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Expert Opinion Article

The Clinical Impact of SGLT2 Inhibitors in Patients with and without Type 2 Diabetes: Systematic Review

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Abstract

Background: Sodium-glucose co-transporter-2 (SGLT2) inhibitors have demonstrated significant benefits in reducing cardiovascular events and delaying kidney disease progression in patients with type 2 diabetes, heart failure, or chronic kidney disease (CKD). However, their impact on non-diabetic populations remains less explored. This systematic review aimed to evaluate the effects of SGLT2 inhibitors in patients with and without type 2 diabetes.

Methods: A comprehensive literature search was conducted using MEDLINE and Embase databases up to September 5, 2022. Randomized, double-blind, placebo-controlled trials with at least 500 participants per arm and a minimum follow-up of six months were included. Primary outcomes were kidney disease progression, acute kidney injury (AKI), and composite cardiovascular outcomes. Data were analyzed using inverse-variance weighting to derive summary relative risks (RRs) with 95% confidence intervals (CIs).

Results: The analysis included 13 trials with 90,413 participants. SGLT2 inhibitors reduced the risk of kidney disease progression by 37% (RR 0.63, 95% CI 0.58–0.69) and AKI by 23% (RR 0.77, 95% CI 0.70–0.84), with consistent benefits observed in both diabetic and non-diabetic populations. Cardiovascular death or heart failure hospitalization was reduced by 23% (RR 0.77, 95% CI 0.74–0.81). Safety outcomes included a higher risk of diabetic ketoacidosis (RR 2.12, 95% CI 1.49–3.04) and limb amputations (RR 1.15, 95% CI 1.02–1.30) in diabetic patients, but no significant risks were noted in non-diabetic individuals.

Conclusion: SGLT2 inhibitors provide significant renal and cardiovascular benefits across diverse patient populations, irrespective of diabetes type II status. These findings support their broader use in managing CKD and heart failure, though careful monitoring for adverse effects is warranted in diabetic patients.

Introduction

Extensive randomized, placebo-controlled research has demonstrated that sodium-glucose co-transporter-2 (SGLT2) inhibitors effectively lower the incidence of cardiovascular events, particularly reducing hospital admissions due to heart failure, in individuals with type 2 diabetes who are at elevated risk for cardiovascular complications, heart failure, or chronic kidney impairment (1, 2, 3, 4, 5). These agents are now recognized as essential in managing patients with heart failure to reduce mortality and hospitalization rates, regardless of their ejection

fraction or diabetic status (1, 2, 3, 4, 5). Furthermore, robust clinical evidence supports their capacity to delay the progression of kidney dysfunction in patients with type 2 diabetes who also exhibit proteinuria (1, 6, 7, 8). However, the available data regarding individuals with chronic kidney disease (CKD) who do not have diabetes remains sparse. Notably, major trials such as CREDENCE and SCORED primarily enrolled participants with both CKD and type 2 diabetes (7, 9), and the DAPA-CKD study, although it included a subset without diabetes, reported relatively few progression events in this population (1, 8, 10). While prior cardiovascular-focused trials included participants with impaired renal function, the number of kidney outcomes in non-diabetic participants was too limited to draw strong conclusions (1, 11).

More recently, two large-scale randomized trials have yielded critical insights into how SGLT2 inhibitors impact kidney outcomes among individuals without diabetes. The DELIVER study, which enrolled individuals with preserved ejection fraction heart failure, included nearly half of its participants without diabetes (4). Similarly, the EMPA-KIDNEY trial, targeting those at risk of CKD progression, also featured a significant proportion of non-diabetic participants (12, 13). Given that the global prevalence of CKD is higher among individuals without diabetes (14, 15), these findings underscore the necessity of reevaluating the evidence base with this population in mind.

Another shortcoming in earlier pooled analyses was the variation in how kidney disease progression was defined across studies, particularly in terms of estimated glomerular filtration rate (eGFR) decline thresholds (1, 6). Additionally, we explored whether baseline kidney function or primary kidney diagnosis influenced the efficacy of SGLT2 inhibitors at the trial level.

Methods

Search Approach and Eligibility Criteria

This analysis was designed and reported in line with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) framework. A comprehensive literature search was carried out using the MEDLINE and Embase databases via Ovid, covering all publications up to September 5, 2022. Eligible trials included randomized, double-blind, placebo-controlled studies (excluding crossover designs) that evaluated the use of SGLT2 inhibitors, including dual SGLT1/2 agents, in adults aged 18 years and older. Studies were required to have at least 500 participants per arm, a minimum duration of six months, and to report on pre-identified clinical outcomes related to efficacy or safety. Initial screening of titles and abstracts for duplication and relevance was performed by a reviewer, while full-text screening and assessment of bias risk (using the Cochrane Risk-of-Bias tool version 2) were independently completed by reviewers, with disagreements resolved through discussion.

