ORIGINAL ARTICLE

Cardiovascular Outcomes with Tirzepatide versus Dulaglutide in Type 2 Diabetes

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ABSTRACT

BACKGROUND

Tirzepatide, a dual incretin agonist of the glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide receptors, has favorable effects on glycemic control and body weight. The effects on cardiovascular outcomes are uncertain.

METHODS

We conducted an active-comparator–controlled, double-blind, noninferiority trial in which patients with type 2 diabetes and atherosclerotic cardiovascular disease were randomly assigned in a 1:1 ratio to receive a weekly subcutaneous injection of tirzepatide (up to 15 mg) or dulaglutide (1.5 mg), an agent that has been shown to reduce the incidence of cardiovascular events. The primary end point was a composite of death from cardiovascular causes, myocardial infarction, or stroke and was tested for noninferiority of tirzepatide to dulaglutide with a margin of 1.05 for the upper limit of the 95.3% confidence interval for the hazard ratio. An upper limit of less than 1.00 was considered to indicate superiority of tirzepatide to dulaglutide.

RESULTS

A total of 13,299 patients underwent randomization; 134 were subsequently excluded because they did not meet inclusion criteria. The modified intention-to-treat population thus included 6586 patients in the tirzepatide group and 6579 in the dulaglutide group. The mean (±SD) age of the patients was 64.1±8.8 years, 29.0% were women, the mean body-mass index (the weight in kilograms divided by the square of the height in meters) was 32.6±5.5, the mean glycated hemoglobin level was 8.4±0.9%, and the mean duration of diabetes was 14.7±8.8 years. A primary end-point event occurred in 801 patients (12.2%) in the tirzepatide group and 862 (13.1%) in the dulaglutide group (hazard ratio, 0.92; 95.3% confidence interval, 0.83 to 1.01; P=0.003 for noninferiority; P=0.09 for superiority). The incidence of adverse events appeared to be similar in the two groups, although more gastrointestinal adverse events were observed in the tirzepatide group.

CONCLUSIONS

Among patients with type 2 diabetes and atherosclerotic cardiovascular disease, tirzepatide was noninferior to dulaglutide with respect to a composite of death from cardiovascular causes, myocardial infarction, or stroke. (Funded by Eli Lilly; SURPASS-CVOT ClinicalTrials.gov number, NCT04255433.)

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*A complete list of the SURPASS-CVOT Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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CME

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Therapies targeting incretin hormone receptors have an increasing role in the management of type 2 diabetes and in strategies to promote weight loss.[1] Clinical trials have shown that glucagon-like peptide-1 (GLP-1) receptor agonists reduce the incidence of major adverse cardiovascular events among patients with high cardiovascular risk and type 2 diabetes,[2-7] chronic kidney disease,[8,9] or obesity.[10] Clinical guidelines have integrated the use of GLP-1 receptor agonists into the treatment of patients at high cardiovascular risk.[11-14]

Tirzepatide is a dual agonist of the GLP-1 and glucose-dependent insulinotropic polypeptide receptors.[15] Clinical trials have shown that tirzepatide leads to incremental benefits with respect to glycemic control, weight, atherogenic lipoprotein levels, blood pressure, and kidney-related outcomes as compared with selective GLP-1 receptor agonists or other glucose-lowering agents.[16-22] These benefits, if sustained over time, could also have incremental effects on the incidence of atherosclerotic events. However, data from a randomized, clinical trial of the effect of tirzepatide on cardiovascular outcomes have been lacking.

The established role of GLP-1 receptor agonists in the management of type 2 diabetes in patients with high cardiovascular risk[2-7] precluded direct comparison of tirzepatide with a placebo control in a large, long-term clinical trial.[23] We conducted the Study of Tirzepatide Compared with Dulaglutide on Major Cardiovascular Events in Participants with Type 2 Diabetes (SURPASS-CVOT) to determine the cardiovascular effects of tirzepatide as compared with those of the selective GLP-1 receptor agonist dulaglutide in patients with type 2 diabetes and established atherosclerotic cardiovascular disease.[24] Because dulaglutide has been shown to reduce the incidence of cardiovascular events as compared with placebo,[5] we sought to determine whether tirzepatide was noninferior to dulaglutide with respect to cardiovascular events, as well as whether tirzepatide was associated with a greater cardiovascular benefit.

Methods

Trial Organization and Oversight

The trial design has been described previously,[24] and the trial protocol and statistical analysis plan are available with the full text of this article at NEJM.org. We conducted this double-blind, randomized, active-comparator–controlled trial at 640 sites in 30 countries (additional details are provided in the Supplementary Appendix, available at NEJM.org). The trial was designed by the sponsor, Eli Lilly, in collaboration with the academic executive committee. The protocol was approved by the ethics committee at each participating site. The sponsor oversaw the conduct of the trial, undertook site monitoring, collected the data, and performed the initial statistical analysis. Subsequently, the database was transferred to Monash University, Melbourne, VIC, Australia, and statisticians affiliated with the university validated the data analyses. An independent data and safety monitoring committee reviewed the safety and efficacy data during the trial. The first author wrote the first draft of the manuscript, which was edited and approved by all the authors. The sponsor reviewed the manuscript and suggested revisions, but the final decision on content was reserved for the first author, who made the decision to submit the manuscript for publication. The first author vouches for the accuracy and completeness of the data and for the fidelity of the trial to the protocol and the statistical analysis plan.

