Aldosterone and Potassium in Heart Failure: Overcoming This Major Impediment in Clinical Practice

Laibah Arshad Khan [1], Adeena Jamil [2], Stephen J Greene [3,4], Muhammad Shahzeb Khan [5,6,7] and Javed Butler [1,7]

1. Department of Medicine, University of Mississippi Medical Center, Jackson, MS, US; 2. Department of Medicine, Dow International Medical College, Dow University of Health Sciences, Karachi, Pakistan; 3. Duke Clinical Research Institute, Durham, NC, US; 4. Division of Cardiology, Duke University Medical Center, Durham, NC, US; 5. Division of Cardiology, The Heart Hospital Plano, Plano, TX, US; 6. Department of Medicine, Baylor College of Medicine, Temple, TX, US; 7. Baylor Scott and White Research Institute, Dallas, TX, US

Abstract

Aldosterone is a key regulator of fluid and electrolyte balance in the body. It is often dysregulated in heart failure (HF) and is a key driver of cardiac remodelling and worse clinical outcomes. Potassium regulation is essential for normal cardiac, gastrointestinal and neuromuscular function. Serum potassium fluctuations are largely determined by aldosterone, the final step of the renin–angiotensin–aldosterone system. Dyskalaemia (i.e. hypokalaemia and hyperkalaemia) is prevalent in HF because of the disease itself, its therapies and related comorbidities such as chronic kidney disease. Prognostic implications of abnormal serum potassium follow a U-shaped curve, where both hypokalaemia and hyperkalaemia are associated with adverse outcomes. Hypokalaemia is associated with increased mortality, starting from potassium <4.0 mmol/l but especially at potassium <3.5 mmol/l. Hyperkalaemia, along with increasing arrhythmia risk, limits the use of lifesaving renin–angiotensin–aldosterone system inhibitors, which may have long-term survival implications. The advent of novel potassium binders aims to manage chronic hyperkalaemia and may allow for uptitration and optimal dosing of guideline-recommended therapy. This review discusses the impacts of dyskalaemia in HF, along with management strategies, including the relevance of potassium binder use in optimising HF treatment. Current and potential future aldosterone-modulating therapies, such as non-steroidal mineralocorticoid receptor antagonists and aldosterone synthase inhibitors, are also discussed.

Keywords

Heart failure, hypokalaemia, hyperkalaemia, potassium binders, aldosterone

Received: 21 May 2024 **Accepted:** 5 October 2024 **Citation:** *Cardiac Failure Review* 2024;10:e18. **DOI:** https://doi.org/10.15420/cfr.2024.09

Disclosures: SJG has received research support from the Duke University Department of Medicine Chair's Research Award, American Heart Association, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Cytokinetics, Merck, Novartis, Pfizer and Sanofi; has served on advisory boards or as consultant for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Corteria Pharmaceuticals, CSL Vifor, Cytokinetics, Eli Lilly, Lexicon, Merck, Novo Nordisk, Roche Diagnostics, Sanofi, scPharmaceuticals, Tricog Health and Urovant Pharmaceuticals; and has received speaker fees from AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Lexicon and Roche Diagnostics. MSK has received fees from Bayer. JB is a consultant to Abbott, American Regent, Amgen, Applied Therapeutic, AskBio, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cardiac Dimension, Cardiocell, Cardior, CSL Bearing, CVRx, Cytokinetics, Daxor, Edwards, Element Science, Faraday, Foundry, G3P, Innolife, Impulse Dynamics, Imbria, Inventiva, Ionis, Levator, Lexicon, Lilly, LivaNova, Janssen, Medtronics, Merck, Occlutech, Owkin, Novartis, Novo Nordisk, Pfizer, Pharmacosmos, Pharmain, Prolaio, Pulnovo, Regeneron, Renibus, Roche, Salamandra, Salubris, Sanofi, SC Pharma, Secretome, Sequana, SQ Innovation, Tenex, Tricog, Ultromics, Vascular Dynamics, Vifor and Zoll; and is on the *Cardiac Failure Review* editorial board; this did not influence peer review. All other authors have no conflicts of interest to declare.

Correspondence: Javed Butler, Baylor Scott and White Research Institute, 3434 Oak St 501, Dallas, TX 75204, US. E: javed.butler@bswhealth.org

The role of aldosterone in driving the pathogenesis and worsening of heart failure (HF) outcomes has been well-established.[1,2] Several drugs have been developed to mitigate the effects of aldosterone for the management of HF and target different steps in aldosterone physiology. Aldosterone is the final product of the renin–angiotensin–aldosterone system (RAAS), where angiotensin II upregulates aldosterone synthesis and release from the zona glomerulosa of the adrenal cortex.[3] The rate-limiting step of aldosterone synthesis, catalysed by the aldosterone synthase enzyme (cytochrome P450 [CYP] 11B2), catalyses the conversion of 11-deoxycorticosterone to aldosterone.[4] Aldosterone exerts its effects largely by binding to intracytoplasmic mineralocorticoid receptors (MRs), which are found in the nephron, heart, colon and brain (including the pituitary gland).[5] In addition to this genomic signalling, aldosterone has been implicated in non-genomic, MR-independent effects on the kidney, heart and vascular smooth muscle.[6]

Several of the guideline-recommended therapies for HF inhibit RAAS (collectively referred to as RAAS inhibitors; RAASi) and include angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs) and angiotensin receptor–neprilysin inhibitors (ARNi), all reducing aldosterone production.[7,8] Moreover, aldosterone's downstream activity is also targeted by MR antagonists (MRAs), which include the steroidal MRAs spironolactone and eplerenone and – more recently – non-steroidal MRAs such as finerenone.[9,10] Finally, a newer class of drugs, aldosterone

synthase inhibitors (ASIs), may be beneficial in reducing both the genomic and non-genomic effects of aldosterone.[11] The use of most of these aldosterone-modulating therapies is limited by their effects on potassium homeostasis and the increased risk of hyperkalaemia.

Potassium is essential for normal cellular functions. Dyskalaemia, i.e. abnormal serum potassium, can lead to cardiac, gastrointestinal and neuromuscular disturbances.[12] Although potassium is the most abundant cation in humans, 98% of it is intracellular (approximately 140 mmol/l) and only 2% is extracellular (approximately 3.8–5.0 mmol/l). Hypokalaemia – defined as potassium ≤4.0 mmol/l – increases cellular excitability, automaticity and depolarisation.[13] In the heart, potassium influx determines cardiac repolarisation, hence, hypokalaemia leads to lengthening of the action potential and the QT interval. In contrast, hyperkalaemia – defined as serum potassium >5.0 mmol/l – leads to rapid repolarisation and QT interval shortening.[13,14] Both hypokalaemia and hyperkalaemia may increase the risk of life-threatening ventricular arrhythmias and sudden cardiac death.[15]

Physiologically, the kidneys are responsible for over 90% of potassium elimination.[16] The colon excretes the remaining potassium, which – in the setting of chronic renal impairment – may increase by threefold.[17] The renal excretion of potassium is largely dependent on aldosterone regulation, along with sodium concentration within the distal tubule.[12] Aldosterone regulation, in turn, is dependent on RAAS and serum potassium fluctuations.[18] Aldosterone is a key hormone in the pathophysiology of HF and – as mentioned earlier – is targeted by RAASi and MRAs. All these drugs, through the eventual inhibition of aldosterone's effects, have the potential to cause hyperkalaemia. Other guideline-recommended therapies also impact potassium concentrations, such as β-blockers (hyperkalaemia) or thiazide and/or loop diuretics (hypokalaemia).[8] HF patients are predisposed to dyskalaemia due to HF itself and related comorbidities such as chronic kidney disease (CKD), diabetes and the older age of the patient population.

In HF, the relationship between potassium concentrations and adverse outcomes is U-shaped, where both hypo- and hyperkalaemia are associated with worse outcomes.[19,20] This is consistent with what has been shown for other cardiovascular (hypertension and myocardial infarction) and non-cardiovascular (CKD and diabetes) pathologies.[19,21–23] Dyskalaemia, along with directly increasing hospitalisation and mortality, also limits the use of optimal guideline-recommended therapies such as RAASi in the case of hyperkalaemia.[24–26] Notably, although hyperkalaemia and the fear of hyperkalaemia is more often a focal point in HF care, hypokalaemia is equally detrimental for HF patients.[27] Hence, the management of serum potassium levels in patients with HF is vital to optimise disease treatment, minimise adverse outcomes and improve survival. This paper seeks to explore the interplay between potassium, aldosterone and HF and suggests how to address these problems from current and new therapeutic options, including the up-and-coming potassium binders patiromer and sodium zirconium cyclosilicate (SZC).

