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TIRZEPATIDE VERSUS SEMAGLUTIDE: A COMPREHENSIVE REVIEW OF COMPARATIVE EFFICACY, SAFETY, AND METABOLIC OUTCOMES IN TYPE 2 DIABETES AND OBESITY

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ABSTRACT

Type 2 diabetes (T2D) and obesity represent chronic, escalating global health crises that necessitate potent pharmacological strategies. This comprehensive review compares the relative efficacy, safety, and overall metabolic benefits of tirzepatide (TZP), a novel dual GIP/GLP-1 receptor agonist, against semaglutide (SEMA), a selective GLP-1 receptor agonist. A systematic review was conducted, synthesizing data from 36 eligible Randomized Controlled Trials (RCTs), Indirect Treatment Comparisons (ITCs), and Real-World Evidence (RWE) studies involving adults with T2D and/or overweight/obesity. Key outcomes assessed included changes in HbA1c, body weight, and gastrointestinal adverse events (AEs). Findings from head-to-head RCTs (e.g., SURPASS-2) definitively demonstrated that all tested doses of once-weekly TZP (5 mg, 10 mg, and 15 mg) achieved statistically significantly greater reductions in both HbA1c and body weight compared to SEMA 1.0 mg. Furthermore, TZP significantly increased the proportion of participants achieving challenging composite endpoints, such as reaching stringent glycemic targets combined with substantial weight loss (e.g., ≥10%), without clinically significant hypoglycemia. ITCs comparing maximal doses also suggested that TZP 15 mg conferred superior efficacy for both weight and glycemic control over SEMA 2.4 mg in patients with T2D/obesity. The safety profile of TZP was generally consistent with the incretin class, characterized predominantly by transient gastrointestinal AEs (nausea, diarrhea, vomiting). In conclusion, tirzepatide, leveraging its dual GIP/GLP-1 agonism, provides consistently superior efficacy for glycemic control and body weight reduction compared to semaglutide, positioning dual incretin agonism as a powerful advance in treating T2D and obesity.

KEYWORDS

Tirzepatide, Semaglutide, Type 2 Diabetes, Obesity, GIP/GLP-1 Agonist

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Introduction

Type 2 Diabetes Mellitus (T2D) and obesity constitute a significant and escalating public health concern worldwide, often attaining pandemic proportions [le Roux et al., 2023; Lingvay et al., 2022]. T2D is a multifactorial chronic condition primarily influenced by insulin resistance [Lingvay et al., 2022], and its development is closely associated with obesity [Ciudin et al., 2025]. The worldwide prevalence of obesity has risen sharply, currently impacting around 890 million adults, with projections indicating that this number will exceed 1.25 billion by 2030 [Papantoniou et al., 2025]. This coexisting burden substantially elevates the risk of cardiometabolic complications [Patel et al., 2023], underscoring the importance of weight management in optimizing T2D outcomes and halting disease progression [Ciudin et al., 2025].

Over recent decades, pharmacological treatments for T2D have evolved considerably, particularly with the emergence of incretin-based therapies [Scheen, 2023]. Among these, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have become central to modern T2D and obesity management, offering proven advantages in glycemic regulation, weight reduction, and potential cardiovascular benefit [Scheen, 2023; Toraih et al., 2025]. Current clinical recommendations frequently position incretin-based agents as first-line injectable therapies aimed at lowering both blood glucose and body weight in individuals with T2D [Patel et al., 2023].

Semaglutide, a leading drug within this category, acts as a selective GLP-1 receptor agonist [Frias et al., 2021; Osumili et al., 2024]. The pharmacodynamic actions of GLP-1 RAs include promoting insulin secretion under hyperglycemic conditions, suppressing glucagon release, delaying gastric emptying, and diminishing appetite—mechanisms that collectively contribute to weight loss [Frias et al., 2021; Toraih et al., 2025]. Building on these advancements, a new generation of incretin-based agents has emerged in the form of dual agonists [Scheen, 2023]. Tirzepatide represents the first once-weekly dual agonist that targets both the glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors (GIP/GLP-1 RA) [Scheen, 2023; Frias et al., 2021; Vadher et al., 2022; Mody et al., 2023; Bull et al., 2022]. This dual action—merging GLP-1 and GIP receptor agonism, which together influence insulin secretion, glucagon regulation, and lipid metabolism [Frias et al., 2021; Bull et al., 2022]—is thought to enhance therapeutic outcomes in terms of glycemic control and body weight reduction relative to selective GLP-1 RAs [Frias et al., 2021; Hoog et al., 2025].

Since tirzepatide has already demonstrated superior efficacy in lowering glucose levels and inducing weight loss compared with semaglutide 1 mg in clinical studies such as SURPASS-2 [Mody et al., 2023; Lingvay et al., 2022], and both agents are identified as highly effective options in current T2D management guidelines [Patel et al., 2023], it is essential to thoroughly assess their comparative benefits. Consequently, the main aim of this review is to systematically analyze the available evidence on the efficacy and safety of tirzepatide and semaglutide [Frias et al., 2021; Azuri et al., 2022; Vadher et al., 2022]. This comparison is particularly relevant given the differences in dosage regimens (e.g., semaglutide 1 mg versus 2.4 mg used for obesity) and the reliance on indirect treatment comparisons to inform clinical decision-making in patients affected by both T2D and obesity [Vadher et al., 2022; Hankosky et al., 2025].

Methodology

Study Design

Eligible research encompassed Randomized Controlled Trials (RCTs), meta-analyses, and Indirect Treatment Comparisons (ITCs) (e.g., employing Bucher or MAIC methodologies), as well as high-quality Real-World Evidence (RWE) studies. Only studies demonstrating strong methodological integrity and clearly defined comparators were included in the analysis.

Intervention and Comparison

Eligible studies were required to present either direct head-to-head comparisons or credible indirect comparisons between tirzepatide (TZP) and semaglutide (SEMA). Priority was given to analyses enabling a meaningful evaluation of the relative efficacy and safety of these two therapeutic agents.

Population

The study population consisted of adults diagnosed with Type 2 Diabetes Mellitus (T2D) and/or individuals categorized as overweight or obese. Studies with mixed cohorts were also considered eligible if they included relevant subgroup analyses pertaining to this population.

Outcomes

Selected studies reported primary efficacy endpoints, including reductions in HbA1c and body weight, as well as safety and tolerability data, with particular attention to gastrointestinal adverse events (AEs). Where available, studies assessing clinically significant composite outcomes were also prioritized.

