JAMA | Original Investigation

# 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

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**IMPORTANCE** The effects of tirzepatide, a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, as an addition to insulin glargine for treatment of type 2 diabetes have not been described.

**OBJECTIVE** To assess the efficacy and safety of tirzepatide added to insulin glargine in patients with type 2 diabetes with inadequate glycemic control.

**DESIGN, SETTING, AND PARTICIPANTS** Randomized phase 3 clinical trial conducted at 45 medical research centers and hospitals in 8 countries (enrollment from August 30, 2019, to March 20, 2020; follow-up completed January 13, 2021) in 475 adults with type 2 diabetes and inadequate glycemic control while treated with once-daily insulin glargine with or without metformin.

**INTERVENTIONS** Patients were randomized in a 1:1:1:1 ratio to receive once-weekly subcutaneous injections of 5-mg (n = 116), 10-mg (n = 119), or 15-mg (n = 120) tirzepatide or volume-matched placebo (n = 120) over 40 weeks. Tirzepatide was initiated at 2.5 mg/week and escalated by 2.5 mg every 4 weeks until the assigned dose was achieved.

**MAIN OUTCOMES AND MEASURES** The primary end point was mean change from baseline in glycated hemoglobin $A_{1c}$ ($HbA_{1c}$) at week 40. The 5 key secondary end points included mean change in body weight and percentage of patients achieving prespecified $HbA_{1c}$ levels.

**RESULTS** Among 475 randomized participants (211 [44%] women; mean [SD] age, 60.6 [9.9] years; mean [SD] $HbA_{1c}$, 8.31% [0.85%]), 451 (94.9%) completed the trial. Treatment was prematurely discontinued by 10% of participants in the 5-mg tirzepatide group, 12% in the 10-mg tirzepatide group, 18% in the 15-mg tirzepatide group, and 3% in the placebo group. At week 40, mean $HbA_{1c}$ change from baseline was −2.40% with 10-mg tirzepatide and −2.34% with 15-mg tirzepatide vs −0.86% with placebo (10 mg: difference vs placebo, −1.53% [97.5% CI, −1.80% to −1.27%]; 15 mg: difference vs placebo, −1.47% [97.5% CI, −1.75% to −1.20%]; $P < .001$ for both). Mean $HbA_{1c}$ change from baseline was −2.11% with 5-mg tirzepatide (difference vs placebo, −1.24% [95% CI, −1.48% to −1.01%]; $P < .001$]). Mean body weight change from baseline was −5.4 kg with 5-mg tirzepatide, −7.5 kg with 10-mg tirzepatide, −8.8 kg with 15-mg tirzepatide and 1.6 kg with placebo (5 mg: difference, −7.1 kg [95% CI, −8.7 to −5.4]; 10 mg: difference, −9.1 kg [95% CI, −10.7 to −7.5]; 15 mg: difference, −10.5 kg [95% CI, −12.1 to −8.8]; $P < .001$ for all). Higher percentages of patients treated with tirzepatide vs those treated with placebo had $HbA_{1c}$ less than 7% (85%-90% vs 34%; $P < .001$ for all). The most common treatment-emergent adverse events in the tirzepatide groups vs placebo group were diarrhea (12%-21% vs 10%) and nausea (13%-18% vs 3%).

**CONCLUSIONS AND RELEVANCE** Among patients with type 2 diabetes and inadequate glycemic control despite treatment with insulin glargine, the addition of subcutaneous tirzepatide, compared with placebo, to titrated insulin glargine resulted in statistically significant improvements in glycemic control after 40 weeks.

**TRIAL REGISTRATION** ClinicalTrials.gov Identifier: NCT04039503

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*JAMA*. 2022;327(6):534-545. doi:10.1001/jama.2022.0078

Basal insulins are widely used in patients with type 2 diabetes and inadequate glycemic control with oral glucose-lowering medications. Although increasing the basal insulin dose often improves glycemic control, it can also be associated with increased risk of hypoglycemia and weight gain, resulting in inadequate intensification of insulin dose in clinical practice.[1]

When added to basal insulin, selective glucagon-like peptide-1 (GLP-1) receptor agonists have demonstrated improved glycemic control and body weight loss without increasing the risk of hypoglycemia and reducing insulin requirements.[2-6] Glucose-dependent insulinotropic polypeptide is the primary incretin hormone responsible for meal-stimulated insulin secretion in healthy individuals.[7] It also suppresses glucagon secretion during hyperglycemia, signals glucagon secretion during hypoglycemia, facilitates postprandial lipid clearance, and promotes satiety.[8-10] Tirzepatide is a novel, once-weekly dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist that is administered via subcutaneous injection and has shown statistically significant reductions in hemoglobin $A_{1c}$ ($HbA_{1c}$) and body weight compared with the GLP-1 receptor agonist semaglutide (1 mg),[11] insulin degludec,[12] and insulin glargine[13] when added to oral glucose-lowering medications. Additionally, tirzepatide was associated with reductions in blood pressure and improvements in lipid profile.[11-14] The safety profile of tirzepatide was found to be similar to that of the GLP-1 receptor agonist class.[11-14]

The SURPASS-5 study evaluated the efficacy and safety of 3 doses of tirzepatide (5 mg, 10 mg, and 15 mg) compared with placebo as an addition to titrated basal insulin in patients with type 2 diabetes inadequately controlled with basal insulin, with or without metformin.

### Key Points

**Question** What is the effect of once-weekly subcutaneous tirzepatide compared with placebo when added to titrated insulin glargine on glycemic control in patients with type 2 diabetes?

**Findings** In this randomized clinical trial that included 475 adults, mean change in hemoglobin $A_{1c}$ at 40 weeks was −2.40% with 10-mg tirzepatide, −2.34% with 15-mg tirzepatide and −0.86% with placebo; the differences between each tirzepatide group vs the placebo group were statistically significant.

**Meaning** Among patients with type 2 diabetes and inadequate glycemic control despite treatment with insulin glargine, the addition of subcutaneous tirzepatide, compared with placebo, to titrated insulin glargine resulted in statistically significant improvements in glycemic control after 40 weeks.

## Methods

This study was a 40-week, phase 3, randomized, double-blind, parallel, multicenter, placebo-controlled study conducted at 45 medical research centers and hospitals in the US, Japan, Czech Republic, Germany, Poland, Puerto Rico, Slovakia, and Spain. The start date of enrollment was August 30, 2019, the last patient was randomized on March 20, 2020, and the date of final follow-up was January 13, 2021. The trial protocol (Supplement 1) was approved by the ethical review board at each site and followed according to the principles laid out in the Declaration of Helsinki, Council for International Organizations of Medical Sciences International Ethical Guidelines, the International Council of Harmonization guidelines, and local laws and regulations. All patients provided written informed consent before participation in the study.

### Participants

Eligible patients were adults with type 2 diabetes, baseline $HbA_{1c}$ of 7.0% to 10.5% (53-91 mmol/mol) inclusive, and body mass index (BMI) of at least 23 receiving stable doses of once-daily insulin glargine (>20 IU/d or >0.25 IU/kg/d) with or without metformin (≥1500 mg/d). Patients needed further insulin glargine dose increase at the randomization visit per the treat-to-target algorithm (median value of the last 3 self-monitored blood glucose values for fasting blood glucose >100 mg/dL; see details in eTable 1 in Supplement 2). Key exclusion criteria included the presence of type 1 diabetes, history of pancreatitis, nonproliferative diabetic retinopathy requiring acute treatment, proliferative diabetic retinopathy, diabetic maculopathy, hepatitis, hypoglycemia unawareness, gastroparesis, estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 $m^2$ (or <45 mL/min/1.73 $m^2$ for patients receiving metformin), and use of any other antihyperglycemia medication in the 3 months before screening (for complete list of eligibility criteria see eAppendix in Supplement 2). The study was not designed to represent the racial diversity of each of the participating countries. To meet regulatory requirements, race and ethnicity were recorded in this study and were determined by the participant according to fixed selection categories.

