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ORIGINAL ARTICLE

Tirzepatide reduces the predicted risk of atherosclerotic cardiovascular disease and improves cardiometabolic risk factors in adults with obesity or overweight: SURMOUNT-1 post hoc analysis

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Abstract

Aim: To assess the effect of tirzepatide on long-term risk of atherosclerotic cardiovascular disease (ASCVD) among people with obesity or overweight without diabetes from SURMOUNT-1.

Materials and Methods: SURMOUNT-1, a phase 3 trial, evaluated the efficacy and safety of tirzepatide in adults with body mass index ≥30 or ≥27 kg/m^2 and at least one weight-related complication, excluding diabetes. Participants were randomly assigned to tirzepatide (5/10/15 mg) or placebo. Changes from baseline in cardiometabolic variables were assessed. The predicted 10-year ASCVD risk scores were calculated (American College of Cardiology/American Heart Association risk engine) at baseline, week 24, and week 72 in SURMOUNT-1 participants without a history of ASCVD. Percent change in risk scores from baseline to weeks 24 and 72 was compared between tirzepatide and placebo using mixed model for repeated measures analysis. Analyses were also conducted in participants with intermediate to high risk at baseline.

Results: Tirzepatide-treated groups demonstrated reductions in cardiometabolic variables over 72 weeks. In participants without a history of ASCVD (N = 2461), the baseline median risk score was low and did not differ across groups (1.5%–1.6%). Relative change in risk from baseline to week 72 was greater for tirzepatide (−23.5% to −16.4%) than placebo (12.7%; $P < 0.001$). Relative change among participants with intermediate-to-high baseline risk was significantly greater for tirzepatide ($P < 0.05$). Intermediate-to-high-risk participants demonstrated similar relative change but greater absolute risk reduction compared to the overall population.

Conclusion: Tirzepatide treatment significantly reduced the 10-year predicted risk of ASCVD versus placebo in patients with obesity or overweight without diabetes.

KEYWORDS
ASCVD, obesity, tirzepatide

1 | INTRODUCTION

Obesity is a chronic, progressive disease with a rising prevalence,[1] and more than 500 million adults are currently impacted worldwide.[2] There are numerous serious complications associated with obesity, including type 2 diabetes (T2D), hypertension, dyslipidaemia, cardiovascular disease (CVD), and CVD mortality.[3–8] Effective obesity treatments may reduce obesity-related morbidity and mortality, including atherosclerotic CVD (ASCVD) and CVD mortality.[3,5,9]

Treatment of obesity requires an individualized, multifaceted approach. Although previous clinical recommendations have focused on lifestyle changes, including dietary modification and increased physical activity, as the first line of treatment, current clinical guidelines increasingly recognize the benefits of anti-obesity pharmacotherapy as an adjunct to lifestyle modification.[10–13] Long-acting glucagon-like peptide-1 (GLP-1) receptor agonists have demonstrated promising weight reduction in recent studies,[14,15] together with improvements in CVD risk factors including waist circumference, systolic blood pressure (SBP), triglycerides, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) in individuals with obesity.[16,17] In addition, commercially available GLP-1 receptor agonists have demonstrated improvements in major adverse cardiovascular events in patients with T2D.[18] Like GLP-1, glucose-dependent insulinotropic polypeptide (GIP) is an incretin hormone involved in energy and nutrient metabolism; combining GLP-1 and GIP receptor agonism has the potential to enhance the weight-loss effects seen with GLP-1 receptor agonism alone.[19,20]

Tirzepatide, a novel, once-weekly GIP and GLP-1 dual receptor agonist, is approved for treatment of T2D and is in development for chronic weight management in patients with obesity. Tirzepatide has previously shown significant glycated haemoglobin (HbA1c) and weight reduction in the SURPASS clinical trial programme in adults with T2D,[21–25] without any indication of an increase in the risk of major cardiovascular events.[25,26] A recent phase 3, randomized clinical trial, SURMOUNT-1, which investigated the safety and efficacy of tirzepatide in people with obesity or overweight, without diabetes, demonstrated substantial and sustained mean body weight reduction of up to 22.5% (NCT04184622).[27] Data from SURMOUNT-1 have also shown improvements in cardiometabolic parameters, including SBP, diastolic blood pressure (DBP), and lipid levels at week 72.

Although the improvements in cardiovascular risk factors in SURMOUNT-1 are promising, the effect of tirzepatide on the long-term risk of ASCVD in people with obesity or overweight is still unknown. Therefore, the aim of this study was to assess the impact of tirzepatide treatment on the 10-year predicted risk of ASCVD among SURMOUNT-1 trial participants with obesity or overweight.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a post hoc analysis of the SURMOUNT-1 clinical trial using patient-level data to compare the percent change in risk for long-term ASCVD outcomes from baseline up to 72 weeks between tirzepatide- and placebo-treated groups. Details of the SURMOUNT-1 study design have been published previously.[27] Briefly, SURMOUNT-1, a phase 3, randomized, double-blind, placebo-controlled study, included adults (age ≥18 years) with obesity (body mass index [BMI] ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2 and at least one weight-related complication) without diabetes. Participants were randomly assigned in a 1:1:1:1 ratio to receive tirzepatide at a dose of 5, 10 or 15 mg, or placebo, administered subcutaneously once weekly for 72 weeks in combination with lifestyle intervention. Tirzepatide treatment was initiated at 2.5 mg and escalated every 4 weeks in 2.5-mg increments during the dose-escalation period.

The original SURMOUNT-1 trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Protocols were approved by independent ethics committees or institutional review boards.

