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Hipertansiyon Diyaliz ve Transplantasyon Vakfı

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Dear Readers,

We are pleased to present the new issue of the Journal of Evidence-Based Internal Medicine Practice (JEIMP), featuring a concise yet comprehensive selection of original articles, reviews, and letters that address current clinical questions in nephrology, cardiology, and metabolic medicine.

A central theme of this issue is the broadening clinical impact of SGLT-2 inhibitors. Original studies and a meta-analysis examine their effects on systemic inflammation in advanced chronic kidney disease, compare commonly used agents in real-world settings, and evaluate their role in heart failure, highlighting benefits that extend beyond glucose lowering.

Renal involvement in complex systemic conditions is another key focus. This issue includes an analysis of renal impairment at the time of multiple myeloma diagnosis, emphasizing the need for early detection and integrated care. In addition, a systematic review discusses the role of sodium zirconium cyclosilicate in the management of hyperkalemia in patients with heart failure and chronic kidney disease, a frequent and clinically relevant challenge.

The Letters to the Editor section provides valuable clinical insights and academic discussion, featuring rare but preventable adverse drug effects, emerging perspectives in diabetes management, and an unusual cause of kidney failure.

Overall, this issue reflects JEIMP's commitment to evidence-based, practice-oriented research with direct relevance to daily clinical decision-making. We hope it will be informative and useful for our readers.

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In This Issue

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Hipertansiyon Diyaliz ve Transplantasyon Vakfı

JEIMP

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Original Article

Impact of SGLT-2 Inhibitors on Aggregate Index of Systemic Inflammation in Patients with Stage 3-4 Chronic Kidney Disease: A Retrospective Cohort Study

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Abstract

Background: Chronic kidney disease (CKD) is characterized by systemic inflammation that contributes to cardiovascular morbidity. The Aggregate Index of Systemic Inflammation (AISI), calculated as (neutrophils × platelets × monocytes)/ lymphocytes, has emerged as a prognostic biomarker. SGLT-2 inhibitors demonstrate anti-inflammatory properties in CKD, yet their impact on AISI remains unexplored. We aim to evaluate the impact of SGLT-2 inhibitor therapy on AISI values in patients with stage 3-4 CKD and type 2 diabetes mellitus.

Methods: This retrospective cohort study included 148 patients with stage 3-4 CKD and type 2 diabetes mellitus who initiated SGLT-2 inhibitor therapy at Gazi University Nephrology Clinic between September 2024 and September 2025. AISI was calculated from complete blood counts at baseline and follow-up (mean 48.0 ± 12.2 days). The primary outcome was change in AISI values. Paired t-test was used for statistical analysis.

Results: Mean age was 67.15 ± 9.20 years, 54.7% were male, and baseline eGFR was 38.9 ± 12.1 mL/min/1.73m². Patients received empagliflozin (n=74) or dapagliflozin (n=74). AISI showed no significant change from baseline to follow-up indicating no significant difference (519.89 ± 319.52 vs. 503.15 ± 442.39, p=0.535).

Conclusions: SGLT-2 inhibitor therapy does not significantly alter AISI values in stage 3-4 CKD patients with diabetes over short-term follow-up. The established cardiovascular and renal benefits of SGLT-2 inhibitors appear to operate through mechanisms not reflected in this composite inflammatory marker.

Keywords: Renal Insufficiency, Chronic, Sodium-Glucose Transporter 2 Inhibitors, Inflammation, Diabetes Mellitus, Type2

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INTRODUCTION

Chronic kidney disease (CKD) represents a major global health burden, affecting approximately 10% of the world's population with particularly high prevalence among patients with diabetes mellitus (1). Beyond progressive decline in kidney function, CKD is characterized by a state of chronic systemic inflammation that contributes substantially to excessive cardiovascular morbidity and mortality observed in this population (2,3). While traditional inflammatory biomarkers such as C-reactive protein (CRP) have demonstrated prognostic value, they capture only limited aspects of the complex inflammatory milieu in CKD (4).

The Aggregate Index of Systemic Inflammation (AISI), calculated as (neutrophils × monocytes × platelets)/ lymphocytes, represents a comprehensive composite biomarker integrating multiple components of the inflammatory cascade (5). By incorporating neutrophils and monocytes, lymphocytes, and platelets, AISI theoretically provides a more comprehensive assessment of systemic inflammatory burden than simpler two-component ratios (6). First introduced in 2018, AISI has demonstrated prognostic value in various conditions including hypertension, heart failure, coronary artery disease, and idiopathic pulmonary fibrosis (7-9).

In CKD populations, AISI demonstrates strong prognostic associations. Analysis of 50,768 participants from the National Health and Nutrition Examination Survey (NHANES) identified a threshold effect at AISI >181.27, above which CKD risk increased sharply (10). Among patients with IgA nephropathy, higher AISI tertiles carried more than double the progression risk compared to lower tertiles (11). Furthermore, in cardiovascular contexts, elevated AISI independently

predicts all-cause and cardiovascular mortality in patients with hypertension, heart failure, and coronary artery disease (7,8,12).

SGLT-2 (Sodium-Glucose Co-Transporter 2) inhibitors have revolutionized CKD management, providing cardiovascular and renal protection across diverse patient populations. The landmark DAPA-CKD, CREDENCE, and EMPA-KIDNEY trials demonstrated consistent 28-44% reductions in kidney disease progression and 29-39% reductions in cardiovascular death or heart failure hospitalization (13-15). These benefits extend to patients with eGFR as low as 20 mL/min/1.73m², establishing SGLT-2 inhibitors as foundational therapy for CKD (16).

SGLT-2 inhibitors exert anti-inflammatory effects through interconnected mechanisms. Metabolic reprogramming increases β-hydroxybutyrate, inhibiting NLRP3 inflammasome activation; concurrent suppression of NF-κB, MKK7/JNK, and JAK2/STAT pathways limits pro-inflammatory gene transcription, while Nrf2/HO-1 activation reduces oxidative stress [17-19]. Clinically, SGLT-2 inhibitors lower IL-6 by 30–65%, TNF-α by ~45%, and CRP by 2–3 mg/L within weeks to months (20,21).

Despite these robust anti-inflammatory effects, the impact of SGLT-2 inhibitors on complete blood count parameters remains unclear. Emerging evidence suggests that while these agents modify cellular function and tissue-level inflammation, they may not significantly alter circulating immune cell populations (22). Since AISI depends on absolute counts of neutrophils, monocytes, platelets, and lymphocytes, it may not capture functional anti-inflammatory changes that occur without quantitative shifts in cell populations (23). This disconnect between functional inflammation and structural hematopoietic parameters represents a fundamental gap in our understanding of SGLT-2 inhibitor mechanisms.

Therefore, this study aimed to evaluate the impact of SGLT-2 inhibitor therapy on AISI values in patients with stage 3-4 CKD and type 2 diabetes mellitus, testing the hypothesis that despite known anti-inflammatory properties, these agents may not significantly alter this composite hematologic marker.

METHODS

Study Design and Participants

This retrospective cohort study was conducted at the Nephrology Clinic of Gazi University Faculty of Medicine, between September 1, 2024, and September 1, 2025. Due to the retrospective nature of the study, the requirement for informed consent was waived by the ethics committee.

Patients were included if they met all of the following criteria:

1.Age ≥18 years
2.Documented stage 3-4 CKD (eGFR 15-59 mL/min/1.73m² calculated using the CKD-EPI equation)
3.Confirmed diagnosis of type 2 diabetes mellitus
4.Initiation of SGLT-2 inhibitor therapy (empagliflozin 10 mg daily or dapagliflozin 10 mg daily) during the study period
5.Available complete blood count data at baseline and follow-up

Patients were excluded if they had any of the following:

1.Active infection at baseline (defined by clinical signs, elevated CRP >10 mg/L, or antibiotic treatment)
2.Recent hospitalization within 3 months prior to baseline
3.Active malignancy or history of malignancy within 5 years
4.Current immunosuppressive therapy (including corticosteroids ≥10 mg/day prednisone equivalent)
5.Discontinuation of SGLT-2 inhibitor before follow-up visit
6.Incomplete laboratory data

Initial screening identified 238 patients with stage 3-4 CKD and type 2 diabetes mellitus who initiated SGLT-2 inhibitor therapy during the study period. After applying exclusion criteria, 148 patients were included in the final analysis (Figure 1). Exclusions comprised: incomplete baseline laboratory data (n=52), lost to follow-up or no control visit (n=48), active infection at baseline (n=24), recent hospitalization within 3 months (n=18), SGLT-2 inhibitor discontinued before follow-up (n=10), active malignancy (n=7), and current immunosuppressive therapy (n=5). Some patients met multiple exclusion criteria.

Data Collection

Demographic and Clinical Data

Baseline demographic data included age, sex, body mass index (BMI), duration of diabetes mellitus, and duration of CKD. Medical history was obtained from electronic medical records, including presence of hypertension, cardiovascular disease, and current medications.

Laboratory Measurements

All laboratory measurements were performed at the Gazi University Hospital Central Laboratory using standardized automated methods. Complete blood counts were obtained using automated hematology analyzers.

Serum creatinine was measured using an enzymatic method, and eGFR was calculated using the 2021 CKD-EPI equation without race adjustment. Glycated hemoglobin (HbA1c) was measured using high-performance liquid chromatography. Serum albumin was measured by bromocresol green method. Urine

albumin-to-creatinine ratio (ACR) was calculated from spot urine samples.

AISI Calculation

AISI was calculated using the following formula:

AISI = (Neutrophils × Monocytes × Platelets) / Lymphocytes

Where all cell counts are expressed as $\times 10^3/\mu L$. AISI was calculated at baseline (before SGLT-2 inhibitor initiation) and at follow-up.

Primary Outcome

The primary outcome was the change in AISI from baseline to follow-up after SGLT-2 inhibitor initiation.

Sample Size Calculation

Sample size calculation was performed using G*Power software (version 3.1). To detect a small-to-moderate effect size (Cohen's d=0.3) in AISI changes with 90% power at a two-tailed significance level of 0.05, a minimum of 119 patients was required. Accounting for an estimated 15% attrition rate, we aimed to enroll at least 140 patients. Our final cohort consisted of 148 patients.

STATISTICAL ANALYSIS

Continuous variables are presented as mean ± standard deviation for normally distributed data. Categorical variables are expressed as frequencies and percentages. Normality of distribution was assessed using the Kolmogorov-Smirnov test. The primary analysis compared baseline and follow-up AISI values using the paired t-test, as data approximated normal distribution.

All statistical analyses were performed using SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

Table 1 presents the baseline characteristics of the 148 patients included in the study. The mean age was 67.15 ± 9.20 years, and 54.7% were male. Mean BMI was 27.3 ± 4.9 kg/m², indicating that most patients were overweight. All patients had type 2 diabetes mellitus with a mean HbA1c of 7.45 ± 0.91% and mean fasting glucose of 130.0 ± 43.6 mg/dL, reflecting generally adequate glycemic control. Baseline mean serum creatinine was 1.82 ± 0.55 mg/dL and mean eGFR of 38.9 ± 12.1 mL/min/1.73m². Serum albumin was at 4.33 ± 0.39 g/dL. Albuminuria was present with mean urine albumin-to-creatinine ratio of 802.5 ± 1118.2 mg/g.

Baseline complete blood count parameters showed mean hemoglobin of 12.5 ± 1.8 g/dL and hematocrit of 38.0 ± 5.5%. Mean white blood cell count was 7.85 ± 2.20 $\times 10^3/\mu L$, with neutrophil percentage of 63.9 ± 9.8% and lymphocyte percentage of 24.1 ± 8.0%. Mean platelet count was 254.9 ± 60.6 $\times 10^3/\mu L$, also within normal limits. Patients received either empagliflozin 10 mg daily (n=74, 50.0%) or dapagliflozin 10 mg daily (n=74, 50.0%). The mean follow-up duration was 48.0 ± 12.2 days.

Primary Outcome: Change in AISI

Table 2 presents the primary outcome results. Baseline AISI was 519.89 ± 319.52, and follow-up AISI was 503.15 ± 442.39. The mean difference was 16.74 ± 327.85 (95% CI: -36.52 to 70.00, p=0.535).

DISCUSSION

This study examined the impact of SGLT-2 inhibitor therapy on the AISI in patients with stage 3-4 CKD and type 2 diabetes mellitus. Our principal finding was that despite initiating SGLT-2 inhibitor therapy, AISI values did not change significantly over a mean follow-up of 48 days. This null result, while perhaps initially counterintuitive given the established anti-inflammatory properties of SGLT-2 inhibitors, provides important mechanistic insights into how these agents exert their cardiovascular and renal protective effects.

Table 1. Baseline Characteristics of Study Population (n=148)

Variable	Mean ± SD or n (%)
Demographics	
Age (years)	67.15 ± 9.20
Male sex	81 (54.7)
Body mass index (kg/m²)	27.3 ± 4.9
Height (cm)	167.3 ± 6.1
Weight (kg)	76.5 ± 14.5
Renal Function	
Serum creatinine (mg/dL)	1.82 ± 0.55
eGFR (mL/min/1.73m²)	38.9 ± 12.1
Serum albumin (g/dL)	4.33 ± 0.39
Urine ACR (mg/g)	802.5 ± 1118.2
Glycemic Control	
Fasting glucose (mg/dL)	130.0 ± 43.6
HbA1c (%)	7.45 ± 0.91
Hematologic Parameters	
Hemoglobin (g/dL)	12.5 ± 1.8
Hematocrit (%)	38.0 ± 5.5
White blood cells ($\times 10^3/\mu L$)	7.85 ± 2.20
Neutrophils (%)	63.9 ± 9.8
Lymphocytes (%)	24.1 ± 8.0
Platelets ($\times 10^3/\mu L$)	254.9 ± 60.6
SGLT-2 Inhibitor	
Empagliflozin 10 mg daily	74 (50.0)
Dapagliflozin 10 mg daily	74 (50.0)

Table 2. Changes in Aggregate Index of Systemic Inflammation Following SGLT-2 Inhibitor Initiation

Variable	Baseline	Follow-up	p-value
AISI	519.89 ± 319.52	503.15 ± 442.39	0.535

AISI, Aggregate Index of Systemic Inflammation

However, the critical finding explaining our results emerges from hematological data: SGLT-2 inhibitors do not significantly alter neutrophil, lymphocyte, monocyte, or platelet counts despite these robust anti-inflammatory effects. This represents a fundamental disconnect between functional cellular changes and circulating cell populations. The EMMY trial post-hoc analysis found no significant changes in neutrophil count, leukocyte count, or neutrophil-lymphocyte ratio with empagliflozin treatment (24). Across all major cardiovascular outcomes trials—EMPA-REG OUTCOME, DECLARE-TIMI 58, CANVAS, CREDENCE, DAPA-CKD, and EMPA-KIDNEY—collectively enrolling over 50,000 participants, no significant platelet count alterations were documented (25).

While SGLT-2 inhibitors modulate lymphocyte function by correcting Th1/Th2 balance and normalizing Th17/Treg ratios, these represent phenotypic and functional changes rather than changes in absolute cell numbers (26). Similarly, functional studies demonstrate that these agents shift monocyte/macrophage polarization from pro-inflammatory M1 toward anti-inflammatory M2 phenotypes and reduce monocyte recruitment from bloodstream to tissues, but circulating monocyte counts remain stable (27). A recent article showed that 15 days of SGLT-2 inhibitor treatment decreased thromboxane B2 by 33.1%, soluble P-selectin by 49.3%, and soluble CD40L by 62.3%, representing potent functional antiplatelet effects without quantitative changes in platelet counts (28).

AISI is calculated as (neutrophils × monocytes × platelets) / lymphocytes, using values (cells $\times 10^3/\mu L$) from routine complete blood counts. Its mathematical structure confers resistance to pathway-specific interventions, as the multiplicative numerator requires concurrent changes in all three cell types for a meaningful effect, while single cell-type targeting has minimal impact. The lymphocyte denominator adds further limitation: although increasing lymphocytes would lower AISI, CKD-related lymphopenia due to thymic involution is largely irreversible with current therapies (29,30).

Biologically, AISI reflects largely irreversible structural immune changes, including thymic involution with reduced naïve T-cell production, myeloid-skewed hematopoiesis due to bone marrow exhaustion, cellular senescence sustaining inflammatory programs, and altered immune trafficking between tissues and circulation (31). These structural alterations are far less modifiable than the functional inflammatory pathways targeted by SGLT-2 inhibitors. Their anti-inflammatory effects arise through reduced cytokine signaling, oxidative stress, endothelial dysfunction, and tissue-level inflammation, without altering circulating immune cell distributions (32).

The one consistent hematological change with SGLT-2 inhibitors involves red blood cells, not AISI components. Hemoglobin and hematocrit increase 2-4 percentage points across all SGLT-2 inhibitor trials through enhanced erythropoiesis mediated by improved renal oxygenation, reversion of myofibroblasts to erythropoietin-producing fibroblasts, and reduced hepcidin levels (33,34).

