Potassium homeostasis and management of dyskalemia in kidney diseases: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

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Potassium disorders are common in patients with kidney disease, particularly in patients with tubular disorders and low glomerular filtration rate. A multidisciplinary group of researchers and clinicians met in October 2018 to identify evidence and address controversies in potassium management. The issues discussed encompassed our latest understanding of the regulation of tubular potassium excretion in health and disease; the relationship of potassium intake to cardiovascular and kidney outcomes, with increasing evidence showing beneficial associations with plant-based diet and data to suggest a paradigm shift from the idea of dietary restriction toward fostering patterns of eating that are associated with better outcomes; the paucity of data on the effect of dietary modification in restoring abnormal serum potassium to the normal range; a novel diagnostic algorithm for hypokalemia that takes into account the ascendency of the clinical context in determining cause, aligning the educational strategy with a practical approach to diagnosis; and therapeutic approaches in managing hyperkalemia when chronic and in the emergency or hospital ward. In sum, we provide here our conference deliberations on potassium homeostasis in health and disease, guidance for evaluation and management of dyskalemias in the context of kidney diseases, and research priorities in each of the above areas.

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A multidisciplinary group of researchers and clinicians met in October 2018 to identify evidence and address controversies in potassium management. Here we provide our overview of potassium homeostasis in health and disease and guidance for evaluation and management of dyskalemias in the context of kidney diseases, and indicate research priorities.

Potassium homeostasis

Potassium homeostasis is achieved by matching intake with excretion and ensuring proper distribution between

extra- and intracellular fluid compartments. Approximately 2% of total body potassium is located in extracellular fluid, whereas 98% of exchangeable potassium is in the intracellular compartment, setting resting plasma membrane potential of cells. The kidney is primarily responsible for maintaining total body potassium content, with shift of potassium between compartments reducing fluctuation (e.g., postprandial insulin shifts dietary potassium into cells by increasing the activity of the Na^+-K^+-adenosine triphosphatase [ATPase] until the kidney excretes the potassium load).[1,2]

Potassium handling by the kidney. Approximately 90% of filtered potassium is reabsorbed along the proximal tubule and ascending loop of Henle, independent of potassium intake.[3] Urinary potassium excretion results primarily from potassium secretion along the aldosterone-sensitive distal nephron.[4] Tubule potassium secretion is mediated by 2 types of apical potassium channels (Figure 1).[5,6]

Electronegative lumen voltage is generated largely by sodium reabsorption through the epithelial sodium channels localized to the apical membrane. Aldosterone stimulates epithelial sodium channel activity via mineralocorticoid receptors, which increase both channel number and open probability.[7]

Major determinants of potassium excretion are factors that regulate potassium secretion along the aldosterone-sensitive distal nephron and include luminal sodium delivery and flow rate, plasma potassium concentration, circulating aldosterone and arginine vasopressin, and acid-base status.[8] A fraction of renal cortical potassium secretion is reabsorbed, primarily in the medulla; potassium deficiency increases potassium reabsorption. The pumps responsible for potassium absorption (H,K-ATPases) are also stimulated by aldosterone or other mineralocorticoids. Elevation of plasma potassium concentration enhances potassium excretion even when aldosterone concentration is held constant.[9] Aldosterone activates epithelial sodium channels,[10] leading to sodium retention and also reducing plasma potassium concentration, but at least during exogenous infusion, this reflects predominantly a shift of potassium into cells.[11] When aldosterone secretion is stimulated by extracellular fluid volume depletion, typically mediated by angiotensin II, decreased sodium delivery to the connecting tubule and collecting duct prevents potassium wasting, despite stimulated secretion.[12] In contrast, when plasma aldosterone secretion is mediated by rises in plasma potassium concentration, it plays a critical role in defending against hyperkalemia through renal and extrarenal effects.[9]

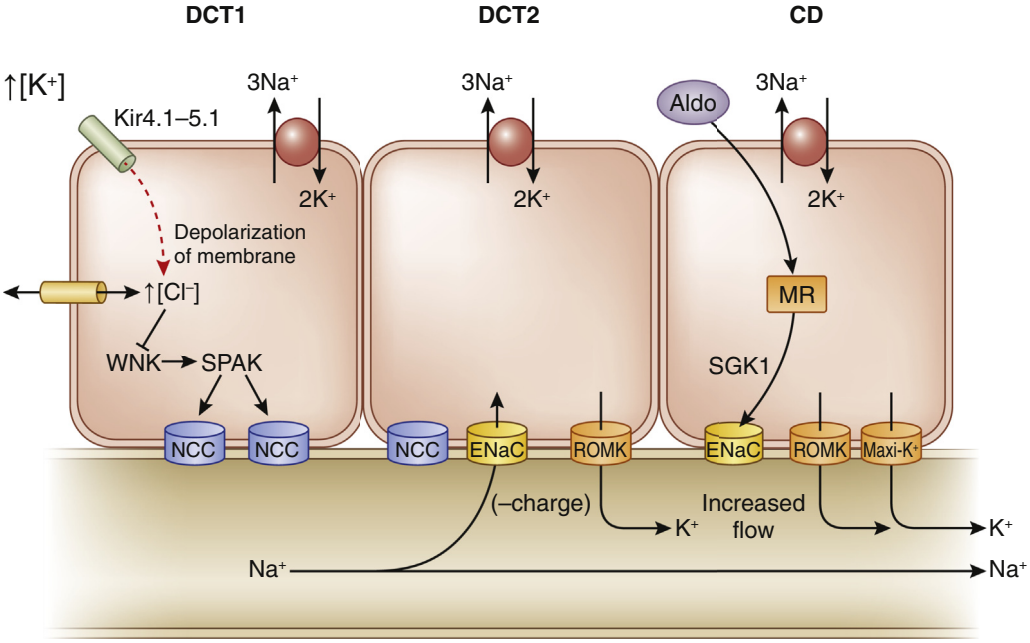


Figure 1 | Mechanisms of potassium secretion by the distal nephron showing distal convoluted tubule (DCT) subsegments 1 and 2 and the connecting tubule/collecting duct (CNT/CD). Sodium is reabsorbed by the DCT primarily by the thiazide-sensitive Na^+/Cl^- cotransporter (NCC). This process is stimulated when plasma K^+ concentration is low, through effects dependent on the K^+ channel Kir4.1-5.1. This reduces cell chloride activating the Ste20-related proline/alanine-rich kinase (SPAK), which activates NCC. When the plasma K^+ concentration rises, the converse happens. Additionally, secreted aldosterone activates epithelial sodium channels (ENaC) in the DCT2 and CNT/CD. There, sodium is reabsorbed electrogenically, which drives K^+ secretion through both the renal outer medullary potassium channel (ROMK) and Maxi-K channels. Aldo, aldosterone; MR, mineralocorticoid receptor; SGK1, serum and glucocorticoid regulated kinase 1; WNK, "with-no-lysine" kinases. Reprinted from *American Journal of Kidney Diseases*, Palmer BF, Clegg DJ. Physiology and pathophysiology of potassium homeostasis: core curriculum 2019, volume 74, pages 682–695. © 2019, with permission from the National Kidney Foundation, Inc.[6]

Recent work has described circadian rhythms[13–16] and sexual dimorphism[17–19] (summarized in Palmer and Clegg[6]) affecting tubular handling and an aldosterone-sensitive colonic BK channel[20–28]; whether these findings will lead to better opportunities for individualization of care or possible novel drug targets is not yet defined.

The potassium switch. Gitelman syndrome and pseudohypoaldosteronism type 2 helped identify a previously unrecognized role for the distal convoluted tubule in modulating renal potassium excretion. In the former, dysfunction of the thiazide-sensitive NaCl cotransporter leads to massive potassium-wasting and hypokalemia.[29] In the latter, enhanced NaCl cotransporter activity leads to potassium retention and hyperkalemia.[30,31] Plasma potassium concentration is a predominant factor that regulates thiazide-sensitive NaCl cotransporter activity;[32] it also controls aldosterone secretion.[33] The effects of plasma potassium concentration on distal potassium secretion are amplified by effects along the proximal tubule and the loop of Henle, thus modulating potassium excretion. Together, these insights have largely resolved the "aldosterone paradox,"[34,35] the observation that a single hormone, aldosterone, can mediate sodium retention in some situations and potassium excretion in others. In other words, hyperkalemia stimulates potassium secretion without sodium retention, and in volume depletion, sodium is retained but potassium is not wasted.

