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Research Article

Cardiorenal Effects of SGLT2 Inhibitors: A Meta-Analysis of Randomized Controlled Trials

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Abstract

Type 2 diabetes (T2D) and hypertension are major causes of end-stage renal disease (ESRD) and cardiovascular complications. Sodium-glucose cotransporter 2 (SGLT2) inhibitors, also known as gliflozins, initially developed as antidiabetic agents, have demonstrated significant cardiorenal protective effects independent of glycemic control. This meta-analysis aimed to evaluate their impact on the prevention of ESRD and major adverse cardiovascular events (MACE). A systematic review and meta-analysis were conducted in accordance with PRISMA 2020 guidelines. PubMed/MEDLINE, Embase, Cochrane Library, and ClinicalTrials.gov databases were searched from 2008 to 2025. Randomized controlled trials comparing SGLT2 inhibitors with placebo were included. The primary outcomes were a composite renal endpoint (progression to ESRD, ≥50% decline in glomerular filtration rate, initiation of renal replacement therapy, or renal death) and MACE (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke). Statistical analyses were performed using RevMan 5.4, applying fixed- or random-effects models depending on heterogeneity (I^2). Results were expressed as odds ratios (OR) with 95% confidence intervals (95% CI). A total of 13 randomized controlled trials including 90,413 participants were analyzed. SGLT2 inhibitors significantly reduced the risk of major renal events (OR = 0.68; 95% CI: 0.59–0.77; I^2 = 61%), major cardiovascular events (OR = 0.88; 95% CI: 0.83–0.93; I^2 = 44%), and all-cause mortality (OR = 0.89; 95% CI: 0.85–0.93). In conclusion, SGLT2 inhibitors confirm their major cardiorenal benefits, independent of glycemic control, significantly reducing progression to ESRD, major cardiovascular events, and overall mortality. These findings support their early use in patients at high cardiorenal risk, in line with recent international recommendations.

Keywords : SGLT2 inhibitors; Gliflozins; End-stage renal disease; Type 2 diabetes; Hypertension; Cardiovascular outcomes; Meta-analysis; PRISMA

Introduction

Type 2 diabetes (T2D) and hypertension are two chronic diseases whose global prevalence continues to rise, representing a major public health challenge [1]. Often associated, they potentiate each other's deleterious effects and significantly increase the risk of cardiovascular and renal complications, particularly end-stage renal disease (ESRD) [2]. ESRD represents the final stage of chronic kidney disease (CKD), a condition affecting nearly 13.4% of the global population and potentially involving up to 7.1 million patients requiring renal replacement therapy (RRT) in the coming years [3]. In Senegal, more than 750,000 people suffer from kidney disease [4]. In response to this growing burden, a comprehensive strategy is required, including early screening, lifestyle modification, improved access to healthcare, and the integration of new therapeutic options aimed at slowing disease progression [5,6].

In this context, a new class of oral antidiabetic agents, known as gliflozins or sodium-glucose cotransporter 2 inhibitors (SGLT2i), was initially developed to improve glycemic control in patients with T2D [7]. Beyond their hypoglycemic effect, these drugs have demonstrated additional benefits, including weight reduction and blood pressure lowering. They have also shown significant protective effects on both cardiovascular and renal systems [8].

To address this issue, the main objective of this study was to evaluate, based on consolidated data from randomized controlled trials, the impact of SGLT2 inhibitors

(gliflozins) on the prevention of ESRD and the reduction of major adverse cardiovascular events (MACE), in order to assess the overall cardiorenal benefit of this therapeutic class in patients with type 2 diabetes and/or hypertension.

Methods

Study Design

This study is a systematic review and meta-analysis of randomized controlled trials conducted in accordance with PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Objective

The primary objective was to evaluate the impact of SGLT2 inhibitors on the prevention of major renal events, including ESRD, and on major cardiovascular events (MACE) in patients with type 2 diabetes, heart failure, or chronic kidney disease.

Search Strategy

A systematic search was performed in PubMed/MEDLINE, Embase, Cochrane Library, and ClinicalTrials.gov databases, covering the period from January 2008 to June 2025. The search strategy combined MeSH terms and free-text keywords related to SGLT2 inhibitors, renal and cardiovascular diseases, and randomized trials. A manual search of references from included studies was also conducted to identify additional relevant articles.

Inclusion and Exclusion Criteria

Included studies were:

- randomized controlled trials,
- double-blind studies,
- comparing an SGLT2 inhibitor with placebo,
- reporting at least one renal or cardiovascular outcome.

Excluded studies were:

- observational studies,
- non-randomized analyses,
- non-peer-reviewed or incomplete publications.