Study Selection

In total, 63 studies underwent screening for eligibility. Of these, 36 met the inclusion criteria and were incorporated into the review, while 27 were excluded. Among the excluded works, 17 were omitted for being review articles, and 2 were excluded because they were conducted using animal models. Two additional studies were excluded for addressing public perceptions or interest in novel therapies rather than reporting clinical outcomes. One study was excluded due to its sole focus on ophthalmologic outcomes, another for concentrating on orthopedic parameters, and one more for addressing oncological conditions. Furthermore, a single study was excluded as it was limited to a Canadian population. Two additional studies were excluded for investigating alternative treatment regimens instead of standard comparators. Ultimately, 36 studies meeting all predefined eligibility criteria were included in both qualitative and quantitative analyses.

Pharmacological Overview

Semaglutide: Mechanism of Action, Dosing, and Clinical Trials

Semaglutide is a well-characterized therapeutic agent that acts as a selective glucagon-like peptide-1 (GLP-1) receptor agonist [Frias et al., 2021]. GLP-1 RAs represent a cornerstone class of incretin-based therapies extensively recommended for managing Type 2 Diabetes Mellitus (T2D) and obesity [Frias et al., 2021]. Their clinical benefits arise from multiple physiological mechanisms, including the stimulation of glucose-dependent insulin secretion, suppression of glucagon release, delayed gastric emptying, and appetite regulation via central pathways [Toraih et al., 2025; le Roux et al., 2023; Forst et al., 2024].

Semaglutide is administered once weekly through subcutaneous injection [Osumili et al., 2024; Hankosky et al., 2025]. The 1.0 mg dose has been thoroughly evaluated for glycemic management in T2D, while higher doses, such as 2.4 mg weekly, have been specifically formulated for long-term weight control in individuals with overweight or obesity [le Roux et al., 2023; Hankosky et al., 2025]. The efficacy of semaglutide in promoting weight reduction and improving cardiometabolic parameters has been firmly supported by findings from the phase 3 STEP (Semaglutide Treatment Effect in People with Obesity) clinical trial program [le Roux et al., 2023; Forst et al., 2024]. In particular, the STEP 2 trial examined the effects of the 2.4 mg dose in adults with overweight or obesity who also had T2D [Frias et al., 2021; Ciudin et al., 2025].

Tirzepatide: Dual GIP/GLP-1 Agonist Mechanism, SURPASS and SURMOUNT Trials

Tirzepatide is an innovative, first-in-class dual agonist targeting both the glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors (GIP/GLP-1 RA) [Frias et al., 2021; Vadher et al., 2022; Bull et al., 2022; Scheen, 2023]. This unimolecular dual receptor agonism represents a pharmacological advancement beyond traditional selective GLP-1 RAs [Scheen, 2023]. Tirzepatide displays greater agonistic activity at the GIP receptor relative to the GLP-1 receptor [Scheen, 2023; Al-Sabah et al., 2024]. The synergistic engagement of both receptors is proposed to amplify therapeutic benefits, as GIP not only enhances insulin secretion and modulates glucagon levels but also contributes to lipid metabolism and improved insulin sensitivity beyond effects attributable solely to weight loss [Scheen, 2023; Lingvay et al., 2022; Forst et al., 2024; Tang et al., 2025]. Furthermore, tirzepatide therapy has been shown to improve β-cell function and insulin sensitivity in individuals with T2D [Henney et al., 2025; Scheen, 2023].

Tirzepatide is likewise administered once weekly via subcutaneous injection, with approved therapeutic doses of 5 mg, 10 mg, and 15 mg [Osumili et al., 2024]. Its efficacy has been comprehensively assessed through phase 3 clinical programs addressing the continuum of metabolic disease:

SURPASS Program (T2D): This phase 3 series primarily evaluated tirzepatide's glycemic efficacy in patients with T2D [Lingvay et al., 2022; Bergman et al., 2024]. The pivotal SURPASS-2 trial directly compared tirzepatide at all three doses (5 mg, 10 mg, and 15 mg) against semaglutide 1.0 mg as an active comparator in adults with T2D [Frias et al., 2021; Osumili et al., 2024].

SURMOUNT Program (Obesity): This parallel program investigated tirzepatide's effects on sustained weight management in individuals with overweight or obesity [le Roux et al., 2023]. The SURMOUNT-2 trial, in particular, enrolled participants with both T2D and obesity/overweight [Hankosky et al., 2025; Tang et al., 2025].

Comparative Profiles: Administration, Pharmacokinetics, and Adverse Events

Tirzepatide and semaglutide share comparable convenience in administration, both being delivered via once-weekly subcutaneous injection [Osumili et al., 2024; Hankosky et al., 2025]. Their pharmacokinetic profiles are optimized through structural modifications that enable extended half-lives and weekly dosing [Toraih et al., 2025].

The safety profile of tirzepatide aligns closely with that of GLP-1 RAs, with gastrointestinal (GI) adverse events (AEs) being the most frequently reported [Patel et al., 2023]. Common GI AEs include nausea, diarrhea, and vomiting, which are typically mild to moderate in severity and tend to resolve with continued therapy or during dose escalation [Frias et al., 2021; Patel et al., 2023].

Data from the 40-week SURPASS-2 trial provide comparative insight into the tolerability of tirzepatide versus semaglutide 1 mg [Osumili et al., 2024; Frias et al., 2021]. Incidence rates of key GI AEs (≥5%) were largely similar between both treatments, with dose-dependent variations observed [Frias et al., 2021]:

Nausea: Occurred in 17.4%–22.1% of tirzepatide-treated participants (5–15 mg), versus 17.9% in the semaglutide 1 mg group.

Diarrhea: Reported in 13.2%–16.4% of tirzepatide users compared to 11.5% with semaglutide 1 mg.

Vomiting: Documented in 5.7%–9.8% of tirzepatide recipients versus 8.3% in the semaglutide group.

Treatment discontinuation due to AEs occurred across all groups, affecting 3% of semaglutide 1 mg participants and 3%–7% of tirzepatide recipients in SURPASS-2 [Frias et al., 2021]. Both agents were associated with a low risk of clinically relevant hypoglycemia in the absence of concomitant insulin or sulfonylurea therapy, with severe hypoglycemic episodes (<54 mg/dL) being infrequent—reported in 0.2%–1.7% of tirzepatide users and 0.4% of semaglutide users [Frias et al., 2021]. Injection-site reactions occurred in 1.9%–4.5% of tirzepatide-treated patients, compared with 0.2% among semaglutide 1 mg recipients [Frias et al., 2021].

