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Tirzepatide Improved Markers of Islet Cell Function and Insulin Sensitivity in People With T2D (SURPASS-2)

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Abstract

Context: In previous SURPASS studies tirzepatide reduced hemoglobin glycated A1c (HbA1c) and body weight and improved markers of insulin sensitivity and β-cell function to a greater extent than comparators.

Objective: Explore changes in biomarkers of β-cell function and insulin sensitivity and in efficacy profiles in baseline biomarker quartile analyses with tirzepatide compared to semaglutide.

Design: Post hoc analysis of SURPASS-2 phase 3 trial (participants randomly assigned to receive weekly subcutaneous tirzepatide or semaglutide for 40 weeks).

Setting: Post hoc analysis of 128 sites in 8 countries.

Participants: A total of 1879 participants with type 2 diabetes.

Interventions: Once-weekly tirzepatide (5, 10, 15 mg) or semaglutide 1 mg.

Main outcomes measures: Change in homeostatic model assessment indices for pancreatic β-cell function (HOMA2-B) and for insulin resistance (HOMA2-IR), fasting glucagon, fasting C-peptide, and fasting insulin.

Results: At week 40, a greater increase in HOMA2-B was seen with tirzepatide (5, 10, 15 mg) doses (96.9-120.4%) than with semaglutide 1 mg (84.0%) ($P < .05$). There was a greater reduction in HOMA2-IR with all doses of tirzepatide (15.5%-24.0%) than with semaglutide 1 mg (5.1%) ($P < .05$). Tirzepatide 10 and 15 mg resulted in a significant reduction in both fasting C-peptide (5.2%-6.0%) and fasting glucagon (53.0%-55.3%) compared with an increase of C–peptide (3.3%) and a reduction of glucagon (47.7%) with semaglutide 1 mg ($P < .05$). HbA1c and body weight reductions were greater with all tirzepatide doses than semaglutide within each HOMA2-B and HOMA2-IR baseline quartile.

Conclusion: In this post hoc analysis, improvements in HbA1c and weight loss were consistent and significantly higher with tirzepatide, regardless of baseline β-cell function and insulin resistance, compared with semaglutide.

Key Words: tirzepatide, beta-cell function, insulin sensitivity, type 2 diabetes, incretin

Abbreviations: BMI, body mass index; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin A1c; HOMA2, homeostatic model assessment; HOMA2-B, homeostatic model assessment for pancreatic β-cell function; HOMA2-IR, homeostatic model assessment for insulin resistance; MMRM, model for repeated measures; Q, quartile; T2D, type 2 diabetes.

Type 2 diabetes (T2D) results from multiple pathophysiological mechanisms, including defects in insulin secretion, insulin resistance, decreased incretin effect, increased glucagon secretion, and adiposity (1, 2). Tirzepatide is a first-in-class, once-weekly, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist approved for treatment of people with T2D and obesity (1, 3, 4). In the SURPASS phase 3 trials, tirzepatide (5, 10, and 15 mg) reduced glycated hemoglobin A1c (HbA1c) up to 2.6% and reduced body weight up to 12.9 kg, significantly more than placebo (SURPASS-1), semaglutide 1 mg (SURPASS-2), insulin degludec (SURPASS-3), insulin glargine (SURPASS-4), and placebo as an add on to insulin glargine (SURPASS-5) (5-9). The safety profile of tirzepatide is consistent with that of GLP-1 receptor agonists, with the most commonly reported adverse events being generally mild to moderate gastrointestinal symptoms, which typically decreased over time (3, 5-8).

A phase 1 mechanistic study demonstrated substantial improvements in β-cell function, insulin sensitivity, and glucagon secretion in response to treatment with tirzepatide, that in combination contributed to the observed glucose-lowering effects (10). In the phase 2 study, tirzepatide improved markers of insulin sensitivity and β-cell function to a greater extent than placebo or dulaglutide (11). Improvements in

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insulin sensitivity were only partly attributable to weight loss. Concordant changes in markers of pancreatic β-cell function and insulin resistance were also observed in the SURPASS-1 and SURPASS-2 trials. β-cell dysfunction and impaired insulin resistance are interrelated in the pathogenesis of diabetes and result in inadequate glucose homeostasis. Current guidelines for the treatment of patients with T2D highlight the importance of individualized treatment and patient-centered care (12). Weight management is an important component of treatment in T2D, whereas glycemic control, in the form of HbA1c, is an indicator of disease status (13, 14).

In this post hoc analysis, we evaluated changes in markers of pancreatic islet cell function and insulin sensitivity over time and the association between these markers and change in HbA1c and body weight by baseline quartile analyses.

Materials and Methods

Trial Design and Participants

A full description of the SURPASS-2 main study baseline characteristics, methods, efficacy, and safety results has been previously published (6). SURPASS-2 was a phase 3, international, multicenter, randomized, open-label, parallel group, 40-week, active-controlled study designed to assess the efficacy and safety of 3 once-weekly doses of tirzepatide (5 mg, 10 mg, 15 mg) compared with once-weekly, subcutaneous semaglutide (1 mg) in patients with T2D who had inadequate glycemic control with metformin monotherapy (≥1500 mg/day). Eligible patients were randomized 1:1:1:1 to once-weekly injectable tirzepatide 5 mg, 10 mg, 15 mg or semaglutide 1 mg. Both tirzepatide and semaglutide followed the dosing escalations recommended in labeling to the randomized dose and remained on that dose through the duration of the trial. These dose escalations are well known, published, and explained from SURPASS-2 (6). The prespecified primary efficacy endpoint was the mean change from baseline in glycated HbA1c at week 40. This study was conducted in accordance with the protocol and consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical guidelines, applicable ICH Good Clinical Practice Guidelines, and applicable laws and regulations. All participants provided signed informed consent and protocols were approved by local ethical review boards. This study is registered with ClinicalTrials.gov (NCT03987919).

