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Liraglutide, Semaglutide, and Tirzepatide in Obesity, Type 2 Diabetes : A Systematic Review and Meta-Analysis

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A Thesis

Presented in Partial Fulfilment of the Requirements for the Bachelor of Science Degree in Pharmacy, Faculty of Pharmacy, Galala University.

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List of Abbreviations and Key Terms

Abbreviation	Meaning
BMI	Body Mass Index
T2DM	Type 2 Diabetes Mellitus
GLP-1	Glucagon-Like Peptide-1
GIP	Glucose-dependent Insulinotropic Polypeptide
GLP-1 RA	Glucagon-Like Peptide-1 Receptor Agonist
HbA1c	Glycated Hemoglobin
FPG	Fasting Plasma Glucose
RCT	Randomized Controlled Trial
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
GRADE	Grading of Recommendations Assessment, Development and Evaluation
MD	Mean Difference
SMD	Standardized Mean Difference
RR	Risk Ratio
OR	Odds Ratio
CI	Confidence Interval
ICER	Incremental Cost-Effectiveness Ratio
QALY	Quality-Adjusted Life Year
NAFLD	Non-Alcoholic Fatty Liver Disease
RevMan	Review Manager Software

Abstract

Background

Obesity is a complex, recurring, and multidimensional disease that is now recognized as one of the most important public health problems across the globe. Obesity has been identified as being strongly linked to a range of metabolic and cardiac complications, including T2DM, hypertension, dyslipidemia, cardiovascular diseases, nonalcoholic fatty liver disease, and obstructive sleep apnea. Recently, incretin therapy such as liraglutide, semaglutide, and tirzepatide has been identified as an efficacious pharmacotherapy for obesity and diabetes patients **.**

Aim

The present systematic review and meta-analysis were conducted to compare the effectiveness and safety of liraglutide, semaglutide, and tirzepatide in adults who had overweight, obesity, and T2DM, focusing especially on their effects in terms of weight loss, glycemic control, cardiometabolic outcomes, and adverse drug events **.**

Methods

A comprehensive search of literature was conducted via PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library. Included articles comprised randomized control trials, clinical trials with comparatives, observational studies, systematic reviews, and meta-analysis studies assessing liraglutide,

semaglutide, and tirzepatide. The inclusion, risk of bias evaluation, data extraction, and synthesis were carried out following PRISMA principles. Potential risk of biases was assessed based on the Cochrane Risk of Bias tool, while evidence certainty was determined by means of GRADE methodology

Results

The results revealed that all the three drugs had been able to show significant changes for body weight, blood glucose, and metabolic measures. Out of the three drugs, tirzepatide had shown the highest percentage reduction in weight at up to 26.6%, while the same was only up to 17.4% for semaglutide and 9.2% for liraglutide. Additionally, tirzepatide had shown the highest percentage reduction in HbA1C levels and high rates of achievement for clinically important weight loss targets as well as normalization of the glucose levels. Semaglutide had shown considerable efficacy and the highest evidence for its cardiovascular and kidney protective properties. Liraglutide had shown considerable efficacy, although smaller compared to the other two drugs. The most common adverse effects were gastrointestinal symptoms such as nausea, vomiting, diarrhea, and constipation.

Conclusion

All three drugs were successful at managing obesity and T2DM. However, it was clear that tirzepatide was more efficient in weight loss, glucose levels management, and diabetes prevention while semaglutide had significant effects on the cardiovascular and renal systems. Although liraglutide was effective as

well, it still proved to be less efficient than the other two drugs. In conclusion, tirzepatide seemed to be the most efficient drug among all three options presented here.

Keywords: Obesity; Overweight; Type 2 Diabetes Mellitus; Liraglutide; Semaglutide; Tirzepatide; GLP-1 Receptor Agonists; GIP/GLP-1 Agonist; Weight Loss; Systematic Review; Meta-analysis.

Introduction

It is worth noting that obesity is considered a chronic, relapsing, and multifactorial disease characterized by a steady increase in body mass index (BMI) of at least 30 kg/m2. It should be noted that more than 650 million people suffer from obesity worldwide, and overweight and obesity become prevalent among all age groups. Obesity contributes greatly to the increased morbidity, mortality, deterioration in the quality of life, and increased costs of health care. **(Ghassan & Hussain, 2026; Tentolouris et al., 2026)**

Metabolic complications of obesity include type 2 diabetes mellitus (T2DM), coronary artery disease, cerebrovascular accidents, hypertension, dyslipidemia, non-alcoholic fatty liver disease (NAFLD), obstructive sleep apnea, and various cancers. All obesity-related diseases increase the risk of disability, early death, and medical complications. **(Tentolouris et al., 2026; Wilson et al., 2026)**

Lifestyle modification through nutrition counseling, exercise, and psychotherapy still remain the cornerstones of the treatment of obesity. At the same time, long-term weight loss is rather complicated for many individuals and, consequently, a lot of people regain lost weight. Therefore, nowadays, the issue of developing new pharmacotherapy strategies is particularly acute to ensure sustainable weight loss. **(Quarenghi et al., 2025; Bonga & Padhan, 2026)**

The recent innovations in obesity pharmacotherapy have resulted in the emergence of powerful incretin-based injectable drugs. From the incretin-based

injectable drugs, liraglutide (Saxenda® /Victoza®), semaglutide (Wegovy®/Ozempic®), and tirzepatide (Zepbound®/Mounjaro®) should be singled out for their efficiency in reducing body mass index and cardiometabolic outcomes improvement. Liraglutide and semaglutide are representatives of the group of glucagon-like peptide-1 receptor agonists (GLP-1 RAs), whereas tirzepatide can be regarded as a novel glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA agent. **(Ciudin et al., 2026; Bonga & Padhan, 2026)**

There are many physiological processes involved in weight loss caused by these drugs. The action of incretin-based drugs is based on the suppression of appetite due to central hypothalamic pathways activation, delayed gastric emptying, improved satiety, decreased calorie intake, enhanced insulin secretion, and glucose regulation improvements. Thanks to these mechanisms, patients manage to significantly lose weight. **(Ghassan & Hussain, 2026; Bonga & Padhan, 2026)**

There is strong scientific evidence through various randomized controlled studies, comparative studies, and meta-analysis showing the effectiveness of liraglutide, semaglutide, and tirzepatide in body weight loss. It has been revealed that the tirzepatide might be more effective in achieving better results than semaglutide while, on the other hand, semaglutide is more effective than liraglutide. Besides weight loss, it also exerts positive influences on body mass

index, glucose regulation, and health-related quality of life. **(Ciudin et al., 2026; Munawar et al., 2025; Shukla et al., 2026)**

Despite the substantial number of evidences provided, there are very few studies making direct comparisons between liraglutide, semaglutide, and tirzepatide. In addition to differences in methodologies, patients involved, outcome measures, and safety reports, the main issues with the use of these drugs include gastrointestinal side effects, potential treatment discontinuation, weight regain post-therapy, and overall drug safety. **(Quarenghi et al., 2025; Ng et al., 2025; Ghassan & Hussain, 2026)**

This leads to the need for a systematic review and meta-analysis of data related to the effectiveness and safety of liraglutide, semaglutide, and tirzepatide, which will contribute to formulating evidence-based conclusions for further guidance in terms of prescribing one of these agents to treat overweight and obesity. **(Ciudin et al., 2026; Karimi et al., 2025)**

Rationale of the Study

Being overweight has emerged as one of the leading public health problems of the 21st century. Millions of people have become overweight worldwide. Besides causing severe harm to the patients' health, it poses a significant burden on the healthcare system. Overweight increases patients' risks of developing different kinds of diseases. These include type 2 diabetes mellitus, hypertension, dyslipidemia, heart disorders, obstructive sleep apnea, fatty liver, and even some cancers. Apart from being damaging to health, being overweight also affects people emotionally and socially. **(Bonga & Padhan, 2026; Ghassan & Hussain, 2026)**

While lifestyle modification programs involving dietary changes and more exercises have been the primary treatment option for obese patients, there is evidence that many patients find it difficult to lose weight successfully by means of such interventions alone. As far as the problem under discussion is concerned, weight regain is quite common even among those patients who initially succeeded in losing extra pounds. There are several reasons for such outcomes. In this regard, pharmacological therapy has been suggested as an important strategy in the fight against overweight. **(Bonga & Padhan, 2026)**

In recent times, incretin drugs have become an important tool in the management of obesity and overweight patients. Examples of incretin-based drugs include liraglutide, semaglutide, and tirzepatide. The former two are glucagon-like peptide-1 receptor agonists (GLP-1 RAs) while the third drug

acts as a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist. Various studies have shown that such incretin medications may result in large weight reductions along with improvement in blood glucose levels, cardiometabolic risk markers, and overall metabolic condition. **(Bonga & Padhan, 2026; Ciudin et al., 2026)**

There exists a considerable amount of evidence concerning the use of those drugs. The literature contains various randomized controlled trials, observational studies, systematic reviews, and meta-analyses aimed at studying the efficacy and safety of incretin medications. Nonetheless, some shortcomings have been revealed with respect to the existing publications. For example, many studies investigate only one of those medications instead of comparing three incretin drugs directly. In addition to that, different populations, body mass index, diabetes status, therapy duration, doses used, endpoints, and ways of recording adverse effects add to the diversity of data obtained. **(Karimi et al., 2025; Ciudin et al., 2026)**

From recent data, it appears that tirzepatide might offer more pronounced weight loss results than semaglutide and liraglutide, thus constituting an important step forward in the treatment of obesity with medication. At the same time, there are concerns regarding the actual clinical effectiveness of the therapy, consistency of results observed among different groups of patients, as well as possible side effects including nausea, treatment discontinuation, etc. In addition, semaglutide is considered highly effective compared to other anti-

obesity drugs, whereas liraglutide remains popular among medical professionals despite a relatively long history. **(Aamir et al., 2025; Munawar et al., 2025)**

The choice of an appropriate drug based on incretins as an active ingredient becomes a critical question facing healthcare providers when it comes to the treatment of overweight or obese patients. Apart from efficacy, this question is shaped by various factors, such as safety, acceptability of the treatment, adherence, availability, costs, etc. An overall synthesis of current evidence is crucial in order to inform practice decisions. A comparison of liraglutide, semaglutide, and tirzepatide along with the analysis of their results will enable clinicians to identify benefits and drawbacks of each treatment modality. **(Munawar et al., 2025)**

A systematic review and meta-analysis would be considered the most advanced way to analyze scientific data. Through the combination of the results of several high-quality studies, one can enhance statistical power, obtain more precise estimations of the effects under consideration, and estimate outcomes based on better scientific data than that obtained by separate trials. Furthermore, heterogeneity, pattern recognition, and the robustness of scientific evidence can be examined using a systematic approach. This method is especially important in the field of rapid development, such as obesity pharmacotherapy. **(Ciudin et al., 2026; Schulz et al., 2025)**

In light of what has been discussed above, a systematic review and meta-analysis on the comparison of liraglutide, semaglutide, and tirzepatide would be particularly topical and clinically important. Specifically, a comprehensive analysis would shed some light on the comparative efficacies and safety of the three pharmaceuticals in terms of the treatment of obesity in adult patients. It should help in forming evidence-based recommendations on drug prescription, provide medical professionals with information useful in making a choice about treatment modality, and highlight gaps in literature. **(Karimi et al., 2025; Ciudin et al., 2026; Schulz et al., 2025)**

Aim of the Study

The main objective of the present study is to assess the efficacy and safety of recently introduced injectable agents for the treatment of overweight or obesity in adults, including liraglutide, semaglutide, and tirzepatide, using systematic review and meta-analysis methods based on the clinical evidence obtained from randomized control trials and comparative clinical studies.

Also, an assessment of the safety of the investigated drugs should be performed by estimating the occurrence of adverse events and other important clinical outcomes. Overall, the purpose of this investigation is to compare the benefits of each therapy with the adverse effects, aiming to determine which treatment provides the best balance between efficacy and safety.

Finally, the results of this study can help with making clinical decisions based on the available evidence, choosing the proper pharmaceuticals for patients suffering from obesity, as well as conducting further research in this area.

Objectives

Main Objective

The primary objective of this study is to ascertain the combined effects of liraglutide, semaglutide, and tirzepatide regarding their ability to induce reductions in body weight in patients with overweight and obesity conditions compared with placebo, standard treatment regimen or alternative treatments for obesity.

Secondary Objectives

1. To compare the effectiveness of the three medications in inducing weight loss by comparing changes in body weight and body weight percentage reductions.
2. Assessing the effect of the mentioned drugs on body mass index (BMI) and waist circumference.
3. Assessing glycemic control improvement measured in fasting plasma glucose and glycated hemoglobin (HbA1c).
4. Comparing the effects of these three medications on cardiometabolic outcomes.
5. Incidence of side effects of liraglutide, semaglutide, and tirzepatide.

6. Rate of discontinuation of treatments due to the occurrence of adverse effects.
7. Overall safety and tolerance of the selected drugs.
8. Determine the most efficient combination of efficacy and safety among the listed medications for patients with overweight or obesity.

Research Questions

Main Research Question

Among adults who are either overweight or obese, what is the comparative effectiveness and safety of liraglutide, semaglutide, and tirzepatide in helping patients lose weight and improve health outcomes related to obesity?

Sub-Research Questions

1. Which drug—liraglutide, semaglutide, or tirzepatide—induces the highest reduction in body weight?
2. Which drug—liraglutide, semaglutide, or tirzepatide—causes the highest percentage of weight loss?
3. What is the impact of these drugs on the body mass index and waist circumference?
4. What is the impact of liraglutide, semaglutide, and tirzepatide on improving glycemic indicators, such as fasting blood glucose and HbA1c levels?
5. Which adverse events occur most frequently with each drug?

6. Is there any difference in terms of safety and tolerance between liraglutide, semaglutide, and tirzepatide?
7. Do the discontinuation of treatment because of adverse events differ among the drugs?
8. Which drug can be considered the best in terms of efficacy and safety in treating obese and overweight adults?
9. Are clinical studies consistent in proving the advantage of one medication over others?
10. What more should be known about the comparative use of these drugs?

PICO Framework

The application of the PICO framework allowed us to develop an appropriate research question and choose the studies that would be used in this systematic review. In particular, this framework helped assess the efficacy and safety of using injectable anti-obesity drugs (liraglutide, semaglutide, and tirzepatide) in adults with overweight or obesity.

Population (P)

The population was adults aged 18 years and older diagnosed with overweight or obesity. The BMI of participants was equal to or above 25 kg/m^2 (overweight) or 30 kg/m^2 (obesity). Adults with obesity-related diseases, including type 2 diabetes mellitus, hypertension, dyslipidemia, cardiovascular

disease, and metabolic syndrome, were also included in most cases if mentioned by the original studies.

The participants had various demographic characteristics in terms of age, sex, and ethnic background. The focus of the review was made on adults; thus, all studies involving only children, pregnant women, or adults with severe diseases that were not associated with obesity were ruled out. **(Bonga & Padhan, 2026)**

Intervention (I)

In this context, the considered interventions were contemporary incretin-based injections that have been approved or studied for the treatment of obesity. They involved the following drugs:

- Liraglutide (Saxenda®, Victoza®)
- Semaglutide (Wegovy®, Ozempic®)
- Tirzepatide (Zepbound®, Mounjaro®)

Specifically, liraglutide and semaglutide belong to glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and tirzepatide acts as a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA. All three drugs contribute to weight loss using multiple mechanisms, namely the stimulation of satiety, delayed gastric emptying, inhibition of appetite, and glycemic modulation.

For this purpose, both studies comparing different dose and duration regimens and alternative forms of drug administration were analyzed in order to provide

a thorough review of therapeutic effectiveness and safety. **(Ciudin et al., 2026; Ghassan & Hussain, 2026)**

Comparison (C)

In this regard, the interventions were compared against one or several of the following:

- Placebo therapy
- Lifestyle modifications
- Nutritional and physical activity interventions
- Traditional pharmacological treatments of obesity
- GLP-1 receptor agonists (excluding liraglutide, semaglutide, and tirzepatide)
- Head-to-head comparison of liraglutide, semaglutide, and tirzepatide

The use of such control measures made it possible to analyze the comparative advantages and disadvantages of each intervention and identify the most effective means of weight control. **(Ciudin et al., 2026; Karimi et al., 2025)**

Outcome Measures (O)

The outcome measures evaluated in this paper were the efficacy and safety measures that pertained to the treatment of obesity.

Primary Outcome Measures

The primary outcomes measured were:

- Change in mean body weight (kg)
- Change in percentage body weight from baseline (%)
- Clinical significance based on weight loss ≥5%, ≥10%, and ≥15% of baseline body weight

These were chosen because they represent some of the commonest outcome measures used in studies of obesity.

Secondary Outcome Measures

The secondary outcome measures included:

- Change in Body Mass Index (BMI)
- Change in waist circumference (cm)
- Change in HbA1c (%)
- Change in fasting plasma glucose levels
- Insulin sensitivity improvement
- Change in blood pressure
- Lipid profile improvements
- Metabolic risks reductions
- Quality of life
- Patient compliance and satisfaction
- Adverse events
- Gastrointestinal side effects (nausea, vomiting, diarrhea, constipation)
- Serious adverse events

- Discontinuations

These outcome measures gave a wider insight into the metabolic benefits and safety profile of injectable anti-obesity drugs. **(Ciudin et al., 2026)**

PICO Research Question

Do the injectable incretin-based medications such as liraglutide, semaglutide, and tirzepatide (I), in comparison to placebo, lifestyle modifications, or other pharmaceuticals (C), provide greater benefits to adults suffering from overweight and obesity (P), with regards to weight loss and metabolic outcomes while ensuring an appropriate safety profile (O)?

PICO Summary Table

Component	Description
Population	Adults aged ≥18 years with overweight or obesity, with or without obesity-related comorbidities
Intervention	Liraglutide, Semaglutide, and Tirzepatide
Comparison	Placebo, lifestyle modification, conventional anti-obesity medications, and head-to-head drug comparisons
Outcomes	Weight loss, BMI reduction, glycemic control, cardiometabolic improvements, adverse events, and treatment adherence

The PICO framework served as the foundation for the literature search strategy, study selection process, and synthesis of evidence presented in the subsequent sections of this review.

Methodology

Design of the Study

For this research, the approach that will be adopted is that of conducting a systematic review and meta-analysis of randomized controlled trials and comparative studies examining the safety and efficacy of liraglutide, semaglutide, and tirzepatide in adults who have been found to have obesity or overweight status. The methodology will follow the PRISMA approach that seeks to enhance transparency, reproducibility, and quality of research in the conduct of systematic reviews and meta-analyses. In this respect, the primary aim of this review will be to analyze the effectiveness of the injectable incretin agonists as far as weight loss and safety of treatment are concerned. **(Karimi et al., 2025; Ciudin et al., 2026)**

Data Sources

A literature search will be undertaken to find eligible articles from several databases, which will include those published in 2026.

The databases to be used are as follows:

- PubMed/MEDLINE
- Scopus

- Web of Science
- Cochrane Library
- ClinicalTrials.gov

Also, manual searches of reference lists from the articles will be made to find more articles. **(Karimi et al., 2025; Schulz et al., 2025)**

Table. Databases Included in the Literature Search

Database	**Purpose**
PubMed/MEDLINE	Biomedical and clinical research
Scopus	Multidisciplinary scientific literature
Web of Science	Citation-indexed journals
Cochrane Library	Clinical trials and systematic reviews
ClinicalTrials.gov	Registered clinical studies

Search Strategy

The searches will be done with the use of Medical Subject Headings (MeSH) and free-text words related to obesity and anti-obesity therapy through injections.

Search Terms

- obesity
- overweight

- GLP-1 receptor agonist
- semaglutide
- liraglutide
- tirzepatide
- weight loss injection
- anti-obesity drug
- randomized controlled trial

Example of Search String

("obesity" OR "overweight") AND ("semaglutide" OR "liraglutide" OR "tirzepatide") AND ("weight loss" OR "anti-obesity drug") AND ("randomized controlled trial")

Boolean operators (AND, OR) will be used to increase the sensitivity and specificity of the search.

Eligibility Criteria

Inclusion Criteria

A study will be included if it:

- Is a RCT or a comparative clinical study.
- Involves patients ≥18 years old suffering from overweight and/or obesity.
- Uses injectable incretin-based drugs (liraglutide, semaglutide, and/or tirzepatide).

- Considers weight loss results.
- Examines safety/adverse effects results.
- Is written in English.
- Contains quantitative data required for further analysis.

Exclusion Criteria

A study will be excluded if it:

- Is a case report or a case series.
- Is a review article.
- Is an editorial/comment.
- Lacks appropriate outcome data.
- Is a duplicate publication.
- Deals with pediatric populations only.

