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# GLP-1 RECEPTOR AGONISTS IN THE TREATMENT OF OBESITY: IMPACT ON WEIGHT LOSS, GLYCEMIC CONTROL, AND CARDIOMETABOLIC OUTCOMES SYSTEMATIC REVIEW AND META-ANALYSIS

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## ABSTRACT

Obesity is a chronic, multifactorial disease associated with the development of type 2 diabetes mellitus, cardiovascular diseases, heart failure, chronic kidney disease, and a reduced quality of life. Glucagon-like peptide-l receptor agonists have shown relevant results in weight and metabolic control. This study aimed to evaluate the efficacy and safety of selective GLP-l receptor agonists for the treatment of overweight and obesity, considering their effects on weight loss, glycemic control, and cardiometabolic outcomes. A systematic review with meta-analysis of randomized clinical trials was conducted in accordance with the PRISMA 2020 recommendations. Forty publications were included, corresponding to 39 independent clinical cohorts, involving semaglutide, liraglutide, dulaglutide, exenatide, lixisenatide, albiglutide, and efpeglenatide. Risk of bias was assessed using the Cochrane RoB 2 tool, and the quantitative syntheses used random-effects models.Analysis of studies of subcutaneous semaglutide 2.4 mg in adults with obesity and no diabetes showed a pooled mean difference of _ll.75 percentage points in the change in body weight compared with placebo, with a 95% confidence interval of _l4.83 to _8.67. The magnitude of weight loss was smaller among participants with type 2 diabetes, although relevant reductions in glycated hemoglobin were observed. In the cardiovascular trials conducted in people with type 2 diabetes, GLP-l receptor agonists reduced the risk of major adverse cardiovascular events by approximately l4%, with a pooled hazard ratio of 0.86 and a 95% confidence interval of 0.79 to 0.94. Gastrointestinal adverse events were the most frequent and contributed to treatment discontinuation. It is concluded that selective GLP-l receptor agonists are effective in reducing weight and improving glycemic control, and may also reduce cardiovascular events in high-risk populations. However, effects vary among molecules, doses, and populations, requiring individualized selection and prolonged clinical follow-up.

**Keywords:**Obesity; Peptide l Receptor Agonists Similar to The glucagon; weight reduction; cardiovascular diseases.

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## INTRODUCTION

Obesity is a chronic, progressive, and multifactorial disease resulting from the interaction between genetic, neuroendocrine, metabolic, behavioral, environmental, and social mechanisms. Its prevalence has increased significantly over the past decades, becoming one of the main global public health challenges. In 2022, more than one billion people worldwide lived with obesity, including adults, children, and adolescents, while approximately 2.5 billion adults had overweight (1,2). In addition to its high frequency, obesity is associated with a reduced life expectancy and quality of life, increased functional disability, and the expansion of costs related to the treatment of chronic diseases.

Although the body mass index is widely used to classify populations with excess weight, this measure does not fully represent the distribution of body fat, visceral adiposity, functional impairment, or the presence of associated organic lesions. In this context, contemporary diagnostic proposals have begun to distinguish pre-clinical obesity, characterized by excess adiposity associated with an elevated risk in the future, from clinical obesity, defined by the presence of functional alterations, symptoms, or limitations directly related to excess adipose tissue (3) . This perspective reinforces that obesity should not be understood only as an anthropometric change, but as a systemic, heterogeneous, and potentially disabling condition.

Excess adipose tissue, especially when located in visceral and ectopic compartments, exerts metabolic and inflammatory effects that contribute to insulin resistance, dysfunction of pancreatic beta cells, arterial hypertension, dyslipidemia, atherosclerosis, heart failure, and chronic kidney disease. Obesity is also associated with the development of prediabetes, type 2 diabetes mellitus, obstructive sleep apnea, fatty liver disease associated with metabolic dysfunction, osteoarthritis, and certain types of cancer. Among the mechanisms involved are low-grade chronic inflammation, alterations in adipokine secretion, lipotoxicity, oxidative stress, endothelial dysfunction, and neuro-hormonal activation.

Sustained weight loss can reduce a substantial portion of this risk. Moderate reductions in body weight are associated with improved blood glucose, blood pressure, lipid profile, and functional capacity, while more substantial losses may favor remission of type 2 diabetes, reduced severity of sleep apnea, and improvement of other complications related to excess body fat. However, isolated behavioral interventions often show limited long-term effectiveness, mainly due to physiological adaptations that promote increased hunger, reduced satiety, decreased energy expenditure, and weight regain. For this reason, pharmacotherapy has come to play an increasingly important role in the longitudinal treatment of obesity and should be integrated with nutritional guidance, physical activity, behavioral interventions, and clinical follow-up clinical of the comorbidities (4) .

Among the available pharmacological strategies, GLP-l receptor agonists stand out for the combination of effects on body weight, glycemic control, and cardiometabolic risk. GLP-l is an incretin hormone produced mainly by the cells enteroendocrine hormones L after the ingestion of nutrients. Their physiological actions include stimulating the secretion of insulin in a glucose-dependent manner, inadequate inhibition of glucagon secretion during hyperglycemia, modulation of gastric emptying, and participation in central mechanisms of satiety and control of food intake. Since endogenous GLP-l undergoes rapid degradation by the enzyme dipeptidyl peptidase-4, were developed agonists resistant to degradation with a prolonged duration of action (5) .

GLP-l receptor agonists exert peripheral and central effects. In the central nervous system, they act on hypothalamic circuits and regions related to food reward, reducing hunger, energy intake, and preference for foods with high energy density. In glucose metabolism, they promote glucose-dependent insulin secretion and reduce glucagon secretion, with a relatively low risk of hypoglycemia when used without insulin or secretagogues. Additionally, their effects on blood pressure, inflammation, endothelial function, albuminuria, and lipid metabolism suggest benefits that go beyond the isol-

ated reduction in body weight and glycosylated hemoglobin (5) .

The first robust evidence of efficacy in the treatment of obesity was obtained with liraglutide. Clinical trials demonstrated that daily administration of 3.0 mg resulted in greater weight loss than that observed with placebo in individuals with obesity, prediabetes, or type 2 diabetes mellitus, and also reduced the progression of prediabetes to diabetes during prolonged follow-up (6–8). Despite these results, the need for daily administration and the moderate magnitude of weight loss prompted

the development of longer-acting molecules.

Weekly subcutaneous semaglutide represented a relevant expansion of pharmacologic efficacy. STEP program trials showed substantial reductions in body weight in adults with overweight or obesity, both in the absence and presence of type 2 diabetes (9–l3). Benefits were also observed when pharmacologic treatment was combined with intensive behavioral intervention and when maintained for periods longer than one year. In direct comparison, weekly semaglutide produced greater weight loss than daily liraglutide, indicating differences in efficacy within the same pharmacologic class (l4).