Aldosterone Homeostasis and Heart Failure Pathophysiology

Aldosterone, a steroid hormone, is synthesised in the zona glomerulosa of the adrenal cortex by a series of enzymatic reactions catalysed by the CYP system.[28–30] The final step, mediated by aldosterone synthase, is the target of hormonal regulation to meet physiological demands.[4,31] Determinants of endogenous aldosterone production include angiotensin II (i.e. RAAS), serum potassium concentration and, at times, adrenocorticotropic hormone (ACTH).[32,33] Aldosterone synthase activity is increased in response to elevated serum potassium and RAAS through the binding of angiotensin II to the angiotensin II receptor type 1 on adrenal cortical cells.[3,32,33] RAAS is activated in response to decreased renal perfusion (i.e. low blood pressure) or low sodium delivery to the macula densa.[3,32] ACTH can also acutely stimulate aldosterone synthesis and release.[34]

Aldosterone exerts its effects both by MR-dependent genomic effects and MR-independent non-genomic effects.[6,35] Intracytoplasmic binding of aldosterone to the MR is followed by translocation to the nucleus where the receptor–ligand complex works as a transcription factor to induce downstream effects.[36] MRs can be found in the nephron, heart, brain and colon and, along with aldosterone, may also be activated by steroid hormone synthesis intermediates and glucocorticoids.[5,28,36,37] Aldosterone's key physiological role is to maintain fluid and electrolyte homeostasis by its effect on the distal nephron (distal convoluted tubule, collecting tubule and collecting duct).[38] In summary, it increases sodium reabsorption and subsequent fluid retention through increased epithelial sodium channel expression, increases potassium excretion by increasing renal outer medullary potassium channels on the apical membrane and increases proton secretion through the intercalated cells.[38–42] Along with these well-documented genomic effects, there is implication of MR-independent, rapid-acting, non-genomic effects of aldosterone. These include production of reactive oxidation species, inflammation, vasoconstriction and apoptosis in tissues such as cardiomyocytes, nephrons and arterial smooth muscle.[6,43,44]

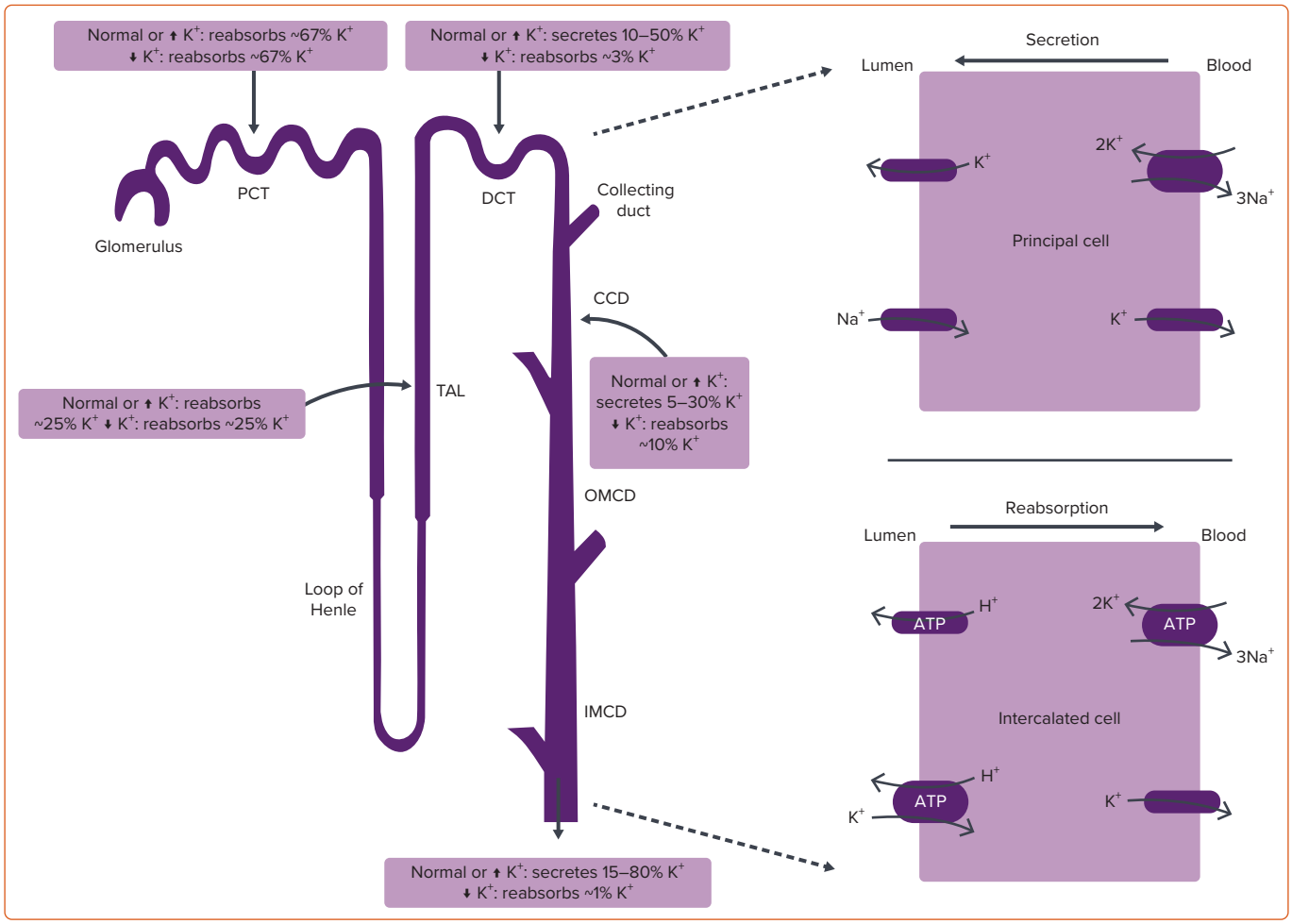
Maladaptive aldosterone regulation is present in cardiovascular diseases.[1] In HF, decreased effective circulatory volume towards juxtaglomerular cells results in chronically elevated aldosterone levels.[2,45] Multiple studies have established hyperaldosteronism's association with cardiac structural changes such as left ventricular hypertrophy.[46–48] Both the genomic and non-genomic effects of aldosterone can result in inflammation, fibrosis and remodelling of the heart, kidney and vasculature.[49–51] These pathological pathways are responsible for both the pathogenesis and progression of HF and CKD, which is a common comorbidity in HF patients.[52]

Potassium Homeostasis and Heart Failure Pathophysiology

Typically, the kidneys filter out approximately 90% of the potassium ingested each day.[16] The majority of ingested potassium gets filtered at the glomerulus, then reabsorbed by the proximal tubule and the loop of Henle, leaving just approximately 10% to continue to the distal tubule.[53] The secretion of excess potassium into the urine occurs within the principal cells of the renal collecting duct. This process is dependent on the luminal potassium channels, influenced by an electrochemical gradient established by the sodium–potassium pump (Na^+/K^+-adenosine triphosphatase [ATP]ase) on the basolateral membrane, working in conjunction with a luminal sodium channel.[53,54] During potassium-depleted states, the principal cells reduce secretion and instead, potassium is reabsorbed by the action of hydrogen–potassium pump (H^+/K^+-ATPase) in the intercalated cells.[54] Segmental handling of potassium within the nephron is illustrated in *Figure 1*.

Potassium secretion in the collecting tubule is determined by serum aldosterone levels and sodium concentrations within the distal tubule.[12] Aldosterone production increases in response to decreased renal perfusion and subsequent RAAS activation.[18,55] Elevated serum potassium

Figure 1: Potassium Regulation in the Nephron



Excess potassium is secreted into the tubular lumen and consequently excreted in urine by the principal cells within the collecting duct. This secretion is mediated by potassium channels present in the luminal membrane, dependent on the electrochemical gradient for potassium created through the coordinated activity of the sodium–potassium ATPase on the basolateral membrane and a sodium channel on the luminal membrane. During potassium-depleted states, potassium secretion by principal cells is inhibited and the luminal membrane hydrogen–potassium ATPase in the intercalated cells becomes activated to reabsorb the remaining potassium in the tubular fluid, thereby reducing urinary potassium loss. ATP = adenosine triphosphate; CCD = cortical collecting duct; DCT = distal convoluted tubule; IMCD = inner medullary collecting duct; OMCD = outer medullary collecting duct; PCT = proximal convoluted tubule; TAL = thick ascending limb of Henle's loop.

also stimulates aldosterone synthesis, increasing potassium secretion in the distal tubule and restoring homeostasis.[18,56] Furthermore, an increase in dietary potassium elevates the elimination of potassium via the urine, suggesting that potassium sensors may also be located in the gastrointestinal tract, the enterohepatic system and the liver.[54] Studies in humans have also revealed that enhanced renal and gastrointestinal elimination of potassium, following an intake of an oral potassium load, persisted even after inhibiting aldosterone activity.[57] These findings indicate the possibility of a gastrointestinal–renal kaliuretic axis that promotes potassium elimination, acting independently of serum potassium and aldosterone alterations.

Potassium levels may vary in HF because of several mechanisms. Decreased renal perfusion pressure in HF can lead to the stimulation of RAAS, upregulating aldosterone production, leading to excess potassium secretion in the collecting tubule and causing hypokalaemia.[58] Potassium-wasting diuretics, such as loop diuretics – common therapeutic drugs in HF – can further contribute to lower potassium levels.[59] Conversely, RAASi use can block aldosterone effects leading to hyperkalaemia.[7] Hyperkalaemia may also be seen due to high serum aldosterone in HF patients causing increased sodium reabsorption in the proximal tubule, leading to decreased sodium delivery to the distal nephron, downregulating potassium secretion.[12] Comorbid renal disease may disrupt renin production, shutting down RAAS and leading to decreased aldosterone and potassium elimination. Other tubulointerstitial diseases may have dysfunctional nephrons that do not adequately respond to the elevated aldosterone levels in HF, leading to resistance and hyperkalaemia.

