Brigham and Women's Hospital
Founding Member, Mass General Brigham

What's New in Obesity Medications, Devices and Procedures

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DISCLOSURES

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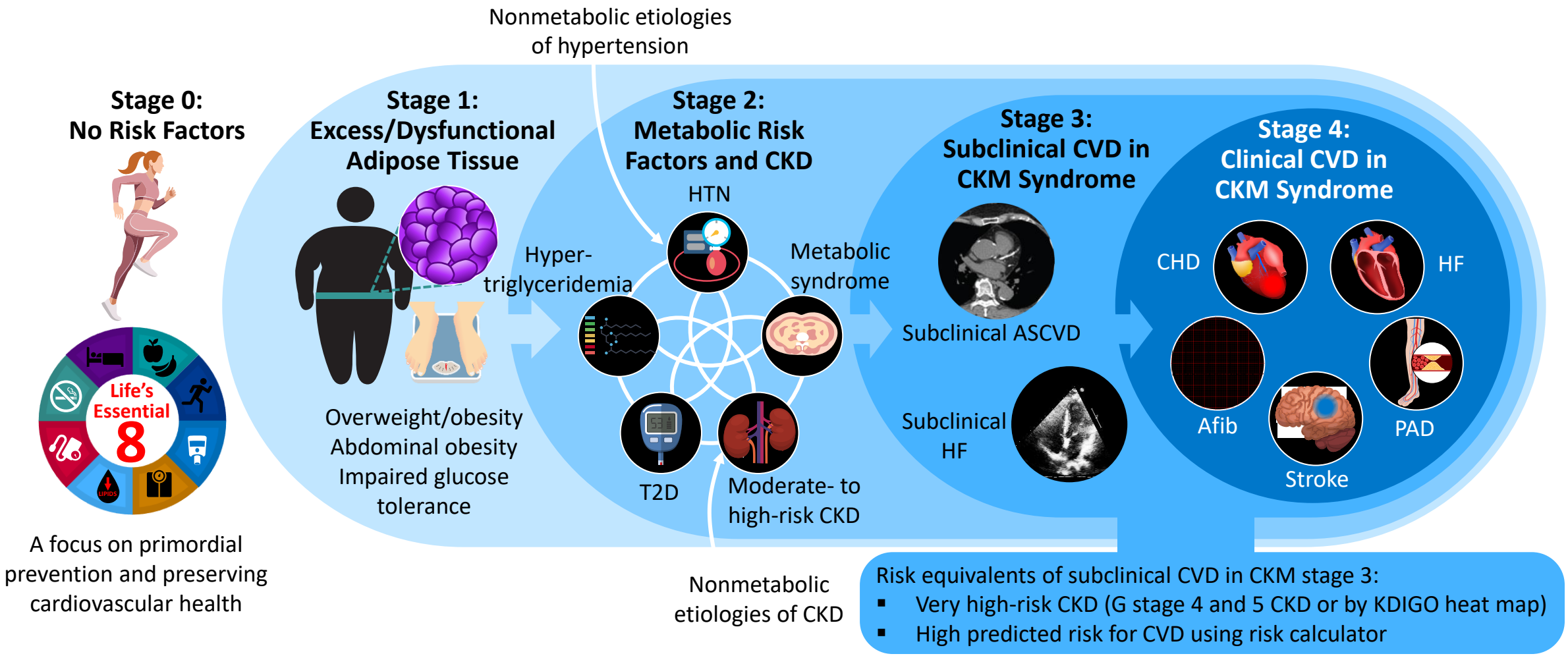
- Clinical focus: Obesity and Post-Bariatric Care
- Research focus: Obesity and Post-Bariatric Care

OBJECTIVES

By the end of this session, participants will be able to:

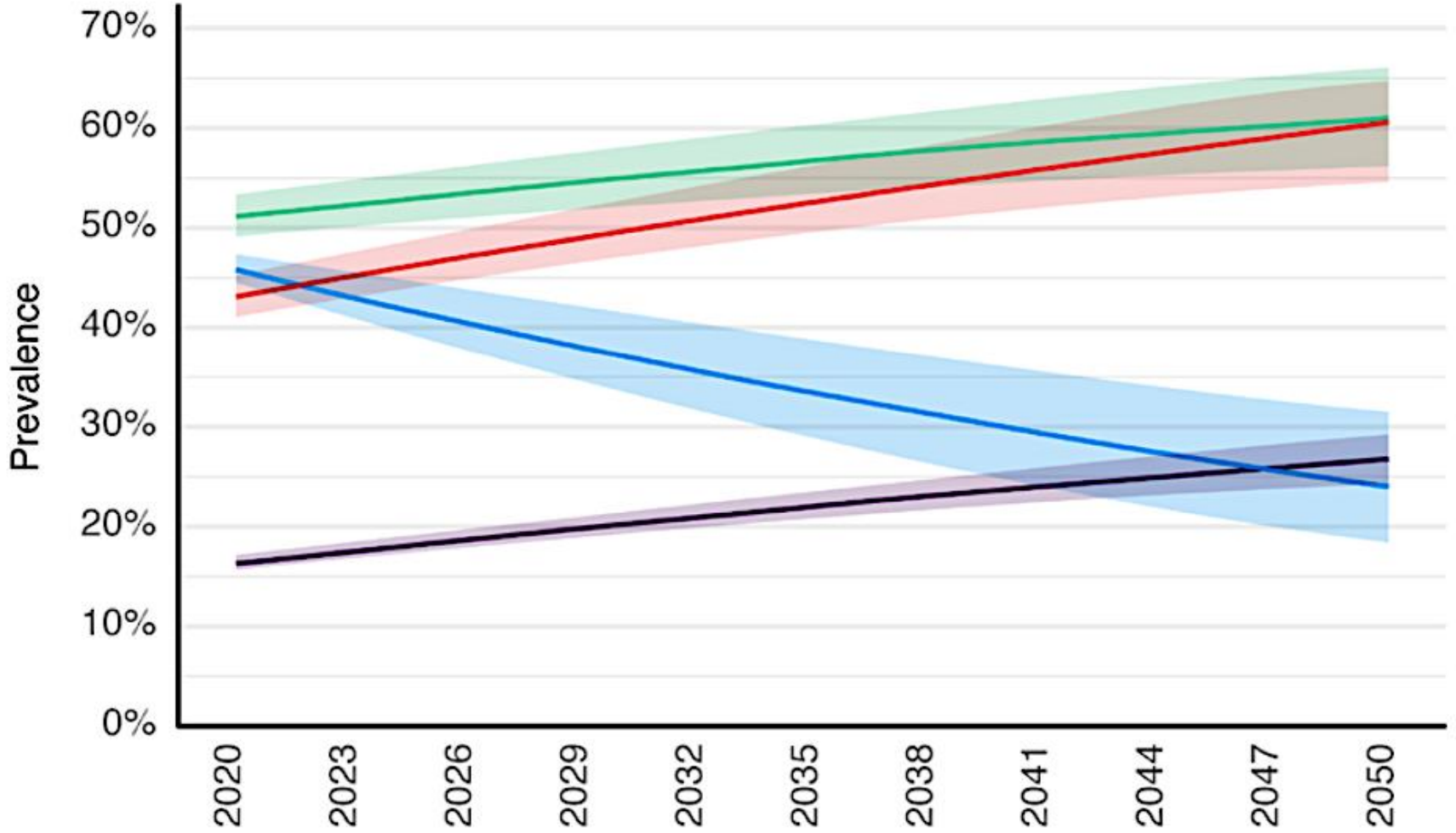
1. **Describe** the mechanisms of action and clinical benefits of emerging obesity treatments, including their impact on cardiometabolic and kidney health outcomes.
2. **Evaluate** strategies to optimize patient outcomes during treatment with obesity medications, including balancing nutrition, preserving lean mass, and mitigating side effects.
3. **Apply** evidence-based, individualized approaches to obesity care that focus on long-term health improvements beyond weight reduction alone.

Excess and Dysfunctional Adipose Tissue Drive CV Disease in the CKM Syndrome



Ndumele et al. Circulation. 2023;148(20):1606-1635

Projected Prevalence of Adverse Cardiovascular Health Factors in US Adults 2020 to 2050



Obesity 43.1% to 60.6%
Diabetes 16.3% to 26.8%

Joynt Maddox et al. Circulation. 2024;149:e00–e00

Magnitude of Weight Reduction and Health Improvements

- Blood glucose
- Triglycerides

3%

- HDL-Cholesterol[1]
- Systolic and diastolic blood pressure
- Hepatic steatosis measured by MRS[2]
- Patient Reported Outcome Measures
  - Symptoms of urinary stress incontinence[3]
  - Measures of sexual function[4,5]
  - Quality of life measures (IWQOL)[6]

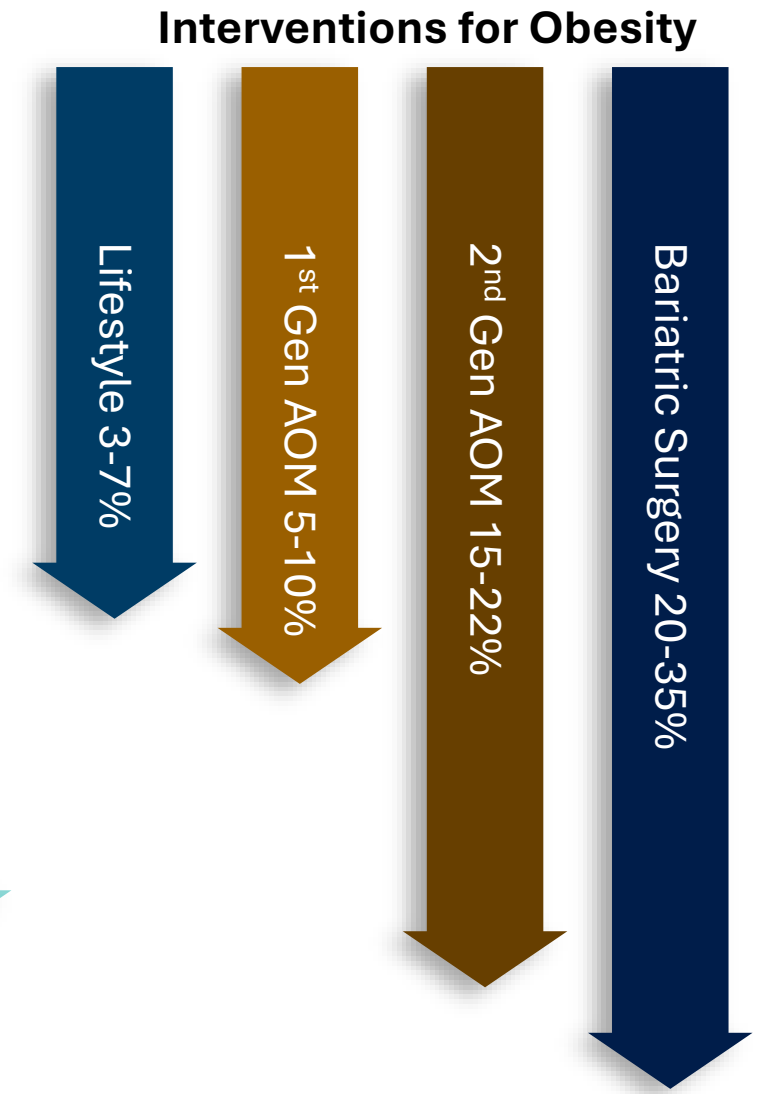
5%

- NASH (MASLD/MASH) Activity Score on biopsy[7]
- OSA Apnea-Hypopnea Index[8]

10%

- Remission of T2D, reduction in CV events, mortality

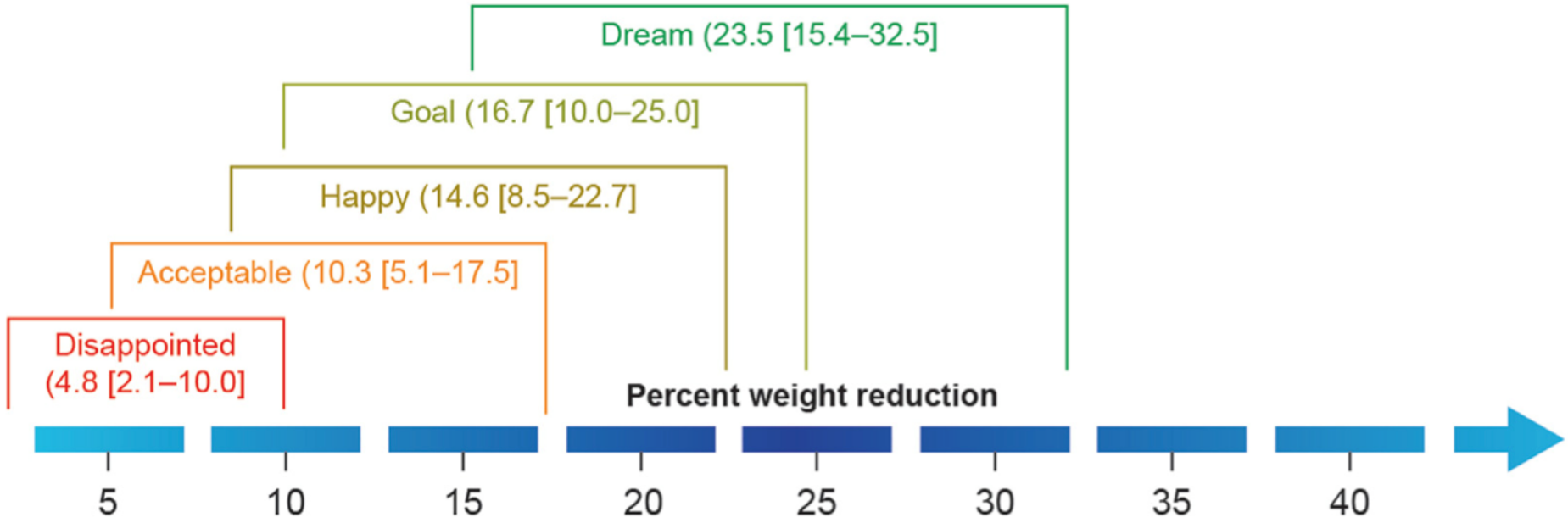
≥15%



1. Wing RR et al. *Diabetes Care*. 2011;34:1481-1486. 2. Lazo M et al. *Diabetes Care*. 2010;33:2156-2163. 3. Phelan S et al. *J Urol*. 2012;187:939-944.
4. Wing RR et al. *Diabetes Care*. 2013;36:2937-2944. 5. Wing RR et al. *J Sex Med*. 2010;7:156-165. 6. Engel SG et al. *Obes Res*. 2003;11:1207-1213.
7. Promrat K et al. *Hepatology*. 2010;51:121-129. 8. Foster GD et al. *Arch Intern Med*. 2009;169:1619-1626. 9. Després JP et al. *BMJ*. 2001;322:716-720.

Patient Preferred Magnitude of Weight Reduction

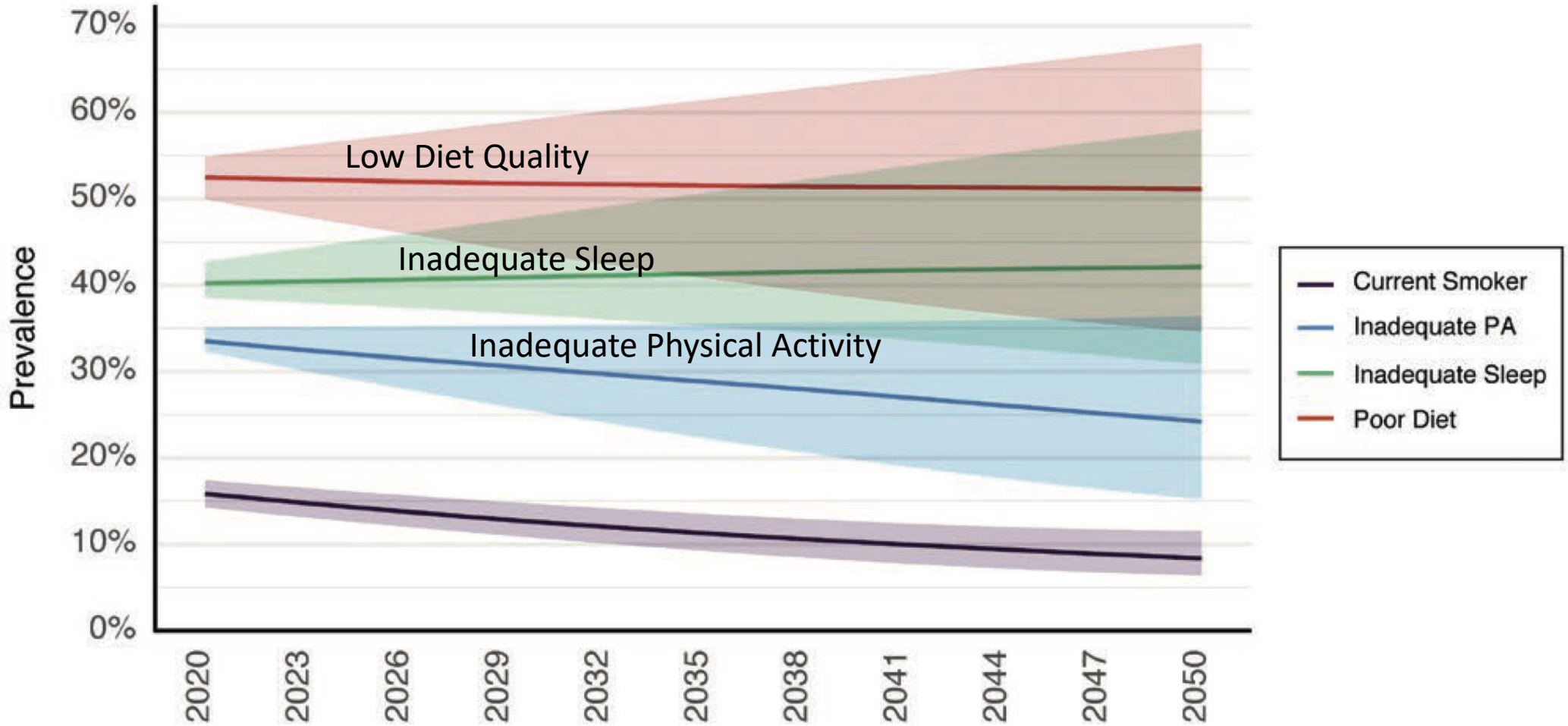
OBSERVE Study



Preferred percent weight reduction by weight class					
BMI categories*	**Dream**	**Goal**	**Happy**	**Acceptable**	**Disappointed**
Overweight	12.3 (8.1–17.5)	8.9 (5.3–14.4)	7.4 (3.6–11.3)	4.4 (1.9–8.4)	2.3 (0.7–4.2)
Class I obesity	20.0 (13.5–26.9)	13.3 (8.5–20.0)	12.5 (6.8–18.3)	8.7 (4.4–13.6)	3.9 (1.8–6.9)
Class II obesity	27.2 (20.4–34.8)	20.0 (14.2–27.3)	17.5 (12.4–24.3)	13.0 (8.9–19.7)	6.5 (3.5–12.5)
Class III obesity	36.9 (28.0–45.1)	27.0 (20.0–36.5)	24.0 (15.5–32.7)	17.5 (10.6–27.7)	9.1 (4.8–16.5)

Gudzune et al. Endocrine Practice. 2024 Jun 18

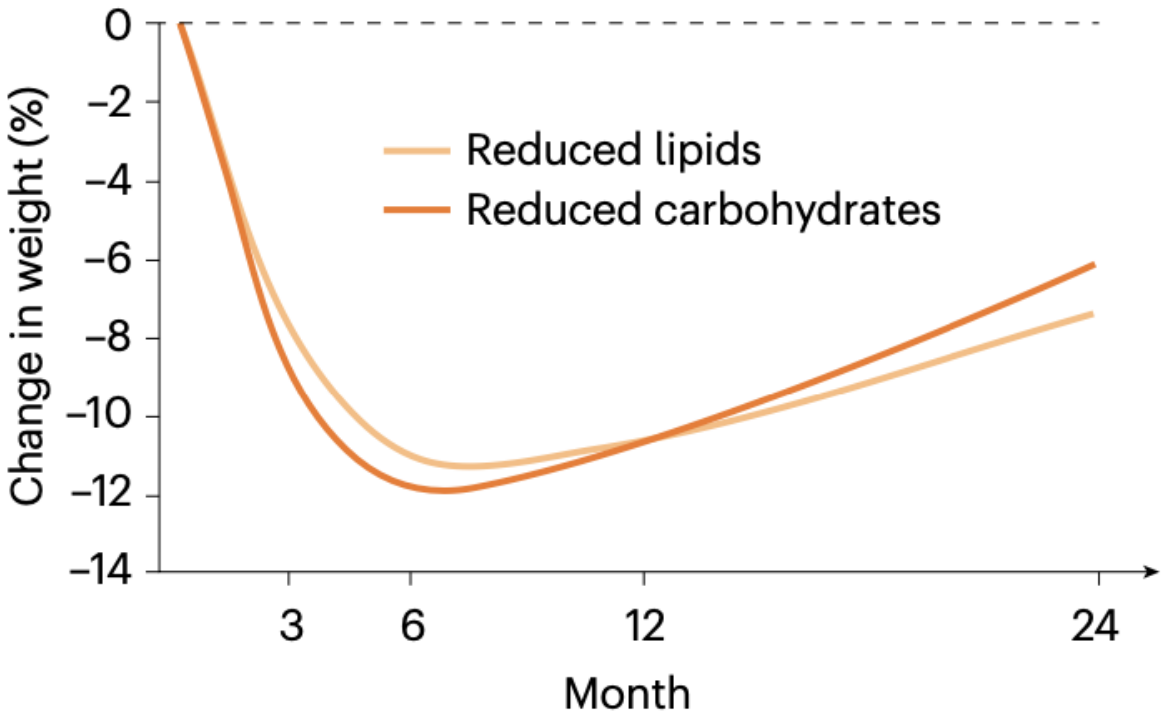
Prevalence of Adverse Health Behaviors in US Adults 2020 to 2050