To assess effects of tirzepatide treatment on fasting biomarkers of pancreatic islet cell function, we measured levels of C-peptide and glucagon (adjusted for fasting glucose). Fasting blood samples were collected for biomarker measures at baseline and at weeks 8, 16, 24, 40, and during the safety follow-up. Biomarker analyses included fasting blood glucose, insulin, C-peptide, and glucagon. Fasting glucagon levels were adjusted for fasting glucose levels (6). Homeostatic model assessment (HOMA2) indices for pancreatic β-cell function (HOMA2-B) and for insulin resistance (HOMA2-IR) were computed with fasting glucose and insulin or fasting glucose and C-peptide using the HOMA2 calculator (15).

Statistical Analyses

Exploratory post hoc analyses of the main study were conducted to assess changes from baseline in HbA1c and body weight across baseline β-cell function (HOMA2-B quartiles) and insulin resistance (HOMA2-IR quartiles). Analyses included data from all randomized patients who received ≥1 treatment dose (modified intention-to-treat [mITT] population), while patients were on treatment without rescue therapy and excluding patients who discontinued study drug because of inadvertent enrollment (efficacy estimand).

HOMA2-B and HOMA2-IR quartiles were calculated from the baseline measurements in the overall population across treatment arms. For stratification of β-cell function (HOMA2-B), quartile 1 indicates lower β-cell function, whereas quartile 4 indicates higher β-cell function. For insulin resistance (HOMA2-IR), quartile 1 (Q1) represents lower insulin resistance, whereas Q4 represents higher insulin resistance. Quartiles were defined as follows: for HOMA2-B, Q1 is defined as ≤25% percentile (≤29.3); Q2: >25% percentile and ≤median (>29.3 and ≤44.2); Q3: >median and ≤75% percentile (>44.2 and ≤64); and Q4: >75% percentile (>64). For HOMA2-IR, the quartiles are defined as Q1: ≤1.35; Q2: >1.35 and ≤2; Q3: >2 and ≤3.1; and Q4: >3.1. Descriptive statistics were provided for demographics and baseline variables by HOMA2-B and HOMA2-IR quartiles. Nominal P values were reported for comparisons among quartiles using χ^2 test for categorical variables and ANOVA for continuous variables.

Least square means for HbA1c and weight change from baseline were calculated from a mixed model for repeated measures (MMRM), with model terms for baseline value, pooled country, treatment group, visit, and treatment by visit interaction. For weight change, the baseline HbA1c group (≤8.5%, >8.5%) was added to the model. This model was performed in the overall population and within each HOMA2-B and HOMA2-IR quartile, respectively.

To assess the interaction between HOMA2-B (or HOMA2-IR) quartiles and treatment group, an MMRM model was run in the overall population with added model terms of HOMA-2B quartile, the 2-way interaction terms of HOMA2-B quartile by treatment and HOMA-2B quartile by visit, and the 3-way interacting term of HOMA2-B quartile by treatment by visit.

Percent change from baseline of glucose metabolism and β-cell function was derived from MMRM model on the log-scale of the biomarkers adjusted for baseline value, pooled country, baseline HbA1c group (≤8.5%, >8.5%), treatment group, visit, and treatment by visit interaction.

Statistical test results were considered significant at the 2-sided α level of 0.05. No adjustment for multiple comparisons was performed. Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

Baseline Demographics and Clinical Characteristics

Baseline characteristics were comparable across HOMA2-B baseline quartiles for some characteristics, but significant differences were observed in weight, body mass index (BMI), HbA1c, fasting serum glucose, and mean duration of diabetes (Table 1). HOMA2-IR baseline quartiles were also comparable for some characteristics except for age, weight, BMI, fasting serum glucose, and duration of diabetes (Table 2). The overall mean duration of diabetes was 8.6 years, with a mean baseline HbA1c of 8.3% and BMI of 34 kg/m^2 in both HOMA2-B and HOMA2-IR baseline quartile groups. The use of each

treatment (tirzepatide 5 mg, 10 mg, 15 mg; semaglutide 1 mg) was equal across HOMA2-B and HOMA2-IR baseline quartiles.

Changes in Markers of Islet Cell Function

In the overall population, fasting glucagon levels progressively decreased over time, and greater and significant reductions were seen with tirzepatide 10 and 15 mg (53.0 to 55.3%) than with semaglutide 1 mg (47.7%) ($P < .05$) at week 40 (Fig. 1A, Table 3).

Fasting C-peptide levels initially increased at lower doses of tirzepatide in the initial stages of dose escalation and subsequently decreased over time. Greater and significant reductions in fasting C-peptide were seen with tirzepatide 10 and 15 mg (5.2%-6.0%) compared with the observed increase with semaglutide 1 mg (3.3%) ($P < .05$) at week 40 (Fig. 1B, Table 3).

HOMA2-B index significantly increased from baseline by 8 weeks in all cohorts. Significantly greater increases in HOMA2-B were observed with tirzepatide (5 mg, 10 mg, 15 mg) doses (96.9%-120.4%) vs semaglutide 1 mg (84.0%) ($P < .05$) at week 40 (Fig. 1C, Table 3).

