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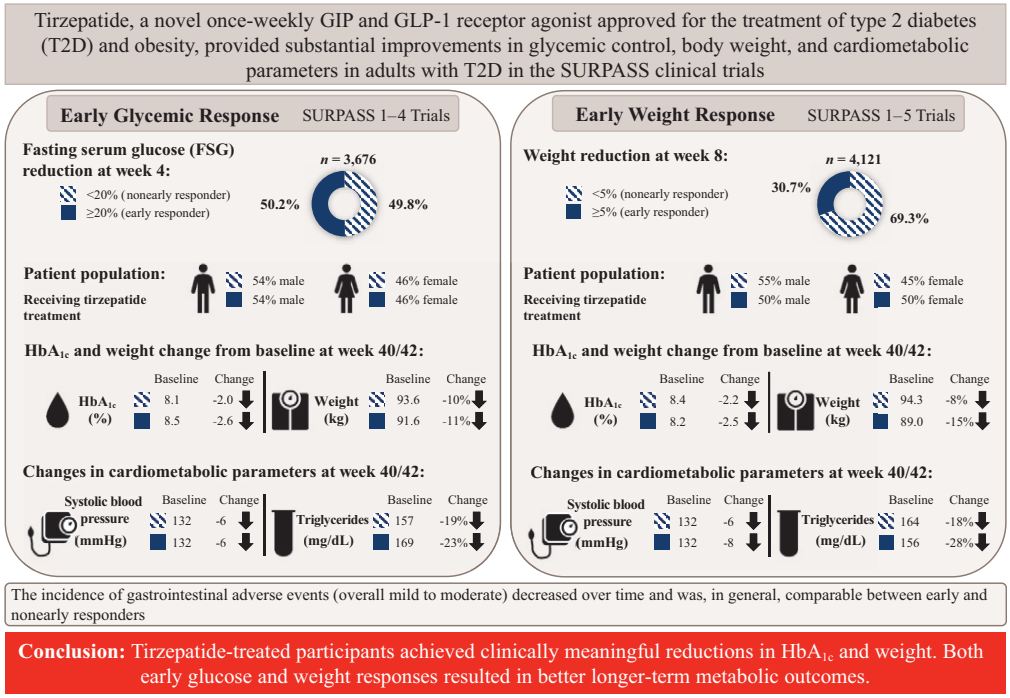

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Identifying characteristics of therapeutic response is of clinical importance towards a more efficient and individualized approach in the treatment of type 2 diabetes. However, the association between the early response to tirzepatide and longer term outcomes in patients with type 2 diabetes is not known.

- **What is the specific questions we wanted to answer?**
  What are late (week 40 or 42) metabolic outcomes, measured by early glycemic and weight response, in study participants with type 2 diabetes treated with tirzepatide?

- **What did we find?**
  Study participants treated with tirzepatide achieved clinically meaningful reductions in HbA_{1c} and weight, regardless of early response. Early responders in terms of fasting serum glucose levels were younger, with higher glycemic parameters and lower weight at baseline. Early responders in terms of weight reduction had lower glycemic parameters and weight at baseline and more frequently were women and White. Early responders in terms of glucose or weight achieved better metabolic outcomes at week 40 or 42.

- **What are the implications of our findings?**
  These findings may help clinicians individualize the treatment of their patients to achieve their therapeutic goals.

- **Why did we undertake this study?**
  Identifying characteristics of therapeutic response is of clinical importance towards a more efficient and individualized approach in the treatment of type 2 diabetes. However, the association between the early response to tirzepatide and longer-term outcomes in patients with type 2 diabetes is not known.

Early Fasting Serum Glucose or Weight Reduction With Tirzepatide and Metabolic Outcomes in People With Type 2 Diabetes: A Post Hoc Analysis of the SURPASS Trials

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ORIGINAL ARTICLE

OBJECTIVE

To evaluate late (week 40 or 42; hereafter, week 40/42) metabolic outcomes by early glycemic response (<20% or ≥20% fasting serum glucose [FSG] reduction at week 4) or weight response (<5% or ≥5% weight reduction at week 8), respectively, in tirzepatide-treated participants with type 2 diabetes in the SURPASS trials.

RESEARCH DESIGN AND METHODS

This post hoc analysis used pooled data across trials. Baseline characteristics, change from baseline to week 40/42 for efficacy parameters, and gastrointestinal (GI) adverse events (AEs) were described and analyzed by early response in terms of FSG (SURPASS-1 to -4; *n* = 3,676) or weight (SURPASS-1 to -5; *n* = 4,121) in the efficacy and safety analysis set, respectively.

RESULTS

Early responders in FSG (50%) were younger, with higher glycemic parameters and lower weight at baseline. Early responders in weight (31%) had lower glycemic parameters and weight at baseline, and a greater percentage were women and White. Early versus nonearly responders in FSG or weight achieved better HbA_{1c} (−2.6% vs. −2.0% or −2.5% vs. −2.2%, respectively) and weight (−11% vs. −10% or −15% vs. −8%, respectively) responses at week 40/42 and greater improvements in blood pressure and lipids profile. Nonearly responders also had clinically meaningful HbA_{1c} and weight reductions with all tirzepatide doses. The incidence of GI AEs (generally mild to moderate events) decreased over time and was, in general, comparable between early and nonearly responders.

