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Achieving Normoglycemia With Tirzepatide: Analysis of SURPASS 1–4 Trials

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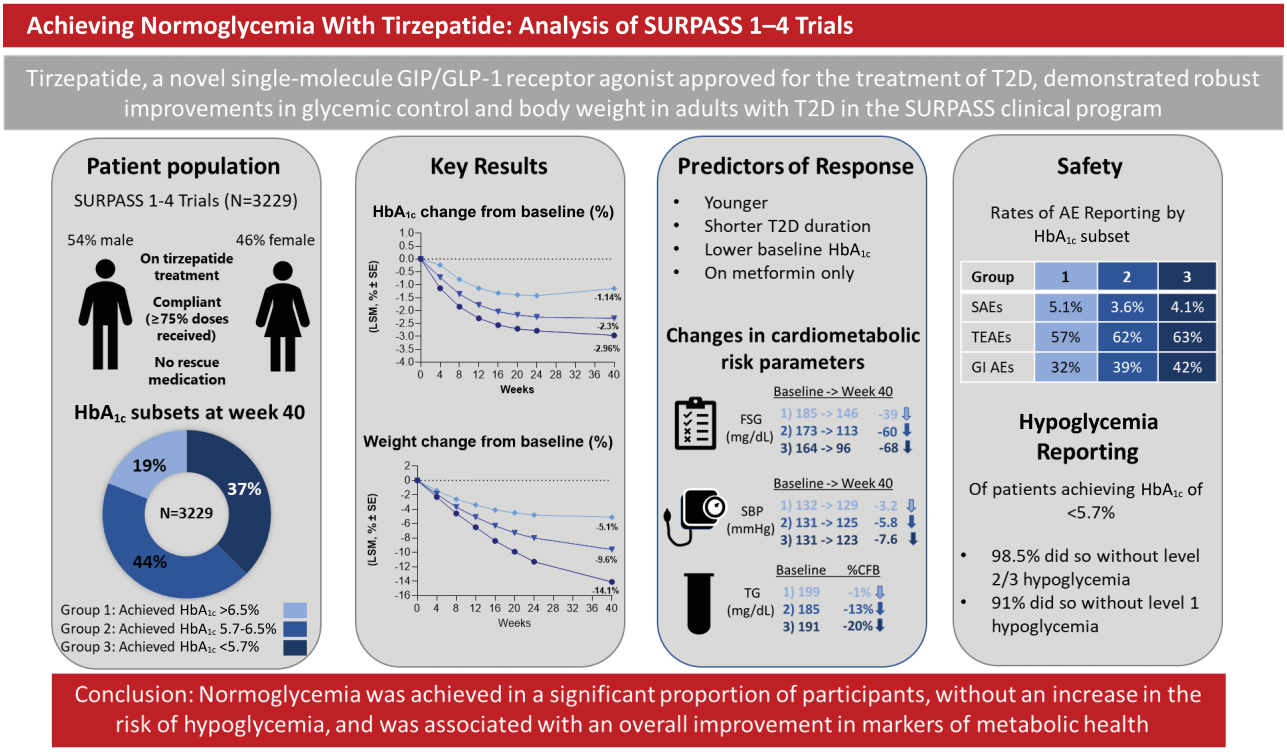

ARTICLE HIGHLIGHTS

- Normoglycemia (HbA_{1c} <5.7%) was achieved by a significant proportion of participants treated with tirzepatide in the SURPASS clinical program.
- We aimed to characterize patients who achieved HbA_{1c} <5.7% and evaluate changes in clinical markers associated with long-term cardiometabolic health.
- Tirzepatide-treated participants who achieved HbA_{1c} <5.7% were slightly younger, with a shorter duration of diabetes and lower HbA_{1c} value at baseline. Moreover, they showed greater improvements in multiple metabolic markers without an increased risk of hypoglycemia.
- Normalization of glucose levels in the context of a broader metabolic improvement may become an achievable goal in people with type 2 diabetes.

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Achieving Normoglycemia With Tirzepatide: Analysis of SURPASS 1–4 Trials

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ORIGINAL ARTICLE

OBJECTIVE

Tirzepatide is a novel single-molecule glucose-dependent insulinotropic polypeptide/glucagon-like peptide 1 receptor agonist, which demonstrated unprecedented improvements in glycemic control and body weight reduction, in the SURPASS phase 3 program. In this exploratory analysis, we aimed to characterize tirzepatide-treated participants who achieved HbA_{1c} <5.7% and evaluate changes in clinical markers associated with long-term cardiometabolic health.

