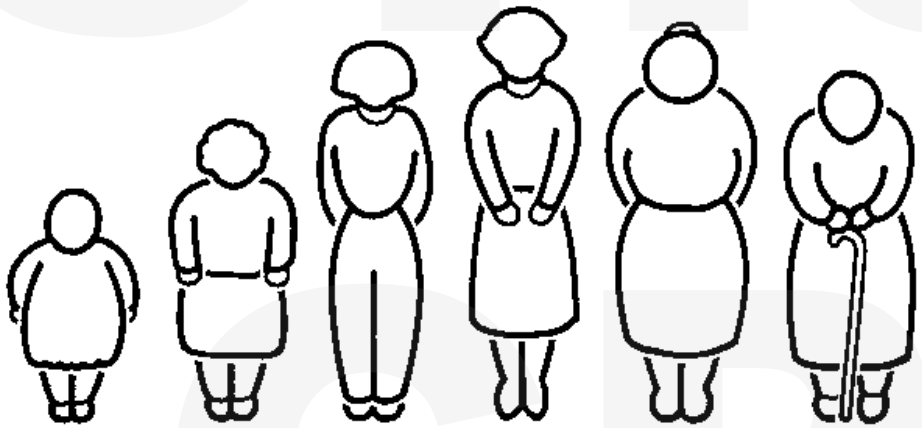
Obesity Medications (including GLP-1's)



DATE: April 2026

PRESENTED BY:

Jonathan Q. Purnell, MD, FTOS, DABOM
Professor, Knight Cardiovascular Institute
Division of Endocrinology, Diabetes, Clinical Nutr
Oregon Health & Science University
Portland, Oregon

Disclosures

Society Member:
- The Obesity Society (VP)
- American Diabetes Association
- Endocrine Society

Research:
- NIH

Consulting / Steering Committee:
- Boehringer Ingelheim
- Novo Nordisk
- Zealand Pharmaceuticals

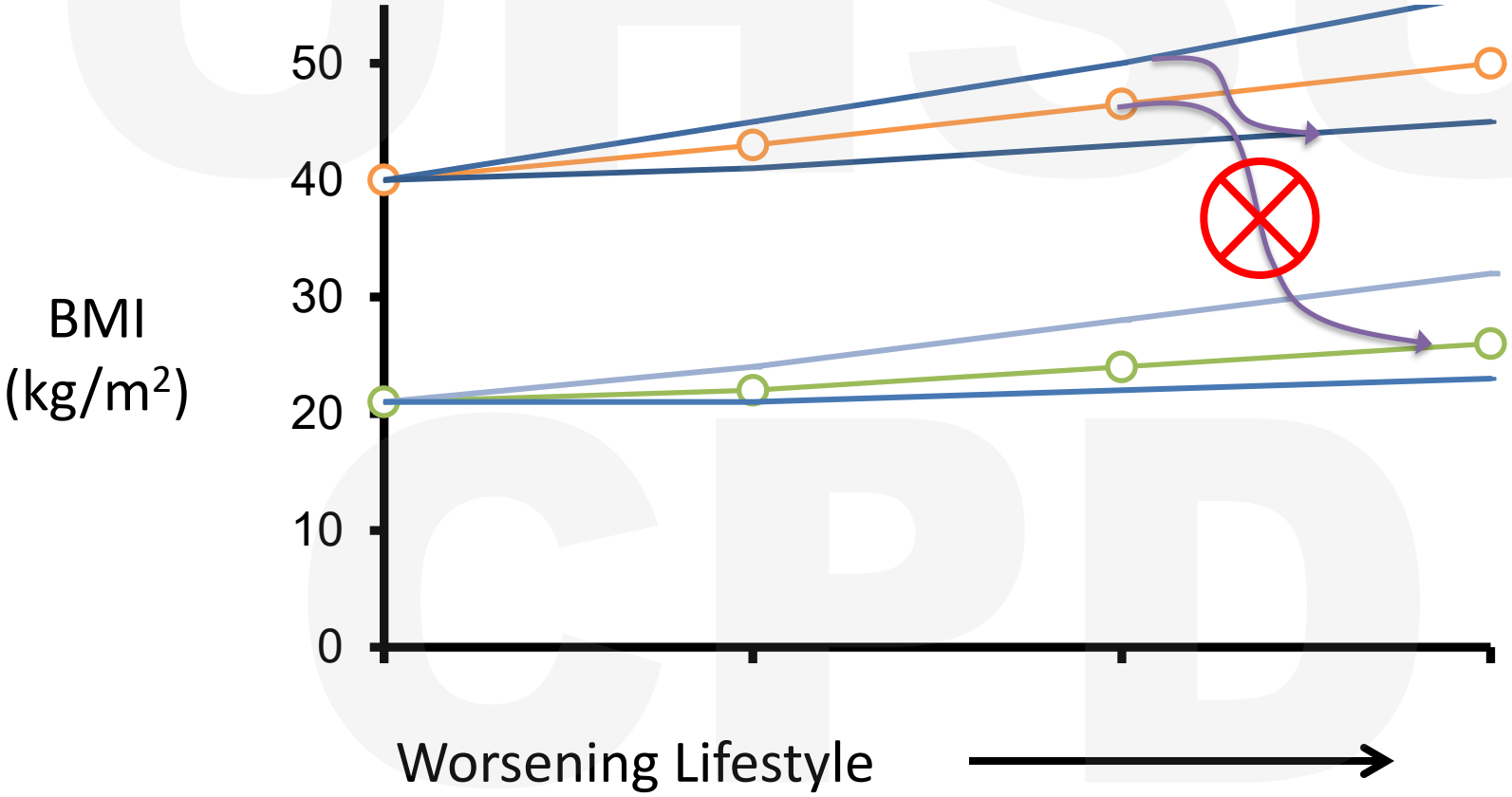
Clinical Trial (PI)
- Novartis
- Amgen

Chronic Disease Management

- Lifestyle (diet, exercise)   ↓ 2-4% total weight loss
  - If started for weight loss alone, it is insufficient by itself.
  - Improves health but has not been shown to reduce MACE.
  - So be prepared to offer more than just “diet and exercise.”

Knowler W, et al. N Engl J Med 346:393–403, 2002.
DPPRG. Lancet. 2009.374:1677-89.

Lifestyle and Obesity: Effect on Body Weight in a "Set-Range"



Chronic Disease Management

- Lifestyle (diet, exercise)

↓ 2-4% total weight loss

- Medications

Knowler W, et al. N Engl J Med 346:393–403, 2002.
DPPRG. Lancet. 2009.374:1677-89.

Becris, srip, Freepik

ORIGINAL ARTICLE OPEN ACCESS

Clinical Trials and Investigations

Joint TOS/OMA/OAC Expert Guidance Statement on the Pharmacological Management of United States Adults With Overweight or Obesity Using the GRADE Approach

Lydia Alexander[1] | Jonathan Q. Purnell[2] | Karlijn Burridge[3] | Marc-André Cornier[4] | Angela Golden[5] | Deborah Bade[6] | Michelle Look[7] | Joe Nadglowski[8] | Camila Ávila-Oliver[9,10] | Francisco Novillo[10,11] | Ana María Rojas-Gómez[10] | Brad Hussey[12] | Ximena Ramos Salas[12]

[1]Enara Health, Inc., San Mateo, California, USA | [2]Oregon Health & Science University, Portland, Oregon, USA | [3]Healthy4Life, Naperville, Illinois, USA | [4]Medical University of South Carolina, Charleston, South Carolina, USA | [5]The Obesity Society, Rockville, Maryland, USA | [6]Obesity Medicine Association, Centennial, Colorado, USA | [7]San Diego Sports Medicine Weight and Wellness, San Diego, California, USA | [8]Obesity Action Coalition, Tampa, Florida, USA | [9]Facultad de Medicina Clínica Alemana, Universidad del Desarrollo, Santiago, Chile | [10]Epistemonikos Foundation, Santiago, Chile | [11]School of Dentistry, Faculty of Health and Dentistry, Universidad Diego Portales, Santiago, Chile | [12]Replica Communications, Hamilton, Ontario, Canada

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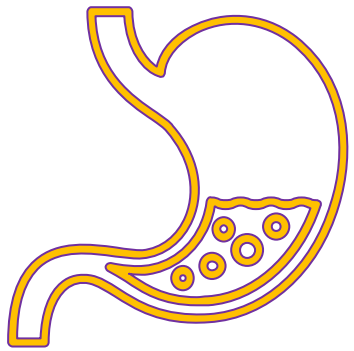
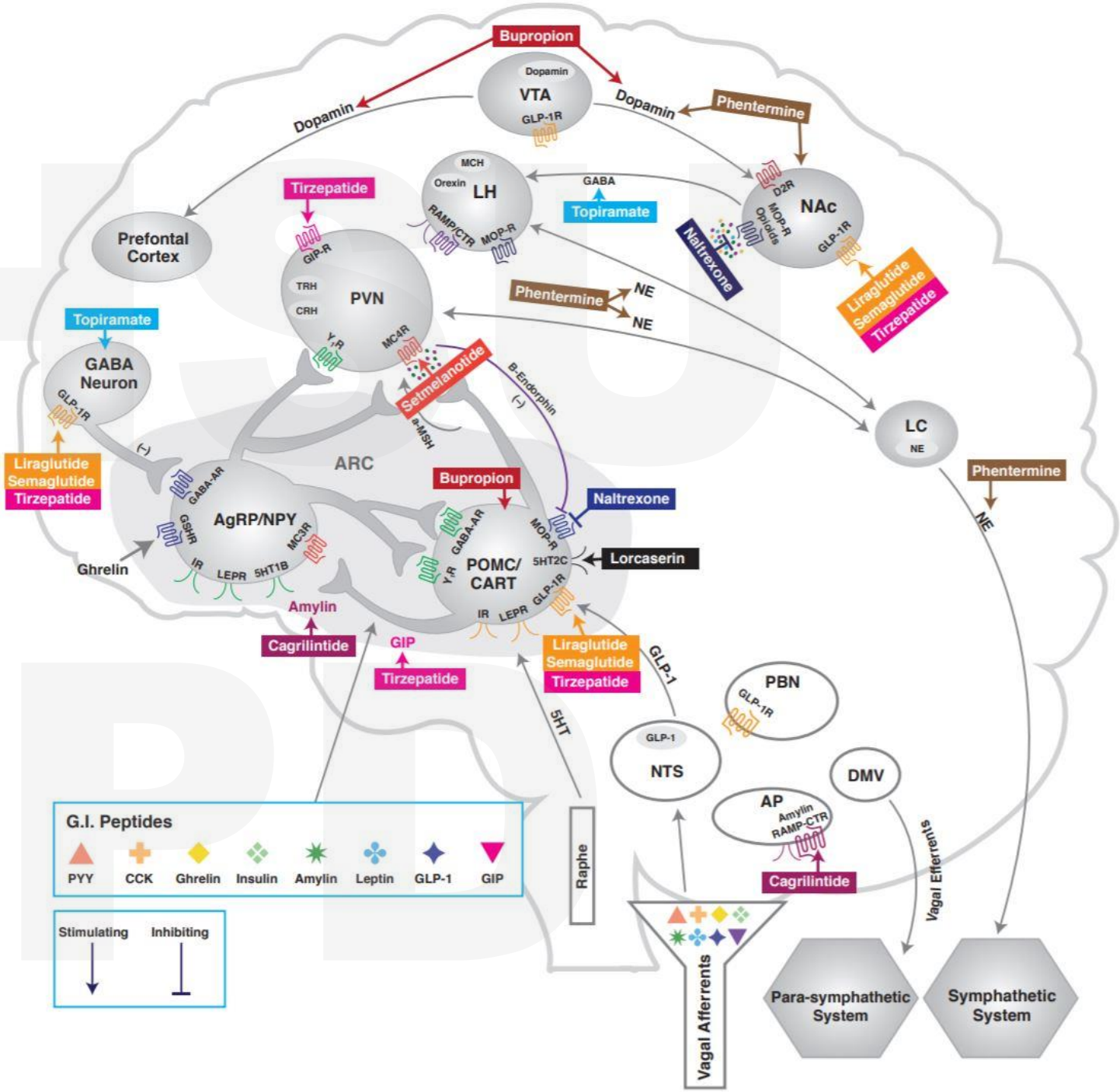
Received: 13 October 2025 | **Revised:** 27 January 2026 | **Accepted:** 27 January 2026

