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Hyperkalemia in chronic kidney disease in the new era of kidney protection therapies

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Abstract

Despite recent therapeutic advances, chronic kidney disease (CKD) is one of the fastest growing global causes of death. This illustrates limitations of current therapeutic approaches and, potentially, unidentified knowledge gaps. For decades, renin-angiotensin-aldosterone system blockers (RAAS) have been the mainstay of therapy for CKD. However, they favor the development of hyperkalemia that is already common in CKD patients due to the CKD-associated decrease in urinary potassium (K^+) excretion and metabolic acidosis. Hyperkalemia may itself be life-threatening as it may trigger potentially lethal arrhythmia, and additionally may limit the prescription of RAAS blockers and lead to low K^+ diets associated to low dietary fiber intake. Indeed, hyperkalemia is associated with adverse kidney, cardiovascular and survival outcomes. Recently, novel kidney protective therapies, ranging from sodium/glucose cotransporter 2 (SGLT2) inhibitors to new mineralocorticoid receptor antagonists have shown efficacy in clinical trials. Herein, we review K^+ pathophysiology and the clinical impact and management of hyperkalemia considering these developments and the availability of the novel K^+ binders patiromer and sodium zirconium cyclosilicate, recent results from clinical trials targeting metabolic acidosis (sodium bicarbonate, veverimer) and an increasing understanding of the role of the gut microbiota in health and disease.

Key points

- Hyperkalemia is a potentially lethal consequence of CKD.
- Some commonly used treatments in CKD patients, like inhibitors of the RAAS system, have a potential effect worsening hyperkalemia
- New treatments available in the nephrologist's armamentarium can be used in order to maintain K levels in the safe range

Declarations:

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1. Introduction

Potassium (K^+) is the most abundant intracellular cation. Around 3,500 mmol (98% of total) K^+ are found within cells in the body. The normal plasma K^+ levels are roughly 4.0-5.0 mmol/l. Hyper and hypokalemia are associated with serious health consequences but, whereas there is wide agreement about the lower safe levels of plasma K^+ (3.5–3.6 mmol/l), this is not the case for the upper limit. Thus, the higher safe level for plasma K^+ has been set at 5.0 to 5.5 mmol/l [1,2] depending on medical specialties, associated comorbidities and acuteness/chronicity of K^+ elevation. In general (except for heart failure settings), physicians are more concerned about hypokalemia and its deleterious effects on arrhythmias, blood pressure and even stroke[3]. However, hyperkalemia is potentially lethal and is common in general practice, especially in individuals with chronic kidney disease (CKD), diabetes, heart failure or myocardial infarction[4]. The kidney is the main organ maintaining the K^+ balance and drugs to treat CKD patients interfere in renal K^+ handling. In the present review, we discuss the physiology of K^+ homeostasis and the most recent data on incidence and prognostic value of hyperkalemia in CKD. Furthermore, new therapeutic options to keep plasma K^+ within safe limits.

2. K^+ homeostasis

The adequate intake of K^+ was established at 4,700 mg/day (120 mmol/day) by the Food and Nutrition Board of the Institute of Medicine[5]. Most of the ingested K^+ is absorbed by the small (80%), or the large intestine (13%). Around 90% of the excess K^+ intake is excreted in the urine,[6] whereas the rest is eliminated by the gastrointestinal tract.[7] The kidney can maintain K^+ homeostasis despite high dietary intake by adjusting urinary K^+ excretion (**Figure 1**). Furthermore, the extracellular levels of K^+ are also buffered by K^+ movement into cells. Therefore, short term regulation of extracellular K^+ levels is achieved by intracellular uptake while long term regulation depends upon renal function.

In CKD, impaired kidney excretion alters K^+ homeostasis. Furthermore, in end stage kidney failure (ESKF) , altered colon handling of K^+ has been reported.[8]

2.1 Transcellular distribution of K^+

The intracellular concentration of K^+ is around 140-150 mmol/L, constituting the major intracellular osmol. The ratio of the intracellular to extracellular concentration of K^+ is the major determinant of the resting membrane potential in all cells. Indeed, increases or decreases in this ratio can hyperpolarize and depolarize cells, affecting especially neural and cardiac function.

The extracellular concentration of K^+ depends largely upon its distribution between the intracellular and the extracellular compartment through the ubiquitous Na^+-K^+ -ATPase pump, as well as on the total body K^+ content. Insulin, catecholamines, and, to a lesser extent, aldosterone are critical regulators of the internal distribution of K^+ (**Figure 1**).[9] Thus, insulin and epinephrin upregulate Na^+-K^+ ATPase activity and expression. Aldosterone also induces a short-term increase in Na^+-K^+ ATPase activity and levels, followed by a long-term increase in newly synthesized Na^+-K^+ ATPase. In addition, during acidosis, cell uptake of H^+ increases extracellular pH and is linked to K^+ release from cells. Alkalosis elicits the opposite effect.[10]

2.2 Renal handling of K^+

K^+ is freely filtered across the glomerulus and reabsorbed by the proximal tubule and thick ascending limb of Henle. Only a small amount reaches the distal nephron (**Figure 1**).[11] Around 80% of filtered K^+ is reabsorbed in the early portions of the proximal tubule, primarily by solvent drag through the paracellular pathway. In the later portions of the proximal tubule, the shift in lumen potential acts as an additional driving force favoring K^+ reabsorption through the same route. In the loop of Henle, most of the remaining K^+ is reabsorbed through both paracellular and transcellular pathways. Within the collecting duct, K^+ is mainly reabsorbed by the luminal H^+-K^+ ATPase and paracellular pathways.

K^+ is secreted in the early distal convoluted tubule (DCT) and secretion progressively increases in magnitude into the cortical collecting duct (CCD).[12]. The later portions of the DCT and the CCD are sensitive to aldosterone. Aldosterone increases the expression of both the luminal epithelial sodium channel and the basolateral Na^+-K^+ ATPase, increasing Na^+ reabsorption and therefore, the electrogenic secretion of K^+ through ROMK channels. Recently, the existence of an enteric sensor which could connect the gut and the kidney has been proposed.[13] Thus, a K^+ load would be followed by an aldosterone-independent inhibition of Na^+ reabsorption in the early portions of the DCT, increasing Na^+ delivery to distal portions of the DCT and therefore, increasing the flow-mediated Maxi-K excretion of K^+ .

3. Epidemiology of hyperkalemia

The incidence and prevalence of hyperkalemia is highly variable and depends to a large extent on the definition used, the condition studied, the presence of co-morbidities, the number of tests done and the clinical practice of individual countries (**Table 1**). All these factors need to be considered when interpreting studies on the incidence and prevalence of hyperkalemia. While there is no universally agreed definition of hyperkalemia, most studies use the European Resuscitation Council definition of a $K^+ >5.5$ mmol/L [14]. Hyperkalemia is further classified into mild (5.5-5.9), moderate (6.0-6.4) or severe (≥ 6.5 mmol/L).

In cohorts of patients admitted to hospital, the prevalence of hyperkalemia was 1.1 to 10% [15-19]. Hyperkalemia is an adverse prognostic marker in admitted patients [19]. In 2013-14 there were around 7,000 hospital admissions for hyperkalemia in England resulting in around 21,000 bed days [20].

4. Hyperkalemia in CKD

The risk factors associated with hyperkalemia were recently systematically review [21]. The most common factors associated with hyperkalemia were the presence of CKD (the prevalence of hyperkalemia increases as kidney function decreases), heart failure, type 2 diabetes mellitus, hypertension and use of angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB) and mineralocorticoid receptor antagonists (MRA). Although acidosis may increase risk of hyperkalemia, most large epidemiological studies do not report impact of bicarbonate levels or prescription on hyperkalemia, possibly due to bicarbonate not being assessed or reported in primary care[18,22-24]. Whilst metabolic acidosis and hyperkalemia are undoubtedly linked[25] on an epidemiological level, it is challenging to dissociate the separate effects of declining eGFR on both metabolic acidosis and risk of hyperkalemia[26].

CKD is a global public health priority. In 2016, CKD was the 13th global cause of death and is expected to become the 5th by 2040 [27,28]. In 2017, the global prevalence of CKD was estimated at 11.1% of the world's population; that is, 850 million people [29]. Patients with CKD are at increased risk of premature mortality, particularly from cardiovascular causes [30]. Hyperkalemia is one of the commonest complications of CKD and is associated with an increased risk of cardiovascular events and mortality [21,22,30]. Hyperkalemia also contributes

indirectly to the increased mortality associated with CKD by limiting the use of kidney- and cardio-protective therapies that increase serum K^+ , including ACEI, ARB and MRA [21-23,31].

4.1 CKD categories G3-G5

In studies in general population, the incidence of hyperkalemia ranges from 2.9 to 40% in patients with an eGFR <30 ml/min/1.73m² (i.e. CKD categories G4-G5) [18,23,24,32-36]. In Nephrology clinics (mean eGFR 35-40 mL/min/1.73 m²), hyperkalemia was resolving in 16-17%, new onset in 15-16% and persistent in 17-22% of patients, despite an increase in use of anti-hyperkalemia strategies[37,38]

Studies looking at repeated measures of serum K^+ are reporting much higher rates of hyperkalemia. In family doctor practices in the United Kingdom, nearly half (45.2%) of patients with CKD had at least one episode of hyperkalemia [22]. In Danish health registries, 16% of newly diagnosed patients with diabetes had at least one episode of hyperkalemia over a mean follow-up period of 4.1 years [39]. The rate was nearly double if there was also a diagnosis of CKD. Indeed, the incidence of hyperkalemia increased as the number of serum K^+ measurements increased [24]. Patients with CKD category G3b (eGFR 30-44 ml/min/1.73m²) and more than 4 tests per year had an incidence of hyperkalemia of 54% over 3 years.

The detected incidence of hyperkalemia also differs across countries [40]. For example, in the systems BIOlogy Study to Tailored Treatment in Chronic Heart Failure (BIOSAT-CHF) study, the prevalence of hyperkalemia showed a distinct geographical distribution independent of risk factors including age, sex, medication usage and the presence of diabetes mellitus and hypertension, suggesting possible differences in serum K^+ monitoring as well as clinical practice across Europe [41].

