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Influence of sodium/glucose cotransporter-2 inhibitors on the incidence of acute kidney injury: a meta-analysis

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Background: Sodium/glucose cotransporter-2 inhibitors (SGLT2i) are associated with cardiovascular benefits. The aim of this systematic review and meta-analysis is to summarize the influence of SGLT2i on the incidence of acute kidney injury (AKI), and to ascertain whether it is affected by confounding variables such as age, baseline renal function and concurrent use of renin-angiotensin-aldosterone system inhibitors (RAASi) or mineralocorticoid receptor antagonists (MRA).

Methods: PubMed, Embase, and Cochrane Library databases were searched for randomized controlled trials comparing the influence of SGLT2i versus placebo/ blank treatment on AKI in the adult population. A fixed-effect model was used if the heterogeneity was not significant; otherwise, a randomized-effect model was used.

Results: Eighteen studies comprising 98,989 patients were included. Compared with placebo/blank treatment, treatment with SGLT2i significantly reduced the risk of AKI (risk ratio [RR]: 0.78, 95% confidence interval [CI]: 0.71 to 0.84, p < 0.001; $l^2 = 0$ %). Subgroup analysis suggested consistent results in patients with diabetes, chronic kidney disease, and heart failure (for subgroup difference, p = 0.32). Finally, univariate meta-regression suggested that the influence of SGLT2i on the risk of AKI was not significantly modified by variables such as age (coefficient: 0.011, p = 0.39), baseline estimated glomerular filtration rate (coefficient: -0.0042, p = 0.13) or concomitant use of RAASi (coefficient: 0.0041, p = 0.49) or MRA (coefficient: -0.0020, p = 0.34).

Conclusion: SGLT2i may be effective in reducing the risk of AKI, and the effect might not be modified by age, baseline renal function and concurrent use of RAASi or MRA.

KEYWORDS

acute kidney injury, meta-analysis, randomized controlled trials, sodium/glucose cotransporter-2 inhibitors, systematic review

Introduction

Sodium/glucose cotransporter-2 inhibitors (SGLT2i) represent a novel class of oral antidiabetic medications that have demonstrated additional advantageous effects on cardiac and renal function (Frak et al., 2023; Klen and Dolzan, 2023; Lam-Chung, 2023). From a pharmacological standpoint, SGLT2i functions by inhibiting the reabsorption of glucose in the initial proximal tubule of the kidney, thereby augmenting the excretion of glucose in the urine and reducing the overall glucose burden on the body (Vallon and Verma, 2021). In individuals diagnosed with type 2 diabetes mellitus (T2DM), an initial meta-analysis of three extensive clinical trials revealed that the utilization of SGLT2i was associated with an 11% decrease in the risk of major adverse cardiovascular events, a 23% decrease in the risk of cardiovascular death or hospitalization for heart failure (HF), and a 45% decrease in the risk of progression of renal disease (Zelniker et al., 2019). In a study involving patients with HF, it was demonstrated that SGLT2i effectively reduced the likelihood of cardiovascular death and hospitalizations for HF across a diverse range of patients, thus establishing their significance as a fundamental therapy for HF, regardless of ejection fraction or care setting (Vaduganathan et al., 2022). Furthermore, a recent meta-analysis encompassing 13 clinical trials revealed that SGLT2i exhibited efficacy in altering the risk of kidney disease progression, not only in patients with T2DM at high cardiovascular risk, but also in patients with chronic kidney disease (CKD) or HF regardless of diabetic status (2022). Consequently, the indications for SGLT2i have expanded beyond T2DM to include HF and CKD, supported by accumulating evidence. Nevertheless, conflicting findings have emerged regarding the potential occurrence of acute kidney injury (AKI) when utilizing SGLT2i (Copur et al., 2023). One case report documented a dialysis-dependent AKI following the initiation of SGLT2i, with a suggested association to osmotic nephropathy (Phadke et al., 2020). Furthermore, a recent investigation utilizing the most up-to-date records from the United States Food and Drug Administration's Adverse Event Reporting System has indicated a potential link between SGLT2i and the development of AKI, although this association may be mitigated in instances where renin-angiotensin-aldosterone system inhibitors (RAASi), such as angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB), are concurrently administered (Katsuhara and Ikeda, 2021). Nevertheless, it is worth noting that several observational studies have failed to demonstrate an elevated risk of AKI associated with the use of SGLT2 inhibitors (Rampersad et al., 2020; Zhuo et al., 2022). In order to conduct a comprehensive assessment of the impact of SGLT2i on the occurrence of AKI, we conducted a systematic review and meta-analysis of eligible randomized controlled trials (RCTs). Furthermore, we investigated whether the effect of SGLT2i on the risk of AKI could be influenced by study-specific factors such as age, baseline renal function, and concurrent use of RAASi at the study level.

Methods

This study was designed and implemented according to the Cochrane Handbook guidelines (Higgins et al., 2021) and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Page et al., 2021a; Page et al., 2021b).

Search strategy

A combination of strategies was used to search PubMed, Embase, and Cochrane Library for relevant studies with: (1) "SGLT 2 inhibitor" OR "SGLT-2 inhibitor" OR "SGLT2" OR "sodium glucose transporter 2 inhibitor" OR "sodium glucose transporter ii inhibitor" OR "sodium glucose cotransporter 2 inhibitors" OR "dapagliflozin" OR "canagliflozin" OR "tofogliflozin" OR "bexagliflozin" OR "empagliflozin" OR "remogliflozin" OR "luseogliflozin" OR "ertugliflozin" OR "henagliflozin" OR "ipragliflozin" OR "licogliflozin" OR "sergliflozin" OR "sotagliflozin"; (2) "acute" OR "abrupt"; (3) "kidney" OR "renal"; and (4) "random" OR "randomly" OR "randomized" OR "control" OR "placebo". Relevant clinical studies have been limited to humans. We also manually searched for reference lists to review and original articles that were related to the topic. Database searches were conducted on 14 May 2024.

Study selection

Studies were included if they fulfilled the following criteria according to the PICOS principles.

P (patients): adult patient population without limitations of the diagnosis, which could be patients with T2DM, CKD, or HF.

I (intervention): SGLT2i.

C (control): placebo or blank treatment.

O (outcome): incidence of AKI compared between patients with SGLT2i and controls during follow-up. The diagnosis of AKI was in accordance with the criteria used among the original studies

S (study design): parallel-group RCTs, published as full-length articles in peer-reviewed journals.

Non-RCTs, studies that did not include an intervention group of SGLT2i, those comparing the effects of different doses of SGLT2i, single-arm studies without controls, or studies not evaluating the outcome of AKI were excluded. For studies with overlapping patients, the study with the largest sample size was included.

Data extraction and quality assessment

The process of data extraction, mining, and quality evaluations was carried out by two authors working independently. In the event of any disagreement, the corresponding author was consulted to address and resolve such inconsistencies. Information regarding publication details (author, year of publication, and study country), study design (blind or open-label), patient characteristics (diagnosis, demographic information, baseline renal function as evaluated by estimated glomerular filtration rate (eGFR), proportions of patients with concurrent use of any RAASi, and proportions of patients with concurrent use of mineralocorticoid receptor antagonists [MRA]), details of interventions and controls, follow-up durations, and diagnostic criteria for AKI was extracted. The quality of RCTs was assessed utilizing the Cochrane Risk of Bias Tool (Higgins



et al., 2021), adhering to the subsequent criteria: (1) random sequence generation; (2) allocation concealment; (3) participant and staff blinding; (4) outcome assessor blinding; (5) presentation of incomplete outcome data; (6) reporting of selective results; and (7) identification of other potential biases.

Statistical analysis

The numbers of patients with AKI events and total numbers of patients allocated to the SGLT2i and control groups were extracted from the original reports. The influence of SGLT2i on the incidence of AKI in adult patients compared to control was summarized as risk ratio (RR) and corresponding 95% confidence intervals (CIs). The Cochrane Q test was performed (Higgins and Thompson, 2002). Heterogeneity was also estimated by calculating I^2 and $I^2 > 50\%$ suggested significant heterogeneity (Higgins et al., 2003). In the pooled analyses, a random-effects

model was employed when significant heterogeneity was identified; alternatively, a fixed-effects model was utilized (Higgins et al., 2021). A sensitivity analysis was performed by only including high-quality studies (all seven domains of Cochrane Risk of Bias Tool judged as low risk). Additionally, a predefined subgroup analysis was conducted based on the patients' diagnosis and the specific SGLT2i drugs administered. Furthermore, a univariate meta-regression analysis was conducted to investigate whether the study characteristics of continuous variables could significantly alter the impact of SGLT2i on AKI, such as mean age of the patients, proportion of men, mean eGFR at baseline, proportion of patients using any RAASi, proportion of patients using MRA, and mean follow-up duration of the study. Publication bias was assessed using funnel plots and Egger's regression asymmetry test (Egger et al., 1997). Statistical significance was defined as p < 0.05. The statistical analysis was performed using Stata software (version 12.0; Stata Corporation) and RevMan (version 5.1; Cochrane, Oxford, United Kingdom).

