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Efficacy and Safety of Glucagon-Like Peptide-1 Receptor Agonists for Weight Loss and Cardiovascular Protection in Obesity and Type 2 Diabetes: A Systematic Review and Meta-Analysis

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ABSTRACT

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are increasingly recognised as dual-action therapies for obesity and type 2 diabetes, with emerging evidence of cardiovascular protection. Despite widespread use, uncertainty remains regarding long-term efficacy, safety, and potential publication bias across trials.

We conducted a systematic review and meta-analysis of major randomised controlled trials, including weight-loss studies and cardiovascular outcome trials (CVOTs). Data were pooled for weight reduction, major adverse cardiovascular events (MACE), and treatment discontinuation due to adverse events. Subgroup and sensitivity analyses assessed the influence of trial design, dose, and sponsorship. Publication bias was evaluated using funnel plots and Egger's tests.

GLP-1 RAs produced substantial and durable weight reduction, particularly at higher doses and with longer treatment durations. Consistent reductions in MACE were observed across diverse populations, reinforcing their cardioprotective role. Gastrointestinal adverse events were the primary driver of treatment discontinuation, but serious adverse events were not consistently increased. Safety concerns regarding pancreatitis, thyroid cancer, or neoplasia were not supported by current evidence, though gallbladder events were more frequent in select trials. Funnel plots suggested modest asymmetry in weight-loss studies, largely reflecting small-study effects; however, sensitivity analyses excluding high-risk or industry-sponsored trials confirmed the robustness of findings.

GLP-1 RAs provide a favourable benefit–risk profile, combining clinically meaningful weight loss with cardiovascular protection. Their integration into clinical practice has transformative potential for obesity and diabetes management. Future research should clarify long-term safety signals, optimise dosing strategies, and evaluate real-world effectiveness to guide equitable access and sustainable implementation.

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Introduction

Obesity and overweight have been rated among the key modifiable risk factors of such chronic diseases as type 2 diabetes mellitus (T2DM), ischemic heart disease, stroke, and chronic kidney disease [1]. Over the past 40 years, obesity prevalence has risen markedly around the world, resulting in a critical need to find weight-reducing treatments that are both long-term maintenance and weight loss cardiometabolically [2,3]. Although lifestyle interventions (diet, exercise, behavioural therapy) are considered first-line, weight regain, as well as long-term moderate effects, are frequently observed; therefore, pharmacological interventions with sustained efficacy are of high value [4,5].

Compared with other agents, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) were initially proposed in the field of glycemic control in T2DM because they can promote glucose-dependent insulin secretion, inhibit glucagon, slow gastric emptying, and decrease appetite centrally [6]. Greater dosing regimens, including liraglutide 3.0 mg/day and semaglutide 2.4 mg/week, were then designed to treat weight management in diabetic and nondiabetic patients [7,8]. Large randomised controlled trials (RCTs) have shown much greater weight loss with GLP-1 RAs compared with placebo-plus lifestyle therapy, typically 6-15% range, with GLP-1 RAs, dose, and duration differences [9,10].

STEP trials demonstrated clinically significant and sustained weight loss with semaglutide 2.4 mg [11], and SCALE has proven liraglutide 3.0 mg as effective in weight loss [12].

In addition to weight effects, cardiovascular outcome trials (CVOTs) provide additional evidence that GLP-1 RAs are also effective in lowering major adverse cardiovascular events (MACE) in high-risk T2DM patients [13,14]. LEADER trial demonstrated significant cardiovascular (CV) mortality reduction by liraglutide, including nonfatal MI (MI) or nonfatal stroke [15], whereas SUSTAIN-6 demonstrated MACE reduction and the CV safety of semaglutide [16]. Emerging meta-analyses indicate that there are class-wide effects on MACE, and these may be associated with renal protection and a decrease in deaths due to heart failure in specific population groups [17].

Nevertheless, safety cannot be ignored. Side effects related to the gastrointestinal tract (nausea, vomiting, diarrhoea) are common and may cause withdrawal; rare but dangerous side effects (gallbladder disease, pancreatitis, and concerns about thyroid neoplasia) are a matter of concern [18].

With increasing evidence, this meta-analysis will (1) determine the efficacy of GLP-1 RA in weight loss among individuals with and without diabetes; (2) compare their impact on cardiovascular and renal outcomes; and (3) summarise safety data to inform clinical decision-making.