RESEARCH DESIGN AND METHODS

Baseline characteristics and change from baseline to week 40 for several efficacy and safety parameters were analyzed according to HbA_{1c} attainment category (<5.7%, 5.7–6.5%, and >6.5%) using descriptive statistics in participants taking ≥75% of treatment doses, without rescue medication, in the SURPASS 1–4 trials (*N* = 3,229). Logistic regression models with tirzepatide doses adjusted as a covariate were used to obtain odds ratios and assess the impact of patient characteristics achieving an HbA_{1c} <5.7%.

RESULTS

Tirzepatide-treated participants who achieved HbA_{1c} <5.7% were slightly younger, with a shorter duration of diabetes and lower HbA_{1c} value at baseline compared with those who did not achieve HbA_{1c} <5.7%. In addition, they showed greater improvements in HbA_{1c}, body weight, waist circumference, blood pressure, liver enzymes, and lipid parameters without increasing hypoglycemia risk.

CONCLUSIONS

Normoglycemia was unprecedently achieved in a significant proportion of participants in the SURPASS clinical program, without increasing hypoglycemia risk, and was associated with an overall improvement in metabolic health.

The goal of glycemic management in people with type 2 diabetes (T2D) is to achieve and maintain blood glucose (BG) levels in a range that would help to prevent disease complications (1). A post hoc analysis of UK Prospective Diabetes Study data reported a continuous association of microvascular and macrovascular diabetes complications as well as mortality rates with HbA_{1c} levels, with the lowest risk in patients with HbA_{1c} values in the close to normal range (<6%) (2). However, achievement of normoglycemia with pharmacotherapy has been hitherto an elusive, almost unthinkable goal in T2D management. Current guidelines for the treatment of patients with T2D recommend improvement in glycemic control to achieve a target HbA_{1c} <7% (American

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Diabetes Association/European Association for the Study of Diabetes) or ≤6.5% (American Association of Clinical Endocrinology/American College of Endocrinology), which still remain above the normal levels, yet have been shown to reduce microvascular complications (3). Whether a lower HbA_{1c} target, if not glucose normalization, can offer any further risk reduction is currently unknown, as no therapeutic tools were available to reach such a bold glycemic target in a safe manner without inducing unwanted hypoglycemia. Indeed, the major barrier to achieving normoglycemia has been the increased risk of hypoglycemia when approaching HbA_{1c} levels of around 6%. In intervention trials striving for an HbA_{1c} <7%, such as in Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), and Veterans Affairs Diabetes Trial (VADT), the significant risk of hypoglycemia was encountered mainly with intensive insulin therapy with or without oral glucose-lowering agents (4–6). However, these trials did not specifically assess the use of newer pharmacological agents, such as sodium–glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide 1 receptor agonists (GLP-1 RAs), or gastrointestinal polypeptide (GIP)/GLP-1 RA, which have demonstrated consistent glucose-lowering efficacy, weight reduction, and a low hypoglycemia risk (7).

Tirzepatide is a single-molecule GIP and GLP-1 receptor agonist approved for the treatment of T2D in adults. In the SURPASS phase 3 program, tirzepatide demonstrated unprecedented clinically meaningful improvements in glycemic control and body weight reduction in adults with T2D. Notably, a prespecified novel secondary end point of these trials was to determine the proportion of participants achieving HbA_{1c} <5.7%. Between 43 and 62% of participants treated with the highest tirzepatide dose (15 mg) achieved HbA_{1c} <5.7% at the primary end point of each SURPASS study (40 or 52 weeks) (8–12), even though study participants were not treated with the purpose of achieving such a specific target.

In this patient-level exploratory analysis of the SURPASS program, we aimed to better characterize participants who achieved HbA_{1c} <5.7% and evaluate changes in clinical markers associated with long-term cardiometabolic health in these people.

RESEARCH DESIGN AND METHODS

Study Design and Participants

Pooled data from four phase 3 trials, SURPASS 1–4 (N = 3,229) were included in this exploratory analysis. Full individual study details are published (9–12). As background insulin dose titration to target is a potential confounder for interpretation of the results, SURPASS 5 was not included in the pooled analysis. The analysis population included participants randomized and treated with any tirzepatide dose from SURPASS 1–4 who were predefined as compliant if they received ≥75% doses, with no rescue medication. Participants with missing HbA_{1c} at week 40 (or 42 in SURPASS 4) and/or who discontinued the study drug were excluded from the analyses. Background medication at baseline included metformin only (63%), a combination of two to three oral antidiabetic medications (26%), no treatment (9%), and patients taking one oral medication that is not metformin (1%).

