ORIGINAL ARTICLE

Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity

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ABSTRACT

BACKGROUND

Obesity increases the risk of heart failure with preserved ejection fraction. Tirzepatide, a long-acting agonist of glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptors, causes considerable weight loss, but data are lacking with respect to its effects on cardiovascular outcomes.

METHODS

In this international, double-blind, randomized, placebo-controlled trial, we randomly assigned, in a 1:1 ratio, 731 patients with heart failure, an ejection fraction of at least 50%, and a body-mass index (the weight in kilograms divided by the square of the height in meters) of at least 30 to receive tirzepatide (up to 15 mg subcutaneously once per week) or placebo for at least 52 weeks. The two primary end points were a composite of adjudicated death from cardiovascular causes or a worsening heart-failure event (assessed in a time-to-first-event analysis) and the change from baseline to 52 weeks in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS; scores range from 0 to 100, with higher scores indicating better quality of life).

RESULTS

A total of 364 patients were assigned to the tirzepatide group and 367 to the placebo group; the median duration of follow-up was 104 weeks. Adjudicated death from cardiovascular causes or a worsening heart-failure event occurred in 36 patients (9.9%) in the tirzepatide group and in 56 patients (15.3%) in the placebo group (hazard ratio, 0.62; 95% confidence interval [CI], 0.41 to 0.95; P=0.026). Worsening heart-failure events occurred in 29 patients (8.0%) in the tirzepatide group and in 52 patients (14.2%) in the placebo group (hazard ratio, 0.54; 95% CI, 0.34 to 0.85), and adjudicated death from cardiovascular causes occurred in 8 patients (2.2%) and 5 patients (1.4%), respectively (hazard ratio, 1.58; 95% CI, 0.52 to 4.83). At 52 weeks, the mean (±SD) change in the KCCQ-CSS was 19.5±1.2 in the tirzepatide group as compared with 12.7±1.3 in the placebo group (between-group difference, 6.9; 95% CI, 3.3 to 10.6; P<0.001). Adverse events (mainly gastrointestinal) leading to discontinuation of the trial drug occurred in 23 patients (6.3%) in the tirzepatide group and in 5 patients (1.4%) in the placebo group.

CONCLUSIONS

Treatment with tirzepatide led to a lower risk of a composite of death from cardiovascular causes or worsening heart failure than placebo and improved health status in patients with heart failure with preserved ejection fraction and obesity. (Funded by Eli Lilly; SUMMIT ClinicalTrials.gov number, NCT04847557.)

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The majority of patients with heart failure and a preserved ejection fraction also have obesity, and visceral adiposity contributes to the evolution and progression of heart failure.[1,2] An increase in adipocyte mass induces a state of systemic inflammation, which may be transduced onto the myocardium through proinflammatory transformation of epicardial adipose tissue.[3,4] The risk of heart failure (especially with preserved ejection fraction) increases as body-mass index (BMI) increases,[1,5] and weight-loss interventions (e.g., gastric bypass surgery and treatment with glucagon-like peptide-1 [GLP-1] receptor agonists) ameliorate systemic inflammation, decrease epicardial adipose volume, reduce the risk of incident heart failure, and alleviate symptoms in patients with established heart failure with preserved ejection fraction.[6-9]

Two trials assessing the use of semaglutide in patients with heart failure with preserved ejection fraction and obesity showed that GLP-1 receptor agonism might not only reduce symptoms but might also lower the risk of major adverse outcomes of heart failure.[8,9] The two trials noted a reduction of 8 to 9% in body weight, improvement in health status and exercise tolerance, and a potential decreased risk of worsening heart failure.[8,9] However, the effect on worsening heart failure was observed in exploratory analyses with follow-up of only 52 weeks.

Tirzepatide is a long-acting agonist of glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors that results in 12 to 21% weight loss in patients with obesity[10,11]; however, data are needed on its effects in patients with obesity and heart failure with preserved ejection fraction. We conducted a long-term trial to examine the effect of tirzepatide on worsening heart-failure events, health status, and functional capacity.

Methods

Trial Design and Oversight

The SUMMIT trial protocol and the statistical analysis plan are available with the full text of this article at NEJM.org. The ethics committee at each investigative site approved the trial, and all patients provided written informed consent.

