Cardiovascular and Renal Outcomes of GLP-1 Receptor Agonist and SGLT2 Inhibitor Combination Therapy in Type 2 Diabetes: From Mechanistic Synergy to Clinical Evidence

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***Abstract*—Type 2 Diabetes (T2D) elevates cardiovascular and renal risk, and combination therapy with Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs) and Sodium-Glucose Cotransporter 2 inhibitors (SGLT2i) is increasingly recommended. This review evaluates evidence from Cardiovascular Outcome Trials (CVOTs) and observational studies on the efficacy and safety of dual therapy. Across the SOUL, AMPLITUDE-O, and FLOW trials, GLP-1 RA-induced reductions in Major Adverse Cardiovascular Events (MACE) and renal outcomes remained consistent regardless of baseline SGLT2i treatment, with no additive safety concerns. In SOUL, oral semaglutide reduced MACE by 14% overall (HR, 0.86), with similar effects in participants receiving and not receiving SGLT2i at baseline (HR, 0.89 vs. 0.84; P-interaction = 0.66). Real-world data further suggest additive benefits on MACE, all-cause mortality, and heart failure with combination therapy compared to either drug alone. While the precise magnitude of additive protection awaits prospective quantification, existing evidence validates combined therapy as a safe and potentially synergistic approach to reducing cardiorenal risks in high-risk type 2 diabetes patients.**

***Keywords*—GLP-1 receptor agonist, SGLT2 inhibitor, combination therapy, cardiovascular outcomes, type 2 diabetes**

I. Introduction

Over the past decade, Cardiovascular Outcome Trials (CVOTs) have demonstrated that glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and Sodium-Glucose Cotransporter 2 inhibitors (SGLT2i) each reduce Major Adverse Cardiovascular Events (MACE) and renal outcomes independent of their hypoglycemic effects [1]. These findings have prompted major clinical practice guidelines to recommend both drug classes as first-line cardiorenal protective therapies for high-risk patients with type 2 diabetes, marking a fundamental shift from glucose-centered glycemic control toward organ-protective therapeutic strategies.

The rationale behind combined use of GLP-1 RAs and SGLT2i lies in their distinct yet complementary mechanisms of action GLP-1. RAs exert antiatherosclerotic and anti-inflammatory effects that translate into consistent reductions in myocardial infarction and stroke, with clinical evidence supporting reductions in circulating C-reactive protein levels [2]. SGLT2i, in contrast, offer pronounced benefits on heart failure hospitalization and renal hemodynamics through natriuresis, glucosuria, and enhanced tubuloglomerular feedback, contributing to lower intraglomerular pressure and improved myocardial energetics [3]. Such non-overlapping pharmacological pathways indicate that dual therapy delivers additive or synergistic cardiorenal protection superior to monotherapy [4].

However, the incremental efficacy and safety benefits of combined therapy versus monotherapy have only recently begun to be systematically investigated. Most available evidence derives from subgroup analyses of trials designed for other purposes and from observational studies, which, although suggestive of additive benefits, leave critical questions unanswered regarding the true magnitude of risk reduction, optimal patient selection, and long-term safety [5]. This review synthesizes and critically assesses existing evidence from randomized controlled trials and real-world cohort studies concerning the combined administration of GLP-1 Ras, predominantly oral semaglutide, and SGLT2i regarding cardiovascular and renal outcomes, identifies remaining evidence gaps, and discusses future trial designs needed to validate this therapeutic strategy.

II. Evolution of Baseline SGLT2i Use Across GLP-1 RA CVOTs

In early GLP-1 RA CVOTs, baseline SGLT2i utilization remained limited, as these drugs had not achieved widespread accessibility or formal guideline endorsement. At that time, the cardiovascular benefits of SGLT2i had not been firmly established, and clinical practice focused

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primarily on glucose-lowering with metformin and insulin. Consequently, trials such as LEADER (liraglutide) and EMPA-REG OUTCOME (empagliflozin, an SGLT2i trial) were conducted in parallel rather than in combination. As SGLT2i gained robust evidence for reducing heart failure hospitalization and slowing chronic kidney disease progression, professional society guidelines began endorsing them as part of standard cardiorenal protective therapy in type 2 diabetes. This therapeutic paradigm shifts consequently raised baseline SGLT2i application rates in subsequent GLP-1 RA trials. For example, while earlier GLP-1 RA CVOTs like EXSCEL (once-weekly exenatide) reported negligible SGLT2i use at baseline (<2%), subsequent trials such as REWIND (dulaglutide) observed a gradual increase. The most notable change occurred in trials initiated after 2018, when SGLT2i adoption accelerated globally. Thus, the temporal evolution of SGLT2i background therapy provides a natural experimental framework to assess the additive or independent effects of GLP-1 RAs when used on top of SGLT2i. By comparing outcomes across trials with low versus high SGLT2i utilization, researchers can infer whether the cardiorenal benefits of GLP-1 RAs are attenuated, preserved, or enhanced by concomitant SGLT2i therapy. This trend expands the evidence pool for combined therapy assessment and lays the groundwork for modern trials with rigorous prespecified subgroup analyses.

