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Early-Onset Type 2 Diabetes and Tirzepatide Treatment: A Post Hoc Analysis From the SURPASS Clinical Trial Program

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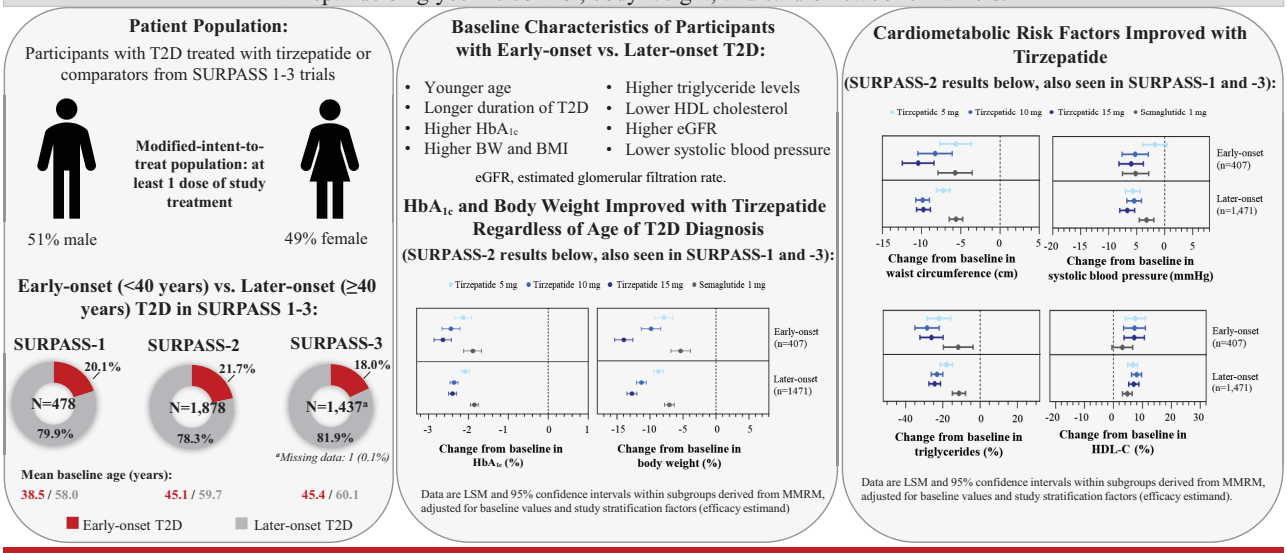
Early-onset type 2 diabetes and tirzepatide treatment: a post hoc analysis from the SURPASS clinical trial program

In the SURPASS Phase 3 clinical trial program for type 2 diabetes (T2D), tirzepatide treatment significantly improved glycemic levels and substantially reduced body weight (BW), with improvements in cardiometabolic markers. This post hoc analysis evaluated baseline characteristics of participants with early-onset T2D (diagnosed before age 40) from SURPASS and assessed the effect of tirzepatide on glycemic control, body weight, and cardiometabolic markers.



Conclusion: Despite younger age, participants with early-onset T2D from the SURPASS program had higher glycemic levels and worse overall metabolic health at baseline compared with those with later-onset T2D. In this post hoc analysis, similar improvements in HbA_{1c}, BW and cardiometabolic markers were observed with tirzepatide, irrespective of age at T2D diagnosis. Future studies are needed to determine long-term outcomes of tirzepatide therapy in people with early-onset T2D.

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Early-onset type 2 diabetes, defined as being diagnosed before the age of 40 years, is associated with greater risks of cardiovascular complications.
- **What is the specific question(s) we wanted to answer?**
  We assessed baseline characteristics of participants with early-onset type 2 diabetes (T2D) from SURPASS trials and the effect of tirzepatide on glycemia, body weight (BW), and cardiometabolic markers.
- **What did we find?**
  Despite younger age, participants with early-onset T2D had higher glycemia and a worse metabolic profile at baseline, including higher BW and similarly abnormal lipids versus later-onset T2D.
- **What are the implications of our findings?**
  Tirzepatide was associated with improved glycemia and BW, irrespective of age at T2D diagnosis. In this post hoc analysis, improvements in HbA_{1c}, BW, lipids, and blood pressure were similar in both subgroups with tirzepatide.

Early-Onset Type 2 Diabetes and Tirzepatide Treatment: A Post Hoc Analysis From the SURPASS Clinical Trial Program

Philip Zeitler,[1] Rodolfo J. Galindo,[2] Melanie J. Davies,[3] Brandon K. Bergman,[4] Vivian T. Thieu,[4] Claudia Nicolay,[4] Sheryl Allen,[4] Robert J. Heine,[4] and Clare J. Lee[4]

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ORIGINAL ARTICLE

OBJECTIVE

We evaluated baseline characteristics of participants with early-onset type 2 diabetes (T2D) from the SURPASS program and tirzepatide's effects on glycemic control, body weight (BW), and cardiometabolic markers.

RESEARCH DESIGN AND METHODS

This post hoc analysis compared baseline characteristics and changes in mean HbA_{1c}, BW, waist circumference (WC), lipids, and blood pressure (BP) in 3,792 participants with early-onset versus later-onset T2D at week 40 (A Study of Tirzepatide [LY3298176] in Participants With Type 2 Diabetes Not Controlled With Diet and Exercise Alone [SURPASS-1] and A Study of Tirzepatide [LY3298176] Versus Semaglutide Once Weekly as Add-on Therapy to Metformin in Participants With Type 2 Diabetes [SURPASS-2]) or week 52 (A Study of Tirzepatide [LY3298176] Versus Insulin Degludec in Participants With Type 2 Diabetes [SURPASS-3]). Analyses were performed by study on data from participants while on assigned treatment without rescue medication in case of persistent hyperglycemia.

RESULTS

At baseline in SURPASS-2, participants with early-onset versus later-onset T2D were younger with longer diabetes duration (9 vs. 7 years, $P < 0.001$) higher glycemic levels (8.5% vs. 8.2%, $P < 0.001$), higher BW (97 vs. 93 kg, $P < 0.001$) and BMI (35 vs. 34 kg/m^2, $P < 0.001$), and a similarly abnormal lipid profile (e.g., triglycerides 167 vs. 156 mg/dL). At week 40, similar improvements in HbA_{1c} (−2.6% vs. −2.4%), BW (−14 vs. −13 kg), WC (−10 vs. −10 cm), triglycerides (−26% vs. −24%), HDL (7% vs. 7%), and systolic BP (−6 vs. −7 mmHg) were observed in both subgroups with tirzepatide.

