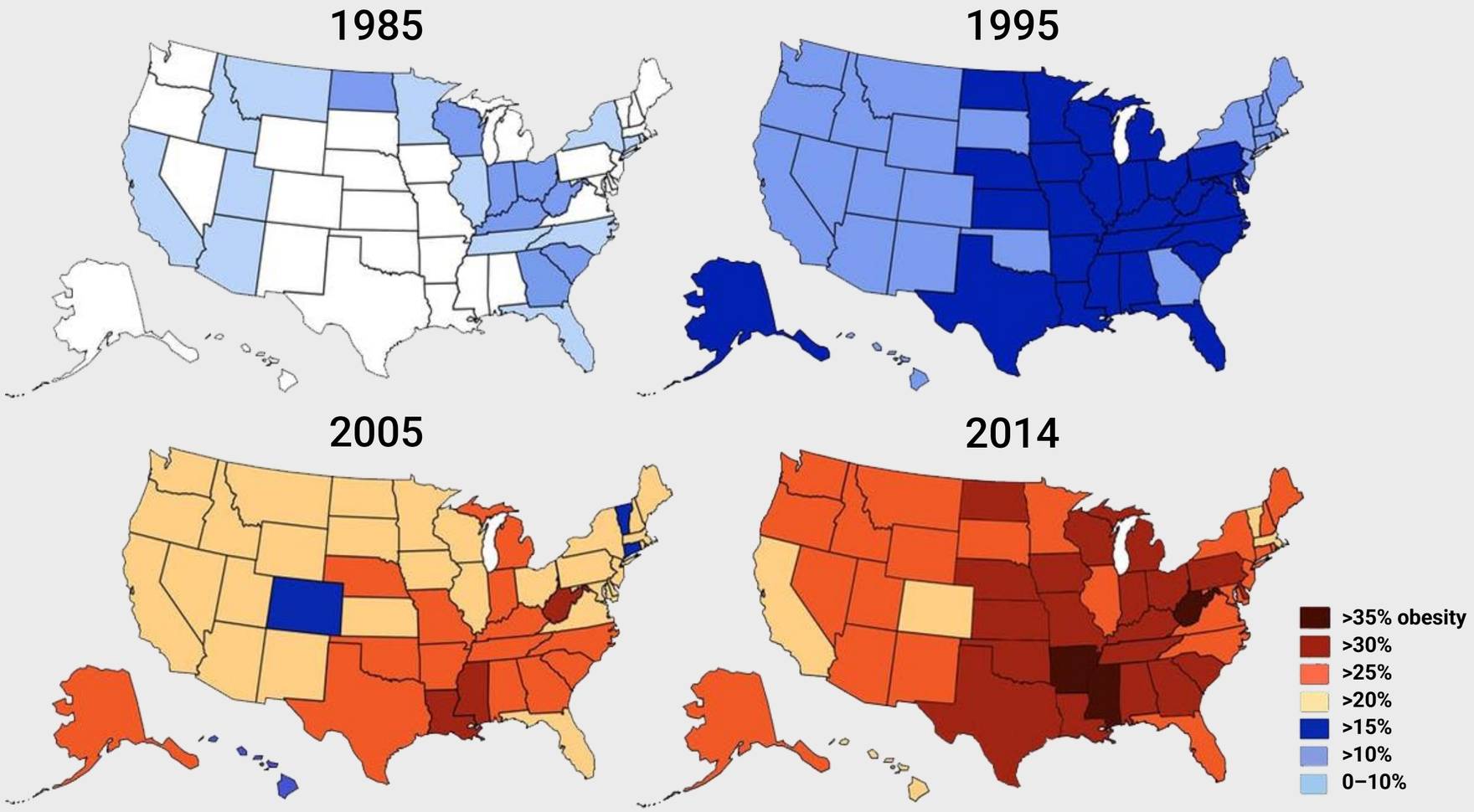
Why Are We Here?

- Obesity (BMI ≥30) is extremely common, affecting >40% of adults in the US
  - 9.4% of adults have *severe* obesity (BMI ≥40)
  - ~20% of children ages 2 to 19 years have obesity
- There are known associations between inflammatory GI conditions and obesity, and response to treatment is also impacted with BMI
- Now more than ever, obesity is a ***modifiable*** risk factor
- If we want to care for our patients with any IMIDs, addressing modifiable comorbid conditions, including obesity, is a necessary role

BMI = body mass index; GI = gastrointestinal.

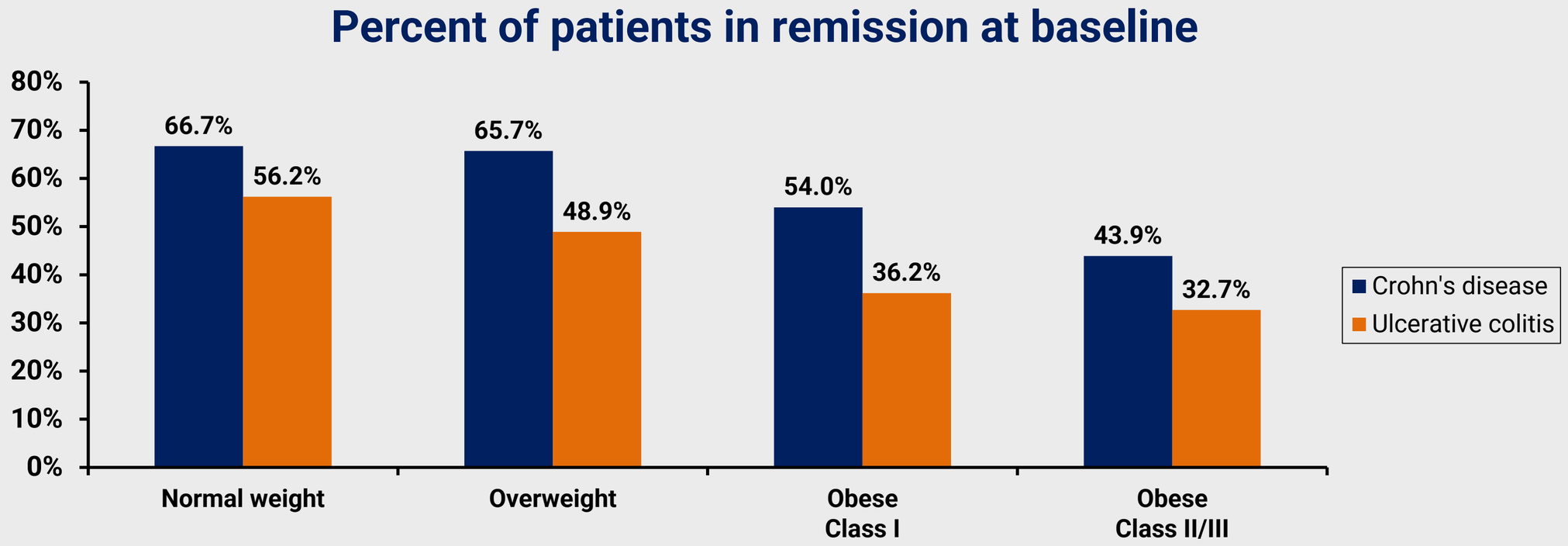
Emmerich SD, et al. *NCHS Data Brief*. 2024;(508):10.15620/cdc/159281. National Institutes of Health (NIH). Overweight and obesity statistics, 2021 (https://www.niddk.nih.gov/health-information/health-statistics/overweight-obesity). URLs accessed 1/9/2026.

Obesity Continues to Rise in the United States



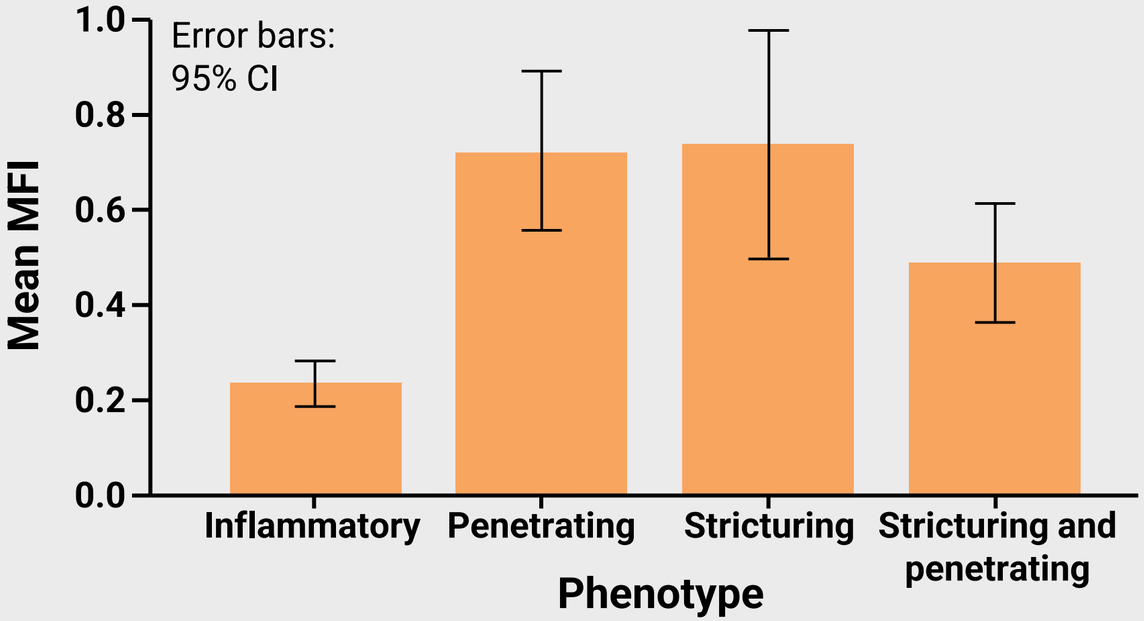
Impact of Obesity on Clinical Course of IBD