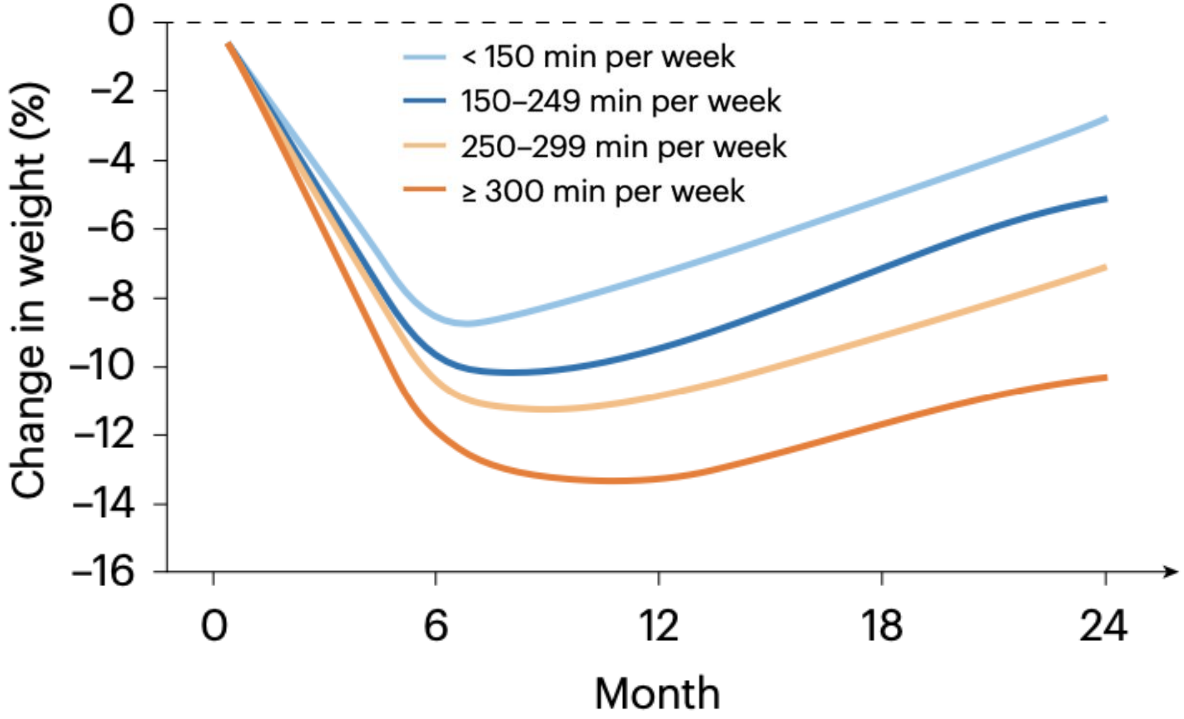
Joynt Maddox et al. Circulation. 2024;149:e00–e00

Weight Loss by Diet and Physical Activity

Dietary Restriction

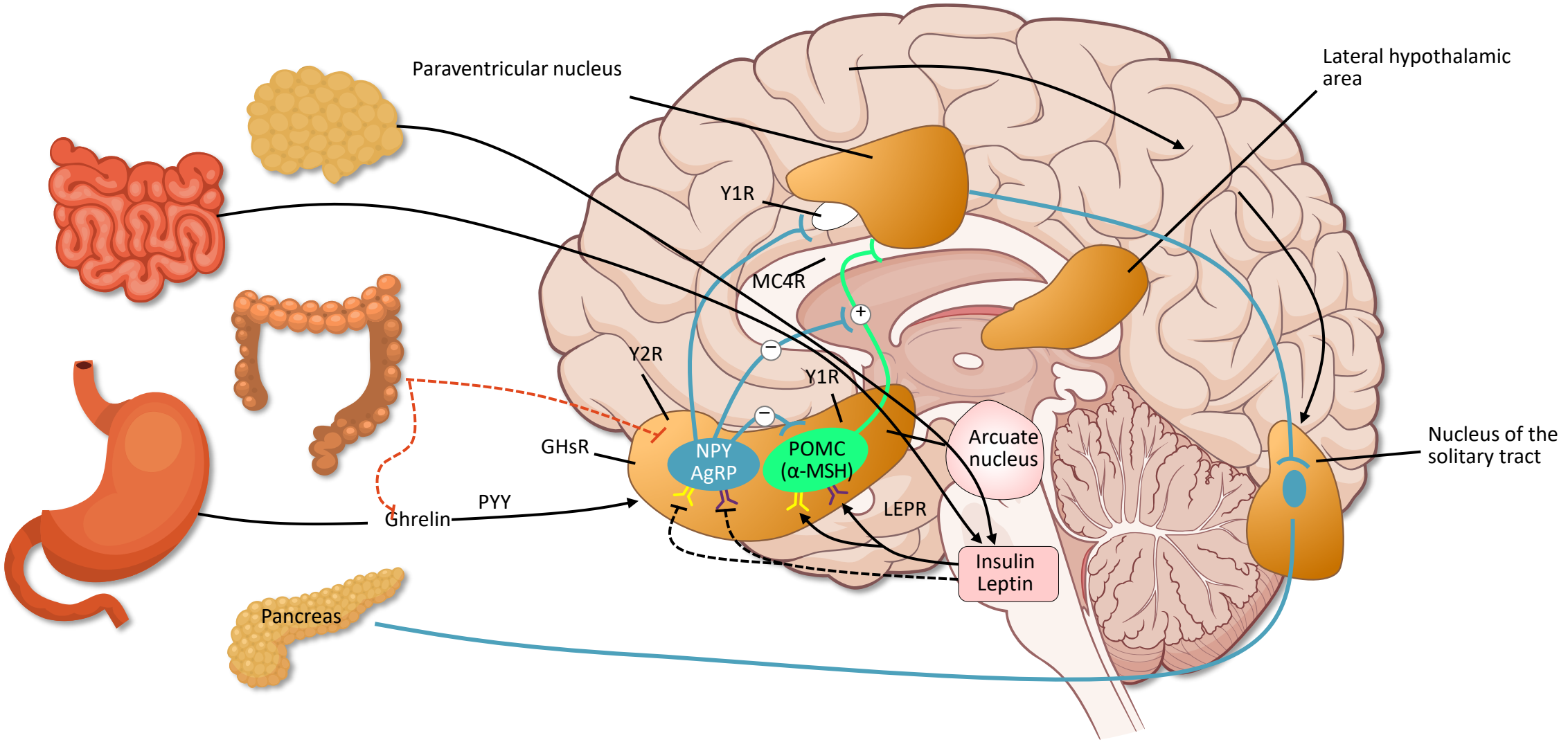


Increased Physical Activity



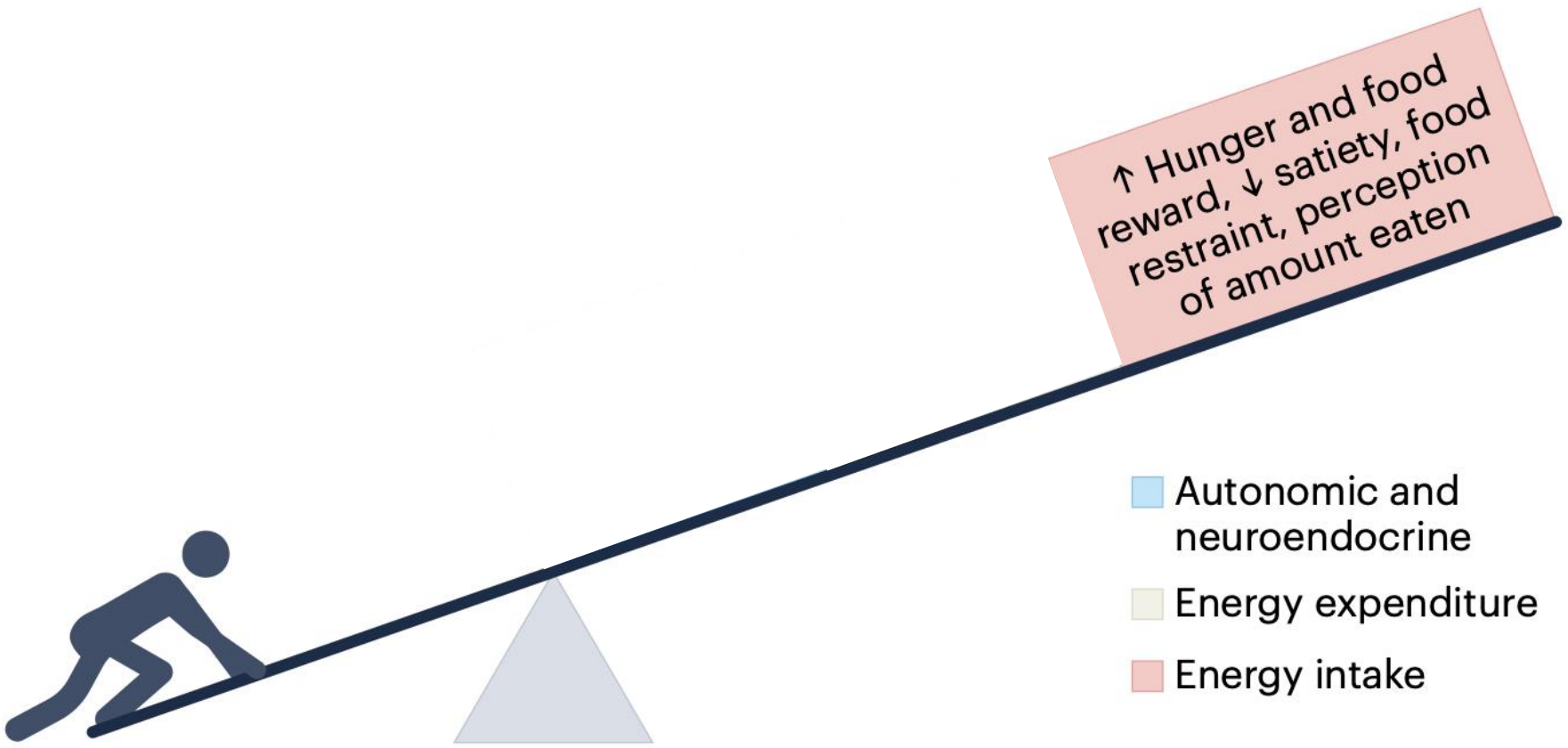
Rosenbaum M, Foster G. Nat Metab. 2023 Aug;5(8):1266-1274

Dysregulation of Energy Balance System



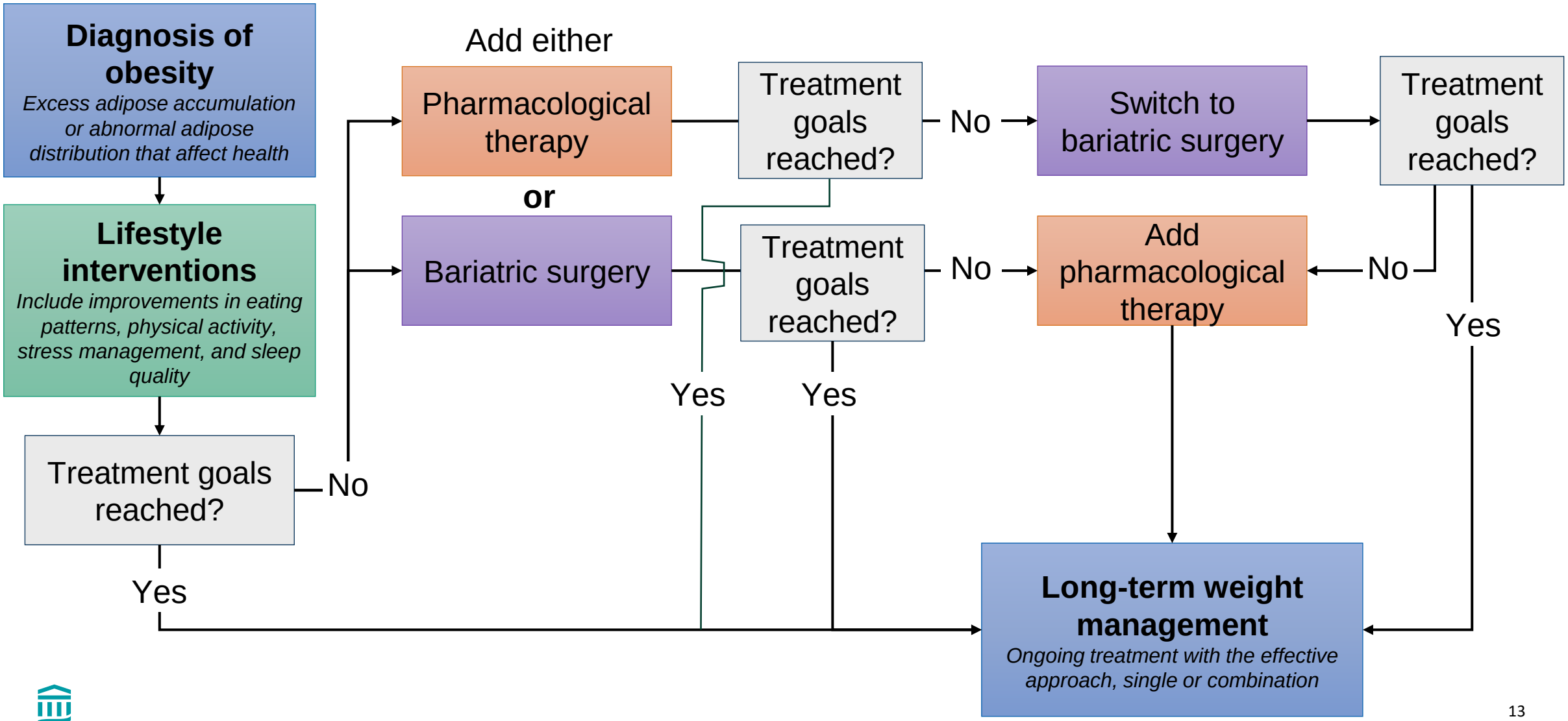
Apovian. J Clin Endocrinol Metab. 2015;100:342; Schwartz. Endocr Rev. 2017;38:267.

Systems Favoring Weight Regain



Rosenbaum M, Foster G.Nat Metab. 2023 Aug;5(8):1266-1274

Conceptual Approach to Treating Obesity

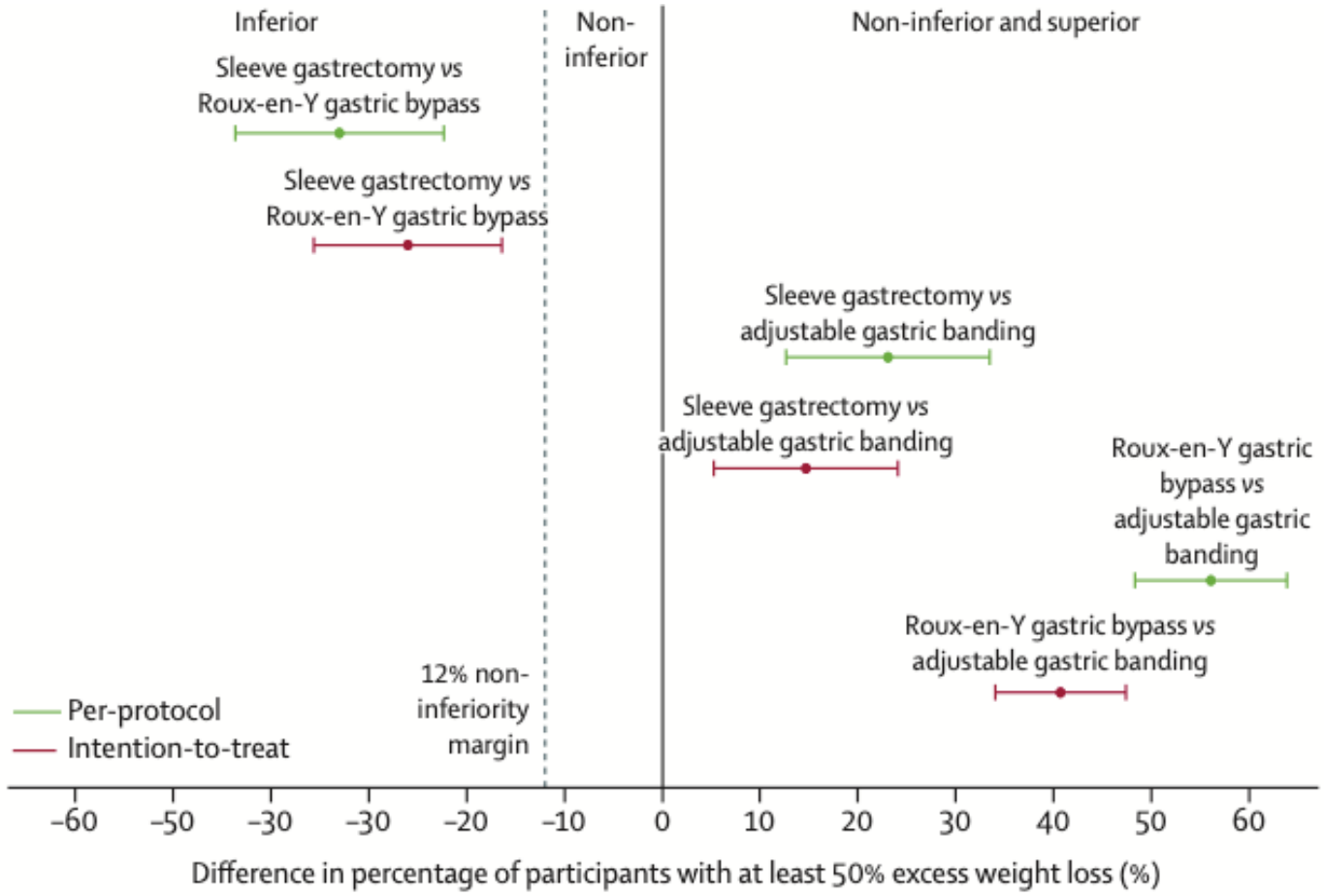


Lingvay I et al. Lancet. 2024;404:972-987.

Gastric Bypass, Adjustable Band or Sleeve

By-Band-Sleeve– multicentre, open label, three-group, randomised controlled trial

Percentage excess weight loss at 3 years

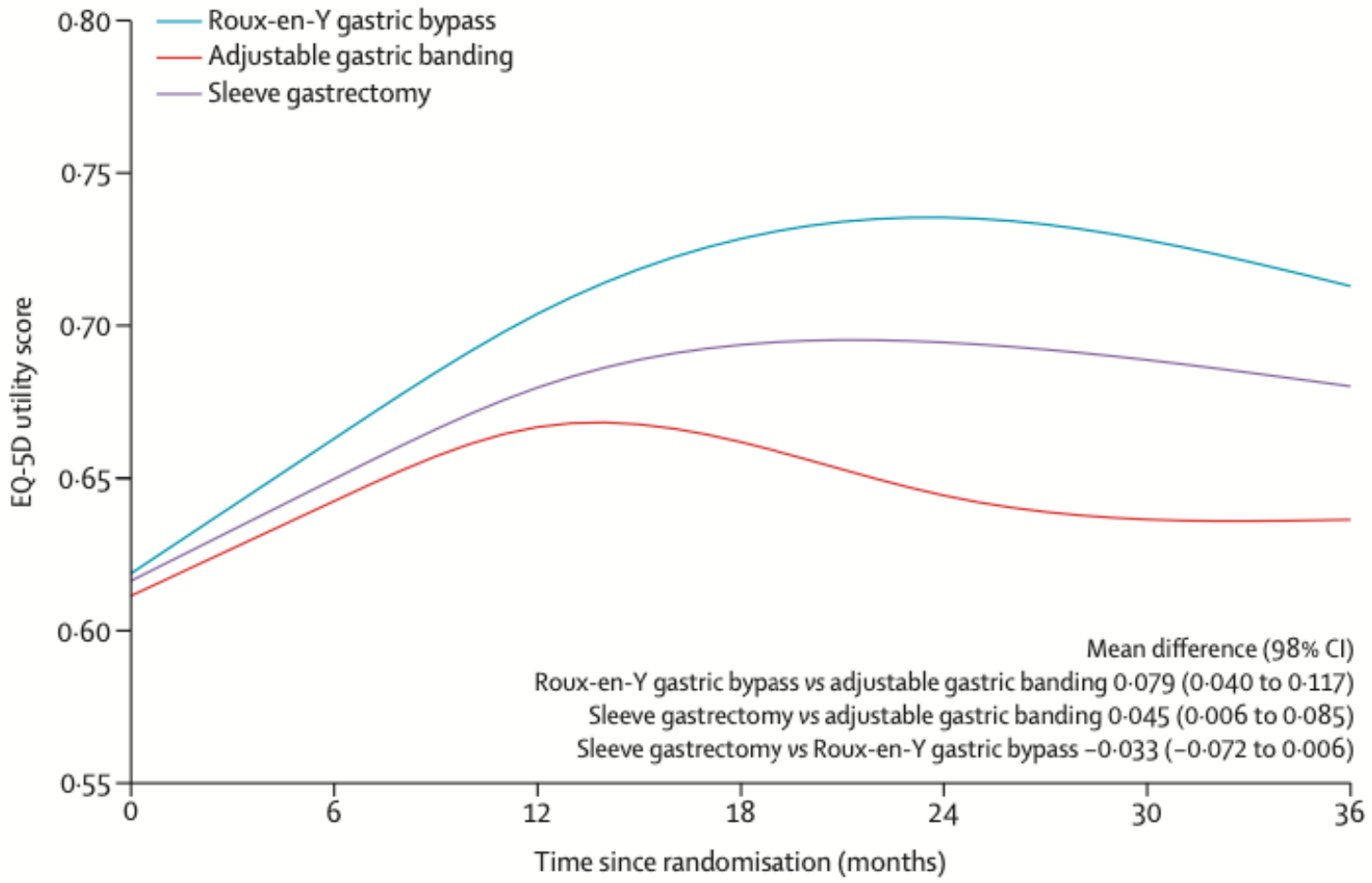


Blazeby et al. The By-Band-Sleeve Collaborative Group. Lancet Diabetes Endocrinol 2025 Published Online March 31, 2025

Gastric Bypass, Adjustable Band or Sleeve

By-Band-Sleeve– multicentre, open label, three-group, randomised controlled trial

EQ-5D utility score to 3 years



Blazeby et al. The By-Band-Sleeve Collaborative Group. Lancet Diabetes Endocrinol 2025 Published Online March 31, 2025

FDA-Approved Obesity Medications

Bupropion/ Naltrexone

Bupropion blocks reuptake of dopamine and norepinephrine in various brain regions, including the mesolimbic reward pathway, prefrontal cortex, and hypothalamus.
Naltrexone inhibits opioids in the mesolimbic dopamine system.

↑ DA/NE

DA/MOP-R

Phentermine-Topiramate

Affects various brain regions involved in mood regulation, including the cortex, hippocampus, and amygdala.

↑ NE/DA/5-HT

GABA-R and CAI

Phentermine

Increases the release of norepinephrine, dopamine and serotonin in the hypothalamus.

