Nefrologia 46 (2026) 501532

Sociedad Española de Nefrología

nefrología

Revista de la Sociedad Española de Nefrología

journal homepage: www.revistanefrologia.com

Review

Sodium zirconium cyclosilicate for renin–angiotensin–aldosterone system inhibitor therapy optimization: A systematic review and meta-analysis with meta-regression

Ciclosilicato de sodio y zirconio en la optimización de la terapia con inhibidores del sistema renina-angiotensina-aldosterona: una revisión sistemática y metaanálisis con metarregresión

Hamlet Ghukasyan [a,*], David Abraham Batista da Hora[b], Syeda Rubab Fatima[c], Kauê Abreu Chagas[d], Taguhi Hayrapetyan[a], Juan Casas Todolí[a], Marina Llopis Sanchis[a], Felemez Arslan[e]

[a] *Hospital Francesc de Borja, Gandía, Spain*
[b] *Federal University of Amazonas, Brazil*
[c] *CMH Lahore, Pakistan*
[d] *Afya Itaperuna University Center, Itaperuna, Rio de Janeiro, Brazil*
[e] *University of Health Science Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Department of Internal Medicine, Istanbul, Turkey*

ARTICLE INFO

Keywords:
Sodium zirconium cyclosilicate
Hyperkalemia
Chronic kidney disease
Heart failure
RAAS inhibitors
Meta-analysis

ABSTRACT

Introduction and objectives: Renin–angiotensin–aldosterone system inhibitors (RAASi) are essential in chronic kidney disease (CKD) and heart failure (HF) management but may increase the risk of hyperkalemia (HK). Sodium zirconium cyclosilicate (SZC), a novel potassium binder, may enable sustained RAASi use and dose optimization. This meta-analysis evaluated the association between SZC therapy and RAASi maintenance and optimization.

Methods: We systematically searched PubMed, Embase, Cochrane, and Web of Science from inception until August 2025 for RCTs, observational studies and post-hoc analyses comparing SZC with placebo or standard care in RAASi-treated patients with HK (PROSPERO registration: CRD42024603403). Six studies (3 RCTs, 3 observational; n = 79,956 patients) with 3–12 months follow-up were included. Primary outcomes were: RAASi maintenance, up-titration, and discontinuation/down-titration. Subgroup analyses and comparator-stratified analyses were performed. An exploratory meta-regression was conducted to evaluate potassium reduction magnitude and RAASi maintenance association.

Results: SZC was associated with a higher likelihood of RAASi maintenance (RR 1.26; 95% CI 1.14–1.40; I^2 = 77%) and up-titration (RR 1.47; 95% CI 1.20–1.80), and with a lower risk of discontinuation or down-titration (RR 0.56; 95% CI 0.46–0.68). Subgroup analyses showed consistent benefits in patients with baseline potassium >5.0 mEq/L and in RCT-only analyses. The exploratory meta-regression revealed a statistically significant ecological association between the magnitude of potassium reduction and RAASi maintenance (p = 0.002).

Conclusion: SZC was associated with improved maintenance and optimization of RAASi therapy, while reducing the risk of down-titration or discontinuation. Randomized trials powered for cardiovascular and renal endpoints are needed to determine whether SZC use translates into improved patient outcomes.

* Corresponding author.
E-mail address: h.h.ghoukasian@gmail.com (H. Ghukasyan).

https://doi.org/10.1016/j.nefroe.2026.501532
Received 16 November 2025; Accepted 11 March 2026
2013-2514/© 2026 Sociedad Española de Nefrología. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Palabras clave:
Ciclosilicato de sodio y zirconio
Hiperpotasemia
Enfermedad renal crónica
Insuficiencia cardíaca
Inhibidores del sistema renina-angiotensina-aldosterona
Metaanálisis

RESUMEN

Introducción: Los inhibidores del sistema renina-angiotensina-aldosterona (iSRAA) son esenciales en el manejo de la enfermedad renal crónica (ERC) y la insuficiencia cardíaca (IC), pero pueden aumentar el riesgo de hiperpotasemia (HP). El ciclosilicato de zirconio y sodio (CZS), un nuevo captador de potasio, puede permitir el uso sostenido de iSRAA y la optimización de la dosis. Este metaanálisis evaluó la asociación entre la terapia con CZS y el mantenimiento y optimización de los ISRAA.

Métodos: Se realizó una búsqueda sistemática en PubMed, Embase, Cochrane y Web of Science desde su inicio hasta agosto 2025, incluyendo ensayos clínicos aleatorizados, estudios observacionales y análisis post hoc que compararan SZC con placebo o tratamiento estándar en pacientes tratados con iRAAS y con HK (registro PROSPERO: CRD42024603403). Se incluyeron seis estudios (3 aleatorizados, 3 observacionales; n = 79.956 pacientes) con un seguimiento de 3 a 12 meses. Los objetivos primarios fueron: mantenimiento, intensificación y suspensión/reducción posológica de iRAAS. Se realizaron análisis de subgrupos y análisis estratificados por comparador. Se llevó a cabo una metarregresión exploratoria para evaluar la asociación entre la magnitud de la reducción de potasio y el mantenimiento de iSRAA.

Resultados: El CZS se asoció con una mayor probabilidad de mantenimiento de iSRAA (RR 1,26; IC 95% 1,14-1,40; I^2 = 77%) y de incremento de dosis (RR 1,47; IC 95% 1,20-1,80), y con un menor riesgo de suspensión/reducción posológica (RR 0,56; IC 95% 0,46-0,68). Los análisis de subgrupos mostraron beneficios consistentes en pacientes con potasio basal >5,0 mEq/L y en los análisis solo con ensayos aleatorizados. La metarregresión exploratoria reveló una asociación ecológica estadísticamente significativa entre la magnitud de la reducción de potasio y el mantenimiento de iSRAA (p = 0,002).

Conclusión: El CZS se asoció con un mejor mantenimiento y optimización de la terapia con iSRAA, al tiempo que redujo el riesgo de reducción de dosis o interrupción. Se necesitan ensayos aleatorizados con potencia estadística para eventos cardiovasculares y renales para determinar si el uso de CSZ se traduce en mejores resultados clínicos.

