

Expert Opinion on the Management of Hyperkalemia in Patients with Cardiorenal Diseases Treated with Renin Angiotensin Aldosterone System Inhibitors: An Indonesian Perspective

Pringgodigdo Nugroho^{1*}, Aida Lydia¹, Haerani Abdul Rasyid², Zulkhair Ali³, Pranawa⁴, Nyoman Paramita Ayu⁵, Birry Karim⁶, Erwin Sukandi⁷, Siti Elkana Nauli⁸, Hary Sakti Muliawan⁹, Edrian Zulkarnain¹⁰

¹Division of Nephrology and Hypertension, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia.

²Division of Nephrology and Hypertension, Department of Internal Medicine, Faculty of Medicine, Universitas Hasanuddin, Makassar, Indonesia.

³Division of Nephrology and Hypertension, Department of Internal Medicine, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia.

⁴Division of Nephrology and Hypertension, Department of Internal Medicine, Faculty of Medicine Airlangga University, Surabaya, Indonesia.

⁵Division of Nephrology and Hypertension, Department of Internal Medicine, Faculty of Medicine, Universitas Udayana, Denpasar, Indonesia.

⁶Division of Cardiology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia.

⁷Division of Cardiology, Department of Internal Medicine, Faculty of Medicine Universitas Sriwijaya, Palembang, Indonesia.

⁸Department of Cardiology and Vascular Medicine, Tangerang District Hospital, Tangerang, Indonesia.

⁹Department of Cardiology and Vascular Medicine, Cardiologist, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia.

¹⁰Department of Cardiology and Vascular Medicine, Mohammad Hoesin General Hospital, Palembang, Indonesia.

*Corresponding Author:

Pringgodigdo Nugroho, MD., PhD. Division of Nephrology and Hypertension, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia. Jl. Salemba Raya No. 6, Jakarta 10430, Indonesia. Email: pringgodigdo.nugroho@ui.ac.id

ABSTRACT

Hyperkalemia (serum potassium >5.0 mEq/l) is a significant complication in patients with heart failure, chronic kidney disease, and diabetes mellitus, particularly when treated with renin-angiotensin-aldosterone system inhibitors (RAASi). Both hyperkalemia and RAASi interruption are associated with increased cardiovascular events, hospitalizations, and mortality. This expert opinion document, developed between January and December 2024 through a systematic process, aims to establish guidance for hyperkalemia treatment in Indonesian patients with cardiorenal diseases receiving RAASi therapy, addressing the unique challenges within the Indonesian healthcare context. A comprehensive literature review of international guidelines and regional studies was conducted by a panel of 11 expert specialists (3 cardiologists, 6 internist-nephrologists, and 2 internist-cardiologists), who evaluated 29 statements covering diagnosis, monitoring, prevention, and treatment of hyperkalemia. Of the 29 statements, 26 reached consensus: 17 statements achieved very high agreement

($\geq 90\%$) and 9 attained high agreement ($\geq 67\% - < 90\%$). The agreed statements covered key areas, including potassium monitoring frequency, RAASi dose optimization strategies, dietary modifications, and treatment thresholds. Three statements regarding alternative therapeutic approaches did not receive agreement ($< 67\%$) due to limited local availability and cost considerations. Key recommendations include structured monitoring protocols for high-risk patients, strategies for RAASi dose optimization while managing hyperkalemia risk, and specific interventions adapted to local resources. This document provides a practical approach for managing hyperkalemia in Indonesian patients with cardiorenal diseases while maintaining optimal RAASi therapy, considering local Indonesian healthcare resources and constraints.

Keywords: Hyperkalemia, Cardio-Renal Syndrome, Renin-Angiotensin System, Indonesia.