Table. Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
Adults ≥18 years	Animal studies
Overweight or obesity	Pediatric studies
Injectable incretin therapies	Case reports
Weight-loss outcomes reported	Narrative reviews
Safety outcomes reported	Editorials
English-language studies	Insufficient data

Risk of Bias Assessment

Quality assessment for randomized controlled trials included in this systematic review will be done through the use of the Cochrane Risk of Bias Tool (RoB 2), and it will include the following aspects of the trials:

- Randomization method
- Allocation concealment
- Blinding of participants and personnel
- Missing outcome data
- Outcome measurement
- Selective outcome reporting

Risk of bias for each trial will be categorized as:

- Low risk of bias
- Some concerns
- High risk of bias

Statistical Analyses

The meta-analysis will be carried out using Review Manager (RevMan) version 5.4 software and R Statistical Software. The statistical analysis of data will be done where appropriate homogeneity among data extracted from the studies is present. The analyses will be conducted in compliance with the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Data Synthesis

The information from relevant research will be combined to make comparisons about the effectiveness and safety of liraglutide, semaglutide, and tirzepatide among adults who are overweight or obese. The effectiveness as well as safety measures will be separately analyzed if there is enough information. In case there is evidence that can be compared, the pooled estimates will be obtained to compare the three treatment methods. Both effectiveness and safety outcome measures will be synthesized separately. Where the synthesis is not possible due to considerable clinical or methodological heterogeneity, the results will be presented descriptively.

Continuous Variables

Continuous variables will be synthesized by applying Mean Difference (MD) with 95% Confidence Intervals (CI) in case studies measure the effect using the same measurement scale. The following outcome measures are considered to be continuous variables:

- Body weight change (kg)
- Percentage weight loss (%)
- Reduction in Body Mass Index (BMI)
- Reduction in waist circumference (cm)
- Reduction in HbA1c (%)
- Fasting plasma glucose levels
- Lipid profile parameters changes

- Blood pressure changes
- Quality-of-life measures where available

In case the studies use different measurement scales, Standardized Mean Difference (SMD) with 95% CI will be utilized.

Dichotomous Endpoints

Dichotomous endpoints will be assessed utilizing Risk Ratios (RR) along with 95% Confidence Interval (CI). They comprise of:

- Overall adverse events
- Adverse events involving the gastrointestinal system
- Serious adverse events
- Treatment discontinuation due to adverse effects
- Nausea, vomiting, diarrhea, and constipation
- Hypoglycemia
- Reaching a clinical weight reduction of at least 5%, 10%, or 15%
- Reaching target HbA1c levels
- Mortality (when applicable)

Odds Ratio (OR) will be determined whenever there is inadequate data from studies to determine Risk Ratio.

Assessment of Heterogeneity

There will be statistical assessment for heterogeneity between studies based on the Chi-Squared (χ^2) test and the I^2 statistic. While the χ^2 will examine the

compatibility of observed differences with the null hypothesis, the I^2 statistic will measure the proportion of variability due to heterogeneity as opposed to sampling error.

Table--. Interpretation of I^2 Statistic

I^2 Value	Interpretation
0–25%	Low heterogeneity
26–50%	Moderate heterogeneity
51–75%	Substantial heterogeneity
>75%	Considerable heterogeneity

If the heterogeneity between the studies is low (I^2 ≤50%), then a fixed-effect model will be used. In case of substantial heterogeneity between studies (I^2 >50%), the random-effects model will be employed due to its consideration of the between-study variability. The sources of heterogeneity will be identified via subgroup and sensitivity analyses.

Subgroup Analysis

In cases where enough data are provided, subgroup analyses will be performed in order to identify possible sources of heterogeneity in relation to:

- Having type 2 diabetes mellitus or not
- BMI levels
- Age group
- Sex

- Dosage schedule of liraglutide, semaglutide, and tirzepatide
- Duration of therapy
- Research design (RCTs vs. observational studies)
- Geographical location of the study

Sensitivity Analysis

Sensitivity analysis will be carried out to examine the reliability of pooled effect estimates from the meta-analysis. Possible types of sensitivity analysis may include:

- Exclusion of studies at a high risk of bias
- Exclusion of studies with a small number of participants
- Exclusion of studies reporting missing or imputed data
- Comparison of fixed- and random-effects models
- Elimination of studies contributing most to heterogeneity

Publication Bias Testing

Publication bias shall be checked in case there are ten or more studies for a particular outcome. Visual inspection of funnel plots for asymmetry will be carried out, while tests such as Egger's regression test and Begg's test may also be used appropriately.

Handling Missing Data

Efforts shall be made to obtain all outcome data from selected studies. In cases where data is incomplete or ambiguous, authors shall be contacted to clear any

confusion. Where missing data is not available, analyses can still be performed, and the possible effect that missing data could have on the findings can be highlighted.

Statistical Significance

All statistical tests in the analysis shall be two-tailed. Statistically significance will be declared where the p-value is below 0.05. Results will then be interpreted by presenting all effect estimates along with their 95% confidence intervals to determine the accuracy of the pooling process.

Certainty of Evidence

Certainty of evidence for all major outcomes will be assessed using the GRADE framework of assessment. Evidence can thus be rated as high, moderate, low, and very low certainty based on factors such as risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Results

Study 1: Ciudin et al., 2026

In the current study, which utilized Bayesian network meta-analysis, six RCTs including 10,355 subjects who had obesity or overweight but no type 2 diabetes were enrolled. The efficacy and safety of tirzepatide, semaglutide, and liraglutide were examined at the follow-up durations of 52 to 72 weeks.

Results on Weight Reduction

As shown in the study results, tirzepatide showed significant weight loss compared with both semaglutide and liraglutide. It was revealed that the maximum weight loss occurred in patients receiving tirzepatide 15 mg with an average of 22.5% decrease from baseline. With semaglutide, 16.6% to 17.1% weight loss was observed, while with liraglutide, 6.6% to 9.2% decrease in body weight occurred.

Table. Percentage Weight Reduction

Treatment	Mean Weight Reduction (%)
Liraglutide	6.6–9.2
Semaglutide	16.6–17.1
Tirzepatide 5 mg	16.0
Tirzepatide 10 mg	21.4
Tirzepatide 15 mg	22.5

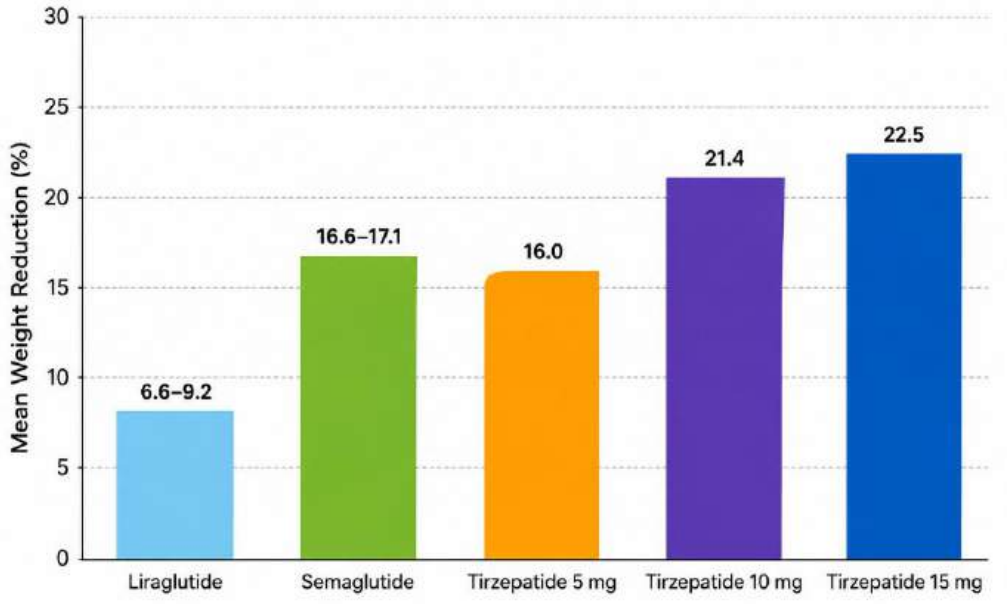


Figure 1. Percentage Weight Reduction Across Treatments

Interpretation

The graph clearly demonstrates the superior efficacy of tirzepatide, particularly at the 10 mg and 15 mg doses. Tirzepatide 15 mg achieved approximately three times the weight reduction observed with liraglutide and substantially greater reductions than semaglutide.

Waist Circumference Outcomes

Tirzepatide was associated with significantly greater reductions in waist circumference compared with both liraglutide and semaglutide.

Table. Waist Circumference Reduction

Comparison	Mean Difference (cm)
Tirzepatide 5 mg vs Liraglutide	-7.02

Tirzepatide 10 mg vs Liraglutide	-11.79
Tirzepatide 15 mg vs Liraglutide	-12.30
Tirzepatide 10 mg vs Semaglutide	-4.81
Tirzepatide 15 mg vs Semaglutide	-5.32

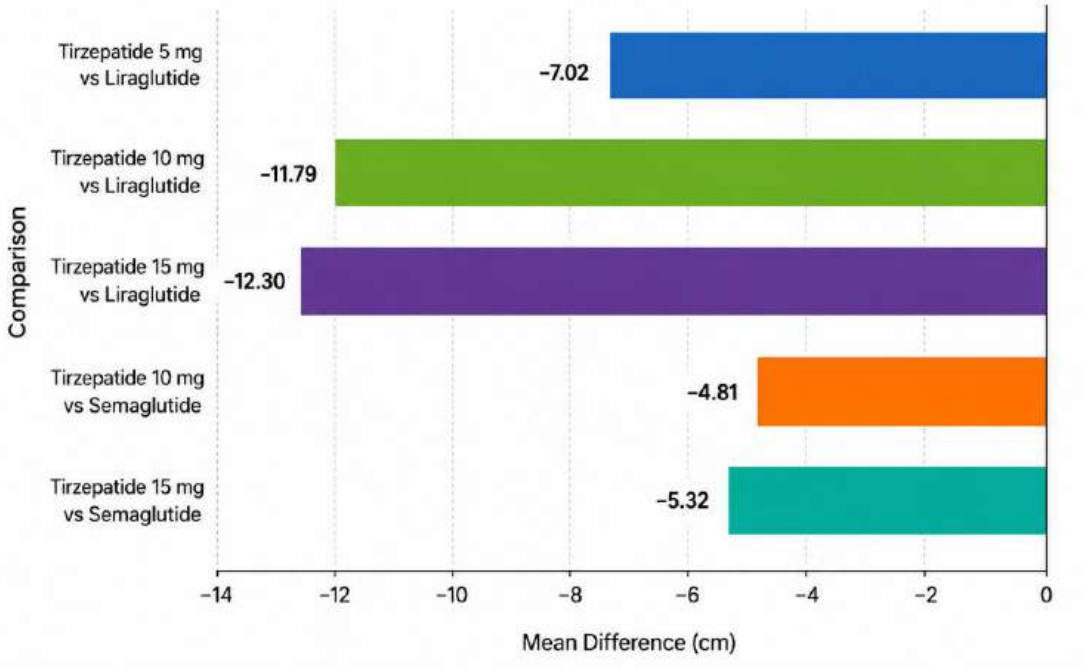


Figure 2. Waist Circumference Reduction

Interpretation

The greatest reduction in waist circumference was observed with tirzepatide 15 mg. These findings indicate superior reduction of central adiposity compared with both liraglutide and semaglutide.

Achievement of Weight-Loss Targets

Participants receiving tirzepatide were significantly more likely to achieve clinically meaningful weight-loss thresholds.

Table. Odds Ratios for Achieving ≥20% Weight Loss

Comparison	Odds Ratio
Tirzepatide 5 mg vs Liraglutide	14.65
Tirzepatide 10 mg vs Liraglutide	39.54
Tirzepatide 15 mg vs Liraglutide	53.50

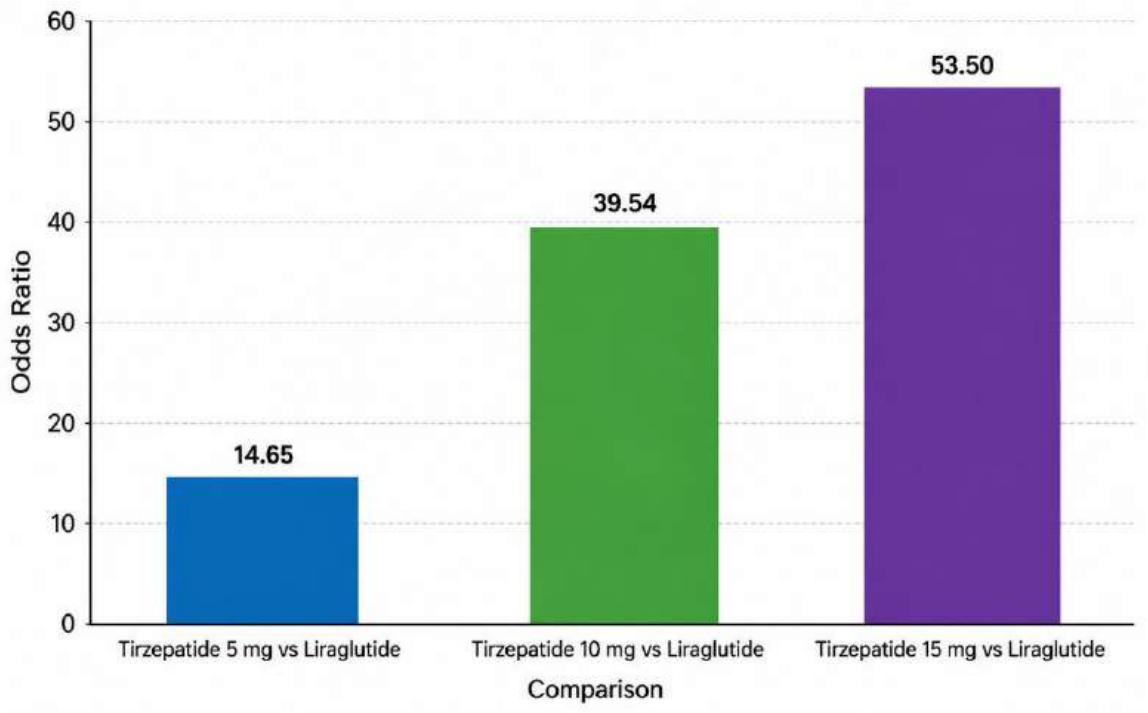


Figure 3. Probability of Achieving ≥20% Weight Loss

Interpretation

Tirzepatide 15 mg showed the highest likelihood of achieving substantial weight reduction, with more than 50-fold higher odds compared with liraglutide.

Safety Outcomes

The safety profiles of tirzepatide, semaglutide, and liraglutide were generally comparable. Gastrointestinal adverse events remained the most frequently reported side effects across all treatments.

Table. Safety Outcomes

Outcome	Tirzepatide vs Comparators
Total GI Adverse Events	Comparable
Severe GI Adverse Events	Slightly Higher
Nausea	Comparable
Treatment Discontinuation	Lower Trend

Interpretation

Although severe gastrointestinal adverse events occurred slightly more frequently with higher doses of tirzepatide, overall treatment discontinuation rates remained low and comparable across treatment groups.

Overall Result

Among all evaluated therapies, tirzepatide 15 mg demonstrated the greatest efficacy for weight reduction, waist circumference reduction, and improvement of cardiometabolic risk factors, while maintaining a safety profile generally comparable to semaglutide and liraglutide.

Study 2: Cetiner, 2026

This real-life comparative trial involved 169 patients suffering from overweight or obesity and prescribed liraglutide (n=55), semaglutide (n=55), or tirzepatide (n=59). The weight loss and waist circumference reductions achieved after 36-week treatment were used as outcome measures.

Patients' Demographic Features

In all, 169 subjects took part in this trial, where 57.9% of the patients were women and 42.1% were male subjects.

The distribution of patients by medication type is shown below:

- Liraglutide: 55 patients (32.5%)
- Semaglutide: 55 patients (32.5%)
- Tirzepatide: 59 patients (34.9%)

Initial body mass index was between 33.37

Table. Baseline Characteristics

Variable	Liraglutide	Semaglutide	Tirzepatide
Sample Size	55	55	59
Female (%)	56.3	60.0	57.6
Age (years)	41.89	41.11	39.42
Weight (kg)	100.08	93.11	99.41
BMI (kg/m²)	36.08	33.37	34.25
HbA1c (%)	5.56	5.64	5.49

Weight Loss Outcomes

Weight loss differed significantly among treatment groups at week 36 ($p < 0.01$).

After adjustment for sex, age, baseline BMI, and hepatic steatosis, tirzepatide achieved the greatest mean weight loss, followed by semaglutide and liraglutide.

Table . Adjusted Mean Weight Loss at Week 36

Treatment	Weight Loss (kg)
Liraglutide	13.18 ± 0.74
Semaglutide	16.63 ± 0.73

Tirzepatide	19.52 ± 0.70

Interpretation

Tirzepatide achieved the greatest reduction in body weight, with approximately 6.3 kg greater weight loss than liraglutide and nearly 3 kg greater weight loss than semaglutide. The difference between treatment groups remained statistically significant after adjustment for potential confounders (p = 0.001).

Distribution of Percentage Weight Loss

The proportion of patients achieving higher weight-loss categories increased progressively from liraglutide to semaglutide and tirzepatide.

Table. Distribution of Percentage Weight Loss

Weight Loss Category	**Liraglutide (%)**	**Semaglutide (%)**	**Tirzepatide (%)**
5–10%	30.9	18.2	5.1
10–15%	30.9	36.4	18.6
15–20%	23.6	25.5	39.0
>20%	14.5	20.0	37.3

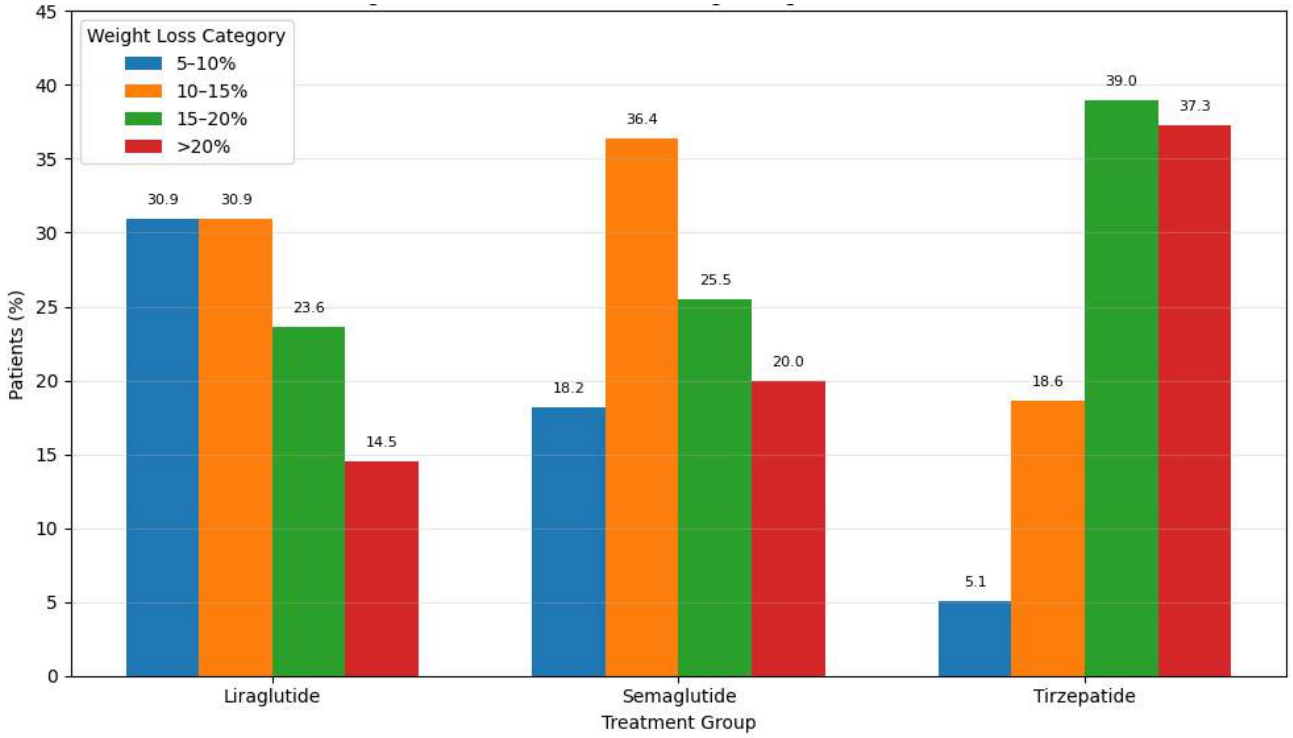


Figure 4. Distribution of Percentage Weight Loss by Treatment Group

Interpretation

Higher levels of weight loss were observed more frequently among patients receiving tirzepatide. More than one-third of tirzepatide-treated patients achieved weight loss exceeding 20%, compared with only 14.5% of liraglutide-treated patients.

Waist Circumference Outcomes

All treatment groups demonstrated significant reductions in waist circumference after 36 weeks ($p < 0.01$).

