APPROCCIO FARMACOLOGICO: INDICAZIONI E LIMITI

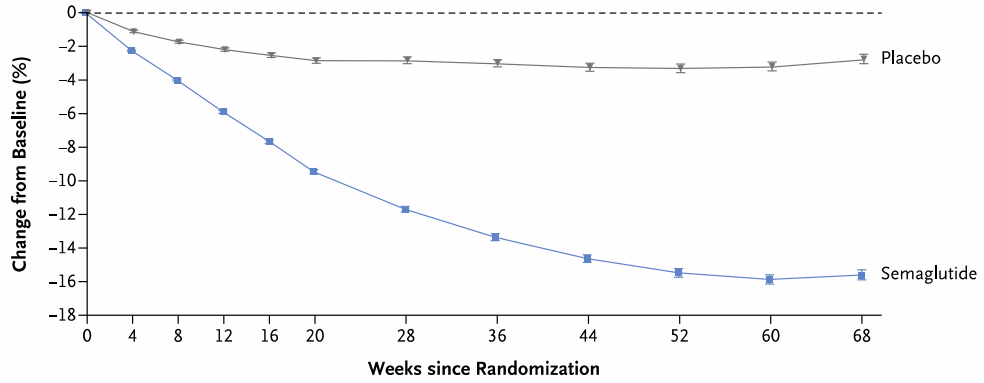
LUCA BUSETTO
DIPARTIMENTO DI MEDICINA
UNIVERSITA' DI PADOVA

Once-Weekly Semaglutide in Adults with Overweight or Obesity

PARTICIPANTS

We enrolled adults (18 years of age or older) with one or more self-reported unsuccessful dietary efforts to lose weight and either a BMI of 30 or greater or a BMI of 27 or greater with one or more treated or untreated weight-related coexisting conditions (i.e., hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease).

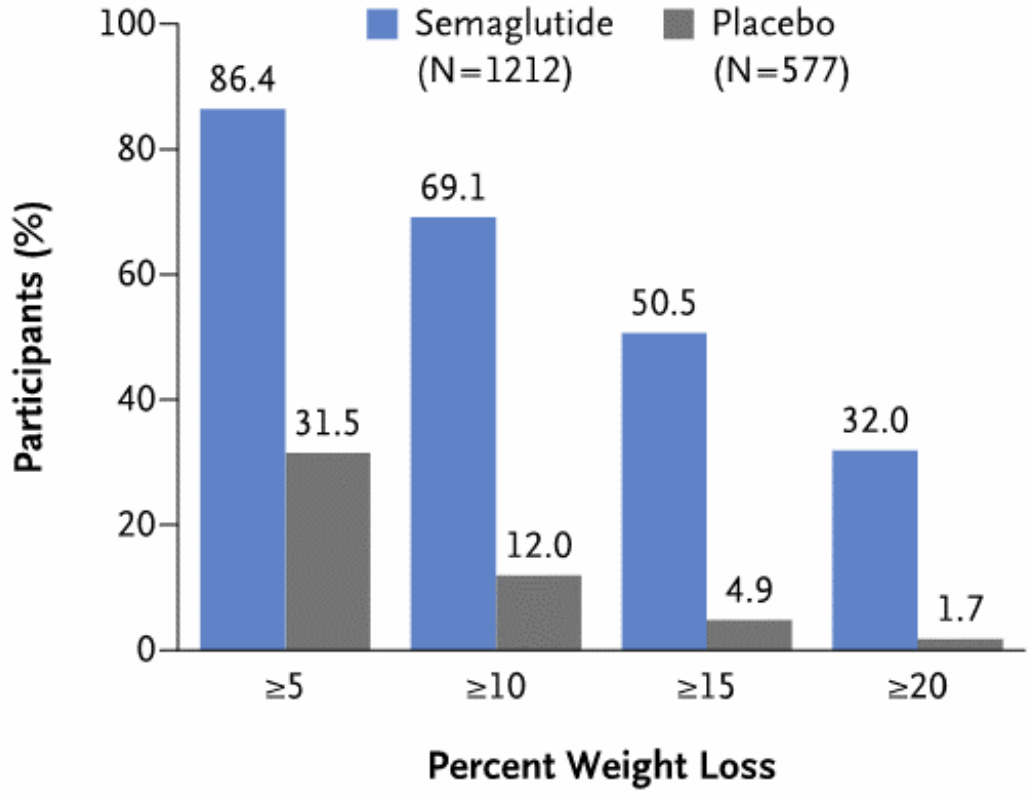
A Body Weight Change from Baseline by Week, Observed In-Trial Data



No. at Risk

Placebo	655	649	641	619	615	603	592	571	554	549	540	577
Semaglutide	1306	1290	1281	1262	1252	1248	1232	1228	1207	1203	1190	1212

