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Perspectives on weight control in diabetes – Tirzepatide

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ABSTRACT

Tirzepatide, a once-weekly glucose-dependent insulinotropic polypeptide (GIP)/glucagon-like peptide-1 (GLP-1) receptor agonist (GIP/GLP-1 RA) improves glycemic control. Besides improvement of glycemic control, tirzepatide treatment is associated with significantly more weight loss as compared to potent selective GLP-1 receptor agonists as well as other beneficial changes in cardio-metabolic parameters, such as reduced fat mass, blood pressure, improved insulin sensitivity, lipoprotein concentrations, and circulating metabolic profile in individuals with type 2 diabetes (T2D). Some of these changes are partially associated with weight reduction. We review here the putative mechanisms of GIP receptor agonism contributing to GLP-1 receptor agonism-induced weight loss and respective findings with GIP/GLP-1 RAs, including tirzepatide in T2D preclinical models and clinical studies. Subsequently, we summarize the clinical data on weight loss and related non-glycemic metabolic changes of tirzepatide in T2D. These findings suggest that the robust weight loss and associated changes are important contributors to the clinical profile of tirzepatide for the treatment of T2D diabetes and serve as the basis for further investigations including clinical outcomes.

1. Introduction

Tirzepatide, a once-weekly glucose-dependent insulinotropic polypeptide (GIP)/glucagon-like peptide-1 (GLP-1) receptor agonist (GIP/GLP-1 RA), is approved in the United States, Europe, Japan and in some other countries for the treatment of type 2 diabetes mellitus (T2D) and is under development for chronic weight management. Tirzepatide treatment results in improvement of glycemic control and weight loss in individuals with T2D. The general effects, particular the glycemic efficacy of tirzepatide were recently presented in several excellent review papers [1-6]. The current review focuses on weight control and various associated aspects of tirzepatide. Preclinical and clinical data about the role of GIP receptor agonism alone and in combination with GLP-1 receptor agonism leading to the development of GIP/GLP-1 RAs with respect to weight changes are summarized. We review the weight and insulin-sensitizing effects of the early representatives of the GIP/GLP-1 RA class and some of their differences to tirzepatide. Subsequently, the mechanistic effects of tirzepatide on weight, fat distribution, insulin resistance and metabolic changes are discussed based on emerging data. We review findings on weight, insulin sensitivity, lipoproteins, circulating metabolites and blood pressure changes in the T2D clinical development program of tirzepatide primarily based on numerous analyses of seven clinical studies: a phase 2 trial ("Tirzepatide Phase 2 Study"), the SURPASS 1–5 phase 3 studies and a phase 1 clamp study ("Tirzepatide Clamp Study", Table 1) [7-13].

2. Obesity, weight changes and type 2 diabetes

The prevalence of obesity and T2D continues to increase worldwide. This increase is mainly due to excess energy intake (high sugar and fat diet) and sedentary lifestyle affecting a growing proportion of the global population [14,15]. Excess weight or obesity is associated with elevated T2D risk. For example, the relative risk of T2D markedly increased in line with the weight gain observed over 10 years in men and 18 years in women compared to a control population without weight change (Health Professionals' Follow-Up study and Nurses' Health study) [16]. In addition to weight gain, weight variability is also an independent risk factor for T2D complications [17,18]. The pathophysiological connection between obesity and the development of T2D is mediated predominantly by the increase in insulin resistance accompanied by elevated insulin secretion followed by β-cell failure and other unfavorable metabolic changes induced by an excessive fat deposition in

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adipose tissues, liver, pancreas, skeletal muscle, and other organs [19,20]. The close interaction between obesity and diabetes, also called "diabesity", suggests the necessity of joint treatment strategies [20]. Obesity is not only an important risk factor for the development of T2D but also negatively affects multiple physiological functions and organs resulting in numerous complications, such as various manifestations of cardiovascular and pulmonary diseases, cancers, osteoarthritis, sleep apnea and nonalcoholic fatty liver disease or steatohepatitis. Adipose tissue insulin resistance plays a key role in the development of metabolic impairment in patients with obesity and nonalcoholic fatty liver disease. The inadequate suppression of lipolysis by insulin increases lipotoxic metabolites in the peripheral organs that result in various inflammatory pathological changes [21-23].

Since excess weight predisposes T2D, it seems plausible that weight reduction could mitigate the severity of T2D. Early studies demonstrated that diet-induced weight loss in individuals with obesity and T2D positively influenced the clinical status. Calorie restriction decreases fasting glucose concentrations effectively, mainly due to a reduced basal hepatic glucose production due to improved hepatic insulin sensitivity as well as a reduction in postprandial glucose excursions due to increase in peripheral glucose uptake by improved skeletal muscle insulin sensitivity [24]. A more effective weight loss (>15 kg) by severe calorie restriction can reduce and, in most patients with recently diagnosed T2D, can normalize fasting blood glucose and HbA1c, and reach remission of T2D after a few months [25]. As weight reduction may be a central element of T2D interventions, the current guidelines for the treatment of T2D and obesity recommend starting with lifestyle modifications including a healthy diet and more physical activity [26]. Moreover, weight reduction does more than achieve remission of T2D. While the primary endpoint was not met (an intensive lifestyle intervention focusing on weight loss failed to reduce the risk of cardiovascular events), a secondary analysis of the Look AHEAD study demonstrated, that participants who lost at least 10% of their bodyweight in the first year of the study, experienced reduced incidence of major adverse cardiovascular events (MACE) [27]. Thus, weight reduction in T2D could be a therapeutic goal to improve glycemic control and reduce complications.

3. Weight effect of diabetes medications

There are numerous classes of medicines to treat hyperglycemia in T2D. All these agents improve glycemic control but have differential effects on weight. Therapies with pioglitazone (the class of thiazolidinediones) and various insulin regimes and secretagogues such as sulphonylureas and meglitinides are associated with weight gain. Dipeptidyl peptidase-4 (DPP-4) inhibitors appear to be weight neutral [26].

Metformin moderately reduces body weight [28]. Metformin is the first-line glucose-lowering medication recommended by most international guidelines [26] and among other mechanisms of action, inhibits gluconeogenesis, decreases hepatic glucose output and also increases peripheral insulin sensitivity [29-31]. Several preclinical and clinical studies suggest a cardioprotective effect of metformin but no adequately powered cardiovascular outcomes study (CVOT) has been conducted [32,33].

When compared to metformin, drugs in two other classes of diabetes medicines, the sodium-glucose co-transporter 2 (SGLT-2) inhibitors and GLP-1-RAs, reduce weight more markedly [34-36]. Moreover, in CVOTs, some SGLT-2 inhibitors and GLP-1-RAs were proven to be associated with low incidence of hypoglycemia and reduction of MACE in patients with T2D [26,34,37].

3.1. Weight effect of GLP-1 receptor agonists

Incretins are polypeptide hormones secreted after a meal by enteroendocrine cells located in the mucosal tissue of various gut regions. They stimulate insulin secretion and reduce postprandial glucose excursion. The two major representatives are GLP-1 (secreted by the L cells) and GIP (secreted by the K cells) [38]. Due to their short half-life, the native hormones are not suitable for therapeutic application. GLP-1 RAs, on the other hand, have longer half-life and achieve effective glycemic control accompanied with significant weight reduction in patients with T2D [38]. The weight reduction of GLP-1 RAs is dose dependent and the maximum dose is restricted mainly due to dose-dependent gastrointestinal tolerability concerns [39]. Notably, the high-dose formulations of two GLP-1 RAs, liraglutide and semaglutide, beyond glycemic control, are also approved for the treatment of obesity [40,41].

3.2. Weight effect of GIP receptor agonism

While GIP plays an important role as one of the physiological incretins in healthy individuals, it appeared to fail as a therapeutic agent

Table 1
Overview of selected clinical studies with tirzepatide [7-13]. Main study characteristics of Tirzepatide Phase 2 Study (Frias et al.), SURPASS 1–5 studies and Tirzepatide Clamp Study (Heise et al.). BMI, body mass index; HbA1c = glycated hemoglobin A1c; PBO, placebo; MET, metformin; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; SU, sulphonylurea.