Clinical Efficacy

Superior Glycemic Control and Weight Reduction in Direct Comparison

The comparative efficacy of tirzepatide versus semaglutide was first established in the head-to-head Phase 3 trial SURPASS-2, which enrolled individuals with Type 2 Diabetes Mellitus (T2D) inadequately controlled on metformin monotherapy [Lingvay et al., 2022; Nicholls et al., 2024; Forst et al., 2024; Ciudin et al., 2025]. This pivotal 40-week investigation demonstrated that tirzepatide achieved superior outcomes compared with semaglutide 1.0 mg across all evaluated doses (5 mg, 10 mg, and 15 mg), both in terms of glycemic control and body weight reduction [Nicholls et al., 2024; Ciudin et al., 2025; Frias et al., 2021].

For glycemic endpoints, tirzepatide induced significantly greater mean reductions in glycated hemoglobin (HbA1c) from baseline across all doses compared with semaglutide 1.0 mg [Forst et al., 2024; Frias et al., 2021]. The mean HbA1c reduction ranged between −2.01% and −2.30% for tirzepatide, versus −1.86% for semaglutide 1.0 mg [Frias et al., 2021]. The estimated treatment difference (ETD) in HbA1c reduction varied from −0.15 to −0.45 percentage points, consistently favoring tirzepatide [Frias et al., 2021]. Moreover, tirzepatide led to greater decreases in fasting serum glucose levels throughout the study compared with semaglutide 1.0 mg [Frias et al., 2021]. Mechanistic analyses further demonstrated that tirzepatide 15 mg produced a larger decrease in incremental blood glucose $AUC_{0–240}$ min following a mixed meal tolerance test compared to semaglutide 1 mg [Heise et al., 2022].

The dual agonist mechanism also translated into consistently greater weight loss across all tirzepatide dose groups within SURPASS-2 [Ciudin et al., 2025]. Body weight reductions of ≥5%, ≥10%, and ≥15% were achieved in 65–80%, 34–57%, and 15–36% of tirzepatide-treated participants, respectively, compared with 54%, 24%, and 8% in the semaglutide 1.0 mg arm [Frias et al., 2021].

Achievement of Composite Endpoints and Sustained Control

Contemporary treatment guidelines increasingly emphasize achieving multidimensional clinical goals—combining effective glycemic control, significant weight loss, and low hypoglycemia risk [Mody et al., 2023; Lingvay et al., 2022]. Post hoc analyses across the entire SURPASS trial series (SURPASS-1 through SURPASS-5) revealed that a significantly higher proportion of tirzepatide-treated patients met these composite efficacy endpoints compared with all comparators, including semaglutide 1.0 mg [Lingvay et al., 2022]. For instance, 32–60% of tirzepatide participants achieved HbA1c ≤6.5% with ≥10% body weight reduction and without clinically significant hypoglycemia, versus 22% of those treated with semaglutide 1.0 mg [Frias et al., 2021]. This advantage persisted across various HbA1c thresholds (<7.0%, ≤6.5%, and <5.7%) combined with weight loss benchmarks of ≥5%, ≥10%, and ≥15% [Lingvay et al., 2022].

In addition, post hoc analyses evaluating the durability of metabolic control showed a sustained advantage for tirzepatide. Participants receiving tirzepatide maintained a longer median proportion of treatment time within target glycemia (HbA1c <7.0%)—approximately 80%—compared with 70% for those on semaglutide 1 mg [Bergman et al., 2024]. Similarly, in SURPASS-2, all tirzepatide dose groups maintained

significantly longer continuous periods meeting the composite goal of HbA1c ≤6.5% with ≥5% weight loss compared to semaglutide 1 mg ($p < 0.001$) [Bergman et al., 2024].

Comparative Weight Reduction in Obesity Trials (SURMOUNT vs. STEP)

Given that both tirzepatide and semaglutide are also indicated at higher doses for obesity management—with or without coexisting T2D—dedicated clinical programs were conducted: the SURMOUNT series for tirzepatide and the STEP program for semaglutide.

In adults with obesity but without T2D, semaglutide 2.4 mg (STEP 1) produced a mean body weight reduction of −14.9% [Forst et al., 2024]. In contrast, tirzepatide 15 mg (SURMOUNT-1) achieved a markedly greater mean reduction of −20.9% over 72 weeks [Forst et al., 2024].

For individuals with both obesity and T2D, SURMOUNT-2 demonstrated mean weight losses of −12.8% and −14.7% for tirzepatide 10 mg and 15 mg, respectively, compared to −3.2% with placebo [Forst et al., 2024; Hankosky et al., 2025]. In STEP 2, semaglutide 2.4 mg achieved a mean reduction of −9.6% [Forst et al., 2024; Hankosky et al., 2025].

Efficacy in Subgroups: Indirect Treatment Comparisons (ITC)

Because no head-to-head trials have yet compared the maximum obesity doses of semaglutide (2.4 mg) and tirzepatide (10 mg or 15 mg), Indirect Treatment Comparisons (ITCs) have played a critical role in guiding clinical interpretation [le Roux et al., 2023].

1. Tirzepatide vs. Semaglutide 2.4 mg (Obesity with T2D):

An ITC comparing tirzepatide 10 mg and 15 mg (SURMOUNT-2) with semaglutide 2.4 mg (STEP 2) in patients with obesity/overweight and T2D demonstrated that higher doses of tirzepatide offered superior efficacy [Hankosky et al., 2025]. Tirzepatide 15 mg yielded significantly greater mean percentage reductions in body weight (mean difference [MD]: −4.83%) and HbA1c (MD: −0.56%) relative to semaglutide 2.4 mg [Ciudin et al., 2025]. Furthermore, tirzepatide 15 mg significantly increased the likelihood of achieving ≥15% weight loss compared to semaglutide 2.4 mg (Odds Ratio: 2.85) [Ciudin et al., 2025].

2. Tirzepatide vs. Semaglutide 2.0 mg (T2D):

An adjusted ITC utilizing data from SURPASS-2 and SUSTAIN FORTE compared tirzepatide (5 mg, 10 mg, and 15 mg) with semaglutide 2 mg in T2D management. Tirzepatide 10 mg and 15 mg were associated with significantly greater reductions in both body weight and HbA1c at week 40. The estimated treatment difference in body weight favored tirzepatide 15 mg by −5.15 kg over semaglutide 2 mg.

