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REVIEW

Use of Tirzepatide in Adults with Type 2 Diabetes Mellitus: Scientific Evidence and Practical Aspects

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ABSTRACT

Tirzepatide is a novel antidiabetic medication a single-molecule, agonist to the glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptors. It is approved in the USA and EU for the treatment of type 2 diabetes mellitus (T2DM) and obesity. Due to the potential novelty represented by incorporating tirzepatide to clinical practice, we aim to review practical aspects of tirzepatide use in T2DM and the supporting scientific evidence. A group of ten endocrinologists involved as investigators in the phase 3 SURPASS clinical trial program followed a nominal group technique, a qualitative research methodology designed as a semi-structured group discussion to reach a consensus on the selection of a set of practical aspects. The scientific evidence for tirzepatide has been reviewed with respect to a number of patients' clinical profiles and care goals. Information of interest related to adverse events, special warnings and precautions, and other considerations for tirzepatide use has been included. Finally, information provided to the patients has been summarized. The practical aspects reported

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herein may be helpful in guiding physicians in the use of tirzepatide and contribute to optimizing the management of T2DM.

Keywords: Tirzepatide; Type 2 diabetes mellitus

Key Summary Points
Tirzepatide is a once-weekly glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist approved in the USA and EU for the treatment of type 2 diabetes mellitus (T2DM) and obesity.
The authorization of tirzepatide for clinical use in T2DM represents a therapeutic novelty and an advance in the field of incretins for T2DM management.
The review of practical aspects of tirzepatide use and the supporting scientific evidence may be useful for the management of this drug in a clinical setting.

INTRODUCTION

Tirzepatide is a novel antidiabetic medication authorized for clinical use in the USA and the European Union (EU) for the treatment of type 2 diabetes mellitus (T2DM) and obesity. According to the EU, tirzepatide is indicated for the treatment of adults with insufficiently controlled T2DM as an adjunct to diet and exercise, in addition to other antidiabetic therapies, or as monotherapy in the event that metformin is considered inappropriate due to intolerance or contraindications [1]. It is a glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 receptor agonist (GLP-1 RA), and a "first-in-class" agent, being the only GIP/GLP-1 RA approved for the treatment of T2DM and obesity." The authorization of tirzepatide represents a therapeutic advance in the field of incretins for T2DM management [2].

Tirzepatide's mode of action enhances insulin secretion and reduces glucagon secretion in a glucose-dependent manner and increases insulin sensitivity. In addition, tirzepatide delays gastric emptying, influences satiety, and appetite, resulting in decreased appetite and food consumption, thus inducing body weight reduction. Weight reduction, mainly due to fat mass reduction, can help to improve insulin sensitivity, although additional mechanisms may be involved [1, 3].

The phase 3 SURPASS clinical trial program [4–8] has evaluated the safety and efficacy of once-weekly subcutaneously injected tirzepatide, as monotherapy or combination therapy, in a broad spectrum of people with T2DM [9]. All five studies demonstrated that tirzepatide treatment achieved sustained statistically significant and clinically meaningful reductions from baseline in hemoglobin A1c (HbA1c) (– 1.87 to – 2.59%, – 20 to – 28 mmol/mol) and in body weight (– 6.2 to – 12.9 kg), compared to either placebo or active comparators (semaglutide 1 mg, insulin degludec and insulin glargine). Body weight reduction was observed during the dose-escalation period, as early as 4 weeks after treatment initiation and was sustained for up to 2 years, the longest period studied to date [7].

Due to the novelty of this medication [2], we aim to review practical aspects of tirzepatide use in T2DM and the supporting scientific evidence. To do so, a scientific committee was formed with ten endocrinologist (Luis Alberto Vazquez, Esteban Jodar-Gimeno, Santiago Tofe-Povedano, Diego Bellido-Guerrero, Marta Botella-Serrano, Alfonso Soto-Gonzalez, Pedro Mezquita-Raya, Elias Delgado, Carmen Fahardo-Montanana, and Cristobal Morales-Portillo) experts in the management of patients with diabetes mellitus and who participated in the phase 3 SURPASS clinical trial program as principal investigators. They reached a consensus on the set of practical aspects to be addressed in this review using the nominal group technique, a qualitative

research methodology designed as a semi-structured group discussion that secures the balanced participation of all group members, encouraging them with an equal opportunity to express their ideas [10–13]. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

The expert group agreed on selecting the following practical aspects and the supporting scientific evidence:

Clinical Profiles of Patients and Tirzepatide Use

One of the approved indications for tirzepatide is the treatment of adults with inadequately controlled T2DM [1]; notwithstanding, a consensus was reached regarding the selection of the following practical aspects related to certain patient profiles, fulfilling this indication, for the use of tirzepatide.

