Consensus-Based Recommendations for the Management of Hyperkalemia in the Hemodialysis Setting

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Hyperkalemia (serum K^+ >5.0 mmol/L) is commonly observed among patients receiving maintenance hemodialysis and associated with increased risk of cardiac arrhythmias. Current international guidelines may not reflect the latest evidence on managing hyperkalemia in patients undergoing hemodialysis, and there is a lack of high-quality published studies in this area. This consensus guideline aims to provide recommendations in relation to clinical practice. Available published evidence was evaluated through a systematic literature review, and the nominal group technique was used to develop consensus recommendations from a panel of experienced nephrologists, covering monitoring, dietary restrictions, prescription of K^+ binders, and concomitant prescription of renin-angiotensin-aldosterone system inhibitors. Recent studies have shown that K^+ binders reduce the incidence of hyperkalemia, but further evidence is needed in areas including whether reduced-K^+ diets or treatment with K^+ binders improve patient-centered outcomes. Treatment of hyperkalemia in the hemodialysis setting is complex, and decisions need to be tailored for individual patients.

Introduction

HYPERKALEMIA, COMMONLY DEFINED as serum K^+ >5.0 mmol/L or >5.5 mmol/L, is a common electrolyte disturbance observed in patients with advanced stages of chronic kidney disease (CKD) and is associated with increased risk of life-threatening cardiac arrhythmias.[1-4] Generally, moderate hyperkalemia is defined as serum K^+ >5.5 mmol/L and severe hyperkalemia defined as serum K^+ >6.0 mmol/L. The risk of hyperkalemia is increased in patients with heart failure and diabetes and in patients receiving maintenance hemodialysis.[5,6] Each month, nearly two-third of patients undergoing hemodialysis experience an episode of hyperkalemia (K^+ >5.5 mmol/L) after the long interdialytic interval.[6,7]

Currently, key approaches to managing hyperkalemia in patients with end-stage kidney disease (ESKD) include changing the dialysis prescription (time, blood flow rate, dialysate flow rate, dialyzer, dialysate K^+ concentration), dietary counseling on K^+ intake, additional dialysis sessions, and, particularly for patients with residual kidney function, adjustment of medications that increase serum K^+ such as nonsteroidal anti-inflammatories, β blockers, and renin-angiotensin-aldosterone system (RAAS) inhibitors.[6,8] However, RAAS inhibitors reduce cardiovascular risk, are efficacious in managing resistant hypertension, and in patients receiving maintenance dialysis, may preserve residual renal function.[9,10] Given the interplay among these many factors influencing serum K^+ concentrations, nephrologists are faced with a difficult decision when

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considering whether to manage hyperkalemia by reducing or discontinuing their patients' RAAS inhibitor dose.

K^+-binding medications have a role in managing hyperkalemia. Until recently, in many regions, the only K^+ binder available for use was sodium polystyrene sulfonate (SPS; Kayexalate® [ADVANZ PHARMA, Ontario, Canada], Resonium A® [Sanofi, Reading, UK], Kionex® [ANI Pharmaceuticals, Baudette, MN, USA). However, relatively poor tolerability, lack of clinical trial evidence for acute and long-term safety and efficacy, poor adherence, lack of specificity with respect to cation binding, potential for binding with other drugs in the intestinal tract, and potentially serious gastrointestinal adverse effects mean that this agent is used with caution.[5,9,11-14] Calcium polystyrene sulfonate (CPS; Resonium Calcium® [Sanofi, Reading, UK], Sorbisterit® [Fresenius Medical Care, Bad Homburg, Germany], Resikali® [CSP, Cournon-d'Auvergne, France, Kalimate® [Kowa Pharmaceutical Company, Tokyo, Japan]) is an alternative to SPS, used in Asia and Europe for the treatment of hyperkalemia, but its efficacy and safety profile have similarly not been systematically determined.[15,16]

In recent years, two newer K^+ binders, patiromer sorbitex calcium (patiromer; Veltassa® [Vifor Pharma, Glattbrugg, Switzerland]) and sodium zirconium cyclosilicate (SZC; Lokelma® [AstraZeneca, Cambridge, UK]), have been approved for use, opening up new avenues for managing chronic hyperkalemia.[9] Large-scale clinical trials across different settings have shown the newer K^+ binders to be well tolerated and efficacious in managing hyperkalemia.[17-30] Patiromer has been demonstrated to allow a higher proportion of patients to continue on RAAS inhibitor therapy than SPS.[31] Specifically in the hemodialysis setting, a real-world retrospective cohort study showed that patiromer was more effective than SPS in reducing severe recurrent hyperkalemia.[32] In a randomized controlled trial (RCT), SZC was well tolerated and efficacious in hyperkalemic patients with ESKD who were receiving maintenance hemodialysis.[22]

Not all current guidelines and recommendations on managing hyperkalemia address the use of newer K^+ binders, or how to treat hyperkalemia in the hemodialysis setting.[33] This consensus statement from experienced nephrologists covers current gaps in clinical practice recommendations regarding the management of hyperkalemia in the hemodialysis setting and identifies areas where future research is needed to further reinforce the evidence base supporting these recommendations.

