

Gestão da Hipercalemia em Contexto de Urgência: Recomendações de Boas Práticas Geradas por Metodologia de Consenso

Management of Hyperkalemia in an Emergency Situation: Best Practices Recommendations Driven by Consensus Methodology

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Resumo:

Introdução: A hipercalemia (HK) é caracterizada por níveis serológicos elevados de potássio e é frequente em doentes com doença renal crónica, diabetes *mellitus* e doenças cardiovasculares, aumentando o risco de complicações cardíacas e morte. Estudos de evidência em mundo real sublinham a necessidade de otimizar a gestão da hipercalemia, no entanto, não existe consenso nesta área, especialmente em relação a novos medicamentos. O nosso objetivo é estabelecer um consenso entre profissionais de saúde em Portugal relativamente à gestão eficaz da HK em situações de urgência e fornecer recomendações para a adoção de melhores práticas.

Métodos: Este estudo qualitativo baseou-se no método Delphi. Especialistas identificaram cinco tópicos relacionados com a gestão da HK e definiram 25 afirmações sobre o seu tratamento. Entre julho e agosto de 2023, foi distribuído um questionário online com as afirmações por médicos que atuam frequentemente no serviço de urgência. O consenso foi definido quando pelo menos 65% dos inquiridos indicaram concordância ou forte concordância com cada afirmação. O inquérito inicial obteve resultados consistentes, obviando a necessidade de rondas suplementares.

Resultados: Participaram 63 médicos especialistas. Observou-se um consenso muito elevado, de mais de 90% dos participantes a concordarem ou a concordarem fortemente com 19 das 25 afirmações. Estas estabelecem que a HK é uma condição crítica para os doentes com doença renal crónica, particularmente para os com taxa de filtração glomerular inferior, idosos e doentes que medicados com inibidores do sistema renina-angiotensina-aldosterona e bloqueadores dos recetores da angiotensina II, entre outros. Houve concordância também sobre o aumento de risco de mortalidade associado à HK, que acresce em doentes com comorbilidades ou HK prolongada. As afirmações relativas ao ciclossilicato de zircónio de sódio, o patirómero e tratamento com insulina tiveram os níveis de consenso mais baixos.

Conclusão: Foi alcançado um consenso entre profissionais de saúde em Portugal relativamente à gestão eficaz da HK. Os especialistas formularam recomendações que destacam aspetos fundamentais para a gestão da HK em situações de urgência. A implementação destas recomendações poderá melhorar a prestação de cuidados médicos harmonizados e baseados na evidência, bem como os resultados clínicos.

Palavras-chave: Consenso; Hipercalemia/diagnóstico; Hipercalemia/tratamento farmacológico; Polímeros; Potássio; Silicatos; Sistema Renina-Angiotensina; Técnica Delphi.

Abstract:

Introduction: Hyperkalemia (HK) is characterized by elevated serum potassium levels and is common in patients with chronic kidney disease, diabetes mellitus and cardiovascular diseases. Severe hyperkalemia increases the risk of cardiac disturbances and mortality. Real-world studies and international expert groups highlight the urgent need to optimize hyperkalemia management however, consensus in this area is lacking, especially concerning new drugs. We aim to establish a consensus among healthcare professionals in Portugal regarding the effective management of HK in emergency settings. Additionally, we aim to provide recommendations for the adoption of best practices in emergency care.

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Methods: This qualitative study was based on Delphi consensus. A panel of experts collaboratively identified and discussed five main topics related to HK management and defined 25 treatment statements. An online questionnaire was distributed to doctors who frequently handle emergencies between July and August 2023. A consensus was defined when at least 65% of respondents indicated agreement or strong agreement with a statement. The initial round produced high agreement levels, obviating the need for additional survey rounds.

