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Effects of Tirzepatide Versus Basal Insulins in People With Type 2 Diabetes and Different Baseline Glycemic Patterns: Post Hoc Analyses of the SURPASS-3 and SURPASS-4 Trials

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Tirzepatide demonstrated superior glycemic control vs. basal insulins, irrespective of baseline glycemic pattern

Context

Both FSG and PPG levels are important for glucose control in T2D

Aim

Evaluate efficacy of tirzepatide vs. basal insulins in people with T2D according to baseline glycemic patterns

Post Hoc Analysis Design

Study	*SURPASS-3*	*SURPASS-4*
Tirzepatide vs.	iDegludec	iGlargine
n	1370	1944

Baseline glycemic pattern subgroups

Defined by median baseline FSG and PPG

- Low FSG/Low PPG
- Low FSG/High PPG
- High FSG/Low PPG
- High FSG/High PPG

Key Findings (Week 52)

- HbA_{1c}, FSG, and PPG ↓ with tirzepatide and basal insulin in all subgroups ($P < 0.05$)
- Differences between tirzepatide and basal insulins were consistent across subgroups

	Within-subgroup differences	
	Tirzepatide vs. iDegludec	Tirzepatide vs. iGlargine
HbA_{1c}	> decrease	> decrease
FSG	≈ decrease	≈ decrease
PPG	> decrease	> decrease

- Within-subgroup differences were generally consistent across tirzepatide doses (5, 10, 15 mg)

Abbreviations: FSG, fasting serum glucose; i, insulin (as in iDegludec); PPG, postprandial glucose; T2D, type 2 diabetes.

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Both fasting serum glucose (FSG) and postprandial glucose (PPG) levels influence glucose control in type 2 diabetes.
- **What is the specific question we wanted to answer?**
  Does the efficacy of tirzepatide and basal insulin differ depending on baseline FSG and PPG patterns?
- **What did we find?**
  In this post hoc analysis, tirzepatide was associated with greater reductions in HbA_{1c} and PPG values than were basal insulins, and similar improvements were noted in FSG levels.
- **What are the implications of our findings?**
  Regardless of baseline glycemic patterns, tirzepatide was associated with superior glycemic control compared with basal insulins in this post hoc analysis. These findings may help inform treatment decisions.

Effects of Tirzepatide Versus Basal Insulins in People With Type 2 Diabetes and Different Baseline Glycemic Patterns: Post Hoc Analyses of the SURPASS-3 and SURPASS-4 Trials

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BRIEF REPORT

OBJECTIVE

This post hoc analysis assessed change from baseline to week 52 in glycemic parameters for tirzepatide (5, 10, 15 mg) versus insulin degludec (SURPASS-3 trial) and glargine (SURPASS-4 trial) in people with type 2 diabetes and different baseline glycemic patterns, based on fasting serum glucose (FSG) and postprandial glucose (PPG) values.

RESEARCH DESIGN AND METHODS

Participant subgroups with low FSG/low PPG, low FSG/high PPG, high FSG/low PPG, and high FSG/high PPG were defined according to the median values of these measures.

RESULTS

All tirzepatide doses and basal insulins were associated with decreased HbA_{1c}, FSG, and PPG values from baseline to week 52 in all subgroups ($P < 0.05$). Within each subgroup, HbA_{1c} and PPG decreases were greater with tirzepatide than insulin ($P < 0.05$). FSG decreases were generally similar. There were no differential treatment effects by FSG/PPG subgroup.

CONCLUSIONS

In this post hoc analysis, tirzepatide was associated with superior glycemic control compared with insulin, irrespective of baseline glycemic pattern.

Both fasting serum glucose (FSG) and postprandial glucose (PPG) levels contribute to glucose control and should be considered in type 2 diabetes (T2D) management (1,2). Although basal insulins act on FSG, effects on PPG are limited (3,4). Dulaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1 RA), demonstrated greater efficacy than insulin glargine on glycated hemoglobin (HbA_{1c}), largely irrespective of baseline FSG and PPG levels, although insulin dose titration was not optimal; consistent effects on FSG and PPG across baseline FSG and PPG subgroups were not observed (5). Tirzepatide, a glucose-dependent insulinotropic polypeptide/GLP-1 RA, showed superior glucose control versus the GLP-1 RA semaglutide 1 mg and basal insulins (6–8).

