The NEW ENGLAND JOURNAL of MEDICINE

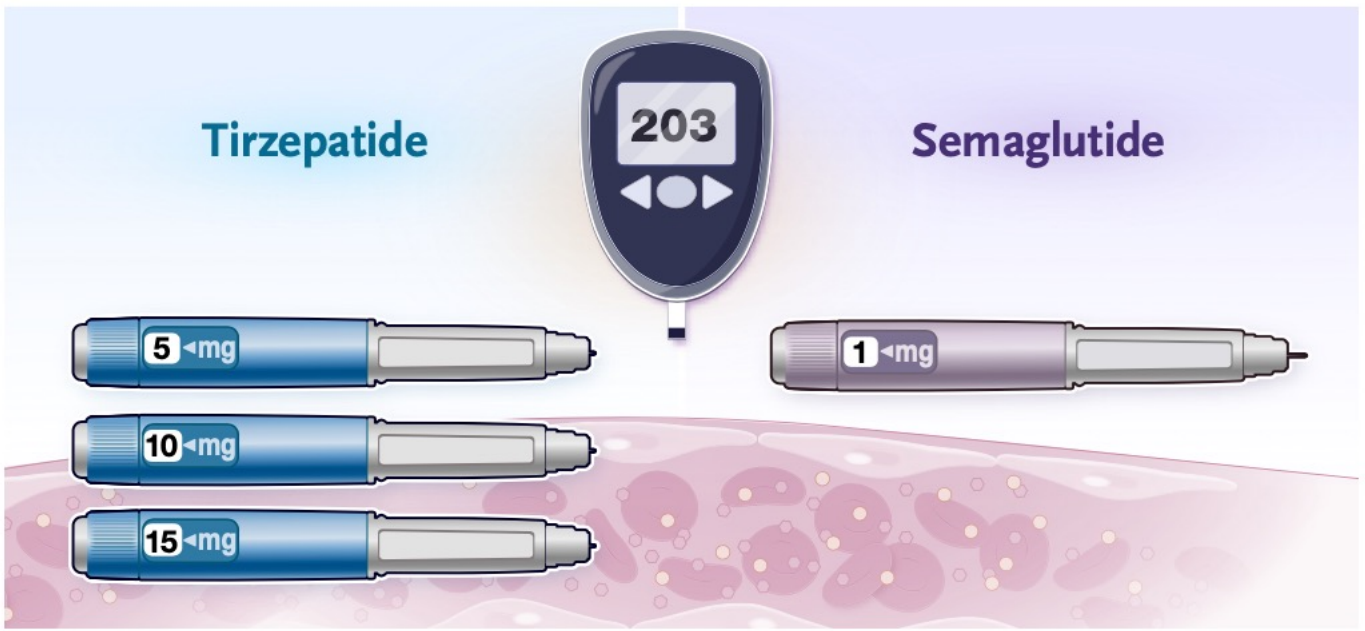
ORIGINAL ARTICLE

Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes

Juan P. Frías, M.D., Melanie J. Davies, M.D., Julio Rosenstock, M.D., Federico C. Pérez Manghi, M.D., Laura Fernández Landó, M.D., Brandon K. Bergman, Pharm.D., Bing Liu, Ph.D., Xuewei Cui, Ph.D., and Katelyn Brown, Pharm.D., for the SURPASS-2 Investigators*

CLINICAL PROBLEM

Not all patients with type 2 diabetes have adequate glucose control with metformin monotherapy. Tirzepatide is a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist under development for treatment of diabetes; how it compares with the selective GLP-1 receptor agonist semaglutide is unknown.



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CLINICAL TRIAL

Design: An international, randomized, open-label, phase 3, noninferiority trial was conducted to compare tirzepatide with semaglutide in adults with type 2 diabetes.

Intervention: 1879 adults with inadequately controlled diabetes despite metformin treatment were assigned to a once-weekly subcutaneous injection of tirzepatide (5, 10, or 15 mg) or semaglutide (1 mg) for 40 weeks. The primary efficacy end point was the change in glycated hemoglobin level from baseline to 40 weeks.

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RESULTS

Efficacy: All three tirzepatide doses were noninferior to and also superior to semaglutide with respect to the mean reduction in glycated hemoglobin level. Patients in the tirzepatide groups also lost more weight than those in the semaglutide group.

Safety: The percentage of patients reporting any adverse event was similar across the groups, with gastrointestinal events most common. However, serious adverse events were reported by 5.3 to 7.0% of patients in the tirzepatide groups and 2.8% of those in the semaglutide group.