↑ NE/DA/5-HT

GLP-1 RA and dual GIP/GLP-1 RA

Liraglutide
Semaglutide

GLP-1 RA

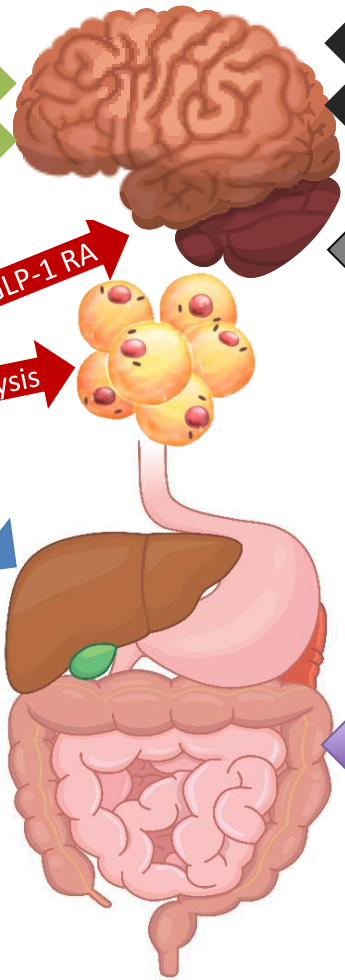
Tirzepatide

GIP/GLP-1 RA

↓ GASTRIC EMPTYING

↓↑ Lipolysis

↓ GASTRIC EMPTYING



GLP-1 RA

Act centrally in the brainstem, hypothalamus, and reward centers of the brain to increase glucose-dependent insulin secretion, inhibit glucagon secretion, and delay gastric emptying.

GIP/GLP-1 dual RA

Augment the central acting effect on appetite suppression.

LIPASE INHIBITION

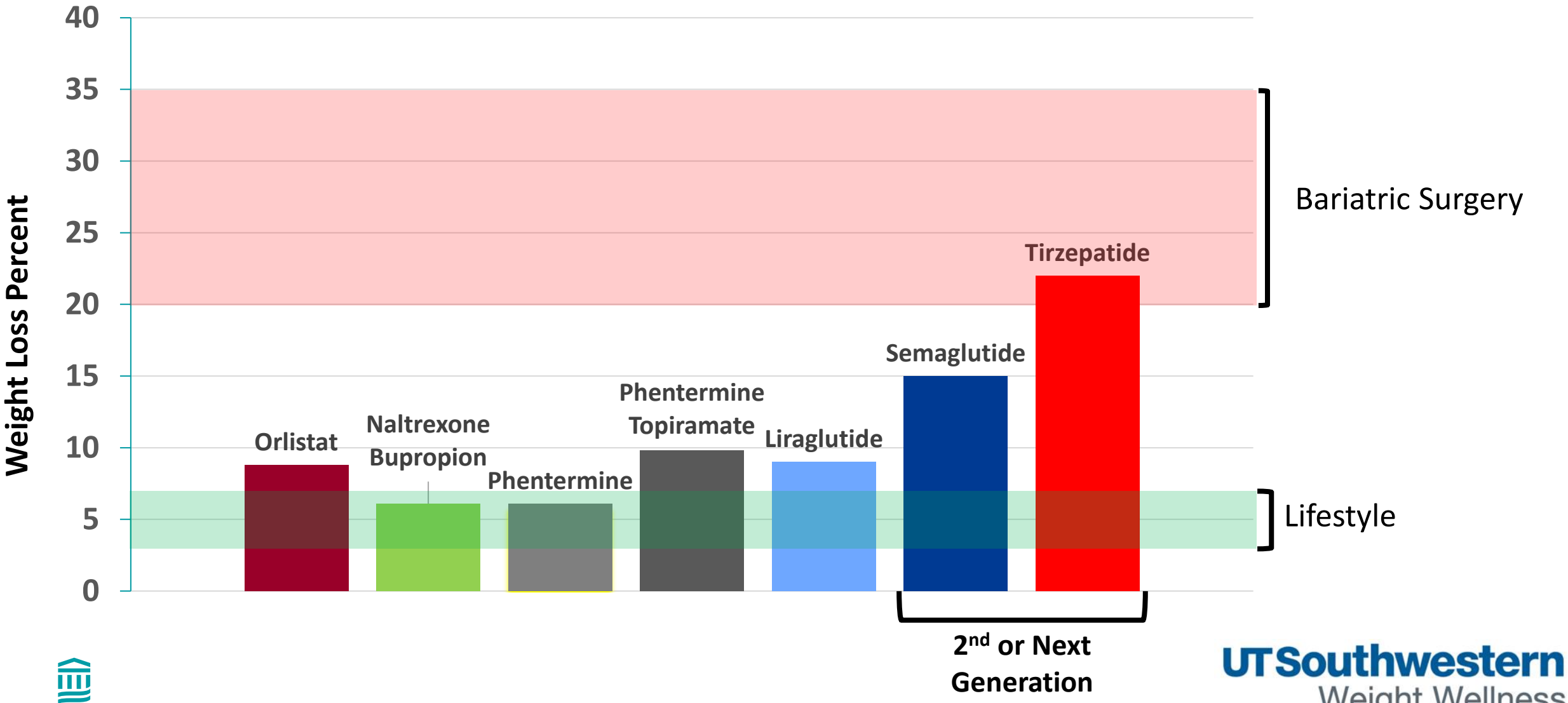
Orlistat

Deactivates pancreatic and gastric lipases that facilitate fat absorption in the small intestine.

Gudzune K, Kushner R, JAMA. 2024;332(7):571-584

UT Southwestern Weight Wellness

Effectiveness of Obesity Medications vs. Lifestyle and Bariatric Surgery for Treating Obesity



UT Southwestern
Weight Wellness

Significant Sustained Weight Loss With Non-GLP-1RA

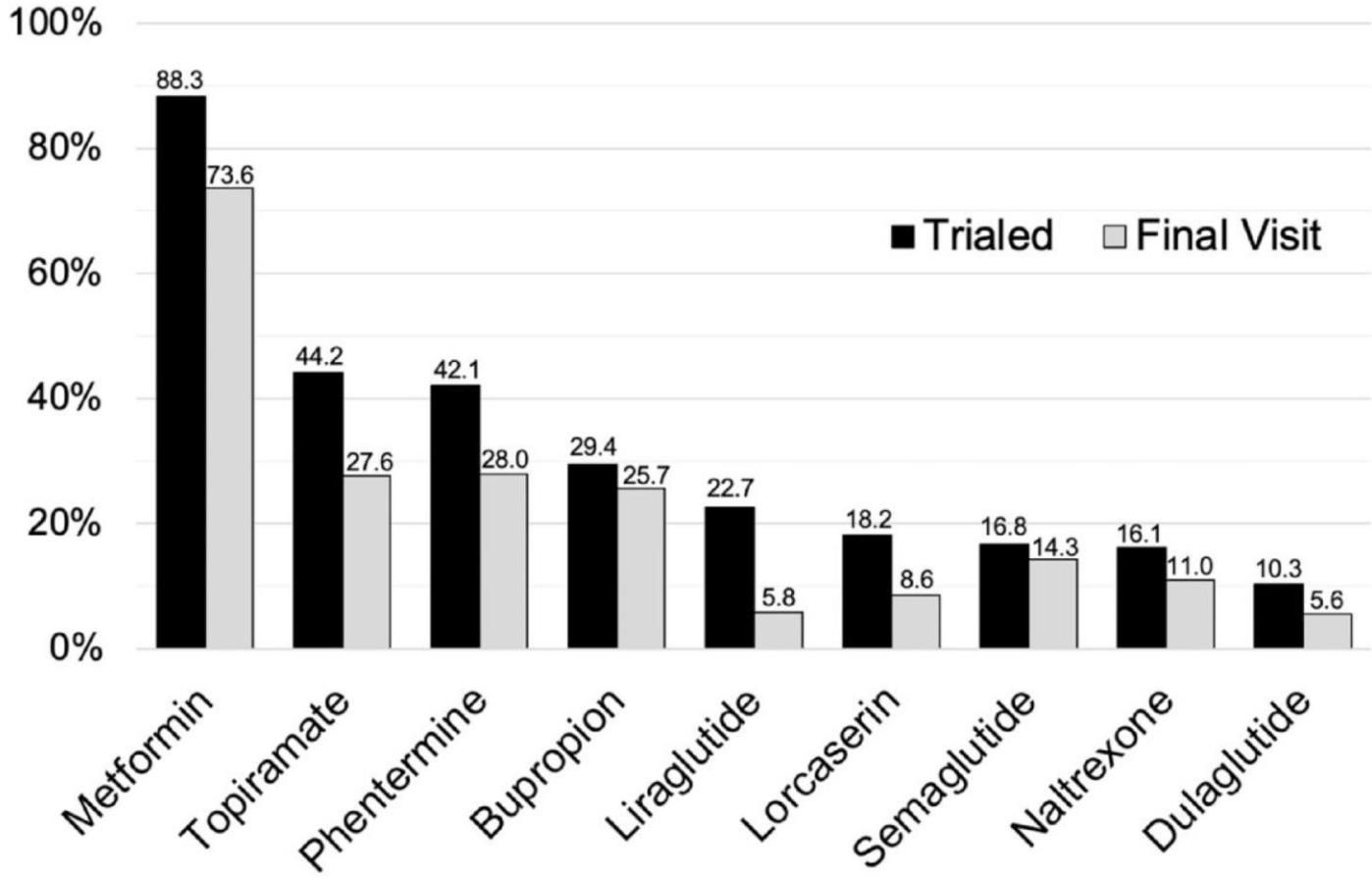
Average weight loss 10.4% with a mean follow-up of 4.4 years

At Final Visit
- Mean OMs at final visit: 2.1
- 65.0% taking ≥2 OM
- Mean number of OM trialed: 4.3

Patients who Maintained ≥10% WL
92 unique OM combinations
13% metformin monotherapy
9% metformin, phentermine, topiramate

Predictors of ≥10% WL
- More clinic visits OR 1.04, *P* = .002
- Metformin OR 1.91, *P* = .009
- Topiramate OR 2.50, *P* < .001
- Bupropion OR 2.06, *P* = .013

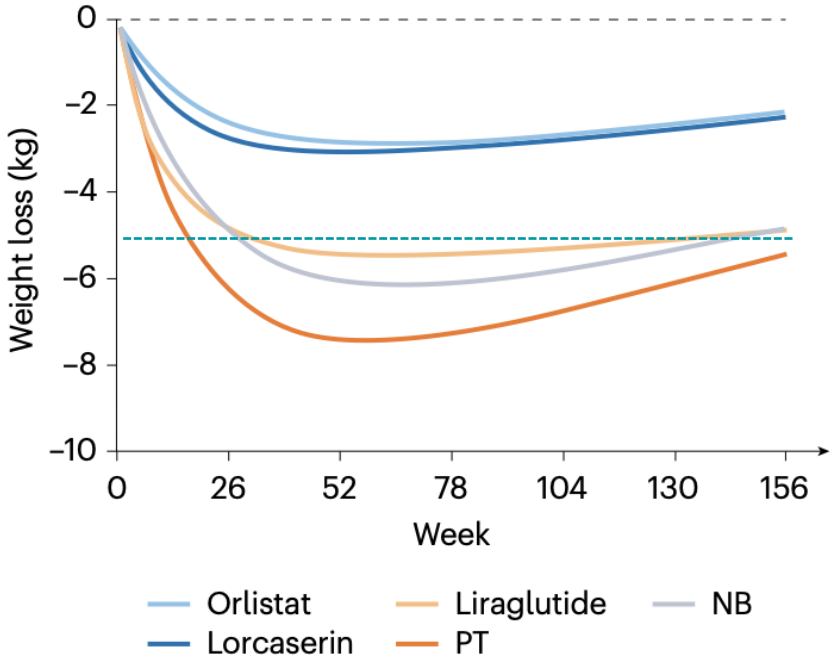
Frequency of Obesity Medications Trialed



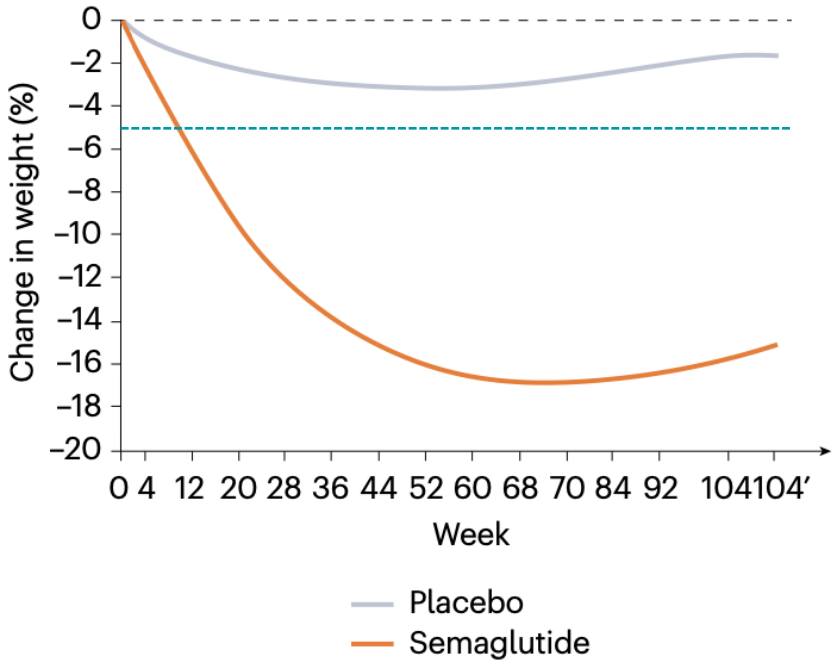
Weintraub et al. JCEM, 2023, 108, e832–e841

Weight Loss with Obesity Medications

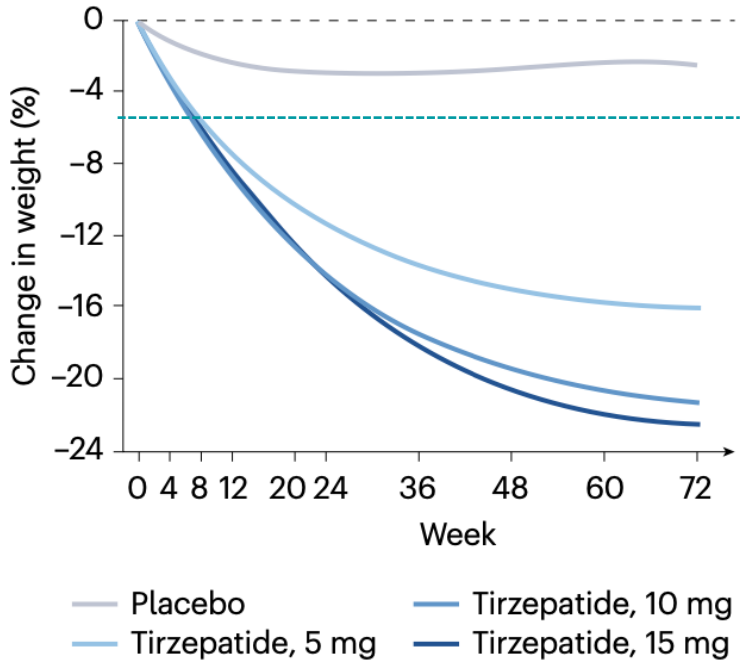
1st Generation AOM



Semaglutide 2.4 mg



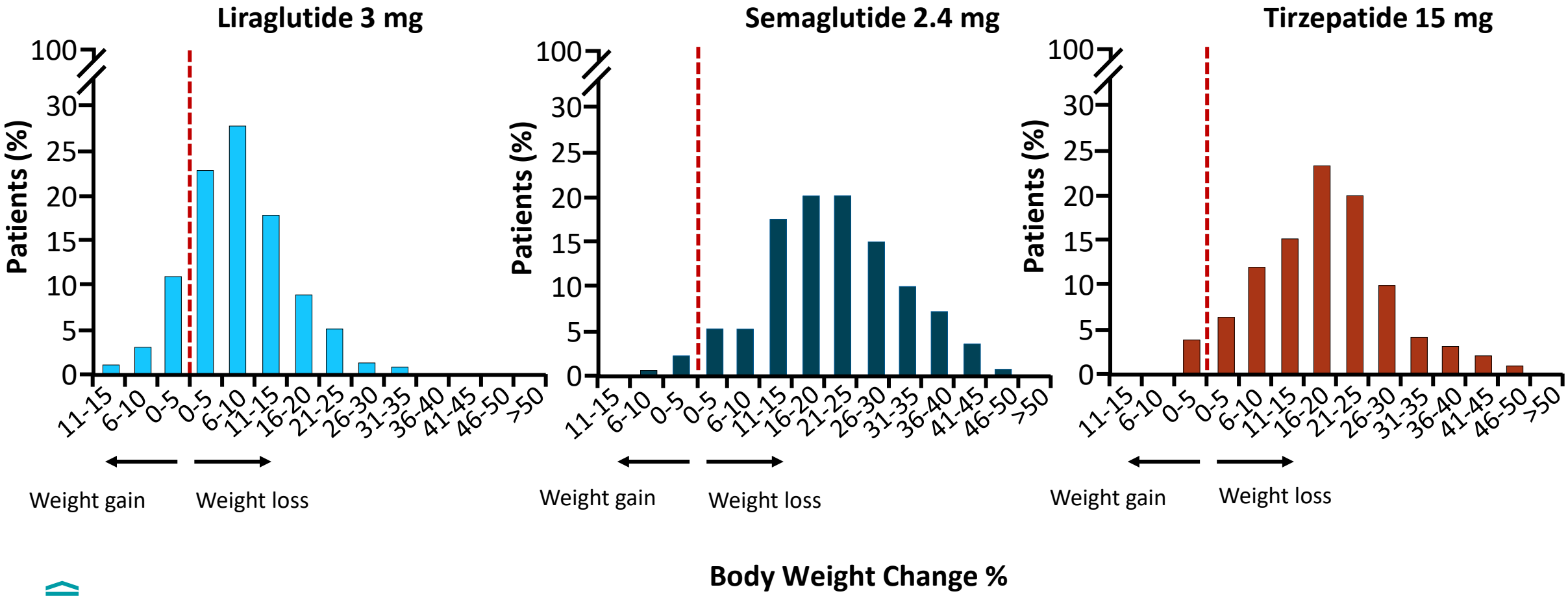
Tirzepatide



2nd Generation AOM

Rosenbaum M, Foster G. Nat Metab. 2023 Aug;5(8):1266-1274

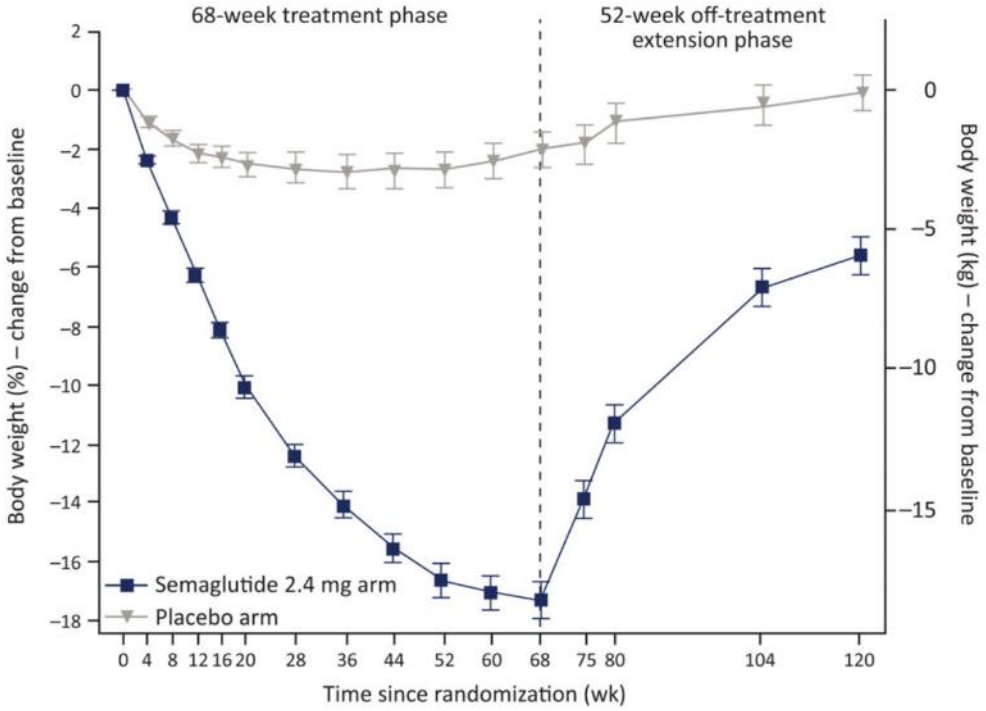
Weight Loss Varies with GLP-1 and GIP/GLP-1 RA



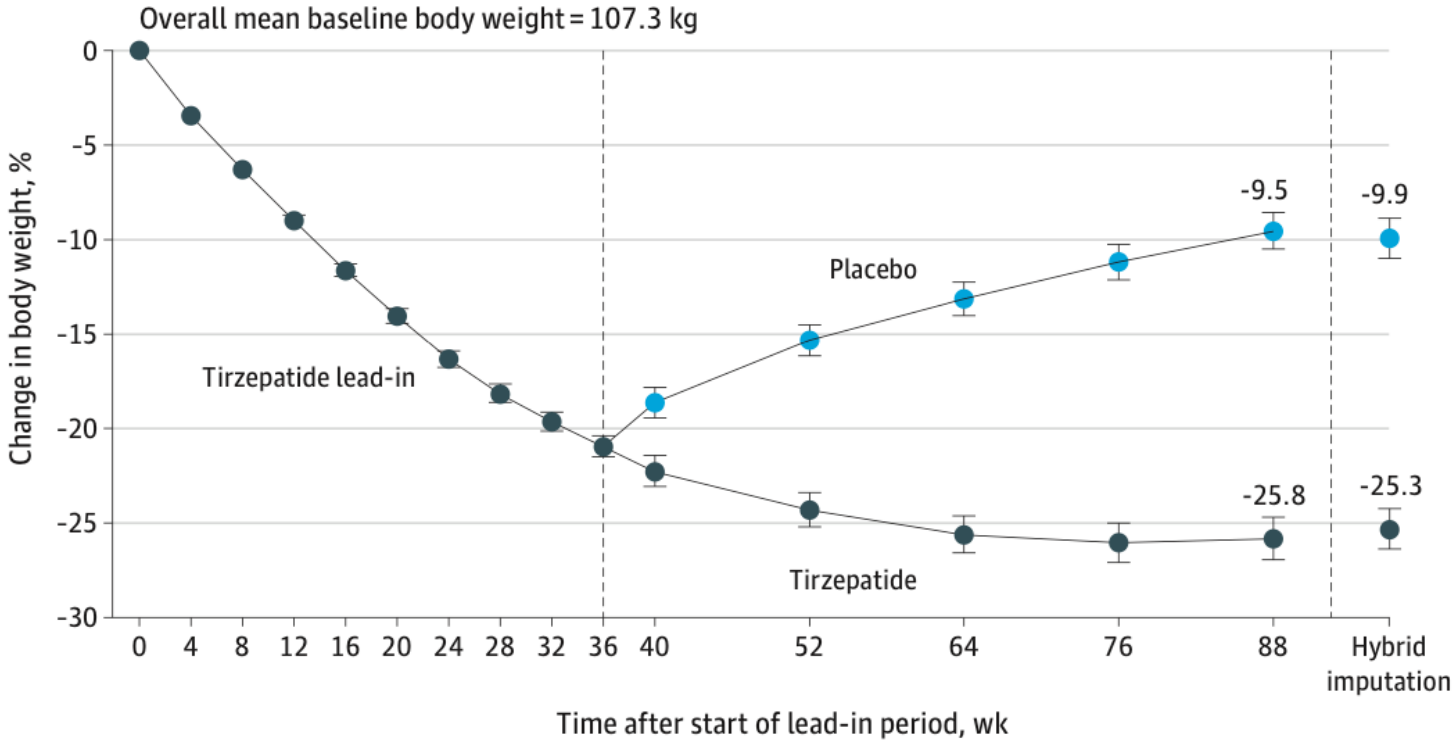
Perdomo et al. Lancet. 2023;401:1116.