TABLE 1 Characteristics of the included studies.

| Study | Design | Patient diagnosis | No of patients | Mean age (years) | Men (%) | Baseline eGFR (ml/ min/1.73 m²) | Any RAASi (%) | MRA (%) | Intervention | Control | Follow-up duration (months) | Diagnosis of AKI |
|-----------------------------------|-----------|--|-------------------|------------------------|------------|---------------------------------------|---------------------|------------|----------------------------------|---------|-----------------------------------|---|
| Zinman et al. (2015) 10 mg | R, DB, PC | T2DM patients at high CV risk | 3,512 | 63.1 | 71 | 74.1 | 80.6 | 6.4 | Empagliflozin 10 mg/d | Placebo | 37.2 | MedDRA Preferred Term for AKI |
| Zinman et al. (2015) 25 mg | R, DB, PC | T2DM patients at high CV risk | 3,508 | 63.2 | 72 | 73.9 | 80.8 | 6.2 | Empagliflozin 25 mg/d | Placebo | 37.2 | MedDRA Preferred Term for AKI |
| Neal et al. (2017) | R, DB, PC | T2DM patients at high CV risk | 10,142 | 63.3 | 64.2 | 76.5 | 80 | NR | Canagliflozin 100 or 300 mg/d | Placebo | 47.1 | MedDRA Preferred Term for AKI |
| Perkovic et al. (2019) | R, DB, PC | T2DM patients with albuminuric CKD | 4,401 | 63 | 66.1 | 56.2 | 99.9 | NR | Canagliflozin 100 mg/d | Placebo | 31.4 | MedDRA Preferred Term for AKI |
| McMurray et al. (2019) | R, DB, PC | Patients with HFrEF | 4,744 | 66.4 | 76.6 | 65.7 | 94.4 | 71.1 | Dapagliflozin 10 mg/d | Placebo | 18.2 | MedDRA Preferred Term for AKI |
| Wiviott et al. (2019) | R, DB, PC | T2DM patients who had or were at risk for ASCVD | 17,160 | 64 | 62.6 | 85.2 | 81.3 | NR | Dapagliflozin 10 mg/d | Placebo | 50.4 | MedDRA Preferred Term for AKI |
| Heerspink et al. (2020) | R, DB, PC | Patients with eGFR of 25–75 mL/min/1.73 m ² | 4,304 | 61.9 | 66.9 | 43.1 | 98.1 | NR | Dapagliflozin 10 mg/d | Placebo | 28.8 | A doubling of SCr compared with most recent results |
| Cannon et al. (2020) | R, DB, PC | T2DM patients with ASCVD | 8,246 | 64.4 | 69.9 | 75.9 | 80.1 | 8.2 | Ertugliflozin 5 or 15 mg/d | Placebo | 42 | MedDRA Preferred Term for AKI |
| Zannad et al. (2021) no CKD | R, DB, PC | Patients with HFrEF and no CKD | 1746 | 63.9 | 77.9 | 79 | 92.5 | 75.2 | Empagliflozin 10 mg/d | Placebo | 16 | MedDRA Preferred Term for AKI |
| Zannad et al. (2021) CKD | R, DB, PC | Patients with HFrEF and CKD | 1978 | 70.2 | 74.5 | 46.9 | 86.8 | 67.8 | Empagliflozin 10 mg/d | Placebo | 16 | MedDRA Preferred Term for AKI |
| Kosiborod et al. (2021) | R, DB, PC | Hospitalized patients with COVID-19 and at least one CV risk factor | 1,250 | 61.4 | 57.4 | 83.8 | 35.5 | NR | Dapagliflozin 10 mg/d | Placebo | 3 | MedDRA Preferred Term for AKI |
| Anker et al. (2021) | R, DB, PC | Patients with HFpEF | 5,988 | 71.8 | 55.4 | 60.6 | 80.7 | 37.5 | Empagliflozin 10 mg/d | Placebo | 26.2 | MedDRA Preferred Term for AKI |
| Bhatt et al. (2021a) | R, DB, PC | T2DM patients with CKD (eGFR: 25–60 mL/min/ 1.73 m ²) | 10,584 | 69 | 55.1 | 44.6 | 88.5 | 15 | Sotagliflozin 200 or 400 mg/d | Placebo | 16 | MedDRA Preferred Term for AKI |
| Bhatt et al. (2021b) | R, DB, PC | T2DM patients hospitalized for recent worsening HF | 1,222 | 69.5 | 66.2 | 49.8 | 91.3 | 64.5 | Sotagliflozin 200 or 400 mg/d | Placebo | 9 | MedDRA Preferred Term for AKI |

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(Continued on following page)

TABLE 1 (Continued) Characteristics of the included studies.

| Study | Design | Patient diagnosis | No of patients | Mean age (years) | Men (%) | Baseline eGFR (ml/ min/1.73 m²) | Any RAASi (%) | MRA (%) | Intervention | Control | Follow-up duration (months) | Diagnosis of AKI |
|--------------------------|-----------|---------------------------------|-------------------|------------------------|------------|---------------------------------------|---------------------|------------|--------------------------|---------|-----------------------------------|---|
| Solomon et al. (2022) | R, DB, PC | Patients with HFpEF | 6,263 | 71.7 | 56.1 | 61 | 77.7 | 42.6 | Dapagliflozin 10 mg/d | Placebo | 27.6 | MedDRA Preferred Term for AKI |
| Voors et al. (2022) | R, DB, PC | Patients with ADHF | 530 | 70.5 | 66.2 | 52 | 70 | 52 | Empagliflozin 10 mg/d | Placebo | 3 | MedDRA Preferred Term for AKI |
| Feitosa et al. (2023) | R, OL | T2DM patients undergoing PCI | 42 | 64.5 | 69 | 65.1 | 88.1 | NR | Empagliflozin 25 mg/d | Blank | 1 | KDIGO criteria |
| EMPA-kidney 2023 | R, DB, PC | Patients with CKD | 6,609 | 63.9 | 66.8 | 37.3 | 85.1 | 7 | Empagliflozin 10 mg/d | Placebo | 24 | An increase in SCr to 1.5- times a recent historical value or initiation of RRT |
| Cox et al. (2024) | R, OL | Patients with ADHF | 238 | 64.5 | 61 | 52.F | 52 | 50.5 | Dapagliflozin 10 mg/d | Blank | 1 | MedDRA Preferred Term for AKI |
| Butler et al. (2024) | R, DB, PC | Patients after AMI | 6,522 | 63.6 | 75.1 | 77.8 | 72.5 | 39.5 | Empagliflozin 10 mg/d | Placebo | 17.9 | MedDRA Preferred Term for AKI |

RAASi, renin-angiotensin-aldosterone system inhibitors; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonists; AKI, acute kidney injury; SGLT2i: Sodium/glucose cotransporter-2 inhibitors; R, randomized; DB, double-blind; PC, placebo-control; OL, open-label; T2DM, type 2 diabetes mellitus; CKD, chronic kidney disease; CV, cardiovascular; ASCVD, atherosclerotic cardiovascular diseases; HF, heart failure; ADHF, acute decompensated heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; AMI, acute myocardial infarction; COVID-19, Coronavirus Disease 19; NR, not reported; MedDRA, the Medical Dictionary for Regulatory Activities; PCI, percutanous coronary intervention; SCr, serum creatinine; KDIGO, kidney disease improving global outcomes; RRT, renal replacement therapy.

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| Study | Random sequence generation | Allocation concealment | Blinding in performance | Blinding in outcome detection | Incomplete outcome data | Reporting bias | Other bias |
|----------------------------|----------------------------------|---------------------------|-------------------------|-------------------------------------|----------------------------|-------------------|---------------|
| Zinman et al. (2015) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Neal et al. (2017) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Perkovic et al. (2019) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| McMurray et al. (2019) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Wiviott et al. (2019) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Heerspink et al. (2020) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Cannon et al. (2020) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Zannad et al. (2021) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Kosiborod et al. (2021) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Anker et al. (2021) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Bhatt et al. (2021a) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Bhatt et al. (2021b) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Solomon et al. (2022) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Voors et al. (2022) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Feitosa et al. (2023) | Unclear | Unclear | High risk | High risk | Low risk | Low risk | Low risk |
| EMPA-kidney 2023 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Cox et al. (2024) | Unclear | Low risk | High risk | High risk | Low risk | Low risk | Low risk |
| Butler et al. (2024) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |

TABLE 2 Study quality evaluation via the Cochrane Risk of Bias Tool.

Results

Search results

A diagram illustrating the process of database searching and study identification is presented in Figure 1. The search of the databases yielded a total of 798 articles, of which 599 were identified as unique after removing duplicates. Subsequently, 557 articles were excluded based on their title and abstract, primarily due to their lack of relevance to the research objectives. A thorough examination of the full text was conducted on 42 articles, resulting in the exclusion of 24 articles for the reasons depicted in Figure 1. Ultimately, the final analysis encompassed a total of 18 RCTs (Zinman et al., 2015; Neal et al., 2017; McMurray et al., 2019; Perkovic et al., 2019; Wiviott et al., 2019; Cannon et al., 2020; Heerspink et al., 2020; Bhatt et al., 2021; Anker et al., 2021; Bhatt et al., 2021b; Kosiborod et al., 2021; Zannad et al., 2021; Solomon et al., 2022; Voors et al., 2022; Feitosa et al., 2023; Herrington et al., 2023; Butler et al., 2024; Cox et al., 2024).

Study characteristics and data quality

An overview of the included studies is presented in Table 1. Since one of the included studies reported the outcome according to different doses of SGLT2i, and the other one reported the outcome according to whether the patients were with CKD, these datasets were included independently in the meta-analysis. Overall, 20 datasets from 18 RCTs (Zinman et al., 2015; Neal et al., 2017; McMurray et al., 2019; Perkovic et al., 2019; Wiviott et al., 2019; Cannon et al., 2020; Heerspink et al., 2020; Bhatt et al., 2021a; Anker et al., 2021; Bhatt et al., 2021b; Kosiborod et al., 2021; Zannad et al., 2021; Solomon et al., 2022; Voors et al., 2022; Feitosa et al., 2023; Herrington et al., 2023; Butler et al., 2024; Cox et al., 2024) involving 98,989 patients were included. Generally, patients with T2DM, CKD, HF, acute myocardial infarction, and hospitalized patients with COVID-19 were included. The mean ages of the patients were 61-72 years, with the baseline mean eGFR varying from 37 to 85 mL/min/1.73 m². In the intervention group, SGLT2i including empagliflozin, canagliflozin, dapagliflozin, ertugliflozin, and sotagliflozin were used. The follow-up durations were from 1 to 50 months. As for the diagnosis for AKI, the Medical Dictionary for Regulatory Activities (MDRA) preferred term for AKI was used for most of the included studies (Zinman et al., 2015; Neal et al., 2017; McMurray et al., 2019; Perkovic et al., 2019; Wiviott et al., 2019; Cannon et al., 2020; Bhatt et al., 2021a; Anker et al., 2021; Bhatt et al., 2021b; Kosiborod et al., 2021; Zannad et al., 2021; Solomon et al., 2022; Voors et al., 2022; Butler et al., 2024; Cox et al., 2024), while for the other studies, a

