TERAPIA FARMACOLOGICA DELL'ECCESSO PONDERALE CON GLP-1 AGONISTI

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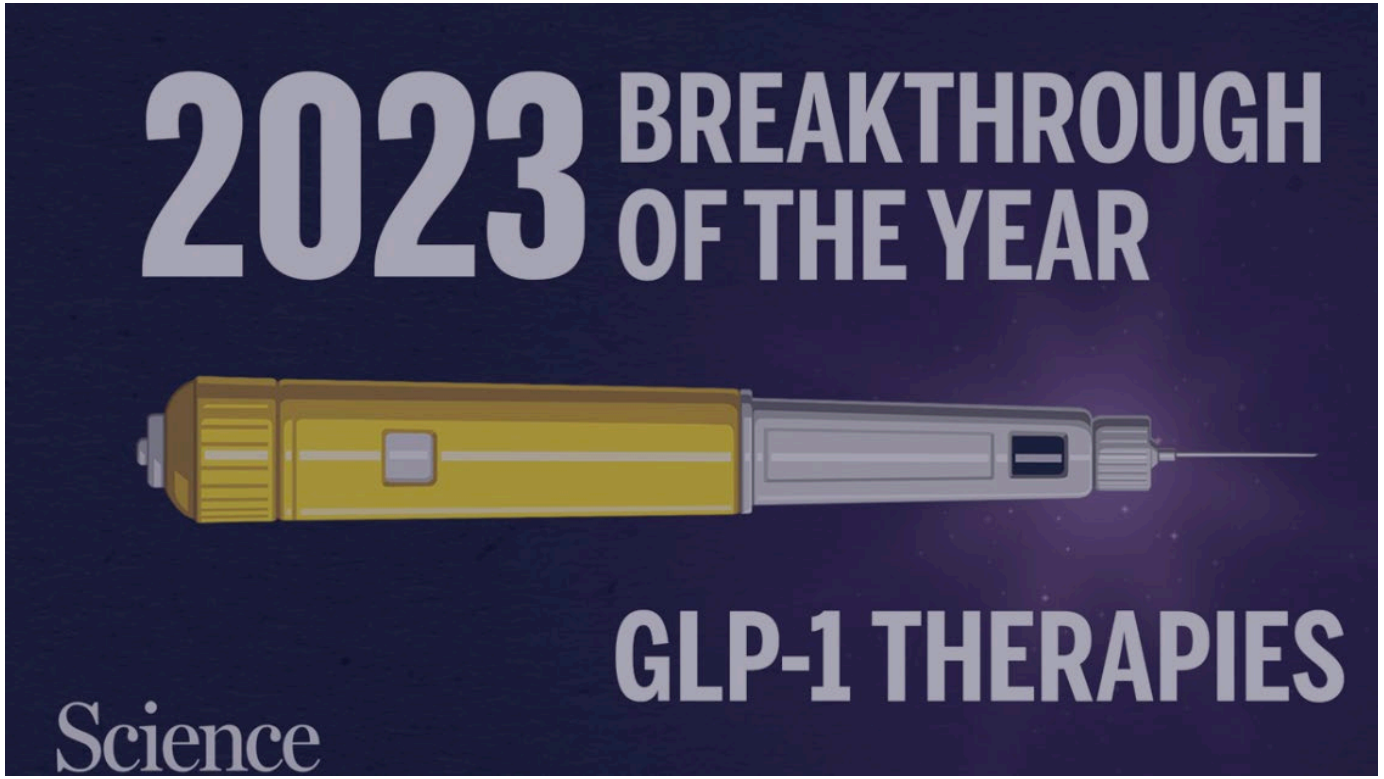
Centro di Riferimento Regionale per il Diabete, ARNAS Garibaldi – Catania


2023 BREAKTHROUGH OF THE YEAR
Check for updates
OBESITY
MEETS ITS
MATCH
Blockbuster weight loss drugs show promise for a wider range of health benefits
By Jennifer Couzin-Frankel
Downloaded from https://www.science.org on January 05, 2024


2023 BREAKTHROUGH OF THE YEAR
GLP-1 THERAPIES
Science

Semaglutide[3]

Semaglutide 2.4 mg

es. h: 1.70 m, w: 78 kg

Overweight

BMI ≥ 27 kg/m²

+ ≥ 1 comorbidities
[such as dysglycaemia (prediabetes or T2D), hypertension, dyslipidaemia, OSAS or CV disease]

es. h: 1.70 m, w: 87 kg

Obesity

BMI ≥ 30 kg/m²

T2D, type 2 diabetes; OSAS, obstructive sleep apnoea; CV, cardiovascular

SmPC, available from https://www.aifa.gov.it/trova-farmaco

Semaglutide is a once-weekly, human GLP-1 analogue

- **94%** homology to human GLP-1[1]
- $t_{½}$ of approximately **1 week**[2,3]

Amino acid substitution at position 8
(alanine to alpha-aminoisobutyric acid)
protects against DPP-4 degradation[1]

Spacer and C-18 fatty di-acid chain to lysine in position 26 provide strong binding to albumin[1]

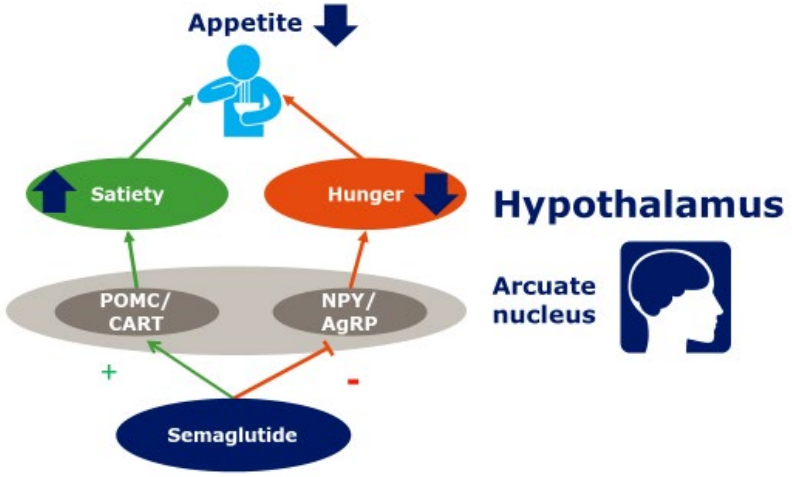
Amino acid substitution at position 34
(lysine to arginine) prevents C-18 fatty di-acid binding at the wrong site[1]

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; t½, half-life.

Lau et al. J Med Chem 2015;58:7370–80; Kapitza et al. J Clin Pharmacol 2015;55:497–504; Marbury et al. Clin Pharmacokinet 2017;56:1381–90.

Semaglutide increases satiety and reduces hunger

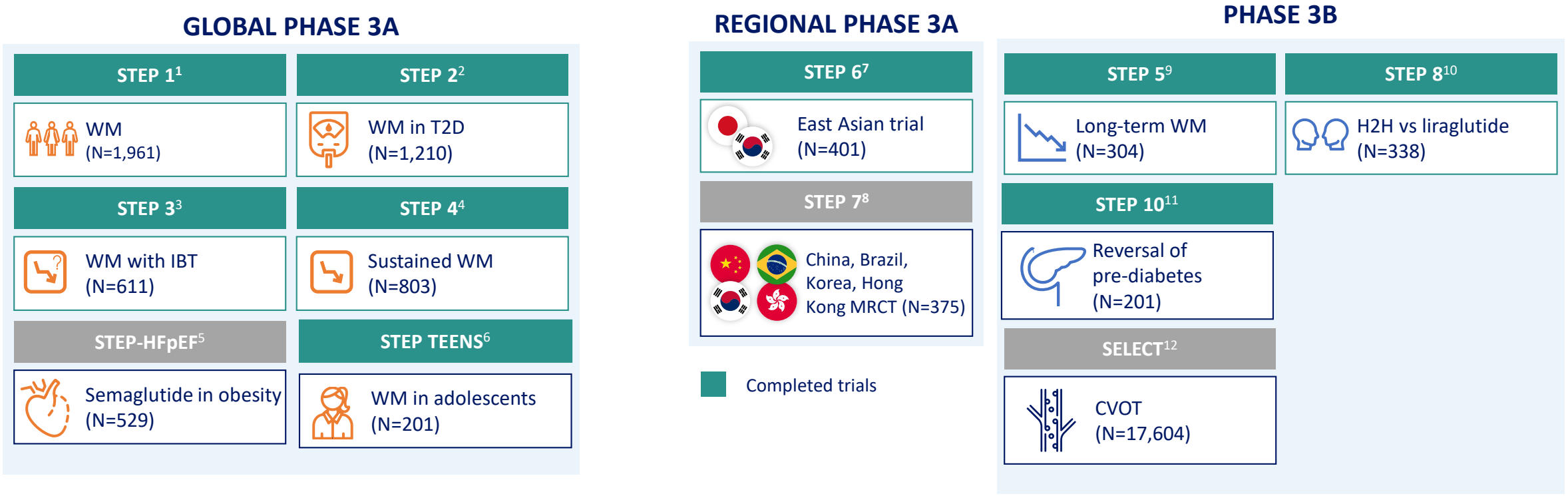
Via neurons in the arcuate nucleus



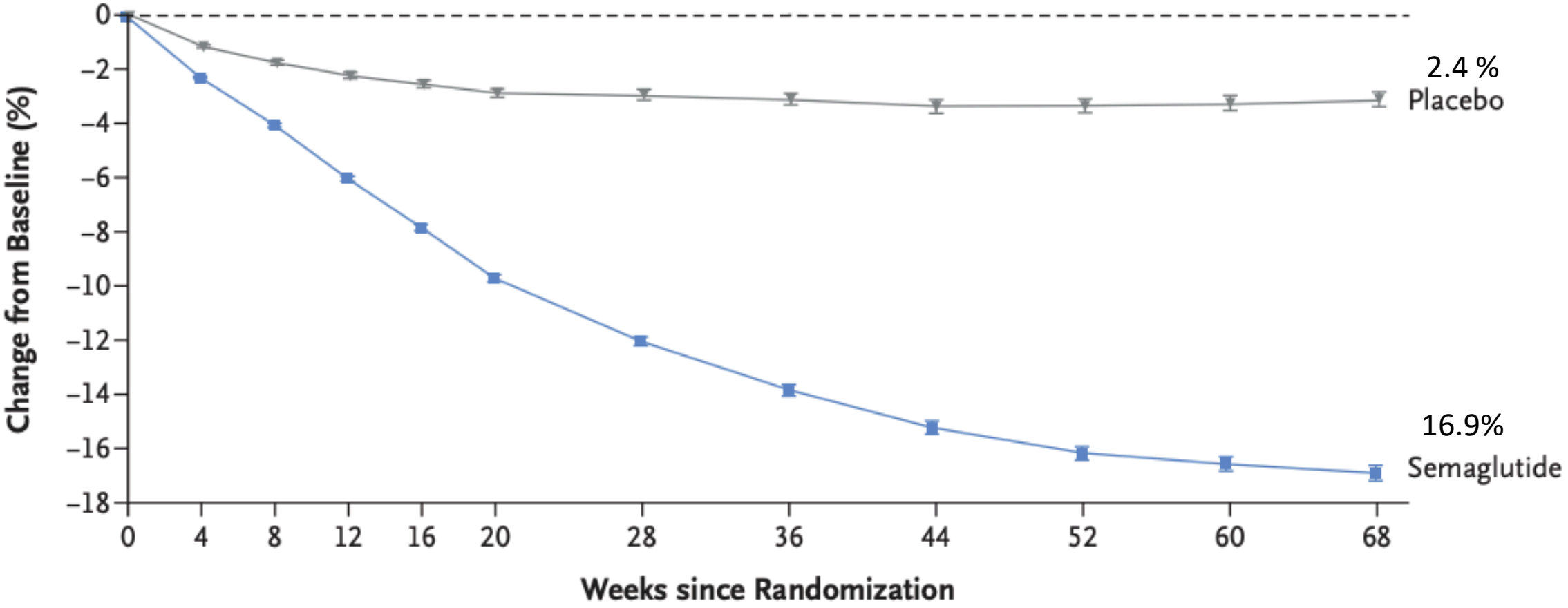
GABA, gamma-aminobutyric acid; GLP-1R, glucagon-like peptide-1 receptor; NPY, neuropeptide Y; POMC, pro-opiomelanocortin

Secher et al. J Clin Invest 2014;124:4473–88; Jensen CB et al. Diabetes 2017;66 (Suppl 1):P-1145. Lu TT et al. Diabetes 2017;66 (Suppl 1):P-1072.

