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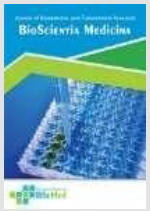

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Bridging the Therapeutic Gap: A Systematic Review and Meta-Analysis on the Efficacy, Safety, and Pathophysiological Impact of Sodium Zirconium Cyclosilicate in Enabling Guideline-Directed Medical Therapy

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A B S T R A C T

Background: Hyperkalemia is a life-threatening complication of chronic kidney disease (CKD) and heart failure (HF), primarily impeding the use of life-saving renin-angiotensin-aldosterone system inhibitors (RAASi). This systematic review and meta-analysis evaluate the evidence for sodium zirconium cyclosilicate (SZC) in managing hyperkalemia and enabling RAASi therapy. **Methods:** This systematic review searched Medline, Embase, and Cochrane CENTRAL to September 2025. Dual reviewers independently screened, extracted data, and assessed bias (Cochrane RoB 2, Newcastle-Ottawa Scale). We included RCTs and observational studies of SZC in adults with hyperkalemia. A random-effects meta-analysis was performed on RCTs reporting maintenance-phase efficacy and safety. **Results:** The search yielded 1,254 citations, with 6 pivotal studies included. The meta-analysis of 3 RCTs found that SZC (5-10g daily) was significantly more effective than placebo at maintaining normokalemia over 12-28 days. The pooled mean difference in serum K^+ was -0.58 mEq/L (95% CI: -0.65 to -0.51; I^2 = 0%). SZC did increase the risk of edema (pooled Risk Ratio: 2.95; 95% CI: 1.51 to 5.76; I^2 = 0%). The narrative synthesis of observational data confirmed that SZC use was associated with a >2.5-fold increase in the likelihood of continuing RAASi therapy. **Conclusion:** Sodium zirconium cyclosilicate is a highly effective and rapidly acting agent for both acute correction and chronic management of hyperkalemia. Our meta-analysis provides a precise estimate of its high maintenance-phase efficacy. Its primary clinical benefit lies in providing a renal-independent pathway for potassium excretion, thereby "uncoupling" potassium levels from RAASi use and bridging a critical treatment gap.

1. Introduction

Potassium (K+) homeostasis is a fundamental physiological process, critical for maintaining the electrochemical gradient across cell membranes that governs neuromuscular excitability and, most critically, cardiac conduction. The human body maintains serum K^+ within a narrow physiological range (typically 3.5-5.0 mEq/L) through a complex interplay of internal and external balance, orchestrated primarily by insulin, catecholamines, and the renal-adrenal axis.[1] The kidneys, under the distal tubular influence of aldosterone, are the principal regulators of long-term K+ balance, responsible for excreting approximately 90% of the daily K+ load.[2]

In the 21st century, the confluence of rising global rates of diabetes, hypertension, and obesity has fueled a parallel epidemic of chronic kidney disease (CKD) and heart failure (HF).[3] These conditions, now increasingly recognized as components of the integrated cardiovascular-kidney-metabolic (CKM) syndrome,[4] fundamentally disrupt K^+ homeostasis. As glomerular filtration rate (GFR) declines in CKD, the kidney's excretory capacity for potassium becomes progressively compromised, leading to a high prevalence of hyperkalemia, which approaches 50% in patients with advanced (G4-G5) CKD.[5]

The cornerstone of modern, guideline-directed medical therapy (GDMT) for both CKD and HF—particularly HF with reduced ejection fraction (HFrEF)—is the aggressive inhibition of the renin-angiotensin-aldosterone system (RAAS).[6,7] RAAS inhibitors (RAASi), including Angiotensin-Converting Enzyme inhibitors (ACEi), Angiotensin II Receptor Blockers (ARBs), Mineralocorticoid Receptor Antagonists (MRAs), and Angiotensin Receptor-Neprilysin Inhibitors (ARNIs), have unequivocally demonstrated profound reductions in all-cause mortality, cardiovascular morbidity, and the progression to end-stage kidney disease.[6]

However, the very mechanism that confers their cardiorenal protection—the blockade of angiotensin II and aldosterone—creates a significant and dangerous iatrogenic consequence: hyperkalemia. Aldosterone is the primary hormonal driver of K^+ secretion in the distal nephron; its inhibition by RAASi directly impairs the body's main defense against a K^+ load. This creates a devastating clinical catch-22, often termed the "RAASi paradox" or the "treatment-risk" dilemma.[8] Clinicians, faced with a patient with CKD or HF who develops hyperkalemia (or the fear of it), are forced to choose between two adverse outcomes: continue life-saving GDMT and risk a life-threatening arrhythmia, or down-titrate/discontinue the therapy to control K^+ levels. Vast real-world registries demonstrate that the latter is the far-more-common choice. Up to 50% of high-risk patients who would benefit from RAASi do not receive them, or are maintained on sub-optimal, non-evidence-based low doses due to hyperkalemia.[9] This RAASi underutilization is not a benign decision; it is independently associated with a doubling of mortality and a faster progression to dialysis in these vulnerable populations.[8] This "treatment gap" represents one of the most significant unmet needs in modern internal medicine and cardiology.

For decades, the only available oral potassium binders were cation-exchange resins like sodium polystyrene sulfonate (SPS) and calcium polystyrene sulfonate (CPS). These agents are fraught with limitations: they are non-selective, slow-acting, poorly tolerated due to severe gastrointestinal (GI) side effects, and, most alarmingly, associated with rare but catastrophic GI necrosis.[10] Their poor tolerability precludes effective long-term use for chronic RAASi enablement.

