ORIGINAL ARTICLE

Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes

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ABSTRACT

BACKGROUND

Tirzepatide is a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist that is under development for the treatment of type 2 diabetes. The efficacy and safety of once-weekly tirzepatide as compared with semaglutide, a selective GLP-1 receptor agonist, are unknown.

METHODS

In an open-label, 40-week, phase 3 trial, we randomly assigned 1879 patients, in a 1:1:1:1 ratio, to receive tirzepatide at a dose of 5 mg, 10 mg, or 15 mg or semaglutide at a dose of 1 mg. At baseline, the mean glycated hemoglobin level was 8.28%, the mean age 56.6 years, and the mean weight 93.7 kg. The primary end point was the change in the glycated hemoglobin level from baseline to 40 weeks.

RESULTS

The estimated mean change from baseline in the glycated hemoglobin level was –2.01 percentage points, –2.24 percentage points, and –2.30 percentage points with 5 mg, 10 mg, and 15 mg of tirzepatide, respectively, and –1.86 percentage points with semaglutide; the estimated differences between the 5-mg, 10-mg, and 15-mg tirzepatide groups and the semaglutide group were –0.15 percentage points (95% confidence interval [CI], –0.28 to –0.03; P=0.02), –0.39 percentage points (95% CI, –0.51 to –0.26; P<0.001), and –0.45 percentage points (95% CI, –0.57 to –0.32; P<0.001), respectively. Tirzepatide at all doses was noninferior and superior to semaglutide. Reductions in body weight were greater with tirzepatide than with semaglutide (least-squares mean estimated treatment difference, –1.9 kg, –3.6 kg, and –5.5 kg, respectively; P<0.001 for all comparisons). The most common adverse events were gastrointestinal and were primarily mild to moderate in severity in the tirzepatide and semaglutide groups (nausea, 17 to 22% and 18%; diarrhea, 13 to 16% and 12%; and vomiting, 6 to 10% and 8%, respectively). Of the patients who received tirzepatide, hypoglycemia (blood glucose level, <54 mg per deciliter) was reported in 0.6% (5-mg group), 0.2% (10-mg group), and 1.7% (15-mg group); hypoglycemia was reported in 0.4% of those who received semaglutide. Serious adverse events were reported in 5 to 7% of the patients who received tirzepatide and in 3% of those who received semaglutide.

CONCLUSIONS

In patients with type 2 diabetes, tirzepatide was noninferior and superior to semaglutide with respect to the mean change in the glycated hemoglobin level from baseline to 40 weeks. (Funded by Eli Lilly; SURPASS-2 ClinicalTrials.gov number, NCT03987919.)

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Glucagon-like peptide-1 (GLP-1) receptor agonists are an effective treatment option for patients with type 2 diabetes. These agents act by stimulating insulin secretion in hyperglycemic states, suppressing glucagon secretion in hyperglycemic or euglycemic states, delaying gastric emptying, decreasing appetite, and reducing body weight.[1-3]

Glucose-dependent insulinotropic polypeptide, the main incretin hormone in healthy persons, is insulinotropic; however, unlike GLP-1, it is glucagonotropic in a glucose-dependent manner. Under hyperglycemic conditions, glucose-dependent insulinotropic polypeptide stimulates the release of insulin, thereby lowering glucagon levels, and under euglycemic or hypoglycemic conditions, glucagon levels are increased.[4] Glucose-dependent insulinotropic polypeptide receptors are abundant in adipose tissue,[5] and glucose-dependent insulinotropic polypeptide enhances both the postprandial lipid-buffering capacity of white adipose tissue and the sensitivity of adipose tissue to insulin, which may prevent ectopic fat deposition.[6] The glucose-dependent insulinotropic polypeptide component of dual glucose-dependent insulinotropic polypeptide–GLP-1 agonism is hypothesized to act centrally to potentiate a GLP-1–induced reduction in food intake.[6-8] In patients with type 2 diabetes, a single molecule combining the glucose-dependent insulinotropic polypeptide receptor and GLP-1 receptor agonism may have a greater effect on glucose levels and weight control than selective GLP-1 receptor agonists.

Tirzepatide is a dual glucose-dependent insulinotropic polypeptide–GLP-1 receptor agonist. Its structure is primarily based on the glucose-dependent insulinotropic polypeptide amino acid sequence and includes a C20 fatty diacid moiety.[7] Its half-life of approximately 5 days allows once-weekly subcutaneous administration.[7] A phase 2b trial involving patients with type 2 diabetes showed that those who received tirzepatide had dose-dependent reductions in the glycated hemoglobin level and weight at 26 weeks.[9]

Once-weekly injectable semaglutide, a selective GLP-1 receptor agonist, is approved for the treatment of type 2 diabetes at doses up to 1 mg. In trials involving patients who received semaglutide, the mean reductions in the glycated hemoglobin level have been reported to be as high as 1.8 percentage points and the mean reductions in body weight have been reported to be as high as 6.5 kg.[10-19]

We conducted the SURPASS-2 trial (A Study of Tirzepatide [LY3298176] versus Semaglutide Once Weekly as Add-on Therapy to Metformin in Participants with Type 2 Diabetes) to compare the efficacy and safety of tirzepatide at doses of 5 mg, 10 mg, and 15 mg with those of semaglutide at a dose of 1 mg in patients with type 2 diabetes that had been inadequately controlled with metformin monotherapy.

METHODS

TRIAL DESIGN AND OVERSIGHT

This 40-week, open-label, parallel-group, randomized, active-controlled, phase 3 trial was conducted in 128 sites in the United States, Argentina, Australia, Brazil, Canada, Israel, Mexico, and the United Kingdom (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The protocol, which is available at NEJM.org, was approved by local institutional review boards, and the trial was conducted in accordance with the principles of the Declaration of Helsinki and in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation. All the patients provided written informed consent. The statistical analysis plan is available with the protocol at NEJM.org.