The STEP programme investigated semaglutide for weight management in people with overweight or obesity

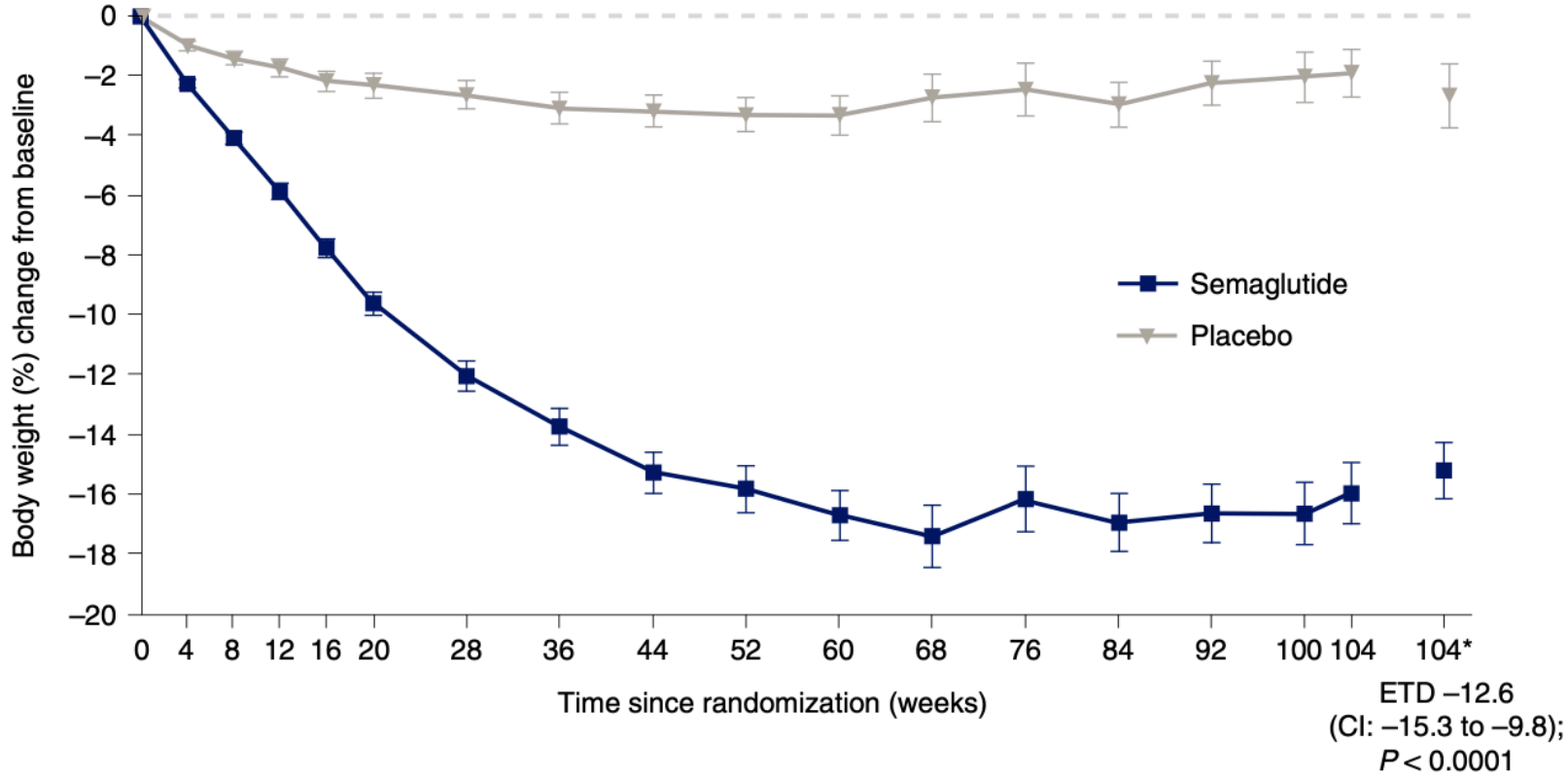


Semaglutide- STEP 1



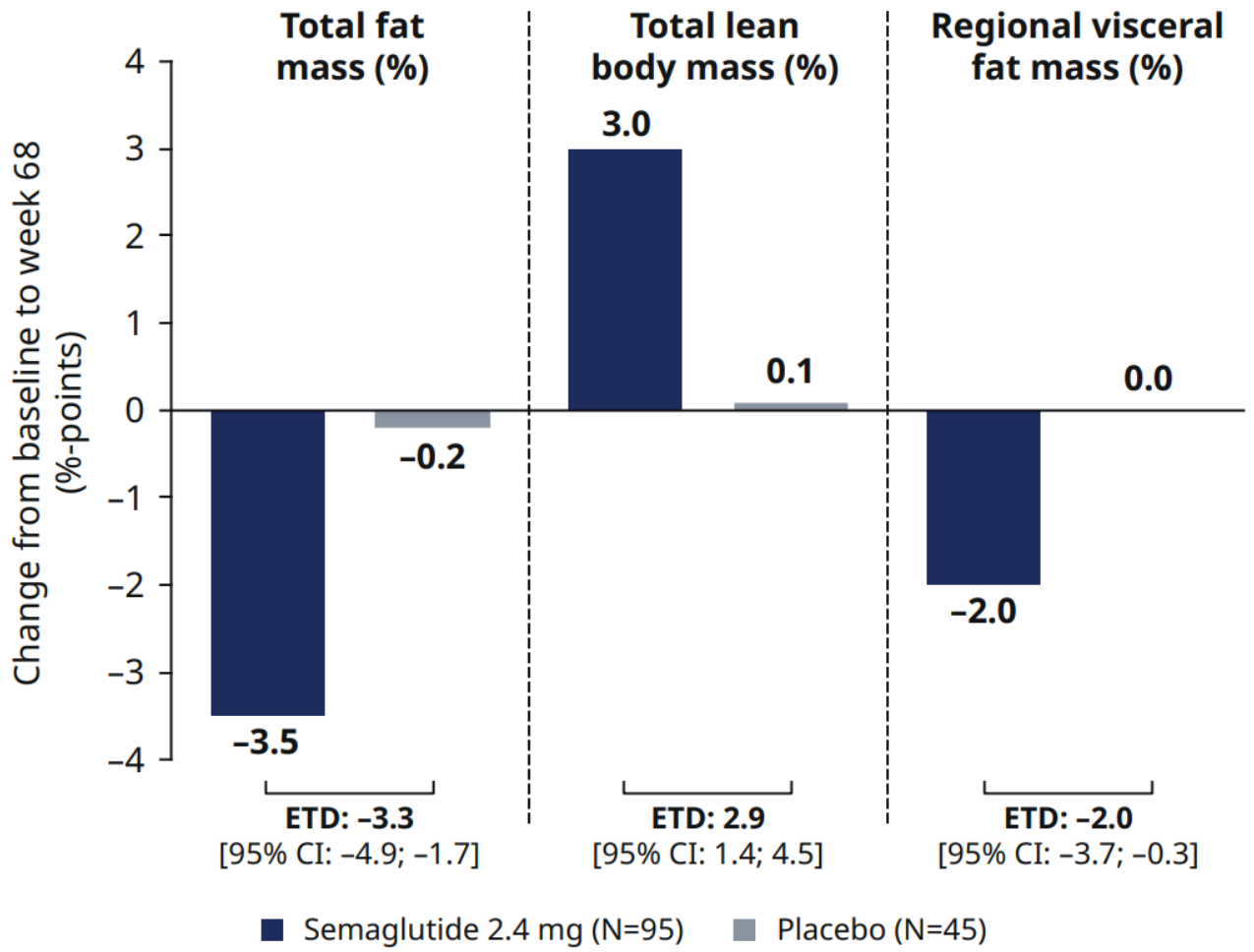
N Engl J Med 2021;384:989-1002

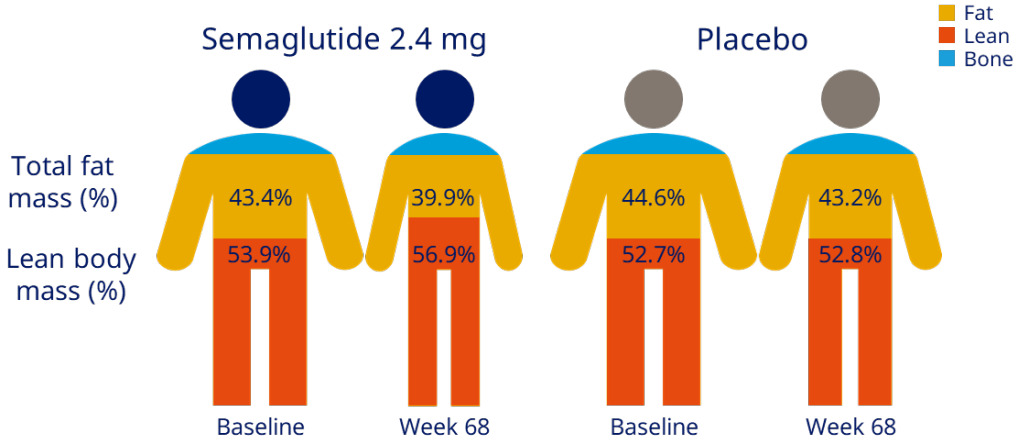
Two-year effects of semaglutide : the STEP 5 trial



Nat Med 28, 2083–2091 (2022)

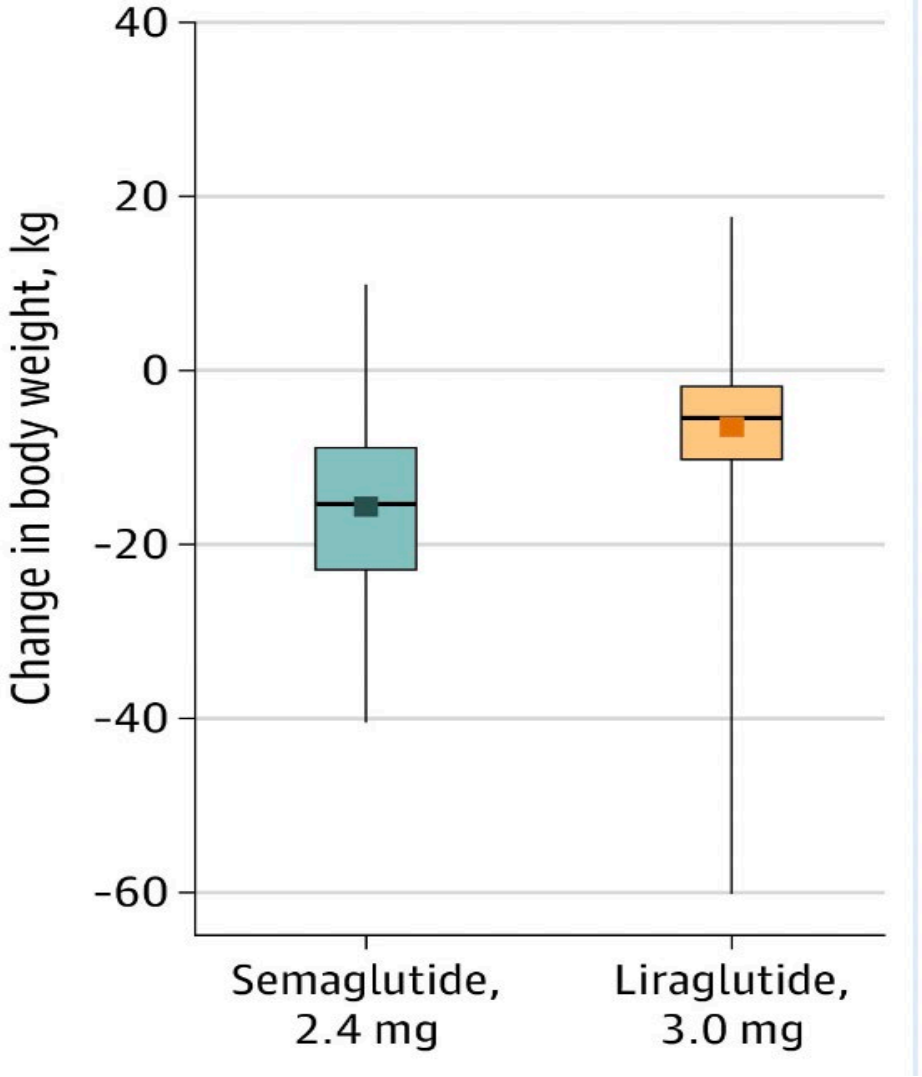
Semaglutide 2.4 mg: body composition changes by DEXA

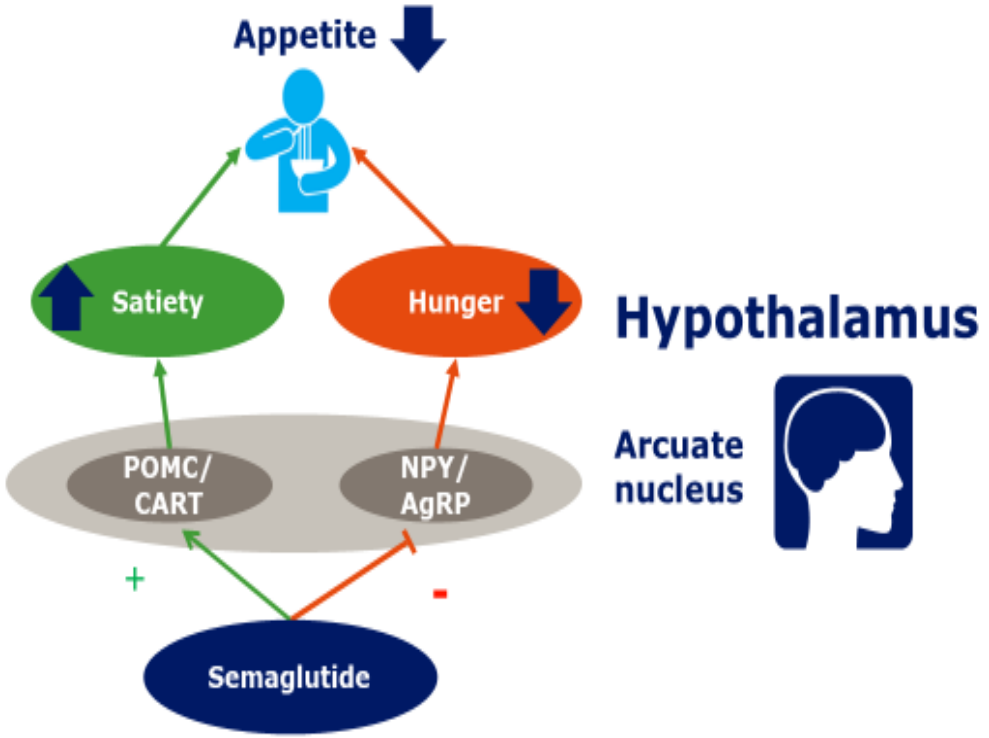




Adapted from Wilding et al. N Engl J Med 2021;384:989-1002.