CONCLUSIONS

Despite younger age, participants with early-onset T2D from the SURPASS program had higher glycemic levels and worse overall metabolic health at baseline versus those with later-onset T2D. In this post hoc analysis, similar improvements in HbA_{1c}, BW, and cardiometabolic markers were observed with tirzepatide, irrespective of age at T2D diagnosis. Future studies are needed to determine long-term outcomes of tirzepatide in early-onset T2D.

Early-onset type 2 diabetes (T2D), which is defined as a diagnosis at <40 years of age, has increased at an alarming rate over the past few decades in parallel with

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increasing prevalence of obesity in this population (1–8). T2D diagnosed at an early age manifests a more aggressive disease course characterized by increased insulin resistance (1,2,7,9) and greater deterioration of β-cell function, resulting in faster rise in glycemic levels (10) and a higher risk for diabetes-related complications (1–3,9,11–15) and early mortality (15–17). Furthermore, there is an unmet clinical need in this population given their reduced response to antihyperglycemic treatment such as metformin and insulin (18). Most data on early-onset T2D are in adolescents and not from individuals aged 19–39 years, and subsequently, adults with early-onset T2D are severely underrepresented in clinical studies (19); however, the epidemiology and clinical course of early-onset and later-onset T2D are thought to be similar (20).

Tirzepatide is a first-in-class once weekly glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) receptor agonist approved in the U.S. for treatment of T2D and obesity. In the SURPASS clinical trial program for T2D, treatment with tirzepatide at all doses studied (5 mg, 10 mg, 15 mg) demonstrated significant and robust improvements in glycemic levels, with 81–97% of participants reaching the American Diabetes Association-recommended HbA_{1c} target of <7% (53 mmol/mol) and 23–62% of participants reaching normoglycemia (i.e., HbA_{1c} <5.7% [39 mmol/mol]) (21–25). This level of glycemic efficacy was observed without increased risk of clinically significant (<54 mg/dL) or severe hypoglycemia (21–26). Furthermore, treatment with tirzepatide resulted in substantial mean reductions in body weight (BW; 7–14%) and improvement in cardiometabolic markers, including blood pressure (BP), lipid profile, and waist circumference (WC) (21–25,27,28).

Based on data from youth-onset (<18 years old) T2D, we hypothesized that individuals with early-onset T2D may have metabolically worse clinical features and treatment response compared with individuals with later-onset T2D. To further investigate this hypothesis, we aimed in this post hoc analysis to compare the baseline demographics and clinical characteristics of participants with early-onset versus later-onset T2D and the effect of tirzepatide on glycemic levels, BW, and cardiometabolic markers in these populations from the SURPASS clinical trial program.

RESEARCH DESIGN AND METHODS

Participants and Study Design

The study design, full inclusion and exclusion criteria, and primary results of the A Study of Tirzepatide (LY3298176) in Participants With Type 2 Diabetes Not Controlled With Diet and Exercise Alone (SURPASS-1), A Study of Tirzepatide (LY3298176) Versus Semaglutide Once Weekly as Add-on Therapy to Metformin in Participants With Type 2 Diabetes (SURPASS-2), and A Study of Tirzepatide (LY3298176) Versus Insulin Degludec in Participants With Type 2 Diabetes (SURPASS-3) clinical trials have been published (21–23). Participants were adults aged ≥18 years with T2D (HbA_{1c} ≥7.0% to ≤10.5% at screening), a BMI ≥23 kg/m^2, and on various oral background medications (e.g., metformin, with or without sodium–glucose cotransporter 2 inhibitors [SGLT2i], or on no background antihyperglycemic therapy) representative of clinical practice. Participants were randomly assigned to receive once-weekly tirzepatide (5 mg, 10 mg, or 15 mg) or one of the following comparator interventions: semaglutide (1 mg), insulin degludec, or placebo. Participants from A Study of Tirzepatide (LY3298176) Once a Week Versus Insulin Glargine Once a Day in Participants With Type 2 Diabetes and Increased Cardiovascular Risk (SURPASS-4) were excluded from this analysis due to confounding factors, such as being an older population with a preselected high cardiovascular risk and the relatively small number of participants meeting the criteria for early-onset T2D (24). Participants from A Study of Tirzepatide (LY3298176) Versus Placebo in Participants With Type 2 Diabetes Inadequately Controlled on Insulin Glargine With or Without Metformin (SURPASS-5) and Study of Tirzepatide (LY3298176) Versus Insulin Lispro (U100) in Participants With Type 2 Diabetes Inadequately Controlled on Insulin Glargine (U100) With or Without Metformin (SURPASS-6) were also excluded due to the relatively older age of the population and background insulin use across all participants that could confound factors examined in this post hoc analysis (25,29).

These SURPASS clinical trials were conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. All participants provided signed informed consent, and protocols were approved by local ethical review boards. These trials are registered with ClinicalTrials.gov (NCT03954834, NCT03987919, and NCT03882970).

Procedures

Age at time of T2D diagnosis was derived by subtracting the duration of T2D from age at study enrollment (both in years). Participants were then categorized by age at time of T2D diagnosis <40 years (early-onset T2D) versus ≥40 years (later-onset T2D).

Baseline demographics and clinical characteristics were assessed in participants with early-onset versus later-onset T2D treated with tirzepatide or comparator, including age, sex, duration of diabetes, race, BW, BMI, HbA_{1c}, fasting serum glucose, systolic and diastolic BP, estimated glomerular filtration rate (eGFR), urine albumin-to-creatinine ratio, hepatic enzymes, lipid profile, biomarker of insulin sensitivity (HOMA of insulin resistance [IR] computed with fasting C-peptide), history of cardiovascular disease, and concomitant use of antihyperglycemic, antihypertensive, and lipid-lowering medications at baseline.

Change from baseline at week 40 (SURPASS-1 and SURPASS-2) or week 52 (SURPASS-3) in HbA_{1c}, BW, and cardiometabolic markers, including WC, lipids, and BP, were analyzed in participants with early-onset versus later-onset T2D treated with tirzepatide. Safety measures, including treatment-emergent adverse events and serious adverse events, were also assessed. Laboratory measurements were performed at a central laboratory.