C In-Trial Data at Wk 68



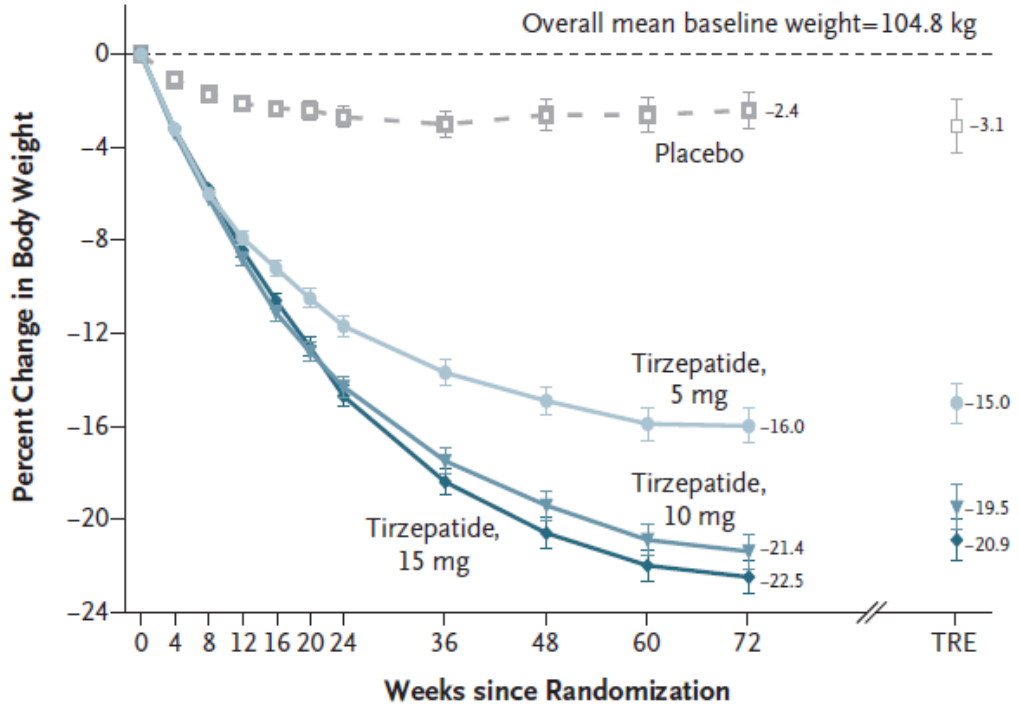
Wilding JPH et al. NEJM 2021;384:989

Tirzepatide Once Weekly for the Treatment of Obesity

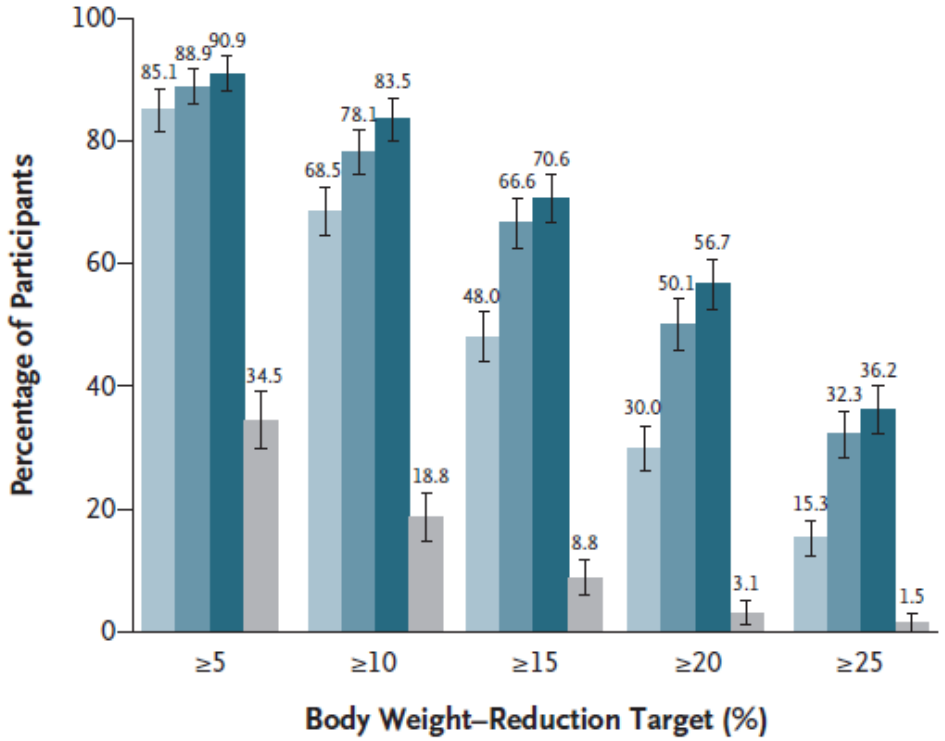
PARTICIPANTS

Adults who were 18 years of age or older, with a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of 30 or more, or a BMI of 27 or more and at least one weight-related complication (e.g., hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease), and who reported one or more unsuccessful dietary effort to lose weight

B Percent Change in Body Weight by Week (efficacy estimand)

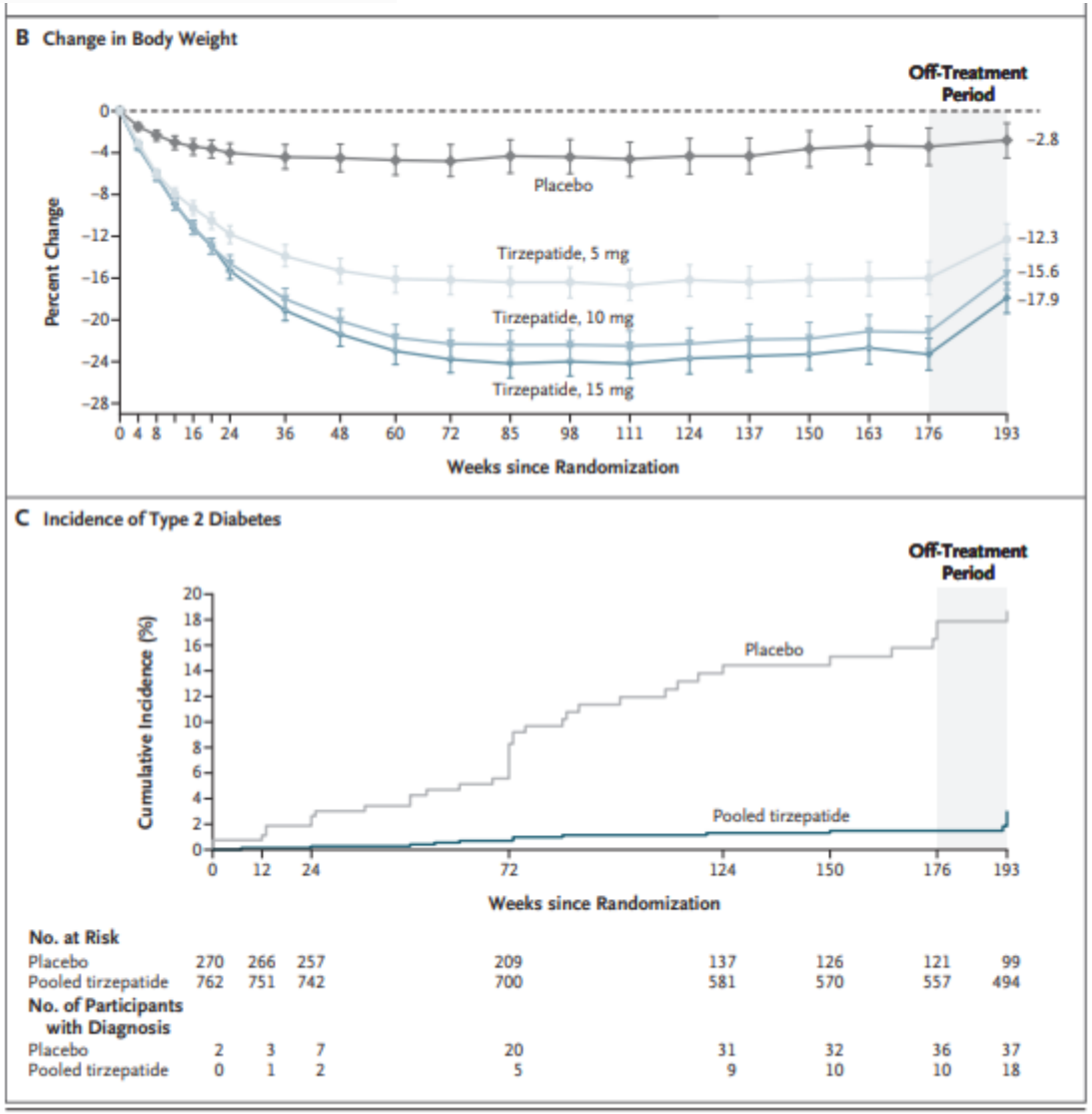


C Participants Who Met Weight-Reduction Targets (treatment-regimen estimand)