Weight Recurrence Following Cessation

STEP-1 Extension Semaglutide

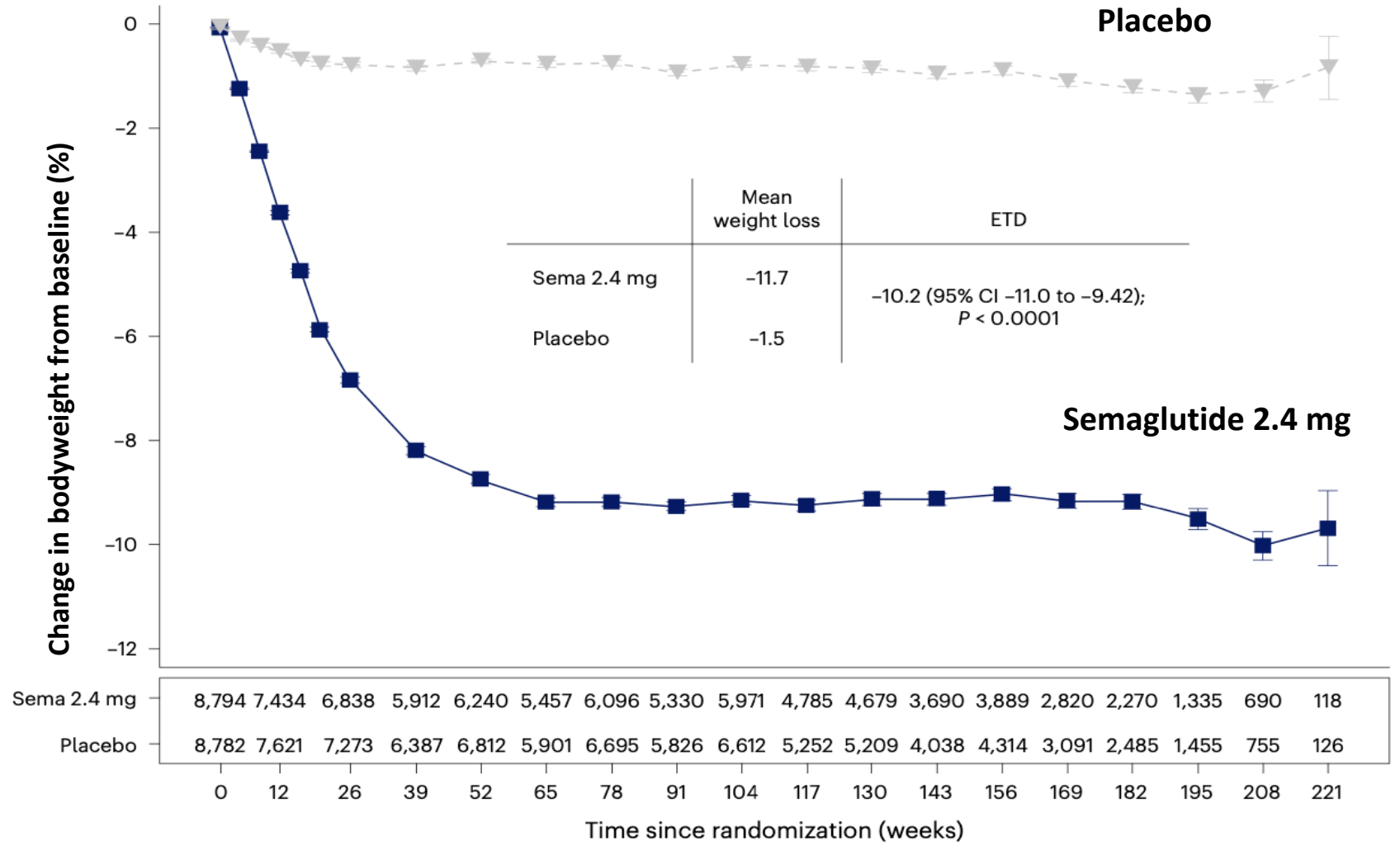


SURMOUNT-4 Tirzepatide



Wilding et al. Diabetes Obes Metab. 2022;24:1553–1564; Aronne et al. JAMA. 2024;331(1):38-48

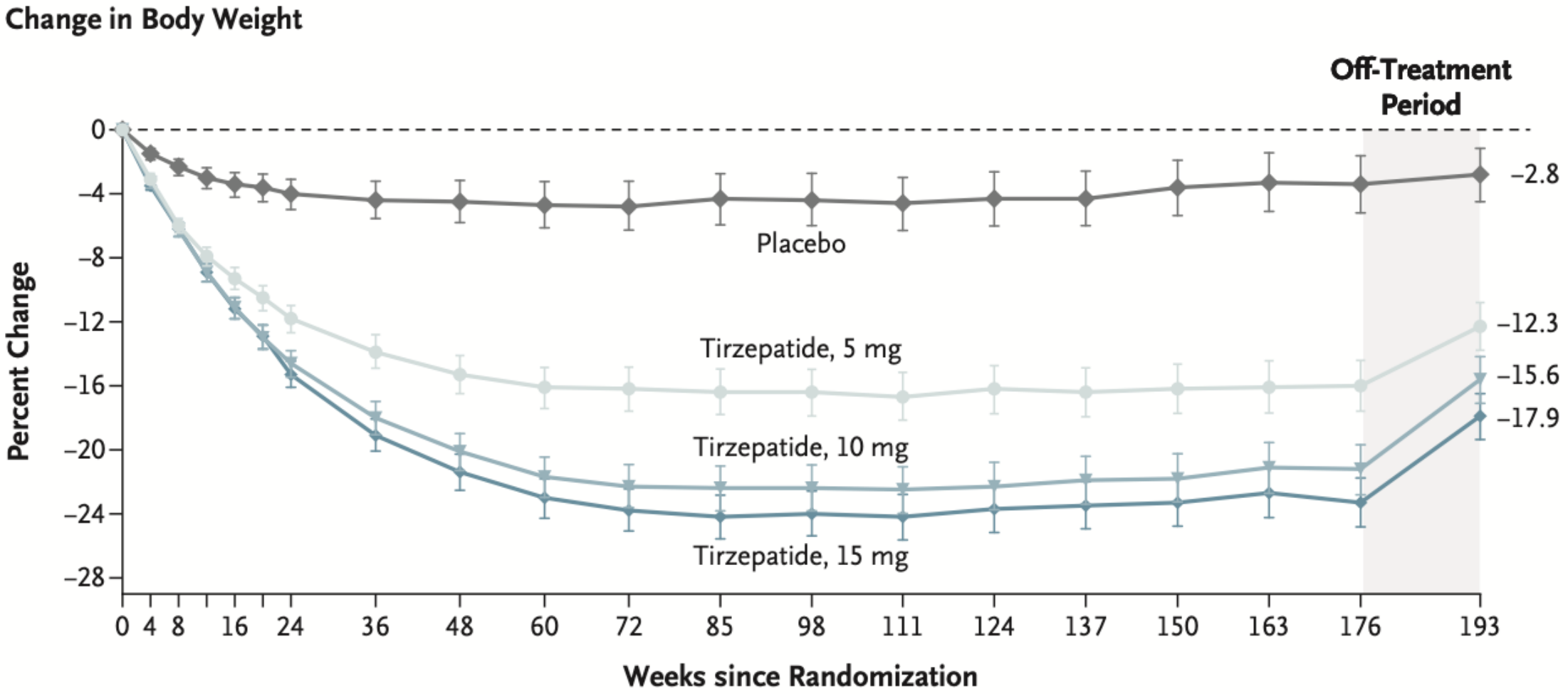
Durable Effectiveness of Semaglutide 2.4 mg



Ryan et al. Nat Med. 2024 Jul;30(7):2049-2057

Tirzepatide for Obesity and T2D Prevention

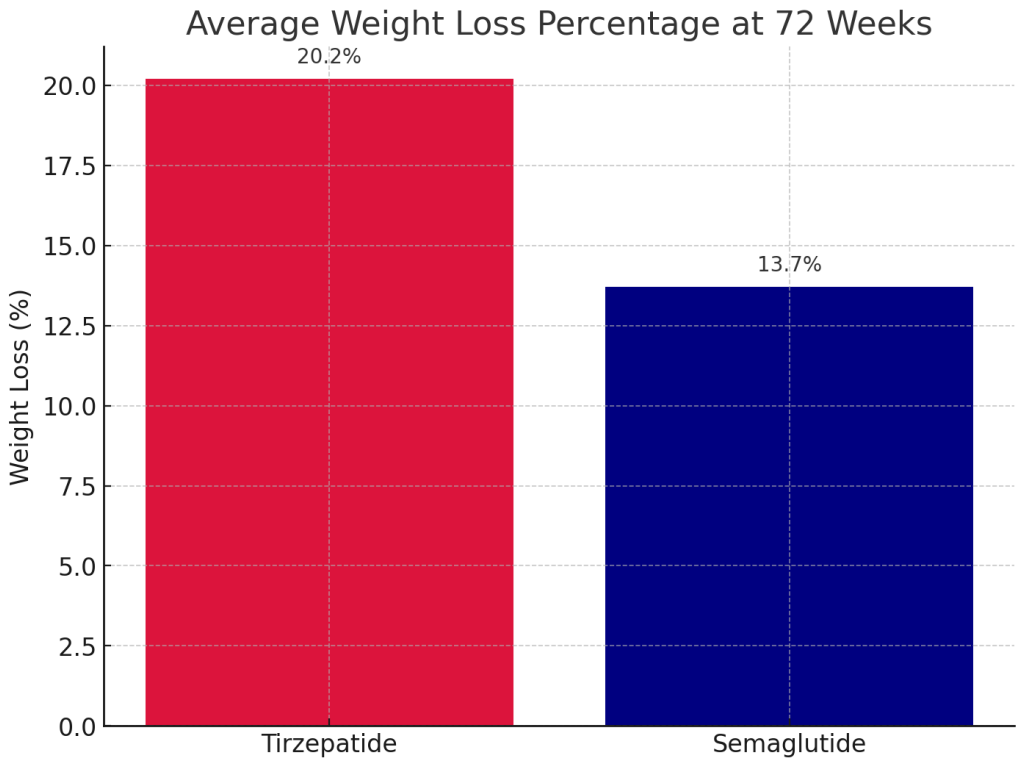
SURMOUNT-1 Trial – 3-year data on weight change and T2D Prevention

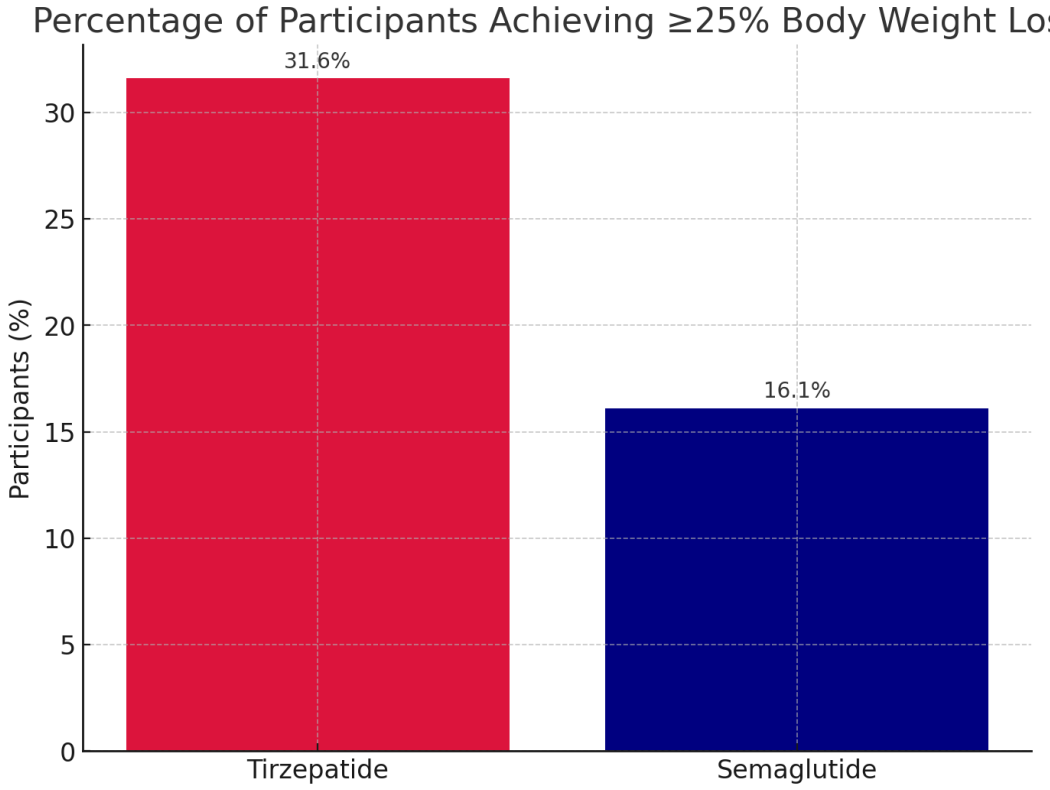


Jastreboff et al. NEJM November 13, 2024

Tirzepatide vs Semaglutide for Obesity

SURMOUNT-3 Trial – 72-week phase 3b trial in people without T2D, tirzepatide vs. semaglutide 2.4 mg





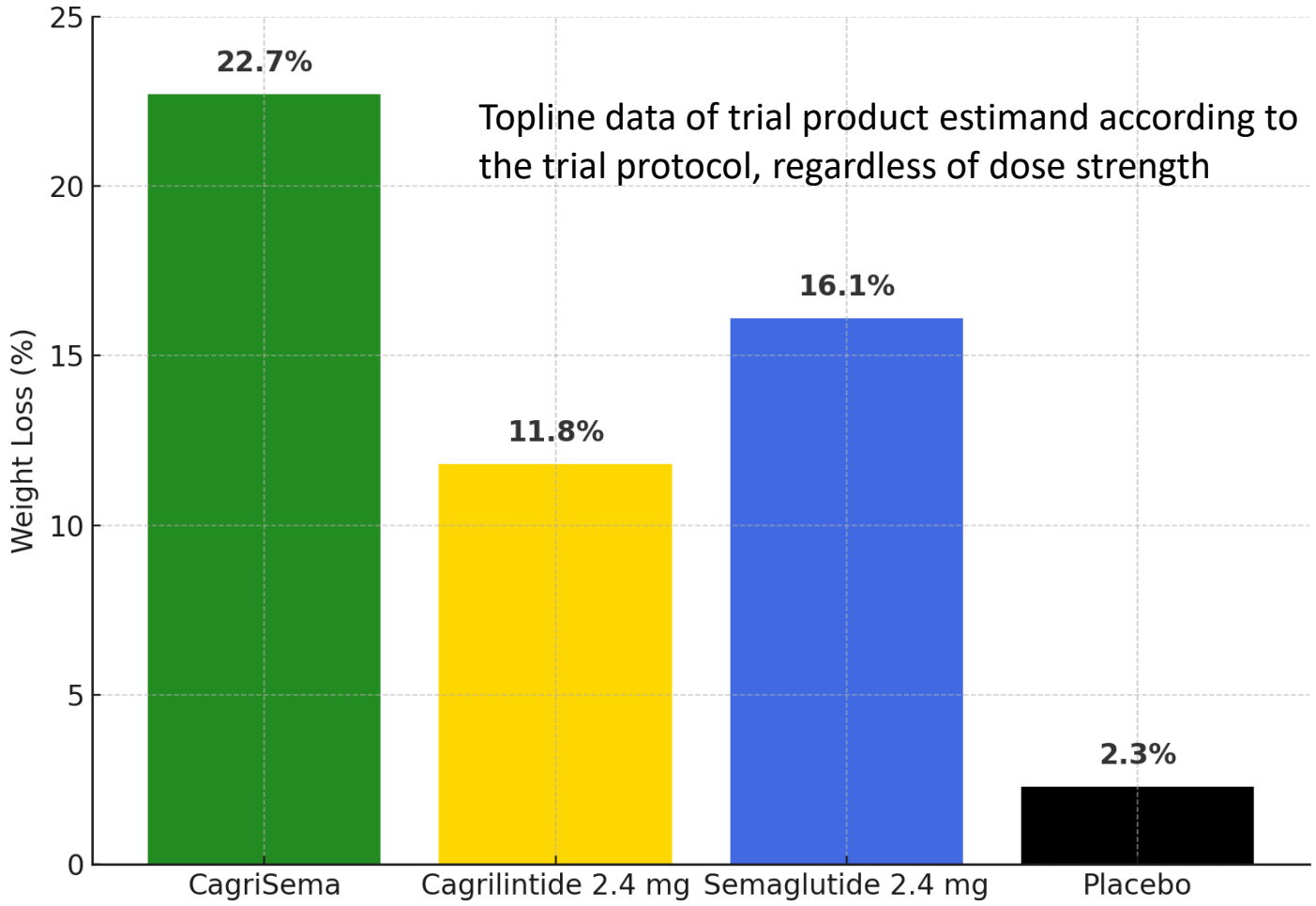
tirzepatide provided a 47% greater relative weight loss compared to semaglutide

T2D, type 2 diabetes.

Eli Lilly Company Announcement December 4, 2024 https://investor.lilly.com/news-releases/news-release-details/lillys-zepboundr-tirzepatide-superior-wegovyr-semaglutide-head

CagriSema for Obesity

REDEFINE-1 Trial – 68-week phase 3 trial in PwO without T2D, CagriSema vs. sema 2.4 mg vs. placebo

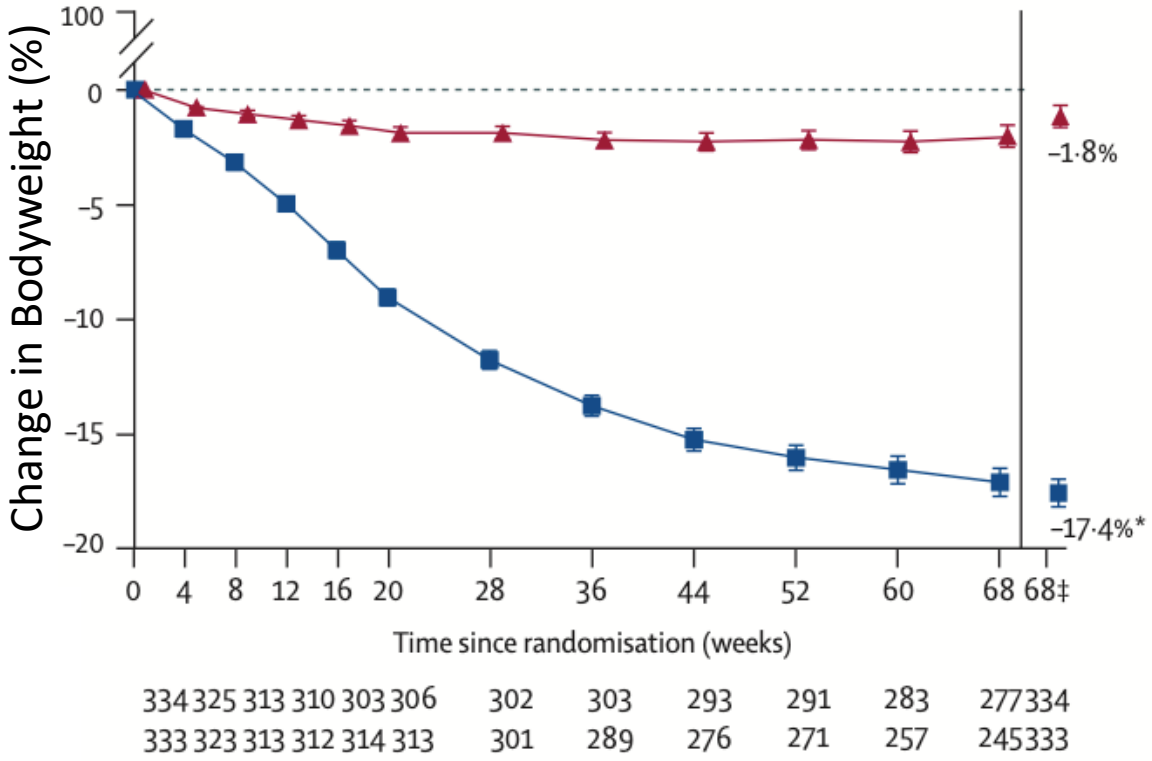


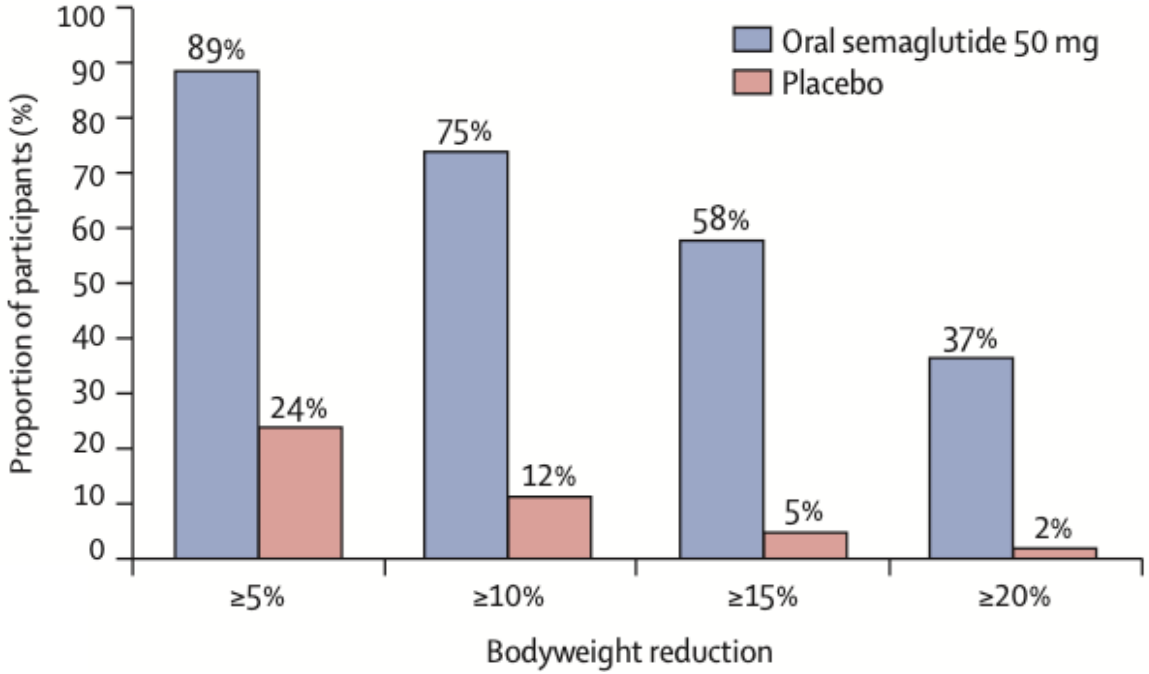
PwO, people with obesity; sema, semaglutide; T2D, type 2 diabetes.