2.2 | Study population

The cardiometabolic outcome analysis used the efficacy analysis set (EAS) from the SURMOUNT-1 trial, which included data obtained during the treatment period from 2539 participants in the modified intention-to-treat (mITT) population. The EAS included all mITT participants (all randomly assigned participants who received at least one dose of study drug), excluding data after discontinuation of study drug (last dose date +7 days). The post hoc risk prediction analysis excluded any participant who had a lifetime history of CVD events at baseline. CVD events at baseline are defined in Supplementary Table S1. The original study participant consent covered the analyses conducted in the present study.

2.3 | Variables and outcomes

The cardiometabolic outcome variables were measured at various time points between baseline and week 72 in the original SURMOUNT-1 mITT population. Changes in antihypertensive and antihyperlipidaemic therapy and cardiometabolic variables, including waist circumference, lipids, blood pressure, HbA1c and fasting glucose, were assessed. The demographic and baseline clinical characteristics were summarized descriptively in the study population by treatment group in participants without CVD events at baseline. The 10-year predicted ASCVD risk was calculated at baseline, week 24 and week 72, and the percent change from baseline to weeks 24 and 72 was compared between tirzepatide 5, 10 and 15 mg and placebo. The risk scores were also grouped into low (<5.0%), borderline (≥5.0% to <7.5%), intermediate (≥7.5% to <20%), or high (≥20.0%) risk categories according to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines. Due to the low overall predicted ASCVD risk scores, the 10-year predicted risk score and percent change from baseline were also assessed in the intermediate-to-high baseline risk score

group. Additionally, the change in risk factors over time were assessed. The model input of smoking status was collected at baseline and assumed to remain constant throughout the study period. Throughout the 72-week study period, the adverse event of T2D was reported in five participants (four in the placebo group, and one in the tirzepatide group). However, since the number of events was low and they were not adjudicated, incidence of T2D was not considered in the trial population for the risk engine.

The ASCVD predicted risk was calculated using a risk engine developed by the ACC/AHA in 2013.[28,29] Several cohorts were used to develop the model, including African American and White participants aged 40 to 79 years. The model inputs included sex, race, age, total cholesterol, HDL, SBP, treatment for blood pressure, presence of diabetes mellitus, and current smoking status. The ACC/AHA risk engine was developed using a Cox regression model. The model inputs were used in a cross-sectional manner, such that the values for a given period are not influenced or calculated relative to other time points. Week 72 was the primary study endpoint and week 24 was an interim visit for the SURMOUNT-1 trial. ASCVD risk was calculated at these time points as all necessary model inputs were collected at both time points. Missing predictors were not imputed. Risk scores for participants with missing predictors were not calculated.

2.4 | Analyses

Mean changes in cardiometabolic parameters were derived from a mixed model for repeated measures (MMRM) analysis of the EAS or the safety analysis set. The lipid parameters were analysed on a log-scale and reported as mean percent change over time. The relative change from baseline of the risk scores was analysed using an MMRM with model terms of baseline risk score, country, treatment group, time point, and treatment-by-time-point interaction. Due to its skewness, the risk scores were analysed on a log-scale in the MMRM analysis and reported as mean percent change. The number and percentage of participants in each risk score category (low, borderline, intermediate and high) were reported by treatment group at each time point. The changes in the participants' risk categories from baseline to weeks 24 and 72 were also analysed using a repeated measurement ordinal logistic regression on the following three ordered outcomes:

1. Improved ASCVD risk profile: participant shifted from a higher risk category at baseline to a lower risk category at week 24 or 72.
2. Worsened ASCVD risk profile: participant shifted from a lower risk category at baseline to a higher risk category at week 24 or 72.
3. Stable ASCVD risk profile: participant stays in the same risk category at baseline and week 24 or 72.

Treatment group (pooled tirzepatide and placebo), time point, treatment-group-by-time-point interaction, and baseline risk score were included as model terms in the regression. The odds ratios of tirzepatide versus placebo were assumed to be the same for the outcome of improved ASCVD risk profile relative to maintaining a stable ASCVD risk profile and for the outcome of stable ASCVD risk profile relative to the worsened risk profile.

The primary analysis was performed among all participants free of CVD at baseline without consideration for CVD events that occurred during the study. Sensitivity analyses evaluated the robustness of this methodological choice. Sensitivity analysis 1 was conducted among participants aged ≥40 to ≤79 years at baseline to reflect the population in which the ACC/AHA risk engine was developed. Sensitivity analysis 2 excluded participants who experienced a CVD event post-baseline. For this sensitivity analysis, participants who experienced a CVD event prior to week 24 were excluded from the risk calculation at weeks 24 and 72, and participants who experienced a CVD event prior to week 72 were excluded from the week 72 risk score calculation. This was consistent with the intended use of the ACC/AHA risk engine for the prediction of primary CVD events. Subgroup analyses examined the 10-year predicted risk of ASCVD by BMI status at baseline and prediabetes status at baseline.

The analysis was conducted using SAS software version 9.4 (2016; SAS Institute Inc., Cary, North Carolina).

3 | RESULTS

3.1 | Cardiometabolic outcomes

Cardiometabolic endpoints were examined in the full mITT SURMOUNT-1 participants (N = 2539). Cardiometabolic outcomes examined during the SURMOUNT-1 trial included waist circumference, fasting serum glucose, SBP, DBP, HbA1c, serum non-HDL cholesterol, serum HDL cholesterol, serum LDL cholesterol, and serum triglycerides.

