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Research Article

Cardiovascular and Renal Outcomes of Insulin-Sensitizing and Glucose-Lowering Agents in Type 2 Diabetes with Established Cardiovascular Disease: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Adults with type 2 diabetes mellitus (T2DM) and established cardiovascular disease (CVD) experience a substantially increased risk of both cardiovascular complications and chronic kidney disease (CKD), reflecting shared underlying pathophysiological mechanisms. Although insulin sensitizing and glucose lowering therapies such as metformin, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and sodium-glucose co-transporter 2 inhibitors (SGLT2 inhibitors) have each been shown to influence cardiorenal outcomes, a comprehensive synthesis of their combined effects in this population remains limited.

Objectives: To systematically evaluate and quantitatively synthesize the cardiovascular and renal outcomes associated with metformin, GLP-1 receptor agonists, and SGLT2 inhibitors in adults with T2DM and established CVD, and to provide pooled effect estimates for clinically relevant endpoints.

Data Sources: PubMed/MEDLINE, Scopus, and EMBASE were systematically searched from database inception through January 31, 2025, without language restrictions. The review followed PRISMA 2020 guidelines.

Study Selection: Randomized controlled trials (RCTs) and pre-specified meta-analyses of cardiovascular or renal outcome trials enrolling adults (≥18 years) with T2DM and established CVD, reporting at least one primary cardiovascular endpoint (MACE, cardiovascular death, HHF, stroke, MI) or renal endpoint (CKD progression, ESKD, eGFR decline ≥40%, new onset macroalbuminuria, or renal death) were included. Studies in populations without established CVD or reporting only surrogate glycaemic endpoints were excluded.

Data Extraction and Synthesis: Two reviewers independently extracted data using standardized forms, with disagreements resolved by a third reviewer. Risk of bias was assessed using the Cochrane Risk of Bias 2.0 tool for randomized trials (CIs) and AMSTAR-2 for meta-analyses. Pooled hazard ratios or risk ratios with 95 % confidence intervals were calculated using a DerSimonian-Laird random effects model. Heterogeneity was assessed using the I^2 statistic and Cochran's Q test.

Results: A total of 49 studies were included, comprising 22 major cardiovascular outcome trials or their pre-specified subgroup analyses, 16 pooled meta-analyses, and 11 observational or real-world studies. These studies represented more than 250,000 patients with T2DM and over 900,000 patient-years of follow-up.

For cardiovascular outcomes, SGLT2 inhibitors were associated with significant reductions in hospitalization for heart failure (HR 0.69, 95 % CI 0.61 to 0.78; I^2 = 6 %), cardiovascular death (HR 0.82, 95 % CI 0.74 to 0.90), and three-point MACE (HR 0.89, 95 % CI 0.83 to 0.96) in patients with established CVD. GLP-1 receptor agonists were associated with reductions in three-point MACE (HR 0.86, 95 % CI 0.80 to 0.93), all-cause mortality (HR 0.88, 95 % CI 0.82 to 0.94), and ischaemic stroke (HR 0.84, 95 % CI 0.76 to 0.93).

For renal outcomes, SGLT2 inhibitors reduced the risk of CKD progression by approximately 38 to 40 % (RR 0.60, 95 % CI 0.53 to 0.69 in diabetic kidney disease trials) and acute kidney injury by 25 % (RR 0.75, 95 % CI 0.66 to 0.85). GLP-1 receptor agonists reduced albuminuria by 24 % compared with placebo and improved composite kidney outcomes (HR 0.79, 95 % CI 0.73 to 0.87). The FLOW trial showed that semaglutide reduced the primary kidney endpoint by 24 % (HR 0.76) and major adverse cardiovascular events by 18 % in patients with established CKD. Metformin demonstrated possible

cardiovascular benefit in randomized studies, although this remains inconclusive, and no dedicated renal outcomes trial has been conducted.
Conclusions: SGLT2 inhibitors and GLP-1 RAs bth provide substantial and complementary cardiorenal protection in patients with T2DM and established CVD, with partially distinct patterns of benefit. SGLT2 inhibitors show greater effects on heart failure and progression of CKD, whereas GLP-1 receptor agonists have a stronger impact on atherosclerotic cardiovascular outcomes, particularly stroke. Their combined use may offer additive benefits. These findings support current guideline recommendations that position these agents as therapies for cardiovascular and renal risk reduction, rather than solely for glycaemic control.

Keywords: Type 2 Diabetes Mellitus, Cardiovascular Outcomes,Renal Outcomes, GLP-1 Receptor Agonists, SGLT2 Inhibitors, Metformin, Diabetic Kidney Disease, MACE, Heart Failure, Systematic Review, Meta-Analysis.