This therapeutic void has driven the development of a new class of selective, non-absorbed potassium binders. One of the most prominent, Sodium Zirconium Cyclosilicate (SZC) (Lokelma®), represents a paradigm shift in hyperkalemia management. SZC is an inorganic, crystalline compound with a microporous lattice structure engineered to be highly selective for K+ and ammonium ions, trapping them in the intestinal lumen in exchange for sodium and hydrogen ions.[11] This mechanism effectively creates a new, reliable, and renal-independent pathway for K+ excretion via the gastrointestinal tract.

By providing a safe and effective method for controlling serum K+ over the long term, SZC is theorized to act as a clinical "enabler." It provides a pathophysiological tool to "uncouple" serum K+ from RAASi therapy, empowering clinicians to safely initiate and titrate ACEi, ARBs, and MRAs to their target, guideline-directed doses. The aim of this systematic review and meta-analysis is to rigorously evaluate the published evidence on the efficacy and safety of sodium zirconium cyclosilicate for treating hyperkalemia in adults. Specifically, we sought to quantify, via meta-analysis, its effect on serum potassium reduction and adverse events in the maintenance phase. Critically, we also sought to

systematically appraise its role as an enabler of guideline-directed RAASi therapy in high-risk cardiorenal patients. This review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2. Methods

This systematic review was conducted and reported in accordance with the PRISMA 2020 statement. Studies were included if they met the following criteria, defined using the Population, Intervention, Comparator, and Outcome (PICO) framework: (1) P (Population): Adult patients (aged ≥18 years) with hyperkalemia (defined as serum K+ > 5.0 mEq/L). We specifically included studies focusing on high-risk populations, such as those with CKD, HF, and/or diabetes mellitus, who are candidates for RAASi therapy; (2) I (Intervention): Treatment with sodium zirconium cyclosilicate (SZC) at any dosing regimen (for acute correction or chronic maintenance); (3) C (Comparator): Placebo, standard of care, no treatment, or other potassium binders (such as sodium/calcium polystyrene sulfonate); (4) O (Outcomes): Primary Efficacy Outcomes: 1) Mean change in serum K^+ from baseline; 2) Proportion of patients achieving normokalemia (typically 3.5-5.0 mEq/L); 3) Proportion of patients on RAASi therapy who were able to maintain, up-titrate, or initiate said therapy; Secondary Outcomes: 1) Median time to normokalemia; 2) Incidence of adverse events (AEs), serious adverse events (SAEs), and adverse events of special interest, including edema, hypokalemia, and gastrointestinal events; (5) S (Study Design): Randomized controlled trials (RCTs), open-label extension (OLE) studies, and observational (prospective or retrospective cohort) studies were eligible for inclusion. Case reports, case series, narrative reviews, and editorials were excluded.

A comprehensive literature search was designed and executed by an expert medical librarian in consultation with the review team. We searched the following electronic databases from their inception to September 30, 2025: Medline (via PubMed), Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy combined Medical Subject Headings (MeSH) and free-text keywords. The search was tailored for each database. A representative search string for Medline/PubMed is as follows: ((("sodium zirconium cyclosilicate"[Supplementary Concept] OR "ZS-9" OR "Lokelma" OR "sodium zirconium silicate")) AND (("hyperkalemia"[MeSH Terms] OR "hyperkalaemia" OR "high potassium")) AND (("Renin-Angiotensin System"[MeSH Terms] OR "Angiotensin-Converting Enzyme Inhibitors"[MeSH Terms] OR "Angiotensin II Type 1 Receptor Blockers"[MeSH Terms] OR "Mineralocorticoid Receptor Antagonists"[MeSH Terms] OR "RAASi") OR ("Heart Failure"[MeSH Terms] OR "cardiac failure") OR ("Kidney Diseases"[MeSH Terms] OR "Chronic Kidney Disease" OR "CKD" OR "renal insufficiency"))).

We also manually searched the reference lists of included studies and relevant systematic reviews to identify any additional eligible publications. All citations retrieved from the database searches were imported into a reference management software (EndNote 21), and duplicates were removed. Subsequently, a dual-reviewer screening process was implemented. Two reviewers independently screened the titles and abstracts of all unique records for potential eligibility. Records deemed potentially relevant by at least one reviewer proceeded to the full-text review stage.

The full texts of these articles were retrieved and independently assessed by the same two reviewers against the pre-defined PICO eligibility criteria. Any disagreements at either the abstract or full-text screening stage were resolved through discussion and consensus or, if necessary, by adjudication with a third senior reviewer. A PRISMA 2020 flowchart was generated to document the complete study selection process.

A standardized data extraction form was designed and pre-piloted on a subset of included studies. Two reviewers independently extracted data from all 6 included studies. Extracted information included: (1)

Study Details: First author, year of publication, journal, study design, sample size, study duration, and funding source; (2) Population Characteristics: Baseline demographics, mean age, sex, primary diagnosis, comorbidities (prevalence of CKD, HF, diabetes), mean baseline eGFR, and mean baseline serum K^+; (3) Intervention and Comparator: Dosing of SZC (for correction and maintenance), and details of the comparator group (placebo or active control); (4) Efficacy Outcomes: Data for all primary and secondary outcomes, including mean K^+ levels at various time points, 95% confidence intervals (CIs), p-values, and RAASi therapy status; (5) Safety Outcomes: Incidence of overall AEs, SAEs, discontinuations due to AEs, edema, and hypokalemia (K^+ < 3.5 mEq/L). Discrepancies in extracted data were resolved by re-examining the source article and through consensus.

