INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Research Article

Comparative Efficacy and Safety of Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors in Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis

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ARTICLE INFO

Published: 18 Sept 2026

Keywords:
SGLT2 inhibitors; type 2 diabetes mellitus; canagliflozin; dapagliflozin; empagliflozin; cardiovascular outcomes; systematic review; meta-analysis

DOI:
10.5281/zenodo.22833228

ABSTRACT

Background: Sodium-glucose cotransporter-2 (SGLT2) inhibitors have transformed the pharmacological management of type 2 diabetes mellitus (T2DM), moving beyond glycaemic control to demonstrate consistent cardiovascular and renal protection across large outcome trials. However, individual agents within this class—canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin—differ in molecular selectivity, trial populations, and reported effect sizes, creating uncertainty about comparative efficacy and safety in routine practice. To systematically review and quantitatively synthesise randomised controlled trial (RCT) evidence on the comparative glycaemic efficacy, cardiovascular and renal outcomes, and safety profile of SGLT2 inhibitors in adults with T2DM. Following PRISMA 2020 guidance, PubMed/MEDLINE, Embase, Cochrane CENTRAL, and Web of Science were searched from inception to March 2026 for RCTs of at least 12 weeks' duration comparing an SGLT2 inhibitor with placebo or an active comparator in adults with T2DM. Two reviewers independently screened studies, extracted data, and assessed risk of bias using the Cochrane RoB2 tool. Random-effects meta-analysis was used to pool mean differences (MD) for glycated haemoglobin (HbA1c), body weight, and blood pressure, and risk ratios (RR) or hazard ratios (HR) for cardiovascular, renal, and safety outcomes, with heterogeneity assessed by I^2. Forty-four RCTs and six major cardiovascular/renal outcome trials, together enrolling more than 190,000 participants, met inclusion criteria. Compared with placebo, SGLT2 inhibitors reduced HbA1c by a pooled 0.62% (95% CI −0.66 to −0.59), body weight by1.8–2.7 kg, and systolic blood pressure by 3–5 mmHg, with canagliflozin 300 mg

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Relevant conflicts of interest/financial disclosures: 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.

showing numerically greater glycaemic and weight effects than empagliflozin 25 mg or dapagliflozin 10 mg. Across cardiovascular outcome trials, SGLT2 inhibitors reduced major adverse cardiovascular events (MACE) by approximately 11% (HR 0.89, 95% CI 0.84–0.94), hospitalisation for heart failure by 28–32%, and composite kidney outcomes by 30–40%, with benefits most pronounced in patients with established atherosclerotic disease, heart failure, or chronic kidney disease. Safety analyses confirmed an increased risk of genital mycotic infection (RR ≈ 3.5–3.75) and diabetic ketoacidosis (RR ≈ 2.4–2.6), a modestly increased risk of lower-limb amputation with canagliflozin, and a reduced risk of severe hypoglycaemia and acute kidney injury relative to comparators. SGLT2 inhibitors provide clinically meaningful and broadly consistent glycaemic, cardiovascular, and renal benefits across the class, with a manageable and largely predictable adverse-event profile. Selection among individual agents should be guided by the dominant clinical priority—cardiorenal protection, weight reduction, or glycaemic potency—rather than by assuming therapeutic interchangeability.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is among the most consequential chronic disorders of the twenty-first century. The International Diabetes Federation estimates that 589 million adults were living with diabetes globally in 2024, a figure projected to rise to 853 million by 2050, with the steepest increases occurring in low- and middle-income countries such as India [1]. T2DM is a progressive disease characterised by insulin resistance and declining beta-cell function, and it is closely linked to microvascular complications (retinopathy, nephropathy, neuropathy) and macrovascular complications (myocardial infarction, stroke, peripheral arterial disease). Cardiovascular disease remains the leading cause of morbidity and mortality among people with T2DM, while diabetic kidney disease is now the single largest cause of end-stage renal disease worldwide.

For decades, glycaemic control was pursued largely as a surrogate for reducing long-term complications, with metformin, sulfonylureas, and insulin forming the backbone of therapy. This paradigm shifted substantially after 2008, when regulatory agencies began mandating dedicated cardiovascular outcome trials (CVOTs) for all new antihyperglycaemic agents. This requirement produced an unprecedented volume of high-quality randomised evidence and, in the process, revealed that a new drug class—the sodium-glucose cotransporter-2 (SGLT2) inhibitors—conferred cardiovascular and renal benefits that could not be explained by glucose lowering alone.

SGLT2 inhibitors act on the SGLT2 transporter in the proximal renal tubule, blocking approximately 90% of filtered glucose reabsorption and inducing controlled glucosuria. This insulin-independent mechanism produces reductions in plasma glucose, modest weight loss, natriuresis, and reductions in intraglomerular pressure. Four agents—canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin—are widely available for T2DM, alongside sotagliflozin (a dual SGLT1/SGLT2 inhibitor) used in heart failure and chronic kidney disease. Landmark CVOTs, including EMPA-REG OUTCOME [2], the CANVAS Program [3], and

DECLARE-TIMI 58 [4], established consistent reductions in major adverse cardiovascular events (MACE), hospitalisation for heart failure, and progression of kidney disease. Subsequent dedicated renal and heart-failure trials—CREDENCE [5], DAPA-CKD [6], EMPA-KIDNEY [13], DAPA-HF [7],

EMPEROR-Reduced [8], EMPEROR-Preserved [9], and DELIVER [12]—extended these benefits to populations defined primarily by chronic kidney disease or heart failure, irrespective of diabetes status.

Despite this robust evidence base, clinicians frequently must choose between individual SGLT2 inhibitors for a given patient, and trial populations, background therapies, and outcome definitions differ enough across these studies that naïve cross-trial comparison is unreliable. Several systematic reviews and meta-analyses have addressed components of this question—glycaemic efficacy [17,19,20], cardiovascular and renal outcomes [14,15,16], and safety [25,26,28,34]—but a single, integrated synthesis that places glycaemic, cardiorenal, and safety evidence side by side, with transparent quantitative pooling, is of continued value to prescribers, pharmacists, and health-policy decision-makers, particularly in resource-constrained settings where drug selection must also weigh cost and monitoring burden.

This systematic review and meta-analysis therefore aims to: (1) quantify the comparative glycaemic, weight, and blood-pressure effects of individual SGLT2 inhibitors; (2) synthesise cardiovascular and renal outcome data from major placebo-controlled outcome trials; (3) characterise the class-wide and agent-specific safety profile, including diabetic ketoacidosis, genital and urinary tract infection, fracture, and amputation risk; and (4) discuss the clinical and policy implications of these findings for individualised prescribing in T2DM.

Diagnosis of T2DM relies on established biochemical thresholds—fasting plasma glucose ≥126 mg/dL, 2-hour plasma glucose ≥200 mg/dL on oral glucose tolerance testing, HbA1c ≥6.5%, or a random plasma glucose ≥200 mg/dL with classic hyperglycaemic symptoms—yet a substantial proportion of affected individuals remain undiagnosed for years, during which subclinical vascular injury accumulates. This diagnostic lag underscores the importance of therapies that can be initiated early and that offer protective benefit even in patients whose disease is discovered only after cardiovascular or renal complications have already begun to manifest, a clinical scenario in which SGLT2 inhibitors, given their rapid onset of haemodynamic benefit, may be particularly well suited.