Changes in Markers of Insulin Sensitivity

Greater reductions in fasting insulin were seen with all doses of tirzepatide, from 8.9% to 20.9% vs an increase of 0.6% with semaglutide ($P < .05$) at week 40 (Fig. 1D, Table 3). An initial increase in fasting insulin levels was seen at week 8 followed by decreases over time as higher doses of tirzepatide were achieved in dose escalation.

Greater reductions in HOMA2-IR (computed with insulin) were seen with all doses of tirzepatide, from 15.5% to 24.0% vs semaglutide (5.1%) ($P < .05$) at week 40 (Fig. 1E, Table 3).

HbA1c Changes Within HOMA2-B and HOMA2-IR Baseline Quartiles

HbA1c reductions were numerically greater with all tirzepatide doses than with semaglutide within each HOMA2-B baseline quartile (Fig. 2A, Supplementary Table S1 (16)). The reduction was significantly greater for tirzepatide 10 mg and 15 mg across all quartiles and for tirzepatide 5 mg in Q2 and Q3 ($P < .05$). Across HOMA2-B quartiles, the extent of HbA1c reductions was related to baseline HbA1c and largest in participants within Q1 (Fig. 2A, Table 1).

HbA1c reductions were numerically greater with all tirzepatide doses than with semaglutide within each HOMA2-IR baseline quartile (Fig. 2B, Supplementary Table S1 (16)). The reduction was significantly greater for tirzepatide 10 and 15 mg across all quartiles and for tirzepatide 5 mg in Q1 and Q2 ($P < .05$).

The interaction between HOMA quartiles and treatment group was not significant for HOMA2-B or HOMA2-IR.

Body Weight Changes Within HOMA2-B and HOMA2-IR Baseline Quartiles

Body weight reductions were numerically greater across HOMA2-B quartiles with all tirzepatide doses (range, 7.9%-14.1%) than with semaglutide (6.4%-7.2%) (Fig. 2C, Table 1). The reduction was significantly greater for tirzepatide 10 and 15 mg in each quartile and for tirzepatide 5 mg in Q3 ($P < .05$).

Body weight reductions were numerically greater across HOMA2-IR quartiles with all tirzepatide doses (range, 8.2%-13.5%) than with semaglutide (6.1%-7.1%) (Fig. 2D, Table 2). The reduction was significantly greater for tirzepatide 10 mg and 15 mg across all quartiles and for tirzepatide 5 mg in Q3 and Q4 ($P < .05$).

No significant interactions were detected between HOMA quartiles and treatment group.

Discussion

In the SURPASS-2 trial, tirzepatide 5 mg, 10 mg, and 15 mg demonstrated significant and clinically relevant enhancements in markers of pancreatic β-cell function and insulin sensitivity in conjunction with improved glycemic control and body weight reduction. These improvements were maintained regardless of the baseline pancreatic β-cell function and insulin sensitivity, and the degree of HbA1c and body weight reduction was comparable across HOMA2-B and HOMA2-IR quartiles.

Recent epidemiologic studies have combined analyses of genetic markers, clinical traits, and circulating biomarkers to propose that people living with T2D can be stratified into consistent phenotypic subtypes or clusters (17). In several independent cohorts, subgroups have been identified that were either characterized by lower pancreatic β-cell function as described by lower HOMA2-B indices or distinct subgroups characterized by higher insulin resistance as described by higher HOMA2-IR indices (17-19). To explore whether treatment with tirzepatide or semaglutide could produce different effects to improve glucose control or decrease body weight in the context of differences in baseline β-cell function or insulin resistance, we conducted post hoc analyses to evaluate participant subgroups in SURPASS-2 stratified by baseline HOMA2 quartiles. Our quartile analyses showed that HbA1c reductions were greater with all tirzepatide 5 -mg, 10-mg, and 15-mg doses than semaglutide 1 mg within each HOMA2-B and HOMA2-IR baseline quartile. HbA1c reductions were related to baseline HbA1c across HOMA2-B quartiles and largest in Q1 (2.3%-3.0%), the quartile with the lowest measure of β-cell function but were similar across all HOMA2-IR quartiles. People with markers of diminished pancreatic β-cell function at baseline had the most glycemic improvement. One possible explanation for this marked HbA1c reduction in the lowest HOMA2-B quartile could be the difference in mean HbA1c at baseline between Q1 and Q4 (9.1% and 8.3%, respectively) (Table 1; $P < .001$). No significant differences were observed in baseline HbA1c between Q1 and Q4 in the HOMA2-IR quartiles (Table 2; $P = .179$). Body weight reductions were greater across HOMA2-B quartiles with all tirzepatide (5 mg, 10 mg, 15 mg) doses than semaglutide 1 mg. Weight reductions were related to baseline weight across HOMA2-B quartiles and the largest reduction was seen in Q4 (quartile with higher β-cell function). This observation could be related to mean baseline weight differences in Q1 and Q4 (Table 1; $P < .001$). Across all HOMA2-IR quartiles, weight reduction differences were not clearly noted within quartiles despite mean baseline weight differences (Table 2; $P < .001$). Additional analyses may be of interest to further explore this observation. The distinct efficacy profile of tirzepatide may be attributed to enhancements in both islet cell function and insulin sensitivity. Although greater HbA1c and weight reductions were marginally associated with certain HOMA2-B quartiles across treatment groups,