Mechanisms of Action of Obesity Medications (OMs)



↑ CNS Fullness Signaling

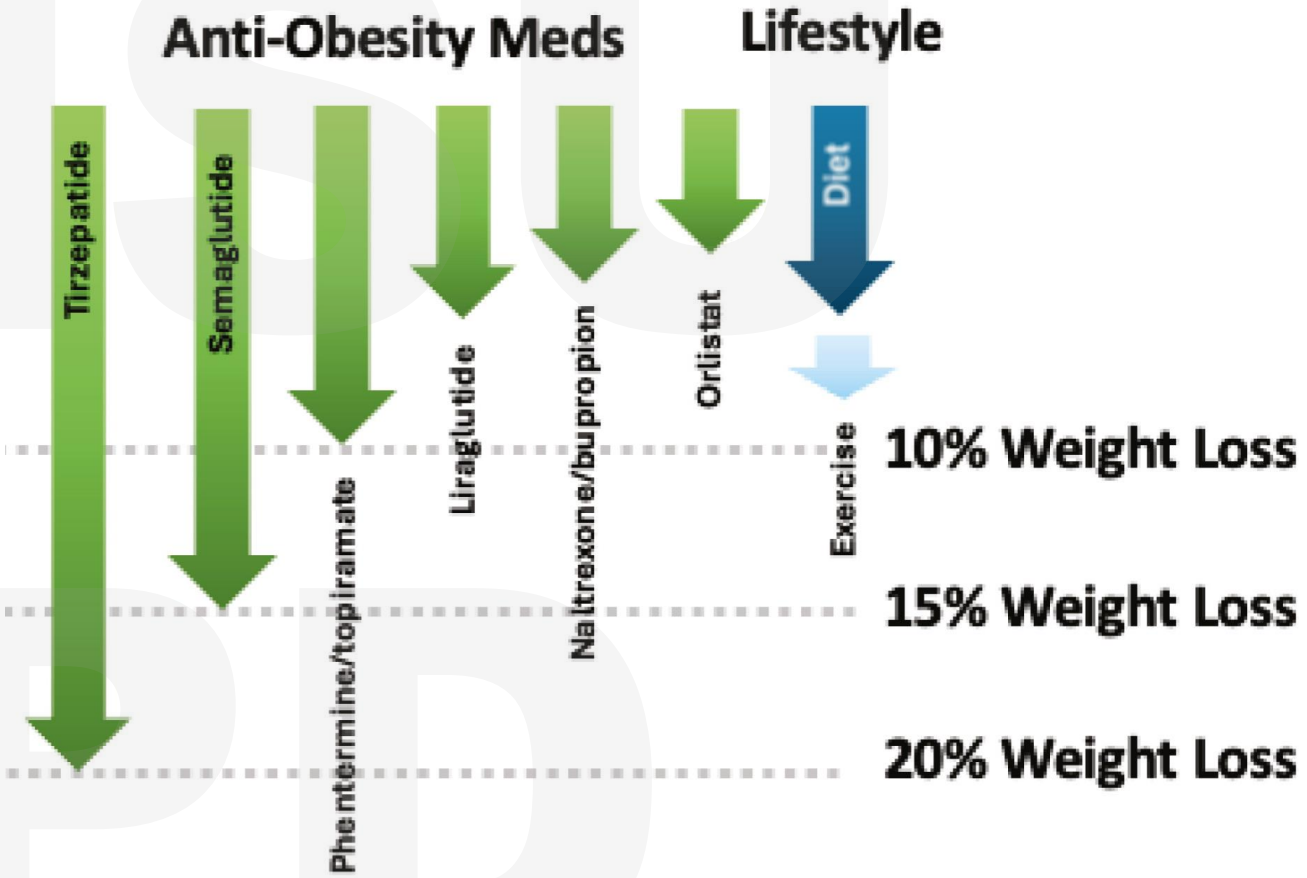
↓ CNS Hunger Signaling



M. Furkan Burak MD. *Handbook of Obesity.* 2023.

US FDA-Approved Obesity Medications (OMs)

Ave Wt Loss	
~ 4-5%	• bupropion + naltrexone
~ 6-7%	• liraglutide 3.0 mg †
~ 10-11%	• phentermine + topiramate
~ 15%	• semaglutide 2.4 mg †
up to 30%	• setmelanotide
~ 20%	• tirzepatide†

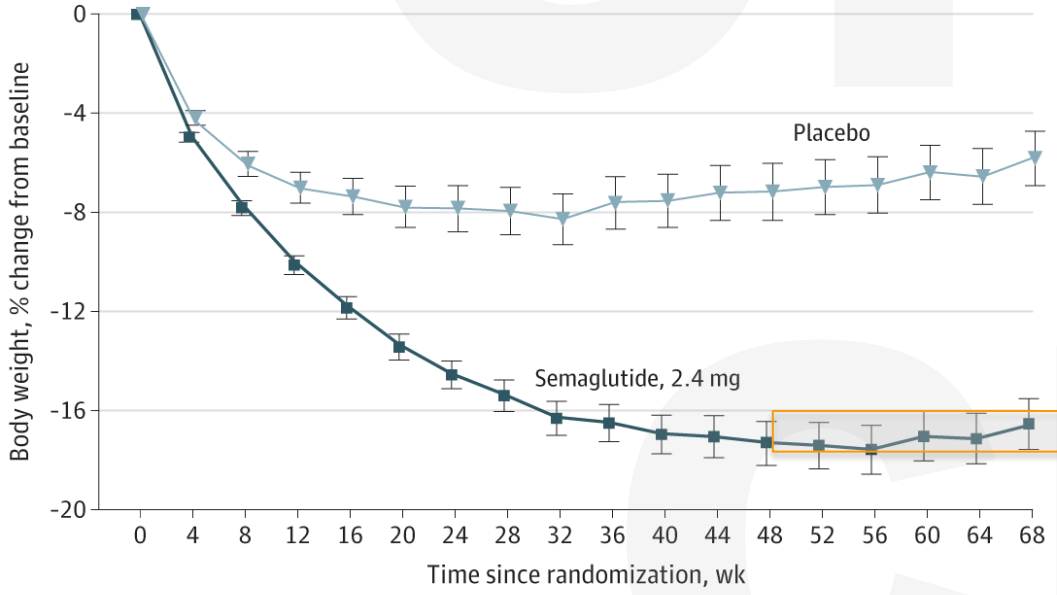


† In patients without diabetes

Nissen SE, et al. JAMA. 2016;315(10):990-1004.
le Roux CW, et al. Lancet. 2017. 8;389(10077):1399-1409.
Monroe, et al. BMJ. 1:352-54. 1968.
Garvey WT, et al. Am J Clin Nutr. 2012;95:297-308.
Wilding JPH, et al. N Engl J Med 2021; 384:989-1002.
Clement K, et al. Lancet Diabetes Endocrinol 2020; 8: 960–70.
Jastreboff AM, et al. N Engl J Med. 2022 Jun 4. doi: 10.1056/NEJMoa2206038. Online ahead of print.

Role of Intensive Lifestyle Intervention in Pharmacological Weight Management

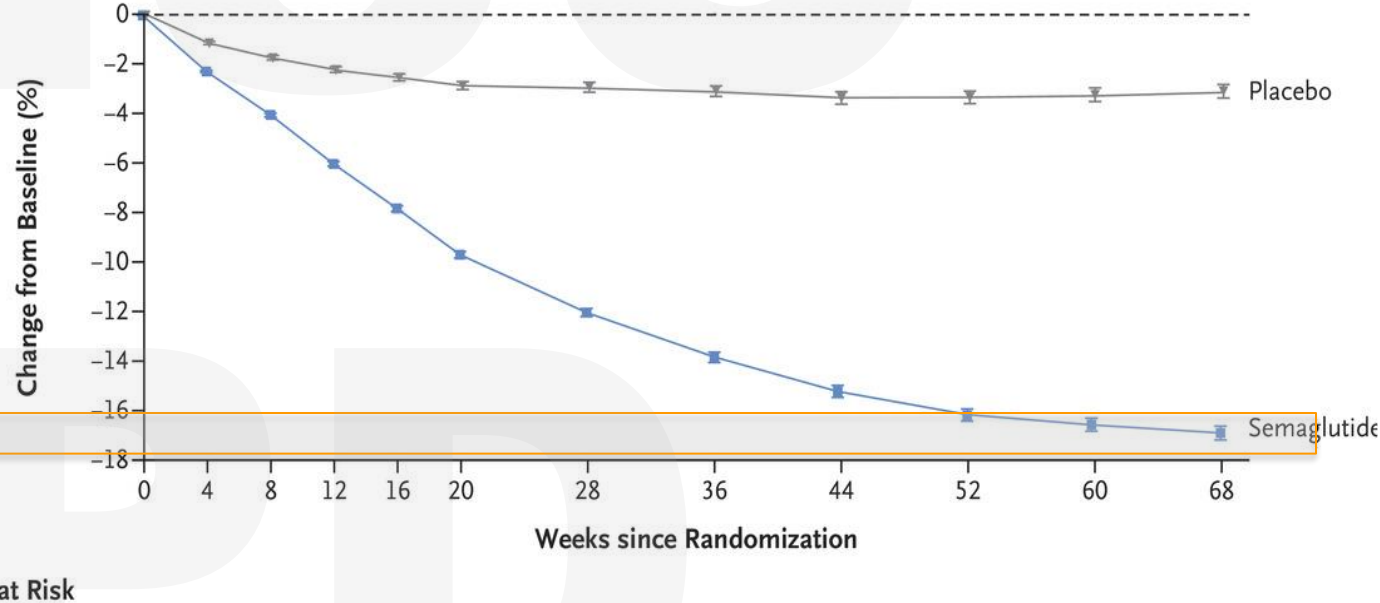
Step 3 trial:
Intensive Behavioral Lifestyle + P or semaglutide 2.4 mg