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In this post hoc analysis, we evaluated the efficacy of tirzepatide versus basal insulin degludec and glargine in participants with T2D and different baseline glycemic patterns.

RESEARCH DESIGN AND METHODS

SURPASS-3 and SURPASS-4 Trial Designs

SURPASS-3 (A Study of Tirzepatide (LY3298176) Versus Insulin Degludec in Participants With Type 2 Diabetes; National Library of Medicine Identifier NCT03882970) and SURPASS-4 (A Study of Tirzepatide (LY3298176) Once a Week Versus Insulin Glargine Once a Day in Participants With Type 2 Diabetes and Increased Cardiovascular Risk; National Library of Medicine Identifier NCT03730662) were open-label, phase 3 clinical trials of once-weekly tirzepatide (7,8). Both trials obtained ethical approval, and all participants provided written informed consent. In both, tirzepatide was initiated at 2.5 mg and then the dose was increased by 2.5 mg every 4 weeks until the allocated treatment dose was reached.

SURPASS-3 was conducted with adults with HbA_{1c} 7.0–10.5% and a BMI $\geq$25 kg/m^2. Participants were insulin-naïve and used metformin alone or in combination with a sodium-glucose cotransporter 2 (SGLT-2) inhibitor. Randomization was 1:1:1:1 to tirzepatide 5, 10, or 15 mg or once-daily insulin degludec (100 U/mL), with a 52-week treatment period.

SURPASS-4 participants were adults treated with any combination of metformin, sulfonylurea, or SGLT-2 inhibitor; HbA_{1c} 7.5–10.5%; BMI $\geq$25 kg/m^2; and established cardiovascular disease or a high risk of cardiovascular events. Randomization was 1:1:1:3 to tirzepatide 5, 10, or 15 mg or insulin glargine (100 U/mL), and all participants were treated for $\geq$52 weeks.

Degludec and glargine were initiated at 10 U/day and titrated weekly to a fasting blood glucose concentration of $<$90 and $<$100 mg/dL, respectively, using treat-to-target algorithms with dose adjustment based on the median value of the last three self-monitored blood glucose values (9–12).

Post Hoc Analyses

Participants were assigned to four subgroup categories defined by baseline glucose values: low FSG/low PPG, low FSG/high PPG, high FSG/low PPG, high FSG/high PPG. Low and high were split using median values of FSG (162 mg/dL and 164 mg/dL) and PPG (187 mg/dL and 197 mg/dL) in SURPASS-3 and SURPASS-4, respectively. FSG levels were measured in a central laboratory. PPG data are the 2-h postmeal daily mean from 7-point self-monitored blood glucose.

Outcomes of interest were change from baseline to week 52 in FSG, PPG, HbA_{1c}, and body weight. Baseline characteristics, insulin use, hypoglycemia (blood glucose $<$54 mg/dL or severe), and gastrointestinal-related safety data are also reported.

Statistical Analyses

Post hoc analyses were performed by trial, including all randomly assigned participants with at least one dose of the assigned study drug with both a PPG and FSG value at baseline. Participants who discontinued the study drug because of inadvertent enrollment were excluded. Efficacy analyses included on-treatment data prior to the use of rescue therapy for persistent hyperglycemia (efficacy estimand).

Baseline demographics and clinical characteristics were summarized and compared across subgroups using ANOVA for continuous variables and a χ^2 test for categorical variables. Insulin use and hypoglycemia were summarized descriptively.

Change from baseline in HbA_{1c} at 52 weeks was assessed within each subgroup using a mixed model for repeated measures (MMRM) with pooled country, baseline SGLT-2 inhibitor use (yes, no), baseline value, treatment group, visit, and treatment-by-visit interaction as fixed effects, and patient as the random effect. The MMRM for FSG, PPG, and body weight included baseline HbA_{1c} group ($\leq$8.5%, $>$8.5%) as a covariate. Missing data were managed within the MMRM. Interactions between treatment and subgroup categories were assessed using the same MMRM in the overall population, with additional terms for subgroup and treatment-by-subgroup, time-by-subgroup, and treatment-by-time-by-subgroup interactions. Hypoglycemia data were summarized as incidence and rate per year; gastrointestinal-related safety data were summarized as number and percentages.

