

ORIGINAL ARTICLE

Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity

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ABSTRACT

BACKGROUND

Obstructive sleep apnea is characterized by disordered breathing during sleep and is associated with major cardiovascular complications; excess adiposity is an etiologic risk factor. Tirzepatide may be a potential treatment.

METHODS

We conducted two phase 3, double-blind, randomized, controlled trials involving adults with moderate-to-severe obstructive sleep apnea and obesity. Participants who were not receiving treatment with positive airway pressure (PAP) at baseline were enrolled in trial 1, and those who were receiving PAP therapy at baseline were enrolled in trial 2. The participants were assigned in a 1:1 ratio to receive either the maximum tolerated dose of tirzepatide (10 mg or 15 mg) or placebo for 52 weeks. The primary end point was the change in the apnea–hypopnea index (AHI, the number of apneas and hypopneas during an hour of sleep) from baseline. Key multiplicity-controlled secondary end points included the percent change in AHI and body weight and changes in hypoxic burden, patient-reported sleep impairment and disturbance, high-sensitivity C-reactive protein (hsCRP) concentration, and systolic blood pressure.

RESULTS

At baseline, the mean AHI was 51.5 events per hour in trial 1 and 49.5 events per hour in trial 2, and the mean body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) was 39.1 and 38.7, respectively. In trial 1, the mean change in AHI at week 52 was –25.3 events per hour (95% confidence interval [CI], –29.3 to –21.2) with tirzepatide and –5.3 events per hour (95% CI, –9.4 to –1.1) with placebo, for an estimated treatment difference of –20.0 events per hour (95% CI, –25.8 to –14.2) ($P < 0.001$). In trial 2, the mean change in AHI at week 52 was –29.3 events per hour (95% CI, –33.2 to –25.4) with tirzepatide and –5.5 events per hour (95% CI, –9.9 to –1.2) with placebo, for an estimated treatment difference of –23.8 events per hour (95% CI, –29.6 to –17.9) ($P < 0.001$). Significant improvements in the measurements for all prespecified key secondary end points were observed with tirzepatide as compared with placebo. The most frequently reported adverse events with tirzepatide were gastrointestinal in nature and mostly mild to moderate in severity.

CONCLUSIONS

Among persons with moderate-to-severe obstructive sleep apnea and obesity, tirzepatide reduced the AHI, body weight, hypoxic burden, hsCRP concentration, and systolic blood pressure and improved sleep-related patient-reported outcomes. (Funded by Eli Lilly; SURMOUNT-OSA ClinicalTrials.gov number, NCT05412004.)

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This article was published on June 21, 2024, and last updated on July 1, 2024, at NEJM.org.

DOI: 10.1056/NEJMoa2404881

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OBSTRUCTIVE SLEEP APNEA IS CHARACTERIZED by repetitive pharyngeal collapse during sleep resulting in apneas and hypopneas, with consequent hypoxemia, hypercapnia, and recurrent arousals.¹ Obstructive sleep apnea is accompanied by clinically relevant symptoms, such as excessive daytime sleepiness, and is an independent risk factor for cardiovascular disease.^{1,2} The disease is common and has major medical and economic effects; more than 900 million persons are affected worldwide, approximately 40% of whom have moderate-to-severe disease.³

The treatment of patients with obstructive sleep apnea has historically focused on mechanical support during sleep. Positive airway pressure (PAP) therapy improves the apnea–hypopnea index (AHI, the number of apneas and hypopneas during an hour of sleep) and reduces symptoms related to obstructive sleep apnea, but its overall effectiveness can be affected by varying adherence to therapy. Randomized, controlled trials have failed to show that PAP reduces occurrences of adverse cardiovascular outcomes and death.^{4–6} Mandibular advancement therapy is predominantly used in patients who are unable or unwilling to adhere to treatment with PAP, but it is not universally efficacious.⁷ Upper-airway surgery, including stimulation of the hypoglossal nerve, may be effective but is an invasive option that may be appropriate for selected patients. At present, there is no pharmaceutical intervention that has been approved for the treatment of obstructive sleep apnea.

Excess adiposity is a major reversible etiologic risk factor for obstructive sleep apnea and its complications.^{8,9} The benefit of substantial weight reduction in the treatment of patients with obstructive sleep apnea is well recognized, and clinical guidelines recommend treatment of obesity in patients with obstructive sleep apnea.⁹ Thus, a pharmacologic intervention that targets obesity and its downstream effects on obstructive sleep apnea, symptoms, blood pressure, and low-grade systemic inflammation may facilitate a holistic approach that is not fully attained with the aforementioned mechanical treatments.^{10–12}

Tirzepatide is a long-acting glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist that selectively binds to and activates both the GIP and GLP-1 receptors. It is an amino acid sequence that includes a C20 fatty diacid moiety that enables albumin binding, which prolongs the half-

life.¹³ Treatment with tirzepatide has led to significant reductions in excess body weight, improvements in blood pressure, and reductions in markers of inflammation and vascular endothelial dysfunction, and may have the potential to be efficacious in persons with obstructive sleep apnea.^{14,15} Here we report the results of the SURMOUNT-OSA phase 3 trials evaluating the safety and efficacy of tirzepatide for the treatment of adults with obstructive sleep apnea and obesity.

METHODS

TRIAL DESIGN

The SURMOUNT-OSA trials were two 52-week, phase 3, multicenter, parallel-group, double-blind, randomized, controlled trials that were conducted at 60 sites across nine countries to evaluate the efficacy and safety of the maximum tolerated dose of weekly tirzepatide (10 mg or 15 mg) in adults with moderate-to-severe obstructive sleep apnea and obesity (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Two participant populations were included in the SURMOUNT-OSA master protocol (available at NEJM.org): trial 1 included participants who were unable or unwilling to use PAP therapy, and trial 2 included participants who had been using PAP therapy for at least 3 consecutive months at the time of screening and who planned to continue PAP therapy during the trial. The master protocol rationale and design have been previously published.¹⁶ The protocols were designed by the sponsor (Eli Lilly) and members of the trial steering committee. The protocol was approved by the relevant institutional review boards, and all the participants provided written informed consent.

The trials were conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation and the principles of the Declaration of Helsinki. Statistical analyses were performed by employees of the sponsor. The first and last authors prepared the first draft of the manuscript, which was reviewed, edited, and approved by all the authors. A medical writer employed by the sponsor provided medical-writing assistance. The investigators and steering committee worked under confidentiality agreements with the sponsor. The sponsor was involved in the collection, management, analyses, and in-

terpretation of the data; the preparation, review, and approval of an earlier version of the manuscript; and the decision to submit the manuscript for publication. Final decisions on preparation of the manuscript for submission were made by the authors, some of whom were employees of the sponsor. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trials to the protocols.

