بنام خداوند جان و خرد

TIRZEPATIDE (MOUNJARO)

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Summer 2022

Outline

- Introduction
- Physiology
- Structure
- Medication
- Studies
- Cost
- Utility

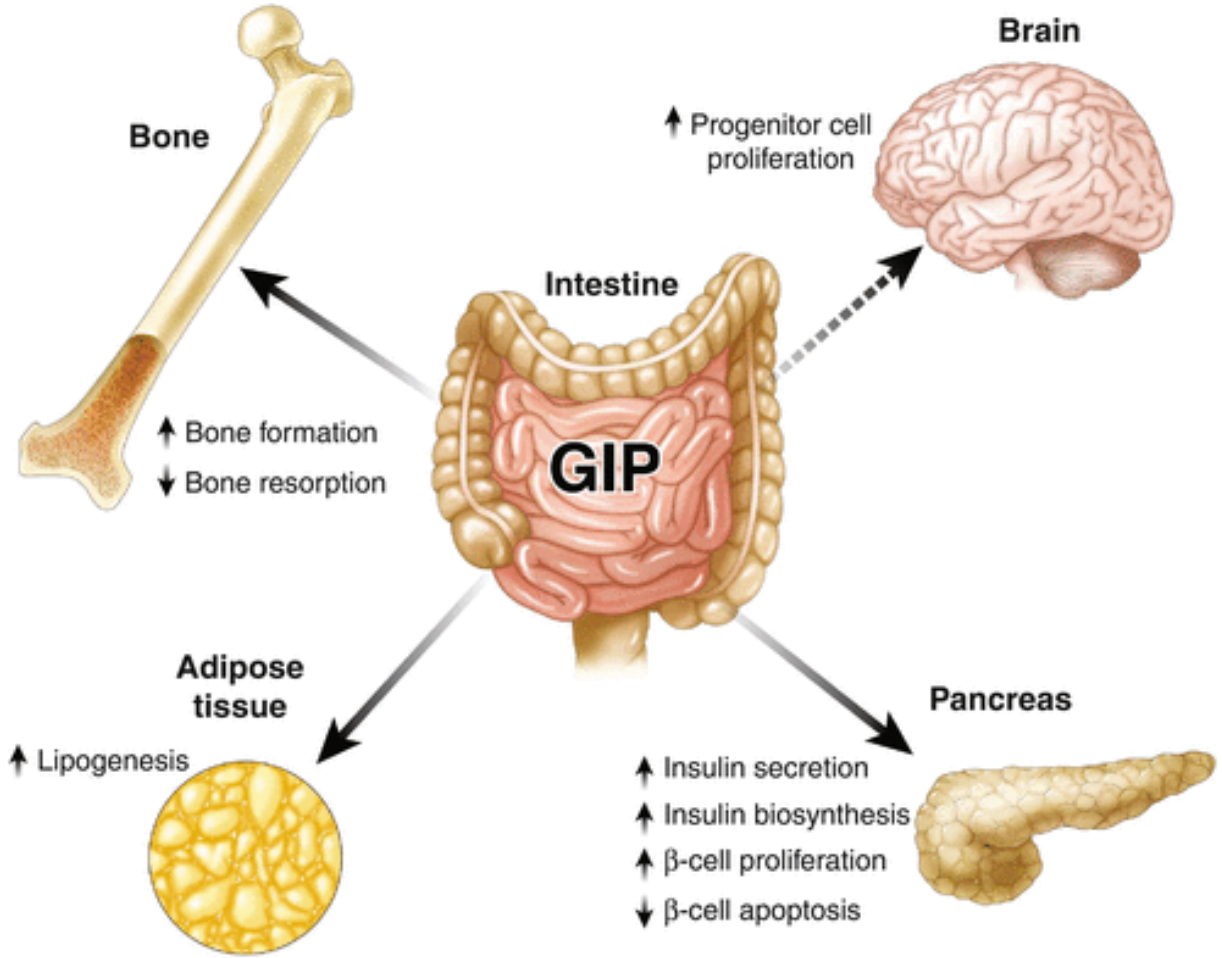
Disclaimer

- There is no conflict of interest.
- Tirzepatide is not available in Iran yet, but many patients ask about it and they have questions regarding Its efficacy and safety both In patients with obesity and type 2 diabetes mellitus.

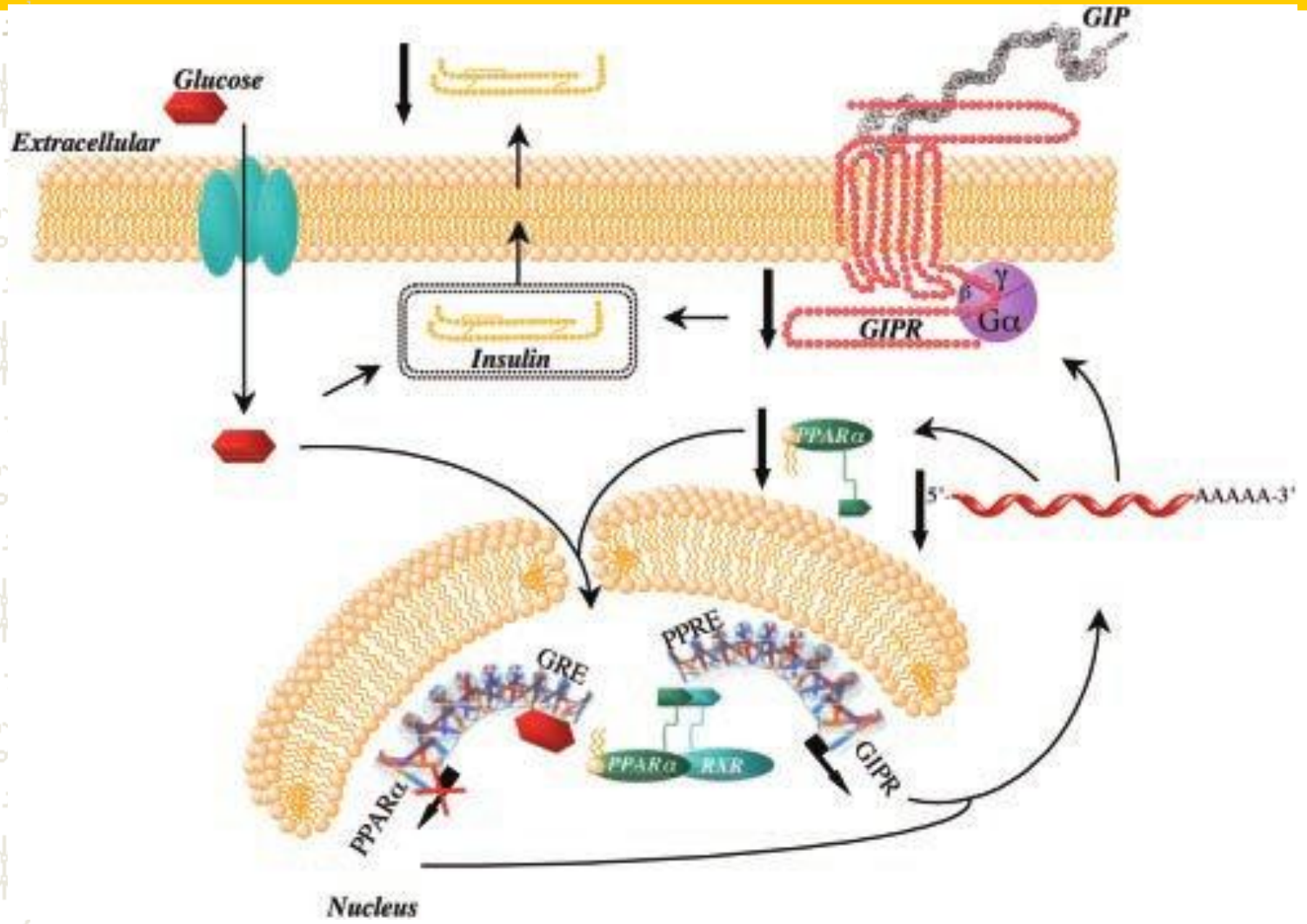
Introduction

- At May 13, 2022, the U.S. Food and Drug Administration approved Mounjaro (tirzepatide) injection to improve blood sugar control in adults with type 2 diabetes, as an addition to diet and exercise.
- Mounjaro was effective at improving blood sugar and was more effective than the other diabetes therapies with which it was compared in clinical studies.
- Tirzepatide (LY3298176) is a fatty-acid-modified, dual incretin receptor agonist that exhibits pharmacology similar to native GIP at the glucose-dependent insulinotropic polypeptide receptor (GIPR) but shows bias toward cyclic adenosine monophosphate signaling at the glucagon-like peptide-1 receptor (GLP-1R).
- In addition to GIPR signaling, the pathway bias at the GLP-1R may contribute to the efficacy of tirzepatide at improving glucose control and body weight regulation in type 2 diabetes mellitus.

