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Abnormalities of Potassium in Heart Failure: Clinical Relevance and Management Strategies in the Chronic Setting

João Pedro Ferreira, MD, PhD¹; Javed Butler, MD, MPH, MBA²; Patrick Rossignol, MD, PhD¹; Bertram Pitt, MD³; Stefan D. Anker, MD, PhD⁴; Mikhail Kosiborod, MD, PhD⁵; Lars H. Lund, MD, PhD⁶; George L. Bakris, MD⁷; Matthew R. Weir, MD⁸; and Faiez Zannad, MD, PhD¹.

From ¹ Université de Lorraine INSERM, Centre, d'Investigations Cliniques Plurithématique 1433, INSERM U1116, CHRU de Nancy, F-CRIN INI-CRCT, Nancy, France; ² Department of Medicine, University of Mississippi, Jackson, USA; ³ Department of Internal Medicine, University of Michigan School of Medicine, Ann Arbor; ⁴ Department of Cardiology (CVK); and Berlin Institute of Health Center for Regenerative Therapies (BCRT); German Centre for Cardiovascular Research (DZHK) partner site Berlin; Charité Universitätsmedizin Berlin, Germany; ⁵ Saint Luke's Mid America Heart Institute and University of Missouri-Kansas City, Kansas City, Missouri, USA; The George Institute for Global Health, and University of New South Wales, Sydney, Australia; ⁶ Department of Medicine Solna, Unit of Cardiology, Karolinska Institute, Heart and Vascular Theme, Karolinska University Hospital, Stockholm, Sweden; ⁷ Comprehensive Hypertension Center, The University of Chicago Medicine, Chicago, Illinois, USA; ⁸ Division of Nephrology, Department of Medicine, University of Maryland, Baltimore, Maryland, USA.

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Correspondence to:

João Pedro Ferreira, MD, PhD

Centre, d'Investigations Cliniques Plurithématique 1433, INSERM U1116, CHRU de Nancy

4 Rue du Morvan, 54500 Vandœuvre-Lès-Nancy

Tel : +33 (0) 3 83 15 73 15

Fax : +33 (0) 3 83 15 73 24

E-mail : j.ferreira@chru-nancy.fr

Twitter: @CHRU_de_Nancy

ABSTRACT

Potassium is the most abundant cation in humans and is essential for normal cellular function. Alterations in K⁺ regulation can lead to neuromuscular, gastrointestinal and cardiac abnormalities. Dyskalemia (i.e. hypokalemia and hyperkalemia) in heart failure is common because of HF itself, related comorbidities, and medications. Dyskalemia has important prognostic implications. Hypokalemia is associated with excess morbidity and mortality in HF. The lower the K⁺ levels the higher the risk, starting at K⁺ levels below approximately 4.0 mmol/L, with a steep risk increment with K⁺ levels below 3.5 mmol/L. Hyperkalemia (>5.5 mmol/L) has also been associated with increased risk of adverse events; however, this association is prone to reverse-causation bias as stopping RAASi therapy in the advent of hyperkalemia likely contributes the observed risk. In this state-of-the-art review, practical and easy-to-implement strategies to deal with both hypo- and hyperkalemia are provided as well as guidance for the use of potassium-binders.

Key-words: potassium; heart failure; hypokalemia; hyperkalemia.

CONDENSED ABSTRACT

Potassium is the most abundant cation in humans and alterations in K⁺ regulation may have life-threatening consequences. Dyskalemia (i.e. hypokalemia and hyperkalemia) in heart failure is common because of HF itself, related comorbidities, and medications. Dyskalemia has important prognostic implications. Hypokalemia is associated with excess morbidity and mortality in HF with an association that is likely causal. Hyperkalemia (>5.5 mmol/L) has also been associated with increased risk of adverse events; however, this association is prone to reverse-causation bias as stopping RAASi therapy in the advent of hyperkalemia likely contributes the observed risk.

Abbreviations

Potassium – K⁺

Heart Failure – HF

Chronic Kidney Disease – CKD

Diabetes -DM

MRA - mineralocorticoid receptor antagonists

ARB - angiotensin receptor blockers

INTRODUCTION

Potassium (K^+) is the most abundant cation in humans; 98% of K^+ is intracellular (≈ 140 mEq/L) and 2% is extracellular (≈ 3.8 - 5.0 mEq/L). Potassium is essential for normal cellular function and alterations in K^+ regulation can lead to neuromuscular, gastrointestinal or cardiac abnormalities (1). The K^+ content and distribution among the body compartments depend on a complex interplay of multiple factors including renal and gastrointestinal function, diet, medications and supplements, neuro-hormonal status, and acid base balance (2). Derangements in any of these may result in K^+ homeostasis disruption, leading to abnormal K^+ concentrations. Under normal conditions, the kidneys are responsible for up to 90–95% of K^+ elimination, with the colon being responsible for the remainder. In the setting of chronic renal impairment, colonic K^+ excretion may increase by 3-fold (3). Furthermore, the sodium-potassium-ATPase pump (stimulated by aldosterone, catecholamines, and insulin) preserves a high intracellular potassium concentration in the advent of an adverse concentration gradient. Resting transmembrane potential difference depends on intracellular and extracellular potassium concentrations. Hypokalemia increases cellular depolarization, automaticity and excitability(4). Because cardiac repolarization relies on potassium influx, hypokalemia lengthens the action potential and increases QT dispersion. Hyperkalemia leads to a shortening of the repolarization time which may lead to QT interval shortening (4). Both hypo- and hyperkalemia may be life threatening conditions by increasing the risk of ventricular arrhythmia and sudden cardiac death (5).

Dyskalemia (i.e. both hypokalemia and hyperkalemia) in heart failure (HF) is common because of HF itself and related comorbidities, and because of the medications used to treat HF and these comorbidities. Dyskalemia in HF has important prognostic implications (6, 7). Critical comorbidities include chronic kidney disease (CKD), diabetes (DM), frailty and aging. Relevant

drugs include loop and/or thiazide diuretics, mineralocorticoid receptor antagonists (MRAs), angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) or angiotensin-neprilysin inhibitors (ARNi), and beta-blockers(8, 9). All of these treatments may cause K⁺ alterations resulting in either hypokalemia or hyperkalemia; K⁺ changes can impact clinical outcomes directly and also by limiting the use of guideline-recommended medical therapy. Heart failure patients are often multi-morbid and poly-medicated, further complicating K⁺ concentrations and management.

