The past, the present and future of anti-obesity pharmacotherapy

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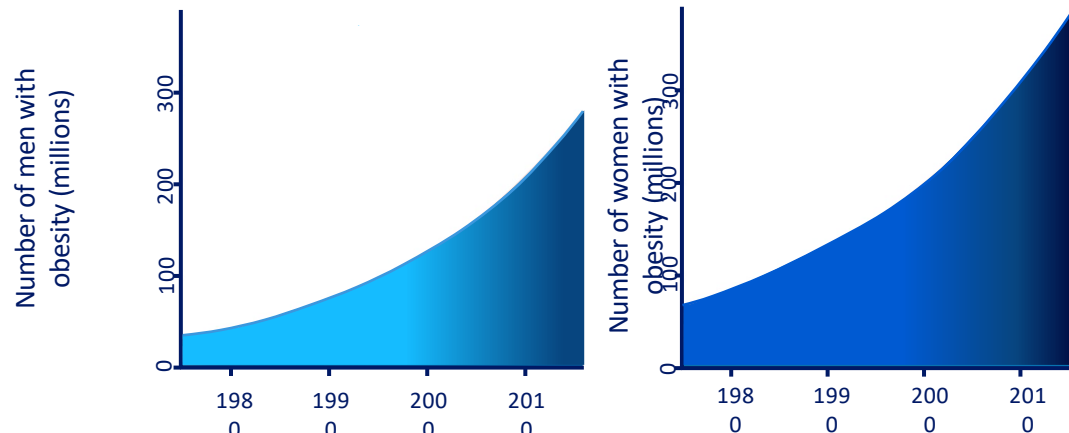Antwerp, Belgium
luc.vangaal@uza.be

Conflict of Interest Disclosures LVG

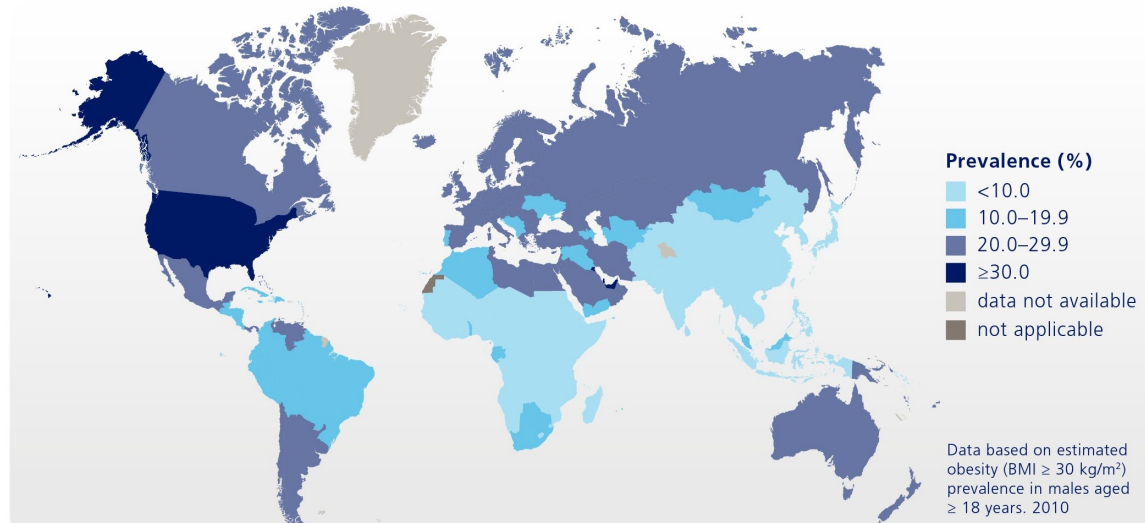Luc Van Gaal is a member of the Speakers Bureau of

- Bayer Pharma

- Boehringer Ingelheim

- Eli Lilly & Co

- Lifescan

- Merck Sharp & Dohme

- Novo Nordisk

Obesity is a Serious Chronic Disease

Global Prevalence of Obesity

Number of men with obesity (millions)

