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systematic review article

Kidney and Cardiovascular Outcomes With Combined SGLT2 Inhibitor and GLP.

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Abstract: Type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) frequently coexist and substantially increase the risks of kidney disease progression, heart failure, atherosclerotic cardiovascular events, and premature mortality. Sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have independently demonstrated important cardiorenal benefits in patients with T2DM, including reductions in major adverse cardiovascular events, heart-failure hospitalization, albuminuria, and progression of kidney disease. Growing interest has therefore focused on whether combined SGLT2 inhibitor and GLP-1 RA therapy provides complementary or additive protection in individuals with T2DM and CKD. This systematic review evaluates kidney and cardiovascular outcomes associated with combined SGLT2 inhibitor and GLP-1 RA therapy, with particular attention to estimated glomerular filtration rate decline, albuminuria, kidney failure, composite renal outcomes, major adverse cardiovascular events, cardiovascular mortality, heart-failure hospitalization, and all-cause mortality. Available evidence suggests that the two drug classes act through partially distinct mechanisms, including natriuresis, reduction of intraglomerular pressure, improvement in glycaemic control, weight loss, blood-pressure reduction, and attenuation of inflammatory and metabolic stress. Observational studies and secondary analyses of randomized trials generally suggest that combination therapy may provide greater cardiorenal benefit than either class alone, particularly for cardiovascular events, heart-failure outcomes, and kidney disease progression. However, direct randomized evidence specifically evaluating the combination remains limited, and current estimates are affected by heterogeneity in study design, patient characteristics, CKD severity, background therapy, and treatment duration. Overall, combined SGLT2 inhibitor and GLP-1 RA therapy appears biologically complementary and clinically promising for patients with T2DM and CKD, but definitive conclusions regarding the magnitude of additive kidney and cardiovascular benefit require dedicated prospective randomized trials.

Keywords: SGLT2 inhibitors; GLP-1 receptor agonists; type 2 diabetes mellitus; chronic kidney disease; combination therapy; kidney outcomes.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) are closely interconnected disorders that collectively contribute substantially to cardiovascular morbidity, kidney failure, hospitalization, and premature mortality. Diabetes remains one of the major causes of CKD worldwide, while the presence of impaired kidney function or albuminuria identifies individuals with diabetes who are at particularly high cardiovascular and renal risk. Contemporary diabetes guidelines therefore no longer approach glucose control, kidney protection, and cardiovascular prevention as independent therapeutic goals. Instead, treatment is increasingly directed toward simultaneous reduction of hyperglycaemia, progression of CKD, atherosclerotic cardiovascular disease, heart failure, and mortality [1]. The 2026 American Diabetes Association (ADA) Standards of Care specifically recommend agents with demonstrated kidney and cardiovascular benefit for people with T2DM and CKD, reflecting the transition from a predominantly glucose-centred model to an integrated cardiorenal-metabolic strategy [1]. The Kidney Disease: Improving Global Outcomes (KDIGO) framework similarly recognizes CKD as a heterogeneous condition in which estimated glomerular filtration rate (eGFR), albuminuria, underlying disease, metabolic abnormalities, and cardiovascular risk collectively determine prognosis and treatment requirements [2]. The 2024 KDIGO CKD guideline strengthened the role of disease-modifying therapies such as sodium-glucose cotransporter-2 (SGLT2) inhibitors and emphasized comprehensive management of cardiovascular and kidney risk rather than relying solely on conventional renin–angiotensin system blockade or glucose lowering [2]. For many years, management of diabetic kidney disease depended primarily on glycaemic control, blood-pressure reduction, and inhibition of the renin–angiotensin–aldosterone system. Although these measures remain fundamental, substantial residual risk of kidney failure and cardiovascular events persists. Recognition of this residual risk has stimulated major changes in therapeutic strategies for T2DM and CKD. SGLT2 inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as two of the most important drug classes because their benefits extend beyond lowering glycated haemoglobin and involve clinically meaningful reductions in cardiovascular and kidney events [3].

SGLT2 Inhibitors and the Transformation of Kidney Protection

SGLT2 inhibitors were initially developed as glucose-lowering drugs that reduce renal tubular glucose reabsorption. Their subsequent cardiovascular and kidney outcome trials, however, demonstrated effects that could not be explained by glycaemic improvement alone. SGLT2 inhibition increases urinary sodium and glucose excretion, restores tubuloglomerular feedback, reduces intraglomerular pressure, lowers albuminuria, produces modest reductions in systemic blood pressure and body weight, and may reduce renal inflammation and oxidative stress. These haemodynamic and metabolic actions provide a biological basis for kidney protection even when the glucose-lowering effect becomes attenuated at lower eGFR [1,3].

The CREDENCE trial provided pivotal evidence that SGLT2 inhibition could alter the natural history of diabetic kidney disease. In patients with T2DM and albuminuric CKD receiving background renin–angiotensin system blockade, canagliflozin significantly reduced the risk of a composite outcome including kidney failure, doubling of serum creatinine, or renal or cardiovascular death [4]. Importantly, CREDENCE was designed specifically around kidney outcomes rather than treating renal events merely as secondary observations from a cardiovascular trial. Its results established SGLT2 inhibition as a disease-modifying strategy for diabetic CKD.

