

## Review

## A Systematic Review of Sodium Zirconium Cyclosilicate for Hyperkalemia Management in Heart Failure and Chronic Kidney Disease

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**Background:** Hyperkalemia is common in chronic kidney disease (CKD) and heart failure (HF) and often limits the initiation, continuation, or up-titration of renin-angiotensin-aldosterone system inhibitors (RAASi). Sodium zirconium cyclosilicate (SZC) is a non-absorbed, selective potassium binder used for both acute correction and maintenance therapy.

**Methods:** We systematically searched PubMed/MEDLINE to identify randomized and real-world clinical studies evaluating SZC for hyperkalemia in adult CKD and/or HF populations; Embase and Cochrane Library were not searched, and no language restrictions were applied. Reporting was guided by the PRISMA 2020 statement, and study selection is summarized in a PRISMA flow diagram. Evidence was synthesized narratively due to heterogeneity in study designs and outcome reporting.

**Results:** Across randomized trials, SZC lowered serum potassium rapidly, with onset within 1 hour and clinically meaningful reductions within 24-48 hours. Maintenance-phase trials demonstrated sustained normokalemia during continued SZC dosing. In CKD with concomitant metabolic acidosis, SZC was associated with higher rates of normokalemia maintenance at 4 weeks and modest increases in serum bicarbonate. In HF with reduced ejection fraction during spironolactone optimization, SZC improved maintenance of normokalemia on guideline-directed mineralocorticoid receptor antagonist therapy. Based on observational real-world evidence, studies reported fewer urgent hyperkalemia interventions and improved RAASi persistence; edema related to sodium load and occasional hypokalemia were the most clinically relevant safety considerations.

**Conclusion:** SZC provides rapid and durable potassium control in CKD and HF and may facilitate continuation of guideline-directed RAASi therapy. Monitoring for sodium-related fluid retention and electrolyte over-correction is warranted, and the lowest effective dose should be used in volume-sensitive patients. Reported clinical outcome benefits remain hypothesis-generating and require confirmation in prospective trials.

**Keywords:** Hyperkalemia, Sodium Zirconium Cyclosilicate, Heart Failure, Renin-Angiotensin System, Chronic Kidney Disease

**Submitted at:** 04.01.2026, **Accepted at:** 20.01.2026, **Published at:** 01.02.2026**INTRODUCTION**

Hyperkalemia is a frequent and clinically consequential electrolyte disorder in patients with chronic kidney disease (CKD) and heart failure (HF). Reduced renal potassium excretion and the widespread use of renin-angiotensin-aldosterone system inhibitors (RAASi) create a setting in which recurrent hyperkalemia is common and can lead to emergency care and discontinuation of therapies that improve outcomes.

Sodium zirconium cyclosilicate (SZC, also known as ZS-9; Lokelma) is a non-absorbed, inorganic cation exchanger that preferentially binds potassium in the

gastrointestinal tract. By lowering serum potassium, SZC may enable clinicians to initiate or maintain RAASi therapy in patients who would otherwise require dose reduction or discontinuation. Pivotal randomized evidence and meta-analytic synthesis support SZC's ability to rapidly lower serum potassium and maintain normokalemia across hyperkalemia populations (1, 2), including comparative real-world data in acute care settings (3) and durable maintenance-phase efficacy in outpatient trials (4).

This systematic review summarizes the efficacy and safety of SZC for acute correction and maintenance

treatment of hyperkalemia in adult CKD and/or HF populations, with specific emphasis on potassium control, RAASi continuation/optimization, and clinically relevant outcomes.

## METHODS

### Protocol and Search Strategy

Reporting was guided by the PRISMA 2020 statement; the PRISMA 2020 checklist is provided as *Supplementary File 1*, and the study selection process is summarized in the PRISMA flow diagram (**Figure 1**). We searched PubMed (MEDLINE) from database inception to 2 January 2026 using the query: (“sodium zirconium cyclosilicate”[Title/Abstract] OR “ZS-9”[Title/Abstract] OR “Lokelma”[Title/Abstract]) AND (“hyperkalemia”[Title/Abstract] OR “hyperkalaemia”[Title/Abstract]). Reference lists of included studies were screened to identify additional eligible reports. Embase and the Cochrane Library were not searched. No language restrictions were applied.

### Study Selection

We included randomized controlled trials and observational real-world studies reporting original adult clinical data on SZC for acute potassium lowering and/or maintenance therapy in hyperkalemia, including CKD and/or HF populations. We excluded narrative reviews, editorials/letters, conference abstracts without full text, pediatric-only studies, and reports without relevant clinical outcomes. Title/abstract screening and full-text eligibility assessment were performed independently by two reviewers; discrepancies were resolved by consensus (with involvement of an additional author when required).

