New options for the management of chronic hyperkalemia

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Hyperkalemia is a frequently detected electrolyte abnormality that can cause life-threatening complications. Hyperkalemia is most often the result of intrinsic (decreased glomerular filtration rate; selective reduction in distal tubule secretory function; impaired mineralocorticoid activity; and metabolic disturbances, such as acidemia and hyperglycemia) and extrinsic factors (e.g., drugs, such as renin-angiotensin-aldosterone system inhibitors, and potassium intake). The frequent use of renin-angiotensin-aldosterone system inhibitors in patients who are already susceptible to hyperkalemia (e.g., patients with chronic kidney disease, diabetes mellitus, or congestive heart failure) contributes to the high incidence of hyperkalemia. There is a need to understand the causes of hyperkalemia and to be aware of strategies addressing the disorder in a way that provides the most optimal outcome for affected patients. The recent development of 2 new oral potassium-binding agents has led to the emergence of a new paradigm in the treatment of hyperkalemia.

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Hyperkalemia is encountered more frequently in current medical practices due to the increasing incidence and prevalence of common chronic diseases, such as diabetes and chronic kidney disease,[1] which (along with common treatment used for their treatment) disturb potassium homeostasis.[2] Hyperkalemia, usually defined as serum potassium concentrations greater than 5.0 to 5.5 mEq/l, is widely recognized as a direct and life-threatening complication, although questions remain about when and how to correct it.[3] Hyperkalemia most often results from the failure of renal adaptation to potassium imbalance resulting from a combination of intrinsic and extrinsic factors.[2,4,5] Intrinsic factors include decreased glomerular filtration rate, decreased distal delivery of sodium, selective reduction in distal tubule secretory function, impaired mineralocorticoid activity, and metabolic disturbances, such as acidemia and hyperglycemia. Common extrinsic factors are drugs that impair physiologic responses to hyperkalemia (e.g., various inhibitors of the renin-angiotensin-aldosterone system (RAAS), and potassium intake (e.g., a diet rich in potassium, or potassium supplements).[4,6] The frequency of chronic hyperkalemia is increased in current medical practice in part because RAAS inhibitors have undisputed beneficial effects in patient groups that are most susceptible to the development of hyperkalemia; for example, patients with chronic kidney disease (CKD), diabetes mellitus, or congestive heart failure.[4] Because hyperkalemia hinders the use of these beneficial agents, and because hyperkalemia can be a life-threatening condition, there is a need to understand the complex causes of hyperkalemia and be aware of strategies to address the disorder in a way that provides the most optimal outcome for affected patients. More than 50 years after the clinical introduction of sodium polystyrene sulfonate as an ion-exchange resin to treat hyperkalemia,[7–9] a new paradigm has emerged in the treatment of hyperkalemia, aided by the development of 2 new oral agents to reduce serum potassium levels.[10,11]

Risk factors and outcomes of chronic hyperkalemia

Potassium is a critical participant in the bioelectricity generated by ion gradients and flows between the extracellular and intracellular compartments and thus essential to all vascular and neuromuscular excitation, contraction, and conduction.[6,12] Hyperkalemia therefore alters a critical gradient and impairs the function of excitable tissues, most notably cardiac. All cells possess the ubiquitous Na^+-K^+ ATPase, which

pumps Na^+ out of, and K^+ into the cell. This leads to a K^+ gradient across the cell membrane ($K^+_{in} > K^+_{out}$), which is partially responsible for maintaining the potential difference across the membrane. This potential difference is important to the function of all cells, but is especially important in excitable tissues such as nerve and muscle. For these reasons, the body has developed numerous mechanisms for defense of normal serum K^+. Total body K^+ is approximately 50 mEq/kg, which in a 70-kg person would be approximately 3500 mEq. Most (98%) of this K^+ is within cells, with only 2% in the extracellular fluid. The normal concentration of K^+ in the extracellular fluid is 3.5 to 5.3 mEq/l. Large deviations from these values are not compatible with life.[6,12]