Outcomes

The primary renal outcome was a composite endpoint including:

- initiation of renal replacement therapy (dialysis or transplantation),
- ≥50% decline in glomerular filtration rate,
- or estimated GFR < 15 mL/min/1.73 m^2.

Cardiovascular outcomes included major adverse cardiovascular events (MACE), defined as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke.

Secondary outcomes included all-cause mortality, doubling of serum creatinine, and changes in the urinary albumin-to-creatinine ratio (UACR).

Data Extraction

Data were independently extracted by two reviewers using a standardized form including study characteristics, demographic data, interventions, comparators, and clinical outcomes. Discrepancies were resolved by consensus.

Risk of Bias Assessment

Risk of bias was assessed using the Cochrane Risk of Bias 2.0 tool. The overall quality of evidence was evaluated using the GRADE approach [10].

Statistical Analysis

Statistical analyses were performed using Review Manager (RevMan) version 5.4. Results were expressed as odds ratios (OR) with 95% confidence intervals (95% CI). A fixed-effect model (Mantel–Haenszel) was used in the absence of significant heterogeneity; otherwise, a random-effects model was applied (I^2 > 50%).

Heterogeneity and Sensitivity Analyses

Heterogeneity between studies was assessed using the I^2 statistic. Sensitivity analyses were conducted to evaluate the robustness of the results. Subgroup analyses were performed according to clinical profiles (diabetes, heart failure, chronic kidney disease).

Results

Study Identification

The study selection process followed PRISMA 2020 guidelines, from initial identification to final inclusion [11]. The flow diagram below summarizes each stage of the selection process.

