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GLP-1 RA and SGLT2 – Inhibitor Treatment

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Abstract **Original Research Article**

Background: GLP-1 receptor agonists and sodium–glucose co-transporter-2 inhibitors independently lower cardiovascular and renal risk in type 2 diabetes. Uptake of concomitant therapy remains limited. ***Methods:*** MEDLINE and Embase (1 Jan 2023–30 Jun 2025) identified studies comparing GLP-1 receptor agonists and sodium–glucose co-transporter-2 inhibitors vs monotherapy in adults with established atherosclerotic cardiovascular disease and type 2 diabetes (many with CKD). Designs included randomised trials, prespecified trial sub-analyses, large registries (≥200 dual-therapy users), and systematic reviews. Evidence was stratified as: (A) add sodium–glucose co-transporter-2 inhibitors S to GLP-1 receptor agonists; (B) add GLP-1 receptor agonists ao sodium–glucose co-transporter-2 inhibitors; (C) head-to-head registries. Random-effects models were applied within strata; heterogeneity was assessed with I^2. ***Results:*** Six studies met criteria. Head-to-head registries (n ≈ 41 800) showed pooled HR for 3-point major adverse cardiovascular events of 0.60 (0.50–0.72) vs monotherapy. Adding an sodium–glucose co-transporter-2 inhibitors to background dual GLP-1 receptor agonists yielded pooled RR 0.64 (0.46–0.90); adding a GLP-1 RA to background SGLT2I produced HR 0.89 (0.71–1.11). A 2025 RCT-rich meta-analysis reported similar magnitudes. No excess serious-adverse-event signal was seen. ***Conclusion:*** Across complementary designs – predominantly in adults with established atherosclerotic cardiovascular disease and type 2 diabetes (many with CKD) – dual GLP-1 receptor agonists and sodium–glucose co-transporter-2 inhibitors confers ~30–40 % additional 3-point major adverse cardiovascular events reduction vs single-agent therapy, with consistent renal benefits and acceptable tolerability. Pending factorial RCTs, early dual initiation is reasonable in highest-risk phenotypes, with staggered titration and renal blood pressure monitoring.

Keywords: GLP-1 receptor agonist; SGLT2 inhibitor; combination therapy; major adverse cardiovascular events; chronic kidney disease.

1. INTRODUCTION

Residual cardiovascular risk remains unacceptably high in adults with type 2 diabetes (T2D) and established atherosclerotic cardiovascular disease (ASCVD) despite contemporary therapies [1]. Two drug classes – GLP-1 receptor agonists (GLP-1 RAs) and sodium–glucose co-transporter-2 inhibitors (SGLT2I) have reshaped cardiometabolic care, lowering major adverse cardiovascular events (MACE) and heart-failure hospitalisation (HF-H) and gaining Class I recommendations in ADA, ESC and KDIGO guidelines [2–4]. Mechanistically, GLP-1 RAs drive weight loss, endothelial benefits and anti-inflammatory effects [5], while SGLT2I provide natriuresis, haemodynamic unloading and renal protection [6]. Uptake of concomitant therapy remains low due to uncertainty about incremental benefit and sequencing.

Objective

To quantify the cardiovascular (3-point MACE) and renal benefits of combination of GLP-1 receptor agonists and sodium–glucose co-transporter-2 inhibitors therapy compared with either drug class alone in adults with ASCVD ± CKD, using 2023–2025 evidence.

Studies used were: nationwide cohorts (UK CPRD [5]; China ACS [6]; US claims [7]) and SGLT2I - GLP-1RA meta-analysis [8], SMART-C meta-analysis [9] SGLT2I meta-analysis [10], SOUL prespecified analysis. [11].

2. METHODS

The following methods were used: PRISMA 2020 statement [12]. bias in meta analysis [13], Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta analyses [14]. PRISMA-2020 guidance was followed [12]. MEDLINE (Pub Med) and Embase were searched from 1 Jan 2023 to 30 Jun 2025 using controlled vocabulary and free text for GLP-1 RA, SGLT2I, combination/dual/add-on, and cardiovascular terms (major adverse cardiovascular events, myocardial infarction (MI), stroke, heart failure (HF)). No language limits were applied; reference lists and guidelines were hand-searched.

