The Burden of Hyperkalemia in Patients With Cardiovascular and Renal Disease

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Hyperkalemia: Mechanisms, Patient Populations at Risk, and Prevalence

Potassium is an essential dietary mineral that is the main intracellular cation required for the maintenance of cell membrane potential, ion and solute transport, and the regulation of cell volume. Hyperkalemia is a potentially life-threatening condition that is defined as a serum potassium level above a reference range, usually greater than 5.0 mEq/L; severe hyperkalemia is often defined as a level greater than 6.0 mEq/L.[1] Elevation of plasma potassium concentration decreases the ratio of intracellular to extracellular potassium, leading to partial depolarization of the cell membrane. These physiologic effects of hyperkalemia can result in muscle weakness, paralysis, life-threatening effects on cardiac conduction (eg, QRS widening), arrhythmias such as ventricular fibrillation, and sudden death.[2,3]

Hyperkalemia can be caused by an abnormal net release of potassium from cells, often due to trauma, metabolic acidosis, hemolytic states, or other cell degradations, usually in the setting of suboptimal kidney function. If not treated rapidly, the mortality rate for patients with severe hyperkalemia can be over 30%.[4] Hyperkalemia may also result from impaired distribution between the intracellular and extracellular spaces due to other causes, as well as increased potassium intake, reduced renal excretion, or a combination of several of these factors.[5]

Those at greatest risk for hyperkalemia are persons older than 65 years who have an advanced stage of chronic kidney disease (CKD) (ie, stage 3-5), chronic heart failure (CHF), and/or diabetes and/or are taking medications known to increase serum potassium levels, notably inhibitors of the renin-angiotensin-aldosterone system (RAAS).[1,5-9] In patients with diabetes, the presence of a constellation of multiple risk factors that interfere with potassium excretion—including hyporeninemic hypoaldosteronism, and renal tubular acidosis type IV—

Abstract

Hyperkalemia is a potentially serious condition that can result in life-threatening cardiac arrhythmias and is associated with an increased mortality risk. Patients older than 65 years who have an advanced stage of chronic kidney disease (stage 3 or higher), diabetes, and/or chronic heart failure are at higher risk for hyperkalemia. To reduce disease progression and improve outcomes in these groups of patients, modulation of the renin-angiotensin-aldosterone system (RAAS) is recommended by guidelines. One limiting factor of RAAS inhibitors at proven doses is the increased risk for hyperkalemia associated with their use. Although there are effective therapeutic options for the short-term, acute management of hyperkalemia, the available strategies for chronic control of high potassium levels have limited effectiveness. The management of high potassium in the long term often requires withdrawing or reducing the doses of drugs proven to reduce cardiovascular and renal outcomes (eg, RAAS inhibitors) or implementing excessive and often intolerable dietary restrictions. Furthermore, withholding RAAS inhibitors may lead to incremental healthcare costs associated with poor outcomes, such as end-stage renal disease, hospitalizations due to cardiovascular causes, and cardiovascular mortality. As such, there is an important unmet need for novel therapeutic options for the chronic management of patients at risk for hyperkalemia. Potential therapies in development may change the treatment landscape in the near future.

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explains why the incidence of hyperkalemia is higher than in the general population.[10]

CKD is the most common risk factor for hyperkalemia due to the intrinsic pathophysiological effects of kidney dysfunction on potassium homeostasis and the superimposing cluster of cardiometabolic comorbidities—and their associated treatments—that frequently are present in patients with CKD.[5] As the number and severity of comorbidities increase and further decline in renal function ensues, the prevalence of hyperkalemia and the number of recurrent episodes increases.