Table. Waist Circumference Changes

Treatment	Baseline (cm)	Week 36 (cm)	Reduction (cm)
Liraglutide	104.36	91.95	12.42
Semaglutide	98.36	86.07	12.29
Tirzepatide	103.81	89.00	14.81

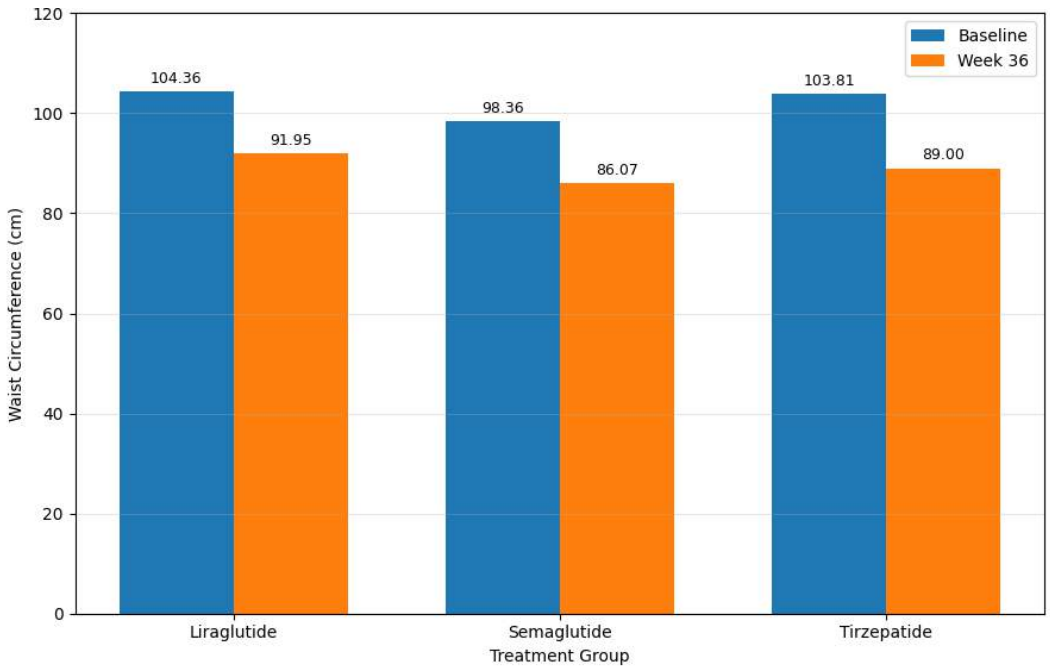


Figure 5. Waist Circumference at Baseline and Week 36

Interpretation

Tirzepatide produced the largest numerical reduction in waist circumference (14.81 cm). However, the differences between treatment groups did not reach

statistical significance ($p > 0.05$), indicating that all three medications were similarly effective in reducing central adiposity.

Statistical Analysis of Weight Loss

ANCOVA analysis demonstrated a significant effect of treatment group on weight loss outcomes.

Table. ANCOVA Results

Variable	F Value	p-value
Sex	8.908	0.003
Age	0.100	0.753
Baseline BMI	32.859	0.001
Hepatic Steatosis	4.874	0.029
Treatment Group	19.185	0.001

Interpretation

Treatment group was one of the strongest predictors of weight loss, with a large effect size (partial $\eta^2 = 0.191$). Baseline BMI also significantly influenced treatment response.

Overall Findings

Among the three therapies evaluated, tirzepatide demonstrated the greatest efficacy for body weight reduction, while semaglutide showed intermediate

efficacy and liraglutide produced the lowest weight-loss outcomes. All treatments significantly reduced waist circumference and improved obesity-related parameters, with generally comparable baseline characteristics across groups.

Study 3: Liu et al., 2025

This paper aimed to assess the cost-effectiveness analysis within a limited period of time for patients suffering from overweight and obesity without diabetes, but not including type 2 diabetes, by comparing the costs, BMI changes, QALYs and ICERs between different treatment options for tirzepatide, oral semaglutide, subcutaneous semaglutide, and liraglutide in the U.S.

BMI Reduction Outcomes

Tirzepatide demonstrated the greatest reduction in BMI among all evaluated therapies.

Table . Total BMI Reduction

Treatment	Total BMI Reduction
Liraglutide	3.0
Semaglutide Injection	5.6
Semaglutide Oral	5.6

Tirzepatide	8.2

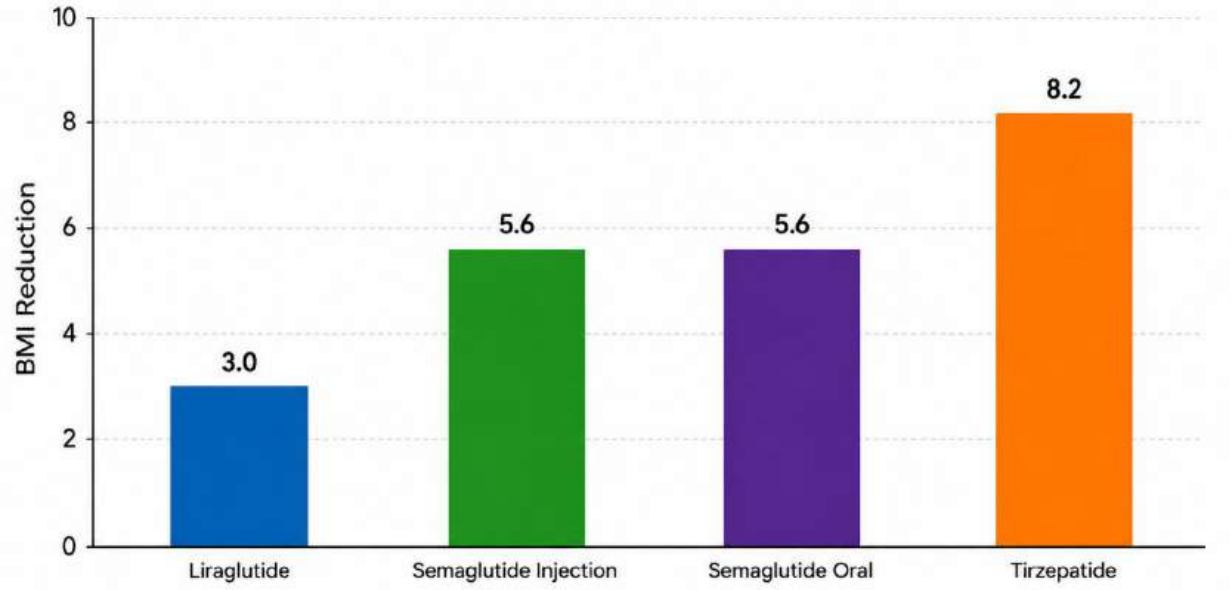


Figure 6. Total BMI Reduction Across Treatments

Interpretation

Tirzepatide achieved the largest BMI reduction (8.2 units), exceeding both injectable and oral semaglutide (5.6 units) and liraglutide (3.0 units).

Early BMI Reduction (Week 20)

Tirzepatide also demonstrated the greatest early treatment effect.

Table. BMI Reduction at Week 20

Treatment	BMI Reduction
Liraglutide	2.7

Semaglutide Injection	3.3
Semaglutide Oral	3.5
Tirzepatide	4.5

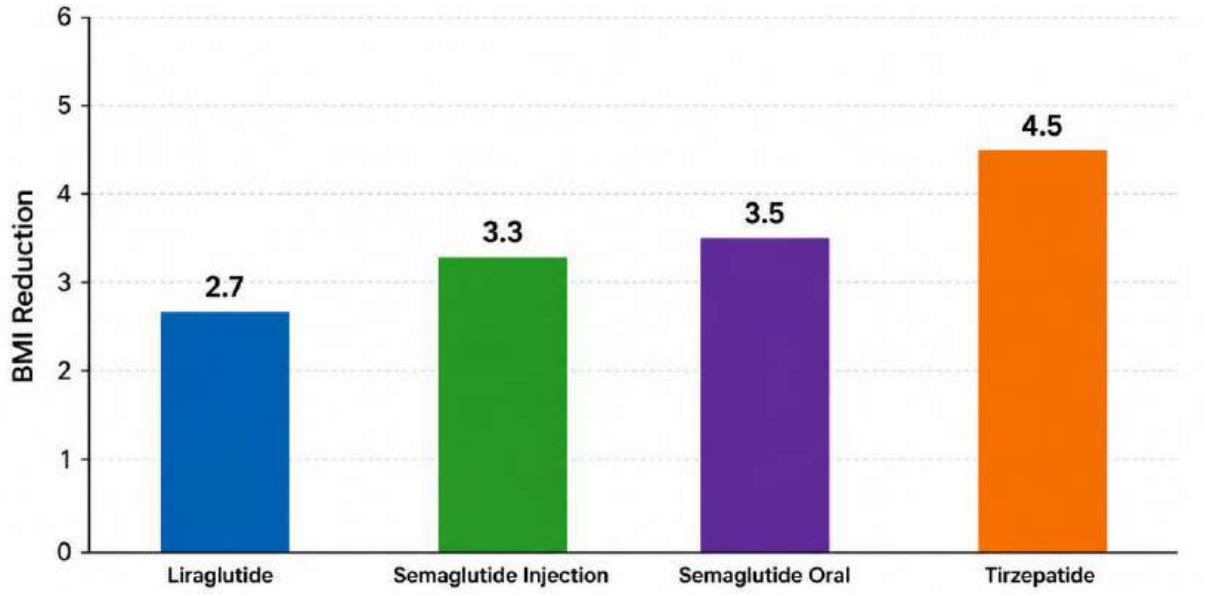


Figure 7. BMI Reduction at Week 20

Interpretation

At week 20, tirzepatide produced the greatest reduction in BMI, indicating a faster onset of weight-loss effect compared with the other therapies.

Cost-Effectiveness Outcomes

Tirzepatide emerged as the most cost-effective treatment strategy.

Table. Cost-Effectiveness Results

Comparison	Result
Tirzepatide vs Oral Semaglutide	Cost-effective
Tirzepatide vs Injectable Semaglutide	Dominant
Tirzepatide vs Liraglutide	Dominant
ICER (Tirzepatide vs Oral Semaglutide)	$34,212/QALY

Interpretation

The ICER of tirzepatide was substantially below the willingness-to-pay threshold of $150,000 per QALY, confirming its economic value.

Probability of Cost-Effectiveness

Probabilistic sensitivity analysis demonstrated a very high probability that tirzepatide would remain cost-effective.

Table. Probability of Cost-Effectiveness

WTP Threshold	Probability
$100,000/QALY	98.4%
$150,000/QALY	97.8%

Interpretation

Across both willingness-to-pay thresholds, tirzepatide maintained a probability greater than 97% of being cost-effective, indicating highly robust economic performance.

Sensitivity Analysis

The model was most sensitive to:

- Cost of oral semaglutide
- Cost of tirzepatide
- BMI reduction achieved by tirzepatide
- BMI reduction achieved by oral semaglutide

Table. Key Drivers of Cost-Effectiveness

Variable	Impact on ICER
Oral Semaglutide Cost	High
Tirzepatide Cost	High
Tirzepatide BMI Reduction	High
Oral Semaglutide BMI Reduction	High

Interpretation

Medication costs and treatment efficacy were the primary determinants of cost-effectiveness outcomes.

From all of the studied treatments, tirzepatide provided the largest BMI change and the best cost-effectiveness ratios. Moreover, the therapy retained its economic efficiency in several sensitivity analysis scenarios and willingness-to-pay levels, confirming its relevance to be considered an effective therapy for adults with overweight/obesity without diabetes.

Study 4: Karimi et al., 2025

Systematic Review and Meta-analysis on Semaglutide vs. Liraglutide, Dulaglutide, and Tirzepatide for Patients With Overweight/Obesity or Type 2 Diabetes Mellitus.

Study Selection

Database searches yielded a total of 1,570 citations. Following the elimination of duplicate studies and title and abstract screening of relevant studies, a total of 16 studies were eligible for inclusion in qualitative and quantitative synthesis.

Table. Glycemic Outcomes (HbA1c)

Comparison	Effect Size (95% CI)	p-value	Main Finding
Semaglutide vs Dulaglutide	3.72 (0.02–7.41)	0.05	Semaglutide superior
Semaglutide vs Liraglutide	0.56 (0.19–0.94)	<0.001	Semaglutide superior

Tirzepatide vs Semaglutide	-0.45 (-0.88 to -0.02)	0.04	Tirzepatide superior

Description

In the comparison of glycemic control, semaglutide demonstrated greater HbA1c reduction than both dulaglutide and liraglutide. When tirzepatide was compared directly with semaglutide, tirzepatide showed a greater reduction in HbA1c levels. These differences reached statistical significance in all three comparisons.

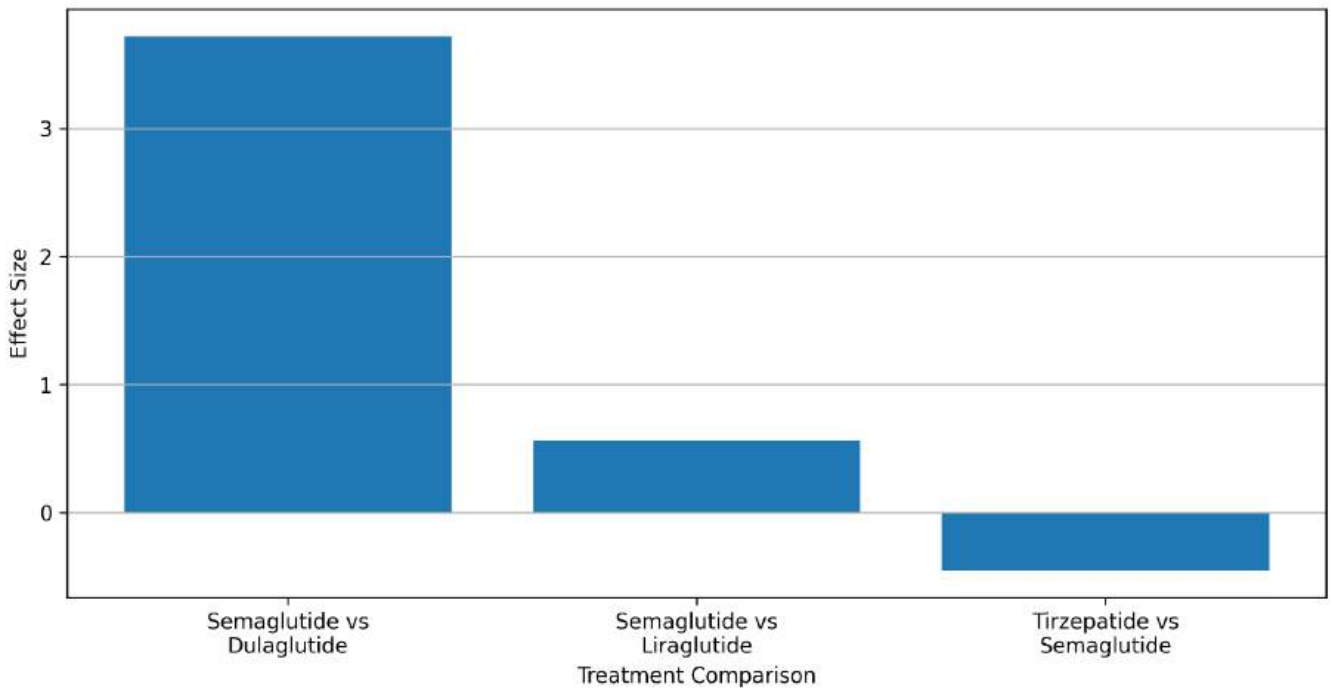


Figure 8. HbA1c Comparison Across Treatments

Table. Weight Reduction Outcomes

Comparison	Effect Size (95% CI)	p-value	Main Finding
Semaglutide vs Dulaglutide	5.53 (-0.45–11.50)	0.07	No significant difference
Semaglutide vs Liraglutide	0.81 (-0.12–1.75)	0.09	No significant difference
Tirzepatide vs Semaglutide	-2.57 (-6.77–1.62)	0.23	No significant difference

Description

Regarding body weight reduction, semaglutide showed numerically greater weight loss than both dulaglutide and liraglutide. Tirzepatide also demonstrated greater numerical weight reduction than semaglutide. However, none of these comparisons reached statistical significance according to the pooled analysis.

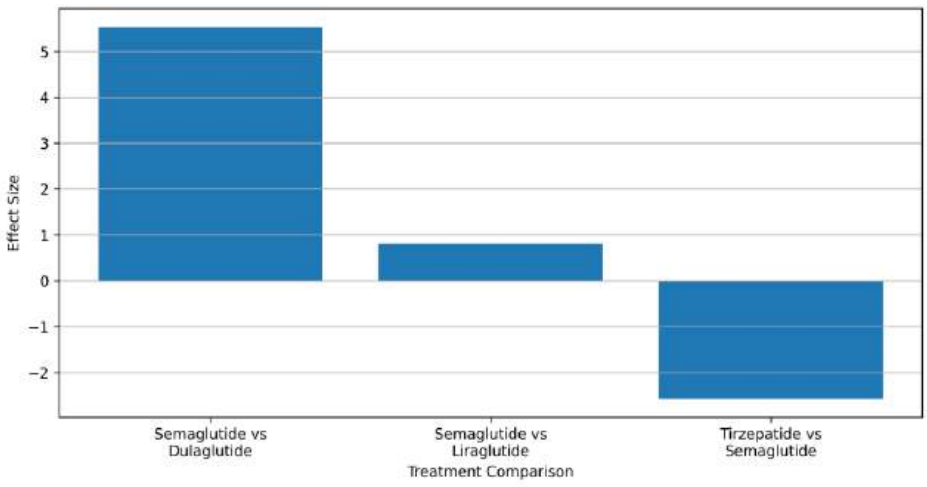


Figure 9. Weight Reduction Comparison Across Treatments

Table. Additional Metabolic Outcomes

Comparison	Outcome	Effect Size (95% CI)	p-value
Semaglutide vs Dulaglutide	FBS	2.66 (0.26–5.07)	0.03
Semaglutide vs Dulaglutide	BMI	5.23 (-0.44–10.89)	0.07
Semaglutide vs Liraglutide	FBS	0.95 (-0.45–2.34)	0.18
Semaglutide vs Liraglutide	BMI	1.17 (-0.73–3.07)	0.23
Tirzepatide vs Semaglutide	FBS	-2.15 (-5.67–1.38)	0.18

Description

Semaglutide produced a significantly greater reduction in fasting blood glucose compared with dulaglutide. For BMI reduction and fasting blood glucose outcomes in the remaining comparisons, no statistically significant differences were observed between treatments.

Overall Findings

The meta-analysis included 16 studies comparing semaglutide, liraglutide, dulaglutide, and tirzepatide. Semaglutide demonstrated superior HbA1c reduction compared with both dulaglutide and liraglutide. Tirzepatide showed greater HbA1c reduction than semaglutide. For weight loss, BMI, and most fasting blood glucose outcomes, the pooled analyses did not demonstrate statistically significant differences between treatments.

Study 5: Wen et al., 2025

Tirzepatide Versus Semaglutide on Weight Loss in Type 2 Diabetes Patients: A Systematic Review and Meta-Analysis of Direct Comparative Studies

Study Characteristics

The initial systematic search identified 696 studies. Four studies were included in the final analysis. Across these studies, 28,827 patients with type 2 diabetes mellitus were evaluated. The mean age was 55.7 years and the mean follow-up duration was 35.9 weeks.

Table. Overall Weight Change

Outcome	Tirzepatide	Semaglutide
Mean Weight Change (%)	-11.4%	-7.3%
Range (%)	-15.3% to -8.2%	-8.3% to -6.08%

Description

The mean weight change across the included studies was -11.4% for tirzepatide and -7.3% for semaglutide.

Table. Meta-analysis of Weight Loss

Outcome	Result
Mean Difference	-4.84 kg

95% CI	-6.21 to -3.47
I^2	78.3%
Tau^2	1.51

Description

The meta-analysis demonstrated an estimated treatment difference of -4.84 kg (95% CI: -6.21 to -3.47) favoring tirzepatide. Individual study estimates ranged from -2.9 kg to -5.6 kg. Heterogeneity was reported as I^2 = 78.3%.