Novo Nordisk Company Announcement December 20, 2024 - https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=915082

Oral Semaglutide for Obesity

OASIS-1 Trial – 68wk phase 3 trial in PwO without T2D – oral semaglutide 50 mg

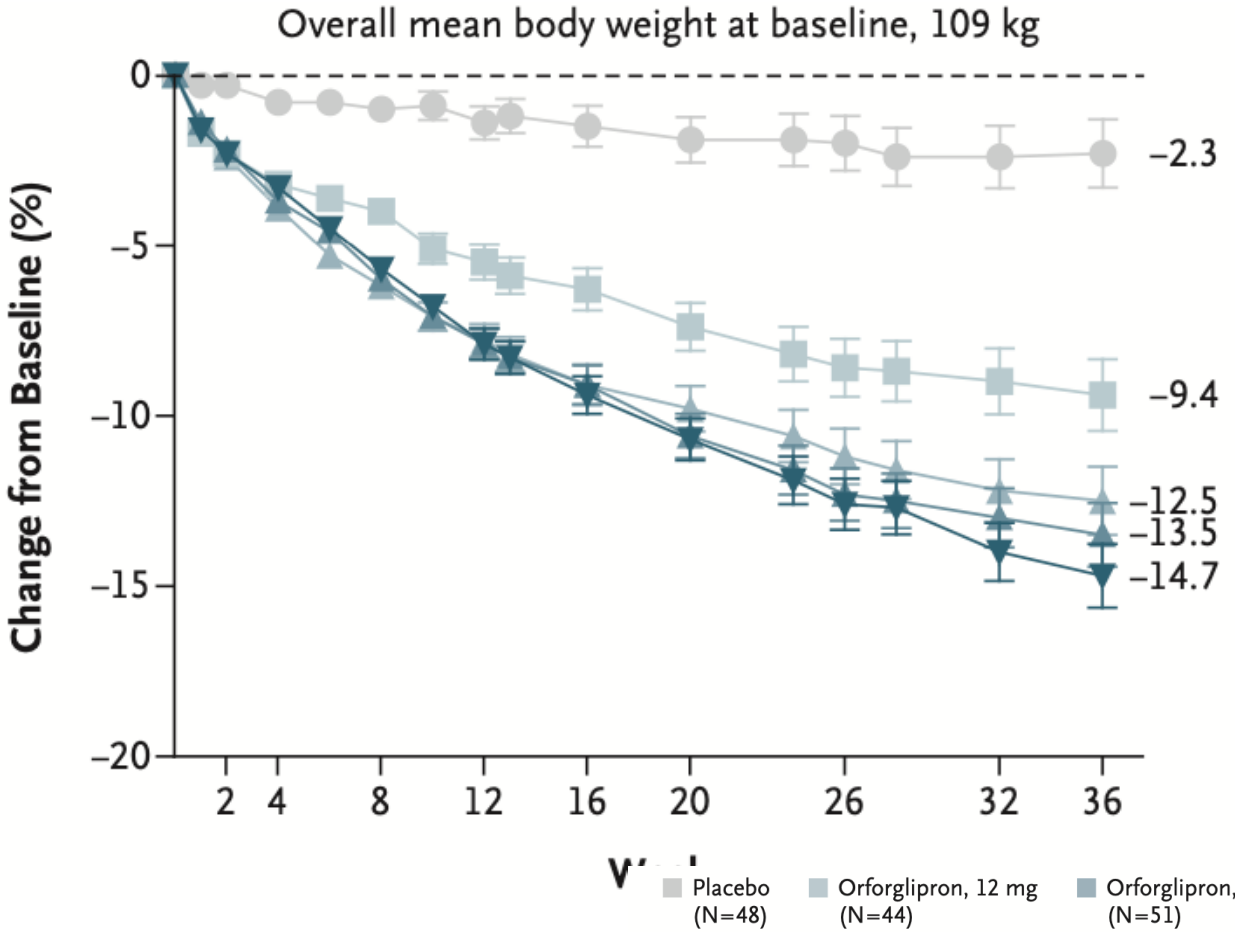




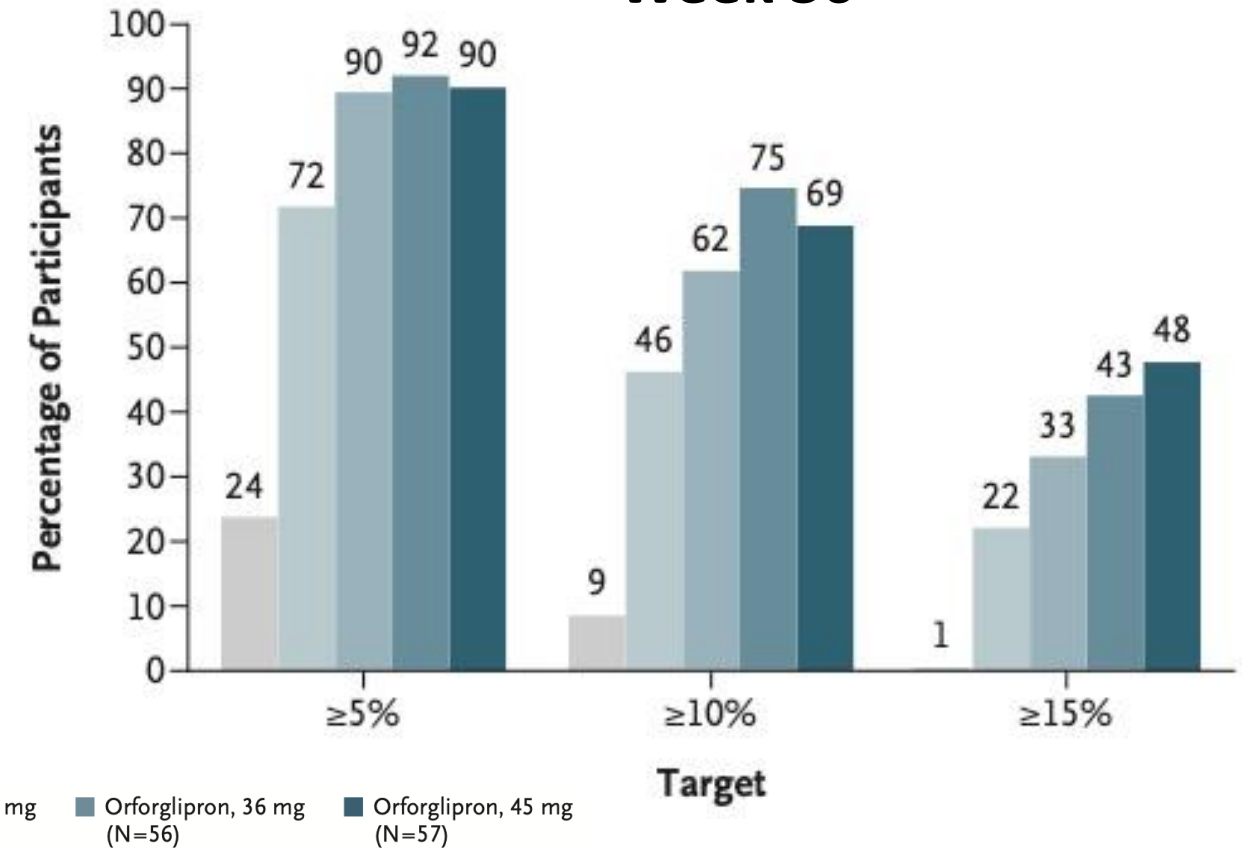
Knopp et al. Lancet. 2023 Aug 26;402(10403):705-719

Orforglipron for Obesity

Phase 2 Trial – 36wk trial in PwO without T2D – oral orforglipron (GLP-1RA)



Week 36

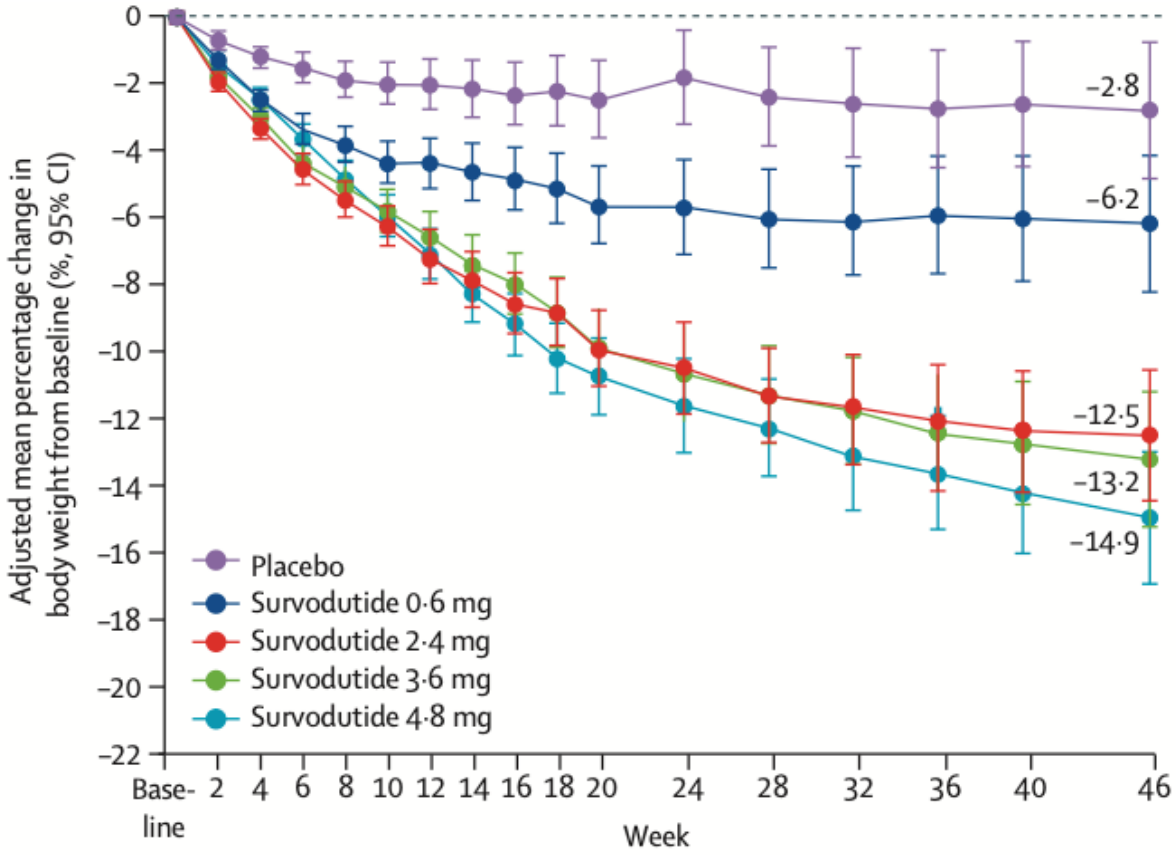


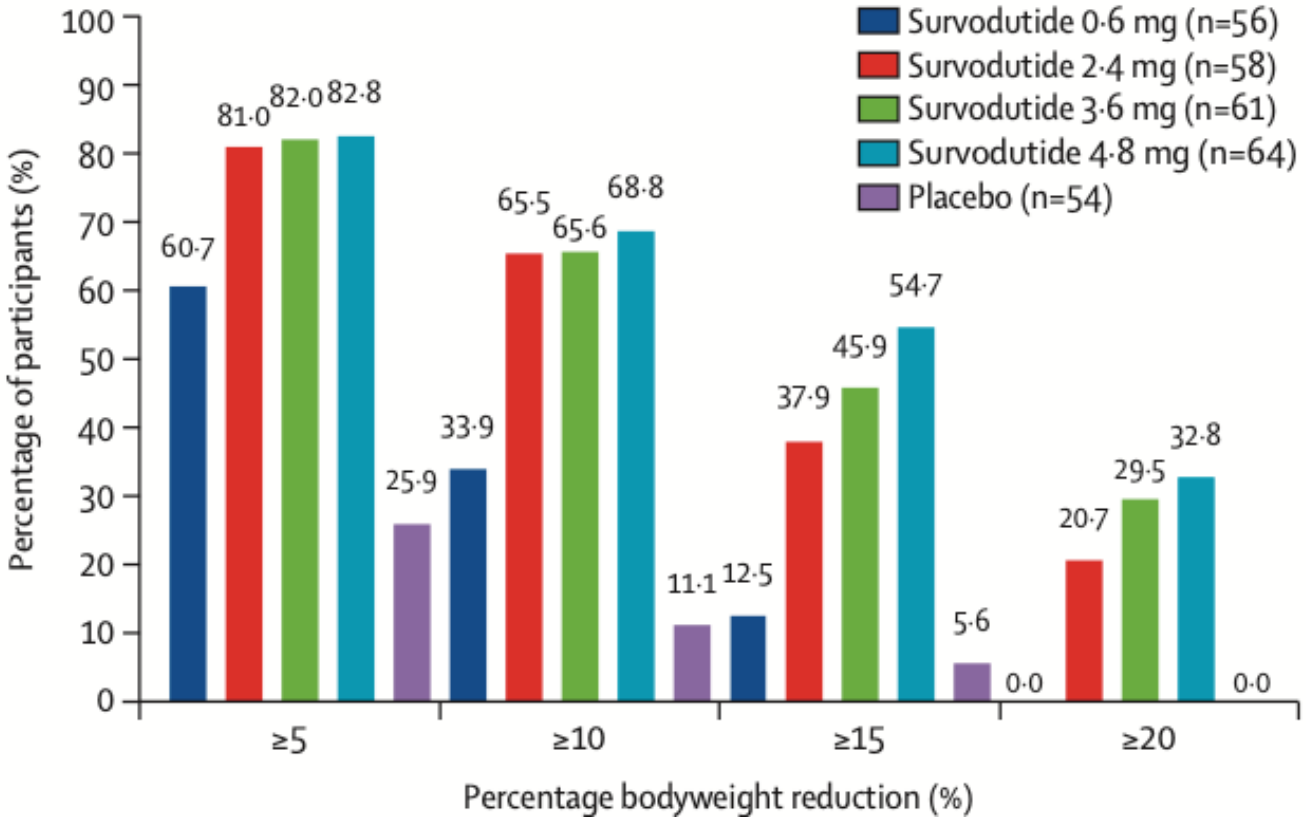
Placebo (N=48) | Orforglipron, 12 mg (N=44) | Orforglipron, 24 mg (N=51) | Orforglipron, 36 mg (N=56) | Orforglipron, 45 mg (N=57)

Wharton et al. N Engl J Med 2023;389:877-888

Survodutide for Obesity

Phase 2 Trial – 46wk trial in PwO without T2D – Survodutide (GCG/GLP1-RA)

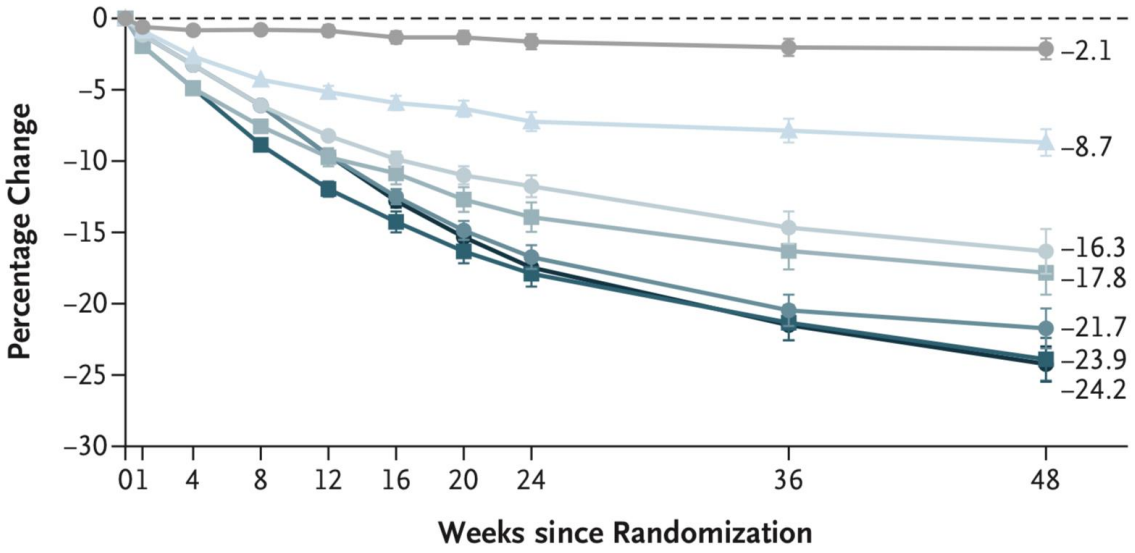


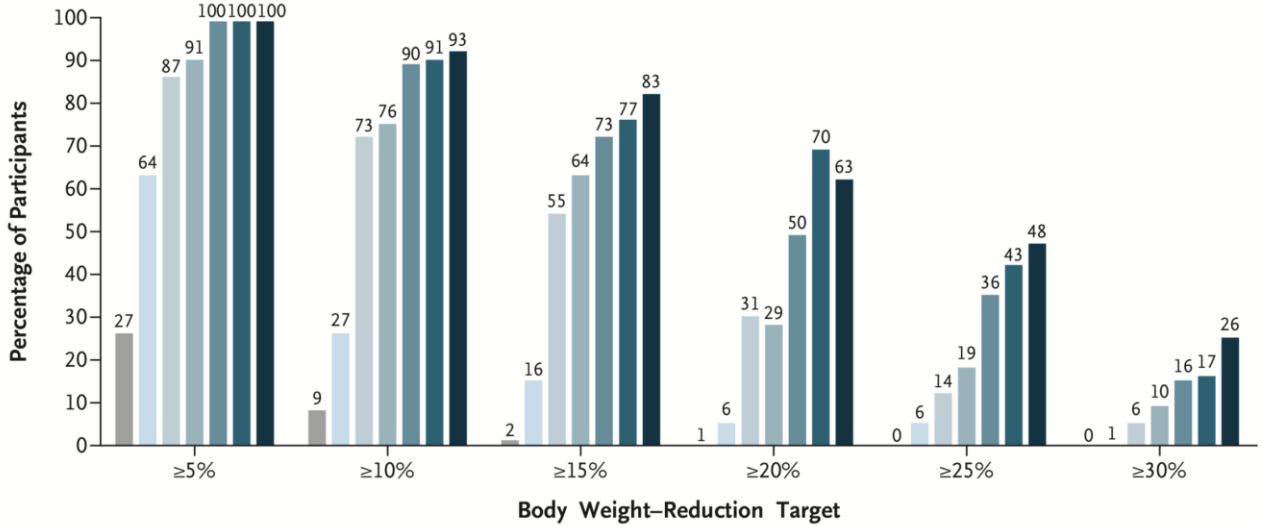


leRoux et al. Lancet Diabetes Endocrinol 2024;12:162–73

Retatrutide for Obesity

Phase 2 Trial – 48wk trial in PwO without T2D – Retatrutide (GIP/GCG/GLP1-RA)





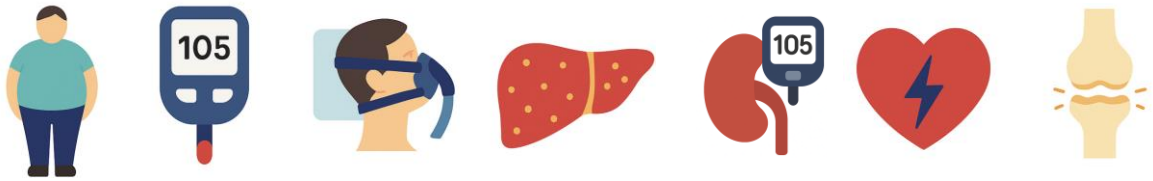
Placebo | Retatrutide, 1 mg | Retatrutide, 4 mg (ID, 2 mg) | Retatrutide, 4 mg (ID, 4 mg) | Retatrutide, 8 mg (ID, 2 mg) | Retatrutide, 8 mg (ID, 4 mg) | Retatrutide, 12 mg (ID, 2 mg)

Jastreboff et al. N Engl J Med 2023;389:514-526

Actions and indications for GLP-1-based therapies

GLP-1 actions

↓ Albuminuria	↓ Gut motility
↓ Atherosclerosis	↓ Inflammation
↓ Body weight	↓↑ Islet hormone secretion
↑ Blood flow	↑ Natriuresis
↓ Blood pressure	↓ Oxidative stress
↑ Cell survival	↑ Plaque stability
↓ Cell death	↓ Platelet aggregation
↓ Fibrosis	↓ Postprandial lipaemia
↓ Glucose	↓ Thrombosis



Established indications

- Obesity
- Type 2 diabetes
- Obstructive sleep apnoea
- **Cardiovascular disease**
  - Myocardial infarction
  - Heart failure
  - Stroke
- Metabolic liver disease
- Diabetic kidney disease
- Osteoarthritis