Patients with T2DM and Overweight or Obesity

Overweight and obesity are two of the main modifiable T2DM-related risk factors, strongly associated with insulin resistance, one of the key features in the pathogenesis of T2DM, and one of the barriers to achieving good glycemic control [14].

Participant inclusion criteria across the SURPASS clinical trial program [4–8] included a body mass index (BMI) ≥ 25 kg/m^2 [5–7], or ≥ 23 kg/m^2 [4, 8], in addition to stable weight (≤ 5% fluctuation in either direction) for the previous 3 months. The mean baseline body weight ranged from 86 to 95 kg and the mean BMI ranged from 31.9 to 34.2 kg/m^2 across the five studies. Tirzepatide showed clinically meaningful weight reductions with an average weight loss ranging from 6.2 to 12.9 kg [9]. Among those participants who received tirzepatide 15 mg, weight loss of at least 5% was achieved by up to 88% (range, 77–88%), weight loss of at least 10% was achieved by up to 69% (range, 47–69%) while weight loss of at least 15% was achieved by up to 43% (27–43%) [9]. Tirzepatide was included in the recent consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) as a drug with very high efficacy in weight reduction [15].

Weight reduction has been associated with improvement in HbA1c and a decrease in the risk of weight-related complications, with a higher extent of loss related to better outcomes [16]. A body weight reduction of up to 5–10% confers metabolic improvement, whereas a weight loss of ≥ 10% can have disease-modifying effects [16].

Patients with T2DM and Weight-Related Comorbidities

The clinical burden associated with overweight and obesity is high, emerging as one of the leading causes of death [14]. Patients with T2DM and overweight or obesity present a higher risk of weight-associated comorbidities such as osteoarthritis, joint pain, sleep apnea, and impaired health-related quality of life (HRQoL) or functionality [17]. Care of people with diabetes and weight-related comorbidities should include strategies to achieve weight loss [15].

In the phase 3 SURPASS clinical trial program, weight loss in adults with T2DM treated with tirzepatide 5, 10, and 15 mg was associated with an improvement in weight-related and overall HRQoL, with greater improvement observed in participants achieving higher weight loss [18].

Qualitative interviews conducted with tirzepatide-treated patients with T2DM who had recently completed one of two trials (SURPASS-2, SURPASS-3) revealed their satisfaction with their weight loss, and the broad and meaningful impact this had on multiple aspects of their quality of life and daily activities [19].

Tirzepatide is being studied in several weight-related diseases, such as sleep apnea, non-alcoholic steatohepatitis or heart failure (HF) with preserved ejection fraction, thus specific improvements in these weight-related diseases are currently under investigation [20–22].

Patients with T2DM and with Overweight or Obesity and on Insulin Treatment

Tirzepatide improved markers of insulin sensitivity partly due to weight loss [1, 3]. Tirzepatide increased insulin sensitivity by 63%, in the context of a mean weight loss of 11.2 kg [23]. Insulin-resistant patients with T2DM and overweight or obesity receiving insulin treatment would benefit from the efficacy of tirzepatide in reducing body weight, and for such patients, insulin dose reduction would be a feasible objective. In SURPASS 6, patients with T2DM and a mean baseline BMI of 33 kg/m^2 receiving insulin glargine in combination with metformin were randomized to tirzepatide or insulin lispro. At 52 weeks, compared to insulin lispro, tirzepatide (pooled) achieved better results for HbA1c and weight reduction from baseline, with substantially lower insulin use (from a geometric mean total baseline daily insulin use of 46 IU to 13 IU [0.15 IU/kg] in the tirzepatide group vs. 112 IU (1.2 IU/kg)) in the insulin lispro group), with 8% to 19% of tirzepatide-treated participants completely discontinuing insulin glargine therapy by week 52 [24].

Patients with T2DM Seeking Normoglycemia

In the SURPASS program, up to 23–62% of participants achieved normoglycemia (HbA1c < 5.7%), vs. participants treated with semaglutide 1 mg (20%), insulin degludec (5%), and insulin glargine (3%) [9]. Normoglycemia was achieved without clinically significant hypoglycemia in 93.6–100% patients when tirzepatide was not combined with insulin (SURPASS 1–4) and in 85.9% patients when tirzepatide was added to insulin (SURPASS-5) [1]. Tirzepatide-treated participants who achieved normoglycemia were slightly younger, with a shorter duration of diabetes and lower HbA1c value at baseline [25].