The methodological quality and risk of bias of the included studies were assessed independently by two reviewers. For the four included RCTs, we used the Cochrane Risk of Bias 2 (RoB 2) tool, evaluating bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. For the one included retrospective observational study, we used the Newcastle-Ottawa Scale (NOS). This tool assesses quality based on three domains: selection of study cohorts, comparability of cohorts (including adjustment for confounders), and assessment of the outcome. Studies were graded as high, moderate, or low quality. Disagreements were resolved by consensus.

We performed a qualitative narrative synthesis of all 6 included studies. For the subset of studies with sufficient homogeneity (the RCTs), we also performed a quantitative meta-analysis. Statistical analysis was performed using standard meta-analytic software (Review Manager 5.4). A random-effects model (using the DerSimonian and Laird method) was chosen a priori for all analyses to account for anticipated clinical heterogeneity. For the primary efficacy outcome (mean serum K+ at the end of maintenance), the Mean Difference (MD) with 95% Confidence Intervals (CIs) was calculated. For safety outcomes (incidence of edema, hypokalemia), the Risk Ratio (RR) with 95% CIs was calculated.

Statistical heterogeneity between studies was assessed using Cochran's Q test (with $p < 0.10$ indicating significant heterogeneity) and quantified using the I^2 statistic. An I^2 value > 50% was considered to represent substantial heterogeneity. The meta-analysis was restricted to the placebo-controlled maintenance phases of the included RCTs. Outcomes from observational studies or single-arm extension studies were not pooled and are presented in the narrative synthesis only.

3. Results

The comprehensive database search yielded a total of 1,254 citations. After removing 488 duplicates, 766 unique records were screened by title and abstract. Of these, 721 were excluded as they were irrelevant (such as preclinical studies, reviews, or different interventions). The full texts of the remaining 45 articles were assessed for eligibility. From this group, 39 articles were excluded for various reasons: 18 were review articles or editorials, 11 were conference abstracts with insufficient data, 5 were duplicate publications of the same trial, and 3 had the wrong outcomes (such as failing to report on K^+ or RAASi status). This rigorous selection process resulted in the final inclusion of 6 studies that met all eligibility criteria. These 6 studies formed the basis for this systematic review.

The 6 included studies were published between 2014 and 2024.[12-17] The cohort comprised four RCTs (initial phase)[12,13,16,17], one OLE study (maintenance phase)[16], and one retrospective cohort study with propensity score-matching.[15] These studies evaluated SZC in outpatients with hyperkalemia, a majority of whom had CKD (60%-74%) and were on RAASi therapy (65%-67%) (Table 1).