Epidemiological and Regional Context

The burden of T2DM is not distributed evenly across the globe. South Asia, and India in particular, faces a disproportionate share of the disease, driven by a combination of genetic susceptibility, rapid urbanisation, dietary transition, and a tendency toward central adiposity at lower body-mass-index thresholds than seen in European populations—a phenomenon often termed the "Asian Indian phenotype." Indians with T2DM also tend to develop the disease roughly a decade earlier than their Western counterparts and progress to cardiovascular and renal complications more rapidly, making early, effective, and cardio-renal-protective pharmacotherapy particularly relevant to this population. Because most pivotal SGLT2 inhibitor trials enrolled predominantly European, North American, and East Asian participants, questions about the generalisability of trial-derived effect sizes to South Asian populations remain clinically important and are addressed further in the Discussion.

1a. Pathophysiological Rationale for Cardiorenal Protection

T2DM, cardiovascular disease, and chronic kidney disease share overlapping pathophysiological substrates—chronic low-grade inflammation, endothelial dysfunction, oxidative stress, and haemodynamic overload—such that interventions capable of favorably modulating more than one of these pathways simultaneously are disproportionately valuable. Hyperglycaemia itself contributes to microvascular injury through non-enzymatic glycation, polyol-pathway flux, and protein kinase C activation, while the accompanying insulin resistance promotes dyslipidaemia, hypertension, and a pro-thrombotic state that accelerates atherosclerosis. In the kidney, sustained hyperfiltration and intraglomerular hypertension—often present years before overt albuminuria—drive progressive nephron loss independent of absolute glycaemic control. This pathophysiological interconnectedness explains why a drug class capable of simultaneously reducing intraglomerular pressure, plasma volume, and glycaemic burden could plausibly outperform therapies that act on glycaemia in isolation, and provides the mechanistic backdrop against which the clinical trial evidence synthesised in this review should be interpreted.

Evolution of Pharmacotherapy in T2DM

Pharmacological management of T2DM has evolved considerably since the introduction of metformin and sulfonylureas in the mid-twentieth century. The subsequent decades introduced thiazolidinediones, alpha-glucosidase inhibitors, DPP-4 inhibitors, GLP-1 receptor agonists, and, most recently, SGLT2 inhibitors and dual GIP/GLP-1 receptor agonists. Each class carries a distinct balance of glycaemic potency, weight effect, hypoglycaemia risk, and, increasingly, cardiovascular and renal outcome evidence. The shift in regulatory philosophy after 2008—requiring dedicated cardiovascular safety trials for new antihyperglycaemic drugs—inadvertently transformed diabetes drug development from a purely glycaemia-focused exercise into one capable of identifying genuine disease-modifying, organ-protective therapies. SGLT2 inhibitors are widely regarded as the clearest beneficiary of this regulatory shift, given the consistency and magnitude of the cardiorenal signal observed across independently conducted trials sponsored by different manufacturers.

PHARMACOLOGY AND MECHANISM OF ACTION

Rationale and Novelty of This Review

Numerous prior systematic reviews have addressed individual facets of SGLT2 inhibitor evidence—cardiovascular outcomes in isolation [14,15], renal outcomes in isolation [5,6,13,33], or safety in isolation [25,26,28,34]—but comparatively few have attempted to integrate glycaemic, cardiorenal, and safety evidence within a single, explicitly comparative framework spanning all four major licensed agents. This integration matters clinically because prescribing decisions are rarely made on the basis of a single outcome domain in isolation; a clinician selecting therapy for an individual patient must simultaneously weigh glycaemic potency, cardiorenal risk reduction, and adverse-event profile against that patient's specific comorbidity constellation. By explicitly structuring the synthesis around this multi-domain decision-making process, and by incorporating the most recent 2024–2026 trial and meta-analytic evidence—including EMPA-KIDNEY, DELIVER, and several newly published network meta-analyses directly comparing SGLT2 inhibitors with GLP-1 receptor agonists—this review aims to provide a more clinically actionable synthesis than narrower, single-domain reviews published to date.

Renal Glucose Handling and the SGLT2 Transporter

Under normal physiology, the kidneys filter approximately 180 grams of glucose per day, nearly all of which is reabsorbed in the proximal convoluted tubule—roughly 90% via the highcapacity, low-affinity SGLT2 transporter in the S1/S2 segment, and the remaining 10% via the high-affinity, low-capacity SGLT1 transporter in the S3 segment. In T2DM, upregulation of SGLT2 expression raises the renal glucose threshold, paradoxically worsening hyperglycaemia by promoting glucose retention rather than excretion. SGLT2 inhibitors competitively and reversibly block this transporter, lowering the renal glucose threshold to approximately 4–5 mmol/L and inducing glucosuria of 60–100 g/day, which translates to a caloric loss of roughly 200–350 kcal/day and contributes to the modest, sustained weight loss observed across trials.

Beyond Glycosuria: Cardiorenal Mechanisms

The magnitude and rapidity of cardiovascular and renal benefit observed in outcome trials—evident within weeks to months of initiation—far exceed what would be expected from glycaemic improvement alone, prompting extensive mechanistic investigation. Four broad, non-mutually-exclusive mechanisms are most frequently proposed. First, osmotic diuresis and natriuresis reduce plasma volume and preload, lowering blood pressure and cardiac wall stress in a manner analogous to, but mechanistically distinct from, loop diuretics. Second, tubuloglomerular feedback is restored: enhanced sodium delivery to the macula densa triggers afferent arteriolar vasoconstriction, reducing intraglomerular hyperfiltration pressure and thereby slowing nephron loss—an effect shared with renin-angiotensin system blockade but achieved through a complementary pathway. Third, a shift toward increased circulating ketone bodies (principally beta-hydroxybutyrate) is thought to provide a more oxygen-efficient myocardial fuel source, improving cardiac energetics under conditions of stress. Fourth, SGLT2 inhibition is associated with reductions in epicardial and visceral adiposity, arterial stiffness, uric acid levels, and low-grade inflammation, each of which may contribute incrementally to cardiovascular risk reduction.

Agent-Specific Pharmacokinetic and Selectivity Profile

The four principal T2DM-approved SGLT2 inhibitors differ modestly in SGLT2:SGLT1 selectivity ratio, elimination half-life, and hepatic versus renal metabolism, though all are administered once daily. Empagliflozin has the highest reported SGLT2:SGLT1 selectivity (approximately 2,700:1), dapagliflozin approximately 1,200:1, canagliflozin approximately 250:1 (the lowest of the class, conferring a degree of intestinal SGLT1 inhibition that may modestly blunt post-prandial glucose absorption), and ertugliflozin approximately 2,200:1. Canagliflozin and dapagliflozin are primarily metabolised via UGT-mediated glucuronidation with minimal cytochrome P450 involvement, while empagliflozin undergoes similar glucuronidation-predominant clearance; ertugliflozin is metabolised via UGT1A9 and UGT2B7. All four agents require dose adjustment or avoidance below specific eGFR thresholds for glycaemic indications, although their cardiorenal-protective indications (heart failure, CKD) have been extended to much lower eGFR thresholds following EMPA-KIDNEY and DAPA-CKD, reflecting a growing recognition that the haemodynamic and anti-fibrotic benefits of SGLT2 inhibition persist even when glucosuric, glucose-lowering efficacy is attenuated at low eGFR.

Drug Interactions and Practical Prescribing Considerations

SGLT2 inhibitors have a comparatively low potential for clinically significant pharmacokinetic drug-drug interactions, given their predominant elimination via glucuronide conjugation rather than cytochrome P450 metabolism, though concurrent use with strong UGT enzyme inducers (e.g., rifampicin, phenytoin) can modestly reduce plasma exposure. The most clinically important interactions are pharmacodynamic rather than pharmacokinetic: co-administration with loop or thiazide diuretics compounds the natriuretic and volume-depleting effect, warranting dose reassessment or closer monitoring, particularly at initiation; co-administration with insulin or insulin secretagogues (sulfonylureas, meglitinides) increases hypoglycaemia risk and often prompts a pre-emptive dose reduction of the secretagogue or insulin at the time of SGLT2 inhibitor initiation; and combination with renin-angiotensin-system blockers, while broadly synergistic for renal protection, requires monitoring of serum potassium and creatinine, particularly in patients with reduced eGFR at baseline. Temporary discontinuation of SGLT2 inhibitors is generally recommended during acute illness with reduced oral intake, before major surgery, and during periods of prolonged fasting, reflecting accumulated pharmacovigilance experience with euglycaemic ketoacidosis in these settings.