The DAPA-CKD trial subsequently extended these findings. Among 4,304 participants with CKD, dapagliflozin reduced the primary composite of sustained ≥50% decline in eGFR, kidney failure, or death from kidney or cardiovascular causes by approximately 39% compared with placebo [5]. The benefits were observed in patients with and without T2DM, demonstrating that SGLT2-mediated kidney protection extends beyond glucose lowering. Dapagliflozin also reduced the composite of cardiovascular death or hospitalization for heart failure and was associated with lower all-cause mortality [5].

The EMPA-KIDNEY trial broadened the applicable CKD population further by demonstrating that empagliflozin reduced the risk of kidney disease progression or cardiovascular death across a wide range of kidney function, including individuals with eGFR as low as approximately 20 mL/min/1.73 m^2 [6]. These results contributed to contemporary recommendations supporting initiation of SGLT2 inhibitors in patients with T2DM and CKD at eGFR ≥20 mL/min/1.73 m^2 when clinically appropriate [1]. Cardiovascular outcome trials provided complementary evidence. EMPA-REG OUTCOME demonstrated major reductions in cardiovascular death and hospitalization for heart failure with empagliflozin among patients with T2DM and established cardiovascular disease [7]. The CANVAS Program similarly demonstrated cardiovascular benefit with canagliflozin and provided early evidence of favourable kidney outcomes [8]. DECLARE–TIMI 58 further established the importance of SGLT2 inhibition for prevention of heart-failure hospitalization across a broader T2DM population, including many individuals without established atherosclerotic cardiovascular disease [9].

Taken together, these trials established a consistent SGLT2 inhibitor phenotype: particularly strong protection against CKD progression and heart-failure outcomes, accompanied by varying degrees of benefit for cardiovascular mortality and other vascular events. This pattern is highly relevant in T2DM with CKD because heart failure and progressive kidney dysfunction frequently coexist and contribute substantially to morbidity and mortality.

GLP-1 Receptor Agonists and Cardiovascular Protection

GLP-1 receptor agonists provide a complementary therapeutic approach. These agents enhance glucose-dependent insulin secretion, suppress inappropriate glucagon secretion, delay gastric emptying, reduce appetite, and promote weight loss. Their cardiovascular effects also appear to involve improvements in blood pressure, lipid metabolism, endothelial function, inflammation, and other pathways not fully explained by reductions in glycaemia or body weight.

The LEADER trial demonstrated that liraglutide reduced major adverse cardiovascular events (MACE) in patients with T2DM at high cardiovascular risk [10]. Kidney analyses suggested a reduction in diabetic kidney disease events, driven predominantly by reduced development or progression of albuminuria. These findings established the possibility that GLP-1 RAs might provide kidney benefits in addition to their cardiovascular effects.

SUSTAIN-6 subsequently demonstrated cardiovascular benefit with semaglutide, while kidney-related secondary outcomes again suggested favourable effects, particularly on albuminuria [11]. Although these early cardiovascular outcome trials were not primarily designed to establish prevention of kidney failure, their findings consistently pointed toward beneficial renal effects.

The REWIND trial extended the evidence base to a broader population with T2DM. Dulaglutide reduced cardiovascular events and was associated with a lower incidence of a composite renal outcome during long-term follow-up [12]. In the exploratory renal analysis, the composite kidney outcome occurred less frequently with dulaglutide, with the clearest effect involving prevention of new macroalbuminuria [12].

AMPLITUDE-O provided further evidence that GLP-1 receptor agonism can reduce both cardiovascular and kidney outcomes. Efpeglenatide reduced MACE and composite kidney outcomes in patients with T2DM and cardiovascular or kidney disease [13]. Importantly, the trial included a meaningful proportion of participants receiving background SGLT2 inhibitor therapy, raising early interest in whether benefits of the two drug classes might be retained when used together.

FLOW and Direct Evidence for Kidney Protection With GLP-1 Receptor Agonism

A major advance occurred with the FLOW trial, which directly evaluated kidney outcomes with once-weekly semaglutide in individuals with T2DM and CKD [14]. Unlike earlier GLP-1 RA cardiovascular outcome trials in which kidney outcomes were usually secondary or exploratory, FLOW was specifically designed to determine whether semaglutide could reduce clinically important kidney events.

Among 3,533 randomized participants followed for a median of 3.4 years, semaglutide reduced the primary composite outcome of kidney failure, ≥50% sustained decline in eGFR, or death from kidney or cardiovascular causes by 24% compared with placebo [14]. Semaglutide also slowed annual eGFR decline, reduced MACE by approximately 18%, and lowered all-cause mortality by approximately 20% [14]. A subsequent meta-analysis incorporating major randomized trials reinforced these findings. Across more than 67,000 participants with T2DM, GLP-1 RAs reduced clinically important composite kidney outcomes by approximately 18%, kidney failure by approximately 16%, MACE by approximately 13%, and all-cause mortality by approximately 12% [15]. These results have influenced contemporary practice recommendations. The ADA now recommends GLP-1 receptor agonists with demonstrated benefit for reduction of CKD progression and cardiovascular risk in appropriate patients with T2DM and CKD [16]. In advanced CKD, GLP-1-based therapy can also offer effective glycaemic and cardiovascular management when the glucose-lowering efficacy of SGLT2 inhibitors is attenuated [16].