Table. Frias et al., 2021 Weight Loss Results

Treatment	**Weight Change (%)**
Tirzepatide 5 mg	8.22
Tirzepatide 10 mg	9.81
Tirzepatide 15 mg	11.94
Semaglutide 1 mg	6.08

Description

A significant decrease in body weight was observed across all groups ($p < 0.001$). Estimated treatment differences versus semaglutide were:

- Tirzepatide 5 mg: -1.9 kg (95% CI: -2.8 to -1.0)
- Tirzepatide 10 mg: -3.6 kg (95% CI: -4.5 to -2.7)
- Tirzepatide 15 mg: -5.5 kg (95% CI: -6.4 to -4.6)

Table. Achievement of Weight-Loss Targets (Frias et al., 2021)

Target	Tirzepatide	Semaglutide
≥5% Weight Loss	65%–80%	54%
≥10% Weight Loss	34%–57%	24%
≥15% Weight Loss	15%–36%	8%

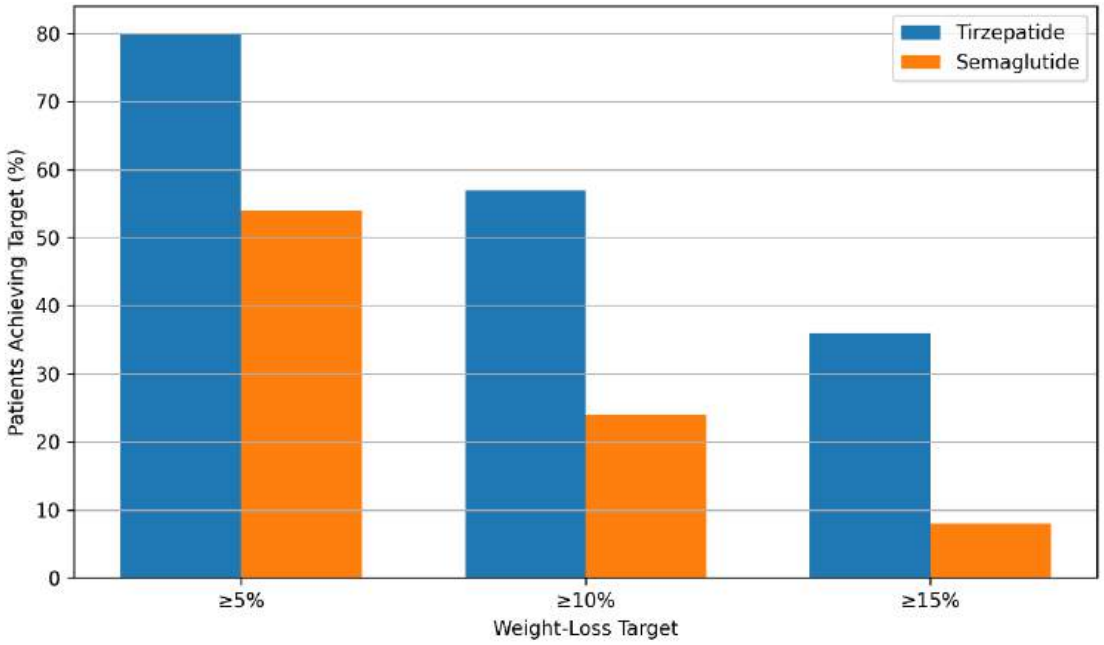


Figure 10. Achievement of Weight-Loss Targets (Frias et al., 2021)

Description

The proportion of patients achieving ≥5%, ≥10%, and ≥15% body weight reduction was higher in the tirzepatide groups than in the semaglutide group.

Table. Rodriguez et al., 2024 Weight-Loss Targets

Target	Tirzepatide	Semaglutide
>5% Weight Loss	81.8%	66.5%
>10% Weight Loss	62.1%	37.1%
>15% Weight Loss	42.3%	18.1%

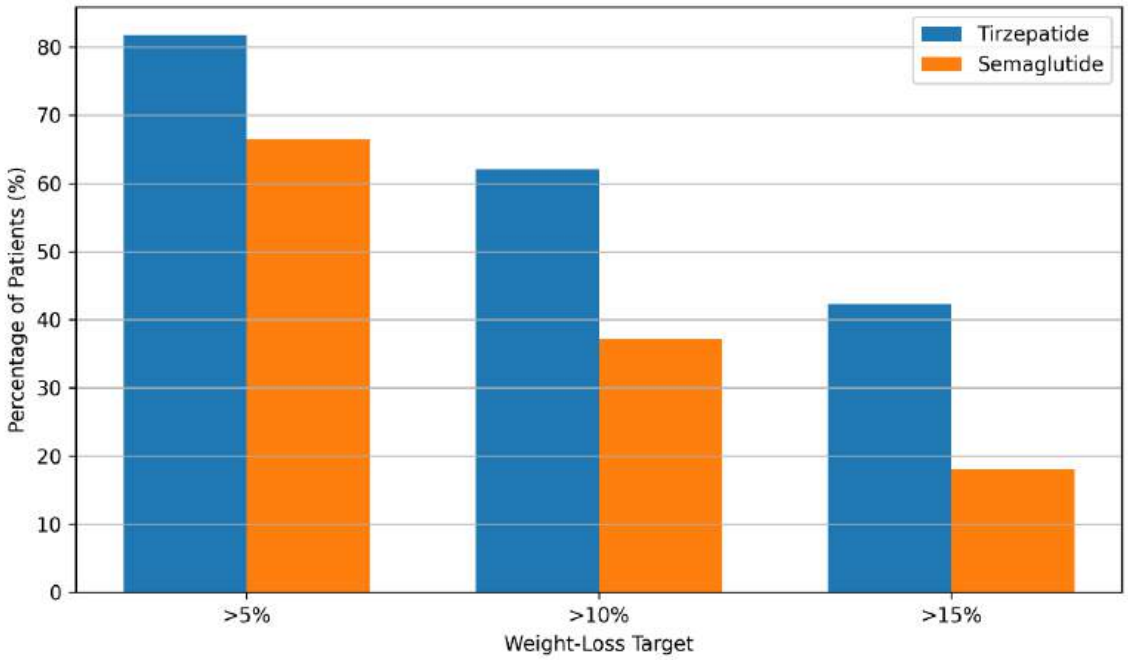


Figure 11. Rodriguez et al., 2024 Weight-Loss Targets

Description

Rodriguez et al. reported higher proportions of patients achieving >5%, >10%, and >15% weight loss in the tirzepatide group compared with the semaglutide group.

Table. Adverse Events

Outcome	Tirzepatide	Semaglutide
≥1 Adverse Event	68.0%	67.1%
Gastrointestinal Adverse Events	53.0%	52.0%

Description

The most common adverse events were gastrointestinal adverse events. Across two studies, at least one adverse event occurred in 68.0% of patients receiving tirzepatide and 67.1% of patients receiving semaglutide. Gastrointestinal adverse events occurred in 53.0% and 52.0% of patients, respectively.

Study 6: Hoog et al., 2025

Study Population

After propensity score matching, 10,702 naïve tirzepatide initiators were matched with 10,702 naïve semaglutide initiators. In the non-naïve cohort, 5,577 tirzepatide initiators were matched with 5,577 semaglutide initiators.

Table. HbA1c Outcomes in GLP-1 RA Naïve Patients

Outcome	Tirzepatide	Semaglutide
Patients with HbA1c data	1,399	1,173
Baseline HbA1c	7.8%	7.8%
Mean HbA1c reduction	1.3%	0.9%

Additional HbA1c decrease	0.4%	—
p-value	<0.001	—

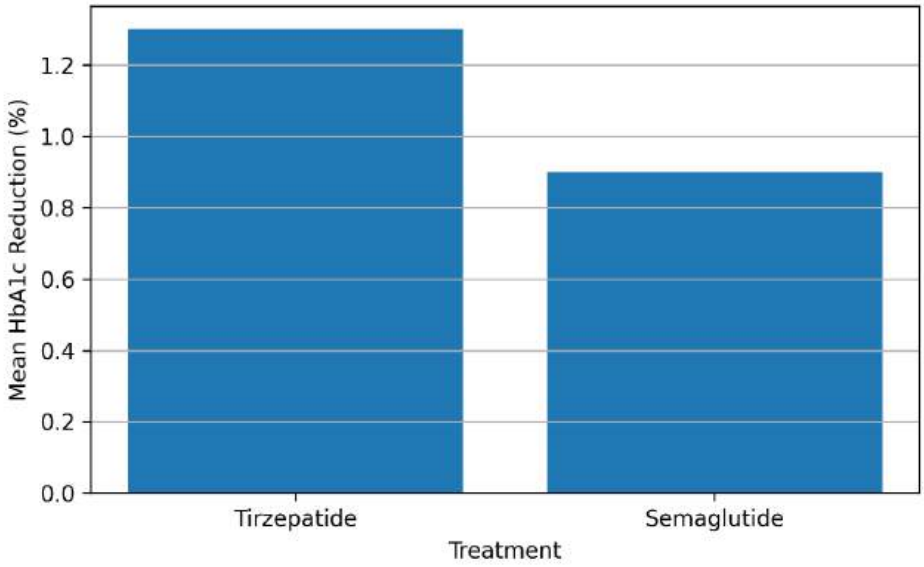


Figure 12. HbA1c Outcomes in GLP-1 RA Naïve Patients

Description

Both groups had a mean baseline HbA1c of 7.8%. Mean HbA1c reduction was 1.3% among tirzepatide initiators and 0.9% among semaglutide initiators. The additional 0.4% decrease observed with tirzepatide was statistically significant ($p < 0.001$).

Table. Weight Outcomes in GLP-1 RA Naïve Patients

Outcome	Tirzepatide	Semaglutide
Patients with weight data	454	432

Baseline weight (kg)	112.4	110.7
Mean weight reduction (kg)	10.2	6.1
Additional weight reduction (kg)	4.1	—
p-value	<0.001	—

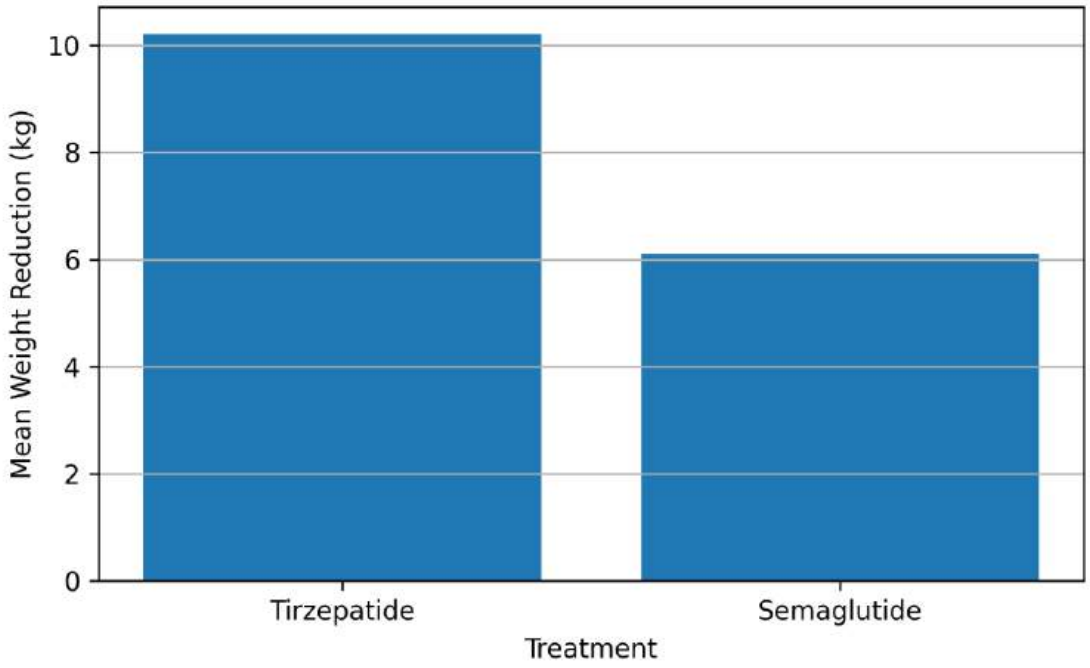


Figure 13. Weight Outcomes in GLP-1 RA Naïve Patients

Description

Mean baseline weight was 112.4 kg in the tirzepatide group and 110.7 kg in the semaglutide group. Mean weight reduction was 10.2 kg and 6.1 kg, respectively. The additional 4.1 kg reduction observed with tirzepatide was statistically significant ($p < 0.001$).

Table. HbA1c Outcomes in GLP-1 RA Non-Naïve Patients

Outcome	Tirzepatide	Semaglutide
Patients with HbA1c data	792	738
Baseline HbA1c	7.7%	7.9%
Mean HbA1c reduction	0.9%	0.6%
Additional HbA1c decrease	0.3%	—
p-value	<0.001	—

Description

Mean baseline HbA1c was 7.7% for tirzepatide initiators and 7.9% for semaglutide initiators. Mean HbA1c reduction was 0.9% and 0.6%, respectively. The additional 0.3% decrease observed with tirzepatide was statistically significant ($p < 0.001$).

Study 7: Hankosky et al., 2025

Tirzepatide 10 & 15 mg versus Semaglutide 2.4 mg in People with Obesity or Overweight and Type 2 Diabetes

Study Population and Baseline Characteristics

The primary indirect treatment comparison included 938 participants from SURMOUNT-2 and 807 participants from STEP 2. Baseline characteristics

including age, sex, body weight, BMI, duration of type 2 diabetes, and HbA1c were generally similar between studies.

Table. Mean Percent Change in Body Weight

Comparison	Mean Difference (%)	95% CI	p-value
Tirzepatide 10 mg vs Semaglutide 2.4 mg	-2.57	-4.24 to -0.90	0.003
Tirzepatide 15 mg vs Semaglutide 2.4 mg	-4.79	-6.47 to -3.12	<0.001

Description

Both tirzepatide doses produced significantly greater reductions in body weight compared with semaglutide 2.4 mg. The largest reduction was observed with tirzepatide 15 mg, which demonstrated a mean difference of -4.79% versus semaglutide.

Table. Achievement of ≥5% Body Weight Reduction

Comparison	Odds Ratio (OR)	95% CI	p-value
Tirzepatide 10 mg vs Semaglutide 2.4 mg	1.24	0.75–2.04	0.407

Tirzepatide 15 mg vs Semaglutide 2.4 mg	1.76	1.04–2.97	0.035

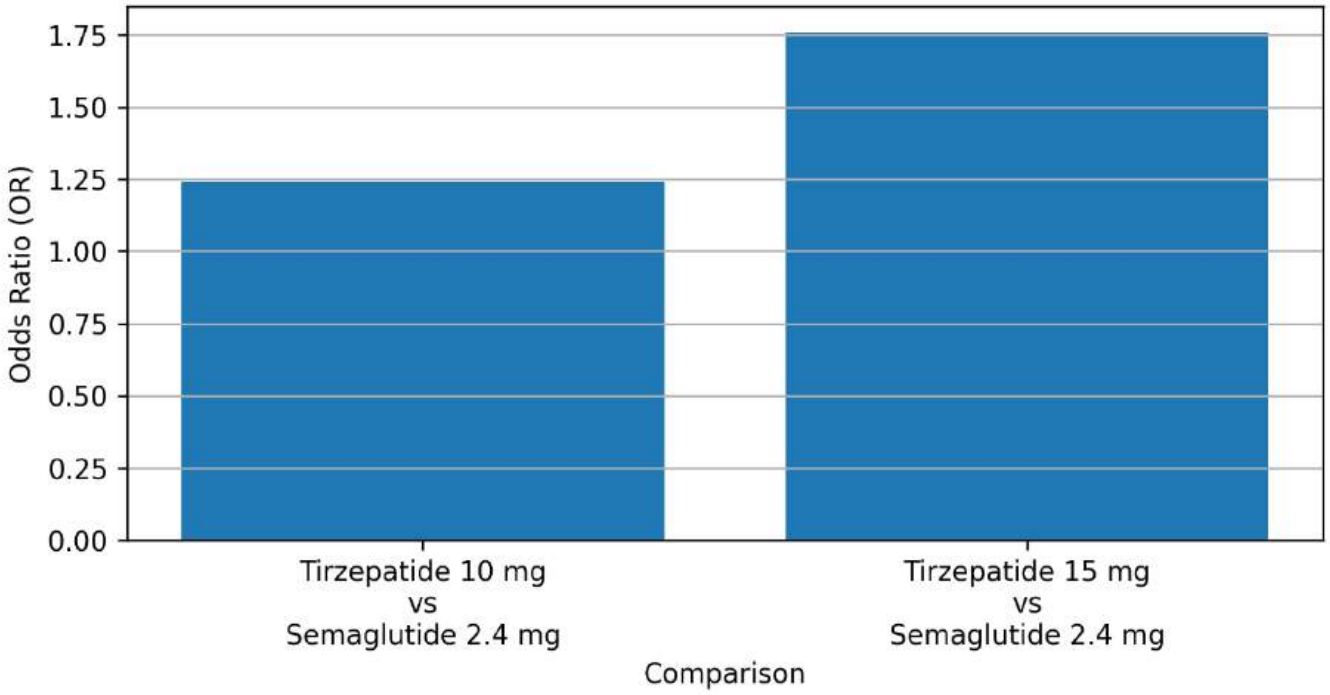


Figure 14. Achievement of ≥5% Body Weight Reduction

Description

Participants receiving tirzepatide 15 mg had significantly higher odds of achieving at least 5% body weight reduction compared with semaglutide 2.4 mg. Although tirzepatide 10 mg also favored weight loss, the difference was not statistically significant.

Table. HbA1c Reduction

Comparison	Mean Difference (%)	95% CI	p-value
Tirzepatide 10 mg vs Semaglutide 2.4 mg	-0.47	-0.70 to -0.24	<0.001
Tirzepatide 15 mg vs Semaglutide 2.4 mg	-0.56	-0.79 to -0.33	<0.001

Description

Both tirzepatide 10 mg and 15 mg achieved significantly greater HbA1c reductions than semaglutide 2.4 mg. The greatest improvement in glycemic control was observed with tirzepatide 15 mg, which reduced HbA1c by an additional 0.56% compared with semaglutide.

- Tirzepatide 10 mg and 15 mg produced significantly greater body weight reduction than semaglutide 2.4 mg.
- Tirzepatide 15 mg significantly increased the likelihood of achieving ≥5% weight loss.
- Both tirzepatide doses resulted in significantly greater HbA1c reduction than semaglutide.
- The strongest efficacy outcomes were consistently observed with tirzepatide 15 mg.

Study 8: Ciudin et al., 2025

Indirect Comparative Efficacy and Safety of Tirzepatide 10 and 15 mg versus Semaglutide 2.4 mg for the Management of Obesity and Overweight in Patients with Type 2 Diabetes

Study Population and Baseline Characteristics

Baseline demographic and clinical characteristics were generally comparable between SURMOUNT-2 and STEP 2. Mean body weight, BMI, waist circumference, HbA1c, age, and sex distribution were similar across both trials.

Table. Body Weight Reduction

Comparison	**Mean Difference (%)**	**95% CI**	**p-value**
Tirzepatide 10 mg vs Semaglutide 2.4 mg	-2.53	-4.20 to -0.86	Significant
Tirzepatide 15 mg vs Semaglutide 2.4 mg	-4.83	-6.50 to -3.16	<0.001

Description

Both tirzepatide doses achieved greater percentage weight reduction than semaglutide 2.4 mg. The largest reduction was observed with tirzepatide 15 mg. The arm-level trial results also showed greater body-weight reductions with tirzepatide 10 mg (-13.43%) and tirzepatide 15 mg (-15.65%) compared with semaglutide 2.4 mg (-10.64%).

Table. HbA1c Reduction

Comparison	Mean Difference (%)	95% CI	p-value
Tirzepatide 10 mg vs Semaglutide 2.4 mg	-0.47	-0.70 to -0.24	<0.001
Tirzepatide 15 mg vs Semaglutide 2.4 mg	-0.56	-0.79 to -0.33	<0.001

Description

Both tirzepatide doses produced significantly greater reductions in HbA1c than semaglutide. The greatest improvement in glycemic control was observed with tirzepatide 15 mg.

Table. Waist Circumference Reduction

Comparison	Mean Difference (cm)	95% CI
Tirzepatide 10 mg vs Semaglutide 2.4 mg	-1.20	-2.92 to 0.52
Tirzepatide 15 mg vs Semaglutide 2.4 mg	-3.76	-5.50 to -2.02

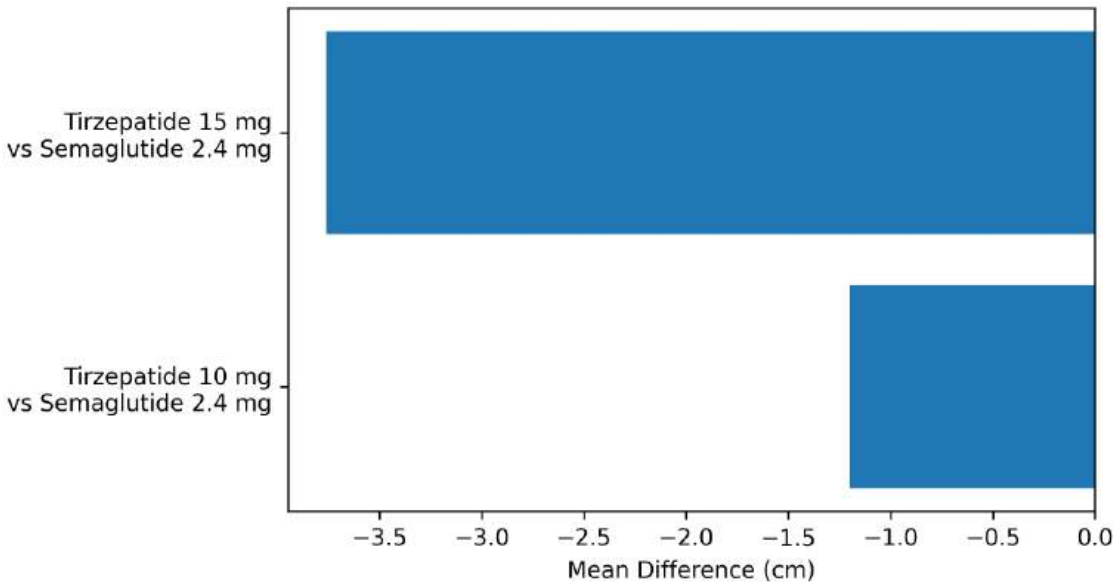


Figure 15. Waist Circumference Reduction

Description

Tirzepatide 15 mg was associated with a significantly greater reduction in waist circumference compared with semaglutide. Tirzepatide 10 mg showed a favorable trend but did not reach statistical significance.