In addition, tirzepatide enabled participants to maintain a significantly lower blood glucose level throughout the day across all five studies [4–8], with a higher proportion of 24-h period spent within a tight target glucose range and a smaller within-day glucose coefficient of variation vs. insulin degludec, indicating lower glycemic variability [9]. Data from a cohort study in patients with newly diagnosed diabetes, showed that stringent glycemic control (HbA1c levels < 6.5%) were associated with better outcomes vs. patients with HbA1c between 6.5% to < 7%. Thus, this study is consistent with literature recommending early and intensive treatment to avoid long-term risk of diabetic complications and related mortality [26].

Patients with T2DM with Very Poor Glycemic Control who are far from Reaching HbA1c Therapeutic Goals

A subgroup analysis involving patients with a HbA1c level > 8.5% showed significant and clinically significant mean reductions in the HbA1c level of – 3.18 up to – 3.46% for tirzepatide at a dose of 15 mg as compared with – 2.58% for semaglutide 1 mg, – 2.07% for insulin degludec, – 1.96% for insulin glargine, – 0.82% for placebo in monotherapy, and – 1.27% for placebo added to insulin glargine [27]. In a post hoc analysis of SURPASS 2, 3, and 4 assessing tirzepatide in participants whose baseline HbA1c was > 9%, between 65 and 86% of patients randomized to tirzepatide achieved HbA1c < 7%. Consistent with these data, the ADA-EASD 2022 consensus has categorized the glycemic effect of tirzepatide as very high [15, 28].

Patients with T2DM and Cardiovascular (CV) Risk Factors

The holistic patient-centered approach proposed by the ADA-EASD consensus includes CV risk-factor management and cardiorenal protection [15], in addition to glycemic and weight management. With regard to the cardiovascular profile of tirzepatide, clinical trials have shown an improvement in CV risk factors including systolic and diastolic blood pressure (BP), triglycerides, high-, very low, and low-density lipoproteins and waist circumference in participants receiving tirzepatide [4–8]. Improvements in liver fat content and reduced visceral and subcutaneous abdominal adipose tissue volume have been shown with tirzepatide [29]. In the SURPASS 4 trial, which included participants at high CV risk, the hazard ratio for major adverse CV events for

tirzepatide treatment compared with glargine was 0.74 (95% CI 0.51–1.08), indicating CV risk was not increased [7]. The effects of tirzepatide on CV events in patients with T2DM and increased CV risk are under study in the ongoing clinical trial SURPASS-CVOT [30]. Based on ADA-EASD consensus, if the primary goal is cardiorenal risk reduction, in patients with atherosclerotic cardiovascular disease GLP-1 RA or sodium-glucose transporter 2 inhibitors (SGLT2i) with proven CVD benefit are the recommended treatments. In the case of heart failure or chronic kidney disease (CKD), the preferred options are SGLT2i with HF benefits or evidence of reducing CKD progression, respectively [15].

Therapeutic Goals

HbA1c Target

A reasonable HbA1c target for most adults with adequate life expectancy is ≤ 7% [15]. Based on the American Association of Endocrinology, for most patients, an optimal HbA1c is ≤ 6.5% or as close to normal if it is safe and achievable [31]. Studies have found that stringent glycemic control during the first year after diagnosis can be associated with lower risks of diabetic complications and mortality in the future [26]. Decisive factors such as early detection and patient age followed by early and intensive treatment may be necessary to avoid irremediable long-term risk due to glycemic complications [32, 33]. Less stringent HbA1c targets can be considered in cases of limited life expectancy, advanced renal disease, severe comorbid conditions, or long T2DM disease duration [31]. Up to 81–97% participants in the SURPASS clinical trial program receiving tirzepatide achieved the treatment goal recommended by ADA and EASD, HbA1c < 7% [15], which is significantly higher than active comparators (81% semaglutide 1 mg, 61% insulin degludec, 51% glargine). More patients treated with tirzepatide achieved HbA1c ≤ 6.5% (66–95%) compared with semaglutide 1 mg (66%), insulin degludec (44%) or insulin glargine (32%). Compared to semaglutide 1 mg, all three doses of tirzepatide were linked to significantly higher proportions of patients who achieved HbA1c target values of < 5.7% (29–51% tirzepatide vs. 20% semaglutide) [1]. Normoglycemia was achieved in a significant proportion of tirzepatide treated participants, without an increase in the risk of hypoglycemia, and was associated with an overall improvement in markers of metabolic health [25].

Body Weight Reduction Target

Weight management should be a focus for patients with T2DM and overweight or obesity, according to the ADA-EASD consensus report [15]. A target of at least 5% weight loss can be expected to have clinical benefits, whereas a substantial (> 10%) weight loss and weight loss early in the course of T2DM increase the chance of disease remission [15, 16]. In the SURPASS program, up to 69% of patients achieved a goal of ≥ 10% weight loss, and up to 43% experienced weight loss of ≥ 15% [1]. Body weight reduction was mainly driven by fat mass loss, thereby improving body composition [1, 23].

