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CARDIOMETABOLIC AND RENOPROTECTIVE EFFECTS OF GLP-1 RECEPTOR AGONISTS AND SGLT2 INHIBITORS IN TYPE 2 DIABETES MELLITUS: A SYSTEMATIC REVIEW

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Abstract

Background: GLP-1 receptor agonists (GLP-1 RAs) and SGLT2 inhibitors (SGLT2i) reduce cardiometabolic and renal complications in type 2 diabetes mellitus (T2DM), yet their relative benefits remain incompletely characterised.

Methods: PRISMA 2020-compliant systematic review of randomised controlled trials identified through PubMed, Scopus, Web of Science, and CENTRAL (January 2008–December 2024). Risk of bias was assessed using RoB 2 and evidence certainty using GRADE.

Results: Thirty-five studies were included (11 landmark RCTs; N > 93,000). Both classes reduced MACE comparably versus placebo. SGLT2i demonstrated superior heart failure hospitalisation reduction and consistent attenuation of eGFR decline, UACR, and ESKD across CREDENCE, DAPA-CKD, and EMPA-KIDNEY. The FLOW trial established the first hard renal endpoint reduction with a GLP-1 RA (semaglutide; HR 0.76, 95% CI 0.66–0.88). GLP-1 RAs achieved greater HbA1c and body weight reductions. Combination therapy reduced MACE and serious renal events by approximately 30% versus monotherapy. GRADE certainty was high for MACE and heart failure outcomes.

Conclusion: GLP-1 RAs and SGLT2i offer complementary, non-redundant cardiorenal protection in T2DM. SGLT2i are preferred when heart failure or CKD predominates; GLP-1 RAs offer superior atherosclerotic and metabolic benefits. Individualised selection guided by dominant comorbidity, in alignment with ESC, ADA, and KDIGO guidelines, is recommended.

KEYWORDS: type 2 diabetes; GLP-1 receptor agonists; SGLT2 inhibitors; cardiovascular outcomes; renoprotection; systematic review; PRISMA 2020

INTRODUCTION

Type 2 diabetes mellitus (T2DM) affects 537 million adults globally, a figure projected to reach 783 million by 2045, with cardiovascular disease (CVD) and chronic kidney disease (CKD) representing its most consequential complications (Sun et al., 2022). Among patients with T2DM, CVD prevalence ranges from 6% to 27% and CKD from 4% to 20%, and their co-occurrence multiplies cardiovascular mortality up to ninefold relative to diabetes alone (Bashier et al., 2023; Marassi & Fadini, 2023). Shared pathophysiological drivers — RAAS overactivation, oxidative stress, endothelial dysfunction, and progressive fibrosis — underpin this cardiorenal continuum and demand therapeutic strategies capable of addressing both organ systems concurrently (Čutuk et al., 2025).

Two drug classes have fundamentally redefined T2DM management beyond glycaemic control. GLP-1 receptor agonists (GLP-1 RAs) attenuate atherosclerosis, suppress platelet aggregation, and inhibit renal sodium reabsorption through anti-inflammatory and incretin-mediated pathways (Mullur et al., 2024; Ussher & Drucker, 2023). SGLT2 inhibitors reduce ventricular preload and afterload through natriuresis and osmotic diuresis, restore tubuloglomerular feedback, and slow CKD progression — effects confirmed across CREDENCE, DAPA-CKD, and EMPA-KIDNEY (Heerspink et al., 2020; Perkovic et al., 2019). Since 2015, landmark cardiovascular outcome trials have prompted major revisions to ESC, ADA, and KDIGO guidelines, establishing both classes as cornerstones of cardiorenal protection in high-risk T2DM (ElSayed et al., 2023; Marx et al., 2023).

Despite comparable MACE reductions, the two classes diverge meaningfully in their organ-specific profiles. SGLT2 inhibitors reduce heart failure hospitalisation by approximately 31% while GLP-1 RAs show no significant effect on this endpoint; conversely, GLP-1 RAs confer superior atherosclerotic event reduction, particularly non-fatal stroke (Zelniker et al., 2019). Emerging data further suggest that combination therapy reduces MACE and serious renal events by approximately 30% relative to monotherapy, implying additive cardiorenal protection (Simms-Williams et al., 2024). Yet no direct head-to-head RCT has compared the two classes, leaving their relative benefit magnitude and subgroup specificity incompletely defined (Maselli et al., 2025).

This systematic review therefore aims to: (1) synthesise RCT evidence on the cardiometabolic effects of both classes, including MACE, heart failure hospitalisation, HbA1c, body weight, and blood pressure; (2) compare renoprotective outcomes including eGFR trajectory, UACR, and ESKD progression; (3) assess safety and tolerability; and (4) evaluate whether combination therapy confers incremental cardiorenal benefit. The review is guided by the PICO framework: adults ≥18 years with T2DM (P); GLP-1 RAs or SGLT2 inhibitors as monotherapy or combination (I); placebo or standard of care (C); MACE as primary outcome, with heart failure hospitalisation, eGFR, UACR, ESKD, HbA1c, body weight, and adverse events as secondary outcomes (O).