Study ClinicalTrials.gov NCT number	Tirzepatide Phase 2 Study 03131687	SURPASS-1 03954834	SURPASS-2 3987919	SURPASS-3 03882970	SURPASS-4 03730662	SURPASS-5 04039503	Tirzepatide Clamp Study 03951753
HbA1c values (%) and BMI (kg/m^2) for inclusion	≥7.0 to ≤ 10.5, and 23–50	≥7.0 to ≤ 9.5, and ≥ 23	≥7.0 to ≤ 10.5, and ≥ 25	≥7.0 to ≤ 10.5, and ≥ 25	≥7.5 to ≤ 10.5, and ≥ 25	≥7.0to ≤ 10.5, and ≥ 23	≥7.0 to ≤ 9.5, and ≥ 23
Participants randomized (N)	318	478	1879	1444	2002	475	117
Study duration (weeks)	26	40	40	52	Up to 104	40	28
Primary objective	Change in HbA1c	Change in HbA1c	Change in HbA1c	Change in HbA1c	Change in HbA1c	Change in HbA1c	Change in clamp disposition index
Baseline diabetes medications	Drug-naïve or MET	Drug-naive or wash-out from any oral drug	MET	MET ± SGLT-2i	± MET ± SGLT-2 i ± SU	Insulin Glargine ± MET	MET ± another oral drug
Comparator	Dulaglutide 1.5 mg and placebo	Placebo	Semaglutide 1 mg	Insulin degludec	Insulin glargine	Placebo	Semaglutide 1 mg and placebo
Baseline characteristics							
Diabetes duration [years]	8.5	4.7	8.6	8.4	11.8	13.3	11.3
Age [years]	57	54	57	57	64	61	62
HbA1c [%]	8.1	7.9	8.3	8.2	8.5	8.3	7.8
BMI [kg/m^2]	32.6	32	34	33	33	33	33

because GIP did not induce a meaningful effect in patients with T2D and hyperglycemia [42]. However, if glycemic status of individuals with insufficiently controlled T2D (mean HbA1c 8.6% [70 mmol/mol] at baseline) was improved by insulin treatment for four weeks, the insulinotropic effect of GIP infused to reach physiological level could increase endogenous insulin secretion albeit below the magnitude of insulin secretion observed in non-diabetic individuals [43]. Nevertheless, this GIP responsiveness of T2D patients inspired the subsequent design and development of GIP and GIP/GLP-1 RAs [44,45].

The evidence for the effect of selective GIP receptor agonists and antagonists on weight is considered conflicting, the results appear to depend on the experimental conditions in preclinical models. Multiple experiments suggested some anti-obesity effect of GIP receptor blockage in lean but less effect in obese rodents [44]. Miyawaki et al showed protection against diet-induced obesity in GIP receptor knock-out mice [46]. Moreover, the GIP antagonist (Pro3)GIP protected against obesity in mice on high-fat diet [47]. On the other hand, some other preclinical studies have suggested a weight neutral effect or weight increase, while others demonstrated a weight decrease with GIP receptor agonism. The administration of ZP4165, a GIP agonist, for example, did not affect body weight and food intake in diet-induced obese (DIO) mice [44]. In a transgenic mouse model, on the other hand, the chronically elevated GIP concentration resulted in increased insulin sensitivity, better glucose tolerance, enhanced β-cell function and weight loss [48]. A recent study, with systematic testing of a series of GIP receptor agonists and antagonists in various preclinical models, created strong evidence that long-acting selective GIP receptor agonists rather than antagonists, induce dose-dependent weight loss, an effect independent of the GLP-1 pathway [49]. The precise mechanism of GIP agonism promoting weight loss is not known. Recent data suggest that GIP receptors in the hypothalamic feeding center of mice may participate in the weight regulation [50,51]. GIP receptor agonist administration increases neuronal activity in the hypothalamic feeding center of DIO mice and is associated with suppressed food intake and weight reduction as well as better glycemic control. Similar changes were observed with GIP/GLP-1 RAs and to a lesser extent, with GLP-1 RAs. In CNS-GIP receptor knockout mice, the effect of GIP/GLP-1 RA was blunted, suggesting the important role of the CNS GIP receptor in the inhibition of food intake in general and by GIP/GLP-1 receptor co-agonists, specifically [52,53].

In addition, GIP receptors are present in both the white and brown adipose tissues [54,55]. GIP enhances glucose uptake, lipolysis, and lipoprotein lipase activity in the adipose tissue and reduces circulating triglyceride concentration [56,57]. GIP receptor agonism increases the perfusion of the adipose tissue, facilitates the removal of triglycerides from the circulation by deposition in the white adipose tissue, preventing the increase of visceral fat content and thus the cascade leading to increased insulin resistance [58]. Considering the weight reduction/obesity protection by both GIP antagonists and agonists, one theory suggests that weight reducing effect of GIP receptor antagonists are through peripheral, adipose tissue related mechanisms while GIP receptor agonists could act centrally to mediate inhibition of food intake. [53]. These complex questions need further research as human data are not supporting the influence of GIP on appetite and energy expenditure. Short-term GIP administrations did not affect energy intake or appetite in overweight or T2D individuals when added to GLP-1 or GLP-1 RA. [59,60]. In summary, preclinical data suggest that the reduced food intake together with the direct effects on adipose tissues may contribute to weight reduction and beneficial metabolic changes observed with GIP receptor agonism. The relevance of these findings on humans remains to be elucidated.

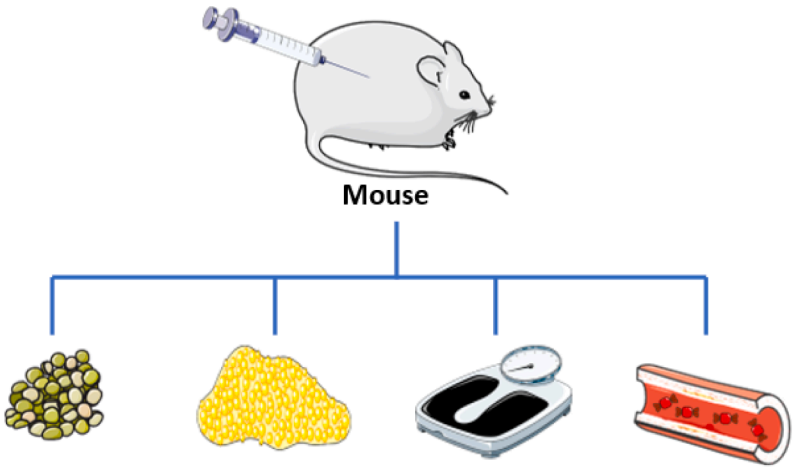
3.3. The modulatory effect of GIP receptor agonists on the weight reduction effect of GLP-1 RAs

Beyond the weight-reducing effects of GIP receptor agonism in preclinical models, the alteration of GLP-1 effects by GIP is of special interest. The administration of GLP-1 RAs both in preclinical and human studies are associated with marked weight loss. In the preclinical model of DIO mice, where GLP-1 RAs are effective, GIP receptor agonist alone did not affect weight. On the other hand, when an equimolar dose of GIP receptor agonist was co-administered for two weeks with an unchanged dose of GLP-1 RA, the weight, food intake and fat mass were reduced more than on GLP-1 RA alone [61].

Similar data have been recently reported with the combination of different GIP and GLP-1 receptor agonists. The combination of the potent, selective, and extended half-life GIP receptor agonist ZP4165 with the established GLP-1 receptor agonist liraglutide resulted in superior weight loss and associated metabolic changes when compared with liraglutide alone in DIO mice [44]. These data, together with other favorable changes in diabetes and metabolic control, supported the strategy to develop GIP/GLP-1 RAs *(*Fig. 1*)* [45].

4. Co-agonists of the GIP receptor and the GLP-1 receptor

The first series of unimolecular GIP receptor and GLP-1 receptor dual agonists was characterized a decade ago. The basic structure, the 40-amino acid glucagon-based polypeptide had similar affinity to both GIP and GLP-1 receptors. Several additional substitutions were made on the amino acid chain to increase the chemical stability and resistance against biological degradation. Moreover, the longer half-life was further prolonged by covalent extension of the polypeptide using either fatty acid (acylation) or polyethylene glycol (PEGylation) [61]. The administration of the basic and extended versions of this co-agonist resulted in dose-dependent reductions in weight, fat mass, and food intake and other improvements in metabolic parameters in rodent models of obesity and diabetes and in cynomolgus monkeys. It was also confirmed that both GIP receptor- and GLP-1 receptor-agonistic pathways were essential for the efficacy [61]. Clinical results of the PEGylated analog demonstrated dose-dependent glycemic control and no inhibition of gastric emptying unlike with GLP-1 RAs [61]. A better gastrointestinal tolerability of this co-agonist versus GLP-1 RAs has also been postulated [61]. Subsequently, a more extensive clinical trial with the acylated version of this co-agonist (RG7697 or NNC0090-2746) confirmed the initial findings of the clinical profile in humans. Participants with T2D were randomized to once-daily subcutaneous injection of 1.8 mg of NNC0090-2746 or placebo. In parallel, an open-label arm of once-daily subcutaneous injections of liraglutide (escalated to 1.8 mg/day) served as a qualitative reference. After 8 weeks, NNC0090-2746 significantly reduced HbA1c levels and body weight relative to baseline values and compared to placebo, with values like those observed in patients on liraglutide [62]. After 12 weeks of treatment with NNC0090-2746 the weight change of −2.86% was not significantly different when compared with −1.19% on placebo (-1.67% difference, $p = 0.06$). Significant reduction (total cholesterol) or trend for lipoprotein lowering on NNC0090-2746 versus placebo was also observed. These changes appeared to be larger than in participants on open label liraglutide. Specifically, plasma leptin was significantly reduced by 22%, a greater change than expected based on the observed body weight reduction. No significant changes in adiponectin and resistin were observed [62]. Interestingly, NNC0090-2746-treated patients with baseline HbA1c values $< 8.5\%$ (69 mmol/mol) lost significantly more weight than those with HbA1c values $\geq 8.5\%$ (69 mmol/mol). This finding could be related to the fact that the effects of GIP receptor activation, including weight reduction, may be realized under normoglycemic or near-normoglycemic conditions [63]. Consistent with clinical studies administering GLP-1 receptor agonists, the most frequently reported adverse events associated with NNC0090-2746 use were gastrointestinal side effects: nausea, vomiting, and diarrhea. The expected diminishing of GI side effects due to the hypothetical advantageous GIP agonistic CNS effect was not apparent [39]. While NNC0090-2746 did show potential for treating hyperglycemia, development of this molecule was discontinued.