CONCLUSIONS

Both early glucose and weight responses with tirzepatide were associated with better longer-term metabolic outcomes. Early response may be a good clinical indicator that could help inform treatment individualization to achieve therapeutic goals.

Type 2 diabetes is often associated with overweight and obesity; therefore, current guidelines recommend a multifactorial approach including correction of hyperglycemia as well as weight management (1). To achieve this, lifestyle intervention and pharmacological therapy with potential for both glycemic control and weight loss are frequently required.

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Tirzepatide is a once-weekly glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist approved for the treatment of type 2 diabetes and obesity. Tirzepatide provided greater glycemic control and body weight reduction compared with placebo and active comparators and led to improvements in cardiometabolic parameters in participants with type 2 diabetes in the phase 3 SURPASS trials (2–7). Up to 62% of tirzepatide-treated participants achieved normal levels of glycated hemoglobin (HbA_{1c} <5.7%) and up to 43% achieved ≥15% body weight reduction from baseline (8). Overall, typically mild to moderate and transient gastrointestinal (GI) adverse events (AEs), such as nausea, vomiting, and diarrhea, were the most common AEs observed with tirzepatide, which is generally consistent with the safety profile of the GLP-1 receptor agonist class (8).

Identifying characteristics of therapeutic response is of clinical importance toward a more efficient and individualized approach in the treatment of type 2 diabetes. However, the association between the early response to tirzepatide and longer-term outcomes in patients with type 2 diabetes is not known. The aim of this analysis is to *1*) identify distinct patient profiles for early glycemic response (<20% or ≥20% fasting serum glucose [FSG] reduction at week 4) and body weight response (<5% or ≥5% weight reduction at week 8), respectively, and *2*) examine the association of early response with longer-term (week 40 or 42) metabolic outcomes observed with tirzepatide in the SURPASS trials.

RESEARCH DESIGN AND METHODS

Study Design and Participants

In this post hoc analysis, data from the 5 phase 3 SURPASS clinical trials (SURPASS-1 to -5) were pooled across studies in participants with type 2 diabetes randomly assigned to receive once-weekly tirzepatide 5, 10, or 15 mg. Tirzepatide was initiated at 2.5 mg once weekly for 4 weeks. Then, the dose was escalated in increments of 2.5 mg every 4 weeks until the randomized dose of 5, 10, or 15 mg was achieved. The background antihyperglycemic medications were none in SURPASS-1, metformin in SURPASS-2, metformin with or without a sodium–glucose cotransporter 2 inhibitor (SGLT2i) in SURPASS-3, any combination of metformin, sulfonylurea, and SGLT2i in SURPASS-4, and titrated insulin glargine with or without metformin in SURPASS-5. The study design of the SURPASS-1 to -5 trials has previously been published (2–6).

Data from tirzepatide-treated participants were categorized into two subgroups: early responders versus nonearly responders. In the analysis by early FSG response, participants from the SURPASS-1 to -4 trials were categorized into <20% or ≥20% FSG reduction from baseline at week 4. A 20% FSG reduction cutoff was thought to represent a clinically meaningful early response. At week 4, all tirzepatide-treated participants had received the 2.5-mg dose for 4 weeks. Data from SURPASS-5 were not included, to avoid the variability in FSG due to the background basal insulin management during the first 4 weeks. In the analysis by early weight response, participants from the SURPASS-1 to -5 trials were categorized into <5% or ≥5% weight reduction from baseline at week 8. A 5% weight reduction cutoff was chosen because this is suggested by current guidelines as the minimum primary target of management for many people living with type 2 diabetes (1) and allowed for a suitable sample size at week 8. At week 8, all tirzepatide-treated participants had received the 2.5-mg dose for the first 4 weeks and 5-mg dose for the following 4 weeks. Because changes in FSG over time occurred faster than changes in body weight (2–6), early response in FSG was defined at week 4 versus week 8 for early response in weight.

The inclusion and exclusion criteria of the SURPASS-1 to -5 trials have previously been published (2–6). Briefly, participants were adults with type 2 diabetes (mean baseline HbA_{1c} ranging from 7.94% to 8.52% and BMI ranging from 31.9 to 34.2 kg/m^2).

The protocols were approved by local institutional review boards, and the trials were conducted in accordance with the Declaration of Helsinki, the Council of International Organizations of Medical Sciences International Ethical Guidelines, and Good Clinical Practice guidelines. All participants provided written informed consent.

Outcomes

The following efficacy outcomes were assessed and compared between subgroups of early and nonearly responders: changes from baseline to week 40 in HbA_{1c} and body weight and the proportion of participants achieving at week 40 an HbA_{1c} <7% (53 mmol/mol) and <5.7% (39 mmol/mol); a weight reduction from baseline of ≥10% and ≥15%; and the composite end point of HbA_{1c} <7% and ≥10% weight reduction from baseline. The HbA_{1c} thresholds were chosen based on either guideline-recommended target (<7%) or the levels considered normal (<5.7%) (1). The weight reduction thresholds were chosen based on guidelines suggesting weight reduction of 5–15% as a primary target of management for many people living with type 2 diabetes (1). Within this recommended range, higher magnitude of weight reduction (10–15% or more) can have a disease-modifying effect (9). In addition, changes from baseline at week 40 in blood pressure and fasting lipids were reported. The actual time points for the assessments were week 40 (SURPASS-1, -2, -3, and -5) or week 42 (SURPASS-4) because this was the last time point with data available for all trials; thus, we refer to week 40/42 where applicable. Safety outcomes included the incidence of treatment-emergent GI AEs (nausea, vomiting, or diarrhea) over time within each subgroup of early and nonearly responders.

