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REVIEW

A Delphi consensus project to capture experts' opinion on hyperkalaemia management across the cardiorenal spectrum

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Abstract

The main purpose of this project was to capture experts' opinion on hyperkalaemia management and form best practice recommendations for cardiorenal patients in Greece. A steering committee of nephrologists and cardiologists developed 37 statements. An online questionnaire completed by 32 experts in cardiorenal management in Greece. Median score used to determine the level of agreement and disagreement index (DI) used to determine the level of consensus for each statement. Statements divided in four sectors: hyperkalaemia risk management, preventative measures, treatment and collaboration between specialties. The rate of the first round of the consensus was 94.6%. Median score was >7 for 36 of 37 statements and DI ≤ 1 for 35 of 37. Among other statements, consensus reached for recognizing levels K+ > 5.0 mEq/L as associated with elevated mortality risk; retaining renin–angiotensin–aldosterone system inhibitors (RAASi) on maximum recommended dose for cardiorenal patients; and using novel K+ binders to help enabling guideline-recommended doses of RAASi therapy. Cardiologists compared to nephrologists showed higher reluctance to discontinue down-titrate RAASi and MRA in patients with K+ levels above 5 mEq/L. Additionally, 88.9% of nephrologists and 71.4% of cardiologists agreed that cross-specialty alignment on a serum K+ concentration level (K > 5.5 mEq/L) is needed to initiate hyperkalaemia treatment. Both cardiologists and nephrologists showed disagreement with the statement on keeping titration in cardiorenal patients with K+ > 5.5 mEq/L or preserving fruit and vegetable consumption when moderate or severe hyperkalaemia exhibits. This Delphi project pointed out nephrologists' and cardiologists' agreement on hyperkalaemia management in cardiorenal patients; thus, it can help a cross-specialty optimal management of cardiorenal patients, with hyperkalaemia not being an obstacle for disease-optimizing therapy. Novel potassium binding agents can enable guideline-recommended doses of potassium-sparing medication.

Keywords Cardiorenal; Delphi method; Hyperkalaemia; Potassium binder; RAAS inhibitor

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Introduction

Potassium (K+) is an essential dietary mineral that is precisely balanced by internal and external homeostatic mechanisms, primarily regulated by the kidney, along with extrarenal mechanisms present in the gastrointestinal track. Hyperkalaemia (HK) is a potentially life-threatening condition; especially patients who have chronic kidney disease (CKD) or diabetes mellitus (DM) or who are taking renin–angiotensin–aldosterone system inhibitors (RAASi) are at increased risk.[1] The incidence of HK in large-scale randomized trials even in patients with heart failure (HF) and reduced ejection fraction (HFrEF) receiving medications of the RAASi is relatively low, mainly due to the pre-selection criteria that excluded patients with CKD.[2] As a result, strategies of management are not evidence-based. In clinical practice, where there is no patient selection and less rigorous serial monitoring of serum K+ exists, HK prevalence is reported increased. In patients with CKD, HK is associated with higher healthcare costs and mortality rates; but in HF patients, the occurrence of HK may lead to postpone up-titration, following by down-titration or even discontinuation of medications essentials for the clinical course

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and survival of those patients.[3] In addition, multiple renin–angiotensin–aldosterone system (RAAS) blockers including mineralocorticoid receptor antagonists (MRAs) and β-blockers may be beneficial in patients with resistant hypertension (HTN) and other cardiovascular disorders. However, RAAS blockers and MRAs are associated with an increased incidence of HK, especially in patients with concomitant CKD.[4–6] Furthermore, dietary intake of K+ or use of other pharmaceutical agents that impair the ability to excrete K+, such as non-steroidal anti-inflammatory drugs, increases the burden of this condition. Dietary restriction of K+ consumption leads to lower adherence to Mediterranean type of diet that has shown beneficial effects on various cardiovascular disease, including kidney dysfunction, HF and resistant HTN.[7] In the field of HF, the implementation of recent findings of STRONG-HF study for high-intensity care with rapid up-titration of guideline-directed medical therapy that has proved reduction in all-cause death or HF readmission can be impended due to HK incidence.[8] Thus, a multidisciplinary consensus from two specialties, nephrologists and cardiologists, that show close collaboration in daily clinical practice for the management of patients with cardiorenal disease coming from a Mediterranean basin country may confer in the better appreciation of recognition and treatment of cardiorenal patients prone to present high serum K+ levels.