Jastreboff AM et al. N Engl J Med 2022;387:205

Tirzepatide for Obesity Treatment and Diabetes Prevention



Jastreboff AM et al. N Engl J Med 2024; Nov 13

Figure 5. Diagnosis and Medical Management of Obesity

DIAGNOSIS		COMPLICATION-SPECIFIC STAGING AND TREATMENT		
Anthropometric Component (BMI kg/m^2)	Clinical Component	Disease Stage	Chronic Disease Phase of Prevention	Suggested Therapy (based on clinical judgment)
<25 <23 in certain ethnicities waist circumference below regional/ ethnic cutoffs		**Normal weight** (no obesity)	**Primary**	• **Healthy lifestyle:** healthy meal plan/ physical activity
25–29.9 23–24.9 in certain ethnicities	Evaluate for presence or absence of adiposity-related complications and severity of complications • Metabolic syndrome • Prediabetes • Type 2 diabetes • Dyslipidemia • Hypertension • Cardiovascular disease • Nonalcoholic fatty liver disease • Polycystic ovary syndrome • Female infertility • Male hypogonadism • Obstructive sleep apnea • Asthma/reactive airway disease • Osteoarthritis • Urinary stress incontinence • Gastroesophageal reflux disease • Depression	**Overweight stage 0** (no complications)	**Secondary**	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/physical activity/ behavioral interventions
≥30 ≥25 in certain ethnicities		**Obesity stage 0** (no complications)	**Secondary**	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/physical activity/ behavioral interventions • **Weight-loss medications:** Consider after lifestyle therapy fails to prevent progressive weight gain. (BMI ≥27)
≥25 ≥23 in certain ethnicties		**Obesity stage 1** (1 or more mild-moderate complications)	**Tertiary**	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/physical activity/ behavioral interventions • **Weight-loss medications:** Consider after lifestyle therapy fails to achieve therapeutic target or initiate concurrent with lifestyle therapy. (BMI ≥27)
≥25 ≥23 in certain ethnicties		**Obesity stage 2** (at least 1 severe complication)	**Tertiary**	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/physical activity/ behavioral interventions • **Add weight-loss medication:** Initiate concurrent with lifestyle therapy. (BMI ≥27) • **Consider bariatric surgery:** (BMI ≥35)

A new framework for the diagnosis, staging and management of obesity in adults

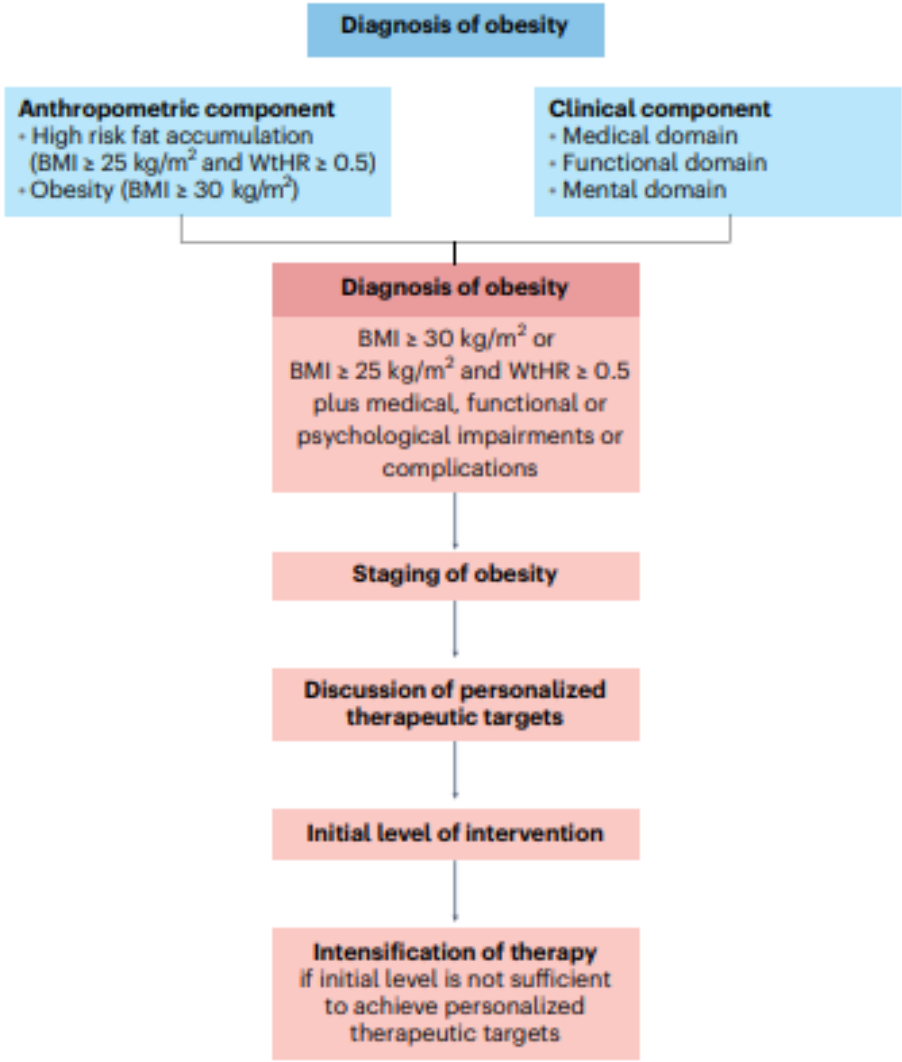


Fig. 1 | A new framework for the diagnosis, staging and management of obesity in adults. This flowchart of the diagnostic and therapeutic pathways results from the statements in Table 1. WtHR, waist-to-height ratio.

