Updates on medical management of hyperkalemia

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Purpose of review
Hyperkalemia is a potentially fatal electrolyte disorder, more commonly present when the potassium excretion capacity is imparied. Hyperkalemia can lead to adverse outcomes, especially due to severe cardiac arrhythmias. It can also impair the cardiovascular effects of renin–angiotensin–aldosterone system inhibitors (RAASis) and potassium rich diets, as hyperkalemia frequently leads to their discontinuation.

Recent findings
Potassium is a predictor of mortality and should be monitored closely for patients who are at risk for hyperkalemia. Acute hyperkalemia protocols have been revised and updated. Randomized trials have shown that the new anti-hyperkalemic agents (patiromer and zirconium cyclosilicate) are effective hyperkalemia treatment options. The use of anti-hyperkalemic agents may allow for a less restrictive potassium diet and lower RAASi discontinuation rates.

Summary
Hyperkalemia should be monitored closely for high-risk patients, as it is associated with adverse outcomes. New therapies have demonstrated effective control, offering hope for potential use in patients that would benefit from diet or medications associated with an increase in serum potassium, indicating that the use of hyperkalemic agents can be associated with better outcomes.

Keywords
hydro-electrolyte disorders, hyperkalemia, kidney disease, potassium

INTRODUCTION

Hyperkalemia is an electrolyte disorder with potentially dire clinical consequences, occurring in high-risk individuals when physiologic mechanisms to maintain serum potassium (K+) homeostasis are impaired. Hyperkalemia can be caused by increased exogenous K+ intake, shift from the intracellular to the extracellular space or impaired excretion. Chronic hyperkalemia, however, requires some degree of impaired renal excretion, as a result of reduced glomerular filtration rate (GFR), some types of renal tubular disorders (drug-induced or congenital) or of inhibition of the renin–angiotensin–aldosterone system (RAAS).

The general aim of management is to reduce the risk of arrhythmias and other severe consequences of hyperkalemia. Although the acute management of hyperkalemia is directed to myocardial stabilization and shift of K+ into the intracellular compartment to avoid cardiac consequences, the chronic management focuses on reducing the risk of extended exposure to hyperkalemia through strategies that induce total body K+ depletion and/or reduced intake.

The human body maintains the K+ concentration within a narrow range, which is crucial for excretion, and of distribution between extracellular and intracellular fluid compartments. Diet is the main source of K+, which is found in most raw fruits and vegetables; beef, poultry and fish can contribute significantly as animal sources.

The intracellular compartment maintains 98% of K+ setting the resting plasma membrane potential of cells, with the interior negative relative to the exterior [1]. The kidney, at large, handles the total body K+ content; gastrointestinal secretion also plays an important part, as well as the kidney gastrointestinal reflex, which allows for an increase in renal excretion even before an increase in K+ load can be detected in the filtrate. Significantly, the

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KEY POINTS

- Hyperkalemia increases the risk of adverse effects in the general population.
- Kidney function is the most important clinical factor associated with hyperkalemia.
- Acute hyperkalemia can result in fatal events, mostly due to cardiac arrhythmias and the management is focused on myocardial stabilization, shift of potassium back to the intracellular compartment and elimination of potassium from the body.
- New anti-hyperkalemic agents have offered new opportunities for the use of RAASi in chronic kidney disease and congestive heart failure patients and to allow for healthier, high potassium, diets in patients at risk of chronic hyperkalemia.

mechanisms that reduce the postprandial hyperkalemic response are particularly impaired in chronic kidney disease (CKD). There is also fine-tuning for body K+ occurring through different physiologic mechanisms that allows for a rapid shift of K+ into cells, that is insulin and noradrenaline.

K+ has a U-shaped association with mortality; the lowest all-cause mortality rates were reported for patients with K+ values between 4.0 and less than 4.5 mEq/l. Even mild hyperkalemia was associated with higher mortality for patients with heart failure, CKD and diabetes mellitus, when compared with patients without these comorbidities, caused by the increase risk of serious or life-threatening cardiac arrhythmias [2]. In this review article, we provide an update of the current recommendations for the clinical management of hyperkalemia.

