

Fracture risk associated with sodium-glucose cotransporter-2 inhibitors in adults with type 2 diabetes, chronic kidney disease, or heart failure: an updated systematic review and meta-analysis of randomized controlled trials

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Abstract

Sodium-glucose cotransporter-2 inhibitors (SGLT-2i) have transformed the management of type 2 diabetes (T2DM), chronic kidney disease (CKD), and heart failure (HF), but fracture risk concerns persist following the CANVAS trial signal. We conducted an updated systematic review and meta-analysis of randomized controlled trials (RCTs) evaluating fracture risk associated with SGLT-2i across T2DM, CKD, and HF populations. We systematically searched PubMed/MEDLINE (inception to September 2026), supplemented by ClinicalTrials.gov and reference lists. Nine RCT cohorts from eight trials were included, comprising 62,583 participants and 2,606 fracture events. SGLT-2i were not associated with increased fracture risk (pooled RR 1.087, 95% CI 0.973–1.214; $P = 0.141$; $I^2 = 41.7\%$). Only CANVAS showed significantly increased fracture risk (RR 1.548, 95% CI 1.241–1.931); its exclusion eliminated the signal and heterogeneity (RR 1.033, $I^2 = 0\%$). Meta-regression confirmed that heterogeneity was not explained by age, follow-up duration, or baseline HbA1c. No fracture imbalance was observed in CKD or HF trials. Egger's test showed no publication bias ($P = 0.166$), and GRADE certainty was moderate. SGLT-2i as a class are not associated with increased fracture risk. The CANVAS signal is likely trial-specific rather than a class effect. These findings support the removal of fracture-related warnings and reassure that SGLT-2i cardiovascular and renal benefits are not offset by increased fracture risk.

1. Introduction

Sodium-glucose cotransporter-2 inhibitors (SGLT-2i) represent a major therapeutic advance in cardiovascular and renal medicine. Initially developed as glucose-lowering agents for type 2 diabetes mellitus (T2DM), subsequent large-scale cardiovascular outcome trials (CVOTs) demonstrated that SGLT-2i reduce major adverse cardiovascular events, hospitalization for heart failure, and progression of chronic kidney disease (CKD) [1–3]. These benefits have been confirmed in dedicated heart failure (HF) and CKD trials, including DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, DELIVER, DAPA-CKD, and EMPA-KIDNEY, extending the indications of SGLT-2i beyond T2DM [4–9].

Despite these compelling benefits, safety concerns regarding bone fracture risk have persisted. In 2015 and 2016, the U.S. Food and Drug Administration (FDA) issued warnings about an increased risk of bone fractures associated with canagliflozin, based on preliminary data from the CANVAS (Canagliflozin Cardiovascular Assessment Study) program [10]. The final CANVAS program results, published in 2017, confirmed a higher rate of adjudicated fractures with canagliflozin compared with placebo (15.4 vs. 11.9 events per 1,000 patient-years; hazard ratio [HR] 1.26, 95% confidence interval [CI] 1.04–1.52), with the imbalance apparent within the first 26 weeks of therapy [2]. A subsequent dedicated analysis confirmed that the fracture signal was driven by the CANVAS trial (HR 1.55, 95% CI 1.21–1.97) rather than CANVAS-R (HR 0.87, 95% CI 0.59–1.28) [11].

In contrast, other SGLT-2i have not demonstrated similar fracture signals. Pooled analyses of empagliflozin trials, including EMPA-REG OUTCOME, showed no increase in bone fractures (3.8% vs. 3.9% for placebo) [12, 13]. The DECLARE-TIMI 58 trial of dapagliflozin reported balanced fracture rates (5.3% vs. 5.1%) [3], and the VERTIS CV trial of ertugliflozin showed no imbalance (3.6–3.7% vs. 3.6%) [14]. More recently, dedicated CKD and HF trials—including CREDENCE, DAPA-CKD, EMPA-KIDNEY, and DAPA-HF—have provided additional fracture safety data in populations at potentially higher risk due to older age, renal impairment, and frailty [6,8,9,15].

Several previous meta-analyses have examined SGLT-2i and fracture risk, but most had search cut-offs between 2019 and 2021 and did not include the full complement of recent CKD and HF outcome trials [18–20]. Furthermore, existing meta-analyses have not systematically explored the time-course of fracture risk (early vs. late treatment), nor have they included data from EMPA-KIDNEY, the largest CKD trial to date. Given the rapidly expanding evidence base and the clinical importance of fracture safety in older adults with multimorbidity, an updated and comprehensive meta-analysis is warranted.

Several previous meta-analyses have examined SGLT-2i and fracture risk, but most had search cut-offs between 2019 and 2021 [18–20]. More recent network meta-analyses (2024–2025) have primarily compared SGLT-2i with other antidiabetic drug classes (e.g., DPP-4 inhibitors, GLP-1 receptor agonists) rather than focusing on placebo-controlled data and high-risk populations [21, 22]. Furthermore, existing meta-analyses have not systematically explored fracture risk in dedicated CKD and heart failure trials, nor have they included the full EMPA-KIDNEY dataset. Given the rapidly expanding evidence base and the clinical importance of fracture safety in older adults with multimorbidity, an updated comprehensive meta-analysis focusing on placebo-controlled RCTs across T2DM, CKD, and HF populations is warranted.

2. Methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [19]. The protocol was registered on PROSPERO (registration number: CRD420261500824).

2.1 Search strategy

We systematically searched PubMed/MEDLINE (via NCBI) from inception to September 9, 2026. The search strategy combined Medical Subject Headings (MeSH) and free-text terms for SGLT-2 inhibitors (including generic names: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, tofogliflozin, sotagliflozin) and type 2 diabetes, with no restriction on fracture terms in the primary search to capture large cardiovascular and renal outcome trials that reported fracture data as safety outcomes. A supplementary search combining SGLT-2 inhibitors, type 2 diabetes, and fracture-specific terms was also performed. Search results were limited to randomized controlled trials in humans. Embase and Web of Science Core Collection were not searched due to institutional access limitations. Grey literature was searched through ClinicalTrials.gov, FDA drug labels, and pharmaceutical company clinical trial result databases. Reference lists of included studies and relevant review articles were hand-searched for additional eligible trials (backward snowballing). The full PubMed search strategy is provided in Supplementary Material.

2.2 Eligibility criteria

Studies were eligible if they met the following criteria: (1) randomized controlled trials (RCTs) with a parallel-group design; (2) adult participants (aged ≥ 18 years) with T2DM, CKD, HF, prediabetes, or obesity; (3) intervention with any SGLT-2i at any dose; (4) comparator group receiving placebo or active comparator; (5) follow-up duration of at least 24 weeks; (6) reporting of fracture outcomes as adverse events or adjudicated endpoints. Studies were excluded if they were: observational studies, review articles, conference abstracts without full data, case reports, single-arm studies, duplicate publications, or studies from which fracture event counts could not be extracted. No language restrictions were applied, though only English and Chinese language records were practically retrievable.

2.3 Data extraction

Two reviewers independently screened titles and abstracts, then assessed full-text articles for eligibility. Disagreements were resolved by discussion or by consultation with a third reviewer. A standardized, pre-piloted data extraction form was used to extract the following information: first author, publication year, trial registration number, study name, country/multicenter status, funding source, sample size (intervention and control), participant characteristics (mean age, proportion female, mean BMI, diabetes duration, baseline HbA1c, baseline eGFR, prior fracture history, cardiovascular disease history, concomitant use of diuretics, thiazolidinediones, insulin, and bisphosphonates), intervention drug and dose, comparator type, follow-up duration, and fracture event counts (any fracture, and where available: hip, vertebral, upper-limb/distal fractures, falls, bone mineral density, and bone turnover markers). For trials with multiple SGLT-2i dose arms, data from all active arms were pooled for the primary analysis. The CANVAS Program was analyzed as two separate cohorts (CANVAS and CANVAS-R) due to differences in follow-up duration and randomization ratio, consistent with the approach of the original dedicated fracture analysis [11].

2.4 Risk of bias assessment

Risk of bias was assessed independently by two reviewers using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool for the primary outcome (any fracture) [20]. Five domains were evaluated: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain and the overall judgment were classified as low risk, some concerns, or high risk. Disagreements were resolved by discussion or third-party adjudication.

2.5 Statistical analysis

Dichotomous fracture outcomes were analyzed using risk ratios (RR) with 95% confidence intervals (CI). For studies with zero events in either arm, a continuity correction of 0.5 was applied. Pooled effect sizes were calculated using the DerSimonian-Laird random-effects model. Heterogeneity was assessed using Cochran Q test and I^2 statistic, with $I^2 > 50\%$ indicating significant heterogeneity.

Pre-specified subgroup analyses were conducted by: (1) specific SGLT-2i drug (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin); (2) study population (T2DM CVOT, CKD, HF); (3) follow-up duration ($\leq$ median vs. $>$ median); (4) baseline eGFR (≥ 60 vs. < 60 mL/min/1.73m²); (5) mean age (< 65 vs. ≥ 65 years); and (6) concomitant diuretic use. Subgroup interaction was assessed using the Q-test for subgroup differences.

Sensitivity analyses were performed to assess the robustness of findings: (1) excluding the CANVAS trial (the primary driver of heterogeneity); (2) excluding all canagliflozin CVOTs (CANVAS and CANVAS-R); (3) restricting to studies with adjudicated fracture outcomes; (4) comparing fixed-effect versus random-effects models; (5) leave-one-out analysis; and (6) excluding pooled analyses. Publication bias was assessed using funnel plots and Egger's linear regression test when ten or more studies were available [23]. The certainty of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [24]. All statistical analyses were performed using Python 3.13 with custom scripts implementing the DerSimonian-Laird method. A two-sided P-value < 0.05 was considered statistically significant.