Three authors employed by the sponsor contributed to the trial design, and two authors employed by the sponsor were responsible for the statistical analyses. The four academic authors and the last author (who was employed by the sponsor) provided medical oversight during the trial. All the authors participated in interpretation of the data and critical review of the manuscript. The investigators were responsible for data collection, and the sponsor undertook site monitoring, data collation, and analysis. The investigators worked under confidentiality agreements with the sponsor, and all the authors had full access to the trial data, drafted the manuscript (with assistance from a medical writer paid by the sponsor), approved the submission of the manuscript for publication, and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

PATIENTS

Key inclusion criteria for this trial were an age of 18 years or older and type 2 diabetes that was inadequately controlled with metformin at a dose of at least 1500 mg per day. Eligible patients had

a glycated hemoglobin level of 7.0 to 10.5% and a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of at least 25, and they had had stable weight (±5%) during the previous 3 months. Key exclusion criteria were type 1 diabetes; an estimated glomerular filtration rate below 45 ml per minute per 1.73 m^2; a history of pancreatitis; and a history of any of the following: nonproliferative diabetic retinopathy that warranted urgent treatment, proliferative diabetic retinopathy, or diabetic maculopathy. A full list of eligibility criteria is provided in the Supplementary Appendix.

PROCEDURES

The patients were randomly assigned in a 1:1:1:1 ratio to receive a once-weekly subcutaneous injection of either tirzepatide (at a dose of 5 mg, 10 mg, or 15 mg; the doses were double-blinded) or semaglutide (1 mg) for a 40-week treatment period, followed by a 4-week safety follow-up period (Fig. S1). The patients were stratified at randomization according to country and baseline glycated hemoglobin level (≤8.5% or >8.5% [≤69 or >69 mmol per mol]).

Tirzepatide was initiated at a dose of 2.5 mg once weekly, and the doses were increased by 2.5 mg every 4 weeks until the randomly assigned dose was reached. The final dose was then maintained for the duration of the trial. Semaglutide was initiated at a dose of 0.25 mg once weekly, and the dose was doubled every 4 weeks until 1 mg was reached. The final dose was then maintained for the duration of the trial.[20] Dose de-escalation was not allowed. The initiation of new antihyperglycemic medications was allowed according to specific criteria that are described in the Supplementary Appendix.

END POINTS

The primary end point was the change in the glycated hemoglobin level from baseline to week 40. The key secondary end points (in a graphical testing scheme, described in the Statistical Analyses Methods section in the Supplementary Appendix, Figs. S2 through S6, and Table S2) were the change in body weight from baseline to week 40 and the attainment of glycated hemoglobin level targets of less than 7.0% and less than 5.7%. Other end points were attainment of a glycated hemoglobin level of 6.5% or less and weight loss of at least 5%, 10%, or 15%; the mean change from baseline in the fasting serum glucose level and in the daily, patient-measured, mean seven-point blood glucose profiles (i.e., the mean of seven measurements); BMI and waist circumference; lipid levels; the results of an updated homeostasis model assessment–insulin resistance (HOMA2-IR); and the fasting glucagon level adjusted for the fasting serum glucose level. A composite end point of a glycated hemoglobin level of 6.5% or less with at least 10% weight loss and without clinically significant hypoglycemia (blood glucose level, <54 mg per deciliter [<3.0 mmol per liter]) or severe hypoglycemia events was also assessed.

The safety end points were adverse events and discontinuation of tirzepatide or semaglutide because of adverse events. Other safety end points were adjudicated pancreatic adverse events; the serum calcitonin level; the incidence of hypersensitivity reactions; the mean changes from baseline in the pulse rate and the systolic and diastolic blood pressure; the occurrence of hypoglycemia events; and the incidence of initiation of rescue antihyperglycemic therapy.

STATISTICAL ANALYSIS

The trial was designed to provide at least 90% power to show noninferiority of tirzepatide at a dose of 10 mg or 15 mg as compared with semaglutide at a dose of 1 mg with respect to the change from baseline in the glycated hemoglobin level at 40 weeks, with a margin of 0.3%, a standard deviation of 1.1%, and a two-sided alpha value of 0.025, assuming no difference between the treatments. We estimated that a sample size of 1872 patients would give the trial this power to show noninferiority, assuming a dropout rate of 28%.

Two "estimands" (i.e., precisely defined estimated measures of treatment effect), which were used to assess treatment efficacy from different perspectives, accounted for intercurrent events differently. First, the treatment-regimen estimand was the treatment effect between tirzepatide and semaglutide, including the effect of any additional antihyperglycemic medication for all patients who underwent randomization, regardless of premature discontinuation of tirzepatide or semaglutide and use of rescue medication. Second, the efficacy estimand was the treatment effect among all patients who underwent randomization, had all the patients continued to receive tirzepatide or semaglutide without rescue medication. All the patients who underwent randomization and re-

ceived at least one dose of tirzepatide or semaglutide (the modified intention-to-treat population) were included in the analyses to assess both estimands. Patients who discontinued tirzepatide or semaglutide because of inadvertent enrollment were excluded from efficacy analyses. Details on estimands and analysis methods are provided in the Supplementary Appendix. All the reported results are for the treatment-regimen estimand, unless stated otherwise.

The type I error rate was strongly controlled within each estimand independently for evaluation of the primary and key secondary end points with a graphical approach. Safety analyses were performed in the modified intention-to-treat population with all the data from the start of treatment to the end of the safety follow-up. For other outcomes that were not covered in the testing strategy, the results are reported as point estimates and 95% confidence intervals when applicable; the widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects.

RESULTS

TRIAL PATIENTS

The trial was conducted between July 30, 2019, and February 15, 2021. In all, 2526 patients were assessed for trial eligibility; 1879 patients underwent randomization, and 1878 patients received at least one dose of tirzepatide or semaglutide (Fig. S7).

