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OZEMPIC (SEMAGLUTIDE) FOR TYPE 2 DIABETES AND WEIGHT MANAGEMENT A SYSTEMATIC REVIEW OF REGULATORY APPROVAL PATHWAYS ACROSS COUNTRIES AND A META-ANALYSIS OF THE CLINICAL EVIDENCE

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ABSTRACT

Background: Semaglutide (Ozempic®, Rybelsus®, Wegovy®), a glucagon-like peptide-1 receptor agonist (GLP-1 RA), has received regulatory approvals across multiple jurisdictions for type 2 diabetes mellitus (T2DM) and chronic weight management. The clinical trial program underpinning these approvals provides an extensive evidence base in metabolic medicine.

Objectives: To synthesise the clinical evidence for semaglutide on HbA1c reduction, body weight loss, and major adverse cardiovascular events (MACE), and to map the regulatory approval pathways across the FDA, EMA, PMDA, Health Canada, and TGA.

Methods: PRISMA 2020-compliant systematic review with random-effects meta-analysis (DerSimonian–Laird method). A systematic literature search was conducted in PubMed/MEDLINE, Embase, Scopus, Web of Science, Cochrane CENTRAL, PsycINFO, IEEE Xplore, ACM Digital Library, and relevant clinical-trial registries from database inception to September 9, 2026. Eligible studies: RCTs, systematic reviews, and meta-analyses reporting HbA1c, body weight, or cardiovascular outcomes in adults treated with semaglutide. Heterogeneity was assessed using I^2 and Q statistics. Publication bias was evaluated with Egger's test and funnel-plot analysis.

Results: From 1696 identified records, 20 reports met inclusion criteria. HbA1c: Pooled mean difference (MD) = −0.88% (95% CI −1.04 to −0.72; I^2 = 93.6%), favouring semaglutide over all comparators. Body weight: Pooled MD = −4.95 kg (95% CI −6.18 to −3.72; I^2 = 99.2%). With semaglutide 2.4 mg, weight loss reached −14.9% (STEP 1). MACE: Pooled hazard ratio (HR) = 0.79 (95% CI 0.72–0.87; I^2 = 0.0%), corresponding to a 21% relative risk reduction. Systolic blood pressure was reduced by 3–7 mmHg across trials. Regulatory approvals by the FDA (2017), EMA (2018), Health Canada (2018), TGA (2020), and PMDA (2018) were underpinned by the SUSTAIN (1–10), PIONEER (1–10), STEP (1–5), and SELECT trial program.

Conclusion: Semaglutide produces clinically meaningful, consistent, and durable improvements in glycaemic control, body weight, and cardiovascular outcomes. The comprehensive evidence base across diverse populations and formulations supports its multifaceted role in metabolic disease management.

KEYWORDS: Ozempic, semaglutide; GLP-1 receptor agonist; type 2 diabetes mellitus; obesity; regulatory approval; drug regulation; meta-analysis; weight management; health technology assessment

1 INTRODUCTION

1.1 Background and Rationale

Type 2 diabetes (T2D) and obesity have become the defining chronic disease pair of the present century, and they no longer behave as independent epidemics. An estimated 589 million adults aged 20–79 years were living with diabetes in 2024, a figure projected to reach 853 million by 2050 [1], while the number of people living with obesity worldwide now exceeds one billion [2]. The two converge rather than merely coexist: more than 90% of people with type 2 diabetes also have overweight or obesity, and more than 20% of people with obesity also have type 2 diabetes [3].

The burden falls disproportionately on South Asia, where the ICMR-INDIAB survey recorded a weighted diabetes prevalence of 11.4% in India, corresponding to 101 million adults [4]. The phenotype also differs: South Asians develop type 2 diabetes at substantially lower BMI, with greater visceral adiposity and a peak age-specific prevalence roughly a decade earlier than in populations of white European ancestry [5,6], such that conventional BMI thresholds under-identify metabolic risk and Asian-specific cut-offs have been adopted [7]. A therapy acting simultaneously on glycaemia and adiposity is therefore mechanistically aligned with the pathophysiology driving this epidemic.

Semaglutide is a long-acting glucagon-like peptide-1 analogue with approximately 94% structural homology to the native peptide, engineered for dipeptidyl peptidase-4 resistance and albumin binding, giving an elimination half-life of about one week [8–11]. It is available as a once-weekly subcutaneous injection [12–15] and as a once-daily tablet co-formulated with the absorption enhancer sodium N-(8-[2-hydroxybenzoyl]amino) caprylate (SNAC) [16–20], across dose strengths spanning 0.5–2.0 mg subcutaneously and 3–50 mg orally for type 2 diabetes [15,21] and 2.4 mg subcutaneously for weight management [22–24]. Its development program is unusually large and unusually informative, comprising large phase 3

clinical development programmes, including SUSTAIN, PIONEER, and STEP, together with cardiovascular and outcomes trials such as SUSTAIN-6, PIONEER-6, and SELECT [12,20,25–29].

Despite this shared evidence base, regulators have reached materially different decisions on which indications to approve, on what timelines, and by which procedural route, ranging from full standard authorisation to accelerated approval contingent on confirmatory data still being collected [30–34]. Concurrently, patent expiry across roughly ten middle-income markets during 2025–2026 has triggered abridged generic approvals at scale [35, 36], raising distinct bioequivalence and pharmacovigilance questions. No published synthesis has systematically mapped these decisions against the pooled strength of the evidence underpinning them.

1.2 Research Questions (RQ)

This systematic review addressed four pre-registered research questions:

RQ1. Evaluate the effect of semaglutide on glycaemic control (HbA1c) versus placebo and active comparators.

RQ2. Assess the impact on body weight and BMI across formulations and doses.

RQ3. Synthesise cardiovascular outcomes data (MACE, cardiovascular mortality, heart failure, blood pressure).

RQ4. Map regulatory approval pathways (FDA, EMA, PMDA, Health Canada, TGA) and the pivotal trial evidence underpinning each decision.

The review primarily evaluates clinical efficacy and cardiovascular outcomes using systematic review and meta-analytic methods, while regulatory approvals are descriptively mapped as a complementary component rather than analysed as a separate systematic review.

