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# Beyond glycemic control: clinical cardiovascular effects of tirzepatide—a narrative review

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***Abstract*:** The risk of cardiovascular disease is significantly increased by both type 2 diabetes mellitus (T2DM) and obesity through overlapping pathways involving insulin resistance, dyslipidemia, systemic inflammation, and endothelial dysfunction. Tirzepatide, the first dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, has shown significant glycemic and weight-reducing effects and is increasingly recognized as a cardiometabolic therapy that extends beyond glucose control. This narrative review summarizes clinical and translational evidence about the cardiovascular and metabolic benefits of tirzepatide and the biologic mechanisms that may underpin its effects. Tirzepatide has consistently shown high improvements in key indicators of glycemic control and body weight across the SURPASS program in patients with T2DM and the SURMOUNT program in patients with obesity. Benefits include marked reduction in glycated hemoglobin and cardiovascular risk factors, such as systolic and diastolic blood pressure, atherogenic lipid parameters, visceral adiposity, and several inflammatory biomarkers. Dual incretin signaling seems to increase endothelial function by enhancing the bioavailability of nitric oxide, reducing oxidative stress, inhibiting pro-inflammatory pathways such as nuclear factor kappa B, and favorably modulating adipokine profiles, collectively supporting cardiovascular protection. Promising data suggest symptomatic and functional improvements in obesity-related heart failure with preserved ejection fraction. Reductions in major adverse cardiovascular events are currently under investigation in dedicated outcome trials, including the SURPASS Cardiovascular Outcomes Trial. Overall, tirzepatide provides broad cardiometabolic benefits, making it a promising treatment in the changing landscape of cardiometabolic disease management.

## Plain language summary

### More Than Blood Sugar Control: How Tirzepatide Affects Heart Health

The risk of developing heart and blood vessel disease, which is a common cause of death worldwide, is very high in obese diabetic patients. Tirzepatide is a new medication that participates in regulation of blood sugar, appetite, and metabolism by causing the same effects of two naturally occurring gastro-intestinal hormones. In addition, Tirzepatide may improve several factors linked to heart health, including blood pressure, lipids, inflammation, blood vessels and heart structure and function. Although its long-term outcomes are still under study, current evidence suggests that Tirzepatide may play an important role in improving cardiometabolic health.

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## Introduction

There is a close interrelationship between type 2 diabetes mellitus (T2DM), obesity, and cardiovascular disease (CVD), with CVD being the chief cause of morbidity and mortality in individuals with T2DM.[1] Over the past decade, major advances in the pathophysiology and mechanisms that connect T2DM to CVD have resulted in significant improvements in pharmacological therapy. CVD development and progression are linked to chronic hyperglycemia, insulin resistance, dyslipidemia, systemic inflammation, and endothelial dysfunction.[2] These interrelated factors enhance the development of atherosclerosis and therefore increase the risk of coronary artery disease, heart failure, and stroke. Recent evidence highlights the cardioprotective effects of some anti-diabetic medications such as sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs), extending their benefits beyond glycemic control.[3] SGLT2 inhibitors such as dapagliflozin have been shown to reduce heart failure hospital admissions and cardiovascular (CV) mortality rates among patients with T2DM and established CVD or heart failure.[4] These effects could be attributed to improved hemodynamics, attenuation of ventricular remodeling, and enhanced natriuresis, independent of the glucose-lowering effect. Likewise, GLP-1RAs such as semaglutide have been shown to decrease major adverse cardiovascular events (MACE), driven by anti-inflammatory effects, weight loss, and reduced arterial blood pressure.[5] Furthermore, a non-steroidal mineralocorticoid receptor antagonist that is recommended for use in patients with T2DM and chronic kidney disease has been shown to decrease renal and cardiovascular outcomes.[6] Lifestyle interventions, particularly Mediterranean dietary patterns and structured physical activity, remain foundational components of T2DM and CVD management.[7] Current guidelines emphasize personalized multidisciplinary approaches that integrate pharmacological and non-pharmacological strategies to address individual risk profiles.

Incretin-based treatment has increased with the introduction of dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1RA. Incretin hormones such as GIP and glucagon-like peptide-1 (GLP-1) are known to increase glucose-stimulated insulin secretion; however, recent evidence indicates that combining GIP and GLP-1 agonism can further improve insulin sensitivity and support greater weight reduction.[8] Early findings suggest that dual-pathway activation provides metabolic advantages that are superior to those of GLP-1RAs alone.[9] Tirzepatide (TZP), the first Food and Drug Administration-approved dual GIP/GLP-1RA, has demonstrated remarkable efficacy. In the SURPASS clinical trials, TZP achieved substantial reductions in glycated hemoglobin (HbA1c; up to 2.58%) and body weight (up to 15.7%), outperforming semaglutide.[9,10] More recent obesity trials have further confirmed TZP's capacity to achieve significant weight loss, even among non-diabetic individuals.[11] The success of this agent has prompted research into next-generation multi-agonists, including triple agonists targeting GIP, GLP-1, and glucagon receptors, with potential implications for metabolic disorders such as non-alcoholic steatohepatitis and cardiovascular risk reduction.[12] As a novel dual incretin therapy, TZP utilizes the synergistic activity of GIP and GLP-1 to promote insulin secretion, inhibit glucagon secretion, and cause excessive weight loss.[9] Clinical data provided through the SURPASS program indicate that TZP offers better improvements in glycated hemoglobin and body weight compared to several known antidiabetic therapies.[9,10,13] Beyond glycemic control, TZP has shown promising cardiometabolic benefits, including improvements in lipid profiles, blood pressure, and reductions in visceral adiposity.[11] Its significant weight loss effects, exceeding 15% in some studies, position it as a potential therapy for obesity, even in non-diabetic individuals.[14] As the first dual GIP/GLP-1 agonist, TZP represents a paradigm shift in metabolic disease management, expanding therapeutic possibilities beyond glucose-lowering effects to