4.2 ESKF requiring dialysis

Hyperkalemia is one of the cardinal metabolic disturbances associated with ESKF requiring dialysis. There are challenges in interpreting data describing incidence and risk factors for hyperkalemia in hemodialysis patients. Most data come from national surveys or registries. Some studies report data based on a single K^+ value, whilst others report a mean value over several months. Variability between countries may reflect differences in use of K^+ binders,

dialysis practices and dietary intake. In the United Kingdom, where use of K^+ binders in dialysis patients has historically been rare, 10.5% of in center hemodialysis patients had a pre-dialysis $K^+ > 6.0$ mmol/L in the 2018 UK Renal Registry Report[42], whilst in a multi-center French study, 4.9% of 527 hemodialysis patients had pre-dialysis $K^+ > 6.0$ mmol/L which may reflect that 61% of these patients were prescribed a K^+ binding resin (sodium polystyrene sulfonate)[43] or a low K^+ bath. Similarly, in a cohort of 81,013 maintenance hemodialysis patients from across the United States, 4.5% had a pre-dialysis $K^+ \geq 6.0$ mmol/L, based on the mean of 3 months sampling[44], whilst 8% of 55,183 patients from 20 countries had pre-dialysis $K^+ \geq 6.0$ mmol/L in the Dialysis Outcomes and Practice Patterns Study (DOPPS) [45]. Timing of sampling may also influence the results as midweek predialysis K^+ may be lower than predialysis K^+ following the weekend. Additionally, a circadian rhythm has been described that could be more prominent in CKD patients, with a nadir at around 9.00 pm and a peak at 1.00 to 3.00 pm[46]. This may generate differences between persons at different hemodialysis shifts. **Table 1** summarizes selected cohort reports on the epidemiology of hyperkalemia in CKD and in hemodialysis.

Although K^+ disorders are common in patients on peritoneal dialysis (PD), hypokalemia tends to be more frequent, with $K^+ < 3.5$ mmol/L reported in 11.1% of patients in Peritoneal DOPPS, compared to $K^+ \geq 5$ mmol/L in 8.8% of them [25]. In large US dialysis providers, $K^+ \geq 5$ mmol/L was present in 20% of PD patients compared to 33% of hemodialysis patients, whilst conversely the prevalence of $K^+ < 3.5$ mmol/L was 10% in PD patients and 2% in hemodialysis[47]. Some reports have demonstrated seasonal variation in the incidence of hyperkalemia in hemodialysis. However, these are contradictory, with higher rates of hyperkalemia observed in summer in France, and in winter in USA[43,48,49]. Dietary K^+ intake shows a major influence on serum K^+ in dialysis patients [50], and seasonal country-specific dietary patterns may be relevant. Whilst the K^+ bath used for dialysis influences serum K^+ , epidemiological studies are challenging to interpret as there is indication bias, whereby patients at highest risk of hyperkalemia are prescribed 2.0 mmol/L K^+ baths to reduce this risk. The corollary of this observation is that prescription of low K^+ baths increases the gradient between serum and dialysate K^+ and may further increase risk of arrhythmia[51]. Similar indication bias may account for K^+ binder prescriptions association to higher K^+ levels[52]. Even in patients on hemodialysis, medications may increase the risk of hyperkalemia. Thus, the use of beta-blockers and inhibitors of the renin angiotensin aldosterone system (RAAS) have been associated with hyperkalemia in dialysis patients [53-58].

5. Hyperkalemia and adverse outcomes in CKD

Hyperkalemia has consistently been associated with an increased risk of adverse events (mainly all-cause and cardiovascular mortality) in patients with CKD. The relevant observational studies are heterogeneous; populations with various comorbidities and medications, no standard definition of hyperkalemia, single or repeated measurements of serum K^+ and short- or long-term follow-up. However, most data support the strongly association of hyperkalemia with adverse clinical outcomes and this association is graded with elevations of K^+ and remains stable with adjustments for many potential confounders across all CKD stages (**Table 2**).

A Japanese retrospective study in ESKD patients[59] was the first to describe an association of serum $K^+ \geq 5.5$ mmol/L with a 2-fold increased risk of death. In a large hemodialysis database[44], both crude all-cause and cardiovascular mortality were higher in patients with hyperkalemia in the overall and all subgroups analyses. The unadjusted association was U-shaped, with the greatest survival in the 4.6 to 5.6 mmol/L serum K^+ levels. In a similar retrospective study[60], the adjusted HR for all-cause mortality became statistically significant when hyperkalemia was defined as serum $K^+ \geq 5.7$ mmol/L (HR 1.13, 95% CI 1.01–1.28). The unadjusted HR for cardiovascular mortality became statistically significant when serum $K^+ \geq 6.0$ mmol/L (HR 1.29, 95% CI 1.01–1.66, $p = 0.04$), but no association was found when adjusted for several factors, probably due to misclassification of CVD events. In peritoneal dialysis populations[47], hyperkalemia is also constantly associated with adverse outcomes[47]. Thus, a U-shaped relationship between time-averaged serum K^+ and all-cause and cardiovascular mortality was indicated (adjusted OR 1.52 and OR 1.51 for $K^+ \geq 5.5$ mmol/L). Likewise, K^+ levels >5.0 mmol/L were associated with 27% higher arrhythmia-related death among non-Hispanic whites and blacks, but not among Hispanic[61].

The long interdialytic interval in hemodialysis is associated with sudden deaths and it has been speculated that K^+ accumulation may be connected. In a three-year study[62], predialytic hyperkalemia ≥ 6.0 mmol/L was associated with a 2.7-fold increase in risk of sudden death, which was more frequent during the first 24 h of the first short interdialytic interval and during the last 24 h of the long interval. In a larger study[63], serum $K^+ \geq 7.0$ mmol/L was independently associated in the short-term with a >3 -fold risk of death and a 2-fold greater risk of ED visits than in the reference category. The association of hyperkalemia (K^+ 5.5- 6.0 mmol/L) with hospitalization was of greater magnitude when assessed on Fridays versus on Mondays or Wednesdays (OR 1.68 vs 1.12 and 1.04, respectively).

The association of mortality with hyperkalemia extends to pre-dialysis CKD patients[18,22,64,65]. In a national cohort of CKD inpatients and outpatients, 1-day odds of death were higher after a hyperkalemic event ($K \geq 5.5$ mmol/L, OR 5.4; 95% CI, 4.72-6.14 vs 2.73; 95% CI, 1.8-4.11) respectively[18]. Similarly, in 55,000 CKD patients there was a statistically significant U-shaped association between serum K^+ and adverse events- the mortality incident rate ratios adjusted for various comorbidities and medication increased with $K \geq 5.0$ mmol/L, the highest IRRs being 3.31 (95%CI, 2.52-4.34) for $K^+ \geq 6.0$ mmol/L[65]. MACE and hospitalization IRRs were significantly increased for the same K^+ levels. In CKD patients who developed hyperkalemia >5.0 mmol/L, six-month hazard ratios for any acute hospitalization or death were 2.11-fold or 4.85-fold higher, respectively [66].

Data seem contradictory in a few prospective studies. In 800 CKD outpatients[32], $K^+ \geq 5.5$ mmol/L was associated with 69% increased risk of cardiovascular event or death, but no association with all-cause mortality was found. In another prospective study from Spain in 1,757 CKD patients, $K^+ \geq 5.2$ mmol/L was associated with cardiovascular events (fatal and non-fatal) (HR 1.54, 95% CI 1.06-2.25)[67]. On the contrary, a prospective study[68] in 2,078 CKD patients under strict optimal nephrology care encompassing reminder of recommended targets for each abnormal value in biological tests to help guide treatment adjustment, found no association between hyperkalemia and mortality.

In various studies[18,64,69,70], hyperkalemic events in patients without CKD were associated with higher mortality than in patients with CKD. Thus, the adjusted 1-day odds of death with severe hyperkalemia ($K \geq 6.0$ mg/dl) in CKD stage 5 was substantially less (OR 8.02) than the risk among those with Stage 3 (OR 19.52) or non CKD (OR 31.64)[18]. This paradox has been attributed to a better tolerance to chronic hyperkalemia in CKD patients than to acute hyperkalemia, due to gradual adaptation of K^+ channels to higher K^+ levels, while acute changes cause a rapid reduction in resting membrane potential leading to increased cardiac depolarization and ECG changes[71,72]. A recent meta-analysis (more than 1 million general and CKD participants followed up for a mean of 6.9 years)[73] found no difference in the mortality risk associated with K^+ by level of eGFR. However, in the whole population the HR for all-cause mortality was 1.22 at K^+ levels >5.5 mmol/L, a consistent conclusion in almost all studies which emphasizes the importance of careful monitoring and management of high K^+ levels.

However, and although the association of hyperkalemia with adverse outcomes has been consistent, there is less information about the effect of normalizing serum K levels and its effect on outcomes[74,75].

6. Causes of Hyperkalemia in CKD

In CKD, different pathophysiological mechanisms, lifestyle habits and pharmacological treatments can increase plasma levels of K^+ . Higher intake of K^+ rich foods, together with an increased transcellular extrusion and a decrease in renal excretion are the main mechanisms involved in CKD-related hyperkalemia (**Figure 2**). Release of K^+ from cells occurs during increased tissue breakdown or fasting which may both lower insulin levels and cause resistance to beta-adrenergic stimulation of K^+ uptake by cells, while oliguria or reduced aldosterone secretion or responsiveness impair the urinary excretion of K^+ [76-78].

6.1 Increased K^+ load

The typical Western diet contains approximately 50–100 mmol (2000–4000 mg) K^+ , which is below the recommended intake [5]. Excessive K^+ ingestion rarely causes hyperkalemia in individuals with normal renal function as normal kidneys can excrete hundreds of millimoles of K^+ daily[79]. When renal K^+ excretion is impaired, excessive K^+ intake can cause hyperkalemia[65]. Thus, in 212 predialysis patients with CKD stage 4-5, the main determinants of normal serum K^+ levels were the K^+ load (intake and absorption minus extrarenal excretion) relative to kidney function and fractional excretion of K^+ [80].

