Review

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A narrative review on tirzepatide's therapeutic potential in glycemic control and cardioprotection

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Abstract

Tirzepatide, a dual glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist, represents a new class of incretin-based therapy for type 2 diabetes mellitus (T2DM), obesity, and related comorbidities. This narrative review synthesizes evidence from the SURPASS, SURMOUNT, and SUMMIT clinical trial programs. Across studies, tirzepatide reduced glycated hemoglobin (HbA1c) by up to 2.5% and body weight by more than 20%. It also improved cardiovascular risk factors (blood pressure, lipids, inflammation) and has demonstrated benefits in patients with heart failure with preserved ejection fraction (HFpEF) and obstructive sleep apnea (OSA), with reductions in the apnea-hypopnea index (AHI) and heart failure hospitalizations. Its safety profile is consistent with that of GLP-1 receptor agonists (GLP-1 RAs), although gastrointestinal side effects, gallbladder events, and thyroid cancer signals warrant monitoring. Ethical concerns related to off-label use, weight regain after discontinuation, and barriers to real-world access remain active issues. Ongoing outcome trials and real-world data will clarify its long-term role and potential integration into future clinical guidelines.

Keywords: cardioprotection, dual incretin agonist, glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP)

Introduction

Metabolic diseases such as type 2 diabetes mellitus (T2DM) and obesity are closely linked to cardiovascular disease (CVD), leading to a global epidemic of morbidity and mortality[1,2]. Despite advances in treatment, many patients still struggle to achieve adequate glycemic control, weight loss, and risk factor reduction[3]. Metabolic and cardiovascular complications (e.g., atherosclerosis and heart failure) remain the leading causes of death worldwide. There is an urgent need for therapies that address multiple aspects of this cardiometabolic syndrome, such as improving blood glucose levels, reducing body weight, and mitigating cardiovascular risk[4,5].

In recent years, incretin-based therapies (such as glucagon-like peptide-1 (GLP-1) receptor agonists) have transformed the management of T2DM by improving glycemic control, promoting weight loss, and reducing cardiovascular risk[6]. Tirzepatide is a novel agent that expands this paradigm. It is a first-in-class dual incretin agonist, often termed a "twincretin," that activates both the GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors[7]. Through this dual mechanism, tirzepatide has demonstrated superior metabolic outcomes, including greater reductions in HbA1c and body weight compared to conventional therapies[8].

Tirzepatide, under the brand name Mounjaro, was first approved in 2022 for adults with T2DM as an adjunct to diet and exercise[8]. In late 2023, the Food and Drug Administration (FDA) approved tirzepatide under the brand name Zepbound for chronic weight management in adults with obesity [Body Mass Index (BMI)

HIGHLIGHTS

- Tirzepatide, a dual GIP and GLP-1 receptor agonist, shows unprecedented glycemic and weight-loss benefits in patients with type 2 diabetes and obesity.
- FDA approvals now include treatment for type 2 diabetes, chronic weight management, and obstructive sleep apnea, expanding its therapeutic footprint.
- Tirzepatide has shown to improve cardiometabolic markers including blood pressure, lipid profile, inflammation, and cardiovascular risk scores.
- Safety concerns include gastrointestinal side effects, potential gallbladder disease, and thyroid neoplasia, warranting close monitoring.
- Real-world data confirm sustained efficacy across diverse populations and suggest promising long-term metabolic benefits.

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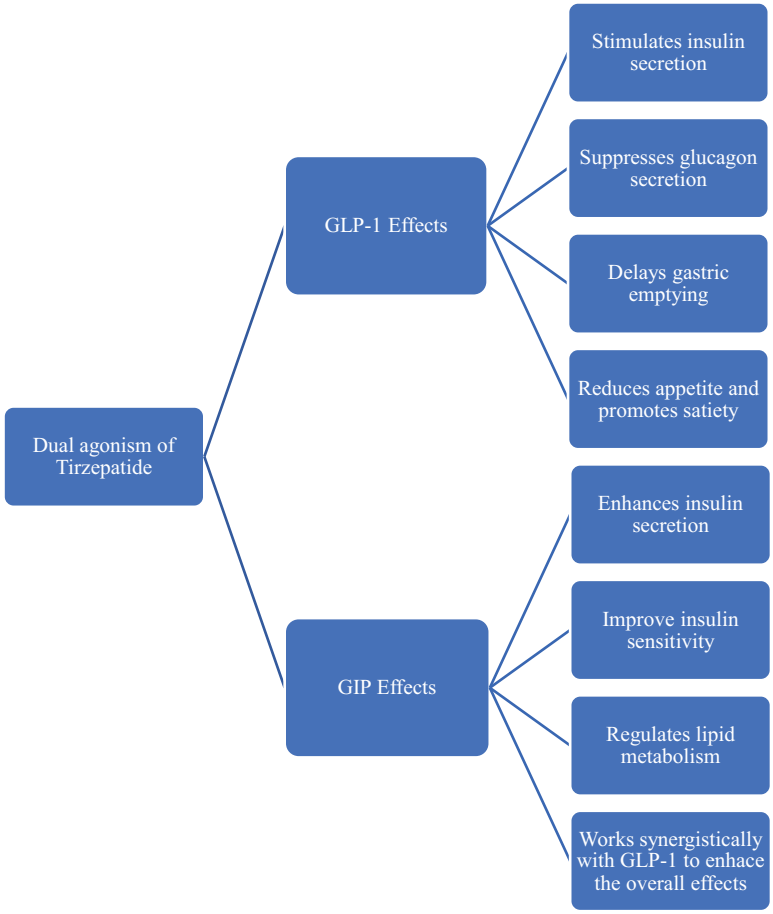