Notably, the discrepancy in serum and plasma potassium measurements warrants a discussion. The evaluation of potassium levels in the bloodstream – and the subsequent determination of dyskalaemia – hinges on the accuracy and method of the test performed. Potassium levels may be assessed in either serum or plasma samples. To analyse serum potassium, blood must first be allowed to clot, whereas plasma potassium can be measured promptly. Clotting results in the release of potassium from cells into the serum, typically raising measured potassium levels by 0.1 to 0.4 mmol/l, with this increment being more pronounced when potassium concentrations are high.[60] As such, reported instances of hyperkalaemia could be falsely elevated due to haemolysis, which can occur if blood samples are not properly handled or if analysis is unduly delayed. This phenomenon, known as 'pseudo-hyperkalaemia,' may result in an erroneous clinical assessment and management.[61] It is therefore crucial to verify the presence of genuine hyperkalaemia through careful analysis and confirmation, unless the patient is facing an immediate threat to life. The current literature concerning dyskalaemia and its

relationship with cardiovascular health is constrained by a lack of clarity and consistency regarding whether serum or plasma levels are reported in the studies or by the interchange of both values without distinction.

Hyperkalaemia

Incidence and Causes

HF patients are predisposed to hyperkalaemia due to the disease, its treatment medications and/or comorbidities. In one large cohort study (n=19,194), 11.3% of HF patients developed hyperkalaemia over a mean follow-up of 3.9 ± 3.2 years.[62] Broadly, hyperkalaemia can be classified into two types: 1. inherent hyperkalaemia that includes CKD, diabetes, other endocrine disorders (e.g. Addison's disease, hyporeninaemic hypoaldosteronism) or other diseases causing potassium shifts;[63,64] and 2. treatment-related hyperkalaemia caused by medications (e.g. RAASis, MRAs, non-steroidal anti-inflammatory drugs [NSAIDs], diuretic agents, heparin).[65] In addition, excess dietary intake of foods high in potassium or sodium supplements containing high potassium content can cause hyperkalaemia.[66] Hyperkalaemia in patients with HF is commonly treatment-related, particularly due to RAASi-like ACEis, ARBs, MRAs and the ARNi sacubitril-valsartan.[7,67,68] Higher dosing and combination use can exacerbate serum potassium elevation.[69,70] Inherent hyperkalaemia factors like advanced age, diabetes and CKD often complicate such patients, which may compound the hyperkalaemia risk.[71]

The advent of hyperkalaemia frequently necessitates the reduction or discontinuation of RAASi therapy, diminishing its potential advantages. Concern over hyperkalaemia, which leads to the under-prescribing or inadequate dosing of RAASi medications, is well-founded as a substantial number of HF patients on RAASi therapy experience moderate to severe hyperkalaemia, especially if complicated by the above-mentioned comorbidities. Research from a broad, international study of the HF population showed that hyperkalaemia, alongside poor kidney function and hypotension, were key reasons for RAASi being underdosed or not prescribed at all.[72] Clinicians are particularly concerned about hyperkalaemia when it comes to using MRAs.[73] An analysis from the Swedish HF Registry revealed that CKD and older age were significant factors in deciding against MRA use, regardless of potassium levels or other influencing factors.[74]

Hyperkalaemia severity can be defined in stages such as mild (5.0–5.5 mmol/l), moderate (5.6–6.0 mmol/l) or severe (>6.0 mmol/l). The threshold at which hyperkalaemia poses a risk of life-threatening arrhythmias or death is not consistent among patients.[75] While it is often believed that the rate at which potassium levels change is more critical than the absolute level in causing rhythm problems, this viewpoint is not universally supported. Observational studies suggest that there might be a correlation between even mild hyperkalaemia and negative health outcomes.[23,27] Considering the variable risk of arrhythmias according to individual potassium levels, it is advisable to perform an ECG in cases of both hyperkalaemia and hypokalaemia to identify any signs of arrhythmia, despite ECGs generally having a low sensitivity to detect rhythm abnormalities seen with hyperkalaemia.[76,77]

Clinical Evidence

Observational Studies

Cohort studies in HF with reduced ejection fraction (HFrEF) highlight that up to one in four patients may not receive treatment with ACEi/ARB/ARNi.[78] Use of MRAs is consistently even lower, with real-world evidence suggesting that 40–70% of patients are not prescribed therapy.[78–80] Hyperkalaemia is cited as the reason for non-prescription in up to 10% of cases for ACEis and ARBs and in up to 35% for MRAs.[72,74,81] Studies indicate that the therapeutic efficacy of both ACEi/ARBs and β-blockers is dose-dependent.[82,83] While the ideal recommendations for maximising patient outcomes with MRAs have not been established, insights from the EMPHASIS-HF study suggest that dosages of certain MRAs, such as eplerenone, should be modified according to renal function, with reduced doses being advisable for patients with renal insufficiency.[84]

Following the publication of RALES, there was a notable surge in the prescription of spironolactone. While one study from Canada showed an increased incidence of hyperkalaemia correlated to increased mortality, a study in Scotland reported a rise in the usage of spironolactone post-RALES without a corresponding rise in hyperkalaemia and even a decrease in outpatient cases.[24,85] This discrepancy might stem from different methods of monitoring potassium levels, variances in disease severity of the target population and demographics such as age. Crucially, the elevated clinical risk associated with hyperkalaemia in HF may be potentially attributed to discontinuation of RAASi after potassium levels start to rise. Hence, hyperkalaemia may be indicative of inability to use RAASi therapy (i.e. a risk marker of suboptimal RAASi use), in addition to any potential direct risk from hyperkalaemia itself.[86,87] Several studies have investigated this scenario. Specifically, the BioStat-CHF study found that, while hyperkalaemia did not directly lead to worse health outcomes, it did contribute to the underuse of optimal doses of ACEis or ARBs.[88] Similarly, the Swedish HF registry identified that both low and high potassium levels correlated with higher mortality rates in the short and long term, which is consistent with a U-shaped curve. However, after adjusting, only hypokalaemia continued to be independently linked to mortality in the short and long term, while hyperkalaemia was only independently related to short-term mortality.[89] This suggests that over time, hyperkalaemia may be more indicative of issues, such as inadequate RAAS inhibitor therapy, rather than being a direct mortality risk.

Hyperkalaemia risk is higher in HF patients with accompanying CKD. More than 60% of the 105,388 HF patients included in the ADHERE study had kidney disease.[90] In individuals with CKD, hyperkalaemia prevalence may reach up to 20%, and it is linked to increased mortality and major adverse cardiovascular events as well as the discontinuation of RAASi.[91] The use of RAASi in patients with cardiovascular conditions, such as MI, HF, diabetes and CKD, can mitigate negative long-term outcomes; however, most trials do not include participants with moderate or severe CKD, despite its common occurrence in the advanced stages of HF.[92]

In a recent observational study focusing on patients beginning treatment with MRAs, the emergence of hyperkalaemia resulted in nearly half (47%) of those patients stopping MRA treatment and another 10% having their doses reduced. After the MRA treatment was halted, the majority of those patients (>75%) did not resume MRA therapy within the next year.[93] Additionally, within the expansive European Society of Cardiology Heart Failure Long-Term Registry, both hypokalaemia and hyperkalaemia were linked to poorer health outcomes. However, when accounting for the discontinuation of RAASi (be it ACEi, ARBs, or MRAs), hyperkalaemia was no longer associated with an increased health risk.[94] This further suggests that the mechanism of potential excess risk with hyperkalaemia may relate more to non-use or discontinuation of RAASi, leading to an increased risk of adverse outcomes, independent of its direct acute cardiotoxic effects.[87,95] Most studies mentioned above show a U-shaped relationship between potassium levels and outcomes, with hyperkalaemia being associated with higher mortality risk. Potassium levels >5.5 mmol/l and especially >6.0 mmol/l have consistently been linked to negative

outcomes. The strength of the associations for potassium >6.0 mmol/l is similar to those observed for potassium <3.5 mmol/l, and correcting hyperkalaemia has also been found to mitigate its associated risks.[19,27]

Clinical Trials

Clinical trials appear to have similar prognostic implications as those seen in observational studies. For instance, a *post hoc* analysis of the TOPCAT trial showed that potassium levels >5.5 mmol/l were linked to a 1.7-fold increase in the risk of death.[96] A similar association with an increased risk of death due to hyperkalaemia (>5.5 mmol/l) was also found in a retrospective analysis from RALES.[25] The EMPHASIS-HF trial showed that, although eplerenone was associated with higher occurrence of hyperkalaemia, this did not eliminate survival benefit.[97] In the PARADIGM-HF trial, <18% of patients had hyperkalaemia throughout follow-up, with approximately 15% of patients in both the ARNi and enalapril arms developing potassium >5.5 mmol/l. However, there was a statistically significant increase in patients developing potassium >6.0 mmol/l with enalapril compared with ARNi.[98] Sacubitril/valsartan appeared to mitigate hyperkalaemia risk among patients taking an MRA.[99] Similar rates of hyperkalaemia were noted across both study groups in PIONEER-HF and there were no statistically significant differences between them.[100] In the PARAGON-HF study, fewer than 16% of patients maintained potassium levels above 5.5 mmol/l during the follow-up period. Potassium levels exceeding 6.0 mmol/l were observed in 3% of patients receiving sacubitril/valsartan and in 4% of those treated with valsartan. Additionally, the risk of hyperkalaemia was similar between the sacubitril/valsartan and valsartan groups for patients taking an MRA medication.[101]

