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Prevalence and management of hyperkalemia in chronic kidney disease and heart failure patients in the Gulf Cooperation Council (GCC)

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Abstract

Hyperkalemia is a frequent complication in patients with chronic kidney disease (CKD) or heart failure (HF) and associated with neuromuscular manifestations, changes in the electrocardiogram, and increased risk of mortality. While data on the prevalence and management of hyperkalemia in the gulf region are scarce, risk factors such as preference for potassium-rich foods (e.g., dates and dried fruits/vegetables), periods of intense fasting (e.g., Ramadan), and diabetes (an ancestor of CKD and HF) are common. Therefore, a panel of nephrologists and cardiologists from countries of the Gulf Cooperation Council (GCC) convened to collate and review available data on the prevalence, regional drivers, and current practice in the management of hyperkalemia in the region. Eventually, this review provides consensus recommendations on a balanced utilization of dietary and pharmacological options including new potassium binders for achieving and sustainably maintaining desirable serum potassium levels in countries of the GCC region. Alignment with regional habits and practice was a key aspect to facilitate the uptake of the recommendations into physicians' practice and patients' lives.

KEYWORDS

chronic kidney disease, heart failure, hyperkalemia, potassium binding

1 | INTRODUCTION

Hyperkalemia is a frequent complication in chronic kidney disease (CKD) and heart failure (HF) patients, particularly those on renin-angiotensin-aldosterone inhibitor (RAASi) therapy.^{1,2} It is associ-

ated with neuromuscular symptoms, changes in the electrocardiogram (ECG), cardiac arrhythmias, and increased all-cause mortality (Figure 1).³⁻⁵ Hyperkalemia also impacts health care systems due to significantly more frequent hospital visits, readmission rates, and longer length of stay.⁶

All authors contributed equally to the preparation of this manuscript.

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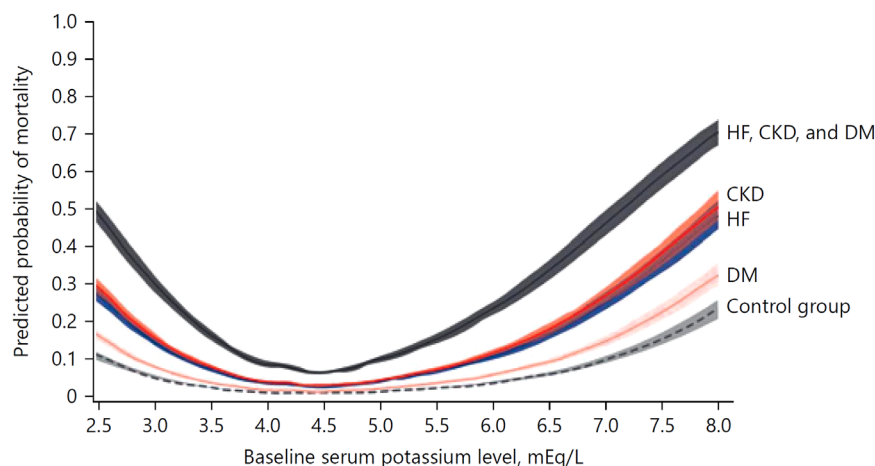


FIGURE 1 Covariate-adjusted probability of all-cause mortality across potassium values (2.5–8.0 mEq/L) in HF, CKD, diabetes mellitus (DM), and combined cohorts compared to controls (from Collins et al.³)

Notably, medications used in CKD and HF patients can affect serum potassium levels in contrasting ways. Whereas RAASi agents increase potassium levels, thiazide and thiazide-like diuretics decrease them.⁴ Furthermore, dietary habits and certain supplements can aggravate unrecognized hyperkalemia.

Unfortunately, lack of a general cutoff level for intervention and neglect of regional factors influencing potassium intake hinder the implementation of hyperkalemia treatment standards. Furthermore, the interplay between heart and kidney function⁷ calls for the harmonization of hyperkalemia management among cardiologists and nephrologists.