Table 1. Baseline characteristics by HOMA2-B baseline quartiles

	Q1	Q2	Q3	Q4	Total	*P*
Range per quartile	≤29.3	29.3–44.2	44.2–64	>64		
N	459	456	461	453	1829	
Age	56.2 (10.5)	56.7 (10.8)	57.2 (10.1)	56.1 (10.4)	56.5 (10.4)	.367
Sex, n (%)						.120
Female	253 (55.1)	220 (48.2)	242 (52.5)	250 (55.2)	965 (52.8)	
Male	206 (44.9)	236 (51.8)	219 (47.5)	203 (44.8)	864 (47.2)	
Duration of type 2 diabetes, years	10.3 (7.1)	8.8 (6.1)	8.2 (6.0)	7.0 (6.0)	8.6 (6.4)	<.001
HbA1c, %	9.1 (1.01)	8.4 (0.90)	8.0 (0.82)	7.6 (0.76)	8.3 (1.03)	<.001
HbA1c, mmol/mol	75.6 (11.1)	68.7 (9.84)	63.5 (8.93)	60.0 (8.32)	67.0 (11.25)	<.001
HbA1c category, n (%)						<.001
≤8.5%	139 (30.3)	261 (57.2)	363 (78.7)	403 (89.0)	1166 (63.8)	
>8.5%	320 (69.7)	195 (42.8)	98 (21.3)	50 (11.0)	663 (36.2)	
FSG, mg/dL	224.03 (50.91)	183.87 (36.21)	155.64 (28.17)	129.37 (28.15)	173.33 (51.01)	<.001
Weight, kg	87.5 (19.3)	93.9 (21.7)	95.4 (21.3)	99.0 (23.6)	93.9 (21.9)	<.001
BMI, kg/m^2	32.1 (6.21)	34.0 (6.79)	34.60 (6.26)	36.2 (7.58)	34.2 (6.89)	<.001
Treatment, n (%)						.713
Tirzepatide 5 mg	128 (27.9)	115 (25.2)	115 (24.9)	104 (23.0)	462 (25.3)	
Tirzepatide 10 mg	113 (24.6)	119 (26.1)	113 (24.5)	112 (24.7)	457 (25.0)	
Tirzepatide 15 mg	113 (24.6)	119 (26.1)	110 (23.9)	114 (25.2)	456 (24.9)	
Semaglutide	105 (22.9)	103 (22.6)	123 (26.7)	123 (27.2)	454 (24.8)	

Data are mean (SD) or n (%). All participants had prior metformin use. *P* values were derived from χ^2 test (categorical variables) and ANOVA (continuous variables) for differences among HOMA2-B baseline quartile groups Q1-Q4.
Abbreviations: BMI, body mass index; FSG, fasting serum glucose; HbA1c, glycated hemoglobin A1c; HOMA2-B, homeostasis model assessment (updated version) for β-cell function (C-peptide); Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile.

Table 2. Baseline characteristics by HOMA2-IR baseline quartiles

	Q1	Q2	Q3	Q4	Total	*P*
Range per quartile	≤1.35	1.35-2	2-3.1	>3.1		
N	446	473	430	435	1784	
Age	58.7 (10.7)	57.6 (10.1)	55.9 (10.3)	54.0 (10.3)	56.6 (10.5)	<.001
Sex, n (%)						.422
Female	223 (50.0)	252 (53.3)	239 (55.6)	228 (52.4)	942 (52.8)	
Male	223 (50.0)	221 (46.7)	191 (44.4)	207 (47.6)	842 (47.2)	
Duration of type 2 diabetes, years	10.1 (7.2)	8.2 (5.9)	8.1 (6.3)	7.9 (6.3)	8.6 (6.5)	<.001
HbA1c, %	8.3 (1.07)	8.2 (1.05)	8.3 (1.05)	8.4 (0.93)	8.3 (1.03)	.179
HbA1c, mmol/mol	66.8 (11.68)	66.3 (11.48)	67.2 (11.44)	67.9 (10.19)	67.0 (11.23)	.179
HbA1c category, n (%)						.294
≤8.5%	293 (65.7)	308 (65.1)	268 (62.3)	262 (60.2)	1131 (63.4)	
>8.5%	153 (34.3)	165 (34.9)	162 (37.7)	173 (39.8)	653 (36.6)	
FSG, mg/dL	164.31 (47.41)	165.31 (46.52)	175.01 (50.80)	186.13 (54.82)	172.47 (50.63)	<.001
Weight, kg	84.7 (17.10)	90.0 (18.10)	96.5 (21.44)	103.7 (24.25)	93.6 (21.54)	<.001
BMI, kg/m^2	31.2 (6.06)	33.2 (6.15)	35.1 (6.43)	37.2 (7.36)	34.1 (6.87)	<.001
Treatment, n (%)						.328
Tirzepatide 5 mg	124 (27.8)	122 (25.8)	94 (21.9)	111 (25.5)	451 (25.3)	
Tirzepatide 10 mg	109 (24.4)	106 (22.4)	116 (27.0)	115 (26.4)	446 (25.0)	
Tirzepatide 15 mg	111 (24.9)	111 (23.5)	117 (27.2)	106 (24.4)	445 (24.9)	
Semaglutide	102 (22.9)	134 (28.3)	103 (24.0)	103 (23.7)	442 (24.8)	

Data are mean (SD) or n (%). All participants had prior metformin use. *P* values were derived from χ^2 test (categorical variables) and ANOVA (continuous variables) for differences among HOMA2-B baseline quartile groups Q1-Q4.
Abbreviations: BMI, body mass index; FSG, fasting serum glucose; HbA1c, glycated hemoglobin A1c; HOMA2-IR, homeostasis model assessment for beta cell function (calculated with insulin); Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile.