CKD leads to suboptimal use of RAASi medication, even in the setting of normokalaemia. In trials such as RALES, EMPHASIS-HF and PARADIGM-HF, there was no significant interaction found between treatment effects and baseline creatinine levels or CKD status (defined as estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m^2). [25,97,98] While these trials excluded patients with eGFR <30 ml/min/1.73 m^2, two large observational studies indicate that RAASi drugs may be equally effective in elderly individuals and those with eGFR <30 ml/min/1.73 m^2.[102,103] Using the EMPHASIS-HF and EPHESUS trials, researchers developed a risk score to determine cardiovascular death. They did so by taking into account history, clinical and biological factors (such as potassium levels, eGFR, anaemia) and medications (diuretic use, MRA, β-blockers). The incorporation of time-updated variables like potassium and MRA treatment significantly enhanced the prediction of cardiovascular death risk in patients with HF eligible for RAASi and MRA therapy when added on top of the MAGGIC score. The authors aimed to introduce this score to attenuate harmful discontinuations of MRAs.[104]

In summary, elevated potassium levels above 5.5 mmol/l and particularly exceeding 6.0 mmol/l may be linked to higher mortality rates in HF, while also indicating poor RAASi use. Lowering potassium levels may, in part, reduce associated risks but does not address the persisting issue of poor RAASi use, highlighting that occasional episodes of hyperkalaemia can have long-term consequences on medication use and persistence. In chronic HFrEF, sacubitril/valsartan probably lowers the risk of hyperkalaemia compared with enalapril, especially when used alongside MRAs.

Management

Acute Management

The treatment of hyperkalaemia depends on the severity and underlying cause. Emergent management is indicated in patients with ECG changes and/or potassium levels >7.0 mmol/l. Firstly, intravenous calcium gluconate is given to stabilise the myocardium and prevent life-threatening arrhythmias. Serum potassium is quickly lowered by administering insulin with glucose and/or β-2 adrenoreceptor agonists, which redistribute potassium from the extracellular to the intracellular space; however, this is a temporary measure.[12] To eliminate potassium from the body, three routes can be adopted: excretion from the urine with the help of potassium-wasting diuretics like loop or thiazide diuretic agents; removal from the blood via haemodialysis, although this is only done in severe renal insufficiency or when the patient is refractory to other methods; and, lastly, elimination via the gastrointestinal tract by using potassium binders.[12,105] In patients with hyperkalaemia and concomitant metabolic acidosis, often seen in CKD, sodium bicarbonate is effective in lowering potassium levels.[106] The management approach for acute hyperkalaemia is summarised in *Table 1*.

Table 1: Acute Management of Hyperkalaemia

Effect	Management
Cardiac membrane stabilisation	• Calcium gluconate (if severe hyperkalaemia or ECG changes are present)
Lowering serum potassium	• Insulin (combined with glucose) • β-2 adrenergic agonists • Sodium bicarbonate (if concomitant metabolic acidosis)
Elimination of potassium from the body	• Potassium-wasting diuretics (thiazides or loop) • Potassium binders • Haemodialysis (only in refractory/severe cases)

Chronic Management

A holistic approach is required for maintenance therapy of hyperkalaemia by optimising diet, hyperkalaemia-causing medications (like RAASi) and potassium-lowering interventions (such as diuretics and potassium binders). A detailed history of diet (including supplements and salt substitutes) and medications should be performed, particularly ruling out those implicated in hyperkalaemia.[65] Restriction of dietary potassium to <2.4 g/day is recommended in patients with stage 3 (eGFR <60 ml/min/1.73 m^2) or higher CKD.[107] Patients on sodium restriction often use salt substitutes including potassium, predisposing them to hyperkalaemia. Dieticians should be involved in health and nutrition education for patients regarding avoidance of high-potassium foods – something often practised in nephrology but less so by cardiologists. Potassium supplements should be discontinued and drugs that may compromise renal function and increase potassium levels, such as NSAIDs, should also be stopped. When starting or re-starting RAASi and ARNi, initiation should be done with a low dose, which should then be titrated to the maximum tolerated evidence-based dose, allowing serum potassium up to 5.5 mmol/l. Current guidelines recommend starting hyperkalaemia patients on non-potassium-sparing diuretics or increasing the diuretic dose if already on one.[107–109] However, care should be taken to prevent or minimise potential volume depletion and subsequent stimulation of RAAS.[110]

Guidelines recommend criteria for dose reduction or discontinuation of RAASi and ARNi.[7,8] In general, it is advised to avoid cessation of RAASi or ARNi therapy when serum potassium levels range between 5.0 and 5.5 mmol/l, unless patient adherence to follow-up is unreliable.[111] In such instances, clinicians may opt to reduce dosage, aiming to stay above 50% of the recommended guideline dose if at all possible. Should a temporary interruption of RAASi or ARNi therapy be warranted, it is imperative to minimise the duration, swiftly reinstating treatment while monitoring

Table 2: Management Strategy for Dyskalaemia

Serum K^+ (mmol/l)	Management Strategy*
<3.5	• If ECG alterations: in-hospital admission • Stop thiazides (prefer loop diuretics if in volume overload) • Stop K^+ binders • Initiate MRA (↑ dose if already on MRA) • ↑ ACEi/ARB/ARNi dose to optimal targets • Monitor K^+ and Cr at 1 week, 1 month, 2 months and 3 months: until K^+ is in the normal range • Initiate K^+ supplement if still in hypokalaemia
3.5–3.9	• Stop thiazides (prefer loop diuretics if in volume overload) • Stop K^+ binders • Initiate MRA (↑ dose if already on MRA) • ↑ ACEi/ARB/ARNi dose to optimal targets • Monitor K^+ and Cr at 1 week, 1 month, 2 months and 3 months: until K^+ is in the normal range
4.0–5.0	• Normal target range • Initiate or maintain MRA and RAASi dose
5.1–5.5	• Individualise management based on patient risk and compliance/follow-up reliability • Can maintain ACEi/ARB, ARNi, MRA • Monitor K^+ and Cr closely • Stop K^+ supplements, NSAIDs and ↓ K^+ rich food† • If unreliable follow-up, consider K^+ binder initiation over decreasing RAASi therapy
5.6–6.0	• If ECG alterations: in-hospital admission • Assess for possible haemolysis and repeat sample, if needed • Initiate or ↑ dose of a diuretic • Stop K^+ supplements, NSAIDs and ↓ K^+ rich food† • If K^+ levels still high after 1 week ○ consider starting a K^+ binder while keeping RAASi to at least 50% of guideline-recommended therapy (do not stop RAASi) • Monitor K^+ and Cr at 1 week. Depending on K^+ trajectory and if back in normal range, monitor at least at 1, 2 and 3 months:

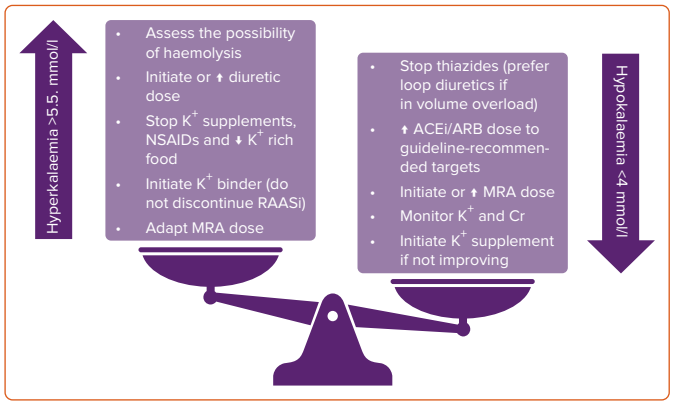
>6.0	• If ECG alterations: in-hospital admission
	• Assess for possible haemolysis and repeat sample, if needed
	• Initiate or ↑ dose of a diuretic
	• Stop K^+ supplements, NSAIDs and ↓ K^+ rich food†
	• Initiate K^+ binder
	• Discontinue or dose reduce MRA/ACEi/ARB/ARNi
	• If K^+ levels still high after 1 week:
	  ○ Maintain or initiate (if not already on) K^+ binder
	  ○ ↓ MRA/ACEi/ARB/ARNi dose further or discontinue
	• If K^+ levels normal at 1 week, reintroduce or dose-escalate MRA/ACEi/ARB/ARNi while co-administering K^+ binder therapy.
	• Monitor K^+ and Cr at 1 week, 1 month, 2 months and 3 months: until K^+ is in the normal range. Once K^+ levels in normal range, reintroduce or dose-escalate MRA/ACEi/ARB/ARNi while co-administering K^+-binder therapy.