Figure 1. Mechanism of action of tirzepatide.

≥30] or overweight (BMI ≥27 with at least one weight-related condition). Zepbound was also approved in December 2024 for the treatment of moderate to severe obstructive sleep apnea (OSA) in adults with obesity[9]. These successive approvals highlight tirzepatide's evolving role as not only a diabetes therapy but also a comprehensive metabolic intervention.

Tirzepatide is a synthetic 39-amino acid peptide engineered to activate both GLP-1 and GIP receptors, influencing pancreatic islet function, gut motility, and brain appetite centers[10]. Figure 1 illustrates this mechanism. Administered as a once-weekly subcutaneous injection at doses of 5, 10, or 15 mg, tirzepatide represents a novel class of antidiabetic agents with the potential to address the

Table 1

Summary of key study design features, populations, comparators, and durations of major tirzepatide trials (SURPASS, SURMOUNT, SUMMIT)

Trial	Design	Duration	Population	Sample size	Primary endpoint
SURPASS-1[12]	Phase 3, double-blind RCT	40 weeks	T2DM (drug-naïve)	478	Change in HbA1c
SURPASS-2[13]	Phase 3, open-label RCT	40 weeks	T2DM (on metformin)	1879	Change in HbA1c
SURPASS-3[14]	Phase 3, open-label RCT	52 weeks	T2DM (on oral meds ± SGLT2i)	1444	Change in HbA1c
SURPASS-4[15]	Phase 3, open-label RCT	52 weeks	T2DM with high CV risk	2002	Change in HbA1c
SURPASS-5[16]	Phase 3, double-blind RCT	40 weeks	T2DM on insulin glargine	475	Change in HbA1c
SURMOUNT-1[11]	Phase 3, double-blind RCT	72 weeks	Obesity (no diabetes)	2539	Percent weight loss
SURMOUNT-2[17]	Phase 3, double-blind RCT	72 weeks	Obesity + T2DM	938	Percent weight loss
SURMOUNT-3[18]	Phase 3, double-blind RCT	72 weeks (12-week lifestyle intervention lead in)	Obesity (after diet/exercise lead-in)	806	Weight maintenance and loss
SURMOUNT-4[19]	Phase 3, double-blind RCT	88 weeks (36-week tirzepatide lead in	Obesity (maintenance study)	783	Sustained weight loss
SUMMIT[20]	Phase 3, double-blind RCT	52 weeks	HFpEF + Obesity	1100	CV death or HF hospitalization

Reference numbers in brackets correspond to the main manuscript reference list.

multisystem complications of diabetes[11]. This review synthesizes evidence from various clinical trials to evaluate tirzepatide's efficacy, safety, and therapeutic potential in the treatment of T2DM, obesity, cardiovascular disease, and related metabolic disorders. Table 1 includes the summary of key study design features, populations, comparators, and durations of major tirzepatide trials (SURPASS, SURMOUNT, SUMMIT).

Methods

This narrative review was conducted by searching the PubMed, Scopus, and Google Scholar databases for relevant articles published between January 2019 and April 2025. Keywords included "Tirzepatide," "GIP/GLP-1 agonist," "SURPASS," "SURMOUNT," "obesity," "type 2 diabetes," "heart failure," "cardiometabolic," and "obstructive sleep apnea." Peer-reviewed randomized controlled trials, meta-analyses, and major guidelines were prioritized. Additional sources were identified through citation tracking (manually screening reference lists of included papers and reviews) and examination of the relevant clinical trial registries (e.g., ClinicalTrials.gov). Studies were excluded if they were not in English, lacked peer review, or consisted solely of case reports, preclinical models, or conference abstracts. When conflicting data were present, we prioritized high-quality evidence (e.g., larger trials, more recent meta-analyses), and confirmed by independent screening by two authors. No formal risk of bias tool was used, but study design and quality were considered in evaluating findings. This review adheres to the 2025 TITAN Guidelines on the transparent and responsible use of artificial intelligence in scholarly writing and authorship practices[21] (Fig. 2).