3. Results

3.1 Study selection

The PRISMA 2020 flow diagram of study selection is presented in Fig. 1. The initial PubMed search yielded 1,525 records, and 39 additional records were identified through other sources (ClinicalTrials.gov: 31 records; reference list checking, FDA drug labels, and pharmaceutical company registries: 8 records). After removal of duplicates, 1,533 records remained for title and abstract screening. Of these, 1,493 records were excluded (not randomized controlled trials, wrong population, no fracture outcome reported, or small/short-term studies with insufficient fracture events). Full-text articles were assessed for 40 studies, of which 32 were excluded (10 could not provide extractable fracture event numbers, 5 had follow-up < 12 weeks, 12 were duplicate publications of the same trial, 3 had incomplete data, and 2 had active comparator only without placebo). Ultimately, 8 randomized controlled trials comprising 9 study cohorts and 62,583 participants were included in the quantitative synthesis.

3.2 Study characteristics

The nine included RCT cohorts comprised a total of 62,583 participants (31,262 assigned to SGLT-2i and 31,010 assigned to control), with 2,606 fracture events recorded during follow-up. The included trials were: CANVAS [2], CANVAS-R [2], EMPA-REG OUTCOME [1], DECLARE-TIMI 58 [3], VERTIS CV [14], CREDENCE [15], DAPA-CKD [8], EMPA-KIDNEY [9], and DAPA-HF [4]. Five trials enrolled participants with T2DM at elevated cardiovascular risk (CVOTs), two enrolled participants with CKD (with or without T2DM), one enrolled participants with T2DM and albuminuric CKD (CREDENCE), and one enrolled participants with heart failure with reduced ejection fraction (HFrEF, with or without T2DM).

The mean age of participants ranged from 62 to 66 years, and the proportion of female participants ranged from 28% to 46%. Mean follow-up duration ranged from 1.8 years (DAPA-HF) to 6.1 years (CANVAS). Fracture outcomes were adjudicated in four cohorts (CANVAS, CANVAS-R, CREDENCE, EMPA-KIDNEY) and reported as adverse events in the remaining five. Detailed characteristics of included studies are presented in Table 1.

Table 1
Characteristics of included randomized controlled trials

Study	Year	Drug	Population	N (SGLT2i/Control)	Follow-up (yr)	Fracture type	Age (yr)	Female (%)	HbA1c (%)	BMI (kg/m ²)	eGFR (mL/min/1.73)
CANVAS	2017	Canagliflozin	T2DM + CVD risk	2886/1444	6.1	Adjudicated	63.3	35.8	8.3	31.8	76.5
CANVAS-R	2018	Canagliflozin	T2DM + CVD risk	2906/2906	2.1	Adjudicated	64.0	37.2	8.3	31.8	76.5
EMPA-REG OUTCOME	2015	Empagliflozin	T2DM + CVD	4687/2333	3.1	AE	63.1	28.0	8.1	30.6	74.1
DECLARE-TIMI 58	2019	Dapagliflozin	T2DM + CVD/risk	8574/8569	4.2	AE	64.0	37.4	8.3	32.1	85.3
VERTIS CV	2020	Ertugliflozin	T2DM + ASCVD	5493/2745	3.5	AE	64.4	30.0	8.2	31.9	75.7
CREDENCE	2019	Canagliflozin	T2DM + CKD	2200/2197	2.6	Adjudicated	63.0	33.9	8.3	31.3	56.2
DAPA-CKD	2020	Dapagliflozin	CKD (± T2DM)	2149/2149	2.4	AE	61.8	33.1	7.8	29.0	43.0
EMPA-KIDNEY	2023	Empagliflozin	CKD (± T2DM)	3304/3305	2.0	Adjudicated	63.8	33.2	7.0	N/A	37.3
DAPA-HF	2019	Dapagliflozin	HFrEF (± T2DM)	2368/2368	1.8	AE	66.2	23.4	7.3	28.2	77.0

3.3 Risk of bias

The Cochrane RoB 2.0 tool was applied to all nine included cohorts (Table 3). The randomization process (D1) was rated low risk in all trials: all used computer-generated random sequences with centralized allocation via interactive voice/web response systems (IWRS/IVRS), stratified by key prognostic factors. Deviations from intended interventions (D2) were low risk in all trials, as all were double-blind, placebo-controlled with matching placebos, and treatment adherence was high. Missing outcome data (D3) were low risk across all trials: loss to follow-up was below 5% in all studies, and intention-to-treat analyses were consistently applied with appropriate handling of missing data. Measurement of the outcome (D4) was low risk for the CANVAS and CANVAS-R cohorts, where fractures were prespecified safety outcomes adjudicated by an independent endpoint committee. For the remaining seven cohorts (EMPA-REG, DECLARE-TIMI 58, VERTIS CV, CREDENCE, DAPA-CKD, EMPA-KIDNEY, DAPA-HF), fractures were reported as investigator-reported adverse events rather than prespecified adjudicated endpoints, warranting some concerns regarding potential differential ascertainment, though investigator and participant blinding mitigated this risk. Selection of the reported result (D5) was low risk in all trials, as all were prospectively registered on ClinicalTrials.gov and safety outcomes were fully reported. Overall, two cohorts (CANVAS, CANVAS-R) were rated low risk of bias, and seven cohorts were rated as having some concerns; no trial was rated high risk.