Aldosterone also activates sodium and potassium transport along the aldosterone-sensitive distal nephron by phosphorylating mineralocorticoid receptors in intercalated cells, which reduces their activity. Under these conditions, aldosterone stimulates electrogenic sodium reabsorption and thereby potassium secretion in principal cells.[36] In contrast, when aldosterone is stimulated in the setting of extracellular fluid volume depletion, angiotensin II dephosphorylates mineralocorticoid receptors in intercalated cells, permitting aldosterone to activate the apical proton pumps (H-ATPase and H,K-ATPases) and the chloride/bicarbonate exchanger, pendrin. This provides a pathway for electroneutral sodium chloride absorption, preventing excess potassium loss.[37]

Diuretic effects. Both loop and distal convoluted tubule diuretics cause potassium wasting. Distal convoluted tubule diuretics are more potent, causing initial kaliuresis by increasing distal flow and sodium delivery. This effect wanes in chronic use, and hypokalemia is closely correlated with the elevation in aldosterone concentration,[38] with typical reduction in plasma potassium concentration of only 0.2 mmol/l.[39] Hyperkalemia may result from potassium-sparing diuretics that inhibit epithelial sodium channel activity in the aldosterone-sensitive distal nephron, especially with older age, concomitant kidney failure, or co-administration of other drugs.[40]

Potassium homeostasis in chronic kidney disease. Hyperkalemia is uncommon when glomerular filtration rate (GFR) is greater than 60 ml/min per 1.73 m^2 and increases in prevalence with lower GFR.[41–43] Hyperkalemia in persons with preserved GFR is less prevalent and most commonly associated with pseudohyperkalemia, transient increases in potassium caused by cell shift, and drug-induced impairment of potassium excretion.[44] Homeostasis in the face of low nephron numbers results from an adaptive increase in the secretion of potassium in remaining nephrons,[45] which is thought to be similar to that which occurs in healthy persons subjected to high dietary potassium intake. Chronic potassium loading augments the secretory capacity of the distal nephron so that renal potassium excretion is significantly increased for any given plasma potassium concentration. Increased potassium secretion under these conditions occurs in association with structural changes characterized by cellular hypertrophy, increased mitochondrial density, and proliferation of the basolateral membrane in cells in the distal nephron and principal cells of the collecting duct.[46] Increased serum potassium and mineralocorticoids independently initiate the amplification process, which is accompanied by an increase in Na^+-K^+-ATPase activity. Loss of kidney mass also leads to an increase in flow and sodium delivery and collecting duct sodium reabsorption in the remaining nephrons.[47] Increased apical sodium entry provides a further stimulatory effect on Na^+-K^+-ATPase activity. Despite this adaptation, the ability to augment potassium secretion in response to an exogenous load is limited such that hyperkalemia can result from even modest increases in potassium intake (Supplementary Figure S1).[48,49] When GFR is $<$15 ml/min per 1.73 m^2, small incremental losses in kidney function require progressively steeper rises in steady state serum potassium concentration to maintain total body potassium balance. Above that threshold, hyperkalemia develops because of decreased distal sodium delivery (as in persons with decompensated heart failure), reductions in mineralocorticoid activity (as in hyporeninemic hypoaldosteronism in people with diabetes), or abnormal collecting duct function (as in persons with tubulointerstitial kidney disease; Figure 2).[44,50,51]

Potassium intake and outcomes in health and disease

Dietary sources and measurement of potassium intake. Fruits and vegetables, meat, poultry, and fish are important sources of potassium (Supplementary Table S1). Food patterns associated with potassium intake and dietary potassium sources vary around the world[52,53]; the estimated daily potassium intake ranges from ~52 mmol (2.1 g) in China, ~68 mmol (2.6 g) in the United States, to ~125 mmol (4.8 g) in Spain.[53–55] Potassium-rich diets are generally consistent with dietary patterns considered healthy; a typical Mediterranean diet can provide up to 155 mmol/d (6 g/d) of potassium, whereas a dietary approaches to stop hypertension (DASH) diet would contribute up to 120 mmol/d (4.7 g/d).[56]

The bioavailability of dietary potassium is influenced by the consumption of other nutrients that affect potassium metabolism (meat intake leads to net acid production, but fruit and vegetable intake leads to net base production) along with other nutrients such as vitamins, antioxidants,

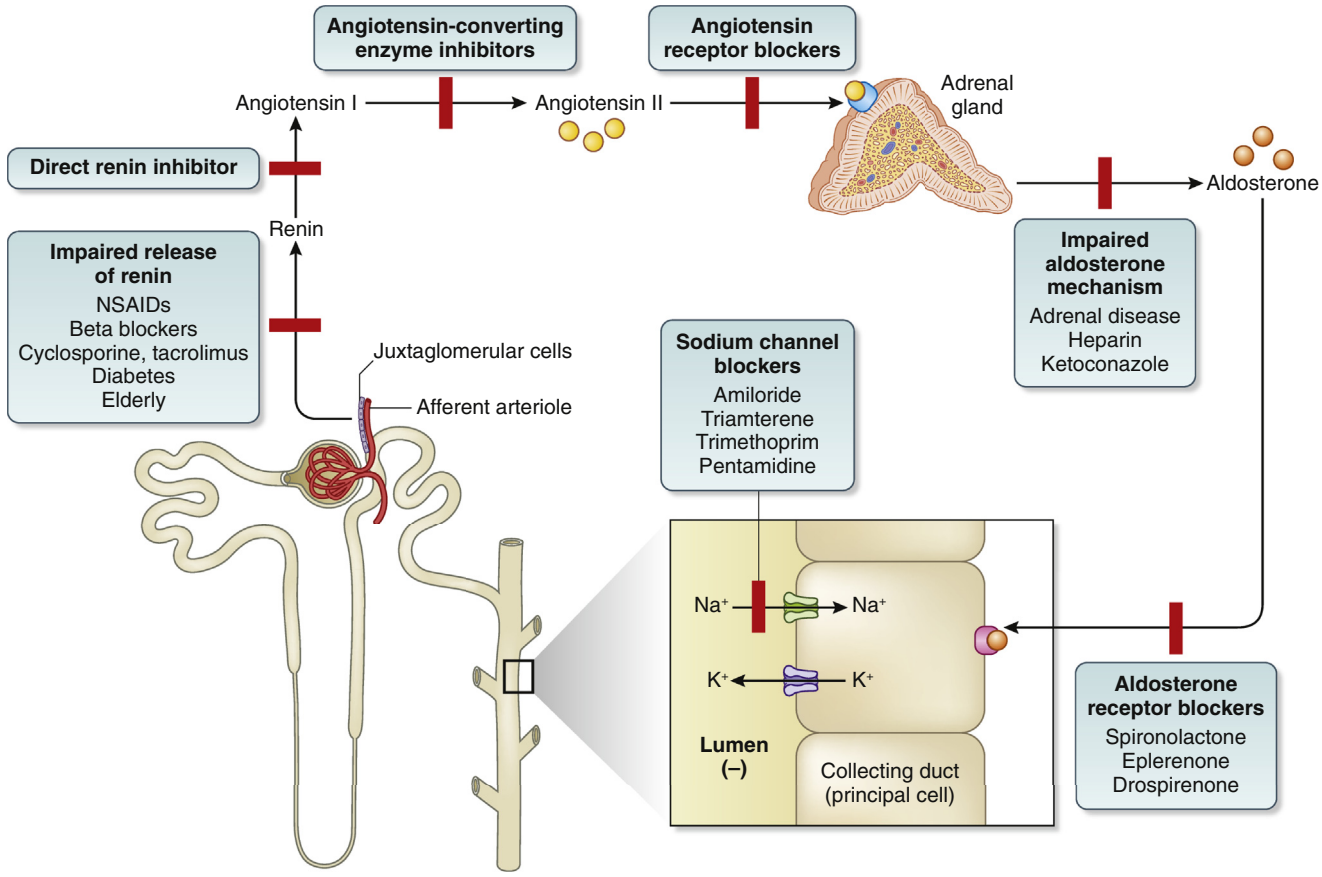


Figure 2 | The renin-angiotensin-aldosterone system and regulation of renal K^+ excretion. Disease states or drugs that interfere at any point along this system can impair renal K^+ secretion and increase the risk of hyperkalemia. In many patients this risk is magnified as a result of disturbances at multiple sites along this system. NSAIDs, nonsteroidal antiinflammatory drugs. Adapted from *The New England Journal of Medicine*, Palmer BF. Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system, volume 351, pages 585–592. Copyright © 2004 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[51]

carbohydrates, and fiber. Compared with high-potassium meat, high-potassium fruits and vegetables may promote intracellular entry of potassium and excretion of potassium in stool by increasing fecal volume through dietary fiber.[57] Salt substitutes, food additives, and preservatives are important hidden sources of potassium that significantly contribute to the total daily intake (e.g., potassium preservatives in prepared meat may add 300–575 mg of potassium per 100 g of intake).[58–60] The use of potassium chloride in salt substitution is increasing, partly as a result of international public health campaigns to reduce sodium consumption. Typically 20% of salt is replaced by potassium chloride, adding ~12 mmol/d (0.45 g/d) to usual intake.[61] The safety of the substitution, particularly in more advanced stages of chronic kidney disease (CKD), requires further investigation.

Supplementary Table S2 describes the advantages and pitfalls of available methods to estimate dietary potassium.