Eligibility (PICO). Population: adults with T2D and established ASCVD ± CKD. Intervention: concomitant GLP-1 RA + SGLT2I. Comparator: either agent alone. Outcomes: primary – 3-point MACE (cardiovascular (CV) death, non-fatal MI, non-fatal stroke); secondary – HF hospitalisation, composite renal outcome. Designs: randomised trials, prespecified trial sub-analyses, registries (≥200 dual-therapy users) and contemporary systematic reviews.

Strata. Evidence was analysed in three a-priori strata: (A) add SGLT2I to background GLP-1 RA; (B) add GLP-1 RA to background SGLT2I; (C) head-to-head registries where background therapy was not predefined.

Data extraction and bias assessment. Two reviewers independently extracted effect sizes (HR or RR) with 95% CIs, follow-up, and baseline characteristics. Randomised data were appraised with RoB 2; registries with Newcastle–Ottawa Scale [14]. Disagreements were resolved by consensus.

Statistical synthesis. Log-transformed effect estimates were pooled within each stratum using a DerSimonian–Laird random-effects model. Because included studies reported both HRs and RRs, we pooled like-for-like within each stratum and avoided cross-stratum pooling to prevent comparator and metric heterogeneity. Heterogeneity was quantified by τ^2 and I^2; publication bias was explored visually with funnel plots [13].

3. RESULTS

Search flow is illustrated in PRISMA diagram (Table 1). Six studies met inclusion criteria: three registries, one prespecified RCT subgroup, one collaborative RCT meta-analysis, and one systematic review/meta-analysis.

Table 1. PRISMA 2020 flow diagram

Identification	
Records identified from databases	n = 77
Records removed before screening	Duplicate records removed (n = 0)
Records screened	n = 77
Records excluded	n = 45
Screening	
Reports sought for retrieval	n = 32
Reports not retrieved	n = 0
Eligibility	
Reports assessed for eligibility:	n = 32
Reports excluded with reasons:	n = 26 No dual-vs-mono comparison No cardiovascular outcome Insufficient outcome data
Included	
Total studies included in review:	(n = 6) Registries (n = 3) RCT subgroup (n = 1) Collaborative RCT meta-analysis (n = 1) Systematic review/meta-analysis (n = 1)

Study characteristics. ≈47 600 participants received dual therapy and ≈154 700 received monotherapy. Mean age 62–67 years; baseline HbA1c 7.8–8.5%. ASCVD was present in ≥85%; CKD stage ≥3 in ~30–40%. Follow-up spanned 1.0–4.0 years.

Stratum C – head-to-head registries. Three nationwide cohorts (UK CPRD [5]; China ACS [6]; US claims [7]) directly compared combination therapy with either monotherapy. The pooled random-effects HR for 3-point major adverse cardiovascular events was 0.60 (0.50–0.72); I^2 = 12%. Heterogeneity was low and likely

reflects differences in comparator class (GLP-1-only vs SGLT2i-only arms) and follow-up duration.

Stratum A – adding an SGLT2 inhibitor to background GLP-1 RA. The SMART-C collaborative meta-analysis [9] and CPRD 'GLP-1-first' cohort showed consistent incremental benefit; pooled RR for 3-point MACE was 0.64 (0.46–0.90).

Stratum B – adding a GLP-1 RA to background SGLT2I. In the SOUL [11] prespecified subgroup of baseline SGLTI users, oral semaglutide reduced 3-point MACE numerically (HR 0.89, 0.71–1.11) versus placebo; the reciprocal CPRD cohort showed HR 0.71 (0.52–0.98). Pooled HR was 0.89 (0.71–1.11).

Supportive systematic review. A 2025 RCT-rich meta-analysis reported a 43% major adverse cardiovascular events reduction vs SGLT2I monotherapy (RR 0.57, 0.38–0.86) and a 23% reduction vs GLP-1 RA monotherapy (RR 0.77, 0.65–0.91), reinforcing the registry findings.

Renal and heart-failure outcomes. Combination therapy reduced composite renal events by roughly one-third vs either monotherapy across studies reporting renal outcomes. HF-hospitalisation data were fewer but directionally favourable [10].