Trearments vs. vehichle	Food intake	Fat mass	Body weight	Blood glucose
GIP receptor agonist	↔↓	↔↓	↔↓	↓↓
GLP-1 receptor agonist	↓	↓	↓	↓↓
Combination of GIP and GLP-1 receptor agonists	↓↓	↓↓	↓↓	↓↓

Fig. 1. Effect of GIP receptor agonists, GLP-1 RAs or the combination of both on food intake, fat mass, body weight and blood glucose in various mouse models. A symbolic presentation. GIP receptor agonist, GLP-1 RA and the combination of the two resulted in significantly lower libitum-fed blood glucose levels. There was either no change or mild to moderate reduction versus vehicle in food intake, fat mass and body weight when GIP receptor agonist was administered. Significantly reduced food intake, fat mass and body weight versus vehicle were observed after GLP-1 RA administration. Significantly reduced food intake, fat mass and body weight versus both vehicle and GLP-1 RA were observed after co-administration of GIP receptor agonist and GLP-1 RA. [44,49,53,58,61,64]. The Figure was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license.

5. Tirzepatide

Tirzepatide is the first unimolecular GIP/GLP-1 RA available for treatment of T2D. Tirzepatide has similar affinity to GIP receptors as native GIP. In contrast, its affinity to GLP-1 receptors is 5-fold lower than native GLP-1. When investigated in signaling studies, the difference is even more marked. In cell lines with recombinantly expressed GIP or GLP-1 receptor, tirzepatide reaches cAMP accumulation similarly to native GIP, but 13-fold less potently than native GLP-1. Despite this imbalance, tirzepatide was as active as semaglutide in GIP receptor knockout mice and was a potent GIP receptor agonist in GLP-1 receptor knockout mice, demonstrating marked activity on both incretin pathways. In DIO mice, 10 nmol/kg tirzepatide resulted in larger weight loss than 30 nmol/kg semaglutide and was accompanied by a greater reduction in food intake, a greater increase in fat oxidation and signs of a moderate increase in energy expenditure mainly at the initial phase of treatments [64]. This reduced appetite with tirzepatide could be related to the simultaneous GIP and GLP-1 agonistic effect on the hypothalamic food intake neuronal circuits [51].

5.1. Weight reduction with tirzepatide in individuals with T2D

In the Tirzepatide Phase 2 Study, tirzepatide 5, 10 and 15 mg improved glycemic control versus placebo and dulaglutide with mean changes in HbA1c from baseline of −1.6%, −2% and −2.4%, respectively. Tirzepatide 5, 10 and 15 mg also significantly reduced body weight when compared to placebo and dulaglutide [7]. The subsequent phase 3 development program for the treatment of T2D included five global SURPASS studies, SURPASS 1–5, evaluating the safety and efficacy of tirzepatide 5, 10 and 15 mg in participants at various stages of T2D, with different background medications, and comparator arms, including placebo (SURPASS-1 and −5), semaglutide (SURPASS-2), insulin degludec (SURPASS-3) and insulin glargine (SURPASS-4) [8-12]. These studies included participants with mean baseline body weights of 86–95 kg and BMI of 31.9–34.2 kg/m^2. Tirzepatide treatment resulted in marked body weight reduction and a significantly higher proportion of study participants achieving>5%, 10% and 15% body weight loss when compared with placebo and active comparators. Weight reduction results from the T2D Phase 3 program of tirzepatide, the SURPASS program (SURPASS 1–5 studies) are summarized in Table 1 and Fig. 2*A*, and some more detailed weight results for the longest-duration study, SURPASS-4, are provided in Fig. 2*B and 2C*. Design and major outcomes of the SURPASS 1–5 studies are summarized in a recent review [4]. Briefly, when compared with baseline, the average weight loss on various (5, 10 and 15 mg) tirzepatide doses in the five studies were between 6.2 and 12.9 kg. Larger weight losses were achieved with higher tirzepatide doses. The dose-dependent weight change was −6.2 to −7.8 kg, −7.8 to −10.7 kg and −9.5 to −12.9 kg for tirzepatide 5, 10 and 15 mg doses, respectively. Weight reduction with tirzepatide was apparent within 4 weeks after starting treatment, during the dose-escalation phase and continued until the end of the studies. SURPASS-4 was the longest duration: participants could be exposed to tirzepatide up to 2 years, with a median exposure of 85 weeks. The results demonstrated increasing weight loss during the first year and constant weight thereafter. Tirzepatide was also studied in participants with overweight (BMI higher than 27 kg/m^2) and weight-related complications or with obesity (BMI higher than 30 kg/m^2), with or without prediabetes and without T2D, in the SURMOUNT-1 trial. In these individuals, the weight reduction with tirzepatide was larger than that of the patients with T2D in the SURPASS program [65]. This is similar to observations with semaglutide where participants with overweight/obesity without diabetes lost more weight than those with T2D [41]. Further data on weight effect of tirzepatide in T2D are expected from SURMOUNT-2 (NCT04657003), a study comparing the efficacy and safety of tirzepatide 10 mg and 15 mg to placebo as an adjunct to a reduced-calorie diet and increased physical activity in adults with T2D