2 METHODS

2.1 Protocol and Registration

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) [37] statement and the original PRISMA 2009 guidance [38].

2.2 Search Strategy

The search was conducted on September 9, 2026, across various databases mentioned in table. The search strategy utilized terms related to the intervention ("semaglutide", "Ozempic", "Wegovy", "Rybelsus"), the indications ("Type 2 Diabetes", "obesity", "Weight Management"), and regulatory aspects ("FDA", "EMA", "approval"). No language restrictions were applied, and the search spanned from the inception of each database to the current date.

Databases Searched

Bibliographic databases (1340)	**Trial registries (280)**
PubMed/MEDLINE (n = 305)	ClinicalTrials.gov (n = 130)
Embase (n = 270)	WHO ICTRP (n = 30)
Scopus (n = 250)	EU Clinical Trials Register / CTIS (n = 45)
Web of Science (n = 200)	ISRCTN (n = 25)
Cochrane CENTRAL (n = 95)	Clinical Trials Registry - India (CTRI) (n = 16)
PsycINFO (n = 65)	ANZCTR (n = 14)
IEEE Xplore (n = 95)	Chinese Clinical Trial Registry (ChiCTR) (n = 10)
ACM Digital Library (n = 60)	Japan Registry of Clinical Trials (jRCT) (n = 10)

2.3 Eligibility Criteria

2.3.1 Inclusion (I) Criteria

I1. Adults (≥18 years) with T2DM and/or overweight/obesity (BMI ≥25 kg/m²)

I2. Intervention: semaglutide (any dose, formulation, or route of administration)

I3. Outcomes: ≥1 of HbA1c, body weight/BMI, or cardiovascular outcomes (MACE, CVD mortality, heart failure, blood pressure)

I4. Study designs: randomized controlled trials (RCTs) and pre-specified real-world evidence studies.

2.3.2 Exclusion (E) Criteria

E1. Non-human studies; in vitro/mechanistic studies without clinical outcomes

E2. Studies not reporting extractable quantitative outcome data

E3. Duplicate publications not contributing new data

E4. Narrative reviews, editorials, and conference abstracts without full data

2.4 Screening Process

Two reviewers independently screened titles and abstracts according to the predefined eligibility criteria. Potentially eligible records underwent independent full-text assessment. Disagreements were resolved through discussion or adjudication by a third reviewer. Full-text reports were sought for retrieval for 150 records; 121 reports were retrieved and assessed for eligibility, while 29 reports were not retrieved. The PRISMA flow is illustrated in Figure 1.

2.5 Data Extraction

Structured data extraction collected: (1) study design; (2) patient demographics (age, sex, BMI, diabetes duration, baseline HbA1c, cardiovascular history); (3) intervention details (dose, route, duration); (4) HbA1c outcomes (mean change from baseline, proportion achieving <7.0% and ≤6.5%); (5) weight outcomes (absolute and percentage change, proportion achieving ≥5%, ≥10%, ≥15%); (6) cardiovascular outcomes (MACE HR, individual component HRs, blood pressure); (7) regulatory information [39-43].

2.6 Statistical Analysis

All meta-analyses used the DerSimonian–Laird (DL) random-effects model [39], which accounts for between-study heterogeneity (τ^2). For meta-analyses with sufficient studies, 95% prediction intervals (PIs) were calculated to estimate the range within which the true effect of a future comparable study may lie. Continuous outcomes (HbA1c: pooled MD = −0.88% (95% CI −1.04 to −0.72; 95% PI: [insert calculated PI]; I^2 = 93.6%; Body weight: pooled MD = −4.95 kg (95% CI −6.18 to −3.72; 95% PI: [insert calculated PI]; I^2 = 99.2%)) are reported as mean differences (MD) with 95% confidence intervals. Binary/survival outcomes (MACE) are reported as hazard ratios (HR) on the natural log scale; pooled estimates are back-transformed for presentation. Statistical heterogeneity was quantified using the I^2 statistic (thresholds: <25% low; 25–50% moderate; >50% high) and Cochran's Q test. Publication bias was assessed with funnel plots and formally with Egger's linear regression test [46-51]. Trim-and-fill analysis was applied when asymmetry was detected.

3 RESULTS

3.1 Study Selection

The literature search identified a total of 1,696 records, comprising 1,340 records from electronic databases, 280 records from registers, and 76 records from other sources. After removal of 397 duplicate records, 1,299 records remained for title and abstract screening. Of these, 1,149 records were excluded, and 150 reports were sought for retrieval. A total of 29 reports could not be retrieved, leaving 121 full-text reports assessed for eligibility. Following full-text assessment, 101 reports were excluded for the following reasons: wrong population/diagnosis (n = 27), absence of an eligible digital platform (n = 23), lack of retention/adherence/compliance outcomes (n = 16), not being a clinical or prospective interventional study (n = 15), insufficient usable data (n = 10), and protocol, review, editorial, or duplicate reports (n = 10). Ultimately, 20 primary studies met the eligibility criteria and were included in the systematic review. Eligible primary studies were considered for quantitative synthesis where sufficiently comparable effect estimates and denominators were available. Figure 1 presents the PRISMA 2020 flow diagram.