300
200
100
0

1980   1990   2000   2010

Number of women with obesity (millions)

300
200
100
0

1980   1990   2000   2010

Obesity rates are increasing globally

Prevalence (%)
- <10.0
- 10.0–19.9
- 20.0–29.9
- ≥30.0
- data not available
- not applicable

Data based on estimated obesity (BMI ≥ 30 kg/m²) prevalence in males aged ≥ 18 years. 2010

- **650 million adults live with obesity(WHO 2016 data)**

- **39-49% of world's population are overweight/obese (2.8-3.5bn people)**

- **Socio-economic factors contribute to obesity which drives health inequalities**
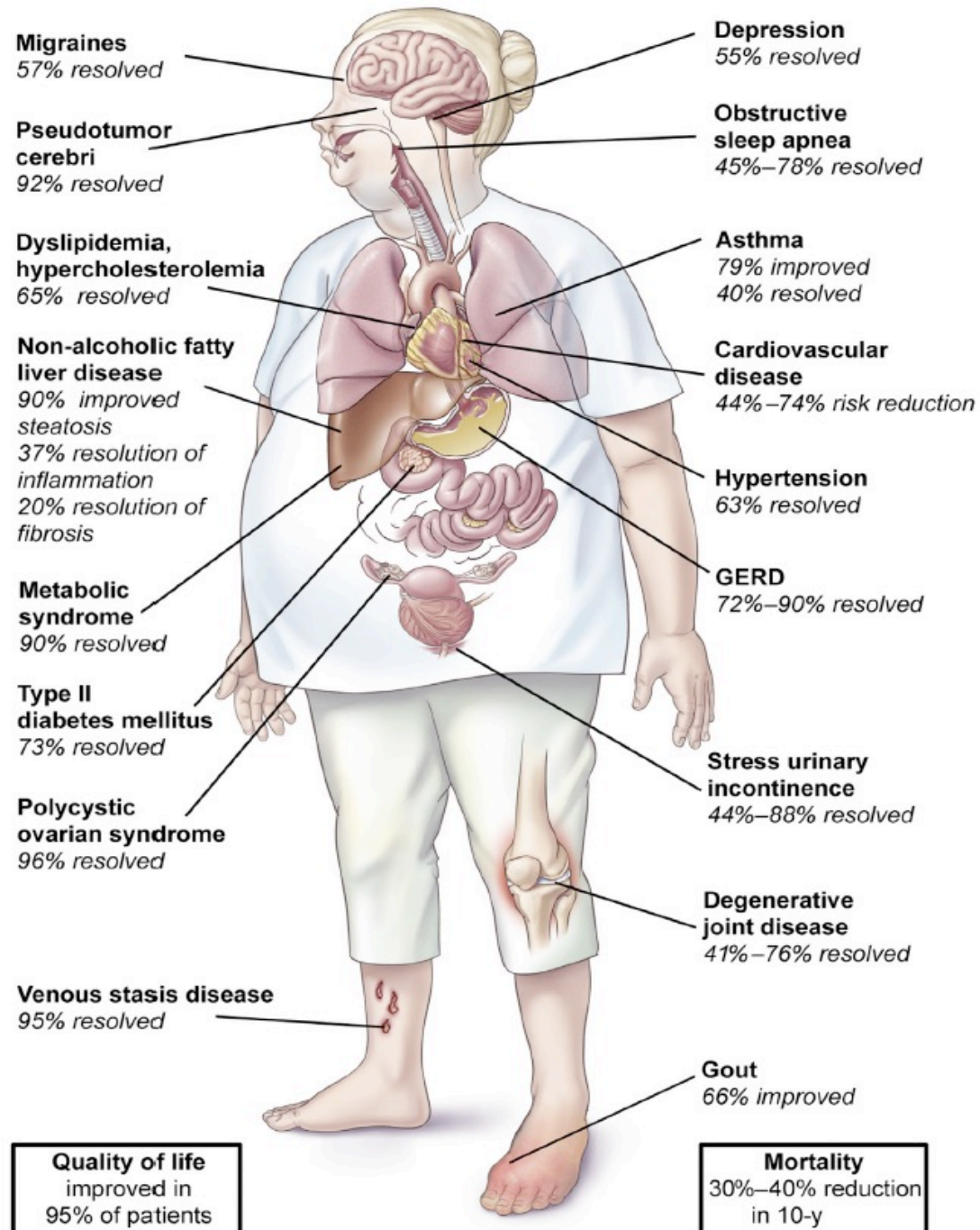
Life expectancy decreases as BMI increases

