

A Chinese Multi-Specialty Delphi Consensus to Optimize RAASi Usage and Hyperkalaemia Management in Patients with Chronic Kidney Disease and Heart Failure

Ming-Hui Zhao^{1*}, Wei Chen², Hong Cheng³, Bi-Cheng Liu⁴, Zhi-Guo Mao⁵, Zhuang Tian⁶, Gang Xu⁷, Jing-Min Zhou⁸

1. Renal Division, Peking University First Hospital, Beijing, 100034, China
2. Renal Division, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, 510080, China
3. Renal Division, Capital Medical University, Beijing, 100029, China
4. Renal Division, Southeast University Zhongda Hospital, Nanjing, 210009, China
5. Renal Division, Shanghai Changzheng Hospital, Shanghai, 200003, China
6. Department of Cardiology, Peking Union Medical College Hospital, Beijing, 100730 China,
7. Renal Division, Tongji Medical College of Huazhong University of Science and Technology, Wuhan, 430030, China
8. Department of Cardiology, Zhongshan Hospital, Fudan University, Shanghai, Department of Cardiology, 200032, China

Received December 5, 2023; accepted April 8, 2024; published online June 7, 2024.

Corresponding author: Ming-Hui Zhao, E-mail: mhzhao@bjmu.edu.cn.

This article has been accepted for publication but has not been through the copy editing, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record.

© The Authors 2024. Published by Chinese Academy of Medical Sciences. This is an open access article attributed under the CC BY-NC license (<https://creativecommons.org/licenses/by-nc/4.0/>).

ABSTRACT

Objective: Variations are present in common clinical practices regarding best practice in managing hyperkalaemia (HK), there is therefore a need to establish a multi-specialty approach to optimal RAASi usage and HK management in patients with chronic kidney disease (CKD) & heart failure (HF). This study aimed to establish a multi-speciality approach to the optimal use of RAASi and how to manage HK in patients with CKD and HF.

Methods A steering expert group of cardiology and nephrology experts from across China convened to discuss challenges to HK management through a nominal group technique. The group then created a list of 41 statements for a consensus questionnaire, which was distributed for a further survey of an extended panel group of cardiologists and nephrologists across China. Consensus was assessed using a modified Delphi technique, with agreement defined as "strong" ($\geq 75\%$ and $< 90\%$) and "very strong" ($\geq 90\%$). The steering group, data collection, and analysis were aided by an independent facilitator.

Results A total of 150 responses from 21 provinces across China were recruited in the survey. Respondents were comprised of an even split ($n=75$, 50%) between cardiologists and nephrologists. All 41 statements achieved the 75% consensus agreement threshold, of which 27 statements attained very strong consensus ($\geq 90\%$ agreement) and 14 attained strong consensus (agreement between 75% and 90%).

Conclusions Based on the agreement levels from respondents, the steering group agreed a set of recommendations intended to improve patient outcomes in the use of RAASi therapy and HK management in China.

Key Words: cardio-renal syndrome; chronic kidney failure; heart failure; hyperkalemia; multidisciplinary communication

INTRODUCTION

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health. This is indicated by a glomerular filtration rate (GFR) below $60 \text{ mL/min/1.73 m}^2$, or the presence of one or more markers of kidney damage. CKD is classified based on cause, glomerular filtration rate category, and albuminuria category^[1]. In China, CKD has been found to have a prevalence of 10.8% of the population over 18 years^[2]. CKD affects an estimated 50% of people with heart failure (HF)^[3] and around 50% of people with type 2 diabetes mellitus (T2DM)^[4].

Heart failure (HF) is not a single pathological diagnosis, but a clinical syndrome consisting of symptoms (*e.g.*, breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (*e.g.*, elevated jugular

venous pressure, pulmonary crackles, and peripheral edema)^[5]. HF has an estimated prevalence of 1.1% of the population aged ≥ 25 years in China, equating to 12.1 million people^[6].

Hyperkalemia (HK) is defined as a serum or plasma potassium level above normal (*i.e.*, >5.0 mmol/L). HK can be classified as mild (serum potassium concentration 5.0 – 5.9 mmol/L), moderate (6.0 – 6.4 mmol/L), or severe (≥ 6.5 mmol/L)^[7]. Mild HK is often asymptomatic, while severe HK may result in life-threatening cardiac arrhythmias, muscle weakness, or paralysis^[8]. CKD is a significant risk factor for HK. Epidemiological data show that the prevalence of HK was about 3.86% among Chinese outpatients but might reach 23% in those with CKD^[9].

Renin–angiotensin–aldosterone system inhibitors (RAASi) is a broad term that includes angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and angiotensin receptor-neprilysin (ARN) inhibitors. RAASi therapy has a complementary effect on both cardiac and renal function and has been shown to reduce blood pressure and proteinuria and slow the decline in estimated glomerular filtration rate (eGFR). It offers cardiorenal protection during the progression of both HF and CKD and reduces the risk of kidney failure, cardiovascular morbidity, and all-cause mortality in individuals with CKD and HF^[10]. For these reasons, RAASi therapy is widely used to treat patients with both HF and CKD.

International guidelines recommend the use of disease-modifying therapies (DMTs) including RAASi and sodium-glucose co-transporter-2 inhibitors (SGLT2i) in patients with CKD and hypertension or diabetes^[5,11-13], and this approach is supported in Chinese guidelines and consensus^[14-18]. The updated 2021 Kidney Disease Improving Global Outcomes (KDIGO) guideline for the management of blood pressure in CKD recommends RAASi as antihypertensive agents for non-dialysis CKD patients with hypertension^[12]. KDIGO 2024 CKD guidelines recommend that CKD patients with moderately or severely increased albuminuria should be started on RAASi therapy, and that RAASi should be considered for those with CKD and normal to mildly increased albuminuria and hypertension or HF with low ejection fraction^[19]. The *2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure* recommends initiation of RAASi therapy for treatment of Stage B: Pre-HF (to prevent progression to symptomatic HF and reduce mortality) and Stage C: Symptomatic HF patients^[20].