Our findings have important implications for understanding AISI's clinical utility. AISI serves powerfully as a prognostic marker identifying high-risk CKD patients requiring aggressive management, as demonstrated by studies showing that elevated AISI independently predicts mortality, cardiovascular events, and CKD progression (8-12). However, AISI appears less responsive as a short-term therapeutic marker.

The lack of AISI change despite proven clinical benefit from SGLT-2 inhibitors underscores the importance of selecting inflammatory markers aligned with therapeutic mechanisms. IL-6, CRP, and oxidative stress markers more accurately reflect SGLT-2 inhibitor–mediated anti-inflammatory activity than AISI. More broadly, anti-inflammatory strategies targeting cellular function, activation states, or signaling pathways may yield substantial clinical benefit without altering composite indices dependent on structural hematopoietic changes. In contrast, CRP, IL-6, TNF-α, and to a variable extent NLR respond to pharmacologic interventions, as they represent soluble or dynamic inflammatory components. AISI, however, requires shifts in circulating cell populations, a threshold largely resistant to current anti-inflammatory therapies.

In CKD populations, studies noted AISI was more effective in detecting CKD presence than simpler inflammatory markers like SII or PLR, suggesting it captures a different aspect of disease burden—likely reflecting chronic structural immune remodeling rather than acute or subacute inflammatory states (10). This distinction becomes crucial when interpreting therapeutic interventions.

The major CKD trials proved SGLT-2 inhibitors reduce hard outcomes by 28-44% for kidney disease progression and 29-39% for cardiovascular death or heart failure

hospitalization without measuring inflammatory biomarkers, demonstrating that mechanistic understanding, while valuable, is not required for evidence-based prescribing (13,14). Our null finding should not deter clinicians from prescribing SGLT-2 inhibitors in appropriate patients, as these agents provide cardiovascular and renal protection through mechanisms that extend beyond what AISI captures.

This study has several strengths. We utilized a well-defined cohort of patients with documented stage 3-4 CKD and type 2 diabetes mellitus, a population known to benefit from SGLT-2 inhibitor therapy. We employed rigorous inclusion and exclusion criteria to minimize confounding from acute inflammatory conditions. Our sample size exceeded the calculated requirement based on power analysis. We calculated AISI using standardized automated laboratory methods, enhancing reproducibility.

However, several limitations merit discussion. The retrospective design introduces potential selection bias, though consecutive enrollment of eligible patients mitigated this risk. The relatively short follow-up duration (mean 48 days) may not capture longer-term inflammatory changes, though previous studies demonstrating

SGLT-2 inhibitor anti-inflammatory effects typically observed changes within 30-90 days (20,21). The single-center design limits generalizability, though our patient population is representative of typical CKD patients seen in nephrology clinics.

We did not measure other inflammatory markers (IL-6, TNF-α, CRP) that might have changed despite stable AISI, preventing direct demonstration of anti-inflammatory effects in our cohort. We captured only single baseline and follow-up measurements rather than serial assessments, potentially missing temporal variability.

The relatively short follow-up precluded assessment of clinical outcomes such as CKD progression or cardiovascular events. Future studies with longer follow-up examining both AISI changes and clinical outcomes would clarify whether AISI dynamics predict response to SGLT-2 inhibitor therapy. Additionally, we did not assess changes in individual complete blood count components, which might have revealed subtle shifts not reflected in the composite AISI calculation.

Mechanistic studies should determine which aspects of systemic inflammation drive AISI's prognostic value whether specific cell types contribute disproportionately and whether targeted hematopoietic interventions could modify AISI. Comparative studies examining AISI versus simpler markers (NLR, PLR) across CKD stages and etiologies would optimize risk stratification approaches. Investigation of interventions that might alter hematopoietic parameters such as senolytic therapies targeting senescent cells or interventions addressing thymic involution could clarify whether structural immune aging represents a modifiable therapeutic target.

CONCLUSION

Our findings indicate that cardiovascular and renal benefits of SGLT-2 inhibitors arise from mechanisms not captured by this composite hematologic marker. Inflammation spans circulating cytokines, cellular activation, and structural immune remodeling, with therapies targeting distinct components. AISI reflects structural immune changes resistant to current anti-inflammatory strategies, whereas SGLT-2 inhibitors modulate functional pathways without altering cell counts.

Clinicians should not expect AISI reductions after SGLT-2 inhibitor initiation despite established anti-inflammatory effects. Stable AISI values alongside improved markers reflect insensitivity rather than treatment failure. Decisions should prioritize eGFR preservation, proteinuria reduction, and cardiovascular event prevention over biomarker fluctuations in practice.

DECLARATIONS

Ethics Committee Approval: TThis study was approved by the Gazi University Ethics Committee (approval number: 2025-1097, approval date: June 17, 2025). The study was conducted in accordance with the Declaration of Helsinki. Due to the retrospective nature of the study using de-identified data from medical records, the requirement for informed consent was waived by the ethics committee.

Data Availability: The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests: The authors declare no competing interests.

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Informed Consent: Not applicable.

Authors' Contributions

BCH: Conceptualization, methodology, data curation, formal analysis, writing—original draft, writing—review and editing. TEC: Data collection, validation, writing—review and editing. AK: Data collection, validation, writing—review and editing, HP: Conceptualization, writing—review and editing. All authors read and approved the final manuscript.

AI Assistance: Portions of manuscript drafting and language editing were supported by an AI tool (OpenAI ChatGPT) used solely for clarity and grammar improvement. All outputs were verified by the authors in line with COPE and ICMJE AI-use guidelines.

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Original Article

Comparison of Dapagliflozin and Empagliflozin in Patients with Type 2 Diabetes and/or Chronic Kidney Disease: A Real-World Observational Study

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Abstract

Background: Sodium-glucose cotransporter-2 (SGLT2) inhibitors provide renal protection in patients with diabetes mellitus (DM) and chronic kidney disease (CKD), but comparative real-world data on dapagliflozin and empagliflozin across different renal diagnoses are limited.

Method: In this retrospective observational study, 328 adults with DM and/or CKD, including diabetic nephropathy, glomerulonephritis, and heart failure, who received dapagliflozin or empagliflozin for at least 12 months were evaluated. Demographic, clinical, and laboratory data, including estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio, were recorded at baseline and 12 months. The primary outcome was ≥50% reduction in albuminuria, and a >50% decline in eGFR was analyzed as a safety endpoint.

Results: Of 328 patients (mean age 60.4 ± 11.1 years, 43.3% female), 165 received dapagliflozin and 163 received empagliflozin. Among 298 patients with DM, 61.4% achieved ≥50% reduction in albuminuria at 12 months, while 86.7% of 30 non-diabetic patients reached this target. High response rates were observed in patients with isolated DM, DM+CKD, and non-diabetic CKD, including those with glomerulonephritis. Only one patient (with DM and CKD in the empagliflozin group) experienced a >50% decline in eGFR; no such decline occurred in other subgroups. There were no significant differences between dapagliflozin and empagliflozin in albuminuria reduction or eGFR decline across diagnostic categories.

Conclusion: In this real-world cohort, dapagliflozin and empagliflozin were similarly effective in substantially reducing albuminuria and preserving eGFR in patients with DM, CKD, glomerulonephritis, and heart failure. These findings support the use of SGLT2 inhibitors as renoprotective therapy across diverse high-risk populations.

Keywords: Sodium-Glucose Transporter 2 Inhibitors, Dapagliflozin, Empagliflozin, Albuminuria, Renal Insufficiency, Chronic

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INTRODUCTION

The prevalence of diabetes mellitus (DM) is increasing in Türkiye, as it is worldwide. With the rise in type 2 DM, the number of individuals at risk of cardiovascular disease and end-stage renal disease also continues to grow (1). According to data from the Turkish Society of Nephrology, DM remains the most common underlying cause among incident hemodialysis patients (2).

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are oral antidiabetic agents used in the management of type 2 DM. These drugs act by inhibiting the SGLT2 cotransporter in the renal proximal tubule, thereby reducing glucose reabsorption and promoting urinary glucose excretion. Beyond their glucose-lowering effects, SGLT2 inhibitors exert renoprotective benefits independent of glycemic control. By blocking the reabsorption of glucose and sodium in the proximal tubule, they increase sodium delivery to the macula densa, which activates the tubuloglomerular feedback mechanism and induces vasoconstriction of the afferent arteriole. The resulting decrease in intraglomerular pressure is expected to reduce proteinuria (3). Considering that DM is the leading cause of chronic kidney disease (CKD), SGLT2 inhibitors (capable of improving glycemic control and lowering proteinuria) have become a preferred therapeutic option for patients with diabetic nephropathy. In Türkiye, the available SGLT2 inhibitors include dapagliflozin and empagliflozin.

It has been reported that 20–40% of individuals diagnosed with DM develop diabetic nephropathy (4).

A decline in estimated glomerular filtration rate (eGFR) and an increase in proteinuria are associated with higher mortality among patients with diabetic nephropathy (5). In a study by Coppo et al., age and proteinuria were identified as the key factors influencing renal prognosis in patients with IgA nephropathy (6). Likewise, a study on membranous glomerulonephritis demonstrated that proteinuria had a significant impact on prognosis (7). Consequently, the use of SGLT2 inhibitors, which effectively reduce proteinuria, has been increasing among patients followed for glomerulonephritis (4). In the treatment of diabetic nephropathy, SGLT2 inhibitors play a crucial role by lowering intraglomerular pressure and thereby contributing meaningfully to disease management.

Accordingly, this study aimed to evaluate and compare the effects of dapagliflozin and empagliflozin on albuminuria and decline in eGFR among patients with CKD, including those with glomerulonephritis and diabetic nephropathy.

METHODS

Study Design and Participants

This retrospective observational study included 328 adult patients who were diagnosed with DM, CKD, including diabetic nephropathy and glomerulonephritis, and had been using a SGLT2i for at least one year at the Nephrology Clinic/Outpatient Unit of Dışkapı Training and Research Hospital between January 2022 and January 2023. Exclusion criteria was stage 5 CKD patients, type 1 DM patients and patients with missing data. The flowchart for the study is presented in **Figure 1**. Ethical approval for the study was obtained from the Gülhane Faculty of Medicine Ethics Committee (Decision No: 146/24, Date: 12/09/2022). Individual consent to participate was waived with the approval of the ethics committee due to the retrospective design of the study.

Patients' diagnosis, treatment, and follow-up data were retrospectively reviewed from medical records and recorded. Clinical and demographic variables such as age at treatment initiation, sex, comorbidities, smoking status, body mass index (BMI), concomitant treatments (RAAS blockers, diuretics, statins) and systolic and diastolic blood pressures were collected. Laboratory parameters including serum creatinine, eGFR, spot urine albumin-to-creatinine ratio (ACR), potassium, hemoglobin, and HbA1c were also recorded. In addition, patients' 12th-month laboratory values for creatinine, eGFR, and, ACR were retrospectively retrieved and documented. eGFR was calculated with the formula CKD-EPI. CKD staging was performed according to the KDIGO 2024 CKD guideline. BMI was calculated as body weight divided by the square of height (kg/m²). The SGLT2i used by each patient—either dapagliflozin or empagliflozin—was recorded. All patients receiving dapagliflozin received 10 mg. Patients with DM without CKD received empagliflozin 25 mg, while patients with CKD received empagliflozin 10 mg.

STATISTICAL ANALYSIS

Data analysis was conducted using SPSS version 26 and a p value <0.05 was considered statistically significant. Continuous variables have been summarized as mean

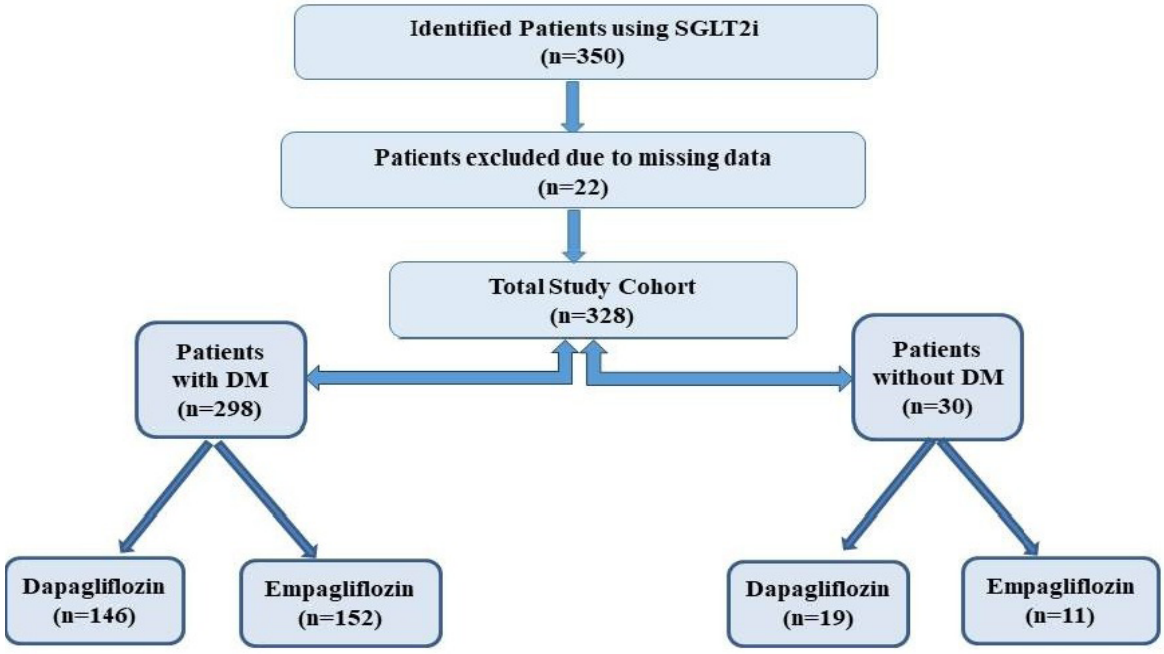

Figure 1. Flowchart of the study

Table 1. Baseline Characteristics of Study Population (n=148)

Parameters	Total (n=328)	Dapagliflozin (n=165)	Empagliflozin (n=163)	p value
Age, years, mean±SD	60.4±11.1	60.1±12.0	60.7±10.2	0.631
Female, n (%)	142(43.3)	74(44.8)	68(41.7)	0.567
Body mass index (kg/m²), mean±SD	30.7±5.8	30.3±6.0	31.0±5.6	0.261
Smoking, n (%)	144(43.9)	68(41.2)	76(46.6)	0.323
Blood pressure (mmHg), mean±SD				
Systolic blood pressure	134.4±19.1	133.7±17.4	135.0±20.8	0.526
Diastolic blood pressure	79.2±12.8	77.8±12.0	80.6±13.6	0.056
Estimated GFR (mL/min/1.73 m²), mean±SD	70.9±24.5	69.4±24.9	72.5±24.2	0.258
Stage 1–2 CKD, n (%), (eGFR≥60)	198(60.4)	97(58.8)	101(62.0)	0.411
Stage 3a CKD, n (%), (eGFR 45-59)	81(24.7)	38(23.0)	43(26.4)	
Stage 3b CKD, n (%), (eGFR 30-44)	38(11.6)	23(13.9)	15(9.2)	
Stage 4 CKD, n (%), (eGFR 15-29)	11(3.4)	7(4.2)	4(2.5)	
Serum creatinine (mg/dL), mean±SD	1.2±0.5	1.2±0.5	1.1±0.5	0.299
Hemoglobin (g/dL), mean±SD	13.5±2.0	13.3±2.0	13.7±2.0	0.065
HbA1c (%), mean±SD	8.3±1.9	8.2±2.0	8.3±1.9	0.671
Potassium (mEq/L), mean±SD	4.6±0.6	4.6±0.5	4.5±0.6	0.147
Urine albumin/creatinine ratio, mean±SD	402.8±836.6	474.5±975.6	330.2±662.4	0.124
< 30 mg/g creatinine, n (%)	75(22.9)	37(22.4)	38(23.3)	0.587
30–300 mg/g creatinine, n (%)	156(47.6)	75(45.5)	81(49.7)	
> 300 mg/g creatinine, n (%)	97(29.6)	53(32.1)	44(27.0)	
Diabetes mellitus, n (%)	298(90.9)	146(88.5)	152(93.3)	0.134
Hypertension, n (%)	251(76.5)	123(74.5)	128(78.5)	0.395
Glomerulonephritis, n (%)	26(7.9)	20(12.1)	6(3.6)	0.043
Heart failure, n (%)	87(26.5)	36(21.8)	51(31.2)	0.221
Reduced EF (≤ 40 %), n (%)	43(49.4)	15(41.6)	28(54.9)	0.149
Mildly reduced EF (41–49 %), n (%)	14(16.0)	6(16.6)	8(15.6)	
Preserved EF (≥ 50 %), n (%)	30(34.4)	17(47.2)	13(25.4)	
Concomitant medications, n (%)				
RAAS blocker	316(96.3)	161(97.6)	155(95.1)	0.231
Diuretic	199(60.7)	95(57.6)	104(63.8)	0.248
Statin	176(53.7)	83(50.3)	93(57.1)	0.220

SD, standard deviation; GFR, glomerular filtration rate; CKD, chronic kidney disease; EF, ejection fraction; RAAS, renin-angiotensin-aldosterone system.