Methods

Literature Review

A systematic literature review investigating the management of hyperkalemia was published by Palaka et al. in 2017[4] and was updated here with literature published between 2017 and 2020. PubMed (including MEDLINE) and the Cochrane Library were searched on April 15, 2020, for a predefined set of query terms relating to the management of hyperkalemia, excluding case studies and commentary or editorial publication types (Supplementary Tables 1 and 2). The eligibility criteria for the systematic literature review included RCTs, observational studies, and systematic reviews reporting outcomes expressed as changes in serum K^+ concentration or prevention of outcomes associated with hyperkalemia in patient populations of adults with or at risk of hyperkalemia (Supplementary Figure 1). In two rounds of review, the titles and abstracts of records identified through the search results were screened against the eligibility criteria by two independent reviewers, and the screen then repeated with the full-text article. Discrepancies were resolved through consensus between reviewers. Literature listed in the study by Palaka et al. (2017) and in the updated systematic review (Supplementary Table 3) was used to identify gaps in the existing evidence base and to assess the level of evidence available for recommendations being made.[4]

Recommendation Development

A panel of eight nephrology experts was convened, representing the United States, UK, and Australia, to provide a global perspective on the treatment of hyperkalemia in patients receiving maintenance hemodialysis. A modified version of the nominal group technique,[34] adapted for a virtual meeting format, was used to establish consensus among the expert panel on a range of topics relating to managing hyperkalemia in patients receiving maintenance hemodialysis.

Key topics for consensus were identified from the literature review, and a set of questions developed to gain insights on best practice across a range of local healthcare systems. The wording of the questions was refined by the lead author to cover relevant practical considerations important for each topic.

Two virtual meetings were held on July 2, 2020, and July 30, 2020. Members of the panel were sent an electronic survey before the virtual meetings to collect their responses to the set of predefined questions regarding treatment recommendations. The panel survey responses were collated and anonymized, and each unique treatment recommendation was discussed in open sessions during the two virtual meetings. In both meetings, at the end of each session, the unique response statements were presented to the panelists as an electronic poll and panel members specified which of the treatment recommendations they supported.

After the meetings, poll results were collated, and the level of consensus on each treatment recommendation was determined. The condition for consensus was set at agreement from at least 75% of the panel. Subsequently, the level of evidence and the strength of each recommendation were weighed and graded according to predefined

Table 1. Classes of Recommendation and Level of Evidence Definitions

Classes of Recommendation*	
Class I	Evidence and/or general agreement that a given treatment is beneficial, useful, effective
Class II	Conflicting evidence and/or divergence of opinion about the usefulness/ efficacy of the treatment
Class IIa	Weight of evidence or opinion is in favor of treatment usefulness/efficacy
Class IIb	Usefulness/efficacy is less well established by evidence or opinion
Class III	Evidence or general agreement that the treatment is not useful or effective and, in some cases, may be harmful
Level of Evidence*	
Level A	Data derived from multiple RCTs or meta-analyses
Level B	Data derived from a single RCT or large nonrandomized studies
Level C	Consensus of opinion of the experts and/ or small studies, retrospective studies, registries

RCT, randomized controlled trial.
*Classes of recommendation and level of evidence definitions adapted from the study by Ponikowski et al., 2016.[35]

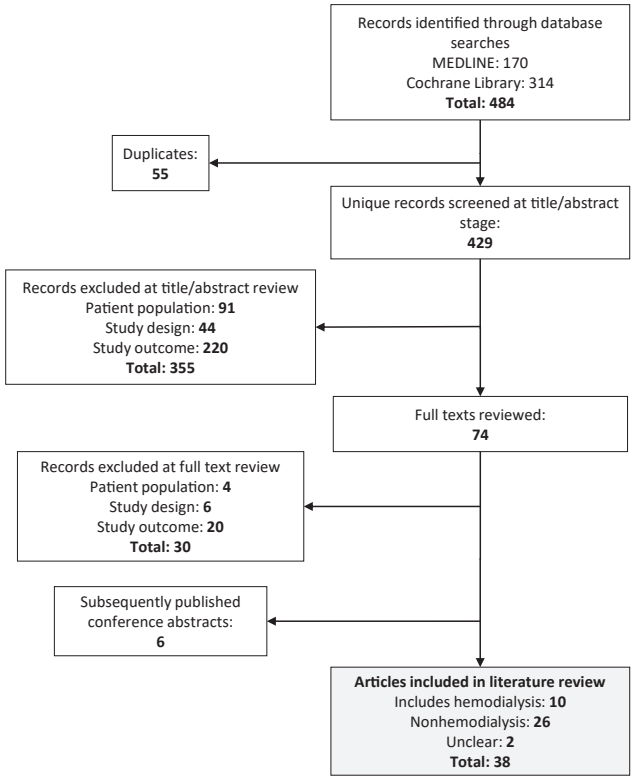

Figure 1. Flowchart for systematic literature review update.

scales (Table 1) through consultation with the relevant literature identified in the systematic literature review. The grading system used was adapted from the study by Ponikowski et al. 2016[35] and combines strength of recommendation with the level of supporting evidence.

Results and Discussion

Systematic Literature Review

The systematic literature review by Palaka et al. (2017) identified 201 publications reporting on 102 unique studies into managing hyperkalemia.[4] Most of these studies investigated short-term temporizing treatments in small cohorts, with few studies on long-term maintenance strategies or robust, high-quality published RCTs.

In our update of this systematic literature review, the initial search of MEDLINE and the Cochrane Library returned 429 unique citations (Figure 1; Supplementary Tables 1 and 2). After screening for a defined set of eligibility criteria (Supplementary Figure 1), 38 eligible records that reported interventional or observational studies of pharmacologic or nonpharmacologic management of hyperkalemia in adults were included (Supplementary Table 3). Of these, ten publications, covering nine unique studies, investigated hyperkalemia in the hemodialysis setting.

