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# Egyptian Consensus on Hyperkalemia Management: Lessons from Recent Evidences

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## Abstract

Acute and chronic hyperkalemia is linked to higher hospitalization rates and mortality rates. It has a high prevalence among dialysis and non-dialysis patients in Egypt. The current therapy options are not that ideal. Moreover, we have a critical management paradox in cardiorenal diseases: *Should we use the optimum dose of RAASi with its higher incidence of HK, or should we decrease the dose or even stop it with all its harmful hazards*? Therefore, in light of the recent updates in different clinical practice guidelines, we, a country-specific (Egypt) task force, gathered to develop a clear, evidence-based, and multi-disciplinary consensus for managing HK. This manuscript illustrates the recommendations of this expert committee. The panel recommends new evidenced K binders like Sodium Zirconium Cyclosilicate (SZC) and patiromer to help manage HK in cardiorenal patients as stated by different international guidelines. In emergency settings, SZC can have a role in managing acute HK; however, it should be used in addition to other drugs like insulin and glucose. Local research studies on the utilization of these novel K binders are highly recommended. The utilization of these novel K binders as prophylaxis should be tested first in a well-designed randomized controlled trial.

## Keywords

Hyperkalemia, Potassium Binders, Sodium Zirconium Cyclosilicate, Patiromer

## 1. Introduction

Hyperkalemia (HK) is an electrolyte imbalance characterized by serum potassium

(K) levels greater than five mmol/L and can be mild (serum K levels between 5.0 and 5.5 mmol/L), moderate (5.5 and 6.0 mmol/L), or severe (beyond 6.0 mmol/L). It is a serious medical disorder that can result in cardiac arrhythmias, muscular weakness, and even paralysis. It is linked to higher hospitalization rates and mortality rates [1] [2] [3] [4] [5].

Hyperkalemia can be acute. It occurs quite frequently in the emergency room. In those cases, cardiac dysrhythmia or conduction abnormalities are the primary cause of death [1] [6].

Heart Failure (HF) and Chronic Kidney Disease (CKD) patients frequently have chronic HK, a significant medical condition that can have detrimental effects, and call for careful management by cardio-nephrologists. The usage of Renin-Angiotensin-Aldosterone System inhibitors (RAASi) and the presence of CKD, HF, or Diabetes (DM) are known to cause this condition [5].

In one study, the prevalence of HK among hemodialysis patients in Egypt was 41.2%, 6.5%, and 66.9% of pre- and post-dialysis and before the next session of dialysis, respectively [7]. Moreover, in the non-dialysis patients, another one-year study was completed among old Egyptian patients who visited the outpatient clinics of Zagazig University from Feb. 2018 to Feb. 2019. The study showed the prevalence of HK to be 25% [8].

The current therapy options could be better as numerous CKD and HF patients have HK [5]. Therefore, in light of the recent updates in different clinical practice guidelines, a country-specific (Egypt) task force was gathered to develop a clear, evidence-based, and multi-disciplinary consensus for managing HK according to recent advances. This manuscript illustrates the recommendations of this expert committee.

## 2. Hyperkalemia: Risk Factors

The main risk factors for chronic HK include CKD, HF, DM, and drug-induced, including Mineralocorticoid Receptor Antagonists (MRA) and RAASi [5].

Patients with CKD frequently have abnormal serum K levels, with 14% - 20% prevalence. The main drivers of serum K in CKD are the severity of CKD, the use of drugs like RAASi, dietary K consumption, and other cardiovascular comorbidities (such as hypertension and HF) and DM [5] [9]. A meta-analysis of data from over 1.2 million individuals with CKD examined the risk factors for HK. The study found a strong correlation between the risk of HK and eGFR. Across the entire range of kidney function (eGFR 15 to 105 mL/min), HK strongly correlated with eGFR. Also, a 15 mL/min decrease in eGFR doubled the odds of developing HK. Albuminuria was also identified as a risk factor, although the association was weaker, with an odds ratio for HK of less than two, even in cases of heavy albuminuria [10].