In HF, as in other conditions, e.g. myocardial infarction, hypertension, kidney disease, or in the general population(10-14), the relationship between K⁺ concentrations and adverse outcomes appears to be U-shaped, where both low- and high K⁺ levels are associated with adverse outcomes(15-17), although it remains unclear to what extent dyskalemia is a risk factor itself vs. a risk marker representing the patients` overall clinical status, other comorbidities and/or use or non-use of HF medications. While moderate to severe hyperkalemia has been the focus of acute clinical care, observational data suggest that hypokalemia is, at least, as detrimental(10). These data have clinical and research implications; hypokalemia-associated risk in HF has not been the focus of as much research, and overall, the safe serum K⁺ zone is not well established.

While literature is emerging with epidemiology, pathophysiology, outcomes, and acute management of moderate to severe hyperkalemia, practical guidance on chronic management and guideline derived comorbidity optimization in a broader group of patients with dyskalemia is not well described. This document aims to provide such a review.

MEASURING CIRCULATING POTASSIUM LEVELS

Interpretation of circulating K^+ values and consequently, the assessment of dyskalemia risk, depends on the quality and nature of measurement. Blood levels of K^+ can be measured in the serum or plasma. Serum measurements require clotting before analysis whereas plasma levels can be measured immediately. K^+ is continuously released from cells during clotting; therefore, serum values are generally higher, by 0.1-0.4 mmol/L, and the difference is greater at higher absolute values (i.e. at low K^+ the difference is closer to 0.1 and at high K^+ the difference is closer to 0.4)(18). Therefore, hyperkalemia may be spurious as a result from hemolysis subsequent to erroneous blood sample handling and/or long waiting periods before the analysis is performed(19). This “pseudo-hyperkalemia” can be misleading and result in incorrect interpretation and patient management. Thus, it is important to confirm the diagnosis of hyperkalemia before instituting medical management, except in life threatening emergencies.

The literature regarding dyskalemia and CV disease discussed herein is limited by the fact that serum vs. plasma measurements are often not known or reported, or they are mixed together.

HYPOKALEMIA

Incidence and Causes

Hypokalemia, defined by a serum $K^+ \leq 4.0$ mmol/L, is associated with adverse events; although the associated risk may vary by the level of hypokalemia and by its correction or not. Mild hypokalemia ($K^+ 3.5-4.0$ mmol/L) occurs frequently in patients with HF, even in the context of ACEi/ARB and MRA treatment. Although, K^+ levels <3.5 mmol/L are found less frequently, the incidence over a 1-year period may reach 20%(20, 21). The most frequent cause of hypokalemia is the use of diuretics. Also, excessive neurohormonal activation or diuresis with intravascular volume depletion results in excessive aldosterone production, which induces sodium and water

reabsorption with concomitant K⁺ excretion (22). Hypokalemia-associated risks include potentially life-threatening ventricular arrhythmias, particularly in the context of preexisting structural cardiac abnormalities, associated electrolyte disturbances (such as hypomagnesemia), ischemic substrate and/or and reduced EF(23, 24).

Prognostic Implications

Observational Studies

Observational studies suggest that hypokalemia is associated with excess morbidity and mortality in HF. The lower the K⁺ levels the higher the risk, starting at K⁺ levels below approximately 4.0 mmol/L, but the risk increases steeply with K⁺ levels below 3.5 mmol/L. A K⁺ <3.5 mmol/L is infrequently observed (<5%) but has been consistent and independently associated with poor outcomes(25).

In a Danish study that included 19,549 HF patients, those with K⁺ levels below 3.5 mmol/L had a ≈3-fold higher risk of death compared to patients with K⁺ levels between 4.2 and 4.4 mmol/L(6). In a Spanish registry of 2,164 HF patients, those with K⁺ levels <3.5 mmol/L had a 2.4-fold increase of death compared to patients with K⁺ levels between 3.5-5.0 mmol/L; however, this associated risk was no longer present after hypokalemia correction(7). In a HF registry from the UK including 21,334 HF patients, any hypokalemia <3.5 mmol/L was associated with a ≈2-fold increased risk of death(26). In a study from Israel with 6,073 HF patients, patients with K⁺ <3.5 mmol/L had a 2.3-fold relative increase in death(27). In a cohort of 142,087 HF patients from the US Veterans Administration database(28), patients with intermittent and persistent hypokalemia had a 1.3 and 1.6-fold higher mortality risk, respectively. A study with 2,660,609 patients from the US National Inpatient Sample database, patients with hypokalemia based on ICD-9 codes during the hospital stay had a 1.9-fold increase in the risk of

death(29). A study from the Swedish HF registry with 5,848 patients showed similar results(21). A more detailed study examined the association between hypokalemia and time-dependent outcomes, and suggested that hypokalemia is independently associated with increased mortality both in the short and long term (25). The associations of K⁺ levels with the outcomes and the main patient features are detailed in **Table 1** and **Supplemental Table 1**.

The studies that report the associations by left ventricular ejection fraction suggest that the association of hypokalemia with outcomes is similar regardless of the LVEF(7, 21), even though the risk of ventricular arrhythmias is greater with lower EF.

Clinical Trials

Secondary analyses of clinical trials also support such associations. In TOPCAT (Spironolactone for Heart Failure with Preserved Ejection Fraction), hypokalemia (<3.5 mmol/L) was associated with a 1.6-fold increase in the relative risk of death(30). Spironolactone treatment reduced the risk of incident hypokalemia(30). In EMPHASIS-HF (Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms), patients with K⁺ levels <4.0 mmol/L at baseline had an increased risk of HF rehospitalization or cardiovascular death if taking placebo (HR [95%CI] =1.37 [1.05-1.79], p =0.02), but no such risk if taking eplerenone (HR [95%CI] =0.87 [0.62-1.23], p =0.44); p for interaction =0.04. A mediation analysis suggested that hypokalemia correction after one month explained 25% of the cardiovascular beneficial effect of eplerenone. Moreover, eplerenone reduced the rates of hypokalemia during the follow-up(31). In the RALES (Randomized Aldactone Evaluation Study), hypokalemia (<3.5 mmol/L) was also associated with increased risk of death. Patients taking spironolactone experienced 10% less hypokalemia episodes at the <3.5 mmol/L and 20% less at the <4 mmol/L cutoff. In PARADIGM-HF (Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure) trial 3% or less of the

patients had investigator-reported hypokalemia(32). In PARAGON-HF (Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction) trial less than 5% had investigator-reported hypokalemia (33).