For subgroup analyses, an interaction $P < 0.006$ was considered statistically significant (Bonferroni-adjusted for multiple comparisons). Analyses were exploratory and performed using SAS, version 9.4.

RESULTS

Baseline Characteristics and Insulin Use

From SURPASS-3, 1,370 participants (95.3% of the SURPASS-3 population) were included in these analyses. The mean duration of diabetes was 8.4 years and mean HbA_{1c} was 8.2% (Supplementary Table 1). From SURPASS-4, 1,944 participants (97.4% of the SURPASS-4 population) were included; they had a mean diabetes duration of 11.8 years and HbA_{1c} of 8.5% (Supplementary Table 2). Among other characteristics, baseline HbA_{1c} values differed significantly between subgroups in both studies ($P < 0.05$).

In SURPASS-3, the daily median (minimum, maximum) degludec dose at week 52 ranged from 40.0 (8.0, 102.0) U in the high FSG/low PPG subgroup to 48.0 (14.0, 148.0) U in the low FSG/high PPG subgroup (Supplementary Table 3). Median glargine doses at week 52 in SURPASS-4 ranged from 34.0 (4.0, 164.0) U in the low FSG/low PPG subgroup to 44.0 (5.0, 226.0) U in the high FSG/high PPG subgroup (Supplementary Table 3).

Changes in Glycemic Measures

In both studies, tirzepatide and basal insulins decreased HbA_{1c} significantly from baseline in all subgroups (all $P < 0.05$) (Fig. 1*A* and *B*). Within each subgroup, reductions were significantly greater with all tirzepatide doses versus the comparator (all $P < 0.05$).

In SURPASS-3, FSG levels decreased significantly with all tirzepatide doses and insulin degludec in all subgroups ($P < 0.05$) (Fig. 2*A*). In the high FSG/high PPG subgroup, FSG levels decreased to a significantly greater extent with degludec than tirzepatide 5 mg ($P < 0.001$). There were no other significant within-subgroup differences between treatments ($P > 0.05$). FSG levels also decreased significantly at 52 weeks with each tirzepatide dose and glargine in SURPASS-4 ($P < 0.05$) (Fig. 2*B*). Within subgroups, reductions with tirzepatide 10 and 15 mg were significantly greater than with glargine in the high FSG/high PPG group ($P < 0.05$), with no significant between-treatment differences in other subgroups.

In both studies, tirzepatide and basal insulin decreased PPG levels significantly