Other risk factors for HK included being male, non-black race, lower body mass index, and a history of smoking, DM, coronary heart disease, or stroke. Certain medications such as Angiotensin-Converting Enzyme inhibitors (ACEi),

Angiotensin Receptor Blockers (ARB), or potassium-sparing diuretics also increase the risk of HK. In contrast, using thiazide or loop diuretics was found to have a protective effect against HK [11].

The chances of death, Cardiovascular Disease (CVD), hospitalization, and the progression of kidney disease are all closely linked to HK. Individuals having CKD, HF, DM, and arterial hypertension using RAASi show a 2 - 3 times higher risk for HK [5] [9].

Due to the increased prevalence of CKD among individuals hospitalized for HF, HF is a common risk factor for CKD-related HK. RAASi and MRA are taken in substantial doses by patients with HF and CKD, contributing to chronic HK. Approximately 30% of CKD, HF, or DM patients receiving RAASi treatment had at least one incident of HK over five years [5] [12] [13].

In the context of HF, ACEi-treated hospitalized patients are at an increased risk of developing HK at around 38% [14]. A greater mortality risk was seen with K levels above 5.5 mmol/L [15].

Also, patients with HF and decreased renal function may experience an increase in the incidence of HK since CKD carries an increased risk of developing chronic HK. More than 60% of HF patients had kidney disease [16].

In DM, HK has a greater incidence than the general population. As far as acidosis, insulin insufficiency, hypertonicity, rhabdomyolysis, and medications (such as B-blockers), redistribution of K from the intracellular to the extracellular compartment can induce HK without a net rise in total body K. Many medications (ACEi, ARB, renin inhibitors, B blockers, and potassium-sparing diuretics) that interfere with K excretion, as well as decreased glomerular filtration of K (due to acute renal injury and CKD), are related to HK. The syndrome of hyporeninemic hypoaldosteronism, defined by mild-to-moderate renal insufficiency, is the most frequent cause of chronic HK in people with diabetes, and patients often present with asymptomatic HK [5] [17] [18].

In patients with CKD and/or chronic HF taking RAASi, moderate to severe initial HK (5.6 mEq/L), low eGFR (45 mL/min per 1.73 $m^2$), DM, and spironolactone use are risk factors for recurring HK within six months of the first occurrence [19].

Moreover, HK was seen in all phenotypes of HF. Savarese *et al.* (2019), in their study of 5848 HF, found that 24.4% of patients have HK. HK was seen in 25.8% of Heart Failure with preserved Ejection Fraction (HFpEF), 22.2% of Heart Failure with mid-range Ejection Fraction (HFmrEF), and 24.7% of Heart Failure with reduced Ejection Fraction (HFrEF) [20].

## 3. Management Paradox: HK and the Need for Optimal Dose of RAASi

Renin-Angiotensin-Aldosterone System inhibitors (RAASi) are proven therapies for various illnesses like hypertension, DM, CKD, and congestive HF. One of the most frequent side effects of RAASi is HK, which is brought on by either decreased aldosterone secretion or elevated aldosterone resistance. The risk for HK

alone is also increased by the disorders for which RAASi are advised. A higher risk of CV events, hospitalizations, and death are linked to RAASi-related HK. Nevertheless, stopping RAASi increases the risk of CV events, hospitalizations, and death in individuals with CKD and congestive HF. As a result, doctors frequently face the difficult decision of managing RAASi-related HK best. Also, offering a suboptimal dose of RAASi can jeopardize better management of these conditions [21]. Failure to convey guideline-recommended RAASi doses could lead to many problems. One study showed that patients who maintained or increased their dose of RAASi had better 6-month survival [22]. Thus, we are left with this management paradox: Should we use the optimum RAASi with its higher incidence of HK or, decrease the dose, or even stop the RAASi with all its harmful hazards?

According to the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure, ACEi/ARNi, a beta-blocker, and an MRA should be up-titrated to the doses used in the clinical trials (or to maximally tolerated doses if that is not possible) for patients with (NYHA Classes II - IV) HFrEF (LVEF ≤ 40%) [23].

Also, according to the 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA) guideline for the management of heart failure, titration of RAASi to achieve target doses shown to be efficacious in RCTs is recommended, to reduce CV mortality and HF hospitalizations, unless not well tolerated in patients with HFrEF (LVEF ≤ 40%). Also, an MRA is recommended in patients with HFrEF and NYHA class II to IV symptoms to reduce morbidity and mortality if eGFR > 30 mL/min/1.73m$^2$ and serum potassium is <5.0 mmol/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely monitored to minimize the risk of hyperkalemia and renal insufficiency [24].