RAASi therapy can suppress potassium excretion and may increase the risk of HK^[21]. In this situation concerned physicians may choose to de-escalate or stop RAASi therapy based on patient safety, but

discontinuation sacrifices the long-term cardiorenal benefits and has proven to be one of the major barriers to achieving optimal control of disease progression^[21]. An alternative approach, which maintains RAASi therapy, is the use of a potassium-lowering therapy. Oral potassium binders are recommended in Chinese hyperkalaemia guidelines and consensuses^[16-18,22,23]. While drugs such as sodium polystyrene sulfonate (SPS) and calcium polystyrene sulfonate (CPS) lack evidence of long-term efficacy and safety, the emergence of new agents with a more favourable safety profile, such as sodium zirconium cyclosilicate (SZC) and patiromer, make the long-term management of HK possible while maintaining the optimal dose of RAASi therapy.

Variations are present in common clinical practices regarding best practice in managing HK, and there is therefore a need to establish a multi-specialty approach to optimal RAASi usage and HK management in patients with CKD & HF.

MATERIALS AND METHODS

A literature review of CKD and HF was performed on PubMed and Google Scholar, with an additional general web search using free-text terms to identify any relevant literature sources. Search terms included but were not limited to "cardio-renal syndrome", "chronic kidney failure", "heart failure", "hyperkalemia", and "multidisciplinary communication". Following the literature search, relevant information was used to generate questions and discussion points for the steering group. The modified Delphi technique used in this study was guided by the *Guidance on Conducting and REporting DElphi Studies* (CREDES). Due to organizational and regional variations across China, a modified Delphi technique^[24] was chosen to bring together experts from different regions and across specialities to reach agreement on a common set of recommendations that can be implemented to both issues of managing patients with CKD and HF and optimal approach to treatment. The overall process is outlined in (**Fig. 1**).

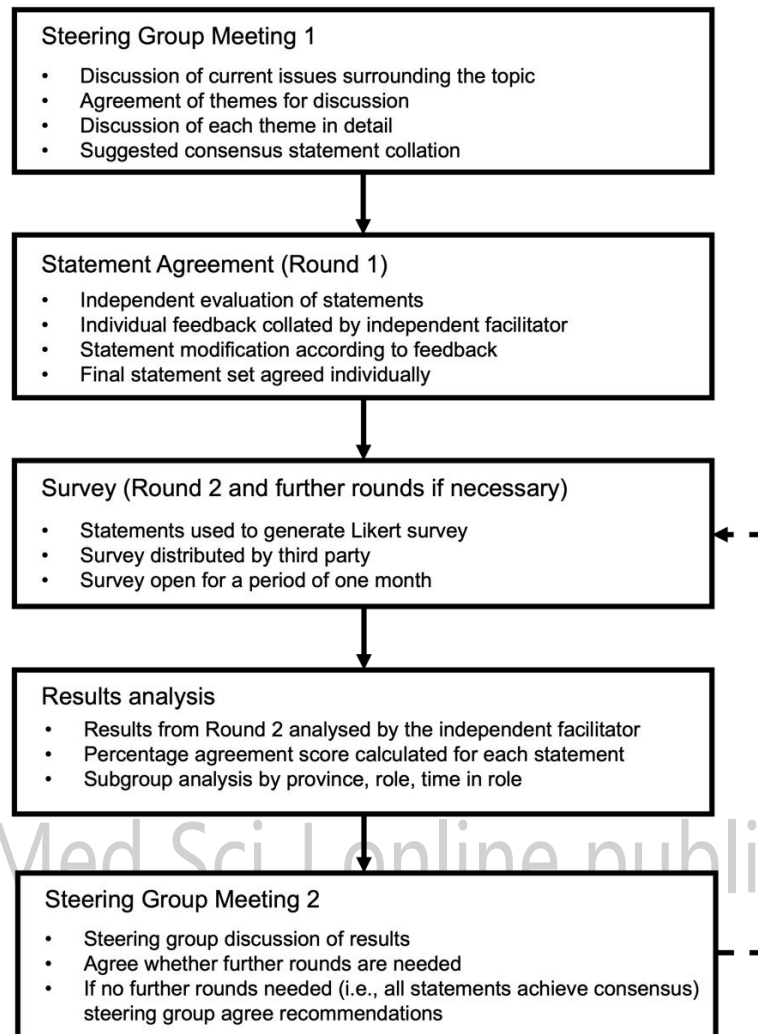


Figure 1. Study flow diagram.

Initial statements

A steering group of cardiology and nephrology experts from across China was convened in August 2022 to discuss current challenges in RAASi use and HK. The meeting was guided by an independent facilitator (Triducive Partners Limited). All the materials needed for the meeting were provided in both English and Chinese. Translation services were provided by Interprefy during the steering group meetings to ensure meetings were accessible for all members. The experts were defined as specialists in nephrology or cardiology who had achieved an appropriate level of seniority within their field (e.g., professors or clinical leads), had published papers related to the management of CKF/HF, or had been involved in guidelines development.

Five themes were agreed and discussed by the group, including: (A) Risk factors and risk stratification for managing HK in the cardiorenal patients; (B) Prevention of HK for at-risk cardiorenal patients ; (C) Correction of HK for at-risk cardiorenal patients with the use of potassium-lowering therapy; (D) Cross-specialty alignment (cardiology & nephrology); (E) Education of clinicians and patients.

The initial statements under each topic were then developed collaboratively. The statements were subsequently collated, and the steering group independently rated the statements as either "accept", "remove", or "reword" with suggested changes. A simple majority agreement was required to uphold suggested changes to the statements. Once finalized, the steering group agreed on the final set of statements for testing. This constituted the initial round of consensus.

Second round consensus

The resulting consensus statements (**Table 1**) were developed into a Likert survey, which was then distributed electronically by Sermo, a specialist medical market research organization, in Round 2. Prior to full distribution, the survey was tested with 10 Round 2 panel members for quality and assurance purposes. As no concerns were raised during this pilot distribution, all received responses were included in the dataset. The steering group members did not provide responses to the Round 2 survey.

Responder panel members for the second round consensus were recruited based on the following criteria: (i) Employed within China as a nephrologist or cardiologist; and (ii) speciality ratio of nephrology to cardiology was set as 1:1. The sample of panel members ($n=150$) was based the need for a comparable number of responses from cardiologists and nephrologists ($n=75$ from each responder group), the desire to gain insights from different provinces within China, and the resource availability. Participants with a variety of clinical experience were engaged in the study to ensure a broad spectrum of perspectives. The identity of respondents was not known to the steering group or the independent facilitator.

The questionnaire presented each statement alongside a 4-point Likert scale ("strongly disagree", "tend to disagree", "tend to agree", and "strongly agree") to allow respondents to indicate their level of agreement. The questionnaire also captured some demographic data (province of work, role, and years in role) to assist further analyses, but no further information was captured to ensure anonymity of responders.

