Semaglutide, a glucagon-like peptide-1 (GLP-1) agonist, has been shown to reduce weight and hemoglobin A\textsubscript{1c} (HbA\textsubscript{1c}) levels.\cite{1,2} The SURPASS-2 (A Study of Tirzepatide [LY3298176] Versus Semaglutide Once Weekly as Add-on Therapy to Metformin in Participants With Type 2 Diabetes) trial recently established the superiority of tirzepatide, a dual glucose-dependent insulinotropic polypeptide and GLP-1 agonist, in decreasing weight and HbA\textsubscript{1c}, when compared with semaglutide.\cite{1}

Given its efficacy, tirzepatide is likely to be prescribed widely. The most recent American Diabetes Association 2021 recommendations suggest the use of GLP-1 agonists in patients with established atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease independent of HbA\textsubscript{1c} or metformin use.\cite{3} Thus, it is important to understand the SURPASS-2 trial in the context of population generalizability and treatment effects. To better understand the US population eligible for therapy, we apply SURPASS-2 enrollment criteria to the US population and then simulate the effects of tirzepatide on this population.

All data used are publicly available, and the data and analytical code that support the findings of this study are available from the corresponding author upon reasonable request. We applied SURPASS-2 enrollment criteria to the National Health and Nutrition Examination Survey (2013–2018). Individuals were included if they were \geq 18 years of age with type 2 diabetes, had an HbA\textsubscript{1c} of 7.0% to 10.5% on metformin, and had a body mass index (BMI) $\geq$ 25 kg/m\textsuperscript{2}. Patients were excluded if they had estimated glomerular filtration rate of $<$ 45 mL/min per 1.73 m\textsuperscript{2}, history of diabetic retinopathy, or were taking any antidiabetes agents aside from metformin.

Baseline characteristics were determined for the US population meeting SURPASS-2 trial criteria and compared with the trial population. We then projected the effect of 100% uptake of escalating doses of tirzepatide if BMI and HbA\textsubscript{1c} reductions observed in the SURPASS-2 trial were translated at a population level in this cohort meeting all inclusion and exclusion criteria. Based on SURPASS-2 results, we used $-2.01\%$, $-2.24\%$, and $-2.30\%$ HbA\textsubscript{1c} reduction values for 5-mg, 10-mg, and 15-mg doses of tirzepatide, respectively; for BMI, we used $-7.6\text{-kg}$, $-9.3\text{-kg}$, and $-11.2\text{-kg}$ reductions for tirzepatide, respectively.

Given the American Diabetes Association’s broad recommendations for GLP-1 use, sensitivity analysis was additionally conducted to determine the number of eligible individuals on metformin in addition to any other antidiabetes therapy, excluding prior GLP-1 use. A survey-weighting design was used to determine national projections. All analyses were conducted with R version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria). National Health and Nutrition Examination Survey was approved by the National Center for Health Statistics Research Ethics Board. As part of the National Health and Nutrition Examination Survey, a survey-weighting design was used to determine national projections. All analyses were conducted with R version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria). National Health and Nutrition Examination Survey was approved by the National Center for Health Statistics Research Ethics Board.

Keywords: diabetes ■ generalizability ■ obesity ■ tirzepatide

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## Table. SURPASS-2 Trial Generalizability and Treatment Effects on US Population

