Expert consensus document on the management of hyperkalaemia in patients with cardiovascular disease treated with RAAS-inhibitors - Coordinated by the Working Group on Cardiovascular Pharmacotherapy of the European Society of Cardiology

Giuseppe M.C. Rosano, MD, PhD, FESC, FHFA[1-2]; Juan Tamargo, MD, FESC[3]; Keld P. Kjeldsen, MD, DSc[4-6]; Mitja Lainscak, MD, FESC, FHFA[7]; Stefan Agewall, MD, FESC[8-9]; Stefan D. Anker, MD, PhD,FESC, FHFA[10]; Claudio Ceconi, MD, FESC[11]; Andrew JS Coats, MD, FESC, FHFA[1]; Heinz Drexel, MD, FESC[12-14]; Gerasimos Filippatos, MD, FESC, FHFA[15]; Juan Carlos Kaski, MD, FESC[1]; Lars Lund, MD, FESC, FHFA[16]; Alexander Niessner, MD, FESC[17]; Piotr Ponikowski, ME, FESC, FHFA[17]; Gianluigi Savarese, MD, FESC, FHFA[16]; Thomas A Schmidt, MD, DSc[19]; Petar Seferovic, MD, FESC, FHFA[20;] Sven Wassmann, MD, FESC[21]; Thomas Walther, PhD[22-23]; Basil S. Lewis MD, FRCP, FESC[24-25],

1. Department of Medical Sciences, IRCCS San Raffaele, Roma, Italy
2. Cardiology Clinical Academic Group, St George's Hospitals NHS Trust University of London, United Kingdom
3. Department of Pharmacology, School of Medicine. University Complutense, CIBERCV, Madrid, Spain
4. Department of Medicine, Copenhagen University Hospital (Holbæk Hospital), Holbæk, Denmark
5. Institute for Clinical Medicine, Copenhagen University, Copenhagen, Denmark
6. Department of Health Science and Technology, Aalborg University, Aalborg, Denmark
7. Faculty of Medicine, University of Ljubljana; Department of Internal Medicine, General Hospital Murska Sobota, Slovenia
8. Oslo University Hospital, Ullevål, Norway
9. Institute of Clinical Sciences, University of Oslo, Oslo, Norway
10. A. Division of Cardiology and Metabolism; Department of Cardiology (CVK); and Berlin-Brandenburg Center for Regenerative Therapies (BCRT); German Centre for Cardiovascular Research (DZHK) partner site Berlin; Charité Universitätsmedizin Berlin, Germany.
    B.Department of Cardiology and Pneumology, University Medicine Göttingen (UMG), Göttingen, Germany
11. University Hospital of Ferrara, U.O. Cardiologia, Ferrara, Italy
12. Vorarlberg Institute for Vascular Investigation and Treatment (VIVIT), Feldkirch, Austria.
13. Department of Internal Medicine, Academic Teaching Hospital Feldkirch, Feldkirch, Austria;
14. University of the Principality of Liechtenstein, Triesen, Liechtenstein
15. National and Kapodistrian University of Athens, School of Medicine, Attikon University Hospital, Athens, Greece
16. Karolinska Institutet, and Karolinska University Hospital, Stockholm, Sweden
17. Division of Cardiology, Department of Internal Medicine II, Medical University of Vienna, Austria
18. Department of Heart Diseases, Wroclaw Medical University, Centre for Heart Diseases, Military Hospital, Wroclaw, Poland
19. Department of Emergency Medicine, Holbaek Hospital, University of Copenhagen, Denmark - Institute of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark
20. Department of Cardiology, University of Belgrade, Belgrade, Serbia
21. Cardiology Pasing, Munich, Germany and University of the Saarland, Homburg/Saar, Germany

22. Department of Pharmacology and Therapeutics, School of Medicine and School of Pharmacy, University College Cork, Cork, Ireland;
23. Institute of Medical Biochemistry and Molecular Biology, University Medicine Greifswald, Greifswald, Germany.
24. Lady Davis Carmel Medical Center, Haifa, Israel
25. Ruth and Bruce Rappaport School of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