Data Collection and Analytical Procedures

Summary-level data were collected from principal publications and associated peer-reviewed sources for each qualifying study. This process was independently conducted by authors, and discrepancies were resolved by consensus. For outcomes not publicly reported, corresponding investigators were contacted to provide unpublished results. The primary efficacy outcomes assessed were progression of kidney disease, incidence of acute kidney injury, and the combined incidence of cardiovascular death or hospital admission for heart failure.

Kidney disease progression was defined uniformly as a persistent reduction in eGFR of ≥50% from baseline, initiation of long-term dialysis, receipt of a kidney transplant, sustained eGFR below defined thresholds (<15 or <10 mL/min/1.73 m^2), or death attributed to kidney failure. In eight of the included trials, this definition of kidney progression was not available in the public domain; therefore, trial investigators provided recalculated estimates based on participant-level eGFR data (3, 4, 7, 8, 12, 17, 18, 19). The component of kidney failure was standardized as including long-term dialysis, transplantation, or sustained low eGFR. Acute kidney injury was regarded as an efficacy metric and was identified using standardized regulatory terminology. The composite cardiovascular outcome excluded emergency heart failure visits to ensure consistent reporting across studies. Mortality was assessed both for cardiovascular and non-cardiovascular causes, while all-cause mortality was included for completeness despite its broader generalizability.

Safety outcomes of interest included those with known or suspected associations with SGLT2 inhibition, such as diabetic ketoacidosis and limb amputations, particularly in light of findings from the CANVAS trial (1, 21). Additional safety parameters included urinary and genital infections, significant hypoglycemia, and bone fractures.

For studies focused on chronic kidney disease, subgroups were analyzed based on the primary cause of kidney disease as reported by investigators when available. In trials like DAPA-CKD and EMPA-KIDNEY, these included diabetic kidney disease, hypertensive or ischemic nephropathy, glomerulonephritis, and other or unspecified types (10, 12, 13). CREDENCE participants were assumed to have diabetic nephropathy, as individuals with suspected non-diabetic kidney disease were excluded (7). SCORED was excluded from some subgroup analyses due to unavailable diagnostic categorization (9). Exploratory subgroup evaluations by glomerular disease subtype (IgA nephropathy,

focal segmental glomerulosclerosis, and other types) were carried out based on available DAPA-CKD data (22, 23).

Analysis was stratified by diabetes status at baseline, except for kidney disease diagnosis subgrouping. Where available, diabetes-specific treatment effects were extracted from Cox regression models; otherwise, log-transformed relative risks (RR) and standard errors were calculated using event data. This approach ensures uniform contribution of participants across trials without assuming effect homogeneity (24, 25).

Previously assessed heterogeneity across trials was based on standard chi-square tests (1). For this update, further heterogeneity testing was conducted by diabetes status, trial population characteristics, and primary kidney disease classification. An additional comparison of amputation rates between CANVAS and all other included studies was also done. Trials were ordered in forest plots based on baseline eGFR to examine effect modification by kidney function. Trend tests were used to detect graded differences across these ordered estimates. For trials presenting medians and IQRs instead of means and SDs for eGFR, standard statistical conversions were applied (43). Sensitivity analyses were also conducted with trials ordered by baseline albuminuria levels.

Event rates were reported per 1000 person-years. For core outcomes such as kidney disease progression, acute kidney injury, cardiovascular death or heart failure hospitalization, and key adverse events (e.g., ketoacidosis, amputation), absolute effects by diabetes status were calculated by applying treatment-specific RRs to mean event rates in the placebo arms. SOLOIST-WHF was omitted from these analyses due to the exceptionally high baseline event risk observed in its patient population (20).

Statistical analyses were conducted using SAS (version 9.4) and R (version 3.6.2).

Role of Study Sponsors

The study sponsors did not contribute to any aspect of the design, execution, data handling, interpretation, or reporting of this research.

Results

PRISMA Flow Diagram

Records identified through database searching (PubMed, Scopus, Web of Science, Cochrane Library): *283*. Additional records identified through other sources (manual search, reference lists): *18*. Total records after duplicates removed: *182*. Records screened (title/abstract): *182*. Records excluded (irrelevant, duplicate topic, not related): *150*. Full-text articles assessed for eligibility: *32*. Full-text articles excluded: *19*. Studies included in the study: *13*.