Methods

Overview

The aim of this project was to establish a national multidisciplinary consensus based on experts' opinions regarding HK management in patients with cardiorenal disease using the Delphi consensus method.[9–13] The Delphi process achieves consensus by using the collective opinion of panel members through an online survey questionnaire, all the while maintaining anonymity thus assuring the free expression of opinions. It usually involves multiple rounds; between rounds, the group's responses are analysed, summarized and communicated back to the participants, a process called controlled feedback. Participants are then allowed to reflect on their response and compare it with the overall direction of the collective group before completing the survey questionnaire again, at which point they can possibly amend their answers. This is repeated until an acceptable level of consensus is reached (no universal agreed cut-off exists) or for a planned number of rounds depending on the research question (typically two to three rounds). For this project, a Delphi survey comprising up to three rounds was planned to be conducted via an online platform.

Results

Participants and consensus rates

The expert panel consisted of 32 physicians (75.0% males, 84.4% < 60 years old) with a balanced representation in terms of specialties (56.3% nephrologists and 43.8% cardiologists), work setting (53.1% practising in publicly owned academic institutions) and location of practice (50.0% practising in institutions located in Attica). Most participants (84.4%) had experience of >15 years of practice in nephrology or cardiology and were focusing on both patient care and research.

Table 1 Characteristics of panel participants, overall and per specialty subgroup

n (%)	Overall (*N* = 32)	Nephrologists (*N* = 18)	Cardiologists (*N* = 14)
Sex			
Male	24 (75.0%)	13 (72.2%)	11 (78.6%)
Female	8 (25.0%)	5 (27.8%)	3 (21.4%)
Age			
30–39	1 (3.1%)		1 (7.1%)
40–49	4 (12.5%)		4 (28.6%)
50–59	22 (68.8%)	13 (72.2%)	9 (64.3%)
60–69	5 (15.6%)	5 (27.8%)	
Area of focus			
Patient care	5 (15.6%)	4 (22.2%)	1 (7.1%)
Both patient care and research	27 (84.4%)	14 (77.8%)	13 (92.9%)
Years of practice in nephrology or cardiology field			
6–10 years	2 (6.3%)		2 (14.3%)
11–15 years	3 (9.4%)		3 (21.4%)
16–20 years	9 (28.1%)	7 (38.9%)	2 (14.3%)
≥21 years	18 (56.3%)	11 (61.1%)	7 (50.0%)
Work setting			
Publicly owned non-academic	12 (37.5%)	8 (44.4%)	4 (28.6%)
Publicly owned academic (university)	17 (53.1%)	8 (44.4%)	9 (64.3%)
Privately owned hospital/institution/clinic	3 (9.4%)	2 (11.1%)	1 (7.1%)
Location of practice			
Attica	16 (50.0%)	10 (55.6%)	6 (42.9%)
Outside Attica	16 (50.0%)	8 (44.4%)	8 (57.1%)