The closing criteria for the study was defined *a priori* in line with best practice principles as: 90% of the final set of the statement, with the widely accepted consensus threshold at 75%^[25]. If these criteria were not met, statements would be modified, and the survey re-issued as necessary for a maximum of three rounds. Consensus was further categorised as "high" at $\geq 75\%$ and "very high" at $\geq 90\%$. Completed surveys were analyzed by the independent facilitator. Microsoft Excel software was used to produce an overall agreement score for each statement and to identify any patterns of agreement when analyzed by role, experience, and region. No further statistical methods were applied. The overall agreement level for each statement was calculated from the number of respondents expressing agreement as a percentage of the overall number of responses for each statement. As the survey was undertaken by a third party, response rate could not be calculated.

As this study only sought the anonymous opinions of physicians and no patient-specific data were captured, ethical approval was not sought. Respondents consented to having their responses included in this study by joining the panel organized by Sermo.

The Steering Group meticulously reviewed the survey results and developed a set of recommendations aimed at enhancing patient care. Given the high levels of agreement observed following the first survey round, the Group determined that additional rounds were not required.

RESULTS

The study collected a total of 150 responses from participants representing 21 provinces in China (**Fig. 2**). The majority of the respondents were based in Beijing ($n=26$), with Shanghai ($n=15$), Guangdong ($n=15$), and Jiangsu ($n=14$) following. The sample was purposefully balanced with an equal number of cardiologists and nephrologists ($n=75$ each).

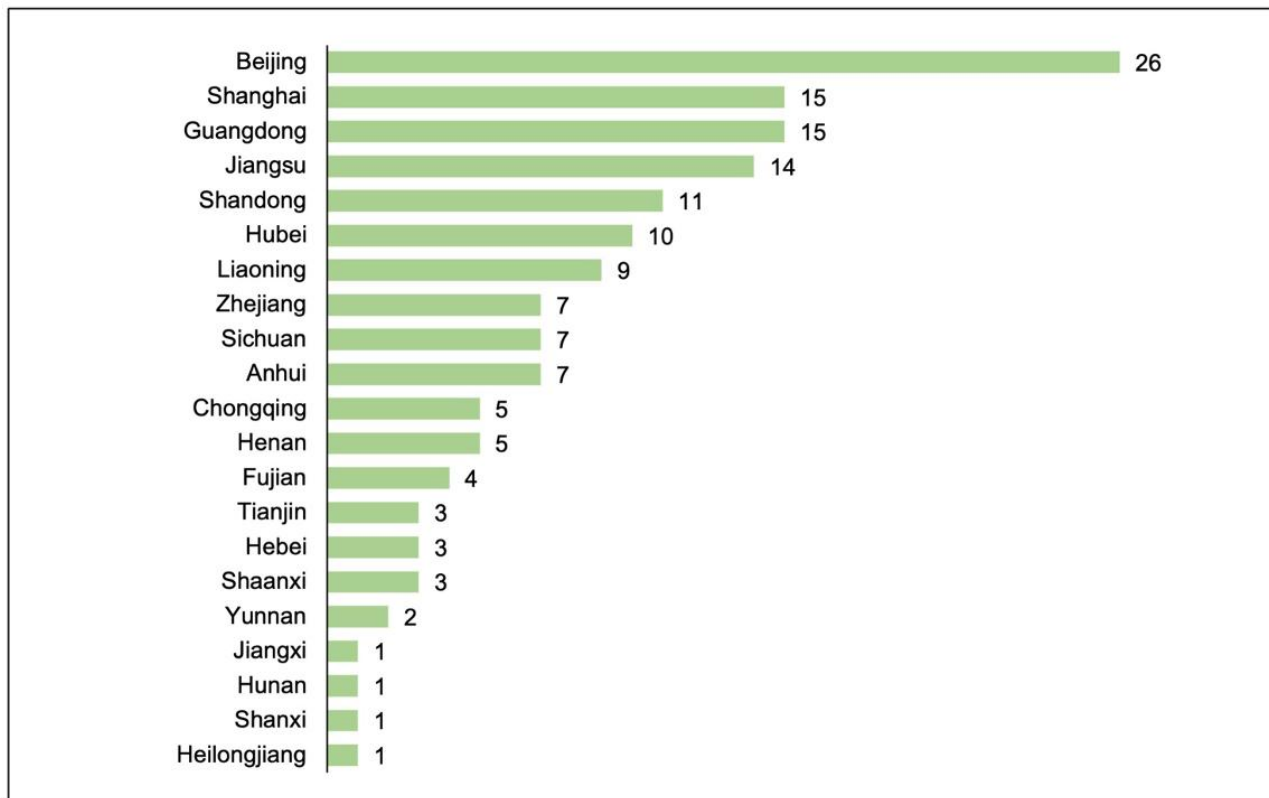


Figure 2. Respondent numbers by province (% of total response).

All statements achieved the 75% consensus agreement threshold (**Table 1; Fig. 3**). Of these, 27 statements attained very strong agreement ($\geq 90\%$ agreement) and 14 attained strong agreement ($\geq 75\%$ and $< 90\%$).

Alignment between the specialities was broadly similar, but some disparities were identified between specialities and provinces when analyzing individual statements, as highlighted within the "Discussion" section.

Table 1. Consensus agreement by statement

No.	Statements	Agreement
Topic A: Risk factors and risk stratification for managing hyperkalaemia in the cardiorenal patient		
1.	Patients with chronic kidney disease, heart failure, or diabetes are at increased risk of hyperkalaemia	97%
2.	Patients on RAASi and MRA treatments are at increased risk of hyperkalaemia	95%