Results: A total of 63 specialist doctors participated in the online questionnaire. There was a very high consensus, with over 90% of participants either agreeing or strongly agreeing with 19 of the 25 statements. These establish that HK is a critical concern for patients with chronic kidney disease, particularly those with a lower estimated glomerular filtration rate (eGFR), elderly population and patients on medications such as inhibitor renin-angiotensin-aldosterone system (iRAAS), angiotensin II receptor blockers (ARBs), mineralocorticoid-receptor antagonists (MRAs), or potassium-sparing diuretics. They also agree that HK is associated with higher mortality risk, which increases in individuals with underlying conditions or prolonged HK. Statements regarding potassium management involving sodium zirconium cyclosilicate (SZC), patiromer, scavengers in patients on iRAAS, and related to insulin treatment had the lowest consensus levels.

Conclusion: A robust consensus among Portuguese healthcare professionals regarding effective HK management in emergency settings was achieved. Experts collaboratively formulated recommendations covering key aspects of the management of HK in emergency settings. Implementing these recommendations will enhance the delivery of harmonized evidence-based medical care and the improvement of clinical outcomes.

Keywords: Consensus; Delphi Technique; Hyperkalemia/diagnosis; Hyperkalemia/drug therapy; Polymers; Potassium; Renin-Angiotensin System; Silicates.

Introduction

Hyperkalemia (HK) is a medical condition characterized by abnormally high levels of serum potassium (K⁺).¹ HK is most commonly caused by reduced urinary excretion of potassium, which is often observed in patients with kidney diseases such as chronic kidney disease (CKD). Other risk factors for HK include male gender, non-black race, lower body mass index, advanced age, smoking, a history of diabetes mellitus, coronary artery disease, or heart failure, and the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and potassium-sparing diuretics.²⁻⁵ The most commonly used definition for the severity of HK can be classified as mild (>5.0

to <5.9 mEq/L), moderate (6.0 to 6.4 mEq/L), and severe at thresholds (>6.5 mEq/L).⁶

HK can lead to serious electrophysiological disturbances, such as cardiac arrhythmias. Specifically, severe HK is an independent predictor of hospitalizations, in-hospital mortality, and all-cause mortality.⁴⁻⁷ It is also important to note that chronic HK can be asymptomatic, so it is important to frequently monitor these patients to detect any changes and prevent potential complications.¹⁻⁷ An increase in K⁺ has several consequences for myocardial action potential, so HK can manifest with different types of electrocardiogram (ECG) abnormalities.^{1,5,7-9}

The treatment of acute HK requires various procedures aiming at preventing or minimizing electrophysiological effects on the heart to reduce the immediate risk of arrhythmias.⁹ This requires intravenous access, continuous cardiac monitoring through ECG, quantifying the absolute concentration of potassium in the blood, as well as the rate of increase in its concentration. However, neither serum potassium levels nor ECG alone are sufficient to determine the need for treatment, and the physician must consider the clinical context. To minimize the damage caused by HK, it is necessary to stabilize cardiac cell membranes, shift extracellular K⁺ into cells (or redistribution), and eliminate K⁺ from the body.¹⁰ One way to do this is through the administration of certain potassium-binding medications.

This part of HK treatment is particularly subject to a lack of consensus among healthcare professionals.^{7,8} This is particularly evident when considering the introduction of new potassium-binding drugs and their application in patients suffering from HK due to CKD or adverse effects of prevalent medications, notably the renin-angiotensin-aldosterone system inhibitors (RAASi).^{2,3} Real-world studies show additional evidence in this regard. The observational REVEAL-ED study found that treatment decisions by healthcare professionals were often influenced by initial potassium levels in patients and confirmed the lack of a standardized treatment protocol for HK in emergency settings, echoing findings from previous studies.¹¹

Defining how to optimally manage HK is crucial. In August 2021, experts from Europe and North America formed a steering group, both cardiologists and nephrologists, aiming to address HK management in cardiorenal disease.¹² Current clinical guidelines recommend different procedures to protect the heart and to eliminate K⁺ and protect the heart allowing for the reversion of the pro-arrhythmogenic effects.^{13,14} In an emergency situation, it is essential to begin dialysis treatment, but there are logistical challenges that need to be addressed before starting this treatment.¹² Despite the existence of some statements regarding the treatment of HK, there is still no unanimous agreement on ideal practices among the Portuguese medical community.^{11,13}

This study aims to define a consensus on the effective management of HK in Portuguese emergency settings among healthcare professionals. Secondly, we aim to develop a comprehensive visual tool with recommendations

to facilitate the understanding and implementation of good practices in emergency setting, with the ultimate goal of improving patient outcomes and optimizing the management of HK-related emergencies.

