

Review

Semaglutide across cardiovascular and kidney outcome trials: a systematic review and stratified synthesis

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Abstract

Semaglutide outcome trials span distinct cardiometabolic populations and endpoint hierarchies, complicating a single pooled interpretation. We synthesized cardiovascular and kidney evidence using prespecified clinical strata. Following PRISMA 2020 and SWiM (PROSPERO CRD420261441534), we included phase 3 randomized, double-blind, placebo-controlled cardiovascular or kidney outcome trials of oral or subcutaneous semaglutide. PubMed/MEDLINE, CENTRAL, ClinicalTrials.gov and WHO ICTRP were searched through 15 July 2026. Risk of bias was assessed with RoB 2 and certainty with GRADE. Within the type 2 diabetes cardiovascular stratum, MACE hazard ratios were combined by inverse-variance common-effect meta-analysis; no estimates were pooled across strata. Five trials (37,267 participants) were included: SUSTAIN-6, PIONEER-6, SOUL, SELECT and FLOW. The type 2 diabetes MACE summary was 0.83 (95% CI 0.76–0.92; $I^2=0\%$). SELECT showed a MACE hazard ratio of 0.80 (0.72–0.90), while FLOW showed a primary kidney composite hazard ratio of 0.76 (0.66–0.88). Semaglutide reduced cardiovascular events in type 2 diabetes and obesity without diabetes and kidney events in type 2 diabetes with chronic kidney disease. Stratified interpretation preserves clinically important differences across trial populations and endpoint hierarchies.

Keywords: type 2 diabetes mellitus, obesity, GLP-1 receptor agonists, major adverse cardiovascular events, chronic kidney disease, cardiorenal risk

Introduction

Cardiovascular disease and chronic kidney disease remain leading causes of morbidity and mortality in people with type 2 diabetes, obesity, and cardiometabolic disease, and substantial residual risk persists despite contemporary risk-factor management [1–3]. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have evolved from glucose-lowering agents into therapies with cardiovascular and kidney benefits [4–8].

Semaglutide, available in subcutaneous and oral formulations, has been evaluated in a series of large randomized placebo-controlled outcome trials: SUSTAIN-6 and PIONEER-6 (cardiovascular safety/non-inferiority trials in type 2 diabetes), SOUL (a car-

diovascular superiority trial of oral semaglutide in high-risk type 2 diabetes), SELECT (a cardiovascular superiority trial in obesity without diabetes), and FLOW (a kidney superiority trial in type 2 diabetes with chronic kidney disease) [9–13].

These trials are clinically related but not interchangeable. They differ in population, formulation and dose, design intent, follow-up duration, background standard of care, and endpoint hierarchy. Recent semaglutide-specific meta-analyses overlap substantially with portions of this evidence base: Tan et al. pooled cardiovascular outcomes from four trials in type 2 diabetes and compared oral with subcutaneous formulations, whereas Marzano et al. synthesized mortality, cardiovascular and kidney outcomes across a broader



cardio-kidney-metabolic spectrum [14, 15]. The present review therefore does not claim novelty from the type 2 diabetes pooled MACE estimate itself. Its purpose is to preserve trial primary-endpoint hierarchy and separate clinically distinct evidence strata rather than generate a universal semaglutide effect estimate.

We therefore conducted a systematic review with stratified evidence synthesis. Cardiovascular outcome trials in type 2 diabetes were synthesized within one stratum, while SELECT and FLOW were retained as stand-alone strata because they address different populations and primary endpoints. This framework is intended to provide a clinically interpretable map of what can reasonably be combined and what should remain trial-specific.

Material and methods

Protocol, registration, and reporting

The review was conducted according to a protocol prepared following PRISMA-P [16] and registered in PROSPERO before formal data extraction and analysis. Reporting follows PRISMA 2020 [17] and, for structured synthesis, the Synthesis Without Meta-analysis (SWiM) guideline [18]. This is a pre-analysis, not a pre-evidence, protocol: the eligible trials were already published, a limitation acknowledged transparently.

