



# Clinical Management of Hyperkalemia

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## Abstract

Hyperkalemia is an electrolyte abnormality with potentially life-threatening consequences. Despite various guidelines, no universally accepted consensus exists on best practices for hyperkalemia monitoring, with variations in precise potassium ( $K^+$ ) concentration thresholds or for the management of acute or chronic hyperkalemia. Based on the available evidence, this review identifies several critical issues and unmet needs with regard to the management of hyperkalemia. Real-world studies are needed for a better understanding of the prevalence of hyperkalemia outside the clinical trial setting. There is a need to improve effective management of hyperkalemia, including classification and  $K^+$  monitoring, when to reinstate previously discontinued renin-angiotensin-aldosterone system inhibitor (RAASi) therapy, and when to use oral  $K^+$ -binding agents. Monitoring serum  $K^+$  should be individualized; however, increased frequency of monitoring should be considered for patients with chronic kidney disease, diabetes, heart failure, or a history of hyperkalemia and for those receiving RAASi therapy. Recent clinical studies suggest that the newer  $K^+$  binders (patiomer sorbitex calcium and sodium zirconium cyclosilicate) may facilitate optimization of RAASi therapy. Enhancing the knowledge of primary care physicians and internists with respect to the safety profiles of these newer  $K^+$  binders may increase confidence in managing patients with hyperkalemia. Lastly, the availability of newer  $K^+$ -binding agents requires further study to establish whether stringent dietary  $K^+$  restrictions are needed in patients receiving  $K^+$ -binder therapy. Individualized monitoring of serum  $K^+$  among patients with an increased risk of hyperkalemia and the use of newer  $K^+$ -binding agents may allow for optimization of RAASi therapy and more effective management of hyperkalemia.

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Hyperkalemia, defined as an elevated serum potassium ( $K^+$ ) concentration of greater than 5.0 or greater than 5.5 mEq/L (mmol/L), is an electrolyte abnormality with potentially life-threatening consequences.<sup>1</sup> The risk for development of hyperkalemia is increased in patients with chronic kidney disease (CKD), diabetes, and heart failure (HF) and in individuals receiving renin-angiotensin-aldosterone system inhibitors (RAASi).<sup>1-3</sup>

Guidelines/consensus statements for hyperkalemia management have been developed.<sup>1,2,4-9</sup> However, no universally accepted consensus exists regarding best practices, particularly in consideration of newer  $K^+$

binders and their use in patients with hyperkalemia due to CKD or the adverse effects of RAASi, a widely used drug class with significant cardiorenal benefits.<sup>1</sup> Thus, new management guidelines are needed to incorporate these  $K^+$  binders into hyperkalemia treatment.

This review summarizes the physiology of hyperkalemia and suggests evidence-based clinical considerations that may provide improvements in care and outcomes in patients with an increased hyperkalemia risk.

## METHODS

We conducted a literature search of the PubMed database for articles published between January 1, 2000, and October 14,

2019. Search terms included *chronic kidney disease, diabetes, heart failure, hyperkalaemia, hyperkalemia, patiromer, potassium, renin-angiotensin-aldosterone system inhibitor, sodium polystyrene sulfonate, SPS, sodium zirconium cyclosilicate, SZC, and ZS9*. The results of this literature search were reviewed by researchers, epidemiologists, clinicians, dietitians, and trialists in the field of hyperkalemia.

## POTASSIUM HOMEOSTASIS AND HYPERKALEMIA

Potassium homeostasis is largely maintained by the kidneys, although the gastrointestinal tract and other systems are also involved to a lesser extent (Figure 1).<sup>7,10</sup> Hyperkalemia has depolarizing effects on the heart,<sup>10</sup> causing shortened action potentials and increasing the risk of arrhythmias.<sup>11</sup> Hyperkalemia causes neuromuscular symptoms,<sup>10,12</sup> metabolic acidosis, and suppression of ammoniogenesis.<sup>13</sup>

The risk of mortality, cardiovascular morbidity, progression of CKD, and hospitalization is increased in patients with hyperkalemia, especially those with CKD, HF, and diabetes.<sup>14,15</sup> A U-shaped curve exists between serum  $K^+$  and mortality, with both hyperkalemia and hypokalemia associated with adverse clinical outcomes (Figure 2).<sup>14</sup> However, the exact  $K^+$  concentration that clinicians should consider to be life-threatening remains controversial. The risk of hyperkalemia and the optimal range for serum  $K^+$  concentrations vary according to individual patient comorbidities, such as CKD, HF, or diabetes. For example, a patient with atrioventricular heart block may experience worsening of cardiac symptoms at a lower  $K^+$  concentration than another patient without the same condition.<sup>16</sup> The rate of increase in  $K^+$  concentrations must also be considered, as a rapid increase in serum  $K^+$  is more likely to result in cardiac abnormalities than a slow steady rise over several months.<sup>17</sup> In patients with CKD, compensatory mechanisms may result in tolerance to elevated circulating  $K^+$ , and several studies have suggested that hyperkalemia is a less threatening condition in CKD.<sup>15,18-22</sup> A retrospective study found a stronger association between hyperkalemia ( $K^+ \geq 5.5$  mEq/L) and

## ARTICLE HIGHLIGHTS

- An unmet need exists for new hyperkalemia management guidelines that effectively incorporate classification and monitoring for hyperkalemia, optimization of renin-angiotensin-aldosterone system inhibitor (RAASi) therapy, and use of the newer potassium ( $K^+$ ) binders.
- Treatment gaps exist between guideline recommendations and RAASi use in clinical practice among patients with an increased risk of hyperkalemia; if discontinued, RAASi therapy should be reinitiated after acute hyperkalemia has resolved.
- The frequency of  $K^+$  monitoring should be individualized on the basis of patient comorbidities and medications (eg, RAASi), particularly in patients at high risk for development of hyperkalemia.
- Patients with chronic hyperkalemia may benefit from long-term  $K^+$ -binding therapy, initiated at the recommended dose and titrated according to serum  $K^+$  levels.
- Use of the newer  $K^+$  binders may enable the optimization of RAASi therapy in more patients with hyperkalemia.

1-day mortality among inpatients and outpatients with normal kidney function than in those with CKD (estimated glomerular filtration rate [eGFR]  $<60$  mL/min per 1.73  $m^2$ ).<sup>18</sup> A U-shaped correlation was found between serum  $K^+$  and overall mortality risk in patients with non-dialysis-dependent CKD,<sup>19</sup> and in a study of consecutive hospitalizations for severe hyperkalemia, a graded decrease in the risk of mortality was observed as CKD stage worsened.<sup>20</sup> In a cohort study of patients with stage 3 to 5 CKD, the risk of pre-end-stage renal disease (ESRD) mortality was lower when serum  $K^+$  concentrations were 4.0 to 5.5 mEq/L compared with 4.0 mEq/L or less and was not increased with serum  $K^+$  levels of 5.5 mEq/L or greater.<sup>21</sup> Lastly, in a large cohort study evaluating the potential reduction in mortality risk from hyperkalemia with worsening CKD in more than 800,000 individuals, an evaluation of 90-day mortality risk in relation to  $K^+$  concentrations revealed that the observed optimal  $K^+$  range was broader toward higher  $K^+$  concentration in patients with stage 4 to 5 CKD (optimal range, 3.3 to 5.5 mEq/L) than in those

with stage 1 to 2 CKD (optimal range, 3.5 to 5.0 mEq/L).<sup>15</sup>

The mechanisms underlying this possible increase in tolerance to hyperkalemia among patients with advanced CKD are not fully understood. It has been suggested that patients with CKD adapt to elevated  $K^+$  concentrations through modifications in gastrointestinal  $K^+$  secretions<sup>10,23</sup> which may favor intracellular  $K^+$  storage,<sup>24</sup> or by increasing insulin-mediated intracellular  $K^+$  uptake in splanchnic and peripheral muscle tissues.<sup>25</sup> However, it is unknown whether these adaptations to increased serum  $K^+$  exist in other cells (eg, cardiomyocytes). Potassium channels in the myocardium are known to be sensitive to shifts in endogenous factors and may change in number or functioning in response to structural<sup>26,27</sup> and environmental<sup>28</sup> alteration. Therefore, future studies should investigate whether these changes in myocardial  $K^+$  channels may explain the observed reductions in the relative risk of death from hyperkalemia in patients with advanced CKD. In addition, given the relationship between serum  $K^+$ , acidosis, and calcium/magnesium concentrations,<sup>29</sup> it would be interesting to examine whether metabolic acidosis affects the association between serum  $K^+$  and mortality risk in patients with CKD.