Dietary potassium in the general population. A recent meta-analysis of 22 clinical trials and 11 cohort studies in the general population concluded that increased potassium intake reduced systolic blood pressure by 3.5 mm Hg (95% confidence interval [CI]: 1.8–5.2) and diastolic blood pressure by 2.0 mm Hg (95% CI: 0.9–3.1),[62] mainly in adult patients with hypertension, and without a clear dose-response relationship.[63,64] Meta-analyses of trials of potassium supplementation versus placebo report a consistent reduction in the risk of stroke (risk ratio, 0.76; 95% CI: 0.66–0.89)[65,66] but not cardiovascular or coronary artery disease.[62]

Dietary potassium in persons with CKD. To prevent hyperkalemia in patients with advanced CKD and end-stage kidney disease (ESKD) who are undergoing hemodialysis, opinion-based guidelines recommend a low-potassium diet (Supplementary Table S3). This practice is widespread, and studies evaluating adherence to dietary recommendations in patients undergoing hemodialysis consistently report low potassium intake with corresponding low intake of fruits, vegetables, and other plant-derived compounds (e.g., fiber, vitamin C, and carotenoids).[67,68] However, observational studies in persons with CKD or ESKD report weak associations between dietary potassium intake and potassium concentration,[69–72] challenging the belief that the amount of potassium consumed strongly influences potassium concentration.

In a 1990 balance study of healthy persons, potassium loading (400 mmol/d) increased potassium excretion by

3.7-fold within 24 hours (which rapidly returned to baseline when supplementation was discontinued) with a 1.1-fold increase in plasma potassium.[73] Similar effects have been reported in meta-analysis of trials of potassium supplementation where the weighted mean difference in urine potassium excretion was 46 mmol/d (95% CI: 38–54) but the corresponding increase in serum potassium was 0.14 mmol/l (95% CI: 0.09–0.19).[74] Comparable studies in patients with CKD are scarce. In the 1940s, potassium balance studies in 15 people with CKD consuming 2 to 5 g of potassium salts showed impaired renal potassium clearance and elevated circulating potassium,[75,76] leading to caution in the use of potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in patients with advanced CKD. In another study of patients undergoing hemodialysis, a 0.25 mmol/kg oral intake of potassium chloride raised serum potassium by 0.4 mmol/l at 3 hours.[77] Multiple compensatory mechanisms are enhanced in the setting of CKD to maintain potassium homeostasis, including intracellular deposition of dietary potassium[78] (e.g., extrarenal buffering [influenced by acid-base balance[79]], insulin secretion[80] [particularly when accompanied by concomitant carbohydrates and sugar[77]]), and increased colonic excretion[20] (attributed to increased numbers of large-conductance potassium channels in colonic epithelial cells).[20,81] All the aforementioned reports used doses of potassium supplements that exceed the differences usually achieved by diet.

Multiple observational reports in different severities of CKD explored the association between dietary potassium intake and outcomes that are important to patients (Table 1).[69,71,82–89] In a majority of them, surrogates of high potassium intake were associated with a lower risk of death or progression of kidney disease.

Table 1 | Studies associating potassium intake, CKD outcomes, and mortality

Study	Population	Dietary K^+ assessment	Outcome definitions	Factors associated with higher K^+ intake
Araki *et al.*, 2015[82]	623 Japanese patients with diabetes and eGFR ≥60 ml/min per 1.73 m^2 enrolled between 1996–2003 and followed up until 2013	Estimated from a single baseline 24-h urine collection	eGFR ↓ ≥50% or progression to CKD G4 or annual rate of eGFR decline	↓ risk of both outcomes Slower rate of annual eGFR decline
Smyth *et al.*, 2014[71]	*Post hoc* analysis of ONTARGET and TRANSCEND studies; >30,000 patients from 18 countries with vascular disease or diabetes with end-organ damage	Estimated 24-h urine K^+ from a single urine sample	eGFR ↓ ≥30% or CD, or eGFR ↓ ≥40% or CD, or rapid progression, or doubling of SCr or CD, or progression of proteinuria	↓ risk of CKD progression
Kieneker *et al.*, 2016[85]	5315 Dutch participants aged 28 to 75 yr in the PREVEND study and followed up for a median of 10.3 yr	Two 24-h urine collections at baseline and midway during follow-up	CKD incidence	↓ risk of incident CKD
Smyth *et al.*, 2016[88]	544,635 participants in the NIH-AARP Diet and Health Study, aged 51–70 yr	FFQ to assess K^+ intake over the preceding year	Death due to renal causes or need for dialysis	↓ risk of both kidney outcomes
Leonberg-Yoo *et al.*, 2017[86]	*Post hoc* analysis of MDRD study; 812 patients aged 15–70 yr with CKD G2–G4	Estimated from 24-h urine collection at baseline and at multiple time points	Initiation of chronic dialysis or kidney transplantation (kidney replacement therapy) Death from all causes	No association with kidney replacement therapy Association with ↓ risk of death
Mirmiran *et al.*, 2018[87]	1780 participants in the Tehran Lipid and Glucose study and followed up for 6.3 yr	Validated 168-item FFQ	CKD incidence	No association
He *et al.*, 2016[84]	3939 participants aged 21–74 yr with CKD (GFR 20–70 ml/min per 1.73 m^2) in the CRIC study	Estimated from 24-h urine collection at baseline and at years 1 and 2	Composite of ESKD or halving of GFR Death from all causes	↑ risk of CKD progression No association with risk of death
Noori *et al.*, 2010[69]	224 chronic HD patients from the NIED Study	Estimated 24-h urine K^+ from FFQ	Death from all causes	↑ risk of death only when comparing extreme intakes
Eisenga *et al.*, 2016[83]	Prospective cohort of 705 stable kidney transplant recipients	A single 24-h urine collection and FFQ	Graft failure Death from all causes	↓ risk of graft failure and death
Kim *et al.*, 2019[89]	1821 participants aged 20–75 yr with CKD G1–G5 (nondialysis) in the KNOW-CKD study	24-hour urine collection at baseline; spot urine	Composite of GFR ↓ ≥ 50% or ESKD	↓ risk of CKD progression

CD, chronic dialysis; CKD, chronic kidney disease; CRIC, Chronic Renal Insufficiency Cohort; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; FFQ, food frequency questionnaire; GFR, glomerular filtration rate; HD, hemodialysis; K^+, potassium; KNOW-CKD, Korean Cohort Study for Outcome in Patients with CKD; MDRD, Modification of Diet in Renal Disease; NIED, Nutritional and Inflammatory Evaluation in Dialysis; NIH-AARP, National Institutes of Health–American Association of Retired Persons; ONTARGET, Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; PREVEND, Prevention of renal and vascular end-stage disease; SCr, serum creatinine; TRANSCEND, Telmisartan Randomized Assessment Study in ACE Inhibitor Intolerant Subjects with Cardiovascular Disease.

It is unclear if the observed associations are explained by potassium intake or by potassium as a proxy for higher plant consumption[90–92] or specific eating patterns,[93–95] both of which have been associated with better outcomes in people with and without kidney disease. Observational studies in patients with CKD,[96] in kidney transplant recipients,[97] and in patients undergoing hemodialysis[98] associated higher plant consumption with lower cardiovascular mortality. Potassium concentrations and the incidence of hyperkalemia were not reported.

Few trials have evaluated the impact of dietary potassium modification in persons with CKD. A recent randomized controlled trial of 42 patients with CKD G3a–G4 compared dietary counseling focusing on potassium restriction (with sodium polystyrene sulfonate if serum potassium ≤4.5 mmol/l was not achieved) with general nutritional advice over 24 months; significant reductions in neuropathy scores were observed with potassium restriction.[99] Another randomized controlled trial of patients with CKD G4, hypertension but no diabetes, compared alkaline-rich fruits and vegetables with sodium bicarbonate over 1 year, observing no change in serum potassium or detected hyperkalemia.[100] Finally, 2 pilot feasibility studies investigating the safety and acceptability of a DASH diet in patients with CKD G3a–G3b reported no change in plasma potassium and no adverse hyperkalemia events after 2 weeks[101] and 5 weeks.[102] Whether potassium supplementation results in renoprotection is also currently being examined in the "K^+ in CKD" study.[72]

Direct evidence in support of the current recommendation for restricting dietary potassium in patients with CKD was lacking; however, we did not find evidence that increased potassium intake, or liberalization of potassium restrictions, in patients with advanced CKD is safe. While we acknowledge that dietary potassium restriction is a valid strategy to treat acute hyperkalemia, we hypothesize that potassium restriction as a general strategy to prevent hyperkalemia in persons with CKD may deprive patients of the beneficial effects associated with potassium-rich diets. We recommend that interventional trials be conducted to clarify optimal dietary potassium advice for patients with CKD (Table 2). In the absence of this work, we suggest developing educational material showing potassium content in foods that promotes low-potassium plant-based foods, especially vegetables, for use when clinicians believe that switching from high-potassium foods is clinically indicated, with an emphasis on overall healthy dietary pattern such as the Mediterranean diet and healthy eating index.