Eligibility criteria

Eligible studies were published phase 3 randomized, double-blind, placebo-controlled cardiovascular or kidney outcome trials of semaglutide (oral or subcutaneous) versus placebo plus standard of care, in adults, reporting adjudicated clinical events. Observational studies, non-randomized and single-arm studies, reviews, conference abstracts without full publication, and trials of other GLP-1 RAs without a dedicated semaglutide arm were excluded. Post hoc, pooled, and secondary analyses were used only to clarify definitions, not as independent studies.

Information sources and search

PubMed/MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, and WHO ICTRP were searched from inception to 15 July 2026, supplemented by reference-list screening. A concept-based strategy was combined with a trial-acronym sensitivity strategy. Embase was not searched

because it was not accessible to the review team. CENTRAL was searched as a supplementary source, but bulk export was unavailable and its records could not be incorporated into the automated deduplication workflow. Search reporting follows PRISMA-S [19].

Study selection and data extraction

Two reviewers independently screened records and full texts against the eligibility criteria, with disagreements resolved by discussion or a third reviewer; selection is summarized in a PRISMA 2020 flow diagram. Two reviewers independently extracted trial design, population, formulation and dose, follow-up, endpoint definitions and hierarchy, event counts, hazard ratios (HRs) with 95% confidence intervals (CIs), safety outcomes, and sponsor involvement, using primary publications as the main source and supplements/registries for clarification. No individual participant data were requested or reconstructed.

Outcomes and endpoint harmonization

Co-primary outcomes were defined by stratum: 3-point MACE (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) for the T2D CVOT stratum and for SELECT, and the trial primary kidney composite for FLOW. Composite outcomes were not pooled solely because they shared a label; components and endpoint role were checked trial by trial. FLOW MACE was treated only as supportive cardiovascular evidence and was not pooled with the T2D CVOT MACE stratum.

Statistical analysis

The unit of synthesis was the prespecified evidence stratum defined in Section 2.5; no analysis pooled estimates across strata. The principal effect measure was the hazard ratio (HR) with its 95% confidence interval (CI) as reported in each trial's primary publication. For quantitative handling within a stratum, HRs and CIs were transformed to the log scale, and the standard error of each log-HR was derived from the reported CI as $(\ln[\text{upper limit}] - \ln[\text{lower limit}]) / (2 \times 1.96)$ [20]. No individual participant data were used and no event-level data were reconstructed; all analyses relied exclusively on published aggregate estimates.

For the type 2 diabetes cardiovascular outcome-trial stratum (SUSTAIN-6, PIONEER-6, SOUL), trial-level log-HRs for 3-point MACE were combined using

inverse-variance common-effect meta-analysis [18]. This within-stratum analysis was prespecified and was not extended across the obesity or chronic kidney disease strata. Because SOUL is substantially larger than SUSTAIN-6 and PIONEER-6, individual trial weights are reported to make its influence on the summary estimate explicit.

Between-trial consistency within this stratum was characterized descriptively using Cochran's Q statistic and the I^2 index, interpreted only as exploratory indicators of directional and magnitude consistency and not as a decision rule for whether to pool [21]. Both statistics have low power and wide uncertainty when the number of trials is small and were therefore not used to justify a random-effects model or any pooled inference.

The obesity-without-diabetes stratum (SELECT) and the chronic kidney disease stratum (FLOW) each comprised a single eligible trial; their estimates are reported as published trial-level HRs with 95% CIs, and no synthesis, weighting, or adjustment was performed. Consistent with the prespecified plan, the FLOW MACE estimate was reported only as supportive cardiovascular evidence within chronic kidney disease and was not combined with the type 2 diabetes cardiovascular stratum. Effect measures of different types (e.g., hazard ratios and risk ratios) were never combined within the same synthesis.

