JUSINDO, Vol. 8 No. 2, February 2026
p-ISSN: 2303-288X, e-ISSN: 2541-7207

Sodium Zirconium Cyclosilicate Compared with Polystyrene Sulfonate for the Management of Hyperkalemia in Chronic Kidney Disease: A Systematic Review

Bella Yanita[1], Januar Ishak Hutasoit[2]
Abdul Moeloek General Hospital Lampung, Indonesia[1]
Universitas Lampung, Indonesia[2]
Email: Bellaynta17@gmail.com

Keywords:
Hyperkalemia; Chronic kidney disease (CKD); Sodium zirconium cyclosilicate (SZC); Potassium binders

ABSTRACT

Background: Hyperkalemia is a common and potentially life-threatening complication in patients with chronic kidney disease (CKD). Methods: This systematic review followed the PRISMA 2020 guidelines. A comprehensive literature search was conducted using PubMed, ScienceDirect, and the Cochrane Library to identify randomized controlled trials and comparative observational studies involving adult patients with CKD and hyperkalemia. Studies comparing sodium zirconium cyclosilicate (SZC) with polystyrene sulfonate–based binders and reporting efficacy or safety outcomes were included. Data extraction and risk of bias assessment were performed, and a qualitative synthesis of results was conducted due to study heterogeneity. Results: Eight studies were included in the qualitative analysis, comprising seven interventional and hospital-based observational studies involving 690 patients and one large nationwide cohort including more than 70,000 patients. In acute settings, SZC achieved rapid reductions in serum potassium, with greater or comparable efficacy to polystyrene sulfonate–based binders. In chronic management, SZC was associated with earlier normalization and more sustained potassium control. Safety outcomes were generally comparable, with favorable tolerability and patient preference observed for SZC. Discussion: The included studies consistently demonstrated effective potassium lowering with SZC across acute and chronic settings. While heterogeneity and the predominance of observational data limit causal inference, the overall findings support the clinical utility of SZC, particularly in facilitating long-term potassium control and treatment adherence. Conclusion: SZC represents an effective and well-tolerated alternative to polystyrene sulfonate–based binders for the management of hyperkalemia in patients with CKD. Further well-designed randomized studies are warranted to confirm long-term clinical benefits.

INTRODUCTION

Hyperkalemia represents a frequent and clinically significant electrolyte abnormality among patients with chronic kidney disease (CKD). Progressive impairment of renal potassium excretion, metabolic acidosis, and the widespread use of renin–angiotensin–aldosterone system inhibitors (RAASi) collectively contribute to its high prevalence across all stages of CKD. (Humphrey, 2022) Importantly, hyperkalemia is associated with an increased risk of cardiac arrhythmias, hospital admission, discontinuation of evidence-based therapies, and all-cause mortality, underscoring the necessity for effective and safe potassium-lowering interventions in this population.

The clinical impact of hyperkalemia is extensive, ranging from life-threatening ventricular arrhythmias to obstacles in the administration of cardioprotective therapy. (Rossignol, 2017), in a prospective survey of 8,510 hemodialysis sessions in France, found that 31% of patients had pre-dialysis potassium levels >5.5 mmol/L, and this condition was independently associated with increased mortality. Furthermore, hyperkalemia often forces clinicians to reduce doses or even discontinue RAASi, whereas RAASi has been shown to slow the progression of CKD. This dilemma between electrolyte safety and cardiorenal benefits lies at the core of the problem in advanced CKD management.

For decades, pharmacological therapy for chronic hyperkalemia has been dominated by polystyrene sulfonate–based potassium binders, both in the form of sodium (SPS) and calcium (CPS). However, the effectiveness of these agents is often questioned. A study by Batter et al. (2013), published in Drug Safety, showed that the onset of action of SPS is slow and unpredictable and is often associated with serious gastrointestinal side effects such as intestinal necrosis. This limitation creates an urgent need for more selective and well-tolerated agents.