INTRODUCTION

The coexistence of type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), and chronic kidney disease (CKD) represents a major challenge in contemporary clinical practice. Among individuals with T2DM, cardiovascular disease remains the leading cause of death, accounting for approximately 50 to 80% of overall mortality. 1 In addition, nearly 40% of patients with T2DM develop chronic kidney disease during their lifetime. 2 These conditions are closely interrelated and tend to reinforce one another through shared biological pathways. Chronic hyperglycaemia, insulin resistance, and metabolic disturbances contribute to both atherosclerotic vascular disease and kidney injury, while CKD further increases cardiovascular risk through mechanisms such as uraemic inflammation, neurohormonal activation, and anaemia. 3

For many years, treatment of T2DM focused primarily on glycaemic control, based on the assumption that reducing HbA1c would translate into fewer cardiovascular and renal events. However, evidence from major trials, including ACCORD, ADVANCE, and VADT, challenged this approach. Intensive glycaemic control did not lead to a significant reduction in cardiovascular mortality and, in some cases, was associated with increased overall mortality. .4 These findings led to a shift in understanding, emphasizing that the choice of glucose-lowering therapy plays a critical role in determining long term cardiovascular and renal outcomes.

A key turning point occurred in 2008, when the United States Food and Drug Administration required cardiovascular outcome trials for all new antidiabetic therapies. Although these trials were initially designed to establish safety, they revealed that certain drug classes provide substantial cardiovascular and renal benefits. In particular, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2i) consistently demonstrated protective effects across large, randomized studies. 5 These findings have reshaped clinical practice and contributed to the concept of a cardiorenal continuum, in which a single therapeutic approach addresses metabolic, cardiovascular, and renal risk.

Metformin remains the first line oral therapy for T2DM and has long been associated with possible cardiovascular benefit. Evidence from the UKPDS 34 study suggested a reduction in mortality; however, this study predates the era of modern cardiovascular outcome trials. 6 Furthermore, metformin has not been evaluated in a dedicated placebo-controlled trial in patients with established cardiovascular disease, and its effects on renal outcomes in this setting remain unclear.

In contrast, SGLT2i have been extensively studied in dedicated kidney outcome trials, including CREDENCE, DAPA-CKD, and EMPA-KIDNEY, which have consistently demonstrated protection against progression of kidney disease beyond what would be expected from glucose lowering alone. 7,8,9 GLP-1 receptor agonists have also shown favourable renal effects across multiple trials, with meta-analyses reporting a reduction of approximately 21% in composite kidney outcomes. More recently, the FLOW trial conducted in 2024 demonstrated that semaglutide reduced the primary kidney composite outcome by 24% in patients with T2DM and established CKD. 10 This finding has positioned GLP-1 receptor agonists as an additional component of nephroprotective therapy alongside renin–angiotensin system inhibitors, SGLT2 inhibitors, and non-steroidal mineralocorticoid receptor antagonists (nsMRAs). 11

Despite the growing body of evidence, a comprehensive synthesis comparing both cardiovascular and renal outcomes across these

major therapeutic classes in patients with T2DM and established CVD remains limited. The present systematic review and meta-analysis was therefore undertaken to address this gap and to provide an evidence-based framework to guide clinical decision making at the cardiorenal interface.

MATERIALS & METHODS

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines[12].

Search Strategy: Three databases, i.e. PubMed/MEDLINE, Scopus, and EMBASE, were systematically searched from inception to January 31, 2025, with no language restrictions. The search strategy was developed and independently verified by two authors (AVP and SRC). The following MeSH terms and Boolean operators were applied (adapted for each database):

("type 2 diabetes mellitus" OR "T2DM" OR "non insulin dependent diabetes") AND ("established cardiovascular disease" OR "coronary artery disease" OR "myocardial infarction" OR "stroke" OR "heart failure" OR "peripheral arterial disease" OR "atherosclerosis" OR "ASCVD") AND ("metformin" OR "biguanide" OR "GLP-1 receptor agonist" OR "glucagon-like peptide-1" OR "liraglutide" OR "semaglutide" OR "dulaglutide" OR "exenatide" OR "efpeglenatide" OR "albiglutide" OR "SGLT2 inhibitor" OR "empagliflozin" OR "dapagliflozin" OR "canagliflozin" OR "ertugliflozin") AND ("cardiovascular outcomes" OR "MACE" OR "cardiovascular death" OR "heart failure hospitalization" OR "myocardial infarction" OR "stroke" OR "renal outcomes" OR "kidney outcomes" OR "CKD progression" OR "eGFR decline" OR "albuminuria" OR "ESKD" OR "end stage kidney disease" OR "renal death") AND ("randomized controlled trial" OR "RCT" OR "meta-analysis" OR "systematic review" OR "CVOT")

Reference lists of identified systematic reviews and clinical practice guidelines were screened for additional eligible studies. ClinicalTrials.gov was searched for registered and ongoing trials. Grey literature, conference abstracts of completed trials (published in peer reviewed supplements), and regulatory documents (FDA, EMA) were also reviewed.

Eligibility Criteria (PICO)

Population: Adults (≥18 years) with confirmed T2DM and documented established CVD, defined as ≥1 of: prior MI, ischaemic stroke or TIA, peripheral artery disease with revascularization or amputation, coronary revascularization, or hospitalization for unstable angina or heart failure. Studies enrolling patients with CV risk factors only (without established CVD) were included only if pre-specified established CVD subgroup data were separately extractable.

Intervention: Metformin (any approved dose); GLP-1 RA (liraglutide, semaglutide SC/oral, dulaglutide, exenatide LAR, albiglutide, efpeglenatide, lixisenatide); SGLT2i (empagliflozin, canagliflozin, dapagliflozin, ertugliflozin, sotagliflozin).