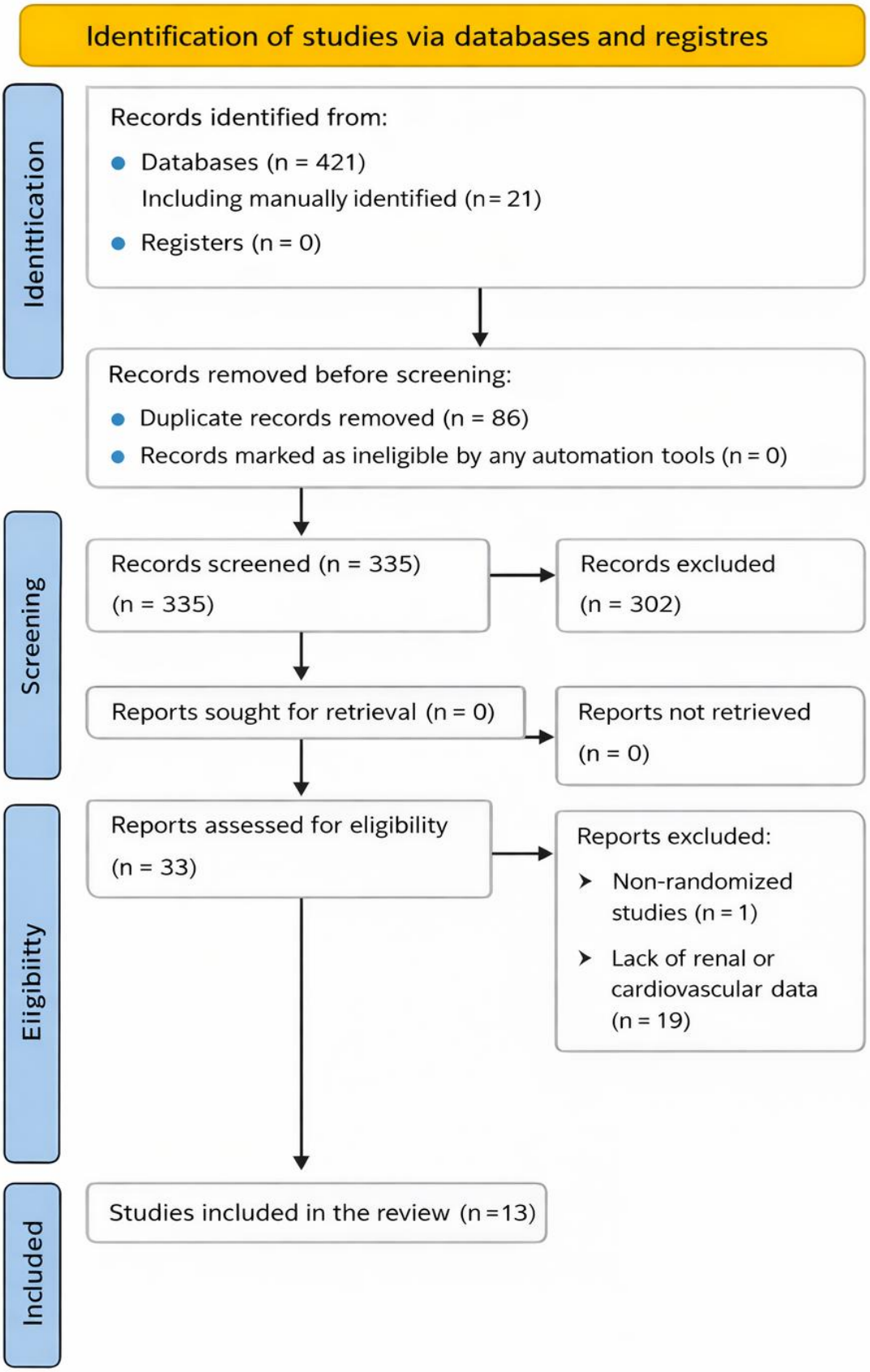

Figure 1 : PRISMA 2020 flow diagram of study selection process

Description of the studies included in the meta-analysis

The 13 randomized controlled trials included involved a total of 90,413 participants (Table I).

Table I: Demographic characteristics according to subgroups (high cardiovascular risk diabetes, heart failure, chronic kidney disease).

Table V: Demographic Characteristics According to Subgroups (High Cardiovascular Risk Diabetes, Heart Failure, Chronic Kidney Disease)

Trial	Year	Duration (years)	Total Population	Treatment Group	Control Group	Female (%)	Mean Age (years)
High Cardiovascular Risk Diabetes							
CANVAS [12,13]	2017	3.6	10,142	5,795	4,347	36	63
DECLARE-TIMI 58 [14]	2018	4.2	17,160	8,582	8,578	37	64
EMPA-REG OUTCOME [15,16]	2015	3.1	7,020	4,687	2,333	28	63
VERTIS CV [17]	2020	3.5	8,246	5,499	2,747	70	64
Heart Failure							
DAPA-HF [18]	2019	1.5	4,744	2,373	2,371	23	66
DELIVER [19,20]	2022	2.3	6,263	3,131	3,132	44	72
EMPEROR-Preserved [21]	2020	2.2	5,988	2,997	2,991	45	72
EMPEROR-Reduced [22]	2020	1.3	3,730	1,863	1,867	25	67
SOLOIST-WHF [23]	2022	0.75	1,222	608	614	34	69
Chronic Kidney Disease							
CREDENCE [24]	2019	2.6	4,401	2,202	2,199	34	63
DAPA-CKD [25]	2020	2.4	4,304	2,152	2,152	33	62
EMPA-KIDNEY [26]	2022	2.0	6,609	3,304	3,305	34	64

Clinical characteristics (Appendix I):

- Moderate chronic kidney disease, with a median estimated glomerular filtration rate (eGFR) ranging from 37.5 to 85 mL/min/1.73 m^2;
- Variable albuminuria, often ≥ 300 mg/g in patients at high renal risk;
- High prevalence of cardiovascular comorbidities, particularly hypertension (>80%) and a history of atherosclerosis.

Risk of Bias Assessment

Each study included in the meta-analysis was evaluated based on seven key methodological criteria to identify potential sources of bias (Table II). A visual coding system was used for each criterion: green (low risk of bias), yellow (unclear risk), and red (high risk of bias).

1. **Random sequence generation**

This criterion assesses whether participants were randomly allocated to groups. It reflects a rigorous method (e.g., computer-generated randomization).

2. **Allocation concealment**

Evaluates whether investigators could predict participant assignment. It indicates whether allocation was adequately concealed (e.g., opaque envelopes, centralized systems).

3. **Double blinding (performance bias)**

Assesses whether participants and healthcare providers were unaware of the assigned treatment, ensuring proper blinding.

4. **Blinding of outcome assessors (detection bias)**

Determines whether outcome evaluators were blinded to treatment allocation, ensuring unbiased assessment.

5. **Incomplete outcome data (attrition bias)**

   Examines how missing data and loss to follow-up were handled. It may indicate proper data handling (e.g., intention-to-treat analysis) or reveal unjustified exclusions or high dropout rates.

6. **Selective reporting (reporting bias)**

   Evaluates whether all pre-specified outcomes were reported. It reflects transparency or highlights omissions and post hoc modifications of outcomes.

7. **Other sources of bias**

   Identifies additional biases (e.g., conflicts of interest, protocol deviations, industry funding).