### Randomization and Blinding

Patients were randomized in a 1:1:1:1 ratio to receive 5 mg, 10 mg, or 15 mg of tirzepatide or volume-matched placebo (**Figure 1**) with a blocking schema (block size of 4) by a computer-generated random sequence using an interactive web response system and stratified based on country, baseline $HbA_{1c}$ (≤8.0% or >8.0% [≤64 mmol/mol or >64 mmol/mol]), and baseline metformin use. Investigators, site staff, clinical monitors, external independent adjudication committee members, sponsors, and patients remained blinded to the treatment assignments until study completion. All cases of suspected pancreatitis and major adverse cardiovascular events were adjudicated by an independent clinical end point committee in a blinded manner (eAppendix in Supplement 2).

### Interventions

Patients were randomized to receive once-weekly subcutaneous injections of the allocated tirzepatide (Eli Lilly and Company) or placebo treatment for 40 weeks, followed by a 4-week safety follow-up period (eFigure 1 in Supplement 2). The treatment period consisted of an initial 4-week insulin stabilization period followed by a 36-week insulin titration

Figure 1. Screening, Randomization, and Flow of Patients in the SURPASS-5 Trial

[a] Includes 1 participant each with absence of type 2 diabetes diagnosis, body mass index <23, serum calcitonin level ≥35 ng/L, not able to meet study requirements or of completing protocol due to drug/alcohol misuse or psychiatric disorder as judged by the investigator, and history of active/untreated malignancy or in remission.

[b] See eTable 3 in Supplement 2 for the details of the adverse events that led to study drug discontinuation.

[c] Study discontinuations include both before and after the primary end point visit.

period. Patients administered their assigned treatment dose using single-dose pens.

All patients were instructed to continue receiving insulin glargine (100 U/mL) once daily for the entire treatment period and measure their fasting blood glucose daily. To minimize risk of hypoglycemia, patients were required to keep the dose of insulin glargine unchanged until week 4, except for safety reasons. Additionally, patients with $HbA_{1c}$ less than or equal to 8.0% at randomization were required to reduce the dose of insulin glargine by 20% to reduce potential risk of hypoglycemia. Between weeks 5 and 40, patients in all treatment groups were instructed to self-adjust the dose of insulin glargine using their self-measured blood glucose values to a target fasting blood glucose of less than 100 mg/dL as per the treat-to-target algorithm (eTable 1 in Supplement 2).

Tirzepatide doses were escalated gradually to improve gastrointestinal tolerability. All patients started tirzepatide at a 2.5-mg dose, which was increased by 2.5 mg every 4 weeks until they reached their randomly assigned dose. For the comparator group, patients received matching doses of placebo using an injection device of identical appearance.

Patients using metformin at baseline were required to continue the same dose and formulation for the entire study duration. Patients were permitted to use concomitant medications as required, except for other antihyperglycemic and weight loss medications to avoid interference with the assessment of efficacy and safety. Rescue therapy with other glucose-lowering agents was allowed per protocol criteria; however, other basal insulins, GLP-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and pramlintide were not permitted (Supplement 1).

## Outcomes

The primary efficacy end point was mean change from baseline in $HbA_{1c}$ at week 40. The primary objective was to compare 10-mg tirzepatide and 15-mg tirzepatide dose groups with placebo. Key secondary objectives, controlled for type I error rate (in a graphical testing scheme described in eAppendix in Supplement 2), included the comparison of 5-mg tirzepatide vs placebo for mean change from baseline in $HbA_{1c}$; comparisons of 5-mg, 10-mg, and 15-mg tirzepatide vs placebo for mean change from baseline in body weight, fasting serum glucose, percentage of patients with $HbA_{1c}$ less than 7.0% (<53 mmol/mol), and comparison of 10-mg and 15-mg tirzepatide vs placebo for the percentage of patients with $HbA_{1c}$ less than 5.7% (<39 mmol/mol), all at week 40. Other secondary and exploratory efficacy objectives not controlled for type I error rate compared 5-mg tirzepatide vs placebo for the percentage of patients with $HbA_{1c}$ less than 5.7% and compared 5-mg, 10-mg, and 15-mg tirzepatide vs placebo for the percentage of patients with $HbA_{1c}$ less than or equal to 6.5% (≤48 mmol/mol) and body weight loss of greater than or equal to 5%, 10%, and 15%; mean change in daily average 7-point self-monitored blood glucose; daily mean change in insulin glargine dose; and mean change in fasting lipids, waist circumference, and BMI. Composite end points of the percentage of patients with $HbA_{1c}$ less than 7.0% or less than or equal to 6.5% without weight gain and clinically significant documented symptomatic hypoglycemia (blood glucose <54 mg/dL) or severe hypoglycemia at week 40 were also assessed.

Safety assessments included treatment-emergent adverse events, early discontinuation of study treatment due to adverse events, adjudicated pancreatitis, serum calcitonin, incidence of injection site reaction and hypersensitivity reactions, mean change from baseline in systolic and diastolic blood pressure and pulse rate, occurrence of hypoglycemic events (including severe hypoglycemic events defined as episodes with severe cognitive impairment requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions), and incidence of initiation of rescue therapy for persistent hyperglycemia. The adjudicated major adverse cardiovascular event results were planned to contribute toward a meta-analysis across all SURPASS trials for the establishment of cardiovascular safety of tirzepatide.

## Sample Size Calculation

A sample size of 472 patients (assuming a dropout rate of up to 28%) was calculated to provide a power of at least 90% to demonstrate statistical superiority of 10-mg and/or 15-mg tirzepatide vs placebo for change from baseline in $HbA_{1c}$ at week 40. The calculation included an assumed difference between treatment groups of 0.6% (6.6 mmol/mol) in $HbA_{1c}$ based on data from the phase 2 trial[15] and from a study with a GLP-1 receptor agonists featuring a similar design.[2]

## Statistical Analyses

Efficacy and safety analyses were performed on the population composed of all randomly assigned patients exposed to at least 1 dose of the study drug. Additionally, for efficacy end points, patients who discontinued the study drug after randomization for not fulfilling any of the eligibility criteria were excluded. The full analysis set comprised data from all randomly assigned patients exposed to at least 1 dose of the study drug during the treatment period, regardless of treatment adherence or use of rescue therapy. The efficacy analysis set comprised data from all randomly assigned patients exposed to at least 1 dose of the study drug receiving treatment without use of rescue therapy. The safety analyses were performed on all randomly assigned patients exposed to at least 1 dose of the study drug with all data from the start of study treatment to the end of safety follow-up (safety analysis set). The primary objective tested the 10-mg and 15-mg tirzepatide doses in parallel, controlled for multiplicity, and were accompanied by 2-sided 97.5% CIs; statistical significance was defined as $P < .025$. All other treatment difference results from statistical analyses were accompanied with 2-sided 95% CIs and $P$ values; statistical significance was defined as $P < .05$.