No. of participants

Semaglutide, 2.4 mg	407	398	396	385	389	385	370	380	363	373	364	364	356	367	343	365	346	373
Placebo	204	200	197	190	194	194	185	189	180	189	180	184	172	183	170	180	166	189

Step 1 trial:
"Usual care: diet and exercise" + P or semaglutide 2.4 mg



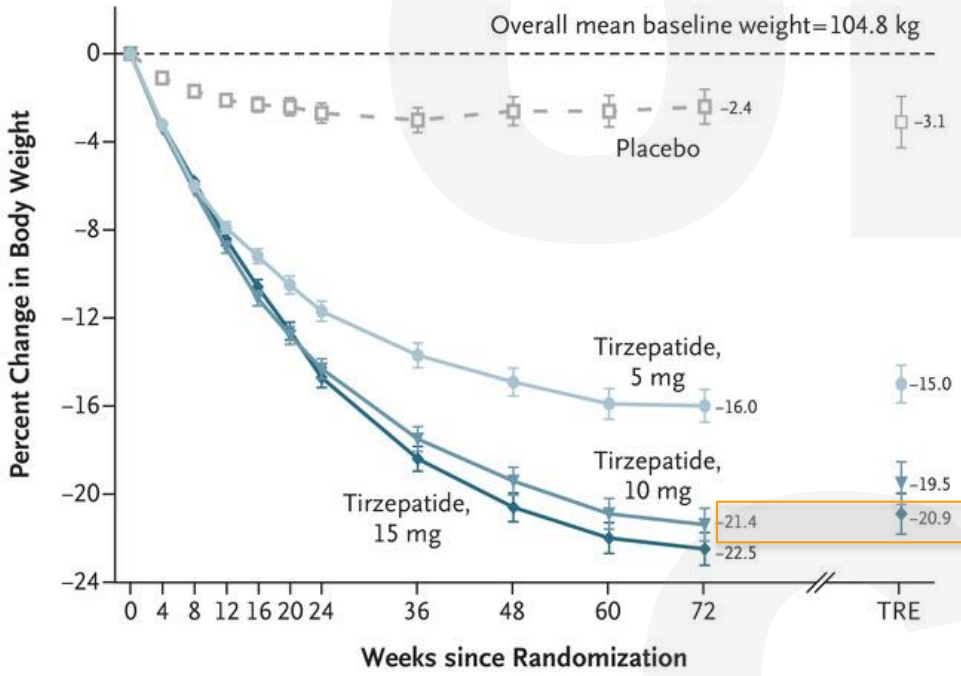
No. at Risk

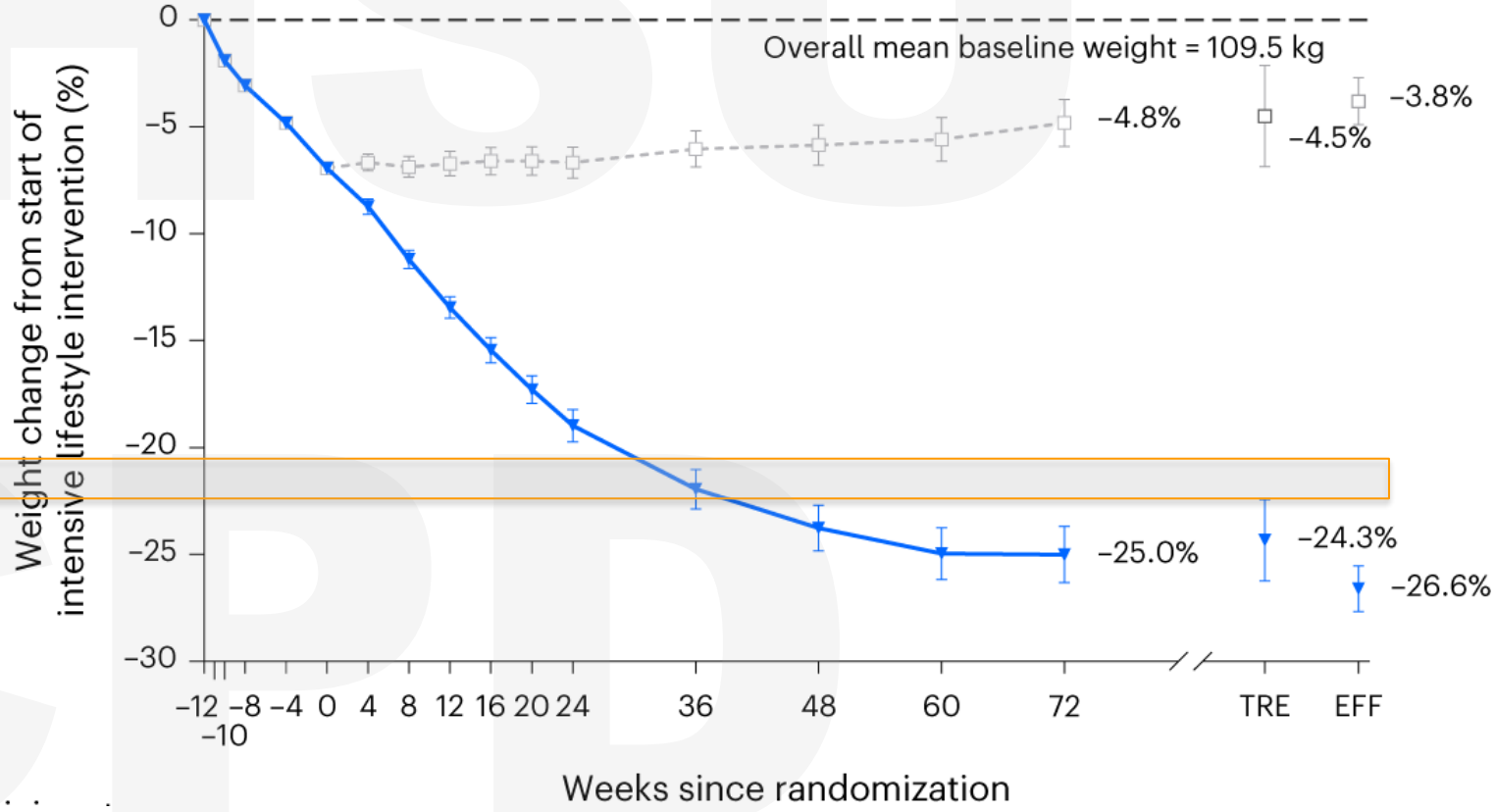
Placebo	655	647	637	613	607	593	576	555	529	520	514	499
Semaglutide	1306	1283	1259	1225	1206	1193	1176	1166	1135	1115	1100	1059

JAMA. 2021;325(14):1403-1413.
N Engl J Med 2021;384:989-1002.

Effect of Tirzepatide + ILI on Body Weight

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

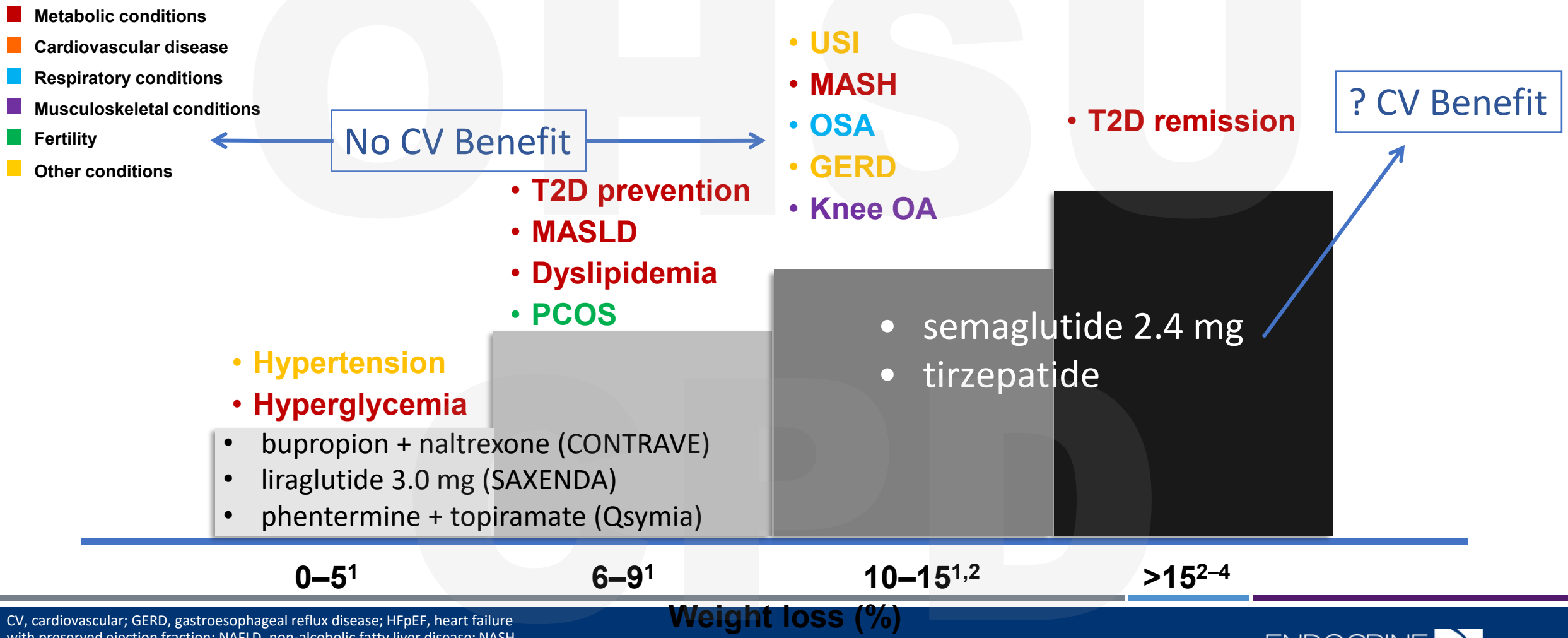




.Jastreboff AM, et al. N Engl J Med. 2022; 387:205-216.

