More Tears Are Shed Over Answered Prayers

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Disclosures

- *Scientific Advisor*: Abbvie, Altimmune, Amgen, AstraZeneca, Boehringer Ingelheim, Biohaven, Calibrate, Carmot/Roche, CINRx, Currax, eMed, Epitomee, Fractyl, Gila, Lilly, Nestle, Novo Nordisk, Pfizer, Regeneron, Scientific Intake, Source Bio, Structure Therapeutics, Tenvie, Wondr Health, Zealand

- *Speaker's Bureau*: Novo Nordisk, Lilly

- *Stock Options*: Epitomee, Calibrate, Roman, Scientific Intake, Xeno Bioscience

- *DSMB*: IQVIA setmelanotide (2); Lilly (1); CinRx (1)

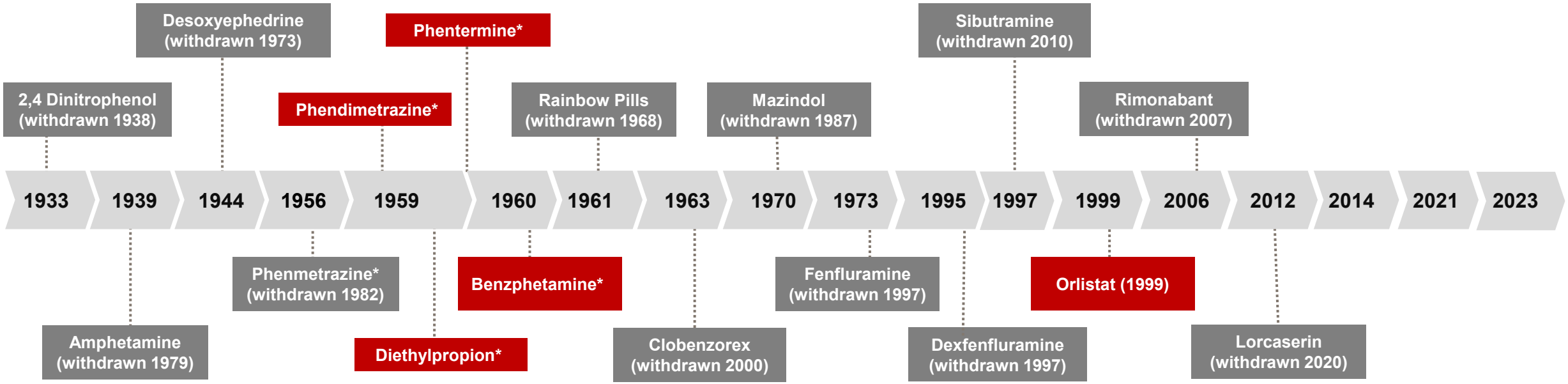
Answered Prayers

The Golden Age of Medications for Obesity

Learning Objectives

Difficult Beginnings	Robust Weight Loss	Disease-modifying	Challenges
Review the difficult path to developing successful medications for weight management;	Describe the weight loss efficacy and safety of semaglutide and tirzepatide and the promise of medications currently in phase 3;	Relate the evidence supporting disease-modifying attributes of the medications derived from nutrient stimulating hormones; and	Describe the challenges presented by these medications and ways we might overcome these challenges.

Early Days of Anti-Obesity Pharmacotherapies[1-3]



*Approved for short term use in the US

Withdrawn AOMs

AOMs on market

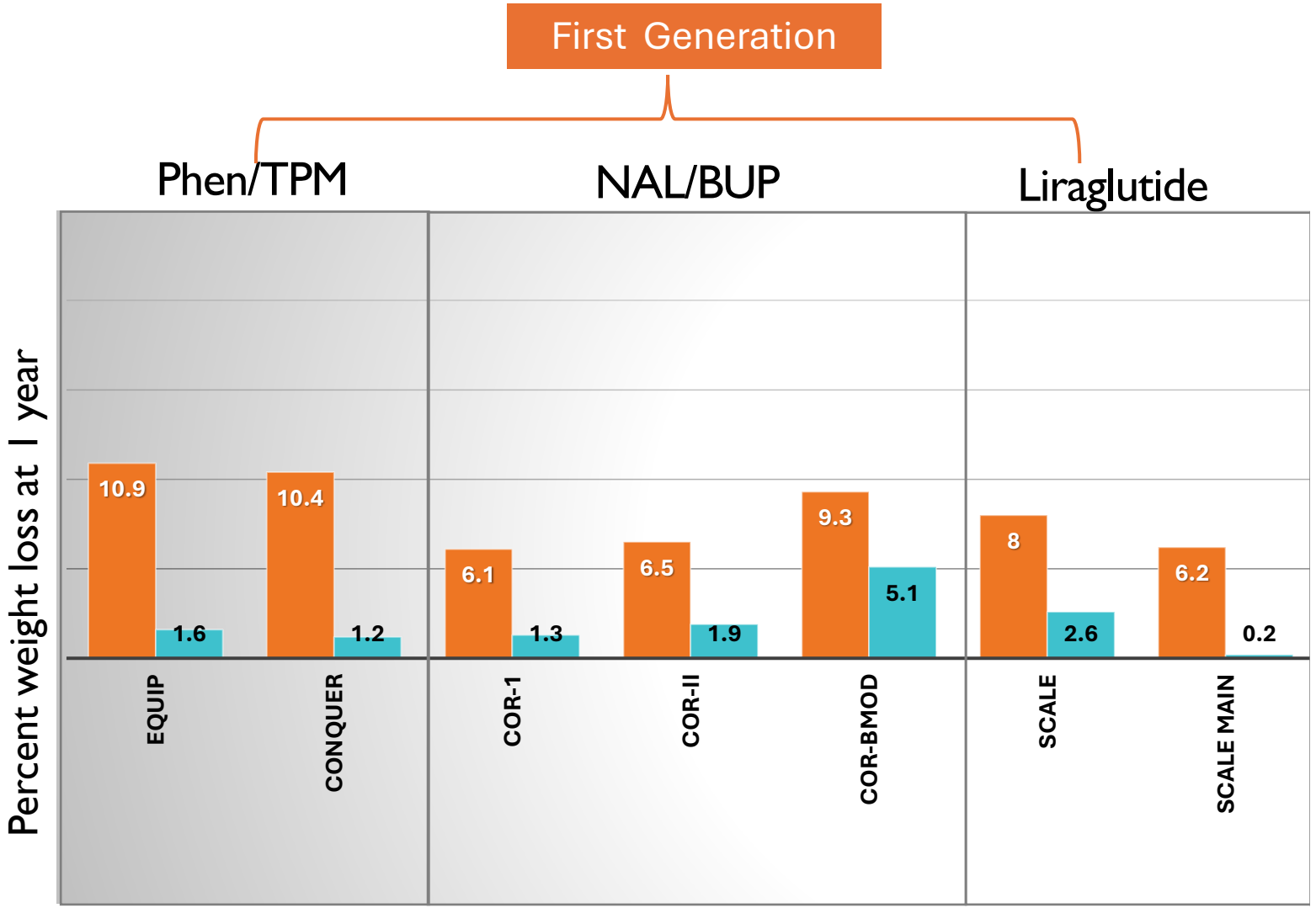
AOMs = Antiobesity medications

Slide adapted from Louis J. Aronne, M.D.

1. Pilitsi E, et al. *Metabolism*. 2019;92:170-192.
2. Müller TD, et al. *Nat Rev Drug Discov.* 2021;1-23.
3. Onakpoya IJ, et al. *BMC Med*. 2016;14:191.

MEDICATIONS INDICATED FOR CHRONIC WEIGHT MANAGEMENT

Percent weight loss (drug vs placebo) for obesity medications

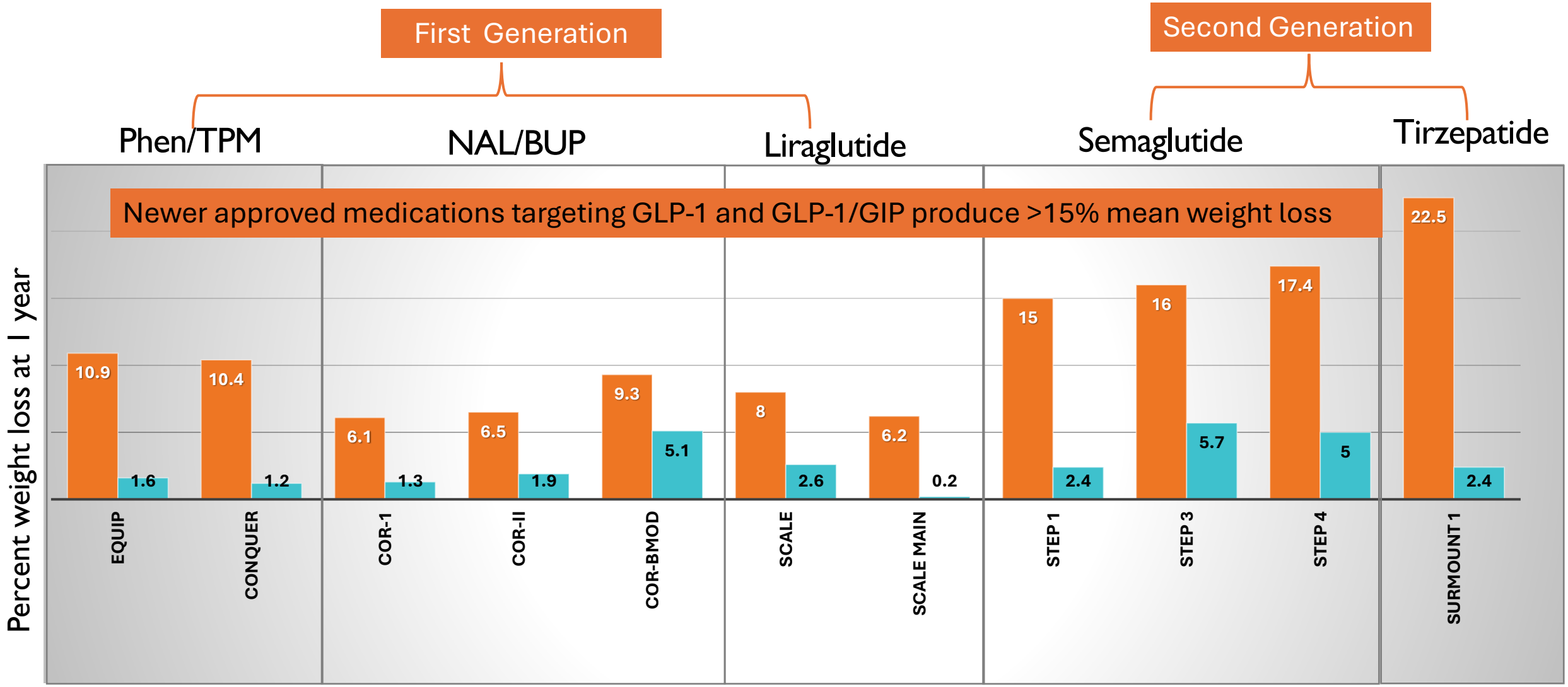


Allison DB, et al. *Obesity*. 2012;20(2):330-342. [EQUIP]. Gadde KM, et al. *Lancet*. 2011;37:1341-1352. [CONQUER]. Greenway FL, et al. *Lancet*. 2010;376:595-605. [COR-I]. Apovian CM, et al. *Obesity*. 2013;21:935-943 [COR-II]. Wadden TA, et al. *Obesity*. 2011;19(1):110-120. [COR-BMOD]. Pi-Sunyer X, et al. *N Engl J Med*. 2015;373(1):11-22. [SCALE]. Wadden TA, et al. *Int J Obes*. 2013;37:1443-1451. [SCALE MAIN]. Wilding JPH, et al. *N Engl J Med*. 2021;384(11):989-1002 [STEP 1]. Wadden TA, et al. *JAMA*. 2021;325(14):1403-1413. [STEP 3]. Rubino E, et al. *JAMA*. 2021;325(14):1414-1425 [STEP 4]. Jastreboff A, et al. *N Engl J Med*. 2022;387(3):205-216 [SURMOUNT1].

"Are we there yet?"

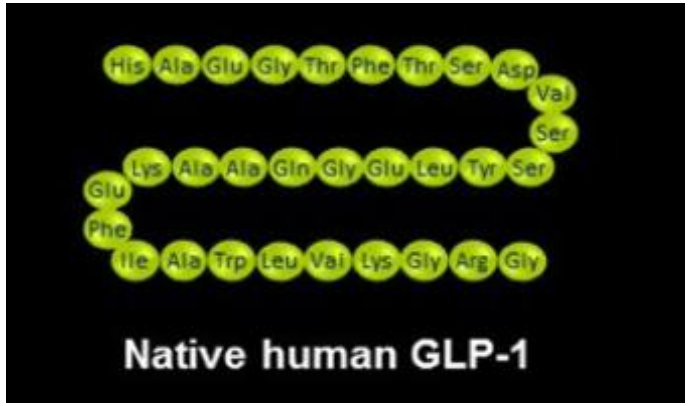
MEDICATIONS INDICATED FOR CHRONIC WEIGHT MANAGEMENT

Percent weight loss (drug vs placebo) for obesity medications

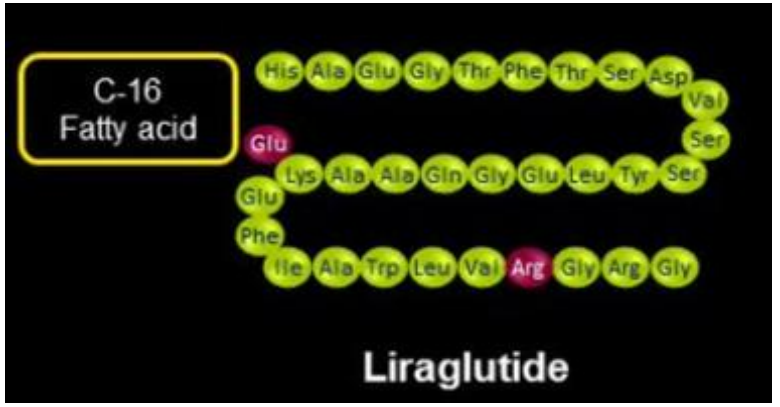


Allison DB, et al. *Obesity*. 2012;20(2):330-342. [EQUIP]. Gadde KM, et al. *Lancet*. 2011;37:1341-1352. [CONQUER]. Greenway FL, et al. *Lancet*. 2010;376:595-605. [COR-I]. Apovian CM, et al. *Obesity*. 2013;21:935-943 [COR-II]. Wadden TA, et al. *Obesity*. 2011;19(1):110-120. [COR-BMOD]. Pi-Sunyer X, et al. *N Engl J Med*. 2015;373(1):11-22. [SCALE]. Wadden TA, et al. *Int J Obes*. 2013;37:1443-1451. [SCALE MAIN]. Wilding JPH, et al. *N Engl J Med*. 2021;384(11):989-1002 [STEP 1]. Wadden TA, et al. *JAMA*. 2021;325(14):1403-1413. [STEP 3]. Rubino E, et al. *JAMA*. 2021;325(14):1414-1425 [STEP 4]. Jastreboff A, et al. *N Engl J Med*. 2022;387(3):205-216 [SURMOUNT1].