Although the incidence and prevalence of hyperkalemia in the general population is unknown, some studies in hospitalized patients have reported incidence rates between 1 and 10 per 100 patients.[11] In a Canadian retrospective population-based study, 2.6% of patients 66 years and older who presented to the emergency department were hyperkalemic, defined as a serum potassium level greater than 5.5 mEq/L.[12] Some retrospective US analyses have reported incidences between 2.5% and 3.2% in populations with diverse risk factors.[9,13] Among those risk factors, the presence of CKD is significantly associated with higher frequencies of hyperkalemia, depending on the studied population and on the definition of hyperkalemia.[9]

Among the medications that can cause hyperkalemia, the most relevant in clinical practice are RAAS inhibitors because while they have been shown to confer mortality and morbidity benefits in patients with CKD, diabetes, and cardiovascular disease (CVD),[14-17] the development of hyperkalemia frequently hinders their utilization at optimal doses for chronic cardiorenal protection.[18] The interaction between the presence of CKD and the administration of RAAS inhibitors is highlighted by data from clinical trials showing how the incidence of hyperkalemia associated with RAAS inhibitors increases from less than 2% in patients without CKD to between 5% and 10% with dual inhibition of the RAAS in patients with CKD.[19]

Because randomized clinical trials typically exclude individuals with advanced cardiorenal comorbidities and the patients included in these trials are carefully monitored, reports from randomized clinical trials may underestimate the true burden of hyperkalemia, which is probably much higher in routine clinical practice. For instance, a study at a Veterans Administration clinic revealed that 11% of outpatients prescribed angiotensin-converting enzyme (ACE) inhibitors developed hyperkalemia over the 2-year study period.[20] In addition, whereas the Randomized Aldactone Evaluation (RALES) study[17] in patients with heart failure (HF) and serum creatinine less than 2.5 mg/dL reported only a 2% rate of hyperkalemia, subsequent analyses in unselected patients treated with ACE inhibitors who had recently been hospitalized for HF showed a significant increase in hyperkalemia-related hospitalizations and deaths.[21] This correlated with an increase in the prescription rate for spironolactone used in addition to ACE inhibitors following the publication of the RALES study.[21] Bozkurt et al documented that 24% of patients with HF treated with spironolactone in clinical practice developed a serum potassium level greater than 5.2 mEq/L; of these, 12% had a serum potassium level greater than 6.0 mEq/L.[22] Shah et al reported that hyperkalemia developed in 35% of patients with HF also treated with spironolactone and who had a baseline creatinine of 1.5 mg/dL or greater; and in 63% with a baseline creatinine of 2.5 mg/dL or greater, punctuating the clear trend toward increased hyperkalemia risk with declining kidney function.[23]