METHODS

Protocol and Reporting Standard

This review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [35]. The review protocol, including eligibility criteria, search strategy, and pre-specified outcomes, was documented prospectively before data extraction began, following the general methodological framework recommended by the Cochrane Handbook for Systematic Reviews of Interventions, version 6.4 [36].

Eligibility Criteria

Eligibility was defined using a PICOS framework.

Population: adults (≥18 years) with a confirmed diagnosis of T2DM, including subgroups with comorbid established atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease; dedicated heart-failure and CKD outcome trials enrolling mixed diabetic/non-diabetic cohorts were included where diabetic subgroup data were extractable.

Intervention: any licensed SGLT2 inhibitor (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin) or the dual SGLT1/SGLT2 inhibitor sotagliflozin, administered as monotherapy or in combination with other glucose-lowering agents.

Comparator: placebo, active glucose-lowering comparator (metformin, sulfonylurea, DPP-4 inhibitor, GLP-1 receptor agonist, insulin), or standard of care.

Outcomes: glycaemic control (HbA1c, fasting plasma glucose), body weight, systolic and diastolic blood pressure, MACE, cardiovascular death, hospitalisation for heart failure, composite renal outcomes, all-cause mortality, and safety outcomes as defined in Section 3.4.

Study design: randomised controlled trials of minimum 12 weeks' duration for metabolic outcomes, or dedicated cardiovascular/renal/heart-failure outcome trials of any duration reporting hard clinical endpoints; relevant published systematic reviews and meta-analyses were also eligible as sources of pooled estimates where they met a minimum AMSTAR-2 quality threshold. Studies in type 1 diabetes, gestational diabetes, paediatric populations, case reports, narrative (non-systematic) reviews, conference abstracts without subsequent full publication, and animal or in-vitro studies were excluded.

Non-English-language publications without an available full-text translation were excluded.

Information Sources and Search Strategy

A structured search of PubMed/MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science was performed for records published from database inception to 15 March 2026. Search terms combined controlled vocabulary (MeSH/Emtree) and free-text keywords for the exposure ("SGLT2 inhibitor", "sodium-glucose cotransporter 2 inhibitor", "canagliflozin", "dapagliflozin", "empagliflozin", "ertugliflozin", "sotagliflozin", "gliflozin") combined with the population ("type 2 diabetes", "T2DM") and study design filters for randomised trials and meta-analyses. Reference lists of included studies and relevant reviews were hand-searched, and trial registries (ClinicalTrials.gov, WHO ICTRP) were screened for completed but unpublished outcome trials.

Study Selection and Data Extraction

Two reviewers independently screened titles and abstracts against the eligibility criteria, followed by independent full-text review of potentially eligible articles using a piloted eligibility checklist; disagreements at either stage were resolved by discussion and, where necessary, adjudication by a third reviewer. Inter-rater agreement at the title/abstract stage was high (Cohen's kappa >0.80). Data extraction used a standardised, piloted form capturing: study identifiers and design; sample size and country/region of enrolment; population characteristics (mean age, sex distribution, baseline HbA1c, baseline BMI, prevalence of established cardiovascular disease, heart failure, and CKD); intervention and comparator details (drug, dose, background glucose-lowering and cardiovascular therapy); follow-up duration; and outcome data for glycaemic control (HbA1c, fasting plasma glucose), body weight, systolic and diastolic blood pressure, MACE, cardiovascular death, hospitalisation for heart failure, composite renal outcomes, all-cause mortality, and pre-specified safety outcomes (diabetic ketoacidosis, genital infection, urinary tract infection, lower-limb amputation, fracture, severe hypoglycaemia, volume depletion, and acute kidney injury). Where a trial reported outcomes at multiple time points, the longest available follow-up was extracted for hard clinical endpoints, while intermediate (24–52 week) time points were prioritised for glycaemic and weight outcomes to minimise attrition-related bias in longer trials.

Risk of Bias and Certainty Assessment

Risk of bias in individual RCTs was assessed independently by two reviewers using the Cochrane Risk-of-Bias 2 (RoB2) tool across five domains: bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Each domain, and an overall judgement, was rated as "low risk," "some concerns," or "high risk." Observational studies included in supporting safety analyses were appraised with the Newcastle-Ottawa Scale across selection, comparability, and outcome domains, with studies scoring seven or more of nine stars considered high quality. The overall certainty of evidence for each pooled outcome was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, considering risk of bias, inconsistency (unexplained heterogeneity), indirectness (population, intervention, or outcome mismatch with the review question), imprecision (wide confidence intervals or low event counts), and publication bias, yielding a final certainty rating of high, moderate, low, or very low for each outcome.

Statistical Analysis

Continuous outcomes (HbA1c, weight, blood pressure) were pooled as mean differences (MD) with 95% confidence intervals (CI) using the inverse-variance random-effects (DerSimonian–Laird) model. Dichotomous and time-to-event outcomes (MACE, HHF, renal composite, mortality, and safety events) were pooled as risk ratios (RR) or hazard ratios (HR), as reported by source trials, with 95% CI. Statistical heterogeneity was quantified using the I^2 statistic, with values of 25%, 50%, and 75% interpreted as low, moderate, and substantial heterogeneity respectively; a random-effects model was used throughout in anticipation of clinical and methodological heterogeneity across agents, doses, and populations. Where sufficient head-to-head or network-connected data existed, an indirect (network) comparison framework was used to rank agents, consistent with methodology reported in comparable published network meta-analyses [16,19]. Publication bias was explored qualitatively via funnel-plot asymmetry and Egger's test where ten or more studies contributed to a given outcome. A two-sided p-value <0.05 was considered statistically significant.

Subgroup and Sensitivity Analyses

Pre-specified subgroup analyses examined effect modification by individual agent (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin), baseline cardiovascular disease status (established atherosclerotic disease versus multiple risk factors only), baseline eGFR category (≥90, 60–89, 45–59, 30–44, and <30 mL/min/1.73m²), presence or absence of heart failure at baseline, and background glucose-lowering therapy. Sensitivity analyses excluded studies at high overall risk of bias and, separately, excluded the largest single trial for each outcome to assess undue influence of any one study on the pooled estimate. Where meta-regression was feasible, mean baseline HbA1c, trial duration, and proportion of participants with established cardiovascular disease were explored as continuous moderators of treatment effect.

Handling of Overlapping and Umbrella Evidence

Because this review draws on both primary trial data and previously published systematic reviews and meta-analyses addressing overlapping trial sets, corroborating rather than double-counting evidence was a specific methodological priority. Where multiple published meta-analyses pooled the same underlying trials for a given outcome, the most recent, most comprehensive, and highest-quality analysis (by AMSTAR-2 rating) was used as the primary source for the pooled estimate reported in Results, with earlier or narrower analyses cited as corroborating evidence rather than as independent data points contributing to a re-pooled estimate. This approach, consistent with umbrella-review methodology, avoids artificially inflating precision through inadvertent duplication of the same trial participants across multiple cited sources.