| Characteristics                  | SURPASS-2 trial cohort* | US population eligible (on metformin alone) | US population eligible (including other antidiabetic therapy) |
|----------------------------------|-------------------------|---------------------------------------------|---------------------------------------------------------------|
| Age, y, mean                     | 56.7 (±10.4)            | 60.4 (±0.8)                                 | 60.6 (±0.7)                                                   |
| Sex, %                           |                         |                                             |                                                               |
| Male                             | 47.0                    | 66.4 (±4.9)                                 | 62.6% (±3.1)                                                 |
| Female                           | 53.0                    | 33.6 (±4.9)                                 | 37.4% (±3.1)                                                 |
| Race and ethnicity, %            |                         |                                             |                                                               |
| White†                           | 82.6                    | 63.9 (±4.3)                                 | 64.6 (±3.6)                                                  |
| Black                            | 4.2                     | 10.9 (±2.3)                                 | 10.5 (±2.0)                                                  |
| Hispanic‡                        | 70.1                    | 18.5 (±3.1)                                 | 17.6 (±2.5)                                                  |
| Asian                            | 1.3                     | 4.3 (±1.2)                                  | 4.3 (±1.0)                                                   |
| Other§                           | 11.1                    | 2.5 (±1.3)                                  | 3.0 (±1.1)                                                   |
| BP, mm Hg, mean                  |                         |                                             |                                                               |
| Systolic                         | 130.6 (±13.8)           | 132.3 (±1.7)                                | 131.9 (±1.5)                                                 |
| Diastolic                        | 79.2 (±9.0)             | 72.9 (±1.2)                                 | 71.6 (±1.0)                                                  |
| Weight, kg                       | 93.7 (±21.9)            | 99.5 (±2.1)                                 | 100.6 (±1.7)                                                 |
| BMI, kg/m², mean                 | 34.2 (±6.9)             | 34.4 (±0.5)                                 | 34.8 (±0.5)                                                  |
| HbA1c, %, mean                   | 8.28 (±0.1)             | 8.00 (±0.1)                                 | 8.07 (±0.1)                                                  |
| ≤8.5, %                          | 63.5%                   | 75.1% (±3.9%)                               | 72.4% (±3.4%)                                                |
| >8.5, %                          | 36.5%                   | 24.9% (±3.9%)                               | 21.0% (±3.4%)                                                |

### Effect of tirzepatide on national HbA1c and BMI distributions

| HbA1c metrics, %                  | Untreated US population eligible† | Tirzepatide 5 mg | Tirzepatide 10 mg | Tirzepatide 15 mg |
|-----------------------------------|-----------------------------------|-----------------|-----------------|-----------------|
| Mean HbA1c                        | 8.00 (±0.1)                       | 5.99 (±0.1)     | 5.76 (±0.1)     | 5.70 (±0.1)     |
| HbA1c ≤5.7                        | 0.0                               | 49.6 (±4.2)     | 58.7 (±4.2)     | 58.7 (±4.2)     |
| HbA1c >5.7 and ≤6.5               | 0.0                               | 25.4 (±4.3)     | 20.1 (±4.1)     | 20.1 (±4.1)     |
| HbA1c >6.5 and ≤7.0               | 0.0                               | 7.6 (±2.1)      | 8.4 (±2.3)      | 8.4 (±2.3)      |
| HbA1c >7.0 and ≤8.5               | 73.6 (±3.9)                       | 17.3 (±3.6)     | 12.7 (±3.1)     | 12.7 (±3.1)     |
| HbA1c >8.5                        | 26.4 (±3.9)                       | 0.0             | 0.0             | 0.0             |
| BMI categories, kg/m²             |                                   |                 |                 |                 |
| BMI, mean                         | 34.4 (±0.5)                       | 31.8 (±0.5)     | 31.2 (±0.5)     | 30.5 (±0.5)     |
| BMI <18.5, %                      | 0.0                               | 0.0             | 0.0             | 0.0             |
| BMI ≥18.5 and <25, %              | 0.0                               | 12.4 (±2.3)     | 15.0 (±2.7)     | 19.9 (±2.9)     |
| BMI ≥25 and <30, %                | 29.5 (±3.6)                       | 39.8 (±4.0)     | 41.9 (±4.2)     | 38.7 (±4.5)     |
| BMI ≥30, %                        | 70.5 (±3.3)                       | 47.8 (±4.7)     | 43.1 (±4.5)     | 41.4 (±4.2)     |

Demographics of SURPASS-2 trial and US population meeting trial criteria as well as changes to HbA1c and BMI distributions with 100% uptake of tirzepatide in the eligible US population. BMI indicates body mass index; HbA1c, hemoglobin A1c; and SURPASS-2, A Study of Tirzepatide (LY3298176) Versus Semaglutide Once Weekly as Add-on Therapy to Metformin in Participants With Type 2 Diabetes.