In collaboration with the sponsor (Eli Lilly), the academic members of the steering committee developed and amended the protocol and statistical analysis plan, oversaw the recruitment of patients and the quality of follow-up, supervised the data analyses, and provided an independent interpretation of the results. A clinical events committee adjudicated events in a blinded manner according to prespecified definitions. An independent data and safety monitoring committee reviewed the safety data. The first author, who had unrestricted access to the data, prepared all drafts of the manuscript, which were then reviewed and edited by all authors. The authors made the decision to submit 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

We included men and women who were at least 40 years of age and had chronic heart failure (defined as New York Heart Association class II to IV heart failure), a left ventricular ejection fraction of at least 50%, and a BMI (the weight in kilograms divided by the square of the height in meters) of at least 30. Enrolled patients had a 6-minute walk distance of between 100 and 425 m and a Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) of 80 or lower (scores range from 0 to 100, with higher scores indicating better quality of life). Patients also met at least one of the following criteria: an elevated N-terminal pro–B-type natriuretic peptide (NT-proBNP) level (defined as >200 pg per milliliter in patients with sinus rhythm or >600 pg per milliliter in patients with atrial fibrillation), left atrial enlargement (assessed on two-dimensional echocardiography), or elevated filling pressures at rest or during exercise (assessed by invasive or noninvasive measurements). Patients were also required to have had heart-failure decompensation within 12 months before baseline or to have an estimated glomerular filtration rate of less than 70 ml per minute per 1.73 m^2 at baseline. Details of the eligibility criteria are provided in the Supplementary Appendix (available at NEJM.org).

Study Procedures

Eligible patients were randomly assigned, in a 1:1 ratio and in a double-blind manner, to receive tirzepatide subcutaneously at a dose of 2.5 mg per week or placebo, in addition to usual therapy. Randomization was stratified according to the

occurrence of heart-failure decompensation within 12 months before baseline (yes or no), a history of type 2 diabetes (yes or no), and BMI (≥35 or <35). The dose of tirzepatide or matching placebo was increased by 2.5 mg every 4 weeks (if there were no unacceptable side effects) up to a dose of 15.0 mg per week after 20 weeks. Patients continued to receive the maximum tolerated dose of double-blind tirzepatide or placebo until the end of the trial; all background treatments could be altered at the discretion of the clinician.

Patients were evaluated every 1 to 6 months for body weight, heart-failure symptoms, worsening heart-failure events, changes in heart-failure medications, and adverse events. The 6-minute walk distance, KCCQ-CSS, and high-sensitivity C-reactive protein (CRP) level were assessed at baseline and at 24 and 52 weeks. All patients who underwent randomization were followed for major heart-failure outcomes for the entire duration of the trial, regardless of whether they continued taking tirzepatide or placebo. The trial was continued until the last patient who had undergone randomization was followed for 52 weeks.

PRESPECIFIED PRIMARY AND SECONDARY END POINTS

The trial originally had two primary end points: the first was a hierarchical composite of death from any cause or worsening heart-failure event (during the entire trial duration) combined with changes at 52 weeks in the KCCQ-CSS and in the 6-minute walk distance, and the second was a change in the 6-minute walk distance at 52 weeks. The original protocol anticipated a 10% annual incidence of worsening heart failure in the placebo group and a 20 to 30% lower risk of heart-failure events in the tirzepatide group, with no effect of treatment on the risk of death.

In August 2023, the STEP-HFpEF (Effect of Semaglutide 2.4 mg Once Weekly on Function and Symptoms in Subjects with Obesity-related Heart Failure with Preserved Ejection Fraction) trial[8] showed that GLP-1 agonism might substantially reduce the risk of cardiovascular death and worsening heart-failure events (observed hazard ratio, 0.08, which was calculated on the basis of 13 events). Accordingly, the steering committee proposed to separate the components of the hierarchical composite end point into two distinct primary end points, one focused on events and the other on health status. After discussions with the Food and Drug Administration (FDA), the sponsor learned that the hierarchical composite would be difficult to interpret because it combined worsening heart-failure events with functional measurements, with the two domains being assessed at different time points. On the basis of the original projections, the steering committee and sponsor believed that the SUMMIT trial would observe a sufficient number of events to test prospectively the effect of tirzepatide on the risk of death from cardiovascular causes and worsening heart-failure events if a composite of these two variables were included as a standalone end point.

Accordingly, on the basis of reasons external to the trial, the primary end points were revised approximately 1 year before the end of the trial, with the investigators and the sponsor having no knowledge of the unblinded data and before the data and safety monitoring committee had conducted any efficacy analyses. After a formal amendment and discussions with the FDA, the two primary end points of the trial were designated as a composite of adjudicated death from cardiovascular causes or a worsening heart-failure event, assessed in a time-to-first-event analysis (with an alpha allocation of 0.04), and the change at 52 weeks in the KCCQ-CSS (with an alpha allocation of 0.01). Deaths adjudicated to be of undetermined causes were included as deaths from cardiovascular causes. An adjudicated worsening heart-failure event was defined as exacerbated symptoms of heart failure resulting in hospitalization, intravenous therapy in an urgent care setting, or intensification of oral diuretic therapy (additional information is provided in the Supplementary Appendix). Intensification of diuretic therapy in the absence of worsening heart failure was not identified as an event.