Compared with placebo, decreases in waist circumference, SBP and DBP from baseline were observed in all three tirzepatide treatment arms (5, 10 or 15 mg/wk) as early as week 4 and continued until week 72 (Figure 1A,C,D). Fasting serum glucose, HbA1c, and serum triglycerides were significantly reduced from baseline, starting at week 12 through to week 72 in all tirzepatide treatment groups (Figure 1B,E,I). Improvements in serum lipids were observed by 24 weeks and maintained until 72 weeks including reductions in LDL and non-HDL cholesterol (Figure 1H,F), while increases in HDL were only demonstrated at the 72-week time point (Figure 1G).

Use of concomitant lipid-lowering and antihypertensive medications was allowed in the SURMOUNT-1 trial. Most participants were not using antihypertensive or lipid-lowering therapies at either baseline or the postbaseline period; however, slightly more tirzepatide-treated participants (2.9%–5.2%) than placebo-treated participants (2.0%) experienced decreased antihypertensive medication use from baseline to safety follow-up (Figure 1J,K).

3.2 | Median 10-year predicted risk of ASCVD

Among the 2539 SURMOUNT-1 mITT participants, 78 participants (3.1%) had previous CVD event history at baseline and were excluded

from ASCVD predicted risk analyses. Of the 2461 participants included in this analysis, 622 were included in the placebo group, 614 were treated with tirzepatide 5 mg, 616 with tirzepatide 10 mg, and 609 with tirzepatide 15 mg. The baseline characteristics were similar across treatment groups for the participants without CVD events at baseline (Table 1). The mean (standard deviation [SD]) age of participants was 44.5 (12.3) years, the mean (SD) BMI was 38.0 (6.8) kg/m^2, and 68.4% were female.