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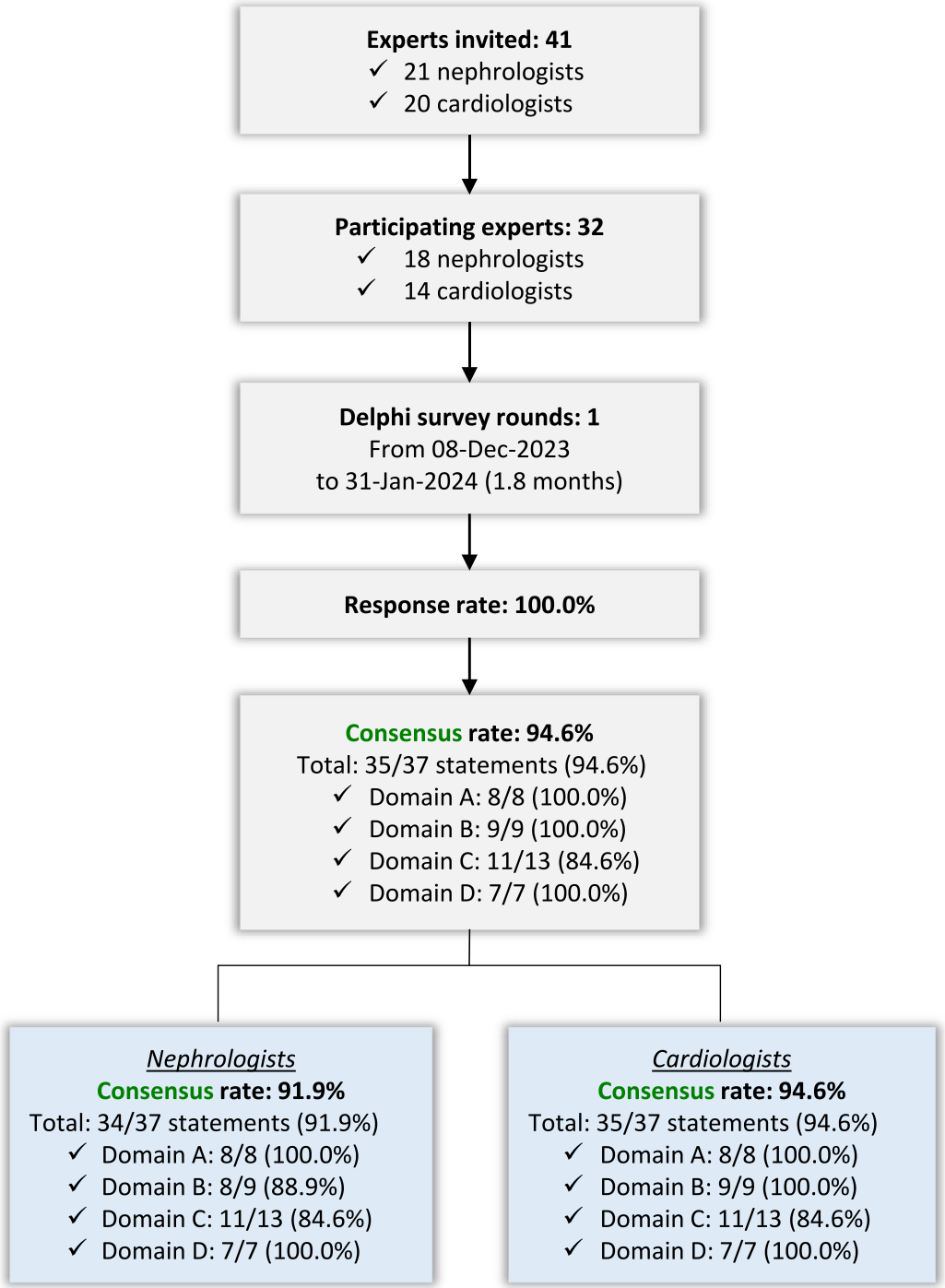
Detailed panellist characteristics are presented in *Table 1*, overall and per specialty subgroup.

As summarized in *Figure 1*, one survey round was performed, starting on 8 December 2023 and ending on 31 January 2024, which was completed by all participants (response rate: 100.0%). All but two of the statements (94.6%; 35/37) reached consensus, referred to hereinafter as 'consensus statements'. The two statements not reaching consensus belonged to Domain C: 'HK treatment in cardiorenal patients'. Similar consensus rates were obtained when analysed separately by specialty subgroup, apart from one statement from Domain B, 'Preventative measures for HK in cardiorenal

Figure 1 Disposition of participating experts and consensus rates.



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patients', which did not reach consensus in the subgroup of nephrologists.

Due to the high consensus rate, no further survey rounds were required.

Consensus and appropriateness of statements

The frequencies of the expert panel ratings per statement are displayed in *Figure 2* and *Tables S1–S3*. The IPRAS method revealed that 35 of the presented statements were 'appropriate'. All but one of those statements (97.1%; 34/35) attained an 'agreement' (rating of 7–9) by >67% (specifically, ≥78.1%) of expert panellists, while nearly two-thirds (65.7%; 23/35) attained an 'agreement' by >90% (specifically, ≥90.6%) of expert panellists (*Figure 2*; *Figure S2A*).