Effect of Semaglutide vs Liraglutide: The STEP 8



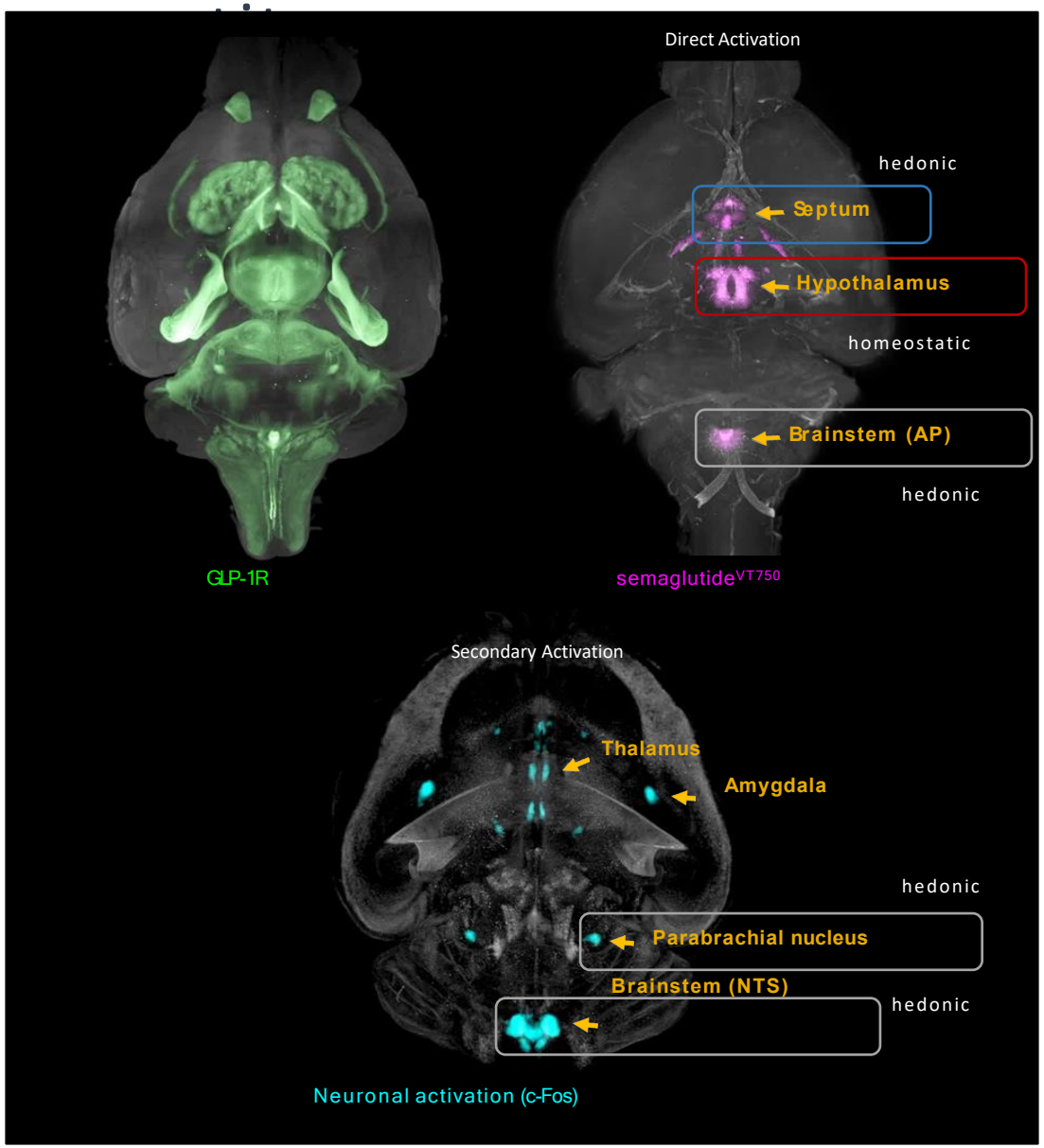


GABA, gamma-aminobutyric acid; GLP-1R, glucagon-like peptide-1 receptor; NPY, neuropeptide Y; POMC, pro-opiomelanocortin

Secher et al. J Clin Invest 2014;124:4473–88; Jensen CB et al. Diabetes 2017;66 (Suppl 1):P-TT45. Lu TT et al. Diabetes 2017;66 (Suppl 1):P-1072.

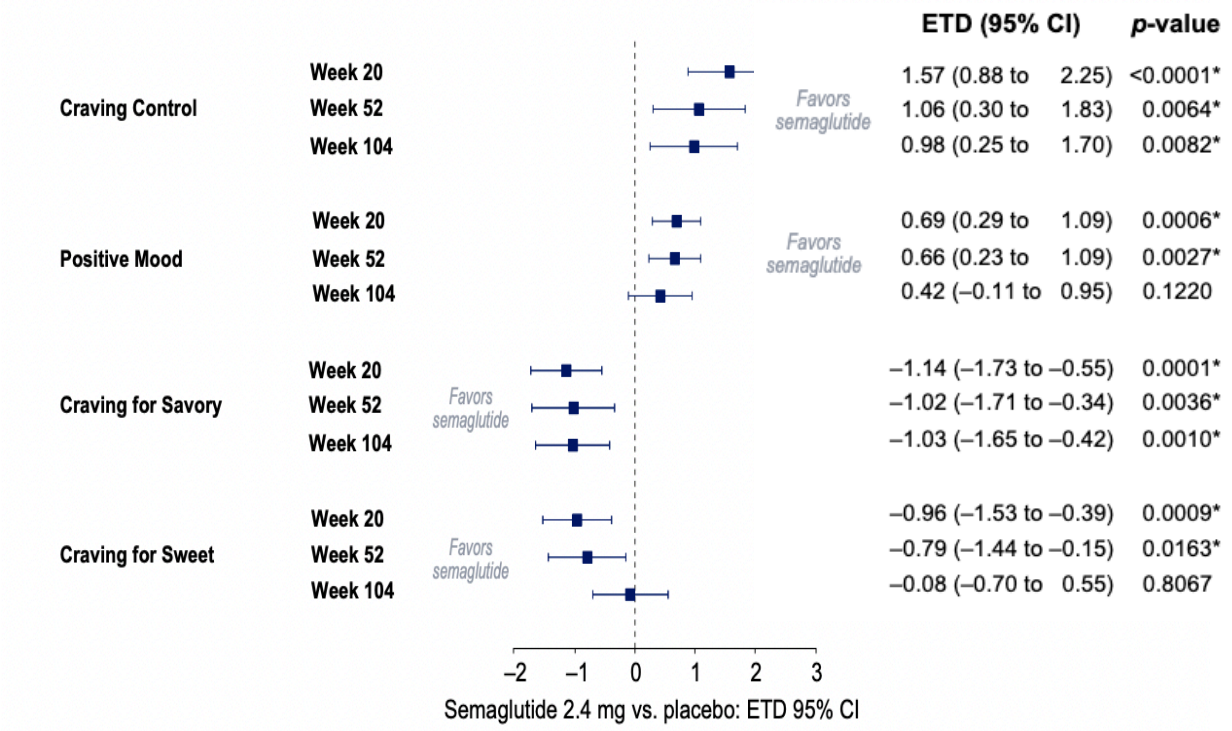
JAMA. 2022 Jan 11;327(2):138-150.

Semaglutide integrates the homeostatic and hedonic control of



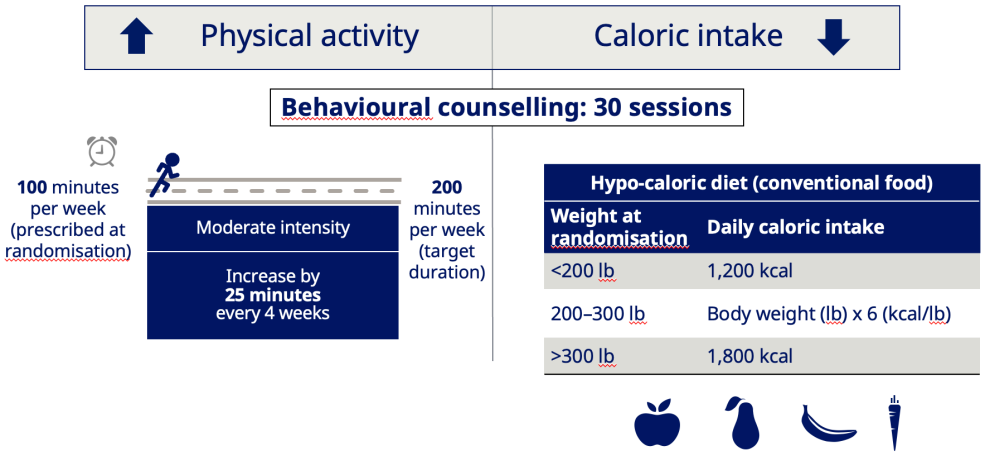
Gabery S et al. JCI Insight 2020;5:e133429.