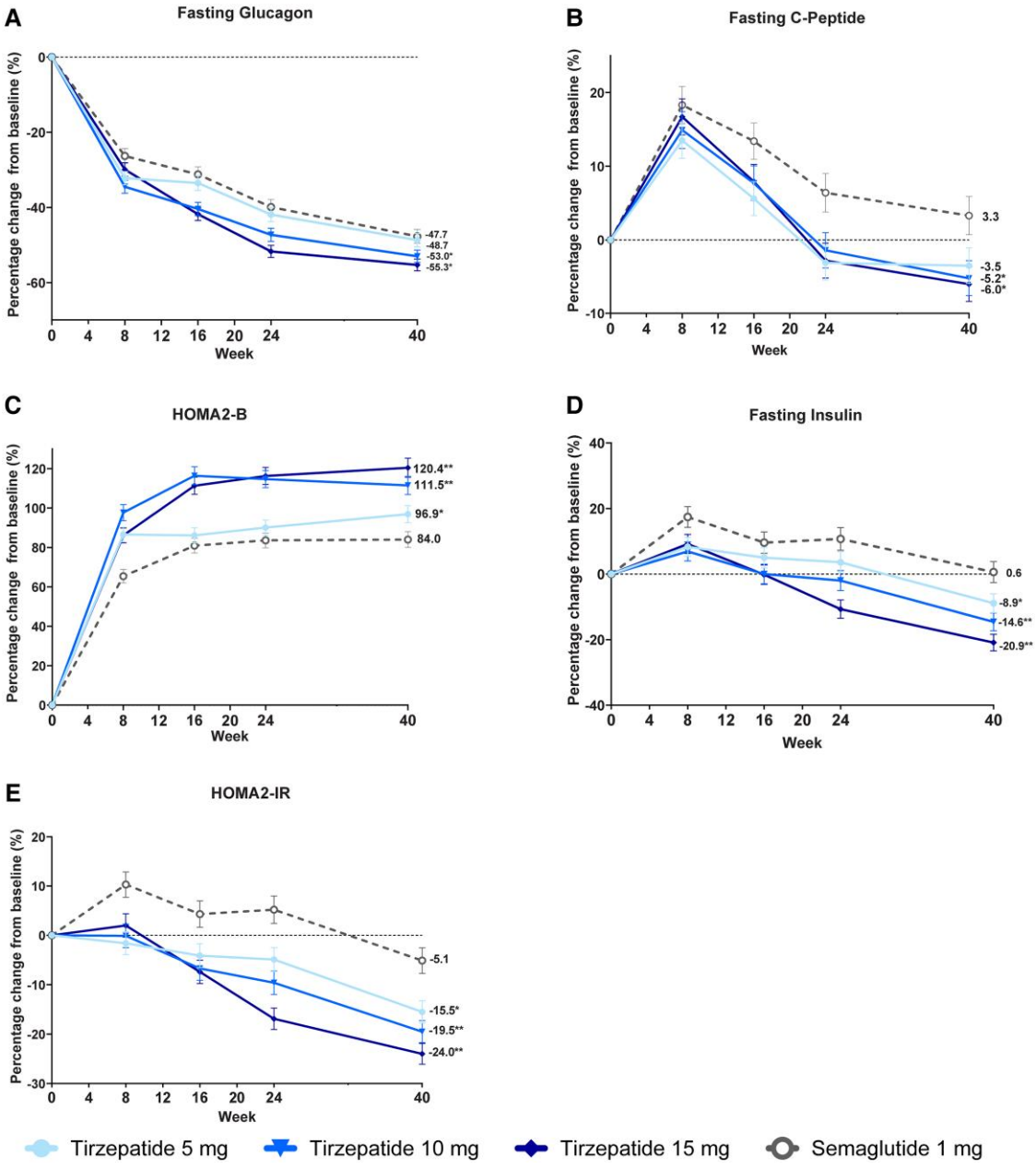

Figure 1. Percent change from baseline over 40 weeks. (A) Fasting glucagon. (B) Fasting C-peptide. (C) HOMA2-B (calculated with C-peptide). (D) Fasting insulin. (E) HOMA2-IR (calculated with insulin). $*P < .05$ and $**P < .001$ for LS mean difference between tirzepatide dose group vs semaglutide. Maintenance doses were achieved at week 4 for tirzepatide 5 mg, week 12 for tirzepatide 10 mg, week 20 for tirzepatide 15 mg, and week 8 for semaglutide. Percent change was derived from the MMRM model for change on log-scale with model terms log (baseline), pooled country, baseline HbA1c group (≤8.5%, vs >8.5%), treatment group, visit, and treatment group by visit interaction. The change from baseline for fasting serum glucose was derived from the MMRM model with model terms of baseline value, pooled country, baseline HbA1c group (≤8.5% vs >8.5%), treatment group, visit, and treatment by visit interaction. HbA1c, glycated hemoglobin A1c; HOMA2-B, homeostasis model assessment (updated version) for β-cell function (C-peptide); HOMA2-IR, homeostasis model assessment for β-cell function (calculated with insulin); LS, least squares; MMRM, mixed model for repeated measures.

no differential treatment effect was observed for tirzepatide vs semaglutide across the HOMA quartiles (ie, no interaction effect between HOMA quartiles and treatment group).

