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ORIGINAL ARTICLE

Executive Summary of the Malaysian Consensus on the Management of Acute and Persistent Hyperkalaemia: A Multidisciplinary Approach

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ABSTRAK

Tahap kalium yang tinggi (hyperkalaemia; hyperK$^+$) adalah keadaan yang berpotensi mengancam nyawa. Ia berpotensi menimbulkan cabaran besar semasa pengurusan hyperK$^+$ akut dan jangka panjang, terutamanya bagi pesakit dengan penyakit buah pinggang kronik, kegagalan jantung dan kencing manis (diabetes melitus). Meskipun ubat perencat sistem renin-angiotensin-aldosteron merupakan terapi perubatan yang disarankan dalam garis panduan untuk pengamalan klinikal dan terbukti membawa manfaat kardiorenal, kebimbangan mengenai peningkatan risiko hyperK$^+$ disebabkan ubat-ubatan ini telah menjejaskan penggunaan optimumnya. Walaupun cabaran ini wujud, pengurusan hyperK$^+$ masih kurang jelas dan menimbulkan keperluan untuk menyeragamkan cara hyperK$^+$ diuruskan. Penyata-penyata konsensus ini menyediakan garis panduan berasaskan bukti terkini bagi pengurusan hyperK$^+$ akut dan kronik yang disesuaikan dengan konteks penjagaan kesihatan tempatan.

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Kata kunci: *Hyperkalaemia; natrium zirkonium siklasilikat; perubatan kecemasan; sindrom kardiorenal*

ABSTRACT

Hyperkalaemia (HyperK$^+$) is a potentially life-threatening condition that poses significant challenges in both acute and chronic care, especially for patients with chronic kidney disease, heart failure and diabetes mellitus. While renin-angiotensin-aldosterone system inhibitors (RAASi) are guideline-directed medical therapy known for their cardiorenal benefits, concerns about the increased risk of hyperK$^+$ associated with these medications have hindered their optimal use. Despite these challenges, ambiguity remains regarding the management of hyperK$^+$, highlighting the need for a standardised approach. This Malaysian consensus provides evidence-based guidelines for managing acute and persistent hyperK$^+$ tailored to the local healthcare context.

Keywords: Cardiorenal syndrome; emergency medicine; hyperkalaemia; sodium zirconium cyclosilicate

INTRODUCTION

Patients with diabetes mellitus (DM), heart failure (HF) and chronic kidney disease (CKD) are at significantly higher risk of developing hyperkalaemia (hyperK$^+$) compared to the general population. (Collins et al. 2017; Fitch et al. 2017; Nilsson et al. 2017) The use of renin-angiotensin-aldosterone system inhibitors (RAASi), which include angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACE-i/ARB), angiotensin receptor/neprilysin inhibitors (ARNI), and mineralocorticoid receptor antagonists (MRA), as part of guideline-directed medical therapy (GDMT) (Heidenreich et al. 2022; KDIGO 2021; KDIGO 2022; McDonagh et al. 2021; National Heart Association of Malaysia 2023) for managing HF, CKD with proteinuria and DM with hypertension, further increases this risk. Chronic (persistent) hyperK$^+$ can lead to adverse cardiac effects, and it is prevalent among patients on RAASi therapy, often necessitating adjustments to their medication (Riccio et al. 2022).

Despite the availability of novel K$^+$-lowering agents such as patiromer and sodium zirconium cyclosilicate (SZC), as well as calcium polystyrene sulfonate (CPS) (Kashihara et al. 2021; Packham et al. 2015; Roger et al. 2019), concerns about hyperK$^+$ risk continue to hinder RAASi optimisation in high-risk populations (Beusekamp et al. 2019; Epstein et al. 2015; Fonseca et al. 2020; Henrysson et al. 2023). This sub-optimal dosing can lead to increased long-term mortality, higher hospitalisation rates in HF patients, more rapid deterioration of kidney function and greater cardiovascular (CV) event risk in CKD patients.

This executive summary offered an overview of recommendations along with detailed practice points that accompany each consensus statement, which elaborate on best practices for managing acute and persistent hyperK$^+$. All content, including these practice points, had been thoroughly reviewed and agreed upon by the committee members, integrating insights from emergency physicians, nephrologists and cardiologists. These recommendations were based on the

latest evidence, international guidelines, and best clinical practices within the Malaysian healthcare system, and can be accessed in full at https://www.msn.org.my/.

MATERIALS AND METHODS

A 12-member steering committee, consisting of emergency physicians, nephrologists, and cardiologists, was formed to develop consensus statements on hyperK$^+$. The committee focused on six key themes: defining hyperK$^+$, diagnosing and managing hyperK$^+$ in emergency settings, preventing hyperK$^+$ in at-risk cardiorenal patients, assessing hyperK$^+$ risk, K$^+$-lowering therapies and collaborative care.

After a review of recent consensus statements and guidelines for managing hyperK$^+$ in cardiorenal patients, a list of 49 consensus statements were presented to the steering committee (Burton et al. 2022; Lindner et al. 2020; Rafique et al. 2021; Rossignol et al. 2022; The Renal Association 2020). After extensive discussions, these statements were refined to 20 statements. The revised 20 statements were then developed into a survey using Microsoft Forms. All submissions were anonymised, and consent was implied when specialists answered the survey on a volunteer basis.