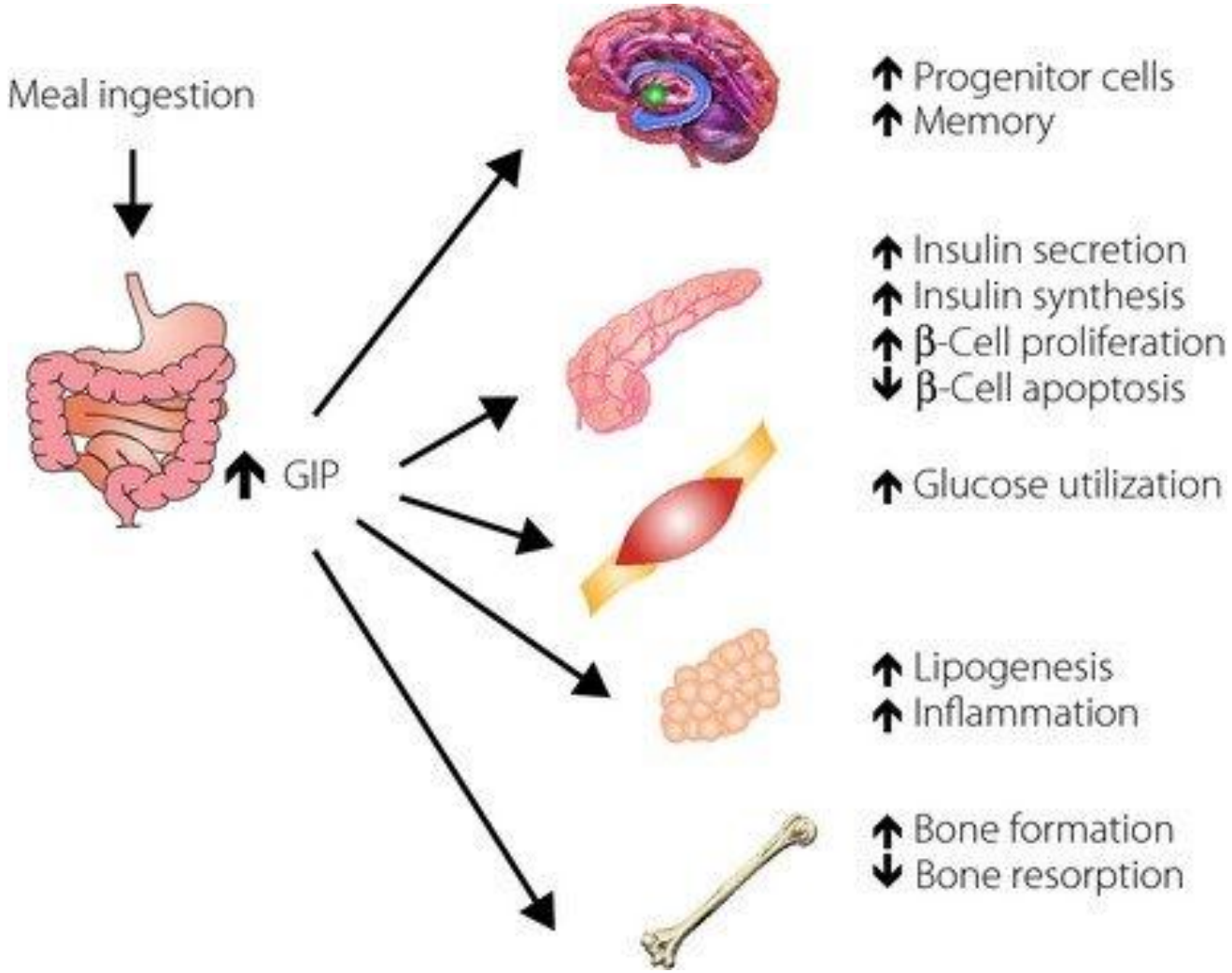
Physiology


Bone
Bone formation
Bone resorption
Brain
Progenitor cell proliferation
Intestine
GIP
Adipose tissue
Lipogenesis
Pancreas
Insulin secretion
Insulin biosynthesis
β-cell proliferation
β-cell apoptosis

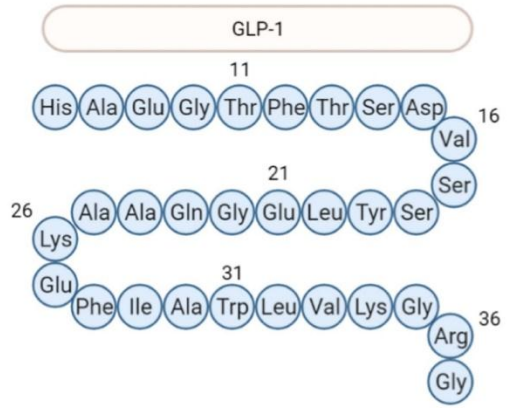
Physiology


GIP
Glucose
Extracellular
GIPR
β
γ
Gα
Insulin
PPARα
5'
AAAAA-3'
PPRE
GRE
PPARα
RXR
GIPR
Nucleus

Physiology


Meal ingestion
GIP
↑ Progenitor cells
↑ Memory
↑ Insulin secretion
↑ Insulin synthesis
↑ β-Cell proliferation
↓ β-Cell apoptosis
↑ Glucose utilization
↑ Lipogenesis
↑ Inflammation
↑ Bone formation
↓ Bone resorption

Structure


GLP-1
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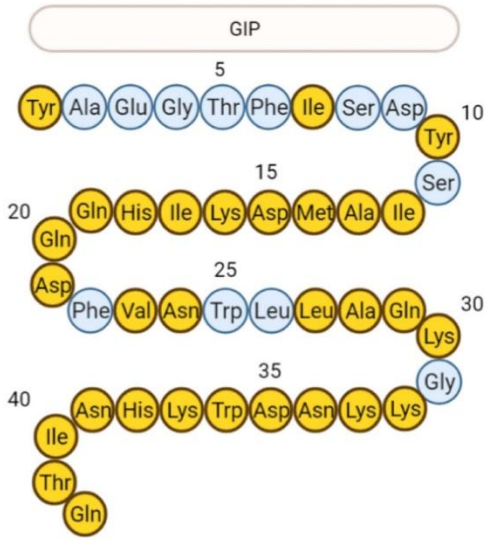
11
16
21
26
31
36


GIP
Tyr Ala Glu Gly Thr Phe Ile Ser Asp Tyr Ser Gln His Ile Lys Asp Met Ala Ile Gln Asp Phe Val Asn Trp Leu Leu Ala Gln Lys Gly Asn His Lys Trp Asp Asn Lys Lys Ile Thr Gln
5
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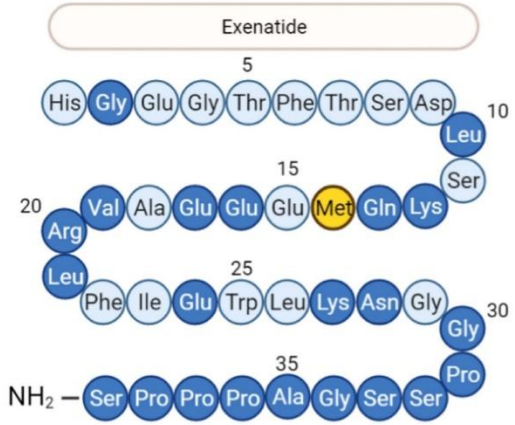
40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5
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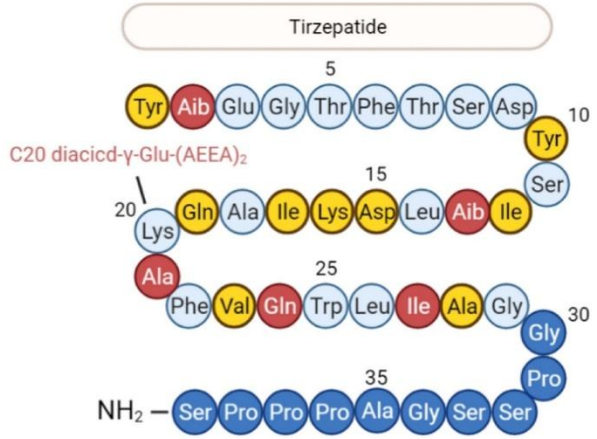
15
20
25
30
35