## EPIDEMIOLOGY OF HYPERKALEMIA

### Hyperkalemia Incidence

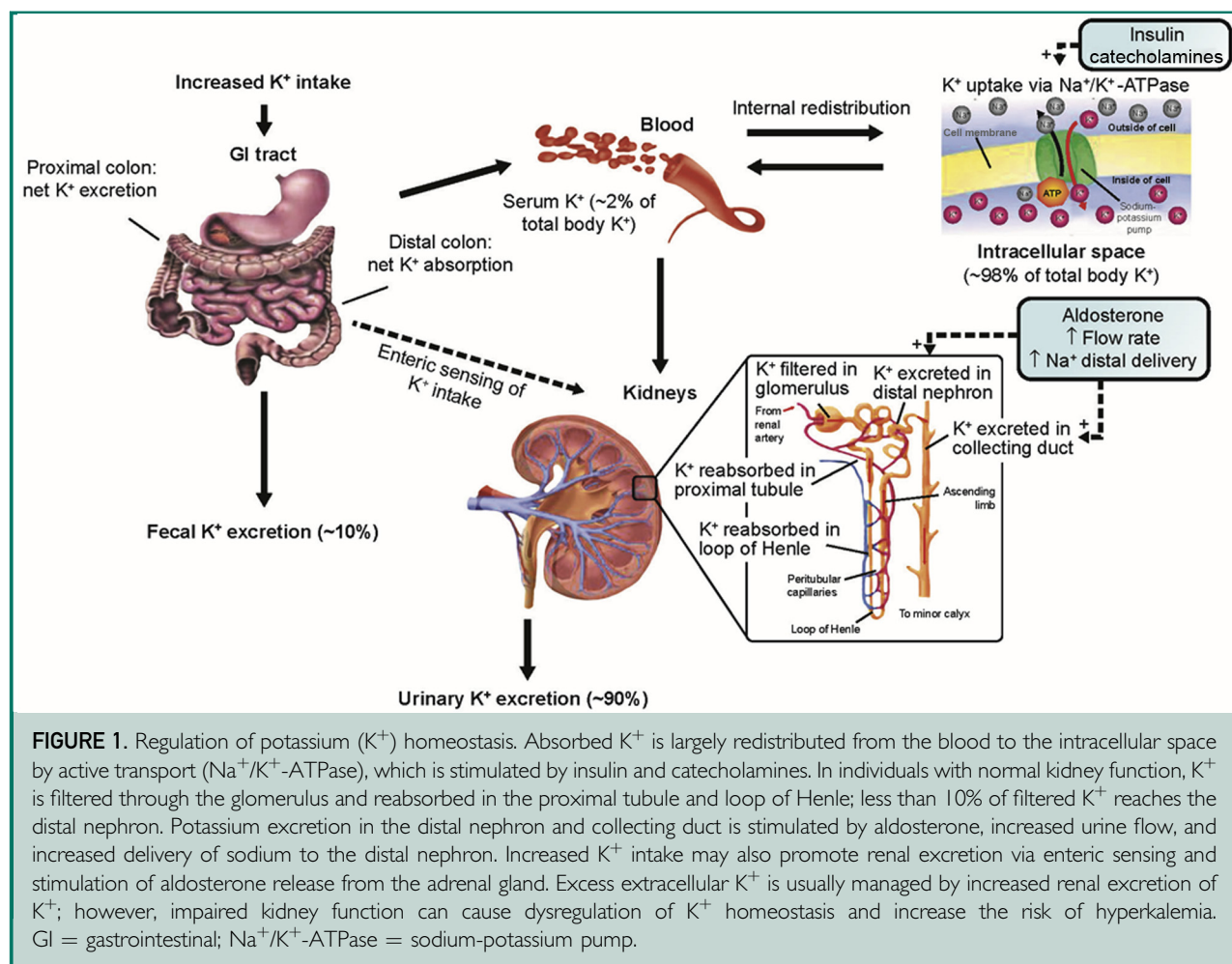
Hyperkalemia is rare in the general population.<sup>7</sup> However, because it is a transient condition, no prospective studies monitoring intraindividual serum  $K^+$  concentrations have been conducted, and therefore, the exact incidence of hyperkalemia in the general population is unclear. Different  $K^+$  thresholds also affect the reported incidence of hyperkalemia. Among hospitalized patients, hyperkalemia incidence has been reported as 3.5% ( $>5.5$  mEq/L) in Canada<sup>16</sup> and 4.9% ( $>5.0$  mEq/L) in Ireland.<sup>17</sup> However, the likelihood of detecting hyperkalemia depends on the frequency of  $K^+$  monitoring. Two studies of inpatients and/or outpatients undergoing  $K^+$  testing over 3 years, one in Sweden<sup>30</sup> and another in the United States,<sup>31</sup> observed higher rates of

hyperkalemia (7%<sup>30</sup> and 11% [ $>5.0$  mEq/L] and 2% [ $>5.5$  mEq/L],<sup>31</sup> respectively). The worldwide incidence of hyperkalemia could be underestimated because of the lack of routine  $K^+$  monitoring even in some high-risk patient populations. Therefore, further epidemiological research in real-world populations is needed to more accurately estimate hyperkalemia incidence, which may be higher than observed in clinical trials because of the lack of consistent  $K^+$  monitoring and the lack of a standardized hyperkalemia definition (eg, serum  $K^+ >5.0$ ,  $>5.5$ , or  $>6.0$  mEq/L).

### Risk Factors

Certain patient populations have an increased risk of hyperkalemia-associated morbidity and mortality, including patients with advanced stages of CKD, HF, resistant hypertension, diabetes, myocardial infarction (MI), and/or combinations of these conditions.<sup>14,32,33</sup> Additional risk factors include RAASi usage, advanced age,<sup>2</sup> and drugs such as heparin,  $\beta$ -blockers, nonsteroidal anti-inflammatory drugs, calcineurin inhibitors, trimethoprim, pentamidine, and  $K^+$ -sparing diuretics.<sup>10,34</sup> The risk of hyperkalemia progressively increases as eGFR decreases.<sup>15</sup> Because chronic loss of kidney function is associated with an adaptive response in the remaining functional nephrons, allowing for an increase in fractional  $K^+$  excretion and maintenance of serum  $K^+$  levels of less than 5.5 mEq/L, the risk of hyperkalemia is generally increased once the eGFR is less than 15 mL/min per 1.73 m<sup>2</sup>.<sup>35</sup> Furthermore, patients receiving RAASi therapy who have an eGFR of less than 60 mL/min per 1.73 m<sup>2</sup> have an elevated hyperkalemia risk, which progressively increases as eGFR decreases.<sup>3,36</sup> In patients with CKD and/or chronic HF receiving RAASi, risk factors for repeated hyperkalemia within 6 months of the first event include moderate to severe initial hyperkalemia ( $\geq 5.6$  mEq/L), low eGFR ( $<45$  mL/min per 1.73 m<sup>2</sup>), diabetes, and spironolactone use.<sup>37</sup>

Hyperkalemia risk is slightly higher in men than in women after initiation of RAASi therapy<sup>3</sup> and differs among racial groups, in whom ethnicity, diet, and socioeconomic factors may contribute.<sup>38</sup> These factors currently do not impact hyperkalemia management;



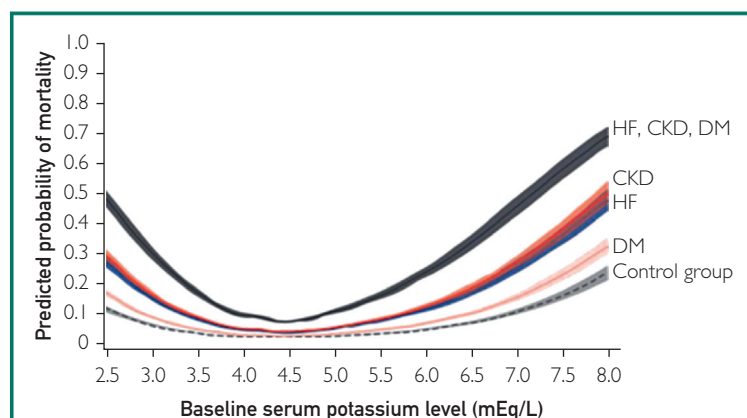
however, the potentially additive effects of these differences may increase hyperkalemia risk.