Address for correspondence:
Giuseppe M.C. Rosano, MD, PhD, FESC, FHFA
Clinical Academic Group
St George's Hospitals NHS Trust University of London
Email: grosano@sgul.ac.uk

Abstract

Renin angiotensin aldosterone system inhibitors/antagonists/blockers (RAASi) are a cornerstone in treatment of patients with cardiovascular diseases especially in those with heart failure (HF) due to their proven effect on surrogate and hard end-points. RAASi are also the basis in treatment of arterial hypertension and they are furthermore indicated to reduce events and target organ damage in patients with diabetes and chronic kidney disease, where they have specific indication because of the evidence of benefit. RAASi therapy, however, is associated with an increased risk of hyperkalaemia. Patients with chronic kidney disease and HF are at increased risk of hyperkalaemia and ~50% of these patients experience two or more yearly recurrences. A substantial proportion of patients receiving RAASi therapy have their therapy down-titrated or more often discontinued even after a single episode of elevated potassium (K^+) level.

Since RAASi therapy reduces mortality and morbidity in patients with cardiovascular disease steps should, when hyperkalaemia develops, be considered to lower K^+ level and enable patients to continue their RAASi therapy. The use of such measures are especially important in those patients with the most to gain from RAASi therapy.

Keywords

Potassium, hyperkalaemia, renin angiotensin aldosterone inhibitors, mineralocorticoid, mineralocorticoid antagonist, heart failure, arterial hypertension, chronic kidney disease

Potassium (K^+) is the most abundant cation in the body (50-75 mEql/kg body weight). Under physiological conditions, approximately 98% of total body K^+ is located in the intracellular space and only 2% in the extracellular space. Hyperkalaemia defined as serum or plasma K^+ > 5 mmol/L (for K^+ 1 mmol/L = 1 mEq/L) is a common electrolyte disorder that may develop due to increased K^+ intake, reduced K^+ excretion and shift of K^+ from intracellular to extracellular space.

Food is the primary source of K^+ intake with the relative amounts of K^+ differing greatly between foods. The highest amounts of K^+ are found in fruits, vegetables and meat. However, a sometimes overlooked dietary K^+ source comes from salt substitutes (i.e. Na^+ chloride substituted by K^+ chloride) and nutritional supplements. High K^+ intake may cause hyperkalaemia if renal K^+ excretion is impaired.

The kidneys are, under normal conditions, responsible for up to 90-95% of K^+ elimination with the colon being responsible for the majority of the remaining K^+ excretion. However, the colonic excretion of K^+ increases when renal function worsens. In fact, in patients with end-stage renal disease faecal K^+ secretion is 3-fold greater as compared to patients with normal renal function. This finding suggests that the colon might assume an accessory K^+ excretory role and a modest compensatory mechanism for reduced renal K^+ excretion. While long-term regulation of K^+ levels occurs mainly in kidneys, short-term regulation mainly occurs in skeletal muscles.

Several common clinical conditions and drugs **(Table 1)** are known to cause or aggravate hyperkalaemia. Amongst these drugs, Renin angiotensin aldosterone system inhibitors/antagonists/blockers (RAASi) are those most frequently associated with hyperkalaemia in patients with cardiovascular disease, but against this must be counter-balanced with the fact that they are among the drugs that confer the most significant survival benefit in patients with cardiovascular disease [1-8] .

Guidance on how best to direct the management of cardiovascular patients in the sub-acute (post-emergency) and chronic phases of hyperkalaemia is in increasing demand due to the increasing use of RAASi. This document is an expert consensus on the optimum management of hyperkalaemia in the post-emergency phase in patients with cardiovascular disease, especially in those receiving or having a compelling indication to receive RAASi.

Hyperkalaemia

K^+ levels were traditionally measured in serum from coagulated blood but are now more often measured in plasma from heparinised blood. Serum levels may be up to ½ mEq/L higher than plasma levels. This is especially the case for high values. In addition, errors associated with blood sampling may also cause erroneously high K^+ levels. These factors must be taken into consideration by the clinician, and must be clarified in any scientific study on hyperkalaemia. In the present document, we mostly use the expression K^+ level since it is unclear in many studies, what was actually measured.

