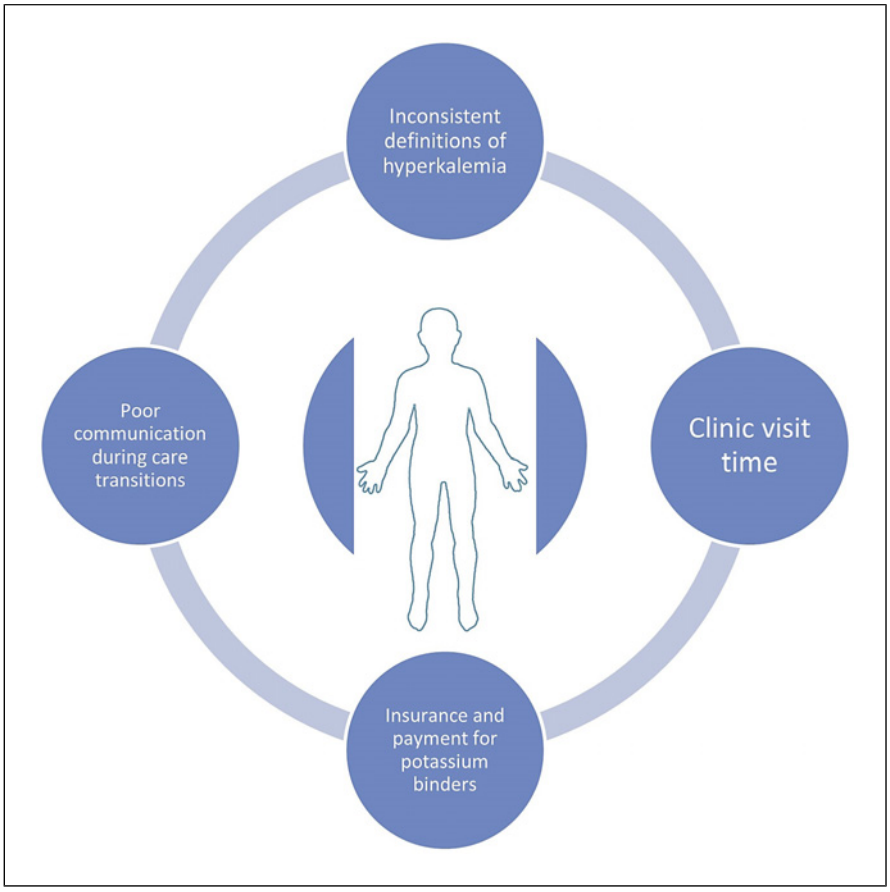


**Fig. 5.** Barriers to utilization of $K^+$ binders to support the optimal treatment of the patient with heart failure. There are numerous barriers that patients face when utilizing $K^+$ binders, including common ones that are listed.

clinicians discontinuing or omitting beneficial HF therapies to address hyperkalemia risk rather than deploying strategies that would allow these therapies to safely continue [67]. The patient needs to be monitored regularly to make sure that their serum potassium concentration remains within the normal range [66, 67].

*Future Directions*

Additional agents may be utilized to reduce episodes of hyperkalemia in patients with CKD or HF. For example, the use of SGLT2 inhibitors as a class of agents are commonly used to improve mortality and morbidity outcomes in CKD and HF through a variety of mechanisms. Specifically, to hyperkalemia, these agents promote tubular flow leading to improved kidney function which impacts potassium secretion. In the FIDELIO-DKD trial, patients who were on an SGLT2 inhibitor while receiving the MRA had lower serum potassium levels compared those not on SGLT2 inhibitors [70]. This result suggests these agents may have independent potassium-lowering ability. Furthermore, two large meta-analysis examining SGLT2 inhibitors in DM and CKD, found SGLT2 inhibitors reduced the risk of serious hyperkalemia [50, 71]. More data need to be derived with this drug class in order to determine if they can be considered potassium-lowering agents; however, it does speak to the importance of getting these initiated and maintained in order to optimize GDMT.

Finerenone is a non-steroidal mineralocorticoid receptor antagonist used in the treatment of CKD in patients with type 2 diabetes [72]. Use of finerenone may result in a lower risk of hyperkalemia and lower rates of discontinuation due to hyperkalemia compared to spironolactone [31, 72–77]. The Mineralocorticoid Receptor Antagonist Tolerability Study (ARTS) was a phase 2 head-to-head comparison of finerenone (2.5–10 mg daily and 5 mg twice daily) with spironolactone (25–50 mg daily for 30 days [31]. In ARTS, the incidence of investigator-reported hyperkalemia was lower with finerenone compared to spironolactone (5.3% versus 12.7%, $p = 0.048$) [31]. Discontinuation due to hyperkalemia occurred in 0% vs. 3.2% of patients, respectively [31]. The FIGARO-DKD trial demonstrated that finerenone led to a reduction in cardiovascular events among patients with type 2 diabetes and CKD who were already on maximal renin-angiotensin



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system blockade therapy [73, 74]. A post hoc comparison from the FIDELITY pooled analysis indicated that finerenone is associated with lower rates of hyperkalemia compared with spironolactone [75, 76]. The lower risk of hyperkalemia may reflect potential differences in tissue distribution that may affect potassium homeostasis, differences in plasma half-life (2.2–2.8 h with finerenone compared with >12 h in healthy volunteers with spironolactone), and that finerenone has no active metabolites, whereas spironolactone has multiple [72, 75, 76]. However, in a recent secondary analysis of the FINEARTS-HF multicenter randomized-controlled trial, authors reported that participants receiving finerenone experienced an increase in serum potassium compared to placebo, so clinicians must still remain vigilant when monitoring potassium levels in patients taking finerenone. Despite this, participants who received finerenone in the FINEARTS-HF study had fewer of the primary endpoint events, which consisted of the composite worsening HF or cardiovascular death [78]. Finerenone is being further evaluated in a number of ongoing cardiovascular outcome studies. In addition, other non-steroidal MRAs are also being investigated in ongoing CV trials [79].

## Conclusions

Hyperkalemia is a common occurrence, particularly in patients with risk factors such as HF and CKD. In these patients, clinicians should maintain RAASi therapy by utilizing potassium binding agents, combining therapies such as SGLT2i and RAASi, and working within a multidisciplinary team to treat individual patients. Our consensus panel identified numerous future needs within the healthcare system that may increase the number of patients who receive guideline-directed therapy. There is a need for a more consistent definition of hyperkalemia, as well as strategies that improve communication among primary care clinicians, subspecialist clinicians, nurses, and pharmacists. It is critical for potassium binding medications to be placed on hospital pharmacy formularies, and for hospitals to improve medication compliance by facilitating the ease of filling prescriptions during care transitions. Nurses who care for patients at risk of, or with hyperkalemia, must be educated in a standardized fashion so that they are empowered to provide guidance during care transitions. Clinicians must receive education about the correct dosing of medications to support the management of patients with acute and chronic hyperkalemia. Lastly, improvements to patient and family education are critical to ensuring the best possible outcomes for patients.

## Conflict of Interest Statement

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## Author Contributions

B.G. conceived of the idea for the consensus gathering and manuscript and obtained grant funding. N.K. and I.P. were the moderators of the consensus panel. N.A., A.A., C.B., R.B., G.F., B.G., K.K., R.M., B.P., C.P., and I.P. all contributed to written sections of the manuscript, participated in panel discussions, and critically reviewed and revised the manuscript. All authors approve of the final manuscript.

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