STATISTICAL ANALYSIS

We anticipated that the occurrence of approximately 70 events would provide the trial with 80% power to discern a hazard ratio of 0.50 for death or a worsening heart-failure event, an effect size that was substantially smaller than that reported in the STEP-HFpEF trial[8] (see the FDA briefing document in the protocol of the SUMMIT trial). The trial would also have 80% power to discern a 5-point difference in the KCCQ-CSS with a standard deviation of 19.

In accordance with the intention-to-treat prin-

ciple, for both primary end points, the analysis was based on all patients who underwent randomization and included the entire planned treatment period, regardless of whether patients continued receiving tirzepatide or placebo. End points were analyzed as the time to first event with the use of a Cox regression model, with three covariates: a history of diabetes, an HFpEF-ABA score of 0.8 or higher or of less than 0.8, and an NT-proBNP level of less than 200 or of 200 pg per milliliter or higher. HFpEF-ABA is a clinical model that estimates the probability of heart failure with preserved ejection fraction (HFpEF) on the basis of age, BMI, and history of atrial fibrillation

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Tirzepatide (N=364)	Placebo (N=367)
Age — yr	65.5±10.5	65.0±10.9
Female sex — no. (%)	200 (54.9)	193 (52.6)
Race or ethnic group — no. (%)†		
Native American, Alaska Native, or Pacific Islander	26 (7.1)	24 (6.5)
Asian	58 (15.9)	73 (19.9)
Black	22 (6.0)	14 (3.8)
White	256 (70.3)	256 (69.8)
Other or multiple	2 (0.5)	0 (0.0)
Region — no. (%)		
United States	83 (22.8)	68 (18.5)
Latin America	193 (53.0)	197 (53.7)
Asia	58 (15.9)	73 (19.9)
Other	30 (8.2)	29 (7.9)
New York Heart Association functional classification — no. (%)		
Class II	262 (72.0)	268 (73.0)
Class III or IV	102 (28.0)	99 (27.0)
Measures of adiposity		
Body weight — kg	102.9±21.7	103.1±22.7
Body-mass index‡	38.3±6.4	38.2±7.0
Waist-to-height ratio	0.73±0.09	0.73±0.09
Left ventricular ejection fraction — %	61.0±6.5	60.6±6.2
HFpEF-ABA score§	0.82±0.16	0.81±0.17
Coronary artery disease — no./total no. (%)	111/359 (30.9)	106/364 (29.1)
Median NT-proBNP level (IQR) — pg/ml	196 (56–488)	169 (64–476)
Estimated glomerular filtration rate — ml/min/1.73 m^2	64.5±23.7	64.3±23.5
KCCQ-CSS score¶	53.9±17.9	53.2±19.0
6-Minute walk distance — m	305.0±80.0	300.6±83.5
High-sensitivity C-reactive protein level — mg/liter	5.8±8.5	5.8±8.4
Systolic blood pressure — mm Hg	127.9±13.1	128.2±13.7
Heart rate — beats/min	71.0±11.2	71.2±10.7
Hospitalization or urgent care visit for worsening heart failure within 12 months before enrollment — no. (%)	171 (47.0)	172 (46.9)
Atrial fibrillation — no. (%)	95 (26.1)	91 (24.8)
Type 2 diabetes — no. (%)	174 (47.8)	178 (48.5)

Table 1. (Continued.)

Characteristic	Tirzepatide (N=364)	Placebo (N=367)
Cardiovascular medications — no. (%)		
Diuretics	267 (73.4)	271 (73.8)
Renin–angiotensin system and neprilysin inhibitors‖	293 (80.5)	295 (80.4)
Beta-blocker	245 (67.3)	263 (71.7)
Mineralocorticoid-receptor antagonist	131 (36.0)	125 (34.1)
Sodium–glucose cotransporter 2 inhibitor	69 (19.0)	57 (15.5)

* Plus–minus values are means ±SD. IQR denotes interquartile rage, and NT-proBNP N-terminal pro–B-type natriuretic peptide.
† Race or ethnic group was reported by the patients; those who reported more than one race or no race were classified as other.
‡ Body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The HFpEF-ABA is a clinical model that estimates the probability that a patient has heart failure with preserved ejection fraction (HFpEF) on the basis of age, body-mass index, and history of atrial fibrillation (ABA); scores range from 0.0 to 1.0, with higher scores indicating a higher probability.
¶ Kansas City Cardiomyopathy Questionnaire clinical summary scores (KCCQ-CSS) range from 0 to 100, with higher scores indicating better quality of life.
‖ Renin–angiotensin system inhibitors include angiotensin-converting–enzyme inhibitors, angiotensin-receptor blockers, and angiotensin receptor–neprilysin inhibitors.