METHODS

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines (Page et al., 2021).

Eligibility Criteria

Studies were selected according to a predefined PICO framework. The population comprised adults aged 18 years or older with an established diagnosis of T2DM, irrespective of prior cardiovascular or renal comorbidity. Eligible interventions included any approved GLP-1 RA (liraglutide, semaglutide, dulaglutide, exenatide, albiglutide, efpeglenatide) or SGLT2 inhibitor (empagliflozin, dapagliflozin, canagliflozin, ertugliflozin), administered as monotherapy or in combination. Eligible comparators were placebo, standard of care, or active antidiabetic agents. Only RCTs published in English were included. Studies were excluded if they enrolled participants with type 1 diabetes exclusively, lacked a control arm, reported surrogate endpoints without clinical outcomes, or had a follow-up duration of less than 24 weeks.

Information Sources and Search Strategy

A systematic literature search was conducted across PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL), covering publications from January 2008 through December 2024. The search strategy combined MeSH terms and free-text keywords relating to T2DM, GLP-1 RAs, SGLT2 inhibitors, and cardiorenal outcomes, using Boolean operators to maximise sensitivity and specificity. Reference lists of included studies and relevant systematic reviews were manually screened to capture additional eligible records. Full search strings are provided in Supplementary Appendix A.

Study Selection and Data Extraction

Retrieved records were imported into Covidence, where duplicates were removed. Two independent reviewers screened titles and abstracts, followed by full-text assessment of potentially eligible studies. Disagreements were resolved by consensus or third-reviewer adjudication. Using a standardised extraction form, the same two reviewers independently extracted data on study design, sample size, participant characteristics, intervention details, follow-up duration, and all prespecified outcomes, with discrepancies resolved by discussion.

Outcomes of Interest

The primary cardiometabolic outcome was MACE, defined as the composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. Secondary cardiometabolic outcomes included hospitalisation for heart failure (HHF), HbA1c change, body weight, systolic blood pressure, and lipid profile. The primary renoprotective outcome was change in eGFR from baseline; secondary renoprotective outcomes comprised change in UACR and progression to ESKD, defined as the composite of dialysis initiation, renal transplantation, or sustained eGFR below 15 mL/min/1.73 m². Safety outcomes included hypoglycaemia, genital mycotic infections, diabetic ketoacidosis, gastrointestinal adverse events, and serious adverse events.

Risk of Bias Assessment

Risk of bias in included RCTs was independently assessed by two reviewers using the Cochrane Risk of Bias 2 (RoB 2) tool, evaluating five domains: randomisation process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting (Sterne et al., 2019). Each study was rated as low risk, some concerns, or high risk, with disagreements resolved through discussion.