This review focuses on regional prevalence, drivers, and management of chronic hyperkalemia in CKD and HF patients in the Gulf Cooperation Council (GCC) region and recommendations for achieving and maintaining sustainable serum potassium levels.

2 | METHODS

Eleven nephrologists and cardiologists from the GCC region and two international guest experts convened to achieve a common, evidence-based treatment approach that is applicable to the GCC region. Available evidence was collated from international CKD and HF treatment guidelines and articles on the prevalence and management of hyperkalemia in GCC countries (Bahrain, Kuwait, Oman, Qatar, Kingdom of Saudi Arabia [KSA], United Arab Emirates [UAE]). Pubmed was searched on September 30, 2021 with the search term “(hyperkalemia) AND (Bahrain OR Kuwait OR Oman OR Qatar OR Arabia OR KSA OR UAE OR Emirates).” From 74 hits, 29 were selected for further review and supplemented with articles on hyperkalemia prevalence in selected neighboring countries (Egypt, Turkey).

In addition, results of a survey on the prevalence and management of hyperkalemia among nephrologists and cardiologists in KSA were available. Overall, 50 nephrologists and 30 cardiologists were enrolled for quantitative interviews (~30 min), and three nephrologists and three cardiologists for qualitative interviews in January/February 2020. On average, participants had 17 years of practice experience and spent 91% of time in direct patient care.

3 | DEFINITION, PREVALENCE, AND RISK FACTORS OF HYPERKALEMIA

3.1 | Definition of hyperkalemia in the GCC region

Frequently used thresholds for the upper limit of normal of serum potassium (5.0 mEq/L) and hyperkalemia (>5.5 mEq/L) cause ambiguity.^{8–10} In medical centers across the GCC, upper limits of normal range from 5.0 to 5.5 mEq/L but changed over time with new analytical procedures or equipment. In the survey in KSA, the majority (nephrologists 92%, cardiologists 83%) described chronic hyperkalemia as potassium >5.5 mmol/L for a prolonged time and 38 and 43%, respectively as recurring episodes of elevated potassium within 1 year. For patients with arrhythmia or a cardiac problem, already potassium levels >5.5 mEq/L were considered severe.

The panel recommends an upper limit of normal of 5.0 mEq/L considering the potassium-dependent increased mortality risk³ and recent consensus statements of medical societies.^{4,8,11} The severity of hyperkalemia shall be classified as mild (>5.0 to <5.5 mEq/L), moderate (5.5–6.0 mEq/L), and severe (>6.0 mEq/L). Potassium levels between current local upper limits of normal and 5.5 mEq/L shall be considered as mild hyperkalemia.

Reading potassium levels requires caution as levels can be influenced by circadian rhythm, fed/fasting status, and hemolysis or thrombocytosis due to suboptimal blood sampling (pseudohyperkalemia).^{12,13} Furthermore, blood gas analyzers tend to report significantly lower potassium levels than biochemistry analyzers.¹⁴ In case of doubt (e.g., in low-risk patients with glomerular filtration rate [GFR] ≥ 60 ml/min or normal ECG) repeating the test from freshly drawn blood is recommended.

3.2 | Prevalence of hyperkalemia in the GCC region

In general, data on the prevalence of hyperkalemia in GCC and neighboring countries are scarce. Reported rates depend on the investigated population, setting and applied cut-off levels (Table 1).^{2,15–21} The