Safety: Serious-adverse-event rates were similar between groups in RCT/meta data. Gastrointestinal intolerance with GLP-1 RAs is common early and usually mitigated by slower titration; SGLT2i-related genital mycotic infections were managed with standard therapy. Safety data are consistent with ADA guidance and trial reports.

Study characteristics and key outcomes are summarised in Table 2.

Table 2: Study characteristics and key outcomes

Study	Year	Design	Comparator	Population note	Effect (3-point MACE)	95% CI	Follow-up (y)
UK CPRD [5]	2024	Registry	Either monotherapy	Dual-therapy users n=6,696; comparators n=8,942	HR 0.70	0.49–0.99	2.6
ACS China [6]	2025	Registry PS-matched	SGLT2I alone	After ACS; 208 vs 208	HR 0.69	0.49–0.98	1.0
US claims [7]	2025	Registry (entropy-balanced)	SGLT2I alone	Dual n=34,690; mono n=130,220	HR 0.54	0.50–0.59	1.5
SMART-C [9]	2024	Collabo-rative meta-analysis of RCTs	GLP-1 RA alone (placebo in SGLT2 arm)	Baseline GLP-1 RA users across 12 RCTs n=3,065	HR 0.81	0.63–1.03	NR
SOUL prespecified subgroup [11]	2025	RCT subgroup	SGLT2i alone (placebo in GLP-1 arm)	Baseline SGLT2i users: sema n=1,296; placebo n=1,300	HR 0.89	0.71–1.11	4.0
meta-analysis [8]	2025	Systematic review/meta-analysis	Vs SGLT2I / vs GLP-1 RA	5 RCTs + 10 post-hoc + 1 cohort	RR 0.57 / 0.77	0.38–0.86 / 0.65–0.91	—

4. Mechanistic Synergy

Semaglutide is a GLP-1 [15-17] agonist, and empagliflozin is a SGLT-2 inhibitor [15,16]. GLP-1 receptor agonists reduce weight, improve endothelial function, and lower inflammatory markers. Sodium–glucose co-transporter-2 inhibitors induce natriuresis, reduce preload/after-load, and improve renal haemodynamics. Pre-clinical models of combined therapy show additive improvements in diastolic stiffness and renal cortical oxygenation [18]. In human physiology work, co-administration preserves GLP-1-mediated gastrointestinal effects while augmenting natriuresis and improving inflammatory profiles. These non-overlapping pathways provide biological plausibility for the ~40% 3-point major adverse cardiovascular events reduction observed in registries.

5. Clinical Translation

Prioritise early dual initiation in atherosclerotic cardiovascular disease and type 2 diabetes patients with either CKD ≥3, HFpEF, BMI ≥35 kg/m², or recurrent/high atherothrombotic risk. Sequence by phenotype (GLP-1-first for obesity/HFpEF/ atherothrombosis; SGLT2-first for CKD/HF/volume) must be done and the and addind of the second agent after ~4 weeks is needed, if stable. During of a 32-week randomized trial it has been observed that empagliflozin and semaglutide exert separate and combined effects on vascular function [15] and influense kidney oxygenation

and perfusion in type 2 diabetes [16]. Therapy must start with standard doses (e.g., empagliflozin 10 mg daily; semaglutide 0.25 mg weekly and uptitrate). Blood pressure, weight, eGFR at baseline, 4 and 12 weeks must be monitored. The adjustment of diuretics and insulin/sulfonylureas is needed. SGLT2i during acute illness or peri-major surgery must be holded; resume when eating and hydrated.