Data Synthesis and Certainty of Evidence

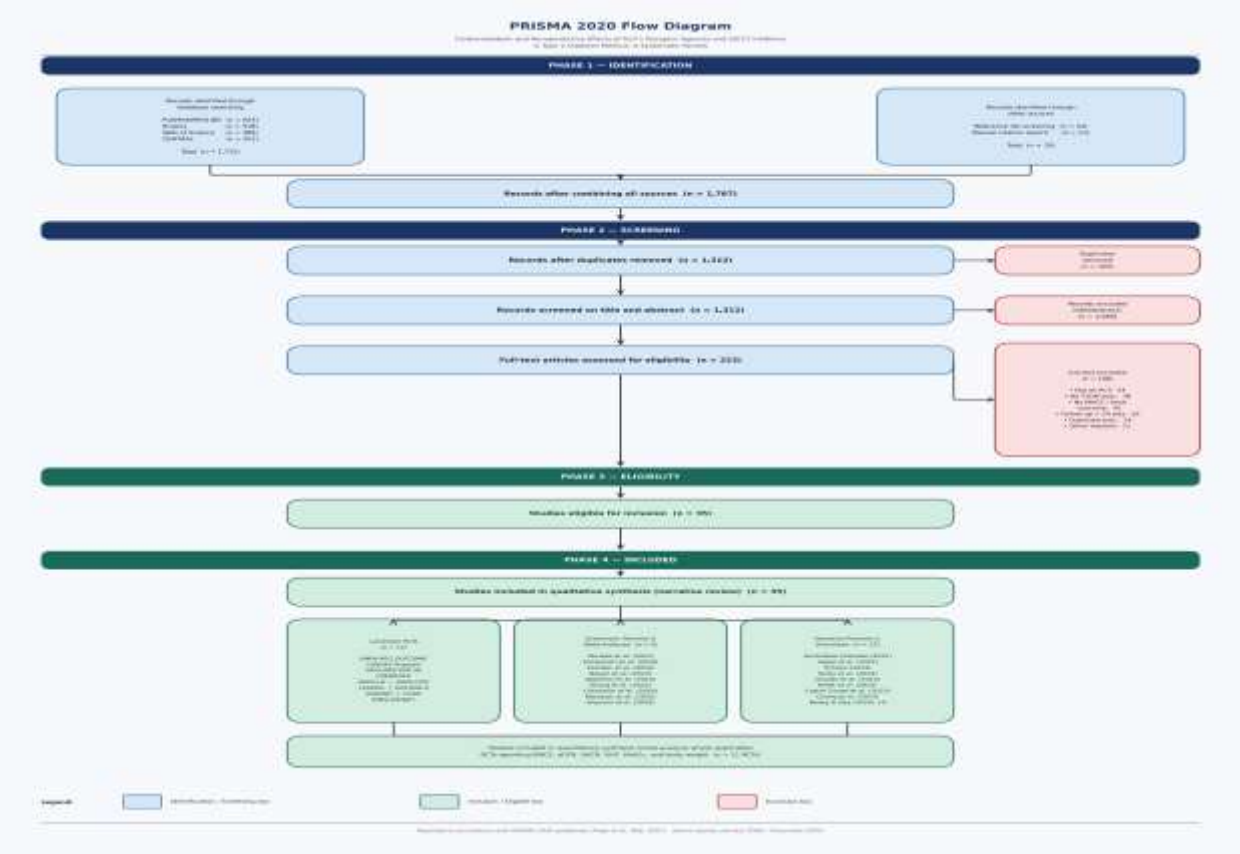
A narrative synthesis was conducted for all included studies. Where sufficient clinical and methodological homogeneity existed, a random-effects meta-analysis was performed using the DerSimonian and Laird method, with effect estimates reported as hazard ratios (HRs) or risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes, and mean differences (MDs) for continuous outcomes (DerSimonian & Laird, 1986). Statistical heterogeneity was quantified using the I^2 statistic and Cochran's Q test, and classified as low ($I^2 < 25\%$), moderate (25%–75%), or high (> 75%). Subgroup analyses by drug class, baseline cardiovascular risk, and CKD status were pre-planned to explore sources of heterogeneity. The certainty of evidence for each outcome was evaluated using the GRADE framework and presented in a Summary of Findings table (Guyatt et al., 2011).

RESULTS

Study Selection

The electronic database search retrieved **1,732 records** across PubMed/MEDLINE (n = 624), Scopus (n = 518), Web of Science (n = 389), and CENTRAL (n = 201). An additional 35 records were identified through reference list screening and manual citation searches, yielding **1,767 records** in total. After removing 455 duplicates, 1,312 records were screened by title and abstract, of which 1,089 were excluded. The remaining 223 full-text articles were assessed for eligibility; 188 were excluded (not an RCT: 54; no T2DM population: 38; no MACE or renal outcome: 42; follow-up < 24 weeks: 29; duplicate publication: 14; other reasons: 11). A final corpus of **35 studies** was included in the qualitative synthesis, comprising 11 landmark RCTs, 9 systematic reviews and meta-analyses, and 15 narrative reviews and comprehensive overviews. Eleven RCTs were included in the quantitative synthesis. The full selection process is presented in the PRISMA 2020 flow diagram (Figure 1).

Figure 1. PRISMA 2020 Flow Diagram — Study Selection Process



Note. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT = randomised controlled trial; MACE = major adverse cardiovascular events; T2DM = type 2 diabetes mellitus.

Study Characteristics

The 11 included RCTs enrolled a combined total of more than 93,000 participants across trials spanning from 2015 to 2024, with follow-up durations ranging from 1.5 to 5.4 years. SGLT2 inhibitor trials included EMPA-REG OUTCOME (empagliflozin; n = 7,020), CANVAS Program (canagliflozin; n = 10,142), DECLARE-TIMI 58 (dapagliflozin; n = 17,160), CREDENCE (canagliflozin; n = 4,401), DAPA-CKD (dapagliflozin; n = 4,304), DAPA-HF (dapagliflozin; n = 4,744), and EMPA-KIDNEY (empagliflozin; n = 6,609). GLP-1 RA trials included LEADER (liraglutide; n = 9,340), SUSTAIN-6 (semaglutide; n = 3,297), REWIND (dulaglutide; n = 9,901), and FLOW (semaglutide; n = 3,533). Mean participant age ranged from 60 to 67 years, with 29% to 40% female participants. Baseline HbA1c ranged from 7.3% to 8.7% and baseline eGFR from 37.3 to 85.4 mL/min/1.73 m² across trials. All trials used placebo or standard of care as the comparator. Full study characteristics are presented in Table 1.

