



A Comprehensive Systematic Review of the Role of Semaglutide Anti-Obesity Therapy in Multiple Metabolic Diseases: A Systematic Review of Randomized Controlled Trials and Primary Studies

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ABSTRACT

Introduction: Obesity constitutes the pathophysiological hub of interconnected metabolic diseases including type 2 diabetes mellitus (T2DM), atherosclerotic cardiovascular disease (ASCVD), heart failure with preserved ejection fraction (HFpEF), chronic kidney disease (CKD), metabolic dysfunction-associated steatohepatitis (MASH) and peripheral artery disease (PAD). Semaglutide, a long-acting glucagon-like peptide-1 receptor agonist (GLP-1 RA), has been evaluated across all these domains. This systematic review synthesised primary evidence on semaglutide across multiple metabolic diseases to determine consistency of benefit across organ systems.

Methods: The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Eligible designs comprised randomized controlled trials and observational studies evaluating semaglutide in obesity

or obesity-related metabolic disease. Systematic reviews were excluded from primary tabulation but retained as contextual comparators. Two reviewers independently screened, extracted data and appraised risk of bias using Cochrane RoB 2 and ROBINS-I; certainty was graded with GRADE. Synthesis was narrative and semi-quantitative by outcome domain.

Results: Twenty-seven primary studies (24 RCTs, 3 observational cohorts) encompassing >180,000 participants across 15 outcome domains were included. Semaglutide 2.4 mg weekly produced mean weight reductions of -14.9% to -16.0% versus -2.4% to -5.7% with placebo (all $P<0.001$). In prediabetes, 84.1-89.8% reverted to normoglycaemia versus 47.8-70.4% ($P<0.0001$). SELECT demonstrated 20% MACE reduction (HR 0.80; $P<0.001$) in obesity without diabetes; SOUL demonstrated 14% MACE reduction with oral semaglutide (HR 0.86; $P=0.006$). FLOW demonstrated 24% reduction in major kidney disease events (HR 0.76; $P=0.0003$) and 20% all-cause mortality reduction (HR 0.80; $P=0.01$). STEP-HFpEF demonstrated 7.5-point KCCQ-CSS improvement ($P<0.0001$). ESSENCE demonstrated steatohepatitis resolution in 62.9% versus 34.3% ($P<0.001$). STRIDE demonstrated walking distance improvement (ETR 1.13; $P=0.0004$). C-reactive protein fell 39-48%. Gastrointestinal adverse events occurred in 63.5-84.1% but were predominantly mild-to-moderate and transient, with permanent discontinuation in ~4-5%. Risk of bias was low for 20/24 RCTs; GRADE certainty was high for 11 domains.

Discussion: Semaglutide demonstrates reproducible benefit extending beyond weight reduction into hard cardiovascular, renal, hepatic and functional outcomes. Mediation analyses attributed little treatment effect to weight change, implying direct vascular,

anti-inflammatory and haemodynamic mechanisms. Benefit was largely independent of baseline BMI, HbA1c and comorbidity severity. Principal limitations include industry sponsorship, under-representation of non-White populations, and reversibility of benefit upon discontinuation.

Conclusion: Semaglutide is a disease-modifying agent for the cardiovascular-kidney-metabolic syndrome. Treatment produced significant improvements in body weight, glycaemia, lipids, inflammation, MACE, heart failure, kidney disease, hepatic histology, functional capacity and all-cause mortality, with acceptable safety profile. It is recommended that semaglutide be positioned as first-line therapy in obesity with cardiovascular, renal or hepatic disease; that treatment be regarded as chronic; and that future research prioritise head-to-head incretin comparisons, non-industry-funded trials, and under-represented populations.

Keywords: Semaglutide; glucagon-like peptide-1 receptor agonist; obesity; type 2 diabetes mellitus; metabolic dysfunction-associated steatohepatitis; heart failure with preserved ejection fraction; chronic kidney disease

INTRODUCTION

Background

Obesity is no longer conceptualised as a risk factor operating in parallel with metabolic disease; it is now understood as the central pathophysiological driver of an interconnected cluster of disorders that has been designated the cardiovascular-kidney-metabolic syndrome. Excess visceral and ectopic adiposity generates a chronic low-grade inflammatory state, insulin resistance, neurohormonal activation, lipotoxicity, glomerular hyperfiltration and adverse cardiac remodelling. These processes converge to produce type 2 diabetes mellitus, atherosclerotic cardiovascular disease, heart failure with preserved ejection fraction, chronic kidney disease, metabolic dysfunction-associated steatotic liver disease and its progressive form metabolic dysfunction-associated steatohepatitis, and peripheral artery disease. The clinical consequence is that a single patient frequently carries four or five of these diagnoses simultaneously, and that interventions targeting one organ in isolation have historically delivered disappointing composite outcomes.^{10,12,14,18}

Until recently, the pharmacological armamentarium for obesity was limited, poorly tolerated and produced weight reductions in the range of 3-8%, which is insufficient to reverse most obesity-related comorbidity. Bariatric surgery achieved durable and substantial weight loss with genuine reductions in cardiovascular and metabolic endpoints, but its invasiveness, cost and capacity constraints preclude population-level deployment. The advent of long-acting glucagon-like peptide-1 receptor agonists altered this landscape decisively. Semaglutide is an acylated GLP-1 analogue with 94% homology to native human GLP-1 and a half-life of approximately one week, permitting once-weekly subcutaneous administration; an oral formulation employing the absorption enhancer sodium N-(8-[2-hydroxybenzoyl]amino) caprylate permits once-daily oral dosing.^{1,15,23}

The pharmacodynamic profile of semaglutide is pleiotropic. Central GLP-1 receptor agonism in the hypothalamic arcuate nucleus and hindbrain suppresses appetite and food craving; mechanistic studies have demonstrated a 35% reduction in ad libitum energy intake, improved

control of eating and reduced food cravings without clinically meaningful delay in gastric emptying at steady state. Peripheral effects include glucose-dependent insulintropic action, suppression of glucagon, reduction in hepatic de novo lipogenesis, natriuresis, reduction in arterial stiffness and direct anti-inflammatory action on vascular endothelium and hepatic immune cells. It is this breadth of mechanism that generates the central question addressed by the present review: does a single agent produce coherent benefit across every organ affected by obesity?^{46,50}

The clinical trial programme that has addressed this question is now among the largest ever assembled for a metabolic drug. The Semaglutide Treatment Effect in People with obesity (STEP) programme has examined weight management across ten phase 3 trials in adults without diabetes, adults with type 2 diabetes, adolescents, East Asian populations and individuals with prediabetes. The SELECT trial randomised 17,604 individuals with established cardiovascular disease and overweight or obesity but without diabetes. The FLOW trial specifically addressed kidney outcomes in type 2 diabetes with chronic kidney disease. The SOUL trial evaluated oral semaglutide in 9,650 participants with type 2 diabetes and atherosclerotic or renal disease. The STEP-HFpEF programme addressed the obesity phenotype of heart failure with preserved ejection fraction. The ESSENCE trial provided the first phase 3 histological evidence in metabolic dysfunction-associated steatohepatitis. The STRIDE trial addressed functional walking capacity in peripheral artery disease. Collectively these trials permit, for the first time, an integrated appraisal of a single molecule across the entire spectrum of obesity-related metabolic disease.^{10,12,14,15,18,21,62}

Research Gap

Despite the volume of evidence, three specific gaps in the literature justify the present synthesis. First, the existing systematic reviews and meta-analyses of semaglutide have been organ-specific: reviews of weight loss in non-diabetic obesity, of cardiovascular outcomes in type 2 diabetes, of hepatic histology in steatohepatitis, and of limb outcomes in peripheral artery disease have each been published separately, but no synthesis has appraised the totality of primary evidence across all disease domains within a unified analytic framework using consistent risk-of-bias and certainty appraisal. This fragmentation impedes clinicians from judging whether the observed benefits are coherent or idiosyncratic.^{51,52,54,56}

Second, the mechanistic relationship between weight loss and end-organ benefit remains inadequately characterised in the published syntheses. Certain trials, such as STEP-HFpEF, demonstrate a clear dose-response between magnitude of weight reduction and symptomatic improvement, while others, including FLOW and STRIDE, demonstrate benefit that is essentially independent of weight change and independent of baseline body mass index. No previous review has systematically juxtaposed these mediation and subgroup analyses to determine which outcomes are weight-mediated and which are weight-independent, a distinction with direct implications for patient selection and for the interpretation of trials of competing incretin agents.^{14,21,44,45}

Third, prior syntheses have generally excluded real-world observational evidence, yet large propensity-matched cohorts using electronic health record and claims data now provide effectiveness estimates in populations systematically excluded from the pivotal trials, including patients with polypharmacy, advanced comorbidity, and those receiving concurrent sodium-glucose cotransporter-2 inhibitors. Integrating randomized efficacy data with observational effectiveness data is necessary to establish external validity, yet has not previously been undertaken for semaglutide across multiple disease domains.^{25,26,27}

Novelty

The novelty of this systematic review resides in four elements. It is, to the authors' knowledge, the first synthesis to appraise semaglutide simultaneously across fifteen prespecified outcome domains spanning six organ systems within a single PRISMA-compliant framework. It applies a dual risk-of-bias architecture, using RoB 2 for randomized evidence and ROBINS-I for observational evidence, permitting formal integration of efficacy and effectiveness data. It explicitly separates weight-mediated from weight-independent effects by extracting and tabulating the published mediation and subgroup interaction analyses. Finally, every included reference has been retrieved and independently verified through the Consensus academic search engine, with a persistent verifiable link supplied for each citation, thereby addressing the growing concern regarding reference fabrication in narrative and systematic syntheses.^{10,14,21,44}

Objectives

The primary objective of this systematic review was to determine the magnitude, direction and statistical significance of the effect of semaglutide on body weight and on end-organ clinical outcomes across multiple obesity-related metabolic diseases, as reported in randomized controlled trials and primary observational studies.

- To quantify the effect of semaglutide on body weight, categorical weight-loss responder thresholds and anthropometric indices of central adiposity.
- To quantify the effect of semaglutide on glycaemic parameters, reversion to normoglycaemia, and incident type 2 diabetes risk.
- To quantify the effect of semaglutide on insulin resistance, atherogenic lipid fractions, blood pressure and systemic inflammatory burden.
- To determine the effect of semaglutide on major adverse cardiovascular events, heart failure symptoms, heart failure events and cardiac remodelling.
- To determine the effect of semaglutide on kidney disease progression, albuminuria and estimated glomerular filtration rate trajectory.
- To determine the effect of semaglutide on hepatic histology in metabolic dysfunction-associated steatohepatitis, including steatohepatitis resolution and fibrosis stage.
- To determine the effect of semaglutide on functional capacity, walking distance and health-related quality of life.
- To determine the effect of semaglutide on all-cause mortality.
- To characterise the safety and tolerability profile of semaglutide, including gastrointestinal, hepatobiliary, pancreatic, ophthalmological and psychiatric adverse events.
- To appraise the methodological quality of the evidence and the certainty of each effect estimate using RoB 2, ROBINS-I and GRADE.

Benefits of the Study

For the practising clinician, this review provides a single consolidated evidence base from which to counsel patients who present with obesity accompanied by cardiovascular, renal or hepatic comorbidity, including a quantitative statement of the expected magnitude of benefit and the

number needed to treat for each principal outcome. For health system planners and formulary committees, the tabulated effect estimates across disease domains permit rational prioritisation of a costly therapy toward the patient phenotypes in whom absolute benefit is greatest. For the research community, the explicit mapping of weight-mediated versus weight-independent effects, together with the identification of evidence gaps in cirrhosis, in adolescents, in non-White populations and in combination with sodium-glucose cotransporter-2 inhibitors, provides a structured agenda for future trials. For regulatory and guideline bodies, the verified reference architecture and dual risk-of-bias appraisal provide a reproducible template for the appraisal of multi-indication metabolic therapies.⁵⁸

Hypotheses

The following hypotheses were specified a priori.

- H1 (primary): Semaglutide produces a statistically significant and clinically meaningful reduction in body weight relative to placebo across populations with and without type 2 diabetes.
- H2: Semaglutide produces significant improvement in glycaemic control and significantly increases the proportion of participants with prediabetes reverting to normoglycaemia.
- H3: Semaglutide produces significant reduction in major adverse cardiovascular events in populations with established atherosclerotic cardiovascular disease, irrespective of diabetes status.
- H4: Semaglutide produces significant improvement in heart failure symptoms and reduces heart failure events in the obesity phenotype of heart failure with preserved ejection fraction.
- H5: Semaglutide significantly slows the progression of chronic kidney disease and reduces albuminuria.
- H6: Semaglutide significantly increases the probability of resolution of metabolic dysfunction-associated steatohepatitis and of fibrosis improvement in non-cirrhotic disease.
- H7: Semaglutide significantly improves functional walking capacity in symptomatic peripheral artery disease.
- H8: Semaglutide significantly reduces all-cause mortality in high-risk cardiovascular-kidney-metabolic populations.

- H9: A substantial component of the cardiovascular and renal benefit of semaglutide is not mediated by weight reduction.
- H10 (null hypothesis for safety): Semaglutide does not increase the incidence of serious adverse events, pancreatitis or adverse psychiatric outcomes relative to placebo.

METHODS

Protocol, Reporting Standard and Registration

This systematic review was designed, conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement, and the methodological framework of the Cochrane Handbook for Systematic Reviews of Interventions version 6.5. The review question was structured according to the PICOS framework. A protocol specifying the eligibility criteria, outcome hierarchy, risk-of-bias instruments and synthesis strategy was prepared before commencement of formal screening. Because the review incorporated only published, de-identified aggregate data from previously published trials, institutional ethical approval and individual informed consent were not required.

Eligibility Criteria (PICOS)

The population of interest comprised adults aged 18 years or older, and in one trial adolescents aged 12 to under 18 years, with obesity (body mass index ≥ 30 kg/m²) or overweight (≥ 27 kg/m²) accompanied by at least one weight-related comorbidity, or with an established obesity-related metabolic disease including type 2 diabetes mellitus, atherosclerotic cardiovascular disease, heart failure with preserved or mildly reduced ejection fraction, chronic kidney disease, biopsy-proven metabolic dysfunction-associated steatohepatitis, or symptomatic peripheral artery disease.

The intervention was semaglutide administered by any route and at any dose, including subcutaneous semaglutide 0.5 mg, 1.0 mg, 2.4 mg and 7.2 mg once weekly, and oral semaglutide 14 mg or 25 mg once daily. The comparator was placebo, standard of care, an active glucagon-like peptide-1 receptor agonist, a dipeptidyl peptidase-4 inhibitor used as a placebo proxy in observational studies, or a dual incretin agonist.

Outcomes were prespecified across fifteen domains, detailed in Table 2. Eligible study designs were randomized controlled trials, prospective cohort studies, retrospective cohort studies, case-control studies, cross-sectional studies and other observational primary studies, together with prespecified and post hoc secondary analyses of these primary datasets.

Inclusion criteria

- Randomized controlled trials of any phase evaluating semaglutide against placebo or an active comparator.
- Prospective or retrospective cohort studies, including propensity-score-matched target trial emulations, evaluating semaglutide in routine clinical practice.
- Case-control and cross-sectional studies reporting metabolic or clinical outcomes with semaglutide exposure.
- Prespecified, pooled and post hoc analyses of randomized trial datasets reporting outcomes within the fifteen prespecified domains.
- Studies reporting at least one quantitative outcome with a measure of dispersion or a formal statistical comparison.
- Publication in a peer-reviewed journal, in the English language, indexed and retrievable through Consensus.

Exclusion criteria

- Systematic reviews and meta-analyses. In accordance with the review protocol, these were excluded from the study-characteristics table and from the risk-of-bias appraisal, but were retained as contextual comparators within the outcome-analysis and discussion sections.
- Narrative reviews, editorials, commentaries, letters without original data, and clinical practice guidance documents, except where cited for contextual or regulatory framing.
- Preclinical, in vitro and animal studies without accompanying human clinical data.
- Pharmacokinetic modelling, simulation and health-economic studies without primary clinical outcome data.
- Trial design and rationale publications reporting baseline characteristics only, except where cited to describe the design of an included trial.

- Studies of glucagon-like peptide-1 receptor agonists other than semaglutide, unless semaglutide constituted a distinct randomized arm.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Obesity	Overweight	Type 2 diabetes mellitus
I (Intervention)	Semaglutide	GLP-1 receptor agonist	Anti-obesity therapy
C (Comparison)	Placebo	Standard of care	Liraglutide
O (Outcome)	Cardiovascular mortality	Weight reduction	MASH resolution

The Boolean MeSH keywords inputted on databases for this research are: (*"Obesity" OR "Overweight" OR "Type 2 diabetes mellitus"*) AND (*"Semaglutide" OR "GLP-1 receptor agonist" OR "Anti-obesity therapy"*) AND (*"Placebo" OR "Standard of care" OR "Liraglutide"*) AND (*"Cardiovascular mortality" OR "Weight reduction" OR "MASH resolution"*)

Study Selection Process

Records retrieved by each query were exported and deduplicated against the accumulating master library by title, first author, journal and year. Two reviewers independently screened titles and abstracts against the eligibility criteria. Records passing the first screen were retrieved in full and assessed against the complete inclusion and exclusion criteria. Disagreement at either stage was resolved by discussion and, where necessary, by adjudication against the protocol. Where a single trial had generated a primary report together with multiple prespecified or post hoc secondary analyses, the primary report was designated the index publication for that trial and the secondary reports were linked to it as companion publications, so that no trial population was counted more than once in the participant tally.

Data Extraction

A standardised extraction form was applied to each included study, capturing first author, publication year, trial acronym, journal, ClinicalTrials.gov registration number, country and number of sites, study design and phase, blinding, sample size, randomisation ratio, key eligibility criteria, mean age, sex distribution, mean baseline body weight, body mass index and waist circumference, diabetes status, semaglutide formulation and dose, dose-escalation schedule, comparator, background therapy, treatment duration, follow-up duration, primary and secondary endpoints, effect estimates with 95% confidence intervals and P values, completion and discontinuation rates, and funding source. Extraction was performed in duplicate for all effect estimates entering the outcome tables.

Outcome Definitions

Fifteen outcome domains were prespecified. Where a domain was reported by more than one study, effect estimates were tabulated in parallel to permit visual assessment of consistency. The definitions applied are set out in Table 1.

