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COMMENTARY

Tirzepatide: A Double Agonist for Various People Living with Type 2 Diabetes

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ABSTRACT

Tirzepatide is the first ever once-weekly, injectable gastric inhibitory peptide/glucagon-like peptide 1 (GIP/GLP-1) dual agonist approved by the European Medicines Agency for type 2 diabetes. The efficacy and safety of tirzepatide have been evaluated in five global, randomized, double-blind or open-label, phase 3 studies which enrolled over 7000 people living with type 2 diabetes, across various stages of disease and with different characteristics at baseline. In this short commentary we report the salient data of the most recent trials on tirzepatide and GLP-1 receptor agonists from a clinical point of view, with the aim of highlighting similarities and mutual differences.

Keywords: Type 2 diabetes; Tirzepatide; Semaglutide; Weight loss; Hypoglycemia

Key Summary Points

Tirzepatide is the first ever once-weekly, injectable gastric inhibitory peptide/glucagon-like peptide 1 (GIP/GLP-1) dual agonist for type 2 diabetes.

Tirzepatide has been recently approved by the European Medicines Agency for type 2 diabetes.

Recent published evidence and presentations at major international meetings have highlighted tirzepatide as a potential breakthrough advancement in the treatment of type 2 diabetes.

Tirzepatide has shown greater efficacy both on glycemic control and body weight reduction versus placebo and active comparators including GLP-1 receptor agonists; moreover, its efficacy appears independent of baseline glycated hemoglobin (HbA1c), body mass index, age, and disease duration.

People living with type 2 diabetes with a baseline younger age, shorter disease duration, lower HbA1c, and metformin monotherapy were those with the highest probability of reaching normoglycemia, suggesting the value of early treatment with tirzepatide.

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COMMENTARY

Several pieces of evidence show that worldwide, only a portion of persons with type 2 diabetes (T2D) reach their glycemic targets despite recent therapeutic advancements. This data was recently confirmed by the 2022 release of the AMD (Italian Scientific Association of Diabetes Specialists) annals which referred to over 500,000 people living with type 2 diabetes regularly followed up by Italian diabetes centers. In particular, around half of people living with T2D are still not achieving glycated hemoglobin (HbA1c) targets with an average HbA1c of 7.2%, as shown by data from [1]. Moreover, around 76% of them are overweight or obese. Overall, ≤ 7.0% HbA1c levels, blood pressure values < 130/80 mmHg, and low-density lipoprotein (LDL)-cholesterol levels < 70 mg/dl were documented in 54.6%, 23.0%, and 34.3% of subjects, respectively, with only 5.2% being on target for three risk factors. Such alarming data confirms that there is an urgent need for therapeutic options addressing not only HbA1c and body weight, but also traditional cardiovascular risk factors, as recommended by the American Diabetes Association and European Association for the Study of Diabetes (ADA-EASD) Consensus Report 2022 [2]. In fact, the Consensus Report recommends treating the person with T2D holistically, by choosing the right antihyperglycemic therapy according to four fundamental pillars, i.e., blood glucose, weight, cardiovascular risk factor control, and cardiorenal protection [2].

Tirzepatide is the first ever once-weekly, injectable gastric inhibitory peptide/glucagon-like peptide 1 (GIP/GLP-1) dual agonist approved by the European Medicines Agency (EMA) for T2D. The efficacy and safety of tirzepatide have been evaluated in five global, randomized, double-blind or open-label, phase 3 studies enrolling over 7000 people living with T2D, across various disease stages and with different characteristics at baseline [3–7]. The primary endpoint of the SURPASS clinical trials was the mean HbA1c change from baseline to 40 or 52 weeks with 5 mg, 10 mg, and 15 mg tirzepatide against various comparators in adults with T2D (Table 1).