Statistical Methods

Achieved HbA_{1c} threshold (<5.7%, 5.7–6.5%, and >6.5%) for each tirzepatide-treated patient was assessed at week 40 (or week 42 in SURPASS 4). Selected baseline characteristics and changes from baseline to week 40 (or week 42 in SURPASS 4) in selected clinical parameters were summarized by the achieved HbA_{1c} thresholds and analyzed using descriptive statistics (mean and SD for continuous variables, and counts and percentages for categorical variables).

Statistical analysis was carried out using SAS 9.4. Mixed models for repeated measures were used to model the trends for the change from baseline over time for HbA_{1c} and percentage change from baseline over time for weight, fasting serum glucose (FSG), and systolic blood pressure (SBP) by the achieved HbA_{1c} threshold. The model terms included baseline values, study, geographical regions, achieved HbA_{1c} category, visit, and HbA_{1c} target-by-visit interaction. Logistic regression models with tirzepatide doses (5 mg, 10 mg, and 15 mg) adjusted as a covariate were used to obtain odds ratios assessing the impact of individual baseline variables on achieving an HbA_{1c} <5.7%. A multivariate logistic regression model was fitted to further assess the joint impact of baseline variables.

Safety analyses by achieved HbA_{1c} threshold were completed including rate of adverse events (AEs) and serious AEs (SAEs), proportion of patients achieving HbA_{1c} <5.7% at primary end point without hypoglycemia, and proportion of patients ≥65 years of age achieving HbA_{1c} <5.7% without hypoglycemia. Level 1 hypoglycemia was defined as having a BG ≤70 mg/dL, level 2 hypoglycemia as having a BG <54 mg/dL, and level 3 (severe) hypoglycemia as an episode with severe cognitive impairment requiring the assistance of another person.

RESULTS

Patient characteristics at baseline for the different subgroups (<5.7%, 5.7–6.5%, and >6.5%) are shown in Table 1. People treated with tirzepatide who achieved HbA_{1c} <5.7% at week 40 were slightly younger (56 ± 10.4 vs. 59 ± 10.1 or 59 ± 10.0 years), with shorter duration of diabetes (7.5 ± 6.2 vs. 9.3 ± 6.9 or 11.0 ± 7.5 years) and lower HbA_{1c} value at baseline (8.0 ± 0.9 vs. 8.4 ± 0.9 or 8.7 ± 1.0%) compared with those who did not achieve an HbA_{1c} <5.7% (Table 1).

The group of patients who achieved HbA_{1c} <5.7% had a mean HbA_{1c} change of −3.0% vs. −2.3% in those who achieved HbA_{1c} between 5.7 and 6.5% or vs. −1.1% in those with HbA_{1c} >6.5% ($P < 0.001$ for all) (Fig. 1*A*). Separation of the different groups in the HbA_{1c} over-time curves is apparent starting at week 4. The HbA_{1c} <5.7% group had a mean body weight change of −14.1% vs. −9.6% in the 5.7–6.5% group or −5.1% in the >6.5% group ($P < 0.001$ for all) at week 40 (Fig. 1*B*). These patients also showed more profound reductions in FSG, BMI, waist circumference, BP, and liver enzymes, as well as substantial improvements in lipid parameters (Fig. 1 and Table 1). Separate analyses performed in SURPASS 1 and 2 showed marked improvements in HOMA-IR and HOMA-B, as well as reductions in fasting plasma insulin concentrations, in participants that achieved an HbA_{1c} <5.7% (Supplementary Table 3).