PARTICIPANTS

Adults who had received a diagnosis of moderate-to-severe obstructive sleep apnea (AHI ≥ 15 events per hour) and obesity (body-mass index [BMI, the weight in kilograms divided by the square of the height in meters] of ≥ 30 [≥ 27 in Japan]) were eligible. Key exclusion criteria were the presence of type 1 or type 2 diabetes, a participant-reported change in body weight of more than 5 kg in the 3 months before screening, planned surgery for sleep apnea or obesity, a diagnosis of central or mixed sleep apnea, and major craniofacial abnormalities. A full list of eligibility criteria is available in the Supplementary Appendix.

TRIAL PROCEDURES

After a 4-week screening period, participants were assigned to trial 1 or trial 2 and randomly assigned in a 1:1 ratio to receive tirzepatide or placebo subcutaneously once weekly with the use of a single-dose pen autoinjector. All the participants received regular lifestyle counseling sessions regarding the maintenance of healthy nutrition while adhering to a 500 kilocalorie per day deficit and at least 150 minutes per week of physical activity.

Randomization was conducted by means of a Web-based interactive response system and stratified according to trial, country or geographic region, baseline AHI severity category, and sex. Enrollment of men was limited to 70% to ensure adequate representation of women. Participants, investigators, and the sponsor were unaware of trial-group assignment. Participants were required to receive tirzepatide or placebo during a planned 52-week period that included a dose-escalation period of up to 20 weeks and a 4-week safety follow-up. The initial dose of tirzepatide was 2.5 mg once weekly and was increased by 2.5 mg every 4 weeks during the dose-escalation period until the participant reached the maximum tolerated dose of 10 mg or 15 mg in week 20. Par-

ticipants in whom doses of 10 mg or more produced unacceptable side effects discontinued tirzepatide or placebo but were encouraged to remain in the trial.

The AHI was measured by laboratory polysomnography at screening, week 20, and week 52. Data from polysomnographic studies were scored centrally with the use of the American Academy of Sleep Medicine rule 1B for identification of hypopneas (which specifies a $\geq 30\%$ reduction in airflow for ≥ 10 seconds and oxygen desaturation of $\geq 4\%$).¹⁷

END POINTS AND ASSESSMENTS

The primary end point was the change in the AHI from baseline. Key secondary end points that were controlled for type 1 errors included the percent change in AHI; the percentage of participants with an AHI reduction of at least 50%; the percentage of participants with an AHI of less than 5 events per hour or with an AHI of 5 to 14 events per hour and a score of 10 or less on the Epworth Sleepiness Scale (ESS; range, 0 to 24, with higher scores indicating greater daytime sleepiness); the percent change in body weight; the change in high-sensitivity C-reactive protein (hsCRP) concentration; the change in sleep apnea-specific hypoxic burden (a measure calculated from a polysomnographic study that comprises frequency, duration, and depth of oxygen saturation related to the respiratory event)¹⁸; the change in scores on the Patient-Reported Outcomes Measurement Information System (PROMIS) Short Form Sleep-related Impairment 8a (PROMIS-SRI) and PROMIS Short Form Sleep Disturbance 8b (PROMIS-SD) scales (higher scores indicate more sleep impairment or sleep disturbance, respectively); and the change in systolic blood pressure. Participants in trial 2 were instructed to suspend PAP therapy for 7 days before polysomnographic and patient-reported outcome (PRO) assessments at baseline, week 20, and week 52 to minimize the confounding effect of PAP therapy on sleep-disordered breathing and other breathing-related and PRO assessments. All end points were assessed from baseline to week 52 except for blood pressure, which was assessed at week 48 to prevent suspension of PAP therapy in trial 2 from confounding the assessment.

In response to a recommendation by a regulatory body, key secondary PRO end points were changed from the hierarchical combination of

change in scores on the Functional Outcomes of Sleep Questionnaire to change in PROMIS-SRI and PROMIS-SD. Owing to the timing of regulatory advice and because the change did not affect how clinical trial investigators conducted the tri-

als, the change in key secondary PRO end points was captured in the final statistical analysis plan, available with the protocol, before the time of the data unblinding, the database lock, and data analyses (details are provided in the Supplemen-