There was a close alignment between responses of nephrologists versus cardiologists with no statistically significant differences between the two subgroups, overall demonstrating they have common opinions in terms of risk factors, prevention as well as management of HK in cardiorenal patients (*Figure 2*). Rates of agreement differed by less than 10% between subgroups in 74.3% (26/35) of the 'consensus statements' (*Figure 2*; *Figure S2B*). Details for the remaining nine 'consensus statements', that is, those having a discordance of >10% in agreement rates between specialties, are outlined in the sections below.

Domain A: Risk management in cardiorenal patients with HK

There was a clear agreement with all the statements in Domain A. Additionally, there was no significant variation in the responses by specialty (*Figure 2*). Specifically, all but one statements (7/8) showed a difference of less than 10% between nephrologists and cardiologists in terms of agreement rates. With regard to 'consensus statement' A7 (association of serum K + concentration >5.0 mEq/L with mortality risk and discontinuation of RAASi and MRA), 100.0% of nephrologists and 85.7% of cardiologists agreed with this statement, but the difference was not statistically significant (P = 0.183) (*Figure 2*).

Domain B: Preventative measures for HK in cardiorenal patients

While all statements pertaining to HK preventative measures achieved consensus agreement, there was one statement (statement B2) with a markedly lower agreement level (*Figure 2*). Specifically, only 65.6% (21/32) of panellists agreed with the use of novel K+ binders together with RAASi therapy in high-risk patients as preventative measure for HK. The remaining panellists were either undecided (18.8%; 6/32) or disagreed with this statement (15.6%; 5/32). The proportion of agreement/uncertainty/disagreement among nephrologists and cardiologists for this statement were 66.7/16.7/16.7% and 64.3/21.4/14.3%, respectively (*Tables S2 and S3*), with no statistically significant differences in the proportions of agreement between subgroups (P > 0.999; *Figure 2*). Notably however, based on the IPRAS method, this statement did not reach a consensus in the nephrologist subgroup (*Table S2*).

Higher agreement rates (>10% difference) were observed among nephrologists compared with cardiologists in the following 'consensus statements', albeit not statistically significantly different:

- B3: Novel K+ binders in patients with resistant HTN and CKD may allow the increase of RAASi medication, if necessary; 100.0% versus 85.7%, P = 0.183.
- B6: Patients with resistant arterial HTN under RAASi treatment should periodically be evaluated for HK; 100.0% versus 78.6%, P = 0.073.
- B7: In patients for whom dietary restrictions may not be appropriate or desired, the use of novel K+ binders may enable a balanced diet; 94.4% versus 64.3%, P = 0.064.
- B8: The Mediterranean diet has been proven beneficial in cardiorenal patients; therefore, it should not be restricted as a preventative measure; 88.9% versus 71.4%, P = 0.365.

Domain C: HK treatment in cardiorenal patients

HK treatment was the only topic that did not generate 100.0% consensus across statements (*Figure 1*). Overall, high levels of agreement were observed, apart from two statements for which a consensus was not reached: C5 (potassium value >5.5 mEq/L should not lead to down-titration or to avoid up-titration) and C12 (cardiorenal patients with moderate or severe HK should not eat fruits and vegetables), with agreement/uncertainty/disagreement rates of 59.4/3.1/37.5% and 43.8/21.9/34.4%, respectively (*Table S1*). A similar pattern was observed for subgroups by specialty. Excluding the two aforementioned 'uncertain' statements, higher agreement rates (>10% difference) were observed among nephrologists compared with cardiologists in the following 'consensus statements', albeit not statistically significantly different:

- C2: It should be a priority for cardiorenal patients to use the maximum recommended dose of RAASi therapy; 100.0% versus 85.7%, P = 0.183.
- C6: Discontinuation of RAASi therapy should not be considered as a permanent strategy in chronic HK; 88.9% versus 78.6%, P = 0.631.
- C8: Novel K+ binders in patients with mild HK can enable guideline-recommended doses of RAASi therapy; 100.0% versus 85.7%, P = 0.183.