Introduction

Maintaining potassium levels within the optimal range (4–4.5 mmol/L) is critical, particularly in patients with chronic kidney disease (CKD) and high cardiovascular risk, as deviations are associated with increased mortality and hospitalization rates.[1–3]

The renin–angiotensin–aldosterone system inhibitors (RAASi) are cornerstone therapies for HF and CKD, slowing disease progression and reducing mortality and hospital readmissions.[4,5] However, despite their benefits, RAASi are frequently associated with hyperkalemia episodes, creating a barrier to therapy optimization and often leading to dose reduction or discontinuation,[2,6–8] which in turn is associated with an increased risk of cardiorenal events and mortality.[9]

International guidelines emphasize that hyperkalemia should not preclude RAASi use and recommend emerging therapies with two novel potassium binders: sodium zirconium cyclosilicate (SZC) and patiromer, that may transform hyperkalemia management to facilitate RAASi therapy optimization.[5]

While several recent meta-analyses have demonstrated that these potassium binders effectively reduce hyperkalemia recurrence and support their effectiveness in RAASi therapy optimization,[10–12] their conclusions were largely driven by studies focused on patiromer, and many included trials with SZC lacked appropriate comparator groups.

In contrast, our meta-analysis is focused exclusively on SZC, evaluating its efficacy in maintaining and optimizing RAASi therapy among patients at high risk of hyperkalemia, using only studies with placebo or other control arms. To the best of our knowledge, this is the first meta-analysis of SZC to incorporate meta-regression, elucidating the quantitative relationship between the magnitude of potassium reduction and RAASi maintenance.

Materials and methods

Study design

This systematic review and meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines[13] and the Cochrane Handbook for Systematic Reviews of Interventions.[14] The study was registered in the PROSPERO database under the registration number CRD42024603403. A completed PRISMA checklist is provided as supplementary material. Statement of human and animal rights was deemed unnecessary.

Eligibility criteria

Studies were eligible for inclusion if they: (1) were randomized or nonrandomized clinical trials (including post-hoc analyses); (2) compared SZC with placebo, other potassium binders, or a potassium binder-free control arm; (3) enrolled patients receiving RAASi with prior hyperkalemia or at elevated risk for hyperkalemia; and (4) reported quantifiable outcomes on SZC's efficacy in maintaining RAASi therapy and preventing its discontinuation; (5) with a minimum follow-up of 3 months.

We excluded (1) studies without control groups; (2) overlapping patient populations; (3) case reports or case series; (4) review articles, comment articles, editorials, and letters to the editor.

Search strategy

A comprehensive and systematic search was conducted in the following electronic databases from their inception: Cochrane Central Register of Controlled Trials (CENTRAL), PubMed/MEDLINE, Embase, and Web of Science (WOS) which were consulted from inception until August 2025. The search strategy was developed in consultation with a medical librarian and utilized a combination of controlled vocabulary (MeSH terms) and free-text keywords. The complete electronic search strategy is described in the supplementary file. The references from all included studies, previous systematic reviews, and meta-analysis were also searched manually for any additional studies. Three authors independently extracted the data following predefined search criteria and quality assessment.

Study selection

All records were imported into Zotero for reference management and deduplicated via Rayyan.ai, which also facilitated collaborative

screening. Three reviewers independently screened titles/abstracts and full texts. Four authors then performed double-blinded, independent data extraction from primary and supplementary materials. Disagreements were resolved by consensus among the authors.

Quality assessment

The risk of bias and quality assessment of the RCTs were conducted using the version 2 of the Cochrane Risk of Bias assessment tool.[15] Nonrandomized clinical trials were assessed with the Risk of Bias in Non-randomized Studies of interventions tool (ROBINS-I).[16] The risk of bias evaluation was independently performed by two authors. While disagreements were resolved through consensus after discussing the reasons for discrepancy. Publication bias was investigated using the Funnel-plot analysis and Egger's regression test.

Statistical analysis

Endpoints were analyzed using risk ratio (RR) with 95% confidence intervals (CIs) to compare treatment effects for categorical endpoints. For the primary analysis, all eligible comparator arms (placebo, other potassium binders and a potassium binder-free control arm) were pooled together to estimate the overall association between SZC use and RAASi-related outcomes. A random-effects model was applied to account for variability in effect sizes across studies. We assessed heterogeneity using the I^2 statistic and Cochran Q test; p-values <0.10 and $I^2 > 25\%$ were considered significant. In the meta-regression the significance of the regression slope was tested using the Q-test (reported as a two-sided p-value). Review Manager 5.4 (Cochrane Center, The Cochrane Collaboration, Denmark) and R version 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analysis.

Outcomes

The primary outcomes included: (1) proportion of patients remaining on any dose of RAASi therapy at the end of follow-up (RAASi maintenance); (2) proportion of patients who up-titrated their RAASi dose during follow-up; (3) proportion of patients who down-titrated or discontinued RAASi therapy. Given potential clinical heterogeneity introduced by differing comparator types, prespecified subgroup analyses were performed, using (4) studies reporting outcomes specifically in patients receiving mineralocorticoid receptor antagonist (MRA) therapy; (5) patients with baseline serum potassium >5.0 mEq/L who remained on any RAASi; and (6) using RCTs only. To explore the potential influence of comparator type, additional subgroup analyses were performed according to control group strategy (placebo or active potassium binder). These analyses were conducted when sufficient studies were available. Given the limited number of head-to-head trials and anticipated heterogeneity, we did not perform network meta-analysis or indirect comparisons between potassium binders. To explore potential effect modification, we conducted an exploratory random-effects univariate meta-regression and examined whether differences in net serum potassium change (ΔK, mmol/L) had any significant impact on the results and explained the heterogeneity in the pooled estimates. ΔK was calculated as mean end follow-up serum potassium minus baseline serum potassium (in mmol/L); thus, negative values indicate potassium reduction. Effects were modelled on the log(RR) scale and reported as RRs per 1.0 mmol/L decrease in potassium (i.e. $\Delta K = -1.0$).