Tirzepatide
C20 diacicd-γ-Glu-(AEEA)2
Tyr Aib Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Gln Ala Ile Lys Asp Leu Aib Ile Ala Phe Val Gln Trp Leu Ile Ala Gly Gly Pro Ser Pro Pro Pro Ala Gly Ser Ser NH2
5
10
15
20
25
30
35

Medication


mounjaro™
(tirzepatide) injection
15 mg 0.5 mL
mounjaro™
(tirzepatide) injection
10 mg 0.5 mL
mounjaro™
(tirzepatide) injection
5 mg 0.5 mL

Studies

- Tirzepatide Once Weekly for the Treatment of Obesity, NEJM
- Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes, NEJM
- Efficacy and Safety of Tirzepatide in Patients with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomized Phase II/III Trials. Pharmaceuticals 2021, 14, 991

Tirzepatide Once Weekly for the Treatment of Obesity

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tirzepatide Once Weekly for the Treatment of Obesity

Ania M. Jastreboff, M.D., Ph.D., Louis J. Aronne, M.D., Nadia N. Ahmad, M.D., M.P.H., Sean Wharton, M.D., Pharm.D., Lisa Connery, M.D., Breno Alves, M.D., Arihiro Kiyosue, M.D., Ph.D., Shuyu Zhang, M.S., Bing Liu, Ph.D., Mathijs C. Bunck, M.D., Ph.D., and Adam Stefanski, M.D., Ph.D., for the SURMOUNT-1 Investigators*

Background

- Obesity is a chronic disease that results in substantial global morbidity and mortality.
- The efficacy and safety of tirzepatide, a novel glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, in people with obesity are not known.

Methods

- In this phase 3 double-blind, randomized, controlled trial, we assigned 2539 adults with a body-mass index of 30 or more, or 27 or more and at least one weight-related complication, excluding diabetes, in a 1:1:1:1 ratio to receive once-weekly, subcutaneous tirzepatide (5 mg, 10 mg, or 15 mg) or placebo for 72 weeks, including a 20-week dose-escalation period.
- Coprimary end points were the percentage change in weight from baseline and a weight reduction of 5% or more. The treatment-regimen estimand assessed effects regardless of treatment discontinuation in the intention-to-treat population.

Results

- At baseline, the mean body weight was 104.8 kg, the mean BMI was 38.0, and 94.5% of participants had a BMI of 30 or higher.
- The mean percentage change in weight at week 72 was −15.0% (95% confidence interval [CI], −15.9 to −14.2) with 5-mg weekly doses of tirzepatide, −19.5% (95% CI, −20.4 to −18.5) with 10-mg doses, and −20.9% (95% CI, −21.8 to −19.9) with 15-mg doses and −3.1% (95% CI, −4.3 to −1.9) with placebo (P<0.001 for all comparisons with placebo).

Results

- The percentage of participants who had weight reduction of 5% or more was 85% (95% CI, 82 to 89), 89% (95% CI, 86 to 92), and 91% (95% CI, 88 to 94) with 5 mg, 10 mg, and 15 mg of tirzepatide, respectively, and 35% (95% CI, 30 to 39) with placebo;
- 50% (95% CI, 46 to 54) and 57% (95% CI, 53 to 61) of participants in the 10-mg and 15-mg groups had a reduction in body weight of 20% or more, as compared with 3% (95% CI, 1 to 5) in the placebo group ($P<0.001$ for all comparisons with placebo).

Results

- Improvements in all prespecified cardiometabolic measures were observed with tirzepatide.
- The most common adverse events with tirzepatide were gastrointestinal, and most were mild to moderate in severity, occurring primarily during dose escalation.
- Adverse events caused treatment discontinuation in 4.3%, 7.1%, 6.2%, and 2.6% of participants receiving 5-mg, 10-mg, and 15-mg tirzepatide doses and placebo, respectively.

Conclusions

- In this 72-week trial in participants with obesity, 5 mg, 10 mg, or 15 mg of tirzepatide once weekly provided substantial and sustained reductions in body weight.
- (Supported by Eli Lilly; SURMOUNT-1 ClinicalTrials.gov number, NCT04184622. opens in new tab.)

Demographic and Clinical Characteristics of the Participants at Baseline.*

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

Characteristic	Tirzepatide, 5 mg (N=630)	Tirzepatide, 10 mg (N=636)	Tirzepatide, 15 mg (N=630)	Placebo (N=643)	Total (N=2539)
Age — yr	45.6±12.7	44.7±12.4	44.9±12.3	44.4±12.5	44.9±12.5
Female sex — no. (%)	426 (67.6)	427 (67.1)	425 (67.5)	436 (67.8)	1714 (67.5)
Race or ethnic group — no. (%)†					
American Indian or Alaska Native	56 (8.9)	58 (9.1)	59 (9.4)	58 (9.0)	231 (9.1)
Asian	68 (10.8)	71 (11.2)	66 (10.5)	71 (11.0)	276 (10.9)
Black or African American	48 (7.6)	47 (7.4)	51 (8.1)	55 (8.6)	201 (7.9)
White	447 (71.0)	452 (71.1)	443 (70.3)	450 (70.0)	1792 (70.6)
Native Hawaiian or other Pacific Islander	2 (0.3)	2 (0.3)	3 (0.5)	2 (0.3)	9 (0.4)
Multiple	9 (1.4)	6 (0.9)	8 (1.3)	7 (1.1)	30 (1.2)
Hispanic or Latino — no. (%)	308 (48.9)	297 (46.7)	299 (47.5)	310 (48.2)	1214 (47.8)
Duration of obesity — yr	14.0±10.81	14.7±11.05	14.8±10.75	14.0±10.71	14.4±10.83
Body weight — kg	102.9±20.71	105.8±23.32	105.6±22.92	104.8±21.37	104.8±22.12
Mean body-mass index	37.4±6.63	38.2±7.01	38.1±6.69	38.2±6.89	38.0±6.81
Body-mass index category — no. (%)					
<30	38 (6.0)	38 (6.0)	40 (6.3)	24 (3.7)	140 (5.5)
≥30 to <35	241 (38.3)	209 (32.9)	199 (31.6)	227 (35.3)	876 (34.5)
≥35 to <40	174 (27.6)	187 (29.4)	179 (28.4)	180 (28.0)	720 (28.4)
≥40	177 (28.1)	202 (31.8)	212 (33.7)	212 (33.0)	803 (31.6)
Waist circumference — cm	113.2±14.25	114.8±15.80	114.4±15.59	114.0±14.92	114.1±15.16
Blood pressure — mm Hg					
Systolic	123.6±12.45	123.8±12.77	123.0±12.94	122.9±12.77	123.3±12.73
Diastolic	79.3±8.14	79.9±8.32	79.3±8.23	79.6±7.95	79.5±8.16
Pulse — beats per min	72.3±9.60	71.8±9.57	72.5±9.95	72.9±9.27	72.4±9.60
Lipid levels — geometric mean mg/dl (coefficient of variation, %)					
Total cholesterol	187.1 (21.1)	190.7 (19.9)	187.4 (19.9)	186.4 (20.3)	187.9 (20.3)
HDL cholesterol	47.6 (26.6)	47.5 (26.1)	47.5 (25.5)	46.5 (26.9)	47.3 (26.3)
LDL cholesterol	108.7 (30.2)	111.5 (30.3)	109.5 (30.0)	108.4 (30.5)	109.5 (30.2)
Triglycerides	128.9 (51.7)	126.5 (51.5)	127.9 (47.5)	130.5 (49.2)	128.4 (50.0)
Estimated GFR — ml/min/1.73 m^2 ‡	97.6±17.87	98.3±18.26	98.2±17.67	98.1±18.28	98.1±18.02
Prediabetes, n (%)	247 (39.2)	262 (41.2)	253 (40.2)	270 (42.0)	1032 (40.6)
Glycated hemoglobin — %	5.6±0.36	5.6±0.37	5.6±0.41	5.6±0.38	5.6±0.38
Fasting glucose — mg/dl	95.4±9.7	95.5±10.7	95.3±10.3	95.7±9.5	95.5±10.1
Fasting insulin — mIU/liter	13.6±10.0	14.1±12.2	14.4±9.3	14.3±9.9	14.1±10.4
SF-36 physical function score	49.6±8.3	49.6±7.5	49.6±7.8	49.7±7.7	49.6±7.8