**Providing stable renal function with eGFR >30 ml/min/1.73 m2 and stable blood pressure and systolic blood pressure >100 mmHg. †Examples of K^+ rich foods include (but are not limited to) beef; processed foods such as meats, sauces and juices; legumes and lentils; certain fruits such as bananas, avocados and dates; and cow's-milk based dairy products. ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNi = angiotensin receptor–neprilysin inhibitor; Cr = creatinine; eGFR = estimated glomerular filtration rate; MRA = mineralocorticoid receptor antagonist; NSAID = non-steroidal anti-inflammatory drug; RAASi = renin–angiotensin–aldosterone inhibitor.*

serum potassium levels.[7,8] Employing potassium binders may facilitate the continuation of RAASi therapy. If serum potassium levels range between 5.5 and 6.0 mmol/l, it is advisable to halve the dosage of MRAs, ACEis/ARBs or ARNis and reassess serum potassium levels within 5–7 days until normalisation occurs. Prolonged discontinuation of MRAs, ACEis/ARBs or ARNis due to persistently elevated serum potassium levels is discouraged, necessitating careful consideration of potassium binder usage to sustain RAASi therapy.[12] Management of dyskalaemia based on the patient's serum potassium can be found in *Table 2* and *Figure 2*.

Along with management, serum potassium monitoring guidelines should be adhered to. As per guidelines for ACEi/ARB/ARNi use, it is recommended that blood chemistry values, including serum creatinine and serum potassium, are measured 1–2 weeks after starting, 1–2 weeks after dose titration and subsequently after every 4 months.[7,27] For MRAs, monitoring of potassium and renal function should be performed according to clinical status, generally after 1 week, then 4 weeks, then every 6 months after MRA initiation or dose escalation, with more frequent testing in clinically unstable patients.[7] After an episode of hyperkalaemia, blood chemistry (including serum creatinine and serum potassium) should be monitored frequently and serially until potassium and creatinine have plateaued. However, the rates of appropriate monitoring are low in clinical practice and an increase in potassium level often leads to dose reduction or permanent discontinuation of RAASi.[25,112,113] Enhanced monitoring strategies, incorporating innovative approaches such as self-monitoring devices or point-of-care assessments, coupled with comprehensive disease management programs that involve specialised HF nursing support for patient education and follow-up (either in-person or via telecommunication), hold promise for optimising the safe usage of RAASi and warrant further exploration.[114]

Figure 2: Management of Dyskalaemia



ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; Cr = creatinine; MRA = mineralocorticoid receptor antagonist; NSAID = non-steroidal anti-inflammatory drug; RAASi = renin–angiotensin–aldosterone inhibitor.

Potassium Binders

The recent availability of gastrointestinal potassium-binding resins with a strong safety profile has opened new avenues for chronic management of hyperkalaemia and may allow RAASi therapy optimisation, possibly decreasing the need for dose reduction or discontinuation.[115–118]

Sodium polystyrene sulfonate (SPS) and calcium polystyrene sulfonate represent widely available cation exchange resins used for potassium removal through the gastrointestinal tract. Despite their longstanding presence, neither SPS nor calcium polystyrene sulfonate have undergone adequately powered randomised trials to evaluate their safety, tolerability and efficacy over the long term.[119–121] In the short term, these agents are poorly tolerated, with unstable onset of action and inconsistent, unpredictable lowering of potassium levels.[122,123] They are also associated with potentially severe gastrointestinal complications, including colonic necrosis, although absolute rates may be low with potential confounding present.[124–126] In addition, SPS usage may be limited due to sodium exchange causing volume expansion, which may worsen oedema.[127]

Two new agents, patiromer (patiromer sorbitex calcium/RLY5016; Veltassa; Relypsa) and SZC (ZS-9; AstraZeneca), also act to remove potassium by exchanging cations (calcium for patiromer, and sodium and hydrogen for SZC) for potassium in the gastrointestinal tract, thus increasing its faecal excretion.[122,128] Patiromer and SZC have been approved by the Food and Drug Administration (FDA) and the European Medicines Agency for the treatment of hyperkalaemia in patients receiving RAASi therapy. The use of these potassium binders may facilitate the preservation of RAASi use and guideline-recommended dosing in patients who would have their RAASi dose lowered or discontinued after hyperkalaemia development.[129–131] Below, we will discuss current evidence from clinical trials for patiromer and SZC. A summary of the clinical trials on these two potassium binders can be found in *Table 3*.

Patiromer

Patiromer is a non-absorbed polymer recently approved by the FDA to treat hyperkalaemia by binding to potassium in the gastrointestinal tract.[131] Patiromer predominantly uses calcium as the exchange cation instead of sodium seen in SZC, although magnesium and sodium cations are also used.[132] Patiromer is administered as a once-daily dose and, according to results from TOURMALINE study, has equal efficacy whether taken with or without food.[133] In the gastrointestinal tract, this resin exchanges its monovalent (sodium) and divalent (calcium, magnesium) cations and binds to potassium. Potassium binding occurs predominantly in the colon, where potassium concentration is the highest.[134] The colonic hypokalaemia stimulates more potassium secretion into the gastrointestinal tract, effectively removing it from the body through faeces.[135,136]

OPAL-HK included 237 CKD patients with potassium levels of 5.1 to 6.4 mmol/l, who were receiving RAASi therapy.[118] There were two phases: a 4-week phase in which patients received 4.2 or 8.4 g of patiromer twice-daily, followed by an 8-week randomised withdrawal phase, in which patients were randomly assigned to either the treatment arm, which continued the initial dose, or were switched to placebo. In phase 1, 76% of patients achieved normokalaemia. During the withdrawal phase, only 15% of patients developed hyperkalaemia, compared with 60% in the control group. At the end of phase 2, 100% of HF patients in the treatment group were on RAASi. A substudy of the OPAL-HK trial studied patiromer efficacy in HF patients.[137] Of the 102 HF patients in the first 4 weeks, 76% achieved normokalaemia; 8% of patients in treatment arm, compared with 52% of patients in the placebo arm, developed hyperkalaemia in phase 2. The OPAL-HK study also reported lower plasma aldosterone levels and reduction in the urine aldosterone-to-creatinine ratio at 4 and 8 weeks of patiromer use.[138]

The AMETHYST-DN study was an open-label, multicentre, open-label, randomised trial with a total of 306 patients with diabetes with CKD (eGFR 15 to <60 ml/min/1.73 m^2), and hyperkalaemia (>5.0 mmol/l), all of whom received RAASi throughout the study.[139] Both mild and moderate hyperkalaemia patients experienced decrease in baseline potassium levels at 4 weeks and up until 52 weeks with patiromer treatment. Hence, in both OPAL-HK and the AMETHYST-DN trials, patients were able to maintain RAASi therapy, regardless of hyperkalaemia. This was also demonstrated in the AMBER trial of 295 patients, in which more patients with CKD and resistant hypertension were able to continue spironolactone in the patiromer group compared with the control group (86% versus 66%; p<0.0001).[130] The PEARL-HF trial studied the effect of patiromer in a chronic HF patient population with either CKD (eGFR <60 ml/min) or a history of RAASi discontinuation due to hyperkalaemia.[131] A total of 155 patients were administered 25 mg/day of spironolactone and were randomised to double-blind treatment with patiromer 30 g/day or placebo for 4 weeks. At 4 weeks, the patiromer treatment group had a lower incidence of hyperkalaemia (7.3% versus 24.5%, respectively; p=0.015), with a larger percentage of patients on increased spironolactone dose of 50 mg/day (91% versus 74%, respectively; p=0.019).

Recently, results from the DIAMOND trial have provided the most robust evidence to date for patiromer benefits in managing hyperkalaemia in HF patients on RAASi.[140] This multinational, multicentre, randomised, double-blind phase 3b trial was the largest and longest study assessing potassium binders, studying 878 HF patients, with a median follow-up of 27 weeks. This study showed an adjusted mean change in potassium of +0.03 mmol/l in the patiromer arm, compared with +0.13 mmol/l in the placebo arm, giving an adjusted mean difference of −0.10 mmol/l (95% CI; −0.13, −0.07; p<0.001) between patiromer and placebo. Patients receiving patiromer also had decreased hyperkalaemia incidence and risk, lower MRA dose reduction and higher RAASi use.