Domain D: Cross-specialty collaboration in HK management

The agreement across all Domain D statements was strong (*Figure 2*). A discordance of >10% between subgroups by specialty was observed in only one statement (D3). Specifically, 88.9% of nephrologists and 71.4% of cardiologists

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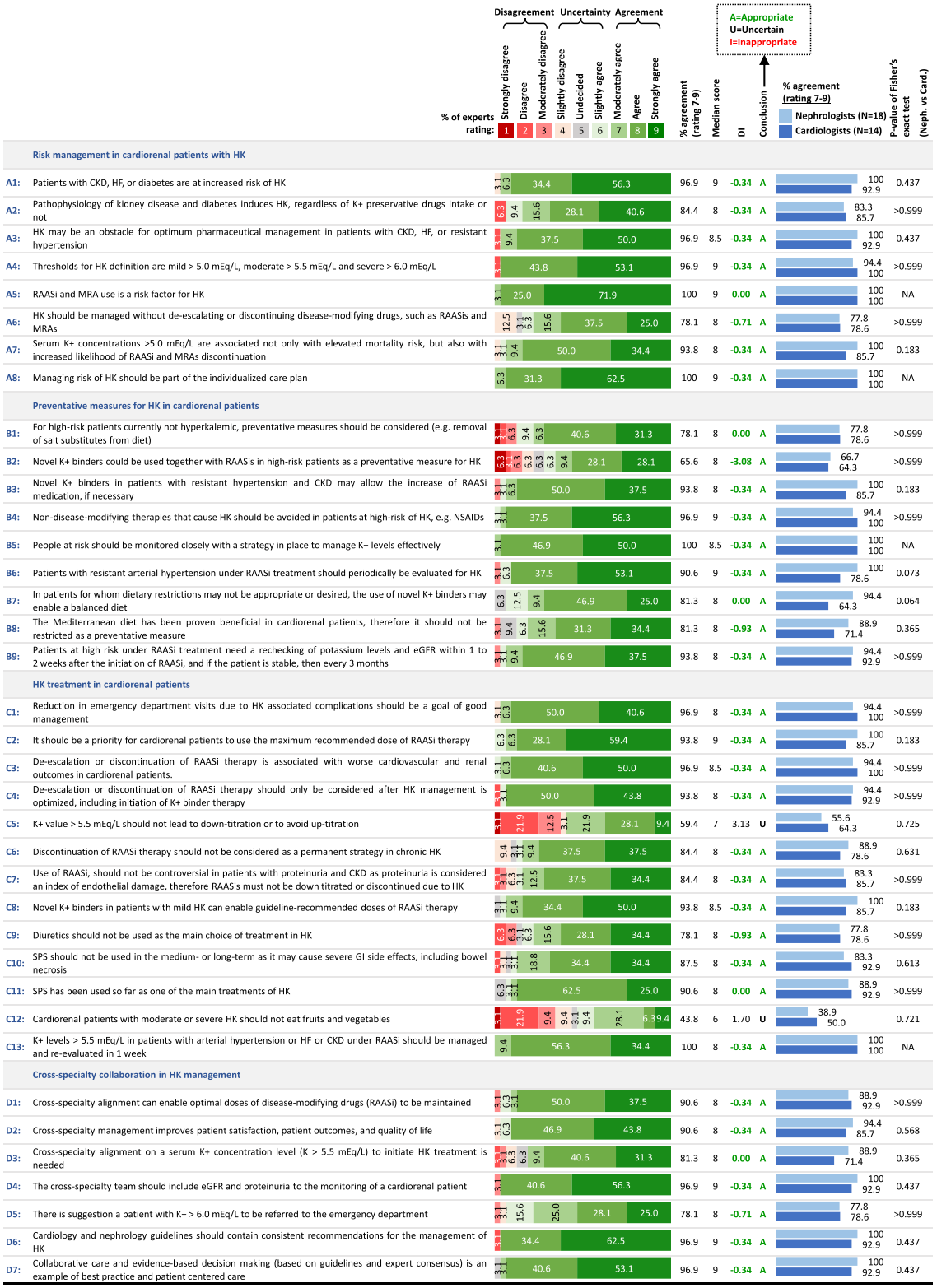
Figure 2 Distribution of ratings, agreement rates and alignment between medical specialties, per statement. CKD, chronic kidney disease; DI, disagreement index; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; HF, heart failure; HK, hyperkalaemia; K+, potassium; MRA, mineralocorticoid receptor antagonists; NA, not applicable; NSAID, non-steroidal anti-inflammatory drug; RAASi, renin–angiotensin–aldosterone system inhibitor; SPS, sodium polystyrene sulfonate.