Results

As illustrated in the PRISMA flow diagram (Fig. 1) our initial search yielded a total of 548 results. After removing duplicate records and ineligible studies based on their titles and abstracts, a total of 17 results remained and were fully reviewed based on the inclusion criteria. Studies were excluded for the following reasons: a focus on short-term or discontinuous SZC use (without an appropriate control group), an incompatible study design, or the absence of relevant outcomes. Furthermore, all identified meta-analyses combined data for patiromer and SZC, and most of their included studies investigated patiromer exclusively, while those including SZC often lacked a true SZC-free control arm, rendering them unsuitable for the present analysis.

In our meta-analysis a total of six studies were included: three observational[17–19] and three RCTs,[20–22] comprising 79,956 patients with a follow-up from 3 to 12 months. Three out of the six studies compared SZC with placebo, two studies included other potassium binders in the control group, one study compared SZC with potassium binder-free arm. For studies reporting outcomes at multiple follow-up timepoints or including more than one control group, we selected the most clinically relevant and methodologically appropriate comparator and timepoint for each pre-specified endpoint.

Full study characteristics are shown in Table 1. For observational studies, propensity score-matched analyses were preferentially included when available to reduce baseline confounding.

The study populations were characterized by a high burden of cardiovascular and renal comorbidities, reflective of a cohort at significant risk for hyperkalemia. The mean age across studies ranged from 59 to 78 years. Diabetes mellitus (DM) was present in 65.0% (n = 51,945) and hypertension in more than 83% (n = 66,933) of patients. Furthermore, a vast majority of patients ($>90\%$) had CKD, and HF was a common comorbidity, affecting 48.8% (n = 38,992) of the cohort.

RAAS inhibitor use was common: at least 73.3% of patients were treated with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). Mineralocorticoid receptor antagonists (MRAs) use was reported in 5.9% of patients. Baseline serum potassium levels ranged from 4.6 to 6.0 mEq/L.

Endpoints

The primary meta-analysis, including six studies, evaluated the association between SZC therapy and maintenance of any RAASi treatment. As described in the forest plot of Fig. 2A, the pooled analysis showed a significant 26% increase in the likelihood of RAASi maintenance in the SZC group compared to the control group (RR, 1.26; 95% CI, 1.14–1.40; $p < 0.0001$). Significant heterogeneity was observed across the included studies (I^2 = 77%).

The benefit of SZC was further demonstrated in therapy optimization. Patients treated with SZC were 47% more likely to undergo up-titration of their RAASi therapy compared to controls (RR, 1.47; 95% CI, 1.20–1.80; p = 0.0002), as shown in Fig. 2B, with moderate heterogeneity (I^2 = 62%, p = 0.05). Conversely, the risk of down-titration or complete withdrawal of RAASi therapy was significantly reduced by 44% in the SZC group (RR, 0.56; 95% CI, 0.46–0.68; $p < 0.00001$, Fig. 2C), with low heterogeneity (I^2 = 18%, p = 0.30).

Absolute risk differences corresponded to numbers needed to treat (Table S4 of the supplementary file) ranging from 3 to 12 for maintenance of RAAS inhibitor therapy, indicating a clinically meaningful improvement across studies. For prevention of RAASi withdrawal, NNT values ranged from 5 to 10.

To investigate the sources of heterogeneity and test the robustness of the primary findings, we performed several subgroup analyses. In the subgroup of patients who remained on MRA therapy, the point

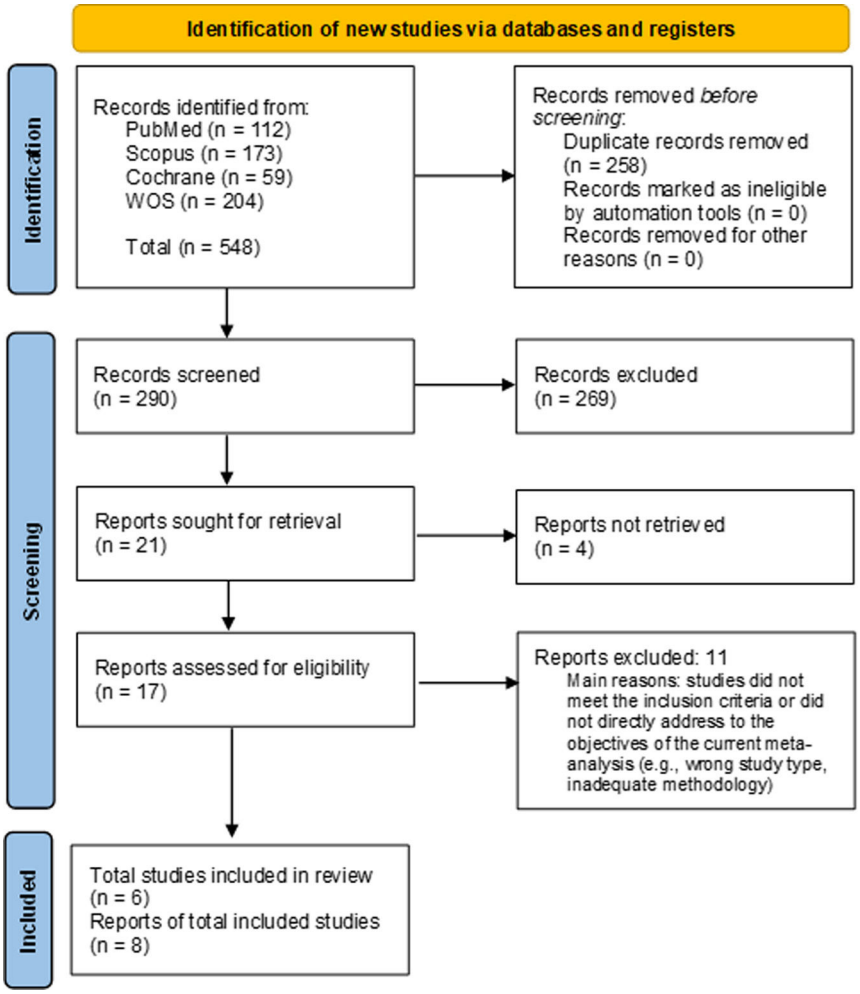

Fig. 1. PRISMA flow diagram of study selection. Flow diagram depicting the identification, screening, eligibility assessment, and inclusion of studies in the meta-analysis, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.

Table 1
Individual study characteristics.