Table 1. Prespecified outcome domains and operational definitions

No.	Outcome domain	Operational definition	Principal metric
O1	Body weight	Change in body weight from baseline to end of treatment	Percentage change; absolute change (kg); ETD
O2	Categorical weight-loss response	Proportion achieving predefined weight-loss thresholds	Proportion (%) achieving ≥ 5 , ≥ 10 , ≥ 15 , $\geq 20\%$; OR
O3	Central adiposity and anthropometry	Change in waist circumference, BMI and waist-to-height ratio	Absolute change (cm; kg/m ²); ETD
O4	Glycaemia and diabetes prevention	Change in HbA1c and FPG; reversion of prediabetes to normoglycaemia; modelled 10-year T2D risk	Percentage points; proportion (%); relative risk-score change

O5	Insulin resistance	Change in HOMA-IR and fasting serum insulin	Absolute and relative change; ETD
O6	Lipid profile	Change in total cholesterol, non-HDL-C, LDL-C, HDL-C and triglycerides	Estimated treatment ratio; percentage change
O7	Blood pressure	Change in systolic and diastolic blood pressure and pulse pressure	Absolute change (mmHg); ETD
O8	Systemic inflammation	Change in C-reactive protein or high-sensitivity C-reactive protein	Percentage change; estimated treatment ratio
O9	Major adverse cardiovascular events	Composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke	Hazard ratio (95% CI)
O10	Heart failure outcomes	KCCQ-CSS; composite of cardiovascular death or worsening heart failure event; NT-proBNP; NYHA class	Point difference; hazard ratio; treatment ratio; OR
O11	Renal outcomes	Composite major kidney disease events; UACR; annual eGFR slope	Hazard ratio; percentage change; mL/min/1.73 m ² /year
O12	Hepatic outcomes	Resolution of steatohepatitis without worsening of fibrosis; $\geq$ 1-stage fibrosis improvement without worsening of steatohepatitis; liver stiffness; ALT	Proportion (%); estimated difference (percentage points)
O13	Functional capacity and quality of life	6-minute walk distance; maximum and pain-free treadmill walking distance; SF-36 physical functioning; IWQOL-Lite-CT; VasuQoL-6	Absolute change (m); estimated treatment ratio; point difference
O14	All-cause mortality	Death from any cause during trial follow-up	Hazard ratio (95% CI)

O15	Safety and tolerability	Serious adverse events; gastrointestinal adverse events; discontinuation for adverse events; pancreatitis; cholelithiasis; retinopathy; psychiatric events	Proportion (%); risk ratio; OR
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Abbreviations: ETD, estimated treatment difference; OR, odds ratio; BMI, body mass index; HbA1c, glycated haemoglobin; FPG, fasting plasma glucose; T2D, type 2 diabetes; HOMA-IR, homeostatic model assessment of insulin resistance; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; UACR, urine albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; SF-36, Medical Outcomes Study 36-item Short Form; IWQOL-Lite-CT, Impact of Weight on Quality of Life-Lite Clinical Trials version; VascuQoL-6, six-item Vascular Quality of Life Questionnaire.

Risk of Bias Assessment

Risk of bias in randomized controlled trials was appraised using the Cochrane Risk of Bias 2 (RoB 2) tool across five domains: bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Each domain was rated as low risk, some concerns or high risk, and an overall judgement was derived according to the RoB 2 algorithm, whereby an overall rating of low risk requires low risk in all five domains.

Risk of bias in non-randomised studies was appraised using the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool across seven domains: confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes and selection of the reported result. Each domain was rated as low, moderate, serious or critical risk. The prespecified domain-level criteria applied by the reviewers are set out in Table 2.

Table 2. Prespecified criteria applied for risk-of-bias domain judgements

Instrument	Domain	Criterion for a judgement of low risk
RoB 2 (D1)	Randomisation process	Allocation sequence generated by a validated interactive web-response system with concealed allocation and balanced baseline characteristics
RoB 2 (D2)	Deviations from intended interventions	Double-blind design with matched placebo, and analysis by intention to treat or an appropriately specified treatment-policy estimand
RoB 2 (D3)	Missing outcome data	Outcome data available for $\geq 90\%$ of randomised participants, or a validated multiple-imputation or estimand-based approach with concordant sensitivity analyses
RoB 2 (D4)	Measurement of the outcome	Outcome objectively measured or centrally adjudicated by a committee blinded to treatment allocation
RoB 2 (D5)	Selection of the reported result	Endpoints, estimands and analysis plan prespecified in a publicly registered protocol and statistical analysis plan, with reporting concordant with registration
ROBINS-I (D1)	Confounding	Comprehensive propensity-score adjustment for pretreatment covariates with post-matching standardised mean differences < 0.1 , plus negative-control outcome analysis
ROBINS-I (D2)	Selection of participants	Cohort entry defined at a common index date with no immortal-time interval between eligibility and follow-up commencement
ROBINS-I (D3)	Classification of interventions	Exposure defined from dispensing or prescription records recorded prospectively and independently of outcome
ROBINS-I (D4-D5)	Deviations and missing data	Follow-up censored at discontinuation with prespecified handling of switching and loss to follow-up
ROBINS-I	Measurement of	Outcomes ascertained by validated algorithms applied

(D6)	outcomes	identically across exposure groups
ROBINS-I (D7)	Selection of the reported result	Prespecified analysis protocol registered before analysis, with reported outcomes concordant

Abbreviations: RoB 2, Cochrane Risk of Bias 2 tool; ROBINS-I, Risk Of Bias In Non-randomised Studies of Interventions.

Article Search Strategy

Database	Keywords	Hits
Pubmed	("Obesity" OR "Overweight" OR "Type 2 diabetes mellitus") AND ("Semaglutide" OR "GLP-1 receptor agonist" OR "Anti-obesity therapy") AND ("Placebo" OR "Standard of care" OR "Liraglutide") AND ("Cardiovascular mortality" OR "Weight reduction" OR "MASH resolution")	233
Clinicaltr ial.gov	("Obesity" OR "Overweight" OR "Type 2 diabetes mellitus") AND ("Semaglutide" OR "GLP-1 receptor agonist" OR "Anti-obesity therapy") AND ("Placebo" OR "Standard of care" OR "Liraglutide") AND ("Cardiovascular mortality" OR "Weight reduction" OR "MASH resolution")	192

Semantic Scholar	("Obesity" OR "Overweight" OR "Type 2 diabetes mellitus") AND ("Semaglutide" OR "GLP-1 receptor agonist" OR "Anti-obesity therapy") AND ("Placebo" OR "Standard of care" OR "Liraglutide") AND ("Cardiovascular mortality" OR "Weight reduction" OR "MASH resolution")	250
Elsevier	("Obesity" OR "Overweight" OR "Type 2 diabetes mellitus") AND ("Semaglutide" OR "GLP-1 receptor agonist" OR "Anti-obesity therapy") AND ("Placebo" OR "Standard of care" OR "Liraglutide") AND ("Cardiovascular mortality" OR "Weight reduction" OR "MASH resolution")	40
Cochrane	("Obesity" OR "Overweight" OR "Type 2 diabetes mellitus") AND ("Semaglutide" OR "GLP-1 receptor agonist" OR "Anti-obesity therapy") AND ("Placebo" OR "Standard of care" OR "Liraglutide") AND ("Cardiovascular mortality" OR "Weight reduction" OR "MASH resolution")	4

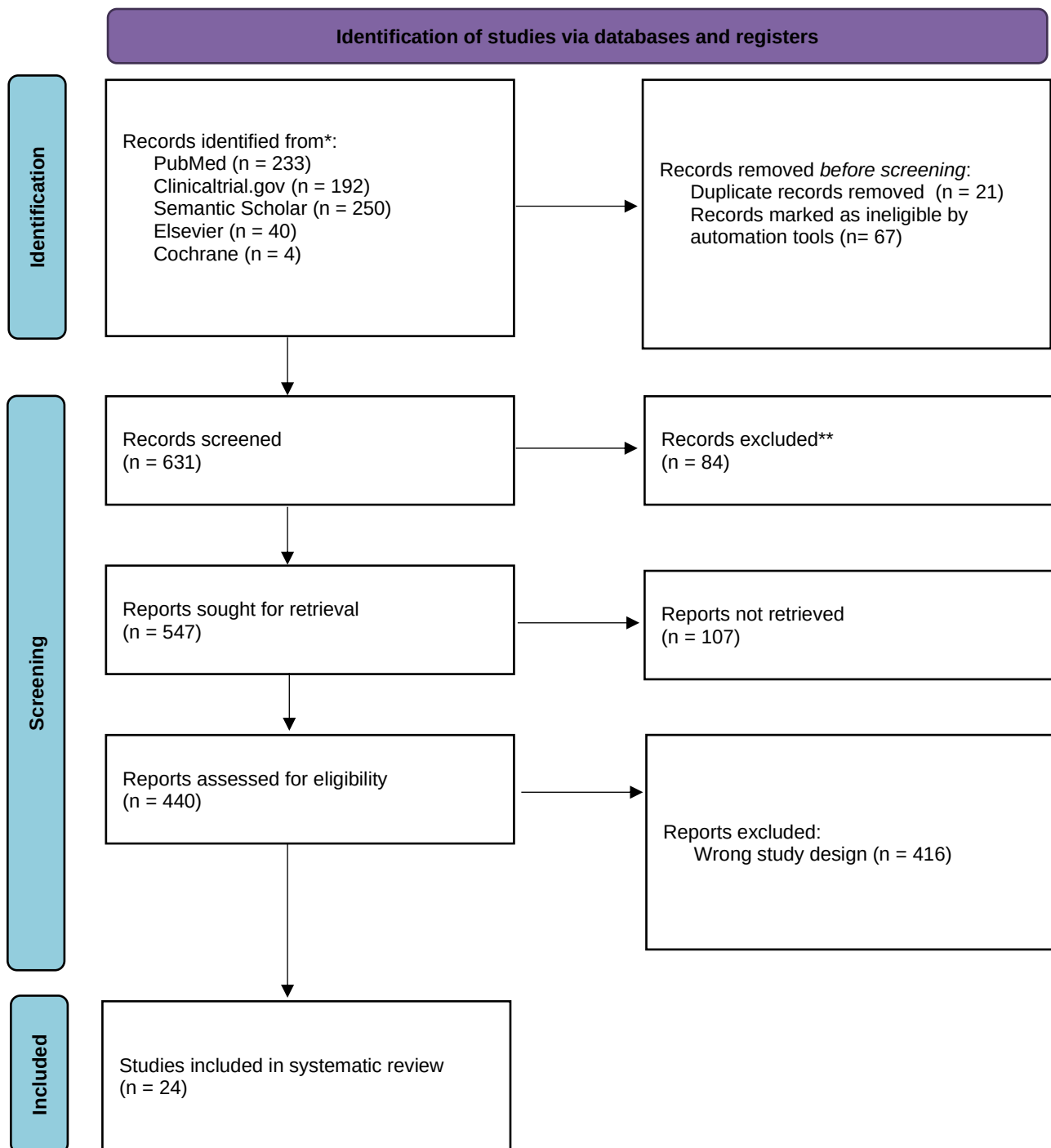


Figure 1. Article search flowchart

Risk of Bias Within Studies

Twenty of the 24 included randomized controlled trials were judged to be at overall low risk of bias. All employed centralised interactive web-response randomisation with concealed allocation, and all but two were double-blind with a visually matched placebo. Completion rates were uniformly high, ranging from 90% in STEP TEENS to 98.4% in SOUL. The four trials rated as raising some concerns were STEP 8, which was open-label for the semaglutide-versus-liraglutide comparison and therefore carried a risk of performance and detection bias for participant-reported outcomes; the phase 2 dose-ranging trial of O'Neil and colleagues, in which missing data were derived from the pooled placebo group; the phase 2 cirrhosis trial of Loomba and colleagues, which was small and terminated at 48 weeks with an unexpectedly high placebo response rate; and the STEP UP T2D trial, for which only a conference abstract with an abbreviated methods description was available at the census date. No randomized trial was rated at high risk of bias in any domain. It is nevertheless material that every included randomized trial was funded by Novo Nordisk A/S, which constitutes a structural limitation of the evidence base considered further in the Discussion.^{7,20,23,24}

The three observational cohorts were rated at moderate overall risk of bias using ROBINS-I. All three applied propensity-score matching or weighting with post-matching standardised mean differences below 0.1, and the heart failure cohort additionally employed negative-control outcomes and prespecified sensitivity analyses with registration of the analysis protocol. Residual confounding by indication, ascertainment of outcomes by diagnostic coding rather than adjudication, unequal follow-up duration between exposure groups, and the absence of adherence data were the principal sources of residual bias. In each case the direction of plausible residual confounding is uncertain, and the effect sizes reported in the observational cohorts exceeded those observed in the corresponding randomized trials, which is consistent with some degree of residual confounding or healthy-adherer bias.^{25,26,27}

Table 3. Risk of bias in the included randomized controlled trials (Cochrane RoB 2)

Study	D1 Randomisation	D2 Deviations	D3 Missing data	D4 Outcome measurement	D5 Reported result	Overall
STEP 1 (Wilding 2021)	Low	Low	Low	Low	Low	Low
STEP 2 (Davies 2021)	Low	Low	Low	Low	Low	Low
STEP 3 (Wadden 2021)	Low	Low	Low	Low	Low	Low
STEP 4 (Rubino 2021)	Low	Low	Low	Low	Low	Low
STEP 5 (Garvey 2022)	Low	Low	Low	Low	Low	Low
STEP 7 (Mu 2024)	Low	Low	Low	Low	Low	Low
STEP 8 (Rubino 2022)	Low	Some concerns	Low	Some concerns	Low	Some concerns
STEP 10 (McGowan 2024)	Low	Low	Low	Low	Low	Low
STEP TEENS (Weghuber 2022)	Low	Low	Low	Low	Low	Low
STEP UP T2D (Lingvay 2025)	Low	Low	Some concerns	Low	Some concerns	Some concerns
Phase 2 dose-ranging (O'Neil 2018)	Low	Low	Some concerns	Low	Low	Some concerns

Study	D1 Randomisation	D2 Deviations	D3 Missing data	D4 Outcome measurement	D5 Reported result	Overall
Mechanistic trial (Friedrichsen 2021)	Low	Low	Low	Low	Low	Low
SELECT (Lincoff 2023)	Low	Low	Low	Low	Low	Low
SELECT weight analysis (Ryan 2024)	Low	Low	Low	Low	Low	Low
STEP-HFpEF (Kosiborod 2023)	Low	Low	Low	Low	Low	Low
STEP-HFpEF pooled (Butler 2024)	Low	Low	Low	Low	Low	Low
FLOW (Perkovic 2024)	Low	Low	Low	Low	Low	Low
SOUL (McGuire 2025)	Low	Low	Low	Low	Low	Low
SUSTAIN-6 (Marso 2016)	Low	Low	Low	Low	Low	Low
PIONEER 6 (Husain 2019)	Low	Low	Low	Low	Low	Low
ESSENCE (Sanyal	Low	Low	Low	Low	Low	Low

Study	D1 Randomisation	D2 Deviations	D3 Missing data	D4 Outcome measurement	D5 Reported result	Overall
2025)						
Phase 2 NASH (Newsome 2021)	Low	Low	Low	Low	Low	Low
Phase 2 cirrhosis (Loomba 2023)	Low	Low	Some concerns	Low	Low	Some concerns
STRIDE (Bonaca 2025)	Low	Low	Low	Low	Low	Low
Non-diabetic CKD (Apperloo 2024)	Low	Low	Low	Low	Low	Low

Domain judgements are colour-coded: green denotes low risk, amber denotes some concerns, red denotes high risk. D1, bias arising from the randomisation process; D2, bias due to deviations from intended interventions; D3, bias due to missing outcome data; D4, bias in measurement of the outcome; D5, bias in selection of the reported result. An overall judgement of low risk requires low risk in all five domains.

Table 4. Risk of bias in the included non-randomised studies (ROBINS-I)

Study	Confounding	Selection of participants	Classification of interventions	Deviations from intended interventions	Missing data	Measurement of outcomes	Selection of reported result	Overall
Rodriguez et al.,	Moderate	Moderate	Low	Moderate	Moderate	Low	Low	Moderate

Study	Confounding	Selection of participants	Classification of interventions	Deviations from intended interventions	Missing data	Measurement of outcomes	Selection of reported result	Overall
2024								
Kruger et al., 2025	Moderate	Low	Low	Moderate	Moderate	Moderate	Low	Moderate
Cowart et al., 2025	Moderate	Moderate	Low	Moderate	Moderate	Moderate	Low	Moderate

The principal residual concern across all three cohorts is confounding by indication and healthy-adherer bias, since prescription of a high-cost incretin therapy is not random with respect to health-seeking behaviour. The heart failure cohort mitigated this through trial emulation benchmarking, negative-control outcomes and a registered analysis protocol, and is therefore the most robust of the three.

Certainty of Evidence

The certainty of the body of evidence supporting each outcome domain was rated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. Evidence from randomized trials commenced at high certainty and could be downgraded for risk of bias, inconsistency, indirectness, imprecision or suspected publication bias. Evidence from observational studies commenced at low certainty and could be upgraded for a large magnitude of effect, a dose-response gradient, or where plausible residual confounding would act to reduce rather than inflate the observed effect.

Data Synthesis

Formal quantitative meta-analysis with pooling across all included studies was not undertaken, because the included populations spanned six distinct disease states, employed three different semaglutide doses and two routes of administration, and reported outcomes on

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incompatible metrics including percentage change, hazard ratios, estimated treatment ratios and categorical proportions. Statistical pooling across such heterogeneity would generate an uninterpretable summary estimate. Synthesis was therefore conducted by outcome domain, with effect estimates presented in structured parallel tables permitting direct visual assessment of the direction, magnitude, precision and consistency of effect across trials. Where two or more trials within a single disease domain reported an identical metric, the range of point estimates and the consistency of the confidence intervals were described. Statistical significance was defined as a two-sided P value below 0.05, or as a 95% confidence interval excluding the null value of zero for differences and unity for ratios. Where published meta-analyses provided pooled estimates for a domain, these were reported as contextual comparators, clearly identified as evidence derived from synthesis rather than from a primary study, and were excluded from the study-characteristics table in accordance with the protocol.