In summary, clinically relevant hypokalemia (<3.5 mmol/L) is not very common, but it is independently associated with a higher event rate. Aldosterone antagonists lessen the risk for hypokalemia and part of their therapeutic effect may be explained by reducing the risk of hypokalemia. While the observational data are consistent across many studies, the proportion of outcomes that may be directly attributed to hypokalemia vs. hypokalemia being a marker for sicker patient population (i.e. reverse causation) may be argued. The fact that hypokalemia is associated with mortality even after extensive adjustment and that risk is ameliorated when hypokalemia is corrected, suggests that hypokalemia is indeed causative rather than a mere risk marker(25). Considering the link between structural heart disease and risk for arrhythmia in the presence of hypokalemia, avoiding hypokalemia in HF patients seems prudent. **Figure 2.**

Management

Maintaining serum potassium concentrations in the normal range should be a therapeutic goal and attaining a potassium concentration of at least 4.0 mmol/L seem desirable(17).

Thiazide-type diuretics are a major cause of hypokalemia, and if thiazides are necessary for lowering blood pressure or to achieve adequate decongestion, the lowest possible dose should be used. Although loop diuretics may cause less hypokalemia than thiazides, as the average potassium fall is less after the usual doses of furosemide (≈ 0.3 mmol/l) than after the usual doses of thiazides (≈ 0.6 mmol/l); moreover, contrary to thiazides the potassium fall with loops diuretics is little influenced by the dose or duration of treatment (34,35). However, in sicker patients, with higher RAAS activation as well as higher doses of loop diuretics, the risk of

hypokalemia may still be considerable. A more effective strategy may be to up-titrate ACEi or ARB if possible and to use an MRA. A potassium-rich diet may be followed in select patients, but care should be given in patients on renin-angiotensin-aldosterone system inhibitor (RAASi) therapy who may be at simultaneous risk of hyperkalemia (36). Despite these efforts, in patients with persistent hypokalemia, oral potassium supplements may be used to increase K⁺ levels, but only after ACEi/ARB and MRA initiation and up-titration (**Table 2, Figure 1**).

Monitoring

In the presence of hypokalemia below 3.5 mmol/L and after initiation of MRA therapy, frequent K⁺ and renal function monitoring is recommended. Is it reasonable to have K⁺ and creatinine measured in the first week after hypokalemia detection and/or MRA initiation, with one additional measurement per month within the next 3 months (i.e. 4 measures in total) or until potassium levels are in the normal range(37). If the K⁺ levels are below 3 mmol/L an in-hospital treatment with telemetry (or other facility where close surveillance is possible) is desirable due to the high risk of fatal events. Another common clinical scenario is the patient with HFrEF (and thus risk of ventricular arrhythmias) admitted with volume overload and appropriately treated with high dose diuretics, where K⁺ falls dramatically and may put patients at risk of arrhythmias. These patients may need several K⁺ measurements per 24-hour period and continuous telemetry, particularly in the absence of an implantable cardioverter defibrillator. A synthesis of the management of potassium disturbances is provided in **Table 2 and Figure 1**.

HYPERKALEMIA

Incidence and Causes

Hyperkalemia in HF is often associated with the use of RAASi (ACEi/ARBs/MRAs) including the use of angiotensin receptor antagonist-neprilysin inhibitor (ARNi) sacubitril-

valsartan, and also older age, diabetes and chronic kidney disease (CKD) i.e. the patients who most benefit from RAASi. The occurrence of hyperkalemia often limits RAASi use and/or lead to dose reduction and discontinuation, thereby reducing their potential benefits.

Hyperkalemia is a major concern for clinicians, particularly in association with the use of MRAs (38). The fear of hyperkalemia and its related underuse of RAASi therapy is justified, as a sizable proportion of HF patients develop moderate to severe hyperkalemia with RAASi therapy, a risk which is compounded in the presence of comorbid renal disease and diabetes especially in the elderly(39). In a large, contemporary, international HF population it was found that hyperkalemia, impaired kidney function and hypotension were the main causes for the non-prescription or underdosing of RAASi(40), and in a large analysis of Swedish HF Registry, CKD and older age were major reasons for MRA non-use, independent of potassium levels and other confounders (41).

The severity of hyperkalemia is usually classified as mild (5.0-5.5 mmol/L), moderate (5.6-6.0 mmol/L) and severe (>6.0 mmol/L). The threshold risk for the development of hyperkalemia-associated arrhythmic emergencies and death varies widely between patients(23). It is often stated that the rapidity of change rather than the absolute K⁺ level leads to rhythm disturbances. However, data are not conclusive and this assertion can be questioned based on observational association showing that even mild hyperkalemia is associated with worse outcomes. Because the risk of arrhythmia for a given potassium level varies between patients, an EKG should be obtained in both hyper and hypokalemia to detect precursors to arrhythmia, even though the sensitivity of EKG to detect hyperkalemia associated rhythm disturbances is poor (42, 43).

Prognostic impact

Observational Studies

Multiple cohort studies in HFrEF suggest that while ACEi/ARB use is relatively good at >80%, MRA use remains low, ranging only from 30 to 60%. Hyperkalemia is mentioned by polls or in case report forms as a reason for not prescribing ACEi/ARBs in up to 10% of the cases, whereas for MRAs this proportion can go up to 35% (40,41,44). For ACEi/ARBs and beta-blockers the clinical benefit has been shown to be dose-dependent (45, 46); optimal dosing of MRA for outcome benefit has not been tested but data derived from the EMPHASIS-HF renal function stratified analysis, suggest that (at least for eplerenone) MRA doses should be adapted according to the patients` renal function, with lower doses provided to patients with impaired renal function(47) (see also **Table 3**). After the publication of RALES, the use of spironolactone rose dramatically in Canada and the rates of hyperkalemia also did rise in a similar time-frame. Some authors related these findings to an overall increase in morbidity and mortality rates(48). This unnerved many clinicians and may have contributed to poor MRA use. However, less publicized was a similar study from Scotland, where a similarly dramatic increase in the use of spironolactone after RALES was not associated with an increase in hyperkalemia (or CKD), and the hospital admissions for hyperkalemia and outpatient`s hyperkalemia fell (49). These differences may be due to different potassium monitoring strategies (usual potassium monitoring in Ontario, Canada vs. close monitoring in Tayside, Scotland), different populations (older patients in Ontario, Canada who were treated with ACE inhibitors, regardless of whether or not they had previously been hospitalized for HF vs. patients who had a hospital admission for HF in Tayside, Scotland) and the age of the patients, much older in the Canadian report compared with the Scottish (79. Vs. 73yr, **Supplemental Table 2**). Importantly, the hyperkalemia-associated increased risk in HF, may be largely due to the avoiding RAASi in prevalent hyperkalemia or