Methods

This is an observational, cross-sectional qualitative study, based on the Delphi consensus methodology.^{15,16} Specifically, we assembled a panel of six Portuguese experts on HK management in emergency situations within the national context, including members of the “Núcleo de Estudos de Urgência e do Doente Agudo” and Directors of emergency care from different hospitals of the country. Based on the European Resuscitation Council Guidelines 2021,¹⁷ the experts identified five main topics: “Who is at risk?”, “Identification of hyperkalemia”, “Protect the heart”, “Remove K⁺ from the body” and “Prevention of hyperkalemia recurrence”. These topics were further discussed by the group and 25 statements to represent crucial applicable steps in the treatment of this clinical condition were defined (Table 1). These informed an anonymous online questionnaire developed using Google Forms.

The questionnaire was distributed through email, among doctors selected based on their expertise on attending HK-related emergencies. Participants were asked to indicate the level of agreement with each statement using a 5-point Likert scale (‘strongly disagree’, ‘disagree’, ‘neither agree or disagree’, ‘agree’, and ‘strongly agree’). The initial round lasted between July and August 2023. The consensus was defined by a concordance of at least 65% for those classified as “agree”/“strongly agree”. The questionnaire results were analyzed by the independent investigator to produce an agreement score for each statement. After this round, the results were reviewed by the expert panel. Survey iterations would be performed until the consensus threshold was achieved; however, due to the levels of agreement received after the first round, the expert panel agreed that further rounds were unnecessary.

Results

A total of 63 specialist doctors participated in the online questionnaire. All participants completed the entire questionnaire, with no missing values.

The 25 predefined statements reached a very high consensus (Fig. 1, Appendix). More than 90% participants agreed/strongly agreed with 19 statements and at least 66% agreed/strongly agreed with the remaining 6 statements. Statements 19, 21 and 23, related to the potassium management by the administration of SZC, patiromer and scavengers in patients on iRAAS, had the lowest consensus with 32%, 21% and 11% of “neither agree or disagree” answers, respectively. The highest rate of disagreement (disagree/strongly disagree) was 19% for statement 13, on insulin treatment. The remaining statements always had a low percentage of disagreement, with 56% of the statements having disagreement rates below 2%.

Table 1: Description of the predefined statements.

A - Who is at risk?	
Statement 1	Patients with a lower estimated glomerular filtration rate (eGFR) and treated with drugs to delay the progression of chronic kidney disease may experience hyperkalemia. When eGFR decreases by at least 15 mL/min, the likelihood of developing hyperkalemia doubles. The presence of a reduced eGFR is a high risk factor for the development of hyperkalemia.
Statement 2	Elderly patients are at risk of hyperkalemia due to decreased renin activity and decreased plasma aldosterone levels, as well as the frequent use of non-steroidal anti-inflammatory drugs (NSAIDs) in this population. However, this population may also present other risk factors for the development of hyperkalemia.
Statement 3	Patients treated with angiotensin-converting enzyme inhibitors (iRAAS), angiotensin receptor antagonists (ARBs), mineralocorticoid receptor antagonists (MRAs) or potassium-sparing diuretics are at risk of hyperkalemia.
Statement 4	Patients with hyperkalemia have a higher mortality risk. Patients with hyperkalemia and heart failure, type 2 diabetes mellitus or chronic kidney disease have an even higher risk of mortality. The longer the time in hyperkalemia, the greater the risk of mortality.
B - Identification of hyperkalemia	
Statement 5	Hyperkalemia is a medical condition characterized by abnormal serum potassium levels (> 5 mEq/L). The most commonly used definition classifies hyperkalemia according to severity as mild (>5.0 to <5.9 mEq/L), moderate (6.0 to 6.4 mEq/L) and severe at thresholds (≥6 .5 mEq/L)
Statement 6	If hyperkalemia is suspected and if the patient is not in cardiac arrest, the ABCDE approach (“Airway, Breathing, Circulation, Disability, Exposure”) should be used, other altered clinical parameters should be corrected and access should be placed. intravenous. At the same time, causes of pseudohyperkalemia (e.g. hemolysis, etc.) must be excluded.
Statement 7	In the presence of moderate (6.0 to 6.4 mEq/L) or severe (≥6.5 mEq/L) hyperkalemia, it is essential to perform an ECG, in order to assess the need to apply measures to stabilize the membrane.
Statement 8	In the absence of electrophysiological changes, measures must be taken to promote the movement of potassium into the cells.