Secondary and component cardiovascular outcomes, and safety outcomes, were summarized descriptively by trial; they were not pooled, not accorded confirmatory status, and not subjected to multiplicity-controlled testing at the synthesis level, within-trial multiplicity having been governed by each trial's own testing hierarchy. By deliberate prespecification, no cross-population pooled effect, no meta-regression or quantitative subgroup meta-analysis, and no causal-mediation or biomarker-based predictive analysis was undertaken, as such quantities cannot be validly derived from published aggregate outcome data.

All confidence intervals are two-sided at the 95% level. Inverse-variance weights, the within-stratum summary, Cochran's Q, and I^2 were computed with the MAJOR meta-analysis module, which implements the R package metafor [22], within jamovi (version 2.7.37; The jamovi project) [23]. No common summary estimate was calculated across the three clinical strata.

Risk of bias and certainty of evidence

Two reviewers independently assessed risk of bias with the Cochrane RoB 2 tool. Certainty of evidence was assessed with GRADE [24, 25]. Commercial spon-

sorship was recorded explicitly as a potential source of publication or reporting bias, but sponsorship alone was not treated as an automatic downgrading rule. Instead, publication bias was judged at the evidence-stratum level together with trial registration, availability of outcome-trial results, reporting completeness, and the concentration of evidence within a single manufacturer. GRADE indirectness considered population, formulation, dose, design intent, endpoint role, and temporal changes in background therapy between 2016 and 2025.

Results

Study selection and characteristics

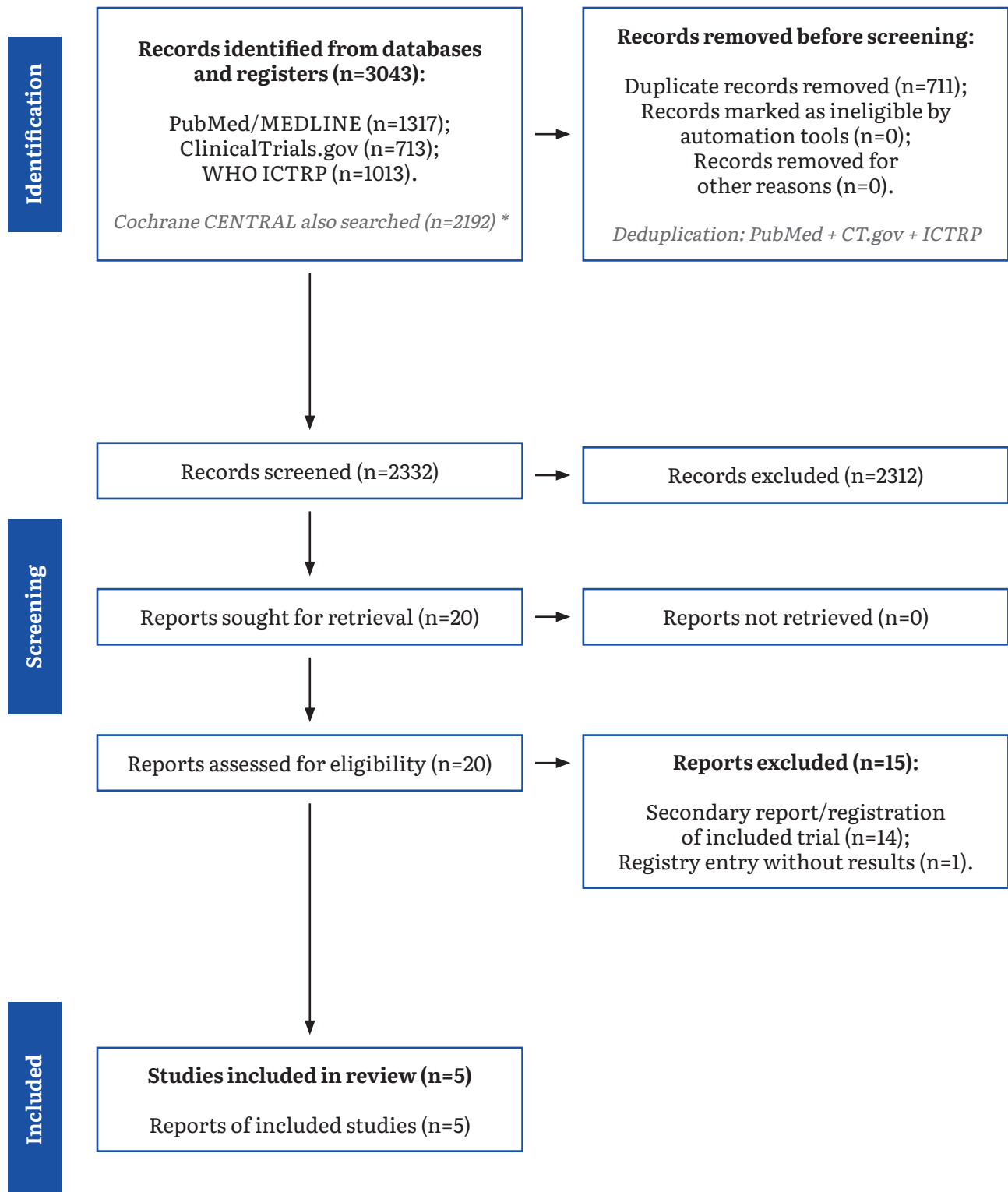
The systematic search and reference screening identified the five eligible phase 3 semaglutide cardiovascular or kidney outcome trials as eligible (Figure 1), comprising 37,267 randomized participants: SUSTAIN-6 [9], PIONEER-6 [10], and SOUL [11] in the type 2 diabetes cardiovascular outcome-trial stratum (16,130 participants), SELECT [12] in obesity without diabetes (17,604 participants), and FLOW [13] in chronic kidney disease (3,533 participants). Trial characteristics are shown in Table 1. All trials were double-blind, placebo-controlled, event-driven, and sponsored by Novo Nordisk; formulations, design intent, and follow-up differed across trials as summarized.