Busetto L et al. Nat Med 2024;30:2395-2399.

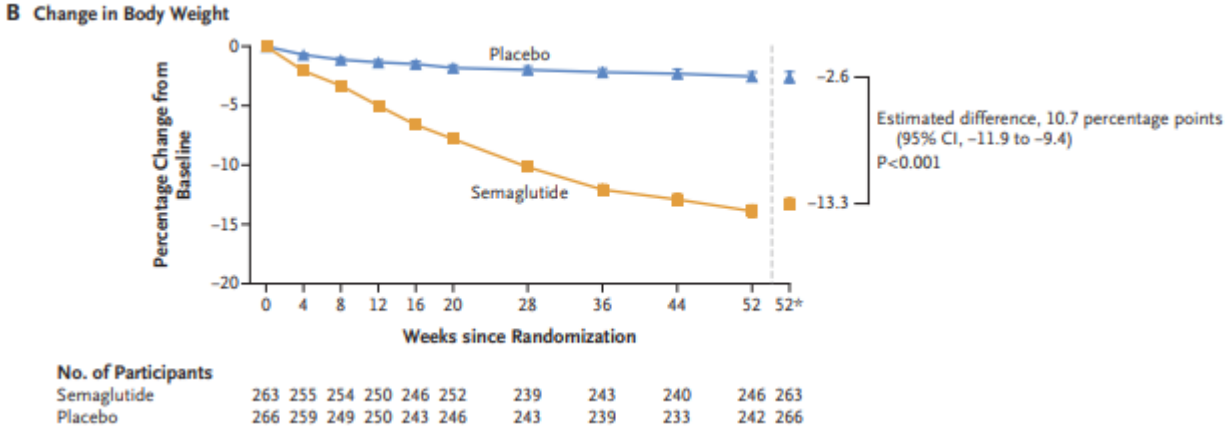
Tirzepatide Once Weekly for the Treatment of Obesity

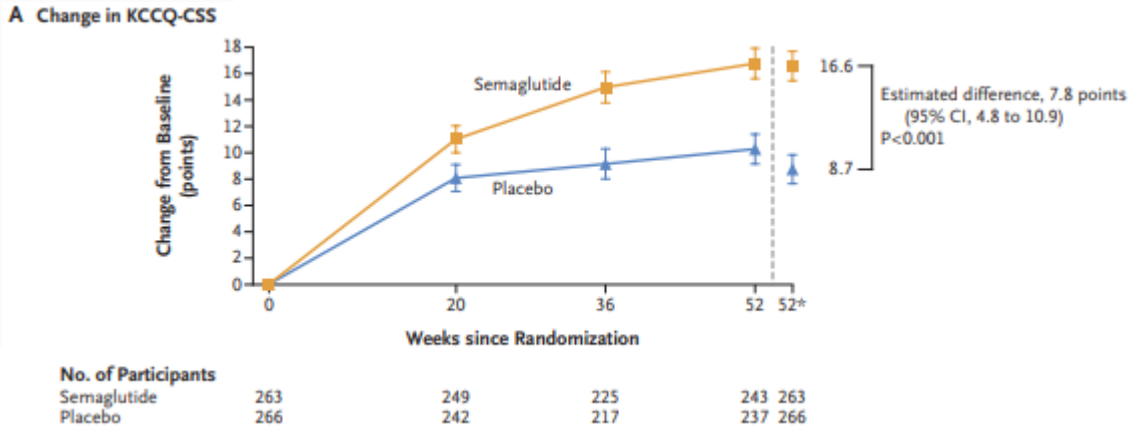
Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

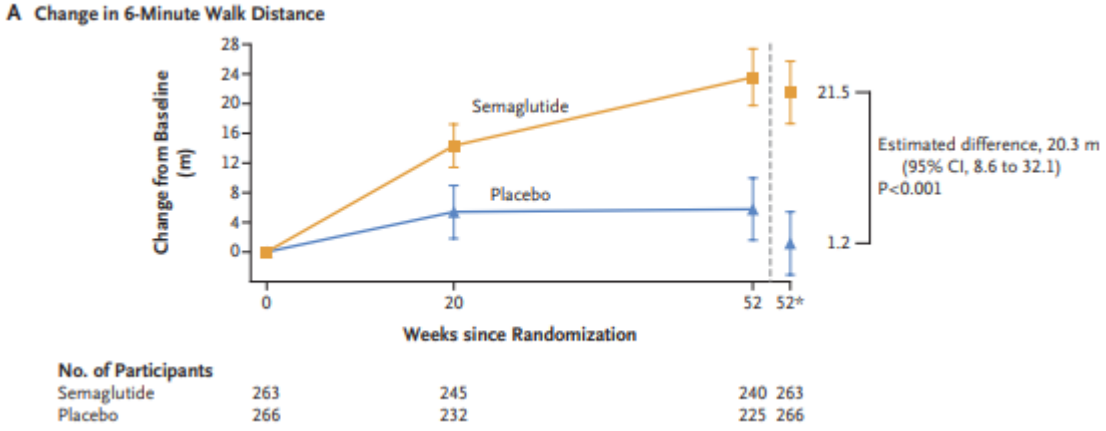
Characteristic	Tirzepatide, 5 mg (N=630)	Tirzepatide, 10 mg (N=636)	Tirzepatide, 15 mg (N=630)	Placebo (N=643)	Total (N=2539)
Age — yr	45.6±12.7	44.7±12.4	44.9±12.3	44.4±12.5	44.9±12.5
Female sex — no. (%)	426 (67.6)	427 (67.1)	425 (67.5)	436 (67.8)	1714 (67.5)
Race or ethnic group — no. (%)†					
American 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)