- Cross-sectional and longitudinal cohort from IBD Partners
- 7296 adults with IBD with at least 1 follow-up of 6 to 12 months
- 65% with CD, 20% obese
- Higher anxiety, depression, fatigue, pain and inferior social function scores in CD and UC



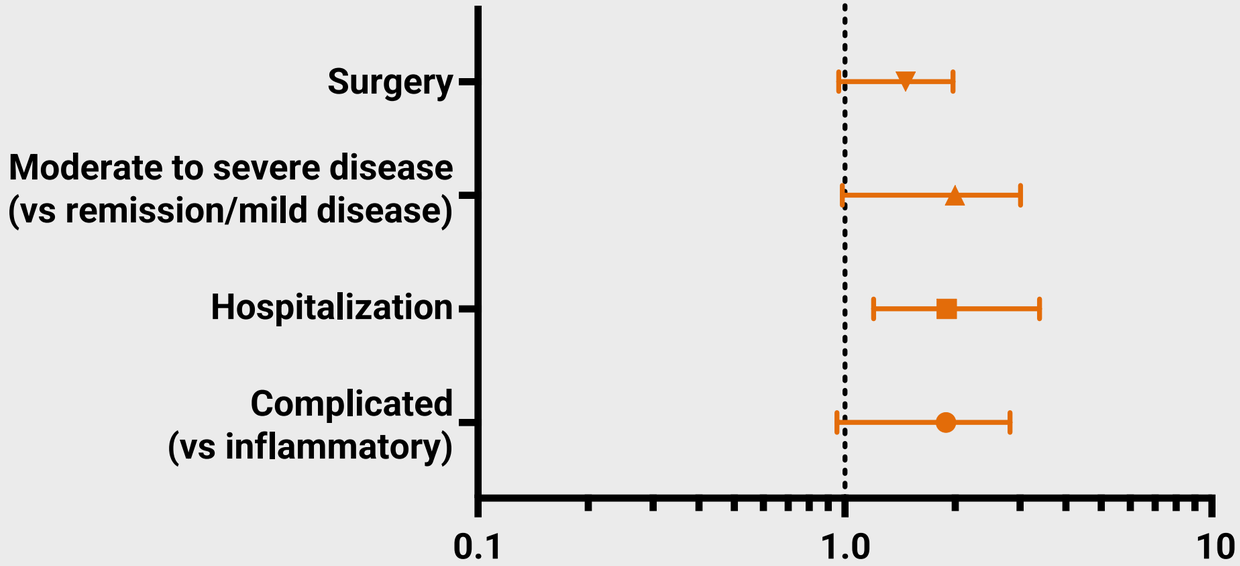
Jain A, et al. *Am J Gastroenterol.* 2019;114(4):630-639.

Impact of Visceral Adiposity in Crohn's Disease



	Complicated	Inflammatory	*p*-value
All patients (n = 50)			
MFI	0.67 ± 0.29	0.23 ± 0.1	.01
Visceral fat area (cm^2)	125.3 ± 89.7	53.1 ± 35.9	.01
Subcutaneous fat area (cm^2)	192.0 ± 102.7	245.4 ± 153.9	.18

CD outcomes, with increasing VAT

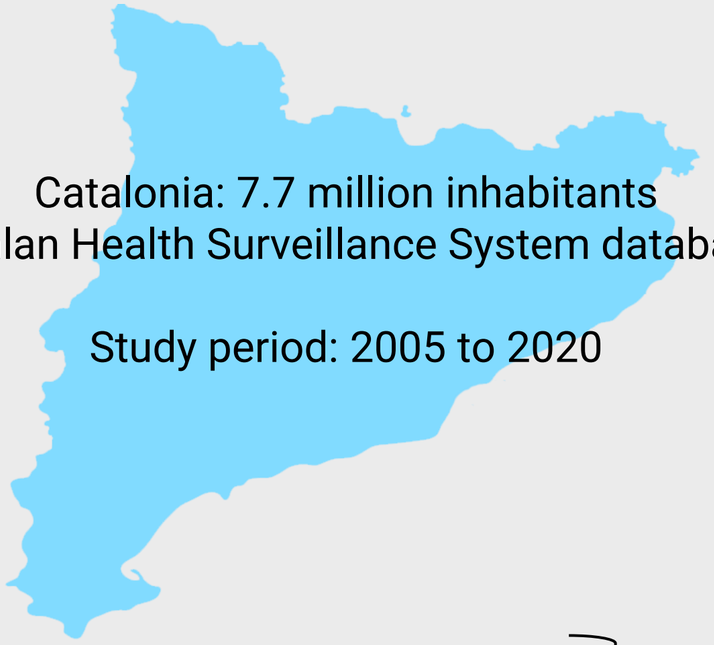


Visceral adiposity (more than overall obesity) may be associated with high-risk phenotype and adverse outcomes in CD.

MFI = mesenteric fat index; VAT = visceral adipose tissue.

Erhayiem B, et al. *Clin Gastroenterol Hepatol*. 2011;9(8):684-687. Uko V, et al. *Inflamm Bowel Dis.* 2014;20:2286-2291.

Severe Obesity, a Susceptibility Factor for Developing Inflammatory Bowel Disease: Results of a Population-Based Study



Catalonia: 7.7 million inhabitants
Catalan Health Surveillance System database

Study period: 2005 to 2020

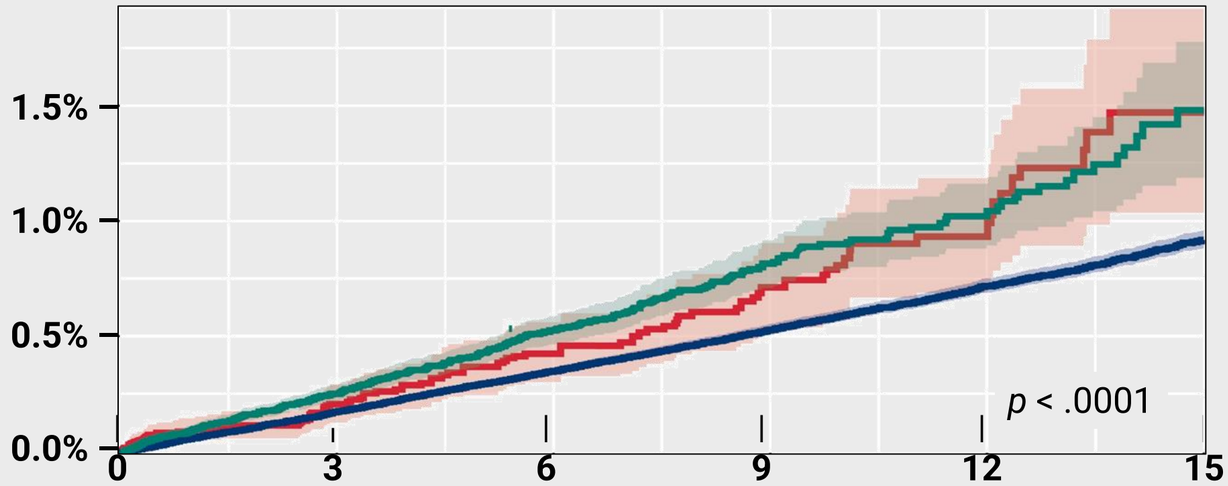
1,009,256
subjects with obesity

93,473
subjects with severe obesity

14,698
subjects with bariatric surgery

Incidence of new IBD cases

Cumulative incidence of new IBD cases



Bariatric surgery
↑
78 new cases of IBD (0.84 cases per 1000 person-years)

Severe obesity
↑
409 new cases of IBD (0.90 cases per 1000 person-years)

Obesity
↑
3,790 new cases of IBD (0.60 cases per 1000 person-years)

Cañete F, et al. *J Crohns Colitis*. 2025;19(2):jjaf010.