A low- $K^+$  diet is recommended in patients with advanced-stage CKD to reduce hyperkalemia risk<sup>39</sup>; however, a recent Kidney Disease: Improving Global Outcomes (KDIGO) conference found that direct evidence supporting a link between dietary  $K^+$  intake and serum  $K^+$  concentrations is limited and that interventional trials are needed to determine optimal recommendations for dietary  $K^+$  in patients with CKD.<sup>40</sup> A low- $K^+$  diet is difficult for patients to adhere to, particularly those who may have additional dietary restrictions due to diabetes and reduced sodium intake for CKD or HF. Furthermore, evidence indicates that a  $K^+$ -rich diet has multiple health benefits including blood pressure reductions and

reduced risks of CKD progression, cardiovascular disease, and stroke.<sup>41</sup> Restriction of dietary  $K^+$  as a general approach to preventing hyperkalemia may therefore deprive patients of these benefits.<sup>40</sup>

#### RAASi Therapy—Benefits and Hyperkalemia Risk

Renin-angiotensin-aldosterone system inhibitors are recommended for patients with hypertension,<sup>42</sup> HF,<sup>43,44</sup> stable coronary artery disease,<sup>45</sup> CKD, diabetic kidney disease (DKD),<sup>46</sup> and diabetes.<sup>47,48</sup> They improve survival in patients with CKD,<sup>49</sup> HF,<sup>50,51</sup> and post-MI status<sup>52</sup> and also provide kidney benefits in patients with non-DKD<sup>53</sup> and DKD.<sup>54,55</sup> Many patients who would otherwise benefit from RAASi either do not receive these medications, receive suboptimal doses,



**FIGURE 2.** The risk of hypokalemia- or hyperkalemia-associated mortality (a) in patients with chronic kidney disease (CKD) and other comorbidities over 18 months. DM = diabetes mellitus; HF = heart failure. From *Am J Nephrol*,<sup>14</sup> with permission.

or discontinue therapy because of the associated increased risk of recurrent hyperkalemia.<sup>1</sup> Treatment gaps exist between guideline recommendations and RAASi use in clinical practice in patients with increased hyperkalemia risk.<sup>36,56,57</sup> Compared with those for maximum RAASi dosing, mortality rates are higher with suboptimal dosing among patients with CKD, diabetes or HF and are highest among patients who discontinue RAASi.<sup>57</sup> In one study, 74% of patients who discontinued mineralocorticoid receptor antagonists (MRAs) because of hyperkalemia did not reinitiate therapy during the subsequent year.<sup>36</sup> Many patients who have had acute MI are not prescribed MRAs at hospital discharge because of hyperkalemia risk.<sup>56</sup> Additionally, patients with HF are often prescribed subtherapeutic MRA doses despite guideline recommendations.<sup>58</sup>

Although hyperkalemia represents a significant barrier to effective use of RAASi,<sup>1,59,60</sup> RAASi therapy is associated with improved survival in patients with HF, particularly in those at risk for hyperkalemia.<sup>61,62</sup> Despite a lack of randomized controlled trial data to document improved clinical outcomes with correction of hyperkalemia and reinitiation of RAASi therapy in patients with an increased hyperkalemia risk, there is an increasing body of real-world evidence of increased morbidity and mortality

among patients with CKD, HF, or diabetes who receive suboptimal or no RAASi therapy because of hyperkalemia.<sup>63-65</sup> For example, in a cohort study of patients who experienced a decline in eGFR to less than 30 mL/min per 1.73 m<sup>2</sup> while receiving RAASi therapy, discontinuation of RAASi therapy was associated with a higher risk of mortality or major adverse cardiovascular events than continuation of RAASi.<sup>63</sup> In addition, a recent consensus report<sup>9</sup> and a position paper<sup>66</sup> suggest that treatment with the newer K<sup>+</sup> binders (discussed subsequently) may allow for optimization of RAASi therapy in patients with HF. Therefore, maximum RAASi therapy, as tolerated, should be considered when RAASi are indicated. Hyperkalemia should be treated if it develops, and reinitiation of RAASi (if discontinued) should be considered after resolution of acute hyperkalemia. Other potential risk factors for hyperkalemia should be identified and removed, whenever possible, and patients should be monitored closely, with reassessment of K<sup>+</sup> concentrations within 1 week.