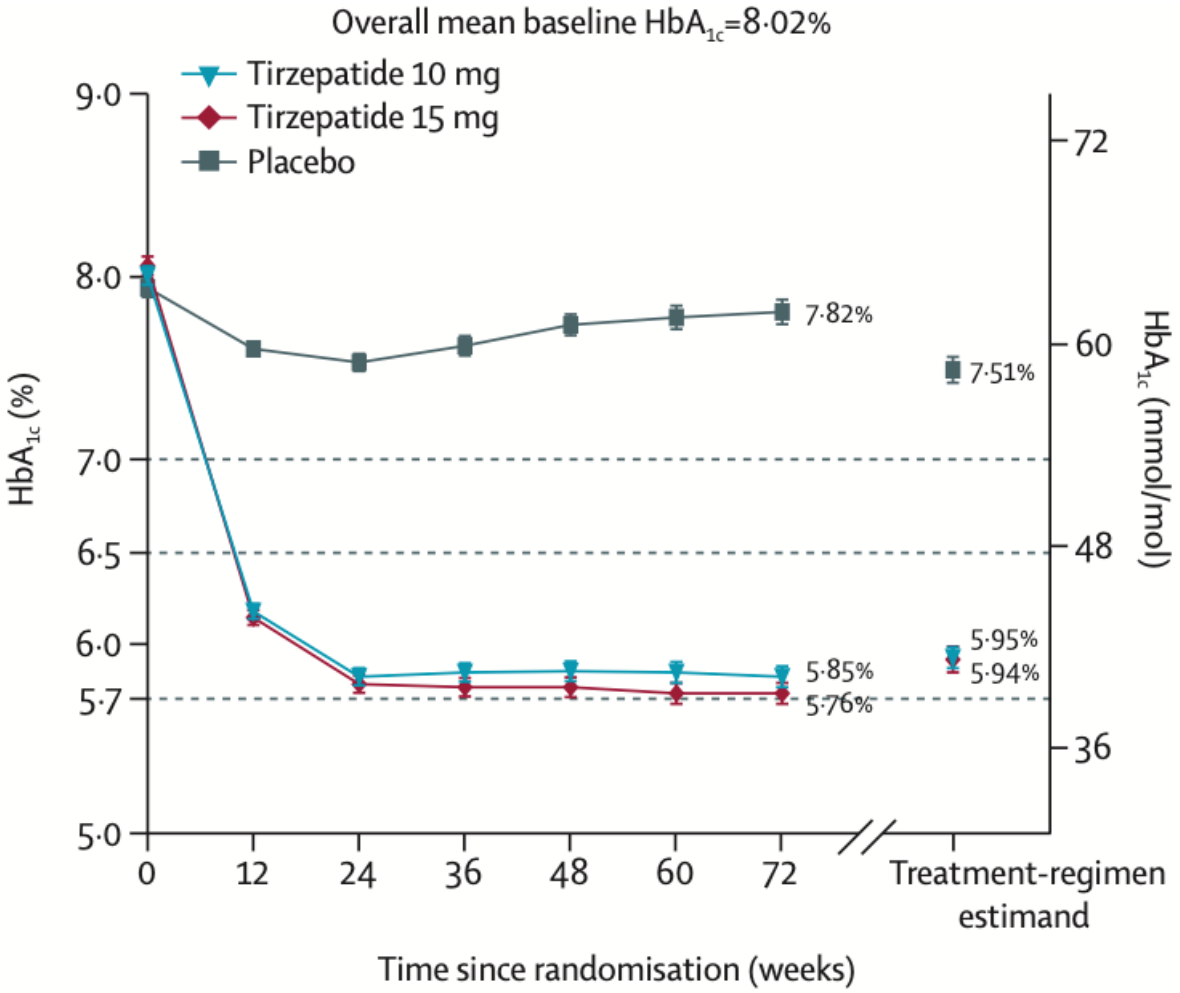
Investigational indications

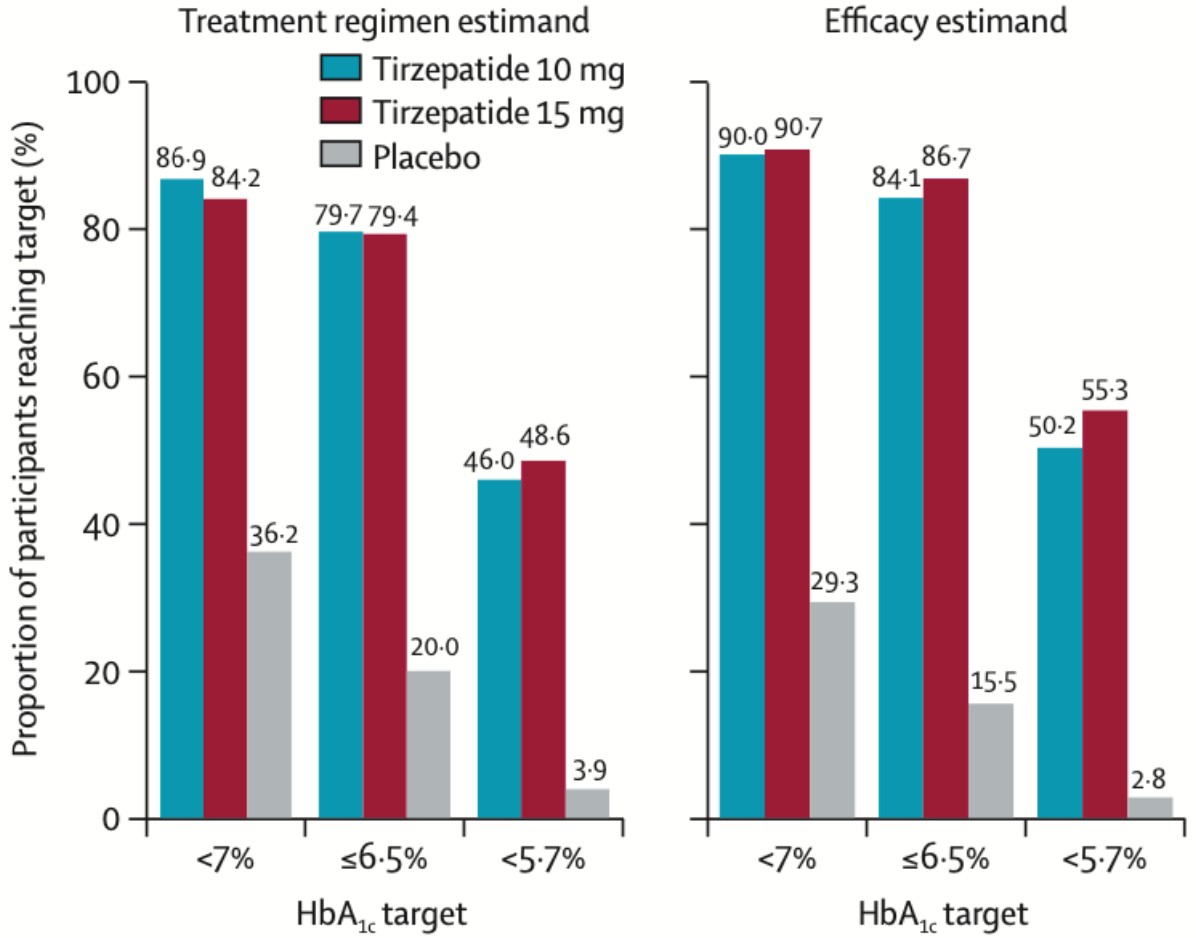
- **CNS disorders**
  - Neurodegenerative disorders
  - Substance use disorders
  - Neuropsychiatric disease
  - Monogenic obesity
- Type 1 diabetes
- Allergic airways disease
- Peripheral artery disease
- Chronic kidney disease
- Hypertension
- Psoriatic arthritis
- Alcohol-related liver disease

Drucker, D.J. GLP-1-based therapies for diabetes, obesity and beyond. *Nat Rev Drug Discov* (2025). https://doi.org/10.1038/s41573-025-01183-8

Tirzepatide for Obesity in PwT2D

Phase 3 Trial – 72 week trial in PwO with T2D – Mean weight loss 14.7% in TZP 15 mg vs. 3.2% PBO



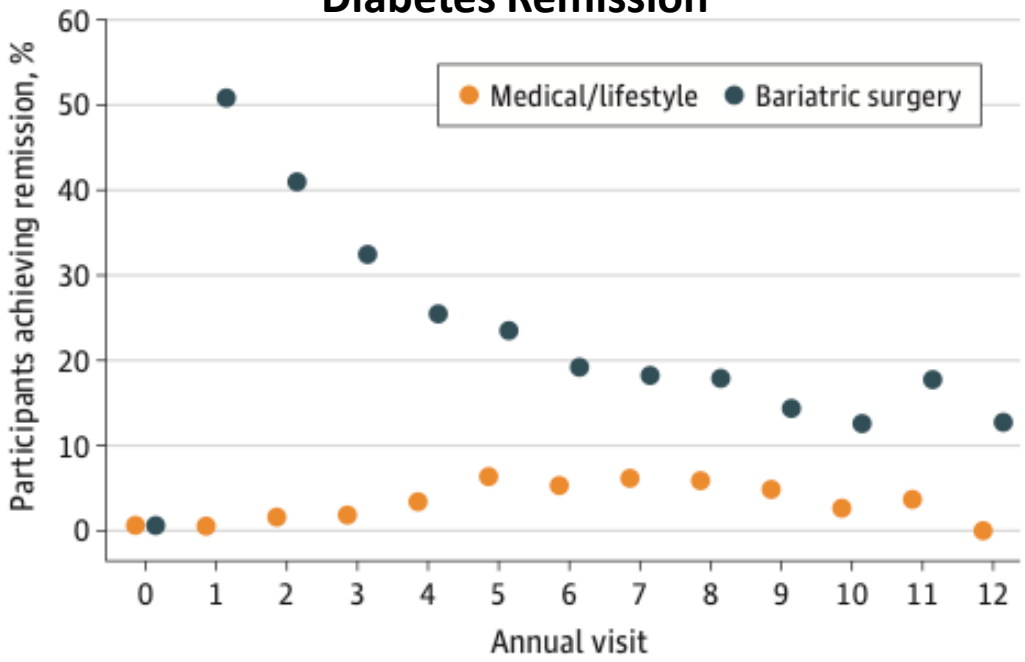


Garvey et al. Lancet 2023; 402: 613–26

Bariatric Surgery vs. Meds for Type 2 Diabetes

ARMMS-T2D – pooled analysis from 4 US single-center randomized trials – 7-year outcomes

	A1c <7%
Medical Management	26.7%
Bariatric Surgery	54.1%

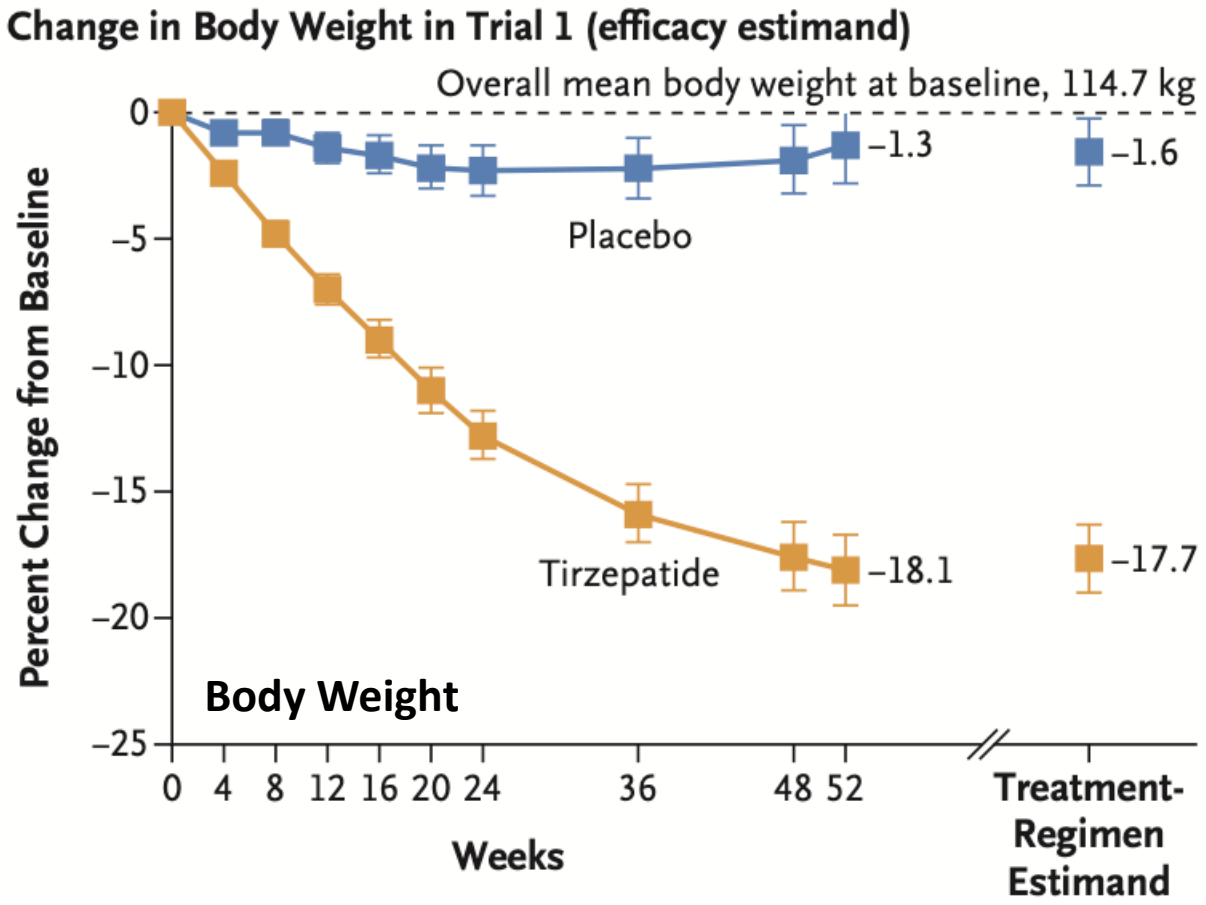


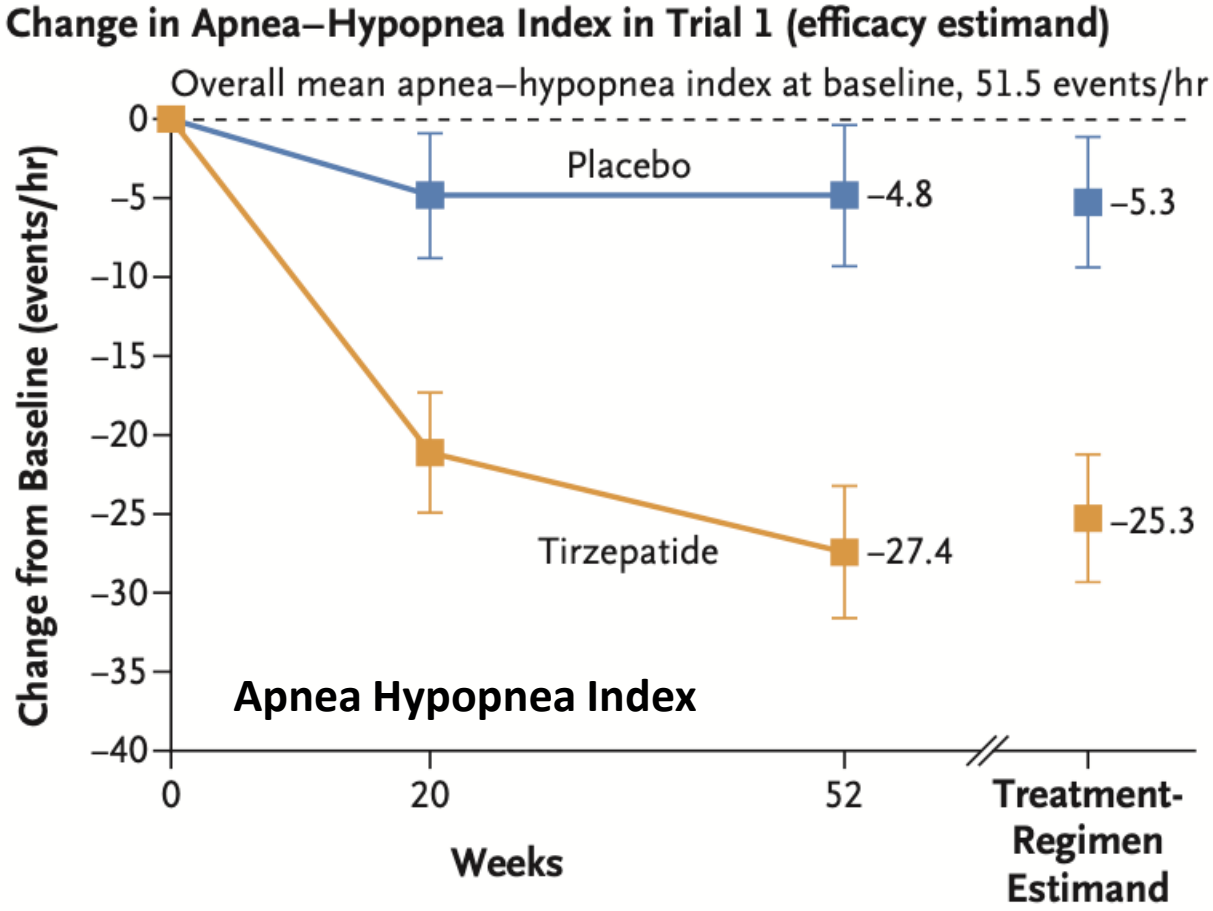
Remission was defined as hemoglobin A_{1c} less than 6.5% and not receiving any medications for diabetes.