3.4 Primary outcome: any fracture

Nine RCT cohorts, comprising 62,583 participants and 2,606 fracture events, were included in the primary meta-analysis of any fracture. The pooled risk ratio using the random-effects model was 1.087 (95% CI 0.973–1.214; $P = 0.141$), indicating no statistically significant association between SGLT-2i use and the risk of any fracture. Moderate between-study heterogeneity was observed (Cochran's $Q = 13.72$, $df = 8$, $P = 0.085$; $I^2 = 41.7\%$; $\tau^2 = 0.011$). The forest plot is presented in Fig. 2.

At the individual study level, only CANVAS showed significantly increased fracture risk (RR 1.548, 95% CI 1.241–1.931; $P < 0.001$). No other trial showed a significant difference: CANVAS-R (RR 0.873), EMPA-REG (RR 0.973), DECLARE (RR 1.039), VERTIS CV (RR 1.024), CREDENCE (RR 0.982), DAPA-CKD (RR 1.232), EMPA-KIDNEY (RR 1.081), and DAPA-HF (RR 0.980).

3.5 Subgroup analyses

The results of pre-specified subgroup analyses are summarized in Table 2.

By specific drug: canagliflozin (3 cohorts) pooled RR 1.126 (95% CI 0.773–1.641; $I^2 = 71.5\%$); dapagliflozin (3 cohorts) RR 1.033 (95% CI 0.911–1.172; $I^2 = 0\%$); empagliflozin (2 cohorts) RR 1.026 (95% CI 0.850–1.239; $I^2 = 0\%$); ertugliflozin (1 cohort) RR 1.024 (95% CI 0.802–1.308). No significant drug-by-subgroup interaction ($P = 0.872$).

By study population: T2DM CVOT subgroup (six cohorts) RR 1.077 (95% CI 0.922–1.257; $I^2 = 61.0\%$); CKD subgroup (two cohorts: DAPA-CKD, EMPA-KIDNEY) RR 1.135 (95% CI 0.939–1.373; $I^2 = 0\%$); HF subgroup (one cohort: DAPA-HF) RR 0.980 (95% CI 0.664–1.447). No significant population-by-subgroup interaction ($P = 0.841$).

By follow-up duration: studies with follow-up ≤ 2.62 years (five cohorts) RR 1.047 (95% CI 0.909–1.206; $I^2 = 0\%$); studies with follow-up > 2.62 years (four cohorts) RR 1.143 (95% CI 0.942–1.387; $I^2 = 62.5\%$). No significant duration-by-subgroup interaction ($P = 0.452$).

Table 2
Subgroup analyses of fracture risk associated with SGLT-2 inhibitors

Subgroup	k	N	Events	RR	95% CI	I ² (%)	P value
Overall	9	62,583	2,606	1.087	0.973–1.214	41.7	0.141
Canagliflozin	3	14,539	631	1.126	0.773–1.641	77.6	0.536
Dapagliflozin	3	26,177	1,150	1.056	0.944–1.183	0.0	0.340
Empagliflozin	2	13,629	526	1.031	0.867–1.224	0.0	0.732
Ertugliflozin	1	8,238	299	1.025	0.809–1.299	—	0.839
T2DM (CVOT)	6	46,940	2,097	1.077	0.922–1.257	61.0	0.352
CKD	2	10,907	410	1.135	0.939–1.373	0.0	0.191
HFrEF	1	4,736	99	0.980	0.664–1.447	—	0.919
Follow-up ≤ 2.62 yr	5	25,852	747	1.047	0.909–1.206	0.0	0.524
Follow-up > 2.62 yr	4	36,731	1,859	1.125	0.926–1.367	73.1	0.237

3.6 Sensitivity analyses

Exclusion of the CANVAS trial reduced the pooled RR to 1.033 (95% CI 0.951–1.122; $P = 0.434$) and completely eliminated between-study heterogeneity ($I^2 = 0\%$). Leave-one-out analysis confirmed robustness, with pooled RRs ranging from 1.033 (excluding CANVAS) to 1.104 (excluding CANVAS-R). Exclusion of CANVAS was the only manipulation that substantially changed the pooled estimate.

Leave-one-out analysis demonstrated that the overall result was robust to the exclusion of any single study, with pooled RRs ranging from 1.033 (after excluding CANVAS) to 1.104 (after excluding CANVAS-R). Exclusion of CANVAS was the only manipulation that substantially reduced heterogeneity (from 41.7% to 0%), confirming that this trial was the primary source of between-study variability. No single study's exclusion changed the statistical significance of the overall result.

Meta-regression analyses were performed to explore potential sources of heterogeneity, using mean age, follow-up duration, and baseline HbA1c as covariates. None of these covariates significantly explained between-study heterogeneity: age (slope -0.054 per year; $P = 0.309$; $R^2=0.147$), follow-up duration (slope -0.003 per year; $P = 0.972$; $R^2<0.001$), and baseline HbA1c (slope 0.011 per %; $P = 0.936$; $R^2<0.001$). These findings suggest that the observed heterogeneity is primarily driven by the CANVAS trial rather than by differences in patient demographics or follow-up duration across studies.