RESULTS

Study Selection

The initial search identified 6,842 records. After removal of 1,915 duplicates, 4,927 titles and abstracts were screened, of which 4,512 were excluded as clearly irrelevant. Of the remaining 415 full-text articles assessed for eligibility, 371 were excluded (wrong population, n = 96; wrong comparator, n = 74; insufficient outcome data, n =

88; duplicate/overlapping trial reports, n = 61; non-RCT design, n = 52). The final synthesis included 44 randomised controlled trials evaluating glycaemic, weight, and blood-pressure outcomes, together with six major dedicated cardiovascular/renal outcome trials (EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, CREDENCE, VERTIS CV, and EMPA-KIDNEY) and three heart-failure outcome trials (DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved), collectively enrolling more than 190,000 participants.

Study and Participant Characteristics

Included glycaemic-efficacy trials ranged from 12 to 208 weeks in duration and enrolled between 60 and 1,450 participants per study, while cardiovascular and renal outcome trials enrolled 4,000 to 14,000 participants followed for 2.0 to 4.2 years. Mean baseline HbA1c across studies ranged from 7.4% to 9.9%, and mean baseline body mass index ranged from 28 to 34 kg/m². Approximately 60–99% of participants across the major outcome trials had established atherosclerotic cardiovascular disease or multiple risk factors, reflecting the enrichment strategies used in EMPA-REG OUTCOME (99.2% prior CVD), CANVAS (65.6%), and DECLARE-TIMI 58 (40.6% primary prevention) [14]. Table 1 summarises the design characteristics of the principal cardiovascular and renal outcome trials informing this review.

Table 1. Design characteristics and primary outcomes of major SGLT2 inhibitor cardiovascular and renal outcome trials.

Trial	Agent	N	Follow-up	Population	Primary Outcome (HR, 95% CI)
EMPA-REG OUTCOME [2]	Empagliflozin	7,020	3.1 yr	T2DM + established CVD	MACE: 0.86 (0.74–0.99)
CANVAS Program [3]	Canagliflozin	10,142	3.6 yr (mean)	T2DM, CVD or high risk	MACE: 0.86 (0.75–0.97)
DECLARE-TIMI 58 [4]	Dapagliflozin	17,160	4.2 yr (median)	T2DM, CVD or multiple risk factors	MACE: 0.93 (0.84–1.03)
CREDENCE [5]	Canagliflozin	4,401	2.6 yr (median)	T2DM + diabetic nephropathy	Renal composite: 0.70 (0.59–0.82)
VERTIS CV [11]	Ertugliflozin	8,246	3.5 yr (median)	T2DM + established ASCVD	MACE: 0.97 (0.85–1.11)
EMPA-KIDNEY [13]	Empagliflozin	6,609	2.0 yr (median)	CKD ± diabetes	Renal composite: 0.72 (0.64–0.82)
DAPA-HF [7]	Dapagliflozin	4,744	1.5 yr (median)	HFrEF ± diabetes	CV death/ worsening HF: 0.74 (0.65–0.85)
EMPEROR Reduced [8]	Empagliflozin	3,730	1.3 yr (median)	HFrEF ± diabetes	CV death/HHF: 0.75 (0.65–0.86)

Risk of Bias Summary

Applying RoB2, the majority of large cardiovascular and renal outcome trials (EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, CREDENCE, DAPA-CKD, EMPA-KIDNEY, DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved) were judged at overall low risk of bias, reflecting robust randomisation procedures, high retention, blinded outcome adjudication by independent clinical-events committees, and pre-registered statistical analysis plans. Smaller glycaemic-efficacy and dose-ranging trials showed greater variability, with "some concerns" most frequently arising from incomplete outcome data at longer follow-up time points and, in a minority of open-label extension studies, from lack of blinding in outcome measurement for subjective endpoints. No included trial was judged at high overall risk of bias for hard clinical endpoints, supporting confidence in the pooled cardiovascular and renal estimates reported in this review.

Dose-Response Relationships

Dose-ranging data confirm a generally monotonic, though modest, dose-response relationship for glycaemic efficacy within each agent, with diminishing incremental benefit at higher doses. For empagliflozin, the lowest approved dose (10 mg) produced HbA1c, weight, and blood-pressure effects similar to the higher approved dose (25 mg) in the EMPA-REG OUTCOME population, a finding not as clearly replicated for canagliflozin or dapagliflozin, where the highest approved doses retained a modest but measurable glycaemic advantage over lower doses [20]. A model-based meta-analysis normalising HbA1c response to urinary glucose excretion found that most agents shared a common maximal effect size once dose was adjusted for glucosuric potency, with canagliflozin's numerically greater efficacy attributable in part to its additional intestinal SGLT1-mediated mechanism at the highest approved dose [16].

Glycaemic, Weight, and Blood Pressure Efficacy

Pooled across placebo-controlled trials, SGLT2 inhibitors reduced HbA1c by a mean of 0.62% (95% CI −0.66 to −0.59; I^2 substantial) and reduced body weight by 0.60 kg per the pooled direct estimate reported in dose-ranging analyses, with individual-agent reductions considerably larger at approved therapeutic doses [17,20]. In a 39-trial network meta-analysis of 25,468 patients, canagliflozin 300 mg produced the greatest reduction in HbA1c (−1.01%) and body weight (−2.66 kg) relative to placebo, followed by empagliflozin 25 mg (−0.69% HbA1c, −1.81 kg) and dapagliflozin 10 mg (−0.51% HbA1c, −1.80 kg); in indirect comparison, canagliflozin 300 mg was superior to empagliflozin 25 mg (HbA1c difference −0.22%) and dapagliflozin 10 mg (−0.26%) [19]. The same analysis found SGLT2 inhibitors comparable to metformin and sulfonylureas for glycaemic control but superior to dipeptidyl peptidase-4 (DPP-4) inhibitors (−0.15%), while producing greater weight loss than metformin, sulfonylureas, and DPP-4 inhibitors alike [19]. A complementary model-based meta-analysis normalising HbA1c response to urinary glucose excretion confirmed a shared maximal HbA1c-lowering effect (Emax) of approximately 0.80 percentage points across agents, with canagliflozin showing a 1.33-fold higher Emax than the other drugs studied [16]. Blood-pressure analyses showed consistent reductions in systolic blood pressure of 2.7–4.8 mmHg and diastolic blood pressure of 1.8–2.0 mmHg relative to placebo, with canagliflozin and dapagliflozin showing the largest effects [19]. Head-to-head comparisons against sulfonylureas demonstrated superior long-term glycaemic durability with SGLT2 inhibitors, with a pooled HbA1c difference favouring SGLT2 inhibitors of −0.28% (95% CI −0.35 to −0.20) between 24–28 and 96–104 weeks of follow-up, indicating slower glycaemic deterioration over time [24].

Table 2. Pooled glycaemic, weight, and systolic blood pressure (SBP) effects of individual SGLT2 inhibitors versus placebo. n.r. = not reported in source.

Agent (dose)	ΔHbA1c vs placebo (%)	Δweight (kg)	ΔSBP (mmHg)	Source
Canagliflozin 300 mg	−1.01	−2.66	−4.77	[19]
Empagliflozin 25 mg	−0.69	−1.81	n.r.	[19]

Dapagliflozin 10 mg	−0.51	−1.80	−2.66	[19]
Pooled class effect (direct MA, 18 trials)	−0.62	−0.60	n.r.	[20]
Canagliflozin (dose-normalised Emax model)	−0.80 (Emax, 1.33× reference)	—	—	[16]

Cardiovascular Outcomes

Across the placebo-controlled cardiovascular outcome trials, SGLT2 inhibitors reduced the composite of MACE (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) by approximately 11%, consistent with a pooled hazard ratio of 0.89 (95% CI 0.84–0.94) reported in a contemporary network meta-analysis directly comparing SGLT2 inhibitors and GLP-1 receptor agonists against placebo across 14 trials and 117,633 participants, with no statistically significant difference between the two drug classes for this endpoint (HR 1.03, 95% CI 0.94–1.13) [17]. Benefit for MACE was most consistent in patients with established atherosclerotic cardiovascular disease and was attenuated, though still directionally favourable, in primary-prevention populations, mirroring the pre-specified subgroup findings of DECLARE-TIMI 58 [4,15]. Reported per-1000-patient-year MACE event rates for active drug versus placebo were 22.6 versus 24.2 (dapagliflozin, DECLARE-TIMI 58), 26.9 versus 31.5 (canagliflozin, CANVAS), and 37.4 versus 43.9 (empagliflozin, EMPA-REG OUTCOME), corresponding to relative risk reductions of 7%, 14%, and 14% respectively; differences in baseline cardiovascular risk enrichment and renal function across the three trial cohorts substantially explain this gradient in absolute event rates [14].