Baseline HbA_{1c}, FSG, estimated glomerular filtration rate (eGFR), duration of diabetes, age, and background therapy showed significant associations when assessed by univariate logistic regression models adjusted by tirzepatide dose (Fig. 2). A higher baseline HbA_{1c} (each 1% increase) and FSG (each 50 mg/dL increase) were associated with decreased odds of achieving an HbA_{1c} <5.7% at week 40 (42% and 24%,

Table 1—Baseline characteristics and change from baseline in efficacy parameters at week 40 by HbA_{1c} subset: <5.7%, 5.7–6.5%, and >6.5%

HbA_{1c} subsets at week 40	Patients who achieved <5.7% (*N* = 1,209)	Patients who achieved 5.7–6.5% (*N* = 1,407)	Patients who achieved >6.5% (*N* = 613)
Baseline characteristics			
Age (years)	56 ± 10.4	59 ± 10.1	59 ± 10.0
Male/female (%)	54/46	54/46	53/47
Duration of diabetes (years)	7.5 ± 6.2	9.3 ± 6.9	11.0 ± 7.5
Baseline antihyperglycemic therapy (%)			
Metformin only	842 (69.6)	845 (60.1)	346 (56.4)
More than one oral medication	247 (20.4)	397 (28.2)	205 (33.4)
No oral medication	112 (9.3)	143 (10.2)	48 (7.8)
Other	8 (0.7)	22 (1.6)	14 (2.3)
Efficacy parameters			
HbA_{1c} (%)			
Baseline	8.0 ± 0.9	8.4 ± 0.9	8.8 ± 1.0
Change from baseline	−2.8 ± 1.0	−2.3 ± 0.9	−1.5 ± 1.2
HbA_{1c} (mmol)			
Baseline	63.9 ± 9.8	68.3 ± 9.8	72.7 ± 10.9
Change from baseline	−29.5 ± 10.9	−25.1 ± 3.8	−16.4 ± 13.1
Fasting glucose (mg/dL)			
Baseline	164 ± 48	173 ± 47	185 ± 55
Change from baseline	−68 ± 48	−60 ± 47	−39 ± 58
Fasting glucose (mmol/L)			
Baseline	9.10 ± 2.7	9.6 ± 2.6	10.3 ± 3.1
Change from baseline	−3.8 ± 2.7	−3.3 ± 2.6	−2.2 ± 3.2
Weight (kg)			
Baseline	93.3 ± 19.9	93.2 ± 20.4	92.3 ± 21.0
Change from baseline	−13.2 ± 7.3	−8.8 ± 6.0	−4.5 ± 4.8
BMI (kg/m^2)			
Baseline	33.8 ± 6.2	33.6 ± 6.4	33.4 ± 6.6
Change from baseline	−4.8 ± 2.7	−3.2 ± 2.2	−1.7 ± 1.8
Waist circumference (cm)			
Baseline	109.3 ± 13.7	109.5 ± 14.9	109.2 ± 15.8
Change from baseline	−11.0 ± 8.6	−7.7 ± 8.8	−4.5 ± 8.4
SBP (mmHg)			
Baseline	131.0 ± 14.5	131.3 ± 14.3	132.3 ± 12.8
Change from baseline	−7.6 ± 15.2	−5.8 ± 14.6	−3.2 ± 13.4
DBP (mmHg)			
Baseline	79.7 ± 9.3	78.8 ± 8.9	78.5 ± 8.5
Change from baseline	−3.5 ± 9.4	−2.1 ± 9.0	−0.9 ± 8.6
eGFR (mL/min/1.73 m^2)			
Baseline	94.4 ± 17.7	90.2 ± 19.7	92.2 ± 20.8
Change from baseline	−3.5 ± 11.4	−3.7 ± 10.4	−3.9 ± 10.5
Triglycerides (mg/dL)			
Baseline	191 ± 136	185 ± 126	199 ± 134
% change from baseline	−21 ± 38	−13 ± 37	0.5 ± 49
HDL-C (mg/dL)			
Baseline	43 ± 11	44 ± 11	44 ± 12
% change from baseline	11 ± 19	7 ± 18	5.5 ± 22
VLDL-C (mg/dL)			
Baseline	36 ± 19.8	35.4 ± 19.2	37.7 ± 21.1
% change from baseline	−20 ± 37.5	−12.3 ± 36.0	0.94 ± 45.4
LDL-C (mg/dL)			
Baseline	92.8 ± 34.2	91.7 ± 35.0	93.2 ± 37.1
% change from baseline	−3.5 ± 39.3	−0.5 ± 41.7	3.0 ± 50.8
ALT (IU/L)			
Baseline	30.6 ± 18.3	28.0 ± 16.3	26.8 ± 18.9
% change from baseline	−25.4 ± 56.7	−15.0 ± 45.4	−0.7 ± 45.1
AST (IU/L)			
Baseline	23.7 ± 13.9	22.3 ± 11.2	21.5 ± 12.3
% change from baseline	−10.6 ± 46.8	−4.3 ± 35.3	4.7 ± 37.8

Data are mean ± SD or (%). ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBP, diastolic blood pressure.