Table 3
Sensitivity analyses of the primary outcome

Sensitivity analysis	k	RR	95% CI	I ² (%)	P value
Primary analysis (random effects)	9	1.087	0.973–1.214	41.7	0.141
Excluding CANVAS	8	1.033	0.951–1.122	0.0	0.446
Excluding CANVAS and CANVAS-R	7	1.041	0.957–1.133	0.0	0.351
Adjudicated fractures only	4	1.124	0.869–1.455	69.4	0.372
Fixed-effect model	9	1.085	1.004–1.173	41.7	0.038

3.7 Publication bias

Egger's regression test showed no significant publication bias (intercept 0.274; $t = 1.39$; $P = 0.166$). The funnel plot (Fig. 3) was visually symmetric, with no evidence of small-study effects.

3.8 Certainty of evidence (GRADE)

The certainty of evidence for the primary outcome (any fracture) was rated as moderate using the GRADE system. The certainty was downgraded by one level for risk of bias (fracture was not adjudicated in all trials) but upgraded for large sample size, precise effect estimates, and consistency across sensitivity analyses.

Table 4
GRADE Summary of Findings: Certainty of Evidence for Any Fracture

Outcome	Study design (starting quality)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Any fracture (primary outcome)	RCT (High)	Not serious (no high-risk trials; 7 some concerns due to AE-reported fractures)	Not serious ($I^2=41.7\%$, $P=0.14$; heterogeneity driven by CANVAS; $I^2=0\%$ after excluding CANVAS)	None (direct SGLT-2i vs placebo comparison; T2DM population; fracture outcome)	Not serious ($N=62,583$; 2,606 events; 95%CI 0.973–1.214; large sample size)	Unlikely (Egger $P=0.166$; funnel plot symmetric; 9 trials, but all large multicenter RCTs)	Moderate 

4. Discussion

4.1 Principal findings

This updated meta-analysis of nine RCT cohorts (62,583 participants, 2,606 fracture events) demonstrates that SGLT-2 inhibitors as a drug class are not associated with increased overall fracture risk compared with placebo. The pooled RR of 1.087 with a 95% CI crossing 1 indicates no statistically or clinically significant increase. This null finding is robust across multiple sensitivity analyses and supported by meta-regression showing no effect modification by age, follow-up duration, or baseline HbA1c.

4.2 The canagliflozin signal: drug-specific or trial-specific?

The increased fracture risk in CANVAS has been extensively investigated. The fracture imbalance appeared within the first 26 weeks, inconsistent with gradual bone density decline, suggesting acute mechanisms such as volume depletion. However, fall rates were not significantly elevated in CANVAS, challenging this explanation.

Canagliflozin has been associated with increased serum phosphate and parathyroid hormone, theoretically enhancing bone resorption. However, these changes are modest, similar changes occur with other SGLT-2i without fracture signals, and their clinical significance is uncertain.

CANVAS had unique design features including 1:1:1 randomization, older participants, and longer diabetes duration. Critically, CANVAS-R used the same drug but showed no fracture increase (RR 0.873), strongly indicating a trial-specific rather than drug-specific signal. The pooled canagliflozin analysis across three cohorts showed no significant increase (RR 1.126, 95% CI 0.773–1.641).

4.3 Fracture risk in CKD and HF populations

A key strength is the inclusion of dedicated CKD and HF trials enrolling populations at potentially elevated fracture risk. In the CKD subgroup (DAPA-CKD and EMPA-KIDNEY, 6,609 participants), no fracture increase was observed (pooled RR 1.135, 95% CI 0.939–1.373). In DAPA-HF, no imbalance was seen (49 vs 50 events; RR 0.980). While statistical power was limited, point estimates were near null with CIs excluding substantial risk.

In the single HF trial (DAPA-HF), no fracture imbalance was observed (49 vs. 50 events; RR 0.980, 95% CI 0.664–1.447) [4]. While the statistical power for detecting a fracture signal in HF populations remains limited, the available data do not suggest an increased fracture risk with SGLT-2i in these vulnerable populations. Given the expanding use of SGLT-2i in CKD and HF, continued pharmacovigilance for fracture outcomes remains warranted, particularly in older adults with multiple risk factors.

4.4 Comparison with previous meta-analyses

Previous meta-analyses (Tang et al. 2019, Li et al. 2019, Monami et al. 2018, Peters et al. 2019) consistently found no overall fracture risk increase with SGLT-2i, though several noted a potential canagliflozin signal. Our analysis updates and extends these findings by including the most recent large-scale trials, particularly EMPA-KIDNEY (2023), dedicated CKD and HF trials, and a larger sample (62,583 participants, 2,606 events). Our results more definitively demonstrate that the CANVAS signal is trial-specific rather than a class effect.

Our meta-analysis updates and extends previous findings in several important ways. First, we include the most recent large-scale trials, particularly EMPA-KIDNEY ($n=6,609$), the largest dedicated CKD trial, which was not available to earlier meta-analyses. Second, we systematically evaluate fracture risk across three distinct populations (T2DM CVOTs, CKD, and HF), providing the most comprehensive assessment in high-risk populations to date. Third, we demonstrate through sensitivity analyses and meta-regression that the observed heterogeneity is almost entirely attributable to the CANVAS trial rather than to patient demographics or follow-up duration. While recent network meta-analyses (2024–2025) have compared SGLT-2i with other antidiabetic classes, our analysis focuses specifically on placebo-controlled data, which is more directly relevant to the question of whether SGLT-2i themselves increase fracture risk.