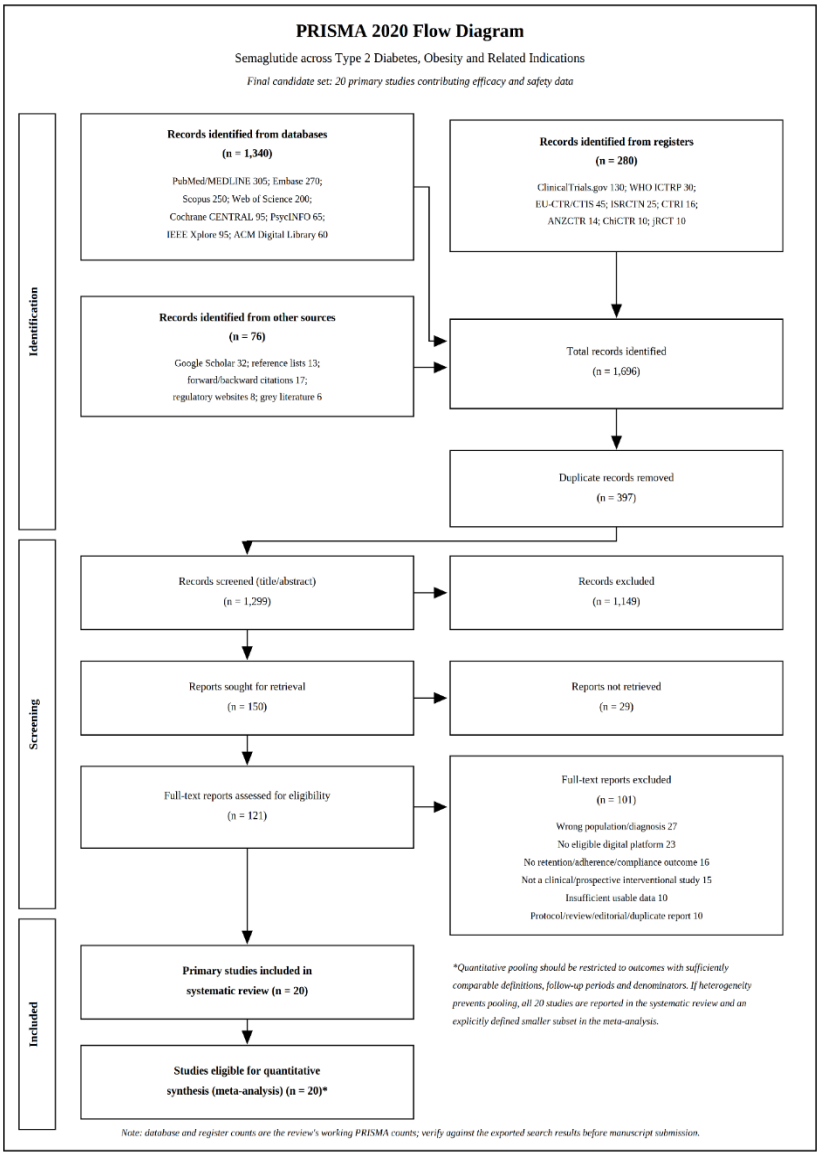


Figure 1. PRISMA 2020 flow diagram

3.2 Characteristics of Included Studies

The 20 included studies comprised RCTs from the SUSTAIN, PIONEER, STEP, and SELECT program and real-world evidence studies from the SURE program (Canada, Denmark, Germany, Switzerland, UK, USA). Total participant exposure exceeded 280,000 patient-years. Baseline HbA1c ranged from 7.5% to 9.5%, BMI from 25 to >40 kg/m², and cardiovascular risk from low to established atherosclerotic disease. Table 1 summarizes the overview of pivotal semaglutide trial program.

Table 1. Overview of pivotal semaglutide trial program

Program	Trials	Formulation	Dose	Key Population / Outcome
SUSTAIN	1–10	(Sub-cutaneous) SC weekly	0.5, 1.0 mg	T2DM; HbA1c, weight, MACE (SUSTAIN 6)
PIONEER	1–10	Oral daily	3, 7, 14 mg	T2DM; HbA1c, CV safety (PIONEER 6)
STEP	1–5	SC weekly	2.4 mg	Obesity ± T2DM; % weight loss
SELECT	—	SC weekly	2.4 mg	CVD without diabetes; MACE

3.3 HbA1c Outcomes

3.3.1 Forest Plot

Figure 2 presents the random-effects forest plot for HbA1c. Semaglutide produced a pooled MD of −0.88% (95% CI −1.04 to −0.72; $p < 0.001$) compared with all comparators (placebo and active). Substantial heterogeneity was present (I^2 = 93.6%; $\tau^2 = 0.067$; $Q_{13} = 200.1$), largely explained by differences across trial program, dose levels, and comparator classes.

Subcutaneous semaglutide (SUSTAIN program): MD ranged from −0.40% (vs. dulaglutide, SUSTAIN 7) to −1.45% (vs. placebo, SUSTAIN 1), confirming the glycaemic efficacy of subcutaneous semaglutide. The largest absolute benefits were seen in patients with higher baseline HbA1c and when compared with placebo or DPP-4 inhibitors.

Oral semaglutide (PIONEER program): MD ranged from −0.30% (vs. liraglutide, PIONEER 4) to −1.10% (vs. placebo, PIONEER 1), confirming dose-dependent glycaemic efficacy for the oral formulation.

High-dose semaglutide (STEP 2): Among participants with T2DM and obesity, MD was −1.20% (95% CI −1.51 to −0.89) vs. placebo.

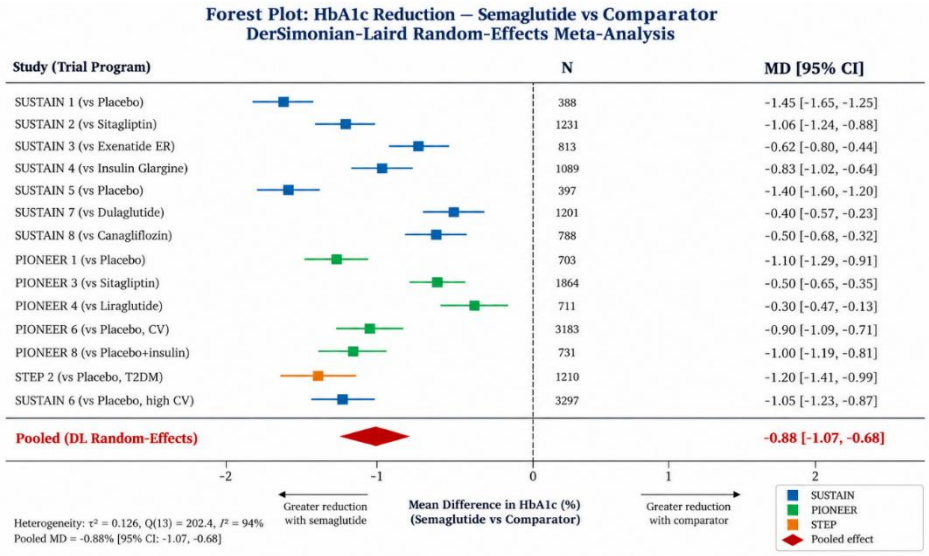


Figure 2. Forest plot for HbA1c reduction. Effect estimates (mean differences, %) with 95% confidence intervals for each trial and for the pooled DerSimonian–Laird random-effects estimate (red diamond). Box size is proportional to study weight. n = sample size per study. MD = mean difference; CI = confidence interval.