3. Real-World and Subpopulation Findings:

Evidence from real-world data (RWD) further supports the superior efficacy of tirzepatide, showing greater mean weight loss than semaglutide during a 6-month follow-up, particularly among individuals without diabetes [Trinh et al., 2024]. Post hoc analyses also revealed a more pronounced decline in the prevalence of metabolic syndrome among tirzepatide-treated patients compared with those receiving semaglutide 1 mg or other comparators, indicating broader cardiometabolic benefits that correlate with the extent of weight loss [Nicholls et al., 2024]. Additionally, tirzepatide appears to enhance β-cell function and insulin sensitivity to a greater degree per unit of weight reduction than selective GLP-1 receptor agonism alone, likely due to its dual GIP/GLP-1 activity [Nicholls et al., 2024].

Safety and Tolerability

Overall Safety Profile

The safety profiles of tirzepatide and semaglutide generally align with the established characteristics of the incretin drug class [Frias et al., 2021; Lingvay et al., 2022; Bull et al., 2022; Patel et al., 2023]. This overall consistency is evident across the range of studied doses, although differences in the frequency of certain adverse events (AEs) and treatment discontinuation rates have been reported [Bull et al., 2022; Vadher et al., 2022; Patel et al., 2023].

Gastrointestinal Adverse Events (GI AEs)

Gastrointestinal (GI) events represent the most frequently observed AEs for both tirzepatide and semaglutide, typically classified as mild to moderate in severity [Frias et al., 2021; Lingvay et al., 2022; Bull et al., 2022; Patel et al., 2023]. These effects are commonly transient and occur predominantly during the initial dose-escalation phase for both agents [Frias et al., 2021; Lingvay et al., 2022; Bull et al., 2022; Patel et al., 2023].

The Phase 3 SURPASS-2 head-to-head trial provides a direct evaluation of GI tolerability between tirzepatide (5 mg, 10 mg, and 15 mg) and semaglutide 1 mg over a 40-week period [Frias et al., 2021]. Reported incidence rates of key GI AEs were as follows: nausea (tirzepatide 17–22% vs. semaglutide 18%) [Frias et al.,

2021]; diarrhea (tirzepatide 13–16% vs. semaglutide 12%) [Frias et al., 2021]; and vomiting (tirzepatide 6–10% vs. semaglutide 8%) [Frias et al., 2021]. Although the overall GI profiles were largely comparable, some analyses noted a slightly higher rate of diarrhea in the tirzepatide 10 mg and 15 mg groups relative to semaglutide 1 mg [Scheen, 2023; Patel et al., 2023].

In trials evaluating obesity doses, indirect treatment comparisons (ITCs) of tirzepatide 10 mg and 15 mg versus semaglutide 2.4 mg suggested that tirzepatide 10 mg was associated with significantly lower odds of total GI AEs compared with semaglutide 2.4 mg, while tirzepatide 15 mg showed a non-significant trend toward lower GI AE incidence [Ciudin et al., 2025].

Treatment discontinuations due to AEs occurred in 6–9% of participants receiving tirzepatide (with higher rates in the 10 mg and 15 mg groups) and in 4% of those treated with semaglutide 1 mg in SURPASS-2 [Frias et al., 2021; Bull et al., 2022; Osumili et al., 2024]. GI events represented the leading cause of premature discontinuation for both therapies [Frias et al., 2021; Bull et al., 2022; Patel et al., 2023]. Importantly, post hoc analyses confirmed that tirzepatide's superior weight loss efficacy is primarily mediated by direct mechanisms—such as appetite suppression—rather than by GI adverse effects like nausea, vomiting, or diarrhea [Patel et al., 2023; Lingvay et al., 2022].

Cardiovascular and Vestibular Risks

Cardiovascular Safety: Semaglutide has a well-established record of cardiovascular (CV) benefit, having demonstrated a significant reduction in major adverse cardiovascular events (MACE) among adults with T2D and pre-existing cardiovascular disease [Reitzel et al., 2023]. Tirzepatide's CV safety profile, based on a pre-specified meta-analysis of SURPASS trials, indicates a favorable trend with fewer MACEs compared to pooled comparators (Hazard Ratio 0.80; 95% CI, 0.57–1.11) [Scheen, 2023; Nicholls et al., 2024; Forst et al., 2024; Bull et al., 2022]. The large-scale, prospective SURPASS-CVOT trial is currently in progress and directly compares tirzepatide with the GLP-1 receptor agonist dulaglutide [Scheen, 2023; Bull et al., 2022].

Both tirzepatide and semaglutide produced generally favorable effects on hemodynamic and lipid parameters. In SURPASS-2, mean pulse rate increases were modest and comparable between groups (2.2–2.6 bpm for tirzepatide vs. 2.5 bpm for semaglutide) [Frias et al., 2021]. Tirzepatide produced slightly greater reductions in systolic (−4.8 to −6.5 mmHg) and diastolic blood pressure (−1.9 to −2.9 mmHg) than semaglutide (−3.6 mmHg and −1.0 mmHg, respectively) [Frias et al., 2021].

Vestibular Disorders: Large real-world cohort analyses have recently explored the association between GLP-1 receptor agonists and incident vestibular disorders such as vertigo and dizziness [Toraih et al., 2025]. While both tirzepatide and semaglutide were linked to an elevated risk compared to matched controls, direct comparison revealed that semaglutide carried a higher relative risk than tirzepatide [Toraih et al., 2025]. This difference widened over time, with the semaglutide-to-tirzepatide risk ratio increasing from 1.53 at 6 months to 2.04 at 3 years [Toraih et al., 2025]. The dual GIP/GLP-1 receptor activity of tirzepatide, along with structural and lipophilic distinctions, may contribute to a comparatively protective or modulatory effect [Toraih et al., 2025].

Rare and Specific Adverse Events

Hypoglycemia: Both drugs show a low incidence of hypoglycemia, particularly in the absence of concomitant sulfonylurea or insulin use [Bull et al., 2022; Lingvay et al., 2022]. In SURPASS-2, clinically significant hypoglycemia (blood glucose <54 mg/dL) occurred in 0.6% (5 mg), 0.2% (10 mg), and 1.7% (15 mg) of tirzepatide-treated individuals, compared with 0.4% in the semaglutide group [Frias et al., 2021; Reitzel et al., 2023].

Pancreatitis and Thyroid Malignancies: The risk of rare but serious events is consistent with the class profile of GLP-1 receptor agonists. In SURPASS-2, only a few non-serious cases of pancreatitis were confirmed (two each in the tirzepatide 10 mg and 15 mg arms, and three in the semaglutide 1 mg arm) [Frias et al., 2021]. Across the SURPASS program, no cases of medullary thyroid carcinoma were observed, and no clinically meaningful elevations in mean calcitonin were detected [Frias et al., 2021; Forst et al., 2024]. Notably, patients with prior pancreatitis or medullary thyroid carcinoma were systematically excluded from these trials [Forst et al., 2024; Henney et al., 2025].