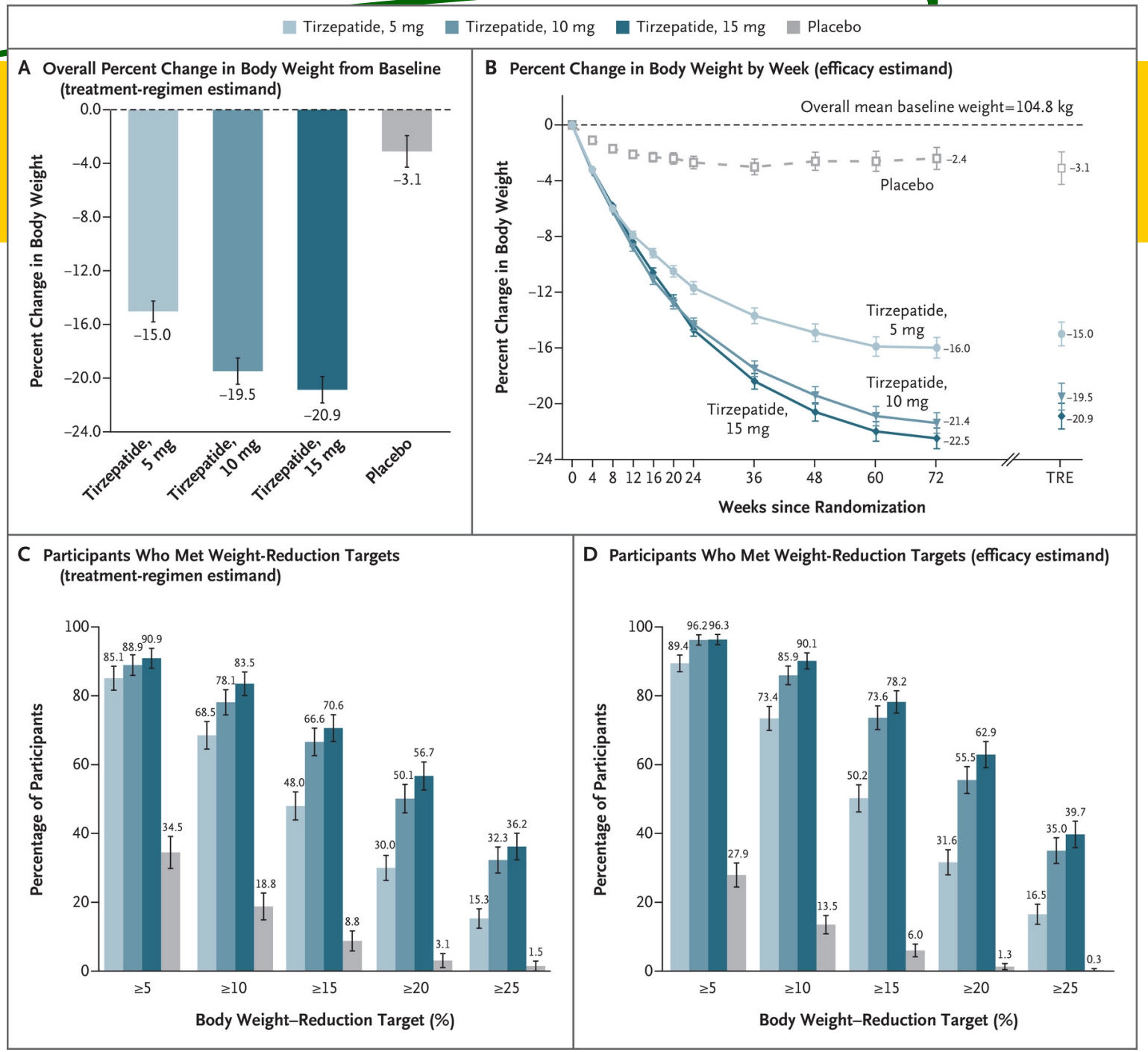


Figure 1. Effect of Once-Weekly Tirzepatide, as Compared with Placebo, on Body Weight.

Least-squares means are presented, unless otherwise noted. Panel A shows the percent change in body weight from baseline to week 72, derived from an analysis of covariance model for the treatment-regimen estimand (TRE). Panel B shows the percent change in body weight according to weeks since randomization, derived from a mixed model for repeated measures (MMRM) analysis for the efficacy estimand; week 72 estimates for the treatment-regimen estimand are also shown. Panels C and D show the percentages of participants who had weight reductions of at least 5%, 10%, 15%, 20%, and 25% from baseline to week 72. For Panel C, the percentage was calculated with the use of Rubin's rules by combining the percentages of participants who met the target in imputed data sets. Missing values at week 72 were imputed with MMRM if the missingness was due solely to Covid-19 and with multiple imputation if the missingness was not due to Covid-19. For Panel D, the percentage of participants who met weight-reduction targets was obtained by dividing the number of participants reaching respective goals at week 72 by the number of participants with a baseline value and at least one nonmissing postbaseline value. Missing values at week 72 were imputed from MMRM analysis. I bars indicate 95% confidence intervals.

Table 2. Primary and Secondary End Points for the Treatment-Regimen Estimand.*

End Points	Tirzepatide, 5 mg (N = 630)	Tirzepatide, 10 mg (N = 636)	Tirzepatide, 15 mg (N = 630)	Placebo (N = 643)
	least-squares mean (95% CI)			
Coprimary end points†				
Percentage change in body weight‡	−15.0 (−15.9 to −14.2)	−19.5 (−20.4 to −18.5)	−20.9 (−21.8 to −19.9)	−3.1 (−4.3 to −1.9)
Difference from placebo in percentage change in body weight — percentage points‡	−11.9 (−13.4 to −10.4)	−16.4 (−17.9 to −14.8)	−17.8 (−19.3 to −16.3)	—
Weight reduction of 5% or more at week 72 — percentage of participants‡§	85.1 (81.6 to 88.6)	88.9 (85.9 to 91.9)	90.9 (88.0 to 93.8)	34.5 (29.8 to 39.2)
Key secondary end points†				
Weight reduction of 10% or more at week 72 — percentage of participants§¶	68.5 (64.5 to 72.5)	78.1 (74.4 to 81.7)	83.5 (80.0 to 86.9)	18.8 (14.9 to 22.7)
Weight reduction of 15% or more at week 72 — percentage of participants§¶	48.0 (43.9 to 52.1)	66.6 (62.6 to 70.6)	70.6 (66.7 to 74.5)	8.8 (5.9 to 11.7)
Weight reduction of 20% or more at week 72 — percentage of participants§¶	30.0 (26.4 to 33.6)	50.1 (46.0 to 54.2)	56.7 (52.6 to 60.8)	3.1 (1.1 to 5.1)
Change in waist circumference — cm¶	−14.0 (−14.9 to −13.1)	−17.7 (−18.7 to −16.8)	−18.5 (−19.3 to −17.6)	−4.0 (−5.1 to −2.8)
Difference from placebo in change in waist circumference — cm ¶	−10.1 (−1.6 to −8.6)	−13.8 (−15.2 to −12.3)	−14.5 (−15.9 to −13.0)	—
Additional secondary end point				
Weight reduction of 25% or more at week 72 — percentage of participants §‖	15.3 (12.5 to 18.1)	32.3 (28.5 to 36.1)	36.2 (32.3 to 40.1)	1.5 (0.1 to 2.9)

Table 3. Key Secondary and Additional Secondary End Points for Pooled Tirzepatide Dose Groups (Treatment-Regimen Estimand).*