6.2 Transcellular shift

Impaired cell uptake of K^+ also contributes to the development of hyperkalemia in advanced CKD. Diminished Na-K-ATPase activity may be particularly important in this setting. Retained uremic toxins may decrease the transcription of mRNA for the alpha1 isoform of the Na-K-ATPase pump in skeletal muscle[78,81].

As little as a 2% shift of intracellular K^+ to the extracellular fluid will result in a serum K^+ of 8 mmol/l. Disturbances in serum K^+ concentration due to cell shifts are generally transient in nature, whereas sustained hyperkalemia is due to impaired renal excretion. Blocking of mechanisms shifting K^+ from the extracellular to the intracellular space results in hyperkalemia. The most common causes are metabolic acidosis, hyperglycemia, β_2 -adrenoreceptor antagonists (β -blockers), α -adrenoreceptor agonists, hyperosmolarity and exercise[9,82].

Metabolic acidosis promotion of K^+ exit from cells depends on the type of acid present. Mineral acidosis (NH_4Cl or HCl) causes a greater decrease in intracellular Na^+ than organic

acidosis as they cannot freely diffuse into the intracellular compartment and, thus, decrease extracellular pH [83]. Low extracellular pH decreases the $\text{Na}^+\text{-H}^+$ exchange and inhibits the inward movement of Na^+ . The subsequent fall in intracellular Na^+ leads to decreased activity of $\text{Na}^+\text{-K}^+\text{-ATPase}$, and thus, to a net decrease in K^+ entry into cells and higher extracellular K^+ levels. In summary, during acidosis there is a significant extracellular shift of intracellular K^+ in exchange for protons leading to hyperkalemia.

Insulin receptor activation stimulates Na-K-ATPase and increase cellular K^+ uptake. Decreased insulin, commonly observed in diabetic patients, but also in fasting, increases extracellular K^+ . Cell shift is also a potential complication of hypertonic states[84]. Hyperglycemia leads to water movement from the intracellular to extracellular compartment together with a mass movement of K^+ , which results in hyperkalemia.

β_2 -adrenergic receptor activation also stimulates Na-K-ATPase and increase cellular K^+ uptake. Activation of the α -1-receptor inhibits $\text{Na}^+\text{-K}^+\text{-ATPase}$, preventing cellular uptake and increasing serum K^+ levels. These effects have important pharmacological implications. Drugs that block β_2 -adrenoreceptor (non-cardioselective β -blockers) inhibit renin production, hamper K^+ redistribution to the intracellular space and tend to increase serum K^+ [85,86].

The onset of exercise is associated with a release of K^+ from contracting skeletal muscle that results in an increase in plasma K^+ [87]. The rate and magnitude of increase in plasma K^+ is dependent on exercise intensity, trained state of the individual, and on drugs such as β_2 -adrenoreceptor blockers and caffeine. During exercise, the uptake of K^+ from the blood by non-contracting tissues may be important in preventing plasma K^+ from rising to excessive levels that will impair skeletal muscle and myocardial excitability and contractility [87]. The rapid increases and decreases in plasma K^+ with onset and cessation of exercise has been implicated in altered myocardial function and sudden cardiac death[87].

6.3 Decreased K^+ excretion

In CKD patients, the ability to maintain near-normal K^+ excretion without developing hyperkalemia after a dietary K^+ load generally persists as long as both the secretion of and responsiveness to aldosterone are intact and distal delivery of sodium and water are maintained[76]. The kidney can maintain K^+ balance until the GFR decreases below 10-15 ml/min[88]. This is counterbalanced by adaptation of remaining nephrons, which increase the ability to excrete K^+ [82].

Acute decreases in GFR in acute kidney injury (AKI) may lead to marked decreases in distal delivery of salt and water, which may secondarily decrease K^+ secretion in distal nephron. Thus, in oliguric AKI, hyperkalemia is frequent; while in nonoliguric, distal delivery is usually sufficient, and hyperkalemia is unusual. In CKD, K^+ handling is more complicated, as decreased GFR coexists with less collecting tubule mass to secrete K^+ .

6.4 RAAS blockade

RAAS blockers improve the outcome in diabetic and non-diabetic CKD, heart failure or post-acute myocardial infarction. However, hyperkalemia often limits RAAS blockade. This is particularly true for advanced CKD, diabetes, congestive heart failure or combined RAAS blockade. The impact of RAAS blockers on K^+ levels may differ for different drugs. Initial reports of a lower increase in K^+ levels with ARBs than with ACEI were not confirmed [89]. Conversely, non-selective MRAs possibly cause a higher increase in serum K^+ than ARBs when added to Lisinopril [90].

In RCTs, the incidence of hyperkalemia on a single RAAS blocker was low. In trials testing the renoprotective effects of ACEi in non-diabetic nephropathies, isolated episodes of K^+ elevation were common, but few patients stopped the drug because of life-threatening hyperkalemia: 1.6 % in the ACEi in Progressive Renal Insufficiency (AIPRI) study [91] and 0.56% in the Ramipril Efficacy In Nephropathy (REIN) study[92,93]. Of note, increased K^+ levels were observed also in the placebo group in both trials. Similar percentages were reported with ARBs in patients with type 2 diabetes and CKD[94,95]. However, in the Reduction of Endpoints in NIDDM with the All Antagonist Losartan (RENAAL), one third of patients treated with losartan had serum K^+ levels ≥ 5.5 mmol/L at 6 months and this was associated with an increased risk of renal outcomes [95,96].

As expected, hyperkalemia is more frequent for dual RAAS blockade, especially in patients with type 2 diabetes. In the ALTITUDE trial [97], addition of aliskiren to either an ACEi or an ARB, increased the proportion of patients with serum K^+ level ≥ 6.0 mmol/L as compared to placebo (11.2% vs. 7.2%). Similarly, in VA NEPHRON-D [98], patients receiving a combination of losartan and lisinopril had a significantly higher risk of hyperkalemia than those on monotherapy with losartan. According to a recent metanalysis [99], the risk of hyperkalemia is increased significantly in patients with diabetic kidney disease with macroalbuminuria but not in those with microalbuminuria.

Of note, the increased risk of hyperkalemia is among the reasons why dual RAAS blockade involving an ACEi and an ARB or a direct renin inhibitor (aliskiren) is not recommended in most CKD patients, especially in presence of diabetic kidney disease. In this respect, in 2014 the European Medicine Agency issued an ad-hoc warning restricting the combination of medicines affecting the RAAS, especially in subjects with diabetes and kidney disease[100]. When the combined use of an ARB and ACE inhibitor is considered essential, as for patients with heart failure who are intolerant to MRAs or those with non-diabetic severe proteinuria, combined use must be supervised by specialists with close monitoring of renal function, electrolytes and blood pressure. **Table 3** summarizes the prevalence of hyperkalemia and the need for drug discontinuation in the main RCTs testing RAAS blockade in CKD patients.

Observational studies also generally showed an increased risk of hyperkalemia with RAAS blockade in CKD. Data from a large laboratory database in the region of Stockholm, Sweden, showed that dual RAAS blockade with ACEi/ARB substantially increased the risk of hyperkalemia for decreasing GFR values [101]. Other factors significantly associated with increased K^+ levels were diabetes, a history of chronic heart failure, the use of K^+ -sparing diuretics and pre-treatment K^+ levels. In a population of more than 700 subjects with CKD stage 2-5, nearly one third had serum K^+ levels > 5.0 mM/L at the start of the observation; in a multivariate model, hyperkalemia at baseline, low venous bicarbonate levels, lower eGFR, and use of ACE inhibitors or ARBs were related to hyperkalemia over time[102]. Metabolic acidosis and the use of RAAS blockers were the strongest modifiable risk factors for preventing hyperkalemia.

The risk of acute kidney injury and hyperkalemia underlie the under prescription of RAAS blockers. In an observational study of 627 patients with moderate to severe CKD and an indication for RAS blockade, one third were not prescribed RAS blockade. This was more likely in diabetic, older and in a more advanced stage of CKD patients[103]. In a historic cohort of 34,676 CKD patients in the three-year period preceding the start of dialysis[104], hyperkalemia was associated with ACEi/ARB withdrawal and lower use. Compared to those continuing or using ACEi/ARB use, ACEi/ARB non-users had higher all-cause mortality risk after dialysis start.

The steroidal MRA class includes the nonselective agent spironolactone, its active metabolite canrenone and the selective agent eplerenone[105]. Spironolactone is used to treat primary aldosteronism due to adrenal hyperplasia or adenomas prior to surgical resection[106] and is currently recommended as the second-line antihypertensive of choice for resistant

hypertension[107]. Spironolactone and eplerenone have received Class 1A recommendation for heart failure with reduced ejection fraction (HFrEF)[108], while they reduce albuminuria or proteinuria in CKD patients[109]. As aldosterone holds a key role in K^+ homeostasis, all MRAs have a propensity to increase serum K^+ [105,110]. An important issue that needs to be considered in this regard is the possible differences in hyperkalemia rates between the strict setting of a clinical trial and the real world. In particular, in the Randomized-Aldactone-Evaluation-Study (RALES) trial showing major decreases of mortality and morbidity in patients with heart failure on spironolactone, the actual incidence of hyperkalemia caused by spironolactone was found to be remarkably low, i.e. around 2%[111]. This could be related to the use of a low dose of spironolactone(25 mg), a decision made after a short, dose-finding study in which hyperkalemia (serum $K^+ \geq 5.5$ mEq/L) occurred in 13%, 20%, and 24% of heart failure patients treated with spironolactone 25, 50, and 75 mg/d, respectively[112]. However, a population-based time-series analysis from a Canadian Health Provider published 4 years after the RALES trial, showed that the increased use of spironolactone for heart failure in the community had largely increased the complications of hyperkalemia. Hospitalization for hyperkalemia rose from 2.4/1000 admitted patients in 1994 to 11/1000 admitted patients in 2001 and in-hospital death from hyperkalemia rose from 0.3/1000 to 2/1000 over the same period[113].