Statistical Analysis

This post hoc analysis used the efficacy analysis set, which included all randomly assigned participants who received at least one dose of tirzepatide and excluded participants who were inadvertently enrolled. Data after initiating rescue antihyperglycemic medication or prematurely stopping tirzepatide (last dose date plus 7 days) were excluded. Safety analyses were performed in all randomly assigned participants who received at least one dose of tirzepatide regardless of initiating rescue antihyperglycemic medication or permanent study discontinuation. Participant population was analyzed by early response to therapy: early response in FSG or weight.

Continuous measurements were assessed using mixed-model repeated measures (MMRM). The model was adjusted for key baseline covariates (e.g., baseline HbA_{1c}, baseline weight, baseline FSG in the analysis by early response in FSG, age, sex, and study) to account for any potential imbalances in baseline characteristics

due to subgroup categorization by post-randomization changes in FSG (week 4) or body weight (week 8). The MMRM model used early FSG or weight reduction subgroup, visit, and early FSG or weight reduction subgroup-by-visit interaction as fixed effects. For the MMRM model, no missing value imputation was used.

For categorical outcomes, the logistic regression model was used with the aforementioned additional covariates to account for potential imbalances. Missing end point measurements were imputed by predictions based on MMRM models using the observed data in the efficacy analysis set from the same treatment group and then dichotomized for each study, respectively, for the responder analysis. Individual covariate adjustment for missing value imputation based on the SURPASS-1 to -5 trials has previously been reported (2–6). All the statistical analyses were carried out using SAS, version 9.4.

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, 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

Participants

The analysis by early response in FSG included 3,676 tirzepatide-treated participants with type 2 diabetes from the SURPASS-1 to -4 clinical trials. Of these, 50% achieved ≥20% FSG reduction at week 4 (Table 1). At baseline, these early responders were younger; a slightly greater percentage were Hispanic or Latino; had higher HbA_{1c}, FSG, triglycerides, and VLDL cholesterol levels; and had lower body weight than those achieving <20% FSG reduction at week 4 (nonearly responders).

The analysis by early response in body weight included 4,121 tirzepatide-treated participants with type 2 diabetes from the SURPASS-1 to -5 clinical trials. Of these, 31% achieved ≥5% body weight reduction at week 8 (Table 1). At baseline, slightly greater percentages of these early responders were women, White, used prior oral antihyperglycemic medication, and had lower HbA_{1c}, FSG, body weight, triglyceride, LDL cholesterol, and VLDL cholesterol levels. Among participants who lost <5% of weight in the first 8 weeks from baseline (nonearly responders), the majority (81.3%) lost >0.5 kg, 11.8% had stable weight, and 7% experienced weight gain.

In both analyses of early response (FSG and body weight), there were slight differences in the use of background antihyperglycemic medication between early and nonearly responders (Table 1). However, the distribution of background antihyperglycemic medication was consistent between early and nonearly responders in both analyses.

Glycemic Outcomes by Early Response

Significantly greater HbA_{1c} reductions from baseline to week 40 were observed with all tirzepatide doses in early versus nonearly responders ($P \leq 0.001$) (Fig. 1*A* and *B*). In the analysis by early response in FSG, decreases from baseline in HbA_{1c} at week 40 ranged from 2.38% to 2.70% vs. 1.73% to 2.17%, respectively (Fig. 1*A*). In the analysis by early response in body weight, decreases from baseline in HbA_{1c} ranged from 2.30% to 2.62% vs. 1.97% to 2.37%, respectively (Fig. 1*B*).

Significantly greater percentages of early versus nonearly responders ($P \leq 0.05$) achieved HbA_{1c} <7% and <5.7% at week 40 with all tirzepatide doses in both analyses of early response (Fig. 1*C*–*F*).

Weight-Related Outcomes by Early Response

Greater weight reductions from baseline to week 40 were observed with all tirzepatide doses in early versus nonearly responders (Fig. 2*A* and *B*). In the analysis by early response in FSG, decreases from baseline in body weight at week 40 ranged from 8.5% to 13.2% vs. 7.5% to 12.6%, respectively (Fig. 2*A*). Comparison between early and nonearly responders in FSG was not statistically different with the tirzepatide 15-mg dose. In the analysis by early response in body weight, decreases from baseline in body weight ranged from 12.4% to 18.0% vs. 5.8% to 10.4%, respectively (Fig. 2*B*).

Greater percentages of early versus nonearly responders achieved ≥10% and ≥15% weight reduction from baseline at week 40 with all tirzepatide doses in both analyses of early response (Fig. 2*C*–*F*). Comparison between early and nonearly responders was not statistically different with the tirzepatide 15-mg dose for the achievement of ≥10% weight reduction threshold in the analysis by early response in FSG.

Composite End Point by Early Response

Significantly greater percentages of early versus nonearly responders ($P \leq 0.01$) achieved the composite end point of HbA_{1c} <7% and ≥10% weight reduction at week 40 with all tirzepatide doses (Supplementary Fig. 1). In the analysis by early response in FSG, 35–62% vs. 24–54% achieved this composite end point (Supplementary Fig. 1*A*), respectively. In the analysis by early response in body weight, 58–84% vs. 16–45% achieved this composite end point (Supplementary Fig. 1*B*), respectively.