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agreed that cross-specialty alignment on a serum K+ concentration level (K > 5.5 mEq/L) is needed to initiate HK treatment, but the difference was not statistically significant (P = 0.365) (*Figure 2*).

Discussion

In this project, using the Delphi consensus method, in the era of establishing a national multidisciplinary consensus report, a team of clinical experienced nephrologists and cardiologists posed its opinion regarding HK incidence and management in patients with cardiorenal disease. The survey questionnaire included 37 statements, all of which employed closed-ended responses and fell into four key domains, regarding risk management, preventive strategies, treatment and cross-specialty collaboration. The survey questionnaire reflected global expertise level on handling cardiorenal patients with HK in Greece. Interestingly, in one survey round, a high proportion of statements reached consensus with a high rate of agreement in almost all parts of the four sectors, with higher agreement rates observed among nephrologists compared to cardiologists. This consensus was targeted to cardiorenal patients, as the incidence of HK in general populations is relatively low (2%–3%); but in patients with CKD, HF, resistant arterial HTN and diabetes or those having combinations of those morbidities is increased.[23,24] Obviously, this risk aggravates with co-existing conditions, type of patient's diet and especially use of RAASi medications and MRAs. In daily clinical practice, patients with HF even in the form of HF with preserved ejection fraction (HFpEF), show increased rates or kidney dysfunction and diabetes mellitus (more than 40%).[25] Furthermore, patients with HF, DM and resistant HTN will progressively present kidney dysfunction of various severity; but even after 5 years of RAAS inhibitors initiation, more than one third of patients will exhibit HK.[26–28]

In the first key domain of this consensus, the topic of risk management in cardiorenal patients was addressed. There was a clear agreement with all the statements, without significant variation of opinions between specialties. In the statement of discontinuation of RAASi and MRA treatment in patients with K+ concentrations above 5 mEq/L, the cardiologists seem to be more reluctant to agree, compared with nephrologists. This difference, although non-significant, may reflects the higher rates of increased K+ levels in heart disease patients in daily clinical practice. At the current time, there is no consensus on the magnitude, duration and frequency of elevated K+ values that define chronicity, which in many cases guide physicians' behaviour. It is well known that HF and CKD often co-exist in cardiorenal disease. Cardiologists and nephrologists recognize the nature of this clinical entity and individualize their approach according to their medical experience.

In the second key domain, any preventative measures for HK in cardiorenal patients were addressed. Most of the preventable statements reached agreement, with the nephrologists showing higher agreement compared to the cardiologists for the non-restriction of the K+-rich Mediterranean diet in cardiorenal patients and the potential use of novel K+ binders in order to maintain healthy dietary habits and up-titrate medications in resistant HTN. Interestingly, both specialties showed low rates of agreement, with the nephrologists failing to come to consensus on the statement for prophylactic initiation of K+ binders in high-risk patients who are under therapy with RAASi to prevent HK occurrence. In fact, patients with kidney dysfunction and HF, as well as patients with kidney dysfunction and DM, show increased probability of HK occurrence, which may lead physicians to show reluctant in up-titration of K+-preserving medications and even down-titration of treatment when HK is detected.[27] Thus, vast majority of HF patients are not optimal managed, while suboptimal dosing of RAASi therapy is associated with doubling of mortality across all patient subtypes.[29,30] One should not forget that HK was the main obstacle with MRA use in HF trials, while it is mainly associated with RAASi use in other at-risk populations beyond HF.[31–34]