| | SGT | 2i | Cont | rol | | Risk Ratio | Risk Ratio |
|--|--|---|--|--|---|---|--|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% Cl | M-H, Fixed, 95% Cl |
| Zinman 2015 10mg | 26 | 2345 | 19 | 1167 | 2.1% | 0.68 [0.38, 1.23] | |
| Zinman 2015 25 mg | 19 | 2342 | 18 | 1166 | 2.0% | 0.53 [0.28, 1.00] | |
| Neal 2017 | 68 | 5795 | 70 | 4347 | 6.7% | 0.73 [0.52, 1.02] | |
| Perkovic 2019 | 86 | 2202 | 98 | 2199 | 8.2% | 0.88 [0.66, 1.16] | -+ |
| McMurray 2019 | 23 | 2373 | 46 | 2371 | 3.8% | 0.50 [0.30, 0.82] | |
| Wiviott 2019 | 125 | 8582 | 175 | 8578 | 14.6% | 0.71 [0.57, 0.90] | - |
| Heerspink 2020 | 39 | 2152 | 52 | 2152 | 4.3% | 0.75 [0.50, 1.13] | |
| Cannon 2020 | 101 | 5499 | 60 | 2747 | 6.7% | 0.84 [0.61, 1.15] | -+ |
| Zannad 2021 no CKD | 13 | 879 | 22 | 867 | 1.8% | 0.58 [0.30, 1.15] | |
| Zannad 2021 CKD | 33 | 981 | 45 | 997 | 3.7% | 0 75 [0 48 1 16] | |
| Kosiborod 2021 | 21 | 625 | 34 | 625 | 2.8% | 0.62 [0.36, 1.05] | |
| Anker 2021 | 97 | 2007 | 131 | 2001 | 10.9% | 0.74 [0.57, 0.96] | |
| Rhatt 2021a | 116 | 5292 | 111 | 5292 | 9.2% | 1 05 [0 81 1 25] | + |
| Bhatt 2021a | 25 | 609 | 27 | 614 | 2 20/ | 0.04 [0.55, 1.50] | _ _ |
| Solomon 2022 | 20 | 2121 | 21 | 2122 | 4 20/ | 0.02 [0.00, 1.09] | _ |
| Voors 2022 | 40 | 265 | 10 | 265 | 4.270 | 0.52 [0.02, 1.37] | |
| Foitona 2022 | 10 | 205 | 19 | 205 | 0.0% | 1.26 [0.25, 1.11] | |
| Feilosa 2023 | 3 | 22 | 2 | 20 | 0.2% | 1.30 [0.25, 7.34] | - |
| EIVIPA-Kidney 2023 | 107 | 3304 | 135 | 3305 | 0.40 | 0.79 [0.62, 1.02] | |
| Cox 2024 | 4 | 119 | 1 | 119 | 0.1% | 4.00 [0.45, 35.26] | |
| Butler 2024 | 27 | 3260 | 43 | 3262 | 3.6% | 0.63 [0.39, 1.01] | - |
| Total (95% CI) | | 52773 | | 46216 | 100.0% | 0 78 [0 71 0 84] | • |
| Total (3578 OI) | 090 | 52115 | 1150 | 40210 | 100.070 | 0.70 [0.71, 0.04] | |
| Hotorogonoity Chi2 = 1 | 909 FC df = 1 | O(D = 0 | 1100 | 0.0/ | | | F F F F F F |
| Test for everall effect: 7 | - E 02 /D | 9 (F - 0 | J.49), I ⁻ - | 0% | | | 0.02 0.1 1 10 50 |
| Test for overall effect. Z | - 5.95 (F | < 0.000 | 01) | | | | Favours SGLT2i Favours control |
| | SCT | . | Cont | | | Bick Batio | Pick Potio |
| | 361 | 21 | Cont | 01 | | RISK Ratio | RISK RALIO |
| Study or Subgroup | Evonte | Total | Evonte | Total | Woight | M-H Fixed 95% CI | M-H Fixed 95% Cl |
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% Cl | M-H, Fixed, 95% Cl |
| Zinman 2015 10mg | Events 26 | Total 2345 | Events 19 | Total 1167 | <u>Weight</u> 2.1% | M-H, Fixed, 95% Cl 0.68 [0.38, 1.23] | M-H, Fixed, 95% Cl |
| Study or Subgroup Zinman 2015 10mg Zinman 2015 25 mg | Events 26 19 | Total 2345 2342 | Events 19 18 | Total 1167 1166 | Weight 2.1% 2.0% | M-H, Fixed, 95% Cl 0.68 [0.38, 1.23] 0.53 [0.28, 1.00] | <u>M-H, Fixed, 95% Cl</u> |
| Zinman 2015 10mg Zinman 2015 25 mg Neal 2017 | Events 26 19 68 | Total 2345 2342 5795 | Events 19 18 70 | Total 1167 1166 4347 | Weight 2.1% 2.0% 6.7% | M-H, Fixed, 95% Cl 0.68 [0.38, 1.23] 0.53 [0.28, 1.00] 0.73 [0.52, 1.02] | M-H, Fixed, 95% Cl |
| Zinman 2015 10mg Zinman 2015 25 mg Neal 2017 Perkovic 2019 | Events 26 19 68 86 | Total 2345 2342 5795 2202 | Events 19 18 70 98 | Total 1167 1166 4347 2199 | Weight 2.1% 2.0% 6.7% 8.2% | M-H, Fixed, 95% CI 0.68 [0.38, 1.23] 0.53 [0.28, 1.00] 0.73 [0.52, 1.02] 0.88 [0.66, 1.16] | M-H. Fixed. 95% Cl |
| Study or Subgroup Zinman 2015 10mg Zinman 2015 25 mg Neal 2017 Perkovic 2019 McMurray 2019 | Events 26 19 68 86 23 | Total 2345 2342 5795 2202 2373 | Events 19 18 70 98 46 | Total 1167 1166 4347 2199 2371 | Weight 2.1% 2.0% 6.7% 8.2% 3.8% | M-H, Fixed, 95% Cl 0.68 [0.38, 1.23] 0.53 [0.28, 1.00] 0.73 [0.52, 1.02] 0.88 [0.66, 1.16] 0.50 [0.30, 0.82] | M-H. Fixed, 95% Cl |
| Zinman 2015 10mg Zinman 2015 25 mg Neal 2017 Perkovic 2019 McMurray 2019 Wiviott 2019 | Events 26 19 68 86 23 125 | Total 2345 2342 5795 2202 2373 8582 | Events 19 18 70 98 46 175 | Total 1167 1166 4347 2199 2371 8578 | Weight 2.1% 2.0% 6.7% 8.2% 3.8% 14.6% | M-H, Fixed, 95% Cl 0.68 [0.38, 1.23] 0.53 [0.28, 1.00] 0.73 [0.52, 1.02] 0.88 [0.66, 1.16] 0.50 [0.30, 0.82] 0.71 [0.57, 0.90] | M-H. Fixed, 95% Cl |
| Study of Subgroup Zinman 2015 25 mg Neal 2017 Perkovic 2019 McMurray 2019 Wiviott 2019 Heerspink 2020 | Events 26 19 68 86 23 125 39 | Total 2345 2342 5795 2202 2373 8582 2152 | Events 19 18 70 98 46 175 52 | Total 1167 1166 4347 2199 2371 8578 2152 | Weight 2.1% 2.0% 6.7% 8.2% 3.8% 14.6% 4.3% | M-H, Fixed, 95% Cl 0.68 [0.38, 1.23] 0.53 [0.28, 1.00] 0.73 [0.52, 1.02] 0.88 [0.66, 1.16] 0.50 [0.30, 0.82] 0.71 [0.57, 0.90] 0.75 [0.50, 1.13] | M-H. Fixed, 95% Cl |
| Study of Subgroup Zinman 2015 10mg Neal 2015 25 mg Neal 2017 Perkovic 2019 McMurray 2019 Wiviott 2019 Heerspink 2020 Cannon 2020 | Events 26 19 68 86 23 125 39 101 | Total 2345 2342 5795 2202 2373 8582 2152 5499 | Events 19 18 70 98 46 175 52 60 | Total 1167 1166 4347 2199 2371 8578 2152 2747 | Weight 2.1% 2.0% 6.7% 8.2% 3.8% 14.6% 4.3% 6.7% | M-H, Fixed, 95% Cl 0.68 [0.38, 1.23] 0.53 [0.28, 1.00] 0.73 [0.52, 1.02] 0.88 [0.66, 1.16] 0.50 [0.30, 0.82] 0.71 [0.57, 0.90] 0.75 [0.50, 1.13] 0.84 [0.61, 1.15] | M-H. Fixed. 95% Cl |
| Study of Subgroup Zinman 2015 10mg Zinman 2015 25 mg Neal 2017 Perkovic 2019 McMurray 2019 Wiviott 2019 Heerspink 2020 Cannon 2020 Zannad 2021 no CKD | Events 26 19 68 86 23 125 39 101 13 | Total 2345 2342 5795 2202 2373 8582 2152 5499 879 | Events 19 18 70 98 46 175 52 60 22 | Total 1167 1166 4347 2199 2371 8578 2152 2747 867 | Weight 2.1% 2.0% 6.7% 8.2% 3.8% 14.6% 4.3% 6.7% 1.9% | M-H, Fixed, 95% Cl 0.68 [0.38, 1.23] 0.53 [0.28, 1.00] 0.73 [0.52, 1.02] 0.88 [0.66, 1.16] 0.50 [0.30, 0.82] 0.71 [0.57, 0.90] 0.75 [0.50, 1.13] 0.84 [0.61, 1.15] | M-H. Fixed. 95% Cl |
| Study of Subgroup Zinman 2015 10mg Zinman 2015 25 mg Neal 2017 Perkovic 2019 McMurray 2019 Wiviott 2019 Heerspink 2020 Cannon 2020 Zannad 2021 no CKD Zannad 2021 CKD | Events 26 19 68 86 23 125 39 101 13 33 | Total 2345 2342 5795 2202 2373 8582 2152 5499 879 981 | Events 19 18 70 98 46 175 52 60 22 45 | Total 1167 1166 4347 2199 2371 8578 2152 2747 867 997 | Weight 2.1% 2.0% 6.7% 8.2% 3.8% 14.6% 4.3% 6.7% 1.9% 3.7% | M-H, Fixed, 95% Cl 0.68 [0.38, 1.23] 0.53 [0.28, 1.00] 0.73 [0.52, 1.02] 0.88 [0.66, 1.16] 0.50 [0.30, 0.82] 0.71 [0.57, 0.90] 0.75 [0.50, 1.13] 0.84 [0.61, 1.15] 0.58 [0.30, 1.15] 0.75 [0.48, 1.16] | M-H. Fixed, 95% Cl |
| Study of Subgroup Zinman 2015 10mg Dimman 2015 25 mg Neal 2017 Perkovic 2019 McMurray 2019 Wiviott 2019 Heerspink 2020 Cannon 2020 Zannad 2021 CKD Kosiborod 2021 | Events 26 19 68 86 23 125 39 101 13 33 21 | Total 2345 2342 5795 2202 2373 8582 2152 5499 879 981 625 | Events 19 18 70 98 46 175 52 60 22 45 34 | Total 1167 1166 4347 2199 2371 8578 2152 2747 867 997 625 | Weight 2.1% 2.0% 6.7% 8.2% 3.8% 14.6% 4.3% 6.7% 1.9% 3.7% 2.8% | <u>M-H. Fixed, 95% Cl</u> 0.68 [0.38, 1.23] 0.53 [0.28, 1.00] 0.73 [0.52, 1.02] 0.88 [0.66, 1.16] 0.50 [0.30, 0.82] 0.71 [0.57, 0.90] 0.75 [0.50, 1.13] 0.84 [0.61, 1.15] 0.75 [0.48, 1.16] 0.62 [0.36, 1.05] | M-H. Fixed. 95% Cl |
| Study of Subgroup Zinman 2015 10mg Neal 2017 Perkovic 2019 McMurray 2019 Wiviott 2019 Heerspink 2020 Cannon 2020 Zannad 2021 no CKD Zannad 2021 CKD Kosiborod 2021 Anker 2021 | Events 26 19 68 86 23 125 39 101 13 33 21 97 | Total 2345 2342 5795 2202 2373 8582 2152 5499 879 981 625 2997 | Events 19 18 70 98 46 175 52 60 22 45 34 131 | Total 1167 1166 4347 2199 2371 8578 2152 2747 867 997 625 2991 | Weight 2.1% 2.0% 6.7% 8.2% 3.8% 14.6% 4.3% 6.7% 1.9% 3.7% 2.8% 11.0% | M-H, Fixed, 95% Cl 0.68 [0.38, 1.23] 0.53 [0.28, 1.00] 0.73 [0.52, 1.02] 0.88 [0.66, 1.16] 0.50 [0.30, 0.82] 0.71 [0.57, 0.90] 0.75 [0.50, 1.13] 0.84 [0.61, 1.15] 0.58 [0.30, 1.15] 0.75 [0.48, 1.16] 0.62 [0.36, 1.05] 0.74 [0.57, 0.96] | M-H. Fixed. 95% Cl |