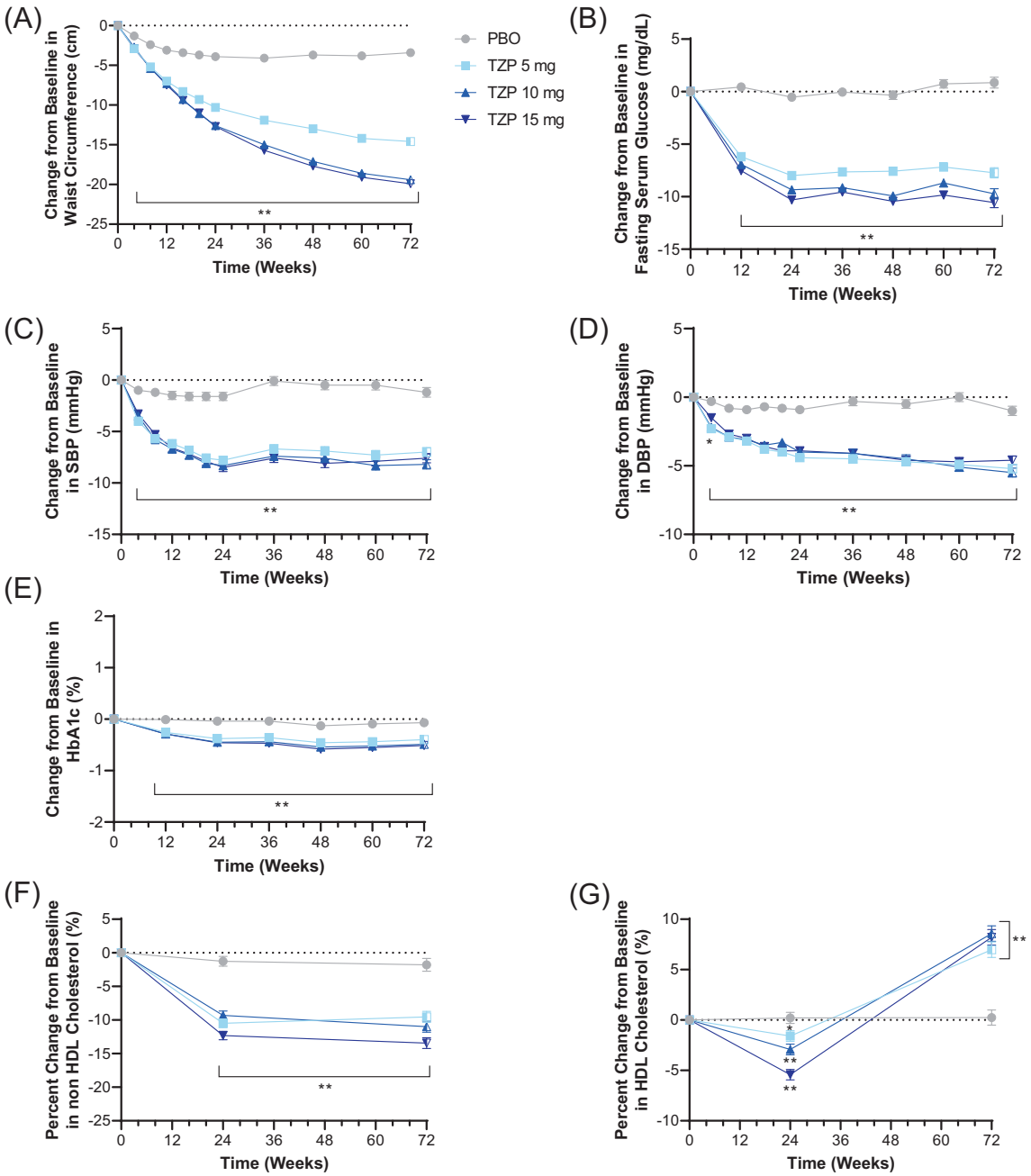

FIGURE 1 Effect of tirzepatide (TZP) on cardiometabolic risk factors in the SURMOUNT-1 population. Mean change from baseline in (A) waist circumference, (B) fasting serum glucose, (C) systolic blood pressure, (D) diastolic blood pressure, and (E) glycated haemoglobin (HbA1c) over time, derived from a mixed model for repeated measures (MMRM) analysis for the efficacy estimand. Percent change from baseline in (F) non-high-density lipoprotein (HDL) cholesterol, (G) HDL cholesterol, (H) low-density lipoprotein (LDL) cholesterol, and (I) triglycerides over time, derived from a MMRM analysis using the efficacy estimand. Error bars indicate standard error. Percentage of participants who changed the status of (J) lipid-lowering or (K) antihypertensive medication. All comparisons between TZP dose groups and placebo (PBO) were significant at $^{**}P < 0.001$. Comparison for change from baseline in diastolic blood pressure (D) between TZP 15 mg vs. PBO at week 4 was significant at $^{*}P < 0.05$. Comparison for change from baseline in HDL (G) between TZP 5 mg vs. PBO at week 24 was significant at $^{*}P < 0.05$. Comparison for change from baseline in LDL (H) between TZP 5 mg vs. PBO at week 72 was significant at $^{*}p < 0.05$. DBP, diastolic blood pressure; SBP, systolic blood pressure. To convert HbA1c% to mmol/mol use: A1C(mmol/mol) = 10.929 * (A1C(%) - 2.15).

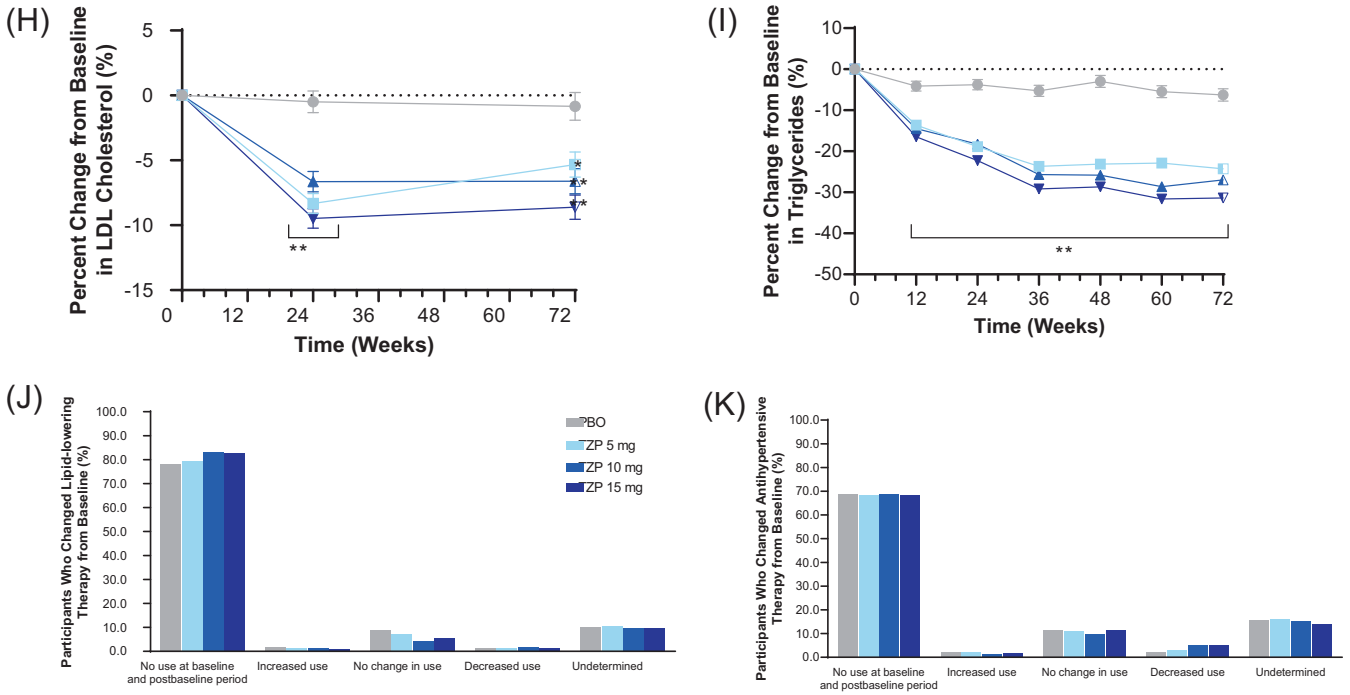

FIGURE 1 (Continued)