Despite these guideline recommendations to optimize RAASi [23] [24], the majority of patients with HFrEF remain below target doses, as shown in the Change the Management of Patients with Heart Failure (CHAMP-HF) registry, Savarese *et al.*'s (2021) cohort study, and the BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF) cohort study [25] [26] [27] [28].

## 4. Magnitude of Recurrence of HK, Persistent HK and Mortality

A significant UK retrospective cohort research included people who used RAASi and/or had CKD, HF, resistant hypertension, dialysis, or DM. About 33.3% had at least one HK event, while 20.2% had recurrences [29]. In another retrospective study, persistent HK in HF patients is linked to a higher mortality risk [30].

A multicenter Egyptian cohort of 1475 patients with acute heart failure was studied as a subgroup of the European Society of Cardiology-Heart Failure (ESC-HF) registry to determine the predictive value of K level in HF. For the

1085 patients who made up the final study cohort, information was available on K at admission and discharge and 12-month mortality. Overall, 71 patients died while receiving medical attention in the hospital, and an additional 256 patients died during the 12-month follow-up. Death after one year was significantly predicted by admission and discharge HK. The lowest mortality was observed between 3.5 and 5 mEq/L of K [31].

## 5. Hyperkalemia Management

Achieving and maintaining normokalemia became a new therapeutic target in HF and other conditions that required RASSi therapy [32] [33] [34] [35].

### 5.1. Current Therapeutic Options

Recently, novel potassium binders, patiromer, and SZC were developed [21]. Both have proven to be effective [36] [37] [38], and their usage is advised by the ESC HF guidelines (2021), the KDIGO guidelines for managing DM in CKD (2020), as well as the KDIGO guidelines for managing blood pressure in CKD (2021) [23] [35] [39]. Moreover, both were recommended by the NICE for treating hyperkalemia in adults [40] [41]. Although sodium polystyrene sulfonate has traditionally been used to treat HK, its safety and effectiveness are under debate [42].

The HARMONIZE trial, a multicenter, randomized, double-blind, and placebo-controlled study, assessed the effectiveness and safety of SZC for 28 days in patients with HK. After comparison to placebo, all three dosages of SZC led to lower serum K levels and a higher percentage of patients with normal K levels for up to 28 days. Serum K was reduced by SZC to normal levels in 48 hours. In order to assess long-term clinical results and gauge the efficacy and safety of SZC beyond the first four weeks, additional research was required. So, for approximately 11 months, an Open-Label Extension (OLE) of the HARMONIZE study assessed SZC's effectiveness and safety. According to the study, most patients kept their mean serum K levels within the normal range for about 11 months while receiving continued SZC medication [43] [44].

### 5.2. Management of HK in the Emergency Setting

HK in the ED is frequently discovered by chance through laboratory electrolyte measurements or venous or arterial blood gas examination. Pseudohyperkalemia should be considered in patients with no known risk factors or when the HK finding appears questionable. An ECG is advised to check for changes brought on by HK. In addition, more actions should be performed to determine the cause of HK. These can involve a thorough review of the patient's medical history and current medications, testing for hemolysis, determining kidney function, and, if necessary, looking into the potential causes of Acute Kidney Injury (AKI) [45].

The UK Renal Association released an update to the clinical practice guideline

on treating acute HK in adults in 2020. International nephrology, cardiology, and emergency medicine experts created an algorithm (Figure 1) for emergency HK management. They recommended novel K binders, SZC and patiromer, in the community out-patients for managing persistent HK and an option in the emergency management of acute life-threatening hyperkalemia [46].