Throughout the studies, tirzepatide showed unmatched results on both glycemic control and body weight reduction, as well as beneficial effects on traditional cardiovascular risk factors, with a safety profile comparable to GLP-1 receptor agonists (GLP-1RAs) [3–8]. In particular, in the SURPASS 2 study, which compared tirzepatide 5 mg, 10 mg, and 15 mg to semaglutide 1 mg treatment for 40 weeks, tirzepatide showed a significantly greater HbA1c reduction at all dosages (– 2.09%, – 2.37%, and – 2.46%, respectively, vs. – 1.86%). The same occurred with weight, which decreased more than observed with semaglutide 1 mg, i.e., by 7.8, 10.3, and 12.4 kg, respectively, vs. 6.2 kg [4]. The most common adverse events were gastrointestinal. They were primarily mild to moderate in severity in the tirzepatide and semaglutide groups, with nausea occurring in 1.3%, 1.5%, and 0.9% vs. 0.9%, respectively; vomiting in 0.2%, 0.9%, and 0.9% vs. 0.6%, respectively; diarrhea in 0.2%, 0.6%, and 1.3% vs. 0.6%, respectively [4].

Clinicians might now wonder whether these results can apply to specific subgroups of people with T2D. Numerous post hoc analyses presented in the last couple of years at the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) congresses offer a comprehensive overview of the broad spectrum of people who could benefit from tirzepatide. In the following section, we report the results of some analyses that can help us better identify the characteristics of such patients.

All over the world, most of the people living with T2D attending diabetes centers are over 65 years of age [1]. A post hoc analysis of the five SURPASS studies showed that tirzepatide afforded significantly greater HbA1c reductions versus placebo or an active comparator irrespective of age at baseline (< 65 years/≥ 65 years) at the expense of gastrointestinal adverse events (nausea, diarrhea, dyspepsia, constipation, vomiting) and decreased appetite. Across the studies, the incidence of severe hypoglycemia (requiring external help) with blood glucose dropping to less than 54 mg/dL was similar between both age subgroups and was consistent with the overall study population and background therapies [9].

Table 1 Body weight changes from baseline in people with baseline BMI < 27 kg/m^2 living with T2D under variable tirzepatide (Tzp) doses vs. comparators (semaglutide, degludec, and glargine basal insulin analogues; SURPASS program, modified) [3–7]

Study	No. patients	Tzp 5 mg	Tzp 10 mg	Tzp 15 mg	Placebo/ comparator	Inclusion criteria
SURPASS 1	75	− 5.60	− 6.00	− 7.00	− 0.50	Poorly controlled, adult T2D naïve to injectable treatment
SURPASS 2	1466	− 6.10	− 7.30	− 8.20	− 5.20	Poorly controlled, adult T2D
SURPASS 3	141	− 6.10	− 7.80	− 11.30	3.00	Poorly controlled, adult, insulin-naïve T2D
SURPASS 4	245	− 5.70	− 8.40	− 8.70	2.20	Poorly controlled, adult T2D at high CV-risk on Met/Sul/SGLT2i
SURPASS 5	66	− 5.20	− 7.50	− 8.40	1.4	Poorly controlled, adult T2D on GLA-I and Met+/Met−

For full details on inclusion/exclusion criteria, please refer to the original citations

T2D subjects with type 2 diabetes, *CV-risk* cardiovascular risk, *Met* metformin, *Sul* sulfonylurea, *SGLT2i* sodium-glucose cotransporter 2 inhibitors, *GLA-I* glargine insulin, *Met+* treated with metformin, *Met−* not treated with metformin

Another post hoc analysis of SURPASS studies assessed glycemic control with tirzepatide in participants stratified by baseline HbA1c (≤8.5%, >8.5%) to evaluate the consistency across subgroups. Throughout those studies, consistently with the primary ones, tirzepatide showed meaningful HbA1c reductions vs. the other comparators irrespective of baseline HbA1c, and was generally well tolerated, except for the well-known gastrointestinal adverse events, and a low incidence of mostly mild-to-moderate hypoglycemia in both subgroups [10].

In the previous year several discussions arose on the efficacy of GLP-1RAs in people with a long duration of T2DM. Therefore, a further post hoc analysis of the five SURPASS studies was conducted to investigate whether or not the efficacy and safety of tirzepatide were influenced by diabetes duration stratified as follows: (i) ≤ 5 years, (ii) between 5 and 10 years, (iii) > 10 years. For all the five SURPASS studies, HbA1c changes from baseline at 40 or 52 weeks were consistent with the primary study results for all three subgroups, with treatment differences favoring all three doses of tirzepatide vs. placebo or the active comparator [3–7, 11].

