JAMA | Original Investigation

Tirzepatide vs Insulin Lispro Added to Basal Insulin in Type 2 Diabetes
The SURPASS-6 Randomized Clinical Trial

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IMPORTANCE Tirzepatide is a glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist used for the treatment of type 2 diabetes. Efficacy and safety of adding tirzepatide vs prandial insulin to treatment in patients with inadequate glycemic control with basal insulin have not been described.

OBJECTIVE To assess the efficacy and safety of tirzepatide vs insulin lispro as an adjunctive therapy to insulin glargine.

DESIGN, SETTING, AND PARTICIPANTS This open-label, phase 3b clinical trial was conducted at 135 sites in 15 countries (participants enrolled from October 19, 2020, to November 1, 2022) in 1428 adults with type 2 diabetes taking basal insulin.

INTERVENTIONS Participants were randomized (in a 1:1:1:3 ratio) to receive once-weekly subcutaneous injections of tirzepatide (5 mg [n = 243], 10 mg [n = 238], or 15 mg [n = 236]) or prandial thrice-daily insulin lispro (n = 708).

MAIN OUTCOMES AND MEASURES Outcomes included noninferiority of tirzepatide (pooled cohort) vs insulin lispro, both in addition to insulin glargine, in HbA_{1c} change from baseline at week 52 (noninferiority margin, 0.3%). Key secondary end points included change in body weight and percentage of participants achieving hemoglobin A_{1c} (HbA_{1c}) target of less than 7.0%.

RESULTS Among 1428 randomized participants (824 [57.7%] women; mean [SD] age, 58.8 [9.7] years; mean [SD] HbA_{1c}, 8.8% [1.0%]), 1304 (91.3%) completed the trial. At week 52, estimated mean change from baseline in HbA_{1c} with tirzepatide (pooled cohort) was −2.1% vs −1.1% with insulin lispro, resulting in mean HbA_{1c} levels of 6.7% vs 7.7% (estimated treatment difference, −0.98% [95% CI, −1.17% to −0.79%]; $P < .001$); results met noninferiority criteria and statistical superiority was achieved. Estimated mean change from baseline in body weight was −9.0 kg with tirzepatide and 3.2 kg with insulin lispro (estimated treatment difference, −12.2 kg [95% CI, −13.4 to −10.9]). The percentage of participants reaching HbA_{1c} less than 7.0% was 68% (483 of 716) with tirzepatide and 36% (256 of 708) with insulin lispro (odds ratio, 4.2 [95% CI, 3.2-5.5]). The most common adverse events with tirzepatide were mild to moderate gastrointestinal symptoms (nausea: 14%-26%; diarrhea: 11%-15%; vomiting: 5%-13%). Hypoglycemia event rates (blood glucose level <54 mg/dL or severe hypoglycemia) were 0.4 events per patient-year with tirzepatide (pooled) and 4.4 events per patient-year with insulin lispro.

CONCLUSIONS AND RELEVANCE In people with inadequately controlled type 2 diabetes treated with basal insulin, weekly tirzepatide compared with prandial insulin as an additional treatment with insulin glargine demonstrated reductions in HbA_{1c} and body weight with less hypoglycemia.

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Supplemental content

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Insulin therapy remains a treatment option in type 2 diabetes, particularly for patients with long-term type 2 diabetes and inadequate glycemic control despite the use of other glucose-lowering therapy. Recent guidelines support adding an injectable incretin-related therapy such as glucagon-like peptide-1 (GLP-1 RA) for glycemic control, rather than basal insulin, when oral medications are inadequate.[1] However, due to cost, gastrointestinal symptoms, and clinician prescribing habits, basal insulins are still widely used as the first-prescribed injectable treatment.[2] Guidelines also recommend the addition of GLP-1 RAs for patients taking more than 0.5 IU/kg per day of basal insulin before intensifying therapy with short-acting insulin before meals (prandial insulin) as basal-bolus insulin therapy.[1] GLP-1 RAs have demonstrated similar or slightly better glycemic control, with lower rates of hypoglycemia and more weight loss or less weight gain, compared with adding prandial insulin in patients receiving basal insulin.[3,4] Nevertheless, adding prandial insulin remains a therapeutic option for patients with type 2 diabetes that is inadequately controlled with basal insulin.[5,6]

Tirzepatide is a once-weekly glucose-dependent insulinotropic polypeptide and GLP-1 RA approved for the treatment of type 2 diabetes and under investigation for long-term weight management. In the phase 3 SURPASS clinical trial program, tirzepatide at all doses tested resulted in significant reductions in mean glycated hemoglobin A_{1c} (HbA_{1c}) ranging from 1.9% to 2.6% with body weight loss ranging from 6 kg to 13 kg (7%-14%) across all stages of diabetes treatment.[7-11] Furthermore, 81% to 97% of participants achieved an HbA_{1c} less than 7.0% and 23% to 62% achieved an HbA_{1c} less than 5.7%.[7-11] The SURPASS-6 trial evaluated the efficacy and safety of adding tirzepatide to background basal insulin vs adding thrice-daily prandial insulin lispro in adults with inadequately controlled type 2 diabetes receiving basal insulin with or without metformin.

Key Points

Question What is the effect on glycemic control of adding once-weekly tirzepatide vs thrice-daily prandial insulin lispro to insulin glargine treatment in inadequately controlled basal insulin–treated type 2 diabetes?

Findings In this randomized clinical trial (N = 1428), mean change in hemoglobin A_{1c} (HbA_{1c}) at week 52 was −2.1% with tirzepatide vs −1.1% with insulin lispro; treatment differences were statistically significant with less hypoglycemia and more body weight reduction with tirzepatide.

Meaning Adding once-weekly tirzepatide vs prandial insulin lispro to insulin glargine in basal insulin-treated patients with type 2 diabetes and inadequate glycemic control resulted in greater reductions in HbA_{1c} along with more weight loss and less hypoglycemia.

Methods

This 52-week, open-label, multicenter, parallel-group, randomized, phase 3b clinical trial (protocol in Supplement 1) was conducted in 135 medical research centers and hospitals in Argentina, Belgium, Brazil, Czech Republic, Germany, Greece, Hungary, Italy, Mexico, Romania, Russia, Slovakia, Spain, Turkey, and the US (eTable 1 in Supplement 2). The protocol was approved by local institutional review boards; the trial was conducted in accordance with the Declaration of Helsinki guidelines on Good Clinical Practice. All participants provided written informed consent.