Outcomes

Main outcomes of interest in this post hoc analysis were changes from baseline at week 40 (SURPASS-1, SURPASS-2) or week 52 (SURPASS-3) in HbA_{1c}, BW, and cardiometabolic markers, including WC, lipids, and BP. Additional outcomes were fasting serum glucose, eGFR, and HOMA2-IR. The proportion of participants reaching HbA_{1c} targets <7.0% and <5.7% was also assessed.

Statistical Analyses

Data were analyzed by trial (data could not be pooled due to the significant differences in study design across the SURPASS trials, such as background antihyperglycemic therapies, study duration, and clinical characteristics, including baseline HbA_{1c} and BW). All analyses were post

hoc and performed on the modified intent-to-treat population, comprising all randomly assigned participants with at least one dose of study drug exposure. Within each subgroup of onset of T2D, we evaluated baseline characteristics, efficacy end points, and safety. Efficacy analyses included on-treatment data prior to the use of rescue therapy for persistent hyperglycemia and excluded participants who discontinued study drug because of inadvertent enrollment (i.e., the efficacy estimand). Safety analyses were performed on the modified intent-to-treat population with all data from the start of treatment to the end of the 4-week safety follow-up.

Baseline demographics and clinical characteristics were summarized and compared in participants with early-onset versus later-onset T2D from the SURPASS-1, SURPASS-2, and SURPASS-3 clinical trials using ANOVA for continuous variables, the χ^2 test for categorical variables, and the Wilcoxon rank sum test for nonnormally distributed variables.

Change from baseline in HbA_{1c} at 40 or 52 weeks was assessed within each onset of T2D subgroup using a mixed-model for repeated measures (MMRM) with pooled country, baseline value, treatment group, visit, and treatment-by-visit interaction as the fixed effect, and patient as the random effect. The MMRM for outcomes other than HbA_{1c} also included baseline HbA_{1c} group ($\leq$8.5% or $>$8.5%) as a covariate. For analyses with SURPASS-1 and SURPASS-3, the MMRM was also adjusted for prior or baseline oral antihyperglycemic medications (OAM) (SURPASS-1: prior use of OAM [yes, no]; SURPASS-3: use of SGLT2i at baseline [yes, no]). Lipid profiles and HOMA2-IR were analyzed on the log scale in the MMRM due to their skewed distributions and then converted back to the percent change. Missing outcomes were not directly imputed but managed within the MMRM assuming that data are missing at random and that the missing data follow the same trend as the participants with the same treatment assignment and baseline characteristics.

The interactions between the treatment and onset of T2D were assessed using the same MMRM model applied to the overall population and included additional terms for onset of T2D (early-onset or later-onset), treatment-by-onset of T2D, time-by-onset of T2D, and treatment-by-time-by-onset of T2D terms. The threshold *P* value for statistical significance of the interaction adjusted for multiple comparisons (Bonferroni method) was $<$0.002.

The proportions of participants who achieved each HbA_{1c} target at the end point week were estimated within each onset of T2D subgroup via logistic regression. Respective models were adjusted for baseline value, pooled country, and prior or baseline OAM use when applicable. Participants who discontinued treatment or started rescue medication earlier than the end point week were imputed for their HbA_{1c} from an MMRM model with the same model terms used in the change from baseline MMRMs.

The percent change from baseline in ALT was summarized with means and 95% CIs, and safety parameters and discontinuations were summarized as counts and proportions. All analyses presented were exploratory in nature. Analyses were performed using SAS 9.4 software (2017 release; SAS Institute, Cary, NC).

Data and Resource 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 U.S. 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 receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, 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.

RESULTS

The analysis included 3,792 participants from the SURPASS-1, SURPASS-2, and SURPASS-3 clinical trials (tirzepatide: *n* = 2,848, comparator: *n* = 944). Overall, 762 participants (20.1%) were $<$40 years of age at onset of T2D, with 582 participants on tirzepatide treatment and 180 participants on comparator treatment.

Baseline Characteristics

Across the SURPASS-1 to SURPASS-3 studies, which included participants at various stages of T2D management, participants with early-onset T2D had longer duration of diabetes (except for SURPASS-1), worse glycemic control, higher mean BW and BMI, and a similarly unfavorable lipid profile (i.e., elevated triglycerides and low HDL-cholesterol [C]) at baseline versus participants with later-onset T2D (Table 1). There were no significant differences in baseline WC between the two groups. With regard to the renal parameters, eGFR was significantly higher across all studies, whereas the proportions with albuminuria were significantly lower in participants from SURPASS-3 with early-onset versus later-onset T2D. A total of 16 participants (0.4%) met the baseline eGFR cutoff in the hyperfiltrating range ($>$135 mL/min/1.73 m^2), of whom 15 were from the early-onset T2D group. In participants with early-onset T2D, systolic BP was significantly lower at baseline in all studies, and diastolic BP was significantly higher in SURPASS-3. Data from SURPASS-1 and SURPASS-2 demonstrated that the marker of insulin resistance, HOMA-IR computed with fasting insulin, was higher in participants with early-onset versus later-onset T2D at baseline, whereas HOMA-IR computed with fasting C-peptide showed similar findings.

Change in Glycemic Parameters and BW Observed With Tirzepatide

Among the three studies included in these analyses, we describe SURPASS-2 data as the main data given that it had the largest number of participants with early-onset T2D, and we describe SURPASS-1 and SURPASS-3 data as supportive evidence herein. In SURPASS-2, tirzepatide at all doses (5 mg, 10 mg, and 15 mg) was associated with similar improvements in HbA_{1c} in participants with early-onset versus later-onset T2D at week 40 (Fig. 1*A*), with an overall least-squares mean (LSM) reduction from baseline in HbA_{1c} of $-$2.6% in the early-onset T2D subgroup versus $-$2.4% in the later-onset T2D subgroup treated with tirzepatide, 15 mg (Supplementary Table 1), reaching a final LSM HbA_{1c} of 5.8% in both subgroups at week 40. Overall, similar results were reported in SURPASS-1 and SURPASS-3 (Supplementary Tables 2 and 3 and Figs. 2 and 3), and no differential treatment effect on HbA_{1c} was observed

Table 1—Baseline demographics and clinical characteristics in participants with early-onset versus later-onset T2D