INTRODUCTION

Hyperkalemia is a potentially life-threatening electrolyte disorder defined as a serum potassium level exceeding 5.0 mEq/L; it occurs if the kidneys cannot efficiently excrete potassium since the body cannot move potassium out of circulation into cells.¹⁻³ KDIGO 2024 guidelines classify the severity of acute hyperkalemia based on potassium concentration along with ECG changes. Hyperkalemia is mild when there exist potassium concentration values of 5.0-6.0 mmol/L lacking ECG changes, yet hyperkalemia is severe when there exist potassium concentration values of 6.1-6.5 mmol/L showing ECG changes.⁴ Hyperkalemia may be classified as either acute or chronic/recurrent according to the onset, and also according to the number of hyperkalemia episodes experienced – K⁺ levels that are > 5 mEq/L repetitively measured over just 1 year define chronic or recurrent hyperkalemia. Severe cases can lead to mortality or paralysis or muscle weakness or cardiac arrhythmias that threaten life, though most cases are asymptomatic, particularly with mild hyperkalemia.^{1,5,6}

Global epidemiological data reveal important regional variations in hyperkalemia prevalence. A recent systematic review as well as meta-analysis reported that the worldwide prevalence was 6.3% (95% CI, 5.8%–6.8%) while Asia showed a higher prevalence (10.4%) than Europe (5.9%) or North America (5.0%). This prominent change implies possible risk factor disparities. Different regions can have different kinds of healthcare practices and monitoring strategies. The higher Asian prevalence warrants particular attention in developing region-specific management approaches. In Indonesia, while nationwide

prevalence data are limited, a recent single-center study in Jakarta demonstrated significant hyperkalemia occurrence among hemodialysis patients, with age and hyperphosphatemia identified as key associated factors.⁸ On the other hand, for non-hemodialysis patients, another unpublished single-center observational data also showed as high as 15% incidence of hyperkalemia among Heart Failure patients. These local data, although limited in scope, highlight the need for more comprehensive surveillance and management strategies within the Indonesian healthcare context.

Hyperkalemia commonly affects patients with cardiovascular diseases such as hypertension, heart failure, coronary artery disease, renal impairment, and diabetes.^{7,9,10} These conditions often coexist, creating a complex clinical scenario that requires careful management. The risk of hyperkalemia is particularly pronounced in patients with reduced kidney function, as the kidneys play a crucial role in maintaining potassium homeostasis.¹¹⁻¹³ A significant contributor to hyperkalemia risk is the use of renin-angiotensin-aldosterone system inhibitors (RAASi), including ACE inhibitors, ARB, MRA, and ARNI.^{14,15} These medications represent cornerstone therapies in heart failure and renal disease management, demonstrating significant benefits in reducing mortality, morbidity, and disease progression by involving the inhibition of aldosterone-dependent potassium excretion, which can lead to potassium retention.^{11,14}

Hyperkalemia management approaches vary based on severity and presentation. Acute cases require immediate intervention

through cardiac monitoring (as there is risk of arrhythmia), membrane stabilizing agents, insulin-glucose combination, administration of adrenoceptor agonist, sodium bicarbonate, potassium-binding agents, or emergency dialysis. The urgency of intervention is determined by potassium levels, the presence of ECG changes, and clinical symptoms.^{4,16} Chronic management involves dietary modifications through controlled potassium intake, nutritional counselling, and regular dietary assessment.¹⁷ Pharmacological interventions include diuretic therapy optimization, use of potassium binders, RAASi dose modification, and elimination of other contributing medications, such as NSAIDs. Regular monitoring of potassium levels, ECG monitoring in high-risk patients, and renal function surveillance are essential.¹⁶ It is mandatory to manage all underlying diseases and comorbidities experienced by the patient.

Traditional approaches focusing on RAASi dose reduction or discontinuation have been challenged by recent evidence showing increased hospitalization rates as well as mortality.^{19,20} This finding has led to a paradigm shift in management strategies, emphasizing the importance of maintaining RAASi therapy while implementing effective hyperkalemia prevention and treatment measures. Managing hyperkalemia in Indonesia is uniquely challenging due to regional disparities in healthcare access, limited facilities, and cost issues in chronic disease management. Clinical practices vary in guideline adherence, resource availability, and the need for localized protocols. Patient factors include cultural dietary habits, socioeconomic impacts on medication access, and differing health literacy levels.