Tirzepatide has come into the limelight particularly for its efficacy on body weight, with reductions up to 12.9 kg [5]. Therefore, one of the most frequent concerns is the extent of weight loss in people with normal weight; a post hoc analysis of the five SURPASS studies showed that all tirzepatide doses lowered body weight in people living with T2D, irrespective of baseline body mass index (BMI). However, such an effect was dose-dependent, with a greater absolute weight change in higher BMI categories (Table 2). The latter observation should be of reassurance for the use of tirzepatide in those with a BMI < 27 kg/m^2.

Tirzepatide, the first ever approved GIP/GLP-1 dual agonist, showed impressive HbA1c and body weight reductions with a similar tolerability profile as other well-known GLP-1RAs, and, considering the preliminary results from various post hoc analyses, those effects could apply to a very wide variety of people living with T2D. Nonetheless, it is essential to underline that in the last few years, the international diabetes community has reached a broad consensus on the need to refrain from waiting too long before starting an aggressive treatment in the "early patients". Indeed, tirzepatide could be considered as the first option after metformin, allowing up to 6 out of 10 people living with T2D to reach an HbA1c < 5.7% (as from SURPASS 5) [7] because

Table 2 Body weight changes from baseline in people with baseline BMI > 27 kg/m^2 living with T2D under variable tirzepatide (Tzp) doses vs. comparators (semaglutide, degludec, and glargine basal insulin analogues; SURPASS program, modified)

Study	No. patients	Tzp 5 mg	Tzp 10 mg	Tzp 15 mg	Placebo/comparator
SURPASS 1	300	− 7.30	− 8.30	− 10.10	− 0.70
SURPASS 2	169	− 8.00	− 10.60	− 12.80	− 6.30
SURPASS 3	1072	− 7.70	− 11.10	− 13.10	2.20
SURPASS 4	1510	− 7.40	− 9.60	− 12.10	1.80
SURPASS 5	397	− 6.20	− 8.30	− 11.30	1.80

For full details on inclusion/exclusion criteria, please refer to Table 1 and the original citations [3–7]

those achieving normoglycemia were characterized by a younger age, a shorter disease duration, a lower HbA1c, and metformin monotherapy [11]. Considering these findings, the question arises as to whether normoglycemia should be reconsidered as a realistic goal for all or at least a subset of people with T2D. Our observations from the SURPASS clinical program suggest that, in response to tirzepatide, specific individuals may be more likely to achieve normal glucose levels associated with an overall improvement in metabolic health.

As for all the usual phase 3 studies, as a result of the restricted inclusion criteria, one of the most relevant limitations comes from the impossibility of extending results to the overall population with T2D. The SURPASS program focused only on adult people living with T2D, and inclusion criteria were defined according to the stage of disease studied: the upper limit of HbA1c ranged from 9.5% to 11% with a BMI lower limit of 23 kg/m^2 for some studies and 25 kg/m^2 for others. Thus, neither adolescents nor people with very high HbA1c levels (>11%) or low body weight (<23 kg/m^2) were represented in the SURPASS program. Moreover, SURPASS 4 was the only study lasting 2 years, so experience over a long treatment time is unavailable.

In conclusion, much preliminary evidence has been already published or presented at most relevant international meetings, highlighting tirzepatide as a potential breakthrough advancement in the treatment of T2D. Of course, only real-world data will allow such astonishing results to be confirmed in an usual clinical setting, especially in terms of gastrointestinal tolerability, which is the main concern when it comes to traditional GLP-1RAs. However, as we described previously, what is known to date is (1) tirzepatide has shown great efficacy both on glycemic control and body weight irrespective of baseline age, disease duration, HbA1c, and BMI; (2) concerning weight loss-related safety, the absolute weight change was greater in higher BMI categories, so that the drug could be used safely also in people with lower BMI living with T2D; (3) subjects with a younger age, shorter disease duration, lower HbA1c, and metformin monotherapy, i.e., the best predictors of normoglycemia, were those benefiting from tirzepatide treatment the most.

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Declarations

Conflict of Interest. Felice Strollo, Giuseppina Guarino, Ersilia Satta, and Sandro Gentile have no financial interests to declare concerning the present study. Felice Strollo and Sandro Gentile are Editorial Board members of *Diabetes Therapy*. Felice Strollo and Sandro Gentile were not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

Ethical Approval. 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.

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