Table 1. Characteristics of Included Randomised Controlled Trials (n = 11)

Trial	Drug / Class	N	Follow-up (yrs)	Mean Age (yrs)	Baseline HbA1c (%)	Baseline eGFR (mL/min/1.73m²)	Prior CVD (%)	Primary Outcome
SGLT2 Inhibitor Trials								
EMPA-REG OUTCOME (2015)	Empagliflozin 10/25 mg	7,020	3.1	63.1	8.1	74.1	100	3-point MACE
CANVAS Program (2017)	Canagliflozin 100/300 mg	10,142	3.6	63.3	8.2	76.5	65.6	3-point MACE
DECLARE-TIMI 58 (2019)	Dapagliflozin 10 mg	17,160	4.2	63.9	8.3	85.4	40.6	3-point MACE; HHF/CV death
CREDENCE (2019)	Canagliflozin 100 mg	4,401	2.6	63.0	8.3	56.3	50.4	Composite renal/CV outcome
DAPA-HF (2019)	Dapagliflozin 10 mg	4,744	1.5	66.3	7.5	65.5	56.3	Worsening HF or CV death
DAPA-CKD (2020)	Dapagliflozin 10 mg	4,304	2.4	61.8	7.6	43.1	37.4	Composite renal/CV outcome
EMPA-KIDNEY (2023)	Empagliflozin 10 mg	6,609	2.0	63.8	6.9	37.3	32.3	Renal progression or CV death
GLP-1 Receptor Agonist Trials								
LEADER (2016)	Liraglutide 1.8 mg	9,340	3.8	64.3	8.7	80.1	81.3	3-point MACE
SUSTAIN-6 (2016)	Semaglutide 0.5/1.0 mg	3,297	2.1	64.6	8.7	72.8	83.0	3-point MACE
REWIND (2019)	Dulaglutide 1.5 mg	9,901	5.4	66.2	7.3	75.0	31.5	3-point MACE
FLOW (2024)	Semaglutide 1.0 mg	3,533	3.4	66.6	8.0	47.2	23.0	Composite renal/CV outcome

Note. N = total randomised; HbA1c = glycated haemoglobin; eGFR = estimated glomerular filtration rate; CVD = cardiovascular disease; MACE = major adverse cardiovascular events; HHF = hospitalisation for heart failure; DKD = diabetic kidney disease; HF = heart failure. HbA1c only in diabetic subgroup.

Risk of Bias Assessment

Risk of bias assessment using the Cochrane RoB 2 tool revealed a low risk of bias in the majority of included RCTs. All 11 trials were double-blind, placebo-controlled, and used pre-specified outcome adjudication by independent committees. Some concerns were noted in two trials regarding potential unblinding due to glucosuria detection with SGLT2 inhibitor treatment, and in one trial regarding selective reporting of secondary outcomes. Overall, the included evidence base was judged to be of high methodological quality, supporting confidence in the observed effect estimates.

Cardiovascular Outcomes

Major Adverse Cardiovascular Events (MACE)

Both drug classes significantly reduced the incidence of three-point MACE compared with placebo. In EMPA-REG OUTCOME, empagliflozin reduced MACE by 14% (HR 0.86; 95% CI 0.74–0.99), a reduction driven predominantly by cardiovascular death (HR 0.62; 95% CI 0.49–0.77) rather than non-fatal myocardial infarction or stroke (Zinman et al., 2015). In SUSTAIN-6, MACE occurred in 6.6% of the semaglutide group compared with 8.9% in the placebo group (HR 0.74; 95% CI 0.58–0.95), confirming both non-inferiority and nominal superiority versus placebo (Marso et al., 2016b). The LEADER trial demonstrated a 13% significant relative risk reduction in MACE with liraglutide (HR 0.87; 95% CI 0.78–0.97; Marso et al., 2016a). In the REWIND trial, dulaglutide reduced MACE (HR 0.88; 95% CI 0.79–0.99) across a broader risk population that included participants without established CVD (Gerstein et al., 2019). A network meta-analysis of 14 large-scale RCTs (N > 117,000) demonstrated comparable MACE reductions with SGLT2 inhibitors (HR 0.89; 95% CI 0.84–0.94) and GLP-1 RAs (HR 0.86; 95% CI 0.80–0.93), with no statistically significant difference between classes (HR 1.03; 95% CI 0.94–1.13; Alqurain et al., 2026).

Heart Failure Hospitalisation

SGLT2 inhibitors demonstrated pronounced and consistent reductions in HHF across the trial programme. In EMPA-REG OUTCOME, empagliflozin reduced cardiovascular death or HHF by 34% (HR 0.66; 95% CI 0.55–0.79) and HHF alone by 35%, irrespective of baseline heart failure status. In DAPA-HF, dapagliflozin reduced the composite of worsening heart failure or cardiovascular death by 26% (HR 0.74; 95% CI 0.65–0.85) in patients with HFrEF (McMurray et al., 2019). In contrast, GLP-1 RA trials consistently showed no significant reduction in HHF; this differential effect (SGLT2i HR 0.75 vs. GLP-1 RA HR ~1.0 for HHF) remained consistent across subgroup analyses and is considered a class-level distinction (Zelniker et al., 2019).