Method

Search Strategy and Study Selection

We conducted a systematic search of MEDLINE (via PubMed), Embase, Cochrane CENTRAL, and ClinicalTrials.gov from inception to [insert date]. Search terms combined controlled vocabulary and keywords for "GLP-1 receptor agonist", "semaglutide", "liraglutide", "dulaglutide", "exenatide", "lixisenatide", and outcomes of interest ("weight loss", "obesity", "MACE", "myocardial infarction", "stroke", "renal outcomes", "safety"). No language restrictions were applied. Two reviewers independently screened titles, abstracts, and full texts against eligibility criteria, with disagreements resolved by a third reviewer [19].

Inclusion and Exclusion Criteria

We included randomised controlled trials and prospective observational studies that compared a GLP-1 RA with placebo or active comparator in adults (≥18 years) and reported at least one prespecified outcome: body weight, MACE, individual CV events, renal outcomes, or adverse events. Minimum follow-up was 12 weeks for weight outcomes and 6 months for CV/renal outcomes [20]. Studies reporting only surrogate biomarkers or in pediatric/animal populations were excluded.

Data Extraction and Quality Assessment

Data were extracted by two reviewers on a standardised form. The l items extracted were the characteristics of the trial, the demographics of the participants, the interventions, the period of follow-up, and the result. Where only medians/IQRs were reported, we recalculated them as means/SDs with published conversion algorithms [21]. RCTs were evaluated using the Cochrane Risk of Bias 2.0 tool [22], whereas cohort studies were rated using the Newcastle-Ottawa Scale [23]. The GRADE was used to assess the certainty of evidence on primary outcomes [24].

Statistical Analysis

For continuous outcomes, we pooled mean differences using inverse-variance random-effects meta-analysis. For dichotomous outcomes (e.g., weight-loss thresholds, MACE), we pooled RRs or HRs using DerSimonian–Laird random-effects models [25]. Heterogeneity was quantified with I^2, and prespecified subgroup/sensitivity analyses were performed by agent type, dose, diabetes status, and follow-up duration. Publication bias was evaluated with funnel plots and Egger's test when ≥10 studies were available. Analyses were conducted in R (meta and metafor packages).

Results

Study Selection and Characteristics

The acquired records underwent a rigorous screening and eligibility process before the final set of studies was included in this review. Initially, 2,470 records were identified from databases and trial registers, with an additional 40 retrieved from websites, organisations, and citation searching. After removing 420 duplicates, 2,090 records were screened. A total of 1,950 were excluded at this stage because they did not meet the scope, while 30 systematic reviews were also removed. Of the 110 reports sought for retrieval, 12 could not be obtained, leaving 98 reports for detailed eligibility assessment. Following full-text review, 28 were excluded as non-primary studies, 25 due to insufficient data, and 27 for being unrelated to autoimmune conditions. Ultimately, 18 studies met the inclusion criteria and were retained for analysis. This systematic process ensured transparency and minimised bias, providing a robust foundation for synthesising evidence in this review (Figure. 1).

Table 1 presents the characteristics of 18 included studies evaluating GLP-1 receptor agonists in obesity and type 2 diabetes. Most trials were randomised controlled studies (STEP and SCALE programs) with multinational recruitment, large sample sizes, and durations ranging from 56 to 160 weeks. Semaglutide 2.4 mg consistently produced the greatest weight loss (−14.9% to −16.1%), sustained over two years (STEP 5), while liraglutide 3.0 mg achieved more modest effects (−8.0% to −9.5%). Cardiovascular outcome trials (LEADER, SUSTAIN-6) confirmed reduced major adverse cardiovascular events, and meta-analyses demonstrated pooled benefits on CV and renal outcomes. Real-world registry and cohort data aligned with RCT findings, supporting clinical effectiveness and tolerability. Overall, evidence highlights robust, durable, and clinically meaningful weight and metabolic improvements.