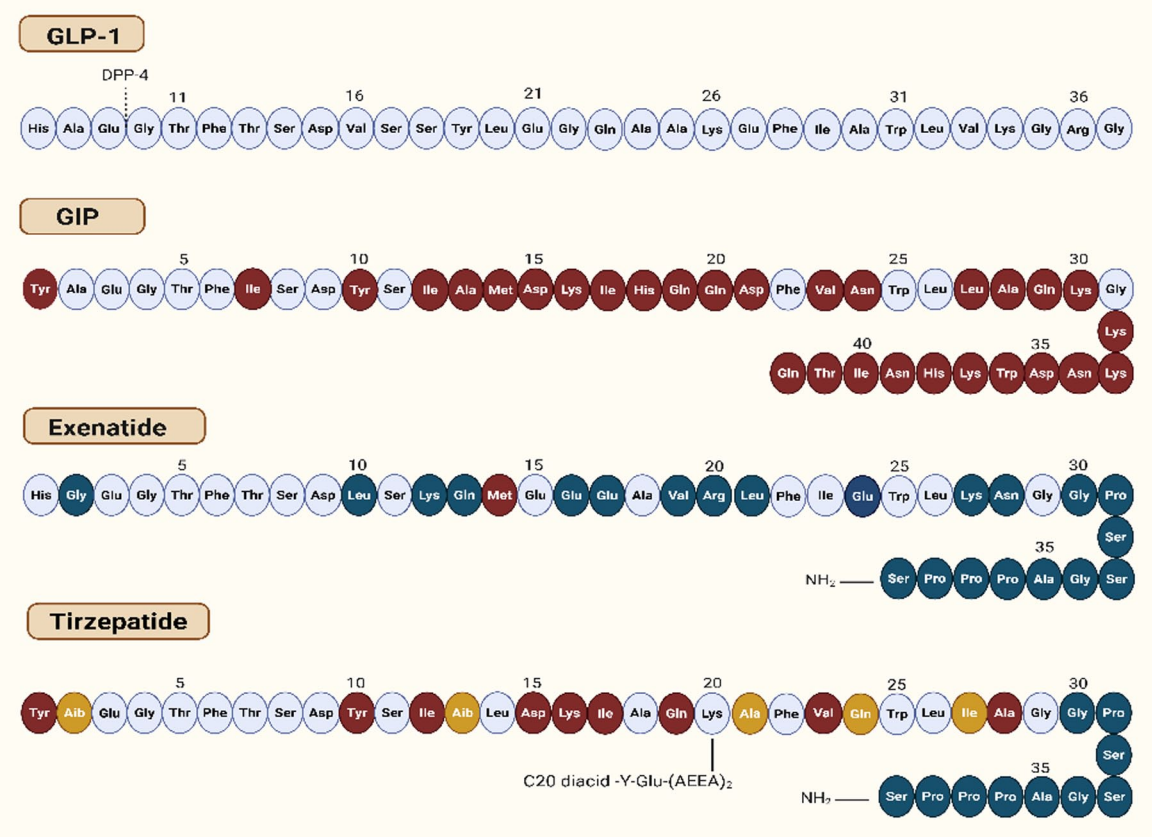



**Figure 1.** Comparative amino acid sequences of native incretin hormones (GLP-1 and GIP) and their therapeutic analogue, tirzepatide, highlighting structural modifications that enhance receptor activity and resistance to enzymatic degradation.
Source: Created with BioRender.com.
GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1.

address obesity, cardiovascular risk, and metabolic syndrome.

## Molecular structure and pharmacology of tirzepatide

TZP is a synthetic peptide engineered to function as a dual receptor agonist for both GIP and GLP-1, thereby combining the effects of the two incretin hormones into one drug.[15] Structurally, TZP consists of 39 amino acids in a linear peptide similar in structure to GIP but incorporates specific modifications to allow binding and activation of both GIP and GLP-1 receptors (GLP-1R).[16,17] These modifications include the substitution of specific amino acids and the addition of a C20 fatty diacid moiety, which is conjugated to a lysine residue via a hydrophilic linker, 2-(2-aminoethoxy)ethoxyacetic acid, which facilitates reversible binding to albumin and extends the drug half-life.[16–18] Specific amino acid substitutions and C-terminal amidation enhance resistance to enzymatic breakdown and improve metabolic stability.[19,20] In addition, the fatty acid chain enables strong albumin binding, thereby prolonging the drug's half-life and permitting once-weekly dosing.[17,18] Figure 1 highlights the structural features that distinguish TZP from native incretins, including amino acid substitutions and a C20 fatty diacid side chain which facilitates activity.

Pharmacologically, TZP exhibits balanced agonism at the GIP receptor and partial agonism at the GLP-1R.[21] This double-receptor activity enabled enhanced glucose-dependent insulin secretion, suppressed glucagon release, improved insulin sensitivity, and reduced appetite.[22–24] The binding affinity for the GIP receptor is high,

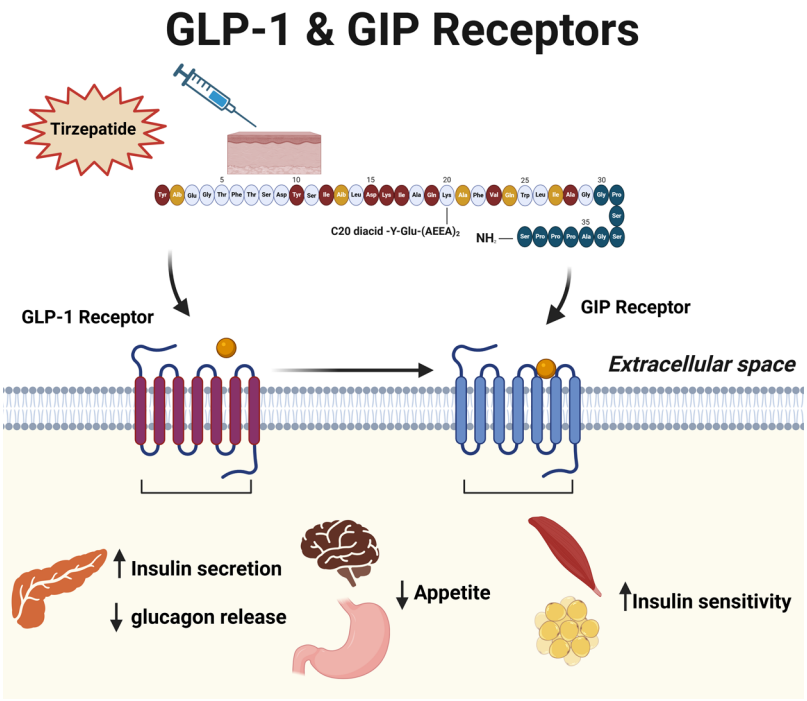



**Figure 2.** Dual agonism of GLP-1 and GIP receptors by tirzepatide. Tirzepatide activates both incretin receptors, leading to enhanced insulin secretion, reduced glucagon release, appetite suppression, and improved insulin sensitivity.
Source: Created with BioRender.com.
GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1.

closely mimicking that of the original hormone, while GLP-1R activation is intentionally less potent than genuine GLP-1RAs such as semaglutide or liraglutide, which helps reduce the incidence of gastrointestinal side effects.[21,25] Figure 2 describes how the dual activation of GIP and GLP-1R by TZP results in multiple integrated effects that include enhanced insulin secretion, reduced glucagon release, appetite suppression, and improved insulin sensitivity.