### Data Extraction

For each eligible study, we extracted study design, population characteristics (including CKD stage, HF phenotype, and baseline RAASi use where reported), SZC regimen and comparator, follow-up duration, efficacy outcomes (potassium change, time to normokalemia, and maintenance of normokalemia), RAASi continuation/optimization, and safety outcomes (including edema/fluid retention, hypokalemia, and gastrointestinal events). Data extraction was performed independently by two reviewers using a standardized extraction framework; discrepancies were resolved by consensus.

### Excluded Data

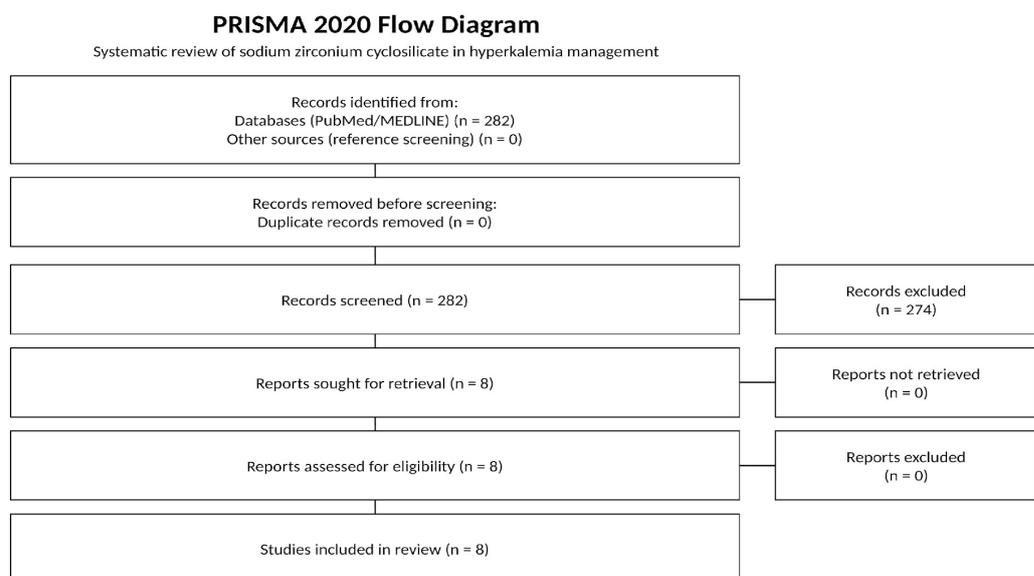
Full-text articles excluded after eligibility assessment were documented with the main reason for exclusion (e.g., wrong population or intervention, no original outcomes, or non-clinical report).

### Data synthesis and analysis

Because of heterogeneity across study designs, populations, comparators, and outcome definitions, evidence was synthesized narratively and grouped by outcome domain: acute potassium lowering, maintenance therapy, CKD-specific outcomes, HF/RAASi optimization, real-world outcomes, and safety.

## STATISTICAL ANALYSIS

Due to the significant clinical and methodological heterogeneity across the included studies (specifically regarding study designs (randomized controlled trials vs. observational real-world cohorts), baseline potassium thresholds, patient populations (CKD stages, HF phenotypes), and varied outcome definitions) a quantitative meta-analysis was not performed. Instead, a



**Figure 1.** PRISMA 2020 flow diagram of study selection.

narrative synthesis approach was employed to summarize the efficacy and safety data. Efficacy outcomes, including mean reduction in serum potassium (K<sup>+</sup>), time to normokalemia, and maintenance of potassium levels, were reported descriptively using the point estimates and 95% confidence intervals (CIs) as provided in the original reports. For observational data, associations between SZC use and clinical outcomes (e.g., RAASi persistence, hospitalization) were reported as odds ratios (OR) or Hazard Ratios (HR) where available

Data were categorized and synthesized based on specific clinical domains: Acute Phase Efficacy: Rapid potassium lowering within 48 hours. Maintenance Phase Efficacy: Stability of normokalemia and RAASi optimization. Safety Profile: Incidence of adverse events, specifically focusing on edema and electrolyte over-correction. All data extraction and qualitative assessments were cross-verified by two independent reviewers to ensure accuracy and minimize reporting bias.