The incidence of any adverse events was similar in the patiromer versus the placebo group of the DIAMOND trial (72.9% versus 74.0%). The most common adverse effect was hypokalaemia (15.0% for patiromer versus 10.7% for placebo), followed by hypomagnesaemia (4.3% patiromer versus 5.0% placebo) and gastrointestinal disturbances; diarrhoea (4.3%

Table 3: Clinical Trials with Potassium Binders

Trial	K+ Binder	Design	Patient Population	Intervention	Primary Endpoints	Efficacy Results
PEARL-HF[131]	Patiromer	RCT Double-blind Phase II	105 HF patients with a history of hyperkalaemia or CKD on spironolactone	Patients randomised to 3 g/day of patiromer versus placebo for 4 weeks	Change in median K^+ levels at 4 weeks	Patiromer group achieved normokalaemia in 24% (12 of 49 patients) versus 7% (4 of 55 patients) in placebo (p=0.015). 91% in the patiromer group were able to reach the target dosage of spironolactone (50 mg/day at 4 weeks, increased from 25 mg/day). More patients in the patiromer group were able to have spironolactone dose uptitration versus the placebo group (91 versus 74%; p=0.019).
HARMONIZE[117]	SZC	RCT Double-blind Phase III	258 patients with hyperkalaemia	All patients were treated with three-times-daily 10 g SZC for 48 h. Patients with normokalaemia at 48 h were randomly assigned to receive once-daily 5, 10, or 15 g of SZC or placebo for 28 days	K^+ levels through 8–29 days in each group	In the 48-h phase 1, mean K^+ levels decreased from 5.6 to 4.5 mmol/l; 84% achieved normokalaemia by 24 h and 98% by 48 h. In the randomised phase 2, K^+ level declined though days 8–29 with all SZC doses versus placebo (4.8, 4.5 and 4.4 mmol/l for 5, 10 and 15 g, respectively; 5.1 mmol/l for placebo. The proportion of patients with mean K^+ <5.1 mmol/l was higher in all SZC groups versus placebo (80, 90 and 94% for the 5-, 10- and 15-g groups, respectively, versus 46% with placebo.
HARMONIZE (HF subgroup)[116]	SZC	RCT Double-blind Phase III	94 patients with hyperkalaemia; 60 on RAASi	All patients were treated with three-times-daily 10 g SZC for 48 h. Patients with normokalaemia at 48 h were randomly assigned to receive once-daily 5, 10, or 15 g of SZC or placebo for 28 days	K^+ levels through 8–29 days in each group	48-h phase 1: 87 (93%) achieved normokalaemia. In the randomised phase 2, despite constant RAASi doses, K^+ level declined through days 8–29 with all SZC doses versus placebo (4.7, 4.5 and 4.4 mmol/l for 5, 10 and 15 g, respectively; 5.2 mmol/l for placebo. The proportion of patients with mean K^+ <5.1 mmol/l was higher in all SZC groups versus placebo (83, 89 and 92% for the 5-, 10- and 15-g dose groups, respectively, versus 40% with placebo.
OPAL-HK[118]	Patiromer	RCT Single-blind Phase III	237 CKD patients on RAASi with hyperkalaemia (K^+ 5.1–6.5 mmol/l)	Phase I: 4-week initial treatment with 4.2 or 8.4 g patiromer twice daily Phase II: 8-week randomised withdrawal phase. Patients who had achieved normokalaemia in phase I received patiromer or placebo	Phase I: mean change in the serum K^+ level from baseline to week 4 Phase II: Between-group difference in the median change in the serum K^+ level after 4 weeks	Phase I: mean (± SE) change in the serum K^+ level was −1.01 ± 0.03 mmol/l (p<0.001). 76% of patients reached normokalaemia. Phase II: Hyperkalaemia (K^+ ≥5.5 mmol/l) recurrence occurred in 60% of the patients in the placebo group compared with 15% in the patiromer group through week 8 (p<0.001). At the end of phase II, 55% of HF patients placebo-group patients and 100% of treatment-group patients were receiving RAASi.
OPAL-HK (HF + CKD subgroup)[137]	Patiromer	RCT Single-blind Phase III	102 CKD patients with comorbid HF	Phase I: 4-week initial treatment with 4.2 or 8.4 g patiromer twice daily Phase II: 8-week randomised withdrawal phase. Patients who had achieved normokalaemia in phase I received patiromer or placebo	Phase I: mean change in the serum K^+ level from baseline to week 4 Phase II: Between-group difference in the median change in the serum K^+ level after 4 weeks	Phase I: mean change in serum K^+ from baseline was −1.06 ± 0.05 mmol/l (p<0.001). Phase II: 52% of patients in the placebo group had a recurrence of hyperkalaemia (K^+ >5.5 mmol/l) versus 8% in the treatment group (p<0.001). At the end of 8 weeks, 55% of HF patients on placebo and 100% of patiromer group patients were receiving RAASi.

Table 3: Cont.

Trial	K+ Binder	Design	Patient Population	Intervention	Primary Endpoints	Efficacy Results
AMETHYST-DN[139]	Patiromer	RCT Open-label Phase II	306 diabetic patients with comorbid CKD on RAASi with hyperkalaemia	Patients were stratified into mild or moderate hyperkalaemia groups and received one of three randomised starting doses of patiromer: Mild hyperkalaemia: 4.2, 8.4 or 12.6 g twice daily. Moderate hyperkalaemia: 8.4, 12.6, or 16.8 g twice daily. Patiromer was titrated to achieve and maintain serum K^+ ≤5.0 mmol/l.	Change in median K^+ levels at 4 weeks or prior to dose titration.	Mild hyperkalaemia group: K^+ reduction from baseline at 4 weeks was 0.35 mmol/l (95% CI [0.22–0.48]), 0.51 (95% CI [0.38–0.64]) and 0.55 (95% CI [0.42–0.68]) mmol/l for the 4.2, 8.4 and 12.6 g twice-daily starting-dosage group respectively. Moderate hyperkalaemia group: K^+ reduction at 4 weeks was 0.87 (95% CI [0.60–1.14]), 0.97 (95% CI [0.70–1.23]) and 0.92 (95% CI [0.67–1.17]) mmol/l for the 8.4, 12.6 and 16.8 g twice-daily starting-dosage groups respectively ($p<0.001$ for all groups). This effect was maintained through week 52.
SCZ Trial[143]	SZC	RCT Double-blind Phase II	90 patients with K^+ 5.0–6.5 mmol/l	Patients were randomly assigned to three-times-daily: SZC treatment with 0.3 (n=12), 3.0 (n=24) or 10 g (n=24) or placebo (n=30) for 48 h.	Potassium levels through 48 h	Mean baseline serum K^+ was 5.1 mmol/l. Serum K^+ was significantly decreased by 0.92 ± 0.52 mmol/l at 38 h. Urinary potassium excretion significantly decreased with 10-g SZC compared with placebo at day 2 (+15.8 ± 21.8 mmol/l/24 h versus +8.9 ± 22.9 mmol/l/24 h).
ZS-003[142]	SZC	RCT Double-blind Phase III	753 patients with K^+ 5.0–6.5 mmol/l. 300 patients had history of HF	Patients were randomly assigned to three-times-daily: 1. SZC treatment with 1.25, 2.5, 5.0 or 10 g or 2. placebo for 48 h Patients with normokalaemia at 48 h were randomly assigned to once-daily SZC or placebo on days 3–14.	Potassium levels through 48 h	Reduction of 0.46, 0.54 and 0.73 mmol/l in the 2.5-, 5- and 10-g groups, respectively and 0.25 mmol/l with placebo. At 48 h, 99% of patients treated with 10 g and 94% with 5 g achieved normokalaemia. In the maintenance phase, the patients who received 5 and 10 g SZC, serum K^+ levels remained in the normal range (4.76 and 4.58 mmol/l), respectively, compared with >5.10 mmol/l in the placebo group ($p<0.01$)
AMBER[130]	Patiromer	RCT Double-blind Phase II	295 patients with CKD, uncontrolled hypertension and on spironolactone	Patients were randomly assigned to spironolactone in addition to double-blind treatment with either placebo (n=148) or patiromer (n=147)	Between-group difference at week 12 in the proportion of patients still on spironolactone	At week 12, 66% patients in the placebo group and 86% patients in the patiromer group remained on spironolactone (between-group difference 19.5; 95% CI [10.0–29.0]; $p<0.0001$).
DIAMOND[140]	Patiromer	RCT Double-blind Phase III	878 patients with HF and history of RAASi-related hyperkalaemia on RAASi therapy (including MRA)	Patients were randomly assigned to patiromer or placebo	Between-group difference in the adjusted mean change in serum K^+	The adjusted mean change in potassium was +0.03 mmol/l in the treatment group and +0.13 mmol/l in the placebo group. Between-group difference −0.10 mmol/l (95% CI [−0.13, −0.07]); $p<0.001$]. In the patiromer arm, there was a lower risk of hyperkalaemia >5.5 mmol/l (HR 0.63; 95% CI [0.45–0.87]; p=0.006), MRA dose reduction (HR 0.62; 95% CI [0.45–0.87]; p=0.006), and total adjusted hyperkalaemia events per 100 person-years (77.7 versus 118.2; HR 0.66; 95% CI [0.53–0.81]; $p<0.001$).