Glycaemic and Metabolic Outcomes

Both drug classes produced clinically meaningful reductions in HbA1c across included trials. GLP-1 RAs generated somewhat larger absolute HbA1c reductions (approximately 0.9% to 1.4%), while SGLT2 inhibitors produced reductions in the range of 0.5% to 1.0%. GLP-1 RAs demonstrated markedly superior body weight reduction, with semaglutide achieving 3 to 4 kg reductions in RCT settings, compared with 2 to 3 kg for SGLT2 inhibitors. Both classes reduced systolic blood pressure by approximately 3 to 5 mmHg, with no meaningful difference between classes. GLP-1 RAs modestly reduced LDL cholesterol and triglycerides, while SGLT2 inhibitors produced small increases in LDL, likely from haemoconcentration. Combination GLP-1 RA and SGLT2i therapy produced significantly greater reductions in HbA1c, body weight, LDL cholesterol, and systolic blood pressure than either monotherapy. Cardiovascular outcomes are summarised in Table 2.

Table 2. Summary of Major Cardiovascular Outcomes Across Included RCTs

Trial	Drug	MACE HR (95% CI)	HHF HR (95% CI)	CV Death HR (95% CI)	All-cause Mortality HR (95% CI)	Key Finding
SGLT2 Inhibitor Trials						
EMPA-REG OUTCOME	Empagliflozin	0.86 (0.74–0.99)	0.65 (0.50–0.85)	0.62 (0.49–0.77)	0.68 (0.57–0.82)	14% MACE reduction; 38% CV death reduction
CANVAS Program	Canagliflozin	0.86 (0.75–0.97)	0.67 (0.52–0.87)	0.87 (0.72–1.06) NS	0.87 (0.74–1.01) NS	HHF reduction; limb amputation signal
DECLARE-TIMI 58	Dapagliflozin	0.93 (0.84–1.03) NS	0.73 (0.61–0.88)	0.98 (0.82–1.17) NS	0.93 (0.82–1.04) NS	HHF/CV death reduction; MACE NS

DAPA-HF	Dapagliflozin	N/A (HF population)	0.70 (0.59–0.83)	0.82 (0.69–0.98)	0.83 (0.71–0.97)	26% reduction in worsening HF or CV death
GLP-1 Receptor Agonist Trials						
LEADER	Liraglutide	0.87 (0.78–0.97)	0.87 (0.73–1.05) NS	0.78 (0.66–0.93)	0.85 (0.74–0.97)	13% MACE reduction; 22% CV death reduction
SUSTAIN-6	Semaglutide	0.74 (0.58–0.95)	1.11 (0.77–1.61) NS	0.98 (0.65–1.48) NS	1.05 (0.74–1.50) NS	26% MACE reduction; driven by stroke reduction
REWIND	Dulaglutide	0.88 (0.79–0.99)	0.93 (0.77–1.12) NS	0.91 (0.78–1.06) NS	0.90 (0.80–1.01) NS	Benefit extended to primary prevention population
FLOW	Semaglutide	0.82 (0.68–0.98)	Not primary	Included in composite	0.80 (0.67–0.95)	18% MACE reduction; 20% all-cause mortality reduction

Note. HR = hazard ratio; CI = confidence interval; MACE = major adverse cardiovascular events; HHF = hospitalisation for heart failure; CV = cardiovascular; NS = not statistically significant; N/A = not applicable. Statistical significance: $p < 0.05$; $p < 0.01$; $p < 0.001$.

Renoprotective Outcomes

eGFR and CKD Progression

SGLT2 inhibitors consistently attenuated eGFR decline and reduced hard renal endpoints across three dedicated renal outcome trials. In DAPA-CKD, dapagliflozin reduced the risks of ≥50% eGFR decline and ESKD by 47% and 36%, respectively, and reduced the composite of cardiovascular death or HHF by 29% and overall mortality by 31% (Heerspink et al., 2020). In CREDENCE, canagliflozin reduced the composite renal outcome by 34% (HR 0.66; 95% CI 0.53–0.81) and ESKD by 36% (Perkovic et al., 2019). In EMPA-KIDNEY, empagliflozin reduced the primary composite of kidney disease progression or cardiovascular death by 28% (HR 0.72; 95% CI 0.64–0.82) across a broad CKD population extending to eGFR ≥ 20 mL/min/1.73 m² (The EMPA-KIDNEY Collaborative Group, 2023).

The FLOW trial provided the first definitive evidence of renoprotection with a GLP-1 RA. Semaglutide reduced the composite primary kidney outcome by 24% (HR 0.76; 95% CI 0.66–0.88; $p = 0.0003$), reduced eGFR decline by 1.16 mL/min/1.73 m² per year (95% CI 0.86–1.47; $p < 0.001$), and reduced UACR by 32% compared to placebo. These benefits were independent of CKD severity, sex, age, BMI, and background medication (Perkovic et al., 2024).

