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Barriers to guideline mandated renin-angiotensin inhibitor use: focus on hyperkalaemia

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Hyperkalaemia in patients with chronic disease states can be caused by both abnormalities of potassium homeostasis as well as extrinsic factors such as medication use and potassium intake. In patients with heart failure (HF), chronic kidney disease (CKD), diabetes mellitus (DM), and in those who use renin-angiotensin-aldosterone system inhibitors (RAASi), there is particularly increased risk of chronic or recurrent hyperkalaemia. Hyperkalaemia is often a reason for the suboptimal dosing or complete discontinuation of RAASi. This review presents current options for the management of hyperkalaemia in patients with chronic disease states. It also explores barriers to guideline-mediated RAASi prescribing patterns in these high-risk patients and highlights the unmet need for agents that adequately manage hyperkalaemia in patients with chronic diseases on concomitant RAASi therapy.

Introduction

Hyperkalaemia, one of the most feared electrolyte abnormalities, can lead to a range of pathophysiological disturbances including muscle weakness and cardiac arrhythmias. Hyperkalaemia has become increasingly recognized as an independent predictor of harm.[1,2] This risk is further heightened by comorbid heart failure (HF), chronic kidney disease (CKD), diabetes mellitus (DM), and use of renin–angiotensin–aldosterone system inhibitors (RAASi) in these conditions.[3-6] RAASi encompass a large class of drugs, including angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors (ARNi), and mineralocorticoid receptor antagonists (MRAs).

It should be noted that the major risk factors for development of hyperkalaemia are an estimated glomerular filtration rate (eGFR) $<$45 mL/min/1.73 m^2 and/or a serum potassium level on appropriate diuretics for kidney function of $>$4.5 mmol/L.[7] Thus, in these settings, hyperkalaemia is a common complication of RAASi therapy and is often a reason for their discontinuation or suboptimal dosing.[6,8] However, these agents offer a proven mortality benefit, slow progression of kidney disease, and decrease risk of hospitalization in people with HF.[5,9] With the current limitations for management of hyperkalaemia, there is a substantial gap between recommendations in treatment guidelines and everyday prescribing patterns for RAASi, given that the patients who would gain the greatest cardiovascular and renal benefit from these therapies are at the highest risk of developing hyperkalaemia.[10,11] The fact that many clinical trials have specifically excluded high-risk patients (such as those with Stage 3b or higher CKD) furthers this therapeutic dilemma.[12]

Regulation of potassium homeostasis and renal handling of potassium

Despite wide variations in potassium intake (~40–200 mmol/day), this cation is strictly regulated by the kidney and maintained such that 98% remains

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intracellular (~140 mmol/L) and only 2% extracellular (~3.5-5.0 mmol/L).[13,14] Such tight control of potassium levels is essential for life. Potassium homeostasis is regulated through a complex network of intracellular/extracellular shifts, with long-term homeostasis where 90% is handled by the kidney and 10% by the distal colon. In the glomerulus, potassium is readily filtered, and the majority of filtered potassium, about 90%, is reabsorbed in the proximal tubule/loop of Henle.[15] The remaining 10% reaches the distal tubule and is secreted in the collecting duct. Potassium secretion is largely influenced by aldosterone, which, in turn, is mediated by the renin-angiotensin system and serum potassium levels.[14]

Abnormalities of potassium homeostasis in chronic disease states

Failure to modulate potassium homeostasis occurs when this fine balance between potassium intake and removal is disrupted. This abnormal modulation is most commonly seen when eGFR is <45 mL/min/1.73 m^2 or if other metabolic issues generally related to diabetes are present. Hyperkalaemia has been typically defined as serum potassium level >5.2 mmol/L. However, recent data from very large databases demonstrate that among those with CKD, HF, and DM, the upper limit should be 4.8 mmol/L as mortality increases above this level.[2] Hyperkalaemia homeostasis is driven by various mechanisms including excess dietary intake of potassium, potassium redistribution in the body (including hyperglycaemic, insulin resistant, or acidotic states), and reduced potassium excretion (due to impaired renal function, RAASi, and HF).[14,16-19]