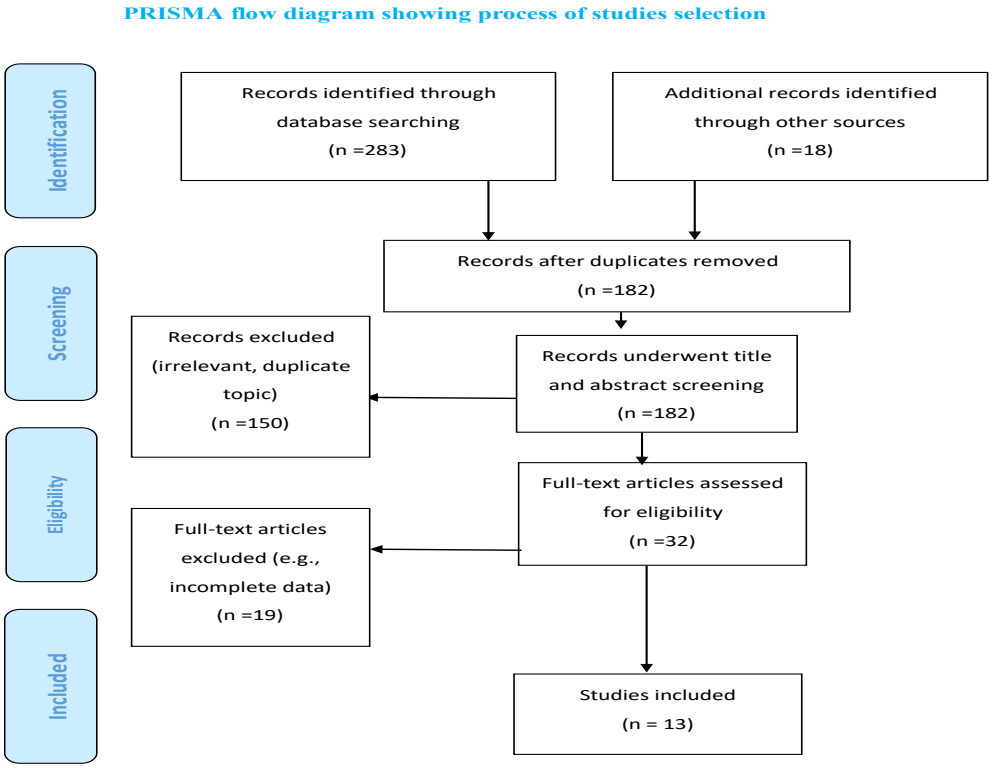


Fig 1: PRISMA Flow

Studies Characteristics

A total of 15 major clinical trials were initially identified in the literature screening (table). Two of these—one involving 1,402 individuals with type 1 diabetes (inTandem3 trial) and another with 1,250 participants hospitalized due to COVID-19 (DARE-19

trial)—were excluded due to having follow-up durations of less than six months (1, 44, 45). The remaining 13 trials formed the basis of the primary analysis and were supported by associated secondary publications (3, 4, 7, 8, 9, 10, 11, 13, 17, 18, 20, 21, 22, 23, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 46), encompassing data from a combined total of 90,413 randomized participants. Women comprised approximately 35.7% (32,238) of the study population, and the average age per trial ranged from 61.9 to 71.8 years. All 13 trials were determined to have a low risk of bias.

These trials were grouped by disease focus: four studies enrolled 42,568 individuals with type 2 diabetes and elevated atherosclerotic cardiovascular risk, five focused on 21,947 patients with heart failure (of whom 11,305 had diabetes and 10,638 did not), and four trials assessed 25,898 patients with chronic kidney disease (20,931 with diabetes, 4,967 without). Those with unclear diabetes status were removed from the analyses, leaving 90,409 individuals in the final dataset. Almost all participants with diabetes had type 2 diabetes. The average baseline estimated glomerular filtration rate (eGFR) ranged from 74 to 85 mL/min/1.73 m^2 in the trials targeting cardiovascular risk, from 51 to 66 mL/min/1.73 m^2 in the heart failure studies, and from 37 to 56 mL/min/1.73 m^2 in the kidney disease trials. Median follow-up times varied by population type, being longest for cardiovascular risk (2.4 to 4.2 years), followed by kidney disease (1.3 to 2.6 years), and shortest for heart failure (0.8 to 2.2 years).

When compared with placebo, the use of SGLT2 inhibitors was linked to a 37% relative reduction in kidney disease progression (RR 0.63, 95% CI 0.58–0.69). In trials centered on chronic kidney disease, the reduction in kidney failure risk specifically was estimated at 33% (RR 0.67, 95% CI 0.59–0.77). These effects were consistent across individuals with (RR 0.62, 95% CI 0.56–0.68) and without diabetes (RR 0.69, 95% CI 0.57–0.82), with no significant variation based on baseline eGFR.