Rationale for the Treatment of Hyperkalemia in Patients Receiving Maintenance Hemodialysis

Potassium homeostasis is achieved by balancing K^+ intake from external sources, with K^+ movement from the blood into the cells, and/or K^+ excretion from the body.[36] As the kidneys are the main route of K^+ excretion, hyperkalemia is commonly reported in patients with advanced CKD, especially patients with concomitant heart failure or type 2 diabetes.[1,4,5] In patients receiving maintenance hemodialysis, dialysis serves a crucial role in restoring K^+ homeostasis through the removal of excess K^+.[4]

A serum K^+ >5.0 mmol/L has been reported as the threshold for increased risk of all-cause mortality in individuals with CKD not on dialysis, heart failure, or type 2 diabetes, with risk increasing linearly with higher serum K^+ concentrations.[37] Across a range of studies, hyperkalemia has been associated with increased risk of composite cardiovascular outcomes in patients with CKD, including those on dialysis.[38] However, evidence is limited as to what K^+ concentration constitutes a concern in patients receiving maintenance hemodialysis. No trials have yet examined the long-term cardiovascular and mortality outcomes of actively lowering K^+ concentration through intervention. The view of the panel was that there are too many unknowns and no applicable evidence for any specific group of patients with hyperkalemia, and so all treatments must be individualized (Box 1).

Box 1
Consensus Statements on the Rationale for the Treatment of Hyperkalemia in Hemodialysis

		Level of Agreement*	Class of Recommendation/Level of Evidence
1.1	K^+ is an important factor to consider in patients receiving maintenance hemodialysis because elevated serum K^+ is associated with arrhythmias, and with morbidity and mortality.	100%	I/A
1.2	In a patient with hyperkalemia, the gradient between elevated serum K^+ and dialysate K^+ concentration can cause rapid extracellular K^+ shifts. This risk is increased when the dialysate has a relatively low K^+ concentration, i.e., <2.0 mmol/L.	75%	III/C
1.3	Any serum K^+ elevation that impacts on diet, morbidity, or other aspects of patient health is problematic in patients receiving maintenance hemodialysis.	75%	IIb/C
1.4	In patients on chronic hemodialysis where dialysis was not immediately available as a treatment option for acute hyperkalemia, it would be appropriate to initiate pharmacological treatment if patient serum K^+ concentration is severely elevated (e.g., >6.0 mmol/L), or if hyperkalemia was accompanied by electrocardiogram changes.	75%	IIa/C
1.5	Initiation of pharmacological treatment for raised K^+ concentration should be individualized for each patient, as an absolute serum K^+ value that would indicate a cause for concern is not known.	75%	IIa/C

*Only statements for which at least 75% agreement was achieved have been included.

The modifiable causes of hyperkalemia will vary among patients receiving maintenance hemodialysis: some may be underdialyzed as a result of inability to attend dialysis, inadequate access, poor adherence, or inappropriate dialysis prescription; others may not be following their prescribed diet; and some may be taking medications for concomitant conditions associated with decreased K^+ excretion. There is a lack of global consensus on the ideal dialysate K^+ concentration required to balance sufficient K^+ removal with minimization of rapid lowering of K^+ during standard 3- to 4-h dialysis, particularly in patients receiving three-times-weekly dialysis treatment. The safety of low-K^+ dialysate (<2.0 mmol/L) has been a focus of concern as the rapid lowering of K^+ during dialysis may potentially provoke cardiac arrhythmias and cardiac mortality.[6,39,40] A prospective multicenter study found that patients with a high predialysis serum K^+ concentration (≥5 mmol/L) prescribed a dialysate K^+ concentration of 1 mmol/L were at higher risk of mortality than patients prescribed 2 mmol/L or 3 mmol/L dialysate.[41] In a large-scale global study, no clinically meaningful difference in mortality or arrhythmias was detected among patients on 3.0 mmol/L or 2.0 mmol/L dialysate at any level of predialysis serum K^+.[42]

Monitoring K^+ in the Hemodialysis Setting

Recommendations on the monitoring of hyperkalemia in patients with CKD are largely indirect,[1,33] and there is no evidence to inform on the ideal timing or frequency in the hemodialysis setting (Box 2). The association between elevated serum K^+ (≥5.5 mmol/L) and hospitalizations has been observed to be stronger when measurements were done on a Friday, rather than a Monday or Wednesday (for patients on a Monday-Wednesday-Friday schedule).[43] In the panelists' experience, taking measurements midweek is the most frequent practice across healthcare systems.

Monthly monitoring does not capture all changes in K^+ levels, but additional monitoring would generate more costs, increase the burden on the patient's healthcare team (especially nurses and dieticians), and could cause more stress for the patient. Healthcare professionals would need to be presented with convincing evidence for the practice of monthly monitoring to change, and comparing measurements taken at different points of the treatment cycle may create confusion.