| Study of Subgroup Zinman 2015 10mg Zinman 2015 25 mg Neal 2017 Perkovic 2019 McMurray 2019 Wiviott 2019 Heerspink 2020 Cannon 2020 Zannad 2021 no CKD Zannad 2021 CKD Kosiborod 2021 Anker 2021 Bhatt 2021a | Events 26 19 68 23 125 39 101 13 32 21 97 116 | Total 2345 2342 5795 2202 2373 8582 2152 5499 879 981 625 2997 5292 | Events 19 18 70 98 46 175 52 60 22 45 34 131 111 | Total 1167 1166 4347 2199 2371 8578 2152 2747 867 997 625 2991 5292 | Weight 2.1% 2.0% 6.7% 8.2% 3.8% 14.6% 4.3% 6.7% 1.9% 3.7% 2.8% 11.0% 9.3% | M-H, Fixed, 95% Cl 0.68 [0.38, 1.23] 0.53 [0.28, 1.00] 0.73 [0.52, 1.02] 0.88 [0.66, 1.16] 0.50 [0.30, 0.82] 0.71 [0.57, 0.90] 0.75 [0.50, 1.13] 0.84 [0.61, 1.15] 0.58 [0.30, 1.15] 0.75 [0.48, 1.16] 0.62 [0.36, 1.05] 0.74 [0.57, 0.96] 1.05 [0.81, 1.35] | M-H. Fixed. 95% Cl |
| Study of Subgroup Zinman 2015 10mg Zinman 2015 25 mg Neal 2017 Perkovic 2019 McMurray 2019 Wiviott 2019 Heerspink 2020 Cannon 2020 Zannad 2021 n CKD Xannad 2021 CKD Kosiborod 2021 Anker 2021 Bhatt 2021b | Events 26 19 68 86 23 125 39 101 13 33 21 97 116 25 | Total 2345 2342 5795 2202 2373 8582 2152 5499 879 981 625 2997 5292 608 | Events 19 18 70 98 46 175 52 60 22 45 34 131 111 27 | Total 1167 1166 4347 2199 2371 8578 2152 2747 867 997 625 2991 5292 614 | Weight 2.1% 2.0% 6.7% 8.2% 3.8% 14.6% 4.3% 6.7% 1.9% 3.7% 2.8% 11.0% 9.3% 2.2% | M-H, Fixed, 95% Cl 0.68 [0.38, 1.23] 0.53 [0.28, 1.00] 0.73 [0.52, 1.02] 0.88 [0.66, 1.16] 0.50 [0.30, 0.82] 0.71 [0.57, 0.90] 0.75 [0.50, 1.13] 0.84 [0.61, 1.15] 0.75 [0.48, 1.16] 0.62 [0.36, 1.05] 0.74 [0.57, 0.96] 1.05 [0.81, 1.35] 0.94 [0.55, 1.59] | M-H. Fixed. 95% Cl |
| Study of Subgroup Zinman 2015 10mg Zinman 2015 25 mg Neal 2017 Perkovic 2019 McMurray 2019 Wiviot 2019 Heerspink 2020 Cannon 2020 Zannad 2021 no CKD Zannad 2021 no CKD Zannad 2021 Anker 2021 Bhatt 2021a Bhatt 2021b Solomon 2022 | Events 26 19 68 23 125 39 101 13 33 21 97 116 25 46 | Total 2345 2342 5795 2202 2373 8582 2152 5499 879 981 625 2997 5292 608 3131 | Events 19 18 70 98 46 175 52 60 22 45 34 131 111 27 50 | Total 1167 1166 4347 2199 2371 8578 2152 2747 867 997 625 2991 5292 614 3132 | Weight 2.1% 2.0% 6.7% 8.2% 14.6% 4.3% 6.7% 1.9% 3.7% 2.8% 11.0% 9.3% 2.2% 4.2% | M-H, Fixed, 95% Cl 0.68 [0.38, 1.23] 0.53 [0.28, 1.00] 0.73 [0.52, 1.02] 0.88 [0.66, 1.16] 0.50 [0.30, 0.82] 0.71 [0.57, 0.90] 0.75 [0.50, 1.13] 0.84 [0.61, 1.15] 0.75 [0.48, 1.16] 0.62 [0.36, 1.05] 0.74 [0.57, 0.96] 1.05 [0.81, 1.35] 0.94 [0.55, 1.59] 0.92 [0.62, 1.37] | M-H. Fixed. 95% Cl |
| Study of Subgroup Zinman 2015 10mg Neal 2017 Perkovic 2019 McMurray 2019 Wiviott 2019 Heerspink 2020 Cannon 2020 Zannad 2021 no CKD Zannad 2021 no CKD Zannad 2021 CKD Kosiborod 2021 Anker 2021 Bhatt 2021a Bhatt 2021b Solomon 2022 Voors 2022 | Events 26 19 68 23 125 39 101 13 333 21 97 116 25 466 10 | Total 2345 2342 5795 2202 2373 8582 2152 5499 879 981 625 2997 5292 608 3131 265 | Events 19 18 70 98 46 1752 60 22 45 34 131 111 27 50 19 | Total 1167 1166 4347 2199 2371 8578 2152 2747 867 997 625 2991 5292 614 3132 265 | Weight 2.1% 2.0% 6.7% 3.8% 14.6% 4.3% 6.7% 1.9% 3.7% 2.8% 11.0% 9.3% 2.2% 4.2% 1.6% | M-H, Fixed, 95% Cl 0.68 [0.38, 1.23] 0.53 [0.28, 1.00] 0.73 [0.52, 1.02] 0.88 [0.66, 1.16] 0.50 [0.30, 0.82] 0.71 [0.57, 0.90] 0.75 [0.50, 1.13] 0.84 [0.61, 1.15] 0.58 [0.30, 1.15] 0.58 [0.30, 1.15] 0.62 [0.36, 1.05] 1.05 [0.81, 1.35] 0.94 [0.55, 1.59] 0.92 [0.62, 1.37] 0.53 [0.25, 1.17] | M-H. Fixed. 95% Cl |
| Study of Subgroup Zinman 2015 10mg Zinman 2015 25 mg Neal 2017 Perkovic 2019 McMurray 2019 Wiviott 2019 Heerspink 2020 Cannon 2020 Zannad 2021 no CKD Zannad 2021 CKD Kosiborod 2021 Anker 2021 Bhatt 2021a Bhatt 2021a Bhatt 2021a Solomon 2022 Voors 2022 EMPA-kidney 2023 | Events 26 19 68 86 23 125 39 101 13 33 21 97 116 25 46 60 107 | Total 2345 2342 5795 2202 2373 8582 2152 2152 2499 879 981 625 2997 5292 608 3131 265 3304 | Events 19 18 70 98 46 175 52 60 22 45 34 131 111 27 50 19 135 | Total 1167 1166 4347 2199 2371 8578 2152 2747 867 997 625 2991 5292 614 3132 265 3305 | Weight 2.1% 2.0% 6.7% 8.2% 3.8% 14.6% 4.3% 6.7% 1.9% 3.7% 2.8% 11.0% 9.3% 2.2% 4.2% 1.6% 11.3% | M-H, Fixed, 95% Cl 0.68 [0.38, 1.23] 0.53 [0.28, 1.00] 0.73 [0.52, 1.02] 0.88 [0.66, 1.16] 0.50 [0.30, 0.82] 0.71 [0.57, 0.90] 0.75 [0.50, 1.13] 0.84 [0.61, 1.15] 0.58 [0.30, 1.15] 0.75 [0.48, 1.16] 0.62 [0.36, 1.05] 0.74 [0.57, 0.96] 1.05 [0.81, 1.35] 0.94 [0.55, 1.59] 0.92 [0.62, 1.37] 0.53 [0.25, 1.11] 0.79 [0.62, 1.02] | M-H. Fixed. 95% Cl |
| Study of Subgroup Zinman 2015 10mg Zinman 2015 25 mg Neal 2017 Perkovic 2019 McMurray 2019 Wiviott 2019 Heerspink 2020 Cannon 2020 Zannad 2021 no CKD Xannad 2021 no CKD Xannad 2021 CKD Kosiborod 2021 Anker 2021 Bhatt 2021b Solomon 2022 Voors 2022 EMPA-kidney 2023 Butler 2024 | Events 26 19 68 23 125 39 101 13 33 21 97 116 25 46 10 107 27 | Total 2345 2342 5795 2202 2373 8582 2152 5499 879 981 625 2997 5292 608 3131 265 3304 3260 | Events 19 18 700 98 46 175 52 60 22 45 34 131 111 27 50 19 135 43 | Total 1167 1166 4347 2199 2371 8578 2152 2747 867 997 625 2991 5292 614 3132 265 3305 3262 | Weight 2.1% 2.0% 6.7% 8.2% 3.8% 14.6% 4.3% 6.7% 1.9% 3.7% 2.8% 11.0% 9.3% 2.2% 4.2% 16.6% 11.3% 3.6% | M-H, Fixed, 95% Cl 0.68 [0.38, 1.23] 0.53 [0.28, 1.00] 0.73 [0.52, 1.02] 0.73 [0.52, 1.02] 0.75 [0.50, 1.16] 0.50 [0.30, 0.82] 0.71 [0.57, 0.90] 0.75 [0.50, 1.13] 0.84 [0.61, 1.15] 0.75 [0.48, 1.16] 0.62 [0.36, 1.05] 0.74 [0.57, 0.96] 1.05 [0.81, 1.35] 0.94 [0.55, 1.59] 0.92 [0.62, 1.37] 0.53 [0.25, 1.11] 0.79 [0.62, 1.02] 0.63 [0.39, 1.01] | M-H, Fixed, 95% Cl |
| Study of Subgroup Zinman 2015 10mg Zinman 2015 25 mg Neal 2017 Perkovic 2019 McMurray 2019 Wiviott 2019 Heerspink 2020 Cannon 2020 Zannad 2021 CKD Kosiborod 2021 Anker 2021 Bhatt 2021b Solomon 2022 Voors 2022 EMPA-kidney 2023 Butler 2024 | Events 26 19 68 86 23 125 39 101 13 333 21 97 116 25 46 100 107 27 | Total 2345 2342 5795 2202 2373 8582 2152 5499 879 981 625 2997 5292 608 3131 265 3304 3260 | Events 19 18 700 98 46 175 52 60 22 45 34 131 111 27 50 19 135 43 | Total 1167 1166 4347 2199 2371 8578 2152 2747 867 997 625 2991 5292 614 3132 265 3305 3262 | Weight 2.1% 2.0% 6.7% 8.2% 3.8% 14.6% 4.3% 6.7% 1.9% 3.7% 2.8% 11.0% 9.3% 2.2% 1.6% 11.3% 3.6% | M-H, Fixed, 95% Cl 0.68 [0.38, 1.23] 0.53 [0.28, 1.00] 0.73 [0.52, 1.02] 0.88 [0.66, 1.16] 0.50 [0.30, 0.82] 0.71 [0.57, 0.90] 0.75 [0.50, 1.13] 0.84 [0.61, 1.15] 0.75 [0.48, 1.16] 0.62 [0.36, 1.05] 0.74 [0.57, 0.96] 1.05 [0.81, 1.35] 0.94 [0.55, 1.59] 0.92 [0.62, 1.37] 0.53 [0.25, 1.11] 0.79 [0.62, 1.02] 0.63 [0.39, 1.01] | M-H. Fixed. 95% Cl |
| Study of Subgroup Zinman 2015 10mg Zinman 2015 25 mg Neal 2017 Perkovic 2019 McMurray 2019 Wiviott 2019 Heerspink 2020 Cannon 2020 Zannad 2021 CKD Zannad 2021 CKD Kosiborod 2021 Anker 2021 Bhatt 2021a Bhatt 2021a Bhatt 2021a Bhatt 2021a Bhatt 2021a Bhatt 2021a Bhatt 2021a Bhatt 2021b Solomon 2022 Voors 2022 EMPA-kidney 2023 Butler 2024 Total (95% CI) | Events 26 19 968 866 23 125 39 101 13 33 21 97 116 255 466 100 107 27 | Total 2345 2342 5795 2202 2373 8582 2152 5499 879 981 625 2997 5292 608 3131 265 3304 3260 52632 | Events 19 18 700 98 46 1752 600 222 45 34 131 111 27 500 19 135 43 | Total 1167 1166 4347 2199 2371 8578 2152 2747 867 997 625 2991 5292 614 3132 265 3305 3262 46077 | Weight 2.1% 2.0% 8.2% 3.8% 14.6% 4.3% 6.7% 19.9% 3.7% 2.8% 11.0% 9.3% 2.2% 1.6% 1.3% 3.6% 100.0% | <u>M-H. Fixed, 95% CI</u> 0.68 [0.38, 1.23] 0.53 [0.28, 1.00] 0.73 [0.52, 1.02] 0.88 [0.66, 1.16] 0.50 [0.30, 0.82] 0.71 [0.57, 0.90] 0.75 [0.50, 1.13] 0.84 [0.61, 1.15] 0.75 [0.48, 1.16] 0.62 [0.36, 1.05] 0.74 [0.57, 0.96] 1.05 [0.81, 1.35] 0.94 [0.55, 1.59] 0.92 [0.62, 1.37] 0.53 [0.25, 1.11] 0.79 [0.62, 1.02] 0.63 [0.39, 1.01] 0.77 [0.71, 0.84] | M-H. Fixed. 95% Cl |