Hypokalemia

Hypokalemia, defined as a potassium concentration <3.5 mmol/l, affects approximately 1% to 3% of the general and CKD populations, and its prevalence and clinical importance are likely underrecognized (Table 3).[103–123] Patients undergoing dialysis, while generally viewed as being at high risk for hyperkalemia, also may develop hypokalemia, with an estimated prevalence of 1% to 2% among those undergoing hemodialysis and being more common (5%–22%) among persons undergoing peritoneal dialysis, although this rate varies by country.[115–117,124]

Renal potassium loss that occurs as a result of medication use is a common cause of hypokalemia in adults (Supplementary Table S4),[125–130] especially with use of thiazide diuretics, which are associated with 5-fold increased risk.[131] Other common diagnoses include mineralocorticoid-driven hypertension, tubulopathies, and gastrointestinal losses.[132,133] Nearly one quarter of high-risk patients experience hypokalemia after bowel preparation for a colonoscopy.[109] In patients undergoing dialysis, the predominant causes of hypokalemia are low potassium dialysate, low dietary potassium intake, and malnutrition.[117,118,123]

In the acute setting, abnormalities such as a U wave on an electrocardiogram (ECG) and ventricular arrhythmias can be present in an estimated 25% to 66% of severe cases.[111,112,134,135] The risk of mortality associated with hypokalemia may be greater than that associated with hyperkalemia, even in patients with CKD and patients undergoing dialysis[103,104,114,116,119,121]; however, studies relating hypokalemia to adverse outcomes are observational and subject to uncontrolled confounding.[105,108,114,136]

We suggest a novel and practical approach to hypokalemia recognizing the most common causes

Table 2 | Summary of evidence and future research recommendations for dietary potassium in CKD

What we know	What we think	Future research
K^+-rich diets are consistent with fruit and vegetable-rich healthy dietary patterns. K^+ supplementation, at a general population level, reduces blood pressure and lowers the risk of stroke. In people with CKD, estimations of dietary K^+ correlate poorly with circulating K^+.	Generalized dietary K^+ restriction in people with CKD may deprive them from other beneficial effects and nutrients of K^+-rich diets.	• Investigate the effect of dietary K^+ restriction in CKD on circulating levels • Investigate the effect of fruit- and vegetable-rich diets in CKD • Develop new methods and validate existing methods to estimate dietary K^+ intake in people with CKD • Evaluate the impact of dietary K^+ on serum concentration in people with CKD • Evaluate the effects of dietary K^+ restriction in people with CKD on clinically important outcomes, including harms • Evaluate the effects of unrestricted fruit/vegetable intake on the risk of hyperkalemia in people with advanced CKD or who are undergoing dialysis

CKD, chronic kidney disease; K^+, potassium.

Table 3 | Summary of studies describing prevalence and outcomes associated with hypokalemia

Study type	No CKD	CKD	HD	PD
Prevalence				
General population	1.9%–2.7%[103,108] Precolonoscopy: 4.2%[109] Preelective bypass: 1.4%[110] Emergency room: 5.5%–11%[111,112] Hospitalizations: 12%[113]	2.0%; 1.6%; 3.0%; 3.2%[103,104,106,114]	1.4%[115]	5.4%–27.9%[115–119]
Specific comorbidities	Primary hyperaldosteronism: 56%[120] Hypertension: 3.8%[121]	CHF: 19% ($K^+ < 4$ mmol/l)[105]		
Outcomes				
All-cause mortality	HR: 1.5 (3 vs. 4.2 mmol/l K^+)[103]; 2.8 (2.9–3.4 vs. 4.1–4.4)[121]; 1.0 (NS) (<3.5 ml vs. ≥3.5 mmol/l)[108]; 1.2 (<3.5 vs. 3.5–5.4 mmol/l)[122]	HR: 1.6 (3 vs. 4.2 mmol/l K^+)[103]; IRR: 3.1 (<3.5 vs. 4.5–4.9 mmol/l)[104]; HR: 1.6 (<4 vs. 4–4.9 mmol/l)[105]; 2.0 (<3.5 vs. 4–4.9 mmol/l)[106]; 1.7 (<3.8 vs. 3.8–5.5 mmol/l)[114]	HR 1.14 (0.88–1.46) (<4.5 vs. ≥4.5 mmol/l)[115]; 1.03 (0.97–1.09) (<4 vs. 4–5 mmol/l)[123]	HR: 1.4 (<4.5 vs. ≥4.5 mmol/l)[115]; 1.1 (NS) (<3.5 vs. 4–4.5 mmol/l)[116]; 1.8 (<3.5 vs. ≥3.5 mmol/l)[118]; 1.8 (3–3.5 vs. 4–4.5 mmol/l)[119]
CVD mortality	HR: 1.1 (3 vs. 4.2 mmol/l K^+)[103]	HR: 1.2 (3 vs. 4.2 mmol/l K^+)[103]; 1.7 (<4 vs. 4–4.9 mmol/l)[105]		HR 1.1 (NS) (<3.5 vs. 4–4.5 mmol/l)[116]
MACE		IRR: 1.9 (<3.5 vs. 4.5–4.9 mmol/l)[104]		
ESRD	HR: 1.4 (3 vs. 4.2 mmol/l K^+)[103]; 0.8 (NS) (<3.5 ml vs. ≥3.5 mmol/l)[108]	HR: 1.2 (3 vs. 4.2 mmol/l K^+)[103]; 1.0 (NS) (<3.5 vs. 4–4.9 mmol/l)[106]		

CHF, congestive heart failure; CKD, chronic kidney disease; CVD, cardiovascular disease; ESRD, end-stage renal disease; HD, hemodialysis; HR, hazard ratio; IRR, incidence rate ratio; MACE, major adverse cardiovascular events; NS, not statistically significant; PD, peritoneal dialysis.

(Figure 3).[29,133,137,138] History and physical examination can diagnose medication-induced and gastrointestinal-related hypokalemia. The presence of hypokalemia in a person with hypertension and normal GFR should raise suspicion for hyperaldosteronism, and a blood aldosterone:renin ratio may be diagnostic.[139] For initial biochemical testing, we suggest that only mineralocorticoid receptor antagonists need to be discontinued; however, in patients with a high pretest probability of hyperaldosteronism and equivocal aldosterone:renin ratio results, aldosterone:renin ratio testing should be repeated after discontinuing diuretics and renin-angiotensin-aldosterone system (RAAS) inhibitors.[140] This strategy may lead to a diagnosis such as a surgically remediable adrenal adenoma.[137,138,141] Of note, the interpretation of the aldosterone:renin ratio is heavily dependent upon local laboratory methods, including the lower limit of detection for renin. In normotensive patients without obvious cause, measurement of a spot urine sodium and chloride level helps distinguish tubulopathy and surreptitious causes,[44,133] and heritable tubulopathies may be confirmed with genetic testing.[142] When a clinical explanation is lacking, urine potassium measurements have been suggested, particularly as a ratio to urine creatinine concentration[29,143-145]; however, recent evidence suggests high intra-individual variability and lack of specificity.[146,147] The trans-tubular potassium gradient was proposed as a diagnostic tool but has too many limitations to be recommended.[133,145,148,149] Rare etiologies are summarized in Supplementary Table S5.

Treatment of hypokalemia is aimed at preventing short- and long-term complications without precipitating hyperkalemia.[113,150] Multiple observational studies suggest that the optimal range of potassium is 4 to 5 mmol/l,[103,105,110,115,119] but potassium thresholds for treatment initiation, postponement of elective procedures, and referral to the emergency department have not been defined. Acutely, treatment decisions generally depend on the severity of hypokalemia and the presence of ECG abnormalities or symptoms.[134] For a patient with severe hypokalemia and paralysis, distinguishing hypokalemic periodic paralysis from other causes of hypokalemia is important because of the risk of post-therapeutic hyperkalemia, and the risk of relapse, in the former.[144] For hypokalemia that results from a potassium deficit, each 0.3 mmol/l lower serum potassium corresponds to approximately 100 mmol lower total body potassium.[134] Oral supplements are safe and generally preferred to intravenous replacement in noncritical scenarios.[74] However, most oral formulations have relatively low potassium content (Supplementary Table S6), and serial monitoring is an important part of management.[122,151] Intravenous potassium chloride at a rate up to 20 mmol/h can be a safe alternative in persons with severe hypokalemia and when oral intake is not possible; note that high concentrations of potassium chloride given peripherally can cause pain or sclerosis.[150,152] Potassium replacement can increase serum sodium concentration,[153] and thus caution is required when correcting hypokalemia in patients with concomitant severe hyponatremia.