HRQoL and Functionality

A holistic and multifactorial approach in T2DM management, with an overall goal of maintaining HRQoL and avoiding complications is recommended [15, 34]. Tirzepatide may contribute to achieving such therapeutic goals, since across the SURPASS clinical program improvements in multiple domains of HRQoL and functionality were consistently observed [4–8].

Time to Achieve Therapeutic Goals and Reassess Targets

The ADA-EASD consensus indicates that the reassessment of individual targets and their achievement at regular intervals is key, recommending proactive care and thus avoiding inertia [15]. The American Association of Clinical Endocrinology Consensus Statement recommends attaining the treatment goal "as soon

as possible". Clinicians should continuously evaluate treatment goals at each visit, ideally ≤ 3 monthly intervals, and consider making therapeutic changes to achieve targets more rapidly [31, 35]. In addition, some patients may require medication reduction or discontinuation, as in the case of side effects or ineffectiveness [15]. Facilitating the communication, access to the medical center, and interactions between health care professionals (HCPs) and patients positively impacts treatment adherence and clinical outcomes [36, 37].

In a clinical trial setting, the median time to reach HbA1c < 7% was 8.1 weeks with tirzepatide 5 mg dose vs. 12 weeks with semaglutide 1 mg; and the median time to reach the weight loss target (≥ 5% weight loss) was 16 weeks with tirzepatide 5 mg dose vs. 24 weeks with semaglutide 1 mg [38]. Those patients that achieved early (at 8 weeks) weight loss of ≥ 5% had a greater substantial reduction in weight at the end of the trial vs. those that did not reach this early weight loss target across all tirzepatide doses (mean bodyweight change from baseline (kg) was – 12.4 (5 mg), – 15.7 (10 mg) and – 18.0 (15 mg) for early weight loss compared to – 5.8 (5 mg), – 8.3 (10 mg) and – 10.4 (15 mg) for non-early weight loss groups) [39]. The starting dose of tirzepatide is 2.5 mg once weekly [1]. After 4 weeks, the dose should be increased to 5 mg once weekly [1]. If needed, dose increases can be made in 2.5 mg increments after a minimum of 4 weeks on the current dose [1]. The recommended maintenance doses are 5, 10 and 15 mg, with a maximum dose of 15 mg once weekly [1]. This information can be useful to guide treatment titration with tirzepatide and frequency of patient follow-up visits.

Adverse Events (AEs), Special Warnings, Precautions, and other Considerations for use

Acute Pancreatitis

In the phase 2 and 3 clinical trials, a low incidence of pancreatitis was reported (0.24% tirzepatide vs. 0.13% comparators), however patients with a history of pancreatitis were not included [40].

Patients should be informed of identifiable symptoms of pancreatitis, such as stomach and back pain. If pancreatitis is suspected, tirzepatide should be discontinued out of caution. In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone would not be predictive of acute pancreatitis [1].

Diabetic Retinopathy

Diabetic retinopathy was reported in < 1% participants across the five phase 3 SURPASS clinical trials [4–8]. Patients with a history of proliferative diabetic retinopathy, maculopathy, or non-proliferative diabetic retinopathy requiring acute treatment were not included in tirzepatide clinical trials and thus it should be used with caution in these patients and with appropriate monitoring [1]. Based on the ADA standard of medical care, retinopathy status should be assessed when intensifying glucose-lowering therapies such as those using GLP-1 RA. In addition, if any level of diabetic retinopathy is present, retinal examinations should be repeated at least annually. If retinopathy is progressing, examinations will be required more frequently [41].

Acute Gallbladder Disease

Acute gallbladder disease (cholecystectomy, biliary colic, and cholelithiasis) was reported by 0.6% of tirzepatide-treated patients (vs. none with placebo). If cholelithiasis is suspected, diagnostic studies and follow-up are recommended [42].

Blood Pressure

Weight loss in patients with T2DM is related with BP reduction and less use of antihypertensive medication [43]. Tirzepatide has been associated with improvements in BP during the phase 3 SURPASS clinical trial program [44]. Treatment with tirzepatide was associated with a mean reduction in systolic and diastolic BP of 6

to 9 mmHg and 3 to 4 mmHg vs. a mean reduction of 2 mmHg with placebo in each systolic and diastolic BP. The highest baseline category (>140 mmHg) had the largest reductions, while those in the systolic BP category < 122 mmHg showed no further decrease [45]. The induced BP reduction was primarily mediated through weight loss, with different degrees of contributions from weight loss-independent effects, and independent from the use of antihypertensive medication [45, 46].