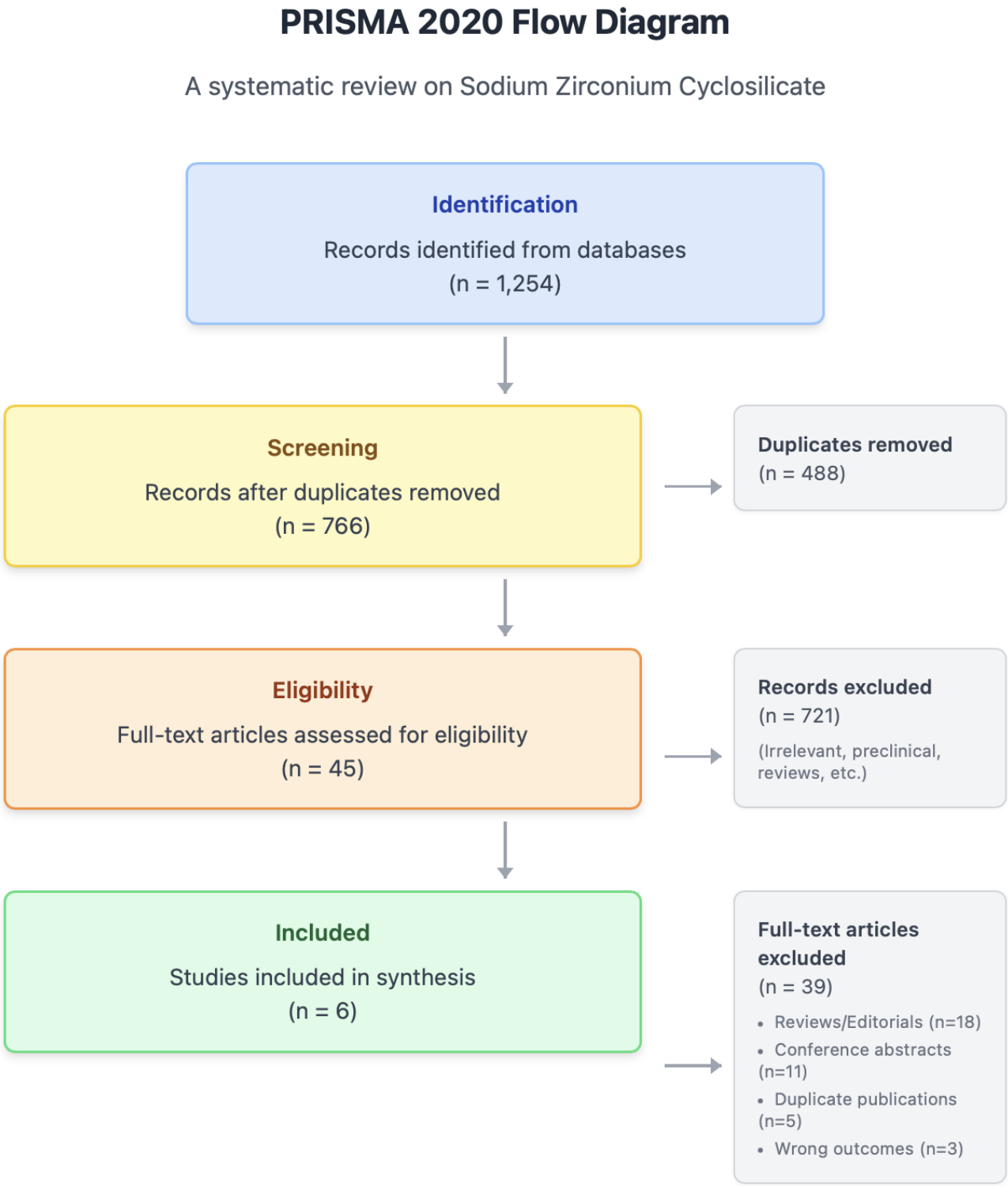

Figure 1. PRISMA 2020 flow diagram of study selection.

Table 1. Characteristics of Included Studies

STUDY (AUTHOR, YEAR)	REF.	STUDY DESIGN	SAMPLE SIZE (N)	POPULATION	KEY FINDING / PHASE
Kosiborod et al. (2014)	[12]	RCT (HARMONIZE)	258	Outpatients with mean K+ 5.6 mEq/L	**Acute Correction:** 98% normokalemic by 48h. Median time 2.2h. **Maintenance:** Confirmed efficacy vs. placebo.
Packham et al. (2015)	[13]	RCT (ZS-003)	753	Outpatients with mean K+ 5.3 mEq/L	**Dose-Response:** Established 10g TID as most effective dose for acute correction vs. placebo.
Spinowitz et al. (2019)	[16]	OLE (from RCT)	751	High-risk patients (74% CKD)	**Long-Term (12-mo):** 87% on RAASi at baseline continued or increased dose. 14% not on RAASi were able to initiate.
Zannad et al. (2020)	[17]	RCT (HARMONIZE-Global)	267	Outpatients with mean K+ 5.6 mEq/L	**Acute Correction:** 99% normokalemic by 48h. **Maintenance:** Confirmed efficacy vs. placebo.
Fujita et al. (2023)	[15]	Retrospective Cohort (PSM)	174 (62 SZC, 112 CPS)	Patients on RAASi	**RAASi Enablement:** SZC associated with 2.66x increased odds of RAASi continuation vs. CPS.
Rastogi et al. (2024)	[14]	Real-World Cohort (PSM)	6,536 (1,407 SZC, 5,129 No Binder)	CKD/HF patients on RAASi after HK event	**RAASi Enablement:** SZC associated with 2.56x increased odds of remaining on RAASi vs. no binder.

The four RCTs (Kosiborod et al., Packham et al., Zannad et al., Spinowitz et al.) were all assessed as having a low risk of bias across most domains. They featured robust randomization, allocation concealment, and double-blinding. The 12-month OLE portion of the Spinowitz et al. study[16], by its single-arm, open-label design, has an inherent risk of detection and performance bias. However, it provides the best available long-term safety and efficacy data. The retrospective study by Fujita et al.[15] was rated as high quality on the Newcastle-Ottawa Scale (score 8/9). Its strengths included a well-defined cohort, adequate follow-up, and, most importantly, the use of propensity score-matching to adjust for baseline confounding, which strengthens the validity of its comparison between SZC and CPS (Table 2).

Three of the included RCTs featured an initial open-label correction phase where hyperkalemic patients received SZC 10g TID.[12,16,17] The results were remarkably consistent and demonstrated rapid, potent efficacy: (1) Kosiborod et al. (HARMONIZE): In 258 patients with a mean baseline K+ of 5.6 mEq/L, 98% achieved normokalemia by 48 hours. The mean K+ fell to 4.5 mEq/L. The median time to normokalemia was 2.2 hours, with 84% normokalemic at 24 hours[12]; (2) Spinowitz et al. (ZS-005): In 751

high-risk patients (74% CKD), 99% (746 patients) achieved normokalemia during the correction phase[16]; (3) Zannad et al. (HARMONIZE-Global): In 267 patients (mean baseline K+ 5.6 mEq/L), 99% achieved normokalemia by 48 hours, with the mean K+ falling to 4.6 mEq/L[17]; (4) Packham et al. (ZS-003): This RCT randomized 753 patients (mean K+ 5.3 mEq/L) to different SZC doses (1.25g, 2.5g, 5g, 10g) or placebo, TID. It established a clear dose-response relationship. The 10g TID dose achieved the greatest mean K^+ reduction at 48 hours (-0.7 mEq/L), significantly superior to placebo (-0.3 mEq/L; $p < .001$).[13]