± standard deviation, and categorical variables as frequency and percentage. Differences between groups were assessed using the appropriate statistical tests for the groups, including the independent samples t-test for continuous variables, and the Chi-square or Fisher's exact test for categorical variables.

RESULTS

A total of 328 patients were included in the study. The mean age of participants was 60.4 ± 11.1 years and 142 (43.3%) patients were female. Among the participants, 165 (50.3%) were using dapagliflozin and 163 (49.7%) were using empagliflozin. The mean serum creatinine level was 1.2 ± 0.5 mg/dL, and the mean eGFR was 70.9 ± 24.5 mL/min/1.73 m². Of the total patients, 298 (90.9%) had DM, 251 (76.5%) had hypertension, 87 (26.5%) had heart failure, and 26 (7.9%) had a diagnosis of glomerulonephritis.

The demographic, clinical, and laboratory characteristics of the patients, along with the comparison of these parameters between those using dapagliflozin and empagliflozin, are presented in **Table 1**.

Among the 298 patients diagnosed with DM, 74 (24.8%) did not have accompanying CKD or heart failure. A total of 210 patients (70.5%) had CKD in addition to DM, 73 (24.5%) had concurrent heart failure, and 6 (2.0%) had a diagnosis of glomerulonephritis alongside DM.

Of the 30 patients without a DM diagnosis, 25 (83.3%) had CKD, 20 (66.6%) had glomerulonephritis, and 14 (46.6%) had heart failure. The comparison of disease frequencies between dapagliflozin and empagliflozin users among patients with and without diabetes is presented in **Table 2**.

A ≥50% reduction in albuminuria at the 12th month was observed in 183 (61.4%) of the 298 patients diagnosed with DM. Among the 30 patients without a DM diagnosis,

Table 2. Comparison of disease frequencies between dapagliflozin and empagliflozin users among patients with and without diabetes mellitus

Patients with DM	Total (n=298)	Dapagliflozin (n =146)	Empagliflozin (n =152)	p value
DM only, n (%)	74 (24.8)	33 (22.6)	41 (27.0)	0.383
DM + CKD, n (%)	210 (70.5)	109 (74.7)	101 (66.4)	0.120
DM + GN, n (%)	6 (2.0)	2 (1.4)	4 (2.6)	0.438
Membranous GN	3 (1.0)	1 (0.7)	2 (1.3)	1.000
MPGN	1 (0.3)	0	1 (0.7)	
FSGS	2 (0.7)	1 (0.7)	1 (0.7)	
DM + Renal Transplant, n (%)	7 (2.3)	5 (3.4)	2 (1.3)	0.275
DM + Heart Failure, n (%)	73 (24.5)	33 (22.6)	40 (26.3)	0.456
Reduced EF (≤40%)	31 (42.5)	12 (36.4)	19 (47.5)	0.128
Mildly Reduced EF (41–49%)	13 (17.8)	4 (12.1)	9 (22.5)	
Preserved EF (≥50%)	29 (39.7)	17 (51.5)	12 (30.0)	
CKD, n (%)	25 (83.3)	15 (78.9)	10 (90.9)	0.397
GN, n (%)	20 (66.6)	18 (94.7)	2 (18.1)	0.002
IgA nephropathy	14 (70.0)	13 (72.2)	1 (50.0)	0.007
Membranous GN	5 (25.0)	4 (22.2)	1 (50.0)	
Minimal Change Disease	1 (3.3)	1 (5.5)	0 (0)	
Heart Failure, n (%)	14(46.6)	3(15.7)	11(100.0)	0.056
Reduced EF (≤40%)	12(85.7)	2(66.6)	10(90.9)	0.333
Mildly Reduced EF (41–49%)	1(7.1)	1(33.3)	0 (0)	
Preserved EF (≥50%)	1(7.1)	0 (0)	1(9.0)	

DM, diabetes mellitus; CKD, chronic kidney disease; GN, glomerulonephritis; MPGN, membranoproliferative glomerulonephritis; FSGS, focal segmental glomerulosclerosis; EF, ejection fraction.

26 (86.7%) showed a ≥50% reduction in albuminuria at the 12th month. The comparison of patients receiving dapagliflozin and empagliflozin who achieved a ≥50% reduction in albuminuria at 12 months across different disease groups is presented in **Table 3**.

Among patients with only DM, as well as those with DM and renal transplantation or DM and heart failure, no patients in either the dapagliflozin or empagliflozin groups experienced a >50% decline in eGFR at the 12th month. In patients diagnosed with both DM and CKD, none of the patients in the dapagliflozin group showed a >50% decrease in eGFR at 12 months, whereas only

Table 3. Comparison of patients showing ≥50% reduction in albuminuria at the first year between dapagliflozin and empagliflozin groups

	Total		Dapagliflozin		Empagliflozin		p value
	Total	≥ %50 reduction in Albuminuria	Total	≥ %50 reduction in Albuminuria	Total	≥ %50 reduction in Albuminuria	
Patients with DM							
Only DM	74	53 (71.6)	33	22 (66.6)	41	31 (75.6)	0,255
Chronic kidney disease	210	123 (58.5)	109	64 (58.6)	101	59 (58.4)	0,126
Renal Transplant	7	3 (42.8)	5	2 (40.0)	2	1 (50.0)	0,516
Heart Failure	73	37 (50.6)	33	16 (48.4)	40	21 (52.5)	0,509
Reduced EF (≤40%)	31	14 (46.6)	12	4 (33.3)	19	10 (52.6)	0.119
Mildly Reduced EF (41–49%)	13	7 (53.8)	4	2 (50.0)	9	5 (55.5)	
Preserved EF (≥50%)	29	16 (55.1)	17	10 (58.8)	12	6 (50.0)	
Patients without DM							
Chronic kidney disease	25	21 (84.0)	15	14 (93.3)	10	7 (70.0)	0.562
Heart Failure	14	12 (85.7)	3	3 (100.0)	11	9 (81.8)	0.365
Glomerulonephritis	20	18 (90.0)	18	17 (94.4)	2	1 (50.0)	0.070
IgA Nephropathy	14	13 (92.8)	13	12 (92.3)	1	1 (100.0)	-
Membranous GN	5	4 (80.0)	4	4 (100.0)	1	0	-
MCD	1	1 (100.0)	1	1 (100.0)	0	0	-

DM, diabetes mellitus; EF, ejection fraction; GN, glomerulonephritis; MCD, minimal change disease

one patient in the empagliflozin group exhibited such a decline. Among patients without a DM diagnosis, no >50% decrease in eGFR at the 12th month was observed in either treatment group.

DISCUSSION

The results of this retrospective cohort revealed the reduction rate of albuminuria ≥50% at 12 months to be notably high across multiple patient groups; including those with only DM, those with DM and CKD and those with only CKD – such as the patients with glomerulonephritis. It is important to note that there was no significant difference between dapagliflozin and empagliflozin in regards to their ability to reduce albuminuria across these subgroups – seemingly showing both molecules to be equally effective. Additionally, only one patient in the entire cohort experienced a >50% decline in estimated eGFR at the 12th month.

Overall, the proportion of patients achieving more than a 50% reduction in albuminuria was high in all diagnostic groups. Our findings support Lin et al., who previously demonstrated that SGLT2 inhibitors effectively reduce albuminuria levels (8). Similarly, a meta-analysis including 12 studies and 89,191 patients confirmed that SGLT2 inhibitors significantly lower albuminuria (9). In our cohort, none of the patients with DM showed a >50% eGFR decline after one year, aligning with the meta-analysis by Toyama et al., which included 27 studies and 7,363 patients and demonstrated that SGLT2 inhibitors attenuate the annual decline in eGFR (10). Another meta-analysis involving six randomized controlled trials further confirmed that SGLT2 inhibitors slow renal function deterioration among patients with DM and CKD (11).

According to the KDIGO guideline for the management of CKD in patients with diabetes, SGLT2 inhibitors are now recommended as the first-line therapy for all individuals with an eGFR ≥20 mL/min/1.73 m² (12). Therefore, patients with DM and/or CKD should be evaluated for the early initiation of SGLT2 inhibitors at diagnosis to mitigate the risk of renal disease progression.

Large multi-center trials such as DAPA-CKD and EMPA-KIDNEY have further expanded the therapeutic scope of SGLT2 inhibitors, demonstrating significant reductions in CKD progression and albuminuria, even among non-diabetic patients (13,14). In glomerulonephritis, a study focusing on IgA nephropathy similarly reported that SGLT2 inhibitors effectively reduce proteinuria (15). In our analysis, although the number of glomerulonephritis patients was limited, these patients showed the highest albuminuria reduction rates. While SGLT2 inhibitors are increasingly incorporated into routine practice for IgA nephropathy, broader randomized prospective studies are still needed to clarify their efficacy across other glomerulonephritis subtypes.

We also observed that among patients with heart failure (regardless of DM statu) albuminuria significantly decreased and furthermore, no cases of >50% eGFR decline were identified. The DAPA-HF trial similarly showed that dapagliflozin provided superior renal outcomes compared to placebo, including reduced risk of >50% eGFR decline, end-stage kidney disease, or renal death (16). Likewise, in the EMPEROR-REDUCED trial involving 3,730 patients, empagliflozin was associated with a lesser decline in eGFR compared with placebo (17). Together, these findings support the growing evidence that the renal benefits of SGLT2 inhibitors extend to patients with heart failure and should not be overlooked in their management.

At baseline, patients using dapagliflozin and those using empagliflozin were similar in terms of demographic, clinical, and laboratory characteristics. After 12 months of treatment, both agents showed comparable efficacy, suggesting equivalent renal benefit. This is consistent with findings from Lim et al., who reported no significant difference in renal endpoints between dapagliflozin and empagliflozin (18). Another study has also demonstrated similar results between the two drugs (8). Conversely, the VERTIS-CV trial, which included non-diabetic CKD patients, found that ertugliflozin did not significantly reduce albuminuria (19). Taken together, our findings and those from the literature suggest that the renal effects of SGLT2 inhibitors are likely class effects rather than molecule-specific differences (20). However, additional head-to-head and mechanistic studies are needed to confirm this observation.

Limitations of The Study

This study has several limitations. The retrospective design, relatively small sample size, and single-center setting may limit the generalizability of the results. The small number of glomerulonephritis cases represents another constraint. Additionally, other antidiabetic agents used by patients with DM were not recorded, which may have influenced renal outcomes. Nevertheless, the principal strength of our study lies in its inclusion of diverse patient populations and the direct comparison between dapagliflozin and empagliflozin users, providing valuable real-world evidence on the renal effects of SGLT2 inhibitors across multiple disease contexts.

CONCLUSION

In our study, we found that SGLT2 inhibitors significantly reduced albuminuria in patients with diabetic nephropathy, heart failure, CKD, and glomerulonephritis. Furthermore, no substantial difference in efficacy was

observed between dapagliflozin and empagliflozin. Consistent with existing literature, our findings support the importance of initiating SGLT2 inhibitors in all eligible patients with appropriate indications.

DECLARATIONS

Ethics Committee Approval: This study was carried out according to the ethical rules and principles of the Declaration of Helsinki. Patient data was retrospectively accessed and anonymized before analysis. Approval for the study protocol was obtained from the Ethics Committee of Gülhane Hospital (approval date: 12 September 2022; approval number: 146/24).

Data Availability: The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests: All authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Informed Consent: Since the study is retrospective, informed consent form is not necessary.

Authors' Contributions: **MY**: Conceptualization, methodology, and writing—original draft. **EY** and **BIA**: Data collection and validation. **EGO**: Writing—review and editing and supervision. **MDA**: Conceptualization, project administration, and writing—review and editing. All authors read and approved the final manuscript.

AI Assistance: We hereby confirm that the content of this article was written entirely by the authors and does not involve the use of artificial intelligence or AI-assisted writing tools. All intellectual contributions, data analysis, and interpretations presented in this manuscript are the result of the authors' original work.

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Original Article

Renal Impairment at Multiple Myeloma Diagnosis: Clinical Characteristics, Contributing Factors in a Retrospective Cohort

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Abstract

Background: This study aimed to examine the frequency and clinical characteristics of kidney dysfunction at the time of multiple myeloma (MM) diagnosis, focusing on factors associated with MM-related nephropathy, to identify factors associated with renal recovery among patients presenting with impaired kidney function.

Methods: This retrospective single-center study included patients diagnosed with MM between 1999 and 2009. Of 204 screened patients, 136 were eligible for analysis after exclusion of cases with incomplete laboratory or imaging data. Kidney dysfunction was defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² at diagnosis. Demographic characteristics, myeloma subtype, International Staging System (ISS) stage and risk category, laboratory parameters, renal ultrasonography findings, and nephrotoxic exposures were evaluated. Renal recovery was assessed in patients with kidney dysfunction at baseline.

Results: Kidney dysfunction was present in 24 patients (17.6%) at diagnosis. Compared with those with preserved renal function, these patients had higher rates of light chain myeloma, and higher β2-microglobulin and CRP levels, and greater proteinuria (all $p \leq 0.05$). Moreover, patients with kidney dysfunction were more likely to have higher ISS Stage, high-risk ISS classification ($p<0.001$). Renal ultrasonography abnormalities including increased cortical echogenicity and reduced kidney size, were significantly more common in the kidney dysfunction group ($p < 0.001$). Among patients with kidney dysfunction, renal recovery occurred in 9 of 24 (37.5%). Lower baseline creatinine and absence of hemodialysis requirement at diagnosis were associated with higher recovery likelihood, whereas increased cortical echogenicity or reduced kidney size predicted persistent dysfunction.

Conclusion: Kidney dysfunction at diagnosis in MM patients is associated with advanced disease stage, and unfavorable laboratory and clinical features. While β2-microglobulin remains a useful prognostic marker, its interpretation in patients with kidney dysfunction should be approached cautiously due to impaired renal clearance. These findings underscore the importance of early recognition and appropriate management of renal impairment in MM..

Keywords: Multiple Myeloma, Renal Insufficiency, Myeloma Kidney, Recovery of Function

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INTRODUCTION

Multiple myeloma (MM) is a malignant plasma cell disorder characterized by clonal proliferation of plasma cells in the bone marrow and the presence of monoclonal immunoglobulins or light chains. Clinically, MM presents with lytic bone lesions, anemia, hypercalcemia, renal dysfunction, and recurrent infections. Following non-Hodgkin lymphoma, it is the second most common hematologic malignancy in adults, typically diagnosed between 60 and 70 years of age (1,2). Globally, MM affects approximately 35,000 individuals annually in the United States and nearly 600,000 worldwide per year (3).

Renal impairment is one of the clinically important complications of MM (4). Renal impairment is observed in approximately 20–40% of patients at diagnosis, and up to 50–75% may experience renal involvement at some point during the disease course (4-6). Kidney involvement in MM may occur either through direct monoclonal light chain–mediated tubular injury or secondary mechanisms such as dehydration, hypercalcemia, infections, nephrotoxic medications, and other comorbid conditions (4,7). Such renal complications substantially worsen the clinical trajectory, as renal failure (RF) ranked as the second most frequent cause of mortality among MM patients (surpassed only by infections) particularly

before widespread access to dialysis became available (4,7).

Lambda and kappa light chains are the two main types of free light chains. Lambda light chains are more frequently associated with severe tubular injury and more aggressive renal involvement, leading to faster progression of renal dysfunction compared with kappa light chains. These pathological changes result from the deposition of monoclonal light chains within the renal tissue, which can give rise to cast nephropathy, light chain deposition disease, or AL amyloidosis (8,9). Chronic structural changes such as increased cortical echogenicity or reduced kidney size, may also develop over time as a result of sustained tubular injury and interstitial fibrosis in MM-related renal involvement 10. Renal failure has been a major contributor to mortality in MM, accounting for a substantial proportion of deaths in historical cohorts. A 12-month follow-up analysis showed that reversibility of renal failure was a more important prognostic factor than chemotherapy response (11,12).

Given the substantial clinical impact of renal involvement in MM, this study therefore aimed to evaluate the clinical characteristics, laboratory features, and disease severity associated with kidney dysfunction at the time of MM diagnosis. The secondary aim was to describe comorbid factors and nephrotoxic exposures that may contribute to impaired renal function in this cohort.

METHODS

Protocol and Search Strategy

This retrospective single-center study was conducted at Gazi University Faculty of Medicine, Department of Internal Medicine, hematology and nephrology divisions, using data from adult patients diagnosed with MM between January 1, 1999, and December 31, 2009. Ethical approval was obtained from the Ankara Keçiören Training and Research Hospital, The Committee of Human Researches, dated 25.11.2009 and numbered 2009/11-110. The study involved analyzing retrospective data, and no budget was required.