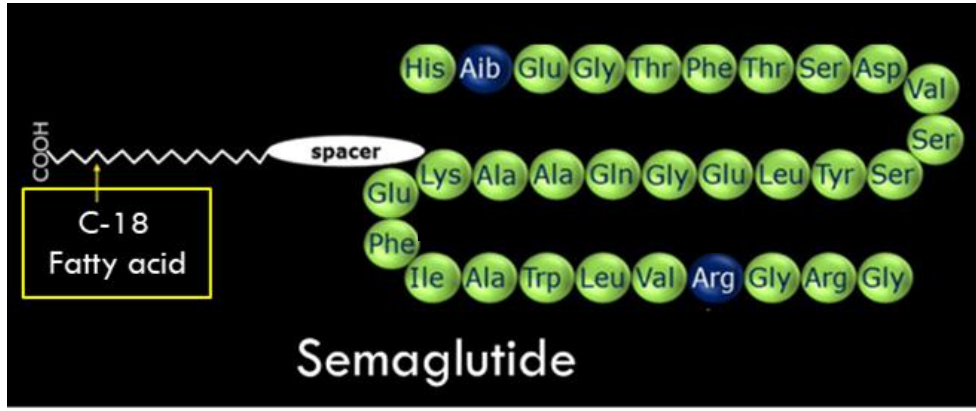
GLP-1 Physiology to Pharmacology



- Half life: 1–2 minutes
- Deactivated by DPP-4



- 97% homology
- Arginine replaces lysine @ 28
- Lysine at 20 conjugated to C-16 palmitic acid via gamma glutamic acid spacer (albumen binding)
- Reduced degradation and clearance
- Half life: 13 hours

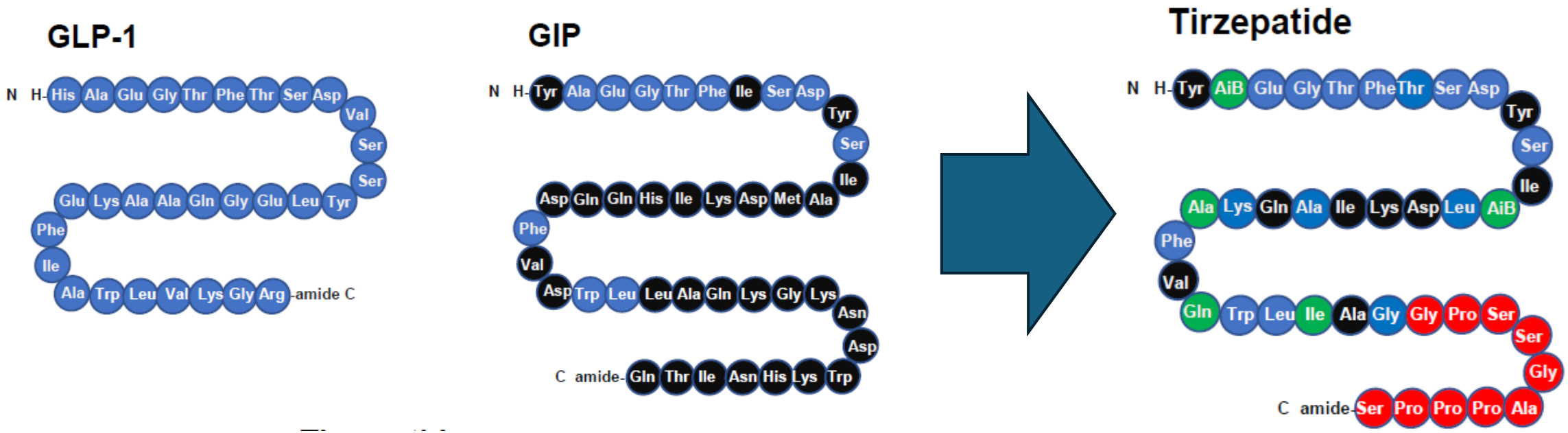


- 94% homology
- Arginine replaces lysine @ 28
- Aminoisobutyric acid replaces glycine at position 2 (resists degradation)
- C-18 fatty acid and lengthier spacer attached to Lysine (albumen binding)
- Reduced degradation and clearance
- Half life: 165 hours

DPP-4, Dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1.

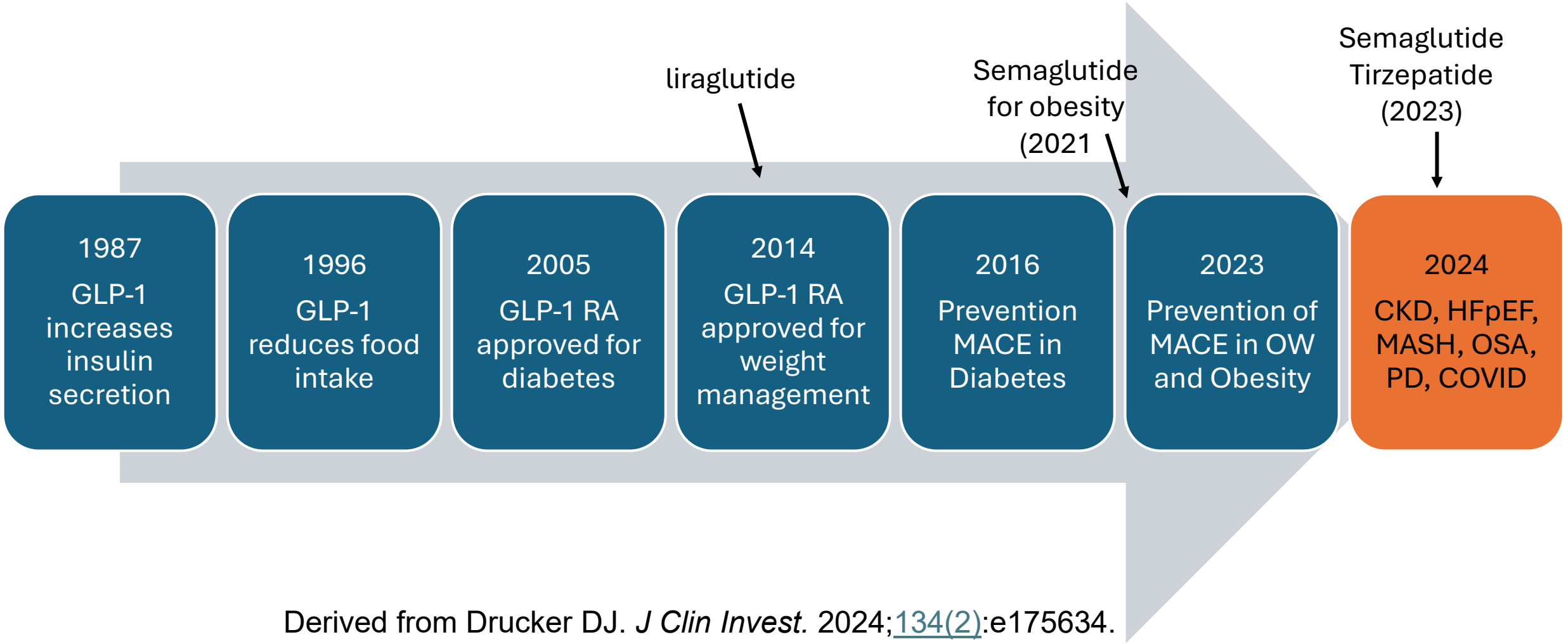
Brandt SJ, et al. Journal Internal Medicine 2018;284:581-602.

Structure of Tirzepatide – GLP-1 and GIP Receptor Dual Agonist



Tschöp et al (2023) Diabetologia DOI 10.1007/s00125-023-05929-0

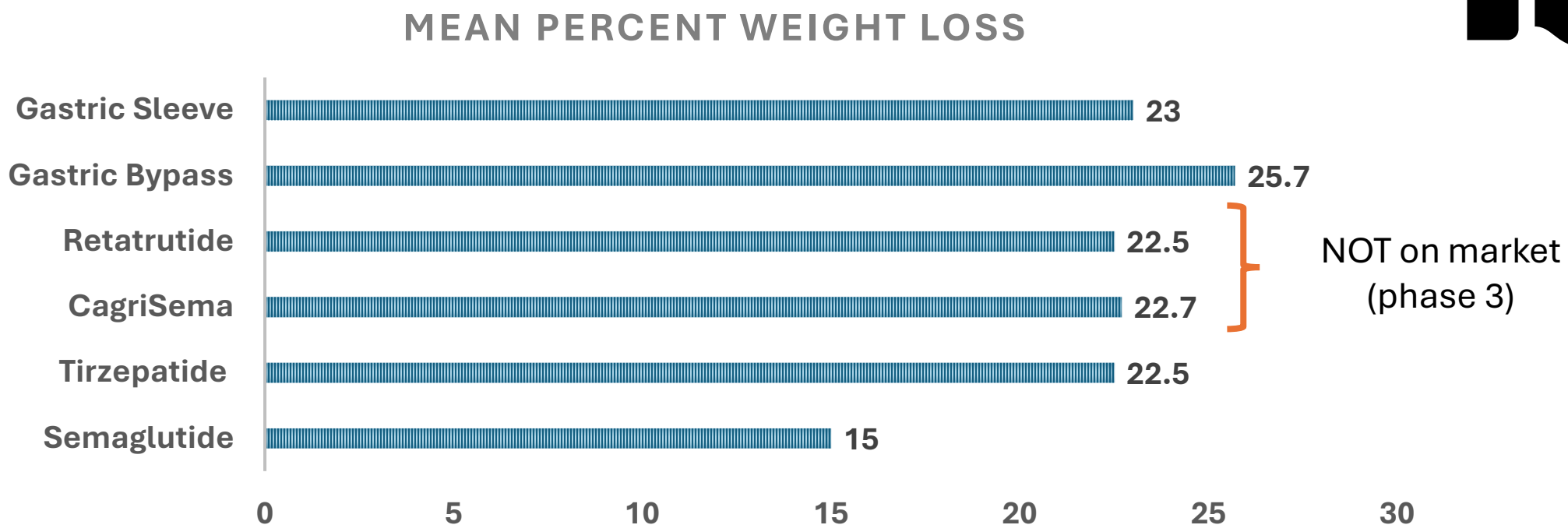
Timeline for GLP-1-based Discoveries and Therapies



Derived from Drucker DJ. *J Clin Invest.* 2024;134(2):e175634.

MACE – major adverse cardiovascular events, CKD – chronic kidney disease, HFpEF – heart failure with preserved ejection fraction, OSA – obstructive sleep apnea, MASH, PD = Parkinson's disease.

Make no mistake: the new GLP-1 medications produce robust mean weight loss



Arterburn DE, et al. Ann Surg. 2021 Dec 1;274(6):e1269-e1276. (Placebo-controlled, 1 year outcomes for surgery)
Cagrisema press release. Dec 20, 2024 https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=915082
Jastreboff A, et al. *N Engl J Med*. 2022;387(3):205-216 [SURMOUNT1].
Wilding JPH, et al. *N Engl J Med*. 2021;384(11):989-1002 [STEP 1].

Importantly: the new GLP-1 medications produce clinically significant weight loss in almost all patients