Potassium homeostasis is maintained by several different mechanisms. As patients ingest approximately 100 mEq of potassium, the kidney is responsible for maintaining total body balance of potassium[13]; however, the gastrointestinal (GI) tract also plays a small contributory role under normal circumstances.[14] As patients lose kidney function, the contribution of the GI tract starts to increase and in dialysis patients it has been estimated that up to 50% of potassium secretion may occur in the colon.[14–16] The kidney has a relatively sluggish ability to excrete a potassium load, as it takes about 4 hours to reestablish total potassium body balance. Following a potassium-rich meal, our body needs mechanisms to prevent rises in extracellular fluid potassium and this is accomplished by shifting potassium into the cells until the kidney has had time to reestablish total body potassium content.[17] There are physiological factors that are responsible for shifting potassium into the cells, including insulin and beta-adrenergic stimulation. Therefore, when eating a meal, insulin is released to not only control serum glucose, but it shifts potassium into the cell until the kidney has had time to establish normal potassium balance at the level of the kidney. The beta-adrenergic role is primarily operative during exercise. Exercise results in potassium leaking from skeletal muscle cells into the interstitial compartment of the skeletal muscle, which exerts a vasodilating effect to increase muscle perfusion during exercise. Exercise also activates the autonomic nervous system, which (among others) serves to keep serum potassium in check. These are physiologic regulators on the internal distribution of potassium homeostasis.[6,12]

Potassium at the level of the kidney is freely filtered by the glomerulus and then reabsorbed by the proximal tubule and thick ascending limb, such that only a small amount reaches the distal nephron.[12] K^+ secretion begins in the early distal convoluted tubule and progressively increases in magnitude into the cortical collecting duct. This secretory component varies and is regulated according to physiologic needs. The normal kidney has a large capacity to excrete potassium and maintain a normal serum potassium concentration. To highlight this statement, we can turn to results of 5 studies conducted in patients with normal kidneys that placed these patients on a high-potassium diet (up to 400 mEq of potassium per day) and illustrated that the potassium serum concentrations stayed constant throughout the study (see Table 1).[18–22] In the setting of high potassium intake, we accumulate potassium in the interstitial compartments of the kidney and the potassium can inhibit thick ascending limb sodium reabsorption, thereby providing more flow and sodium delivery to the downstream segments.[23–25] However, it is unlikely that inhibiting sodium in this segment will have the fidelity needed to selectively modulate potassium transport and not cause overexcretion of sodium and water and resulting volume depletion. Given this fact, there is now an increased focus on the distal convoluted tubule as a more regionalized site by which dietary potassium intake may modulate potassium secretion. Recent evidence has identified the distal nephron as a K^+ sensor whereby small changes in extracellular K^+ concentration can lead to direct changes in the K^+ secretory mechanism through alterations in activity of the with no lysine (WNK) family of kinases and their regulatory proteins SPAK and OxSR1.[13] After a high dietary intake of potassium, subtle rises of potassium (even within the normal range) result in a slight polarization of the distal convoluted tubule cell leading to a higher intracellular chloride content. The WNK proteins are sensitive to changes in chloride content, resulting in an inhibitory effect on the thiazide-sensitive Na^+-Cl^- cotransporter with an increase in sodium delivery to the more distal (aldosterone-sensitive) segments of the distal convoluted tubule and the collecting duct, increasing luminal electronegativity and providing luminal potassium secretion, and increasing luminal flow leading to enhanced potassium secretion through the Maxi-K channel.[26–28] The distal nephron thus may possess an intrinsic potassium-sensing capacity to modulate potassium transport in a regionalized manner.[13]

In addition to this potassium-sensing mechanism in the distal nephron, the ability to handle potassium loads might

Table 1 | Effect of prolonged K^+ intake in healthy humans

Reference	Number of subjects	Method of increasing K^+ intake	Baseline K^+ intake (mEq/d)	Final K^+ intake (mEq/d)	Duration of intervention (days)	Baseline serum K^+ (mmol/l)	Final serum K^+ (mmol/l)
Rabelink 1990[20]	6	KCL supplement 300 mEq/d	100	400	20	3.75	4.22
Witzgall 1986[22]	16	K citrate + $KHCO_3$ 2000 mEq/d	60	260	6	4.2	4.6
Sebastian 1994[21]	6	$KHCO_3$ 120 mEq/d	59	179	18	3.92	4.15
Jenkins 2001[19]	10	Grain-free vegetarian diet	98	341	14	4.26	4.03
Hene 1986[18]	6	K citrate 220 mEq/d	80	300	14	4.07	4.48

actually begin at the level of the stomach. When potassium enters into the stomach, it leads to rapid dephosphorylation of the Na^+-Cl^- cotransporter, allowing increased potassium secretion even though the blood potassium or mineralocorticoid levels have remained unchanged.[29–31] This mechanism is highlighted in a recent study in which patients were placed on a mineralocorticoid blocker removing the effect of aldosterone, and then given a potassium load with a meal.[32] Despite no change in the serum potassium level, there was a rapid increase in urinary excretion, supporting the presence of a gastric renal-sensing mechanism.