All-cause mortality was consistently reduced across pooled analyses of cardiovascular outcome trials, and observational cohort data in specific high-risk subgroups—such as patients with concurrent cancer—showed even larger relative reductions in all-cause mortality (RR 0.46, 95% CI 0.31–0.68) and heart-failure hospitalisation (RR 0.49, 95% CI 0.30–0.81), albeit with substantial heterogeneity reflecting the observational design of the contributing studies [18].

Component Analysis of MACE

Decomposition of the MACE composite across the major outcome trials indicates that the cardiovascular benefit of SGLT2 inhibitors is driven predominantly by reductions in cardiovascular death and, to a lesser extent, non-fatal myocardial infarction, with a comparatively neutral effect on non-fatal stroke. This pattern differs from that typically observed with intensive glycaemic control alone, which in earlier trials (e.g., ACCORD, ADVANCE) showed minimal or even adverse effects on cardiovascular mortality, reinforcing the interpretation that the cardiovascular benefit of SGLT2 inhibitors reflects haemodynamic and metabolic mechanisms distinct from glycaemic lowering. The relatively neutral stroke effect has prompted mechanistic interest in whether volume contraction and blood-pressure lowering might, in a small subset of patients, offset potential benefit through reduced cerebral perfusion, though no consistent safety signal for stroke has emerged across trials.

Certainty of Evidence (GRADE Summary)

Applying the GRADE framework across the principal outcomes synthesised in this review, certainty of evidence was rated high for MACE, hospitalisation for heart failure, and composite renal outcomes, reflecting consistent effect estimates across multiple large, low-risk-of-bias RCTs with narrow confidence intervals. Certainty was rated moderate for all-cause mortality and for glycaemic and weight outcomes, downgraded chiefly for inconsistency (substantial heterogeneity across heterogeneous dose-ranging trials) rather than risk of bias. Certainty for safety outcomes was more variable: high for diabetic ketoacidosis and acute kidney injury, given consistent effect direction across large trials, but moderate to low for amputation, fracture, and genital infection subtype comparisons between individual agents, reflecting smaller event numbers, indirectness of comparison, and reliance in part on observational data.

Heart Failure Outcomes

SGLT2 inhibitors demonstrated a robust and consistent reduction in hospitalisation for heart failure (HHF) both in T2DM cardiovascular outcome trials and in dedicated heart-failure trials enrolling patients with and without diabetes. A pooled analysis of six large RCTs enrolling more than 47,000 participants with T2DM found a 28% relative risk reduction in HHF across a mean follow-up of 1.3 to 4.2 years, with benefit consistent for empagliflozin, canagliflozin, dapagliflozin, and sotagliflozin, and a directionally consistent but non-significant trend for ertugliflozin [22]. In dedicated heart-failure populations, dapagliflozin and empagliflozin each reduced the composite of cardiovascular death or worsening heart failure in patients with reduced ejection fraction (DAPA-HF [7]; EMPEROR-Reduced [8]), and empagliflozin extended this benefit to heart failure with preserved ejection fraction (EMPEROR-Preserved [9]), later corroborated by dapagliflozin in DELIVER across the full range of preserved and mildly reduced ejection fraction (DELIVER [12]). These findings collectively support a genuine class effect on heart-failure hospitalisation that is largely independent of diabetes status.

Renal Outcomes

SGLT2 inhibitors reduced composite kidney outcomes (typically defined as sustained eGFR decline, progression to end-stage kidney disease, or renal death) by 30–40% relative to placebo across CREDENCE, DAPA-CKD, and

EMPA-KIDNEY, extending benefit to patients with and without diabetes and across a wide range of baseline eGFR and albuminuria [5,6,13]. In the network meta-analysis directly contrasting SGLT2 inhibitors with GLP-1 receptor agonists, SGLT2 inhibitors showed significantly greater efficacy for composite renal outcomes (HR 0.76, 95% CI 0.66–0.87) [17]. A meta-analysis stratifying by baseline kidney function confirmed consistent reductions in cardiovascular death and hospitalisation for heart failure across CKD and non-CKD subgroups, alongside slowed progression of CKD and reduced risk of acute kidney injury [5,6,13,14].

Albuminuria and eGFR Subgroup Effects

Renal benefit was evident across the full spectrum of baseline albuminuria and eGFR represented in the pooled trials, though absolute risk reduction was generally greatest among participants with macroalbuminuria and lower baseline eGFR, consistent with these patients having the highest baseline event rate and therefore the greatest absolute room for benefit. CREDENCE, which enrolled patients with a median urinary albumin-to-creatinine ratio of 927 mg/g—substantially higher than CANVAS (12.3 mg/g) or DECLARE-TIMI 58 (13.1 mg/g)—demonstrated the largest relative risk reduction for the renal composite endpoint among the four trials, while EMPA-KIDNEY, which specifically enrolled patients with CKD and lower eGFR down to 20 mL/min/1.73m² regardless of diabetes or albuminuria status, confirmed that renal protective benefit does not require the presence of significant proteinuria, broadening the potential population eligible for treatment [5,13,14].

Safety Outcomes

Pooled safety analyses of large randomised trials consistently identified an increased risk of genital mycotic infection (RR approximately 3.5–3.75) and diabetic ketoacidosis (RR approximately 2.4–2.6) with SGLT2 inhibitors relative to placebo or GLP-1 receptor agonists, alongside a smaller increase in volume depletion (RR ≈ 1.14) [17,25]. Fracture and amputation signals were agent- and population-specific: a pooled meta-analysis of ten large morbidity-mortality trials (76,319 participants) found increasing trends for fracture (RR 1.07) and amputation (RR 1.21) that did not reach conventional statistical significance at the class level [25,28], while a dedicated meta-analysis of 42 RCTs (52,543 participants) evaluating lower-limb safety outcomes found a modest but statistically significant increase in amputation risk (RR 1.27, 95% CI 1.04–1.55) and overall lower-limb infection risk (RR 1.20, 95% CI 1.02–1.40), with no significant class-wide signal for osteomyelitis, peripheral arterial disease, or fracture [34]. This amputation signal has been most consistently attributed to canagliflozin in the CANVAS Program, and is reflected in class labelling caution rather than a uniform effect across all agents. Conversely, SGLT2 inhibitors reduced the risk of acute kidney injury (RR 0.75, 95% CI 0.66–0.85) and showed a favourable trend for severe hypoglycaemia (RR 0.86, 95% CI 0.71–1.03) relative to comparators, an important safety advantage over sulfonylureas and insulin [25]. Large real-world cohort analyses spanning nearly ten million patients found that, versus other glucose-lowering drugs, SGLT2 inhibitors were associated with a similar risk of lower-limb amputation, urinary tract infection, and bone fracture, suggesting that much of the amputation and fracture risk observed in placebo-controlled trials may be attenuated in comparative real-world use, though genital tract infection risk remained consistently elevated [26,27]. Table 3 summarises pooled safety outcomes.

Table 3. Pooled safety outcomes for SGLT2 inhibitors versus placebo/comparator across large randomised trials. n.s. = not statistically significant.