Trial Population

Patients at least 40 years of age were eligible if they had type 2 diabetes with a glycated hemoglobin level between 7.0% (53 mmol per mole) and 10.5% (91 mmol per mole), a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of at least 25, and established atherosclerotic cardiovascular disease in at least one vascular territory. Among the exclusion criteria were any cardiovascular event in the 60 days before screening, use of a GLP-1 receptor agonist or pramlintide in the 3 months before screening, planned treatment for diabetic retinopathy or macular edema, chronic advanced heart failure, a history of pancreatitis, a clinically significant abnormality in gastric emptying or previous bariatric surgery, active liver disease (not including metabolic dysfunction–associated steatohepatitis), an estimated glomerular filtration rate (eGFR) of less than 15 ml per minute per 1.73 m^2 of body-surface area or use of long-term dialysis, or a family or personal history of multiple endocrine neoplasia or medullary thyroid carcinoma. All the patients provided written informed consent. Additional details with regard

to inclusion and exclusion criteria, as well as criteria for established atherosclerotic cardiovascular disease, are provided in the Supplementary Appendix.

RANDOMIZATION AND TRIAL REGIMEN

Eligible patients were randomly assigned in a 1:1 ratio to receive weekly subcutaneous injections of tirzepatide at a dose adjusted up to 15 mg or dulaglutide at a dose of 1.5 mg. Randomization was stratified according to country and the use of sodium–glucose cotransporter 2 (SGLT2) inhibitors at baseline. Tirzepatide was initiated at a dose of 2.5 mg and increased by 2.5 mg every 4 weeks to a maximum of 15 mg or to the maximum tolerated dose. Because the dose of dulaglutide remained at 1.5 mg throughout the trial, a sham dose-escalation scheme was used to maintain trial blinding. Discontinuation of dipeptidyl peptidase 4 inhibitors was recommended at the time of randomization. The glucose-control regimen was adjusted during the trial, at the discretion of the site investigator, with the use of open-label nonincretin agents in accordance with national guidelines for glycemic control. Adjustment of the blinded trial medication dose was permitted at the discretion of the investigator. Patients were monitored at trial visits every 4 weeks for the first 24 weeks and every 3 months thereafter (Fig. S1 in the Supplementary Appendix).

TRIAL END POINTS

The primary end point was a composite of death from cardiovascular causes, myocardial infarction, or stroke, assessed in a time-to-first-event analysis. Key secondary end points included death from cardiovascular causes; myocardial infarction; stroke; death from any cause; a composite of death from cardiovascular causes, myocardial infarction, stroke, or coronary revascularization; a composite of death from cardiovascular causes or hospitalization or urgent visit for heart failure; the change from baseline to 36 months in the eGFR according to the Chronic Kidney Disease Epidemiology Collaboration creatinine–cystatin equation 2021[25] in patients with high-risk or very-high-risk chronic kidney disease as defined by the Kidney Disease: Improving Global Outcomes 2024 guideline (an eGFR of ≥60 ml per minute per 1.73 m^2 and a urinary albumin-to-creatinine ratio of >300 [with albumin measured in milligrams and creatinine measured in grams], an eGFR of 45 to <60 ml per minute per 1.73 m^2 and a urinary albumin-to-creatinine ratio of >30, or an eGFR of <45 ml per minute per 1.73 m^2 at baseline)[26]; the change from baseline in the glycated hemoglobin level, body weight, and systolic blood pressure at 36 months; and the change from baseline in the triglyceride level and in the low-density lipoprotein (LDL) cholesterol level at 24 months. End points were adjudicated by an independent committee in which the members were unaware of treatment assignments (additional details are provided in the Supplementary Appendix).

STATISTICAL ANALYSIS

The trial was designed with an event-driven approach to test for noninferiority of tirzepatide to dulaglutide.[23] Noninferiority to dulaglutide was determined by an upper limit of less than 1.05 for the 95.3% confidence interval for the hazard ratio for death from cardiovascular causes, myocardial infarction, or stroke with tirzepatide as compared with dulaglutide, with adjustment for the interim efficacy analysis. The noninferiority margin of 1.05 was chosen conservatively in consultation with the Food and Drug Administration to be consistent with guidance that required the chosen margin to ensure putative superiority of tirzepatide to placebo and preserve at least 50% of the efficacy of dulaglutide after adjustment for effects with placebo.[23] If noninferiority was met, the superiority of tirzepatide to dulaglutide would be concluded if the upper limit of the confidence interval was less than 1.0.

We calculated that a minimum of 1615 primary end-point events would provide the trial with 90% power to determine the noninferiority of tirzepatide to dulaglutide (with a 10.5% lower risk of a primary end-point event with tirzepatide) and the superiority of tirzepatide to dulaglutide (with a 15% lower risk of a primary end-point event with tirzepatide) at a two-sided alpha level of 0.05. Enrollment of 12,500 patients with follow-up for an average estimated duration of 4 years was planned with the assumption that the annual event rate in the dulaglutide group would be 3.5%. One prespecified interim efficacy analysis for superiority with respect to the primary end point at a two-sided alpha level of 0.01 was performed when 1078 primary end-point events had occurred.