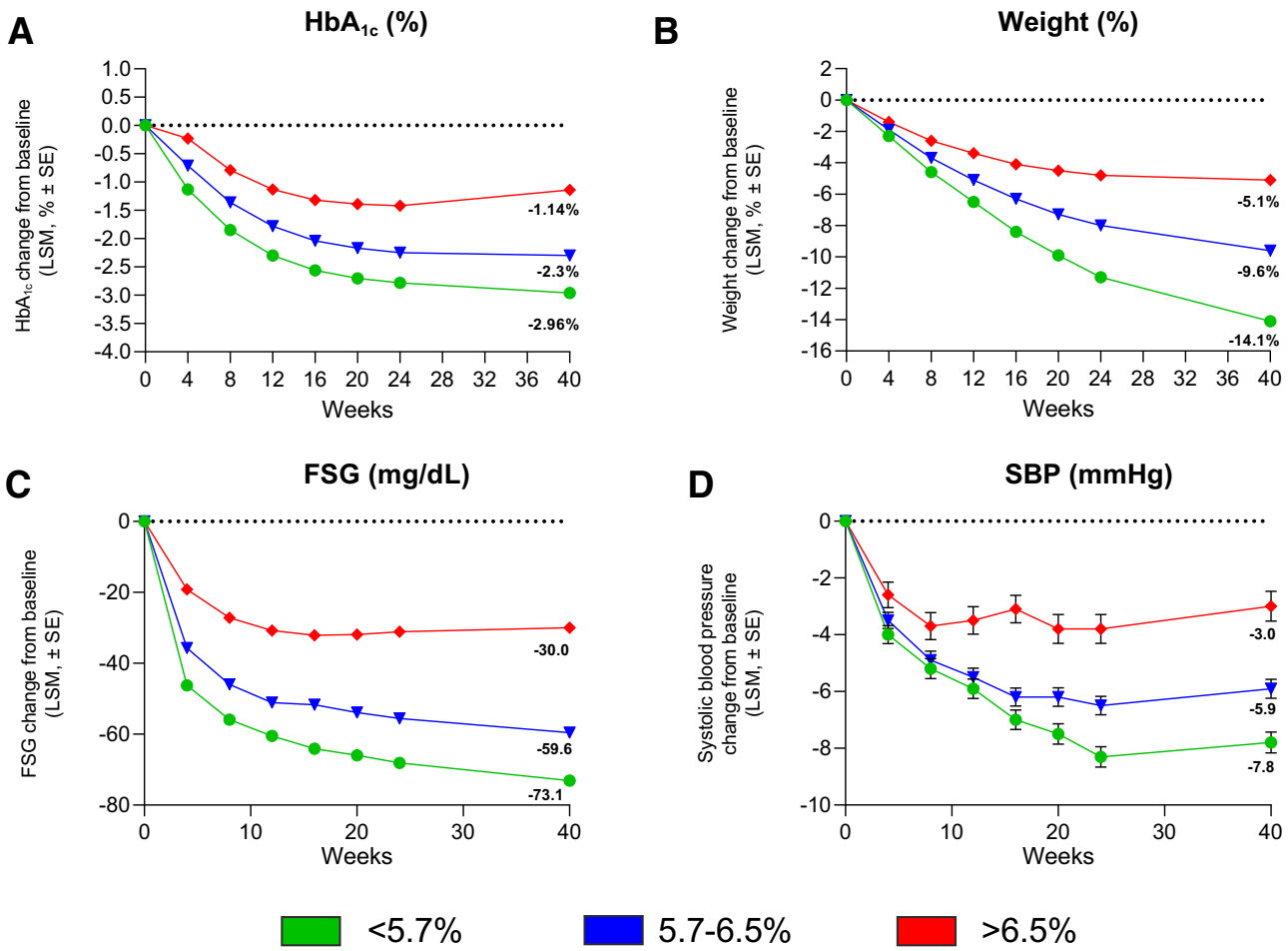

Figure 1—Change from baseline in HbA_{1c}, body weight, FSG, and SBP over time at week 40 (by HbA_{1c} subset; <5.7%, 5.7–6.5%, and >6.5%). HbA_{1c} (*A*), body weight (*B*), FSG (*C*), and SPB (*D*), over time from baseline to week 40 (or 42). Change from baseline values represent LSM change (SE) and not error bar range values. LSM, least squares mean.

respectively). Odds of achieving an HbA_{1c} <5.7% were reduced by 13% and 24% with every 5-year increase in age or diabetes duration, respectively. Patients receiving metformin only had a greater chance of achieving an HbA_{1c} <5.7% (Fig. 2). A multivariate logistic regression model including age, duration of diabetes, background medication, baseline HbA_{1c}, and baseline weight demonstrated similar findings (data not shown).