The third key domain the issue of HK treatment was addressed, where both specialties did not consented with the statement that they should not down-titrate or avoid up-titration in patients with K+ levels above 5.5 mEq/L, although they also did not come in agreement to discourage cardiorenal patients with moderate or severe HK from eating fruits and vegetables. The first statement not reaching consensus actually follows previous statements that emphasize on the importance of RAAS therapy. This may reflect the individualized approach to the K+ level threshold that indicates intervention in RAASi treatment. As mentioned above, the second statement not reaching consensus is concerning diet; despite this result, it is clear from other answers that the positive role of Mediterranean diet for cardiorenal patients has been upgraded. It seems that both specialties are concerned how to handle diet and medical therapy in patients with elevated K+ levels. It is well known that renal dysfunction and HK are the major causes of underuse of RAAS inhibitors, particularly MRA, in clinical practice. In recent ESC guidelines, the initiation of K+ binders in HK patients can permit administration of optimal medical treatment in HF patients.[35] According to KDIGO 2024, there is a strong relationship between the quantity of urine albumin with both kidney and CVD risk and observed CVD even at very low levels of urine albumin. RAAS therapy has a strategic role in the management of albuminuria and in CKD progression in general.[36] Along with this, both specialties agreed that it should be a priority for cardiorenal patients to use the maximum recommended dose of RAASi therapy, a therapy that should be discontinued in chronic HK as novel K+ binders even in patients with mild HK can enable guideline-recommended doses of RAASi therapy.

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Finally, in the fourth key domain of cross-specialty collaboration in HK management, both nephrologists and cardiologists agreed that cross-specialty alignment on a serum K+ concentration level above 5.5 mEq/L is mandatory to initiate HK treatment and to maintain optimal medical treatment of the main condition.

In conclusion, this Delphi project illustrated that both nephrologists' and cardiologists' agree on HK management in cardiorenal patients by promoting cross-specialty alignment in order to offer optimal management of cardiorenal patients, as HK should not be an obstacle for modifying medical therapy according to scientific evidence.

Participants

Steering committee (SC)

The Project Initiator Group of this Delphi consensus initiative consisted of four national nephrology and cardiology experts, who also acted as the steering committee (SC). They were actively involved in every step of the Delphi process, including systematic literature review to identify and define the topics to be addressed, drafting of protocol and survey questionnaire, definition of eligibility criteria for panellist selection, preparation of initial list of experts to be invited, invitation of experts, formation of final list of participating experts (panel), agreement on consensus decision rules and corresponding actions after each survey round. They were also responsible for selecting and appointing the independent external vendor, who was responsible for the conduct and analysis of the online survey following all applicable data protection regulations and requirements. Complete confidentiality and anonymity was ensured since (a) the SC did not have voting rights, (b) expert panellists were unaware of the identity of other panellists and (c) none of the responses of individual panellists were disclosed to anyone involved in the project (neither SC members nor expert panellists). The overall coordination of all project phases was moderated by two SC members, one from each medical specialty.

Expert panel

There are no clear recommendations on the optimal size of the expert group for Delphi studies since representativeness is assessed based on the quality characteristics.[14–16] In line with prior suggestions of 5–10 experts per professional group category or 15–30 experts for a homogeneous sample from the same discipline,[17,18] panel selection herein initially included a minimum of 40 experts (excluding the SC members) equally distributed across the two specialties (i.e. 20 cardiologists and 20 nephrologists), aiming at ensuring at least 30 experts participating in the first round and at least 24 experts completing the full Delphi process. A non-acceptance rate during the invitation process of 20%–30% and a dropout rate of 20% across all rounds were assumed, in accordance with previous Delphi studies.[19,20]

Eligible panel members were cardiology and nephrology experts in Greece, representatives of their medical specialty with impact on decision-making in HF/CKD care, professional recognition for their experience and scientific opinion and special interest in the cardiorenal field. Experts having any conflict of interest with the present project, such as current or upcoming employment in the pharmaceutical industry or ownership in the pharmaceutical company, were excluded.