(ABA); scores range from 0.0 to 1.0, with higher scores indicating a higher probability.[12] Treatment effects were calculated as hazard ratios with 95% confidence intervals; the data of patients were censored at the time of their final visit or, if lost to follow-up, at the time of last contact. Between-group differences in changes in the KCCQ-CSS were analyzed with the use of the stratified Wilcoxon rank-sum test, and the Hodges–Lehmann method, with multiple imputation of missing data, was used to estimate the median difference regardless of patient adherence to the trial regimen, along with two-sided 95% confidence intervals. The proportional hazards assumption was tested and validated (Table S1 in the Supplementary Appendix).

If the effect on the primary outcome was significant for either primary end point, the following key secondary end points were to be analyzed according to a graphical stepwise testing procedure to preserve the overall type I error rate: the change in the 6-minute walk distance at 52 weeks, the percent change in body weight at 52 weeks, and the percent change in the high-sensitivity CRP level at 52 weeks. These end points were analyzed as described in the Supplementary Appendix. For measurements not listed above, there was no adjustment for multiplicity, and the data are presented as point estimates and 95% confidence intervals; the widths of the confidence intervals should not be used to infer treatment effect. Additional information on statistical analyses is provided in the Supplementary Appendix.

RESULTS

PATIENT CHARACTERISTICS AND DISPOSITION

Between April 20, 2021, and June 30, 2023, a total of 1494 patients were screened, and 731 patients were randomly assigned to receive tirzepatide (364 patients) or placebo (367 patients) at 129 centers in nine countries (Fig. S1). The baseline characteristics of the treatment groups appeared to be similar (Table 1) and were representative of patients with heart failure with preserved ejection fraction and obesity (Tables S2 and S3). The mean age of the patients was 65.2 years, 53.8% were women, and the mean BMI was 38.3. The mean KCCQ-CSS was 53.5 points, the mean 6-minute walk distance was 302.8 m, and 46.9% of patients had had a hospitalization or urgent care visit for worsening heart failure in the previous 12 months.

A total of 332 patients (91.2%) in the tirzepatide group and 331 patients (90.2%) in the placebo group attended the final trial visit. By the end of the trial, 70 patients (19.2%) in the tirzepatide group and 78 patients (21.3%) in the placebo group had discontinued the trial regimen. At the final visit, 212 (72.1%) of the 294 patients in the

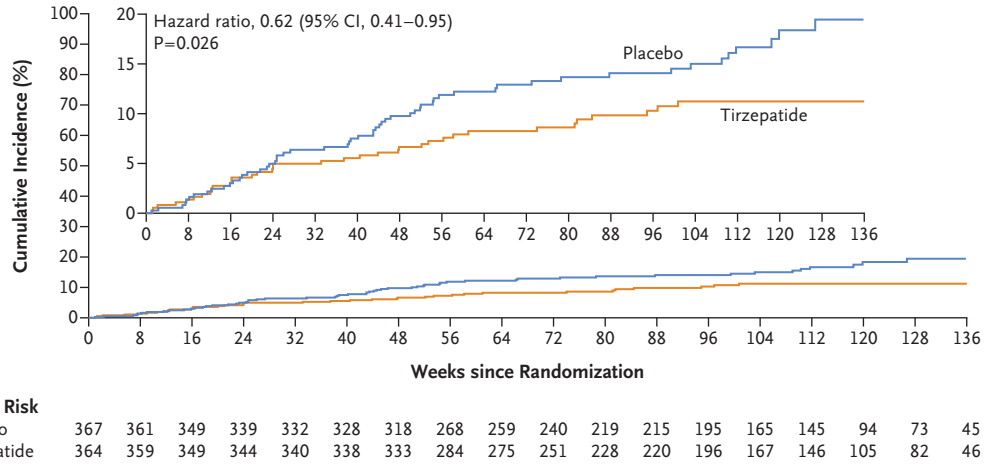


Figure 1. Composite of Death from Cardiovascular Causes or a Worsening Heart-Failure Event.

Shown is the cumulative incidence of death from cardiovascular causes or a worsening heart-failure event (the composite primary end point), assessed in a time-to-first-event analysis, among 364 patients who received tirzepatide and 367 patients who received placebo. The inset shows the same data on an expanded y axis.

tirzepatide group who were still receiving treatment were receiving the target dose of 15 mg, and 289 patients (78.7%) were still taking placebo. The median duration of follow-up was 104 weeks; 11 patients in the placebo group and 4 patients in the tirzepatide group were lost to follow-up for assessment of vital status.