## RESULTS

### Study selection (PRISMA summary)

The PubMed search (last run 2 January 2026) retrieved 282 records. After title/abstract screening, 274 records were excluded. Eight full-text reports were assessed for eligibility and all met inclusion criteria, yielding 8 studies for the primary synthesis (PRISMA flow diagram, Figure 1). These studies are summarized in Tables 1-2: 4 randomized trials (ZS-003; HARMONIZE; NEUTRALIZE; REALIZE-K) and 4 observational real-world studies/registries (UK CPRD, Japan claims database, ZORA registry, and an Italian administrative database study). Additional publications (meta-analyses, pharmacovigilance analyses, and case reports) were used to contextualize safety signals and practice considerations but were not counted among the primary included studies.

### Risk of Bias (Summary)

Overall, trial evidence was judged as having generally low risk of bias (randomized designs with blinding and prespecified outcomes), whereas observational studies were at moderate-to-high risk of confounding and selection bias despite adjustment strategies (e.g., propensity weighting and multivariable models). Accordingly, estimates from real-world studies should be interpreted as associative rather than causal.

### Study Characteristics

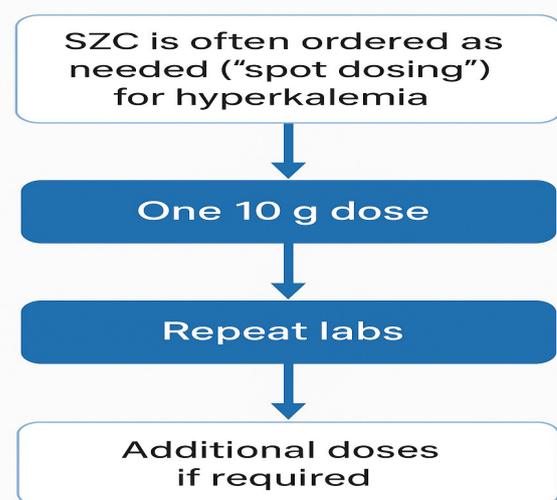
Key trial and real-world evidence included in this review is summarized in Table 1 (clinical trials) and Table 2 (real-world studies). The included trials evaluated SZC for rapid correction of hyperkalemia and for maintenance of normokalemia, including CKD and HF subgroups and

RAASi optimization settings.

### Acute Potassium Lowering

Clinical trials have demonstrated SZC's efficacy in treating hyperkalemia in general populations (patients with varied causes of hyperkalemia, often CKD and/or HF). In a pivotal Phase 3 trial, Packham et al. reported a dose-dependent potassium decrease over 48 hours compared with placebo (1). A meta-analysis of randomized controlled trials estimated the mean difference in K<sup>+</sup> reduction between SZC and placebo to be approximately -0.42 mmol/L overall, though significant advantages over placebo were more consistently observed after the 4-hour mark at the correction phase (2). Clinical response can be evident within hours after initiation; in a retrospective inpatient cohort comparing SZC versus sodium polystyrene sulfonate (SPS), mean serum potassium was lower at 8 hours with SZC (4.6 vs 5.0 mmol/L; P = 0.005), while 24-hour normokalemia rates were similar (80% vs 77%; P = 0.56) (3). These key Phase 3 and extension trials of SZC in hyperkalemia are summarized in **Table 1**.

SZC starts lowering serum K<sup>+</sup> within 1 hour of the first dose (1, 4). This rapid onset is a key advantage in acute care. Direct head-to-head randomized evidence comparing SZC with sodium polystyrene sulfonate (SPS) remains limited; available comparative observational data suggest earlier potassium reduction with SZC in the first 8 hours, while 24-hour normokalemia rates may be similar (3). A randomized head-to-head trial protocol has been published, highlighting the need for higher-quality comparative evidence (5). In clinical practice, SZC is often ordered on an as-needed basis ("spot-dosing")



**Figure 2.** Example of a spot-dosing approach for sodium zirconium cyclosilicate (SZC) in hyperkalemia (single 10 g dose with repeat laboratory assessment and additional dosing if required).

**Table 1.** Key clinical trials of sodium zirconium cyclosilicate in hyperkalemia, including general, chronic kidney disease, and heart failure populations, with primary endpoint domain.