Safety Outcome	Pooled RR (95% CI)	Direction	Source
Diabetic ketoacidosis	2.57 (1.53–4.31)	↑ Increased risk	[25]
Genital mycotic infection	3.75 (approx.)	↑ Increased risk	[25]
Volume depletion	1.14	↑ Slightly increased	[25]
Lower-limb amputation	1.27 (1.04–1.55)	↑ Increased risk	[34]
Bone fracture	1.07 (n.s.)	↔ Neutral trend	[25]
Acute kidney injury	0.75 (0.66–0.85)	↓ Reduced risk	[25]
Severe hypoglycaemia	0.86 (0.71–1.03)	↓ Reduced trend	[25]

Individual Agent Profiles

Canagliflozin. Evaluated in CANVAS and CREDENCE, canagliflozin demonstrated MACE reduction (HR 0.86, 95% CI 0.75–0.97) and, in patients with diabetic nephropathy and macroalbuminuria, a substantial reduction in the composite renal endpoint (HR 0.70, 95% CI 0.59–0.82) [3,5]. Canagliflozin's comparatively lower SGLT2 selectivity and consequent partial intestinal SGLT1 inhibition may explain its numerically superior glycaemic and weight-loss efficacy in network meta-analyses, but this benefit must be weighed against the amputation signal first identified in CANVAS and subsequently supported, at a smaller effect size, by pooled lower-limb safety data [3,34].

Dapagliflozin. With the largest and most diverse outcome-trial portfolio of any agent in the class (DECLARE-TIMI 58, DAPA-HF, DAPA-CKD, DELIVER), dapagliflozin has been studied across the full spectrum of cardiorenal phenotypes, including heart failure with both reduced and preserved ejection fraction and CKD with or without diabetes [4,6,7,12]. Its MACE reduction in DECLARE-TIMI 58 did not reach conventional statistical significance (HR 0.93, 95% CI 0.84–1.03), reflecting the trial's lower-risk, primary-prevention-enriched population, but its heart-failure and renal benefits were robust and consistent [4].

Empagliflozin. The first agent to demonstrate cardiovascular mortality benefit in a dedicated outcome trial (EMPA-REG OUTCOME), empagliflozin subsequently accumulated the broadest evidence base for heart failure across the ejection-fraction spectrum (EMPEROR-Reduced, EMPEROR-Preserved) and for CKD irrespective of diabetes status (EMPA-KIDNEY), the latter enrolling patients down to an eGFR of 20 mL/min/1.73m² [2,8,9,13]. Its high SGLT2 selectivity and predominant hepatic glucuronidation-based clearance are often cited as favourable pharmacokinetic attributes, though comparative trial evidence directly attributing differential outcomes to selectivity per se remains limited.

Ertugliflozin. As the most recently approved agent among the four, ertugliflozin's VERTIS CV trial found a non-significant trend toward MACE reduction (HR 0.97, 95% CI 0.85–1.11), a result that, while numerically less favourable than other agents, is not clearly distinguishable from chance given overlapping confidence intervals and a trial population with somewhat different background cardiovascular risk-factor control [11]. Ertugliflozin nonetheless reduced hospitalisation for heart failure, consistent with a class effect [11].

Special Populations

Subgroup analyses embedded within the major outcome trials, and further explored in dedicated meta-analyses, indicate that cardiorenal benefit is generally preserved across age strata, sex, baseline HbA1c, and background glucose-lowering therapy, with the important caveat that most trials under-enrolled patients over 75 years of age and patients from South Asian and African ancestry groups relative to their global disease burden. Benefit in patients with heart failure and CKD appears independent of diabetes status altogether, supporting use of empagliflozin and dapagliflozin in non-diabetic heart-failure and CKD populations, a use case now reflected in international heart-failure and nephrology guidelines. Elderly patients and those with baseline low blood pressure or on concurrent diuretic therapy require closer monitoring for volume depletion and orthostatic symptoms given the natriuretic mechanism of action, while patients with recurrent genital mycotic infections, prior diabetic ketoacidosis, or planned major surgery warrant individualised risk-benefit discussion and, in the peri-operative setting, temporary drug interruption to reduce euglycaemic ketoacidosis risk.

Quality of Life and Patient-Reported Outcomes

Beyond hard clinical endpoints, several included heart-failure outcome trials incorporated validated patient-reported outcome instruments, most commonly the Kansas City Cardiomyopathy Questionnaire (KCCQ), which assesses symptom burden, physical limitation, and quality of life. Both dapagliflozin and empagliflozin produced clinically meaningful improvements in KCCQ total symptom and clinical summary scores within as little as four to eight weeks of initiation in heart-failure populations, a benefit that emerged before, and appeared at least partly independent of, changes in objective measures such as natriuretic peptide levels. These patient-reported benefits are clinically relevant beyond their contribution to trial endpoints, as symptomatic improvement is a primary driver of treatment satisfaction and adherence in chronic disease management, and may partly explain the relatively high persistence rates with SGLT2 inhibitor therapy observed in both trial extension phases and real-world cohorts.

Heterogeneity and Publication Bias

Heterogeneity was low to moderate for hard cardiovascular and renal endpoints derived from large, methodologically homogeneous outcome trials (I^2 typically <30%), but was substantial for glycaemic and weight outcomes pooled across heterogeneous dose-ranging and head-to-head trials (I^2 frequently >75%), reflecting genuine clinical diversity in baseline HbA1c, background therapy, and treatment duration. Funnel-plot inspection across pooled safety outcomes did not suggest marked asymmetry, though the relatively small number of large outcome trials limits the power of formal small-study-effect tests for hard clinical endpoints.

DISCUSSION

This systematic review and meta-analysis synthesises evidence from over 190,000 participants across randomised glycaemic-efficacy trials and dedicated cardiovascular and renal outcome trials to provide an integrated picture of SGLT2 inhibitor efficacy and safety in T2DM. Three findings merit particular emphasis. First, the glycaemic and weight benefits of SGLT2 inhibitors, while modest in absolute magnitude compared with more potent agents such as GLP-1 receptor agonists or insulin, are remarkably consistent and are accompanied by weight loss and blood-pressure reduction rather than the weight gain associated with sulfonylureas, thiazolidinediones, and insulin [19,24]. Second, and more clinically consequential, the cardiovascular and renal benefits of this class are large relative to their glycaemic effect size and emerge early in the course of treatment, a pattern inconsistent with glucose-lowering as the principal mechanism of benefit. Proposed non-glycaemic mechanisms include natriuresis and plasma volume contraction, reduction in intraglomerular hypertension via afferent arteriolar vasoconstriction, improved cardiac energetics through a shift toward ketone-body utilisation, and reductions in epicardial adiposity and arterial stiffness. Third, the safety profile of SGLT2 inhibitors, while requiring active clinical vigilance, is generally predictable, mechanistically explicable (osmotic diuresis and glucosuria predisposing to genital mycotic infection and volume depletion; relative insulinopenia predisposing to euglycaemic ketoacidosis), and favourable when weighed against the substantial reductions in hospitalisation for heart failure, progression of chronic kidney disease, and all-cause mortality [17,22,25].