C - Protect the heart	
Statement 9	In the presence of electrocardiographic changes (such as, for example, increased T wave amplitude, QRS widening, PR prolongation, flattening and loss of P wave and sinusoidal waves) it is necessary to promote rapid intravenous administration of calcium gluconate or calcium chloride, with the aim of stabilizing the cell membrane in order to prevent the occurrence of arrhythmias.
Statement 10	In order to identify, avoid or reverse the potentially arrhythmogenic effects caused by hyperkalemia, in addition to intravenous therapeutic intervention, it is also necessary to carry out continuous cardiac monitoring.
Statement 11	The need to stabilize the membrane should not condition the initiation of measures to promote the movement of potassium into the cells.
Statement 12	An assessment of cardiac function and possible urinary tract obstructions must be carried out, as well as an assessment of the patient's hydration status.
Statement 13	To promote the movement of potassium into cells, administration of 10 IU of rapid-acting insulin + 25 g of glucose (for example, a 250 mL solution of 10% glucose) should be administered in 15-30 minutes. If blood glucose is found to be higher than 250 mg/dL, this glucose procedure should not be applied. Start of action: 30 minutes; Duration of action: 2-4 hours.
Statement 14	In patients without hyperglycemia (glucose levels < 250 mg/dL) and to avoid post-treatment hypoglycemia, insulin treatment must be accompanied by the administration of 25 g of glucose (50 mL of a 50% solution) within 5 hours.
Statement 15	In the presence of severe hyperkalemia, a beta-2 agonist should be used, such as salbutamol 10-20 mg nebulized. Onset of action: 15-30 minutes; Duration of action: 4-6 h).
Statement 16	In the presence of metabolic acidosis (pH<7.1 and HCO ₃ <10), intravenous administration of 50-100 mmol of sodium bicarbonate should be considered.
D - Remove K+ from the body	
Statement 17	Diuretics may be considered for the treatment of mild to moderate hyperkalemia in individuals with adequate renal function. In patients with volume overload or hypertension, it may be possible to administer furosemide 40 mg or an equivalent dose of another diuretic one or more times. In some cases, it may be necessary to apply furosemide infusion continuously. It is necessary to consider the risk of hypovolemia and worsening of renal function.
Statement 18	Oral administration of potassium scavengers can promote the removal of excess potassium from the body, depending on their availability and the intended objective.

Statement 19	The administration of sodium zirconium cyclosilicate (SZC) (10 g tid for 48 hours) reduces serum potassium concentrations after 1 hour and normokalemia can be achieved, in most patients, within a period of 24 to 48 hours.
Statement 20	The use of cation exchange resins, such as sodium polystyrene sulfonate or calcium polystyrene sulfonate (onset of action > 4 hours), may be considered.
Statement 21	Administration of patiromer (8.4, 16.8, or 25.2 g) may be considered (onset of action: 4-7 hours).
Statement 22	If it is impossible to achieve the potassium reduction objectives using the previous strategies, emergency dialysis should be considered, as long as it is available and the patient has criteria for it.
E- Prevention of hyperkalemia recurrence	
Statement 23	The administration of potassium scavengers is indicated as a strategy after initiating iRAAS therapy in patients at high risk of hyperkalemia and can be used when initiating or increasing iRAAS titration. iRAAS dose reduction or discontinuation should be performed as a last resort.
Statement 24	In patients with chronic kidney disease or heart failure, a post-event assessment must be carried out to allow the reintroduction of prognosis-modifying therapies and the risk of recurrence to be reassessed.
Statement 25	Hyperkalemia recurrence events are common, especially in the first 6 months after discharge. Persistent and recurrent increase in potassium values is associated with a high risk of mortality.