Tirzepatide in type 2 diabetes mellitus

Tirzepatide's efficacy in T2DM has been evaluated in the SURPASS program, a series of large, global, multicenter phase 3 randomized controlled trials (RCTs; Table 2). Across these trials, participants received once-weekly tirzepatide at doses of 5, 10, or 15 mg and were compared against placebo or active comparators[12–16].

In terms of glycemic control, tirzepatide consistently achieved robust reductions in glycated hemoglobin (HbA1c), typically ranging from 1.5 to 2.5% with the 15 mg dose yielding ~2.3–2.5% reductions. In SURPASS-1, a double-blind, placebo-controlled trial, patients achieved a mean HbA1c decrease of about 2.07% with tirzepatide 15 mg[12]. SURPASS-2 directly compared tirzepatide with semaglutide 1 mg and found tirzepatide to be superior, with reductions of 2.46% versus 1.86%, respectively[13]. Similarly, SURPASS-3 demonstrated superiority over insulin degludec[14], while SURPASS-4 showed greater efficacy than insulin glargine in patients with high cardiovascular risk[15]. Finally, SURPASS-5, which evaluated tirzepatide as an add-on to insulin glargine, reported HbA1c reductions of approximately 2.59%[16].

Tirzepatide also produced consistent, dose-dependent weight loss across the SURPASS program. On average, participants lost approximately 5.0 kg with the 5 mg dose and 11–12 kg with the 15 mg dose. In SURPASS-2, weight loss with tirzepatide 15 mg was particularly notable, averaging 11.2 kg compared with 5.7 kg for semaglutide 1 mg[12]. In comparison, older diabetes agents such as insulin or sulfonylureas are associated with weight gain, and even GLP-1 receptor agonists typically produce weight loss in the 4–6 kg range, except for high-dose semaglutide[22].

Despite the compelling results of the SURPASS program, several limitations must be considered. The majority of trials were of 40–52 week duration, meaning that the long-term durability of glycemic and weight benefits remains uncertain. Moreover, cardiovascular outcomes were not designated as primary endpoints, limiting the ability to draw firm conclusions regarding event reduction. Finally, study populations often excluded patients with severe renal or hepatic dysfunction, making the generalizability of findings to these groups less certain.

Tirzepatide in obesity and weight-related outcomes

Encouraged by substantial weight loss in patients with diabetes, SURMOUNT trials evaluated tirzepatide in people with obesity, with or without diabetes[11]. The SURMOUNT-1 trial enrolled adults with obesity (or overweight with comorbidities) without diabetes and treated them with tirzepatide 5, 10, or 15 mg versus placebo for 72 weeks. The results, published in 2022, are notable, with average weight reductions of 16% (5 mg), 21.4% (10 mg), and 22.5% (15 mg) of initial body weight, compared to ~2.4% with placebo[11].

The SURMOUNT-2 trial focused on participants with obesity plus T2DM. SURMOUNT-2 showed an average weight reduction of ~15% in body weight with tirzepatide 15 mg over 72 weeks[17]. In addition, glycemic control improved markedly; baseline HbA1c ~8.0% improved to ~5.9% at 72 weeks, and about half of the participants were able to reach normal HbA1c levels (<5.7%) without significant hypoglycemia[17]. SURMOUNT-3 showed that adding tirzepatide after an initial diet-and-exercise program can yield significant additional weight reduction (averaging 20–25% of body weight)[18].

While tirzepatide has demonstrated substantial and sustained weight loss during active treatment, emerging data underscore the challenge of weight regain upon cessation. The SURMOUNT-4 trial specifically evaluated this by incorporating a 36-week open-label tirzepatide run-in phase (10 or 15 mg weekly), after which participants were randomized to either continue tirzepatide or switch to placebo for an additional 52 weeks. Those who discontinued tirzepatide experienced a mean weight regain of 14% of initial body weight, effectively reversing over half of the weight lost during active treatment[19]. In contrast, participants who continued tirzepatide maintained or even slightly increased their weight loss, achieving a total mean reduction of 27.1% over the full 88 weeks[19]. These findings suggest that chronic or maintenance dosing may be necessary to sustain weight loss. Future research is needed to evaluate optimal maintenance strategies, such as dose tapering, re-initiation thresholds, or integration with structured lifestyle and behavioral support programs to minimize regain while reducing long-term medication burden.