Almost all patients taking tirzepatide have meaningful weight loss

96.3% ≥5% loss

90.1% ≥10% loss

2.3% gained weight

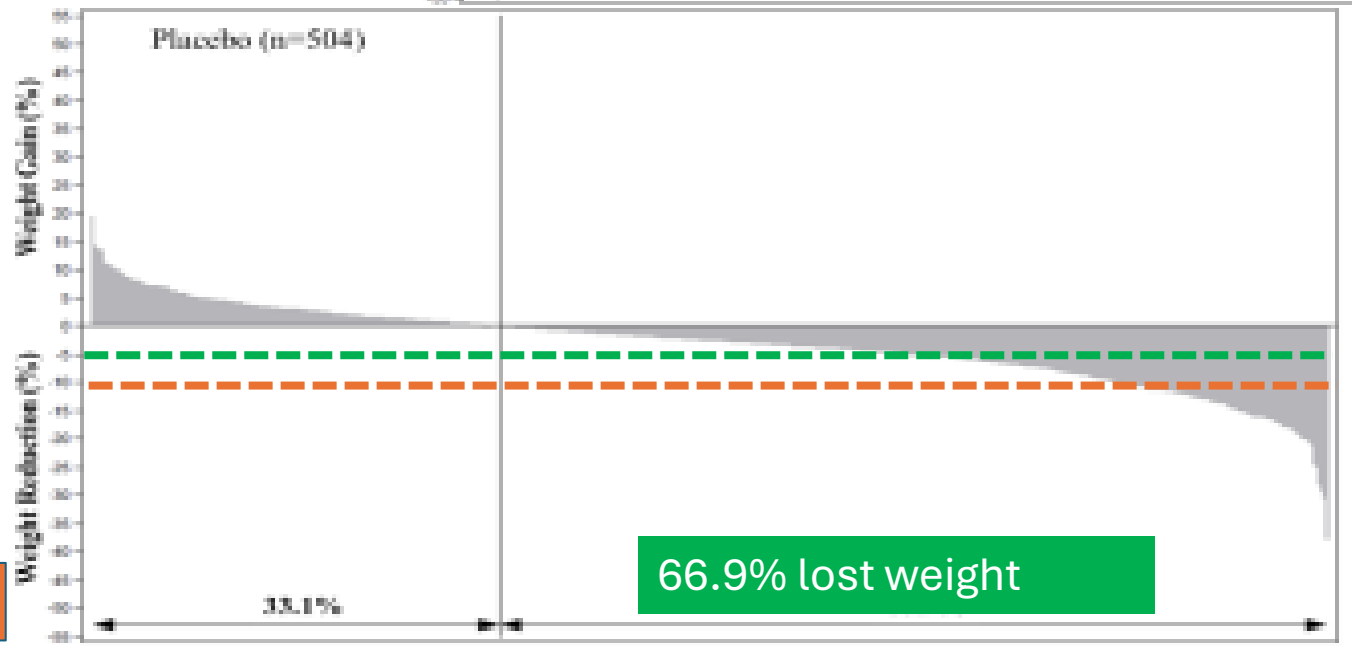
97.7% lost weight

Placebo

27.9% ≥5% loss

13.5% ≥10% loss

33.1% gained weight



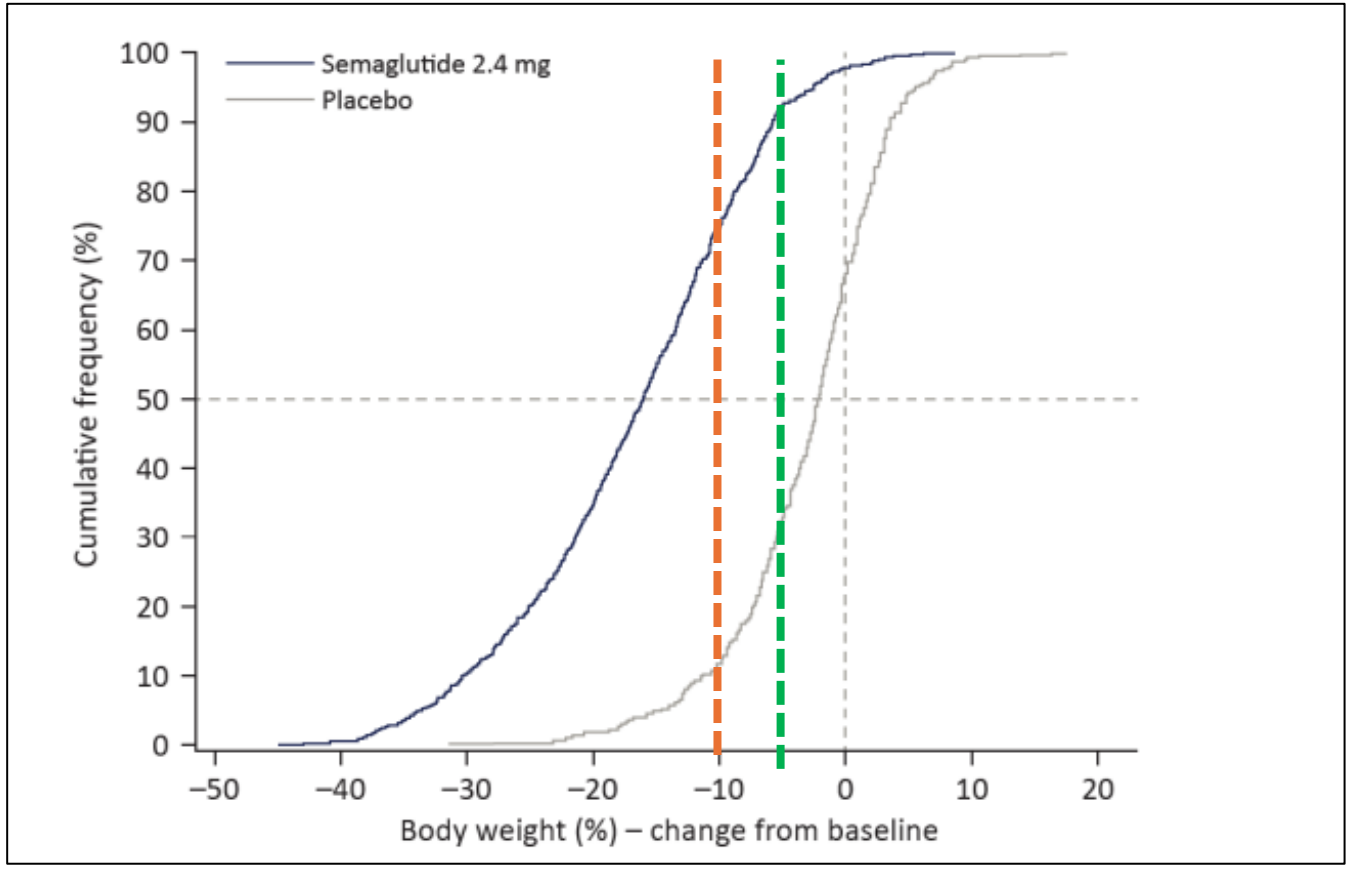
66.9% lost weight

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

On-Treatment Analysis

Cumulative distribution plot: STEP 1: Semaglutide 2.4 mg in adults with obesity

Percentage change in weight for semaglutide 2.4 mg vs placebo



Almost all patients taking semaglutide have meaningful weight loss

Semaglutide
92.4% ≥5% loss
74.8% ≥10% loss

Placebo
33.1% ≥5% loss
11.4% ≥10% loss

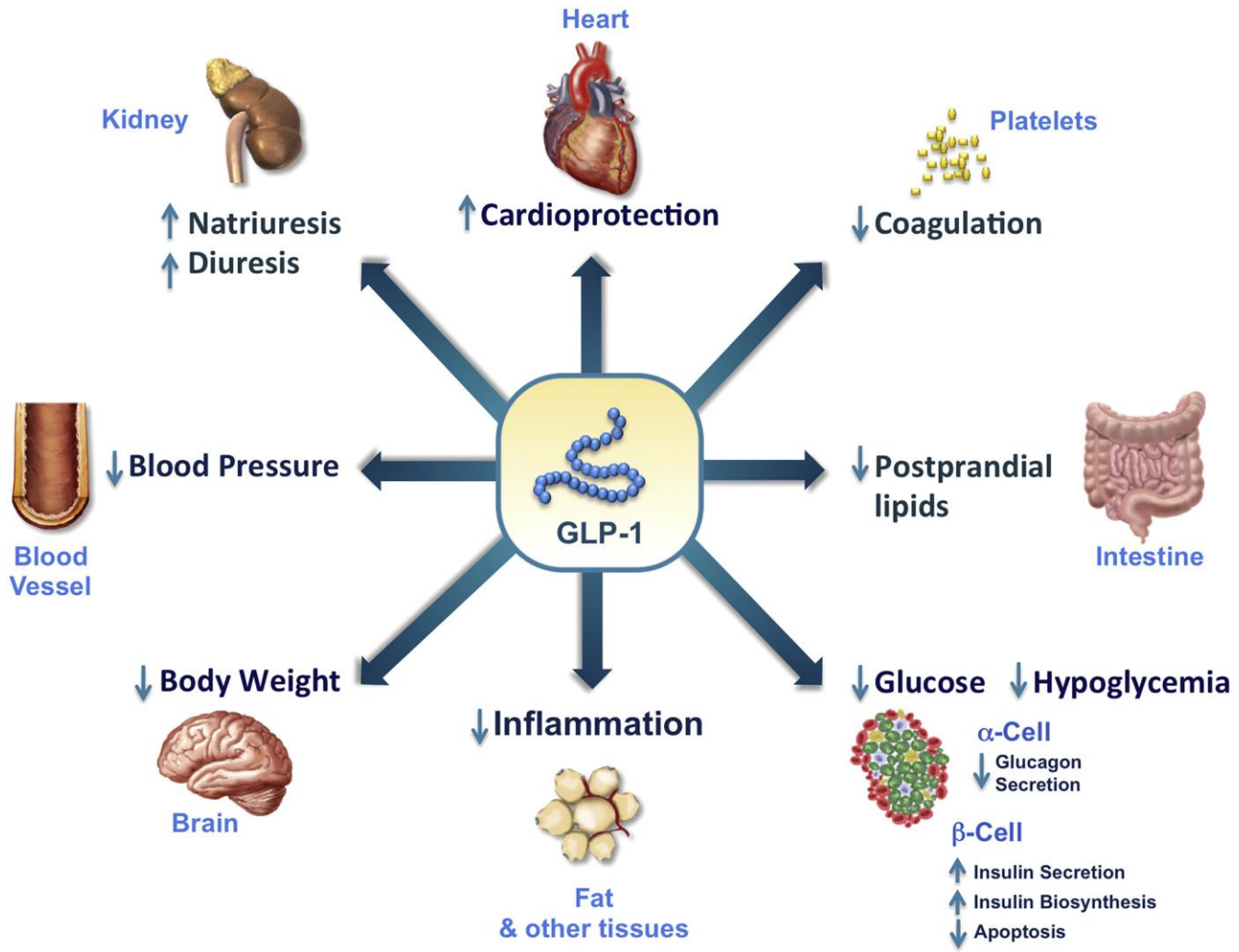
Wilding JPH, et al. *N Engl J Med*. 2021;384:989-1002.

On-Treatment Analysis

Even more importantly: the new GLP-1 medications are showing evidence of disease-modifying properties

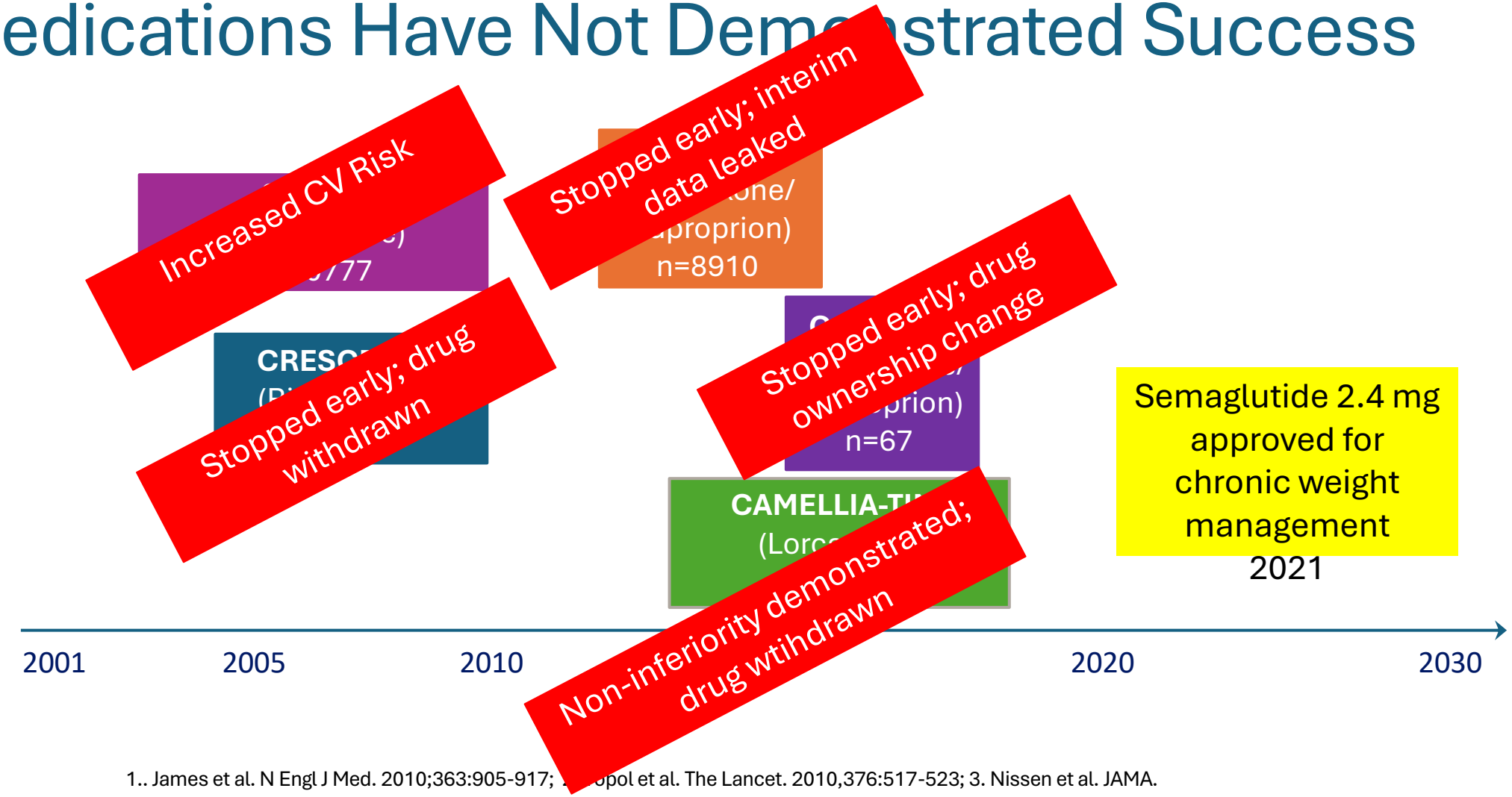
Society minimizes the potential of these drugs; its much more than weight loss

Native GLP-1 Has Pleiotropic Effects



Drucker DJ, *Cell Metabolism* 2016;24(1):15-30.

Cardiovascular Outcome Trials with Anti-obesity Medications Have Not Demonstrated Success

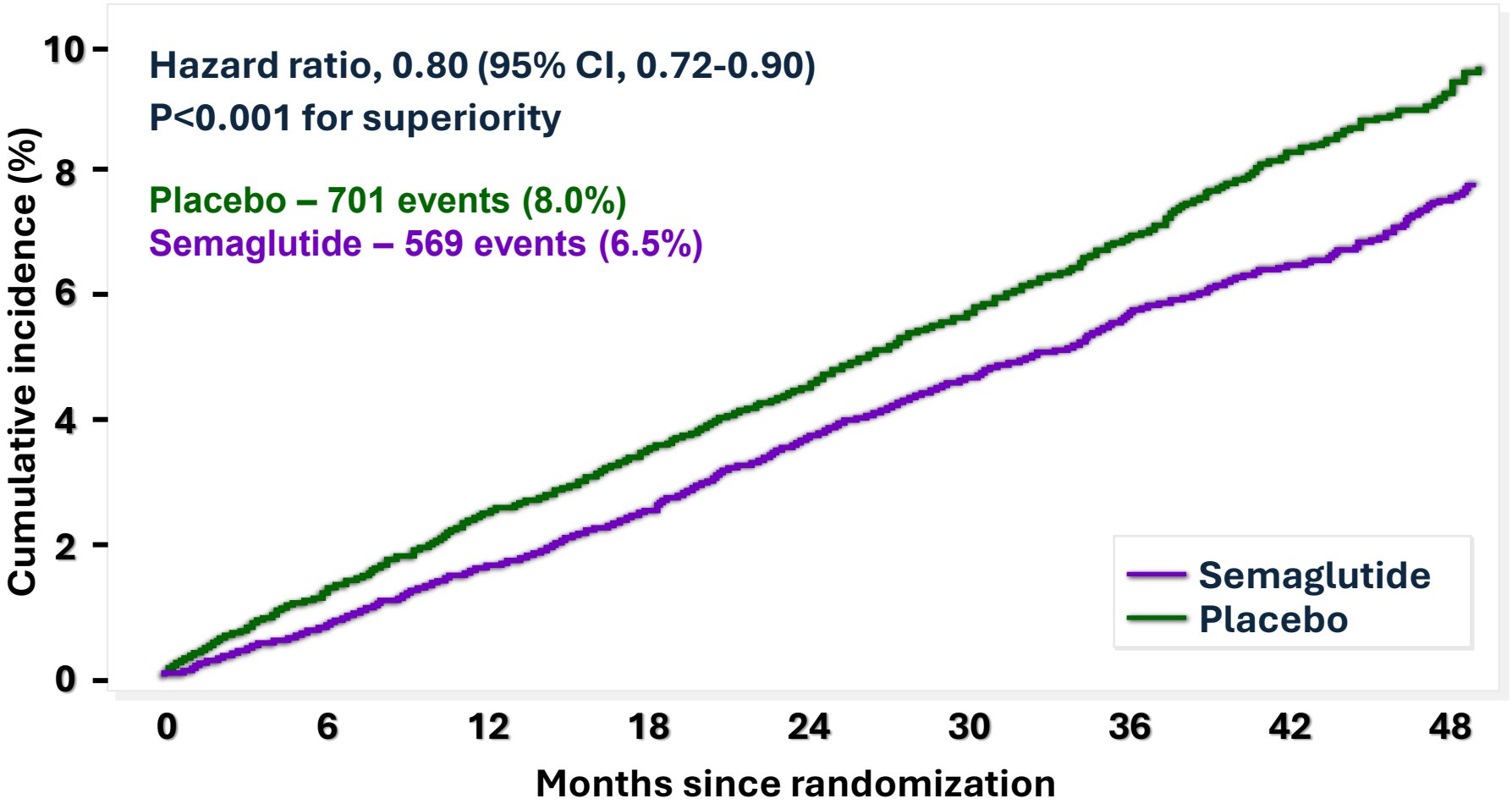


1.. James et al. N Engl J Med. 2010;363:905-917; 2. Lopol et al. The Lancet. 2010,376:517-523; 3. Nissen et al. JAMA. 2016;315:990-1004; 4.https://clinicaltrials.gov/ct2/show/NCT02638129; 5. Bohula et al. Am Heart J. 2018,202:39-48; 6. https://www.fda.gov/drugs/fda-drug-safety-podcasts/fda-requests-withdrawal-weight-loss-drug-belviq-belviq-xr-lorcaserin-market 7. https://www.tctmd.com/news/another-cv-outcomes-trial-testing-weight-loss-drug-contrave-terminated-early

SELECT trial – cardiovascular efficacy

CV death, nonfatal MI, or nonfatal stroke

Primary cardiovascular composite endpoint



20%
reduction in risk of MACE

Semaglutide 2.4 mg significantly reduced
the risk of MACE by 20%
compared with placebo in people with obesity and established CVD, without T2D

All three components (death from CV causes, nonfatal MI, and nonfatal stroke) contributed to MACE risk reduction

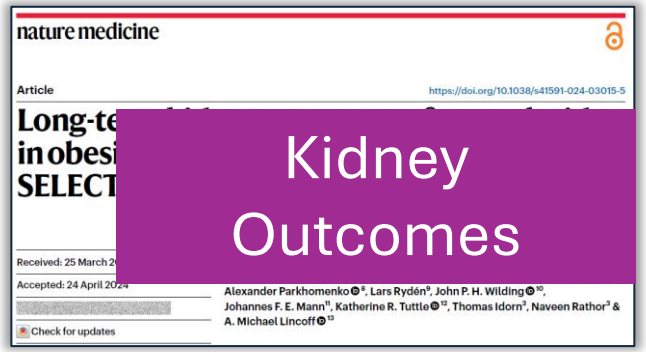
Mean follow-up time was 39.8 months

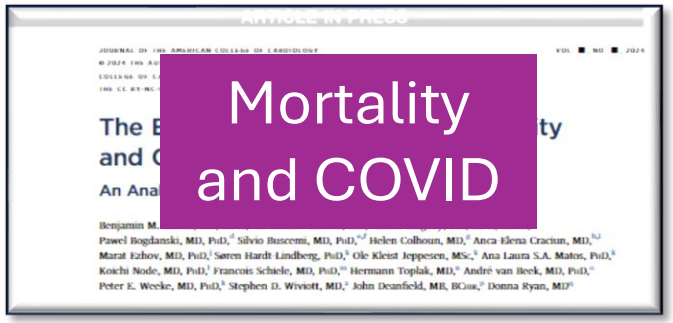
Lincoff AM, et al. *N Engl J Med*. 2023;389:2221-2232.