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Trial 1			Trial 2		
	Tirzepatide (N=114)	Placebo (N=120)	Total (N=234)	Tirzepatide (N=120)	Placebo (N=115)	Total (N=235)
Age — yr	47.3±11.0	48.4±11.9	47.9±11.5	50.8±10.7	52.7±11.3	51.7±11.0
<50 yr	63 (55.3)	62 (51.7)	125 (53.4)	54 (45.0)	45 (39.1)	99 (42.1)
≥50 yr	51 (44.7)	58 (48.3)	109 (46.6)	66 (55.0)	70 (60.9)	136 (57.9)
Female sex — no. (%)	36 (31.6)	41 (34.2)	77 (32.9)	33 (27.5)	32 (27.8)	65 (27.7)
Race or ethnic group — no. (%)						
American Indian or Alaska Native	9 (7.9)	9 (7.5)	18 (7.7)	10 (8.3)	9 (7.9)	19 (8.1)
Asian	23 (20.2)	24 (20.0)	47 (20.1)	17 (14.2)	16 (14.0)	33 (14.1)
Black or African American	6 (5.3)	7 (5.8)	13 (5.6)	8 (6.7)	3 (2.6)	11 (4.7)
White	74 (64.9)	80 (66.7)	154 (65.8)	85 (70.8)	86 (75.4)	171 (73.1)
Multiple	2 (1.8)	0	2 (0.9)	—	—	—
Hispanic or Latino	51 (44.7)	47 (39.2)	98 (41.9)	38 (31.7)	38 (33.0)	76 (32.3)
Body weight — kg	116.7±24.6	112.8±22.6	114.7±23.7	115.8±21.5	115.1±22.7	115.5±22.0
Body-mass index						
Mean value	39.7±7.3	38.6±6.7	39.1±7.0	38.6±6.1	38.7±6.0	38.7±6.0
Distribution — no. (%)†						
<35	33 (28.9)	44 (36.7)	77 (32.9)	33 (27.7)	33 (28.9)	66 (28.3)
≥35 to <40	39 (34.2)	35 (29.2)	74 (31.6)	47 (39.5)	41 (36.0)	88 (37.8)
≥40	42 (36.8)	41 (34.2)	83 (35.5)	39 (32.8)	40 (35.1)	79 (33.9)
Waist circumference — cm	122.6±16.6	119.8±14.8	121.2±15.7	120.7±13.1	121.0±14.0	120.9±13.5
AHI — events/hr	52.9±30.5	50.1±31.5	51.5±31.0	46.1±22.4	53.1±30.2	49.5±26.7
Obstructive sleep apnea severity — no. (%)‡						
No apnea	0	1 (0.8)	1 (0.4)	—	—	—
Mild: AHI <15 events/hr	1 (0.9)	2 (1.7)	3 (1.3)	0	2 (1.8)	2 (0.9)
Moderate: AHI ≥15 events/hr	39 (34.2)	43 (36.1)	82 (35.2)	35 (29.4)	37 (32.5)	72 (30.9)
Severe: AHI ≥30 events/hr	74 (64.9)	73 (61.3)	147 (63.1)	84 (70.6)	75 (65.8)	159 (68.2)
Missing data	0	1 (0.8)	1 (0.4)	1 (0.8)	1 (0.9)	2 (0.9)
PROMIS Sleep-related Impairment T score§	53.2±7.5	54.3±8.5	53.8±8.1	55.3±8.4	55.0±9.5	55.2±8.9
PROMIS Sleep Disturbance T score¶	53.8±6.0	53.5±7.4	53.6±6.7	56.0±7.6	55.7±7.6	55.9±7.6
ESS score	10.3±5.3	10.8±5.2	10.6±5.3	10.8±4.6	9.5±4.4	10.2±4.5
Sleep apnea-specific hypoxic burden — % min/hr**	153.6 (102.7)	137.8 (104.1)	145.3 (103.4)	132.2 (83.4)	142.1 (112.5)	137.0 (97.5)
Systolic blood pressure — mm Hg	128.4±12.2	130.3±10.7	129.4±11.5	130.5±14.3	130.5±12.8	130.5±13.5
Diastolic blood pressure — mm Hg	83.7±8.9	84.0±8.6	83.8±8.7	83.2±8.2	80.5±8.6	81.8±8.5
Hypertension — no. (%)	84 (73.7)	93 (77.5)	177 (75.6)	91 (75.8)	91 (79.1)	182 (77.4)

Table 1. (Continued.)

Characteristic	Trial 1			Trial 2		
	Tirzepatide (N=114)	Placebo (N=120)	Total (N=234)	Tirzepatide (N=120)	Placebo (N=115)	Total (N=235)
hsCRP concentration — mg/liter ^{††}	3.5 (120.0)	3.6 (124.6)	3.5 (122.0)	3.0 (124.3)	2.7 (127.5)	2.8 (125.8)
Prediabetes — no. (%)	74 (64.9)	78 (65.0)	152 (65.0)	69 (57.5)	64 (55.7)	133 (56.6)
Glycated hemoglobin — %	5.69±0.37	5.64±0.35	5.67±0.36	5.62±0.37	5.65±0.44	5.63±0.41
Dyslipidemia — no. (%)	91 (79.8)	98 (81.7)	189 (80.8)	100 (83.3)	97 (84.3)	197 (83.8)

* Plus-minus values are mean ±SD. Categories include all participants who underwent randomization unless otherwise noted.

[†] Trial 2 had one missing participant value for body-mass index for each of the two trial groups.

[‡] Participants with an apnea–hypopnea index (AHI, the number of apneas and hypopneas during an hour of sleep) of less than 15 events per hour were determined to have been enrolled in error and were withdrawn from the trial.

[§] The PROMIS Short Form Sleep-related Impairment 8a consists of eight factors that the participant can recall in the past 7 days, with each factor rated on a 5-point scale from “not at all” to “very much.” Scores for individual factors were totaled to obtain a raw score that was then converted to a T score (with the use of response-pattern scoring), with a mean score of 50 and a standard deviation of 10, with higher scores indicating more sleep-related impairment.²³

[¶] The PROMIS Short Form Sleep Disturbance 8b consists of eight factors that the participant can recall in the past 7 days, with each factor rated on a 5-point scale from “not at all” to “very much,” “never” to “always,” or “very poor” to “very good.” Scores for individual factors were totaled to obtain a raw score that was then converted to a T score (with the use of response-pattern scoring), with a mean score of 50 and a standard deviation of 10, with higher scores indicating more sleep disturbance.²³

^{||} The Epworth Sleepiness Scale (ESS) is an eight-factor participant-reporting measure that asks the participant to rate, on a scale of 0 (would never doze) to 3 (high chance of dozing), their recent typical likelihood of dozing in eight different daytime situations. The ESS total score is the sum of the eight factor scores and ranges from 0 to 24, with higher scores indicating greater daytime sleepiness.

^{**} Hypoxic burden is defined as the total respiratory-event–related area under the oxygen-desaturation curve from a pre-event baseline and is expressed as % min/hr — the time (in minutes) spent in oxygen desaturation (%) per hour of sleep. This measure is calculated from a polysomnographic study that encapsulated frequency, duration, and depth of respiratory event–related oxygen desaturation, and data are geometric means (coefficient of variation, %).

^{††} High-sensitivity C-reactive protein (hsCRP) data are geometric means (coefficient of variation, %).

tary Appendix). Safety assessments included adverse events and serious adverse events that occurred during the reporting period.

STATISTICAL ANALYSIS

The statistical analysis plan, including all the end points and assessments, was finalized and submitted before the time of the database lock and data unblinding. We calculated that a sample size of 206 participants per trial would provide the trial with at least 90% power to show the superiority of tirzepatide to placebo relative to the primary end point at a two-sided significance level of 0.05. In calculating the sample size for the primary end point, we assumed a mean 50% reduction in AHI, with a common standard deviation of 50% and a dropout rate of up to 25%. The updated primary end point was also deemed to have sufficient power; therefore, no adjustments to the sample-size calculation were made.