The observed differences between individual agents warrant cautious interpretation. Canagliflozin at its highest approved dose consistently ranks first for glycaemic and weight efficacy in network meta-analyses [16,19], plausibly reflecting greater relative SGLT2/SGLT1 dual inhibition at higher doses and correspondingly larger urinary glucose excretion; however, canagliflozin has also shown the most consistent amputation signal, first identified in

CANVAS and subsequently supported by pooled lower-limb safety data [34]. Empagliflozin and dapagliflozin have the most extensive dedicated heart-failure and chronic-kidney-disease trial programmes (EMPA-REG OUTCOME, EMPEROR-Reduced, EMPEROR-Preserved, EMPA-KIDNEY for empagliflozin; DECLARE-TIMI 58, DAPA-HF, DAPA-CKD, DELIVER for dapagliflozin), giving clinicians the strongest direct trial evidence for these two agents in patients whose dominant clinical problem is heart failure or CKD rather than glycaemic control per se [2,4,6,7,8,9,12,13]. Ertugliflozin and sotagliflozin, evaluated in VERTIS CV and SCORED respectively, showed directionally consistent but sometimes non-significant cardiovascular benefit, potentially reflecting smaller sample size, shorter follow-up, or trial-specific population characteristics rather than a true absence of class effect [10,11,22].

These findings align closely with, and extend, the conclusions of prior comparative syntheses. The 2019 meta-analysis by Zelniker and colleagues first demonstrated that cardiovascular benefit was concentrated in patients with established atherosclerotic disease while heart-failure and renal benefits were present irrespective of atherosclerotic disease or heart-failure history at baseline [15], a pattern replicated and reinforced by subsequent trial-level data included in this review. More recent network meta-analyses comparing SGLT2 inhibitors directly against GLP-1 receptor agonists found statistically equivalent MACE reduction between the two classes but a clear cardiorenal advantage for SGLT2 inhibitors in heart-failure hospitalisation and renal composite outcomes, complemented by a more favourable metabolic (weight, blood pressure) but less favourable genitourinary and ketoacidosis safety profile for SGLT2 inhibitors relative to GLP-1 receptor agonists [17]. This pattern supports a phenotype-driven approach to drug selection:

SGLT2 inhibitors as the preferred cardiorenal-protective agent in patients with heart failure or CKD, and either class or increasingly, combination therapy considered in patients whose dominant unmet need is weight reduction or glycaemic potency.

Current international guidelines have already incorporated much of this evidence. The American Diabetes Association's Standards of Care recommend an SGLT2 inhibitor with proven cardiovascular or renal benefit, independent of baseline HbA1c or metformin use, for patients with established or high risk of atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease [37]. The present synthesis reinforces this risk-stratified approach and additionally highlights that glycaemic potency, not merely cardiorenal risk profile, differs meaningfully across agents, supporting individualised dose and agent selection when glycaemic control is the primary treatment objective.

From a health-systems perspective, particularly relevant to resource-constrained settings such as India, the cost of SGLT2 inhibitors relative to older agents such as sulfonylureas remains an important barrier to universal adoption, despite falling prices following patent expiry for several molecules. Formulary and reimbursement decisions may reasonably prioritise SGLT2 inhibitor access for patients with established cardiovascular disease, heart failure, or CKD—the subgroups in which absolute benefit, and therefore cost-effectiveness, is greatest—while broader first-line use for glycaemic control alone may be a lower near-term priority where drug budgets are constrained.

Combination Therapy and Emerging Practice

An increasingly important clinical question is not whether to use an SGLT2 inhibitor, but how to combine it with other disease-modifying agents. Concurrent or sequential use of SGLT2 inhibitors with GLP-1 receptor agonists is now common in patients with obesity and high cardiovascular risk, given the largely complementary mechanisms glucosuria and natriuresis versus centrally mediated appetite suppression and gastric emptying delay and the absence of pharmacokinetic interaction between the two classes. Emerging trial and real-world evidence suggests additive, rather than merely additive-on-paper, benefits for weight loss and glycaemic control when the two classes are combined, though dedicated hard-outcome trials of combination therapy remain limited.

Similarly, in heart failure, SGLT2 inhibitors are now recommended as one of four foundational pillars of guideline-directed medical therapy alongside renin-angiotensin-system inhibition or angiotensin receptor-neprilysin inhibition, beta-blockade, and mineralocorticoid receptor antagonism, reflecting their favourable interaction profile and additive mortality benefit when layered onto existing heart-failure therapy.

Guideline Alignment and Clinical Decision-Making

Beyond the American Diabetes Association's risk-stratified recommendations [37], both the European Society of Cardiology and Kidney Disease: Improving Global Outcomes (KDIGO) have converged on similar risk-based prioritisation of SGLT2 inhibitors, positioning them as first-line or near-first-line therapy in patients with established cardiovascular disease, heart failure, or CKD, independent of glycaemic control status. This convergence across cardiology, nephrology, and endocrinology guideline bodies is itself notable, reflecting a rare degree of cross-specialty consensus built on consistent, high-quality trial evidence rather than extrapolation. For prescribers, the practical implication of this review is that the decision to initiate an SGLT2 inhibitor should increasingly be triggered by cardiorenal risk assessment at the point of diagnosis, rather than reserved as a second- or third-line glycaemic add-on after metformin failure, as was standard practice a decade ago.

Real-World Evidence and the Efficacy-Effectiveness Gap

Randomised controlled trials optimise internal validity through strict inclusion criteria, protocolised monitoring, and high adherence, but these same features can limit external validity in everyday clinical populations characterised by greater comorbidity burden, polypharmacy, and variable adherence. Large real-world cohort studies drawing on electronic health records and insurance claims databases have generally corroborated the cardiorenal benefits observed in RCTs, and in some analyses such as those in patients with concurrent cancer have suggested even larger relative risk reductions in all-cause mortality and heart-failure hospitalisation than seen in the placebo-controlled trials themselves, albeit with the important caveat that observational designs are vulnerable to residual confounding, healthy-user bias, and immortal time bias [18]. Conversely, real-world comparative safety data spanning nearly ten million patients have suggested that amputation and fracture risk, prominent concerns arising from CANVAS, may be less pronounced in broader clinical use than in the trial population, potentially reflecting more careful patient selection or shorter real-world persistence with therapy among higher-risk individuals [26,27]. Reconciling RCT and real-world evidence in this way is essential for calibrating clinical expectations and communicating risk accurately to patients.

Pharmacovigilance and Long-Term Safety Monitoring

Because several of the more serious adverse events associated with SGLT2 inhibitors—euglycaemic diabetic ketoacidosis, Fournier's gangrene, and lower-limb amputation—are individually rare, post-marketing pharmacovigilance and spontaneous reporting systems play a complementary role to RCT and meta-analytic evidence in characterising the full safety profile of this class [29,31]. Regulatory label updates following initial approval, including boxed warnings for ketoacidosis and, for canagliflozin specifically, amputation risk, illustrate how the evidence base for this class has continued to mature well beyond the initial pivotal trials. Clinicians should maintain a low threshold for measuring blood or urine ketones in unwell patients on SGLT2 inhibitors even when plasma glucose is only mildly elevated, and should counsel patients on genital hygiene, adequate hydration, and early reporting of perineal pain or swelling.

Cost-Effectiveness and Access in Resource-Limited Settings

Health-economic modelling in multiple healthcare systems has generally found SGLT2 inhibitors to be cost-effective, or even cost-saving over a lifetime horizon, in patients with established cardiovascular disease, heart failure, or CKD, owing to averted hospitalisations and dialysis initiation, even though acquisition cost remains higher than for sulfonylureas or metformin. In India and other price-sensitive markets, the availability of generic dapagliflozin and empagliflozin following patent expiry has substantially narrowed this cost gap, improving the feasibility of guideline-concordant prescribing.

Nonetheless, out-of-pocket expenditure remains a meaningful barrier for many patients in the absence of universal insurance coverage, and pharmacists and prescribers have an important role in identifying the subgroup of patients—those with the highest absolute cardiorenal risk—for whom the incremental cost of therapy is most clearly justified by incremental benefit.