Table 2 summarizes the amount of weight loss and HbA1c reduction at various tirzepatide doses across different trials compared to placebo and other medications. Weight loss seen in these trials rivaled the outcomes of metabolic surgery which typically result in 25–30% weight reduction[23], and high-dose semaglutide (2.4 mg) which resulted in ~15.3 kg mean weight reduction compared to placebo in STEP 1 trial[22]. Participants on tirzepatide showed significant reductions in waist circumference, blood pressure (BP), triglycerides, and markers of inflammation (like C-reactive protein) compared to placebo (Table 3).

TITAN Guideline Checklist 2025			
Topic	**Item**	**Description**	**Page number**
Artificial Intelligence (AI) (some journals may prefer this in the methods and/or acknowledgments section and it should also be declared in the cover letter)	1	**Declaration of whether any AI was used in the research and manuscript development** **State no, if that's the case.** **If yes, proceed to item 1a.**	Not used
	1a	**Purpose and Scope of AI Use** - Precisely state why AI was employed (e.g. development of research questions, language drafting, statistical analysis/summarisation, image annotation, etc). - Was generative AI utilised and if so, how? - Clarify the stage(s) of the reporting workflow affected (planning, writing, revisions, figure creation). - Confirmation that the author(s) take responsibility for the integrity of the content affected/generated	Not used
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	1d	**Human Oversight and Verification** - Identify the supervising author(s) who reviewed every AI output. - Detail the process for fact-checking, clinical accuracy checks - State whether any AI-generated text/figures were edited or discarded. - Acknowledge the limitations of AI and its use	Not used
	1e	**Bias, Ethics and Regulatory Compliance** - Outline steps taken to detect and mitigate algorithmic bias (e.g. cross-checking against under-represented populations). - Affirm adherence to relevant ethical frameworks. - Disclose any conflicts of interest or financial ties to AI vendors.	Not used
	1f	**Reproducibility and Transparency** - Provide the exact prompts or code snippets (as supplementary material if lengthy). - Supply version-controlled logs or model cards where possible. - if applicable, state repository, hyperlink or digital object identifier (DOI) where AI-generated artefacts can be accessed, enabling attempts at independent replication of the query/input.	Not used

Figure 2. TITAN guideline checklist 2025.

Although randomized trials have demonstrated efficacy in controlled settings, real-world data is increasingly supportive. A large real-world retrospective study of over 4000 U.S. patients without diabetes who were prescribed tirzepatide for weight management found an average weight loss of nearly 13% of body weight in 6 months[24]. Similarly, in patients with T2DM,

Table 2

Average weight loss (kg) and HbA1c reduction at different tirzepatide doses across SURPASS and SURMOUNT trials

Trial	Parameter	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Comparator
SURPASS-1[12]	Weight ↓	−7.0 kg	−7.8 kg	−9.5 kg	Placebo: − 0.7 kg
	HbA1c ↓	1.87%	2.00%	2.07%	
SURPASS-2[13]	Weight ↓	−7.6 kg	−9.3 kg	−11.2 kg	Semaglutide 1 mg: −5.7 kg
	HbA1c ↓	2.09%	2.37%	2.46%	
SURPASS-3[14]	Weight ↓	−7.5 kg	−10.7 kg	−12.9 kg	Insulin degludec: +2.3 kg
	HbA1c ↓	2.07%	2.37%	2.43%	
SURPASS-4[15]	Weight ↓	−7.1 kg	−9.5 kg	−11.7 kg	Insulin glargine: +1.9 kg
	HbA1c ↓	2.43%	2.58%	2.59%	
SURPASS-5[16]	Weight ↓	−5.4 kg	−7.5 kg	−8.8 kg	Placebo: +1.6 kg
	HbA1c ↓	1.93%	2.20%	2.34%	
SURMOUNT-1[11]	Weight ↓	−16.1 kg	−22.2 kg	−23.6 kg	Placebo: −2.4 kg
	HbA1c ↓	N/A	N/A	N/A	
SURMOUNT-2[17]	Weight ↓	N/A	−13.5 kg	−15.6 kg	Placebo: −3.2 kg
	HbA1c ↓	N/A	~1.9%	2.1%	
SURMOUNT-3[18]	Weight ↓	N/A	N/A	−22.8 kg[a]	Placebo: −3.5 kg
	HbA1c ↓	N/A	N/A	N/A	
SURMOUNT-4[19]	Weight ↓	N/A	N/A	−27.1 kg[a]	Placebo after tirzepatide lead-in: −10.6 kg
	HbA1c ↓	N/A	N/A	N/A	

[a]MTD, Maximum Tolerated Dose (typically 10 or 15 mg, titrated individually).
Reference numbers in brackets correspond to the main manuscript reference list.

tirzepatide has shown >10% weight reduction in a significant proportion of users by 6–12 months, along with substantial A1c declines (often bringing patients to goal A1c <7%). Additionally, real-world data suggest that its effectiveness is sustained across diverse populations, including those with long-standing diabetes and those previously treated with insulin or GLP-1 receptor agonists (GLP-1 RAs)[24].

