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*Letter to Editor*

# Comment On: "a Systematic Review of Sodium Zirconium Cyclosilicate for Hyperkalemia Management in Heart Failure and Chronic Kidney Disease"

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Dear Editor,

We read with great interest the systematic review by Çankaya et al. on the efficacy and safety of sodium zirconium cyclosilicate (SZC) for hyperkalemia management in patients with chronic kidney disease (CKD) and heart failure (HF) (1). The authors provide a comprehensive synthesis of available evidence supporting SZC as an effective potassium binder that facilitates renin-angiotensin-aldosterone system inhibitor (RAASi) continuation. We wish to complement this review with an important comparative perspective regarding the safety profile of SZC versus patiromer in the CKD and HF population.

Both SZC and patiromer are approved novel potassium binders, yet they differ meaningfully in their mechanisms and safety profiles. SZC operates via sodium-potassium exchange, delivering approximately 400 mg of sodium per 5 g dose, which may contribute to fluid retention — a concern the authors duly acknowledge (1). Patiromer, in contrast, operates via calcium-mediated exchange and does not carry a sodium load, potentially offering a more favorable hemodynamic profile in volume-sensitive patients.

A large real-world comparative effectiveness study including approximately 50% of patients with CKD stage 3–5 in each treatment arm reported that SZC initiation was associated with significantly higher risks of hospitalization for HF (adjusted HR 1.373; 95% CI 1.337–1.410), major edema encounters (HR 1.330; 95% CI 1.298–1.363), and all-cause mortality (HR 1.287; 95% CI 1.255–1.320) compared with patiromer (2). These findings were consistent across subgroups with and without preexisting HF, raising the hypothesis that the sodium load inherent to SZC may contribute to these outcome differences, although the precise mechanism has not been established. An earlier propensity score-matched cohort study similarly reported a numerically higher rate of hospitalization for HF and significantly greater risk of severe edema with SZC compared to patiromer, providing further support for this safety signal (3). Both studies are observational rather than randomized head-to-head comparisons, and residual confounding by indication (including differences in baseline HF severity, CKD stage, diuretic use, and treatment persistence) cannot be excluded.

While the authors appropriately highlight the REALIZE-K safety signal regarding fluid-related events in patients with markedly elevated NT-proBNP, these observational data raise the possibility that patiromer may be preferable in selected volume-sensitive CKD and HF patients, although confounding by indication cannot be excluded and this comparative evidence merits explicit discussion (1). These comparative safety considerations do not diminish the established efficacy of SZC in rapidly and durably lowering serum potassium or its value in facilitating RAASi continuation; rather, they inform individualized agent selection when both SZC and patiromer are available. Clinicians selecting between these agents should consider not only potassium-lowering efficacy but also the patient's volume status, cardiac function, and residual renal sodium handling capacity.

In conclusion, future guideline discussions should consider comparative safety and effectiveness data between SZC and patiromer, particularly for patients with HF, edema risk, or advanced CKD, while recognizing the observational nature of the current evidence. Patiromer may be preferred in selected volume-sensitive patients, whereas SZC remains a useful potassium binder when rapid potassium lowering, tolerability, access, cost, or other patient-specific factors favor it.

## DECLARATIONS

**Conflict of interest:** None
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