Among the chronic kidney disease-focused trials, benefit was observed regardless of primary kidney disease etiology. For those with diabetic kidney disease, SGLT2 inhibitors reduced progression by 40% (RR 0.60, 95% CI 0.53–0.69). Similar outcomes were noted in non-diabetic subgroups, including reductions of 30% for ischemic and hypertensive kidney disease (RR 0.70, 95% CI 0.50–1.00), 40% for glomerular diseases (RR 0.60, 95% CI 0.46–0.78), and 26% for other or unspecified kidney conditions (RR 0.74, 95% CI 0.51–1.08). Differences among subtypes of glomerular disease were not statistically significant.

Across all included trials, SGLT2 inhibitors were associated with a 23% relative reduction in acute kidney injury risk compared to placebo (RR 0.77, 95% CI 0.70–0.84). The benefit was seen in both diabetic (RR 0.79, 95% CI 0.72–0.88) and non-diabetic populations (RR 0.66, 95% CI 0.54–0.81), with little evidence of differences linked to baseline eGFR.

The analysis also showed that SGLT2 inhibitors reduced the combined risk of cardiovascular death or hospitalization due to heart failure by 23% (RR 0.77, 95% CI 0.74–0.81), with nearly identical risk reductions in patients regardless of diabetic status—diabetic (RR 0.77, 95% CI 0.73–0.81) and non-diabetic (RR 0.79, 95% CI 0.72–0.87). Cardiovascular mortality alone decreased by 14% (RR 0.86, 95% CI 0.81–0.92), again consistently across both groups. There was no significant impact on non-cardiovascular death (RR 0.94, 95% CI 0.88–1.02).

While the risk of diabetic ketoacidosis was low in absolute terms (0.2 cases per 1000 patient-years among placebo-treated individuals with diabetes), SGLT2 inhibitors doubled the relative risk (RR 2.12, 95% CI 1.49–3.04). No similar increase was detected in non-diabetic patients, with only one recorded case among them during the follow-up period.

Regarding lower limb amputations, a notable increase was observed only in one trial (CANVAS), where risk doubled (6.3 vs. 3.4 cases per 1000 patient-years). Across all other trials, there was no significant association (RR 1.06, 95% CI 0.93–1.21). Overall, SGLT2 inhibitor use was linked to a 15% higher relative risk of amputation (RR 1.15, 95% CI 1.02–1.30), primarily among individuals with diabetes.

Additional findings included a modest increase in urinary tract infections (RR 1.08, 95% CI 1.02–1.15), no significant increase in serious urinary tract infections (RR 1.07, 95% CI 0.90–1.27), a higher incidence of genital mycotic infections (RR 3.57, 95% CI 3.14–4.06), a small reduction in severe hypoglycemia (RR 0.89, 95% CI 0.80–0.98), and no substantial effect on bone fractures (RR 1.07, 95% CI 0.99–1.14).

In terms of absolute effects, SGLT2 inhibitors provided greater clinical benefits for patients with diabetes due to higher baseline risks. Among those with chronic kidney disease and diabetes, treatment over one year for every 1,000 individuals prevented approximately 11 cases of kidney disease progression, four cases of acute kidney injury, and 11 events of cardiovascular death or heart failure hospitalization, but resulted in roughly one additional case each of ketoacidosis and limb amputation. For non-diabetic individuals with chronic kidney disease, the benefits included prevention of 15 cases of kidney disease progression, five cases of acute kidney injury, and two fewer cardiovascular deaths or hospitalizations per 1,000 patient-years, with no increased risk of ketoacidosis or amputation. Benefits for patients with heart failure were consistently substantial regardless of diabetes status.