With regards to patients with CKD, in a systematic review of 4 studies that added spironolactone or eplerenone to ACEIs or ARBs, the overall incidence of hyperkalemia was about 5.5%, ranging between 3% and 17% depending on the cut-off level for reporting hyperkalemia in each of the included studies[114]. However, in a real-life study in 46 patients with resistant hypertension and stages 2 or 3 CKD (mean eGFR 56 ml/min/1.73 m²) addition of an MRA was associated a 17.3% higher hyperkalemia rate, defined as serum $K^+ > 5.5$ mEq/l[115]. Predictors of hyperkalemia included a baseline eGFR of <45 ml/min/1.73 m² and baseline serum $K^+ > 4.5$ mmol/l on appropriately dosed non- K^+ sparing diuretics. The above clearly suggest that the incidence of hyperkalemia may be largely different in clinical trials and everyday clinical practice, following the expected differences in population characteristics, patient adherence to instructions and monitoring density.

6.4.1 New therapeutic interventions in the RAAS: nonsteroidal MRAs

Among nonsteroidal MRAs, finerenone displayed different pharmacological properties from steroidal MRAs, such as greater receptor selectivity than spironolactone and better receptor

affinity than eplerenone, more potent antiinflammatory and antifibrotic effects in preclinical models, and lower hyperkalemia incidence compared to spironolactone in clinical trials[116,117].

The efficacy and safety of finerenone has been tested in recent trials. In a phase II trial, 392 patients with heart failure with reduced ejection fraction (HFrEF) and moderate CKD (eGFR 30-60 mL/min/1.73 m²) were randomized to finerenone (2.5, 5, or 10 mg q.d., or 5 mg twice daily), placebo or open-label spironolactone (25 or 50 mg/day) (8). Finerenone was associated with significantly smaller mean increases in serum K⁺ concentration than spironolactone (0.04-0.30 versus 0.45 mmol/L, respectively, P<0.0001-0.0107) and lower incidences of hyperkalemia (5.3 versus 12.7%, P=0.048). In a subsequent phase 2b study, 821 patients with diabetic CKD treated with ACEI or ARB and serum K⁺ ≤4.8 mmol/L were randomized to 7 different doses of finerenone (from 1.25 to 20 mg) or placebo for 90 days[118]. Finerenone dose-dependently reduced albuminuria up to 33% and 38% in the 15 and 20 mg groups with only small increases in serum K⁺ (+0.17±0.46 and +0.23±0.37, respectively). The incidence of hyperkalemia defined as serum K⁺ ≥5.6 mmol/L was 1.5% (12 out of 821 patients), with no cases observed with placebo. Only two cases of serum K⁺ >6.0 mmol/L were observed, both in the 1.25 mg/d group. No differences in the incidence of eGFR decrease >30% or of other adverse events between the placebo and finerenone groups were noted. In a similar study in 96 Japanese patients[119], all doses of finerenone numerically reduced UACR after 90 days compared to placebo. Small increases in serum K⁺ levels were observed with finerenone (up to 0.17 mmol/L) but no patient developed serum K⁺ ≥5.6 mmol/L.

The Finerenone in reducing kidney failure and disease progression in Diabetic Kidney Disease (FIDELIO-DKD) phase III study randomized 5734 patients with type 2 DM and either UACR 300-5000 mg/g and eGFR 25 to <75 mL/min/1.73 m² or UACR 30 to <300 mg/g, eGFR 25 to <60 mL/min/1.73 m² and diabetic retinopathy to finerenone (10 mg increased to 20 mg if serum K⁺ stable) or placebo [120,121]. All patients were on maximum tolerated doses of an ACEI or an ARB and had serum K⁺ ≤4.8 mmol/L at both, run-in and screening visits. At baseline 12.1% of the patients had high and 87.5% very high albuminuria; mean eGFR was 44.3±12.6 mL/min/1.73m²[120,121]. Over a median of 2.6 years, finerenone significantly reduced the primary outcome, a composite of kidney failure, eGFR decrease of ≥40% from baseline, or death from renal causes (HR, 0.82; 95%CI 0.73-0.93, p=0.001). Significant reductions were also noted in the main secondary renal outcome, a composite of kidney failure, eGFR decrease of ≥57% or renal death (HR 0.76; 95%CI 0.65-0.90) and the main secondary cardiovascular

outcome (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure, HR, 0.86; 95%CI 0.75 to 0.99)[121]. The cardiovascular effects of finerenone were consistent across various subgroups including type of underlying CVD, history of heart failure, region, baseline eGFR, UACR, systolic blood pressure, sex, age (above and below 65 years) and glycated haemoglobin[122].

In FIDELIO-DKD total and serious adverse event rates were similar in the finerenone and placebo groups. A higher serum K^+ level with finerenone was noted (maximal difference of 0.23 mmol/L at month 4, remaining stable thereafter). The prespecified outcome of hyperkalemia leading to discontinuation of the trial was 2.3% with finerenone vs 0.9% with placebo. The incidences of serum $K^+ > 5.5$ mmol/L were 21.7% vs 9.8% and those of > 6.0 mmol/L 4.5% vs 1.4%, respectively. Hospitalization due to hyperkalemia was 1.4% vs 0.3%. No fatal hyperkalemia events were reported[121]. Despite the significantly higher hyperkalemia rates with finerenone, given the size, duration and average eGFR in participants of the trial, finerenone could be considered well-tolerated. In fact, hyperkalemia leading to discontinuation of finerenone was less frequent than in dual RAAS blockade with aliskiren/ACE or ARB in ALTITUDE (4.8%) or losartan/lisinopril in the NEPHRON-D (9.9%) trials[97,98], despite inclusion of more advanced CKD patients and the fact that FIDELIO-DKD had no protocol recommendations to restrict dietary K^+ . Furthermore, the rate of hospitalization due to hyperkalemia was much lower than in the general population with spironolactone[113].

The exact reasons why finerenone is associated with less hyperkalemia risk need to be elucidated. An important contributor could be that FIDELIO-DKD[120,121] and its pilot trials[118,119] enrolled only patients with baseline serum $K^+ \leq 4.8$ mmol/L. However, unique characteristics of finerenone may be involved, including its tissue distribution (equal to heart and kidneys, in contrast to spironolactone and eplerenone that accumulate more in the kidney), its short half-life, and lack of active metabolites[123-125]. Furthermore, the non-steroidal structure of finerenone leads to a distinct mode of MR antagonism with recruitment inhibition of transcriptional co-factors involved more in expression of profibrotic and proinflammatory pathways rather in regulation of K^+ excretion, thus offering protection against heart and kidney disease progression with lower risk of hyperkalemia[125,126].

The Finerenone in Reducing CV Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trial is a randomized, double-blind, placebo-controlled trial, designed as a twin trial to FIDELIO-DKD with a primary cardiovascular outcome. FIGARO-DKD randomized 7,437 patients

with an eGFR ≥ 25 mL/min/1.73 m² and moderately or severely increased albuminuria (UACR ≥ 30 to $\leq 5,000$ mg/g) to finerenone or placebo and is expected to report in 2021, offering further information on the drug's safety [127]. A recent press release indicated that finerenone reduced the composite risk of time to first occurrence of CV death or non-fatal CV events, defined as myocardial infarction, stroke, or hospitalization for heart failure.

7. Treatment of hyperkalemia in CKD

There are lifestyle and pharmacological approaches to prevent or treat chronic hyperkalemia in CKD patients.

7.1 Dietary modifications

Essentially all foods contain K⁺ although in varying amounts (**Figure 3**). Animal (meat and dairy) and plant foods, such as fruits, vegetables, legumes, and nuts, are its main sources. To prevent hyperkalemia, CKD patients are advised to reduce their K⁺ intake to 50-75 mmol/day (2000–3000 mg/day)[128]. Dietary recommendations to CKD patients restrict plant-based foods, such as seeds, nuts, beans, and peas, as well as fruits and vegetables[128,129]. However, plant-based foods should not be excluded from the diet since they are also sources of vitamins, minerals, fibers and other bioactive compounds. When prescribing a low K⁺ diet is important to keep in mind that a higher intake of fibers provided by foods containing K⁺ is associated with the regulation of bowel transit and at the very end they may increase fecal excretion of K⁺ via increasing bowel motility [129-131]. Indeed, constipation, rather than K⁺ dietary load, seems to be a key determinant of hyperkalemia in CKD and ESRD patients.[131] Fiber is additionally key to maintaining a healthy microbiota. In addition, plant-based diets may have specific health benefits for CKD patients, related in part to their alkalinizing effects, which may explain the reductions in metabolic acidosis and kidney disease progression in nondiabetic CKD patients who were acidemic [130]. Consumption of fresh food rather than processed food will limit the exposure to additives in processed foods containing K⁺, and also phosphate and sodium which should also be limited in CKD patients. Processed meats may contain up to 3-fold more K⁺ than unprocessed meat [132]. Thus, dietary recommendations should be individualized and focused on promoting autonomy for choosing or combining foods and stimulating changes within the dietary repertoire.

The cooking technique may also reduce K^+ in plant-based foods. Cooking vegetables in abundant water, discarding the cooking water to remove part of the K^+ content may provide most of the benefit as compared to performing the maneuver twice.

Dietary K^+ restrictions are the most common strategy to control hyperkalemia in CKD. However, dietary restrictions are poorly tolerated especially when extended for long and unpredictable periods, sometimes for the entire life. In fact, dietary restrictions are among the most challenging interventions in chronic patients and may not be sustainable on the long run. More recently, dietary intervention in patients with CKD has been questioned [133]. In a cross-sectional analysis including a non-dialysis-dependent CKD and a hemodialysis cohort, dietary K^+ intake assessed by 3-day food records was not associated to serum K^+ levels. However, multiple confounders may be at play, including the precision of dietary recalls. In any case, caution is needed in prescribing rigid and hard-to-follow diets for hyperkalemia in CKD, but knowledge of the patient dietary habits may identify key modifiable factors. Thus, K^+ supplements and salt substitutes contain 10-13 mmol/g [132]. K^+ chloride has been widely used to replace sodium chloride to reduce dietary sodium, either in the form of “light” salt or in food products described as having a reduced sodium content. It is of paramount importance to underline that salt substitutes to replace sodium chloride in the food in patients with CKD, even in the earliest stages, must be strongly discouraged or even forbidden because they may cause hyperkalemia that may be fatal.