The survey was distributed to all registered specialists through their respective professional societies: the College of Emergency Physicians, the Malaysian Society of Nephrology and the National Heart Association of Malaysia (Round 1). Based on the combined number of registered specialists, the steering committee agreed that a response rate of approximately 30% would be acceptable. The survey duration was set for two months to allow optimal response time.

The statements were evaluated using a 4-point Likert scale, "Strongly agree, Agree, Disagree and Strongly disagree", with an option to provide comments for each statement. Votes of "Strongly agree" and "Agree" were totalled to determine the level of agreement. Statements with 75% agreement were included in the consensus. All 20 statements achieved a level of agreement of 75% or higher among the respondents.

Following the review of all comments by the respondents and an extensive discussion (Round 2), the steering committee further revised the statements to the final set of 16 statements with 100% agreement from the committee (Table 1).

RESULTS AND DISCUSSION

Definition of Hyperkalaemia

The definitions of hyperK$^+$ are - mild: K$^+$ 5.5-5.9 mmol/L; moderate: K$^+$ 6.0-6.4 mmol/L; and severe: K$^+$ ≥6.5 mmol/L. This section outlines the consensus on the classification of hyperK$^+$ based on serum K$^+$ levels, categorising it into mild (5.5-5.9 mmol/L), moderate (6.0-6.4 mmol/L), and severe (≥6.5 mmol/L) stages. These definitions excluded the use of electrocardiogram (ECG) changes in determining the severity of hyperK$^+$. Additionally, it emphasises the importance of ruling out pseudohyperK$^+$, which may result from factors like improper blood draw techniques or sample handling (Lindner et al. 2020). The guidance provides practical recommendations for clinicians to differentiate true hyperK$^+$ from false readings, ensuring accurate diagnosis and management.

Diagnosing and Managing Hyperkalaemia in Emergency Settings

The algorithm for the emergency management of hyperK$^+$ is presented in Figure 1. In this

TABLE 1: Consensus statements

Definition of hyperK⁺
1. The definitions of hyperK⁺ are – mild: K⁺ 5.5-5.9 mmol/L, moderate: K⁺ 6.0-6.4 mmol/L and severe: K⁺ ≥ 6.5 mmol/L
Diagnosing and managing hyperK⁺ in emergency settings
2. It is essential to consider the entire clinical picture when diagnosing and treating patients with hyperK⁺ because it can manifest with non-specific symptoms or be asymptomatic
3. All patients presenting to the ED with serum K⁺>5.5 mmol/L should undergo an ECG
4. Initiating treatment strategies in the ED is recommended for patients with serum K⁺>6.0 mmol/L regardless of ECG changes and in all patients with hyperkalaemic ECG changes
5. Reassess serum K⁺ levels, and monitor ECG, vital signs, and plasma glucose at a frequency appropriate to the clinical context until the serum K⁺ improves to <5.5 mmol/L
6. Patients who have responded to treatment (i.e., serum K⁺<5.5 mmol/L), are stable, with no indication for admission or risk of recurrent hyperK⁺ may be discharged with preventive care and a follow-up appointment
Preventing hyperK⁺ in the at-risk cardiorenal patients
7. Consider preventive strategies for patients at risk of hyperK⁺
8. Consider using a novel K⁺ binder for RAASi optimisation in patients with known hyperK⁺ when basic preventive strategies fail
Assessing risk and managing hyperK⁺ in cardiorenal patients
9. When RAASi are initiated, closer serum K⁺ monitoring is recommended for high-risk patients (patients with CKD, HF, and/or DM)
10. In an individualised care plan, effectively managing hyperK⁺ is recommended to optimise GDMT
11. In cases of mild and moderate hyperK⁺, consider decreasing the RAASi dosage if mitigation strategies prove ineffective for normalising serum K⁺ levels
12. In cases of severe hyperK⁺, consider de-escalating or discontinuing RAASi when the risks outweigh the benefits of continuation
K⁺-lowering therapies for hyperK⁺ in cardiorenal patients
13. Managing persistent hyperK⁺ with long-term use of novel K⁺ binders (SZC or patiromer) may enable cardiorenal patients to experience the proven benefits of guideline-recommended doses of RAASi therapy
14. CPS is an option for short-term hyperK⁺ management. Exercise caution when using CPS in the medium- or long-term due to concerns about GI side effects
Collaborative care
15. In all cases presenting to the ED with moderate and severe hyperK⁺ which are unresponsive to treatment, a physician consultation is recommended
16. To optimise GDMT, and align medication prescriptions and adjustments relating to hyperK⁺, cross-specialty communication is essential

CKD: chronic kidney disease; CPS: calcium polystyrene sulfonate; DM: diabetes mellitus; ECG: electrocardiogram; ED: emergency department; GDMT: guidelines-directed medical therapy; GI: gastrointestinal; HF: heart failure; hyperK⁺: hyperkalaemia; K⁺: potassium; RAASi: renin-angiotensin-aldosterone system inhibitors; SZC: sodium zirconium cyclosilicate