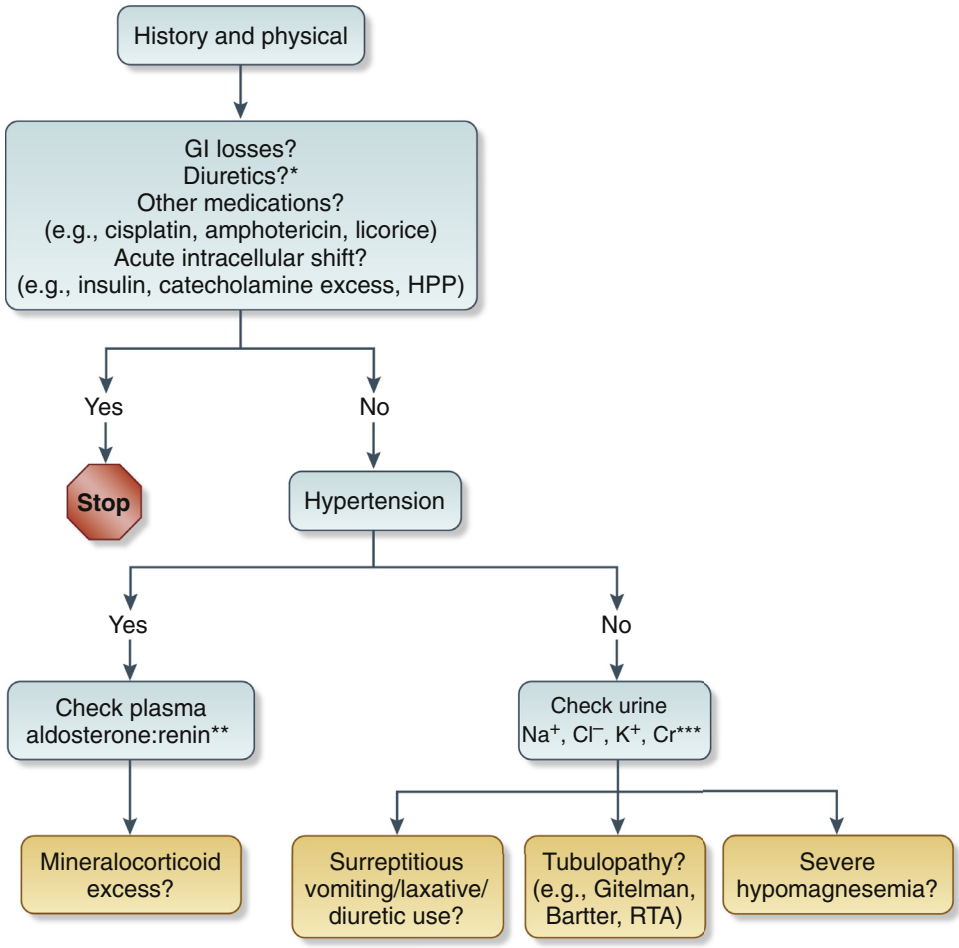


Figure 3 | Pragmatic diagnostic algorithm for hypokalemia. *If hypokalemia seems disproportionately severe to the dose of diuretic, one may still consider aldosterone excess. **Ideally, after correcting serum potassium levels, with the patient not taking mineralocorticoid receptor antagonists. Other medications, including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, may be continued in most cases; interpretation is dependent upon local laboratory methods and reporting.[137,138] ***Typical presentations: vomiting: urine Na/Cl > 1.6, low urine Cl; laxative: urine Na/Cl < 0.7, high urine Cl; active diuretic use: similar to tubulopathy; tubulopathy: urine K/creatinine (Cr) > 2.5 mmol/mmol, with urine Na/Cl ∼1. Tubulopathy may be confirmed via genetic testing.[29,133] Cr, creatinine; HPP, hypokalemic periodic paralysis; RTA, renal tubular acidosis.

Strategies to treat chronic hypokalemia should be tailored to the underlying cause (e.g., discontinuation of diuretics where alternative therapies exist). Chronic potassium repletion can be costly, poorly tolerated, and involve a large pill burden. Initiation of RAAS inhibitors is an alternative, as are mineralocorticoid receptor antagonists/potassium-sparing diuretics, with the latter generally more efficacious and possibly better tolerated than potassium supplementation.[154–159] Concomitant hypomagnesemia is likely under-recognized yet important to address when correcting hypokalemia.[160,161]

Localization and removal of an aldosterone-producing adenoma in patients with primary hyperaldosteronism will correct the hypokalemia and may improve cardiovascular outcomes.[120] The management of tubulopathies can be complex, and hypokalemia may not be fully correctable.[162] For patients with hypokalemia who are undergoing dialysis, spironolactone has been used effectively.[163,164] In contrast, there may be little effect on potassium concentration by RAAS inhibition in patients receiving peritoneal dialysis.[165] An increase in dietary potassium also should be considered.[151,166]

Because of time constraints, emergency management of hypokalemia was not addressed at the conference. However, current evidence and future research priorities in this area are included in Table 4.

Acute hyperkalemia

We defined acute hyperkalemia as a potassium result above the upper limit of normal that is not known to be chronic. Acute hyperkalemia is a relatively common occurrence in the emergency department. In the United States the prevalence of potassium >5.0 mmol/l was 3.6%,[112] whereas in Switzerland the prevalence of potassium >4.5 mmol/l, the upper limit of normal, was 8.8%.[167]

Risk factors. Factors associated with an increased likelihood of the development of hyperkalemia are summarized in Supplementary Table S7. CKD as early as G3a and G3b is

Table 4 | Summary of evidence and future research recommendations for hypokalemia

What we know	What we think	Future research
Hypokalemia is common, especially with diuretic use and pericolonoscopy. Hypokalemia is morbid: Mortality is the same or higher than hyperkalemia and is associated with arrhythmias, stroke, infection, and ESKD. Most hypokalemia is due to a few common etiologies; urine K^+ has high within-person variability and does not reliably distinguish between causes. Management differs by cause: Hypokalemia due to diuretics can be treated by K^+ supplements, K^+-sparing diuretics/MRAs (most effective), or ACEi/ARBs; hypokalemia due to tubulopathies may not be fully correctable; hypokalemia due to hypokalemic periodic paralysis should be corrected very cautiously because it has high risk for overcorrection. Potassium replacement is relatively safe.	Unexplained hypokalemia merits investigation: • Concomitant hypomagnesemia is important. • Hyperaldosteronism is underdiagnosed. • Hypokalemia in patients on PD is often exacerbated by low K^+ in diet and malnutrition. Pragmatic algorithms should incorporate prevalence of underlying etiologies. Management protocols should be implemented (preferably in electronic orders): • ECG and magnesium should be checked. • Intervene when potassium <3.5 mmol/l. • Address concomitant hypomagnesemia (this may be harder with PPI use). • For diuretic-induced hypokalemia, first consider discontinuation of diuretic. • Diet should always be considered given the evidence for low K^+ intake in PD, CKD, and general population overall.	• Consensus definition of hypokalemia • Frequency and implications of concomitant hypomagnesemia • Methods to promote awareness of hypokalemia, particularly among diuretic users and pericolonoscopy • Validity of the pragmatic diagnostic algorithm • Standardization of clinical laboratory measurement and reporting of diagnostic biomarkers • Risk-based approach to guide treatment of hypokalemia, postponement of elective procedures, ED referral, and monitoring in high-risk patients (e.g., diuretic users and pericolonoscopy) • Effectiveness of potassium repletion protocols and dietary interventions in pragmatic trials • Frequency of rebound hyperkalemia • Outcome-based evidence for the treatment of chronic hypokalemia

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; ECG, electrocardiogram; ED, emergency department; ESKD, end-stage kidney disease; K^+, potassium; MRA, mineralocorticoid receptor antagonists; PD, peritoneal dialysis; PPI, proton-pump inhibitor.

among the most important predictors of hyperkalemia.[103,126,168–171] Potassium-sparing diuretics and RAAS inhibitors are the drugs most frequently associated with hyperkalemia.

Diagnosis. Serum or plasma measurement is acceptable; research reports should state clearly which was used (serum potassium is 0.1–0.7 mmol/l higher).[172–174] Point-of-care devices have limited accuracy and precision,[175–178] which should limit their widespread adoption; however, some devices have been shown to be sufficiently accurate, with mean differences of 0.1 to 0.5 mmol/l when compared with laboratory measurements, to be useful in acute settings.[179,180] A falsely elevated potassium level may occur with fist clenching during the blood draw, mechanical trauma, tourniquet use >1 minute, blood clotting, or elevated white blood cell or platelet counts.[181–183]

The ECG manifestations of acute hyperkalemia relative to potassium concentration have been described.[184–189] The sequence is reported to be peaked T waves, prolonged PR interval, progressive widening of QRS complex, followed by sine wave patterns, ventricular fibrillation, and asystole. The most common ECG change is peaked T waves, followed by prolonged QRS[187,190] (Supplementary Figure S2). Conduction block patterns also are described. A retrospective study of 188 patients found that bradycardia (relative risk, 12.3), junctional rhythms (relative risk, 7.5), and QRS widening (relative risk, 4.7, but not peaked T waves) were associated with adverse outcomes.[191] For this reason we suggest classifying hyperkalemia as mild, moderate, or severe based on the potassium concentration and the presence or absence of ECG changes (Figure 4). However, normal ECGs also have been reported in patients with severe chronic hyperkalemia,[192] and it is not known whether ECG changes are sensitive in the prediction of potentially lethal arrhythmia.