	SURPASS-1		SURPASS-2		SURPASS-3[a]	
	Early-onset (*n* = 96)	Later-onset (*n* = 382)	Early-onset (*n* = 407)	Later-onset (*n* = 1,471)	Early-onset (*n* = 259)	Later-onset (*n* = 1,177)
Age, years	38.5 (8.5)**	58.0 (9.0)	45.1 (9.6)**	59.7 (8.2)	45.4 (9.2)**	60.1 (8.1)
Male sex, *n* (%)	42 (43.8)	205 (53.7)	182 (44.7)	700 (47.6)	138 (53.3)	663 (56.3)
Race, *n* (%)						
White	34 (35.4)	136 (35.6)	326 (80.1)	1,225 (83.3)	229 (88.4)	1,078 (91.6)
American Indian or Alaska Native	22 (22.9)	96 (25.1)	59 (14.5)	149 (10.1)	1 (0.4)	3 (0.3)
Asian	34 (35.4)	134 (35.1)	7 (1.7)	18 (1.2)	18 (6.9)	58 (4.9)
Black or African American	6 (6.3)	16 (4.2)	12 (2.9)	67 (4.6)	11 (4.2)	32 (2.7)
Other	0	0	3 (0.7)	12 (0.8)	0	6 (0.5)
T2D duration, years	2.8 (0.7–6.2)	2.9 (0.7–7.3)	9.0 (4.3–15.1)**	6.8 (3.8–10.8)	9.6 (5.5–14.6)**	6.7 (3.6–10.7)
HbA_{1c}, %	8.1 (0.9)	7.9 (0.9)	8.5 (1.1)**	8.2 (1.0)	8.4 (1.0)**	8.1 (0.9)
HbA_{1c}, mmol/mol	64.6 (10.2)	63.0 (9.2)	69.0 (12.0)	66.5 (11.0)	68.4 (10.9)	65.2 (9.7)
Fasting serum glucose, mg/dL	156.1 (46.0)	153.0 (38.2)	184.4 (60.5)**	169.7 (48.2)	176.4 (48.0)*	167.9 (45.3)
BW, kg	91.5 (22.6)*	84.5 (18.7)	97.3 (24.0)**	92.7 (21.2)	97.9 (21.8)*	93.5 (19.6)
BMI, kg/m^2	33.7 (7.5)*	31.4 (6.3)	35.4 (7.8)**	33.9 (6.6)	34.5 (6.2)*	33.3 (6.0)
WC, cm	105.8 (15.0)	102.6 (13.8)	109.7 (16.8)	109.2 (14.9)	110.8 (15.1)	110.1 (13.9)
Systolic BP, mmHg	121.2 (13.5)**	129.3 (13.8)	127.2 (13.8)**	131.6 (13.7)	127.9 (13.3)**	132.4 (13.2)
Diastolic BP, mmHg	80.0 (8.6)	79.2 (8.9)	79.6 (9.5)	79.1 (8.9)	80.4 (8.7)*	78.9 (8.9)
eGFR, mL/min/1.73 m^2	111.8 (15.8)**	89.6 (18.0)	109.1 (14.8)**	92.4 (15.8)	107.9 (15.1)**	91.1 (15.9)
Hyperfiltration,[b] *n* (%)	5 (5.2)	0	5 (1.2)	1 (0.1)	5 (1.9)	0
Urine albumin-to-creatinine ratio, g/kg	28.8 (56.2)	40.9 (156.8)	76.1 (226.0)	76.4 (267.0)	129.6 (559.8)*	66.2 (319.0)
Macroalbuminuria, *n* (%)	0	8 (2.1)	20 (5.7)	66 (5.3)	22 (8.5)**	41 (3.5)
Microalbuminuria, *n* (%)	22 (23.2)	74 (19.4)	78 (22.1)	295 (23.6)	51 (19.7)**	288 (24.5)
Normal, *n* (%)	73 (76.8)	299 (78.5)	255 (72.2)	889 (71.1)	186 (71.8)**	845 (72.0)
ALT, IU/L	29 (19–47)*	24 (17–35)	24 (17–38)	24 (17–35)	25 (18–39)	24 (17–35)
Triglycerides, mg/dL	162 (117–227)	148 (108–195)	167 (119–239)	156 (117–216)	159 (110–234)	156 (114–218)
HDL-C, mg/dL	37.9 (32.1–42.0)	44.0 (36.0–52.0)	41.0 (35.2–48.0)	43.0 (37.0–51.0)	41.0 (35.2–49.1)	43.0 (37.1–52.0)
LDL-C, mg/dL	106.6 (83.0–126.0)	106.0 (88.0–127.0)	95.0 (74.0–117.0)	93.0 (70.0–116.0)	94.0 (74.3–118.2)	89.3 (67.0–118.0)
HOMA2-IR						
Computed with fasting insulin	2.3 (1.7–3.2)	1.8 (1.2–2.7)	2.2 (1.5–3.3)	2.0 (1.3–3.0)	N/A	N/A
Computed with fasting C-peptide	2.0 (1.6–2.4)	1.8 (1.3–2.5)	2.0 (1.4–2.7)	2.0 (1.4–2.7)	N/A	N/A

Data are mean (SD) or median (first quartile–third quartile), unless otherwise noted. Comparisons of subgroups within studies included ANOVA and Wilcoxon rank sum test (continuous variables) and χ^2 test (categorical variables). "Other" race includes multiple or native Hawaiian or other Pacific Islander. N/A, not available. [a]One patient was excluded due to missing information on age at T2D onset. [b]Hyperfiltration is defined as an eGFR >135 mL/min/1.73 m^2 (Chronic Kidney Disease Epidemiology Collaboration creatinine-based equation). *$P < 0.05$ and **$P < 0.001$ early-onset vs. later-onset T2D.

between the two subgroups (Supplementary Fig. 1). Estimated treatment differences for change in HbA_{1c} by subgroup are presented in Supplementary Tables 4–6). At the primary end point, 85–94% of participants on tirzepatide, 15 mg, with early-onset T2D reached an HbA_{1c} target <7.0% compared with 89–94% of participants with later-onset T2D (Supplementary Table 1). Furthermore, 46–65% of participants with early-onset T2D on tirzepatide, 15 mg, reached an HbA_{1c} target <5.7% compared with 47–51% of participants with later-onset T2D (Supplementary Table 1). Estimated treatment differences for proportion of participants reaching HbA_{1c} targets by subgroup are presented in Supplementary Tables 4–6).