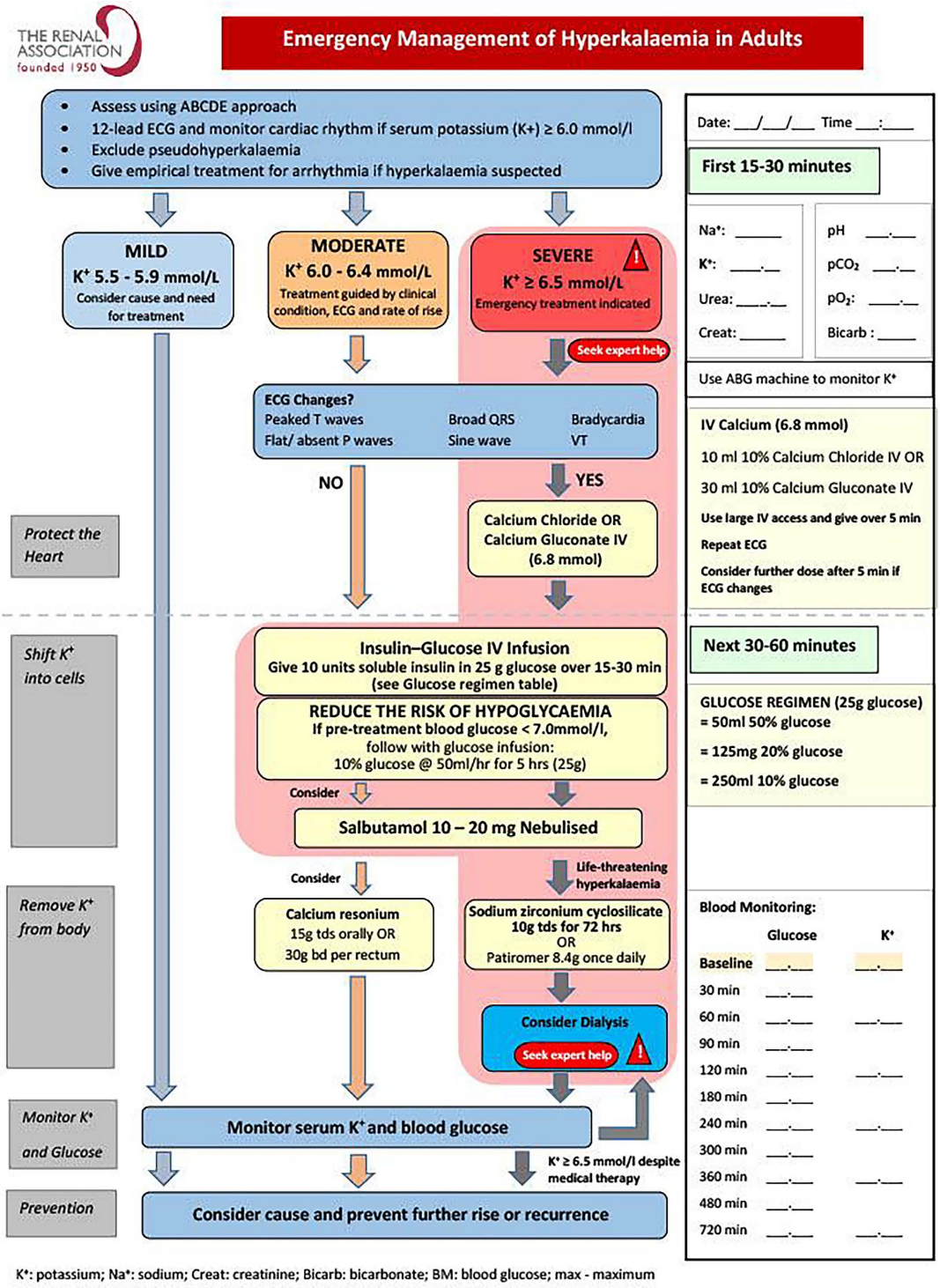


**Figure 1.** Emergency management of hyperkalemia [46].

Also, the NICE recommended the uptake of novel K binders, SZC & patiromer, in emergency care for acute life-threatening HK alongside standard care [40] [41].

- **Stabilization of cell membrane**

When hyperkalemic patients come with ECG abnormalities that may indicate HK, intravenous calcium salts should be given right away [46] [47]. As a result of its lower tissue toxicity, calcium gluconate is preferred by certain authorities over calcium chloride. However, calcium chloride is preferred by others due to its potential for better bioavailability [48]. It is important to remember that calcium chloride contains roughly three times as much calcium as calcium gluconate [46]. The European Resuscitation Council advises administering 10 ml of 10% calcium chloride over 2 - 5 minutes to inhibit ventricular fibrillation/tachycardia by stabilizing the cardiac cell membrane [47].