Normal potassium homeostasis is altered in CKD. In an animal model with 1 intact kidney and 1 kidney 50% removed, most potassium secretion initially originated in the intact kidney.[33] After removing the intact kidney and leaving only the remnant kidney in place, there was a fourfold increase in potassium excretion within 1 day and a sixfold increase within 7 days,[33] suggesting that in a patient with decreased nephron mass, the remaining nephrons undergo adaptive changes to enhance their potassium secretory capacity. This adaptation is mediated by enhanced sodium and flow through the remaining nephrons, with increased number and activity of the Na^+-K^+ ATPase in the distal tubule.[34,35] Although the adaptation to decreased nephron mass is quite profound and able to maintain potassium homeostasis under steady-state circumstances even with advanced CKD, the diseased kidney has much less capacity to handle acute potassium loads.[36] This can be extrapolated to what we observe clinically where potassium excursions in patients with CKD are higher and more prolonged than in patients with normal renal function, and potentially leading to increased mortality. Such excursions can be even higher in patients with CKD who have additional exacerbating factors for hyperkalemia, such as receiving a RAAS inhibition blocker.

When evaluating the renal mechanisms of hyperkalemia, we should consider 3 causes: (i) primary decrease in mineralocorticoid activity; (ii) primary decrease in distal sodium delivery; and (iii) intrinsic abnormalities of the cortical collecting duct. Aldosterone interacts in the distal nephron and facilitates sodium reabsorption, and it enhances the luminal negative charge, which is a driving force for potassium secretion. Common causes of hyperkalemia include conditions impairing renin and aldosterone levels, such as diabetes, adrenal disease, numerous drugs (e.g., nonsteroidal anti-inflammatory drugs, beta blockers, renin inhibitors, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor blockers, amiloride, triamterene, cyclosporine, tacrolimus, heparin, ketoconazole, and trimethoprim), and elderly age (even if otherwise healthy). Despite age-related changes in potassium homeostasis, serum potassium is typically not elevated in elderly patients at baseline.[37] However, slight perturbations in these homeostatic mechanisms can induce abrupt and life-threatening hyperkalemia. Another clinically relevant cause of hyperkalemia is the oral contraceptive drospirenone, which possesses anti-mineralocorticoid properties, and which has been associated with hyperkalemia when used in combination with RAAS inhibitors.[4,38]

Hyperkalemia is regarded as a medical emergency due to its propensity to cause malignant arrhythmias.[39,40] Indeed, hyperkalemia is associated with a substantial number of emergency department visits and hospital admissions.[41] More importantly, hyperkalemia has been associated with increased short-term death rates in patients with and without CKD or end-stage renal disease,[3,42–47] and with an increased risk of ventricular fibrillation.[48] Most studies indicated that the potassium concentration associated with the best survival is approximately 4.0 to 4.5 mEq/l.[42,44,47,48] Compounding the arrhythmogenic effects of hyperkalemia in patients with CKD and especially end-stage renal disease, there are various other exacerbating factors that frequently accompany abnormal potassium levels, such as hypocalcemia, hypomagnesemia, and metabolic alkalosis,[49,50] and the presence of underlying comorbidities, such as left ventricular hypertrophy,[51] which together may conspire to result in a very high risk of malignant arrhythmias in this population.[52,53]

Besides its link to increased mortality and a heightened propensity for malignant arrhythmias, hyperkalemia is also able to cause other physiologic perturbations, such as muscle weakness and impaired renal acidification.[54] Hyperkalemia suppresses proximal ammoniagenesis and the medullary transfer of ammonia leading to metabolic acidosis.[55] This is especially important because metabolic acidosis may contribute to the progression of CKD[56] and treatment of metabolic acidosis has been shown in small studies to slow progression of CKD.[57,58] Besides its link to increased mortality and a heightened propensity for malignant arrhythmias, hyperkalemia is also able to cause other physiologic perturbations, such as muscle weakness and impaired renal acidification.[54] Hyperkalemia suppresses proximal ammoniagenesis and the medullary transfer of ammonia leading to metabolic acidosis.[55] This is especially important because metabolic acidosis contributes to the progression of CKD[56] and treatment of metabolic acidosis has been shown to prevent progression of CKD.[57,58]