Jastreboff AM et al. N Engl J Med 2022;387:205

Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity

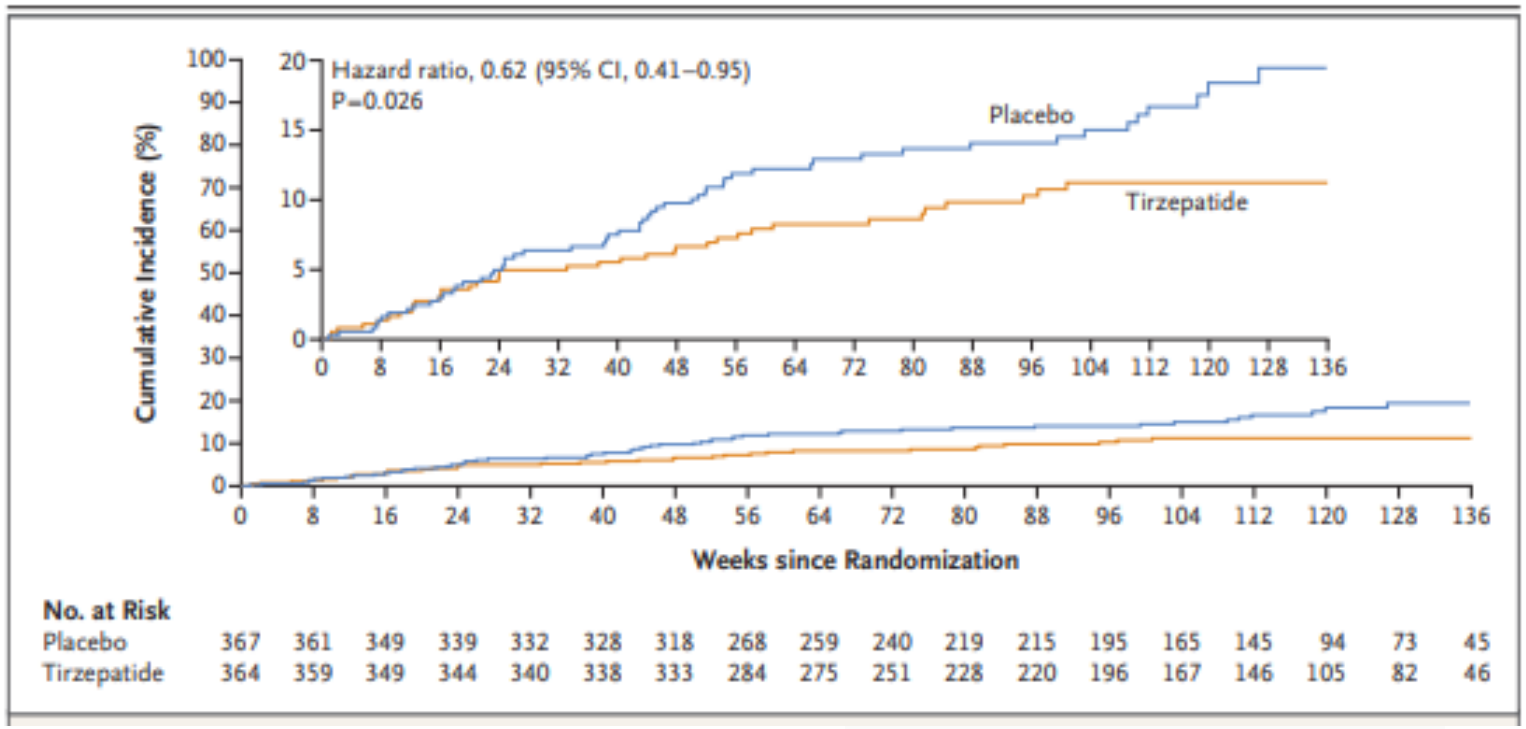






Kosiborod MN et al. NEJM 2023;389:1069

Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity



Packer M et al. NEJM 2024 Nov 16.

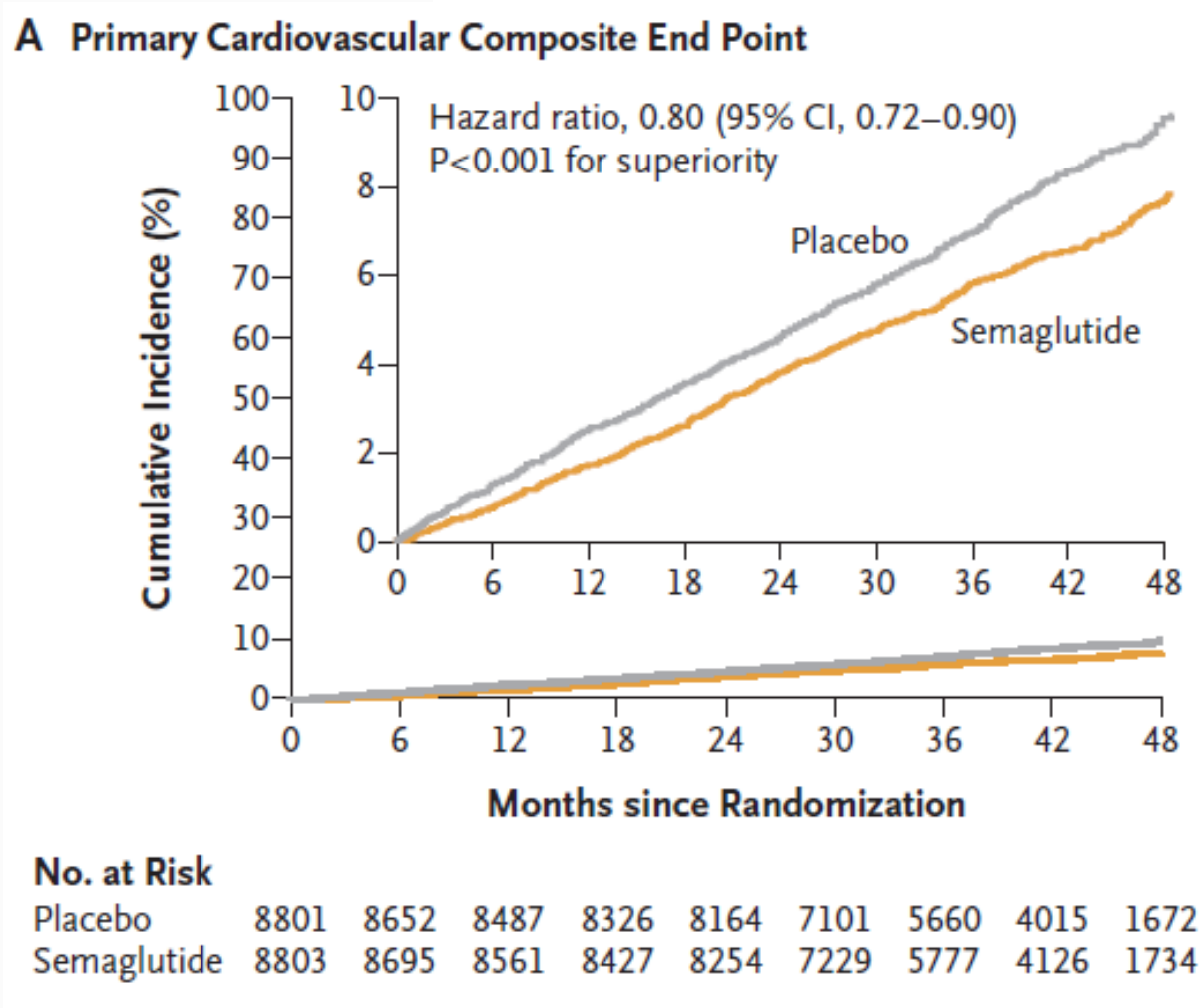
Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