Normal BMI
80%

BMI 35–40 kg/m²
60%

BMI 40–50 kg/m²
50%

chance of reaching age 70
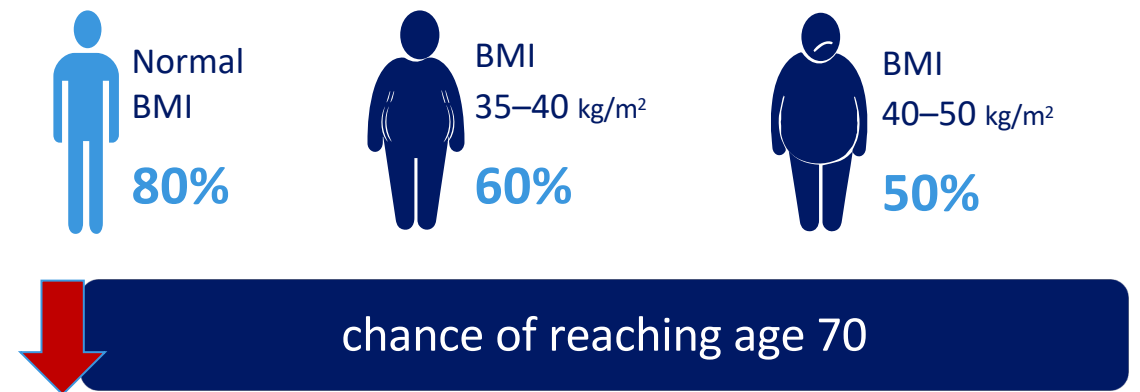
- Adapted from NCD Risk Factor Collaboration (NCD-RisC). Lancet 2017:390 (Supplement);2627–42; WHO. Global Health Observatory (GHO) data; WHO, Obesity & Overweight; Prospective Studies.ollaboration. Lancet 2009;373:1083–96.

Weight loss success

Migraines
57% resolved

Pseudotumor cerebri
92% resolved

Dyslipidemia, hypercholesterolemia
65% resolved

Non-alcoholic fatty liver disease
90% improved steatosis
37% resolution of inflammation
20% resolution of fibrosis

Metabolic syndrome
90% resolved

Type II diabetes mellitus
73% resolved

Polycystic ovarian syndrome
96% resolved

Venous stasis disease
95% resolved

Depression
55% resolved

Obstructive sleep apnea
45%–78% resolved

Asthma
79% improved
40% resolved

Cardiovascular disease
44%–74% risk reduction

Hypertension
63% resolved

GERD
72%–90% resolved

Stress urinary incontinence
44%–88% resolved

Degenerative joint disease
41%–76% resolved

Gout
66% improved

Quality of life
improved in
95% of patients

Mortality
30%–40% reduction
in 10-y

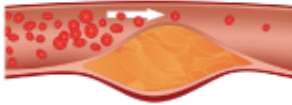Le Roux & Heneghan, Med Clin N Am, 2018

What are the effects of weight loss?