First author (year)	Kimura et al. (2023)	Onogi et al. (2024)	Rastogi et al. (2024)	Tardif et al. (2022)	Hao et al. (2025)	Kosiborod (2024)
Intervention	SZC	SZC	SZC	SZC	SZC	SZC
Comparator	CPS	CPS and SPS	Placebo	Placebo	No potassium binder	Placebo
Study design	Retrospective observational study	Retrospective cohort study	Retrospective cohort study	RCT, double-blind, phase 2	RCT, open label, phase 3	RCT, double-blind, phase 4
Population	70	73,118	6297	182	86	203
Follow-up	3 months	12 months	6 months	3 months	6 months	6 months
Mean age	78	72	73	72	58.7	71
DM (patients)	32	46,241	5452	82	All	52
HT (patients)	68	66,515	N/A	171	79	NA
HF (patients)	N/A	35,083	3524	All	NA	All
eGFR, ml/min/1.73 m^2	18.5 (14–30)	N/A	N/A	41.4 ± 11.3	35.5	54.8
CKD (patients)	All	All	5608	All	All	NA
Beta blocker	N/A	18,747	N/A	166	37	194
ACEIs/ARBs	All	35,100	5860	150	All	73
ARNi	N/A	N/A	442	30	NA	130
MRA	6	3580	1001	34	NA	All
Diuretics	N/A	N/A	N/A	155	32	143
Serum potassium level [mEq/L or mmol/L]	5.8–5.9	5.7–6	≥5	4.85–4.87	4.64	5.0 ± 0.5

ACEi: angiotensin converting enzyme inhibitor; ARBs: angiotensin II receptor blockers; ARNi: angiotensin receptor-neprilysin inhibitor; CKD: chronic kidney disease; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; HF: heart failure; HT: hypertension; MRA: mineralocorticoid receptor antagonist; SPS: sodium polystyrene sulfonate; CPS: calcium polystyrene sulfonate; SZC: sodium zirconium cyclosilicate.

estimate favored SZC, but the result was not statistically significant (RR, 1.38; 95% CI, 0.98–1.93), with high heterogeneity (I^2 = 90%, Fig. 3A). A sensitivity analysis including only patients with serum potassium levels >5.0 mEq/L at baseline showed a consistent and significant 26% higher rate of RAASi maintenance with SZC (RR, 1.26; 95% CI, 1.06–1.49; Fig. 3B), with moderate heterogeneity (I^2 = 51%, p = 0.11). Furthermore, an analysis restricted to the three RCTs demonstrated a significant 31% benefit for RAASi continuation with

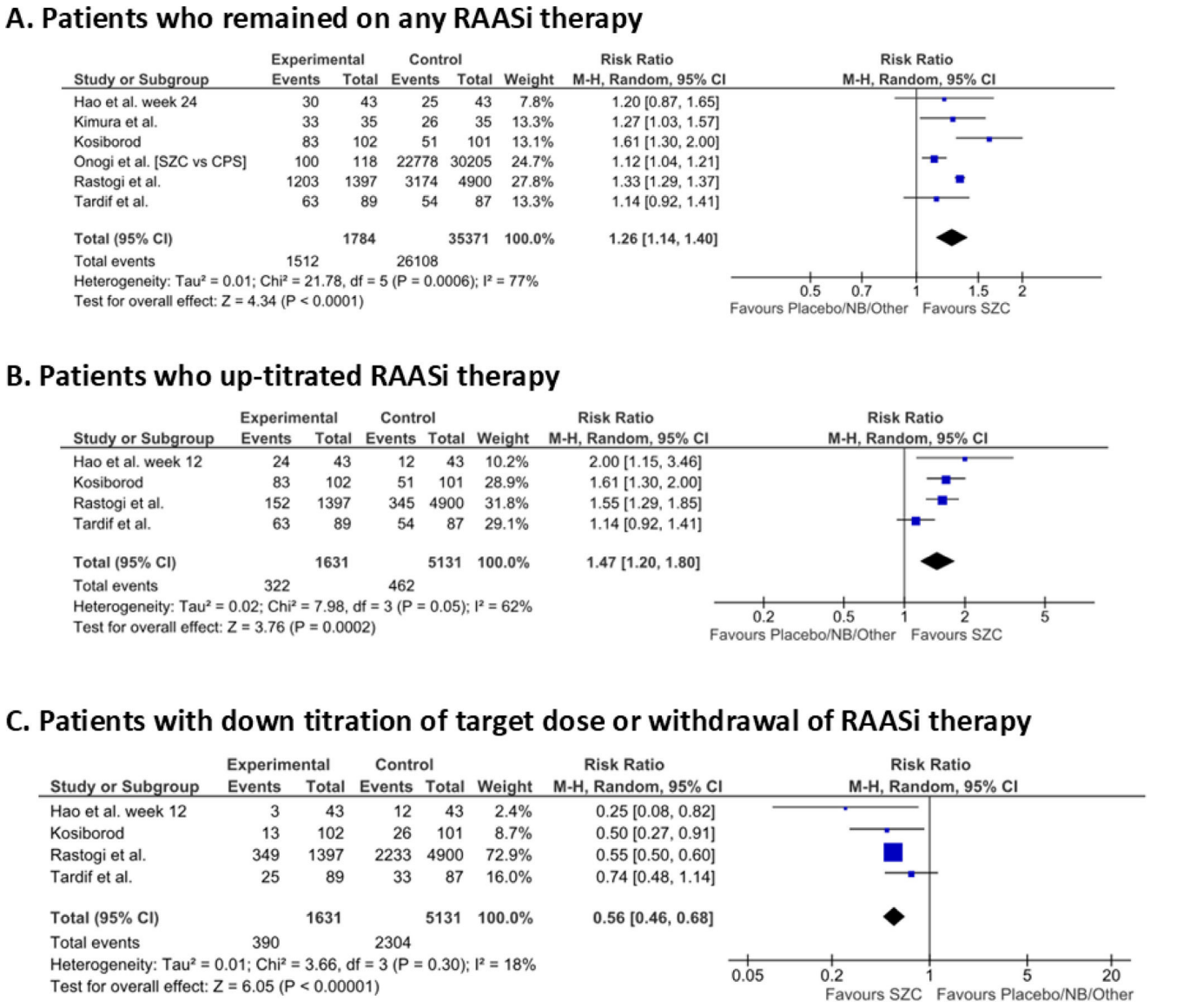

Fig. 2. Forest plots of primary endpoints: (A) RAASi maintenance: pooled risk ratio (RR) for remaining on any dose of RAASi at end of follow-up. (B) RAASi up-titration: RR for dose escalation during follow-up. (C) RAASi discontinuation or down-titration: RR for therapy reduction or withdrawal. Results are shown as risk ratios with 95% confidence intervals. The size of each square is proportional to the study's weight in the meta-analysis; horizontal lines represent 95% CI. The diamond represents the pooled estimate using a random-effects model.