End Points	Pooled Tirzepatide Groups†	Placebo (N = 643)	Estimated Treatment Difference from Placebo (95% CI)
	least-squares mean (95% CI)		
Key secondary end points‡			
Change from baseline to week 20 in body weight — kg§	−12.8 (−13.1 to −12.5)	−2.7 (−3.2 to −2.2)	−10.1 (−10.7 to −9.6)
Change in measure			
SF-36 physical function score§¶	3.6 (3.2 to 4.0)	1.7 (0.8 to 2.6)	1.9 (1.0 to 2. 9)
Systolic blood pressure — mm Hg	−7.2 (−7.8 to −6.7)	−1.0 (−2.3 to −0.3)	−6.2 (−7.7 to −4.8)
Percentage change in level‖			
Triglycerides — mg/dl	−24.8 (−26.3 to −23.1)	−5.6 (−10.0 to −1.2)	−20.3 (−24.3 to −16.1)
Non-HDL cholesterol — mg/dl	−9.7 (−10.7 to −8.6)	−2.3 (−4.9 to −0.2)	−7.5 (−10.1 to −4.9)
HDL cholesterol — mg/dl	8.0 (6.9 to 9.1)	−0.7 (−2.9 to 1.5)	8.8 (6.1 to 11.5)
Fasting insulin — mIU/liter**	−42.9 (−44.9 to −40.9)	−6.6 (−15.3 to 2.2)	−38.9 (−44.8 to −32.4)
Additional secondary end points††			
Change in diastolic blood pressure — mm Hg	−4.8 (−5.2 to −4.4)	−0.8 (−1.6 to 0.0)	−4.0 (−4.9 to −3.1)
Percentage change in level‖			
Total cholesterol — mg/dl	−4.8 (−5.6 to −4.0)	−1.8 (−3.7 to 0.1)	−3.1 (−5.2 to −1.0)
LDL cholesterol — mg/dl	−5.8 (−6.9 to −4.6)	−1.7 (−4.6 to 1.3)	−4.2 (−7.2 to −1.0)
VLDL cholesterol — mg/dl	−24.4 (−25.9 to −22.9)	−4.8 (−9.2 to −0.4)	−20.6 (−24.6 to −16.4)
Free fatty acids — mmol/liter	−7.5 (−10.7 to −4.3)	9.5 (3.8 to 15.3)	−15.6 (−20.8 to −9.9)

Table 4. Adverse Events and Safety.

Table 4. Adverse Events and Safety.

Variable	Tirzepatide, 5 mg (N = 630)	Tirzepatide, 10 mg (N = 636)	Tirzepatide, 15 mg (N = 630)	Placebo (N = 643)
	number (percent)			
Participants with ≥1 adverse event during treatment period	510 (81.0)	520 (81.8)	497 (78.9)	463 (72.0)
Serious adverse events	40 (6.3)	44 (6.9)	32 (5.1)	44 (6.8)
Death*	4 (0.6)	2 (0.3)	1 (0.2)	4 (0.6)
Adverse events leading to discontinuation of trial drug or placebo†	27 (4.3)	45 (7.1)	39 (6.2)	17 (2.6)
Nausea	6 (1.0)	7 (1.1)	12 (1.9)	2 (0.3)
Diarrhea	2 (0.3)	5 (0.8)	3 (0.5)	0
Abdominal pain	0	2 (0.3)	3 (0.5)	0
Vomiting	0	4 (0.6)	0	0
Adverse events occurring in at least 5% of participants in any treatment group†				
Nausea	155 (24.6)	212 (33.3)	195 (31.0)	61 (9.5)
Diarrhea	118 (18.7)	135 (21.2)	145 (23.0)	47 (7.3)
Covid-19	94 (14.9)	98 (15.4)	82 (13.0)	90 (14.0)
Constipation	106 (16.8)	109 (17.1)	74 (11.7)	37 (5.8)
Dyspepsia	56 (8.9)	62 (9.7)	71 (11.3)	27 (4.2)
Vomiting	52 (8.3)	68 (10.7)	77 (12.2)	11 (1.7)
Decreased appetite	59 (9.4)	73 (11.5)	54 (8.6)	21 (3.3)
Headache	41 (6.5)	43 (6.8)	41 (6.5)	42 (6.5)
Abdominal pain	31 (4.9)	34 (5.3)	31 (4.9)	21 (3.3)
Alopecia	32 (5.1)	31 (4.9)	36 (5.7)	6 (0.9)
Dizziness	26 (4.1)	35 (5.5)	26 (4.1)	15 (2.3)
Eructation	24 (3.8)	33 (5.2)	35 (5.6)	4 (0.6)
Injection-site reaction‡	18 (2.9)	36 (5.7)	29 (4.6)	2 (0.3)
Adverse events of special interest				
Hepatic events§	2 (0.3)	2 (0.3)	0	0
Cancer	9 (1.4)	3 (0.5)	5 (0.8)	7 (1.1)
Pancreatitis (adjudication-confirmed)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Major adverse cardiovascular events (adjudication-confirmed)	4 (0.6)	5 (0.8)	0	5 (0.8)
Cardiac disorders¶	0	1 (0.2)	2 (0.3)	1 (0.2)
Severe or serious gastrointestinal events	11 (1.7)	20 (3.1)	21 (3.3)	7 (1.1)
Gallbladder disease§	5 (0.8)	11 (1.7)	6 (1.0)	5 (0.8)
Renal events§	2 (0.3)	2 (0.3)	2 (0.3)	1 (0.2)
Major depressive disorder or suicidal ideation§	1 (0.2)	2 (0.3)	2 (0.3)	0
Hypersensitivity‖	0	1 (0.2)	1 (0.2)	0
Hypoglycemia (blood glucose <54 mg/dl)	9 (1.4)	10 (1.6)	10 (1.6)	1 (0.2)