Table. Summary of included trials

	Size, n	Median follow-up, years	Proportion with diabetes, n (%)	Proportion with heart failure, n (%)	Mean (SD) eGFR, mL/min per1·73 m²	Median (IQR) uACR, mg/g	Key eligibility criteria
Type 2 diabetes at high risk of atherosclerotic cardiovascular disease							
DECLARE-TIMI 58[18] (dapagliflozin 10 mg)	17 160	4·2	17 160 (100%)	1724 (10%)	85 (16)	13·1 (6·0–43·6)	• Type 2 diabetes • Age ≥40 years and history of coronary, cerebral, or peripheral vascular disease; or age ≥55 years in men or ≥60 years in women with at least one cardiovascular risk factor Creatinine clearance ≥60 mL/min
CANVAS Program[21, 26, 27, 28, 29] (canagliflozin 100–300 mg)	10 142	2·4	10 142 (100%)	1461 (14%)	77 (21)	12·3 (6·7–42·1)	• Type 2 diabetes • History of coronary, cerebral, or peripheral vascular disease; or age >50 years with at least two cardiovascular risk factors • eGFR ≥30 mL/min per 1·73 m²
VERTIS CV[19, 30] (ertugliflozin 5 mg or 15 mg)	8246	3·0	8246 (100%)	1958 (24%)	76 (21)	19·0 (6·0–68·0)	• Type 2 diabetes • History of coronary, cerebral, or peripheral vascular disease • eGFR ≥30 mL/min per 1·73 m²
EMPA-REG OUTCOME[31, 32, 33] (empagliflozin 10 mg or 25 mg)	7020	3·1	7020 (100%)	706 (10%)	74 (21)	17·7 (7·1–72·5)	• Type 2 diabetes • History of coronary, cerebral, or peripheral vascular disease • eGFR ≥30 mL/min per 1·73 m²
Heart failure							
DAPA-HF[34, 35] (dapagliflozin 10 mg)	4744	1·5	2139 (45%)*	4744 (100%)	• Overall: 66 (19) • Diabetes: 63 (19) • No diabetes: 68 (19)	NA	• Symptomatic chronic heart failure (NYHA class II–IV) with LVEF ≤40% (ie, reduced ejection fraction) • NT-proBNP ≥600 pg/mL • eGFR ≥30 mL/min per 1·73 m² Appropriate doses of medical therapy and use of medical devices
EMPEROR-REDUCED[11, 17, 36, 37] (empagliflozin 10 mg)	3730	1·3	1856 (50%)	3730 (100%)	• Overall: 62 (22) • Diabetes: 61 (22) • No diabetes: 63 (21)	22·1 (8·0–81·3)	• Chronic heart failure (NYHA class II–IV) with LVEF ≤40% (ie, reduced ejection fraction) • NT-proBNP above a defined threshold (stratified by LVEF) • Appropriate doses of medical therapy and use of medical devices

EMPEROR-PRESERVED[3, 11, 38] (empagliflozin 10 mg)	5988	2·2	2938 (49%)	5988 (100%)	• Overall: 61 (20) • Diabetes: 60 (21) • No diabetes: 62 (19)	21·0 (8·0–71·6)	• Symptomatic chronic heart failure (NYHA class II–IV) with LVEF >40% • Echocardiographic evidence of structural heart disease or hospitalisation for heart failure in the last year • NT-proBNP >300 pg/mL (or >900 pg/mL if in atrial fibrillation) • eGFR ≥20 mL/min per 1·73 m² No recent coronary event
DELIVER[4] (dapagliflozin 10 mg)	6263	2·3	3150 (50%)†	6263 (100%)	• Overall: 61 (19) • Diabetes: 60 (20) • No diabetes: 63 (19)	NA	Symptomatic heart failure (NYHA class II–IV) with LVEF >40% (ambulatory or hospitalised) Echocardiographic evidence of structural heart disease NT-proBNP ≥300 pg/mL (or ≥600 pg/mL if in atrial fibrillation)
SOLOIST-WHF[20] (sotagliflozin 200–400 mg)	1222	0·8	1222 (100%)	1222 (100%)	51 (17)‡	NA	• Hospitalised for heart failure requiring intravenous therapy (ie, a heart failure population with a wide range of LVEFs) Type 2 diabetes • eGFR ≥30 mL/min per 1·73 m² No recent coronary event
Chronic kidney disease							
CREDENCE[7, 39, 40] (canagliflozin 100 mg)	4401	2·6	4401 (100%)	652 (15%)	56 (18)	927 (463–1833)	• Type 2 diabetes • eGFR 30–90 mL/min per 1·73 m² • uACR 300–5000 mg/g Stable maximally tolerated RAS blockade Excluded suspected non-diabetic kidney disease
SCORED[9] (sotagliflozin 200–400 mg)	10 584	1·3	10 584 (100%)	3283 (31%)	44 (11)‡	74 (17–481)	• Type 2 diabetes • eGFR 25–60 mL/min per 1·73 m² At least one cardiovascular risk factor
DAPA-CKD[8, 10, 22, 23, 41, 42] (dapagliflozin 10 mg)	4304	2·4	2906 (68%)	468 (11%)	• Overall: 43 (12) • Diabetes: 44 (13) • No diabetes: 42 (12)	949 (477–1885)	• eGFR 25–75 mL/min per 1·73 m² • uACR 200–5000 mg/g • Stable maximally tolerated RAS blockade, unless documented intolerance Excluded polycystic kidney disease, lupus nephritis, or anti-neutrophil cytoplasmic antibody-associated vasculitis
EMPA-KIDNEY[12, 13] (empagliflozin 10 mg)	6609	2·0	3040 (46%)†	658 (10%)	• Overall: 37 (14) • Diabetes: 36 (13) • No diabetes: 39 (15)	329 (49–1069)	eGFR 20–45 mL/min per 1·73 m² or eGFR 45–90 mL/min per 1·73 m² with uACR ≥200 mg/g at screening§ Clinically appropriate RAS blockade, unless not indicated or not tolerated Excluded polycystic kidney disease

Median follow-up is reported without IQR as these data were not always available. eGFR=estimated glomerular filtration rate. LVEF=left ventricular ejection fraction. NA=not available. NT-proBNP=N-terminal prohormone brain natriuretic peptide. NYHA=New York Heart Association. RAS=renin angiotensin system. uACR=urinary albumin:creatinine ratio.