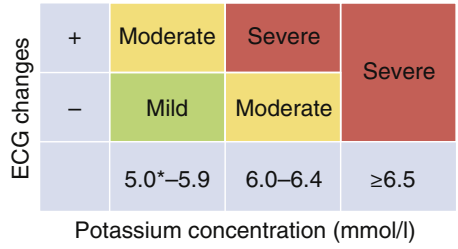
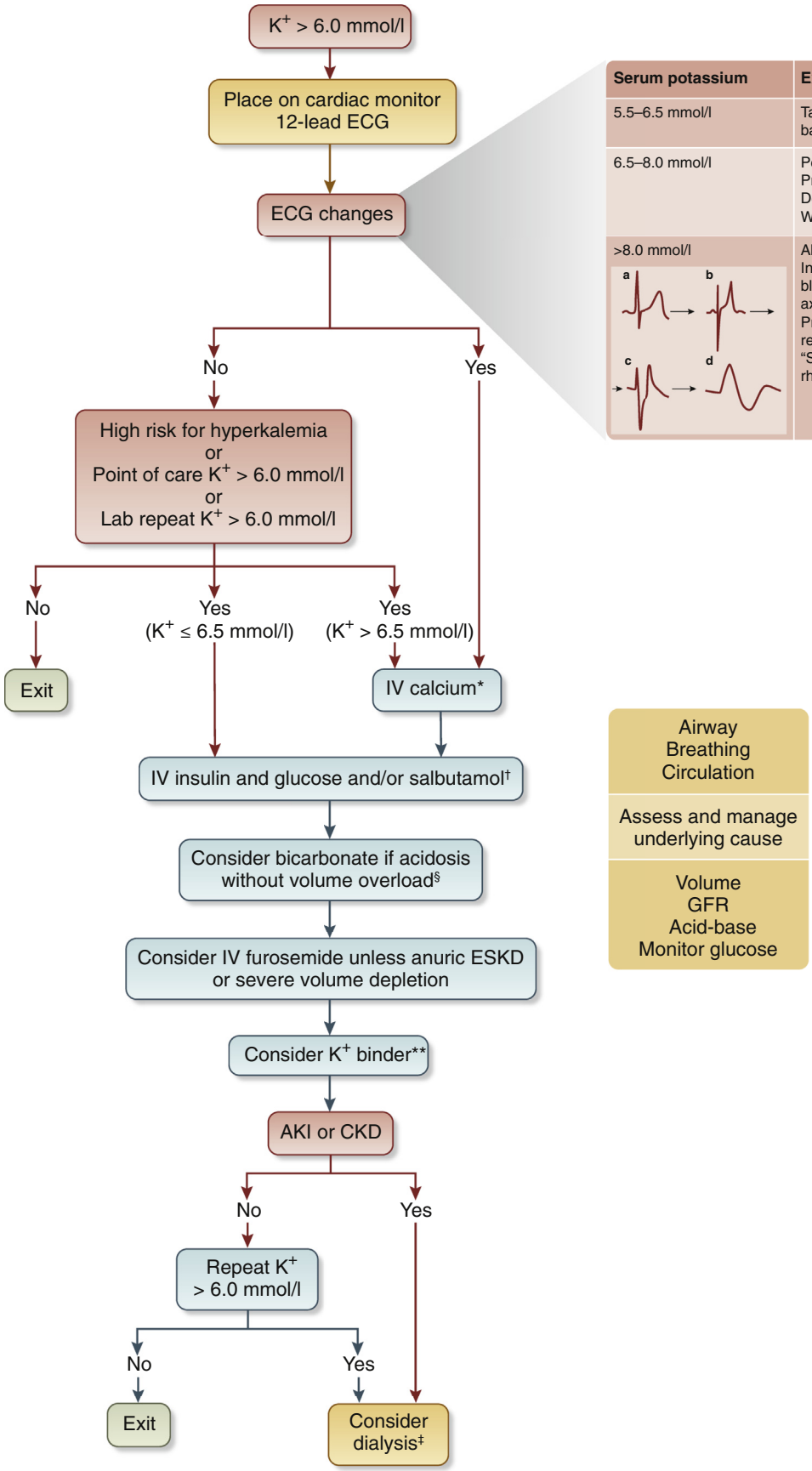


Figure 4 | Severity of acute hyperkalemia: expert opinion-based risk classification. *5.0 or upper limit of normal range. ECG, electrocardiogram.

Management. We suggest that outpatients with acute hyperkalemia who have a potassium concentration of >6.0 mmol/l, or hyperkalemia with any new ECG changes, should be referred to a facility with cardiac monitoring, usually an emergency department that can address this urgently.[184] We base our suggestions for management (Figure 5[184–189,193–195]) on available evidence but note that most evidence was generated in convenience samples of stable patients with predialysis hyperkalemia and that our synthesis into an algorithm is untested. We recommend monitoring of the vital signs, continuous cardiac monitoring and performing a 12-lead ECG.[184] We suggest repeating the potassium measurement to rule out pseudohyperkalemia, or if hemolysis is present, using clinical judgment and the presence of ECG changes to balance the importance of verification against the potential for delay of treatment.

In hyperkalemic patients with ECG changes, we suggest the administration of calcium salts (1000–3000 mg of



Serum potassium	Expected ECG abnormality
5.5–6.5 mmol/l	Tall, "peaked" T waves with narrow base, best seen in precordial leads
6.5–8.0 mmol/l	Peaked T waves Prolonged PR interval Decrease amplitude of P waves Widening of QRS complex
>8.0 mmol/l	Absence of T wave Intraventricular blocks, fascicular blocks, bundle branch blocks, QRS axis shift Progressive widening of QRS resulting in bizarre morphology "Sine wave" patterns (sinoventricular rhythm), VF, asystole

calcium gluconate or 1000 mg of calcium chloride).[195] Subsequent doses should be considered if ECG changes persist after 5 minutes or recur. We prefer the use of calcium gluconate to calcium chloride because the latter has been associated with skin necrosis.[196] We suggest intravenous administration of insulin and glucose to shift potassium intracellularly.[195] Administration of 5 units of regular insulin appears as effective in lowering potassium concentration as the administration of 10 units, although evidence is limited; hypoglycemia is a potential complication.[197,198] In addition, or as an alternative to insulin-glucose, administration of β-agonists is suggested.[195] Use of 10 mg salbutamol via nebulizer results in significant reduction of potassium at a peak of 120 minutes after use (90 minutes for 20 mg).[197] Increased heart rate, tremors, palpitations, and mild anxiety were reported adverse effects.[193] Concomitant use of insulin-glucose and salbutamol is feasible, additive, and internationally recommended.[199,200] In patients with concomitant metabolic acidemia, sodium bicarbonate can be considered, although data on its efficacy are conflicting.[201,202]

Subsequently, potassium-binding agents and loop diuretics can be considered; evidence of effectiveness in the acute setting is lacking. During the treatment of acute hyperkalemia, frequent reassessments of potassium, glucose (in cases of insulin administration), and the ECG are suggested. The underlying cause for acute hyperkalemia should be evaluated. We suggest considering dialysis in cases of persistently elevated potassium concentration exceeding 6 mmol/l or ECG changes that are not responsive to medical management.

Research recommendations are summarized in Table 5.[99]

Chronic hyperkalemia

The definition of hyperkalemia is generally based on the distribution of potassium values in the general population. Notwithstanding the validity of this approach, a prognostic-based definition[203] would convey the graded association with adverse events: risk increases continuously with higher potassium concentrations, and CKD modifies both the distribution of potassium concentration[103] and the associated risk.[169,204–207] Incorporating risk factors[103,126,204] into prediction models may help achieve better individual risk stratification.[168,208] There is no consensus on the magnitude, duration, and frequency of elevated potassium values that define chronicity.

Monitoring strategies and measurement methods. Chronic hyperkalemia is usually asymptomatic and is more likely to be detected in patients who undergo more frequent testing,[126] although this may represent confounding by indication. In patients at risk for hyperkalemia, testing potassium concentration before and 1 to 2 weeks after initiation of RAAS inhibition is recommended, based on expert opinion in several guidelines.[209,210] However, population-based data show that adherence to these guidelines is limited.[168,211]

Clinical significance of chronic hyperkalemia. The development of hyperkalemia is associated with increased risk of adverse events. These associations have been described in numerous observational studies, consistently showing U-shaped associations between serum potassium and mortality,[103,169,205] The plausibility of the association being in part causal is supported by the electrophysiological role of potassium and the known cardiac abnormalities that can be induced by both high and low potassium concentrations; however, uncontrolled confounding also likely plays an important role, in that greater disturbances in physiology would be expected to produce greater changes in potassium.

Because of the potential for hyperkalemia to cause life-threatening arrhythmias, the detection of preprocedure hyperkalemia may lead to delays and cancellations. One study observed a nonsignificant tendency toward increased cardiopulmonary resuscitations and death in (the very few) patients undergoing surgical interventions with a preoperative serum potassium concentration of >5.3 mmol/l,[110] and in patients undergoing dialysis, a preoperative serum potassium concentration of >5.5 mmol/l was associated with higher risk of major adverse cardiovascular events.[212] We were unable to identify any studies examining the impact of correcting preoperative hyperkalemia.

Risks and benefits of antihyperkalemia therapies. Therapeutic options are summarized in Table 6.[168,204,213–224] People with advanced CKD and ESKD who experience elevated potassium concentrations are commonly advised to follow low-potassium diets. However, randomized evidence about whether this approach is effective is lacking and needed. An unintended consequence of this advice may be a shift toward lower dietary quality, which should be specifically examined in any trials of dietary intervention, along with dietary satisfaction, patient experience, costs, illness intrusiveness, and abdominal side effects.