The severity of hyperkalaemia can be classified as mild (>5.0 to <5.5 mEq/L) to moderate (5.5 to 6.0 mEq/L) and to severe at thresholds (>6.0 mEq/L) **(Figure 1)**. The risk for the development of arrhythmic emergencies and sudden arrhythmic death in patients with hyperkalaemia is widely variable as life-threating arrhythmias may occur at different thresholds and vary between different patients. Often K^+ levels up to 6 mEq/L are found in patients without any signs of arrhythmia, especially if they have chronic kidney disease, diabetes or heart failure. In these patients, hyperkalaemia is often incidentally discovered whilst performing routine blood tests. Besides, the definition based on K^+ levels, hyperkalaemia can be classified as acute or chronic or recurrent according to the onset and the number of hyperkalaemia episodes experienced. Chronic or recurrent hyperkalaemia is defined as K^+ levels >5 mEq/L repetitively measured over a one-year period. Pseudo-hyperkalaemia refers to high K^+ level in the test tube without hyperkalaemia in the body. This may be caused by release of K from blood or tissue during sampling. If pseudo-hyperkalaemia is suspected measurement should be repeated with blood sampled appropriately or eventually taken as an arterial sample. In case of haemolysis, the clinician should consider whether it occurs in the test tube or in the body [6-10].

The occurrence of hyperkalaemia differs between in- and outpatients. It is present in 2-4% of the general population, and in 10-55% of patients hospitalized for any cause depending on the K^+ level used to define hyperkalaemia in the different studies. Both the prevalence of hyperkalaemia and risk of recurrence increase as severity and number of comorbidities increase [11-28]. The incidence of hyperkalaemia increases with the severity of renal impairment, it is often iatrogenic, caused by concurrent drugs and nutritional/herbal supplements **(Table 1)**. In clinical practice, hyperkalaemia occurs in up to 73% of patients with advanced chronic kidney disease and in up to 40% of patients with chronic heart failure. It

leads to more frequent hospitalisations and increased mortality, especially when stringent monitoring is not performed [3,5,11-35].

Hyperkalaemia frequently occurs in patients with cardiovascular diseases (e.g. heart failure, arterial hypertension, coronary artery disease), in particular when combined with renal function impairment, diabetes and advanced age. Hyperkalaemia may be responsible for cardiac arrhythmias leading to cardiac arrest and death, with a resulting mortality rate of up to 30%. Severe hyperkalaemia is an independent predictor of all-cause and in-hospital mortality and hospitalizations.

Life-threatening hyperkalaemia requires immediate treatment with a combination of calcium carbonate and hyperosmolar sodium (if the individual has hyponatraemia) to stabilise the myocardial cell membrane; insulin w/wo glucose and/or beta adrenoceptor agonists (e.g. salbutamol) (off-label use in some EU Countries) and sodium bicarbonate to transfer K^+ into the cells [17,22,30,36]. However, insulin salbutamol, and bicarbonate do not increase K^+ excretion and only provide temporary benefit (1-4 hours). Thus, rebound hyperkalaemia can occur after 2 hours. This suggests that treatment with a K^+ lowering agent should be initiated as early as possible. Loop diuretics and potassium binders [mainly sodium polystyrene sulfonate (SPS), calcium polystyrene sulfonate (CPS) or patiromer sorbitex calcium (PSC) (Veltassa®) or sodium zirconium cyclosilicate (SZC) or (ZS-9)] can be used to promote the excretion via renal or gastrointestinal route, respectively. K^+ increasing medicine should be stopped and K^+ intake via food, drinks etc. should be reduced to a minimum. If these measures are ineffective, haemodialysis may be needed (**Table 2**).

Despite being recommended for use, RAASi drugs are unfortunately seldom re-instated following an episode of hyperkalaemia at or after discharge even if a different clear precipitating cause of hyperkalaemia was detected and eliminated. The most common clinical scenario is that doses of RAASi are reduced, or they are simply discontinued; this is particularly true for MRAs. Although RAASi dose reduction or discontinuation may reduce the risk of reoccurrence of hyperkalaemia, discontinuation of RAASi is associated with an increased risk of worsening of the underlying cardiovascular condition and mortality [13,14,37-39].