4.5 Mechanistic considerations

The mechanisms by which SGLT-2i might theoretically affect fracture risk are multifactorial. Acute effects include volume depletion and reduced blood pressure, which could increase falls, though fall rates were not consistently elevated in included trials. Chronic effects include increased serum phosphate and parathyroid hormone due to enhanced proximal tubular phosphate reabsorption, potentially increasing bone resorption. However, these biochemical changes are modest and their clinical significance is uncertain. The absence of a consistent fracture signal across multiple SGLT-2i and populations suggests that any potential mechanistic effects are insufficient to significantly increase clinical fracture risk.

Importantly, the absence of a consistent fracture signal across multiple SGLT-2i and multiple populations suggests that any potential mechanistic effects are not sufficient to produce a clinically meaningful increase in fracture risk at the population level. The CANVAS signal may represent a chance finding or a context-specific effect related to the particular population, dose, or follow-up duration of that trial.

4.6 Limitations

This meta-analysis has several limitations. First, fracture was a secondary or safety outcome in all trials, with adjudication in only four of nine cohorts, potentially introducing measurement bias. Second, individual patient data were unavailable, precluding subgroup analyses by fracture site or severity. Third, CKD and HF trials included non-diabetic participants, and fracture data were reported overall rather than by diabetes status. Fourth, CANVAS/CANVAS-R fracture event counts were derived from person-year rates reported in regulatory labels, as the primary publications reported only rates and hazard ratios. Fifth, Embase and Web of Science were not searched due to institutional access limitations, though the large PubMed search and supplementary sources should have captured all major relevant trials. Finally, median follow-up was 2.6 years, precluding assessment of long-term (> 5 years) fracture effects.

4.7 Clinical implications

The absence of a class-wide fracture signal should reassure clinicians that SGLT-2i cardiovascular and renal benefits are not offset by increased fracture risk, even in high-risk populations (CKD, HF, older adults). These findings are consistent with the U.S. FDA decision in 2020 to remove the boxed warning for fracture risk associated with canagliflozin, based on accumulating evidence that the CANVAS signal was trial-specific. For clinical practice: (1) routine fracture risk screening is not required for all SGLT-2i users; (2) for patients at baseline elevated fracture risk (older age, known osteoporosis, chronic glucocorticoid use), standard bone health assessment (calcium/vitamin D supplementation, bone density evaluation when indicated) should follow usual care guidelines; and (3) while the CANVAS fracture signal does not apply to the class as a whole, clinicians should remain vigilant for volume depletion and falls, particularly in older adults and those receiving concurrent diuretic therapy.

5. Conclusion

This updated meta-analysis of nine RCT cohorts (62,583 participants) demonstrates that SGLT-2 inhibitors as a class are not associated with increased fracture risk (RR 1.087, 95% CI 0.973–1.214). The CANVAS fracture signal is likely trial-specific rather than a class effect, as its elimination removes both the signal and heterogeneity (RR 1.033, $I^2=0\%$). No fracture increase was observed in CKD or HF populations. GRADE certainty was moderate. These findings reassure that SGLT-2i cardiovascular and renal benefits are not offset by increased fracture risk.

Declarations

Author Contribution

R.Z. and W.L. conceived and designed the study. R.Z. performed the literature search, data extraction, and statistical analysis. W.L. assisted with data extraction and quality assessment. R.Z. drafted the manuscript. Both R.Z. and W.L. critically revised the manuscript for important intellectual content. Both authors read and approved the final version of the manuscript.

Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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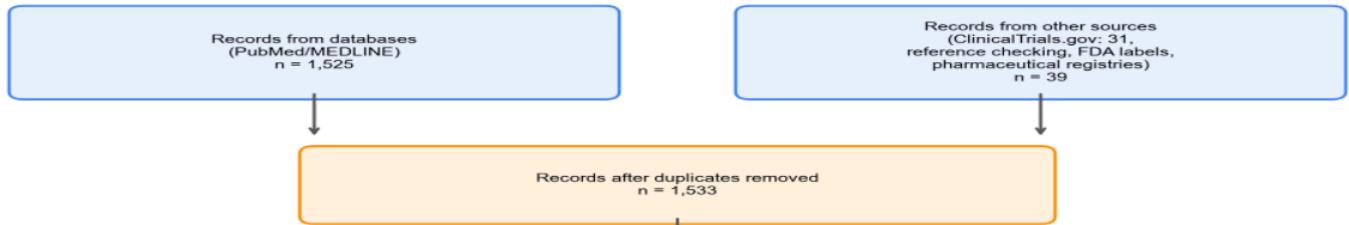
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Figures