Table. Achievement of Weight-Loss Targets

Outcome	Tirzepatide 15 mg vs Semaglutide
≥5% Weight Reduction	Significantly higher odds
≥15% Weight Reduction	Significantly higher odds

Description

Participants treated with tirzepatide 15 mg had significantly greater odds of achieving both ≥5% and ≥15% body-weight reduction compared with

semaglutide 2.4 mg. Tirzepatide 10 mg showed favorable trends but without statistical significance.

Study 9: Wilson et al., 2026

Semaglutide and Tirzepatide Effects on Cardiovascular Outcomes in People with Overweight or Obesity in the Real World (STEER)

Table. Study Population After Propensity Score Matching

Characteristic	Semaglutide	Tirzepatide
Matched Patients	10,625	10,625
Mean Age (years)	58.5	58.3
Female (%)	61.8%	61.6%
Hypertension (%)	72.7%	71.1%
Dyslipidemia (%)	71.2%	70.3%
Mean Follow-up (months)	8.3	8.6

Description

After propensity score matching, both treatment groups were well balanced regarding demographic and clinical characteristics. Hypertension and dyslipidemia were highly prevalent in both cohorts, and the average follow-up period was approximately eight months.

Table. Revised Major Adverse Cardiovascular Events (rMACE)

Outcome	Semaglutide	Tirzepatide	Hazard Ratio (HR)	p-value
rMACE-3 Incidence (per 1000 patient-years)	7.6	10.8	0.71	0.046
rMACE-5 Incidence (per 1000 patient-years)	16.7	21.0	0.78	0.040

Description

Semaglutide was associated with significantly lower cardiovascular risk compared with tirzepatide. The risk of rMACE-3 was reduced by 29%, while the risk of rMACE-5 was reduced by 22% among semaglutide users.

Table. Individual Cardiovascular Event Rates

Outcome (per 1000 patient-years)	Semaglutide	Tirzepatide
Myocardial Infarction (MI)	3.8	5.4
Hospitalization for Heart Failure	4.3	6.1
Stroke	2.4	3.9
Coronary Revascularization	7.6	8.7
All-Cause Mortality	1.5	1.7

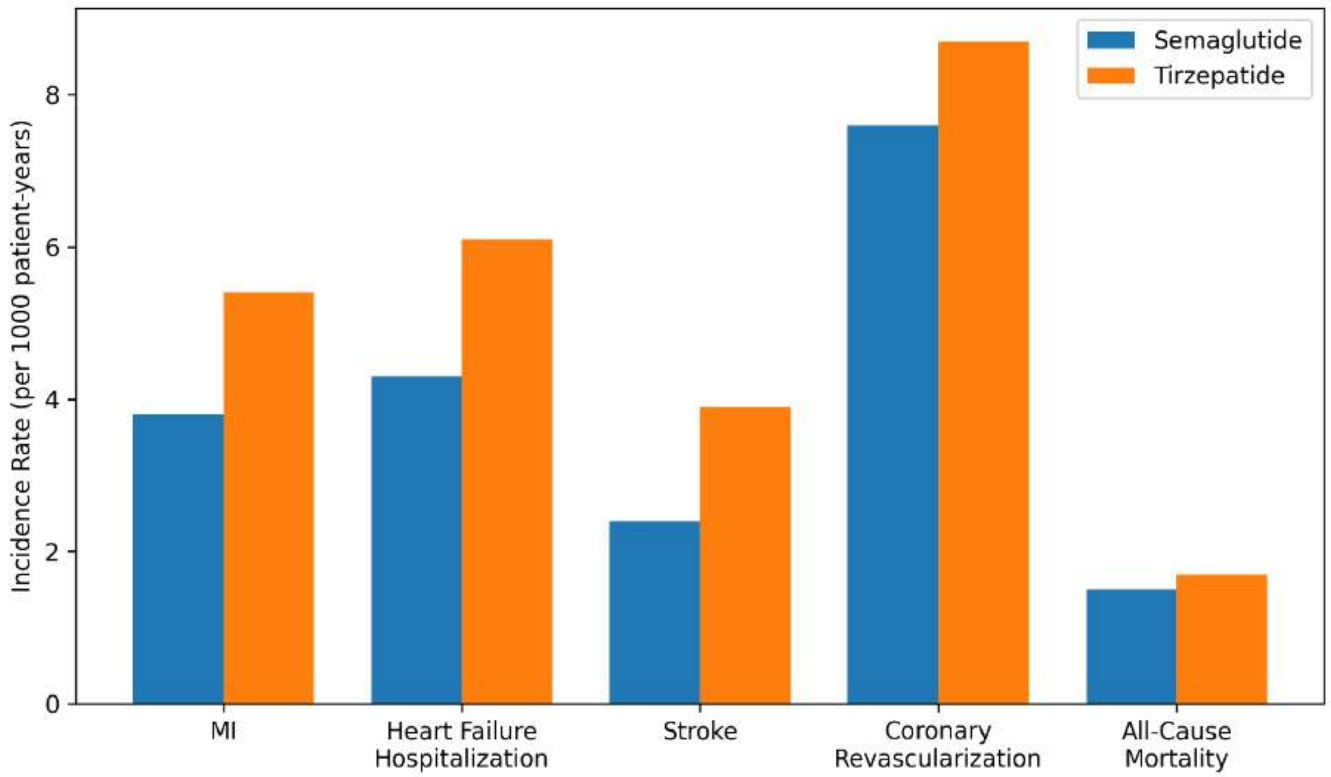


Figure16. Individual Cardiovascular Event Rates

Description

Although differences in individual cardiovascular outcomes did not reach statistical significance, all event rates consistently favored semaglutide. Lower incidences of myocardial infarction, stroke, heart failure hospitalization, coronary revascularization, and all-cause mortality were observed in the semaglutide group.

Table. Per-Protocol Cardiovascular Outcomes

Outcome	Hazard Ratio (HR)	p-value	Main Finding
rMACE-3	0.43	0.005	Semaglutide superior
rMACE-5	0.57	0.003	Semaglutide superior
Myocardial Infarction	0.38	0.019	Semaglutide superior
Heart Failure Hospitalization	0.34	0.020	Semaglutide superior

Description

The per-protocol analysis demonstrated stronger cardiovascular benefits with semaglutide. Compared with tirzepatide, semaglutide reduced the risk of rMACE-3 by 57%, rMACE-5 by 43%, myocardial infarction by 62%, and heart failure hospitalization by 66%.

- Both cohorts included 10,625 matched patients after propensity score matching.
- Semaglutide showed a significantly lower risk of rMACE-3 and rMACE-5 compared with tirzepatide.

- Cardiovascular event rates consistently favored semaglutide across all individual outcomes.
- Per-protocol analyses confirmed greater cardiovascular protection with semaglutide.
- Exploratory analyses reported greater weight loss with tirzepatide, whereas cardiovascular outcomes favored semaglutide.

Study 10: Shukla et al., 2026

Improved Health-Related Quality of Life with Tirzepatide versus Semaglutide in Adults with Obesity or Overweight (SURMOUNT-5)

Baseline Characteristics of the Study Population

Baseline demographic and clinical characteristics were well balanced between the tirzepatide and semaglutide groups. More than half of participants had prediabetes, and approximately half had at least two obesity-related complications.

Table. Depression Outcomes (PHQ-9) at Week 72

Outcome	Tirzepatide	Semaglutide
Participants with no/minimal depression at baseline	77.5%	76.6%

Remained in no/minimal depression category at Week 72	65.5%	66.8%
Increase in depression category during study	12.5%	11.0%
Discontinued due to PHQ-9 score	0	0

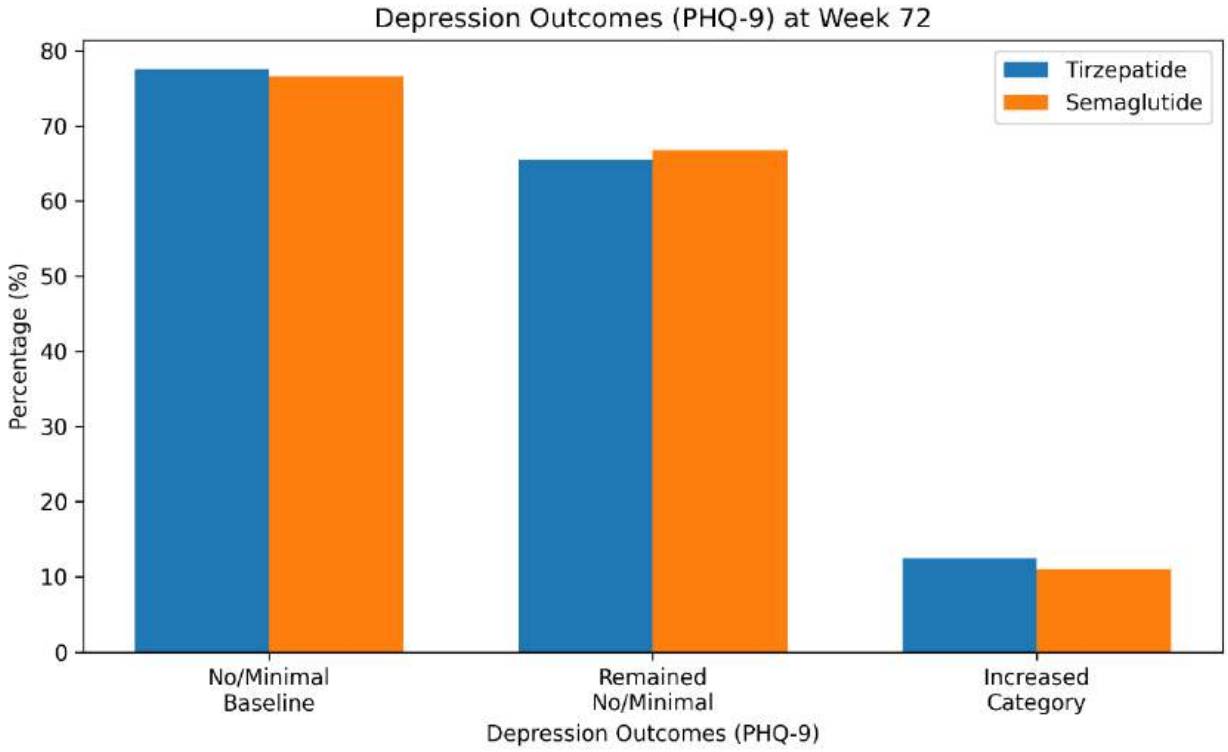


Figure 17. Depression Outcomes (PHQ-9) at Week 72

Description

The onset or worsening of depressive symptoms was similar between treatment groups. Most participants who had no or minimal depression at baseline remained in the same category through Week 72. No participant discontinued treatment because of PHQ-9 scores.

Table. Health-Related Quality of Life Outcomes (Week 72)

Outcome	Main Result
SF-36v2 Physical Health Domains	Significant improvement in both groups
SF-36v2 Mental Health Domains	Significant improvement in both groups
General Health Score	Greater improvement with Tirzepatide
Physical Component Summary (PCS)	Improved significantly in both groups
Mental Component Summary (MCS)	No significant difference between groups

Description

Both tirzepatide and semaglutide significantly improved health-related quality of life across multiple physical and mental health domains. Improvements were generally similar between treatments; however, tirzepatide showed a significantly greater improvement in General Health scores.

Table . Quality of Life in Participants with Baseline Physical Limitations

Outcome	Result
Physical Functioning	Greater improvement with Tirzepatide
General Health	Greater improvement with Tirzepatide
Physical Component Summary (PCS)	Significantly higher with Tirzepatide
Mental Component Summary (MCS)	No significant difference

Description

Among participants who reported physical limitations at baseline, both treatments improved quality-of-life measures. Tirzepatide produced significantly greater improvements in physical functioning, general health, and overall physical health status compared with semaglutide.

- Both treatments significantly improved physical and mental quality-of-life measures over 72 weeks.
- Depression outcomes were similar between tirzepatide and semaglutide.
- Most participants maintained or improved their baseline depression status.

- Tirzepatide demonstrated greater improvement in General Health scores compared with semaglutide.
- In participants with baseline physical limitations, tirzepatide produced greater improvements in physical functioning and physical health status.
- Greater weight reduction was associated with greater improvements in physical functioning, bodily pain, general health, vitality, and overall physical quality-of-life outcomes.

Study 11: Tentolouris et al., 2026

Semaglutide and Tirzepatide in Prediabetes: Evidence for Diabetes Prevention and Cardiovascular Protection

Table. Diabetes Prevention Outcomes

Outcome	**Result**
Semaglutide 2.4 mg (STEP 1, STEP 5, SELECT)	Increased regression to normoglycemia (up to 84%)
Semaglutide 2.4 mg	Reduced progression from prediabetes to diabetes
Tirzepatide (SURMOUNT-1)	Reduced diabetes incidence by nearly 90%
Tirzepatide Hazard Ratio	0.07

p-value	<0.001

Description

Across the STEP 1, STEP 5, and SELECT trials, semaglutide substantially increased the proportion of participants returning to normoglycemia and reduced progression to type 2 diabetes compared with placebo. In the SURMOUNT-1 trial, tirzepatide produced a marked reduction in diabetes incidence, with the authors noting that this benefit was largely associated with the significant weight loss achieved during treatment.

Table. Cardiovascular Outcomes

Outcome	**Result**
Trial	SELECT
Participants with Prediabetes	66.4%
Primary CV Outcome HR	0.80
95% CI	0.72–0.90
Main Finding	Semaglutide reduced CV events versus placebo

Description

The SELECT trial demonstrated that semaglutide significantly reduced the risk of the composite cardiovascular endpoint consisting of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. Importantly, a prespecified

analysis showed that the cardiovascular benefit was independent of baseline HbA1c levels, suggesting that semaglutide may provide cardiovascular protection even in individuals with prediabetes.

- Semaglutide increased regression from prediabetes to normoglycemia and reduced progression to diabetes.
- Tirzepatide reduced the incidence of diabetes by nearly 90% in the SURMOUNT-1 trial.
- The diabetes prevention effect of tirzepatide was largely linked to substantial weight reduction.
- In the SELECT trial, semaglutide significantly reduced major cardiovascular events compared with placebo.
- Cardiovascular risk reduction with semaglutide was observed regardless of baseline HbA1c levels, supporting benefits in individuals with prediabetes.
- The ongoing SURMOUNT-MMO trial is expected to provide further evidence regarding the cardiovascular effects of tirzepatide in people with obesity without diabetes.

Study 12: Johansson et al., 2026

Cost-effectiveness of tirzepatide versus semaglutide for patients with obesity or overweight in the US: evidence from the SURMOUNT-5 head-to-head phase-3 trial

Table. Prediabetes Outcomes at 72 Weeks

Sample Size (n)	Duration	Outcome	Tirzepatide	Semaglutide
Simulation of 1,000 patients	72 weeks	Return to normoglycemia (%)	87.50%	76.88%

Description

This table presents the glycemic outcomes at 72 weeks. The model estimated that 87.50% of patients treated with tirzepatide returned to normoglycemic levels compared with 76.88% of patients treated with semaglutide.

Table. Cost-Effectiveness Outcomes

Sample Size (n)	Duration	Outcome	Tirzepatide
Simulation of 1,000 patients	Lifetime horizon	Incremental QALYs	0.506
Simulation of 1,000 patients	Lifetime horizon	Incremental Life Years Gained (LYGs)	0.195

Simulation of 1,000 patients	Lifetime horizon	Incremental Net Health Benefit (iNHB)	0.784
Simulation of 1,000 patients	Lifetime horizon	Cost Difference	$41,688 lower

Description

This table summarizes the cost-effectiveness outcomes over the lifetime horizon. Tirzepatide was associated with 0.506 incremental quality-adjusted life years (QALYs), 0.195 life-years gained, an incremental net health benefit of 0.784, and lower total costs by $41,688 compared with semaglutide.

Table. Obesity-Related Clinical Outcomes

Sample Size (n)	Duration	Outcome	Tirzepatide	Semaglutide
Simulation of 1,000 patients	Lifetime horizon	Type 2 Diabetes Cases	70 fewer cases	Reference
Simulation of 1,000 patients	Lifetime horizon	Cardiovascular Disease Cases	10 fewer cases	Reference
Simulation of 1,000 patients	Lifetime horizon	Angina Cases per 1,000 Patients	128	127
Simulation of 1,000 patients	Lifetime horizon	Overall Obesity-Related Clinical Events	5–46% reduction	Reference

Description

This table presents the modeled obesity-related clinical outcomes. Tirzepatide was associated with 70 fewer cases of type 2 diabetes and 10 fewer cases of cardiovascular disease per 1,000 patients compared with semaglutide. Angina incidence was similar between treatments, while overall obesity-related clinical events were reduced by 5–46% with tirzepatide.

Table. Weight, Sleep Apnea, and Productivity Outcomes

Sample Size (n)	Duration	Outcome	Tirzepatide	Semaglutide
Simulation of 1,000 patients	Lifetime horizon	Weight Change	Greater reduction	Lower reduction
Simulation of 1,000 patients	Lifetime horizon	Years Lived with Moderate/Severe OSA	3.07 fewer years	3.07 more years
Simulation of 1,000 patients	Annual outcome	Lost Productivity Days	5 fewer days/year	Reference

Description

This table summarizes additional health and productivity outcomes. Tirzepatide produced greater weight reduction than semaglutide, reduced the number of years lived with moderate-to-severe obstructive sleep apnea by 3.07 years, and was associated with five fewer lost productivity days per patient annually due to absenteeism and presenteeism.

Study 13: Quarenghi et al., 2025

Weight Regain After Liraglutide, Semaglutide or Tirzepatide Interruption: A Narrative Review of Randomized Studies

Table. Weight Regain After Semaglutide Withdrawal (STEP Studies)

Duration	Outcome	Semaglutide	Placebo
20-week run-in	Mean weight reduction during treatment	-10.6%	—
Week 20–68	Mean weight change	-7.9%	+6.9%
Week 0–68	Mean weight loss	-17.3%	-2.0%
Week 68–120 (off-treatment)	Weight regain	+11.6%	+1.9%
Week 0–120	Net weight loss	-5.6%	-0.1%

Description

This table summarizes weight changes reported in the STEP studies. Semaglutide treatment resulted in substantial weight reduction during the treatment period. Following treatment withdrawal, participants regained 11.6 percentage points of body weight, although a net weight loss of 5.6% from baseline was maintained at week 120.

Table. Weight Regain After Liraglutide Withdrawal (SCALE Studies)

Duration	Outcome	Liraglutide	Placebo
Week 56	Mean weight loss	-8.0%	-2.6%
Week 56–68	Continued liraglutide	-0.69%	—
Week 56–68	Switched from liraglutide to placebo	+2.91% regain	—
Week 56–68	Placebo continued	+0.28%	+0.28%
Week 160	Weight loss during treatment	-6.1%	-1.9%
Week 172	Treatment difference after cessation	-3.2%	Reference

Description

This table presents the weight outcomes observed in the SCALE studies. Participants receiving liraglutide achieved greater weight loss than placebo during treatment. After discontinuation, weight regain occurred; however, a significant treatment difference remained at week 172.

Table . Weight Outcomes Following Tirzepatide Withdrawal (SURMOUNT-4)

Duration	Outcome	Tirzepatide	Placebo
First 36 weeks	Mean weight reduction	-20.9%	—

Week 36–88	Mean weight change	-5.5%	+14.0%
Week 36–88	Treatment difference	-19.4%	Reference

Description

This table summarizes the results of the SURMOUNT-4 study. Participants treated with tirzepatide experienced a mean weight reduction of 20.9% during the initial treatment period. Continued treatment resulted in an additional 5.5% reduction in body weight, whereas participants switched to placebo regained 14.0% of body weight.

Table. Additional Studies Reporting Weight Regain After Treatment Cessation

Duration	Treatment	Outcome
68 weeks	Liraglutide 1.8 mg	Weight change at follow-up: -3.6%
68 weeks	Liraglutide 3.0 mg	Weight change at follow-up: -4.7%
68 weeks	Placebo	Weight change at follow-up: -2.7%
59 weeks	Semaglutide	Weight change ranged from -4.9% to -15.5% depending on dose
28 weeks	Beinaglutide	Weight regain of 0.78% during 12-week observation period

Description

This table summarizes additional phase 2 and phase 3 studies that reported follow-up outcomes after treatment discontinuation. Weight regain was observed following treatment cessation across different GLP-1 receptor agonists, although the magnitude varied according to treatment type, dose, and study duration.