In CKD, the ability of the kidneys to excrete potassium is significantly compromised as the eGFR decreases.[20] Patients with CKD face increased comorbidity burden including DM, HF, metabolic acidosis, and anaemia requiring blood transfusion, which further exacerbate hyperkalaemia.[21] In DM, hyperglycaemia related to insulin resistance is associated with an altered ability to adequately shift potassium into intracellular space in large part to due to acidosis.[22]

In HF, the relationship between serum aldosterone concentration and sodium delivery to the distal tubules is altered such that the standard inverse relationship is no longer seen, and increased aldosterone in patients with HF causes increased absorption of sodium in proximal tubules (thus decreased amounts reaching the distal tubules), which results in decreased potassium excretion. In addition to this development of aldosterone resistance, medications including RAASi decrease aldosterone secretion, and therefore, can potentiate the already increased risk of hyperkalaemia in patients with HF.[21]

Renin-angiotensin-aldosterone system inhibitors, chronic disease states, and hyperkalaemia risk

Therapy with RAASi reduces all-cause mortality by 15–30% in patients with chronic heart failure with reduced ejection fraction (HFrEF), rendering them a fundamental component of HFrEF treatment.[23,24] Due to this, they have a Class I recommendation for use in this high-risk population.[24,25] However, in everyday practice, although use of ACEi and ARBs remains acceptable, the dosing and maintenance of these therapies is poor, with only approximately 25–45% of patients reaching target dosing and upwards of 10% of patients stopping therapy altogether.[26,27] MRAs, particularly, are notoriously underutilized in patients with HFrEF, with studies showing approximately 50% overall adherence.[26,28,29] Non-adherence to therapy has been largely attributed to hyperkalaemia and renal dysfunction.[27] In both inpatient and outpatient settings, studies have shown that 10–38% of hospitalized patients on an ACEi developed hyperkalaemia during hospitalization and 10% of patients prescribed an ACEi developed severe hyperkalaemia (serum potassium >6.0 mmol/L) within 1 year of follow-up.[30-32] This risk is even more significant in HF patients with concomitant CKD and DM.[2,3,33-35] Even in the absence of comorbid diseases, the Prospective Comparison of ARNI (Angiotensin Receptor-Neprilysin Inhibitor) with ACEI (Angiotensin-Converting-Enzyme Inhibitor) to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial showed that approximately 15% of patients in both ARNi and ACEi arms developed hyperkalaemia irrespective of kidney function.[36] Furthermore, given the intersection between HFrEF and comorbid CKD, RAASi therapies are often being used in patients with at least some degree of renal dysfunction.[37] Even in randomized controlled trials, approximately 33% of enrolled patients had mild CKD (Stages 1–2), and 30–35% of patients had CKD Stage 3.[38]

The prevalence of CKD in patients with HF increases with increasing age.[38] However, most randomized clinical trials evaluating RAASi in HF patients excluded patients with advanced CKD (eGFR <30 mL/min/1.73 m^2) and those with baseline hyperkalaemia (serum potassium >5.0–5.2 mmol/L).[38] Subsequently, current European Society of Cardiology (ESC) guidelines for ACEi, ARB, ARNi recommend dose reduction in patients in patients with eGFR <25 mL/min/1.73 m^2 or serum potassium >5.0 mmol/L, and dose discontinuation in patients with eGFR <20 mL/min/1.73 m^2 or serum potassium >5.5 mmol/L.[39]

With MRA use in particular, secondary analyses of the Randomized Aldactone Evaluation Study (RALES) and the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trials showed that MRAs maintained their benefits for serum potassium levels of at least up to 5.5 mmol/L, suggesting that perhaps the benefits of MRA therapy outweigh risks of hyperkalaemia.[40,41] These trials have provided strong data that led to guideline changes. The current ESC guidelines recommend dose reduction in patients with eGFR <30 mL/min/1.73 m^2 or serum potassium >5.5 mmol/L, and dose discontinuation in patients with eGFR <20 mL/min/1.73 m^2 or serum potassium >6.0 mmol/L.[39] However, subsequent observational data demonstrate a U-shaped relationship between potassium levels and mortality, showing a higher risk of mortality with serum potassium levels >5 mmol/L across many groups of patients with varied comorbidities.[1,2,42] Given increasing observational data highlighting the risks of hyperkalaemia, there is a growing discrepancy between current guidelines and evidence and an increasing need to more adequately manage hyperkalaemia once it develops.[43,44]