Another potential cause of hyperkalemia is total parenteral nutrition in patients with CKD. In these patients, the K^+ recommended in normal individuals usually should be reduced.

7.2 Diuretics

Thiazide and loop diuretics increase urinary K^+ excretion and hypokalemia is a potential adverse effect. Concurrent use of loop or thiazide diuretics is associated with reduced risk of hyperkalemia in patients on RAAS blockade [134]. Diuretics to limit the risk of hyperkalemia may additionally improve the effectiveness of RAAS blockade. Thiazides further decreased albuminuria by 42% when added to RAAS blockade in short term (4 weeks) studies [135] and are a recommended combination to improve the anti-hypertensive efficacy of RAAS blockers [107]. The K^+ lowering efficacy of thiazides will be limited in patients with lower eGFR values, although serum K^+ in these patients may still respond to loop diuretics. Of note, K^+ -sparing diuretics such as triamterene, amiloride and those targeting the mineralocorticoid receptor may increase the risk of hyperkalemia [135].

7.3 SGLT2 inhibitors

Impressive nephroprotection and cardioprotection by SGLT2 inhibitors were demonstrated in patients with diabetic and non-diabetic CKD and heart failure as well as in diabetic patients at high cardiovascular risk in trials assessing long-term hard outcomes[136,137]. As a result, they have become standard therapy for DKD and heart failure as recommended by clinical guidelines and will likely become standard therapy for non-diabetic CKD in the near future[138,139]. SGLT2 inhibitors were associated with lower serum K^+ levels in patients with CKD. Thus, in DKD, canagliflozin addition to RAAS blockade was associated with a hazard ratio for hyperkalemia of 0.80 (0.65–1.00)[140] while dapagliflozin on top of RAAS blockade decreased the risk of hyperkalemia by 50% in a CKD population comprised of diabetic and non-diabetic patients[141]. The impact of SGLT2 inhibitors on serum K^+ appears to be larger in clinical trials enrolling patients with CKD than in high cardiovascular risk trials, as in the CANVAS Program there were no meaningful effects of canagliflozin on serum K^+ in the overall population or key subgroups[142]. In summary, SGLT2 inhibitors effect on serum K^+ is neutral or may even decrease hyperkalemia in patients with CKD.

7.4 Correction of metabolic acidosis

Metabolic acidosis facilitates K^+ exit from the intracellular space. Metabolic acidosis is common in advanced CKD and KDIGO guidelines suggest treatment with oral bicarbonate supplementation when people with CKD have serum bicarbonate concentrations <22 mmol/l to maintain serum bicarbonate within the normal range, unless contraindicated[143]. Indeed, clinical trials have observed protection from GFR decline in patients randomized to sodium bicarbonate for metabolic acidosis[144]. Smaller trials observed lower serum K^+ in patients on sodium bicarbonate despite no differences in GFR[145]. However, other trials did not observe an impact of sodium bicarbonate on serum K^+ , likely because additional therapeutic maneuvers were implemented to control hyperkalemia[146]. Of note, sodium bicarbonate may be a source of sodium. In this regard, veverimer is a novel acid binder non-absorbed polymer undergoing clinical trials for metabolic acidosis in CKD[147] (NCT03710291). However, no changes in serum K^+ were observed in short-term or long-term clinical trials or in animal models [148-151]. This would suggest, in the absence of additional evidence, that veverimer would not be the base of choice for CKD patients with metabolic acidosis and hyperkalemia. In any case, the mechanisms of action of veverimer is not completely understood, since there is a

lack of dose dependency in the increase in serum bicarbonate concentration and it induces an isochloremic increase in serum bicarbonate concentration that is accompanied by a decrease in serum anion gap[147]. Further studies should address the mechanism of action, including the potential impact on the microbiota and on serum K^+ . A prolonged-release formulation of K^+ citrate/ K^+ hydrogen carbonate recently received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP)[152]. However, while it corrects metabolic acidosis over 24 h, it contains K^+ as it is intended for distal renal tubular acidosis which is associated with low serum K^+ .

7.5 K^+ binders

Two new K^+ binders were recently approved for the treatment of hyperkalemia: the cation-exchange polymer Patiromer (FDA-approved in 2015, EMA-approved in 2017[153]) and the non-polymeric crystalline compound sodium zirconium cyclosilicate (SZC) (EMA-[154] and FDA-approved 2018). Both followed a streamlined clinical development that confirmed the efficacy and safety in non-emergency hyperkalemia[155].

Older generation K^+ binders were cation-exchange resins (i.e. sodium polystyrene sulfonate (SPS) and calcium polystyrene sulfonate (CPS)) approved decades ago, albeit with no placebo-RCTs to ascertain their safety and efficacy. These resins exchange sodium (SPS) or calcium (CPS) for secreted K^+ in the colon lumen. As a result, they display limitations in use for CKD patients with sodium overload (SPS) while certain brands of CPS (e.g. ResinCalcio®) are contraindicated in CKD associated with hypercalcemia or vascular calcification[156]. Although resins are effective in reducing serum K^+ , their effects remain unpredictable[3,157]. SPS is the most used old-generation K^+ binder in several countries while CPS is more commonly used in Spain. Based on observational “real-life” data, safety concerns were raised with regard to the -rare- occurrence of colonic necrosis[158] and to the impact of sodium load on congestion[159]. Adherence is negatively impacted by poor palatability and high incidence of constipation. There is a high worldwide heterogeneity in resin prescription rates. In prospectively data in non-dialysis patients prior to new K^+ binder availability in Europe, K^+ binder prescription was more common in France (13%) than in Germany (6%) despite a much higher percentage of CKD Stage 4 patients in Germany (74% vs. 42% in France) in this study. Such heterogeneity was confirmed by a five-European country retrospective survey of recurrent hyperkalemia in non-dialysis patients with the highest prescription rate recorded in

France (45.4%), followed by Spain (21.5%), Italy (13.4%), Germany (8.1%) and UK (7.5%)[31]. This heterogeneity was also observed in chronic dialysis patients[43,52].

Patiromer exchanges K^+ for calcium while SZC exchanges K^+ for sodium. Four- to eight-week placebo-controlled RCTs respectively demonstrated SZC[160] and Patiromer[161] to be effective and safe in lowering serum K^+ in patients with non-emergent hyperkalemia (**Table 4**). Efficacy, safety and adherence were observed up to 12 months in open-label studies[162-164]. Patiromer and SZC appear to offer tolerability advantages over SPS, although direct comparative clinical studies are not available. Both SZC and Patiromer are free-flowing powders that do not swell appreciably in the gastrointestinal tract. Mild to moderate constipation has been reported in 1–11% of patients enrolled in pivotal clinical trials with no reported cases of colonic necrosis. Other adverse effects include hypokalemia (5–10%, depending on drug and dose) and hypomagnesaemia (3–7%, depending on Patiromer dose). A thorough biological monitoring is therefore warranted[159] along with good patient compliance. Importantly, serum K^+ does not increase until day 3 post-treatment discontinuation).[162]

SZC has also been associated with an increased incidence of edema [155] likely associated with sodium exchange. SZC contains approximately 400 mg sodium per 5 g dose, equivalent to 20% of the WHO recommended maximum daily sodium intake, and is considered high in sodium by the EMA Summary of Product Characteristics[154]. In a long-term open-label study, peripheral edema occurred in 13% and 8% of CKD patients with eGFR below or above 30 mL/min/1.73 m² and were thought to be treatment-related in 2% in both[165]. SZC also increased serum bicarbonate concentrations and reduced patient prevalence of metabolic acidosis, likely due to SZC-binding of gastrointestinal ammonium, providing a further mechanism to decrease serum K^+ [166].

An enabling effect of Patiromer on RAAS blockade has been demonstrated by RCTs[161,167,168]. In the AMBER phase II trial, Patiromer enabled a persistent use of a higher dose of spironolactone than placebo in 295 patients with advanced CKD (eGFR 25 to 45 mL/min/1.73m²) and resistant hypertension. Two-thirds of the patients in the placebo group developed hyperkalemia over the 12-week follow-up, the risk being halved by Patiromer.[168] Whether this strategy may translate into improved cardiovascular outcomes in heart failure patients is being tested by the DIAMOND placebo-controlled trials (NCT03888066)[3]. The AMBER trial also provided insights on the pharmacokinetics of spironolactone in patients with advanced CKD: active metabolites of spironolactone were detectable in the urine even 2 weeks

after the administration of the last dose. This may explain both the persistent BP-lowering effect and hyperkalemia after spironolactone discontinuation. Additionally, the RELIEHF phase IV RCT will investigate the potential for Patiromer-facilitated use of higher doses of MRA in addition to standard care to improve congestion, well-being and mortality in people who have worsening congestion due to heart failure and hyperkalemia (NCT04142788)(Table 5).

8. Conclusions

In conclusion, hyperkalemia continues to be common and associated with adverse outcomes in CKD patients. Hyperkalemia can trigger potentially lethal arrhythmia, but also can negatively affect patient survival by limiting the prescription of RAAS blockers and lead to the recommendation of low K⁺ diets, associated to low dietary fiber intake. In CKD, both reduced kidney K⁺ excretion and impaired cellular uptake contribute to hyperkalemia.