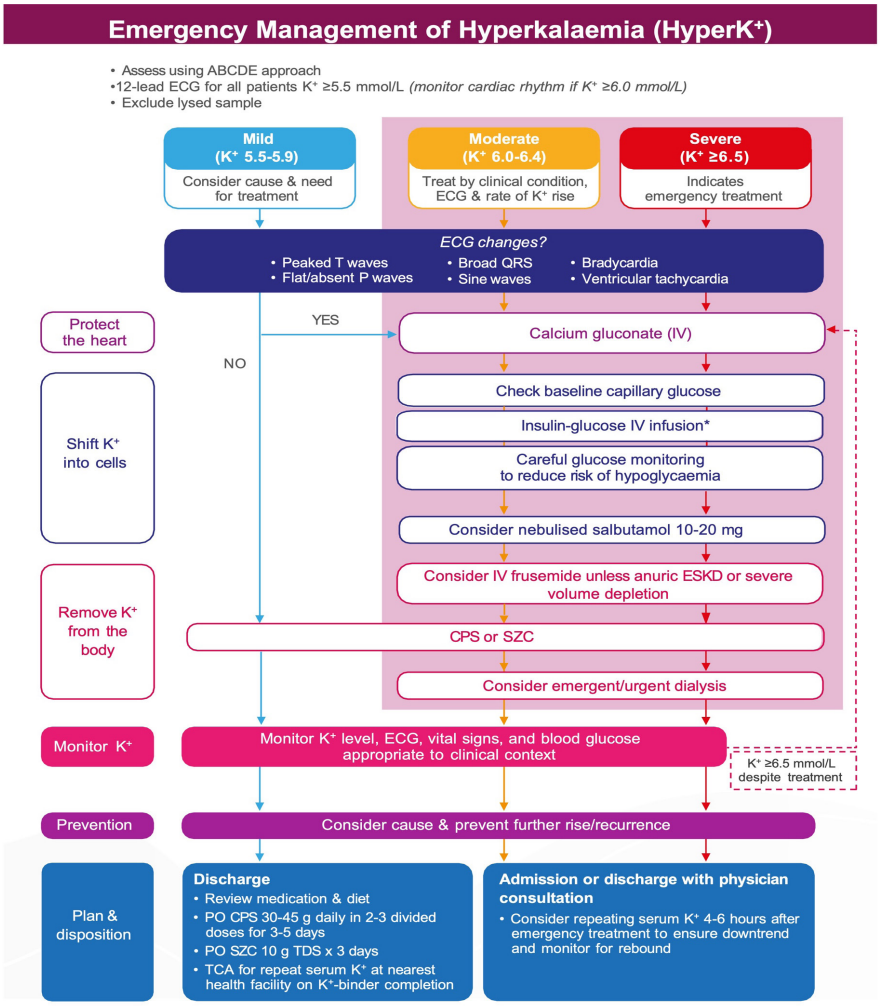

FIGURE 1: All K+ levels are in mmol/L. *Give 10 U soluble insulin + 50 ml Dextrose 50% (or equivalent strength) through a slow bolus. [ABCDE: Airway, Breathing, Circulation, Disability, Exposure approach; CPS: calcium polystyrene sulfonate; ECG: electrocardiogram; ESKD: end-stage kidney disease; ICU: intensive care unit; IV: intravenous; K+: potassium; PO: orally; SZC: sodium zirconium cyclosilicate; TCA: to come again; TDS: three times daily). Adapted from The Renal Association UK. Clinical Practice Guidelines.

theme, we emphasise the importance of a comprehensive clinical approach when diagnosing and managing hyperK+ in emergency settings. HyperK+ can often present asymptomatically or with non-specific symptoms making laboratory tests and ECG vital in early detection (Campese & Adenuga 2016; Simon et al. 2024 ; Te Dorsthorst et al. 2019). ECG screening is recommended for all patients with serum K+ >5.5 mmol/L, though the absence of ECG abnormalities does not rule out hyperK+ (Campese & Adenuga 2016; Van Mieghem et al. 2004)

Emergency treatment should be initiated for patients with serum K+ >6.0 mmol/L or with hyperkalaemic ECG changes. Continuous

monitorings of serum K^+, ECG and vital signs are crucial throughout treatment. Patients stabilised with serum K^+ <5.5 mmol/L and no risk of recurrence may be discharged with preventive care and follow-up. Those with persistent or new ECG abnormalities, hemodynamic instability, or severe hyperK^+ require further evaluation or admission.

It is essential to consider the entire clinical picture when diagnosing and treating patients with hyperK^+ because it can manifest with non-specific symptoms or be asymptomatic. Practice points are: (2.1.1) assess patients for hyperK^+ even in the absence of symptoms, as life-threatening cardiac arrhythmias may occur at lower serum K^+ levels and in patients with persistent hyperK^+; (2.1.2) be aware of non-specific hyperkalaemic symptoms for timely diagnosis and management.

All patients presenting to the ED with serum K^+>5.5 mmol/L must undergo an ECG. Practice points is: (2.2.1) although ECG sensitivity for mild hyperK^+ is low, increased serum K^+ can induce detectable ECG changes.