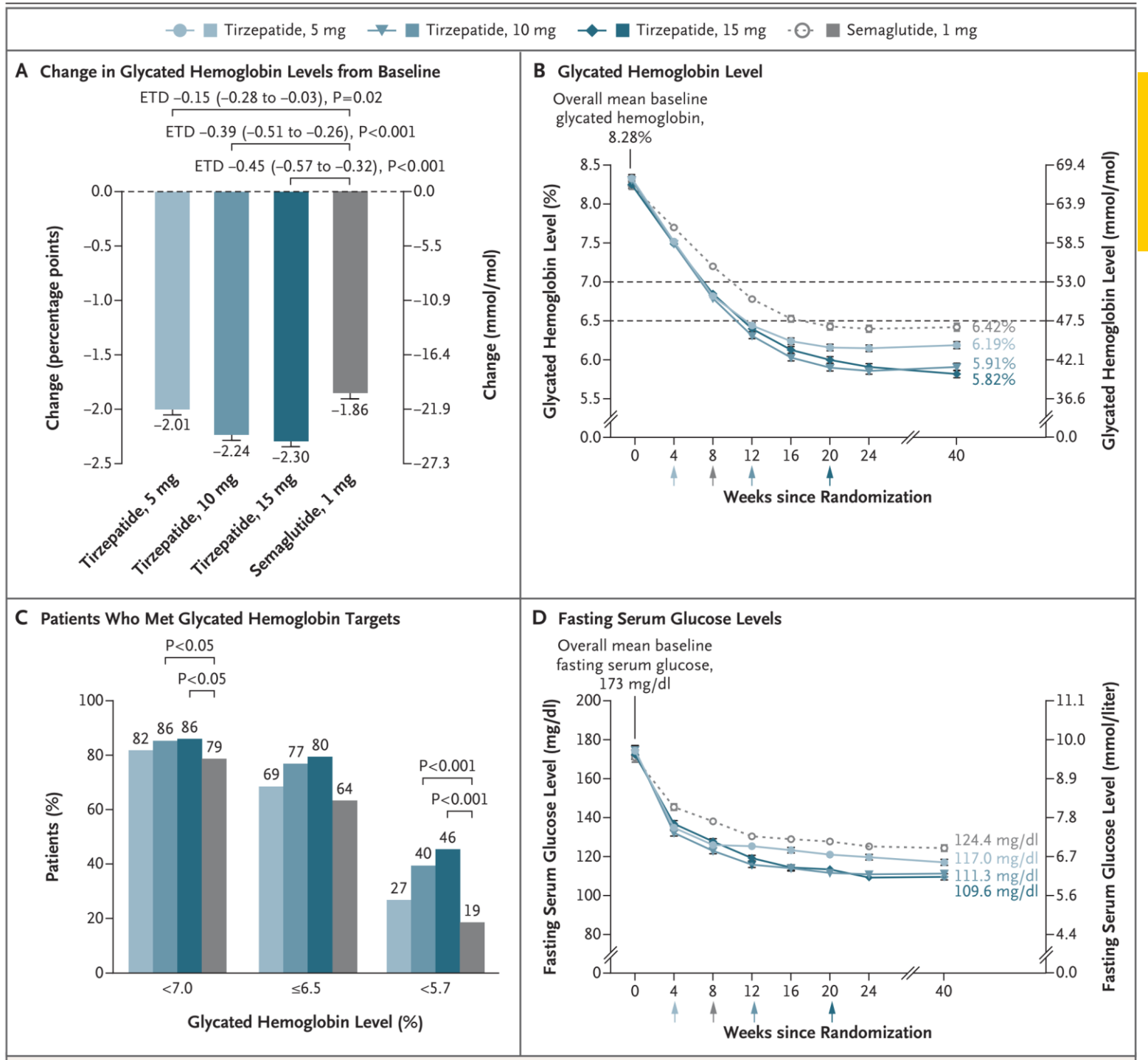
The NEW ENGLAND JOURNAL of MEDICINE

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*

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.



Conclusions

- In patients with type 2 diabetes, tirzepatide was noninferior and superior to semaglutide with respect to the mean change in the glycated hemoglobin level from baseline to 40 weeks.
- (Funded by Eli Lilly; SURPASS-2 ClinicalTrials.gov number, NCT03987919. opens in new tab.)

Efficacy and Safety of Tirzepatide in Patients with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomized Phase II/III Trials

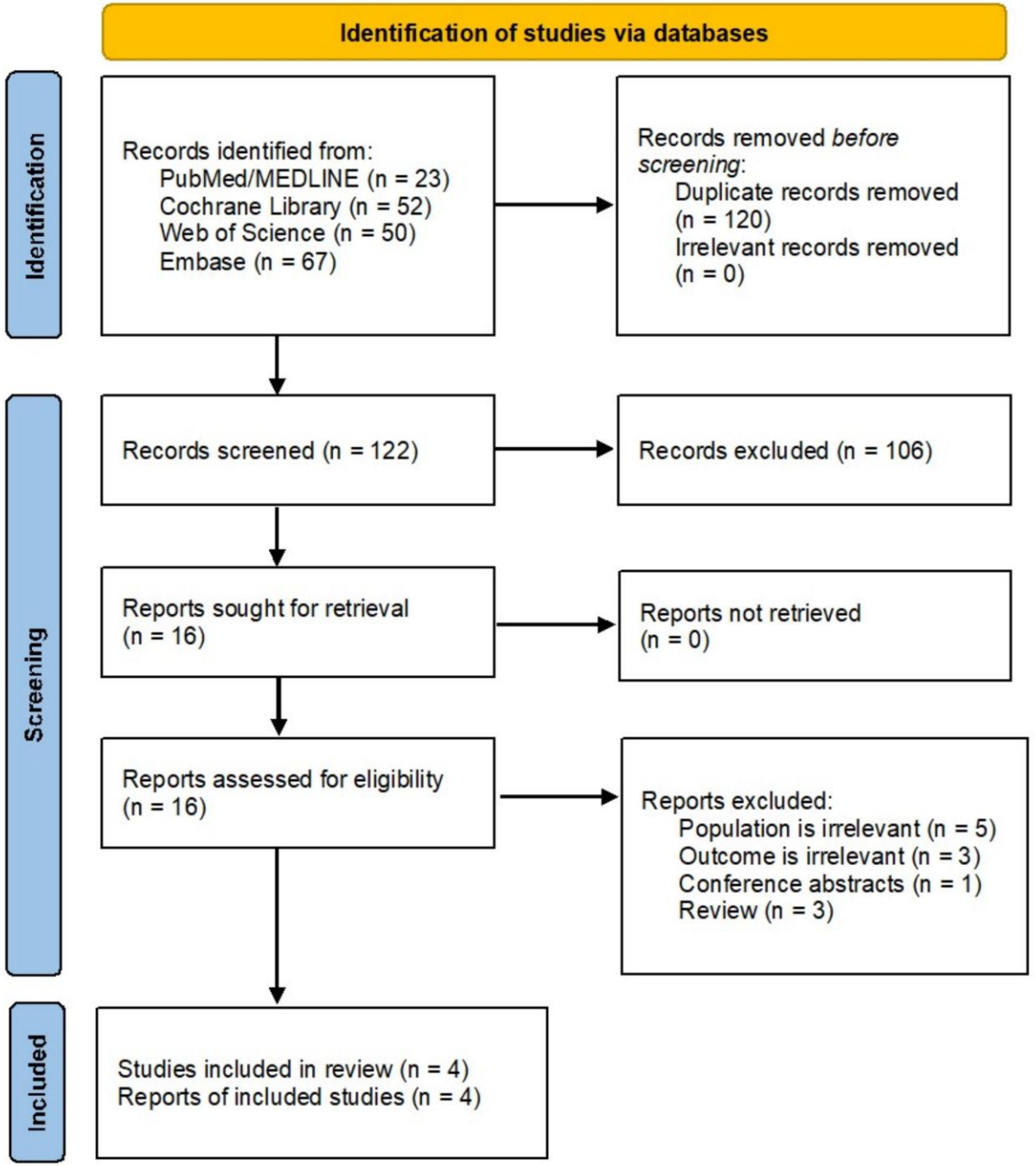
- Tirzepatide is a novel once-a-week dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, currently under trial to assess glycemic efficacy and safety in people with type 2 diabetes.
- A systematic review and meta-analysis were conducted to investigate the efficacy of tirzepatide on glycated hemoglobin (HbA1c, %), fasting serum glucose (mg/dL), and body weight (kg) in patients with uncontrolled type 2 diabetes (HbA1c > 7.0%).

Efficacy and Safety of Tirzepatide in Patients with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomized Phase II/III Trials

- Mean changes for efficacy and proportions (safety) with corresponding 95% confidence intervals (CIs) were used to provide pooled estimates.
- A total of four randomized controlled trials, comprising 2783 patients of whom 69.4% (n = 1934) were treated with 5 mg (n = 646), 10 mg (n = 641), or 15 mg (n = 647) of tirzepatide, were compared to the placebo (n = 192) or the selective GLP-1 receptor agonist (n = 523).

Efficacy and Safety of Tirzepatide in Patients with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomized Phase II/III Trials

- The pooled analysis showed that tirzepatide treatment resulted in a greater lowering of the HbA1c (−1.94%, 95% CI: −2.02 to −1.87), fasting serum glucose (−54.72 mg/dL, 95% CI: −62.05 to −47.39), and body weight (−8.47, 95% CI: −9.66 to −7.27).
- We also found that improvement in the HbA1c levels was still maintained at weeks 26 and 40 from the long-term trials.
- As for safety, only 3% experienced hypoglycemia, and 4% (95% CI: 2 to 6) experienced serious adverse events, while the discontinuation of therapy percentage was 7% (95% CI: 5 to 8).
- Tirzepatide significantly improved glycemic control and body weight and had an acceptable safety profile, indicating that it is an effective therapeutic option for glucose-lowering in patients with type 2 diabetes mellitus.


Identification of studies via databases
Identification
Records identified from:
PubMed/MEDLINE (n = 23)
Cochrane Library (n = 52)
Web of Science (n = 50)
Embase (n = 67)
Records removed *before screening*:
Duplicate records removed (n = 120)
Irrelevant records removed (n = 0)
Screening
Records screened (n = 122)
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Reports excluded:
Population is irrelevant (n = 5)
Outcome is irrelevant (n = 3)
Conference abstracts (n = 1)
Review (n = 3)
Included
Studies included in review (n = 4)
Reports of included studies (n = 4)

Table 1. Study characteristics of included studies.