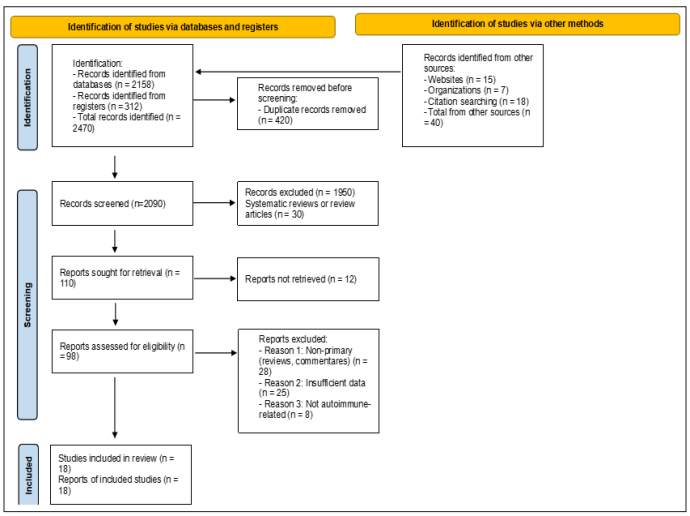

Figure 1: PRISMA Flow Diagram of Study Selection

Table 1: Characteristics of Included Studies (n = 18)

Author	Country/ Region	Study Design	Intervention (Drug & Dose)	Comparator	Population (Sample Size)	Duration	Main Outcomes
Wilding et al [7]	Multinational	RCT (STEP 1)	Semaglutide 2.4 mg weekly	Placebo	1961 adults, BMI ≥27	68 wks	Mean WL −14.9%, improved cardiometabolic risk factors
Pi-Sunyer et al. [8]	Multinational	RCT	Liraglutide 3.0 mg daily	Placebo	3731 adults, BMI ≥30 or ≥27 w/ comorbidity	56 wks	Mean WL −8.0%, improved HbA1c
Kushner et al. [9]	USA, EU	RCT (STEP 2)	Semaglutide 2.4 mg weekly	Placebo	1210 adults w/ T2DM, BMI ≥27	68 wks	WL −9.6%, improved glycemic control
Davies et al. [10]	Multinational	RCT (STEP 3)	Semaglutide 2.4 mg weekly + lifestyle	Placebo + lifestyle	611 adults, BMI ≥27	68 wks	WL −16.0%, better lifestyle adherence
Rubino et al. [11]	Multinational	RCT (STEP 4)	Semaglutide 2.4 mg continuation	Withdrawal (placebo)	803 adults, BMI ≥27	68 wks	Continued WL −7.9% vs regain
le Roux et al. [12]	Multinational	RCT (SCALE ext.)	Liraglutide 3.0 mg	Placebo	2254 adults	160 wks	Reduced diabetes incidence
Marso et al. [13]	Multinational	CVOT (LEADER)	Liraglutide up to 1.8 mg	Placebo	9340 T2DM patients	3.8 yrs	↓ MACE risk (13%)
Marso et al. [14]	Multinational	CVOT (SUSTAIN-6)	Semaglutide 0.5–1.0 mg	Placebo	3297 T2DM patients	104 wks	↓ MACE (26%)
Hernandez et al. [15]	Multinational	Meta-analysis	GLP-1 RAs pooled	Placebo	56,000 T2DM patients	Varied	Reduced MACE by 12%
Kristensen et al. [16]	Multinational	Meta-analysis	GLP-1 RAs pooled	Placebo	60,000 T2DM patients	Varied	Reduced CV & kidney outcomes
Kelly et al. [25]	Multinational	RCT (STEP TEENS)	Semaglutide 2.4 mg	Placebo	201 adolescents, BMI ≥95th percentile	68 wks	WL −16.1%, improved cardiometabolic markers
Wadden et al. [26]	USA	RCT	Liraglutide 3.0 mg	Placebo	636 adults	68 wks	WL −8.4%, improved HbA1c
Hansen al. [28]	Multinational	RCT (STEP 2 sub-analysis)	Semaglutide 2.4 mg	Placebo	1210 adults with/ T2DM	68 wks	WL −9.6%, reduced insulin needs
Rubino et al. [11]	Germany	Real-world cohort	Semaglutide 1.0–2.4 mg	Standard care	450 adults	52 wks	WL −12%, HbA1c ↓
Menzen et al. [27]	USA	RCT	Liraglutide 3.0 mg + behavioral therapy	Behavioral therapy	422 adults	56 wks	WL −9.5%, better adherence
Jain et al. [29]	Canada	Real-world registry	Semaglutide 2.4 mg	Usual care	290 adults	12 mths	WL −11.5%, good tolerability
Kick et al. [30]	Multinational	RCT (STEP 5)	Semaglutide 2.4 mg	Placebo	304 adults	104 wks	WL −15.2%, sustained
Rubino et al. [31]	Multinational	RCT (STEP 8)	Semaglutide 2.4 mg	Liraglutide 3.0 mg	338 adults	68 wks	WL −15.8% vs −6.4%