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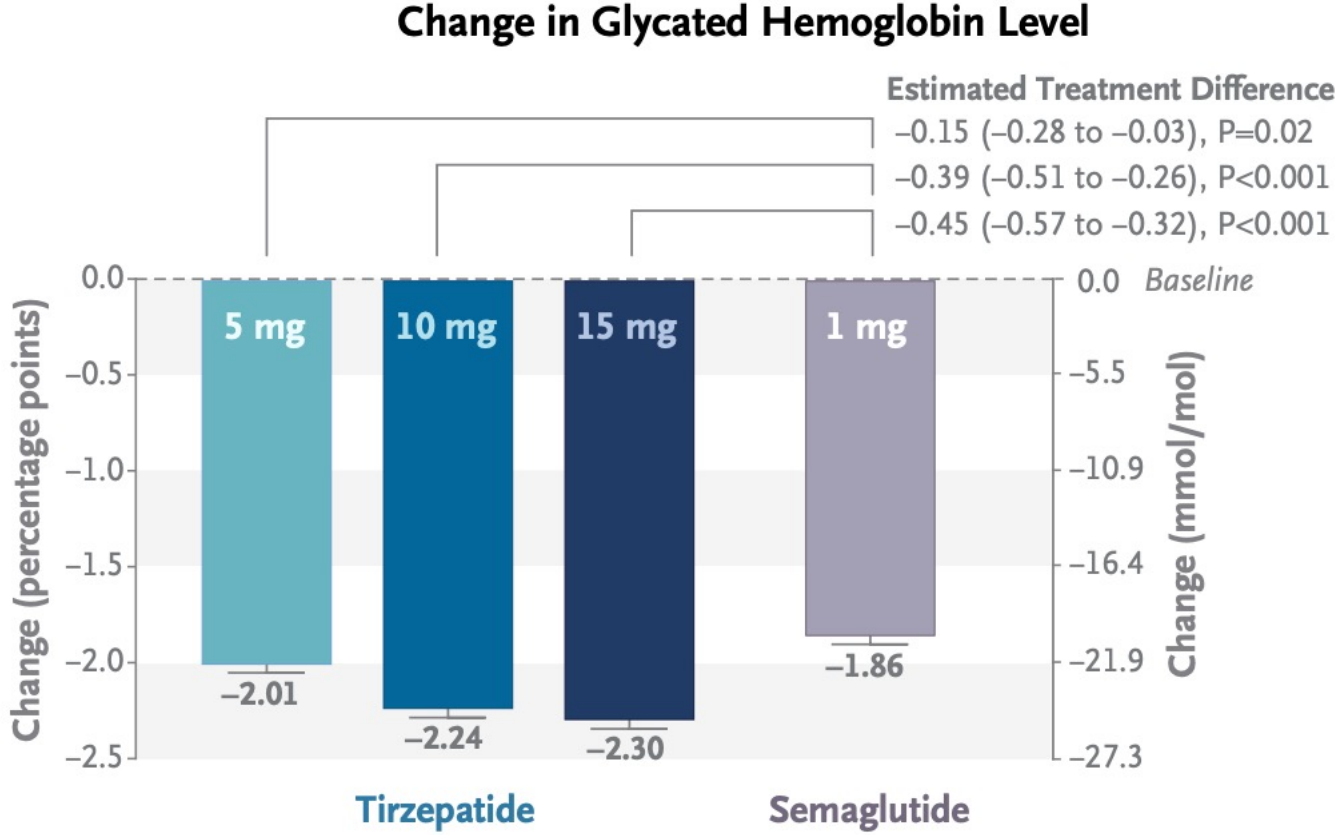