3.	Cardiorenal patients should have their serum potassium levels tested at least every 6 months or more according to disease severity	89%
4.	Cardiorenal patients undergoing RAASi up-titration should have their serum potassium levels tested at least every two weeks during the up-titration period and monitored routinely thereafter	97%
5.	Patients with CKD stage 4/5 should have their serum potassium levels tested at least every 3 months	89%
6.	Patients who have an episode of hyperkalaemia should have their serum potassium levels tested two weeks later and at least every 3 months thereafter	89%
Topic B: Prevention of hyperkalaemia for at-risk cardiorenal patients		
7.	For those patients with a known history of hyperkalaemia preventing optimisation of RAASi therapy, a novel potassium binder can be used to enable RAASi optimisation	98%
8.	For those patients at risk of hyperkalaemia using RAASi therapy, advice about dietary considerations and the impact on potassium levels should be provided	96%
9.	While a low potassium diet is commonly advised this approach may be counter to a heart healthy diet that is beneficial to cardiorenal patients	81%
10.	Low potassium diets can be difficult to follow, especially during certain seasons where different fruits are more readily available	93%
11.	Advising a low potassium diet to control hyperkalaemia is increasingly controversial: the evidence for the effectiveness of a low-potassium diet is not strong	84%
Topic C: Correction of hyperkalaemia for at-risk cardiorenal patients with the use of potassium lowering therapy		
12.	Hyperkalaemia should be recognised as a predictable, treatable, and manageable side effect of optimal heart failure/chronic kidney disease therapy	96%
13.	Optimising and maintaining RAASi therapy provides better outcomes for cardiorenal patients including morbidity and mortality	97%
14.	In practice, the occurrence of hyperkalaemia may lead to the down-titration or discontinuation of RAASi therapy	97%
15.	When managing mild-to-moderate hyperkalaemia in cardiorenal patients, RAASi therapy should be maintained due to the cardioprotective benefit in this patient type	79%
16.	A goal for the management of cardiorenal patients should be to utilise the maximum recommended dose of RAASi therapy	86%
17.	Action to manage hyperkalaemia should be taken when the serum potassium level exceeds 5.0 mmol/L	97%
18.	RAASi use should not be de-escalated or discontinued due to hyperkalaemia unless alternative methods of hyperkalaemia management have been optimised, including initiation of potassium binder therapy	88%

19.	Novel potassium binders enable guideline recommended RAASi dosing and the proven benefits that they bring to patients	97%
20.	When potassium levels exceed 6.5 mmol/L, RAASi treatment down-titration, suspension, or cessation should be considered	97%
21.	When treating cardiorenal patients, permanent discontinuation of RAASi therapy should be considered a last resort strategy	75%
22.	Where disease modifying therapy has been reduced or ceased due to hyperkalaemia, it should be reinstated once normokalaemia is achieved	89%
23.	Prolonged use of SPS should be avoided due to the association with severe gastrointestinal side effects, including bowel necrosis	89%
24.	Prolonged use of SPS should be avoided due its poor palatability and poor patient acceptance	81%
Topic D: cross-specialty alignment (Cardiology & Nephrology)		
25.	Continuity of care is important in the management of hyperkalaemia	97%
26.	Significant variation in approach to cardiorenal diseases and hyperkalaemia management in China leads to variable patient outcomes	93%
27.	There is a need for a consistent and agreed understanding of hyperkalaemia management within the hospital setting, especially between Cardiology & Nephrology	97%
28.	Cardiology and Nephrology guidelines should contain aligned recommendations for the management of hyperkalaemia	95%
29.	Patients with cardiorenal comorbidities should be managed by a multi-disciplinary team (MDT) with an agreed management plan	99%
30.	Cross-specialty alignment can enable optimal doses of disease-modifying drugs (RAASi) to be maintained	96%
31.	Primary care is an important component of the multi-disciplinary team (MDT) for the management of cardiorenal patients	95%
32.	Endocrinology is an important component of the multi-disciplinary team (MDT) for the management of cardiorenal patients	88%
33.	Emergency care is an important component of the multi-disciplinary team (MDT) for the management of cardiorenal patients	89%
34.	Before making a treatment decision regarding down-titration or cessation of a disease modifying therapy (RAASi), primary care should refer to a specialist cardiologist or nephrologist	97%
Topic E: Education of clinicians and patients		
35.	Up-to-date education on the management of hyperkalaemia and guidelines for RAASi therapy is needed	100%
36.	Structured education of HCPs on routine serum potassium testing and hyperkalaemia management improves patient outcomes	99%

37.	Education for patients at risk of hyperkalaemia improves their outcomes	99%
38.	Education of hyperkalaemia management is best delivered by cardiology or nephrology specialists	96%
39.	Education of non-specialist HCPs (e.g., primary care physicians, emergency physicians, endocrinology physicians, dialysis centre nurses) regarding hyperkalaemia improves patient outcomes	97%
40.	Patients need to understand the consequences of hyperkalaemia and how to avoid it through lifestyle modification and appropriate use of potassium lowering therapies	99%
41.	Patients should be aware of the potential impact that herbal medicines may have on the risk of hyperkalaemia	97%

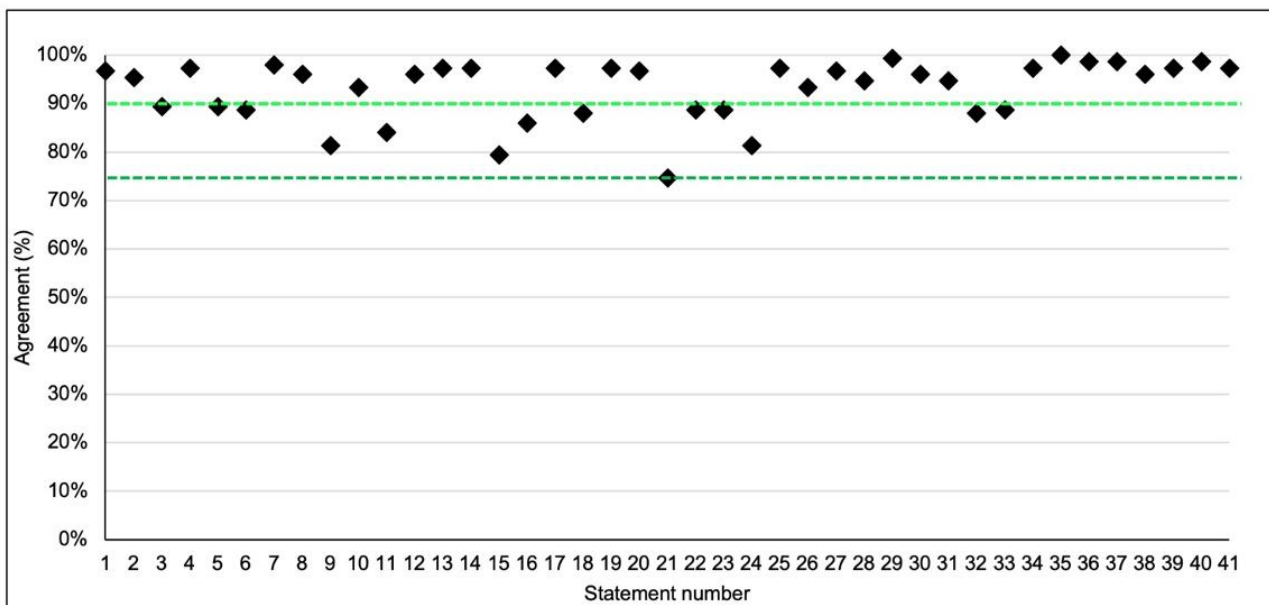


Figure 3. Combined consensus agreement scores. The dark green line represents consensus threshold of 75% and the light green line represents the threshold for very strong consensus (90%).