Participants

Key inclusion criteria were adults 18 years or older with type 2 diabetes inadequately controlled with basal insulin (insulin NPH, insulin glargine, insulin detemir, or insulin degludec), with or without any combination of up to 2 of the following oral glucose-lowering medications: metformin of at least 1500 mg per day, sulfonylurea, or dipeptidyl peptidase-4 inhibitors. Eligible participants had an HbA_{1c} level of 7.5% to 11% (58-97 mmol/mol) at visit 1 and a body mass index of 23 to 45. Key exclusion criteria included the diagnosis of type 1 diabetes, history of pancreatitis, proliferative diabetic retinopathy, diabetic macular edema, nonproliferative diabetic retinopathy that required immediate treatment, severe hypoglycemia and/or hypoglycemia unawareness, and an estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m^2 (or less than 45 mL/min/1.73 m^2 for participants receiving metformin). For a complete list of eligibility criteria, see the eAppendix in Supplement 2. Information on sex was self-reported. To meet regulatory requirements, race and ethnicity were recorded and determined by the participant according to fixed categories.

Randomization and Blinding

Eligible participants switched their diabetes treatment to a standardized therapy of insulin glargine (100 IU/mL) and discontinued glucose-lowering medications, except for metformin, during a stabilization period up to 10 weeks before randomization. During this insulin stabilization period, investigators adjusted the dose of insulin glargine per their clinical judgement to a target fasting blood glucose of 100 to 125 mg/dL. Patients with an HbA_{1c} of 7.5% or greater were randomized using a computer-generated random sequence through an interactive web-response system based at Eli Lilly and Company. Participants were randomized to receive subcutaneous injection of once-weekly tirzepatide (5 mg, 10 mg, or 15 mg) or thrice-daily prandial insulin lispro (100 IU/mL) for 52 weeks, followed by a 4-week safety follow-up period (eFigure 1 in Supplement 2). Stratification was performed by country, prerandomization HbA_{1c} (≤8.5% or >8.5%), and baseline metformin use (yes or no).

Interventions

Tirzepatide was initiated at 2.5 mg once weekly with the dose increased by 2.5 mg every 4 weeks until the randomized dose was achieved and maintained until 52 weeks.

Insulin lispro was initiated at 4 IU prior to the 3 largest meals of the day. Doses were adjusted twice weekly until week

24 and at least once weekly after week 24 to achieve a prelunch, predinner, and bedtime blood glucose target of 100 to 125 mg/dL following a standardized titration algorithm (eTable 2 and 3 in Supplement 2).

At randomization, participants reduced insulin glargine doses by 30% in all groups to lower hypoglycemia risk due to study treatment initiation. Basal insulin glargine doses were titrated weekly to a prebreakfast blood glucose target of 100 to 125 mg/dL (eTable 4 in Supplement 2). Tirzepatide-treated participants were restricted from any up-titration of insulin glargine for 4 weeks after randomization.

Outcomes

The primary objective was to demonstrate statistical noninferiority of tirzepatide (pooled cohort) to insulin lispro in change from baseline in HbA_{1c}. Key secondary objectives, controlled for type I error (described in a graphical testing scheme in eAppendix in Supplement 2), included demonstrating statistical superiority of tirzepatide (pooled cohort) to insulin lispro in change from baseline in HbA_{1c} and body weight and percentage of participants reaching HbA_{1c} less than 7.0% at week 52; demonstrating statistical noninferiority of individual tirzepatide doses (5 mg, 10 mg and/or 15 mg) to insulin lispro in change in HbA_{1c} from baseline to week 52; and demonstrating statistical superiority of individual tirzepatide doses (5 mg, 10 mg and/or 15 mg) to insulin lispro in change in HbA_{1c} and body weight from baseline to week 52 (eAppendix and eFigure 2 in Supplement 2). Other secondary end points not controlled for type I error were the percentage of participants achieving an HbA_{1c} target of 6.5% or less, the percentage of participants with weight loss of 5% or greater, mean change from baseline in fasting serum glucose, daily mean 7-point self-monitored blood glucose levels, lipid levels, body mass index, and waist circumference. A composite end point of an HbA_{1c} level less than 7.0% without clinically significant hypoglycemia events (defined as blood glucose level <54 mg/dL or severe hypoglycemia) was also assessed. To assess any difference in treatment response based on glycemic status, a subgroup analysis was conducted for the HbA_{1c} based on baseline HbA_{1c} category (≤8.5% or >8.5%) to test for any treatment × subgroup interaction at week 52.

Exploratory end points not included in the original protocol were change in insulin dose, the percentage of participants achieving an HbA_{1c} target of 5.7% or less, the percentage of participants with weight loss of 10% or more, and the percentage of participants with weight loss of 15% or more.

Safety assessments included adverse events, treatment discontinuation due to adverse events, independently adjudicated pancreatitis, hypersensitivity reactions, vital signs, and hypoglycemia events (eAppendix in Supplement 2).

Throughout, to convert glucose from mg/dL to mmol/L, multiply values by 0.0555. To convert HbA_{1c} to mmol/mol, use the following equation: $10.93 \times HbA_{1c} - 23.50$.

Sample Size Calculation

This trial was designed with a planned sample size of 1182 participants randomized in a 1:1:1:3 ratio to receive 5-mg tirzepatide, 10-mg tirzepatide, 15-mg tirzepatide, and insulin lispro to provide 80% power to show noninferiority of each tirzepatide dose vs insulin lispro with respect to change from baseline in HbA_{1c} at week 52. Power was assessed assuming a 1-sided significance level of .025 using a 2-sample *t* test with a noninferiority margin of 0.3% and an SD of 1.3% and assuming no difference in HbA_{1c} between treatment groups. This sample size ensured 97% power to achieve the primary objective.