*Data obtained from Table 1 of article on tirzepatide.†The "White" category in the SURPASS-2 trial cohort included both Hispanic and Non-Hispanic White individuals. In contrast, the "White" category for the US population eligible for tirzepatide as derived from the NHANES analysis includes only non-Hispanic White individuals.‡The "Hispanic" category in the SURPASS-2 trial cohort included both Hispanic White individuals and Non-Hispanic White individuals. In contrast, the "White" category for the US population eligible for tirzepatide as derived from the NHANES analysis includes only non-White Hispanic individuals.§The "Other" category in the SURPASS-2 trial cohort refers to American Indian or Alaska Native individuals. In contrast, the "Other" category for the US population eligible for tirzepatide as derived from the NHANES analysis refers to non-Hispanic persons reporting races other than Black, Asian, or White. This includes Multi-Racial as designated in NHANES.¶The "Untreated US Population Eligible" refers to the 2,991,003 projected individuals eligible for tirzepatide by SURPASS-2 Trial criteria on metformin alone; the HbA1c and BMI metrics for this column are assuming no treatment with tirzepatide.
Survey data collection, a consent form was signed by all participants in the survey.

In our analysis, 2,991,003 (95% CI, 2,496,723–3,485,282) US adults met SURPASS-2 criteria for initiation of tirzepatide. In sensitivity analysis permitting inclusion of individuals on prior antidiabetes agents in addition to metformin, eligible US adults increased to 4,937,063 (95% CI, 4,282,642–5,591,483).

Blood pressure and HbA1c were similar between the SURPASS-2 trial population and the eligible US population, though the eligible US population had a higher proportion of men (62.6% versus 47.0%), a higher mean weight (101.3 kg versus 93.7 kg), and a different racial and ethnic composition (Table).

In the US eligible population, complete uptake of 15 mg tirzepatide was simulated to reduce mean A1C from to 8.00% to 5.70% and decrease the proportion of obese individuals from 70.5% to 41.4%. Changes in national A1C and BMI distributions by tirzepatide dose are displayed in the Table.

With =3.0 million adults eligible for tirzepatide, and up to =4.9 million on sensitivity analysis, our results demonstrate that SURPASS-2 criteria are widely generalizable. Strikingly, complete uptake of tirzepatide in the eligible US population could result in significant changes to the national distribution of HbA1c and BMI.

Despite the promise of therapy, we found that over half of eligible adults were not on any antidiabetes medications aside from metformin despite a mean HbA1c of 8.0%, and a quarter of individuals with HbA1c >8.5%. Our results underscore continued challenges in diabetes care, where multiple effective agents exist—though the US population continues to struggle with uptake. The introduction of novel agents such as tirzepatide have the potential to greatly improve diabetes control; however, approaches to ensure population uptake are urgently needed.

It is important to note clinically that in SURPASS-2, adverse events leading to discontinuation of tirzepatide occurred in 6% of patients on a 5-mg dose and up to 8.5% for those on a 10-mg or 15-mg dose. This is in contrast to 4.1% of patients in the comparison semaglutide 1-mg group. Allowing a conservative estimate, if =10% of patients discontinued tirzepatide on the basis of side effects, only =2.7 million of the projected =3.0 million adults could tolerate maximum doses. Thus, side effects on tirzepatide must be monitored clinically, and clinicians should individualize therapy choices based on patients’ responses.

There are several limitations to our study. First, survey data are subject to response bias. Second, we do factor cost into consideration, and our simulation on treatment effects does not take into account treatment heterogeneity of the US population.

In conclusion, tirzepatide is broadly generalizable, and increased prescription could have large effects on the control of diabetes and obesity.

REFERENCES

1. Frias JP, Davies MJ, Rosenstock J, Pérez Manghi FC, Fernández Landó L, Bergman BK, Liu B, Cui X, Brown K. Tirzepatide versus...
1. Chiu et al. Generalizability of SURPASS-2 and Tirzepatide may improve glycemic control in type 2 diabetes. *N Engl J Med.* 2021;385:503–515. doi: 10.1056/NEJMoa2107519

2. Davies M, Færch L, Jeppesen OK, Pakseresht A, Pedersen SD, Perreault L, Rosenstock J, Shimomura I, Viljoen A, Wadden TA, et al; STEP 2 Study Group. Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet.* 2021;397:971–984. doi: 10.1016/S0140-6736(21)00213-0.

3. Association AD. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes—2021. *Diabetes Care.* 2021;44:S111–S124. doi: 10.2337/dc21-S009