Changes in clinical practice that modulate the incidence and consequences of hyperkalemia are expected soon or are already ongoing. Overall, it is expected that hyperkalemia will cease to condition the therapeutic approach to kidney and heart protection. Updated clinical guidelines and regulatory clearance to treat CKD and heart failure with SGLT2 inhibitors even in patients without diabetes, the likely future availability of novel MRAs with more limited impact on serum K⁺, and the recently approved novel K⁺ binders are expected to decrease the incidence of hyperkalemia and limit its negative impact on compliance with clinical guidelines for heart and kidney protection (Figure 4). Further potential players include novel agents for metabolic acidosis and the trend towards avoiding recommendations to lower the intake of healthy foods that contain K⁺. Overall, the combination of these factors is expected to lower the prevalence of hyperkalemia and independently decrease the adverse impact of hyperkalemia on outcomes. The ongoing changes offer opportunities for further research aimed at establishing the optimal combination of new agents that maximize kidney and heart protection while minimizing hyperkalemia (Table 6). Identifying optimal combination therapies will require novel clinical trials, as trials available so far have compared interventions to a standard of therapy that is no longer considered optimal. Additionally, the impact of the different therapeutic approaches to hyperkalemia on the gut microbiota and the microbiota contribution to benefit or harm can no longer be ignored. Microbiota modulation is rapidly entering the clinical realm and its analysis should be part of hyperkalemia research[169]. Thus, the existence of kidney and heart protective strategies that limit the negative impact of RAAS blockers on hyperkalemia in CKD patients (i.e. SGLT2 inhibitors), of safer MRAs and of well

tolerated K^+ binders will allow a liberalization of K^+ intake that will facilitate fiber-rich diets that promote a healthier microbiota. This may further improve outcomes by itself and its potential contribution to overall outcomes should be quantified. Conversely, novel drugs, especially oral binders have the potential to influence the gut microbiota, as recently demonstrated for phosphate binders (reviewed in 152). These potential effects on the microbiota and their biological significance should be monitored.

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Table 1: Main epidemiological studies showing the prevalence of hyperkalemia in CKD patients.

Study	Population	Setting	N	Prevalence K >5.0 mmol/L (%)	Prevalence K >5.5 mmol/L (%)	Prevalence K >6 mmol/L (%)	Mean or median K	Associations with ↑K	Association with outcomes
Furuland[22]	Non dialysis CKD 3-5	GP research database in UK	191,964	12.4	2.7	0.5	4.5	-	↑ K ⁺ associated with increased mortality and RAASi discontinuation
Belmar [23]	Non dialysis CKD 3-5	Nephrology clinic	1088	-	9.6	3.1	-	CKD, RAASi therapy, DM	-
Einhorn [18]	≥1 hospitalisation in 2005	US Veterans	245 808	-	13.7	-	-	CKD, RAASi therapy	Serum K ⁺ >5.5 associated with ACM
Sarafidis [33]	Low clearance CKD	Nephrology clinic	238	-	31.5	-	5.1	Lower GFR	-
Loutradis[36]	CKD 1-4	Nephrology clinic Greece	360	23.6	3.3	-	-	Stage 4 CKD, ACEi use, and smoking	-
Chang [24]	Outpatients with BP measurement	Geisinger Health System	194 456	10.8	2.3	-	-	CKD, male, higher BP, low BMI, DM	↑ K ⁺ led to discontinuation/dose reduction RAASi or MRA
Beusekamp [41]	LVEF <40%	Multinational HF cohort	1666	8	2	-	-	Low GFR, male	-
UKKR [42]	HD	Audit of in centre HD patients	13,978	-	-	10.5%	4.9	-	-
Rosignol[43]	HD	Cohort study of 14 centres in France	527	26.4%	13.8%	4.9%	4.8	Patients requiring K ⁺ binder	-
Kovesdy [44]	HD	DaVita dialysis clinics in USA	81,013	-	12.5%	4.5%	-	Greater protein intake	Serum K ⁺ >5.5 associated with ACM and CVM
Karaboyas [45]	HD	20 countries in DOPPS	55,183	38%	-	8%	-	-	Serum K ⁺ >5.5 associated with ACM K ⁺ >6.0 with arrhythmic events

CKD chronic kidney disease; GP general practitioner; HF heart failure; HD hemodialysis; RAASi renin angiotensin aldosterone system inhibitors; DM diabetes mellitus; ACEi angiotensin converting enzyme inhibitors; GFR glomerular filtration rate; BP blood pressure; BMI body mass index; ACM all-cause mortality; CVM cardiovascular mortality

Table 2: Main epidemiological studies showing the association of hyperkalemia with adverse events of CKD patients.

Author	Type of study	Number of patients	Population	Definition of hyperkalemia (mmol/L)	Adverse event	HR, OR or IRR (95% CI)
Iseki [59]	Retrospective (1971-1990)	1406	CKD-5 (non-dialysis)	≥5.5	Mortality	RR 2.15(1.17-3.96)
Kovesdy [44]	Retrospective (2001-2004)	74219	HD	5.6-6.0	CV mortality	13% in 3years
Yusuf [60]	Retrospective (2007-2010)	28774-36388	HD	≥5.7	All-cause mortality	32% in 3years
				≥5.8	All-cause mortality	HR 1.13(1.01-1.28)
				≥5.9		1.18(1.03-1.35)
				≥6.0		1.29(1.12-1.5)
						1.37(1.16-1.62)
				≥5.7	CV mortality	HR 1.09 (0.91-1.31)
				≥5.8		1.13 (0.93-1.39)
				≥5.9		1.20 (0.95-1.5)
				≥6.0		1.28 (0.99-1.64)
Torlen [47]	Retrospective (2001-2006)	10468	PD	>5.5	All-cause mortality	OR 1.52 (1.32-1.75)
					CV mortality	1.51(1.23-1.87)
		111651	HD		All-cause mortality	OR 1.26(1.21-1.30)
					CV mortality	1.39(1.32-2.01)
Eriguchi [61]	Retrospective (2007-2011)	17664	PD	>5.0	All-cause mortality	HR 1.15(1.06-1.25)
					Arrhythmia-related death	1.65(1.41-1.93)
				>6.0	All-cause mortality	HR 1.23(1.03-1.46)
					Arrhythmia-related death	1.64(1.18-2.27)
Genovesi [62]	Prospective	476	HD	≥6.0	Sudden death	HR 2.7(1.3-5.9)
Brunelli [63]	Retrospective (2010-2011)	52734	HD	5.5-6.0	Hospitalizations	OR 1.68/ 1.04/1.12
				6.0-6.5	(Friday/Wednesday/	1.63 /1.37/1.22
				6.5-7.0	Monday)	2.19 / 1.91/1.7
				≥7.0		3.51 /2.09/2.78
				≥7.0	Death	OR 3.37(1.67-7.0)
					Emergency department visit	2.62(2.22-3.09)
Einhorn [18]	Retrospective (2004-2005)	70873	CKD (stage3-5)	≥5.5-6.0	Death(1-day) (CKD stage3/4/5)	OR 5.35 / 5.73 /2.31
				≥6.0		OR 19.52 / 11.56 /8.02
Nakhoul[64]	Retrospective (2005-2009)	36359	CKD (stage 3-4)	5.0-5.4	Mortality	HR 1.12(1.03-1.21)
				≥5.5		1.65(1.48-1.84)
Luo [65]	Retrospective (2009-2013)	55000	CKD (stage3-5)	5.0-5.4	Mortality	IRRs 1.14(1.04-1.26)
				5.5-5.9		1.6(1.37-1.88)
				≥6.0		3.31(2.57-4.34)
Furuland [22]	Retrospective (2006-2015)	192000	CKD (stage 3-5)	5.5-6.0	Mortality	HR 1.6(1.52-1.68)
					MACE	2.88(2.61-3.18)
				>6.0	Mortality	HR1.07(1.00-2.15)
					MACE	1.15(0.98-1.36)

Valdivielso [170]	Prospective	1757	CKD	>5.2	CV event	HR 1.54(1.06-2.25)
Thomsen [66]	Retrospective (2000-2012)	157766	CKD	>5.0	Acute hospitalizations	HR 3.78(3.69-3.87)
					Arrhythmia	3.43(2.96-3.97)
					Cardiac arrest	5.41 (4.08-7.16)
					Death	4.85 (4.65-5.05)
Korgaonkar [32]	Prospective (2000-2006)	820	CKD (stage 3-5)	≥5.5	CV event or mortality	HR 1.69(1.62-2.6)
Wagner [68]	Prospective (2000-2012)	2078	CKD (stage1-5)	>5	All-cause mortality	HR 0.79(0.48-1.32)
					CV mortality	1.47(0.67-3.24)
Gasparini [70]	Retrospective (2006-2011)	70403	CKD (stage 3)	Out of range	Mortality (90days)	HR 2.53(2.39-2.68)
		8594	CKD (stage 4-5)	(95% distribution)		

CV cardiovascular; HD hemodialysis; PD peritoneal dialysis; CKD chronic kidney disease; MACE major adverse cardiac event; HR hazard ratio, adjusted for various confounders; OR odds ratio, adjusted for various confounders; IRR incident rate ratio, adjusted for various confounders

Table 3: The prevalence of hyperkalemia and the need for drug discontinuation in the main randomized clinical trials using ACE inhibitors, angiotensin II receptor blockers, aliskiren of their combination in patient with chronic kidney disease