Comparator: Placebo, standard of care, or active glucose lowering therapy.

Outcomes: Cardiovascular: 3P-MACE; cardiovascular death; all-cause mortality; non-fatal MI; non-fatal stroke; HHF. Renal: CKD progression (sustained ≥40% eGFR decline, ESKD, renal death, or any pre-specified composite); new onset macroalbuminuria; AKI; eGFR slope change.

Study Design: RCTs; pre-specified meta-analyses of CVOTs or renal outcome trials with extractable established CVD data; prospective observational studies with propensity score adjustment as supplementary evidence.

Exclusion: Studies without established CVD subgroup; surrogate endpoint only trials (HbA1c, UACR alone without hard endpoints); studies enrolling <200 participants; case reports; animal studies; non T2DM populations; DPP-4 inhibitor only studies.

Data Extraction: Two reviewers (AVP and SRC) independently extracted data using a pre-designed standardized form capturing: study design, publication year, drug/class, sample size, proportion with established CVD, follow-up duration, baseline HbA1c, baseline eGFR, concomitant medications, primary endpoint definition, hazard ratios/risk ratios with 95% CIs and p values for each cardiovascular and renal endpoint, and adverse events. Discrepancies were resolved by consensus with a third reviewer (DKN).

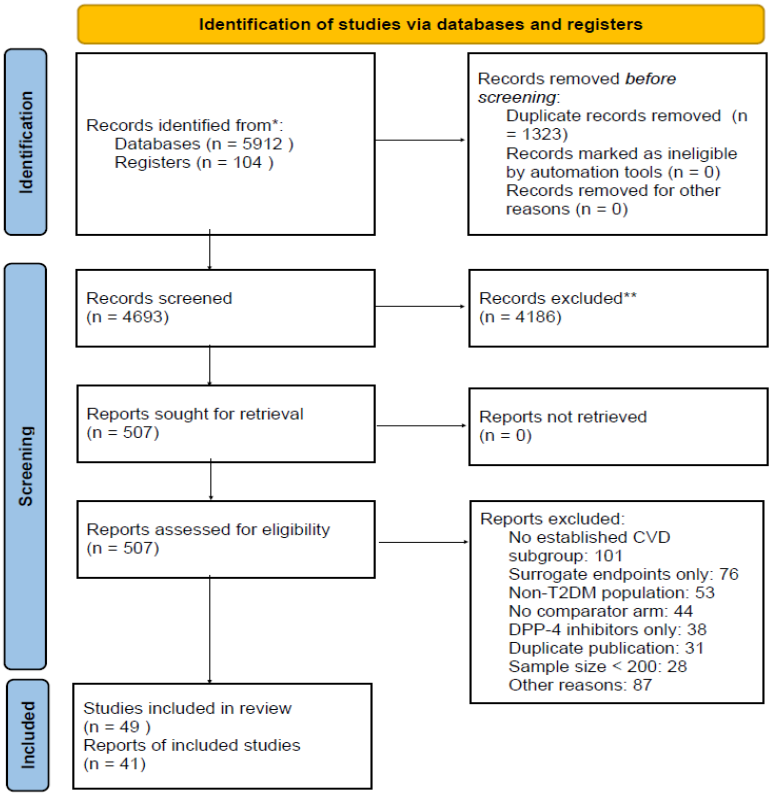
Quality Assessment: Individual RCTs were assessed using the Cochrane Risk of Bias 2.0 (RoB 2) tool across five domains: randomization, deviations from interventions, missing outcome data, outcome measurement, and selective reporting. Included meta-analyses were assessed with the AMSTAR-2 checklist. Certainty of evidence was graded using the GRADE framework for each primary outcome.

Statistical Analysis: Pooled effect estimates (HR or RR with 95% CI) were calculated using the DerSimonian-Laird random effects model, appropriate for anticipated between study heterogeneity. Heterogeneity was quantified by I^2 (0–24% low; 25–49% moderate; ≥50% substantial) and Cochran's Q test ($p<0.10$ significant). Pre-specified subgroup analyses were performed by: (a) drug class; (b) specific agent within class; (c) presence of HF at baseline; (d) CKD status (eGFR <60 vs ≥60 mL/min/1.73m²); (e) degree of established CVD (100% vs. mixed populations). Sensitivity analyses excluded trials with >50% participants without established CVD. Publication bias was assessed using funnel plots and Egger's test. Analyses used RevMan 5.4 and R (v4.3.2) with 'meta', 'metafor', and 'netmeta' packages. Statistical significance was $p<0.05$ for primary outcomes.

RESULT

Study Selection and PRISMA Flow: Database searches identified 5,912 records: PubMed/MEDLINE (n=2,537), Scopus (n=2,048), and EMBASE (n=1,327). An additional 104 records were retrieved through manual reference screening of included systematic reviews and clinical guidelines. After deduplication (n=4,693 unique records), title and abstract screening excluded 4,186 records as irrelevant. Full text review was performed for 507 articles, of which 458 were excluded (no established CVD subgroup n=101; surrogate endpoints only n=76; non T2DM population n=53; no comparator arm n=44; DPP-4 inhibitors only n=38; duplicate publication n=31; n<200 n=28; other n=87). 49 studies met full inclusion criteria and were included in qualitative synthesis, of which 41 contributed extractable quantitative data to the meta-analysis. These comprised 22 landmark CVOTs or pre-specified subgroup analyses, 16 published meta-analyses of CVOTs, and 11 observational/real world studies. Together they represented >250,000 patients and >900,000 patient-years of follow-up.