Tirzepatide in obstructive sleep apnea

In December 2024, the FDA approved tirzepatide (Zepbound) as the first pharmacologic therapy for moderate-to-severe OSA in adults with obesity to be used in combination with diet and exercise[9]. This approval makes tirzepatide the first drug treatment option for OSA in this patient population.

SURMOUNT-OSA, a phase 3 randomized controlled study, enrolled adults with moderate-to-severe OSA and obesity[9]. Key findings from this 52-week trial include a substantial reduction in the apnea-hypopnea index (AHI) and the number of breathing interruptions per hour, compared to placebo. After 52 weeks, patients taking tirzepatide (10 mg or 15 mg) had approximately 20–24 fewer apnea/hypopnea events per hour than at baseline, whereas placebo patients had only ~5 fewer events/hour[9]. This amounted to a 50–60% reduction in AHI with tirzepatide versus minimal change with placebo, a highly significant improvement ($P < 0.001$)[9].

As expected from a weight-management drug, tirzepatide led to pronounced weight reduction. Participants treated with tirzepatide lost approximately 16–20% of their body weight (~45–50 lbs) over the year, versus only ~2% (~4–6 lbs) in the placebo

Table 3

Summary of key metabolic and cardiovascular outcomes with tirzepatide reported in phase 3 clinical trials

Effect	Magnitude of Change	Duration	Dose (mg, weekly)	Population	Study
HbA1c reduction (%)	−1.5% to −2.5%	40–52 weeks	5, 10, 15 mg (weekly)	Adults with T2DM	SURPASS 1-5[12–16]
Fasting plasma glucose reduction (mg/dl)	−50 to −60 mg/dl	40–52 weeks	5, 10, 15 mg (weekly)	Adults with T2DM	SURPASS 1-5[12–16]
Weight loss (kg)	−5.4 to −25 kg	40–72 weeks	5, 10, 15 mg (weekly)	T2DM and non-T2DM obese patients	SURPASS 1-5[12–16], SURMOUNT 1-4
≥10% Weight loss (% of patients)	~60% (at 15 mg in SURMOUNT-1)	72 weeks	15 mg (weekly)	Obesity (non-diabetic)	SURMOUNT-1[11]
Waist circumference reduction (cm)	−9 to −13 cm	72 weeks	10, 15 mg (weekly)	Obesity (non-diabetic)	SURMOUNT-1[11]
Systolic BP (mmHg)	−6.8 to −7.2 mmHg	24–72 weeks	5, 10, 15 mg (weekly)	Obesity (non-diabetic)	SURMOUNT-1[11]
LDL cholesterol (%)	−5.8%	72 weeks	15 mg (weekly)	Obesity (non-diabetic)	SURMOUNT-1[11]
Triglycerides (%)	−24.8%	72 weeks	15 mg (weekly)	Obesity (non-diabetic)	SURMOUNT-1[11]
CRP reduction (%)	−38.8 %	52 weeks	15 mg (weekly)	Obesity with HFpEF	SUMMIT[20]
Troponin T reduction (%)	−10.2%	52 weeks	15 mg (weekly)	Obesity with HFpEF	SUMMIT[20]

Reference numbers in brackets correspond to the main manuscript reference list.

group. This degree of weight loss is likely the primary driver of OSA improvement regardless of whether patients use continuous positive airway pressure (CPAP)[9]. The clinical implications of AHI reduction include lower daytime sleepiness, improved cognitive function and mood, decreased BP and cardiovascular risk, and potentially reduced CPAP dependence or improved adherence among dual users.

However, there are several limitations to consider. The trial population consisted exclusively of individuals with obesity (BMI ≥30), which limits the generalizability of findings to normal-weight or lean patients with OSA. In addition, CPAP use was not uniformly controlled; most participants were either non-users or non-adherent at baseline. As a result, further studies are needed to clarify whether tirzepatide should be considered primarily as a complement to, or potential alternative for, CPAP therapy. Finally, although the trial demonstrated significant improvements in the AHI, the long-term durability of these benefits, and whether they translate into reduced cardiovascular events or mortality remains uncertain. Longer follow-up studies and post-marketing surveillance will be essential to answer these questions.

Despite these limitations, tirzepatide represents a paradigm shift in OSA management: for the first time, a medication targets the metabolic root cause rather than bypassing the anatomic consequences. Given the shared pathophysiology of cardiometabolic diseases, it is essential to examine its role in cardiovascular health and prevention.