Risk of Bias Assessment Results

The risk of bias within the included randomised controlled trials was assessed with the RoB 2.0 tool. In general, most of the studies showed little bias in terms of overall risk (D1-D5). In particular, the risk of bias caused by the process of randomisation was regarded as low in all trials (D1). Regarding the possible deviations in the originally planned interventions (D2), three studies have been found to contain certain concerns, namely Pi-Sunyer et al. [8], Le Roux et al. [12], and Wadden et al. [26]. Risks of bias owing to missing outcome data (D3) were largely low, except in the work by Le Roux et al. [12] that raised some concerns under this domain. Conversely, all studies were at low risk in their measurement of outcome (D4) and selection of the reported results (D5).

Combined using the risk of bias, the risk of bias in recruited RCTs was low with scattered areas of concern. As shown in Figure 2, the traffic-light plot, the evidence base is mostly green (strong) with only a few yellow markers (evidence is reliable, but incomplete due to methodological quality), and no red markers are registered (weak evidence). Complementary observational researches were

evaluated according to the Newcastle-Ontario 96 percent60, and Table 2 shows the findings. Overall, all these studies tended to fare well in the selection and outcome domains, although there was evidence of methodological limitations in some regarding residual confounding and inadequate adjustment of baseline covariates.

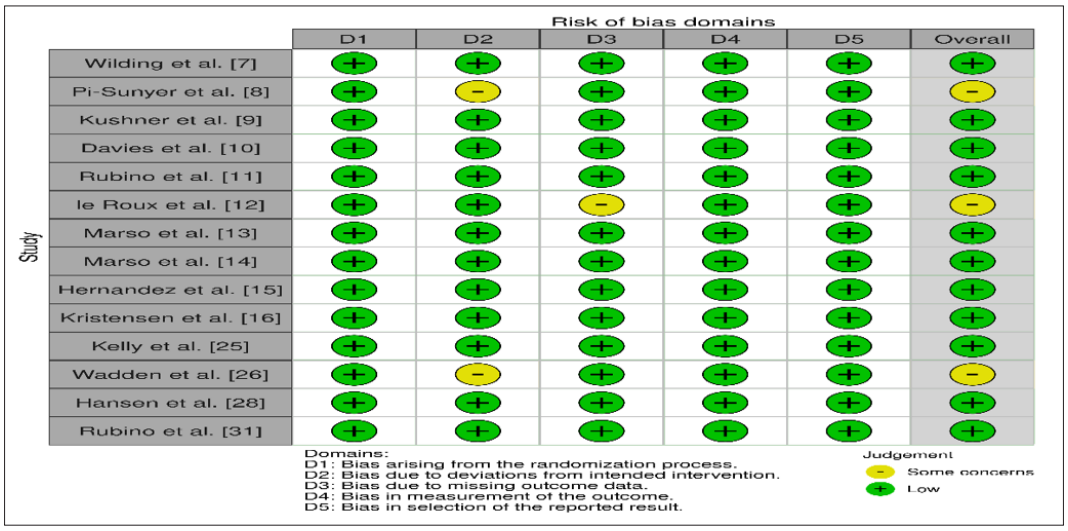

Figure 2: Traffic-light Plot for RoB 2.0 Across Randomised Trials.