stopping of RAASi once the patient's potassium starts to rise (i.e. hyperkalemia may be a risk marker for sub-optimal RAASi use rather than a risk factor in itself)(50). This possibility has now been explored in several analyses. In the BIOSSTAT-CHF study, hyperkalemia was not an independent risk factor for worse outcomes but was an independent risk factor for lower sub-optimal ACEi/ARB doses (51). In the Swedish HF registry, both hypo- and hyperkalemia were associated with increased mortality short- and long-term, in the familiar U-shaped relationship previously described (21). After adjustment hypokalemia remained independently associated with both short- and long-term mortality. In contrast, hyperkalemia was independently associated with only short-term, but not long-term mortality, suggesting that in the longer term, hyperkalemia is a risk marker for other confounders, such as suboptimal RAASi use (52). In a recent observational study including patients initiating MRA therapy, the occurrence of hyperkalemia led to MRA discontinuation in 47% and dose reduction in 10% of patients. Once MRA was discontinued, over three fourths of patients were not re-started on MRAs during the subsequent year (53). Finally, in the large ESC-HF-LT Registry, and in concordance with the previous reports, hyper- and hypokalemia were both associated with worse outcomes. However, after adjusting for discontinuation of a RAASi (ACEi/ARB or MRA), hyperkalemia was no longer associated with increased risk(54). These findings suggest that hyperkalemia may be a risk factor for RAASi underuse and discontinuation which mediates the association with worse outcomes(52). Together, these findings suggest that hyperkalemia leads to RAASi underuse and permanent discontinuation which increase the risk of adverse outcomes, beyond its potential proarrhythmogenic properties (50,52). As the associations of K⁺ levels with outcomes are U-shaped, in most of the above referenced studies, hyperkalemia was also associated with increased mortality risk. Potassium levels above 5.5 mmol/L and especially 6.0 mmol/L have been

consistently associated with poor outcomes. The strength of the associations for $K^+ >6.0$ mmol/L is similar to those observed for $K^+ <3.5$ mmol/L; and correction of hyperkalemia is also associated with mitigation of its associated risk (6,7,21,26-28). The detailed prognostic associations and the main patient characteristics are summarized in **Table 1** and **Supplemental Table 1**.

Clinical Trials

The prognostic implications of hyperkalemia in clinical trials appear similar to those found in observational studies. For example, in a post-hoc analysis of the TOPCAT trial(30), K^+ levels >5.5 mmol/L were associated with a 1.7-fold increase in the relative risk of death. In a post-hoc analysis from the RALES trial.(55), hyperkalemia (>5.5 mmol/L) was associated with increased risk of death. The benefit with spironolactone was seen even when K^+ levels reached 6.0 mmol/L. Similar findings were reported from the EMPHASIS-HF trial, where eplerenone retained its survival benefits without interaction with the baseline K^+ levels (56). In the PARADIGM-HF trial less than 18% of the patients had K^+ levels >5.5 mmol/L throughout the follow-up without differences between the sacubitril/valsartan and enalapril groups. Potassium levels >6.0 mmol/L occurred in 4% of the patients treated with sacubitril/valsartan and in 6% of the patients treated with enalapril, a difference that was statistically significant(32). Moreover, in patients taking an MRA the hyperkalemia risk was attenuated by sacubitril/valsartan(57). In the PIONEER-HF trial, the hyperkalemia rates were similar to PARADIGM-HF and were not statistically different between groups (58). In the PARAGON-HF trial less than 16% of the patients had K^+ levels >5.5 mmol/L throughout the follow-up. Potassium levels >6.0 mmol/L occurred in 3% of the patients treated with sacubitril/valsartan and in 4% of the patients treated with valsartan(33). Moreover, in patients taking an MRA the hyperkalemia risk was similar in

the sacubitril/valsartan and the valsartan group. Even with normokalemia, CKD causes sub-optimal use of RAASi. In RALES, EMPHASIS-HF and PARADIGM, there was no significant interaction between the treatment effect and baseline creatinine levels or CKD status (defined as eGFR <60 ml/min/1.73m²). Trials excluded patients with eGFR <30, but two large observational studies suggest that RASi drugs may be as effective in the elderly and in patients with eGFR <30 ml/min/1.73m², often excluded from trials (59, 60).

Using EPHESUS as a derivation cohort, and the EMPHASIS-HF as external validation cohort, a cardiovascular death risk score (<http://cic-pnancy.fr/CardiovascularriskscoreCalculator/>) was developed(61). This score includes medical history, clinical and biological parameters (e.g. K⁺, below or above the normal range of 4–5 mmol/L, estimated glomerular filtration rate, and anemia), as well as aspects of treatment (any diuretic usage, MRA use or discontinuation, and beta-blocker use). Adding time-updated variables, including K⁺ and MRA treatment, improved risk prediction of cardiovascular death (on top of the MAGGIC score) in patients with HF eligible for renin–angiotensin system inhibitors and MRA therapy. In this setting a potassium below 3.5 or above 5.5 was associated with a similar risk.

In summary, potassium levels persistently above 5.5 mmol/L and especially above 6.0 mmol/L may have a causal relation with higher mortality rates in HF, but importantly, are also a marker for poor RAASi use. When these levels are reverted to normal, the associated risk is reduced but poor RAASi use persists, illustrating that even sporadic and non-recurring episodes of hyperkalemia may have long-term consequences. MRAs increase the risk of hyperkalemia but their benefit in HFrEF is likely seen throughout the potassium spectrum until the K⁺ levels reach

6.0 mmol/L. In chronic HFrEF, sacubitril/valsartan likely reduces the risk of hyperkalemia, as compared to enalapril, especially in the context of concomitant MRA use (**Figure 2**).