Figure 5 | Management of acute hyperkalemia in adults. The thresholds for actions are opinion based. Suggested drug doses are based on a 2010 systematic review[193] and a subsequent observational study.[194] Electrocardiogram (ECG) changes commonly reported with increasing potassium concentrations have been described in the literature.[184–189] *IV 1 g calcium gluconate (3 × 10 ml of 10% solution, each containing 93 mg elemental calcium, 2.3 mmol) or calcium chloride (10 ml of 10% solution, 273 mg elemental calcium, 6.8 mmol). †IV regular insulin 5 units plus 25 g glucose (50 ml of 50%) is as effective as albuterol (salbutamol) 10 mg nebulized; insulin and albuterol may have an additive effect. Beware of hypoglycemia. §IV bicarbonate (1 amp of 50 ml of 8.4% solution, Na^+ 50 mmol, HCO_3^- 50 mmol) over 15 minutes. **Potassium binders: sodium polystyrene sulphonate 15–60 g p.o./p.r. (do not give with sorbitol) or zirconium cyclosilicate 10 g 3×/d (patiromer not advisable as onset of action is 7 hours). This guidance is suggestive as there are limited data on onset of action with no head-to-head studies between potassium binders. ‡Hemodialysis is the modality of preference. AKI, acute kidney injury; CKD, chronic kidney disease; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; IV, intravenous; K^+, potassium; VF, ventricular fibrillation. Adapted from *Resuscitation*, volume 95, Truhlář A, Deakin CD, Soar J, et al. European Resuscitation Council Guidelines for Resuscitation 2015: Section 4. Cardiac arrest in special circumstances, pages 148–201, © 2015, with permission from the European Resuscitation Council.[195]

Table 5 | Future questions for hyperkalemia research

Acute hyperkalemia	
Understanding the burden of disease	• Determine the prevalence of hyperkalemia in patients with acute kidney injury
Testing the efficacy of acute management	• Compare the efficacy and safety of calcium chloride and calcium gluconate for management of acute hyperkalemia with ECG changes • Evaluate the efficacy of loop diuretics for treatment of acute hyperkalemia
Understanding the measurement properties of ECG in the prediction of clinical outcomes	• Determine the ECG changes that warrant administration of intravenous calcium salts
Testing the efficacy of noninvasive screening for hyperkalemia	• Evaluate use of artificial intelligence and smart phone technology for noninvasive monitoring to detect hyperkalemia in the outpatient setting
Chronic hyperkalemia	
Testing the efficacy and harms of dietary intervention	• Including PROs and clinically important cardiorenal outcomes, as well as serum potassium concentration
Testing the efficacy of newer agents for potassium reduction in populations not well represented in current trials	• In ESKD people receiving maintenance hemodialysis • In people with functioning kidney transplants, test efficacy and harms, investigate impact on immunosuppressant levels • In diverse populations (differing by clinical context, ethnicity, or diet) • In people with type 4 RTA and normal or reduced eGFR
Evaluating the risks and benefits of maintaining and optimizing RAAS blockade despite hyperkalemia	• In people with heart failure for cardiovascular outcomes • In people at risk of progression for preventing CKD progression
Preventing clinical events arising from hyperkalemia	• In people with hyperkalemia (e.g., diabetes with type 4 RTA, advanced CKD, ESKD receiving hemodialysis) for survival and prevention of arrhythmias
Preventing health service utilization arising from hyperkalemia	• Reduction of hospitalizations, emergency department presentations, investigations, and management arising as a response to hyperkalemia
Testing the impact of the newer agents on the patient experience using patient reported outcomes	• PROs for standard of care vs. newer strategies • Gut symptoms, pill burden, illness intrusiveness (medication timing away from binders, monitoring, possible diet liberalization), peripheral neuropathy[99]
Testing the relative role of the newer agents	• Important to compare with placebo and with SPS (lower cost; wide experience) • In broad populations head-to-head trials, including comparison with SPS (lower cost; wide experience) • Directly assessing and modeling the impact of ability to continue RAAS blockade
Understanding the dynamics of potassium	• Monitoring frequency; novel continuous monitoring devices may provide data for modeling studies to define optimal monitoring frequencies • Deprescribing trials

CKD, chronic kidney disease; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; PROs, patient reported outcomes; RAAS, renin-angiotensin-aldosterone system; RTA, renal tubular acidosis; SPS, sodium polystyrene sulfonate.

The concept that chronic hyperkalemia can be alleviated in people with normal or reduced estimated GFR is supported by randomized trial evidence, with durations of up to 1 year for the newer agents, patiromer and sodium zirconium cyclosilicate, with less compelling evidence from short-term studies (up to a week) for sodium polystyrene sulfonate (SPS).[225–230] There is limited evidence of the efficacy and safety of these agents in people with ESKD.[227,229] Relatively common and potentially clinically relevant adverse events reported for patiromer include constipation and hypomagnesemia, and for sodium zirconium cyclosilicate include edema.[231] Adverse events for SPS are less well clarified, although there are concerns about associations with rare but serious conditions of intestinal necrosis when given with sorbitol, which prompted a Food and Drug Administration warning in 2009 and withdrawal of formulations including 70% sorbitol.[220,231] A subsequent retrospective single-center study of around 125,000 patients found a low incidence rate of colonic necrosis overall that was not significantly different in people who had or had not been exposed to SPS (0.14% in patients who had received SPS and 0.07% in patients who had not received it; relative risk 2.1; 95% CI: 0.7–6.5).[232] In a linked-data cohort study of 28,000 propensity-matched SPS users between 2003 and 2015, outpatient SPS prescription was associated with increased hospitalization for adverse GI events (19 per 10,000 in the 30 days following prescription, compared with 9 per 10,000 in control subjects);[233] this was independently confirmed in a similar administrative cohort.[234] After release of these findings, some have strongly recommended that SPS no longer be used.[235] Although these analyses are not randomized and residual confounding cannot be excluded, the small absolute rates (7–10 per 10,000) mean that randomized evidence to exclude or confirm these concerns is unlikely; similarly, parallel data from large-scale postmarketing studies for the newer agents will not be available for some time. We suggest the evidence priorities should be to definitively establish the benefit of potassium control for clinically meaningful events through randomized trials in order to inform assessments of risk tolerance to rare but serious events.

Data are also limited on safety signals, including rates of low potassium and magnesium concentrations, edema, and potentially associated clinical events. Drug interactions are common, resulting from direct binding (patiromer and SPS) and alteration in gastric pH (sodium zirconium cyclosilicate), resulting in a manufacturers' recommendation to take all other oral drugs at least 3 hours before or after patiromer[222] and SPS[236] and at least 2 hours before or after sodium zirconium cyclosilicate for drugs whose

Table 6 | Approaches to the management of chronic hyperkalemia

Strategy	Comment
Dietary potassium restriction	• Reliant on lifestyle change • Uncertainty on degree and reliability of response • Poor evidence base to support the practice • Financial cost of special diets • Practical issues in implementation • Potential for harm because of impact of diet on intake of other beneficial nutrients, healthy dietary pattern • Potential for harm through loss of enjoyment in food and impact on social activities
Permissive approach (no additions or changes to management despite awareness of hyperkalemia)	• The extent of practice poorly documented • Potentially could be tested in randomized trials given the uncertainty on benefits and harms of approaches based on tolerance of different potassium thresholds
Discontinuation of medications elevating potassium (e.g., RAAS inhibitors)	• Common strategy • Effect on outcomes unknown[168,204]
Use of potassium-wasting diuretics	• Dependent on kidney function; RCT evidence of no impact on potassium concentrations in people on PD with residual kidney function[213]; small pre-post studies suggest that metolazone but not thiazides may be kaliuretic in patients with GFR <20 ml/min per 1.73 m^2 [214,215] • Degree and predictability of response uncertain • Clearest role when diuresis or an additional antihypertensive agent is also a desired effect • In between-study comparisons, high-dose furosemide was more kaliuretic than metolazone in patients with GFR <20 ml/min per 1.73 m^2 [214,216]
Mineralocorticoid agonists	• Dependent on kidney function • Weak (small observational studies and clinical trials) and inconsistent data about efficacy[217,218] • Possibly harmful, given the hypothesis that mineralocorticoid antagonism may reduce CV outcomes in ESKD
Gastrointestinal potassium wasting	• Potential management option • Scant evidence • One small pre-post study[219] found that increasing the number of stools from 1 to 2–4 per day with laxatives lowered potassium from mean 5.9 ± 0.2 to 5.5 ± 0.2 mmol/l without inducing diarrhea
Correction of coincident acidosis	• No evidence
Use of low potassium dialysate	• Observational evidence of increased risk of mortality, arrhythmias and emergency department visits at dialysate potassium concentration <2 mmol/l and with higher serum-dialysate gradients (see text)
Older potassium binder: SPS	• Concern about rare but serious adverse gastrointestinal effects from postmarketing studies • FDA warning in 2009 against use with sorbitol[220] • Use only in patients with normal bowel function • Limited randomized evidence for efficacy • Binds other medications; other oral medications to be taken at least 3 h before or 3 h after SPS, 6 hours in patients with gastroparesis[221]
Newer potassium binders: patiromer, zirconium cyclosilicate	• Evidence for efficacy in reducing hyperkalemia incidence of up to 12 mo • Evidence of adverse effects for exposure of up to 12 mo • Lack of large-scale postmarketing studies • Patiromer binds other medications; other oral medications to be taken at least 3 h before or 3 h after patiromer[222] • Zirconium cyclosilicate affects the absorption of drugs whose bioavailability is dependent on gastric pH[a]; these oral medications should be taken at least 2 h before or 2 h after zirconium cyclosilicate[223]