ACUTE HYPERKALEMIA AND ITS MANAGEMENT

An acute episode of hyperkalemia (defined as high serum K+ levels without previous knowledge of this condition), occurs when there is a rise in extracellular K+ concentration from the result of a defect in the internal redistribution, a sudden decrease in net excretion, or both disturbances happening at once, in a patient with previously normal serum K+ levels [3▪]. A rapid shift of K+ to the extracelular compartment, usually the result of a massive cell turnover or in the critical illness setting can lead to potentially fatal consequences related to ventricular arrhythmias.

The severity of acute hyperkalemia is classified as mild (≥5–5.5 mEq/l) moderate (5.5–6 mEq/l) or severe (≥6 mEq/l) taking into account the presence or absence of ECG changes. In outpatients with acute hyperkalemia with a serum K+ measurement at least 6.0 mEq/l, or any hyperkalemia with new EKG changes, should be referred to the emergency department for vital signs observation, cardiac monitoring [4]. We suggest to always repeat the K+ measurement to rule out pseudohyperkalemia, as long as this is feasible and does not result in delay of treatment, especially when a severe case of hyperkalemia is likely. The summary of acute hyperkalemia management is listed, by the mechanism of action in Table 1.

In hyperkalemic patients with EKG changes, we suggest the intravenous administration of calcium salts for cellular membrane stabilization, which prevents ventricular arrhythmias (1 g of calcium chloride or 3 mg of calcium gluconate over 2–5 min) [5]. A second dose can be administered if EKG changes persist after 5 min. Calcium gluconate is the preferred choice of calcium salt, due to lesser local tissue toxicity [5,6]. To shift the K+ to the intracellular compartment, we suggest an intravenous administration of insulin and glucose [7]. Administration of 5 U of regular insulin appears as effective in lowering K+ levels as the administration of 10 U, although evidence is limited. In select cases, as an alternative (or addition) to insulin and glucose, administration of β-agonists is suggested [5]. Use of 10-mg salbutamol via nebulizer or metered-dose inhaler results in significant reduction of K+ at a peak at 120 min after use (90 min if 20 mg applied) [7]. Sodium bicarbonate should be considered, only in hyperkalemic patients with metabolic acidosis [8,9].

In addition to the measures cited, focused on a prompt shift, anti-hyperkalemic agents (particularly zirconium cyclosilicate due it rapid action) and use of loop diuretics can be considered in the acute setting [10]. During the treatment of acute hyperkalemia, frequent reassessments of K+, glucose (in cases of insulin administration) and EKG are suggested. The underlying cause for acute hyperkalemia should also be evaluated. Dialysis should be considered for patients with persistent renal dysfunction and elevated K+ at least 6 mEq/l or EKG changes, not responsive to medical management.

CHRONIC HYPERKALEMIA AND ITS MANAGEMENT

Patients at risk for high serum K+, can be exposed to persistently increased blood K+ detected over serial measurements, during clinical evaluation and follow-up. Recurrent or relapsing hyperkalemia, with some values fluctuating within normal ranges is also a frequent occurrence, and these clinical scenarios are both associated with increased risk of hospitalization and mortality [2,11▪▪,12,13]. Among risk factors for

Table 1. Summary of the management of acute hyperkalemia

Early management
Exclude the possibility of pseudo hyperkalemia
Perform an EKG – if there are changes, or K+ ≥ 6 mEq/dl: maintain continuous EKG, BP and oxygen saturation monitoring
Calcium gluconate, 1000 mg for an IV infusion of 2–5 min
Measures to increase intracellular potassium shift
Insulin and glucose infusion
Bolus of 10 U of insulin, accompanied by 50 ml of 50% dextrose
Infusion of 10% dextrose at 50–75 ml/h
Frequent monitoring of blood glucose for 6 h
Consider beta agonists
10-mg salbutamol via nebulizer or metered-dose-inhaler
Potassium excretion measures
Diuretics for hypervolemic patients
0.9% Sodium Chloride (Saline) for hypovolemic patients
0.9% Sodium Chloride (Saline) and IV diuretics (furosemide) to euvolemic patients without severe renal impairment
Gastrointestinal anti-hyperkalemic agents – consider especially for patients with renal impairment, in whom hemodialysis cannot be swiftly performed
Hemodialysis – should be considered for patients with kidney failure

BP, blood pressure; EKG, eletrocardiogram; IV, intravenous; K+, potassium.

hyperkalemia (listed in Table 2), low GFR is the strongest predictor of hyperkalemia. The prevalence of hyperkalemia in a cohort of 238 patients with mean estimated GFR of 14 ml/min was reported to be 54%, for K+ at least 5 mEq/l, and 8% for K+ at least 6 mEq/l [14]. Once a patient's GFR falls to less than 15 ml/min/1.73 m^2, an inflection point is reached, where small increments of CKD progression would require progressive rises in the steady state serum K+ concentration.