The development of oral semaglutide and research into higher subcutaneous doses expanded therapeutic possibilities. Trials from the OASIS program showed that the oral formulation can promote a clinically relevant reduction in body weight, while more recent studies evaluated weekly doses higher than those initially used in the treatment of obesity (l5–l9). However, the expansion of formulations and therapeutic regimens also increased the heterogeneity of the literature, particularly regarding dose, route of administration, the population included, the comparator used, the duration of follow-up, and the statistical method adopted to estimate efficacy.

In addition to weight loss, GLP-l receptor agonists demonstrated relevant effects on glycemic control. In individuals with type 2 diabetes, different molecules and doses reduced glycated hemoglobin and fasting glucose, often accompanied by weight reduction and a lower need for treatment intensification. However, the magnitude of weight loss tends

to be smaller among participants with diabetes when compared with that observed in people without the disease, possibly due to metabolic differences, concomitant therapies, and baseline clinical characteristics. This variation justifies a separate analysis of populations with and without diabetes.

The cardiovascular effects are also not uniform among different agonists. Large-scale clinical trials have shown a reduction in major adverse cardiovascular events with liraglutide, semaglutide, dulaglutide, albiglutide, and efpeglenatide in populations with type 2 diabetes and high cardiovascular risk (20–25). In contrast, lixisenatide and exenatide mainly demonstrated cardiovascular safety, with no unequivocal superiority over placebo in reducing the composite cardiovascular outcome (26,27). These differences suggest that cardiovascular benefits should not automatically be assigned homogeneously to all representatives of the class.

The SELECT study expanded on this discussion by demonstrating a reduction in major cardiovascular events with semaglutide 2.4 mg in individuals with overweight or obesity, established cardiovascular disease, and no diabetes (28). This finding indicated that cardiovascular benefit may occur independently of diabetes treatment and reinforced the relevance of obesity as a cardiovascular therapeutic target. Studies conducted in patients with heart failure with preserved ejection fraction and obesity also showed improvements in symptoms, functional capacity, and body weight, suggesting additional applications in specific cardiometabolic phenotypes.

Despite the overall consistency of the evidence, questions remain regarding the magnitude and sustainability of the benefits, weight recovery after discontinuation, and tolerability gastrointestinal, discontinuation of therapy, and less frequent adverse events. There are also important differences between adults, children, and adolescents; between participants with or without diabetes; between oral and subcutaneous formulations; and between trials of initial treatment, maintenance, or withdrawal of the medication. The combined interpretation of these studies therefore requires methods that can control for clinical heterogeneity and avoid the inappropriate combination

of different populations and study designs.

Previous reviews have often focused on a specific molecule, on exclusively weight-based outcomes, or on populations with type 2 diabetes. The rapid incorporation of new trials involving oral formulations, higher doses, obesity without diabetes, heart failure, and kidney disease makes it necessary to produce an updated and comprehensive synthesis. In addition, an integrated analysis of weight loss, glycemic control, cardiovascular events, and safety can clarify whether the observed benefits represent effects predominantly related to weight reduction or broader cardiometabolic actions.

Against this backdrop, the aim of this systematic review with meta-analysis was to assess the efficacy and safety of selective GLP-1 receptor agonists for the treatment of overweight and obesity, considering their effects on weight loss, glycemic control, and outcomes cardiometabolic.

Secondarily, we sought to analyze the occurrence of adverse events and treatment discontinuations, as well as to investigate potential sources of heterogeneity related to the molecule, the dose, the formulation, the presence of diabetes, the age range, the duration of follow-up, and the type of comparator.

## METHODOLOGY

A systematic review with meta-analysis of randomized clinical trials was conducted, structured according to the recommendations of the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses*- PRISMA 2020 and the methodological guidance of the *Cochrane Handbook for Systematic Reviews of Interventions*(29,30). The protocol was defined before the quantitative synthesis, including formulation of the research question, eligibility criteria, information sources, search strategy, study selection process, data extraction, risk-of-bias assessment, and the statistical analysis plan. The review investigated the effects of selective glucagon-like peptide-1 (GLP-1) receptor agonists in the treatment of overweight and obesity, considering weight loss, glycemic control, and outcomes

cardiovascular, parameters cardiometabolic and safety.

The research question was structured according to the PICOS strategy. The population consisted of children, adolescents, or adults with overweight or obesity, with or without prediabetes, type 2 diabetes mellitus, cardiovascular disease, heart failure, chronic kidney disease, or other related cardiometabolic conditions. The intervention included selective GLP-1 receptor agonists, including semaglutide, liraglutide, dulaglutide, exenatide, lixisenatide, albiglutide, and efpeglenatide, regardless of formulation, dose, or frequency of administration. The comparators considered were placebo, usual clinical treatment usual, intervention
behavioral, structured diet, different dose of the same agonist or another selective GLP-1 receptor agonist. The outcomes of interest included change in body weight, body mass index, waist circumference, glycated hemoglobin, fasting blood glucose, incidence of type 2 diabetes mellitus, blood pressure, lipid profile, major adverse cardiovascular events, mortality, heart failure, renal outcomes, adverse events, and treatment discontinuation. Were considered trials clinical randomized and controlled, with parallel groups, active comparisons, or a randomized withdrawal design.

The initial identification of the studies was based on a comprehensive matrix search developed for systematic reviews on GLP-1 receptor agonists in the treatment of obesity. This strategy included the MEDLINE, Embase, Cochrane Central Register of Controlled Trials CENTRAL, and LILACS databases, as well as international clinical trial registries. The search was complemented by targeted reference tracking from the main clinical programs, including STEP, OASIS, SCALE, SUSTAIN, PIONEER, AWARD, and the large cardiovascular outcomes trials, as well as by checking the reference lists of eligible studies, secondary publications, supplementary materials, and clinical trial registries. The targeted update included studies published up to June 2026, with no initial language restriction.

The search terms combined controlled vocabulary and free-text words related to GLP-1 receptor agonists, obesity, overweight, weight reduction, glycemic

control, cardiovascular outcomes, and randomized clinical trials. The conceptual strategy combined the terms "glucagon-like peptide-1 receptor agonist" OR "GLP-1 receptor agonist" OR semaglutide, liraglutide, dulaglutide, exenatide, lixisenatide, albiglutide, and efpeglenatide with the terms obesity, overweight, adiposity, body weight, weight loss, and body mass index, in addition to descriptors related to randomization, placebo, and clinical trial. A complementary strategy associated the intervention terms with expressions related to type 2 diabetes mellitus, glycated hemoglobin, blood glucose, cardiovascular events, mortality, heart failure and renal outcomes. The strategies were adapted to the syntax and controlled vocabulary of each source consulted.

Randomized clinical trials were included that assessed selective GLP-1 receptor agonists in participants with overweight or obesity and that reported at least one outcome related to weight loss, glycemic control, risk cardiometabolic outcomes or safety. For the weight-loss and glycemic-control analyses, studies with a minimum duration of 20 weeks were prioritized. This restriction was not applied to mechanistic studies or to specific clinical populations when they presented relevant metabolic outcomes and randomized design. The studies needed to provide a comparator group and sufficient quantitative data to calculate an effect measure or obtain the published estimate with its corresponding confidence interval.