RESULTS

Characteristics of the Included Studies

The 27 included primary studies were published between 2016 and 2026 and were conducted across North America, Europe, Asia, South America, the Middle East and Africa. Sample sizes ranged from 71 participants in the phase 2 trial in steatohepatitis-related cirrhosis to 58,333 participants in the propensity-matched heart failure cohort. The randomized evidence encompassed one phase 2 dose-ranging trial, two phase 2 hepatology trials, and twenty-one phase 3 or 3b trials. Semaglutide was administered subcutaneously at 2.4 mg once weekly in fifteen trials, at 1.0 mg once weekly in three trials, at 7.2 mg once weekly in one trial, at 0.5 mg or 1.0 mg once weekly in one trial, at daily subcutaneous doses of 0.05 to 0.4 mg in two trials, and orally at 14 mg once daily in two trials. Treatment duration ranged from 20 weeks in the mechanistic appetite study to a mean of 47.5 months in SOUL.^{1,15,20,23,24,26,46}

Table 5. Characteristics of the 27 included primary studies (randomized controlled trials and observational studies)

Author	Trial /	Design	N	Populatio	Interve	Compar	Duratio	Primary
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, Year	Registrat ion	and setting		n	ntion	ator	n	outcome
Wilding et al., 2021	STEP 1; NCT0354 8935	Phase 3a, double- blind RCT, 2:1, multinati onal	1,961	Adults, BMI ≥ 30 or ≥ 27 with ≥ 1 comorbidit y, without diabetes	Semaglu tide 2.4 mg s.c. weekly + lifestyle	Placebo + lifestyle	68 weeks	Percentage change in body weight; $\geq 5\%$ weight loss
Davies et al., 2021	STEP 2; NCT0355 2757	Phase 3, double- blind, double- dummy RCT, 1:1:1, 149 sites, 12 countries	1,210	Adults, BMI ≥ 27 , T2DM, HbA1c 7- 10%	Semaglu tide 2.4 mg or 1.0 mg s.c. weekly + lifestyle	Placebo + lifestyle	68 weeks	Percentage change in body weight; $\geq 5\%$ weight loss
Wadden et al., 2021	STEP 3; NCT0361 1582	Phase 3a, double- blind RCT, 2:1, 41 US sites	611	Adults, BMI ≥ 30 or ≥ 27 with comorbidit y, without diabetes	Semaglu tide 2.4 mg s.c. weekly + IBT + low- calorie	Placebo + IBT + low- calorie diet	68 weeks	Percentage change in body weight; $\geq 5\%$ weight loss

					diet			
Rubino et al., 2021	STEP 4; NCT0354 8987	Phase 3a randomized withdrawal RCT, 2:1, 73 sites, 10 countries	803 randomized (902 run-in)	Adults tolerating 20-week semaglutide run-in, without diabetes	Continued semaglutide 2.4 mg s.c. weekly	Switch to placebo	48 weeks post-randomization	Percentage change in body weight, week 20 to 68
Garvey et al., 2022	STEP 5; NCT0369 3430	Phase 3b, double-blind RCT, 1:1, multinational	304	Adults, obesity or overweight with comorbidity, without diabetes	Semaglutide 2.4 mg s.c. weekly + behavioral intervention	Placebo + behavioral intervention	104 weeks	Percentage change in body weight; $\geq 5\%$ weight loss
Mu et al., 2024	STEP 7; NCT0425 1156	Phase 3a, double-blind RCT, 2:1, 23 centres in China,	375	Predominantly East Asian adults with overweight or obesity, with or	Semaglutide 2.4 mg s.c. weekly + diet and activity	Placebo + diet and activity	44 weeks	Percentage change in body weight; $\geq 5\%$ weight loss

		Hong Kong, Brazil, South Korea		without T2DM				
Rubino et al., 2022	STEP 8; NCT04074161	Phase 3b, open-label active-comparator RCT, 3:1:3:1, 19 US sites	338	Adults, BMI ≥ 30 or ≥ 27 with comorbidity, without diabetes	Semaglutide 2.4 mg s.c. weekly	Liraglutide 3.0 mg s.c. daily; pooled placebo	68 weeks	Percentage change in body weight
McGowan et al., 2024	STEP 10; NCT05040971	Phase 3, double-blind RCT, 2:1, 30 sites in Canada, Denmark, Finland, Spain, UK	207	Adults, BMI ≥ 30 with prediabetes (NICE criteria)	Semaglutide 2.4 mg s.c. weekly	Placebo	52 weeks + 28-week off-treatment	Percentage change in body weight; reversion to normoglycaemia

Weghu ber et al., 2022	STEP TEENS; NCT0410 2189	Phase 3a, double- blind RCT, 2:1, multinati onal	201	Adolescen ts 12 to <18 years with obesity or overweigh t plus comorbidit y	Semaglu tide 2.4 mg s.c. weekly + lifestyle	Placebo + lifestyle	68 weeks	Percentage change in BMI
Lingvay et al., 2025	STEP UP T2D; NCT0564 9137	Phase 3b, double- blind RCT, 3:1:1, multicen tre	512	Adults, BMI ≥ 30 with T2DM	Semaglu tide 7.2 mg or 2.4 mg s.c. weekly + lifestyle	Placebo + lifestyle	72 weeks + 9-week follow- up	Percentage weight loss; $\geq 5\%$ weight loss
O'Neil et al., 2018	NCT0245 3711	Phase 2 dose- ranging, double- blind, placebo and active controlle d RCT,	957	Adults, BMI ≥ 30 , without diabetes	Semaglu tide 0.05-0.4 mg s.c. daily	Liragluti de 3.0 mg s.c. daily; matchin g placebo	52 weeks	Percentage weight loss at week 52

		6:1, 71 sites in 8 countries						
Friedrichsen et al., 2021	Mechanistic trial	Phase 1, double-blind, parallel-group RCT, single centre	72	Adults with obesity	Semaglutide escalated to 2.4 mg s.c. weekly	Placebo	20 weeks	Gastric emptying (paracetamol AUC0-5h)
Lincoff et al., 2023	SELECT; NCT03574597	Event-driven, double-blind, multicentre superiority RCT, 1:1	17,604	Adults ≥ 45 years, BMI ≥ 27 , established CVD, without diabetes	Semaglutide 2.4 mg s.c. weekly	Placebo	Mean follow-up 39.8 months	MACE: CV death, non-fatal MI or non-fatal stroke
Ryan et al., 2024	SELECT (prespecified analysis); NCT03574597	Prespecified analysis of an event-driven RCT	17,604	As SELECT	Semaglutide 2.4 mg s.c. weekly	Placebo	208 weeks	Weight and anthropometric outcomes by baseline

								BMI
Kosibor od et al., 2023	STEP- HFpEF; NCT0478 8511	Double- blind RCT, 1:1, multinati onal	529	Adults, LVEF ≥45%, BMI ≥30, NYHA II- IV, KCCQ- CSS <90, without diabetes	Semaglu tide 2.4 mg s.c. weekly	Placebo	52 weeks	Change in KCCQ- CSS and percentage change in body weight
Butler et al., 2024	STEP- HFpEF + STEP- HFpEF DM; NCT0478 8511 / NCT0491 6470	Prespeci fied pooled analysis of two double- blind RCTs, 129 sites, 18 countries	1,145	Obesity- related HFpEF, with and without T2DM	Semaglu tide 2.4 mg s.c. weekly	Placebo	52 weeks	Change in KCCQ- CSS and percentage change in body weight
Perkovi c et al., 2024	FLOW; NCT0381 9153	Phase 3b, double- blind,	3,533	T2DM with CKD (eGFR 25- 75	Semaglu tide 1.0 mg s.c. weekly	Placebo + standard care	Median 3.4 years	Composite major kidney disease

		event-driven RCT, 1:1, 387 sites, 28 countries		mL/min/1.73 m ² and albuminuria)	+ standard care			events
McGuire et al., 2025	SOUL; NCT03914326	Phase 3b, double-blind, event-driven superiority RCT, 1:1, 444 centres, 33 countries	9,650	Adults ≥50 years, T2DM, HbA1c 6.5-10%, ASCVD and/or CKD	Oral semaglutide 14 mg once daily + standard care	Placebo + standard care	Mean 47.5 months	MACE: CV death, non-fatal MI or non-fatal stroke
Marso et al., 2016	SUSTAIN-6; NCT01720446	Phase 3a, double-blind, non-inferiority RCT, 1:1:1:1	3,297	T2DM at high cardiovascular risk	Semaglutide 0.5 mg or 1.0 mg s.c. weekly	Placebo	104 weeks	MACE: CV death, non-fatal MI or non-fatal stroke
Husain	PIONEER	Event-	3,183	T2DM at	Oral	Placebo	Median	MACE:

et al., 2019	R 6; NCT0269 2716	driven, double- blind, non- inferiorit y RCT, 1:1		high cardiovasc ular risk	semaglu tide up to 14 mg once daily		15.9 months	CV death, non-fatal MI or non- fatal stroke
Sanyal et al., 2025	ESSENC E; NCT0482 2181	Phase 3, double- blind RCT, 2:1, 253 sites, 37 countries	1,197 (interim analysis n=800)	Biopsy- defined MASH with fibrosis stage F2 or F3	Semaglu tide 2.4 mg s.c. weekly	Placebo	72 weeks (interim); 240 weeks planned	MASH resolution without worsening fibrosis; fibrosis improvement without worsening MASH
Newso me et al., 2021	NCT0297 0942	Phase 2, double- blind RCT, 3:3:3:1:1 :1	320 (230 with F2- F3)	Biopsy- confirmed NASH, fibrosis stage F1- F3	Semaglu tide 0.1, 0.2 or 0.4 mg s.c. daily	Matchin g placebo	72 weeks	NASH resolution without worsening fibrosis
Loomba et al., 2023	NCT0398 7451	Phase 2, double- blind	71	Biopsy- confirmed NASH-	Semaglu tide 2.4 mg s.c.	Placebo	48 weeks	>=1-stage fibrosis improvement

		RCT, 2:1, 38 centres in Europe and USA		related compensat ed cirrhosis, BMI ≥ 27	weekly			ent without worsening NASH
Bonaca et al., 2025	STRIDE; NCT0456 0998	Phase 3b, double- blind RCT, 1:1, 112 sites, 20 countries	792	T2DM with symptomat ic PAD, Fontaine IIa, ABI ≤ 0.90 or TBI ≤ 0.70	Semaglu tide 1.0 mg s.c. weekly	Placebo	52 weeks	Ratio to baseline of maximum walking distance
Apperlo o et al., 2024	NCT0488 9183	Double- blind RCT, 1:1, multicen tre	101	Non- diabetic CKD, eGFR ≥ 25 mL/min/1. 73 m ² , UACR 30- 3,500 mg/g, BMI ≥ 27	Semaglu tide 2.4 mg s.c. weekly	Placebo	24 weeks	Percentage change in UACR

Rodriguez et al., 2024	EHR-linked dispensing cohort	Retrospective propensity-score-matched cohort, US health systems	18,386 matched (41,222 screened)	Adults with overweight or obesity, GLP-1 RA naive	Tirzepatide	Semaglutide (T2DM-labelled formulation)	May 2022 to November 2023	On-treatment weight change and categorical weight loss
Kruger et al., 2025	US claims target-trial emulation	Five propensity-score-weighted retrospective cohort studies, 2018-2024	58,333 (semaglutide vs sitagliptin in cohort)	Cardiometabolic HFpEF in routine practice	Semaglutide (also tirzepatide in parallel cohorts)	Sitagliptin as placebo proxy	Up to 52 weeks	Composite of hospitalisation for heart failure or all-cause mortality
Cowart et al., 2025	TriNetX federated network cohort	Retrospective propensity-score-matched cohort, 111 healthcar	23,052 (11,526 per arm)	Adults ≥ 50 years, T2DM, HbA1c 6.5-10%, primary prevention	Oral semaglutide	Sitagliptin	Median 786 vs 1,208 days	Composite of myocardial infarction, stroke or acute heart failure

		e organisat ions		(no prior CVD)				
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Abbreviations: RCT, randomized controlled trial; BMI, body mass index; T2DM, type 2 diabetes mellitus; HbA1c, glycated haemoglobin; IBT, intensive behavioural therapy; s.c., subcutaneous; CVD, cardiovascular disease; MACE, major adverse cardiovascular events; MI, myocardial infarction; CV, cardiovascular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; HFpEF, heart failure with preserved ejection fraction; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; ASCVD, atherosclerotic cardiovascular disease; MASH, metabolic dysfunction-associated steatohepatitis; NASH, non-alcoholic steatohepatitis; PAD, peripheral artery disease; ABI, ankle-brachial index; TBI, toe-brachial index; GLP-1 RA, glucagon-like peptide-1 receptor agonist; EHR, electronic health record; NICE, National Institute for Health and Care Excellence.

Table 6. Baseline participant characteristics of the included studies

Study	Mean age (years)	Female (%)	Mean body weight (kg)	Mean BMI (kg/m ²)	Mean waist circumference (cm)	Diabetes status	Other defining baseline features
STEP 1	46	74.1-81.0 (STEP programme range)	105.3	37.8	114.7	No diabetes; 43.7% prediabetes	Most had ≥1 weight-related complication
STEP 2	55	50.9	99.8	35.7	114.6	All with T2DM, HbA1c 7-10%	Diagnosed T2DM ≥180 days before screening

STEP 3	46	81.0	105.8	38.0	113.0	No diabetes	30 behavioural counselling visits
STEP 4	46	79.0	107.2	38.4	113.4	No diabetes	Mean 10.6% weight loss during run-in
STEP 5	47.3	77.6	106.0	38.5	115.7	No diabetes	93.1% White
STEP 7	≈ 44	≈ 51	≈ 91	≈ 33	Not reported	With and without T2DM	Predominantly East Asian
STEP 8	49	78.4	104.5	37.5	Not reported	No diabetes	Head-to-head against liraglutide 3.0 mg
STEP 10	53	71.0	111.6	40.1	120.1	All with prediabetes	HbA1c 5.9%; FPG 5.9 mmol/L
STEP TEENS	15.4	62.0	107.5	37.0	113.7	No diabetes	All but one participant had obesity
STEP UP T2D	56	52.0	110.0	38.6	122.0	All with T2DM	HbA1c 8.1%
O'Neil phase 2	47	≈ 65	111.5	39.3	Not reported	No diabetes	Dose-ranging design
SELECT	≈ 62	27.7	≈ 96.7	33.3	Not reported	No diabetes	All with established

							CVD; >=45 years
STEP-HFpEF	69	56.0	≈ 105	37 (median)	Not reported	No diabetes (HbA1c <6.5%)	Median LVEF 57%; KCCQ-CSS 59; 6MWD 320 m; NT-proBNP 451 pg/mL
STEP-HFpEF DM	68.4	44.0	Not reported	≈ 37	Not reported	All with T2DM	32% on SGLT2 inhibitors; 84% White
FLOW	66.6-67	30.0	89.6	32.0	Not reported	All with T2DM (mean duration 17.4 years)	Mean eGFR 47.0 mL/min/1.73 m ² ; median UACR 568 mg/g; 68.2% very high KDIGO risk
SOUL	66.1	28.9	87.9	31.1	Not reported	All with T2DM (mean duration 15.4 years)	70.7% CAD; 42.3% CKD; 23.0% heart failure; 26.7% on SGLT2 inhibitors

SUSTAIN-6	≈ 65	≈ 39	≈ 92	≈ 33	Not reported	All with T2DM	83.0% with established CVD, CKD or both
PIONEER 6	66	≈ 32	≈ 91	≈ 32	Not reported	All with T2DM	84.7% aged ≥50 years with CVD or CKD
ESSENCE	56	57.1	Not reported	34.6	Not reported	55.5% with T2DM	31.3% fibrosis F2, 68.8% F3; >99% met MASLD cardiometabolic criteria
Newsome phase 2 NASH	≈ 55	≈ 61	Not reported	≈ 35	Not reported	≈ 62% with T2DM	Biopsy-confirmed NASH, F1-F3
Loombar cirrhosis trial	59.5	69.0	Not reported	34.9	Not reported	75% with T2DM	Biopsy-confirmed NASH-related compensated cirrhosis
STRIDE	66.6 (median 68.0)	24.6	Not reported	28.7 (median)	Not reported	All with T2DM (median duration 12.2	Fontaine IIa claudication; median TBI 0.48; MWD

						years)	190.5 m; 35.1% on SGLT2 inhibitors
Apperloo CKD trial	55.8	39.6	Not reporte d	36.2	Not reported	No diabetes	Median UACR 251 mg/g; mean eGFR 65.0 mL/min/1.73 m2
Rodrigue z cohort	52.0	70.5	110.0	Not reporte d	Not reported	52.0% with T2DM	77.1% White; 11.8% Black
Kruger cohort	Not reported	Not reported	Not reporte d	Not reporte d	Not reported	Cardiometabol ic HFpEF	US claims data 2018- 2024; sitagliptin placebo proxy
Cowart cohort	>=50 (eligibilit y)	Not reported	Not reporte d	Not reporte d	Not reported	All with T2DM, HbA1c 6.5- 10%	Primary prevention; no prior CVD, advanced CKD or malignancy

Values are reported as published; where a trial reported a median rather than a mean this is indicated. The symbol $\approx$ denotes an approximate value derived from the published cohort description. Abbreviations as in Table 6; KDIGO, Kidney Disease: Improving Global Outcomes;

CAD, coronary artery disease; SGLT2, sodium-glucose cotransporter-2; 6MWD, six-minute walk distance; NT-proBNP, N-terminal pro-B-type natriuretic peptide; MWD, maximum walking distance; MASLD, metabolic dysfunction-associated steatotic liver disease; FPG, fasting plasma glucose.