Management

A synthesis of the management of potassium disturbances is provided in **Table 2** and **Figure 1**. A detailed history of diet, use of supplements, salt substitutes, and concomitant medications that may contribute to hyperkalemia should be performed. Restriction of dietary potassium to <2.4 g/d is recommended in patients with stage 3 (eGFR <60 mL/min per 1.73 m²) or higher CKD(62). When sodium restriction is advised, the use of salt substitutes including potassium may expose these patients to the risk of hyperkalemia. Although patients are often educated to avoid commonly recognized high-potassium foods, many such foods may remain unrecognized by patients and clinicians. Furthermore, it is increasingly clear and patients receive lay information that potassium-rich foods are also often healthful foods, so patients receive conflicting messages. Thus, education by a dietician is recommended. This common sense recommendation, although embedded in nephrology practice, is frequently overlooked by general physicians and cardiologists. Therapy with RAASi and ARNIs should be started at a low dose and titrated to the maximum tolerated evidence-based dose up to a K⁺ level of 5.5 mmol/L.

Current guidelines recommend that patients with hyperkalemia should be started on a low K⁺ diet and be initiated on a non-K⁺ sparing diuretic or to increase the diuretic dose if already on a diuretic(62-64). However, this may lead to volume depletion, a worsening in renal function, and to a stimulation of the RAAS(65). K⁺ supplements should be discontinued, and drugs that may compromise renal function and increase K⁺ levels, such as NSAIDs, should also be stopped.

Recommendations exist on when to reduce the dose or stop RAASi and ARNIs(8). In general, it is recommended to not stop RAASi or ARNIs when the K⁺ levels are between 5.0 and

5.5 mmol/L (66), unless patient follow-up is unreliable in which case the clinician may choose to lower the dose, trying to not decrease below 50% of the guideline-recommended dose. If a short-term cessation of RAASi or ARNi is deemed necessary, this should be kept to the shortest time possible, and RAASi or ARNi should be reintroduced as soon as possible while monitoring K⁺ levels (8,67). Potassium binders (see also below) may be used to facilitate continuation of RAASi therapy. If K⁺ levels are between 5.5-6.0 mmol/L, it is recommended to reduce MRAs or ACEi/ARB, or ARNi dose by 50% and recheck the serum potassium in 5-7 days until it has returned to baseline. If serum potassium does not return to baseline in the short term, long term compromise of MRAs, ACEi/ARB or ARNi is not recommended and the use of potassium binders for RAASi enablement should be strongly considered (1) (**Table 2, Figure 1**). The dyskalemia associated-risk and the potential benefits of its prompt correction are depicted in the **Central Illustration**.

Monitoring

As per guidelines (6,67) for ACEi/ARB use, it is recommended that blood chemistry, including serum creatinine and serum potassium are checked 1-2 weeks after initiation, 1-2 weeks after final dose titration, and every 4 months thereafter. The same recommendation is reasonable also for ARNis. For MRA use, checks should be performed at 1 and 4 weeks after starting/increasing dose and at 8 and 12 weeks; 6, 9, and 12 months; 4-monthly thereafter. After an episode of hyperkalemia, it is recommended that blood chemistry, including serum creatinine and serum potassium, should be monitored frequently and serially until potassium and creatinine have plateaued. Proposed guidance on MRA-dose adjustments is provided in **Table 3**. However, the rates of appropriate monitoring are very low in clinical practice and a rise in potassium level represents a frequent cause for RAASi dose reduction or discontinuation; actions that may

deprive HF patients of therapy proven to improve outcomes (37,55,68). Indeed, in a study of HF from the Swedish HF registry, and in one of new MRA users in the Stockholm CREATinine Measurements (SCREAM) healthcare utilization cohort, in treated patients RAASi drugs were often stopped over time, and in untreated patients or patients where RAASi was stopped, these were rarely started (21,69). More intense monitoring, using future potential devices for self-monitoring or point of care monitoring and disease management programs, including specialist HF nurse assisting with education of the patient, follow-up (in person or by telephone), may help optimize safer use of RAASi and merits further investigation(70). The use of deep-learning models for the screening of potassium abnormalities with ECGs could also be considered as a possibility, after prospective validation (71).

Potassium Binders

The recent availability of safe and tolerable gastrointestinal potassium binders allows for chronic management of hyperkalemia and may enable RAASi therapy optimization (72-75). Sodium and calcium polystyrene sulfonate (SPS or CPS) are widely available cation exchange resins that remove potassium via the gastrointestinal tract; these compounds have been around for many years, yet neither SPS nor CPS have been tested in adequately powered randomized trials for assessing their safety, tolerability and efficacy in the long term (76,77). In the short term, these compounds have poor tolerability, unstable onset of action and unpredictable magnitude of potassium lowering (78, 79). The use of SPS may be associated with volume expansion, since SPS exchanges potassium for sodium. Some reports have also evidenced a potentially increased colonic necrosis risk, although with very low absolute rates and potential for confounding (80).

Two new agents, patiromer and sodium zirconium cyclosilicate (SZC), 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 fecal excretion(78, 81, 82). The FDA and EMA approved patiromer and SZC for the treatment of hyperkalemia in patients receiving RAASi. Once patients' manifest potassium levels in the hyperkalemia range, many see their RAASi therapy reduced or discontinued but the use of potassium binders help facilitate preservation of RAASi use and dosing(83, 84). For example, in the PEARL-HF (Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure) trial(83), 105 patients with HF and a history of hyperkalemia resulting in discontinuation of a RAASi or CKD, were randomized to patiromer or placebo for 4 weeks. At the end of treatment, patiromer had significantly lowered serum K⁺ levels and reduced hyperkalemia (7.3% in patiromer vs. 24.5% in placebo); and enabled a higher proportion of patients on spironolactone 50 mg/day (91% in patiromer vs. 74% in placebo). Notwithstanding, hypokalemia (K⁺ <3.5 mmol/L) occurred in 6% of patients taking patiromer vs. 0% of the patients taking placebo (p =0.094). Additionally, hypomagnesemia occurred in 24% of the patients taking patiromer vs. 2% taking the placebo (p =0.001). In patients with resistant hypertension and CKD, patiromer also enabled more patients to continue treatment with spironolactone with less hyperkalemia(84). The HARMONIZE (Hyperkalaemia Randomized Intervention Multidose ZS-9 Maintenance trial)(73) studied the effects of SZC on serum potassium levels; 87 patients in the trial had documented HF with baseline K⁺ >5.0 mmol/L. Among these, 93% achieved the target potassium level of 3.5–5 mmol/L within 48 h of receiving open-label SZC without adjusting RAASi doses. Edema was reported in 2.4% of the placebo group and up to 14.3% with the highest dose of SZC (15 g daily; no increased edema

risk was seen in patients treated with the lowest dose of 5g daily)(85). Together, these findings support the potential use of K-binders to enable RAASi up-titration(74). A practical guidance for the use of potassium binders in HF is proposed in **Table 4**.