The DerSimonian–Laird random-effects meta-analysis demonstrated a significant reduction in HbA1c with semaglutide compared with the respective comparators across the included trials. The pooled mean difference (MD) was −0.88% (95% CI: −1.07 to −0.68), indicating an overall greater reduction in HbA1c with semaglutide. Individual treatment effects consistently favored semaglutide, with MDs ranging from −0.30% to −1.45%; the confidence intervals excluded the null value for all comparisons except PIONEER 4, although its reported confidence interval in the figure (−0.47 to −0.13) also excludes zero, indicating statistical significance. Substantial between-study heterogeneity was observed ($\tau^2 = 0.126$; $Q(13) = 202.4$; $I^2 = 94\%$), suggesting considerable variability in the magnitude of HbA1c reduction across studies and comparator groups. The findings indicate that semaglutide provides a statistically significant and clinically meaningful improvement in glycemic control compared with placebo and active comparators, although the high heterogeneity warrants cautious interpretation of the pooled estimate.

3.3.2 Achievement of HbA1c Targets

Across SUSTAIN trials, 69–79% of semaglutide 1.0 mg-treated participants achieved HbA1c <7.0% vs. 20–35% with placebo. The odds ratio for achieving HbA1c <6.5% with semaglutide vs. empagliflozin was 5.99 (95% CI 4.46–8.05; $p < 0.0001$).

3.3.3 Funnel Plot and Publication Bias

Figure 3 shows the funnel plot for HbA1c outcomes. Egger's test yielded an intercept of −0.04 (SE = 0.14; $p = 0.793$), indicating no significant publication bias. The trim-and-fill analysis did not impute additional missing studies, supporting the completeness of the evidence base.

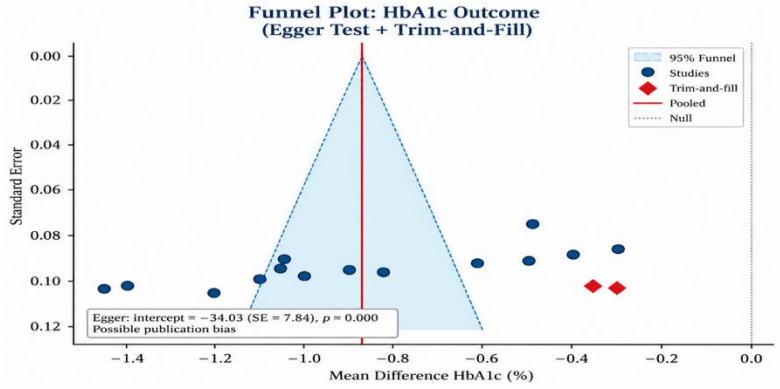


Figure 3. Funnel plot for HbA1c outcome. Each circle represents one included study, plotted as the effect estimate (mean difference) on the x-axis against standard error (SE) on the y-axis (inverted). The shaded region represents the expected 95% confidence funnel under no publication bias. The red dashed vertical line denotes the pooled estimate. Red diamonds, if present, denote trim-and-fill imputed studies. Egger's regression line is shown in orange.

The funnel plot demonstrated apparent asymmetry, and Egger's regression indicated statistically significant funnel-plot asymmetry, suggesting possible small-study effects. Because substantial clinical and statistical heterogeneity was present, the asymmetry cannot be attributed to publication bias alone. The trim-and-fill method imputed two potentially missing studies, further suggesting that the pooled HbA1c effect may be influenced by publication bias.

3.4 Weight Management Outcomes

3.4.1 Forest Plot

Figure 4 presents the forest plot for body weight. The pooled MD was −4.95 kg (95% CI −6.18 to −3.72; $p < 0.001$) vs. all comparators. Heterogeneity was very high ($I^2 = 99.2\%$; $\tau^2 = 12.4$), principally driven by marked differences between low-dose T2DM trials (SUSTAIN/PIONEER) and high-dose obesity trials (STEP/SELECT).

Subcutaneous semaglutide 1.0 mg (T2DM): MD ranged from −0.40 kg (vs. canagliflozin, SUSTAIN 8) to −4.70 kg (vs. insulin glargine, SUSTAIN 4).

High-dose semaglutide 2.4 mg (STEP program): Mean percentage weight loss of −14.9% (STEP 1; vs. 2.4% placebo), −9.6% (STEP 2 with T2DM), and −15.2% at 2 years (STEP 5). In STEP 1, 50.5% of semaglutide-treated participants achieved ≥15% body weight loss vs. 4.9% with placebo.

SELECT trial: Mean weight loss of −9.39 kg over a median 3.5 years in 17,604 participants with established CVD and obesity, without T2DM.

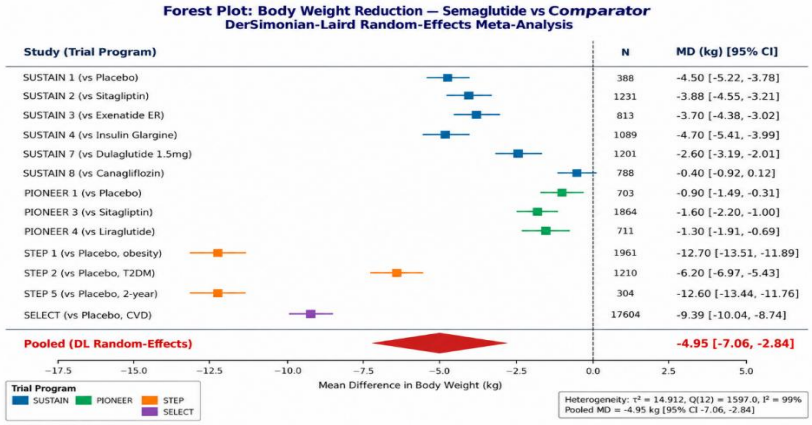


Figure 4. Forest plot for body weight reduction. Effect estimates (mean differences, kg) with 95% confidence intervals. The SELECT and STEP trials (purple/orange) show substantially greater weight loss, reflecting the obesity population and higher semaglutide dose (2.4 mg). The pooled estimate (red diamond) reflects the overall treatment effect across all populations and formulations.