MACE:

701 on 8801 pts (8.0%) in placebo
569 on 8803 pts (6.5%) in semaglutide

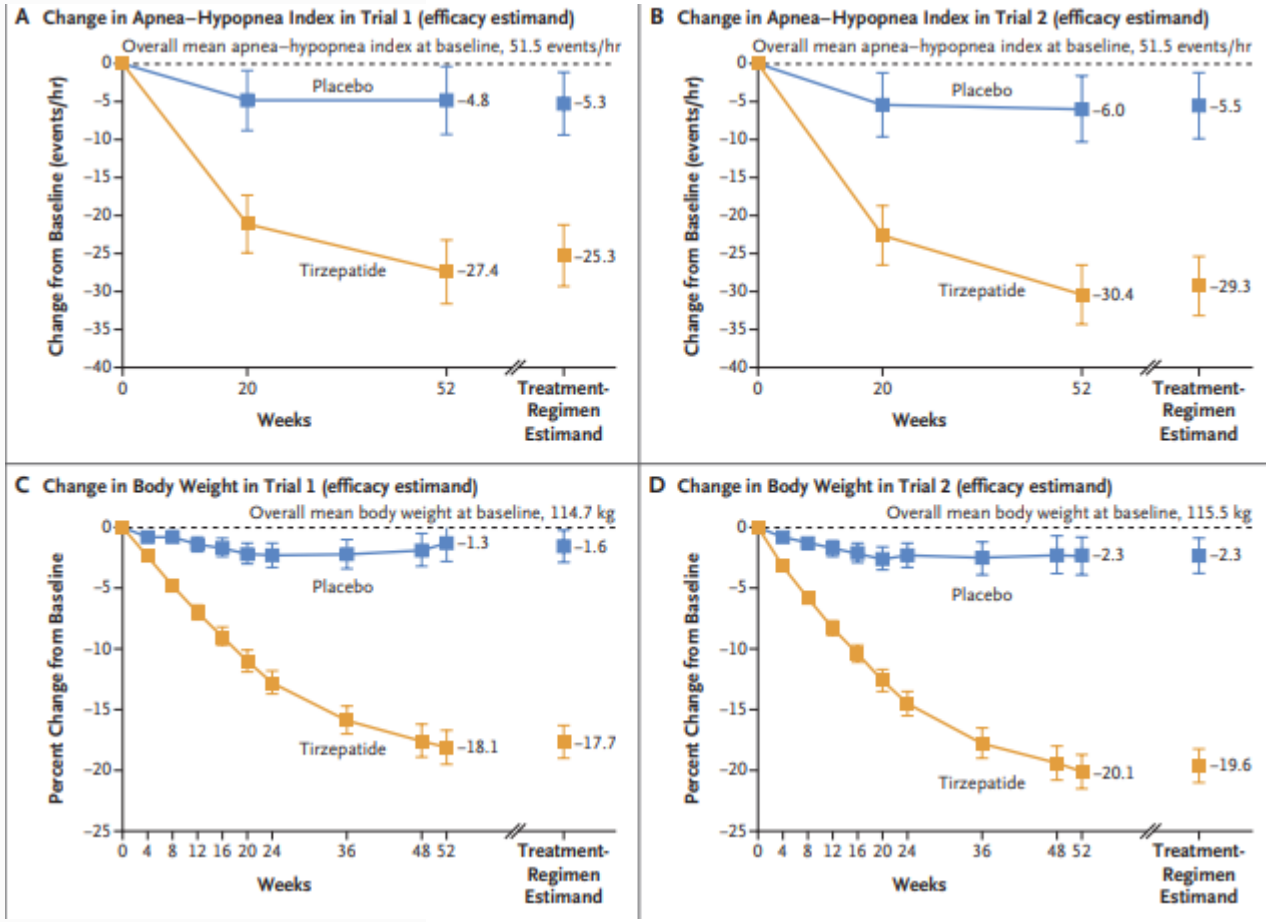
ABR: 1.5%

NNT: 67



Lincof AM et al. N Engl J Med. 2023;389:2221.

Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity



Malhotra A et al. NEJM 2024;391:1193

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Semaglutide (N=8803)	Placebo (N=8801)
Age — yr	61.6±8.9	61.6±8.8
Male sex — no. (%)	6355 (72.2)	6377 (72.5)
Race or ethnic group — no. (%)†		
White	7387 (83.9)	7404 (84.1)
Asian	720 (8.2)	727 (8.3)
Black	348 (4.0)	323 (3.7)
Other	253 (2.9)	273 (3.1)
Hispanic or Latino	914 (10.4)	908 (10.3)
Body weight — kg	96.5±17.5	96.8±17.8
BMI‡	33.3±5.0	33.4±5.0

Lincof AM et al. N Engl J Med. 2023;389:2221.

Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Tirzepatide (N=364)	Placebo (N=367)
Age — yr	65.5±10.5	65.0±10.9
Female sex — no. (%)	200 (54.9)	193 (52.6)
Race or ethnic group — no. (%)†		
Native American, Alaska Native, or Pacific Islander	26 (7.1)	24 (6.5)
Asian	58 (15.9)	73 (19.9)
Black	22 (6.0)	14 (3.8)
White	256 (70.3)	256 (69.8)
Other or multiple	2 (0.5)	0 (0.0)
Region — no. (%)		
United States	83 (22.8)	68 (18.5)
Latin America	193 (53.0)	197 (53.7)
Asia	58 (15.9)	73 (19.9)
Other	30 (8.2)	29 (7.9)
New York Heart Association functional classification — no. (%)		
Class II	262 (72.0)	268 (73.0)
Class III or IV	102 (28.0)	99 (27.0)
Measures of adiposity		
Body weight — kg	102.9±21.7	103.1±22.7
Body-mass index‡	38.3±6.4	38.2±7.0

Packer M et al. NEJM 2024 Nov 16.