Propensity Score Matched Cohort of 5128 Obese vs. 5128 Non-obese Hospitalized Patients with IBD

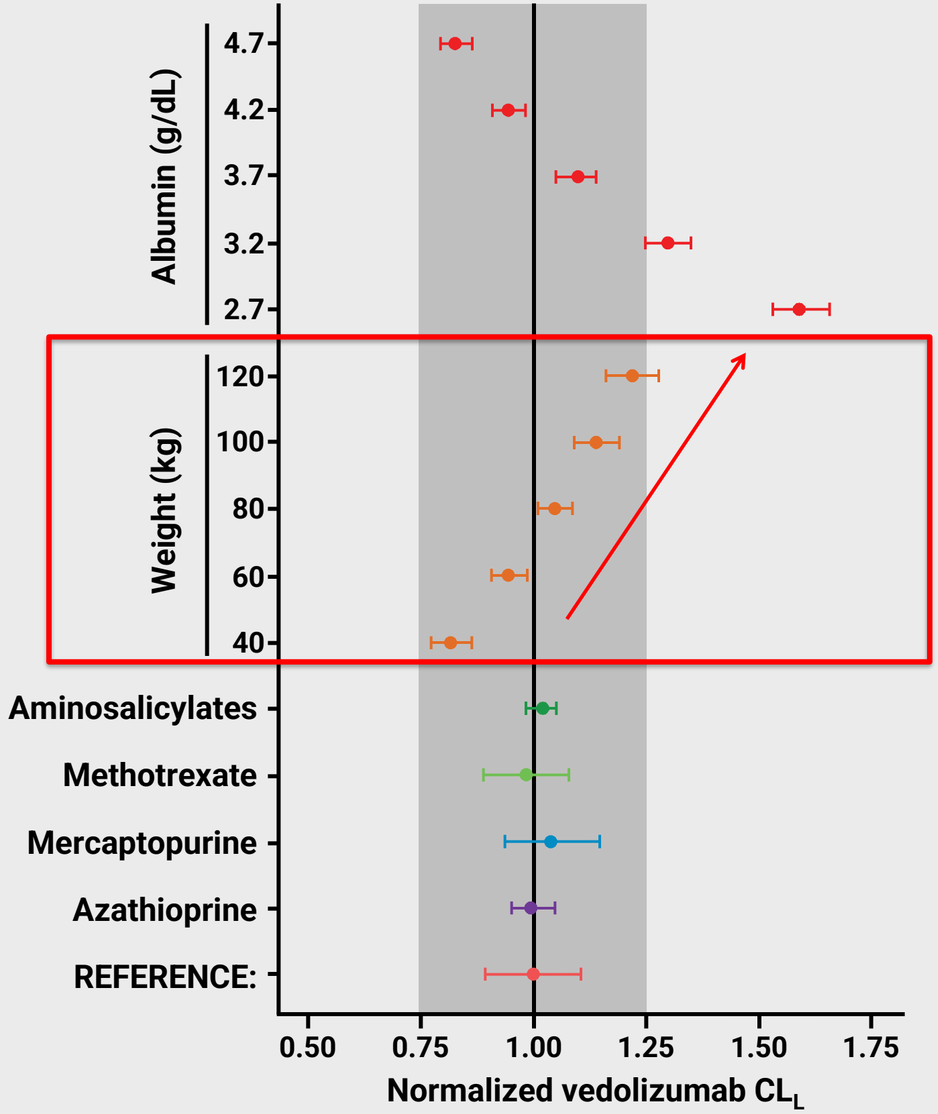
Outcomes (median, IQR)	Obese (n=5128)	Non-obese (n=5128)
Total **days spent in hospital**/year	8 (4-17)	5 (3-12)
Total **number of hospitalizations**/year	3 (2-4)	2 (2-3)
Total **costs of hospitalization**/year	17,277 (8,414-35,034)	11,847 (6,088-24,010)

$p < .01$ for all comparisons

Obese patients with IBD have a higher burden and costs of hospitalization as compared to non-obese patients

Nguyen … Singh. *Clin Gastroenterol Hepatol* 2019;17:709

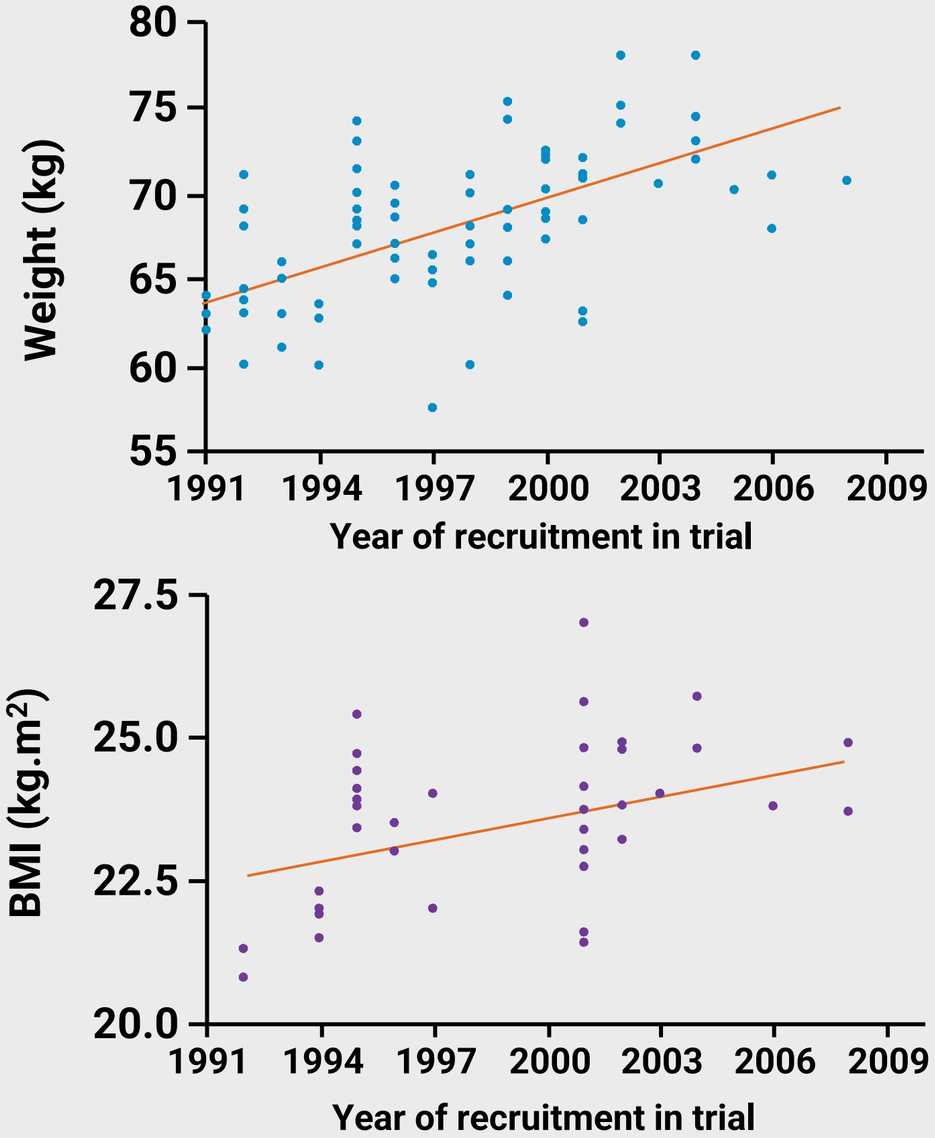
Obesity Impacts Pharmacokinetics of Biologic Agents



- Obesity modifies systemic drug exposure and absorption:
  - Weight-based dosing vs fixed dose
  - Intravenous vs subcutaneous
- High body weight is associated with pharmacokinetic effects across several biologics, with alterations in drug clearance and trough concentrations:
  - E.g., adalimumab, certolizumab, golimumab, infliximab, natalizumab, ustekinumab, vedolizumab
  - The effects of obesity on newer agents (e.g., mirikizumab and risankizumab) are still being investigated

Bassi M, et al. *BioDrugs*. 2022;36:197-203. Rosario M, et al. *Aliment Pharmacol Ther.* 2015;42:188-202. Sarmiento K, et al. *Cureus*. 2026;18:e105055. Harper JW, et al. *World J Gastroenterol*. 2016;22:7868-7881. Foley JF, et al. *Neurol Neuroimmunol Neuroinflamm*. 2024;11:e200321.

Time-Trends in Obesity in IBD – Clinical Trials



- 40 trials in CD
- 1991 to 2008
- 10,282 patients
- Average weight increased from 57.1 kg (1991) to 89.1 kg (2008)

Moran GW, et al. *Inflamm Bowel Dis.* 2013;19:2949-2956.