Table 1 Acute and chronic treatment options for management of hyperkalaemia organized by level of acuity and clinical setting

Acuity		Therapies	Goal	Limitations
Inpatient	Acute	Calcium gluconate	Membrane stabilization	Temporizing measure and no reduction of total K+
		Insulin-dextrose	K+ intracellular shift	Temporizing measure, no reduction of total K+, and risk of hypoglycaemia
		Beta-2 receptor agonists	K+ intracellular shift	Temporizing measure and no reduction of total K+
	Subacute	Sodium bicarbonate	K+ intracellular shift, urinary K+ excretion	No significant short-term effect and risk of alkalosis
Outpatient		Loop/thiazide diuretics	Urinary K+ excretion	Risk of volume contraction and WRF
		Dialysis	K+ elimination	Safety concerns of cardiac arrhythmias and sudden cardiac death
	Chronic	Diet modification	Reduce K+ intake	Difficult to remain compliant and contradicts DASH diet
		Medication adjustment	Prevent drug-induced hyperkalaemia	Stopping RAASi therapy results in poorer outcomes
		Potassium binders (SPS)	K+ elimination	Unclear efficacy, results in sodium retention and dangerous side effects including colonic necrosis

DASH, dietary approaches to stop hypertension; K+, potassium; RAASi, renin-angiotensin-aldosterone system inhibitors; SPS, sodium polystyrene sulfonate; WRF, worsening renal function.

Current approach to management

The management of chronic hyperkalaemia can be difficult, and current options for management are largely limited to acute, inpatient situations. Longer-term solutions for management of patients at risk for recurrent hyperkalaemia focus on identifying the underlying pathophysiology of hyperkalaemia and restoring potassium homeostasis by eliminating aggravating factors. This is achieved through dietary modification, i.e. reducing high potassium foods,[45,46] chronic diuretic administration appropriate for kidney function, and up-titration (especially in patients with comorbid HF). Additionally, it is also achieved by dose reduction or discontinuation of culprit medications that play a role in impairing renal potassium excretion, including RAASi, non-steroidal anti-inflammatory agents, and heparin.[47]

Patients with hyperkalaemia in an acute setting can present with vague symptoms including weakness, nausea, chest pain, dyspnoea, and paralysis.[48] However, most patients are asymptomatic. Electrocardiographic changes seen can include 'peaked' T-waves (representing increased repolarization rate), widened PR or QRS intervals (representing conduction delay), progressive P-wave flattening and subsequent absence, and eventual presence of a 'sine wave' pattern.[49,50] Electrocardiograms (ECGs) remain insensitive markers of the severity of hyperkalaemia.[49]

Given that hyperkalaemia can have lethal consequences with mortality rates of over 30% if left untreated,[48] the immediate management of an acute or severe electrolyte disturbance focuses on stabilizing myocardial conduction in an effort to prevent cardiac excitability and instability and reduce arrhythmogenicity. Following this immediate stabilization, the next step in acute management is redistribution of potassium from extracellular to intracellular compartments to avoid the immediate consequences of elevated serum potassium levels. Subsequent care focuses on excretion of excess potassium from the body and limiting intake.[51] The various treatments used for management of hyperkalaemia, organized by acuity and clinical setting, are outlined in *Table 1*.

Acute treatment options

Acute management of hyperkalaemia focuses on the immediate and abrupt lowering of extracellular potassium to prevent life-threatening complications. These are largely temporizing measures. They can be further categorized by their onset of action, ranging from immediate to minutes to hours.