Wadden T, et al. Nat Med. 2023. (11):2909-2918.

HEALTH BENEFITS BEGIN AT 2-5% TOTAL WEIGHT LOSS



CV, cardiovascular; GERD, gastroesophageal reflux disease; HFpEF, heart failure with preserved ejection fraction; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OA, osteoarthritis; OSA, obstructive sleep apnea; PCOS, polycystic ovary syndrome; T2D, type 2 diabetes; USI, urinary stress incontinence.

1. Garvey WT et al. Endocr Pract 2016;22(Suppl. 3):1–203; 2. Look AHEAD Research Group. Lancet Diabetes Endocrinol 2016;4:913–21; 3. Lean ME et al. Lancet 2018;391:541–51; 4. Benraoune F and Litwin SE. Curr Opin Cardiol 2011;26:555–61.

Courtesy L Arrone

ENDOCRINE SOCIETY
Hormone Science to Health

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

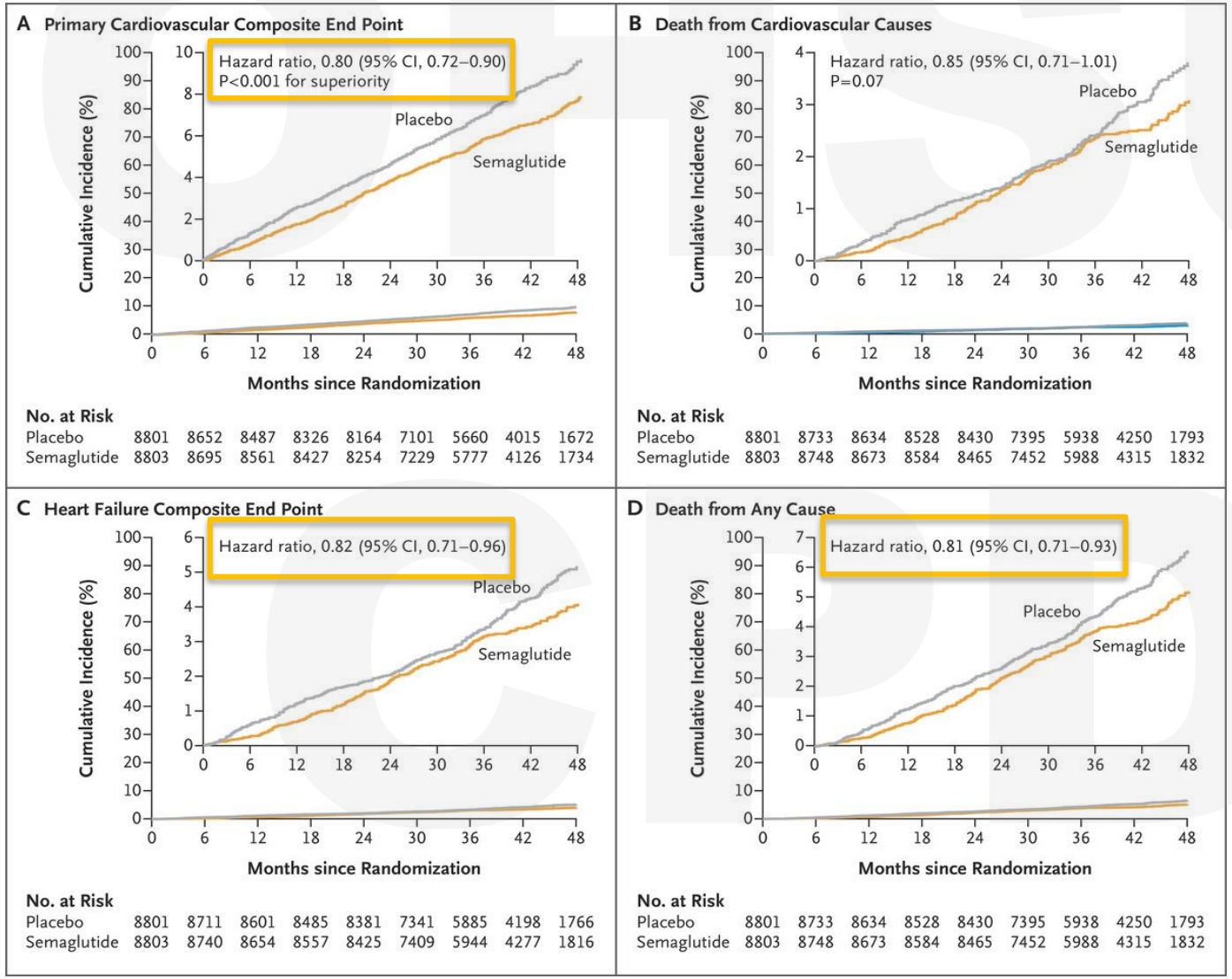
A. Michael Lincoff, M.D., Kirstine Brown-Frandsen, M.D., Helen M. Colhoun, M.D., John Deanfield, M.D., Scott S. Emerson, M.D., Ph.D., Sille Esbjerg, M.Sc., Søren Hardt-Lindberg, M.D., Ph.D., G. Kees Hovingh, M.D., Ph.D., Steven E. Kahn, M.B., Ch.B., Robert F. Kushner, M.D., Ildiko Lingvay, M.D., M.P.H., Tugce K. Oral, M.D., Marie M. Michelsen, M.D., Ph.D., Jorge Plutzky, M.D., Christoffer W. Tornøe, Ph.D., and Donna H. Ryan, M.D., for the SELECT Trial Investigators*

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
Waist circumference — cm	111.3±13.1	111.4±13.1
Glycated hemoglobin level — %	5.78±0.34	5.78±0.33
Distribution — no. (%)		
<5.7%	2925 (33.2)	2980 (33.9)
≥5.7%	5877 (66.8)	5819 (66.1)
Median high-sensitivity CRP level (IQR) — mg/liter	1.87 (0.89–4.18)	1.80 (0.86–4.06)
Cardiovascular inclusion criteria — no. (%)		
Myocardial infarction only	5962 (67.7)	5944 (67.5)
Stroke only	1578 (17.9)	1556 (17.7)
Peripheral arterial disease only	376 (4.3)	401 (4.6)
Two or more inclusion criteria	718 (8.2)	719 (8.2)
Other§	169 (1.9)	181 (2.1)
eGFR — ml/min/1.73 m²	82.4±17.5	82.5±17.3
Median lipid level (IQR) — mg/dl		
Total cholesterol	153 (131–182)	153 (131–183)
HDL cholesterol	44 (37–52)	44 (37–52)
LDL cholesterol	78 (61–102)	78 (61–102)
Triglycerides	134 (99–188)	135 (100–190)
Systolic blood pressure — mm Hg	131.0±15.6	130.9±15.3
Diastolic blood pressure — mm Hg	79.4±10.0	79.2±9.9

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes: SELECT

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



↓ ~20% for:

- 3-point MACE
- Heart failure
- Total Mortality

Semaglutide and CV Outcomes in SELECT by Baseline and Changes in Adiposity Measurements: BMI, WC

Deanfield J, et al. Lancet 2025; 406: 2257–68

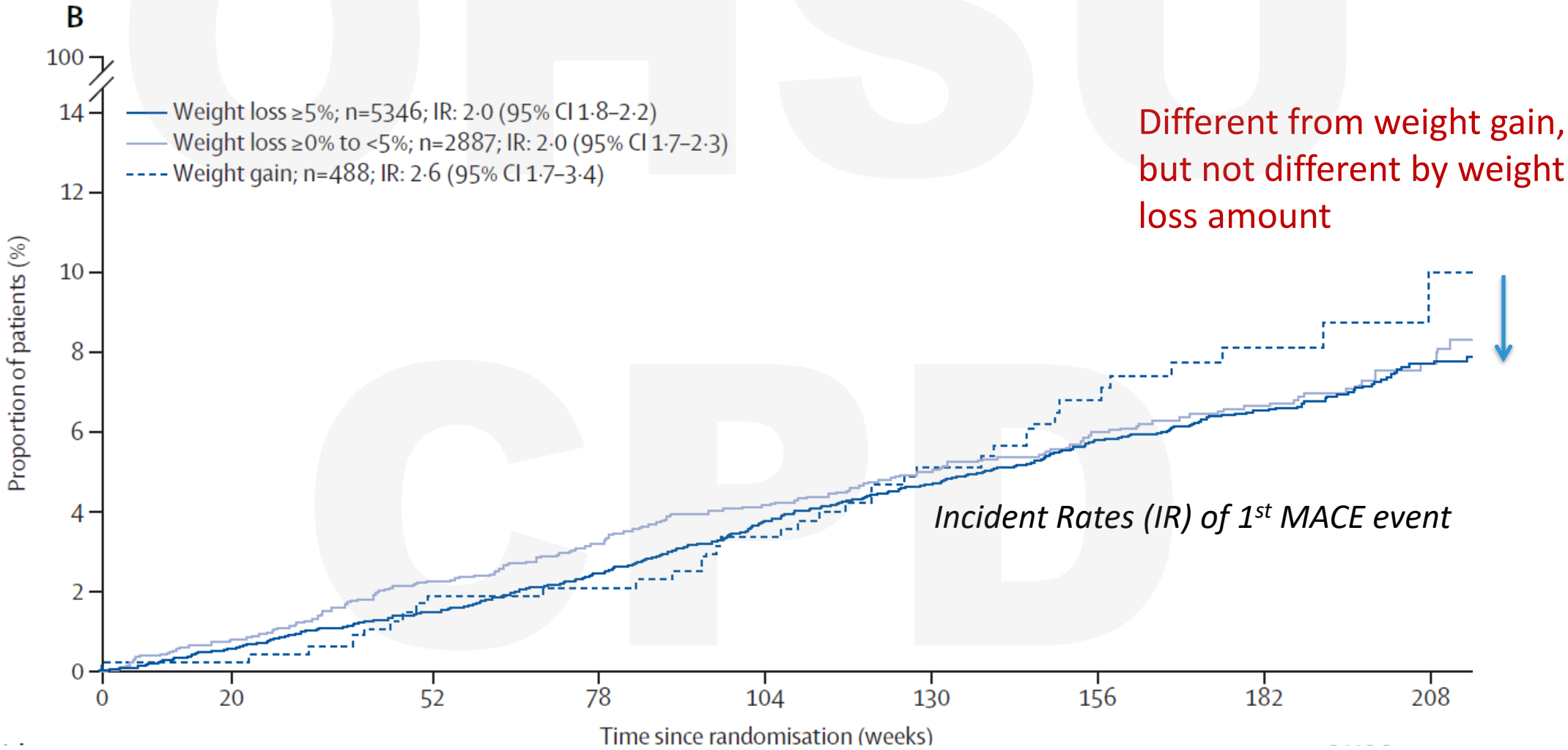
Question:

Could evidence support weight and adiposity-independent effects of semaglutide on MACE outcomes?