Data from all the participants who received at least one dose of tirzepatide or placebo (the intention-to-treat population) were used to analyze the efficacy and safety end points. For each trial, two estimands — the treatment-regimen estimand

and efficacy estimand — were used to assess the primary and key secondary end points from different perspectives, and the two estimands accounted for intercurrent events differently. The treatment-regimen estimand represented the average treatment effect of tirzepatide relative to placebo for all participants who had received at least one dose of tirzepatide or placebo regardless of whether they discontinued trial treatment or placebo for any reason. The efficacy estimand represented the average treatment effect of tirzepatide relative to placebo for all the participants if the treatment or placebo was administered as intended for the entire planned 52-week trial duration. All results are reported with the use of the treatment-regimen estimand unless otherwise specified. For the primary and key secondary end points, the type 1 error rate was controlled at a two-sided alpha level of 0.05 within each estimand and within each trial by means of a graphical testing procedure.¹⁹ PROMIS-SRI and PROMIS-SD end points from both trials that were controlled for type 1 errors were pooled and tested with the use of a distinct graphical testing scheme to provide relevant power for

analysis under the submission-wise type 1 error-rate-control strategy (Fig. S2).^{20,21} The populations of the two trials were suitable for pooling because of similar baseline PRO characteristics. The potential issue of PAP confounding of the PROMIS outcomes in trial 2 was minimized by a 7-day PAP washout period.²²

Statistical analyses were conducted with the use of an analysis of covariance model, with the end point as a response variable, trial-group assignment and randomization strata as fixed effects (except for the severity of obstructive sleep apnea for AHI-related end points), and the baseline value as a covariate. Categorical variables of the proportion of participants who had at least 50% reduction in AHI and an AHI of less than 5 events per hour or an AHI of 5 to 14 events per hour with an ESS of 10 or less were evaluated with the use of logistic regression analysis with trial-group assignment, geographic region, baseline AHI, and sex as covariates. Baseline or post-baseline data were assumed to be missing at random or not at random depending on the reason for missingness. Data that were missing at random were handled through a multiple-imputation approach with the use of data from the same trial group. Data that were missing but not at random were imputed with the use of a placebo-based multiple-imputation approach. Full details on the estimands, handling of missing values, and statistical analysis methods are provided in the Supplementary Appendix.

RESULTS

PARTICIPANTS

The trials were conducted from June 21, 2022, through March 29, 2024. A total of 469 participants were randomly assigned to receive tirzepatide or placebo in trial 1 (234 participants) or trial 2 (235 participants) (Table 1). Overall, 82.9% of the participants completed the trial (91.5% in the tirzepatide groups and 74.4% in the placebo groups) and 79.7% adhered to the assigned regimen (87.6% in the tirzepatide groups and 71.9% in the placebo groups) (Fig. S3).

Demographic and baseline characteristics of the participants are shown in Table 1. In trial 1, the mean age of the participants was 47.9 years; most were male (67.1%) and White (65.8%), with a mean BMI of 39.1 and a mean AHI of 51.5 events per hour. In trial 2, the mean age was 51.7

years; most were male (72.3%) and White (73.1%), with a mean BMI of 38.7 and a mean AHI of 49.5 events per hour. Details regarding the geographic distribution and representativeness of the trial participants are shown in Tables S1 and S2.

SLEEP-DISORDERED BREATHING-RELATED END POINTS

For the trial 1 treatment-regimen estimand, the change in AHI at week 52 was −25.3 events per hour (95% confidence interval [CI], −29.3 to −21.2) with tirzepatide and −5.3 events per hour (95% CI, −9.4 to −1.1) with placebo, for an estimated treatment difference of −20.0 events per hour (95% CI, −25.8 to −14.2), ($P < 0.001$) (Fig. 1A and Table 2). For the efficacy estimand, the change in AHI at week 52 was −27.4 events per hour (95% CI, −31.6 to −23.2) with tirzepatide and −4.8 events per hour (95% CI, −9.3 to −0.3) with placebo, for an estimated treatment difference of −22.5 events per hour (95% CI, −28.7 to −16.4).

For the trial 2 treatment-regimen estimand, the change in AHI at week 52 was −29.3 events per hour (95% CI, −33.2 to −25.4) with tirzepatide and −5.5 events per hour (95% CI, −9.9 to −1.2) with placebo, for an estimated treatment difference of −23.8 events per hour (95% CI, −29.6 to −17.9), ($P < 0.001$) (Fig. 1B and Table 2). For the efficacy estimand, the change in AHI at week 52 with tirzepatide was −30.4 events per hour (95% CI, −34.3 to −26.5) with tirzepatide and −6.0 events per hour (95% CI, −10.3 to −1.6) with placebo, for an estimated treatment difference of −24.4 events per hour (95% CI, −30.3 to −18.6). The change over time in AHI in the efficacy estimand is shown in Figures 1A and 1B.

Participants in both trials who received tirzepatide had significant reductions in AHI and in the sleep apnea-specific hypoxic burden (Table 2). The percentages of participants who had a reduction in the AHI of 50% or more at week 52 and the percentages who had an AHI of less than 5 events per hour or an AHI of 5 to 14 events per hour and an ESS of 10 or less at week 52 are reported in Table 2.

CHANGE IN PROS AND CARDIOVASCULAR RISK FACTORS

In a pooled trial 1 and trial 2 analysis, participants who received tirzepatide had significant reductions in PROMIS-SRI and PROMIS-SD T scores (Table 3). PROMIS data that were analyzed separately for