The pharmacokinetic profile of TZP supports its clinical effects. Following subcutaneous administration, TZP demonstrates slow absorption and an extended half-life of approximately 5 days, which facilitates weekly dosing.[26] It is primarily metabolized via proteolytic metabolism and β-oxidation, with minimal renal elimination of the intact compound.[27,28] Recent studies indicate consistent pharmacokinetic exposure across a range of populations, including those with hepatic or renal impairment, indicating that dose adjustment is usually unnecessary in these groups.[29,30] Compared to traditional GLP-1RAs and other antidiabetic therapies, TZP showed better results in reducing both HbA1c and body weight.[9,10,13,31] The dual-receptor mechanism also appears to contribute to improved β-cell function, insulin secretion, and potential cardiovascular effects beyond those seen with GLP-1RAs alone.[32,33] In addition, TZP's molecular design allows for a smoother dose-escalation protocol and potentially better gastrointestinal tolerability, particularly during the early treatment phases.[34] These features collectively distinguish TZP as a next-generation incretin-based therapy with a broader metabolic and clinical impact.[35]

## Doses and mechanism of action

TZP is injected subcutaneously as a once-weekly dose and is approved for two primary indications: T2DM and obesity management in individuals with or without diabetes.[36] The drug was manufactured by Eli Lilly and Company and received approval for treatment of T2DM in the US (May 2022),[37] European Union (September 2022),[38,39] Canada (November 2022),[38,40] and Australia

(December 2022).[38,41] It is marketed under the brand names "Mounjaro" for diabetes and "Zepbound" for obesity management and obstructive sleep apnea in adults with obesity.[42,43]

For the treatment of T2DM dosing typically begins at 2.5 mg weekly.[44] This starting dose is used for a 4-week period to allow for gastrointestinal adaptation, not for glycemic control.[26] The dose is then increased in 2.5 mg every 4 weeks to reach maintenance doses of 5, 10, and a maximum of 15 mg weekly, depending on patient tolerability and therapeutic goals.[45] Real-world data show that most patients initiating TZP therapy start with low doses (2.5 or 5 mg), consistent with clinical recommendations. The 5, 10, and 15 mg maintenance doses of TZP are typically reached at 4, 12, and 20 weeks, respectively, after treatment initiation.[44] This gradual escalation schedule is clinically relevant as it influences the time required to achieve glycemic and weight-loss targets, especially considering that treatment guidelines recommend reassessing therapy every 3 months based on HbA1c results.[44,46] The most common side effects during the initiation and dose-escalation phases are gastrointestinal symptoms that include nausea, vomiting, and diarrhea.[47] To mitigate these effects and improve tolerability, treatment is initiated at a low dose and gradually increased.[48] For weight management, TZP follows a similar titration strategy but may be escalated up to 15 mg depending on the clinical protocols in various countries.[49] Notably, the same titration schedule is generally used, but the primary outcome targeted is weight reduction rather than glycemic control. The eligibility criteria for obesity treatment include individuals with a body mass index of $\geqslant$30, or $\geqslant$27 kg/m$^2$ with a weight-associated comorbidity such as hypertension, dyslipidemia, or obstructive sleep apnea.[50] The injection is delivered subcutaneously into the abdomen, thigh, or upper arm using a user-friendly prefilled pen.[51] The convenience of once-weekly dosing has been shown to improve patient adherence and satisfaction in both diabetes and obesity management.[52,53] Despite the high comorbidity burden and prior exposure to similar antidiabetic agents, a large proportion of patients adhered to TZP as prescribed, and only a minority discontinued treatment within the first 6 months.[54] As described above, patients with renal impairment, including those with end-stage renal disease, and individuals with severe hepatic impairment do not require dose adjustments.[29,30] Additionally, TZP delays gastric emptying, which may transiently affect the absorption of co-administered oral drugs. A single 5-mg dose reduced the systemic exposure of oral contraceptives by approximately 20%, coinciding with the maximal gastric emptying delay.[55] However, this effect decreases with repeated dosing due to tachyphylaxis, limiting its long-term clinical significance.[26]

## Mechanistic insights: Cardiovascular biology of GIP and GLP-1 signaling

The physiological effects of GIP and GLP-1 are linked to the sites of their corresponding receptors across different tissues and organs.[56] These are distributed in the gastrointestinal (including pancreatic B-cells), cardiovascular, nervous, musculoskeletal, and immune systems.[57] GIP and GLP-1R are classified within the class B family of the seven-transmembrane G protein-coupled receptors.[57] Hormone binding to the extracellular domain results in G protein engagement and activation. Both receptors stimulate intracellular cyclic AMP signaling pathways that promote insulin secretion and metabolic regulation.[58] Figure 3 illustrates the intracellular incretin-mediated effects in pancreatic β-cells that link GIP and GLP-1R activation to increased insulin synthesis and secretion via exocytosis, thus resulting in glucose-lowering effects.

Both hormones (GIP and GLP-1) have direct effects on the cardiovascular system and vascular smooth muscle cells.[59] GIP promotes cell growth in vascular endothelial cells without influencing intracellular cAMP concentrations and enhances nitric oxide (NO) production by activating AMP-activated protein kinase. This process can be facilitated by phospholipase C and calcium/calmodulin-dependent protein kinase kinase.[59] Moreover, GIP inhibits reactive oxygen species (ROS) production by decreasing gene expression levels of the receptor for advanced glycation end products (AGEs).[59] With regard to the effect on arterial blood pressure, GIP decreased the average arterial blood pressure, while elevating the heart rate in subjects with normal glucose tolerance, impaired glucose tolerance, and T2DM.[59] In contrast, GLP-1R activation offers cardioprotective benefits, supporting heart function and mitigating adverse cardiac remodeling.[60] These effects are mediated by the fact that GLP-1R decreases oxidative stress and prevents apoptosis