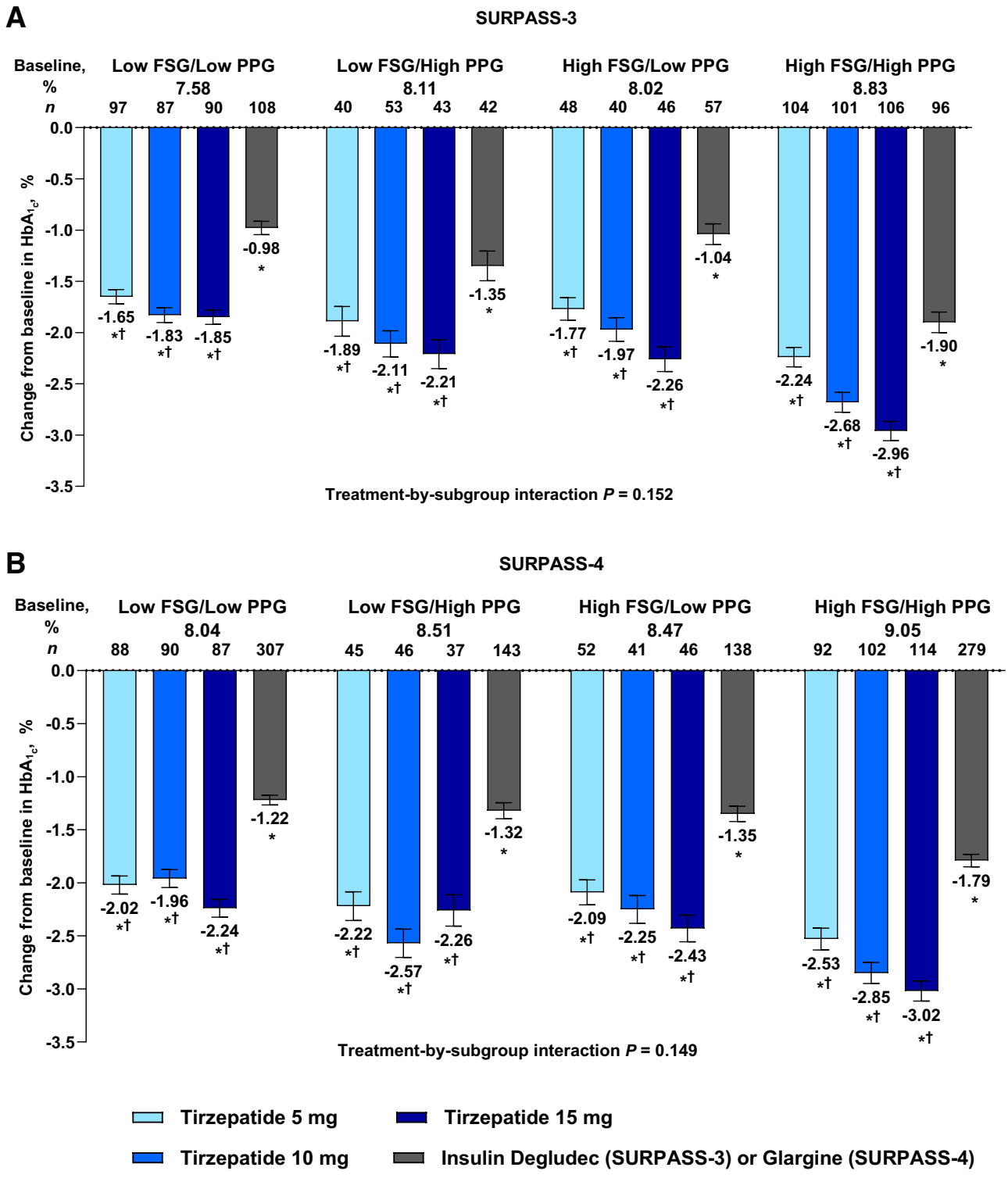

Figure 1—Change from baseline in HbA_{1c} at 52 weeks by subgroups in (*A*) SURPASS-3 and (*B*) SURPASS-4. Data are presented as the mean at baseline and least-squares mean (SE) from the modified intent-to-treat population efficacy analysis set with both a PPG and FSG value at baseline. *$P < 0.05$ vs. baseline and †$P < 0.05$ vs. insulin degludec or glargine. PPG data are given as the 2-h postmeal daily mean. *n*, number of individuals in the population with baseline and postbaseline values at week 52.

($P < 0.05$). Reductions with each tirzepatide dose were significantly greater versus insulin in all subgroups ($P < 0.05$) (Fig. 3*A* and *B*).

The extent of FSG, PPG, and HbA_{1c} reductions in each subgroup depended on baseline values, with larger decreases being associated with higher baseline values (Supplementary Tables 4 and 5). There was no significant treatment-by-subgroup interaction for any glycemic measure.