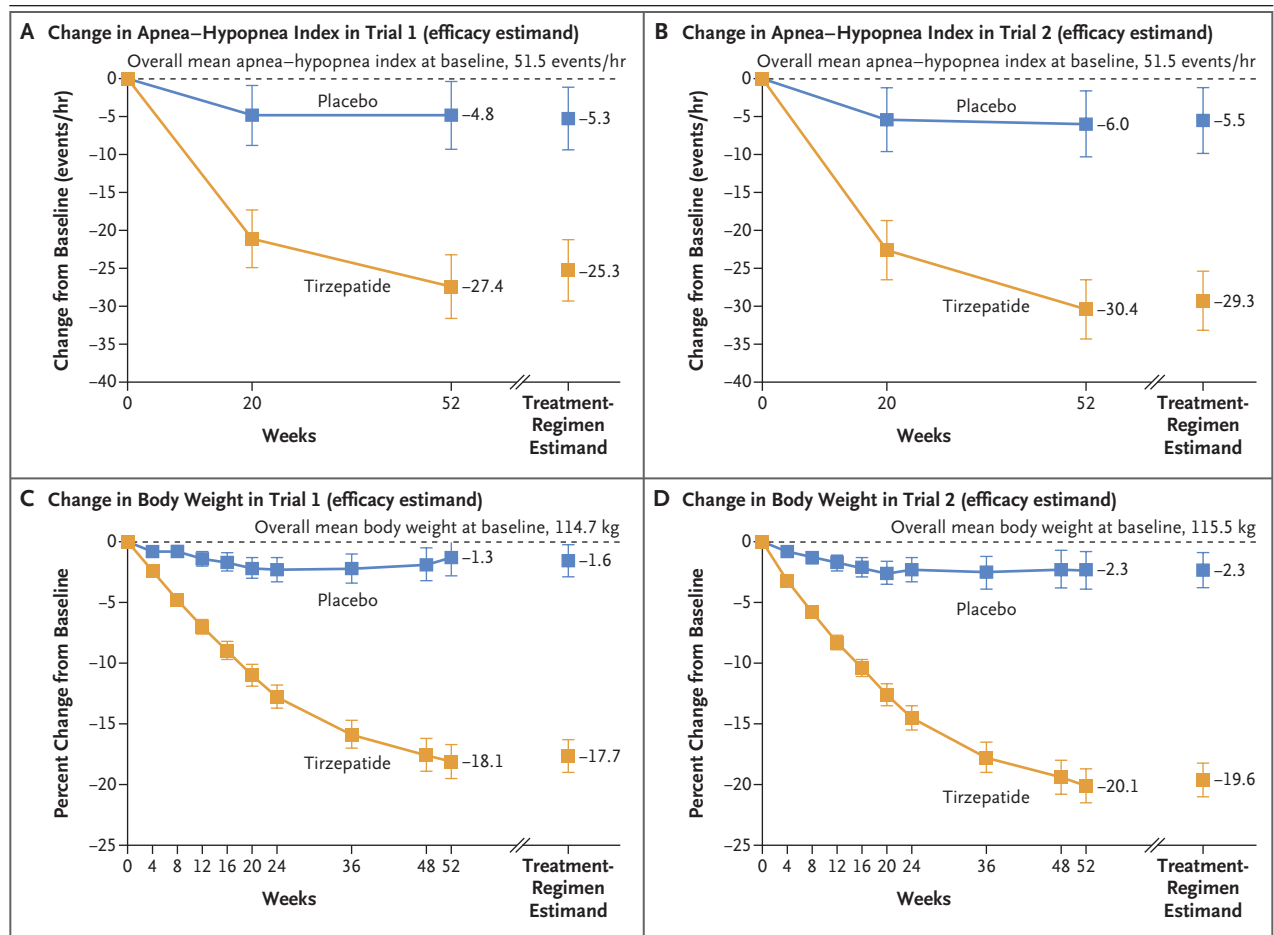


Figure 1. Change in AHI and Body Weight.

The change in the apnea–hypopnea index (AHI, the number of apneas and hypopneas during an hour of sleep) (Panels A and B) and body weight (Panels C and D) from baseline to week 52 for trial 1 and trial 2 are shown according to the weeks since randomization, derived from a mixed-model-for-repeated-measures analysis for the efficacy estimand, and no explicit imputations were performed for missing data. Week 52 estimates for the treatment-regimen estimand are also shown. For the treatment-regimen estimand, missing data at week 52 due to coronavirus disease 2019, missing data at week 52 from participants in the tirzepatide and placebo groups who completed the study period, missing data at week 52 after trial discontinuation due to the participant having undergone randomization in error, or missing data at baseline were assumed to be missing at random and were imputed with the use of multiple imputation from the same trial group. All other missing data at week 52 were considered to be not missing at random, and a placebo-based multiple imputation method was implemented. Least-squares means are shown unless otherwise noted. I bars indicate 95% confidence intervals.

each trial showed reductions similar to those shown in analysis of the pooled data (Table S4). Participants in both trials who received tirzepatide had significant reductions in body weight (Figs. 1C and 1D), systolic blood pressure, and hsCRP concentrations (Table 2).

SAFETY

Adverse events that occurred during the receipt of tirzepatide or placebo were reported by 79.8% of the participants who received tirzepatide and 76.7% of those who received placebo in trial 1

and by 83.2% of the participants who received tirzepatide and 72.8% of those who received placebo in trial 2 (Table 4). The most frequently reported adverse events were generally gastrointestinal and occurred more frequently in the participants who received tirzepatide. These events were generally mild-to-moderate in severity and occurred most frequently during the dose-escalation phase.

Serious adverse events were reported by 35 participants (7.5%) overall. Similar percentages of participants in the tirzepatide and placebo groups

Table 2. Primary and Key Secondary End Points According to Trial Group for the Treatment-Regimen Estimand.*

End Point	Trial 1		Trial 2	
	Tirzepatide N = 114	Placebo N = 120	Tirzepatide N = 120	Placebo N = 115
Primary end point				
Change in AHI (95% CI) — no. of events/hr	–25.3 (–29.3 to –21.2)	–5.3 (–9.4 to –1.1)	–29.3 (–33.2 to –25.4)	–5.5 (–9.9 to –1.2)
Key secondary end points				
Percent change in AHI (95% CI)	–50.7 (–62.3 to –39.1)	–3.0 (–16.9 to 10.9)	–58.7 (–69.1 to –48.4)	–2.5 (–16.2 to 11.2)
Reduction of ≥50% in AHI events at wk 52 — no. (%)	70 (61.2)	23 (19.0)	86 (72.4)	27 (23.3)
AHI of <5 or AHI of 5 to 14 with ESS ≤10 at wk 52 — no. (%)	48 (42.2)	19 (15.9)	60 (50.2)	16 (14.3)
Percent change in body weight (95% CI)	–17.7 (–19.0 to –16.3)	–1.6 (–2.9 to –0.2)	–19.6 (–21.0 to –18.2)	–2.3 (–3.8 to –0.9)
Change in hsCRP concentration at wk 52 (95% CI) — mg/liter	–1.4 (–1.7 to –1.1)	–0.7 (–1.1 to –0.3)	–1.4 (–1.6 to –1.1)	–0.3 (–0.8 to 0.1)
Change in sleep apnea-specific hypoxic burden at wk 52 (95% CI) — % min/hr	–95.2 (–103.2 to –87.2)	–25.1 (–44.3 to –5.9)	–103.0 (–110.3 to –95.6)	–41.7 (–63.9 to –19.5)
Change in systolic blood pres- sure at wk 48 (95% CI) — mm Hg	–9.5 (–11.5 to –7.5)	–1.8 (–3.9 to 0.2)	–7.6 (–9.7 to –5.6)	–3.9 (–6.3 to –1.6)
Additional secondary end point†				
Change in diastolic blood pres- sure at wk 48 (95% CI) — mm Hg	–4.9 (–6.4 to –3.5)	–2.1 (–3.6 to –0.6)	–3.3 (–4.7 to –1.9)	–2.2 (–3.8 to –0.6)
				–1.1 (–3.2 to 1.0)

* Data are least-squares means with 95% confidence intervals or numbers and percents of patients, unless otherwise stated. Relative risks are calculated using g-computation methods²⁴ from logistic regression. P values for categorical end points are based on a logistic regression model. All changes are from baseline to week 52 with the exception of blood pressure, which was change from baseline to week 48 to prevent suspension of PAP therapy in trial 2 from confounding the assessment.