Study 14: Torres-Pirela, 2025

Semaglutide and Tirzepatide: Revolutionary Therapies for Obesity and Type 2 Diabetes Mellitus Management

Table. STEP Clinical Trials of Semaglutide

Trial	Sample Size (n)	Duration	Outcome	Semaglutide	Comparator
STEP 1	1,961	68 weeks	Weight loss (%)	14.9	2.4 (placebo)
STEP 1	1,961	68 weeks	Participants achieving ≥20% weight loss (%)	32.0	1.7 (placebo)
STEP 2	1,210	68 weeks	Weight loss (%)	9.6 (2.4 mg)	3.4 (placebo)

STEP 2	1,210	68 weeks	HbA1c reduction (%)	1.6–1.7	0.4 (placebo)
STEP 2	1,210	68 weeks	Participants achieving HbA1c <7 (%)	78.5	26.5 (placebo)
STEP 3	611	68 weeks	Weight loss (%)	16.0	5.7 (placebo)
STEP 4	902	20 weeks	Initial weight loss (%)	10.6	—
STEP 4	803	68 weeks	Additional weight change (%)	-7.9	+6.9 (placebo)
STEP 4	803	68 weeks	Total cumulative weight loss (%)	17.4	5.7 (placebo)

Description

This table summarizes the numerical outcomes reported in the STEP clinical trials. Weight loss ranged from 9.6% to 17.4% with semaglutide treatment. In STEP 1, 32% of participants achieved at least 20% weight loss compared with

1.7% in the placebo group. In STEP 2, HbA1c reductions of 1.6–1.7% were observed, and 78.5% of participants achieved HbA1c levels below 7%.

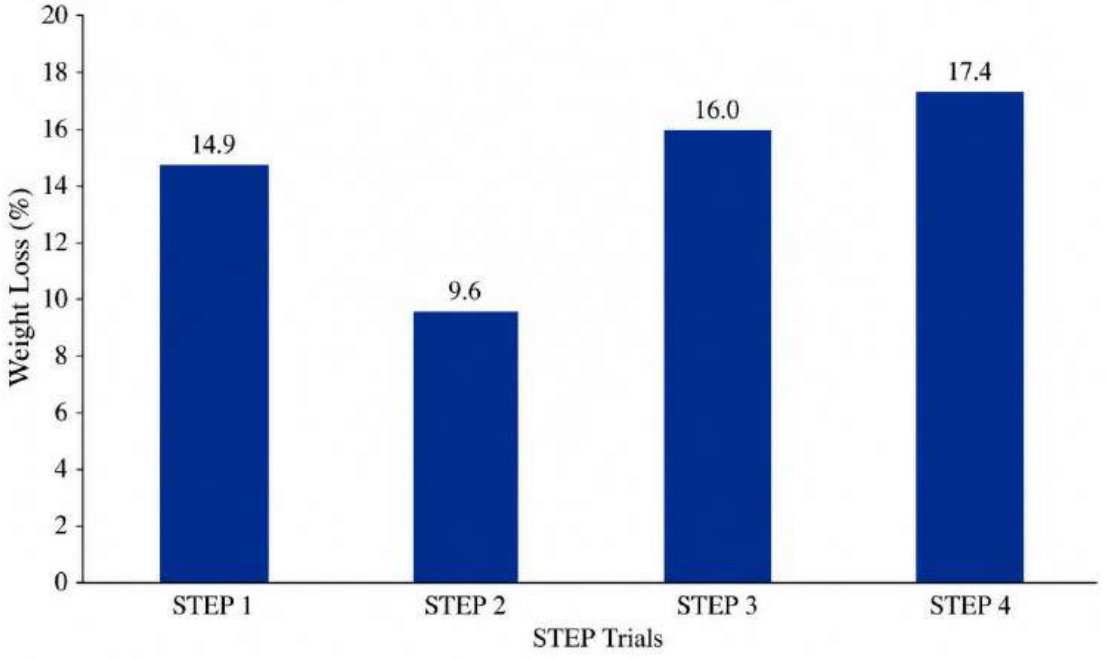


Figure 18: Weight Loss in STEP Trials (Semaglutide)

Table. SURPASS Clinical Trials of Tirzepatide

Trial	Sample Size (n)	Duration	Weight Loss	HbA1c Reduction
SURPASS-1	478	40 weeks	9.5 kg	2.07%
SURPASS-2	1,879	40 weeks	12.4 kg	2.46%
SURPASS-3	1,444	52 weeks	12.9 kg	2.37%
SURPASS-4	2,002	104 weeks	11.7 kg	2.58%

SURPASS-5	475	40 weeks	10.9 kg	2.59%

Description

This table summarizes the outcomes reported in the SURPASS clinical trials. Tirzepatide produced weight reductions ranging from 9.5 kg to 12.9 kg and HbA1c reductions ranging from 2.07% to 2.59% across the included studies.

Table. SURMOUNT-1 Trial

Sample Size (n)	Duration	Outcome	Result
2,539	72 weeks	Weight loss (%)	20.9

Description

The SURMOUNT-1 trial included 2,539 participants and evaluated tirzepatide over 72 weeks. Participants receiving the 15 mg dose achieved an average weight loss of 20.9%.

Study 15: Aamir et al., 2025

Comparative Efficacy of Tirzepatide vs. Semaglutide in Reducing Body Weight in Humans: A Systematic Review and Meta-Analysis of Clinical Trials and Real-World Data

Table. Study Selection and Included Evidence

Total Studies Retrieved	After Deduplication	Excluded in Initial Screening	Excluded in Full-Text Screening	Included Studies	Study Types

751	668	514	147	7	2 RCTs and 5 retrospective cohort studies

Description

This table summarizes the study selection process. A total of 751 studies were retrieved, and after screening, seven studies were included in the meta-analysis, consisting of two randomized controlled trials and five retrospective cohort studies.

Table. Overall Pooled Effect on Weight Loss

Tirzepatide Participants	Semaglutide Participants	Outcome	Mean Difference (MD)	95% CI	P-value	Heterogeneity
36,754	106,057	Weight loss (%)	4.23	3.22–5.25	<0.05	$I^2 = 100\%$

Description

This table presents the overall pooled effect. Tirzepatide produced a significantly greater weight loss percentage than semaglutide, with a mean difference of 4.23%.

Table. Subgroup Analysis by Tirzepatide Dose

Subgroup	Outcome	Mean Difference (MD)	95% CI	P-value	Heterogeneity
Tirzepatide ≤10 mg	Weight loss (%)	3.89	2.12–5.65	<0.01	I^2 = 0%
Tirzepatide >10 mg	Weight loss (%)	6.50	5.93–7.08	<0.01	I^2 = 100%

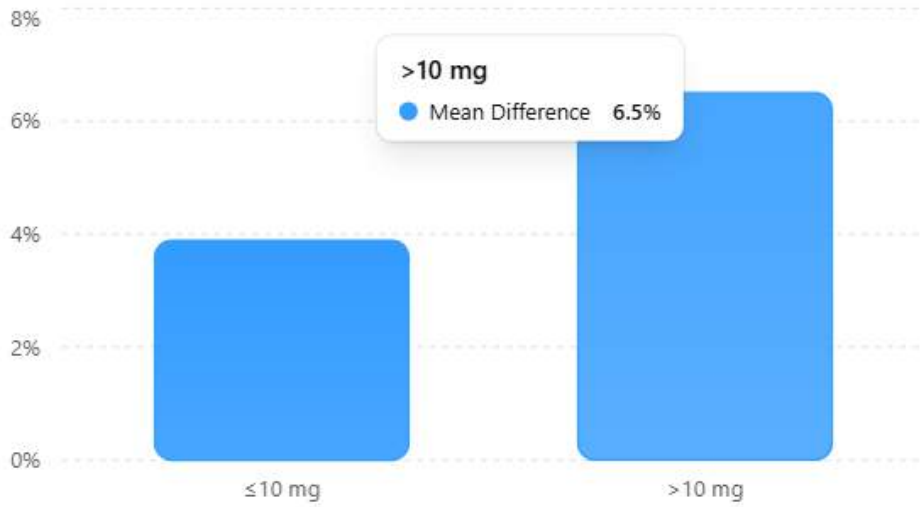


Figure 19: Weight Loss by Tirzepatide Dose

Description

This table shows the subgroup analysis based on tirzepatide dose. Higher doses of tirzepatide were associated with greater weight loss compared with semaglutide, indicating a dose-response relationship.

Table. Subgroup Analysis by Duration

Subgroup	Outcome	Mean Difference (MD)	95% CI	P-value	Heterogeneity
Tirzepatide ≤6 months	Weight loss (%)	3.50	2.24–4.75	<0.01	I^2 = 97%
Longer duration	Weight loss (%)	5.00	3.48–6.52	<0.01	I^2 = 100%

Description

This table presents the subgroup analysis by treatment duration. Tirzepatide showed greater weight loss than semaglutide in both duration groups, with a larger mean difference reported in the longer-duration subgroup.

Table. Subgroup Analysis by Study Design

Study Design	Outcome	Mean Difference (MD)	95% CI	P-value	Heterogeneity
RCTs	Weight loss (%)	4.73	2.31–7.15	<0.01	I^2 = 100%
Retrospective cohort studies	Weight loss (%)	4.07	2.92–5.22	<0.01	I^2 = 97%

Description

This table summarizes subgroup results by study design. Tirzepatide remained superior to semaglutide in both randomized controlled trials and retrospective cohort studies.

Table. Sensitivity Analysis and Publication Bias

Analysis	**Result**
Sensitivity analysis	Results did not change after sequential removal of any study
Minimum MD after study omission	4.00
Maximum MD after study omission	4.48
Egger’s test P-value	0.94
Egger’s test t-value	-0.08
Degrees of freedom	12

Description

This table presents sensitivity analysis and publication bias findings. The superiority of tirzepatide remained stable after removing individual studies. No publication bias was detected visually or by Egger’s test.

Study 16: Ng et al., 2025

Real-World Weight Loss Observed With Semaglutide and Tirzepatide in Patients with Overweight or Obesity and Without Type 2 Diabetes (SHAPE)

Table. Patient Population and Baseline Weight

Variable	Semaglutide 2.4 mg	Tirzepatide
Sample size (n)	6,794	3,122
Mean age (years)	47.8 (10.3)	49.5 (10.9)
Female (%)	79.8	77.9
Obesity (%)	97.1	93.8
Mean baseline weight (kg)	104.5	104.9

Description

This table summarizes the baseline characteristics of patients included in the SHAPE study. A total of 6,794 patients received semaglutide 2.4 mg and 3,122 received tirzepatide. Mean baseline body weight was 104.5 kg and 104.9 kg, respectively.

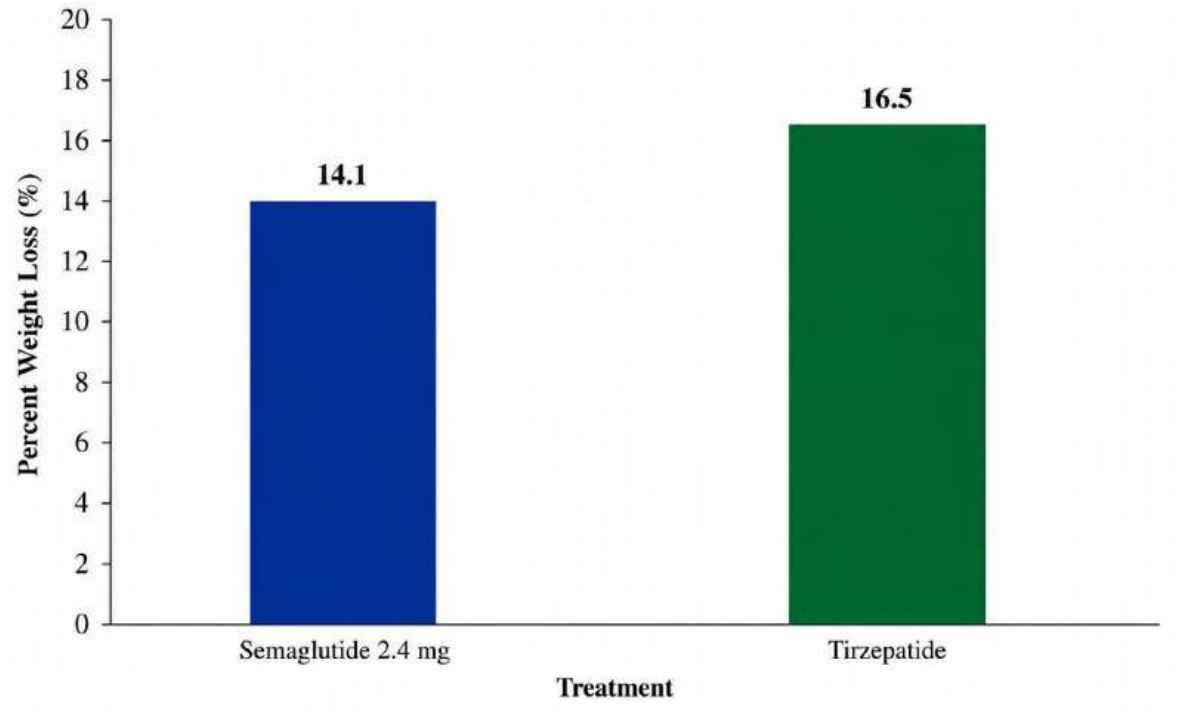


Figure 20. Percentage Weight Loss After One Year

Table. Weight Outcomes After One Year

Variable	Semaglutide 2.4 mg	Tirzepatide
Follow-up weight (kg)	89.9 (22.4)	87.6 (22.6)
Absolute weight loss (kg)	-14.6 (9.9)	-17.2 (11.7)
Percent weight loss (%)	-14.1 (9.6)	-16.5 (10.8)
Patients achieving ≥5% weight loss (%)	84.1	86.2

Description

This table presents weight outcomes after one year of continuous treatment. Mean body weight decreased from baseline in both treatment groups. Patients

receiving tirzepatide experienced greater absolute and percentage weight loss than patients receiving semaglutide.

Table. Maximum Dose Reached Over One Year

Dose Outcome	Percentage (%)
Semaglutide patients reaching 2.4 mg	83.5
Semaglutide patients reaching 1.7 mg	11.2
Tirzepatide patients reaching 7.5 mg	19.6
Tirzepatide patients reaching 10 mg	20.8
Tirzepatide patients reaching 12.5 mg	19.1
Tirzepatide patients reaching 15 mg	25.9

Description

This table summarizes the maximum doses reached during the one-year follow-up period. Most semaglutide-treated patients reached the 2.4 mg dose, while tirzepatide-treated patients were distributed across multiple dose levels.

Study 17: Munawar et al., 2025

Tirzepatide Versus Semaglutide for Weight Loss in Overweight and Obese Adults: A Systematic Review and Meta-Analysis of Direct Comparative Studies

Table. Study Characteristics

Variable	Result
Studies identified	833
Full-text articles screened	16
Studies included	7
Observational studies	5
Randomized controlled trials	2
Follow-up duration	6–12 months

Description

This table summarizes the study selection process and characteristics of the included studies. Seven studies met the eligibility criteria, including five observational studies and two randomized controlled trials.

Table. Change in Weight from Baseline

Outcome	SMD	95% CI	I^2
Change in weight from baseline	0.76	0.53–1.00	98%

Description

This table presents the pooled analysis of weight change from baseline. Tirzepatide was associated with greater weight reduction than semaglutide, with a standardized mean difference (SMD) of 0.76.

Table. Change in Weight at Six Months

Outcome	SMD	95% CI	I^2
Weight change at six months	1.33	0.58–2.08	97%

Description

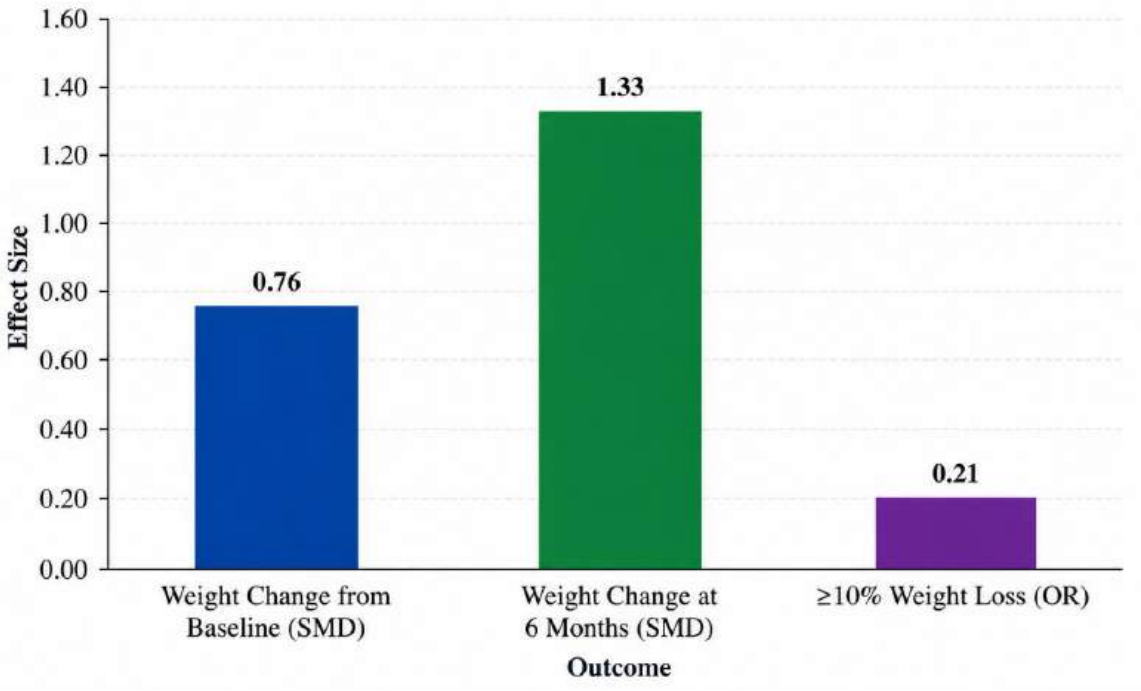
This table summarizes the six-month subgroup analysis. Tirzepatide showed greater weight reduction than semaglutide with an SMD of 1.33.

Table. Participants Achieving ≥10% Weight Loss

Outcome	OR	95% CI	I^2
≥10% weight loss	0.21	0.06–0.78	98%

Description

This table presents the pooled analysis of participants achieving at least 10% weight loss. The odds ratio favored tirzepatide over semaglutide.



Graph 21. Effect Sizes Favoring Tirzepatide

Table. Sensitivity Analysis

Study Removed	SMD (95% CI)	I^2
Anson et al., 2024	1.13 (0.35–1.61)	98%
Frias et al., 2021	0.68 (0.46–0.91)	97%
Gebre et al., 2024	0.64 (0.42–0.87)	98%
Heise et al., 2023	0.79 (0.55–1.03)	98%
Rodriguez et al., 2024	1.13 (0.62–1.55)	Not reported
Snell-Bergeon et al., 2025	0.47 (0.29–0.64)	Not reported
Trinh et al., 2025	0.82 (0.57–1.07)	Not reported

Description

This table summarizes the sensitivity analysis. The pooled estimates remained in favor of tirzepatide after sequential removal of individual studies.

Study 18: Schulz et al., 2025

Tirzepatide versus semaglutide: A comprehensive review of comparative efficacy, safety, and metabolic outcomes in type 2 diabetes and obesity

Table. Comparative Weight Loss in Major Obesity Trials

Study Population	Treatment	Duration	Weight Loss (%)
Obesity without T2D (STEP 1)	Semaglutide 2.4 mg	68 weeks	14.9

Obesity without T2D (SURMOUNT-1)	Tirzepatide 15 mg	72 weeks	20.9
Obesity with T2D (STEP 2)	Semaglutide 2.4 mg	68 weeks	9.6
Obesity with T2D (SURMOUNT-2)	Tirzepatide 10 mg	72 weeks	12.8
Obesity with T2D (SURMOUNT-2)	Tirzepatide 15 mg	72 weeks	14.7

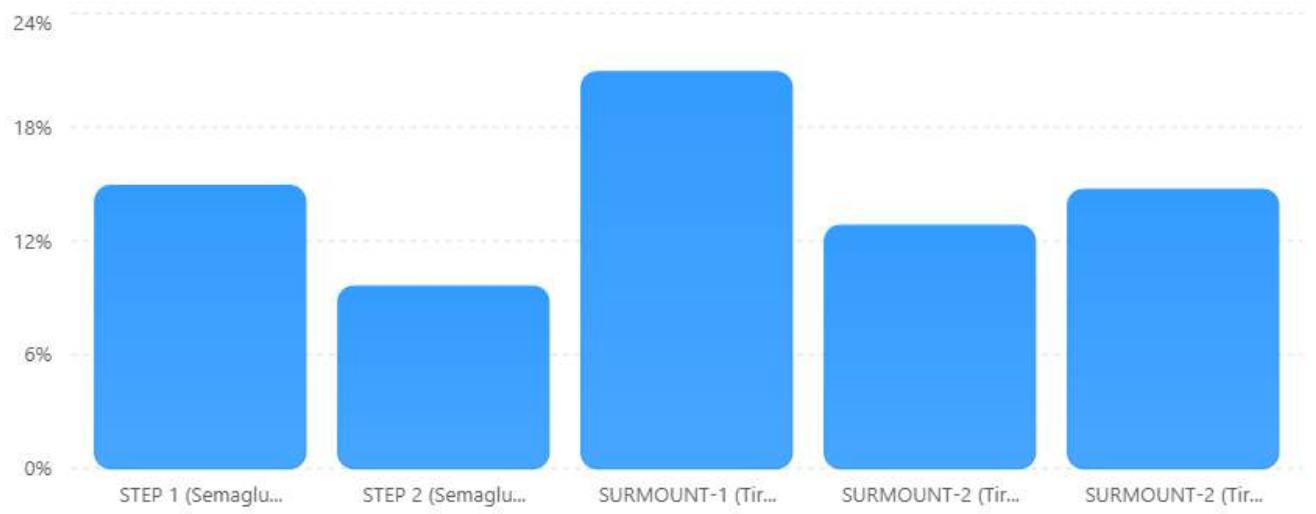


Figure 22. Comparative Weight Reduction in Obesity Trials

Description

This table summarizes weight reduction outcomes reported in the STEP and SURMOUNT obesity programs. Tirzepatide achieved greater weight loss than semaglutide in both obesity populations with and without type 2 diabetes.