Across SURPASS 1–4, 63% of patients who achieved HbA_{1c} <5.7% similarly experienced at least one AE vs. 62% and 57% in the group of patients achieving HbA_{1c} between 5.7 and 6.5% and >6.5%, respectively (Supplementary Table 2). The most common AEs were gastrointestinal-related (42% vs. 39% vs. 32%, respectively). A similar number of patients experienced SAEs across groups (4.1% vs. 3.6% vs. 5.1%, respectively). Of the patients who achieved HbA_{1c} <5.7%, 98.5% did so without level 2 clinically significant (<54 mg/dL) or level 3 severe hypoglycemia, with 91% doing so without level 1 hypoglycemia (≤70 mg/dL) (Table 2). Out of 18 patients who experienced level 2 and/or 3 hypoglycemia, 12 were on a sulfonylurea as background therapy (data not shown). In patients ≥65 years of age, 98.5% of those who achieved HbA_{1c} <5.7% did so without level 2 and/or 3 hypoglycemia (Table 2).

CONCLUSIONS

Achievement of normoglycemia (HbA_{1c} <5.7%) has hitherto not been assessed in any T2D clinical development programs of glucose-lowering agents, as it was not considered a safe, realistic goal with the therapeutic options available. The unprecedented proportions of study participants achieving normoglycemia with tirzepatide in the SURPASS clinical program provide the opportunity to assess such a bold glycemic target with respect to potential benefits and safety. To our knowledge, this is the first analysis looking at a large sample of subjects achieving normoglycemia in a phase 3 clinical research program. The large sample size allowed for thorough exploratory analyses to better describe the characteristics of these subjects as well as the factors associated with this outcome that may have predictive clinical value. Importantly, the participants that achieved HbA_{1c} values of <5.7% in SURPASS 1–4 did so in response to their randomly assigned weekly dose of tirzepatide, as achievement of normoglycemia was not a specifically planned goal by design of the studies.

Our findings suggest that individuals who achieved normoglycemia at the end of the treatment period tend to be younger, with shorter duration of the disease and a lower baseline HbA_{1c} and on treatment only with metformin. Analyses of glycemic response typically show greater reductions in those individuals with higher baseline HbA_{1c} values (10,11,13). The categorization according to achieved HbA_{1c}