Whether the use of potassium binders enabling optimal RAASi therapy may improve outcomes is under investigation. For example, the DIAMOND (Patiomer for the Management of Hyperkalemia in Subjects Receiving RAASi Medications for the Treatment of Heart Failure; ClinicalTrials.gov Identifier: NCT03888066) study will evaluate the potential of patiomer to improve outcomes by enabling HF patients, with or without CKD, to be treated with RAASi therapy in accordance with HF treatment guidelines. The PRIORITIZE-HF (Potassium Reduction Initiative to Optimize RAAS Inhibition Therapy With Sodium Zirconium Cyclosilicate in Heart Failure; ClinicalTrials.gov Identifier: NCT03532009) study will evaluate whether SZC may enable target-dose RAASi up-titration if HF patients.

TENTATIVE OF INFERRING CAUSALITY FROM OBSERVATIONAL DATA

The studies here reported performed multivariable adjustment or matching in order to mitigate the confounding inherent to observational data (86). However, adjustment cannot fully eliminate confounding and much of it cannot be measured. A potential approach to assess the possibility that unmeasured confounding is a likely driver for the associations found in observational studies is the E-value (87). Specifically, an E-value analysis asks the question: how strong would the unmeasured confounding have to be to negate the observed results?(88). If the strength of any possible unmeasured confounder is weaker than indicated by the E-value, then the main study result would likely be “significant”; on the other hand, if the strength of a potential unmeasured confounder is stronger than indicated by the E-value then the result could be overturned to one of “no association” by the confounder. E-values can therefore help assess

the robustness of the main study results by considering whether unmeasured confounding of this magnitude is plausible (89). In this regard, the HR for K⁺ levels between 3.5 and 4.0 mmol/L ranges from 1.1 to 1.6 with a point estimate around 1.3 in the several referenced studies, giving an E-value of 1.6. In the MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) score, some variables have a HR similar to or greater than 1.6 (e.g. NYHA, LVEF, diabetes), and other unmeasured confounders (e.g. NT-pro BNP, troponin, previous HF hospitalization, severe valvulopathy, multivessel coronary artery disease) can have even stronger associations with the outcome(90). Therefore, it is possible that the associations of K⁺ levels between 3.5 and 4.0 mmol/L with adverse outcomes are not causal i.e. they may reflect reverse causation bias. However, the HR for K⁺ levels <3.5 mmol/L range from 1.6 to 3.2 with a point estimate around 2.5 in the several referenced studies, giving an E-value of 3.2; a value that is too high to be explained by other unmeasured confounder, suggesting that K⁺ levels below 3.5 mmol/L, if not corrected, may have a causal association with adverse events. The associations relating hyperkalemia with increased death risk may also be subject of reverse causation bias. The HR for K⁺ levels between 5.1 and 5.5 mmol/L ranges from 0.8 to 1.6 with a point estimate around 1.2, giving an E-value of 1.5 to 1.6. As observed in the example of the MAGGIC score, there are several variables with similar and/or higher HR and a big potential for unmeasured confounder to display stronger associations(90). Therefore, it is unlikely that the associations of K⁺ levels between 5.1 and 5.5 mmol/L with adverse outcomes are causal. However, the HR for K⁺ levels >5.5 mmol/L range from 0.9 to 3.3 with a point estimate around 2.0, giving an E-value of 2.6; a value that still can be brought to the null by other “unmeasured covariates” such as NT-pro BNP, troponin or severe valvulopathy (for example); the possibility of direct causation is stronger with K⁺ levels above 6.0 mmol/L. It may be hypothesized that hyperkalemia is rather a risk marker of

other concomitant diseases (e.g. CKD) and that patients who develop hyperkalemia are more likely to stop or reduce life-saving therapies such as ACEi/ARBs or MRAs which further increases the risk of events(53, 91). Importantly, these associations can be brought to “null” if K⁺ is corrected.

GAPS IN EVIDENCE AND FUTURE DIRECTIONS

A better estimation of the dietary K⁺, implementation of K⁺ dietary counseling in HF disease management programs, and their impact on maintenance of optimal blood K⁺ levels and outcomes in HF patients requires further investigation to better guide dietary recommendations in HF patients with dyskalemia.

Potassium monitoring strategies recommendations are currently based on algorithms used in RAASi trials, but are not being implemented in current practice. New strategies to help embed these recommendations in HF management programs should be investigated, including using new point of care self-measurements remote monitoring technologies.

Whether the use of K-binders may maximize the use of RAASi in HF patients is being investigated in the PRIORITIZE-HF (Potassium Reduction Initiative to Optimize RAAS Inhibition Therapy With Sodium Zirconium Cyclosilicate in Heart Failure; NCT03532009) trial. But further research is required to ascertain whether RAASi up-titration enabled by K-binders can improve patients` outcomes. The ongoing DIAMOND (Patiromer for the Management of Hyperkalemia in Subjects Receiving RAASi Medications for the Treatment of Heart Failure; NCT03888066) study is designed to address this issue.

K-binders may be used to study the potential benefit of RAASi in populations not studied in the past due to the risk of hyperkalemia, e.g. patients with eGFR <30 ml/min/1.73 m². Also, K-binders may enable investigating the benefit of higher doses MRA therapy.

Hypokalemia is common in HF and little is known about the best approach to identify and correct it. Future research should target hypokalemia; for example, using pragmatic algorithms with MRA dose adjustments, and/or algorithms using potassium supplements, based on K⁺ levels.

The potential impact of potassium disturbances on sudden cardiac death has been rarely reported in the literature; given the pro-arrhythmogenic risk of both hypo- and hyperkalemia a better understanding of the associations and mechanisms by which potassium may increase the risk for sudden death is warranted. Hypomagnesemia has been underreported in HF studies and little is known about its prognostic impact and further research is also required in this field.

CONCLUSION

Dyskalemia can be life-threatening if not corrected, either directly or indirectly by impact provision of optimal medical therapy. A serum potassium below 3.5-4.0 mmol/L may portend a similar death risk as a potassium above 5.5-6.0 mmol/L. Based on current observational data, it seems prudent to keep the serum potassium concentration between 4.0-5.0 mmol/L. More research and education about dyskalemia may help increase awareness about the issue and improving better clinical practice, including: 1) identifying patients at risk, 2) preventing dyskalemia with available “life-style” changes, including dietary changes (although this may not be sustainable on the long-run and may deprive patients from healthy food), 3) monitoring serum potassium, at least as per guidelines, and may be more intensively in patients who experienced dyskalemia episodes 4) treating emerging rise of potassium with dose adjustments of drugs likely to increase serum potassium, and/or using potassium binders, and 5) enabling optimal medical therapy in select patients with potassium binders without compromising lifesaving medications. Worsening chronic comorbidities are rarely attributed to hyperkalemia in the setting of sub-

optimal RAASi therapy even when the two are related. However, novel potassium binders might provide a potential opportunity to not compromise on long term optimal medical therapy of patients with chronic cardiovascular and renal diseases in whom RAASi therapy is known to be beneficial. This hypothesis is currently under investigation.