In SURPASS-2, tirzepatide at all doses (5 mg, 10 mg, and 15 mg) was associated with similar improvements in BW in participants with early-onset versus later-onset T2D at week 40 (Fig. 1*B*), with an overall LSM reduction from baseline in BW of −13.5 kg (−14.0%) in the early-onset T2D subgroup versus −12.0 kg (−12.7%) in the later-onset T2D subgroup treated with tirzepatide, 15 mg (Supplementary Table 1), reaching a final LSM BW of 83.6 kg vs. 81.0 kg at week 40, respectively.

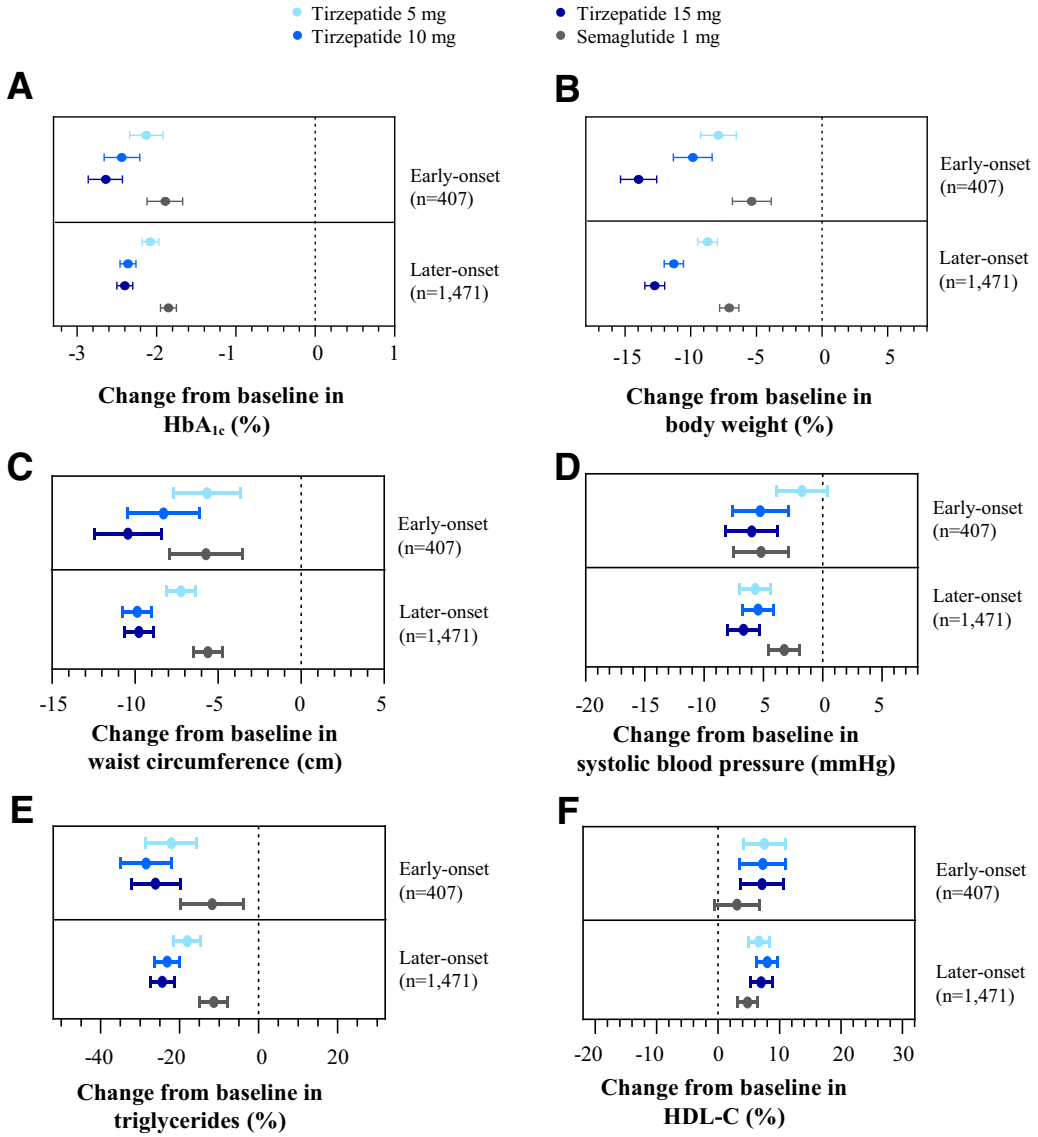

Figure 1—Change from baseline in HbA_{1c}, BW, and cardiometabolic parameters at week 40 in people with early-onset vs. later-onset T2D in SURPASS-2. Analysis based on data from participants while on assigned treatment without rescue medication (efficacy estimand). Data are LSM and 95% CIs within subgroups and treatment arms derived from MMRM, adjusted for baseline values and study stratification factors. Lipid profiles were analyzed on the log scale and then converted back to the percent change. The interactions between the treatment and onset of T2D were assessed using the same MMRM model applied to the overall population with additional terms for onset of T2D (early-onset or later-onset), treatment-by-onset of T2D, time-by-onset of T2D, and treatment-by-time-by-onset of T2D terms. Background therapy was metformin. (*A*) Change from baseline in HbA_{1c} in people with early-onset vs. later-onset T2D at week 40 in SURPASS-2. The treatment-by-early-onset interaction at week 40 was $P = 0.436$. (*B*) Percent change from baseline in BW in people with early-onset vs. later-onset T2D at week 40 in SURPASS-2. The treatment-by-early-onset interaction at week 40 was $P = 0.011$. (*C*) Change from baseline in WC in people with early-onset vs. later-onset T2D at week 40 in SURPASS-2. The treatment-by-early-onset interaction at week 40 was $P = 0.300$. (*D*) Change from baseline in systolic BP in people with early-onset vs. later-onset T2D at week 40 in SURPASS-2. The treatment-by-early-onset interaction at week 40 was $P = 0.032$. (*E*) Percent change from baseline in triglycerides in people with early-onset vs. later-onset T2D at week 40 in SURPASS-2. The treatment-by-early-onset interaction at week 40 was $P = 0.837$. (*F*) Percent change from baseline in HDL-C in people with early-onset vs. later-onset T2D at week 40 in SURPASS-2. The treatment-by-early-onset interaction at week 40 was $P = 0.811$.