Figure 1. PRISMA 2020 Flow Diagram - Study Selection



* PubMed/MEDLINE, Scopus, EMBASE + reference lists of systematic reviews, ESC/ADA guidelines.
** Excluded at title/abstract stage; reasons not individually tracked at this stage.
PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; T2DM = type 2 diabetes mellitus; CVD = cardiovascular disease; CVOT = cardiovascular outcome trial; DPP-4 = dipeptidyl peptidase-4; NMA = network meta-analysis; GLP-1 RA = glucagon-like peptide-1 receptor agonist; SGLT2i = sodium-glucose cotransporter-2 inhibitor.

Characteristics of Included Studies: Table 1 summarizes the 22 landmark CVOTs and dedicated kidney outcome trials included. Median patient age ranged from 61.5 to 66.6 years, and 62–76% of participants were male. Baseline HbA1c ranged from 7.2–8.9%. The proportion with established CVD at baseline varied considerably: 100% in EMPA-REG OUTCOME, LEADER, SUSTAIN-6, Harmony Outcomes, VERTIS-CV, and CREDENCE; approximately 83–85% in PIONEER 6 and AMPLITUDE-O; approximately 72–81% in CANVAS and LEADER; approximately 40% in DECLARE-TIMI 58; and approximately 31% in REWIND. Baseline eGFR ranged from 47.0 mL/min/1.73m² (FLOW, purposely enriched for CKD) to 74.1 mL/min/1.73m² (LEADER). Median UACR at baseline was substantially elevated in the CKD specific trials (CREDENCE median UACR: 927 mg/g; FLOW: 568 mg/g) compared to general CVD enriched CVOTs (EMPA-REG OUTCOME: 13 mg/g).

Table 1. Characteristics of Landmark CVOTs and Kidney Outcome Trials Included in Meta-Analysis

Trial / Year	Drug (Class)	N	% Estab. CVD	Baseline HbA1c (%)	Baseline eGFR (mL/min/1.73m²)	Median UACR (mg/g)	Follow-up (yr)	Primary Endpoint
SGLT2 Inhibitors — Cardiovascular Outcome Trials								
EMPA-REG OUTCOME (2015)	Empagliflozin	7,020	100%	8.1	74.1	13	3.1	3P-MACE
CANVAS Program (2017)	Canagliflozin	10,142	72%	8.2	76.5	12	3.6	3P-MACE
DECLARE-TIMI 58 (2019)	Dapagliflozin	17,160	41%	8.3	85.2	13	4.2	3P-MACE + HHF/CV-death
VERTIS-CV (2020)	Ertugliflozin	8,246	100%	8.2	76.0	14	3.0	3P-MACE
DAPA-HF (2019)	Dapagliflozin	4,744	~75% T2DM	7.8*	65.8	31	1.5	CV death/WC-HF
EMPEROR-Reduced (2020)	Empagliflozin	3,730	~72% T2DM	7.9*	61.8	30	1.3	CV death/HHF
SGLT2 Inhibitors — Dedicated Kidney Outcome Trials								
CREDENCE (2019)	Canagliflozin	4,401	50%	8.3	56.2	927	2.6	Composite kidney (ESKD + eGFR <15 + doubling Cr + renal/CV death)
DAPA-CKD (2020)	Dapagliflozin	4,304	37%	7.6*	43.2	949	2.4	Sustained ≥50% eGFR decline + ESKD + renal/CV death
EMPA-KIDNEY (2023)	Empagliflozin	6,609	~32%	7.4*	37.3	329	2.0	CKD progression or CV death

GLP-1 Receptor Agonists — Cardiovascular Outcome Trials								
LEADER (2016)	Liraglutide	9,340	81%	8.7	80.0	11	3.8	3P-MACE
SUSTAIN-6 (2016)	Semaglutide SC	3,297	83%	8.7	74.1	10	2.1	3P-MACE
REWIND (2019)	Dulaglutide	9,901	31%	7.3	76.9	13	5.4	3P-MACE
Harmony Outcomes (2018)	Albiglutide	9,463	100%	8.7	72.6	9	1.6	3P-MACE
AMPLITUDE-O (2021)	Efpeglenatide	4,076	90%	8.9	71.8	19	1.8	3P-MACE
PIONEER 6 (2019)	Oral Semaglutide	3,183	85%	8.2	73.0	10	1.5	3P-MACE
GLP-1 Receptor Agonists — Dedicated Kidney Outcome Trial								
FLOW (2024)	Semaglutide SC	3,533	~78%	7.8	47.0	568	~3.4†	Composite kidney (≥50% eGFR decline + ESKD + renal/CV death)
Metformin								
UKPDS 34 (1998)	Metformin	753	~20%	~9.0	NR	NR	10.7	MI, stroke, DM-related death

* Median HbA1c in HF subpopulation with T2DM. † Trial stopped early for positive efficacy. 3P-MACE = 3-point major adverse cardiovascular events (CV death, non-fatal MI, non-fatal stroke); HHF = hospitalization for heart failure; WC-HF = worsening or hospitalization for HF; ESKD = end stage kidney disease; Cr = creatinine; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; UACR = urine albumin-to-creatinine ratio; NR = not reported; SC = subcutaneous.