Risk of bias

All five trials were judged at low overall risk of bias on RoB 2 across the domains of randomization, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported result, consistent with large, adjudicated, double-blind designs. This within-trial assessment does not capture the concentration of the entire evidence base in a single commercial sponsor, which is addressed separately under certainty of evidence.

Stratum 1 — Type 2 diabetes cardiovascular outcome trials (3-point MACE)

For 3-point MACE, hazard ratios were 0.74 (95% CI 0.58–0.95) in SUSTAIN-6, 0.79 (0.57–1.11) in PIONEER-6, and 0.86 (0.77–0.96) in SOUL (Figure 2, Table 2). The inverse-variance common-effect summary was 0.83 (0.76–0.92), with no detectable statistical heterogeneity (Cochran $Q=1.30$, $df=2$, $P=0.52$; $I^2=0\%$). SOUL contributed 76.4% of the inverse-variance weight (SUSTAIN-6



* Cochrane CENTRAL was searched (n=2192) but records were not exported (access restriction) and overlap substantially with MEDLINE. Deduplication was performed by reproducible record linkage (matching on registry identifier or normalized title).

Reference-list (citation) searching of included trials and relevant reviews identified no additional eligible studies (n=0 via other methods).

Figure 1: PRISMA 2020 flow diagram of study identification, screening, and inclusion. Deduplication was performed across exportable records from PubMed, ClinicalTrials.gov, and WHO ICTRP. CENTRAL was searched (n=2192), but bulk export was unavailable and CENTRAL records were therefore not included in the automated deduplication count.

Table 1: Characteristics of included trials.

Trial	Stratum	Population/ formulation	Design (intent)	N (sema/placebo); follow-up	Primary endpoint
SUSTAIN-6 (2016)	1 · T2D CVOT	T2D, high CV risk; SC 0.5/1.0 mg weekly	Phase 3, CV safety/ non-inferiority	3297 (1648/1649); 2.1 y	3-point MACE
PIONEER-6 (2019)	1 · T2D CVOT	T2D, high CV risk; oral 14 mg daily	Phase 3, CV safety/ non-inferiority	3183 (1591/1592); 1.3 y	3-point MACE
SOUL (2025)	1 · T2D CVOT	T2D+ASCVD and/or CKD; oral 14 mg daily	Phase 3, CV superiority	9650 (4825/4825); 49.5 mo	3-point MACE
SELECT (2023)	2 · Obesity, no diabetes	Overweight/ obesity+CVD, no diabetes; SC 2.4 mg weekly	Phase 3, CV superiority	17604 (8803/8801); 39.8 mo	3-point MACE
FLOW (2024)	3 · CKD kidney	T2D+CKD; SC 1.0 mg weekly	Phase 3, kidney superiority	3533 (1767/1766); 3.4 y	Major kidney disease event (5-component)