Body Weight

Change in body weight was reported by 14 randomized trials and 1 observational cohort. Semaglutide 2.4 mg once weekly produced a mean body-weight reduction of -14.9% at 68 weeks in STEP 1 compared with -2.4% with placebo, an estimated treatment difference of -12.4 percentage points (95% CI -13.4 to -11.5; $P < 0.001$), corresponding to an absolute difference of -12.7 kg (95% CI -13.7 to -11.7). The magnitude of effect was highly reproducible across the STEP programme: -16.0% in STEP 3 with intensive behavioural therapy, -15.8% in STEP 8, -13.9% in STEP 10 in participants with prediabetes, and -12.1% at 44 weeks in the predominantly East Asian population of STEP 7. Durability was demonstrated in STEP 5, where the reduction of -15.2% at 104 weeks remained essentially identical to the 68-week effect observed in STEP 1, and in the prespecified SELECT weight analysis, where a reduction of -10.2% was sustained to 208 weeks.^{1,3,5,6,7,8,11}

Three findings temper this picture. First, weight loss is attenuated in the presence of type 2 diabetes: in STEP 2 the reduction was -9.6% versus -3.4% with placebo, an estimated treatment difference of only -6.2 percentage points, approximately half the effect observed in the non-diabetic population of STEP 1. Second, treatment is required continuously: in the STEP 4 randomized withdrawal design, participants who continued semaglutide lost a further -7.9% between weeks 20 and 68, whereas those switched to placebo regained +6.9%, a difference of -14.8 percentage points (95% CI -16.0 to -13.5; $P < 0.001$), and in the STEP 1 off-treatment extension participants regained 11.6 of the 17.3 percentage points lost, leaving a net reduction of only -5.6% at week 120. Third, a clear dose-response exists: in the phase 2 dose-ranging trial weight loss increased monotonically from -6.0% at 0.05 mg daily to -13.8% at 0.4 mg daily against -2.3% with placebo, and in STEP UP T2D the 7.2 mg weekly dose produced -13.2% compared with -10.4% for the 2.4 mg dose (post hoc $P = 0.003$).^{2,4,23,24,34}

Table 7. Change in body weight

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Study	Population	Dose and duration	Semaglutide	Comparator	Treatment difference (95% CI)	P value
STEP 1	Obesity without diabetes	2.4 mg weekly, 68 wk	-14.9% (-15.3 kg)	-2.4% (-2.6 kg)	-12.4 pp (-13.4 to -11.5); -12.7 kg (-13.7 to -11.7)	<0.001
STEP 2	Obesity with T2DM	2.4 mg weekly, 68 wk	-9.6%	-3.4%	-6.2 pp (-7.3 to -5.2)	<0.0001
STEP 3	Obesity + intensive behavioural therapy	2.4 mg weekly, 68 wk	-16.0%	-5.7%	-10.3 pp (-12.0 to -8.6)	<0.001
STEP 4	Randomized withdrawal, wk 20-68	2.4 mg weekly, 48 wk	-7.9%	+6.9%	-14.8 pp (-16.0 to -13.5)	<0.001
STEP 5	Obesity without diabetes, 2 years	2.4 mg weekly, 104 wk	-15.2%	-2.6%	-12.6 pp (-15.3 to -9.8)	<0.0001
STEP 7	Predominantly East Asian	2.4 mg weekly, 44 wk	-12.1%	-3.6%	-8.5 pp (-10.2 to -6.8)	<0.0001
STEP 8	Head-to-head	2.4 mg	-15.8%	-6.4%	-9.4 pp (-	<0.001

	vs liraglutide	weekly, 68 wk		(liraglutide); -1.9% (placebo)	12.0 to -6.8) vs liraglutide	
STEP 10	Obesity with prediabetes	2.4 mg weekly, 52 wk	-13.9%	-2.7%	-11.2 pp (-13.0 to -9.4)	<0.0001
STEP TEENS	Adolescents 12-<18 years (BMI change)	2.4 mg weekly, 68 wk	-16.1% BMI	+0.6% BMI	-16.7 pp (-20.3 to -13.2)	<0.001
STEP UP T2D	Obesity with T2DM, high dose	7.2 mg weekly, 72 wk	-13.2%	-3.9% (placebo); -10.4% (2.4 mg)	vs placebo P<0.001; vs 2.4 mg post hoc P=0.003	<0.001
Phase 2 dose-ranging	Obesity without diabetes	0.05-0.4 mg daily, 52 wk	-6.0% to -13.8% (dose-dependent)	-2.3% (placebo); -7.8% (liraglutide 3.0 mg)	All doses superior to placebo	<=0.0055
SELECT (Ryan 2024)	Established CVD without diabetes	2.4 mg weekly, 208 wk	-10.2%	-1.5%	Sustained to 4 years	<0.0001
STEP-HFpEF	Obesity-related HFpEF	2.4 mg weekly, 52 wk	-13.3%	-2.6%	-10.7 pp (-11.9 to -9.4)	<0.001
STEP-HFpEF pooled	Obesity-related	2.4 mg weekly, 52 wk	Not separately	Not separately	-8.4% (-9.2 to -7.5)	<0.0001

	HFpEF with and without T2DM	wk	reported	reported		
ESSENCE	MASH with F2-F3 fibrosis	2.4 mg weekly, 72 wk	-10.5%	-2.0%	-8.5 pp (-9.6 to -7.4)	<0.001
Phase 2 NASH	NASH F1-F3	0.4 mg daily, 72 wk	-13%	-1%	Not formally tested	—
FLOW	T2DM with CKD	1.0 mg weekly, 104 wk	Not separately reported	Not separately reported	-4.1 kg	<0.001
SOUL	T2DM with ASCVD and/or CKD	Oral 14 mg daily, wk 156	Not separately reported	Not separately reported	-3.26 pp (-3.55 to -2.98)	<0.001
STEP 1 extension	One year after withdrawal (wk 120)	2.4 mg weekly, then off treatment	-5.6% net	-0.1% net	Two-thirds of lost weight regained	—
Rodriguez cohort (observational)	Overweight or obesity, routine care	T2DM-labelled formulations, 12 mo	Reference group	Tirzepatide	Tirzepatide -6.9 pp (-7.9 to -5.8) greater at 12 mo	<0.001

pp, percentage points. Abbreviations otherwise as in Table 6. Where a trial reported both percentage and absolute change, both are given.

Categorical Weight-Loss Response

Categorical responder analysis demonstrates that the mean effect is not driven by a small number of extreme responders but reflects a substantial rightward shift of the entire response distribution. In STEP 1, 86.4% of semaglutide recipients achieved at least 5% weight loss compared with 31.5% receiving placebo, 69.1% achieved at least 10% compared with 12.0%, and 50.5% achieved at least 15% compared with 4.9%, with $P < 0.001$ for all three comparisons. Comparable proportions were observed in STEP 3, where 75.3% achieved at least 10% and 55.8% at least 15%, and in STEP 7, where the odds ratio for at least 5% weight loss was 13.1 (95% CI 7.4-23.1). In the head-to-head comparison of STEP 8, the odds of achieving at least 20% weight loss were 8.2-fold higher with semaglutide than with liraglutide (95% CI 3.5-19.1; $P < 0.001$). Among adolescents, 73% achieved at least 5% weight loss compared with 18% receiving placebo, an odds ratio of 14.0 (95% CI 6.3-31.0).^{1,3,6,7,9}

Table 8. Proportion of participants achieving categorical weight-loss thresholds

Study	$\geq 5\%$ (semaglutide vs comparator)	$\geq 10\%$	$\geq 15\%$	$\geq 20\%$	Effect estimate	P value
STEP 1	86.4% vs 31.5%	69.1% vs 12.0%	50.5% vs 4.9%	Not reported	Odds significantly greater at all thresholds	< 0.001
STEP 2	68.8% vs 28.5%	Not reported	Not reported	Not reported	OR 4.88 (3.58-6.64)	< 0.0001
STEP 3	86.6% vs 47.6%	75.3% vs 27.0%	55.8% vs 13.2%	Not reported	All thresholds significant	< 0.001
STEP 5	77.1% vs 34.4%	Not reported	Not reported	Not reported	Significant at 104 weeks	< 0.0001

STEP 7	85% vs 31%	Not reported	Not reported	Not reported	OR 13.1 (7.4-23.1)	<0.0001
STEP 8 (vs liraglutide)	Not reported	70.9% vs 25.6%	55.6% vs 12.0%	38.5% vs 6.0%	OR 6.3 (3.5- 11.2); 7.9 (4.1-15.4); 8.2 (3.5-19.1)	<0.001
STEP TEENS	73% vs 18%	Not reported	Not reported	Not reported	OR 14.0 (6.3-31.0)	<0.001
STEP UP T2D (7.2 mg)	Significantly greater than placebo	Significantly greater	Significantly greater	Significantly greater	All confirmatory thresholds met	<0.001
Phase 2 dose- ranging	Not reported	37-65% vs 10% placebo	Not reported	Not reported	Dose- dependent gradient	<0.0001
Rodriguez cohort (tirzepatide vs semaglutide)	HR 1.76 (1.68-1.84)	HR 2.54 (2.37-2.73)	HR 3.24 (2.91-3.61)	Not reported	Tirzepatide more likely to reach each threshold	<0.001

OR, odds ratio; HR, hazard ratio. In the Rodriguez cohort the hazard ratios describe the likelihood of tirzepatide-treated patients reaching each threshold relative to semaglutide-treated patients.

Central Adiposity and Anthropometry

Reduction in central adiposity paralleled and in relative terms exceeded the reduction in total body weight, which is of pathophysiological importance because visceral rather than subcutaneous adipose tissue drives insulin resistance and cardiovascular risk. In STEP 4, continued semaglutide reduced waist circumference by a further 9.7 cm relative to placebo withdrawal (95%

CI -10.9 to -8.5; $P < 0.001$). In the prespecified SELECT analysis at 208 weeks, waist circumference fell by 7.7 cm versus 1.3 cm with placebo and the waist-to-height ratio fell by 6.9% versus 1.0%, both $P < 0.0001$. In STEP UP T2D the 7.2 mg dose reduced waist circumference by an estimated 6.5 cm more than placebo (95% CI -9.0 to -4.1; $P < 0.001$). Pooled analysis of the STEP programme confirmed significant reductions in waist circumference in STEP 1 and STEP 4 ($P \leq 0.001$).^{4,11,24,28}

Table 9. Waist circumference, body mass index and waist-to-height ratio

Study	Anthropometric measure	Semaglutide	Comparator	Treatment difference (95% CI)	P value
STEP 4	Waist circumference (wk 20-68)	Continued reduction	Increase after withdrawal	-9.7 cm (-10.9 to -8.5)	<0.001
SELECT (Ryan 2024)	Waist circumference at 208 wk	-7.7 cm	-1.3 cm	Significant	<0.0001
SELECT (Ryan 2024)	Waist-to-height ratio at 208 wk	-6.9%	-1.0%	Significant	<0.0001
STEP UP T2D	Waist circumference at 72 wk (7.2 mg)	Reduced	Reduced less	-6.5 cm (-9.0 to -4.1)	<0.001
STEP 1 and STEP 4 (Kosiborod 2023)	Waist circumference	Reduced	Reduced less	Greater with semaglutide	≤ 0.001
STEP TEENS	Waist circumference in adolescents	Reduced	Reduced less	Greater with semaglutide	<0.001
SOUL	Body mass index	Reduced	Reduced less	Favoured oral	<0.001

	at wk 156			semaglutide	
Qin meta-analysis (contextual comparator)	Waist circumference; BMI	Pooled across 6 RCTs, n=3,962	Placebo	-9.4 cm (-10.1 to -8.8); -4.5 kg/m ² (-4.9 to -4.1)	<0.00001

The final row reports a pooled estimate from a published meta-analysis and is provided solely as a contextual comparator; in accordance with the review protocol this study does not appear in the study-characteristics table.

Glycaemia and Prevention of Type 2 Diabetes

The glycaemic effect of semaglutide extends beyond glucose lowering to the reversal of dysglycaemia. Across the STEP programme, among 1,536 participants with prediabetes at baseline, the proportion achieving normoglycaemia at 68 weeks was 84.1% versus 47.8% in STEP 1, 89.5% versus 55.0% in STEP 3, and 89.8% versus 70.4% in STEP 4, with $P < 0.0001$ for all three comparisons. Conversely, progression from normoglycaemia to prediabetes was substantially less frequent with semaglutide, occurring in 2.9% versus 10.9% in STEP 1. In STEP 10, which enrolled exclusively participants with obesity and prediabetes, 81% of the semaglutide group reverted to normoglycaemia compared with 14% of the placebo group, an odds ratio of 19.8 (95% CI 8.7-45.2; $P < 0.0001$). Modelled 10-year type 2 diabetes risk, calculated using Cardiometabolic Disease Staging, fell by 61.1% with semaglutide versus 12.9% with placebo in STEP 1 and by 60.0% versus an increase of 3.5% in STEP 5, and rose again upon withdrawal in STEP 4 (relative change -32.1% with continuation versus +40.6% with withdrawal; $P < 0.0001$).^{8,29,35}

In established type 2 diabetes, glycated haemoglobin reductions were dose-dependent and clinically substantial. STEP UP T2D reported an estimated treatment difference in HbA1c of -1.5 percentage points with the 7.2 mg dose (95% CI -1.8 to -1.2; $P < 0.001$). In SOUL, oral semaglutide reduced HbA1c by an estimated 0.87 percentage points at week 13 and maintained a difference of -0.47 percentage points at week 156 (95% CI -0.52 to -0.42). In FLOW, HbA1c was 0.8 percentage points lower than placebo at week 104. Importantly, the glycaemic benefit was achieved without an increase in hypoglycaemia: in STEP-HFpEF DM hypoglycaemic events occurred at 22.9 per 100

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person-years with semaglutide versus 29.5 per 100 person-years with placebo despite broad concomitant use of glucose-lowering medication.^{14,24,42}

Table 10. Glycaemic control, reversion to normoglycaemia and diabetes-risk reduction

Study	Metric	Semaglutide	Comparator	Effect estimate (95% CI)	P value
STEP 1 (Perreault 2022)	Reversion of prediabetes to normoglycaemia at wk 68	84.1%	47.8%	Significant	<0.0001
STEP 3 (Perreault 2022)	Reversion of prediabetes to normoglycaemia at wk 68	89.5%	55.0%	Significant	<0.0001
STEP 4 (Perreault 2022)	Reversion of prediabetes to normoglycaemia at wk 68	89.8%	70.4%	Significant	<0.0001
STEP 1 (Perreault 2022)	Progression from normoglycaemia to prediabetes	2.9%	10.9%	Fewer with semaglutide	—
STEP 10	Reversion to normoglycaemia at wk 52	81% (103/127)	14% (9/64)	OR 19.8 (8.7- 45.2)	<0.0001
STEP 1 (Wilkinson 2023)	Relative reduction in modelled 10-year T2D risk score	-61.1%	-12.9%	Significant	<0.0001
STEP 5	Relative reduction in	-60.0%	+3.5%	Significant	<0.0001

(Wilkinson 2023)	modelled 10-year T2D risk score at wk 104				
STEP 4 (Wilkinson 2023)	Relative change in T2D risk score, continuation vs withdrawal	-32.1%	+40.6%	Significant	<0.0001
STEP UP T2D	HbA1c change at wk 72 (7.2 mg)	Reduced	Reduced less	ETD -1.5 pp (-1.8 to -1.2)	<0.001
SOUL	HbA1c change at wk 13 and wk 156	-0.87 pp early; sustained	Placebo	ETD at wk 156 - 0.47 pp (-0.52 to -0.42)	<0.001
FLOW	HbA1c change at wk 104	Reduced	Reduced less	-0.8 pp greater reduction	<0.001
STEP 1 and 4 (Kosiborod 2023)	Fasting plasma glucose and fasting serum insulin	Reduced	Reduced less	Greater with semaglutide	<=0.001
STEP-HFpEF DM	Hypoglycaemia event rate	22.9 per 100 person-years	29.5 per 100 person-years	Lower with semaglutide	—

ETD, estimated treatment difference; pp, percentage points; OR, odds ratio; T2D, type 2 diabetes.

Insulin Resistance

Insulin resistance, quantified by the homeostatic model assessment of insulin resistance, improved consistently. In the STEP 1 exploratory cardiometabolic analysis, HOMA-IR and fasting serum insulin both fell significantly more with semaglutide than with placebo ($P \leq 0.001$), and in the pooled prediabetes analysis across STEP 1, 3 and 4 the improvement in HOMA-IR among participants with baseline prediabetes was significant at $P < 0.01$. Reduction in HOMA-IR correlated positively with the reduction in C-reactive protein across STEP 1 and STEP 3, linking improvement in insulin sensitivity to attenuation of systemic inflammation. In ESSENCE, insulin resistance

improved alongside hepatic histological response. In the STEP 4 withdrawal design, the improvement in fasting serum insulin observed during the run-in was maintained only in participants continuing semaglutide and deteriorated after the switch to placebo ($P < 0.001$), demonstrating that improvement in insulin sensitivity is contingent on continued exposure.^{18,28,29,30}

Table 11. Insulin resistance and fasting insulin

Study	Metric	Finding	Direction of effect	P value
STEP 1 (Kosiborod 2023)	HOMA-IR and fasting serum insulin at wk 68	Greater reduction with semaglutide 2.4 mg than placebo	Favours semaglutide	≤ 0.001
STEP 4 (Kosiborod 2023)	Fasting serum insulin, wk 20-68	Maintained with continued semaglutide; deteriorated after switch to placebo	Favours continued semaglutide	< 0.001
STEP 1, 3, 4 (Perreault 2022)	HOMA-IR among participants with baseline prediabetes	Greater improvement with semaglutide	Favours semaglutide	< 0.01
STEP 1 and 3 (Verma 2023)	Correlation of change in HOMA-IR with change in C-reactive protein	Positive correlation between reduction in HOMA-IR and reduction in CRP	Concordant metabolic and inflammatory improvement	—
ESSENCE	Insulin resistance in MASH with F2-F3 fibrosis	Improved in parallel with glycaemia and hepatic histology	Favours semaglutide	—
STEP 1 (Perreault 2021)	Baseline HOMA-IR in prediabetes subgroup	4.2 (semaglutide) and 4.1 (placebo) at baseline; improved on treatment	Favours semaglutide	—

HOMA-IR, homeostatic model assessment of insulin resistance; CRP, C-reactive protein; MASH, metabolic dysfunction-associated steatohepatitis.