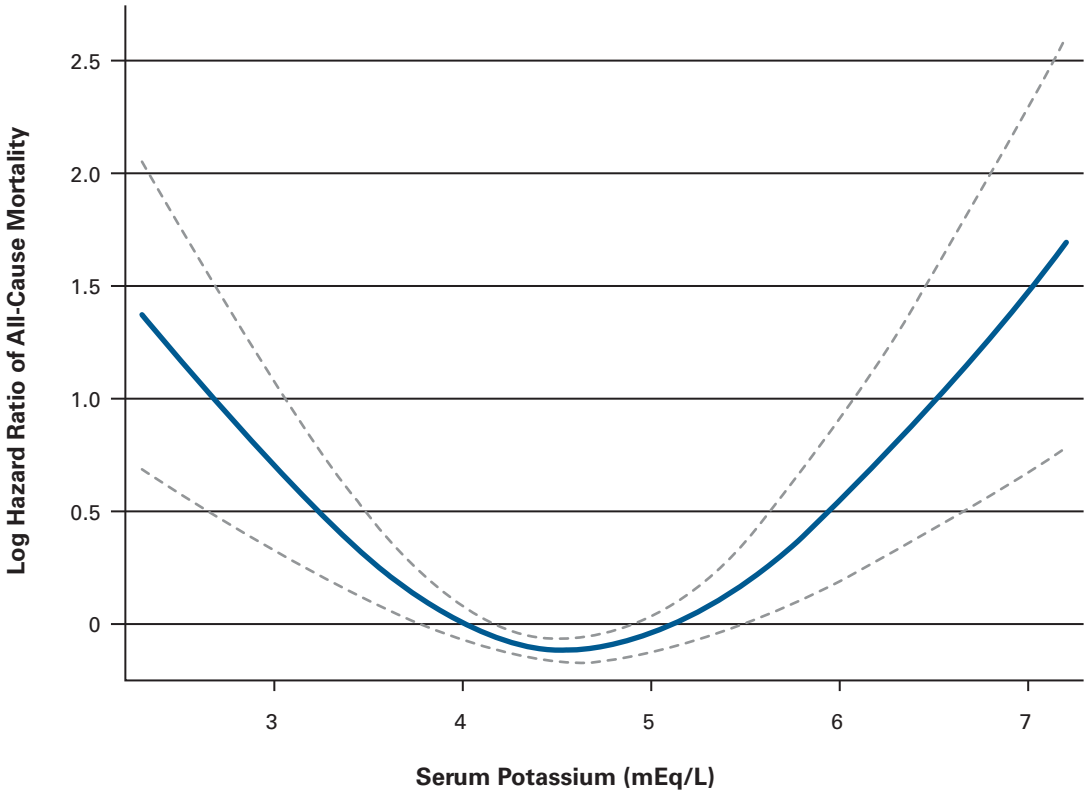
Consequences of Hyperkalemia

Hyperkalemia is often a silent condition that goes undetected until a patient exhibits serious consequences, such as ventricular arrhythmias, or may be detected incidentally upon laboratory testing. In patients with cardiorenal comorbidities, the risk for developing hyperkalemia is an ongoing concern. Hyperkalemia is associated with both clinical and economic consequences, including increased emergency department (ED) visits, hospitalizations, and mortality. These have a direct bearing on the overall cost of managing patients, especially in a managed care setting.

In 2011, approximately 67,000 visits to the ED were a direct result of elevated potassium levels.[24] Of patients who visited the ED, 50% were admitted to the hospital, with an average length of stay of 3.2 days and mean in-hospital charges of $24,178 per stay. A total of 84% of individuals hospitalized were older than 45 years. Thus, persons older than 45 years who are at risk for hyperkalemia should be monitored closely. The estimated total annual hospital charges for Medicare admissions with hyperkalemia as the primary diagnosis were approximately $697 million (US) in 2011.[24]

Clinical evidence shows that increases in serum potassium above the normal range are associated with higher mortality rate, especially as an individual ages and in patients with comorbidities (**Figure 1**[8]).[7,8] Other studies have noted that hyperkalemia is one of the greatest risk factors associated with all-cause mortality in patients with pre-existing CVD, advanced CKD,[6] patients without CKD,[9] and patients undergoing dialysis (**Figure 2**[26]).[25,26] A

■ **Figure 1.** All-Cause Mortality Associated With Serum Potassium Levels in Non-Dialysis Dependent Patients with Chronic Kidney Disease (n = 1227)[8,a]