Cardiometabolic Outcomes by Early Response

Decreases from baseline to week 40 in systolic and diastolic blood pressures were not statistically different between early and nonearly responders in tirzepatide-treated participants in the analysis by early response in FSG (Supplementary Table 1). Significantly greater systolic and diastolic blood pressure reductions were observed in early versus nonearly responders ($P \leq 0.001$) in the analysis by early response in body weight (Supplementary Table 1).

Significantly greater improvements from baseline to week 40 in triglyceride, HDL cholesterol, and VLDL cholesterol levels were observed in early versus nonearly responders ($P \leq 0.01$) in both FSG and weight analyses of early response (Supplementary Table 1). Decreases in LDL cholesterol were not statistically

Table 1—Demographics and baseline clinical characteristics pooled across SURPASS trials[a] by early response in FSG or body weight in tirzepatide-treated participants

	Response: FSG reduction at week 4[b]		Response: body weight reduction at week 8[b]	
	<20%	≥20%	<5%	≥5%
Characteristic	*n* = 1,829	*n* = 1,847	*n* = 2,856	*n* = 1,265
Age, years	58.9 (10.4)	57.8 (10.4)*	58.5 (10.4)	58.4 (10.4)
Female sex, *n* (%)	844 (46)	857 (46)	1,278 (45)	636 (50)**
Race, *n* (%)				
American Indian or Alaska Native	159 (9)	154 (8)	271 (10)	75 (6)*
Asian	116 (6)	128 (7)	215 (8)	94 (7)
Black or African American	70 (4)	75 (4)	118 (4)	37 (3)
Multiple	9 (1)	20 (1)	21 (1)	8 (1)
Native Hawaiian or other Pacific Islander	3 (<1)	3 (<1)	4 (<1)	2 (<1)
White	1,471 (81)	1,466 (79)	2,226 (78)	1,048 (83)*
Ethnicity, *n* (%)				
Hispanic or Latino	864 (47)	947 (51)†	1,338 (47)	573 (45)
Not Hispanic or Latino	923 (51)	862 (47)†	1,413 (50)	660 (52)
Not reported	42 (2)	38 (2)	105 (4)	32 (3)
Duration of type 2 diabetes, years	9.0 (6.9)	8.9 (6.8)	9.4 (7.0)	9.2 (7.0)
HbA_{1c}, %	8.1 (0.9)	8.5 (1.0)**	8.4 (1.0)	8.2 (0.9)**
FSG, mg/dL	149.5 (39.6)	191.6 (49.6)**	172.7 (50.9)	164.8 (48.5)**
Prior use of oral antihyperglycemic medication, *n* (%)	1,726 (94)	1,759 (95)	2,663 (93)	1,208 (96)*
Background antihyperglycemic medication, *n* (%)				
None	781 (43)	864 (47)*	1,499 (53)	585 (46)**
Metformin only	157 (9)	154 (8)	202 (7)	113 (9)
SGLT2i ± metformin	269 (15)	197 (11)*	299 (11)	167 (13)
Sulfonylurea (any)[b]	622 (34)	632 (34)	856 (30)	400 (32)
Body weight, kg	93.5 (21.3)	91.6 (19.7)*	94.3 (20.7)	89.1 (20.1)**
BMI, kg/m^2	33.8 (6.7)	33.1 (6.0)*	33.9 (6.4)	32.4 (6.1)**
Blood pressure, mmHg				
Systolic	131.6 (14.4)	131.5 (14.0)	132.1 (14.5)	131.8 (14.4)
Diastolic	78.7 (9.0)	79.3 (9.0)	79.2 (9.1)	78.7 (9.3)
Pulse rate, beats/min	73.7 (9.9)	74.7 (10.1)*	74.4 (10.2)	74.0 (10.1)
Fasting lipids, mg/dL, geometric mean (coefficient of variation [%])				
Triglycerides	157.4 (51.6)	168.6 (57.0)**	164.1 (54.9)	156.4 (53.1)*
HDL cholesterol	42.2 (25.2)	41.9 (25.3)	42.3 (25.3)	42.6 (25.5)
LDL cholesterol	84.1 (46.4)	85.7 (43.9)	86.5 (45.3)	82.0 (43.2)**
VLDL cholesterol	31.0 (47.9)	33.0 (51.6)**	32.2 (50.2)	30.8 (49.7)†

Data from participants randomized to tirzepatide who took at least one dose of study drug and excluding data after rescue or discontinuation of study drug. Percentages might not add up to 100 due to rounding. [a]Data by early response in fasting serum glucose were pooled across SURPASS-1 to -4 trials. Data by early response in body weight were pooled across SURPASS-1 to -5 trials. Data are reported as mean (SD) unless otherwise indicated. [b]"Any" refers to sulfonylurea only, with or without SGLT2i use, and with or without metformin use. †$P \leq 0.05$, *$P \leq 0.01$, **$P \leq 0.001$ between early and nonearly responders.

different between early and nonearly responders in both analyses of early response.

GI AEs by Early Response

In tirzepatide-treated participants, the incidence of self-reported nausea, vomiting, or diarrhea decreased over time in early and nonearly responders in both analyses of early response (Fig. 3). Most of these GI events were mild to moderate in severity and were reported more frequently during the first few weeks corresponding to the tirzepatide dose-escalation period (≤20 weeks). The incidence and distribution of nausea, vomiting, or diarrhea were consistent between early and nonearly responders in both analyses of early response.