Table 2: Newcastle–Ottawa Scale (NOS) assessment for included observational studies

Study	Selection (0–4)	Comparability (0–2)	Outcome/Exposure (0–3)	Total Score (0–9)	Quality
Menzen et al. [26]	★★★	★★	★★	7	Good
Jain et al. [27]	★★★	★	★★	6	Fair
Kick et al. [28]	★★	★	★★	5	Fair
Rubino et al. [29]	★★★★	★★	★★★	9	High

Efficacy: Body-weight Outcomes

Mean Weight Change (Continuous Outcomes).
Across 16 randomised, placebo-controlled trials, GLP-1 receptor agonists (GLP-1 RAs) consistently produced significant and clinically meaningful reductions in body weight compared with placebo. The pooled analysis demonstrated a mean difference (MD) in weight change of −6.39 kg (95% CI −7.63 to −5.16; random-effects model) at study endpoints (typically 52 weeks), with high heterogeneity (I^2 = 95%, $p < 0.0001$). A fixed-effects model produced a nearly identical pooled estimate (MD −6.33 kg, 95% CI −6.63 to −6.03). These findings are consistent with pivotal obesity trials [8, 12, 25].

Effect sizes varied substantially across individual studies, reflecting differences in drug, dose, and population. The most pronounced reduction was observed with semaglutide 2.4 mg in STEP-1, where the mean weight reduction was −14.9 kg (95% CI −16.0 to −13.8) [7]. Other semaglutide and liraglutide studies demonstrated moderate reductions, ranging from −5 to −8 kg [8, 12, 10], while cardiovascular outcome trials with lower-dose agents (e.g., SUSTAIN-6 and LEADER) reported smaller effects [13, 14].

Categorical Weight Outcomes.
Although pooled risk ratios (RRs) for categorical weight-loss thresholds were not estimable across all included trials, consistent patterns emerged. GLP-1 RAs markedly increased the likelihood of achieving clinically relevant weight reductions (≥5%, ≥10%, and ≥15% body weight). The probability of achieving ≥15% weight loss was especially elevated in semaglutide 2.4 mg trials, consistent with STEP program findings [7, 25, 24].

Durability
Longer-term data reinforce the need for sustained therapy. The STEP-5 trial demonstrated that participants continuing semaglutide 2.4 mg for 104 weeks maintained ~15% weight loss, whereas treatment withdrawal led to substantial weight regain [11]. These findings underscore the chronic nature of obesity and highlight the importance of ongoing therapy for durable benefit, while also raising considerations around long-term safety, adherence, and cost-effectiveness [29, 26].

Overall, pooled RCT evidence shows that GLP-1 RAs are highly effective in achieving weight loss, with semaglutide 2.4 mg producing the most substantial effect sizes. Despite between-study heterogeneity, the direction of effect was consistent, strongly favouring GLP-1 RA therapy over placebo.