SZC (RR, 1.31; 95% CI, 1.04–1.66; Fig. 3C), although, with higher heterogeneity ($I^2 = 64\%$, $p = 0.06$). Subgroup analyses stratified by comparator type were performed to explore potential differences according to control strategy (supplementary file, Fig. S1). Effect estimates in placebo-controlled studies were consistent with the primary analysis.

Meta-regression analysis

An exploratory meta-regression of four studies was performed to assess whether the magnitude of serum potassium reduction (ΔK, in mmol/L) explained the treatment effect of SZC on RAASi maintenance. As shown in Fig. 4, the meta-regression slope was −0.39 (SE = 0.126, $p = 0.002$), i.e. for every 1.0 mmol/L increase in ΔK the ln(RR) decreases by 0.39. Because ΔK is defined as (follow-up − baseline) potassium, a 1.0 mmol/L decrease corresponds to $\Delta K = -1.0$, which increases the log(RR) by +0.39. Equivalently, for every 1.0 mmol/L decrease in serum potassium the RR for RAASi persistence is multiplied by exp(0.39) = 1.48 (RR, 1.48; 95% CI, 1.16–1.90), corresponding to an estimated 48% higher relative likelihood of remaining on RAASi therapy. The model explained a large proportion of between-study variance ($\tau^2 \approx 0$, $R^2 = 100\%$), suggesting a dose-dependent relationship (supplementary file, Tables S1–S3). However, given the limited number of studies and use of study-level data, these findings should be interpreted as exploratory.

Quality assessment

RCTs showed low risk of bias, with only one of them showing some concerns, particularly in reporting and randomization. Observational studies demonstrated high risks of bias, especially for confounding, deviations from intended interventions, and selection of participants (supplementary file). Publication bias of the primary endpoint was investigated using the Funnel-plot analysis showing a symmetric distribution of studies with similar weights (supplementary file). Egger's regression test for funnel plot asymmetry was non-significant ($z = 0.28$, $p = 0.78$), suggesting no evidence of small-study effects or publication bias.

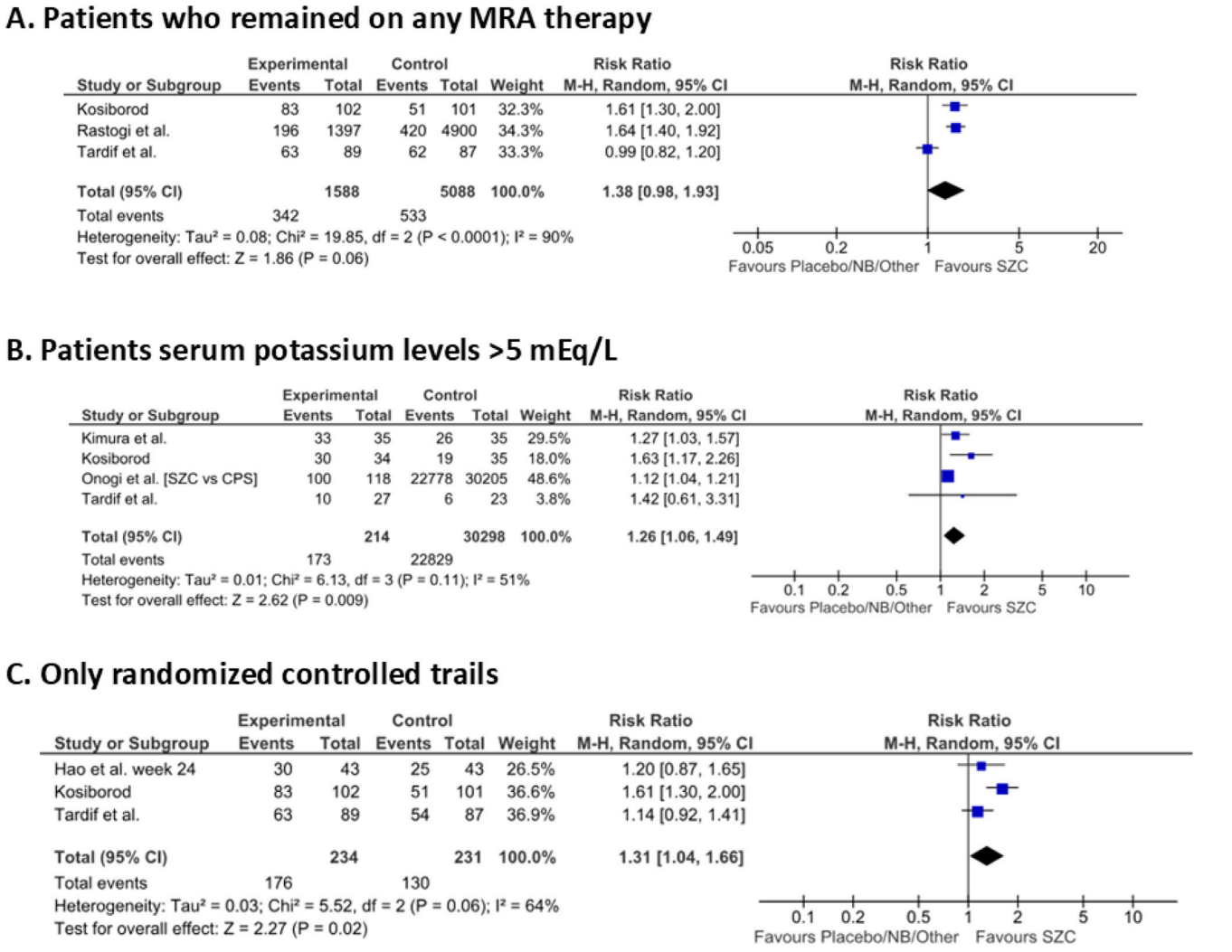

Fig. 3. Subgroup analyses of RAASi persistence with SZC. (A) Effect in patients receiving mineralocorticoid receptor antagonists (MRAs). (B) Effect in patients with baseline serum potassium >5.0 mmol/L. (C) Analysis restricted to randomized controlled trials (RCTs) only. Data are presented as risk ratios (RR) with 95% confidence intervals. Heterogeneity was assessed using the I^2 statistic.