III. Prespecified Subgroup Analyses: A Consistent Signal of Independent Benefit

A. The AMPLITUDE-O and Harmony Outcomes Trials

The AMPLITUDE-O trial, which evaluated efpeglenatide versus placebo in 4076 participants with T2D and established CVD or CKD, was the first GLP-1 RA CVOT to stratify randomization by baseline SGLT2i use. This prespecified design aimed to clarify whether the therapeutic effects of efpeglenatide varied with baseline SGLT2i treatment. The rationale stemmed from the complementary mechanisms of the two drug classes: while GLP-1 RAs reduce atherothrombotic events through pleiotropic effects on vascular inflammation and endothelial function, SGLT2i primarily lower intraglomerular pressure and improve cardiac preload/afterload. Theoretically, combined administration could generate synergistic benefits or diminished efficacy owing to overlapping pharmacological pathways. The AMPLITUDE-O investigators therefore planned subgroup analyses by baseline SGLT2i use to examine this issue. In a prespecified exploratory analysis, efpeglenatide reduced MACE consistently in participants receiving and not receiving SGLT2i at baseline (HR, 0.70 [95% CI, 0.37–1.30] and HR, 0.74 [95% CI, 0.58–0.94], respectively; P-interaction = 0.70). The point estimates were nearly identical, and the wide confidence interval in the SGLT2i subgroup reflected the relatively small number of SGLT2i users (n = 619, 15.2% of the trial population). Notably, the reduction in heart failure hospitalization appeared particularly pronounced among SGLT2i users (HR, 0.23 [95% CI, 0.05–0.97]), although the interaction P-value did not reach statistical significance. This signal, while hypothesis-generating, raised the possibility that the combination might confer special benefit for heart failure outcomes beyond what either drug achieves alone. Similarly, the Harmony Outcomes trial, which examined albiglutide in 9463 participants, demonstrated consistent MACE reduction irrespective of baseline SGLT2i use (HR, 0.89 [95% CI, 0.45–1.77] with SGLT2i; HR, 0.78 [95% CI, 0.67–0.90] without SGLT2i) [6]. Harmony Outcomes enrolled a smaller proportion of SGLT2i users (6.1%), which weakened statistical precision, yet the lack of qualitative interaction still validated the conclusion that GLP-1 RA benefits are preserved on an SGLT2i background.

B. The FLOW Trial: Renal Outcomes by Baseline SGLT2i Use

The FLOW trial stands as the first specialized renal outcome trial of GLP-1 RA, which randomized 3533 patients with T2D and CKD to weekly subcutaneous semaglutide or placebo. Unlike previous CVOTs that included renal endpoints as secondary or exploratory outcomes, FLOW was powered for a primary composite kidney outcome, making it uniquely suited to examine renoprotection. A prespecified analysis by baseline SGLT2i use demonstrated that semaglutide reduced the primary composite kidney outcome—defined as a sustained ≥50% decline in estimated glomerular filtration rate (eGFR), kidney failure, or death from kidney or cardiovascular causes—consistently regardless of SGLT2i status. Specifically, among participants using SGLT2i at baseline (15.6% of the cohort), the hazard ratio for the primary kidney outcome was 0.78 (95% CI 0.58–1.05), compared with 0.81 (95% CI 0.70–0.94) among non-users (P-interaction = 0.76). The annualized rate of eGFR decline was also slowed to a similar extent in participants with and without background SGLT2i use, providing important evidence that the renoprotective effects of semaglutide are independent of concurrent SGLT2i therapy [5]. These findings are clinically meaningful because patients with CKD often already receive SGLT2i for renal protection. Demonstrating that adding a GLP-1 RA provides additional slowing of eGFR loss, even on top of an SGLT2i, supports a sequential or upfront combination strategy in high-risk renal populations. Furthermore, the FLOW results helped resolve earlier uncertainty about whether GLP-1 RA renal protective effects become redundant under concurrent SGLT2i medication; the data clearly indicate they are not.