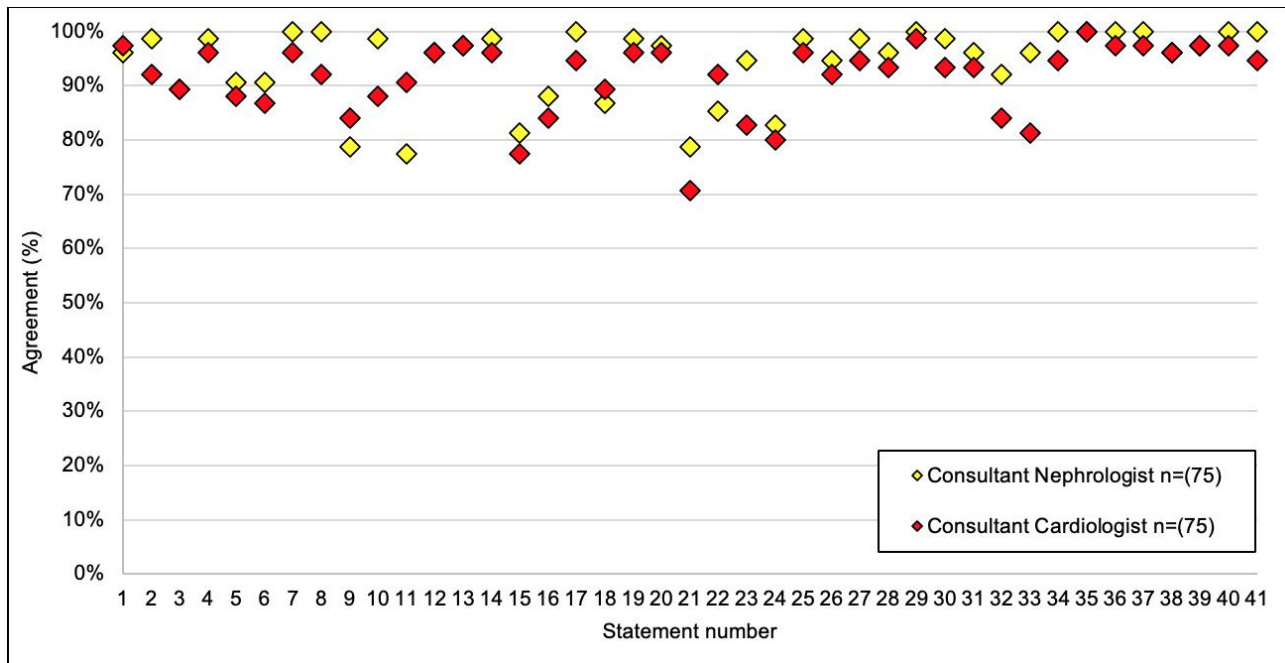


Figure 4. Consensus agreement by role.

DISCUSSION

This modified Delphi study engaged a group of representative experts to reach consensus on the management of patients with CKD and HF in China. The first survey round yielded unexpectedly high levels of agreement (75% – 100%) across all statements, negating the need for additional survey rounds. The results support the adoption of some basic principles for both specialist and general medicine practitioners to improve the delivery of care for cardiorenal patients in China. When analyzing the results by sub-group, cardiologists and nephrologists appeared to demonstrate similar opinions across the majority of statements (**Fig. 4**). However, cardiologists did not achieve consensus agreement regarding the discontinuation of RAASi therapy as a last resort, suggesting that cardiologists may be more willing than nephrologists to stop RAASi therapy in practice. The steering group were surprised by the overall levels of agreement achieved, particularly as, to minimize bias, a third party was used to distribute the survey and respondents remained anonymous throughout the process.

Statement 4 (S4) within topic A stands out as a key statement, emphasizing the importance of monitoring serum potassium levels every two weeks during initiation of RAASi. Very strong agreement for statements 1 & 2 (97% & 95%, respectively) demonstrates good respondent awareness of the increase in HK risk for patients with CKD, HF, and T2DM. This is supported further by strong agreement for statements 3, 5,

& 6 (range: 89% – 97%) supporting the need for regular monitoring of serum potassium at intervals determined by individual risk factors.

There are challenges in China regarding the long-term follow-up of some patients, due to the current low levels of downward referral. A 2019 study found that 84% of patients with chronic diseases went without downward referral (that is, a referral from specialist/hospital to a family doctor/general practitioner)^[26], and this is recognised by policymakers, for example, the Healthy China 2030 initiative is intended to build innovative patient referral models for health care reform in China^[27]. The lack of downward referral for ongoing management means that a physician may stop RAASi treatment in the interests of patient safety. But for the longer-term benefit of the patient, serum potassium management should be the approach. In the management of CKD, HF and chronic HK, follow-up should be seen as the key to achieving the optimal patient outcomes.

The lowest agreement in Topic B was seen for statement 9 (81%). This may have been due to the phrasing and translation into Chinese, or that efficacy and safety of a low potassium diet is not clear within the literature. Response to statement 11 (84%) suggests that this is well recognised but analysis by specialty shows some differences, with 91% agreement amongst cardiologists compared with 77% for nephrologists. This could be due to nephrologists being comfortable with providing step-wise advice according to HK severity and rate of serum potassium change, or it may be a reflection that potassium lowering treatments are not easily available for use and that in the absence of this option the nephrologist may attempt to address all contributory factors to elevated serum potassium. In contrast, cardiologists may exercise caution and choose not to follow a treatment course that is not supported by the evidence base.

Observational studies report weak associations between dietary potassium intake and potassium concentration and this approach may deprive patients of the beneficial cardiovascular effects associated with potassium-rich diets^[28]. This is where pharmaceutical management, including the use of potassium binders (S7, 98%), can play an important role. There is evidence to support the use of SZC in HK, and appropriate use can maintain the safety of patients on RAASi by reducing serum potassium^[29].