Improvements were similarly seen in SURPASS-1 and SURPASS-3 (Supplementary Tables 2 and 3 and Figs. 2 and 3), and no differential treatment effect on BW was observed between the two subgroups (Supplementary Fig. 2). Estimated treatment differences for change in BW by subgroup are presented in Supplementary Tables 4–6.

Change in Cardiometabolic Parameters and Insulin Sensitivity

In SURPASS-2, tirzepatide at all doses (5 mg, 10 mg, and 15 mg) was associated with similar improvements in WC, systolic BP, and lipids (triglycerides and HDL-C) in participants with early-onset versus later-onset T2D at week 40 (Fig. 1*C*–*F*). In participants treated with tirzepatide, 15 mg, LSM reductions from baseline in WC were −10.4 cm in the early-onset T2D subgroup versus −9.8 cm in the later-onset T2D subgroup (Supplementary Table 1). Furthermore, systolic BP reduced by −6.0 mmHg vs. −6.7 mmHg (LSM), triglycerides reduced by −26.1% vs. −24.4% (LSM), and HDL-C increased by 7.2% vs. 7.0% (LSM), respectively

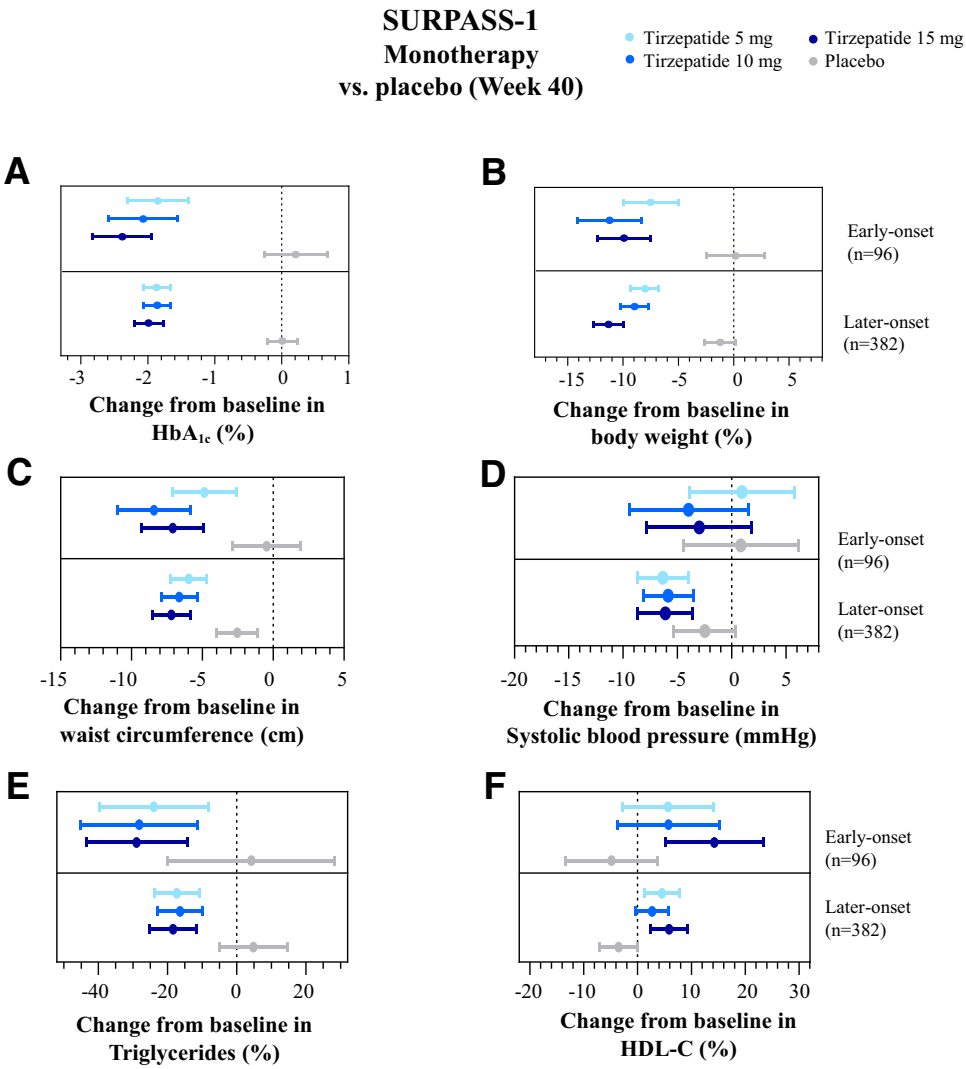

Figure 2—Change from baseline in HbA_{1c}, BW, and cardiometabolic parameters in people with early-onset vs. later-onset T2D in SURPASS-1. Analysis based on data from participants while on assigned treatment without rescue medication (efficacy estimand). Data are LSM and 95% CIs within subgroups and treatment arms derived from MMRM, adjusted for baseline values and study stratification factors. Lipid profiles were analyzed on the log-scale and then converted back to the percent change. The interactions between the treatment and onset of T2D were assessed using the same MMRM model applied to the overall population with additional terms for onset of T2D (early-onset and later-onset), treatment-by-onset of T2D, time-by-onset of T2D, and treatment-by-time-by-onset of T2D terms. (*A*) Change from baseline in HbA_{1c} in people with early-onset vs. later-onset T2D at week 40 in SURPASS-1. The treatment-by-early-onset interaction at week 40 was $P = 0.378$. (*B*) Percent change from baseline in BW in people with early-onset vs. later-onset T2D at week 40 in SURPASS-1. The treatment-by-early-onset interaction at week 40 was $P = 0.292$. (*C*) Change from baseline in WC in people with early-onset vs. later-onset T2D at week 40 in SURPASS-1. The treatment-by-early-onset interaction at week 40 was $P = 0.284$. (*D*) Change from baseline in systolic BP in people with early-onset vs. later-onset T2D at week 40 in SURPASS-1. The treatment-by-early-onset interaction at week 40 was $P = 0.569$. (*E*) Percent change from baseline in triglycerides in people with early-onset vs. later-onset T2D at week 40 in SURPASS-1. The treatment-by-early-onset interaction at week 40 was $P = 0.794$. (*F*) Percent change from baseline in HDL-C in people with early-onset vs. later-onset T2D at week 40 in SURPASS-1. The treatment-by-early-onset interaction at week 40 was $P = 0.476$. Early-onset means diagnosis of T2D before age 40 years. *n* is the number of participants in the subgroup across all treatment arms.