Initiating treatment strategies in the ED is recommended for patients with serum K^+ >6.0 mmol/L regardless of ECG changes and in all patients with hyperkalaemic ECG changes. Practice points are: (2.3.1) accurately differentiating between acute and persistent hyperK^+ is essential to guide appropriate emergency treatments; (2.3.2) promptly initiates emergency management strategies for hyperK^+ based on the serum K^+ level to prevent ECG changes and potential lethal arrhythmia; (2.3.3) to manage hyperK^+ in the emergency setting, treat reversible causes, reduce membrane excitability (e.g. with IV calcium gluconate), and start measures for lowering serum K^+.

Reassess serum K^+ levels, and monitor ECG, vital signs, and plasma glucose at a frequency appropriate to the clinical context should be done until the serum K^+ improves to <5.5 mmol/L. Practice points are: (2.4.1) monitoring ECG continuously at and during emergency management of hyperK^+ is advisable; (2.4.2) monitors other clinical parameters at appropriate intervals on a case-to-case basis; (2.4.3) monitors glucose levels at regular intervals if the patient is given insulin during the emergency treatment of hyperK^+; (2.4.4) monitors serum K^+ levels as early 2-4 hours after initiating K^+-lowering agents and then reassess to determine the frequency of monitoring.

Patients who have responded to treatment (i.e., serum K^+ <5.5 mmol/L), are stable, with no indication for admission or risk of recurrent hyperK^+ may be discharged with preventive care and a follow-up appointment. Practice points are: (2.5.1) healthcare providers may discharge patients who have a repeat serum K^+ <5.5 mmol/l, resolved ECG changes, and stable vital parameters, with K^+ binders and close follow-up; (2.5.2) hemodynamic instability, new or persistent ECG changes, and new onset hyperK^+ require admission.

Preventing HyperK^+ in the At-risk Cardiorenal Patients

For this theme we focus on preventive strategies for hyperK^+ in patients with conditions such as CKD, HF, DM with hypertension, especially those on RAASi (Di Lullo et al. 2019; Palmer et al. 2021; Wang 2019; Weinstein et al. 2021). These patients face higher risks due to their underlying conditions, medications (e.g. β-blockers, non-steroid anti-inflammatory drugs, and trimethoprim/sulfamethoxazole), and other contributing factors like advanced age and K^+ intake (Neuen et al. 2022; Palmer et al. 2021; Wang 2019). Preventive measures include regular blood monitoring, dietary modifications, education about hidden

K^+ in processed foods and cautious use of medications that may induce hyperK^+ (Ben Salem et al. 2014; Clase et al. 2020; Ikizler et al. 2020; Martínez-Pineda et al. 2021; The Renal Association 2020; Weinstein et al. 2021).

Additional strategies such as optimising diuretic use and addressing metabolic acidosis (Larivée et al. 2023; Weinstein et al. 2021) are included, along with the recommendation to consider novel K^+ binders when basic preventive measures fail. Optimising RAASi doses, even at full or higher levels, is critical to managing CKD and HF effectively, as it has been shown to reduce albuminuria, CKD progression, and mortality (Bhatt et al. 2021; Packer et al. 1999; Parving et al. 2001; Zannad et al. 2011). Novel K^+ binders like SZC and patiromer have demonstrated efficacy in maintaining normal serum K^+ levels, allowing continued RAASi therapy without compromising patient outcomes. (Butler et al. 2022; Spinowitz et al. 2019).

Consider preventive strategies for patients at risk of hyperK^+. Practice points are: (3.1.1) considers regular blood monitoring for patients at risk of hyperK^+ and introduce preventive strategies when serum K^+ is $\geq$5.0 mmol/L; (3.1.2) RAASi should be carefully dosed, and serum K^+ levels should be monitored closely after initiation and up-titration; (3.1.3) using diuretics can mitigate hyperK^+ in patients with volume overload; (3.1.4) addresses modifiable risk factors such as avoiding medications and drug combinations that may cause hyperK^+, avoiding constipation, and correcting metabolic acidosis; (3.1.5) dietary modification limiting K^+-rich foods, withdrawing K^+-containing supplements and educating patients about hidden K^+ in processed foods are also preventive strategies.

Consider using a K^+ binder for RAASi optimisation in patients with known hyperK^+ when basic preventive strategies fail. Practice points are: (3.2.1) uses optimal doses of RAASi for managing CKD because it reduces albuminuria, increases the rate of albuminuria normalisation and slows CKD progression; (3.2.2) optimises RAASi for managing HF as it reduces hospitalisations for HF, CV mortality and all-cause mortality; (3.2.3) considers initiating K^+ binders to facilitate RAASi optimisation in patients with hyperK^+.

Assessing Risk and Managing Hyperkalaemia in Cardiorenal Patients

The importance of optimising RAASi therapy for patients with CKD, HF and DM, while carefully managing the associated risk of hyperK^+ is the primary focus of this theme. We recommend closer serum K^+ monitoring (Table 2) as it is crucial for high-risk patients, especially those with multiple comorbidities (Figure 2).