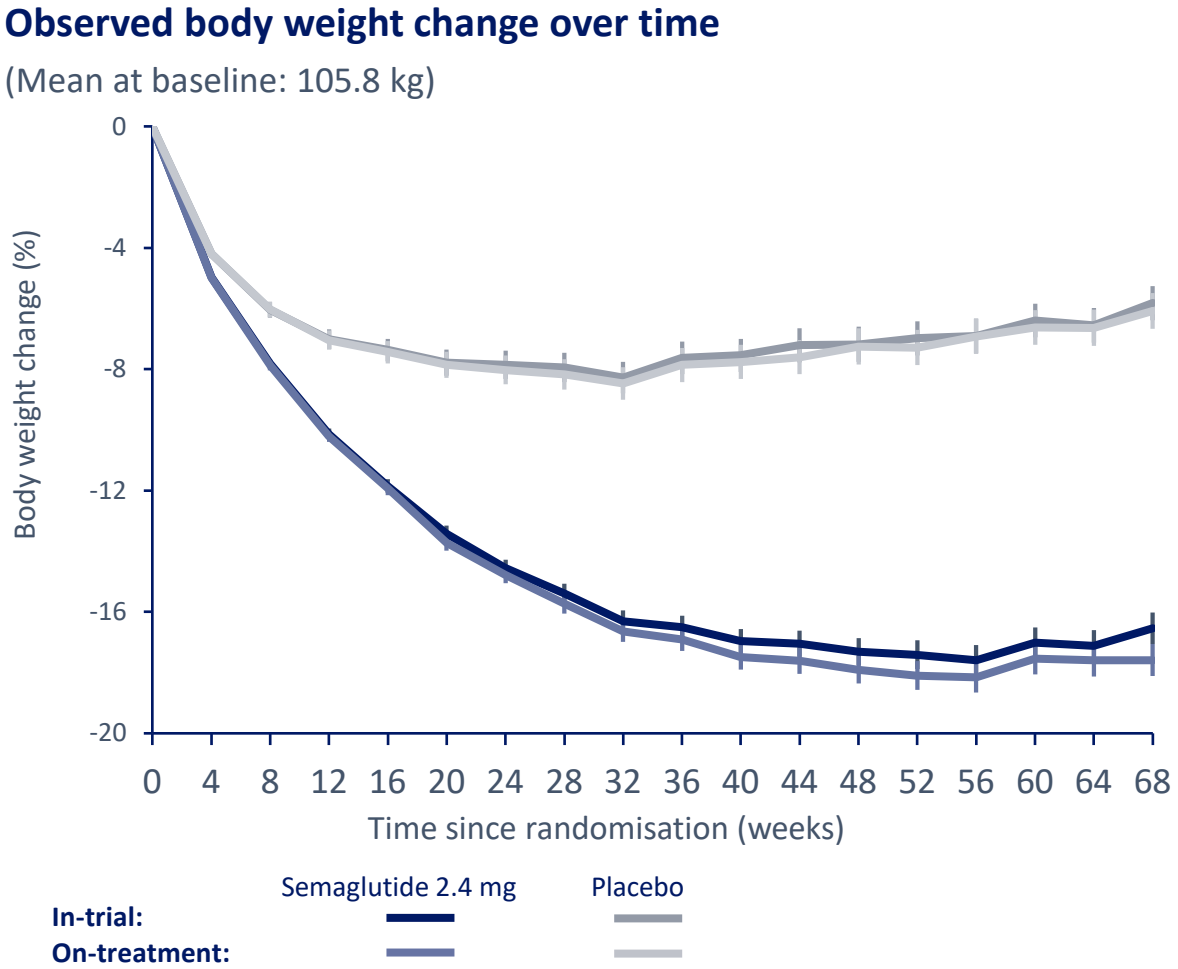
Control of eating- STEP 5



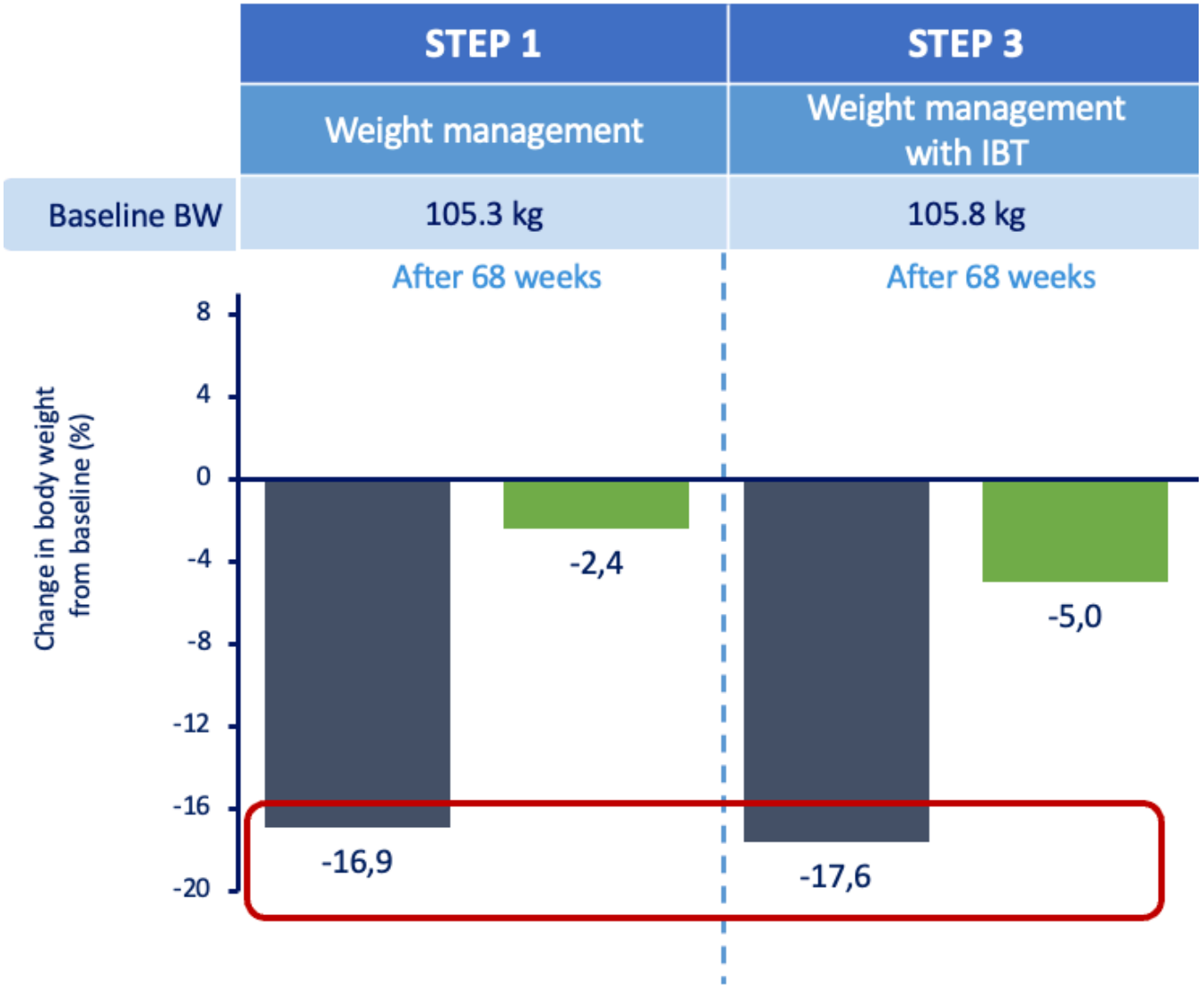
Obesity (Silver Spring). 2023;31:703–715.

the STEP 3 trial:
the weight management with intensive behavioral therapy



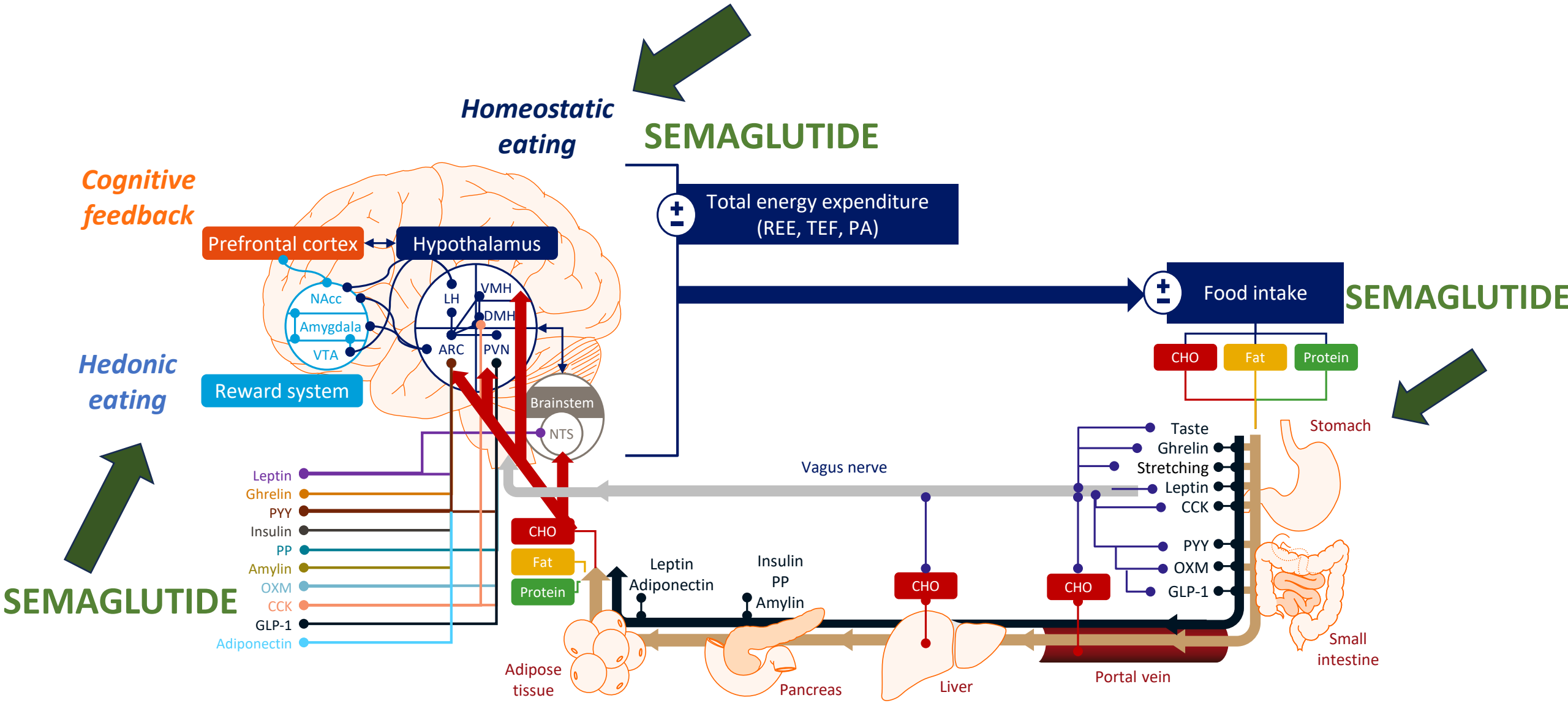


STEP 3 vs STEP 1

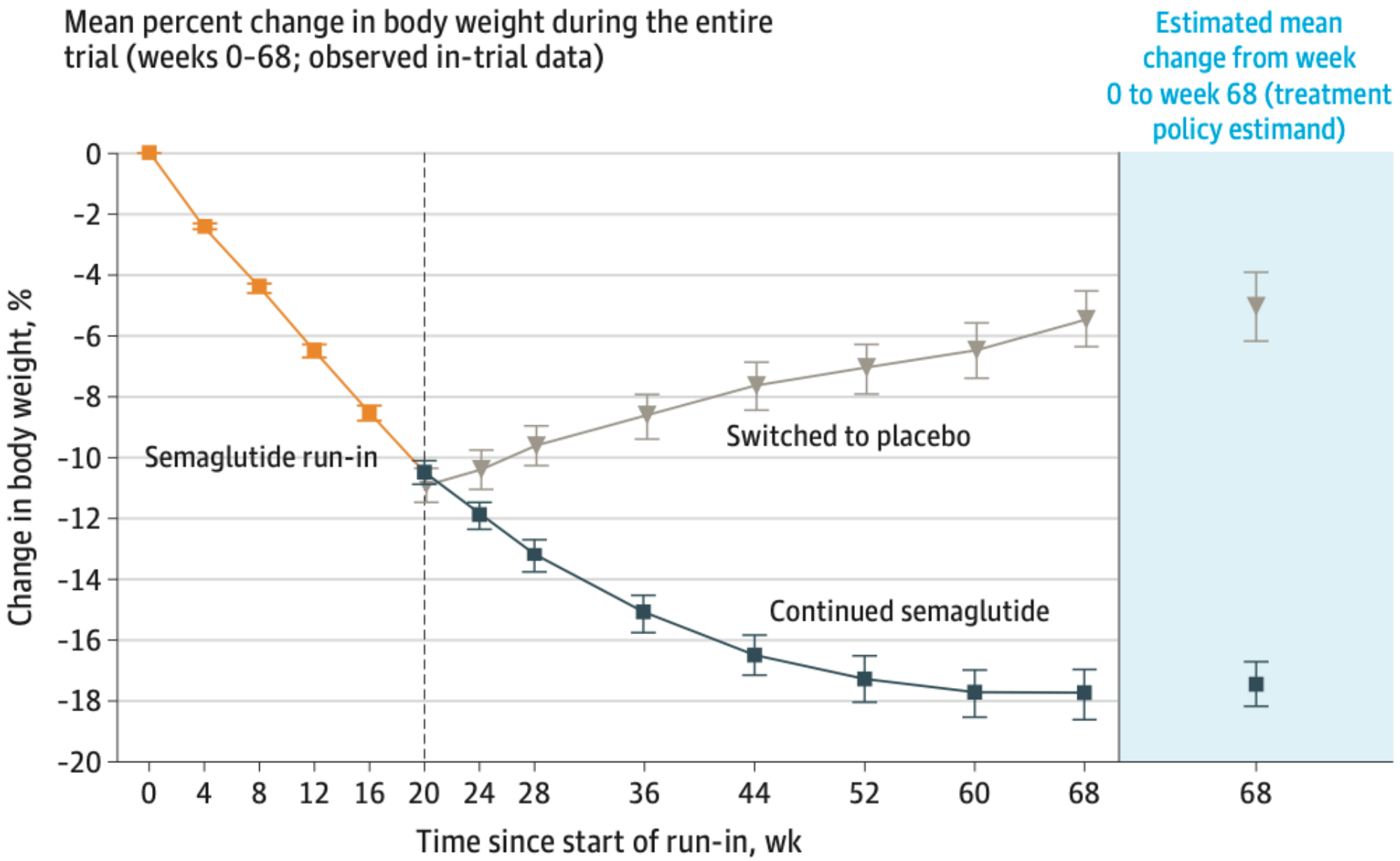


Wilding et al. N Engl J Med 2021;384:989-1002; Davies et al. Lancet 2021;397:971-84..