PRIMARY END POINTS

Death from cardiovascular causes or a worsening heart-failure event (the composite primary end point) occurred in 36 patients (9.9%) in the tirzepatide group and in 56 patients (15.3%) in the placebo group (5.5 and 8.8 events per 100 patient-years of follow-up, respectively; hazard ratio, 0.62; 95% confidence interval [CI], 0.41 to 0.95; P=0.026) (Fig. 1, Table 2, and Table S4). When events managed only with intensification of oral diuretic therapy were removed from the primary end-point analysis, the hazard ratio was 0.57 (95% CI, 0.34 to 0.95) (Fig. S2 and Table S5). The hazard ratio for a worsening heart-failure event was 0.54 (95% CI, 0.34 to 0.85) and for a worsening heart-failure event resulting in hospitalization was 0.44 (95% CI, 0.22 to 0.87) (Fig. S3 and Table 2). Of the 15 cardiovascular deaths (adjudicated deaths from cardiovascular causes and adjudicated deaths from undetermined causes), 11 were not preceded by worsening heart failure, and 2 (both in the tirzepatide group) occurred after patients had stopped taking the trial medication for more than 15 months (Table 2). Death from any cause occurred in 19 patients in tirzepatide group and in 15 patients in the placebo group (hazard ratio, 1.25; 95% CI, 0.63 to 2.45) (Table 2 and Fig. S4).

At 52 weeks, the mean increase in the KCCQ-CSS was 19.5 points in the tirzepatide group and 12.7 points in the placebo group (between-group median difference, 6.9; 95% CI, 3.3 to 10.6; P<0.001) (Table 2 and Fig. 2). The effects of tirzepatide on both primary outcomes appeared to be consistent across prespecified subgroups (Fig. 3).

KEY SECONDARY END POINTS

At 52 weeks, the mean percent change in body weight was –13.9% in the tirzepatide group and –2.2% in the placebo group (between-group difference, –11.6 percentage points; 95% CI, –12.9 to –10.4; P<0.001). The mean increase in the 6-minute walk distance was 26.0 m in the tirzepatide group and 10.1 m in the placebo group (between-group median difference, 18.3; 95% CI, 9.9 to 26.7; P<0.001), and the mean percent decrease in the high-sensitivity CRP level was –38.8% and –5.9%, respectively (between-group difference, –34.9 percentage points; 95% CI, –45.6 to –22.2; P<0.001) (Table 2 and Figs. S5 through S7).

Table 2. Primary and Secondary End Points.*

End Point	Tirzepatide (N=364)		Placebo (N=367)		Hazard Ratio or Difference (95% CI)†	P Value
	Value	Events/100 patient-yr	Value	Events/100 patient-yr		
Primary end points and components						
Adjudicated death from cardiovascular causes or a worsening heart-failure event resulting in hospitalization, intravenous drugs in an urgent care setting, or intensification of oral diuretic therapy — no. (%)	36 (9.9)	5.5	56 (15.3)	8.8	0.62 (0.41 to 0.95)	0.026
Adjudicated death from cardiovascular causes — no. (%)	8 (2.2)	1.2	5 (1.4)	0.7	1.58 (0.52 to 4.83)	
Adjudicated death from undetermined cause — no. (%)	2 (0.5)	0.3	0	0	—	
Adjudicated worsening heart-failure event resulting in hospitalization, intravenous drugs in an urgent care setting, or intensification of oral diuretic therapy — no. (%)	29 (8.0)	4.5	52 (14.2)	8.2	0.54 (0.34 to 0.85)	
Adjudicated worsening heart-failure event resulting in hospitalization — no. (%)	12 (3.3)	1.8	26 (7.1)	3.9	0.44 (0.22 to 0.87)	
Adjudicated worsening heart-failure event resulting in intravenous diuretic therapy in an urgent care setting — no. (%)	5 (1.4)	0.7	12 (3.3)	1.8	0.41 (0.14 to 1.16)	
Adjudicated worsening heart-failure event resulting in intensification of oral diuretic therapy in an outpatient setting — no. (%)	17 (4.7)	2.6	21 (5.7)	3.2	0.80 (0.42 to 1.52)	
Death from any cause — no. (%)	19 (5.2)	2.8	15 (4.1)	2.2	1.25 (0.63 to 2.45)	
Change at 52 weeks in KCCQ-CSS	19.5±1.2	—	12.7±1.3	—	6.9 (3.3 to 10.6)‡	<0.001§
Key secondary end points						
Change at 52 weeks in 6-minute walk distance — m	26.0±3.8	—	10.1±3.9	—	18.3 (9.9 to 26.7)‡	<0.001§
Percent change at 52 weeks in body weight — %	−13.9±0.4	—	−2.2±0.5	—	−11.6 (−12.9 to −10.4)	<0.001
Percent change at 52 weeks in high-sensitivity C-reactive protein level — %	−38.8±4.5	—	−5.9±5.3	—	−34.9 (−45.6 to −22.2)¶	<0.001
Adjusted change at 52 weeks in physiological and laboratory measurements						
NT-proBNP — ratio of geometric means‖	0.93±0.04	—	1.04±0.04	—	0.90 (0.79 to 1.01)¶	
Systolic blood pressure — mm Hg	−4.6±0.8	—	0.1±0.8	—	−4.7 (−6.8 to −2.5)	
Heart rate — beats/min	3.0±0.5	—	0.3±0.5	—	2.8 (1.3 to 4.3)	