Large cardiovascular trials were considered even when obesity did not constitute a mandatory inclusion criterion, provided that they evaluated GLP-1 receptor agonists and presented relevant data on weight, glycemic control, or cardiovascular outcomes in populations metabolically related to the scope of the review. These studies were analyzed separately from trials specifically intended for obesity treatment. Observational studies, case reports and case series, reviews, editorials, letters, protocols without results, preclinical research, exclusively animal studies, trials without a randomized group, isolated surgical interventions, and studies without recoverable quantitative data were excluded. Trials that evaluated exclusively dual or triple agonists, such as tirzepatide and retatrutide, were also excluded when there was no independent arm with a

selective GLP- 1 receptor agonist. Duplicate publications or secondary analyses without additional relevant information were not treated as independent studies.

The identified records were gathered into a single database and subjected to duplicate removal. The selection took place in two stages. Initially, titles and abstracts were assessed for possible eligibility, and subsequently, the full texts of potentially relevant records were examined according to the preestablished criteria. The reasons for exclusion after full-text review were recorded and grouped into categories, including incompatible population, non-eligible intervention, non-randomized design, absence of an appropriate comparator, insufficient duration, unavailable quantitative data, duplicated publication, secondary analysis without additional data, or another methodologically justified reason. The process of identification, screening, eligibility, and inclusion was represented in a PRISMA 2020 flow diagram (29).

The clinical trial was considered the primary unit of analysis. When different publications reported results from the same population, the articles were linked to a common study identifier. The main publication was used for methodological characteristics and for the primary outcome, while extensions, secondary analyses, and follow-up studies provided additional information only when they did not produce double counting of participants. In trials with multiple eligible arms, the groups were analyzed according to the clinical comparison of interest. When necessary, the shared control group was divided proportionally among the comparisons, or the intervention arms were combined, avoiding double weighting of the same sample. Randomized withdrawal trials were analyzed separately from studies that performed randomization before treatment began.

Data extraction was performed using a standardized form. Information was collected on authorship, year of publication, country, essay acronym, clinical phase, number of centers, sample size, population characteristics, age, sex, baseline weight, body mass index, presence of diabetes, cardiovascular disease, intervention, dose, route of administration, frequency, comparator, duration, loss to

follow-up, analytical method, funding, and conflicts of interest. For efficacy outcomes, we extracted the absolute change in body weight, the percentage change in weight, the change in body mass index, the change in waist circumference, the proportion of participants with loss of at least 5%, l0%, l5%, and 20% of body weight, the change in glycated hemoglobin, the change in fasting glucose, the incidence of type 2 diabetes mellitus, return to normoglycemia, the change in blood pressure, and the change in the lipid profile.

For cardiovascular and renal outcomes, major adverse cardiovascular events, cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, all-cause mortality, hospitalization or worsening of heart failure, albuminuria, and composite renal outcomes were extracted. For safety, data on gastrointestinal adverse events, nausea, vomiting, diarrhea, constipation, pancreatitis, gallbladder disease, severe hypoglycemia, diabetic retinopathy, serious adverse events, and treatment discontinuation due to adverse events were collected. When a trial presented more than one estimand, the treatment policy estimand was prioritized because it represents the effect of assignment to intervention regardless of discontinuation or the use of additional therapies. Efficacy estimands were used in supplementary or sensitivity analyses.

The primary outcomes were the percent change in body weight, the proportion of participants with a reduction of at least l0% of their baseline weight, the change in glycated hemoglobin, and the occurrence of major adverse cardiovascular events across three components, defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. The secondary outcomes included absolute weight change, weight response of at least 5%, l5%, and 20%, body mass index, waist circumference, fasting blood glucose, progression to diabetes, return to normoglycemia, blood pressure, lipid profile, cardiovascular mortality, all-cause mortality, myocardial infarction, stroke, heart failure, renal outcomes, serious adverse events, gastrointestinal events, and discontinuation of treatment.

The risk of bias was assessed by the Cochrane Risk of Bias 2 tool, RoB 2, considering the primary outcome of each

trial (31). The domains related to the randomization process, deviations from the intended interventions, missing data, outcome measurement, and selection of the reported outcome were examined. Each domain was classified as low risk, some concerns, or high risk, and the overall judgment followed the tool's algorithm, without the use of a numerical score. In obesity studies, special attention was given to missing data, interruptions of the medication, the use of additional anti-obesity therapies, and imputation methods. In cardiovascular trials, event adjudication, maintenance of follow-up after discontinuation, and intention-to-treat analysis were examined.

For the continuous outcomes reported in the same unit, mean differences were used with 95% confidence intervals. The percentage change in weight was expressed in percentage points, while absolute weight, glycated hemoglobin, blood glucose, blood pressure, and lipid parameters were kept in their original units. When the studies used incompatible metrics, the use of the standardized mean difference, corrected by Hedges, was planned. For dichotomous outcomes, such as weighted response and adverse events, relative risks were calculated with 95% confidence intervals. For time-to-event outcomes, including major adverse cardiovascular events, mortality, and heart failure, hazard ratios were combined, transformed to the logarithmic scale, and weighted by the inverse of the variance.

The meta-analyses were conducted when at least two studies showed sufficient clinical compatibility regarding the population, intervention, comparator, and the definition of the outcome. Was used primarily a random-effects model, considering the expected heterogeneity between molecules, doses, populations, and follow-up durations. The variance between studies was estimated using the restricted maximum likelihood method, with the Hartung-Knapp adjustment applied when appropriate. Combined estimates were presented, including the 95% confidence interval, p value, heterogeneity I 2, variance between studies $\tau$ 2, Cochran's Q test, and a 95% prediction interval.

The analyses were stratified in adults with overweight or obesity without

diabetes, adults with type 2 diabetes mellitus, children and adolescents, prevention or reversal of prediabetes, large cardiovascular trials, obesity-associated heart failure, renal outcomes, and safety. Pediatric studies were analyzed separately, using percent change in body mass index, body mass index z-score, or an equivalent measure. Withdrawal trials were kept separate from studies with randomization from baseline.

Subgroup analyses were planned according to the molecule used, dose, oral or subcutaneous formulation, presence or absence of diabetes, age range, placebo or active comparator, duration less than or greater than 52 weeks, standard or intensive behavioral intervention, presence of established cardiovascular disease, and risk of bias. When the number of studies allowed, exploratory meta-regressions were planned to investigate the influence of dose, treatment duration, initial body mass index, mean age, prevalence of diabetes, initial glycated hemoglobin, proportion of women, and baseline cardiovascular risk.

When standard deviations were not available, they were calculated from standard errors, confidence intervals, p values, or other statistical measures. When necessary, formulas were used to convert median and interquartile range to mean and standard deviation, along with sensitivity analyses. Change-from-baseline values were prioritized. In the absence of these data, final values could be combined provided they were expressed in the same unit and came from comparable groups after randomization.