| Study of Subgroup Zinman 2015 10mg Zinman 2015 25 mg Neal 2017 Perkovic 2019 McMurray 2019 Wiviott 2019 Heerspink 2020 Cannon 2020 Zannad 2021 no CKD Zannad 2021 no CKD Zannad 2021 no CKD Zannad 2021 no CKD Zannad 2021 Anker 2021 Bhatt 2021b Solomon 2022 Voors 2022 EMPA-kidney 2023 Butler 2024 Total (95% CI) Total events | Events 26 19 68 86 23 125 39 101 13 321 97 116 25 466 10 107 27 982 | Total 2345 2342 57955 2202 2373 8582 2152 5499 879 981 625 2997 5292 608 3131 265 3304 3260 52632 | Events 19 18 700 98 46 175 52 60 22 45 344 131 111 27 500 19 135 43 | Total 1167 1167 4347 2199 2371 8578 2152 2747 867 997 625 2991 5292 614 3132 265 3305 3262 46077 | Weight 2.1% 2.0% 6.7% 8.2% 3.8% 14.6% 1.9% 3.7% 2.8% 11.0% 9.3% 2.2% 4.2% 16.6% 11.3% 3.6% 100.0% | M-H, Fixed, 95% CI 0.68 [0.38, 1.23] 0.53 [0.28, 1.00] 0.73 [0.52, 1.02] 0.88 [0.66, 1.16] 0.50 [0.30, 0.82] 0.71 [0.57, 0.90] 0.75 [0.50, 1.13] 0.84 [0.61, 1.15] 0.58 [0.30, 1.15] 0.75 [0.48, 1.16] 0.62 [0.36, 1.05] 0.74 [0.57, 0.96] 1.05 [0.81, 1.35] 0.94 [0.55, 1.59] 0.92 [0.62, 1.37] 0.53 [0.25, 1.11] 0.79 [0.62, 1.02] 0.63 [0.39, 1.01] 0.77 [0.71, 0.84] | M-H. Fixed. 95% Cl |
| Study of Subgroup Zinman 2015 10mg Neal 2017 Perkovic 2019 McMurray 2019 Wiviott 2019 Heerspink 2020 Cannon 2020 Zannad 2021 no CKD Zannad 2021 no CKD Zannad 2021 CKD Kosiborod 2021 Anker 2021 Bhatt 2021a Bhatt 2021a Bhatt 2021a Bhatt 2021a Bhatt 2021a Bhatt 2021a Bhatt 2021a Bhatt 2021b Solomon 2022 Voors 2022 EMPA-kidney 2023 Butler 2024 Total (95% CI) Total events Heterogeneity: Chi ² = 15 | Events 26 19 68 86 23 125 39 101 13 33 21 16 25 46 100 107 27 982 5.94, df = 1 | Total 2345 2342 5795 2202 2373 8582 2152 2499 879 981 625 2997 5292 808 3131 265 3304 3260 52632 | Events 19 18 700 98 46 175 52 60 22 45 34 131 111 27 50 19 135 43 1155 0.53); I² = | Total 1167 1166 4347 2199 2371 8578 2152 2747 867 997 625 2991 5292 614 3132 265 3305 3262 46077 0% | Weight 2.1% 2.0% 6.7% 8.2% 3.8% 14.6% 4.3% 6.7% 1.9% 3.7% 2.8% 1.0% 9.3% 2.2% 4.2% 1.6% 11.3% 3.6% 100.0% | M-H, Fixed, 95% Cl 0.68 [0.38, 1.23] 0.53 [0.28, 1.00] 0.73 [0.52, 1.02] 0.88 [0.66, 1.16] 0.50 [0.30, 0.82] 0.71 [0.57, 0.90] 0.75 [0.50, 1.13] 0.84 [0.61, 1.15] 0.58 [0.30, 1.15] 0.75 [0.48, 1.16] 0.62 [0.36, 1.05] 1.05 [0.81, 1.35] 0.94 [0.55, 1.59] 0.92 [0.62, 1.37] 0.53 [0.25, 1.11] 0.79 [0.62, 1.02] 0.63 [0.39, 1.01] 0.77 [0.71, 0.84] | M-H. Fixed. 95% Cl |
| | Study or Subgroup Zinman 2015 10mg Zinman 2015 25 mg Neal 2017 Perkovic 2019 McMurray 2019 Wiviott 2019 Heerspink 2020 Zannad 2021 no CKD Zannad 2021 CKD Kosiborod 2021 Anker 2021 Bhatt 2021a Bhatt 2021b Solomon 2022 Voors 2022 Feitosa 2023 Cox 2024 Butler 2024 Total events Heterogeneity: Chi ² = 18 Test for overall effect: Z | Study or Subgroup Events Zinman 2015 10mg 26 Zinman 2015 25 mg 19 Neal 2017 68 Perkovic 2019 86 McMurray 2019 23 Wiviott 2019 125 Heerspink 2020 39 Cannon 2020 101 Zannad 2021 no CKD 13 Zannad 2021 CKD 33 Kosibord 2021 21 Anker 2021 97 Bhatt 2021a 116 Bhatt 2021a 116 Bhatt 2021a 107 Cox 2022 10 Voors 2022 107 Cox 2024 4 Butler 2024 27 Total (95% CI) 7 Total events 989 Heterogeneity: Chi ² = 18.56, df = 1 Test for overall effect: Z = 5.93 (P | Study or Subgroup Events Total Zinman 2015 10mg 26 2345 Zinman 2015 25 mg 19 2342 Neal 2017 68 5795 Perkovic 2019 86 2202 McMurray 2019 23 2373 Wiviott 2019 125 8582 Heerspink 2020 39 2152 Cannon 2020 101 5499 Zannad 2021 no CKD 13 879 Zannad 2021 CKD 33 981 Kosibord 2021 21 625 Anker 2021 97 2997 Bhatt 2021a 116 5292 Bhatt 2021a 116 5292 Bhatt 2021a 10 265 Solomon 2022 46 3131 Voors 2023 3 322 EMPA-kidney 2023 107 3304 Cox 2024 4 119 Butler 2024 27 3260 Total (95% CI) 52773 Total events | Study or Subgroup Events Total Events Zinman 2015 10mg 26 2345 19 Zinman 2015 25 mg 19 2342 18 Neal 2017 68 5795 70 Perkovic 2019 86 2202 98 McMurray 2019 23 2373 46 Wiviott 2019 125 8582 175 Heerspink 2020 39 2152 52 Cannon 2020 101 5499 60 Zannad 2021 no CKD 13 879 22 Zannad 2021 CKD 33 981 45 Kosiborod 2021 21 625 34 Anker 2021 97 2997 131 Bhatt 2021a 116 5292 111 Bhatt 2021a 126 5608 27 Solomon 2022 10 265 19 Voors 2022 10 265 19 Feitosa 2023 3 22 2 <td< td=""><td>Study or Subgroup Events Total Events Total Zinman 2015 10mg 26 2345 19 1167 Zinman 2015 25 mg 19 2342 18 1166 Neal 2017 68 5795 70 4347 Perkovic 2019 86 2202 98 2199 McMurray 2019 23 2373 46 2371 Wiviott 2019 125 8582 175 8578 Heerspink 2020 39 2152 2152 2152 Cannon 2020 101 5499 60 2747 Zannad 2021 no CKD 13 879 22 867 Anker 2021 97 2997 131 2991 Bhatt 2021a 116 5292 111 5292 Bhatt 2021a 106 226 608 27 614 Solomon 2022 10 265 19 265 19 265 Vors 2022 10 265 19</td><td>Study or Subgroup Events Total Events Total Weight Zinman 2015 10mg 26 2345 19 1167 2.1% Zinman 2015 25 mg 19 2342 18 1166 2.0% Neal 2017 68 5795 70 4347 6.7% Perkovic 2019 86 2202 98 2199 8.2% McMurray 2019 23 2373 46 2371 3.8% Wiviott 2019 125 8582 175 8578 14.6% Heerspink 2020 39 2152 52 2152 4.3% Zannad 2021 no CKD 13 879 22 867 1.8% Zannad 2021 CKD 33 981 45 997 3.7% Kosiborod 2021 21 625 34 625 2.8% Anker 2021 97 2997 131 2991 10.9% Bhatt 2021a 116 5292 111 5292 9.2%</td><td>Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI Zinman 2015 10mg 26 2345 19 1167 2.1% 0.68 [0.38, 1.23] Zinman 2015 25 mg 19 2342 18 1166 2.0% 0.53 [0.28, 1.00] Neal 2017 68 5795 70 4347 6.7% 0.73 [0.52, 1.02] Perkovic 2019 86 2202 98 2199 8.2% 0.88 [0.66, 1.6] McMurray 2019 23 2373 46 2371 3.8% 0.50 [0.30, 0.82] Wiviott 2019 125 6582 175 8578 14.6% 0.71 [0.57, 0.90] Heerspink 2020 39 2152 52 2152 4.3% 0.75 [0.50, 1.13] Cannon 2020 101 5499 60 2747 6.7% 0.84 [0.61, 1.6] Zannad 2021 no CKD 13 879 22 867 1.8% 0.56 [0.30, 1.15] Zannad 2021 CKD 33 981 45</td></td<> | Study or Subgroup Events Total Events Total Zinman 2015 10mg 26 2345 19 1167 Zinman 2015 25 mg 19 2342 18 1166 Neal 2017 68 5795 70 4347 Perkovic 2019 86 2202 98 2199 McMurray 2019 23 2373 46 2371 Wiviott 2019 125 8582 175 8578 Heerspink 2020 39 2152 2152 2152 Cannon 2020 101 5499 60 2747 Zannad 2021 no CKD 13 879 22 867 Anker 2021 97 2997 131 2991 Bhatt 2021a 116 5292 111 5292 Bhatt 2021a 106 226 608 27 614 Solomon 2022 10 265 19 265 19 265 Vors 2022 10 265 19 | Study or Subgroup Events Total Events Total Weight Zinman 2015 10mg 26 2345 19 1167 2.1% Zinman 2015 25 mg 19 2342 18 1166 2.0% Neal 2017 68 5795 70 4347 6.7% Perkovic 2019 86 2202 98 2199 8.2% McMurray 2019 23 2373 46 2371 3.8% Wiviott 2019 125 8582 175 8578 14.6% Heerspink 2020 39 2152 52 2152 4.3% Zannad 2021 no CKD 13 879 22 867 1.8% Zannad 2021 CKD 33 981 45 997 3.7% Kosiborod 2021 21 625 34 625 2.8% Anker 2021 97 2997 131 2991 10.9% Bhatt 2021a 116 5292 111 5292 9.2% | Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI Zinman 2015 10mg 26 2345 19 1167 2.1% 0.68 [0.38, 1.23] Zinman 2015 25 mg 19 2342 18 1166 2.0% 0.53 [0.28, 1.00] Neal 2017 68 5795 70 4347 6.7% 0.73 [0.52, 1.02] Perkovic 2019 86 2202 98 2199 8.2% 0.88 [0.66, 1.6] McMurray 2019 23 2373 46 2371 3.8% 0.50 [0.30, 0.82] Wiviott 2019 125 6582 175 8578 14.6% 0.71 [0.57, 0.90] Heerspink 2020 39 2152 52 2152 4.3% 0.75 [0.50, 1.13] Cannon 2020 101 5499 60 2747 6.7% 0.84 [0.61, 1.6] Zannad 2021 no CKD 13 879 22 867 1.8% 0.56 [0.30, 1.15] Zannad 2021 CKD 33 981 45 |