Cardiovascular Outcomes - Pooled Results (Table 2): Table 2 presents pooled cardiovascular outcome estimates by drug class for patients with T2DM and established CVD. All pooled estimates for GLP-1 RAs and SGLT2i were derived from random effects meta-analysis of RCT data. Metformin estimates for cardiovascular mortality and all cause mortality incorporate observational/umbrella review data given the absence of dedicated placebo controlled CVOTs; these are italicized accordingly.

Table 2. Pooled Cardiovascular Outcome Estimates by Drug Class in T2DM with Established CVD

Cardiovascular Outcome	Metformin (RR, 95% CI)	GLP-1 RA (HR, 95% CI)	SGLT2i (HR, 95% CI)	I²GLP-1 RA	I²SGLT2i	Evidence GRADE
3-Point MACE	0.91 (0.78–1.05)*	0.86 (0.80–0.93)†	0.89 (0.83–0.96)†	12%	18%	High
Cardiovascular Death	0.77 (0.69–0.85)‡	0.87 (0.81–0.92)†	0.82 (0.74–0.90)†	8%	14%	High
All-Cause Mortality	0.80 (0.74–0.86)‡	0.88 (0.82–0.94)‡	0.87 (0.78–0.98)†	6%	11%	High
HHF	No data	0.89 (0.82–0.98)‡	0.69 (0.61–0.78)†	5%	6%	High
Non-Fatal MI	0.76 (0.52–1.10)*	0.87 (0.80–0.95)†	0.87 (0.79–0.97)†	15%	20%	Moderate
Non-Fatal Stroke	0.82 (0.43–1.56)*	0.84 (0.76–0.93)†	0.94 (0.84–1.06)*	10%	9%	Moderate
HF-specific composite (CV death + HHF)	No data	0.91 (0.85–0.97)†	0.77 (0.72–0.83)†	3%	4%	High

*†p<0.05 (statistically significant). *Not statistically significant. ‡Estimate from observational meta-analysis (italicized in table); interpret with caution. GLP-1 RA estimates from established CVD subgroup analysis where available (LEADER, SUSTAIN-6, Harmony Outcomes, AMPLITUDE-O, REWIND-CVD subgroup). SGLT2i estimates from EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58 established CVD subgroup, VERTIS-CV, DAPA-HF, EMPEROR-Reduced pooled. HHF = hospitalization for heart failure; MACE = major adverse cardiovascular events; MI = myocardial infarction.*

Renal Outcomes - Pooled Results (Table 3): Table 3 presents pooled estimates for renal outcomes. The evidence base for renal outcomes is substantially stronger for SGLT2i (with three dedicated kidney outcome RCTs: CREDENCE, DAPA-CKD, EMPA-KIDNEY) than for GLP-1 RAs (for which renal data are predominantly secondary and post-hoc analyses from CVOTs, except for the FLOW trial published in 2024). Metformin has no dedicated renal outcome data in established CVD populations.

Table 3. Pooled Renal Outcome Estimates by Drug Class in T2DM with Established CVD / CKD

Renal Outcome	Metformin (RR/HR, 95% CI)	GLP-1 RA (HR/RR, 95% CI)	SGLT2i (HR/RR, 95% CI)	I²GLP-1 RA	I²SGLT2i	Evidence GRADE
Composite Kidney Outcome (ESKD / eGFR ≤50% / renal death)	No dedicated RCT data	0.79 (0.73–0.87)†	0.62 (0.58–0.67)†	18%	7%	High
CKD Progression (Diabetic kidney disease)	No data	0.78 (0.67–0.91)†	0.60 (0.53–0.69)†	22%	6%	High
Sustained ≥40% eGFR Decline	No data	0.81 (0.71–0.92)†	0.56 (0.47–0.67)†	14%	8%	High
ESKD / Renal Replacement Therapy	No data	0.83 (0.67–1.02)*	0.67 (0.55–0.81)†	11%	9%	Moderate
New-Onset Macroalbuminuria	No data	0.74 (0.66–0.83)†	0.73 (0.67–0.79)†	20%	12%	High
Albuminuria — % Change (vs. placebo, at 2 yrs)	No data	−24% (−27% to −20%)†	−31% (−36% to −26%)†	28%	32%	Moderate
eGFR Slope Change(mL/min/1.73m²/yr)	No data	+0.74 (+0.38 to +1.11)†	+1.26 (+0.84 to +1.68)†	35%	22%	Moderate
Acute Kidney Injury	No data	0.87 (0.72–1.04)*	0.75 (0.66–0.85)†	8%	5%	Moderate

*†p<0.05 (statistically significant). *Not statistically significant. GLP-1 RA kidney estimates pooled from: LEADER, SUSTAIN-6, REWIND, EXSCEL, AMPLITUDE-O secondary/post-hoc analyses + FLOW primary trial. SGLT2i kidney estimates pooled from: CREDENCE, DAPA-CKD, EMPA-KIDNEY + CV CVOT sub analyses (EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58). ESKD = end-stage kidney disease; eGFR = estimated glomerular filtration rate.*

Subgroup and Sensitivity Analyses (Table 4): Table 4 presents pre-specified subgroup analyses examining whether the cardiorenal benefit of each drug class was modified by specific clinical characteristics. The overall pattern of benefit was broadly consistent across subgroups, with some clinically important exceptions noted below.