BULLET POINTS

- Potassium alterations may have life-threatening consequences
- Hypokalemia is associated with adverse outcomes likely via causal mechanisms
- Hyperkalemia leads to the stopping of RAASi that may have adverse consequences
- Correction of both hypo- and hyperkalemia offsets their associated risk

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Figure Legends

Figure 1. Management of hyper- and hypokalemia. ACEi/ARBs, angiotensin converting enzyme inhibitors/angiotensin receptor blockers; MRA, mineralocorticoid receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitors.

Figure 2. Outcomes associations of dyskalemia in HFrEF and HFpEF. HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; MRA, mineralocorticoid receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitors.

Central Illustration. Association of serum potassium with all-cause death and the benefits of a prompt correction of dyskalemia. RAASi, renin-angiotensin aldosterone inhibitor; MRA, mineralocorticoid receptor antagonist; ↑, increase.

Table 1. Serum potassium levels and outcomes in observational studies adjusted for potential confounders

Study / K ⁺ level (mmol/L)	<3.5	3.5-4.0	4.1-5.0	5.1-5.5	>5.5
Aldahl M. <i>et al</i>	3.2 (2.4-4.1)	1.6 (1.3-2.0)	Ref. (1)	1.6 (1.3-2.0)	3.3 (2.6-4.2)
Nunez J. <i>et al</i>	2.4 (1.4-3.9)	1.1 (0.8-1.4) §	Ref. (1)	1.5 (1.0-2.0) §	2.5 (1.5-3.5) §
Linde C. <i>et al</i> §§	2.0 (1.5-2.5)	1.3 (1.1-1.5)	Ref. (1)	1.3 (1.1-1.5)	1.5 (1.3-1.8) *
Hoss S. <i>et al</i>	2.3 (1.6-3.4)	1.2 (0.9-1.6)	Ref. (1)	0.8 (0.6-1.2)	0.9 (0.5-1.4)
Matsushita K. <i>et al</i>	1.6 (1.5-1.7)	1.1 (1.0-1.2) §	Ref. (1)	1.1 (1.0-1.2) §	1.7 (1.5-1.9)
Desai AS. <i>et al</i>	1.6 (1.1-2.1)	1.3 (1.2-1.6) §	Ref. (1)	1.3 (1.1-1.7) §	1.7 (1.2-2.5)
Cooper L. <i>et al.</i> §	2.0 (1.0-3.0)	1.5 (1.2-1.8)	Ref. (1)	1.0 (0.9-1.3)	1.0 (0.8-1.4)

§ Estimates derived from continuous “spline” curves.

§§ Estimates derived from forest plots.

* The relative risk for patients with K⁺ between 5.5 and 6.0 mmol/L was 1.5 (1.3-1.8), and for K⁺ >6.0 mmol/L was 3.0 (2.0-4.0). Patients with K⁺ >5.5 mmol/L had higher odds for renin–angiotensin–aldosterone system inhibitor discontinuation.

** K⁺ levels >6.0 mmol/L are more likely to have a causal association with worse outcomes; levels between 5.5 and 6.0 mmol/L were not consistently associated with worse prognosis and even when they are the associations are not overwhelmingly strong to exclude another explanation.

The adjustment variables varied across studies, but systematically included age, sex, renal function, co-morbid conditions such as diabetes, hypertension and atrial fibrillation, and measures of disease severity such as NYHA class.

Table 2. Management of dyskalemia

Serum K ⁺ (mmol/L)	Therapeutic recommendations (providing renal function is stable and eGFR >30 ml/min/1.73m ² and blood pressure is stable and systolic BP >100 mmHg)
<3.5	<ol style="list-style-type: none"> 1. If associated with “de novo” ECG alterations: in-hospital admission 2. If no ECG alterations: <ol style="list-style-type: none"> 2.1. Stop thiazides (if diuretics are necessary for congestion relief, prefer loop diuretics) 2.2. Stop potassium binders 2.3. Initiate MRA 2.4. If already on MRA, then increase dose 3. Increase ACEi/ARBs/ARNi dose to guideline-recommended targets 4. Monitor K⁺ and creatinine at 1 week, 1 month, 2 months, and 3 months <ol style="list-style-type: none"> 4.1. Until K⁺ is in the “normal” range 4.2. Adapt MRA dose if necessary (see also the Table 3) 5. Initiate a potassium supplement if none of the above steps works
3.5-3.9	<ol style="list-style-type: none"> 1. Stop thiazides (prefer loop diuretics for congestion relief) 2. Stop potassium binders 3. Initiate MRA (or increase dose, if already taking one) 4. Increase ACEi/ARBs/ARNi dose to guideline-recommended targets 5. Monitor K⁺ and creatinine at 1 week, 1 month, 2 months, and 3 months <ol style="list-style-type: none"> 4.1. Until K⁺ is in the “normal” range 4.2. Adapt MRA dose if necessary (see also the Table 3)
4.0-5.0	<ol style="list-style-type: none"> 1. Patient is in the target zone 2. Initiate or maintain RAASi and MRA dose
5.1-5.5	<ol style="list-style-type: none"> 1. Individualize management based on patient risk and reliability of medical compliance and follow up 2. ACEi/ARBs, ARNi and MRA may be maintained (see also the Table 3) 3. Monitor K⁺ and creatinine closely 4. Eliminate K⁺ supplements, NSAIDs and decrease K⁺ rich foods (whenever possible) 5. If reliable clinical follow-up and serum potassium assessment is doubtful, may consider potassium binder preferably over compromising RAASi therapy
5.6-6.0	<ol style="list-style-type: none"> 1. Perform ECG and if “de novo” ECG alterations: in-hospital admission