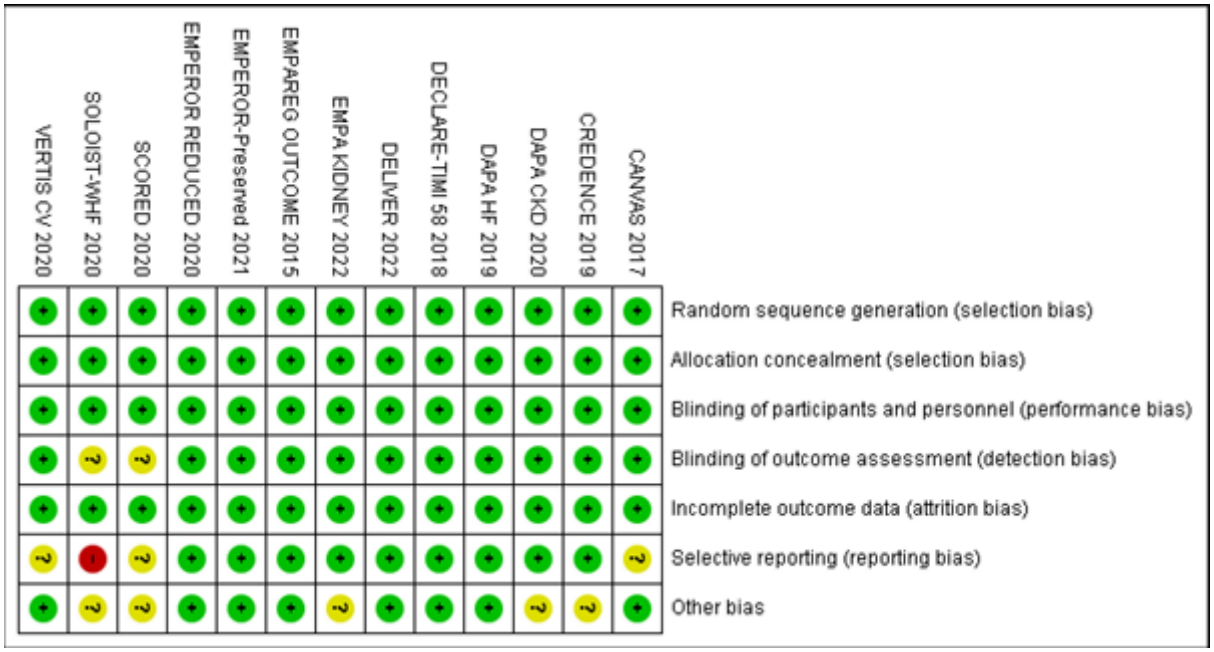

Figure 2: Assessment of each risk of bias domain, presented as percentages across all included studies.

Comparison of the efficacy of SGLT2 inhibitors versus placebo

Major renal events

The meta-analysis including 12 randomized controlled trials showed that SGLT2 inhibitors significantly reduce the risk of major renal events compared with placebo. These events were defined as progression to end-stage renal disease (ESRD), a ≥50% decline in glomerular filtration rate (GFR), initiation of renal replacement therapy (dialysis or transplantation), or renal death (Figure 3).

Overall, 1,236 events were observed in the SGLT2 inhibitor group compared with 1,725 in the placebo group, across a combined population of 47,871 patients receiving SGLT2 inhibitors and 41,312 receiving placebo. The event rate was lower in the treatment group, with a pooled odds ratio (OR) of 0.68 (95% CI: 0.59–0.77). Heterogeneity among studies was high (I^2 = 61%, p = 0.003), justifying the use of a random-effects Mantel–Haenszel (M–H) model.

Subgroup analysis revealed the following:

- **In patients with type 2 diabetes at high cardiovascular risk**, a significant effect in favor of SGLT2 inhibitors was observed (OR = 0.56; 95% CI: 0.48–0.66), with no heterogeneity (I^2 = 0%), suggesting a consistent effect.
- **In patients with heart failure**, the effect was not statistically significant (OR = 0.82; 95% CI: 0.73–1.11), with high heterogeneity (I^2 = 65%), likely reflecting heterogeneity in cardiac phenotypes.
- **In patients with chronic kidney disease**, the effect was particularly pronounced (OR = 0.66; 95% CI: 0.58–0.75), with low heterogeneity (I^2 = 34%).

The test for subgroup differences (Chi^2 = 5.17; p = 0.08) indicated a trend toward variation between subgroups, with substantial heterogeneity (I^2 = 61.3%).