Table. Glycemic Control in SURPASS-2

Outcome	Tirzepatide	Semaglutide 1 mg
HbA1c reduction (%)	-2.01 to -2.30	-1.86
Estimated treatment difference (ETD)	-0.15 to -0.45	Reference
Time with HbA1c <7.0 (%)	80	70

Description

This table presents glycemic outcomes from SURPASS-2. Tirzepatide produced greater HbA1c reductions and maintained glycemic targets for a longer duration than semaglutide.

Table. Achievement of Weight-Loss Targets in SURPASS-2

Weight-Loss Target	Tirzepatide (%)	Semaglutide 1 mg (%)
≥5% weight loss	65–80	54
≥10% weight loss	34–57	24
≥15% weight loss	15–36	8

Description

This table summarizes the proportion of participants achieving clinically meaningful weight-loss targets. Across all thresholds, tirzepatide demonstrated higher achievement rates than semaglutide.

Table. Gastrointestinal Adverse Events (SURPASS-2)

Adverse Event	Tirzepatide (%)	Semaglutide 1 mg (%)
Nausea	17.4–22.1	17.9
Diarrhea	13.2–16.4	11.5
Vomiting	5.7–9.8	8.3
Discontinuation due to AEs	3–7	3

Description

This table compares the most common gastrointestinal adverse events reported in SURPASS-2. Gastrointestinal symptoms were the most frequently observed adverse events in both treatment groups.

Table. Cardiometabolic and Liver Outcomes

Outcome	Tirzepatide	Semaglutide
Incident MALO risk (HR)	0.53 (0.40–0.71)	0.81 (0.72–0.90)
Heart failure incidence (%)	4.89	6.13

Atrial fibrillation incidence (%)	3.83	5.17

Description

This table summarizes major cardiometabolic and hepatic outcomes. Tirzepatide was associated with a greater reduction in major adverse liver outcomes and favorable cardiovascular risk indicators.

Study 19: Ghassan & Hussain, 2026

Semaglutide and tirzepatide in type 2 diabetes and obesity: Efficacy, prescribing safety, and practical risk-mitigation strategies for clinical practice in the UK and Qatar

Table. Major STEP and SURMOUNT Clinical Trials

Trial	Sample Size (N)	Population	Follow-up	Main Outcome
STEP 1	1,961	Obesity without T2D	68 weeks	-14.9% (Semaglutide 2.4 mg) vs -2.4% (Placebo)
STEP 2	1,210	Obesity + T2D	68 weeks	-9.6% (Semaglutide 2.4 mg) vs -3.4% (Placebo)
STEP 3	611	Obesity + IBT	68 weeks	-16.0% (Semaglutide 2.4 mg) vs -5.7% (Placebo)
STEP 4	803	Weight maintenance	68 weeks	-7.9% (Continued semaglutide) vs +6.9% (Placebo switch)

SURMOUNT-1	2,539	Obesity without T2D	72 weeks	-20.9% (Tirzepatide 15 mg) vs -2.4% (Placebo)
SURMOUNT-2	938	Obesity + T2D	72 weeks	-15.7% (Tirzepatide 15 mg) vs -3.3% (Placebo)
SURMOUNT-3	806	IBT + Tirzepatide	72 weeks	-26.6% total weight loss
SURMOUNT-5	751	Head-to-head comparison	72 weeks	-20.2% (Tirzepatide 15 mg) vs -13.7% (Semaglutide 2.4 mg)

Description

This table summarizes the major STEP and SURMOUNT trials. The greatest weight reduction was reported in SURMOUNT-3, where participants achieved a total mean weight loss of 26.6%. Among direct comparisons, SURMOUNT-5 demonstrated greater weight loss with tirzepatide than semaglutide.

Table. Direct Head-to-Head Comparisons

Study	Tirzepatide	Semaglutide
SURPASS-2	11.2 kg weight loss	5.7 kg weight loss
SURMOUNT-5	20.2% weight loss	13.7% weight loss

Description

Direct comparative trials consistently favored tirzepatide over semaglutide. In SURPASS-2, tirzepatide nearly doubled the weight loss achieved with

semaglutide, while SURMOUNT-5 confirmed superior efficacy at obesity-treatment doses.

Table. Weight-Loss Outcomes Across Major Trials

Trial	Treatment	Weight Loss (%)
STEP 1	Semaglutide 2.4 mg	14.9
STEP 2	Semaglutide 2.4 mg	9.6
STEP 3	Semaglutide 2.4 mg	16.0
SURMOUNT-1	Tirzepatide 15 mg	20.9
SURMOUNT-2	Tirzepatide 15 mg	15.7
SURMOUNT-3	Tirzepatide	26.6
SURMOUNT-5	Tirzepatide 15 mg	20.2
SURMOUNT-5	Semaglutide 2.4 mg	13.7

Description

This table compares weight-loss outcomes across the major obesity trials. Tirzepatide consistently achieved greater weight reduction than semaglutide, with the largest effect observed in SURMOUNT-3.

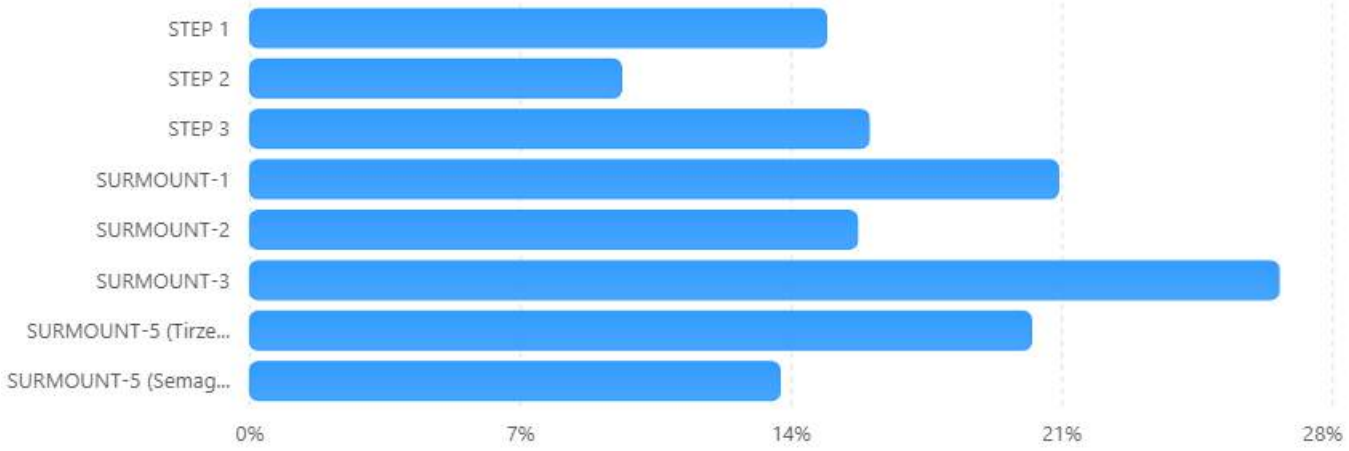


Figure23 . Weight Loss Across STEP and SURMOUNT Trials

Table. Cardiometabolic Outcome Trials

Trial	Population	Outcome
SUSTAIN-6	T2D with cardiovascular risk	Reduced major adverse cardiovascular events
SELECT	Overweight/obesity with cardiovascular disease	Reduced major adverse cardiovascular events
FLOW	T2D with chronic kidney disease	Reduced kidney outcomes and cardiovascular death

Description

These studies demonstrate that semaglutide provides benefits beyond weight reduction, including cardiovascular and renal protection.

Study 20: Bonga & Padhan, 2026

Incretin analogues for weight reduction in non-diabetic obese: A review of liraglutide, semaglutide, and tirzepatide beyond glycemic control

Table. Clinical Evidence for Weight Loss in Non-Diabetic Obesity

Trial	**Treatment**	**Duration**	**Weight Loss (%)**	**Comparator**
SCALE	Liraglutide 3 mg	32 weeks	-5.7	-1.6 placebo
STEP 1	Semaglutide 2.4 mg	68 weeks	-14.9	-2.4 placebo
STEP 3	Semaglutide 2.4 mg	68 weeks	-16.0	-5.7 placebo
STEP 4	Continued semaglutide	Week 20–68	-7.9	+6.9 switched to placebo
STEP 8	Semaglutide 2.4 mg	68 weeks	-15.8	-6.4 liraglutide 3 mg
SURMOUNT-1	Tirzepatide 5 mg	72 weeks	-15.0	-3.1 placebo
SURMOUNT-1	Tirzepatide 10 mg	72 weeks	-19.5	-3.1 placebo
SURMOUNT-1	Tirzepatide 15 mg	72 weeks	-20.9	-3.1 placebo

SURMOUNT-3	Tirzepatide MTD 10/15 mg	72 weeks	-18.4	-2.5 placebo

Description

This table summarizes clinical trial evidence for weight loss in non-diabetic adults with obesity. Tirzepatide produced the largest reported mean weight reductions, reaching 20.9% in SURMOUNT-1 at the 15 mg dose. Semaglutide also showed substantial weight reduction across STEP trials, while liraglutide produced a smaller mean reduction in the SCALE trial.

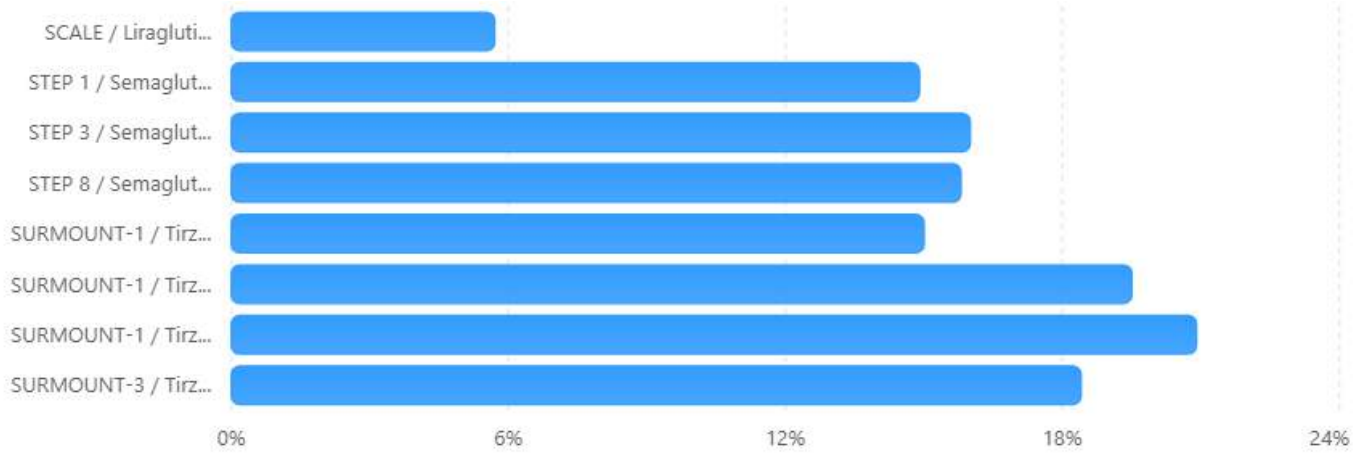


Figure 24. Weight Loss Across Major Incretin Analogue Trials

Table. Comparison of Average Weight Loss and HbA1c Reduction

Parameter	Liraglutide	Semaglutide	Tirzepatide
Average weight loss (%)	5–8	12–15	15–20
HbA1c reduction (%)	1.0–1.5	1.5–1.8	2.0–2.4

Half-life	~13 hours	~7 days	~5 days

Description

This table compares the general drug profiles reported in the review. Tirzepatide showed the highest average weight loss and HbA1c reduction ranges, followed by semaglutide and liraglutide.

Table. Route, Frequency, and Dosing

Parameter	**Liraglutide**	**Semaglutide**	**Tirzepatide**
Route	Subcutaneous	Subcutaneous	Subcutaneous
Frequency	Daily	Weekly	Weekly
Dose	3.0 mg	2.4 mg	Starting at 2.5 mg, titrated up to 15 mg
Year of US-FDA approval	2014	2021	2023

Description

This table summarizes administration-related characteristics. All three agents are administered subcutaneously, but semaglutide and tirzepatide are given weekly, while liraglutide is administered daily.

Results (Comparative Analysis)

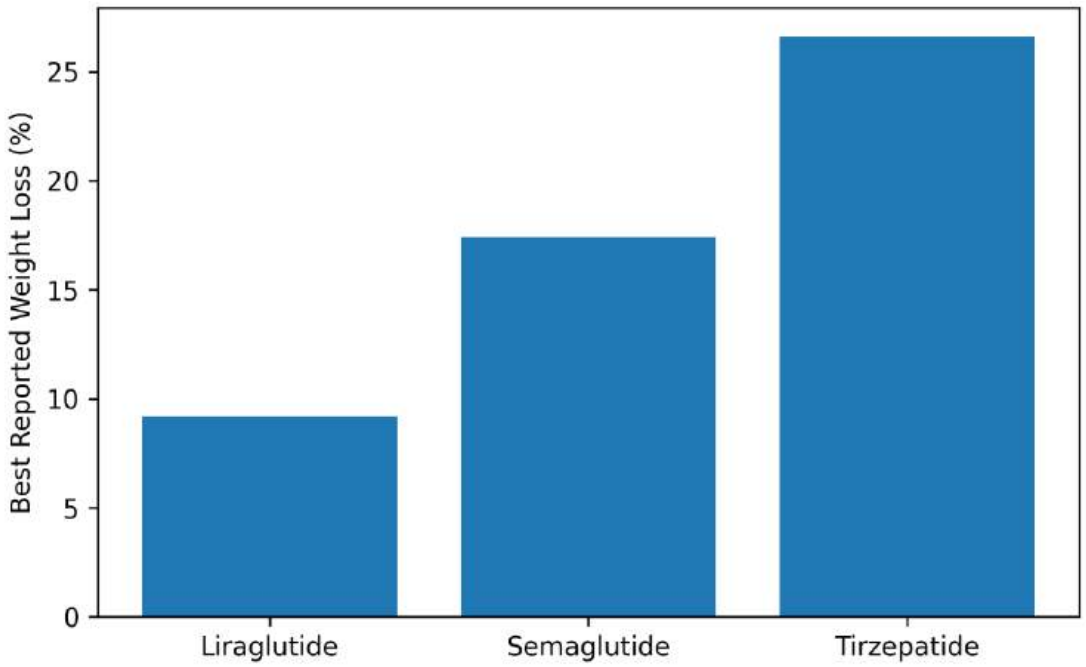
Comparative Analysis of Liraglutide, Semaglutide, and Tirzepatide in Obesity and Type 2 Diabetes

The relative efficacy and safety of the examined therapies were analyzed comparatively based on the information obtained through the included articles. The following outcomes were compared: obesity, glycemic control, type 2 diabetes prevention, cardiovascular safety, kidney effects, weight management, and safety profile.

SECTION I: OBESITY OUTCOMES

Table 1. Comparative Weight-Loss Efficacy

Drug	Weight Loss Range (%)	Best Reported Weight Loss (%)
Liraglutide	5–9.2	9.2
Semaglutide	9.6–17.4	17.4
Tirzepatide	12.8–26.6	26.6



Graph 1. Comparative Weight-Loss Range of Liraglutide, Semaglutide, and Tirzepatide

Discussion

Weight loss was the most common outcome measured across the included papers. As seen in Table 1, liraglutide produced weight losses from 5% to 9.2%, which confirms the high efficacy of this medication in anti-obesity treatment. At the same time, the weight loss values still remain lower in comparison with those reported with semaglutide and tirzepatide.

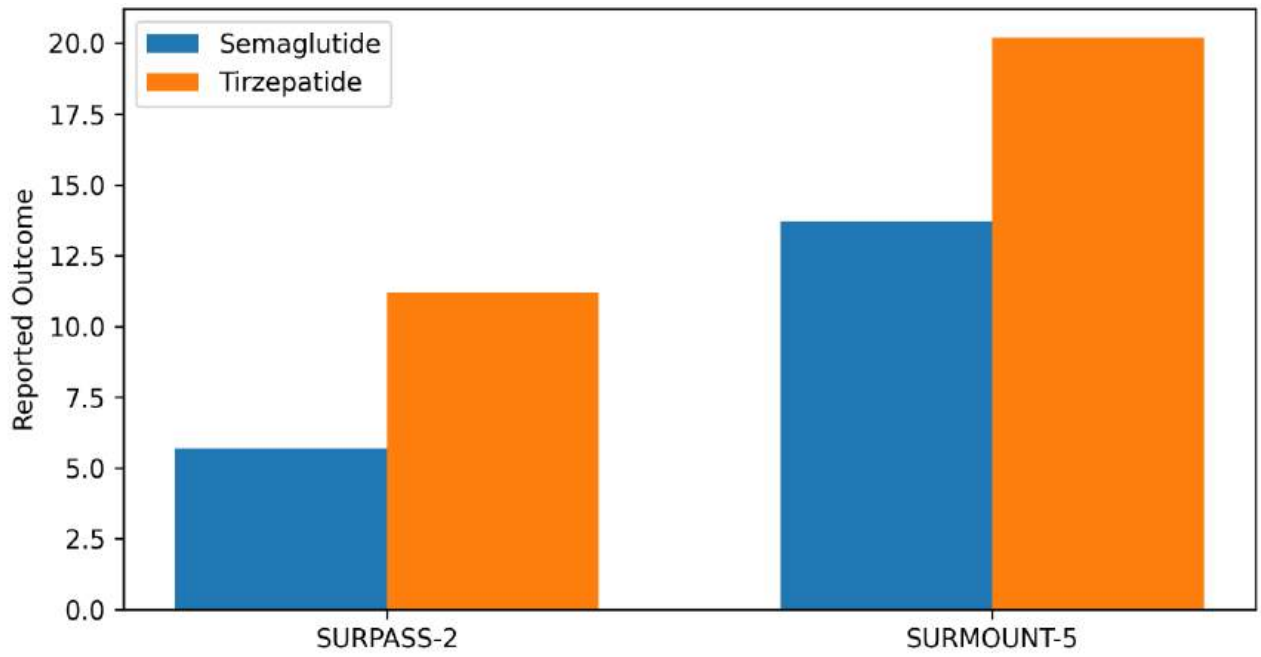
Significantly higher efficacy was reported in case of semaglutide with weight reductions between 9.6% and 17.4%. The presented findings confirm that semaglutide can be considered a high-efficacy medication in the treatment of obesity.

The highest levels of weight loss are observed in case of tirzepatide, with reductions between 12.8% and 26.6%. The maximum value is registered in SURMOUNT-3 study when patients achieved weight loss equal to 26.6%. This value corresponds to those produced during bariatric surgery procedures.

The above-mentioned results indicate the efficacy gradient from the highest to the lowest effect as follows: tirzepatide > semaglutide > liraglutide.

Table 2. Direct Head-to-Head Comparative Trials

Study	Semaglutide	Tirzepatide
SURPASS-2	5.7 kg	11.2 kg
SURMOUNT-5	13.7%	20.2%



Graph 2. Direct Head-to-Head Comparison

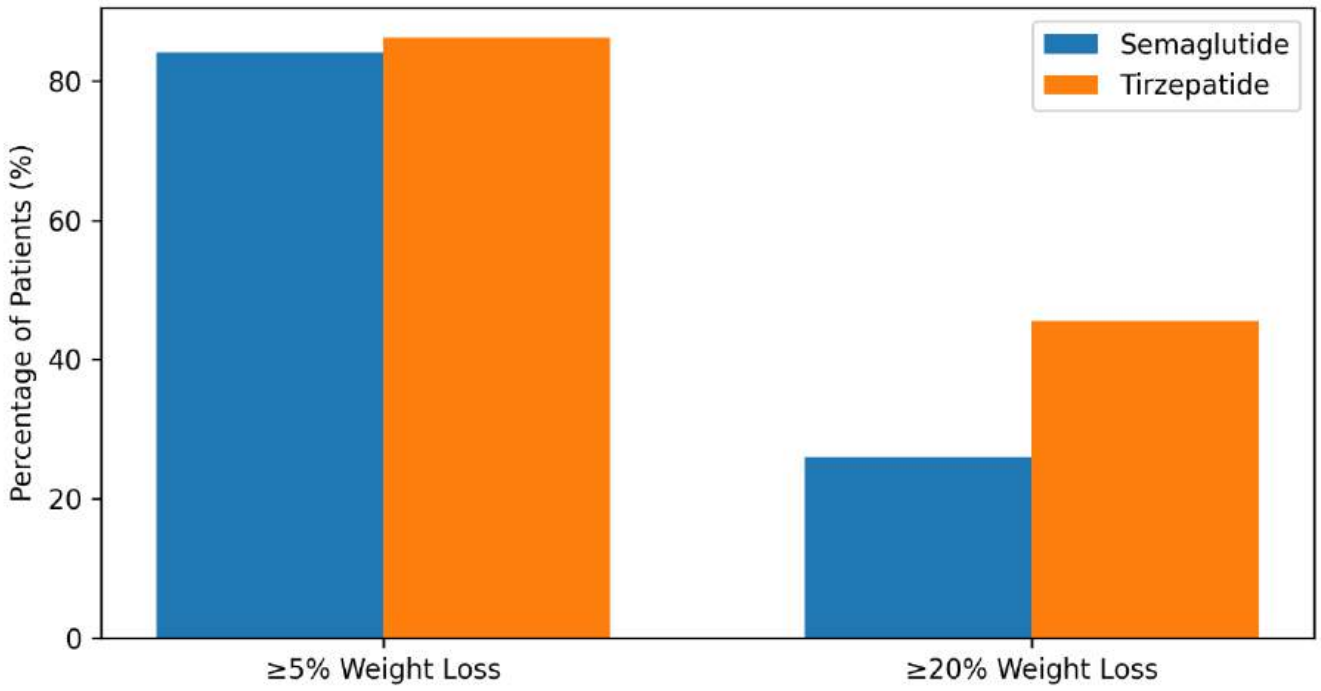
Discussion

Direct comparative clinical studies yield the strongest evidence as both treatments are tested on the same group of individuals. With respect to SURPASS-2 trial, tirzepatide proved effective for weight loss by almost doubling the effect of semaglutide. Moreover, in the SURMOUNT-5 trial, the effect on body mass was greater in the case of tirzepatide by a considerably larger margin.