TABLE 1 Prevalence of hyperkalemia in GCC and neighboring countries

Country [Ref.]	Population	Prevalence (definition)	Remarks
KSA ¹⁵	300 hospitalized adult patients	47.3% (≥ 5.1 mEq/L)	Among hyperkalemic patients, 94.4% > 55 years, 80.2% hypertensive, 73.9% diabetic, 56.3% CVD, 45.8% CKD
UAE ²⁰	102 adult patients with HF, reduced ejection fraction with LVEF $\leq 40\%$, and prescription for sacubitril/valsartan	> 11.8% (> 4.8 mEq/L)	Enrollment of patients with hyperkalemia should have been delayed until normalization. However, 11.8% of patients were reported as deviation due to hyperkalemia. Accordingly, the actual prevalence must be > 11.8%.
Qatar ¹⁶	161 adult patients with GFR ≥ 60 ml/min/1.73 m ² who received at least two doses co-trimoxazole	28.6% (> 5.5 mEq/L)	Among those, 76% on potassium-increasing medications such as β -blockers, heparin, ACE inhibitors, or angiotensin II receptor blockers.
GCC region ²	947 patients on maintenance HD	72% (≥ 5.1 mEq/L) 46% (≥ 5.6 mEq/L)	Peak potassium of monthly predialysis measures observed during the 4-month "exposure interval"
Egypt ¹⁷	400 patients on maintenance HD	41.2% and 66.9% predialysis at the first and subsequent HD session	6.5% post-dialysis
Turkey ¹⁸	9045 hospitalized patients	7.3% (> 5.0 mEq/L)	Among those, 73.0% with mild, 8.8% moderate, and 8.2% severe hyperkalemia ^a
Iran ¹⁹	338 HD patients	58% (> 5.2 mEq/L)	
Tunisia ²¹	66 chronic HD patients	28.8% (pre-HD) (≥ 5.5 mEq/L)	Prolonged QTc interval was significantly correlated with serum potassium ($p = 0.046$).

Abbreviations: ACE, angiotensin-converting enzyme; CKD, chronic kidney disease; CVD, cardiovascular disease; GCC, Gulf Cooperation Council (Bahrain, Kuwait, Oman, Qatar, KSA, and United Arab Emirates); GFR, glomerular filtration rate; HD, hemodialysis; HF, heart failure; KSA, Kingdom of Saudi Arabia; LVEF, left ventricular ejection fraction; UAE, United Arab Emirates.

^aMild (5.0–5.49 mEq/L), moderate (5.5–5.99 mEq/L), severe HK (≥ 6.0 mEq/L).

scarcity of data is a limitation for the awareness about hyperkalemia in the GCC region and its appropriate management. Well-designed studies to explore the prevalence of hyperkalemia in the GCC and potential relations with complications in patients with HF or CKD are warranted.

In the survey among nephrologists and cardiologists in KSA, hyperkalemia was reported in 50% of CKD patients and 42% of chronic HF patients, with CKD patients showing a trend toward more severe hyperkalemia (severe 22 vs. 12%, mild 39 vs. 59%). The majority of hyperkalemic patients (60%) were considered having chronic hyperkalemia (CKD 64%, HF 55%).

3.3 | Medical conditions associated with hyperkalemia

Conditions and risk factors associated with hyperkalemia, including CKD, chronic metabolic conditions, HF, and medications are reflected in the populations with available prevalence data (Table 1). Indeed, hyperkalemia associated with RAASi medications and cardiac risks was the most frequent safety issue (10.6 and 9%, respectively) discussed in direct health care professional letters of the Saudi Food and Drug Authority in June 2020.²² Among hyperkalemic, hospitalized, adult, nondialysis patients in KSA, 31.0% used β -blockers, 30.3% ACE inhibitors, and 12.0% spironolactone/eplerenone, and the use of β -blockers correlated significantly with hyperkalemia.¹⁵

In the survey in KSA, the most frequently stated causes of hyperkalemia were CKD (94%) and medications (87%), and 28% considered

hyperkalemia being caused by RAASi treatment most of the time. Other causes of hyperkalemia comprised untreated diabetes (41%) and HF (47%).