CONCLUSIONS

The early assessment of response to diabetes treatment is of clinical importance to

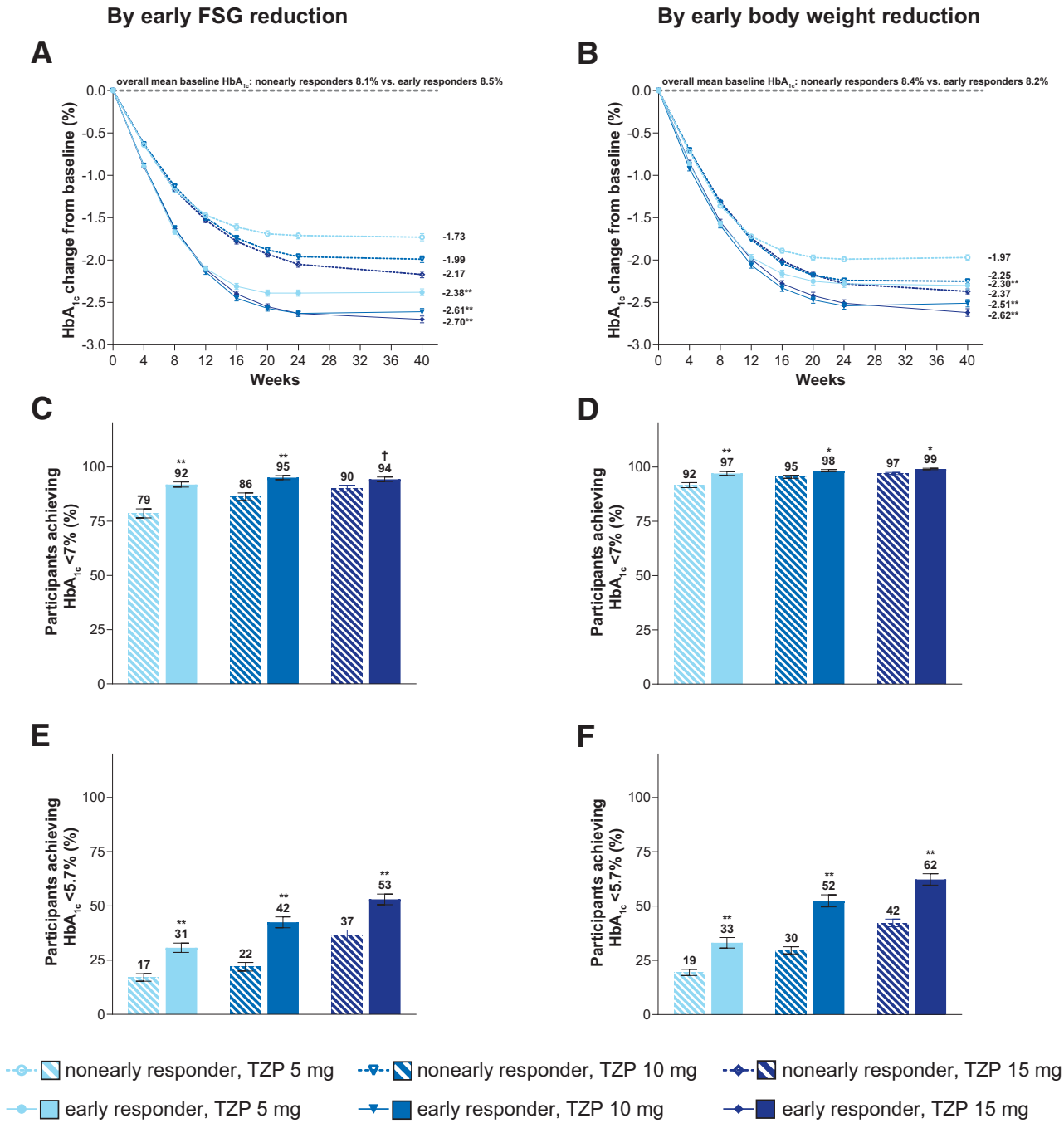

Figure 1—Change from baseline in HbA_{1c} and percentage of participants achieving HbA_{1c} <7% and <5.7% at week 40 by early response in FSG (<20% or ≥20% reduction at week 4) (*A*, *C*, *E*) or body weight (<5% or ≥5% reduction at week 8) (*B*, *D*, *F*) in tirzepatide (TZP)-treated participants. Data by early response in FSG were pooled across SURPASS-1 to -4 trials. Data by early response in body weight were pooled across SURPASS-1 to -5 trials. Data are shown as least-squares mean (*A*, *B*) or estimate (*C*–*F*), and error bars are SE from participants randomized to tirzepatide who took at least one dose of study drug and excluding data after rescue or discontinuation of study drug. †$P \leq 0.05$, *$P \leq 0.01$, **$P \leq 0.001$ between early and nonearly responders.

achieve an efficient and individualized treatment approach. Because weight management is also part of the holistic approach in the treatment of type 2 diabetes, early assessment of FSG and/or weight reduction seems relevant in understanding the effect on late metabolic outcomes.