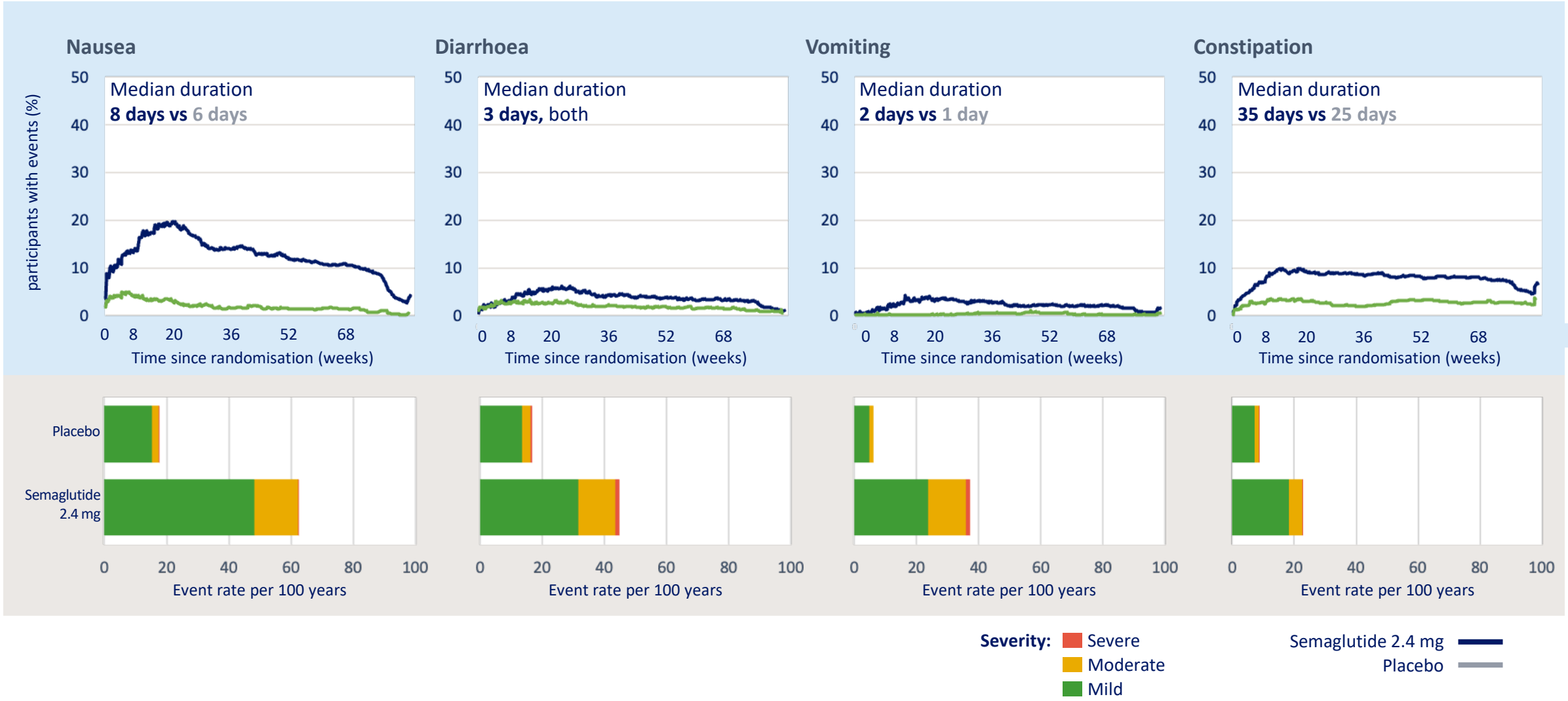
Current pharmacological therapy targets



Effect of Continued Semaglutide vs Placebo - STEP 4

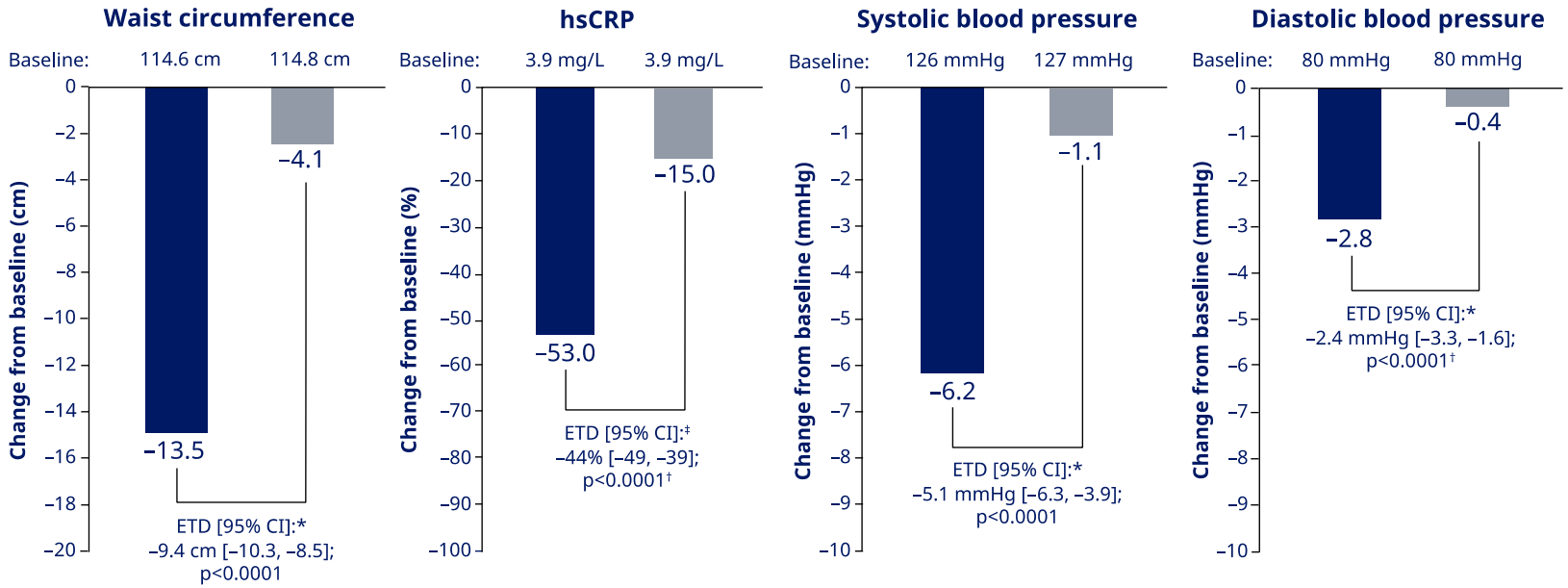


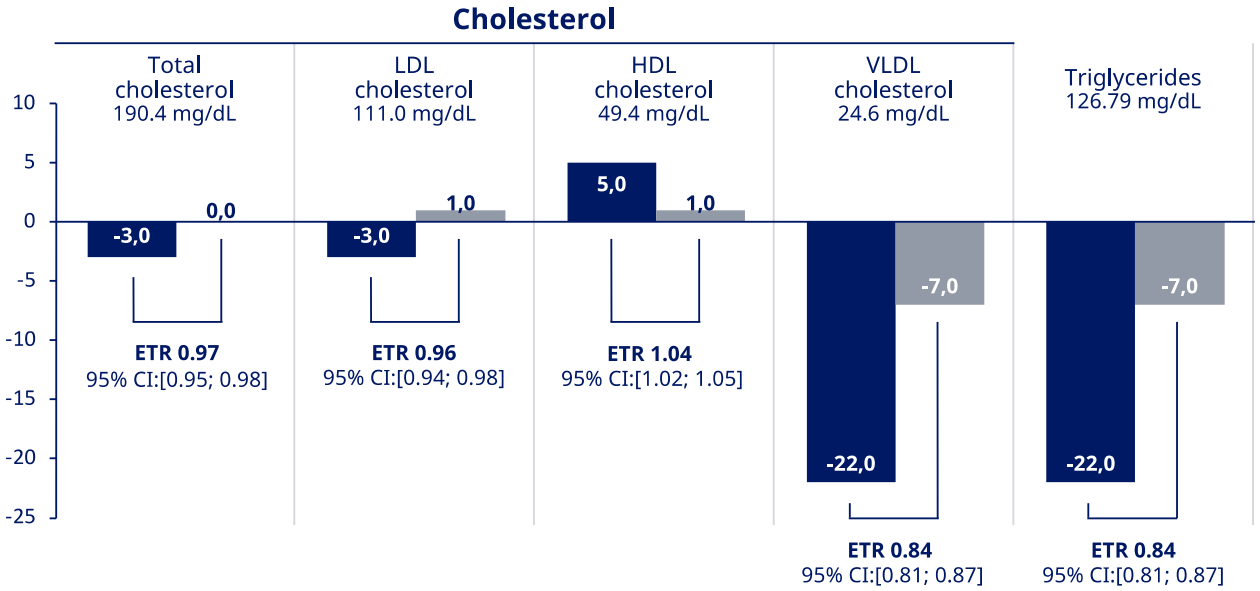
Semaglutide 2.4 mg- AE



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

Semaglutide- CV risk factors





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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

SELECT

semaglutide effects on cardiovascular outcomes in people with overweight or obesity

SELECT

N=17,604

Male | Female

72.3 | 27.7%

Mean age

61.6 years

Mean BMI[1]

33.3 kg/m²

Mean HbA_{1c}[1]

5.8%

With prediabetes[1]

66.4%

MI only

67.6%

Stroke only

17.8%

PAD only

4.4%

≥2 CV inclusion criteria

8.2%

Chronic heart failure[1]

24.3%

Subclass[2]
HFpEF| HFrEF | Unknown

12.9 | 7.7 | 3.8

Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

Therapeutic impact on top of optimized evidence-based therapy

Baseline characteristic	Semaglutide 2.4 mg (N = 8,803)	Placebo (N = 8,801)
Systolic blood pressure – mmHg	131.0 ± 15.6	130.9 ± 15.3
Diastolic blood pressure – mmHg	79.4 ± 10.0	79.2 ± 9.9
Pulse – bpm	68.9 ± 10.6	68.6 ± 10.7
Total cholesterol – mg/dL	153 (131–182)	153 (131–183)
HDL cholesterol – mg/dL	44 (37–52)	44 (37–52)
LDL cholesterol – mg/dL	78 (61–102)	78 (61–102)
Triglycerides – mg/dL	134 (99–188)	135 (100–190)
hsCRP – mg/L	1.87 (0.89–4.18)	1.80 (0.86–4.06)

Baseline CV medications (%, n)	Semaglutide 2.4 mg (N = 8,803)	Placebo (N = 8,801)
Platelet aggregation inhibitors	86.5 (7,612)	86.0 (7,569)
- Acetylsalicylic acid	78.5 (6,909)	77.9 (6860)
- P2Y12 receptor inhibitors	33.2 (2,925)	34.1 (2,998)
Anti-thrombotic medications	12.3 (1,086)	13.1 (1,150)
- Vitamin K antagonists	3.8 (336)	3.9 (340)
- Direct oral anticoagulants	8.4 (738)	8.9 (784)
Lipid-lowering drugs	90.1 (7,928)	90.1 (7,929)
- Statins	87.7 (7,716)	87.6 (7,709
- Ezetimibe	13.5 (1,188)	13.0 (1,144)
- Fibrates	2.4 (213)	3.0 (266)
- PCSK-9 inhibitors	2.0 (177)	1.8 (162)
Beta blockers	70.2 (6,182)	70.2 (6,175)
ACE inhibitors	45.0 (3,963)	45.1 (3,966)
ARBs	29.7 (2,618)	29.2 (2,569)
CCBs	27.3 (2,407)	26.5 (2,331)

ACE, angiotensin-converting-enzyme; ARB, angiotensin-receptor blockers;
CCB, calcium channel blockers. LDL, low-density lipoprotein; hsCRP, high-sensitivity C-reactive protein

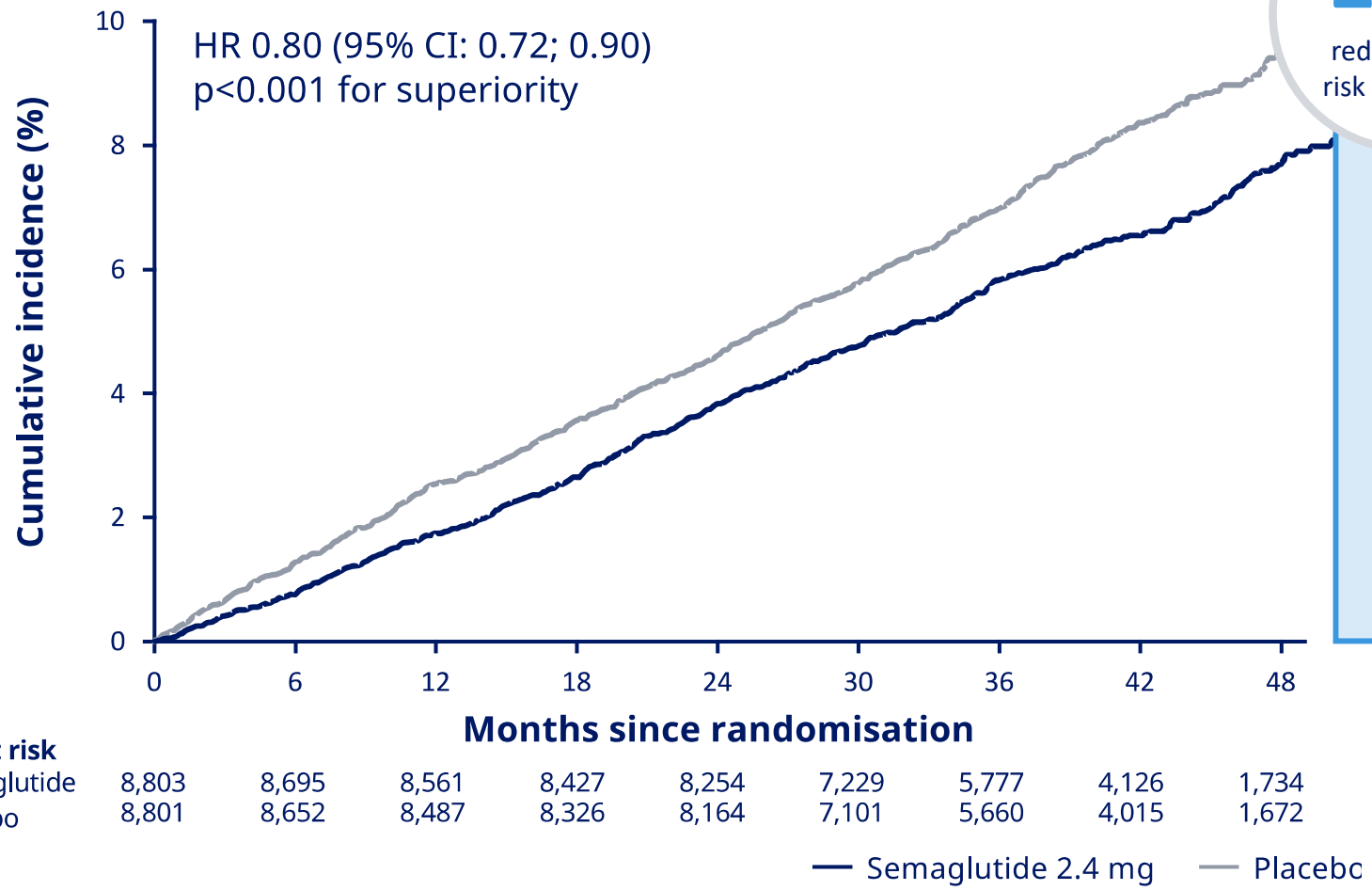
Adapted from Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563 supplementary;

SELECT

SELECT

Primary cardiovascular composite endpoint

Cumulative incidence of MACE



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[1]