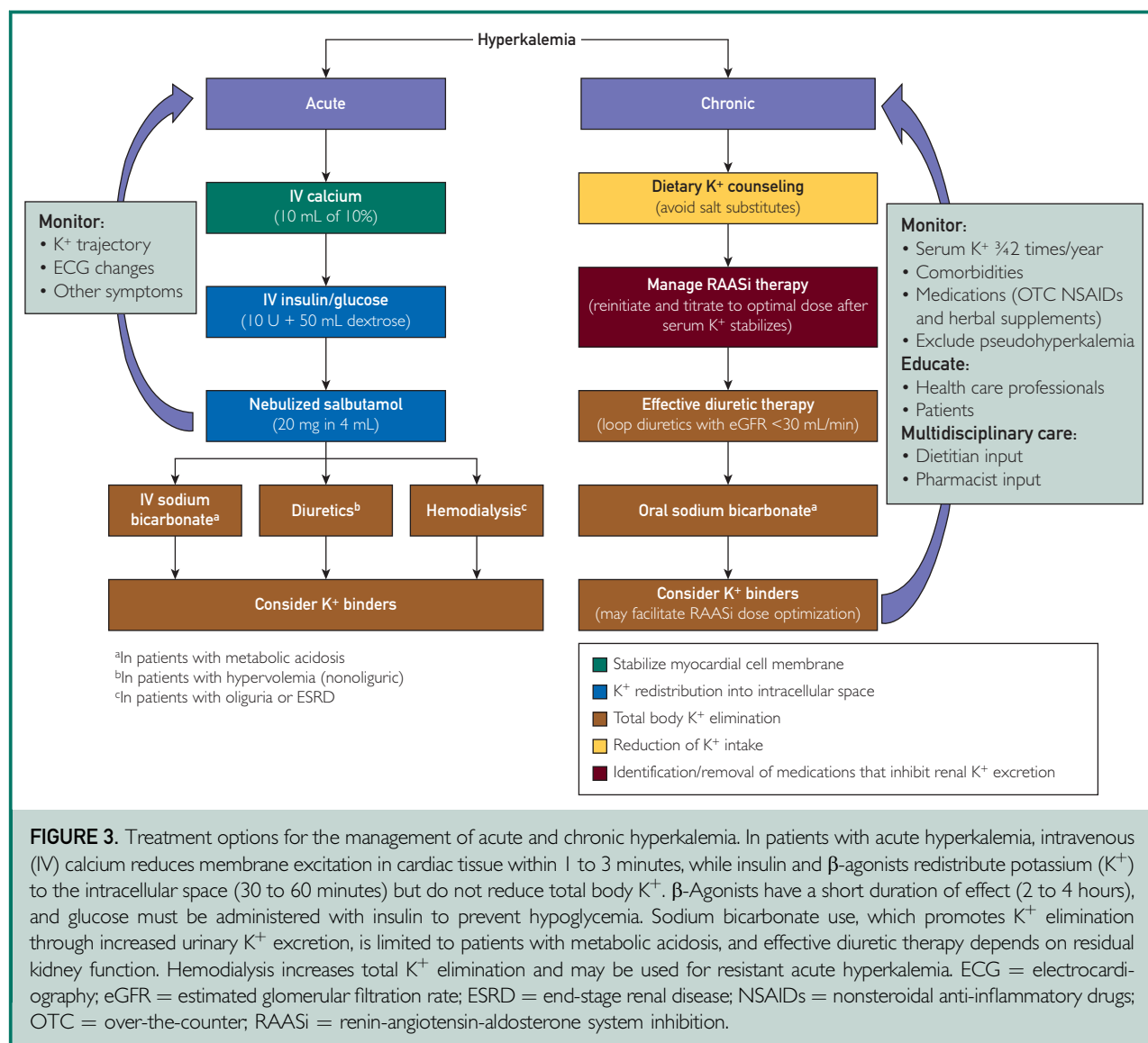
## HYPERKALEMIA MANAGEMENT

Management of hyperkalemia occurs across a continuum ranging from urgent to short-term treatment and then long-term treatment and involves both inpatient and outpatient settings. Different management strategies are utilized in patients with acute vs chronic hyperkalemia (Figure 3).

### Classification of Hyperkalemia

Although the precise K<sup>+</sup> concentration thresholds for mild, moderate, and severe hyperkalemia vary among current guidelines,<sup>1,4-6</sup> a serum K<sup>+</sup> level of 5.5 mEq/L or greater is widely accepted as the threshold for hyperkalemia.<sup>6</sup> Hyperkalemia-associated adverse outcomes may extend beyond hyperkalemia thresholds (serum K<sup>+</sup> >5.0 or >5.5 mEq/L) and include high “normal” K<sup>+</sup> concentrations in patients with acute or chronic HF,<sup>32,67</sup> hypertension,<sup>33</sup> or CKD.<sup>15</sup> When deciding how to treat hyperkalemic episodes, it may be useful to focus on hyperkalemia with clinical impact, as well as rapid fluctuations in serum K<sup>+</sup>, rather than rigid and somewhat arbitrary serum K<sup>+</sup> thresholds.





Potassium concentration thresholds for the classification of mild, moderate, and severe hyperkalemia are useful; however, patient risk- and clinical impact-based classification may also guide clinical intervention. Clinicians should consider using individualized serum K<sup>+</sup> concentration thresholds that take into account patient comorbidities and “normal” K<sup>+</sup> concentration ranges, as well as the rate or degree of change in serum K<sup>+</sup> levels over time, which enables proactive or preventive interventions and is a useful clinical variable for hyperkalemia management.

### Frequency of K<sup>+</sup> Monitoring

The use of serum or plasma for determination of K<sup>+</sup> concentrations affects laboratory results. Plasma K<sup>+</sup> concentrations are usually 0.1- to 0.4-mEq/L lower than serum levels,<sup>7</sup> which is caused by the release of K<sup>+</sup> from platelets during coagulation.<sup>68</sup> The methods used for K<sup>+</sup> determination are not standardized, with wide variations in reference ranges.<sup>7</sup> Complications such as pseudohyperkalemia (resulting from repeated fist clenching and poor phlebotomy techniques), hemolysis, slow specimen processing, and other factors<sup>7,10,69</sup>

need to be assessed prior to hyperkalemia treatment. The timing of sample collection may influence  $K^+$  results because of the circadian rhythm of  $K^+$  homeostasis.<sup>7</sup>

Clinical guidelines recommend  $K^+$  measurement in at-risk patients prior to initiation of drugs that influence hyperkalemia risk and periodically thereafter.<sup>4,46,70,71</sup> For example, the 2012 KDIGO guidelines advocate serum  $K^+$  measurement within 1 week of starting or dose escalation of RAASi in patients with CKD.<sup>46</sup> Repetitive consecutive measurements facilitate determination of whether hyperkalemia is a chronic or transient event<sup>5</sup>; however, there is no consensus on the number of tests required to document chronic hyperkalemia risk.<sup>59</sup> Potassium monitoring frequency should vary depending on patient comorbidities (eg, diabetes, HF, CKD stage, and the need for dialysis) and medications (eg, RAASi therapy).

Individualized  $K^+$  monitoring frequency based on the presence of comorbidities and medications should be considered, with more frequent monitoring in patients with increased hyperkalemia risk (eg, those with CKD, diabetes, HF, or a history of hyperkalemia and those taking RAASi). In particular, serum  $K^+$  concentrations should be assessed 7 to 10 days after starting RAASi therapy and increasing RAASi doses.

### Acute Hyperkalemia

Acute hyperkalemia is defined as a serum  $K^+$  concentration exceeding the upper limit of normal that is not known to be chronic.<sup>40</sup> Management of acute hyperkalemia depends on the magnitude or severity of the increase in  $K^+$  concentration, especially when combined with marked electrocardiographic (ECG) changes and severe muscle weakness.<sup>4,40</sup> The most commonly observed changes in ECG are peaked T waves and prolonged QRS complexes.<sup>40</sup> However, as noted in the observational REVEAL-ED (Real World Evidence for Treatment of Hyperkalemia in the Emergency Department) study of emergency department patients who presented with  $K^+$  concentrations of 5.5 mEq/L or greater,<sup>72</sup> the symptoms of hyperkalemia can be nonspecific, and although recommended for determining

the clinical relevance of elevated serum  $K^+$ , ECG findings can be highly variable and not as sensitive as a laboratory test in predicting hyperkalemia or its associated complications. A deep learning model that may allow for noninvasive screening for hyperkalemia using ECG is currently being developed<sup>73</sup>; however, this tool is not yet available for use in routine clinical practice. Therefore,  $K^+$  measurements should be conducted on the basis of the patient's risk factors rather than clinical symptoms (Figure 3).

The goal of managing acute hyperkalemia is to prevent or minimize electrophysiologic effects on the heart to reduce the immediate risk of arrhythmias.<sup>2,5,7</sup> Treatment options for acute hyperkalemia include intravenous calcium gluconate, insulin/glucose, inhaled  $\beta$ -agonists (eg, salbutamol), intravenous sodium bicarbonate, and hemodialysis (Figure 3). Intravenous calcium gluconate administration rapidly reduces the membrane excitatory effects of  $K^+$  on cardiac tissue within 1 to 3 minutes, thereby minimizing the potential for cardiac arrhythmia, but only minimally reduces serum  $K^+$  concentrations.<sup>2,74</sup> If no effect is observed within 5 to 10 minutes, another dose of calcium gluconate may be given.<sup>75</sup> Intravenous insulin (plus glucose) and inhaled  $\beta$ -agonists act within 30 minutes to promote redistribution of serum  $K^+$  into the intracellular space but do not change total body  $K^+$  levels.<sup>74</sup> Short-term treatment with oral sodium bicarbonate may be used to promote  $K^+$  elimination through increased urinary  $K^+$  excretion in patients with concurrent metabolic acidosis,<sup>2</sup> countering the release of  $K^+$  into the blood that is caused by metabolic acidosis by decreasing blood acidity and promoting  $K^+$  excretion through increased distal sodium delivery.<sup>76</sup> Dialysis increases  $K^+$  elimination from the body and may be used as an adjunctive therapy in acute hyperkalemia after instituting other approaches.<sup>2</sup>

Several deficiencies associated with current management of acute hyperkalemia were highlighted by the REVEAL-ED study, including a lack of standard, universally accepted treatment protocols or algorithms for managing

hyperkalemia in the emergency department.<sup>72</sup> The study documented the use of different treatments, alone or in combination, depending on the institution and initial blood  $K^+$  concentration, including intravenous calcium, inhaled  $\beta_2$ -agonists, oral sodium polystyrene sulfonate (SPS), intravenous sodium bicarbonate, dialysis, and intravenous diuretics. Insulin/glucose (alone or in combination with other therapy) was the most commonly utilized option (64% of patients) within the first 4 hours,<sup>72</sup> whereas the treatment option most likely to achieve normokalemia within 4 hours was dialysis.