All efficacy analyses were conducted in a modified intention-to-treat population that excluded 134 patients who had undergone randomization in error and discontinued the trial early according to regulatory request. The primary efficacy end point and the secondary end points that were assessed in time-to-clinical-event analyses were analyzed with Cox proportional-hazards models with treatment as the factor of interest and stratification according to SGLT2 inhibitor use at baseline. Cumulative incidence was estimated with the Kaplan–Meier method. P values were calculated with the use of Wald tests. Proportionality of hazards assumptions was assessed within each stratum on the basis of SGLT2 inhibitor use at baseline, Schoenfeld residual plots, and a Kolmogorov-type supremum test. At the request of the *Journal* editors, data were also analyzed with appropriate adjustment for competing risks with the Fine–Gray model.[27] The change from baseline to 36 months in the eGFR and glycated hemoglobin level and the percentage of weight loss were assessed with analysis of covariance models with treatment group, SGLT2 inhibitor use at baseline, country, and baseline value as covariates, with multiple imputation of missing data at 24 or 36 months (additional details are provided in the Supplementary Appendix).

A graphical testing approach was prespecified to evaluate each of the primary and key secondary efficacy end points, with preservation of the familywise type I error rate at 5% (Fig. S2). The widths of the confidence intervals were not adjusted for multiplicity and should not be used in place of hypothesis testing. Safety was evaluated in all patients who had undergone randomization and received treatment with a trial drug. The statistical analyses were performed with SAS software, version 9.4 or higher (SAS Institute), and RStudio software, version 4.4.2 (Posit).

RESULTS

RANDOMIZATION, PATIENT CHARACTERISTICS, AND FOLLOW-UP

Between May 29, 2020, and June 27, 2022, a total of 16,979 patients were screened and 13,299 underwent randomization: 6648 were assigned to the tirzepatide group and 6651 to the dulaglutide group. A total of 134 patients (62 in the tirzepatide group and 72 in the dulaglutide group) discontinued the trial after a median of 85 days and were excluded from efficacy analyses because they were deemed not to have been eligibile according to the inclusion and exclusion criteria; the 13,165 remaining patients were included in the modified intention-to-treat population (6586 in the tirzepatide group and 6579 in the dulaglutide group). Screening, randomization, and follow-up are summarized in Figure S3.

The characteristics of the patients at baseline appeared to be similar in the two treatment groups (Table 1). The mean (±SD) age of the patients was 64.1±8.8 years, 29.0% were women, the mean BMI was 32.6±5.5, 65.0% of the patients had coronary artery disease, 19.2% had a history of stroke, 25.3% had peripheral artery disease, 20.3% had a history of heart failure, and the mean duration of diabetes was 14.7±8.8 years. The representativeness of the patients is shown in Table S1.

At the time of enrollment, 97.3% of the patients were receiving glucose-lowering medications: 81.4% were receiving metformin, 30.6% were receiving an SGLT2 inhibitor, 21.6% were receiving a sulfonylurea, and 48.8% were receiving insulin (Table S2). Baseline risk factors included a mean glycated hemoglobin level of 8.4±0.9% (68±10 mmol per mole), a mean LDL cholesterol level of 80.6 mg per deciliter (2.08 mmol per liter), mean systolic blood pressure of 135.3±15.7 mm Hg, and a mean eGFR of 78.9±23.8 ml per minute per 1.73 m^2; 22.7% of the patients met the criteria for high-risk or very-high-risk chronic kidney disease.

EFFICACY END POINTS

Patients were followed for a median of 4.0 years. Premature discontinuation of the trial drug occurred in 21.6% patients in the tirzepatide group and 19.8% in the dulaglutide group. At 36 months, 72.7% of the patients in the tirzepatide group were receiving the 15-mg dose (Fig. S4); metformin was being used in 71.4% of the patients in the tirzepatide group and 78.8% in the dulaglutide group; an SGLT2 inhibitor in 33.8% and 41.1%, respectively; a sulfonylurea in 15.0% and 21.4%; and insulin in 39.2% and 47.8%. The median duration of exposure to the trial drug was 47.6 months in the tirzepatide group and 47.7 months in the dulaglutide group. Complete assessment for the primary end point was available for 99.0% of the patients, and the vital status was known for 99.7%.

A primary end-point event occurred in 801 patients (12.2%) in the tirzepatide group and 862