CV, cardiovascular; ESKD, end-stage kidney disease; FDA, US Food and Drug Administration; GFR, glomerular filtration rate; PD, peritoneal dialysis; RAAS, renin-angiotensin-aldosterone system; RCT, randomized controlled trial; SPS, sodium polystyrene sulfonate.
Conference participants were unable to provide evidence-based recommendations or suggestions on preferential strategies because of a lack of evidence for most of the strategies, the absence of evidence on comparative efficacy of alternative strategies, and the potential for harm with at least some of them.
[a]Zirconium cyclosilicate interferes with the absorption of drugs that exhibit pH-dependent bioavailability, e.g., atorvastatin; the azole antifungals ketoconazole, itraconazole, and posaconazole; dabigatran; furosemide; some drugs for HIV (atazanavir, nelfinavir, indinavir, ritonavir, saquinavir, raltegravir, ledipasvir, and rilpivirine); and the tyrosine kinase inhibitors (erlotinib, dasatinib, and nilotinib). We were unable to identify a comprehensive reference permitting clinicians to identify whether an individual drug has gastric pH-dependent bioavailability. In 2018 the FDA initiated a process to improve approaches to the assessment of this issue.[224]

absorption is dependent on gastric pH (e.g., atorvastatin, azole antifungals, dabigatran, furosemide, protease inhibitors, and tyrosine kinase inhibitors).[223,237] This poses a practical challenge, particularly for those who take critical medications such as immunosuppressive drugs.

Improvement in potassium control could lead to increased use of RAAS inhibitors in patients with an evidence-based indication. In observational cohorts, hyperkalemia is associated with reduction or cessation of RAAS inhibitors,[43,168,204,238,239] while a small, exploratory analysis of 107 people with CKD receiving RAAS inhibitors and hyperkalemia controlled with patiromer found that only 44% of those randomized to withdrawal from patiromer continued on RAAS inhibitors compared with 94% of those randomized to ongoing patiromer.[240] In an uncontrolled study of the use of sodium zirconium cyclosilicate in 746 patients with

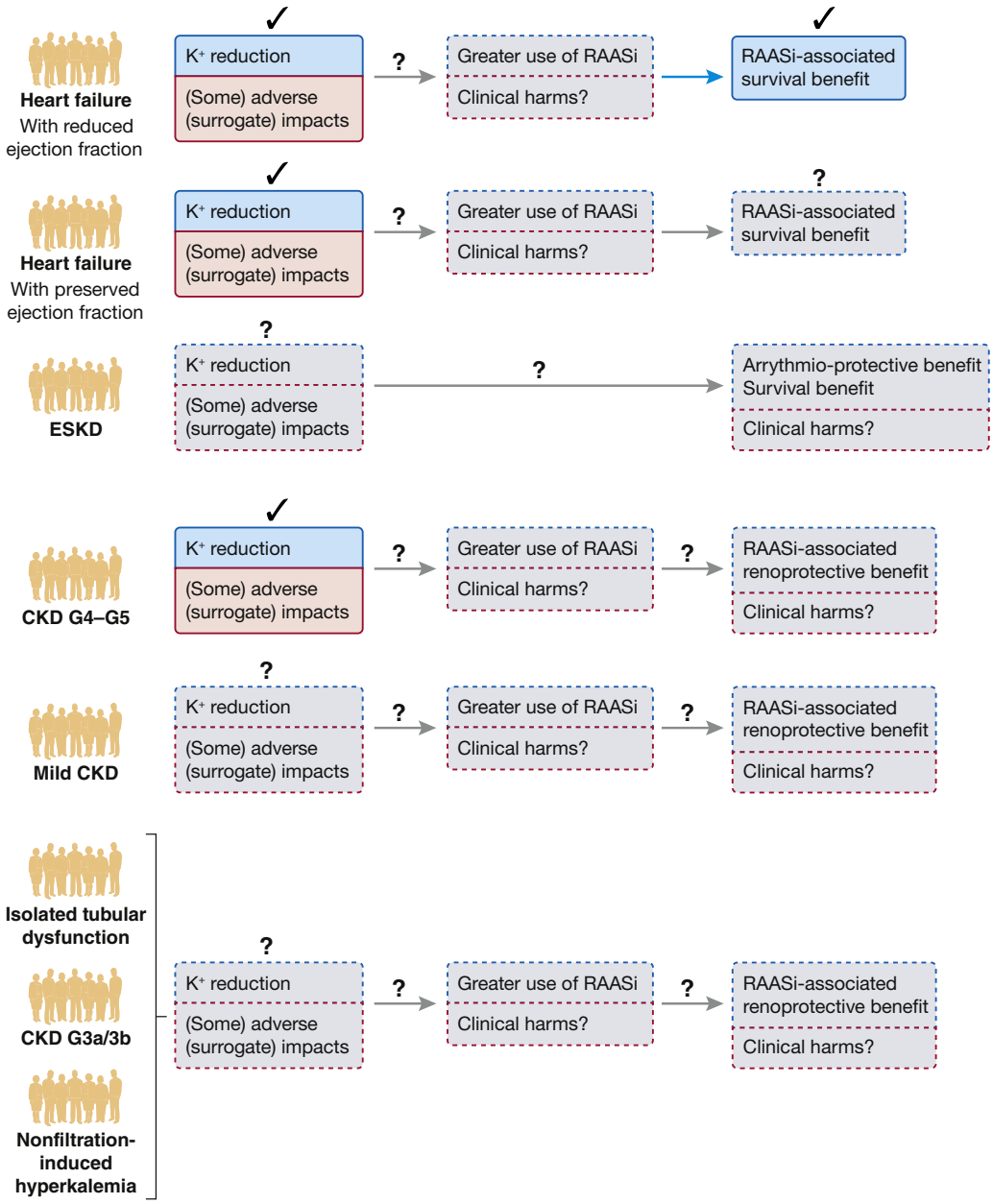


Figure 6 | Pathways to potential clinical benefit. Solid borders indicate propositions supported by evidence. Dotted lines indicate hypotheses that need testing in randomized trials. Arrows indicate causal pathways. Question marks indicate those that are not proven. CKD, chronic kidney disease; ESKD, end-stage kidney disease; K^+, potassium; RAASi, renin-angiotensin-aldosterone system inhibitors.

hyperkalemia, 38% of participants discontinued the drug for patient or protocol reasons. Of those who completed 12 months, final potassium was <5.1 mmol/l in 87%; 87% of those taking RAAS inhibitors continued on therapy or had their dose increased.[241] Results from the AMBER trial showed that in patients with resistant hypertension and advanced CKD (25 to ≤ 45 ml/min per 1.73 m^2), concomitant use of patiromer, compared with placebo, resulted in a larger proportion of patients using spironolactone at 12 weeks.[242]

RAAS inhibition clearly improves outcomes in patients with heart failure and reduced ejection fraction[238] and in patients with proteinuric kidney disease, including diabetes,[243] although its role in advanced CKD is less clear, based on evidence from a single trial of 224 participants with proteinuric CKD G4.[244] We regard it as critical to test whether such strategies to reduce the risk of hyperkalemia (e.g., examining existing or extended clinical indications for RAAS inhibition) improves patient-important outcomes (Figure 6).

Further light on the role of RAAS inhibition in advanced CKD will come from the ongoing UK STOP-ACEi trial, which will study 410 participants with CKD G4–G5 who currently are receiving RAAS inhibitors, randomizing them to continuation or cessation of RAAS inhibition.[245]

Among people with ESKD, low potassium dialysate (1.0–1.5 mmol/l) in observational studies is associated with mortality[246] and arrhythmias[123]; larger gradients between serum and dialysate potassium are associated with mortality and emergency department attendances[247]; and postdialysis hypokalemia is associated with mortality.[248]

Areas of further research on chronic hyperkalemia are outlined in Table 5.

Conclusion

We summarized here the evidence and controversies in the physiology, identification, and management of disturbances of potassium in the context of kidney diseases and hope that this report serves as a useful reference and outlines research priorities that will further strengthen the evidence base in this area.

APPENDIX

Other Conference Participants

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DISCLOSURES

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SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Figure S1. Studies in experimental animals show minimal change in the plasma K^+ concentration following a reduction in renal mass due to an adaptive increase in K^+ secretion by remaining nephrons.
Figure S2. Frequency of electrocardiogram abnormalities in acute hyperkalemia.
Table S1. Nutrient composition of selected foods.
Table S2. Advantages and pitfalls of current methods to estimate dietary potassium intake.
Table S3. Dietary potassium intake recommendations for adults in the general population and in persons with CKD.
Table S4. Common kaliuretic diuretics, their dosages, and duration of action.
Table S5. Additional causes of dyskalemias via a variety of mechanisms: interesting examples in the literature.
Table S6. Common oral potassium supplements and their formulations.
Table S7. Risk factors for hyperkalemia.
Supplementary References.

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