GENERAL ASSESSMENT

Patients at high risk should be managed with dietary advice and possible reduction or avoidance of medications associated with hyperkalemia. Food patterns associated with high K^+ intake vary among different populations. The estimated daily K^+ intake ranges from approximately 52 mEq/day in China to 125 mEq/day in Spain [15,16]. Yet, K+ additives have also been a component of processed foods. Their K+ concentration, in some cases, far exceeds and is more bioavailable than that of whole foods [17]. It is important to point out that potassium-rich diets seem to be consistent with cardioprotective dietary patterns advocated in healthier diets, and the potential harm of restricting K+ should be always considered in the management of chronic hyperkalemia [18]. In situations where diet modification is not a viable option, monitoring through frequent visits with laboratory exams is advised.

Table 2. Clinical factors and medications commonly associated with hyperkalemia

Clinical risk factors	Medications
Acute and chronic kidney disease	Nonsteroidal anti-inflammatory drugs
Congestive heart failure	RAAS inhibitors
Diabetes mellitus	Beta blockers
Acidosis	Heparin
	Amiloride
Male sex	Trimethropin
Rhabdomyolysis	Pentamidine
Tumor necrosis	Penicillin G
Urinary obstruction	Triamterene

RAAS, renin–angiotensin–aldosterone system.

When a selected patient falls into a category where a RAAS inhibitor (RAASi) is highly suggested (i.e. proteinuric kidney disease, heart failure), we recommend that cautious monitoring of K+ levels should be performed to avoid discontinuation, especially in advanced CKD, and those with a prior history of acute hyperkalemia. In CKD patients prone to hyperkalemia, a prescription containing a combination of two or more RAASi agents should be avoided; considering the risk and the unproven benefit when compared with the use of a single agent.

Recent clinical trials that focused on use of the new potassium-binding polymers patiromer and zirconium cyclosilicate in outpatients with hyperkalemia and specific groups, such as those on hemodialysis and with resistant hypertension have shown

Table 3. Summary of recent trials involving potassium lowering agents

Trial reference and objective	Summary of methods	Conclusion
Weir *et al.* [22] Objective: To test differences in the effect of patiromer treatment on serum aldosterone, blood pressure and albuminuria in patients with CKD on renin–angiotensin system inhibitors with hyperkalemia (serum potassium 5.1–6.5 mEq/l)	Placebo-controlled, 12-week phase 3 study evaluating patiromer treatment Sequential randomized controlled trial, divided in 2-part (4-week initial treatment phase of 243 patients; 8-week randomized withdrawal phase) Main outcome: mean serum potassium and aldosterone levels *N* = 243	Patiromer reduced serum potassium and aldosterone levels independent of plasma renin activity in patients with CKD and hyperkalemia on renin–angiotensin system inhibitors
Agarwal *et al.* [21]: AMBER trial Objective: To evaluate the efficacy of the potassium-binding polymer patiromer used concomitantly with spironolactone in patients with resistant hypertension and CKD prevents hyperkalemia and allows more persistent spironolactone use for hypertension management	Patiromer and spironolacone vs. placebo and spironolactone in patients with uncontrolled resistant hypertension and CKD Main outcome: between-group difference (spironolactone and patiromer vs. spironolactone and placebo) in the proportion of patients remaining on spironolactone at week 12 *N* = 295	At week 12, 66% of patients in the placebo group remained on spironolactone compared with 86% of patients in the patiromer group, with patiromer use also allowing patients to use 385 mg more of spironolactone during this time
Kosiborod *et al.* [20]: HARMONIZE trial Objective: To evaluate the efficacy and safety of zirconium cyclosilicate for 28 days in outpatients with hyperkalemia (serum potassium ≥5.1 mEq/l)	Double blind randomized controlled study Intervention: sodium zirconium cyclosilicate vs. placebo Main outcome: mean serum potassium level during days 8–29 of the randomized phase *N* = 495	Among outpatients with hyperkalemia, open-label sodium zirconium cyclosilicate reduced serum potassium to normal levels within 48 h; compared with placebo, all 3 doses of zirconium cyclosilicate resulted in lower potassium levels and a higher proportion of patients with normal potassium levels for up to 28 days
Fishbane *et al.* [19]: DIALIZE study Objective: evaluate the efficacy and safety of zirconium cyclosilicate in stable patients with ESRD managed by adequate HD	Randomized, double blind, placebo-controlled, phase 3b trial Main outcome: maintained serum potassium of 4.0–5.0 mmol/l for 4 weeks, during three or more of four HD treatments after the long interdialytic interval and who did not require rescue therapy Intervention: sodium zirconium cyclosilicate vs. placebo *N* = 443	Compared with placebo, sodium zirconium cyclosilicate significantly increased the proportion of patients who maintained predialysis serum potassium 4.0–5.0 mmol/l during ≥3 of 4 HD treatments following the long interdialytic interval and who did not require urgent rescue therapy The drug was well tolerated, indicating that it could be a viable option for the management of hyperkalemia in this setting