UACR and Albuminuria

Both drug classes produced significant reductions in UACR. SGLT2 inhibitors reduced UACR by 20% to 31% across CREDENCE, DAPA-CKD, and EMPA-KIDNEY. GLP-1 RAs reduced UACR by 26% (LEADER) to 32% (FLOW). The magnitude of UACR reduction was broadly comparable between classes; however, the SGLT2 inhibitor evidence base is more robust, having been replicated across multiple trials powered for hard renal endpoints including ESKD. Renoprotective outcomes are summarised in Table 3.

Table 3. Summary of Renoprotective Outcomes Across Included RCTs

Trial	Drug	Composite Renal Outcome HR (95% CI)	eGFR Slope Change (mL/min/1.73m²/yr)	UACR Reduction (%)	ESKD Risk Reduction (%)	Key Finding
SGLT2 Inhibitor Trials						

CREDENCE (2019)	Canagliflozin	0.66 (0.53–0.81)	−1.52 vs −4.01 (favours active)	−31%	−36%	First dedicated DKD trial for SGLT2i; stopped early
DAPA-CKD (2020)	Dapagliflozin	0.61 (0.51–0.72)	−1.73 vs −3.38 (favours active)	−29%	−47%	Benefit independent of T2DM; 31% mortality reduction
EMPA-KIDNEY (2023)	Empagliflozin	0.72 (0.64–0.82)	−1.37 vs −2.75 (favours active)	−20%	−28%	Broadest eGFR range; benefit down to eGFR 20
GLP-1 Receptor Agonist Trials						
LEADER (2016)	Liraglutide	0.78 (0.67–0.92) (nephropathy composite)	Modest attenuation	−26%	Not reported separately	Reduction in new macroalbuminuria; no hard ESKD endpoint
FLOW (2024)	Semaglutide	0.76 (0.66–0.88)	+1.16 mL/min/yr less decline	−32%	Included in composite	First GLP-1 RA trial with hard renal composite; stopped early for efficacy

Note. HR = hazard ratio; CI = confidence interval; eGFR = estimated glomerular filtration rate; UACR = urinary albumin-to-creatinine ratio; ESKD = end-stage kidney disease; DKD = diabetic kidney disease; CV = cardiovascular; NS = not statistically significant. Statistical significance: $p < 0.01$; $p < 0.001$.

Combination Therapy

Emerging evidence from post-hoc analyses of placebo-controlled RCTs and large population-based cohort studies indicates that combined GLP-1 RA and SGLT2 inhibitor therapy confers incremental cardiorenal benefit relative to monotherapy. A large population-based cohort study demonstrated that combination therapy was associated with approximately 30% lower risk of MACE and serious renal events compared with monotherapy (Simms-Williams et al., 2024). The SMART-C collaborative meta-analysis confirmed that the cardiovascular and kidney benefits of SGLT2 inhibitors were consistent regardless of background GLP-1 RA use, supporting additive organ protection (Apperloo et al., 2024). A 2024 meta-analysis of more than 110,000 patients across 13 investigations found that combination therapy was associated with a significant reduction in all-cause mortality (odds ratio 0.49; 95% CI 0.41–0.60; $p < 0.00001$) relative to comparators, with additional reductions in BMI, blood pressure, HbA1c, and fasting glucose (Aristizábal-Colorado et al., 2025).

Safety and Tolerability

The safety profiles of the two drug classes were distinct and clinically informative. SGLT2 inhibitors were associated with a more than three-fold increase in the risk of genital mycotic infections (RR 3.49; 95% CI 2.63–4.55) and a two-fold rise in the risk of diabetic ketoacidosis (RR 2.36; 95% CI 1.33–4.17) compared with GLP-1 receptor agonists. The CANVAS Program identified an elevated risk of lower limb amputation with canagliflozin (HR 1.97; 95% CI 1.41–2.75), a signal considered agent-specific rather than class-wide. GLP-1 RAs were predominantly associated with gastrointestinal adverse effects—nausea, vomiting, and diarrhoea—which were dose-dependent and typically transient. In SUSTAIN-6, semaglutide was associated with a higher incidence of diabetic retinopathy complications (HR 1.76; 95% CI 1.11–2.78), attributed to rapid glycaemic improvement. Neither class significantly increased the risk of severe hypoglycaemia when used without concurrent insulin or sulfonylurea therapy. The comparative safety profile is presented in Table 4.

Table 4. Comparative Safety Profile of SGLT2 Inhibitors and GLP-1 Receptor Agonists

Adverse Event	SGLT2 Inhibitors	GLP-1 Receptor Agonists	Clinical Note
Genital mycotic infections	↑↑↑ RR 3.49 (2.63–4.55)	No significant increase	Highest risk in women; candidiasis; responds to antifungals
Diabetic ketoacidosis (DKA)	↑↑ RR 2.36 (1.33–4.17)	Rare; not class risk	Euglycaemic DKA; hold peri-operatively; monitor ketones
Gastrointestinal events	Mild (nausea with polyuria)	↑↑↑ Nausea, vomiting, diarrhoea	GLP-1 RA GI events are dose-dependent, transient, peak during up-titration