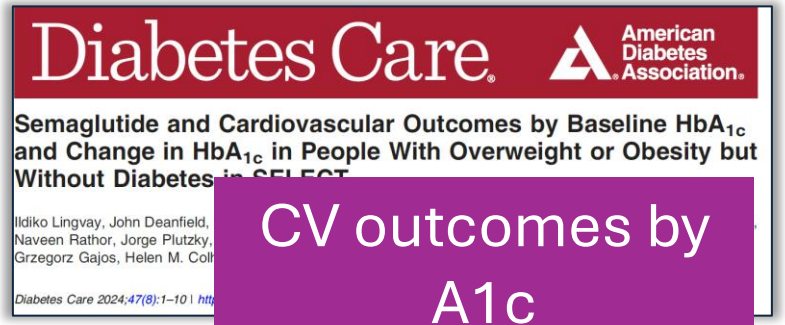
August 7, 2023

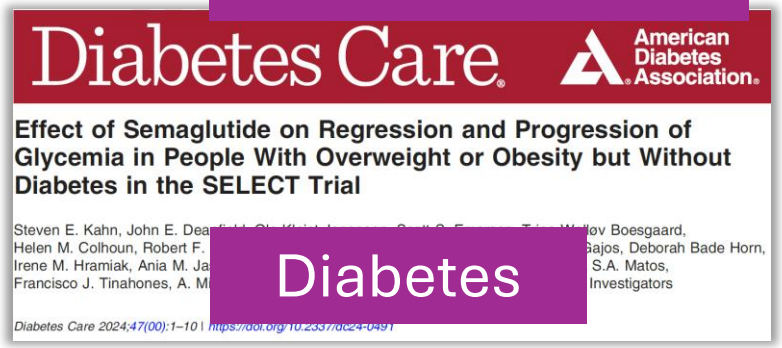

THE GAME CHANGER
Medicare will pay for coverage for OW and Obesity and CVD secondary prevention

Secondary Analyses from SELECT









COMING SOON

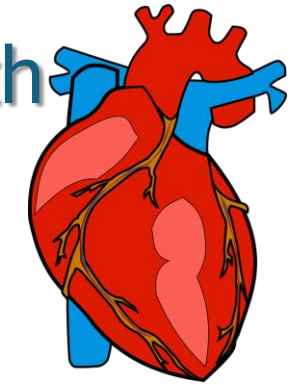
- Hospitalizations
- Effect of weight loss on MACE
- Inflammation
- Smoking Cessation
- Predictors of Weight Loss
- Mediation Analyses

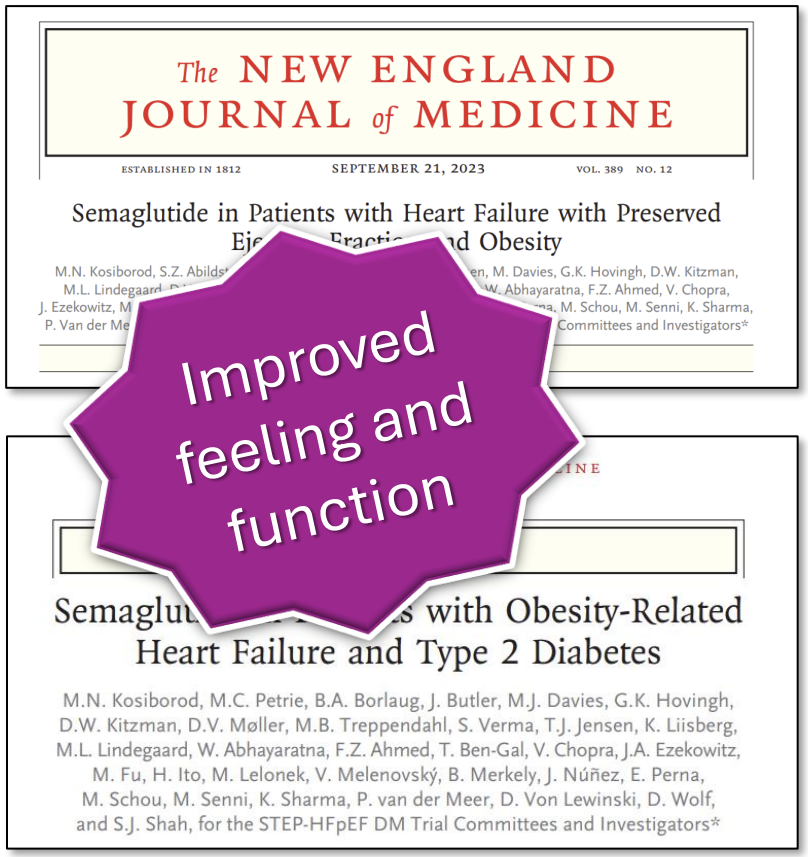
Ryan DH, et al. *Nat Med* 30, 2049–2057 (2024).
Colhoun HM, et al. *Nat Med* 30, 2058–2066 (2024)..
Lingvay I, et al. D*iabetes Care* 2024;47(8):1360–1369.

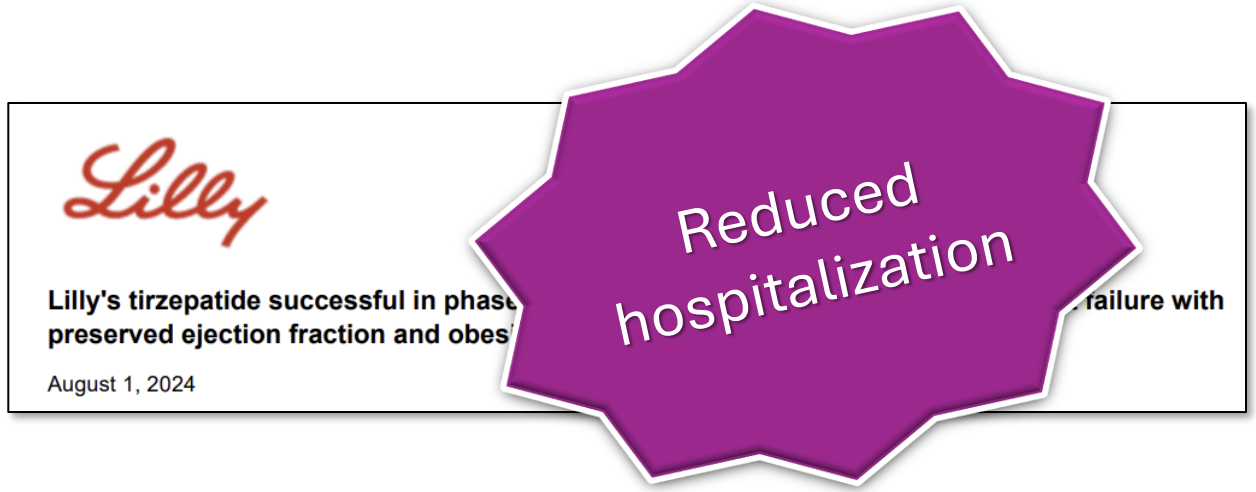
Kahn SE, et al *Diabetes Care* 2024;47(8):1350–1359
Scirica, B et al. *JACC*. 2024 Oct, 84 (17) 1632–1642.
Deanfield J et al. Lancet 2024;404:773.

Kushner RF, et al. Obesity. 13 February 2025 https://doi.org/10.1002/oby.24222

Semaglutide and Tirzepatide Effects on Heart failure with preserved ejection fraction
STEP HFpEF, STEP HpEF DM and SUMMIT

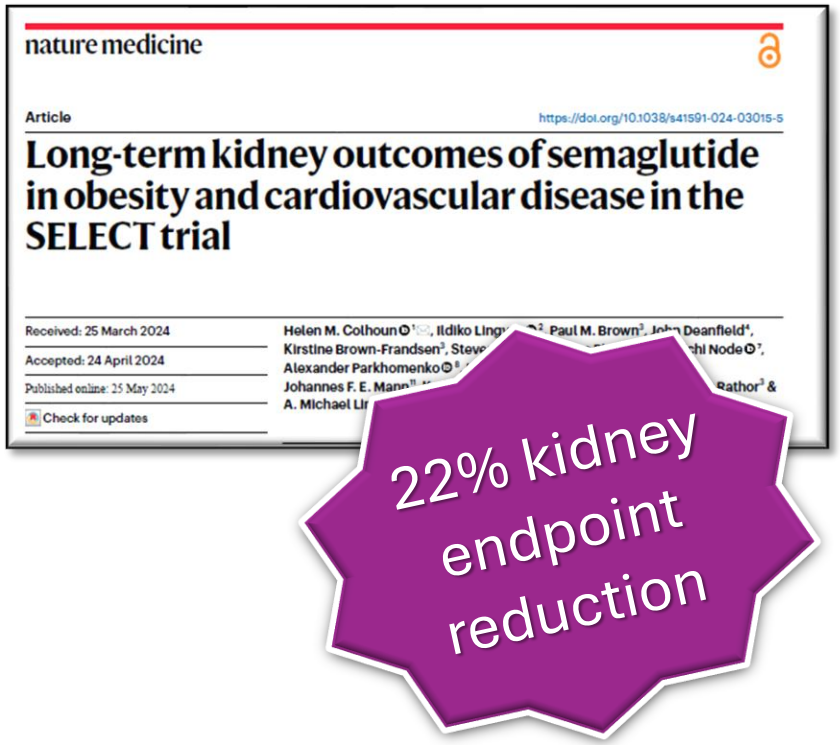






Kosiborod MN, et al. *N Engl J Med*. 2023;389:1069-1084.
Kosiborod MN, et al. *N Engl J Med.* 2024:390:1394-1407.
https://investor.lilly.com/node/51151/pdf

SELECT and FLOW: Semaglutide Effects on Chronic Kidney Disease

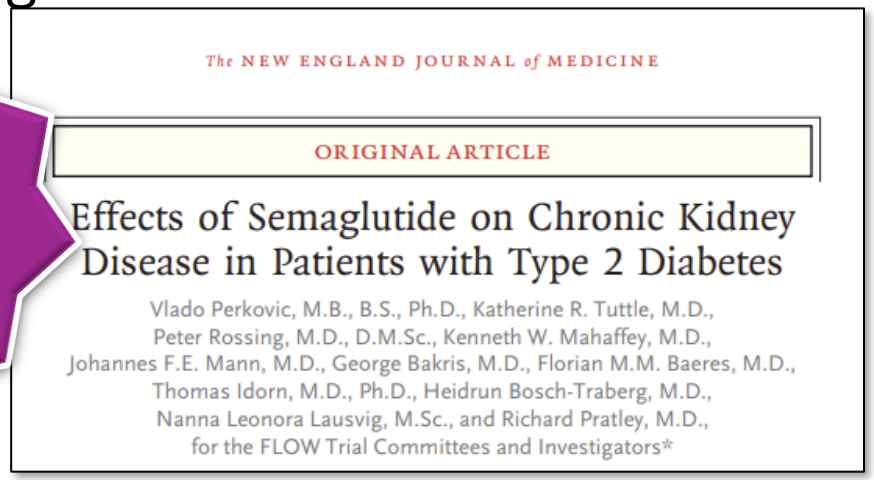


22% kidney endpoint reduction

FLOW: Semaglutide in patients with T2D

- In patients with CKD and T2D, semaglutide reduced the risk of the primary outcome* by 24% compared to placebo
- Benefits occurred regardless of SGLT2i use

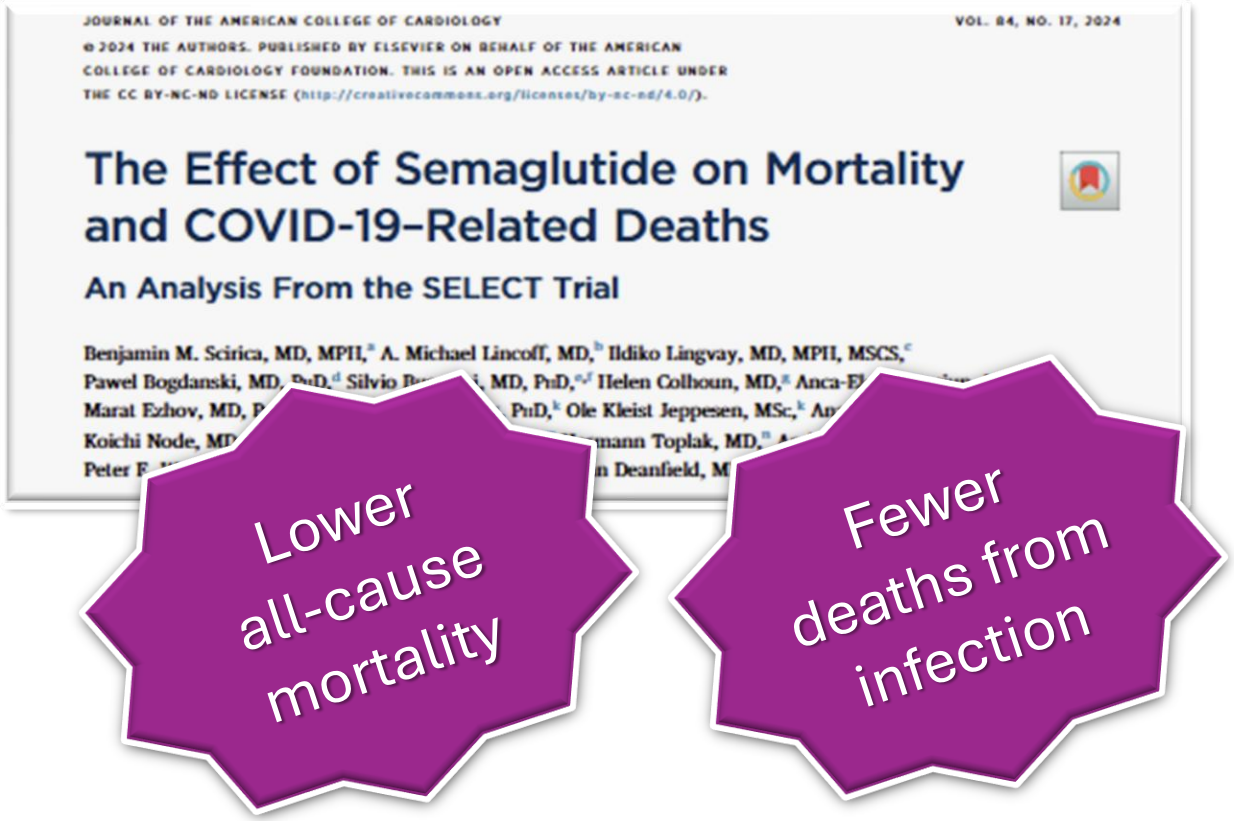
24% risk reduction



CKD, chronic kidney disease;T2D type 2 diabetes; SGLT2i, sodium-glucose cotransporter-2 inhibitor; T2D, type 2 diabetes.