Management of Hyperkalemia in Patients Receiving Maintenance Hemodialysis

Global Guidelines and Recommendations for Managing Hyperkalemia in Patients Receiving Maintenance Hemodialysis

Guidelines on the chronic and acute management of hyperkalemia often lack specific recommendations for patients in the hemodialysis setting. The National Kidney Foundation lists interventions for the treatment of chronic

Box 2
Consensus Statements on Monitoring K^+ in the Hemodialysis Setting

		Level of Agreement*	Class of Recommendation/Level of Evidence
2.1	Patient K^+ concentration should be monitored at least monthly in the hemodialysis setting, and it would be appropriate to measure more frequently in a patient with recurrent severe hyperkalemia.	88%	IIa/C
2.2	In most patients, it is sufficient to measure K^+ concentration before hemodialysis after the short interdialytic interval, but in some patients, it is clinically important to also measure K^+ concentration after the long interdialytic interval as this is when hyperkalemia more commonly occurs.[7]	88%	IIa/C
2.3	Patients with diabetes who receive hemodialysis may be more prone to developing hyperkalemia due to insulin resistance and impaired cellular redistribution and should be given additional consideration as to whether more frequent monitoring may be indicated.	88%	IIa/C
2.4	In patients with CKD but not yet on renal replacement therapy, hyperkalemia may indicate the need for hemodialysis initiation if control with medical measures fails to maintain normokalemia.	75%	IIb/C

*Only statements for which at least 75% agreement was achieved have been included.

and acute hyperkalemia in patients with CKD, but the only recommendation on their use in the hemodialysis setting is that sodium bicarbonate may not be efficacious for acute treatment.[44] Both the Kidney Disease: Improving Global Outcomes (KDIGO) organization and Kidney Health Australia list management strategies for treatment of hyperkalemia in patients with CKD, including dietary K^+ restriction, changes in K^+-elevating medications (e.g., RAAS inhibitors), and prescription of K^+ binders.[36,45] The 2020 Kidney Disease Outcomes Quality Initiative clinical practice guideline for nutrition in CKD recommends individualized adjustment of dietary K^+ intake for patients with CKD and dyskalemia and suggests that future research is needed into the effect of dialysate K^+ concentration on outcomes in patients receiving maintenance hemodialysis.[46] However, none of these three guidelines provide recommendations for managing hyperkalemia in patients receiving maintenance hemodialysis. In cases of severe acute hyperkalemia (serum K^+ $\geq$6.5 mmol/L) and electrocardiogram changes in patients receiving maintenance hemodialysis, the UK Renal Association recommends intravenous calcium salt to reduce risk of arrhythmias, urgent hemodialysis where available, standard treatment with insulin-glucose and salbutamol where hemodialysis is not available, or K^+ binders to reduce the risk of hyperkalemia during the interdialytic interval.[47] A recent position statement from the Italian Society of Nephrology states that inadequate dialysis, resulting from suboptimal prescription, reduced patient adherence to dialysis treatments, and/or dysfunctional vascular access, is a common risk factor for hyperkalemia in patients receiving maintenance hemodialysis. Regular assessment of dialysis efficiency and prescription plays a crucial role in managing hyperkalemia in the hemodialysis setting (Box 3).[8]

Managing Hyperkalemia Through Dietary K^+ Restrictions in Patients Receiving Maintenance Hemodialysis

It is common in most healthcare systems to assess patient diet routinely, but this is part of a general assessment of patient health and may not be specifically focused on K^+ concentration (Box 4). Most of the guidelines listed in the previous section recommend dietary K^+ restriction as one of the first steps in management of hyperkalemia; however, the benefits of this practice are not supported by rigorous RCTs.[48] A prospective multicenter cohort study of patients receiving hemodialysis has suggested that excessive dietary K^+ restriction is associated with higher mortality risk.[49] This is in contrast with an earlier study that found higher dietary K^+ intake to be associated with increased 5-year risk of mortality in patients receiving maintenance hemodialysis.[50] In a cross-sectional analysis, dietary K^+ intake was not found to be associated with serum K^+ concentration or hyperkalemia (serum K^+ $>$5.0 mmol/L) in patients receiving hemodialysis.[51] Furthermore, the targeting of high-K^+ foods is based on the assumption that all dietary K^+ is therapeutically equivalent, which is not necessarily the case.[48] Despite their higher K^+ content, a renoprotective effect of plant-rich

diets has been shown in patients with normal or near-normal kidney function, and also in patients with CKD without kidney replacement therapy.[52] The absorption of K^+ is affected by intestinal transit time, potentially explaining why diets high in fiber are less prone to causing hyperkalemia despite their higher K^+ content, and also why laxative use is associated with lower risk of hyperkalemia.[53,54] An additional factor to consider is the effect of diet on acid-base balance. While some vegetables are high in K^+, these foods are also alkalinizing, which may be another mechanism that alleviates their effect on hyperkalemia.[53] The intake of other foods such as carbohydrates during meals might also modulate the effect of dietary K^+ on serum K^+ concentration. Pilot studies have demonstrated that in a controlled environment, stimulation of insulin production through the intake of glucose can mitigate the acute rise in serum K^+ after an oral K^+ load in uremic patients.[55–57] Taken together, these studies suggest that dietary K^+ is a complex issue and that other factors may be significant contributors to hyperkalemia. Further research is needed to evaluate the extent to which different aspects of diet influence serum K^+ concentration in patients receiving hemodialysis before any firm recommendations can be made on the role of dietary modulation in the management of chronic hyperkalemia.