Personalised care plans (Figure 3) are recommended for managing hyperK^+ without interrupting GDMT (KDIGO, 2022). In cases where prevention strategies fail, dose reduction

TABLE 2: Frequency of serum K^+ monitoring for ACEi, ARB and MRAs

Serum K^+ monitoring
· At treatment initiation · 2-4 weeks after initiation · At regular intervals, thereafter, based on the patient's individual risk

ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; K^+: potassium; MRA: mineralocorticoid antagonists

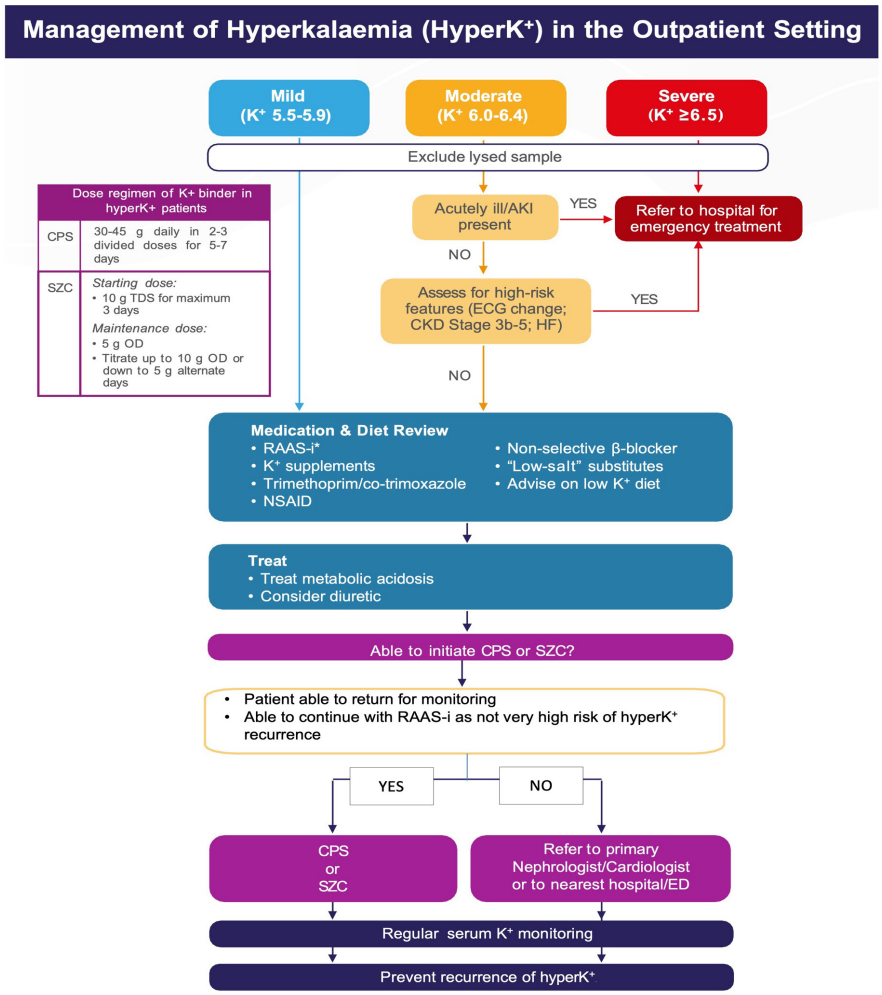

FIGURE 2: All K^+ levels are in mmol/L. *RAAS-i = ACE-i/ARB, ARNI and MRA. [ACE-i: angiotensin-converting enzyme inhibitor; AKI: acute kidney injury; ARB: angiotensin II receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; CKD: chronic kidney disease; CPS: calcium polystyrene sulfonate; ECG: electrocardiogram; ED: emergency department; HF: heart failure; K^+: potassium; MRA: mineralocorticoid receptor antagonist; NSAID: non-steroidal anti-inflammatory drug; PO: orally; TDS: three times daily; RAAS-i: renin-angiotensin-aldosterone system inhibitor; SZC: sodium zirconium cyclosilicate. Adapted from The Renal Association UK. Clinical Practice Guidelines

or temporary discontinuation of RAASi may be considered. The use of K^+ binders can help to maintain RAASi therapy while minimising the risk of hyperK+. For patients with severe hyperK+ (serum K^+ >6.5 mmol/L), discontinuing RAASi and initiating emergency treatment may be required, with potential re-initiation once serum K^+ levels normalise (Rosano et al. 2018).

When RAASi are initiated, closer serum K^+ monitoring is recommended for high-risk patients (patients with CKD, HF, and/or diabetes mellitus). Practice points is: (4.1.1) RAASi elevates hyperK+ risk in patients with comorbidities like CKD, HF, and DM,