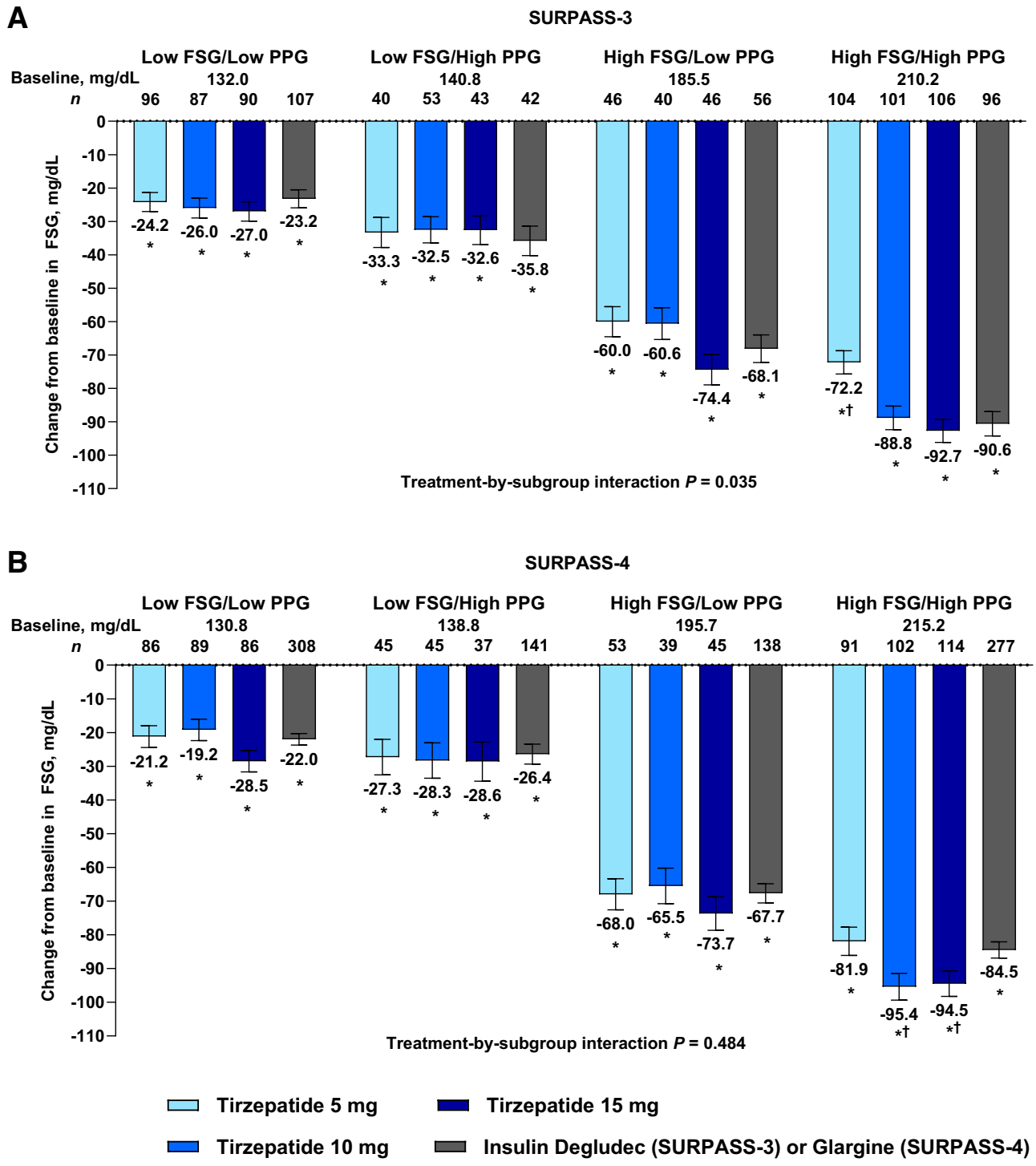

Figure 2—Change from baseline in FSG at 52 weeks by subgroups in (*A*) SURPASS-3 and (*B*) SURPASS-4. Data are presented as the mean at baseline and least-squares mean (SE) from the modified intent-to-treat population efficacy analysis set with both a PPG and FSG value at baseline. *$P < 0.05$ vs. baseline and †$P < 0.05$ vs. insulin degludec or glargine. PPG data reported as 2-h postmeal daily means. *n*, number of individuals in the population with baseline and postbaseline values at week 52.

Changes in Body Weight

In both studies and all subgroups, each tirzepatide dose significantly decreased, whereas insulin increased, body weight, with significant between-treatment differences (all $P < 0.05$) (Fig. 4*A* and *B*). There was a statistically significant treatment-by-subgroup interaction in SURPASS-4 ($P < 0.001$), but not SURPASS-3 ($P = 0.640$).