† Differences between the groups are presented as the estimated treatment difference with the exception of the week-52 categories of reduction of ≥50% in AHI events and AHI of <5 or 5 to 14 with ESS ≤10, which are shown as relative risk. Estimated treatment differences for the secondary end points are the differences in the least-squares mean changes. P<0.001 for the primary and key secondary end points with the exceptions of the change in hsCRP concentration at week 52 in trial 1 (P=0.004) and the change in systolic blood pressure at week 48 in trial 2 (P=0.02).

‡ The confidence intervals for this end point have not been adjusted for multiplicity and should not be used to make inferences.

Table 3. Pooled Trial 1 and Trial 2 Patient-Reported Outcomes.*

Variable	Tirzepatide (N = 234)	Placebo (N = 233)	Estimated Treatment Difference (95% CI)	P Value
Change in PROMIS Sleep-related Impairment T score	−7.5 (−8.8 to −6.3)	−3.6 (−4.9 to −2.3)	−3.9 (−5.7 to −2.2)	<0.001
Change in PROMIS Sleep Disturbance T score	−5.7 (−6.8 to −4.7)	−2.7 (−3.8 to −1.6)	−3.1 (−4.5 to −1.5)	<0.001

* Data are least-squares means (95% confidence interval) unless otherwise stated. All changes shown are from baseline to week 52 in the modified intention-to-treat population.

reported serious adverse events. There were two adjudicated confirmed cases of acute pancreatitis in the trial 2 tirzepatide group. No cases of medullary thyroid cancer were reported. There were five cases of severe or serious depressive disorder or suicidal ideation or behavior events across both trials (two with tirzepatide and three with placebo). There were no deaths reported in either trial.

DISCUSSION

In the present trials involving adults with moderate-to-severe obstructive sleep apnea and obesity, the AHI decreased significantly by up to 29.3 events per hour (a 58.7% change from baseline) among the participants who received tirzepatide, as compared with a decrease of up to 5.3 events per hour (a 3.0% change from baseline) among those who received placebo. This change is considered clinically relevant; the American Academy of Sleep Medicine defines the clinical significance threshold for the AHI as 15 or more events per hour,²⁵ and other sources have proposed a 50% improvement in AHI as clinically relevant.^{26,27} A meaningful percentage of participants who received tirzepatide (up to 50.2%) in both SURMOUNT-OSA trials met the combined key secondary end-point criteria of fewer than 5 AHI events per hour or 5 to 14 AHI events per hour and an ESS of 10 or less, which is relevant because these thresholds for disease severity represent a level at which PAP therapy may not be recommended.^{2,3,28,29} The reductions in AHI were also accompanied by meaningful improvements in hypoxic burden, which better captures the obstructive sleep apnea–related risk of cardiovascular complications and death.^{18,30} These reductions were consistent in both trials regardless of concomitant PAP therapy and may inform

treatment decisions about patients with or without PAP therapy. Patients with obstructive sleep apnea are sometimes unable or unwilling to adhere to PAP treatment, and PAP has not been shown to affect cardiovascular complications and death in obstructive sleep apnea; therefore, there is a need for additional treatment options.^{4-6,10}

Symptoms of obstructive sleep apnea represent a substantial disease burden and increased risk of injury, including increased risk of motor vehicle accidents and work-related injuries.³¹ The symptom severity in obstructive sleep apnea may also be a predictor of increased risk of cardiovascular complications.³² Therefore, it is clinically relevant that in the current trials, positive effects of tirzepatide on the participants' sleep-related functioning and sleep disturbance were detected on the basis of PROMIS-SRI and PROMIS-SD scores.

Obstructive sleep apnea and obesity are two distinct but closely related diseases, and both have independent etiologic roles in the development of cardiovascular complications.¹⁰ Current guidelines recommend weight reduction of 7 to 11% for patients with obstructive sleep apnea^{8,33}; however, a recent meta-analysis reports additional weight reduction can further reduce the AHI.³⁴ This level of weight reduction has been difficult to accomplish with lifestyle intervention alone.³⁵ Bariatric surgery has shown benefits in adults with obstructive sleep apnea³⁶; however, owing to the invasive nature of surgery, it is not a feasible approach for many persons with obstructive sleep apnea and obesity. In SURMOUNT-OSA, tirzepatide reduced blood pressure and inflammation, which are important risk factors for cardiovascular complications of obstructive sleep apnea with obesity.

The safety profile of tirzepatide was consistent with that observed in previous trials.^{14,37-39} As

Table 4. Adverse Events and Safety.*				
Variable	Trial 1		Trial 2	
	Tirzepatide N=114	Placebo N=120	Tirzepatide N=119	Placebo N=114
	number (percent)			
≥1 Adverse event while receiving tirzepatide or placebo	91 (79.8)	92 (76.7)	99 (83.2)	83 (72.8)
Death	0	0	0	0
Serious adverse events	9 (7.9)	7 (5.8)	7 (5.9)	12 (10.5)
Adverse events leading to discontinuation of trial drug or placebo	5 (4.4)	2 (1.7)	4 (3.4)	8 (7.0)
Adverse events occurring in ≥5% of participants in any trial group				
Diarrhea	30 (26.3)	15 (12.5)	26 (21.8)	10 (8.8)
Nausea	29 (25.4)	12 (10.0)	26 (21.8)	6 (5.3)
Vomiting	20 (17.5)	5 (4.2)	11 (9.2)	1 (0.9)
Constipation	18 (15.8)	3 (2.5)	18 (15.1)	5 (4.4)
Eructation	9 (7.9)	0	10 (8.4)	1 (0.9)
Gastroesophageal reflux disease	9 (7.9)	1 (0.8)	6 (5.0)	0
Injection-site reaction	8 (7.0)	1 (0.8)	6 (5.0)	0
Abdominal pain	7 (6.1)	4 (3.3)	5 (4.2)	2 (1.8)
Upper respiratory tract infection	7 (6.1)	10 (8.3)	5 (4.2)	8 (7.0)
Coronavirus disease 2019	6 (5.3)	10 (8.3)	8 (6.7)	11 (9.6)
Nasopharyngitis	3 (2.6)	8 (6.7)	15 (12.6)	12 (10.5)
Dyspepsia	5 (4.4)	2 (1.7)	11 (9.2)	1 (0.9)
Gastroenteritis	3 (2.6)	4 (3.3)	8 (6.7)	1 (0.9)
Upper abdominal pain	4 (3.5)	2 (1.7)	7 (5.9)	2 (1.8)
Influenza	4 (3.5)	8 (6.7)	3 (2.5)	3 (2.6)
Arthralgia	3 (2.6)	6 (5.0)	4 (3.4)	5 (4.4)
Bronchitis	0	0	3 (2.5)	7 (6.1)
Hypertension	1 (0.9)	8 (6.7)	2 (1.7)	2 (1.8)
Other adverse events of special interest				
Severe hypoglycemia	0	0	0	0
Adjudication-confirmed MACE†	0	0	0	1 (0.9)
Arrhythmias or cardiac conduction disorders	7 (6.1)	9 (7.5)	6 (5.0)	2 (1.8)
Severe or serious gastrointestinal events‡	4 (3.5)	0	4 (3.4)	0
Severe or serious hepatic events	0	0	0	0
Severe or serious acute renal events	0	0	1 (0.8)	0
Adjudication-confirmed acute pancreatitis	0	0	2 (1.7)	0
C-cell hyperplasia or thyroid cancer	0	0	0	0
Severe or serious major depressive disorder or suicidal behavior and ideation events	2 (1.8)	1 (0.8)	0	2 (1.8)
Severe or serious allergic or hypersensitivity reactions§	0	0	0	0