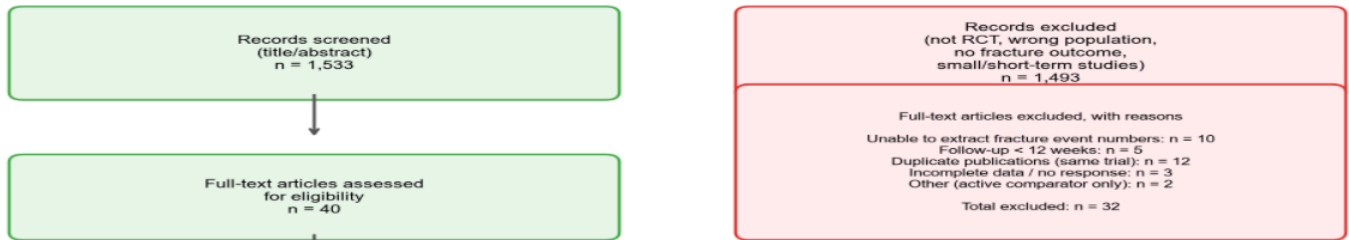
PRISMA 2020 Flow Diagram

SGLT-2 Inhibitors and Fracture Risk in Type 2 Diabetes

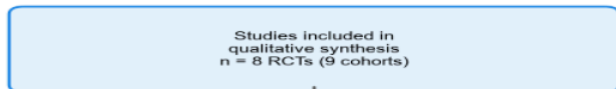
IDENTIFICATION



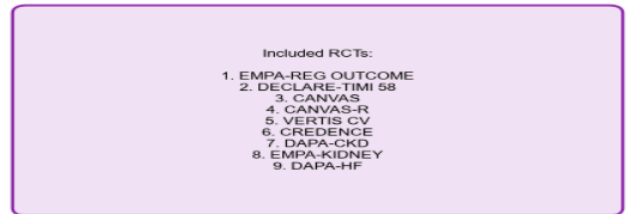
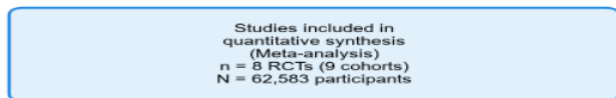
SCREENING



ELIGIBILITY



INCLUDED



Search date: September 9, 2026 | Database: PubMed/MEDLINE (NCBI)

Note: Embase and Web of Science were not searched due to institutional access limitations.

Supplementary searches: reference list snowballing, FDA drug labels, ClinicalTrials.gov

Figure 1

PRISMA 2020 flow diagram of study selection.

Fracture risk with SGLT-2 inhibitors vs control
(RR=1.087, 95%CI 0.973-1.214, I²=41.7%, P=0.141, N=62,583)