Calhoun HM, et al. Nature Medicine
Perkovic V, et al. N Engl J Med 2024;91(2):109-21; Mann JFE, et al. Nat Med 2024;30(10):2849-56

SELECT: Semaglutide Effects on Mortality and COVID



- **4,258 patients (24.2%) reported COVID-19**
  - No difference in reported cases of COVID between arms (2108 vs 2150 events; P=0.46)

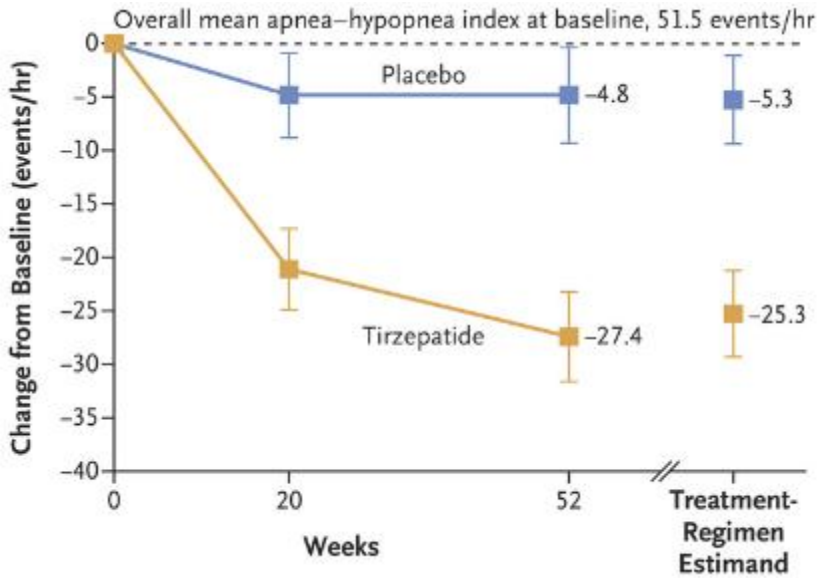
- Fewer COVID SAEs with semaglutide (232) vs. placebo (277)
- Fewer COVID deaths with semaglutide (19 vs. 65)
- Fewer infection deaths with semaglutide (62 vs. 87)

SAE, serious adverse event.

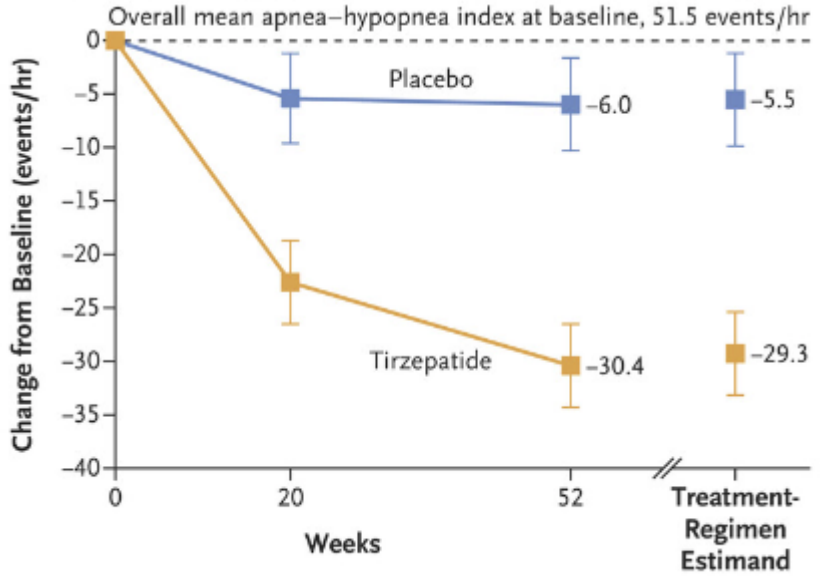
Scirica BM, et al. J Am Coll Cardiol 2024;84(17):1632-42.

Obstructive Sleep Apnea: SURMOUNT OSA: Tirzepatide in OSA

Patients not on CPAP



Patients receiving CPAP

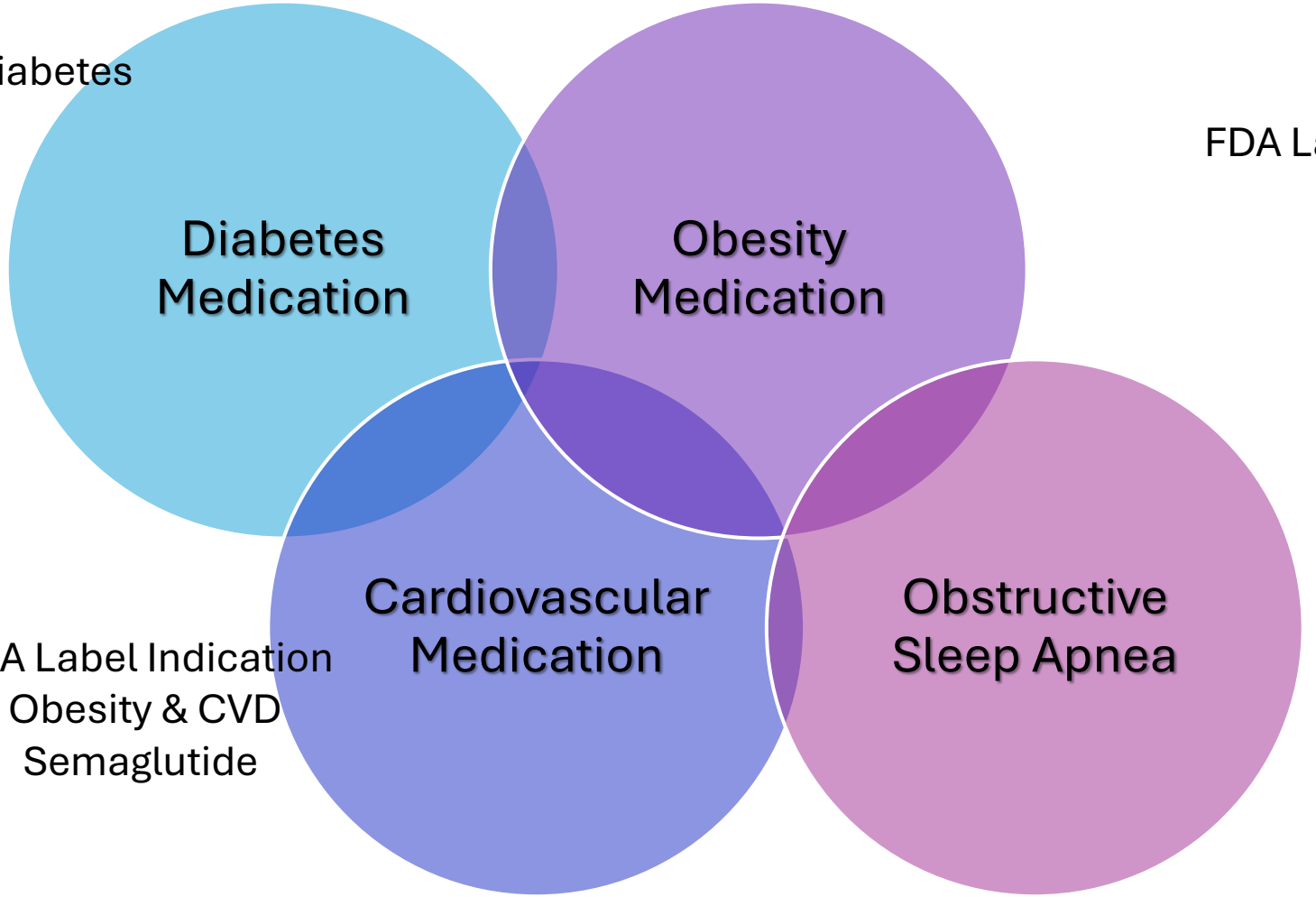


Semaglutide also reduced body weight, hypoxic burden, hsCRP concentration, and systolic blood pressure and improved sleep-related patient-reported outcomes.

Malhotra A, Grunstein RR, Fietze I, et al. *N Engl J Med*.. *N Engl J Med*. 2024; **Published June 21, 2024. DOI: 10.1056/NEJMoa2404881**

What kind of medications are GLP-1RAs?

FDA Label Indication Diabetes
Exenatide
Liraglutide
Efpeglenitide
Lixisentitde
Albiglutide
Dulaglutide
Semaglutide
Tirzepatide

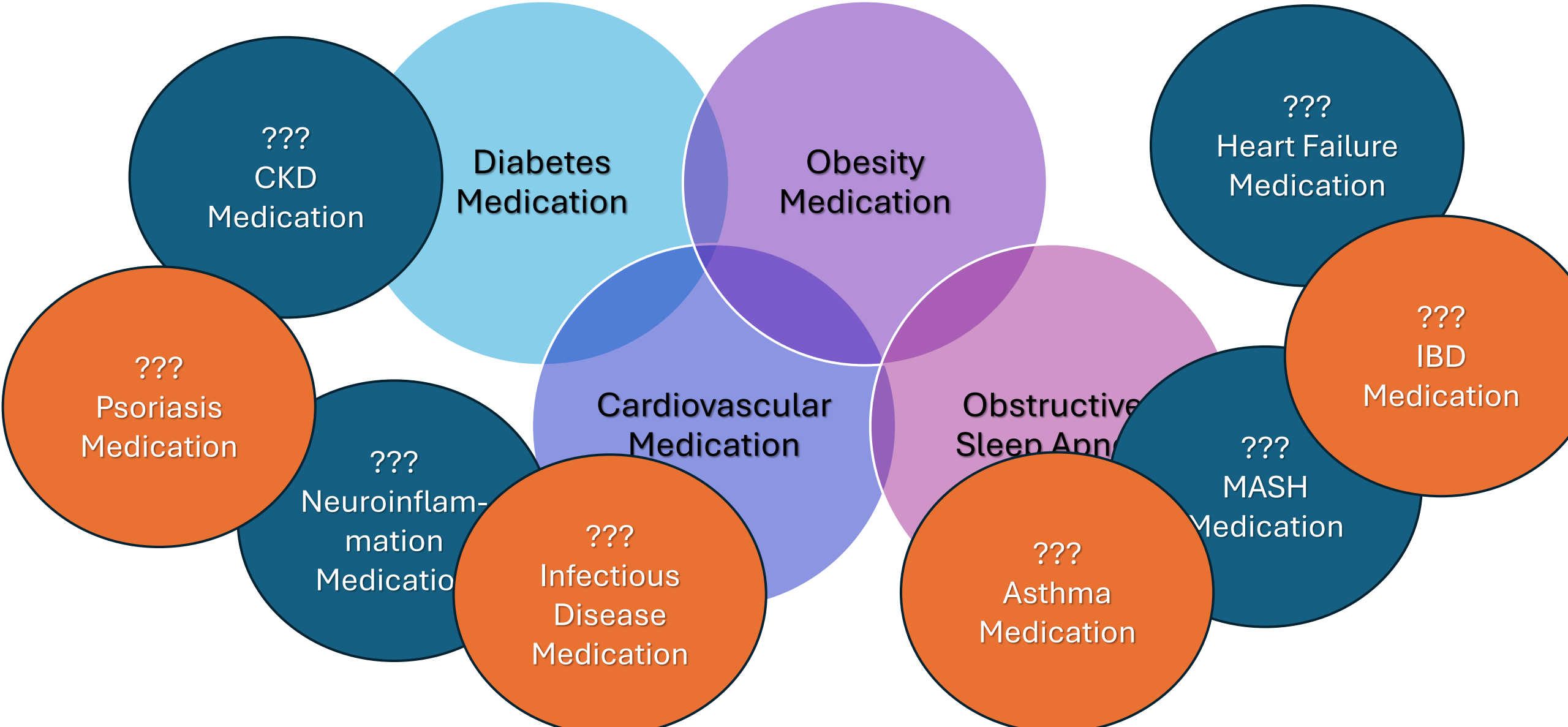


FDA Label Indication Obesity
Liraglutide
Semaglutide
Tirzepatide

FDA Label Indication
Obesity & CVD
Semaglutide

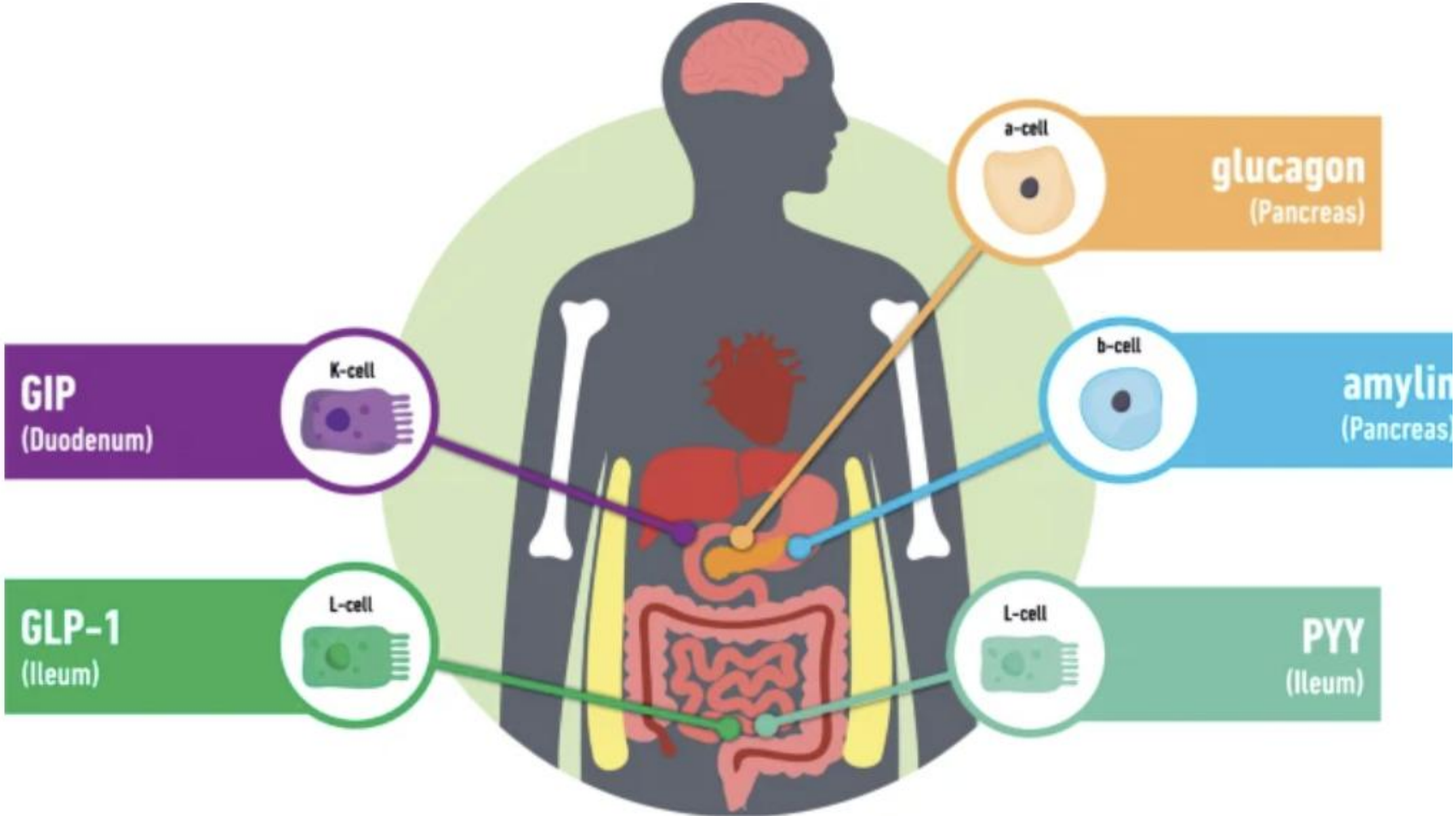
FDA Label Indication
Obesity & OSA
Tirzepatide

What kind of medications are GLP-1RAs?