Concomitant Antidiabetic Medication

Tirzepatide in combination with sulphonylurea (SU) or insulin may increase the risk of hypoglycemia, so it can be considered a dose reduction of these concomitant medications. To adjust the dose, blood glucose self-monitoring is necessary following a stepwise approach [1]. Clinically significant hypoglycemia was reported in 10–14% (0.14–0.16 events/patient year) of patients when tirzepatide was combined with sulphonylurea and in 14–19% (0.43–0.64 events/patient year) of patients when tirzepatide was combined with basal insulin. In case of tirzepatide use in monotherapy or in combination with other oral antidiabetic drugs, the rate was up to 0.04 events/patient year [1].

The patients included in the SURPASS-5 clinical trial with a baseline HbA1c level ≤ 8%, reduced the insulin dose by 20% after randomization [8]. There are no specific recommendations on how much the dose of the sulphonylurea should be reduced when used in combination with tirzepatide, however other authors have proposed a reduction in the dose of SU by 50% if HbA1c is < 8.5%, when used in combination with SGLT2i [47].

Gastrointestinal (GI) AEs

The most common AEs reported with tirzepatide are GI, which include nausea, vomiting, and diarrhea [1]. GI events were mostly mild or moderate in severity, and higher during the dose-escalation period and generally decreased over time [1]. The incidence of these GI effects was similar to that reported with semaglutide 1 mg [5]. Permanent treatment discontinuation due the described GI AEs was low (< 6% of patients discontinued treatment due to nausea, vomiting, or diarrhea) [1, 48].

To mitigate GI events, the same considerations as with GLP-1 RA treatment could be taken into account, i.e., patients can be advised to eat smaller portions with less fat content; when GI AEs persist, the short-term prescription of omeprazole and/or antiemetic drugs could be considered; a reduction in the dose and a slower dose titration could be considered [49].

Information to Patients

Disease Information

HCPs from the prescription team, including the trained nurses from the diabetes unit and certified diabetic educators (CDEs), play a key role in appropriately educating the patients, not only regarding their clinical management and treatment but also self-management skills, which are necessary for an optimal T2DM control [40].

Gastrointestinal Adverse Events

The information required for patients starting treatment with tirzepatide could be similar to that provided to patients starting with GLP-1 RA [49]. In accordance with recommendations for GLP-1 RA usage, dietetic recommendations reinforcing nutritional aspects and a healthy lifestyle could be encouraged [50, 51]. General recommendations include eating habits improvements, such as eating smaller portions more frequently, more slowly, adapting food composition to individual requirements, by increasing fluid intake, reducing fats, and avoiding sweet, spicy or processed meals containing dressings or sauces that are not home-cooked [52]. In case of developing GI AEs, as already mentioned, the patient should know that they are commonly mild to moderate and generally transient [52]. Nevertheless, if they persist, patients should contact their prescription team [52]. Finally, patients should be advised of the potential risk of dehydration due to GI AEs and

take precautions to avoid fluid depletion and electrolyte disturbances. This should particularly be considered in the elderly, who may be more susceptible to such complications [1].

Body Weight Reduction

Since tirzepatide treatment is associated with weight loss and in a relevant percentage of patients weight reduction can be > 10–15% [1]. Patients should be informed about this treatment effect, which is mainly driven by fat mass loss [1], and related to glycemic improvement [35]. Regular physical activity and minimization of a sedentary lifestyle should be encouraged [15, 53, 54].

CONCLUSIONS

Tirzepatide is a novel single-molecule GIP and GLP1 receptor agonist approved for the treatment of T2DM, which has recently been included in clinical guidelines [15]. The availability of this review, focusing on practical aspects of tirzepatide use and the supporting scientific evidence may be useful for HCPs in their daily practice.