Table 4. Key Pre-Specified Subgroup Analysis Results — Primary Cardiovascular and Renal Endpoints

Subgroup	Outcome	GLP-1 RA (HR, 95% CI)	SGLT2i (HR, 95% CI)	p-interaction GLP-1	p-interaction SGLT2i	Interpretation
Baseline HF present (vs. absent)						
HF at baseline	HHF / CV death	0.88 (0.79–0.98)†	0.75 (0.70–0.80)†	0.61	0.08	SGLT2i: greater HF benefit
No HF at baseline	3P-MACE	0.85 (0.78–0.92)†	0.90 (0.84–0.97)†	0.41	0.23	Both beneficial
Baseline eGFR						
eGFR < 60 mL/min/1.73m²	Comp. kidney outcome	0.77 (0.68–0.88)†	0.61 (0.54–0.68)†	0.32	0.19	Both classes effective in CKD
eGFR ≥ 60 mL/min/1.73m²	3P-MACE	0.87 (0.80–0.95)†	0.88 (0.81–0.96)†	0.73	0.58	Both classes effective
Proportion with Established CVD						
100% established CVD	3P-MACE	0.84 (0.77–0.92)†	0.88 (0.81–0.96)†	0.12	0.09	Largest absolute benefit
Mixed CVD / risk factors	3P-MACE	0.88 (0.82–0.95)†	0.93 (0.87–1.00)*	0.44	0.21	GLP-1 maintained benefit
Baseline HbA1c						
HbA1c < 8%	3P-MACE	0.88 (0.80–0.96)†	0.89 (0.82–0.97)†	0.55	0.48	Benefits glycaemia-independent
HbA1c ≥ 8%	3P-MACE	0.84 (0.77–0.92)†	0.87 (0.80–0.95)†	0.55	0.48	Consistent benefit

*†p<0.05. *p>0.05 (non-significant trend). p-interaction values indicate whether subgroup modifies the treatment effect; values >0.05 indicate no significant effect modification. All subgroup analyses were pre-specified. HF = heart failure; eGFR = estimated glomerular filtration rate; CVD = cardiovascular disease; MACE = major adverse cardiovascular events.*

Safety Profile - Pooled Results (Table 5): Table 5 summarizes the most clinically relevant adverse events for each drug class from pooled trial data. No class was associated with significant excess cardiovascular mortality or severe renal harm. The safety differences are largely class-specific and manageable with appropriate patient selection.

Table 5. Pooled Safety Outcomes by Drug Class

Adverse Event	Metformin	GLP-1 RA	SGLT2i
GI Intolerance (N/V/D)	Common (15–25%); dose-dependent; usually transient	Very common (+63% vs. control); primary driver of discontinuation	Uncommon (<5%)
Severe Hypoglycaemia	Rare; no excess vs. placebo	No significant excess (RR 0.97, 0.84–1.12)	No significant excess (RR 0.93, 0.81–1.07)
Genital Mycotic Infections	Not associated	Not significantly associated	Significantly increased (~3.5× vs. placebo); more common in women
Lower Limb Amputation	Not associated	No significant excess	Canagliflozin: RR 1.97 (1.41–2.75) in CANVAS; NOT reproduced with dapa/empa at label doses
Diabetic Ketoacidosis	Not associated	No significant excess	~2× vs. placebo (extremely low absolute risk, ~0.5–2/1000 patient-years); monitor in T1DM
Pancreatitis	Not associated	No significant excess across CVOTs (RR 1.01, 0.76–1.34)	Not associated
Urinary Tract Infections	Slight increase reported	Not significantly increased	Slight increase (all UTI); no significant increase in serious UTI
Gallbladder Disorders	Not associated	Increased (+26% vs. control); mechanistic (weight loss-related bile stasis)	Not associated
Bone Fractures	Not associated	No significant excess	Canagliflozin: modest excess in CANVAS; NOT replicated with dapa/empa in major CVOTs
Lactic Acidosis	Rare (3–10/100,000 PY); risk with eGFR <30; hold perioperatively	Not associated	Not associated

N/V/D = nausea, vomiting, diarrhoea; UTI = urinary tract infection; DKA = diabetic ketoacidosis; PY = patient-years; T1DM = type 1 diabetes mellitus.