Onset of action

Immediate (3 min). Calcium gluconate. Calcium serves as an antagonist to the effect of potassium on myocardial cell membranes.[52] It is recommended as an immediate therapy in the presence of ECG changes and/or serum potassium >7.0 mmol/L.[44] It acts rapidly and lasts only 30-60 min. ECG monitoring is advised, and it can be re-administered if no changes or adverse effects are observed.[53]

Within Minutes (30 min). Insulin-dextrose. Insulin works to redistribute potassium into intracellular compartments, thereby quickly reducing the extracellular levels of potassium, with dextrose co-administered to minimize risk of hypoglycaemia.[54] This therapy works within 15–30 min and lasts for 4–6 h.[55]

Beta-2 receptor agonists. Beta-2 receptor agonists also work as a temporizing measure to promptly shift potassium into cells and lower serum potassium levels. This therapy works within 30 min, but lasts only for about 2-4 h.[54]

Within hours (subacute). Sodium bicarbonate. In certain populations (i.e. in patients who have hyperkalaemia as a result of metabolic acidosis), prolonged administration of bicarbonate (1–2 h) promotes potassium redistribution to intracellular space and has also been shown to enhance urinary potassium excretion, which occurs due to urine alkalinization.[56] However, bicarbonate therapy is controversial, as short-term treatment with bicarbonate infusion did not demonstrate significant short-term effect.[55]

Loop diuretics. Loop diuretics (i.e. intravenous furosemide) have variable onset of action (varies with onset of diuresis) and work to both enhance kaliuresis and control volume overload. In an acute setting, diuretics are administered intravenously, and fluid requirements and renal function are closely monitored. Since diuretics work to remove excess potassium from the body, they can also be used orally in chronic management of hyperkalaemia, but prolonged use can lead to volume contraction, precipitate worsening renal function, and cause diuretic resistance, making them a suboptimal choice.[55]

Dialysis. In patients with advanced Stage 5 kidney disease (eGFR $<$15 mL/min/1.73 m^2) or patients with very high potassium values (i.e. $>$6.0 mmol/L) who have ECG changes or other symptoms who have failed to adequately reduce potassium or alleviate symptoms with conventional approaches, dialysis is the most reliable therapeutic option. The onset of action is within 15–20 min after initiation, with hemodialysis removing potassium at a significantly faster rate than peritoneal dialysis.[57] The amount of potassium removed with dialysis is highly variable and depends on many factors, hence cannot always be predicted.[58] Additionally, there are some safety concerns raised as to whether fast removal of potassium by a very low potassium bath during dialysis can lead to cardiac arrhythmias or sudden cardiac death.[55,59,60]

Chronic treatment options

In contrast to short-term goals of serum potassium stabilization, the goal of chronic management of hyperkalaemia is preventing recurrent hyperkalaemia in high-risk patients and enabling use of RAASi in diseases that mandate their use. This is achieved through correction of imbalances in potassium homeostasis, which often occur in chronic disease states, and identification/correction of modifiable causes of hyperkalaemia. Options include dietary potassium restriction, reducing doses, or discontinuing medications that affect renal handling of potassium (i.e. RAASi), prolonged diuretic therapy, and use of novel potassium binders.

Dietary management

A diet rich in potassium can contribute to hyperkalaemia, particularly in the setting of impaired renal excretion of potassium. In patients with advanced CKD (Stage 3 or higher, with eGFR $<$60 mL/min per 1.73 m^2), current guidelines recommend restriction of dietary potassium to $<$2.4 g/day and discontinuation of salt substitutes including potassium chloride.[61] There are no specific guidelines in dietary management of hyperkalaemia in other high-risk groups including those with HF and DM. Certain fruits (such as bananas, melons, oranges, grapefruit, and mangos), vegetables (such as Brussels sprouts, kale, spinach, potatoes, and avocadoes), meats, nuts, and yogurt have especially high potassium content and should be restricted in patients at high risk for recurrent hyperkalaemia.[62] Certain herbal supplements and remedies can also contain high levels of potassium, which can precipitate hyperkalaemia, and patients should be counselled regarding such supplements.[63] Healthcare providers may not always recognize all foods rich in potassium.[62] Therefore, patients may benefit from referral to a dietician to discuss avoiding or limiting intake of high potassium food products. Dietary modification has been shown in animal studies to manage even severe hyperkalaemia.[64,65] However, patient adherence to such a restrictive diet may be questionable. It is also important to note that dietary potassium restriction can contradict the recommendations of a healthy cardiovascular diet, such as the Dietary Approaches to Stop Hypertension (DASH) diet.[62]