Case selection: ≥ 18-year-old adult patients with MM. Patients diagnosed at Gazi University School of Medicine, Department of Internal Medicine were included in the study.

Staging and Risk stratification for MM: International Staging System (ISS) for Multiple Myeloma was utilized for staging (Accessed at: 24.06.2024, https://www.myeloma.org/international-staging-system-iss-reivised-iss-r-iss) (13).

Definition of Kidney Dysfunction: Kidney dysfunction was defined primarily by eGFR <60 mL/min/1.73 m² at diagnosis. Among patients with eGFR <60 mL/min/1.73 m² at diagnosis, four individuals with clearly documented long-standing chronic kidney disease (persistently reduced eGFR for >1year prior to MM diagnosis) were excluded from the renal dysfunction group in statistical analyses, in order to focus on kidney impairment present at or newly recognized at MM diagnosis. This exclusion was intended to minimize confounding by pre-existing CKD and to better capture kidney impairment present at or newly recognized at MM diagnosis, which is more likely to reflect MM-related renal involvement. Creatinine clearance and 24-hour proteinuria levels were used to further stage CKD, in accordance with KDIGO principles (14).

Exclusion criteria: Monoclonal gammopathy of undetermined significance, Waldenström macroglobulinemia, incomplete patient data, and an external diagnosis of MM were considered for exclusion. Data collection: Demographical features of the patients, stage of the disease, comorbidities, nephrotoxic drug, and radiocontrast agent use were noted. The treatment protocols and responses to the treatment and ISS stage and ISS risk category were also noted. Ig G, A, and M levels measured at the time of diagnosis, serum protein, albumin, globulin, β2 microglobulin, hemoglobin (Hgb), white blood cell (WBC), platelet (PLT), erythrocyte sedimentation rate (ESR), C-reactive protein [CRP]), blood urea nitrogen (BUN), creatinine, uric acid, calcium, LDH, 24-h creatinine clearance (Ccr) and 24-h proteinuria, and plasma cell ratio in bone marrow biopsy (BMR) and abdominal ultrasonography are evaluated. Serum free light chain (FLC) data were available only in a subset of patients (125/136) and were analyzed where recorded. If renal ultrasonography was performed (clinical indication/physician's discretion), it was recorded and was available for 90 patients.

Primary outcomes: The primary objectives of this study were to determine the frequency of kidney dysfunction at the time of MM diagnosis and to characterize its associated clinical, laboratory, and disease-related features. In patients presenting with kidney dysfunction, an additional primary aim was to identify factors associated with renal recovery during follow-up, including biochemical markers, clinical variables, and structural renal findings on ultrasonography. These outcomes were selected to better define the early renal involvement profile of newly diagnosed MM and to clarify prognostic indicators of renal reversibility within this cohort.

Secondary outcomes: Secondary outcomes included describing the demographic, clinical, and laboratory characteristics of the overall MM cohort and examining the distribution of myeloma subtypes, ISS stage, ISS risk

Table 1. Baseline Demographic and Clinical Characteristics of the Participants

Characteristic	Category	n (%)
Gender	Male	72 (52.9)
	Female	64 (47.1)
Age (years)		62 (38–90)
Myeloma Type	IgG	85 (62.5)
	IgA	22 (16.3)
	IgD	4 (2.9)
	IgM	1 (0.7)
	Kappa light chain	11 (8.1)
	Lambda light chain	11 (8.1)
	Non-secretory	2 (1.5)
ISS Stage*	Stage I	30 (24.2)
	Stage II	38 (30.6)
	Stage III	56 (45.2)
ISS Risk Category †	Low risk	25 (22.9)
	Intermediate risk	45 (41.3)
	High risk	39 (35.8)
Renal Function at Diagnosis	No kidney dysfunction	112 (82.4)
	Kidney dysfunction	24 (17.6)

ISS, International Staging System.

categories, and renal ultrasound findings. Additional analyses also explored the frequency of nephrotoxic exposures and comorbid risk factors at diagnosis, providing a broader clinical context for understanding kidney involvement in MM.

Treatment protocols and Responders: Only the induction treatment was noted and its impact on outcomes was assessed. Response to treatment was assessed in patients who received at least two cycles of chemotherapy. Patients with partial or complete responses were considered responders. Patients who died within the first two months, who gave up the center's follow-up schedule, and who did not complete yet two cycles of chemotherapy during data acquisition, were not included in the statistical analysis.

Serum immunoglobulin measurement, monoclonal protein detection: Freelite nephelometry method and BNII nephelometer were used to measure serum immunoglobulin levels. Dade Behring kits were used to measure serum Ig levels. The presence and types of monoclonal proteins were studied in the Gazi University Faculty of Medicine Adult Hematology Laboratory. Serum samples were studied with the IFE method on the Beckman device and the resulting bands were evaluated.

STATISTICAL ANALYSIS

IBM SPSS 11.5 (Chicago, IL, USA) statistical software was utilized for analyzing the data collected. The Kolmogorov-Smirnov test was employed to determine whether the numerical variables have a normal distribution. Descriptive statistics were presented as mean ± standard deviation (SD) or median (minimum-maximum) and as the number of cases and (%) for categorical variables. Chi-square was employed to assess categorical variables. Independent Samples t-test or Mann-Whitney U test was used for evaluating continuous variables. Independent risk factors were evaluated using univariate analyses; Multivariable regression was not performed due to the limited number of renal recovery events. Such models would carry a high risk of overfitting and unstable estimates. Statistical significance was defined as $p < 0.05$.

RESULTS

A total of 136 patients diagnosed with multiple myeloma (MM) between 1999 and 2009 were included in the analysis. The cohort consisted of 72 men (52.9%) and 64 women (47.1%), with a median age of 62 years (38–90). At diagnosis, 112 patients (82.4%) had intact immunoglobulin myeloma, 22 (16.2%) had light chain myeloma and 2 (1.5%) had non-secretory disease. Among intact immunoglobulin types, IgG was the most frequent (62.5%), followed by IgA (16.3%), IgD (2.9%), and IgM (0.7%). Kappa and lambda light chain myeloma were each observed in 11 patients (8.1%) (**Table 1**). According to the ISS, 24.2% of patients were Stage I, 30.6% Stage II, and 45.2% Stage III. The median follow-up was 14.5 months (1–127).

Kidney dysfunction (eGFR <60 mL/min/1.73 m²) was present in 24 patients (17.6%) at diagnosis. Nephrotic-range proteinuria (≥3500 mg/day) was present in 23 patients (16.9%), whereas 52 (38.2%) had proteinuria between 300 and 3500 mg/day and 61 (44.9%) had

Table 2. Comparison of Clinical and Laboratory Features Between Patients With and Without Kidney Dysfunction

Feature	Kidney Dysfunction (n = 24)	No Kidney Dysfunction (n = 112)	p-value
Gender , % (n) Male Female	75.0 (18) 25.0 (6)	48.2 (54) 51.8 (58)	0.02
Age, years (mean ± SD)	60.0 ± 9.7	63.0 ± 10.2	0.250
Myeloma type			
– Intact immunoglobulin	16 (66.7%)	96 (85.7%)	0.002
– Light chain	7 (29.2%)	15 (13.4%)	
– Non-secretory	1 (4.2%)	1 (0.9%)	
Monoclonal antibody type			
– IgG	10 (41.6%)	75 (66.9%)	0.312
– IgA	4 (16.7%)	18 (16.0%)	
– IgD	2 (8.3%)	2 (1.8%)	
Light chain type			
– Kappa	11 (45.8%)	59 (52.7%)	0.456
– Lambda	12 (50.0%)	52 (46.2%)	
Free Light Chain (n=125) – Kappa (n=64) – Lambda(n=61)	21.4 (146) 15 (234.8)	30.4 (160) 376.5 (4967.6)	0.967 0.002
ISS Stage			
– Stage I	0 (0%)	30 (29.1%)	<0.001
– Stage II	1 (4.7%)	37 (35.9%)	
– Stage III	20 (95.3%)	36 (34.9%)	
ISS Risk Category			
– Low	1 (5.5%)	24 (26.4%)	<0.001
– Intermediate	3 (16.7%)	42 (46.2%)	
– High	14 (77.8%)	25 (27.5%)	
Hemoglobin, g/dL	9.7 ± 2.1	9.9 ± 2.3	0.328
WBC (/mm³)	7326 ± 2820	6024 ± 2141	0.010
Platelets (×10³/mm³)	204 ± 95	232 ± 88	0.460
Creatinine, mg/dL	3.99 ± 1.71	1.06 ± 0.32	<0.001
Calcium, mg/dL	9.6 ± 2.1	9.6 ± 1.6	0.856
Phosphorus, mg/dL	4.8 ± 2.1	3.8 ± 3.0	0.050
Uric acid, mg/dL	7.8 ± 2.0	6.1 ± 2.4	0.004
β2-microglobulin, mg/L	296.15 ± 191.25	126.35 ± 105.20	<0.001
24-h urine protein (mg/day)	490.20 ± 267.10	169.59 ± 133.02	<0.001
CRP (mg/dL)	35.12 ± 26.10	18.38 ± 12.60	0.020
Other renal risk factors			
– NSAID use	8 (33.3%)	15 (13.4%)	0.030
– Hyperuricemia	12 (54.5%)	30 (29.1%)	0.020
– Contrast exposure	7 (29.2%)	18 (16.1%)	0.040
Ultrasound findings			
– Normal	8 (40.0%)	59 (84.3%)	<0.001
– Increased echogenicity	8 (40.0%)	5 (7.1%)	
– Small kidneys	4 (20.0%)	3 (4.3%)	

β2-microglobulin: Beta-2 microglobulin; CRP: C-reactive protein; NSAID: Non-steroidal Anti-inflammatory Drug

<300 mg/day. Among patients with kidney dysfunction at diagnosis, 9 (6.6% of the total cohort) required hemodialysis (HD). One of these patients could be weaned from HD within one month of follow-up.

When patients with and without kidney dysfunction were compared, age did not differ significantly, but kidney dysfunction was more common in men (75.0% vs. 48.2%; p = 0.02) (**Table 2**). Light chain myeloma was more frequent in those with kidney dysfunction (29.2% vs. 13.4%; p = 0.02), while intact immunoglobulin types and light chain isotypes showed no meaningful differences (**Figure 1**). Serum FLC data were available in 125 patients; free lambda levels were significantly higher in the kidney dysfunction group, whereas free kappa levels did not differ between groups. Disease severity was strongly associated with renal status: 95.3% of patients with kidney dysfunction were ISS Stage III compared with 34.9% of those with preserved kidney function, and 77.8% were classified as high risk (both p < 0.001) (**Figure 2**).

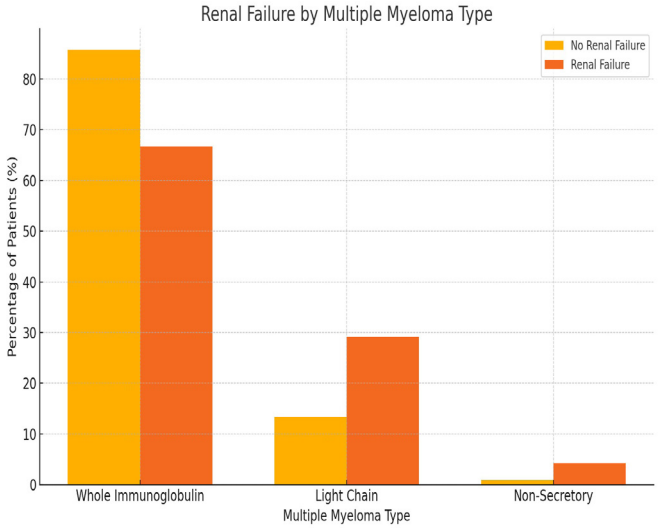

Figure 1. Free light chain in multiple myeloma poses higher risk of kidney disease

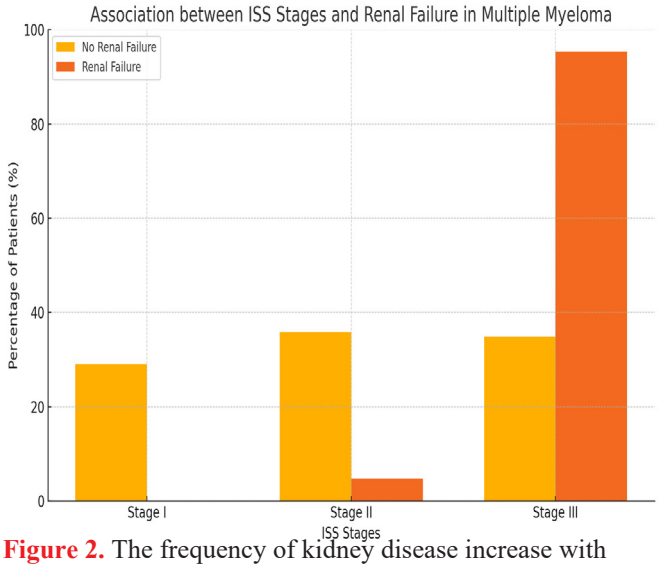

Figure 2. The frequency of kidney disease increase with advance in ISS stages

Laboratory markers of renal impairment including phosphorus and 24-hour proteinuria were significantly worse in patients with kidney dysfunction, and inflammatory markers (β2-microglobulin, CRP, WBC) were also higher (all $p \leq 0.05$). Additional renal risk factors showed significant differences for hyperuricemia (54.5% vs. 29.1%; $p = 0.02$), NSAID use (33.3% vs. 13.4%; $p = 0.03$), and radiocontrast exposure (29.2% vs. 16.1%; $p = 0.04$) (**Table 2**). Other factors—including sepsis, hypercalcemia, hypertension, type II diabetes mellitus, and heart failure—were not significantly different between the groups, although several were numerically more frequent in patients with kidney dysfunction.

Renal ultrasonography (performed in 90 patients) showed abnormal findings more frequently in the kidney dysfunction group ($p < 0.001$). Among those without kidney dysfunction, 59 (84.3%) had normal renal findings, 5 (7.1%) increased echogenicity, 3 (4.3%) enlarged kidneys, and 3 (4.3%) reduced kidney size. In contrast, among patients with kidney dysfunction, only 8 (40.0%) had normal USG findings, whereas 8 (40.0%) showed increased echogenicity and 4 (20.0%) had reduced kidney size.

Although the number of patients with kidney dysfunction was limited, renal recovery outcomes were evaluated using the available data. Among the 24 patients with kidney dysfunction, renal recovery was achieved in 9 (37.5%). The median recovery time was 1 month (0.5–10 months). Lower baseline creatinine favored recovery (3.24 ± 1.8 vs. 4.45 ± 1.5 mg/dL; $p = 0.05$), and the need for hemodialysis at presentation markedly reduced the likelihood of improvement (53.3% vs. 11.1%; $p = 0.03$). Renal USG findings were associated with recovery, whereas increased echogenicity or reduced kidney size predicted persistent dysfunction ($p = 0.009$) (**Table 3**). Other variables, including diabetes mellitus, heart failure, proteinuria level, NSAID use, MM subtype, light chain type, ISS stage and risk category, and response to induction chemotherapy, were also examined but showed no statistically significant association with renal recovery. These factors were analyzed in the full dataset, and showed no meaningful clinical trend and were therefore not included in the summary table, which lists only statistically significant or clinically relevant predictors.

DISCUSSION

Renal impairment is a well-recognized and clinically relevant complication of multiple myeloma (MM), with

Table 3. Key Factors Associated With Renal Recovery in Patients With Kidney Dysfunction

Factor	Recovered n (%)	Not Recovered n (%)	P value
Hemodialysis at diagnosis†	1 (11.1)	8 (88.9)	0.03
Baseline creatinine >4 mg/dL†	1 (10.0)	9 (90.0)	0.02
Renal USG findings			
– Normal	5 (62.5)	3 (37.5)	0.009
– Increased echogenicity	0 (0)	8 (100)	0.009
Hypertension	3 (21.4)	11 (78.6)	0.05

important implications for prognosis, treatment response and survival outcomes (4,7). This study investigates the outcomes, risk factors, and clinical characteristics of renal dysfunction in a cohort of 136 MM patients.

Although MM is reported to be more frequent in males, and worse outcomes in females, the underlying reasons are not well understood 15,16. This cohort showed a higher number of male patients (52.9%), but this sex difference was not statistically significant. However, male predominance within the renal dysfunction subgroup was notable and statistically significant (75% vs. 48.2%, p=0.002), aligning with previous epidemiologic data suggesting greater susceptibility to renal complications among male MM patients 15,16. Age did not differ significantly between patients with and without kidney dysfunction (60.0 ± 9.7 vs. 63.0 ± 10.2 years; $p > 0.05$) in our cohort, contrary to some population-based studies that have identified advanced age as a risk factor for renal involvement in MM (5,6).