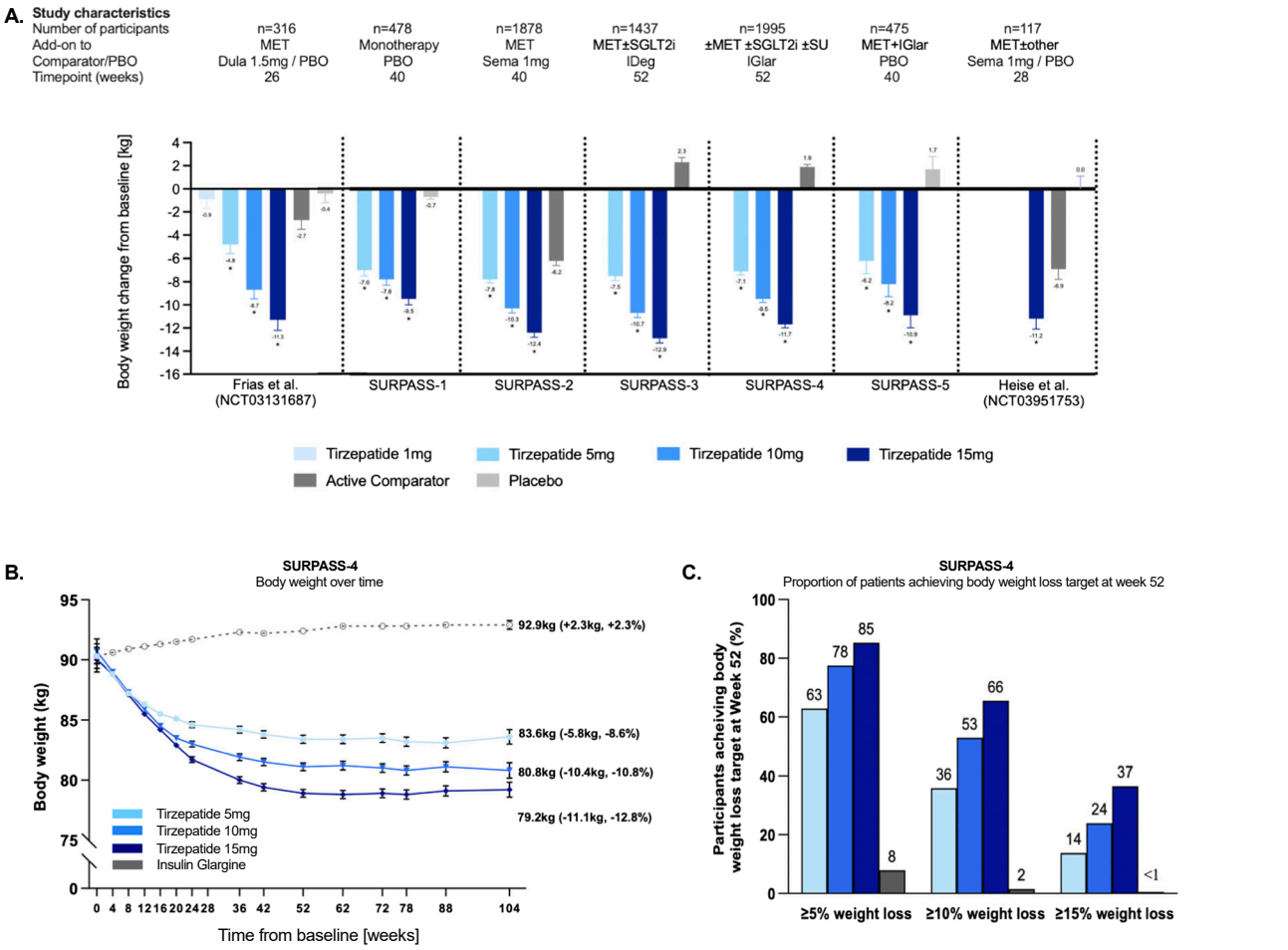


Fig. 2. Effect of tirzepatide on body weight in selected clinical studies [7-13]. (A) Main study characteristics and body weight changes from baseline at primary endpoint for Tirzepatide Phase 2 Study (Frias et al.), SURPASS 1–5 studies and Tirzepatide Clamp Study (Heise et al.); (B) body weight change from baseline over time in the study with longest duration, SURPASS-4; (C) proportion of participants achieving ≥ 5%, ≥10% and ≥ 15% weight loss at the primary study endpoint in SURPASS-4. n, number of patients who were randomly assigned and received at least one dose of study drug; Dula, dulaglutide; PBO, placebo; MET, metformin; Sema, semaglutide; SGLT-2i, sodium-glucose co-transporter 2 inhibitor; IDeg, insulin degludec; IGlar, insulin glargine 100 U/ml; SU, sulphonylurea. * indicates statistical significance $p < 0.05$ for tirzepatide vs. comparator/PBO.

who have obesity or overweight, and from SURPASS-PEDS (NCT05260021), a study to evaluate tirzepatide in pediatric and adolescent participants with T2D inadequately controlled with metformin or basal insulin or both.

5.1.1. *Weight reduction on tirzepatide versus GLP-1 RAs*

The comparison of tirzepatide to GLP-1 RAs is of special interest. Three studies and one indirect comparison analysis reported such results. In the Tirzepatide Phase 2 Study, tirzepatide 1, 5, 10 and 15 mg was compared to dulaglutide 1.5 mg/week. Tirzepatide 5, 10 and 15 mg administration for 26 weeks resulted in −4.8, −8.7 and −11.3 kg mean weight change, respectively. All these changes were significant when compared to −2.7 kg mean weight change on dulaglutide 1.5 mg/week. Correspondingly, 20.8%, 67.6%, 66.2% and 11.7% of the study participants lost>10% of their original weight on 5, 10, 15 mg tirzepatide and 1.5 mg/week dulaglutide, respectively. When compared to dulaglutide, tirzepatide significantly reduced the fasting concentration of insulin and affected the Homeostasis Model Assessment (HOMA) indexes: increased HOMA-B, and reduced HOMA-IR [7]. The HOMA measurements reflects some aspect of the beta cell function and insulin resistance with important limitations. In the SURPASS-2 study, in patients with T2D on metformin therapy at baseline, 40 weeks of treatment with all three tirzepatide doses significantly reduced mean body weight when compared with semaglutide 1 mg/week: the mean weight change with tirzepatide 5, 10 and 15 mg (-7.8, −10.3, −12.4 kg) was significantly larger than with semaglutide 1 mg/week (−6.2 kg). The percentage of patients who lost more than 10% of their body weight was 34%, 47%, 57% and 24% of participants on 5, 10, 15 mg tirzepatide and 1 mg/week semaglutide, respectively [9]. In the Tirzepatide Clamp Study, 28 weeks of treatment with tirzepatide 15 mg or semaglutide 1 mg/week resulted in a weight change of −11.2 and −6.9 kg, respectively [13]. Meanwhile, semaglutide 2 mg/week became approved for the treatment of patients with T2D. In the SUSTAIN FORTE study, the mean change in body weight from baseline at week 40 was − 6.9 kg with semaglutide 2 mg/week, demonstrating statistically significant incremental weight reduction compared to −6.0 kg with semaglutide 1 mg/week [66]. No study has been conducted so far comparing weight loss with tirzepatide versus semaglutide 2 mg/week. In an adjusted indirect comparison in patients with T2D, tirzepatide 5 mg treatment resulted in similar, while tirzepatide 10 and 15 mg in larger, weight loss when compared with semaglutide 2 mg/week [67].

5.1.2. *Weight reduction and fat distribution with tirzepatide in patients with T2D*

The change in various fat compartments has been measured by MRI technique in the SURPASS-3 substudy of patients with T2D on metformin ± SGLT-2 inhibitors with fatty liver index>60 [68]: visceral adipose tissue, liver fat content, and abdominal subcutaneous adipose tissue.

After 52 weeks of treatment, all three doses of tirzepatide (5, 10, and 15 mg) had statistically greater changes in liver fat content (with relative change from baseline ranging from –29.8% to –47.1%), in visceral adipose tissue (–16.3% to –25.1%) and in abdominal subcutaneous adipose tissue (–12.6% to –20.9%) when compared with titrated insulin degludec (–11.2%, +8.1% and + 7.6%, respectively). Moreover, the body weight reduction (kg) and the improvement in glycemic control (HbA1c) achieved on tirzepatide was significantly correlated with the reduction in liver fat content. A post hoc analysis of the Tirzepatide Phase 2 Study in patients with T2D showed improvement in non-alcoholic steatohepatitis-related biomarkers (serum alanine aminotransferase, aspartate aminotransferase, keratin-18, procollagen III and total adiponectin) after 26 weeks of treatment with tirzepatide [69]. All of these findings could represent a potential therapeutic benefit of tirzepatide in non-alcoholic steatohepatitis. These evaluations are ongoing in a study specifically focused on that target population (SYNERGY-NASH; NCT04166773).

A recent analysis of the Tirzepatide Clamp Study has compared the effect on body composition of weight reduction by tirzepatide 15 mg and semaglutide 1 mg/week in participants with T2D when compared with placebo. After 28 weeks of treatment, body weight was significantly reduced from baseline with tirzepatide (-11.2 kg) and semaglutide (-6.9 kg) while no change could be observed in the placebo group (see also Section 5.1.1). More importantly, body composition analyses showed that the body weight loss was overwhelmingly fat mass reduction, −9.7 kg and −5.9 kg on tirzepatide and semaglutide, respectively. The overall weight and the fat mass reductions were significantly larger with tirzepatide than with semaglutide. The fasting appetite reduction for both drugs and the energy intake during ad libitum buffet-style lunch was significantly reduced with tirzepatide (−348 kcal) and with semaglutide (-284 kcal) versus placebo, but the magnitude of the reduction was not different between the two drugs. Thus, factors other than profound reduction in appetite and caloric intake with tirzepatide versus semaglutide could contribute for the more pronounced weight loss.

5.1.3. Associations between baseline characteristics and magnitude of weight loss with tirzepatide

A clinically meaningful proportion of participants with T2D on tirzepatide achieved substantial body weight reduction in the SURPASS program. In a pooled analysis of SURPASS 1–4 clinical trials, 792 individuals (25%) achieved ≥ 15% reduction of their baseline body weight. Higher doses of tirzepatide, females, White or Asian race, participants with better glycemic status, lower non-HDL cholesterol value, and those on metformin at baseline had a higher chance of losing ≥ 15% of the baseline body weight [70]. Moreover, patients on tirzepatide reaching higher weight loss categories (analyzing groups with < 5%, ≥5 to < 10%, ≥10 to < 15%, and ≥ 15% weight loss) achieved greater improvements in glycemic control, blood pressure, serum triglycerides and alanine aminotransferase. There was a significant correlation between body weight loss and HbA1c decrease in SURPASS-2, −3 and −4 studies [71,72].