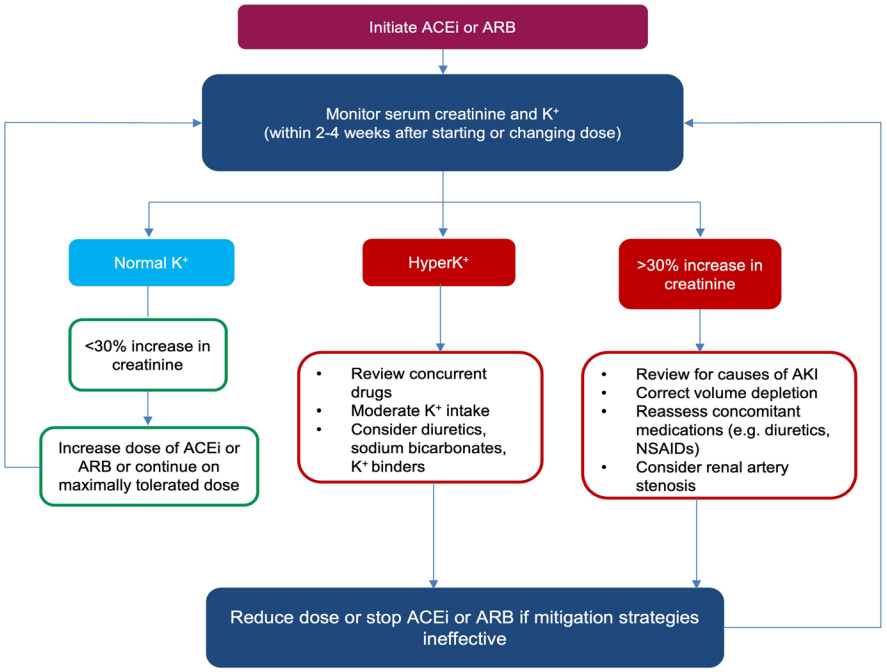

FIGURE 3: Monitoring serum creatinine and K^+ during ACEi or ARB treatment with dose adjustment and monitoring of side effects. [ACE: angiotensin converting enzyme inhibitor; AKI: acute kidney injury; ARB: angiotensin receptor blockers; hyperK+: hyperkalaemia; K^+: potassium; NSAIDs: non-steroidal anti-inflammatory drugs] Source: KDIGO 2022 Clinical Practice Guidelines for Diabetes Management in Chronic Kidney Disease.

necessitating closer serum K^+ monitoring.

In an individualised care plan, effectively managing hyperK+ is recommended to optimise GDMT. Practice points are: (4.2.1) patients with HF on GDMT require regular laboratory monitoring for hyperK+ and preventive actions against AKI; (4.2.2) to manage hyperK+ effectively without interrupting GDMT, prioritise managing all modifiable risk factors.

In cases of mild and moderate hyperK+, consider decreasing the RAASi dosage if mitigation strategies prove ineffective. Practice points are: (4.3.1) ensures that all other strategies to mitigate hyperK+ have been optimised (see Statements 3.1, 3.2); (4.3.2) consider a K^+ binder, if available, to avoid RAASi dose reduction (see Statements 5.1 and 5.2); (4.3.3) considers reducing RAASi dose and monitor serum K^+ level if long-term use of K^+ binder is not feasible.

In cases of severe hyperK+, consider discontinuing RAASi when the risks outweigh the benefits of continuation. Practice points are: (4.4.1) ensures all other strategies to mitigate hyperK+ have been optimised (see Statements 3.1, 3.2); (4.4.2) to determine if RAASi can be restarted, temporarily discontinue RAASi and evaluate renal function before deciding on a treatment approach; (4.4.3) considers a K^+ binder, if available, to facilitate reinitiating RAASi (see Statements 5.1 and 5.2)

Potassium Lowering Therapies for Hyperkalaemia in Cardiorenal Patients

This theme primarily focuses on the different K^+-lowering therapies available that can manage hyperK^+ in patients with cardiorenal conditions, particularly those on RAASi therapy. Despite guidelines recommending the continuation of RAASi after a hyperK^+ episode, discontinuation or dose reduction is common, leading to worse outcomes, including increased hospitalisations and a higher risk of cardiorenal events. (Kanda et al. 2023; Svensson et al. 2023)

Novel potassium binders, such as SZC and patiromer, are effective for long-term management of persistent hyperK^+, allowing patients to continue RAASi therapy and experience its benefits (Kashihara et al. 2021; Packham et al. 2015; Roger et al. 2019). These binders have demonstrated safety and efficacy in reducing serum K^+ levels over extended periods, supporting GDMT optimisation in patients with CKD, DM, or HF (Tables 3 & 4; Figure 1 & 2).

For short-term management, CPS (Table 5; Figure 1 & 2) is an option, (National Pharmaceutical Regulatory Agency 2025; Wang et al. 2018; Wang et al. 2023) though its use in the medium- or long-term is limited due to concerns about gastrointestinal (GI) side effects, including constipation and rare cases of intestinal necrosis (Joo et al. 2009; Takeuchi et al. 2013; Yu et al. 2017). Close monitoring is recommended when CPS is prescribed, and it should be discontinued if severe GI symptoms occur (National Pharmaceutical Regulatory Agency 2025).

Managing persistent hyperK^+ with long-term use of novel K^+ binders (SZC or patiromer) may enable cardiorenal patients to experience the proven benefits of guideline-recommended

TABLE 3: Patiromer Phase III trials

No	Trial	Design	Population	Duration	Findings
1.	OPAL-HK (Pitt et al. 2015)	Multicentre phase 1: single group, single arm. Phase 2: randomised, single-blind, placebo-controlled withdrawal phase.	Phase 1: N=243 Phase 2: N=107 eGFR <60 (91%), RAASi (100%), DM (57%), HTN (97%), hyperK^+	Phase 1: 4 weeks Phase 2: 8 weeks	Mean serum K^+ reduction in phase 1 was -1.01 mmol/L (p<0.001). Between group difference in serum K^+ during the withdrawal phase was 0.72 mmol/L (95% CI 0.46-0.99, p<0.001). 60% of the placebo group compared with 15% of the patiromer group had a serum K^+ reading ≥5.5 mmol/L.
2.	DIAMOND (Butler et al. 2022)	Multicentre Phase 1: open label, run in. Phase 2: randomised triple-blind placebo-controlled withdrawal phase.	Phase 1: N=1195 Phase 2: N=878 RAASi (100%), MRA (100%), HTN (91%), HF (100%), hyperK^+	Phase 1: up to 12 weeks Phase 2: 13 to 43 weeks (median: 27 weeks)	Serum K^+ was 0.10 mmol/L higher in the placebo group (p<0.001). Serum K^+ >5.5 mmol/L and discontinuation or dose reduction of MRA was less frequent in the patiromer group (HR 0.63 and 0.62, with p=0.006 for both).