Further considerations when evaluating the effect of recommended dietary K^+ restriction are levels of patient adherence and patient quality of life (QoL). In patients with CKD, nonadherence to treatment, medication, and dietary recommendations ranges between 22% and 74%.[58] A recent survey reported that individuals with CKD and hyperkalemia (serum K^+ $\geq$5.3 mmol/L) who were aware of the need for dietary restrictions did not consume less K^+ than those without hyperkalemia. Despite this observation, their K^+ intake was only slightly above recommended levels.[59] It is important to encourage patients to follow a healthy diet to lower cardiovascular risk and improve QoL; however, many such diets are higher in K^+.[36] Patients receiving maintenance hemodialysis do not rank diet as a top priority,[60] but diet remains a consideration in optimizing patient QoL in the burdensome hemodialysis setting and so needs to be re-evaluated regularly and the importance of monitoring K^+ intake

Box 3
Consensus Statements on General Management of Hyperkalemia in Patients Receiving Maintenance Hemodialysis

		Level of Agreement*	Class of Recommendation/Level of Evidence
3.1	Dialysis prescription should be re-evaluated as a matter of routine after diagnosis of chronic hyperkalemia.	100%	IIa/C
3.2	Signs of poor clearance should be considered when evaluating dialysis prescription (e.g., PO_4, urea, and so on), and Kt/V or urea reduction ratio measured.	100%	IIa/C
3.3	After diagnosis of hyperkalemia in patients receiving maintenance hemodialysis at home, compliance with dialysis prescription, hours and frequency of dialysis, and vascular access should be assessed, and patients and/or caregivers educated about removal rates to maximize compliance with dialysis prescription.	75%	IIa/C
3.4	In the ongoing management of hyperkalemia in patients receiving hemodialysis at home, the type of treatment, the amount of clearance received, and the frequency of hemodialysis need to be considered.	100%	IIa/C

*Only statements for which at least 75% agreement was achieved have been included.

Box 4
Consensus Statements on Dietary K^+ Restriction in Patients Receiving Maintenance Hemodialysis

		Level of Agreement*	Class of Recommendation/Level of Evidence
4.1	A key part of dietary management is to interrogate patient diet upon diagnosis of hyperkalemia, to identify where patients have a diet high in K^+ or are ingesting a specific high-K^+ food that they can easily exclude from their diet.	88%	IIa/C
4.2	Dietary K^+ restriction is part of routine recommendations in management of hyperkalemia in patients receiving standard 3- to 4-h, three-times-weekly maintenance hemodialysis treatment.	88%	IIb/C
4.3	In the general population, a diet high in fruit and vegetables is associated with reduced cardiovascular risk, but there is a lack of evidence that this also holds true in individuals with ESKD, and high K^+ intake in such a diet increases the risk of hyperkalemia.	75%	IIb/C

*Only statements for which at least 75% agreement was achieved have been included.

reinforced to the patient. To support patient awareness of dietary K^+, resources such as handouts require regular updating to ensure that information on K^+ sources and recommendations for dietary restriction are in line with current guidelines and recent clinical trial data.[61] Socioeconomic and cultural barriers to patient adherence with dietary advice should also be considered.[52]

Reflecting on the potential to adjust patient diet after prescription of K^+ binders, the panel asserted that there is limited evidence that a low-K^+ diet is associated with reductions in serum K^+ in hemodialysis patients; there is also a lack of evidence that liberalization of K^+ restrictions is safe.[12,36] In two recent observational studies of patients on maintenance hemodialysis, one found no association between a healthy plant-based diet and serum K^+ concentration or risk of hyperkalemia, while the other found a greater consumption of fruit and vegetables to be associated with lower mortality.[62,63] However, further research is needed to evaluate the effects of unrestricted fruit and vegetable intake on the risk of hyperkalemia in patients receiving maintenance hemodialysis.[36] In most cases, K^+ binders are not prescribed to allow liberalization of diet, but rather because the patient has uncontrolled hyperkalemia despite making all reasonable management changes. The panel agreed that it is important to counsel the patient not to relax their dietary K^+ intake without first consulting with their nephrologist and other healthcare providers, as increased dietary K^+ could interfere with the purpose of the of the K^+ binder prescription. It is important to note that in the experience of the panel, many patients have difficulty adhering to prescribed low-K^+ diets.

The Influence of Hyperkalemia Risk on the Use of RAAS Inhibitors in Patients on Hemodialysis

RAAS inhibitors, including mineralocorticoid receptor antagonists, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs), are effective for treatment of hypertension and are recommended to reduce the risk of cardiovascular complications and mortality.[35,64] ACE inhibitors, β blockers, and mineralocorticoid receptor antagonists have been shown to reduce mortality in patients with heart failure with reduced ejection fraction; however, patients with severe kidney dysfunction are often excluded from RCTs of RAAS inhibitors, and so their efficacy in the setting of ESKD is less well established than in other settings (Box 5).[35] In patients receiving maintenance hemodialysis, ARBs and, to a lesser extent, ACE inhibitors appear to preserve residual renal function, and ARB therapy has been associated with cardiovascular protection and reduced risk of heart failure in this population.[10]

Despite their cardiovascular and renoprotective benefits, RAAS inhibitors are associated with increased risk of hyperkalemia; thus, dosage may be reduced or treatment stopped in patients experiencing recurrent hyperkalemia while receiving maintenance hemodialysis.[35,65,66] Although there is a lack of evidence for patients undergoing hemodialysis, in patients not on dialysis who receive RAAS inhibitor therapy, treatment with newer K^+ binders maintains normal serum K^+ concentration and reduces the risk of hyperkalemia over 1 year of follow-up.[19,24,25,29,67] Prescription of K^+ binders also increases the number of patients with hyperkalemia who remain on RAAS inhibitor therapy.[17,68]

Use of K^+ Binders to Manage Hyperkalemia in Patients Receiving Maintenance Hemodialysis