Study (Year)	Population & Design	Primary Endpoint Domain	Key Efficacy Findings	Notes
Packham et al., 2015 (ZS-003) (1)	Phase 3 randomized controlled trial in acute hyperkalemia (mixed CKD/HF; baseline K <sup>+</sup> ~5.6 mmol/L).	Biochemical (potassium control)	Correction phase: dose-dependent reduction in serum K <sup>+</sup> over 48 hours compared with placebo; maintenance phase: continued SZC helped maintain normokalemia over 28 days compared with placebo withdrawal (1).	First pivotal SZC trial; demonstrated dose-dependent potassium reduction during the 48-hour correction phase. Edema was reported more often at higher maintenance doses.
HARMONIZE 2014 and Extension (4,8)	HARMONIZE: 28-day RCT in outpatients with hyperkalemia. Extension: open-label 12-month study including many CKD and HF patients.	Biochemical (potassium control / maintenance)	SZC rapidly normalized K <sup>+</sup> in most patients and maintained normokalemia for 28 days. In the 12-month extension, normokalemia was maintained and 87% could continue/increase RAASi at 1 year.	Demonstrated long-term efficacy and compatibility with ongoing RAASi therapy; supports chronic SZC use for potassium control.
NEUTRALIZE, 2024 (7)	Phase 3b RCT in CKD stages 3-5 with hyperkalemia and metabolic acidosis (HCO <sub>3</sub> <sup>-</sup> 16-20 mmol/L).	Biochemical (potassium + bicarbonate endpoints)	88% on SZC vs 20% on placebo remained normokalemic at 4 weeks; 35.3% vs 5.0% achieved normokalemia with a ≥3 mmol/L increase in serum bicarbonate (7).	Trial was stopped early (n=37) but suggests SZC corrects K <sup>+</sup> and modestly improves metabolic acidosis in CKD.
REALIZE-K, 2025 (15)	RCT in HFrEF (EF <40%) with current or prior hyperkalemia during up-titration of spironolactone (MRA).	RAASi enablement/optimization (with potassium control)	Primary response at end of treatment: 71% (SZC) vs 36% (placebo) (OR 4.45).	Designed to enable spironolactone optimization in HFrEF with prior hyperkalemia; not powered for clinical outcomes. Exploratory composite cardiovascular death or worsening HF was numerically higher with SZC (11 vs 3); interpret cautiously.

CKD, Chronic Kidney Disease; EF, Ejection Fraction; HCO<sub>3</sub><sup>-</sup>, Bicarbonate; HF, Heart Failure; HFrEF, Heart Failure with reduced Ejection Fraction; K<sup>+</sup>, Potassium; MRA, Mineralocorticoid Receptor Antagonist; RAASi, Renin-Angiotensin-Aldosterone System inhibitor; RCT, Randomized Controlled Trial; SZC, Sodium Zirconium Cyclosilicate

for hyperkalemia, with an initial 10 g dose followed by repeat laboratory testing and additional doses if required (Figure 2).

#### Dosing

The typical regimen for acute potassium reduction is 10 g three times daily for up to 48 hours (as used in trials), though in practice many patients achieve normokalemia with fewer doses (3). For maintenance therapy, the approved starting dose is 10 g once daily, titrated in 5 g increments to maintain K<sup>+</sup> in the target range. Maintenance doses of 5-15 g daily can be used chronically. Importantly, SZC should be taken separately from other oral medications by at least 2 hours, as it may transiently bind some co-administered drugs in the gut (6).

In acute care, SZC should be used as an adjunct to temporizing measures and definitive potassium elimination strategies, particularly when sustained control is needed to prevent rebound hyperkalemia.

#### Maintenance of Normokalemia

After initial correction, SZC is effective at maintaining normal potassium if continued. In clinical trials, patients who achieved normokalemia were randomized to continued SZC versus placebo: the vast majority on SZC stayed normokalemic over 2-4 weeks, whereas placebo patients often rebounded (4). One trial reported 88% of patients remained at K<sup>+</sup> 3.5-5.0 mmol/L at 4 weeks on SZC, versus only 20% on placebo (7). This demonstrates that ongoing SZC can prevent recurrence of hyperkalemia. Open-label extensions and subsequent studies have shown this effect can be sustained with longer therapy; normokalemia was maintained for up to 12 months in patients treated chronically with SZC (8). These long-term data also showed that 87% of patients were able to continue or even up-titrate their RAASi inhibitor therapy while on SZC, reflecting the drug's ability to control K<sup>+</sup> in the background of RAASi use (8). The key phase 3 and extension trials of SZC