- **Potassium shift to the intracellular compartment**

Since the introduction of calcium salts does not reduce K concentrations, other strategies, such as insulin and beta-adrenergic agonists, must be used to move K from the extracellular to the intracellular compartment. The optimal dose and procedure for intravenous short-acting insulin to lower K in HK were examined in a systematic review by Harel and Kamel. The authors concluded that using a larger dose was associated with a higher risk for hypoglycemia. At the same time, the administration of 10 insulin units produced results comparable to those of 20 units. The patient should also receive 25 - 50 g of glucose intravenously in addition to insulin [49]. Studies from an ED in the USA found that a low insulin regimen (5 units) is comparable to 10 units in the amount of K lost but with less hypoglycemia [50] [51].

As an alternative to or in addition to the administration of insulin and glucose, $\beta$-adrenergic agonists have been proposed [47]. Salbutamol can be administered intravenously or nebulized, according to a 2015 Cochrane review results. Using a nebulizer to provide 10 mg of salbutamol causes a considerable decrease in K that peaks 120 minutes after administration [52]. Salbutamol with insulin may have additive effects [53]. The potential side effects of this high salbutamol dose need to be watched.

Although there is mixed evidence regarding sodium bicarbonate's efficacy, it activates the Na-K pump and corrects an underlying metabolic acidosis, which may lower serum potassium levels. Only individuals with metabolic acidosis who are anticipated to tolerate the sodium load required should use sodium bicarbonate [45].

- **Potassium elimination**

The only methods for removing potassium from the body are loop diuretics, dialysis, and potassium-binding drugs. Although loop diuretics are frequently used to treat acute HK, studies still need to be done to determine how well they work to remove potassium. Loop diuretics may be helpful following fluid resuscitation in other individuals and hyperkalemic patients with volume overload, such as those with heart failure [45].

Large RCTs have yet to be conducted to examine sodium polystyrene sulfonate's effectiveness. Two observational studies [54] [55] have reported adverse Gastrointestinal (GI) effects. Novel potassium binders like patiromer and SZC have been licensed with promising results in removing potassium. SZC appears to have an adequately quick onset of action [56] [57] [58] [59]. In a study by Kosiborod *et al.*, a subset of 45 patients with severe HK (>6 mmol/L) received a 10 g dose of SZC. A serum potassium level of 6.0 mmol/L was reached on average in 1.1 h, and a level of 5.5 mmol/L was reached on average in 4.0 h [56].

The ENERGIZE study suggested that SZC with insulin and glucose may provide an incremental benefit in the emergency treatment of HK over insulin and glucose alone [60]. The use of patiromer in ED patients with HK was studied in a recent small trial despite the drug's slower onset of action. It was discovered that patiromer considerably reduced serum potassium concentrations after two hours without adverse effects [61].

In patients with HK, K is removed from the blood through dialysis. We advise nephrology consultation for all patients who present to the ED with HK and receive dialysis treatment. Furthermore, individuals with AKI or therapy-refractory HK should be sent to nephrology for consideration of dialysis [45].

### 5.3. Management of Chronic, Recurrent or Persistent HK

The different therapeutic options available for the management of non-acute HK, as well as their algorithmic presentations, were illustrated by the UK Renal Association in their updated clinical practice guideline in 2020. **Figure 2** depicts the HK management in the community setting [46].

**1) Management of chronic HK for RAASi maximization: CKD/HF**

According to the evidence, HK can be challenging to reach and maintain the maximum tolerated doses of RAASi therapy advised by CKD and HF treatment guidelines recommendations to improve patient outcomes. Therefore, using novel K binders is recommended for HK control in CKD and HF treatment recommendations based on the available evidence to facilitate the best possible RAASi therapy [23] [24] [35] [39] [62]-[67].

**Novel potassium binders: their place in the trajectory of cardiorenal diseases**

Patiromer and SZC, the two more recent gastrointestinal potassium binders, remove K by exchanging cations (calcium for patiromer and sodium and hydrogen for SZC), resulting in enhanced fecal excretion. Both medications have FDA approval for the management of HK in RAASi-receiving patients [24].