Based on these highly consensual 25 statements, the involved experts developed a visual tool with the recommendations for the management of HK in an emergency context (Fig. 2). Consensus was defined as at least 65% of agree/strongly agree.

Discussion

The results show strong recognition that HK is predictable, treatable and manageable through treatment optimization. This study yielded consistent results on the 25 predefined statements related to HK management in Portuguese emergency settings. Notably, statements regarding the administration of SZC, patiromer and potassium scavengers in patients on iRAAS treatment had the lowest consensus levels and the statement with the highest rate of disagreement was about insulin treatment. The results obtained informed the recommendations presented in Fig. 2.

There is overall consensus on the populations in higher risk of HK and poor clinical outcomes. HK is a critical concern for

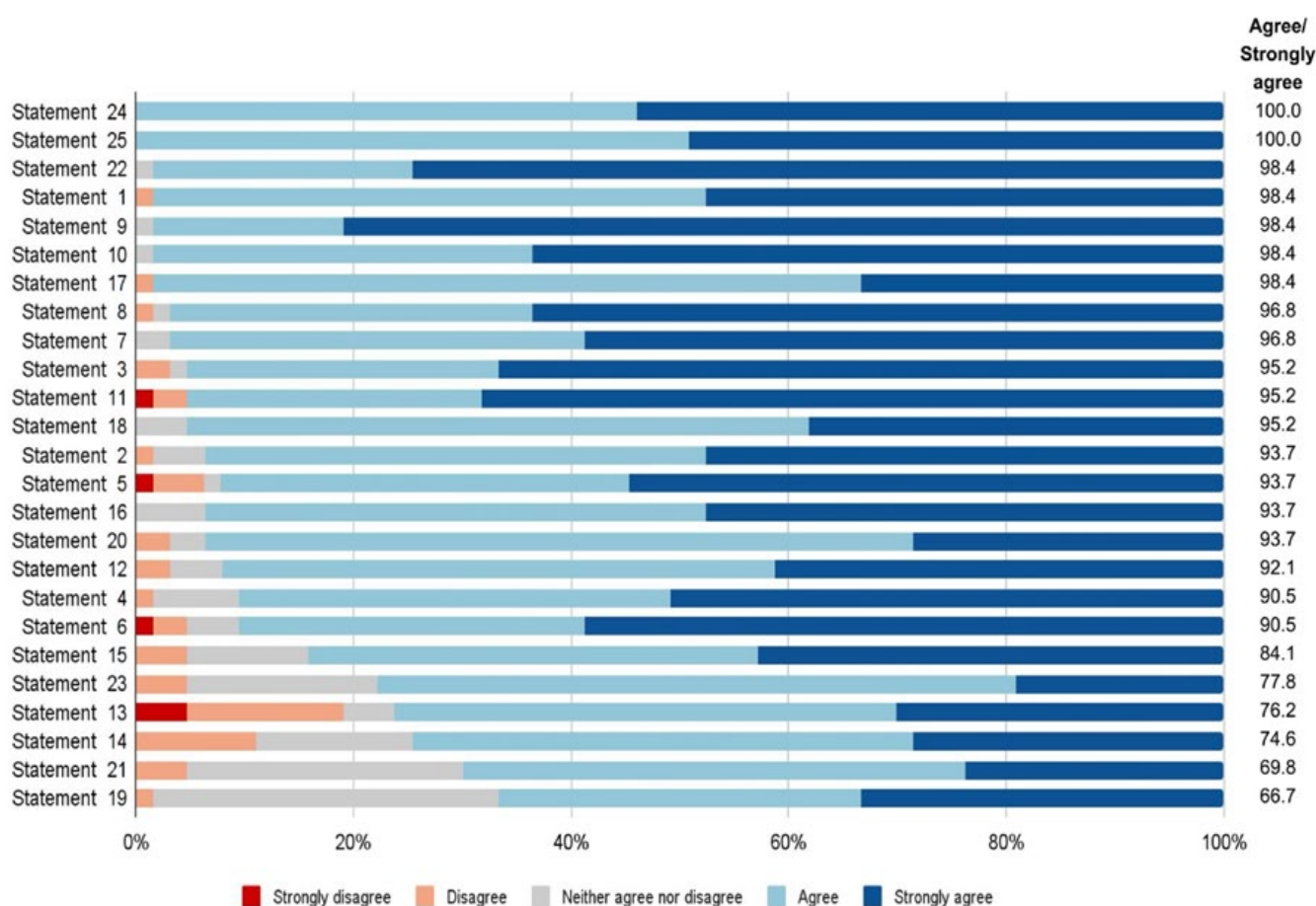


Figure 1: Percentage of responses to each statement (n = 63) and percentage of consensus.

patients with chronic kidney disease, particularly those with a lower eGFR.

Also, that the elderly population faces an elevated risk due to factors like reduced renin activity, decreased plasma aldosterone levels, and the frequent use of non-steroidal anti-inflammatory drugs (NSAIDs). Moreover, patients on medications such as iRAAS, ARBs, MRAs, or potassium-sparing diuretics are also susceptible to hyperkalemia. Importantly, hyperkalemia is associated with higher mortality risk, and individuals with both hyperkalemia and underlying conditions like heart failure, type 2 diabetes, or chronic kidney disease face even greater mortality risks. Additionally, prolonged exposure to hyperkalemia further escalates mortality risk, underscoring the importance of prompt management and monitoring. These results are in line with literature. The risk factors associated with hyperkalemia, including reduced eGFR, advanced age, medication use, and underlying medical conditions like heart failure, diabetes, and chronic kidney disease, are widely recognized in medical literature.