Statistical Analyses

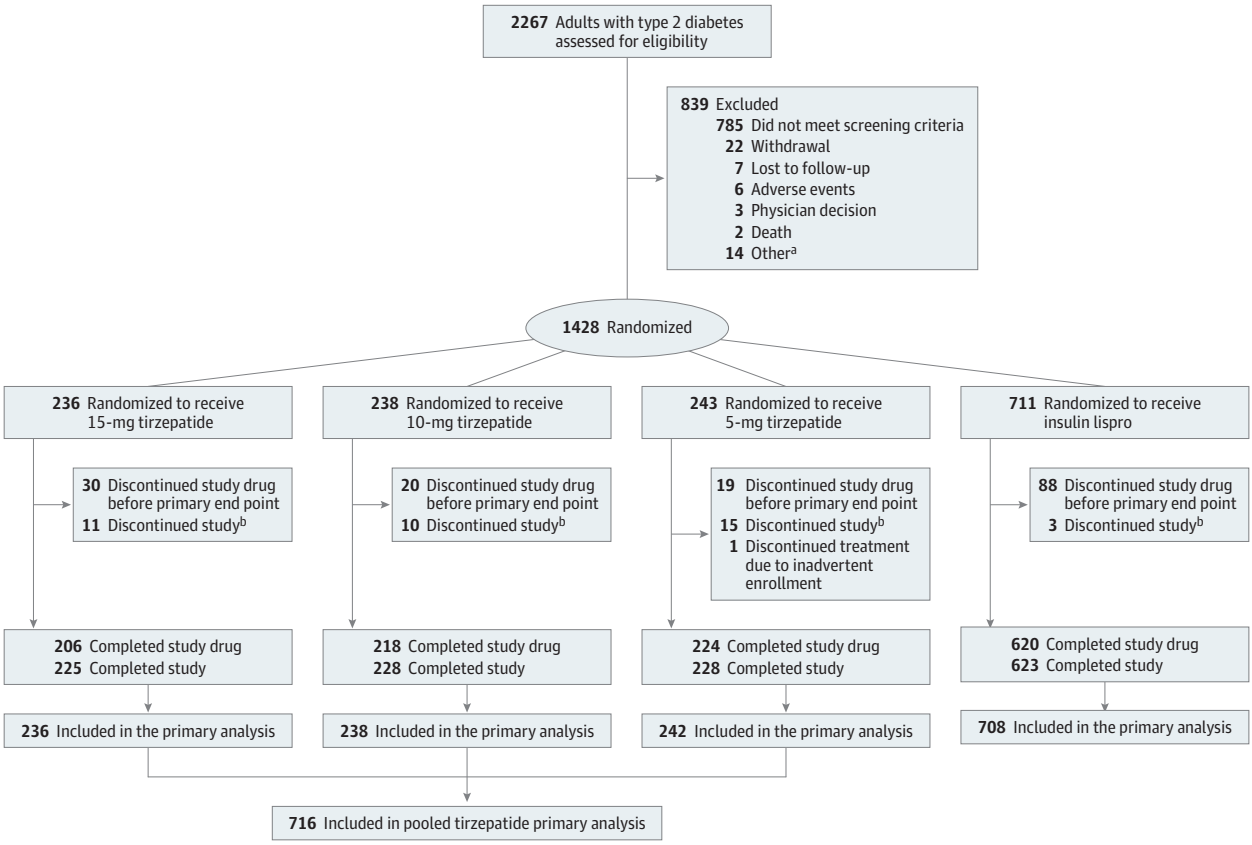
Primary and key secondary end points were evaluated for 2 estimands (treatment-regimen estimand and efficacy estimand). Type I error rate was controlled within each estimand for evaluation of primary and key secondary objectives using a graphical approach (eAppendix in Supplement 2). For other secondary and exploratory end points, the efficacy estimand was evaluated unless specified otherwise. Safety analyses were performed on all randomized patients who received at least 1 dose of the study drug with all data from start of study treatment to end of safety follow-up. All treatment difference results from statistical analyses were accompanied with 2-sided 95% CIs and *P* values, with statistical significance defined as $P < .05$. All statistical analyses were performed using SAS, version 9.4 (SAS Institute).

The treatment-regimen estimand evaluated the treatment effect of tirzepatide relative to insulin lispro irrespective of adherence to investigational product or introduction of rescue therapy. Statistical models used data during the treatment period regardless of treatment adherence or use of rescue therapy in participants who received at least 1 dose of the study treatment and did not discontinue study treatment due to inadvertent enrollment. For continuous end points, an analysis of covariance model with treatment, country, baseline metformin use (yes or no), and baseline HbA_{1c} (≤8.5% or >8.5%; excluding HbA_{1c} end point) as fixed effects and baseline end point value as a covariate was used. For categorical end points, after missing data imputation, logistic regression with the same fixed effects and covariate as continuous end points was used.

The efficacy estimand evaluated the treatment effect of tirzepatide treatments relative to insulin lispro if all patients had adhered to treatment and had not received rescue therapy. Statistical models used data during the treatment period excluding data after initiating rescue therapy or early discontinuation of the study drug in participants receiving at least 1 dose of study treatment who did not discontinue study treatment due to inadvertent enrollment. Continuous end points used a mixed model for repeated measures on the efficacy analysis set with treatment, visit, treatment × visit interaction, country, baseline metformin use (yes or no), and baseline HbA_{1c} category (≤8.5% or >8.5%; excluding HbA_{1c} end point) as fixed effects and baseline end point value as a covariate. For categorical end points, after missing data imputation, logistic regression was used with the same factors and covariate (excluding visit effects) as continuous end points.

Analyses details, including imputation methods, are provided in the eAppendix in Supplement 2.

Figure 1. Flow of Participants in the SURPASS-6 Trial



See Table 3 for the details of the adverse events that led to study treatment discontinuation.

[a] Includes 1 participant each who did not meet baseline age criteria, had chronic or acute pancreatitis or hepatitis, receiving drugs that directly affect gastrointestinal motility, or have a known clinically significant gastric emptying abnormality, have history of history of diabetic ketoacidosis or hyperosmolar state/coma, have family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, have evidence of an autoimmune abnormality, have a history of any other condition that may preclude the participant from following and completing the protocol, are pregnant or breastfeeding, have participated in a clinical study involving an investigational product, or have previously completed/discontinued from this study or any other study investigating tirzepatide.

[b] Study discontinuations before, after, or at the primary end point visit were included.

Results

Baseline Characteristics

This trial was conducted between October 19, 2020, and November 1, 2022. Overall, 2267 participants were assessed for trial eligibility, 1428 participants were randomized, and 1425 participants received at least 1 dose of the study treatment (**Figure 1**). Baseline demographics and clinical characteristics were similar across groups (overall mean age, 59 years; 824 [58%] women; mean diabetes duration, 14 years; mean HbA_{1c}, 8.8%; mean body weight, 90.5 kg; mean fasting serum glucose, 157 mg/dL; and median insulin glargine dose, 46 IU/d [0.53 IU/kg/d]) (**Table 1**; eTable 5 in Supplement 2). Racial and ethnic groups within the US were well represented (13% of participants were Black and 53% were Hispanic). A total of 89% of participants completed trial treatment (87%-92% across tirzepatide groups and 87% in the insulin lispro group) (Figure 1). The leading cause of premature treatment discontinuation with tirzepatide was adverse events (mainly gastrointestinal) (eTable 6 in Supplement 2).