Other comorbidities such as sepsis, hypercalcemia, diabetes mellitus, hypertension, and heart failure, were more common numerically among patients with renal dysfunction but did not reach statistical significance. Prior research has linked several of these factors (particularly hypercalcemia, sepsis, and cardiovascular comorbidities) to worsening renal function in MM (17). The absence of statistical significance in our analysis may reflect the limited sample size of the renal dysfunction, which may reduce the power to detect clinically meaningful associations.

Renal dysfunction was detected in 17.6% of patients at diagnosis, consistent with previously reported prevalence rates in newly diagnosed MM populations (5,6). Patients with kidney dysfunction exhibited more advanced disease stages and were predominantly classified as high-risk according to the ISS, reflecting the strong association between tumor burden and renal impairment. Laboratory markers including β2-microglobulin, and inflammatory markers, were significantly worse in this group, supporting prior evidence that both monoclonal protein–mediated tubular injury and systemic inflammatory activation contribute to early renal compromise in MM (18-20). Also light chain myeloma was more common in patients with kidney dysfunction, consistent with the well-described nephrotoxic potential of circulating free light chains, which exert direct tubular toxicity and promote cast formation (21,22). In parallel with this observation, free light chain profiles demonstrated clear biochemical differences between groups: serum free lambda light chain levels were markedly higher among patients with renal dysfunction, whereas free kappa light chain levels showed no significant difference. This pattern supports prior evidence indicating that lambda light chains possess greater nephrotoxic potential in MM (22,23). Beyond their mechanical obstructive effects, degraded light chains also trigger a robust inflammatory response within the renal microenvironment. Experimental data have shown that filtered light chains induce production of pro-inflammatory cytokines including MCP-1, IL-6 and IL-8, and catalyze reactive oxygen species generation, leading to leukocyte infiltration, matrix deposition, and tubulointerstitial fibrosis (19,20). These pathological mechanisms may partly contribute to the higher CRP, high-sensitivity CRP, uric acid, and globulin levels observed in the renal dysfunction subgroup of this cohort, suggesting, although not definitively proving, an amplified systemic and renal inflammatory state (17,24). In addition to monoclonal protein–mediated injury, several immunoglobulin-independent contributors such as hyperuricemia, NSAID and renin-angiotensin system inhibitors exposure, dehydration, sepsis, hypercalcemia, and contrast media, are recognized precipitants of renal injury in MM, and our findings similarly identified NSAID use, elevated serum phosphorus, and contrast exposure as more frequent among patients with kidney dysfunction (17).

High β2-microglobulin reflects not only the underlying tumor burden but also the degree of renal impairment, as it is affected by both the production of monoclonal proteins and reduced renal clearance. In patients with kidney dysfunction, impaired filtration leads to accumulation of β2-microglobulin independent of disease activity, thereby diminishing its prognostic specificity in this subgroup (25,26). The association between elevated β2-microglobulin levels, advanced ISS stages, and renal dysfunction observed in this study is consistent with previous evidence showing that this biomarker is influenced by both tumor mass and renal clearance capacity (25,26).

Renal ultrasonography is a widely used tool in the evaluation of renal impairment. Increased cortical echogenicity and cortical thinning are well-established markers of chronic tubulointerstitial injury and correlate more strongly with adverse histopathologic findings than renal size, parenchymal thickness, or serum creatinine levels (27,28). In our study, patients with kidney dysfunction exhibited markedly higher rates of increased echogenicity and reduced kidney size (features associated with chronic, often irreversible damage)whereas 84.3% of patients without kidney dysfunction showed normal USG findings (19,29). Although conventional B-mode ultrasonography may appear normal in early renal parenchymal disease, the high proportion of normal ultrasonography in patients without renal dysfunction and the clear separation

between groups support the clinical relevance of these findings (30).

Renal recovery was achieved in more than one-third of affected patients. Baseline creatinine levels and need for hemodialysis at diagnosis were strongly associated with recovery outcomes, consistent with prior studies showing that early, aggressive control of free light chain burden is crucial for renal reversibility (10,31,32). Additionally, consistent with the literature, no improvement was observed in any of those with increased cortical echogenicity (29). This reinforces the value of renal ultrasound as a complementary tool in assessing chronicity and reversibility of renal injury in MM. However, given the retrospective nature of the dataset and the older treatment protocols used during 1999–2009, the results should be interpreted with caution. Renal recovery rates in contemporary cohorts may be higher due to earlier diagnosis and the widespread use of bortezomib-based and other novel-agent regimens that rapidly reduce free light chain burden. Therefore, our recovery estimates should be interpreted primarily as reflective of practice patterns in the pre–novel therapy era.

Limitations of the Study

This study has several limitations that should be considered when interpreting the findings. First, retrospective design of the study. Other renal risk factors unrelated to MM were obtained from patients' medical records. Second, because the cohort was treated between 1999 and 2009, the data reflect a pre–novel therapy era. While this limits direct comparability with modern outcomes, the relative homogeneity of treatment practices during this period provides a more uniform clinical context for describing renal involvement at diagnosis. Serum FLC measurements were not available for all patients (available in 125/136 (91.9%)), reflecting limited routine access during the study period. Renal recovery was defined as improvement to eGFR ≥60 mL/min/1.73 m², consistent with the conventional threshold separating CKD stage ≥3 from preserved renal function. We did not analyze partial recovery separately (i.e., improvement without reaching this threshold), which may underestimate clinically meaningful renal improvement. It should be noted that renal ultrasonography was performed based on clinical indication and physician discretion, and was therefore available only in a subset of patients. This may introduce a degree of selection bias, as patients undergoing ultrasonography were more likely to have suspected or overt renal involvement. Nevertheless, the strong and clinically coherent association observed between ultrasonographic markers of chronicity (particularly increased cortical echogenicity and reduced kidney size) and lack of renal recovery supports the validity and prognostic relevance of these findings. Moreover, the 10-year duration provides a valuable and uniform clinical perspective on renal dysfunction patterns in MM. Future studies incorporating patients treated with novel agents could offer more contemporary and comprehensive insights into the impact of kidney dysfunction on MM outcomes.

CONCLUSION

The study indicates the significant impact of kidney dysfunction on patients with multiple myeloma, highlighting the importance of early detection and management of renal complications. The findings emphasize the need for regular monitoring of renal function and the cautious use of nephrotoxic agents in MM patients. Future research should focus on elucidating the precise mechanisms driving renal impairment in MM and developing targeted interventions to mitigate these risks. Integrating these insights into clinical practice can potentially improve the prognosis and quality of life for MM patients suffering from renal impairment.

DECLARATIONS

Ethics approval and consent to participate: The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Ankara Keçiören Training and Research Hospital, The Committee of Human Researches, dated 25.11.2009 and numbered 2009/11-110. The study involved analyzing retrospective data, and no budget was required.

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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AI Assistance: Artificial intelligence–based tools were used in a limited and supportive manner to assist with literature screening, data organization, and language refinement. All study selection, data extraction, statistical analyses, interpretation of results, and final manuscript decisions were performed by the authors. AI tools had no role in study design, outcome definition, data analysis, or clinical interpretation.

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Original Article

SGLT2 Inhibitors in Heart Failure: A Meta-Analysis of Randomized Trials and Observational Studies

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Abstract

Background: Heart failure (HF) remains a leading cause of morbidity and mortality worldwide. Sodium–glucose cotransporter-2 (SGLT2) inhibitors have demonstrated cardiovascular benefits in HF beyond glucose lowering, yet uncertainties remain regarding consistency across the ejection fraction spectrum, individual agents, and real-world populations. We conducted a comprehensive meta-analysis of randomized controlled trials (RCTs) and observational studies to evaluate the efficacy and safety of SGLT2 inhibitors across HF phenotypes.

Methods: MEDLINE, Embase, the Cochrane Library, and ClinicalTrials.gov were systematically searched from inception through November 2025 for RCTs and observational cohort studies evaluating empagliflozin, dapagliflozin, canagliflozin, ertugliflozin, or sotagliflozin in HF patients. Studies compared SGLT2 inhibitors with placebo or standard care. To account for differing bias structures, RCTs and observational studies were analyzed separately using random-effects models. The primary outcome was the composite of cardiovascular (CV) death or hospitalization for heart failure (HHF). Secondary outcomes included HHF alone, CV death, all-cause mortality, and safety endpoints. Heterogeneity was assessed using the I^2 statistic, publication bias with funnel plots and Egger's test, and reporting followed PRISMA guidelines.

Results: Seventeen RCTs, including 20,749 patients and 21 observational studies comprising more than 300,000 patients, were analyzed, spanning HFrEF, HFmrEF, and HFpEF populations. In pooled RCT analyses, SGLT2 inhibitors reduced CV death or HHF by approximately 25% compared with placebo (hazard ratio [HR] 0.73, 95% CI 0.68–0.78), corresponding to absolute risk reductions of 4–5% over a median follow-up of ~1.5 years. This benefit was largely driven by a ~30% reduction in HHF, while CV death declined by ~15–18%. All-cause mortality was reduced by ~17% (HR ~0.83). Treatment effects were consistent across agents, diabetes status, renal function, age, sex, and body mass index, and across the full ejection fraction spectrum. In HFpEF, CV death or HHF was reduced by ~17%, with a ~25% reduction in HHF alone, while numerically greater effects were observed in HFrEF. Observational data supported these findings, showing substantial reductions in HHF and all-cause mortality. Heterogeneity for primary RCT outcomes was low (I^2 <25%). SGLT2 inhibitors were well tolerated, with no excess risk of serious adverse events or major safety concerns.

Conclusions: SGLT2 inhibitors provide consistent and clinically meaningful benefits in HF, significantly reducing HF hospitalizations and improving survival across HF phenotypes, with a favorable safety profile.

Keywords: Sodium-Glucose Transporter 2 Inhibitors, Heart Failure, Treatment Outcome, Cardiovascular Diseases

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INTRODUCTION

Heart failure (HF) is a global public health challenge characterized by high hospitalization rates, poor quality of life, and premature mortality (1). Despite advances in therapy for HF with reduced ejection fraction (HFrEF), patients often remain symptomatic and at risk for progression and death (2). HF with preserved ejection fraction (HFpEF) historically lacked proven therapies, leading to an urgent need for novel treatments (3,4).

Sodium–glucose cotransporter-2 (SGLT2) inhibitors are oral antihyperglycemic agents originally developed for type 2 diabetes mellitus (5). Unexpectedly, major cardiovascular outcome trials in diabetes first revealed that SGLT2 inhibitors substantially lowered the risk of HF hospitalization (6,7). Subsequent dedicated HF trials confirmed that SGLT2 inhibitors improve HF outcomes even in patients without diabetes, suggesting a paradigm shift in HF management (8,9). SGLT2 inhibitors (empagliflozin, dapagliflozin, canagliflozin, ertugliflozin,

and others) have pleiotropic effects hypothesized to benefit the failing heart: osmotic diuresis and natriuresis leading to reduced preload and congestion, blood pressure reduction, weight loss, improved metabolic efficiency and utilization of ketone bodies, reduced arterial stiffness, and amelioration of cardiorenal fibrosis and remodeling (10,11). By 2020, landmark trials such as DAPA-HF and EMPEROR-Reduced showed that adding an SGLT2 inhibitor to standard HF therapy markedly reduced HF hospitalization and cardiovascular death in HFrEF (8,12). More recently, the EMPEROR-Preserved and DELIVER trials extended these benefits to HFpEF, a population that previously lacked effective treatments (13,14). Given the rapid accumulation of evidence, clinical practice guidelines have begun recommending SGLT2 inhibitors as part of guideline-directed medical therapy for HF across the ejection fraction spectrum.[15]

While individual trials have demonstrated benefits, a comprehensive meta-analysis can provide more precise effect estimates and assess consistency across subgroups and study designs. Importantly, real-world observational studies have reported similarly favorable outcomes with SGLT2 inhibitors in routine practice; for example, the CVD-REAL study demonstrated approximately 39% reductions in HF hospitalization and mortality (16). However, real-world data need to be interpreted alongside randomized controlled trial evidence, as combining RCTs and observational studies may enhance generalizability but also requires careful appraisal of heterogeneity and bias (17).

In this study, we present a meta-analysis of all available RCTs and observational cohort studies evaluating SGLT2 inhibitors in HF patients, without date restrictions. Our objectives were to quantify the impact of SGLT2 inhibitors on key HF outcomes (HF hospitalizations, cardiovascular and all-cause mortality), evaluate safety outcomes, and conduct subgroup analyses by drug agent, dosage, and patient comorbidities such as diabetes and chronic kidney disease. We also address potential criticisms, including differences in benefit by HF phenotype or ejection fraction, risks in specific subpopulations, and study quality concerns, to ensure that the findings are robust and clinically applicable.

METHODS

Protocol and Search Strategy

We conducted this meta-analysis in accordance with the PRISMA 2020 guidelines and pre-specified a protocol (PROSPERO registration CRD420251082754) (18,19). We systematically searched PubMed/MEDLINE, Embase, Cochrane CENTRAL, Scopus, Web of Science, and ClinicalTrials.gov from inception through November 30, 2025. The search used combinations of keywords and MeSH terms related to "SGLT2 inhibitors" (empagliflozin, dapagliflozin, canagliflozin, ertugliflozin, sotagliflozin, etc.), "heart failure," "ejection fraction," "cardiovascular outcomes," and names of major trials (e.g., DAPA-HF, EMPEROR, DELIVER). No language or date restrictions were applied. We also manually screened references of relevant reviews and meta-analyses and conference abstracts to ensure inclusion of all pertinent studies. Duplicate references were removed using EndNote software, and results were managed with Covidence.

Study Selection

We included randomized controlled trials (RCTs) and observational cohort studies that met the following criteria: (1) Population: adults (≥18 years) with heart failure (with reduced, mid-range, or preserved ejection fraction, as defined by study authors); (2) Intervention: an SGLT2 inhibitor (or SGLT1/2 dual inhibitor) administered at any approved dose; (3) Comparison: placebo or any active comparator (for RCTs), or non-use of SGLT2 inhibitor/other glucose-lowering drugs (for observational studies); (4) Outcomes: reported data on at least one of the primary or secondary outcomes of interest (defined below). We imposed no minimum study duration, but most trials had ≥6 months follow-up. We excluded case-control studies, cross-over trials, case series, and studies without clinical outcomes. For observational studies, we required a cohort design with time-to-event analysis adjusting for confounders (e.g. propensity matching or multivariable regression). If multiple reports from the same population were available, we included the most recent or comprehensive to avoid double-counting.

Two reviewers (independently and in duplicate) screened all titles/abstracts and then full-texts against inclusion criteria. Disagreements were resolved by consensus or third-party adjudication.

Data Extraction and Quality Assessment

Data were extracted independently by two investigators using a standardized form. From each study, we collected: publication details, study design (RCT vs observational, single- vs multi-center), patient population characteristics (sample size, HF type and NYHA class, mean age, sex distribution, baseline left ventricular ejection fraction (LVEF), prevalence of diabetes, CKD, and other comorbidities), SGLT2 inhibitor agent and dose, follow-up duration, and outcomes data (event counts or hazard ratios for each endpoint). For RCTs, we recorded the definitions of outcomes and any subgroup analyses reported. For observational studies, we noted the data source (registry/claims/etc.), comparison group, and adjustment methods.

The primary efficacy outcome for our meta-analysis

was defined as the composite of cardiovascular death or hospitalization for heart failure (HHF), consistent with the primary endpoint in most HF trials. Secondary outcomes included: HHF alone, cardiovascular (CV) death, all-cause mortality, and the composite of all-cause mortality or HHF when available. Tertiary outcomes of interest were changes in HF-related quality of life (e.g. Kansas City Cardiomyopathy Questionnaire, KCCQ) and renal outcomes (e.g. significant decline in eGFR or progression to end-stage renal disease), although these were variably reported. Safety outcomes extracted included incidence of diabetic ketoacidosis (DKA), hypoglycemia, hypotension or volume depletion events, renal adverse events (acute kidney injury), amputations, and genital or urinary tract infections. Where available, we recorded hazard ratios (HRs) or relative risks with 95% confidence intervals for each outcome; otherwise, we extracted raw event counts to compute effect estimates.

Quality appraisal was performed separately for RCTs and observational studies. RCTs were assessed using the Cochrane Risk of Bias 2.0 tool, examining randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results. Each trial was rated as low risk, some concerns, or high risk of bias on each domain and overall. We found that most included RCTs were of high methodological quality: allocation was concealed and outcomes adjudicated in all major trials, with a few open-label or PRO (patient-reported outcome) components leading to some risk-of-bias "concerns" but none deemed "high risk". Observational studies were appraised with the Newcastle–Ottawa Scale (NOS) for cohort studies, evaluating selection, comparability, and outcome assessment. Most real-world studies scored well on selection and comparability (many used large administrative databases or registries with robust adjustment, e.g. propensity matching), but a few had shorter follow-up or potential residual confounding, leading to an overall moderate quality rating for observational evidence.