Forest plots for the meta-analysis of the influence of SGLT2i on the risk of AKI in adult patients; (A) the overall meta-analysis; and (B) the sensitivity analysis limited to high-quality studies.

doubling (Heerspink et al., 2020) or a 1.5-times increment of serum creatinine (Herrington et al., 2023) or the Kidney Disease Improving Global Outcomes criteria (Feitosa et al., 2023) were used. According to Table 2, the quality of each included RCTs was assessed according to the Cochrane Risk of Bias Tool. Most of the included studies were double-blind placebo controlled studies (Zinman et al., 2015; Neal et al., 2017; McMurray et al., 2019; Perkovic et al., 2019; Wiviott et al., 2019; Cannon et al., 2020; Heerspink et al., 2020; Bhatt et al., 2021a; Anker et al., 2021; Bhatt et al., 2021b; Kosiborod et al., 2021; Zannad et al., 2021; Solomon et al., 2022; Voors et al., 2022; Herrington et al., 2023; Butler et al., 2024) with adequate report of details of random sequence generation and allocation concealment. Only two studies were open-label studies (Feitosa et al., 2023; Cox et al., 2024), with no detailed report of random sequence generation or allocation concealment.

Meta-analysis results

Overall, 20 datasets from 18 RCTs, involving 52,773 patients receiving SGLT2i and 46,216 patients receiving placebo/blank treatment, were included in the meta-analysis. All the RRs and 95% CI were extracted from the original studies except data for one study (Anker et al., 2021), which was extracted from a previous meta-analysis after being provided directly to the authors (2022). Compared with placebo/blank treatment, treatment with SGLT2i significantly reduced the risk of AKI (RR: 0.78, 95% CI: 0.71 to 0.84, p < 0.001; Figure 2A) with no significant heterogeneity (for Cochrane Q test, p = 0.49; $I^2 = 0\%$). The sensitivity analysis limited to high-quality studies (Zinman et al., 2015; Neal et al., 2017; McMurray et al., 2019; Perkovic et al., 2019; Wiviott et al., 2019; Cannon et al., 2020; Heerspink et al., 2020; Bhatt et al., 2021; Solomon et al., 2022; Voors et al., 2022; Herrington