Sodium and calcium polystyrene sulfonate (SPS/CPS) have traditionally been used as potassium binders; however, their clinical utility is limited by inconsistent efficacy, delayed and unpredictable onset of action, suboptimal tolerability, and concerns regarding gastrointestinal adverse events. (Packham, 2015) Sodium zirconium cyclosilicate (SZC) is a newer, highly selective potassium binder that has demonstrated rapid potassium-lowering effects and a favorable tolerability profile in both acute and chronic settings. Nevertheless, existing comparative evidence between SZC and polystyrene sulfonate–based binders remains heterogeneous, with variations in study design, patient populations, clinical contexts, and outcome measures. (Agarwal, 2019; Kosiborod, 2019; Pitt, 2015; Weir, 2015) Accordingly, a systematic synthesis of the available evidence is warranted to clarify the relative efficacy and safety of SZC compared with conventional polystyrene sulfonate–based binders in patients with CKD and hyperkalemia.

Sodium zirconium cyclosilicate (SZC) is a non-polymeric inorganic cation exchanger with high selectivity for potassium ions. Unlike polystyrene sulfonate, which acts throughout the large intestine, SZC acts specifically in the upper gastrointestinal tract by trapping potassium in its microcrystalline framework. Phase III clinical trials such as HARMONIZE and ZS-005 have proven the efficacy of SZC in achieving normokalemia within 24–48 hours. Despite this, the trials mostly used placebo as a comparator rather than directly comparing SZC with SPS/CPS.

The research gap lies in the lack of a systematic synthesis that directly compares SZC with polystyrene sulfonate. A study by (Cañas, 2023; Rafique, 2020) in BMC Nephrology did attempt to compare the two agents, but it focused only on acute hyperkalemia in the emergency room and had a small sample size. To date, there has been no systematic review integrating current evidence from randomized controlled trials conducted between 2024 and 2025, as well as large-scale real-world data reported by Onogi et al. (2024).

The urgency of this research is increasing as access to SZC expands in various countries following FDA and EMA approval. Although SZC has become more widely available, the question of whether this agent is truly clinically superior to the much cheaper generic polystyrene sulfonate remains frequently debated in scientific forums. Without solid

comparative evidence, policymakers in hospitals face difficulties developing formularies and clinical practice guidelines.

The novelty of this systematic review lies in its scope and inclusion of the most up-to-date evidence. Unlike previous reviews that focused on a single agent, this study exclusively includes direct head-to-head comparisons. We integrated findings from a double-blind randomized controlled trial by Elsayed et al. (2025) in Egypt, the appetite palatability study by Wheeler et al. (2024), and the Japanese national cohort by Onogi et al. (2024), which included more than 70,000 patients. This broad scope allows for a more comprehensive analysis.

The purpose of this study is to synthesize qualitative evidence regarding the efficacy and safety of SZC compared with SPS/CPS in CKD patients with hyperkalemia. Specifically, this study aims to compare the rate of potassium decline, the duration required to achieve normokalemia, the side-effect profiles, and clinical outcomes such as hospitalization and mortality.

RESEARCH METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The review aimed to compare the efficacy and safety of sodium zirconium cyclosilicate (SZC) versus polystyrene sulfonate–based potassium binders (sodium or calcium polystyrene sulfonate) in patients with chronic kidney disease (CKD) and hyperkalemia.

1. Search Strategy

A comprehensive literature search was performed across multiple electronic databases, including PubMed, Science Direct, and Cochrane Library. The search covered studies published from database inception to the most recent update to ensure inclusion of all relevant evidence. Keywords used in the search included: “sodium zirconium cyclosilicate” OR “zirconium cyclosilicate”, “polystyrene sulfonate” OR “sodium polystyrene sulfonate” OR “calcium polystyrene sulfonate”, “hyperkalemia”, “chronic kidney disease” OR “CKD” OR “renal failure”. Boolean operators (AND, OR) were applied to combine search terms appropriately. The search was restricted to English-language full-text articles. In addition, the reference lists of relevant studies were manually screened to identify any additional eligible articles.

2. Inclusion Criteria

Studies were eligible for inclusion if they enrolled adult patients (aged ≥18 years) with chronic kidney disease, irrespective of dialysis status, who were diagnosed with hyperkalemia. Eligible studies were required to include a direct comparison between sodium zirconium cyclosilicate and polystyrene sulfonate–based potassium binders (sodium or calcium polystyrene sulfonate) and to report quantitative data on at least one clinically relevant efficacy or safety outcome related to potassium management (Clase, 2020; Epstein, 2016). Both randomized controlled trials and comparative observational studies, including prospective and retrospective designs, were considered for inclusion.