Study	Population	Baseline renal function	Drug	K ⁺ increase	Hyperkalemia prevalence	Drug withdrawal
AIPRI [91]	Non-diabetic CKD (n= 583)	GFR 30-60 ml/min	Benazepril vs placebo	Average increase of 0.5 mmol/l in the benazepril group	NA	5 (1.6%) in the benazepril group and 3 (1%) in the placebo group
REIN [92]	Non-diabetic, proteinuria ≥3 g/day, (n= 117)	GFR 20-70 ml/min	Ramipril vs placebo	NA	NA	1 (18%) in the ramipril group and 1 (16%) in the placebo group
REIN [93]	Non-diabetic, proteinuria <3 g/day (n= 186)	GFR 20-70 ml/min	Ramipril vs placebo	NA	NA	0 (%) in the ramipril group and 1 (11%) in the placebo group
AASK [171]	Hypertensive kidney disease, African American (n=1,094)	GFR, 20-65 mL/min	Ramipril, vs metoprolol vs amlodipine	NA	NA	3 (0.7%) in the ramipril group, 1 (0.2%) in the metoprolol group, 0 in the amlodipine group
RENAAL[94,172]	Type II diabetic CKD (n=1,513)	Serum creatinine of 1.3 - 3.0 mg/dl	Losartan vs placebo	NA	K ⁺ ≥5.5 mmol/l increased from 22 (2.9%) at baseline to 73 (10.8%) at month 6 with losartan; in placebo remained stable (35 (4.6%) to 34 (5.1%))	NA
IDNT [96]	Type II diabetic CKD (n=1,715)	Serum creatinine of 1.0 - 3.0 mg/dl in women and 1.2 - 3.0 mg/dl in men	Irbesartan, amlodipine or placebo	NA	NA	11 (1.9%) with irbesartan, 3 (0.5%) with amlodipine, 2 (0.4%) with placebo
ONTARGET [89]	Vascular disease or high-risk diabetes without heart failure (n=25,720)	Serum creatinine < 3 mg/dl	Ramipril, telmisartan or their combination	At week 6, mean K ⁺ increase of – 4 mmol/L for monotherapy, +2 mmol/l for the combination; <i>p</i> < 0.001	K ⁺ ≥5.5 mmol/l in 283 (3.29%) patients of the ramipril group, 287 (3.35%) of the telmisartan group, 480 (5.79%) in the combination-therapy group; <i>P</i> <0.001	NA

HALT PKD [173]	ADPKD (n=486)	25-60 ml/min	Lisinopril in combination with telmisartan or placebo	NA	41 (16.9%) in the lisinopril plus placebo group and 46 (18.9%) in the lisinopril/telmisartan group	NA
VA NEPHRON-D [98]	Type 2 diabetes and macroalbuminuria (n=1,448)	GFR 30.0-89.9 ml/min	Losartan in combination with lisinopril or placebo	Significantly higher mean K ⁺ levels r the combination therapy	32 (4.4%) in losartan monotherapy vs 72 (9.9%) for the combination; p<0.001	NA
ALTITUDE [97]	Type 2 diabetes and CKD, CVD, or both (n=8,561)	GFR ≥ 30 ml/min	Aliskiren or placebo plus an ACEi or ARB	NA	1670 (39.1%) in the aliskiren group, 1244 (29%) in the placebo group; p<0.001	205 (4.8%) in the aliskiren group, 111 (2.6%) in the placebo group; p<0.001

ADPKD, autosomal dominant polycystic kidney disease; GFR, glomerular filtration rate; ACEi, ACE inhibitor; CKD, chronic kidney disease; CVD, cardiovascular disease; NA, not available; AIPRI, The Angiotensin-converting-enzyme Inhibition on Progressive Renal Insufficiency; REIN, Ramipril Efficacy In Nephropathy; AASK, African American Study of Kidney; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; IDNT, Irbesartan Diabetic Nephropathy Trial; ONTARGET, Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; HALT PKD, Halt Progression of Polycystic Kidney Disease; VA NEPHRON-D, Veterans Affairs Nephropathy in Diabetes; ALTITUDE, Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints

Table 4: Phase III pivotal trials of novel K⁺ binders

	Inclusion criteria and design	Baseline comorbidities		RAASi use at baseline		Primary endpoint	Efficacy results	Safety results
OPAL-HK phase III pivotal trial patiromer [161].	Patients with CKD receiving RAAS inhibitors with serum K ⁺ 5.1 to < 6.5 mmol/L received patiromer (at an initial dose of 4.2 g or 8.4 g twice a day) for 4 weeks (initial treatment phase: part A); Eligible patients at the end of week 4 (those with a baseline K ⁺ level of 5.5 to <6.5 mmol/L in whom the level decreased to 3.8 to <5.1 mmol/L) entered an 8-week randomized Part B withdrawal phase in which they were randomly assigned to continue patiromer or switch to placebo.	DT2	139 (57)	Any RAASi	243 (100)	Part A primary endpoint: Mean change in serum K ⁺ from baseline to Week 4 Part B primary endpoint: Treatment group differences in median change in serum K ⁺ from start of Part B to Part B Week 4 or first visit where serum K ⁺ was <3.8 or ≥5.5 mmol/L	Part A: In the initial treatment phase, among 237 patients receiving patiromer who had at least one K ⁺ measurement at a scheduled visit after day 3, the mean (±SE) change in the serum K ⁺ level was -1.01 [±] 0.03 mmol/L (p<0.001). Part B: Subsequently, 107 patients were randomly assigned to patiromer (55 patients) or placebo (52 patients) for the randomized withdrawal phase. The median increase in the K ⁺ level from baseline of that phase was greater with placebo than with patiromer (<0.001).	Mild-to-moderate constipation was the most common adverse event (in 11% of the patients); hypokalemia occurred in 3% of the patients.
		HF nb	102 (42)	Dual RAAS blockade	41 (17)			
		HTN	236 (97)					
		CKD	243 (100)					

ZS004 (ZSC) phase III pivotal trial[160]	Outpatients with hyperkalemia (serum K ⁺ ≥5.1mEq/L; n = 258) received 10 g of zirconium cyclosilicate 3 times daily in the initial 48-hour open-label phase. Patients achieving normokalemia (3.5-5.0 mEq/L; n = 237) were then randomized to receive zirconium cyclosilicate, 5 g (n = 45), 10 g (n = 51), or 15 g (n = 56), or placebo (n = 85) daily for 28 days.	DT2 nb (%)	170 (66%)	Any RAASi n(%)	180 (70)	The comparison of mean serum K ⁺ levels between placebo and each treatment group (highest to lowest) during days 8 through 29 of the randomized phase	In the open-label phase, serum K ⁺ levels declined from 5.6mEq/L at baseline to 4.5mEq/L at 48 hours. In the randomized phase, serum K ⁺ was significantly lower during days 8-29 with all 3 zirconium cyclosilicate doses vs placebo (4.8mEq/L [95%CI, 4.6-4.9], 4.5mEq/L [95%CI, 4.4-4.6], and 4.4mEq/L [95%CI, 4.3-4.5] for 5 g, 10g, and 15 g; 5.1mEq/L [95%CI, 5.0-5.2] for placebo; p<0.001 for all comparisons).	Adverse events were comparable between zirconium cyclosilicate and placebo, although edema was more common in the 15-g group (placebo: 2/85 [2%], 5g: 1/45 [2%], 10g: 3/51 [6%], and 15g: 8/56 [14%]. Hypokalemia developed in 5/51 (10%) and 6/56 patients (11%) in the 10-g and 15-g zirconium cyclosilicate groups, vs none in the 5-g or placebo groups.
		HF nb (%)	94 (36%)	Dual RAAS blockade	?			
		HTN nb (%)	?					
		CKD nb (%)	169 (66%)					

CV cardiovascular; RAASi renin angiotensin aldosterone system inhibitors; DT2 type 2 diabetes mellitus; HF heart failure; HTN hypertension

Table 5. Planned or ongoing randomized clinical trials of novel K⁺ binders with primary endpoint clinical events.

NCT Number	Title	Status	Conditions	Interventions	Primary outcome	Phase	Enrollment	Estimated Completion Date
NCT03888066	Patiromer for the Management of Hyperkalemia in Subjects Receiving RAASi Medications for the Treatment of Heart Failure (DIAMOND)	Recruiting	Heart failure/Hyperkalemia	Patiromer vs Placebo	Time to first occurrence of CV death or CV hospitalization (or equivalent in outpatient clinic)	3	2388	March 2022
NCT04142788	RELieving Increasing oEdema Due to Heart Failure (RELIEHF)	Not yet recruiting	Heart Failure/Congestive	Patiromer/high dose MRA vs standard dose MRA	"Congestion index", Morbidity/mortality	4	2000	November 2025

Table 6. Current research questions

- What is the optimal combination of nephroprotective therapies that improves kidney and cardiovascular outcomes while minimizing the risks associated with hyperkalemia?
- Do novel K⁺ binders improve kidney or cardiovascular outcomes in CKD patients? On top of which nephroprotective regimen?
- Does correction of acidosis with veverimer lower serum K⁺?
- What is the impact of novel non-absorbable binders on the gut microbiota and may this have clinical consequences?