### Chronic Hyperkalemia

Chronic hyperkalemia is defined as recurrent episodes of elevated serum  $K^+$  concentrations that require ongoing maintenance therapy; however, based on the recent KDIGO report,<sup>40</sup> there is no consensus on the frequency, severity, or duration of these episodes that describes chronicity. In general, chronic hyperkalemia is more likely to be identified in individuals who have more frequent testing and is often asymptomatic.<sup>40</sup> Current recommendations regarding the management of chronic hyperkalemia (long-term elevated serum  $K^+$ ) include the use of loop or thiazide diuretics, modification of RAASi dose, and removal of other hyperkalemia-causing medications (Figure 3).<sup>2,34,40</sup> Diuretics promote urinary excretion of  $K^+$  in patients with CKD or DKD by stimulating the flow and delivery of  $K^+$  to the renal collecting ducts.<sup>76</sup> Fludrocortisone can also increase  $K^+$  excretion but is associated with an increased risk of fluid retention, hypertension, and vascular injury.<sup>2,11</sup>

These long-term treatment options have limitations.<sup>2</sup> Despite the beneficial effects of diuretics on volume status and blood pressure in patients with CKD or HF, these agents may increase the risk of gout, volume depletion, decreased distal nephron flow, worsening kidney function, and reduced  $K^+$  excretion, and their effectiveness in managing hyperkalemia relies on residual kidney function. Discontinuation or dose reduction of RAASi therapy may lead to adverse cardiorenal outcomes, and current guidelines differ with regard to

recommendations on when to reinitiate RAASi (Table 1).<sup>4,44,46,71</sup> Recently US Food and Drug Administration–approved  $K^+$ -binding agents may provide benefits for the management of chronic hyperkalemia while avoiding these limitations. Educational initiatives on the safety and efficacy of the newer  $K^+$  binders are needed for primary care physicians and internists to increase their knowledge of hyperkalemia management, especially in regions where specialist services may not be readily available. A team approach for chronic hyperkalemia management is optimal, which may include specialists (eg, cardiologists, nephrologists), primary care physicians, nurses, pharmacists, social workers, or dietitians.

### Potassium Binders

All  $K^+$  binders used for hyperkalemia management are nonabsorbed and consist of a counterion that is exchanged for  $K^+$ , facilitating the elimination of bound  $K^+$  in feces.<sup>77-79</sup> Until recently, SPS (Kayexalate)<sup>78,80</sup> was the only  $K^+$  binder available for hyperkalemia management and may continue to be the only agent available in parts of the world. However, 2 other  $K^+$  binders, patiomer sorbitex calcium (Veltassa)<sup>77</sup> and sodium zirconium cyclosilicate (SZC; Lokelma [formerly ZS-9]),<sup>79</sup> are now approved in the United States and the European Union. The characteristics of these 3  $K^+$ -binding agents are summarized in Table 2.<sup>12,59,60,79-81</sup> The efficacy of patiomer and SZC has been documented in clinical trials, whereas clinical data for SPS is limited (discussed subsequently and summarized in Table 3).<sup>82-94</sup> The newer  $K^+$ -binding agents are also more palatable than SPS, facilitating adherence and efficacy and potentially leading to improved outcomes.<sup>89,90,92,95</sup> The National Institute for Health and Care Excellence has recently provided recommendations regarding SZC and patiomer use for the treatment of acute life-threatening hyperkalemia, stating that these agents may be considered for use in conjunction with standard care.<sup>95,96</sup>

The initiation of newer  $K^+$ -binding agents should be considered in patients with chronic hyperkalemia despite optimized diuretic therapy and correction of metabolic acidosis. After starting therapy at the recommended dose,  $K^+$



TABLE 1. Summary of Guideline Recommendations for RAASi Therapy<sup>a</sup>

Society	Serum K <sup>+</sup> (mEq/L)	Recommendations for RAASi therapy
American College of Cardiology/American Heart Association/ Heart Failure Society of America <sup>44</sup>	>5.0	Use ACEis and ARBs with caution MRAs are not recommended
Canadian Cardiovascular Society <sup>4</sup>	Mild HK (K <sup>+</sup> 5.0-5.5)	RAASi not usually stopped If RAASi therapy is stopped, reinstate therapy once any concurrent condition contributing to changes in K <sup>+</sup> is under control AND serum K <sup>+</sup> has decreased to <5.0 mEq/L or to within patient's usual range (whichever is higher)
	Moderate (K <sup>+</sup> 5.6-5.9) or severe (K <sup>+</sup> >5.9) HK	Reinstate RAASi therapy once any concurrent condition contributing to changes in K <sup>+</sup> is under control AND serum K <sup>+</sup> has decreased to <5.0 mEq/L or to within patient's usual range (whichever is higher) Reintroduce RAASi agents one at a time with monitoring of kidney function and electrolytes
European Society of Cardiology <sup>1</sup>	4.5-5.0 <sup>b</sup>	If not taking maximum-tolerated guideline-recommended dose, initiate/up-titrate RAASi therapy and closely monitor K <sup>+</sup> ; start K <sup>+</sup> -lowering therapy if K <sup>+</sup> increases to >5.0 mEq/L
	>5.0 to ≤6.5	If receiving maximum-tolerated guideline-recommended RAASi dose, initiate K <sup>+</sup> -lowering therapy; closely monitor K <sup>+</sup> and continue K <sup>+</sup> -lowering therapy unless another treatable etiology for hyperkalemia is identified If not taking maximum-tolerated guideline-recommended RAASi dose, start K <sup>+</sup> -lowering therapy and titrate RAASi when K <sup>+</sup> is <5.0 mEq/L; closely monitor K <sup>+</sup> and maintain K <sup>+</sup> -lowering therapy unless another etiology for hyperkalemia is identified
	>6.5	Discontinue or reduce RAASi therapy; K <sup>+</sup> -lowering therapy may be started as soon as K <sup>+</sup> is >5.0 mEq/L; closely monitor serum K <sup>+</sup>
Kidney Disease: Improving Global Outcomes <sup>46</sup>	NS	Assess GFR and measure serum K <sup>+</sup> within 1 week of starting RAASi or following any dose escalation
National Institute for Health and Care Excellence <sup>71</sup>	>5.0	Do not initiate RAASi therapy in patients with CKD
	≥6.0	Discontinue RAASi therapy once other drugs known to increase the risk of hyperkalemia have been stopped

<sup>a</sup>ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CKD = chronic kidney disease; GFR = glomerular filtration rate; HK = hyperkalemia; K<sup>+</sup> = potassium; MRA = mineralocorticoid receptor antagonist; NS = not specified; RAASi = renin-angiotensin-aldosterone system inhibitor.

<sup>b</sup>Serum or plasma K<sup>+</sup>.

binders should be titrated for optimization of serum K<sup>+</sup> concentration, with individualized monitoring of serum or plasma K<sup>+</sup>. Long-term K<sup>+</sup>-binder therapy may be considered in patients with chronic hyperkalemia. The use of one of the newer K<sup>+</sup>-binding agents (patiomer or SZC) may allow for the continuation and optimization of RAASi therapy in patients with hyperkalemia. Consideration of the costs of patiomer or SZC may influence their use in clinical practice for some patients.