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Tirzepatide (N=6586)	Dulaglutide (N=6579)
Age — yr	64.0±8.8	64.1±8.7
Female sex — no. (%)	1891 (28.7)	1926 (29.3)
White race — no./total no. (%)†	5299/6501 (81.5)	5282/6492 (81.4)
Hispanic or Latino ethnic group — no. (%)†	1988 (30.2)	1981 (30.1)
Geographic region — no. (%)		
North America	970 (14.7)	970 (14.7)
South America	1896 (28.8)	1897 (28.8)
Europe	3047 (46.3)	3034 (46.1)
Asia–Pacific	673 (10.2)	678 (10.3)
History of ASCVD — no. (%)		
Coronary artery disease	4286 (65.1)	4267 (64.9)
Myocardial infarction	3097 (47.0)	3119 (47.4)
Coronary revascularization	3756 (57.0)	3773 (57.3)
Stroke	1253 (19.0)	1272 (19.3)
Peripheral artery disease	1660 (25.2)	1674 (25.4)
Previous heart failure	1310 (19.9)	1368 (20.8)
Hypertension — no. (%)	5941 (90.2)	5932 (90.2)
Dyslipidemia — no. (%)	5685 (86.3)	5611 (85.3)
Current tobacco use — no. (%)	963 (14.6)	996 (15.1)
Duration of diabetes — yr	14.8±8.8	14.7±8.7
Cardiovascular risk factors		
Weight — kg	92.6±18.9	92.5±18.8
Body-mass index	32.6±5.5	32.6±5.5
Blood pressure		
Systolic — mm Hg	135.1±15.5	135.5±15.8
Diastolic — mm Hg	77.9±9.7	78.1±9.7
Glycated hemoglobin level — %	8.40±0.92	8.38±0.93
LDL cholesterol level — mg/dl	80.5±36.8	80.7±38.0
Median triglyceride level (IQR) — mg/dl	160.3 (116.0–225.9)	159.4 (116.0–224.1)
Estimated GFR		
Mean value — ml/min/1.73 m^2	78.5±24.2	79.2±23.5
Value of <60 ml/min/1.73 m^2 — no./total no. (%)	1516/6492 (23.4)	1412/6512 (21.7)
Urinary albumin-to-creatinine ratio (IQR)‡	22.0 (9.0–86.0)	22.0 (9.0–81.0)
Microalbuminuria — no./total no. (%)	2072/6472 (32.0)	2070/6482 (31.9)
Macroalbuminuria — no./total no. (%)	754/6472 (11.7)	737/6482 (11.4)

* Plus–minus values are means ±SD. Total numbers indicate numbers of patients with available data. To convert the values for glycated hemoglobin to millimoles per mole, multiply by 10.93 and then subtract 23.5. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. ASCVD denotes atherosclerotic cardiovascular disease, GFR glomerular filtration rate, IQR interquartile range, and LDL low-density lipoprotein.

† Race and ethnic group were reported by the patients.

‡ For the urinary albumin-to-creatinine ratio, albumin was measured in milligrams and creatinine was measured in grams.

(13.1%) in the dulaglutide group (hazard ratio for death from cardiovascular causes, myocardial infarction, or stroke, 0.92; 95.3% confidence interval [CI], 0.83 to 1.01; P=0.003 for noninferiority; P=0.09 for superiority) (Table 2 and Fig. 1). Death from cardiovascular causes occurred in 367 patients (5.6%) in the tirzepatide group and 408 (6.2%) in the dulaglutide group (hazard ratio, 0.89; 95% CI, 0.77 to 1.02). Myocardial infarction occurred in 311 patients (4.7%) and 357 patients (5.4%), respectively (hazard ratio, 0.86; 95% CI, 0.74 to 1.00). Stroke occurred in 229 patients (3.5%) and 249 patients (3.8%), respectively (hazard ratio, 0.91; 95% CI, 0.76 to 1.09). Death from cardiovascular causes, myocardial infarction, stroke, or coronary revascularization (a composite secondary end point) occurred in 1089 patients (16.5%) in the tirzepatide group and 1217 (18.5%) in the dulaglutide group (hazard ratio, 0.88; 95% CI, 0.81 to 0.96) (Fig. S5). Death from cardiovascular causes or hospitalization or urgent visit for heart failure (an additional composite secondary end point) occurred in 512 patients (7.8%) in the tirzepatide group and 557 (8.5%) in the dulaglutide group (hazard ratio, 0.91; 95% CI, 0.81 to 1.03).

Death from any cause occurred in 566 patients (8.6%) in the tirzepatide group and 669 (10.2%) in the dulaglutide group (hazard ratio, 0.84; 95% CI, 0.75 to 0.94) (Fig. S6 and Table S3). Death that was adjudicated to be due to noncardiovascular causes occurred in 199 patients (3.0%) in the tirzepatide group and 261 (4.0%) in the dulaglutide group (hazard ratio, 0.75; 95% CI, 0.63 to 0.91) (Fig. S7). No significant deviation in the proportionality of hazards according to the use of SGLT2 inhibitors at baseline was noted (P=0.82 with SGLT2 inhibitor use; P=0.62 without SGLT2 inhibitor use) (Fig. S8). Analyses that accounted for noncardiovascular causes of death as a competing risk yielded findings that were similar to those of the primary analyses for the primary end point (hazard ratio, 0.92; 95% CI, 0.84 to 1.02) and for the key secondary end points that involved major adverse cardiovascular events (Table S4). Subgroup analysis of the primary end point is shown in Figure S9.