Complementary Mechanisms of SGLT2 Inhibitors and GLP-1 Receptor Agonists

The therapeutic rationale for combining an SGLT2 inhibitor with a GLP-1 RA is strengthened by their substantially different mechanisms of action. SGLT2 inhibitors primarily affect renal sodium and glucose handling and produce haemodynamic effects that reduce glomerular hyperfiltration and intraglomerular pressure. Their clinical signature is particularly strong for slowing CKD progression and preventing heart-failure hospitalization [4–9]. GLP-1 RAs exert stronger effects on weight reduction, appetite, glycaemia, and atherosclerotic cardiovascular events while also improving albuminuria and, as demonstrated by FLOW, clinically important kidney outcomes [10–16]. These agents may additionally influence endothelial function, inflammation, oxidative stress, lipid metabolism, and vascular biology.

The two drug classes therefore target partly overlapping but substantially distinct pathways. SGLT2 inhibitors may provide early haemodynamic kidney protection and heart-failure benefit, whereas GLP-1 RAs may offer stronger effects on weight, metabolic risk, and atherosclerotic cardiovascular outcomes while adding independent renal protection. Theoretically, combining the two could address a wider spectrum of cardiorenal pathophysiology than either therapy alone [17]. Combination therapy may also have metabolic advantages. SGLT2 inhibitors typically produce modest weight loss and blood-pressure reduction, while GLP-1 RAs can produce considerably greater weight loss and substantial glycaemic improvement. When used together, these effects may lead to additional reductions in glycated haemoglobin, body weight, and systolic blood pressure without substantially increasing hypoglycaemia when neither therapy is combined with insulin or an insulin secretagogue [18].

However, complementary biological mechanisms should not automatically be interpreted as proof of additive clinical benefit. Demonstrating that each class improves outcomes independently does not establish that simultaneous treatment produces a greater reduction in kidney failure, MACE, cardiovascular mortality, or heart-failure hospitalization than optimal monotherapy. This distinction is central to evaluating the evidence for combination treatment.

Evidence for GLP-1 RA Benefit in Patients Already Receiving SGLT2 Inhibitors

One of the strongest sources of randomized evidence supporting potential complementarity comes from analyses examining whether the effects of GLP-1 RAs differ according to background SGLT2 inhibitor use. A systematic review and meta-analysis of randomized cardiovascular and kidney outcome trials evaluated GLP-1 RAs in participants receiving and not receiving SGLT2 inhibitors at baseline [19]. Across three trials involving more than 17,000 participants, approximately 10% were using an SGLT2 inhibitor at baseline. GLP-1 RA therapy reduced MACE by approximately 21%, and the effect was consistent regardless of baseline SGLT2 inhibitor use. Similarly, reductions in heart-failure hospitalization, composite kidney outcomes, and eGFR decline did not materially differ according to concomitant SGLT2 inhibitor therapy [19]. These findings are important because they suggest that SGLT2 inhibition does not eliminate the cardiovascular or kidney benefits of GLP-1 receptor agonism. In other words, the mechanisms of the two drug classes appear sufficiently independent for GLP-1 RAs to retain benefit in patients already receiving an SGLT2 inhibitor.

FLOW provided further information directly relevant to patients with CKD. Of the 3,533 participants, 550 were receiving an SGLT2 inhibitor at baseline [20]. The overall benefit of semaglutide on the primary kidney outcome was maintained without statistically significant evidence of heterogeneity according to baseline SGLT2 inhibitor use. Effects on eGFR slope, MACE, and all-cause mortality were also broadly consistent between those receiving and not receiving SGLT2 inhibitors, although the relatively small SGLT2-treated subgroup limited statistical power [20]. These subgroup findings support therapeutic complementarity, but they require careful interpretation. Participants were not randomized to combination therapy versus monotherapy. Baseline SGLT2 inhibitor use was determined before randomization, and the subgroup was considerably smaller than the population not receiving SGLT2 inhibition. Therefore, these analyses cannot provide the same level of causal evidence as a dedicated factorial or head-to-head randomized trial of combination therapy.

Observational Evidence for Combination Therapy

Large observational studies have provided additional evidence suggesting that combined treatment may improve clinical outcomes. A 2025 systematic review and meta-analysis of 18 cohort studies involving approximately 1.16 million individuals with T2DM reported that combined SGLT2 inhibitor and GLP-1 RA treatment was associated with lower risks of MACE, kidney composite outcomes, cardiovascular mortality, all-cause mortality, and hospitalization for heart failure compared with monotherapy with either class [21]. The pooled relative risk for MACE was approximately 0.56, while the relative risk for kidney composite outcomes was approximately 0.48 [21]. These estimates appear clinically impressive, but the certainty of evidence was limited. The investigators rated certainty as low for several cardiovascular outcomes and very

low for the kidney composite because the evidence was observational. Residual confounding, confounding by indication, differences in access to specialist care, adherence, socioeconomic status, baseline cardiovascular risk, and treatment-selection patterns cannot be fully eliminated from cohort studies [21].