**Table 2.** Selected real-world studies of sodium zirconium cyclosilicate in chronic kidney disease and heart failure.

Study	Population / Design	Key Findings	Notes
Marshall et al., 2024 (UK) (12)	Adults with emergent hyperkalemia in secondary care; propensity-score matched retrospective cohort; ~30% on dialysis	SZC use associated with lower odds of emergency hemodialysis and temporary CVC insertion compared with no SZC (OR 0.23 and 0.27, respectively)	Observational; residual confounding possible; reflects acute-care practice
Onogi et al., 2024 (Japan) (9)	Japanese medical claims database; retrospective cohort of CKD patients prescribed potassium binders (includes hemodialysis and non-RRT subgroups)	SZC use associated with lower mortality and fewer hyperkalemia-associated hospitalizations vs non-use	Generalizability may differ by dialysis practice patterns
Pollack et al., 2025 (ZORA program) (13)	International real-world cohort after hyperkalemia episode; comparative effectiveness analysis	Longer duration of SZC treatment associated with higher likelihood of RAASi continuation/persistence after hyperkalemia	Treatment duration may reflect clinical stability; indication and adherence confounding
Gnesi et al., 2025 (Italy) (10)	Italian clinical practice cohort; healthcare resource utilization analysis	SZC initiation associated with improved RAASi maintenance and potentially reduced hyperkalemia-related resource use	Administrative data; outcomes depend on coding; effect sizes may vary

CKD, Chronic Kidney Disease; EF, Ejection Fraction; HCO<sub>3</sub><sup>-</sup>, Bicarbonate; HF, Heart Failure; HFrEF, Heart Failure with reduced Ejection Fraction; K<sup>+</sup>, Potassium; MRA, Mineralocorticoid Receptor Antagonist; RAASi, Renin-Angiotensin-Aldosterone System inhibitor; SZC, Sodium Zirconium Cyclosilicate; CVC, Central Venous Catheter

in hyperkalemia, including CKD and HF subgroups, are summarized in **Table 1**.

As summarized in **Table 1**, SZC consistently outperformed placebo in lowering serum potassium and preventing recurrent hyperkalemia, and in HF populations (e.g. REALIZE-K) it improved the ability to maintain RAASi therapy while requiring careful monitoring of fluid status.

#### CKD-specific Outcomes

Hyperkalemia is especially prevalent in CKD due to reduced renal potassium excretion, often compounded by RAASi therapy used for kidney and cardiac protection. Recent evidence highlights SZC's benefits in CKD patients: it effectively controls potassium, may confer acid-base benefits, and is associated with improved clinical outcomes in real-world CKD settings (7,9,10).

Many CKD patients experience metabolic acidosis alongside hyperkalemia. Notably, SZC may help correct both. In the NEUTRALIZE trial of CKD stages 3-5, patients on SZC had a greater rise in serum bicarbonate than those on placebo; a nominally significant increase in HCO<sub>3</sub><sup>-</sup> was seen (7). Post-hoc analyses of earlier phase 3 trials similarly showed a dose-dependent bicarbonate increase with SZC therapy. Mechanistically, SZC might enhance acid excretion by binding ammonium in the gut - it has an affinity for NH<sub>4</sub><sup>+</sup> and was shown in vitro and in mouse models to bind and remove ammonium along with potassium (7, 11). Overall, CKD patients treated with SZC often exhibit a modest increase in serum bicarbonate, typically ranging from 1.1 to 2.6 mmol/L depending on the dose, especially in those with baseline metabolic acidosis (6,7).

SZC is also being used in some dialysis patients, even

though early trials excluded dialysis. For CKD stage 5D patients, SZC can manage inter-dialytic hyperkalemia - for instance, giving 5-10 g on non-dialysis days to prevent K<sup>+</sup> surges. In the Glasgow "emergent hyperkalemia" study (Marshall et al., 2024), about 30% of the hyperkalemic patients were on maintenance dialysis - yet SZC still averted many urgent dialysis sessions in this group (12). This off-label use in dialysis patients is becoming more common to mitigate dietary K<sup>+</sup> between sessions, although formal randomized studies in dialysis are limited. Randomized evidence specifically in CKD stage 5D (maintenance dialysis) remains limited; therefore, dialysis-focused effectiveness and safety conclusions should be considered primarily observational and hypothesis-generating.

In summary, SZC is highly effective for CKD patients, acutely lowering K<sup>+</sup> and maintaining normal levels chronically. It offers the added benefit of mild metabolic acidosis improvement, which can improve overall CKD management. Real-world data signal that SZC may improve survival and reduce hospitalizations in CKD, likely by permitting safer use of RAASi and preventing life-threatening hyperkalemia episodes (9,10,12,13).