METABOLIC RISK FACTORS

The glycated hemoglobin level decreased to 6.73% (50 mmol per mole) in the tirzepatide group (change from baseline, –1.66 percentage points) and to 7.51% (59 mmol per mole) in the dulaglutide group (change from baseline, –0.88 percentage points), with a between-group difference of –0.78 percentage points (–9 mmol per mole; 95% CI, –0.84 to –0.72 [–9 to –8]) (Fig. 2A). Body weight decreased by 11.6% in the tirzepatide group and 4.8% in the dulaglutide group (between-group difference, –6.8 percentage points; 95% CI, –7.1 to –6.5) (Fig. 2B). The triglyceride level decreased by 24.2% and 10.2%, respectively (difference, –15.6 percentage points; 95% CI, –16.9 to –14.3) (Fig. S10). In patients with high-risk or very-high-risk chronic kidney disease, the eGFR decreased by 5.72 ml per minute per 1.73 m^2 in the tirzepatide group and 8.90 ml per minute per 1.73 m^2 in the dulaglutide group (difference, 3.17 ml per minute per 1.73 m^2; 95% CI, 2.09 to 4.26). Systolic blood pressure decreased by 6.2 mm Hg in the tirzepatide group and 4.1 mm Hg in the dulaglutide group (difference, –2.1 mm Hg; 95% CI, –2.6 to –1.5) (Fig. S11). The LDL cholesterol level decreased by 1.2 mg per deciliter (0.03 mmol per liter) in the tirzepatide group and 2.1 mg per deciliter (0.05 mmol per liter) in the dulaglutide group (difference, 0.9 mg per deciliter [0.02 mmol per liter]; 95% CI, –0.2 to 2.0 [–0.01 to 0.05]) (Fig. S12).

ADVERSE EVENTS

Adverse events that emerged during treatment are reported in Table 3. There appeared to be no substantial differences between the two treatment groups in the incidence of adverse events, serious adverse events, or adverse events that led to discontinuation of the trial drug. Severe hypoglycemia occurred in 0.7% (49 patients) in the tirzepatide group and 0.7% (48 patients) in the dulaglutide group. Gastrointestinal adverse events were reported by 42.5% of the patients in the tirzepatide group and 35.9% of those in the dulaglutide group; nausea was reported by 25.1% and 22.4%, respectively, and diarrhea by 24.8% and 19.1%. Episodes of pancreatitis, adjudicated by a central committee, were reported in 0.6% of the patients in each group. Investigator-reported acute kidney injury occurred in 3.4% of the patients in the tirzepatide group and 2.7% in the dulaglutide group. Medullary thyroid cancer was reported in 2 patients who had received tirzepatide; one tumor was positive for a RET (rearranged during transfection) proto-oncogene mutation.

Table 2. Primary and Key Secondary End Points.*

End Point	Tirzepatide (N=6586)	Dulaglutide (N=6579)	Hazard Ratio (95% CI)	Difference (95% CI)
Primary end point				
Death from cardiovascular causes, myocardial infarction, or stroke — no. of patients with event (%)	801 (12.2)	862 (13.1)	0.92 (0.83 to 1.01)†	—
Key secondary end points				—
Death from cardiovascular causes — no. (%)	367 (5.6)	408 (6.2)	0.89 (0.77 to 1.02)	—
Myocardial infarction — no. (%)	311 (4.7)	357 (5.4)	0.86 (0.74 to 1.00)	—
Stroke — no. (%)	229 (3.5)	249 (3.8)	0.91 (0.76 to 1.09)	—
Death from cardiovascular causes, myocardial infarction, stroke, or coronary revascularization — no. (%)	1089 (16.5)	1217 (18.5)	0.88 (0.81 to 0.96)	—
Death from cardiovascular causes or hospitalization or urgent visit for heart failure — no. (%)	512 (7.8)	557 (8.5)	0.91 (0.81 to 1.03)	—
Death from any cause — no. (%)	566 (8.6)	669 (10.2)	0.84 (0.75 to 0.94)	—
Change in eGFR from baseline to 36 mo — ml/min/1.73 m^2‡	−5.72±0.44	−8.90±0.39	—	3.17 (2.09 to 4.26)
Change in metabolic risk factors§				
Glycated hemoglobin level				
Value at baseline (95% CI) — %	8.40 (8.38 to 8.43)	8.38 (8.36 to 8.40)	—	NA
Change at 36 mo (95% CI) — percentage points	−1.66 (−1.70 to −1.62)	−0.88 (−0.92 to −0.83)	—	−0.78 (−0.84 to −0.72)
Body weight				
Value at baseline (95% CI) — kg	92.6 (92.2 to 93.1)	92.5 (92.1 to 93.0)	—	NA
Change at 36 mo (95% CI) — %	−11.6 (−11.8 to −11.4)	−4.8 (−5.0 to −4.6)	—	−6.8 (−7.1 to −6.5)¶
Triglyceride level				
Value at baseline (95% CI) — mg/dl	166.2 (164.1 to 168.4)	165.2 (163.1 to 167.4)	—	NA
Change at 24 mo (95% CI) — %	−24.2 (−25.1 to −23.3)	−10.2 (−11.2 to −9.1)	—	−15.6 (−16.9 to −14.3)¶
Systolic blood pressure				
Value at baseline (95% CI) — mm Hg	134.8 (13.4 to 135.2)	135.3 (134.9 to 135.6)	—	NA
Change at 36 mo (95% CI) — mm Hg	−6.2 (−6.6 to −5.8)	−4.1 (−4.6 to −3.7)	—	−2.1 (−2.6 to −1.5)
LDL cholesterol level				
Value at baseline (95% CI) — mg/dl	72.2 (71.3 to 73.1)	72.1 (71.2 to 73.0)	—	NA
Change at 24 mo (95% CI) — %	−1.6 (−2.7 to −0.5)	−2.9 (−4.0 to −1.8)	—	1.3 (−0.2 to 2.8)¶