3. Exclusion Criteria

Studies were excluded if they were review articles, editorials, letters, conference abstracts without full-text availability, case reports, or case series. Studies conducted in pediatric populations, animal models, or in vitro settings were also excluded. Furthermore, studies that did not directly compare sodium zirconium cyclosilicate with polystyrene sulfonate–based binders, or that failed to report quantitative efficacy or safety outcomes, were excluded. Study protocols without reported results and non–English-language publications were not eligible for inclusion.

4. Data Extraction and Quality Assessment

The following data were extracted from each eligible study: 1) authors and year of publication; 2) study design; 3) country where the study was conducted; 4) inclusion criteria; 5) number of patients in each treatment group (SZC and SPS/CPS); 6) follow-up duration; 7) study outcomes, including changes in serum potassium levels, achievement of normokalemia, time to potassium normalization, adverse events, and other clinically relevant outcomes such as hospitalization or mortality when available; 8) key findings reported by the authors. Data extraction was performed independently by two reviewers, and discrepancies were resolved through discussion and consensus.

Risk of bias assessment was conducted using the Cochrane Risk of Bias 2 (RoB 2) tool for randomized controlled trials and the ROBINS-I tool for non-randomized studies. A study was considered good if it received 3 or 4 stars in the selection domain AND 1 star in the comparability domain AND 2 or 3 stars in the outcome domain. A study was considered fair if it received 2 stars in the selection domain AND 1 star in the comparability domain AND 2 or 3 stars in the outcome domain. A study was considered poor if it received 0 or 1 star in the selection domain AND 0 stars in the comparability domain AND 0 or 1 star in the outcome domain. Extracted data were summarized in tables and narrative synthesis was performed to describe the data. Due to the heterogeneity of the included articles concerning outcomes of interest to our review, we are unable to analyze and synthesize the data quantitatively. We analyzed and reported (qualitative) data following our study objectives regarding the safety and efficacy of the intervention, which included overall survival, progression-free survival, response rate, and safety in terms of adverse events.

5. Ethical Considerations

As this study involved the analysis of previously published data, ethical approval and informed consent were not required. The findings of this systematic review are expected to provide clinically relevant evidence regarding the comparative effectiveness and safety of sodium zirconium cyclosilicate and polystyrene sulfonate–based binders, thereby supporting evidence-based decision-making in the management of hyperkalemia in patients with chronic kidney disease.

RESULTS AND DISCUSSION

Results

The systematic review included a total of eight studies after a comprehensive screening process. These studies comprised seven interventional and hospital-based observational studies

involving 690 patients, along with one large nationwide claims-based cohort including more than 70,000 patients with chronic kidney disease and hyperkalemia. The primary outcomes assessed were changes in serum potassium concentration and achievement or time to normokalemia, while secondary outcomes included safety outcomes and additional clinically relevant endpoints.

1. Study Selection

The literature search across three databases resulted in 327 hits. After removal of 24 duplicate records, 303 records were screened based on titles and abstracts. Of these, 241 records were excluded for not meeting the inclusion criteria. A total of 62 reports were sought for full-text retrieval; however, 34 reports could not be retrieved. Consequently, 28 full-text articles were assessed for eligibility. Among these, 20 articles were excluded, primarily due to unavailable full text (n = 12) and lack of a control group (n = 8). Following full-text assessment, 8 studies met the eligibility criteria and were included in the qualitative synthesis (Figure 1).

2. Study Characteristics and Risk of Bias

Among the eight included studies, one was a randomized controlled trial and eight were observational studies. Studies were conducted in Egypt, Japan, China, the United States, and multinational settings. Patient populations included both dialysis-dependent and non–dialysis-dependent patients with chronic kidney disease and hyperkalemia. Follow-up duration ranged from 2 hours in acute management studies to 1 year in long-term observational cohorts.