There were 232 (9.4%) and 497 patients (20.2%) who had missing risk scores at weeks 24 and 72, respectively, primarily due to discontinuation of treatment or initiation of rescue therapy. The placebo group tended to have more missing data than the tirzepatide groups, consistent with greater treatment and study discontinuation in the placebo group in the SURMOUNT-1 study. The baseline median 10-year ASCVD predicted risk scores ranged from 1.5% to 1.6%, with no difference among the four treatment groups (Figure 2A). The majority of patients (80.4%) were in the low-risk group (risk score <5%), 8.6% of patients were in the borderline-risk group (risk score ≥5% and <7.5%), 10.0% of patients were in the intermediate-risk group (risk score ≥7.5% and <20%), and only 1.0% patients were in the high-risk group (risk score ≥20%). The median risk scores for tirzepatide 5, 10, 15 mg and placebo groups were 1.4%, 1.2%, 1.3% and 1.6% at week 24, and 1.3%, 1.2%, 1.1% and 1.7% at week 72, respectively. The relative change in predicted risk from baseline to week 24 was −16.7%, −19.0%, −17.0% and 2.5% for tirzepatide 5, 10, 15 mg and placebo, respectively (Figure 2B). At week 72, the relative change in predicted risk was −16.4%, −23.5%, −22.4% and 12.7%, respectively. There were significantly greater relative reductions in risk for tirzepatide groups at weeks 24 and 72 compared with placebo ($p < 0.001$). The change in risk factors over time are shown in Supplementary Table S2.