CKD, chronic kidney disease; ESRD, end stage renal disease; HD, hemodialysis.

favorable and sustained result in lowering serum potassium [19–22]. There is a potential role for the anti-hyperkalemic agents in the chronic management of hyperkalemia, with the particular focus of RAASi use. We have made a selection of the most relevant trials released recently in Table 3.

SPECIFIC MANAGEMENT IN CHRONIC KIDNEY DISEASE PATIENTS

To account for the repeated exposure, patients with CKD develop adaptive physiologic mechanisms to avoid hyperkalemia, to make them less prone to its adverse, and potentially fatal, effects increases in circulating catecholamines, aldosterone and renal and gastrointestinal K+ elimination are meant to blunt the adverse effects of K+ and occur more frequently in the CKD population [23–27]. Yet, patients with CKD are predisposed to metabolic derangements and structural heart disease that lower the arrhythmogenic potential with concurrent hyperkalemia. Thus, despite of the fact that there is a sense of lower risk due to K+ adaptation in CKD patients, hyperkalemia is a major contributor to cardiac mortality in CKD [28].

Hyperkalemia in patients with CKD is also managed by restricting K+ intake, use of effective diuretic therapy for hypervolemic patients with an adequate residual renal function. Use of bicarbonate is also recommended in individuals with metabolic acidosis. RAASi use in preventing adverse outcomes in advanced CKD is not clear, with only one trial of 224 participants with CKD G4 testing the role of an angiotensin-converting enzyme (ACEi) [29]. However, hyperkalemia is known to lead to reduction or cessation of RAASi in observational CKD cohorts, and may be the reason for not achieving an ideal dose of the medication [13,30,31].

New anti-hyperkalemic agents (patiromer and zirconium cyclosilicate) are particularly useful in this population, as they reduce serum K+ effectively in patients with kidney impairment [32,33]. Randomized trials need to test the impact of controlling chronic hyperkalemia in advanced CKD and end stage kidney disease (ESKD) on possible benefits of RAASi use. An exploratory analysis of 107 people with CKD receiving RAASi and hyperkalemia control with patiromer found only 44% of the randomized patients who withdrew from patiromer continued on RAASi compared with 94% of those randomized to ongoing patiromer, until 8 weeks [22]. Randomized clinical trials with longer follow-up are needed to establish that the control of chronic hyperkalemia with anti-hyperkalemic agents can result in both increase the uptake of RAASi and affect their beneficial effects on clinical outcomes. Clinically relevant adverse events, such as constipation and hypomagnesemia, were reported for patiromer in randomized clinical trials [22,34▪,35]; edema and hypertension are common side effect for zirconium cyclosilicate [34▪]. The evidence for K+ control with sodium polystyrene sulfonate is much less compelling. The trials that allowed the use of the medication in clinical practice were underpowered and the length of follow-up is very short, with studies being conducted for a few weeks.