The randomized controlled trial (RCT) demonstrated a low overall risk of bias across all domains assessed using the Cochrane Risk of Bias 2 tool (Figure 2). Observational studies were judged to have moderate to serious risk of bias, primarily due to confounding and deviations from intended interventions, as assessed using the ROBINS-I tool (Figure 3). Measurement of outcomes was consistently judged to be at low risk of bias, as serum potassium and other key outcomes were objectively assessed.

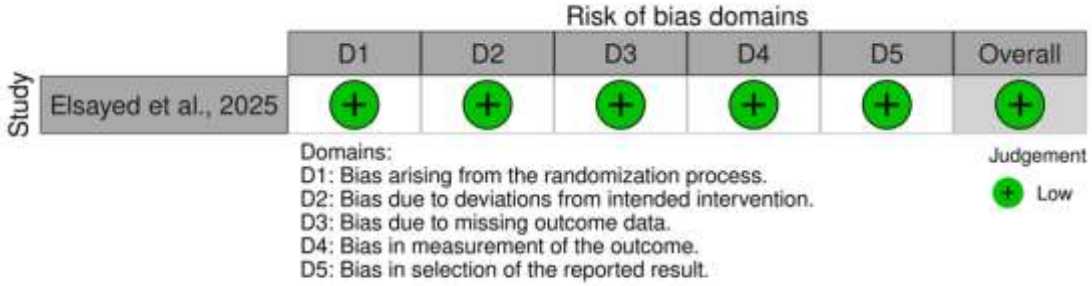

Figure 1. Risk of Bias Assessment of Included Studies Using the Cochrane Risk of Bias 2 tool for RCT