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). Because of the potential for type I error due to multiple comparisons,

findings for analyses of other secondary and lower end points should be interpreted as exploratory. For other secondary and exploratory end points, the efficacy estimand was evaluated unless specified otherwise. All statistical analyses were performed using SAS, version 9.4 (SAS Institute).

The treatment regimen estimand evaluated the treatment effect of tirzepatide treatments relative to placebo, irrespective of adherence to investigational product or introduction of rescue therapy. Statistical models used the full analysis set for analysis relative to the treatment regimen estimand. For continuous end points, an analysis of covariance model with treatment, country, baseline metformin use (yes or no), and baseline $HbA_{1c}$ (≤8.0% or >8.0%; excluding $HbA_{1c}$ end point) as fixed effects and baseline end point value as a covariate was used. For categorical end points, logistic regression with the same fixed effects and covariate as continuous end points was used. Missing values at week 40 were imputed 100 times using the method of multiple imputation based on the placebo group. Statistical inference over imputed data was guided by the Rubin rule. A post hoc mixed-effects regression analysis of the primary end point with site as a random effect was performed to account for multiple sites.

The efficacy estimand evaluated the treatment effect of tirzepatide treatments relative to placebo if all patients adhered to treatment and had not received rescue therapy. Statistical models used the efficacy analysis set for analysis relative to the efficacy estimand. 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 (≤8.0% or >8.0%; excluding $HbA_{1c}$ end point) as fixed effects and baseline end point value as a covariate. For categorical end points, we used logistic regression with the same factor and covariate (excluding visit effects) as continuous end points, where missing end points were dichotomized after they were predicted from the continuous end point mixed model for repeated measures analysis explained above. A subgroup analysis was conducted for the primary end point based on baseline $HbA_{1c}$ category (≤8.0% or >8.0%) to test for any treatment × subgroup interaction at week 40, because patients with baseline $HbA_{1c}$ less than or equal to 8.0% reduced the dose of insulin glargine by 20% after randomization.

## Results

### Patient Disposition and Baseline Characteristics

Of the 586 patients assessed for eligibility, 475 were randomized and received at least 1 dose of study drug (Figure 1). A total of 451 (94.9%) patients completed the study and 424 (89.3%) completed the study treatment. Key reasons for premature study treatment discontinuation across treatment groups in decreasing order of frequency were adverse events, withdrawal by patients, and protocol deviation.

At baseline, the demographics and clinical characteristics of patients were balanced across the 4 treatment groups (**Table 1**). Overall, at baseline, patients had a mean age of 61 years, mean BMI of 33.4, mean duration of diabetes of 13.3 years, mean $HbA_{1c}$ of 8.31% (67 mmol/mol), and median insulin glargine dose of 30.0 IU/d, and 394 (82.9%) were using metformin.

### Primary Outcome

For the treatment regimen estimand, at week 40, the mean $HbA_{1c}$ change from baseline was −2.40% with 10-mg tirzepatide and −2.34% with 15-mg tirzepatide vs −0.86% with placebo (**Table 2**; **Figure 2**A). Tirzepatide doses of 10 mg and 15 mg showed significantly greater change in $HbA_{1c}$ from baseline at week 40 vs placebo (10 mg: difference, −1.53% [97.5% CI, −1.80% to −1.27%]; $P < .001$; 15 mg: difference, −1.47% [97.5% CI, −1.75% to −1.20%]; $P < .001$). For the efficacy estimand, corresponding changes were −2.59% with both 10-mg and 15-mg tirzepatide vs −0.93% with placebo (10 mg: difference, −1.66% [97.5% CI, −1.91% to −1.40%]; $P < .001$; 15 mg: difference, −1.65% [97.5% CI, −1.91% to −1.40%]; Figure 2B; eTables 2 and 3 and eFigure 2A in Supplement 2). A post hoc sensitivity analysis with study site as a random effect revealed a mean change from baseline in $HbA_{1c}$ of −2.39% for 10-mg tirzepatide and −2.33% for 15-mg tirzepatide compared with −0.86 for placebo (10 mg: difference, −1.52% [97.5% CI, −1.79% to −1.26%]; $P < .001$; 15 mg: difference, −1.46% [97.5% CI, −1.74% to −1.19%]; $P < .001$).

### Key Secondary Outcomes

For the treatment regimen estimand, the mean change in $HbA_{1c}$ from baseline to week 40 with 5-mg tirzepatide was −2.11% (difference vs placebo, −1.24% [95% CI, −1.48% to −1.01%]; $P < .001$; Table 2, Figure 2A). For the efficacy estimand, the corresponding change was −2.23% (difference vs placebo, −1.30% [95% CI, −1.52% to −1.07%]; $P < .001$; Figure 2B; eTable 2 and eFigure 2A in Supplement 2). A significantly greater percentage of patients receiving 5-mg, 10-mg, and 15-mg tirzepatide vs placebo met the $HbA_{1c}$ target of less than 7.0% at week 40 (85%-90% vs 34%; $P < .001$ for all; treatment-regimen estimand; Table 2, Figure 2C). Similarly, more patients receiving 10-mg and 15-mg tirzepatide met the $HbA_{1c}$ target of less than 5.7% vs placebo at week 40 (42% and 50% vs 3%; $P < .001$ for all; treatment-regimen estimand; Table 2, Figure 2C). Consistent results were observed for the percentage of patients reaching $HbA_{1c}$ targets of less than 7% and less than 5.7% for 10-mg and 15-mg tirzepatide groups vs the placebo group using the efficacy estimand (eTable 2 and eFigure 2B in Supplement 2). At week 40, tirzepatide significantly reduced mean fasting serum glucose by −58.2 mg/dL for the 5-mg dose, −64.0 mg/dL for the 10-mg dose, and −62.6 mg/dL for the 15-mg dose, compared with −39.2 mg/dL for placebo (5 mg: difference, −19.0 mg/dL [95% CI, −26.6 to −11.4]; $P < .001$; 10 mg: difference, −24.9 mg/dL [95% CI, −32.3 to −17.4]; $P < .001$; 15 mg: difference, −23.4 mg/dL [95% CI, −31.0 to −15.8]; $P < .001$; treatment-regimen estimand; Table 2). The results were consistent when fasting serum glucose was assessed using the efficacy estimand (Figure 2D; eTable 2 in Supplement 2). At week 40, the mean body weight change from

Table 1. Baseline Demographics and Clinical Characteristics in a Study of the Effect of Subcutaneous Tirzepatide vs Placebo Added to Titrated Insulin Glargine on Glycemic Control