While the 2023 Heart Failure Guideline from the Indonesian Heart Association addresses hyperkalemia management briefly,²¹ a multispecialist expert opinion is needed for managing RAASi therapy in the context of current, imminent, or previous hyperkalemia episodes. A multidisciplinary panel of Indonesian internist-nephrologists, internist-cardiologists, and cardiologists was convened to develop evidence-based expert opinion for managing hyperkalemia in patients with cardiorenal diseases requiring RAASi therapy. This expert

opinion aims to provide guidance on maintaining optimal RAASi therapy, address specific challenges in the Indonesian healthcare context, implement practical monitoring strategies, define clear thresholds for intervention, and represents a crucial step toward improving the care of patients with cardiorenal diseases in Indonesia.

KEY AREAS AND PRACTICAL RECOMMENDATIONS IN HYPERKALEMIA MANAGEMENT

Strong expert opinion reflects alignment in hyperkalemia management approaches among cardiorenal specialists across Indonesia's diverse healthcare landscape. This alignment is underpinned by recognizing the predictable and manageable nature of hyperkalemia in cardiorenal disease, especially as the prevalence of hyperkalemia in Asian populations (10.4%) exceeds global rates (6.3%).⁶ The current perspectives are consistent with international guidelines, including KDIGO 2022 for diabetes management in CKD²⁷ and ESC 2021 HF guidelines,²⁸ but adapted for Indonesia's multilayered healthcare system, spanning primary health centers to tertiary referral hospitals.

A crucial understanding is that hyperkalemia risk increases in patients with chronic kidney disease, heart failure, or diabetes, especially when treated with RAASi.^{8,29} This understanding is even more relevant in Indonesia, where healthcare delivery differs between urban and rural areas. Urban centers may have regular access to laboratory monitoring and specialist care, while rural facilities face limitations in diagnostic capabilities and specialist access.³⁰ High agreement on risk stratification approaches signals a shared commitment to continuing optimal RAASi therapy despite hyperkalemia concerns^{8,31} and marks an important shift from previous practice, where hyperkalemia episodes often led to immediate withdrawal of beneficial therapies.

In prevention strategies, there is high support for dietary counseling and medication review protocols. However, some recommendations are controversial, such as the prophylactic use of novel potassium binders in high-risk

but normokalemic patients. The ongoing debate reflects both clinical and health-economic considerations, as well as the varying capabilities of Indonesia's healthcare institutions. The implementation of preventive strategies must consider Indonesia's healthcare system^{32,33}, which has protocols feasible within its resource environment. This fact calls for primary care facilities, the main point of patient contact, to implement practical strategies, while secondary and tertiary hospitals may incorporate more advanced preventive and management options.

A pragmatic preference among Indonesian experts is the prioritization of intensive monitoring strategies over routine use of prophylactic interventions, particularly where economic and logistic constraints exist. This is important considering the challenges involved in implementing strict dietary potassium limitations, which may conflict with heart-healthy diets like DASH³⁴ and carry significant psychosocial burdens for patients.³⁵⁻³⁷ Recognizing that local diets are diverse and deeply rooted in tradition^{38,39}, effective dietary guidance must be sensitive and tailored to each region's dietary cultures.

For correction strategies, particularly the treatment of established hyperkalemia, there is strong agreement on following standardized protocols, such as proposed by Palmer et al.⁴⁰ Nevertheless, implementation must be tailored based on resources of each type of healthcare setting: tertiary hospitals can deploy more comprehensive protocols, while smaller facilities require practical, actionable guidelines for initial management and clear criteria for referral to higher-level care.