CI: confidence interval; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; HF: heart failure; HR: hazard ratio; HTN: hypertension; hyperK^+: hyperkalaemia; K^+: potassium; MRA: mineralocorticoid antagonists; RAASi: renin angiotensin-aldosterone system inhibitors

TABLE 4: SZC Phase III trials

No	Trial	Design	Population	Duration	Findings
1.	ZS-003 (Packham et al. 2015)	Phase 1: multicentre, double-blind correction phase. Phase 2: randomised controlled, multicentre, double-blind maintenance phase.	Phase 1: N=753 Phase 2: N=543 eGFR 60 (74.5%), RAASi (67%), DM (60%), hyperK$^+$	Phase 1: 48 hours Phase 2: 12 days	In the correction phase, SZC reduced serum K$^+$ by 0.30% per hour while placebo reduced serum K$^+$ by 0.09% per hour (p<0.001). During the maintenance phase, SZC 5 g and 10 g significantly decreased mean serum K$^+$ at days 9 and 15 (5.11 mmol/L vs 4.62 mmol/L and 5.11 mmol/L vs 4.60 mmol/L, respectively; p<0.001 for both) but not at day 21 (5.14 mmol/L vs 4.96 mmol/L, p=0.221). There were no significant between group changes in arrhythmias.
2.	HARMONIZE (Kosiborod et al. 2014)	Phase 1: multicentre, open-label correction phase. Phase 2: randomised controlled, multicentre, double-blind maintenance phase.	Phase 1: N=251 Phase 2: N=237 eGFR ≤60 (69%), RAASi (72%), DM (68%), hyperK$^+$	Phase 1: 48 hours Phase 2: 28 days	By the end of Phase 1, the mean reduction in serum K$^+$ was - 1.1 mmol/L (p<0.001). In Phase 2, normal serum K$^+$ levels were obtained more often in the SZC arms (71%, p=0.01; 76%, p=0.002; 85%, p<0.001 for 5 g, 10 g and 15 g, respectively). The differences remained significant in the HF subgroup.
3.	HARMONIZE Open-label extension (Roger et al. 2019)	Multicentre, open-label, single-arm, maintenance phase extension.	N=121 eGFR ≤60 (74%), RAASi (69%), DM (67%), hyperK$^+$	≥11 months	Mean serum K$^+$ ≤5.1 mmol/L was achieved by 76.6% to 87.5% of participants, and mean serum K$^+$ ≤5.5 mmol/L was obtained by all participants.
4.	ZS-005 (Spinowitz et al. 2019)	Phase 1: multicentre, open-label correction phase. Phase 2: multicentre, open-label, maintenance phase.	Phase 1: N=751 Phase 2: N=746 eGFR 60 (73%), RAASi (64%), DM (63%), HTN (82%), hyperK$^+$	Phase 1: 24-72 hours Phase 2: up to 12 months	At completion of the correction phase, 78% of the patients had a normal serum K$^+$. During the maintenance phase, 74% of participants maintained their RAASi dose.
5.	Kashihara et al. (2020)	RCT, multicentre, double-blind (Phase II/III)	N=103 eGFR 60 (97%), RAASi (78%), DM (60%)	48 hours	At 48 hours, the proportion of patients with normal serum K$^+$ was higher in the SZC 5 g and 10 g arms versus placebo (85.3% and 91.7% vs 15.2%, respectively; p<0.0001).
6.	Kashihara et al. (2021)	Multicentre, open-label, single arm correction and maintenance phase.	N=150 eGFR 60 (93%), RAASi (71%), DM (58%), hyperK$^+$	Phase 1: 1-3 days Phase 2: 1 year	99% of the patients in the correction phase had normal serum K$^+$ after 72 hour. ≥65.5% of patients had normokalaemia throughout.

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...continuing

7.	DIALIZE (Fishbane et al. 2019)	RCT, multicentre, double-blind.	N=196 mHD (100%), pre-dialysis hyperK+	8 weeks	More participants in the SZC arm had pre-dialysis serum K+ levels between 4 and 5 mmol/L in at least 3/4 long interdialytic intervals without requiring rescue therapy versus placebo (41.2% vs 1.0%; p<0.001). Rescue therapy for hyperK+ was similar in both arms.
8.	ENERGIZE (Peacock et al. 2020)	RCT, multicentre, double-blind.	N=70 Emergency room, hyperK+	10 hours	There was no statistically significant reduction in serum K+ between SZC and placebo at 10 hours

CI: confidence interval; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; HF: heart failure; HR: hazard ratio; HTN: hypertension; hyperK+: hyperkalaemia; K+: potassium; mHD: maintenance haemodialysis; MRA: mineralocorticoid antagonists; RAASi: renin-angiotensin-aldosterone system inhibitors; RCT: randomised controlled trial; SZC: sodium zirconium cyclosilicate.