#### HF and RAASi Optimization

Heart failure patients frequently develop hyperkalemia, especially when on RAASi therapy (ACE inhibitors, ARBs, angiotensin receptor-neprilysin inhibitors, and MRAs like spironolactone) that are essential for improving HF outcomes. Even moderate K<sup>+</sup> elevations can prompt physicians to down-titrate or stop RAASi, depriving patients of prognostic benefits. The introduction of SZC (and patiromer) has provided a strategy to mitigate increases in serum potassium and keep HF patients on RAASi. Recent real-world studies

and meta-analyses confirm that SZC is accomplishing the goal of maintaining RAASi therapy despite hyperkalemia risk.

In heart failure with reduced ejection fraction (HFrEF) during spironolactone optimization, randomized evidence (REALIZE-K) indicates that SZC increases the likelihood of maintaining normokalemia while receiving guideline-directed MRA dosing, supporting its role as an adjunct to enable RAASi optimization in appropriate patients.

#### *Real-World Outcomes*

Beyond controlled trials, real-world experience provides insight into SZC's impact on clinical endpoints like emergency interventions, hospitalizations, and mortality. The evidence from registries and cohort studies in the past 2-3 years has been largely positive (9,10,12,13).

In an inpatient propensity-weighted analysis from the United Kingdom (Marshall et al.), SZC use in acute hyperkalemia was associated with fewer urgent interventions, including reduced emergency dialysis and reduced emergency central venous catheter placement.

As mentioned in the CKD section, the large Japanese database study observed improved 1-year survival with SZC vs SPS/CPS (9). Similarly, a multi-country observational analysis (Pollack et al., 2025) of 7,980 patients in the US, Japan, and Spain (the ZORA program) found that longer-duration SZC use correlated with significantly lower rates of RAASi therapy discontinuation and subsequent clinical events (13).

In the US cohort, staying on SZC beyond 60 days increased the likelihood of remaining on RAASi at 4 months (120 days) to ~70%, compared to ~59% if SZC was stopped within 30 days ( $p < 0.001$ ). Japan showed a similar pattern (86-87% vs 82% RAASi continuation at 120 days for long- vs short-duration SZC). The risk of losing RAASi therapy increased soon after stopping SZC, indicating that SZC's protective effect persists only while treatment continues. Notably, prior ZORA analyses reported that hyperkalemia patients on SZC had ~2.5-fold higher odds of being on RAASi six months later compared to similar patients not treated with any new binder (14). This suggests a real-world class effect: potassium binders keep patients on guideline therapy and reduce the risk of adverse events, which likely translates to fewer cardiorenal events. Indeed, the Italian study (Gnesi 2025) also showed lower hospitalization costs in those continuing SZC, hinting at fewer HF or CKD decompensations requiring admission (10).

As shown in **Table 2**, real-world use of SZC is associated with fewer emergency interventions for hyperkalemia, improved continuation of RAASi therapy, and lower healthcare utilization in high-risk CKD and HF

populations.

#### *Safety*

SZC's safety profile has been favorable in both trials and post-marketing surveillance, especially when compared with older potassium binders.

Importantly, safety in HF requires attention. The REALIZE-K trial reported a numerical imbalance in the exploratory composite of cardiovascular death or worsening HF (11 vs. 3 patients on placebo). While the trial was not primarily powered for clinical outcomes, post-hoc exploratory analyses identified a critical 'Red Flag': HFrEF patients with baseline NT-proBNP levels  $>4,000$  pg/mL were at a substantially higher risk for adjudicated fluid-related HF events (7 of 24 on SZC vs. 1 of 16 on placebo) (15). This finding mandates heightened clinical vigilance by nephrologists and cardiologists when managing sodium-related fluid load during spironolactone titration in volume-sensitive populations. Accordingly, careful patient selection is recommended in advanced HF (particularly in patients with markedly elevated NT-proBNP and/or clinical volume sensitivity), and SZC should be used at the lowest effective dose with dose minimization strategies whenever feasible, alongside close volume-status monitoring.

SZC contains sodium (~400 mg per 5 g dose) and can cause fluid retention in susceptible individuals (6). HF patients, especially those with reduced ejection fraction, may be sensitive to even mild increases in blood volume. Edema was a known side effect in earlier trials (often mild to moderate), and cases of peripheral edema on SZC are more common at higher doses or with prolonged use. In practice, clinicians should monitor HF patients on SZC for any signs of volume overload - particularly if they require frequent dosing. Strategies like adjusting diuretics or advising dietary sodium restriction can mitigate this risk. Despite this caution, the consensus in cardiology and nephrology practice is that the benefit of maintaining RAASi therapy generally outweighs the manageable risk of edema, as long as patients are properly monitored (13,14,16-18). Overall, SZC represents a valuable tool to optimize HF therapy, with the REALIZE-K trial demonstrating that a significantly higher proportion of patients can achieve and maintain guideline-directed MRA dosing when a potassium binder is utilized (15).