Primary Outcome

For the treatment-regimen estimand, from a mean baseline HbA_{1c} of 8.8% (73 mmol/mol), the pooled tirzepatide group demonstrated a mean change in HbA_{1c} of −2.1% vs −1.1% with insulin lispro, with a mean HbA_{1c} at week 52 of 6.7% vs 7.7% (**Figure 2**A; eFigure 3A in Supplement 2). The pooled tirzepatide group was statistically superior to insulin lispro, with an estimated treatment difference of −0.98% (95% CI, −1.17% to −0.79%; $P < .001$) (**Table 2**).

Key Secondary Outcomes

At week 52, from a baseline HbA_{1c} of 8.8% (73 mmol/mol), the mean changes in HbA_{1c} were −1.9% with 5-mg tirzepatide, −2.2% with 10-mg tirzepatide, and −2.3% with 15-mg tirzepatide (Table 2). Tirzepatide was statistically superior

Table 1. Baseline Demographics and Clinical Characteristics

Characteristic	Mean (SD)				
	Tirzepatide				
	15 mg (n = 236)	10 mg (n = 238)	5 mg (n = 243)	Pooled (n = 717)	Insulin lispro (n = 708)
Age, y	58.2 (9.6)	59.6 (9.4)	58.0 (10.2)	58.6 (9.8)	59.0 (9.7)
Women, No. (%)	133 (56.4)	149 (62.6)	144 (59.3)	426 (59.4)	396 (55.9)
Men, No. (%)	103 (43.6)	89 (37.4)	99 (40.7)	291 (40.6)	312 (44.1)
Race, No. (%)[a]					
American Indian or Alaska Native	1 (0.4)	0	0	1 (0.1)	2 (0.3)
Asian	2 (0.8)	0	2 (0.8)	4 (0.6)	4 (0.6)
Black or African American	11 (4.7)	9 (3.8)	11 (4.5)	31 (4.3)	26 (3.7)
Multiple	2 (0.8)	5 (2.1)	0	7 (1.0)	8 (1.1)
White	220 (93.2)	224 (94.1)	230 (94.7)	674 (94.0)	668 (94.4)
Hispanic or Latino, No. (%)[a]	149 (63.1)	142 (59.7)	148 (60.9)	439 (61.2)	443 (62.6)
Diabetes duration, y[b]	13.4 (7.6)	13.9 (7.3)	13.4 (6.9)	13.6 (7.2)	14.0 (7.4)
Body weight, kg	91.2 (18.7)	89.1 (18.8)	91.7 (17.9)	90.7 (18.5)	90.3 (17.7)
BMI	33.0 (5.3)	33.4 (5.5)	33.5 (5.3)	33.3 (5.4)	33.0 (5.2)
Use of metformin, No. (%)	201 (85.2)	195 (81.9)	202 (83.1)	598 (83.4)	606 (85.6)
Daily insulin glargine dose, median (IQR), IU	47.0 (36.0-61.0)	46.0 (34.0-60.0)	46.0 (36.0-60.0)	46.0 (36.0-60.0)	46.0 (36.0-60.0)
Daily insulin glargine dose, median (IQR), IU/kg	0.52 (0.41-0.69)	0.54 (0.41-0.69)	0.51 (0.41-0.66)	0.52 (0.41-0.68)	0.53 (0.42-0.68)
HbA_{1c}, %[c]	8.74 (1.01)	8.78 (0.98)	8.89 (0.97)	8.80 (0.99)	8.80 (0.96)
HbA_{1c} >8.5%, No. (%)	132 (55.9)	133 (55.9)	146 (60.1)	411 (57.3)	407 (57.5)
Fasting serum glucose, mg/dL[d]	155.9 (54.3)	155.8 (55.5)	163.3 (59.2)	158.4 (56.4)	156.3 (56.1)
eGFR, mL/min/1.73 m^2[e]	89.3 (19.9)	89.5 (18.0)	89.0 (20.7)	89.3 (19.6)	88.8 (18.8)
eGFR <60 mL/min/1.73 m^2, No. (%)	24 (10.2)	14 (5.9)	27 (11.1)	65 (9.1)	65 (9.2)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); eGFR, estimated glomerular filtration rate (calculated with use of the serum creatinine–based Chronic Kidney Disease Epidemiology Collaboration equation); HbA_{1c}, glycated hemoglobin A_{1c}.

[a] To meet regulatory requirements, race and ethnicity were recorded in this study and were determined by the participant according to fixed selection categories.

[b] Duration of diabetes was based on the first diagnosis of type 2 diabetes.

[c] Normal value for HbA_{1c} was <6.5%. To convert HbA_{1c} values to mmol/mol, use the following equation: 10.93 × HbA_{1c} − 23.50.

[d] Normal value for fasting serum glucose was 74-106 mg/dL for those younger than 60 years and 82-115 mg/dL for those aged 60-90 years.

[e] Normal value for eGFR was ≥60 mL/min/1.73 m^2. Participants with a baseline eGFR less than 30 mL/min/1.73 m^2 were excluded from the study.

toinsulin lispro, with estimated treatment differences of −0.79% (95% CI, −1.01% to −0.56%) for 5-mg tirzepatide, −1.01% (95% CI, −1.26% to −0.77%) for 10-mg tirzepatide, and −1.13% (95% CI, −1.37% to −0.90%) for 15-mg tirzepatide (P < .001 for all doses) (Table 2). Observed HbA_{1c} values over time with individual tirzepatide doses are presented in eFigure 4A in Supplement 2. Target HbA_{1c} of less than 7.0% was achieved in 68% of tirzepatide-treated participants (483 of 716) vs 36% receiving insulin lispro (256 of 708) (Table 2; eFigure 3B in Supplement 2).

From a mean baseline body weight of 90 kg, the pooled estimated mean change in body weight was −9.0 kg with tirzepatide vs 3.2 kg with insulin lispro at week 52 (Figure 2B; eFigure 3C in Supplement 2). Mean change in body weight was −6.7 kg for 5-mg tirzepatide, −9.2 kg for 10-mg tirzepatide, and −11.0 kg for 15-mg tirzepatide (Table 2). All tirzepatide doses demonstrated superiority to insulin lispro (Table 2). Observed changes from baseline in body weight over time with individual tirzepatide doses are presented in eFigure 4B in Supplement 2.