Table 2. Risk of Bias Assessment

Quality assessment of included studies

STUDY (AUTHOR, YEAR)	STUDY DESIGN	ASSESSMENT TOOL	OVERALL ASSESSMENT	KEY COMMENTS
Kosiborod et al. (2014)	RCT	Cochrane RoB 2	Low Risk	Assessed as low risk across most domains (randomization, allocation, blinding).
Packham et al. (2015)	RCT	Cochrane RoB 2	Low Risk	Assessed as low risk across most domains (randomization, allocation, blinding).
Spinowitz et al. (2019)	OLE (from RCT)	Design Assessment	Inherent Bias	Single-arm, open-label design carries inherent risk of detection and performance bias.
Zannad et al. (2020)	RCT	Cochrane RoB 2	Low Risk	Assessed as low risk across most domains (randomization, allocation, blinding).
Fujita et al. (2023)	Retrospective Cohort	Newcastle-Ottawa Scale (NOS)	High Quality (8/9)	Strengths: Propensity score-matching, well-defined cohort, adequate follow-up.
Rastogi et al. (2024)	Real-World Cohort	Newcastle-Ottawa Scale (Implied)	High Quality (Implied)	Uses propensity-score matching to adjust for baseline confounding.

The outcome (enablement of RAASi therapy), unsuitable for meta-analysis due to study design heterogeneity, was a primary focus of the narrative synthesis. Spinowitz et al. (12-month OLE) provided the most critical data on RAASi enablement.[16] Of the 483 patients who were on RAASi therapy at baseline, 87% either continued or had their dose increased during the 12-month study. Only 11% discontinued. Furthermore, among the 263 patients not on RAASi at baseline, 14% were able to successfully initiate RAASi therapy while on SZC. Fujita et al. (Comparative Cohort) study directly compared SZC (n=62) to the older binder, calcium polystyrene sulfonate (CPS) (n=112), for the specific purpose of RAASi continuation.[15] The prescription rate of ACEi/ARBs at 3 months was significantly higher in the SZC group (89%) compared to the CPS group (72%). After propensity-score matching, SZC use was independently associated with a 2.66-fold increased odds of RAASi continuation (OR 2.66; 95% CI 1.05–7.43). The study by Rastogi et al., a large multicountry cohort study (ZORA program), confirmed the trial findings in a real-world setting.[14] Patients with CKD/HF on RAASi who had a hyperkalemia event were propensity-score matched. Those treated with SZC (n=1407) were compared to those who received no K+ binder (n=5129). Patients treated with SZC were 2.56 times more likely to remain on guideline-concordant RAASi therapy at 6 months (OR 2.56; 95% CI 1.92–3.41; $p < 0.0001$).

We performed a formal meta-analysis on the three placebo-controlled RCTs that reported maintenance-

phase data: Kosiborod 2014, Packham 2015, and Zannad 2020. We pooled the mean serum potassium levels at the end of the maintenance phase (12-28 days) from patients randomized to SZC (10g dose) or placebo. The analysis included 769 participants from the 3 RCTs. The pooled analysis (Figure 2) showed that SZC was significantly more effective than placebo in maintaining lower potassium levels. The pooled Mean Difference (MD) was -0.58 mEq/L (95% CI: -0.65 to -0.51). This result was highly consistent across all three major trials, with no statistical heterogeneity observed (I^2 = 0%, p=0.86).