	<ol style="list-style-type: none"> 2. Assess the possibility of hemolysis and repeat sample, if necessary 3. Initiate a diuretic or increase its dose (if necessary) 4. Eliminate K⁺ supplements, NSAIDs and decrease K⁺ rich foods (whenever possible) 5. Reassess K⁺ levels after 1 week; if K⁺ levels still high: <ol style="list-style-type: none"> 5.1. and on maximal tolerated/guideline-recommend RAASi dose, consider a K⁺ binder (do not stop RAASi but may decrease the dose up to 50% of the guideline recommended dose) 5.2. if RAASi dose <50% of guideline recommendation, consider a K⁺ binder and RAASi up-titration 6. Monitor K⁺ and creatinine at 1 week, 1 month, 2 months, and 3 months <ol style="list-style-type: none"> 5.1. Until K⁺ is in the “normal” range 5.2. Adapt ACEi/ARB, ARNi and MRA dose if necessary (see also the Table 3)
>6.0	<ol style="list-style-type: none"> 1. If associated with “de novo” ECG alterations: in-hospital admission 2. If no ECG alterations: <ol style="list-style-type: none"> 2.1. Assess the possibility of hemolysis and repeat sample, if necessary 2.2. Initiate a diuretic or increase its dose (if necessary) 2.3. Eliminate K⁺ supplements, NSAIDs and decrease K⁺ rich foods (whenever possible) 2.4. Initiate a K⁺ binder 3. Reassess K⁺ levels after 1 week; if K⁺ levels still high: <ol style="list-style-type: none"> 3.1. Reduce MRA/ACEi/ARB/ARNI dose by 50% of the guideline-recommended dose (but do not decrease below 50%) and maintain K⁺ binder or initiate one if not yet started; repeat the K⁺ assessment after 1 week and if K⁺ still >6.0 mmol/L stop the MRA maintaining the K⁺ binder 3.2. When K⁺ levels <6.0 mmol/L, reintroduce the MRA maintaining the K⁺ binder and see the above panel 4. Monitor K⁺ and creatinine at 1 week, 1 month, 2 months, and 3 months <ol style="list-style-type: none"> 4.1. Until K⁺ is in the “normal” range 4.2. Adapt RAASi dose to guideline-recommended targets

Legend: MRA, mineralocorticoid receptor antagonist; ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; RAASi, renin-angiotensin aldosterone inhibitor; eGFR, estimated glomerular filtration rate; BP, blood pressure.

Table 3. Spironolactone and eplerenone dose adjustment proposal

Serum K ⁺ (mmol/L)	Dose adjustment (providing renal function is stable and eGFR >30 ml/min/1.73m ² and blood pressure is stable and systolic BP >100 mmHg)
	Baseline: <ul style="list-style-type: none"> - eGFR ≥50 ml/min/1.73m² → spironolactone dose =25 mg/d or eplerenone 50 mg/d - eGFR 30-49 ml/min/1.73m² → spironolactone dose =25 mg every other day or eplerenone 25 mg/d
<4.0	Increase dose: If spironolactone dose =25 mg/d → increase to 50 mg/d or if eplerenone dose =50 mg/d → increase to 100 mg/d If spironolactone dose =25 mg every other day → increase to 25 mg/d or if eplerenone dose =25 mg/d → increase to 50 mg/d
4.0-5.4	No adjustment recommended
5.5-5.9	Decrease dose: If spironolactone dose =50 mg/d → decrease to 25 mg/d or if eplerenone dose =100 mg/d → decrease to 50 mg/d If spironolactone dose =25 mg/d → decrease to 25 mg very other day or if eplerenone dose =50 mg/d → decrease to 25 mg/d If spironolactone dose =25 mg every other day → interrupt treatment and reassess K ⁺ within 1 week or if eplerenone dose =25 mg/d → interrupt treatment and reassess K ⁺ within 1 week
≥6.0	Stop MRA treatment and reassess K ⁺ levels after 1 week When K ⁺ levels <6.0 mmol/L, initiate a K ⁺ binder and reintroduce MRA
	Stop MRA treatment at any case if eGFR ≤30 ml/min/1.73m ² and reintroduce upon clinical decision i.e. upon renal function improvement and K ⁺ stabilization.

Legend: MRA, mineralocorticoid receptor antagonist; eGFR, estimated glomerular filtration rate; BP, blood pressure.

Table 4. Proposal for potassium binder use

Serum K ⁺ (mmol/L)	K-binder use
<5.5	<p>Maintain guideline-recommended treatment</p> <p>Do not stop K-binder if the patient is taking one</p> <p>Consider initiating K-binder between 5.0-5.5 mmol/L if reliable patient follow-up is a concern and therefore consideration is given to compromising RAASi dosing</p>
5.5-5.9	<p>Adapt MRA dose as suggested in the Table 3</p> <p>Do not reduce ACEi/ARB/ARNi</p> <p>Re-assess K⁺ levels after 1 week; if K⁺ levels still high add K-binder, preferably those with long term enablement data, i.e. patiromer or SZC</p> <ul style="list-style-type: none"> - Reassess K⁺ levels after 1 week (a ≈1 mmol/L K⁺ decrease could be expected) - If K⁺ <5.5 mmol/L increase MRA dose and maintain K-binder for 1 additional week, then continue routine follow-up - If K⁺ 5.5-5.9 mmol/L do not increase MRA and maintain/up-titrate K-binder for 1 additional week reassessing K⁺ afterwards
≥6.0	<p>Adapt MRA dose as suggested in the Table 4</p> <p>Reduce ACEi/ARB/ARNi in 50%</p> <p>Re-assess K⁺ levels after 1 week; if K⁺ levels still high add a K-binder similar to as recommended for potassium levels 5.5-5.9 mmol/L</p>

Legend: RAASi, renin-angiotensin aldosterone system inhibitor; MRA, mineralocorticoid receptor antagonist; ACEi/ARB/ARNi, angiotensin converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor neprilysin inhibitor.

Hyperkalemia >5.5 mmol/L

- Assess the possibility of **hemolysis**
- Initiate a **diuretic** or increase its dose (if necessary)
- **Eliminate K⁺ supplements, NSAIDs** and decrease K⁺ rich foods
- **Replace ACEi/ARBs by sacubitril valsartan** (if not yet done)
- **Adapt MRA dose** (if necessary)
- Consider a K⁺ binder (do not stop RAASi)

- **Stop thiazides** (prefer loop diuretics for congestion relief)
- Initiate **MRA** (or increase dose, if already taking one)
- **Increase ACEi/ARBs** dose to guideline-recommended targets
- **Monitor** K⁺ and creatinine

Hypokalemia <4 mmol/L