Among the population of ESKD patients, elevated K+ concentrations may contribute directly to adverse clinical events arising from arrhythmic disturbances. Observational studies have raised concerns about the association of high serum K+ concentrations with mortality and arrhythmias [36]. Aggressive dialysis prescriptions of low K+ baths (1.0–1.5 mEq/l), leading to a higher serum dialysate K+ gradient are by strongly associated with adverse outcomes [37]. In these patients, K+ restriction is important and commonly applied to avoid adverse effects of hyperkalemia. A recent study by Noori *et al.* [38] examined the association between dietary K+ intake and at the end of a 5-year follow-up, a direct association of dietary K+ with mortality was observed, even after adjustment for pre-hemodialysis serum K+ and phosphorus levels. Chronic management of hyperkalemia with the new classes of anti-hyperkalemic agents could conceptually lead to improvement in outcomes also in dialysis and transplant patients. A summary of the reasoning behind managing chronic hyperkalemia is posted in Fig. 1.

CONGESTIVE HEART FAILURE

Nearly 40% of patients with heart failure develop hyperkalemia, and many patients have recurrent hyperkalemia episodes [39,40]. An analysis of nearly 32 thousand heart failure patients in Denmark confirmed important risk factors for hyperkalemia in this populations, including CKD (prevalence ratio = 1.46), diabetes mellitus (1.38) and spirolactone use (1.48). Hyperkalemia is associated with severe clinical outcomes and death in heart failure; in patients with heart failure who developed hyperkalemia, 53% had any acute-care hospitalization 6 months before the hyperkalemia event, increasing to 74% 6 months after. Compared with heart failure patients without hyperkalemia, adjusted 6-month hazard ratio was 2.75-fold higher for acute-care hospitalization and 3.39-fold higher for death [40].

Inhibition of the RAAS is a key strategy in treating hypertension and cardiovascular disease, and to slow the progression of CKD. However, RAASi can potentially increase the risk of hyperkalemia (serum K+ > 5.5 mEq/l). In a study of 118 patients with mild-to-moderate hypertension, treatment with the ACEi lisinopril 20 mg/day was associated with a small but statistically significant increase in serum K+ of 0.2 mEq/l from baseline [41]. The risk of hyperkalemia with angiotensin II receptor blockers (ARB) monotherapy was assessed by Goldberg *et al.* [42] in a pooled analysis of 16 randomized, double-blind, clinical trials in 2085 patients with hypertension; rates of serum K+ at least 5.5 mEq/l were 1.5% in those receiving the ARB losartan and 1.3% in patients treated with an ACEi.

Clinical trials point to a slightly higher risk of hyperkalemia in heart failure patients on a single site RAAS inhibition less than 2%; there is scarce evidence to indicate that these are associated with adverse outcomes [35]. The effects of ACEi/ARB combination therapy on hyperkalemia in patients with heart failure were assessed in a meta-analysis of data from the Valsartan Heart Failure Trial, CHARM-Added, Valsartan in Acute Myocardial Infarction Trial and Randomized Evaluation of Strategies for Left Ventricular Dysfunction study. The analysis showed a statistically significant increased risk of serum K+ at least 5.5 mEq/l with ACEi/ARB combination therapy compared with control treatment in