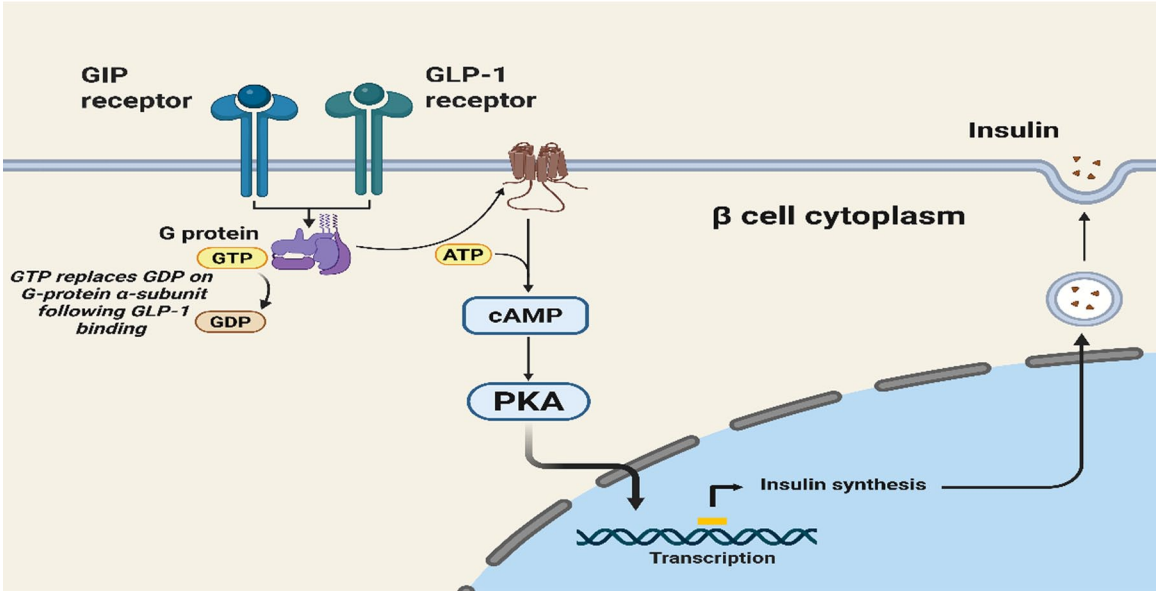



**Figure 3.** Incretin signaling in pancreatic β-cells. Activation of GIP and GLP-1 receptors increases cAMP and PKA signaling, enhancing insulin gene transcription, synthesis, and secretion.
Source: Created with BioRender.com.
cAMP, cyclic adenosine monophosphate; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1.

in cardiomyocytes.[60] Recent data suggest that active GIP inhibits the proliferation of human aortic smooth muscle cells stimulated by growth factors.[59] GLP-1R activation promotes vasodilation by enhancing the synthesis of endothelial NO, resulting in relaxation of blood vessels and an increase in coronary blood flow.[60] While GIP induces fat accumulation in adipose tissues, possibly via activation of lipoprotein lipase, the activation of GLP-1R in adipocytes does not affect lipoprotein lipase activity.[61] Regarding their effects on the gastrointestinal system, GLP-1 and to a lesser extent, GIP slow gastric emptying and gastric acid secretion.[61] In addition, GLP-1R activation decreases food intake.[62,63] and facilitates weight loss by curbing appetite in the hypothalamus and promotes a sense of fullness through the reduction of gastric emptying, thereby lowering calorie consumption.[64] In contrast, the direct effects of GIP on body weight are not fully understood.[65] While some studies considered GIP as an obesity-inducing hormone,[65] others have found that it significantly reduces weight on a long-term basis.[66] Owing to the substantial weight-loss outcomes of GLP-1-based therapies, GLP-1RAs have been approved for the treatment of obesity in individuals with or without T2DM.[67]

## Cardiovascular effects of tirzepatide

### *Anti-inflammatory effects of tirzepatide*

TZP exerts systemic anti-inflammatory effects by activating GLP-1 and GIP receptors, which interfere with certain pro-inflammatory signaling pathways.[68] This decreases transcription and release of inflammatory cytokines from immune and endothelial cells, helping to reduce the ongoing low-grade inflammation associated with CVD. GLP-1RAs reduce infiltration of inflammatory cells in the blood vessels and lower pro-inflammatory monocytes and neutrophils in models of hypertension and cardiac stress.[69] In T2DM, hyperglycemia and insulin resistance enhance signaling through AGEs and their receptor for AGEs, leading to increased oxidative stress and contributing to myocardial inflammation and fibrosis.[70] TZP counteracts these processes by reducing ROS generation, limiting the activity of nicotinamide adenine dinucleotide phosphate oxidase-4, and attenuating interleukin-1 beta (IL-1β)-induced oxidative stress in cardiomyocytes.[71] In addition, GLP-1–based therapies also exert anti-atherogenic actions, with liraglutide and semaglutide significantly reducing plaque burden and suppressing pro-inflammatory myeloid gene

expression in atherosclerosis models.[72] Notably, these protective effects persisted even when endothelial or myeloid GLP-1R expression was deficient, indicating broader immunomodulatory mechanisms beyond direct receptor signaling.

*Impact on inflammatory biomarkers (C-reactive protein, interleukin-6, tumor necrosis factor-alpha).* Previous studies have shown that GLP-1–based therapies, including TZP, caused significant reductions in key inflammatory markers, such as C-reactive protein (CRP), which is a recognized predictor of cardiovascular events.[73] Studies have shown that CRP reduction parallels improvements in cardiovascular outcomes, suggesting that the attenuation of inflammation may contribute to cardio-protection.[74] In the SURPASS trials, the significant reduction in CRP persisted even after adjusting for weight loss and glycemic control, indicating the presence of a weight-loss-independent anti-inflammatory effect.[73] In addition, the rapid appearance of cardiovascular benefits after initiating therapy suggests partial independence from weight loss. Another inflammatory marker that declines with TZP treatment is interleukin-6 (IL-6), which contributes to endothelial dysfunction and plaque instability.[73] A significant reduction in IL-6 was observed following 72 weeks of TZP therapy in the SURMOUNT-1 trial that enrolled non-diabetic participants with obesity.[75] Tumor necrosis factor-alpha (TNF-α), a key mediator of insulin resistance and vascular inflammation, was similarly reduced.[76] Additional inflammatory biomarkers including growth differentiation factor-15, intercellular adhesion molecule-1, and leptin also decreased following TZP therapy, with reductions exceeding those observed with placebo or dulaglutide.[77]

*Adipose tissue mediated anti-inflammatory effects.* The substantial decrease in visceral fat following initiation of TZP therapy is associated with reduction in pro-inflammatory adipokines such as leptin, resistin, and monocyte chemoattractant protein-1.[78,79] At the same time, the level of the anti-inflammatory adipokine (adiponectin) is elevated.[80] This shift in the adipokine profile contributes to an anti-inflammatory environment, reinforcing TZP's cardiometabolic benefits. The anti-inflammatory effect may also be mediated through activation of the GIP receptor, which has been shown to reduce endothelial oxidative stress and suppress cytokine release from the visceral adipose tissue.[81] TZP also restores specific protective intracellular signaling pathways in diabetic myocardium, highlighting its potential in reversing inflammation-related cardiac injury.[82]

*Cardiac anti-inflammatory and cardioprotective implications.* GLP-1 therapies reduce acute cardiac inflammation after myocardial infarction, thus decreasing atrial IL-6 expression and circulating IL-6 levels shortly after injury.[83] In models of pressure overload and early heart failure, GLP-1RAs attenuate ventricular hypertrophy and inflammatory activation, suggesting benefit beyond glucose regulation.[84] Both semaglutide and TZP improve symptoms and severity of heart failure with preserved ejection fraction (HFpEF), although the specific contribution of anti-inflammatory pathways remains under investigation.[85] Emerging evidence indicates that anti-inflammatory effects may act through endothelial GLP-1R in mice, while in humans, the presence of GLP-1R on cardiomyocytes suggests additional potential for direct myocardial protection.[86] Figure 4 shows the molecular and cellular mechanisms through which TZP exerts anti-inflammatory and anti-atherogenic effects, showing how the dual GIP and GLP-1R activation modulates inflammatory mediators, oxidative stress, adipokines, and endothelial dysfunction, thereby contributing to cardiovascular protection.