Therapies for chronic hyperkalemia in chronic kidney disease/end-stage renal disease: something old, something new

The therapeutic approach to hyperkalemia consists of acute and chronic management. The goals of acute management are the prevention of life-threatening arrhythmias and the immediate lowering of serum potassium into safe ranges. The treatments used for acute management of hyperkalemia can be divided into 3 categories[59]: (i) membrane stabilization through the administration of i.v. calcium; (ii) facilitation of potassium redistribution from extracellular to intracellular compartments by using insulin, beta-adrenergic agonists, and sodium bicarbonate (only if the pH is <7.2); and (iii) enhanced potassium elimination using diuretics, polystyrene sulfonate, or dialysis.[60,61] A detailed discussion of acute hyperkalemia management is beyond the scope of this symposium, which is focused primarily on chronic hyperkalemia.

As discussed previously, there are several well-described risk factors for the development of chronic hyperkalemia, such as low glomerular filtration rate, diabetes, the use of RAAS blockage, and various other medications.[2] A high-potassium diet can contribute, but only when there is also decreased ability to excrete potassium.[2] Also, the major disease states that benefit from RAAS inhibition frequently coexist especially in older individuals with reduced glomerular filtration rate from aging or the cumulative effects of chronic diseases. Therefore, the nephrology community faces a paradoxical and clinically significant challenge because those patients who would benefit most from treatment with RAAS agents are those with the highest risk of adverse effects.

Randomized controlled clinical trials of RAAS inhibitors often implement systematic serum potassium monitoring and protocolized interventions for hyperkalemia, and therefore offer valuable insight into the risks of hyperkalemia associated with RAAS inhibitor therapy and the efficacy of various intervention strategies to mitigate this complication. In the Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) study, 1448 patients with type II diabetic kidney disease (stage 2–3) with albuminuria >300 mg/g on losartan 100 mg were randomly assigned to the addition of lisinopril or placebo to assess the effects on renal and safety endpoints.[62] This study excluded patients with baseline serum potassium >5.5 mmol/l. On routine study laboratory testing, hyperkalemia (>5.5 mmol/l) was observed in 18.4% of patients on losartan monotherapy and in 31.5% of those on combination therapy with lisinopril. Given how common hyperkalemia occurs in patients on RAAS blockade, the investigators developed a stepwise approach to managing hyperkalemia: (i) avoid interacting medications, (ii) low-potassium diet, and (iii) enhance excretion of potassium through the kidneys or the GI tract.[62]

For mild hyperkalemia (potassium >5.0 mmol/l), the first step involved a review (and discontinuation, if feasible) of medications known to cause hyperkalemia, such as nonsteroidal anti-inflammatory drugs, and implementation of a low-potassium diet. A low-potassium diet is the mainstay of chronic hyperkalemia therapy; however, it does remove food items from the diet that are known to be healthy, such as fruits, vegetables, beans, nuts, and dairy.[6] In everyday practice it may be difficult for patients to strictly maintain such a diet; it is thus important to provide proper education about how to substitute lower-potassium foods for the higher-potassium foods and to help them understand the importance of portion control. For example, high-potassium fruits, which include bananas, oranges, mango, apricots, and cantaloupe, can be substituted with one-half cup of apples, grapes, peaches, pears, and cranberries instead.

The next step in the VA NEPHRON-D for serum potassium >5.5 mmol/l was to add conservative treatment measures that enhance potassium excretion or potassium redistribution, such as the addition or enhanced dosing of diuretics if volume depletion was not a concern, chronic alkali therapy, liberalization of salt intake in select patients for whom volume status and hypertension was not a concern, and chronic low-dose sodium polystyrene sulfonate (15–30 g 3 times per week).[62] For serum potassium >6.0 mmol/l the VA NEPHRON-D study required the withholding of RAAS inhibitor medications and the performance of an electrocardiogram. If there were no electrocardiogram changes typical of hyperkalemia[63–65] and the serum potassium concentration was below 6.5 mmol/l, investigators administered 60 g sodium polystyrene sulfonate. If the serum potassium concentration was greater than 6.5 mmol/l or if there were electrocardiogram changes typical of hyperkalemia, then the investigators implemented the acute hyperkalemia protocol described previously.