In this post hoc analysis, we also found that regardless of the percent change from baseline of HOMA2-B index, a marker of fasting β-cell function, all doses of tirzepatide significantly increased HOMA2-B (96.9% to 120.4%) to a greater extent than with the selective GLP-1R agonist semaglutide 1 mg (84%) at week 40. In exploratory linear correlation analyses, changes in HOMA2-B were moderately negatively correlated with changes in HbA1c in the SURPASS-2 study population at week 40 (data not shown), suggesting that improvements in pancreatic β-cell function in response to treatment were associated with, and may have contributed to, reductions in hyperglycemia. In a previous analysis of tirzepatide vs the selective GLP-1R agonist dulaglutide 1.5 mg, percent change from baseline in HOMA2-B (computed with fasting C-peptide) increases ranged from 93% to 163% for tirzepatide 5-mg, 10-mg, and 15-mg doses vs 72% with dulaglutide 1.5 mg ($P < .05$) (11). Furthermore, treatment with tirzepatide 10 or

Table 3. HbA1c, body weight, and markers of islet cell function and insulin sensitivity at baseline and week 40

	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Semaglutide 1 mg
HbA1c (%)				
Baseline	8.33 (0.048)	8.31 (0.048)	8.25 (0.048)	8.24 (0.048)
At week 40	6.19 (0.047)	5.91 (0.048)	5.82 (0.048)	6.42 (0.048)
Change from baseline at week 40	−2.09 (0.047)††	−2.37 (0.048)††	−2.46 (0.048)††	−1.86 (0.048)††
ETD vs semaglutide (95% CI) at week 40	−0.23 (−0.36, −0.10)**	−0.51 (−0.64, −0.38)**	−0.60 (−0.73, −0.47)**	
Body weight (kg)				
Baseline	92.6 (1.02)	94.9 (1.02)	93.9 (1.02)	93.8 (1.02)
At week 40	86.2 (0.28)	83.7 (0.29)	81.6 (0.29)	87.8 (0.28)
Change from baseline at week 40	−7.8 (0.33)††	−10.3 (0.34)††	−12.4 (0.34)††	−6.2 (0.33)††
ETD vs semaglutide (95% CI) at week 40	−1.7 (−2.6, −0.7)**	−4.1 (−5.0, −3.2)**	−6.2 (−7.1, −5.3)**	
Fasting serum glucose, mg/dL				
Baseline	174.2 (2.39)	174.6 (2.40)	172.3 (2.39)	170.9 (2.40)
At week 40	117.0 (1.57)	111.3 (1.60)	109.6 (1.59)	124.4 (1.58)
Change from baseline at week 40	−56.0 (1.57)††	−61.6 (1.60)††	−63.4 (1.59)††	−48.6 (1.58)††
ETD vs semaglutide (95% CI) at week 40	−7.3 (−11.7, −3.0)**	−13.0 (−17.4, −8.6)**	−14.7 (−19.1, −10.3)**	
Fasting C-peptide, µg/L				
Baseline	1.98 (0.051)	2.16 (0.056)	2.02 (0.052)	2.08 (0.054)
At week 40	1.99 (0.050)	1.95 (0.049)	1.94 (0.049)	2.13 (0.053)
Percent change from baseline at week 40	−3.5 (2.40)	−5.2 (2.39)†	−6.0 (2.38)†	3.3 (2.59)
ETD vs semaglutide (95% CI) at week 40	−6.6 (−12.9, 0.1)	−8.3 (−14.4, −1.6)*	−9.0 (−15.1, −2.4)*	
Fasting glucagon,[a] pmol/L × mmol/L				
Baseline	100.6 (2.89)	104.3 (3.00)	99.3 (2.85)	102.0 (2.95)
At week 40	52.2 (1.81)	47.8 (1.68)	45.5 (1.60)	53.2 (1.85)
Percent change from baseline at week 40	−48.7 (1.78)††	−53.0 (1.65)††	−55.3 (1.57)††	−47.7 (1.82)††
ETD vs semaglutide (95% CI) at week 40	−1.9 (−10.9, 8.0)	−10.0 (−18.3, −0.9)*	−14.5 (−22.4, −5.8)*	
HOMA2-B (C-peptide)				
Baseline	40.7 (1.14)	43.1 (1.22)	42.6 (1.19)	44.1 (1.24)
At week 40	83.9 (1.83)	90.2 (1.99)	94.0 (2.09)	78.4 (1.72)
Percent change from baseline at week 40	96.9 (4.28)††	111.5 (4.66)††	120.4 (4.89)††	84.0 (4.04)††
ETD vs semaglutide (95% CI) at week 40	7.0 (0.7, 13.7)*	15.0 (8.2, 22.2)**	19.8 (12.7, 27.4)**	
Fasting insulin, mU/L				
Baseline	13.1 (0.43)	14.7 (0.49)	13.9 (0.45)	13.7 (0.45)
At week 40	12.6 (0.40)	11.8 (0.38)	10.9 (0.35)	13.9 (0.44)
Percent change from baseline at week 40	−8.9 (2.88)†	−14.6 (2.73)††	−20.9 (2.54)††	0.6 (3.20)
ETD vs semaglutide (95% CI) at week 40	−9.5 (−17.1, −1.1)*	−15.1 (−22.3, −7.3)**	−21.4 (−28.0, −14.1)**	
HOMA2-IR (computed with insulin)				
Baseline	1.94 (0.055)	2.08 (0.060)	2.01 (0.058)	1.95 (0.056)
At week 40	1.68 (0.045)	1.60 (0.044)	1.51 (0.042)	1.88 (0.052)
Percent change from baseline at week 40	−15.5 (2.28)††	−19.5 (2.23)††	−24.0 (2.10)††	−5.1 (2.60)
ETD vs semaglutide (95% CI) at week 40	−11.0 (−17.5, −4.0)*	−15.2 (−21.4, −8.5)**	−19.9 (−25.8, −13.6)**	