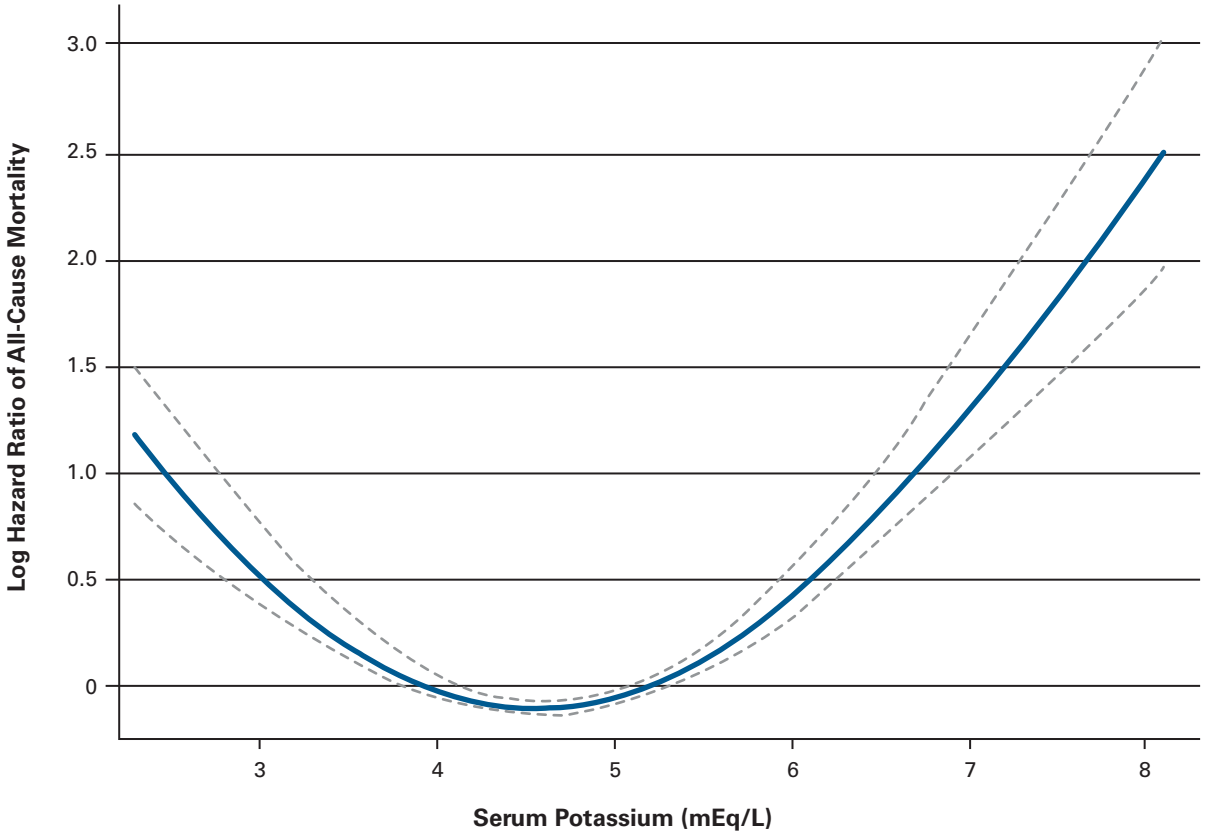
[a]Multivariable adjusted log hazards (solid line) and 95% confidence intervals (dashed lines) of all-cause predialysis mortality associated with serum potassium levels in the entire study population (n = 1227). Associations were examined in time-varying Cox models adjusted for age, race, smoking status, Charlson comorbidity index, diabetes, cardiovascular disease, body mass index, the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, potassium supplements, nonsteroidal anti-inflammatory agents, beta-blockers, estimated glomerular filtration rate, serum albumin, bicarbonate, calcium, phosphorus, blood hemoglobin, and 24-hour urine protein. Association of serum potassium with all-cause mortality in the overall patient population was significant and nonlinear (P <.001 for the quadratic term). Study population included all male patients with serum potassium measurements referred for evaluation and treatment of nondialysis-dependent chronic kidney disease to the nephrology department at Salem Veteran Affairs Medical Center between January 1, 1990, and June 30, 2007. Patients were followed until April 1, 2009.