It is important to recognize HK as a manageable consequence of both CKD and the use of optimal RAASi therapy (S12, 96%). Those who regularly use SPS may feel that the palatability and patient acceptance concerns do not arise in practice (S24, 81%), but still agree that SPS should be avoided for long-term use

due to the established side effect profile (S23, 89%).

The levels of agreement suggest that for mild-to-moderate HK, RAASi therapy should be maintained at therapeutic dose and managed with a potassium lowering agent where necessary. A serum potassium level above 6.5 mmol/L is considered to be severe HK, in this situation RAASi treatment should be discontinued and potassium lowering therapy should be started immediately. Once serum potassium has lowered to an acceptable level, RAASi should be reinstated where possible (S22, 89%). Some physicians may consider reinstatement of RAASi to be a risk, while others may be unsure of how long an interval is required (if any) once normokalaemia is achieved. Education programmes should be put in place to address these knowledge gaps.

Agreement with statement 25 (97%) emphasises the importance of continuity of care. A consistent cross-specialty approach is key for the long-term management of HK, the maintenance of heart and kidney health, and the associated long-term patient outcomes. It is encouraging to see the high agreement for the alignment of professional guidelines on HK management (S28, 95%). Ideally, cardiologists and nephrologists should agree a common tiered treatment approach based on serum potassium levels and risk factors. Where possible, the optimal course of action for cardiorenal patients should be agreed by a multidisciplinary team (MDT).

High agreement levels for topic E highlight the desire for targeted education programmes for HK for both patients and HCPs. These education programmes are best delivered by cardiologists and nephrologists (S38, 96%) with experience of managing HK. Physician education has been shown to improve patient outcomes in other areas of medicine^[30] and could prove beneficial to the holistic management of cardiorenal patients. Education initiatives can also be supported by pharmacologists, who have additional valuable insights to support the optimization of treatment for HK.

When considering lifestyle factors which could influence serum potassium levels, the use of herbal medicines should be included, as these may contain significant amounts of potassium. For this reason, herbal medicine use should be investigated in all CKD stage 4 and 5 patients, and any potential side-effects of herbal medicine should be fully discussed with patients.

The findings of this modified Delphi consensus echo those of an expert panel in Portugal. Given the

guiding principle of maintaining or up-titrate RAASi therapy to maximum target doses the authors recommend the use of novel potassium binders to help to achieve this target in the face of HK. The group also propose treatment algorithm for chronic HK that recommends the use of novel potassium binders in both Mild (serum K⁺ = 5.1-5.5 mEq/L) and moderate HK (serum K⁺ = 5.6-6.0 mEq/L) to maintain RAASi therapy. The algorithm only recommends the discontinuation of RAASi where serum K⁺ is > 6 mEq/L (e.g., severe and life-threatening HK)^[31].

Comparison with results of a similar study from Europe and North America

A similar consensus exercise was previously carried out in Europe and North America (E&NA) with responses from 268 cardiologists and 252 nephrologists across 7 countries^[32]. Analysis of responses to common statements showed the following differences:

The key areas of divergence were around the utility of RAASi in practice. Respondents from E&NA tended to agree that RAASi therapy should be maintained for mild-to-moderate HK in cardiorenal patients and were more likely to agree that maintenance of maximal RAASi dose is a goal in these patients. Cessation or down-titration of RAASi therapy seems to be more acceptable in China, and the potential reasons for this may include:

- In E&NA, there is usually a referral system in place with a family/ primary care physician responsible for ongoing patient care and making referrals for access to a specialist, providing greater opportunity for patient follow-up. In China, follow-up is difficult to implement and so decisions may be made primarily on short-term safety grounds rather than long-term benefits.
- In China, the use of herbal medicine has a strong tradition, but these treatments may potentially expose the patient to elevated dietary potassium.
- Medical schools in China tend to emphasise the danger associated with acute HK and the need for a cautious approach, this may lead to risk aversion when it comes to HK. As the availability and experience with potassium lowering therapies increases, it is expected that this practice will change, and HK will be regarded as a chronic and manageable condition.
- Organisation of health services in China can make follow up of patients difficult, some patients may struggle to fund repeat visits, particularly when the distance to see a specialist is considerable, and this

can be further complicated by issues of insurance coverage, which can vary significantly between provinces.

Recommendation statements

1. Hyperkalaemia should be recognized as a predictable, treatable, and controllable side effect of optimal RAASi therapy
2. Cardiorenal patients undergoing RAASi up-titration should have their serum potassium levels tested at least every two weeks during the up-titration period
3. Patients with a history of hyperkalaemia or who have CKD stage 4/5 should have their serum potassium tested at least every 3 months
4. A novel potassium binder can be used to support RAASi optimisation in patients with a history of hyperkalaemia
5. A low potassium diet is counter to a heart healthy diet that is beneficial to cardiorenal patients
6. When treating cardiorenal patients, permanent discontinuation of RAASi therapy should be considered a last resort strategy
7. Prolonged use of SPS should be avoided due to the association with severe gastrointestinal side effects, including bowel necrosis
8. Cardiology and Nephrology guidelines should contain aligned recommendations for the management of hyperkalaemia
9. Continuity of care is important in the management of hyperkalaemia
10. Structured education of HCPs on routine serum potassium testing and hyperkalaemia management improves patient outcomes
11. Cardiorenal patients should be educated on hyperkalaemia and how to avoid it through lifestyle modification and appropriate use of potassium lowering therapies
12. Patients with CKD stage 4/5 should cease the use of herbal medicines

These principles can be used to underpin a pathway of care, the broad principles of which are shown in Figure 5, this demonstrates the importance of both a multidisciplinary approach and continuity of care in patients with chronic and progressive disease such as CKD & HF (with or without HK).