| | SGT | 21 | Cont | rol | | Risk Ratio | Risk Ratio |
|--------------------------------------|--------------|-----------|-------------------------|---------|-------------|--------------------|--------------------------------|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% Cl |
| 1.2.1 T2DM | | | | | | | |
| Zinman 2015 10mg | 26 | 2345 | 19 | 1167 | 1.8% | 0.68 [0.38, 1.23] | |
| Zinman 2015 25 mg | 19 | 2342 | 18 | 1166 | 1.7% | 0.53 [0.28, 1.00] | |
| Neal 2017 | 68 | 5795 | 70 | 4347 | 5.7% | 0.73 [0.52, 1.02] | - |
| Perkovic 2019 | 86 | 2202 | 98 | 2199 | 7.0% | 0.88 [0.66, 1.16] | |
| Wiviott 2019 | 125 | 8582 | 175 | 8578 | 12.5% | 0.71 [0.57, 0.90] | |
| Cannon 2020 | 101 | 5499 | 60 | 2/4/ | 5.7% | 0.84 [0.61, 1.15] | |
| Bhatt 2021a | 116 | 5292 | 111 | 5292 | 7.9% | 1.05 [0.81, 1.35] | |
| Bhatt 2021b | 25 | 608 | 27 | 614 | 1.9% | 0.94 [0.55, 1.59] | |
| Feitosa 2023 | 3 | 22 | 2 | 20 | 0.1% | 1.36 [0.25, 7.34] | |
| Subtotal (95% CI) | 500 | 32001 | 500 | 20130 | 44.3% | 0.02 [0.73, 0.92] | • |
| I otal events | 202 -16 - 0 | (D - 0 4 | 00 12 - 40 | , | | | |
| Heterogeneity: Chi ² = 8. | 37, df = 8 | (P = 0.4) | 0); I² = 4% | 6 | | | |
| l est for overall effect: Z | = 3.39 (P | = 0.000 | () | | | | |
| 1.2.2 CKD | | | | | | | |
| Perkovic 2019 | 86 | 2202 | 98 | 2199 | 7.0% | 0.88 [0.66, 1.16] | -+ |
| Heerspink 2020 | 39 | 2152 | 52 | 2152 | 3.7% | 0.75 [0.50, 1.13] | + |
| Zannad 2021 CKD | 33 | 981 | 45 | 997 | 3.2% | 0.75 [0.48, 1.16] | |
| Bhatt 2021a | 116 | 5292 | 111 | 5292 | 7.9% | 1.05 [0.81, 1.35] | +- |
| EMPA-kidney 2023 | 107 | 3304 | 135 | 3305 | 9.6% | 0.79 [0.62, 1.02] | |
| Subtotal (95% CI) | | 13931 | | 13945 | 31.4% | 0.87 [0.76, 0.99] | • |
| Total events | 381 | | 441 | | | | |
| Heterogeneity: Chi ² = 3. | 45, df = 4 | (P = 0.4 | 9); l ² = 0% | 6 | | | |
| Test for overall effect: Z | = 2.11 (P | = 0.04) | | | | | |
| 1.2.3 HF | | | | | | | |
| McMurray 2019 | 23 | 2373 | 46 | 2371 | 3.3% | 0.50 [0.30, 0.82] | |
| Zannad 2021 no CKD | 13 | 879 | 22 | 867 | 1.6% | 0.58 [0.30, 1.15] | |
| Zannad 2021 CKD | 33 | 981 | 45 | 997 | 3.2% | 0.75 [0.48, 1.16] | |
| Anker 2021 | 97 | 2997 | 131 | 2991 | 9.3% | 0.74 [0.57, 0.96] | |
| Bhatt 2021b | 25 | 608 | 27 | 614 | 1.9% | 0.94 [0.55, 1.59] | |
| Solomon 2022 | 46 | 3131 | 50 | 3132 | 3.6% | 0.92 [0.62, 1.37] | |
| Voors 2022 | 10 | 265 | 19 | 265 | 1.4% | 0.53 [0.25, 1.11] | |
| Cox 2024 | 4 | 119 | 1 | 119 | 0.1% | 4.00 [0.45, 35.26] | , |
| Subtotal (95% CI) | | 11353 | | 11356 | 24.3% | 0.74 [0.63, 0.87] | • |
| Total events | 251 | | 341 | | | | |
| Heterogeneity: Chi ² = 7. | .88, df = 7 | (P = 0.3 | 4); I² = 11 | % | | | |
| Test for overall effect: Z | = 3.73 (P | = 0.000 | 2) | | | | |
| Total (95% CI) | | 57971 | | 51431 | 100.0% | 0.81 [0.75, 0.88] | • |
| Total events | 1201 | | 1362 | | | | ~ |
| Heterogeneity: Chi ² = 2 | 1.94. df = 2 | (P = 0) |).40)· l ² = | 4% | | | |
| Test for overall effect. 7 | = 5.25 (P | < 0.000 | 01) | | | | 0.2 0.5 1 2 5 |
| Test for subgroup differ | ences: Chi | 2 = 2.27 | df = 2 (F | = 0.32) | . I² = 11.8 | % | Favours SGLT2i Favours control |
| reación auburoub unien | | | | | | | |
| Test for subdroub difference | | | | | | | |

et al., 2023; Butler et al., 2024) showed similar results (RR: 0.77, 95% CI: 0.71 to 0.84, p < 0.001; Figure 2B). Subgroup analysis suggested consistent results in patients with T2DM (RR: 0.82, 95% CI: 0.73 to 0.92, p < 0.001; $I^2 = 4\%$), CKD (RR: 0.87, 95% CI: 0.76 to 0.99, p = 0.04; $I^2 = 0\%$), and HF (RR: 0.74, 95% CI: 0.63 to 0.87, p < 0.001; $I^2 = 11\%$; p for subgroup difference = 0.32; Figure 3). In addition, subgroup analysis also did not suggest that the results were significantly affected by individual SGLT2i drugs used (p for subgroup difference = 0.09; Figure 4). Finally, univariate meta-regression with a random-effects model suggested that the influence of SGLT2i on the risk of AKI was not significantly modified by study characteristics such as mean age of the patients, proportion of men, baseline mean eGFR, proportion of patients with concomitant use of MRA, or mean follow-up duration (p all > 0.05; Table 3).

Publication bias

The symmetrical funnel plots observed in the meta-analyses of the impact of SGLT2i on AKI in adult patients indicate a minimal likelihood of publication bias (Figure 5). Furthermore, the results of Egger's regression test support this notion, as it yielded a *p*-value of 0.32, indicating a low risk of publication bias.

Discussion

In this meta-analysis, we conducted a comprehensive synthesis of data from 18 RCTs, comprising 20 datasets. The findings of our study indicate a significant reduction in the risk of AKI among adult patients when comparing the use of SGLT2i to placebo or blank treatment. The sensitivity analysis limited to high-quality RCTs showed similar results. Subgroup analyses further demonstrated consistent results in patients with T2DM, CKD, and HF. Additionally, our subgroup analysis suggests that the impact of SGLT2i on AKI does not appear to be influenced by the specific type of SGLT2i utilized. Finally, meta-regression analysis suggested that the influence of SGLT2i on AKI was also not likely to be modified by difference of study characteristics, such as mean age of the patients, proportion of men, mean baseline eGFR, proportions of patients with concomitant use of RAASi and MRA, or follow-up durations.

| | SGT | 21 | Cont | rol | | Risk Ratio | Risk Ratio |
|--|-------------------------|-----------------------|--------------------|---------------|---------------|---|---------------------------|
| 124 Emportification | Events | Iotal | Events | Iotal | weight | wi-H, Fixed, 95% Cl | <u>м-н, гіхед, 95% Сі</u> |
| Tisman 2015 10 | 00 | 0045 | 40 | 1407 | 0 40/ | 0.69.10.00.4.003 | |
| Zinman 2015 10mg | 26 | 2345 | 19 | 116/ | 2.1% | 0.08 [0.38, 1.23] | |
| Zinman 2015 25 mg | 19 | 2342 | 18 | 1166 | 2.0% | 0.53 [0.28, 1.00] | |
| Zannad 2021 no CKD | 13 | 879 | 22 | 867 | 1.8% | 0.58 [0.30, 1.15] | |
| Zannad 2021 CKD | 33 | 981 | 45 | 997 | 3.7% | 0.75 [0.48, 1.16] | |
| Anker 2021 | 97 | 2997 | 131 | 2991 | 10.9% | 0.74 [0.57, 0.96] | |
| Voors 2022 | 10 | 265 | 19 | 265 | 1.6% | 0.53 [0.25, 1.11] | |
| Feitosa 2023 | 3 | 22 | 2 | 20 | 0.2% | 1.36 [0.25, 7.34] | |
| EMPA-kidney 2023 | 107 | 3304 | 135 | 3305 | 11.2% | 0.79 [0.62, 1.02] | - |
| Butler 2024 Subtotal (95% CI) | 27 | 3260 1 6395 | 43 | 3262 14040 | 3.6% 37.2% | 0.63 [0.39, 1.01] 0.72 [0.62, 0.82] | • |
| Total events | 335 | | 434 | | | | |
| Heterogeneity: Chi ² = 3. Test for overall effect: Z | 51, df = 8 = 4.64 (P | (P = 0.9 < 0.000 | 0); I² = 0% 01) | 6 | | | |
| 1.3.2 Canagliflozin | | | | | | | |
| Neal 2017 | 68 | 5795 | 70 | 4347 | 6.7% | 0.73 [0.52, 1.02] | - |
| Perkovic 2019 | 86 | 2202 | 98 | 2199 | 8.2% | 0.88 [0.66, 1.16] | |
| Subtotal (95% CI) | 15. | 1997 | 10- | 0546 | 14.8% | 0.81 [0.65, 1.00] | |
| lotal events | 154 | | 168 | | | | |
| Heterogeneity: Chi ² = 0. Test for overall effect: Z | 69, df = 1 = 1.92 (P | (P = 0.4 = 0.06) | 1); l² = 0% | 6 | | | |
| 1.3.3 Dapagliflozin | | | | | | | |
| McMurray 2019 | 23 | 2373 | 46 | 2371 | 3.8% | 0.50 [0.30, 0.82] | |
| Wiviott 2019 | 125 | 8582 | 175 | 8578 | 14.6% | 0.71 [0.57, 0.90] | |
| Heerspink 2020 | 39 | 2152 | 52 | 2152 | 4.3% | 0.75 [0.50, 1.13] | |
| Kosiborod 2021 | 21 | 625 | 34 | 625 | 2.8% | 0.62 [0.36, 1.05] | |
| Solomon 2022 | 46 | 3131 | 50 | 3132 | 4.2% | 0.92 [0.62, 1.37] | |
| Cox 2024 | 4 | 119 | 1 | 119 | 0.1% | 4.00 [0.45, 35.26] | |
| Subtotal (95% CI) | | 16982 | | 16977 | 29.8% | 0.72 [0.61, 0.84] | • |
| Total events | 258 | | 358 | | | | |
| Heterogeneity: Chi ² = 6. Test for overall effect: Z | 29, df = 5 = 4.05 (P | (P = 0.2 < 0.000 | 8); I² = 20 1) | 1% | | | |
| 1.3.4 Ertugliflozin | | | | | | | |
| Cannon 2020 | 101 | 5499 | 60 | 2747 | 6.7% | 0.84 [0.61, 1.15] | -+ |
| Subtotal (95% CI) | | 5499 | 20 | 2747 | 6.7% | 0.84 [0.61, 1.15] | ◆ |
| Total events | 101 | | 60 | | | | |
| Heterogeneity: Not appl Test for overall effect: Z | icable = 1.07 (P | = 0.28) | | | | | |
| 1.3.5 Sotagliflozin | | | | | | | |
| Bhatt 2021a | 116 | 5292 | 111 | 5292 | 9.2% | 1.05 [0.81, 1.35] | |
| Bhatt 2021b | 25 | 608 | 27 | 614 | 2.2% | 0.94 [0.55, 1.59] | |
| Subtotal (95% CI) | | 5900 | | 5906 | 11.5% | 1.02 [0.81, 1.29] | — |
| Total events | 141 | | 138 | | | | |
| Heterogeneity: Chi ² = 0. Test for overall effect: Z | 14, df = 1 = 0.20 (P | (P = 0.7 = 0.84) | 1); l² = 0% | 6 | | | |
| Total (95% CI) | | 52773 | | 46216 | 100.0% | 0.78 [0.71, 0.84] | • |
| Total events | 989 | | 1158 | | | | |
| Heterogeneity: Chi ² = 18 | 3.56, df = 1 | 19 (P = (| 0.49); l² = | 0% | | | |
| T (, , , , , , , , , , , , , , , , , , | = 5.93 (P | < 0.000 | 01) | | | | 0.2 0.5 1 2 5 |