For cases of severe hyperkalemia, especially in patients without kidney function, hemodialysis may be indicated to lower serum potassium. Furthermore, maintenance dialysis also ensures chronic potassium balance in patients with end-stage renal disease. In typical clinical practice, dialysis uses a dialysate potassium concentration that is lower than the serum potassium concentration, therefore creating a gradient across the semipermeable membrane that induces diffusive removal of potassium molecules from the body. Notwithstanding the importance of maintaining long-term potassium mass balance, the rapid dialytic removal of potassium typical of thrice-weekly hemodialysis regimens has raised concerns about the electrophysiologic consequences of rapid potassium shifts, especially in patients presenting with high predialysis serum potassium who are then dialyzed with low dialysate potassium baths. The Dialysis Outcomes and Practice Patterns Study (DOPPS) reported an increased risk of sudden death associated with low potassium dialysate compared with dialysate potassium ≥3.0 mmol/l, especially if predialysis potassium was greater than 5.0 mmol/l.[66] However, a more recent DOPPS report found no association of low potassium dialysate with mortality and arrhythmia.[67] Both high and low predialysis serum potassium levels were associated with increased mortality in this study, but after multivariable adjustments, only serum potassium >6.0 mmol/l was associated with increased mortality and arrhythmia. In another large study of patients with chronic maintenance hemodialysis, a mismatch between predialysis serum potassium and dialysate potassium (i.e., high predialysis serum potassium combined with higher [≥3.0 mmol/l] dialysate potassium, presumably resulting in inadequate dialytic removal and long-term accumulation of potassium) was also associated with higher risk of long-term mortality, underscoring the importance of potassium mass balance.[47]

Recently, there has been a shift in chronic hyperkalemia treatment paradigms, centered on GI elimination using cation exchangers. The old mainstay cation exchanger used to treat hyperkalemia has been sodium or calcium polystyrene sulfonate (with or without sorbitol).[2] Sodium polystyrene sulfonate was approved for the treatment of acute hyperkalemia in the United States in 1958, based on fairly weak experimental evidence. At the time of approval, the use

of dialysis was not common and there were few to no alternative treatment options. One of the first studies of sodium polystyrene sulfonate was published in 1961 and evaluated a total of 32 patients.[9] Of the patients included, 30 patients had oliguria, with 22 patients receiving oral and 8 patients receiving rectal sodium polystyrene sulfonate as an acute intervention; the remaining 2 patients received oral doses chronically. The mean decrease in serum potassium was 1 mmol/l.[9] Although sodium polystyrene sulfonate is approved for the treatment of acute hyperkalemia, data on its efficacy and safety as a chronic therapy are very sparse. In a study of 33 patients with estimated glomerular filtration rate <40 ml/min per 1.73 m^2 and serum potassium 5.0 to 5.9 mmol/l, patients received either placebo or 30 g sodium polystyrene sulfonate daily for 7 days.[68] Patients treated with sodium polystyrene sulfonate experienced a reduction in serum potassium of approximately 1 mmol/l, and experienced more frequent GI side effects. The lack of larger and longer-term randomized controlled clinical trials of sodium polystyrene sulfonate makes it difficult to systematically assess its safety profile. The most concerning risk of sodium polystyrene sulfonate is intestinal (colonic necrosis), which may be increased if administered with sorbitol or if there are other risk factors for intestinal adverse effects.[69–73] The risk for colonic necrosis is estimated to be 0.27% to 1.8%,[74] but the true incidence is not known and this agent should be used only in patients with normal bowel function. The more common adverse effects with sodium polystyrene sulfonate include GI side effects of constipation if used without sorbitol or diarrhea if used with sorbitol.[73,75] There is also a theoretical risk of drug binding, but this has not been well studied.