### Vascular effects

*Endothelial function enhancement.* TZP improves function of the vascular endothelium by enhancing NO production and reducing oxidative stress and vascular inflammation.[71] This leads to better vascular tone, reduced leukocyte adhesion, and a lower risk of developing atherosclerotic plaques. The expression of GLP-1 and GIP receptors in the vascular endothelium and smooth muscle cells facilitates direct vasodilation.[87] GLP-1RAs and other GLP-1-based therapies have been shown to improve endothelial function, as assessed by flow-mediated dilation.[88] In addition, experimental data indicate that both GLP-1 and its metabolite GLP-1(9-36) can exert vasodilatory effects that may involve NO-cyclic guanosine monophosphate signaling.[89] In contrast, GIP regulates vascular inflammation by endothelin-1 signaling and promotes vasodilation through increased NO secretion, suggesting a complementary role in vascular homeostasis.[90] Preclinical studies have demonstrated

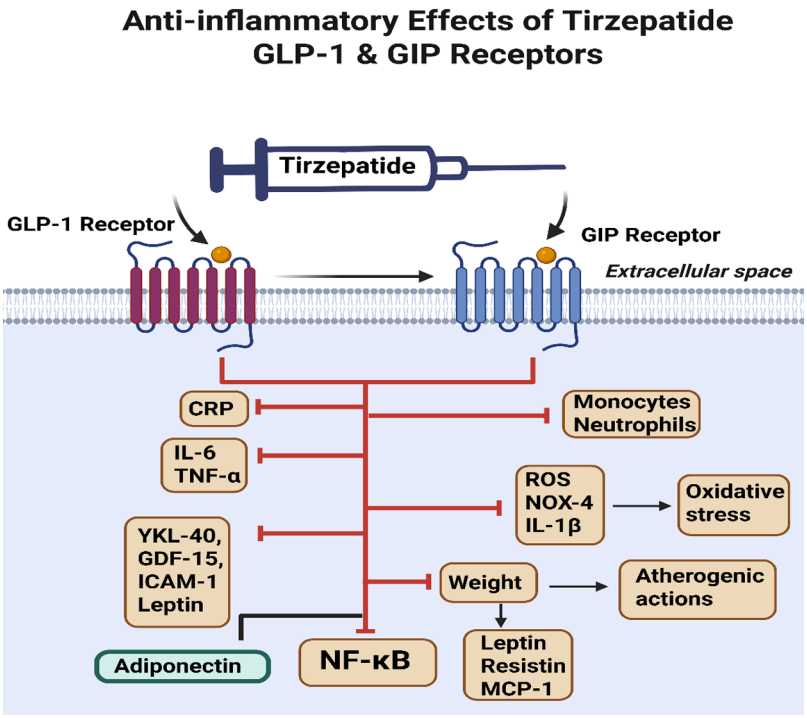



**Figure 4.** Anti-inflammatory effects of tirzepatide mediated through dual activation of GLP-1 and GIP receptors, leading to suppression of NF-κB signaling, reduction of pro-inflammatory cytokines, oxidative stress, and immune cell activation, with favorable effects on adipokine profiles.
Source: Created with BioRender.com.
cAMP, cyclic adenosine monophosphate; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; NF-κB, nuclear factor kappa B.

that TZP reduces endothelial oxidative stress, suppresses inflammatory cytokine production, and protects cardiomyocytes from high-glucose-induced injury, reinforcing its vascular protective profile.[91]

*Blood pressure regulation and effects on arterial stiffness.* TZP has been consistently associated with reductions in both systolic and diastolic arterial blood pressure across multiple clinical trials.[92] While this effect can be loosely attributed to weight loss and improved insulin sensitivity, TZP exerts direct vasodilatory actions that improve vascular tone.[71,89] In the SURPASS program, TZP lowered the mean systolic blood pressure by −2.8 to −12.6 mm Hg and mean diastolic blood pressure by −0.8 to −4.5 mm Hg.[93] These reductions reflect a combination of mechanisms, including natriuresis, decreased inflammation, and enhanced endothelial NO availability.[90] Moreover, TZP promotes endothelial health through dose-dependent reductions in inflammatory biomarkers.[77] Clinical ambulatory blood pressure monitoring analyses showed sustained reductions in 24-h systolic blood pressure with no associated increase in the risk of atrial fibrillation.[94] Notably, larger BP reductions in the Japanese populations suggest a potential ethnicity-related vascular responsiveness to TZP.[95] In addition to blood pressure, TZP contributes to reduced arterial stiffness, a key determinant of cardiovascular risk.[96] By improving endothelial health and decreasing oxidative stress, TZP enhances NO production, thereby promoting vasodilation and maintaining vascular elasticity.[90] The complementary effects of GIP receptor activation, including stimulation of endothelial nitric oxide synthase (eNOS), suppression of inducible NOS (iNOS), and reduction in endothelial oxidative stress, further support improved vascular compliance.[81] Additionally, genetic evidence linking GIP receptor variants to cardiometabolic

traits, along with increased blood flow to adipose tissue and enhanced triglyceride clearance, suggests a broader mechanistic role for GIP signaling in reducing atherogenic lipid burden and improving vascular stiffness.[97]

*GIP-mediated endothelial protection and anti-atherosclerotic effects.* Emerging evidence suggests that TZP's cardiovascular benefits may be partly attributed to its GIP receptor agonism. GIP reduces oxidative stress in human umbilical vein endothelial cells by suppressing the generation of ROS induced by advanced glycation end-products.[98] Furthermore, GIP decreases the expression of plasminogen activator inhibitor-1, a pro-atherogenic molecule, and limits the secretion of inflammatory cytokines by endothelial cells and visceral adipose tissue.[99] At nanomolar concentrations, GIP increases NO production by activating eNOS and suppressing iNOS.[100] These findings support the hypothesis that GIP receptor activation by TZP contributes to vascular homeostasis and may play a role in the prevention of atherosclerosis, even in the context of obesity and insulin resistance. Preclinical studies further show that GIP receptor activation reduces aortic atherosclerotic lesion size and macrophage infiltration, suggesting direct anti-atherosclerotic effects mediated through GIP receptor signaling.[101] Given the shared pathophysiological mechanisms underlying aortic, coronary, cerebrovascular, and peripheral arterial disease, TZP may also attenuate atherosclerosis in all these arteries; however, direct evidence regarding its effects on cerebrovascular and peripheral vascular outcomes requires further investigation.[102] Ongoing trials evaluating semaglutide's effect on plaque composition support the potential for incretin-based therapies including TZP to attenuate progression of atherosclerotic CVD.