Use in the Chronic Setting

While K^+ binders can be used to treat hyperkalemia when it arises, there are numerous underlying causes of hyperkalemia that should be addressed separately from, and before, the use of K^+ binders. The panel discussed how all potential causes of hyperkalemia such as diet,

Box 5
Consensus Statements on the Influence of Hyperkalemia Risk on the Use of RAAS Inhibitors in Patients Receiving Maintenance Hemodialysis

		Level of agreement*	Class of Recommendation/Level of Evidence
5.1	The indication and dosing for RAAS inhibitor therapy should be reviewed in patients receiving maintenance hemodialysis after diagnosis of hyperkalemia.	75%	IIb/C
5.2	In patients with recurrent hyperkalemia, it is preferable to investigate diet and other factors before changing RAAS inhibitor dose.	75%	IIa/C
5.3	The need for RAAS inhibitors and/or β blockers for treatment of patients with heart failure with reduced ejection fraction receiving maintenance hemodialysis could be an indication for control of predialysis or interdialytic hyperkalemia with K^+ binders.	75%	IIa/C
5.4	More data are needed on the use of mineralocorticoid receptor antagonists (MRAs) to treat heart failure in patients with ESKD and to demonstrate the benefits of RAAS blockade in patients receiving maintenance hemodialysis before recommendations can be made on the role of K^+ binders in patients receiving maintenance hemodialysis with heart failure.	75%	IIb/C
5.5	In patients who have residual renal function, K^+ normalization with binders could allow optimal dosing of RAAS inhibitors.	88%	IIa/B
5.6	More data are needed to demonstrate optimal dosing of RAAS inhibitors in patients receiving maintenance hemodialysis.	100%	IIb/C

*Only statements for which at least 75% agreement was achieved have been included.

Box 6
Consensus Statements on the Use of K^+ Binders to Manage Hyperkalemia in Patients Receiving Maintenance Hemodialysis

		Level of Agreement*	Class of Recommendation/Level of Evidence
6.1	K^+ binders should play a role in the conservative management of hyperkalemia in ESKD.	100%	IIa/C
6.2	Prescription of K^+ binders for chronic treatment of hyperkalemia is appropriate in patients who experience frequent K^+ concentration $\geq$6.0 mmol/L during the long interdialytic interval.	75%	IIa/B
6.3	Proven efficacy, safety, tolerability, availability, and calcium versus sodium load should all be considered when selecting which K^+ binder to prescribe.	75%	IIa/C
6.4	K^+ binders should preferentially be used on nondialysis days.	75%	IIa/C
6.5	When K^+ binders are used, dialysate composition should not be changed immediately, and changes with ongoing monitoring of K^+ concentration were only considered.	88%	IIa/C
6.6	If K^+ binders are to be considered for the treatment of acute hyperkalemia, they should not be used alone but rather as part of a broader management plan.	88%	IIa/C
6.7	In cases where hemodialysis is not immediately available to treat a patient with severe hyperkalemia with electrocardiogram changes, K^+ binders could potentially form an important part of an alternative treatment strategy.	100%	IIa/C
6.8	The prescription of K^+ binders needs to be individualized, as the benefits will depend on the cause of each patient's hyperkalemia.	88%	IIa/C
6.9	Diet should not initially be adjusted after initiation of K^+-binder treatment.	75%	IIa/C
6.10	In rare cases where hyperkalemia is the single factor driving initiation of hemodialysis, K^+ binders could delay the start of renal replacement therapy.	88%	IIa/C
6.11	Prospective studies are needed to demonstrate the efficacy of using K^+ binders to allow adjustment of dialysate K^+ concentration, showing an effect on cardiovascular outcomes or arrhythmia measured by loop recorder or similar.	88%	IIa/C

*Only statements for which at least 75% agreement was achieved have been included.

dialysis prescription, dialysis clearance, and prescribed medication should be investigated and addressed as thoroughly as possible before K^+ binders are prescribed (Box 6).

In Japan, where SZC and patiromer are not yet available, CPS is often preferentially used over SPS to treat chronic hyperkalemia because of concerns over sodium overload with SPS; however, a direct comparison found that SPS was more effective than CPS in lowering serum K^+.[16] At higher doses, sodium and calcium load need to be considered when prescribing both older and newer K^+ binders.[16,69]

In the chronic treatment of hyperkalemia, both SZC and patiromer are efficacious for up to 1 year in patients not undergoing hemodialysis, with or without concurrent RAAS inhibitor therapy restrictions.[21,29,67,70] The DIALIZE trial (NCT03303521) is the only randomized clinical trial to date to evaluate newer K^+ binders in the hemodialysis setting. In patients with persistent predialysis hyperkalemia receiving in-center, three-times-weekly maintenance hemodialysis, 4-week administration of SZC resulted in 41% of patients achieving predialysis normokalemia (K^+ 3.5–5.0 mmol/L) after at least three out of four long interdialytic intervals, compared with 1% in the placebo group.[22]

Despite the available observational evidence that newer K^+ binders are effective for ongoing maintenance K^+ reduction, there is currently no evidence indicating whether this translates to reduced hospitalization rates, cardiac arrhythmia, and/or other cardiovascular events in patients receiving maintenance hemodialysis.[22] There is potential cardiovascular benefits in using K^+ binders to adjust dialysate K^+ concentration, avoiding the risks associated with baths at K^+ <2.0 mmol/L. However, prospective studies are needed to demonstrate a reduced risk of cardiovascular events or arrhythmia measured by loop recorder or similar techniques.