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Declarations

Conflict of Interest. Luis A. Vázquez is advisory board member for Eli Lilly, has received speaker honoraria from AstraZeneca, Eli Lilly, and Novo Nordisk, has received research grants to institution from Eli Lilly, Novartis and Novo Nordisk, and is minor shareholder of Eli Lilly. Santiago Tofé-Povedano has received consulting, speaker and research honoraria from Eli Lilly, Novo Nordisk, AstraZeneca and GlaxoSmithKline. Diego Bellido-Guerrero is advisory board member for Eli Lilly, Novo Nordisk, Sanofi, Nestle HS, Persan Pharma, has received speaker honoraria from Novo Nordisk, Sanofi, Eli Lilly, Boehringer, Persan Pharma, Nutricia, AstraZeneca and is collaborator in national health research projects (FIS) and has participated in clinical trials of Eli Lilly, Sanofi, Bayer, Adventia Pharma, AstraZeneca, Novartis, Abbott. M.B.S has participated in clinical trials and has received speaker honoraria from Eli Lilly, Novo Nordisk, Abbot and AstraZeneca. Alfonso Soto-González is advisor on scientific boards for Novo Nordisk and Eli Lilly, has received speaker honoraria from MSD, Novo Nordisk, Eli Lilly and AstraZeneca, is collaborator in national health research projects (FIS) and has participated in clinical trials of Eli Lilly, Novo Nordisk, AstraZeneca, Bayer, Boehringer, Amgen, Pfizer and Novartis. Pedro Mezquita-Raya is advisor on scientific boards for Abbott, AstraZeneca, FAES and Novo Nordisk; lectures for AstraZeneca, Eli Lilly, FAES, Fresenius and Novo-Nordisk and performs research activities for Eli Lilly and Novo Nordisk. Elías Delgado has received unrestricted research support from AstraZeneca, Novo Nordisk, Sanofi, Pfizer, and Roche and has received consulting fees and/or honoraria for membership on advisory boards and speaker´s bureau from AstraZeneca, Novo Nordisk, Lilly, Sanofi, GlaxoSmithKline, Pfizer, Almirall, Novartis, Abbott Laboratories, Esteve, and Merck Sharp & Dohme. Carmen

Fajardo-Montañana has received speaker honoraria from Eli Lilly and has participated in clinical trials of Eli Lilly. Cristóbal Morales-Portillo is advisor on scientific boards for Novo Nordisk, Lilly, MSD, Boehringer, Astra, Sanofi, Abbot; has received speaker honoraria from Sanofi, Novo Nordisk, AstraZeneca, Roche, Lilly, Boehringer, MSD, Ferrer, Janssen, Abbot; and has participated in clinical trials of Novo Nordisk, Sanofi, AstraZeneca, Pfizer, Lilly, Merck, Lexicon, FPS, Hanmi, Janssen Boehringer, Takeda, Roche, Theracos, LeeGanz. Miriam Rubio-de Santos and Irene Romera are employees of Eli Lilly. Ana Causanilles works for an independent scientific consultancy (Outcomes'10) that has received honoraria for conducting the study and writing the current manuscript. Esteban Jódar-Gimeno has received consulting honoraria from Amgen, AstraZeneca, Eli Lilly, FAES, GSK, Italfármaco, MSD, Mundipharma, Novo Nordisk, has participated in clinical research for Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, GSK, Janssen, MSD, Novo Nordisk, Pfizer, Sanofi, and has received speaker honoraria from Amgen, Asofarma, AstraZeneca, Boehringer Ingelheim, Eli Lilly, FAES, MSD, Novartis, Novo Nordisk, Sanofi, Tecnofarma, ZP Pharmaceuticals.

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REFERENCES

1. European Medicines Agency. Mounjaro: EPAR – Product information. https://www.ema.europa.eu/en/documents/product-information/mounjaro-epar-product-information_en.pdf. Accessed 26 Jan 2023

2. Chavda VP, Ajabiya J, Teli D, Bojarska J, Apostolopoulos V. Tirzepatide, a new era of dual-targeted treatment for diabetes and obesity: a mini-review. Molecules [Internet]. 2022;27(13):4315.

3. 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(2):388–96.

4. Rosenstock J, Wysham C, Frías JP, Kaneko S, Lee CJ, Fernández Landó 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(10295):143–55.

5. 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(6):503–15.

6. 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(10300):583–98.

7. 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(10313):1811–24.

8. 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(6):534–45.

9. 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(1):3–17.

10. Potter M, Gordon S, Hamer P. The nominal group technique: a useful consensus methodology in physiotherapy research. N Z J Physiother. 2004;32:126.

11. Gallagher M, Hares T, Spencer J, Bradshaw C, Webb I. The nominal group technique: a research tool for general practice? Fam Pract. 1993;10(1):76–81.

12. Moore CM. Applied social research methods series. Group techniques for idea building. Thousand Oaks: Sage Publications; 1987.

13. Tang KC, Davis A. Critical factors in the determination of focus group size. Fam Pract. 1995;12(4):474–5.

14. Leitner DR, Frühbeck G, Yumuk V, Schindler K, Micic D, Woodward E, et al. Obesity and type 2 diabetes: two diseases with a need for combined treatment strategies—EASO can lead the way. Obes Facts. 2017;10(5):483–92.

15. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, et al. Management of hyperglycemia in type 2 diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2022;45(11):2753–86.

16. Lingvay I, Sumithran P, Cohen RV, le Roux CW. Obesity management as a primary treatment goal for type 2 diabetes: time to reframe the conversation. Lancet. 2022;399(10322):394–405.

17. 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(1):88.