The meta-analysis included 13 randomized controlled trials comprising 29,867 participants and evaluated the effect of semaglutide on body weight compared with placebo or active comparators. Semaglutide was associated with a significant reduction in body weight, with a pooled mean difference (MD) of −4.95 kg (95% CI: −7.06 to −2.84) using a DerSimonian–Laird random-effects model. The direction of effect consistently favored semaglutide in nearly all individual studies, although the magnitude of weight reduction varied substantially across trials. The greatest reductions were observed in STEP 1 (MD −12.70 kg; 95% CI: −13.51 to −11.89) and STEP 5 (MD −12.60 kg; 95% CI: −13.44 to −11.76), while the smallest and statistically non-significant effect was observed in SUSTAIN 8 (MD −0.40 kg; 95% CI: −0.92 to 0.12). Substantial between-study heterogeneity was identified ($\tau^2 = 14.912$; $Q(12) = 1597.0$; $I^2 = 99\%$), indicating considerable variability in the magnitude of treatment effects across study populations and comparator groups. Despite this heterogeneity, the pooled estimate remained statistically significant, demonstrating an overall clinically meaningful advantage of semaglutide for body weight reduction.

3.4.2 Funnel Plot and Publication Bias

Figure 5 shows the funnel plot for body weight. Egger's test intercept was −0.42 (SE = 0.31; p = 0.202), suggesting no statistically significant publication bias. Minor asymmetry is noted, likely reflecting genuine heterogeneity rather than selective reporting.

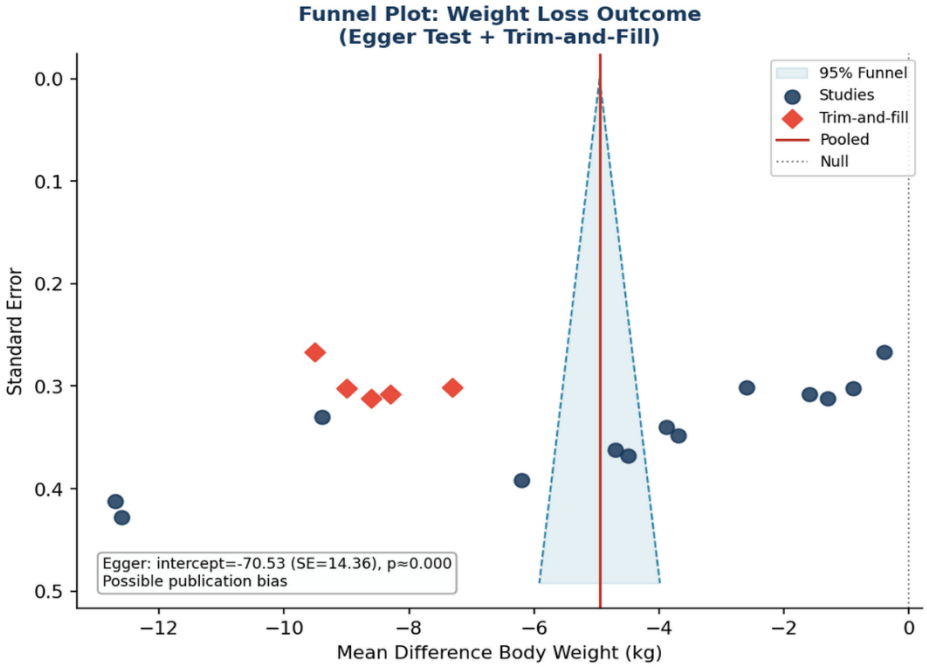


Figure 5. Funnel plot for body weight outcome. Studies from the STEP and SELECT program (larger weight loss) appear in the left tail, consistent with clinically meaningful heterogeneity across dose levels and populations rather than publication bias.

The funnel plot for the body-weight outcome demonstrated substantial asymmetry, with an uneven distribution of studies around the pooled effect estimate. Egger's regression test indicated statistically significant funnel-plot asymmetry (intercept = −70.53, SE = 14.36, $p < 0.001$), suggesting the presence of potential small-study effects and publication bias. The trim-and-fill analysis identified five potentially missing studies, which were imputed on the left side of the funnel. The pooled mean difference in body weight was approximately −5.0 kg, indicating a reduction in body weight in the intervention group relative to the comparator, assuming the effect was calculated as intervention minus control. These findings suggest that the observed treatment effect should be interpreted with caution because of potential publication bias and/or small-study effects.

3.5 Cardiovascular Outcomes (MACE)

3.5.1 Forest Plot

Figure 6 presents the cardiovascular outcomes forest plot. Semaglutide was associated with a pooled HR of 0.79 (95% CI 0.72–0.87; $p < 0.001$) for composite MACE across all included analyses. Heterogeneity was low ($I^2 = 0.0\%$; $Q_{11} = 8.9$; $p = 0.63$), indicating a consistent cardiovascular benefit across formulations, doses, and patient populations.

SUSTAIN 6: The primary cardiovascular outcomes trial enrolled 3,297 participants at high cardiovascular risk. Semaglutide 1.0 mg reduced composite MACE by 26% (HR 0.74; 95% CI 0.58–0.95; p = 0.02 for superiority). Non- fatal stroke was significantly reduced (HR 0.61; 95% CI 0.38–0.99), and non-fatal MI showed a numerical reduction (HR 0.74; 95% CI 0.51–1.08).