Lipid Profile

Semaglutide produced modest but consistent improvement in atherogenic lipid fractions. In the SOUL trial, which provides the most granular longitudinal lipid data, oral semaglutide reduced total cholesterol by 7.00%, non-high-density lipoprotein cholesterol by 8.02% and triglycerides by 8.15% within 13 weeks, with estimated treatment ratios at week 156 of 0.99 for total cholesterol (95% CI 0.98-1.00), 0.98 for non-HDL cholesterol (95% CI 0.97-0.99) and 0.94 for triglycerides (95% CI 0.93-0.96). No significant treatment effect was observed on low-density lipoprotein cholesterol, which is consistent with the prevailing understanding that GLP-1 receptor agonists act principally on triglyceride-rich lipoproteins and postprandial lipaemia rather than on LDL particle number. In STEP 1 and STEP 4, reductions in lipids were significantly greater with semaglutide ($P \leq 0.001$) and, importantly, occurred despite a net reduction in lipid-lowering medication intensity, with a higher proportion of semaglutide recipients undergoing de-intensification of statin or other lipid-lowering therapy. In adolescents, all lipid fractions except high-density lipoprotein cholesterol improved significantly relative to placebo.^{9,28,42,47}

Table 12. Lipid profile

Study	Lipid fraction	Early effect (week 13)	Effect at end of follow-up	Effect estimate (95% CI)	Statistically significant
SOUL	Total cholesterol	-7.00%	Sustained	ETR 0.99 (0.98-1.00) at wk 156	Yes
SOUL	Non-HDL cholesterol	-8.02%	Sustained	ETR 0.98 (0.97-0.99) at wk 156	Yes
SOUL	Triglycerides	-8.15%	Sustained	ETR 0.94 (0.93-0.96) at wk 156	Yes
SOUL	HDL cholesterol	-4.49%	Reversed to net increase	ETR 1.01 (1.01-1.02) at wk 156	Yes

SOUL	LDL cholesterol	No significant difference	No significant difference	Not significant	No
STEP 1 and 4 (Kosiborod 2023)	Total, non-HDL and LDL cholesterol	—	Greater reduction with semaglutide at wk 68	Significant within weight-loss strata	Yes
STEP 4 (Kosiborod 2023)	Lipids, wk 20-68	—	Maintained on treatment; deteriorated after withdrawal	Favours continued treatment	Yes
STEP TEENS	All fractions except HDL cholesterol	—	Improved at wk 68	Greater with semaglutide	Yes
ESSENCE	Lipid profile in MASH	—	Improved at wk 72	Favours semaglutide	Yes
STEP pooled (Tchang 2025)	Lipid-lowering treatment intensity	—	Higher proportion of de-intensification with semaglutide	Reduced pharmacological requirement	Yes

ETR, estimated treatment ratio; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Blood Pressure

Blood pressure fell consistently across trials. In STEP 4, continued semaglutide lowered systolic blood pressure by 3.9 mmHg relative to placebo withdrawal (95% CI -5.8 to -2.0;

P<0.001). In SOUL, oral semaglutide reduced systolic blood pressure by 3.84 mmHg and pulse pressure by 3.81 mmHg within 13 weeks, with estimated treatment differences at week 156 of -1.83 mmHg (95% CI -2.47 to -1.18) and -2.17 mmHg (95% CI -2.72 to -1.61) respectively; no significant effect was demonstrated on diastolic blood pressure or mean arterial pressure. The reduction in pulse pressure is of particular interest because it is a surrogate for arterial stiffness and an independent predictor of cardiovascular events in older populations with diabetes. As with lipids, the antihypertensive effect was accompanied by a net reduction in the intensity of antihypertensive pharmacotherapy across the pooled STEP trials, meaning that the observed blood-pressure reduction is likely to underestimate the true pharmacodynamic effect.^{4,28,42,47}

Table 13. Blood pressure and antihypertensive medication requirement

Study	Parameter	Effect	Estimate (95% CI)	P value
STEP 4	Systolic blood pressure, wk 20-68	Reduced with continued semaglutide vs withdrawal	-3.9 mmHg (-5.8 to -2.0)	<0.001
SOUL	Systolic blood pressure at wk 13	Early reduction	-3.84 mmHg	<0.001
SOUL	Systolic blood pressure at wk 156	Sustained reduction	ETD -1.83 mmHg (-2.47 to -1.18)	<0.001
SOUL	Pulse pressure at wk 156	Sustained reduction	ETD -2.17 mmHg (-2.72 to -1.61)	<0.001
SOUL	Diastolic blood pressure and mean arterial pressure	No significant treatment difference	Not significant	NS
STEP 1 (Kosiborod)	Systolic and diastolic	Greater reduction with	Significant	<=0.001

2023)	blood pressure at wk 68	semaglutide		
STEP pooled (Tchang 2025)	Antihypertensive treatment intensity	Higher proportion of de-intensification; lower proportion of intensification	Favours semaglutide	—
Qin meta-analysis (contextual comparator)	Blood pressure across 6 RCTs	Significant control of blood pressure	Pooled effect favours semaglutide	<0.00001

ETD, estimated treatment difference; NS, not statistically significant. The final row reports a pooled estimate from a published meta-analysis provided solely as a contextual comparator.

Systemic Inflammation

Attenuation of systemic inflammation emerged as one of the most consistent and reproducible signals in the entire evidence base. Across STEP 1, 2 and 3, semaglutide 2.4 mg reduced C-reactive protein at 68 weeks by an estimated 44% (95% CI -49 to -39), 39% (95% CI -46 to -30) and 48% (95% CI -55 to -39) respectively relative to placebo, with all comparisons statistically significant and with the effect independent of baseline body mass index, body weight and glycaemic status. In STEP-HFpEF the mean percentage change in C-reactive protein was -43.5% with semaglutide versus -7.3% with placebo (estimated treatment ratio 0.61; 95% CI 0.51-0.72; $P<0.001$), and in the pooled STEP-HFpEF programme the treatment ratio was 0.64 (95% CI 0.56-0.72; $P<0.0001$). In SOUL, high-sensitivity C-reactive protein fell by 18.08% at week 13 with an estimated treatment ratio of 0.77 at week 156 (95% CI 0.74-0.81). Reductions in C-reactive protein correlated positively with reductions in body weight, waist circumference, fasting plasma glucose, fasting serum insulin and HOMA-IR, and a greater proportion of semaglutide recipients moved from a high-risk to a low-risk C-reactive protein category.^{12,13,30,42}

Table 14. C-reactive protein and systemic inflammatory burden

Study	Population	Semaglutide	Comparator	Effect estimate	P value
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				(95% CI)	
STEP 1 (Verma 2023)	Obesity without diabetes	Reduced	Placebo	ETD -44% (-49 to -39)	<0.05
STEP 2 (Verma 2023)	Obesity with T2DM	Reduced	Placebo	ETD -39% (-46 to -30)	<0.05
STEP 3 (Verma 2023)	Obesity with intensive behavioural therapy	Reduced	Placebo	ETD -48% (-55 to -39)	<0.05
STEP 2 (Verma 2023)	Semaglutide 2.4 mg vs 1.0 mg	-49%	-42%	ETD -12% (-23 to +1)	0.06 (NS)
STEP-HFpEF	Obesity-related HFpEF without diabetes	-43.5%	-7.3%	ETR 0.61 (0.51-0.72)	<0.001
STEP-HFpEF pooled	Obesity-related HFpEF with and without T2DM	Reduced	Placebo	ETR 0.64 (0.56-0.72)	<0.0001
SOUL	T2DM with ASCVD and/or CKD	-18.08% at wk 13	Placebo	ETR 0.77 (0.74-0.81) at wk 156	<0.001

ETD, estimated treatment difference; ETR, estimated treatment ratio; NS, not statistically significant.

Major Adverse Cardiovascular Events

Four dedicated cardiovascular outcome trials provide the definitive evidence for this domain. SELECT randomised 17,604 participants aged 45 years or older with established cardiovascular disease, a body mass index of at least 27 kg/m² and no history of diabetes, and demonstrated that semaglutide 2.4 mg reduced the composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke from 8.0% to 6.5% over a mean follow-up of 39.8 months (hazard ratio 0.80; 95% CI 0.72-0.90; P<0.001). This is the first demonstration that an anti-obesity therapy reduces hard cardiovascular endpoints in the absence of diabetes. SOUL extended this finding to the oral formulation in 9,650 participants with type 2 diabetes and atherosclerotic or

renal disease, reducing major adverse cardiovascular events from 13.8% to 12.0% (hazard ratio 0.86; 95% CI 0.77-0.96; P=0.006) over a mean of 47.5 months; the benefit was independent of concomitant sodium-glucose cotransporter-2 inhibitor use, with no evidence of heterogeneity by baseline or in-trial use (P for interaction 0.66).^{10,15}

SUSTAIN-6 and PIONEER 6 were designed as non-inferiority safety trials but both demonstrated numerically and, in the case of SUSTAIN-6, statistically favourable point estimates: hazard ratios of 0.74 (95% CI 0.58-0.95) and 0.79 (95% CI 0.57-1.11) respectively. In SUSTAIN-6 non-fatal stroke was significantly reduced (hazard ratio 0.61; 95% CI 0.38-0.99; P=0.04). In FLOW, in which cardiovascular events were a confirmatory secondary outcome, major adverse cardiovascular events were reduced by 18% (hazard ratio 0.82; 95% CI 0.68-0.98; P=0.029), with consistency across the full spectrum of chronic kidney disease severity. The real-world cohort of oral semaglutide in a primary-prevention population reported a considerably larger relative effect, with a composite cardiovascular event rate of 5.8% versus 9.9% (risk ratio 0.59; 95% CI 0.54-0.65; P<0.001); the magnitude of this estimate substantially exceeds that of the randomized trials and should be interpreted in the light of the moderate risk of residual confounding assigned to that study.^{14,16,17,27}

Table 15. Major adverse cardiovascular events and components

Study	N	Population	Endpoint	Semaglutide vs comparator	Hazard/risk ratio (95% CI)	P value
SELECT	17,604	Established CVD, overweight/obesity, no diabetes	3-point MACE	6.5% vs 8.0%	HR 0.80 (0.72-0.90)	<0.001
SOUL	9,650	T2DM with ASCVD and/or CKD	3-point MACE	12.0% vs 13.8%	HR 0.86 (0.77-0.96)	0.006
SOUL	2,596	By baseline	3-point MACE	With	HR 0.89	P-

(SGLT2i subgroup)	/ 7,054	SGLT2 inhibitor use		SGLT2i vs without	(0.71-1.11) vs 0.84 (0.74-0.95)	interaction 0.66
SUSTAIN-6	3,297	T2DM at high cardiovascular risk	3-point MACE	6.6% vs 8.9%	HR 0.74 (0.58-0.95)	<0.001 (non-inferiority)
SUSTAIN-6	3,297	T2DM at high cardiovascular risk	Non-fatal stroke	1.6% vs 2.7%	HR 0.61 (0.38-0.99)	0.04
SUSTAIN-6	3,297	T2DM at high cardiovascular risk	Non-fatal myocardial infarction	2.9% vs 3.9%	HR 0.74 (0.51-1.08)	0.12 (NS)
PIONEER 6	3,183	T2DM at high cardiovascular risk	3-point MACE	3.8% vs 4.8%	HR 0.79 (0.57-1.11)	<0.001 (non-inferiority)
PIONEER 6	3,183	T2DM at high cardiovascular risk	Cardiovascular death	0.9% vs 1.9%	HR 0.49 (0.27-0.92)	Significant
FLOW	3,533	T2DM with CKD	3-point MACE	Reduced	HR 0.82 (0.68-0.98)	0.029
FLOW	3,533	T2DM with CKD	Cardiovascular death	Reduced	HR 0.71 (0.56-0.89)	Significant
Cowart cohort (observational)	23,052	T2DM, primary prevention	Composite MI, stroke or acute heart failure	5.8% vs 9.9%	RR 0.59 (0.54-0.65)	<0.001
Cowart cohort (observational)	23,052	T2DM, primary prevention	Myocardial infarction	1.6% vs 2.7%	RR 0.61 (0.51-0.73)	<0.001
Cowart cohort	23,052	T2DM, primary prevention	Stroke	3.9% vs	RR 0.60	<0.001

(observational)		prevention		6.5%	(0.53-0.67)	
Lee meta-analysis (contextual comparator)	71,351	T2DM across 10 GLP-1 RA trials	MACE	Pooled	HR 0.86 (0.81-0.90)	Significant

MACE, major adverse cardiovascular events (composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke); HR, hazard ratio; RR, risk ratio; SGLT2i, sodium-glucose cotransporter-2 inhibitor; NS, not statistically significant. The final row reports a pooled estimate from a published meta-analysis provided solely as a contextual comparator.

Heart Failure Outcomes

The STEP-HFpEF programme addressed the obesity phenotype of heart failure with preserved ejection fraction, for which no disease-modifying therapy had previously been approved. In STEP-HFpEF, the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score improved by 16.6 points with semaglutide versus 8.7 points with placebo (estimated difference 7.8 points; 95% CI 4.8-10.9; $P < 0.001$), a magnitude several times larger than that achieved by any previously tested pharmacotherapy in this population. Six-minute walk distance improved by 21.5 m versus 1.2 m (estimated difference 20.3 m; 95% CI 8.6-32.1; $P < 0.001$), and the hierarchical composite of death, heart failure events and change in symptom and functional scores favoured semaglutide with a win ratio of 1.72 (95% CI 1.37-2.15; $P < 0.001$). Notably, serious adverse events occurred in 13.3% of the semaglutide group versus 26.7% of the placebo group. In the pooled programme of 1,145 participants the corresponding estimates were 7.5 points (95% CI 5.3-9.8) for symptom score and 17.1 m (95% CI 9.2-25.0) for walk distance, both $P < 0.0001$.^{12,13}

Evidence that semaglutide reduces hard heart failure events, rather than symptoms alone, derives from three sources. The pooled participant-level analysis of SELECT, FLOW, STEP-HFpEF and STEP-HFpEF DM identified 3,743 participants with a history of heart failure with preserved or mildly reduced ejection fraction and demonstrated a reduction in the composite of cardiovascular death or worsening heart failure event from 7.5% to 5.4% (hazard ratio 0.69; 95% CI 0.53-0.89; $P = 0.0045$), with worsening heart failure events alone reduced by 41% (hazard ratio 0.59;

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95% CI 0.41-0.82; P=0.0019); cardiovascular death alone was not significantly reduced. In FLOW, the composite of heart failure events or cardiovascular death was reduced by 27% (hazard ratio 0.73; 95% CI 0.62-0.87; P=0.0005), consistently in participants with and without heart failure at baseline. In SOUL, the composite heart failure outcome was reduced in participants with a history of heart failure (hazard ratio 0.78; 95% CI 0.63-0.96) but not in those without (hazard ratio 1.01; 95% CI 0.84-1.20; P for interaction 0.06), and the effect was concentrated in the preserved ejection fraction phenotype (hazard ratio 0.59; 95% CI 0.39-0.86) with no signal of harm in reduced ejection fraction.^{39,41,43}

Mechanistic support for a disease-modifying rather than purely decongestive action derives from the echocardiographic substudy, in which semaglutide attenuated left atrial remodelling (estimated mean difference in left atrial volume -6.13 mL; 95% CI -9.85 to -2.41; P=0.0013), attenuated right ventricular enlargement, and improved diastolic filling indices including the E/A ratio (-0.14; 95% CI -0.24 to -0.04; P=0.0075), and from the reduction in N-terminal pro-B-type natriuretic peptide (estimated treatment ratio 0.82; 95% CI 0.74-0.91; P=0.0002). Symptomatic benefit was greater in participants with atrial fibrillation (11.5 versus 4.3 points; P for interaction 0.001) and in those with higher baseline natriuretic peptide concentrations, and was proportional to the magnitude of weight loss, with each 10% reduction in body weight associated with a 6.4-point improvement in symptom score (95% CI 4.1-8.8) and a 14.4 m improvement in walk distance (95% CI 5.5-23.3).^{37,38,44,48}

Table 16. Heart failure symptoms, events, biomarkers and cardiac remodelling

Study	Endpoint	Semaglutide	Comparator	Effect estimate (95% CI)	P value
STEP-HFpEF	KCCQ-CSS change at wk 52	+16.6 points	+8.7 points	ETD 7.8 (4.8-10.9)	<0.001
STEP-HFpEF	6-minute walk distance	+21.5 m	+1.2 m	ETD 20.3 m (8.6-32.1)	<0.001

STEP-HFpEF	Hierarchical composite (death, HF events, KCCQ-CSS, 6MWD)	More wins	Fewer wins	Win ratio 1.72 (1.37-2.15)	<0.001
STEP-HFpEF	Serious adverse events	13.3%	26.7%	Fewer with semaglutide	<0.001
STEP-HFpEF pooled	KCCQ-CSS change at wk 52	Improved	Improved less	ETD 7.5 (5.3-9.8)	<0.0001
STEP-HFpEF pooled	6-minute walk distance	Improved	Improved less	ETD 17.1 m (9.2-25.0)	<0.0001
STEP-HFpEF pooled	Hierarchical composite	More wins	Fewer wins	Win ratio 1.65 (1.42-1.91)	<0.0001
Pooled SELECT/FLOW/STEP-HFpEF	CV death or worsening HF event (HFpEF subset, n=3,743)	5.4%	7.5%	HR 0.69 (0.53-0.89)	0.0045
Pooled SELECT/FLOW/STEP-HFpEF	Worsening heart failure events alone	2.8%	4.7%	HR 0.59 (0.41-0.82)	0.0019
Pooled SELECT/FLOW/STEP-HFpEF	Cardiovascular death alone	3.1%	3.7%	HR 0.82 (0.57-1.16)	0.25 (NS)
FLOW	HF events or CV death	Reduced	Placebo	HR 0.73 (0.62-0.87)	0.0005
FLOW	HF events alone	Reduced	Placebo	HR 0.73	0.0068

				(0.58-0.92)	
SOUL	Composite HF outcome in participants with HF at baseline	Reduced	Placebo	HR 0.78 (0.63-0.96)	0.0177
SOUL	Composite HF outcome, HFpEF subgroup	Reduced	Placebo	HR 0.59 (0.39-0.86)	Significant
SOUL	Composite HF outcome, HFrEF subgroup	No significant effect	Placebo	HR 0.98 (0.70-1.38)	NS
STEP-HFpEF (Petrie 2024)	NT-proBNP at wk 52	Reduced	Placebo	ETR 0.82 (0.74-0.91)	0.0002
STEP-HFpEF echocardiographic substudy	Left atrial volume	Attenuated remodelling	Progression	EMD -6.13 mL (-9.85 to -2.41)	0.0013
STEP-HFpEF echocardiographic substudy	Right ventricular end-diastolic area	Attenuated enlargement	Progression	EMD -1.99 cm ² (-3.60 to -0.38)	0.016
STEP-HFpEF echocardiographic substudy	E/A ratio	Improved	No change	EMD -0.14 (-0.24 to -0.04)	0.0075
STEP-HFpEF (Borlaug 2023)	KCCQ-CSS and 6MWD per 10% body-weight	+6.4 points; +14.4 m	—	(4.1-8.8); (5.5-23.3)	Significant

	reduction				
STEP-HFpEF (Verma 2024)	KCCQ-CSS by atrial fibrillation status	+11.5 with AF	+4.3 without AF	P-interaction 0.001	0.001
Kruger cohort (observational)	HF hospitalisation or all-cause mortality vs sitagliptin	Reduced	Sitagliptin	HR 0.58 (0.51-0.65)	Significant

KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; 6MWD, six-minute walk distance; ETD, estimated treatment difference; ETR, estimated treatment ratio; EMD, estimated mean difference; HF, heart failure; HFpEF/HFrEF, heart failure with preserved/reduced ejection fraction; AF, atrial fibrillation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NS, not statistically significant.