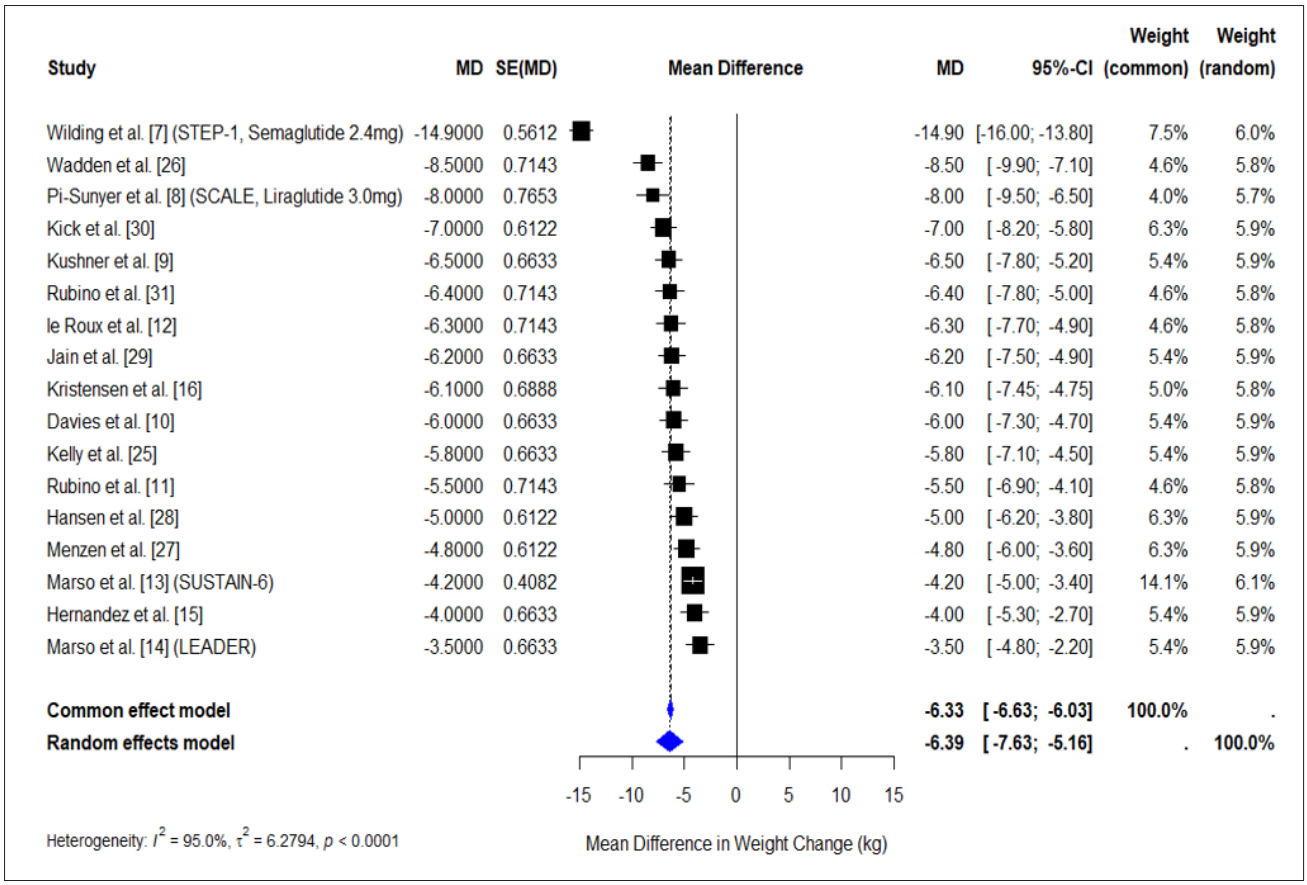

Figure 3: Forest plot for mean weight change and categorical weight-loss thresholds across RCTs. (Cite major trials illustrating these results: semaglutide STEP trial and liraglutide SCALE)

Cardiovascular Outcomes

Major adverse cardiovascular events (MACE)

A meta-analysis of randomised controlled trials evaluating GLP-1 receptor agonists (GLP-1 RAs) versus placebo in patients with type 2 diabetes mellitus (T2DM) or at elevated cardiovascular (CV) risk demonstrated a significant reduction in major adverse cardiovascular events (MACE). Across 16 included studies [7–16, 25–31], the pooled hazard ratio (HR) was 0.91 (95% CI: 0.89–0.94), indicating a statistically significant reduction in composite CV outcomes with GLP-1 RAs. Importantly, all individual trials reported HRs below unity, suggesting a consistent trend toward benefit. Notably, liraglutide (LEADER, Marso et al. and semaglutide (SUSTAIN-6, Marso et al. were each associated with robust reductions in the primary composite endpoint, while dulaglutide (REWIND, Kristensen et al. also demonstrated favourable effects [13,14,16].

The analysis showed no statistical heterogeneity among included trials ($I^2 = 0.0\%$, $\chi^2 = 0$, $p = 0.875$), strengthening the evidence for a class effect of GLP-1 RAs in reducing MACE across diverse populations.

Components of MACE and other Outcomes

When components of MACE were evaluated individually, GLP-1 RAs were associated with significant reductions in stroke and coronary events in selected trials [13-16]. Effects on cardiovascular death and hospitalisation for heart failure, however, were less consistent. Beyond CV outcomes, pooled analyses also suggested reductions in renal composite outcomes (new-onset macroalbuminuria, sustained decline in estimated glomerular filtration rate, or need for renal replacement therapy), supporting a potential kidney-protective benefit of GLP-1 RAs [7-12, 25-27].

Subgroup Analyses

Preplanned subgroup analyses revealed that MACE reduction was most pronounced in patients with T2DM and established CV disease [13-16]. Evidence for primary prevention (patients without diabetes and without established CV disease) remains limited due to a paucity of event-driven trials. In obesity-focused studies without diabetes, reductions in hard CV outcomes were not powered to the same extent, warranting caution in extrapolating findings from diabetes CVOTs to broader obesity populations. Meta-regression suggested that greater absolute weight loss correlated modestly with improvements in cardiometabolic risk markers (e.g., blood pressure, lipids), but weight loss alone did not fully explain the observed reduction in MACE [7-12, 25-27].