RAASi and hyperkalaemia

RAASi are the cornerstone of the treatment of patients with cardiovascular diseases (heart failure with reduced ejection fraction (HFrEF), arterial hypertension, coronary artery disease,

myocardial infarction (MI), left ventricular (LV) hypertrophy), with a class IA recommendation in current clinical guidelines due to the proven reduction of mortality and morbidity in HFrEF [16,20,40]. RAASi are the basis of the treatment of arterial hypertension, and in hypertensive patients an MRA must be implemented before resistant hypertension is diagnosed [15]. RAASi are also indicated to reduce events and target organ damage in patients with diabetes and chronic kidney disease where they have a specific indication because of the overwhelming evidence of benefit [15,17].

Since RAASi increase K^+ levels, RAASi-induced hyperkalaemia often limits the use of these drugs thereby offsetting their survival benefits. In hypertensive patients without risk factors for hyperkalaemia, the incidence of hyperkalaemia with RAASi monotherapy is $\leq$2% and increases to ~5% with dual RAAS inhibition and to 5%-10% when dual therapy is administered in patients with heart failure or chronic kidney disease [14,31]. According to current guidelines MRAs should be implemented in therapy after an ACEi (or an ARB in intolerant patients) has been already initiated [15-17]. In patients with chronic HFrEF, in NYHA functional class II, and meeting specific inclusion and exclusion criteria, including an eGFR >30 ml/min/1.73 m^2 and K^+ level <5.0 mmol/L, eplerenone was both efficacious and safe when carefully monitored, even in subgroups at high risk of developing hyperkalaemia or worsening renal function [13]. Furthermore, in the RALES trial, the benefit of spironolactone was maintained in the setting of moderate hyperkalaemia, and clinical outcomes with spironolactone were superior to placebo when K^+ levels remained <6.0 mEq/L [41]. In this trial, 13.5% and 40% of participants exhibited hyperkalaemia when treated with 25 and 50 mg daily of spironolactone. This finding suggests that limiting the maximum dose to 25 mg daily may reduce the risk of hyperkalaemia and argues against automatic discontinuation of MRAs when K^+ levels rise >5.0 mmol/L. Indeed, the clinical benefit of spironolactone and eplerenone remained even in those who developed modest elevations in K^+ level in the RALES and EMPHASIS-HF trials [14,38,39]. Up to one third of New York Heart Association (NYHA) class II-IV heart failure patients starting an MRA develop hyperkalaemia (>5.0 mEq/L) over two years [14,42,43].

Patients with cardiovascular disease and chronic kidney disease are at risk of hyperkalaemia and ~50% of these patients have two or more recurrences within 1 year [42-45]. Incidence rates of hyperkalaemia have been shown to be higher in HFrEF patients on MRA in the real world setting than in clinical trials (6-12%), i.e. when they are administered to higher-risk and unselected populations which did not receive K^+ level and/or creatinine monitoring [44-47]. In

the real world setting the incidence of hyperkalaemia can be as high as 50% in unselected population of patients receiving RAASi [32, 34]. Despite this evidence and guideline recommendations, K+ levels are frequently under-monitored in patients treated with RAASi [35,48]. Therefore, quality improvement programs are needed to improve rates of laboratory monitoring for patients initiated on MRA therapy, particularly in high-risk patients.

Hyperkalaemia and discontinuation of RAASi

Hyperkalaemia or borderline high K^+ levels are, together with symptomatic hypotension and worsening renal function, the main reasons that result in discontinuation, dose reduction or even non-initiation of RAASi therapy in patients with renal and cardiovascular diseases offsetting the survival benefits conferred by these drugs.

A substantial proportion of heart failure (HF) patients are facing a RAASi dose adjustment even after a single instance of elevated serum K^+ levels. According to the European Society of Cardiology Heart Failure Long-Term Registry recruiting 12,440 patients with HFrEF, RAASi were used in 92.2% and 67.0% of patients, respectively [48]. Less than one-third of patients were on guideline-recommended target doses (29.3% for ACEi, 24.1% for ARB and 30.5% for MRA). In about a third of the patients not achieving the target dosages, a clear reason was not reported (28.8% for ACEi, 29.3% for ARB, and 46.9% for MRA). Hyperkalaemia was the reason for non-use of ACEi/ARB and MRA in 8.5% and 35.1% of patients, respectively [48].