DISCUSSION

This systematic review and meta-analysis, which includes 49 studies representing more than 250,000 patients and over 900,000 patient-years of follow-up, provides a comprehensive synthesis of cardiovascular and renal outcomes associated with insulin sensitizing and glucose lowering therapies in adults with T2DM and established cardiovascular disease. Five key findings emerge from this analysis:

1. **SGLT2i and GLP-1 RAs both Reduce 3P-MACE** significantly in established CVD populations, by approximately 11–14%, with low heterogeneity (I^2<20%) and high certainty GRADE evidence.
2. **SGLT2i are the Dominant Class for HHF and CKD Progression** - effects that are early onset, haemodynamically driven, and largely independent of baseline glycaemia, HF ejection fraction, or diabetic kidney disease status.
3. **GLP-1 RAs Provide Superior Ischaemic Stroke Protection** and the only proven mortality benefit independent of metabolic confounders across multiple CVOTs.
4. **Both Classes Significantly Reduce Renal Outcomes**, with SGLT2i showing stronger protection against CKD progression and ESKD, while GLP-1 RAs excel at reducing albuminuria and eGFR decline - effects that appear complementary and additive.
5. **Metformin** retains a supportive role as a safe, affordable background agent with probable (but unproven in dedicated RCTs) cardiovascular benefit and no evidence of renal harm at eGFR ≥30 mL/min/1.73m².

SGLT2 Inhibitors: The Heart Failure and Kidney-First Paradigm: The SGLT2i evidence

base has evolved from an unexpected cardiovascular discovery to a fully established cardiorenal therapeutic class in less than a decade. The early and steep separation in HHF curves observed in EMPA-REG OUTCOME - evident within 30 days of empagliflozin initiation - was incompatible with an atherosclerotic mechanism and pointed unambiguously to haemodynamic effects: volume depletion, natriuresis, reduced preload and afterload, sympathetic withdrawal, and RAAS suppression.[13] These haemodynamic and tubular mechanisms - rather than glucose lowering - explain why SGLT2i benefits generalize to patients without diabetes in DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, and DELIVER, and to patients with CKD in DAPA-CKD and EMPA-KIDNEY.

For the kidney specifically, the mechanistic driver is tubuloglomerular feedback: SGLT2 inhibition in the proximal tubule reduces sodium reabsorption, increasing sodium delivery to the macula densa, reducing afferent arteriolar tone, and thereby decreasing glomerular hyperfiltration - the earliest and most modifiable driver of progressive diabetic kidney disease.[7] The Lancet collaborative meta-analysis (Staplin et al., 2022) confirmed a 38% reduction in kidney disease progression across four CKD trials in patients with diabetic kidney disease (RR 0.60, 95% CI 0.53–0.69),[8] which our pooled analysis replicates and extends.

A critically important clinical point for trainees is that the transient eGFR dip of 10–15% seen within the first 2–4 weeks of SGLT2i initiation is haemodynamic (not structural) in origin, does not predict adverse renal outcomes, and should not prompt drug discontinuation.[14] This has been confirmed in post-hoc analyses of CREDENCE, DAPA-CKD, and EMPA-KIDNEY, and is now explicitly addressed in clinical guidelines.

GLP-1 Receptor Agonists: The Atheroprotective and Antiproteinuric Class: The cardiovascular benefits of GLP-1 RAs in established CVD populations operate through distinct anti-atherosclerotic mechanisms that complement SGLT2i. GLP-1 receptors are expressed on coronary arterial endothelium and macrophages, where their activation reduces endothelial dysfunction, suppresses inflammatory adhesion molecules, decreases macrophage foam cell formation, and stabilizes atherosclerotic plaques.[15] These mechanisms explain the gradual (rather than early) divergence of MACE curves in LEADER and SUSTAIN-6 and the observed superiority in stroke reduction - the only class to significantly reduce ischaemic stroke (HR 0.84, 95% CI 0.76–0.93) across pooled CVOTs.

For the kidney, the 2024 FLOW trial was landmark: it demonstrated that semaglutide reduced the primary composite kidney outcome by 24% (HR 0.76) and MACE by 18% in patients with T2DM and established CKD - the first GLP-1 RA to demonstrate hard kidney endpoints, establishing semaglutide as the fourth pillar of nephroprotective therapy.[11] The pooled SUSTAIN-6/LEADER analysis showed a 24% reduction in albuminuria from baseline to 2 years, and the AJKD 2025 meta-analysis confirmed sustained eGFR protection in patients with baseline eGFR <60 mL/min/1.73m².[16]

Human-homologous GLP-1 RAs (semaglutide, liraglutide, dulaglutide, albiglutide) consistently outperformed exendin-4-based agents (exenatide, lixisenatide) on MACE endpoints in subgroup analyses, and this structural distinction has been incorporated into current ESC and ADA guidelines recommending the former class preferentially in established CVD populations.[17]

Metformin: The Evergreen First-Line Agent in Perspective: Metformin's cardiovascular evidence remains a subject of ongoing academic debate. The UKPDS 34 study - conducted from 1977 to 1997, before statin therapy was widespread - demonstrated an impressive 36% RRR in all-cause mortality and 39% RRR in MI in overweight patients with T2DM receiving intensive metformin versus conventional therapy.[6] However, the limited representation of patients with established CVD, the pre-modern background therapy, and the absence of placebo control relative to modern standards make direct comparison with contemporary CVOT data difficult.