| Characteristic | No. (%) | | | |
|---|---|---|---|---|
| | Tirzepatide | | | |
| | 5 mg (n = 116) | 10 mg (n = 119) | 15 mg (n = 120) | Placebo (n = 120) |
| Age, mean (SD), y | 62 (10) | 60 (10) | 61 (10) | 60 (10) |
| Women | 55 (47) | 47 (39) | 55 (46) | 54 (45) |
| Men | 61 (53) | 72 (61) | 65 (54) | 66 (55) |
| Race[a] | | | | |
| American Indian or Alaska Native | 0/116 (0.0) | 1/118 (0.8) | 1/120 (0.8) | 0/119 (0.0) |
| Asian | 20/116 (17.2) | 21/118 (17.8) | 22/120 (18.3) | 22/119 (18.5) |
| Black or African American | 1/116 (0.9) | 2/118 (1.7) | 3/120 (2.5) | 0/119 (0.0) |
| White | 95/116 (81.9) | 94/118 (79.7) | 94/120 (78.3) | 97/119 (81.5) |
| Ethnicity | | | | |
| Hispanic or Latino | 4/98 (4.1) | 8/103 (7.8) | 5/98 (5.1) | 5/103 (4.9) |
| Not Hispanic or Latino | 94/98 (95.9) | 95/103 (92.2) | 93/98 (94.9) | 98/103 (95.1) |
| Duration of diabetes, mean (SD), y[b] | 14.1 (8.1) | 12.6 (6.2) | 13.7 (7.5) | 12.9 (7.4) |
| Pulse rate/min, mean (SD) | 75 (12) | 75 (10) | 76 (12) | 75 (11) |
| Blood pressure, mean (SD), mm Hg | | | | |
| Systolic | 137 (16) | 138 (15) | 137 (16) | 140 (15) |
| Diastolic | 79 (12) | 81 (10) | 80 (11) | 83 (10) |
| Weight, mean (SD), kg | 95.8 (19.8) | 94.5 (22.2) | 96.3 (22.8) | 94.1 (21.8) |
| BMI, mean (SD) | 33.6 (5.9) | 33.4 (6.2) | 33.4 (5.9) | 33.2 (6.3) |
| Receiving metformin | 99 (85.3) | 99 (83.2) | 97 (80.8) | 99 (82.5) |
| Metformin dose, mean (SD), mg/d | 2018 (397) | 2077 (416) | 2046 (392) | 2051 (411) |
| Insulin glargine dose, median (IQR) | | | | |
| IU | 30.0 (24.0-45.0) | 29.0 (22.0-43.0) | 32.0 (22.0-47.0) | 30.0 (23.0-44.5) |
| IU/kg/d | 0.34 (0.28-0.46) | 0.32 (0.25-0.51) | 0.34 (0.26-0.49) | 0.36 (0.26-0.46) |
| $HbA_{1c}$[c] | | | | |
| Mean (SD), % | 8.30 (0.88) | 8.36 (0.83) | 8.23 (0.86) | 8.37 (0.84) |
| ≤8.0% | 52 (44.8) | 49 (41.5) | 52 (43.3) | 48 (40.0) |
| >8.0% | 64 (55.2) | 69 (58.5) | 68 (56.7) | 72 (60.0) |
| Mean (SD), mmol/mol | 67.2 (9.6) | 67.9 (9.1) | 66.5 (9.5) | 68.0 (9.1) |
| Fasting serum glucose, mg/dL[d] | | | | |
| Mean (SD) | 162.9 (53.9) | 162.3 (52.0) | 160.3 (54.2) | 164.1 (45.0) |
| Median (IQR) | 154.0 (124.3-186.3) | 150.0 (127.9-189.2) | 150.4 (124.3-185.6) | 151.3 (133.3-192.0) |
| eGFR, mean (SD), mL/min/1.73 $m^2$ | 86.1 (18.1) | 87.1 (18.2) | 84.1 (17.2) | 84.7 (17.8) |
| <60 | 11 (9.5) | 9 (7.6) | 11 (9.2) | 16 (13.3) |
| ≥60[e] | 105 (90.5) | 110 (92.4) | 109 (90.8) | 104 (86.7) |

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); eGFR, estimated glomerular filtration rate; $HbA_{1c}$, 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%.

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

[e] Normal value for eGFR was ≥60 mL/min/1.73 $m^2$.

baseline was −5.4 kg with 5-mg tirzepatide, −7.5 kg with 10-mg tirzepatide, and −8.8 kg with 15-mg tirzepatide vs 1.6 kg with placebo (5 mg: difference, −7.1 kg [95% CI, −8.7 to −5.4]; 10 mg: difference, −9.1 kg [95% CI, −10.7 to −7.5]; 15 mg: difference, −10.5 kg [95% CI, −12.1 to −8.8]; $P < .001$ for all; treatment-regimen estimand; Table 2; eFigure 3A in Supplement 2). For the efficacy estimand, the corresponding change in mean body weight with 5-mg tirzepatide was −6.2 kg, 10-mg tirzepatide was −8.2 kg, and 15-mg tirzepatide was −10.9 kg vs 1.7 kg with placebo (5 mg: difference, −7.8 kg [95% CI, −9.4 to −6.3]; 10 mg: difference, −9.9 [95% CI, −11.5 to −8.3]; 15 mg: difference, −12.6 [95% CI, −14.2 to −11.0]; $P < .001$ for all; Figure 2E; eTable 2 in Supplement 2).

## Additional Secondary and Exploratory End Points

A significantly greater percentage of patients receiving 5-mg, 10-mg, and 15-mg tirzepatide met the $HbA_{1c}$ target of less than or equal to 6.5% compared with those receiving placebo (74%-86% vs 17%; $P < .001$ for all; treatment-regimen estimand). Likewise, significantly more patients receiving 5-mg tirzepatide met an $HbA_{1c}$ target of less than 5.7% vs those receiving placebo (24% vs 3%; $P < .001$; treatment-regimen

Table 2. Primary and Secondary Efficacy Outcomes at 40 Weeks in a Study of the Effect of Subcutaneous Tirzepatide vs Placebo Added to Titrated Insulin Glargine on Glycemic Control