Among patients with chronic kidney disease RAASi were prescribed at the target guideline recommended dose in 19% to 26% of patients, at submaximal dose in 58% to 65% of patients and were discontinued during follow-up in 14% to 16% of patients [49]. Cardio-renal adverse events/mortality and mortality occurred in 34.3% and 11.0% of patients who discontinued RAASi inhibitors, 24.9% and 8.2% of patients on submaximal doses, and 24.9% and 4.1% of patients on maximum doses, respectively [49].

Recently, the BIOSTAT-CHF reported that only 22% of patients with HFrEF achieved the recommended treatment dose for ACEi /ARB [50]. Reaching <50% of the recommended dose of ACEi/ARB doses was associated with an increased risk of death and/or heart failure hospitalization compared with patients reaching ≥100% [50].

The importance of guideline adherence on prognosis has been recently highlighted by the QUALIFY global survey in 7,092 patients with HFrEF [51]. In this registry good adherence to guidelines was associated with a significant prognostic benefit, the adherence score was good

in 67%, moderate in 25%, and poor in 8% of patients and the proportion of patients at target dose and at ≥50% of target dose was 27.9% and 63.3% for ACEi and 6.9% and 39.5% for ARBs, respectively [51].

Data from registries usually provide a more accurate picture than clinical trials on 'real life' situations. However, even registries can identify populations that are receiving better care compared to the general population. Indeed, a recent comparison of patients enrolled and those not enrolled in the Swedish Heart Failure Registry showed that survival was substantially higher in the registry setting, and this was most likely due to better use of RAASi drugs in registry included patients [52].

Current guidelines and management of hyperkalaemia

Current clinical guidelines recommend that patients with chronic hyperkalaemia should be started on a low K^+ diet and have to be initiated on a non-K^+ sparing diuretic or if already on a diuretic, to increase the dose [53-55]. All guidelines also suggest to eliminate K^+ supplements and to discontinue drugs that compromise renal function such as NSAIDs and those that may increase K^+ levels such as RAASi therapy, especially MRAs **(Table 3).**

The ESC Heart Failure Guidelines suggest that if a short-term cessation of K^+-retaining agents and RAASi is deemed necessary, this should be minimized and RAAS inhibitors should be carefully reintroduced as soon as possible while monitoring K^+ levels [20].

As recommended by several regulatory agencies, the chronic use of SPS alone or in conjunction with sorbitol should be avoided because its prolonged use may be associated with severe gastrointestinal side effects such as bowel necrosis [56]. SPS has never undergone rigorous testing in placebo-controlled clinical trials to prove its efficacy and safety for treatment of acute or chronic hyperkalaemia [57,59]. In addition, because Na^+ is the counter exchange ion in SPS, caution is advised if it is administered to patients who do not tolerate even a small increase in Na^+ load (i.e., those with heart failure, severe hypertension, or marked oedema) [59]. Here K^+ binders with a different counter exchange ion (i.e. PSC) may be alternatives.

Consensus on the implementation of RAASi therapies in patients with episodes of hyperkalaemia

Since RAASi therapy reduces mortality and morbidity in patients with cardiovascular disease but can increase K^+ levels, therapies aimed at lowering K^+ levels and enabling patients to

continue RAASi therapy should be considered. Such an approach is already implemented in other fields of medicine, e.g in cancer where symptomatic therapy is used to enable use of cancer directed therapy (antiemetics and cytostatic drugs). The use of such an approach in patients with cardiovascular disease, who develop hyperkalaemia or borderline high K^+ level under RAASi therapy may be of benefit to many including those who benefit most from RAASi therapy.

Thus, the recent availability of two new effective and safe K^+ binders, PSC (Veltassa®) approved for clinical use in Europe and the USA, and sodium zirconium cyclosilicate (SZC) or (ZS-9), approved by European Medicines Agency (EMA) and under final stages of review (at the moment of writing of this manuscript) by United States Food and Drug Administration (US-FDA), are both developed to increase faecal K^+ excretion mainly in the colon, and open new opportunities for the treatment of hyperkalaemia [60,61]. In clinical trials, both compounds have been shown to be effective to normalize elevated K^+ levels, maintain normo-kalaemia over time and prevent the recurrences of hyperkalaemia in patients with hyperkalaemia on RAASi therapy [62,68].