5.2. Weight reduction and increased insulin sensitivity with tirzepatide

5.2.1. Preclinical data on insulin sensitivity with tirzepatide

In preclinical experiments with obese insulin-resistant mice, neither tirzepatide (in Glp-1r–/– animals), nor the selective GIP receptor agonist LAGIPRA (in wild-type animals) reduced weight. The lack of weight reduction in these experiments is consistent with earlier findings that the GLP-1 receptor agonistic effect is required as a sensitizer for GIP receptor agonist-induced weight reduction. Despite the constant weight, both compounds increased insulin sensitivity when evaluated by hyperinsulinemic-euglycemic clamp technique. In addition, when the insulin-sensitizing effect of tirzepatide and the GLP-1 RA, semaglutide, were compared in a setting of equivalent weight reduction, tirzepatide was a more effective insulin sensitizer [58]. This effect could be associated with the GIP receptor agonism-mediated increase in glucose disposal in white adipose tissue and the upregulation of genes associated with glucose, lipid and branched-chain amino acids (branched-chain amino acid aminotransferase 2 and branched-chain alpha-keto acid dehydrogenase) catabolism in brown adipose tissue [73]. A recent in vivo study evaluating this mechanism in obese insulin-resistant mice using stable-isotope tracer confirmed that tirzepatide treatment in rodents stimulates the catabolism of branched-chain amino acids in brown adipose tissue [74].

5.2.2. Clinical evidence on insulin sensitivity with tirzepatide

The effect of tirzepatide on insulin sensitivity has been investigated in a dedicated clinical study, in the Tirzepatide Clamp Study. One hundred and seventeen participants with T2D were randomized to weekly tirzepatide 15 mg, semaglutide 1 mg, or placebo. Insulin sensitivity was measured at baseline and after 28 weeks of treatment by monitoring the glucose infusion rate required to maintain a constant glucose concentration during the hyperinsulinemic-euglycemic clamp. Insulin sensitivity increased by 65.7% with tirzepatide 15 mg and 37.5% with semaglutide 1 mg. Part of the difference could be explained by the larger weight reduction observed with tirzepatide (-11.2 kg) when compared with semaglutide (-6.9 kg). Indeed, the improvement in insulin sensitivity with both drugs correlated with the magnitude of weight reduction. Similar weight reduction, however, was associated with significantly larger improvement in insulin sensitivity with tirzepatide 15 mg when compared with semaglutide 1 mg, [1,13,75]. In the Tirzepatide Phase 2 Study, β-cell function, measured by homeostatic model assessment (HOMA) 2-B, was increased both with the selective GLP-1 RA, dulaglutide (1.5 mg), and tirzepatide (5, 10 and 15 mg) vs placebo. Insulin resistance (HOMA-IR), on the other hand, was reduced significantly only with tirzepatide 10 mg versus dulaglutide and placebo ($P \leq 0.02$). The improvements in insulin resistance (HOMA-IR) with tirzepatide 10 or 15 mg was explained only partially (13–21%) by weight loss in individuals with T2D [76]. GLP-1 RAs also improve insulin resistance in subjects with T2D and these improvements are mainly related to weight reduction [77].

Post hoc analyses of the Tirzepatide Phase 2 Study found that additional biochemical markers of improved insulin sensitivity, such as adiponectin, IGFBP-1, and IGFBP-2, were significantly increased by one or more doses of tirzepatide ($P < 0.05$) [76]. Further, tirzepatide-mediated insulin sensitization in participants with T2D is accompanied by lowering of several circulating biomarkers associated with systemic insulin resistance, including branched-chain amino acids and branched-chain ketoacids [78].

5.3. Lipoprotein changes with tirzepatide

More weight loss with tirzepatide is associated with larger reduction in serum triglycerides in pooled analyses of the SURPASS 1–4 and SURPASS 1–5 studies [71,72]. Moreover, tirzepatide dose-dependently improved the levels of numerous lipoproteins. In the Tirzepatide Phase 2 Study, triglycerides, apolipoprotein (apo)B, and apoC-III levels were reduced significantly, and serum preheparin lipoprotein lipase (LPL) was increased when compared with placebo. In addition, higher doses of tirzepatide (10 and 15 mg) decreased large triglyceride-rich lipoprotein particles (TRLP) and small low-density lipoprotein particles (LDLP). The lipoprotein insulin resistance (LPIR) score, a weighted combination of six lipoprotein subclass measures, was reduced with tirzepatide 10 and 15 mg when compared with both placebo and dulaglutide. There was a dose-dependent decrease in triglycerides with tirzepatide, with 23% reduction in the tirzepatide 15 mg group. This is a higher value when compared with selective GLP-1 RAs or other anti-hyperglycemic medications. Triglyceride reduction was higher in individuals with increased baseline triglyceride (≥150 mg/dL [1.7 mmol/L]) [79]. The mechanism for decreased triglyceride concentration with tirzepatide could be partially weight-loss mediated: SURPASS study

participants on tirzepatide reaching higher weight-loss categories (analyzing groups with < 5%, ≥5 to < 10%, ≥10 to < 15%, and ≥ 15% weight loss) achieved greater improvements in serum triglycerides [71,72]. On the other hand serum triglyceride reduction with tirzepatide could also be related to the direct GIP receptor agonistic effect on adipose tissues, increased lipolysis and LPL activity [54–57]. It is clinically important that the triglyceride-lowering effect of tirzepatide appears to be additive to the effect of fibrates. To reduce triglyceride concentration, fibrates lower hepatic apoC-III production and increase LPL-mediated lipolysis via activation of specific transcription factors belonging to the nuclear hormone receptor superfamily, termed peroxisome proliferator-activated receptors (PPARs) and similar effects have been observed with tirzepatide [79]. Post hoc analyses of the SURPASS-4 study, conducted in participants with T2D and high CV risk, demonstrated that for participants not on fibrate therapy, tirzepatide 5, 10 and 15 mg lowered triglycerides (-16.5% to –22.3%) more effectively than insulin glargine (-7.1%). The reduction of triglycerides in participants on fibrate therapies at baseline were similar (Fig. 3). Analogous findings could be observed in the same study regarding changes in LDL cholesterol in patients with or without statin use at baseline: tirzepatide reduced LDL cholesterol irrespective of statin use [80]. In a similar observation for NNC0090-2746, no interaction of lipid parameter changes with statin was found [62]. These results could be of interest when patients with T2D with increased triglyceride and/or LDL cholesterol values despite fibrate and/or statin treatments are treated with tirzepatide.

5.4. *Weight reduction and blood pressure and cardiovascular outcomes with tirzepatide*

In clinical studies, tirzepatide therapy resulted consistently in meaningful reduction of both systolic and diastolic blood pressure. In the SURPASS 1–5 trial program, the reduction in systolic blood pressure versus baseline was dose dependent and between −4 and −13 mmHg. The largest reductions were observed in SURPASS-5, which enrolled participants with the highest blood pressure and the longest duration of T2D. The lowest decrease in blood pressure was observed in SURPASS-1, which enrolled individuals with the lowest blood pressure and the shortest duration of T2D. The blood pressure change for all tirzepatide doses was significantly larger when compared with active controls like insulin glargine (SURPASS-4), insulin degludec (SURPASS-3) or semaglutide 1 mg (SURPASS-2) [9-11]. A recent analysis investigated the association between weight and blood pressure reduction in patients treated with tirzepatide. These reductions in systolic blood pressure were partially mediated by weight reduction in the SURPASS 1–5 studies. In pooled analyses of these studies and tirzepatide doses, the body weight reduction also correlated with the decrease in systolic blood pressure ($r = 0.21$, $p < 0.0001$) [81]. Several studies demonstrated that weight loss in diabetes improves glycemic control, reduces blood pressure, and improves blood lipids [27]. While the main driver of systolic blood pressure reduction could be the concomitant weight loss with tirzepatide, additional mechanisms could also contribute: improvement in insulin sensitivity, lipoproteins, and cardiovascular biomarkers as well as the reduction in visceral and liver fat [81].

The weight reduction and associated metabolic improvements could be cardioprotective in T2D. While the primary endpoint was not met, the results of a post hoc analysis of the Look AHEAD study suggested a relationship between marked weight loss and incidence of cardiovascular disease (the composite of death from cardiovascular causes, non-fatal acute myocardial infarction, non-fatal stroke, or hospitalization for angina) in a subset of people with T2D. In 10.2 years of follow-up those participants who lost at least 10% of their body weight in the first year of the study had a significant 21% lower risk for a cardiovascular incident [27]. Several GLP-1 RAs, which reduce weight, were proven to reduce the risk of MACE in outcomes trials of people with T2D [82]. It is not clear, however, if weight reduction is necessary for such cardio-protection by these GLP-1 RAs [83]. Beyond weight, metabolic syndrome, a composite of at least 3 of the 5 obesity-associated cardiovascular risk factors including obesity, impaired glucose tolerance, increased triglyceride, decreased HDL cholesterol and hypertension, elevates the risk of severe cardiovascular complications [84]. Tirzepatide significantly reduced the number of participants fulfilling the criteria of metabolic syndrome versus insulin glargine in SURPASS-4 [85] (Fig. 4). Moreover, in SURPASS-4 tirzepatide slowed the rate of estimated glomerular filtration rate (eGFR) decline and reduced urine albumin-creatinine ratio (UACR), cardiovascular risk factors, in clinically meaningful ways compared with insulin glargine [86]. Tirzepatide has an established safety profile as far as cardiovascular risk is concerned as there was no increased risk of MACE identified in the SURPASS-4 trial with participants at increased cardiovascular risk randomized to tirzepatide or insulin glargine. Adjudicated MACE-4 events (cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina) occurred in 109 participants and were not increased with tirzepatide compared with glargine (hazard ratio 0.74, 95% CI