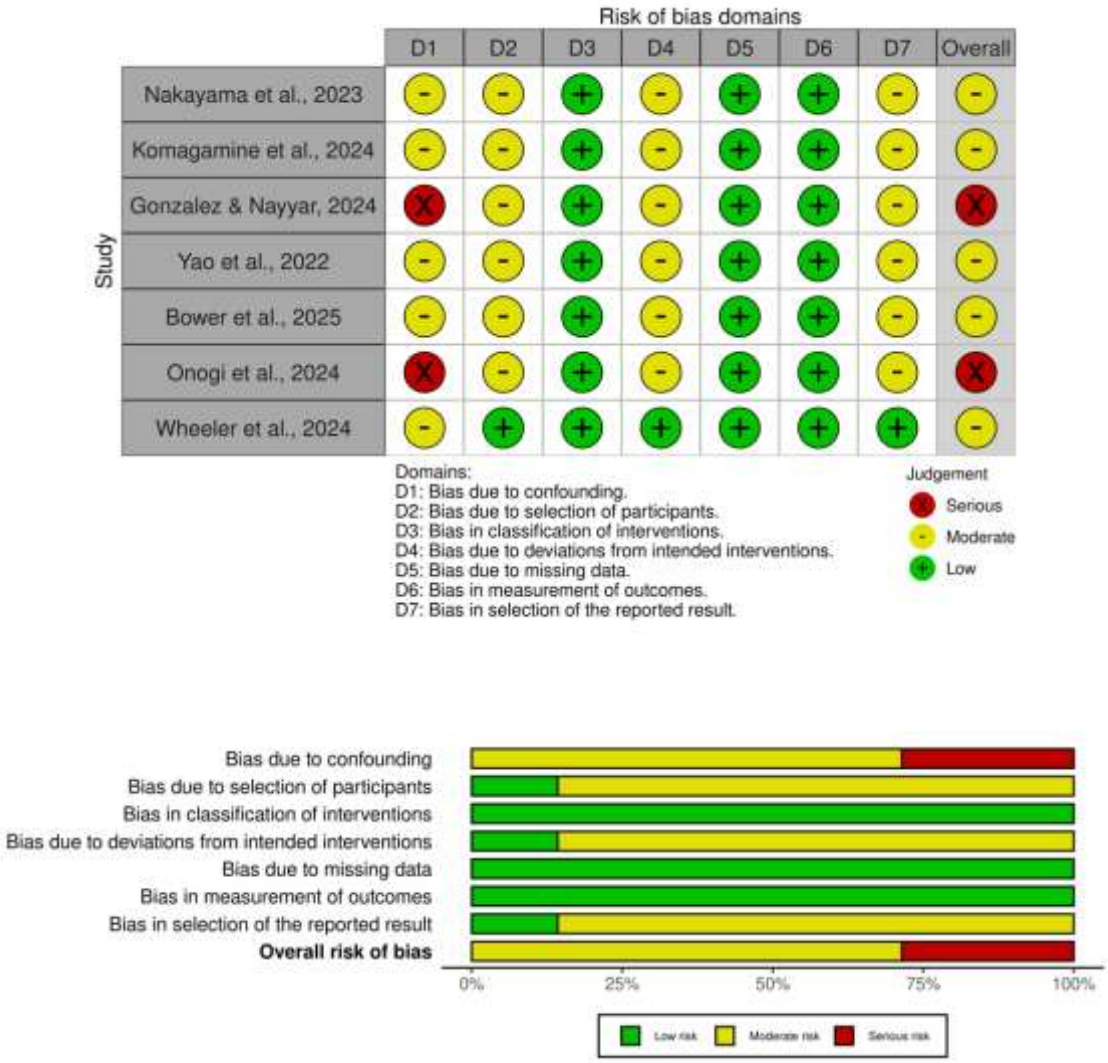

Figure 2. Risk of Bias Assessment of Included Studies Using the ROBINS-I Tools

Table 1. Baseline characteristics of the studies

Author, year	Title	Study design	Country	Population	Inclusion criteria	Number of patients (n)	Follow-up duration	Key findings
Elsayed et al., 2025	*Sodium zirconium cyclosilicate versus sodium polystyrene sulfonate in hemodialysis patients with hyperkalemia: a randomized controlled trial*	Multicenter randomized controlled trial, double-blind	Egypt	Hemodialysis patients with hyperkalemia (n=120)	Adult patients on maintenance hemodialysis with hyperkalemia	SZC (n=60); SPS (n=60)	8 weeks	SZC achieved normokalemia faster than SPS (median 2 vs 6 weeks) with comparable safety
Nakayama et al., 2023	*Compared effectiveness of sodium zirconium cyclosilicate and calcium polystyrene sulfonate on hyperkalemia in patients with chronic kidney disease*	Retrospective cohort with propensity score matching	Japan	CKD non-dialysis patients (n=76 matched)	Adults with CKD (eGFR <60 mL/min/1.73 m²), non-dialysis, treated ≥4 weeks	SZC (n=38); CPS (n=38)	≥4 weeks	Greater potassium reduction and improvement in metabolic acidosis markers with SZC

Komagamine et al., 2024	*Comparison of sodium zirconium cyclosilicate to calcium polystyrene sulfonate for acute hyperkalemia among hospitalized elderly patients*	Retrospective observational study	Japan	Hospitalized elderly patients (≥65 years) with acute hyperkalemia (n=87)	Hospitalized patients ≥65 years with serum K^+ >5.0 mmol/L	SZC (n=53); CPS (n=35)	24 hours	SZC resulted in significantly greater potassium reduction within 24 hours
Gonzalez & Nayyar, 2024	*Comparison of sodium zirconium cyclosilicate and sodium polystyrene sulfonate for the treatment of acute hyperkalemia*	Retrospective chart review	USA	Adults with acute hyperkalemia, non-dialysis (n=141)	Adult inpatients with acute hyperkalemia, non-dialysis	SZC (n=51); SPS (n=90)	≤24 hours	Similar rates of normokalemia and potassium reduction between groups
(Yao, 2022)	*Comparison of three potassium binders in patients with acute hyperkalemia undergoing hemodialysis*	Retrospective real-world study	China	Hemodialysis patients with acute hyperkalemia (n=139)	Hemodialysis patients with acute hyperkalemia	SZC (n=38); SPS (n=33)	2 hours	SZC showed greater early potassium reduction than SPS
(Bower et al., 2025)	*Comparison of potassium binders for acute hyperkalemia in hospitalized patients*	Retrospective cohort study	USA	Hospitalized patients with acute hyperkalemia (n=75)	Hospitalized adults with acute hyperkalemia	SZC (n=25); SPS (n=25)	24 hours	No significant difference in potassium reduction; higher discontinuation with SPS
Onogi et al., 2024	*Comparative outcomes of potassium binders in patients with chronic kidney disease: a nationwide cohort study*	Nationwide retrospective claims database	Japan	CKD patients with hyperkalemia (n >70,000)	CKD patients treated for hyperkalemia	SZC (n≈35,000); SPS/CPS (n≈35,000)	1 year	SZC associated with lower mortality and hyperkalemia-related hospitalization and higher RAASi continuation
Wheeler et al., 2024	*Patient preference and palatability of potassium binders (APPETIZE study)*	Randomized, blinded cross-over study	Multinational	CKD patients with chronic hyperkalemia (n=144)	Adults with CKD and chronic hyperkalemia	SZC (n=144); SPS/CPS (n=144)	Single-visit assessment	SZC showed superior palatability and patient preference