Although such data are limited, cost-effectiveness analysis from the US payer perspective found that the benefits of adding patiomer to treatment in patients with HF and hyperkalemia outweighed the incremental total costs, with lower hospitalization costs, improved survival, and increased quality of life.<sup>97</sup>

**Sodium Polystyrene Sulfonate.** Sodium polystyrene sulfonate is a polymeric

TABLE 2. Selected Characteristics of K<sup>+</sup>-Binding Agents for Hyperkalemia

Characteristic	SPS	Patiomer	SZC
Approval date	1958	US, 2015; EU, 2017	US, 2018; EU, 2018
Mechanism of action	K <sup>+</sup> binding in exchange for Na <sup>+</sup> in GI tract (↑ fecal excretion)	K <sup>+</sup> binding in exchange for Ca <sup>2+</sup> in GI tract (↑ fecal excretion)	K <sup>+</sup> binding in exchange for H <sup>+</sup> and Na <sup>+</sup> in GI tract (↑ fecal excretion)
Site of action	Colon	Colon	Small and large intestines
Selectivity for K <sup>+</sup>	Nonselective; also binds Ca <sup>2+</sup> and Mg <sup>2+</sup>	Nonselective; also binds Na <sup>+</sup> and Mg <sup>2+</sup>	Highly selective; also binds NH <sub>4</sub> <sup>+</sup>
Onset of action	Variable; several hours	7 h	1 h
Na <sup>+</sup> content	1500 mg per 15-mg dose	None	400 mg per 5-g dose
Ca <sup>2+</sup> content	None	1.6 g per 8.4-g dose	None
Sorbitol content	20,000 mg per 15-g dose	4000 mg per 8.4-g dose	No sorbitol content
Dosing	15 g 1-4 times (oral); 30-50 g 1-2 times (rectal)	8.4 g QD (oral), titrate up to 16.8 g or 25.2 g QD	10 g TID (oral) for initial correction of hyperkalemia (for ≤48 h), then 5 g QOD to 15 g QD for maintenance
Serious AEs	Cases of fatal GI injury reported	None reported	None reported
Most common AEs	GI disorders (constipation, diarrhea, nausea, vomiting, gastric irritation), hypomagnesemia, hypokalemia, hypocalcemia, systemic alkalosis	GI disorders (abdominal discomfort, constipation, diarrhea, nausea, flatulence), hypomagnesemia	GI disorders (constipation, diarrhea, nausea, vomiting), mild to moderate edema

AE = adverse event; Ca<sup>2+</sup> = calcium; EU = European Union; GI = gastrointestinal; H<sup>+</sup> = hydrogen ion; K<sup>+</sup> = potassium; Mg<sup>2+</sup> = magnesium; Na<sup>+</sup> = sodium; NH<sub>4</sub><sup>+</sup> = ammonium; QD = once daily; QOD = every other day; SPS = sodium polystyrene sulfonate; SZC = sodium zirconium cyclosilicate; TID = three times daily; US = United States; ↑ = increased.

Data from references 12, 59, 60, and 79 to 81.

cation-exchange resin that binds K<sup>+</sup> ions in exchange for sodium ions in the distal colon.<sup>12,78</sup> It is nonselective for K<sup>+</sup>, with affinity for calcium and magnesium ions. Sodium polystyrene sulfonate may be administered either orally or rectally,<sup>78</sup> although the oral suspension has poor palatability.<sup>98</sup> With only one small randomized, double-blind, 7-day trial, clinical studies supporting its long-term use in patients with hyperkalemia are lacking (Table 3).<sup>82</sup> Its short-term efficacy is also inconsistent,<sup>2</sup> and the onset of action is variable (hours to days).<sup>78</sup> Its use varies widely among countries, ranging from 42% of patients in France to less than 1% in the United Kingdom, Spain, and Japan.<sup>99</sup>

Sodium polystyrene sulfonate has been associated with adverse events (AEs), including intestinal ischemia and colonic necrosis,<sup>100,101</sup> a doubling in the risk of hospitalization for serious gastrointestinal AEs,<sup>102</sup> and a reported overall mortality rate of 33%

for patients with serious gastrointestinal injury.<sup>103</sup> However, although cohort studies have reported a higher relative risk of gastrointestinal AEs with SPS use, the incidence of events with SPS was rare (16 or 23 events per 1000 person-years).<sup>101,102</sup> Because of its potential to cause constipation, SPS was often previously coadministered with the laxative sorbitol.<sup>12</sup> However, in 2009, the US Food and Drug Administration added a warning label to SPS regarding the concomitant use of sorbitol and the associated risk of colonic necrosis and other serious gastrointestinal AEs (bleeding, ischemic colitis, and perforation).<sup>104</sup> Coadministration of SPS with sorbitol is currently not recommended,<sup>78</sup> although gastrointestinal injury has been reported in patients receiving SPS without sorbitol.<sup>101-103</sup> The nonselective binding properties of SPS may also lead to hypocalcemia and hypomagnesemia,<sup>12</sup> and because orally administered SPS potentially binds to other oral medications, their administration should be

TABLE 3. Summary of Key Clinical Studies of K<sup>+</sup>-Binding Agents<sup>a</sup>

Study name; design (duration)	Patient population	Study treatment	Primary efficacy outcomes
SPS			
Phase 4, randomized, double-blind, placebo-controlled (7 d) <sup>82</sup>	Outpatients with CKD and mild hyperkalemia (K <sup>+</sup> 5.0-5.9 mEq/L); N=33	SPS 30 g or placebo QD	Mean change in serum K <sup>+</sup> : –1.25 mEq/L with SPS –0.21 mEq/L with placebo Mean difference (95% CI) vs placebo: –1.04 mEq/L (–1.37 to 0.71 mEq/L); P<.001
Patiromer			
Phase 4, randomized, open-label, single-blind (10 h) <sup>83</sup>	Emergency department patients with ESRD and serum K <sup>+</sup> ≥6.0 mEq/L; N=43	Single dose of patiromer 25.2 g + SOC or SOC alone	Adjusted mean serum K <sup>+</sup> at 6 h: 5.81 mEq/L with patiromer + SOC 6.32 mEq/L with SOC alone; P=.155 vs SOC alone Adjusted mean serum K <sup>+</sup> at 2 h: 5.90 mEq/L with patiromer + SOC 6.51 mEq/L with SOC alone; P=.009 vs SOC alone
PEARL-HF; phase 2, randomized, double-blind, placebo-controlled (28 d) <sup>84</sup>	Patients with chronic HF with (1) history of hyperkalemia leading to RAASi and/or β-blocker withdrawal or (2) CKD; N=105	Patiromer 15 g or placebo BID (+ spironolactone 25 mg/d <sup>b</sup> )	LS mean change in serum K <sup>+</sup> : –0.22 mEq/L with patiromer +0.23 mEq/L with placebo LS mean difference vs placebo: –0.45 mEq/L; P<.001
AMETHYST-DN; phase 2, randomized, open-label (28 d) <sup>85</sup>	Outpatients with DKD and mild (K <sup>+</sup> 5.0-5.5 mEq/L) or moderate (K <sup>+</sup> 5.5-6.0 mEq/L) hyperkalemia; N=306	Mild hyperkalemia: patiromer 4.2, 8.4, or 12.6 g BID <sup>c</sup>	Mild hyperkalemia: LS mean change in serum K <sup>+</sup> : –0.35 mEq/L with patiromer 4.2 g –0.51 mEq/L with patiromer 8.4 g –0.55 mEq/L with patiromer 12.6 g
		Moderate hyperkalemia: patiromer 8.4, 12.6, or 16.8 g BID <sup>c</sup>	Moderate hyperkalemia: LS mean change in serum K <sup>+</sup> : –0.87 mEq/L with patiromer 8.4 g –0.97 mEq/L with patiromer 12.6 g –0.92 mEq/L with patiromer 16.8 g
AMBER; phase 2, randomized, double-blind, placebo-controlled (12 wk) <sup>86</sup>	Patients with CKD, K <sup>+</sup> 4.3-5.1 mEq/L, and resistant hypertension; N=295	Patiromer 8.4 g or placebo QD (+ open-label spironolactone 25 mg/d <sup>d</sup> )	Patients remaining on spironolactone: 86% with patiromer 66% with placebo Difference vs placebo: 19.5%; P<.0001 More patients in placebo vs patiromer with serum K <sup>+</sup> ≥5.5 mEq/L: P<.001
OPAL-HK; phase 3, 2 stages: (1) treatment, single-group, single-blind (4 wk) and (2) withdrawal, randomized, single-blind, placebo-controlled (8 wk) <sup>87</sup>	Patients with CKD on RAASi therapy with mild (K <sup>+</sup> 5.1-5.5 mEq/L) or moderate to severe (K <sup>+</sup> 5.5-6.5 mEq/L) hyperkalemia; N=237	Treatment stage: patiromer 4.2 g (mild hyperkalemia) or 8.4 g (moderate to severe hyperkalemia) BID	Treatment stage: Mean change in serum K <sup>+</sup> at wk 4: Overall: –1.01 mEq/L (P<.001 vs baseline) Mild hyperkalemia: –0.65 mEq/L Moderate to severe hyperkalemia: –1.23 mEq/L