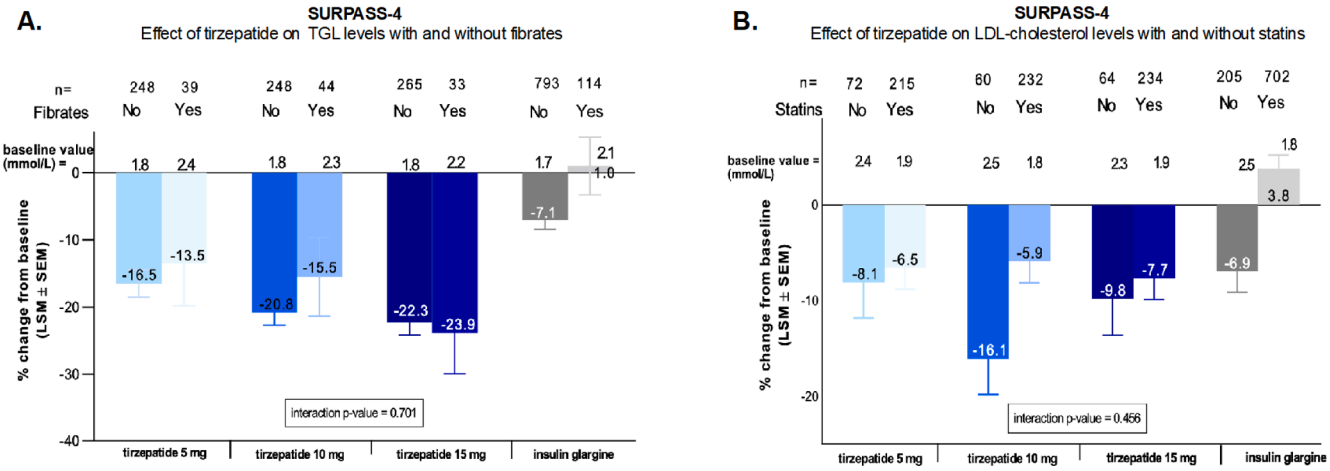


Fig. 3. Effect of tirzepatide on triglyceride and LDL-cholesterol levels in SURPASS-4 [80]. Post hoc analysis assessed percent change from baseline to week 52 (primary endpoint) of (A) triglycerides and (B) LDL-cholesterol across subgroup categories in participants while on assigned treatment without rescue medication. In participants with T2D and high cardiovascular risk, tirzepatide lowered triglycerides and LDL-cholesterol more effectively than insulin glargine, regardless of concomitant use of fibrates or statins, respectively. TGL, triglyceride; LDL, low-density lipoproteins; LSM, least-squares mean; n, population size; SEM, standard error of the mean.

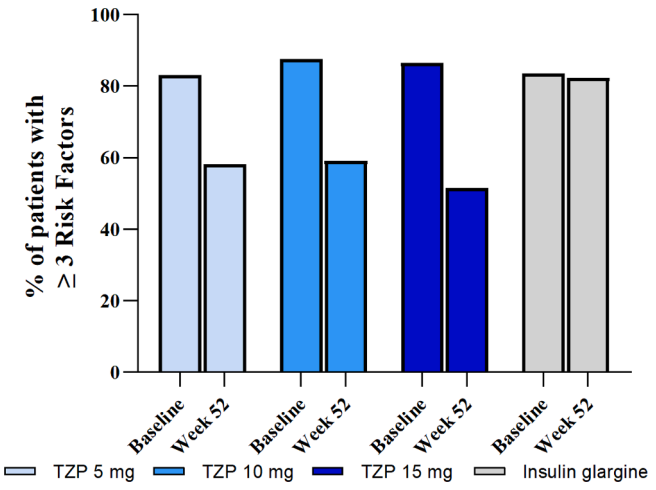


Fig. 4. Effect of tirzepatide on the prevalence of metabolic syndrome* in SURPASS-4 [85]. The prevalence of metabolic syndrome* at baseline was 83–88% across all groups with a significant dose-dependent reduction at 52 weeks of 52–59% with tirzepatide while no change was observable with insulin glargine ($p < 0.001$). *Defined the presence of at least 3 of the components: (1) waist circumference > 102 cm (2) fasting serum glucose ≥ 100 mg/dL or HbA1c ≥ 5.7% (39 mmol/mol), (3) systolic blood pressure > 130 mm Hg and diastolic blood pressure > 85 mm Hg, (4) serum triglycerides > 150 mg/dL (1.7 mmol/L) and (5) HDL cholesterol > 40 mg/dL (1.0 mmol/L).

0.51–1.08) [11]. The *meta*-analysis of the SURPASS program for cardiovascular risk demostrated similar results: the MACE-4 hazard ratio for tirzepatide versus comparator groups was 0.80 (95% CI, 0.57–1.11) [87]. In order to evaluate the cardiovascular safety and potential cardioprotection of tirzepatide, SURPASS-CVOT, a cardiovascular outcomes study comparing tirzepatide with the cardioprotective GLP-1 RA, dulaglutide, is ongoing (A Study of Tirzepatide (LY3298176) Compared With Dulaglutide on Major Cardiovascular Events in Participants With Type 2 Diabetes, SURPASS-CVOT); NCT04255433). [88,89].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Nauck MA, D'Alessio DA. Tirzepatide, a dual GIP/GLP-1 receptor co-agonist for the treatment of type 2 diabetes with unmatched effectiveness regrading glycaemic control and body weight reduction. Cardiovasc Diabetol 2022;21:169.

[2] Forzano I, Varzideh F, Avvisato R, Jankauskas SS, Mone P, Santulli G. Tirzepatide: a systematic update. Int J Mol Sci 2022:23.

[3] Gallwitz B. Clinical perspectives on the use of the GIP/GLP-1 receptor agonist tirzepatide for the treatment of type-2 diabetes and obesity. Front Endocrinol 2022; 13:1004044.

[4] De Block C, Bailey C, Wysham C, Hemmingway A, Allen SE, Peleshok J. Tirzepatide for the treatment of adults with type 2 diabetes: An endocrine perspective. Diabetes Obes Metab 2023;25:3–17.

[5] Zaffina I, Pelle MC, Armentaro G, Giofrè F, Cassano V, Sciacqua A, et al. Effect of dual glucose-dependent insulinotropic peptide/glucagon-like peptide-1 receptor agonist on weight loss in subjects with obesity. Front Endocrinol 2023;14:1095753.

[6] Sinha R, Papamargaritis D, Sargeant JA, Davies MJ. Efficacy and safety of tirzepatide in Type 2 diabetes and obesity management. J. Obesity Metabolic Syndrome 2023;32:25–45.

[7] Frias JP, Nauck MA, Van J, Kutner ME, Cui X, Benson C, et al. Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial. Lancet 2018;392:2180–93.

[8] Rosenstock J, Wysham C, Frias JP, Kaneko S, Lee CJ, Fernandez Lando L, et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. Lancet 2021;398:143–55.

[9] Frías JP, Davies MJ, Rosenstock J, Pérez Manghi FC, Fernández Landó L, Bergman BK, et al. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. N Engl J Med 2021;385:503–15.

[10] Ludvik B, Giorgino F, Jódar E, Frias JP, Fernández Landó L, Brown K, et al. Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial. Lancet 2021;398:583–98.

[11] Del Prato S, Kahn SE, Pavo I, Weerakkody GJ, Yang Z, Doupis J, et al. Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. Lancet 2021;398:1811–24.

[12] Dahl D, Onishi Y, Norwood P, Huh R, Bray R, Patel H, et al. Effect of Subcutaneous Tirzepatide vs Placebo Added to Titrated Insulin Glargine on Glycemic Control in Patients With Type 2 Diabetes: The SURPASS-5 Randomized Clinical Trial. JAMA 2022;327:534–45.

[13] Heise T, Mari A, DeVries JH, Urva S, Li J, Pratt EJ, et al. Effects of subcutaneous tirzepatide versus placebo or semaglutide on pancreatic islet function and insulin sensitivity in adults with type 2 diabetes: a multicentre, randomised, double-blind, parallel-arm, phase 1 clinical trial. Lancet Diabetes Endocrinol 2022;10:418–29.

[14] Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract 2022;183:109119.

[15] Ogurtsova K, Guariguata L, Barengo NC, Ruiz PL, Sacre JW, Karuranga S, et al. IDF diabetes Atlas: global estimates of undiagnosed diabetes in adults for 2021. Diabetes Res Clin Pract 2022;183:109118.