Figure legends

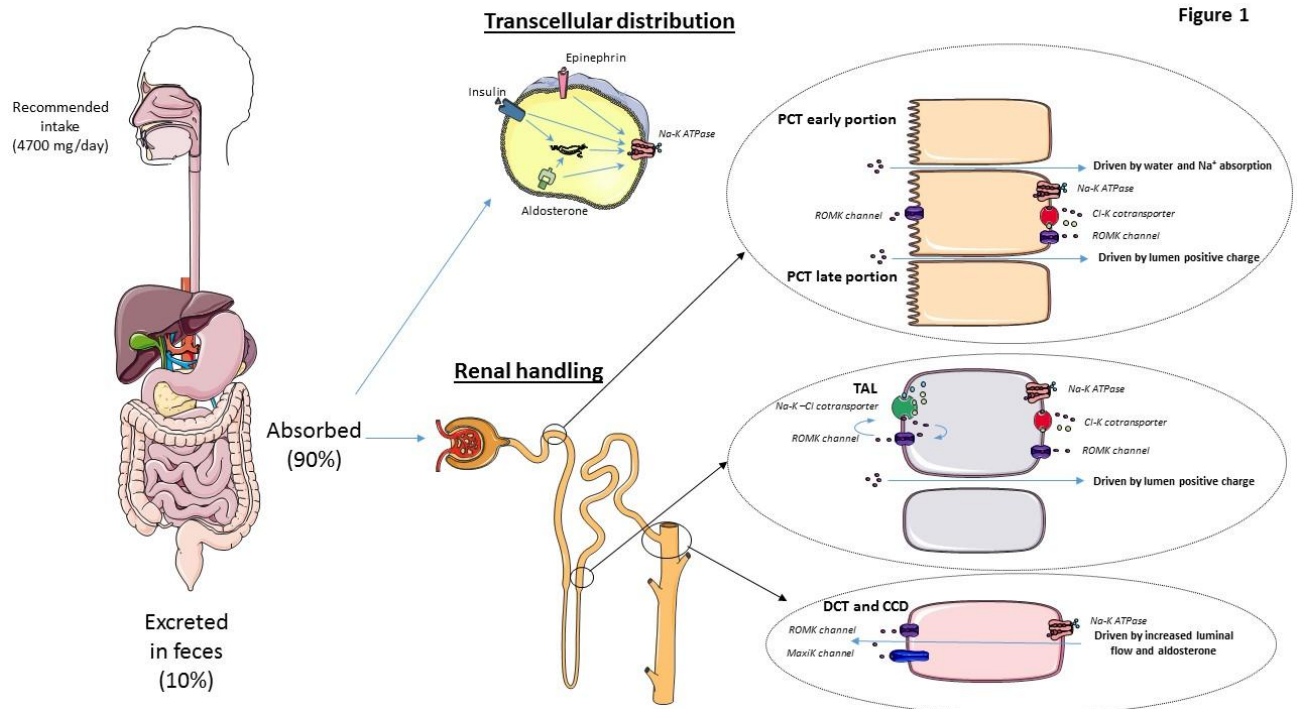


Figure 1

Figure 1: Physiology of normal K^+ handling. In the kidneys, K^+ freely filtered in glomeruli is mostly reabsorbed in the proximal convoluted tubule (PCT), driven by the absorption of Na and water in the early portion and by the shift to luminal positive charge in the late portion. The rest is absorbed in the thick ascending limb of Henle by both paracellular and transcellular pathways. The transcellular pathway is mediated by the luminal $Na^+-K^+-2Cl^-$ cotransporter, activated by the low intracellular concentration of Na^+ generated by the basolateral Na^+-K^+ ATPase. Reabsorbed K^+ then crosses the basolateral membrane cotransported with Cl^- , although a portion is recycled into the luminal space through the renal outer medullary K^+ (ROMK) channel to maintain the luminal $Na^+-K^+-2Cl^-$ cotransporter activity. The different permeability to Cl^- and K^+ between the luminal and basolateral membranes creates a lumen positive charge which in turn drives K^+ reabsorption through the paracellular pathway. The fine adjustment of K^+ excretion is regulated by aldosterone levels in the distal convoluted tubule (DCT) and the cortical collecting duct (CCD), where K^+ excretion depends on electrogenic secretion through ROMK channels and stimulation of Maxi-K channels by increased tubular flow.

Figure 2

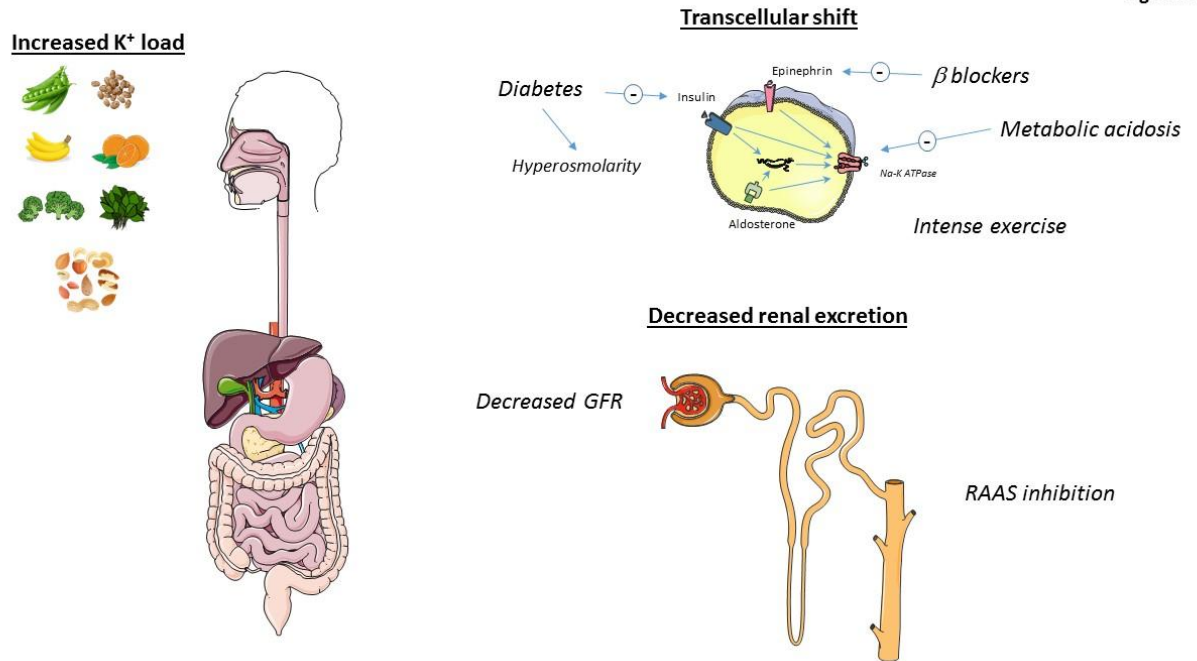


Figure 2: Contributors to hyperkalemia in CKD. Decreased urinary K^+ excretion is caused by decreased glomerular filtration and inhibitors of the RAAS. β -blockers, metabolic acidosis, low insulin activity and hyperosmolarity (e.g. from hyperglycemia) promote a shift of K^+ from inside the cell to the extracellular fluid. Finally, excess dietary K^+ mat also contribute.

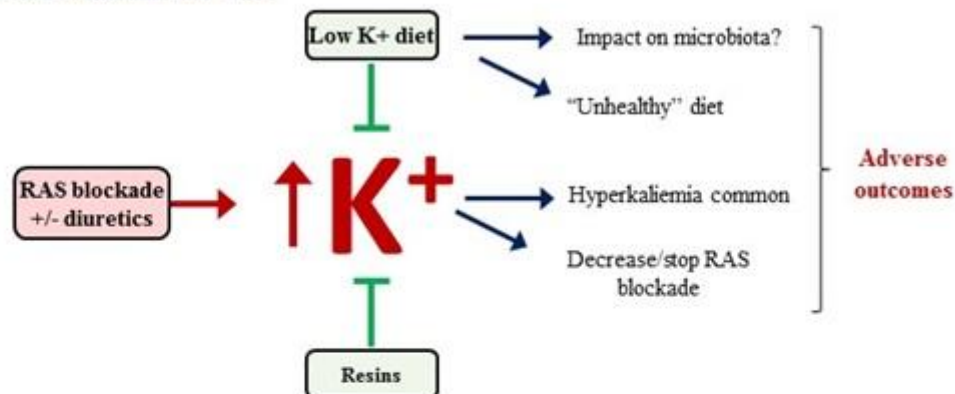
High Potassium content [>1000 mg (25 mmol/100g)]		Low Potassium content [>250 mg (6.2 mmol/100g)]	
Sun-dried tomatoes Lima beans, mature Molasses Wheat bran crude	Vegetables	Plantains Avocados Potatoes Sweet potatoes Beets Carrots Broccoli Cauliflower Tomatoes Summer Squash	
Medium Potassium content [>500 mg (12.5 mmol/100g)]	Fruits	Bananas Purple Passion fruit Kiwis Cantaloupe Mangos Oranges Grapefruit	
Plums, dried (Prunes) Dates Peanuts, raw Cashews, raw Dried figs Oat bran, raw Spinach, raw Walnuts, black dried	Meats	Lamb Lean pork Steak Veal	

Figure 3

Figure 3: K⁺ contents in different foods. K⁺ contents in food varies from very low (<6.2 mmol/100g) to high (25 mmol/100g).

Figure 4

A) Current: hyperkalemia and CKD



B) The evolving landscape: hyperkalemia and CKD

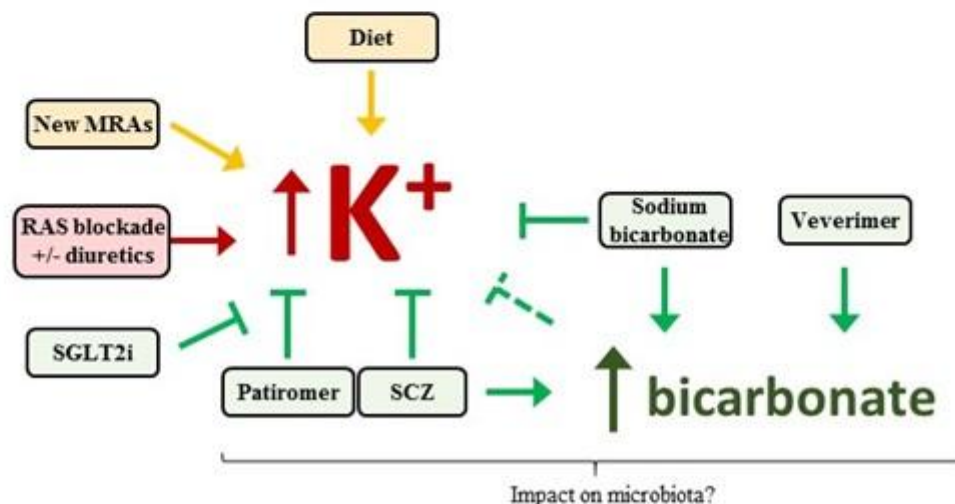


Figure 4: Expected impact of recent and future therapeutic developments on hyperkalemia on CKD. A) Current approach to hyperkalemia and CKD. RAAS blockade is the standard nephroprotective approach but promotes hyperkalemia. Hyperkalemia may be milder when thiazide or loop diuretics are concomitantly prescribed. Prescription of low K^+ /low fiber diets is common. Resin use is widely variable. Implementation of bicarbonate prescription to correct metabolic acidosis is suboptimal. Hyperkalemia is common, may lead to stopping or decreasing RAAS blockade and is associated with adverse outcomes. **B) The evolving landscape.** SGLT2 inhibitors have become key agents in the treatment of CKD and heart failure on top of RAAS blockade. They may decrease serum K^+ in CKD patients. The novel MRA finerenone has a lesser impact on serum K^+ than currently available MRAs. Patiromer and sodium zirconium cyclosilicate (SZC) K^+ binders are now available. These developments may allow a more liberal diet regarding K^+ intake.