⁸ The increased mortality risk associated with hyperkalemia, especially in patients with comorbidities, is also well-documented.

Regarding lower agreement on the management of potassium elevation in patients with CKD on iRAAS treatment is in line with the general uncertainty on this subject. This is particularly

evident when considering the introduction of new potassium-binding drugs (such as SZC and patiromer) or adverse effects of prevalent medications such as iRAAS.^{7,8} The medical community lacks consistent guidelines on managing HK in cardio-renal patients, leading to varied practices among cardiologists and nephrologists.¹⁸ The use of iRAAS is critical for the kidney and cardiovascular protection in patients with chronic kidney disease.¹⁴ However, these agents can lead to hyperkalemia, and the risk may be potentially enhanced in patients with high potassium levels such as patients receiving potassium-sparing diuretics and potassium supplements, concomitantly with iRAAS.¹² Clear strategies to minimize hyperkalemia risk that do not interfere with optimal iRAAS therapy should be prioritized in patients with CKD. These strategies may include the use of potassium-binders, based on evidence of these agents to effectively achieve normokalemia while optimizing RAASi treatment¹⁸ however their adoption is not yet widely applied, possibly due to limited access to these potassium binders.¹⁹ Interestingly, in individuals with CKD, there is a lower risk of death related to high potassium levels when compared to those with normal kidney function. However, it is important to note that in CKD situations, high potassium still significantly increases the risk of both short-term and long-term mortality.⁵