Courcoulas et al. *JAMA. 2024;331(8):654-664*

Tirzepatide for Moderate to Severe OSA

SURMOUNT-OSA Trial – Phase 3



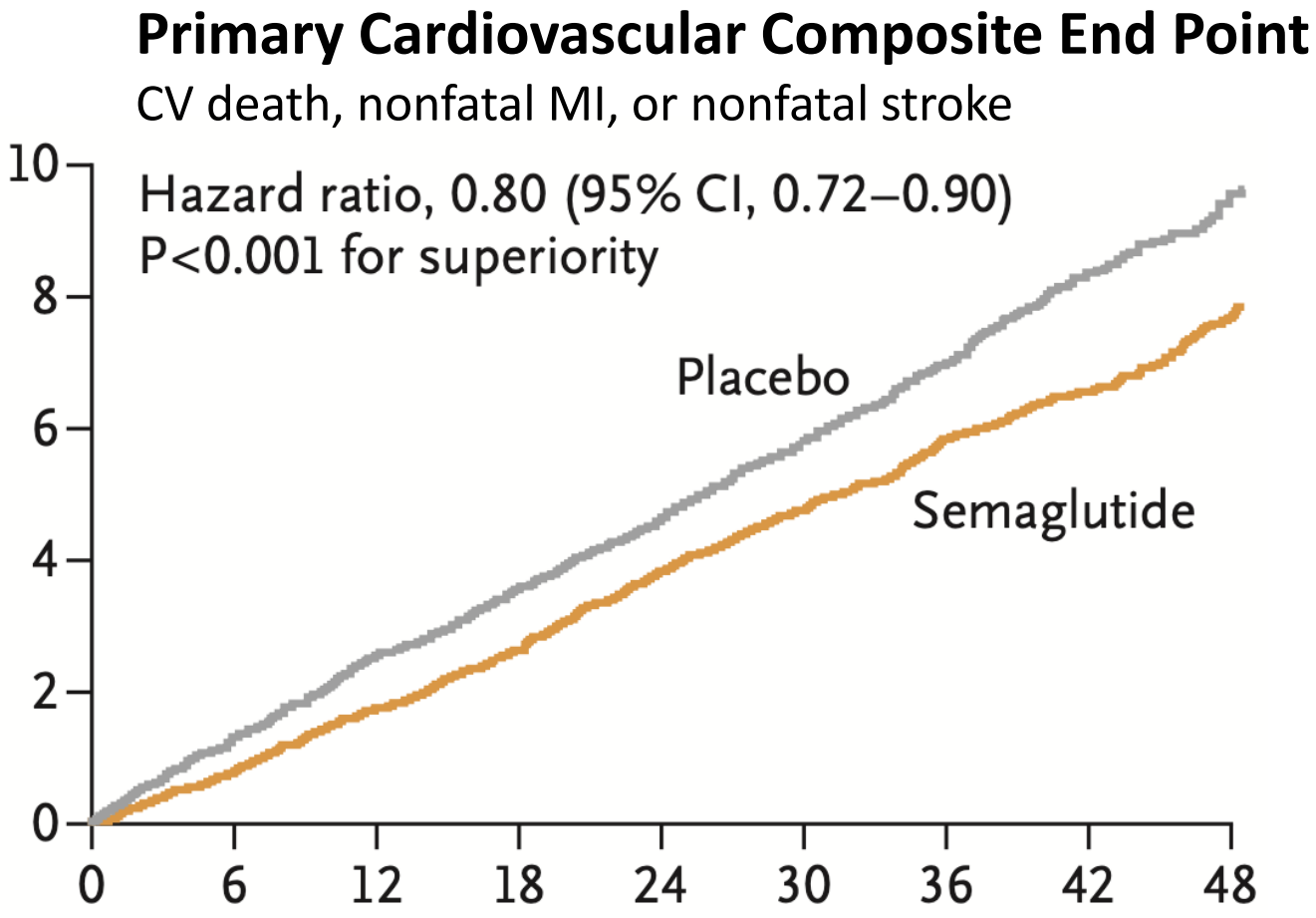


42% of those treated with TZP no longer met CPAP criteria vs. 16% with PBO

Malhotra et al. N Engl J Med 2024;391:1193-1205

Semaglutide 2.4mg for CV Risk Reduction

SELECT Trial – 20% Reduction in MACE with semaglutide 2.4 mg vs. placebo



Semaglutide 2.4 mg

Weight -9.4%

WC -8 cm

SBP -3.82 mmHg

DBP -1.0 mmHg

HR 3.8 bpm

A1c -0.31%

hs-CRP -39%

TC -4.6%

HDL 4.9%

LDL -5.3%

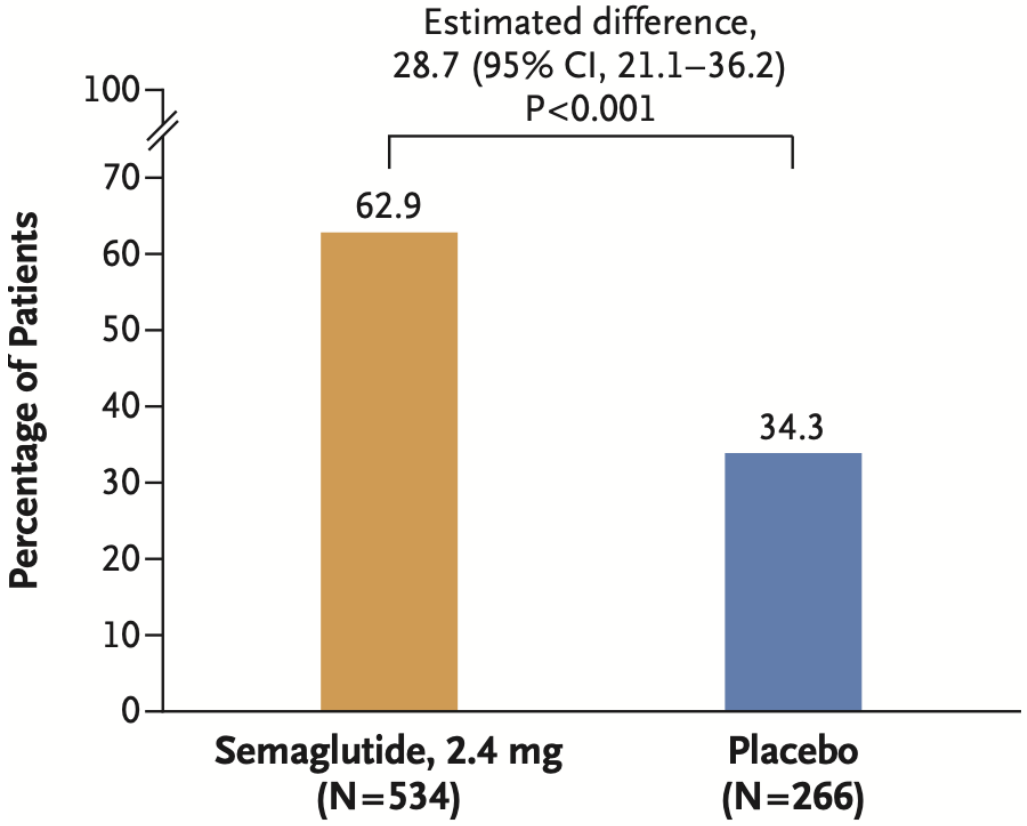
TG -18.3%

Lincoff AM et al. N Engl J Med 2023;389:2221-2232

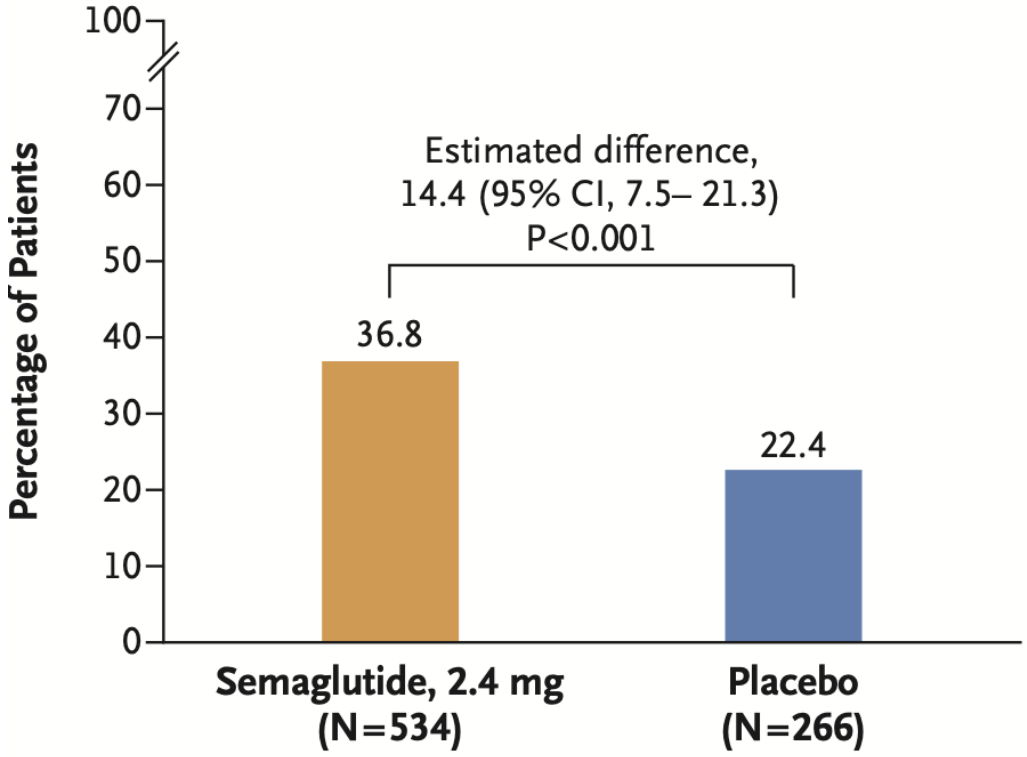
Semaglutide 2.4mg for MASH F2-3

ESSENCE Trial – Phase 3 interim results from first 800 patients completing 72 weeks of treatment

Resolution of Steatohepatitis with No Worsening of Liver Fibrosis



Reduction in Liver Fibrosis with No Worsening of Steatohepatitis

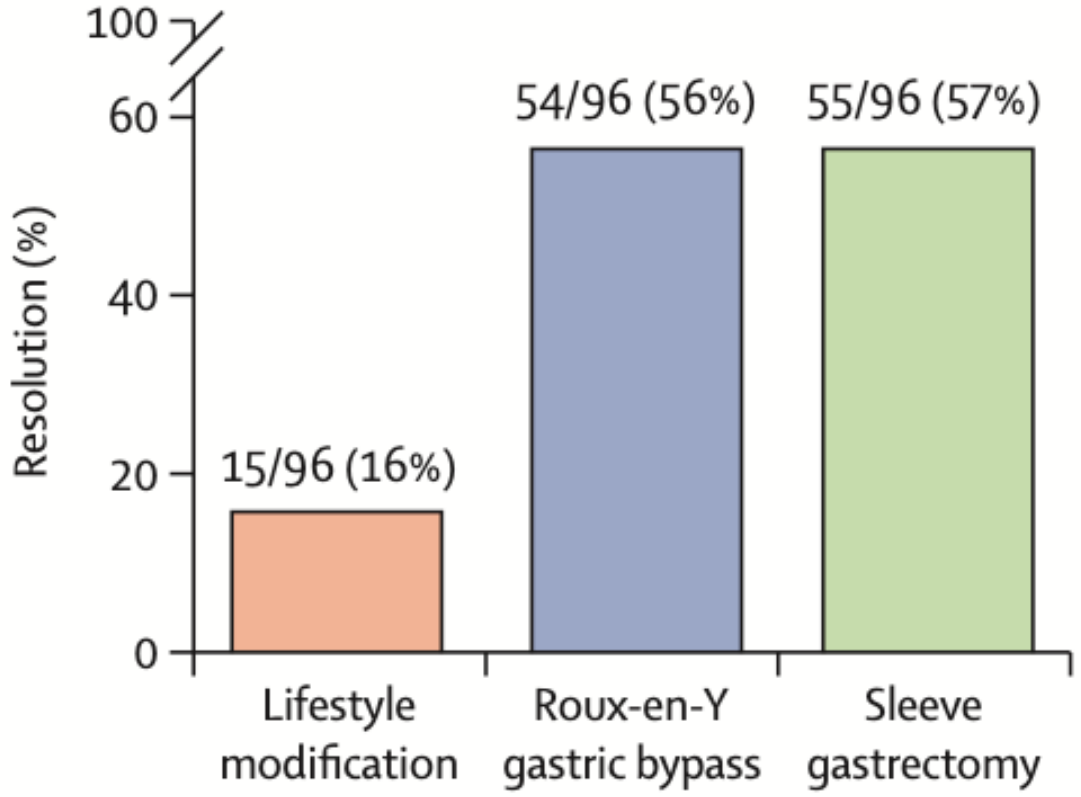


Sanyal et al. NEJM published on April 30, 2025

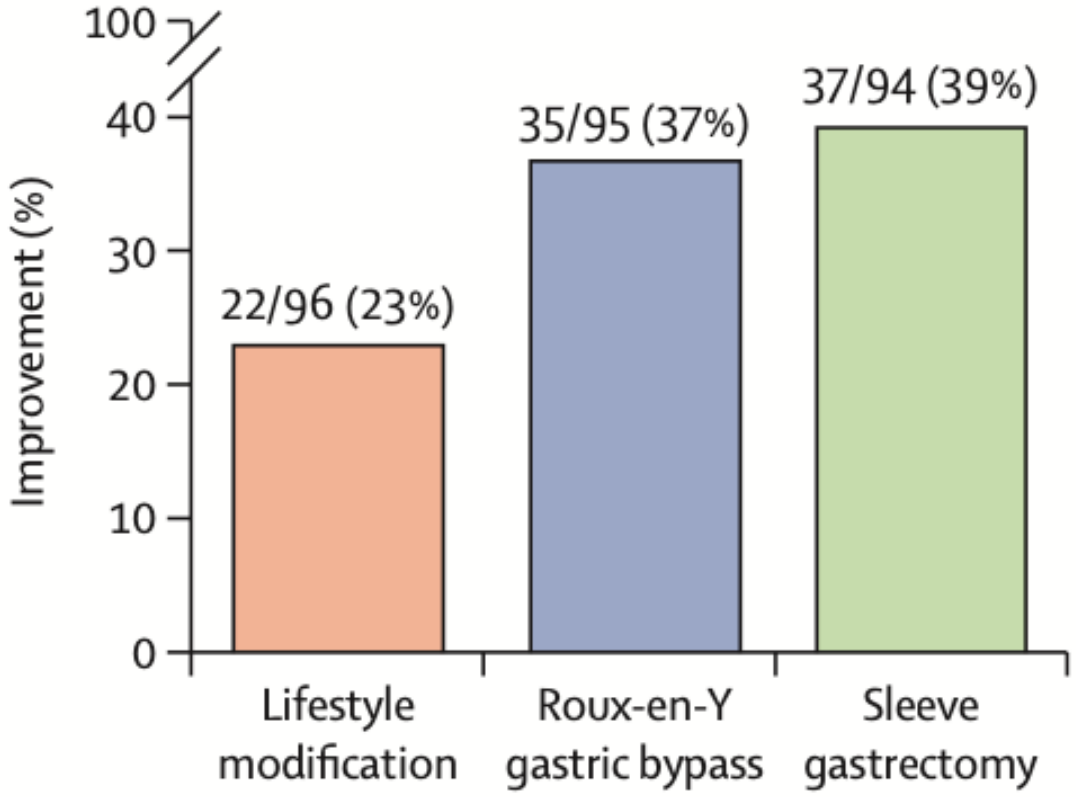
Bariatric Surgery for MASH (NASH)

BRAVES– multicentre, open label, randomised trial – lifestyle vs. gastric bypass vs. sleeve – 1-year outcomes

MASH resolution without worsening of fibrosis (ITT population)



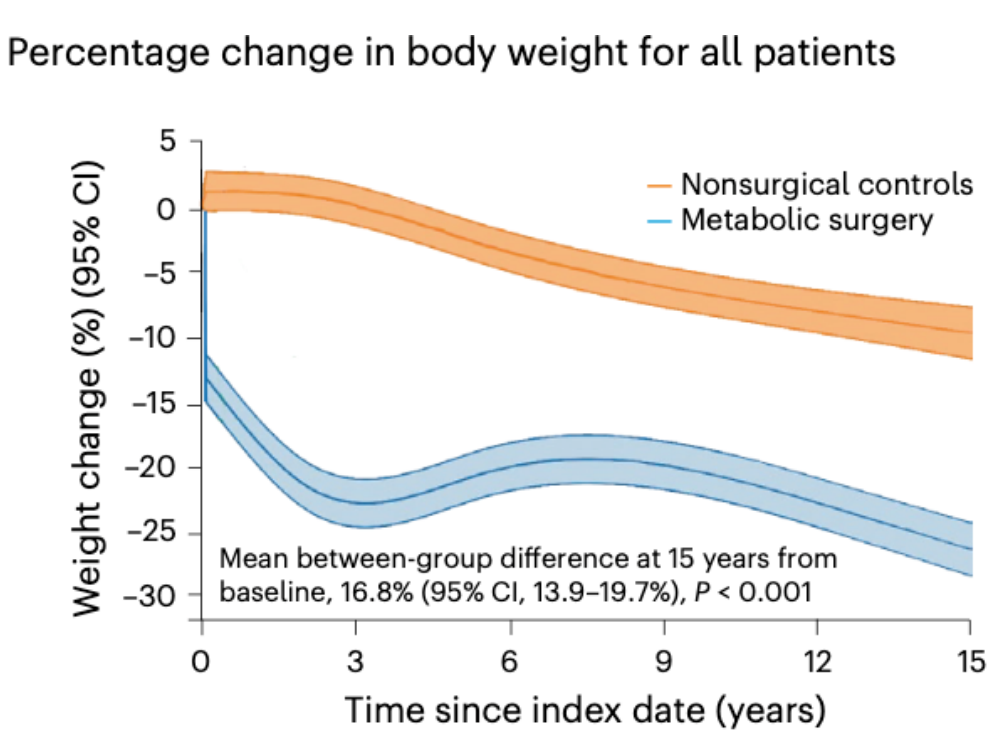
Improvement of at least one stage of liver fibrosis without worsening of MASH (ITT population)

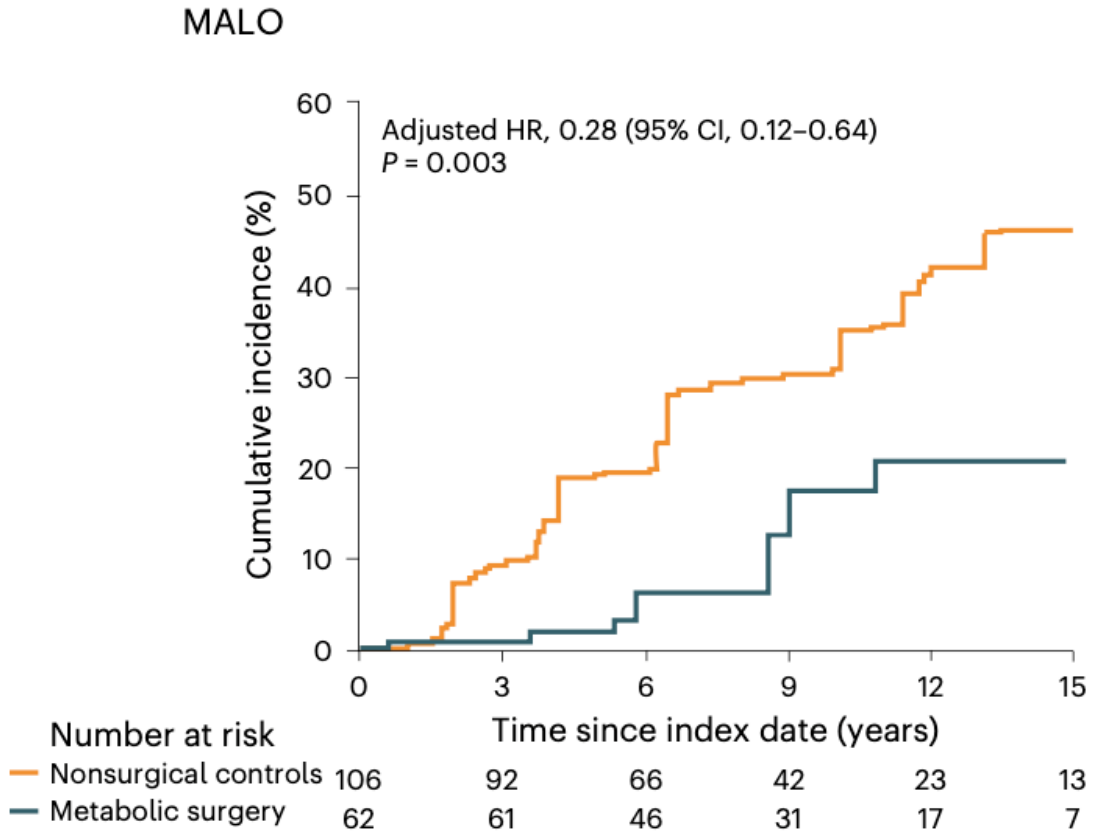


Verrastro et al. *Lancet* 2023; 401: 1786–97

Bariatric Surgery for MASH Outcomes

SPECCIAL– observational study surgery vs nonsurgical treatment in patients with MASH-related cirrhosis



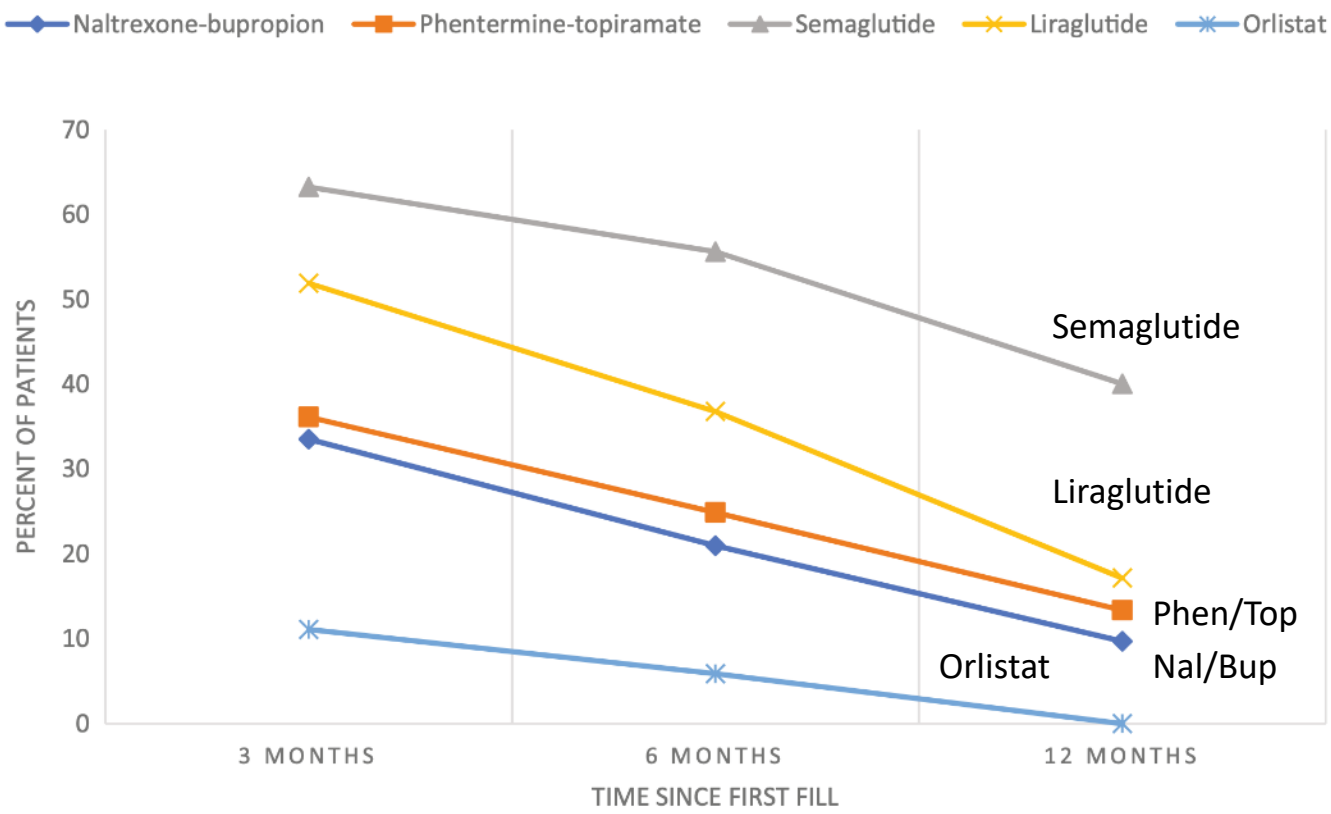


Aminian et al. *Nat Med* 2025; **31**, 988–995

Persistence with Obesity Medications

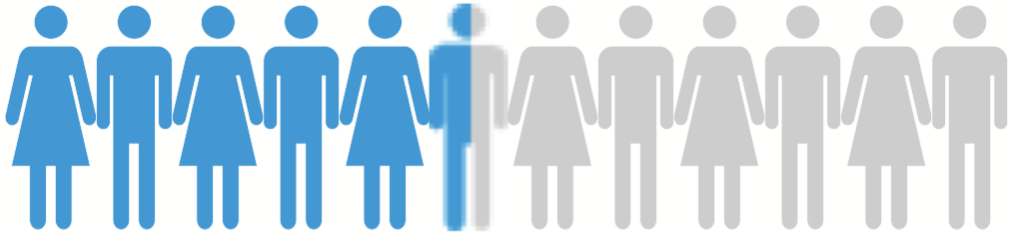
Obesity Medication Persistence at 1 year

Variable	Adjusted odds ratio	95% CI	*p* value
Medication type			
Phentermine-topiramate	Reference		
Naltrexone-bupropion	0.68	0.46–1.00	0.049
Semaglutide	4.26	3.04–6.05	<0.001
Liraglutide	1.40	0.90–2.16	0.13
Orlistat	N/A		



Gasoyan et al. Obesity. 2024 Mar;32(3):486-493

GLP-1 Medication Persistence: Factors Affecting Discontinuation



LESS THAN HALF of those prescribed stay on the medication for 12 weeks or more.

Those who receive their medication from an endocrinologist or obesity medicine specialist were MORE LIKELY to continue longer.

Loss of Employer Sponsored Coverage

THE WALL STREET JOURNAL.