Semaglutide and Tirzepatide are the Beginning

Nutrient Stimulated Hormones “NuSH”



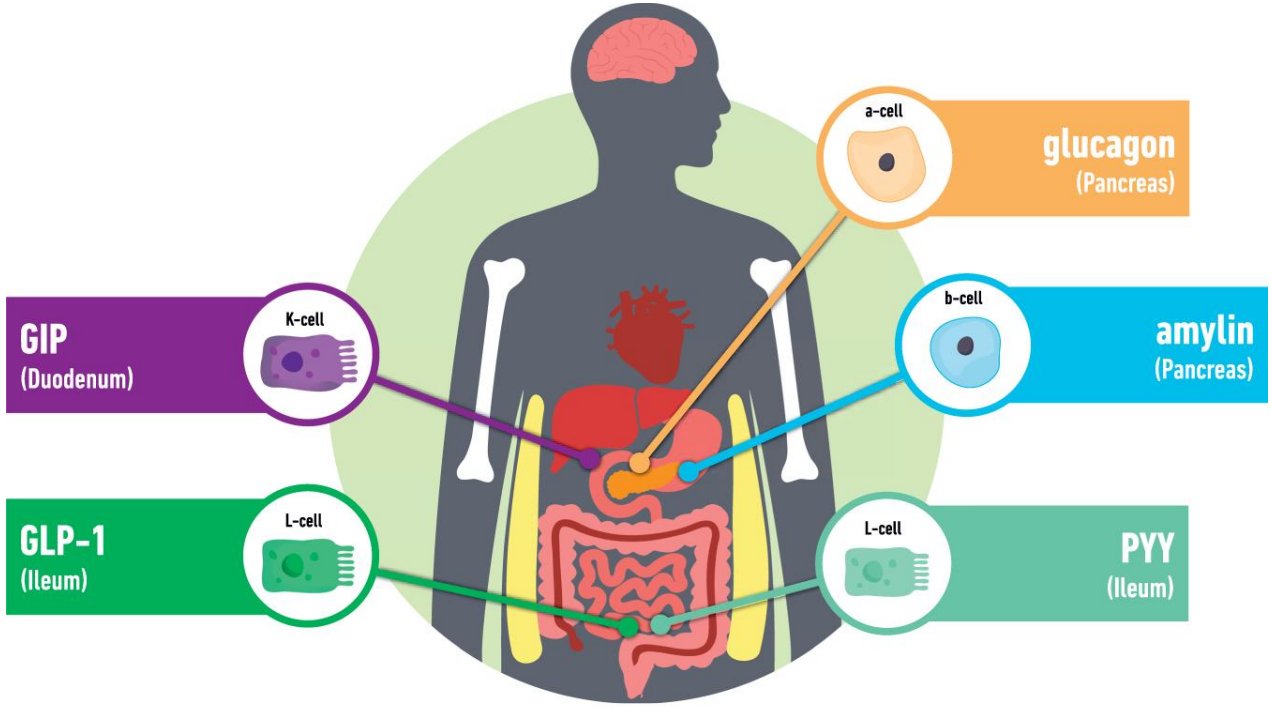
GLP-1 seems to be the backbone, adding other incretins (GIP, PYY) and NUSH-Nutrient Stimulated Hormones (amylin, glucagon)

Marketed:

- GLP-1 (liraglutide and semaglutide)
- GLP-1/ GIP (tirzepatide, single molecule dual agonist)

Phase 3

- GLP-1/amylin (cagri-sema, two drug combo)
- GLP-1,glucagon/GIP (retatrutide, single molecule triple agonist)
- GLP-1 non-peptide oral agonist (orforglipron)
- GLP-1/Glucagon (survodutide, mazdutide, pemvidutide)
- GLP-1/GIP (MariTide)

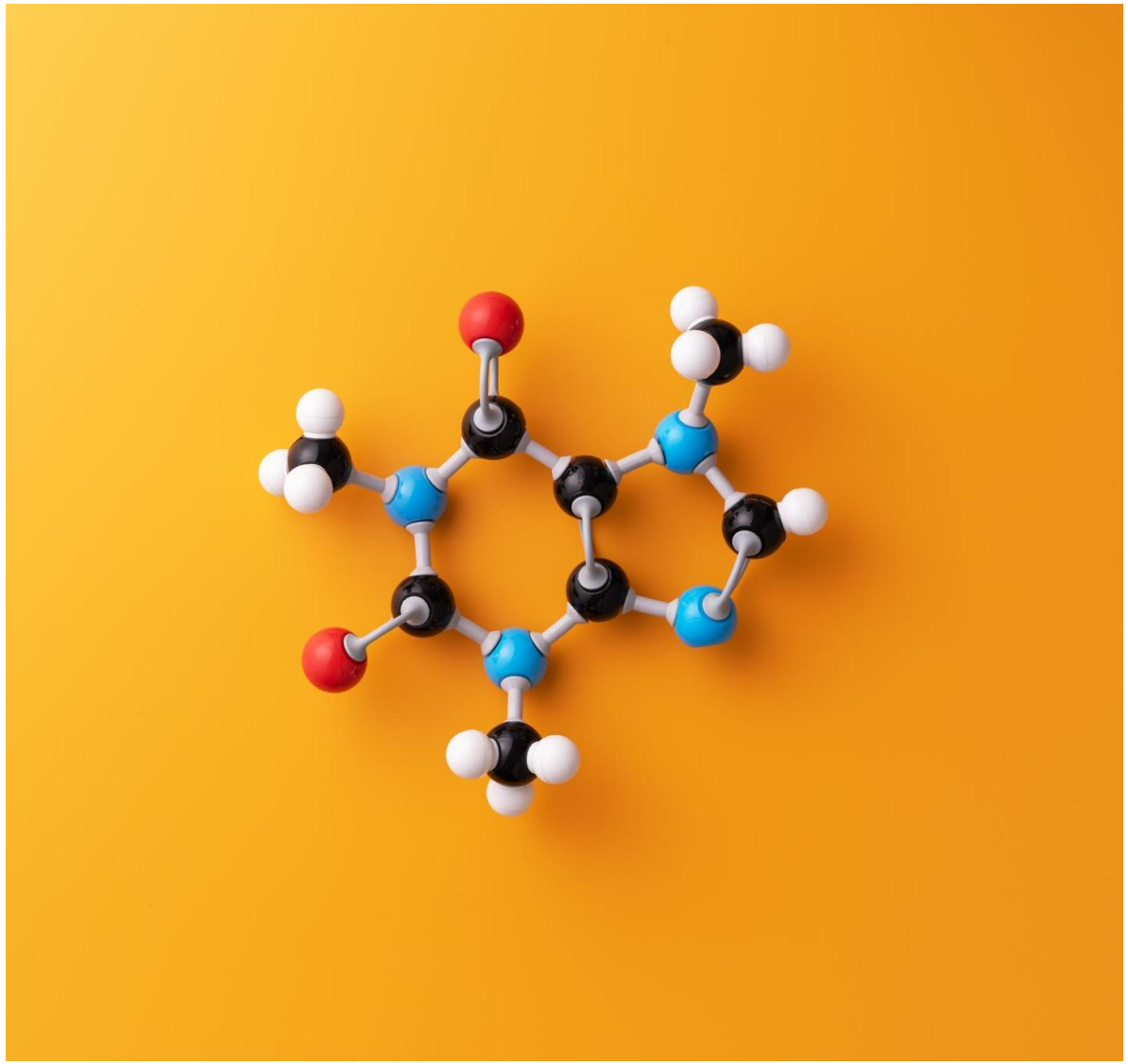


Melson, E., *et al.* What is the pipeline for future medications for obesity?. *Int J Obes* (2024). https://doi.org/10.1038/s41366-024-01473-y

Interesting approaches to NUSH development

- Oral small molecules
- Oral peptide molecules
- Monthly injection monoclonal antibody

- Still in preclinical: GLP-1 gene therapy



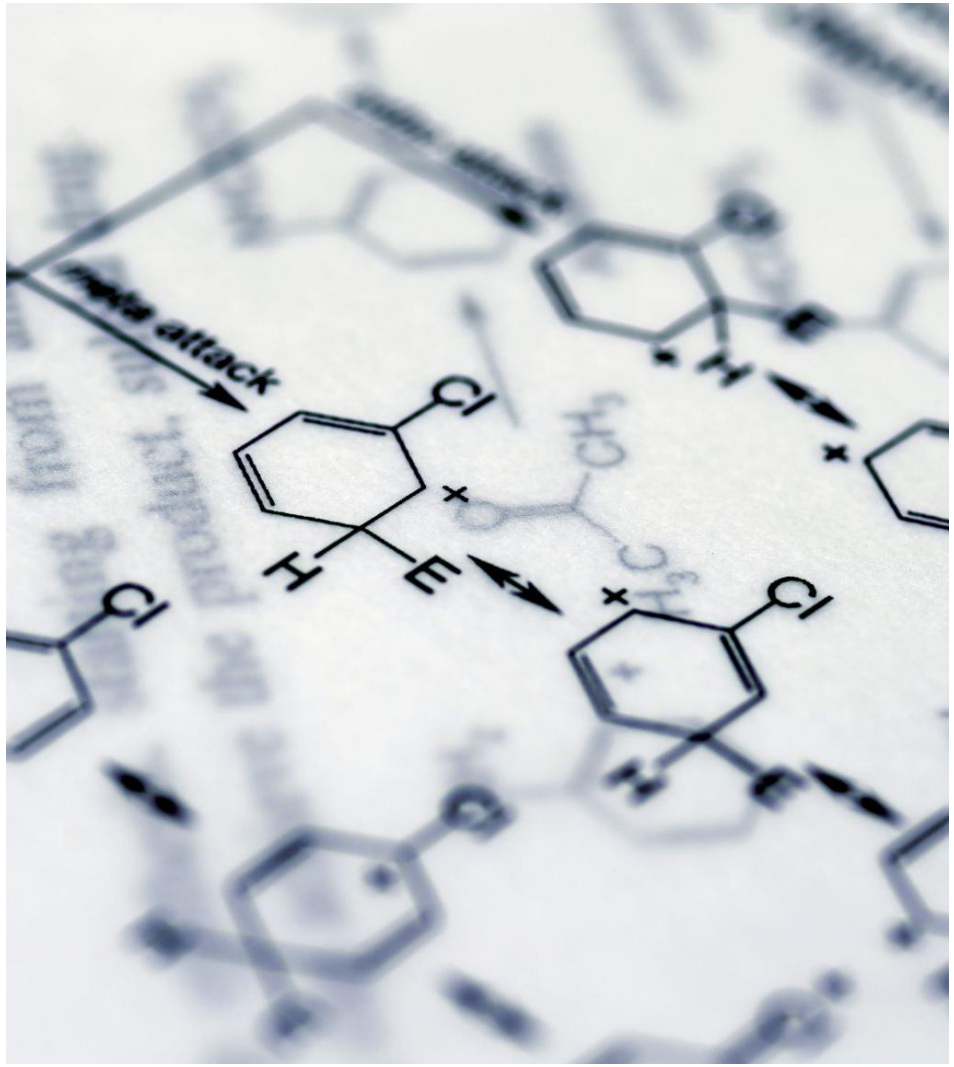
What's coming?
Fat loss with muscle preservation

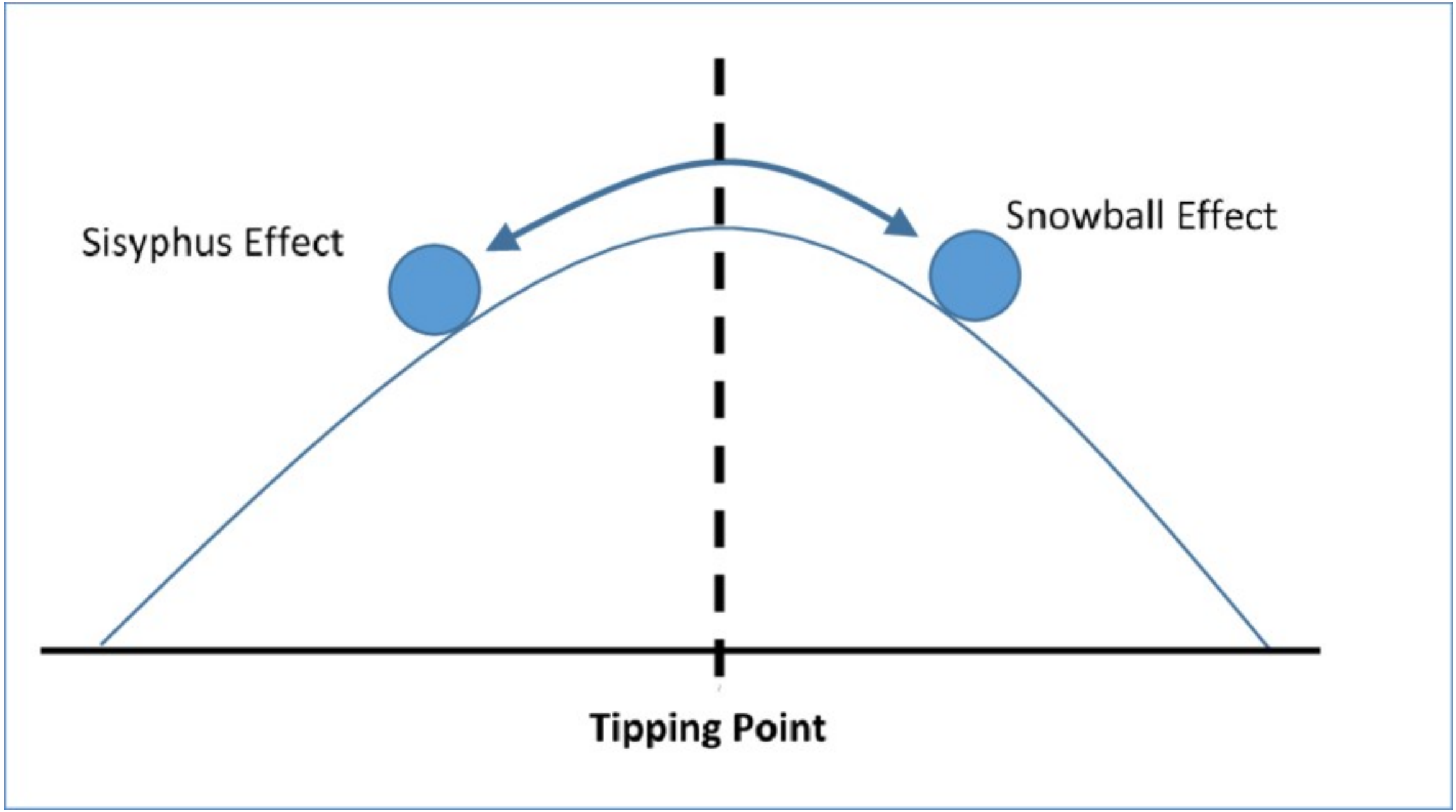
Activin – Myostatin inhibitors

- Bimagrumab Phase 2 results coming soon
- Apitogromab (NCT06445075),
- Mivabademab (NCT06373146),
- Trevogrumab and Garetosmab (NCT06299098)