* Plus–minus values are means ±SE. Data from randomization to the end of follow-up are shown for the modified intention-to-treat population. End points assessed in a time-to-event analysis were analyzed with a Cox proportional-hazards model with treatment as a factor and with stratification according to use of sodium–glucose cotransporter 2 (SGLT2) inhibitors at baseline. Continuous end points that were used to assess changes from randomization to the landmark time point were analyzed with an analysis of covariance model with treatment group, use of SGLT2 inhibitors at baseline, country, and baseline value as covariates, with multiple imputation of missing values. The widths of the confidence intervals were not adjusted for multiplicity and should not be used in place of hypothesis testing. NA denotes not assessed.

† The confidence level for the primary end point was adjusted for the interim efficacy analysis; shown is the 95.3% confidence interval, which corresponds to the nominal two-sided significance level of 0.047. P=0.003 for noninferiority; P=0.09 for superiority.

‡ Data are shown for 1520 patients in the tirzepatide group and 1403 patients in the dulaglutide group with high-risk or very-high-risk chronic kidney disease, as defined by the Kidney Disease: Improving Global Outcomes 2024 guideline: an eGFR of 60 ml per minute per 1.73 m^2 of body-surface area or higher and a urinary albumin-to-creatinine ratio above 300, an eGFR of 45 to less than 60 ml per minute per 1.73 m^2 and a urinary albumin-to-creatinine ratio above 30, or an eGFR of less than 45 ml per minute per 1.73 m^2 at baseline.

§ Values are model-based estimates.

¶ The difference is reported in percentage points.

DISCUSSION

In patients with type 2 diabetes and atherosclerotic cardiovascular disease, treatment with tirzepatide was noninferior to treatment with dulaglutide with respect to the primary composite end point — death from cardiovascular causes, myocardial infarction, or stroke — at a median follow-up of 4.0 years. The results appeared to be consistent among subgroups stratified according to cardiovascular and diabetes-related clinical characteristics. The incidence of adverse events or serious adverse events that emerged during treatment did not appear to differ substantially between the two treatment groups, although gastrointestinal events were reported more frequently by patients assigned to the tirzepatide group.

These findings extend previous observations of the effects of tirzepatide as compared with GLP-1 receptor–selective agonists on metabolic