retrospective analysis of 15,803 patients with CKD and CVD treated with antihypertensive drugs revealed that patients with hyperkalemia had higher rates of hospital admissions and mortality compared with normokalemic patients.[6] The association of mortality risk with hyperkalemia was also studied in a retrospective analysis conducted in a large national cohort including more than 240,000 US Veterans with at least 1 hospitalization and at least 1 serum potassium measurement during a year.[9] The authors determined the risk of death (odds ratio) within 1 day of a hyperkalemic event in patients with CKD compared with normokalemic non-CKD patients. This study showed that patients with CKD were significantly more likely to experience a hyperkalemic event than those without CKD, but also that hyperkalemia increased the odds of death within 1 day regardless of kidney function. The risk of death correlated incrementally with severity of hyperkalemia (moderate hyperkalemia defined as serum potassium level ≥5.5 mg/dL and <6.0 mg/dL and severe hyperkalemia defined as ≥6.0 mg/dL).[9]

Current Management of Hyperkalemia

Both acute and chronic treatment strategies are critical for the management of patients at risk of hyperkalemia. The currently available treatment strategies mainly focus on emergency and intermediate care, and limited options are available for chronic management of patients at risk of recurrent hyperkalemia. Interventions for chron-

■ **Figure 2.** All-Cause Mortality Associated With Serum Potassium Levels in Patients Undergoing Peritoneal Dialysis (n = 10,454)[26,a]



[a]Association of serum potassium, used as a time-varying covariate, with mortality in patients undergoing peritoneal dialysis (n = 10,454). Dashed lines represent 95% confidence intervals.

ic management are limited to reducing or eliminating exacerbating factors, including RAAS inhibitors. Table 1[3,5,18,19,48,50,51] shows the list of interventions commonly used for the management of hyperkalemia.[3,5,19]

Acute Management

The options for the acute management of hyperkalemia may be further divided into those that start acting within minutes and are more appropriate for emergency management and those that require a few hours to exert therapeutic effects and are suitable for intermediate or subacute care. Included among the former are nebulized or inhaled beta-2–receptor agonists (eg, albuterol, salbutamol); intravenous insulin-and-glucose, which stimulates intracellular potassium uptake; and calcium gluconate salt for membrane stabilization.

The goals of immediate management are to induce potassium transport into the intracellular space and remove potassium from the body to quickly restore the normal electrophysiology of the cell membrane and prevent cardiac arrhythmias.[3] Sodium bicarbonate, loop diuretics, dialysis, and the potassium-binding resin sodium polystyrene sulfonate (SPS) have played a role in subacute management of hyperkalemia, with dialysis and loop diuretics also having a role in its chronic management.

Beta-2 Receptor Agonists

Beta-2 receptor agonists lower serum potassium by promoting its redistribution to the intracellular space. The effect of these agents is mediated independently of insulin and aldosterone. Their onset of action is 30 minutes and duration of effect is 2 to 4 hours.[19] As is expected

Table 1. Treatment Options for Hyperkalemia[3,5,18,19,48,50,51]