CKD = chronic kidney disease; HF = heart failure; K^+ = potassium; MRA = mineralocorticoid receptor antagonist; RAASi = renin–angiotensin–aldosterone inhibitor; RCT = randomised controlled trial; SZC = sodium zirconium cyclosilicate.

versus 3.4%), constipation (2.5% versus 1.1%) and nausea (0.9% in both). These are similar to the findings seen with the OPAL-HK trial, where the withdrawal phase showed constipation, diarrhoea and nausea (4% each) with patiromer, whereas these events occurred in none of the patients receiving placebo. In the PEARL-HF trial, the most common adverse events were gastrointestinal complaints (12%, n=21: flatulence, diarrhoea, constipation or vomiting), hypokalaemia (6% for patiromer versus 0% for placebo) and hypomagnesaemia (24% versus 2.1%). Although hypomagnesaemia is reported in clinical trials, usually, no significant neuromuscular or cardiac abnormalities are noted with treatment.[105]

Drug–drug interactions of patiromer have been thoroughly discussed in a previous review.[105] In summary, some drugs have shown binding to patiromer in *in vitro* studies, including 30–50% binding to clopidogrel, furosemide, metformin, warfarin, metoprolol, verapamil and lithium and >50% binding to amlodipine, cinacalcet, ciprofloxacin, levothyroxine, quinidine, thiamine and trimethoprim. However, a phase I study in healthy volunteers did not show reduced absorption. Based on *in vitro* studies, taking patiromer within 6 hours of administration of any of these medications is not recommended.[105]

Sodium Zirconium Cyclosilicate

SZC is an inorganic, insoluble, orally administered potassium-binder, with a structure that mimics potassium ion channels in the body and selectively captures potassium ions as it passes through the gastrointestinal tract after once-daily administration.[141] The ZS-003 study demonstrated the effect of SZC over 14 days, including at the 48-hours acute by studying 753 patients with hyperkalaemia.[142] Various doses were administered and potassium levels were measured at 48 hours, showing dose-related reduction in potassium levels. Approximately 90 to 100% of patients achieved normokalaemia. Another similar short-term phase II study of 90 patients used lower doses of SZC and demonstrated significant reductions in potassium concentration.[143] The HARMONIZE trial enrolled 258 ambulatory patients with hyperkalaemia.[117] In the initial phase (first 48 hours), all patients received 10 g of SZC three times a day, which resulted in normokalaemia in 98% of patients at 48 hours. In the next maintenance phase, patients who achieved normokalaemia were randomised to receive three different doses of SZC or placebo for 28 days. The results showed maintenance of normokalaemia with each once-daily dose of SZC at 5, 10 and 15 g, with serum potassium levels of 4.8, 4.5 and 4.4 mmol/l, respectively, versus placebo (5.1 mmol/l). It was also demonstrated that patients with higher baseline potassium concentration experienced greater absolute reductions. A subgroup analysis of the HARMONIZE trial including only patients with HF (n=94) showed that SZC helped achieve and maintain normokalaemia, regardless of RAASi use.[116] A recent single-arm study assessing the efficacy of SZC in long-term treatment and maintenance therapy of hyperkalaemia in 751 CKD patients demonstrated that SZC corrects hyperkalaemia and maintains normokalaemia in outpatients, regardless of CKD stage.[144] The PRIORITIZE-HF trial was designed to assess RAASi optimisation in HF patients using SZC. However, it was terminated early because of the COVID-19 pandemic.[145]

SZC appears to be safe and tolerable. In the ZS-003 trial, the rates of adverse events were similar between the SZC (12.9%) and placebo groups (10.8%), with diarrhoea being the most common complication. In the HARMONIZE trial, adverse events occurred in 53%, 29% and 44% of patients receiving SZC doses of 5, 10 and 15 g, respectively, compared with 32% in the placebo group. Oedema was most common in the 15-g group (14.3% compared with 2.4% in the placebo group). Gastrointestinal adverse effects were similar in both groups.

Based on the above discussion of both patiromer and SZC, it can be concluded that potassium binders can be used as needed to enable RAASi (including MRA) uptitration and persistence in patients susceptible to hyperkalaemia, allowing optimal HF management.[115]

Hypokalaemia

Incidence and Causes

Hypokalaemia, characterised by a serum potassium level ≤4.0 mmol/l, is linked with adverse clinical outcomes, with the associated risk varying by severity of hypokalaemia and whether correction is undertaken. Mild hypokalaemia (potassium levels ranging from 3.5 to 4.0 mmol/l) is commonly observed in HF patients, even in those receiving ACEis/ARBs and MRAs. While potassium levels <3.5 mmol/l are less frequently encountered, the incidence over a 1-year period may escalate up to 20%.[89,146] The principal aetiology for hypokalaemia in HF is diuretic use. Both diuresis-related intravascular volume depletion and independent neurohormonal activation lead to excessive aldosterone secretion, promoting sodium and water reabsorption and potassium excretion.[147] The primary risk associated with hypokalaemia is the potential development of life-threatening ventricular arrhythmias, particularly in patients with pre-existing structural cardiac anomalies, concurrent electrolyte imbalances (such as hypomagnesaemia), ischaemia and/or reduced ejection fraction (EF).[148,149]

Clinical Evidence

Observational studies suggest that hypokalaemia is associated with excess morbidity and mortality in HF, with risk starting at potassium <4.0 mmol/l, but sharply increasing at potassium <3.5 mmol/l, which, although rare, has consistently and independently been associated with poor outcomes.[150] Three large HF registries from Europe showed a twofold to threefold increase in death in HF patients with potassium <3.5 mmol/l compared with those within the normal range.[27,151,152] Moreover, this risk was nullified with the correction of hypokalaemia.[151] Findings from American registries also demonstrated an increased mortality risk with both intermittent (1.3-fold) and persistent (1.6-fold) hypokalaemia, and a 1.9-fold risk of death in patients with hypokalaemia during hospitalisation.[153,154] A study from the Swedish HF registry (n=5,848) showed similar results.[89] A more detailed study examining time-dependent outcomes of hypokalaemia in HF patients suggested that hypokalaemia is independently associated with increased mortality both in the short and long term.[150] Studies have shown that, even though the risk for ventricular arrhythmias is greater with a lower EF, hypokalaemia seemed to have similar outcomes in HF patients regardless of left ventricular EF.[89,151]

Secondary analyses of clinical trials also support such associations. Several trials on MRAs showed a higher risk of hypokalaemia and adverse events in the placebo group compared with the treatment group, and trials with ARNi showed a decreased incidence of hypokalaemia in the treatment group.[96,98,101,155,156] Evidence suggests that significant hypokalaemia (potassium <3.5 mmol/l) is infrequent but is independently linked with an increased incidence of adverse events. MRAs mitigate the risk of hypokalaemia, and their therapeutic efficacy may partly stem from their ability to reduce this risk. It may be questioned whether hypokalaemia directly causes harm or is a risk marker present in the critically ill population. Because hypokalaemia remains associated with mortality even after extensive adjustments and this risk diminishes upon correction of potassium levels, hypokalaemia likely plays a causative role rather than solely serving as a risk marker.[150] Given the established link between structural heart disease and the heightened risk of arrhythmias in the presence of hypokalaemia, it is imperative to prevent hypokalaemia in patients with HF.

Management

Although normal serum potassium levels fall in the range of 3.5–5.0 mmol/l, attaining potassium concentration >4.0 mmol/l is the ideal therapeutic goal.[157] Because diuretics are the most common cause of hypokalaemia, lowering their dose is the first approach. Hypokalaemia risk has been demonstrated to be higher with thiazides compared with loop diuretics, and hypokalaemia seen with loop diuretics is independent of dose or treatment duration.[158,159] Given that most HF patients are on

RAASis, another effective strategy is dose escalation of ACEis or ARBs or the addition of an MRA if not already prescribed. Dietary modifications, including a potassium-rich diet or potassium supplements may be considered in select patients, although care must be taken to not overshoot the potassium levels in these populations already predisposed to hyperkalaemia due to RAASi use. Hence, exogenous potassium replacement should only be prescribed after ACEi/ARB uptitration and MRA initiation.[160] Management of dyskalaemia based on the patient's serum potassium can be found in *Table 2* and *Figure 2*.

When potassium is <3.5 mmol/l and MRA has been initiated, frequent monitoring of potassium concentration and renal function (with serum creatinine) is prudent. In the chronic setting, this can be done at 1 week, 1 month, 2 months and 3 months after the detection of hypokalaemia, until potassium falls within the reference range.[112]. However, if there are acutely low potassium levels (<3.0 mmol/l) or ECG changes are present, hospitalisation and frequent measurements along with telemetry are recommended. This is also the case in patients being managed with acute decompensation of HF, where multiple administrations of high-dose diuretics may increase the risk of arrhythmias in patients with HFrEF. For such patients, multiple measurements over a 24-hour period are important because of the increased risk of mortality.[86]

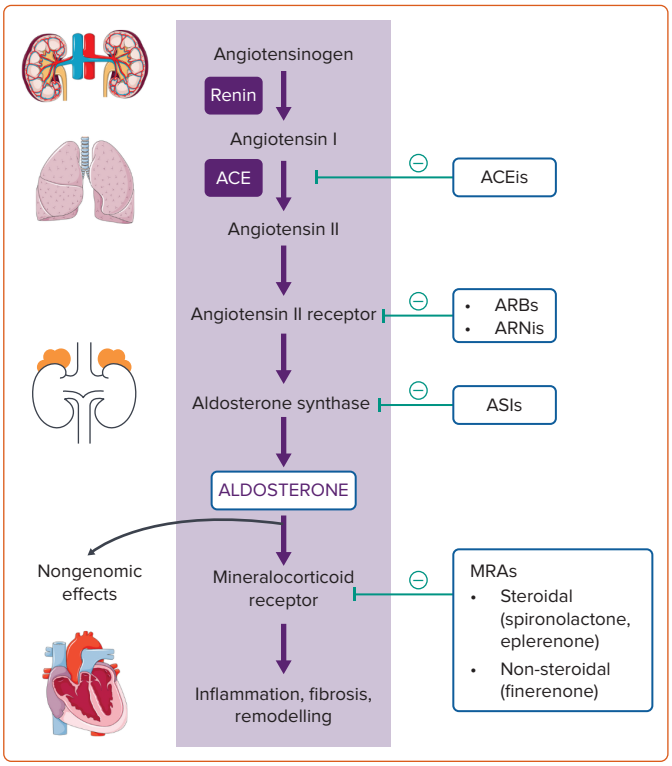
Aldosterone-modulating Therapies

Given the established role of aldosterone in the pathogenesis of HF, mitigating its effects in this patient population has become one of the primary goals of HF management.[45,49,50] Several drug classes targeting different steps in the normal physiology of aldosterone synthesis and action have been developed and are illustrated in *Figure 3*.