Cardiovascular benefits

Atherosclerosis and cardiovascular risk factors

A post hoc analysis of SURMOUNT-1 calculated each participant's 10-year atherosclerotic cardiovascular disease (ASCVD) risk at baseline and after 72 weeks. They found that tirzepatide treatment significantly reduced the 10-year predicted risk of cardiovascular events compared with placebo[25]. For instance, in the tirzepatide 10 mg group, the estimated 10-year risk dropped by ~23.5% (from ~1.5 to ~1.1%), whereas the placebo group's risk slightly increased. The absolute risk reductions were greatest among those who had a higher baseline risk[25].

Hypertension

A post hoc analysis of the SURMOUNT-1 trial found that tirzepatide treatment was associated with a reduction in systolic and diastolic BP over the first 24 weeks, followed by BP stabilization until the end of the observation period, resulting in a significant net reduction by 72 weeks of 6.8 mm Hg systolic and 4.2 mm Hg diastolic BP versus placebo[26]. Participants randomly assigned to any tirzepatide group were more likely than those assigned to placebo to have normal BP at week 72 (58.0% vs 35.2%, respectively). Additionally, by 72 weeks, compared to placebo, there was a greater reduction in the proportion of tirzepatide participants with stage 1 or 2 hypertension[26].

A 2023 meta-analysis by Kanbay *et al* of seven randomized control trials found that 5, 10, and 15 mg of tirzepatide administered once weekly resulted in clinically significant decreases in systolic BPs of median −4.20, −5.34, and −5.77 mmHg, respectively, as well as significant decreases in total cholesterol and triglycerides with increased high-density lipoprotein (HDL) cholesterol levels[27].

Lipid profile

Lipid changes included reductions in triglycerides and small improvements in low-density lipoprotein (LDL) and HDL levels (Table 3). A meta-analysis by Mahar *et al* (2024) demonstrated dose-dependent reductions in total cholesterol, LDL, and triglycerides, and increased HDL compared to placebo[28]. However, a comparison with GLP-1 receptor agonists revealed no significant superiority[28].

Inflammation and endothelial dysfunction

Tirzepatide-treated patients showed lower levels of inflammatory markers, which likely reflects reduced adipose tissue inflammation and possibly the direct anti-inflammatory effects of incretins (Table 3).

A recent meta-analysis of SURPASS trials (~7 trials, up to 2 years of follow-up) evaluated major adverse cardiovascular events (MACE), including cardiovascular death, nonfatal MI, stroke, and unstable angina. Tirzepatide was associated with a Hazard Ratio of ~0.80 versus pooled comparators. However, this result did not reach statistical significance, largely due to the low number of MACE events and relatively short trial durations, which were primarily designed to assess glycemic and weight endpoints rather than cardiovascular outcomes[29]. These findings suggest a favorable trend, but definitive cardiovascular benefit cannot be concluded until results from dedicated CVOTs, such as SURPASS-CVOT, become available.

Heart failure and cardiac function

Notably, tirzepatide has shown considerable promise in patients with heart failure with preserved ejection fraction (HFpEF). The SUMMIT trial specifically tested tirzepatide in patients with HFpEF and obesity (BMI ≥30); the results were presented in late 2024[20]. In SUMMIT, tirzepatide 15 mg weekly was compared to placebo in HFpEF patients (ejection fraction >50%, New York Heart Association II-III) over 52 weeks[20]. The primary endpoint (a composite of cardiovascular death or heart failure hospitalization) was significantly reduced: 9.9% of tirzepatide patients vs 15.3% of placebo patients had an event. This ~38% relative risk reduction was mostly driven by fewer heart failure hospitalizations (8.0% vs 14.2%)[20].

By 1 year, they had a much larger improvement in the Kansas City Cardiomyopathy Questionnaire clinical summary score (+19.5 vs +12.7 points, $P < 0.001$), reflecting a better quality of life and symptom burden[20]. Additionally, tirzepatide significantly reduced body weight by ~14% and lowered systolic BP by ~5 mmHg more than the placebo[20]. A secondary analysis by Borlaug *et al* (2025) showed that tirzepatide reduced markers of circulatory overload, such as NT-proBNP, and improved the left ventricular diastolic function[30].

A cardiac MRI sub-study found that tirzepatide led to a reduction in left ventricular mass and regression of cardiac hypertrophy compared with placebo[31]. It also reduced the pericardial fat. These changes suggest that weight loss and metabolic improvements translate into a healthier cardiac structure and a less stiff heart, which are important in HFpEF pathophysiology.

Tirzepatide's cardiovascular effects appear to arise not from a singular pathway, but through multi-modal mechanisms. Substantial weight reduction (~10–25%) leads to improvements in hemodynamic load, reduction in visceral and pericardial

adiposity, and decreases in inflammatory markers such as CRP[30]. These changes contribute to improved endothelial function, reduced arterial stiffness, and better left ventricular compliance, especially relevant in HFpEF[30]. Furthermore, incretin pathways, particularly GIP signaling, may exert direct anti-inflammatory and vasodilatory effects, although the full mechanistic profile remains under investigation.