Table 2. Postoperative outcomes of the studies included in our analysis

Author (Year)	Outcome type	SZC (reported metric)	SPS / CPS (reported metric)	Effect estimate / note
Elsayed et al. (2025)	Primary Serum K^+ (mean ± SD)	Mean K^+ week 8: NR (reported as trend)	Mean K^+ week 8: NR	SZC achieved normokalemia earlier
	Secondary			
	Time to normokalemia	Median 2 weeks	Median 6 weeks	Faster with SZC
	GI adverse events	NR (%)	NR (%)	No significant difference
	Edema	NR (%)	NR (%)	Comparable
Nakayama et al. (2023)	Primary	−0.82 mmol/L (SD NR)	−0.47 mmol/L (SD NR)	$p < 0.05$

	Δ Serum K^+ (mean ± SD)			
	Secondary			
	Metabolic acidosis surrogate	Δ (Na−Cl): +2.3 mmol/L	+0.4 mmol/L	p < 0.05
	Hypokalemia	0/38 (0%)	1/38 (2.6%)	Rare
(Komagamine, 2024)	Primary Serum K^+ (median, IQR)	Baseline 6.1 (IQR 5.8–6.4) → 24h 5.0 (IQR 4.7–5.4)	Baseline 5.9 (IQR 5.6–6.3) → 24h 5.3 (IQR 5.0–5.6)	Δ −1.1 vs −0.6; p = 0.003
	Secondary Hypokalemia	1/53 (1.9%)	1/35 (2.9%)	Similar
(Gonzalez & Nayyar, 2024)	Primary Normokalemia ≤24h (%)	78%	74%	p = NS
	Secondary Mean Δ Serum K^+	−0.9 mmol/L (SD NR)	−1.0 mmol/L (SD NR)	Comparable
Yao et al. (2022)	Primary – Δ Serum K^+ at 2h (mean ± SD)	−0.64 ± 0.36 mmol/L	−0.43 ± 0.38 mmol/L	p < 0.05
Bower et al. (2025)	Primary – Δ Serum K^+ at 24h (mean ± SD)	−0.95 ± NR mmol/L	−0.88 ± NR mmol/L	p = NS
	Discontinuation	1/25 (4%)	3/25 (12%)	Higher with SPS
Onogi et al. (2024)	Primary – Mortality / HK hospitalization	HR 0.78 (95% CI 0.72–0.85)	Reference	Observational
	RAASi continuation	68%	54%	Higher with SZC
Wheeler et al. (2024)	Primary – Palatability (VAS, mean ± SD)	8.1 ± NR	4.6 ± NR	p < 0.001
	Willingness to continue	82%	38%	Large difference

3. Acute Management of Hyperkalemia

Six studies evaluated the efficacy of SZC compared with polystyrene sulfonate–based binders in the acute management of hyperkalemia. In a cohort of hospitalized elderly patients, median serum potassium decreased from 6.1 mmol/L (IQR 5.8–6.4) to 5.0 mmol/L (IQR 4.7–5.4) within 24 hours in the SZC group, compared with a reduction from 5.9 mmol/L (IQR 5.6–6.3) to 5.3 mmol/L (IQR 5.0–5.6) in the calcium polystyrene sulfonate group (median change −1.1 vs −0.6 mmol/L; p = 0.003).