Some issues remain, including perception of hyperkalemia as a barrier to therapy optimization and the need for mortality benefit data for novel potassium binders. Evolving perspectives on whether hyperkalemia should restrict RAASi optimization highlight the importance of continuing medical education and dissemination of up-to-date evidence across different healthcare settings. Current data suggest that down-titration of RAASi may reduce acute hyperkalemia risk but is associated with worse outcomes in underlying cardiorenal conditions.⁴¹⁻⁴³ While international evidence supports their role in facilitating normokalemia and enabling continued RAASi therapy,^{8,44,45} the utilization should consider cost-effectiveness in real-world contexts.

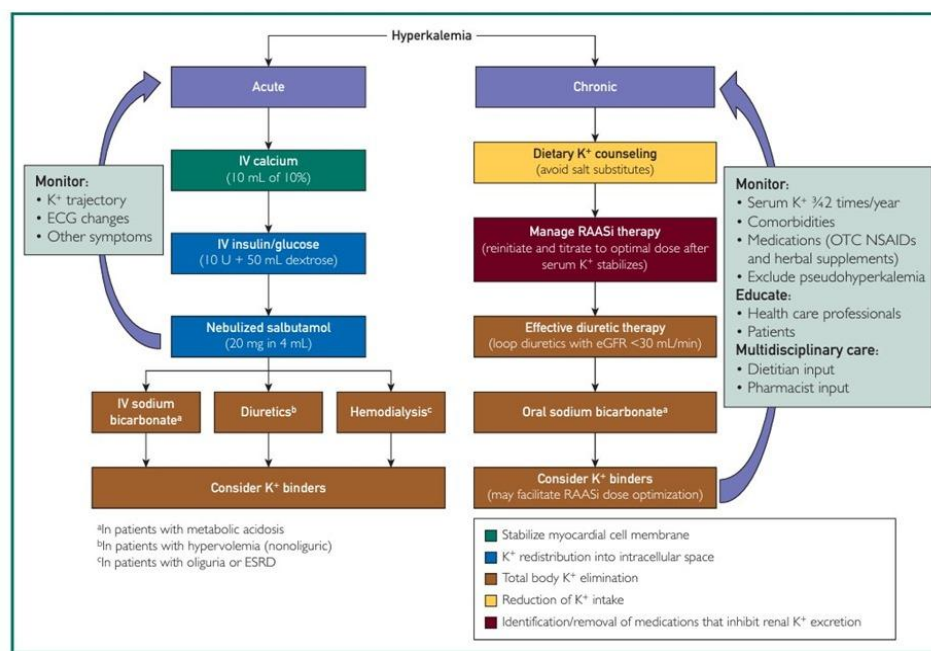


Figure 1. Treatment options for the management of acute and chronic hyperkalemia.⁴⁰