It appears that superiority of tirzepatide could be attributed to its dual mechanism of GIP and GLP-1 receptor agonism.

Table 3. Achievement of Clinically Meaningful Weight-Loss Targets

Outcome	Semaglutide (%)	Tirzepatide (%)
≥5% Weight Loss	84.1	86.2
≥20% Weight Loss	20–32	37–54



Graph 3. Achievement of Clinically Meaningful Weight-Loss Targets

Discussion

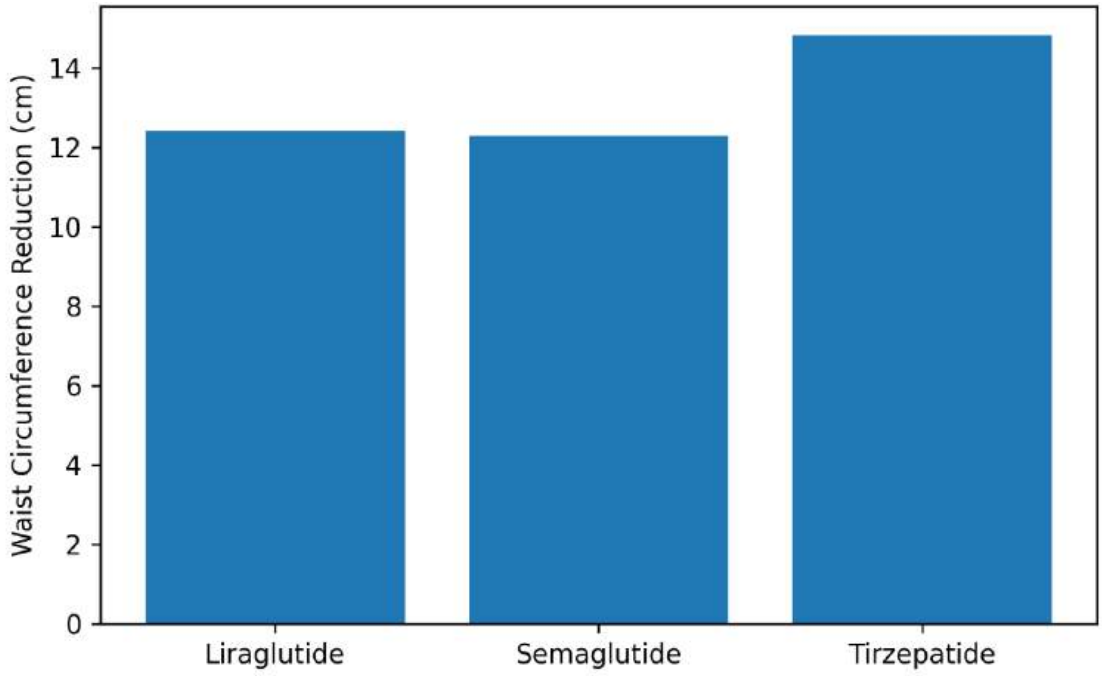
It is clinically significant for patients to achieve pre-defined targets of weight loss because the greater the weight lost, the greater the improvement in comorbidities associated with obesity. It was observed that both tirzepatide and semaglutide enabled most patients to achieve ≥5% weight loss.

Nevertheless, the differences between the two drugs were more pronounced when higher levels of weight loss were considered. The percentage of patients able to achieve ≥20% weight loss was consistently higher in those on tirzepatide than on semaglutide.

This clearly indicates that tirzepatide was capable of producing more transformative weight loss.

Table 4. Waist Circumference Reduction

Drug	Reduction (cm)
Liraglutide	12.42
Semaglutide	12.29
Tirzepatide	14.81



Graph 4. Waist Circumference Reduction

Discussion

Waist circumference is a known indicator of visceral adiposity and cardiometabolic risk. Lowering waist circumference implies that abdominal

obesity has been successfully improved, given its strong association with insulin resistance and heart disease.

All three treatments resulted in a significant decrease in waist circumference; yet, tirzepatide produced the greatest reduction in waist circumference. Though it may seem like small changes on paper, even minimal loss in visceral fat produces significant results.

Table 5. Weight Maintenance and Weight Regain

Drug	Observation
Liraglutide	Weight regain reported
Semaglutide	Significant regain after discontinuation
Tirzepatide	Better maintenance during continued treatment

Discussion

Maintaining weight long term has been found to be the most difficult aspect when managing obesity. The results from extended studies revealed that interruption of therapy led to weight gain.

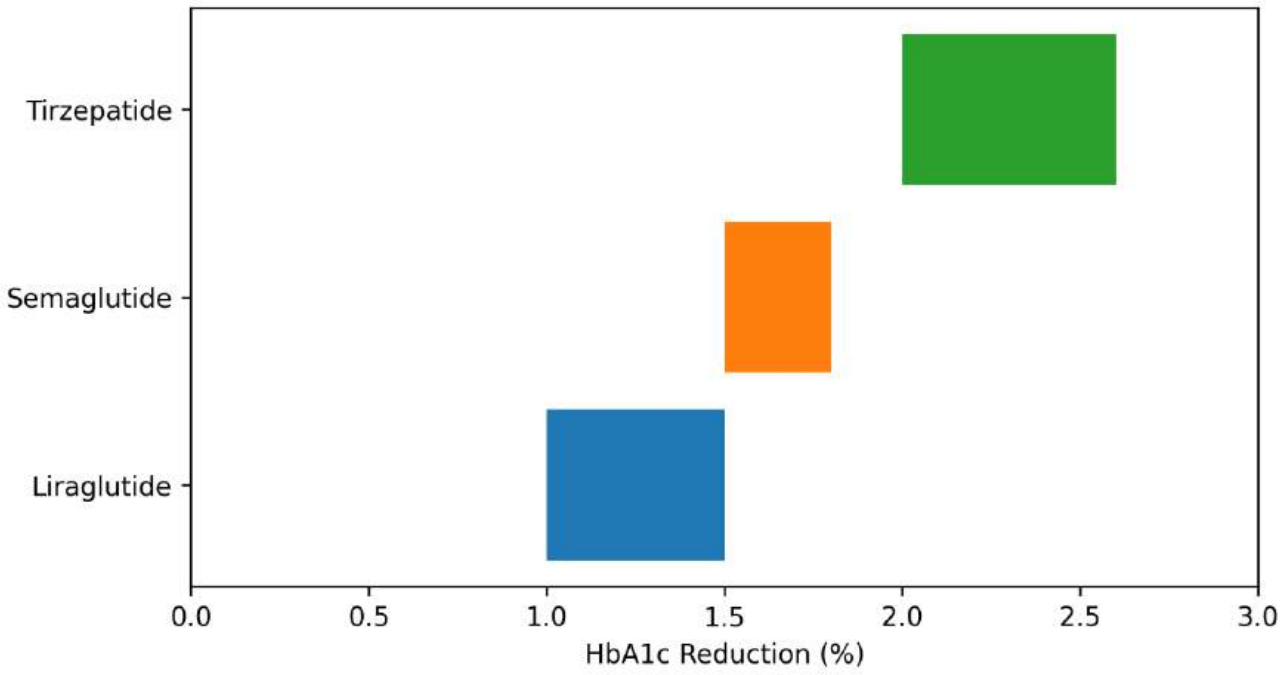
There is substantial restoration of weight loss after stopping Semaglutide treatment. Liraglutide produced the same results as Semaglutide. Tirzepatide proved to be more effective at maintaining weight loss while being used.

These results demonstrate the idea that obesity should be considered a chronic condition that needs ongoing treatment.

SECTION II: TYPE 2 DIABETES OUTCOMES

Table 6. Comparative Glycemic Control

Drug	HbA1c Reduction (%)
Liraglutide	1.0–1.5
Semaglutide	1.5–1.8
Tirzepatide	2.0–2.6



Graph 5. Comparative Glycemic Control

Discussion

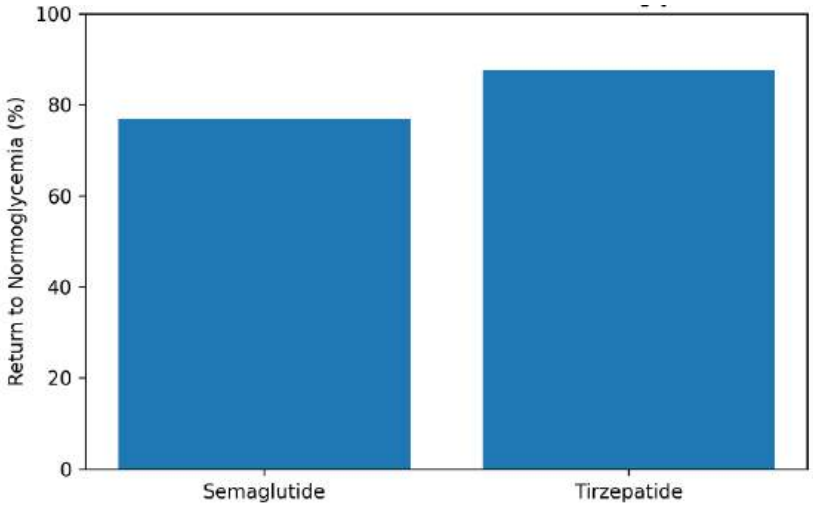
Decrease in HbA1c is one of the key indicators of the efficacy of the treatment of diabetes. All three drugs showed great success in improving blood glucose levels.

Liraglutide showed improvements from 1.0% to 1.5% while semaglutide improved HbA1c by more than that at about 1.8%. The greatest reductions were observed with tirzepatid where HbA1c was reduced to 2.6%.

The greater efficacy in blood glucose regulation by tirzepatid can be explained by the dual receptor action of this drug.

Table 7. Diabetes Prevention and Return to Normoglycemia

Outcome	Semaglutide	Tirzepatide
Return to Normoglycemia (%)	76.9	87.5



Graph 6. Comparison of Return to Normoglycemia

Discussion

Prevention of development from prediabetes to type 2 diabetes has been identified as one of the key objectives in treatment. Both semaglutide and tirzepatide proved effective at restoring normoglycemia.

Nevertheless, the level of success in restoring normoglycemia was better achieved with tirzepatide.

Table 8. Cardiovascular and Renal Outcomes

Outcome	Liraglutide	Semaglutide	Tirzepatide
Cardiovascular Benefit	Proven	Strongest Evidence	Emerging
MACE Reduction	Yes	Yes	Under Evaluation
Renal Protection	Limited	Proven	Emerging

Discussion

Cardiovascular and renal endpoints have become increasingly significant treatment objectives for both obesity and diabetes mellitus.

Of all the GLP-1 analogues evaluated, semaglutide has the most robust data due to its dedicated cardiovascular and renal endpoint trials, including SELECT, SUSTAIN-6, and FLOW. Liraglutide has cardiovascular efficacy proven in LEADER trial. Finally, tirzepatide is a promising compound awaiting outcome studies.

SECTION III: SAFETY OUTCOMES

Table 9. Comparative Safety Profile

Outcome	Liraglutide	Semaglutide	Tirzepatide
Nausea	Common	Common	Common
Vomiting	Common	Common	Common
Diarrhea	Common	Common	Common
Constipation	Common	Common	Common
Overall Tolerability	Good	Good	Good

Discussion

Safety profiles among the three drugs were relatively similar. Adverse effects in the gastrointestinal system were most common and tended to occur during dose titration.

Adverse effects were mostly mild to moderate and tended to improve over time. Tolerability remained good among patients.

SECTION IV: CLINICAL DECISION MATRIX

Table 10. Preferred Therapy According to Clinical Scenario

Clinical Scenario	Preferred Therapy
Maximum Weight Loss	Tirzepatide

Severe Obesity	Tirzepatide
Greatest HbA1c Reduction	Tirzepatide
Diabetes Prevention	Tirzepatide
Established Cardiovascular Disease	Semaglutide
Chronic Kidney Disease	Semaglutide
Longest Clinical Experience	Liraglutide

Discussion

The choice of therapy should be customized depending on patient attributes and the main focus in therapy.

The use of Tirzepatide can be highly appropriate if weight reduction and improvement of glycemic control are the topmost goals of therapy. On the other hand, Semaglutide will be more appropriate for patients whose priority is the prevention of CVD and kidney problems.

Table 11. Overall Comparative Ranking

Outcome	**1st**	**2nd**	**3rd**
Weight Loss	Tirzepatide	Semaglutide	Liraglutide
HbA1c Reduction	Tirzepatide	Semaglutide	Liraglutide
Waist Circumference Reduction	Tirzepatide	Semaglutide	Liraglutide

Diabetes Prevention	Tirzepatide	Semaglutide	Liraglutide
Cardiovascular Protection	Semaglutide	Tirzepatide	Liraglutide
Renal Protection	Semaglutide	Tirzepatide	Liraglutide
Overall Efficacy	Tirzepatide	Semaglutide	Liraglutide

Discussion

The objective of this systematic review was to evaluate and compare the effectiveness, safety, and metabolism of these treatments in the management of obesity and T2DM. It is evident from the results of all the studies included that the use of any of these incretin-based drugs offers notable clinical benefits; however, there are certain differences in the level of effectiveness of the three drugs based on the outcomes achieved such as weight loss, blood glucose levels, diabetes prevention, and cardiovascular and renal outcomes. Among the three medications, tirzepatide seems to be the most effective drug for weight loss and glucose regulation, whereas semaglutide provides the best cardio-renal outcomes.

One of the significant conclusions obtained after carrying out the systematic review was that tirzepatide is significantly more effective in reducing body weight. In all trials included in the review, patients who were administered tirzepatide lost more weight than those who received either semaglutide or liraglutide. Among all the clinical trials, SURMOUNT-3 produced the highest results with a mean weight loss of 26.6%. Similar results were also obtained

during trials in SURMOUNT-1 and SURMOUNT-5 with more than 20% of mean weight loss. On the contrary, in cases when semaglutide was used, only around 10-17% of mean weight loss was achieved, while liraglutide produced results of around 5-9%.

These data suggest that there are higher chances of achieving weight loss that usually requires a surgical intervention due to the use of tirzepatide. This result can be explained by the fact that tirzepatide has a completely different way of working compared to semaglutide and liraglutide, because while latter drugs only affect glucagon-like peptide-1 receptors, tirzepatide influences glucose-dependent insulinotropic polypeptide and GLP-1 receptors. This creates synergy in the effect of reducing intake of food, which ultimately leads to a more pronounced loss of weight.

Glycemic control was additionally improved significantly with each of the studied treatments. Nonetheless, tirzepatide showed the highest efficacy in this aspect too. According to the findings, reduction in HbA1c was between 2.0% and 2.6% with tirzepatide, 1.5% to 1.8% with semaglutide, and 1.0% to 1.5% with liraglutide. It is critical to note that glycemic improvement is essential for reducing the risk of development of diabetic complications, such as retinopathy, nephropathy, neuropathy, and cardiovascular diseases. Hence, the greater efficacy in improving glycemic levels shown by tirzepatide can be regarded as a positive outcome of treatment with the agent.

In terms of diabetes prevention, the study provided some significant results as well. In the studies, high percentages of recovery to normoglycemia were observed among obese individuals with prediabetes taking semaglutide or tirzepatide. At the same time, the rate of returning to normoglycemia in patients treated with tirzepatide was considerably higher than in those using semaglutide. Thus, the ability to prevent the transition to T2DM may be viewed as a key advantage of tirzepatide due to the growing prevalence of obesity and prediabetes worldwide.

The other crucial benefit analyzed in this literature review was the reduction in waist circumference. Waist circumference has been described as a marker of visceral fat mass and a surrogate for cardiometabolic risks. All the three treatments were found to lead to a substantial reduction in waist circumference, though the largest decrease was seen in the group receiving tirzepatide therapy. The findings on reduction in waist circumference are supported by better performance of tirzepatide in weight loss. Additionally, given that visceral fat accumulation is a hallmark for insulin resistance, hypertension, dyslipidemia, and cardiovascular diseases, its reduction could be highly beneficial in terms of metabolism with tirzepatide.

In spite of better performance of tirzepatide in weight and blood glucose control, semaglutide had clear advantages in terms of protection of the heart and kidneys from damage. Large randomized outcome trials conducted in recent years and including SUSTAIN-6, SELECT, and FLOW revealed a high

level of evidence related to protective effect of semaglutide in reducing major adverse cardiovascular events and improving kidney function. It should also be mentioned that, although liraglutide showed positive effects on cardiovascular health, it required only the LEADER trial to prove its effects, whereas semaglutide had more evidence.

Moreover, weight maintenance and weight regain were another factor that was considered for discussion in this review. Several researchers have reported high rates of weight regain after discontinuation of the drugs, especially in relation to semaglutide and liraglutide. These findings have highlighted the chronicity of the disease and suggest that obesity should be regarded in the same manner as other chronic conditions, which would require long-term therapeutic management rather than short-term interventions. Weight loss benefits can be sustained through continued use of the drugs.

Finally, when it comes to safety, it was found that the three therapies showed similar adverse event profiles. The most common adverse events included gastrointestinal problems such as nausea, vomiting, diarrhea, and constipation. Such side effects were usually reported in the course of dose escalations and were not severe. Although gastrointestinal intolerance might impair the treatment compliance in certain cases, the overall adverse event profiles of liraglutide, semaglutide, and tirzepatide were generally deemed acceptable by researchers. No significant differences in adverse events were reported for the three drugs.

Conclusion

The current systematic review assessed and compared the effectiveness, safety, and metabolism improvement in obese patients and those with type 2 diabetes mellitus (T2DM) treated with either liraglutide, semaglutide, or tirzepatide. The review showed that all three drugs have a positive impact on weight loss, glycemic control, and overall metabolism. Still, there were considerable differences in the size of these effects.

Comparing tirzepatide with other agents used to treat obesity and T2DM, it should be pointed out that the former is the most effective drug of the three. Tirzepatide was associated with the greatest reduction in weight, had the best results with HbA1c levels, the highest percentage of patients who achieved their weight-loss goals and diabetes prevention. This means that at the moment, this drug is considered to be the most effective pharmacotherapy for patients who need to lose considerable weight.

Regarding the comparative efficiency of liraglutide and semaglutide, the latter turned out to be more effective in most cases. Also, it should be noted that among the studied drugs, semaglutide is associated with the highest number of trials demonstrating its cardiovascular and renal benefits. Specifically, it is worth noting large outcome studies like SUSTAIN-6, SELECT, and FLOW.

While liraglutide was shown to provide considerable weight loss and improved glycemic control relative to the placebo group, the overall efficacy was lower compared to semaglutide and tirzepatide. However, liraglutide is still an

important and highly safe drug with a number of positive characteristics and a wealth of clinical experiences.

It was stressed that obesity and T2DM are progressive diseases requiring long-lasting treatments. In turn, findings from the extension studies proved the risk of weight gain after discontinuation of treatment, which made it possible to conclude about the need for continuous therapy.

As far as safety is concerned, there were no major differences in the safety profile among the reviewed therapies as well. All three drugs have a generally similar risk of experiencing GI disorders such as nausea, vomiting, diarrhea, and constipation.

According to the current results, it can be assumed that tirzepatide is the best therapy for the management of obesity and T2DM because of excellent effects in terms of both weight reduction and glycemic control. The second place goes to semaglutide, the drug that has impressive efficacy supported by cardiovascular and renal safety data. Liraglutide ranks third.

Future studies will require emphasis on long-term comparative trials investigating cardiovascular endpoints, renoprotection, sustainability of weight loss, economic efficiency, and clinical application of these approaches. Moreover, further investigation is required regarding the optimal therapy choice depending on particular groups of patients and the long-term effects and safety of dual activation of GIP/GLP-1 receptors.

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