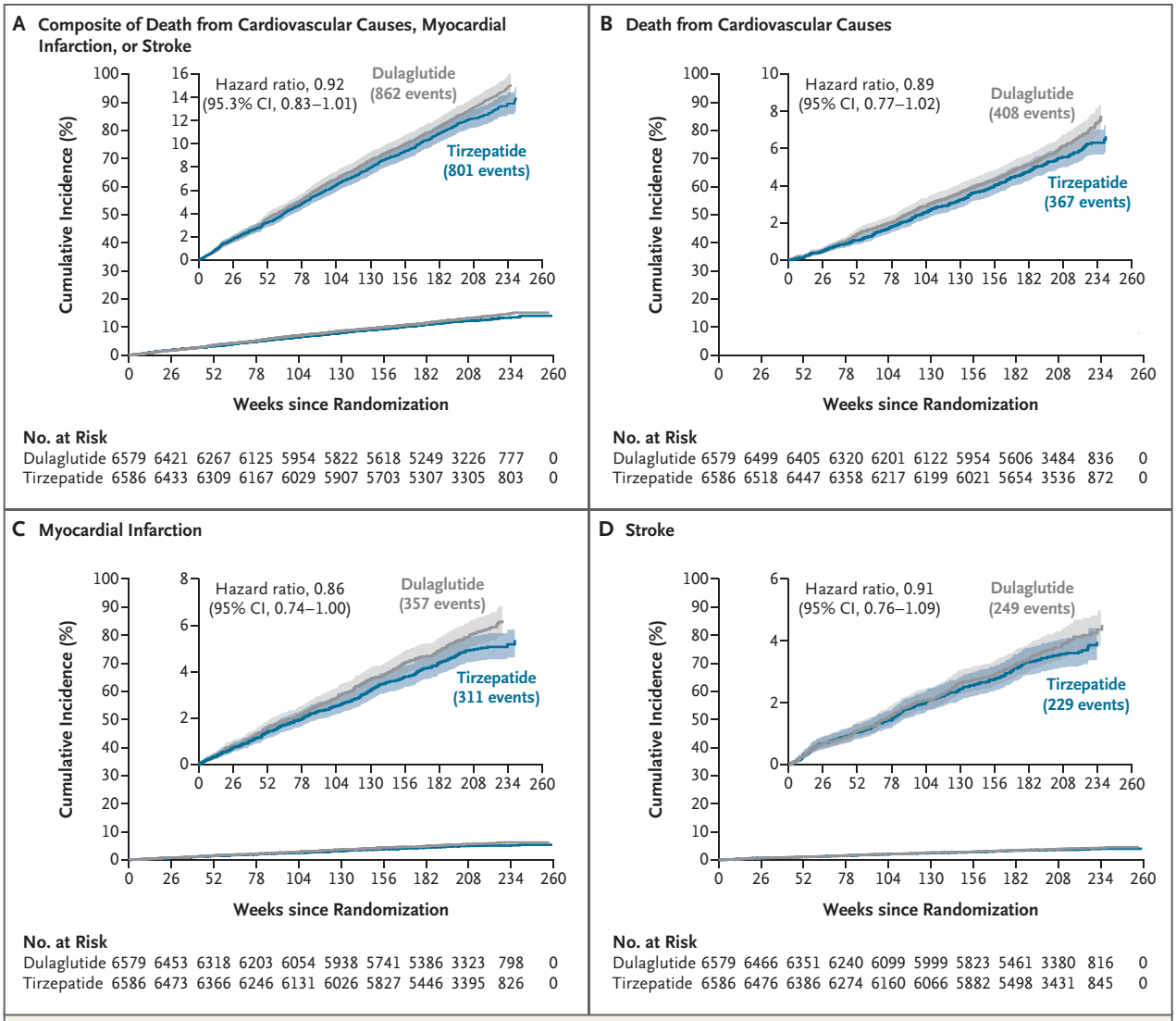

Figure 1. Cumulative Incidence of Cardiovascular Events (Primary and Key Secondary End Points).

Panel A shows the cumulative incidence of a composite of death from cardiovascular causes, myocardial infarction, or stroke (the primary efficacy end point). Panels B, C, and D show the cumulative incidence of the components of the primary end point. In each of the panels, the inset shows the same data on an enlarged y axis. Shading indicates 95% confidence intervals. Cumulative incidence was estimated with the Kaplan–Meier method. The widths of the confidence intervals were not adjusted for multiplicity and should not be used in place of hypothesis testing.

risk factors.[16-21] Although a pooled analysis of previous trials of tirzepatide has examined the effect of tirzepatide on cardiovascular events,[28] those trials were small and short in duration. The noninferior effect of tirzepatide as compared with dulaglutide on the primary cardiovascular outcome provides additional evidence that targeting the incretin axis with multiple approaches has a favorable effect on cardiovascular risk in patients with type 2 diabetes. The results of the current trial also suggest that an incretin therapy that includes activation of the glucose-dependent insulinotropic polypeptide receptor was noninferior to dulaglutide with respect to cardiovascular risk.[1,29,30]

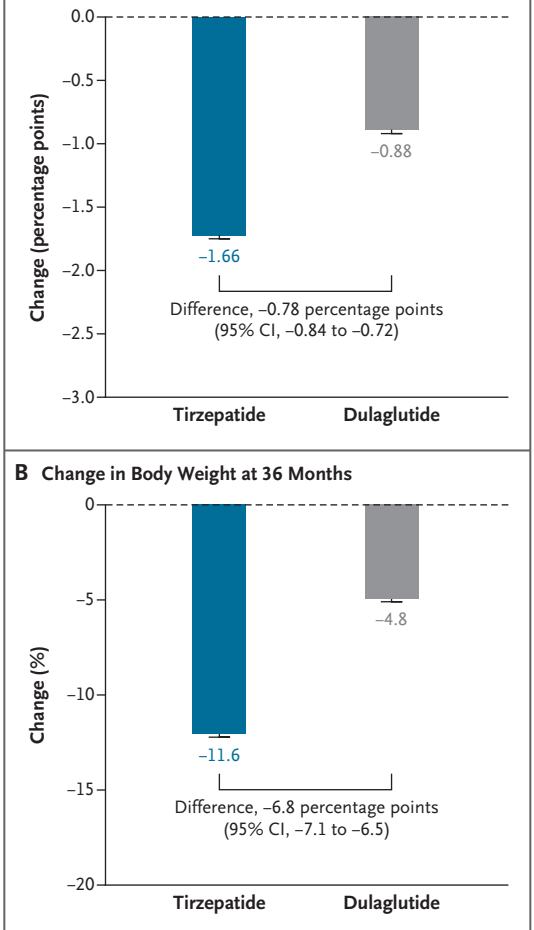

Figure 2. Changes in Glycated Hemoglobin Level and Body Weight over Time.

Panel A shows the change in the glycated hemoglobin level from baseline to 36 months in the tirzepatide group and the dulaglutide group. The mean glycated hemoglobin level in both groups at baseline was 8.4% (68 mmol per mole). Panel B shows the percent change in body weight in the two groups from baseline to 36 months. The mean body weight at baseline was 92.6 kg in the tirzepatide group and 92.5 kg in the dulaglutide group. Colored bars indicate least-squares means, and I bars indicate standard errors. Changes from baseline to the landmark time point were analyzed with an analysis of covariance model with treatment group, use of sodium–glucose cotransporter 2 inhibitors at baseline, country, and baseline value as covariates, with multiple imputation of missing values. The widths of the confidence intervals were not adjusted for multiplicity and should not be used in place of hypothesis testing.