OHSU

Semaglutide and CV Outcomes in SELECT by Baseline and Changes in Adiposity Measurements: BMI, WC

Deanfield J, et al. Lancet 2025; 406: 2257–68



Different from weight gain, but not different by weight loss amount

Incident Rates (IR) of 1st MACE event

Semaglutide and CV Outcomes in SELECT by Baseline and Changes in Adiposity Measurements: BMI, WC

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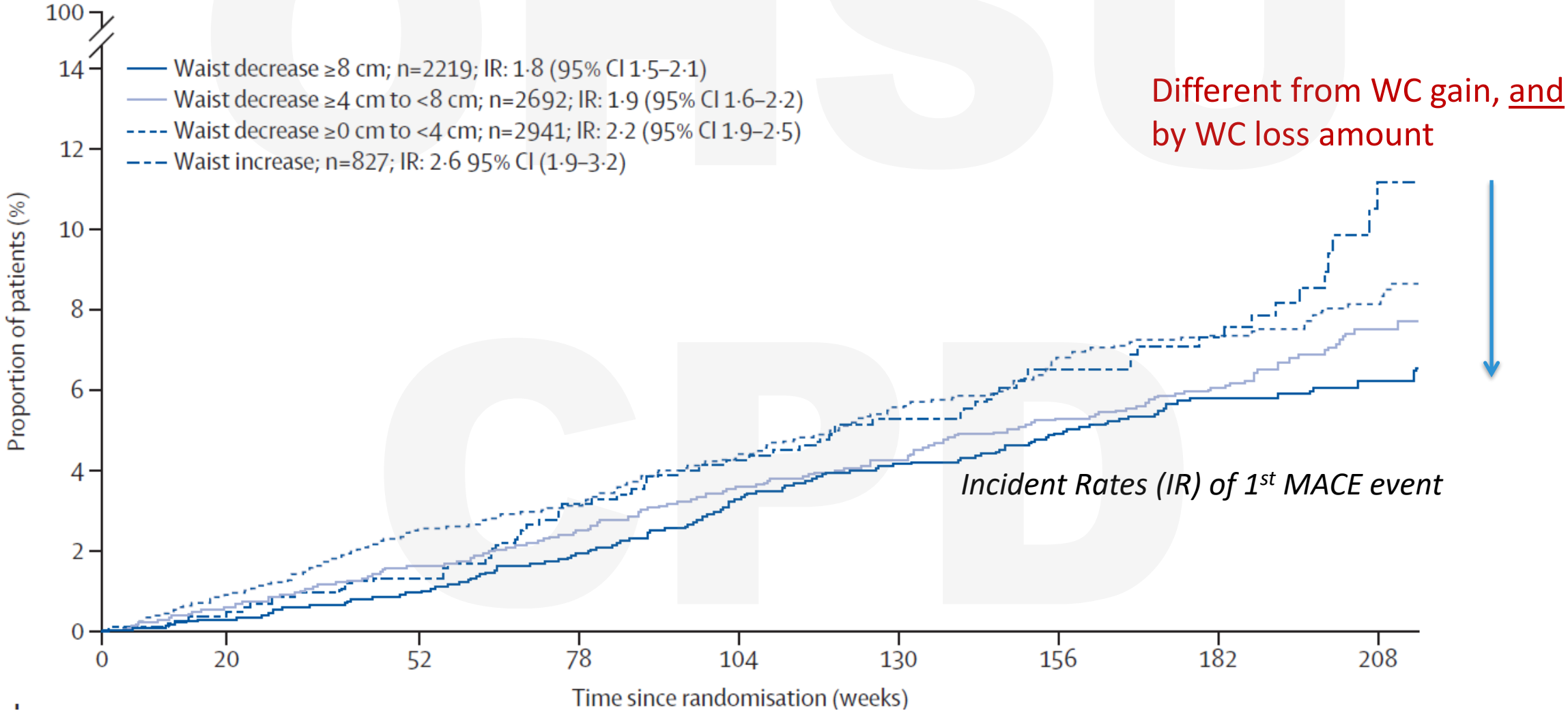


Different from WC gain, and by WC loss amount

Incident Rates (IR) of 1st MACE event

Semaglutide and CV Outcomes in SELECT by Baseline and Changes in Adiposity Measurements: BMI, WC

Deanfield J, et al. Lancet 2025; 406: 2257–68

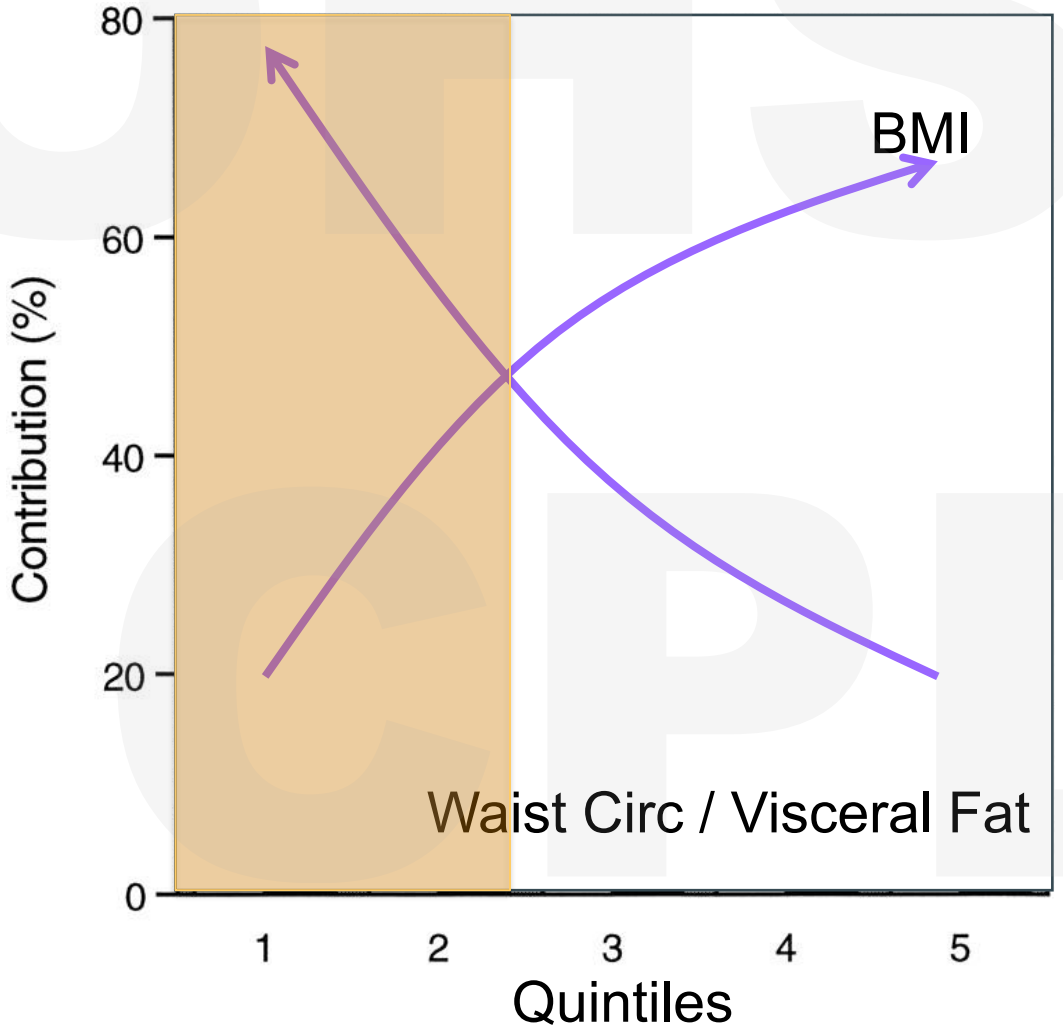
Explanation:

Even though total weight (BMI) loss did not predict time to first MACE event, MACE events were still influenced by loss of central weight (WC).

This is still weight (adiposity) loss!

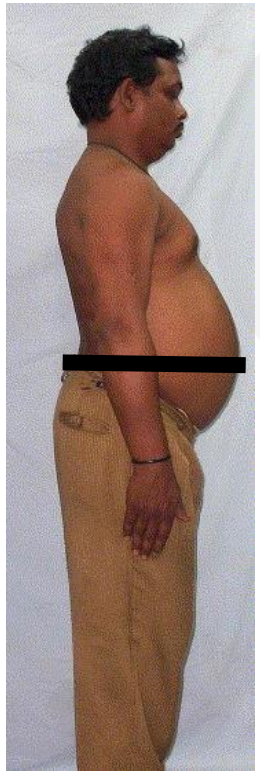
Relative Contribution of Total BMI and Central Fat to Type 2 Diabetes, CVD, and Mortality

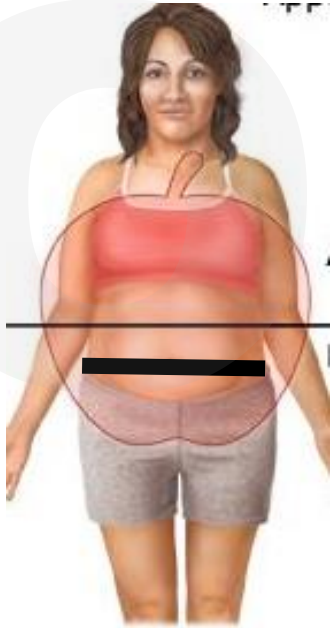
Type 2 Diabetes
CVD
Mortality



Willet, et al. NEJM. 341:427-34, 1999
Lancet. 2009. 373:1083-96.
NEJM. 2017; 377:13-27.
Larsson, et al. BMJ. 288.1401, 1984.