ACEi and ARBs are the mainstays of guideline-recommended therapy in HF and have been shown to decrease mortality and improve outcomes in HF and its comorbidities, such as CKD and diabetes.[7] ARNi use has also been subsequently shown to improve outcomes both in HF, incremental to ACEi/ARB, particularly among patients with EFs below normal.[98,101] All three drugs work upstream to inhibit aldosterone production by targeting the action of its primary regulator, angiotensin II. However, as discussed above, their use is at times limited because of hyperkalaemia and only one of these three drug classes is usually prescribed at a time due to limited benefit and higher hyperkalaemia risk. Moreover, these patients may experience a rise in aldosterone levels after initial decrease during long-term RAASi use, a phenomenon referred to as aldosterone escape.[161,162]

MRA have the most direct effect in inhibiting the pathological effects of aldosterone. Since the landmark results of RALES trial, which demonstrated substantial mortality benefit with spironolactone in HFrEF patients, MRAs have been used to improve outcomes in HF.[156] Steroidal MRAs, derived from progesterone, include first-generation spironolactone and second-generation eplerenone. Spironolactone also demonstrated modest benefit in HF with preserved EF in the TOPCAT trial.[163] Eplerenone, with a better adverse effect profile, has also demonstrated benefit in both HFrEF in EPHESUS and EMPHASIS trials.[164,165] Non-steroidal MRAs are an emerging class of therapeutic agents that are discussed in the next section. It is important to note that, although promising, MRA use remains suboptimal. Steroidal MRAs, especially spironolactone, have multiple potential off-target adverse effects (gynaecomastia, impotence). Use of both steroidal MRAs is often limited by hyperkalaemia or fear of hyperkalaemia, although importantly, there is evidence suggesting a lower risk of hyperkalaemia with non-steroidal MRAs.[166] Moreover, the non-genomic effects of aldosterone remain unaddressed by MRAs.

Figure 3: Aldosterone-modulating Therapies



Several drug classes have been developed to inhibit aldosterone at different steps in its physiology. Renin, produced by the juxtaglomerular cells in the kidney, converts angiotensinogen to angiotensin I, which is converted to angiotensin II by ACE in the pulmonary vasculature. Angiotensin II binds to its receptor in the adrenal cortical cells, increasing aldosterone synthase activity to induce aldosterone production and secretion. Aldosterone binds to intracytoplasmic MRs (genomic) and also exerts MR-independent (non-genomic) effects, which result in cardiac inflammation, fibrosis and remodelling. ACEi block the synthesis of angiotensin II. ARBs and ARNis directly block angiotensin II receptors. Steroidal and non-steroidal MRAs block MR at the final step, but do not mitigate non-genomic effects. Newer class drugs such as ASI may be able to inhibit both genomic and non-genomic effects by inhibiting aldosterone synthesis.
ACE = angiotensin-converting enzyme; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNi = angiotensin receptor–neprilysin inhibitor; ASI = aldosterone synthase inhibitor; MR = mineralocorticoid receptor; MRA = mineralocorticoid receptor antagonist.
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ASIs are a novel class of drugs that may address these concerns by potentially decreasing both genomic and non-genomic effects of aldosterone. Although there has been difficulty in developing a drug with high specificity for aldosterone synthase over other CYP enzymes, there is promise in the preliminary trials conducted so far, including phase II trials for osilodrostat, baxdrostat, lorundrostat, BI 690517 and DP13, which have demonstrated low hyperkalaemia risk and improved blood pressures in hypertension patients.[11]

Non-steroidal Mineralocorticoid Receptor Antagonists

The promising results from RALES and EPHESUS trials, along with the limitations presented by higher incidence of hyperkalaemia and off-target adverse effects prompted extensive research for the development of potent and selective non-steroidal MRAs with a more favourable benefit–risk profile. High-throughput screening techniques led to the discovery of novel non-steroidal MRAs.[167] Several non-steroidal MRAs have been developed since then, such as esaxerenone, finerenone and ocedurenone (KBP-5074).[168,169] Among these, finerenone has shown the most promise in improving cardiorenal outcomes in high-risk groups, such as type 2 diabetes (T2D) and CKD.[170]

There are key differences present between traditional steroidal MRA and non-steroidal MRAs, such as finerenone. Molecular studies demonstrate

higher selectivity and potency of finerenone than spironolactone or eplerenone, with greater inhibition of cofactor recruitment in the MR signalling pathway.[167,171] Moreover, animal studies show greater inhibition of cardiac and renal inflammation, fibrosis and structural remodelling with finerenone compared with steroidal MRAs.[172,173]

Large phase III clinical trials studying finerenone have further provided evidence regarding the promising clinical implications of finerenone. The FIDELIO-DKD and Figaro-DKD trials showed substantial improvement in cardiovascular and renal endpoints in patients with CKD and T2D.[10,174] These findings resulted in the addition of finerenone in the European guidelines as class 1 for the prevention of HF hospitalisation in patients with CKD and T2D.[175] Very recently, results from the FINEARTS-HF trial found that, in HF patients with mildly reduced or preserved EF, finerenone resulted in a significant reduction in the composite of total worsening HF events and death from cardiovascular causes compared with placebo.[176] Regarding potassium balance, the finerenone group had double the incidence of hyperkalaemia compared with placebo, although there was a more comparable and lower risk of hospitalisation due to hyperkalaemia in the finerenone group versus placebo and there were no deaths due to hyperkalaemia.[176] Moreover, finerenone decreased the risk of hypokalaemia compared with placebo. Earlier studies have demonstrated lower risk of hyperkalaemia with non-steroidal MRAs compared with steroidal MRAs in animal models.[166] More head-to-head comparison studies are needed to contrast the effects of non-steroidal versus steroidal MRAs on serum potassium levels.

Future Direction and Gaps in Evidence

There needs to be a better assessment of specific dietary interventions to optimise potassium levels in HF patients. Investigations can be done to establish proper guidelines regarding potassium supplementation, potassium-rich food intake or avoidance (depending on the dyskalaemia), and – with the upcoming use of potassium binders – how to integrate dietary recommendations. Point-of-care remote monitoring and artificial intelligence technology need to be investigated to potentially provide accurate, non-invasive measures of the potassium status of HF patients. Artificial intelligence models using ECG for screening and diagnosis of various cardiovascular diseases are increasingly gaining recognition.[177] Current literature regarding deep learning modalities for assessing potassium abnormalities shows promise, although large, randomised clinical trials are needed before integration can be made into current guidelines.[178,179]

Implementation of findings from the DIAMOND trial are needed, where potassium binders can be used to offset the hyperkalaemia risk and enable long-term treatment with RAASi and MRAs. Although evidence has supported approach, there is a need for improvement in widespread clinical practice. Moreover, there needs to be an evaluation of whether addition of patiromer (in conjunction with MRAs) to pre-existing guideline-recommended HF management can improve HF outcomes, such as cardiovascular death and hospitalisations.

With increased use of potassium binders, there is a need to investigate the consequence of abrupt discontinuation or noncompliance, which may lead to rebound hyperkalaemia, especially in patients uptitrated to RAASi therapy. The PLATINUM trial is a phase IV, multicentre, randomised double-blind trial that will assess the use of patiromer for acute hyperkalaemia management in the emergency department (NCT04443608).[180]

Several new ASI trials are under way, such as the phase II FigHTN-CKD trial for baxdrostat (NCT05432167) and a phase III trial assessing baxdrostat with dapagliflozin for CKD patients with hypertension (NCT06268873); the phase III Launch-HTN trial (NCT06153693) evaluating the safety and efficacy of lorundrostat in patients with uncontrolled or resistant hypertension; a phase III clinical program, EASi-KIDNEY, (NCT06531824) to evaluate the safety and efficacy of BI 690517 (an empagliflozin plus ASI compound) in CKD; and a phase II trial of DP13 is ongoing in 36 patients with primary aldosteronism (NCT04007406).[11] These trials will bring new insight into the potential of these drugs to inhibit aldosterone pathogenetic pathways and open avenues for possible exploration in HF patients.

Conclusion

Aldosterone is a key hormone that drives the pathophysiology behind HF. Many drugs in current and potential future HF management strategies target this adrenal steroid hormone to mitigate its adverse effects on the heart, kidney and vasculature. However, their use is sometimes limited by potassium disturbances. Dyskalaemia is a common complication in HF patients and, if not corrected, can be life-threatening. Hyperkalaemia can be harmful in the acute setting because of its effects on the cardiac membrane potential and increasing arrhythmia risk. However, more of a concern might be the impact of hyperkalaemia leading to the decrease or discontinuation of RAASi therapy, which has a well-established mortality benefit. In contrast, hypokalaemia, although often overlooked, seems to play an independent role in adverse outcomes in HF patients. This is why it is imperative to maintain potassium concentration between 4.0 and 5.0 mmol/l. Novel potassium binders such as patiromer may play an important role in optimising potassium levels without compromising on life-saving medications. Non-steroidal MRAs and ASIs are novel drugs targeting aldosterone and may prove beneficial in HF management. ❑

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