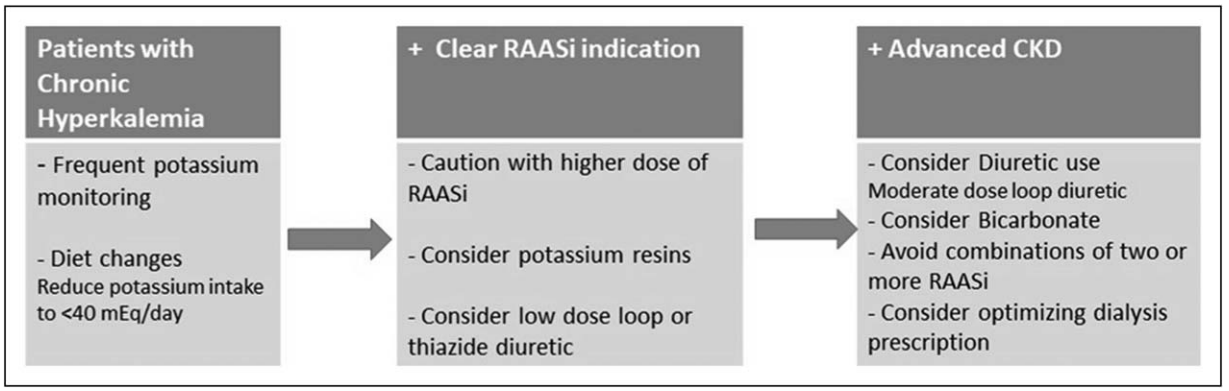

FIGURE 1. Recommendations for the management of chronic hyperkalemia, according to patient characteristics. Figure key: management of chronic hyperkalemia involves identifying patients at risk, before taking actions [3▪]. The first line of action is to confirm high serum potassium levels, by monitoring laboratory values for patients at risk (refer to Table 2 of this article). Once confirmed, it is advised to modify a patient's diet, when appropriate [13]. For patients with a clear indication for renin–angiotensin–aldosterone system inhibitor, there should be caution with achieving high doses of this class of medications. Therapies focused on the excretion of body potassium should be the first line of medical therapy [10,31]. The evidence points to use of anti-hyperkalemic agents as an adjuvanct for renin–angiotensin–aldosterone system inhibitor, especially for chronic kidney disease progression, when there is a clear indication. Diuretics should be considered, both loop and thiazide diuretics are effective in this scenario [7]. For patients with advanced chronic kidney disease (stages 4 and 5), we advise using a moderate dose of loop diuretic, as there's a need for a higher dose to be effective [10]. Bicarbonate is recommended for patients with metabolic acidosis, associated with chronic kidney disease [8,9]. Combinations of two or more renin–angiotensin–aldosterone system inhibitor have been shown to increase potassium and may not benefit patients, in terms of progression; they should be avoided for patients with risk for hyperkalemia [31]. In refractory cases of hyperkalemia, in patients with end-stage kidney diseases, dialysis initiation can be considered; for those on dialysis, the prescription should be optimized, avoiding low potassium baths [34▪].

patients with chronic heart failure (3.5 vs. 0.7%; risk ratio: 4.87; 95% confidence interval: 2.39–9.94) [43]. The recent amber trial that evaluated the effect of patiromer in spironolactone prescription showed that he potassium-binding polymer can effectually keep patients from developing hyperkalemia (86% remained using spironolactone vs. 66% in the control group) compared with placebo [21].

CONCLUSION

Hyperkalemia is a condition associated with CKD, heart failure and their management. Clinicians should be aware of the risk factors to make therapeutic decisions. Acute hyperkalemia can lead to increased mortality, prompting emergency measures. There are risks associated with chronic treatment; however, new anti-hyperkalemic agents may offer hope to patients who could benefit from the use of RAAS inhibitors to prevent disease progression.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ▪ of special interest
- ▪▪ of outstanding interest

1. Palmer BF, Clegg DJ. Physiology and pathophysiology of potassium homeostasis. Adv Physiol Educ 2016; 40:480–490.
2. Collins AJ, Pitt B, Reaven N, *et al.* Association of serum potassium with all-cause mortality in patients with and without heart failure, chronic kidney disease, and/or diabetes. Am J Nephrol 2017; 46:213–221.
3. Montford JR, Linas S. How dangerous is hyperkalemia? J Am Soc Nephrol ▪ 2017; 28:3155–3165.

The review article summarizes the acute and chronic consequences of high-serum potassium and the need of action in the clinical setting. It highlights common situations that physicians can encounter and what was published previously in the literature to help guide decisions.

4. Mattu A, Brady WJ, Robinson DA. Electrocardiographic manifestations of hyperkalemia. Am J Emerg Med 2000; 18:721–729.
5. Truhlar A, Deakin CD, Soar J, *et al.* European Resuscitation Council guidelines for resuscitation 2015: section 4. Cardiac arrest in special circumstances. Resuscitation 2015; 95:148–201.
6. Lin CY, Hsieh KC, Yeh MC, *et al.* Skin necrosis after intravenous calcium chloride administration as a complication of parathyroidectomy for secondary hyperparathyroidism: report of four cases. Surg Today 2007; 37:778–781.