Therefore, for most patients with cardiovascular disease and chronic or recurrent hyperkalaemia, RAASi therapy should be optimised whenever possible and treatment with PSC or SZC (when approved) may be initiated. In the absence of clinical guidelines and of ad hoc randomised clinical trials with hard end points this consensus is based on inferred available evidence but will need to be confirmed by appropriate clinical trials [69-70] .

In patients with hyperkalaemia an evaluation should be made of the patient´s diet, use of supplements, salt substitutes and nutraceuticals that contain K^+ as well as of concomitant medications that may contribute to hyperkalaemia. Co-administration of drugs known to promote hyperkalaemia or reduce kidney function are not absolute contraindications but should prompt more frequent monitoring of K^+ levels. Kidney function must be determined and monitored. A low-K^+ diet and loop or thiazide diuretics that increase K^+ excretion to reduce the occurrence of hyperkalaemia may be considered. Whenever K^+ lowering therapy is initiated K^+ levels should be closely monitored not only to follow the K^+ lowering effect, but also to protect against development of hypokalaemia, which may be even more dangerous than hyperkalaemia.

In general, RAASi therapy should be started at a low dosage starting an ACEi (ARB when indicated) first and an MRA thereafter and titrated to the maximum tolerated evidence-based

doses shown to reduce the risk of cardiovascular and renal events in clinical trials.

In patients with K^+ levels between 4.5 and 5 mEq/L not on maximum tolerated, guideline-recommended target dose of RAASi therapy, it is recommended to titrate/start RAASi therapy and closely monitor K^+ levels. If K^+ levels raise above 5.0 mEq/L, K^+ lowering measures should be initiated.

In patients with as K^+ levels >5 on maximum tolerated, guideline-recommended dose of RAASi therapy, treatment with a K^+ lowering agent may be initiated as soon as K^+ levels >5 mEq/L. K^+ level should be monitored according to the clinical status and K^+ lowering treatment should be maintained unless another aetiology for hyperkalaemia is identified.

Finally, in patients with K^+ levels >5 mEq/L not on maximum tolerated, guideline-recommended target dose of RAASi, therapy with K^+ lowering agents should also be initiated and when K^+ levels are <5 mEq/L titration of RAASi therapy should be implemented. Thereafter, K^+ levels and renal function should be closely monitored and drug dose adjusted **(Figure 2)**.

Conclusion

This consensus document is based on the available evidence and on expert opinion on the beneficial effect of RAASi therapies in patients with cardiovascular disease. The use of the new K^+ lowering agents may be of help in optimising RAASi therapies in patients with hyperkalaemia or at increased risk of developing it. However, the benefit of K^+ lowering agents enabling and optimizing RAASi therapies on long term outcomes should be further evaluated in randomised clinical trials.

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Table 1

Drugs/substances that may cause hyperkalaemia

1. **Decreased potassium excretion:**
    a. Potassium-sparing diuretics (eg, spironolactone, triamterene, amiloride)
    b. Beta-blockers
    c. NSAIDs
    d. Sacubitril/valsartan
    e. Renin-angiotensin-aldosterone inhibitors (RAASi): ACE inhibitors, Angiotensin-receptor blockers, mineralocorticoid receptor antagonists
    f. Direct Renin inhibitors (Aliskiren)
    g. Mannitol
    h. Cyclosporine or tacrolimus
    i. Pentamidine
    j. Trimethoprim-sulfamethoxazole
    k. Heparin
    l. Digitalis
    m. Calcineurin inhibitors
    n. Penicillin G
2. **Increased potassium intake/administration**
    a. Potassium Supplements
    b. Salt Substitute (e.g. DASH)
    c. Fruits (Bananas, melons, orange juice)
    d. Alfalfa
    e. Amino Acids (Aminocaproic acid, Arginine, Lysine)
    f. Dandelion
    g. Dried toad skin
    h. Hawthorne Berry
    i. Horsetail
    j. Liliy of the Valley
    k. Milkweed
    l. Nettle
    m. Noni Juice
    n. Siberian Ginseng
    o. Stored blood products