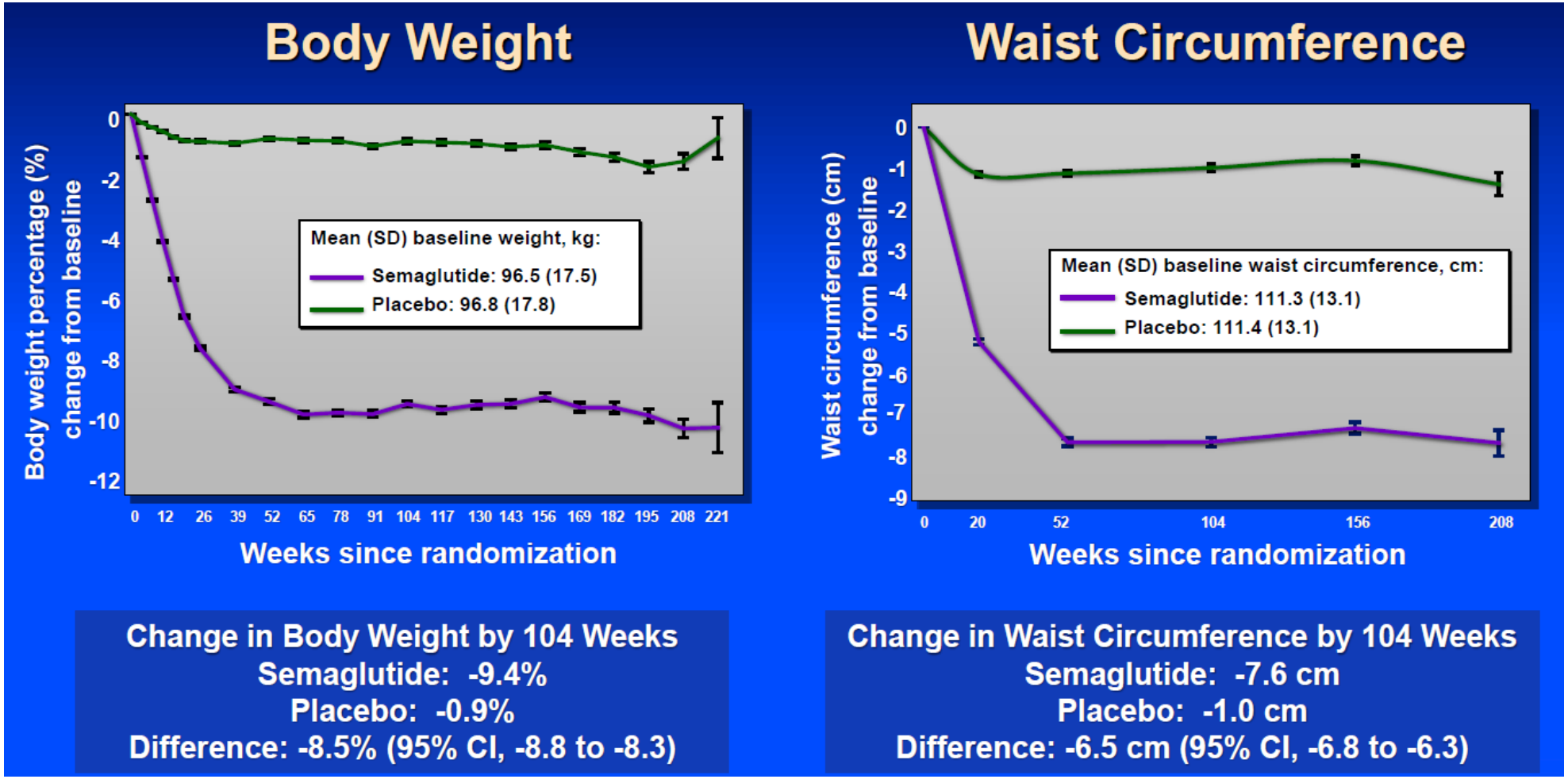
All three components (death from CV causes, non-fatal MI and non-fatal stroke) contributed to MACE risk reduction

Mean follow-up time was 39.8 months

Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

SELECT[20]

Change in body weight and waist circumference (%)



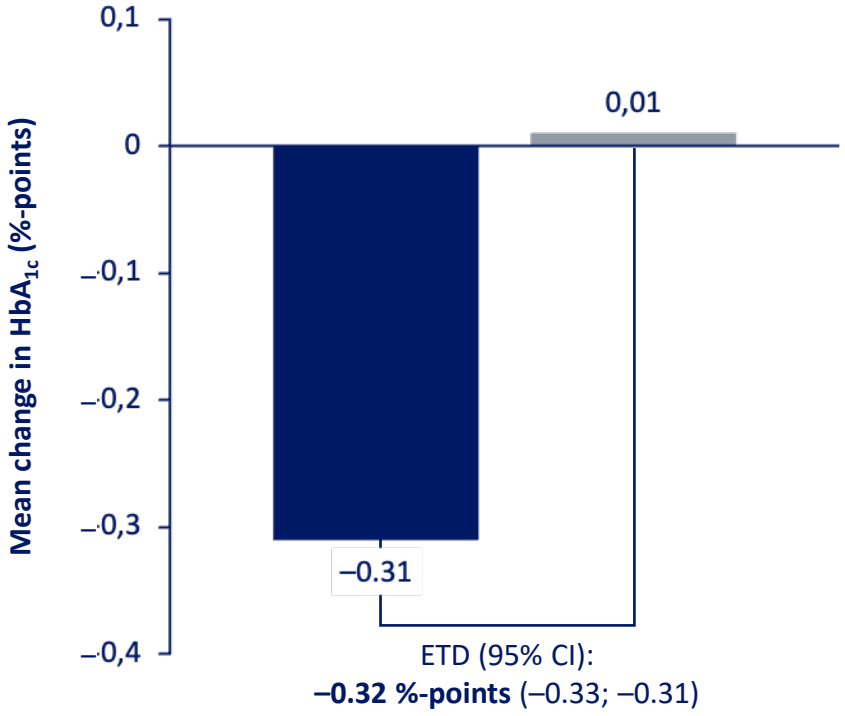
*Error bars in the left-hand figure are 95% CI as calculated by 1.96 times the standard error. *Estimated using an ANCOVA with treatment as factor and the baseline value as covariate, using multiple imputation for missing values under a missing-at-random assumption. CIs have not been adjusted for multiplicity. ANCOVA, analysis of covariance; CI, confidence interval; ETD, estimated treatment difference; SD, standard deviation.*

Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563;

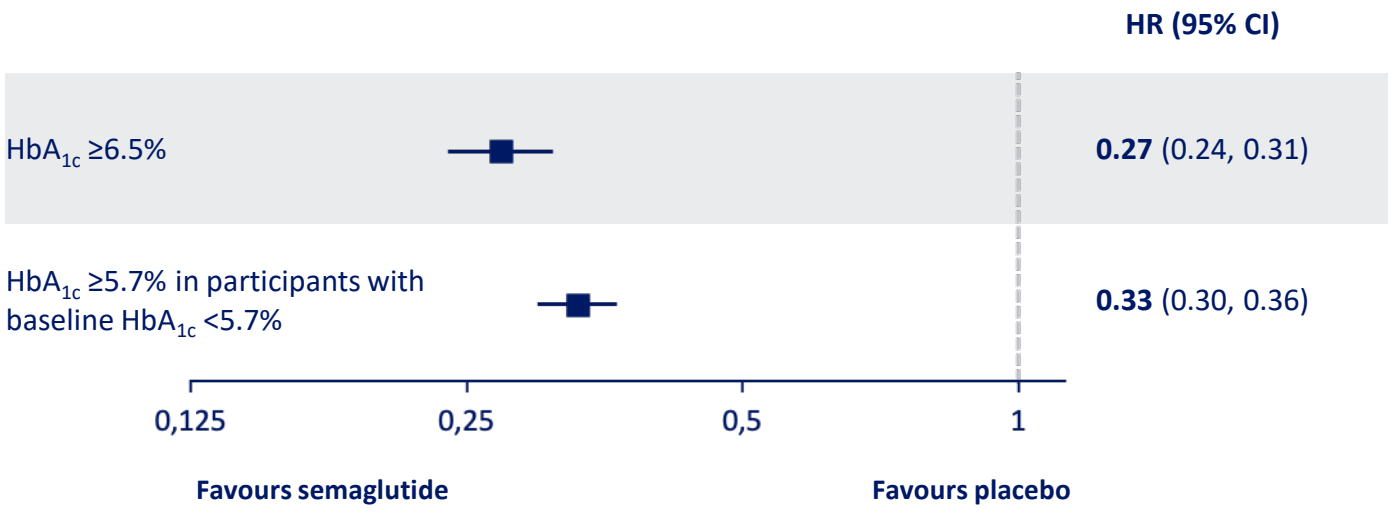
SELECT

Change in glycaemic status

Change in HbA_{1c}*



Time to glycaemic events†

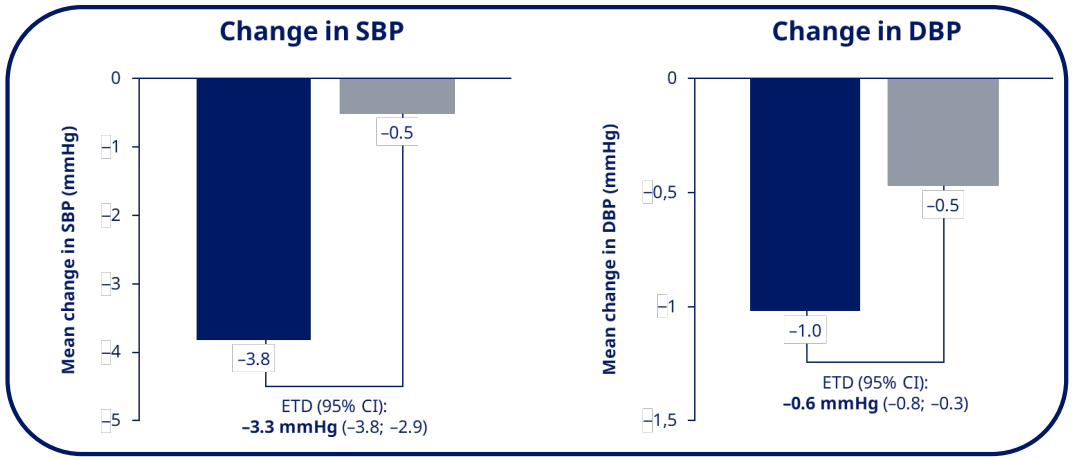


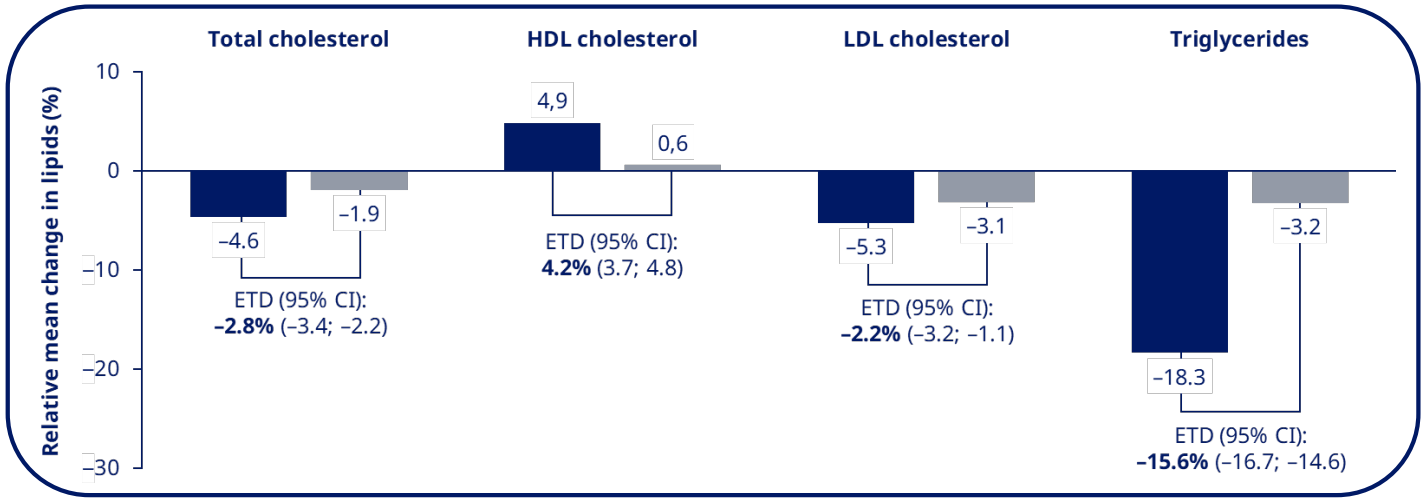
Semaglutide 2.4 mg Placebo

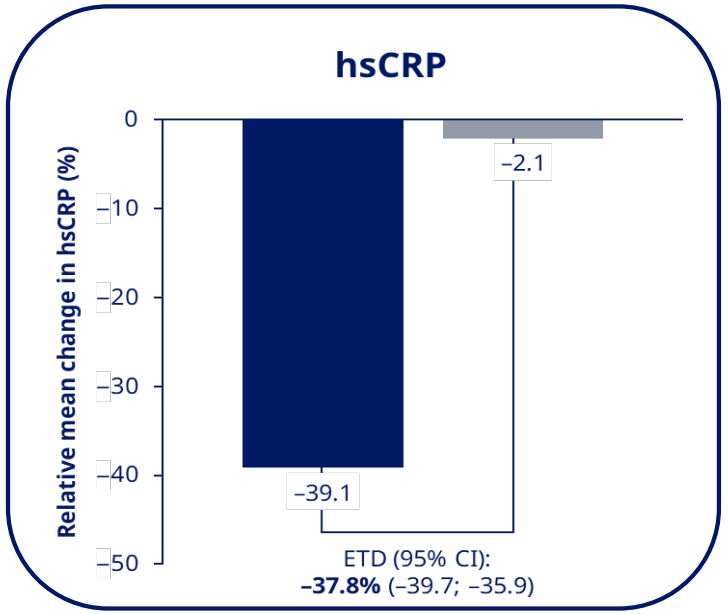
Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563;