Sensitivity analyses were performed by excluding studies with high risk of bias, experimental doses, withdrawal trials, special clinical populations, studies with high treatment discontinuation, and analyses based exclusively on efficacy estimands. An influence analysis with individual study withdrawal was also planned. When a meta-analysis included at least ten studies, publication bias was investigated by visual inspection of the funnel plot and Egger's test, acknowledging that asymmetry could also result from clinical heterogeneity or from the effects of small studies.

The certainty of the body of evidence was assessed using the GRADE

system, considering risk of bias, inconsistency, indirectness of evidence, imprecision, and publication bias (32). The evidence was rated as high, moderate, low, or very low for each critical outcome. The statistical analyses were planned in R software, using specific packages for meta-analysis and generation of graphs. A two-sided significance level of 5% was adopted, although the interpretation considered the effect magnitude, confidence intervals, prediction intervals, heterogeneity, and clinical relevance together.

Because it used exclusively aggregated data from previously published studies, the review did not involve recruiting participants or accessing personally identifiable information, and therefore did not require submission to a research ethics committee.

## RESULTS

The Final Selection Resulted in the Inclusion of 40 Publications Related to Randomized Clinical Trials on Selective GLP-l Receptor Agonists. One of the Publications Corresponded to The Prolonged follow-up of participants previously enrolled in the SCALE Obesity and Prediabetes program, so that the base represented 39 independent clinical cohorts. The studies encompassed pharmacological treatment of obesity, obesity associated with type 2 diabetes mellitus, pediatric populations, prediabetes, heart failure, chronic kidney disease, and large cardiovascular outcome trials.

Sample sizes ranged from 82 participants in the pediatric study with liraglutide, compared to l7,604 participants in SELECT. The duration of Follow-up ranged from l4 weeks in mechanistic metabolic trials to approximately 5.4 years in REWIND. Semaglutide was the most frequently evaluated intervention, followed by liraglutide. Dulaglutide, exenatide, lixisenatide, albiglutide, and efpelenatide were investigated primarily in populations with type 2 diabetes mellitus and high cardiovascular risk.

**Table 1 - Distribution of included publications according to the main clinical axis.**

| Clinical axis | Publications, n | Predominant characteristics |
|---|---|---|
| Semaglutide and weight control | 14 | Adults or adolescents with obesity, with or without diabetes |
| Liraglutide and weight control | 10 | Obesity, prediabetes, diabetes, and associated conditions |
| Major cardiovascular outcomes | 9 | Type 2 diabetes or obesity with cardiovascular disease |
| Heart failure and kidney disease | 3 | Obesity associated with HFpEF or chronic kidney disease |
| Dose-response and metabolic mechanisms | 4 | HbA1c, insulin sensitivity, and dose response |

The risk of bias assessment, conducted with the RoB 2 tool, classified nine publications as having overall low risk and 31 as presenting some concerns. No study was classified as having overall high risk. The main limitations were related to missing data and treatment discontinuation in obesity trials. The risk of bias in measurement was predominantly low, since body weight, body mass index, glycated hemoglobin, and laboratory parameters served as objective outcomes. In major cardiovascular trials, blinded event adjudication, longitudinal follow-up, and intention-to-treat analysis supported more favorable methodological judgments.

Subcutaneous semaglutide promoted consistent weight loss in adults with overweight or obesity without diabetes. In STEP 1, the mean change in weight at 68 weeks was _14.9% with semaglutide 2.4 mg and _2.4% with placebo, corresponding to an estimated difference of _ 12.4 percentage points (9). In STEP 3, in which both groups received intensive behavioral therapy, the reductions were _ 16.0% and _5.7%, respectively, with a difference of _10.3 percentage points (11). In STEP 5, the effect persisted for 104 weeks, with a reduction of _15.2% in the semaglutide group and _2.6% in the

placebo group, a difference of _12.6 percentage points (12).

The quantitative synthesis of studies STEP 1, STEP 3, and STEP 5, restricted to adults without diabetes treated with subcutaneous semaglutide 2.4 mg or placebo, showed a pooled mean difference of **_11.75 percentage points** in the change in body weight, favoring semaglutide (95% CI:_14.83 to _8.67; p=0.004). Heterogeneity was moderate ($I^2$=57.4%), possibly due to differences in the intensity of the behavioral intervention and the duration of follow-up.

The magnitude of weight loss was smaller among participants with type 2 diabetes mellitus. In STEP 2, the mean reduction was _9.6% with semaglutide 2.4 mg and _3.4% with placebo, a difference of approximately _6.2 percentage points (10). This result supported maintaining separate analyses for participants with and without diabetes.

Oral semaglutide also demonstrated efficacy. In OASIS 1, the estimated mean weight reduction at 68 weeks was _15.1% with oral semaglutide 50 mg and _2.4% with placebo, resulting in a _12.7 percentage-point difference (15). The oral formulations were maintained in an independent stratum due to differences in pharmacokinetics, dosing, and adherence compared with subcutaneous administration.

Liraglutide showed a lower weight-loss effect than that observed with semaglutide, but consistently higher than placebo. In the SCALE Obesity and Prediabetes, the average reductions were approximately _8.0% with liraglutide 3.0 mg and _2.6% with placebo (6). In the direct comparison of STEP 8, semaglutide 2.4 mg produced an average loss of _15.8%, whereas liraglutide 3.0 mg resulted in _6.4%, a difference of _9.4 percentage points in favor of semaglutide (14).

The categorical results followed the continuous findings. In STEP 1, 69.1% of participants treated with semaglutide achieved at least 10% weight loss, compared with 12.0% in the placebo group. At least 15% loss was observed in 50.5% and 4.9%, respectively (9). In STEP 8, 70.9% of participants treated with semaglutide lost at least 10% of their weight, compared with 25.6% among those treated with liraglutide; for the 20% threshold, the proportions were 38.5% and 6.0%, respectively (14).

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**Table 2 - Synthesis of the main efficacy results**

| Study or analysis | Population | Primary outcome | Estimate |
|---|---|---|---|
| STEP 1 | Obesity without diabetes | Weight change | _14.9% vs _2.4% |
| STEP 2 | Obesity and type 2 diabetes | Weight change | _9.6% vs _3.4% |
| STEP 5 | Obesity without diabetes | Weight change over 104 weeks | _15.2% vs _2.6% |
| OASIS 1 | Obesity without diabetes | Weight change | _15.1% vs _2.4% |
| SCALE Obesity | Obesity with or without prediabetes | Weight change | _8.0% vs _2.6% |
| STEPs 1, 3 and 5 grouped | Obesity without diabetes | Average difference in weight | _11.75 percentage points; 95% CI _14.83 to _8.67 |
| SELECT | Obesity, CVD, and absence of diabetes | MACE | HR 0.80; 95% CI 0.72–0.90 |
| CVOTs in type 2 diabetes | Diabetes and cardiovascular risk | Grouped MACE | HR 0.86; 95% CI 0.79–0.94 |

**Legend:**CVOTs: cardiovascular outcomes trials; CVD: cardiovascular disease; HR: hazard ratio; 95% CI: 95% confidence interval; MACE: major adverse cardiovascular events; percentage points.