The demographic and clinical characteristics were similar across the groups (Table 1 and Table S4). The overall mean duration of diabetes was 8.6 years, the mean glycated hemoglobin level was 8.28%, and the mean body weight was 93.7 kg. In all the treatment groups, the most common reasons for premature discontinuation of tirzepatide or semaglutide were adverse events (mainly gastrointestinal events) (Table 2 and Table S3).

GLYCEMIC END POINTS

At 40 weeks, reductions in the mean glycated hemoglobin level with tirzepatide at a dose of 5 mg, 10 mg, and 15 mg were –2.01 percentage points, –2.24 percentage points, and –2.30 percentage points, respectively, as compared with –1.86 percentage points with semaglutide (Fig. 1A). All tirzepatide doses were found to be superior to semaglutide, with estimated treatment differences of −0.15 percentage points (95% confidence interval [CI], −0.28 to −0.03; P=0.02) with tirzepatide 5 mg, −0.39 percentage points (95% CI, −0.51 to −0.26; P<0.001) with tirzepatide 10 mg, and −0.45 percentage points (95% CI, −0.57 to −0.32; P<0.001) with tirzepatide 15 mg. The glycated hemoglobin level over time is shown in (Fig. 1B). A total of 82 to 86% of the patients who received tirzepatide and 79% of those who received semaglutide had a decrease in the glycated hemoglobin level to less than 7.0%. A total of 69 to 80% of the patients who received tirzepatide and 64% of those who received semaglutide had a decrease in the glycated hemoglobin level to 6.5% or less, and 27 to 46% and 19%, respectively, had a decrease in the glycated hemoglobin level to less than 5.7% (Fig. 1C). A subgroup analysis involving patients with a glycated hemoglobin level above 8.5% showed mean reductions in the glycated hemoglobin level of –3.22 percentage points with tirzepatide at a dose of 15 mg as compared with –2.68 percentage points with semaglutide (Fig. S8).

With the use of the efficacy estimand at 40 weeks, greater reductions in the fasting serum glucose level were observed with all tirzepatide doses than with semaglutide (Fig. 1D and Fig. S9). In addition, all the tirzepatide doses resulted in greater reductions than those with semaglutide in the patient-measured mean blood glucose levels at all seven time points (Fig. S10A). Reductions from baseline in the mean daily 2-hour postprandial glucose level from the seven-point blood glucose profile ranged from –71.6 to –81.9 mg per deciliter (–4.0 to –4.5 mmol per liter) with tirzepatide to –67.2 mg per deciliter (–3.7 mmol per liter) with semaglutide (Fig. S10B).

BODY-WEIGHT END POINTS

Reductions in body weight with tirzepatide were dose-dependent (Fig. 2A and 2B). At 40 weeks, the mean reductions in body weight with tirzepatide at a dose of 5 mg, 10 mg, and 15 mg were –7.6 kg, –9.3 kg, and –11.2 kg, respectively, as compared with –5.7 kg with semaglutide. At all doses, tirzepatide was superior to semaglutide, with estimated treatment differences of –1.9 kg (95% CI, –2.8 to –1.0) with tirzepatide at a dose of 5 mg, –3.6 kg (95% CI, –4.5 to –2.7) with tirzepatide at a dose of 10 mg, and –5.5 kg (95% CI, –6.4 to –4.6) with tirzepatide at a dose

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline in the Modified Intention-to-Treat Population.*

Characteristic	Tirzepatide			Semaglutide	Total (N=1878)
	5 mg (N=470)	10 mg (N=469)	15 mg (N=470)	1 mg (N=469)	
Age — yr	56.3±10.0	57.2±10.5	55.9±10.4	56.9±10.8	56.6±10.4
Female sex — no. (%)	265 (56.4)	231 (49.3)	256 (54.5)	244 (52.0)	996 (53.0)
Race or ethnic group — no. (%)†					
American Indian or Alaska Native	53 (11.3)	53 (11.3)	57 (12.1)	45 (9.6)	208 (11.1)
Asian	6 (1.3)	11 (2.3)	5 (1.1)	3 (0.6)	25 (1.3)
Black	28 (6.0)	21 (4.5)	15 (3.2)	15 (3.2)	79 (4.2)
White	382 (81.3)	376 (80.2)	392 (83.4)	401 (85.5)	1551 (82.6)
Hispanic	325 (69.1)	322 (68.7)	334 (71.1)	336 (71.6)	1317 (70.1)
Non-Hispanic	145 (30.9)	147 (31.3)	136 (28.9)	133 (28.4)	561 (29.9)
Glycated hemoglobin level					
Glycated hemoglobin level — %	8.32±1.08	8.30±1.02	8.26±1.00	8.25±1.01	8.28±1.03
≤8.5% — no. (%)	293 (62.3)	294 (62.7)	303 (64.5)	302 (64.4)	1192 (63.5)
>8.5% — no. (%)	177 (37.7)	175 (37.3)	167 (35.5)	167 (35.6)	686 (36.5)
Glycated hemoglobin level — mmol/mol	67.46±11.84	67.20±11.20	66.78±10.97	66.69±10.99	67.03±11.25
Fasting serum glucose level					
In mg/dl	173.8±51.87	174.2±49.79	172.4±54.37	171.4±49.77	172.9±51.46
In mmol/liter	9.65±2.88	9.67±2.76	9.57±3.02	9.51±2.76	9.60±2.86
Duration of diabetes — yr	9.1±7.16	8.4±5.90	8.7±6.85	8.3±5.80	8.6±6.46
BMI‡	33.8±6.85	34.3±6.60	34.5±7.11	34.2±7.15	34.2±6.93
Weight — kg	92.5±21.76	94.8±22.71	93.8±21.83	93.7±21.12	93.7±21.86
Waist circumference — cm	108.06±14.81	110.55±16.05	109.55±15.60	109.04±14.90	109.30±15.36
Estimated GFR§					
Mean value — ml/min/1.73 m^2	96.6±17.51	95.5±16.62	96.3±16.92	95.6±17.25	96.0±17.07
Value <60 ml/min/1.73 m^2 — no. (%)	19 (4.0)	15 (3.2)	11 (2.3)	19 (4.1)	64 (3.4)
Value ≥60 ml/min/1.73 m^2 — no. (%)	451 (96.0)	454 (96.8)	459 (97.7)	450 (95.9)	1814 (96.6)
Urinary albumin-to-creatinine ratio — no. (%)¶					
<30	340 (72.3)	353 (75.3)	357 (76.0)	364 (77.6)	1414 (75.3)
30 to ≤300	111 (23.6)	87 (18.6)	85 (18.1)	90 (19.2)	373 (19.9)
>300	18 (3.8)	29 (6.2)	27 (5.7)	15 (3.2)	89 (4.7)
Use of metformin — no. (%)	470 (100.0)	469 (100.0)	470 (100.0)	469 (100.0)	1878 (100.0)
Blood pressure — mm Hg					
Systolic	130.53±14.11	131.47±13.77	130.45±14.32	129.96±12.99	130.60±13.81
Diastolic	78.61±8.89	80.03±9.59	78.97±8.97	79.33±8.61	79.23±9.03
Pulse rate — bpm	74.88±9.37	74.55±10.75	74.46±9.86	75.10±10.25	74.75±10.07