A total of 244 participants were considered to have intermediate-to-high risk for ASCVD (risk score ≥7.5%) at baseline. For this intermediate-to-high-risk group, the median predicted risk scores in tirzepatide groups ranged from 10.5% to 11.3%, 9.4% to 10.0%, and 9.0% to 11.3% at baseline, week 24, and week 72, respectively (Figure 2C). The median predicted risk score was 10.1%, 10.7% and 11.7% for the placebo group at baseline, week 24 and week 72, respectively. The relative change in predicted risk from baseline at week 24 was between −22.2% and −16.0% for the tirzepatide groups and −0.7% for placebo (Figure 2D). At week 72, the relative changes in predicted risk were −10.3%, −20.6%, −16.1% and 6.4% for tirzepatide 5, 10 and 15 mg, and placebo groups, respectively. With tirzepatide treatment, there was a significantly greater relative reduction in risk for the intermediate-to-high-risk ASCVD group compared with placebo ($p < 0.05$), consistent with the primary overall analysis.

Changes in participants' ASCVD risk category classifications from baseline were examined at week 24 and week 72 (Tables 2 and S3). At week 24, 6.9% of participants treated with tirzepatide and 2.9% in the placebo group had improved ASCVD risk profiles, indicating that participants treated with tirzepatide had 2.2 times greater odds (95% confidence interval [CI] 1.6, 3.0; $P < 0.001$) of improving their risk score category from baseline to week 24 than placebo-treated participants. Similarly, at week 72, 7.3% of participants treated with tirzepatide and 3.1% in the placebo group had improved ASCVD risk profiles; participants treated with tirzepatide had 2.4 times greater odds (95% CI 1.7, 3.5; $P < 0.001$) of improving their risk score category from baseline to week 72 than those in the placebo group.

A similar pattern with a larger magnitude was observed among the subgroup of participants with intermediate-to-high baseline ASCVD risk. At week 24, participants treated with tirzepatide had 2.8 times greater odds (95% CI 1.4, 5.6; $P = 0.003$) of improving their ASCVD risk score category from baseline (31.5%) compared to the placebo group (13.3%). At week 72, participants in the tirzepatide group had 2.9 times greater odds (95% CI 1.3, 6.2; $P = 0.008$) of

TABLE 1 Demographic and baseline clinical characteristics of study population

	Placebo (N = 622)	TZP 5 mg (N = 614)	TZP 10 mg (N = 616)	TZP 15 mg (N = 609)	Total (N = 2461)
Age, years	44.1 ± 12.5	45.2 ± 12.5	44.3 ± 12.2	44.4 ± 12.1	44.5 ± 12.3
Female	428 (68.8)	420 (68.4)	418 (67.9)	418 (68.6)	1684 (68.4)
Current smoker, yes	66 (10.6)	91 (14.8)	73 (11.9)	84 (13.8)	314 (12.8)
Antihypertensive medications, yes	167 (26.9)	182 (29.6)	178 (28.9)	175 (28.7)	702 (28.5)
Race					
White	434 (69.8)	432 (70.4)	437 (70.9)	428 (70.3)	1731 (70.3)
Asian	69 (11.1)	67 (10.9)	67 (10.9)	64 (10.5)	267 (10.8)
Black or African American	55 (8.8)	48 (7.8)	47 (7.6)	49 (8.0)	199 (8.1)
Native Hawaiian or other pacific islander	2 (0.3)	2 (0.3)	2 (0.3)	3 (0.5)	9 (0.4)
American Indian or Alaska native	56 (9.0)	56 (9.1)	57 (9.3)	57 (9.4)	226 (9.2)
Multiple	6 (1.0)	9 (1.5)	6 (1.0)	8 (1.3)	29 (1.2)
Ethnicity					
Hispanic or Latino	301 (48.4)	303 (49.3)	293 (47.6)	291 (47.8)	1188 (48.3)
Not Hispanic or Latino	271 (43.6)	265 (43.2)	272 (44.2)	268 (44.0)	1076 (43.7)
Not reported	50 (8.0)	46 (7.5)	51 (8.3)	50 (8.2)	197 (8.0)
Country/Region					
United States	279 (44.9)	273 (44.5)	279 (45.3)	274 (45.0)	1105 (44.9)
Brazil	57 (9.2)	58 (9.4)	60 (9.7)	60 (9.9)	235 (9.5)
China	6 (1.0)	8 (1.3)	6 (1.0)	6 (1.0)	26 (1.1)
India	8 (1.3)	9 (1.5)	9 (1.5)	6 (1.0)	32 (1.3)
Japan	32 (5.1)	30 (4.9)	29 (4.7)	30 (4.9)	121 (4.9)
Mexico	106 (17.0)	110 (17.9)	106 (17.2)	106 (17.4)	428 (17.4)
The Russian Federation	30 (4.8)	27 (4.4)	27 (4.4)	24 (3.9)	108 (4.4)
Taiwan	15 (2.4)	12 (2.0)	13 (2.1)	16 (2.6)	56 (2.3)
Argentina	89 (14.3)	87 (14.2)	87 (14.1)	87 (14.3)	350 (14.2)
HbA1c, %	5.6 ± 0.4	5.6 ± 0.4	5.5 ± 0.4	5.6 ± 0.4	5.6 ± 0.4
eGFR, mL/min/1.73 m^2	98.5 ± 18.3	98.1 ± 17.7	98.8 ± 17.9	98.7 ± 17.5	98.5 ± 17.8
Baseline ASCVD risk score group					
Low risk	495 (79.6)	475 (77.4)	505 (82.0)	503 (82.6)	1978 (80.4)
Borderline risk	59 (9.5)	56 (9.1)	45 (7.3)	51 (8.4)	211 (8.6)
Intermediate risk	62 (10.0)	76 (12.4)	60 (9.7)	49 (8.0)	247 (10.0)
High risk	6 (1.0)	7 (1.1)	6 (1.0)	6 (1.0)	25 (1.0)