| Efficacy end point[a] | Tirzepatide 5 mg (n = 116) | Tirzepatide 10 mg (n = 119) | Tirzepatide 15 mg (n = 120) | Placebo (n = 120) |
|---|---|---|---|---|
| **Primary** | | | | |
| $HbA_{1c}$, %[b,c] | | | | |
| Baseline | 8.30 | 8.36 | 8.22 | 8.38 |
| Change from baseline at week 40 (95% CI) | −2.11 (−2.28 to −1.94) | −2.40 (−2.56 to −2.23) | −2.34 (−2.51 to −2.16) | −0.86 (−1.03 to −0.70) |
| Difference vs placebo (95% CI)[d] | −1.24 (−1.48 to −1.01) | −1.53 (−1.77 to −1.30) | −1.47 (−1.71 to −1.23) | |
| *P* value | <.001 | <.001 | <.001 | |
| $HbA_{1c}$, mmol/mol[b,c] | | | | |
| Baseline | 67.2 | 67.9 | 66.4 | 68.1 |
| Change from baseline at week 40 (95% CI) | −23.0 (−24.9 to −21.2) | −26.2 (−28.0 to −24.4) | −25.6 (−27.4 to −23.7) | −9.5 (−11.2 to −7.6) |
| Difference vs placebo (95% CI)[d] | −13.6 (−16.2 to −11.0) | −16.8 (−19.3 to −14.2) | −16.1 (−18.7 to −13.5) | |
| **Secondary** | | | | |
| Patient met $HbA_{1c}$ target at week 40[b] | | | | |
| <7.0% [<53 mmol/mol], No. (%) | 101 (87.3) | 106 (89.6) | 100 (84.7) | 41 (34.5) |
| Absolute difference vs placebo, % | 52.8 | 55.1 | 50.2 | |
| Odds ratio vs placebo (95% CI)[d] | 14.7 (7.0 to 30.6) | 19.5 (9.2 to 41.3) | 11.5 (5.6 to 23.3) | |
| *P* value | <.001 | <.001 | <.001 | |
| ≤6.5% [≤48 mmol/mol], No. (%) | 86 (74.3) | 101 (85.9) | 94 (79.5) | 21 (17.3) |
| Absolute difference vs placebo, % | 57.0 | 68.6 | 62.2 | |
| Odds ratio vs placebo (95% CI)[e] | 13.7 (7.1 to 26.2) | 29.5 (14.4 to 60.6) | 18.5 (9.3 to 36.6) | |
| *P* value | <.001 | <.001 | <.001 | |
| <5.7% [<39 mmol/mol], No. (%) | 28 (24.4) | 49 (41.6) | 59 (49.6) | 3 (2.7) |
| Absolute difference vs placebo, % | 21.7 | 38.9 | 47.0 | |
| Odds ratio vs placebo (95% CI)[f] | 10.4 (3.3 to 32.1) | 22.8 (7.5 to 69.5) | 30.7 (10.1 to 93.6) | |
| *P* value | <.001 | <.001 | <.001 | |
| Fasting serum glucose, mg/dL[b] | | | | |
| Baseline | 162.9 | 162.6 | 160.4 | 164.4 |
| Change from baseline at week 40 (95% CI)[d] | −58.2 (−63.7 to −52.6) | −64.0 (−69.3 to −58.8) | −62.6 (−68.0 to −57.1) | −39.2 (−44.4 to −33.9) |
| Difference vs placebo (95% CI)[d] | −19.0 (−26.6 to −11.4) | −24.9 (−32.3 to −17.4) | −23.4 (−31.0 to −15.8) | |
| *P* value | <.001 | <.001 | <.001 | |
| Body weight, kg[b] | | | | |
| Baseline | 95.8 | 94.6 | 96.0 | 94.2 |
| Change from baseline at week 40 (95% CI)[d] | −5.4 (−6.6 to −4.3) | −7.5 (−8.6 to −6.3) | −8.8 (−10.0 to −7.7) | 1.6 (0.5 to 2.8) |
| Difference vs placebo (95% CI)[d] | −7.1 (−8.7 to −5.4) | −9.1 (−10.7 to −7.5) | −10.5 (−12.1 to −8.8) | |
| *P* value | <.001 | <.001 | <.001 | |
| Patient met body weight loss targets at week 40[b] | | | | |
| ≥5% loss, No. (%) | 56 (47.9) | 68 (57.9) | 85 (71.6) | 7 (6.0) |
| Absolute difference vs placebo, % | 41.9 | 51.9 | 65.7 | |
| Odds ratio vs placebo (95% CI)[e] | 13.8 (6.0 to 31.4) | 20.9 (9.2 to 47.8) | 38.5 (16.5 to 89.8) | |
| *P* value | <.001 | <.001 | <.001 | |
| ≥10% loss, No. (%) | 24 (20.7) | 49 (41.6) | 48 (40.7) | 1 (0.8) |
| Absolute difference vs placebo, % | 19.9 | 40.8 | 39.9 | |
| Odds ratio vs placebo (95% CI)[e] | 21.5 (4.2 to 111.6) | 65.0 (12.7 to 331.7) | 63.3 (12.4 to 323.3) | |
| *P* value | <.001 | <.001 | <.001 | |
| ≥15% loss, No. (%) | 8 (6.9) | 28 (23.7) | 27 (22.9) | 0 |
| Absolute difference vs placebo, % | 6.9 | 23.7 | 22.9 | |
| Odds ratio vs placebo (95% CI)[e] | 18.8 (1.2 to 298.6) | 79.7 (5.3 to 1203.1) | 78.0 (5.2 to 1179.2) | |
| *P* value | .038 | .002 | .002 | |

(continued)

Table 2. Primary and Secondary Efficacy Outcomes at 40 Weeks in a Study of the Effect of Subcutaneous Tirzepatide vs Placebo Added to Titrated Insulin Glargine on Glycemic Control (continued)

| Efficacy end point[a] | Tirzepatide 5 mg (n = 116) | Tirzepatide 10 mg (n = 119) | Tirzepatide 15 mg (n = 120) | Placebo (n = 120) |
|---|---|---|---|---|
| Insulin glargine dose[g] | | | | |
| Baseline, IU | 34.3 | 32.0 | 35.0 | 32.9 |
| Change from baseline at week 40 (95% CI), IU[e] | 4.4 (−0.46 to 9.19) | 2.7 (−1.90 to 7.34) | −3.8 (−7.66 to 0.04) | 25.1 (17.84 to 32.44) |
| Percent change from baseline at week 40, % | 13.0 | 8.1 | −11.4 | 75.0 |
| Difference vs placebo (95% CI)[e] | −35.4 (−46.0 to −22.8) | −38.2 (−48.3 to −26.1) | −49.3 (−57.7 to −39.4) | |
| *P* value | <.001 | <.001 | <.001 | |
| Insulin glargine dose[g] | | | | |
| Baseline, IU/kg/d | 0.37 | 0.35 | 0.37 | 0.36 |
| Change from baseline at week 40 (95% CI), IU/kg/d[e] | 0.08 (0.02 to 0.13) | 0.07 (0.01 to 0.12) | 0.00 (−0.05 to 0.05) | 0.26 (0.19 to 0.34) |
| Percent change from baseline at week 40, % | 20.9 | 19.0 | 0.0 | 72.3 |
| Difference vs placebo (95% CI)[e] | −29.8 (−41.1 to −16.4) | −31.0 (−42.1 to −17.7) | −42.0 (−51.4 to −30.7) | |
| *P* value | <.001 | <.001 | <.001 | |

Abbreviations: $HbA_{1c}$, glycated hemoglobin $A_{1c}$; IU, international units.

[a] Data presented are estimated mean unless specified otherwise.

[b] Data presented are using treatment-regimen estimand. Treatment-regimen estimand (corresponding analyses used the full analysis set) evaluated treatment effects regardless of treatment adherence or use of rescue therapy. Missing values at week 40 were imputed 100 times using method of multiple imputation based on the placebo group. For continuous variables, analysis of covariance model used with treatment, country, baseline metformin use, and baseline $HbA_{1c}$ category (≤8.0% or >8.0%) (except for analyses related to $HbA_{1c}$) as fixed effects and baseline value as a covariate. For categorical end points, logistic regression was used with the same fixed effects and covariate as that for the analysis of covariance model and included the unadjusted differences between tirzepatide and placebo. See eTable 2 in Supplement 2 for corresponding data for the efficacy estimand.

[c] $HbA_{1c}$ data was missing at primary end point for 7 participants in the 5-mg tirzepatide group, 3 in the 10-mg tirzepatide group, 8 in the 15-mg tirzepatide group, and 2 in the placebo group.

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

[e] Tested for superiority and not controlled for type I error.

[f] Tested for superiority and controlled for type I error only for 10-mg and 15-mg tirzepatide vs placebo. Differences vs placebo reflect simple differences between end point values (tirzepatide minus placebo).