* Includes patients with HbA_{1c} ≥6·5% at enrolment.

† Includes patients with HbA_{1c} ≥6·5% at baseline, or with history or prevalent use of a glucose-lowering agent; DELIVER had four participants with uncertain diabetes status who were excluded from all analyses; 68 patients in EMPA-KIDNEY had type 1 diabetes.

‡ The mean and SD were estimated from reported median and IQR.

§ 254 participants with an eGFR <20 mL/min per 1·73 m^2 at their randomisation visit.

Risk of Bias Assessment

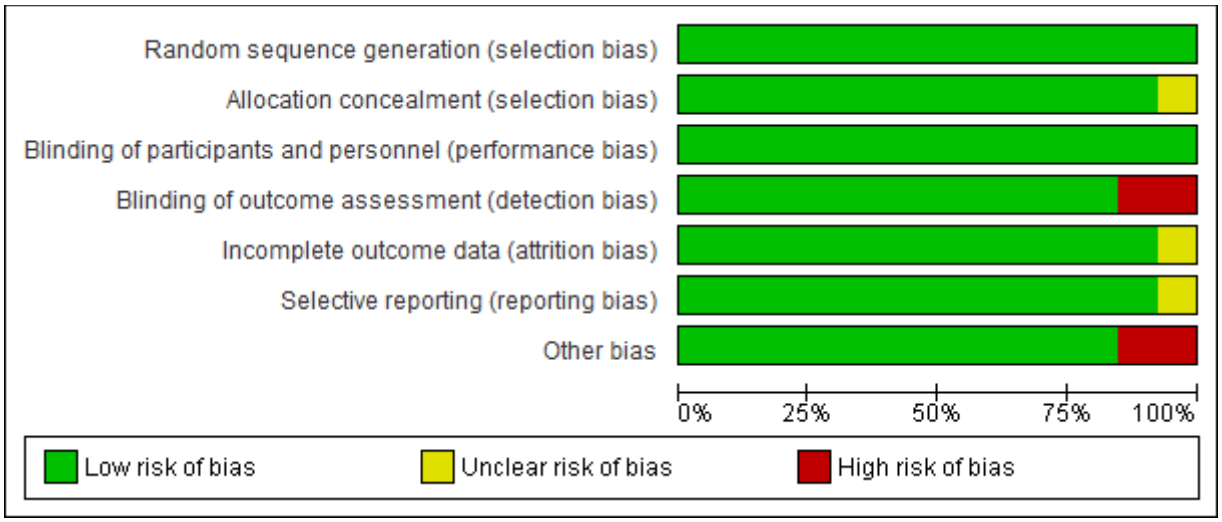
The Risk of Bias (RoB) assessment table () and Figure (a&b) provides a comprehensive evaluation of 13 landmark randomized controlled trials (RCTs) investigating the efficacy and safety of SGLT2 inhibitors across cardiovascular, renal, and heart failure populations. The majority of the included trials demonstrated low risk of bias across all five domains, reflecting rigorous methodological design, high adherence to CONSORT standards, and transparent reporting of prespecified outcomes. Specifically, trials such as DECLARE–TIMI 58, CANVAS, VERTIS CV, EMPA-REG OUTCOME, DAPA-HF, CREDENCE, DAPA-CKD, and EMPA-KIDNEY were rated as low risk across all domains, with clear documentation of randomization procedures, effective blinding, minimal missing outcome data, blinded outcome adjudication, and adherence to preregistered analysis plans.

Conversely, two trials—SOLOIST-WHF and SCORED—were identified as having high overall risk of bias, primarily due to lack of event adjudication, changes to primary outcomes during the study, and early termination due to funding constraints. These limitations introduced risks particularly in the domains of outcome measurement and reporting bias, reducing the internal validity of effect estimates. Although these trials were double-blinded and randomized, their reliance on investigator-reported outcomes and unadjudicated event data warrants caution in interpreting the findings.

Importantly, even trials that stopped early for benefit (e.g., CREDENCE, DAPA-CKD) maintained low bias ratings due to independent data monitoring, prespecified stopping rules, and comprehensive outcome adjudication. Overall, the robustness of these trials—especially the consistency across independently funded and industry-sponsored studies—reinforces the reliability of their results and supports their inclusion in meta-analyses or clinical guidelines. However, sensitivity analyses excluding high-risk trials should be considered to assess the stability of pooled estimates.