This post hoc analysis showed that tirzepatide-treated participants with type 2 diabetes and early response in either FSG or body weight had a different baseline profile. Early versus nonearly responders in FSG were younger; had higher glycemic parameters and higher levels of triglycerides and VLDL cholesterol at baseline; and had lower body weight. These characteristics are in line with previous subgroup analyses in SURPASS-2 and SURPASS-3 showing greater HbA_{1c} reductions at weeks 40 and 52, respectively, in participants with higher baseline HbA_{1c} values (3,4). On the other hand, early versus nonearly responders in weight had lower glycemic parameters; lower levels of triglycerides, LDL cholesterol, VLDL cholesterol at baseline; lower body weight at baseline; were more

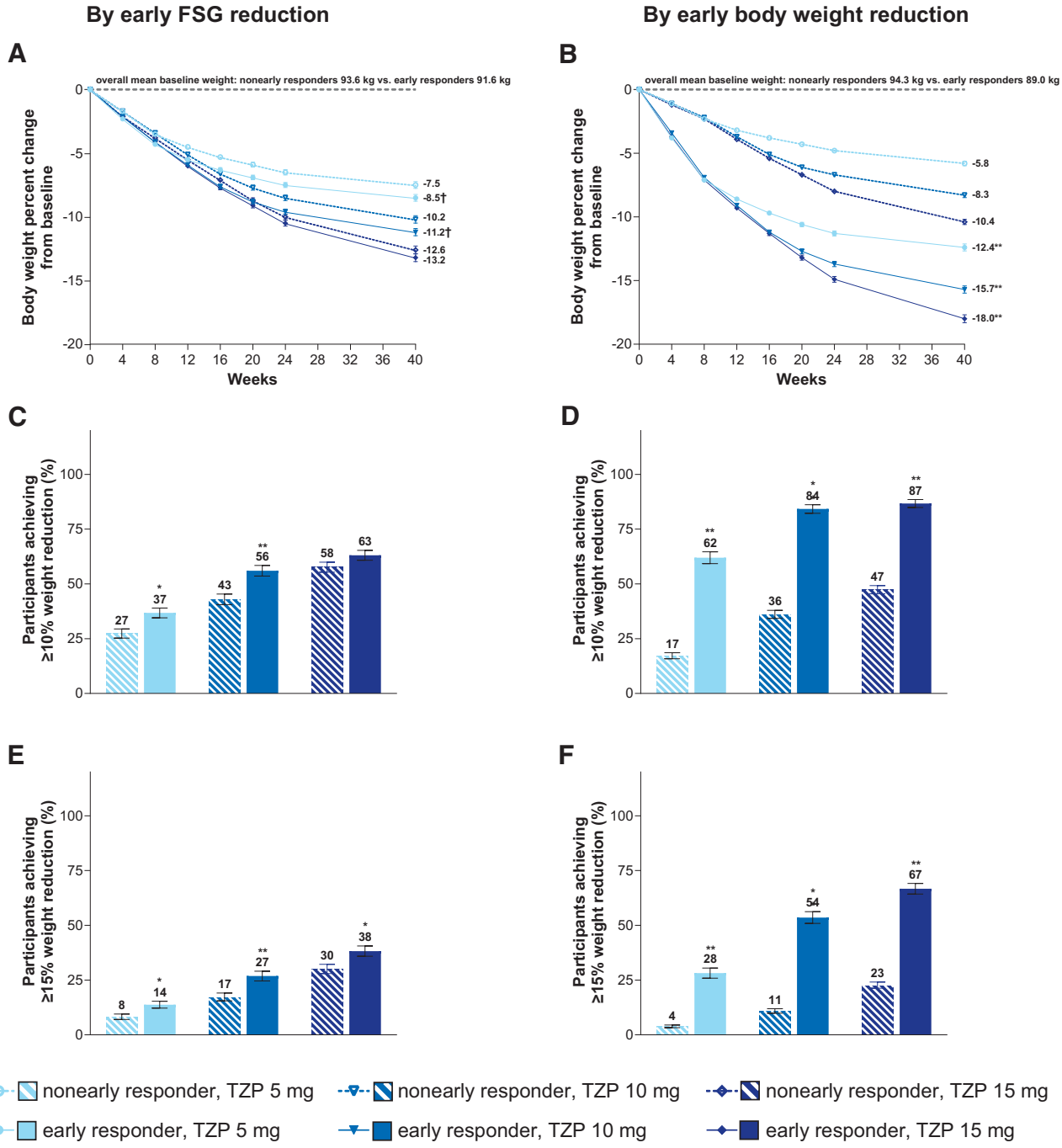

Figure 2—Percent change from baseline in body weight and percentage of participants achieving ≥10% and ≥15% weight reduction at week 40 by early response in FSG (<20% or ≥20% reduction at week 4) (*A*, *C*, *E*) or body weight (<5% or ≥5% reduction at week 8) (*B*, *D*, *F*) in tirzepatide (TZP)-treated participants. Data by early response in FSG were pooled across SURPASS-1 to -4 trials. Data by early response in body weight were pooled across SURPASS-1 to -5 trials. Data are shown as least-squares mean (*A*, *B*) or estimate (*C*–*F*), and error bars are SE from participants randomized to tirzepatide who took at least one dose of study drug and excluding data after rescue or discontinuation of study drug. †$P \leq 0.05$, *$P \leq 0.01$, **$P \leq 0.001$ between early and nonearly responders.

frequently women and White; and more frequently used prior oral antihyperglycemic medication. Previous findings from the SURPASS trials showed that tirzepatide-treated participants achieving greater body weight reduction at week 40/42 were more likely to be women, White, and taking metformin with better glycemic control and lower non-HDL cholesterol level at baseline (10). In turn, participants achieving greater body weight reduction at week 40/42 had also achieved greater weight reduction at week 8 (10). This post hoc analysis is the first time, to our knowledge, that specific baseline clinical profiles are associated with distinct time trajectories in terms of FSG and weight changes focusing on early responses.