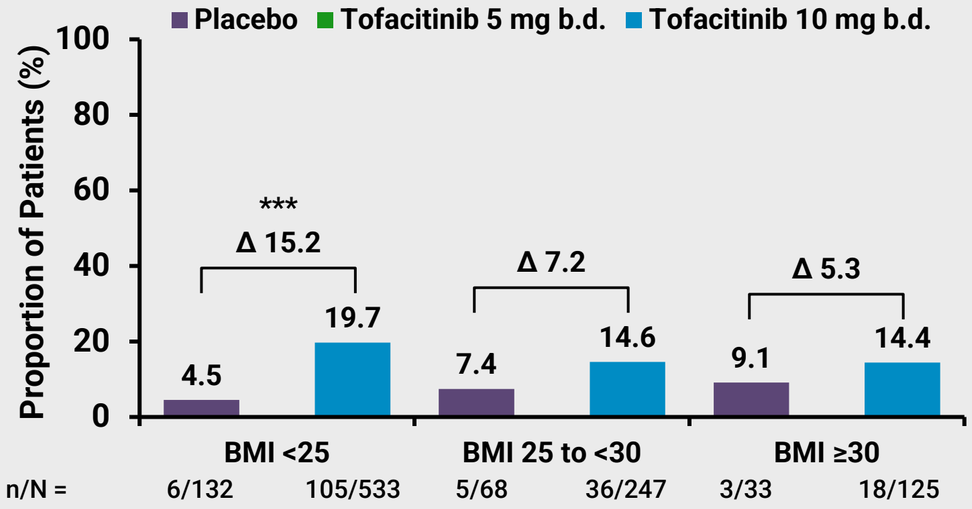
Impact of Obesity on Response to Biologic Agents in UC

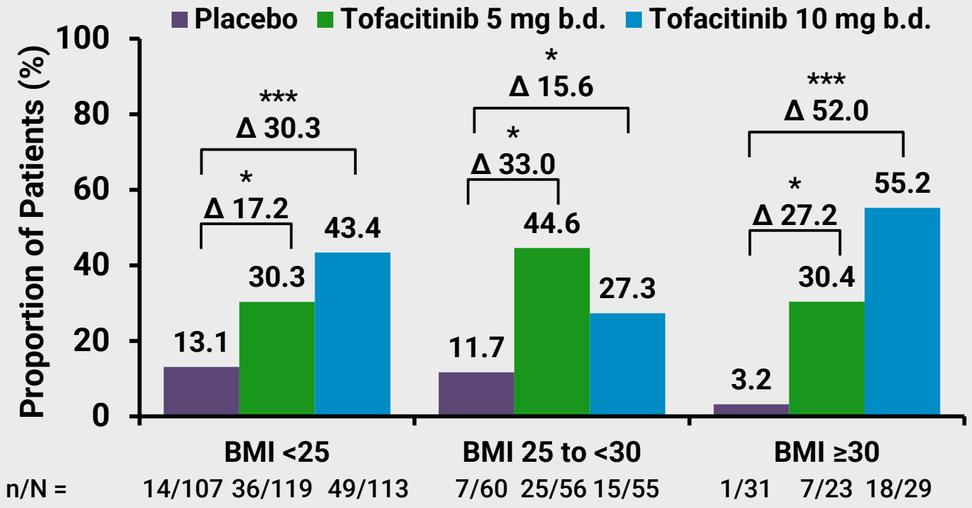
- Single-center, retrospective cohort study, 2011 to 2016
- 160 patients with UC, 55% on weight-based therapy (infliximab), 45% on fixed dose therapy (adalimumab, golimumab, vedolizumab)
- 1 kg/m^2 increase in BMI associated with a **4% higher risk of treatment failure** (HR, 1.04; 95% CI, 1.00–1.08), and an **8% higher risk of surgery or hospitalization** (HR, 1.08; 95% CI, 1.02–1.14) (adjusting for age, sex, disease duration, hospitalization, prior anti-TNF therapy, steroid use, albumin)
- 1 kg/m^2 increase in BMI associated with a **6% lower risk of achieving endoscopic remission** (adjusted odds ratio [OR], 0.94; 95% CI, 0.87–1.00)

1kg/m^2 increase in BMI	Weight-based dosing	Fixed dose regimens
Treatment failure	1.05 (1.00-1.10)	1.05 (0.99-1.12)
Surgery/hospitalization	1.10 (1.03-1.19)	1.09 (0.99-1.20)
Endoscopic remission	0.98 (0.96-0.99)	0.96 (0.85-1.10)

Kurnool S, et al. *Aliment Pharmacol Ther*. 2018;47(11):1472-1479.

The Impact of BMI on Efficacy and Safety in the Tofacitinib OCTAVE UC Clinical Program





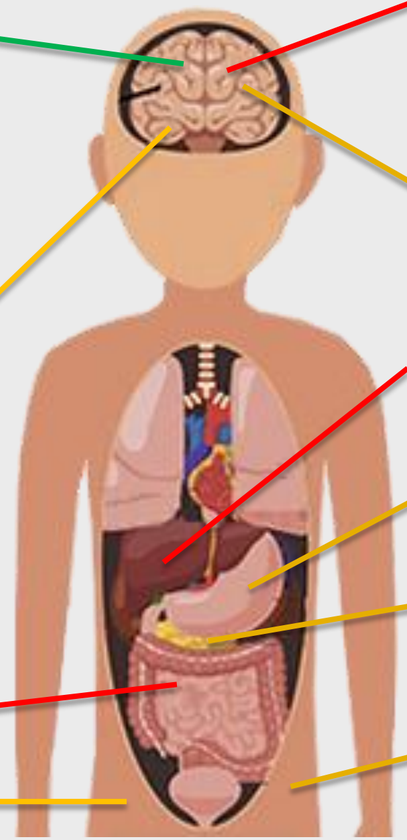
Post-hoc analysis of OCTAVE trials

- OCTAVE 1 and 2, OCTAVE Sustain
- 15% obese
- BMI was not associated with likelihood of achieving effectiveness outcomes (clinical remission/ response, endoscopic improvement, steroid-free remission)
- High BMI → higher risk of serious infections (though only 4 serious infections in obese category)

Odds ratio (OR) for OCTAVE Sustain – all patients (full analysis set [FAS], no imputation)				
Weight	1.00 (0.99, 1.01) [0.94]	1.00 (0.99, 1.01) [0.95]	1.00 (0.99, 1.01) [0.44]	1.01 (0.99, 1.03) [0.23]
BMI (continuous)	1.01 (0.97, 1.05) [0.59]	1.01 (0.97, 1.04) [0.75]	1.00 (0.96, 1.03) [0.79]	1.07 (0.99, 1.15) [0.077]
BMI (<25 vs ≥30)	0.90 (0.51, 1.57) [0.70]	0.94 (0.54, 1.64) [0.84]	0.96 (0.55, 1.65) [0.87]	0.39 (0.15, 1.06) [0.066]
BMI (25 to <30 vs ≥30)	0.84 (0.46, 1.56) [0.58]	0.89 (0.49, 1.63) [0.71]	0.82 (0.45, 1.49) [0.52]	0.33 (0.11, 1.03) [0.056]

Farraye FA, et al. *Aliment Pharmacol Ther.* 2021;54:429-440.

Drug-Induced Weight Loss Mechanism



↓ Food intake by inhibiting norepinephrine reuptake in hypothalamus

↓ Food intake by modulating on signaling pathway of NPY neurons, leptin, and GLP-1

↓ Food intake by inhibiting NPT/AgRP neurons and stimulating POMC/CART neurons

↓ Food intake by stimulating GABA secretion, thereby inhibiting AMPA/kainite excitatory glutamate receptors