* Plus–minus values are least-squares means ±SE and show the change at 52 weeks as assessed with the use of analysis of covariance, with missing data at week 52 imputed with the use of multiple imputation. The effect of tirzepatide on the first primary end point and its components was assessed in time-to-first-event analyses. Specific contributors to the time-to-first-event analysis of the primary end-point events are shown in Table S4. First events included 11 of the 15 deaths from cardiovascular causes and from undetermined causes, 34 of the 38 hospitalizations for heart failure, 13 of the 17 worsening heart-failure events resulting in intravenous diuretics in an urgent care setting, and 34 of the 38 worsening heart-failure events resulting in intensification of oral diuretics. Because there was no prespecified plan to adjust for multiple comparisons for analyses other than the primary and key secondary end points, results are reported as point estimates and 95% confidence intervals. The widths of these confidence intervals have not been adjusted for multiplicity; therefore, the intervals should not be used in place of a hypothesis test.

† Values are hazard ratios for the first primary end point and its components; all other values are differences, except for NT-proBNP, which is the ratio of the adjusted geometric mean ratios. The treatment differences are shown as medians for all key secondary end points and physiological and laboratory measurements.

‡ Values are the Hodges–Lehmann estimate of the median difference and corresponding 95% confidence interval.

§ P values were calculated with the use of the stratified Wilcoxon test, with the analysis stratified according to recent heart-failure decompensation, history of type 2 diabetes, and baseline body-mass index (<35 or ≥35).

¶ The data were log-transformed before the analysis.

‖ NT-proBNP was measured in picograms per milliliter.

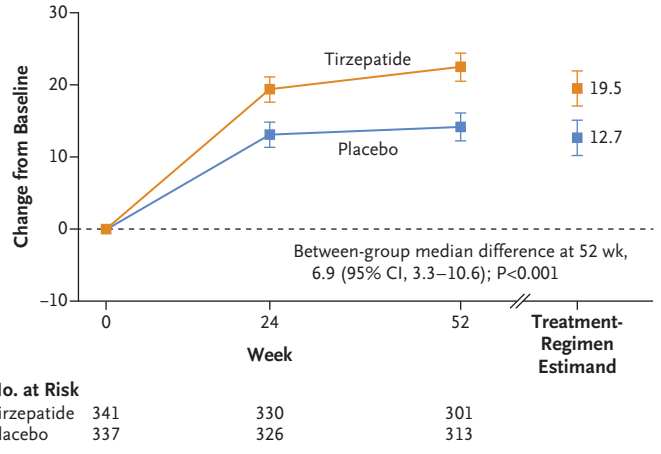


Figure 2. Change in Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS).

The KCCQ-CSS was assessed at baseline and at 24 and 52 weeks. Shown is the mean change from baseline, assessed in a primary prespecified analysis. The changes at 24 and 52 weeks are derived from a mixed-model, repeated-measures analysis without imputations of missing data. The treatment-regimen estimand is the change in the KCCQ-CSS at 52 weeks as assessed with an analysis of covariance, with missing data at 52 weeks imputed with the use of multiple imputation. The between-group difference in the change in the KCCQ-CSS was analyzed with the use of the Hodges–Lehmann method, with multiple imputation of missing data, to estimate the median difference regardless of patient adherence to the regimen, along with two-sided 95% confidence intervals. I bars indicate 95% confidence intervals.

Figure 3 (facing page). Effect of Tirzepatide on Primary End Points.