Other Adverse Events: In SURPASS-2, cases of cholelithiasis were reported in four participants from each tirzepatide group and in two from the semaglutide group [Frias et al., 2021]. Two cases of diabetic retinopathy were also recorded in the tirzepatide 10 mg arm [Frias et al., 2021]. Serious adverse events occurred in 5–7% of tirzepatide-treated participants and 3% of those on semaglutide [Frias et al., 2021]. Deaths were reported in both treatment groups, though none were deemed related to study medication [Frias et al., 2021].

Long-Term Safety Comparison

While short-term efficacy trials such as SURPASS-2 provide comparative safety data over 40 weeks, longer-term assessments of tirzepatide and semaglutide—particularly regarding sustained efficacy, adherence, and cumulative safety—are needed [Frias et al., 2021; Bull et al., 2022]. The ongoing SURPASS-CVOT trial, with its extensive duration and large sample size, aims to further clarify tirzepatide's cardiovascular safety profile [Scheen, 2023; Bull et al., 2022]. Considering the relatively short observation periods of pivotal studies (e.g., 40 weeks in SURPASS-2) [Frias et al., 2021], continuing real-world investigations—such as analyses assessing vestibular outcomes—are essential for delineating the long-term and real-world safety differences between these agents [Toraih et al., 2025].

Cardiometabolic Effects of Novel Incretin-Based Therapies

Obesity and Type 2 Diabetes Mellitus (T2DM) constitute a major global health burden, closely associated with a diverse range of cardiovascular and metabolic complications, including hypertension, dyslipidaemia, and cardiovascular disease (CVD) [Azuri et al., 2022; Forst et al., 2024; Hankosky et al., 2025]. Pharmacological agents that achieve modest but sustained weight reductions (typically 5–10% or more of baseline body weight) have been shown to yield clinically meaningful improvements in glycated haemoglobin (HbA1c), blood pressure, and lipid parameters [Baser et al., 2023; Osumili et al., 2024; Ciudin et al., 2024; Hankosky et al., 2025]. Among emerging incretin-based treatments, dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonists (GIP/GLP-1 RAs), such as tirzepatide, represent a major therapeutic advancement, offering pronounced weight loss alongside robust cardiometabolic benefits [Scheen, 2023; Al-Sabah et al., 2023; Toraih et al., 2025].

Impact on CVD, Major Adverse Cardiovascular Events (MACE), and Heart Failure with Preserved Ejection Fraction (HFpEF)

Both glucagon-like peptide-1 receptor agonists (GLP-1 RAs), such as semaglutide, and the dual GIP/GLP-1 RA tirzepatide—originally developed for glycaemic control in T2DM—have demonstrated notable cardiovascular benefits, largely attributable to their weight-reducing effects and improved metabolic regulation [Baser et al., 2023; Tang et al., 2025]. Evidence from clinical and real-world studies supports the role of these agents in reducing cardiovascular risk. A pre-specified meta-analysis confirmed tirzepatide's favorable cardiovascular safety profile throughout its clinical development program [Hoog et al., 2025; Scheen, 2023; Bull et al., 2022; Forst et al., 2024]. Additionally, a real-world retrospective cohort evaluating antiobesity medications (AOMs)—including semaglutide (Ozempic/Wegovy) and tirzepatide (Mounjaro)—found an 8% relative risk reduction in composite CVD outcomes compared to non-AOM users [Baser et al., 2023]. The use of these agents was also linked to a lower incidence of heart failure (4.89% vs. 6.13%) and atrial fibrillation (3.83% vs. 5.17%). In individuals with obesity but without T2DM, GLP-1 RA therapy was further associated with reduced risks of acute coronary syndrome (HR 0.70), heart failure (HR 0.81), and stroke (HR 0.66) compared with other AOMs [Tang et al., 2025]. Tirzepatide's definitive effect on MACE outcomes is currently being assessed in the ongoing phase 3 SURPASS-CVOT trial (NCT04255433) [Forst et al., 2024; Nicholls et al., 2024].

A particularly meaningful therapeutic advantage has been observed in heart failure with preserved ejection fraction (HFpEF), a condition commonly linked to obesity [Duhan et al., 2025]. A recent meta-analysis integrating data from the SUMMIT trial for tirzepatide and several semaglutide studies (e.g., STEP-HFpEF) demonstrated a consistent class benefit of GLP-1 RAs in patients with HFpEF and obesity [Duhan et al., 2025]. GLP-1 RA therapy significantly reduced heart failure exacerbations, with the composite endpoint of major adverse cardiovascular events (cardiovascular death or worsening heart failure) primarily driven by the decline in heart failure events [Duhan et al., 2025]. Treatment was associated with enhanced functional capacity, reflected by significant improvements in the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) and 6-minute walk test, corresponding with an approximate 10% body weight reduction observed across studies [Duhan et al., 2025].

Hepatic Effects: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) and Major Adverse Liver Outcomes (MALO)

The management of metabolic dysfunction-associated steatotic liver disease (MASLD, formerly NAFLD) and its inflammatory subtype, metabolic dysfunction-associated steatohepatitis (MASH, previously NASH), is of growing clinical importance, as both can advance to cirrhosis and severe liver-related outcomes (MALO) [Scheen, 2023; Henney et al., 2025]. MALO encompasses serious hepatic endpoints such as

compensated or decompensated cirrhosis, chronic liver failure, hepatocellular carcinoma, or liver transplantation [Henney et al., 2025].

Tirzepatide has demonstrated substantial hepatoprotective effects. In a substudy of the SURPASS-3 trial utilizing NMR imaging, tirzepatide significantly reduced visceral adipose tissue and hepatic fat content compared to basal insulin degludec [Scheen, 2023; Azuri et al., 2022; Forst et al., 2024]. The therapy also decreased circulating biomarkers indicative of MASH progression, including alanine and aspartate aminotransferases, keratin-18, and procollagen III [Forst et al., 2024; Bull et al., 2022]. Histologic assessments confirmed that tirzepatide achieved a higher rate of MASH resolution without worsening fibrosis relative to placebo among patients with moderate or severe fibrosis [le Roux et al., 2023; Henney et al., 2025].