### Cardiac effects

*Improvements in cardiac metabolism and structure.* TZP improves cardiac energy metabolism by promoting more efficient fuel utilization, particularly in individuals with diabetes and obesity.[103] This results in improved myocardial energy efficiency and reduction in harmful fat accumulation within cardiac cells.[97] Structural benefits include reduced left ventricular (LV) mass and improved myocardial relaxation.[104] Preclinical data show that TZP protects cardiomyocytes from high-glucose-induced apoptosis, fibrosis, and hypertrophy, suggesting a direct role in preventing diabetic cardiomyopathy.[105] TZP may improve myocardial calcium handling and attenuate adverse cardiac remodeling.[105] In addition, TZP enhances branched-chain amino acid (BCAA) catabolism, which is associated with smaller infarct size, reduced cardiomyocyte necrosis, and lower post-MI mortality. Notably, a low-BCAA diet produced similar myocardial benefits and demonstrated additive cardio-protection when combined with TZP.[106]

*Potential effects on heart rate and LV function.* TZP causes a modest increase in resting heart rate (typically 2–5 beats/min), appearing early in treatment and remaining relatively stable.[107] These changes appear to be physiological, potentially enhancing cardiac output and vascular perfusion, and have not been associated with increased cardiovascular events or opposing its cardiovascular benefits in clinical trials.[108] It also shows promising effects on diastolic LV function, which is commonly impaired in metabolic heart disease.[85] Evidence from GLP-1-based therapies indicates improvements in functional capacity (e.g., 6-min walk test performance) and modest reductions in LV filling pressures, supporting a beneficial effect on myocardial relaxation.[85] However, the effects on systolic function (LVEF) remain inconsistent across trials, with some studies showing no significant improvement despite favorable metabolic changes.[85]

*Cardioprotective implications in heart failure.* Previous studies have shown that GLP-1RAs reduce heart failure hospitalization and improve exercise tolerance in some populations, suggesting that these effects could be observed with TZP.[109] Emerging evidence further indicates that TZP may exert cardioprotective effects, particularly in patients at risk of HFpEF.[85,110] Its ability to target multiple pathophysiological processes that include obesity, inflammation, insulin resistance, and endothelial dysfunction makes it a promising candidate for cardiovascular risk reduction. Early data from HFpEF-focused trials (e.g., SUMMIT) indicate that TZP may improve symptoms and reduce congestion in obese patients with HFpEF.[96] Current studies are assessing the effect of TZP in both HFpEF and Heart Failure with Reduced Ejection Fraction populations, where its weight-loss and metabolic benefits may offer

additive advantages.[111] HFpEF (LV ejection fraction ⩾50%) is strongly associated with obesity-related structural remodeling, including increased epicardial and pericardial fat deposition.[112] TZP's potent weight-reducing effects therefore align with key mechanisms underlying obesity-related HFpEF. Unlike semaglutide, which did not reduce LV mass or epicardial adipose tissue in previous HFpEF studies, TZP is now being evaluated as the first dual GIP/GLP-1 agonist in this population.[104] The SUMMIT trial findings demonstrated that TZP reduced worsening events of heart failure and improved functional status in this phenotype.[96] Meta-analytic and pooled data further reinforce TZP's cardiovascular safety profile, demonstrating no increased risk of major cardiovascular adverse events or mortality, alongside significant improvements in cardiometabolic risk factors.[113,114]

### Clinical evidence: Cardiovascular and metabolic outcomes with tirzepatide

TZP is a promising therapy for the management of T2DM and obesity in adults. In the course of the SURPASS program, efficacy and safety have been well tested (SURPASS-1 through SURPASS-6, including regional and Japanese subtypes) and the SURMOUNT program (weight management among overweight and obese adults, with or without T2DM).[115] The SURPASS trials consistently demonstrated good results in glycemic control, and statistically significant declines in HbA1c and glucose levels (fasting or postprandial) across patients without prior glucose-lowering therapy, those on metformin, and individuals requiring insulin intensification.[9,10,13] Importantly, TZP showed superiority over both other GLP-1RAs (e.g., semaglutide) and basal or prandial insulin, achieving greater HbA1c reduction while minimizing hypoglycemia risk. These trials also included high CV risk populations (e.g., SURPASS-4), providing preliminary evidence that TZP may offer cardiometabolic benefits beyond glycemic control.[10] Similarly, the SURMOUNT trials highlighted the profound weight loss effects of TZP.[52,116,117] Significant reductions in body weight were observed across populations with overweight or obesity, with many participants achieving ⩾5% weight loss or even ⩾20% with higher doses.[52,116,117] This effect was evident in participants with and without T2DM, including those with comorbidities such as obstructive sleep apnea or mobility limitations, demonstrating the broad applicability of TZP in metabolic health management.[52,116,117] Cardiovascular-related secondary endpoints were consistently evaluated, particularly in high-risk populations, supporting a favorable safety profile. Ongoing studies, most notably the SURPASS-CVOT trial, are expected to provide evidence on cardiovascular outcomes, including MACEs, thereby informing future clinical guidelines.[118] Collectively, the integrated evidence from the SURPASS and SURMOUNT programs emphasizes TZP's dual benefits that include effective glucose lowering and substantial weight reduction, with potential cardioprotective effects. These findings position TZP as a novel agent capable of addressing multiple interrelated cardiometabolic risk factors, offering a paradigm shift in the treatment of T2DM and obesity. However, from clinical perspective, TZP may be particularly useful for patients with T2DM and/or obesity who require both weight reduction and glycemic control. When compared to SGLT2 inhibitors in patients with heart failure or chronic renal disease, the use of SGLT2 inhibitors is preferred because of their established cardiorenal benefits.[3,4] Therefore, treatment selection should be individualized according to the patient's metabolic, cardiovascular, renal, and weight-management needs. Tables 1 and 2 summarize the key features and primary outcomes of the SURPASS and SURMOUNT clinical trial programs, respectively, across diverse populations.

Table 1 provides an overview of the SURPASS clinical trials evaluating TZP in adults with T2DM. Trials such as SURPASS-1 and SURPASS-2 demonstrated significant reductions in both HbA1c and body weight compared to placebo or active comparators, while ongoing trials (e.g., SURPASS-CVOT) aim to assess cardiovascular outcomes.

Table 2 summarizes the key SURMOUNT clinical trials investigating TZP for chronic weight management in adults with overweight or obesity, with or without type 2 diabetes (T2DM). Notably, SURMOUNT-1 and SURMOUNT-2 demonstrated clinically meaningful weight reductions, with a substantial proportion of participants achieving ⩾5% or ⩾20% weight loss. Other trials, including ongoing studies (SURMOUNT-5 and SURMOUNT-MM), are assessing dose optimization, long-term safety, and functional outcomes.