At week 40/42, tirzepatide-treated participants achieved clinically meaningful reductions in HbA_{1c} and body weight, regardless of the early response. However, both early glucose and weight responses

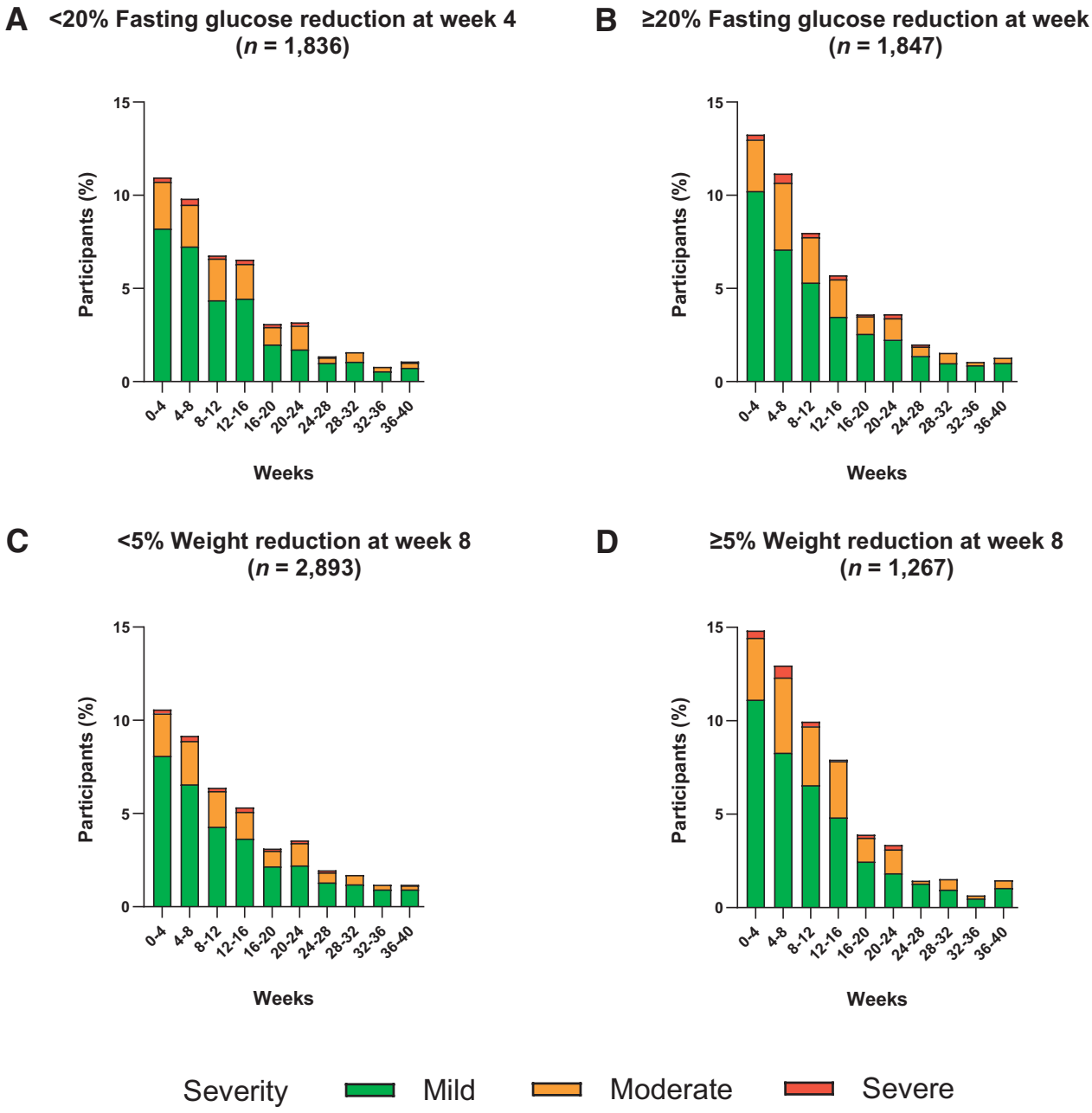

Figure 3—Incidence of any nausea, vomiting, or diarrhea events over time by early response in FSG [<20% (*A*) or ≥20% (*B*) reduction at week 4], or body weight [<5% (*C*) or ≥5% (*D*) reduction at week 8] in pooled tirzepatide-treated participants. Data by early response in FSG were pooled across SURPASS-1 to -4 trials. Data by early response in body weight were pooled across the SURPASS-1 to -5 trials. Data are shown as the proportion of participants who reported a new event relative to participants at risk during a time interval. Participants with multiple events within a time interval were counted once.