This large cardiovascular outcomes trial included an active comparator, the GLP-1 receptor agonist dulaglutide. Previous comparative trials have shown the relative benefits of tirzepatide for metabolic risk factors, including weight, glycemic control, and atherogenic lipoprotein levels,[16-21] yet we did not observe a significantly lower incidence of primary end-point events with tirzepatide than with dulaglutide. Whether this result reflects mechanisms beyond glycemic control or reduction in body weight that mediate the effects of incretin-targeted therapies on cardiovascular outcomes or whether it reflects the active comparison with dulaglutide, an existing agent shown to reduce cardiovascular risk in previous trials involving patients with type 2 diabetes, is uncertain and warrants further investigation. Additional analyses will be required to determine the contribution of different metabolic effects of tirzepatide and dulaglutide to the observed cardiovascular outcomes. These metabolic effects are factors that can be considered when clinicians and patients decide on the use of glucose-lowering therapies.

Although tirzepatide did not meet the criterion for superiority to dulaglutide with respect to the primary end point, a prespecified secondary analysis suggested a possible lower incidence of death from any cause and of death from noncardiovascular causes in the tirzepatide group than in the dulaglutide group. This finding should be considered exploratory and warrants further investigation. Results of the analyses that accounted for competing risks with the Fine–Gray model[27] did not meaningfully differ from the findings of the prespecified analyses of the primary and key secondary end points.

Our trial has limitations. The trial did not include a placebo group because the role of GLP-1 receptor agonists in the treatment of patients with

Table 3. Adverse Events.*

Event	Tirzepatide (N=6647)	Dulaglutide (N=6647)
	number of patients (percent)	
Any adverse event that emerged during treatment	5956 (89.6)	5894 (88.7)
Serious adverse event†	2117 (31.8)	2121 (31.9)
Adverse event leading to drug discontinuation	878 (13.2)	672 (10.1)
Prespecified adverse events of special interest		
Severe hypoglycemia	49 (0.7)	48 (0.7)
Gastrointestinal adverse event‡	2827 (42.5)	2387 (35.9)
Severe gastrointestinal adverse event	171 (2.6)	118 (1.8)
Nausea	1667 (25.1)	1486 (22.4)
Severe nausea	76 (1.1)	51 (0.8)
Vomiting	772 (11.6)	642 (9.7)
Severe vomiting	60 (0.9)	37 (0.6)
Diarrhea	1651 (24.8)	1267 (19.1)
Severe diarrhea	79 (1.2)	53 (0.8)
Pancreatic events		
Pancreatitis§	41 (0.6)	39 (0.6)
Pancreatic carcinoma¶	17 (0.3)	17 (0.3)
Gallbladder-related adverse events		
Cholelithiasis	158 (2.4)	134 (2.0)
Cholecystitis‖	91 (1.4)	84 (1.3)
Thyroid events		
Medullary thyroid cancer	2 (<0.1)	0
Other thyroid carcinoma	9 (0.1)	2 (<0.1)
Serious atrial fibrillation	59 (0.9)	58 (0.9)
Hypersensitivity reactions**		
Anaphylactic reaction	12 (0.2)	15 (0.2)
Hypersensitivity	377 (5.7)	330 (5.0)
Renal events		
Acute kidney injury	226 (3.4)	178 (2.7)
Chronic kidney disease	147 (2.2)	170 (2.6)

* Adverse events are defined according to preferred terms in the *Medical Dictionary for Regulatory Activities* (MedDRA), version 28.0.

† Data shown exclude cardiovascular end-point events confirmed by a clinical end-point committee. The severity of adverse events was determined by the investigators.

‡ Gastrointestinal events included nausea, vomiting, and diarrhea.

§ Pancreatitis was adjudicated by a clinical end-point committee.

¶ Pancreatic carcinoma represents a cluster of terms that includes pancreatic carcinoma; pancreatic carcinoma, metastatic; pancreatic carcinoma, stage IV; pancreatic carcinoma, recurrent; pancreatic neuroendocrine tumor; adenocarcinoma, pancreas; and pancreatic neoplasm.

‖ Cholecystitis represents a cluster of terms that includes cholecystitis, acute; cholecystitis, chronic; cholecystitis; and acute cholecystitis.

** Hypersensitivity was determined with the use of the standardized MedDRA queries "anaphylactic reaction" and "hypersensitivity."

diabetes and cardiovascular risk had been established. Although patients were recruited from 30 countries, the level of diversity with respect to sex and race was not fully representative of the global patient population (more than 80% of the patients in each treatment group were White), a limitation shared by other trials that have assessed cardiovascular outcomes. The effect of tirzepatide on major adverse cardiovascular events in patients with type 2 diabetes was not assessed in patients who were candidates for primary prevention, and the only GLP-1 receptor agonist evaluated was dulaglutide. Imbalances between the treatment groups with respect to the addition of an SGLT2 inhibitor after randomization may have affected results. The trial was limited to patients with type 2 diabetes; a placebo-controlled cardiovascular outcomes trial of tirzepatide in patients without type 2 diabetes who have high cardiovascular risk and overweight or obesity is currently in progress.[31]

Among patients with type 2 diabetes and atherosclerotic cardiovascular disease, tirzepatide was noninferior to dulaglutide with respect to a composite of death from cardiovascular causes, myocardial infarction, or stroke.

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