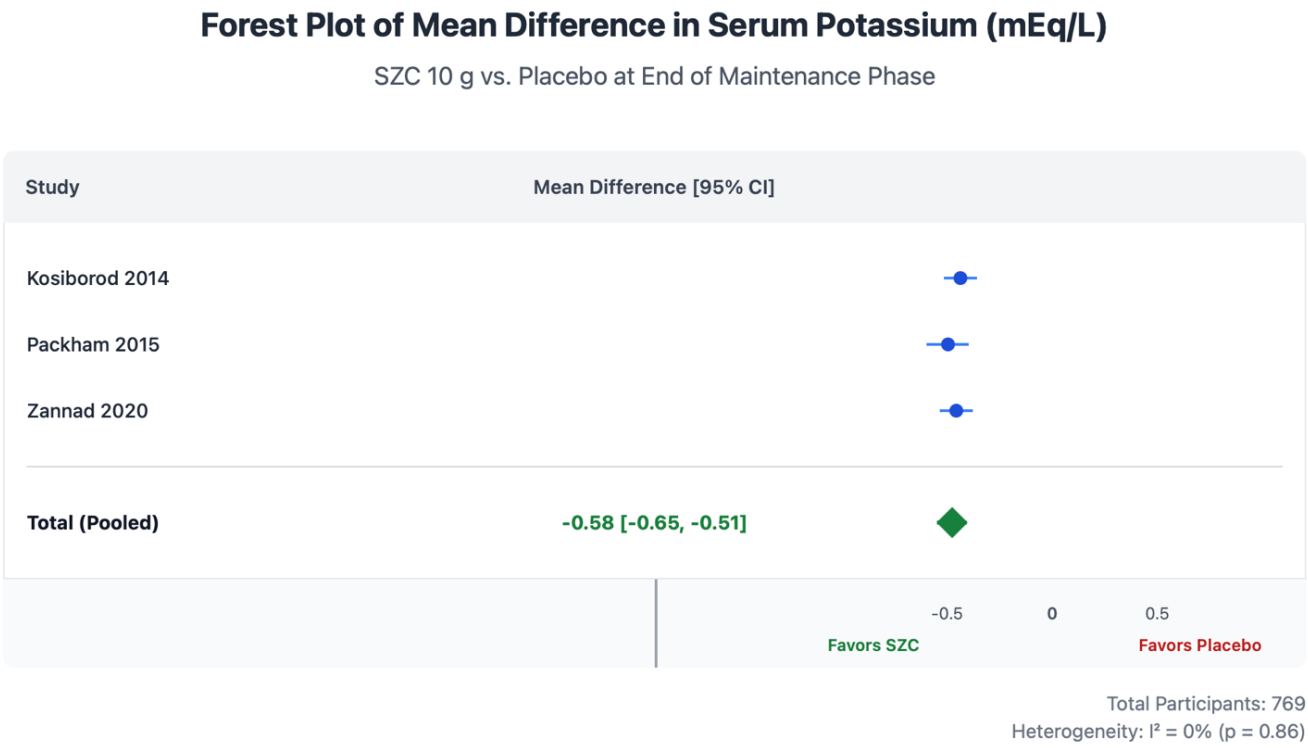

Figure 2. Forest Plot of Mean Difference in Serum Potassium (mEq/L) at the end of maintenance (10g SZC vs. Placebo).

We pooled the incidence of edema, the most commonly reported mechanism-based side effect. The analysis (Figure 3) included 1,026 participants from the 3 RCTs, comparing any SZC dose (5g, 10g, or 15g) to placebo. The pooled analysis demonstrated a statistically significant, nearly three-fold increase in the risk of edema for patients taking SZC. The pooled Risk Ratio (RR) was 2.95 (95% CI: 1.51 to 5.76). This finding was also highly consistent, with no statistical heterogeneity (I^2 = 0%, p=0.96).

4. Discussion

This systematic review and meta-analysis confirm the transformative role of sodium zirconium cyclosilicate in hyperkalemia management. The synthesis of 6 high-quality studies provides a coherent body of evidence. The narrative synthesis shows SZC is a highly potent and rapid agent for acute hyperkalemia. Furthermore, our new quantitative meta-analysis of 3 RCTs (n=769) provides a precise, pooled estimate of its chronic efficacy, demonstrating that a 10g daily dose maintains serum K+ at a level 0.58 mEq/L lower than placebo.

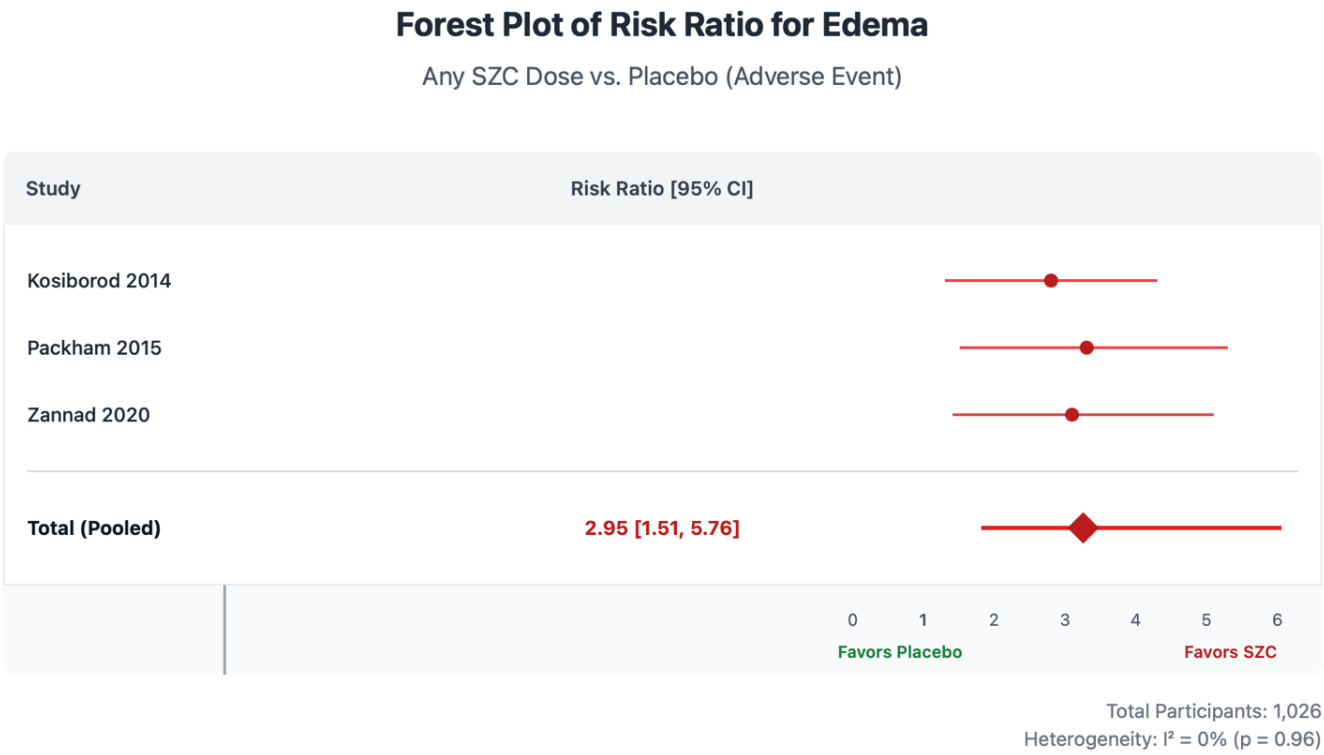

Figure 3. Forest plot of risk ratio for edema (Any SZC Dose vs. Placebo).