Note: Data are n (%) or mean ± SD and include all patients in the efficacy analysis set with no baseline CVD, unless indicated otherwise. To convert HbA1c% to mmol/mol use: A1C(mmol/mol) = 10.929 * (A1C(%) - 2.15)

Abbreviations: CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; N, number of participants in population; n, number of participants in the specified category; SD, standard deviation; TZP, tirzepatide.

improving their ASCVD risk score (31.9%) compared to those in the placebo group (12.8%).

3.3 | Ten-year predicted risk of ASCVD subgroup and sensitivity analyses

The effect of tirzepatide treatment on 10-year risk of ASCVD by baseline BMI (<35 kg/m^2, ≥35 and <40 kg/m^2, or ≥40 kg/m^2) and by baseline prediabetes status (with or without prediabetes) was examined. Similar to the primary analysis, all tirzepatide treatment groups demonstrated significantly greater relative reduction in ASCVD predicted risk compared with placebo when stratified by BMI or by prediabetes status (Supplementary Figure S1). Two sensitivity analyses were conducted. For the first sensitivity analysis, only participants aged between 40 and 79 years were included; 892 (35.1%) of mITT participants aged <40 or >79 years were excluded from the analysis. For the second analysis, data from participants who

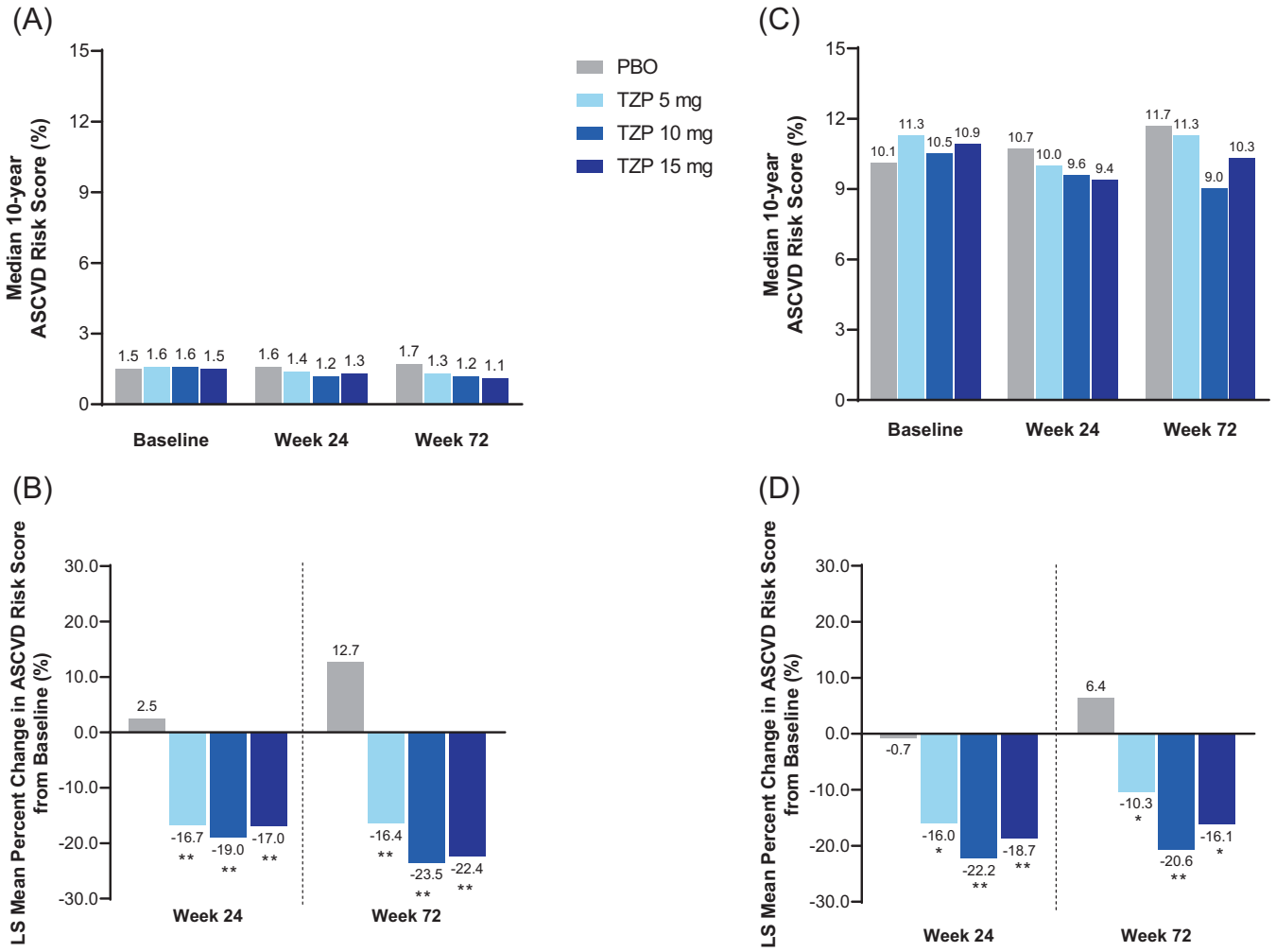

FIGURE 2 Effect of tirzepatide (TZP) on 10-year predicted risk of atherosclerotic cardiovascular disease (ASCVD) in participants with obesity or overweight. (A) Median ASCVD risk scores at baseline, week 24, and week 72 in participants with obesity or overweight. (B) Percent change in ASCVD risk scores from baseline at weeks 24 and 72 in participants with obesity or overweight. (C) Median ASCVD risk scores at baseline, week 24, and week 72 in participants with obesity or overweight and intermediate-to-high risk at baseline. (D) Percent change in ASCVD risk scores from baseline at weeks 24 and 72 in participants with obesity or overweight and intermediate-to-high risk at baseline. All comparisons of risk reductions from baseline between TZP dose groups and placebo (PBO) were significant at $^{**}P < 0.001$, $^{*}P < 0.05$ vs. placebo. Least squares (LS) means are presented in the figures. Percent change in 10-year predicted ASCVD risk from baseline to week 24 and week 72 was derived from a mixed model for repeated measures (MMRM) using the efficacy analysis set (EAS). The EAS included data obtained during the treatment period from the modified intention-to-treat population (all randomly assigned participants who received at least 1 dose of study drug), excluding data after discontinuation of study drug (last dose date +7 days). Change from baseline was calculated on the log-scale and used as the outcome in the MMRM model with model terms of log baseline score, country, treatment group, time point, and treatment-group-by-time-point interaction. N, number of subjects in the population with baseline and post-baseline value at the specified time point.

experienced a CVD event during the study treatment period (three participants at week 24 and 10 at week 72) were excluded. These results were also consistent with the primary analysis (Supplemental Figure S2).

4 | DISCUSSION

This post hoc analysis of SURMOUNT-1 demonstrated that tirzepatide significantly reduces the 10-year predicted risk of ASCVD compared with placebo in people with obesity or overweight. Importantly, participants with higher ASCVD risk at baseline demonstrated even larger reductions in risk with tirzepatide treatment. Participants treated with tirzepatide also showed favourable profiles with respect to changes in their risk categories. Specifically, more participants' ASCVD risk categories improved and fewer worsened at weeks 24 and 72 with tirzepatide compared to placebo. The improvement in the ASCVD risk score was accompanied by significant improvements in multiple cardiometabolic risk factors (waist circumference, blood pressure, fasting glucose, HbA1c, and lipid levels) in the full SURMOUNT-1 population. The subgroup and sensitivity analyses pertaining to ASCVD risk score were consistent with the primary analysis and indicate that tirzepatide

TABLE 2 Shift in atherosclerotic cardiovascular disease risk categories from baseline to weeks 24 and 72

Visit/time	Outcome	Observed proportion, n (%)		Odds ratio (vs. placebo)	
		Placebo	Pooled TZP	Estimate (95% CI)	*P* value
All participants					
Week 24	Improved	16 (2.9)	116 (6.9)	2.2 (1.6, 3.0)	<0.001
	Stable	495 (91.0)	1528 (90.7)		
	Worsened	33 (6.1)	41 (2.4)		
	Total, N	544	1685		
Week 72	Improved	14 (3.1)	111 (7.3)	2.4 (1.7, 3.5)	<0.001
	Stable	391 (87.9)	1336 (88.0)		
	Worsened	40 (9.0)	72 (4.7)		
	Total, N	445	1519		
Participants with intermediate-to-high risk at baseline					
Week 24	Improved	8 (13.3)	57 (31.5)	2.8 (1.4, 5.6)	0.003
	Stable	51 (85.0)	122 (67.4)		
	Worsened	1 (1.7)	2 (1.1)		
	Total, N	60	181		
Week 72	Improved	6 (12.8)	52 (31.9)	2.9 (1.3, 6.2)	0.008
	Stable	40 (85.1)	105 (64.4)		
	Worsened	1 (2.1)	6 (3.7)		
	Total, N	47	163		

Note: The ASCVD risk scores were grouped into low (<5%), borderline (≥5–<7.5%), intermediate (≥7.5–<20%), or high (≥20%) risk categories. Improved: Participant shifted from a higher risk category at baseline to a lower risk category at week 24 or 72; Stable: Participant stayed in the same risk category at baseline and week 24 or 72; Worsened: Participant shifted from a lower risk category at baseline to a higher risk category at week 24 or 72. The odds ratios were estimated from a repeated measurement ordinal logistic regression using the generalized estimating equations method where the ordered outcome category was modelled. The model terms included baseline risk score, TZP treatment group, time point, and TZP treatment group * time point interaction. Participants who had baseline cardiovascular disease history were excluded from analysis. The adjusted mean proportions from the model for each treatment group are reported in Supplementary Table S3.
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; N, number of participants in the population in the specified treatment group; n, number of participants in the specified category; TZP, tirzepatide.