Urinary tract infections	↑ Mild increase	No increase	Usually mild; surveillance recommended
Lower limb amputation	↑ Canagliflozin only HR 1.97 (1.41–2.75)	No increase	Agent-specific signal (canagliflozin); caution in PAD
Diabetic retinopathy	No increase	↑ Semaglutide HR 1.76 (1.11–2.78)	Rapid HbA1c lowering in pre-existing retinopathy; monitor
Severe hypoglycaemia	No increase (without SU/insulin)	No increase (without SU/insulin)	Risk increases with concurrent secretagogues; class-wide
Volume depletion / hypotension	↑ Osmotic diuresis	No increase	Monitor BP and hydration; adjust antihypertensives

Note. RR = relative risk; HR = hazard ratio; CI = confidence interval; DKA = diabetic ketoacidosis; SU = sulfonylurea; PAD = peripheral artery disease. Symbols: ↑ = increased risk; ↑↑ = moderately increased risk; ↑↑↑ = substantially increased risk.

Certainty of Evidence (GRADE)

The certainty of evidence for primary cardiometabolic outcomes (MACE, HHF) was rated as HIGH for both drug classes, supported by consistently low risk of bias across large-scale RCTs with narrow confidence intervals. Evidence for renoprotective outcomes was rated as HIGH for SGLT2 inhibitors across CREDENCE, DAPA-CKD, and EMPA-KIDNEY, and as MODERATE for GLP-1 RAs, where FLOW represented the primary evidence source. Evidence for combination therapy outcomes was rated as MODERATE, reflecting the predominance of observational and meta-analytic data in the absence of direct randomised head-to-head trials. The full GRADE Summary of Findings is presented in Table 5.

Table 5. GRADE Summary of Findings — Certainty of Evidence by Outcome

Outcome	SGLT2i Certainty	GLP-1 RA Certainty	Effect Direction	No. of Trials	Key Concern
3-point MACE reduction	⊕⊕⊕⊕ HIGH	⊕⊕⊕⊕ HIGH	Both favour treatment	7	Indirect comparison only
Hospitalisation for heart failure	⊕⊕⊕⊕ HIGH	⊕⊕ LOW	SGLT2i favoured; GLP-1 RA neutral	7	GLP-1 RA trials underpowered for HHF
eGFR decline attenuation	⊕⊕⊕⊕ HIGH	⊕⊕⊕ MODERATE	Both favour treatment	5	FLOW = primary GLP-1 RA source
UACR / albuminuria reduction	⊕⊕⊕⊕ HIGH	⊕⊕⊕ MODERATE	Both favour treatment	6	Heterogeneity in UACR entry criteria
Prevention of ESKD	⊕⊕⊕⊕ HIGH	⊕⊕⊕ MODERATE	SGLT2i stronger evidence	4	FLOW composite includes CV death
HbA1c reduction	⊕⊕⊕⊕ HIGH	⊕⊕⊕⊕ HIGH	Both; GLP-1 RA greater magnitude	11	Background therapy varies
Body weight reduction	⊕⊕⊕ MODERATE	⊕⊕⊕⊕ HIGH	GLP-1 RA clearly favoured	11	None
Combination therapy outcomes	⊕⊕⊕ MODERATE (both)		Additive benefit suggested	13 (meta-analysis)	Predominantly observational

Note. GRADE certainty ratings: ⊕⊕⊕⊕ HIGH = further research unlikely to change confidence; ⊕⊕⊕ MODERATE = further research likely to impact confidence; ⊕⊕ LOW = further research very likely to change confidence. SGLT2i = sodium-glucose cotransporter-2 inhibitor; GLP-1 RA = glucagon-like peptide-1 receptor agonist; MACE = major adverse cardiovascular events; HHF = hospitalisation for heart failure; eGFR = estimated

glomerular filtration rate; UACR = urinary albumin-to-creatinine ratio; ESKD = end-stage kidney disease; SU = sulfonylurea.

DISCUSSION

This systematic review synthesised evidence from 11 landmark RCTs and 24 additional systematic reviews and narrative analyses encompassing more than 93,000 participants across diverse cardiometabolic and renal risk profiles. The principal findings confirm that both GLP-1 RAs and SGLT2 inhibitors reduce MACE and cardiovascular mortality in patients with T2DM, while their protective profiles diverge meaningfully at the level of heart failure and renal disease — a distinction with direct implications for personalised therapeutic decision-making.

Principal Findings in Context

The MACE reductions observed across GLP-1 RA and SGLT2 inhibitor trials were broadly equivalent in magnitude, consistent with network meta-analytic data demonstrating no statistically significant between-class difference (Alqurain et al., 2026). However, the mechanistic substrates underlying this shared outcome are distinct. Aristizábal-Colorado et al. (2025) confirmed that SGLT2 inhibitors have shown robust effects in reducing heart failure hospitalisation and slowing the progression of CKD, while GLP-1 RAs have demonstrated superior efficacy in reducing atherothrombotic events, particularly non-fatal stroke. This mechanistic divergence — SGLT2 inhibitors acting principally through haemodynamic, natriuretic, and tubuloglomerular pathways, and GLP-1 RAs through anti-atherosclerotic, anti-inflammatory, and metabolic reprogramming mechanisms — explains why each class fills a distinct therapeutic niche despite comparable MACE event rates.