Additional Secondary and Exploratory End Points

Greater reductions in fasting serum glucose were observed with all tirzepatide doses vs insulin lispro at week 52 (eTable 7 in Supplement 2). Reductions in mean daily 2-hour postprandial glucose from the 7-point self-monitored blood glucose profile ranged from 65 to 78 mg/dL with tirzepatide vs 65 mg/dL with insulin lispro (eFigure 5 in Supplement 2).

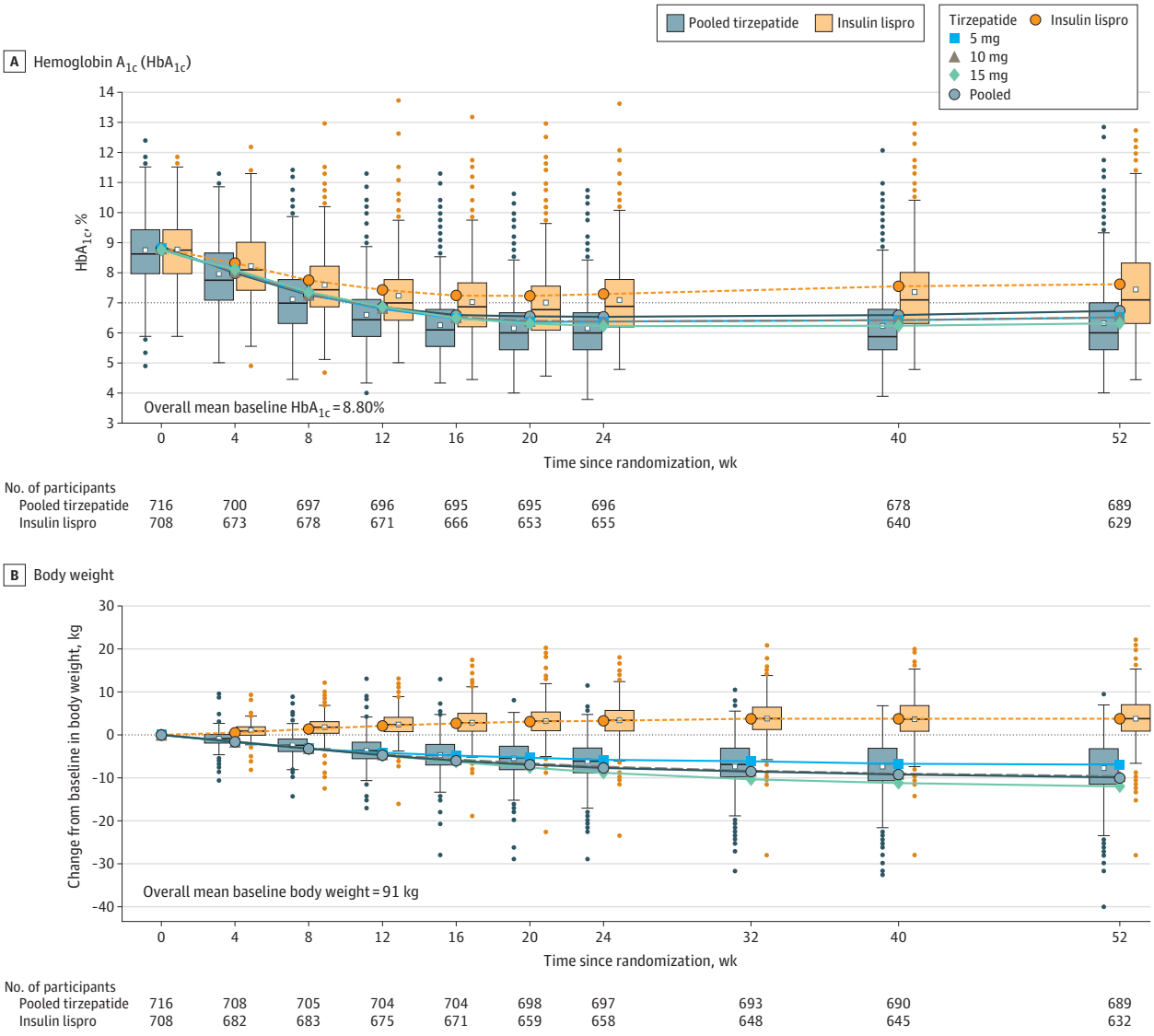
An HbA_{1c} target of 6.5% or less was achieved in 56% of tirzepatide-treated participants and 22% with insulin lispro and an $HbA1_c$ target of less than 5.7% (exploratory endpoint) was achieved in 18% of participants in the tirzepatide group and 3% of those in the insulin lispro group (eTable 7 and eFigure 3B in Supplement 2). For the efficacy estimand, more participants achieved a composite end point of an HbA_{1c} value of less than 7.0% without clinically significant hypoglycemia with tirzepatide (53%-75%) vs insulin lispro (13%) (eTable 8 in Supplement 2).

Body weight reduction of at least 5% was met by 62% to 78% of participants in the tirzepatide group (eTable 7 in Supplement 2). Body weight reduction of at least 10% was met by 32% to 57% and reduction of at least 15% was met in 13% to 37% of the tirzepatide group (exploratory end point). Mean body mass index and waist circumference also significantly decreased with tirzepatide and increased with insulin lispro (eFigure 6 and eTable 7 in Supplement 2).

Similar results for HbA_{1c}, body weight, HbA_{1c} targets, and weight loss targets were reported for the efficacy estimand (eFigure 7 and eTable 9 in Supplement 2). No significant treatment × subgroup interaction was observed for mean HbA_{1c} change from baseline between the subgroups (baseline HbA_{1c} ≤8.5% or >8.5%) (eTable 10 in Supplement 2).