↓ Hepatic gluconeogenesis

↓ Gastric emptying

↑ Insulin secretion
↓ Glucagon secretion

↓ Intestinal glucose uptake

↑ Resting energy expenditure

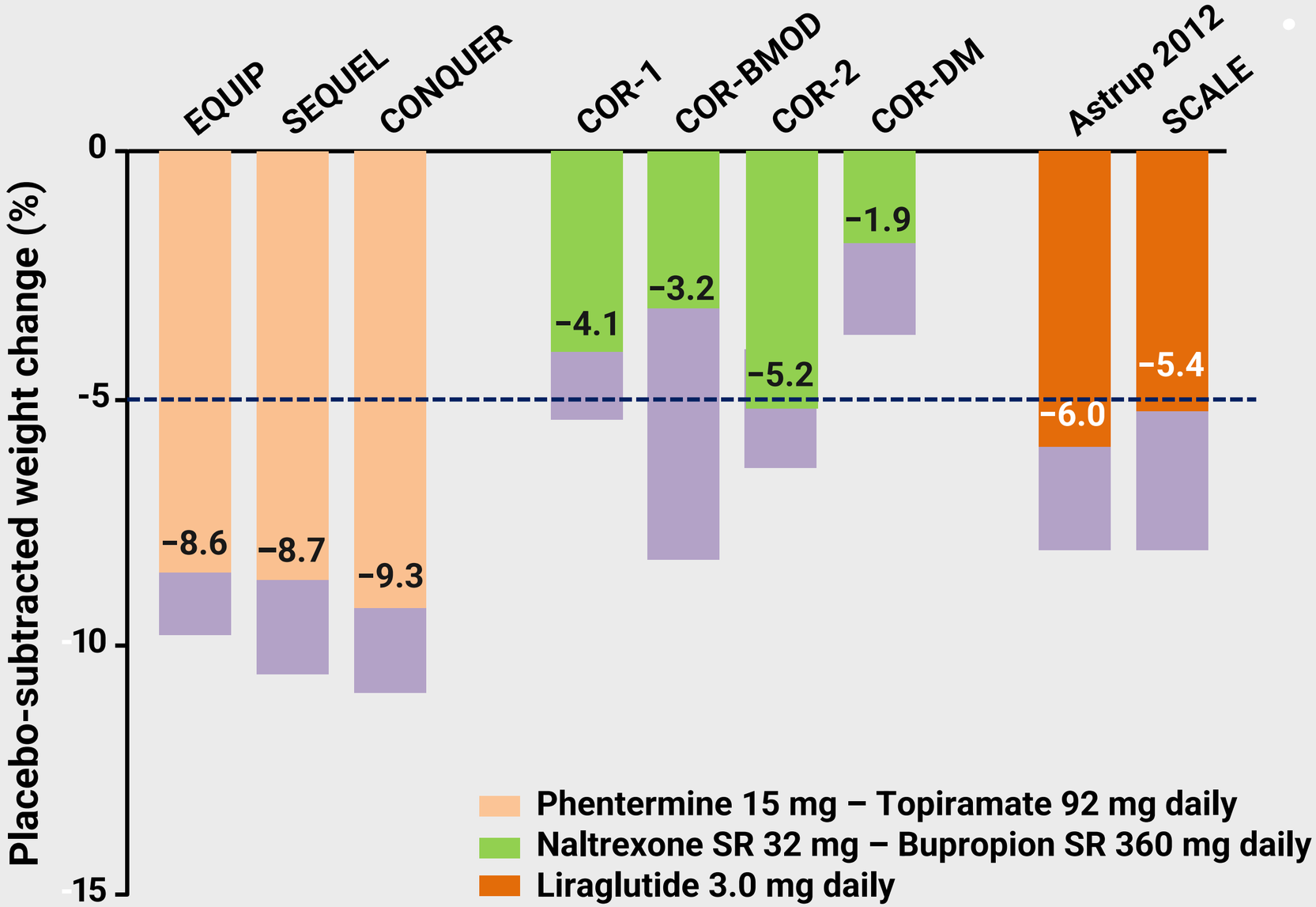
↑ Browning of white adipose tissue
↑ Thermogenesis of brown adipose tissue
↑ Resting energy expenditure

GLP-1 RA
Phentermine
Topiramate
Metformin

AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA = gamma-aminobutyric acid; GLP-1 RA = GLP-1 receptor agonist; NPT/AgRP = neuropeptide Y/agouti-related peptide; POMC/CART = proopiomelanocortin/cocaine-and amphetamine-regulated transcript.

Grandone A, et al. *Best Pract Res Clin Endocrinol Metab*. 2018;32:535-549.

Modest Weight Loss With Antiobesity Medications



SR = sustained-release.

Adapted from Rueda-Clausen CF, et al. *Nat Rev Endo.* 2013;9:467-478. Astrup A, et al. *Int J Obes.* 2012;36:843-854. Pi-Sunyer X, et al. *N Engl J Med.* 2015;373:11-22.

FDA-Approved Antiobesity Pharmacotherapy Agents

Drug	Main mechanism of action
Phentermine with topiramate*	Noradrenaline releaser and anticonvulsant
Diethylpropion*	Secondary to CNS effects, including stimulation of hypothalamus to release norepinephrine
Phendimetrazine*	Stimulates release of norepinephrine
Benzphetamine*	Stimulates release of norepinephrine
Bupropion with naltrexone	Noradrenaline/dopamine reuptake inhibitor and opioid receptor antagonist
Orlistat	Gastric and pancreatic lipase inhibitor
Liraglutide	GLP-1 receptor agonist
Semaglutide	GLP-1 receptor agonist
Tirzepatide	GLP-1/GIP dual agonist

* Controlled substance.

CNS = central nervous system; GLP-1 = glucagon-like peptide 1.

Adan RAH. *Trends Neurosci*. 2013;36:133-140. FDA. News release 6/4/2021 (www.fda.gov/news-events/press-announcements/fda-approves-new-drug-treatment-chronic-weight-management-first-2014). Accessed 12/11/2025.

Guidelines for Selecting Obesity Treatment

Treatment	BMI category (kg/m^2)				
	25–26.9	27–29.9	30–34.9	35–39.9	≥40
Diet, physical activity, and behavioral therapy	With comorbidities	With comorbidities	+	+	+
Antiobesity pharmacotherapy		With comorbidities	+	+	+
Metabolic and bariatric surgery			With comorbidities		

+ = Use of indicated treatment regardless of comorbidities.

Jensen MD, et al. *Circulation*. 2014;129(25 suppl 2):S102-S138. Jensen MD, et al. *Obesity*. 2014;22(suppl 2):S5-S39.

WHO and ADA/TOS Guidelines on GLP-1/GIP Therapies for Obesity Treatment

December 2025

WHO Guidelines
"In adults living with obesity, GLP-1 therapies may be used as a long-term treatment for obesity." ***Conditional recommendation; moderate certainty evidence***
"In adults living with obesity who are prescribed GLP-1 therapies, intensive behavioral therapy may be provided as part of a comprehensive multimodal clinical algorithm." ***Conditional recommendation; low certainty evidence***

January 2026

ADA/Obesity Association Guidelines
"Obesity medications should be offered as part of initial treatment for obesity to adults with or at high risk of obesity-related diseases or complications." ***A recommendation***
"In adults with overweight or obesity and T2DM, the preferred obesity medication should be a GLP-1 RA or dual GLP-1/GIP RA given their weight reduction and glucose-lowering efficacy." ***A recommendation***
Note: this guideline includes many other recommendations surrounding lifestyle intervention, treatment goals, medications, dosing, comorbidities, special populations, and counseling.

Please see guidelines for full recommendations and context.

ADA = American Diabetes Association; GIP = glucose-dependent insulinotropic polypeptide; TOS = The Obesity Society

Celletti F, et al. *JAMA*. 2025 (htpps://doi.org/10.1001/jama.2025.24288). ADA Professional Practice Committee for Obesity. 2026. https://diabetesjournals.org/docm-care/article/doi/10.2337/doci25-0008/164233/Pharmacologic-Treatment-of-Obesity-in-Adults. Accessed 1/14/26.

American Diabetes Association/Obesity Association: 2026 Guidelines on Obesity Pharmacotherapy

Goal: achievement and maintenance of weight reduction and prevention of obesity-related diseases and complications

Without related diseases or complications

Weight-reducing effect of obesity medication beyond 3% weight loss with lifestyle change alone*

High (>10%)	**Moderate (5–10%)**	**Modest (<5%)**
Tirzepatide (A)	Phentermine-topiramate (A)	Naltrexone-bupropion (**A**)
Semaglutide (A)		Liraglutide (**A**)
		Phentermine (**C**)
		Orlistat (**A**)