Author Name	NCTID	Location	Design	Participants Condition at Baseline	Disease Duration (years)	Primary Outcome	Treatment Duration (weeks)	Intervention	Patients on Metformin Therapy (%)	Number Randomized	Age (Years)	Male (%)	Average Change in HbA1c (%) From Baseline
Rosenstock J et al., 2021 [17]	NCT03954834 (SURPASS-1)	India, Japan, Mexico, and USA	Multicenter, double-blind, randomized, placebo-controlled, phase 3 trial	T2DM ([HbA1c] 7.0–9.5%) that was inadequately controlled with diet and exercise alone. They were naive to injectable diabetes therapy.	4.7	Change in HbA1c	40	Tirzepatide 5 mg/day	NR	121	54.1	46	−1.87
								Tirzepatide 10 mg/day	NR	121	55.8	60	−1.89
								Tirzepatide 15 mg/day	NR	121	52.9	52	−2.07
								Placebo	NR	115	53.6	49	0.04
Frias JP et al., 2018 [18]	NCT03131687	Poland, Puerto Rico, Slovakia, and USA	Multicenter, phase 2b, randomized, double-blind study	T2DM for at least 12 months ([HbA1c] 7.0–10.5%) that was inadequately controlled with diet and exercise alone or with stable metformin therapy for at least 3 months before screening.	9.0	Change in HbA1c	26	Tirzepatide 1 mg/day	88.5	52	57.4	56	−0.7
								Tirzepatide 5 mg/day	89.1	55	57.9	62	−1.6
								Tirzepatide 10 mg/day	86.3	51	56.5	59	−2.0
								Tirzepatide 15 mg/day	96.2	53	56.0	42	−2.4
								Dulaglutide 1.5 mg/day	88.1	54	58.7	44	−1.1
								Placebo	92.2	51	56.6	57	0.1
Frias JP et al., 2020 [19]	NCT03311724 (SURPASS)	USA	Multicenter, phase 2, randomized, double-blind, placebo-controlled	T2DM for at least 6 months ([HbA1c] 7.0–10.5%) that was inadequately controlled with diet and exercise alone or with stable metformin therapy.	9.1	Change in HbA1c	12	Tirzepatide 12 mg/day	86.2	29	61.2	51.7	−1.7
								Tirzepatide 15 mg/day-1	89.3	28	55.5	57.1	−2
								Tirzepatide 15 mg/day-2	82.1	28	56.6	82.1	−1.8
								Placebo	88.5	26	56	46.2	0.2
Frias JP et al., 2021 [20]	NCT03987919 (SURPASS-2)	USA, UK, Argentina, Australia, Brazil, Canada, Israel, Mexico	Multicenter, phase 3, open-label, parallel-group, randomized, active-controlled	T2DM for at least 6 months ([HbA1c] 7.0–10.5%) that was inadequately controlled with metformin therapy.	8.6	Change in HbA1c	40	Tirzepatide 5 mg/day	100	470	56.3	43.6	−2.01
								Tirzepatide 10 mg/day	100	469	57.2	50.7	−2.24
								Tirzepatide 15 mg/day	100	470	55.9	45.5	−2.3
								Semaglutide 1 mg/day	100	469	56.9	48	−1.86

NR: Not reported; HbA1c: Glycated hemoglobin; T2DM: Type 2 diabetes mellitus; UK: United Kingdom; USA: United States of America.

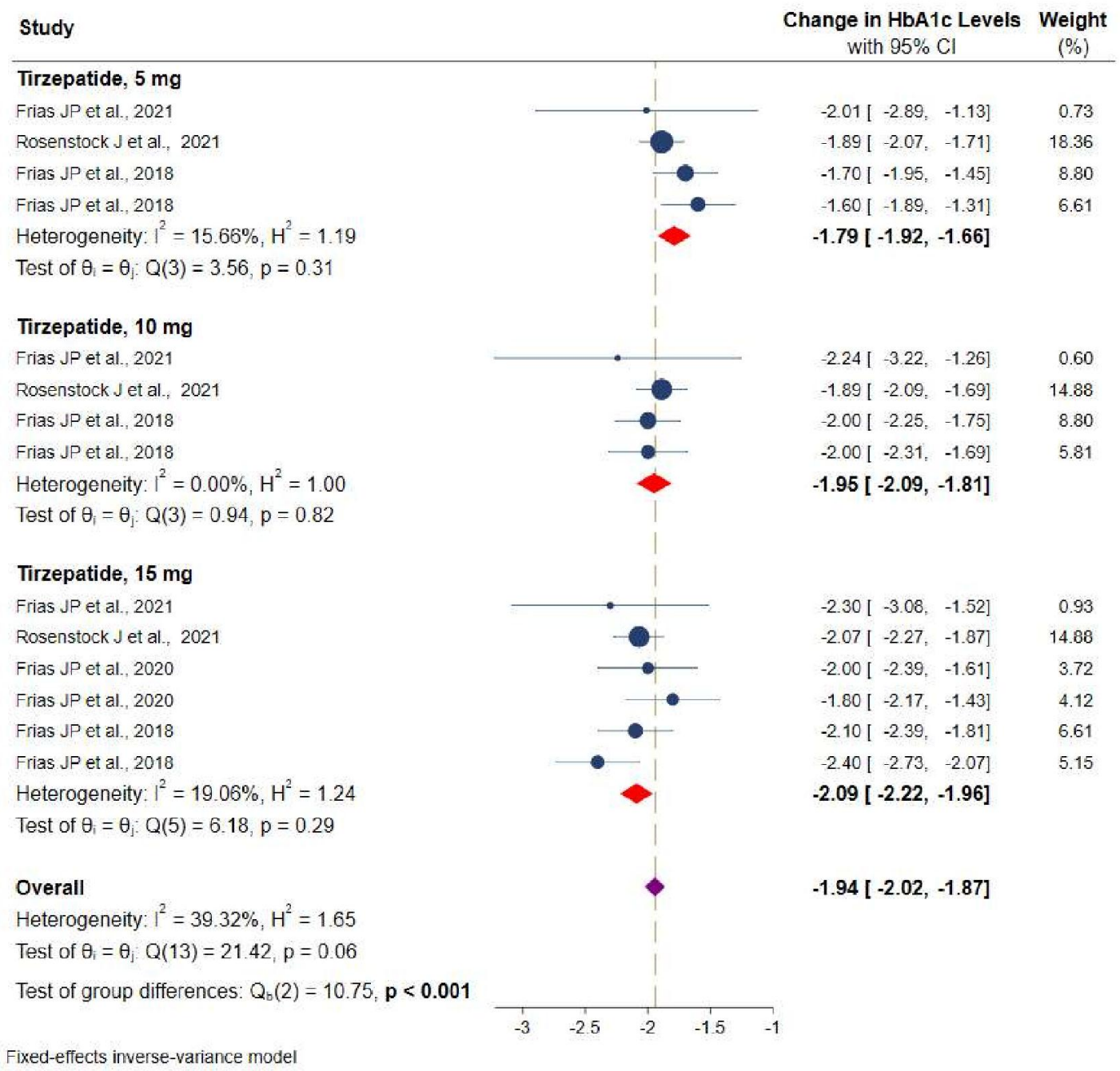

Figure 3. Effect of once-weekly tirzepatide on glycated hemoglobin (HbA1c).