HEALTH | HEALTHCARE

Employers Cut Off Access to Weight-Loss Drugs for Workers

As costs mount for popular drugs such as Wegovy, a cousin of Ozempic, health plans are restricting coverage to save money

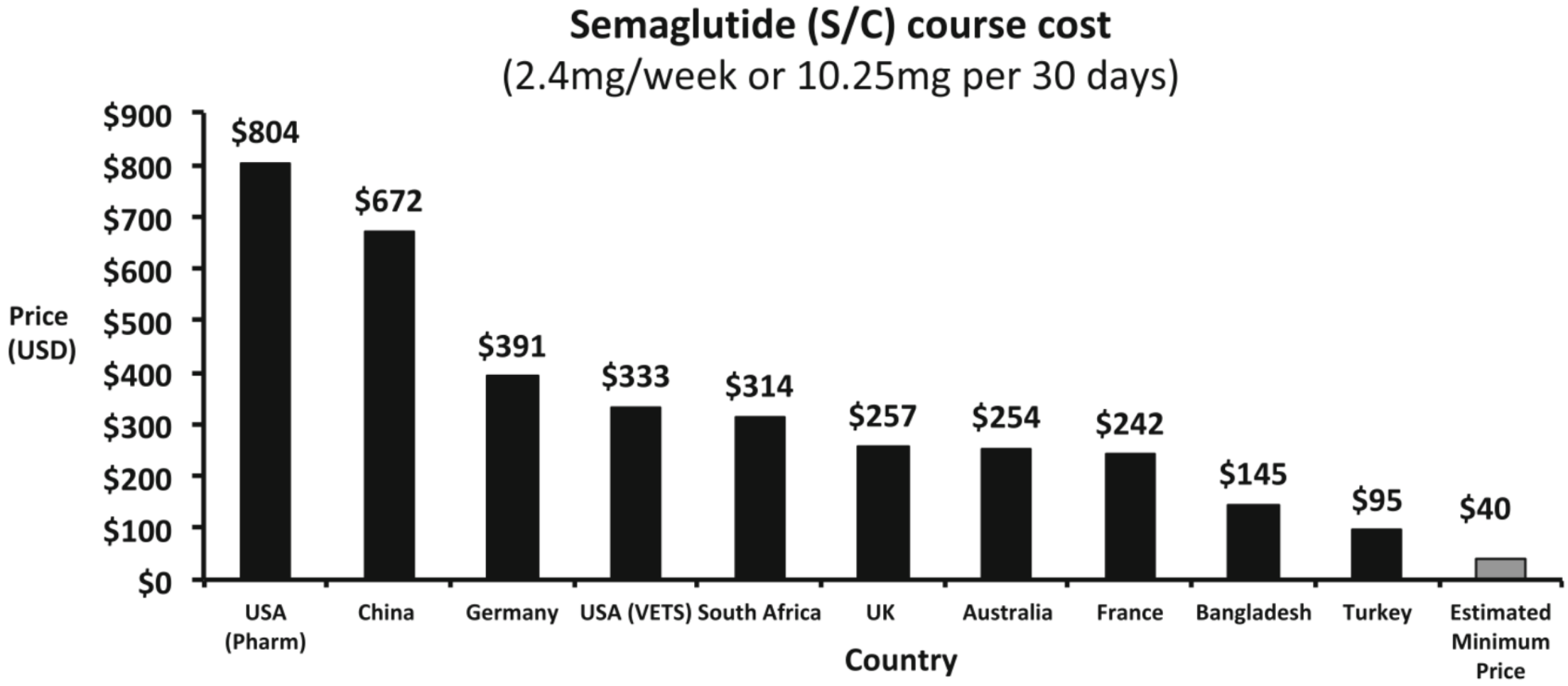
By Peter Loftus Follow

Aug. 2, 2023 at 5:30 am ET

The University of Texas System said it would end coverage of Novo Nordisk's Wegovy and Saxenda for its employees and others covered by its healthcare plans. PHOTO: BILL MCCULLOUGH FOR THE WALL STREET JOURNAL

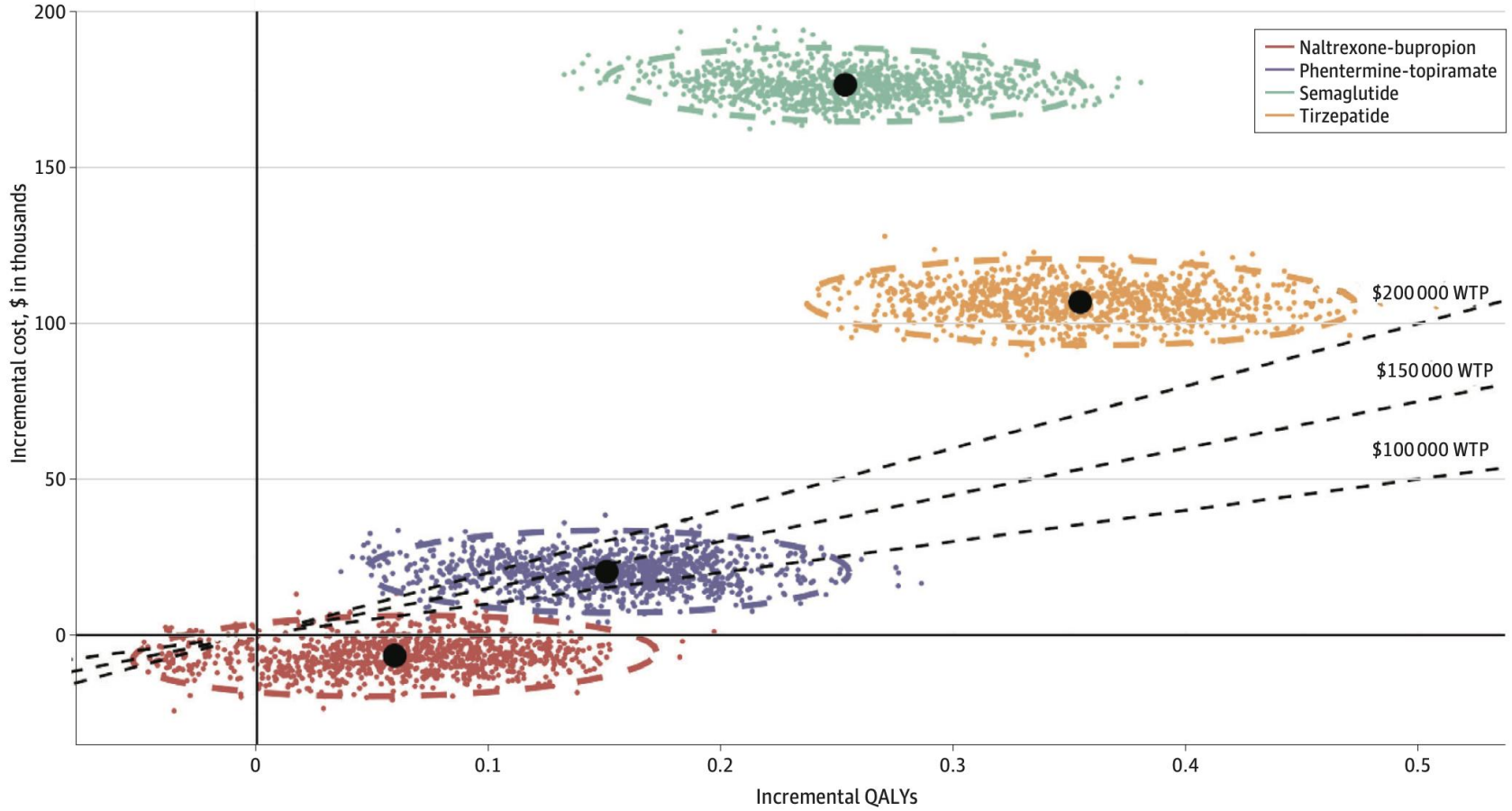
Wall Street Journal, August 2, 2023

Variable Global Pricing for GLP-1 Obesity Medications



Levi et al. *Obesity (Silver Spring). 2023;31:1270–1279*

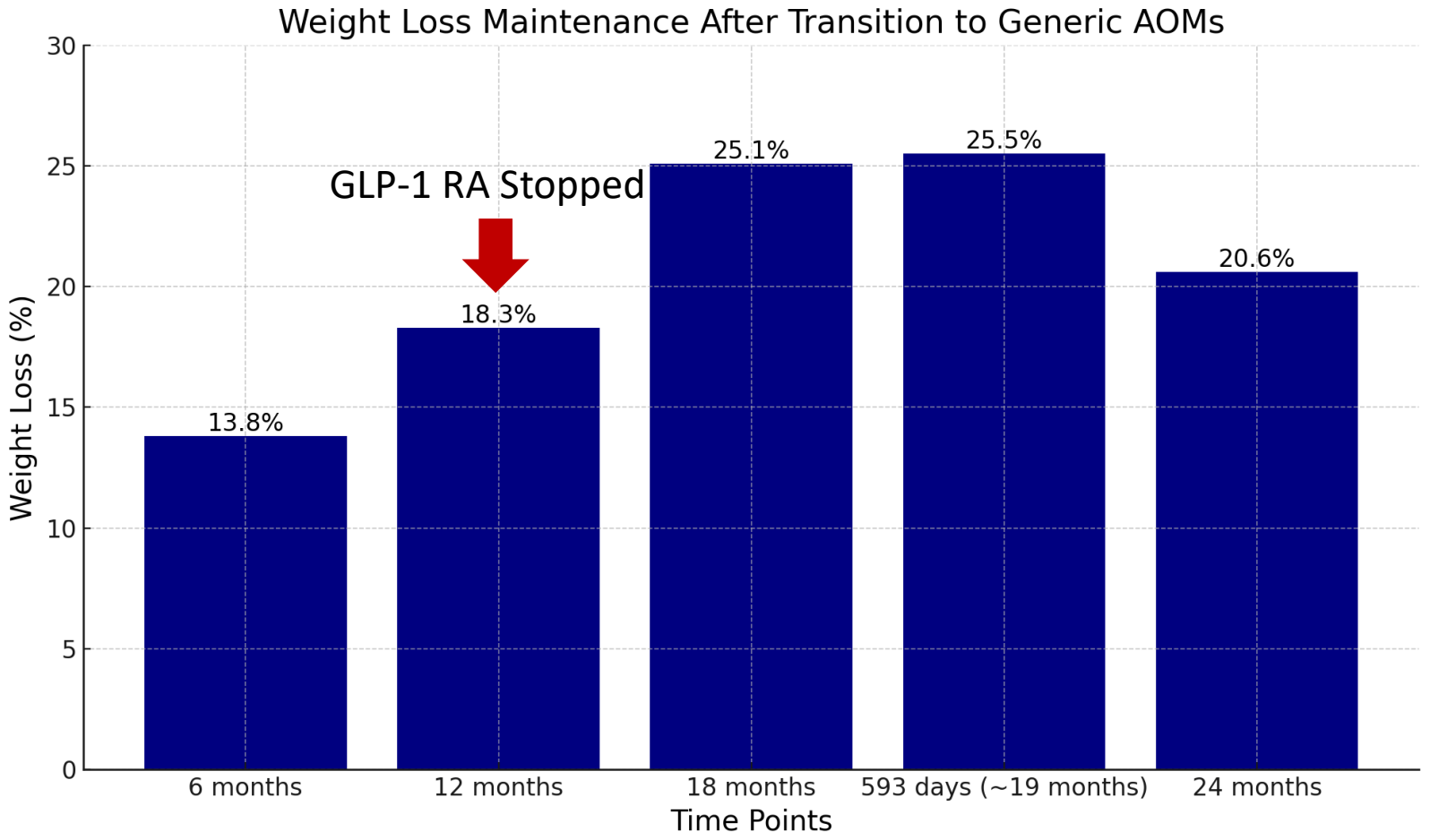
Cost-Effectiveness of the Obesity Medications vs Lifestyle Modification Over a Lifetime



In this economic evaluation of 4 obesity medications, tirzepatide and semaglutide were found to generate greater lifetime health gains by preventing diabetes, cardiovascular complications, and death compared with phentermine-topiramate and naltrexone-bupropion; however, they are not cost-effective at their current net prices.

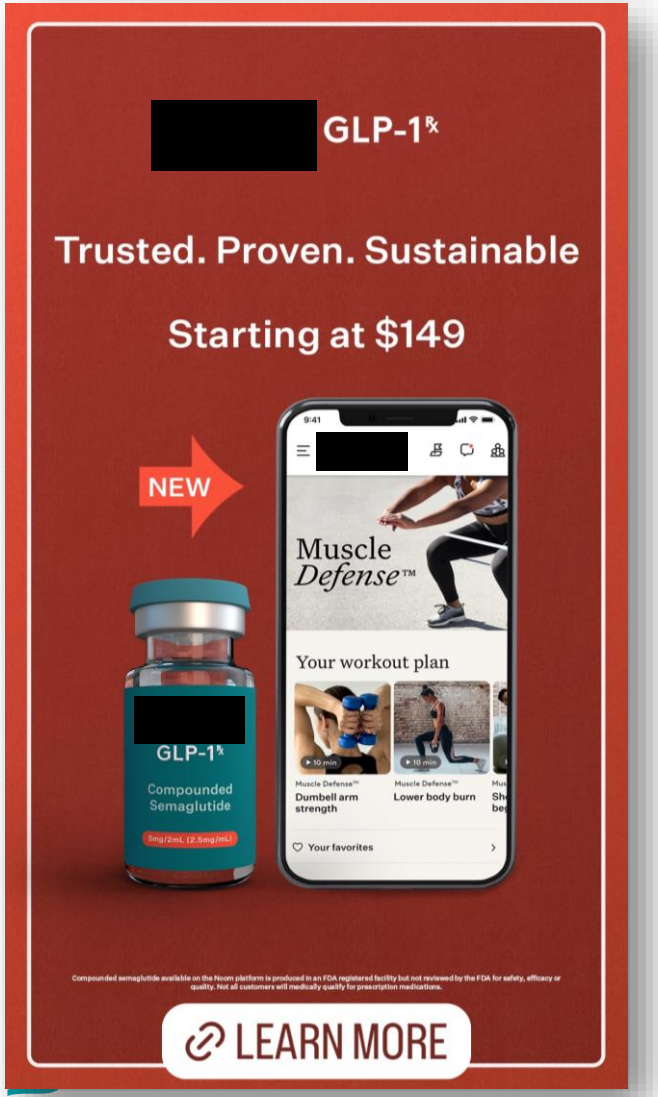
Hwang et al. *JAMA Health Forum.* 2025;6(3):e245586

Weight maintenance on cost-effective antiobesity medications after 1 year of GLP-1 RA therapy



Paddu et al. Obesity (Silver Spring). 2024;32:2255–2263.

Don’t Conflate Access to Drugs with High Quality Care



Focus on Balance Not Restriction with OM

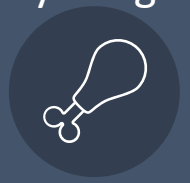
Most individuals in the US do not meet recommendations for a healthy dietary

Energy requirements vary by age, sex, body weight, and activity level, among other factors

- 1200-1500 kcal/day for women is recommended as safe during weight reduction
- 1500-1800 kcal/day for men is recommended as safe during weight reduction

Macronutrient recommendations include[1,2]

Protein*	Carbohydrates	Fat	Fiber
10%-35% total energy ≥60 g/day (up to >1.5 g/kg body weight per day)	45%-65% total energy 135-290 g/day	20%-35% total energy 25-70 g/day	Women 21-25 g/day Men 30-38 g/day




Drink at least 2-3 L of fluids per day[1]

- Consume water, low-calorie beverages, or nutrient-dense beverages
- Limit sugar-sweetened beverages, alcohol, and caffeine[2]

Taking a complete multivitamin is associated with a reduced risk of deficiencies

Supplementation may not be sufficient to correct pre-existing deficiencies in people consuming a low-calorie diet[2]

1. Almandoz JP, et al. *Obesity (Silver Spring). 2024;1–19*. 2. USDA and US Department of HHS. *Dietary guidelines for Americans*, *2020-2025. 9th edition*. 2020.

Perform Baseline Assessment and Visit Regularly with Patients During OM Therapy

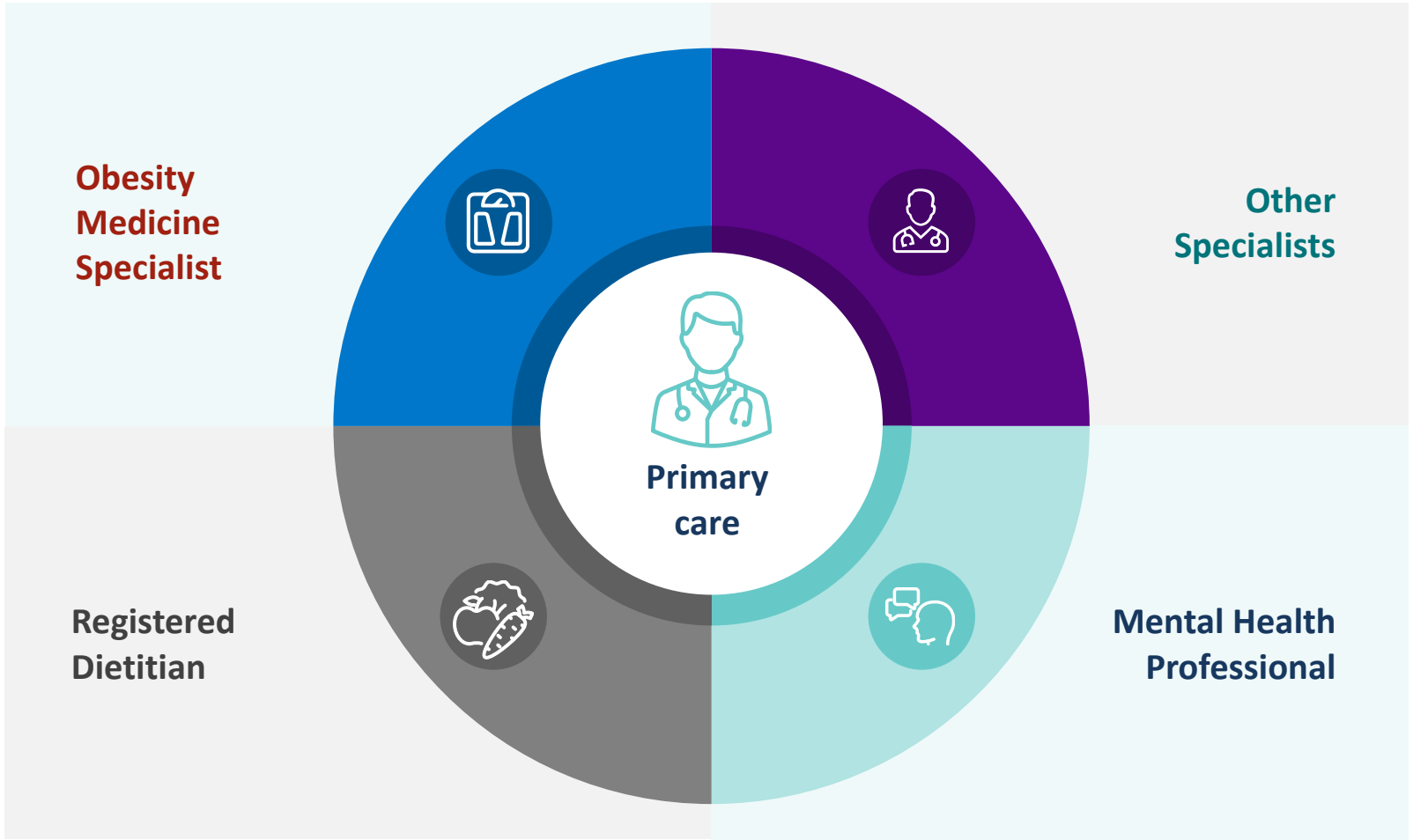
Management of AOM-Associated Adverse GI Events

- Dietary modification: eat smaller nutrient-rich meals more frequently and limit high-fat foods, spicy foods, alcoholic or carbonated beverages
- Dose reduction, slower dose escalation, treatment cessation or switching to alternative therapy
- May consider OTC medications for short-term symptom control
- Ensure patient meets needs for protein, fiber, fluids, and micronutrients.
- If unable to meet needs, consider short-term dietary supplementation (such as protein shakes, multivitamin) until symptoms resolve

Almandoz JP, et al. Obesity 2024 Sep;32(9):1613-1631

Interdisciplinary Team Can Optimize Outcomes for Patients on OM

Support should be individualized to the patient's health, goals and needs



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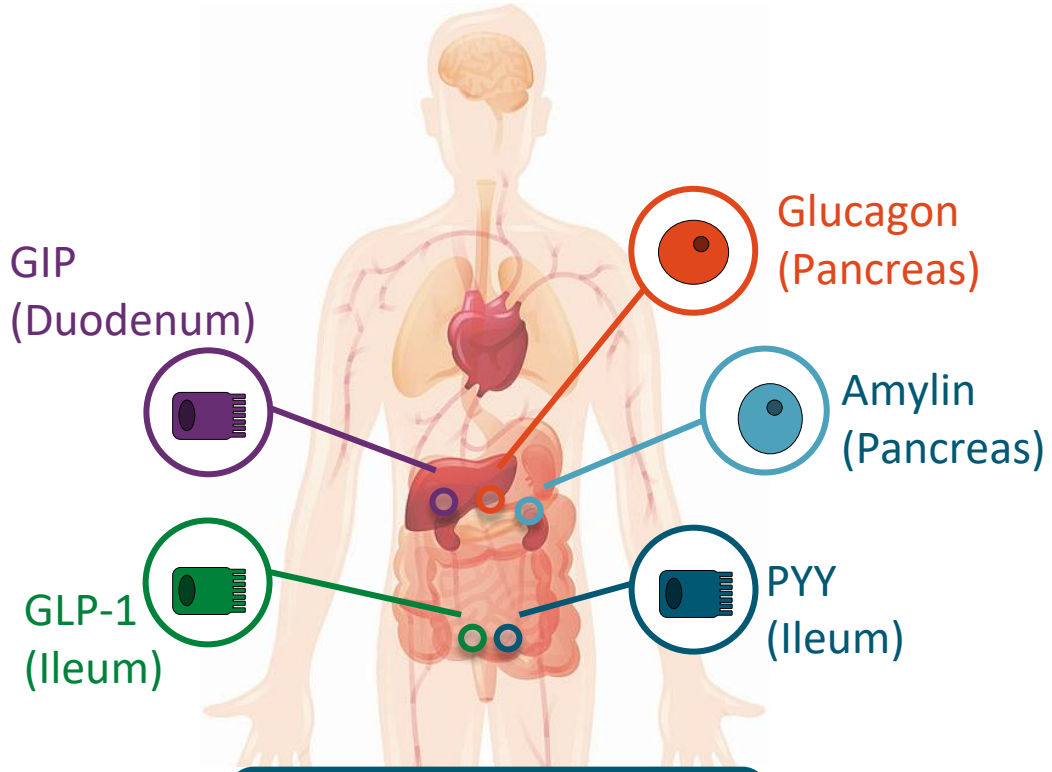
Secretion and Proposed Actions of Nutrient Stimulated Hormones in Pipeline for Obesity

GIP

- ↓ appetite ↓ nausea
- ↑ insulin ↑ glucagon
- ↓ gastric acid secretion
- ↑ lipid deposition ↑ lipogenesis
- ↓ bone resorption

GLP-1

- ↓ appetite ↑ nausea ↓ food intake
- ↑ insulin ↓ glucagon
- ↓ gastric emptying
- ↑ lipolysis
- ↑ cardioprotection ↓ heart rate



PYY

- ↓ appetite ↑ nausea ↓ food intake
- ↓ gastric emptying
- ↑ energy expenditure

Glucagon

- ↓ appetite ↑ nausea ↓ food intake
- ↑ insulin
- ↑ hepatic glucose production ↑ lipid oxidation ↓ hepatic lipid synthesis
- ↓ gastric emptying
- ↑ energy expenditure
- ↑ heart rate

Amylin

- ↓ appetite ↓ food intake
- ↓ glucagon
- ↑ energy expenditure
- ↓ gastric emptying
- ↓ osteoclast activity ↑ osteoblast activity

Melson. Int J Obes (Lond). 2024 Feb 1:1-9

Take Home Messages

Clinically significant weight reduction is challenging to achieve and maintain with lifestyle alone because obesity is a chronic and complex disease

New obesity medications and bariatric surgery can facilitate ≥15% average weight loss and should be considered as part of a comprehensive obesity care plan

Beyond weight reduction with medications and surgery treat a variety of obesity complications and may have weight loss independent effects on health outcomes

Treat obesity using evidence-based therapies that prioritize improving health and quality of life, rather than focusing solely on weight loss

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