In glycemic control studies, GLP-1 receptor agonists reduced glycosylated hemoglobin and body weight. In SUSTAIN FORTE, semaglutide 2.0 mg produced an approximately 2.2 percentage-point reduction in HbA1c, compared with 1.9 percentage point with semaglutide 1.0 mg, an estimated difference of _0.23 percentage point (19). In AWARD-11, the reductions in HbA1c were progressively greater with dulaglutide 1.5 mg, 3.0 mg, and 4.5 mg, accompanied by a dose-dependent response on body weight. Because both studies used active comparators and different doses of the same molecule, their results were not combined

with placebo-controlled trials.

The nine major cardiovascular trials included showed differences regarding the presence of diabetes, baseline risk, the molecule used, and the duration of follow-up. In the SELECT trial, conducted in participants with overweight or obesity, established cardiovascular disease, and no diabetes, semaglutide 2.4 mg reduced the relative risk of MACE by 20% compared with placebo (HR 0.80; 95% CI 0.72–0.90) (28) .

Among the eight trials conducted in people with type 2 diabetes mellitus, the random-effects model meta-analysis showed a pooled 14% reduction in the risk of MACE, with an HR of **0.86**(95% CI: 0.79–0.94; p=0.006) . Heterogeneity was moderate ($I^2$=44.5%) . LEADER, SUSTAIN 6, REWIND, Harmony Outcomes and AMPLITUDE-O showed favorable results regarding cardiovascular superiority, whereas ELIXA and EXSCEL primarily demonstrated cardiovascular non-inferiority and safety (20–27) .

The exploratory combination of the nine cardiovascular trials, including SELECT, resulted in a pooled HR of **0.85**(95% CI: 0.79–0.92; p=0.002), with 45.5% heterogeneity. Despite the overall favorable direction, the presence or absence of diabetes was considered a clinically relevant effect modifier; therefore, SELECT was interpreted separately from the main synthesis of studies in type 2 diabetes.

In participants with heart failure with preserved ejection fraction associated with obesity, the STEPHFpEF and STEP-HFpEF DM studies demonstrated improvement in heart-failure-related health status, greater weight reduction, and increased functional capacity with semaglutide compared with placebo. These trials were not combined with the CVOTs because their primary outcomes evaluated symptoms, physical limitations, and functional capacity, rather than major adverse cardiovascular events.

The events adverse gastrointestinal were the most frequent adverse effects. Nausea, vomiting, diarrhea, and constipation occurred mainly during dose escalation. Discontinuations due to adverse events were generally more frequent in the groups treated with GLP-1 receptor agonists, although most events were classified as mild or moderate. Serious adverse events occurred in a

smaller proportion and showed no uniform pattern of increase across all trials. Safety data were interpreted separately by molecule and population due to heterogeneity in definitions and exposure periods.

Taken together, the results demonstrated that selective GLP-1 receptor agonists produced clinically relevant weight loss, with a greater magnitude in semaglutide studies and among participants without diabetes. The class also improved glycemic control and reduced major cardiovascular events, although the magnitude of these effects varied across molecules, populations, and experimental designs. The observed heterogeneity supported the use of stratified analyses and prevented the interpretation of different class members as therapeutically equivalent.

## DISCUSSION

This systematic review with meta-analysis demonstrated that selective GLP-1 receptor agonists produce a clinically relevant reduction in body weight, improved glycemic control, and a decreased risk of major cardiovascular events in selected populations. The magnitude of the effects, however, was not uniform across studies, varying according to the molecule, dose, formulation, presence of type 2 diabetes mellitus, baseline cardiovascular profile, treatment duration, and experimental design. The synthesis of trials of subcutaneous semaglutide 2.4 mg in adults with obesity and without diabetes showed an additional mean weight reduction of 11.75 percentage points versus placebo, while the large cardiovascular trials conducted in people with type 2 diabetes indicated a pooled reduction of approximately 14% in the risk of major adverse cardiovascular events.

The most pronounced weight-loss efficacy was observed with semaglutide, especially at the subcutaneous dose of 2.4 mg and in oral formulations or experimental doses developed specifically for the treatment of obesity. In the STEP studies, mean reductions close to or greater than 15% of baseline weight were achieved in participants without diabetes, a substantially greater magnitude than that traditionally observed with previous pharmacological therapies (9,11–14) .

Results similar were found with oral formulation in the OASIS program, indicating that adequate pharmacological exposure to the agonist can generate an anti-obesity response relevant regardless of route of administration (l5–l7). The STEP UP studies suggest that higher subcutaneous doses may further increase weight loss, although the incremental benefit should be interpreted together with tolerability, therapy discontinuation, and the clinical cost of dose intensification (l8, l9).

Liraglutide also demonstrated consistent efficacy, but with a smaller magnitude compared with semaglutide. In the SCALE studies, daily administration of liraglutide 3.0 mg was associated with weight reduction and a higher frequency of clinically relevant responses compared with placebo, both in participants without diabetes and in those with type 2 diabetes (6–8,39–42). The superiority of semaglutide was confirmed directly in STEP 8, reducing the likelihood that differences between the two molecules arise exclusively from indirect comparisons between different trials (l4). The greater efficacy of semaglutide may be related to its prolonged pharmacokinetics, continuous receptor exposure, and differences in appetite modulation and energy intake, although the present review was not designed to establish mechanistic superiority.

The difference in response between participants with and without diabetes was one of the most consistent findings. The weight loss observed in STEP 2 was less than that reported in trials with individuals without diabetes, a pattern also identified in liraglutide studies (7, l0). This attenuation may be related to greater insulin resistance, the duration of diabetes, the use of insulin or other medications associated with weight gain, the metabolic limitations imposed by dysfunction of pancreatic beta cells, and differences in baseline characteristics. Consequently, the presence of diabetes should be considered an important modifier of the effect, and estimates from populations without diabetes should not be automatically applied to people with type 2 diabetes.

Despite the smaller weighted reduction in this group, GLP-l receptor agonists showed robust glycemic benefits. The SUSTAIN FORTE and AWARD-ll studies demonstrated dose-response relat-

ionships for reducing glycated hemoglobin and body weight, although the incremental benefits of higher doses were relatively smaller than the differences observed between active treatment and placebo (46,47). These findings suggest that dose intensification may be useful in patients with insufficient glycemic control, but its adoption should consider individual response, tolerability, and the predominant therapeutic objectives. In people whose clinical priority is weight loss, specific doses and formulations for obesity tend to produce better results than regimens initially developed for glycemic treatment.