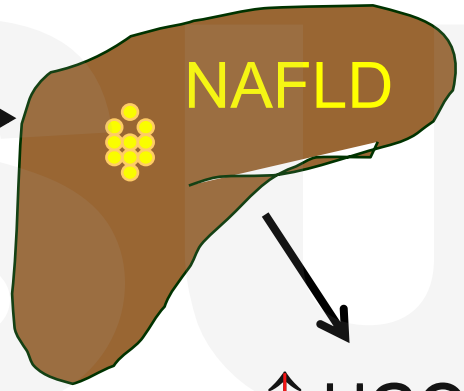
Central Adiposity





Visceral Adiposity

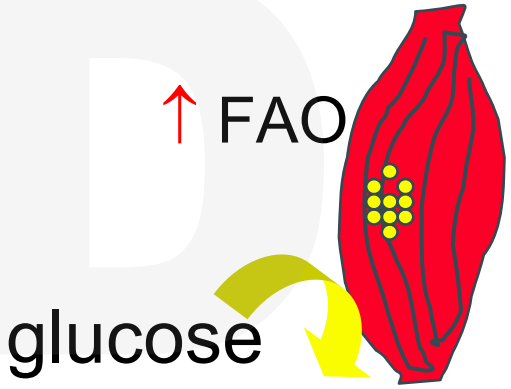
Ectopic Adiposity



↕ HGO → ↕ Glucose

↕ VLDL-TG → ↕ CETP → ↕ HDL-C

↑ Adiponectin



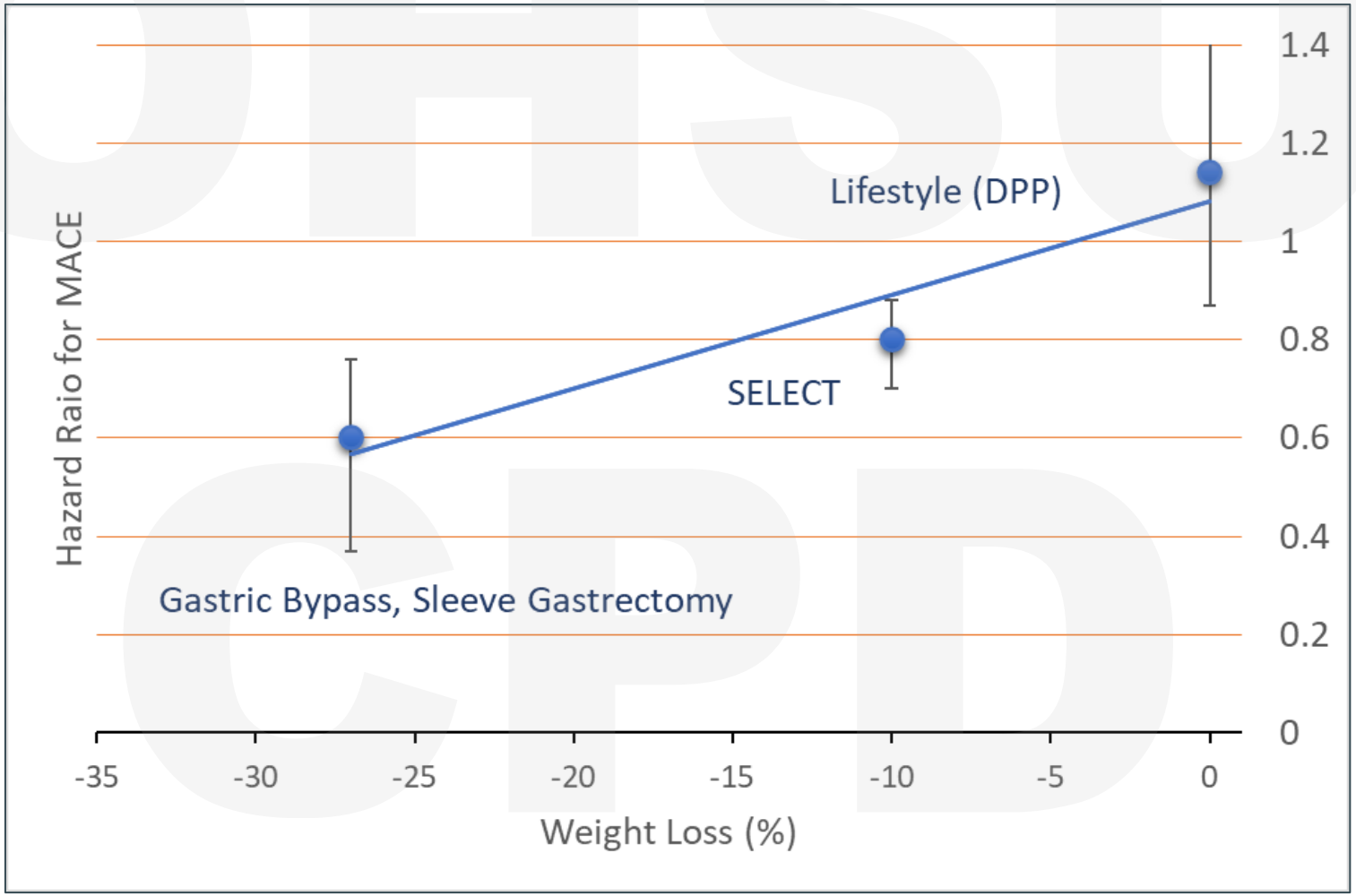
Dyslipidemia

T2D

Inflammation

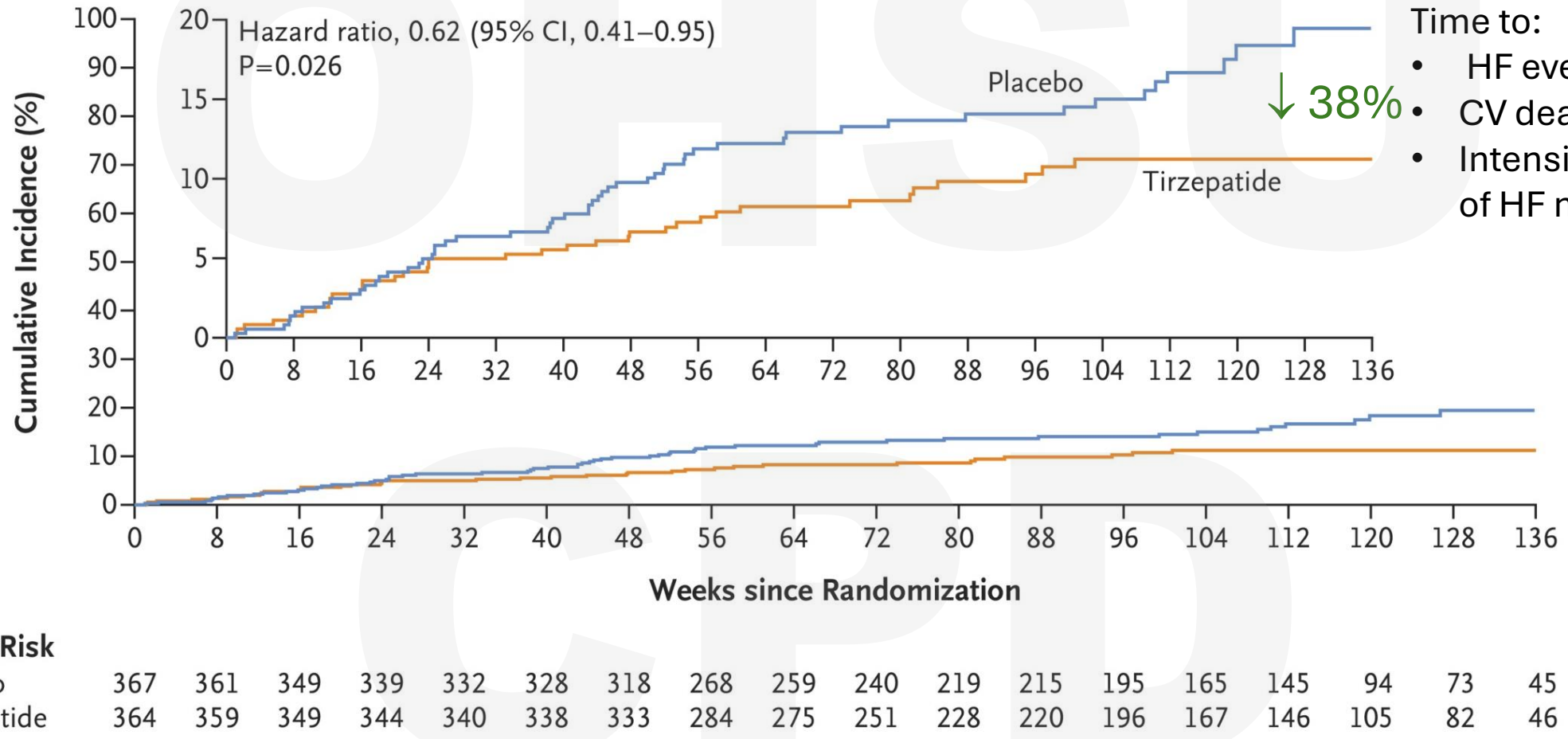
Intervention, Weight Loss, and Relationship to Major Adverse Cardiac Events (3 Point-MACE)

No Diabetes



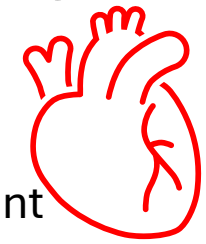
Purnell JQ and Camacho SA. J Clin Lipidology. 2024. 18:e5-e9.