In patients with HF, the 2021 ESC guideline for diagnosing and treating acute and chronic HF stated that using K binders to manage chronic or recurrent HK may enable RAASi therapy. Also, the guideline recommended that RAASi be optimized when K levels are less than 5.0 mmol/L. An approved K-lowering agent may be initiated once K levels are confirmed as >5.0 mmol/L. Close monitoring of K levels is recommended. Maintaining K lowering treatment unless alternative treatable etiology for HK is identified [23]. On the other hand, the 2022

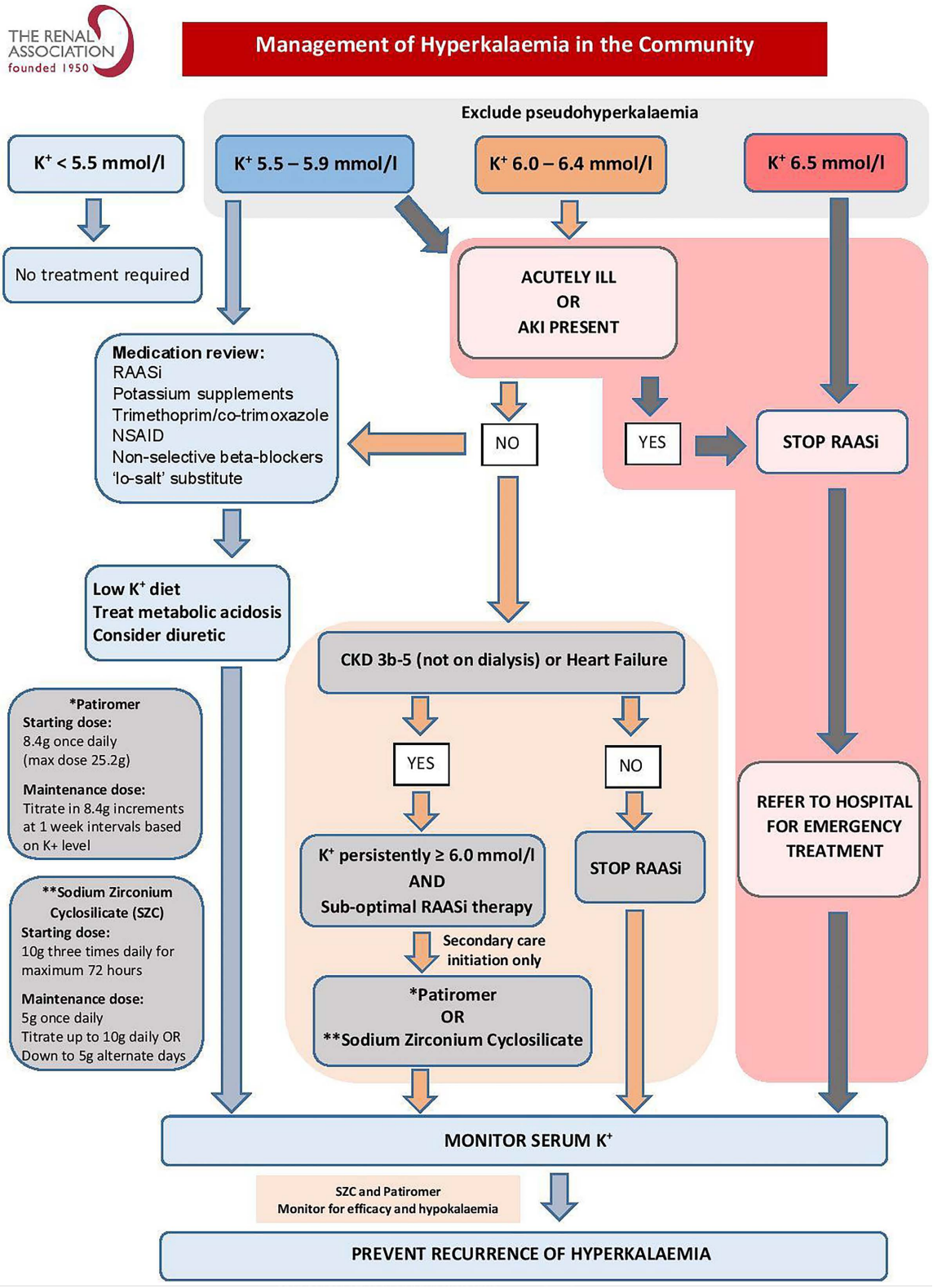


**Figure 2.** Management of hyperkalemia in the community [46].

AHA/ACC/HFSA guideline for the management of HF stated that in patients with HF who experience HK (serum K ≥ 5.5 mmol/L) while taking a RAASi, the