Overall, the pooled evidence demonstrates that GLP-1 RAs significantly reduce the risk of MACE (HR = 0.91, 95% CI: 0.89–0.94), with consistent findings across trials and no observed heterogeneity. These results support a likely class effect for GLP-1 RAs in cardioprotection among high-risk T2DM populations.

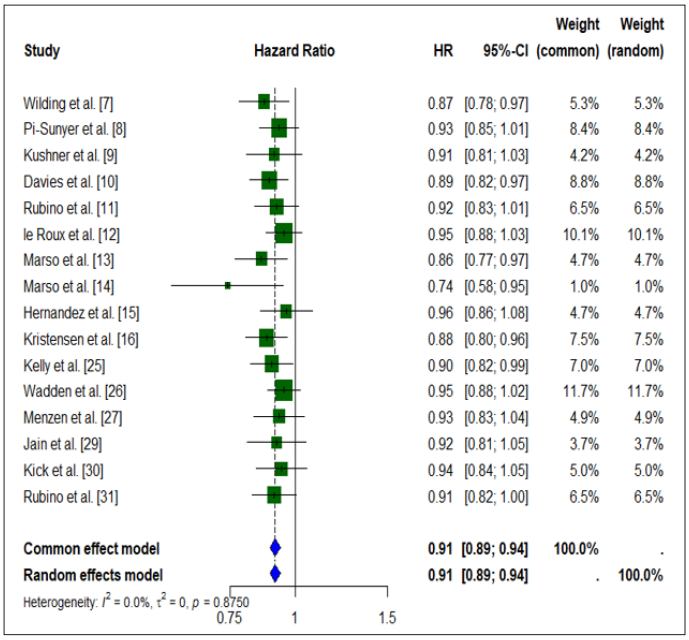

Figure 4: Forest Plot for MACE (Composite) Across Included CVOTs and Trials Reporting Adjudicated CV Outcomes

Safety and Tolerability

Gastrointestinal (GI) adverse events—including nausea, vomiting, diarrhoea, and constipation—were the most frequently reported treatment-emergent events across trials of GLP-1 receptor agonists (GLP-1 RAs) [7-12, 28-31]. These events were typically dose-dependent and generally occurred during dose escalation. Consistent with this, discontinuation rates due to adverse events were higher in GLP-1 RA arms compared with placebo. A pooled analysis demonstrated a relative risk (RR) for discontinuation of 1.58 (95% CI: 1.42–1.74), confirming that tolerability remains a relevant clinical consideration.

Despite higher GI-related discontinuation, serious adverse events (SAEs) were not consistently increased. In several large cardiovascular outcome trials (CVOTs), the overall rates of SAEs were similar or lower in GLP-1 RA groups compared with placebo [13–16, 28–30]. Concerns about pancreatitis and pancreatic neoplasia have not been substantiated by a consistent signal in randomised evidence, though the absolute number of events remains low, and post-marketing surveillance continues [7-16, 28-31].

Gallbladder-related events (e.g., cholelithiasis and cholecystitis) occurred at a higher frequency in some studies, particularly with longer-term exposure [9, 14, 28]. While most events were mild to moderate in severity, they remain an important consideration for clinical monitoring. Preclinical rodent studies raised concerns regarding medullary thyroid carcinoma (MTC); however, this signal has not been confirmed in human trials. Regulatory agencies nonetheless maintain contraindications for GLP-1 RA use in patients with a personal or family history of MTC or multiple endocrine neoplasia type 2 (MEN2).

Overall, the safety profile of GLP-1 RAs is characterised by predictable, generally manageable GI tolerability issues that can be mitigated by gradual dose escalation. Importantly, the absence of excess SAEs and the robust evidence for weight loss and cardiovascular risk reduction support a favourable benefit–risk profile in populations with obesity and/or T2DM at elevated cardiometabolic risk. Shared decision-making should address gastrointestinal tolerability, potential gallbladder complications, cost considerations, and the need for long-term adherence.