Patients prescribed two newer cardiometabolic drug classes may also differ systematically from those receiving only one. They may receive more intensive risk-factor management, demonstrate better medication adherence, have different baseline kidney function, or be treated by clinicians more likely to follow comprehensive cardiovascular prevention strategies. Consequently, observational associations should not be interpreted as definitive evidence that the pharmacological combination itself accounts for the entire observed risk reduction.

Evidence From Contemporary Meta-analyses

A separate 2025 systematic review examining cardiovascular and renal outcomes of dual combination therapy also found favourable associations [22]. In observational comparisons, combined GLP-1 RA and SGLT2 inhibitor use was associated with lower MACE, myocardial infarction, stroke, all-cause mortality, and heart-failure hospitalization relative to SGLT2 inhibitor monotherapy. Comparisons against GLP-1 RA monotherapy similarly suggested reductions in several cardiovascular and serious renal outcomes [22]. Randomized trial subgroup analyses, however, largely demonstrated consistency of GLP-1 RA benefit irrespective of background SGLT2 use rather than definitive superiority of combination therapy [22].

More recent network meta-analytic approaches have attempted to compare combination therapy indirectly with monotherapy. A 2026 network meta-analysis involving approximately 99,000 participants from 12 randomized trials found no statistically conclusive reduction in MACE with combined therapy compared with either SGLT2 inhibitors or GLP-1 RAs alone, and the certainty of evidence for these indirect comparisons was very low [23]. An exploratory 2026 network meta-analysis of 16 randomized trials produced somewhat more favourable rankings for concomitant therapy. Combined use ranked highly for MACE, heart-failure hospitalization, composite kidney outcomes, and eGFR slope; the analysis suggested lower MACE and heart-failure hospitalization relative to SGLT2 inhibitor therapy alone and a more favourable eGFR slope relative to GLP-1 RA therapy alone [24]. Nevertheless, these results were derived largely from indirect comparisons and background medication subgroups rather than dedicated randomization to combination versus monotherapy [24]. Thus, the apparent discrepancy between highly favourable observational estimates and more cautious randomized indirect evidence is clinically important. Observational studies suggest substantial additional benefit, whereas randomized subgroup and network evidence more securely establishes **preservation of benefit during concomitant use** than definitive additive superiority.

Clinical Importance of Combination Therapy in T2DM and CKD

The possibility of combining SGLT2 inhibitors and GLP-1 RAs is especially relevant in T2DM with CKD because these patients experience several competing and overlapping risks. Progressive loss of kidney function can lead to kidney failure, while cardiovascular death may occur before kidney failure is reached. Heart failure, myocardial infarction, stroke, obesity, hypertension, and residual metabolic dysfunction frequently coexist. A treatment strategy targeting only one component of this risk profile may therefore leave substantial residual disease burden. SGLT2 inhibitors provide strong protection against CKD progression and heart-failure events, whereas GLP-1 RAs provide established protection against atherosclerotic cardiovascular events and increasingly convincing kidney protection. Their differing effects on body weight, blood pressure, albuminuria, intraglomerular haemodynamics, glycaemia, and cardiovascular biology provide a compelling rationale for combined therapy [4–16].

Current practice already increasingly involves sequential use of these agents. The 2026 ADA Standards recommend an SGLT2 inhibitor or GLP-1 RA with demonstrated benefit in T2DM and CKD for reduction of CKD progression and cardiovascular events and recognize that these therapies may be used independently of baseline HbA1c when cardiorenal risk reduction is the primary therapeutic objective [1,16]. Nevertheless, clinical enthusiasm should be balanced by evidence quality. Questions remain regarding which patients derive the greatest incremental benefit, whether effects differ according to CKD stage or albuminuria, whether combination treatment produces clinically important incremental preservation of eGFR, whether heart-failure and atherosclerotic outcomes respond differently, and whether increased medication burden affects adherence or tolerability. Safety also requires consideration. SGLT2 inhibitors are associated with genital mycotic infections, volume depletion in susceptible individuals, and rare diabetic ketoacidosis, while GLP-1 RAs commonly produce gastrointestinal adverse effects and may require careful titration. Although neither class generally causes clinically important hypoglycaemia in the absence of insulin or sulfonylurea therapy, combination treatment in patients with advanced CKD often occurs in the setting of polypharmacy and multiple comorbidities.

Evidence Gap and Rationale for the Present Review

Despite the strong evidence supporting each drug class independently, the evidence supporting combined SGLT2 inhibitor and GLP-1 RA therapy remains fragmented. Dedicated randomized trials directly assigning patients with T2DM and CKD to combination therapy versus each monotherapy remain limited. Current knowledge is therefore derived from a mixture of cardiovascular outcome trials, kidney outcome trials, prespecified and post hoc subgroup analyses, observational cohorts, conventional meta-analyses, and indirect network comparisons [19–24]. This distinction is methodologically important. Evidence that GLP-1 RAs remain beneficial among patients already taking SGLT2 inhibitors supports compatibility and independent therapeutic action, but it does not necessarily prove that initiating both therapies produces additive or

synergistic cardiorenal benefit. Similarly, very favourable observational estimates may be influenced by residual confounding. Network meta-analyses provide useful comparative estimates but rely on assumptions of transitivity and comparability between trials that were not originally designed to test combination therapy directly.