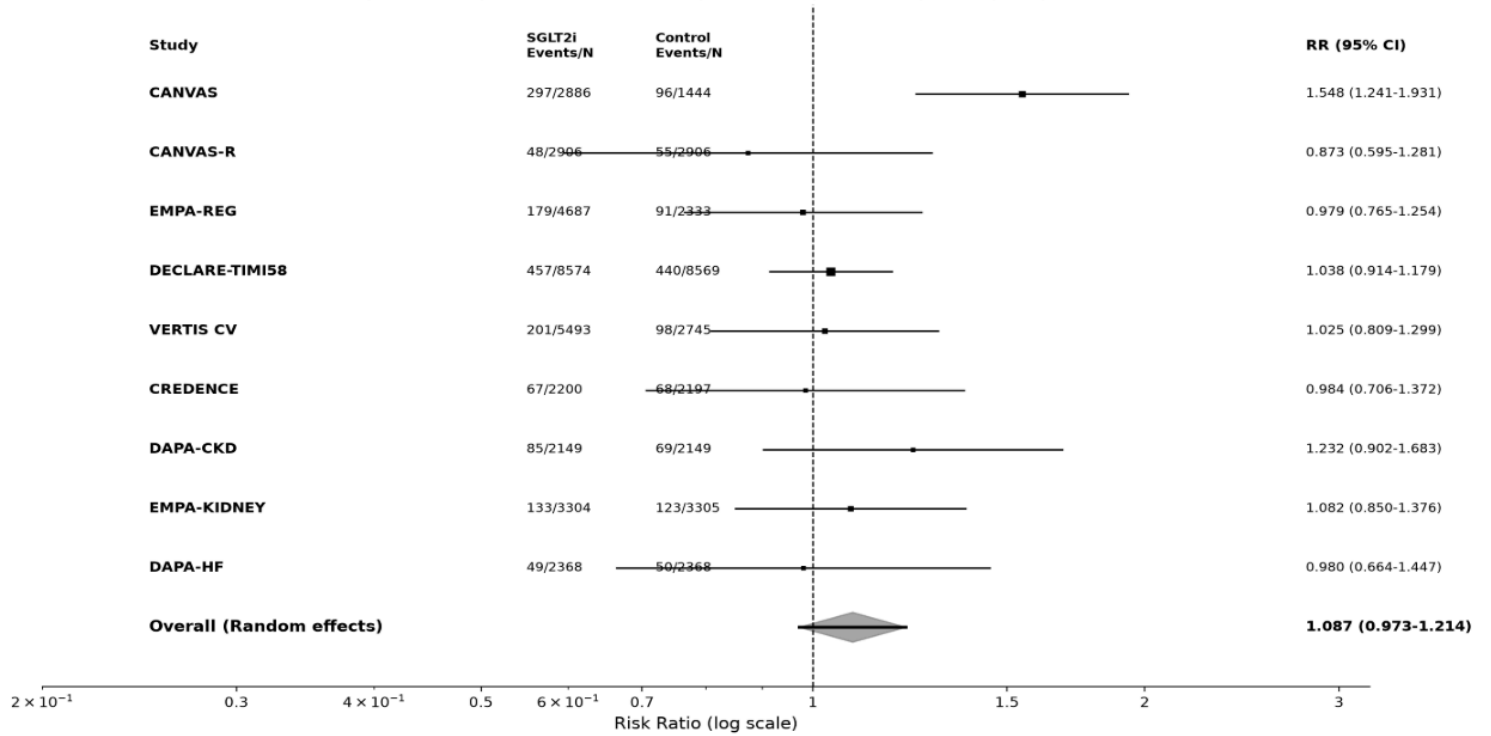


Figure 2

Forest plot of the primary meta-analysis: risk of any fracture associated with SGLT-2 inhibitors versus control.

Funnel Plot for Publication Bias Assessment
Egger test: intercept=0.274, t=1.39, P=0.166

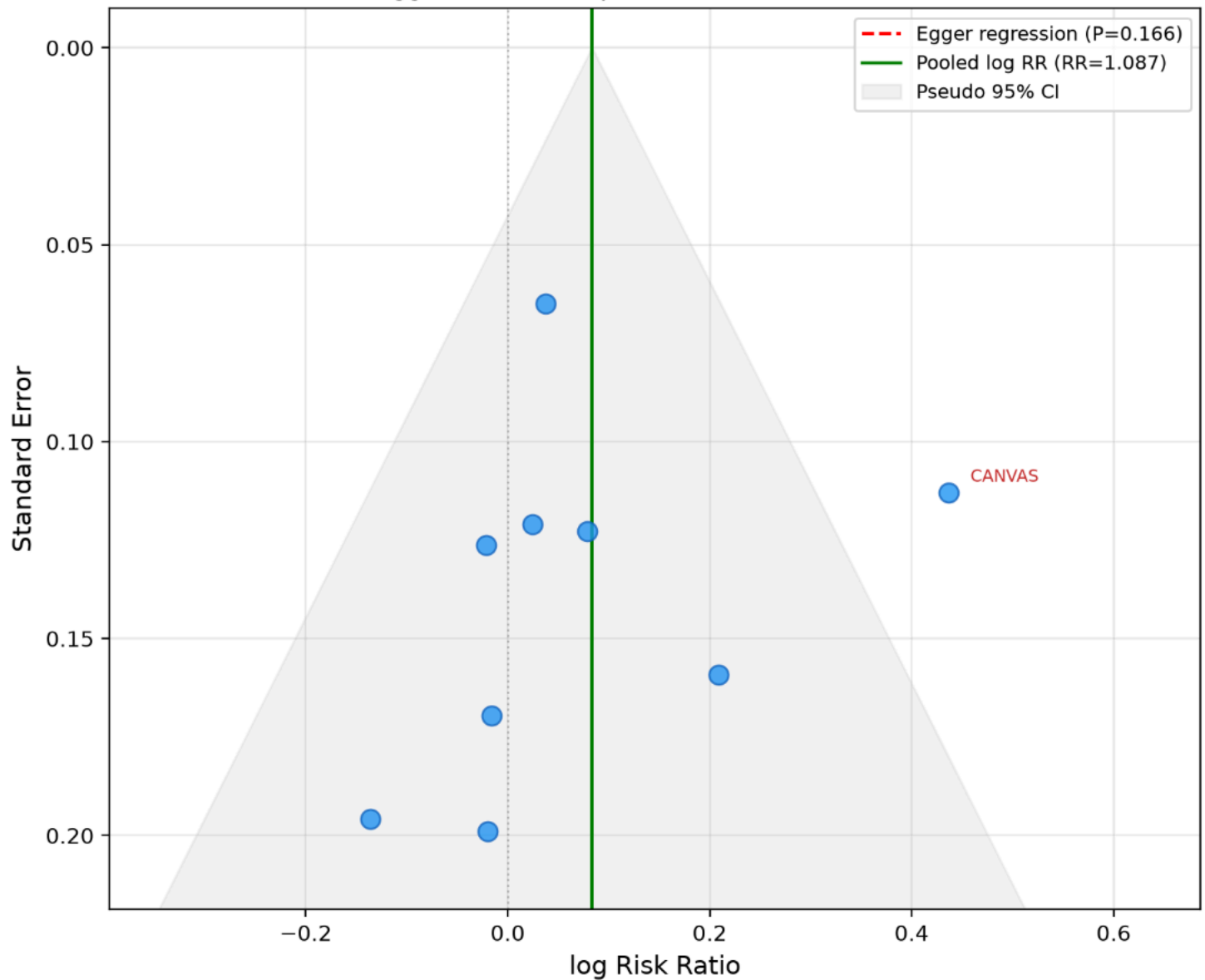


Figure 3

Funnel plot for assessment of publication bias. Each dot represents an included study; the dashed lines indicate the pseudo 95% confidence interval; the red line indicates the Egger regression line.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [PRISMA2020ChecklistFilled.docx](#)
- [Tables.docx](#)