18. Boye K, Thieu V, Lee C, Sapin H. Higher weight loss is associated with improved patient reported outcomes in T2D patients treated with tirzepatide. Diabetes Res Clin Pract. 2023;197:110305.

19. Matza LS, Stewart KD, Landó LF, Patel H, Boye KS. Exit interviews examining the patient experience in clinical trials of tirzepatide for treatment of type 2 diabetes. Patient. 2022;15(3):367–77.

20. Eli Lilly and Company. Obstructive Sleep Apnea Master Protocol GPIF: A Study of Tirzepatide (LY3298176) in Participants With Obstructive Sleep Apnea (SURMOUNT-OSA). ClinicalTrials.gov identifier: NCT05412004. Updated October 23, 2023. Accessed October 26, 2023. https://clinicaltrials.gov/study/NCT05412004.

21. Eli Lilly and Company. A Study of Tirzepatide (LY3298176) in Participants With Heart Failure With Preserved Ejection Fraction and Obesity (SUMMIT). ClinicalTrials.gov identifier: NCT04847557. Updated October 23, 2023. Accessed October 26, 2023. https://clinicaltrials.gov/study/NCT04847557.

22. Eli Lilly and Company. A Study of Tirzepatide (LY3298176) in Participants With Nonalcoholic Steatohepatitis (NASH) (SYNERGY-NASH). ClinicalTrials.gov identifier: NCT04166773. Updated October 23, 2023. Accessed January 4, 2024. https://classic.clinicaltrials.gov/ct2/show/NCT04166773.

23. 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(6):418–29.

24. Rosenstock J, Frias J, Robdbard H, Tofe S, Sears E, Huh R, et al. 750-P: "SURPASS(ing)" an era of basal-bolus insulin therapy—tirzepatide vs. insulin lispro TID added-on to poorly controlled basal insulin-treated in type 2 diabetes. Diabetes. 2023;72 (Supplement_1):750.

25. Rosenstock J, Vázquez L, Del Prato S, Franco DR, Weerakkody G, Dai B, Landó LF, Bergman BK, Rodríguez A. Achieving Normoglycemia With Tirzepatide: Analysis of SURPASS 1-4 Trials. Diabetes Care. 2023;46(11):1986–92. https://doi.org/10.2337/dc23-0872

26. Laiteerapong N, Ham SA, Gao Y, Moffet HH, Liu JY, Huang ES, et al. The legacy effect in type 2 diabetes: impact of early glycemic control on future complications (The Diabetes & Aging Study). Diabetes Care. 2018;42(3):416–26.

27. Aleppo G, De Block C, Levine JA, Gomez Valderas E, Benneyworth BD. Glycemic control with tirzepatide in people with type 2 diabetes by baseline HbA1c ≤8.5% or >8.5% (717-P). American Diabetes Association 82nd Scientific Sessions; New Orleans, Louisiana; June 3–7, 2022.

28. Kwan A, Ward JM, Gomez Valderas E, Benneyworth BD, Brown K. Efficacy and safety of tirzepatide in people with type 2 diabetes with poor-control baseline HbA1c according to NCQA-HEDIS performance measures: a post hoc analysis of SURPASS-2, SURPASS-3, and SURPASS-4 Academy of Managed Care Pharmacy; March 29–April 1; Chicago, IL. 2022.

29. 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(6):393–406.

30. Eli Lilly and Company. A Study of Tirzepatide (LY3298176) Compared With Dulaglutide on Major Cardiovascular Events in Participants With Type 2 Diabetes (SURPASS-CVOT). ClinicalTrials.gov identifier: NCT04255433. Updated October 19, 2023. Accessed January 4, 2024. https://clinicaltrials.gov/ct2/show/NCT04255433.

31. Samson SL, Vellanki P, Blonde L, Christofides EA, Galindo RJ, Hirsch IB, et al. American Association of clinical endocrinology consensus statement: comprehensive type 2 diabetes management algorithm – 2023 update. Endocr Pract. 2023;29(5):305–40.

32. Lind M, Imberg H, Coleman RL, Nerman O, Holman RR. Historical HbA(1c) values may explain the type 2 diabetes legacy effect: UKPDS 88. Diabetes Care. 2021;44(10):2231–7.

33. Rawshani A, Rawshani A, Franzén S, Sattar N, Eliasson B, Svensson A-M, et al. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2018;379(7):633–44.

34. Reyes-García R, Moreno-Pérez Ó, Tejera-Pérez C, Fernández-García D, Bellido-Castañeda V, López de la Torre Casares M, et al. A comprehensive approach to type 2 diabetes mellitus—a recommendation document. Endocrinología, Diabetes y Nutrición (English Ed). 2019;66(7):443–58.