Addressing the shortcomings of sodium polystyrene sulfonate, an emerging new treatment paradigm for management of chronic hyperkalemia centers around new oral agents: patiromer (RLY5016) and zirconium cyclosilicate (ZS-9). Patiromer is a nonabsorbed polymer-based binder that is formulated as a powder for oral suspension that binds potassium in the colon in exchange for calcium.[10] Patiromer (Veltassa) 8.4 g orally daily was approved by the US Food and Drug Administration for the management of nonemergent hyperkalemia in October 2015. This agent has an onset of action of 7 hours and a theoretical drug-binding risk, so the prescribing information suggests that it be separated by 3 hours from other medications. Based on *in vitro* studies, its binding capacity is about twice that of sodium polystyrene sulfonate.[76] The OPAL-HK trial evaluated the short-term efficacy of patiromer in 237 patents with stage 3–4 CKD on RAAS inhibitors and with baseline serum potassium >5.0 and <6.5 mmol/l.[77] There were 2 phases to the study: a 4-week single-group, single-blind study with treatment with patiromer and an 8-week, randomized, single-blind study. Overall, the potassium decreased from 5.6 to 4.6 mmol/l at week 4 with 76% of patients achieving the potassium target of <5.1 mmol/l. The 107 patients who achieved their target potassium in the initial short-term efficacy trial were randomized to the longer-term efficacy trial to receive patiromer or placebo for 8 weeks. Recurrence of hyperkalemia occurred in 60% of patients randomized to placebo compared with 15% of those randomized to patiromer ($P < 0.001$). In the 8-week phase 2, more individuals withdrawn from patiromer needed to stop RAAS inhibitors. The overall adverse event rates were similar between the treatment and placebo groups, with GI side effects seen more often in the patiromer group. The incidence of hypokalemia (serum potassium <3.0 mmol/l) was 5% and hypomagnesemia (serum magnesium <1.4 mg/dl) was 3%.[77] Patiromer has been generally well tolerated when administered chronically over 52 weeks to 306 patients with diabetic nephropathy.[78]

Microporous zirconium cyclosilicate is an oral sorbent that is highly selective to trap potassium ions throughout the GI tract.[10] Because of its high selectivity, zirconium cyclosilicate may bind potassium in the upper GI tract where the amount of potassium is high but the concentration is low.[79] This agent is not currently approved in the United States, but recently received a positive opinion from the Europe Committee for Medicinal Products for Human Use. Zirconium cyclosilicate is being developed for the treatment of acute and chronic hyperkalemia. The HARMONIZE Study had an open-label acute treatment phase (10 g zirconium cyclosilicate thrice daily for 48 hours) in 258 patients with serum potassium ≥5.1 mmol/l and a second phase in those who achieved normal potassium in the first phase (92%), who were randomized to chronic treatment (placebo, and 5 g, 10 g, or 15 g per day of zirconium cyclosilicate).[80] Zirconium cyclosilicate exerted its potassium-lowering effect relatively quickly, with a median time to potassium normalization of 2.2 hours, and showed a dose-response relationship in the chronic treatment phase. The overall adverse event rates were similar across the different groups, except for edema and hypokalemia and a suggestion of increased risk of urinary tract infections.[80] In another randomized, double-blind, placebo-controlled clinical trial, 753 patients with serum potassium levels of 5.0 to 6.5 mmol/l were assigned to 3 different doses of zirconium cyclosilicate thrice daily for 48 hours versus placebo.[79] Serum potassium decreased by a mean of 0.73 mmol/l in patients receiving 10 g zirconium cyclosilicate. After the initial 48 hours, 543 patients who achieved normokalemia were randomized to the original zirconium cyclosilicate dose administered once daily versus placebo, for 12 days. In this chronic phase, significantly more patients receiving 5 and 10 g zirconium cyclosilicate maintained normokalemia compared with placebo.[79]

Summary

In conclusion, hyperkalemia is an important electrolyte abnormality most often affecting patients with CKD, especially if combined with exacerbating factors, such as diabetes mellitus and treatment with RAAS inhibitors. Hyperkalemia is associated with higher mortality and with higher incidence of malignant arrhythmias, and also with metabolic abnormalities such as metabolic acidosis. The

serum potassium level that is associated with the lowest risk for adverse clinical outcomes is approximately 4 mmol/l.

Although every episode of hyperkalemia warrants clinical assessment, in the absence of systematic studies, a variety of clinical observations support the concept that mild hyperkalemia can be defined as serum potassium between 5.0 and 6.0 mmol/l and is generally amenable to outpatient management. Serum potassium levels above this range warrant more comprehensive assessment and may or may not be suitable for outpatient management. Electrocardiogram changes related to hyperkalemia are useful to determine the electrophysiologic relevance of the serum potassium level. The availability of newer, fully evaluated oral ion exchangers is likely to expand the opportunities for safe and effective outpatient management of hyperkalemia, and a wider application of RAAS inhibitors in patients with CKD and congestive heart failure. The long-term clinical effects of a strategy focusing on chronic potassium binder use in the face of RAAS inhibitor–induced hyperkalemia will need to be evaluated in future trials.

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