SELECT

Change in traditional CV risk factors







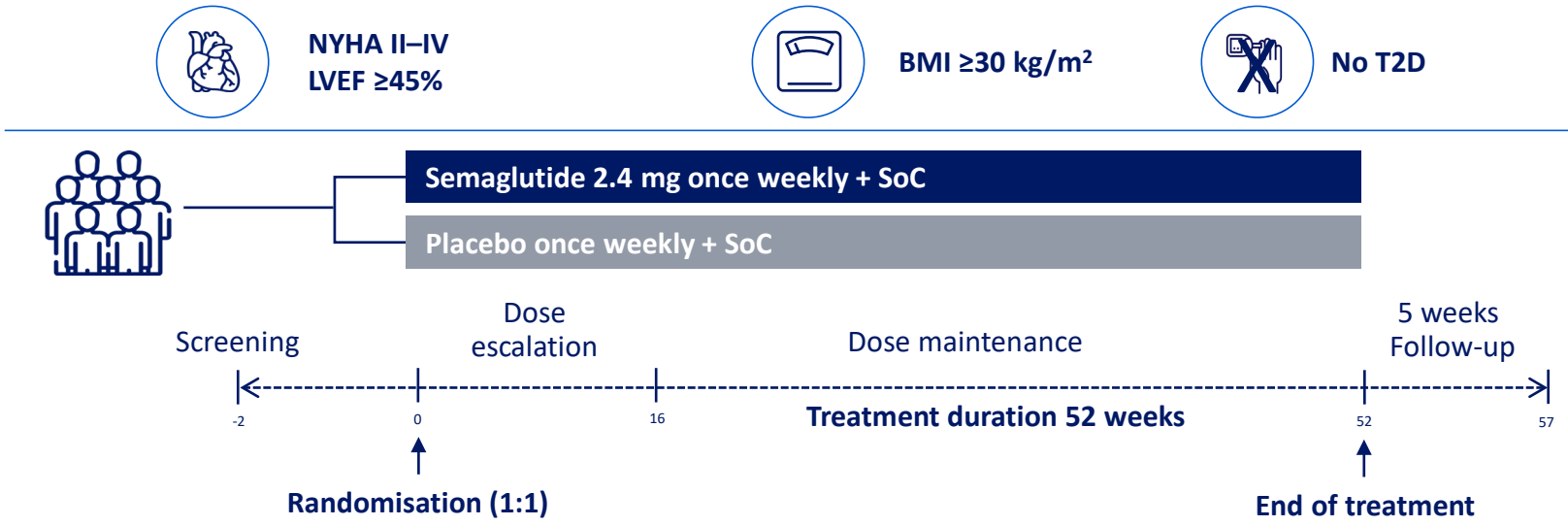
Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563;

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

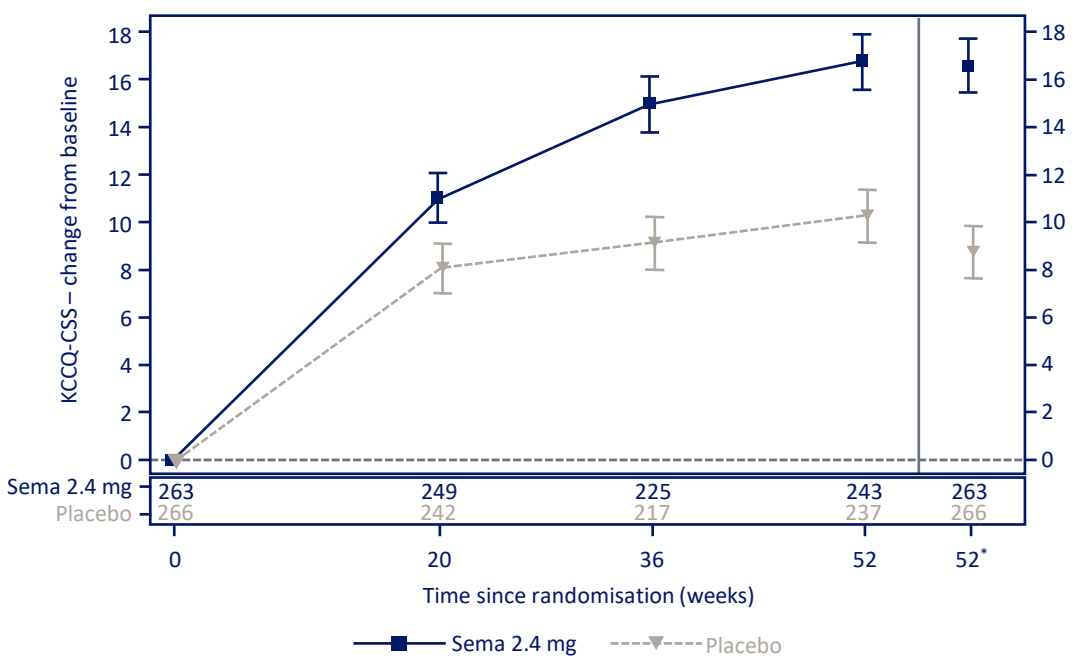
Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity

n=529

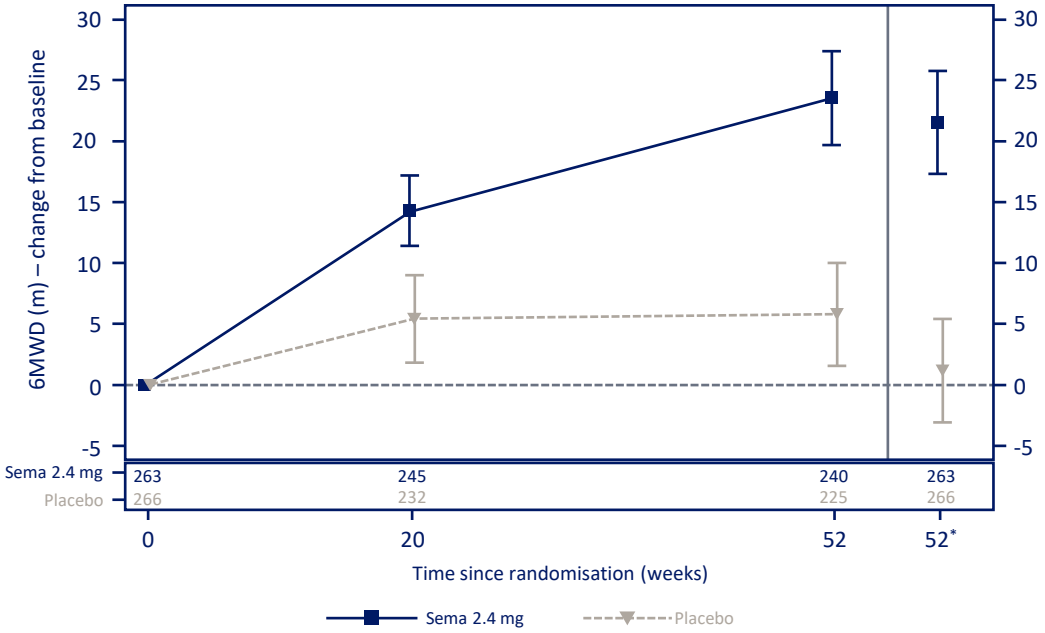


STEP HFpEF

Primary endpoint



Confirmatory secondary endpoint



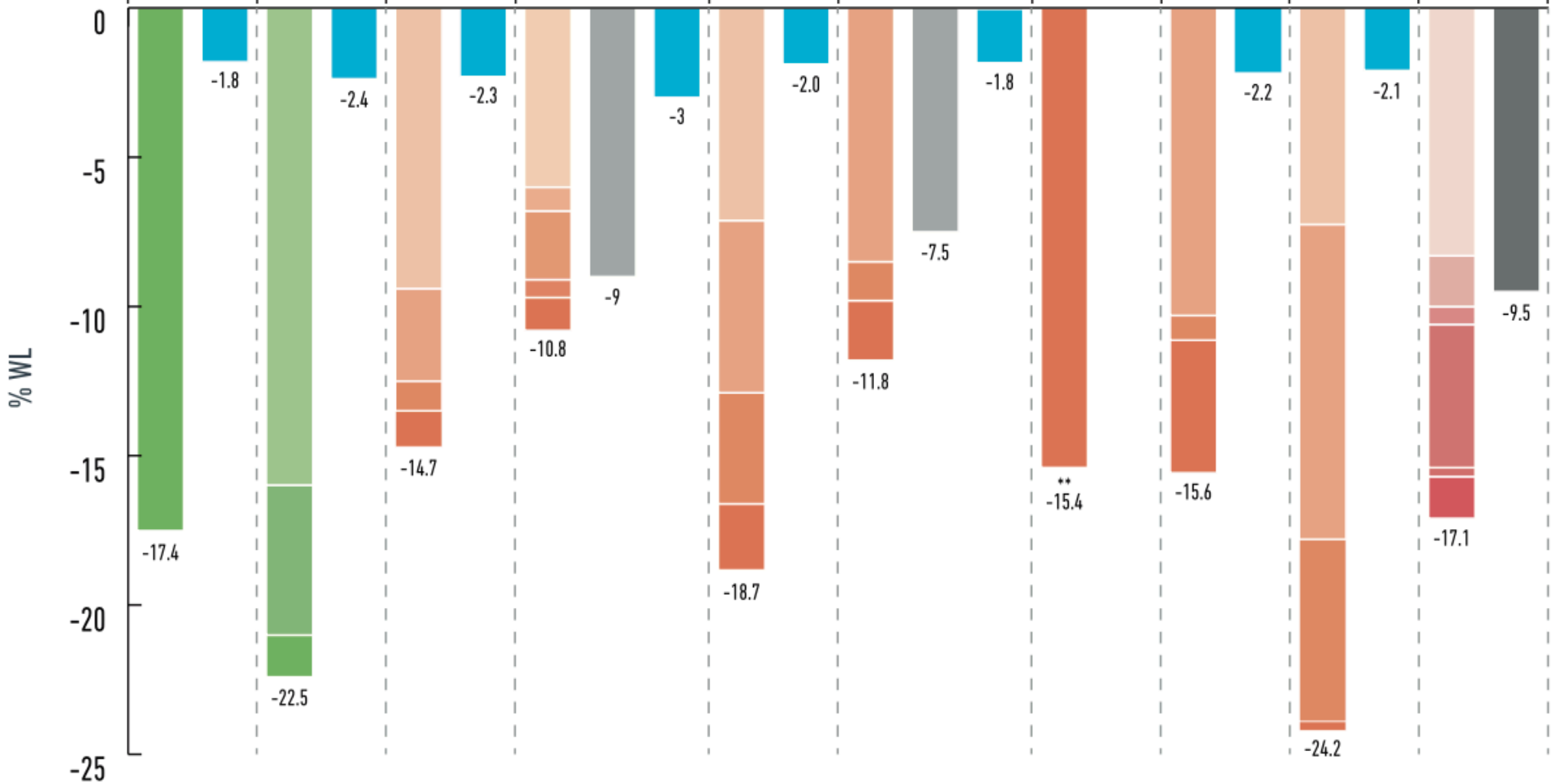
Significant improvement in mean KCCQ-CSS at week 52

Significant increase in mean 6MWD

	Sema 2.4 mg	Placebo	OR (95% CI)
Change from baseline to week 52 in NT-proBNP (% reduction)	-20.9	-5.3	0.84 (0.71; 0.98)
Participants with KCCQ-CSS improvement ≥15 points at week 52 (%)	50.6	35.9	2.2 (1.5; 3.2)

Future perspectives

	Oral Semaglutide[A]	Tirzepatide[A]	Orfoglipron[A]	Cagrilintide[A]	Survodutide[A*]	Efinopegdutide[B]	Mazdutide[C*]	Pemvidutide[A*]	Retatrutide[A]	CagriSema[B]
Dose and frequency	50mg OD	5/10/15mg OW	12/24/36/45mg OD	0.3/0.6/1.2/2.4/4.5mg OW	0.6/2.4/3.6 4.8mg OW	5/7.4/10mg OW	9mg OW	1.2/1.8/2.4mg OW	1/4/8/12mg OW	0.16/0.3/0.6/ 1.2/2.4/4.5 +SEMA 2.4mg OW
Route	PO	SC	PO	SC	SC	SC	SC	SC	SC	SC
Mechanism of action	GLP-1	GLP-1 + GIP	GLP-1	Amylin	GLP-1 + GCG	GLP-1 + GCG	GLP-1 + GCG	GLP-1 + GCG	GLP-1 + GIP + GCG	GLP-1 + Amylin
Comparator	PBO	PBO	PBO	LIRA 3.0mg / PBO	PBO	LIRA 3.0mg / PBO	PBO	PBO	PBO	PBO+SEMA 2.4mg