Real-world comparative studies have reinforced these findings. A target trial emulation evaluating tirzepatide, semaglutide, and liraglutide versus DPP-4 inhibitors in T2DM populations revealed that tirzepatide significantly lowered the risk of incident MALO (Hazard Ratio [HR] 0.53, 95% CI 0.40–0.71) [Henney et al., 2025]. Semaglutide similarly reduced MALO risk, albeit to a lesser extent (HR 0.81, 95% CI 0.72–0.90) [Henney et al., 2025], while liraglutide did not demonstrate a comparable benefit (HR 1.04, 95% CI 0.79–1.36) [Henney et al., 2025]. The protective effect of tirzepatide and semaglutide was primarily attributed to reductions in both compensated and decompensated cirrhosis rates [Henney et al., 2025].

Potential Mechanisms of Beneficial Cardiometabolic Effects

The extensive cardiometabolic benefits conferred by dual GIP/GLP-1 RAs are linked to their distinctive pharmacodynamic profile, which promotes metabolic improvements surpassing those of selective GLP-1 RAs [Al-Sabah et al., 2023]. The principal driver of these effects is significant, sustained body weight reduction [Baser et al., 2023; Hankosky et al., 2025]. Tirzepatide consistently yields greater weight loss compared with semaglutide [le Roux et al., 2023; Vadher et al., 2022], primarily through mechanisms involving appetite suppression, enhanced satiety, and decreased caloric intake [Heise et al., 2023; Patel et al., 2023; Forst et al., 2024].

Beyond weight reduction, tirzepatide's dual receptor activation results in deeper metabolic remodeling. Notably, tirzepatide enhances insulin sensitivity more effectively per unit of weight loss than semaglutide [Tang et al., 2025; Mather et al., 2025; Nicholls et al., 2024], suggesting additive or synergistic effects arising from concurrent GIP and GLP-1 receptor stimulation [Forst et al., 2024].

This metabolic superiority manifests as substantial reductions in cardiovascular risk factors associated with metabolic syndrome (MetS) [Nicholls et al., 2024]. A post-hoc analysis of the SURPASS trials demonstrated that all tirzepatide doses markedly decreased the prevalence of MetS compared with placebo and active comparators (semaglutide 1 mg, insulin glargine, insulin degludec) [Nicholls et al., 2024]. These reductions correlated with the magnitude of body weight loss and included improvements in waist circumference, fasting glucose, triglyceride levels, and HDL cholesterol [Nicholls et al., 2024]. Tirzepatide also significantly reduced systolic blood pressure (SBP) and improved lipid profiles, including reductions in triglycerides and total cholesterol [Forst et al., 2024; Nicholls et al., 2024; Ciudin et al., 2025]. Furthermore, the hepatic benefits of tirzepatide are mechanistically linked to these systemic effects—specifically, to reductions in abdominal fat and improved insulin sensitivity, which collectively mitigate MASLD progression [Azuri et al., 2022; Forst et al., 2022; Al-Sabah et al., 2024].

Cost-effectiveness and Patient Perspective

The emergence of potent dual agonists such as tirzepatide (TZP) and selective GLP-1 receptor agonists such as semaglutide (SEMA) necessitates comprehensive economic evaluation to guide healthcare policy and optimize resource distribution [Papantoniou et al., 2025]. Standard frameworks for economic assessment include Cost-Utility Analysis (CUA), which quantifies outcomes in Quality-Adjusted Life Years (QALYs) and determines the Incremental Cost-Effectiveness Ratio (ICER) [Papantoniou et al., 2025; Betensky et al., 2025]. For analyses with shorter time horizons, more pragmatic indicators such as Cost of Control (CoC) and Cost Needed to Treat (CNT) are often applied [Papantoniou et al., 2025].

Economic Models and Comparative Cost-Effectiveness

Evidence from U.S.-based evaluations indicates that TZP may represent a more cost-efficient option for achieving rigorous clinical targets in Type 2 Diabetes (T2D) management [Mody et al., 2023]. Short-term analyses revealed that TZP at 10 mg and 15 mg doses had significantly lower costs per responder compared with SEMA 1 mg when achieving intensive glycaemic goals (HbA1c $\leq$ 6.5% and <5.7%) [Mody et al., 2023]. Across all evaluated doses, TZP demonstrated a statistically significant advantage in cost per responder for composite outcomes—defined as attainment of HbA1c targets combined with $\geq$10% weight loss and absence

of hypoglycemia—relative to SEMA 1 mg [Mody et al., 2023]. Long-term projections further suggest that TZP is likely to remain cost-effective compared with SEMA 1 mg for T2D treatment in the United States [Valentine et al., 2023]. In chronic weight management among patients with T2D, the CNT per 1% weight loss was substantially lower with TZP 15 mg ($985) compared to SEMA 2.4 mg ($1845) [Azuri et al., 2022].

However, cost-effectiveness outcomes differ considerably between regions due to local price structures and reimbursement systems [Mody et al., 2023]. A CoC evaluation across several European settings (Austria, the Netherlands, and Lithuania) found that SEMA 1 mg generally yielded greater economic value (lower CoC) than any TZP dose for composite T2D endpoints [Reitzel et al., 2023]. Conversely, a Greek analysis in the context of obesity treatment observed that while SEMA presented numerically lower CoC values at moderate weight loss thresholds (≥10% and ≥15%), TZP was favored at higher thresholds (≥20%, ≥25%, ≥30%); however, probabilistic sensitivity analysis showed no statistically significant difference in overall CoC between the two treatments [Papantoniou et al., 2025]. In contrast, a Chinese pharmacoeconomic evaluation concluded that TZP 5 mg and 10 mg were not cost-effective compared to SEMA 1 mg under local willingness-to-pay thresholds [Wang et al., 2025].

Patient Perspective, Adherence, and Accessibility

Therapeutic adherence and patient satisfaction are strongly influenced by the perceived balance between efficacy and tolerability [Gelhorn et al., 2023]. A discrete choice experiment (DCE) conducted among individuals with T2D identified reductions in HbA1c and body weight, alongside lower rates of nausea and hypoglycemia, as key factors shaping treatment preference [Gelhorn et al., 2023]. Based on these attributes, patients expressed a pronounced preference for the TZP profile compared with that of SEMA 1 mg [Gelhorn et al., 2023].

Regarding tolerability, gastrointestinal adverse events (GI AEs)—including nausea, vomiting, and diarrhea (N/V/D)—are characteristic of incretin-based therapies but typically remain mild to moderate in severity [Frias et al., 2021]. Importantly, data from the SURPASS program demonstrated that the majority of patients continued therapy despite GI symptoms, with discontinuation due to such events reported in only approximately 3% of participants [Patel et al., 2023].