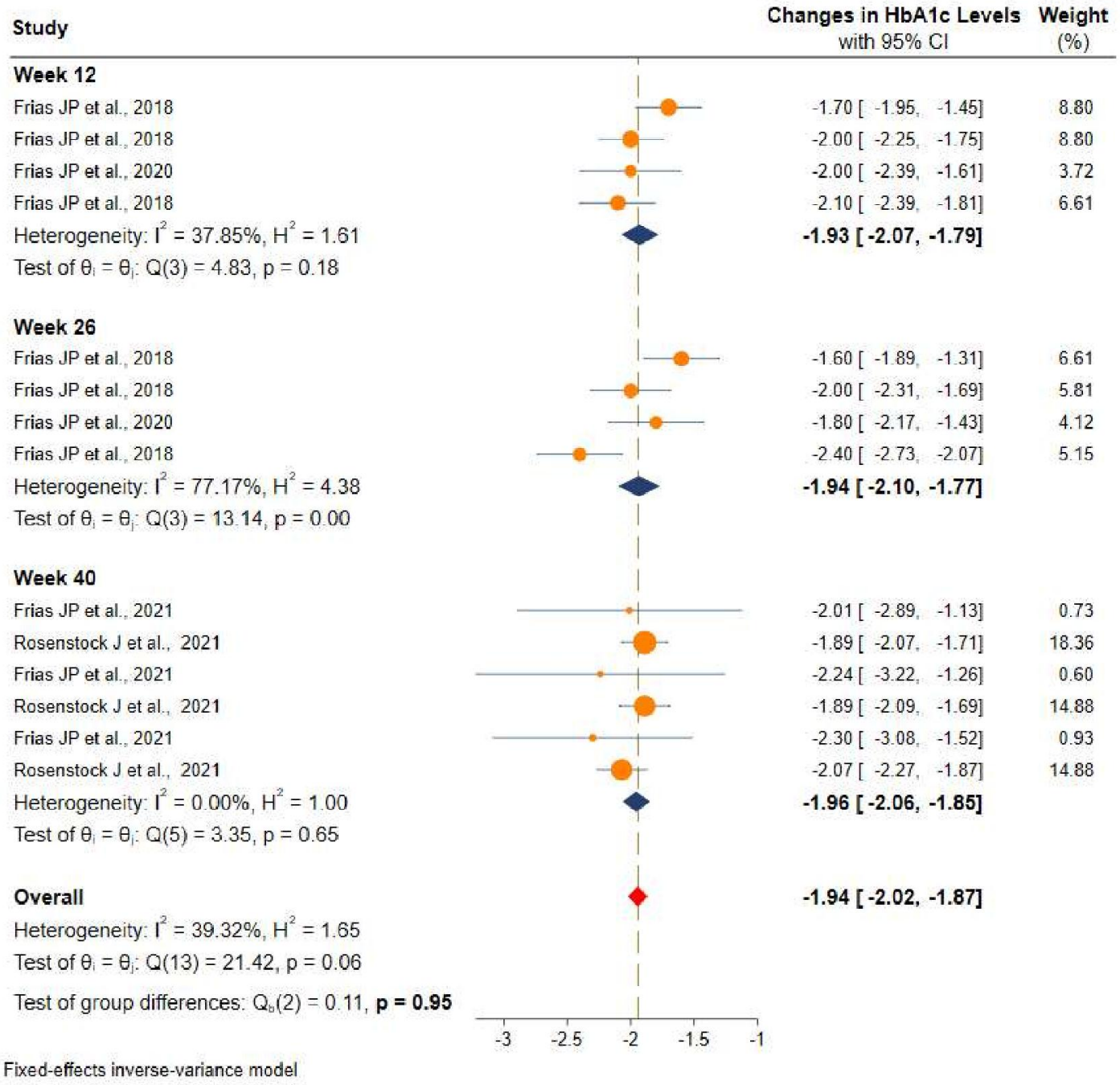

Figure 4. Efficacy of once-weekly tirzepatide on glycated hemoglobin (HbA1c) based on duration of intervention.

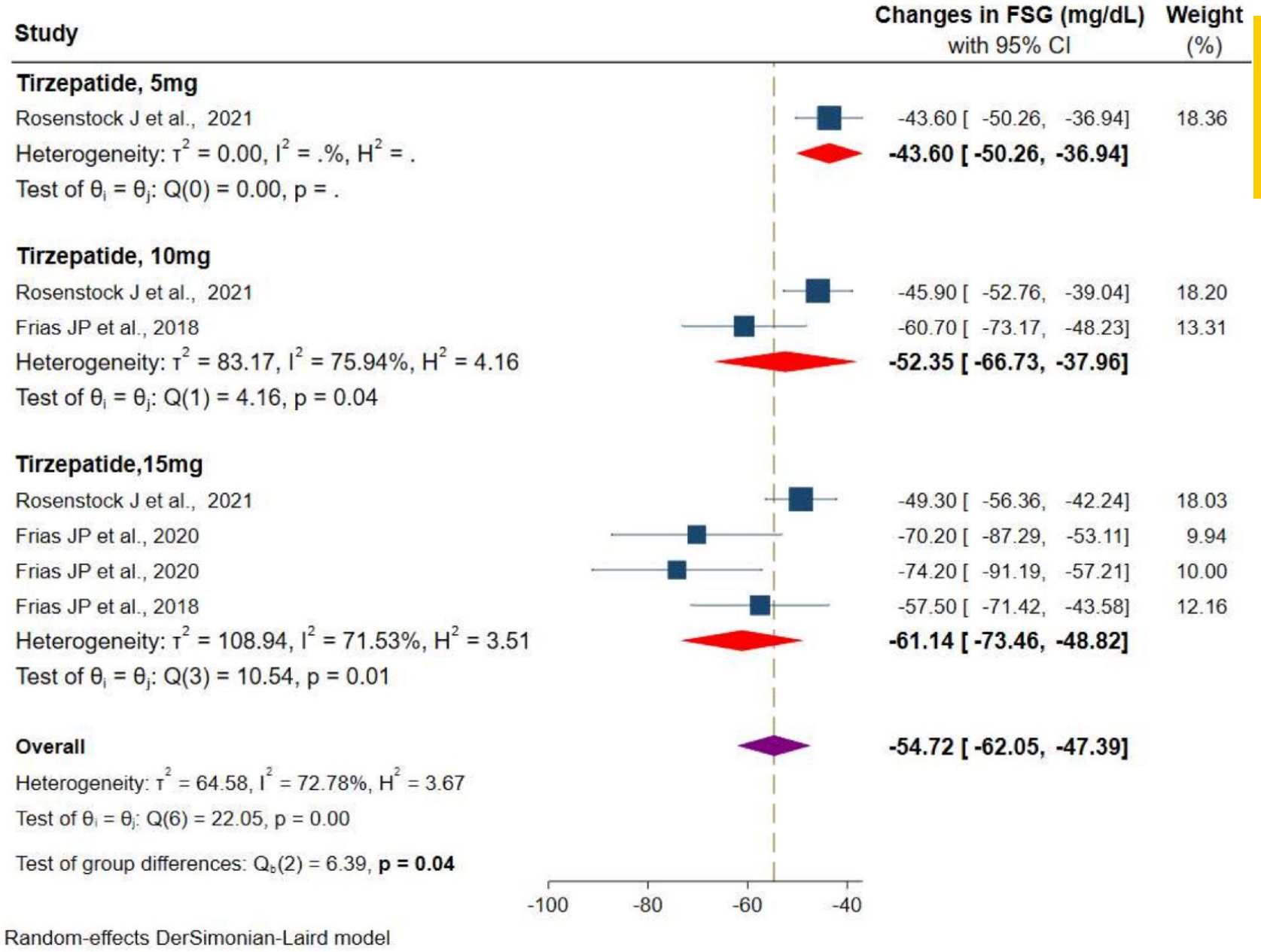

Figure 5. Effect of once-weekly tirzepatide on fasting serum glucose levels (mg/dL).

Costs

- Another common question around tirzepatide, and its potential obesity drug counterpart, is pricing.
- The current list price of Mounjaro is $974 for a four-week prescription of all doses.
- “Each person’s individual insurer and plan will determine the out-of-pocket costs for Mounjaro,” says Pfeiffer, adding some people may qualify for savings cards to reduce out-of-pocket costs.

Costs

- Disparities in affordability of new diabetes and obesity medications, as well as bariatric surgery, for underinsured or people without insurance was a topic among experts at ADA Scientific Sessions.

Utility

- It is not known if Mounjaro is safe and effective in children.
- Mounjaro can cause nausea, vomiting, diarrhea, decreased appetite, constipation, upper abdominal discomfort and abdominal pain.
- Mounjaro causes thyroid C-cell tumors in rats. It is unknown whether Mounjaro causes such tumors, including medullary thyroid cancer, in humans. Mounjaro should not be used in patients with a personal or family history of medullary thyroid cancer or in patients with Multiple Endocrine Neoplasia syndrome type 2.
- Mounjaro has not been studied in patients with a history of pancreas inflammation (pancreatitis), and it is not indicated for use in patients with type 1 diabetes.
- Based on animal reproduction studies, there may be risks to the fetus from exposure to tirzepatide during pregnancy.
- Mounjaro should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Utility

- It depends on availability and affordability in Iran.
- Long term cardio metabolic outcomes are needed.
- Long term safety profile should be established.
- Insurance coverage is another challenge.

Thank you and hope for a good rain