Triglycerides, total cholesterol, low-density lipoprotein cholesterol, very-low-density lipoprotein cholesterol, and non–high-density lipoprotein cholesterol significantly decreased with all tirzepatide doses and high-density lipoprotein

Figure 2. Effect of Tirzepatide vs Insulin Lispro on Hemoglobin A_{1c} (HbA_{1c}) and Body Weight



A, Lines show the values for least-squares mean HbA_{1c} levels over time derived from a mixed-model repeated-measures analysis (efficacy estimand). To convert HbA_{1c} values to mmol/mol, use the equation 10.93 × HbA_{1c}) − 23.50. Boxplots represent observed HbA_{1c} actual values over time for randomized patients from the pooled tirzepatide and insulin lispro groups, irrespective of treatment discontinuation or initiation of rescue therapy, using the full analysis set. The middle lines within each box represent the median observed HbA_{1c}, the symbols in the boxes represent the mean observed HbA_{1c}, the top and bottom of the boxes represent the interquartile range, the whiskers extend to the most extreme observed values with 1.5 times the IQR of the nearer quartile, and the symbols beyond these points represent the observed values outside that range. B, Lines show least-squares mean change from baseline in body weight over time, derived from a mixed-model repeated measures analysis (efficacy estimand). Boxplots represent observed changes from baseline in body weight over time for randomized patients from the pooled tirzepatide and insulin lispro groups, irrespective of treatment discontinuation or initiation of rescue therapy, using the full analysis set. The middle lines within each box represent the median observed changes from baseline; the symbols in the boxes represent the mean observed percentage change; the box tops and bottoms represent the interquartile range; the whiskers extend to the most extreme observed values with 1.5 times the IQR of the nearer quartile; and the symbols beyond these points represent the observed values outside that range. More negative values indicate greater reductions. Due to the large y-axis scale and number of individual data points shown in panel B, some outliers are overlapping and not visualized within the boxplot.

cholesterol significantly increased with tirzepatide at the 10 mg and 15 mg doses vs insulin lispro at week 52 (eTables 7 and 11 and eFigure 8 in Supplement 2).

Background insulin glargine dose decreased over time from a geometric mean baseline of 46 IU with tirzepatide (geometric mean daily insulin glargine dose at week 52: pooled tirzepatide, 13 IU [0.15 IU/kg]; 5-mg tirzepatide, 20 IU [0.24 IU/kg]; 10-mg tirzepatide, 12 IU [0.15 IU/kg]; 15-mg tirzepatide, 8 IU [0.10 IU/kg]), with 8% to 19% of tirzepatide-treated participants completely discontinuing insulin glargine therapy by week 52 (eFigure 9 in Supplement 2). At week 52, geometric mean daily dose of insulin lispro was

Table 2. Glycemic and Cardiometabolic Parameters at Week 52

Parameter	Tirzepatide				Insulin lispro (n = 708)
	15 mg (n = 236)	10 mg (n = 238)	5 mg (n = 242)	Pooled (n = 716)	
Primary end point					
HbA_{1c}, %[a,b]					
Baseline, mean (SD)				8.80	8.80
Week 52, mean (95% CI)				6.69 (−2.2 to −2.0)	7.67 (−1.3 to −1.0)
Change from baseline at week 52 (95% CI)				−2.11 (−2.2 to −2.0)	−1.13 (−1.3 to −1.0)
Difference vs insulin lispro (95% CI)				−0.98 (−1.17 to −0.79)	
P value				<.001	
Confirmatory secondary end points					
HbA_{1c}, %[a,b]					
Baseline, mean (SD)	8.74	8.78	8.88		
Week 52, mean (95% CI)	6.53 (−2.4 to −2.1)	6.65 (−2.3 to −2.0)	6.88 (−2.1 to −1.8)		
Change from baseline at week 52 (95% CI)	−2.27 (−2.4 to −2.1)	−2.15 (−2.3 to −2.0)	−1.92 (−2.1 to −1.8)		
Difference vs insulin lispro (95% CI)	−1.13 (−1.37 to −0.90)	−1.01 (−1.26 to −0.77)	−0.79 (−1.01 to −0.56)		
P value	<.001	<.001	<.001		
Participants met HbA_{1c} target <7.0% at week 52, No. (%)[a,c]	172 (73)	171 (72)	140 (58)	483 (68)	256 (36)
Odds ratio vs insulin lispro (95% CI)	5.2 (3.6 to 7.5)	5.1 (3.5 to 7.4)	2.8 (2.0 to 3.9)	4.2 (3.2 to 5.5)	
P value	<.001	<.001	<.001	<.001	
Body weight, kg[a,b]					
Baseline, mean (SD)	91.2	89.1	91.7	90.7	90.3
Week 52, mean (95% CI)	79.5 (−11.9 to −10.0)	81.2 (−10.2 to −8.3)	83.8 (−7.7 to −5.7)	81.5 (−9.5 to −8.4)	93.6 (2.1 to 4.2)
Change from baseline at week 52 (95% CI)	−11.0 (−11.9 to −10.0)	−9.2 (−10.2 to −8.3)	−6.7 (−7.7 to −5.7)	−9.0 (−9.5 to −8.4)	3.2 (2.1 to 4.2)
Difference vs insulin lispro (95% CI)	−14.2 (−15.6 to −12.7)	−12.4 (−13.9 to −11.0)	−9.9 (−11.4 to −8.4)	−12.2 (−13.4 to −10.9)	
P value	<.001	<.001	<.001	<.001	

Abbreviations: HbA_{1c}, glycated hemoglobin A_{1c}; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

[a] Data presented are using the treatment-regimen estimand.

[b] Tested for superiority and controlled for type I error.

[c] Tested for superiority; controlled for type I error only for pooled tirzepatide vs insulin lispro.

62 IU (0.67 IU/kg) and of insulin glargine was 42 IU (0.45 IU/kg) (Table 2; eFigure 3D in Supplement 2), corresponding to a geometric mean total daily insulin use of 112 IU (1.2 IU/kg) in the insulin lispro group (eFigure 10 in Supplement 2). Protocol-defined blood glucose targets were achieved by 51% to 61% of participants in the lispro insulin group across fasting and postmeal points.

Adverse Events and Tolerability

Reports of adverse events were higher among the tirzepatide groups vs the insulin lispro group (**Table 3**). More serious adverse events were reported with insulin lispro, with the most frequent event being hypoglycemia (Table 3; eTable 12 in Supplement 2). Eighteen (1.3%) deaths occurred during the trial (3 in the 5-mg tirzepatide group, 3 in the 10-mg tirzepatide group, 1 in the 15-mg tirzepatide group, and 11 in the insulin lispro group) (Table 3). None of the deaths were considered to be related to the study treatment by investigators.

The most frequently reported adverse events with tirzepatide were gastrointestinal (including nausea [14%-26%], diarrhea [11%-15%], and vomiting [5%-13%]) (Table 3). Most cases of nausea, vomiting, and diarrhea were mild to moderate in severity as judged by the investigator, transient, and occurred during the dose-escalation period (eFigure 11 and eTable 13 in Supplement 2).