The benefits on glycemia do not seem to result exclusively from weight loss. Mechanistic studies indicated improved insulin sensitivity and components of glycemic physiology during treatment with liraglutide, although the small sample size and short duration limit the generalizability of these observations (49) . GLP-1 receptor agonists stimulate glucose-dependent insulin secretion, reduce inappropriate glucagon secretion, and modulate food intake, establishing complementary

mechanisms for metabolic improvement (5) . However, the proportion of glycemic and cardiovascular benefits directly mediated by weight loss remains uncertain and likely varies among outcomes and populations.

The grouped reduction of major cardiovascular events reinforces that the clinical relevance of the class goes beyond control of intermediate risk factors. In trials conducted in people with type 2 diabetes, the combined effect favored GLP-1 receptor agonists, but the heterogeneity among molecules was clinically important. Liraglutide, semaglutide, dulaglutide, albiglutide, and efpeglenatide showed favorable results for reducing cardiovascular events, while lixisenatide and exenatide mainly demonstrated noninferiority and cardiovascular safety (20–27). Therefore, the results do not support the interpretation of complete equivalence among all class representatives.

Cardiovascular differences may

stem from pharmacological characteristics, duration of exposure, adherence, recruited population, definition of the outcome, baseline risk, and follow-up time. Trials such as ELIXA included participants after acute coronary syndr-

ome, whereas REWIND evaluated a population with a lower proportion of established cardiovascular disease and longer follow-up (23,25). Thus, an unadjusted comparison of hazard ratio magnitudes can lead to inadequate conclusions. Even in the presence of a favorable pooled effect, the therapeutic decision should prioritize molecules that have demonstrated direct cardiovascular benefit in the population corresponding to the patient.

THE SELECT trial represented a particularly relevant advance by demonstrating a reduction in major cardiovascular events in individuals who were overweight or obese, had established cardiovascular disease, and had no diabetes (28). This outcome weakens the hypothesis that cardiovascular protection depends exclusively on reducing hyperglycemia. Weight loss, lower blood pressure, improved inflammatory markers, effects on endothelial function, and systemic metabolic modifications may jointly contribute to the benefit. However, the study does not allow establishing the isolated causal contribution of each mechanism, and its results apply mainly to people with preexisting cardiovascular disease and should not be directly extrapolated to primary prevention in low-risk individuals.

The STEP-HFpEF and STEPHFpEF DM studies also expanded the scope of semaglutide by demonstrating improvements in symptoms, physical limitations, functional capacity, and weight in patients with heart failure with preserved ejection fraction associated with obesity (36,37). These findings are consistent with the recognition that adiposity may directly contribute to the pathophysiology of this heart failure phenotype. However, the primary outcomes of these trials were related to health status and physical function, not mortality or hospitalization as isolated events. Thus, the findings should not be interpreted as definitive evidence of reduced mortality in heart failure.

The study conducted in people with obesity and chronic kidney disease without diabetes also suggested favorable effects on albuminuria, weight, and renal parameters (38). Although these results support a possible renal benefit, the sample size and duration were smaller than those of the large outcomes trials,

and changes in albuminuria do not necessarily equate to the prevention of end-stage renal failure. Confirmation of renal protection in populations without diabetes requires larger trials, with prolonged follow-up and definitive clinical renal outcomes.

The effectiveness of GLP-1 agonists should be interpreted as part of a chronic treatment. STEP 4 showed that continuing semaglutide was associated with additional weight loss, while switching to placebo resulted in progressive weight regain (34). This pattern is consistent with the chronic, relapsing nature of obesity and suggests that stopping the medication removes some of the pharmacological mechanisms that controlled hunger and energy intake. Weight recovery after interruption does not necessarily represent treatment failure, but it shows that its effects do not fully persist after discontinuation.

This dependence on continued therapy has clinical and economic implications. The indication for a GLP-1 agonist should consider not only the initial response, but also the feasibility of maintenance, adherence, access, patient expectations, and strategies to preserve benefits when interruption is necessary. The included trials provided robust evidence over one to two years for weight loss, but information on safety, adherence, and maintenance for much longer periods is still comparatively limited.

In pediatric populations, semaglutide and liraglutide reduced body mass index in adolescents and children with obesity (35,43,44). However, these findings should be interpreted with caution, taking into account growth, pubertal development, bone health, body composition, eating behavior, and the need for family and multiprofessional follow-up. The duration of pediatric trials is still insufficient to determine the effects of prolonged treatment on development and weight maintenance during the transition to adult life.

The safety profile was characterized predominantly by gastrointestinal events, including nausea, vomiting, diarrhea, and constipation. These events occurred mainly during dose escalation and were

generally mild to moderate, but they contributed to discontinuations in some participants. The frequency and intensity of symptoms varied across molecules, doses, and populations, making it difficult to produce a single representative estimate for the class. Gradual dose escalation and dose individualization may improve tolerability, but they do not eliminate the possibility of discontinuation.

Less frequent events, such as pancreatitis, gallbladder disease, severe hypoglycemia, and related complications involving retinopathy, showed less statistical power for assessment. The absence of a significant increase in an isolated trial does not rule out rare risks. In people with diabetes, interpretation of retinopathy should also consider that rapid and marked reductions in glycated hemoglobin may cause transient worsening in susceptible individuals. Safety should be evaluated on an individualized basis, especially in patients with a history of pancreatic, biliary, gastrointestinal, or retinal disease.

Another relevant aspect is that weight loss does not correspond exclusively to a reduction in adipose tissue. Although the largest portion of weight loss associated with GLP-l receptor agonists is attributed to fat reduction, a decrease in lean mass can also occur. The included studies did not evaluate body composition uniformly, preventing a robust quantitative synthesis of this outcome. Associating treatment with adequate protein intake, resistance exercise, and functional monitoring may be particularly important in older adults, people with sarcopenia, or patients experiencing substantial weight loss.

This review presents, as strengths, the inclusion of 40 randomized trial publications, the combined analysis of body weight, glycemic control, cardiovascular events, and safety, the separation between populations with and without diabetes, and the assessment of risk of bias using RoB 2. Stratification by design and population reduced the risk of combining studies clinically incompatible ones. The use of random-effects models was also appropriate given the expected heterogeneity across molecules, doses, and treatment durations.

Some limitations should be recognized. The first was the clinical and methodological heterogenei-

ty, including differences in obesity criteria, behavioral interventions, doses, comparators, duration, imputation methods, and statistical estimands. The second was the dependence on published aggregated data, which prevented individualized analyses by sex, age, ethnicity, visceral adiposity, diabetes duration, and cardiovascular risk. The third was the small number of direct comparisons between molecules, which limits definitive conclusions
relative superiority.

Most of the major clinical programs received industrial funding, a condition that does not invalidate their results, but requires attention to the selection of endpoints, the reporting of estimands, and the interpretation of secondary analyses. In addition, the predominance of participants from specialized centers and the rigorous eligibility criteria may limit generalizability to populations with complex multimorbidity, low adherence, reduced access to multiprofessional follow-up, or difficulties maintaining treatment. The assessment of rare events and long-term safety also remained limited.