**Table 1.** Summary of SURPASS clinical trials of tirzepatide in adults with type 2 diabetes.

| Trial name | Population | Duration/dose | Primary outcomes/remarks |
|---|---|---|---|
| SURPASS-1[46] | Adults with type 2 diabetes, drug-naïve | ~ 40 weeks; tirzepatide 5, 10, or 15 mg/week | Significant reduction in HbA1c and body weight vs placebo |
| SURPASS-2[9] | Adults with T2DM on metformin | 40 weeks; tirzepatide 5, 10, 15 mg/week | Tirzepatide superior to semaglutide in HbA1c and weight reduction |
| SURPASS-3[13] | T2DM on metformin ± SGLT2i | 52 weeks; tirzepatide 5–15 mg/week | Improved HbA1c and weight reduction |
| SURPASS-4[10] | T2DM with high cardiovascular risk | 52 weeks; tirzepatide 5–15 mg/week | Better glycemic control, fewer hypoglycemia events, weight loss benefit |
| SURPASS-5[119] | T2DM on insulin glargine ± metformin | 40 weeks; tirzepatide 5–15 mg/week | Additional HbA1c reduction + weight loss |
| SURPASS-6[120] | T2DM on basal insulin requiring intensification | 52 weeks; tirzepatide 5–15 mg/week | Good glycemic efficacy with weight benefit |
| SURPASS-J-mono[121] | Japanese adults with T2DM | 52 weeks | Confirmed efficacy in Japanese population |
| SURPASS-J-combo[122] | Japanese adults with T2DM on background therapy | 52 weeks | Significant HbA1c and weight reduction |
| SURPASS-AP (Asia-Pacific) Combo[123] | Asia-Pacific adults with T2DM | 40–52 weeks | Similar efficacy across ethnic groups |
| SURPASS-CVOT (ongoing)[118] | T2DM with high CV risk | Multi-year | CV safety and superiority endpoints |

CV, cardiovascular; HbAlc, glycated hemoglobin; SGLT, sodium-glucose cotransporter; T2DM, type 2 diabetes mellitus.

## Clinical implications and cardiovascular outcomes

Beyond its influences on HbA1c and body weight, TZP exerts several additional effects that may have important clinical implications. It improves blood pressure, lipid parameters, systemic inflammation, and endothelial function, thus expanding its clinical application, especially for patients with multiple CVD risk factors. However, these benefits should be distinguished from hard cardiovascular outcomes such as cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure, which are evaluated in dedicated cardiovascular outcome trials (CVOTs). For example, in SURPASS-CVOT, TZP was found to be non-inferior, but not superior, to dulaglutide with respect to MACE, comprising cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.[128] Lower rates of composite cardiovascular and kidney outcomes were later reported in a post hoc analysis.[129] In addition, an imputed placebo analysis using SURPASS-CVOT and REWIND data suggested reductions in MACE and all-cause mortality with TZP compared with placebo.[130] However, these findings should be interpreted carefully since they were derived from indirect analyses rather than controlled trials. Ongoing studies such as SURMOUNT-MMO will further clarify the long-term cardiovascular and mortality benefits of TZP.[131]

## Mechanisms underlying the cardiovascular effects of tirzepatide

TZP, through its GIP and GLP-1R-mediated actions, influences cardiovascular risk factors and cardiac function through interconnected metabolic and molecular mechanisms.[97] Its potent weight-lowering effect is mediated through suppression of the appetite center in the hypothalamus (involving activation of pro-opiomelanocortin

**Table 2.** Summary of SURMOUNT clinical trials of tirzepatide in adults with overweight or obesity.

| Trial name | Population | Duration/dose | Primary outcomes/remarks |
|---|---|---|---|
| SURMOUNT-1[117] | Adults with obesity or overweight (no diabetes) | 72 weeks; tirzepatide 5, 10, 15 mg/week | Mean weight loss up to 22.5%; many achieved ⩾5% or ⩾20% weight reduction |
| SURMOUNT-2[52] | Adults with obesity + type 2 diabetes | 72 weeks; tirzepatide 10, 15 mg/week | Significant weight loss despite diabetes; clinically meaningful results |
| SURMOUNT-3[124] | Obesity after ⩾5% weight loss via lifestyle intervention | 72 weeks after lifestyle lead-in | Additional weight loss beyond lifestyle |
| SURMOUNT-4[125] | Obesity (no diabetes) after open-label tirzepatide lead-in | 36-week open-label + 52-week randomized period | Maintenance of weight loss with ongoing tirzepatide; regain if switched to placebo |
| SURMOUNT-OSA[126] | Obesity + OSA (with and without PAP therapy) | ~52 weeks tirzepatide (dose-escalation up to 10 or 15 mg) | Weight reduction + improvement in OSA severity (in progress/secondary outcomes) |
| SURMOUNT-5 (ongoing)[127] | Obesity or overweight with complications | Ongoing; once-weekly tirzepatide | Dose optimization, comparative efficacy, durability of weight loss, and long-term safety |
| SURMOUNT-MM (ongoing) | Obesity with mobility limitations | Ongoing; once-weekly tirzepatide | Functional outcomes + weight results under investigation |

OSA, obstructive sleep apnea.

and cocaine- and amphetamine-regulated transcript neurons and inhibition of neuropeptide Y and agouti-related peptide neurons), delayed gastric emptying, and modulation of energy expenditure.[132] Reduction in visceral and ectopic fat decreases pro-inflammatory cytokines that are derived from the adipose tissue, such as TNF-α and IL-6; therefore, attenuating systemic low-grade inflammation, which plays a key role in endothelial dysfunction and atherogenesis.[73,75,76,133] At the vascular level, activation of GLP-1R increases NO production via cyclic adenosine monophosphate-protein kinase A signaling and phosphatidylinositol 3-kinase–Akt–eNOS pathways, thus improving endothelial-dependent vasodilation, arterial compliance, and overall vascular function.[134] GIP receptor agonism may further optimize adipose tissue perfusion and lipid partitioning, contributing to improved vascular homeostasis.[135] These mechanisms support the observed reductions in systolic and diastolic arterial blood pressure that is partly independent of weight loss. In contrast, TZP modulates lipid metabolism by enhancing insulin sensitivity, reducing hepatic de novo lipogenesis, suppressing very-low-density lipoprotein secretion, and promoting peripheral lipid uptake. This results in reductions in LDL-cholesterol and triglycerides, modest increases in HDL-cholesterol, and improved postprandial lipid handling, contributing to a less atherogenic lipid profile.[135] The anti-inflammatory and anti-atherogenic effects are evident through reductions in circulating high-sensitivity CRP levels, modulation of macrophage polarization from a pro-inflammatory M1 phenotype toward an anti-inflammatory M2 phenotype (which attenuates vascular inflammation, enhances plaque stability, and limits atherosclerotic progression), and inhibition of nuclear factor kappa B-driven signaling pathways (which reduces transcription of pro-inflammatory cytokines, chemokines, and adhesion molecules involved in endothelial dysfunction and plaque formation).[136] These processes collectively reduce vascular inflammation, oxidative stress, and the progression of atherosclerotic lesions. The direct cardiovascular benefits of TZP extend to cardiac structure and function. Recent studies reported attenuation of cardiac remodeling, improvements in substrate utilization, and reduction of cardiac lipids.[137,138] These effects may enhance diastolic function, preserve cardiac contractility, and reduce the risk of heart failure in treated patients. Furthermore, improved endothelial function and reduced systemic inflammation contribute