effectiveness of K binders to improve outcomes by facilitating the continuation of RAASi therapy is uncertain [24].

The Kdigo 2020 guideline for DM management in CKD and Kdigo 2021 guideline for BP management in CKD stated that in patients with CKD, HK associated with ACEi or ARB use could often be managed by measures to reduce K rather than decreasing the dose or stopping the ACEi or ARB. In addition, oral K binders (SZC or patiromer) can be used in many patients, with the effect that ACEi/ARB can be continued at the recommended dose. Close monitoring of the K level is also recommended [35] [39].

**2) Management of chronic HK: cases not on RAASi therapy**

Some categories of patients who are not on RAASi therapy, like some cases of HF, CKD, DM, and those with hypoaldosteronism, obstructive uropathy, and also those taking the following drugs ($\beta$-adrenergic receptor blocker, digitalis glycoside, heparin, NSAID, trimethoprim, pentamidine, cyclosporine, tacrolimus, ketoconazole) may also have chronic HK [5] [68]. Monitoring and managing HK is essential in those patients with chronic conditions or on continuous utilization of certain drugs. Limiting dietary K intake modifying drugs that raise serum K levels are the main therapeutic strategies. However, novel K binders could help after the failure of those mentioned strategies.

**3) Management of persistent predialysis HK**

Patients with ESRD have severely reduced renal potassium excretion and require Hemodialysis (HD) and peritoneal dialysis to maintain normal serum K levels. However, despite dialysis, many cases have persistent predialysis HK [69] [70].

Effectively managing HK in dialysis patients comes with several problems and difficulties. The main therapeutic strategies are monitoring and limiting dietary K intake, optimizing the dialysis prescription, and modifying drugs that raise serum K levels. Controlling these modifiable factors is essential to preventing HK. Novel K binders could lessen the necessity for a severely limited diet in ESRD patients and the risk of potentially fatal HK and cardiovascular problems resulting from the quick changes in serum K levels. Long-term treatment with the novel K binder medications can optimize RAASi therapy while lowering the risk of HK and cardiovascular complications following the lengthy interdialytic interval [71].

The K binder, SZC, was examined in the double-blind, placebo-controlled, multicenter DIALIZE study for treating HK in hemodialysis patients. It revealed that 2.1% of patients receiving SZC needed rescue therapy to lower serum K during the treatment period, compared to 5.1% of patients receiving placebo. In ESRD patients receiving sufficient hemodialysis, SZC is an efficient and well-tolerated therapy for predialysis HK [72].

## 6. Conclusions and Practical Considerations for the Management of HK

***Statement* 1:** *Because the current therapy options for managing HK are not*

*that ideal, introducing new K binders like SZC and patiromer is highly appreciated.*

***Statement* 2:** *Cardiorenal patients are at risk for chronic HK. The presence of new evidenced drugs like SZC and patiromer can help in their management as recommended by different international guidelines to optimize RAASi therapy.*

***Statement* 3:** *In emergency settings, SZC can have a role in managing acute HK, as evidenced by the ENERGIZE study, and because it has a rapid onset of action than other K binders like patiromer. However, it should be used with other drugs like insulin and glucose.*

***Statement* 4:** *In dialysis patients, novel K binders like SZC and patiromer may play a significant role in managing predialysis HK, as evidenced by the DIALIZE study for SZC.*

## 7. Future Directions

We look forward to seeing the results of all outcome studies for SZC in the management of HK. The utilization of SZC as prophylaxis for HK may be considered. However, prospective studies proving this idea are needed first as it has yet to be a guideline recommendation. Furthermore, local research studies are highly needed.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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