Incidence of clinically significant hypoglycemia was reported in 12% of participants (29 of 243) in the 5-mg tirzepatide group, 9% (22/238) in the 10-mg tirzepatide group, and 11% (25/236) in the 15-mg tirzepatide group vs 48% (340/708) in the insulin lispro group, and event rates were less with tirzepatide than insulin lispro (0.4 vs 4.4 events/patient-year) (**Table 4**). Severe hypoglycemia was reported in 30 insulin lispro-treated participants (89 events) and 3 tirzepatide-treated participants (all in 10-mg group; 17 events).

There were no cases of adjudicated pancreatitis (Table 3). Reductions in serum alanine aminotransferase and aspartate aminotransferase were observed with tirzepatide (eTable 14 in Supplement 2). Other laboratory measures are presented in eTable 14 in Supplement 2. Nine tirzepatide-treated participants and 2 insulin lispro-treated participants reported cholelithiasis (Table 3). No clinically relevant changes in mean calcitonin levels or cases of thyroid malignancies were reported. Two tirzepatide-treated participants and 4 insulin

Table 3. Summary of Adverse Events and Safety Parameters Through Safety Follow-Up 4 Weeks After Treatment Discontinuation

Parameter	Tirzepatide				Insulin lispro (n = 708)
	15 mg (n = 236)	10 mg (n = 238)	5 mg (n = 243)	Pooled (n = 717)	
Participants with ≥1 serious adverse event[a]	15 (6.4)	14 (5.9)	15 (6.2)	44 (6.1)	77 (10.9)
Death[b]	1 (0.4)	3 (1.3)	3 (1.2)	7 (1.0)	11 (1.6)
Adverse event leading to study treatment discontinuation	3 (1.3)	4 (1.7)	5 (2.1)	12 (1.7)	15 (2.1)
Participants with ≥1 adverse event leading to study treatment discontinuation	22 (9.3)	11 (4.6)	10 (4.1)	43 (6.0)	17 (2.4)
Nausea	6 (2.5)	1 (0.4)	3 (1.2)	10 (1.4)	0
Vomiting	5 (2.1)	0	0	5 (0.7)	0
Weight decreased	2 (0.8)	0	0	2 (0.3)	0
Pancreatic enzymes increased	2 (0.8)	1 (0.4)	0	3 (0.4)	0
Decreased appetite	1 (0.4)	1 (0.4)	0	2 (0.3)	0
Dyspepsia	1 (0.4)	1 (0.4)	0	2 (0.3)	0
Gastritis	1 (0.4)	1 (0.4)	0	2 (0.3)	0
Acute coronary syndrome	1 (0.4)	0	0	1 (0.1)	0
COVID-19	0	0	0	0	3 (0.4)
Death	0	0	1 (0.4)	1 (0.1)	1 (0.1)
Diarrhea	0	0	2 (0.8)	2 (0.3)	0
Lung neoplasm malignant	0	0	0	0	2 (0.3)
Acute kidney injury	0	1 (0.4)	0	1 (0.1)	0
Participants with ≥1 treatment-emergent adverse event[c]	177 (75.0)	168 (70.6)	170 (70.0)	515 (71.8)	394 (55.6)
Treatment-emergent adverse events occurring in ≥5% of participants in any treatment group by preferred term					
Nausea	61 (25.8)	49 (20.6)	33 (13.6)	143 (19.9)	8 (1.1)
Decreased appetite	40 (16.9)	28 (11.8)	20 (8.2)	88 (12.3)	1 (0.1)
Vomiting	30 (12.7)	21 (8.8)	11 (4.5)	62 (8.6)	4 (0.6)
Dyspepsia	27 (11.4)	27 (11.3)	15 (6.2)	69 (9.6)	4 (0.6)
Diarrhea	26 (11.0)	36 (15.1)	29 (11.9)	91 (12.7)	17 (2.4)
COVID-19	22 (9.3)	19 (8.0)	29 (11.9)	70 (9.8)	77 (10.9)
Constipation	14 (5.9)	8 (3.4)	6 (2.5)	28 (3.9)	4 (0.6)
Urinary tract infection	12 (5.1)	2 (0.8)	9 (3.7)	23 (3.2)	27 (3.8)
All gastrointestinal adverse events	108 (45.8)	114 (47.9)	81 (33.3)	303 (42.3)	61 (8.6)
Other treatment-emergent adverse events of interest					
Major adverse cardiovascular events (adjudication confirmed)[d]	3 (1.3)	7 (2.9)	5 (2.1)	15 (2.1)	12 (1.7)
Hypersensitivity	6 (2.5)	7 (2.9)	4 (1.6)	17 (2.4)	9 (1.3)
Cholelithiasis	4 (1.7)	3 (1.3)	2 (0.8)	9 (1.3)	2 (0.6)
Injection-site reactions	4 (1.7)	3 (1.3)	1 (0.4)	8 (1.1)	1 (0.1)
Acute cholecystitis	1 (0.4)	1 (0.4)	1 (0.4)	3 (0.4)	1 (0.1)
Diabetic retinopathy[e]	0	0	2 (0.8)	2 (0.3)	4 (0.6)
Adjudication-confirmed pancreatitis	0	0	0	0	0

[a] A serious adverse event was defined as any adverse event that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent disability or incapacity, was a congenital anomaly or birth defect, or medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes previously listed.

[b] Deaths were included as serious adverse events and discontinuations due to adverse event. No deaths were considered related to the study treatment by the investigator. All deaths were adjudicated by an external committee of physicians with cardiology expertise.

[c] A treatment-emergent adverse event was defined as an untoward medical occurrence that emerged during the defined treatment period, having been absent before treatment, or worsens relative to the pretreatment state and does not necessarily have to have a causal relationship with this treatment.

[d] Major adverse cardiovascular events include cardiovascular death, myocardial infarction, hospitalization due to unstable angina and stroke.

[e] Confirmed by ophthalmoscopic examination.

lispro-treated participants reported new or worsening retinopathy confirmed by fundoscopic examination (Table 3).

Significant increases in mean pulse rate reached up to 4.5 per minute with tirzepatide and 2.0 per minute with insulin lispro during the trial, with the difference in mean pulse rate from baseline ranging from 1.4 to 2.6 per minute with tirzepatide compared with 1.0 per minute with insulin lispro at week 52 (eFigure 12A in Supplement 2). Tirzepatide treatment resulted in a significant decrease in mean systolic blood pressure (5.9-9.0 mm Hg) and diastolic blood pressure (1.0-3.3 mm Hg) vs no significant change with insulin lispro at week 52 (eTable 7 and eFigure 12B-C in Supplement 2).