7. Batterink J, C TA, Taylor RAI. Pharmacological interventions for the acute management of hyperkalemia in adults. Cochrane Database Syst Rev 2015; 10.
8. Kaplan JL, Braitman LE, Dalsey WC, *et al.* Alkalinization is ineffective for severe hyperkalemia in nonnephrectomized dogs. Hyperkalemia Research Group. Acad Emerg Med 1997; 4:93–99.
9. Kim HJ. Acute therapy for hyperkalemia with the combined regimen of bicarbonate and beta(2)-adrenergic agonist (salbutamol) in chronic renal failure patients. J Korean Med Sci 1997; 12:111–116.
10. Watson M, Abbott KC, Yuan CM. Damned if you do, damned if you don't: potassium binding resins in hyperkalemia. Clin J Am Soc Nephrol 2010; 5:1723–1726.
11. ■■ Kovesdy CP, Matsushita K, Sang Y, *et al.* Serum potassium and adverse outcomes across the range of kidney function: a CKD prognosis consortium meta-analysis. Eur Heart J 2018; 39:1535–1542.

The meta-analysis overviews the role of potassium as a predictor of adverse outcomes in the outpatient setting, and its relationship with estimated glomerular filtration rate and albuminuria. The study includes a large sample and concludes that hyperkalemia is a concern, independent of kidney function.

12. Gasparini A, Evans M, Barany P, *et al.* Plasma potassium ranges associated with mortality across stages of chronic kidney disease: the Stockholm CREAtinine Measurements (SCREAM) project. Nephrol Dial Transplant 2018. [Epub ahead of print]
13. Lazich I, Bakris GL. Prediction and management of hyperkalemia across the spectrum of chronic kidney disease. Semin Nephrol 2014; 34:333–339.
14. Sarafidis PA, Blacklock R, Wood E, *et al.* Prevalence and factors associated with hyperkalemia in predialysis patients followed in a low-clearance clinic. Clin J Am Soc Nephrol 2012; 7:1234–1241.
15. Welch AA, Fransen H, Jenab M, *et al.* Variation in intakes of calcium, phosphorus, magnesium, iron and potassium in 10 countries in the European Prospective Investigation into Cancer and Nutrition study. Eur J Clin Nutr 2009; 63(Suppl 4):S101–S121.
16. Yin X, Neal B, Tian M, *et al.* Sodium and potassium content of 24 h urinary collections: a comparison between field- and laboratory-based analysers. Public Health Nutr 2018; 21:1036–1042.
17. Picard K. Potassium additives and bioavailability: are we missing something in hyperkalemia management? J Ren Nutr 2019; 29:350–353.
18. Tyson CC, Nwankwo C, Lin PH, Svetkey LP. The dietary approaches to stop hypertension (DASH) eating pattern in special populations. Curr Hypertens Rep 2012; 14:388–396.
19. Fishbane SFM, Fukagawa M, McCafferty K, *et al.* A phase 3b, randomized, double-blind, placebo-controlled study of sodium zirconium cyclosilicate for reducing the incidence of predialysis hyperkalemia. J Am Soc Nephrol 2019. [Epub ahead of print]
20. Kosiborod M, Rasmussen HS, Lavin P, *et al.* Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. JAMA 2014; 312:2223–2233.
21. Agarwal R, Rossignol P, Garza D, *et al.* Patiromer to enable spironolactone use in the treatment of patients with resistant hypertension and chronic kidney disease: rationale and design of the AMBER study. Am J Nephrol 2018; 48:172–180.
22. Weir MR, Bakris GL, Gross C, *et al.* Treatment with patiromer decreases aldosterone in patients with chronic kidney disease and hyperkalemia on renin–angiotensin system inhibitors. Kidney Int 2016; 90:696–704.
23. Gennari FJ, Segal AS. Hyperkalemia: an adaptive response in chronic renal insufficiency. Kidney Int 2002; 62:1–9.
24. Salem MM, Rosa RM, Batlle DC. Extrarenal potassium tolerance in chronic renal failure: implications for the treatment of acute hyperkalemia. Am J Kidney Dis 1991; 18:421–440.
25. Grimm PR, Sansom SC. BK channels in the kidney. Curr Opin Nephrol Hypertens 2007; 16:430–436.
26. Foster ES, Jones WJ, Hayslett JP, Binder HJ. Role of aldosterone and dietary potassium in potassium adaptation in the distal colon of the rat. Gastroenterology 1985; 88(1 Pt 1):41–46.
27. Butterfield I, Warhurst G, Jones MN, Sandle GI. Characterization of apical potassium channels induced in rat distal colon during potassium adaptation. J Physiol 1997; 501(Pt 3):537–547.
28. Korgaonkar S, Tilea A, Gillespie BW, *et al.* Serum potassium and outcomes in CKD: insights from the RRI-CKD cohort study. Clin J Am Soc Nephrol 2010; 5:762–769.
29. Hou FF, Zhang X, Zhang GH, *et al.* Efficacy and safety of benazepril for advanced chronic renal insufficiency. N Engl J Med 2006; 354:131–140.
30. Bandak G, Sang Y, Gasparini A, *et al.* Hyperkalemia after initiating renin–angiotensin system blockade: the stockholm creatinine measurements (SCREAM) project. J Am Heart Assoc 2017; 6:.
31. Savarese G, Vasko P, Jonsson A, *et al.* The Swedish Heart Failure Registry: a living, ongoing quality assurance and research in heart failure. Ups J Med Sci 2019; 124:65–69.
32. Pitt B, Bakris GL. New potassium binders for the treatment of hyperkalemia: current data and opportunities for the future. Hypertension 2015; 66:731–738.
33. Beccari MV, Meaney CJ. Clinical utility of patiromer, sodium zirconium cyclosilicate, and sodium polystyrene sulfonate for the treatment of hyperkalemia: an evidence-based review. Core Evid 2017; 12:11–24.
34. ■ Georgianos PI, Agarwal R. Revisiting RAAS blockade in CKD with newer potassium-binding drugs. Kidney Int 2018; 93:325–334.