Questionnaire and analysis methodology

Before beginning to answer the survey questionnaire, all experts had to provide key demographic information and a few details about their practice in HF/CKD care.

The survey questionnaire included 37 statements, all of which employed closed-ended responses and fell into four key domains (*Figure S1A*):

A Risk management in cardiorenal patients with HK (comprising eight statements)
B Preventative measures for HK in cardiorenal patients (comprising nine statements)
C HK treatment in cardiorenal patients (comprising 13 statements)
D Cross-specialty collaboration in HK management (comprising seven statements)

As a 9-point scale is most frequently used in Delphi studies,[11,20,21] we chose a 9-point Likert-type ordinal scale (1 = *strongly disagree*; 5 = *undecided*; 9 = *strongly agree*) to rate each statement (*Figure S1A*), in accordance with the RAND/UCLA appropriateness method.[22] This method was also used to analyse the responses for each statement, based on the median score, interpercentile range (IPR), IPR adjusted for symmetry (IPRAS), and disagreement index (DI) (IPR divided by IPRAS). The DI was calculated as shown in *Figure S1B*.

For a given statement, the median score shows level of appropriateness, while DI shows presence/lack of consensus. Specifically, *consensus* was considered when DI $\leq$ 1 (i.e. IPR $\leq$ IPRAS, indicating no extreme dispersion of ratings), while *lack of consensus* was established when DI $>$ 1 (i.e. IPR $>$ IPRAS, indicating extreme variation across ratings). As a result, the conclusion for each item could be *appropriate* when the panel median was 7–9 and DI $\leq$ 1 (i.e. consensus about agreement with statement), *uncertain* when the panel median was 4–6 or any median with DI $>$ 1 (i.e. lack of consensus) and *inappropriate* when the panel median was 1–3

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with DI $\leq$ 1 (i.e. consensus about disagreement with statement).

Key definitions for this study were the following:

- Consensus statement = statement reaching consensus;
- IPRAS method = composite measure based on median of ratings and DI level (*Figure S1B*) to derive a conclusion about a statement (i.e. appropriate, uncertain or inappropriate);
- Rate (%) of agreement (for a given statement) = proportion of expert panellists rating 7–9 for that item.

The aforementioned analyses were stratified per medical specialty and the alignment between the two specialties was also examined using Fisher's exact test to compare rates of agreement (i.e. proportion of expert panellists rating 7–9). Statistical analysis was performed by the external vendor using SAS® v.9.4 (SAS Institute Inc., Cary, NC, USA).

No formal ethics approval was required for this project. Survey responses were collected online using a secure internet server and retained for the duration of the project; responses were collated anonymously with an identifying number that was known only to the participant and the web-based system administrator and data processor. The Hellenic Societies of Cardiology and Nephrology were notified of this initiative and granted their favourable opinion based on the scientific integrity and scope of the project.

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Design and hosting of the online platform, data analysis/reporting and editorial assistance was provided by Qualitis SA, member of Optimapharm Group.

Conflict of interest

Christina Chrysohoou served on advisory boards for Medtronic and Roche Diagnostics and speakers engagements for AstraZeneca, Menarini and Roche Diagnostics. Maria Marketou received honorariums from AstraZeneca, Boehringer Ingelheim and Medtronic. Maria Aktsiali served on speakers engagements for Genesis Pharma. Ioannis Griveas served on advisory boards and speakers engagements for AstraZeneca.

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This project was funded by AstraZeneca. The role of AstraZeneca was restricted to financing, with no involvement in any phase or process of the project including expert recruitment, questionnaire formulation, administration or evaluation, analysis, report preparation, results interpretation and publication writing.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Statement ratings and indexes, in the overall set of 32 panelists.
Table S2. Statement ratings and indexes, in the subgroup of 18 nephrologists.
Table S3. Statement ratings and indexes, in the subgroup of 14 cardiologists.
Figure S1. (A) Survey questionnaire overview, and (B) calculation of consensus and appropriateness for each statement (IPRAS method).
Figure S2. Proportion of expert panelists who agreed with each statement (rating of 7–9 in the 9-point Likert-type ordinal scale), (A) among the overall expert panel and (B) per specialty subgroup.

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