Hypoglycemia and Gastrointestinal-Related Safety

In SURPASS-3, across all subgroups, the hypoglycemia incidence (blood glucose <54 mg/dL or severe) was generally

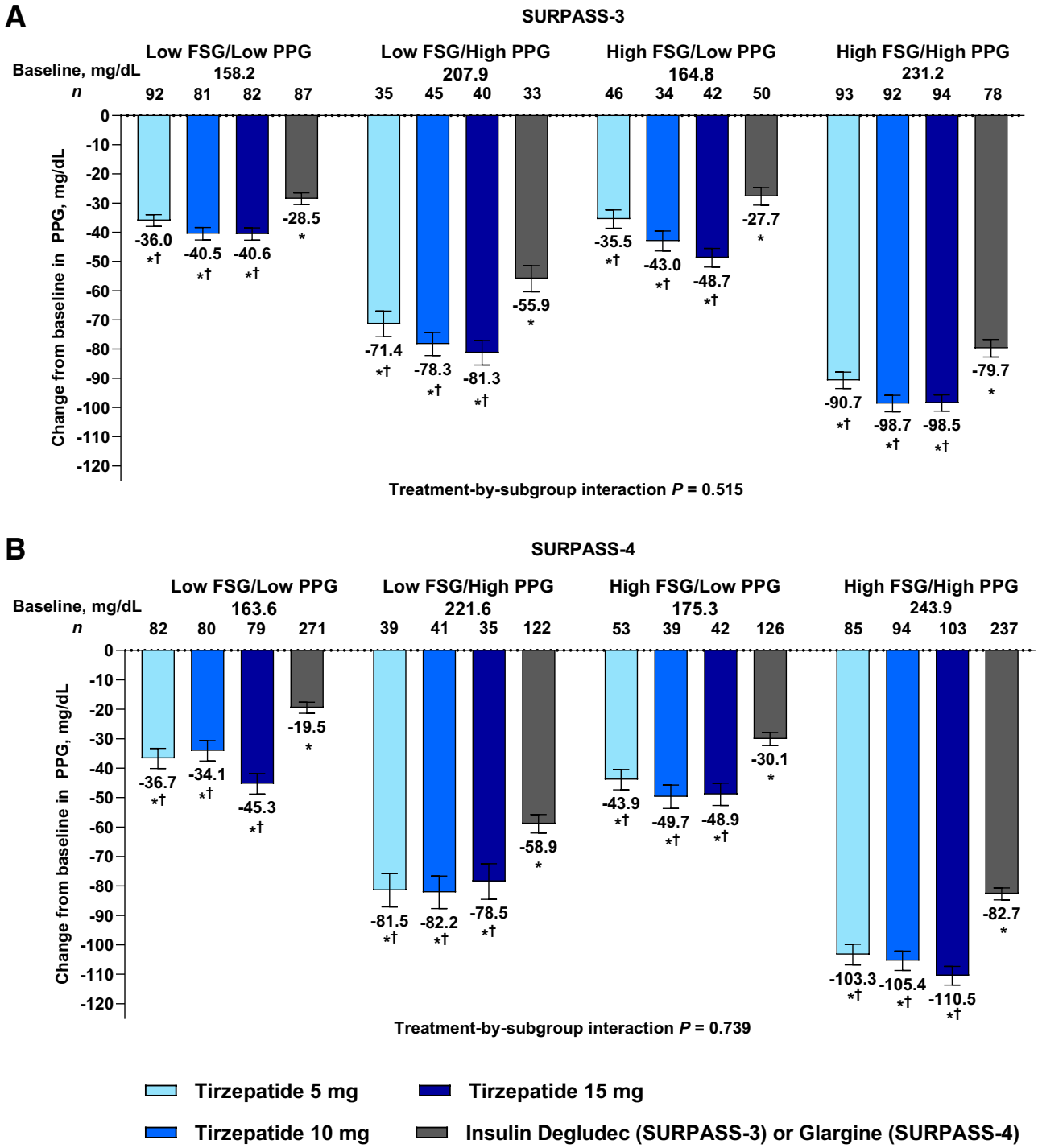

Figure 3—Change from baseline in PPG at 52 weeks by subgroups in (*A*) SURPASS-3 and (*B*) SURPASS-4. Data are presented as the mean at baseline and least-squares mean (SE) from the modified intent-to-treat population efficacy analysis set with both a PPG and FSG value at baseline. *$P < 0.05$ vs. baseline and †$P < 0.05$ vs. insulin degludec or glargine. PPG data are reported as the 2-h postmeal daily means. *n*, number of individuals in the population with baseline and postbaseline values at week 52.