Diabetes is a prevalent risk factor in HF patients (25%–49%) and particularly prevalent in the Arabian Gulf region (Bahrain 16.3%, Kuwait 22.0%, Qatar 15.5%, KSA 18.3%, UAE 15.4%).^{23,24} Only Oman (8.0%) has a moderate diabetes prevalence, but an increase of cases is foreseeable. Among HD patients in GCC countries, diabetes prevalence ranges even from 45 to 74% (median 68%).²⁵

Since also physical inactivity, a key driver of the above-mentioned conditions, is widespread in the region (Kuwait 67%, KSA 53%),²⁶ the panel supports all efforts to increase physical activity and reduce obesity. Furthermore, checks of potassium levels during regular visits of patients with these conditions are recommended.

Nonmedical risk factors of hyperkalemia

– Dietary aspects: The Middle Eastern preference for dates, a rich source of potassium and the large differences in potassium content of different sorts (exceeding 600 or even 1000 mg/100 g)^{27–29} need to be considered in diet plans and patient education. While traditional diets in the GCC region are rich in fruits, vegetables, and legumes, dietary patterns have changed toward processed food over the past decades. However, unlike for phosphorus, no specific recommendations for potassium in processed food are given although additives increase the potassium content of food almost three-fold

and may have greater bioavailability than phosphorus from whole foods.³⁰ Furthermore, attempts to decrease sodium in processed food enhanced the use of potassium to maintain the salty taste. Unfortunately, only 47% of Arab countries have mandatory food labeling regulations.³¹

– Fasting during Ramadan: The effect of daily and partial versus nonfasting during Ramadan has been evaluated in 269 HD patients in Palestine (groups adjusted for diabetes, hypertension, and predictors of clinical and biochemical parameters).³² Mean serum potassium was significantly greater in the fasting than the nonfasting group (5.38 vs. 4.90 mEq/L; $p < 0.001$) and slightly elevated in the partial fasting group (5.03 mEq/L). Potential reasons included the increased consumption of traditional, potassium-rich Ramadan's festive foods (dates, dried apricot, etc.), and fasting-related insulin suppression, shifting potassium from the intracellular to the extracellular compartment.³³

A prospective study in KSA evaluated 32 HD and 39 CKD patients (85% stage 3 or 4) before, during, and after Ramadan.³⁴ Among HD patients, potassium levels increased from 5.1 to 5.3 mEq/L ($p = 0.07$). Hyperkalemia was detected in 25.0% during (Day 15) and 15.6% after Ramadan. Among CKD patients, potassium levels remained stable. An early study of 40 HD patients in KSA reported a significant increase of mean serum potassium from 5.05 mEq/L before to 5.76 mEq/L during Ramadan.³⁵ Notably, 35% presented with potassium ≥ 6.5 mEq/L during Ramadan, compared to 10% before Ramadan. Overall, the reported elevated potassium levels over Ramadan were not associated with important clinical complications and other reports show stable potassium levels.³⁶

In the survey among nephrologists and cardiologists in KSA, high potassium intake (55%) and diet (41%) were the most frequent non-medical causes of hyperkalemia. Notably, high potassium intake was twice as frequent among patients of cardiologists than those of nephrologists (73 vs. 36%).

4 | RAAS BLOCKADE IN CKD AND HF TREATMENT PRACTICE IN THE GCC REGION

In the survey in KSA, 87% of CKD and 70% of HF patients were on RAASi therapy. However, only 70 and 54% of those were considered to be on an optimal dose. In response to hyperkalemia, 60% of surveyed physicians (nephrologists 74%, cardiologists 47%) switched to another medication, 27% (18 and 37%, respectively) reduced the RAASi dose, and 11% (8 and 13%, respectively) discontinued RAASi without switching to another medication (2% referred patients to another specialist). Calcium channel blockers were the most frequently used alternative (26%) followed by vasodilators (23%), diuretics (21%), and beta blockers (12%).

International CKD and HF guidelines^{4,37} and this panel recommend administration of RAASi at the highest locally approved or tolerated dose because the benefits from lower RAASi doses are less certain.³⁷ Serum potassium and eGFR should be assessed before and 7–10 days after the initiation of RAASi or MRAs to avoid hyperkalemia or acute kidney injury. In patients developing hyperkalemia (>5.0 mEq/L),

strategies to lower potassium levels should prevail over RAASi dose reduction or interruption.