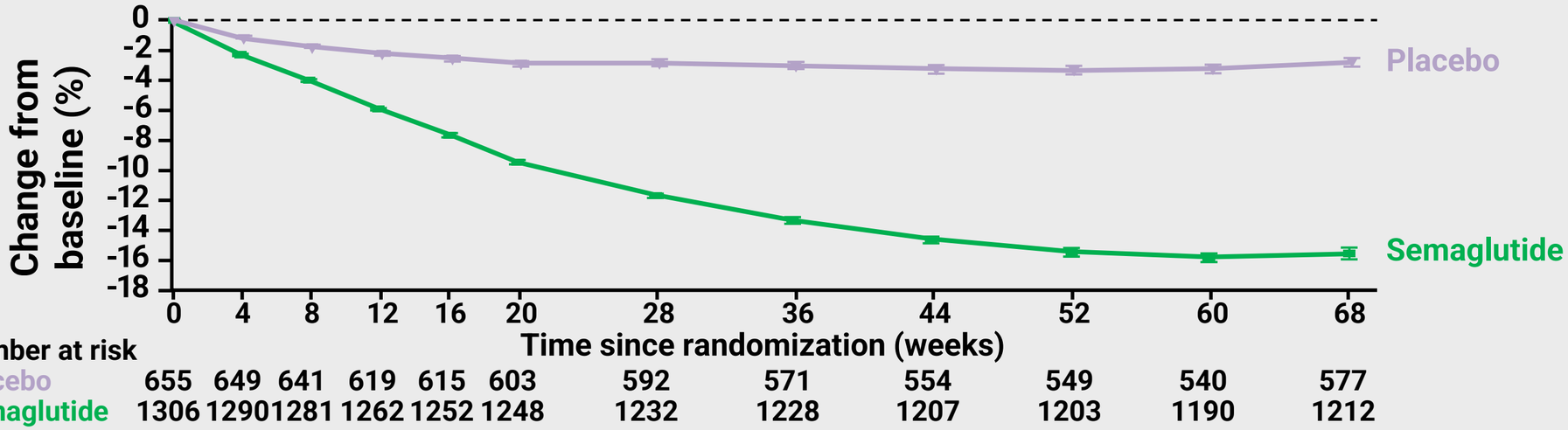
Select obesity medication that aligns with individual goals and does not present barriers to its long-term use

Levels of evidence: A = demonstrated benefit; B or C = potential benefit

ADA Professional Practice Committee for Obesity. 2026. https://diabetesjournals.org/docm-care/article/doi/10.2337/doci25-0008/164233/Pharmacologic-Treatment-of-Obesity-in-Adults. Accessed 1/14/26.

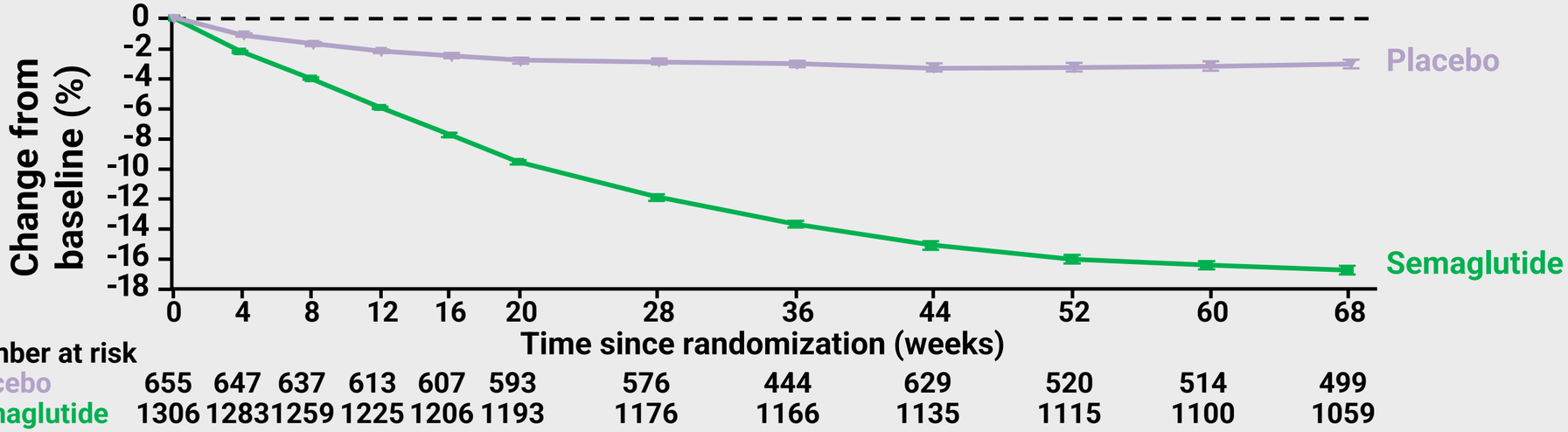
Effect of Once-Weekly Semaglutide vs Placebo on Body Weight (STEP-1)

Body weight change from baseline by week, observed in-trial data



Number 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

Body weight change from baseline by week, on-treatment data



Number at risk												
Placebo	655	647	637	613	607	593	576	444	629	520	514	499
Semaglutide	1306	1283	1259	1225	1206	1193	1176	1166	1135	1115	1100	1059

Wilding JPH, et al. *N Engl J Med*. 2021;384(11):989-1002.

Oral Semaglutide: Significant Weight Loss in OASIS 4
Approved by the FDA December 2025

- 71-week randomized controlled trial (RCT) (N = 205 patients with obesity, without diabetes)

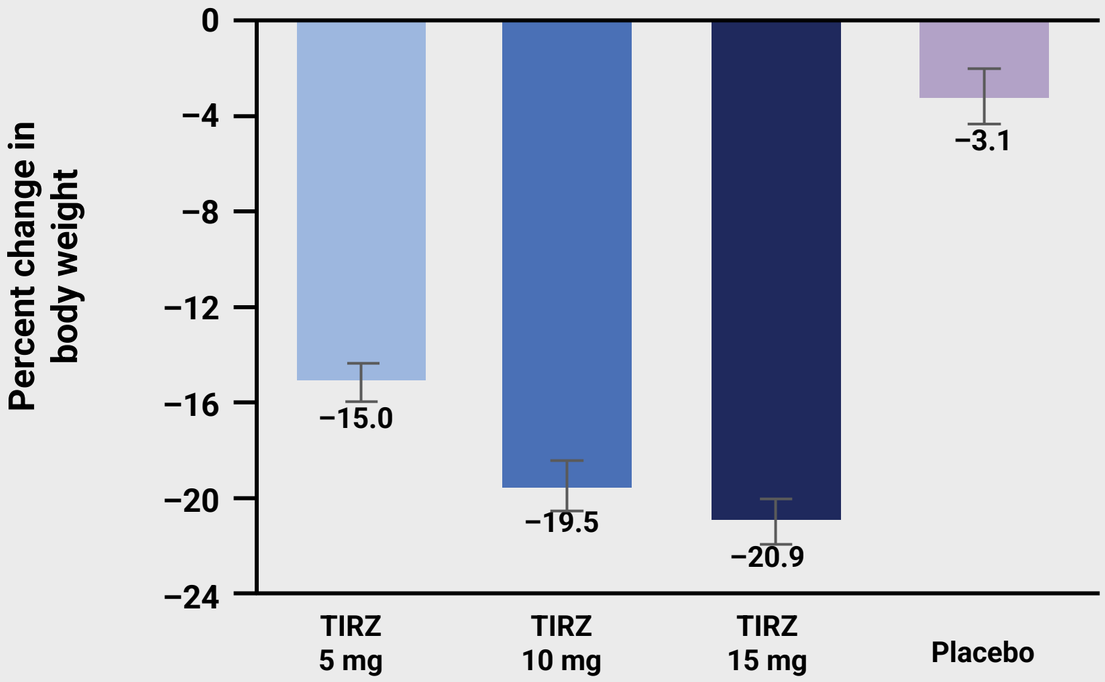
Semaglutide 25 mg	Placebo	95% CI	*P*-value
–13.6%	**–2.2%**	**–13.9 to –9.0**	**< .001**

- Semaglutide group
  - Significantly more likely to achieve 5%, 10%, 15%, and 20% weight reduction
  - Significantly higher improvement in physical function
  - Gastrointestinal (GI) events more common (74% vs 42% placebo)

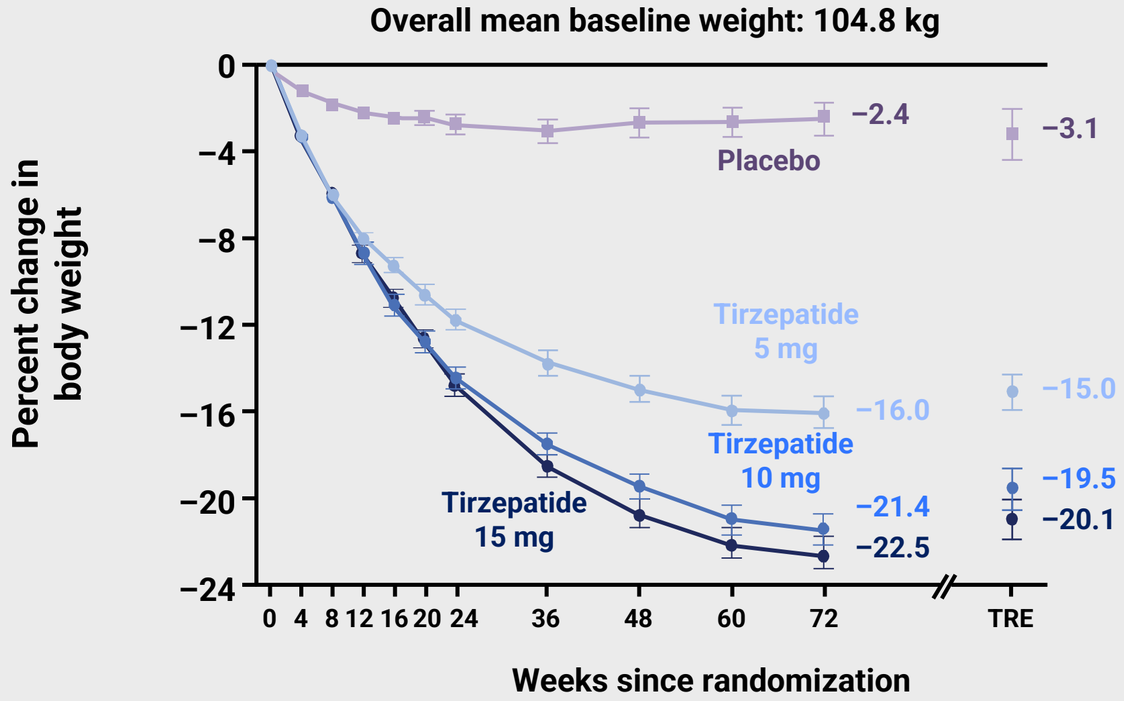
Wharton S, et al. *N Engl J Med*. 2025;393:1077-1087.