Continued on next page

TABLE 3. Continued

Study name; design (duration)	Patient population	Study treatment	Primary efficacy outcomes
		Withdrawal stage: patiromer (at same dosage) or placebo ( $K^+$ 3.8-5.1 mEq/L)	Withdrawal stage: Median change in $K^+$ to wk 4: 0 mEq/L with patiromer +0.72 mEq/L with placebo $P<.001$ vs placebo
SZC			
ENERGIZE; phase 2, randomized, double-blind, placebo-controlled (24 h) <sup>88</sup>	Emergency department patients with serum $K^+ \geq 5.8$ mEq/L; N=70	SZC 10 g ( $\leq 3$ doses in 10 h) or placebo (+ insulin + glucose)	LS mean change in serum $K^+$ at 4 h: −0.41 mEq/L with SZC −0.27 mEq/L with placebo LS mean difference vs placebo: −0.13 mEq/L (95% CI −0.44 to 0.17 mEq/L)
Phase 3, 2-stage, randomized, double-blind, placebo-controlled (14 d) <sup>89</sup>	Patients with hyperkalemia ( $K^+$ 5.0-6.5 mEq/L); N=754	Correction phase: SZC 1.25, 2.5, 5, or 10 g or placebo TID for 48 h  Maintenance phase: SZC (same dose) or placebo QD ( $K^+$ 3.5-4.9 mEq/L) for 14 d	Correction phase: Exponential rate of change in mean serum $K^+$ at 48 h: −0.11% with SZC 1.25 g −0.16% with SZC 2.5 g −0.21% with SZC 5 g −0.30% with SZC 10 g −0.09% with placebo $P<.001$ vs placebo for 3 highest doses  Maintenance phase: Exponential rate of change in mean serum $K^+$ : +0.14% per hour with SZC 10 g +1.04% per hour with placebo $P<.001$ +0.09% per hour with SZC 5 g +0.47% per hour with placebo $P=.008$
HARMONIZE; phase 3, 2-stage, randomized, double-blind, placebo-controlled (28 d) <sup>90</sup>	Outpatients with hyperkalemia ( $K^+ \geq 5.1$ mEq/L); N=258	Initial phase (open-label): SZC 10 g TID for 48 h  Maintenance phase (double-blind): SZC 5, 10, or 15 g or placebo QD for 28 d ( $K^+$ 3.5-5.0 mEq/L)	Initial phase (open-label): Mean change in serum $K^+$ over 48 h: −1.1 mEq/L; $P<.001$ vs baseline  Maintenance phase (double-blind): Mean serum $K^+$ during days 8-29: 4.8 mEq/L with SZC 5 g QD 4.5 mEq/L with SZC 10 g QD 4.4 mEq/L with SZC 15 g QD 5.1 mEq/L with placebo $P<.001$ vs placebo for each dose
HARMONIZE-OLE; phase 3, open-label (11 mo) <sup>91</sup>	Patients from HARMONIZE with $K^+$ 3.5-6.2 mEq/L; N=123	SZC 10 g QD, titrated in 5-g amounts to maintain $K^+$ 3.5-5.0 mEq/L (min, 5 g QD; max, 15 g QD)	93% of patients achieved mean serum $K^+ \leq 5.1$ mEq/L across days 8-337
HARMONIZE-Global; phase 3, randomized,		Correction phase (open-label): SZC 10 g TID for 48 h	Correction phase (open-label): Mean change in serum $K^+$ over 48 h:

Continued on next page

TABLE 3. Continued

Study name; design (duration)	Patient population	Study treatment	Primary efficacy outcomes
double-blind, placebo-controlled (28 d) <sup>92</sup>	Outpatients with hyperkalemia ( $K^+ \geq 5.1$ mEq/L); N=267	Maintenance phase (double-blind): SZC 5 or 10 g or placebo QD for 28 d ( $K^+ 3.5$ -5.0 mEq/L)	–1.28 mEq/L; $P<.001$ vs baseline  Maintenance phase (double-blind): Mean serum $K^+$ during days 8-29: 4.8 mEq/L with SZC 5 g QD 4.4 mEq/L with SZC 10 g QD 5.3 mEq/L with placebo $P<.001$ vs placebo for each dose
ZS-005; phase 3, 2-stage, open-label (12 mo) <sup>93</sup>	Outpatients with hyperkalemia ( $K^+ \geq 5.1$ mEq/L); N=751	Correction phase: SZC 10 g TID for 24-72 h  Maintenance phase: SZC 5 g QD <sup>e</sup>	Correction phase: 78% of patients had serum $K^+ 3.5$ -5.0 mEq/L at 72 h  Maintenance phase: 88% of patients had serum $K^+ <5.1$ mEq/L over 3-12 mo
DIALIZE; phase 3b, randomized, double-blind, placebo-controlled (4 wk) <sup>94</sup>	Patients with ESRD on hemodialysis with hyperkalemia <sup>f</sup> ; N=196	SZC 5, 10, or 15 g or placebo QD on nondialysis days for 4 wk	Maintenance of predialysis serum $K^+$ 4.0-5.0 mEq/L during $\geq 3$ of 4 hemodialysis sessions after long interdialytic interval without requiring rescue therapy: 41% with SZC 1% with placebo $P<.001$ vs placebo

<sup>a</sup>AMBER = Spironolactone With Patiomer in the Treatment of Resistant Hypertension in Chronic Kidney Disease; AMETHYST-DN = Patiomer in the Treatment of Hyperkalemia in Patients With Hypertension and Diabetic Nephropathy; BID = twice daily; CKD = chronic kidney disease; DIALIZE = A Study to Test Whether ZS (Sodium Zirconium Cyclosilicate) Can Reduce the Incidence of Increased Blood Potassium Levels Among Dialyzed Patients; DKD = diabetic kidney disease; ENERGIZE = A Study to Evaluate a Potassium Normalization Treatment Regimen Including Sodium Zirconium Cyclosilicate (ZS) Among Patients With S-K  $\geq 5.8$ ; ESRD = end-stage renal disease; HARMONIZE = Hyperkalemia Randomized Intervention Multidose ZS-9 Maintenance; HARMONIZE-OLE = HARMONIZE open-label extension; HF = heart failure;  $K^+$  = potassium; LS = least squares; max = maximum; min = minimum; OPAL-HK = A Two-Part, Single-Blind, Phase 3 Study Evaluating the Efficacy and Safety of Patiomer for the Treatment of Hyperkalemia; PEARL-HF = Evaluation of Patiomer in Heart Failure Patients; QD = once daily; RAASi = renin-angiotensin-aldosterone system inhibitor; SOC = standard of care; SPS = sodium polystyrene sulfonate; SZC = sodium zirconium cyclosilicate; TID = three times daily.

<sup>b</sup>Spironolactone dosage increased to 50 mg/d after 2 weeks in patients with serum  $K^+ >3.5$  to  $\leq 5.1$  mEq/L.

<sup>c</sup>Patiomer was titrated to achieve and maintain serum  $K^+ \leq 5.0$  mEq/L.

<sup>d</sup>Spironolactone dosage increased to 50 mg/d after 3 weeks in patients with systolic blood pressure  $\geq 120$  mm Hg and serum  $K^+ \leq 5.1$  mEq/L.

<sup>e</sup>SZC was titrated to maintain serum  $K^+ 3.5$ -5.0 mEq/L.