Selective Androgen Receptor Modulators

- Enobosarm



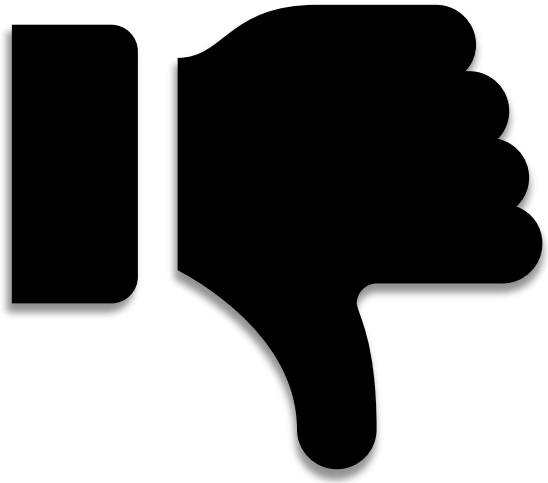

Sisyphus Effect
Snowball Effect
Tipping Point

“More tears are shed over answered prayers”

…*Saint Teresa of Avila*

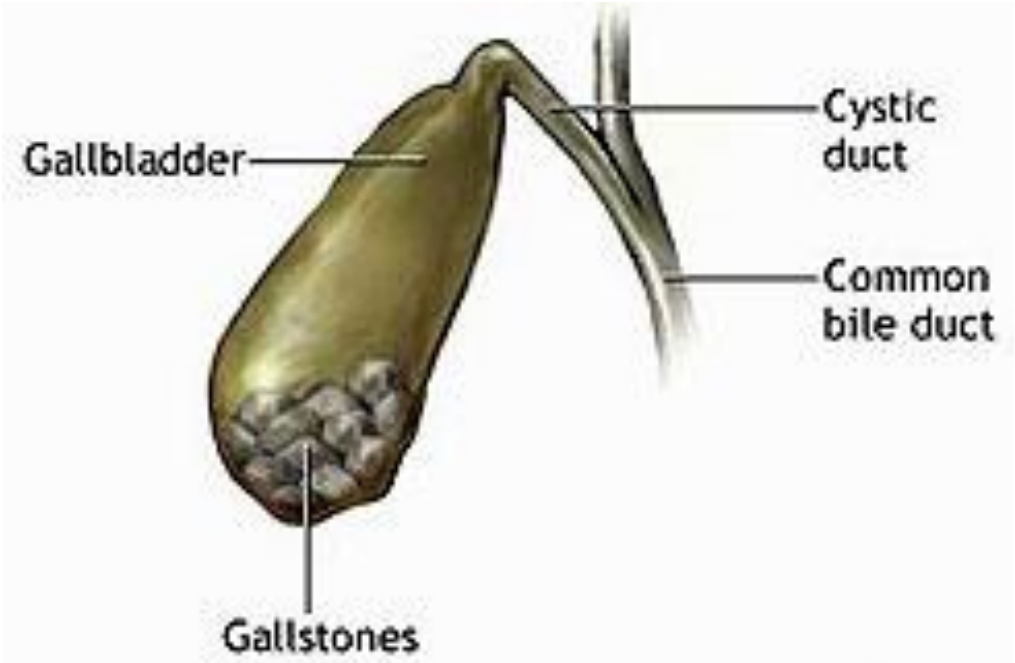
Safety Issues with GLP-1 Medications
(from the labels of semaglutide and tirzepatide)

- Boxed warning: contraindicated in persons with MEN type 2 and in those with personal or family history of medullary thyroid cancer
- Contraindicated in those with allergic reactions (fortunately these are rare)
- Should not be used in pregnancy
- Pancreatitis warning in all labels.
- Gall bladder disease (cholelithiasis and cholecystitis
- Acute renal injury, secondary to dehydration from nausea and vomiting.
- Suicidality warning



Obesity, Weight Loss, GLP-1s and Gall Bladder Disease

- Obesity increases risk for gall stones.
- Weight loss, especially rapid weight loss, increases risk for gall stones and acute gall bladder disease.
- The risk of gallbladder disease with GLP 1 medications that that which can be attributed to weight loss.



Gall Bladder Stones

Everhart JE. Et al. Ann Intern Med. 1993 Nov 15;119(10):1029-35.

Mental Health Adverse Outcomes: Review of 32 studies of bariatric surgery

“Post-bariatric surgery patients had higher self-harm/suicide attempt risk compared to age-, sex-, and BMI-matched controls.”

Castaneda D, Popov VB, Wander P, Thompson CC. Risk of Suicide and Self-harm Is Increased After Bariatric Surgery-a Systematic Review and Meta-analysis. Obes Surg. 2019 Jan;29(1):322-333.

Weight loss that is too rapid or too large

From the Protein-Sparing-Modified-Fast experience:

- Lack of high-quality protein: heart failure and sudden death associated with semi-starvation diets
- Diuresis occurs early in negative energy balance: initial weight loss does not reflect fat loss: electrolyte imbalance and hypotension
- Ketosis develops as glycogen stores are depleted and shift to fat oxidation occurs: anorexic effect
- For individuals with <30 kg fat, shift to protein source of gluconeogenesis can occur and accelerate weight loss and muscle loss

Consequences of Negative Energy Balance

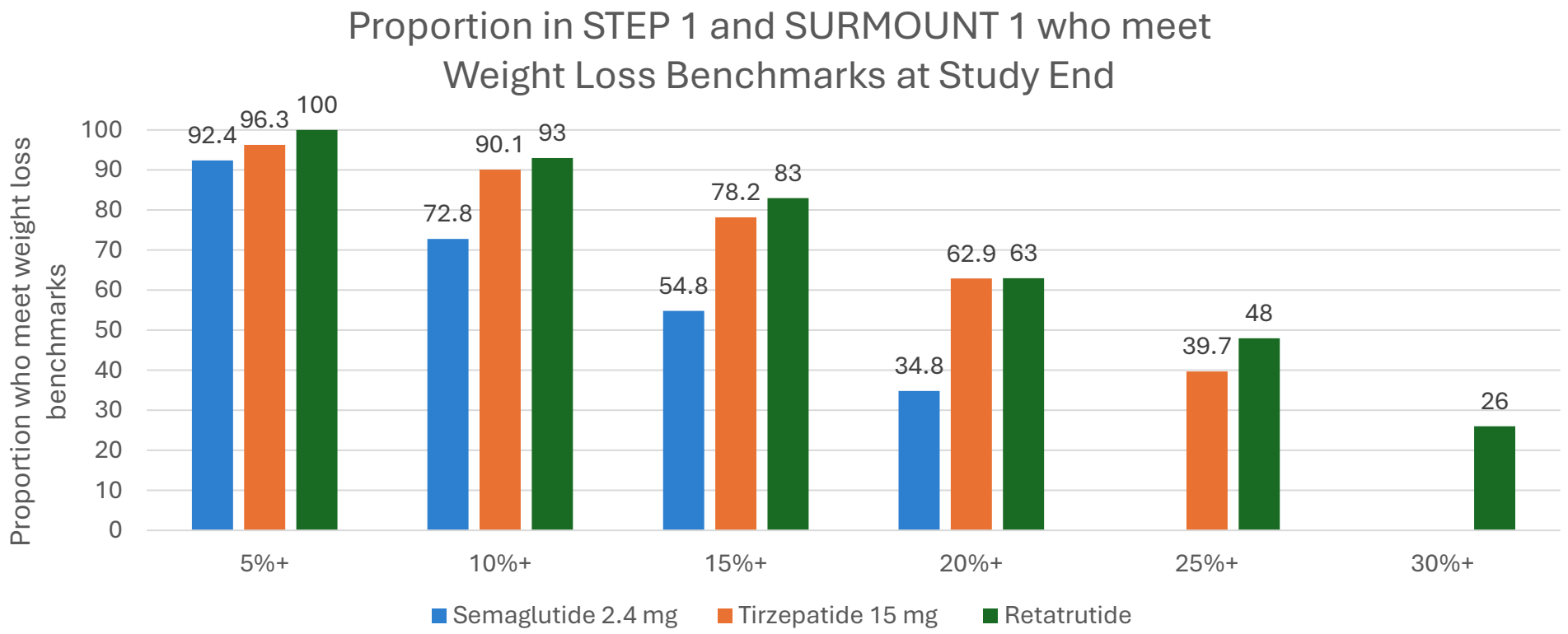
Acute Effects

- Reduction in insulin needs
  - Sulfonylureas and insulin pose danger of hypoglycemia
- Depletion of glycogen stores
  - Rapid water mobilization, diuresis
  - Diuretics may pose danger of hypotension
- Diuresis and electrolyte imbalance
  - Cardiac arrythmia
- Constipation

Chronic Effects

- Gall bladder disease
- Exacerbation of retinopathy
- Loss of muscle mass

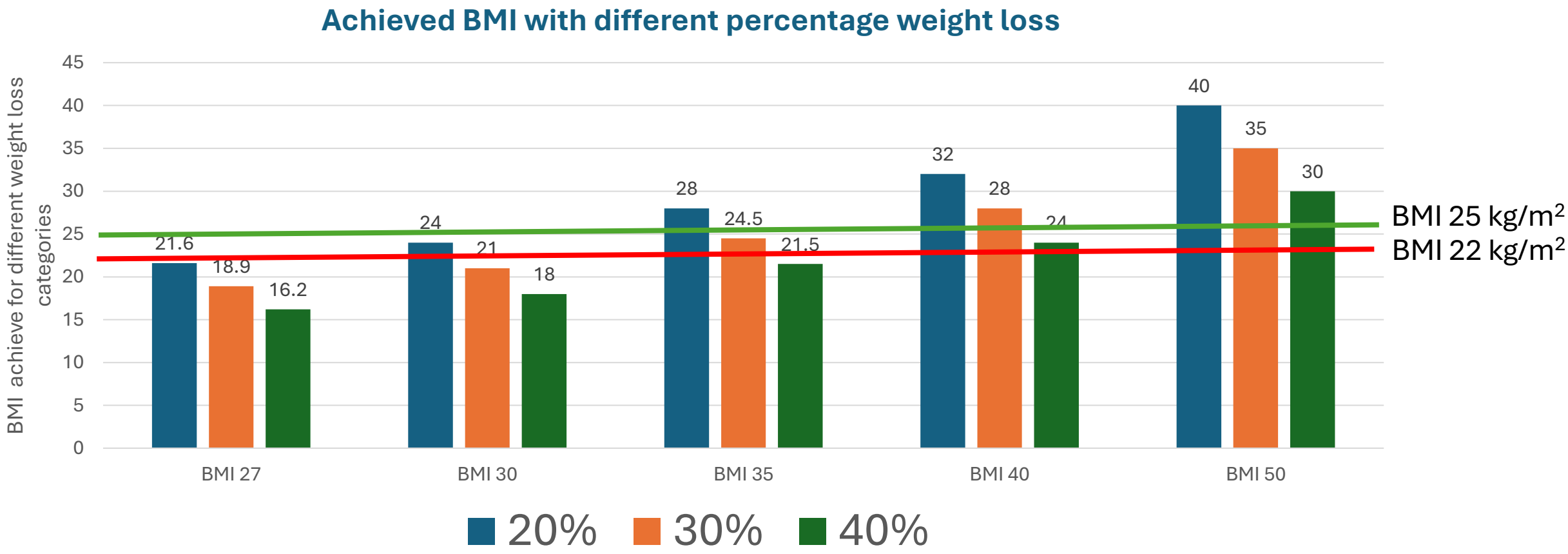
Categorical Weight Loss with Semaglutide and Tirzepatide and Retatrutide



Jastreboff A, et al. *N Engl J Med*. 2022;387(3):205-216 [SURMOUNT1].
Wilding JPH, et al. *N Engl J Med*. 2021;384(11):989-1002 [STEP 1].

On Treatment Analysis

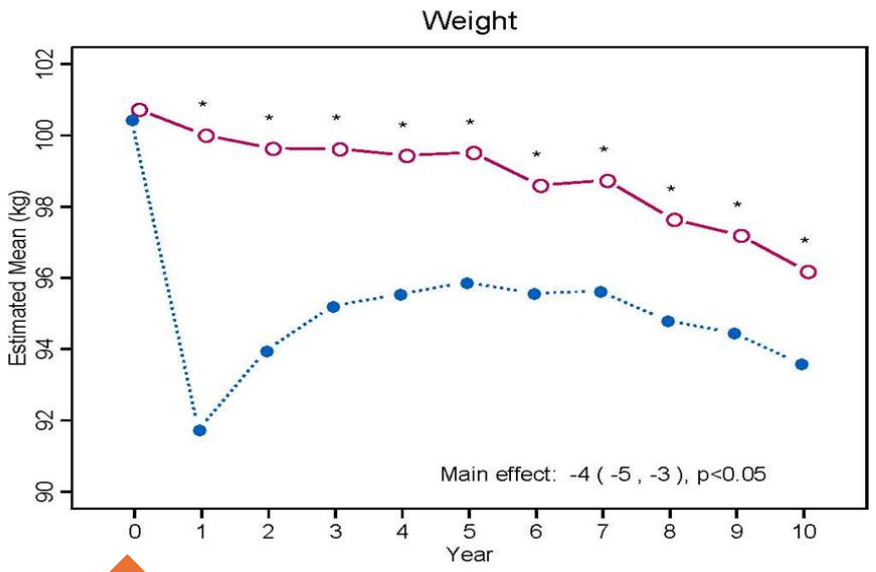
When is Enough, Enough?