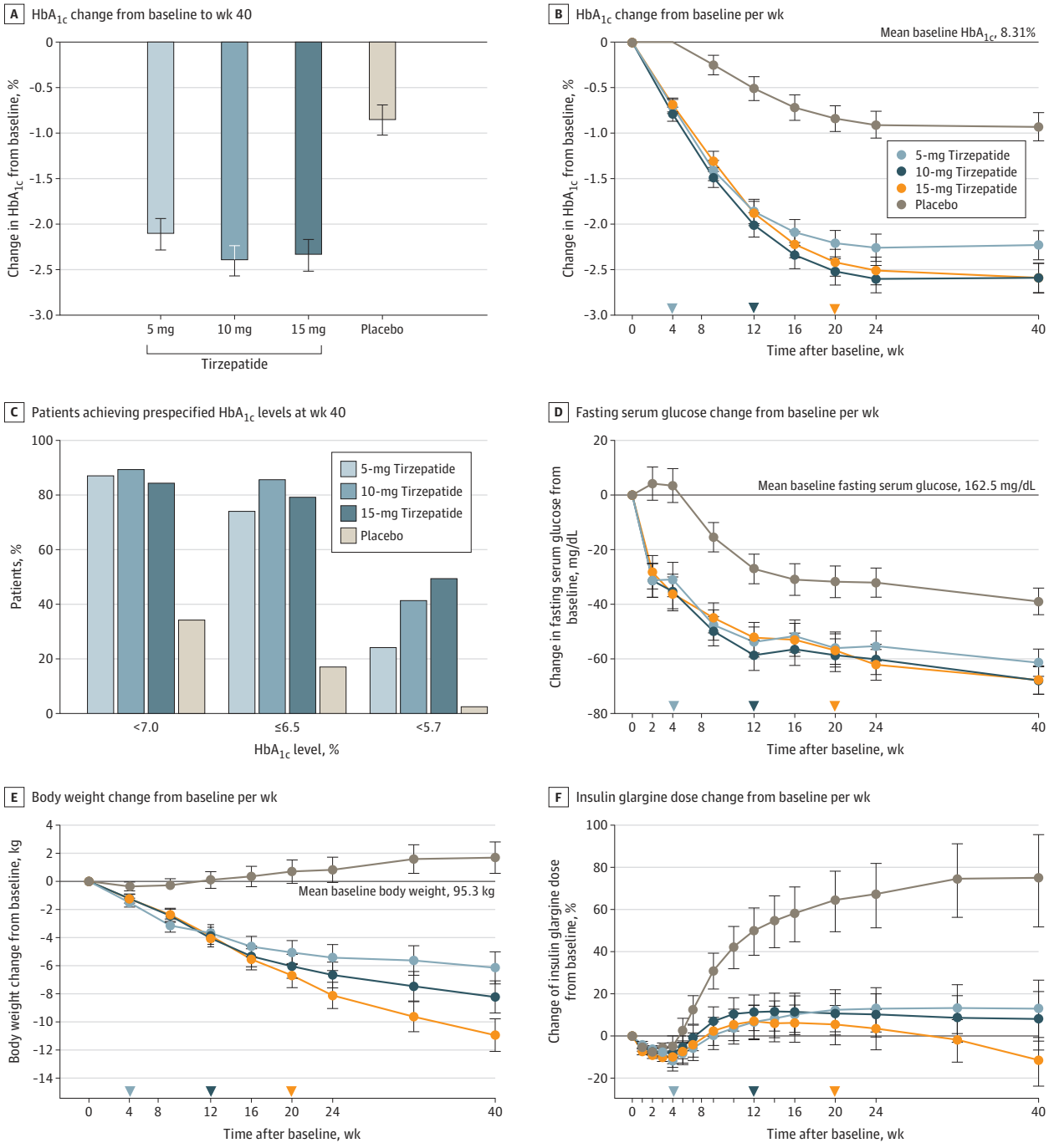
[g] Data presented used the efficacy estimand. The efficacy estimand (corresponding analyses used the efficacy analysis set) evaluated treatment effects using treatment data without use of rescue therapy. Mixed model for repeated measures was used with log-transformed data using treatment, visit, treatment × visit interaction, country, baseline metformin use, and baseline $HbA_{1c}$ category (≤8.0% or >8.0%) as fixed effects and baseline end point value as a covariate. Insulin doses were log-transformed before analysis to account for their skewed distribution and estimated ratio to baseline were transformed back for interpretation expressed as percent change from baseline to week 40 and estimated percent difference vs placebo. Additional secondary efficacy outcomes are presented in Supplement 2.

estimand; Figure 2C). Patients receiving tirzepatide, compared with placebo, were more likely to achieve body weight loss of 5% (48%-72% vs 6%), 10% (21%-42% vs 1%), and 15% (7%-24% vs 0%) ($P < .05$ for all; treatment-regimen estimand; Table 2; eFigure 3B in Supplement 2). Similarly, a significantly greater percentage of patients receiving tirzepatide vs placebo achieved the 2 composite outcomes, $HbA_{1c}$ less than 7.0% (78%-80% vs 12%) or less than or equal to 6.5% (67%-78% vs 8%) without body weight gain and without clinically significant documented hypoglycemia or severe hypoglycemia ($P < .001$ for all; efficacy estimand; eTable 2 in Supplement 2). At week 40, the mean daily, premeal, and postmeal self-monitored blood glucose readings in all the 3 tirzepatide groups reduced significantly from baseline vs the placebo group, with values of less than 140 mg/dL (eTable 2 and eFigure 2D in Supplement 2). A subgroup analysis based on baseline $HbA_{1c}$ of less than or equal to 8% or greater than 8% revealed no significant treatment × subgroup interaction between subgroups for mean $HbA_{1c}$ change from baseline (eTable 4 in Supplement 2).

The data for insulin glargine dose, lipids, pulse rate, blood pressure, BMI, and waist circumference presented below correspond to the efficacy estimand. Mean daily insulin glargine dose decreased from baseline to week 4 in all treatment groups, primarily due to 20% reduction of insulin dose for patients with baseline $HbA_{1c}$ less than or equal to 8.0% (Figure 2F; eTable 5 in Supplement 2). At week 40, the mean percent change from baseline in insulin dose was 13.0% for 5-mg tirzepatide, 8.1% for 10-mg tirzepatide, −11.4% for 15-mg tirzepatide, and 75.0% for placebo (5 mg: difference, −35.4% [95% CI, −46.0% to −22.8%]; 10 mg: difference, −38.2% [95% CI, −48.3% to −26.1%]; 15 mg: difference, −49.3% [95% CI, −57.7% to −39.4%]; $P < .001$ for all; Table 2; Figure 2F; eFigure 4 in Supplement 2).

All doses of tirzepatide were associated with statistically significant improvements from baseline in total cholesterol, low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, and triglycerides at week 40 (eFigure 5 and eTable 6 in Supplement 2). Mean pulse rate change from baseline at week 40 was 1.3 to 5.6 beats per minute with tirzepatide groups and −0.8 beats per minute with the placebo group (eTable 7 and eFigure 6 in Supplement 2). Mean pulse rate values returned to baseline levels 4 weeks after treatment discontinuation for all doses of tirzepatide. At week 40, mean change in systolic and diastolic blood pressure was −6.1 to −12.6 mm Hg and −2.0 to −4.5 mm Hg for tirzepatide

Figure 2. Outcomes in a Study of the Effect of Subcutaneous Tirzepatide vs Placebo Added to Titrated Insulin Glargine on Glycemic Control




Arrowheads on the x-axis indicate the time points when maintenance doses of 5-mg, 10-mg, and 15-mg tirzepatide were achieved. Error bars represent 95% CI for the estimated mean. A and C, Treatment regimen estimand (corresponding analyses used the full analysis set) that evaluated treatment effects regardless of treatment adherence or use of rescue therapy. Missing values at week 40 were imputed 100 times using method of multiple imputation based on the placebo group. Analysis of covariance model was used with treatment, country, and baseline metformin use as fixed effects and baseline glycated hemoglobin A1c ($HbA_{1c}$) value as a covariate. C, Logistic regression was used with the same fixed effects and covariate as that for analysis of covariance model. See eFigure 2 in Supplement 2 for corresponding data for the efficacy estimand. B, D, E, and F, Efficacy estimand (corresponding analyses used the efficacy analysis set) that evaluated treatment effects using on-treatment data without use of rescue therapy. Mixed-model for repeated measures was used with treatment, visit, treatment × visit interaction, country, baseline metformin use, baseline $HbA_{1c}$ category (≤8.0% or >8.0% [≤64 mmol/mol or >64 mmol/mol]) (except for $HbA_{1c}$ related analyses) as fixed effects and baseline endpoint value as a covariate. The number of patients assessed at each time point for $HbA_{1c}$, fasting serum glucose, body weight, and insulin glargine dose over time are described in eTable 3 in Supplement 2. F, Insulin doses were log-transformed before analysis to account for their skewed distribution and estimated ratio to baseline were transformed back for interpretation expressed as percent change from baseline to week 40 and estimated percent difference vs placebo.