Tirzepatide Once Weekly for the Treatment of Obesity

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

Jastreboff AM et al. N Engl J Med 2022;387:205

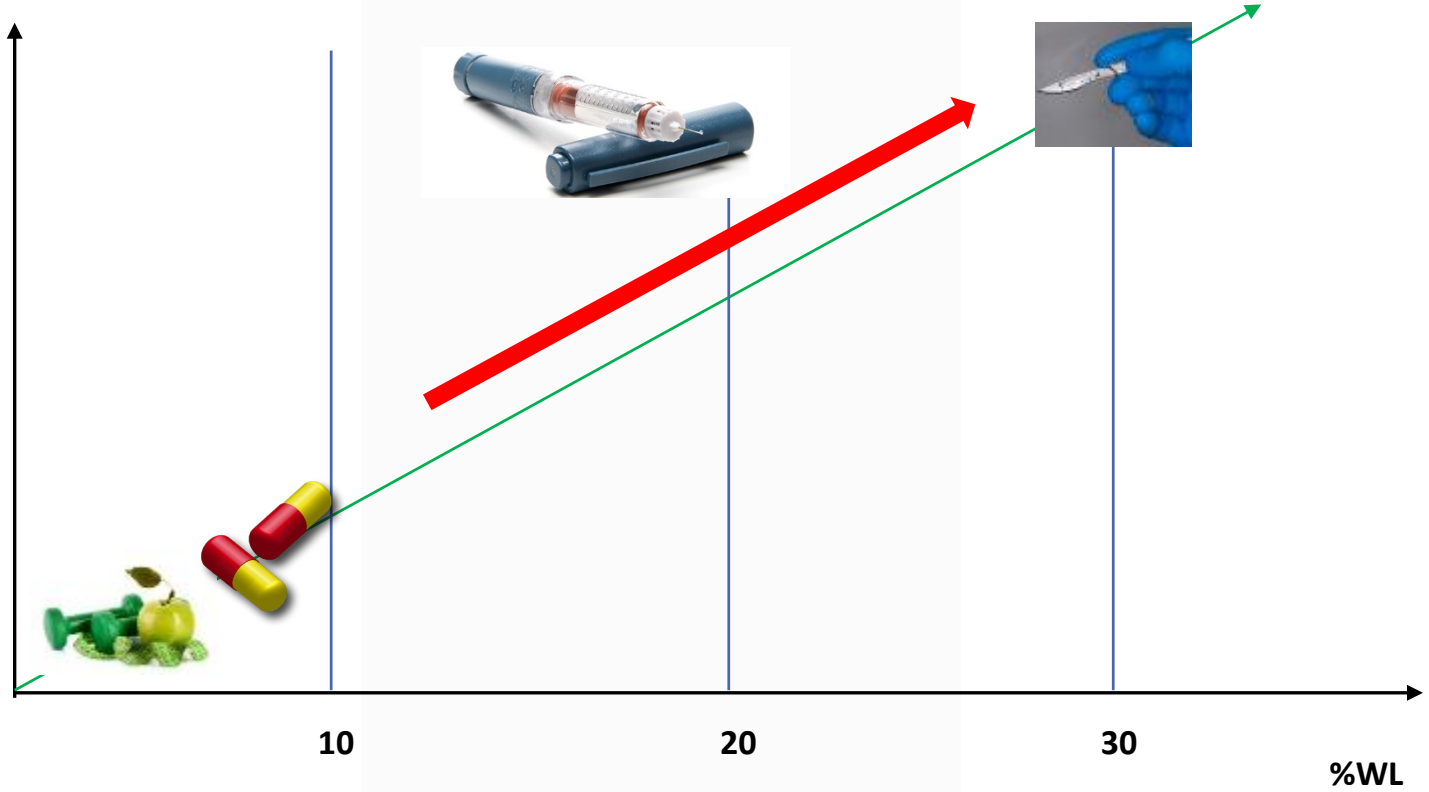
Tirzepatide Once Weekly for the Treatment of Obesity

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)			
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)

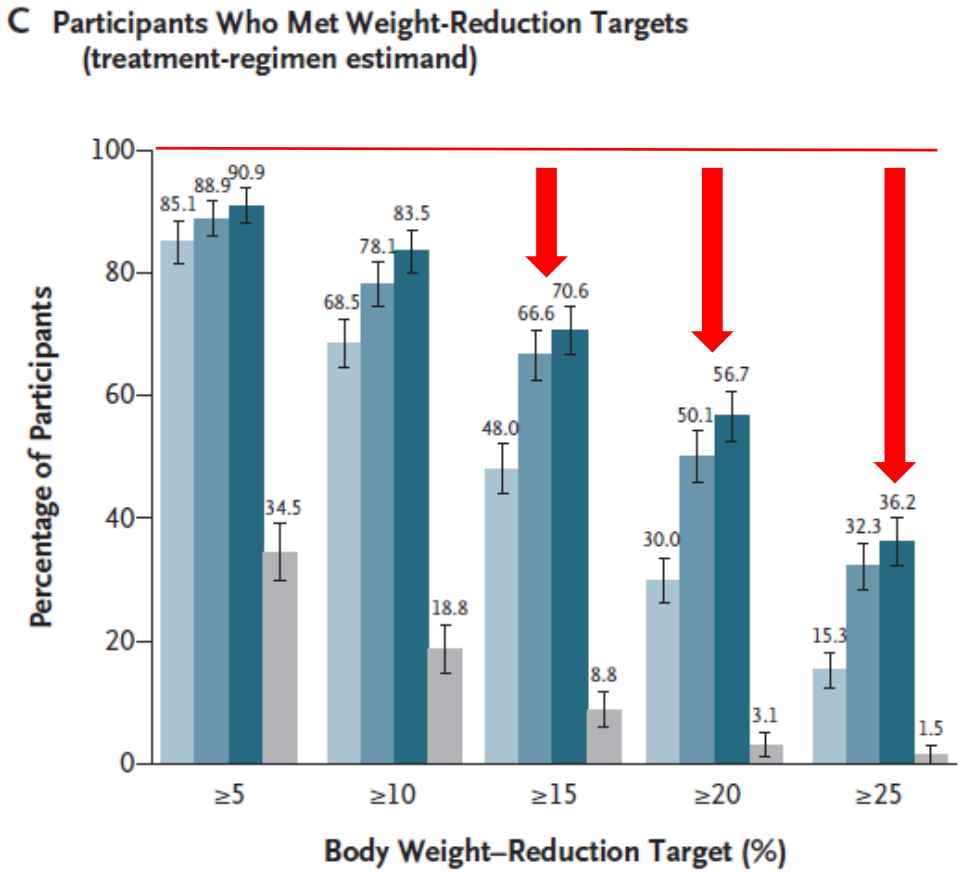
Jastreboff AM et al. N Engl J Med 2022;387:205