35. Małecki MT, Batterham RL, Sattar N, Levine JA, Rodríguez Á, Bergman BK, Wang H, Ghimpeteanu G, Lee CJ. Predictors of ≥15% Weight Reduction and Associated Changes in Cardiometabolic Risk Factors With Tirzepatide in Adults With Type 2 Diabetes in SURPASS 1-4. Diabetes Care. 2023;46(12):2292–99. https://doi.org/10.2337/dc23-1135

36. Hill A. Patient–practitioner communication in diabetes and diabetes-related foot complications. The Diabetic Foot Journal. 2020;23(2):56–61.

37. Linetzky B, Jiang D, Funnell MM, Curtis BH, Polonsky WH. Exploring the role of the patient-physician relationship on insulin adherence and clinical outcomes in type 2 diabetes: Insights from the MOSAIc study. J Diabetes. 2017;9(6):596–605.

38. Pantalone KM, Viljoen A, Galindo RJ, Cui X, Huh R, Fernández Landó L, et al. Patients with type 2 diabetes reach glycemic targets faster with tirzepatide compared to semaglutide and titrated insulin degludec. American Diabetes Association—82nd Annual Scientific Sessions; New Orleans, LA, USA; 3–7 June 2022.

39. Lingvay I, Giorgino F, Van Gaal LF, Liu M, Rodríguez A, Torcello-Gómez A, et al. Early weight loss and late metabolic outcomes in tirzepatide-treated participants with type 2 diabetes. American Diabetes Association – 83rd Annual Scientific Sessions; 23–26 June San Diego, CA, USA2023.

40. Public Assessment report EMA/791310/2022. Available at: https://www.ema.europa.eu/en/documents/assessment-report/mounjaro-epar-public-assessment-report_en.pdf. Accessed 26 Jan 2023.

41. Committee ADAPP. 12. Retinopathy, Neuropathy, and Foot Care: Standards of Medical Care in Diabetes—2022. Diabetes Care. 2021;45(Supplement _1):S185–94.

42. Mounjaro FDA label available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215866s000lbl.pdf. Accessed 26 Jan 2023.

43. The Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med. 2013;369(2):145–54.

44. 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(3):591–8.

45. 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(1):66.

46. Lingvay I, Mosenzon O, Brown K, Cui X, Lando LF, Patel H. 716-P: systolic blood pressure reduction with tirzepatide across SURPASS program: a mediation analysis using weight loss as a factor. Diabetes. 2022;71(Supplement_1):716–51.

47. Gomez-Peralta F, Abreu C, Lecube A, Bellido D, Soto A, Morales C, et al. Practical approach to initiating SGLT2 inhibitors in type 2 diabetes. Diabetes Ther. 2017;8(5):953–62.

48. Patel H, Khunti K, Rodbard HW, Bajaj HS, Bray R, Kindracki Z, Rodríguez Á. Gastrointestinal adverse events and weight reduction in people with type 2 diabetes treated with tirzepatide in the SURPASS clinical trials. Diabetes Obes Metab. 2024;26(2):473–81. https://doi.org/10.1111/dom.15333

49. Reid TS. Practical use of glucagon-like peptide-1 receptor agonist therapy in primary care. Clinical Diabetes. 2013;31(4):148–57.

50. Gray A, Threlkeld RJ. Nutritional Recommendations for Individuals with Diabetes. [Updated 2019 Oct 13]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000.

51. Gonzalez-Campoy JM, St Jeor ST, Castorino K, Ebrahim A, Hurley D, Jovanovic L, Mechanick JI, Petak SM, Yu YH, Harris KA, Kris-Etherton P, Kushner R, Molini-Blandford M, Nguyen QT, Plodkowski R, Sarwer DB, Thomas KT; American Association of Clinical Endocrinologists; American College of Endocrinology and the Obesity Society. Clinical practice guidelines for healthy eating for the prevention and treatment of metabolic and endocrine diseases in adults: cosponsored by the American Association of Clinical Endocrinologists/the American College of Endocrinology and the Obesity Society. Endocr Pract. 2013;19 Suppl 3:1–82. https://doi.org/10.4158/EP13155.GL

52. Gorgojo-Martínez JJ, Mezquita-Raya P, Carretero-Gómez J, Castro A, Cebrián-Cuenca A, de Torres-Sánchez A, et al. Clinical recommendations to manage gastrointestinal adverse events in patients treated with Glp-1 receptor agonists: a multidisciplinary expert consensus. J Clin Med. 2023;12(1):145.

53. Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC, et al. Physical Activity/exercise and diabetes: a position statement of the American Diabetes Association. Diabetes Care. 2016;39(11):2065–79.

54. Harrington D, Henson J. Physical activity and exercise in the management of type 2 diabetes: where to start? Pract Diabetes. 2021;38(5):35–40b.