The superiority of SGLT2 inhibitors for heart failure hospitalisation, consistently demonstrated across EMPA-REG OUTCOME, CANVAS, DAPA-HF, and DECLARE-TIMI 58, stands in sharp contrast to the neutral HHF effect of GLP-1 RAs across all available CVOTs. Caturano et al. (2025) affirmed that SGLT2 inhibitors are particularly effective in reducing heart failure hospitalisations and slowing the progression of renal disease, largely due to their natriuretic, diuretic, and renal haemodynamic effects. This differential has been embedded in international guidelines; the 2023 ESC guidelines and 2025 ADA Standards of Care both recommend SGLT2 inhibitors as the preferred agent when heart failure or significant CKD coexists with T2DM (ElSayed et al., 2023; Marx et al., 2023).

The FLOW trial represents a landmark advance for GLP-1 RAs, establishing for the first time that semaglutide reduces hard renal endpoints — including ESKD and sustained eGFR decline — with a 24% reduction in the composite kidney outcome comparable in direction, though not in absolute magnitude, to SGLT2 inhibitor renal outcome trials. Consistent with this, KDIGO (2024) updated its clinical practice guideline to recommend GLP-1 receptor agonists for their kidney-protective effects alongside SGLT2 inhibitors and RAAS inhibitors in patients with T2DM and CKD, a recognition that fundamentally reshapes the renoprotective armamentarium.

Complementarity and Combination Therapy

Gajjar et al. (2025) established that each agent targets different aspects of cardiometabolic-renal syndrome: SGLT2 inhibitors have a more pronounced renoprotective effect and robust effect on heart failure hospitalisation, while GLP-1 receptor agonists excel at cardiovascular protection and weight loss, providing the mechanistic rationale for combining them. Simms-Williams et al. (2024) demonstrated that combined SGLT2 inhibitor and GLP-1 receptor agonist use was associated with approximately 30% lower risk of major adverse cardiovascular and serious renal events compared with monotherapy. Apperloo et al. (2024) further confirmed through the SMART-C meta-analysis that SGLT2 inhibitor benefits were consistent irrespective of background GLP-1 RA use, suggesting additive rather than redundant protection. However, Mantsiou et al. (2025) cautioned that much of the current evidence supporting combination benefits is derived from post-hoc or subgroup analyses rather than prospective randomised combination trials, and that concerns persist regarding safety, tolerability, cost-effectiveness, and adverse events. A definitive head-to-head combination trial remains absent and represents the most significant gap in the current evidence base.

Safety Considerations

The distinct safety profiles of the two classes are clinically actionable. SGLT2 inhibitors carry risks of genital mycotic infections, euglycaemic diabetic ketoacidosis, and volume depletion that warrant pre-emptive counselling and peri-operative withholding, while GLP-1 RAs carry predominantly gastrointestinal burden and the retinopathy signal observed with semaglutide in the context of rapid HbA1c lowering. Neither safety concern should preclude treatment initiation in guideline-eligible patients, but they do inform individualised drug selection — particularly in patients with recurrent candidiasis, prior DKA, or pre-existing retinopathy.

Limitations

Several limitations must be acknowledged. First, Alqurain et al. (2026) noted that the evidence supporting comparative MACE efficacy between classes was rated as moderate certainty, downgraded due to indirectness, as no head-to-head trials were included in the primary network, meaning all between-class comparisons rely on indirect or network meta-analytic inference. Second, the included trials differed substantially in baseline cardiovascular risk, CKD severity, and background therapy, introducing clinical heterogeneity that limits the generalisability of pooled estimates. Third, the predominance of placebo-controlled designs means that comparative effectiveness against newer agents — including finerenone — remains largely unexplored within this synthesis. Fourth, combination therapy evidence remains predominantly observational, with residual confounding by indication an inherent limitation. Finally, the underrepresentation of older adults, women, and populations from low- and middle-income countries across CVOTs limits the external validity of findings.

Future Directions

Priority research needs include: (1) a large-scale, prospective head-to-head RCT comparing GLP-1 RAs and SGLT2 inhibitors across pre-specified cardiovascular and renal endpoints; (2) a dedicated combination trial powered for hard outcomes; (3) investigations into optimal sequencing and timing of combination therapy initiation; (4) studies in patients with T2DM and CKD stages 4 to 5 where current evidence remains sparse; and (5) real-world effectiveness analyses in older adults and under-represented populations. As observed by a real-world prescribing study, improving systematic cardiometabolic risk assessment and enhancing interdisciplinary care pathways may expand appropriate access to these therapies and support better cardiovascular and kidney outcomes (Al-Qahtani et al., 2026).

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