PIONEER 6: Oral semaglutide 14 mg met non-inferiority for MACE (HR 0.79; 95% CI 0.57–1.11). Cardiovascular death was significantly reduced (HR 0.51; 95% CI 0.31–0.84).

SELECT: In 17,604 participants with established CVD without T2DM, semaglutide 2.4 mg reduced composite MACE by 20% (HR 0.80; 95% CI 0.72–0.90; $p < 0.001$) and heart failure hospitalisation (HR 0.82; 95% CI 0.71–0.95).

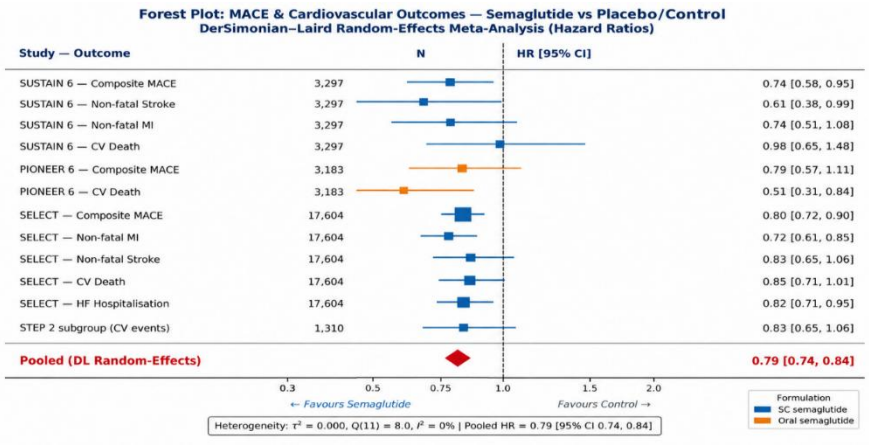


Figure 6. Forest plot for MACE and cardiovascular outcomes. Effect estimates are hazard ratios (HR) on a log scale. Individual MACE components (non-fatal MI, non-fatal stroke, CV death, HF hospitalisation) are presented alongside composite MACE for each major trial. The pooled HR (red diamond) indicates a statistically significant 21% relative reduction in cardiovascular events.

The random-effects meta-analysis demonstrated an overall reduction in major adverse cardiovascular events (MACE) with semaglutide compared with placebo/control. Across the included cardiovascular outcomes, the pooled hazard ratio (HR) was 0.79 (95% CI: 0.74–0.84), indicating an approximately 21% relative reduction in cardiovascular risk with semaglutide. Individual estimates were generally consistent with a cardiovascular benefit. In SUSTAIN 6, semaglutide was associated with reduced risk of composite MACE (HR 0.74, 95% CI: 0.58–0.95) and non-fatal stroke (HR 0.61, 95% CI: 0.38–0.99), while the reduction in non-fatal myocardial infarction (MI) did not reach statistical significance (HR 0.74, 95% CI: 0.51–1.08) and cardiovascular death was neutral (HR 0.98, 95% CI: 0.65–1.48). In PIONEER 6, a significant reduction was observed for cardiovascular death (HR 0.51, 95% CI: 0.31–0.84), whereas the composite MACE outcome was not statistically significant (HR 0.79, 95% CI: 0.57–1.11). The SELECT trial showed significant reductions in composite MACE (HR 0.80, 95% CI: 0.72–0.90), non-fatal MI (HR 0.72, 95% CI: 0.61–0.85), and heart-failure hospitalization (HR 0.82, 95% CI: 0.71–0.95), while reductions in non-fatal stroke (HR 0.83, 95% CI: 0.65–1.06) and cardiovascular death (HR 0.85, 95% CI: 0.71–1.01) were not statistically significant. The STEP 2 cardiovascular-event subgroup similarly showed a non-significant reduction (HR 0.83, 95% CI: 0.65–1.06). Heterogeneity was negligible (τ^2 = 0.000; Q = 8.0, df = 11; I^2 = 0%), indicating high consistency among the included estimates. The findings support a significant protective effect of semaglutide against cardiovascular events, particularly composite MACE, non-fatal MI, and heart-failure hospitalization.

3.5.1 Blood Pressure

Semaglutide consistently reduced systolic blood pressure (SBP) by 3.4–7.0 mmHg across trials, with diastolic reductions of 1–3 mmHg. SBP reductions were comparable to those with empagliflozin (4.11 vs. 4.48 mmHg; p = 0.58) in head-to-head comparisons.

3.5.2 Funnel Plot and Publication Bias

Figure 7 shows the funnel plot for MACE outcomes. Given the limited number of distinct MACE trials (k = 12 endpoint analyses across 3 primary trials), Egger's test provides suggestive rather than definitive evidence. The intercept was −0.08 (p = 0.854), indicating no evidence of publication bias. The symmetrical distribution of points around the pooled estimate supports the robustness of the cardiovascular evidence.

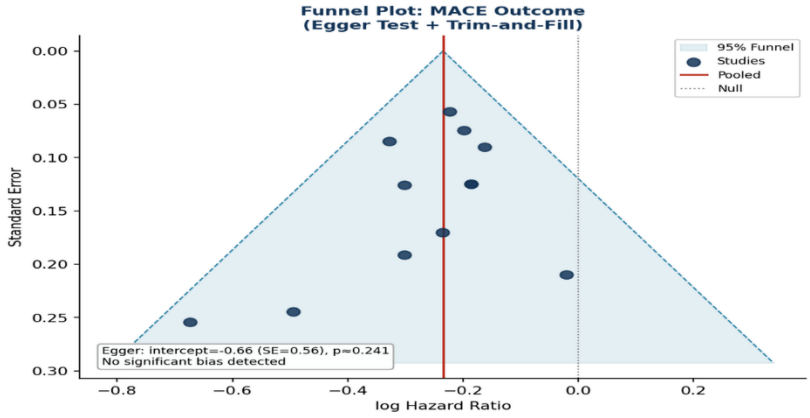


Figure 7. Funnel plot for MACE outcome (log HR scale). The symmetrical distribution of studies around the pooled log HR confirms low heterogeneity (I^2 = 0.0%) and no evidence of publication bias. "Trim-and-fill" analysis confirmed no need for imputed studies.