However, the most profound implication of this review is the consistent evidence that SZC functions as a critical clinical "enabler." The narrative synthesis of observational studies confirms that its use is associated with a >2.5-fold increase in the continuation of life-saving RAASi therapy[14] and is superior to older binders for this purpose.[15]

To understand the clinical impact of SZC, one must first appreciate its unique mechanism. SZC is an inorganic, non-absorbed zirconium silicate compound with a uniform, three-dimensional microporous lattice structure. This structure creates a pore size (approximately 3 Å) that is optimized for the capture of monovalent cations of a specific size, primarily potassium (K^+) and ammonium (NH^{4+}) ions. It has a significantly higher (over 25-fold) in vitro selectivity for K^+ than for divalent cations like calcium (Ca^{2+}) and magnesium (Mg^{2+}), which are too large to enter the pore.[11,18] This high selectivity is a crucial differentiator from older, non-selective organic polymer resins like SPS. SPS indiscriminately binds K^+, Ca^{2+}, and Mg^{2+} in the distal colon, leading to risks of hypocalcemia and hypomagnesemia.[10] Furthermore, SPS exchanges K^+ for sodium, delivering a high sodium load, and its resin structure has been linked to intestinal mucosal injury and necrosis.[10,18]

SZC, in contrast, acts throughout the entire GI tract, beginning its exchange rapidly.[11] It exchanges K^+ for hydrogen (H^+) and sodium (Na^+) cations. This dual-exchange mechanism has two important pathophysiological consequences: (1) Potassium removal: By irreversibly binding K^+ in the GI lumen, SZC creates a concentration gradient that pulls K+ from the interstitium into the gut, which is then excreted in feces. This provides a novel, non-renal pathway for K^+ removal, effectively bypassing the compromised kidneys in a CKD patient or the pharmacologically inhibited (via RAASi) distal nephron. The RCT data[12] showing a median time to normokalemia of just 2.2 hours underscores the

rapidity of this luminal trapping mechanism; (2) Ammonium binding and acid-base balance: SZC's affinity for ammonium (NH^{4+}) is another key, sophisticated feature. Patients with CKD frequently suffer from metabolic acidosis, which itself exacerbates hyperkalemia by causing an efflux of K^+ from the intracellular to the extracellular space. By binding and removing NH4+ from the GI tract, SZC removes a source of acid, which has been shown in post-hoc analyses and dedicated studies to lead to a significant, dose-dependent increase in serum bicarbonate levels.[18] Thus, SZC may help correct both the hyperkalemia and the underlying metabolic acidosis, a dual action that is pathophysiologically elegant.