* Plus–minus values are means ±SD. Patients with a baseline estimated glomerular filtration rate (GFR) of less than 45 ml per minute per 1.73 m^2 were excluded from the trial.
† Race or ethnic group was reported by the patients.
‡ Body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.
§ The mean value of the estimated GFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.
¶ For the calculation of the urinary albumin-to-creatinine ratio, the amount of albumin measured in milligrams per deciliter was divided by the amount of creatinine measured in grams per deciliter.

Table 2. Adverse Events and Safety.*

Event	Tirzepatide						Semaglutide		Total (N=1878)	
	5 mg (N=470)		10 mg (N=469)		15 mg (N=470)		1 mg (N=469)			
	No. of patients (%)	*No. of events*	*No. of patients (%)*	*No. of events*	*No. of patients (%)*	*No. of events*	*No. of patients (%)*	*No. of events*	*No. of patients (%)*	*No. of events*
Patients with ≥1 adverse event	299 (63.6)	—	322 (68.7)	—	324 (68.9)	—	301 (64.2)	—	1246 (66.3)	—
Patients with ≥1 serious adverse event	33 (7.0)	—	25 (5.3)	—	27 (5.7)	—	13 (2.8)	—	98 (5.2)	—
Death†	4 (0.9)	—	4 (0.9)	—	4 (0.9)	—	1 (0.2)	—	13 (0.7)	—
Adverse events leading to discontinuation of tirzepatide or semaglutide	28 (6.0)	—	40 (8.5)	—	40 (8.5)	—	19 (4.1)	—	127 (6.8)	—
Adverse events occurring in ≥0.2% of the overall population (i.e., 3 patients) and leading to discontinuation of tirzepatide or semaglutide										
Nausea	6 (1.3)	—	7 (1.5)	—	4 (0.9)	—	4 (0.9)	—	21 (1.1)	—
Vomiting	1 (0.2)	—	4 (0.9)	—	4 (0.9)	—	3 (0.6)	—	12 (0.6)	—
Diarrhea	1 (0.2)	—	3 (0.6)	—	6 (1.3)	—	1 (0.2)	—	11 (0.6)	—
Abdominal pain	2 (0.4)	—	1 (0.2)	—	2 (0.4)	—	4 (0.9)	—	9 (0.5)	—
Dyspepsia	2 (0.4)	—	1 (0.2)	—	2 (0.4)	—	0	—	5 (0.3)	—
Decreased appetite	1 (0.2)	—	2 (0.4)	—	2 (0.4)	—	0	—	5 (0.3)	—
Fatigue	1 (0.2)	—	1 (0.2)	—	1 (0.2)	—	1 (0.2)	—	4 (0.2)	—
Elevated blood calcitonin level	1 (0.2)	—	1 (0.2)	—	1 (0.2)	—	0	—	3 (0.2)	—
Constipation	0	—	2 (0.4)	—	0	—	1 (0.2)	—	3 (0.2)	—
Covid-19–related pneumonia	1 (0.2)	—	1 (0.2)	—	0	—	1 (0.2)	—	3 (0.2)	—
Injection-site reaction	0	—	2 (0.4)	—	1 (0.2)	—	0	—	3 (0.2)	—

Adverse events occurring in ≥5% of patients in any treatment group, according to preferred term										
Nausea	82 (17.4)	111	90 (19.2)	124	104 (22.1)	136	84 (17.9)	126	360 (19.2)	497
Diarrhea	62 (13.2)	120	77 (16.4)	99	65 (13.8)	102	54 (11.5)	68	258 (13.7)	389
Vomiting	27 (5.7)	35	40 (8.5)	56	46 (9.8)	61	39 (8.3)	53	152 (8.1)	205
Dyspepsia	34 (7.2)	—	29 (6.2)	—	43 (9.1)	—	31 (6.6)	—	137 (7.3)	—
Decreased appetite	35 (7.4)	—	34 (7.2)	—	42 (8.9)	—	25 (5.3)	—	136 (7.2)	—
Constipation	32 (6.8)	—	21 (4.5)	—	21 (4.5)	—	27 (5.8)	—	101 (5.4)	—
Abdominal pain	14 (3.0)	—	21 (4.5)	—	24 (5.1)	—	24 (5.1)	—	83 (4.4)	—
All gastrointestinal adverse events	188 (40.0)	—	216 (46.1)	—	211 (44.9)	—	193 (41.2)	—	808 (43.0)	—
Other adverse events										
Hypoglycemia, blood glucose level <54 mg/dl	3 (0.6)	3	1 (0.2)	2	8 (1.7)	10	2 (0.4)	2	14 (0.7)	17
Severe hypoglycemia	1 (0.2)	1	0	0	1 (0.2)‡	1‡	0	0	2 (0.1)	2
Injection-site reaction	9 (1.9)	—	13 (2.8)	—	21 (4.5)	—	1 (0.2)	—	44 (2.3)	—
Adjudicated pancreatitis	0	—	2 (0.4)	—	2 (0.4)	—	3 (0.6)	—	7 (0.4)	—
Cholelithiasis	4 (0.9)	—	4 (0.9)	—	4 (0.9)	—	2 (0.4)	—	14 (0.7)	—
Hypersensitivity§	9 (1.9)	—	13 (2.8)	—	8 (1.7)	—	11 (2.3)	—	41 (2.2)	—
Diabetic retinopathy¶	0	—	2 (0.4)	—	0	—	0	—	2 (0.1)	—