The LS mean change or percent change from baseline and ETD were derived from MMRM model with model terms of baseline value, pooled country, baseline HbA1c group (≤8.5% vs >8.5%), treatment group, visit, and treatment by visit interaction. Baseline HbA1c group was not included for HbA1c model.
Abbreviations: ETD, estimated treatment difference; HbA1c, glycated hemoglobin A1c; HOMA2-B, homeostasis model assessment (updated version) for β-cell function (C-peptide); HOMA2-IR, homeostasis model assessment for β-cell function (calculated with insulin); LS, least squares; MMRM, mixed model for repeated measures; N, number of randomized participants who received at least 1 dose of study drug.
Fasting serum glucose, fasting C-peptide, [a]fasting glucagon (adjusted for fasting glucose), HOMA2-B, fasting insulin, and HOMA2-IR were analyzed in MMRM on log-scale and transformed into percent change.
†$P < .05$ and ††$P < .001$ for LS mean change vs baseline.
*$P < .05$ and **$P < .001$ for LS mean difference between tirzepatide dose group vs semaglutide.

15 mg significantly reduced proinsulin/C-peptide ratios, indicators of pancreatic β-cell stress, greater than dulaglutide (11). These observations suggest dual agonism of both GLP-1 and GIP receptors has the potential to provide additional improvement in pancreatic β-cell function compared with selective agonism of GLP-1 receptors alone for some people with T2D. Consistent with these clinical observations, recent studies indicate that agonism of the GIP receptor is important for maximal stimulation of insulin secretion from human pancreatic β cells (20, 21). Furthermore, in