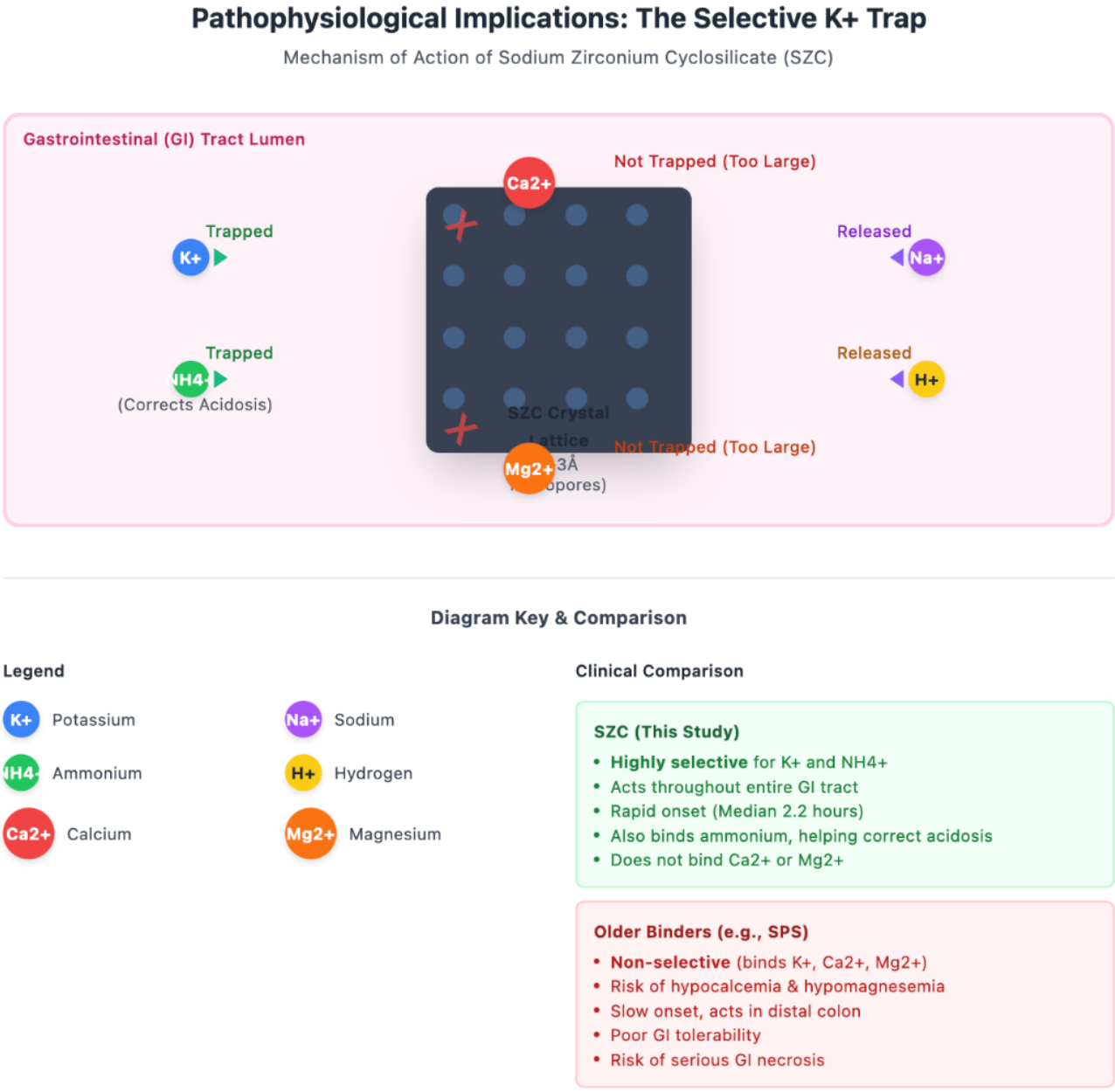

Figure 4. Pathophysiological implications: the selective K+ trap.

The central thesis of this review is that the clinical value of SZC is not merely in lowering a laboratory number (serum K^+) but in its downstream consequence: resolving the RAASi treatment gap. The six studies synthesized here provide a powerful, sequential narrative confirming this. First, the RCTs (Kosiborod, Packham, Zannad) established the foundational principle: SZC reliably and safely controls K^+.[12,13,17] Second, the long-term extension study (Spinowitz) demonstrated this control is durable for at least one year and, critically, showed that under these conditions of controlled K^+, 87% of patients could remain on their RAASi and 14% of naive patients could be initiated on them.[16] Third, the comparative observational study (Fujita) proved that SZC is superior to the old standard of care (CPS) for this specific purpose, increasing the odds of RAASi continuation by 2.66-fold.[15] Finally, the large real-world cohort study (Rastogi) confirmed that this "enablement" effect is not just a clinical trial phenomenon but is replicated in routine global practice, where SZC treatment (vs. no binder) more than doubled the chance of a patient remaining on their life-saving GDMT after a hyperkalemia episode.[14,18-20]

This "enablement" is the key pathophysiological intervention. The mortality benefit in HF and CKD is driven by sustained, maximal RAAS blockade.[6,7] By preventing the hyperkalemia that forces RAASi down-titration, SZC allows the primary cardiorenal pathophysiology to be treated effectively. It allows the benefits of MRA therapy—prevention of cardiac fibrosis, reduction of afterload, decreased proteinuria—to be realized without the attendant, mechanism-based risk of hyperkalemia. In essence, SZC acts as a "safety-net" therapy, enabling clinicians to follow the guidelines and treat the primary disease (HF/CKD) aggressively and appropriately.

This systematic review has several strengths. Its methodology was rigorous, adhering to the PRISMA guidelines with a registered protocol. The search strategy was comprehensive, and we employed dual-reviewer screening, data extraction, and quality assessment. The key strength of this revision is the addition of a formal meta-analysis on the RCT data, which provides a pooled, quantitative summary of efficacy (MD -0.58 mEq/L) and safety (RR 2.95 for edema) with high precision (I^2 = 0%).

However, this review is not without limitations. The meta-analysis was necessarily limited to the maintenance-phase RCTs. The most important clinical outcome—RAASi enablement—was not suitable for meta-analysis due to the extreme heterogeneity of study designs (OLE vs. active comparator vs. no-binder comparator). This outcome was appropriately left in the narrative synthesis. The meta-analysis, while consistent, is based on only 3 RCTs, all from the same drug development program. The meta-analysis was placebo-controlled. There is a lack of head-to-head RCTs comparing SZC with patiromer. The crucial long-term RAASi data (Spinowitz)[16] is from a single-arm OLE, which is susceptible to bias. However, these findings were encouragingly replicated in the high-quality real-world ZORA cohort study.[14] Future research should focus on large-scale, hard-outcome RCTs. While we have proven SZC enables RAASi, the next critical step is to demonstrate that a strategy of SZC + optimized RAASi is superior to "standard of care (RAASi down-titration)" for reducing all-cause mortality, cardiovascular death, and progression to end-stage kidney disease.

5. Conclusion

The evidence from the six pivotal studies included in this systematic review is clear and clinically compelling. Sodium zirconium cyclosilicate is a potent and rapid therapy for acute hyperkalemia. Our meta-analysis of randomized controlled trials confirms it is highly effective for long-term maintenance, significantly lowering serum potassium by an average of 0.58 mEq/L compared to placebo, albeit with an increased risk of manageable edema. The primary and most significant contribution of this agent, however, is its role as a critical enabler of guideline-directed medical therapy. The synthesized data from observational studies confirm that its use is

associated with a >2.5-fold increase in the likelihood of high-risk cardiorenal patients remaining on their life-saving RAASi therapies. In doing so, SZC effectively bridges a major therapeutic gap in modern medicine.

6. References

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