* Patients may be counted in more than one category. The number of events was reported if available. To convert blood glucose values to millimoles per liter, multiply by 0.05551.
† Deaths are also included as serious adverse events and discontinuations due to adverse events. No deaths were considered by the investigators to be related to tirzepatide or semaglutide. All deaths were adjudicated by an external committee of physicians with cardiology expertise.
‡ This patient had a hypoglycemic event that was not considered by the investigator to be severe, but it was reported as a serious adverse event.
§ This category includes immediate (<24 hours after trial drug administration) and nonimmediate (>24 hours after trial drug administration) hypersensitivity events. One immediate event was reported in the tirzepatide 15-mg group.
¶ Diabetic retinopathy was confirmed by funduscopic examination.

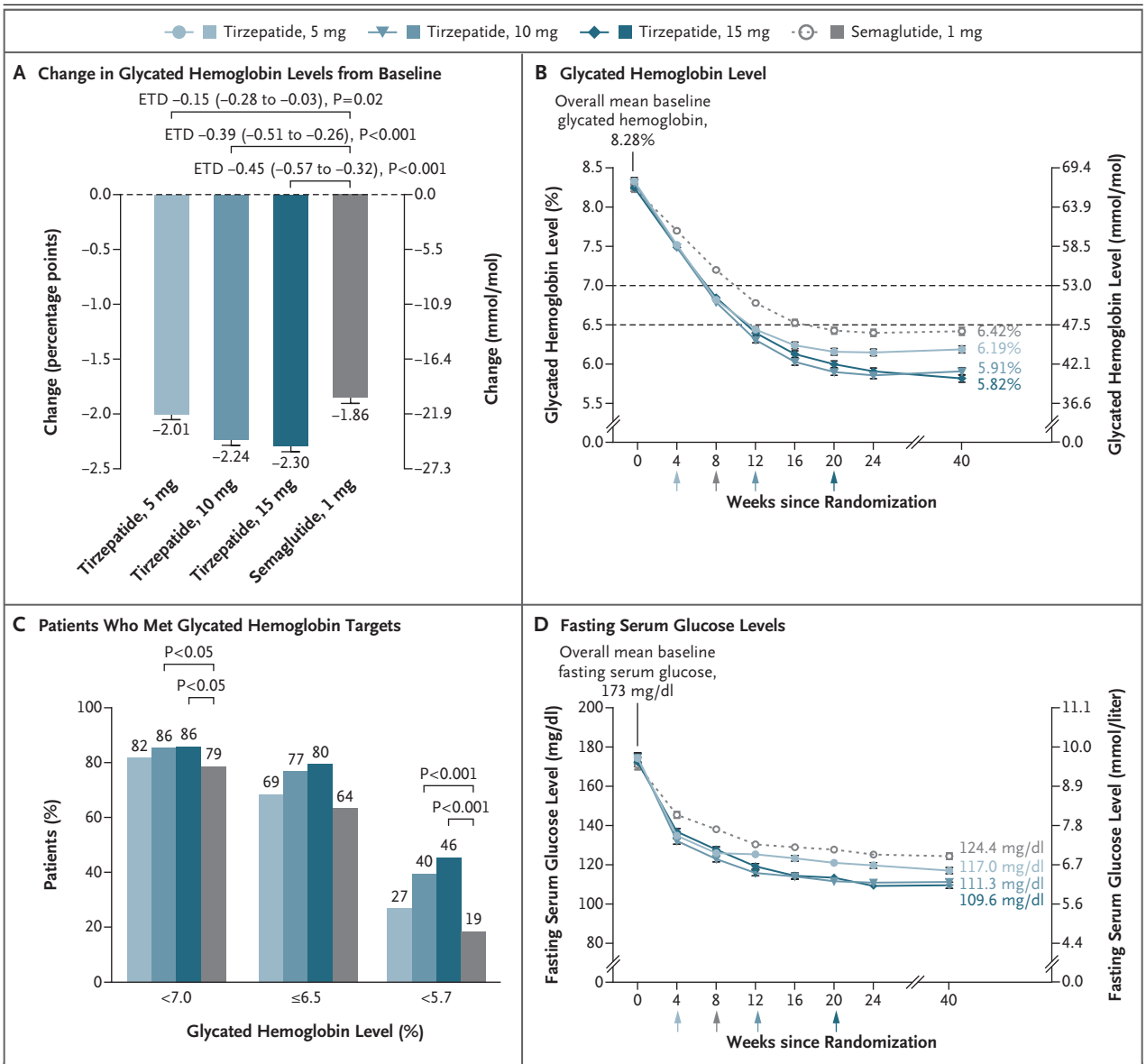

Figure 1. Effect of Once-Weekly Tirzepatide, as Compared with Semaglutide, on the Glycated Hemoglobin Level, Percentage of Patients Who Met Glycated Hemoglobin Level Targets, and Fasting Serum Glucose Levels.