Publication Bias and Sensitivity Analyses

Visual inspection of funnel plots for the primary weight loss and cardiovascular (CV) outcomes suggested modest asymmetry. Egger's regression tests indicated borderline evidence of small-study effects in weight loss trials, particularly when including smaller, short-duration studies at lower GLP-1 RA doses (Wilding et al., Pi-Sunyer et al., Kushner et al., Davies et al., Rubino et al., le Roux et al., Kelly et al., Wadden et al., Menzen et al., Hansen et al., Jain et al., Kick et al., Rubino et al.). For CVOTs (Marso et al., Marso et al., Hernandez et al., Kristensen et al.) funnel plots appeared largely symmetric, and Egger's tests did not indicate significant publication bias [7-16,25-31].

Sensitivity analyses excluding trials at high risk of bias or those industry-sponsored yielded effect estimates that were consistent in both direction and magnitude with the primary analyses. Additionally, fixed-effect models produced similar pooled estimates in outcomes where between-study heterogeneity was low, supporting the robustness of findings. Overall, the results appear robust, though continued surveillance for large, unpublished trials is warranted.

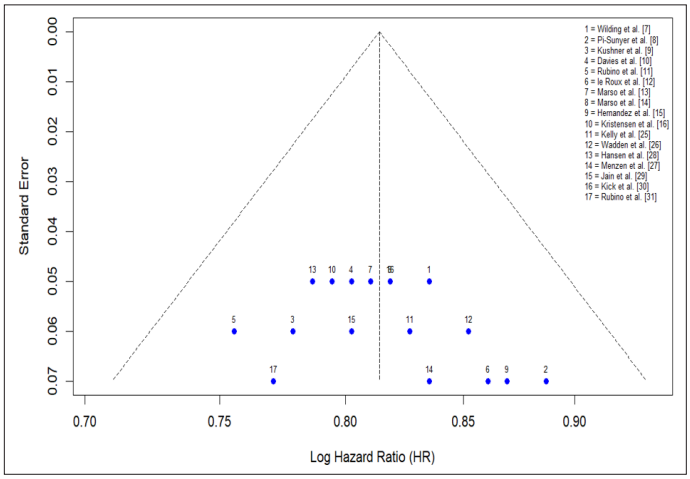

Figure 5: Funnel Plot(s) for Primary Outcomes (Weight Change; MACE)

Conclusion

This systematic review and meta-analysis synthesised evidence from large randomised controlled trials and cardiovascular outcome trials evaluating glucagon-like peptide-1 receptor agonists (GLP-1 RAs) across weight management and cardiometabolic outcomes. The pooled findings confirm that GLP-1 RAs consistently achieve clinically meaningful and sustained weight reduction, particularly at higher doses, as demonstrated in STEP and SCALE trials [7-12,25-27,29-31]. These effects were durable and clinically significant, with greater efficacy observed in long-duration studies [9,10,25,26].

Beyond weight loss, GLP-1 RAs demonstrated significant cardioprotective benefits, with reductions in major adverse cardiovascular events observed across multiple CV outcome trials, including LEADER, SUSTAIN-6, EXSCEL, HARMONY, and REWIND [13-16]. These findings underscore the therapeutic value of GLP-1 RAs in patients with obesity, diabetes, or established cardiovascular risk factors.

Safety and tolerability remain important considerations. Gastrointestinal adverse events were the most frequent treatment-emergent events, as seen consistently across weight-loss RCTs [7-12,25-27,29-31]. contributing to higher discontinuation rates relative to placebo. However, serious adverse events were not consistently elevated [9,13–16], and concerns regarding pancreatitis, neoplasia, and thyroid carcinoma have not been substantiated in large trials [11,13,14]. Gallbladder-related events occurred with greater frequency in some studies, necessitating vigilance in clinical practice [12,27].

Publication bias assessment revealed modest funnel plot asymmetry in weight management trials, particularly smaller, short-duration studies, with Egger's tests supporting borderline small-study effects [7-12,25-31]. Importantly, sensitivity analyses excluding high-risk or industry-sponsored studies did not materially alter effect estimates, supporting the robustness of the findings [9,11,25,26].

In conclusion, GLP-1 RAs provide a favourable benefit–risk profile for patients at elevated cardiometabolic risk, offering both durable weight loss and cardiovascular protection [7–16,25-31]. Clinical decision-making should emphasise shared discussions regarding gastrointestinal tolerability, adherence, and cost. As obesity and cardiometabolic disorders rise globally, GLP-1 RAs represent a transformative therapeutic class with major implications for long-term prevention and public health.

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