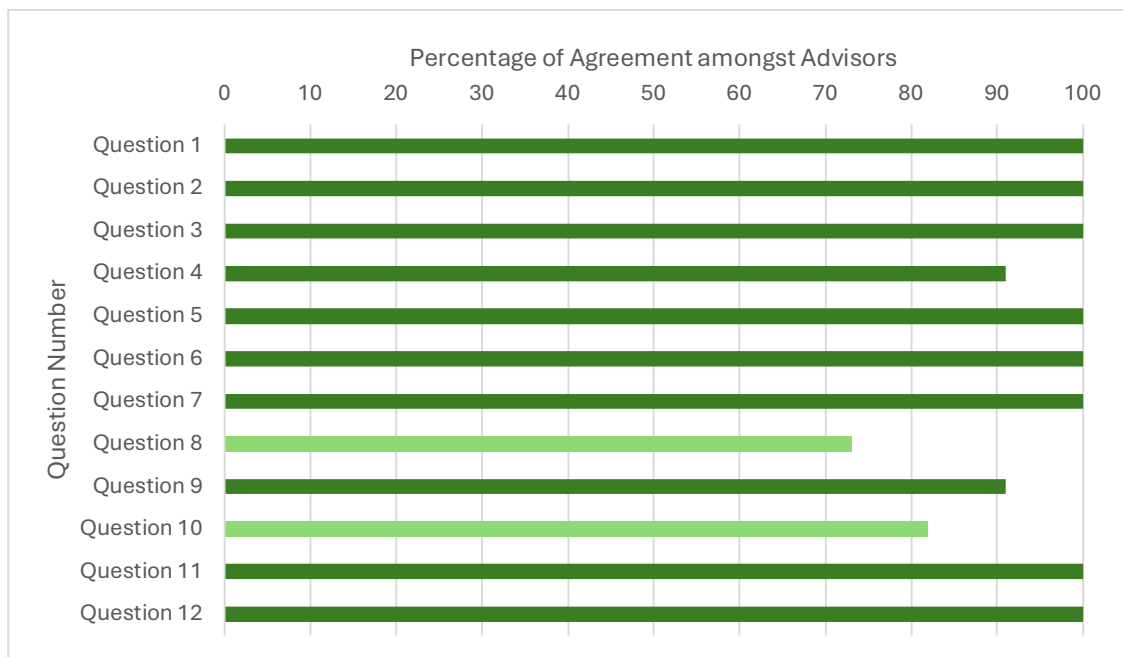


Figure 2. Levels of agreements: risk factors and risk stratification for managing hyperkalemia in cardiorenal patients (Topic A)

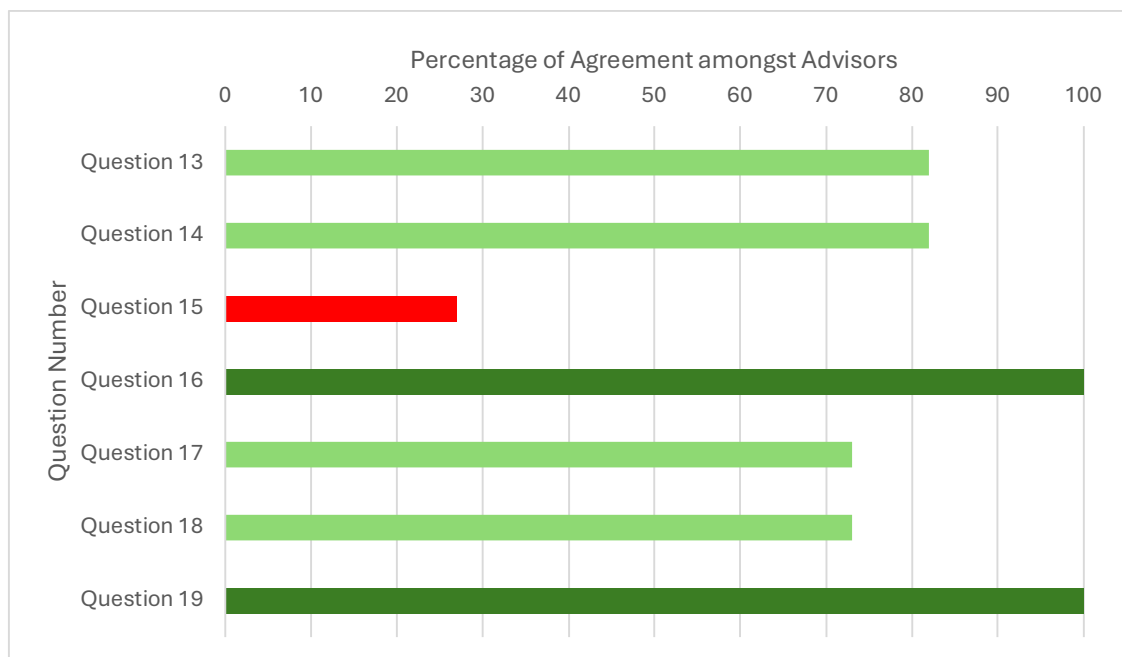


Figure 2. Levels of agreements: risk factors and risk stratification for managing hyperkalemia in cardiorenal patients (Topic A)