Least-squares means (±SE) are presented, unless otherwise noted. Error bars indicate the standard error. Estimated treatment differences (ETDs) are least-squares means (95% confidence interval) at 40 weeks in the modified intention-to-treat population. Panel A shows the change from baseline in the glycated hemoglobin level at 40 weeks, as assessed with the use of analysis of covariance with multiple imputation according to treatment for the missing glycated hemoglobin level at 40 weeks (treatment-regimen estimand). Panel B shows the values for glycated hemoglobin levels over time, derived from a mixed-model repeated-measures analysis (efficacy estimand). Arrows indicate the times at which the maintenance doses of tirzepatide (5 mg, 10 mg, or 15 mg) and semaglutide 1 mg were achieved. Panel C shows the percentage of patients who met glycated hemoglobin level targets of less than 7.0%, 6.5% or less, and less than 5.7% at 40 weeks (treatment-regimen estimand). The percentage was calculated with the use of Rubin's rules by combining the percentages of patients who met the target in imputed data sets. The glycated hemoglobin levels of 6.5% or less and less than 5.7% (tirzepatide 5-mg group only) were not controlled for type 1 errors; thus, P values are not presented. Panel D shows fasting serum glucose values over time, derived from mixed-model repeated-measures analysis (efficacy estimand). Arrows indicate the times at which the maintenance doses of tirzepatide (5 mg, 10 mg, or 15 mg) and semaglutide 1 mg were achieved.

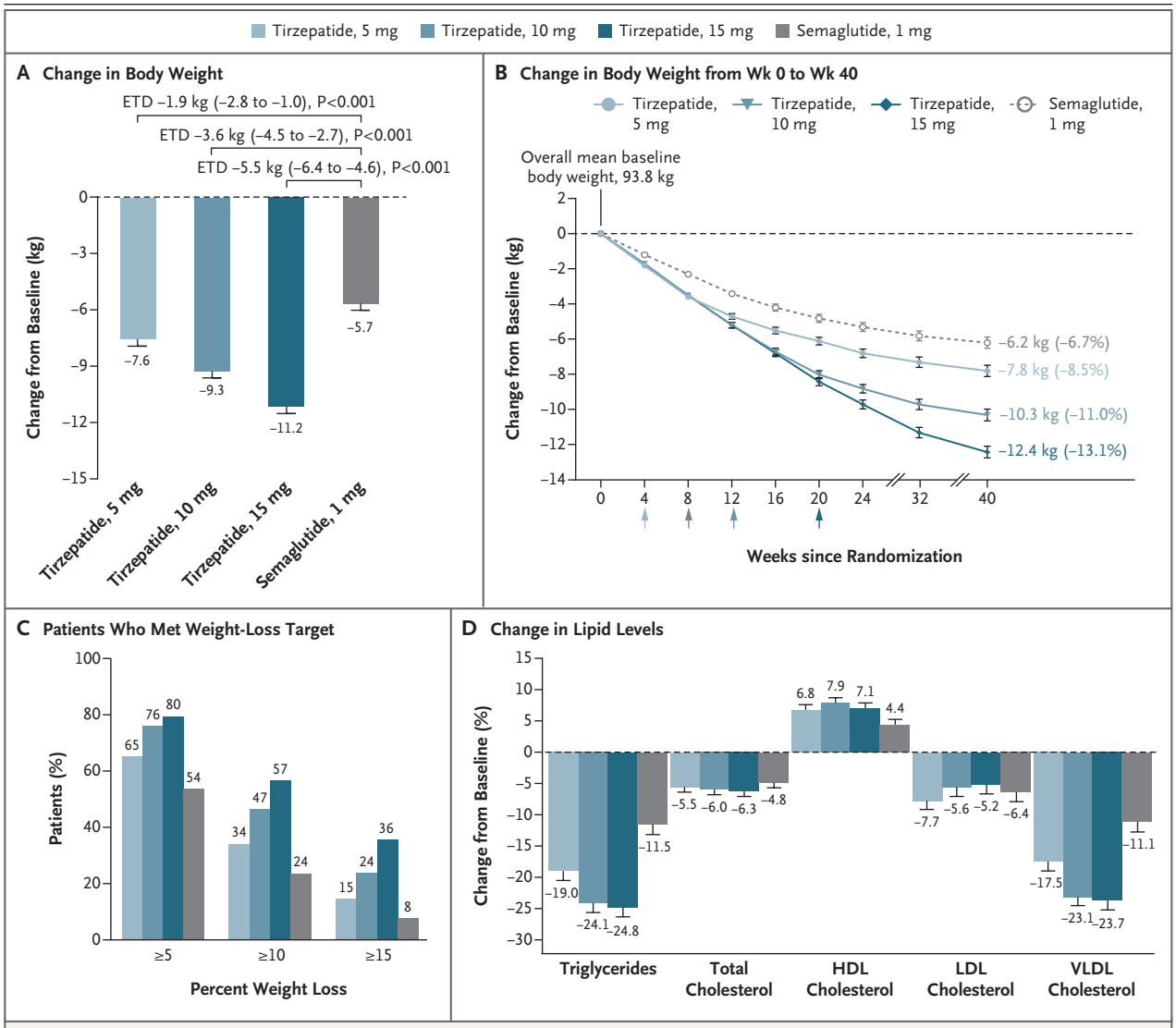

Figure 2. Effect of Once-Weekly Tirzepatide, as Compared with Semaglutide, on Body Weight, the Percentage of Patients Who Met Weight-Loss Goals, and the Lipid Profile.