Effect of Once-Weekly Tirzepatide vs Placebo on Body Weight (SURMOUNT-1)

Overall percent change in body weight from baseline (treatment-regimen estimand)



Percent change in body weight by week (efficacy estimand)



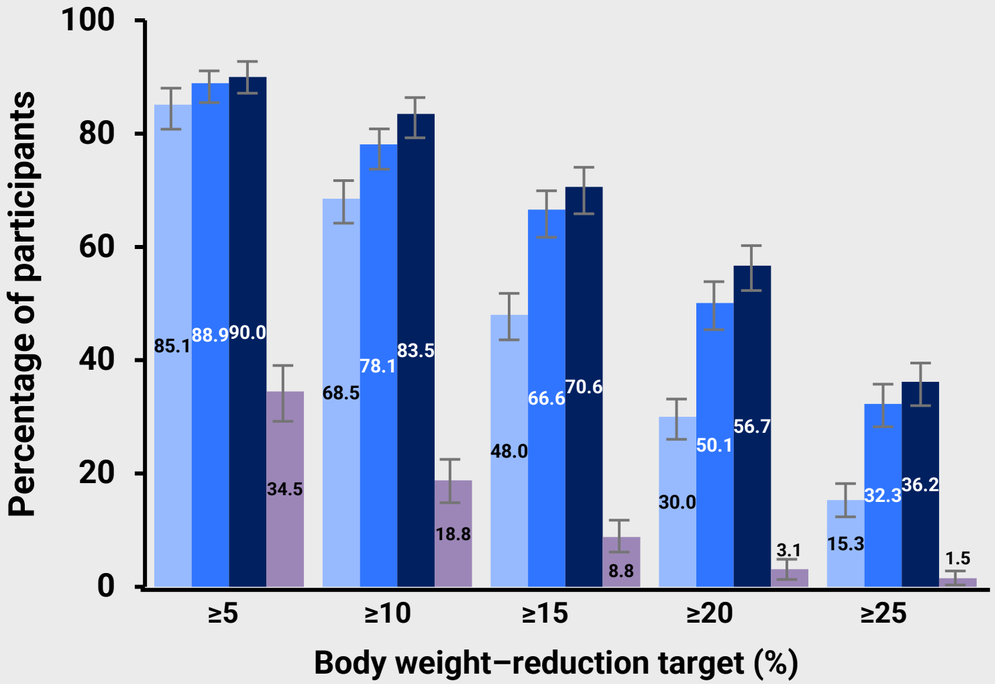
Tirzepatide 5 mg | Tirzepatide 10 mg | Tirzepatide 15 mg | Placebo

TIRZ = tirzepatide; TRE = treatment-regimen estimand.

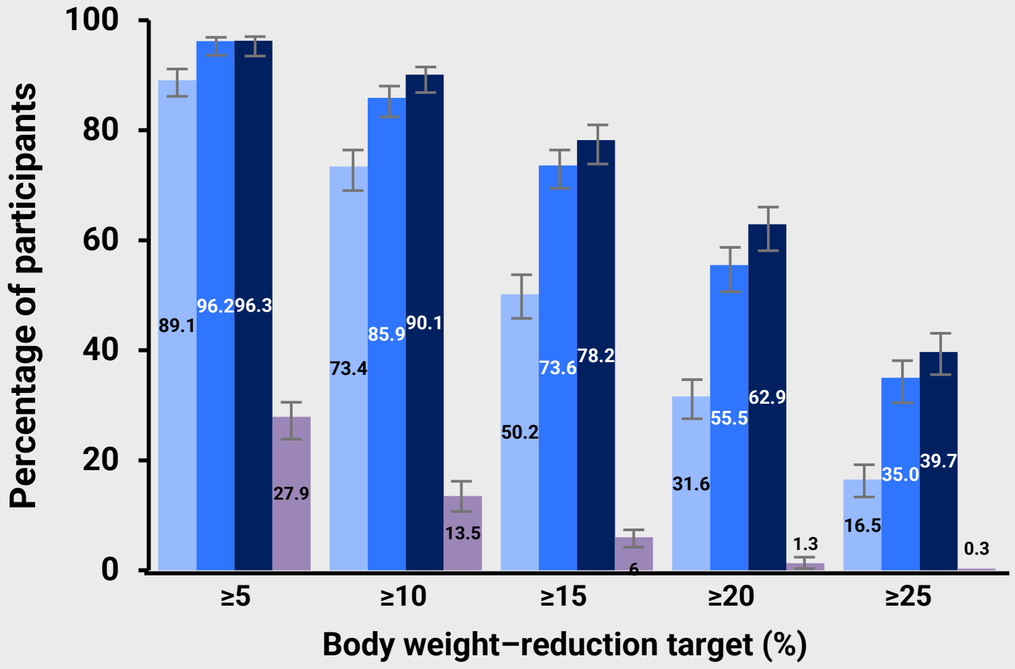
Jastreboff AM, et al. *N Engl J Med*. 2022;387(3):205-216.

Effect of Once-Weekly Tirzepatide vs Placebo on Body Weight (SURMOUNT-1)

Participants who met weight-reduction targets (treatment-regimen estimand)



Participants who met weight-reduction targets (efficacy estimand)