Note: SC – subcutaneous; MACE – major adverse cardiovascular events.

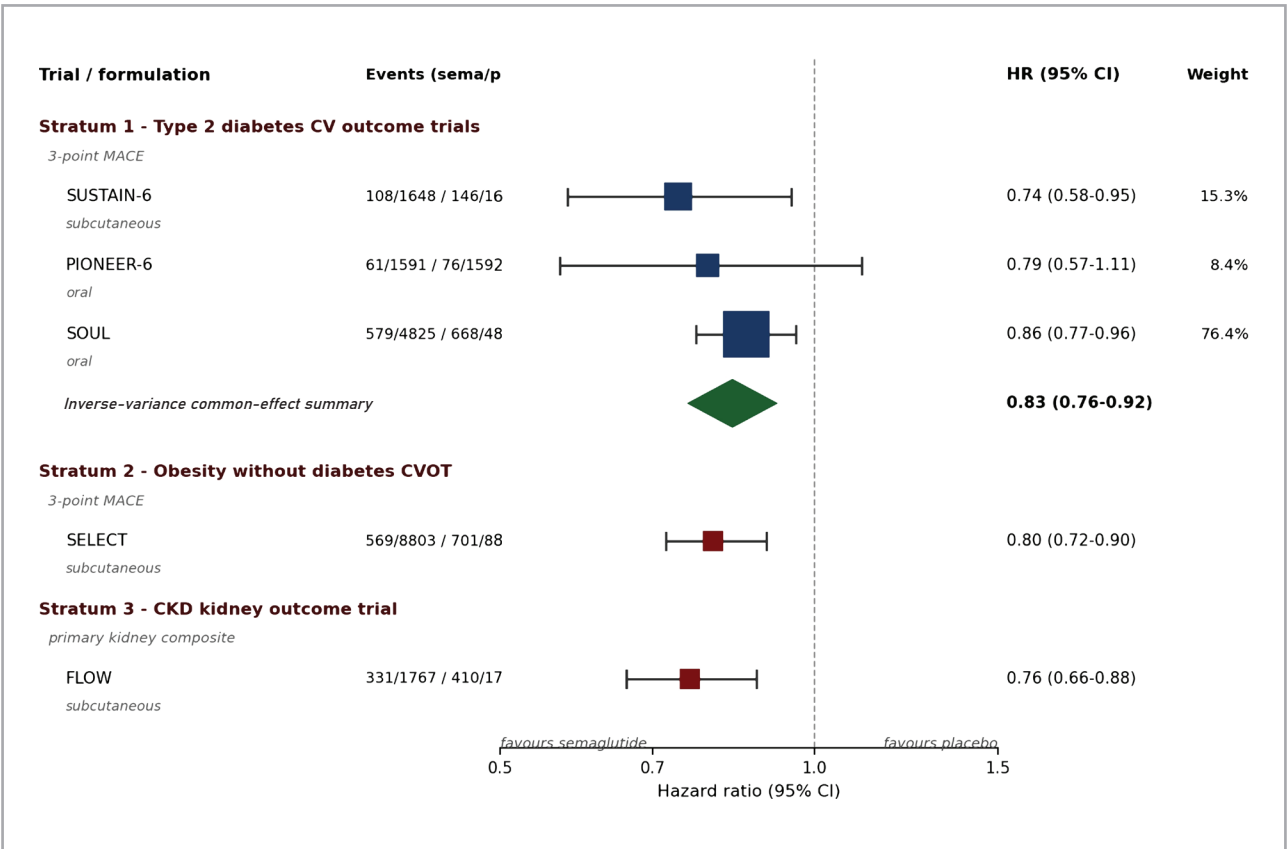


Figure 2: Stratified presentation of semaglutide versus placebo across prespecified evidence strata. Hazard ratios (95% CI) are shown for 3-point MACE in the type 2 diabetes cardiovascular outcome trials (SUSTAIN-6, PIONEER-6, SOUL), together with the within-stratum inverse-variance common-effect summary; for 3-point MACE in SELECT (obesity without diabetes); and for the primary kidney composite in FLOW (chronic kidney disease). Estimates are not pooled across strata.

Table 2: Co-primary and selected secondary outcomes by stratum.

Trial	Outcome	HR (95% CI)	Events sema/placebo	Endpoint role
SUSTAIN-6	3-point MACE	0.74 (0.58–0.95)	108/146	Primary (NI)
PIONEER-6	3-point MACE	0.79 (0.57–1.11)	61/76	Primary (NI)
SOUL	3-point MACE	0.86 (0.77–0.96)	579/668	Primary (superiority)
Stratum 1	MACE — IV common-effect summary	0.83 (0.76–0.92)	748/890	Within-stratum meta-analysis
SELECT	3-point MACE	0.80 (0.72–0.90)	569/701	Primary (superiority)
FLOW	Major kidney disease event	0.76 (0.66–0.88)	331/410	Primary (superiority)
FLOW	MACE	0.82 (0.68–0.98)	—	Confirmatory secondary

Note: SC – subcutaneous; NI – non-inferiority; MACE – major adverse cardiovascular events; HR – hazard ratio; CI – confidence interval. The Stratum 1 estimate is an inverse-variance common-effect summary restricted to the type 2 diabetes cardiovascular outcome-trial stratum; no estimate is pooled across clinical strata.

15.3%, PIONEER-6 8.4%), so the summary is driven primarily by the largest superiority trial. The direction of effect was concordant across all three trials despite differences in formulation and design intent.