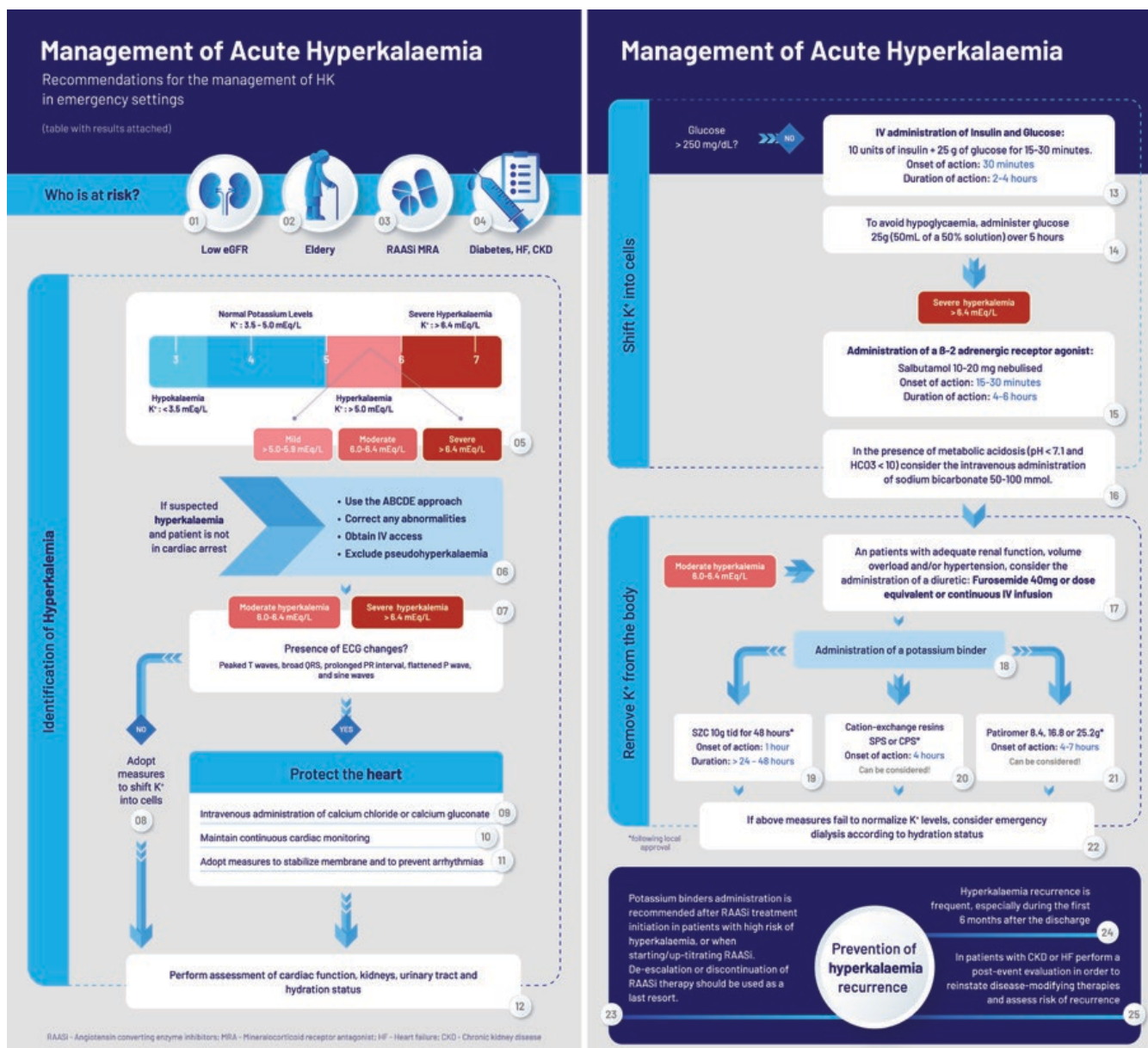


Figure 2: Recommendations for the management of hyperkalemia in emergency settings.

The insulin-glucose treatment to manage HK is less consensual than other statements which may be related to the risk of hypoglycemia after treatment.¹⁵ Patients in higher risk of post treatment hypoglycemia include age (>60 years old), pretreatment blood glucose ≤ 100 mg/dL (≤ 5.6 mmol/L), and pretreatment potassium > 6 mmol/L.¹⁶ In high-risk groups glucose must be monitored for at least 4-6 hours after administration.

This study illustrates a high degree of alignment among experts, emphasizing the potential for improving HK management in emergency contexts. However, it has some limitations, namely a potential selection bias as the participants in the consensus process are all internal medicine specialists. It would be valuable to explore the perspectives of cardiologists and nephrologists despite their attendance in general emergency rooms being less common in the Portuguese context. One

might suggest that setting a more stringent consensus criteria would necessitate an additional round for achieving more robust results. The decision to conduct only one round was based on the observation that the results obtained already reflected significant consensus among the experts, surpassing the 65% cut-off point for consensus. Nonetheless, we acknowledge that additional rounds could potentially enrich the dialogue among experts and further strengthen the study's findings. However, it's important to note that the Delphi consensus method commonly encompasses a range of 55% to 100%, with the standard threshold typically considered at 70%.^{15,16}