[16] Willett WC, Dietz WH, Colditz GA. Guidelines for healthy weight. N Engl J Med 1999;341:427–34.

[17] Prattichizzo F, Frigé C, La Grotta R, Ceriello A. Weight variability and diabetes complications. Diabetes Res Clin Pract 2023;199:110646.

[18] Ceriello A, Lucisano G, Prattichizzo F, La Grotta R, Franzén S, Gudbjörnsdottir S, et al. Risk factors variability and cardiovascular risk among patients with diabetes: a nationwide observational study. Eur J Prev Cardiol 2023.

[19] Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Gómez JM, et al. Bioelectrical impedance analysis–part I: review of principles and methods. Clin Nutr (Edinburgh, Scotland) 2004;23:1226–43.

[20] Astrup A, Finer N. Redefining type 2 diabetes: 'diabesity' or 'obesity dependent diabetes mellitus'? Obes Rev 2000;1:57–9.

[21] Khan SS, Ning H, Wilkins JT, Allen N, Carnethon M, Berry JD, et al. Association of body mass index with lifetime risk of cardiovascular disease and compression of morbidity. JAMA Cardiol 2018;3:280–7.

[22] Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC Public Health 2009;9:88.

[23] Rosso C, Kazankov K, Younes R, Esmaili S, Marietti M, Sacco M, et al. Crosstalk between adipose tissue insulin resistance and liver macrophages in non-alcoholic fatty liver disease. J Hepatol 2019;71:1012–21.

[24] Markovic TP, Jenkins AB, Campbell LV, Furler SM, Kraegen EW, Chisholm DJ. The determinants of glycemic responses to diet restriction and weight loss in obesity and NIDDM. Diabetes Care 1998;21:687–94.

[25] Steven S, Taylor R. Restoring normoglycaemia by use of a very low calorie diet in long- and short-duration Type 2 diabetes. Diabetic Med: A J Brit Diabetic Assoc 2015;32:1149–55.

[26] Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, et al. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2022;2022(45): 2753–86.

[27] Gregg EW, Jakicic JM, Blackburn G, Bloomquist P, Bray GA, Clark JM, et al. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. Lancet Diabetes Endocrinol 2016;4:913–21.

[28] Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006;355:2427–43.

[29] Stumvoll M, Nurjhan N, Perriello G, Dailey G, Gerich JE. Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. N Engl J Med 1995;333: 550–4.

[30] Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. Diabetologia 2017;60:1577–85.

[31] Pavo I, Jermendy G, Varkonyi TT, Kerenyi Z, Gyimesi A, Shoustov S, et al. Effect of pioglitazone compared with metformin on glycemic control and indicators of insulin sensitivity in recently diagnosed patients with type 2 diabetes. J Clin Endocrinol Metab 2003;88:1637–45.

[32] Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–89.

[33] Kooy A, de Jager J, Lehert P, Bets D, Wulffelé MG, Donker AJ, et al. Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. Arch Intern Med 2009;169:616–25.

[34] Tsapas A, Karagiannis T, Kakotrichi P, Avgerinos I, Mantsiou C, Tousinas G, et al. Comparative efficacy of glucose-lowering medications on body weight and blood pressure in patients with type 2 diabetes: A systematic review and network meta-analysis. Diabetes Obes Metab 2021;23:2116–24.

[35] Maruthur NM, Tseng E, Hutfless S, Wilson LM, Suarez-Cuervo C, Berger Z, et al. Diabetes medications as monotherapy or metformin-based combination therapy for Type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2016;164: 740–51.