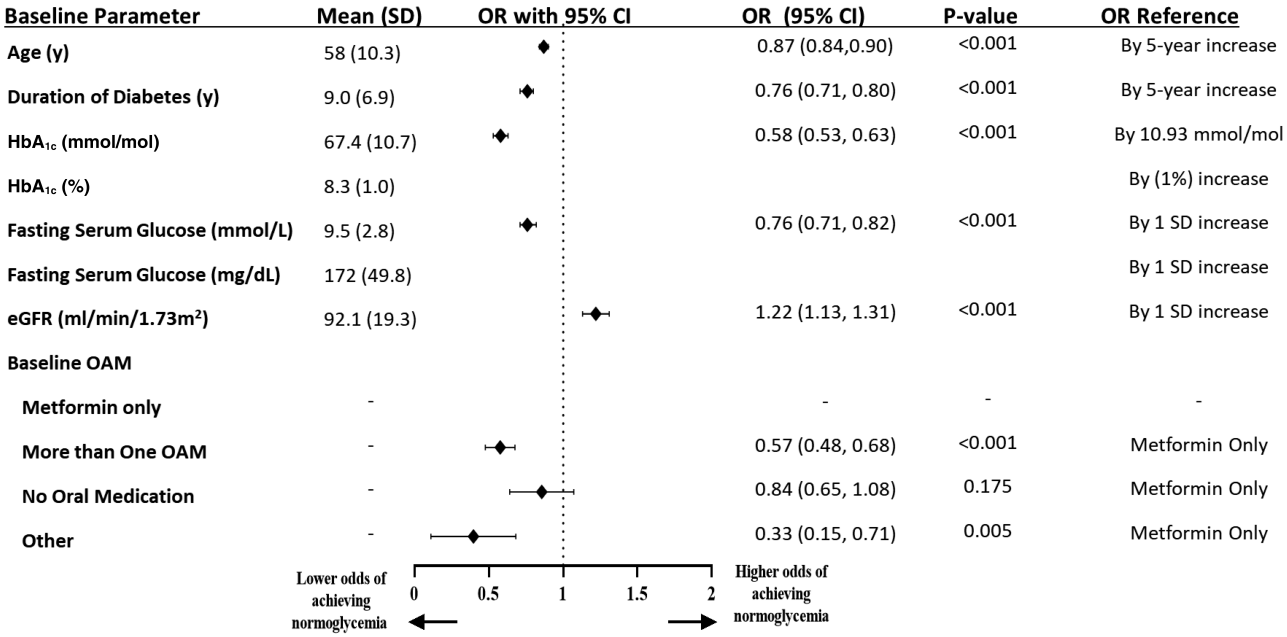

Figure 2—Odds ratio of baseline characteristics for achieving $HbA_{1c} < 5.7\%$. The "Other" category for baseline antihyperglycemic medication refers to patients taking one oral medication that is not metformin. OAM, oral antidiabetic medication; OR, odds ratio; y, years.

provides a novel perspective, as it shows that, despite lower baseline values, there was a more profound reduction in HbA_{1c} in those participants that eventually achieved an HbA_{1c} <5.7%. This indicates these individuals achieved normoglycemia not only because they had better glycemic control at baseline but also because they had a better overall metabolic response (13). We also found that higher eGFR seems to be associated with greater odds of achieving normoglycemia. Our interpretation would be that hyperfiltration is probably another marker associated with shorter duration of disease, and it would be consistent with the rest of the predictors mentioned above. All these observations would support the concept of an earlier treatment initiation in the course of the disease to potentially enable better glycemic outcomes and prevent longer-term complications.

Data from both the SURPASS 1 and 2 studies showed greater improvements in HOMA-IR and HOMA-B in the lower HbA_{1c} categories at week 40. Consistent with other analyses/studies, the combination of improvements in insulin resistance and better β-cell function may explain why patients achieved different degrees of glycemic control (14,15). The over-time plot clearly demonstrates that the improvement in glucose control is observed very early in all groups, but with a clear separation of curves already apparent at 4–8 weeks. Weight curves do not show the same early differences between groups, suggesting that any improvement in insulin resistance during the first few weeks would not be driven solely by weight reduction (16).

Individuals achieving an HbA_{1c} <5.7% with tirzepatide showed a more profound improvement in several cardiometabolic risk markers, implying a potential

Table 2—Proportion of patients achieving HbA_{1c} <5.7% without hypoglycemia (integrated analysis)

	SURPASS 1–4 integrated analysis, compliant patients on treatment without rescue medication at week 40 achieving HbA_{1c} <5.7%			
	TZP 5 mg	TZP 10 mg	TZP 15 mg	Total
N (all patients)	300	410	499	1,209
Achieved HbA_{1c} without severe hypoglycemia, *n* (%)	300 (100)	410 (100)	497 (99.6)	1,207 (99.8)
Achieved HbA_{1c} without level 2 (<54 mg/dL) or severe hypoglycemia, *n* (%)	297 (99)	403 (98.3)	491 (98.4)	1,191 (98.5)
Achieved HbA_{1c} without level 1 (≤70 mg/dL) or severe hypoglycemia, *n* (%)	278 (92.7)	376 (91.7)	446 (89.4)	1,100 (91.0)
N (patients ≥65 years of age)	75	95	94	264
Achieved HbA_{1c} without severe hypoglycemia, *n* (%)	75 (100)	95 (100)	93 (98.9)	263 (99.6)
Achieved HbA_{1c} without level 2 (<54 mg/dL) or severe hypoglycemia, *n* (%)	74 (98.7)	93 (97.9)	93 (98.9)	260 (98.5)
Achieved HbA_{1c} without level 1 (≤70 mg/dL) or severe hypoglycemia, *n* (%)	65 (86.7)	85 (89.5)	82 (87.2)	232 (87.9)

Tirzepatide patients on treatment at the 40-week visit with ≥75% compliance. *N*, number of participants achieving HbA_{1c} <5.7% at week 40; *n*, number of patients in the category; TZP, tirzepatide.

risk reduction of both microvascular and macrovascular complications (17). This emphasizes how normalization of glucose values cannot be separated from the potential benefits of a multifactorial improvement in BP, lipids, weight, waist circumference, and liver enzymes. In fact, this very much aligns with the latest update to the American Diabetes Association/European Association for the Study of Diabetes 2022 hyperglycemia management consensus report, which places a strong emphasis on a holistic approach to T2D management (1).