Table 3. Adverse Events Through 4 Weeks After Treatment Discontinuation in a Study of the Effect of Subcutaneous Tirzepatide vs Placebo Added to Titrated Insulin Glargine on Glycemic Control

| | No. (%) | | | |
|---|---|---|---|---|
| | Tirzepatide | | | |
| Adverse event | 5 mg (n = 116) | 10 mg (n = 119) | 15 mg (n = 120) | Placebo (n = 120) |
| Serious adverse events[a] | 9 (7.8) | 13 (10.9) | 9 (7.5) | 10 (8.3) |
| Adverse events leading to study drug discontinuation | 7 (6.0) | 10 (8.4) | 13 (10.8) | 3 (2.5) |
| Gastrointestinal disorder | 4 (3.4) | 7 (5.9) | 8 (6.7) | 0 |
| Nausea | 1 (0.9) | 2 (1.7) | 4 (3.3) | 0 |
| Vomiting | 1 (0.9) | 2 (1.7) | 2 (1.7) | 0 |
| Diarrhea | 1 (0.9) | 1 (0.8) | 1 (0.8) | 0 |
| Dyspepsia | 1 (0.9) | 1 (0.8) | 0 | 0 |
| Abdominal pain upper | 0 | 1 (0.8) | 0 | 0 |
| Gastroesophageal reflux disease | 0 | 0 | 1 (0.8) | 0 |
| Patients with ≥1 treatment-emergent adverse event[b] | 85 (73.3) | 81 (68.1) | 94 (78.3) | 81 (67.5) |
| Treatment-emergent adverse events occurring in ≥5% of patients | | | | |
| Nasopharyngitis | 18 (15.5) | 8 (6.7) | 15 (12.5) | 23 (19.2) |
| Nausea | 15 (12.9) | 21 (17.6) | 22 (18.3) | 3 (2.5) |
| Diarrhea | 14 (12.1) | 15 (12.6) | 25 (20.8) | 12 (10.0) |
| Decrease appetite | 8 (6.9) | 15 (12.6) | 17 (14.2) | 2 (1.7) |
| Vomiting | 8 (6.9) | 9 (7.6) | 15 (12.5) | 3 (2.5) |
| Dyspepsia | 8 (6.9) | 10 (8.4) | 6 (5.0) | 2 (1.7) |
| Constipation | 7 (6.0) | 8 (6.7) | 8 (6.7) | 2 (1.7) |
| Back pain | 6 (5.2) | 6 (5.0) | 4 (3.3) | 7 (5.8) |
| Eructation | 6 (5.2) | 4 (3.4) | 7 (5.8) | 1 (0.8) |
| Arthralgia | 6 (5.2) | 4 (3.4) | 3 (2.5) | 2 (1.7) |
| Lipase increased | 4 (3.4) | 2 (1.7) | 10 (8.3) | 2 (1.7) |
| Flatulence | 3 (2.6) | 6 (5.0) | 7 (5.8) | 0 |
| Hypertension | 3 (2.6) | 3 (2.5) | 1 (0.8) | 7 (5.8) |
| Hyperglycemia | 2 (1.7) | 0 | 1 (0.8) | 16 (13.3) |
| Other treatment-emergent adverse events of interest[c] | | | | |
| Hypoglycemia[d] | | | | |
| Blood glucose <54 mg/dL | 18 (15.5) | 23 (19.3) | 17 (14.2) | 15 (12.5) |
| Blood glucose ≤70 mg/dL | 70 (60.3) | 75 (63.0) | 72 (60.0) | 73 (60.8) |
| Severe hypoglycemia[d] | 0 | 2 (1.6) | 1 (0.8) | 0 |
| Injection site reactions | 4 (3.4) | 3 (2.5) | 8 (6.7) | 1 (0.8) |
| Hypersensitivity reactions | 8 (6.9) | 3 (2.5) | 6 (5.0) | 3 (2.5) |
| Cholelithiasis[e] | 1 (0.9) | 0 | 0 | 0 |
| Adjudication-confirmed pancreatitis | 0 | 0 | 0 | 0 |
| Adjudication-confirmed MACE-4[f] | 0 | 1 (0.8) | 1 (0.8) | 1 (0.8) |
| Malignant neoplasm | 2 (1.7) | 1 (0.8) | 0 | 2 (1.7) |

Abbreviation: MACE, major adverse cardiovascular events.

[a] Serious adverse event was defined as any adverse event that resulted in death, initial or prolonged inpatient hospitalization, a life-threatening experience, persistent or significant disability or incapacity, congenital anomaly or birth defect, or medical events that may not be immediately life-threatening or result in death or hospitalization but jeopardized the patient's health or required intervention to prevent the previously listed events.

[b] Treatment-emergent adverse event was defined as an untoward medical occurrence that first occurred or worsened in severity after the first dose.

[c] Other adverse events of interest were adverse events that were considered of special clinical relevance considering the therapeutic class of tirzepatide.

[d] Hypoglycemic events occurring after start of new antihyperglycemic drug were excluded. Severe hypoglycemic events were defined as episodes with severe cognitive impairment requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

[e] Medical Dictionary for Regulatory Activities–preferred term.

[f] MACE-4 is a composite end point of death from cardiovascular or undetermined causes, myocardial infarction, stroke, and hospitalization for unstable angina.

groups and −1.7 mm Hg and −2.1 mm Hg for the placebo group (eTable 7 in Supplement 2). Statistically significant improvements were observed in BMI and waist circumference with all doses of tirzepatide vs placebo at week 40 (eFigure 7 in Supplement 2).

## Adverse Events and Tolerability

Overall, 68.1% to 78.3% of tirzepatide-treated patients experienced at least 1 treatment-emergent adverse event compared with 67.5% of placebo-treated patients. The most frequent treatment-emergent adverse event in the tirzepatide groups were gastrointestinal, including diarrhea (12%-21% vs 10% in the placebo group), nausea (13%-18% vs 2.5% in the placebo group), vomiting (7%-13% vs 2.5% in the placebo group), and decreased appetite (7%-14% vs 1.7% in the placebo group) (**Table 3**). Most gastrointestinal events were mild to moderate in severity, and incidence of new events decreased over time in all tirzepatide groups (eTable 8 and eFigures 8 and 9 in Supplement 2). No deaths occurred during the study. Overall, 8% to 11% of tirzepatide-treated

patients reported serious adverse events compared with 8% of placebo-treated patients.