Taken together, the results support the selective agonists ofthe
GLP-l receptor as one of the most effective pharmacological strategies for the treatment of obesity, particularly when molecules and doses developed for weight management are used. The benefits include weight loss, glycemic improvement, and, for certain medications and populations, reduction of cardiovascular events. However, the heterogeneity of the class, the need for prolonged treatment, the occurrence of gastrointestinal events, and uncertainties regarding maintenance, body composition, and long-term safety reinforce the need for individualized selection and ongoing monitoring. The therapeutic decision should integrate the severity of obesity, the presence of diabetes, cardiovascular risk, comorbidities, tolerability, clinical goals, and the feasibility of maintaining treatment.

## CONCLUSION

Selective GLP-l receptor agonists demonstrated clinically relevant efficacy
in the treatment of overweight and obesity, with consistent benefits regarding weight loss, glycemic control, and certain outcomes cardiometabolic. A
The magnitude of the weighted response was greater with semaglutide, especially

in the doses and formulations developed specifically for the treatment of obesity, while liraglutide showed a more moderate effect, although higher than placebo. Participants with type 2 diabetes mellitus had a smaller reduction in body weight compared with those without diabetes, although they achieved a significant improvement in glycated hemoglobin and other metabolic parameters.

The synthesis of the major cardiovascular trials indicated a reduction in the risk of major adverse cardiovascular events with certain GLP-l receptor agonists, especially liraglutide, semaglutide, dulaglutide, albiglutide, and efpeglenatide. However, the results were not uniform across all molecules, reinforcing that cardiovascular benefits should not be automatically considered as a homogeneous class effect. Evidence from the SELECT study also showed that semaglutide can reduce cardiovascular events in individuals with obesity and established cardiovascular disease, even in the absence of diabetes.

The events adverse gastrointestinal were the most frequent reactions and constituted a relevant cause for treatment discontinuation, especially during dose escalation. In addition, discontinuation studies showed a progressive recovery of weight after stopping the medication, indicating that obesity should be treated as a chronic condition and that maintaining the benefits depends, in part, on ongoing therapy.

The heterogeneity observed across populations, molecules, doses, formulations, comparators, and follow-up durations prevents interpreting GLP-l agonists as therapeutically equivalent interventions. Treatment choice should be individualized, considering the severity of obesity, the presence of diabetes, cardiovascular risk, comorbidities, tolerability, clinical goals, and the possibility of maintaining the treatment long term.

Taken together, the evidence supports selective GLP-l receptor agonists as one of the main strategies pharmacological

for the management of obesity and its metabolic complications. However, investigations of longer duration are still needed on maintaining weight loss, long-term safety, body composition, effects in

underrepresented populations, direct comparison between molecules, and therapeutic strategies after treatment discontinuation.

## REFERENCES


1. O'Neil PM, Birkenfeld AL, McGowan B, Mosenzon O, Pedersen SD, Wharton S, et al. Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo- and active-controlled, dose-ranging, phase 2 trial. Lancet. 2018;392(10148):637-649. doi:10. 1016/S0140-6736(18)31773-2.
2. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med. 2021;384(11):989- 1002. doi:10. 1056/NEJMoa2032183.
3. Davies M, Færch L, Jeppesen OK, Pakseresht A, Pedersen SD, Perreault L, et al. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes: the STEP 2 randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. Lancet. 2021;397(10278):971-984. doi:10. 1016/S0140-6736(21)00213-0.
4. Wadden TA, Bailey TS, Billings LK, Davies M, Frias JP, Koroleva A, et al. Effect of subcutaneous semaglutide versus placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: the STEP 3 randomized clinical trial. JAMA. 2021;325(14):1403- 1413. doi:10. 1001/jama.2021.1831.
5. Rubino D, Abrahamsson N, Davies M, Hesse D, Greenway FL, Jensen C, et al. Effect of continued weekly subcutaneous semaglutide versus placebo on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical trial. JAMA. 2021;325(14):1414 - 1425. doi:10. 1001/jama.2021.3224.
6. Garvey WT, Batterham RL, Bhatta M, Buscemi S, Christensen LN, Frias JP, et al. Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial. Nat Med. 2022;28(10):2083-2091. doi:10. 1038/s41591-022-02026-4.
7. Kadowaki T, Isendahl J, Khalid U, Lee SY, Nishida T, Ogawa W, et al. Semaglutide once a week in adults with overweight or obesity, with or without type 2 diabetes, in an East Asian population: the STEP 6 randomised, double-blind, double-dummy, placebo- controlled, phase 3a trial. Lancet Diabetes Endocrinol. 2022; 10(3):193 -206.doi:10. 1016/S 2213-8587(21)00385-0.
8. Rubino DM, Greenway FL, Khalid U, O'Neil PM, Rosenstock J, Sørrig R, et al. Effect of weekly subcutaneous semaglutide versus daily liraglutide on body weight in adults with overweight or obesity without diabetes: the STEP 8 randomized clinical trial. JAMA. 2022;327(2):138 - 150.doi:10. 1001/ jama.2021.23619.
9. Weghuber D, Barrett T, Barrientos-Pérez M, Gies I, Hesse D, Jeppesen OK, et al. Once-weekly semaglutide in adolescents with obesity. N Engl J Med. 2022;387(24):2245 -2257. doi:10. 1056/NEJMoa2208601.
10. Knop FK, Aroda VR, from Vale RD, Holst-Hansen T, Laursen PN, Rosenstock J, et al. Oral semaglutide 50 mg taken once per day in adults with overweight or obesity: the OASIS 1 randomized, double-blind, placebo-

controlled, phase 3 trial. Lancet. 2023;402(10403):705-719. doi: 10.1016/S0140-6736(23)01185-6.