5 | MANAGING HYPERKALEMIA

5.1 | Diagnosis and monitoring of serum potassium

The KSA survey showed that most nephrologists rely on ECG (80%) and blood gas testing (40%) to diagnose hyperkalemia while cardiologists use them almost equally (63 and 67%, respectively). Serum potassium is tested by 32 and 23%, respectively. Interviews suggest that serum potassium is rather used to confirm ECG findings and response to potassium-lowering measures.

In patients at risk of hyperkalemia (e.g., eGFR < 30 ml/min per 1.73 m^2), potassium levels should be tested initially, within 1–2 weeks after RAASi dose changes and at intervals up to 6 months.^{4,37} Furthermore, potassium should be measured prior to initiation of a potassium-lowering agent and 2–3 days and 1 week after initiation. After potassium decreased to < 5.0 mEq/L, monitoring is recommended after 1 month and then every 3–6 months (target level 3.5–5.0 mEq/L).³⁸ If potassium-lowering agents are discontinued while maintaining RAASi treatment, serum potassium can rapidly increase within 1–3 days and should be tested at least once during that period. Others suggest even a daily test during this 3-day period to ensure that levels remain < 5.0 mEq/L.³⁸ An approved device can allow for daily potassium measurements and documentation of hyperkalemia episodes.³⁹

5.2 | Managing potassium levels and concomitant blood pressure medication

RAASi dose reduction or cessation to manage hyperkalemia deprives patients from the benefits of RAASi therapy.⁴⁰ Accordingly, restriction of dietary potassium and potassium-containing supplements, and use of potassium-wasting diuretics and oral potassium binders should be considered.^{4,37}

– Dietary potassium restriction: Definitions of populations that should restrict daily potassium intake vary among experts.^{41,42} Furthermore, general restrictions on potassium intake bear the risk of depriving traditional diets of plant-based but potassium-rich components. Notably, these diets are usually also high in alkaline content and fiber, which can correct CKD-associated metabolic acidosis and improve bowel transit time, constipation, colonic epithelium integrity, and the gut microbiome.⁴³ Suggestions for a gradual and less coercive introduction of potassium intake restriction are summarized in Table 2.^{43,44} In general, active nutritional counseling by an experienced renal dietitian in addition to optimum medical therapy can benefit patients and reduce the prevalence of hyperkalemia.⁴⁵

Before and during Ramadan, cardiologists, nephrologists, and diabetologists should pro-actively ask patients about their intention to fast, and advice on fasting and cautionary measures based on the

TABLE 2 Strategies to gradually introduce a dietary plan to reduce potassium intake

1. Involve the patient	<ul style="list-style-type: none"> • Individualize the dietary plan according to the patient's lifestyle, education, and religious and sociocultural background • Explain the plan's benefits and limitations and give the patient adequate time to accept and start changing dietary habits • Consider a broad range of individual health literacy and potential difficulties with comprehension, communication, and the use of digital technology
2. Involve renal dietitians, psychologists, pharmacists, and social workers to ensure the patient's understanding, acceptance, adaptation, and adherence, if resources allow	
3. Identify potassium content of foods	<ul style="list-style-type: none"> • Check patient's typical serving size/weight (a large serving of low-potassium food may have more potassium than a small serving of high-potassium food) • Normalize potassium contents of food per unit fiber • Soy-, rice-, and almond-based beverages tend to have less potassium and phosphorus than milk • Overall, a stepwise reduction in potassium intake is advised to ensure a balanced intake of fresh fruit, vegetables, and fiber
4. Emphasize food preparation methods that may reduce potassium content of food	<ul style="list-style-type: none"> • Leaching or dialysis of vegetables • Cook vegetables in large volume of water (1:5 w/v) • Soak legumes 12 h in water (1:15 w/v) then cook in the same amount of fresh water
5. Supporting factors in the implementation of food plan	<ul style="list-style-type: none"> • Translate information about nutrients into food, pictures, and recipes • Invite the person responsible for buying and preparing food to appointments with the dietitian • Engage both patients and family members • Adopt a stepwise approach to allow patients to adapt to the recommendations over time • Talk less about what is not allowed and more about what is • Raise awareness about an increasing number of restaurants that have plant-based options • Consider social life and allow occasional freedom to improve long-term adherence • Simplify nutrition education and avoid weighing or counting servings if possible • Recommend cooking classes with food recipes desired by patients • Offer positive feedback and show how diet affects laboratory values or intradialytic weight over time (if applicable) • Meal delivery services may benefit patients who live alone and have to follow special diets