Discussion

Tirzepatide as an add-on to basal insulin treatment at individual and pooled doses resulted in statistically and clinically significant reductions in mean HbA_{1c} and a higher percentage of participants meeting an HbA_{1c} target of less than 7.0%,

Table 4. Hypoglycemia Events[a]

Hypoglycemia event	Tirzepatide								Insulin lispro (n = 708)	
	15 mg (n = 236)		10 mg (n = 238)		5 mg (n = 243)		Pooled (n = 717)			
	No. (%)	Episodes (events/ patient-year of exposure)	No. (%)	Episodes (events/ patient-year of exposure)	No. (%)	Episodes (events/ patient-year of exposure)	No. (%)	Episodes (events/ patient-year of exposure)	No. (%)	Episodes (events/ patient-year of exposure)
Severe hypoglycemia[b]	0	0	3 (1.3)	17 (0.05)	0	0	3 (0.4)	17 (0.01)	30 (4.2)	89 (0.16)
Relative rate (95% CI)		0		0.29 (0.07 to 1.18)		0		0.08 (0.02 to 0.26)		NA
Severe hypoglycemia that required hospitalization or documented medical help or was life threatening)[a]	0	0	2 (0.8)	11 (0.03)	0	0	2 (0.3)	11 (0.01)	25 (3.5)	36 (0.06)
Relative rate (95% CI)		0		0.46 (0.11 to 1.84)		0		0.14 (0.04 to 0.53)		NA
Blood glucose level less than 54 mg/dL or severe hypoglycemia	25 (10.6)	54 (0.23)	22 (9.2)	156 (0.41)	29 (11.9)	158 (0.59)	76 (10.6)	368 (0.41)	340 (48.0)	2796 (4.38)
Relative rate (95% CI)		0.05 (0.03 to 0.09)		0.09 (0.04 to 0.24)		0.13 (0.04 to 0.46)		0.09 (0.05 to 0.18)		NA
Blood glucose level 70 mg/dL or less or severe hypoglycemia	88 (37.3)	604 (2.3)	89 (37.4)	699 (2.6)	86 (35.4)	736 (2.6)	263 (36.7)	2039 (2.5)	519 (73.3)	12716 (18.4)
Relative rate (95% CI)		0.13 (0.09 to 0.18)		0.14 (0.09 to 0.23)		0.14 (0.09 to 0.22)		0.14 (0.10 to 0.18)		NA

Abbreviation: NA, not applicable.

[a] Data include safety follow-up using the safety analysis set from the safety population and exclude hypoglycemia episodes occurring after initiation of new antihyperglycemic therapy. Events per patient-year of exposure are presented as group mean.

[b] Severe hypoglycemia was defined as an episode with severe cognitive impairment requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

compared with prandial lispro insulin, in participants with type 2 diabetes inadequately controlled with basal insulin. This glycemic efficacy was associated with weight loss and a lower rate of clinically significant hypoglycemia. The effects of tirzepatide on glycemic control, weight loss, and other cardiometabolic parameters were consistent with other SURPASS trials.[7-11]

In the current trial, with an overall mean baseline HbA_{1c} of 8.8%, the recommended HbA_{1c} target of less than 7.0% was achieved by 68% of tirzepatide-treated participants. Treatment guidelines recommend simplifying complex treatment regimens, especially when using insulin to reduce the risk of hypoglycemia, polypharmacy, and overall burden of disease.[1] Tirzepatide treatment demonstrated reductions in basal insulin use in a dose-dependent manner, with 8% to 19% of participants completely discontinuing basal insulin therapy.

It is possible that the body weight loss induced by tirzepatide therapy and its reported effect in reducing liver fat content[12] may have led to an improvement in insulin sensitivity and decreased insulin requirements. In a similarly designed trial for semaglutide, 1 mg, the mean change in HbA_{1c} was −1.5%, with mean weight loss of 4.1 kg and reductions in daily basal insulin use from 40 IU to 31 IU at week 52.[4] Higher insulin sparing observed with tirzepatide in the current trial compared with 1-mg semaglutide was likely due to greater weight loss and greater improvements in insulin sensitivity.[4,5] However, direct comparison of these trials should be made with caution, and semaglutide, 2 mg, is now the highest approved dose for glycemic control.

Sustained weight loss of more than 10% has disease-modifying effects and possible remission of type 2 diabetes, likely improving long-term microvascular and cardiovascular morbidity and mortality.[1,13] Weight loss of 5% or more was achieved by 72% of participants in the tirzepatide group at week 52 compared with 10% in the prandial lispro group and was accompanied by clinically relevant improvements in cardiometabolic parameters. In an exploratory analysis, weight loss of 10% or more was achieved by 32% to 57% of tirzepatide-treated participants at week 52.

Hypoglycemia risk and the weight gain observed with complex insulin regimens that include prandial insulin have been main limitations to optimally up-titrate insulin therapy in clinical practice.[3] In the current trial, the rate of clinically significant hypoglycemia was lower with tirzepatide vs insulin lispro add-on therapy, despite achieving lower HbA_{1c} levels. All participants had reduced their basal insulin dose by 30% irrespective of baseline HbA_{1c}, which differs from the common practice of reducing dose of basal insulin by 10%[1] or 20%,[11,14] only for people with HbA_{1c} less than 8%, when adding a GLP-1 receptor agonist. The safety profile of tirzepatide was consistent with that reported previously in other SURPASS trials.[7-11]

This trial had several strengths. This was a global trial with a high completion rate. Titration of insulin, the percentage of participants who reached titration goals, and the overall glycemic efficacy in the prandial lispro insulin group were consistent with a larger trial that had similar blood glucose targets.[4]

Limitations

This trial had limitations. First, study treatments were not masked due to the different dosing frequency, titration

schemes, and drug delivery devices. Second, use of the standardized insulin algorithm and blood glucose targets may not be generalizable to participants outside of the trial setting. Third, this trial was not designed to discontinue insulin therapy. Fourth, patients using sodium-glucose cotransporter-2 inhibitors were excluded from this study.

Conclusions

In people with inadequately controlled type 2 diabetes treated with basal insulin, weekly tirzepatide compared with prandial insulin as an add-on to insulin glargine demonstrated reductions in HbA_{1c} and body weight with less hypoglycemia.

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Acquisition, analysis, or interpretation of data: All authors.
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Critical review of the manuscript for important intellectual content: All authors.
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