synergistically to cardio-protection.[71,74] Collectively, TZP exerts multi-dimensional cardiometabolic and cardiovascular benefits. Weight reduction and visceral fat loss decrease insulin resistance and systemic inflammation, whereas blood pressure improvements are mediated via enhanced endothelial NO signaling and vascular compliance.[135] Lipid metabolism is favorably modulated, with reductions in LDL and triglyceride levels, increases in HDL levels, and improved postprandial lipid handling.[135] The combined anti-inflammatory and anti-atherogenic effects, together with direct myocardial metabolic benefits, including improved cardiac substrate utilization and attenuation of adverse remodeling, collectively contribute to enhanced cardiovascular health.[133] The ongoing trials, particularly SURPASS-CVOT, explore whether these molecular, metabolic, and direct cardiac mechanisms translate into significant reductions in cardiovascular complications and improved long-term cardiovascular outcomes in high-risk populations.[118]

## Safety profile of tirzepatide and incretin-based therapies

While a definitive reduction in MACEs is still awaited, a previous meta-analysis by Wang et al.[139] suggested increased arrhythmic susceptibility through undefined mechanisms. GLP-1RAs are associated with atrial fibrillation as well as worsening ischemic heart disease.[140] However, incretin-based therapies were not found to increase the risk of ischemic heart disease in diabetic patients.[141] In addition to cardiovascular concerns, incretin-based therapies are associated with several non-cardiovascular adverse effects, most of which are gastrointestinal and dose-dependent. GLP-1RAs were known to cause transient nausea, diarrhea, vomiting, and constipation.[142,143] The risk of hypoglycemia is generally low.[142] Concerns about pancreatitis and pancreatic cancer have been extensively investigated, with the preponderance of evidence supporting pancreatic safety.[144,145] Furthermore, while research involving animal models has shown that prolonged administration of GLP-1 can lead to thyroid hyperplasia and medullary thyroid carcinoma,[146] a recent meta-analysis didn't show an increased risk of cancer in T2DM treated patients.[147] In addition, the immunomodulatory and anti-inflammatory roles of GLP-1, GLP-2, and GIP receptor agonists may be responsible for reduced impact of autoimmune diseases.[148] It was proposed that GLP RAs suppress the mononuclear phagocyte system and reduce inflammatory cell infiltration, in addition to reprogramming innate immunity and suppressing gamma interferon and IL-4 production by natural killer cells.[149] Moreover, they inhibit the production of cytokines, cell adhesion molecules, transforming growth factor-β, and other profibrotic factors.[150] Interestingly, GLP-1 and GIP receptors could be responsible for the local reaction, pruritus, and nodules at the injection site.[151,152]

## Future perspectives

The therapeutic potential of TZP continues to expand while CVOTs are ongoing to explore its long-term effects by comparing TZP with dulaglutide in patients with T2DM and established CVD or high cardiovascular risk.[128] The results will be crucial for confirming the superior cardioprotective role of TZP in high-risk cardiometabolic populations.

Beyond diabetes, there is growing interest in TZP's role in non-diabetic CVD, particularly in populations with obesity, HFpEF, and metabolic syndrome. TZP may emerge as a valuable agent in these conditions due to its dual impact on weight and cardiometabolic markers.

While GLP-1RAs are not currently approved for type 1 diabetes, early-phase studies have explored their adjunctive use in selected patients with residual β-cell function. Though TZP has not yet been formally evaluated in this context, its potent incretin-based mechanism raises questions about its feasibility in specific type 1 diabetes populations, especially those with obesity and insulin resistance.

Looking forward, the future of TZP therapy may lie in personalized medicine, with individualized cardiometabolic profiling used to maximize therapeutic benefit. Patients with significant obesity, insulin resistance, or early-stage cardiovascular dysfunction may derive the most pronounced benefits. Stratification tools, including genomic and biomarker-based assessments, may guide clinicians in identifying patients who will respond best, further advancing the era of precision cardiometabolic care.

## Conclusion

TZP has been described as the "twin-cretin" because of its double effects on both GIP and GLP-1R. Its dual receptor activation more closely copies the endogenous incretin response compared to other drugs that activate only GLP-1R. Its synthetic design ensures sustained receptor activation and prolonged pharmacological action, allowing for once-weekly dosing that provides robust glucose-lowering and weight-reduction benefits. TZP stimulates insulin secretion while concurrently inhibiting glucagon secretion, leading to improved glycemic control with a low risk of hypoglycemia. It exerts significant body weight-lowering effects by delaying gastric emptying, reducing appetite through central hypothalamic pathways, and promoting satiety. In the long-term, TZP improves pancreatic β-cell function and insulin sensitivity, which are essential for prolonged diabetes management. These effects are likely mediated by reducing glucotoxicity, lipotoxicity, and systemic inflammation. Beyond glycemic control, TZP favorably modulates multiple factors that affect cardiovascular health, including obesity, blood pressure, systemic inflammation, endothelial function, as well as cardiac metabolism and structural remodeling, thus supporting its potential cardioprotective role, particularly in heart failure-related phenotypes.

## Declarations

### *Ethics approval and consent to participate*

Not applicable.

### *Consent for publication*

Not applicable.

### *Author contributions*

**Azza O. Alawad:** Conceptualization; Investigation; Methodology; Project administration; Writing – original draft.

**Tarig H. Merghani:** Methodology; Resources; Supervision; Visualization; Writing – review & editing.

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## Appendix

### *Abbreviations*

| | |
|---|---|
| AGEs | advanced glycation end products |
| CVD | cardiovascular disease |
| CVOT | cardiovascular outcome trial |
| eNOS | endothelial nitric oxide synthase |
| GIP | glucose-dependent insulinotropic polypeptide |
| GLP-1 | glucagon-like peptide-1 |
| GLP-1R | glucagon-like peptide-1 receptor |
| GLP-1RA | glucagon-like peptide-1 receptor agonist |
| HbA1c | glycated hemoglobin |
| HDL | high-density lipoprotein |
| HFpEF | heart failure with preserved ejection fraction |
| IL-6 | interleukin-6 |
| iNOS | inducible nitric oxide synthase |
| LDL | low-density lipoprotein |
| MACE | major adverse cardiovascular events |
| NF-κB | nuclear factor kappa B |
| NO | nitric oxide |
| ROS | reactive oxygen species |
| SGLT2 | sodium-glucose cotransporter-2 |
| T2DM | type 2 diabetes mellitus |
| TNF-α | tumor necrosis factor-alpha |
| TZP | tirzepatide |
| VLDL | very-low-density lipoprotein |

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