While the safety profiles of newer K^+ binders have been demonstrated in clinical trials,[17-30] these have not yet been fully established through widespread use in clinical practice, and no head-to-head randomized trials comparing newer versus older K^+ binders have been performed. The potential adverse effects of SPS and CPS are better known, which may lead to these being perceived as less safe than SZC and patiromer.

Use in the Acute Setting When Hemodialysis Is Not Immediately Available

The prescribing information for both SZC and patiromer states that these K^+ binders should not be used for emergency treatment of life-threatening hyperkalemia because of their delayed onset of action.[70,71] On administration of SZC (10 g), significant reduction in serum K^+ was observed within 1 hour, but median time to normokalemia was 2.2 hours, with 66% of patients achieving normokalemia in 24 hours and 88% in 48 hours.[23,72] Administration of patiromer (8.4 g) led to significant reduction in serum K^+ within 7 hours, and 80% of patients achieved normokalemia within 24 hours.[73,74]

A pilot real-world open-label evaluation of the acute use of patiromer to treat hyperkalemia in the emergency department found a reduction in serum K^+ within 2 hours, but no difference between the treatment and standard-of-care control groups at 6 hours. The authors concluded that K^+ binders are potentially useful in acute treatment of hyperkalemia, but more rigorous studies are required.[27] An evidence-based review of patiromer, SZC, and SPS for the treatment of hyperkalemia, published in 2017, found stronger evidence supporting the use of patiromer in chronic management of hyperkalemia but suggested that SZC might be the preferred agent for acute treatment owing to its more rapid onset.[2] Guidelines issued by the UK Renal Association and National Institute for Health and Care Excellence in the UK recommend the use of patiromer or SZC alongside insulin-glucose and salbutamol for acute treatment of life-threatening hyperkalemia (serum K^+ ≥6.5 mmol/L).[47] Recent clinical guidance published by KDIGO lists SZC and SPS as potential treatment options for acute hyperkalemia in the emergency department, with the use of patiromer not advised owing to its slower onset of action.[75]

The panel envisaged multiple potential scenarios in which intermittent use of K^+ binders would be beneficial, such as an episode of hyperkalemia when hemodialysis is unavailable or during the long interdialytic interval, a case in which a high serum K^+ concentration might delay life-saving surgery or other procedures, or in a patient who cannot undergo hemodialysis because of a thrombosed dialysis vascular access or reduced medical services in situations such as inclement weather periods. In a recent survey, nephrologists in the UK described how newer K^+ binders provided increased flexibility to bridge delays in dialysis schedules and reduce dialysis frequency from three times to twice weekly while access to hemodialysis units and intensive care unit beds was restricted during the Coronavirus 2019 (COVID-19) pandemic.[76] Future studies should evaluate the use of K^+ binders in urgent or life-threatening cases of hyperkalemia, to allow healthcare professionals time to treat the cause of the patient's elevated K^+ concentration. The panel expressed concern that patients may come to view it as acceptable to miss hemodialysis sessions if K^+ binders were to be routinely used to manage missed sessions.

Overview and Future Directions

A previous systematic review of clinical studies evaluating the use of K^+ binders for treatment of chronic hyperkalemia in patients with CKD concluded that the current evidence is insufficient to inform clinical care or policy decision-making in the setting of peritoneal dialysis,

hemodialysis, home-based hemodialysis, or transplantation.[3] While there is evidence that hyperkalemia (serum K^+ >5.0 mmol/L) is associated with an increased risk of adverse cardiovascular events in patients receiving maintenance hemodialysis,[38,77] the available evidence base and recommendations on how hyperkalemia should be managed in such patients are very limited. To address the gap in recommendations, this expert consensus statement was developed to provide healthcare professionals with guidance on best practice in serum K^+ monitoring, concomitant prescription of RAAS inhibitors, dietary K^+ restriction, prescription of K^+ binders, and other aspects of managing hyperkalemia in patients receiving maintenance hemodialysis.

Study Limitations

The small expert panel provided clinical expertise, and although the panel covered a range of geographical regions, recommendations may not be relevant outside of the areas of panel practice (United States, UK, Australia). A lack of published data limited the number and strength of recommendations that could be proposed and supported.

Gaps in the Evidence Base and Future Directions

A recurrent barrier throughout this consensus statement has been a lack of evidence to allow the panel to make firm recommendations on managing hyperkalemia in patients on maintenance hemodialysis. Hyperkalemia is associated with increased risk of arrhythmias and cardiac arrest and is prevalent in patients undergoing hemodialysis.[6] However, there is limited evidence on how best to manage these risks. Even at the initial stages of hyperkalemia management, there are no clear guidelines on what level of K^+ constitutes a concern, specifically in patients receiving maintenance hemodialysis, and what frequency of monitoring would most meaningfully capture fluctuations in patient serum K^+. Although healthcare professionals use multiple strategies to lower K^+ concentration in patients receiving maintenance hemodialysis, trials have not yet been conducted to examine whether hospitalization rates, cardiac arrhythmia, or other clinical outcomes are reduced when K^+ concentration is lowered through these interventions.

Reliable evidence on whether routine dietary restriction has K^+-reducing benefits in patients receiving maintenance hemodialysis would be of value to clinicians. Further research into patients' QoL priorities in managing hyperkalemia in the hemodialysis setting is also needed to help clinicians prioritize management and care approaches. For example, while there may not be an overall positive effect on K^+ concentration if binders allow patients to eat more foods high in K^+, patient QoL would be expected to improve.