* Adverse events are classified according to the preferred terms in the *Medical Dictionary for Regulatory Activities*, version 26.1.

† Key major adverse cardiac events (MACE) were cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, and hospitalization for heart failure.

‡ In trial 1, two participants had diarrhea, one had gastroesophageal reflux disease, and one had nausea. In trial 2, three participants had diarrhea, two had nausea, and one had acute pancreatitis. Participants could be counted in more than one category.

§ This category includes injection-site reactions and antidrug antibody formation.

typically observed with tirzepatide and GLP-1 receptor agonists, mild-to-moderate gastrointestinal events were the most frequently reported adverse events, occurring primarily during the dose-escalation period. There were no differences observed between tirzepatide recipients and placebo recipients with regard to reported gallbladder-related events or hepatic and renal events.

The current trials have several strengths. They were conducted globally, were adequately sized, ensured relevant representation of women (who typically represent a minority in obstructive sleep apnea trials), and assessed multiple obstructive sleep apnea-related, patient-reported, and cardiovascular-related end points that covered the burden of obstructive sleep apnea. Therefore, we believe that our findings are generalizable. The weight reduction among the participants who received placebo was similar to the results with placebo in other antiobesity medication studies, a finding that suggests a similar level of adherence to the lifestyle intervention. On the basis of the current evidence regarding PAP treatment, the American Academy of Sleep Medicine guidelines prioritize treatment with PAP for patients with symptoms of obstructive sleep apnea.²⁵ Future treatments of obstructive sleep apnea should also address obstructive sleep apnea-related cardiovascular risk, which is associated with moderate-to-severe obstructive sleep apnea regardless of symptoms.⁴⁰ Therefore, it is important that the enrollment in our trials was not limited to participants with current symptoms, and the results may inform broader treatment decisions in future clinical practice. Finally, the design of two independent trials involving participants with and without current PAP therapy provides insights into the effect of tirzepatide treatment in these patient populations that are prevalent in clinical practice.

Interpretation of the current findings should take into account the potential limitations of our

trials. First, the design and shorter duration of the current trials does not support the assessment of long-term cardiovascular outcomes. The ongoing SURMOUNT-Morbidity and Mortality in Obesity trial (ClinicalTrials.gov number, NCT05556512) may provide additional information. Second, our trials excluded participants who did not have obesity and did not analyze the effect of the intervention in people with overweight or normal BMI. Third, trial 2 was not designed to investigate the potential effect of treatment interventions on adherence to PAP treatment, and this was not prespecified as an end point for analysis in trial 2. Fourth, the trials were not designed to assess whether the results differed according to the presence of participant's symptoms at baseline. Fifth, the thresholds for the minimum clinically important changes for PROMIS-SRI and PROMIS-SD have not been established in clinical practice yet. Therefore, the clinical importance of the observed improvements remains to be evaluated. Finally, although obstructive sleep apnea affects patients' lives over a period of many years, the trials did not investigate a period of treatment with tirzepatide longer than 52 weeks.

In two trials, the participants who received tirzepatide had a clinically meaningful change in sleep-disordered breathing and alleviation of perceived sleep disturbance and sleep-related impairment, as well as reductions in common obstructive sleep apnea-related cardiovascular risk factors.

Presented in part at the 84th Scientific Sessions of the American Diabetes Association, Orlando, FL, June 21–24, 2024.

Supported by Eli Lilly.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the participants and caregivers involved in the trial, as well as Eli Lilly employees Casey J. Mast, Pharm.D., for medical writing and editorial assistance; Bram Brouwers, Ph.D., and Meri Kay Scott, Ph.D., for trial design advice; and Angel Rodriguez, M.D., Ph.D., for a critical review of an earlier version of the manuscript.

REFERENCES

1. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. *Lancet* 2014;383:736-47.
2. Veasey SC, Rosen IM. Obstructive sleep apnea in adults. *N Engl J Med* 2019;380:1442-9.
3. Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med* 2019;7:687-98.
4. McEvoy RD, Antic NA, Heeley E, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnoea. *N Engl J Med* 2016;375:919-31.
5. Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunström E. Effect of positive airway pressure on cardiovascular outcomes in coronary artery disease patients with nonsleepy obstructive sleep apnoea: the RICCADSA randomized controlled trial. *Am J Respir Crit Care Med* 2016;194:613-20.
6. Sánchez-de-la-Torre M, Sánchez-de-la-Torre A, Bertran S, et al. Effect of obstructive sleep apnoea and its treatment with continuous positive airway pressure on