Medication reconciliation

Drug-induced hyperkalaemia is one of the most frequent causes of hyperkalaemia.[66] One of the first steps taken by providers in the management of hyperkalaemia is dose reduction or discontinuation of medications that induce it. One of the most commonly used and clinically significant medications in this realm include RAASi. Discontinuing these medications or down-titrating their doses may improve chronic hyperkalaemia; however, the consequences resulting in increased mortality of certain diseases is a concern.[11] A gap between guideline-based recommendations for initiation/optimization of RAASi therapy and actual prescription patterns is already present.[28]

Common barriers to prescription and maintenance of RAASi therapy include hyperkalaemia. In a retrospective review of 279 patients with advanced CKD (Stages 3–5), hyperkalaemia was cited as the main reason for discontinuation of RAASi therapy (34 patients, 66.6%).[8] In another database analysis of 205 108 patients over the age of five and with at least two serum potassium readings found that in patients on RAASi therapy who experienced a hyperkalaemia event, RAASi were reduced to suboptimal dose or discontinued 47% of the time with a moderate-severe hyperkalaemia event (serum potassium $\geq$5.5 mmol/L) and 38% of the time with a mild hyperkalaemia event (serum potassium 5.1–5.4 mmol/L). Furthermore, this analysis found those with reduced dosing or discontinuation of RAASi had worse outcomes than those on optimized therapy.[11] Unfortunately, hyperkalaemia with concomitant use of RAASi poses a challenge, since the patients who would benefit most from their effects are the ones at highest risk of adverse events.

Close surveillance of serum potassium levels is recommended for all patients on ACEi, ARB, or MRA therapy. When first initiating therapy, current guidelines recommend surveillance of potassium and creatinine levels within 3 days, 1 week and every month for the first 3 months of therapy and every 3 months thereafter.[10] Subsequently, if any change is made to dosing, current recommendations are to monitor serum potassium and creatinine levels within 1 week of the change and regularly thereafter (i.e. every 3–6 months). Initiation of therapy is only recommended in patients with serum potassium $<$5 mmol/L and eGFR $\geq$30 mL/min/1.73 m^2. Subsequent dose reduction or discontinuation is recommended for serum potassium >5.5 mmol/L.[10] Close surveillance of potassium levels has been associated with fewer serious hyperkalaemia-associated adverse events compared with patients who did not receive close monitoring.[67]

Other medications that have been associated with precipitating hyperkalaemia include non-steroidal anti-inflammatory agents, trimethoprim, pentamidine, azole antifungals, and heparin. These agents should be discontinued or prescribed at decreased dose in the setting of a hyperkalaemia event.[68]

Additional measures/correction of other causes of hyperkalaemia

In specific patients with identified aldosterone deficiency, fludrocortisone acetate can be an effective therapy to prevent recurrent hyperkalaemia. Fludrocortisone has also been shown to have some efficacy in tacrolimus-induced hyperkalaemia and heparin-induced hyperkalaemia.[69,70] Other studies showed no clinically significant decrease in potassium levels with use of fludrocortisone in end-stage renal disease patients on maintenance hemodialysis therapy.[71,72] Furthermore, fludrocortisone is associated with detrimental side effects including sodium retention, oedema, and hypertension.

In certain cohorts with hyperkalaemia resulting from metabolic acidosis, sodium bicarbonate can be considered as an intermediate to long-term therapeutic option. Additionally, loop/thiazide diuretic combinations can be considered as an option, but the association between prolonged use and worsening renal function and volume contraction limit their potential for long-term use for hyperkalaemia management.[55]

Potassium binders

A detailed analysis and review of novel potassium binders is presented elsewhere.[62] These agents should be used if the above measures are unsuccessful. Until recently, sodium polystyrene sulfonate (SPS) was the only treatment for management of hyperkalaemia approved by the US Food and Drug Administration (FDA).[68] SPS, initially approved for hyperkalaemia management in 1958, is an ion-exchange resin that exchanges sodium for potassium in the colon, thereby increasing faecal elimination of potassium. The onset of action for this agent is several hours after administration. Treatment with SPS has been the mainstay of chronic hyperkalaemia management for the past five decades.