Moving Forward: Implementation and Research Needs

Successful hyperkalemia management, as articulated through these collective expert perspectives, depends not only on guideline

adaptation but also on improving education, communication, and referral pathways throughout Indonesia's health system. Training, resource needs, and thus strategies must be designed for flexibility; for example, tertiary centers can take

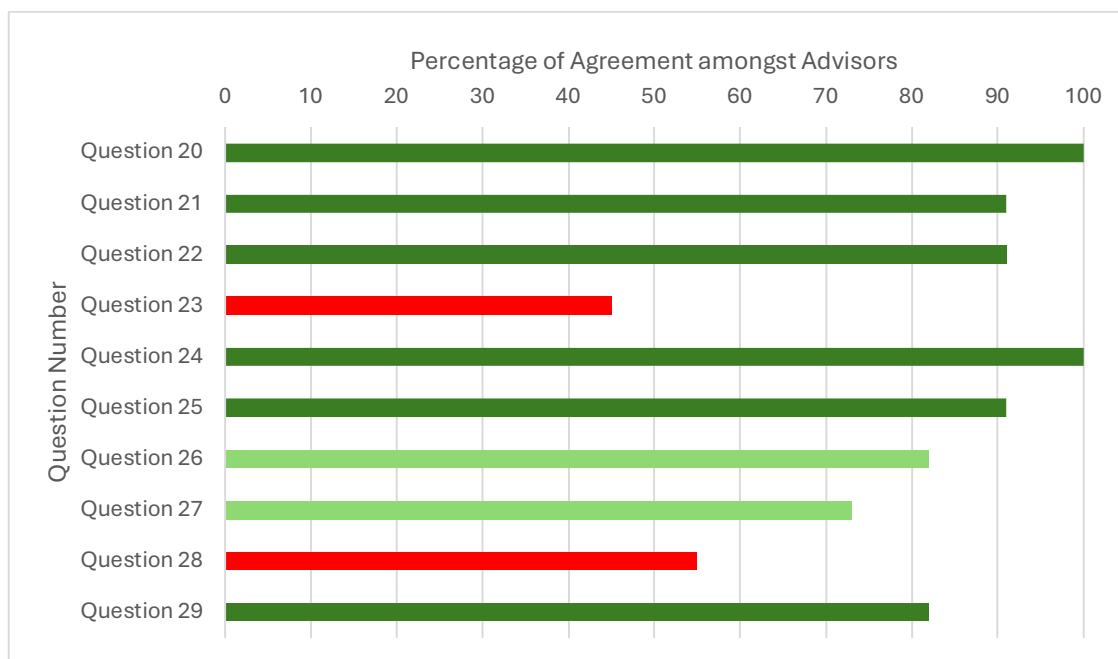


Figure 4. Levels of agreement: correction of hyperkalemia for at-risk cardiorenal patients with the potassium-lowering therapy (Topic C)

on more advanced management and monitoring roles, while primary and secondary sites must be empowered with practical protocols and clear escalation criteria.

Priorities going forward include real-world evaluation of the implementation of these practical recommendations, health-economic studies specific to the Indonesian context, and ongoing research into patient outcomes. Additional investigation into the sociocultural and dietary factors that influence hyperkalemia risk and management is needed to further tailor interventions for Indonesia's population.

CONCLUSION

This expert opinion provides evidence-based statements for managing hyperkalemia in Indonesian patients with cardiorenal diseases receiving RAASi therapy. The strong agreement across most statements demonstrates that hyperkalemia can be effectively managed without compromising essential RAASi therapy. This expert opinion aims to optimize care while considering local resources and constraints, ultimately working to improve outcomes for patients with cardiorenal diseases across Indonesia.

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CONFLICTS OF INTERESTS

The authors report participation in an advisory board for AstraZeneca Indonesia, which manufactures novel potassium binders, one of the drugs discussed in this expert opinion paper. Honoraria for this advisory role were paid to the authors.