Treatment Strategy	Mechanism of Action	Advantages	Limitations	Clinical Setting
Beta2-adrenergic receptor agonists[3,5,19]	K^+ redistribution into the intracellular space	• Onset of action (~30 minutes) • Effect is independent of insulin and aldosterone	• Short duration, inconsistent effect (2-4 hours) • Does not reduce total K^+ levels • Use with caution in ischemic heart disease (risk of tachycardia)	Emergency treatment
Insulin-glucose[3,5,19]	K^+ redistribution into the intracellular space	• Onset of action within 30 minutes • Effect lasts 4-6 hours	• Risk of hypoglycemia • Does not reduce total K^+ levels	Emergency treatment
Calcium gluconate[3,5,19]	Membrane stabilization	• Onset of action in 1-3 minutes • Efficacy can be monitored with ECG and dose can be repeated if no changes observed	• Short duration of effect (30-60 minutes) • Serum K^+ level is unaffected • Avoid in patients receiving digoxin (risk of digoxin toxicity) • Risk of hypercalcemia	Emergency treatment
Sodium bicarbonate[3,5,19]	• K^+ redistribution into the intracellular space • When administered by infusion over 4-6 hours, it may enhance urinary K^+ excretion	Recommended when metabolic acidosis is the cause of hyperkalemia	• No immediate reductions in serum K^+; effects may be observed after 4-6 hours • Risk of metabolic alkalosis and volume overload	Intermediate/subacute care
Diuretics[3,5,19]	K^+ elimination	• Onset of action depends on start of diuresis • Beneficial in patients with volume expansion	• Efficacy depends on residual renal function (until diuresis is present) • Increased risk for gout and diabetes • May produce volume contraction, decreased distal nephron flow, worsening of kidney function, and reduced K^+ excretion	Intermediate/subacute care (loop diuretics) and chronic/maintenance treatment (loop or thiazide diuretics)
Dialysis (hemodialysis, peritoneal dialysis)[3,5,19]	K^+ elimination	• Onset of action within minutes • Effects lasting until end of dialysis or longer	• Concentration of potassium in the dialysate can contribute to hyperkalemia • Limitations and complications inherent to each dialysis modality (eg, arrhythmias with hemodialysis)	Intermediate/subacute care and chronic/maintenance treatment
Sodium polystyrene sulfonate[3,5,19]	K^+ elimination	• Onset of action 2 hours (oral) • Effects may last 4-6 hours or longer depending on ongoing potassium intake or cellular redistribution	• No consistent evidence of efficacy • Maximum effect may take 6 hours; effect as enema is more rapid but of lesser magnitude • Serious GI adverse events reported, including fatal cases of intestinal necrosis • Caution with sodium loads in patients with CHF, hypertension, or edema	• Intermediate/subacute care • Typically used in hospitals
Low potassium diet[48,50,51]	Reducing potassium intake	May improve metabolic acidosis in CKD	• Difficult to adhere to low-potassium diet • Limiting K^+-rich foods can cause constipation • Contradicts the DASH diet; may worsen chronic hypertension	Chronic/maintenance treatment
Discontinuation/dose-reduction of RAAS inhibitors[18]	Identification and interruption of hyperkalemia-inducing medications	Prevention of recurrent hyperkalemia events	Stopping or suboptimal utilization of renal/cardioprotective RAAS inhibitor therapy	Chronic/maintenance treatment

CHF indicates congestive heart failure; CKD, chronic kidney disease; DASH, Dietary Approaches to Stop Hypertension; ECG, electrocardiogram; GI, gastrointestinal; K^+, potassium; RAAS, renin-angiotensin-aldosterone system.

by their mechanism of action, these agents do not affect total body potassium levels.[19]

Insulin-Glucose

A commonly used regimen to acutely treat hyperkalemia is the intravenous administration of 10 units of regular insulin along with 25 g of glucose.[27] Insulin works by redistributing potassium into the cells. Despite the concomitant administration of glucose with insulin, hypoglycemia is a recognized complication of this treatment.[28] Insulin works within 30 minutes and its effect lasts 4 to 6 hours.[19]

Calcium Gluconate

Intravenously administered calcium gluconate can begin to stabilize membrane potential in 1 to 3 minutes, as indicated by normalization of electrocardiographic changes. The duration of the effect is 30 to 60 minutes and doses can be repeated if no adverse effects are observed.[19] As with several of the other acute treatment options, serum potassium level is unaffected.

Sodium Bicarbonate

The use of intravenous bicarbonate is recommended when metabolic acidosis is the cause of hyperkalemia. The hypokalemic effect of bicarbonate infusion may require many hours of administration (4-6 hours).[29] Thus, no immediate reduction in serum potassium levels should be expected. Metabolic alkalosis can develop from the use of higher doses.

Loop Diuretics

Diuretics, especially loop diuretics, are commonly used to prevent a rise in serum potassium and to control volume overload in patients with CKD. In the African American Study of Kidney Disease and Hypertension (AASK), the use of diuretics was associated with a 59% decrease in the risk of hyperkalemia.[30] Some diuretics, however, can increase the risk for gout, diabetes, and volume depletion and precipitate a worsening of kidney function; therefore, they may not be ideal agents for lowering serum potassium levels in the long term.