Shown is the effect of tirzepatide on the dual primary end points in prespecified subgroups defined according to baseline variables. Because there was no prespecified plan to adjust for multiple comparisons for these subgroups, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used in place of a hypothesis test. The HFpEF-ABA is a clinical model that estimates the probability that a patient has heart failure with preserved ejection fraction (HFpEF) on the basis of age, body-mass index, and history of atrial fibrillation (ABA), with higher scores indicating a higher probability. Recent heart-failure decompensation refers to hospitalization or urgent care visit for worsening heart failure within the 12 months before enrollment. GFR denotes glomerular filtration rate, and NT-proBNP N-terminal pro–B-type natriuretic peptide.

PHYSIOLOGICAL MEASUREMENTS AND SAFETY

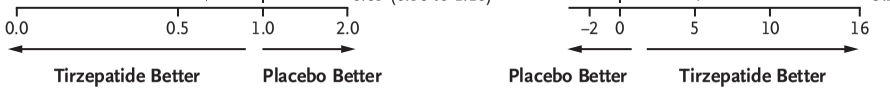
The effects of tirzepatide on systolic blood pressure and heart rate at 52 weeks are shown in Table 2. The number of serious adverse events appeared to be similar in the two groups (Table S6). Nonfatal adverse events leading to discontinuation of the regimen occurred in 23 patients (6.3%) in the tirzepatide group and in 5 patients (1.4%) in the placebo group; 15 patients (4.1%) in the tirzepatide group, but none in the placebo group, discontinued the regimen because of gastrointestinal symptoms.

DISCUSSION

The SUMMIT trial was designed to evaluate prospectively the long-term effects of tirzepatide on major adverse heart-failure outcomes, with death from cardiovascular causes and worsening heart-failure events originally assessed as part of a composite end point that included functional assessments and later assessed as a stand-alone primary composite end point. We observed a lower risk of a composite primary end-point event with tirzepatide than with placebo over a median of 2 years, in particular with respect to fewer worsening heart-failure events resulting in hospitalization or use of intravenous drugs in an urgent care setting. This benefit was paralleled by an improvement in health status (assessed by the KCCQ-CSS) and exercise tolerance (assessed by the 6-minute walk distance) and by a decrease in body weight and in high-sensitivity CRP level, a marker of systemic inflammation. These results were similar to those reported in meta-analyses of the effects of semaglutide in patients with heart failure with preserved ejection fraction.[8,9,13]

In contrast to earlier trials, the SUMMIT trial did not require patients to have increased levels of natriuretic peptides, because these peptides may not be meaningfully elevated in many patients with obesity-related heart failure with preserved ejection fraction, despite increased cardiac filling pressures and substantial functional impairment.[1,14-16] Among patients who are likely to have heart failure with preserved ejection fraction, the measurement of natriuretic peptides does not add meaningfully to the identification of the disease.[12] Although the median NT-proBNP level at baseline in the SUMMIT trial was less than 200 pg per milliliter, patients had marked limitation of health status and exercise tolerance, and nearly half had had worsening heart failure resulting in hospitalization or intravenous treatment within the previous 12 months. The patients

Subgroup	Tirzepatide	Placebo	Hazard Ratio for Death from Cardiovascular Causes or a Worsening Heart-Failure Event (95% CI)	KCCQ-CSS Treatment Difference (95% CI)
	no. of patients with event/ no. of patients at risk			
Age				
<65 yr	13/158	17/166	0.79 (0.38 to 1.64)	6.41 (1.29 to 11.53)
≥65 yr	23/206	39/201	0.53 (0.32 to 0.89)	7.86 (3.45 to 12.25)
Sex				
Female	20/200	29/193	0.66 (0.38 to 1.18)	8.11 (3.50 to 12.72)
Male	16/164	27/174	0.61 (0.33 to 1.13)	5.50 (0.87 to 10.12)
Body-mass index				
<35	12/147	23/148	0.47 (0.23 to 0.95)	4.56 (–0.52 to 9.65)
≥35	24/217	33/219	0.72 (0.43 to 1.23)	8.30 (3.99 to 12.62)
History of type 2 diabetes				
Yes	16/174	28/178	0.58 (0.31 to 1.07)	6.23 (1.77 to 10.70)
No	20/190	28/189	0.66 (0.37 to 1.18)	7.47 (2.67 to 12.26)
HFpEF-ABA score				
<0.8	8/133	12/140	0.68 (0.28 to 1.67)	3.60 (–1.66 to 8.87)
≥0.8	28/231	44/227	0.60 (0.38 to 0.97)	8.91 (4.69 to 13.12)
Recent heart-failure decompensation				
Yes	19/171	24/172	0.75 (0.41 to 1.38)	7.22 (2.33 to 12.11)
No	17/193	32/195	0.52 (0.29 to 0.95)	6.49 (2.03 to 10.95)
Ejection fraction				
<60%	18/141	28/144	0.60 (0.33 to 1.09)	5.30 (–0.12 to 10.73)
≥60%	18/223	28/223	0.60 (0.33 to 1.09)	8.08 (3.97 to 12.19)
NT-proBNP				
<200 pg/ml	11/186	24/197	0.44 (0.22 to 0.90)	6.56 (2.13 to 11.00)
≥200 pg/ml	25/178	32/170	0.77 (0.45 to 1.29)	7.38 (2.37 to 12.40)
KCCQ-CSS				
<Median	20/173	39/192	0.52 (0.30 to 0.90)	9.07 (3.71 to 14.43)
≥Median	16/191	17/174	0.79 (0.40 to 1.56)	4.43 (0.05 to 8.81)
Estimated GFR				
<60 ml/min/1.73 m^2	22/167	34/168	0.61 (0.36 to 1.05)	7.85 (3.06 to 12.65)
≥60 ml/min/1.73 m^2	14/197	22/199	0.64 (0.33 to 1.26)	6.00 (1.39 to 10.60)
Systolic blood pressure				
<130 mm Hg	18/185	36/189	0.47 (0.27 to 0.83)	7.27 (2.44 to 12.10)
≥130 mm Hg	18/179	20/178	0.90 (0.48 to 1.70)	6.21 (1.64 to 10.77)
Use of mineralocorticoid receptor antagonist				
Yes	16/131	24/125	0.58 (0.31 to 1.09)	10.10 (4.56 to 15.65)
No	20/233	32/242	0.63 (0.36 to 1.10)	5.22 (1.09 to 9.34)