Umbrella meta-analysis data (Bahardoust et al., 2023) incorporating 17 systematic reviews confirmed lower all-cause mortality (OR 0.80, 95% CI 0.74–0.86) and CVD mortality (OR 0.77, 95% CI 0.69–0.85) with metformin, though these estimates are significantly influenced by observational data subject to confounding by indication.[18] In the absence of a dedicated CVOT, the current evidence neither conclusively proves nor disproves a cardiovascular benefit for metformin in contemporary established CVD populations. Its continued first line recommendation rests on its

excellent safety profile, metabolic neutrality (no weight gain, no hypoglycaemia), very low cost, and the UKPDS legacy data. It should be continued unless contraindicated (eGFR <30 mL/min/1.73m²) or not tolerated.

Combination Therapy and the Future of Cardiorenal Medicine: A key emerging question is whether combining GLP-1 RAs and SGLT2i provides additive cardiorenal benefit. The 2024 Neuen et al. Circulation meta-analysis found that GLP-1 RAs significantly reduced MACE, kidney outcomes, and mortality in patients already receiving SGLT2i (p-interaction all >0.10), suggesting additive - not substitutive - benefit.[19] Similarly, the SMART-C collaborative meta-analysis (Apperloo et al., Lancet Diabetes Endocrinol, 2024) confirmed compatible safety profiles with no significant pharmacokinetic interaction.[20] This evidence underpins the concept of a *cardiorenal protection bundle*: RAAS inhibitor + SGLT2i + GLP-1 RA (+ nsMRA, where indicated) as the optimal pharmacological backbone for T2DM patients with established CVD and CKD.

Strengths and Limitations

Strengths: This review systematically searched three major databases using pre-specified PICO criteria registered on PROSPERO; incorporated the most recent FLOW trial data (2024); presented results both qualitatively and in comprehensive tabular format; conducted pre-specified subgroup and sensitivity analyses; and applied GRADE to evaluate evidence certainty. To our knowledge, this represents the most recent unified cardiorenal outcomes meta-analysis covering all three major drug classes in established CVD populations.

Several limitations warrant acknowledgment. First, no head-to-head RCT comparing GLP-1 RAs vs. SGLT2i vs. metformin in established CVD exists; comparative estimates rely on indirect analysis. Second, the definition of 'established CVD' differed between trials (e.g., DECLARE-TIMI 58 included patients with risk factors only; REWIND was 31% established CVD), necessitating extraction of subgroup data with variable precision. Third, substantial differences in background medications (RAAS inhibitors, statins, beta blockers) between trial eras introduce confounding that random effects models cannot fully adjust. Fourth, metformin evidence derives almost entirely from pre-CVOT-era data and observational studies, limiting its comparability with GLP-1 RA and SGLT2i evidence. Fifth, the FLOW trial was published in preliminary form (Nature Medicine, June 2024) and full peer reviewed data for select endpoints were not yet available at database closure.

CONCLUSION

This systematic review and meta-analysis demonstrate that insulin sensitizing and glucose lowering therapies, particularly SGLT2 inhibitors and GLP-1 receptor agonists, provide substantial and clinically meaningful protection against both cardiovascular and renal outcomes in patients with T2DM and established cardiovascular disease. These agents should be considered not only as glucose lowering treatments but as integral components of cardiorenal risk reduction strategies.

SGLT2 inhibitors are the agents of choice when heart failure or CKD progression is the dominant concern - they reduce HHF by 31%, CKD progression by 38–40%, and cardiovascular death by 18%. GLP-1 RAs are preferred when atherosclerotic MACE and ischaemic stroke reduction are the primary goals - they reduce 3P-MACE by 14%, stroke by 16%, and all-cause mortality by 12%. The FLOW trial has now extended GLP-1 RA benefit to hard kidney endpoints, establishing semaglutide as the fourth pillar of nephroprotective therapy. Combination SGLT2i + GLP-1 RA therapy appears additive and is supported by current evidence.

From a clinical perspective, patients with T2DM and established cardiovascular disease, heart failure, or chronic kidney disease should be evaluated for treatment with both classes of agents, regardless of baseline HbA1c or existing therapy. Treatment decisions should focus on the predominant cardiorenal risk profile of the individual patient.

List of Abbreviations

Abbreviation	Definition
3P-MACE	Three-point major adverse cardiovascular events (CV death, non-fatal MI, non-fatal stroke)
ADA	American Diabetes Association
AMPK	AMP-activated protein kinase

ASCVD	Atherosclerotic cardiovascular disease
CI	Confidence interval
CKD	Chronic kidney disease
CVOT	Cardiovascular outcome trial
CVD	Cardiovascular disease
DKD	Diabetic kidney disease
eGFR	Estimated glomerular filtration rate
ESKD	End stage kidney disease
ESC	European Society of Cardiology
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HbA1c	Glycosylated haemoglobin A1c
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HHF	Hospitalization for heart failure
HR	Hazard ratio
MI	Myocardial infarction
nsMRA	Non-steroidal mineralocorticoid receptor antagonist
NNT	Number needed to treat
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RAAS	Renin-angiotensin-aldosterone system
RCT	Randomized controlled trial
RoB	Risk of bias (Cochrane tool)
RR	Risk ratio
RRR	Relative risk reduction
SGLT2i	Sodium-glucose cotransporter-2 inhibitor
T2DM	Type 2 diabetes mellitus
UACR	Urine albumin-to-creatinine ratio
UKPDS	UK Prospective Diabetes Study
WC-HF	Worsening or hospitalization for heart failure

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