C. Meta-Analytical Confirmation of Consistent GLP-1 RA Effects

A 2024 systematic review and meta-analysis by Neuen *et al*. [6] pooled individual trial data from Harmony Outcomes, AMPLITUDE-O, and FLOW—the three GLP-1 RA CVOTs with the largest numbers of participants receiving SGLT2i at baseline—yielding a combined population of 1743 SGLT2i users among 17,072 total participants. By using individual participant data, this meta-analysis overcame the limitations of trial-level subgroup analyses, which can suffer from ecological bias

and low statistical power. Researchers adopted unified diagnostic criteria for MACE, heart failure hospitalization and renal endpoints throughout included trials, ensuring consistency. The analysis demonstrated that GLP-1 RAs reduced MACE by 21% overall (HR, 0.79 [95% CI, 0.71–0.87]), with consistent effects irrespective of SGLT2i use (HR, 0.77 [95% CI, 0.54–1.09] with SGLT2i; HR, 0.79 [95% CI, 0.71–0.87] without; P-heterogeneity = 0.78). The confidence interval for the SGLT2i subgroup, while wider, was fully contained within that of the non-user subgroup, and the test for heterogeneity was convincingly negative. Effects on hospitalization for heart failure, cardiovascular death, all-cause mortality, and the composite kidney outcome were similarly consistent across subgroups, with all *P*-values for heterogeneity exceeding 0.05 [6]. This pooled analysis stands as the most authoritative evidence concerning the synergistic effects of GLP-1 RAs combined with SGLT2i, and it provides a robust quantitative synthesis that clinicians can use to inform treatment decisions. Notably, the authors also performed sensitivity analyses excluding trials with very low SGLT2i use, and the results remained unchanged, reinforcing the robustness of the conclusion.

IV. The SOUL Trial: Validating Combination Therapy in the Contemporary Era

The temporal increase in baseline SGLT2i use is clearly reflected in SOUL. Earlier trials, including Harmony Outcomes and AMPLITUDE-O, recorded relatively moderate SGLT2i application rates, while FLOW reported 15.6% [7]. SOUL enrolled 9650 participants with T2D and established ASCVD or CKD, achieving the highest baseline SGLT2i utilization at 26.9%, with an additional 22% initiating SGLT2i during follow-up-so nearly half of all participants had SGLT2i exposure [8]. It constitutes the largest single-trial dataset to assess dual therapy outcomes under modern clinical conditions.

A. Primary Findings on MACE Reduction by Baseline SGLT2i Status

SOUL showed a 14% MACE reduction overall (HR, 0.86 [0.77–0.96]). Prespecified subgroup analyses presented comparable hazard ratios among patients with or without baseline SGLT2i treatment (0.89 [0.71–1.11] and 0.84 [0.74–0.95], respectively; P-interaction = 0.66). The wider confidence interval in the SGLT2i subgroup reflects its smaller size rather than an attenuated treatment effect. Analyses considering any in-trial SGLT2i use confirmed this consistency [8].

B. Secondary Outcomes and Safety Profile of the Combination

Individual MACE components, all-cause mortality, as well as changes in glycated hemoglobin and body weight remained comparable across subgroups (all interaction $P > 0.30$). Safety data were reassuring: serious adverse event rates did not differ meaningfully between semaglutide and placebo arms regardless of SGLT2i background. Severe hypoglycemia and ketoacidosis remained infrequent and evenly distributed, indicating no additive safety concerns with the combination [8].

C. Clinical Implications for Guideline-Directed Combination Therapy

These results carry direct clinical relevance. As the first CVOT to demonstrate MACE reduction with an oral GLP-1 RA, the SOUL trial expands therapeutic choices for patients favoring or necessitating non-injectable regimens. The demonstration that oral semaglutide retains its cardiovascular benefit when added to an SGLT2i fills an important evidence gap on combination efficacy and validates existing guideline suggestions on combined medication administration for type 2 diabetes patients complicated by ASCVD or CKD [7].

V. Discussion

A. Integrating RCT Evidence with Real-World Observational Data on Dual Therapy

The randomized evidence from CVOT subgroup analyses is corroborated by several large observational studies. A population-based cohort study drawing on UK primary care data adopted the prevalent new-user design to mimic randomized trial conditions, comparing GLP-1 RA and SGLT2i combination therapy against either drug class alone. The combination was associated with a 30% lower risk of MACE compared with GLP-1 RAs alone (HR, 0.70 [95% CI, 0.49–0.99]) and a 29% lower risk compared with SGLT2i alone (HR, 0.71 [95% CI, 0.52–0.98]). Reductions in serious renal events and heart failure were also observed, although confidence intervals were wider for some secondary endpoints [9]. A 2025 systematic review and meta-analysis by Shokravi *et al*. [5] that incorporated both RCTs and observational studies further confirmed these findings, revealing steady declines in MACE, myocardial infarction, stroke, all-cause mortality, and heart failure-related events among patients receiving dual therapy versus monotherapy in real clinical practice [5].