#### *Gastrointestinal Tolerability*

SZC was generally well tolerated in clinical trials, with gastrointestinal adverse-event rates similar to placebo. It is an odorless, tasteless powder that is typically administered as a suspension in water. Common mild side effects reported in long-term studies include nausea (8%), constipation (6%), vomiting (5%), and diarrhea (4%),

although rates were generally comparable to placebo across major clinical trials (4, 8). Unlike patiomer, SZC is not associated with hypomagnesemia. Overall, SZC's selectivity largely spares other electrolytes, but serum potassium should be monitored to avoid over-correction (4,8).

A rare but noteworthy GI event reported is intestinal obstruction or perforation in predisposed patients. A recent case report described a patient with advanced rectal cancer and tumor-related stenosis who developed a sigmoid colon perforation while on SZC, with SZC crystal deposition noted histologically at the perforation site (19). Although causality cannot be established from a single report, this highlights the need for caution with any potassium binder in patients with severe GI narrowing, obstruction, or markedly impaired motility.

#### *Edema and Sodium Load*

Edema is the most consistently increased adverse event with SZC compared with placebo in meta-analyses (2). This is mechanistically plausible given that SZC exchanges potassium partly for sodium; each 5 g dose contains approximately 400 mg of sodium (equivalent to 1 g of salt) (6). Edema is usually mild and peripheral but can be clinically relevant in HF or advanced CKD. In trials, edema incidence was dose-related (for example, in one study ~14% of patients on 15 g SZC had edema vs ~2% on lower doses) (4). In long-term open-label use, mild peripheral edema is reported in some patients, particularly those with heart failure, stage 4-5 CKD, or those on higher doses (8). Edema due to SZC is usually manageable with diuretic dose adjustments or dietary counseling. Monitoring weight and blood pressure is advisable for patients on chronic SZC; if significant edema or hypertension develops, the dose or dosing frequency should be reduced. Importantly, no clear differences in serious cardiovascular events (aside from the HF hospitalization imbalance in REALIZE-K) have been definitively linked to SZC in trials (15). The pharmacovigilance analysis of FAERS reports also detected "cardiac failure" as a safety signal among SZC case reports (20,21). This likely correlates with the HF exacerbations discussed earlier. Thus, patients with compromised cardiac function should be followed closely while on SZC, and those who develop worsening edema or dyspnea may require dose reduction or discontinuation (6,20,21).

#### *Electrolyte Disturbances*

Over-correction leading to hypokalemia can occur if SZC is not titrated appropriately. Clinical trials and long-term extension studies showed that serum potassium dropped below 3.5 mmol/L in approximately 4–6% of patients, necessitating periodic monitoring during maintenance therapy (6,8,21,22). FAERS-based analyses suggest

that many reported adverse events occur within the first weeks to months after initiation, underscoring the importance of periodic potassium monitoring during maintenance therapy (21). It is prudent to monitor serum K<sup>+</sup> periodically during maintenance use (for example, check after the first 1–2 weeks, then monthly) and instruct patients to report symptoms of low K<sup>+</sup> (muscle weakness, palpitations). If hypokalemia occurs, holding SZC for a day or two or reducing the dose usually suffices.

#### *Drug–drug Interactions*

SZC can transiently bind other medications in the GI tract, potentially reducing their absorption. The product information recommends separating SZC from other oral drugs by at least 2 hours before or after administration (6). This is particularly important for drugs with a narrow therapeutic index. Clinicians should review patients' medication lists and counsel them about appropriate timing.

#### *Post-marketing Pharmacovigilance*

Post-marketing safety studies using the FDA Adverse Event Reporting System (FAERS) have reinforced SZC's known adverse-event profile and suggested additional potential signals in real-world use (20, 21). Across these analyses, edema/fluid overload and hypokalemia remain among the more frequently reported and clinically relevant events, broadly consistent with product information and clinical trial experience (6,20,21). While spontaneous reporting systems cannot establish causality and are subject to reporting bias, these analyses support ongoing vigilance—particularly in patients at risk of fluid overload or electrolyte disturbances.

Another radiology-focused report described SZC as a "new dual-energy X-ray absorptiometry confounder": the drug's radiopaque crystals in the gastrointestinal tract can appear on imaging and potentially interfere with bone density or abdominal scans (23). Being aware of this can prevent misinterpretation of imaging in patients recently taking SZC.