Overall, a numerically higher rate of AEs, particularly gastrointestinal AEs, was observed in the groups achieving HbA_{1c} $<$5.7% or 5.7–6.5%. These events were self-reported, consistent with the mechanism of action of tirzepatide and unlikely to have any meaningful contribution to weight reduction weight reduction, similar to what has been shown with some GLP-1 RAs (18). Moreover, gastrointestinal AEs with tirzepatide were transient and mostly occurred during the dose escalation period, yet glycemic control was maintained for the duration of the trials. It is noteworthy that 98.5% of participants that achieved normoglycemia did so without any level 2 or level 3 hypoglycemia. Additionally, this was also the case for the subset of participants above 65 years of age.

These results are reassuring, as the main concern about "getting too low" has always been the potential increase in the occurrence of hypoglycemia and related acute complications. Evidence from the ACCORD trial where a near-normal glucose target of HbA_{1c} $<$6.0% was actively pursued pointed to a higher risk of cardiovascular (CV) complications in those people randomized to the arm aiming for the strict glycemic control (19). The type of pharmacological intervention as well as the patient population and the study design may have contributed to those observations. We did not observe any increase in CV AEs in the group that achieved lower HbA_{1c} values, although the study populations in SURPASS 1–3 were not at high risk of events, and the follow-up was too short to come to any conclusion in this regard. The SURPASS-CVOT (cardiovascular outcome) trial (NCT04255433) testing tirzepatide versus dulaglutide in people with T2D at high CV risk will provide a more comprehensive assessment of the CV outcomes and potential cardioprotective effects of tirzepatide.

Another potential matter of concern with "getting too low" if glucose improvement occurs rapidly is accelerating the progression of diabetic retinopathy. No increased risk of progression of diabetic retinopathy has been observed within the whole SURPASS clinical development program, although it must be noted that people with clinically significant or nonstable retinopathy were excluded in these trials.

Considering these findings, the question would be whether normoglycemia should be reconsidered as a realistic target for people with T2D, or at least for a subset of patients. Our observations from the SURPASS clinical program indicate that certain individuals may have a higher probability of achieving normal glucose values in response to tirzepatide, in association with an overall improvement of metabolic health. Longer-term implications of safely achieving normal glucose values are unknown; however, we would hypothesize that there should be long-term benefits associated with an improved cardiometabolic risk profile. Whether this is the case should be tested in long-term pragmatic clinical trials.

This study has several strengths and limitations. The SURPASS 1–4 studies provide the largest patient-level data set of people achieving normoglycemia in a phase 3 clinical trial program. The study population was heterogenous, allowing relative generalizability in patients at varying stages across the T2D treatment continuum. Similar study designs allowed for pooling of data at consistent time points for evaluation. Limitations include the exploratory nature of these analyses, which makes our findings hypothesis generating. The population analyzed included participants who were on study treatment and were compliant, with no rescue medication and with available HbA_{1c} at week 40, and therefore the results may not be generalizable to the overall treated population. Additionally, the analyses involved a relatively short follow-up of 40 weeks across studies, which did not allow the assessment of the durability of this improvement nor the potential longer-term benefits of achieving normoglycemia, particularly with respect to diabetes microvascular and macrovascular complications. More evidence about the relationship of achieving normoglycemia and microvascular and macrovascular complications will be available from the ongoing SURPASS-CVOT trial.

In conclusion, this comprehensive exploratory analysis using patient-level data from the SURPASS clinical program shows that normoglycemic status was achieved in a significant proportion of tirzepatide-treated participants, without an increase in the risk of hypoglycemia, and was associated with an overall improvement in markers of metabolic health. Younger age, shorter duration of the disease, lower HbA_{1c} values, and treatment with only metformin were baseline factors associated with a higher likelihood of achieving normoglycemia, pointing to the early stages of the disease. As more evidence from newer pharmacological treatments becomes available, normalization of glucose levels in the context of a broader metabolic improvement may be considered an achievable goal in people with T2D.

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the data, and edited, reviewed, and approved the final version of the manuscript. G.W. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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