Tirzepatide for HFpEF and Obesity: SUMMIT Trial



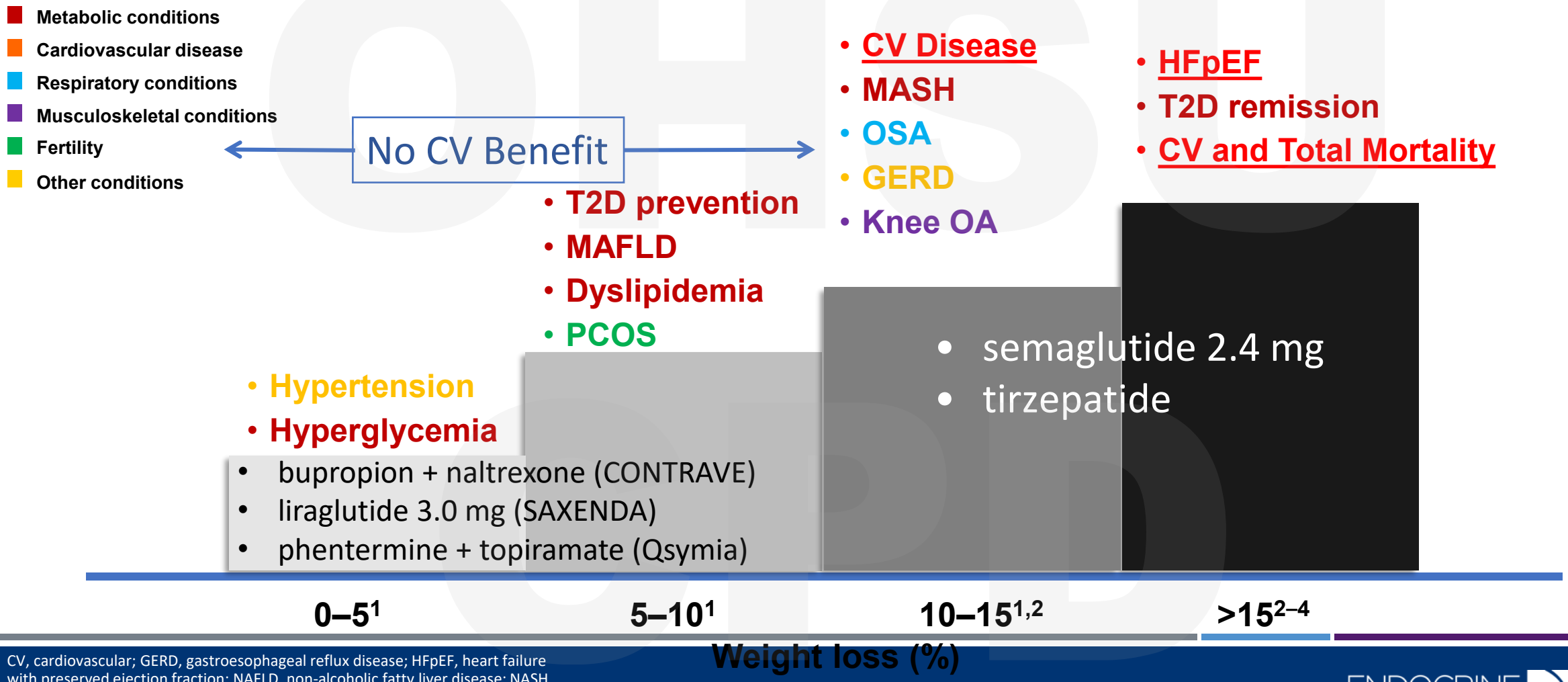
Time to:

- HF event
- CV death
- Intensification of HF meds



Packer M et al. N Engl J Med. 2025;392:427-437

HEALTH BENEFITS BEGIN AT 2-5% TOTAL WEIGHT LOSS



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Courtesy L Arrone

ENDOCRINE SOCIETY
Hormone Science to Health

Treating Obesity First: The Health Halo Effect

MASLD / MASH

Weight loss without “food noise”

Pre-diabetes / Diabetes

OSA

Quality of Life

OA

Cardiovascular Risks and Disease

US FDA-Approved Obesity Medications (OMs)

Ave Wt Loss		Side effects
~ 4-5%	• bupropion + naltrexone	• Nausea, increased adrenergic tone
~ 6-7%	• liraglutide 3.0 mg †	• GI, pancreatitis (?), ↑ HR, theoretical MCT
~ 10-11%	• phentermine + topiramate	• Increase adrenergic tone, mood/cognition
~ 15%	• semaglutide 2.4 mg †	• GI (20%-40%), ↑ HR, theoretical MCT
up to 30%	• setmelanotide	• Skin darkening, increased BP, priapism
~ 20%	• tirzepatide†	• GI (40%-50%), ↑ HR, theoretical MCT

† In patients without diabetes

Nissen SE, et al. JAMA. 2016;315(10):990-1004.
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Monroe, et al. BMJ. 1:352-54. 1968.
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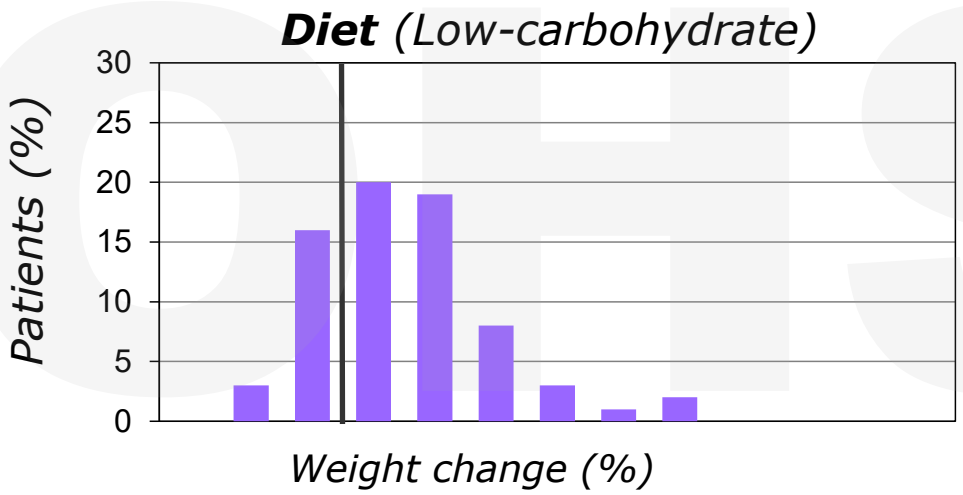
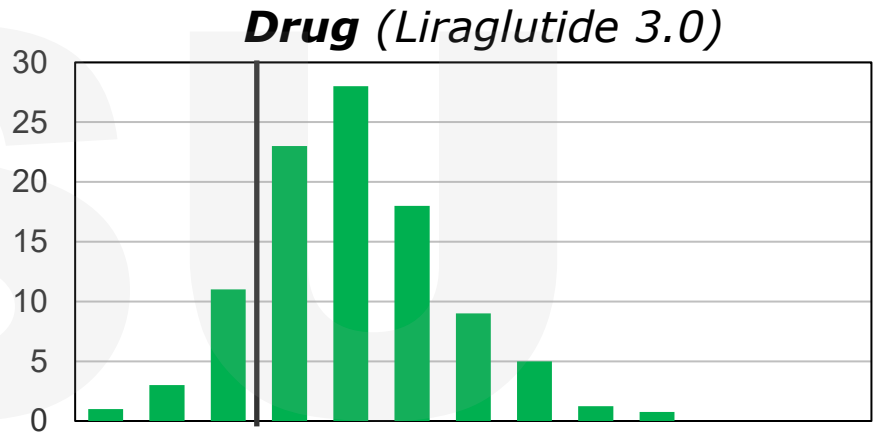
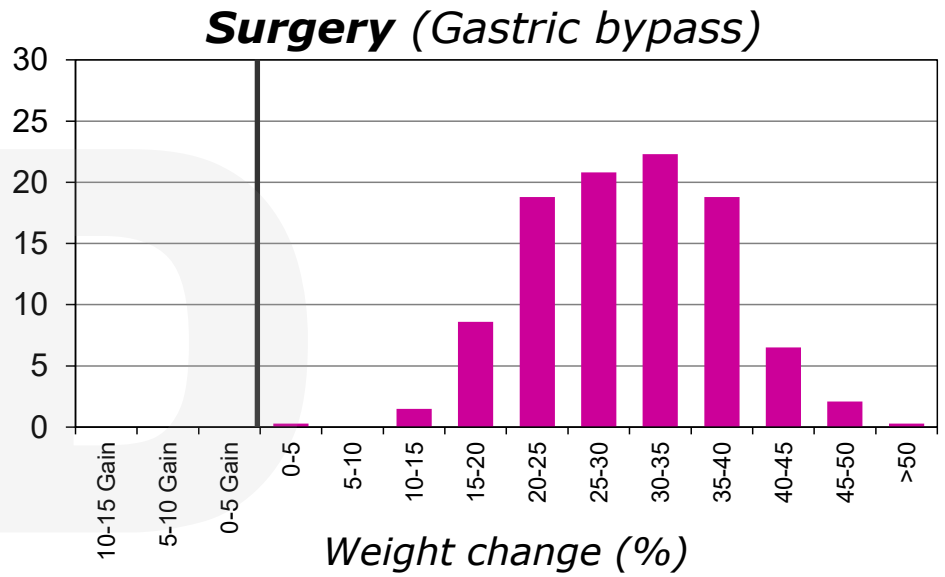
Chronic Disease Management: Variable Response