Table (): Risk of Bias Assessment:

Trial	Random ization	Blinding of participants and personnel	Incomplete outcome	Blinding of outcome assessment	Allocation concealment	Overall Risk of Bias
EMPEROR-Reduced	Low	Low	Low	Low	Low	Low
SCORED	Low	Low	Low	High	Some concerns	High
SOLOIST-WHF	Low	Low	Some concerns	High	Some concerns	High
VERTIS CV	Low	Low	Low	Low	Low	Low
EMPEROR-Preserved	Low	Low	Low	Low	Low	Low
EMPA-REG OUTCOME	Low	Low	Low	Low	Low	Low
EMPA-KIDNEY	Low	Low	Low	Low	Low	Low
DELIVER	Low	Low	Low	Low	Low	Low
DECLAREâ €“TIMI 58	Low	Low	Low	Low	Low	Low
DAPA-HF	Low	Low	Low	Low	Low	Low
DAPA-CKD	Low	Low	Low	Low	Low	Low
CREDENCE	Low	Low	Low	Low	Low	Low
CANVAS Program	Low	Low	Low	Low	Low	Low



Figure(): Risk of Bias graph

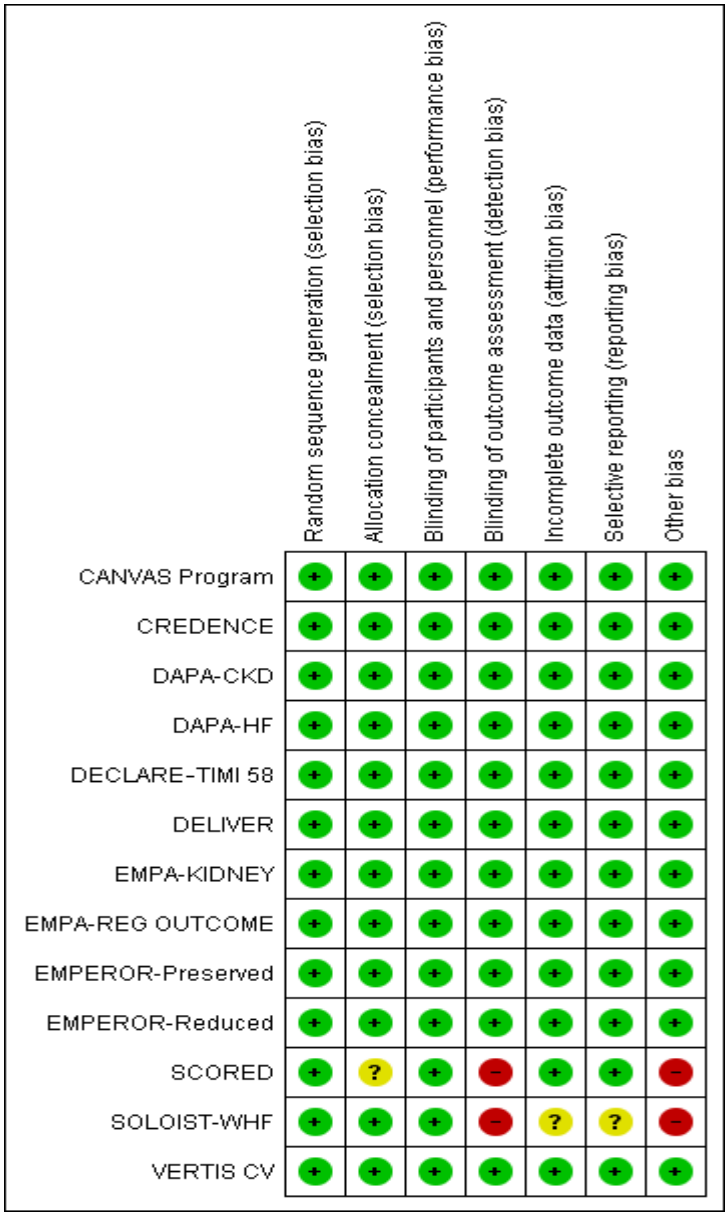


Figure (): Risk of Bias Summary

Discussion

While extensive randomized controlled trials of SGLT2 inhibitors have previously targeted individuals with type 2 diabetes, chronic kidney disease (CKD), and heart failure, no earlier research has specifically been powered to evaluate kidney and cardiovascular outcomes in patients without diabetes. The central aim was to synthesize data from major trials of SGLT2 inhibitors across populations with CKD, heart failure, and type 2 diabetes who were at high cardiovascular risk. This was done to compare the impact of these drugs on kidney disease progression, acute kidney injury (AKI), and related outcomes in those with and without diabetes. Our findings encompass nearly 90,000 participants, including around 16,000 non-diabetic individuals.