Side effects

Like any potent therapy, the benefits of tirzepatide must be weighed against its risks and side-effect profile[32]. Overall, tirzepatide has been found to have a safety and tolerability profile consistent with the GLP-1 receptor agonist (GLP-1 RA) class, with no major unexpected adverse events emerging in trials to date[33]. Key points on safety are as follows:

Gastrointestinal side effects

The most common adverse effects of tirzepatide are gastrointestinal (GI) symptoms, notably nausea, vomiting, diarrhea, and constipation. These effects are similar to those observed with GLP-1 RAs (since both incretins modulate GI motility and appetite)[34,35]. In trials, the majority of patients experienced at least one transient GI symptom, particularly during dose escalation[36]. Most events were mild to moderate and tended to improve over time. Slower up-titration can help mitigate these effects[36]. Patients should be counseled on dietary adjustments (smaller meals and avoiding rich/fatty foods) to manage nausea.

Hypoglycemia

Tirzepatide does not usually cause hypoglycemia because its insulin release is glucose dependent[37]. In trials without concomitant sulfonylureas or insulin, clinically significant hypoglycemia was very rare (<2% of patients, similar to placebo)[37]. It is recommended that the dose of sulfonylurea or insulin be reduced when starting tirzepatide[13]. Overall, for monotherapy or with metformin, the risk is minimal, which is a safety advantage over many older diabetes drugs[14].

Pancreatitis and gallbladder disease

Incretin therapies, including tirzepatide, have been associated with a small risk of acute pancreatitis, though rates are low and comparable to placebo. In pooled phase 3 trials, pancreatitis occurred in ~0.2–0.3% of tirzepatide users versus 0.1–0.2% in placebo (Risk Ratio: 1.46, $P = 0.436$)[36]. A 2023 meta-analysis by Zeng *et al* found no significant increase in pancreatitis, but did report a higher incidence of gallbladder complications, such as cholelithiasis and cholecystitis[38]. In SURMOUNT-1, gallbladder-related adverse events were reported in ~1.4–2.2% of patients on tirzepatide vs 0.6% on placebo. Patients should be monitored for symptoms of biliary colic, especially during rapid weight loss. Slower titration and dietary fat moderation may reduce incidence.

Thyroid tumors

Similar to GLP-1 RAs, tirzepatide carries a class warning about medullary thyroid carcinoma (MTC). Tirzepatide is contraindicated in patients with a personal or family history of MTC or Multiple Endocrine Neoplasia type 2 (MEN 2). A recent pharmacovigilance analysis by Abi Zeid Daou *et al* (2025) using the FDA Adverse Event Reporting System (FAERS) found an increased reporting odds ratio (ROR = 2.09) for thyroid cancer among tirzepatide users, compared to other glucose-lowering medications. While this signal is consistent with known GLP-1 RA class warnings, causality has not been established, and the absolute incidence remains low[39]. Nonetheless, tirzepatide remains contraindicated in individuals with a personal or family history of MTC 2 or MEN 2.

Retinopathy considerations

A rapid improvement in blood glucose has been associated with transient worsening of diabetic retinopathy in some cases (observed with insulin initiation and in the semaglutide SUSTAIN-6 trial)[40]. Tirzepatide's robust A1c drop raises this concern[41]. It is prudent to ensure that diabetic patients have up-to-date retinal examinations before starting tirzepatide and to monitor vision changes.

Mental health effects

Emerging post-marketing data and anecdotal reports have flagged potential psychiatric side effects, including anxiety, mood disturbances, and depression[42]. The exact pathophysiological mechanism remains unclear, although hypotheses include central nervous system effects due to GLP-1 receptor activity in the brain, metabolic shifts, or rapid weight loss affecting neurochemical pathways[42].

Ethical and safety risks

The rise of tirzepatide as a "cosmetic weight loss" agent introduces serious ethical dilemmas and public health concerns. There is a risk that patients may neglect foundational lifestyle interventions, such as physical activity, balanced dietary patterns, and behavioral modification. This may blunt long-term sustainability of weight loss, as discontinuation of the drug has been associated with weight regain unless lifestyle strategies are continued[19]. Clinical stewardship, regulatory oversight, and public education are critical for preventing misuse and safeguarding patient well-being.

Safety versus other agents

Compared to older diabetes medications, tirzepatide avoids many serious side effects (no inherent hypoglycemia as seen with insulin/sulfonylureas and no CHF risk as seen with thiazolidinediones)[37]. Compared to pure GLP-1 RAs, tirzepatide's GI side effect frequency might be slightly higher at the highest dose (because of its potency), but the overall adverse event types and rates are similar to those of GLP-1 analogs[34,35]. Notably, discontinuation rates due to side effects were low to moderate (~5–15% range across doses, higher at 15 mg), somewhat higher than placebo, however, comparable to high-dose semaglutide[32]. With patient education and support during titration, many patients can successfully continue therapy.