- the prevalence of cardiovascular events in patients with acute coronary syndrome (ISAACC study): a randomised controlled trial. *Lancet Respir Med* 2020;8:359-67.
7. Francis CE, Quinnell T. Mandibular advancement devices for OSA: an alternative to CPAP? *Pulm Ther* 2021;7:25-36.
 8. Hudgel DW, Patel SR, Ahasic AM, et al. The role of weight management in the treatment of adult obstructive sleep apnea: an official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med* 2018;198(6):e70-e87.
 9. Morgenthaler TI, Kapen S, Lee-Chiong T, et al. Practice parameters for the medical therapy of obstructive sleep apnea. *Sleep* 2006;29:1031-5.
 10. Javaheri S, Barbe F, Campos-Rodriguez F, et al. Sleep apnea: types, mechanisms, and clinical cardiovascular consequences. *J Am Coll Cardiol* 2017;69:841-58.
 11. Heinzer R, Eckert D. Treatment for obstructive sleep apnoea and cardiovascular diseases: are we aiming at the wrong target? *Lancet Respir Med* 2020;8:323-5.
 12. Yeghiazarians Y, Jneid H, Tietjens JR, et al. Obstructive sleep apnea and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation* 2021;144(3):e56-e67.
 13. Coskun T, Sloop KW, Loghin C, et al. LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: from discovery to clinical proof of concept. *Mol Metab* 2018;18:3-14.
 14. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med* 2022;387:205-16.
 15. Wilson JM, Lin Y, Luo MJ, et al. The dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist tirzepatide improves cardiovascular risk biomarkers in patients with type 2 diabetes: a post hoc analysis. *Diabetes Obes Metab* 2022;24:148-53.
 16. Malhotra A, Bednarik J, Chakladar S, et al. Tirzepatide for the treatment of obstructive sleep apnea: rationale, design, and sample baseline characteristics of the SURMOUNT-OSA phase 3 trial. *Contemp Clin Trials* 2024;141:107516.
 17. Berry R, Brooks R, Gamaldo C, et al. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications, version 2.0.2. Darien, IL: American Academy of Sleep Medicine, 2012.
 18. Azarbarzin A, Sands SA, Stone KL, et al. The hypoxic burden of sleep apnoea predicts cardiovascular disease-related mortality: the Osteoporotic Fractures in Men Study and the Sleep Heart Health Study. *Eur Heart J* 2019;40:1149-57.
 19. Bretz F, Maurer W, Brannath W, Posch M. A graphical approach to sequentially rejective multiple test procedures. *Stat Med* 2009;28:586-604.
 20. Bretz F, Xi D. Commentary on "Statistics at FDA: reflections on the past six years." *Stat Biopharm Res* 2019;11:20-5 (<https://www.tandfonline.com/doi/full/10.1080/19466315.2018.1562369>).
 21. Vandemeulebroecke M, Häring DA, Hua E, Wei X, Xi D. New strategies for confirmatory testing of secondary hypotheses on combined data from multiple trials. *Clin Trials* 2024;21:171-9.
 22. Schwarz EI, Stradling JR, Kohler M. Physiological consequences of CPAP therapy withdrawal in patients with obstructive sleep apnoea—an opportunity for an efficient experimental model. *J Thorac Dis* 2018;10:Suppl 1:S24-S32.
 23. Donovan LM, Yu L, Bertisch SM, Buysse DJ, Rueschman M, Patel SR. Responsiveness of patient-reported outcomes to treatment among patients with type 2 diabetes mellitus and OSA. *Chest* 2020;157:665-72.
 24. Ye T, Bannick M, Yi Y, Shao J. Robust variance estimation for covariate-adjusted unconditional treatment effect in randomized clinical trials with binary outcomes. *Stat Theory Relat Fields* 2023;7:159-63.
 25. Patil SP, Ayappa IA, Caples SM, Kimoff RJ, Patel SR, Harrod CG. Treatment of adult obstructive sleep apnea with positive airway pressure: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. *J Clin Sleep Med* 2019;15:301-34.
 26. Ramar K, Dort LC, Katz SG, et al. Clinical practice guideline for the treatment of obstructive sleep apnea and snoring with oral appliance therapy: an update for 2015. *J Clin Sleep Med* 2015;11:773-827.
 27. Lin H-C, Friedman M, Chang H-W, Gulpinar B. The efficacy of multilevel surgery of the upper airway in adults with obstructive sleep apnea/hypopnea syndrome. *Laryngoscope* 2008;118:902-8.
 28. Epstein LJ, Kristo D, Strollo PJ Jr, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med* 2009;5:263-76.
 29. Centers for Medicare and Medicaid Services. Positive airway pressure (PAP) devices: complying with documentation & coverage requirements. October 2016 (https://www.cms.gov/files/document/papdoccvfactsheetcn905064_textonlypdf).
 30. Azarbarzin A, Sands SA, Taranto-Montemurro L, et al. The sleep apnea-specific hypoxic burden predicts incident heart failure. *Chest* 2020;158:739-50.
 31. Bonsignore MR, Randerath W, Schiza S, et al. European Respiratory Society statement on sleep apnoea, sleepiness and driving risk. *Eur Respir J* 2021;57:2001272.
 32. Baratta F, Pastori D, Fabiani M, et al. Severity of OSAS, CPAP and cardiovascular events: a follow-up study. *Eur J Clin Invest* 2018;48(5):e12908.
 33. Garvey WT, Mechanick JI, Brett EM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocr Pract* 2016;22:Suppl 3:1-203.
 34. Malhotra A, Curtis A, Dunn J, Bunck MC, Bednarik J. Weight reduction and the impact on apnea-hypopnea index: a meta-analysis. *Sleep* 2023;46:Suppl 1:A251-A252 (https://academic.oup.com/sleep/article/46/Supplement_1/A251/7182261).
 35. Dombrowski SU, Knittle K, Avenell A, Araújo-Soares V, Sniehotta FF. Long term maintenance of weight loss with non-surgical interventions in obese adults: systematic review and meta-analyses of randomised controlled trials. *BMJ* 2014;348:g2646.
 36. Zhang Y, Wang W, Yang C, Shen J, Shi M, Wang B. Improvement in nocturnal hypoxemia in obese patients with obstructive sleep apnea after bariatric surgery: a meta-analysis. *Obes Surg* 2019;29:601-8.
 37. Garvey WT, Frias JP, Jastreboff AM, et al. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 2023;402:613-26.
 38. Wadden TA, Chao AM, Machineni S, et al. Tirzepatide after intensive lifestyle intervention in adults with overweight or obesity: the SURMOUNT-3 phase 3 trial. *Nat Med* 2023;29:2909-18.
 39. Aronne LJ, Sattar N, Horn DB, et al. Continued treatment with tirzepatide for maintenance of weight reduction in adults with obesity: the SURMOUNT-4 randomized clinical trial. *JAMA* 2024;331:38-48.
 40. Young T, Palta M, Dempsey J, Peppard PE, Nieto FJ, Hla KM. Burden of sleep apnea: rationale, design, and major findings of the Wisconsin Sleep Cohort study. *WMJ* 2009;108:246-9.

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