In the past, SPS was administered with sorbitol (a laxative) due to the propensity of SPS to cause constipation.[73] There are major concerns over the years regarding the safety profile of SPS. Multiple reports surfaced demonstrating increased association of SPS with serious gastrointestinal events including colonic necrosis. Sorbitol has been believed to be the contributing factor to this colonic necrosis, prompting the FDA in 2009 to change their safety labelling of this agent and mandate a reformulation of manufacturers' premixed SPS resin to lower sorbitol content.[74] In addition to these detrimental side effects, the efficacy of SPS in treatment of hyperkalaemia has not been well-characterized.[74] Furthermore, SPS promotes increased sodium levels in the body, which would not be ideal in patients with HF, volume overload, or hypertension.[75] Due to such significant limitations, SPS has not been a feasible selection for routine, long-term management of hyperkalaemia in patients with chronic diseases.

Novel potassium binding agents, including patiromer and sodium zirconium cyclosilicate, have been approved by the Food and Drug Administration (FDA) for treatment of hyperkalaemia.[68] Patiromer is a calcium binding resin that has shown very good chronic tolerability of RAASi in HF and CKD.[76] In the AMETHYST-DN trial, patients with DM2, CKD, and hyperkalaemia with baseline serum potassium >5.0-5.5 mmol/L (mild) or >5.5 to <6.0 mmol/L (moderate) with or without HF on ACEi/ARB, were randomized to patiromer, divided twice daily.[76,77] Overall, 105/304 (35%) patients had HF (of which 75% had New York Heart Association Class II HF), with mean ejection fraction (EF) 44.9% (standard deviation 8.2) ($n = 81$). Twenty-six patients had EF ≤40%. In HF patients, mean serum potassium decreased by Day 3 through Week 52. At 1 month, mean serum potassium was reduced by 0.64 mmol/L in mild and 0.97 mmol/L in moderate hyperkalaemia (both $P < 0.0001$). Most HF patients with mild (>88%) and moderate (≥73%) hyperkalaemia had normokalaemia at each visit from weeks 12 to 52. The most common patiromer-related adverse event was hypomagnesaemia, with a reduction in serum magnesium of 0.16 mEq/L (8.6%).[77] In the Phase 3 OPAL-HK study, the use of patiromer was examined in older patients on RAASi required for CKD and HF.[78] In this study, patiromer reduced recurrent hyperkalaemia and was well-tolerated in older CKD patients taking RAASi.[78]

Thus, data is emerging in this high-risk subgroup of the newer better-tolerated binders as 'enablers' of RAASi therapy. However, the long-term clinical efficacy of these novel agents for treatment of hyperkalaemia in the setting of RAASi use and mortality outcomes has not yet been evaluated.[79]

A second agent very recently approved in 2018 for hyperkalaemia management sodium zirconium cyclosilicate. Sodium zirconium cyclosilicate (SZC) is an inorganic polymer which selectively attracts potassium ions to its negatively charged crystalline lattice structure and exchanges potassium for sodium and hydrogen.[62] It is formulated as a free-flowing, insoluble powder that is not absorbed systemically.