[36] Palmer SC, Tendal B, Mustafa RA, Vandvik PO, Li S, Hao Q, et al. Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. BMJ (Clinical research ed) 2021;372:m4573.
[37] Ceriello A, Prattichizzo F, Phillip M, Hirsch IB, Mathieu C, Battelino T. Glycaemic management in diabetes: old and new approaches. Lancet Diabetes Endocrinol 2022;10:75–84.
[38] Nauck MA, Meier JJ. The incretin effect in healthy individuals and those with type 2 diabetes: physiology, pathophysiology, and response to therapeutic interventions. Lancet Diabetes Endocrinol 2016;4:525–36.
[39] Samms RJ, Coghlan MP, Sloop KW. How May GIP Enhance the Therapeutic Efficacy of GLP-1? Trends Endocrinol Metab 2020;31:410–21.
[40] Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, et al. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. N Engl J Med 2015;373:11–22.
[41] Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med 2021;384:989–1002.
[42] Nauck MA, Heimesaat MM, Orskov C, Holst JJ, Ebert R, Creutzfeldt W. Preserved incretin activity of glucagon-like peptide 1 [7-36 amide] but not of synthetic human gastric inhibitory polypeptide in patients with type-2 diabetes mellitus. J Clin Invest 1993;91:301–7.
[43] Hojberg PV, Vilsboll T, Rabol R, Knop FK, Bache M, Krarup T, et al. Four weeks of near-normalisation of blood glucose improves the insulin response to glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide in patients with type 2 diabetes. Diabetologia 2009;52:199–207.
[44] Norregaard PK, Deryabina MA, Tofteng Shelton P, Fog JU, Daugaard JR, Eriksson PO, et al. A novel GIP analogue, ZP4165, enhances glucagon-like peptide-1-induced body weight loss and improves glycaemic control in rodents. Diabetes Obes Metab 2018;20:60–8.
[45] Tschop MH, Finan B, Clemmensen C, Gelfanov V, Perez-Tilve D, Muller TD, et al. Unimolecular Polypharmacy for Treatment of Diabetes and Obesity. Cell Metab 2016;24:51–62.
[46] Miyawaki K, Yamada Y, Ban N, Ihara Y, Tsukiyama K, Zhou H, et al. Inhibition of gastric inhibitory polypeptide signaling prevents obesity. Nat Med 2002;8:738–42.
[47] Gault VA, McClean PL, Cassidy RS, Irwin N, Flatt PR. Chemical gastric inhibitory polypeptide receptor antagonism protects against obesity, insulin resistance, glucose intolerance and associated disturbances in mice fed high-fat and cafeteria diets. Diabetologia 2007;50:1752–62.
[48] Kim SJ, Nian C, Karunakaran S, Clee SM, Isales CM, McIntosh CH. GIP-overexpressing mice demonstrate reduced diet-induced obesity and steatosis, and improved glucose homeostasis. PLoS One 2012;7:e40156.
[49] Mroz PA, Finan B, Gelfanov V, Yang B, Tschop MH, DiMarchi RD, et al. Optimized GIP analogs promote body weight lowering in mice through GIPR agonism not antagonism. Mol Metab 2019;20:51–62.
[50] Adriaenssens AE, Gribble FM, Reimann F. The glucose-dependent insulinotropic polypeptide signaling axis in the central nervous system. Peptides 2020;125:170194.
[51] Adriaenssens AE, Biggs EK, Darwish T, Tadross J, Sukthankar T, Girish M, et al. Glucose-Dependent insulinotropic polypeptide receptor-expressing cells in the hypothalamus regulate food intake. Cell Metab 2019;30:987–96.
[52] NamKoong C, Kim MS, Jang BT, Lee YH, Cho YM, Choi HJ. Central administration of GLP-1 and GIP decreases feeding in mice. Biochem Biophys Res Commun 2017;490:247–52.
[53] Zhang Q, Delessa CT, Augustin R, Bakhti M, Colldén G, Drucker DJ, et al. The glucose-dependent insulinotropic polypeptide (GIP) regulates body weight and food intake via CNS-GIPR signaling. Cell Metab 2021;33:833–44.
[54] Rudovich N, Kaiser S, Engeli S, Osterhoff M, Gögebakan O, Bluher M, et al. GIP receptor mRNA expression in different fat tissue depots in postmenopausal non-diabetic women. Regul Pept 2007;142:138–45.
[55] Beaudry JL, Kaur KD, Varin EM, Baggio LL, Cao X, Mulvihill EE, et al. Physiological roles of the GIP receptor in murine brown adipose tissue. Molecular metabolism 2019;28:14–25.
[56] Song DH, Getty-Kaushik L, Tseng E, Simon J, Corkey BE, Wolfe MM. Glucose-dependent insulinotropic polypeptide enhances adipocyte development and glucose uptake in part through Akt activation. Gastroenterology 2007;133:1796–805.
[57] Kim SJ, Nian C, McIntosh CH. Activation of lipoprotein lipase by glucose-dependent insulinotropic polypeptide in adipocytes. A role for a protein kinase B, LKB1, and AMP-activated protein kinase cascade. J Biol Chem 2007;282:8557–67.
[58] Samms RJ, Christe ME, Collins KA, Pirro V, Droz BA, Holland AK, et al. GIPR agonism mediates weight-independent insulin sensitization by tirzepatide in obese mice. J Clin Invest 2021;131.
[59] Bergmann NC, Gasbjerg LS, Heimburger SM, Krogh LSL, Dela F, Hartmann B, et al. No acute effects of exogenous glucose-dependent insulinotropic polypeptide on energy intake, appetite, or energy expenditure when added to treatment with a long-acting glucagon-like peptide 1 receptor agonist in men with Type 2 diabetes. Diabetes Care 2020;43:588–96.
[60] Bergmann NC, Lund A, Gasbjerg LS, Meessen ECE, Andersen MM, Bergmann S, et al. Effects of combined GIP and GLP-1 infusion on energy intake, appetite and energy expenditure in overweight/obese individuals: a randomised, crossover study. Diabetologia 2019;62:665–75.
[61] Finan B, Ma T, Ottaway N, Muller TD, Habegger KM, Heppner KM, et al. Unimolecular dual incretins maximize metabolic benefits in rodents, monkeys, and humans. Sci Transl Med 2013;5:209ra151.
[62] Frias JP, Bastyr 3rd EJ, Vignati L, Tschöp MH, Schmitt C, Owen K, et al. The sustained effects of a dual GIP/GLP-1 receptor agonist, NNC0090-2746, in patients with Type 2 diabetes. Cell Metab 2017;26:343–52.
[63] Knop FK, Vilsbøll T, Højberg PV, Larsen S, Madsbad S, Holst JJ, et al. The insulinotropic effect of GIP is impaired in patients with chronic pancreatitis and secondary diabetes mellitus as compared to patients with chronic pancreatitis and normal glucose tolerance. Regul Pept 2007;144:123–30.
[64] Coskun T, Sloop KW, Loghin C, Alsina-Fernandez J, Urva S, Bokvist KB, et al. LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: from discovery to clinical proof of concept. Mol Metab 2018;18:3–14.
[65] Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, et al. Tirzepatide once weekly for the treatment of obesity. N Engl J Med 2022;387:205–16.
[66] Frías JP, Auerbach P, Bajaj HS, Fukushima Y, Lingvay I, Macura S, et al. Efficacy and safety of once-weekly semaglutide 2·0 mg versus 1·0 mg in patients with type 2 diabetes (SUSTAIN FORTE): a double-blind, randomised, phase 3B trial. Lancet Diabetes Endocrinol 2021;9:563–74.
[67] Vadher K, Patel H, Mody R, Levine JA, Hoog M, Cheng AY, et al. Efficacy of tirzepatide 5, 10 and 15 mg versus semaglutide 2 mg in patients with type 2 diabetes: An adjusted indirect treatment comparison. Diabetes Obes Metab 2022;24:1861–8.
[68] Gastaldelli A, Cusi K, Fernández Landó L, Bray R, Brouwers B, Rodríguez Á. Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial. Lancet Diabetes Endocrinol 2022;10:393–406.
[69] Hartman ML, Sanyal AJ, Loomba R, Wilson JM, Nikooienejad A, Bray R, et al. Effects of Novel Dual GIP and GLP-1 Receptor Agonist Tirzepatide on Biomarkers of Nonalcoholic Steatohepatitis in Patients With Type 2 Diabetes. Diabetes Care 2020;43:1352–5.
[70] Malecki M, Batterham R, Sattar N, Levine J, Rodríguez A, Bergman B, et al. IDF2022-0369 Predictors of achieving weight loss ≥15% with tirzepatide in people with type 2 diabetes from SURPASS 1–4. Diabetes Res Clin Pract 2023;197.
[71] Batterham R, Małecki M, Sattar N, Lee C, Rodríguez A, Bergman B, et al. IDF2022-0370 Characterization of tirzepatide-treated patients achieving different categorical measures of weight loss in SURPASS 1–4. Diabetes Res Clin Pract 2023;197.
[72] Pedersen SUE, Umpierrez GE, Giorgino F, RodrÍGuez Á, Thieu V, Sapin H, et al. 729-P: Relationship between Body Weight Change and Glycemic Control with Tirzepatide Treatment in People with Type 2 Diabetes. Diabetes 2022;71:729 -P.
[73] White PJ, McGarrah RW, Herman MA, Bain JR, Shah SH, Newgard CB. Insulin action, type 2 diabetes, and branched-chain amino acids: A two-way street. Molecular metabolism 2021;52:101261.
[74] Samms RJ, Zhang G, He W, Ilkayeva O, Droz BA, Bauer SM, et al. Tirzepatide induces a thermogenic-like amino acid signature in brown adipose tissue. Mol Metab 2022;64:101550.
[75] Mather KJ, Mari A, Li J, Heise TIM, De Vries JH, Urva S, et al. 714-P: Greater Improvement in Insulin Sensitivity Per Unit Weight Loss with Tirzepatide Compared with Selective GLP-1 Receptor Agonism. Diabetes 2022;71:714 -P.
[76] Thomas MK, Nikooienejad A, Bray R, Cui X, Wilson J, Duffin K, et al. Dual GIP and GLP-1 Receptor Agonist Tirzepatide Improves Beta-cell Function and Insulin Sensitivity in Type 2 Diabetes. J Clin Endocrinol Metab 2021;106:388–96.
[77] Fonseca VA, Capehorn MS, Garg SK, Jódar Gimeno E, Hansen OH, Holst AG, et al. Reductions in insulin resistance are mediated primarily via weight loss in subjects with type 2 diabetes on semaglutide. J Clin Endocrinol Metab 2019.
[78] Pirro V, Roth KD, Lin Y, Willency JA, Milligan PL, Wilson JM, et al. Effects of Tirzepatide, a Dual GIP and GLP-1 RA, on Lipid and Metabolite Profiles in Subjects With Type 2 Diabetes. J Clin Endocrinol Metab 2022;107:363–78.
[79] Wilson JM, Nikooienejad A, Robins DA, Roell WC, Riesmeyer JS, Haupt A, et al. The dual glucose-dependent insulinotropic peptide and glucagon-like peptide-1 receptor agonist, tirzepatide, improves lipoprotein biomarkers associated with insulin resistance and cardiovascular risk in patients with type 2 diabetes. Diabetes Obes Metab 2020;22:2451–9.
[80] Kahn S, Varkonyi T, Pavo I, Nicolay C, Wiese RJ, Del Prato S. IDF2022-0918 Tirzepatide reduces serum triglyceride irrespective of fibrate use in people with T2D at high CV risk (SURPASS-4). Diabetes Res Clin Pract 2023;197:110401.
[81] Lingvay I, Mosenzon O, Brown K, Cui X, O'Neill C, Fernández Landó L, et al. Systolic blood pressure reduction with tirzepatide in patients with type 2 diabetes: insights from SURPASS clinical program. Cardiovasc Diabetol 2023;22:66.
[82] Sattar N, Lee MMY, Kristensen SL, Branch KRH, Del Prato S, Khurmi NS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. Lancet Diabetes Endocrinol 2021;9:653–62.
[83] Buse JB, Bain SC, Mann JFE, Nauck MA, Nissen SE, Pocock S, et al. Cardiovascular Risk Reduction With Liraglutide: An Exploratory Mediation Analysis of the LEADER Trial. Diabetes Care 2020;43:1546–52.
[84] Tune JD, Goodwill AG, Sassoon DJ, Mather KJ. Cardiovascular consequences of metabolic syndrome. Transl Res 2017;183:57–70.
[85] Nicholls Stephen J, D'Alessio D, Wiese R, Pavo I, Zeytinoglu M, Romera I, et al. Compared to Insulin Glargine, Tirzepatide Reduces the Prevalence of the Metabolic Syndrome in Patients with Type 2 Diabetes and High Cardiovascular Risk: Post-hoc Analysis of SURPASS-4. J Am Coll Cardiol 2023;81:1628.
[86] Heerspink HJL, Sattar N, Pavo I, Haupt A, Duffin KL, Yang Z, et al. Effects of tirzepatide versus insulin glargine on kidney outcomes in type 2 diabetes in the

SURPASS-4 trial: post-hoc analysis of an open-label, randomised, phase 3 trial. Lancet Diabetes Endocrinol 2022;10:774–85.
[87] Sattar N, McGuire DK, Pavo I, Weerakkody GJ, Nishiyama H, Wiese RJ, et al. Tirzepatide cardiovascular event risk assessment: a pre-specified meta-analysis. Nat Med 2022;28:591–8.
[88] Kaneko S. Tirzepatide: A Novel, Once-weekly Dual GIP and GLP-1 Receptor Agonist for the Treatment of Type 2 Diabetes. TouchREVIEWS Endocrinol 2022;18:10–9.
[89] McGuire DK, D'Alessio D, Nicholls SJ, Nissen SE, Riesmeyer JS, Pavo I, et al. Transitioning to active-controlled trials to evaluate cardiovascular safety and efficacy of medications for type 2 diabetes. Cardiovasc Diabetol 2022;21:163.