TABLE 3 Advice on fasting during the month of Ramadan depending on eGFR levels*

eGFR > 60	Fasting is permissible, but patients shall be advised on sufficient fluid intake at night and restriction of potassium-rich food like dates and dried vegetables
eGFR 15–60	Fasting is not recommended in case of concomitant uncontrolled DM, use of insulin for blood sugar control, uncontrolled hypertension, HF, severe liver disease, or pregnancy
eGFR < 15	Fasting is not recommended due to the risk of deteriorating kidney function as a consequence of reduced fluid intake

*eGFR in ml/min/1.73 m².

patient's eGFR level as summarized in Table 3. Patients insisting to fast must be closely monitored for clinical status and laboratory values and advised to check their lower limbs for signs of edema and monitor blood pressure and body weight. Patients on HD shall not fast to avoid the risk of volume overload and blood pressure elevation after excessive fluid intake.

- Adding potassium-wasting diuretics: Compared to calcium carbonate and/or sodium bicarbonate, insulin, and beta adrenoceptor agonists, only loop diuretics can facilitate potassium loss.⁴ Combinations of loop diuretics and thiazides effectively induce diuresis, but also can lead to reduction of GFR, hypokalemia, hypomagnesemia, and hyponatremia.³⁷
- Oral potassium binders: The introduction of modern potassium binders (patiromer, sodium zirconium cyclosilicate) enables the initiation, up-titration, and maintenance of RAASi and spironolactone doses in more patients.^{4,37}

Patiromer is a polymer that absorbs and eliminates potassium in exchange for calcium. It has proven potassium lowering efficacy (minus .7–1.2 mEq/L) in RAASi-treated patients with CKD and/or HF and mild or moderate hyperkalemia, lowers frequency of hyperkalemia, and allows maintenance or increase of spironolactone and RAASi medication.^{46–51} In hyperkalemic HD patients undergoing hemodialysis receiving once daily patiromer or SPS on nondialysis days, both treatments significantly reduced serum potassium but patiromer showed a better subjective tolerability score and compliance.⁵² In a recently published placebo-controlled study in HF patients with reduced ejection fraction and hyperkalemia or recent hyperkalemia, patiromer-treated patients showed lower serum potassium levels, less incidences of severe hyperkalemia, and a favorable RAASi use score (85% on guideline-directed RAASi doses) with patiromer compared to placebo.⁵³ Sodium zirconium cyclosilicate is a crystalline compound that binds potassium in exchange for sodium. It showed potassium lowering efficacy in adult, hyperkalemic, outpatients, and predialysis

TABLE 4 Recommendations for managing potassium levels in hypertensive patients in the GCC region

4.0–5.0 mEq/L (target range)	RAASi or mineralocorticoid receptor antagonists should be initiated or maintained as needed. Patients shall be advised on the role of potassium, its dietary sources, and a reduction of dietary potassium intake considering a range of strategies to introduce a dietary plan (Table 2). If potassium levels increase toward the upper limit of normal, potassium-wasting loop diuretics may be initiated (if combined with thiazides, potassium, and sodium levels shall be monitored after initiation).
5.1–5.5 mEq/L (mild HK)	A potassium binder should be initiated in accordance with locally approved labels. Potassium sources and NSAIDs shall be eliminated.
5.6–6.0 mEq/L (moderate HK)	Potential hemolysis should be excluded as a cause of falsely elevated potassium levels (pseudohyperkalemia). A potassium binder should be initiated and/or diuretics initiated or increased. RAASi should be continued unchanged. If a dose reduction is deemed necessary, it should not go below 50% of the recommended dose.
>6.0 mEq/L (severe HK)	An ECG should be performed, and a potassium binder initiated or increased and maintained until normal levels are reached. If serum potassium remains high after 1 week, RAASi should be reduced, but not below 50% of the recommended dose.