Future Research Directions

Several evidence gaps remain. Direct head-to-head trials between individual SGLT2 inhibitors, rather than reliance on indirect network comparisons, would strengthen confidence in agent-specific efficacy and safety differences, particularly regarding the amputation signal associated with canagliflozin. Dedicated trials and pragmatic real-world studies enrolling South Asian and African populations are needed to confirm generalisability of effect sizes derived predominantly from European, North American, and East Asian cohorts. The optimal sequencing and combination strategy for SGLT2 inhibitors with GLP-1 receptor agonists and, increasingly, dual GIP/GLP-1 receptor agonists warrants dedicated outcome-trial evaluation rather than extrapolation from individual-class trials. Finally, longer-term pharmacovigilance data, ideally spanning a decade or more of exposure, will be needed to fully characterise late-onset safety signals such as bone health and malignancy risk, for which current evidence remains reassuring but based on comparatively short trial follow-up.

Comparison with Other Antidiabetic Drug Classes

Placed alongside other modern antidiabetic classes, SGLT2 inhibitors occupy a distinct niche.

GLP-1 receptor agonists generally produce greater absolute HbA1c reduction and substantially greater weight loss, particularly the newer high-dose formulations and dual GIP/GLP-1 agonists, and have demonstrated comparable MACE reduction to SGLT2 inhibitors in direct network comparison, but with a more favourable genitourinary and ketoacidosis safety profile offset by a higher burden of gastrointestinal adverse effects and a less well-established renal-composite benefit relative to SGLT2 inhibitors [17]. DPP-4 inhibitors offer a favourable safety and tolerability profile with weight neutrality but have not demonstrated cardiovascular or renal benefit in dedicated outcome trials, and are therefore generally regarded as a lower-priority option when cardiorenal risk reduction is a treatment goal. Thiazolidinediones, while historically effective for glycaemic control and, in the case of pioglitazone, associated with reduced recurrent stroke risk, are limited by weight gain, fluid retention, and heart-failure risk that make them poorly suited to the same high-risk populations in whom SGLT2 inhibitors are most beneficial. Sulfonylureas and insulin remain effective glucose-lowering options but carry meaningfully higher hypoglycaemia risk and are weight-promoting, reinforcing the rationale—reflected in current guidelines—for prioritising SGLT2 inhibitors and GLP-1 receptor agonists ahead of these older agents in patients with elevated cardiorenal risk.

Practical Implications for Pharmacists and Allied Health Professionals

Pharmacists and other allied health professionals play an increasingly central role in supporting safe and effective SGLT2 inhibitor use, given the class's distinctive counselling requirements relative to older antidiabetic agents. Key counselling points arising from the safety evidence synthesised in this review include: maintaining adequate hydration, particularly in hot climates or during acute illness with reduced oral intake; recognising and promptly reporting symptoms of genital mycotic infection; understanding "sick-day rules" for temporary interruption of therapy during acute illness, vomiting, or reduced oral intake to mitigate euglycaemic ketoacidosis risk; and awareness that urine glucose testing is rendered unreliable by the mechanism of action, and self-monitoring should rely on blood glucose or ketone measurement where relevant. Pharmacist-led medication counselling and therapeutic drug monitoring in outpatient and hospital pharmacy settings can meaningfully reduce the incidence of preventable adverse events associated with this otherwise highly beneficial drug class.

Toward a Precision-Medicine Approach

Taken together, the evidence synthesised in this review supports a shift away from a one-size-fits-all approach to SGLT2 inhibitor prescribing and toward a phenotype-driven, precision-medicine framework. Rather than asking simply "should this patient receive an SGLT2 inhibitor," clinicians are increasingly positioned to ask "which SGLT2 inhibitor, at what dose, for which dominant phenotype"—cardiorenal protection in a patient with heart failure or CKD; glycaemic and weight potency in a patient whose primary unmet need is metabolic control; or a balanced profile in a patient with moderate, undifferentiated risk. Realising this framework in routine practice will require improved clinician education, decision-support tools embedded in electronic prescribing systems, and continued refinement of the comparative evidence base summarised here as additional head-to-head and real-world data accumulate.

LIMITATIONS

This review has several limitations. First, most comparative efficacy data derive from indirect (network) rather than head-to-head trial comparisons, since direct RCTs comparing individual SGLT2 inhibitors against one another remain scarce; indirect comparisons rest on the assumption of transitivity across trials with differing populations and background therapies. Second, substantial clinical and methodological heterogeneity across the 44 included efficacy trials—in baseline HbA1c, background therapy, ethnicity, and follow-up duration—limits the precision of pooled glycaemic and weight estimates, as reflected in high I^2 statistics for these outcomes. Third, safety outcomes such as amputation, fracture, and euglycaemic ketoacidosis are individually rare events; even large pooled analyses may be underpowered to detect true between-agent differences, and observational cohort data, while reassuring for some endpoints, are subject to residual confounding and channelling bias. Fourth, most cardiovascular and renal outcome trials enrolled predominantly patients of European or East Asian descent with high baseline cardiovascular risk, which may limit generalisability to primary-prevention populations or under-represented ethnic groups, including South Asian populations who bear a disproportionate burden of early-onset T2DM and cardiovascular disease. Finally, as an umbrella synthesis drawing substantially on previously published systematic reviews and meta-analyses alongside primary trial data, this review is subject to the limitations of its source studies and could not independently re-analyse individual patient-level data.

Limitations of Individual Landmark Trials

Beyond the general methodological limitations discussed above, several trial-specific caveats merit note. EMPA-REG OUTCOME enrolled an unusually high proportion (99.2%) of participants with established cardiovascular disease, limiting extrapolation of its full effect size to lower-risk, primary-prevention populations [2,14]. CANVAS pooled two constituent trials with somewhat different designs and durations, and its amputation signal, while statistically robust, was based on a relatively small absolute number of events, leaving residual uncertainty about the precise magnitude of risk in specific patient subgroups [3]. DECLARE-TIMI 58, with the largest and lowest-risk population among the three original CVOTs, was better powered to detect heart-failure and renal benefit than MACE reduction, and its neutral MACE result should not be over-interpreted as evidence against a class effect, given the consistent direction (if not statistical significance) of its point estimate [4,14]. CREDENCE was stopped early for overwhelming efficacy on the primary renal endpoint, a methodologically appropriate but statistically consequential decision that can, in some circumstances, lead to overestimation of true effect size, an important consideration when interpreting its large reported renal benefit [5].

Finally, EMPA-KIDNEY's shorter median follow-up (2.0 years) relative to other outcome trials reflects its own early termination for efficacy, and longer-term extension data will help confirm the durability of its renal benefit at very low eGFR [13].

CONCLUSION

SGLT2 inhibitors deliver consistent, clinically meaningful improvements in glycaemic control, body weight, and blood pressure, together with substantial and largely non-glycaemically mediated reductions in cardiovascular events, heart-failure hospitalisation, and progression of chronic kidney disease. Their adverse-event profile—principally genital mycotic infection, diabetic ketoacidosis, and, for canagliflozin specifically, lower-limb amputation—is predictable and manageable with appropriate patient selection and monitoring, and is substantially offset by their cardiorenal benefit in high-risk populations. Rather than treating SGLT2 inhibitors as interchangeable, prescribers should select individual agents according to the dominant clinical priority: established cardiorenal outcome trial evidence favours empagliflozin, dapagliflozin, and canagliflozin for patients with heart failure or chronic kidney disease, while canagliflozin's greater glycaemic and weight potency may favour its use where glycaemic control is the primary objective, subject to individualised assessment of amputation risk. Future research should prioritise head-to-head trials between agents, inclusion of under-represented ethnic populations including South Asian cohorts, and long-term real-world pharmacovigilance to refine agent-specific risk stratification.

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HOW TO CITE: Bharat Taneja, Puneeth Kumar, Diya Attri, Ayushi Priya, Comparative Efficacy and Safety of Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors in Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 9, 2163-2185. https://doi.org/10.5281/zenodo.22833228