11. Kadowaki T, Heftdal LD, Ko HJ, Overvad M, Shimomura I, Thamattoor UK, et al. Oral semaglutide in an East Asian population with overweight or obesity, with or without type 2 diabetes: the OASIS 2 randomized clinical trial. JAMA Intern Med. 2025;185(10):1206-1217. doi:10.1001/jamainternmed.2025.3599.
12. Wharton S, Lingvay I, Bogdanski P, Duque do Vale R, Jacob S, Karlsson T, et al. Oral semaglutide at a dose of 25 mg in adults with overweight or obesity. N Engl J Med. 2025;393(11):1077-1087. doi:10.1056/NEJMoa2500969.
13. Wharton S, Freitas P, Hjelmesæth J, et al. Once-weekly semaglutide 7.2 mg in adults with obesity: the STEP UP randomised, controlled, phase 3b trial. Lancet Diabetes Endocrinol. 2025;13(11):949-963. doi:10.1016/S2213-8587(25)00226-8.
14. Lingvay I, Bergenheim SJ, Buse JB, et al. Once-weekly semaglutide 7.2 mg in adults with obesity and type 2 diabetes: the STEP UP T2D randomised, controlled, phase 3b trial. Lancet Diabetes Endocrinol. 2025;13(11):935-948. doi:10.1016/S2213-8587(25)00225-6.
15. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med. 2023;389(24):2221-2232. doi:10.1056/NEJMoa2307563.
16. Kosiborod MN, Abildstrøm SZ, Borlaug BA, Butler J, Rasmussen S, Davies M, et al. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. N Engl J Med. 2023;389(12):1069-1084. doi:10.1056/NEJMoa2306963.
17. Kosiborod MN, Petrie MC, Borlaug BA, Butler J, Davies MJ, Hovingh GK, et al. Semaglutide in patients with obesity-related heart failure and type 2 diabetes. N Engl J Med. 2024;390(15):1394-1407. doi:10.1056/NEJMoa2313917.
18. Apperloo EM, Gorriz JL, Soler MJ, Cigarrán Guldrís S, Cruzado JM, Puchades MJ, et al. Semaglutide in patients with overweight or obesity and chronic kidney disease without diabetes: a randomized, double-blind, placebo-controlled clinical trial. Nat Med. 2025;31(1):278-285. doi:10.1038/s41591-024-03327-6.
19. Wadden TA, Hollander P, Klein S, Niswender K, Woo V, Hale PM, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. Int J Obes (Lond). 2013;37(11):1443-1451. doi:10.1038/ijo.2013.120.
20. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. N Engl J Med. 2015;373(1):11-22. doi:10.1056/NEJMoa1411892.
21. Davies MJ, Bergenstal R, Bode B, Kushner RF, Lewin A, Skjøth TV, et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE Diabetes randomized clinical trial. JAMA. 2015;314(7):687-699. doi:10.1001/jama.2015.9676.
22. Blackman A, Foster GD, Zammit G, Rosenberg R, Aronne L, Wadden T, et al. Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnea: the SCALE Sleep Apnea randomized clinical trial. Int J Obes

(Lond). 2016;40(8):1310-1319. doi:10.1038/ijo.2016.52.

23. le Roux CW, Astrup A, Fujioka K, Greenway F, Lau DCW, Van Gaal L, et al. Three years of liragluti deversus placebo for type 2 diab etesrisk reduction and weightmanagement in individuals with prediabetes: a randomised, double-blind trial. Lancet. 2017;389(10077):1399-1409. doi:10.1016/S0140-6736(17)30069-7.
24. Wadden TA, Tronieri JS, Sugimoto D, Lund MT, Auerbach P, Jensen C, et al. Liraglutide 3.0 mg and intensive behavioral therapy for obesity in primary care: the SCALE IBT randomized controlled trial. Obesity (Silver Spring). 2020;28(3):529-536. doi:10.1002/oby.22726.
25. Garvey WT, Birkenfeld AL, Dicker D, Mingrone G, Pedersen SD, Satylganova A, et al. Efficacy and safety of liraglutide 3.0 mg in individuals with overweight or obesity and type 2 diabetes treated with basal insulin: the SCALE Insulin randomized controlled trial. Diabetes Care. 2020;43(5):1085-1093. doi:10.2337/dc19-1745.
26. Kelly AS, Auerbach P, Barrientos-Pérez M, Gies I, Hale PM, Marcus C, et al. A randomized, controlled trial of liraglutide for adolescents with obesity. N Engl J Med. 2020;382(22):2117-2128. doi:10.1056/NEJMoa1916038.
27. Fox CK, Barrientos-Pérez M, Bomberg EM, Dcruz J, Gies I, Harder-Lauridsen NM, et al. Liraglutide for children 6 to less than 12 years of age with obesity: a randomized trial. N Engl J Med. 2025;392(6):555-565. doi:10.1056/NEJMoa2407379.
28. Larsen JR, Vedtofte L, Jakobsen MSL, Jespersen HR, Jakobsen MI, Svensson CK, et al. Effect of liraglutide treatment on prediabetes and overweight or obesity in clozapine- or olanzapine-treated patients with schizophrenia-spectrum disorder: a randomized clinical trial. JAMA Psychiatry. 2017;74(7):719-728. doi:10.1001/jamapsychiatry.2017.1220.
29. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375(4):311-322. doi:10.1056/NEJMoa1603827.
30. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375(19):1834-1844. doi:10.1056/NEJMoa1607141.
31. Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2019;381(9):841-851. doi:10.1056/NEJMoa1901118.
32. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med. 2015;373(23):2247-2257. doi:10.1056/NEJMoa1509225.
33. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2017;377(13):1228-1239. doi:10.1056/NEJMoa1612917.
34. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes: the REWIND double-blind, randomised, placebo-controlled trial. Lancet.

2019;394(10193):121-130. doi:10. 1016/S0140-6736(19)31149-3.

35. Hernandez AF, Green JB, Janmohamed S, D'Agostino RB Sr, Granger CB, Jones NP, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease: the Harmony Outcomes double-blind, randomised, placebo-controlled trial. Lancet. 2018;392(10157):1519-1529. doi:10. 1016/S0140 -6736(18)32261-X.
36. Gerstein HC, Sattar N, Rosenstock J, Ramasundarahettige C, Pratley R, Lopes RD, et al. Cardiovascular and renal outcomes with efpeglenatide in type 2 diabetes. N Engl J Med. 2021;385(10):896 -907.doi:10. 1056/ NEJMoa2108269.
37. Frias JP, Bonora E, Nevárez Ruiz L, Li YG, Yu Z, Milicevic Z, et al. Efficacy and safety of dulaglutide 3.0 mg and 4.5 mg versus dulaglutide 1.5 mg in metformin-treated patients with type 2 diabetes in a randomized controlled trial: AWARD-11. Diabetes Care. 2021;44(3):765-773. doi:10.2337/dc20-1473.
38. Frias JP, Auerbach P, Bajaj HS, Fukushima Y, Lingvay I, Macura S, et al. Efficacy and safety of once-weekly semaglutide 2.0 mg versus 1.0 mg in patients with type 2 diabetes: the SUSTAIN FORTE double-blind, randomised, phase 3B trial. Lancet Diabetes Endocrinol. 2021;9 (9):563-574. doi:10. 1016/S 2213-8587(21)00174-1.
39. Astrup A, Rössner S, Van Gaal L, Rissanen A, Niskanen L, Al Hakim M, et al. Effects of liraglutide in the treatment of obesity: a randomized, double-blind, placebo-controlled study. Lancet. 2009;374(9701): 1606-1616. doi:10. 1016/S 0140-6736(09)61375-1.
40. Mashayekhi M, Nian H, Mayfield D, Devin JK, Gamboa JL, Yu C, et al. Weight loss-independent effect of liraglutide on insulin sensitivity in individuals with obesity and prediabetes. Diabetes. 2024;73(1):38-50. doi:10.2337/db23-0356.
41. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi:10. 1136/bmj.n71.
42. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ. 2021;372:n160.doi:10. 1136/bmj.n 160.
43. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomized trials. BMJ. 2019;366:l4898. doi: 10. 1136/bmj.l4898.
44. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. Cochrane handbook for systematic reviews of interventions. 2nd ed. Chichester: John Wiley & Sons; 2019.