Kidney disease progression was operationalized using a composite outcome of sustained ≥50% eGFR decline from baseline, initiation of dialysis, kidney transplant, persistently low eGFR, or death attributed to kidney failure. Our results revealed that SGLT2 inhibitors lowered the risk of kidney disease progression by 37% and reduced the incidence of AKI by 23%. Notably, these protective effects were consistent regardless of diabetes status. Despite the expected reduction in glycosuric efficacy in those with lower baseline kidney function (47), we found no substantial diminution in renal benefits across trials sorted by initial eGFR. Importantly, SGLT2 inhibitors demonstrated safety even at reduced eGFR levels, down to at least 20 mL/min/1.73 m^2, and non-diabetic patients appeared particularly unlikely to develop complications like ketoacidosis or amputation—regardless of treatment status.

The ≥50% sustained eGFR reduction threshold has been widely used to reflect kidney disease progression in post hoc analyses of the DAPA-CKD trial (1, 8, 10, 22, 23). This threshold offers greater specificity for end-stage kidney disease progression compared to lower eGFR reduction cutoffs (≥30% or ≥40%) that might be confounded by acute dips associated with SGLT2 inhibitor initiation (48, 49, 50). The DAPA-CKD trial also demonstrated that dapagliflozin's effects were consistent across several CKD subtypes, including diabetic nephropathy, glomerular disease, hypertensive nephrosclerosis, and idiopathic CKD (10). Additionally, benefits were observed among 270 patients with IgA nephropathy—the most common glomerulonephritis worldwide—where 25 progression events were recorded (22). The EMPA-KIDNEY trial extended these findings with data on 817 patients with IgA nephropathy and 80 progression outcomes (appendix p 18). Our results confirms that SGLT2 inhibitors exert renal protective effects irrespective of diabetes status or the underlying cause of CKD.

Based on event rates observed across trials, we estimate that for every 1000 CKD patients treated for one year with an SGLT2 inhibitor, approximately 11 kidney disease progression events are averted among those with diabetes and 15 among those without. Additionally, treatment could prevent roughly four to five AKI episodes per 1000 patients, regardless of diabetic status. Past trials have also demonstrated that these renal benefits correspond to fewer patients needing dialysis or transplant (7, 8), and modeling data indicate that such outcomes can be cost-effective in diabetic CKD populations (51). We found no strong evidence suggesting that renal benefit was influenced by baseline kidney function. Importantly, EMPA-KIDNEY and DAPA-CKD included nearly 3,000 participants with an eGFR between 20–30 mL/min/1.73 m^2, among whom 489 kidney disease progression events were observed (7, 8, 52). Although some clinical guidelines now support initiating SGLT2 inhibitors at eGFR as low as 20 mL/min/1.73 m^2 (53, 54), others still recommend higher cutoffs such as 25 or 30 mL/min/1.73 m^2 (55, 56, 57). Since individuals with lower eGFR face the greatest absolute risk of progression (58), our findings support earlier initiation and continued use of SGLT2 inhibitors in this high-risk population, even below 20 mL/min/1.73 m^2. In fact, over 250 EMPA-KIDNEY participants had eGFRs below that threshold at baseline, offering indirect evidence supporting this strategy.

Our study has several methodological strengths. It uniquely incorporates a standardized definition for kidney disease progression—something lacking in earlier reviews—and aggregates all available large-scale randomized evidence, covering approximately 90,000 participants from 13 major trials. The inclusion of recent EMPA-KIDNEY and DELIVER trial data has more than doubled the number of kidney events recorded in non-diabetic patients (1). However, there are limitations. The number of cardiovascular deaths and hospitalizations due to heart failure in CKD patients without diabetes was low. Also, most studies did not adjudicate AKI events. The absence of individual-level trial data restricts our ability to evaluate long-term eGFR trajectories (59), particularly in patients with slower disease progression or those with minimal proteinuria. Furthermore, SGLT2 inhibitors' efficacy and safety in patients requiring dialysis or with kidney transplants remain unproven (e.g., NCT05374291), and evidence is sparse for those with specific excluded diagnoses such as polycystic kidney disease or type 1 diabetes (appendix p 8) (44, 60). Lastly, while our absolute risk reductions are trial-specific, relative risks (RRs) are more broadly applicable. Thus, clinicians can apply our RRs alongside individual risk estimates from validated prediction models to inform treatment decisions.

In summary, this comprehensive synthesis of large placebo-controlled SGLT2 inhibitor trials illustrates that these agents effectively reduce risks of kidney

disease progression, AKI, cardiovascular mortality, and heart failure hospitalization in patients with CKD or heart failure—regardless of diabetes status. These benefits were observed across a wide spectrum of kidney function and primary renal diagnoses. The findings strongly support a prominent therapeutic role for SGLT2 inhibitors in CKD management across varied clinical contexts.

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