TABLE 5: CPS clinical trials

No	Trial	Design	Population	Duration	Findings
1.	Wang et al. (2018)	Prospective, randomised, crossover clinical trial with a 1-week washout period.	58 haemodialysis patients with hyperK+ (≥5.5 mol/L).	3-week CPS (3 x 5 g/day) or a blank control, with a 1-week washout period.	Compared with the control group, CPS treatment significantly reduced serum K+ levels (p <0.01). More patients in the CPS group had lower serum K+ levels than the safety level of <5.5 mmol/L (32% for control vs. 61% for CPS, p <0.01).
2.	Wang et al. (2023)	Prospective, open, randomised, controlled, single-centre clinical observational study.	107 stage 3–5 non-dialysis CKD patients with hyperK+ group A (15 g/day) or group B (30 g/day).	1 week	After 3 days of treatment, the serum K+ levels in groups A and B had decreased by 0.68 ± 0.46 and 0.75 ± 0.43 mmol/L, respectively. After 7 days, the serum K+ levels in groups A and B had decreased by 0.64 ± 0.37 and 0.94 ± 0.49 mmol/L, respectively.

CKD: chronic kidney disease; CPS: calcium polystyrene sulfonate; K+: potassium.

doses of RAASi therapy. Practice points are: (5.1.1) persistent hyperK+ is one of the most important causes of RAASi dosage de-escalation or discontinuation; (5.1.2) considers using novel K+ binders to optimise the use of RAASi as they have demonstrated long-term efficacy and safety.

CPS is an option for short-term hyperK+ management. Exercise caution when using CPS in the medium- or long-term due to concerns about GI side effects. Practice points are (5.2.1) the K+ binder, CPS, is an option for the short-term management of hyperK+; (5.2.2) CPS is administered orally. If the oral route

is not feasible or a rapid onset of action is needed, the rectal route can be used; (5.2.3) CPS use in the medium- and long-term should be done with caution as it may cause bowel necrosis, GI intolerance, hypercalcaemia, and hypomagnesemia.

Collaborative Care

The use of RAASi in managing conditions like HF and CKD requires a collaborative, cross-specialty approach to ensure optimal patient outcomes. While the risk of hyperK$^+$ is relatively low with monotherapy, it increases significantly with RAASi combination therapy (Vardeny et al. 2012), particularly in patients with both HF and CKD. In real-world settings, the incidence of hyperK$^+$ is much higher (Cooper et al. 2015; Palmer 2004; Raebel 2012; Shah et al. 2005), largely due to inadequate patient selection and monitoring.

Collaborative care, including cross-specialty communication between cardiology, nephrology, endocrinology, and other specialties, is critical for optimising GDMT and managing the risks associated with RAASi therapy. In addition, it should include developing clinical pathways tailored to local resources, which may benefit local needs.

For patients presenting with moderate to severe hyperK$^+$ who are unresponsive to treatment, referral to a nephrologist or cardiologist is recommended to address persistent ECG abnormalities or arrange for dialysis if needed. Patients at higher risk, such as those with severe hyperK$^+$ or exhibiting haemodynamic instability, should be monitored in intensive care settings. Additionally, involving dietitians and pharmacists helps to address dietary factors, supplements, and medications that may exacerbate hyperK$^+$.

In all cases presenting to the ED with moderate and severe hyperK$^+$ and are unresponsive to treatment, a physician consultation is recommended. Practice points are: (6.1.1) refers patients unresponsive to emergency hyperK$^+$ management to nephrologists/physicians; (6.1.2) ensures referral/follow-up of patients to work up the cause of acute hyperK$^+$ and prevent its recurrence; (6.1.3) refers patients with persistent ECG abnormalities to the relevant specialities.

To optimise GDMT, and align medication prescriptions and adjustments relating to hyperK$^+$, cross-specialty communication is essential. Practice points is: (6.2.1) clears channels of communication between cardiology, nephrology, endocrinology, internal medicine, pharmacists and dietetics is essential to optimise patient care and manage comorbidities associated with hyperK$^+$ and RASS-i therapy

CONCLUSION

The effective management of hyperK$^+$ is essential for improving patient outcomes, especially in those with cardiorenal conditions. Optimal management should aim to reduce ED visits and unplanned hospitalisations due to hyperK$^+$ and its associated complications. This multidisciplinary set of consensus statements provide comprehensive guidelines based on the latest evidence and best practices specific to the context of the Malaysian healthcare system. By standardising the approach to diagnosing and treating both acute and persistent hyperK$^+$, these recommendations aim to reduce complications, optimise the use of GDMTs like RAASi, and ultimately improve the quality of care for at-risk patients. The availability of novel K$^+$ binders, such as patiromer and SZC, provides clinicians with effective long-term options that enable the safe and optimal use of RAASi in high-risk populations. Through these efforts, healthcare providers can better prevent

and manage hyperK+, minimising its impact on patients and the healthcare system.

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