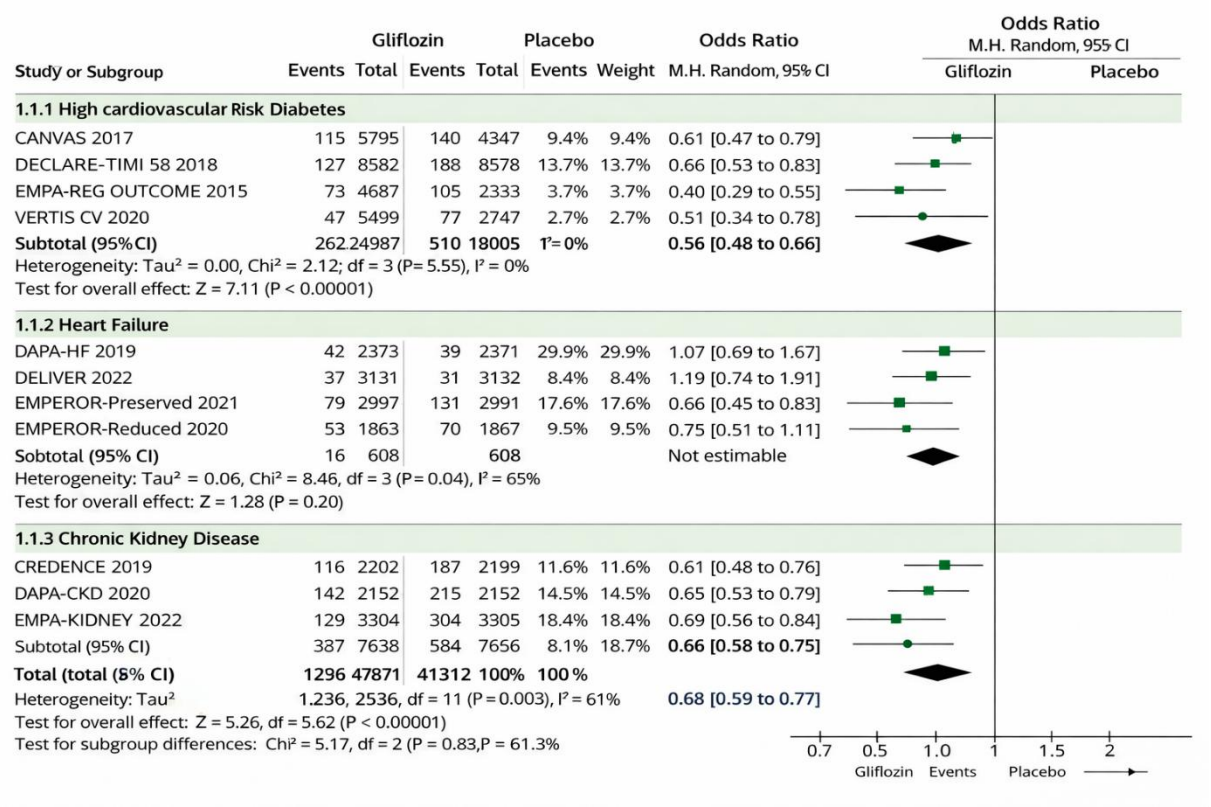

Figure 3: Forest plot of major renal events according to clinical subgroups (high cardiovascular risk diabetes, heart failure, chronic kidney disease).

Major cardiovascular events

The meta-analysis including 7 randomized controlled trials evaluated the effect of SGLT2 inhibitors on major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) (Figure 4).

A total of 3,220 events were observed in the SGLT2 inhibitor group compared with 2,828 in the placebo group, across a combined population of 35,355 patients receiving SGLT2 inhibitors and 28,799 receiving placebo. The event rate was significantly reduced in the treatment group compared with placebo, with a pooled odds ratio (OR) of 0.88 (95% CI: 0.83–0.93). Heterogeneity among studies was moderate (I^2 = 44%, p = 0.10).

- In patients with type 2 diabetes at high cardiovascular risk, the effect was statistically significant (OR = 0.91; 95% CI: 0.85–0.97), with moderate heterogeneity (I^2 = 32%).
- No data were available from trials conducted in heart failure populations.
- In patients with chronic kidney disease, the effect was also significant (OR = 0.81; 95% CI: 0.71–0.91), with low heterogeneity (I^2 = 29%).

The test for subgroup differences (Chi^2 = 3.70; p = 0.05) suggests a trend toward variation in treatment effects across clinical profiles, with substantial between-subgroup heterogeneity (I^2 = 73%).