Among components and related cardiovascular outcomes reported across the stratum, effects were generally directionally consistent but individually imprecise in the two smaller non-inferiority trials; cardiovascular death showed a notably lower point estimate in PIONEER-6 (0.49, 0.27–0.92) than in SUSTAIN-6 (0.98, 0.65–1.48) or SOUL (0.93, 0.80–1.09), underscoring the instability of component-level estimates in the smaller trials and the need for cautious, non-pooled interpretation. These secondary outcomes are reported descriptively (Table 2) and were not accorded confirmatory status.

Stratum 2 — Obesity without diabetes (SELECT)

In SELECT, semaglutide 2.4 mg reduced 3-point MACE, with a hazard ratio of 0.80 (95% CI 0.72–0.90; 569 vs. 701 events) over a mean follow-up of 39.8 months in patients with overweight or obesity and established cardiovascular disease but without diabetes. As a single large superiority trial in a distinct population, SELECT is reported as a stand-alone co-primary stratum and was not pooled with the type 2 diabetes trials.

Stratum 3 — Chronic kidney disease (FLOW)

In FLOW, semaglutide 1.0 mg reduced the primary major kidney disease composite, with a hazard ratio of 0.76 (95% CI 0.66–0.88; 331 vs. 410 first events) over a median 3.4 years in patients with type 2 diabetes and chronic kidney disease. FLOW also reduced MACE as a confirmatory secondary outcome (0.82, 0.68–0.98); consistent with the prespecified plan, this MACE result is reported only as supportive cardiovascular evidence in chronic kidney disease and was not combined with the type 2 diabetes cardiovascular stratum, because FLOW was designed around a kidney primary endpoint.