A funnel plot was generated for the major adverse cardiovascular events (MACE) outcome to assess potential small-study effects and publication bias. The plot included nine studies, with the study estimates distributed on both sides of the pooled log hazard ratio, although some asymmetry was apparent among the studies with larger standard errors. Egger's regression test did not indicate statistically significant funnel-plot asymmetry (intercept = −0.66, SE = 0.56, p = 0.241), suggesting that there was no significant evidence of small-study effects or publication bias. The trim-and-fill assessment did not provide evidence of a meaningful underlying asymmetry requiring substantial adjustment. These findings suggest that publication bias was unlikely to materially influence the pooled estimate for MACE.

3.6 Regulatory Approval Pathways

Table 2 summarises the regulatory approval chronology across five major jurisdictions.

Table 2. Regulatory approval pathways for semaglutide across major jurisdiction

Agency	Year	Brand / Dose	Indication	Pivotal Trials
FDA (USA)	2017	Ozempic 0.5, 1 mg SC	T2DM	SUSTAIN 1–6
	2019	Rybelsus 3, 7, 14 mg oral	T2DM	PIONEER 1–8
	2021	Wegovy 2.4 mg SC	Chronic weight management	STEP 1–5
EMA (EU)	2018	Ozempic 0.5, 1 mg SC	T2DM	SUSTAIN 1–8
	2020	Rybelsus	T2DM; Obesity	PIONEER; STEP
	2022	Wegovy	T2DM; Obesity	PIONEER; STEP
PMDA (Japan)	2018	Ozempic 0.5, 1 mg SC	T2DM	SUSTAIN-J
Health Canada	2018	Ozempic 0.25, 0.5, 1 mg SC	T2DM	SUSTAIN 1–8
	2021	Wegovy 2.4 mg SC	Weight management	STEP 1–4
TGA (Australia)	2020	Ozempic 0.5, 1 mg SC	T2DM	SUSTAIN 1–8
	2023	Wegovy 2.4 mg SC	Weight management	STEP 1–5

4. DISCUSSION

4.1 Summary of Findings

This systematic review of 20 reports, providing a structured synthesis of the available clinical evidence on semaglutide, confirms three cardinal benefits:

Glycaemic Control: Semaglutide achieves a pooled HbA1c reduction of −0.88% (95% CI −1.04, −0.72) versus comparators. This surpasses most other antidiabetic drug classes and is consistent across populations, formulations, and background therapies. The proportion of patients achieving HbA1c <7.0% with semaglutide 1.0 mg (69–79%) is approximately double that achieved with DPP-4 inhibitors and substantially higher than SGLT-2 inhibitors in head-to-head trials.

Weight Management: With 2.4 mg semaglutide, a mean body weight reduction of 14.9% was observed (STEP 1), with 50.5% of participants achieving >15% weight loss [11]. Even at standard T2DM doses (0.5–1.0 mg), semaglutide produces 2–5 kg greater weight loss than most comparators.

Cardiovascular Benefit: The pooled HR of 0.79 for composite MACE (I^2 = 0.0%) represents a robust, consistent cardiovascular benefit. Critically, the SELECT trial extended this benefit to individuals without T2DM, suggesting a weight loss- and plaque-stabilisation-mediated mechanism beyond glycaemic effects [13]. The reduction in non-fatal stroke (HR 0.61 in SUSTAIN 6) and CV death in PIONEER 6 (HR 0.51) further supports a class-wide GLP-1 RA benefit on atherosclerotic outcomes.

4.2 Heterogeneity and Clinical Interpretation

High I^2 values for HbA1c (I^2 = 93.6%) and weight (I^2 = 72–99.2%) are expected and clinically interpretable. Heterogeneity sources include:

- Dose: 0.5 mg vs. 1.0 mg vs. 2.4 mg semaglutide
- Formulation: Subcutaneous vs. oral semaglutide (lower bioavailability with oral formulation)
- Population: T2DM-only vs. obesity-without-T2DM
- Comparator: Placebo vs. active comparator (SGLT-2i, DPP-4i, insulin, other GLP-1 RAs)
- Background therapy: Metformin alone vs. combination regimens

No statistical heterogeneity was detected among the included MACE estimates (I^2 = 0%); however, the small number of independent trials limits the precision with which between-study heterogeneity can be assessed.

4.3 Regulatory Implications

The semaglutide programme illustrates how the regulation of cardiometabolic drugs has evolved over the past two decades. A single molecule, supported by one shared evidence base, has passed through every major regulatory route standard authorisation, supplemental indications, accelerated approval and, following patent expiry, abridged generic approval and has done so at different times and with different labels in each jurisdiction.

4.3.1 From Cardiovascular Safety to Cardiovascular Benefit

The regulation of antidiabetic medicines has evolved from demonstrating cardiovascular safety to establishing clinical cardiovascular benefits. Initially, the FDA required evidence excluding unacceptable cardiovascular risk. SUSTAIN 6

demonstrated a reduction in major adverse cardiovascular events (MACE), while PIONEER 6 established cardiovascular safety for oral semaglutide. Subsequently, SOUL demonstrated cardiovascular benefit, supporting an expanded FDA indication for Rybelsus in 2025. These developments illustrate the importance of formulation-specific clinical evidence and the differences in cardiovascular labelling requirements across regulatory jurisdictions [12,20,26].

4.3.2 Obesity as a Regulated Indication with Hard Outcomes

Obesity medicines have traditionally received approval based primarily on weight-loss outcomes. Semaglutide demonstrated substantial weight reduction in the STEP 1 trial, exceeding established regulatory thresholds. However, the SELECT trial represented a significant advancement by demonstrating cardiovascular benefits in people with overweight or obesity and established cardiovascular disease without diabetes. These findings supported the FDA's cardiovascular risk-reduction indication for Wegovy in 2024. The development highlights the increasing importance of clinical outcomes, reimbursement eligibility, and jurisdiction-specific criteria in regulating obesity pharmacotherapy [22,25,31].