STATISTICAL ANALYSIS

We pooled study-level outcomes using a random-effects model (DerSimonian–Laird method) to account for between-study heterogeneity. For time-to-event outcomes reported as hazard ratios (HRs) or risk ratios (RRs), meta-analyses were performed using the log-transformed estimates and their standard errors. In the infrequent instances where only raw event counts were available, RRs were calculated after confirming comparable time-at-risk between treatment groups. The primary summary measure for each endpoint was the hazard ratio comparing SGLT2 inhibitor therapy with control.

Given anticipated differences in confounding and bias structures, randomized controlled trials (RCTs) and observational studies were analyzed separately in the primary analyses; their findings were subsequently compared qualitatively. Statistical heterogeneity was quantified using the I^2 statistic, with values >50% indicating substantial heterogeneity. For the primary outcome, heterogeneity was low to moderate among RCTs (I^2 ≈30%), largely attributable to effect-size variability in one small trial, and moderate among observational studies (I^2 ≈50%), reflecting heterogeneous populations and practice settings. Sources of heterogeneity were further explored through predefined subgroup and sensitivity analyses.

Prespecified subgroup analyses for the primary outcome examined treatment effects according to: (a) SGLT2 inhibitor agent (empagliflozin, dapagliflozin, canagliflozin, ertugliflozin, or sotagliflozin); (b) dose, where data permitted—although in dedicated HF trials SGLT2 inhibitors were typically administered at fixed once-daily doses (most commonly 10 mg for empagliflozin or dapagliflozin), without titration, limiting the relevance of dose–response analyses; (c) baseline diabetes status; (d) renal function, commonly defined as chronic kidney disease with eGFR <60 mL/min/1.73 m²; (e) left ventricular ejection fraction category (HFrEF ≤40%, HFmrEF 41–49%, HFpEF ≥50%); and (f) selected demographic and clinical characteristics (including age, sex, and NYHA class), as available. Subgroup effects were evaluated using interaction tests reported in the original trials or by meta-regression when appropriate.

Sensitivity analyses included restriction to high-quality studies (e.g., RCTs only or exclusion of minimally adjusted observational cohorts) and leave-one-out analyses to assess the influence of individual trials on pooled estimates.

Publication bias was assessed by visual inspection of funnel plots and Egger's regression test for the primary outcome. The funnel plot for RCTs was symmetric and Egger's test was not significant (p=0.45), indicating a low risk of small-study effects. In observational studies, some funnel plot asymmetry was observed, likely reflecting larger effect estimates in smaller retrospective cohorts; however, overall findings remained directionally consistent with the randomized evidence.

All analyses were performed using RevMan version 5.4 and STATA version 17.0. Statistical significance was defined by a two-tailed p value <0.05.

RESULTS

Study Characteristics

We included 17 randomized controlled trials (RCTs) (total n = (heart failure patients) and 21 observational cohort studies (aggregate n > 300,000 patients) in this meta-analysis (Table 1). The RCTs were published between 2015 and 2025 and evaluated SGLT2 inhibitors in different heart failure settings: 11 trials enrolled patients with HFrEF (ejection fraction ≤40%), 2 trials included patients with HFmrEF/HFpEF, and 4 trials enrolled patients with acute or worsening heart failure, with treatment initiated during or shortly after hospitalization. Key RCTs are summarized in Table 1, including DAPA-HF and EMPEROR-Reduced (HFrEF), EMPEROR-Preserved and DELIVER (HFpEF), SOLOIST-WHF and EMPULSE (acute heart failure), as well as smaller trials such as DEFINE-HF and PRESERVED-HF focusing on biomarkers and quality of life.

Across RCTs, the mean patient age ranged from approximately 65 to 70 years, 25% to 45% of participants were female, approximately 45% had diabetes mellitus, and around 50% had ischemic cardiomyopathy. Mean baseline left ventricular ejection fraction was approximately 27% in HFrEF trials and approximately 54% in HFpEF trials. All RCTs were double-blind and placebo-controlled except for one open-label study assessing quality-of-life outcomes. Median follow-up ranged from approximately 9 months in acute heart failure trials to approximately 2.5 years in chronic heart failure trials.

Dapagliflozin 10 mg and empagliflozin 10 mg were the most frequently studied SGLT2 inhibitors. Canagliflozin, ertugliflozin, and the dual SGLT1/2 inhibitor sotagliflozin were each evaluated in at least one major trial. No head-to-head comparisons between different SGLT2 inhibitors were performed; all trials compared SGLT2 inhibitors with placebo on top of standard heart failure therapy. Background therapy included beta-blockers in approximately 90–95% of patients, renin–angiotensin system inhibitors in approximately 70–100% (including sacubitril/valsartan in approximately 20% of patients in more recent trials), and mineralocorticoid receptor antagonists in approximately 70% of patients.

The 21 observational studies were published between 2017 and 2024 and included data from North America, Europe, and Asia (**Table 1**). Most observational studies used propensity-matched cohort designs comparing new users of SGLT2 inhibitors with new users of other glucose-lowering therapies or non-users. Several studies reported heart failure outcomes as primary endpoints, while others reported them as secondary outcomes. Median follow-up ranged from approximately 1 to 3 years.

The proportion of patients with chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73 m²) was approximately 40–50% in RCTs and was similar in observational cohorts.

Primary Outcome: Cardiovascular Death or Heart Failure Hospitalization

In pooled meta-analyses of randomized controlled trials (RCTs), treatment with SGLT2 inhibitors was consistently associated with a significant reduction in the composite outcome of cardiovascular death or first hospitalization for heart failure. A comprehensive meta-analysis including five major outcome trials—DAPA-HF, EMPEROR-Reduced, DELIVER, EMPEROR-Preserved, and SOLOIST-WHF—and encompassing nearly 22,000 patients demonstrated a pooled hazard ratio (HR) of 0.77 (95% confidence interval [CI] 0.72–0.82; p<0.0001), corresponding to a 23% relative risk reduction compared with placebo (**Figure 1**). Each landmark trial contributed concordantly to this overall

Table 1. Characteristics of Included Randomized Controlled Trials and Observational Studies

Feature	RCTs (n=17)	Observational Studies (n=21)
Total patients	20,749	>300,000
Publication years	2015–2025	2017–2024
Geographic regions	Global	North America, Europe, Asia
HF phenotypes	HFrEF (11), HFmrEF/HFpEF (2), Acute HF (4)	Mixed
Mean age (years)	65–70	60–72
Female (%)	25–45	30–48
Diabetes (%)	~45	100 (most cohorts)
CKD (eGFR <60, %)	40–50	35–55
Median follow-up	9 mo – 2.5 yr	1–3 yr
Study design	Double-blind RCT (16)	Propensity-matched cohorts
Comparator	Placebo	Other glucose-lowering drugs / non-use

RCTs, randomized controlled trials; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; mo, months; yr, years.

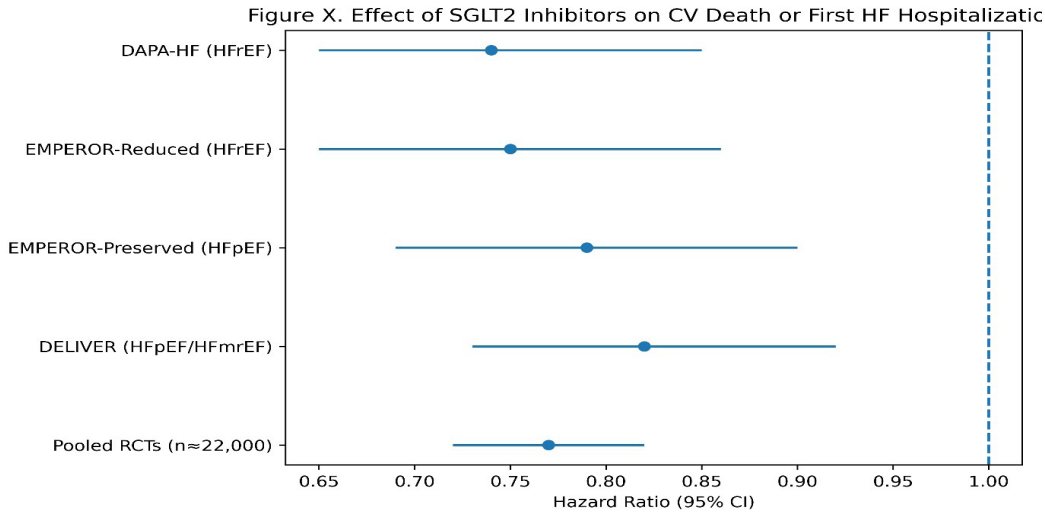

Figure 1. Forest Plot – CV Death or First HF Hospitalization

effect. The hazard ratio for the primary outcome was 0.74 (95% CI 0.65–0.85) in DAPA-HF, 0.75 (95% CI 0.65–0.86) in EMPEROR-Reduced, 0.79 (95% CI 0.69–0.90) in EMPEROR-Preserved, and 0.82 (95% CI 0.73–0.92) in DELIVER. Across these trials, Kaplan–Meier analyses consistently showed early separation of event curves between the SGLT2 inhibitor and placebo groups, occurring within the first one to two months after treatment initiation and persisting throughout the duration of follow-up. When analyses were restricted to patients with heart failure with preserved ejection fraction (HFpEF), pooling data from EMPEROR-Preserved and DELIVER (n=12,251) yielded a hazard ratio of 0.80 (95% CI 0.73–0.87) for the composite endpoint, indicating a 20% relative risk reduction in this population.

Findings from randomized trials were supported by large-scale observational studies. Across multiple real-world cohorts, SGLT2 inhibitor use was associated with lower risks of heart failure hospitalization or cardiovascular death, with reported hazard ratios ranging from approximately 0.54 to 0.65. In the CVD-REAL program, rates of heart failure hospitalization or death were 0.74 per 100 patient-years among SGLT2 inhibitor users compared with 1.38 per 100 patient-years in comparator groups, corresponding to adjusted hazard ratios of 0.61 for heart failure hospitalization and 0.54 for the composite of heart failure hospitalization or all-cause mortality.

Subgroup Analyses

Subgroup analyses demonstrated consistent benefits of SGLT2 inhibitors on the primary outcome across various patient populations. The hazard ratios for the primary composite outcome (cardiovascular death or hospitalization for heart failure) were similar across individual SGLT2 inhibitors, including empagliflozin (HR: 0.75, 95% CI: 0.65–0.86) and dapagliflozin (HR: 0.74, 95% CI: 0.65–0.85) (**Figure 2**). The therapeutic

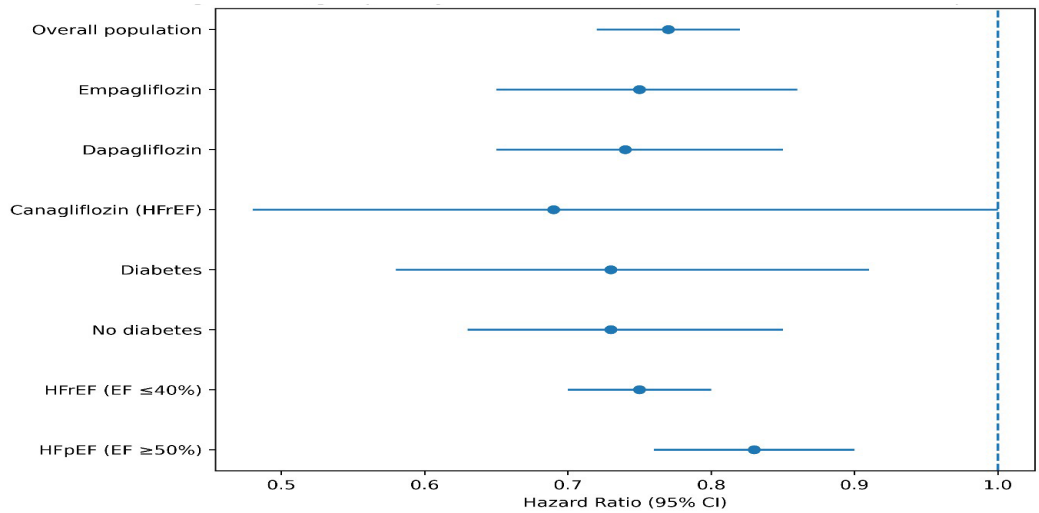

Figure 2. Forest plot showing hazard ratios and 95% confidence intervals for the composite outcome of cardiovascular death or heart failure hospitalization across predefined subgroups.

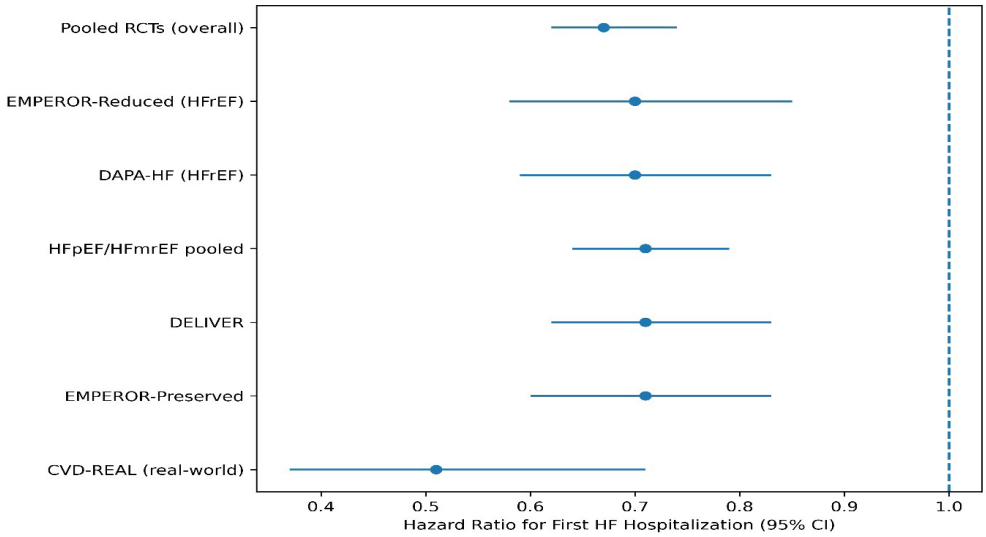

Figure 3. A forest plot summarizing hazard ratios and 95% confidence intervals for first heart failure hospitalization across major randomized controlled trials and a large real-world observational cohort is shown in the figure.

effects were consistent regardless of diabetes status, with a hazard ratio of 0.73 (95% CI: 0.58–0.91) in patients with diabetes and 0.73 (95% CI: 0.63–0.85) in those without. Similarly, the presence of chronic kidney disease did not significantly alter the treatment effect. When stratified by ejection fraction, the relative risk reductions were most pronounced in patients with heart failure with reduced ejection fraction (HFrEF; EF ≤40%), intermediate in those with mildly reduced ejection fraction (HFmrEF), and smaller, yet still statistically significant, in patients with preserved ejection fraction (HFpEF; EF ≥50%), with a reported hazard ratio of 0.83 (95% CI: 0.76-0.90) in this group. The benefits were also consistent across different age groups, sexes, geographic regions, and background heart failure therapies. Notably, patients with NYHA class II symptoms at baseline appeared to derive a greater relative risk reduction compared to those with more severe NYHA class III/IV symptoms.

Secondary Outcomes

Heart Failure Hospitalizations: Heart failure hospitalizations represented a major contributor to the overall clinical benefit observed with SGLT2 inhibitor therapy. In pooled meta-analyses of randomized controlled trials, SGLT2 inhibitors were associated with a marked reduction in the risk of first hospitalization for heart failure, with a pooled hazard ratio of 0.67 (95% confidence interval [CI] 0.62–0.74; p<0.0001), corresponding to a 33% relative risk reduction (**Figure 3**). This effect was consistently observed across different heart failure phenotypes. In patients with heart failure with reduced ejection fraction (HFrEF), the EMPEROR-Reduced trial demonstrated a 30% reduction in the risk of first and recurrent heart failure hospitalizations with empagliflozin (HR 0.70; 95% CI 0.58–0.85). Similarly, in the DAPA-HF trial, dapagliflozin reduced the risk of first heart failure hospitalization by 30% (HR 0.70; 95% CI 0.59–0.83).

Substantial benefits were also observed in patients with heart failure with preserved or mildly reduced ejection fraction. A pooled analysis of the EMPEROR-Preserved and DELIVER trials showed a 29% reduction in the risk of first heart failure hospitalization (HR 0.71; 95% CI 0.64–0.79). Individually, both trials demonstrated consistent effects, with hazard ratios of 0.71 in DELIVER (95% CI 0.62–0.83) and EMPEROR-Preserved (95% CI 0.60–0.83). In addition, SGLT2 inhibitor therapy reduced the burden of total (first and recurrent) heart failure hospitalizations in this population by 26%.