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Supplementary Table. Questionnaire statements

No	Statement
A) Risk factors and risk stratification for managing hyperkalemia in cardiorenal patients	
1	Optimizing RAASi therapy provides better outcomes for patients.
2	Patients with chronic kidney disease, heart failure, or diabetes are at increased risk of hyperkalemia.
3	RAASi use is a risk factor for hyperkalemia.
4	Hyperkalemia can be effectively managed to optimize disease-modifying therapies, which improve morbidity, mortality, and outcomes.
5	New risk prediction tools are needed if clinicians are to fully individualize risk assessment for their cardiorenal patients.
6	Managing the risk of hyperkalemia should be part of the individualized care plan already in place or planned.
7	There is a need for consistent thresholds for defining and treating hyperkalemia among physicians.
8	Hyperkalemia is associated with down-titration or discontinuation of RAASi therapy.
9	When managing mild-to-moderate hyperkalemia in cardiorenal patients, RAASi should be maintained due to the inherent benefit in this patient type.
10	Mild-to-moderate hyperkalemia should be managed without de-escalating or discontinuing disease-modifying drugs, such as RAASi.
11	Hyperkalemia is a known and manageable side effect of RAASi treatment.
12	Hyperkalemia should be recognized as a predictable, treatable, and manageable side effect of optimal heart failure/chronic kidney disease therapy in patients with a history or at high risk of hyperkalemia.
B) Prevention of hyperkalemia for at-risk cardiorenal patients	
13	For high-risk patients currently not hyperkalemic, preventative measures should be considered (e.g., removal of salt substitutes from diet, and considering diuretics for people with hypertension or some volume expansion)
14	For those patients who have a known history of hyperkalemia, preventing optimization of RAASi therapy, a novel K ⁺ binder can be used to enable a trial of RAASi optimization.
15	For high-risk patients currently not hyperkalemic, the use of a novel K ⁺ binder can be considered when starting/up-titrating RAASi
16	Non-disease-modifying therapies that cause hyperkalemia should be avoided in patients at high risk of hyperkalemia, e.g., NSAIDs, amiloride, and herbal supplements.
17	A low K ⁺ diet is often advised to help manage K ⁺ levels, with no/little evidence to support, and is counter to a healthy diet that is beneficial to cardiorenal patients.
18	In people for whom dietary restrictions may not be appropriate or desired, the use of novel K ⁺ binders may enable a balanced diet.
19	People at risk should be monitored closely with a strategy in place to manage K ⁺ levels effectively.

C) Correction of hyperkalemia for at-risk cardiorenal patients with the potassium-lowering therapy	
20	A reduction in emergency department visits and unplanned hospitalizations due to complications associated with hyperkalemia should be a goal of good management
21	A goal for the management of high-risk cardiorenal patients should be to utilize the maximum recommended dose of RAASi therapy.
22	De-escalation or discontinuation of RAASi therapy is associated with worse cardiovascular and renal outcomes in cardiorenal patients.
23	Hyperkalemia should no longer be seen as a barrier to optimization of guideline-directed therapy.
24	Novel K ⁺ binders enable guideline-recommended RAASi dosing and the proven benefits that this brings to patients.
25	Use of novel K ⁺ binders in patients with mild hyperkalemia can enable guideline-recommended doses of RAASi therapy.
26	RAASi use should not be de-escalated or discontinued due to hyperkalemia unless alternative measures of hyperkalemia management have been optimized, including initiation of K ⁺ binder therapy.
27	Novel K ⁺ binders can enable optimization of RAASi therapy in a similar way that antiemetics can enable optimization of chemotherapy.
28	Novel K ⁺ binders should not need to show mortality benefit; they enable RAASis, which have already proven mortality benefit.
29	Calcium Polystyrene Sulfonate (CPS) should not be used in the medium- or long-term as it may cause severe GI side effects, including bowel necrosis.