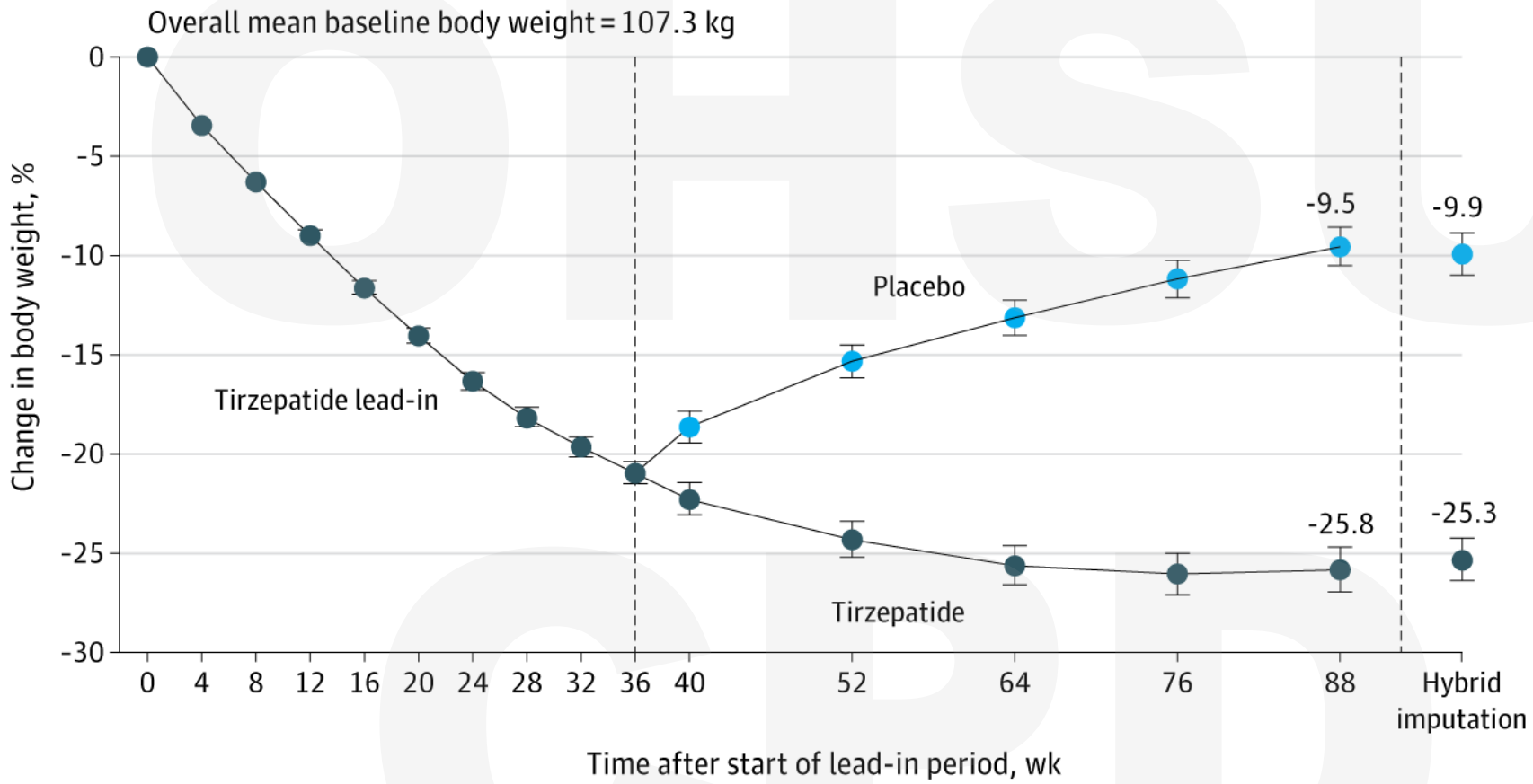
Weight loss is variable

- This is completely expected in chronic disease management.
- Prepare your patients
- Not indicative of lifestyle non-compliance or patient “failure”

Slide courtesy of Lee Kaplan, MD, PhD

MASSACHUSETTS GENERAL HOSPITAL

Chronic Disease Management: Long-term



No. at risk

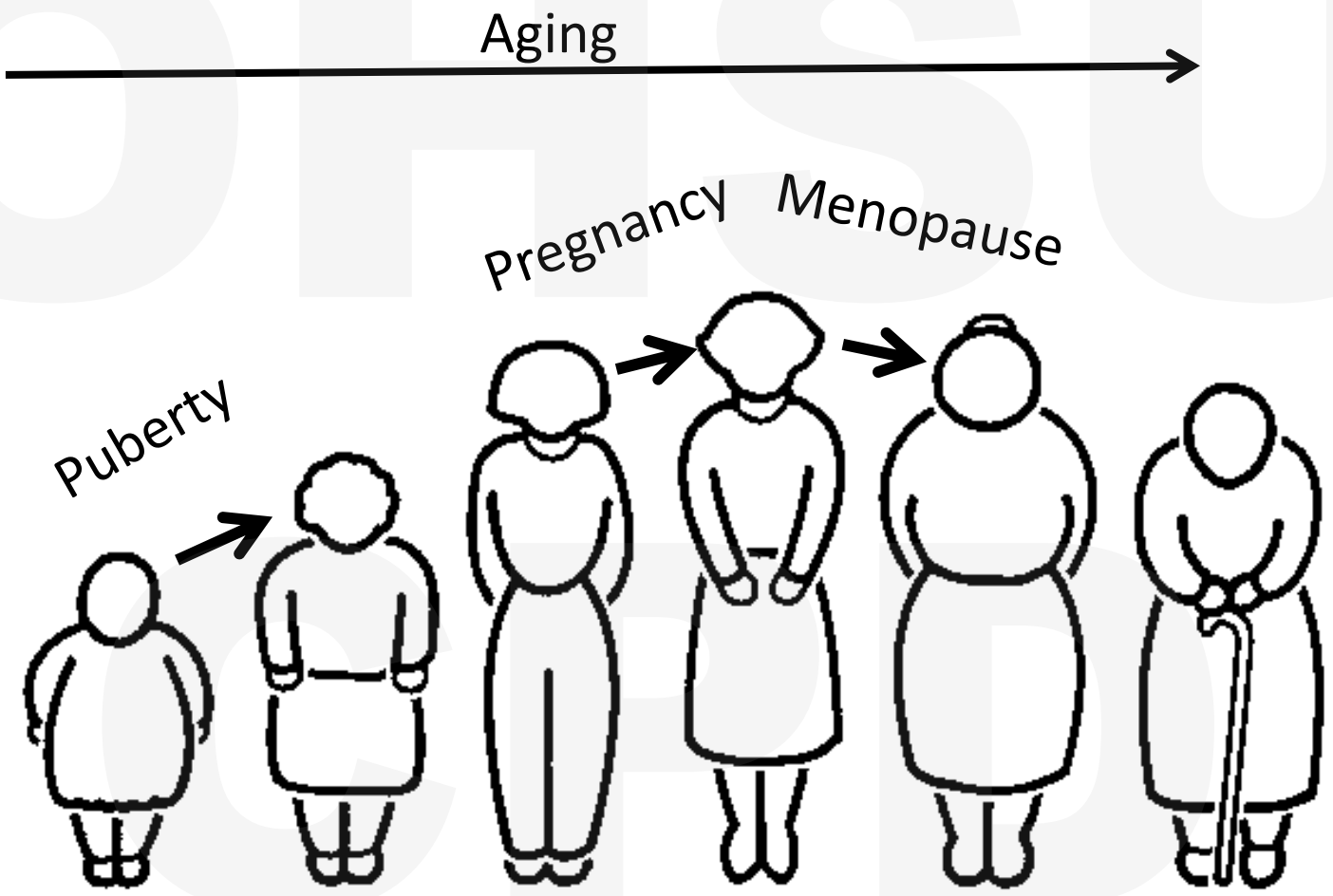
Tirzepatide lead-in	670	666	669	668	667	667	669	663	659	670
Tirzepatide							335	333	328	317	310	310	335
Placebo							335	330	317	303	292	289	335

Aronne LJ, et al. JAMA. 2024. 331:38-48.

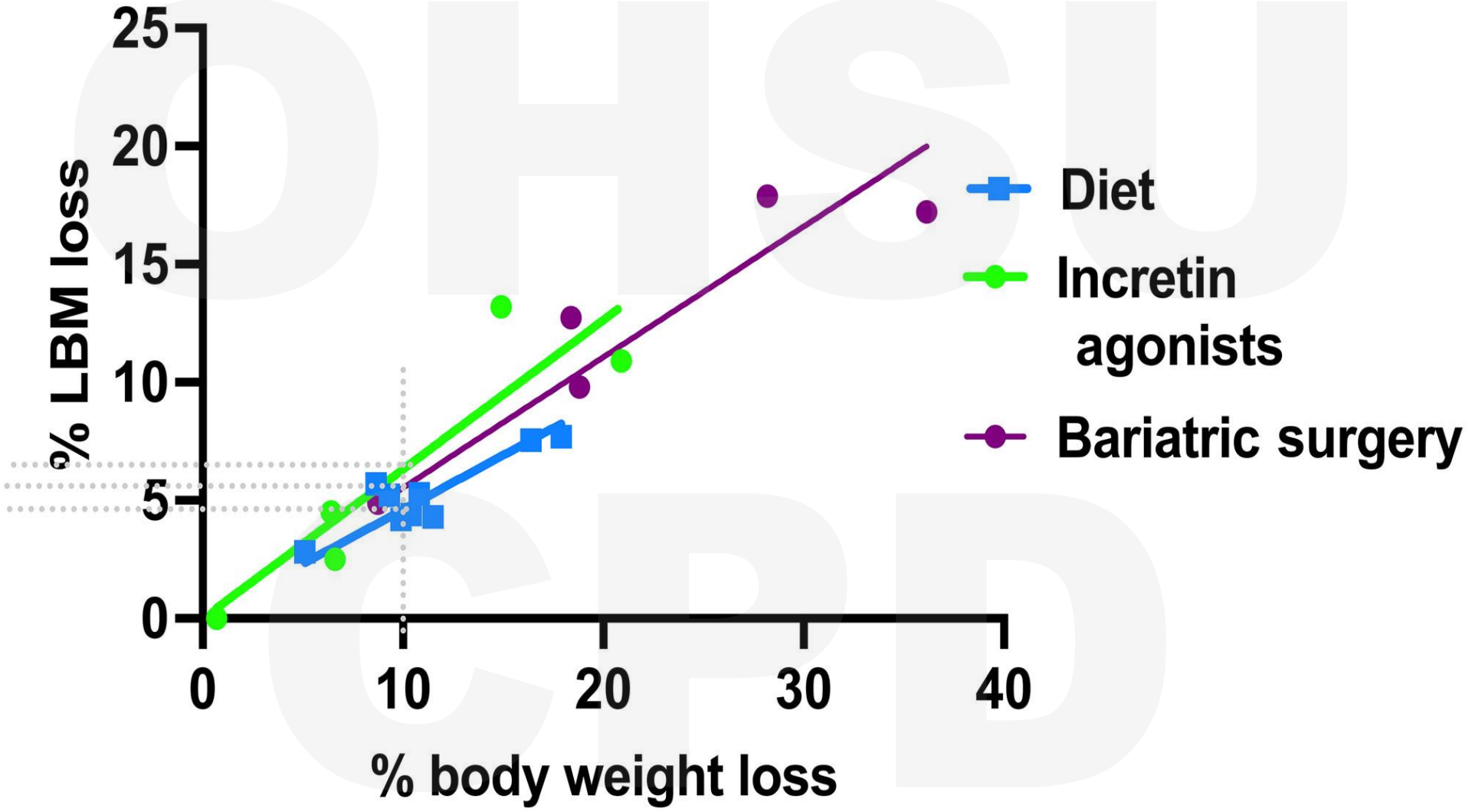
Chronic Disease Management: Combinations

- No one medication is expected to work in everyone
- Each drug has a limit of efficacy—cannot just "dial up the dose to dial down the weight"
- Combination anti-obesity medication therapy is and will be the norm
  - Use separate and complementary MOA's
    - Brain, brainstem, muscle, fat tissue, microbiome by organ site and receptor
    - Energy intake (appetite control) and energy expenditure
  - Reduce side effects

Key Periods in Women's Lives for Weight Gain



Changes in Lean Body Mass Following Weight Loss



Diabetes Obesity Metabolism, Volume: 26, Issue: S4, Pages: 16-27, First published: 27 June 2024, DOI: (10.1111/dom.15728)

Thank You