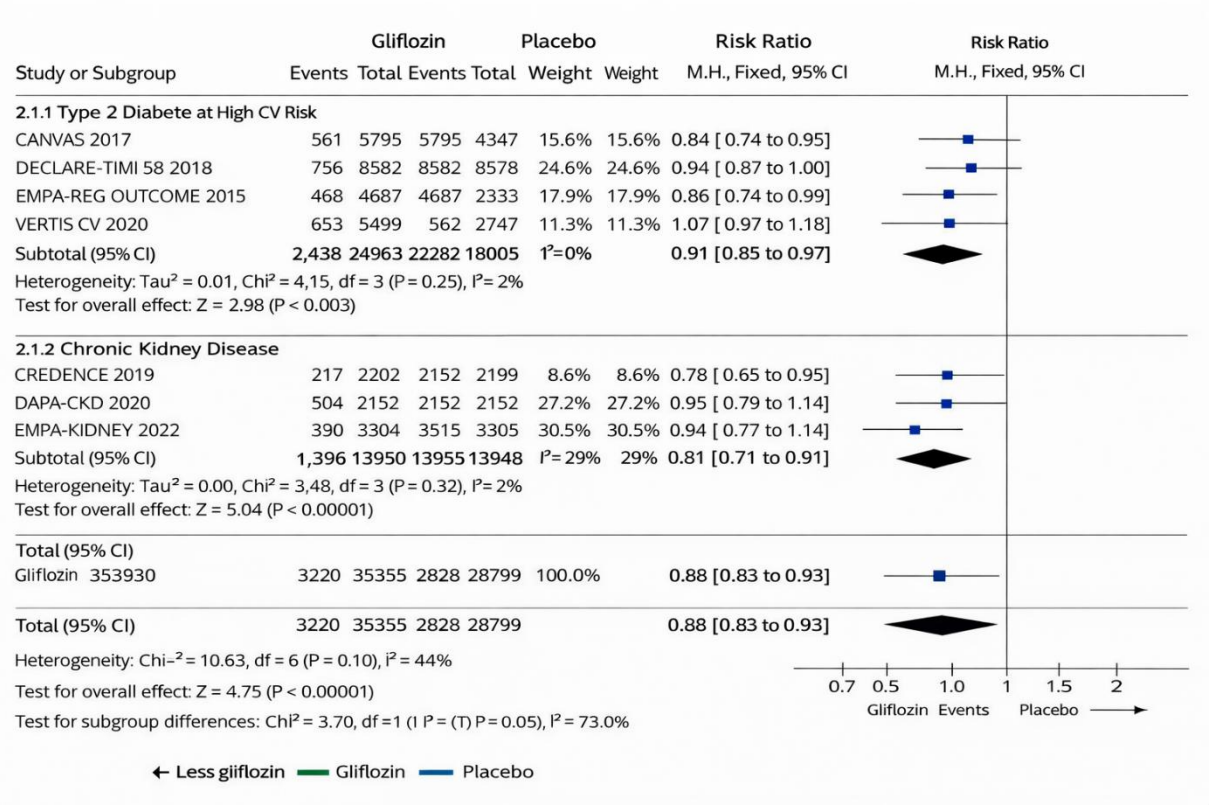

Figure 4: Forest plot of major adverse cardiovascular events (MACE) according to clinical subgroups (high cardiovascular risk diabetes, heart failure, chronic kidney disease).

All-cause mortality

The meta-analysis of all-cause mortality compared with placebo included 13 randomized controlled trials (Appendix II). A total of 3,803 deaths were observed in the SGLT2 inhibitor group compared with 3,707 in the placebo group, across a combined population of 48,479 patients receiving SGLT2 inhibitors and 41,926 receiving placebo. Mortality was significantly lower in the treatment group, with a pooled odds ratio (OR) of 0.89 (95% CI: 0.85–0.93). Overall heterogeneity was moderate (I^2 = 36%).

- **In patients with type 2 diabetes at high cardiovascular risk**, the odds ratio was 0.87 (95% CI: 0.81–0.94), with moderate heterogeneity (I^2 = 65%).
- **In heart failure trials**, a significant effect was observed (OR = 0.92; 95% CI: 0.70–0.92), with no heterogeneity (I^2 = 0%).
- **In patients with chronic kidney disease**, the effect was also significant (OR = 0.86; 95% CI: 0.78–0.96), with moderate heterogeneity (I^2 = 51%).

The test for subgroup differences (Chi^2 = 1.27; p = 0.53; I^2 = 0%) showed no statistically significant variation between subgroups.

Exploratory outcomes

Doubling of serum creatinine

The meta-analysis including the CANVAS 2017 and CREDENCE 2019 trials showed that SGLT2 inhibitors significantly reduced the risk of doubling of serum creatinine (OR = 0.59; 95% CI: 0.47–0.73), with no heterogeneity (I^2 = 0%), indicating strong consistency between studies (Appendix VI) [65], [24].

Urinary albumin-to-creatinine ratio (UACR)

The meta-analysis of the CANVAS 2017 and VERTIS CV 2020 trials showed that SGLT2 inhibitors significantly reduced UACR compared with placebo (OR = 0.57; 95% CI: 0.53–0.61) (Appendix VII). Although the effect was robust, heterogeneity was high (I^2 = 87%), suggesting substantial differences between studies. Nevertheless, the overall benefit remains statistically and clinically relevant [12, 13, 17].

Assessment of the Quality of Evidence (GRADE)

Table II: Overall quality of evidence assessed using the GRADE approach for renal outcomes, major adverse cardiovascular events (MACE), and all-cause mortality.