Future directions

The success of tirzepatide across the metabolic and cardiovascular domains opens compelling avenues for ongoing and future research. Most notably, the SURPASS-CVOT trial comparing

tirzepatide to dulaglutide in individuals with T2DM and established ASCVD will determine whether tirzepatide provides additional protection against MACE beyond existing GLP-1 receptor agonists[43]. Similarly, tirzepatide's phase 2 results in the SYNERGY-NASH trial have laid the groundwork for phase 3 development in metabolic steatohepatitis[44].

Renal endpoints are another area of active investigation[45]. Early data from the SUMMIT trial suggested improvements in estimated glomerular filtration rate (eGFR) and albuminuria, particularly in obese patients with HFpEF[30]. A pooled post-hoc analysis of SURPASS 1-5 clinical trials in patients with T2DM, including those with chronic kidney disease, showed a clinically relevant decreased urine albumin-to-creatinine ratio (UACR) with tirzepatide[46]. A dedicated phase 3 trial, TREASURE-CKD, is now underway to evaluate the renal protective potential of tirzepatide in people with obesity and chronic kidney disease, with or without diabetes[47].

The dual agonism model has spurred interest in triple agonists (e.g., GIP/GLP-1/glucagon) and other multihormone strategies[48]. Combination therapies with sodium-glucose cotransporter-2 (SGLT2) inhibitors may yield synergistic benefits in glycemia, cardiovascular outcomes, and renal protection. Furthermore, development of oral tirzepatide formulations or longer-acting injectables (e.g., biweekly or monthly dosing) may improve adherence and expand access.

Despite the promising therapeutic potential of tirzepatide, its real-world adoption faces several challenges. The cost of therapy remains a significant barrier, with prices comparable to other GLP-1 receptor agonists[49]. Insurance coverage restrictions, prior authorization hurdles, and regional variability in reimbursement policies may limit timely patient access. In low- and middle-income countries, access to injectable incretin therapies is particularly limited, underscoring the need for global pricing strategies and generic pathways.

Health equity is another critical consideration. Marginalized populations including those with lower socioeconomic status, racial/ethnic minorities, and individuals in rural or under-resourced areas may face systemic barriers to tirzepatide access. These include reduced access to specialists, lower rates of insurance, and gaps in patient education. Future research should explore real-world effectiveness, cost-effectiveness, and health equity including how access to advanced therapies like tirzepatide may vary across populations and health systems. Recent modeling studies underscore both tirzepatide's cost-effectiveness in controlled settings and the urgent need for real-world data to validate its broader economic and societal impact[49,50].

Additionally, several key gaps remain in the evidence base:

a. Long-term safety data, especially beyond 2 years, are limited.
b. Pediatric populations have been excluded from all major clinical trials.
c. The efficacy and safety of tirzepatide in hospitalized or critically ill patients with hyperglycemia remain underexplored.

Addressing these gaps will be essential for informing clinical guidelines, payer coverage decisions, and the broader integration of tirzepatide into routine care. As additional data emerge, tirzepatide's role may expand beyond a breakthrough innovation to a cornerstone of comprehensive, cardiometabolic disease management.

Conclusion

Tirzepatide represents a significant advancement in the management of T2DM, obesity, and cardiometabolic comorbidities. By combining potent glucose-lowering and weight-reducing effects with improvements in BP, lipids, and inflammation, tirzepatide offers a multi-pronged approach to addressing the complex pathophysiology of metabolic syndrome. Its benefits in heart failure, obstructive sleep apnea, and emerging signals in non-alcoholic steatohepatitis (NASH) suggest broad clinical utility across traditionally siloed disease areas.

However, its use is not without challenges. Concerns regarding long-term safety, including risks of gallbladder disease, thyroid malignancy, and weight regain following discontinuation, highlight the need for ongoing pharmacovigilance. Additionally, questions remain regarding accessibility, cost-effectiveness, and use in special populations, including pediatric patients, and those with multiple comorbidities.

As outcome trials such as SURPASS-CVOT, TREASURE-CKD, and SYNERGY-NASH conclude, they will clarify tirzepatide's long-term role in cardiovascular and renal protection. Meanwhile, future research should prioritize evaluating real-world effectiveness, health equity, and cost-containment strategies to ensure that this therapeutic innovation reaches its full potential.

In this evolving therapeutic landscape, tirzepatide may serve not only as a powerful metabolic therapy, but also as a platform agent for developing future multi-targeted, disease-modifying treatments.

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