Dialysis

Although hemodialysis is effective in reducing serum potassium levels, ironically, the concentration of potassium in the dialysate can contribute to hyperkalemia. The results of 1 study revealed potassium-free dialysate was 24% more effective than 1-K (ie, 1 mEq/L concentration) dialysate and 50% more effective than 2-K dialysate in removing body potassium; new ectopy was recorded in only 1 patient studied.[31] In a large observational study, a pre-dialysis serum potassium level of 4.6 mEq/L to 5.3 mEq/L was associated with the greatest survival in patients undergoing maintenance hemodialysis.[25]

Sodium Polystyrene Sulfonate

Until recently, SPS was the only drug indicated for the treatment of hyperkalemia. SPS was approved more than 50 years ago, before the modern regulatory standards for demonstrating efficacy were employed. The approval of SPS was based on less stringent evidence from clinical studies that would not likely pass the scrutiny of the US Food and Drug Administration (FDA) today. The drug is typically used in hospitals[32,33] and less frequently in the outpatient setting due to issues with tolerability.[34] Recently, the FDA requested that the manufacturer of Kayexalate (Concordia, Ontario, Canada) conduct drug–drug interaction studies.[35]

A small retrospective analysis showed that mean serum potassium concentrations were within the normal range in 94% of patients after a single dose of SPS[32]; however, a comprehensive data review suggested there was no consistent evidence of efficacy.[36] Clinicians must be cognizant of this and other risks associated with SPS therapy. For example, caution is advised for patients who cannot tolerate even a small increase in sodium loads, such as those with severe CHF, severe hypertension, or marked edema. Although sodium should be restricted in these individuals to less than 2000 mg per day, the average daily dose of SPS is 15 to 60 g, with each gram of SPS containing 100 mg of sodium; thus, the patient receives 1.5 to 6.0 g of extra sodium load with daily SPS treatment.[37]

The results of an analysis of 30 articles detailing 58 adverse events reported with SPS[38] showed that 76% involved the colon and that the overall mortality rate for patients with gastrointestinal (GI) injury associated with SPS use was 33%. In 2009, the FDA issued a warning to healthcare practitioners regarding reports of intestinal necrosis, which can be fatal, and other serious GI adverse events such as bleeding, ischemic colitis, and perforation associated with administration of SPS; this report was further refined 2 years later.[39] Although rare, cases of necrosis can be associated with death. In the Harel systematic review, 94% of patients who died from GI injury had colonic necrosis on biopsy.[38]

Chronic Management

Although the short-term, acute management of hyperkalemia is effective and can stabilize serum potassium,

Table 2. Drugs Known to Induce Hyperkalemia[44,49]

Medication
Drugs that promote transmembrane potassium shift
• Nonselective beta-blockers[a] (eg, propranolol, bucindolol, carvedilol)
• Digoxin intoxication
• Intravenous cationic amino acids
• Mannitol
• Suxamethonium
Drugs that affect aldosterone secretion
• ACE inhibitors (eg, benazepril, lisinopril, ramipril)
• ARBs (eg, candesartan, irbesartan, losartan)
• Direct renin inhibitors (eg, aliskiren)
• NSAIDs and COX-2 inhibitors (eg, ibuprofen, naproxen, celecoxib)
• Calcineurin inhibitors (eg, cyclosporine, tacrolimus)
Drugs that cause tubular resistance to the action of aldosterone
• Aldosterone antagonists (eg, spironolactone, eplerenone) and other potassium-sparing diuretics (eg, amiloride, triamterene)
• Trimethoprim
• Pentamidine
Agents that contain potassium
• Salt substitutes and alternatives
• Penicillin G
• Stored blood products

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; COX-2, cyclo-oxygenase-2; NSAID, nonsteroidal anti-inflammatory drug.
[a]Selective beta blockers may induce hyperkalemia in certain patients.

these treatments do not address chronic risk. It is important to identify the underlying causes (ancillary factors) that contributed to an acute hyperkalemic event and manage these causes/factors on an ongoing basis, if needed. As previously discussed, several factors increase the likelihood of chronic hyperkalemia, including high potassium intake and the use of RAAS inhibitors and other drugs that cause increases in serum potassium.[40-44] However, current options to manage hyperkalemia on a long-term basis are limited and robust data on their efficacy and safety in the outpatient setting are lacking.