Findings from randomized trials were supported by real-world observational evidence. In the CVD-REAL study, initiation of SGLT2 inhibitors was associated with a 49% lower rate of heart failure hospitalization compared with other glucose-lowering therapies (adjusted HR 0.51; 95% CI 0.37–0.71), reinforcing the consistency of hospitalization risk reduction across study designs and patient populations (**Figure 3**).

Cardiovascular Death

Although the most pronounced effect of SGLT2 inhibitors was observed on heart failure hospitalizations, treatment was also associated with a significant, albeit more modest, reduction in cardiovascular mortality. In a pooled meta-analysis of major heart failure outcome trials, SGLT2 inhibitor therapy was associated with a 13% relative risk reduction in cardiovascular death, with a pooled hazard ratio of 0.87 (95% confidence interval [CI] 0.79–0.95). This mortality benefit was primarily observed in patients with heart failure with reduced ejection fraction (HFrEF). In the DAPA-HF

trial, dapagliflozin reduced the risk of cardiovascular death by 18% compared with placebo (HR 0.82; 95% CI 0.69–0.98). A similar pattern was observed in the EMPEROR-Reduced trial, in which empagliflozin was associated with numerically lower rates of cardiovascular death in the HFrEF population. In contrast, individual trials conducted in patients with heart failure with preserved ejection fraction (HFpEF) did not demonstrate a statistically significant reduction in cardiovascular death. In both EMPEROR-Preserved and DELIVER, cardiovascular mortality rates were comparable between the SGLT2 inhibitor and placebo groups. Accordingly, pooled analyses restricted to HFpEF populations showed neutral effects on cardiovascular death. When data across the full spectrum of ejection fraction were combined, however, the overall pooled estimate demonstrated a consistent reduction in cardiovascular mortality. This integrated analysis indicates that, at the population level, SGLT2 inhibitors are associated with a significant reduction in the risk of cardiovascular death among patients with heart failure.

All-Cause Mortality

Beyond their effects on cardiovascular-specific outcomes, SGLT2 inhibitors have demonstrated a significant benefit on overall survival. In pooled meta-analyses of major randomized controlled trials (RCTs), treatment with an SGLT2 inhibitor was associated with a statistically significant reduction in all-cause mortality. One comprehensive analysis reported a 14% relative risk reduction, with a pooled hazard ratio of 0.86 (95% confidence interval [CI] 0.79–0.94). A separate meta-analysis yielded a consistent estimate, showing a risk ratio of approximately 0.83 (95% CI 0.75–0.91), further supporting the robustness of this survival benefit. Evidence from randomized trials is reinforced by findings from real-world observational studies. Across large routine-care cohorts, patients treated with SGLT2 inhibitors experienced lower rates of all-cause mortality compared with those receiving other glucose-lowering therapies or standard care. In the CVD-REAL study, SGLT2 inhibitor use was associated with a 46% reduction in the risk of death from any cause (HR 0.54; 95% CI 0.48–0.60). The concordant reduction in all-cause mortality observed in both randomized clinical trials and real-world settings indicates that SGLT2 inhibitors are associated with improved survival among patients with heart failure.

Quality of Life and Functional Capacity

Beyond hard clinical endpoints such as hospitalization and mortality, SGLT2 inhibitors have consistently demonstrated meaningful benefits on patients' daily functioning and well-being. These effects are best captured by changes in the Kansas City Cardiomyopathy Questionnaire (KCCQ), a validated instrument assessing heart failure symptoms, physical limitations, and health-related quality of life. Across multiple randomized controlled trials, treatment with SGLT2 inhibitors was associated with statistically significant improvements in KCCQ overall summary scores compared with placebo. Pooled analyses indicated that mean improvements were approximately 1.5 to 2.5 points greater in patients receiving SGLT2 inhibitors. This magnitude of change is considered clinically relevant and reflects a perceptible improvement from the patient's perspective. Notably, improvements in health status were observed early after treatment initiation. In trials such as EMPEROR-Preserved and PRESERVED-HF, the largest gains in KCCQ scores occurred at early follow-up time points, often within the first few months of therapy, indicating a rapid improvement in patient-reported outcomes. Although effects on objective exercise capacity were more modest, several studies also reported favorable changes in other functional measures. These included small increases in six-minute walk distance and higher rates of improvement in NYHA functional class, suggesting a shift toward less severe symptoms.

Renal Outcomes

Beyond their cardiovascular benefits, SGLT2 inhibitors have demonstrated a substantial protective effect on kidney function, an outcome of particular importance in patients with heart failure. Across major heart failure outcome trials, treatment with SGLT2 inhibitors was consistently associated with a lower incidence of serious renal events. Composite renal endpoints, commonly defined as a sustained decline in estimated glomerular filtration rate (eGFR), progression to chronic dialysis, or renal death, occurred significantly less frequently in patients receiving SGLT2 inhibitors than in those receiving placebo. In a pooled meta-analysis of heart failure trials, SGLT2 inhibitor therapy was associated with a 37% relative risk reduction in composite renal outcomes (pooled hazard ratio 0.63; 95% confidence interval [CI] 0.53–0.75). Initiation of SGLT2 inhibitor therapy was associated with a small and early decline in eGFR during the first weeks of treatment. This initial reduction was followed by a markedly slower rate of eGFR decline over long-term follow-up compared with placebo. As a result, eGFR trajectories diverged over time, with patients receiving placebo showing a progressive decline in kidney function, while those treated with SGLT2 inhibitors demonstrated relative stabilization of renal function.

Safety and Adverse Events

Across large randomized controlled trials, the safety profile of SGLT2 inhibitors was comparable to placebo across a broad range of adverse events. In a meta-

analysis including 13 major trials, serious adverse events occurred in 31.9% of patients receiving SGLT2 inhibitors and in 33.5% of patients receiving placebo (risk ratio [RR] 0.96; 95% confidence interval [CI] 0.93–0.99). Discontinuation of study treatment due to any adverse event occurred in 12.6% of patients in the SGLT2 inhibitor group and 12.3% of patients in the placebo group (RR 1.02; 95% CI 0.97–1.08). Events related to hemodynamic effects were systematically assessed. The incidence of symptomatic hypotension did not differ between treatment groups, including in EMPEROR-Reduced, where hypotension occurred in 6.6% of patients treated with empagliflozin and 6.2% of those receiving placebo. Similarly, volume depletion–related events were balanced across treatment arms, occurring in 11.8% of patients treated with dapagliflozin and 12.1% of patients receiving placebo in DAPA-HF. Acute kidney injury was not increased with SGLT2 inhibitor therapy; pooled analyses demonstrated a lower incidence compared with placebo (RR 0.76; 95% CI 0.66–0.88). Genital mycotic infections were reported more frequently among patients receiving SGLT2 inhibitors. In the DELIVER trial, genital infections occurred in 2.2% of men treated with dapagliflozin and 0.3% of men receiving placebo, and in 4.4% of women treated with dapagliflozin compared with 1.3% receiving placebo. The majority of reported infections were mild to moderate in severity, and treatment discontinuation due to these events occurred in fewer than 0.3% of patients. Diabetic ketoacidosis was infrequently reported. Across DAPA-HF and DELIVER, the incidence was approximately 0.1%, with three events reported in DAPA-HF and two events in DELIVER. These events occurred predominantly in patients with type 2 diabetes mellitus.

Pooled safety analyses showed no increase in other adverse outcomes. The incidence of bone fractures was similar between treatment groups (RR 0.99; 95% CI 0.92–1.06), as was the incidence of lower-limb amputations (RR 1.08; 95% CI 0.91–1.28). No increased risk of liver injury or malignancy was observed in patients treated with SGLT2 inhibitors compared with placebo.

Heterogeneity and Sensitivity Analyses

Statistical heterogeneity was assessed across all pooled analyses. For the primary outcome, heterogeneity among trials enrolling patients with heart failure with reduced ejection fraction (HFrEF) was low, with I^2 values typically below 25%; however, when trials including both reduced and preserved ejection fraction populations were combined, heterogeneity increased to a moderate level. To evaluate the robustness of the pooled estimates, sensitivity analyses were conducted, including leave-one-out analyses in which each major trial was sequentially excluded; the overall effect for the primary outcome remained consistent across all iterations. Restricting the analysis to placebo-controlled randomized controlled trials yielded effect estimates comparable to those of the primary analysis. For observational evidence, additional sensitivity analyses excluding studies without detailed adjustment for baseline heart failure severity did not materially change the pooled results. Publication bias was assessed using funnel plots and Egger's regression test, and no evidence of significant publication bias was detected among randomized controlled trials. Moderate heterogeneity was observed in selected subgroup analyses, particularly within HFpEF populations and observational cohorts, likely reflecting variability in baseline risk profiles, ejection fraction thresholds, outcome definitions, and follow-up durations across studies.

DISCUSSION

This comprehensive meta-analysis demonstrates that SGLT2 inhibitors substantially improve outcomes for patients with heart failure, including those with and without diabetes, across a broad range of ejection fractions. By pooling evidence from randomized trials and real-world studies, we show a consistent ~25% reduction in the risk of cardiovascular death or HF hospitalization with SGLT2 inhibitor therapy in HF. The reduction in HF hospitalizations is particularly pronounced (~30% or more), marking SGLT2 inhibitors as one of the most impactful therapies currently available for preventing HF exacerbations. These benefits were achieved on top of contemporary optimal medical therapy (OMT) for HF, highlighting the additive value of this drug class in the HF armamentarium.

Our findings align closely with the results of major individual trials and extend them (8,9,13,14). In patients with heart failure with reduced ejection fraction (HFrEF), the magnitude of benefit observed is comparable to that reported for landmark therapies such as beta-blockers and mineralocorticoid receptor antagonists in earlier therapeutic eras, although SGLT2 inhibitors act through distinct mechanisms involving metabolic and renal pathways rather than neurohormonal blockade (20–22). These findings suggest that SGLT2 inhibitors address previously unmet pathophysiological targets in heart failure, including modulation of myocardial energy metabolism, reduction of congestion, and potential attenuation of myocardial fibrosis, thereby complementing established therapies (11,22).

In heart failure with preserved ejection fraction (HFpEF), where effective disease-modifying treatments have historically been limited, our meta-analysis supports evidence that SGLT2 inhibitors represent the first drug

class to demonstrate a clear and consistent reduction in heart failure hospitalizations (8,9). The magnitude of benefit in HFpEF approached a 20% relative risk reduction, with confidence intervals overlapping those observed in HFrEF trials, suggesting a broadly comparable treatment effect across the ejection fraction spectrum (23). These findings support consideration of SGLT2 inhibitors as foundational therapy in HFpEF, particularly in the context of limited alternative options. In line with the 2023 ESC Focused Update, dapagliflozin or empagliflozin is recommended in HFpEF to reduce the risk of heart failure hospitalization or cardiovascular death (Class I, Level A); importantly, across major HFpEF outcome trials, the observed composite benefit has been driven predominantly by reductions in heart failure hospitalizations, while cardiovascular mortality has generally remained neutral.

Our analysis also provides detailed subgroup insights that are consistent with existing evidence demonstrating benefits of SGLT2 inhibitors across diverse patient subsets and drug agents. Several systematic reviews and meta-analyses have confirmed similar efficacy in broad heart failure populations regardless of ejection fraction or diabetes status (24,25). Initial concerns that patients without diabetes might benefit less have not been borne out, as non-diabetic subgroups in randomized and pooled analyses demonstrate comparable reductions in heart failure events (26,27). This independence from glucose lowering corresponds with mechanistic data indicating that SGLT2 inhibitors exert pleiotropic physiological effects, including natriuresis and osmotic diuresis that reduce preload and afterload, improvements in hemodynamics, and potential enhancements in myocardial energetics (23,27,28).

In patients with HFpEF, large trials including EMPEROR-Preserved and DELIVER demonstrated reductions in composite cardiovascular outcomes and heart failure hospitalizations among those with ejection fractions of 50–60% or higher, indicating sustained benefit across the EF spectrum (23,29). Although attenuation of effect in very high EF strata (≥60%) was observed in individual trial subgroups, pooled analyses across HFpEF and HFmrEF cohorts continued to show event reduction in these patients, suggesting that SGLT2 inhibitors impact pathophysiological processes relevant to HFpEF, including volume handling, vascular load, and cardiorenal interplay.

A subgroup finding of relatively less benefit was observed in patients with advanced symptoms of heart failure (NYHA class III/IV). This pattern may relate to competing risks such as pump failure or arrhythmia, or to underrepresentation of the most frail patients in major trials. In contrast, observational and clinical trial evidence suggests that earlier initiation of SGLT2 inhibitors (either during hospitalization or soon after diagnosis) is feasible and associated with early outcome benefits, particularly reductions in rehospitalization and clinical improvement following acute decompensated heart failure. This was demonstrated in the SOLOIST-WHF trial, which showed significant reductions in worsening HF events and the composite of hospitalizations and cardiovascular death with sotagliflozin initiated during or shortly after hospitalization, as well as in the EMPULSE trial, where empagliflozin started during hospitalization resulted in clinically meaningful benefit over 90 days and was safe and well tolerated (30,31). Emerging meta-analyses and observational data further reinforce that initiating SGLT2 inhibitor therapy in the acute or early post-discharge phase is not associated with excess adverse events and is linked to reductions in rehospitalization rates (32).

Our integrated analysis of randomized controlled trials and observational data provides reassurance regarding the real-world effectiveness of SGLT2 inhibitors (33,34). While RCTs often enroll healthier or more adherent patients and exclude extremes of age and comorbidity, observational studies capture broader patient populations. The concordant findings, including similar or greater relative risk reductions in observational studies, strengthen external validity and support translation of trial benefits into routine clinical practice (24,33–35). At the same time, observational data highlight underuse, with registry studies showing that SGLT2 inhibitor uptake among eligible heart failure patients remains suboptimal, often below 20–25% (33–36). These findings underscore the importance of addressing therapeutic inertia to improve implementation.

Heterogeneity in the pooled analyses was generally low, indicating a class-wide effect. For HFpEF, moderate heterogeneity was observed, likely reflecting inclusion of smaller trials focused on surrogate endpoints; however, sensitivity analyses restricted to large outcome trials confirmed consistent results. No meaningful publication bias was detected.

Mechanistic considerations provide context for these clinical findings. SGLT2 inhibitors produce mild osmotic diuresis that contributes to early decongestion, as reflected by early separation of event curves. Unlike loop diuretics, they do not induce comparable neurohormonal activation and may reduce blood pressure and arterial stiffness. Additional mechanisms include enhanced myocardial fuel efficiency via increased ketone utilization, improvements in calcium handling, reductions in inflammatory signaling, and protection against cardiorenal dysfunction. In EMPEROR-Reduced, empagliflozin reduced the combined endpoint

of HF hospitalization or persistent decline in renal function by 50%, highlighting the integrated cardiorenal benefits of this drug class.

Our meta-analysis supports the incorporation of SGLT2 inhibitors as standard therapy for heart failure with reduced ejection fraction, alongside beta-blockers, ACE inhibitors or ARNIs, and MRAs. In HFpEF, they should now be considered first-line therapy given their consistent effect on heart failure hospitalizations. Initiation is straightforward, as SGLT2 inhibitors are administered once daily, are generally well tolerated, and do not require dose titration. Key considerations include baseline renal function and avoidance in patients at high risk for diabetic ketoacidosis.

Several potential concerns warrant clarification. Initial skepticism following early reports of reduced HF hospitalizations in EMPA-REG OUTCOME has been addressed by consistent findings across multiple independent trials, including in non-diabetic populations. Although HFpEF is a heterogeneous syndrome, the broad inclusion criteria of EMPEROR-Preserved and DELIVER support generalizability. While long-term data beyond five years remain limited, available evidence has not identified cumulative toxicity, and post-marketing surveillance continues. SGLT2 inhibitors provide incremental benefit regardless of background therapy, including ARNI and MRAs, and their early initiation may help prevent first and recurrent hospitalizations. Cost and adherence remain considerations, although cost-effectiveness analyses suggest favorable value due to reduced hospitalizations.

The strengths of this meta-analysis include its comprehensive evidence base, rigorous methodology, and focus on clinically meaningful outcomes. Limitations include reliance on observational studies that sometimes did not isolate heart failure populations and potential overlap among real-world datasets. We did not perform head-to-head comparisons between individual SGLT2 inhibitors, as the objective was to assess class effects.

could offer more contemporary and comprehensive insights into the impact of kidney dysfunction on MM outcomes.

CONCLUSION

SGLT2 inhibitors substantially improve outcomes in patients with heart failure, reducing heart failure hospitalizations and improving survival across the ejection fraction spectrum and irrespective of diabetes status. Evidence from both randomized controlled trials and real-world observational cohorts supports their role as cornerstone therapy in HFrEF and as an effective disease-modifying option in HFpEF and HFmrEF, with a favorable safety profile. Overall, our findings support a class effect of SGLT2 inhibitors in heart failure; however, agent- or dose-specific superiority cannot be inferred given the predominantly fixed-dose designs of heart failure trials and the absence of head-to-head comparisons. Wider implementation of SGLT2 inhibitor therapy has the potential to meaningfully reduce the global burden of heart failure and improve patient-centered outcomes.