Certainty of evidence

Certainty was rated moderate for each co-primary stratum. Risk of bias was low and the co-primary estimates were sufficiently precise; no further downgrade was made for inconsistency or indirectness within the prespecified strata. One level was deducted for suspected publication/reporting bias after domain-level judgment, reflecting the concentration of all eligible outcome-trial evidence within a single manufacturer and the absence of independently sponsored outcome trials. This judgment was not based on sponsorship as an automatic rule. Certainty for secondary and component

outcomes was not rated above that of the corresponding co-primary outcome.

Discussion

In this systematic review of semaglutide cardiovascular and kidney outcome trials, semaglutide reduced cardiovascular events in type 2 diabetes (within-stratum HR 0.83, 95% CI 0.76–0.92) and in obesity without diabetes (SELECT, 0.80, 0.72–0.90), and reduced kidney events in chronic kidney disease (FLOW, 0.76, 0.66–0.88). The direction of benefit was concordant across clinical settings, but no single effect was calculated across these distinct populations and primary endpoints.

The type 2 diabetes summary estimate is not itself novel: it is essentially concordant with the pooled MACE estimate reported by Tan et al. in their semaglutide meta-analysis [14]. This concordance provides an external consistency check rather than a new efficacy signal. The distinguishing feature of the present review is the organization of evidence according to trial population and primary-endpoint hierarchy: SELECT is retained as obesity-without-diabetes cardiovascular evidence, and FLOW is retained primarily as kidney-outcome evidence rather than being folded into a universal cardio-kidney-metabolic estimate. This contrasts with broader semaglutide meta-analyses that intentionally pool across heterogeneous clinical settings [15].

The clinical reading is stratum-specific. In type 2 diabetes, the cardiovascular benefit is anchored by SOUL, which contributes roughly three-quarters of the statistical weight; the smaller non-inferiority trials are directionally concordant but individually imprecise, so the descriptor should be understood as consistent supportive evidence rather than as independent confirmation. In obesity without diabetes and in chronic kidney disease, the evidence rests on one large, rigorous superiority trial each (SELECT and FLOW), and is best interpreted as high-quality single-trial evidence rather than meta-analytic replication.

These stratum-specific findings are consistent with class-level meta-analyses of GLP-1 receptor agonists in type 2 diabetes [7, 8], and complement the distinct cardiorenal mechanism of SGLT2 inhibitors [26–28]. They also sit alongside the broader semaglutide programme in heart failure with preserved ejection fraction [29] and peripheral artery disease [30], and the emergence of dual GIP/GLP-1 receptor agonism, for which the recently reported SURPASS-CVOT trial confirmed car-

diovascular benefit [31, 32]. Contemporary guidelines now position these agents for cardiovascular and kidney protection in type 2 diabetes and chronic kidney disease [3, 33–37].

Strengths and limitations

Strengths include pre-analysis registration, pre-specified strata and endpoint harmonization, duplicate risk-of-bias assessment, and explicit consideration of sponsorship within GRADE. Several limitations must be emphasized. First, the entire eligible evidence base was sponsored by a single manufacturer, which raises a potential publication/reporting-bias concern even though the trials were prospectively registered and at low within-trial risk of bias. Second, the type 2 diabetes summary is dominated by SOUL and should be interpreted alongside the individual trial estimates. Third, registration followed publication of all eligible trials, so prespecification protects the analysis and reporting stages but not prior knowledge of the evidence. Fourth, Embase was not searched, and CENTRAL records could not be exported for automated deduplication; these are search-process limitations. Finally, secondary and safety outcomes were heterogeneous in definition and ascertainment and were treated descriptively.

Conclusion

Across prespecified clinical strata, semaglutide reduced cardiovascular events in type 2 diabetes and obesity without diabetes and reduced kidney events in type 2 diabetes with chronic kidney disease. The type 2 diabetes pooled estimate confirms previously reported findings, while the stratified presentation preserves differences in population, trial intent, and primary-endpoint hierarchy. A single cross-population effect estimate is not reported.

Conflict of interest

The authors declare no conflict of interest.

Data availability

All data analysed in this review are derived from the primary publications of the included trials and their supplementary materials, which are publicly

available. The extracted dataset and analysis files are available from the corresponding author on reasonable request.

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