reduces the risk of ASCVD, irrespective of baseline BMI or prediabetes status. This is the first study to provide indirect evidence on the benefit of tirzepatide treatment for the long-term risk of ASCVD in a population without diabetes. The results of the present study suggest favourable effects of tirzepatide on long-term risk of ASCVD and additional potential of tirzepatide to positively impact patients' quality of life.[30]

Previous analyses have explored the potential effect of tirzepatide on cardiovascular events in individuals with T2D. Specifically, in a phase 3 study, participants with T2D and increased cardiovascular risk treated with tirzepatide showed no increase in major adverse cardiovascular events compared with insulin glargine (hazard ratio 0.74, 95% CI 0.51–1.08).[25] Furthermore, in a meta-analysis, which included five phase 3 tirzepatide trials conducted in patients with T2D, tirzepatide did not increase the risk of major cardiovascular events in participants compared with controls (hazard ratio 0.80, 95% CI 0.57–1.11).[26]

In a phase 3 study investigating the effect of semaglutide, a GLP-1 receptor agonist, on weight loss in patients with obesity or overweight, participants who received semaglutide demonstrated improvements in cardiometabolic risk factors.[15] A separate study assessing the predicted 10-year ASCVD risk in people with obesity or overweight treated with semaglutide showed a trend towards improvement in ASCVD risk, but this trend was nonsignificant.[31] In contrast, the results of a small retrospective study demonstrated a significant decrease in predicted ASCVD risk between baseline and 1 year after initiating semaglutide treatment.[32] The effects of semaglutide on cardiovascular outcomes in people with obesity or overweight without T2D were assessed in a large phase 3 study; patients treated with semaglutide demonstrated a 20% reduction in the risk of major adverse cardiovascular events compared with placebo (SELECT; NCT03574597).[33]

To our knowledge, this is the first analysis aimed at evaluating the effects of tirzepatide on long-term ASCVD risk in people with obesity or overweight. Together, the results indicate that tirzepatide treatment could reduce the 10-year predicted risk of ASCVD for people with obesity or overweight as early as 6 months after treatment

commencement. Although the statistically significant results are promising, the clinical significance of predicted ASCVD risk reduction needs to be confirmed. Currently, the cardiovascular benefits of tirzepatide are being investigated in large, international, phase 3 studies in people with obesity or overweight without diabetes (SURMOUNT-MMO; NCT05556512) and in people with T2D (SURPASS-CVOT; NCT04255433).

This study was strengthened by several factors. First, this analysis used validated models that incorporate multiple risk factors to quantitatively assess risk.[28] The ACC/AHA model was selected over the Framingham model due to its broader generalizability across populations. Second, the analysis included a large, global sample size originally recruited for the SURMOUNT-1 trial, which further increased the generalizability of these results. Finally, the consistency of results from the primary, subgroup, and sensitivity analyses indicates that the data are robust.

Despite the power of the tool used in this study, post hoc analyses have intrinsic limitations. The ACC/AHA risk engine was not developed or validated in populations of people with obesity or overweight exclusively, but the validation cohorts did include large, diverse populations.[29] Additionally, the risk engine calculates the predicted risk of ASCVD but needs to be confirmed with a randomized trial against hard outcomes. Also, a minimum of 2 years (104 weeks) is the US Food and Drug Administration recommendation for a cardiovascular outcomes trial. The duration of the SURMOUNT-1 trial was 72 weeks. Furthermore, while the study focused on both people with obesity and overweight, 95% of the participants had obesity (BMI ≥30 kg/m^2). Finally, the SURMOUNT-1 patient population had a low ASCVD risk profile at baseline, indicating a relatively healthy CVD risk profile in this population, and hence the absolute change in the predicted ASCVD risk score was generally small. This limitation is partially addressed with the subgroup analysis in the intermediate-to-high risk group as well as the analysis on ASCVD risk category changes, as the large sample size of SURMOUNT-1 study still provided a reasonable number of patients with higher risk profiles.

Overall, treatment with tirzepatide significantly reduced the 10-year predicted risk of ASCVD compared with placebo in people with obesity or overweight but without diabetes. The absolute reduction in risk was greater for participants with higher ASCVD risk at baseline.

AUTHOR CONTRIBUTIONS

All authors participated in the interpretation of study results, and in the drafting, critical revision, and approval of the final version of the manuscript. All named authors meet the International Committee of Medical Journal Editors criteria for authorship for this article, take responsibility for the integrity of the entire work, and have given their approval for this version to be published. Emily R. Hankosky, Lisa M. Neff, Hong Kan, Adam Stefanski, Nadia N. Ahmad and W. Timothy Garvey contributed to study design and interpretation. Fangyu Wang contributed to data collection, statistical analysis and interpretation. Hui Wang contributed to interpretation and statistical analysis. Ryan Griffin contributed to the interpretation. All authors were involved in the drafting, critical revision, and approval of the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

Emily R. Hankosky, Lisa M. Neff, Hong Kan, Fangyu Wang, Nadia N. Ahmad, Ryan Griffin and Adam Stefanski are employees and shareholders of Eli Lilly and Company. Hui Wang is an employee of Tech-Data Service Company which is contracted by Eli Lilly and Company. W. Timothy Garvey has served as a consultant on advisory boards for Boehringer-Ingelheim, Eli Lilly and Company, Novo Nordisk, Pfizer, Fractyl Health, Alnylam Pharmaceuticals, Inogen and Merck, and has received research grant support for clinical trials sponsored through his university and funded by Novo Nordisk A/S, Eli Lilly and Company, Epitomee, Neurovalens and Pfizer.

DATA AVAILABILITY STATEMENT

Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, for the SURMOUNT-1 study (NCT04184622) will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at https://www.vivli.org.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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