The study focuses on the challenge of hyperkalemia associated with renin–angiotensin–aldosterone system inhibitor (RAASi) in chronic kidney disease (CKD). The author suggests that randomized controlled trials are needed, to show that the new potassium binders could offer the possibility of using RAASi, in doses that could slow CKD progression.

35. Weir MR, Rolfe M. Potassium homeostasis and renin–angiotensin–aldosterone system inhibitors. Clin J Am Soc Nephrol 2010; 5:531–548.
36. Karaboyas A, Zee J, Brunelli SM, *et al.* Dialysate potassium, serum potassium, mortality, and arrhythmia events in hemodialysis: results from the dialysis outcomes and practice patterns study (DOPPS). Am J Kidney Dis 2017; 69:266–277.
37. Ferrey A, You AS, Kovesdy CP, *et al.* Dialysate potassium and mortality in a prospective hemodialysis cohort. Am J Nephrol 2018; 47:415–423.
38. Noori N, Kalantar-Zadeh K, Kovesdy CP, *et al.* Dietary potassium intake and mortality in long-term hemodialysis patients. Am J Kidney Dis 2010; 56:338–347.
39. Desai AS. Hyperkalemia in patients with heart failure: incidence, prevalence, and management. Curr Heart Fail Rep 2009; 6:272–280.
40. Thomsen RW, Nicolaisen SK, Hasvold P, *et al.* Elevated potassium levels in patients with congestive heart failure: occurrence, risk factors, and clinical outcomes: a Danish population-based cohort study. J Am Heart Assoc 2018; 7:.
41. Fogari R, Zoppi A, Malamani GD, *et al.* Effects of different antihypertensive drugs on plasma fibrinogen in hypertensive patients. Br J Clin Pharmacol 1995; 39:471–476.
42. Goldberg AI, Dunlay MC, Sweet CS. Safety and tolerability of losartan potassium, an angiotensin II receptor antagonist, compared with hydrochlorothiazide, atenolol, felodipine ER, and angiotensin-converting enzyme inhibitors for the treatment of systemic hypertension. Am J Cardiol 1995; 75:793–795.
43. Phillips CO, Kashani A, Ko DK, *et al.* Adverse effects of combination angiotensin II receptor blockers plus angiotensin-converting enzyme inhibitors for left ventricular dysfunction: a quantitative review of data from randomized clinical trials. Arch Intern Med 2007; 167:1930–1936.