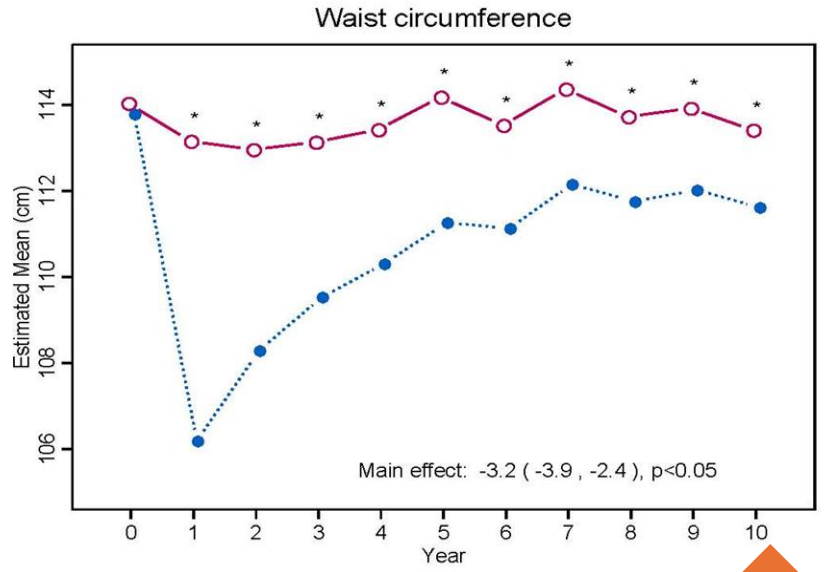


Who is at risk for too much weight loss?

- Lower BMI (<35) (because they start with less fat mass and lower lean mass)
- Older individuals (because they start with lower lean mass)
- Older women (because of the higher risk of osteoporosis)
- Women (because of the cultural drive for slimness driving unrealistic body image)

Look AHEAD: Weight Loss Over 10 Years in 5145 Patients With T2DM





Mean age 59 years

-o- support and education

...●... lifestyle intervention

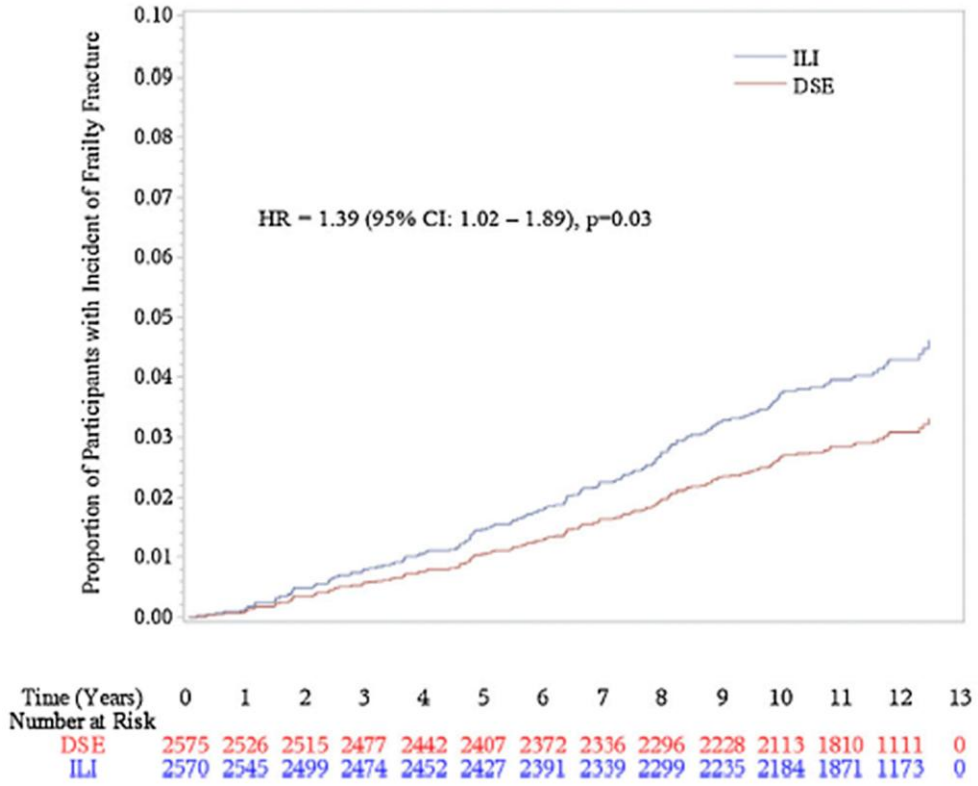
Mean age 69 years

T2DM = type 2 diabetes mellitus.

Look AHEAD Research Group, et al. *N Engl J Med.* 2013;369(2):145-154.

Frailty Fractures in Weight Loss

Increased Risk of Frailty Fractures in Look AHEAD Intensive Lifestyle Intervention



Johnson KC, et al.. *J Bone Miner Res* 2017;32:2278-2287.

Increased Risk of Fractures in SELECT Cardiovascular Outcome Trial

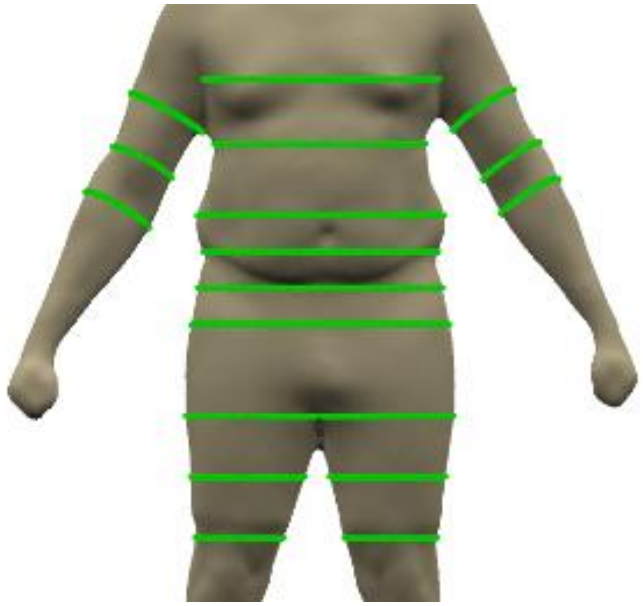
- SELECT study hip and pelvic fractures from SAE reports
- Average age 61.5 years at start
- Average weight loss 9.3%
- Female patients
  - 1.0% (24/2448) vs 0.2% (5/2424)
- Patients age 75+
  - 2.4% (17/703) vs. 0.6% (4/663

Kushner RK et al.

Phenotyping needed!

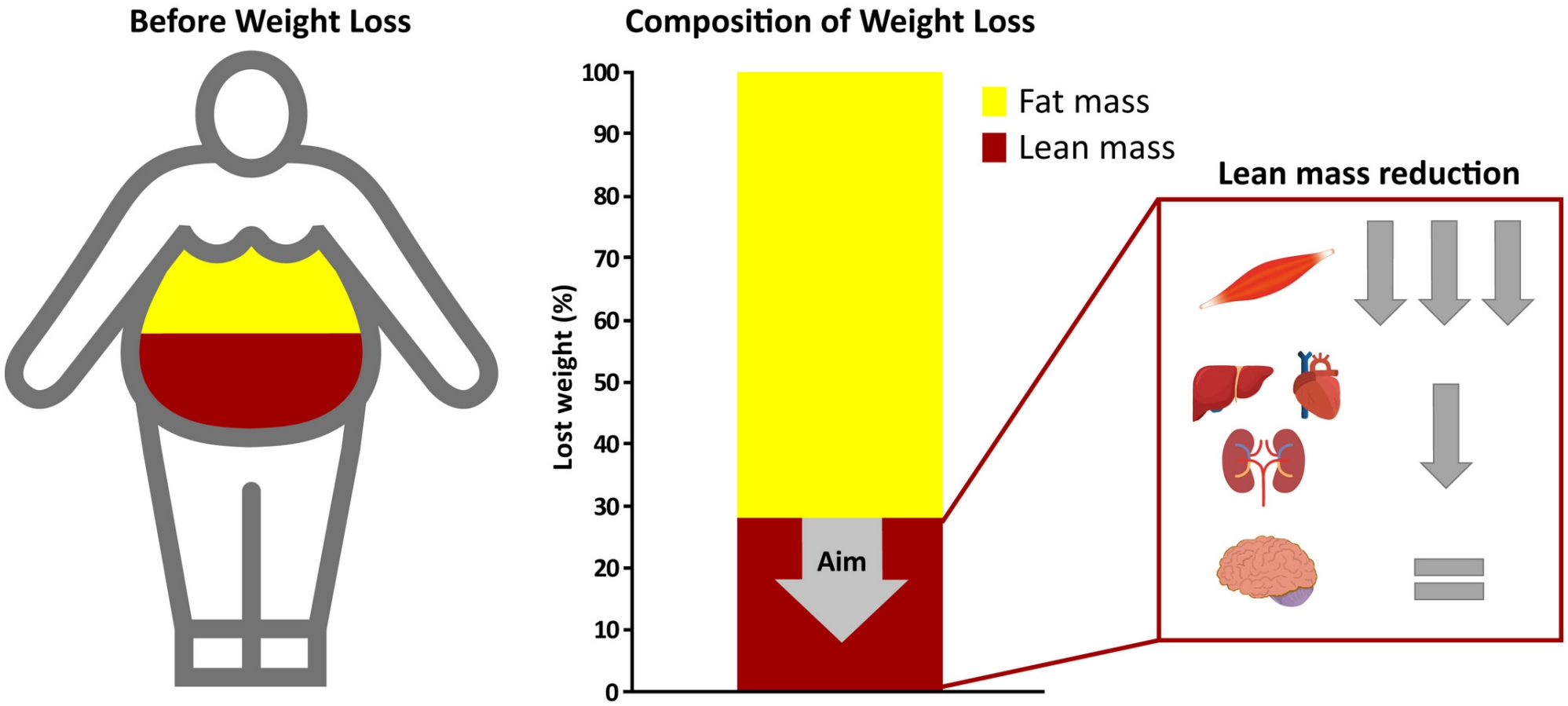
What are the best diagnostic criteria for treatment?

…the best endpoints for judging success?



IN OBESITY, WE NEED A BETTER DEFINITION OF SUCCESS (TREAT TO TARGET)

GOAL: **Loss of excess abnormal fat mass, preservation of lean mass, optimizing organ function**



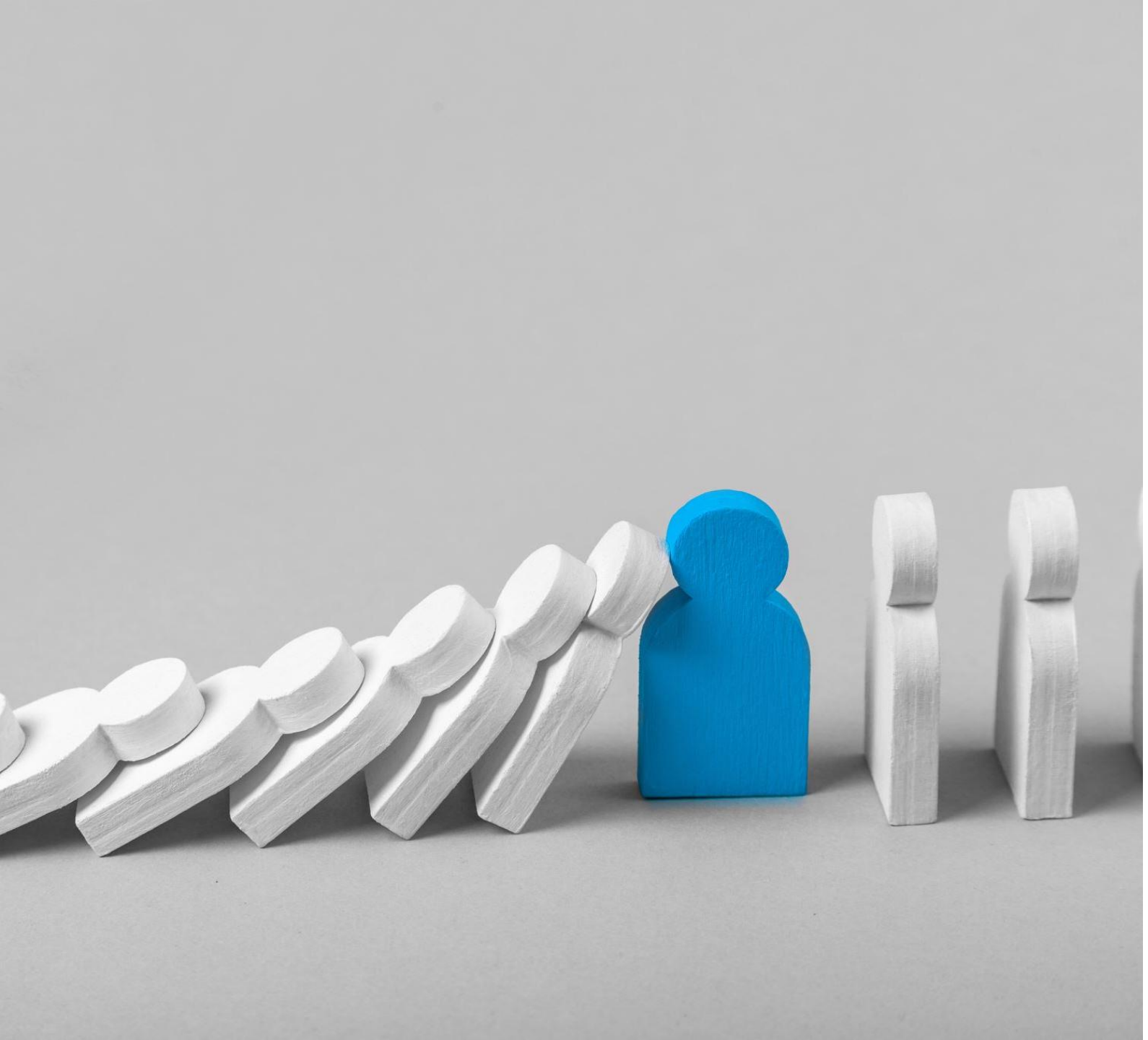
Christoffersen BØ, et al. Obesity (Silver Spring). 2022 Apr;30(4):841-857.

Is more always better?

No, better is better!


More Weight Loss
Exit Now


Better Weight Loss
Next Exit



Challenges to be confronted, Barriers to be overcome

Powerful therapies need a skilled workforce

Society minimizes the potential of these drugs; its much more than weight loss

Three Important Areas Needing Attention

- Access
- Access
- Access


Can we meet the challenge?

“More tears are shed over answered prayers”

…*Saint Teresa of Avila*

- Can we develop the educated workforce needed?
  - More skill is required beyond writing a prescription.
- Can we develop policies to assure that these medications are not a luxury product, that all patients who need them have access?
- Can we develop a continuing research agenda that seeks to answer…
  - What is the best diagnosis for clinical obesity
  - What is the best target for weight loss?


ngiyabonga
danke
謝謝
teşekkür ederim
спасибо
dank je
gracias
thank you
tapadh leat
mochchakkeram
bedankt
dziękuje
go raibh maith agat
sukriya
kop khun krap
obrigado
arigaló
dakujem
terima kasih
grazie
мерси
merci
감사합니다