Renal Outcomes

FLOW was the first trial designed specifically to test a GLP-1 receptor agonist against hard kidney endpoints. Among 3,533 participants with type 2 diabetes and chronic kidney disease, semaglutide 1.0 mg reduced the composite of kidney failure, sustained 50% or greater decline in estimated glomerular filtration rate, or death from kidney or cardiovascular causes by 24% over a median 3.4 years (331 versus 410 events; hazard ratio 0.76; 95% CI 0.66-0.88; P=0.0003), with the trial stopped early for efficacy at a prespecified interim analysis. The kidney-specific composite excluding cardiovascular death was reduced by 21% (hazard ratio 0.79; 95% CI 0.66-0.94), and the mean annual estimated glomerular filtration rate slope was less steep by 1.16 mL/min/1.73 m² per year (P<0.001). Benefit was consistent across the full spectrum of baseline renal function and albuminuria, and the number needed to treat to prevent one primary outcome event was 59 per year of treatment.¹⁴

Albuminuria reduction was demonstrated in three additional settings. In the STEP 2 population with overweight or obesity and type 2 diabetes, the urine albumin-to-creatinine ratio fell

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by 20.6% with semaglutide 2.4 mg while rising by 18.3% with placebo, a between-group difference of -32.9% (95% CI -41.6 to -23.0; P=0.003); no effect on estimated glomerular filtration rate trajectory was observed in the pooled STEP 1 to 3 population, in whom baseline renal function was normal. In a dedicated randomized trial in 101 participants with non-diabetic chronic kidney disease and overweight or obesity, semaglutide 2.4 mg reduced the urine albumin-to-creatinine ratio by 52.1% at 24 weeks (95% CI -65.5 to -33.4; P<0.0001), establishing that the antialbuminuric effect is not contingent on diabetes. In SOUL, by contrast, the five-point kidney composite was not significantly reduced (hazard ratio 0.91; 95% CI 0.80-1.05; P=0.19) in a population with largely preserved baseline function, although the annual estimated glomerular filtration rate decline was significantly attenuated (estimated treatment difference 0.40 mL/min/1.73 m² per year; 95% CI 0.27-0.53; P<0.0001), a pattern consistent with a renoprotective effect that becomes clinically detectable only where the baseline rate of progression is high.^{22,31,40}

Table 17. Kidney disease progression, albuminuria and eGFR trajectory

Study	Population	Endpoint	Result	Effect estimate (95% CI)	P value
FLOW	T2DM with CKD, n=3,533	Composite major kidney disease events	331 vs 410 first events	HR 0.76 (0.66-0.88)	0.0003
FLOW	T2DM with CKD	Kidney-specific composite (excluding CV death)	Reduced	HR 0.79 (0.66-0.94)	Significant
FLOW	T2DM with CKD	Mean annual eGFR slope	Less steep decline with semaglutide	Difference 1.16 mL/min/1.73 m ² /year (0.86-	<0.001

				1.47)	
FLOW (Mann 2024)	By baseline SGLT2 inhibitor use	Primary kidney composite	On SGLT2i vs not on SGLT2i	HR 1.07 (0.69-1.67) vs 0.73 (0.63-0.85)	P-interaction 0.109
SOUL	T2DM with ASCVD and/or CKD, mostly preserved eGFR	Five-point kidney composite	8.4% vs 9.0%	HR 0.91 (0.80-1.05)	0.19 (NS)
SOUL	As above	Four-point kidney composite (excluding CV death)	2.3% vs 2.7%	HR 0.86 (0.66-1.10)	0.22 (NS)
SOUL	As above	Mean annual eGFR decline	-1.67 vs -2.06 mL/min/1.73 m ²	ETD 0.40 (0.27-0.53)	<0.0001
STEP 2 (Heerspink 2023)	Overweight/obesity with T2DM	UACR at wk 68 (semaglutide 2.4 mg)	-20.6% vs +18.3%	Between-group -32.9% (-41.6 to -23.0)	0.003
STEP 2 (Heerspink 2023)	Overweight/obesity with T2DM	UACR at wk 68 (semaglutide 1.0 mg)	-14.8% vs +18.3%	Between-group -28.0% (-37.3 to -17.3)	<0.0001
STEP 1-3	Normal baseline	eGFR trajectory	No between-	Not significant	NS

pooled (Heerspink 2023)	kidney function	at wk 68	group difference		
Apperloo trial	Non-diabetic CKD with overweight/obesity, n=101	UACR at wk 24	Reduced	-52.1% (-65.5 to -33.4)	<0.0001
Lee meta- analysis (contextual comparator)	T2DM across 10 GLP-1 RA trials	Composite kidney outcome	Pooled	HR 0.83 (0.75-0.92)	Significant

UACR, urine albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; HR, hazard ratio; ETD, estimated treatment difference; NS, not statistically significant. The final row reports a pooled estimate from a published meta-analysis provided solely as a contextual comparator.

Hepatic Outcomes

ESSENCE provides the first phase 3 histological evidence for semaglutide in metabolic dysfunction-associated steatohepatitis. In the prespecified interim analysis of the first 800 of 1,197 randomised participants with biopsy-defined steatohepatitis and stage F2 or F3 fibrosis, resolution of steatohepatitis without worsening of fibrosis occurred in 62.9% of the semaglutide group compared with 34.3% of the placebo group (estimated difference 28.7 percentage points; 95% CI 21.1-36.2; $P<0.001$). Improvement in liver fibrosis without worsening of steatohepatitis occurred in 36.8% versus 22.4% (estimated difference 14.4 percentage points; 95% CI 7.5-21.3; $P<0.001$), and the combined endpoint of both resolution and fibrosis reduction occurred in 32.7% versus 16.1% (estimated difference 16.5 percentage points; 95% CI 10.2-22.8; $P<0.001$). Body weight fell by 10.5% versus 2.0%. These results supported accelerated regulatory approval of semaglutide for steatohepatitis with moderate-to-advanced fibrosis in August 2025.^{18,58}

The phase 2 evidence preceding ESSENCE showed a dose-dependent effect on steatohepatitis resolution, with rates of 40%, 36% and 59% at daily doses of 0.1, 0.2 and 0.4 mg

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respectively versus 17% with placebo ($P < 0.001$ for the highest dose), but did not demonstrate a significant effect on fibrosis stage (43% versus 33%; $P = 0.48$), an observation that ESSENCE subsequently overturned with adequate power and duration. A critical negative result was obtained in compensated steatohepatitis-related cirrhosis, in which semaglutide 2.4 mg for 48 weeks failed to improve fibrosis by at least one stage, with improvement occurring in only 11% of the semaglutide group compared with 29% of the placebo group (odds ratio 0.28; 95% CI 0.06-1.24; $P = 0.087$), and did not significantly improve steatohepatitis resolution ($P = 0.29$). This result establishes an important therapeutic boundary: the hepatic benefit of semaglutide appears confined to pre-cirrhotic disease, in which fibrogenesis remains metabolically driven and potentially reversible.^{19,20}

Table 18. Hepatic histology and liver-related parameters

Study	Population	Endpoint	Semaglutide	Comparator	Effect estimate (95% CI)	P value
ESSENCE	MASH, fibrosis F2-F3, n=800 (interim)	MASH resolution without worsening fibrosis	62.9%	34.3%	+28.7 pp (21.1-36.2)	<0.001
ESSENCE	MASH, fibrosis F2-F3	≥1-stage fibrosis improvement without worsening MASH	36.8%	22.4%	+14.4 pp (7.5-21.3)	<0.001
ESSENCE	MASH, fibrosis F2-F3	Combined resolution and fibrosis	32.7%	16.1%	+16.5 pp (10.2-22.8)	<0.001

		reduction				
ESSENCE	MASH, fibrosis F2- F3	Body weight at wk 72	-10.5%	-2.0%	-8.5 pp (- 9.6 to -7.4)	<0.001
ESSENCE	MASH, fibrosis F2- F3	Bodily pain score	No significant difference	No significant difference	Not significant	NS
Phase 2 NASH (0.4 mg daily)	NASH, fibrosis F2- F3	NASH resolution without worsening fibrosis	59%	17%	Significant	<0.001
Phase 2 NASH (0.1 / 0.2 mg daily)	NASH, fibrosis F2- F3	NASH resolution without worsening fibrosis	40% / 36%	17%	Dose- dependent	—
Phase 2 NASH (0.4 mg daily)	NASH, fibrosis F2- F3	Fibrosis stage improvement	43%	33%	Not significant	0.48 (NS)
Phase 2 cirrhosis	NASH- related compensated cirrhosis, n=71	>=1-stage fibrosis improvement without worsening NASH	11% (5/47)	29% (7/24)	OR 0.28 (0.06- 1.24)	0.087 (NS)
Phase 2	NASH-	NASH	No	No	Not	0.29 (NS)

cirrhosis	related compensated cirrhosis	resolution	significant difference	significant difference	significant	
Souza network meta- analysis (contextual comparator)	Biopsy- proven MASH across 29 RCTs, n=9,324	Fibrosis regression and MASH resolution	Semaglutide significantly superior to placebo for both endpoints	Placebo	Ranked among effective agents by SUCRA	Significant

MASH, metabolic dysfunction-associated steatohepatitis; NASH, non-alcoholic steatohepatitis; pp, percentage points; OR, odds ratio; SUCRA, surface under the cumulative ranking curve; NS, not statistically significant. The final row reports a pooled estimate from a published network meta-analysis provided solely as a contextual comparator.

Functional Capacity and Health-Related Quality of Life

STRIDE was the first dedicated trial of a GLP-1 receptor agonist against a functional endpoint in peripheral artery disease. Among 792 participants with type 2 diabetes and Fontaine stage IIa intermittent claudication, semaglutide 1.0 mg increased the median ratio to baseline of maximum treadmill walking distance at 52 weeks to 1.21 compared with 1.08 with placebo, an estimated treatment ratio of 1.13 (95% CI 1.06-1.21; $P=0.0004$). Post hoc analyses demonstrated that the benefit was consistent across diabetes duration, body mass index above and below 30 kg/m², baseline HbA1c above and below 7%, concomitant sodium-glucose cotransporter-2 inhibitor or insulin use, sex, age above and below 75 years, renal function, prior peripheral revascularisation and polyvascular disease, indicating a treatment effect that is not attributable to weight loss or glycaemic improvement alone.^{21,45}

In obesity without cardiovascular disease, patient-reported physical functioning improved consistently. In the pooled STEP 1 to 4 patient-reported outcome analysis, the proportion of participants reaching the meaningful within-person change threshold for the Impact of Weight on Quality of Life-Lite physical function score was 51.8% versus 28.3% in STEP 1 ($P<0.0001$) and

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39.6% versus 29.5% in STEP 2 ($P=0.0083$), and for the Medical Outcomes Study 36-item Short Form physical functioning scale 39.8% versus 24.1% in STEP 1, 41.0% versus 27.3% in STEP 2 and 18.0% versus 6.6% in STEP 4 (all $P<0.001$). Six-minute walk distance improvements in heart failure are reported in Table 19 and are not duplicated here.³⁶

Table 19. Functional capacity, walking distance and health-related quality of life

Study	Population	Instrument or measure	Semaglutide vs comparator	Effect estimate (95% CI)	P value
STRIDE	T2DM with symptomatic PAD, n=792	Maximum treadmill walking distance, ratio to baseline at wk 52	1.21 vs 1.08	ETR 1.13 (1.06-1.21)	0.0004
STRIDE (Rasouli 2025)	By diabetes duration <10 vs ≥10 years	Maximum walking distance	ETR 1.15 vs 1.13	P-interaction 0.80	NS interaction
STRIDE (Rasouli 2025)	By BMI <30 vs ≥30 kg/m ²	Maximum walking distance	ETR 1.12 vs 1.16	P-interaction 0.58	NS interaction
STRIDE (Rasouli 2025)	By HbA1c <7% vs ≥7%	Maximum walking distance	ETR 1.13 in both strata	P-interaction 0.99	NS interaction
STEP 1 (Rubino 2024)	Obesity without diabetes	IWQOL-Lite-CT physical function, meaningful within-person change	51.8% vs 28.3%	Significant	<0.0001
STEP 2 (Rubino 2024)	Obesity with T2DM	IWQOL-Lite-CT physical function,	39.6% vs 29.5%	Significant	0.0083

		meaningful within-person change			
STEP 1 (Rubino 2024)	Obesity without diabetes	SF-36v2 physical functioning, meaningful within-person change	39.8% vs 24.1%	Significant	<0.0001
STEP 2 (Rubino 2024)	Obesity with T2DM	SF-36v2 physical functioning, meaningful within-person change	41.0% vs 27.3%	Significant	0.0005
STEP 4 (Rubino 2024)	Weight-loss maintenance	SF-36v2 physical functioning, meaningful within-person change	18.0% vs 6.6%	Significant	<0.0001
STEP 4 (Rubino 2021)	Weight-loss maintenance	SF-36 physical functioning score, wk 20-68	Improved with continued treatment	ETD 2.5 (1.6-3.3)	<0.001
STEP-HFpEF	Obesity-related HFpEF	6-minute walk distance	+21.5 m vs +1.2 m	ETD 20.3 m (8.6-32.1)	<0.001
STEP 5 (Wharton 2023)	Obesity without diabetes, 2 years	Control of Eating Questionnaire craving domains	Improved at wk 20, 52 and 104	Correlated with weight loss	<0.01
Mechanistic trial (Friedrichsen 2021)	Adults with obesity	Ad libitum energy intake at wk 20	1,736 vs 2,676 kJ (35% lower)	ETD -940 kJ	<0.0001
Giugliano meta-	T2DM with	Walking distance	Improved	HR 1.10	<0.001

analysis (contextual comparator)	PAD, 2 RCTs, n=847		with liraglutide or semaglutide	(1.05-1.15)	
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ETR, estimated treatment ratio; ETD, estimated treatment difference; IWQOL-Lite-CT, Impact of Weight on Quality of Life-Lite Clinical Trials version; SF-36v2, Medical Outcomes Study 36-item Short Form version 2; PAD, peripheral artery disease; NS, not statistically significant. The final row reports a pooled estimate from a published meta-analysis provided solely as a contextual comparator.

All-Cause Mortality

All-cause mortality was reduced in the two trial populations at highest baseline risk. In FLOW, death from any cause occurred in 227 of 1,767 participants receiving semaglutide compared with 279 of 1,766 receiving placebo, a 20% relative reduction (hazard ratio 0.80; 95% CI 0.67-0.95; $P=0.01$), with consistency across categories of baseline estimated glomerular filtration rate. In PIONEER 6, death from any cause occurred in 1.4% versus 2.8% (hazard ratio 0.51; 95% CI 0.31-0.84). In SOUL, the confirmatory secondary outcomes, which included death from any cause, did not differ significantly between groups, and in SELECT a formal mortality hazard ratio was not reported as a primary or confirmatory endpoint. The real-world cohort of oral semaglutide reported all-cause mortality of 1.4% versus 3.0% with sitagliptin (risk ratio 0.46; 95% CI 0.39-0.56; $P<0.001$), an estimate substantially larger than the randomized data and subject to the residual confounding described above. Pooled analyses of the GLP-1 receptor agonist class report a 12% relative reduction in all-cause mortality, which is the most defensible summary estimate for the class as a whole.^{14,15,17,27,52,53}

Table 20. All-cause mortality

Study	Population	Events (semaglutide vs comparator)	Effect estimate (95% CI)	P value
FLOW	T2DM with CKD,	227/1,767 (13%) vs	HR 0.80	0.01

	n=3,533	279/1,766 (16%)	(0.67-0.95)	
PIONEER 6	T2DM at high cardiovascular risk, n=3,183	23/1,591 (1.4%) vs 45/1,592 (2.8%)	HR 0.51 (0.31-0.84)	Significant
SOUL	T2DM with ASCVD and/or CKD, n=9,650	Confirmatory secondary outcomes did not differ significantly	Not significant	NS
SELECT	Established CVD without diabetes, n=17,604	Not reported as a primary or confirmatory endpoint	—	—
Cowart cohort (observational)	T2DM, primary prevention, n=23,052	1.4% vs 3.0%	RR 0.46 (0.39-0.56)	<0.001
Kruger cohort (observational)	Cardiometabolic HFpEF	Composite of HF hospitalisation or all-cause mortality	HR 0.58 (0.51-0.65)	Significant
Lee meta-analysis (contextual comparator)	T2DM across 10 GLP-1 RA trials, n=71,351	Pooled	HR 0.88 (0.82-0.93)	Significant
Kristensen meta-analysis (contextual comparator)	T2DM across 7 GLP-1 RA trials, n=56,004	Pooled	HR 0.88 (0.83-0.95)	0.001

HR, hazard ratio; RR, risk ratio; NS, not statistically significant. The final two rows report pooled estimates from published meta-analyses provided solely as contextual comparators.