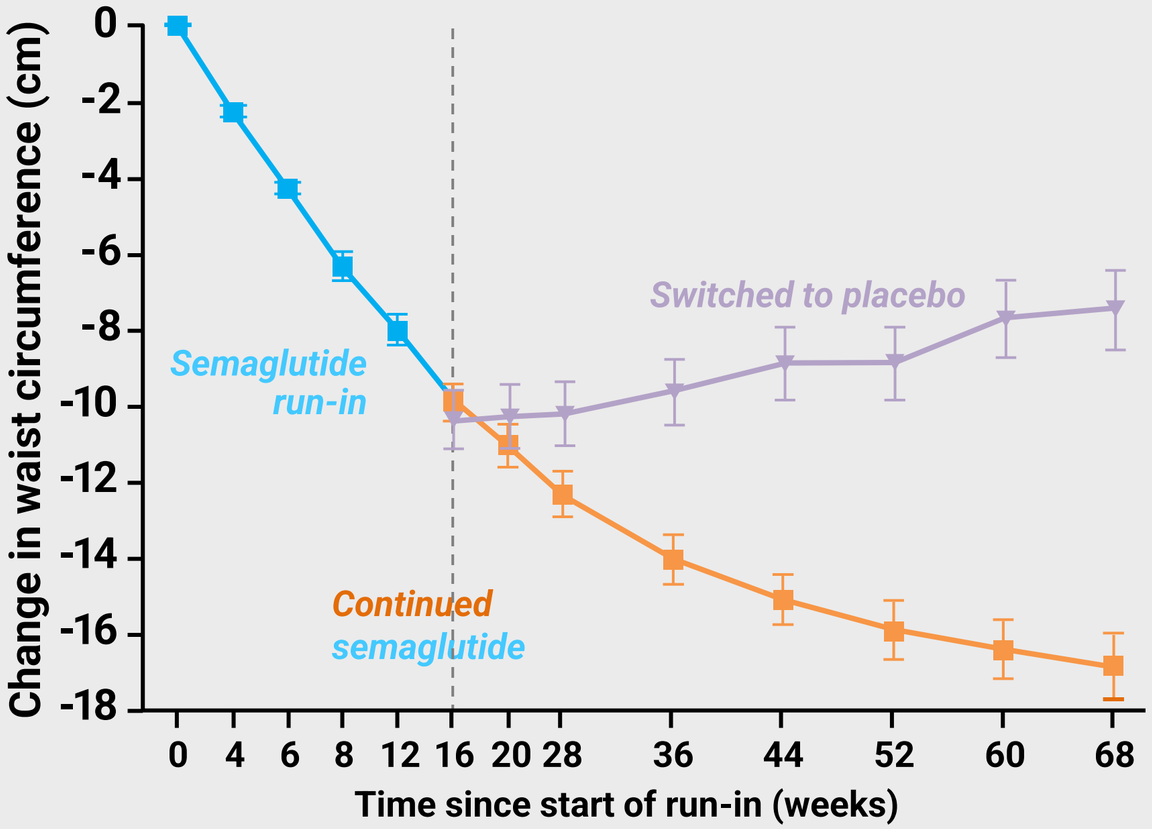


Tirzepatide 5 mg | Tirzepatide 10 mg | Tirzepatide 15 mg | Placebo

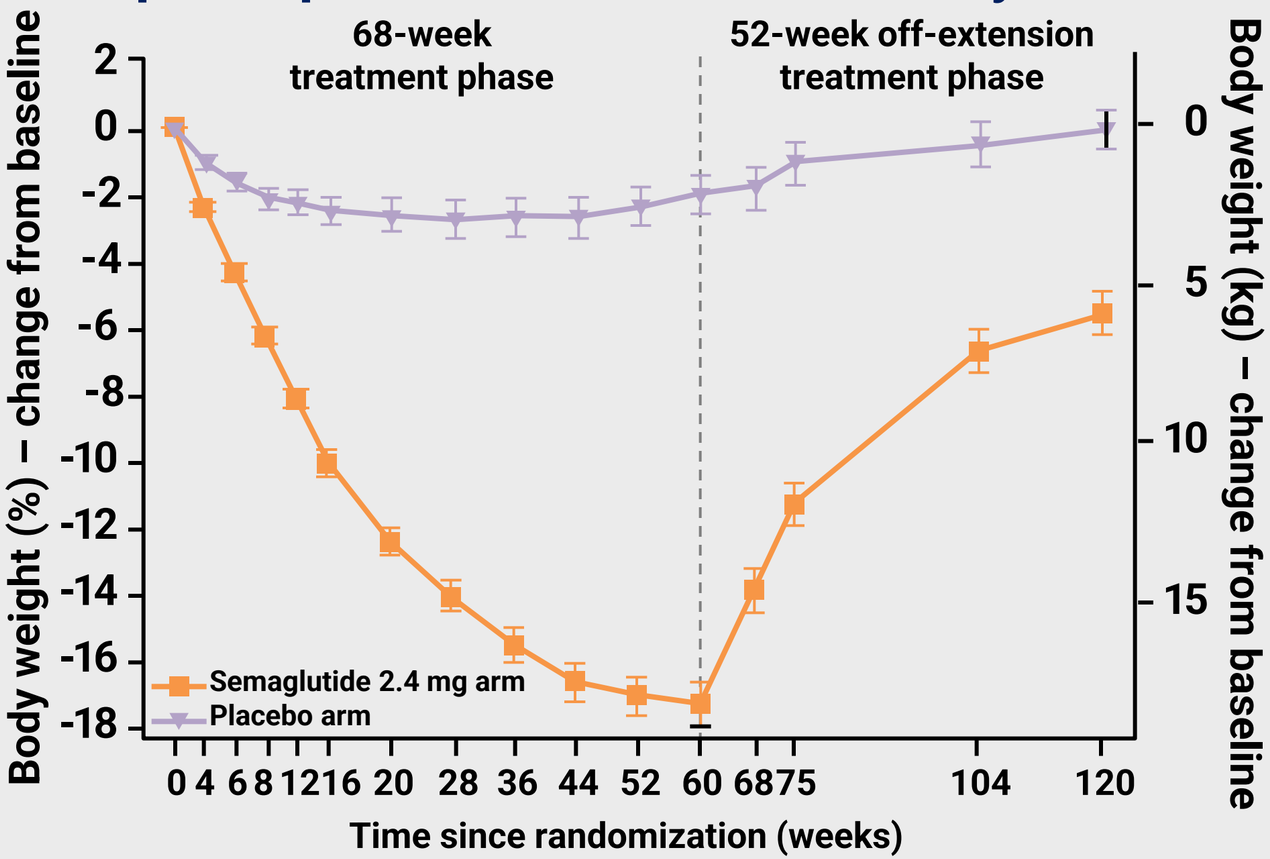
Jastreboff AM, et al. *N Engl J Med*. 2022;387(3):205-216.

Weight Regain After Drug Withdrawal?

Mean change in waist circumference Weeks 0 to 68, observed in-trial data



Change from baseline in body weight for all participants in the extension analysis



Rubino D, et al. *JAMA*. 2021;325:1414-1425. Wilding JPH, et al. *Diabetes Obes Metab*. 2022;24(8):1553-1564.

ATTAIN-1: Significant Weight Loss With Oral Orforglipron

- 72-week RCT (N = 3127 patients with obesity, without diabetes)

Orforglipron (95% CI)		Placebo	*P*-value
6 mg	**−7.5%** (−8.2 to −6.8)	**−2.1%** (−2.8 to −1.4)	**< .001**
12 mg	**−8.4%** (−9.1 to −7.7)		**< .001**
36 mg	**−11.2%** (−12.0 to −10.4)		**< .001**

- Orforglipron group
  - Significantly more likely to achieve 10%, 15%, and 20% weight reduction
  - Significantly higher improvement in waist circumference, systolic blood pressure (SBP), triglycerides, and non-high-density lipoprotein (HDL)
  - GI effects were most common, mostly mild/moderate

Not FDA approved for obesity.

Wharton S, et al. *N Engl J Med*. 2025;393:1796-1806.

GLP-1 RA Meta-Analysis: Cardiovascular (CV) and Non-CV Outcomes

Parameter	Hazard ratio (95% CI)	NNT (95% CI)	*p* value
3-point MACE	0.86 (0.80–0.93)	65 (45–130)	< .0001
Cardiovascular death	0.87 (0.80–0.94)	163 (103–353)	.0010
Fatal or non-fatal myocardial infarction	0.90 (0.83–0.98)	175 (103–878)	.020
Fatal or non-fatal stroke	0.83 (0.76–0.92)	198 (140–421)	.0002
All-cause mortality	0.88 (0.82–0.94)	114 (76–228)	.0001
Hospital admission for heart failure	0.89 (0.82–0.98)	258 (158–1422)	.013
Composite kidney outcome including macroalbuminuria	0.79 (0.73–0.87)	47 (37–77)	< .0001
Worsening of kidney function	0.86 (0.72–1.02)	241 (120 to −1694)	.089

Trials

ELIXA
LEADER
SUSTAIN-6
EXSCEL
Harmony Outcomes
REWIND
PIONEER 6
AMPLITUDE-O

MACE = major adverse cardiovascular events; NNT = number needed to treat.

Sattar N, et al. *Lancet Diabetes Endocrinol*. 2021;9(10):653-662.

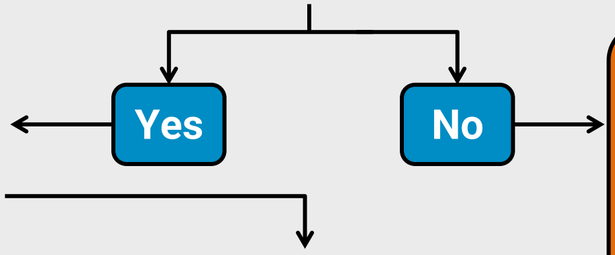
Suggested Script for Initiating Discussion of Obesity

Pre-screen: BMI and weight trajectory; 24-hour dietary recall; personal weight history; medications; physical activity; existing comorbidities or risk factors (eg, stress, sleep, quality of life, depression)

"Is now a good time for us to discuss how your weight and health may be affecting each other and how we can work together on it?"

Questions for the patient

- What concerns you most about your weight?
- What is the single most important outcome that you hope to achieve with weight loss?
- What would stand in the way of achieving this outcome?
- Is there a first step that you are ready to take?
- What impact will the changes we have discussed have on your life?
- Obesity is a chronic problem. What frequency and type of follow-up would be most helpful?



Provider response

- Acknowledge concerns
- Link obesity to diabetes and other comorbidities
- Provide resources
- Schedule follow-up or referral

Provider response

"I understand that you may not be ready to discuss your weight right now; however, I am concerned about the impact of your weight on your health. There may be some things that we can do together in the future. Please make a follow-up appointment if you'd like to discuss this later."

Modified from Gallagher C, et al. *Obesity (Silver Spring)*. 2021;29:821-824.