Table 2

Treatment of acute or chronic hyperkalaemia

Promote uptake of K^+ into the intracellular space	Stimulate Na+/K+-ATPase: • β2-adrenergic agonists (IV, nebulized) • Insulin (IV) ± glucose • Sodium bicarbonate (if metabolic acidosis) • Combination cocktails
Cardiac membrane stabilization	• Calcium chloride or gluconate (IV) • Hypertonic saline (3%-5%)
Increase K^+ elimination	• Loop diuretics (IV, oral) to increase renal K^+ excretion • Hemodialysis for removal of K^+ from blood • Cation-exchange resins (sodium polystyrene sulfonate) to enhance fecal K^+ excretion (PO, PR) • Sodium bicarbonate alkalinizes the urine and increases urinary K^+ excretion • New K^+ binders: patiromer, sodium zirconium cyclosilicate
Other	• Fludrocortisone (PO) in aldosterone deficiency

IV: intravenous. PO: per os (orally). PR: per rectum

Table 3

Existing recommendations on RAASi use according to K^+ levels

K^+ levels	Recommendation
>6	Stop RAASi (ESC HF [20], NICE [7])
>5.5 mEq/L	Reduce dose of/stop ACEI/ARB (K/DOQI [55-57])
5.1-5.5	K/DOQI (e): take measures to lower K^+ when initiating RAASI
>5	Do not start RAASis if >5.0 (K/DOQI [55-57], HFSA HF [63], NICE [7])
	Reduce dose of/stop RAASi if >5-0 (ACCF/AHA HF [18], ESC HF [20], K/DOQI [55-57])
	MRA not recommended if >5.0 (HFSA HF [63])
	Maintain MRA between 4.0-5.0 (ACA/AHA [18])
	Do not routinely offer a RAASi to people with CKD if their pre-treatment K^+ levels are > 5.0 mEq/L A K^+ lowering agent should be started.
4.5-5	In patients not on maximal guideline-recommended target dose of RAASI therapy, it is recommended to up-titrate/start RAASi therapy and closely monitor K^+ levels.