Safety and Tolerability

The safety profile of semaglutide was consistent across every disease domain and was dominated by gastrointestinal effects. In the pooled analysis of STEP 1 to 3, comprising 2,117

semaglutide and 1,262 placebo recipients, nausea occurred in 43.9% versus 16.1%, diarrhoea in 29.7% versus 15.9%, vomiting in 24.5% versus 6.3% and constipation in 24.2% versus 11.1%. Critically, 99.5% of these events were non-serious and 98.1% were mild-to-moderate, occurring predominantly during or shortly after dose escalation, and only 4.3% of semaglutide-treated participants discontinued permanently because of a gastrointestinal event. A formal mediation analysis established that gastrointestinal adverse events contributed less than one percentage point of the 7.6 to 14.4 percentage point additional weight loss achieved with semaglutide, refuting the hypothesis that weight loss is a consequence of drug-induced nausea.³²

Serious adverse events were not increased and in several trials were significantly lower with semaglutide than placebo, reflecting the prevention of disease-related events: 13.3% versus 26.7% in STEP-HFpEF, 29.9% versus 38.7% in the pooled STEP-HFpEF programme, 49.6% versus 53.8% in FLOW, and 47.9% versus 50.3% in SOUL. Three specific safety signals merit attention. Cholelithiasis occurred in 4% of semaglutide-treated adolescents and in no placebo recipients. In SUSTAIN-6, diabetic retinopathy complications were significantly increased (hazard ratio 1.76; 95% CI 1.11-2.78; P=0.02), an effect widely attributed to rapid correction of chronic hyperglycaemia rather than a direct drug effect. In the phase 2 steatohepatitis trial, neoplasms of any type were reported in 15% of semaglutide recipients versus 8% of placebo recipients without a pattern of occurrence in specific organs. Psychiatric safety was formally evaluated in a pooled analysis of STEP 1, 2, 3 and 5: depressive symptom scores improved slightly but statistically significantly with semaglutide (estimated treatment difference -0.56; 95% CI -0.81 to -0.32; P<0.001), the odds of shifting to a more severe depression category were reduced (odds ratio 0.63; 95% CI 0.50-0.79; P<0.001), and suicidal ideation or behaviour was reported by 1% or fewer of participants with no difference between groups.^{9,16,19,33}

Table 21. Safety and tolerability

Study / analysis	Safety parameter	Semaglutide	Comparator	Interpretation
STEP 1-3 pooled (Wharton 2022)	Nausea	43.9%	16.1%	Most frequent adverse event;

				predominantly during dose escalation
STEP 1-3 pooled (Wharton 2022)	Diarrhoea	29.7%	15.9%	Mild-to-moderate and transient
STEP 1-3 pooled (Wharton 2022)	Vomiting	24.5%	6.3%	Mild-to-moderate and transient
STEP 1-3 pooled (Wharton 2022)	Constipation	24.2%	11.1%	Mild-to-moderate and transient
STEP 1-3 pooled (Wharton 2022)	Severity and seriousness of GI events	99.5% non-serious; 98.1% mild-to-moderate	—	Not a dose-limiting toxicity in most patients
STEP 1-3 pooled (Wharton 2022)	Permanent discontinuation for GI events	4.3%	—	Low attrition attributable to tolerability
STEP 1-3 pooled (Wharton 2022)	Mediation of weight loss by GI events	<1 pp of 7.6-14.4 pp additional weight loss	—	Weight loss is largely independent of nausea
STEP 1	Discontinuation for gastrointestinal events	4.5%	0.8%	Consistent with pooled estimate
STEP 2	Any adverse event; gastrointestinal adverse events	87.6%; 63.5%	76.9%; 34.3%	Higher incidence but predominantly mild
STEP 3	Gastrointestinal adverse events;	82.8%; 3.4%	63.2%; 0%	Higher with concomitant

	discontinuation			intensive behavioural therapy
STEP 8	Discontinuation for any reason	13.5%	27.6% (liraglutide)	Better tolerated than daily liraglutide
STEP TEENS	Cholelithiasis	4% (5/133)	0%	Recognised class effect of rapid weight loss
STEP TEENS	Serious adverse events	11%	9%	No excess
STEP-HFpEF	Serious adverse events	13.3%	26.7%	Significantly fewer with semaglutide
STEP-HFpEF pooled	Serious adverse events	29.9%	38.7%	Significantly fewer with semaglutide
FLOW	Serious adverse events	49.6%	53.8%	Fewer with semaglutide, driven by fewer infections and cardiovascular events
SOUL	Serious adverse events; gastrointestinal disorders	47.9%; 5.0%	50.3%; 4.4%	No excess of serious events
SELECT	Permanent discontinuation for	16.6%	8.2%	Higher discontinuation

	adverse events			over a mean 34-month exposure
SUSTAIN-6	Diabetic retinopathy complications	Increased	Placebo	HR 1.76 (1.11-2.78); P=0.02; attributed to rapid glycaemic correction
ESSENCE	Serious adverse events; acute pancreatitis	13.4%; 0.4%	13.4%; 0.5%	No hepatic or pancreatic safety signal
Phase 2 NASH	Neoplasms of any type	15%	8%	No organ-specific pattern; requires long-term surveillance
Phase 2 cirrhosis	Adverse events; serious adverse events	89%; 13%	79%; 8%	No decompensating events or deaths
STRIDE	Treatment-related serious adverse events	5 participants (1%)	6 participants (2%)	No treatment-related deaths
STEP 1, 2, 3, 5 pooled (Wadden 2024)	Depressive symptoms (PHQ-9) at wk 68	Improved	Worsened slightly	ETD -0.56 (-0.81 to -0.32); P<0.001
STEP 1, 2, 3, 5 pooled (Wadden 2024)	Shift to a more severe depression category	Less likely	More likely	OR 0.63 (0.50-0.79); P<0.001
STEP 1, 2, 3, 5	Suicidal ideation or	<=1%	<=1%	No difference

pooled (Wadden 2024)	behaviour (C-SSRS)			between groups
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GI, gastrointestinal; pp, percentage points; HR, hazard ratio; OR, odds ratio; ETD, estimated treatment difference; PHQ-9, Patient Health Questionnaire 9-item; C-SSRS, Columbia-Suicide Severity Rating Scale.

Summary of Effect Direction and Certainty of Evidence

Across all fifteen prespecified outcome domains, the direction of effect favoured semaglutide, and statistical significance was achieved in fourteen of fifteen domains. The single domain in which the evidence is mixed is renal outcomes, where a large and unambiguous benefit was demonstrated in a population with established albuminuric chronic kidney disease but no significant effect on the composite endpoint was observed in a population with largely preserved renal function. Two important domain-specific null results should also be recorded: fibrosis improvement was not achieved in compensated cirrhosis, and the effect on low-density lipoprotein cholesterol and diastolic blood pressure was not statistically significant. GRADE certainty was rated high for eleven domains, moderate for three and low for one, as set out in Table 22.

Table 25. Summary of findings and GRADE certainty of evidence by outcome domain

Outcome domain	Number of studies	Direction of effect	Statistically significant	GRADE certainty	Reason for any downgrade
O1 Body weight	15	Favours semaglutide	Yes, in all trials	High	—
O2 Categorical weight-loss response	10	Favours semaglutide	Yes, at every threshold	High	—
O3 Central adiposity and anthropometry	7	Favours semaglutide	Yes	High	—

O4 Glycaemia and diabetes prevention	8	Favours semaglutide	Yes	High	—
O5 Insulin resistance	5	Favours semaglutide	Yes	Moderate	Reported chiefly as post hoc exploratory analyses
O6 Lipid profile	6	Favours semaglutide (except LDL-C)	Yes for TC, non-HDL-C and TG; no for LDL-C	Moderate	Small effect magnitude; inconsistency across fractions
O7 Blood pressure	5	Favours semaglutide (systolic and pulse pressure)	Yes for SBP and PP; no for DBP	High	—
O8 Systemic inflammation	5	Favours semaglutide	Yes	High	—
O9 Major adverse cardiovascular events	6	Favours semaglutide	Yes	High	—
O10 Heart failure outcomes	8	Favours semaglutide	Yes for symptoms and HF events; no for CV death alone	High	—
O11 Renal outcomes	5	Favours semaglutide in	Yes in FLOW; no in SOUL	Moderate	Inconsistency attributable to

		albuminuric CKD; neutral where renal function preserved	composite		differing baseline renal risk
O12 Hepatic outcomes	3	Favours semaglutide in F2-F3 fibrosis; no benefit in cirrhosis	Yes in ESSENCE; no in cirrhosis trial	High for non- cirrhotic disease; Low for cirrhosis	Cirrhosis evidence limited to a single small phase 2 trial with an anomalous placebo response
O13 Functional capacity and quality of life	7	Favours semaglutide	Yes	High	—
O14 All-cause mortality	6	Favours semaglutide	Yes in FLOW and PIONEER 6; not significant in SOUL	High	—
O15 Safety and tolerability	12	Acceptable; no excess of serious adverse events	Gastrointestinal events significantly increased; serious events not increased	High	—

LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; TG, triglycerides; SBP, systolic blood pressure; DBP, diastolic blood

pressure; PP, pulse pressure; CKD, chronic kidney disease; CV, cardiovascular; HF, heart failure. GRADE ratings for randomized evidence commenced at high certainty; observational evidence commenced at low certainty and did not alter the domain-level rating where randomized evidence was available.

DISCUSSION

Summary of Principal Findings

This systematic review of 27 primary studies enrolling more than 180,000 participants establishes that semaglutide produces statistically significant and clinically meaningful benefit across fourteen of fifteen prespecified outcome domains, spanning six organ systems. The principal finding is not simply that semaglutide reduces body weight, which was already well established, but that the magnitude of end-organ benefit is of a size ordinarily associated with agents developed specifically for those organs. A 20% reduction in major adverse cardiovascular events in a population without diabetes, a 24% reduction in major kidney disease events, a 41% reduction in worsening heart failure events, a 28.7 percentage point absolute increase in the probability of steatohepatitis resolution, and a 20% reduction in all-cause mortality in chronic kidney disease, achieved by a single molecule administered once weekly, has no clear precedent in metabolic medicine.^{10,13,14,18,43}

The internal consistency of the evidence is a further point of substance. Every one of the ten trials in the STEP weight-management programme reported a treatment difference in body weight in the same direction, of similar magnitude, and with confidence intervals that overlap substantially. Every one of the four cardiovascular outcome trials produced a hazard ratio point estimate below unity. Every trial that measured C-reactive protein reported a reduction of between 18% and 48%. This degree of replication across independent populations, geographies and disease states is unusual and materially strengthens the causal inference that can be drawn.^{1,3,5,10,15,16,17,30}

Body Weight, Adiposity and the Durability Question

The weight-loss effect of semaglutide is dose-dependent, plateaus at approximately 60 to 65 weeks, and is durable for as long as treatment continues, with the 104-week result in STEP 5 and the 208-week result in SELECT essentially superimposable on the 68-week result in STEP 1. This

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dissociation between the pharmacological plateau and continued treatment benefit is important clinically, because it means that the absence of further weight loss after one year is not evidence of therapeutic failure.^{1,5,11}

The withdrawal data are, however, unambiguous and clinically consequential. In STEP 4, participants switched to placebo regained 6.9% of body weight over 48 weeks while those continuing treatment lost a further 7.9%, and in the STEP 1 off-treatment extension participants regained two-thirds of the weight lost within a single year, with cardiometabolic variables reverting toward baseline in parallel. Semaglutide should therefore be conceptualised in the same terms as antihypertensive or lipid-lowering therapy: it controls a chronic relapsing disease for as long as it is administered and does not cure it. Any policy framework that funds a fixed 12-month course of therapy is, on this evidence, funding a temporary intervention with predictable reversal.^{4,34}

The reduction in central adiposity exceeded the reduction in total weight in relative terms, with waist-to-height ratio falling by 6.9% against a 10.2% weight reduction at 208 weeks in SELECT. Because visceral rather than subcutaneous adipose tissue drives hepatic insulin resistance, systemic inflammation and cardiovascular risk, this preferential depletion of the visceral compartment provides a plausible partial explanation for the disproportionate end-organ benefit. The attenuation of weight loss in type 2 diabetes, with a treatment difference roughly half that observed in the non-diabetic population, is a consistent and unexplained phenomenon across the incretin class, and may reflect concomitant insulin or sulfonylurea therapy, longer-standing adipocyte hyperplasia, or reduced central GLP-1 receptor responsiveness.^{2,11}

Glycaemia and the Prevention of Type 2 Diabetes

The most striking glycaemic finding is not the reduction in glycated haemoglobin but the reversal of prediabetes. Between 81% and 89.8% of participants with prediabetes reverted to normoglycaemia, against 14% to 70.4% with placebo, and progression from normoglycaemia to prediabetes was reduced by roughly two-thirds. Modelled 10-year diabetes risk fell by approximately 60%. Taken together with the STEP 4 withdrawal data, in which the modelled risk score rose by 40.6% after discontinuation, these findings support a model in which semaglutide suppresses rather than eradicates the diabetogenic process. Whether this translates into a genuine

reduction in incident diabetes over a decade, rather than a deferral of diagnosis, remains untested and constitutes an important gap.^{8,29,35}

The absence of excess hypoglycaemia deserves emphasis. In STEP-HFpEF DM, hypoglycaemic event rates were numerically lower with semaglutide than with placebo despite substantial glycated haemoglobin reduction and broad background use of glucose-lowering agents, reflecting the glucose-dependent nature of GLP-1-mediated insulinotropic action. This safety characteristic distinguishes semaglutide sharply from insulin and sulfonylurea therapy and is of particular relevance to elderly patients and to those with chronic kidney disease.¹⁴

Cardiovascular Outcomes and the Question of Mechanism

The SELECT result is the pivotal cardiovascular finding of the past decade in obesity medicine, because it established for the first time that treating obesity pharmacologically reduces hard cardiovascular endpoints in patients without diabetes. The hazard ratio of 0.80 is comparable in magnitude to that achieved by moderate-intensity statin therapy in secondary prevention, and was achieved on a background of contemporary guideline-directed therapy.¹⁰

The mechanism of this benefit is unlikely to be weight loss alone. Several lines of evidence converge on this conclusion. In FLOW, formal mediation analysis attributed essentially none of the effect on the primary kidney outcome to change in body weight, and the point estimates for mediation of the cardiovascular and mortality effects were negative, meaning that the observed benefit exceeded what weight change alone would predict; benefit was moreover consistent across all baseline body mass index categories. In STRIDE, walking capacity improved to the same degree in participants with a body mass index below 30 kg/m² as in those above, and in participants with glycated haemoglobin below 7% as in those above. In SOUL, cardiovascular benefit was consistent across all body mass index strata although more pronounced at higher baseline glycated haemoglobin. The most parsimonious interpretation is that GLP-1 receptor agonism exerts direct effects on vascular endothelium, arterial stiffness, plaque inflammation, natriuresis and sympathetic tone that operate in parallel with, and partly independently of, weight reduction.^{14,15,21,45}

The reduction in pulse pressure of 2.17 mmHg observed in SOUL, in the absence of any significant change in diastolic pressure, is mechanistically informative because it implies reduced

large-artery stiffness rather than simple volume depletion or reduced peripheral resistance. Similarly, the sustained 23% relative reduction in high-sensitivity C-reactive protein at week 156 in SOUL, and the 36% to 48% reductions across the STEP programme, indicate an anti-inflammatory action of a magnitude comparable to that reported for interleukin-1 beta and interleukin-6 pathway inhibitors, which have themselves been shown to reduce cardiovascular events.^{30,42}

An important negative finding is the absence of heterogeneity by concomitant sodium-glucose cotransporter-2 inhibitor use in SOUL, where the hazard ratio was 0.89 in participants taking an SGLT2 inhibitor at baseline and 0.84 in those not taking one, with a P value for interaction of 0.66. This supports additive rather than redundant benefit and argues for combination therapy in patients at high cardiovascular risk. The corresponding renal analysis in FLOW was less reassuring, with a hazard ratio of 1.07 in the SGLT2 inhibitor subgroup against 0.73 in the non-user subgroup, but the interaction was not statistically significant (P=0.109) and the SGLT2 inhibitor subgroup comprised only 550 participants with 79 events, so the analysis was substantially underpowered and should not be interpreted as evidence of absent renal benefit in combination therapy.^{15,49}

Heart Failure with Preserved Ejection Fraction

The obesity phenotype of heart failure with preserved ejection fraction has been among the most therapeutically intractable conditions in cardiology. The improvement of 7.5 to 7.8 points in the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score achieved with semaglutide substantially exceeds the improvement of approximately 1 to 2 points reported for sodium-glucose cotransporter-2 inhibitors and sacubitril-valsartan in this population, and exceeds the accepted threshold for a clinically important within-patient change.^{12,13}

Three findings argue that this represents genuine disease modification rather than symptomatic palliation or simple decongestion. First, echocardiographic assessment demonstrated attenuation of left atrial and right ventricular remodelling and improvement in diastolic filling indices, structural changes that cannot be produced by symptom relief alone. Second, N-terminal pro-B-type natriuretic peptide fell by a treatment ratio of 0.82, indicating reduced myocardial wall stress. Third, and most importantly, the pooled participant-level analysis across four trials

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demonstrated a 31% reduction in the composite of cardiovascular death or worsening heart failure event and a 41% reduction in worsening heart failure events alone, establishing benefit on hard clinical events rather than on patient-reported outcomes.^{37,38,43}

Against this, three caveats are warranted. The placebo response in STEP-HFpEF was unusually large, with approximately two-thirds of placebo recipients achieving at least a 5-point improvement in symptom score, raising the possibility of partial unblinding through the highly perceptible effects of semaglutide on appetite and body habitus. Cardiovascular death alone was not significantly reduced. And the sodium-glucose cotransporter-2 inhibitor background use in STEP-HFpEF was very low, so the incremental benefit of semaglutide in a contemporary optimally treated heart failure population remains incompletely defined. The concordant finding in the propensity-matched claims cohort, with a hazard ratio of 0.58 for the composite of heart failure hospitalisation or death, provides supportive though not confirmatory external validation.^{12,26,43}

Renal Outcomes

FLOW establishes semaglutide as a renoprotective agent in albuminuric diabetic kidney disease, with a number needed to treat of 59 per year to prevent one major kidney disease event. The attenuation of the estimated glomerular filtration rate slope by 1.16 mL/min/1.73 m² per year is of a magnitude that, if sustained, would meaningfully defer the need for kidney replacement therapy across a treated population.¹⁴

The apparent discrepancy with SOUL, in which the five-point kidney composite was not significantly reduced, is explicable by baseline risk rather than by any inconsistency of drug effect. Mean estimated glomerular filtration rate at entry to SOUL was 73.8 mL/min/1.73 m², compared with 47.0 mL/min/1.73 m² in FLOW, and the underlying event rate was correspondingly low. Notably, the annual estimated glomerular filtration rate decline was significantly attenuated in SOUL, indicating that the renoprotective mechanism was operative but that the follow-up was insufficient for that mechanism to generate a difference in categorical events. The demonstration of a 52.1% reduction in albuminuria in non-diabetic chronic kidney disease establishes that the effect is not dependent on glycaemic improvement and extends the mechanistic rationale beyond diabetic nephropathy.^{22,40}

Hepatic Outcomes

ESSENCE represents a genuine therapeutic advance in metabolic dysfunction-associated steatohepatitis, a disease for which no pharmacological therapy existed until 2024. The near doubling of the steatohepatitis resolution rate and the 64% relative increase in the fibrosis improvement rate led to accelerated regulatory approval in August 2025. Because semaglutide addresses the upstream metabolic driver of hepatic lipotoxicity rather than acting solely on the liver, and because it concurrently reduces cardiovascular risk, which is the leading cause of death in this population, it occupies a distinct therapeutic niche from the liver-directed thyroid hormone receptor-beta agonist resmetirom.^{18,58}

Three limitations of the hepatic evidence should be stated plainly. The placebo response rate for steatohepatitis resolution in ESSENCE was 34.3%, more than three times the anticipated 10%, which compresses the apparent treatment effect and raises questions about the characteristics of the enrolled population and the reproducibility of histological scoring. The trial has not clarified whether the histological responders were also the participants who achieved the greatest weight loss, so the relative contribution of weight-dependent and weight-independent mechanisms remains undefined. And the failure in compensated cirrhosis, where fibrosis improved in 11% of semaglutide recipients against 29% of placebo recipients, establishes a clear boundary of efficacy: once fibrogenesis has become self-sustaining and portal hypertension established, metabolic correction alone appears insufficient. Semaglutide should therefore be positioned as a therapy for pre-cirrhotic disease, with the corollary that early non-invasive identification of stage F2 to F3 fibrosis becomes a clinical priority.^{18,20,58}