Overall, SZC's safety profile is favorable and well characterized in clinical trials and product information (24). It compares favorably with sodium polystyrene sulfonate (which has been associated with rare but serious gastrointestinal adverse events, including intestinal necrosis, particularly when administered with sorbitol) or even patiomer (with its GI tolerability issues) (25). SZC's adverse effects are generally mild and manageable. It is critical, however, to tailor use to the patient: for instance, in a frail HF patient prone to fluid overload, use the lowest effective dose and monitor weight; in a constipated CKD patient, watch for any change in bowel habits. With proper monitoring, SZC can be used chronically with a low incidence of serious

complications, as evidenced by clinical trials and the growing body of real-world experience.

## DISCUSSION

This review consolidates randomized and real-world evidence on sodium zirconium cyclosilicate (SZC) for the management of hyperkalemia in patients with chronic kidney disease (CKD) and/or heart failure (HF), where hyperkalemia frequently constrains renin-angiotensin-aldosterone system inhibitor (RAASi) use. Across trials, SZC demonstrates rapid potassium lowering with maintenance of normokalemia during continued therapy, supporting its role as a bridging and maintenance strategy alongside guideline-directed medical therapy (**Table 1**).

However, the evidence base differs by clinical question. For biochemical endpoints (serum potassium reduction and maintenance), randomized trials provide the strongest support. For ‘hard’ outcomes (mortality, HF hospitalization, progression of CKD), the current evidence is predominantly observational and therefore vulnerable to residual confounding. A 2024 meta-analysis in HF pooled studies of modern potassium binders (including SZC and patiomer) and suggested improved RAASi/MRA optimization and fewer hyperkalemia-related interruptions, but heterogeneity in populations and outcome definitions limits causal inference (18).

### *Limitations of the Study*

Despite clinically meaningful potassium lowering, several limitations should be highlighted. First, the systematic search was limited to a single database (PubMed/MEDLINE) (Embase and the Cochrane Library were not searched) and may have missed eligible studies indexed elsewhere; additionally, no prospective protocol registration was performed. Second, heterogeneity in study design, setting (acute vs chronic), baseline potassium thresholds, and outcome definitions precluded quantitative pooling. Third, most data relevant to clinical outcomes and RAASi persistence are derived from observational cohorts, which cannot fully address confounding by indication. Fourth, evidence in CKD stage 5D (maintenance dialysis) remains sparse and is predominantly observational/off-label.

From a clinical standpoint, SZC also introduces trade-offs. It delivers a sodium load (approximately 400 mg per 5 g dose), which may contribute to edema and fluid retention, particularly in HF or advanced CKD; close monitoring of weight, blood pressure, and volume status is warranted, with diuretic adjustment as clinically indicated (6,15).

SZC can transiently increase gastric pH and should be separated from other oral medications (typically by at

least 2 hours) to minimize absorption interactions, which may challenge adherence in patients with polypharmacy (6,24).

In contrast, sodium polystyrene sulfonate (SPS) has been associated with serious gastrointestinal injury, including colonic necrosis, particularly when administered with sorbitol; this safety profile has contributed to increased use of newer potassium binders in many practice settings (25).

Long-term persistence in routine practice may be limited by cost, pill burden, tolerability, and fluctuating potassium levels. Real-world analyses highlight that short-term use is common and that benefits on RAASi continuation and costs appear more pronounced with longer persistence, underscoring the need for structured follow-up and patient education (10,13).

## CONCLUSION

SZC is an effective potassium binder with a rapid onset that can correct hyperkalemia and maintain normokalemia in patients with CKD and/or HF. The strongest evidence supports biochemical efficacy and maintenance therapy, while evidence for downstream clinical outcomes is still emerging and remains largely observational. In CKD populations, real-world studies suggest that SZC use may be associated with fewer emergency dialysis interventions and reduced hyperkalemia-related hospitalization, and may facilitate RAASi continuation; however, these findings require confirmation in controlled prospective studies (9,12).

In HF, SZC may enable continuation or up-titration of mineralocorticoid receptor antagonists and other RAASi therapies in patients who develop hyperkalemia, but clinicians should actively monitor for edema, hypokalemia, and volume overload, especially at higher or prolonged dosing (6,15,17,18).

Overall, SZC represents a useful component of hyperkalemia management in cardiorenal disease when integrated into an individualized monitoring strategy; further trials should clarify its comparative effectiveness, optimal treatment duration, and impact on clinical outcomes. Any apparent “hard” clinical outcome benefits suggested by observational studies should be regarded as hypothesis-generating pending adequately powered prospective trials.

## DECLARATIONS

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