Discussion

Main findings

In this systematic review and meta-analysis of RCTs and observational studies including nearly 80,000 patients, SZC was associated with a 26% higher likelihood of remaining on RAASi therapy, 47% greater probability of up-titration, and 44% lower risk of dose reduction or discontinuation. Subgroup analyses, including restriction to randomized trials and stratification by comparator type, yielded results consistent with the primary findings. However, heterogeneity across studies was substantial, reflecting differences in study design, populations, and clinical settings. Reporting absolute risks with NNT values alongside relative risks improves interpretation of the magnitude and clinical relevance of treatment effects. However, NNT values should be interpreted in the context of study design heterogeneity.

The meta-regression analysis provides exploratory insights into the relationship between potassium reduction and RAASi maintenance. Our findings suggest a statistically significant ecological association between the magnitude of potassium reduction and RAASi maintenance across studies (coefficient = −0.39, $p = 0.002$; $R^2 = 100\%$). While the result is based on only four studies and reflects group-level trends, it suggests that better potassium control may facilitate continued RAASi therapy and thus support cardiorenal protective strategies. Leave-one-out analysis (supplementary file, Table S3) revealed that the association remained statistically significant when any single study was omitted, except when the Kosiborod et al. trial was excluded (RR, 1.42, $p = 0.34$), suggesting the overall result is sensitive to this trial, which reported the largest potassium reduction ($\Delta K = -1.0$ mmol/L). Although causal relationships cannot be established, the observed dose–response pattern indicates a link between potassium reduction and RAASi persistence, that align with the clinical importance of achieving and maintaining potassium levels within the target range (4.0–4.5 mmol/L).[23,1] These findings should be considered hypothesis-generating and require confirmation in patient-level analyses and prospective studies.

Clinical implications and limitations

Hyperkalemia is common in CKD and HF, affecting up to half of patients with CKD, and is associated with its recurrence and adverse prognosis.[3,6,7,24] SZC is a non-systemically absorbed potassium binder with generally favorable gastrointestinal tolerability in clinical and real-world settings,[25] supporting its use in cardiorenal patients requiring chronic potassium control. Despite international guidelines discouraging RAASi withdrawal due to hyperkalemia and supporting use of newer potassium binders,[5] registry data indicate that a

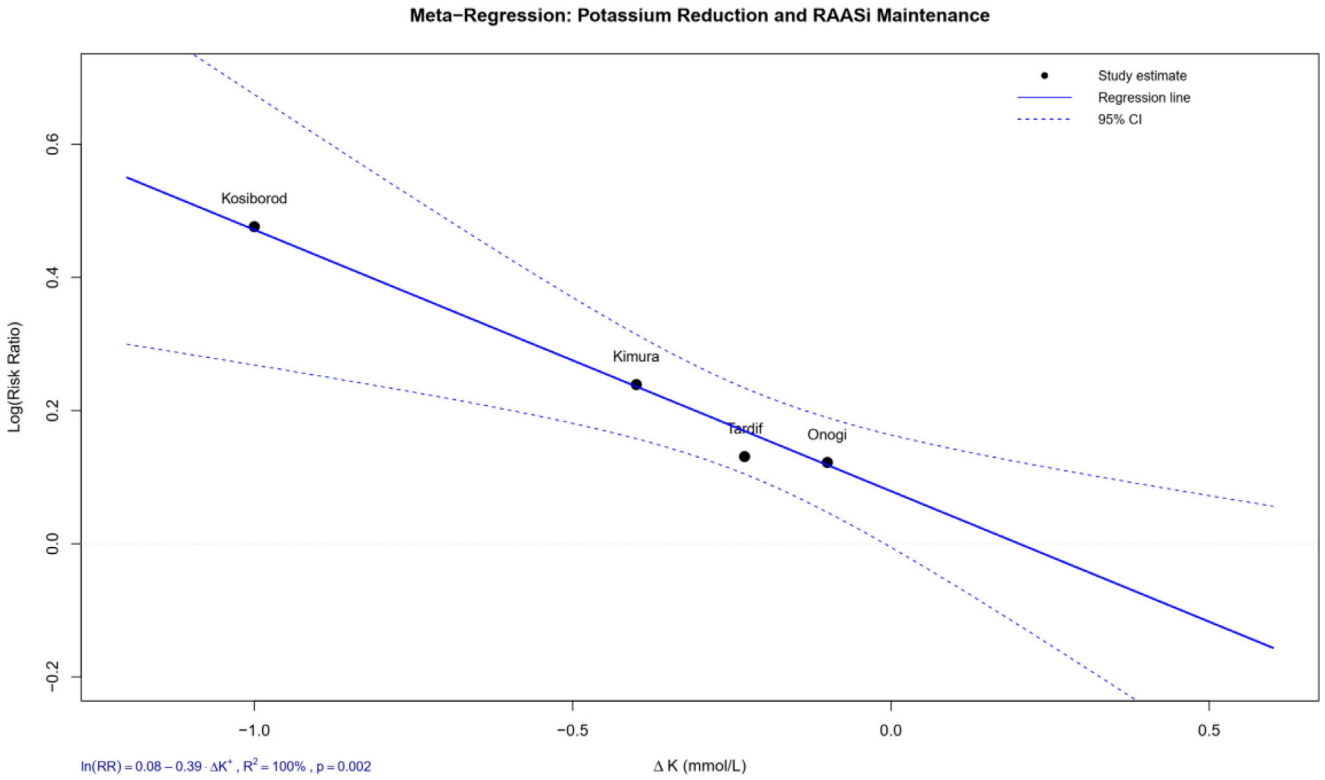

Fig. 4. Meta-regression of potassium reduction and RAASi persistence. Scatter plot showing the association between mean change in serum potassium (Δ*K*, mmol/L; defined as follow-up minus baseline) and the log risk ratio for RAASi persistence across four studies. Each circle represents a study, positioned at its mean potassium change (Δ*K*, mmol/L) and log risk ratio for RAASi persistence. Bubble area is proportional to study precision (inverse variance). The regression line (blue) shows the association between potassium reduction and RAASi maintenance, with dashed lines = 95% CI. A 1 mmol/L decrease in potassium was associated with a 48% higher likelihood of maintaining RAASi (RR, 1.48; 95% CI, 1.16–1.90).