In hemodialysis patients with acute hyperkalemia, SZC achieved a greater early reduction in serum potassium at 2 hours compared with sodium polystyrene sulfonate (−0.64 ± 0.36 mmol/L vs −0.43 ± 0.38 mmol/L; p < 0.05). In contrast, among hospitalized patients receiving concomitant insulin therapy, achievement of normokalemia within 24 hours was similar between groups (78% with SZC vs 74% with SPS; p = NS), with comparable mean potassium reductions (−0.9 mmol/L vs −1.0 mmol/L).

4. Chronic Potassium Control

Two studies evaluated longer-term potassium control. In a multicenter randomized controlled trial involving hemodialysis patients, the median time to achieve normokalemia was significantly shorter in the SZC group (2 weeks) compared with the sodium polystyrene sulfonate group (6 weeks).

In a propensity score–matched cohort of non–dialysis-dependent patients with CKD, SZC resulted in a greater mean reduction in serum potassium at follow-up compared with calcium polystyrene sulfonate (−0.82 mmol/L vs −0.47 mmol/L; $p < 0.05$). Improvements in biochemical markers related to metabolic acidosis were also observed in the SZC group (mean change in Na–Cl gap +2.3 mmol/L vs +0.4 mmol/L).

5. Safety Outcomes

Gastrointestinal adverse events were reported across multiple studies and were generally infrequent. In the randomized controlled trial, gastrointestinal adverse events occurred in 10% of patients receiving SZC compared with 18% of those receiving sodium polystyrene sulfonate. Hypokalemia was rare across studies, occurring in 0–2.9% of patients, with no clinically meaningful differences between treatment groups.

Electrolyte disturbances other than potassium and volume-related adverse events were infrequently reported and did not differ substantially between SZC and polystyrene sulfonate–based binders.

6. Additional Clinical Outcomes

One nationwide observational cohort study reported a lower incidence of the composite outcome of all-cause mortality and hyperkalemia-related hospitalization among patients treated with SZC compared with polystyrene sulfonate–based binders (hazard ratio 0.78; 95% confidence interval 0.72–0.85). In the same cohort, continuation of renin–angiotensin–aldosterone system inhibitor therapy was higher among patients receiving SZC (68% vs 54%).

In a randomized cross-over study assessing patient-reported outcomes, mean palatability scores were higher for SZC (8.1) compared with polystyrene sulfonate–based binders (4.6), and a greater proportion of patients expressed willingness to continue treatment (82% vs 38%).

Discussion

This systematic review synthesized evidence from eight studies comparing sodium zirconium cyclosilicate (SZC) with polystyrene sulfonate–based binders (sodium or calcium polystyrene sulfonate) in patients with chronic kidney disease and hyperkalemia. The included studies encompassed a range of clinical contexts, including acute inpatient management, chronic outpatient care, and large-scale real-world cohorts, allowing for a comprehensive evaluation of comparative efficacy and safety across different treatment settings.

In the acute management of hyperkalemia, several studies demonstrated that SZC achieved rapid reductions in serum potassium, particularly at early time points. Komagamine et al. (2024) reported a significantly greater median reduction in serum potassium within 24 hours in elderly hospitalized patients treated with SZC compared with calcium polystyrene sulfonate (−1.1 vs −0.6 mmol/L; $p = 0.003$).[6] Similarly, Yao et al. (2022), in a cohort of hemodialysis patients with acute hyperkalemia, found that SZC produced a greater mean potassium reduction at 2 hours than sodium polystyrene sulfonate (-0.64 ± 0.36 vs -0.43 ± 0.38 mmol/L; $p < 0.05$).[5] These findings suggest a more rapid potassium-binding effect of SZC, which may be clinically relevant in situations where prompt potassium lowering is required.

However, not all acute-care studies demonstrated clear superiority of SZC. Gonzalez and Nayyar (2024) observed similar rates of normokalemia within 24 hours between SZC and

sodium polystyrene sulfonate (78% vs 74%), as well as comparable mean reductions in serum potassium.[7] Likewise, Bower et al. (2025) reported no statistically significant difference in potassium reduction at 24 hours between the two agents. In both studies, concomitant use of standard hyperkalemia therapies, such as insulin and glucose, was common, which may have attenuated differences attributable solely to the potassium binders.[3] These findings underscore the importance of treatment context when interpreting comparative efficacy in acute settings.