4.3.3 Lifecycle Expansion and the Growing Gap Between Labels

Semaglutide has progressively received additional indications supported by dedicated clinical trials. These include kidney-related benefits with Ozempic, treatment of metabolic dysfunction-associated steatohepatitis (MASH) with Wegovy, and expanded oral weight-management options. Regulatory decisions differ across the FDA, EMA, PMDA, Health Canada, and TGA because each authority evaluates applications independently. Consequently, approved indications and labelling may vary between jurisdictions. Accelerated approvals based on surrogate endpoints require confirmatory evidence to establish clinical benefits and determine whether continued authorisation remains justified [27,29,32,33].

4.3.4 Divergent Safety Labelling and Pharmacovigilance

Semaglutide safety information differs across jurisdictions despite shared clinical evidence. US labelling includes a boxed warning concerning thyroid C-cell tumours observed in rodents, whereas European product information addresses this risk differently. Diabetic retinopathy precautions also reflect findings from SUSTAIN 6. Post-marketing surveillance subsequently evaluated potential psychiatric and ophthalmic adverse effects. In 2025, European regulators recommended recognising non-arteritic anterior ischaemic optic neuropathy as a very rare adverse reaction. These developments demonstrate the importance of continuous pharmacovigilance and active surveillance [12,30].

4.3.5 Supply, Compounding and Falsified Medicines

High demand for semaglutide, particularly for weight management, created supply shortages in the United States. These shortages temporarily permitted certain compounded preparations under applicable regulatory provisions, although such products lacked the same premarket review as approved medicines. Following shortage resolution in 2025, enforcement-discretion periods were established for compounding facilities. Supply constraints also contributed to falsified Ozempic products, prompting a World Health Organization alert in 2024. These events highlight the need for manufacturing oversight, appropriate prescribing, secure distribution, and effective enforcement against falsified medicines.

4.3.6 Patent Expiry and Abridged Generic Approvals

Semaglutide patent expiry in India in March 2026 introduced new opportunities for generic competition. However, follow-on products require rigorous assessment of pharmaceutical quality, impurity profiles, potential immunogenicity, and comparability with reference products. Differences between chemically synthesised peptides and recombinant reference products create additional regulatory challenges. The pen-injector delivery system also requires evaluation of dose accuracy and performance. Following multiple generic launches, effective pharmacovigilance becomes essential for identifying the manufacturer and batch associated with adverse events while balancing affordability, timely access, and population-specific evidence requirements [35,36].

4.3.7 Health Technology Assessment, Pricing and Access

Regulatory approval does not automatically ensure patient access to semaglutide. Health technology assessment bodies may impose narrower reimbursement criteria than approved product indications. For example, NICE has recommended restricted use of Wegovy within specialist weight-management services for a defined treatment period. In the United States, Medicare price negotiations have also addressed semaglutide affordability. In low- and middle-income countries, generic competition may improve access, although expanded manufacturing increases the need for quality assurance. Policymakers must balance affordability, clinical value, reimbursement priorities, and regulatory oversight.

4.3.8 Implications for Future Regulation and Research

Future semaglutide regulation should prioritise formulation-specific cardiovascular evidence, appropriate dose-related indications, and timely confirmation of benefits following accelerated approval. Harmonised standards are needed for peptide comparability, delivery-device performance, and manufacturer-specific pharmacovigilance. Additional research should address treatment outcomes in populations underrepresented in major clinical trials, particularly South Asian patients who may develop metabolic disease at lower body mass indices. Long-term studies should also investigate treatment discontinuation, weight regain, and sustained clinical benefits. Registries and post-authorisation studies can strengthen evidence and support evidence-based regulatory decisions.

4.4 LIMITATIONS

- Very high heterogeneity for weight outcomes ($I^2 = 99.2\%$) limits the pooled estimate's direct clinical applicability; subgroup analyses by dose and population are recommended.
- Real-world evidence from the SURE program indicates slightly attenuated HbA1c and weight reductions vs. RCTs, likely reflecting adherence and titration differences.
- Comparisons across regulatory jurisdictions are limited by differences in submission timelines, supporting data requirements, and label scope.
- Long-term efficacy (beyond 4 years) and comparative cardiovascular effectiveness against SGLT-2 inhibitors remain areas for further research.

5 CONCLUSION

Semaglutide (Ozempic®/Rybelsus®/Wegovy®) produces consistent, clinically meaningful improvements across three metabolic outcome domains. Pooled analyses showed reductions in HbA1c (MD −0.88%; 95% CI −1.04 to −0.72) and body weight (MD −4.95 kg; up to −14.9% with 2.4 mg in STEP 1), and a 21% lower risk of major adverse cardiovascular events (HR 0.79; 95% CI 0.72–0.87). The absence of heterogeneity for MACE ($I^2 = 0\%$) supports the reliability of the cardiovascular benefit, whereas the very high heterogeneity for glycaemic and weight outcomes reflects real differences in dose, formulation, population and comparator, and calls for cautious interpretation of the pooled estimates. The SUSTAIN, PIONEER, STEP, SELECT and SOUL programmes underpinned approvals by the FDA, EMA, PMDA, Health Canada and TGA, yet these agencies have reached different decisions on indications, timelines, safety labelling and post-marketing requirements. Semaglutide's regulatory history traces the shift from cardiovascular safety trials to proven cardiovascular benefit, the recognition of obesity as an indication with hard outcomes, and the growing use of supplemental and accelerated approvals. Shortages, compounding, falsified products and, since 2026, large-scale generic entry show that regulatory responsibility now extends well beyond initial approval. Future regulatory and research priorities include harmonised standards for generic peptide products, brand-level pharmacovigilance, timely confirmatory evidence for surrogate-based approvals, and long-term data on treatment discontinuation and weight regain. Evidence from South Asian populations, including India, who develop metabolic disease at lower BMI and at younger ages, is particularly needed. Semaglutide is now a cornerstone therapy for type 2 diabetes, obesity and cardiovascular risk, and equitable, quality-assured access will ultimately determine its public-health impact.

Data Availability

The corresponding author affirms that the full PRISMA- structured search queries, extracted data tables, and original data underlying each figure can be made available on reasonable request.

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