DECLARATIONS

This study is a systematic review and meta-analysis of previously published randomized controlled trials and observational cohort studies. No new data were collected, and no individual patient-level data were accessed. All included studies had obtained approval from their respective institutional review boards or ethics committees, and were conducted in accordance with the principles of the Declaration of Helsinki and relevant regulatory standards.

Because this meta-analysis relied exclusively on aggregated data from published literature and publicly available sources, no additional ethical approval or informed consent was required for the present study. The review protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD420251082754), ensuring transparency and adherence to predefined methodological standards.

The conduct and reporting of this meta-analysis followed the PRISMA 2020 guidelines. All efforts were made to ensure methodological rigor, minimize bias, and accurately represent the findings of the original studies. No ethical concerns related to patient safety, privacy, or data integrity were identified in the execution of this work.

Informed Consent Statement: Not applicable. This study did not involve direct interaction with human participants, nor did it include identifiable individual-level data.

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Review

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

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Abstract

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

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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

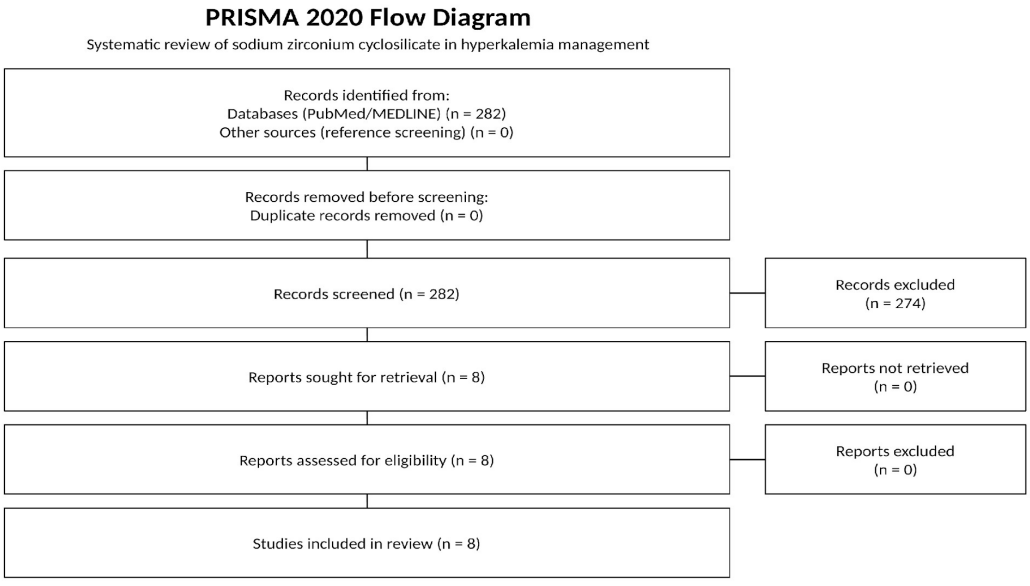

Figure 1. PRISMA 2020 flow diagram of study selection.

narrative synthesis approach was employed to summarize the efficacy and safety data. Efficacy outcomes, including mean reduction in serum potassium (K+), 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^+ 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^+ 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")

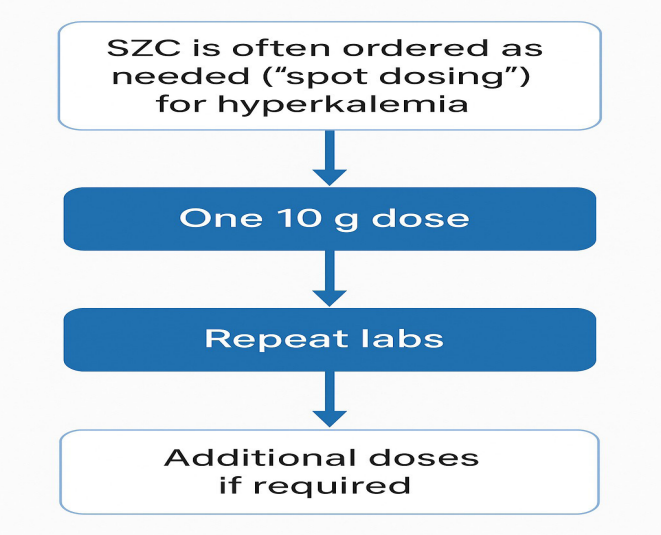

Figure 2. Example of a spot-dosing approach for sodium zirconium cyclosilicate (SZC) in hyperkalemia (single 10 g dose with repeat laboratory assessment and additional dosing if required).

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^+ ~5.6 mmol/L).	Biochemical (potassium control)	Correction phase: dose-dependent reduction in serum K^+ 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^+ 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_3^- 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^+ 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_3, Bicarbonate; HF, Heart Failure; HFrEF, Heart Failure with reduced Ejection Fraction; K+, 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^+ 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^+ 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^+ 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_3, Bicarbonate; HF, Heart Failure; HFrEF, Heart Failure with reduced Ejection Fraction; K+, 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_3^- 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_4^+ 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^+ 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^+ 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^+ 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^+ 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 patiromer, 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^+ periodically during maintenance use (for example, check after the first 1–2 weeks, then monthly) and instruct patients to report symptoms of low K^+ (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 patiromer (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 patiromer) 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

Ethics Committee Approval: Not applicable (systematic review of published data).

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authors. Writing—original draft: all authors. Writing—review and editing: all authors. Final approval: all authors.

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Informed consent form: Not applicable.

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Protocol and registration: The review protocol was not prospectively registered.

Data availability: Extracted data tables and analytic notes are available from the corresponding author upon reasonable request.

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Letter to Editor

Severe Hypernatremia Associated with Intravenous Fosfomycin: A Preventable Adverse Effect in the Intensive Care Setting

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Dear Editor,

In patients followed in intensive care units (ICU), electrolyte disturbances are common and often result from complex polypharmacy, impaired renal handling, or the use of broad-spectrum antibiotics. With the increasing use of fosfomycin for multidrug-resistant (MDR) infections, hypernatremia has emerged as a recurrent and clinically significant problem (1). We present two illustrative ICU cases to highlight this underrecognized yet preventable complication.

Fosfomycin is a broad-spectrum bactericidal antibiotic commonly used against Enterobacteriaceae and Pseudomonas aeruginosa (2). Each gram of intravenous fosfomycin disodium contains about 0.33 g (14.3 mEq) of sodium, meaning that a 16 g/day regimen provides more than 230 mEq of sodium daily, equivalent to 1 L of 3% saline (2). This sodium load can precipitate iatrogenic hypernatremia, particularly in critically ill or oliguric patients (3).

Case 1: A 69-year-old male with diabetes, chronic kidney disease (baseline creatinine 3.5 mg/dL), and laryngeal carcinoma was admitted to the ICU with respiratory failure after CABG. Due to MDR isolates, he received fosfomycin (4 g every 12 hours, total 8 g/day). His serum sodium rose from 141 to 155 mmol/L despite stable renal function and fluid balance. After discontinuation of fosfomycin, sodium levels decreased to 144 mmol/L. The clear temporal association suggested fosfomycin-induced hypernatremia. During this period, the patient was clinically euvolemic, was not receiving diuretics, hypertonic saline, or sodium bicarbonate, and enteral nutrition and fluid prescriptions remained unchanged. Fosfomycin therapy was discontinued prematurely due to progressive hypernatremia rather than completion of the planned treatment course.

Case 2: A 49-year-old paraplegic male with diabetes, hypertension, coronary artery disease, and prior Pott abscess surgery was admitted to the ICU after debridement of an infected pressure ulcer. Following initiation of intravenous fosfomycin (4 g every 12 hours, total 8 g/day), sodium rose from 139 to 163 mmol/L, then gradually decreased to 136 mmol/L after the drug was withdrawn, without other medication changes. The patient was clinically euvolemic, did not receive diuretics or additional sodium-containing infusions, and no changes in nutritional support or fluid management were observed during fosfomycin therapy. Treatment was discontinued early because of marked hypernatremia, after which serum sodium levels gradually normalized.

In conclusion, fosfomycin-induced hypernatremia is an underrecognized but preventable adverse effect. High-risk patients include those with renal dysfunction, oliguric states, or additional sodium loads (4). Regular sodium monitoring, dose adjustment, and avoiding sodium-containing diluents are essential preventive strategies. Early recognition and interdisciplinary collaboration among intensivists, nephrologists, and infectious disease specialists can minimize morbidity and improve outcomes.

This report aims to emphasize a side effect that we frequently observe in practice yet should never overlook, as timely awareness can make a significant clinical difference.

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Letter to Editor

Response to the Letter to the Editor Entitled "What's Missing in Diabetes Treatment? A Novel Agent, Finerenone?"

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Dear Editor,

I would like to thank Akgul and Aylı for their insightful comments and for highlighting the potential therapeutic benefits of finerenone beyond diabetic kidney disease, thereby contributing to our previous article (1,2). The findings from the FINEARTS-HF and CONFIDENCE trials indeed provide important perspectives on the cardiovascular and metabolic benefits of non-steroidal mineralocorticoid receptor antagonists (MRAs).

Furthermore, a recent article published in Nephrology Dialysis Transplantation in September 2025 has attracted attention by suggesting that these agents might also have potential therapeutic roles in a new patient population (3). This publication serves as a preliminary introduction to the ongoing phase 3 FINE-ONE trial, which explores the efficacy and safety of finerenone in patients with type 1 diabetes (T1DM) and chronic kidney disease (CKD). It is well known that both the FIDELIO-DKD and FIGARO-DKD trials were conducted in patients with type 2 diabetes (T2DM) and CKD, excluding those with T1DM.

Nevertheless, the prevalence of diabetic nephropathy among individuals with T1DM remains substantial. A recent study from the United States reported a prevalence of 27.1% (4). The use of sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists in this population is still controversial. This is because the available data in this population are limited, routine clinical use is not supported by sufficient evidence, and safety concerns limit their widespread use in T1D patients (5). Consequently, beyond renin–angiotensin–aldosterone system (RAAS) blockade and glycemic control with insulin, there are no proven therapeutic options for managing CKD in patients with T1DM.

Given the similar pathophysiological basis of CKD in T1DM and T2DM, the hypothesis that finerenone may offer renal protection in T1DM is biologically plausible. The ongoing FINE-ONE phase 3 trial aims to investigate this potential. Although the results have not yet been published, they are eagerly awaited by the nephrology community.

I would like to thank the authors and the editor for providing an opportunity to discuss these evolving therapeutic strategies in nephrology. Hopefully, we will have the chance to revisit this important topic once the FINE-ONE trial results become available.

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Letter to Editor

A Shocking Cause of Kidney Failure: Antiphospholipid Antibody Syndrome

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Dear Editor,

Acute kidney injury (AKI), often originating from vasculitis or thromboembolism, rarely results from antiphospholipid syndrome (APS) manifesting as thrombotic microangiopathy. Although catastrophic APS occurs in <1% of cases, it remains a frequently overlooked cause of AKI.

A 64-year-old male smoker with chronic kidney disease presented with a one-week history of diarrhea, dyspnea, and weakness. Physical examination revealed hypertension (150/104 mmHg), tachycardia (142 bpm), icterus, and basal rales. Laboratory results (Table 1) showed acute kidney injury (creatinine 5.59 mg/dL, eGFR 10 mL/min), hyperkalemia (6.2 mmol/L), thrombocytopenia (48,000/µL), and liver dysfunction (AST 656 U/L, ALT 826 U/L, total bilirubin 6.62 mg/dL). Peripheral smear identified schistocytes (3-4/HPF). CT imaging suggested a main pulmonary artery thrombus, massive pleural effusion, and pulmonary infarcts.

On Day 1, the patient was started on enoxaparin and hemodialysis (HD). Due to suspected thrombotic microangiopathy, plasmapheresis was initiated immediately post-HD. On Day 2, high-dose pulse steroid therapy was added. On Day 5, livedo racemosa developed (Figure 1). Skin biopsy results on Day 7 revealed fibrinoid thrombi in superficial and mid-dermis vessels, confirming systemic microvascular involvement.

The clinical presentation, along with negative ADAMTS13 activity and positive antiphospholipid antibodies (lupus anticoagulant, anti-beta2-glycoprotein IgA), fulfilled the criteria for 'probable Catastrophic Antiphospholipid Syndrome (CAPS)'. Despite the immediate initiation of comprehensive 'triple therapy' (comprising therapeutic anticoagulation, high-dose glucocorticoids, and plasma exchange/intravenous immunoglobulin), the patient's condition deteriorated due to widespread thromboembolic events. The patient succumbed to cardiopulmonary arrest in the intensive care unit.

APS is an autoimmune disorder leading to a prothrombotic state (thrombophilia) (1).In women of childbearing age, it frequently presents with clinical manifestations such as recurrent miscarriages, early pregnancy loss, and preeclampsia (2).

APS also constitutes a significant portion of thromboembolic diseases. The prevalence of antiphospholipid antibodies was found to be 10% among patients with deep vein thrombosis (DVT) and 14% in individuals who had experienced a stroke. In cases of obstetric morbidity, the prevalence of these antibodies ranged from 6% to 9% (3).

The commonly observed clinical features of APS include thrombocytopenia, cardiac valve disease, transient ischemic attack, and livedo racemosa (4). A rare, life-threatening manifestation of APS is CAPS, which presents with widespread thrombosis and multiorgan failure (5).CAPS is an autoimmune disease characterized by symptoms developing in less than one week, involving three or more organs, and histologically confirmed small vessel occlusion in at least one organ. It is also defined by the presence of aPL antibodies, documented as positive at least twice, with a minimum of 12 weeks between tests (6).In our case, a second antibody test after 12 weeks could not be performed. Consequently, this case is classified as 'probable CAPS' based on the preliminary positive aPL titers and the severity of the clinical manifestation. This highlights a significant diagnostic pitfall in clinical practice: the high

early mortality rate often prevents patients from meeting formal criteria, necessitating rapid clinical judgment and aggressive empirical therapy before definitive classification can be achieved.

The clinical presentation of thrombotic microangiopathy (TMA) in this case necessitated a rigorous differential diagnosis. Thrombotic thrombocytopenic purpura (TTP) was excluded due to ADAMTS13 activity levels being within the normal range (>10%). Although the patient presented with severe acute kidney injury, the rapid multi-organ involvement and the presence of high-titer antiphospholipid antibodies shifted the diagnosis away from atypical hemolytic uremic syndrome (aHUS). Furthermore, while the patient exhibited systemic inflammatory features, the absence of overt consumption coagulopathy (normal fibrinogen levels and absence of significant PT/aPTT prolongation) helped differentiate this condition from primary sepsis-induced disseminated intravascular coagulation (DIC). The hallmark finding of livedo racemosa, combined with multi-visceral thrombosis, strongly pointed toward CAPS as the primary etiology of the TMA.

In addition to conditions like stroke and kidney infarction, CAPS can also lead to macrovascular involvement and multi-organ thrombosis, distinguishing it from APS. The disease process can be triggered by complement activation, which in turn can be stimulated by factors such as infection, inflammation, surgery, or pregnancy (7, 8). The standard approach, often referred to as "triple therapy," includes anticoagulation, glucocorticoids, and either therapeutic plasma exchange (TPE) or intravenous immunoglobulin (IVIG). As demonstrated in our case management, despite applying the triple therapy approach, the progressive nature of the disease necessitated considering rituximab, a treatment option for refractory cases. Rituximab may be the preferred choice in select patients with severe thrombosis and thrombocytopenia (9). Given the pivotal role of complement activation in the pathogenesis, eculizumab may be preferred over rituximab as an adjunctive therapeutic option to the core treatment regimen.

In conclusion, CAPS is an autoimmune disease with high mortality that can lead to progressive multiorgan failure, requiring careful and experienced management. Livedo racemosa is a critical cutaneous marker that should alert clinicians to underlying systemic microvascular thrombosis and the potential onset of CAPS. In fulminant cases, early mortality may preclude the 12-week confirmatory testing for antiphospholipid antibodies. In such scenarios, the diagnosis of "probable CAPS" should be sufficient to initiate aggressive multimodal therapy. Severe acute kidney injury in the setting of multisystem failure and thrombotic microangiopathy requires immediate differentiation from TTP and aHUS to avoid delays in starting life-saving plasmapheresis and anticoagulation. A high index of suspicion and early intervention with the triple therapy is the cornerstone of managing a "thrombotic storm," even when all definitive criteria are not yet met. Despite its rarity, the fatal outcome for this patient underscores the critical importance of effective and rapid treatment initiation based on a solid understanding of the diagnostic process.

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