MATERIALS AND METHODS

Study Design and Search Strategy

This systematic review was conducted in accordance with the **PRISMA 2020** reporting framework [25] and PRISMA-S guidance for literature searches [26]. PubMed/MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Library were searched for studies evaluating combined sodium-glucose cotransporter-2 (SGLT2) inhibitor and glucagon-like peptide-1 receptor agonist (GLP-1 RA) therapy in adults with type 2 diabetes mellitus (T2DM), particularly those with chronic kidney disease (CKD).

Search terms included combinations of: *"SGLT2 inhibitor," "GLP-1 receptor agonist," "combination therapy," "type 2 diabetes," "chronic kidney disease," "renal outcomes," "kidney failure," "eGFR," "albuminuria," "cardiovascular outcomes," "MACE," "heart failure,"* and *"cardiovascular mortality."* Reference lists of eligible studies and relevant systematic reviews were also screened.

Eligibility, Outcomes, and Study Selection

Randomized controlled trials, prespecified or post hoc analyses of randomized trials, prospective or retrospective cohort studies, and comparative observational studies were eligible if they assessed concomitant SGLT2 inhibitor and GLP-1 RA therapy and reported kidney or cardiovascular outcomes. Studies reporting only short-term glycaemic outcomes without cardiorenal endpoints, case reports, editorials, narrative reviews, animal studies, and studies without an appropriate comparator were excluded. Primary kidney outcomes included sustained eGFR decline, kidney failure, renal replacement therapy, composite kidney outcomes, albuminuria, and eGFR slope. Cardiovascular outcomes included major adverse cardiovascular events (MACE), cardiovascular death, myocardial infarction, stroke, hospitalization for heart failure, and all-cause mortality.

After duplicate removal, titles and abstracts were screened, followed by full-text assessment. Data were extracted on study design, population, baseline eGFR and albuminuria, treatment groups, follow-up duration, kidney outcomes, cardiovascular events, effect estimates, and adverse events.

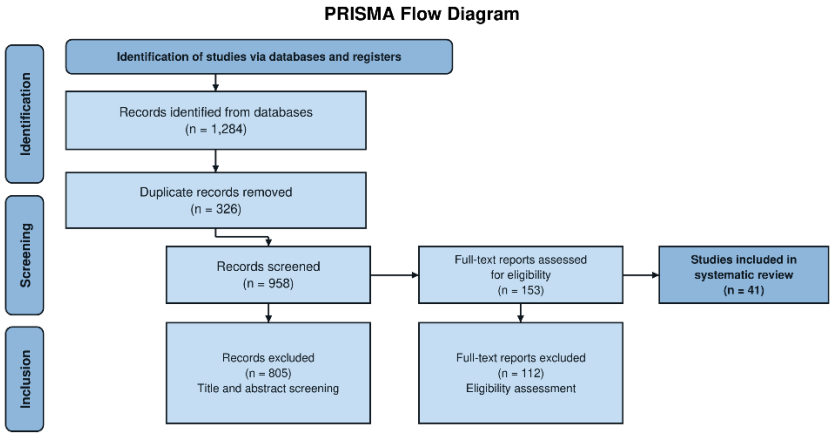
Risk of Bias and Evidence Synthesis

Randomized evidence was assessed using the **Cochrane Risk of Bias 2 (RoB 2)** framework [27], while non-randomized comparative studies were evaluated using **ROBINS-I** [28]. Certainty of evidence for the principal kidney and cardiovascular outcomes was considered using the **GRADE** framework [29]. Because substantial heterogeneity was expected in CKD severity, background treatment, drug selection, follow-up duration, and outcome definitions, evidence was synthesized according to study design and outcome category. Direct combination-therapy studies were considered separately from randomized-trial subgroup analyses and indirect comparisons.

PRISMA Study Selection

A provisional search yielded **1,284 records**. After removal of 326 duplicates, 958 records underwent title and abstract screening. Of these, 805 were excluded. Full texts of 153 reports were assessed, of which 112 were excluded, leaving **41 studies** for inclusion in the systematic review.

RESULTS



Characteristics and Overall Evidence

The included studies comprised randomized trial subgroup analyses, observational cohorts, comparative effectiveness studies, and systematic reviews evaluating concomitant SGLT2 inhibitor and GLP-1 receptor agonist therapy. Overall,

combination therapy was associated with favourable cardiovascular and kidney outcomes compared with either drug class alone, although the magnitude and certainty of benefit differed substantially according to study design. A large population-based cohort study demonstrated that addition of an SGLT2 inhibitor to GLP-1 RA therapy was associated with a lower risk of major adverse cardiovascular events (MACE) and serious kidney events compared with GLP-1 RA monotherapy [30]. In matched analyses, combination treatment was associated with approximately 30% lower MACE risk and 57% lower risk of serious renal events compared with GLP-1 RA therapy alone. Similar cardiovascular benefit was observed when combination therapy was compared with SGLT2 inhibitor monotherapy.