Rates of premature treatment discontinuation due to adverse events were 6.0% (7/116) in the 5-mg tirzepatide group, 8.4% (10/119) in the 10-mg tirzepatide group, 10.8% (13/120) in the 15-mg tirzepatide group, and 2.5% (3/120) in the placebo group (Table 3).

Incidence (rates) of hypoglycemia (blood glucose <54 mg/dL or severe hypoglycemia) ranged from 14.2% to 19.3% (0.43 to 0.64 events/patient-year) in the tirzepatide groups compared with 12.5% (0.44 events/patient-year) in the placebo group (Table 3; eTable 9 in Supplement 2). Three episodes of severe hypoglycemia were reported in 3 patients: 2 in the 10-mg tirzepatide group and 1 in the 15-mg tirzepatide group (Table 3). Rescue therapy for severe persistent hyperglycemia was required for 1 patient each in the 5-mg and 15-mg tirzepatide groups compared with 5 patients in the placebo group. There were no reported cases of adjudication-confirmed pancreatitis and 3 adjudication-confirmed major adverse cardiovascular events (composite end point of death from cardiovascular or undetermined causes, myocardial infarction, stroke, and hospitalization for unstable angina) were reported (Table 3).

Three patients in tirzepatide groups and 2 in the placebo group reported malignant neoplasms (eTable 10 in Supplement 2). No cases of diabetic retinopathy were reported in the tirzepatide groups. About 3% to 7% of patients treated with tirzepatide and 1% in the placebo group reported injection site reactions. No severe cases of hypersensitivity or injection site reactions were reported. Additional adverse event findings and supportive safety information are described in Table 3 and eTable 7 in Supplement 2.

## Discussion

In adults with type 2 diabetes and inadequate glycemic control despite treatment with insulin glargine with or without metformin, the addition of once-weekly tirzepatide, compared with placebo, resulted in statistically significant improvements in glycemic control and body weight reduction after 40 weeks.

To the authors' knowledge, this is the first trial to assess the efficacy and adverse event profile of a dual glucose-dependent insulinotropic polypeptide/GLP-1 receptor agonist in combination with a basal insulin regimen. Although treatment guidelines generally recommend using GLP-1 receptor agonists prior to basal insulin in most cases, the treatment sequence may vary because the latter is still widely used as the first injectable therapy in clinical practice due to cost, reimbursement issues, and prescribing habits.[16] The results from the current study provide clinically relevant information relative to the use of tirzepatide in combination with a basal insulin that should be of help to clinicians when this treatment option is considered.

The significant glycemic improvements in the tirzepatide groups were associated with significantly lower insulin glargine use and significant body weight reduction compared with placebo. Despite the differences in glycemic control between the tirzepatide and placebo groups, the rate of clinically significant or severe hypoglycemia was below 1 event per patient-year in all treatment groups, which also needs to be considered in the context of mean end point $HbA_{1c}$ values of patients receiving tirzepatide. There was no proactive insulin dose reduction implemented in response to meeting or approaching a glycemic target, and therefore further research is warranted to explore whether this approach could result in substantial insulin sparing while providing adequate glycemic control and potentially reducing hypoglycemia risk.

The effects of tirzepatide on glycemic control, body weight, lipid levels, and blood pressure on a background of titrated basal insulin in this trial were consistent with previously reported studies of tirzepatide[11-14] and further validate its effectiveness across different patient populations differing in the duration of the disease, background glucose-lowering therapies, or comorbidities.

The most commonly reported treatment-emergent adverse events for patients receiving tirzepatide were gastrointestinal in nature and decreased over time, especially after reaching maintenance doses. Overall, the adverse events observed in this study are generally consistent with the known safety profile of tirzepatide and GLP-1 receptor agonists.[2-6]

Strengths of the study include the randomized, double-blind, placebo-controlled design and titration of background basal insulin using a treat-to-target algorithm.

### Limitations

This study has several limitations. First, the patients enrolled in this study were treated with insulin glargine with or without metformin, and therefore the observations may not be directly extrapolated to other regimens using different oral antihyperglycemic medications. Second, the lack of adjustment of insulin dose for the first 4 weeks of treatment may have initially favored patients receiving tirzepatide, although this was compensated during the remainder of the 40-week treatment period. Third, the postprandial glucose excursions observed in the placebo group suggest an additional prandial intervention was likely needed in some patients, despite the strict inclusion criteria and the treat-to-target-approach used in the study. Fourth, although gastrointestinal adverse events and their severity are typically self-reported in most clinical trials, this approach has limitations. Fifth, blinding may have been partially affected by the observed gastrointestinal adverse events, body weight loss, and glycemic improvement with little or no increment in insulin dose. Sixth, due to the global nature of the study and the countries participating in it, the percentage of participants identifying as certain racial or ethnic groups was low.

## Conclusions

Among patients with type 2 diabetes and inadequate glycemic control despite treatment with insulin glargine, the addition of subcutaneous tirzepatide, compared with placebo, to titrated insulin glargine resulted in statistically significant improvements in glycemic control after 40 weeks.

## ARTICLE INFORMATION

**Accepted for Publication:** January 6, 2022.

**Author Contributions:** Dr Dahl had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.
*Concept and design:* Bray, Patel, Rodríguez.
*Acquisition, analysis, or interpretation of data:* Dahl, Onishi, Norwood, Huh, Bray, Patel, Rodríguez.
*Drafting of the manuscript:* Huh, Patel, Rodríguez.
*Critical revision of the manuscript for important intellectual content:* All authors.
*Statistical analysis:* Huh, Bray.
*Administrative, technical, or material support:* Rodríguez.
*Supervision:* Dahl, Onishi, Norwood, Patel, Rodríguez.
*Other - Clinical and scientific contributions:* Patel.

**Conflict of Interest Disclosures:** Dr Dahl reported receiving personal fees from Eli Lilly during the conduct of the study and personal fees from Afimmune, Novo Nordisk, and Novartis outside the submitted work. Dr Onishi reported receiving personal fees from Sumitomo Dainippon Pharma and Novo Nordisk outside the submitted work. Dr Norwood reported receiving grants from Eli Lilly during the conduct of the study and owning stock shares in Eli Lilly outside the submitted work. Dr Huh reported being an employee and shareholder of Eli Lilly and Company. Dr Bray reported being an employee and shareholder of Eli Lilly and Company. Dr Patel reported being an employee of and shareholder in Eli Lilly and Company during the conduct of the study. Dr Rodríguez reported being an employee and shareholder in Eli Lilly and Company. No other disclosures were reported.

**Funding/Support:** This study was sponsored by Eli Lilly and Company.

**Role of the Funder/Sponsor:** Eli Lilly and Company was involved in the study design and conduct; data collection, management, analyses, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The sponsor did not have the right to veto publication or to control the decision regarding to which journal the manuscript was submitted. Final decisions resided with the authors, which included employees of the sponsor.

**Meeting Presentations:** Part of the data presented in this article was presented at the 81st Scientific Sessions of the American Diabetes Association; June 25-29, 2021; and the 57th European Association for Study of Diabetes; September 28-October 01, 2021.

**Data Sharing Statement:** See Supplement 3.

**Additional Contributions:** We thank the patients participating in the trial as well as the collaborating research coordinators and investigators who supported this work. We thank Weiguo Zhu, PhD, and Liping Liu, MS, for their contributions to the data preparation and analysis, for which they were compensated as part of their salary as employees of Eli Lilly and Company. Dr Shirin Ghodke, PhD, provided writing and editorial assistance, for which she was compensated as part of her salary as employee of Eli Lilly India Services Private Limited.

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