Reimbursement and Access Considerations

Reimbursement outcomes and accessibility are largely determined by national Health Technology Assessment (HTA) frameworks, which often emphasize short-term payer perspectives and direct medical costs, particularly in systems such as Greece's EOPYY [Papantoniou et al., 2025]. Local drug pricing policies and reimbursement tariffs substantially influence cost-effectiveness results, accounting for regional discrepancies in economic favorability—whereby a therapy may appear cost-advantageous in the U.S. yet less so in certain European contexts [Mody et al., 2023].

Discussion

The rapidly advancing field of anti-diabetic and anti-obesity pharmacotherapy has positioned the dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 receptor agonist (GIP/GLP-1 RA) tirzepatide (TZP) as a benchmark for comparison against selective GLP-1 receptor agonists (GLP-1 RAs), most notably semaglutide (SEMA). The synthesis of current evidence, predominantly derived from randomized controlled trials (RCTs) and indirect treatment comparisons (ITCs), consistently demonstrates that the dual agonism of TZP confers superior efficacy across key metabolic endpoints relative to established GLP-1 RAs. The pivotal SURPASS-2 head-to-head trial showed that once-weekly TZP (5 mg, 10 mg, and 15 mg) achieved significantly greater reductions in glycated hemoglobin (HbA1c) and body weight than SEMA 1.0 mg in individuals with Type 2 Diabetes Mellitus (T2D) [Frias et al., 2021; Gelhorn et al., 2023]. These results translate into meaningful clinical benefit, as post hoc analyses across the SURPASS program confirmed that TZP markedly increased the proportion of participants attaining stringent composite outcomes—such as achieving HbA1c <7.0% or ≤6.5% while concurrently reaching ≥5% or ≥10% weight loss without hypoglycemia [Lingvay et al., 2022]. Moreover, exploratory analyses demonstrated that TZP-treated participants sustained these composite goals for a considerably longer proportion of study duration than those on SEMA 1.0 mg (median 35%–60% vs. 7%) [Bergman et al., 2025]. Mechanistically, TZP's enhanced efficacy is attributed to its pronounced effects on reducing energy intake and fat mass [Heise et al., 2023], supported by exploratory data indicating greater improvement in insulin sensitivity per unit of weight loss compared with SEMA [Tang et al., 2025]. Beyond primary endpoints, TZP exerts broad cardiometabolic benefits, including a significant reduction in the prevalence of metabolic syndrome across the SURPASS trials [Nicholls et al., 2024].

The overall safety and tolerability profile of TZP is broadly comparable to that of SEMA and other incretin-based therapies, with gastrointestinal adverse events (GI AEs)—including nausea, vomiting, and diarrhea—being the most frequent side effects [Frias et al., 2021; Hankosky et al., 2025]. In SURPASS-2, discontinuation rates due to adverse events were somewhat higher for TZP (6.0%–8.5%) than for SEMA 1.0 mg (4.1%) [Frias et al., 2021]. Nonetheless, pooled analyses from the SURPASS program confirm that TZP's robust weight loss efficacy occurs independently of gastrointestinal symptom occurrence, suggesting that these effects are mechanistically distinct [Lingvay et al., 2022; Patel et al., 2023]. Real-world evidence further indicates that both TZP and SEMA are associated with reduced risk of incident Major Adverse Liver Outcomes (MALO)—including decompensated cirrhosis—compared with dipeptidyl peptidase-4 inhibitors (DPP4i) among patients with T2D, with TZP showing a stronger association (TZP Hazard Ratio [HR] 0.53 [95% CI 0.40–0.71]; SEMA HR 0.81 [95% CI 0.72–0.90]) [Henney et al., 2025]. From an economic standpoint, early analyses assessing the cost per percentage of weight loss in the U.S. demonstrated that TZP offered greater value for achieving 1% body weight reduction ($985 for TZP vs. $1845 for SEMA) [Azuri et al., 2022].

Despite the compelling evidence from direct head-to-head comparisons with SEMA 1.0 mg, a major limitation of the current evidence base is the scarcity of direct data comparing higher doses of TZP (10 mg and 15 mg) with the obesity-approved dose of SEMA (2.4 mg). Such comparisons are largely derived from pivotal obesity trials—SURMOUNT-1/2 and STEP 1/2—using Indirect Treatment Comparisons (ITCs) based on the Bucher method or Matching-Adjusted Indirect Comparison (MAIC) [le Roux et al., 2023; Vadher et al., 2022; Hankosky et al., 2025]. The reliance on ITCs inherently introduces potential residual confounding due to unmeasured inter-trial differences [Osumili et al., 2024; Hankosky et al., 2025]. For example, discrepancies in trial duration (e.g., 72 weeks for SURMOUNT-1/2 vs. 68 weeks for STEP 1/2) [le Roux et al., 2023; Hankosky et al., 2025], demographic composition (e.g., ethnic distribution), and concomitant medication use contribute to interpretive limitations [Osumili et al., 2024; Ciudin et al., 2025; Hankosky et al., 2025]. Additionally, formal quantitative comparisons of safety outcomes (e.g., severe GI AEs) are typically avoided in ITCs due to inconsistencies in adverse event collection methods (e.g., self-reported vs. standardized assessment) [Ciudin et al., 2025; le Roux et al., 2023; Vadher et al., 2022]. Furthermore, many of the analyses illustrating TZP's durability and magnitude of effect—such as composite goal achievement or time in control—are post hoc and exploratory, thus considered hypothesis-generating given the lack of multiplicity adjustment [Lingvay et al., 2022; Bergman et al., 2025].

The robust efficacy and consistent clinical benefits observed with TZP position it as a promising therapeutic option for patients requiring intensive glycemic management coupled with substantial weight reduction. Ongoing research is directed toward generating definitive long-term, head-to-head evidence to overcome current limitations. The SURMOUNT-5 trial (NCT05822830), a direct randomized controlled comparison of TZP 10/15 mg versus SEMA 2.4 mg in individuals with obesity but without T2D, is expected to provide conclusive evidence superseding current ITC data [Trinh et al., 2025; Hankosky et al., 2025]. Likewise, the ongoing SURPASS-CVOT trial is pivotal for establishing TZP's long-term cardiovascular outcomes, paralleling the favorable findings already documented for SEMA in studies such as SELECT and aggregated data from FLOW and STEP-HFpEF [Nicholls et al., 2024; Duhan et al., 2025; Tang et al., 2025]. Furthermore, the SUMMIT trial is designed to evaluate TZP's cardiorenal effects in heart failure populations [Duhan et al., 2025]. Collectively, these forthcoming data, in conjunction with long-term modeling analyses projecting sustained metabolic benefits and reduced diabetes complications over a five-year horizon [Niu et al., 2023; Bergman et al., 2025], are anticipated to further establish dual GIP/GLP-1 receptor agonism as a cornerstone in the comprehensive management of T2D and obesity.