GRADE Domain	Renal Outcome (OR = 0.68; 95% CI: 0.59–0.77)	Major Cardiovascular Events (MACE) (OR = 0.88; 95% CI: 0.83–0.93)	All-Cause Mortality (OR = 0.89; 95% CI: 0.85–0.93)	Justification
Risk of bias	Low to high	Low to high	Low to high	Randomized, controlled, double-blind studies. Variable risks observed (Figure 2), including early termination for efficacy, incomplete adjudication, changes in primary outcomes, and loss of funding.
Inconsistency (heterogeneity)	Moderate (I^2 = 61%)	Moderate (I^2 = 44%)	Low to moderate (I^2 = 36%)	Consistent direction of effects; heterogeneity explained by differences in populations (CKD, heart failure, diabetes).
Imprecision	Low	Low	Low	Narrow confidence intervals and large sample sizes.
Publication bias	Unlikely	Unlikely	Unlikely	Symmetrical funnel plots (Appendices III–V), no significant asymmetry; Egger's test not performed.
Directness	High	High	High	Results directly applicable to clinical practice (patients at high cardiorenal risk).
Overall quality of evidence	High	Moderate to high	Moderate to high	Robust, consistent, statistically significant, and clinically relevant effects.

Discussion

Risk of bias assessment

Among the thirteen included trials, seven were classified as having a low risk of bias (Figure 2), indicating generally high methodological quality. Identified biases were limited, notably early trial termination for efficacy observed in CREDENCE 2019, DAPA-CKD 2020, and EMPA-KIDNEY 2022 [24, 25, 26].

Changes in primary outcomes and loss of funding resulted in an unclear risk of bias for SCORED 2024 and a high risk of bias for SOLOIST-WHF 2020 [23], [79]. These two trials, characterized by incomplete event adjudication, require cautious interpretation due to potential bias [70], [79].

Efficacy of SGLT2 inhibitors versus placebo

Major renal events

The meta-analysis including 12 randomized controlled trials confirms that SGLT2 inhibitors significantly reduce the risk of major renal events, including progression to ESRD, ≥50% decline in GFR, need for renal replacement therapy, and renal mortality. The overall effect (OR = 0.68; 95% CI: 0.59–0.77) is statistically robust despite moderate heterogeneity (I^2 = 61%), justifying the use of a random-effects model.

A relative risk reduction of 37% for ESRD and 23% for acute kidney injury has been reported in previous meta-analyses, independent of glycemic status [29].

The DAPA-CKD 2020 and EMPA-KIDNEY 2022 trials confirmed these findings. In DAPA-CKD, renal events were reduced in both diabetic (OR = 0.64; 95% CI: 0.52–0.79) and non-diabetic patients (OR = 0.50; 95% CI: 0.35–0.72). EMPA-KIDNEY showed similar effects (OR = 0.64; 95% CI: 0.54–0.77 and OR = 0.82; 95% CI: 0.68–0.99) [25, 26].

The benefit was consistent across GFR levels. In DAPA-CKD, patients with GFR <45 mL/min/1.73 m^2 (OR = 0.63; 95% CI: 0.51–0.78) and ≥45 (OR = 0.49; 95% CI: 0.34–0.69) both benefited. EMPA-KIDNEY confirmed this effect across all GFR strata, including <30 (OR = 0.73; 95% CI: 0.62–0.86), 30–45 (OR = 0.78; 95% CI: 0.62–0.97), and ≥45 (OR = 0.64; 95% CI: 0.44–0.93) [25, 26].

Analysis according to baseline UACR showed stronger effects in patients with higher albuminuria. In DAPA-CKD, patients with UACR >1000 mg/g had a marked reduction (OR = 0.62; 95% CI: 0.50–0.76), while those

with ≤1000 mg/g also benefited (OR = 0.54; 95% CI: 0.37–0.77) [25]. In EMPA-KIDNEY, the effect was strongest in patients with UACR >300 mg/g (OR = 0.67; 95% CI: 0.58–0.78), compared with lower UACR groups [26].

These findings suggest a stronger protective effect in patients with advanced glomerular damage, likely related to reductions in intraglomerular pressure and hyperfiltration.

The impact on renal replacement therapy (RRT) was also significant, with an OR of 0.65 (95% CI: 0.56–0.75) (Appendix VIII), supporting a clinically meaningful benefit in delaying dialysis or transplantation [24–28].

Major cardiovascular events

SGLT2 inhibitors significantly reduced the risk of MACE (OR = 0.88; 95% CI: 0.83–0.93; I^2 = 44%). These findings are consistent with major trials such as CANVAS 2017 and EMPA-REG OUTCOME 2015, which showed reductions in cardiovascular mortality (OR = 0.62; 95% CI: 0.49–0.77) [12–16]. In CKD populations, CREDENCE 2019 confirmed this benefit [24].