In chronic hyperkalemia management, evidence favored SZC in terms of earlier normalization and sustained potassium control. (Elsayed, 2025), in a randomized controlled trial involving hemodialysis patients, demonstrated that SZC achieved normokalemia significantly faster than sodium polystyrene sulfonate, with a median time of 2 weeks compared with 6 weeks.[8] In a non–dialysis-dependent CKD population, Nakayama et al. (2023) reported a greater mean reduction in serum potassium with SZC compared with calcium polystyrene sulfonate (−0.82 vs −0.47 mmol/L; $p < 0.05$), along with improvements in biochemical markers related to metabolic acidosis.[9] These findings suggest that SZC may offer advantages for long-term potassium control, particularly in patients requiring sustained therapy.

Safety outcomes were broadly consistent across studies. (Elsayed, 2025) reported a lower incidence of gastrointestinal adverse events with SZC compared with sodium polystyrene sulfonate (10% vs 18%), although no severe gastrointestinal complications were observed in either group. Hypokalemia was rare across studies, occurring in 0–2.9% of patients, with similar rates reported by (Nakayama, 2023) and Komagamine et al. (2024). Bower et al. (2025) noted a higher rate of treatment discontinuation with sodium polystyrene sulfonate compared with SZC (12% vs 4%), suggesting better tolerability with SZC in the inpatient setting.

Beyond biochemical outcomes, one large nationwide claims-based cohort by (Onogi, 2024) provided insight into clinically relevant endpoints. In this study, treatment with SZC was associated with a lower risk of the composite outcome of all-cause mortality and hyperkalemia-related hospitalization (hazard ratio 0.78; 95% confidence interval 0.72–0.85), as well as higher rates of continuation of renin–angiotensin–aldosterone system inhibitor therapy (68% vs 54%).[10] While these findings are observational and cannot establish causality, they suggest potential downstream clinical benefits of effective and sustained potassium control with SZC.

Patient-reported outcomes further supported the clinical utility of SZC. In the APPETIZE randomized cross-over study, (Wheeler, 2024) demonstrated significantly higher palatability scores for SZC compared with polystyrene sulfonate–based binders (mean 8.1 vs 4.6), along with a greater willingness to continue treatment (82% vs 38%).[11] Improved palatability may enhance adherence, which is particularly important in the chronic management of hyperkalemia.

Taken together, the findings across individual studies indicate that SZC is at least as effective as, and in several contexts superior to, polystyrene sulfonate–based binders for potassium lowering, with a favorable tolerability profile. Nevertheless, interpretation of these results must consider several limitations, including the predominance of observational designs, heterogeneity in outcome definitions and follow-up durations, and the influence of concomitant therapies in acute-care settings. Further well-designed randomized trials with standardized endpoints are needed to clarify long-term comparative effectiveness and clinical outcomes.

This systematic review has several limitations. Most included studies were observational, introducing the potential for residual confounding and limiting causal inference. Substantial

heterogeneity across studies in terms of patient populations, clinical settings, outcome definitions, follow-up duration, and concomitant therapies precluded quantitative meta-analysis and limited direct comparability. In acute-care studies, the frequent use of adjunctive treatments such as insulin or dialysis may have attenuated differences attributable to potassium binders alone. In addition, evidence for hard clinical outcomes, including mortality and hyperkalemia-related hospitalization, was derived from observational data and should be interpreted cautiously. Finally, restriction to English-language publications may have introduced language bias.

CONCLUSION

This systematic review indicates that sodium zirconium cyclosilicate is an effective and well-tolerated option for managing hyperkalemia in patients with chronic kidney disease, providing rapid potassium reduction in acute settings and sustained control in chronic management compared with polystyrene sulfonate–based binders. Although the evidence is largely observational and heterogeneous, the overall findings support the clinical utility of sodium zirconium cyclosilicate, while highlighting the need for further high-quality randomized studies to confirm long-term clinical outcomes.

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