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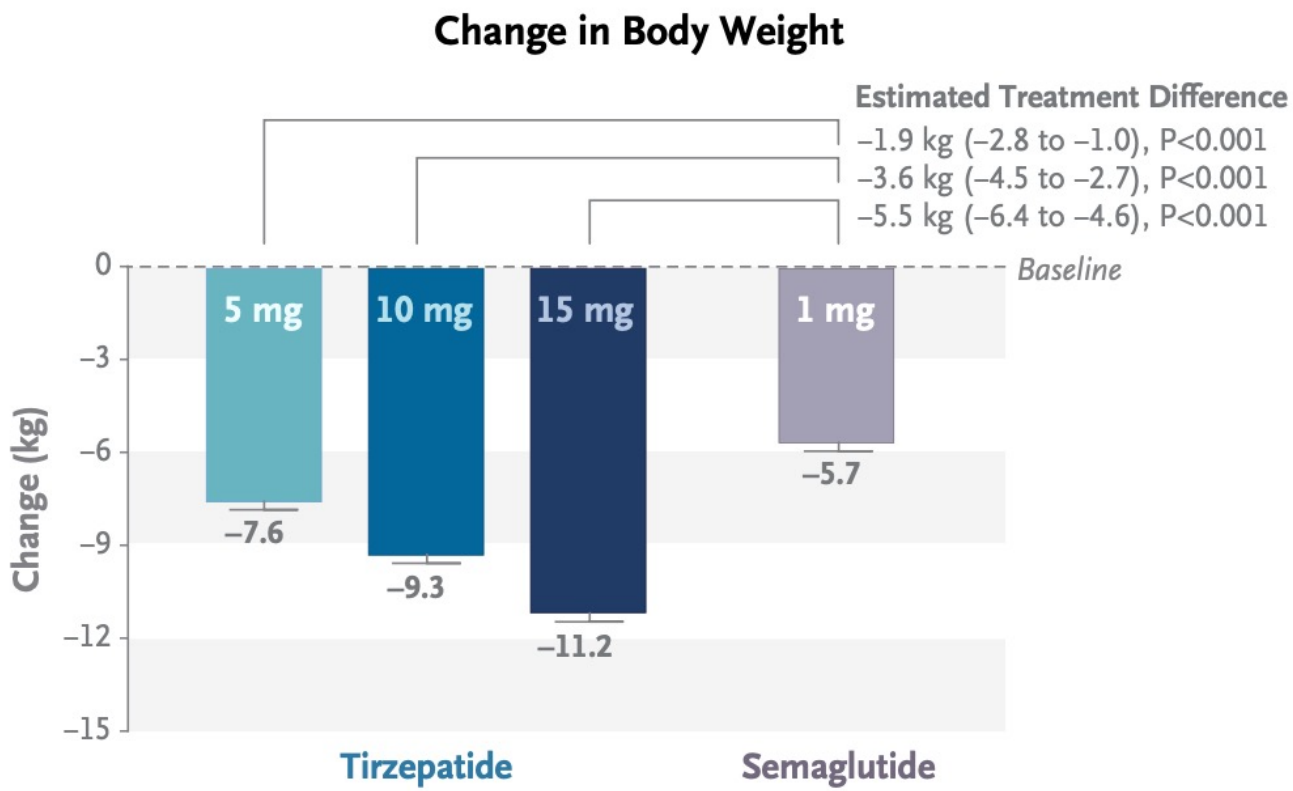

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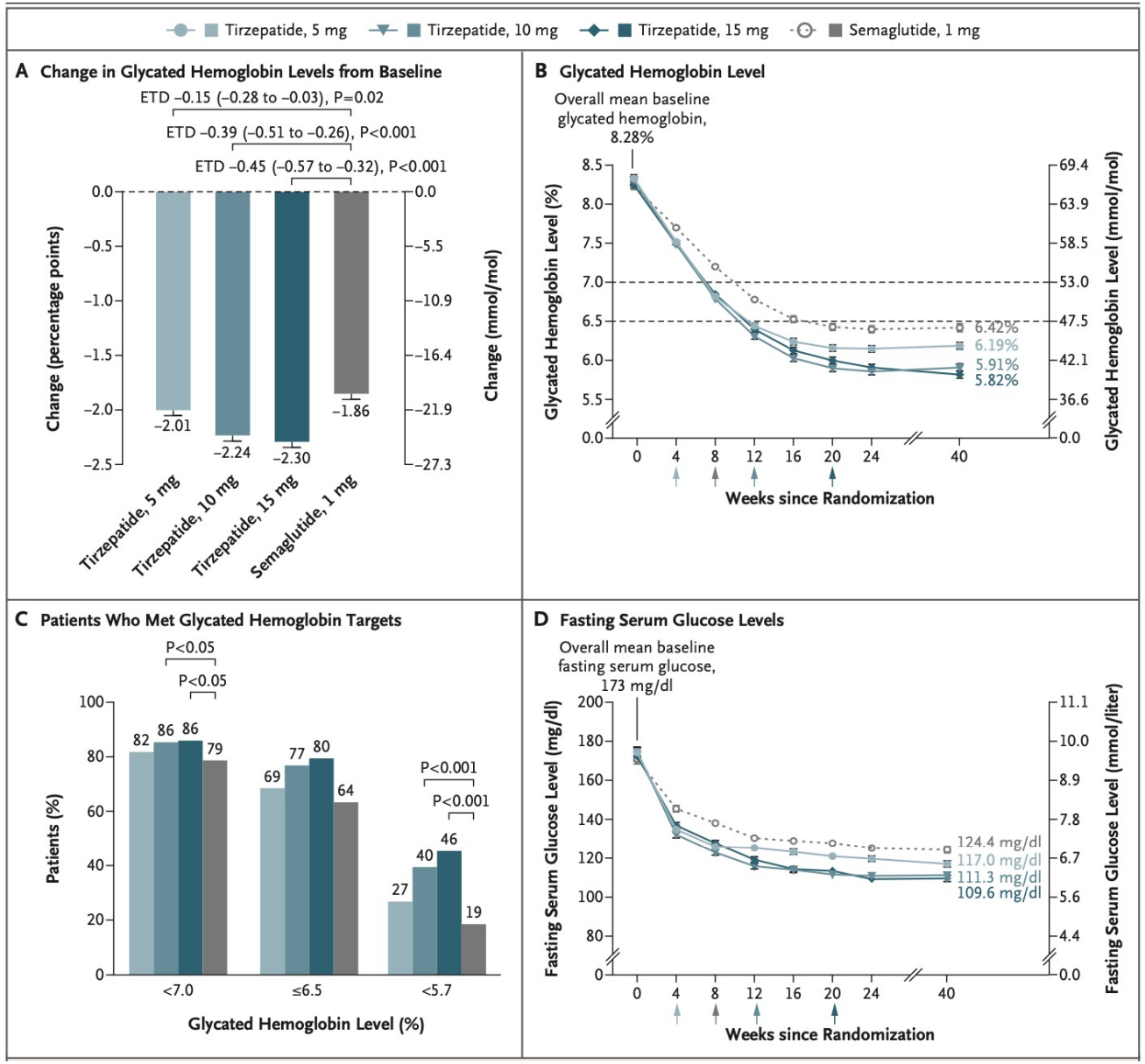