low with tirzepatide treatment, ranging from 0.0–6.3%, versus 1.6–10.2% with degludec (Supplementary Table 6). The respective hypoglycemia incidence in SURPASS-4 was 4.0–13.3% with tirzepatide and 13.5–16.6% with glargine (Supplementary Table 7), and was higher in those using sulfonylureas (tirzepatide: 3.2–22.7%; glargine: 13.0–23.7%) than not using sulfonylureas (tirzepatide: 0.0–5.3%; glargine: 10.1–16.9%) at baseline.

The incidence of gastrointestinal-related treatment-emergent adverse events overall was 29.0% in SURPASS-3 and 22.1% in SURPASS-4, with data across subgroups reported in Supplementary Table 8.

CONCLUSIONS

In these post hoc analyses, tirzepatide was associated with greater reductions

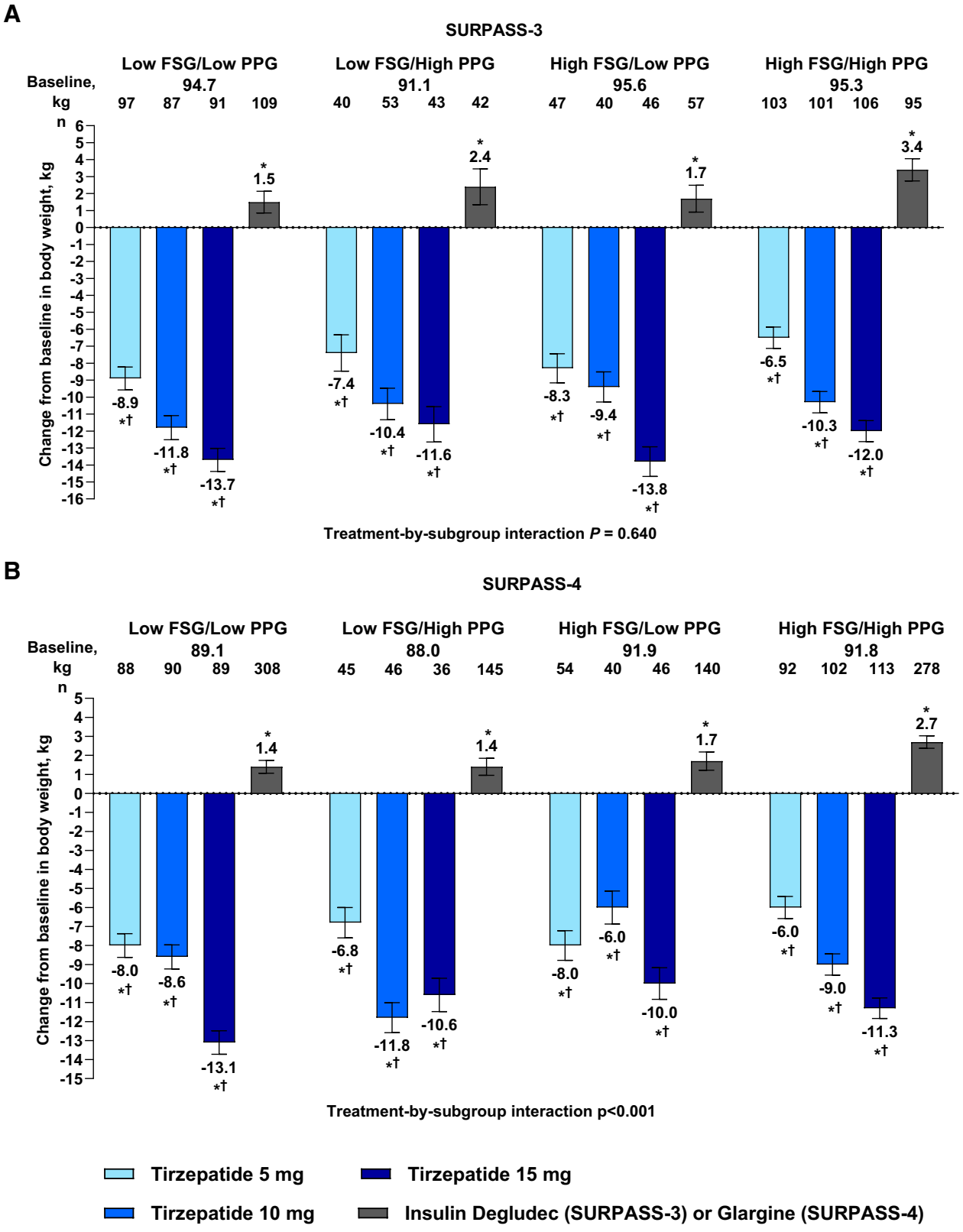

Figure 4—Change from baseline in body weight at 52 weeks by subgroups in (*A*) SURPASS-3 and (*B*) SURPASS-4. Data are presented as the mean at baseline and least-squares mean (SE) from the modified intent-to-treat population efficacy analysis set with both a PPG and FSG value at baseline. *$P < 0.05$ vs. baseline and †$P < 0.05$ vs. insulin degludec or glargine. *n*, number of individuals in the population with baseline and postbaseline values at week 52.

in HbA_{1c} and PPG values than were titrated basal insulins, and similar improvements in FSG levels, regardless of baseline glycemic patterns.

To our knowledge, this is the first time a noninsulin drug has performed as well as intensively titrated basal insulin in reducing FSG levels. In the Assessment of Weekly Administ Ration of LY2189265 (Dulaglutide) in Diabetes-2 (AWARD-2) trial, dulaglutide had similar efficacy on FSG levels as glargine (5); however, FSG levels were higher than would be expected after 1 year of insulin treatment, at ∼125 and 140 mg/dL in the low and high FSG subgroups, respectively, compared with ∼110 and 130 mg/dL in the glargine arm of SURPASS-4, despite a higher median baseline value (171 mg/dL) than in AWARD-2 (158 mg/dL). In SURPASS-3, after 1 year of degludec treatment, FSG levels were ∼108 and 120 mg/dL in the high and low groups, respectively. More intensive insulin titration in SURPASS-3 and SURPASS-4 (both median 0.4 units/kg/day at week 52) than in AWARD-2 (median ∼0.3 units/kg/day at week 52) (13), and, indeed, other studies that use glargine comparators, such as Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes 4 (SUSTAIN 4) (14), highlight the robustness of findings in these analyses.