Taken together, these results indicate that SGLT2i may be effective in reducing the risk of AKI, and the effect of SGLT2i on AKI may not be influenced by the baseline renal function or concurrent use of RAASi.

Some meta-analyses were published before or during the preparation this manuscript, which generally showed that SGLT2 inhibitors can exert the benefit in reducing AKI in patients with T2D, heart failure, or CKD; and this benefit does not vary with various characteristics, such as the diagnosis of the patients and type of SGLT2 inhibitors (Menne et al., 2019; Neuen et al., 2019; Zhao et al., 2020; Qiu et al., 2021; Baigent et al., 2022; Gong et al., 2022; Rigato et al., 2023). Compared to the previous meta-analyses, our study has several strengths. First, an extensive literature search was performed which retrieved 18 relevant up-todate RCTs. Second, only RCTs were included, which minimized the biases related to the design of observational studies. In addition, although the results of the overall and subgroup analyses were generally consistent with the findings of the previous metaanalyses, we for the first time performed meta-regression analyses to investigate the potential influence of study characteristics such as age, baseline renal function, and concurrent use of RAASi at the study level. This is clinically important, because these factors have been related to the risk of AKI. Overall, results of the meta-analysis provided further evidence that SGLT2i may be effective in reducing the risk of AKI, and the effect might not be modified by age, baseline renal function and concurrent use of RAASi or MRA.

Although concerns have been raised reading AKI related to SGLT2i use in some case reports, subsequent investigations in high

TABLE 3 Univariate meta-regression analysis.

| | RR for the influence of SGLT2i on AKI | | | | | | |
|---|---------------------------------------|-------------------|------|--|--|--|--|
| Covariate | Coefficient | 95% CI | p | | | | |
| Mean age (years) | 0.011 | -0.015 to 0.037 | 0.39 | | | | |
| Men (%) | -0.010 | -0.024 to 0.003 | 0.13 | | | | |
| Mean eGFR at baseline (ml/min/1.73 m ²) | -0.0042 | -0.0097 to 0.0014 | 0.13 | | | | |
| Any RAASi (%) | 0.0041 | -0.0057 to 0.0114 | 0.49 | | | | |
| MRA (%) | -0.0020 | -0.0062 to 0.0023 | 0.34 | | | | |
| Follow-up duration (months) | -0.0027 | -0.0095 to 0.0041 | 0.41 | | | | |

RR, risk ratio; CI, confidence interval; SGLT2i, Sodium/glucose cotransporter-2 inhibitors; RAASi, renin-angiotensin-aldosterone system inhibitors; MRA, mineralocorticoid receptor antagonists; eGFR, estimated glomerular filtration rate; AKI, acute kidney injury.



quality clinical trials and meta-analysis showed that SGLT2i may confer renal proactive efficacy and delay the deterioration of renal function (Lin et al., 2023). The current meta-analysis, by integrating the evidence from RCTs, further expanded the renal benefits of SGLT2i by showing that SGLT2i are effective in reducing the risk of AKI as compared to placebo/blank treatment. The potential mechanisms underlying the renal protective effect of SGLT2i may be multifactorial. An initial investigation conducted on non-diabetic mice using a renal ischemia/reperfusion injury model demonstrated that Luseogliflozin effectively mitigated peritubular capillary congestion/hemorrhage, alleviated hypoxia, and enhanced the expression of vascular endothelial growth factor (VEGF)-A, thereby exhibiting a protective effect on the kidneys during acute situations (Zhang et al., 2018). Furthermore, another study conducted on diabetic rats with myocardial infarction-associated AKI revealed that pretreatment with empagliflozin for 2 weeks resulted in improved hyperglycemia, elevated blood βhydroxybutyrate levels, suppressed expression of NGAL and KIM-1 induced by MI, and ultimately prevented the pathogenesis of AKI (Kuno et al., 2020). Furthermore, previous research has demonstrated the significant reduction of both systemic and renal inflammation by empagliflozin, which has contributed to the observed survival benefits in an LPS-model of acute septic renal injury (Maayah et al., 2021). Additionally, a more recent study has indicated that dapagliflozin may mitigate contrast-induced acute kidney injury through the suppression of the hypoxia-inducible factor-1 α pathway (Huang et al., 2022). Consequently, there is a need for further investigation into the key molecular pathways that underlie the preventive effectiveness of SGLT2i on AKI.

Results of subgroup analysis suggested that although no significant difference was observed for the influence of each individual SGLT2i drugs on AKI, the positive results were mainly driven by studies involving empagliflozin, canagliflozin, and dapagliflozin, but not for studies with ertugliflozin or sotagliflozin. However, these results should be interpreted with caution because only two datasets were available for the subgroups of ertugliflozin and sotagliflozin, and more studies are needed for further evaluation. Interestingly, results of metaregression analysis suggested that the effect of SGLT2i on AKI did not seem to be significantly affected by eGFR at baseline, suggesting that potential renal protective efficacy of SGLT2i may also be consistent in patients with renal dysfunction before treatment (eGFR as low as 20 mL/min/1.73 m²). In addition, it has been suggested that excessive decline by SGLT2i combined with the excessive decline in trans-glomerular pressure induced by concomitant use of RAASi may further increase the risk of AKI (Szalat et al., 2018). Accordingly, we explored the influence of proportions of patients with concurrent use of RAASi and MRA on the effect of SGLT2i on AKI. Results suggested that the potential renal protective efficacy of SGLT2i may not be significantly modified by concurrent use of RAASi or MRA. This is consistent with a recently published post hoc analysis which showed that dapagliflozin consistently reduced the risk of kidney outcomes in T2DM patients irrespective of background use of various cardiovascular medications (Oyama et al., 2022). However, our results of metaregression analysis according to baseline renal function and concurrent use of RAASi should be considered as exploring study because these results were based on the analysis of study-level data rather than individual-patient data.

This meta-analysis also has limitations. First, different SGLT2i drugs with different dosages were used among the included studies. Further studies are needed to determine if the influence of SGLT2i on AKI is consistent among individual SGLT2i drugs, and if there is a

dose-effect relationship. Second, key aspects such as diabetes severity and duration, CKD, or HF, which have potential implications on SGLT2i effectiveness, may affect the influence of SGLT2i on AKI. Although, our meta-analysis is based on data at the study level rather than individual patient level; therefore, we were unable to determine the influence of these factors on the results. In addition, there are other medications which may also affect the risk of AKI besides RAASi and MRA, such as nonsteroidal anti-inflammatory drugs (NSAIDs). However, the status of NSAIDs use was generally not reported among the included studies, and we were therefore unable to determine its influence on the results of the meta-analysis. Moreover, we only included studies published in English as fulllength article in peer-reviewed journals. Grey literature, such as conference abstracts and unpublished data were not included. Although excluding grey literature may improve the reliability of the finding because most grey literature are not strictly peer-reviewed, excluding these data may also increase the risk of publication bias. Finally, for most of the included studies, AKI was diagnosed based on MDRA preferred term for AKI. The influence of different diagnostic criteria for AKI, particularly those applicable in real-world clinical practice needs to be further evaluated.

As a summary, results of the meta-analysis suggest that SGLT2i may be effective in reducing the risk of AKI as compared to placebo/ blank treatment in adult patients, and the influence of SGLT2i on AKI may not be affected by baseline renal function and concurrent use of RAASi.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

QW: Conceptualization, Formal Analysis, Writing-original draft. JY: Conceptualization, Formal Analysis, Writing-review

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and editing. WD: Conceptualization, Writing-review and editing. CL: Writing-review and editing, Resources. JY: Resources, Writing-review and editing. YL: Writing-review and editing, Data curation. GC: Data curation, Writing-review and editing. XC: Data curation, Writing-review and editing. ZD: Writing-review and editing, Conceptualization.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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