(Supplementary Table 1). Improvements were similarly seen in SURPASS-1 and SURPASS-3 (Supplementary Tables 2 and 3 and Figs. 2 and 3). Among the 16 individuals with baseline eGFR in hyperfiltrating range (>135 mL/min/1.73 m^2), 8 no longer had eGFR in the hyperfiltrating range (5 from tirzepatide, 2 from placebo, and 1 from the semaglutide group) at the primary end point (week 40 or 52).

Similar improvements in insulin resistance were observed in those with early-onset versus later-onset T2D, as demonstrated by reductions of HOMA2-IR (computed with fasting C-peptide) of −23.4% vs. −17.8% in SURPASS-2 (Supplementary Table 1). Similar findings were observed in SURPASS-1 (Supplementary Table 2). HOMA2-IR data were not collected in SURPASS-3.

For all evaluated cardiometabolic parameters as well as insulin sensitivity, there was no evidence of a differential treatment effect between the subgroups. Estimated treatment differences for additional cardiometabolic parameters and insulin sensitivity by subgroup are presented in Supplementary Tables 4–6.

Safety

Across the populations analyzed, at least one treatment-emergent adverse event was reported by 60–74% of participants with early-onset T2D versus 64–68% of participants with later-onset T2D (Supplementary Table 7). Nausea and diarrhea