Least-squares means (±SE) are presented, unless otherwise noted. Error bars indicate the standard error. Panel A shows the change from baseline in body weight at 40 weeks, as assessed with analysis of covariance with multiple imputation for treatment for missing weight at 40 weeks (treatment-regimen estimand). ETDs are least-squares means (95% confidence interval) at 40 weeks in the modified intention-to-treat population. Panel B shows the change from baseline in body weight over time, derived from a mixed-model repeated-measures analysis (efficacy estimand). The percent changes from baseline values at 40 weeks are shown in parentheses. Arrows indicate the times at which the maintenance doses of tirzepatide (5 mg, 10 mg, or 15 mg) and semaglutide 1 mg were achieved. Panel C shows the percentage of patients who had body-weight reductions of at least 5%, 10%, or 15% from baseline to week 40 (treatment-regimen estimand). The percentage was calculated with the use of Rubin's rules by combining the percentages of patients who met the target in imputed data sets. Panel D shows the percent change (±SE) from baseline in lipid levels at 40 weeks, as estimated with the use of log transformation. HDL denotes high-density lipoprotein, LDL low-density lipoprotein, and VLDL very-low-density lipoprotein.

of 15 mg (P<0.001 for all comparisons). A total of 65 to 80% of the patients who received tirzepatide and 54% of those who received semaglutide had reductions in body weight of at least 5%; 34 to 57% and 24%, respectively, had reductions of at least 10%; and 15 to 36% and 8%, respec-

tively, had reductions of at least 15% (Fig. 2C). With the use of the efficacy estimand, more patients who received tirzepatide than those who received semaglutide met a composite end point of a glycated hemoglobin level of 6.5% or less with at least 10% weight loss and without clinically significant hypoglycemia (blood glucose level, <54 mg per deciliter) or severe hypoglycemia (32 to 60% vs. 22%, respectively) (Table S5). The mean BMI and waist circumference over time are shown in Fig. S11.

OTHER END POINTS AND SAFETY

At 40 weeks, the triglyceride and serum very-low-density lipoprotein levels were lower and the high-density lipoprotein cholesterol levels were higher in patients who received tirzepatide than in those who received semaglutide (Fig. 2D, Fig. S12, and Table S6). The total cholesterol and low-density lipoprotein cholesterol levels did not differ significantly among the treatment groups.

The percentages of patients who reported any adverse events were similar in the four treatment groups (Table 2). There was a higher number of serious adverse events among patients who received tirzepatide than among those who received semaglutide (Table 2 and Table S7); the most frequent serious adverse event was coronavirus disease 2019 (Covid-19)–related pneumonia in all groups.

The most frequent adverse events reported were gastrointestinal-related events (Table 2). Nausea was reported in 17 to 22% of patients who received tirzepatide and in 18% who received semaglutide, diarrhea was reported in 13 to 16% and 12%, respectively, vomiting in 6 to 10% and 8%, respectively, and decreased appetite in 7 to 9% and 5%. Most cases of nausea, vomiting, and diarrhea were mild to moderate in severity and transient and occurred during the dose-escalation period in all groups (Fig. S13 and Tables S8 and S9).

A total of 13 deaths (0.7%) occurred in the total population during the trial (4 patients in each of the three tirzepatide groups and 1 patient in the semaglutide group) (Table 2). None of the deaths were considered by the investigators to be related to tirzepatide or semaglutide. All the deaths were adjudicated by an external committee of physicians. Five deaths were related to Covid-19, and the death of a sixth patient with suspected Covid-19 was adjudicated as being from cardiovascular causes. These 6 deaths occurred in 1 patient who received tirzepatide at a dose of 5 mg, 2 patients who received tirzepatide at a dose of 10 mg, 2 patients (including the patient with presumptive Covid-19) who received tirzepatide at a dose of 15 mg, and 1 patient who received semaglutide. Four other deaths were adjudicated as cardiovascular-related deaths (1 in the tirzepatide 5-mg group, 1 in the tirzepatide 10-mg group, 2 in the tirzepatide 15-mg group, and none in the semaglutide group), and 2 deaths were considered to be indeterminate (1 each in the tirzepatide 5-mg and 10-mg groups) (Table S10). Of these 2 patients with deaths that were considered to be indeterminate, 1 had coronary artery disease. Two patients with cardiovascular-related deaths had no previous cardiovascular risk factors other than type 2 diabetes.

Clinically significant hypoglycemia (blood glucose level, <54 mg per deciliter) was reported in 3 patients (0.6%), 1 patient (0.2%), and 8 patients (1.7%) who received tirzepatide at a dose of 5 mg, 10 mg, and 15 mg, respectively, as compared with 2 patients (0.4%) who received semaglutide (Table 2). Two events of severe hypoglycemia were reported (1 each in the tirzepatide 5-mg and 15-mg groups). Both patients recovered and completed the trial while receiving the assigned trial drug. Rescue therapy for persistent hyperglycemia was warranted for 1.3 to 1.5% of patients who received tirzepatide and 2.8% of those who received semaglutide.

Adjudication-confirmed cases of pancreatitis were reported in patients who received tirzepatide (2 cases each in the 10-mg and 15-mg groups) and in 3 patients who received semaglutide (Table 2). No cases were serious. Changes in serum alanine aminotransferase levels ranged from –22 to –30% with tirzepatide as compared with –22% with semaglutide; and changes in aspartate aminotransferase ranged from and –9 to –14% with tirzepatide as compared with –9% with semaglutide (Table S11). Four patients from each tirzepatide group and 2 patients from the semaglutide group reported cholelithiasis (Table 2). No clinically relevant changes in mean calcitonin levels were observed, and no cases of medullary thyroid cancer were reported. Two cases of diabetic retinopathy were reported (both with tirzepatide at a dose of 10 mg) (Table 2 and Table S12).