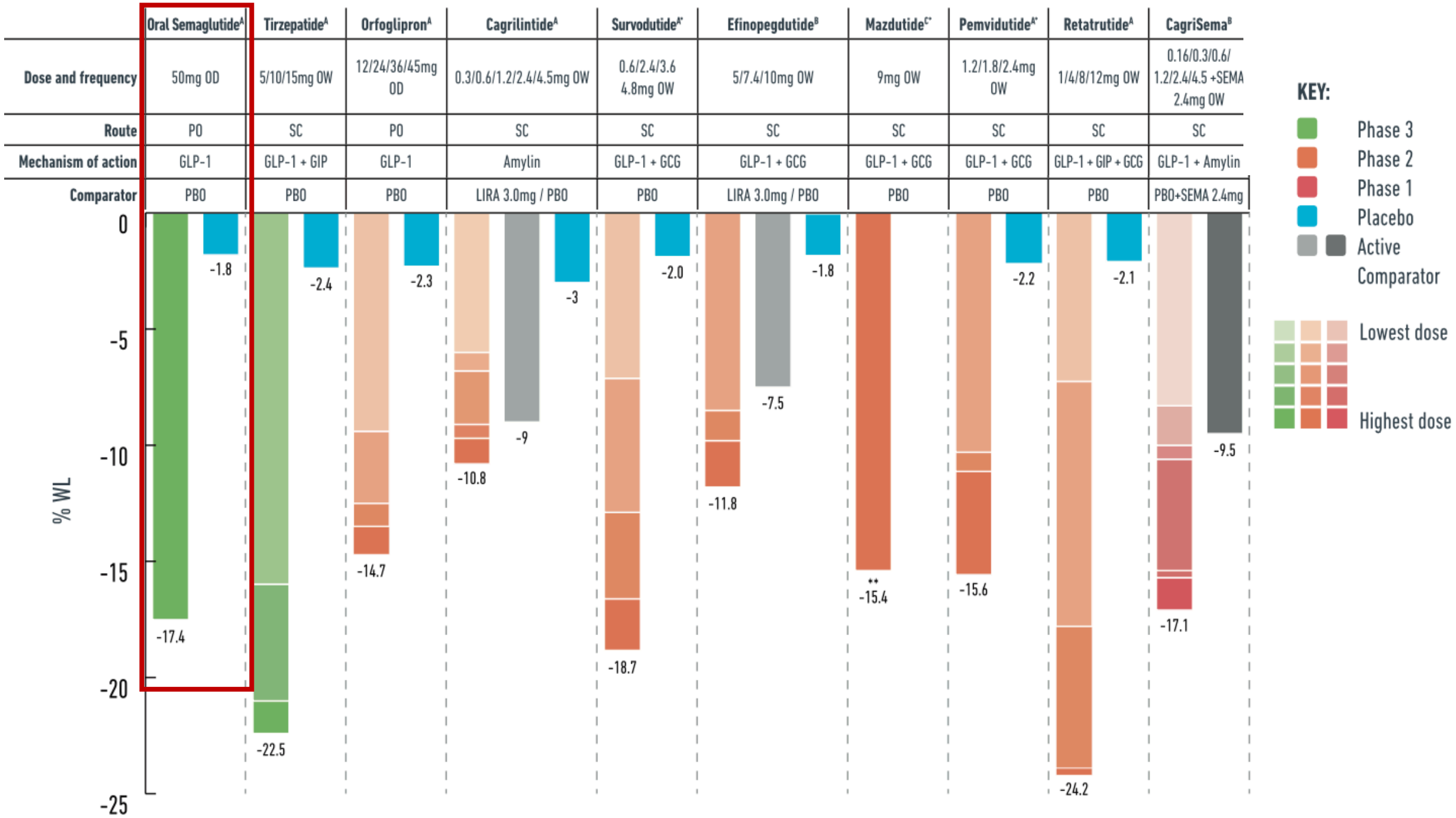
KEY:

- Phase 3
- Phase 2
- Phase 1
- Placebo
- Active Comparator

Lowest dose

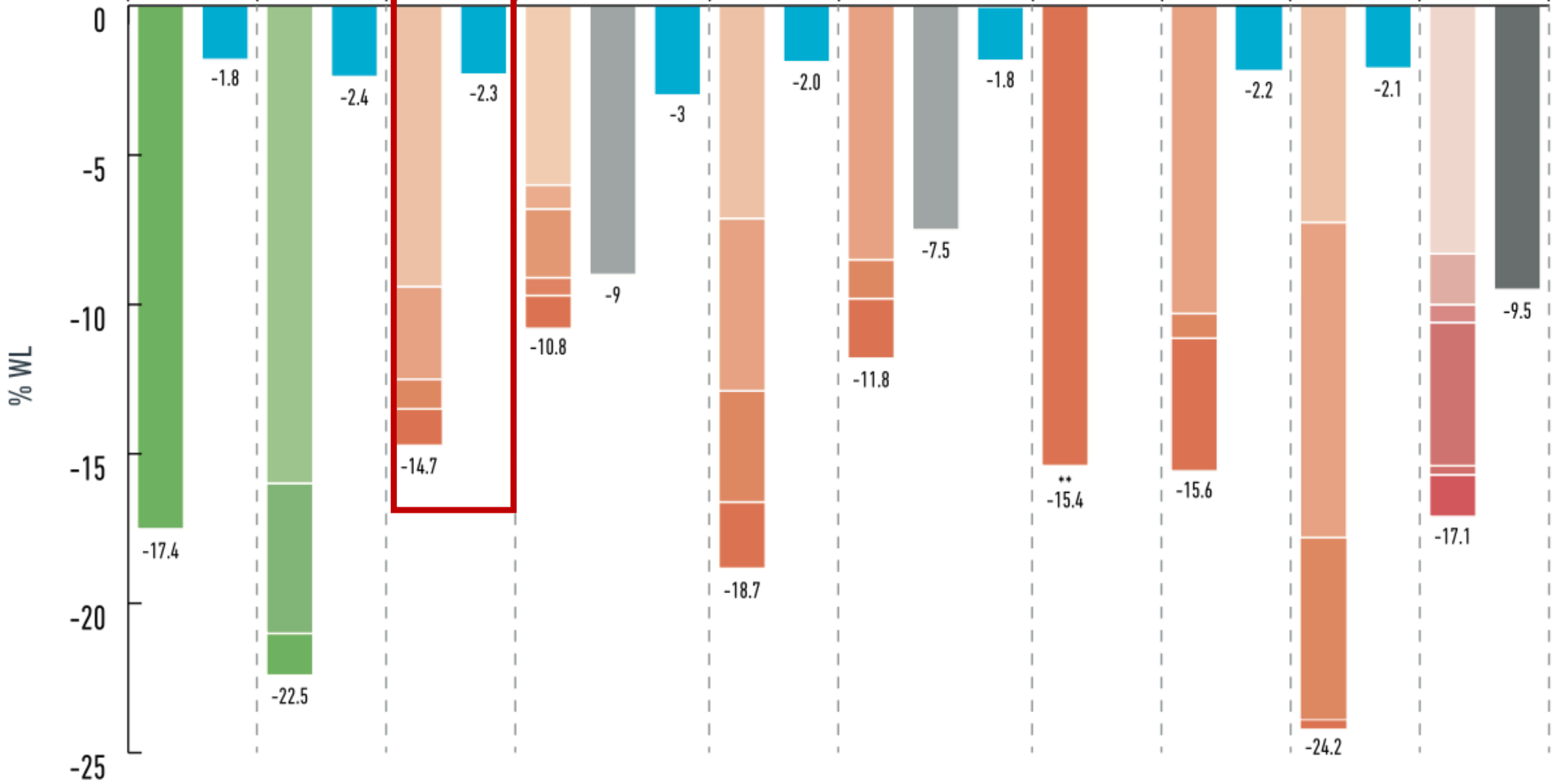
Highest dose

International Journal of Obesity; https://doi.org/10.1038/s41366-024-01473-y



International Journal of Obesity; https://doi.org/10.1038/s41366-024-01473-y

	Oral Semaglutide[A]	Tirzepatide[A]	Orfoglipron[A]	Cagrilintide[A]	Survodutide[A*]	Efinopegdutide[B]	Mazdutide[C*]	Pemvidutide[A*]	Retatrutide[A]	CagriSema[B]
Dose and frequency	50mg OD	5/10/15mg OW	12/24/36/45mg OD	0.3/0.6/1.2/2.4/4.5mg OW	0.6/2.4/3.6 4.8mg OW	5/7.4/10mg OW	9mg OW	1.2/1.8/2.4mg OW	1/4/8/12mg OW	0.16/0.3/0.6/ 1.2/2.4/4.5 +SEMA 2.4mg OW
Route	PO	SC	PO	SC	SC	SC	SC	SC	SC	SC
Mechanism of action	GLP-1	GLP-1 + GIP	GLP-1	Amylin	GLP-1 + GCG	GLP-1 + GCG	GLP-1 + GCG	GLP-1 + GCG	GLP-1 + GIP + GCG	GLP-1 + Amylin
Comparator	PBO	PBO	PBO	LIRA 3.0mg / PBO	PBO	LIRA 3.0mg / PBO	PBO	PBO	PBO	PBO+SEMA 2.4mg



KEY:

- Phase 3
- Phase 2
- Phase 1
- Placebo
- Active Comparator

Lowest dose

Highest dose

International Journal of Obesity; https://doi.org/10.1038/s41366-024-01473-y

Obesity Surgery (2024) 34:303–309
https://doi.org/10.1007/s11695-023-07053-9

ORIGINAL CONTRIBUTIONS

Efficacy of High-dose Liraglutide 3.0 mg in Patients with Poor Response to Bariatric Surgery: Real-world Experience and Updated Meta-analysis

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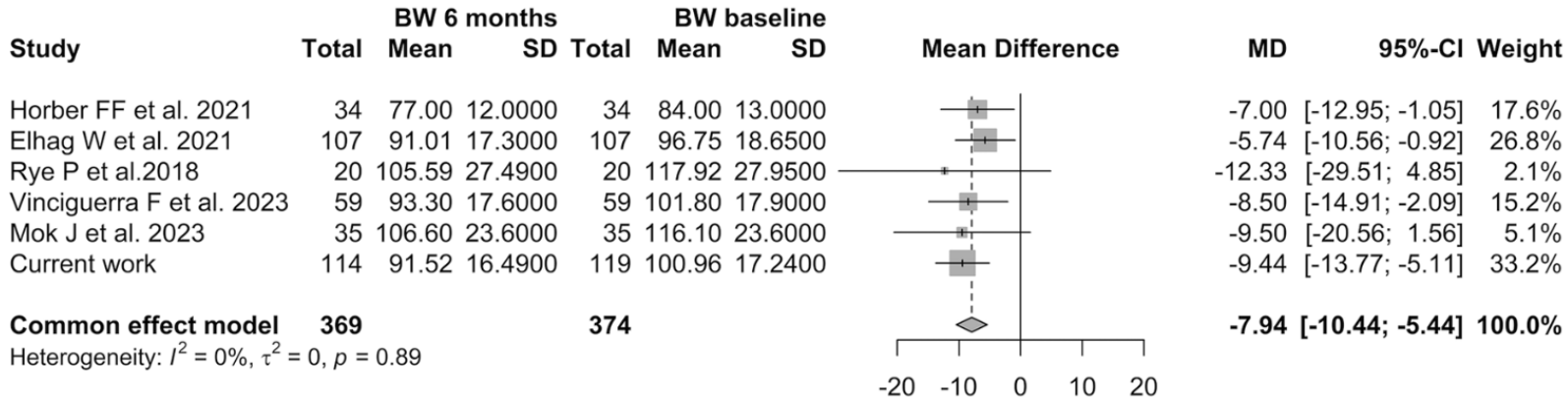

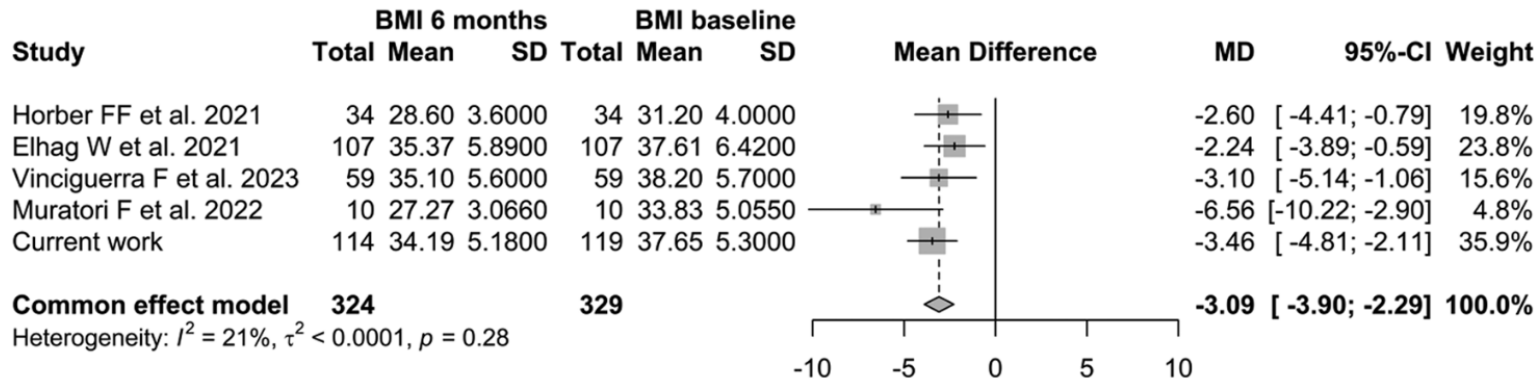

International Obesity Collaborative

CONSENSUS STATEMENT

Obesity Care vs. Weight Loss

Obesity care and weight loss are not the same.

Obesity care delivered by qualified clinicians consists of evidence-based options that address comorbidities of obesity (diabetes, hypertension, hyperlipidemia, etc.) and improve well-being. Obesity care is about health, not weight. Weight loss is just one outcome of obesity care.

People with obesity deserve care, free from stigma and shame.

International Obesity Collaborative Members

OAC Obesity Action Coalition · ASMBS · EASO · eat right. · GOPA Global Obesity Patient Alliance · obesity canada · obésité canada · Obesity Medicine Association · SOPHIA · STOP Obesity Alliance · The Obesity Society

Global Obesity Consensus Statement: Obesity Care vs. Weight Loss, 2023. : https://easo.org/new-global-obesity-consensus-statements