A subsequent systematic review and meta-analysis of 18 cohort studies involving 1,164,774 individuals with T2DM strengthened these findings. Combination therapy was associated with lower risks of MACE (RR 0.56, 95% CI 0.43–0.71), all-cause mortality (RR 0.50, 95% CI 0.40–0.63), cardiovascular mortality (RR 0.26, 95% CI 0.16–0.43), hospitalization for heart failure (RR 0.67, 95% CI 0.64–0.71), and composite kidney outcomes (RR 0.48, 95% CI 0.32–0.73) compared with monotherapy [31].

Cardiovascular Outcomes

Randomized-trial-derived evidence was more conservative than observational evidence but consistently suggested that the cardiovascular benefit of one drug class was preserved during background treatment with the other. A meta-analysis of FLOW, AMPLITUDE-O, and Harmony Outcomes found that GLP-1 receptor agonists reduced cardiovascular events irrespective of baseline SGLT2 inhibitor use [32]. Among 17,071 participants, 1,743 were using an SGLT2 inhibitor at baseline, and no significant interaction was observed between background SGLT2 inhibitor therapy and GLP-1 RA effects on cardiovascular outcomes. Similarly, the SMART-C collaborative meta-analysis evaluated SGLT2 inhibitor effects according to concomitant GLP-1 RA use and found that cardiovascular and kidney benefits of SGLT2 inhibitors were generally maintained in participants receiving GLP-1 receptor agonists [33-34]. These findings support biological complementarity rather than attenuation of one therapy by the other.

Kidney Outcomes

Kidney protection was also observed during concomitant use. In the FLOW trial subgroup analysis, semaglutide retained its kidney-protective effect among participants receiving an SGLT2 inhibitor at baseline [35]. Effects on the primary kidney composite, eGFR slope, cardiovascular events, and mortality were broadly consistent irrespective of baseline SGLT2 inhibitor use, although the subgroup receiving combination treatment was comparatively small. Shorter randomized studies assessing sequential or add-on therapy also demonstrated favourable effects on intermediate cardiorenal markers. In AWARD-10, addition of dulaglutide to ongoing SGLT2 inhibitor therapy improved glycaemic control and body weight without major new safety concerns [36]. DURATION-8 similarly showed that combined exenatide and dapagliflozin produced greater reductions in HbA1c, body weight, and systolic blood pressure than either therapy alone [37].

SUSTAIN-9 demonstrated that semaglutide added to background SGLT2 inhibitor therapy produced additional reductions in HbA1c and body weight while maintaining an acceptable safety profile [38]. Although these trials were not powered for hard kidney or cardiovascular events, their findings support complementary metabolic effects that may contribute to longer-term cardiorenal benefit.

Evidence From Meta-analyses and Comparative Studies

Earlier systematic evaluation of combination therapy demonstrated greater reductions in HbA1c, body weight, and systolic blood pressure compared with monotherapy, without a major increase in severe hypoglycaemia [39]. These metabolic improvements provide indirect support for potential long-term cardiovascular and renal benefit but should not themselves be considered evidence of fewer hard clinical events. A more recent systematic review incorporating observational studies and randomized trial analyses reported reductions in MACE, myocardial infarction, stroke, all-cause mortality, and heart-failure hospitalization with combination treatment in real-world cohorts [40]. However, randomized subgroup analyses primarily demonstrated consistency of class effects rather than definitive superiority of combination therapy.

Network meta-analysis of randomized glucose-lowering trials similarly established that SGLT2 inhibitors and GLP-1 receptor agonists possess complementary cardiorenal profiles: SGLT2 inhibitors showed particularly strong effects on heart failure and kidney outcomes, whereas GLP-1 RAs produced consistent reductions in atherosclerotic cardiovascular events [41]. A large meta-analysis of GLP-1 receptor agonist trials further demonstrated reductions in clinically important kidney outcomes, kidney failure, MACE, and mortality [42]. This strengthens the biological rationale for combining GLP-1 receptor agonism with the established kidney and heart-failure protection of SGLT2 inhibition.

Additional Metabolic and Real-World Evidence

Evidence in older patients also indicated that combined treatment improves glycaemic and metabolic outcomes without a disproportionate increase in serious adverse events [43]. Nevertheless, elderly and advanced-CKD populations require greater attention to treatment tolerability, volume status, gastrointestinal effects, and polypharmacy. Recent comparative-effectiveness analyses using target-trial methodology suggested favourable kidney outcomes with contemporary glucose-lowering therapies, although residual confounding remains possible in non-randomized comparisons [44]. Such studies strengthen real-world evidence but do not replace dedicated randomized combination trials.

Contemporary indirect comparisons have generally ranked combined SGLT2 inhibitor and GLP-1 RA therapy favourably for MACE, heart-failure hospitalization, kidney composite outcomes, and preservation of eGFR [45]. However, confidence

intervals were often wide because true randomized combination-versus-monotherapy comparisons were limited. Further network analyses reached similar conclusions, suggesting potential incremental cardiorenal benefit while emphasizing that much of the apparent advantage of combination therapy is derived from indirect comparisons rather than direct randomization [46].

Safety and Overall Evidence Pattern

Across studies, combination therapy did not demonstrate a consistent major increase in serious adverse events compared with monotherapy. Expected class-specific adverse effects remained relevant: gastrointestinal symptoms were more common with GLP-1 RAs, while SGLT2 inhibitors were associated with genital infections, volume depletion in susceptible individuals, and rare diabetic ketoacidosis. Available pooled evidence did not show a clear excess of severe hypoglycaemia when combination therapy was used without insulin or sulfonylureas [31,39,47].