Transient increases in the mean pulse rate of 1.1 to 4.6 beats per minute were observed during the trial. At 40 weeks, the mean pulse rate had increased by 2.3 beats per minute with tirzepatide at a dose of 5 mg, by 2.2 beats per minute at a dose of 10 mg, and by 2.6 beats per minute at a dose of 15 mg, as compared with an increase of 2.5 beats per minute with semaglutide; the mean pulse rate did not differ significantly among the treatment groups (Fig. S14A). Systolic and diastolic blood pressure decreased with tirzepatide at a dose of 5 mg (−4.8 mm Hg and −1.9 mm Hg, respectively), at a dose of 10 mg (−5.3 mm Hg and −2.5 mm Hg, respectively), and at a dose of 15 mg (−6.5 mm Hg and −2.9 mm Hg, respectively) as compared with semaglutide (−3.6 mm Hg and −1.0 mm Hg, respectively) (Fig. S14B and C).

Hypersensitivity reactions occurred in 1.7 to 2.8% of the patients who received tirzepatide and in 2.3% of those who received semaglutide. Injection-site reactions occurred in 1.9 to 4.5% of the patients who received tirzepatide and in 0.2% of those who received semaglutide; these reactions were mild to moderate in severity (Table 2). No serious cases of hypersensitivity or injection-site reactions were reported. Similar results for glycated hemoglobin level, body weight, and the percentage of patients who met the targets for glycated hemoglobin level and weight loss were reported with the efficacy estimand (Fig. 1B and 2B, and Fig. S15 and Table S13).

DISCUSSION

In the current trial, tirzepatide at a dose of 5 mg, 10 mg, or 15 mg was noninferior and superior to semaglutide at a dose of 1 mg, with respect to a reduction in the glycated hemoglobin level in patients with type 2 diabetes who were receiving metformin. Tirzepatide was also superior to semaglutide with respect to reductions in body weight. A total of 82 to 86% of the patients who received tirzepatide and 79% of those who received semaglutide reached the glycated hemoglobin level target of less than 7.0% that is recommended by the American Diabetes Association and the European Association for the Study of Diabetes.[21] The glycated hemoglobin level target of less than 5.7% (normoglycemia) was met in 27 to 46% of the patients who received tirzepatide and in 19% of those who received semaglutide. The patients who received tirzepatide at a dose of 15 mg had almost twice the weight loss of those who received semaglutide at a dose of 1 mg. Weight reduction did not plateau in any of the four treatment groups at 40 weeks.

A glycated hemoglobin level of less than 5.7% without an increased risk of hypoglycemia has not been considered attainable with current treatment options. In our trial, this goal was met with a gastrointestinal-related side-effect profile that was similar to that reported with GLP-1 receptor agonists.[22] In addition, many patients who received tirzepatide were noted to have an improved lipid profile as well as improved blood pressure, biomarkers of insulin sensitivity, and liver-enzyme levels. We speculate that dual agonism (glucose-dependent insulinotropic polypeptide receptor and GLP-1 receptor) may allow some patients to reach near-normal glycemia with potential long-term benefits. The SURPASS-4 trial (ClinicalTrials.gov number, NCT03730662), which compared tirzepatide with insulin glargine, enrolled patients with increased cardiovascular risk, and the SURPASS-CVOT trial (NCT04255433) is ongoing to compare tirzepatide with dulaglutide and to provide a more comprehensive assessment of cardiovascular safety.

The dose-escalation scheme in the current trial of the phase 3 SURPASS clinical program, which included a lower starting dose and slower dose escalation in smaller increments,[23] was associated with a better gastrointestinal-related side-effect profile than the scheme in the phase 2 trial, which involved more rapid escalation.[9] Gastrointestinal adverse events reported with tirzepatide and semaglutide were consistent with those that would be expected with the GLP-1 receptor agonist class and were mostly mild to moderate and occurred during the escalation period with both trial drugs. The most common reason for premature discontinuation of tirzepatide or semaglutide was adverse events, which were more common with tirzepatide at a dose of 10 mg and 15 mg than with tirzepatide at a dose of 5 mg and with semaglutide. Although there were numerically more deaths with tirzepatide, Covid-19 was a confounder in five of the deaths and presumptively involved in a sixth death. Five deaths were adjudicated to be related to cardiovascular causes, all in the tirzepatide groups; in

addition to type 2 diabetes, three of those patients had previous risk factors and established cardiovascular disease, and a fourth was a smoker and was overweight.

The limitations of our trial were that treatments could not be blinded because of differences in devices and dose-escalation schemes (tirzepatide doses were blinded) and the relatively short duration of 40 weeks, which allowed only 16 weeks at a steady state for the assessment of the highest tirzepatide dose. In addition, the number of Black patients was low. Higher doses of semaglutide were not available as comparators at the time of this trial.

Our trial has several strengths. The reductions in glycated hemoglobin level and body weight observed with semaglutide were consistent with the results already reported in the SUSTAIN (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes) clinical trial program.[10-17,19] In addition, in the 68-week STEP 2 (Semaglutide Treatment Effect in People with Obesity) trial, which assessed semaglutide at doses of 1 mg and 2.4 mg in addition to lifestyle intervention for long-term weight management in patients with type 2 diabetes, the estimated treatment difference in weight loss was –2.7 percentage points with semaglutide at a dose of 2.4 mg as compared with semaglutide at a dose of 1 mg (–9.6% vs. –7.0%) and –6.2 percentage points with semaglutide at a dose of 2.4 mg as compared with placebo (–9.6% vs. –3.4%).[24] These results are consistent with those reported in our trial with semaglutide at a dose of 1 mg for weight reduction. Other strengths of our trial include an active comparator (semaglutide at a dose of 1 mg) and a large sample size with a large number of patients who completed the trial.

In patients with type 2 diabetes who were receiving metformin, the novel once-weekly dual glucose-dependent insulinotropic polypeptide–GLP-1 receptor agonist tirzepatide was noninferior and superior to the selective GLP-1 receptor agonist semaglutide (at a dose of 1 mg) with respect to the mean change in the glycated hemoglobin level from baseline to 40 weeks.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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