Figure 1. Effect of Once-Weekly Tirzepatide, as Compared with Semaglutide, on the Glycated Hemoglobin Level, Percentage of Patients Who Met Glycated Hemoglobin Level Targets, and Fasting Serum Glucose Levels.

Least-squares means (±SE) are presented, unless otherwise noted. Error bars indicate the standard error. Estimated treatment differences (ETDs) are least-squares means (95% confidence interval) at 40 weeks in the modified intention-to-treat population. Panel A shows the change from baseline in the glycated hemoglobin level at 40 weeks, as assessed with the use of analysis of covariance with multiple imputation according to treatment for the missing glycated hemoglobin level at 40 weeks (treatment-regimen estimand). Panel B shows the values for glycated hemoglobin levels over time, derived from a mixed-model repeated-measures analysis (efficacy estimand). Arrows indicate the times at which the maintenance doses of tirzepatide (5 mg, 10 mg, or 15 mg) and semaglutide 1 mg were achieved. Panel C shows the percentage of patients who met glycated hemoglobin level targets of less than 7.0%, 6.5% or less, and less than 5.7% at 40 weeks (treatment-regimen estimand). The percentage was calculated with the use of Rubin's rules by combining the percentages of patients who met the target in imputed data sets. The glycated hemoglobin levels of 6.5% or less and less than 5.7% (tirzepatide 5-mg group only) were not controlled for type 1 errors; thus, P values are not presented. Panel D shows fasting serum glucose values over time, derived from mixed-model repeated-measures analysis (efficacy estimand). Arrows indicate the times at which the maintenance doses of tirzepatide (5 mg, 10 mg, or 15 mg) and semaglutide 1 mg were achieved.