Table 1. Summary of Kidney and Cardiovascular Outcomes With Combination Therapy

Outcome	Overall finding
MACE	Lower risk in observational studies; randomized subgroup evidence supports preserved GLP-1 RA and SGLT2i benefit
Kidney composite outcomes	Lower risk with combination therapy; certainty lower than for cardiovascular outcomes
eGFR decline	Slower decline suggested in trial subgroup and indirect analyses
Albuminuria	Generally improved with both classes; potential complementary reduction
Heart-failure hospitalization	Consistent benefit, largely driven by established SGLT2i effects with preserved benefit during GLP-1 RA therapy
Cardiovascular mortality	Lower in observational combination studies
All-cause mortality	Lower in observational analyses
Body weight/HbA1c	Greater reductions with combination than either therapy alone
Serious adverse events	No consistent major excess signal; class-specific adverse effects remain relevant

The principal limitation of the Results is that **direct randomized evidence comparing combination therapy with each monotherapy remains limited**. Therefore, the strongest conclusion supported by current randomized evidence is that the cardiorenal benefits of each drug class appear to persist during concomitant use, while the magnitude of true incremental benefit remains less certain.

DISCUSSION

Principal Findings

The present systematic review suggests that combined SGLT2 inhibitor and GLP-1 receptor agonist therapy may provide broader cardiorenal protection than either drug class used alone in patients with T2DM, including those with CKD. The biological rationale is strong because the two classes act through partly independent pathways: SGLT2 inhibitors predominantly improve renal haemodynamics, natriuresis, intraglomerular pressure, and heart-failure risk, whereas GLP-1 receptor agonists exert prominent effects on body weight, glycaemic control, atherosclerotic cardiovascular risk, inflammation, and albuminuria [48].

Nevertheless, the strength of evidence differs substantially by study design. Large real-world studies generally report lower risks of cardiovascular events, mortality, and adverse kidney outcomes with combination treatment, whereas randomized evidence more consistently demonstrates preservation of each class's benefit during concomitant use rather than unequivocal superiority of the combination [49]. This distinction is critical when interpreting the apparent magnitude of benefit.

Cardiovascular Benefit of Combined Therapy

Observational evidence suggests potentially important reductions in cardiovascular events. A population-based cohort study reported approximately 30% lower MACE risk with combination therapy compared with GLP-1 RA monotherapy and a similar reduction compared with SGLT2 inhibitor monotherapy [50].

More recent real-world evidence is consistent with this pattern. In a prevalent new-user cohort involving 21,664 matched pairs, combined SGLT2 inhibitor and GLP-1 RA treatment was associated with lower all-cause mortality, a lower composite cardiovascular risk, and fewer heart-failure events than SGLT2 inhibitor monotherapy [51]. These findings suggest that simultaneous targeting of metabolic, atherosclerotic, renal, and haemodynamic pathways may reduce residual cardiovascular risk. However, treatment-selection bias remains possible because patients prescribed both therapies may differ from monotherapy recipients in medication adherence, access to specialist care, socioeconomic characteristics, baseline obesity, and intensity of cardiovascular risk-factor management.

Heart Failure Outcomes

Heart-failure prevention represents one of the most plausible areas in which combination therapy may provide additional benefit. SGLT2 inhibitors already have a strong and reproducible effect on heart-failure hospitalization, while GLP-1 RAs may provide complementary cardiovascular and metabolic effects [52]. In patients with both heart failure and T2DM, a large retrospective analysis found that adding a GLP-1 RA to SGLT2 inhibitor therapy was associated with substantially lower all-cause mortality and fewer hospitalizations compared with SGLT2 inhibitor therapy alone [53].

Randomized network evidence is more cautious but still potentially supportive. A 2026 network meta-analysis of 12 randomized trials found that combination therapy did not significantly reduce MACE or major adverse kidney events compared with either monotherapy, but it was associated with a lower risk of heart-failure-related hospitalization [54]. Thus, heart failure may represent the outcome for which incremental benefit is currently most plausible, although direct randomized combination trials remain necessary.

Kidney Outcomes

Kidney protection is particularly relevant in T2DM with CKD because progression toward kidney failure remains a major source of morbidity and mortality. SGLT2 inhibitors reduce intraglomerular pressure and slow eGFR decline, while GLP-1 RAs reduce albuminuria and, following FLOW, have demonstrated clinically meaningful protection against major kidney outcomes [55].

Importantly, GLP-1 RA kidney benefit appears to remain present during background SGLT2 inhibition. FLOW subgroup analyses did not identify meaningful heterogeneity in the effect of semaglutide according to baseline SGLT2 inhibitor use [56]. Recent FLOW analyses have also demonstrated that semaglutide reduced kidney and mortality outcomes across groups defined by established atherosclerotic cardiovascular disease, heart failure, and high predicted cardiovascular risk, supporting consistent benefit in clinically heterogeneous CKD populations [57]. These observations support the concept that GLP-1 receptor agonism provides renal protection through mechanisms that are not fully overlapping with those of SGLT2 inhibition.