Figure 1

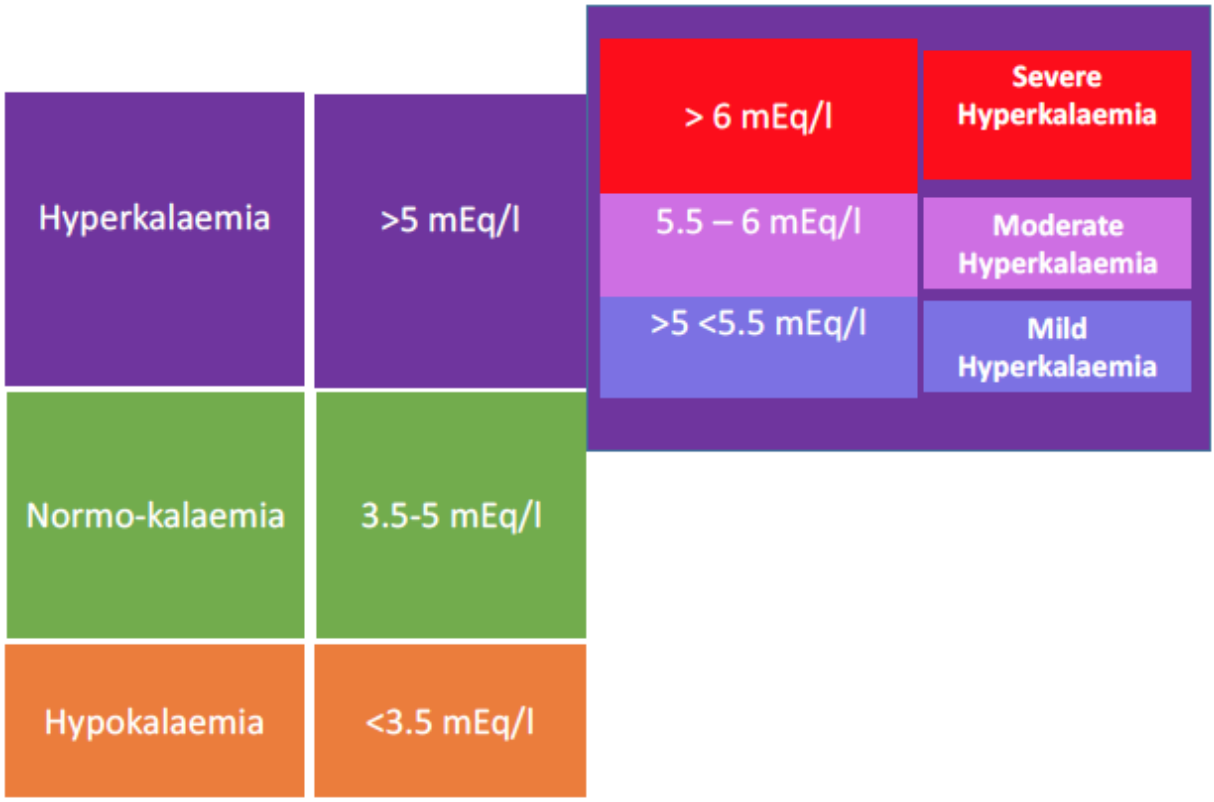

Figure 2

Flow diagram on the management of hyperkalaemia in patients with indication for RAASi

Patients	Recommendation
Chronic or recurrent hyperkalaemia on RAASi therapy	An approved K^+-lowering agent may be initiated as soon as K^+ levels are confirmed as >5.0 mEq/L. Closely monitor K^+ levels. Maintain treatment unless alternative treatable aetiology is identified
Chronic or recurrent hyperkalaemia not on maximal tolerated guideline-recommended target dose of RAASi	RAASi should be optimised and an approved K^+-lowering agent may be initiated as soon as confirmed K^+ levels are >5.0 mEq/L. Closely monitor K^+ levels. Maintain treatment unless alternative treatable aetiology is identified
K+ levels of 4.5–5.0 mEq/L not on maximal tolerated, guideline-recommended target dose of RAASi therapy	Initiate/up-titrate RAASi therapy and closely monitor K^+ levels. If K^+ levels rise above 5.0 mEq/L, initiate an approved K^+-lowering agent
K+ levels of >5.0–≤6.5 mEq/L not on maximal tolerated, guideline-recommended target dose of RAASi therapy	Initiate an approved K^+-lowering agent. If levels <5.0 mEq/L are detected, up-titrate RAASi - K+ level should be closely monitored and K+ lowering treatment should be maintained unless another aetiology for hyperkalaemia is identified
K+ levels of >5.0–≤6.5 mEq/L on maximal tolerated, guideline-recommended target dose of RAASi therapy	Treatment with a K^+ lowering agent may be initiated. K^+ level should be closely monitored and K+ lowering treatment should be maintained unless alternative treatable aetiology for hyperkalaemia is identified
K+ levels of >6.5 mEq/L on either maximal sub-maximal tolerated, guideline-recommended target dose of RAASi therapy	Discontinue/reduce RAASi. Treatment with a K^+ lowering agent may be initiated as soon as K^+ levels >5.0 mEq/l. K^+ level should be closely monitored

Legends

Table 1
Drugs/substances that may cause hyperkalaemia.
NSAIDs=non-steroidal anti-inflammatory drugs
DASH= Dietary Approach to Stop Hypertension

Table 2
Treatment of acute or chronic hyperkalaemia.
Na= sodium, K=potassium, IV= intra-venous, PO= per os, PR= per rectum

Table 3
Existing recommendations on RAASi use according to serum K+ levels
RAASi= Renin angiotensin aldosterone system inhibitor
K=potassium
MRA= mineralocorticoid receptor antagonists

Figure 1
Definitions of normo-kalaemia, hyperkalaemia and hypokalaemia.
Hyperkalaemia can be classified as mild, moderate or severe. Thresholds for the definition of the severity of hyperkalaemia differ between different classifications. This may mainly be due to different methods used to determine K^+ levels

Figure 2
Flow diagram on the management of hyperkalaemia in patients with indication for RAASi therapy.