patients with mild or moderate hyperkalemia (minus .8–1.2 mEq/L) that were only partly on concomitant RAASi therapy at baseline.^{54–56} In one study, most patients on RAASi medication could maintain or increase doses.⁵⁵

Both potassium binders can be taken with or without food.^{57,58} Gastrointestinal side effects are generally mild to moderate, a substantial improvement compared to sodium or calcium polystyrene sulfonate (SPS) preparations.⁵⁹ Main differences in the safety profiles are mild-to-moderate hypomagnesemia (patiromer; as it also binds some magnesium) and edema and hypokalemia (zirconium cyclosilicate; maybe due to high sodium content of 400 mg per 5-g dose). Notably, a recent analysis of nondialysis patients found significantly higher rates of edema-related hospitalizations and a trend for higher heart-failure hospitalizations in sodium zirconium cyclosilicate- versus patiromer-treated patients.⁶⁰

Whether potassium lowering improves clinical outcomes, hospitalization, cost of care, and quality of life remains to be investigated.

Qualitative interviews among nephrologists and cardiologists (KSA survey) suggest that hyperkalemia treatment is started at potassium >5.1 mEq/L, and physicians get really concerned at levels ≥6.0 mEq/L. Potassium lowering treatment is considered successful if levels decrease by 1.0–1.4 mEq/L and patients can be stabilized and discharged from hospital. Calcium resonium and SPS were the most frequently used treatment options with intolerance as most frequently cited barrier.

6 | RECOMMENDATION FOR MANAGING HYPERKALEMIA IN RAASI-TREATED CKD AND HF PATIENTS

Recommended options to maintain normal or reduce elevated potassium levels of hypertensive patients depending on the severity of hyperkalemia are listed in Table 4.

Patients shall be informed that uncontrolled discontinuation of potassium binders while maintaining RAASi medications lead to the rapid increase of potassium levels and can put them at risk of cardiac effects. Monitoring of magnesium levels is advised for patients given

patiromer whereas sodium zirconium cyclosilicate-treated patients should be monitored for edema.

AUTHOR CONTRIBUTIONS

All authors contributed equally to the literature search, data interpretation, and review of the manuscript.

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CONFLICTS OF INTEREST

AlSahow, Ali: speaker honoraria. Al-Ghamdi, Saeed: speaker honoraria Vifor Pharma, AstraZeneca and Astellas. AlJoburi, Harith: speaker honoraria AstraZeneca. AlMogbel, Osama: advisory board and speaker honoraria Vifor Pharma, AstraZeneca. Al-Rowaie, Fadel: speaker honoraria Vifor Pharma. Attallah, Nizar: speaker honoraria Vifor Pharma. Weir, Matthew: scientific advisor AstraZeneca, Akebia, Bayer, Janssen, Boehringer-Ingelheim, Vifor, NovoNordisk, Merck, GSK. Zannad, Faiez: personal fees for trial oversight committees, advisory boards, or speakers' bureau from Acceleron, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer, Cardior, Cereno Scientific, Cellprothera, CVRx, G3 Pharmaceuticals, Merck, Merck AG, Novartis, NovoNordisk, Pfizer, Servier, Vifor Fresenius, and is a Co-Founder of CardioRenal, CVCT. AbdulShafy, Mohammad; Bader, Feras; Hassan, Mohamed; Hussein, Hisham. Taha, Khaldoun: declared no conflict of interest.

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