Treatment with tirzepatide was consistently associated with more reduced PPG levels compared with insulin treatment across subgroups, including in participants with lower baseline PPG levels, in turn leading to greater HbA_{1c} reductions. Mechanisms of action facilitating this may include glucose-dependent insulin secretion, decreased glucagon levels, decreased insulin resistance, and slowed gastric emptying (15–17). In the SURPASS-3 continuous glucose monitoring substudy, tirzepatide improved time in range and tight target range and decreased glycemic variability compared with degludec, indicating a general improvement in glycemic profile (18).

Although hypoglycemia was less frequent with tirzepatide than with basal insulin across the different subgroups, there appeared to be a higher incidence in SURPASS-4 than SURPASS-3, likely reflecting the patient population, because hypoglycemia occurred more frequently in participants using sulfonylureas.

Strengths of this analysis include use of two large, randomized clinical trials with intensively titrated basal insulin comparators and distinct participant populations, with different T2D durations and cardiovascular disease prevalence. Limitations include the relatively short 1-year treatment duration and its post hoc nature. High/low FSG and PPG values were defined by the median because the use of standard cutoff points for elevated FSG and PPG would result in very small subgroups. The SURPASS-3 and -4 trials included people with T2D with a BMI $\geq$25 kg/m^2; therefore, we cannot extrapolate to other populations.

In conclusion, in this post hoc analysis, tirzepatide was associated with superior glycemic control compared with titrated insulin degludec and glargine, regardless of baseline glycemic patterns.

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