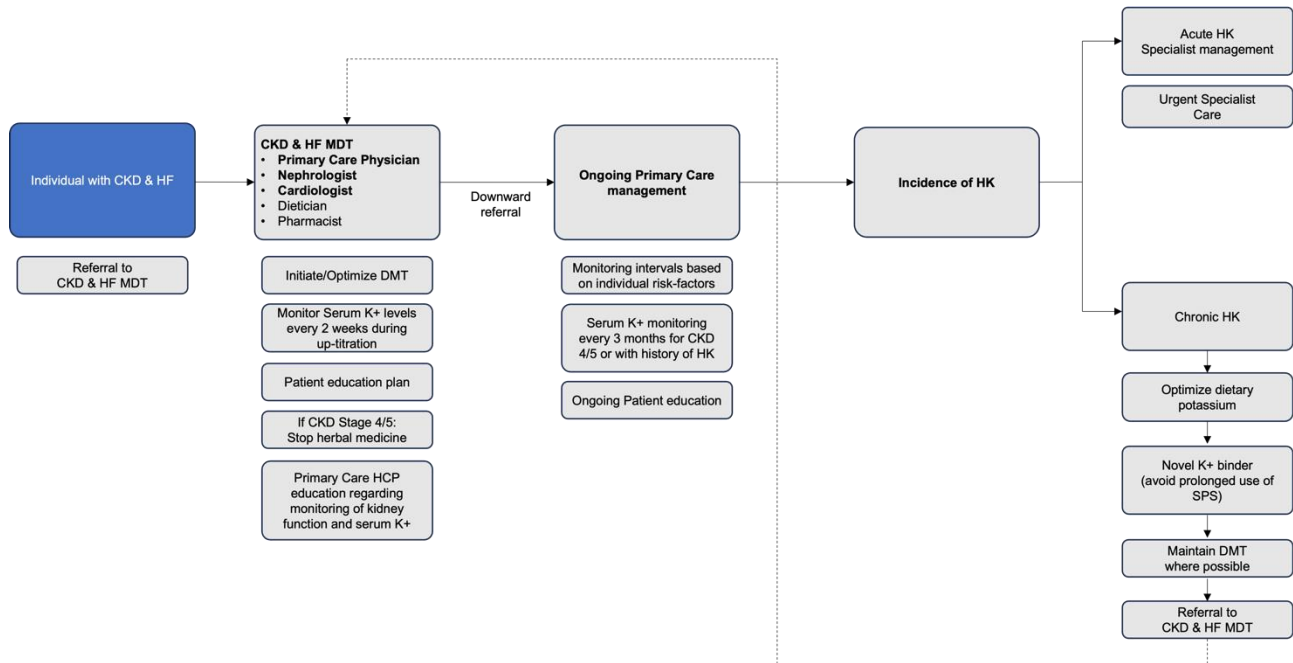


Figure 5. Model pathway of care for chronic kidney disease & heart failure (with or without hyperkalaemia).

CKD: chronic kidney disease; HF: heart failure; HK: hyperkalaemia; MDT: multi-disciplinary team; DMT: disease-modifying therapies.

Chin Med Sci J online publication

Strengths and Limitations

The 150 responses with even representation from cardiology and nephrology across 21 provinces in China is a strong basis for consensus. The majority of respondents (146/150) had at least 5 years' experience in role and 91/150 saw >50 patients with HK in a 3-month period, suggesting an experienced and suitably expert panel. Distributing the survey via Sermo meant that responder identities were not known to the steering group, thereby minimising selection bias, and also the steering group were not able to provide responses as part of the expert panel, further limiting undue influence. A four-point Likert scale was used in the survey, while this was specifically chosen to force a choice (either agreement or disagreement) and avoid neutral responses, it also may have led to a greater level of general agreement with statements than is reflected in practice.

This study had some key limitations. Very high levels of agreement were achieved across the statements, this which may suggest that the statements were constructed as to achieve agreement (confirmation bias), or that perhaps they represent previously established good practice, or that specialists in

China agree with the statements but community physicians and primary care practitioners, who may have a lower awareness of CKD and the use of RAASi treatments, are not able or lack the resources to reflect this best practice. A suggested improvement may have been to allow the panel to comment on the statements and make suggestions. There was also low representation from some provinces, making identification of geographic variations difficult. Further work could be undertaken to look specifically at geographic variation in practice within China and suggest how this can be reduced.

The opinions of patients and consideration of the patient experience (outside of treatment outcomes) were not sought, this can be considered a limitation as the patient perspective may have significant bearing on the identification of barriers and opportunities in HK management in China.

Conclusions

This consensus document is based on expert opinion from 150 cardiologists and nephrologists across 21 provinces in China. The attitude towards HK management in China appears to be moving towards that of HK as a chronic and controllable condition, and mild-to-moderate HK should not result in the stopping of disease-modifying treatments such as RAASi. Collaboration between cardiologists and nephrologists in the treatment of cardiorenal patients should be encouraged, with the coordinated development of guidelines on HK management and the delivery of educational programmes being two important initiatives in improving the consistency of care in China. The high agreement levels achieved from 150 experienced specialists provides basis for the recommendations made by the authors.

ARTICLE INFORMATION

Acknowledgments

The authors wish to thank Dal Singh and Ian Walker from Triducive Partners Ltd. for their support in data collection, analyses and scientific writing.

Conflicts of interest

The study was initiated and funded by AstraZeneca. AstraZeneca commissioned Triducive Partners Limited to facilitate the project and analyse the responses to the consensus statements in line with the Delphi methodology. AstraZeneca made no contribution to the study design and development, and had no involvement in the selection of survey respondents or the distribution of questionnaires. AstraZeneca took no part in the analysis and interpretation of results, or in the writing, revision or editing of the manuscript except checking that the manuscript contained no promotion of specific medicines and that all recommendations were appropriate to drug label. All authors received personal fee from AstraZeneca during conduct of the study. Zhao MH has received honoraria and speaker fees from AstraZeneca, BioMap, GSK, Kira, Novartis, and SanReno. Cheng H, Liu BC, Tian Z, Mao ZG, Xu G, Zhou JM, He Q, Jin W, and Chen W have no further disclosures to make.

Author contributions

Zhao MH: Conceptualization, methodology, validation, writing - review & editing, and supervision; Chen W, Cheng H, Liu BC, Mao ZG, Tian T, Xu G, and Zhou JM: conceptualization, methodology, and writing - review & editing.

REFERENCES

1. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int* 2022; 102 (5S): S1-S127. doi: 10.1016/j.kint.2022.06.008.
2. Expert Group on Kidney Clinical Quality Control Center in Shanghai. Guidelines for early screening, diagnosis, and prevention of chronic kidney disease (2022 edition). *Chin J Nephrol* 2022; 38(5): 453-64. doi: 10.3760/cma.j.cn441217-20210819-00067.
3. van de Wouw J, Broekhuizen M, Sorop O, et al. Chronic kidney disease as a risk factor for heart failure with preserved ejection fraction: a focus on microcirculatory factors and therapeutic targets. *Front Physiol* 2019; 10: 1108. doi: 10.3389/fphys.2019.01108.
4. Thomas MC, Cooper ME, Zimmet P. Changing epidemiology of type 2 diabetes mellitus and associated chronic kidney disease. *Nat Rev Nephrol* 2016; 12(2): 73-81. doi: 10.1038/nrneph.2015.173.

5. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021; 42(36): 3599-726. doi: 10.1093/eurheartj/ehab368.
6. Wang H, Chai K, Du M, et al. Prevalence and incidence of heart failure among urban patients in China: a national population-based analysis. *Circ Heart Fail* 2021;14(10): e008406. doi: 10.1161/CIRCHEARTFAILURE.121.008406.
7. Clase CM, Carrero JJ, Ellison DH, et al. Potassium homeostasis and management of dyskalemia in kidney diseases: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2020; 97(1): 42-61. doi: 10.1016/j.kint.2019.09.018.
8. Simon LV, Hashmi MF, Farrell MW. Hyperkalemia. [Updated 2022 Oct 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 January.
9. Bian J, Zuo L, Zhao H, et al. Epidemiology and treatment pattern of hyperkalemia among outpatients in China: a descriptive study using an administrative database in China. *Chin J Blood Purif* 2020; 19(11): 726-9. doi: 10.3969/j.issn.1671-4091.2020.11.002. (Chinese)
10. Kanda E, Rastogi A, Murohara T, et al. Clinical impact of suboptimal RAASi therapy following an episode of hyperkalemia. *BMC Nephrol* 2023; 24(1): 18. doi: 10.1186/s12882-022-03054-5.
11. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int* 2020; 98(4S): S1-S115. doi: 10.1016/j.kint.2020.06.019.
12. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. *Kidney Int* 2021; 99(3S): S1-S87. doi: 10.1016/j.kint.2020.11.003.
13. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022; 145(18):e895-e1032. doi: 10.1161/CIR.0000000000001063.
14. Chinese Society of Nephrology. Guidelines for early screening, diagnosis, prevention and treatment of chronic kidney disease (2022 Edition). *Chin J Nephrol* 2022; 38(5): 453-64. doi: 10.3760/cma.j.cn441217-20210819-00067.
15. Chinese Society of Nephrology. Guidelines for hypertension management in patients with chronic kidney disease in China (2023). *Chin J Nephrol* 2023; 39(1): 48-80. doi: 10.3760/cma.j.cn441217-20220630-00650.
16. Heart Failure Group of Cardiovascular Physician Branch of Chinese Medical Doctor Association, Expert Consensus Working Group on Management of Hyperkalemia in Patients with Heart Failure in China. Expert consensus on management of hyperkalemia in patients with heart failure in China. *Chin J Med* 2021; 101 (42):3451-8. doi: 10.3760/cma.j.cn112137-20210624-01430.

17. Chinese Medical Doctor Association Heart Failure Professional Committee, National Cardiovascular Expert Committee Heart Failure Professional Committee, Chinese Journal of Heart Failure and Cardiomyopathy Editorial Board. Expert consensus on ion management for patients with heart failure in China. *Chin J HF CM* 2020; 4(1): 16-31. doi: 10.3760/cma.j.cn101460-20200114-00004.
18. Expert Group of Nephrology Branch of Chinese Medical Association. Expert consensus on serum potassium management practice in patients with chronic kidney disease in China. *Chin J Nephrol* 2020; 36 (10): 781-92. doi: 10.3760/cma. j.cn441217-20200721-00139.
19. Kidney Disease: Improving Global Outcomes (KDIGO) 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int* 2024, 105(Suppl 4S): S117–S314.
20. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. *Circulation*. 2022;145:e895–e1032. doi: 10.1161/CIR.0000000000001063
21. Zhang J, He X, Wu J. The impact of hyperkalemia on mortality and healthcare resource utilization among patients with chronic kidney disease: a matched cohort study in China. *Front Public Health* 2022;10: 855395. doi: 10.3389/fpubh.2022.855395.
22. Expert Group of Guidelines on the Management of Hyperkalemia in Maintenance Hemodialysis Patients in China. Guideline on the management of hyperkalemia in maintenance hemodialysis patients in China. *Chin J Blood Purif* 2022; 21(Suppl): S1-S16. (Chinese)
23. Xue C, Mei C. Long-term management of hyperkalemia in chronic kidney disease. *Chin J Nephrol*. 2021, 37(4): 380-4. DOI: 10.3760/cma.j.cn441217-20200623-00056.
24. Dalkey N, Helmer O. An experimental application of the Delphi method to the use of experts. *Management Sci* 1963; 9: 458-67.
25. Diamond IR, Grant RC, Feldman BM, et al. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. *J Clin Epidemiol* 2014; 67(4): 401-9.
26. Jing X, Xu L, Qin W, et al. The willingness for downward referral and its influencing factors: a cross-sectional study among older adults in Shandong, China. *Int J Environ Res Public Health* 2020; 17(1): 369. doi: 10.3390/ijerph17010369.
27. Xiao Y, Chen X, Li Q, et al. Towards Healthy China 2030: modeling health care accessibility with patient referral. *Soc Sci Med* 2021; 276: 113834. doi: 10.1016/j.socscimed.2021.113834.
28. Bernier-Jean A, Wong G, Saglimbene V, et al. Dietary potassium intake and all-cause mortality in adults treated with hemodialysis. *Clin J Am Soc Nephrol* 2021; 16: 1851-61. doi: 10.2215/CJN.08360621.
29. Yuan Lu, Bi-Cheng Liu & Hong Liu. An evaluation of sodium zirconium cyclosilicate: a new treatment option for hyperkalemia in China. *Expert Opin Pharmacother* 2023; doi:10.1080/14656566.2022.2161884
30. Brown R, Bratton SL, Cabana MD, et al. Physician asthma education program improves outcomes for children of low-income families. *Chest*. 2004;126(2): 369-74. doi: 10.1378/chest.126.2.369.

31. Silva-Cardoso J, Brito D, Frazão JM, et al. Management of RAASi-associated hyperkalemia in patients with cardiovascular disease. *Heart Fail Rev* 2021; 26(4): 891-6. doi: 10.1007/s10741-020-10069-3.
32. Burton JO, Coats AJS, Kovesdy CP, et al. An international Delphi consensus regarding best practice recommendations for hyperkalaemia across the cardiorenal spectrum. *Eur J Heart Fail*. 2022; 24(9): 1467-77. doi: 10.1002/ejhf.2612.

(Edited by Liang-Jun Gu)

Chin Med Sci J online publication