enrolled in the STEP-HFpEF trials that assessed semaglutide had a baseline NT-proBNP level twice that of patients in the SUMMIT trial,[8,9] but the SUMMIT trial had higher percentages of patients with heart-failure events because we specified additional criteria to enrich the risk of heart failure in our trial population. The effects of tirzepatide on the two primary end points did not appear to be attenuated in patients with NT-proBNP levels of less than 200 pg per milliliter (Fig. 3). Taken collectively, these findings suggest that a requirement for markedly elevated levels of natriuretic peptides to initiate treatment might exclude many patients with obesity-related heart failure with preserved ejection fraction from the benefits of tirzepatide.

Although gastrointestinal symptoms were common with tirzepatide, in general they dissipated over time and led to treatment discontinuation in only 4% of patients. Serious adverse events appeared to occur with similar frequency in the two groups. Death from cardiovascular causes and death from undetermined causes (which were grouped together as death from cardiovascular causes, in contrast with the design in other trials involving patients with heart failure with preserved ejection fraction) occurred in 10 patients in the tirzepatide group and in 5 patients in the placebo group, but only four of these deaths were preceded by worsening heart failure, a finding consistent with the premise that death from cardiovascular causes in patients with heart failure with preserved ejection fraction may not reflect the progression of heart failure.[17] The results of analyses of the composite primary end point that excluded deaths from undetermined causes were consistent with our reported treatment effects (Table S5). Of note, in trials that assessed long-term outcomes, patients with diabetes or obesity who were treated with GLP-1 receptor agonists had a decreased risk of death from cardiovascular causes and death from any cause.[18,19]

The effects of tirzepatide are probably related to its ability to reduce fat mass, thus diminishing the resulting expansion of plasma volume and inflammatory response that appear to underlie the pathogenesis of heart failure with preserved ejection fraction. Patients treated with tirzepatide had a decline in high-sensitivity CRP level, as was observed in trials with semaglutide.[8,9] Independent of weight loss, agonism of GLP-1 receptors may reverse the proinflammatory biologic features of adipocytes,[20] thus muting their ability to cause microvascular rarefaction and fibrosis in the myocardium.[3,4,21] GIP receptors are abundant in epicardial adipocytes,[22] and it is possible that the addition of GIP receptor agonism to GLP-1 receptor agonism not only results in additional weight loss but also suppresses inflammation in adjacent heart tissue.[23,24] The effects of tirzepatide on lowering systolic blood pressure and increasing heart rate[11,25] may contribute to its beneficial effects in patients with heart failure with preserved ejection fraction.[26-28]

An important limitation of the trial is that we specified BMI of at least 30 as an eligibility criterion; however, many patients with heart failure with preserved ejection fraction have a BMI of less than 30 but have an abnormal waist-to-height ratio (i.e., >0.5),[29] which is a more reliable indicator of excess visceral adiposity.[30] Further studies involving such patients are needed.

In this trial, weekly treatment with tirzepatide for a median of 2 years reduced the risk of a composite of worsening heart-failure events or death from cardiovascular causes while improving health status in patients with heart failure with preserved ejection fraction, obesity, and functional impairment.

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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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