Clinical trials have been performed with this agent by Packham *et al.*[80] who conducted a 2-phase study of SZC in patients with serum potassium of 5.0–6.5 mmol/L. Patients on dialysis were excluded, but no requirements for eGFR or RAASi use were specified. Patients were randomized to double-blind SZC (1.25 g, 2.5 g, 5 g, or 10 g three times daily) or placebo for 48 h. Patients in the SZC group whose serum potassium was 3.5–4.9 mmol/L at 48 h were randomized to either continue their current SZC dose once daily or placebo for 12 days. The primary endpoint of the initial phase was the between-group difference in the exponential rate of change in mean serum potassium for 48 h, and the maintenance phase primary endpoint was the between-group difference in mean serum potassium level during the 12-day treatment interval. A total of 754 patients entered the initial phase, and 543 patients continued to the 12-day maintenance phase. The population reflected patients with risk factors for hyperkalaemia, including CKD (61%), HF (42%), DM2 (61%), and RAASi use (64%). The mean rate of change (decrease) in serum potassium from baseline was greater for the SZC 2.5 g, 5 g, and 10 g groups compared with placebo ($P < 0.001$), and normokalaemia was reached within 48 h for all these dosing groups compared with placebo ($P < 0.001$).[80] During the maintenance phase, normokalaemia was maintained in the SZC 5 g and 10 g dosing groups compared with patients who were subsequently randomized to placebo. Recurrent hyperkalaemia was observed within 1 week among patients treated with SZC 10 g who discontinued the study drug at the end of the study.[16] Gastrointestinal side effects were the most commonly reported adverse events in both the initial treatment and maintenance phases. Hypokalaemia, with serum potassium <3.5 mmol/L, was reported in two SZC patients, one at the 2.5-g dose (maintenance), and one at the 10-g dose (initial treatment).[80] A dose-dependent increase in serum bicarbonate was observed. There were no reports of hypomagnesaemia.

The Hyperkalaemia Randomized Intervention Multidose SZC Maintenance (HARMONIZE) study was a randomized, double-blind, placebo-controlled trial in patients with serum potassium of ≥5.1 mmol/L.[81] Patients were treated with SZC 10 g three times daily for 48 h during an open-label initial phase, and patients who achieved serum potassium 3.5–5.0 mmol/L were randomized to double-blind SZC (5 g, 10 g, or 15 g) or placebo for 28 days. The primary endpoint was the comparison of mean serum potassium levels between placebo and SZC from days 8 to 29. A total of 258 patients entered the open-label phase, and 237 were randomized into the maintenance phase. The mean baseline serum potassium was 5.6 mmol/L, mean eGFR was 46 mL/min per 1.73 m^2, with 69% of patients with eGFR <60 mL/min per 1.73 m^2. CKD was present in 66%, 36% had HF, 66% had DM2, and 70% were treated with ≥1 RAASi. SZC reduced serum potassium from baseline at 48 h (−1.1 mmol/L, 95% confidence interval −1.1 to −1.0; $P < 0.001$), and normokalaemia (serum potassium 3.5–5.0 mmol/L) was achieved in 84% and 98% within 24 and 48 h, respectively. The median time to normokalaemia was 2.2 h. During the maintenance phase, mean serum potassium was lower in all the SZC groups compared with placebo ($P < 0.001$). SZC was well tolerated. Gastrointestinal side effects were reported, but they did not differ between the placebo and SZC groups (14% placebo, 7% 5 g, 2% 10 g, and 9% 15 g). During the maintenance phase, oedema was reported in 2.4% of the placebo group and 2.2%, 5.9%, and 14.3% of the 5 g, 10 g, and 15 g dosing groups, respectively. Serum potassium of <3.5 mmol/L was observed in 10% of patients in the SZC 10 g group and 11% of patients in the SZC 15 g group vs. no cases in the 5 g or placebo groups. No clinically significant changes in serum magnesium or phosphate were observed.[81]

Future direction

The burden of hyperkalaemia has been increasingly recognized, especially in high-risk groups such as patients with CKD, HF, and DM and patients on RAASi therapy. We now have agents, such as potassium binders, that enable the use of RAASi in high-risk groups. We already provide evidence for use of these agents in such groups to take guideline RAASi meds and with no issues related to hyperkalaemia. Future trials need to focus on use of these agents to see if outcomes can change in Stages 4 and 5 CKD or advanced HF.

The management of hyperkalaemia that develops in patients on RAASi often involves discontinuing or reducing doses of these drugs. Fear of this adverse side effect prevents adherence to guideline-recommended prescription of RAASi therapy in patients who would gain most benefit from these agents. These new agents will help long-term management of hyperkalaemia that SPS, because of tolerability issues, has been unable to achieve. Thus, there is a significant, unmet need for novel therapeutic agents for long-term management of hyperkalaemia in patients with chronic diseases on concomitant RAASi therapy.

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