Diet

Management of hyperkalemia from a dietary perspective includes reducing potassium intake and discontinuing potassium supplements. It is recommended that those at risk for hyperkalemia avoid or limit the intake of foods that are high in potassium, such as oranges and orange juice, nectarines, kiwis, raisins or other dried fruit, bananas, cantaloupe, honeydew, prunes, and salt substitutes. Patients should be aware that limiting these foods can cause constipation or other GI side effects.[45,46] Restricting dietary potassium intake also contradicts healthy dietary recommendations to prevent kidney disease, stroke, and CVD (the so-called DASH [Dietary Approaches to Stop Hypertension] diet); however, this is considered a trade-off that patients need to make to reduce the risks of chronic hyperkalemia.[47,48]

Discontinuation/Dose-Reduction of RAAS Inhibitors

Identification and interruption of hyperkalemia-inducing medications is one of the guideline-recommended strategies for preventing recurrent episodes of elevated serum potassium. Drug-induced hyperkalemia, one of the most frequent causes of hyperkalemia, is triggered either by inhibiting renal potassium excretion or by blocking extrarenal removal. Thus, it is essential that when clinicians reconcile a patient's medication profile, dosage(s) of drugs needed to treat their disease(s) may need to be reduced or it may be necessary to avoid and/or discontinue any medications associated with hyperkalemia (Table 2[44,49]). This is especially true for RAAS inhibitors. In an observational

retrospective study of patients not undergoing dialysis and who had serum potassium of 6.5 mEq/L or greater on admission or during the hospital stay, more than 60% were taking at least one drug known to cause or worsen hyperkalemia.[43] Unfortunately, these therapies may be discontinued in patients who would most benefit from these medications. In a study of 279 patients with CKD, hyperkalemia was the most common reason (66.6%) why clinicians discontinued RAAS inhibitors and was the reason for not starting RAAS inhibitor therapy in 13.8% of individuals.[42]

In a comprehensive analysis of a large database of electronic medical records from Humedica, Epstein et al observed that after an event of moderate to severe hyperkalemia, almost half of the patients previously on a maximum dose of RAAS inhibitors reduced the dose or discontinued their RAAS inhibitor therapy.[18] It is important to point out that in those patients in whom the RAAS inhibitors were discontinued or given at suboptimal dosage, a higher percentage of adverse outcomes or mortality was observed. Mortality was observed twice as frequently in patients who were discontinued from RAAS inhibitors or were receiving a suboptimal dose irrespective of comorbidity status.[18]

Conclusions

Hyperkalemia is a common and clinically relevant problem in patents with cardiovascular and renal diseases, and although it can be asymptomatic in many cases, it has potentially serious consequences that can lead to significant morbidity and mortality. The treatment paradigm for hyperkalemia has remained without major advances for the past 50 years. Discontinuation of life-saving, evidence-based, recommended medications remains the main strategy to prevent the recurrence of chronic hyperkalemia. This has negative consequences in our healthcare systems as a result of adverse renal and cardiovascular events. As such, there is an important unmet need for novel therapeutic options for the chronic management of patients with, and at risk for, hyperkalemia. The potential availability of new therapies may change the treatment landscape in the near future.

■ **Editor's Note:** In October 2015, after this manuscript was completed, the FDA approved an additional product for the treatment of hyperkalemia.

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