Conclusion

This study established a consensus on the effective management of HK in Portuguese emergency settings among 63

healthcare professionals. Our panel of distinguished Portuguese experts has worked collaboratively to formulate and endorse recommendations, covering critical aspects including the epidemiology, underlying mechanisms, optimal management, and treatment strategies for acute HK. Remarkably, most of the statements reached consensus levels of at least 90% agreement, which reinforces the credibility and reliability of our recommendations. We have also developed a visually informative tool, designed to foster a more unified clinical approach among Portuguese health professionals. We believe the implementation of these recommendations will contribute for optimization of the management of HK-related emergencies, improving patient clinical outcomes. ■

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MLB, CM, IA, JLA, NBV, SNM - Participaram como peritos e deram feedback crítico sobre o documento.

ASS - Feedback crítico e edição do manuscrito.

IF - Conceção do estudo, recolha de dados, redação do rascunho do manuscrito

Todos os autores aprovaram a versão final a ser publicada.

Contributorship Statement

MLB, CM, IA, JLA, NBV, SNM - Participated as experts, provided critical feedback of the paper.

ASS - Critical feedback and editing of the manuscript.

IF - Participated as experts, provided critical feedback of the paper.

All authors approved the final draft.

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Appendix

Appendix: Results of the first round of the Delphi questionnaire (n=63).

Statements, n %	Strongly disagree		Disagree		Neither agree nor disagree		Agree		Strongly agree		Agree/ Strongly agree	
Statement 1	0	0.0	1	1.6	0	0.0	32	50.8	30	47.6	62	98.4
Statement 2	0	0.0	1	1.6	3	4.8	29	46.0	30	47.6	59	93.7
Statement 3	0	0.0	2	3.2	1	1.6	18	28.6	42	66.7	60	95.2
Statement 4	0	0.0	1	1.6	5	7.9	25	39.7	32	50.8	57	90.5
Statement 5	1	1.6	3	4.8	1	1.6	24	38.1	35	55.6	59	93.7
Statement 6	1	1.6	2	3.2	3	4.8	20	31.7	37	58.7	57	90.5
Statement 7	0	0.0	0	0.0	2	3.2	24	38.1	37	58.7	61	96.8
Statement 8	0	0.0	1	1.6	1	1.6	21	33.3	40	63.5	61	96.8
Statement 9	0	0.0	0	0.0	1	1.6	11	17.5	51	81.0	62	98.4
Statement 10	0	0.0	0	0.0	1	1.6	22	34.9	40	63.5	62	98.4
Statement 11	1	1.6	2	3.2	0	0.0	17	27.0	43	68.3	60	95.2
Statement 12	0	0.0	2	3.2	3	4.8	32	50.8	26	41.3	58	92.1
Statement 13	3	4.8	9	14.3	3	4.8	29	46.0	19	30.2	48	76.2
Statement 14	0	0.0	7	11.1	9	14.3	29	46.0	18	28.6	47	74.6
Statement 15	0	0.0	3	4.8	7	11.1	26	41.3	27	42.9	53	84.1
Statement 16	0	0.0	0	0.0	4	6.3	29	46.0	30	47.6	59	93.7
Statement 17	0	0.0	1	1.6	0	0.0	41	65.1	21	33.3	62	98.4
Statement 18	0	0.0	0	0.0	3	4.8	36	57.1	24	38.1	60	95.2
Statement 19	0	0.0	1	1.6	20	31.7	21	33.3	21	33.3	42	66.7
Statement 20	0	0.0	2	3.2	2	3.2	41	65.1	18	28.6	59	93.7
Statement 21	0	0.0	3	4.8	16	25.4	29	46.0	15	23.8	44	69.8
Statement 22	0	0.0	0	0.0	1	1.6	15	23.8	47	74.6	62	98.4
Statement 23	0	0.0	3	4.8	11	17.5	37	58.7	12	19.0	49	77.8
Statement 24	0	0.0	0	0.0	0	0.0	29	46.0	34	54.0	63	100.0
Statement 25	0	0.0	0	0.0	0	0.0	32	50.8	31	49.2	63	100.0