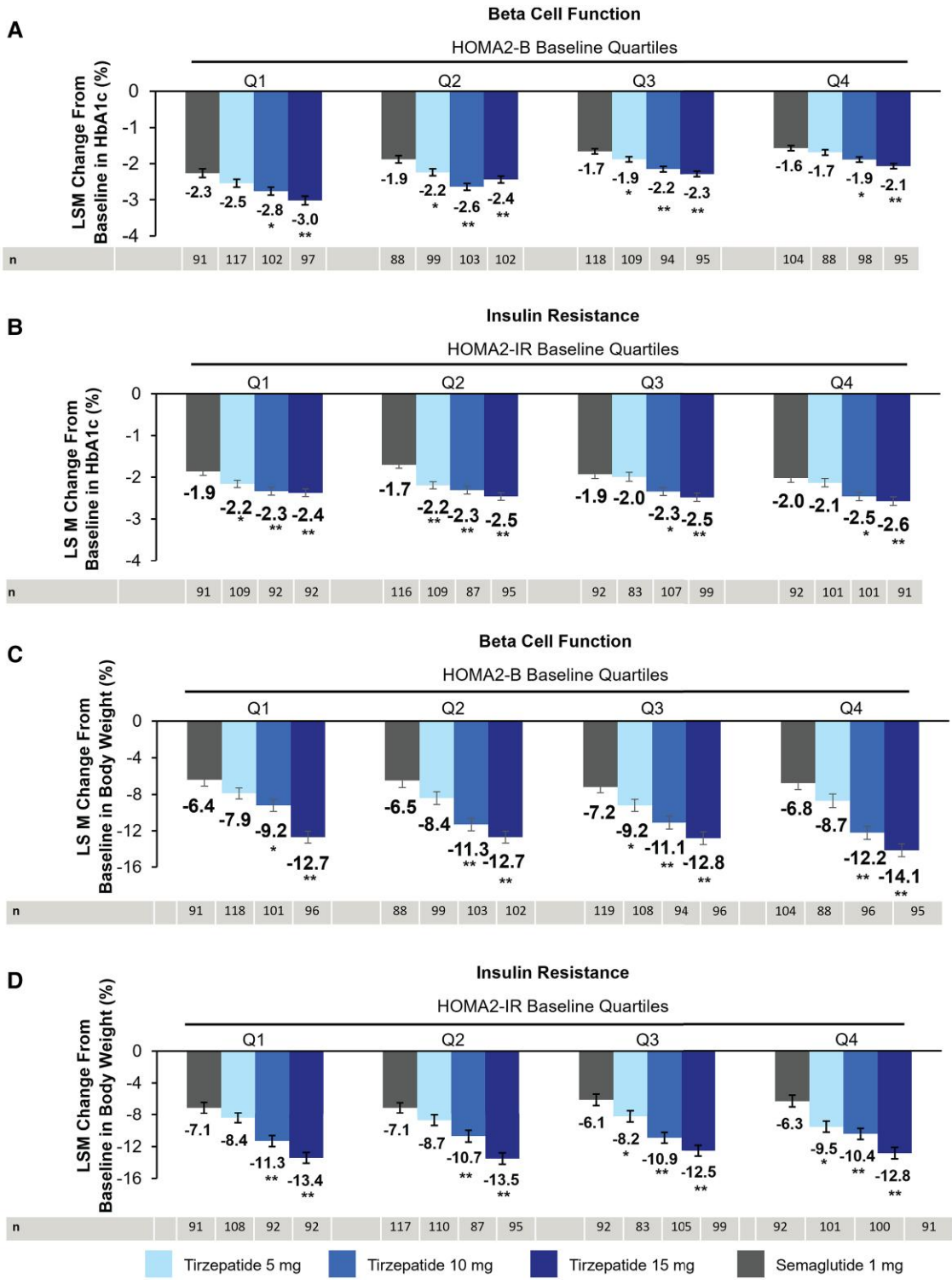

Figure 2. (A) HbA1c change from baseline to week 40 by HOMA2-B baseline quartile. (B) HbA1c change from baseline to week 40 by HOMA2-IR baseline quartile. (C) Body weight change from baseline to week 40 by HOMA2-B baseline quartile. (D) Body weight change from baseline to week 40 by HOMA2-IR baseline quartile. * $P < .05$ and ** $P < .001$ for LS mean difference between tirzepatide dose group vs semaglutide. Notes: n values are for week 40. LS means were calculated from MMRM model with model terms of baseline value, pooled country, treatment group, visit, and treatment by visit interaction within each baseline quartile. Weight analysis also included baseline HbA1c group (≤8.5% vs >8.5%) in the model. HbA1c, glycated hemoglobin A1c; HOMA2-B, homeostasis model assessment (updated version) for β-cell function (calculated with C-peptide); HOMA2-IR, homeostasis model assessment for β-cell function (calculated with insulin); LS, least squares; MMRM, mixed model for repeated measures; quartiles from low to high: Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile.

mechanistic studies in people with T2D treated for 28 weeks with tirzepatide dose escalated to 15 mg or semaglutide 1 mg, administration of tirzepatide resulted in significantly greater increases in total insulin secretion from pancreatic β cells in hyperglycemic clamp studies and in the disposition index than did semaglutide (10).

It is well recognized that hyperglucagonemia is characteristic in T2D, promoting hepatic glucose output and exacerbating hyperglycemia (22, 23). In this post hoc analysis, tirzepatide demonstrated significant and rapid improvement in hyperglucagonemia and related α-cell dysfunction, as indicated by reductions in fasting glucagon levels adjusted for fasting glucose ranging from 48.7% to 55.3%. This finding is consistent with studies that demonstrated greater reductions in fasting and postprandial glucagon levels with tirzepatide treatment compared with selective GLP-1 receptor agonists in adults with T2D (10, 11). In a recently published post hoc analysis of markers of β-cell function, in SURPASS-1, tirzepatide, as monotherapy, improved islet cell function, as demonstrated by greater reductions in hyperglucagonemia (24).

Significantly greater reductions in HOMA2-IR, fasting insulin, and C-peptide concentrations were seen with each tirzepatide dose compared with semaglutide at week 40 in SURPASS-2. These observations were consistent with observed greater numerical improvements in additional metabolic measures often associated with insulin resistance in people living with diabetes, including fasting triglyceride and high-density lipoprotein cholesterol levels as well as body mass indices, following treatment with tirzepatide compared with semaglutide (6). These findings are also consistent with observations seen in the post hoc analysis by Lee et al (24), of the SURPASS-1 study, demonstrating tirzepatide monotherapy vs placebo achieved significant improvements in biomarkers of both pancreatic β-cell function and insulin sensitivity in people with T2D. In the same paper, the authors also reported reductions in HOMA2-IR and fasting insulin levels and increases in total adiponectin and IGF-binding protein 2 levels with tirzepatide vs placebo at week 40. In hyperinsulinemic euglycemic clamp studies, treatment of people with T2D with tirzepatide 15 mg for 26 weeks produced a large and significant increase in insulin sensitivity measured by M-value that was greater than that observed for treatment with semaglutide 1 mg (10). Collectively these results support the hypothesis that GIP receptor agonism may confer additional insulin-sensitizing actions beyond the effects of activating the GLP-1R alone.

In this post hoc analysis, we did not conduct additional analyses of the occurrence of adverse events; however, from the SURPASS-2 trial, Frias et al previously summarized the safety assessments (6). The most frequent adverse events reported were gastrointestinal in nature in the tirzepatide and semaglutide groups (nausea, 17%-22% and 18%; diarrhea, 13%-16% and 12%; and vomiting, 6%-10% and 8%, respectively). Most were mild to moderate in severity and generally occurred during the dose-escalation period.

Limitations of this study include the exploratory nature of the post hoc biomarker analysis. Biomarkers in this phase 3 study were collected only under fasting conditions, limiting the analysis to surrogate fasting markers of β-cell function and insulin sensitivity that were not able to incorporate dynamic or postprandial responses. Additional studies are warranted to further define mechanisms by which tirzepatide results in improved glucose control and insulin sensitivity. The analysis also does not account for social determinants of health, which may impact the glycemic and weight outcomes in this population (25). Findings are consistent with findings of in vitro, preclinical, mechanistic, and other randomized clinical trials assessing changes in β-cell function and insulin sensitivity with tirzepatide.

Conclusion

In this post hoc analysis of the SURPASS 2 trial, treatment with tirzepatide at doses of 5 mg, 10 mg, and 15 mg significantly improved biomarkers of β-cell function and insulin sensitivity as well as glycemic control and body weight loss compared with the selective GLP-1 receptor agonist, semaglutide 1 mg, in people with T2D on concomitant metformin. Improvement in HbA1c and weight loss were consistent and significantly higher with tirzepatide regardless of baseline β-cell function and insulin resistance biomarkers.

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Data Availability

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 United States and European Union 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 a receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, and blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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