substantial proportion of cardiorenal patients receive suboptimal RAASi therapy, with complete discontinuation in 14–16% of cases,[4,9] particularly among those treated with MRAs.[26]

Our findings suggest that SZC may help mitigate hyperkalemia-related barriers to RAASi optimization, hence, facilitating the achievement of optimal quadruple therapy in HF and maximal renoprotective dosing in CKD, both linked to improved survival and fewer hospitalizations.[5,27,28] However, RAASi persistence represents a process measure and surrogate outcome; this meta-analysis did not evaluate mortality, hospitalization, or renal endpoints. Therefore, the results should be interpreted as reflecting treatment optimization rather than demonstrated clinical benefit.

The inclusion of the ZORA real-world multicenter observational study[19] and the REALIZE-K double-blinded randomized trial,[21] enhances the clinical relevance and novelty of our findings. Notably, the effect of SZC was also observed in patients with baseline potassium >5.0 mEq/L, supporting the early initiation (proactive approach) of the novel potassium binders in patients with higher potassium levels.[29]

Several limitations should be acknowledged. First, the evidence base is largely derived from observational studies, introducing potential residual confounding despite adjustment methods. Although analysis restricted to RCTs showed consistent results, their number remains limited. Second, the substantial heterogeneity in the primary analysis ($I^2 = 77\%$), though reduced by subgroup and sensitivity analyses, highlights variability in study design, populations, and clinical practice.

Third, evidence directly comparing SZC with other potassium binders was limited to only two studes.[17,18] In the Onogi et al. study,[18] the CPS arm was selected for analysis to avoid double counting and ensure methodological consistency. Although pharmacologic differences between SZC and patiromer have been described,[25] this study was not designed to evaluate comparative effectiveness of these two novel potassium binders, highlighting the need for direct comparative trials.

Although dosing regimens were not specifically analyzed, most included studies used maintenance doses of 5–10 g/day targeting serum potassium 4.0–4.5 mmol/L, consistent with KDIGO 2024 guidance.[5]

Finally, while the meta-regression demonstrates a statistically significant ecological association between the magnitude of potassium reduction and RAASi persistence, this relationship is derived from a small number of studies using aggregate data, not individual patient effects. Therefore, the findings are exploratory and should not be interpreted as evidence of a causal or mechanistic relationship.

Conclusions

This meta-analysis suggests that SZC may facilitate maintenance and optimization of RAAS inhibitor therapy in patients with hyperkalemia and cardiorenal disease. These findings reflect treatment optimization as a process outcome, and adequately powered randomized trials are required to determine whether potassium-lowering strategies that enable RAASi maintenance translate into improved cardiovascular and renal outcomes.

ORCID ID

David Abraham Batista da Hora: 0000-0002-4261-2617
Kauê Abreu Chagas: 0009-0009-1828-4375
Juan Casas Todolí: 0000-0002-8967-1577
Felemez Arslan: 0000-0001-8318-1860

Hamlet Ghukasyan: 0009-0006-8648-4254
Taguhi Hayrapetyan: 0009-0007-8765-9439

CRediT authorship contribution statement

Hamlet Ghukasyan contributed to the study conception and design. Material review and editing, data collection and analysis were performed by Hamlet Ghukasyan, David Abraham Batista da Hora, Syeda Rubab Fatima and Felemez Arslan. Data curation and visualization were performed by Hamlet Ghukasyan, David Abraham Batista da Hora, Syeda Rubab Fatima, Kauê Abreu Chagas and Taguhi Hayrapetyan. The first draft of the manuscript was written by Hamlet Ghukasyan and David Abraham Batista da Hora and all authors commented on previous versions of the manuscript. Supervision and project administration was performed by Juan Casas Todolí, Marina Llopis Sanchis and Felemez Arslan. All authors approved the final version and agree to be accountable for the work.

Ethical considerations and consent to participate

Not applicable.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interests

We claim that there were no conflicts of interest from any author or institution in this research.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.1016/j.nefroe.2026.501532.