Invasivity/Risk/Cost



Tirzepatide Once Weekly for the Treatment of Obesity

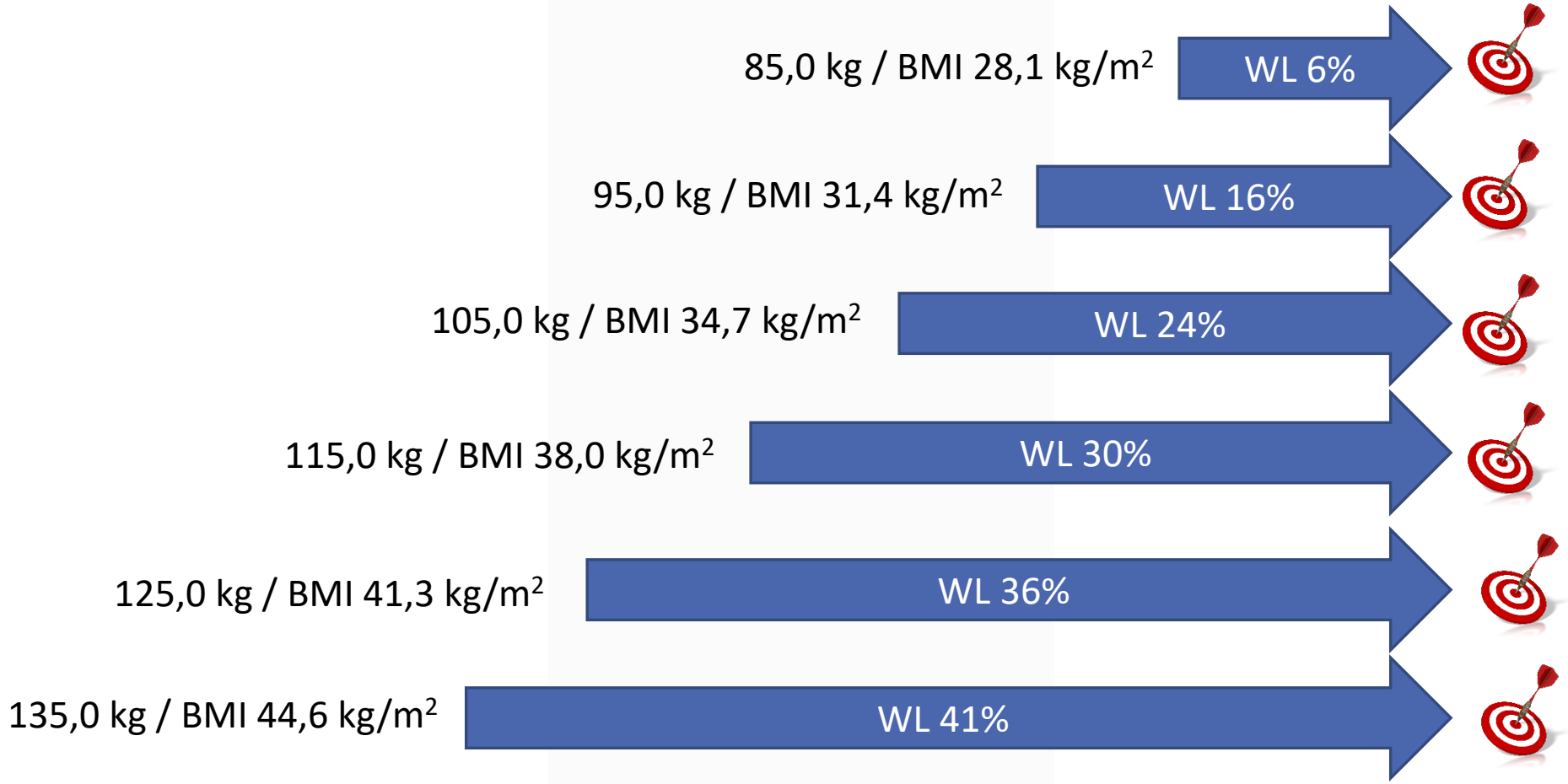
A significant proportion of patients do will not achieve the target with obesity management medications



Jastreboff AM et al. N Engl J Med 2022;387:205

%WL AS A DISTANCE TO TARGET

Patients with height 174 cm, BMI target 26 kg/m² (corresponding to a BW of 80.0 kg) and different baseline body weight / BMI.

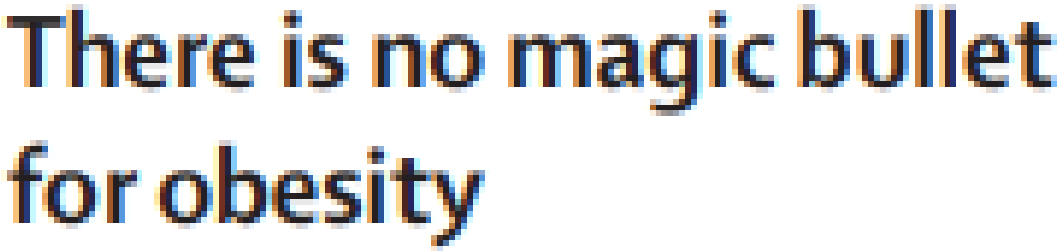


If we agree on individualised BMI or WHtR target, do we should propose as initial level of intervention a therapeutic modality with a reasonable chance to achive the BMI or WHtR target?

Patient with height 174 cm and BMI target 26 kg/m^2 (corresponding to a BW of 80.0 kg)

Initial BW	Initial BW	Requested % weight loss
85.0 kg	28.1 kg/m^2	6%
95.0 kg	31.4 kg/m^2	16%
105.0 kg	34.7 kg/m^2	24%
115.0 kg	38.0 kg/m^2	30%
125.0 kg	41.3 kg/m^2	36%
135.0 kg	44.6 kg/m^2	41%

Will new pharmacological treatment for obesity and early diabetes replace bariatric surgery?



Lingway I et al. Lancet Diabetes Endocrinol 2023;11:541

NAPLES, MARCH 6–7, 2025

1ST INTERNATIONAL BARIATRIC MEETING

Bariatric Surgery and Pharmacological approach to Morbid Obesity: An open debate

Grazie per l'attenzione !!!

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