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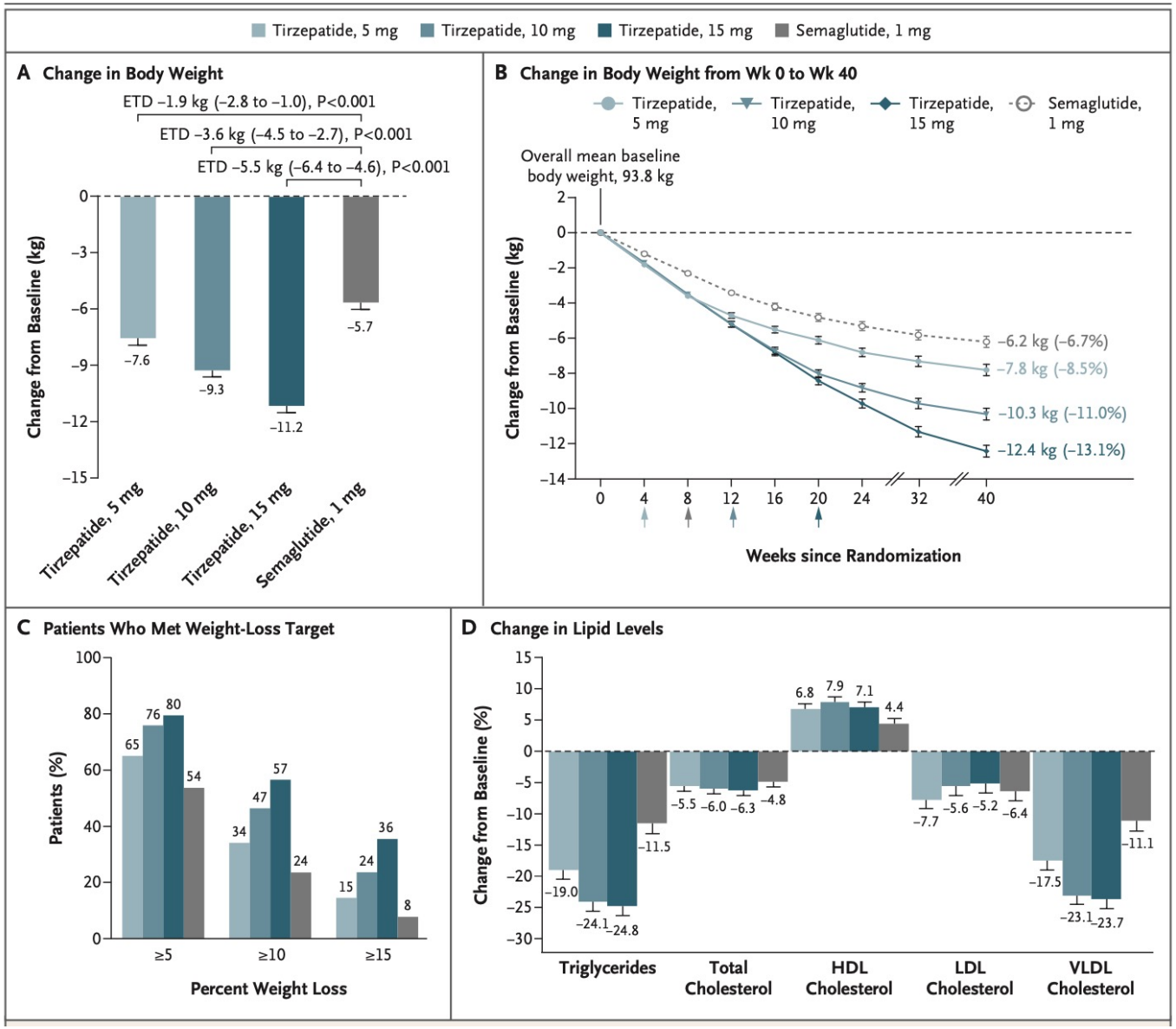

Figure 2. Effect of Once-Weekly Tirzepatide, as Compared with Semaglutide, on Body Weight, the Percentage of Patients Who Met Weight-Loss Goals, and the Lipid Profile.

Least-squares means (±SE) are presented, unless otherwise noted. Error bars indicate the standard error. Panel A shows the change from baseline in body weight at 40 weeks, as assessed with analysis of covariance with multiple imputation for treatment for missing weight at 40 weeks (treatment-regimen estimand). ETDs are least-squares means (95% confidence interval) at 40 weeks in the modified intention-to-treat population. Panel B shows the change from baseline in body weight over time, derived from a mixed-model repeated-measures analysis (efficacy estimand). The percent changes from baseline values at 40 weeks are shown in parentheses. Arrows indicate the times at which the maintenance doses of tirzepatide (5 mg, 10 mg, or 15 mg) and semaglutide 1 mg were achieved. Panel C shows the percentage of patients who had body-weight reductions of at least 5%, 10%, or 15% from baseline to week 40 (treatment-regimen estimand). The percentage was calculated with the use of Rubin's rules by combining the percentages of patients who met the target in imputed data sets. Panel D shows the percent change (±SE) from baseline in lipid levels at 40 weeks, as estimated with the use of log transformation. HDL denotes high-density lipoprotein, LDL low-density lipoprotein, and VLDL very-low-density lipoprotein.

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LIMITATIONS AND REMAINING QUESTIONS

- Treatments were not blinded because of differences in devices and dose-escalation schemes (although individual tirzepatide doses were blinded).
- Higher doses of semaglutide were not compared with tirzepatide.
- Black patients accounted for only 4% of the trial population, so generalizability of the findings is limited.
- How tirzepatide performs in patients with increased cardiovascular risk requires further study.

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CONCLUSIONS

Tirzepatide was noninferior and also superior to semaglutide in reducing glycated hemoglobin levels in adults with type 2 diabetes.

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