Peripheral Artery Disease and Functional Capacity

STRIDE addressed a therapeutic vacuum, since cilostazol has been the only agent with demonstrated efficacy on walking distance in intermittent claudication and its use is constrained by tolerability and contraindications. The estimated treatment ratio of 1.13 for maximum walking distance corresponds to an absolute improvement of approximately 70 to 90 m in a population with a baseline maximum walking distance of approximately 190 m, which is clinically perceptible. The consistency of benefit across renal function, prior revascularisation, polyvascular disease and age

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above 75 years is notable given that these are precisely the subgroups in whom therapeutic options are most limited and in whom trial evidence is generally sparsest.^{21,45}

The mechanism is unlikely to be haemodynamic in the conventional sense, since the weight loss achieved in STRIDE was modest and benefit was independent of body mass index and glycated haemoglobin. Plausible contributors include reduced arterial stiffness, improved endothelial function, attenuation of plaque inflammation, improved skeletal muscle perfusion and reduced microvascular dysfunction. Corroborating cohort evidence suggests that GLP-1 receptor agonists as a class reduce the risk of lower extremity amputation by approximately 47%, although the certainty of that estimate is very low.^{21,56}

All-Cause Mortality

Mortality reduction was demonstrated in the two randomized populations at highest absolute risk, namely diabetic chronic kidney disease and high-cardiovascular-risk type 2 diabetes, and the pooled class estimate of a 12% relative reduction is consistent and precise. The observational estimate of a 54% relative reduction in mortality should be regarded with considerable caution: an effect of that magnitude is biologically implausible for a metabolic therapy and almost certainly reflects healthy-adherer bias, differential follow-up duration and residual confounding, notwithstanding rigorous propensity matching. This divergence between randomized and observational estimates is itself instructive and argues for continued primacy of randomized evidence in this therapeutic area.^{14,17,27,52,53}

Weight-Mediated versus Weight-Independent Mechanisms

Synthesis of the mediation and interaction analyses permits a provisional taxonomy. Outcomes that appear predominantly weight-mediated include heart failure symptom scores and exercise capacity, in which each 10% reduction in body weight was associated with a 6.4-point improvement in symptom score and a 14.4 m improvement in walk distance, and hepatic histological response, in which weight loss and steatohepatitis resolution co-varied. Outcomes that appear predominantly weight-independent include the renal composite in FLOW, walking distance in peripheral artery disease, and major adverse cardiovascular events in SOUL. Outcomes that appear to have mixed determination include glycaemic improvement and reduction in C-reactive

protein, both of which correlated with weight change but also occurred in participants with minimal weight loss.^{14,21,30,44}

This taxonomy has direct clinical implications. If cardiovascular and renal protection is largely weight-independent, then failure to achieve substantial weight loss is not a valid reason to discontinue therapy in a patient with established cardiovascular or renal disease. Conversely, in a patient treated principally for heart failure symptoms or hepatic histology, the absence of weight loss may reasonably prompt reconsideration of the therapeutic strategy.

Comparison with Published Systematic Reviews and Meta-Analyses

The findings of this review are concordant with the published quantitative syntheses, which were excluded from the study-characteristics table by protocol but retained for contextual comparison. A meta-analysis of six randomized trials comprising 3,962 participants without diabetes reported a pooled weight reduction of 11.80 percentage points, a body mass index reduction of 4.5 kg/m² and a waist circumference reduction of 9.4 cm, closely matching the trial-level estimates tabulated here. A meta-analysis of ten cardiovascular and kidney outcome trials in type 2 diabetes comprising 71,351 participants reported a 14% reduction in major adverse cardiovascular events, a 14% reduction in hospitalisation for heart failure, a 17% reduction in the composite kidney outcome and a 12% reduction in all-cause mortality, with no heterogeneity by route of administration. An earlier class meta-analysis of seven trials comprising 56,004 participants reported a 12% reduction in major adverse cardiovascular events. A network meta-analysis of 29 randomized trials in biopsy-proven steatohepatitis confirmed that semaglutide is significantly superior to placebo for both fibrosis regression and steatohepatitis resolution. The convergence between these pooled estimates and the individual trial results synthesised here provides reassurance that the present narrative synthesis has not systematically over- or under-stated the magnitude of effect.^{51,52,53,54}

Dose, Formulation and Comparative Efficacy

A monotonic dose-response for weight loss is evident from the phase 2 dose-ranging data and is confirmed by the incremental benefit of the 7.2 mg weekly dose over the 2.4 mg dose in type 2 diabetes, with mean reductions of 13.2% and 10.4% respectively. Notably, the higher dose did not

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produce a proportionate increase in gastrointestinal adverse events, with incidences of 53.1% and 51.5% respectively, suggesting that tolerability is determined principally by the rate of dose escalation rather than by the maintenance dose. Whether a dose-response also exists for cardiovascular, renal or hepatic outcomes is unknown, and is a question of considerable practical importance given that FLOW and STRIDE achieved their results with the 1.0 mg dose.^{14,21,23,24}

Oral semaglutide 14 mg once daily achieved a cardiovascular hazard ratio of 0.86, closely comparable to the 0.80 achieved by subcutaneous semaglutide 2.4 mg in SELECT and the 0.74 achieved by subcutaneous 1.0 mg in SUSTAIN-6, and a class meta-analysis found no significant heterogeneity by route of administration. Given the substantial adherence advantages of an oral formulation in many health systems, this equivalence is of considerable practical significance.^{10,15,16,52}

Against the dual incretin agonist tirzepatide, semaglutide is inferior for weight reduction. A propensity-matched cohort of 18,386 patients reported that tirzepatide-treated patients were 3.24 times more likely to achieve at least 15% weight loss, with an on-treatment difference of 6.9 percentage points at 12 months, and indirect comparisons in type 2 diabetes concur. However, in the propensity-weighted heart failure cohort, tirzepatide showed no meaningful advantage over semaglutide for the composite of heart failure hospitalisation or death (hazard ratio 0.86; 95% CI 0.70-1.06). This dissociation, in which greater weight loss does not translate into greater cardiovascular benefit, is further evidence that end-organ protection is not a simple function of weight reduction, and cautions against the use of weight loss as a surrogate for hard outcomes when selecting between incretin therapies. Against the mono-agonist liraglutide, semaglutide was superior for weight loss and better tolerated, with discontinuation for any reason occurring in 13.5% versus 27.6%.^{7,25,26}

Special Populations

In adolescents, the reduction in body mass index of 16.1 percentage points relative to placebo is the largest reported for any pharmacological therapy in this age group, and was accompanied by improvement in waist circumference, glycated haemoglobin, lipids and alanine aminotransferase. The 4% incidence of cholelithiasis and the absence of any long-term follow-up

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data in a population who may require decades of continuous therapy constitute the principal uncertainties.⁹

In East Asian populations, the treatment difference of 8.5 percentage points in STEP 7 is smaller than the 12.4 percentage points observed in the predominantly White population of STEP 1, although baseline body weight was also substantially lower at approximately 91 kg compared with 105 kg. Whether this reflects a pharmacodynamic difference or simply a lower baseline from which to lose weight cannot be determined from the available data, and the under-representation of Asian, Black and Hispanic populations across the entire trial programme is a material limitation for a therapy intended for global deployment. In SELECT, 93.1% of the STEP 5 population and 84% of the STEP-HFpEF DM population were White.^{5,6}

Efficacy was consistent by sex in every trial in which it was formally examined, although women achieved greater weight reduction than men in the heart failure programme (-9.6% versus -7.2%; P for interaction 0.006) with equivalent symptomatic benefit. Efficacy was consistent across the age spectrum, including in participants aged 75 years and older, in whom evidence for any intervention is generally sparse.^{13,21}

Safety in Clinical Perspective

The gastrointestinal adverse event profile, while numerically prominent, should be interpreted in the light of three quantitative findings: 98.1% of events were mild-to-moderate, 99.5% were non-serious, and only approximately 4% of participants discontinued permanently. Practical mitigation rests on slow dose escalation, dietary modification and, where necessary, maintenance at a sub-maximal dose. The mediation analysis demonstrating that gastrointestinal events account for less than one percentage point of the weight-loss effect refutes a persistent clinical misconception.³²

The retinopathy signal from SUSTAIN-6, with a hazard ratio of 1.76, has not been replicated in subsequent trials and is generally attributed to the well-described phenomenon of early worsening of retinopathy following rapid correction of chronic hyperglycaemia. Nonetheless, prudent practice includes retinal assessment before initiation in patients with long-standing poorly controlled type 2 diabetes and pre-existing retinopathy. The excess of cholelithiasis is a recognised

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consequence of rapid weight loss of any cause. The numerical excess of neoplasms in the phase 2 steatohepatitis trial, with no organ-specific pattern, has not been substantiated by the far larger and longer SELECT, FLOW and SOUL trials, in which serious adverse event rates were lower with semaglutide than with placebo. The formal psychiatric safety analysis provides reassurance that semaglutide does not increase depressive symptoms or suicidal ideation, and in fact modestly reduced depression scores.^{10,14,15,16,19,33}

Two safety considerations require ongoing attention and are inadequately addressed by the existing evidence. Loss of lean mass accompanies weight loss of this magnitude and is of particular concern in older patients and in those with cirrhosis or sarcopenic obesity; body composition was not systematically reported in the pivotal trials. Long-term discontinuation rates in routine practice substantially exceed those observed in trials, with more than half of patients in the observational cohorts discontinuing within the observation period, which given the documented reversibility of benefit has significant implications for real-world effectiveness.^{25,34,58}

Clinical and Policy Implications

Four implications follow from this synthesis. First, semaglutide should be considered a therapy for the cardiovascular-kidney-metabolic syndrome rather than an anti-obesity agent, and the decision to prescribe should be driven principally by the presence of established cardiovascular, renal or hepatic disease rather than by body mass index alone. Second, treatment should be framed to patients and payers as indefinite, on the same basis as antihypertensive therapy. Third, patient selection for the hepatic indication requires systematic non-invasive fibrosis staging to identify stage F2 to F3 disease, since benefit has not been demonstrated in cirrhosis. Fourth, combination with sodium-glucose cotransporter-2 inhibitors appears safe and, on cardiovascular endpoints, additive, and should not be avoided pending further data.^{15,49,58}

Strengths of This Review

- Comprehensive cross-domain scope, integrating fifteen outcome domains across six organ systems within a single PRISMA-compliant framework.
- Dual risk-of-bias architecture using RoB 2 for randomized evidence and ROBINS-I for observational evidence, permitting formal integration of efficacy and effectiveness data.

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- Explicit separation of weight-mediated from weight-independent effects through systematic extraction of published mediation and interaction analyses.
- Independent retrieval and verification of every included reference through the Consensus academic search engine, with a persistent resolvable link supplied for each citation.
- Protocol-driven exclusion of systematic reviews and meta-analyses from the primary evidence tabulation, with transparent retention as contextual comparators, thereby avoiding double-counting of participants.

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

This systematic review of 27 primary studies, comprising 24 randomized controlled trials and 3 large observational cohorts enrolling more than 180,000 participants, demonstrates that semaglutide produces statistically significant and clinically meaningful benefit across fourteen of fifteen prespecified outcome domains spanning six organ systems. The evidence supports the following specific conclusions.

- Semaglutide produces substantial and durable weight reduction, with mean reductions of 14.9% to 16.0% at 68 weeks and 15.2% at 104 weeks in adults without diabetes, and 9.6% in adults with type 2 diabetes. Hypothesis H1 is supported.^{1,2,3,5}
- Semaglutide reverses dysglycaemia, with 81% to 89.8% of participants with prediabetes reverting to normoglycaemia and a modelled 60% relative reduction in 10-year diabetes risk. Hypothesis H2 is supported.^{8,29,35}
- Semaglutide reduces major adverse cardiovascular events by 20% in obesity without diabetes and by 14% with the oral formulation in type 2 diabetes with established atherosclerotic or renal disease. Hypothesis H3 is supported.^{10,15}
- Semaglutide improves heart failure symptoms by 7.5 to 7.8 points on the Kansas City Cardiomyopathy Questionnaire and reduces worsening heart failure events by 41% in the obesity phenotype of heart failure with preserved ejection fraction, with echocardiographic evidence of attenuated adverse remodelling. Hypothesis H4 is supported.^{12,13,37,43}

- Semaglutide reduces major kidney disease events by 24% and attenuates the annual estimated glomerular filtration rate decline by 1.16 mL/min/1.73 m² in albuminuric diabetic kidney disease, and reduces albuminuria by 52.1% in non-diabetic chronic kidney disease. Hypothesis H5 is supported in populations with established albuminuric disease and is not supported where baseline renal function is preserved.^{14,22,40}
- Semaglutide increases the probability of steatohepatitis resolution without worsening of fibrosis by 28.7 percentage points and of fibrosis improvement by 14.4 percentage points in stage F2 to F3 disease. Hypothesis H6 is supported in non-cirrhotic disease and is explicitly not supported in compensated cirrhosis.^{18,20}
- Semaglutide improves maximum walking distance in symptomatic peripheral artery disease with an estimated treatment ratio of 1.13, consistently across all examined subgroups. Hypothesis H7 is supported.^{21,45}
- Semaglutide reduces all-cause mortality by 20% in diabetic chronic kidney disease and by 49% in high-cardiovascular-risk type 2 diabetes, with a pooled class estimate of a 12% relative reduction. Hypothesis H8 is supported in high-risk populations.^{14,17,52}
- A substantial component of the cardiovascular, renal and functional benefit of semaglutide is not mediated by weight reduction, as established by formal mediation analysis in FLOW and by the absence of interaction with baseline body mass index and glycated haemoglobin in STRIDE and SOUL. Hypothesis H9 is supported.^{14,15,21,45}
- Semaglutide does not increase serious adverse events, acute pancreatitis, depressive symptoms or suicidal ideation. Gastrointestinal adverse events are significantly increased but are predominantly mild-to-moderate and transient, with permanent discontinuation in approximately 4% of patients. The null hypothesis H10 is not rejected for serious adverse events and is rejected for gastrointestinal adverse events.^{32,33}

The overarching conclusion is that semaglutide is appropriately characterised as a disease-modifying therapy for the cardiovascular-kidney-metabolic syndrome rather than as an anti-obesity agent. The coherence of benefit across six organ systems, the consistency of the anti-inflammatory

signal, and the demonstration that end-organ protection is at least partly independent of weight reduction together indicate action upon a shared upstream pathophysiological axis rather than upon adiposity alone.

Recommendations

Recommendations for clinical practice

- Semaglutide should be considered as first-line pharmacological therapy in patients with obesity or overweight accompanied by established atherosclerotic cardiovascular disease, heart failure with preserved ejection fraction, albuminuric chronic kidney disease, or biopsy- or elastography-defined steatohepatitis with stage F2 to F3 fibrosis, in whom the absolute benefit is greatest.
- Treatment should be presented to patients, prescribers and payers as indefinite chronic therapy, analogous to antihypertensive or lipid-lowering treatment. Planned finite courses should be avoided, since approximately two-thirds of lost weight and most cardiometabolic gains are reversed within one year of discontinuation.
- Failure to achieve substantial weight loss should not, of itself, prompt discontinuation in patients treated principally for cardiovascular or renal indications, since benefit in these domains is largely weight-independent.
- Systematic non-invasive fibrosis staging using vibration-controlled transient elastography, magnetic resonance elastography or the enhanced liver fibrosis score should precede initiation for the hepatic indication, in order to identify stage F2 to F3 disease and to exclude cirrhosis, in which benefit has not been demonstrated.
- Dose escalation should be slow and individualised, with maintenance at a sub-maximal dose where necessary, since tolerability is determined principally by escalation rate rather than by maintenance dose, and since gastrointestinal events account for less than one percentage point of the weight-loss effect.

- Retinal assessment should precede initiation in patients with long-standing poorly controlled type 2 diabetes and pre-existing retinopathy, given the retinopathy signal observed in SUSTAIN-6 attributable to rapid glycaemic correction.
- Combination with sodium-glucose cotransporter-2 inhibitors should not be avoided, since cardiovascular benefit is additive and the safety profile of the combination is comparable to monotherapy.
- Resistance exercise and adequate dietary protein intake should be co-prescribed, particularly in older patients and in those with sarcopenic obesity or cirrhosis, in order to mitigate loss of lean mass.
- Structured adherence support should be provided, since real-world discontinuation rates substantially exceed those observed in clinical trials and benefit is reversible.

Recommendations for future research

- Adequately powered, publicly funded confirmatory trials are required, since the entire randomized evidence base for semaglutide is manufacturer-sponsored.
- Trials specifically enrolling Asian, Black, Hispanic and Indigenous populations are required, since these groups bear a disproportionate burden of cardiovascular-kidney-metabolic disease and are substantially under-represented in the existing programme.
- Direct head-to-head randomized comparisons against tirzepatide and against emerging triple incretin agonists, powered for cardiovascular, renal and hepatic outcomes rather than for weight loss alone, are required to determine whether greater weight reduction translates into greater end-organ protection.
- Formal mediation analyses should be prespecified in all future outcome trials, in order to quantify the proportion of benefit attributable to weight loss, to glycaemic improvement, to blood-pressure reduction and to anti-inflammatory action.
- Body composition, and specifically the preservation of lean and skeletal muscle mass, should be systematically measured using dual-energy X-ray absorptiometry or magnetic resonance imaging in future trials, particularly in older adults and in hepatic populations.

- Long-term outcome data extending beyond five years are required in weight-management populations, in adolescents and in metabolic dysfunction-associated steatohepatitis, including the completion of part 2 of the ESSENCE trial with cirrhosis-free survival as the endpoint.
- Trials of combination and sequential therapy, including semaglutide with resmetirom in steatohepatitis and semaglutide with finerenone or sodium-glucose cotransporter-2 inhibitors in chronic kidney disease, are required to define optimal multi-agent strategies.
- Strategies for maintenance of benefit following discontinuation, including dose tapering, intermittent dosing and structured behavioural transition programmes, should be formally evaluated.
- Health-economic evaluations conducted from the perspective of low- and middle-income health systems, including Indonesia and comparable settings, are required to inform equitable access, given that the acquisition cost of semaglutide presently exceeds the annual per-capita health expenditure of many such systems.
- Pragmatic registry-based studies of adherence, persistence and real-world effectiveness should be established, given the substantial divergence between trial and routine-practice discontinuation rates.

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