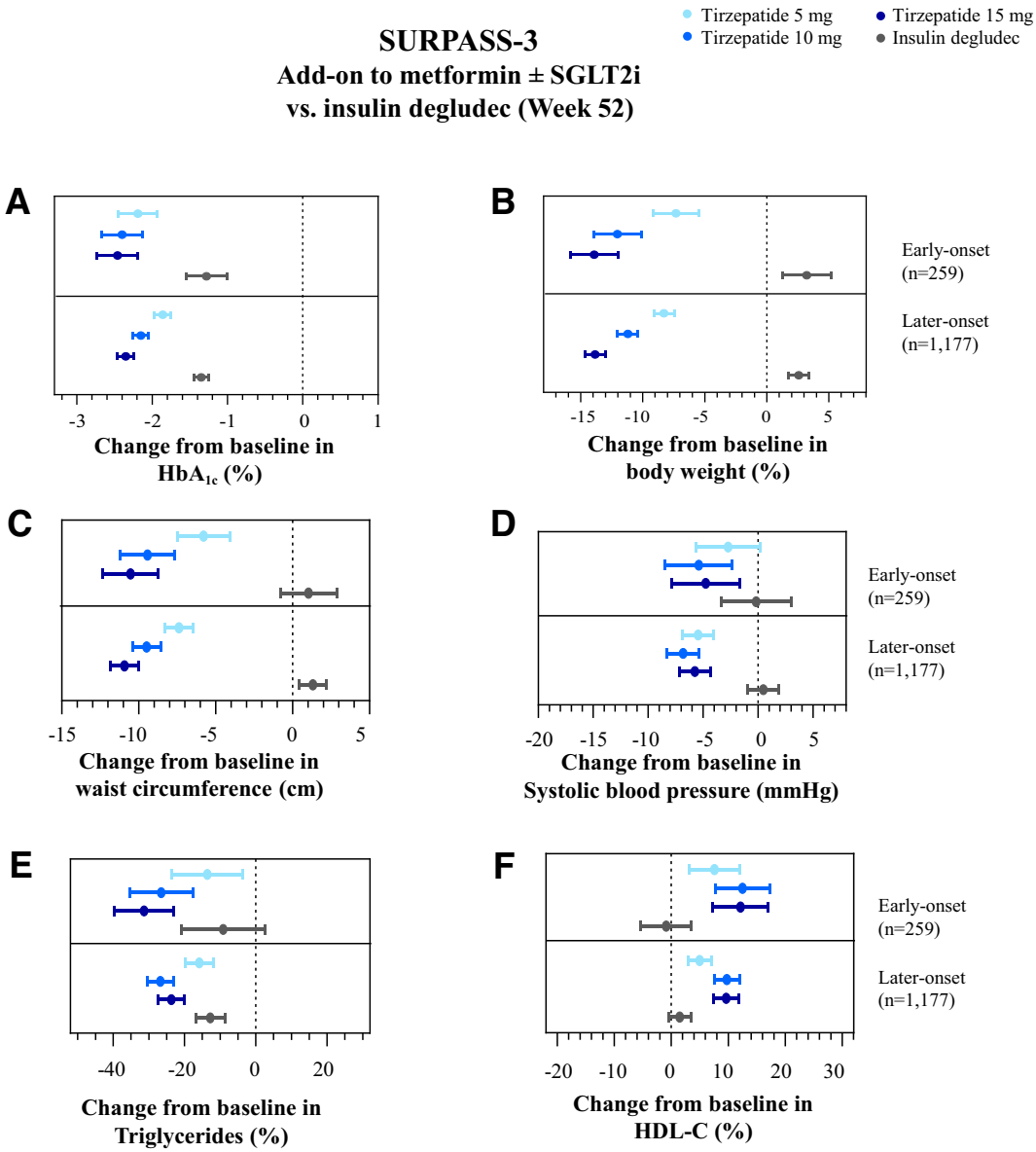

Figure 3—Change from baseline in HbA_{1c}, BW, and cardiometabolic parameters in people with early-onset vs. later-onset T2D in SURPASS-3. Analysis based on data from participants while on assigned treatment without rescue medication (efficacy estimand). Data are LSM and 95% CIs within subgroups and treatment arms derived from MMRM, adjusted for baseline values and study stratification factors. Lipid profiles were analyzed on the log scale and then converted back to the percent change. The interactions between the treatment and onset of T2D were assessed using the same MMRM model applied to the overall population with additional terms for onset of T2D (early-onset and later-onset), treatment-by-onset of T2D, time-by-onset of T2D, and treatment-by-time-by-onset of T2D terms. Background therapy was metformin with or without SGLT2i. (*A*) Change from baseline in HbA_{1c} in people with early-onset vs. later-onset T2D at week 52 in SURPASS-3. The treatment-by-early-onset interaction at week 52 was $P = 0.132$. (*B*) Percent change from baseline in BW in people with early-onset vs. later-onset T2D at week 52 in SURPASS-3. The treatment-by-early-onset interaction at week 52 was $P = 0.521$. (*C*) Change from baseline in WC in people with early-onset vs. later-onset T2D at week 52 in SURPASS-3. The treatment-by-early-onset interaction at week 52 was $P = 0.692$. (*D*) Change from baseline in systolic BP in people with early-onset vs. later-onset T2D at week 52 in SURPASS-3. The treatment-by-early-onset interaction at week 52 was $P = 0.681$. (*E*) Percent change from baseline in triglycerides in people with early-onset vs. later-onset T2D at week 52 in SURPASS-3. The treatment-by-early-onset interaction at week 52 was $P = 0.280$. (*F*) Percent change from baseline in HDL-C in people with early-onset vs. later-onset T2D at week 52 in SURPASS-3. The treatment-by-early-onset interaction at week 52 was $P = 0.320$.

were the most commonly reported treatment-emergent adverse events among participants, irrespective of T2D onset (nausea: 14–19% vs. 11–20%; diarrhea: 12–19% vs. 9–14% for early-onset vs. later-onset T2D, respectively). A similar number of participants experienced serious adverse events across groups (1–5% vs. 3–7%, respectively) (Supplementary Table 7). Study discontinuation rates ranged from 4–13% vs. 5–10%, and treatment discontinuation rates ranged from 6–13% to 12–15% of participants with early-onset T2D versus later-onset T2D, respectively (Supplementary Table 7).

CONCLUSIONS

In this post hoc analysis, we report the characteristics of people with early-onset T2D in SURPASS studies and their response to treatment with tirzepatide, a once-weekly GIP and GLP-1 receptor agonist. Approximately one in five participants included in this analysis met

the definition of early-onset T2D, which is a relatively high representation of this group that has otherwise been severely underrepresented in previous clinical studies (19,20). The analysis demonstrated that people with early-onset T2D had overall worse metabolic health status at baseline, including higher glycemic levels, higher mean BW and BMI, and a similarly atherogenic lipid profile (i.e., elevated triglycerides and low HDL-C). Nevertheless, improvements in HbA_{1c}, BW, and cardiometabolic parameters, including WC, lipids, and BP, were similar in participants with early-onset T2D compared with those with later-onset T2D treated with tirzepatide, and there was no indication of a differential treatment effect for any of the investigated parameters.

The observation that people with early-onset T2D have worse metabolic health status compared with individuals with later-onset T2D is consistent with the current literature, predominantly focused on individuals with T2D diagnosed in adolescence. Early-onset T2D is a more aggressive disease marked by faster pancreatic β-cell deterioration (30,31) and is less responsive to antihyperglycemic treatment, such as metformin, compared with later-onset T2D (18). In turn, people with early-onset T2D may be at higher risk of uncontrolled hyperglycemia over the course of T2D and at higher risk of long-term complications of T2D (10,12). Indeed, studies have shown that individuals with early-onset T2D had a twofold higher mortality compared with type 1 diabetes or age-matched control subjects (32). Furthermore, earlier diagnosis of diabetes was associated with lower life expectancy in a large observational study, thus underscoring the urgency of early diagnosis and effective treatment of people with early-onset T2D (17).

Notably, the glycemic and BW loss responses observed with tirzepatide treatment were equally robust in the early-onset T2D group compared with the later-onset T2D group. Furthermore, these responses appeared dose dependent. Regarding glycemic targets, the proportion reaching HbA_{1c} $<7\%$ or $<5.7\%$ was similarly high with tirzepatide, 15 mg, treatment between the two groups, with nearly half or more of participants with early-onset T2D reaching HbA_{1c} $<5.7\%$ with tirzepatide treatment. In addition, use of tirzepatide, 15 mg,′ was associated with similarly improved cardiometabolic risk factors, including WC, lipids, BP, and insulin sensitivity between the two groups, as shown with tirzepatide in other studies (33,34). In previous studies, youth with T2D experienced a higher prevalence of glycemic failure despite being on metformin, with or without added rosiglitazone (10,11). Combined, these results support the efficacy of tirzepatide in early-onset T2D and support future studies on the long-term health effects of early use of tirzepatide in this group.

There are several important clinical implications to treating individuals with early-onset T2D to achieve early glycemic control. First, early tight glycemic control (HbA_{1c} $<5.7\%$) led to improved long-term glycemic control in the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study of teens with newly diagnosed T2D (35,36). By achieving early sustained glycemic control, this population may be more likely to avoid long-term complications (12,35). Second, early glycemic control and improved insulin sensitivity in this population may attenuate the loss of pancreatic β-cell function, as suggested by rapid β-cell deterioration otherwise observed in this population despite conventional therapies such as metformin, insulin, or intensive lifestyle intervention (18,35). Additionally, early glycemic control in individuals with early-onset T2D has the potential to reduce the adverse impact of T2D on pregnancy outcomes given the reproductive age of this population (37). However, the safety and efficacy of tirzepatide treatment has not been studied among pregnant individuals or on pregnancy outcomes.

The strengths of the study are the inclusion of a sufficient number of participants with early-onset T2D in the data set with detailed baseline and efficacy data over a 40- to 52-week time period. Limitations include the post hoc nature of the data analysis from the SURPASS clinical trial program, lack of longitudinal data on whether the treatment effects are durable, and the potential role of the longer duration of T2D in the early-onset T2D group compared with the later-onset T2D group to confound the study observations.

In conclusion, despite younger baseline age, participants with early-onset T2D from the SURPASS program were relatively well represented with one in five categorized as having early-onset T2D, and these participants had an overall worse metabolic health status at baseline (e.g., worse glycemic control, higher mean BW and BMI, and similarly atherogenic lipid profile) compared with those with later-onset T2D. Notably, in this post hoc analysis, HbA_{1c}, BW, and cardiometabolic markers improved substantially with tirzepatide, showing improvement irrespective of age at T2D diagnosis, which contrasts with less response to antihyperglycemic treatment previously reported in people diagnosed with T2D in early age. Future studies are warranted to determine whether treating individuals with early-onset T2D earlier to achieve and sustain health goals will improve long-term outcomes.

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and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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