B. Safety and Tolerability of Combined GLP-1 RA and SGLT2i Treatment

Across all CVOT subgroup analyses and observational studies, the combination of GLP-1 RAs and SGLT2i has been consistently well-tolerated, with no evidence of synergistic toxicity. In the SOUL trial, serious adverse events were reported in 48.3% versus 48.6% of participants receiving semaglutide versus placebo among those using SGLT2i at baseline, and 47.8% versus 50.9% among those not using SGLT2i. The incidence rates of severe hypoglycemia and diabetic ketoacidosis remained low and comparable across groups irrespective of baseline SGLT2i administration. The AMPLITUDE-O and Harmony Outcomes trials similarly reported no safety signals of concern when GLP-1 RAs were added to background SGLT2i therapy [8]. This favorable safety performance stems from the divergent and non-overlapping adverse reaction characteristics, with gastrointestinal symptoms being the most common adverse effects of GLP-1 RAs and genitourinary infections being more frequent with SGLT2i.

C. Unresolved Questions: Patient Selection, Additivity, and Long-Term Outcomes

Despite the robust and reassuring body of evidence, several key clinical questions remain unanswered. The true additive magnitude of benefit on hard clinical endpoints beyond what is achieved by optimized monotherapy has yet to be quantified in a prospective, randomized setting specifically designed to evaluate combination therapy as a primary objective. Most available evidence derives from subgroup analyses of trials designed for other purposes, inherently limiting the statistical power to detect interactions and raising the possibility of confounding by indication in observational studies [3]. Furthermore, the optimal patient populations, sequencing, and timing of combination therapy initiation remain to be defined. The cost-effectiveness of initial dual therapy versus stepwise treatment strategies also warrants rigorous investigation, particularly amid growing financial constraints on healthcare systems [3].

D. The Case for Dedicated Prospective Trials and Novel Active-Controlled Designs

The rapidly evolving therapeutic landscape, coupled with the well-established cardiorenal benefits of GLP-1 RAs and SGLT2i, has rendered traditional placebo-controlled CVOTs ethically and clinically infeasible. Future trials will increasingly need to employ active-controlled designs that compare investigational therapies with agents of proven cardiovascular efficacy [10]. The SURPASS-CVOT, which is evaluating tirzepatide against dulaglutide using a novel non-inferiority and imputed placebo comparison design, represents a methodological model for such future investigations. Specially designed prospective trials are urgently warranted to evaluate the incremental efficacy of initial combination therapy versus stepwise monotherapy escalation on hard clinical endpoints and fill the existing evidence gaps [10].

VI. Conclusion

Growing evidence from randomized controlled trials and real-world cohort studies consistently shows that the cardiorenal benefits of GLP-1 RAs are independent of background SGLT2i use, suggesting an additive protective effect that is achievable without compromising safety [6]. The SOUL trial, in particular, provides robust contemporary data confirming that oral semaglutide maintains its MACE reduction efficacy irrespective of concomitant SGLT2i therapy, which validates outcomes of prior cardiovascular outcome trials and offers clinicians the most robust evidence for adopting this combined therapeutic regimen [8].

The clinical implications of these findings are substantial. For patients with type 2 diabetes and established atherosclerotic cardiovascular disease or chronic kidney disease, the combination of a GLP-1 RA and an SGLT2i offers the potential to simultaneously target multiple pathophysiological pathways, addressing residual cardiovascular and renal risk that persists despite monotherapy with either agent alone. Real-world observational data further corroborate findings from randomized trials, demonstrating consistent reductions in MACE, all-cause mortality, and heart failure hospitalization events in patients receiving dual therapy versus monotherapy [9].

Nevertheless, several critical evidence gaps remain that warrant careful consideration. The true magnitude of synergistic benefits in hard clinical endpoints beyond optimized monotherapy remains unquantified in prospective randomized trials specifically powered to evaluate combination therapy as the primary endpoint. Most available evidence derives from subgroup analyses of trials designed for other purposes, inherently limiting the statistical power to detect interactions and raising the possibility of confounding by indication in observational studies [3]. Furthermore, the cost-effectiveness and optimal sequencing of these agents in an increasingly complex therapeutic landscape require dedicated investigation [3].

Well-designed prospective controlled trials are urgently required to firmly confirm the additional clinical value of initial combined therapy and to identify the patient populations most likely to derive meaningful clinical benefit. Until such evidence becomes available, the totality of current data provides clinicians with reasonable confidence to utilize this dual strategy as a cornerstone of comprehensive cardiorenal risk management in appropriately selected high-risk patients [2].

Conflict of Interest

The author declares no conflict of interest.

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