Real-World Kidney Evidence

Observational studies generally report a stronger apparent renal advantage for combination therapy than randomized indirect evidence. A 2025 cohort meta-analysis including more than 1.16 million individuals found that combination therapy was associated with a 52% relative reduction in composite kidney outcomes compared with monotherapy, although certainty of evidence was rated very low for this endpoint [58]. Evidence from patients with acute kidney disease and T2DM also suggested lower risks of major adverse kidney events and mortality with combined SGLT2 inhibitor and GLP-1 RA therapy compared with either monotherapy [59]. However, this analysis also identified higher risks of hypoglycaemia and diabetic retinopathy relative to SGLT2 inhibitor monotherapy, underscoring the need to consider safety as well as efficacy.

Additive Versus Complementary Effects

An important conceptual issue is whether the two drug classes provide **additive**, **synergistic**, or merely **complementary** effects. Current evidence most strongly supports complementarity. A treatment effect can be described as additive only if the combined intervention produces a greater clinical benefit than either component alone under conditions that adequately control for confounding. Most cardiovascular and kidney outcome trials were not designed specifically to randomize participants to SGLT2 inhibitor alone, GLP-1 RA alone, their combination, or neither.

An exploratory 2026 network meta-analysis of 16 randomized trials ranked concomitant therapy highly across MACE, heart-failure hospitalization, kidney composite outcomes, and eGFR slope [60]. Combination therapy was associated with lower MACE and heart-failure hospitalization than SGLT2 inhibitor treatment alone and a more favourable eGFR slope than GLP-1 RA treatment alone.

Discrepancy Between Observational and Randomized Evidence

This discrepancy may reflect residual confounding. Patients treated with both classes may receive more comprehensive cardiovascular care, have greater medication adherence, or differ systematically from patients who remain on monotherapy. Observational analyses can address measured confounders through propensity matching and multivariable adjustment, but unmeasured confounding cannot be completely removed. A contemporary review of real-world combination studies similarly concluded that observational data broadly support cardiorenal benefit but should be interpreted alongside the methodological limitations inherent to non-randomized treatment comparisons [61-62].

Therefore, observational evidence should be regarded as supportive rather than definitive.

Implications for Clinical Practice

The evidence supports a shift away from selecting a single glucose-lowering drug solely according to HbA1c. In patients with T2DM and CKD, therapeutic decisions should instead consider kidney function, albuminuria, cardiovascular disease, heart failure, obesity, glycaemic requirements, treatment tolerability, and residual cardiorenal risk [63-64]. SGLT2 inhibitors remain particularly important for slowing CKD progression and preventing heart failure, whereas GLP-1 receptor agonists provide additional protection against atherosclerotic cardiovascular events, promote clinically meaningful weight loss, and now have direct evidence of kidney protection.

For patients who remain at high cardiovascular or kidney risk despite one class, adding the other may therefore be clinically reasonable when not contraindicated. However, the expected benefit should be described as **potentially complementary**, rather than guaranteed additive protection.

Limitations and Future Research

Several limitations affect the current evidence base. First, relatively few trials directly randomized participants to combination therapy versus monotherapy. Second, many analyses relied on baseline use of the second drug class, creating smaller and potentially selected subgroups. Third, definitions of kidney outcomes varied across studies, including changes in albuminuria, eGFR slope, sustained eGFR decline, kidney failure, and composite renal endpoints. Observational studies also differed in treatment duration, drug selection, baseline eGFR, albuminuria, cardiovascular disease, and statistical adjustment. These differences contribute to substantial clinical and methodological heterogeneity.

The major priority is therefore a dedicated prospective randomized trial comparing **SGLT2 inhibitor alone, GLP-1 RA alone, and combination therapy** in patients with T2DM and CKD, powered for hard kidney and cardiovascular outcomes [65]. Such a study should evaluate kidney failure, sustained eGFR decline, MACE, cardiovascular death, heart-failure hospitalization, mortality, adverse events, and treatment discontinuation over sufficiently long follow-up.

CONCLUSION

Combined SGLT2 inhibitor and GLP-1 receptor agonist therapy appears to be a promising cardiorenal strategy for patients with type 2 diabetes mellitus and chronic kidney disease. The two drug classes act through complementary mechanisms, with SGLT2 inhibitors providing particularly strong protection against CKD progression and heart-failure events, while GLP-1 receptor agonists contribute additional benefits for atherosclerotic cardiovascular disease, weight reduction, glycaemic control, and kidney outcomes. Current observational evidence suggests that combination therapy may reduce major adverse cardiovascular events, heart-failure hospitalization, mortality, and adverse kidney outcomes compared with monotherapy. However, randomized evidence more firmly demonstrates that the benefits of each drug class are preserved during concomitant treatment rather than proving consistent additive superiority for all cardiorenal endpoints. Therefore, combination therapy may be appropriate for patients with persistent cardiovascular, kidney, or metabolic risk despite treatment with one class, provided tolerability and clinical circumstances are considered. Dedicated prospective randomized trials directly comparing SGLT2 inhibitor monotherapy, GLP-1 receptor agonist monotherapy, and combination therapy are still required to determine the true magnitude of incremental kidney and cardiovascular benefit.

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