overall were associated with better longer-term metabolic outcomes, with some differences observed between both analyses of early response. Early responders in FSG had more evident later reductions in HbA_{1c} at week 40/42, and early responders in body weight had more evident later reductions in weight and blood pressure, as well as improvements in lipids at week 40/42. The HbA_{1c} plots over time (Fig. 1*A* and *B*) show that the improvement in glycemic control occurred as early as 4 weeks in early and nonearly responders in both analyses, but with a clear separation of curves already apparent at 4 weeks for early versus nonearly responders in FSG and not for early versus nonearly responders in weight. This suggests that any early improvement in insulin resistance and overall glycemic control may not be driven solely by weight reduction (11). On the other hand, the weight plots over time (Fig. 2*A* and *B*) show clear separation of curves already apparent at 4 weeks for early versus nonearly responders in weight and not for early versus nonearly responders in FSG. This and the more evident late improvements in blood pressure and lipids for early weight response collectively suggest weight reduction may exert benefits that extend beyond glycemic management to improve cardiometabolic parameters (9), while acknowledging there is a weight-dependent effect on blood pressure (12) and lipids. These findings

are consistent with those observed for early versus nonearly responders in weight with the GLP-1 receptor agonist liraglutide 3.0 mg in people with obesity and with or without type 2 diabetes (13), with semaglutide 2.4 mg in people with obesity (14), and with exenatide in women with obesity (15). Overall, these criteria for assessment of early response may help clinicians make decisions early in the course of therapy as they seek to optimize treatment (e.g., dose escalations, targets) according to individual needs and degree of response.

It should be highlighted, however, that nonearly responders also benefited from clinically meaningful long-term reductions in HbA_{1c} and body weight with all tirzepatide doses. Notably, up to approximately 50% of nonearly responders met the American Diabetes Association and European Association for the Study of Diabetes dual treatment goals of HbA_{1c} $<7\%$ and $\geq 10\%$ weight reduction at week 40 (1). This is an important observation, indicating that some people may take longer to reach their individual goals, and, ultimately, the clinician may consider optimizing the treatment by choosing the appropriate dose of tirzepatide to meet the goals for that patient. Understanding how an early response is associated with longer-term outcomes may guide clinical care in several ways. Our findings may help set up patients' expectations, because results observed in the first months might either motivate or discourage to continue therapy. Patients with lower-than-expected initial glycemic improvement may still achieve their goals in the long term with continued therapy. In addition, weight reduction is highly anticipated by patients initiating treatment with tirzepatide. Similarly to early glycemic response, patients with lower-than-expected early weight reduction may still benefit from significant weight reduction in the long term with continued treatment. Clinicians should be aware of this heterogeneity in clinical response. Our findings may also help guiding clinicians in dose management based on individual needs and degree of response. Although in clinical trials participants' treatment was escalated at 4-week intervals, escalation periods in clinical practice are often slower and more varied because patients are seen in clinic less often than in trials. Patients with an initial early response might be able to delay dose escalation, whereas patients with minimal response should be seen sooner in the clinic for dose escalation.

Generally mild to moderate nausea, vomiting, or diarrhea were reported more frequently during the first weeks, regardless of the occurrence of an early response. The incidence of GI AEs decreased over time and was, in general, comparable between early and nonearly responders. This suggests that changes in GI tolerability of tirzepatide did not contribute to the distinct FSG or weight response trajectories over time. This also supports the concept from previous post hoc analyses indicating that GI AEs have limited association with tirzepatide-induced body weight reduction (16).

Finally, we explored further the subsets of tirzepatide-treated participants who were early responders in either FSG or weight reduction or both (Supplementary Fig. 2). Only 17% of participants were early responders for both end points, further supporting heterogeneity in response to tirzepatide and suggesting that weight reduction alone as a target of therapy is not enough to assess early response from a glycemic standpoint. For early responders in both FSG and weight reduction, the participant population was similar to early responders in either FSG or weight reduction and achieved numerically greater reductions in HbA_{1c} and weight at week 40/42 compared with early responders in either FSG or weight reduction.

This analysis has some strengths. First, it includes a large number of participants across the disease continuum in the phase 3 SURPASS clinical trial program and a well-balanced number of participants in the early and nonearly responder subgroups. Furthermore, the analysis of early responses for glucose and weight was carried out in largely the same population, which allowed for comparisons.

This analysis also has several limitations. First, this was a post hoc analysis; thus, it was not powered to detect differences in treatment effect between early and nonearly responders. Second, there was a limited sample size of race groups other than White. Third, although most of the effect had already occurred by week 40/42, weight reduction outcomes may be underestimated, given the knowledge that nadir occurs after about 1.5 years of treatment. Fourth, whether treatment adherence differed between early and nonearly responders was beyond the scope of this analysis, and we do not know whether this could have affected our findings. However, 86% of tirzepatide-treated participants completed treatment in the SURPASS trials (2–6), indicating good adherence. The findings from the current analysis might be helpful in conversations with patients to encourage adherence even if the initial results do not meet their expectations.

In conclusion, in this post hoc analysis, in people with type 2 diabetes, all doses of tirzepatide led to substantial reductions in HbA_{1c} and body weight at week 40/42, regardless of their early response in either FSG or body weight. This post hoc analysis in tirzepatide-treated participants also showed that early versus nonearly responders in either FSG or body weight had greater reductions of HbA_{1c} and weight at week 40/42 as well as greater improvements in blood pressure and lipids profile. Early assessment of response may be a good indicator for clinicians to set up patients' expectations and optimize tirzepatide therapy according to patients' needs.

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