While the body of evidence currently available supports the efficacy of SZC and patiromer in managing chronic hyperkalemia, evidence to support their role in the hemodialysis setting is limited.[3] To date, only one RCT has investigated newer K^+ binders in the hemodialysis setting, showing that SZC is efficacious in reducing serum K^+ concentration in patients receiving maintenance hemodialysis.[22] A prospective, randomized, open-label trial is underway to evaluate the efficacy of patiromer to reduce hyperkalemia in patients receiving maintenance hemodialysis (NCT03781089). Further clinical trials underway or being planned will address other gaps in evidence raised in this study, although few include patients undergoing hemodialysis. The PRIORITIZE HF (NCT03532009; terminated early due to COVID-19) and DIAMOND (NCT03888066) RCTs are evaluating the use of SZC and patiromer, respectively, to manage hyperkalemia in patients with heart failure and on RAAS inhibitor therapy, but both trials exclude participants undergoing hemodialysis. Two trials are planned to investigate the use of K^+ binders for the acute treatment of hyperkalemia in the emergency department setting (NCT04443608 [PLATINUM] and NCT04585542 [KBindER]), while others will evaluate the use of patiromer and SZC to transition patients with CKD and hyperkalemia to plant-rich diets (NCT03183778 and NCT04207203 [HELPFUL]) (Table 2).

Summary

This consensus statement provides treatment recommendations and suggests areas for future research that will enable healthcare professionals to effectively manage hyperkalemia and reduce the associated risks in their patients in the hemodialysis setting. The decisions made for the care of each patient will need to be individualized as treatment of hyperkalemia in patients receiving maintenance hemodialysis is complex.

Practical Application

This article is a consensus statement developed to address disparities between current international guidelines on the management of hyperkalemia in patients undergoing maintenance hemodialysis and the most recent published evidence in this field. Furthermore, we address that many aspects of hyperkalemia management in the hemodialysis setting, including dietary potassium restriction, remain poorly researched. To address the gap in recommendations, this expert consensus statement was based on a systematic review of the available evidence. However, because data in this patient population are scarce, we also seek to share our clinical experience of treating hyperkalemia in patients undergoing hemodialysis, to provide healthcare professionals with guidance on best practice in areas including serum potassium monitoring, concomitant prescription of RAAS inhibitors, dietary potassium restriction, and prescription of potassium binders.

Table 2. Clinical Trials of K^+ Binders Currently Planned or Underway

Trial	Number	Type	Drug	Description and Patient Characteristics	Hemodialysis Included?	Estimated Completion
PRIORITIZE HF	NCT03532009	Phase 2	SZC	SZC to initiate and intensify RAAS inhibitor therapy in patients with heart failure	Excluded	Terminated early owing to COVID-19
APPETIZE	NCT04566653	Observational	SZC, patiromer, SPS, CPS	Measure the palatability and preference of SZC versus patiromer versus SPS/CPS in patients with dialysis and nondialysis CKD and hyperkalemia	Included	February 2021
	NCT03781089	Phase 4	Patiromer	Patiromer to reduce the frequency of hyperkalemic episodes in patients with ESKD who receive conventional hemodialysis	Included	June 2021
	NCT03183778	Phase 4	Patiromer	Use of patiromer to maintain normokalemia in patients with CKD who are transitioned to a plant-rich diet	Excluded	June 2021
DIALIZE China	NCT04217590	Phase 3	SZC	Efficacy and safety of SZC in Chinese patients with ESKD on chronic hemodialysis	Included	October 2021
PLATINUM	NCT04443608	Phase 4	Patiromer	Use of patiromer to help lower potassium levels while patients with hyperkalemia are in the emergency department	Included, except within 6 h of study treatment protocol	October 2021
ZIRCUS	NCT04063930	Phase 4	SZC	Effect of concomitant SZC treatment on the efficacy of standard blockade of the renin-angiotensin system in patients with type 2 diabetes, diabetic nephropathy, and hyperkalemia	Excluded	December 2021
KBindER	NCT04585542	Phase 4	SPS, patiromer, SZC, polyethylene glycol 3350	Compare efficacy of three oral potassium binders on lowering blood potassium, in patients presenting to the emergency room with acute hyperkalemia	Included, except within 4 h after randomization	December 2021
DIAMOND	NCT03888066	Phase 3	Patiromer	Patiromer to reduce cardiovascular outcomes in patients developing hyperkalemia while receiving RAAS inhibitor medication for treatment of heart failure	Excluded	March 2022
HELPFUL	NCT04207203	Feasibility study	SZC	Use of SZC to maintain normokalemia in patients with CKD who are transitioned to a diet including fruits, vegetables, whole grains, nuts, white meat, fish, and eggs	Excluded	March 2022
TWOPLUS-hemodialysis	NCT03740048	Phase 3	Patiromer	Hemodialysis initiation comparing twice-weekly hemodialysis plus dialysis-sparing therapy (patiromer) versus thrice-weekly hemodialysis	Included	June 2023
RELIEHF	NCT04142788	Phase 4	Patiromer	Potential for patiromer-facilitated use of higher doses of MRAs in addition to standard care to improve congestion, well-being, and mortality in people who have worsening congestion due to heart failure and hyperkalemia	Excluded	November 2025

CKD, chronic kidney disease; CPS, calcium polystyrene sulfonate; ESKD, end-stage kidney disease; MRA, mineralocorticoid receptor antagonist; RAAS, renin-angiotensin-aldosterone system; SPS, sodium polystyrene sulfonate; SZC, sodium zirconium cyclosilicate.

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Supplementary Data

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