<sup>f</sup>Defined as predialysis serum  $K^+ >5.4$  mEq/L after the long interdialytic interval and predialysis serum  $K^+ >5.0$  mEq/L after  $\geq 1$  short interdialytic interval.

separated by 3 or more hours.<sup>78</sup> Of note, the release of sodium from SPS during  $K^+$  exchange may potentially increase sodium and volume load. Sodium polystyrene sulfonate should be used with caution in patients with congestive HF, severe hypertension, edema, or decreased kidney function who may not tolerate increased sodium loads.<sup>12,78</sup>

**Patiomer Sorbitex Calcium.** The efficacy of patiomer was established in randomized, placebo-controlled, phase 2 and 3 trials of

patients with hyperkalemia, including those with CKD and HF, and/or receiving RAASi (Table 3). In a pilot study of emergency department patients with ESRD and serum  $K^+$  levels of 6.0 mEq/L or higher, single-dose administration of patiomer, 25.2 g, in addition to standard of care effectively reduced serum  $K^+$  concentrations over 6 hours.<sup>83</sup> In patients with chronic hyperkalemia, patiomer, 4.2 to 16.8 g twice daily, provided significant dose-dependent reductions in serum  $K^+$  levels by 0.2 to 1.0 mEq/L over 4 weeks<sup>84,85,87</sup> and



effectively maintained normokalemia ( $K^+$  levels of 3.8 to 5.1 mEq/L) for a further 4 weeks.<sup>87</sup> In patients with advanced CKD and resistant hypertension, significantly more patients continued spironolactone, 25 to 50 mg once daily, while receiving patiomer, 8.4 g once daily, vs placebo for 12 weeks.<sup>86</sup> Among patients with diabetes and CKD, including those with HF receiving RAASi, normokalemia was maintained with patiomer therapy for up to 12 months.<sup>105</sup> In a real-world study of patients undergoing long-term hemodialysis, serum  $K^+$  concentrations were significantly reduced following initiation of patiomer over three 30-day periods, and the proportion of patients with serum  $K^+$  levels of 6.0 mEq/L or higher decreased from approximately 50% before patiomer initiation to 22% at 90 days after patiomer initiation.<sup>106</sup>

Oral patiomer contains a calcium-sorbitol counterion that exchanges calcium for  $K^+$  as it passes through the colon.<sup>77</sup> Similar to SPS, patiomer is a polymer that is nonselective for  $K^+$  and may also bind magnesium and small amounts of sodium.<sup>77,107</sup> The time to onset of action with patiomer is approximately 7 hours.<sup>108</sup> Patiomer administration should also be separated from other oral medications by 3 or more hours because of the potential for binding with patiomer.<sup>77</sup>

No serious AEs have been associated with patiomer therapy in randomized trials. The most common AEs include gastrointestinal events (constipation, diarrhea, nausea/vomiting, abdominal discomfort, and flatulence) and electrolyte disturbances (hypokalemia and hypomagnesemia).<sup>12,77,81</sup> Because patiomer exchanges calcium for  $K^+$  in the colon, theoretically it may also increase the risk of hypercalcemia.<sup>12</sup> Although rare, cases of patiomer-induced hypercalcemia have been reported,<sup>109,110</sup> suggesting that it may be an underreported AE that clinicians should be aware of when initiating patiomer therapy. Currently, there are no real-world safety data for patiomer.

**Sodium Zirconium Cyclosilicate.** Sodium zirconium cyclosilicate (SZC) is the most recently approved  $K^+$ -binding agent, with its

efficacy and safety established in phase 2 and 3 clinical trials of patients with hyperkalemia including those with CKD, HF, and/or diabetes or those receiving RAASi (Table 3).<sup>88-94</sup> In a study of emergency department patients with serum  $K^+$  concentrations of 5.8 mEq/L or higher, SZC therapy (up to three 10-g doses within 10 hours) added to insulin plus glucose provided reductions in mean serum  $K^+$  levels of 0.72 mEq/L within 2 hours.<sup>88</sup> In studies of patients with chronic hyperkalemia, 3-times-daily SZC significantly reduced serum  $K^+$  concentrations within 48 hours, and a once-daily 5- or 10-g SZC dose effectively maintained normokalemia over 14 to 28 days.<sup>89,90,92</sup> Significant reductions in serum  $K^+$  levels were observed within 1 hour of a single SZC 10-g dose in the overall patient populations<sup>89,90,92</sup> and in those with severe hyperkalemia ( $\geq 6.0$  mEq/L).<sup>111</sup> The efficacy and safety of SZC over 12 months have also been documented.<sup>91,93</sup> In the DIALIZE (A Study to Test Whether ZS [Sodium Zirconium Cyclosilicate] Can Reduce the Incidence of Increased Blood Potassium Levels Among Dialyzed Patients) study of patients with ESRD and persistent hyperkalemia, once-daily SZC on nondialysis days effectively maintained normal predialysis serum  $K^+$  levels over 8 weeks.<sup>94</sup> Sustained increases in serum bicarbonate have been observed with SZC,<sup>112</sup> which may provide an added benefit for patients with metabolic acidosis.

Unlike SPS and patiomer, SZC is nonpolymeric with high selectivity for  $K^+$  and ammonium ions (1.25-fold higher affinity for  $K^+$  than ammonium) in exchange for hydrogen and sodium throughout the gastrointestinal tract.<sup>79</sup> Sodium zirconium cyclosilicate binds monovalent cations ( $K^+$ ) as opposed to divalent cations (eg, calcium and magnesium).<sup>113</sup> Because SZC may affect absorption of other oral medications with pH-dependent solubility due to a transient increase in gastric pH, SZC administration should be separated from these medications by 2 or more hours.<sup>79</sup>

Sodium zirconium cyclosilicate has not been associated with any serious AEs in randomized trials. The most common AEs were hypokalemia and a dose-dependent increase in edema.<sup>89,90,93</sup> Because SZC was only

recently launched in US and other markets, postmarketing safety data are currently very limited.

### Hyperkalemia Education

The National Kidney Foundation recommends improvements in patient awareness of hyperkalemia.<sup>114</sup> These actions include using educational tools to facilitate communication about hyperkalemia (eg, <https://www.kidney.org/atoz/content/what-hyperkalemia>) and encouraging nurse practitioners, physicians, physician assistants, pharmacists, and dietitians to proactively engage patients in dialogue about the associated risk of hyperkalemia and provide ongoing dietary and other lifestyle information relevant to patients with increased hyperkalemia risk.<sup>114</sup>

Educational initiatives and campaigns are needed to improve patient awareness of hyperkalemia risk and its potentially life-threatening consequences, including awareness that hyperkalemia is often asymptomatic and that routine K<sup>+</sup> monitoring is important. Allied health care professional involvement in patient education may help to increase awareness of the hyperkalemia risk associated with RAASi and other medications. Health care practitioners should be involved in patient education regarding hyperkalemia to promote shared care responsibility and treatment planning.

### CONCLUSION

Critical unmet needs exist regarding effective hyperkalemia management, including classification and monitoring for hyperkalemia, reinitiation and maximization of RAASi therapy, and use of K<sup>+</sup>-binding agents. Hyperkalemia incidence may be higher than previously reported, and the risks associated with acute and chronic hyperkalemia may be reduced through vigilant individualized serum K<sup>+</sup> monitoring. With the availability of newer K<sup>+</sup>-binding agents, clinicians have increased need for education on their use as well as to increase patient awareness about the signs, symptoms, and risks of hyperkalemia. Newer K<sup>+</sup>-binding agents may enable the optimization of RAASi therapy in more patients with hyperkalemia.

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**Abbreviations and Acronyms:** AE = adverse event; CKD = chronic kidney disease; DKD = diabetic kidney disease; ECG = electrocardiographic; eGFR = estimated glomerular filtration rate; HF = heart failure; K<sup>+</sup> = potassium; KDIGO = Kidney Disease: Improving Global Outcomes; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; RAASi = renin-angiotensin-aldosterone system inhibitor; SPS = sodium polystyrene sulfonate; SZC = sodium zirconium cyclosilicate

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