The lack of estimable data in heart failure trials limits subgroup interpretation, although DAPA-HF 2019 and EMPEROR-Reduced 2020 demonstrated significant reductions in heart failure hospitalizations [18, 22].

All-cause mortality

SGLT2 inhibitors significantly reduced all-cause mortality (OR = 0.89; 95% CI: 0.85–0.93; I^2 = 36%). The effect was consistent across clinical profiles, with no significant subgroup differences (p = 0.53).

Exploratory outcomes

Exploratory endpoints confirmed these findings, with significant reductions in serum creatinine doubling and UACR, supporting direct renal protective mechanisms independent of glycemic control.

Pathophysiological interpretation

The observed benefits can be explained by multiple mechanisms. Increased urinary glucose excretion induces natriuresis and diuresis, improving hemodynamic balance. This leads to a reduction in intraglomerular pressure and albuminuria.

Additionally, anti-inflammatory and antioxidant effects, including reductions in IL-6, NF-κB, KIM-1, and TGF-β, contribute to reduced fibrosis and improved endothelial function. Increased erythropoietin and hematocrit may further enhance cardiovascular and renal protection [30].

A complementary meta-analysis by Fall et al. found no significant drug–drug or disease interactions, supporting the stability of SGLT2 inhibitor effects across different clinical settings [31].

Clinical implications

These findings align with recent ADA (2025) and KDIGO (2022) guidelines, which recommend SGLT2 inhibitors as a cornerstone therapy beyond glycemic control. Their use is now advised in patients with cardiovascular disease, heart failure, or chronic kidney disease, regardless of HbA1c levels, including non-diabetic patients at high risk [32, 33].

Notably, trials such as CREDENCE and DAPA-CKD demonstrated efficacy down to an eGFR of approximately 20 mL/min/1.73 m^2, expanding their therapeutic applicability [34].

Limitations of the meta-analysis

Several limitations should be considered when interpreting the results of this meta-analysis. The lack of specific data prevented the analysis of the hypertensive patient subgroup, and the SOLOIST-WHF 2020 trial did not provide sufficient data to isolate renal function outcomes [23].

No data were available regarding major adverse cardiovascular events (MACE) in patients with heart failure, including in the DAPA-CKD 2020 trial, which limits comparisons across clinical profiles [25]. Some trials were prematurely terminated due to demonstrated efficacy, and event adjudication procedures were sometimes incomplete. The risk of bias varied across studies (Figure 2), which may affect the robustness of the estimates.

Although some trials included participants from South Africa (SCORED 2020), no study was specifically conducted on the African continent, limiting geographic representativeness [27, 28]. In addition, several data were derived from post hoc analyses (SCORED 2020 and EMPA-REG OUTCOME 2015) [75], [76], [64], [65]. Some missing information could not be retrieved due to the lack of contact with study authors.

Finally, heterogeneity remained high for the primary renal outcome (I^2 = 61%) (Figure 3), and adverse event analysis was not performed. Although publication bias appeared unlikely based on visual inspection (Appendices III–V), it was not formally assessed using Egger's test, which represents an additional limitation.

Conclusion and perspectives

This meta-analysis confirms the major role of SGLT2 inhibitors in reducing the risk of end-stage renal disease and major cardiovascular events in patients at high cardiorenal risk. Their benefit, independent of glycemic control, is supported by complementary pathophysiological mechanisms, including hemodynamic and anti-inflammatory effects.

These findings reinforce the role of gliflozins as a cornerstone therapy, including in patients with advanced chronic kidney disease. Their efficacy and safety profile supports early use within integrated therapeutic strategies.

However, certain limitations, particularly the heterogeneity of renal endpoints and the lack of data in specific populations, especially in Africa, should be considered when interpreting these results.

Further studies are needed to better define their efficacy in underrepresented populations, particularly in Africa,

as well as in specific clinical contexts such as non-diabetic or pediatric patients.

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Ethical Approval: This study is a systematic review and meta-analysis based exclusively on previously published data. It does not involve direct human or animal participation. Therefore, ethical approval was not required.

Conflicts of Interest: The authors declare that they have no conflict of interest.

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Author Contributions

MF: conceptualization, methodology, literature search, data extraction, statistical analysis, writing of the original draft. MT: methodology, validation, critical review of the manuscript. NAD: data extraction, validation, review and editing. SA: methodology, statistical analysis, review and editing. MD: literature search, data curation, review. DF: literature search, data curation, review. AMD: supervision, validation, critical revision, and final approval of the manuscript. All authors have read and approved the final version of the manuscript.

Data Availability Statement: All data analyzed in this meta-analysis are derived from previously published randomized controlled trials, which are publicly available through the original publications cited in the references. Additional details, including extracted data and analysis files, are available from the corresponding author upon reasonable request.

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