Conclusions

The integration of key clinical evidence, primarily from studies directly comparing the dual GIP/GLP-1 receptor agonist tirzepatide (TZP) with the selective GLP-1 receptor agonist semaglutide (SEMA), demonstrates that TZP offers superior metabolic efficacy in the management of Type 2 Diabetes Mellitus (T2D) and obesity [Frias et al., 2021; Scheen, 2023; Bull et al., 2022]. Head-to-head investigations, including the pivotal SURPASS-2 trial, have conclusively shown that all evaluated doses of once-weekly TZP (5 mg, 10 mg, and 15 mg) produced significantly greater reductions in glycated hemoglobin (HbA1c) and body weight compared with once-weekly SEMA 1.0 mg in patients with T2D [Frias et al., 2021; Trinh et al., 2025; Mody et al., 2023; Hoog et al., 2025; Osumili et al., 2024]. Consistent post hoc analyses across the SURPASS program further indicate that TZP-treated individuals were substantially more likely to achieve demanding composite endpoints—simultaneously meeting stringent glycemic thresholds (HbA1c ≤6.5% or <5.7%) and

significant weight loss targets (≥5%, ≥10%, or ≥15%) without hypoglycemia [Lingvay et al., 2022]. Moreover, exploratory findings revealed that TZP enabled participants to maintain these composite goals for a markedly longer continuous duration compared with SEMA 1.0 mg (median 35%–60% vs. 7% of the study period achieving HbA1c ≤6.5% with ≥5% weight reduction) [Bergman et al., 2025].

The enhanced clinical outcomes associated with TZP are mechanistically explained by its dual GIP/GLP-1 receptor activation, which appears to exert synergistic metabolic effects surpassing those of selective GLP-1 receptor agonism [Scheen, 2023; le Roux et al., 2023; Hankosky et al., 2025]. Mechanistic investigations have shown that TZP elicits greater reductions in fasting appetite, satiety, and fullness scores relative to SEMA 1 mg, correlating with decreased energy intake and a pronounced reduction in fat mass [Al-Sabah et al., 2024; Forst et al., 2024]. Additionally, exploratory analyses suggest that TZP may deliver superior improvements in insulin sensitivity per unit of weight loss compared with SEMA [Tang et al., 2025]. From a tolerability standpoint, both agents share a predictable and largely transient safety profile characterized mainly by mild to moderate gastrointestinal adverse events (GI AEs) such as nausea, diarrhea, and vomiting [Frias et al., 2021; Hoog et al., 2025]. Importantly, pooled safety analyses from the SURPASS trials have demonstrated that TZP-induced weight reduction occurred independently of self-reported GI AEs, indicating that the weight loss effect is not mediated by intolerance [Lingvay et al., 2022; Patel et al., 2023]. Beyond glycemic and weight endpoints, TZP also conferred notable cardiometabolic advantages, significantly decreasing the proportion of patients meeting diagnostic criteria for metabolic syndrome compared with SEMA 1.0 mg and other comparators [Nicholls et al., 2024]. Furthermore, real-world emulation studies have indicated that both SEMA and TZP are associated with a reduced incidence of Major Adverse Liver Outcomes (MALO), particularly decompensated cirrhosis, compared with dipeptidyl peptidase-4 inhibitors (DPP4i) among patients with T2D [Henney et al., 2025]. Preliminary pharmacoeconomic evaluations reveal mixed findings: while TZP demonstrated greater cost-efficiency in achieving clinically meaningful weight reduction (Cost Needed to Treat [CNT] for 1% weight loss: ≈$985 for TZP vs. ≈$1845 for SEMA in U.S. settings) [Azuri et al., 2022], multinational cost analyses indicated that SEMA 1 mg achieved the lowest cost per 1% HbA1c reduction in selected European and Middle Eastern markets [Reitzel et al., 2023].

Collectively, these data position dual GIP/GLP-1 receptor agonists as high-efficacy pharmacologic options, particularly for patients with T2D or obesity requiring intensive glycemic and weight management. Nonetheless, a significant evidence gap persists due to the absence of definitive head-to-head Randomized Controlled Trials (RCTs) comparing the highest approved doses of TZP (10 mg and 15 mg) directly against SEMA 2.4 mg, which is indicated for chronic weight management [le Roux et al., 2023; Vadher et al., 2022; Ciudin et al., 2025; Hankosky et al., 2025]. Current comparative data at maximal dosing levels therefore rely predominantly on Indirect Treatment Comparisons (ITCs) [le Roux et al., 2023; Vadher et al., 2023; Hankosky et al., 2025], employing methodologies such as Matching-Adjusted Indirect Comparison (MAIC) or the Bucher approach [Vadher et al., 2022; le Roux et al., 2023; Hankosky et al., 2025]. However, such analyses remain subject to potential residual confounding and between-trial heterogeneity, including differences in study duration, baseline demographics, and concomitant therapies (e.g., SURMOUNT-1/2 vs. STEP 1/2) [le Roux et al., 2023; Vadher et al., 2022; Ciudin et al., 2025]. To address this limitation, the ongoing SURMOUNT-5 trial (NCT05822830)—a direct, head-to-head RCT comparing TZP and SEMA 2.4 mg in individuals with obesity without T2D—is expected to yield conclusive evidence regarding their relative weight efficacy [Hankosky et al., 2025; Trinh et al., 2025]. Moreover, long-term outcome studies remain essential for fully delineating TZP's cardiometabolic impact: results from the SURPASS-CVOT trial will clarify its cardiovascular safety profile [Forst et al., 2024], while the SUMMIT trial is anticipated to provide critical data on TZP's efficacy in patients with heart failure with preserved ejection fraction (HFpEF) [Duhan et al., 2025]. Future research priorities include determining optimal weight maintenance strategies following goal achievement, assessing potential excessive lean mass reduction associated with these agents [Forst et al., 2024], and defining their therapeutic role in specific clinical subgroups such as patients with nonalcoholic fatty liver disease (NAFLD) [Henney et al., 2025] or post-bariatric surgery weight regain [Forst et al., 2024].

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