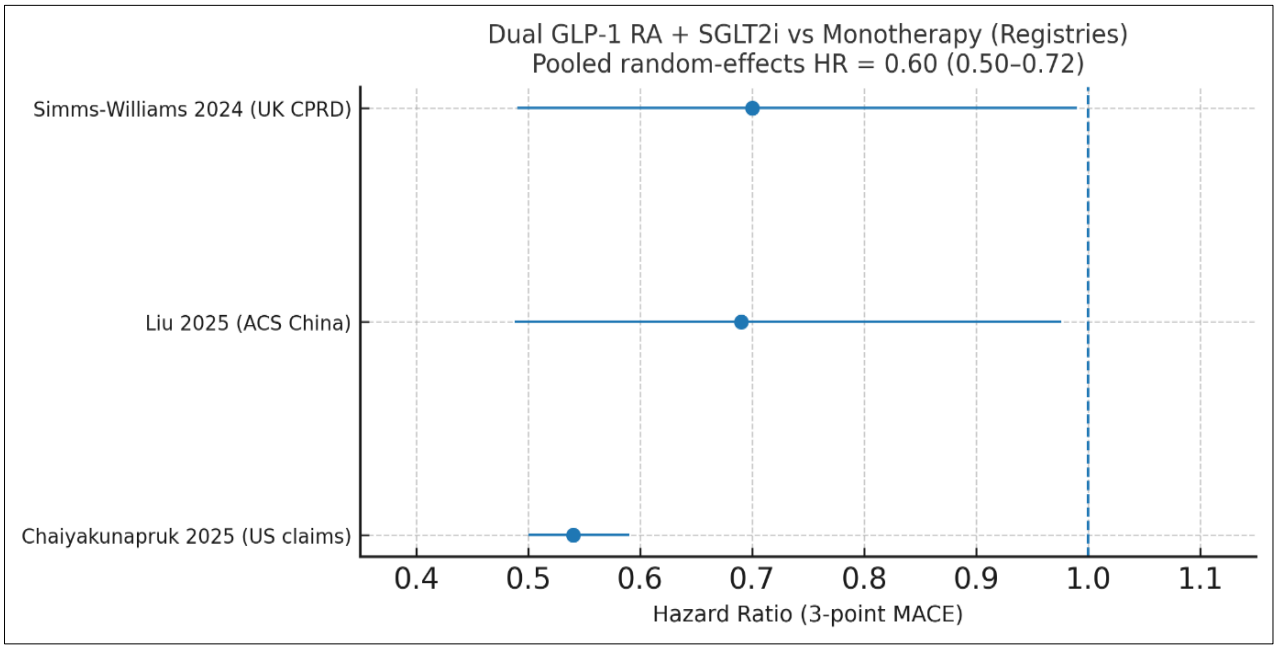

Figure 1: presents forest plot (direct head-to-head registries - dual-therapy with GLP-1 receptor agonists (GLP-1 RAs) and sodium–glucose co-transporter-2 inhibitors (SGLT2I) vs monotherapy

6. DISCUSSION

Across three head-to-head registries, dual GLP-1 receptor agonists and sodium–glucose co-transporter-2 inhibitors therapy reduced 3-point major adverse cardiovascular events with a pooled HR of 0.60 (95% CI 0.50–0.72). Two incremental-addition strata were directionally consistent. An randomized clinical trial (RCT)-rich systematic review corroborated these magnitudes. Biological plausibility is strong given complementary mechanisms. Key limitations include lack of a dedicated factorial RCT, residual confounding in registries, fewer HF outcomes, and potential publication bias.

Clinical implications include a reasonable case for early dual initiation in very-high-risk atherosclerotic cardiovascular disease and type 2 diabetes phenotypes, delivered via staggered starts and routine monitoring. Research priorities include factorial trials of combination vs monotherapy, sequence trials, implementation strategies to improve uptake, and cost-effectiveness analyses. GLP-1 receptor agonists possess beneficial effect for ASCVD risk reduction in type 2 diabetes [17].

7. CONCLUSION

In adults primarily with atherosclerotic cardiovascular disease and type 2 diabetes many with CKD - concomitant GLP-1 receptor agonists and sodium–glucose co-transporter-2 inhibitors therapy provides additional cardiovascular protection beyond either agent alone, with acceptable tolerability. Pending definitive trials, prioritising early dual therapy in highest-risk phenotypes with careful sequencing and monitoring is reasonable.

Abbreviations

ASCVD: atherosclerotic cardiovascular disease
CV: cardiovascular
GLP-1 RAs GLP-1: receptor agonists
HF-H: heart-failure hospitalisation
MACE: major adverse cardiovascular events (MACE)
MI: myocardial infarction
SGLT2I: sodium–glucose co-transporter-2 inhibitors
T2D: type 2 diabetes (T2D

Additional information

Conflict of interest: The authors have declared that no competing interests exist.