References

1. Kovesdy CP, Matsushita K, Sang Y, Brunskill NJ, Carrero JJ, Chodick G, et al. Serum potassium and adverse outcomes across the range of kidney function: a CKD Prognosis Consortium meta-analysis. Eur Heart J. 2018;39:1535–42, http://doi.org/10.1093/eurheartj/ehy100
2. Collins AJ, Pitt B, Reaven N, Funk S, McGaughey K, Wilson D, et al. Association of serum potassium with all-cause mortality in patients with and without heart failure, chronic kidney disease, and/or diabetes. Am J Nephrol. 2017;46:213–21, http://doi.org/10.1159/000479802
3. Thomsen RW, Nicolaisen SK, Hasvold P, Garcia-Sanchez R, Pedersen L, Adelborg K, et al. Elevated potassium levels in patients with congestive heart failure: occurrence, risk factors, and clinical outcomes. J Am Heart Assoc. 2018;7, http://doi.org/10.1161/JAHA.118.008912. e008912.
4. Linde C, Bakhai A, Furuland H, Evans M, McEwan P, Ayobkhani D, et al. Real-world associations of renin–angiotensin–aldosterone system inhibitor dose, hyperkalemia, and adverse clinical outcomes in a cohort of patients with new-onset chronic kidney disease or heart failure in the United Kingdom. J Am Heart Assoc. 2019;8, http://doi.org/10.1161/JAHA.119.012655. e012655.
5. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. 2024;105:S117–314, http://doi.org/10.1016/j.kint.2023.10.018
6. Kovesdy CP. Management of hyperkalaemia in chronic kidney disease. Nat Rev Nephrol. 2014;10:653–62, http://doi.org/10.1038/nrneph.2014.168
7. Tafesse E, Hurst M, Hoskin L, Badora K, Sugrue D, Qin L, et al. Risk factors associated with the incidence and recurrence of hyperkalaemia in patients with cardiorenal conditions. Int J Clin Pract. 2021;75, http://doi.org/10.1111/ijcp.13941. e13941.
8. Epstein M, Reaven NL, Funk SE, McGaughey KJ, Oestreicher N, Knispel J. Evaluation of the treatment gap between clinical guidelines and the utilization of renin–angiotensin–aldosterone system inhibitors. Am J Manag Care. 2015;21:S212–20.
9. Kanda E, Rastogi A, Murohara T, Lesén E, Agiro A, Arnold M, et al. Clinical impact of suboptimal RAASi therapy following an episode of hyperkalemia. BMC Nephrol. 2023;24:18, http://doi.org/10.1186/s12882-022-03054-5
10. Paolillo S, Basile C, Dell'Aversana S, Esposito I, Chirico AS, Colella A, et al. Novel potassium binders to optimize RAASi therapy in heart failure: a systematic review and meta-analysis. Eur J Intern Med. 2024;119:109–17, http://doi.org/10.1016/j.ejim.2023.08.022
11. Montagnani A, Frasson S, Gussoni G, Manfellotto D. Optimization of RAASi therapy with new potassium binders for patients with heart failure and hyperkalemia: rapid review and meta-analysis. J Clin Med. 2021;10:23, http://doi.org/10.3390/jcm10235483
12. Abuelazm M, Badr A, Turkmani M, Amin MA, Amin AM, Aboutaleb A, et al. The efficacy and safety of new potassium binders on renin–angiotensin–aldosterone system inhibitor optimization in heart failure patients: a systematic review and meta-analysis. ESC Heart Fail. 2024;11:28–43, http://doi.org/10.1002/ehf2.14588
13. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71, http://doi.org/10.1136/bmj.n71
14. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. Cochrane handbook for systematic reviews of interventions, version 6.3. Cochrane; 2022. Available from: www.training.cochrane.org/handbook. [Updated February 2022]
15. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366, http://doi.org/10.1136/bmj.l4898. l4898.
16. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2023. Available from: https://www.bmj.com/content/355/bmj.i4919. [Accessed 11 July]
17. Kimura W, Minatoguchi S, Mizuno T, Koide S, Hayashi H, Hasegawa M, et al. Sodium zirconium cyclosilicate reconciles management of hyperkalemia and continuity of renin–angiotensin–aldosterone system inhibitors: a retrospective observational study. J Nephrol. 2024;37:171–9, http://doi.org/10.1007/s40620-023-01743-4
18. Onogi C, Watanabe Y, Tanaka A, Furuhashi K, Maruyama S. Mortality and hyperkalaemia-associated hospitalisation in patients with chronic kidney disease: comparison of sodium zirconium cyclosilicate and sodium/calcium polystyrene sulfonate. Clin Kidney J. 2024;17, http://doi.org/10.1093/ckj/sfae021. sfae021.
19. Rastogi A, Pollack CV, Lázaro IJS, Lesén E, Arnold M, Franzén S, et al. Maintained renin–angiotensin–aldosterone system inhibitor therapy with sodium zirconium cyclosilicate following a hyperkalaemia episode: a multicountry cohort study. Clin Kidney J. 2024;17, http://doi.org/10.1093/ckj/sfae083
20. Hao X, Liu J, Gu L, Zang X, Liu N, Pan Y, et al. Sodium zirconium cyclosilicate (Lokelma) to enable ACEIs/ARBs use in the treatment of patients with diabetic kidney disease. Diab Res Clin Pract. 2025;227, http://doi.org/10.1016/j.diabres.2025.112413
21. Kosiborod MN, Cherney DZI, Desai AS, Testani JM, Verma S, Chinnakondepalli K, et al. Sodium zirconium cyclosilicate for management of hyperkalemia during spironolactone optimization in patients with heart failure. J Am Coll Cardiol. 2025;85:971–84, http://doi.org/10.1016/j.jacc.2024.11.014
22. Tardif JC, Rouleau J, Chertow GM, Al-Shurbaji A, Lisovskaja V, Gustavson S, et al. Potassium reduction with sodium zirconium cyclosilicate in patients with heart failure. ESC Heart Fail. 2023;10:1066–76, http://doi.org/10.1002/ehf2.14268
23. Association of serum potassium with all-cause mortality in patients with and without heart failure, chronic kidney disease, and/or diabetes. Am J Nephrol. 2025. Available from: https://karger.com/ajn/article/46/3/213/41456/Association-of-Serum-Potassium-with-All-Cause. [Accessed 22 September]
24. Thomsen RW, Nicolaisen SK, Hasvold P, Garcia Sanchez R, Pedersen L, Adelborg K, et al. Elevated potassium levels in patients with chronic kidney disease: occurrence, risk factors and clinical outcomes – a Danish population-based cohort study. Nephrol Dial Transplant. 2018;33:1610–20, http://doi.org/10.1093/ndt/gfx312
25. Meaney CJ, Beccari MV, Yang Y, Zhao J. Systematic review and meta-analysis of patiromer and sodium zirconium cyclosilicate: a new armamentarium for the treatment of hyperkalemia. Pharmacotherapy. 2017;37:401–11, http://doi.org/10.1002/phar.1906
26. Rates of hyperkalemia after publication of the randomized aldactone evaluation study. N Engl J Med. 2025, http://doi.org/10.1056/NEJMoa040135 [Accessed 22 September].
27. 2023 focused update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2025. Available from: https://academic.oup.com/eurheartj/article/44/37/3627/7246292?login=false. [Accessed 22 September]
28. 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. 2025, http://doi.org/10.1161/CIR.0000000000001063 [Accessed 22 September].
29. Almenar Bonet L, González-Franco Á. Consensus on the management of hyperkalemia in patients with heart failure: recommendations from the SEC-SEMI. Rev Clin Esp. 2022;222:235–40, http://doi.org/10.1016/j.rceng.2020.11.012