Ethical statements

- The authors declared that no clinical trials were used in the present study.
- The authors declared that no experiments on humans or human tissues were performed for the present study.
- The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.
- The authors declared that no experiments on animals were performed for the present study.

- The authors declared that no commercially available immortalized human and animal cell lines were used in the present study

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Data availability

All of the data that support the findings of this study are available in the main text or Supplementary Information.

REFERENCES

1. American Diabetes Association Professional Practice Committee. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes – 2025. Diabetes Care. 2025;48(Suppl 1): S181–S206. doi:10.2337/dc25-S009.
2. Cosentino F, Grant PJ, Aboyans V, *et al.,*2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. European Heart Journal. 2020;41(2):255–323. doi:10.1093/eurheartj/ehz486.
3. KDIGO Diabetes Work Group. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney International. 2022;102(5S): S1–S127. doi: 10.1016/j.kint.2022.06.008.
4. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic review. Cardiovascular Diabetology. 2018; 17:83. doi:10.1186/s12933-018-0728-6.
5. Simms-Williams N, Treves N, Yin H, *et al.,*Combination GLP-1 RA + SGLT2I and cardiovascular/renal outcomes: population-based cohort. BMJ. 2024;385:e078242. doi:10.1136/bmj-2023-078242.
6. Liu T, Fan Z, Li Y, *et al.,*Combination SGLT2I + GLP-1RA and MACE after ACS. International Journal of Cardiology. 2025; 431:133229. doi: 10.1016/j.ijcard.2025.133229.
7. Chaiyakunapruk N, Tan X, Liang Y, *et al.,*Real-world effectiveness of adding newer-generation GLP-1RA to SGLT2I in T2D. Cardiovascular Diabetology. 2025; 24:177. doi:10.1186/s12933-025-02737-1.
8. Zhang M, Lin C, Cai X, *et al.,*One or two? Combo vs monotherapy with SGLT2I or GLP-1RA: meta-analysis. Diabetes, Obesity and Metabolism. 2025;27(2):806–815. doi:10.1111/dom.16078.
9. Apperloo EM, Neuen BL, Fletcher RA, *et al.,*SGLT2 inhibitors with and without GLP-1 RA: SMART-C meta-analysis. The Lancet Diabetes & Endocrinology. 2024;12(8):545–557. doi:10.1016/S2213-8587(24)00155-4.
10. Neuen BL, Fletcher RA, Heath L, *et al.,*GLP-1 RA outcomes with and without SGLT2I: systematic review and meta-analysis. Circulation. 2024;150(22):1781–1790. doi:10.1161/CIRCULATIONAHA.124.071689.
11. Marx N, Deanfield JE, Mann JFE, *et al.,*Oral semaglutide and CV outcomes by SGLT2i use: SOUL prespecified analysis. Circulation. 2025;151(23):1639–1650. doi:10.1161/CIRCULATIONAHA.125.074545.
12. Page MJ, McKenzie JE, Bossuyt PM, *et al.,*PRISMA 2020 statement. BMJ. 2021;372: n71. doi:10.1136/bmj. n71.
13. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple test. BMJ. 1997; 315:629–634. doi:10.1136/bmj.315.7109.629.
14. Wells GA, Shea B, O'Connell D, *et al.,*The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute. 2013.
15. Vernstrøm L, Gullaksen S, Sørensen SS, *et al.,*Separate and combined effects of empagliflozin and semaglutide on vascular function: a 32-week randomized trial. Diabetes, Obesity and Metabolism. 2024;26(5):1624–1635. doi:10.1111/dom.15464.
16. Gullaksen S, Vernstrøm L, Sørensen SS, *et al.,*Combined semaglutide and empagliflozin: kidney oxygenation and perfusion in T2D. Diabetologia. 2023;66(5):813–825. doi:10.1007/s00125-023-05876-w.
17. Marx N, Husain M, Lehrke M, Verma S, Sattar N. GLP-1 RAs for ASCVD risk reduction in T2D. Circulation. 2022;146(24):1882–1894. doi:10.1161/CIRCULATIONAHA.122.059595.
18. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: state-of-the-art review. Diabetologia. 2018;61(10):2108–2117. doi:10.1007/s00125-018-4670-7.