Benefits of 5–10% weight loss

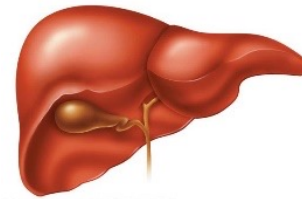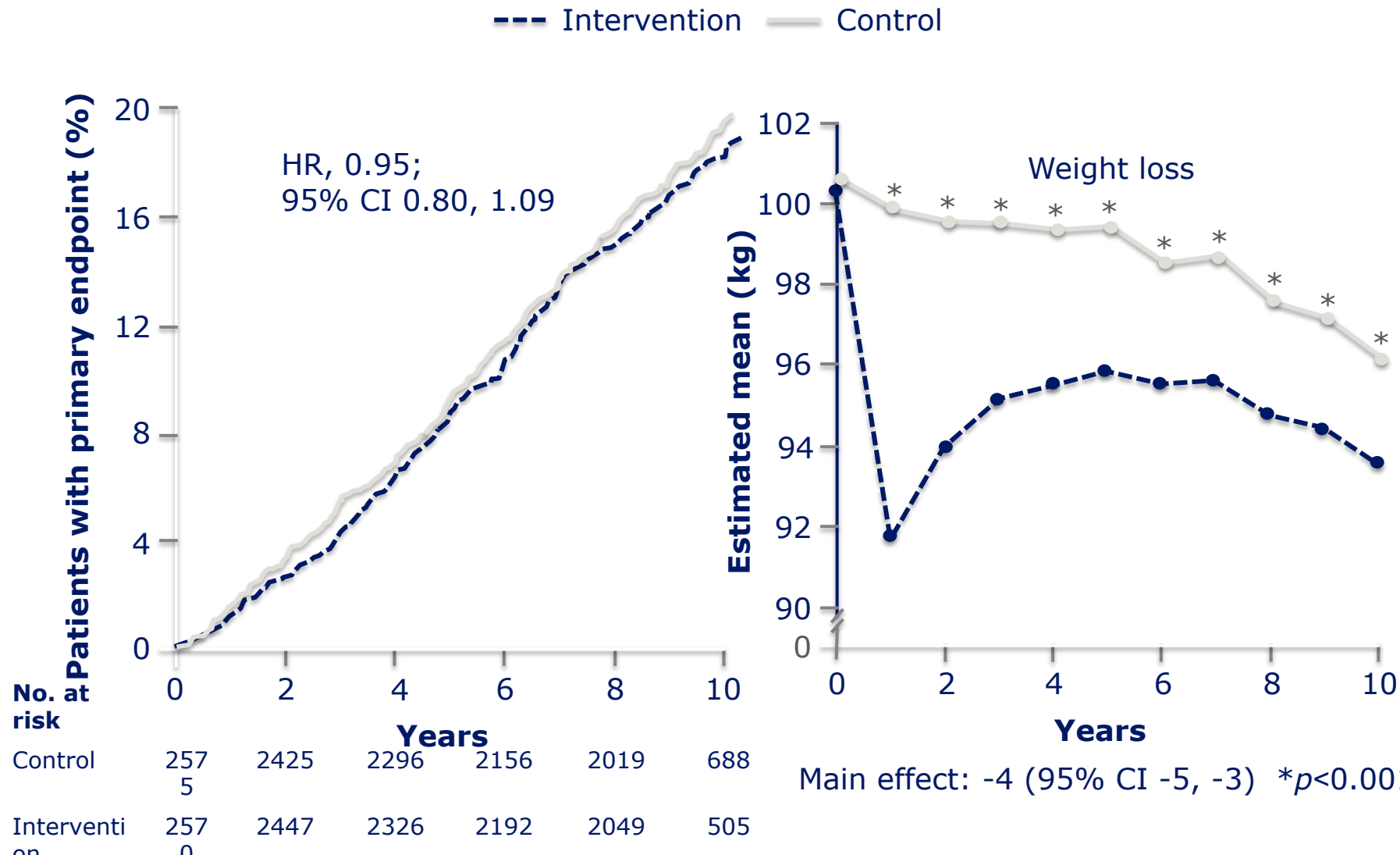| Reduction in risk of type 2 diabetes[1,2] | Improvements in blood lipid profile[3] | Improvements in blood pressure[4] | Improvements in abnormal NAFLD liver histology[5,6] | Improvements in health-related quality of life[7,8] | Improvements in severity of obstructive sleep apnoea[9,10] | Reduction in CV mortality[11] |

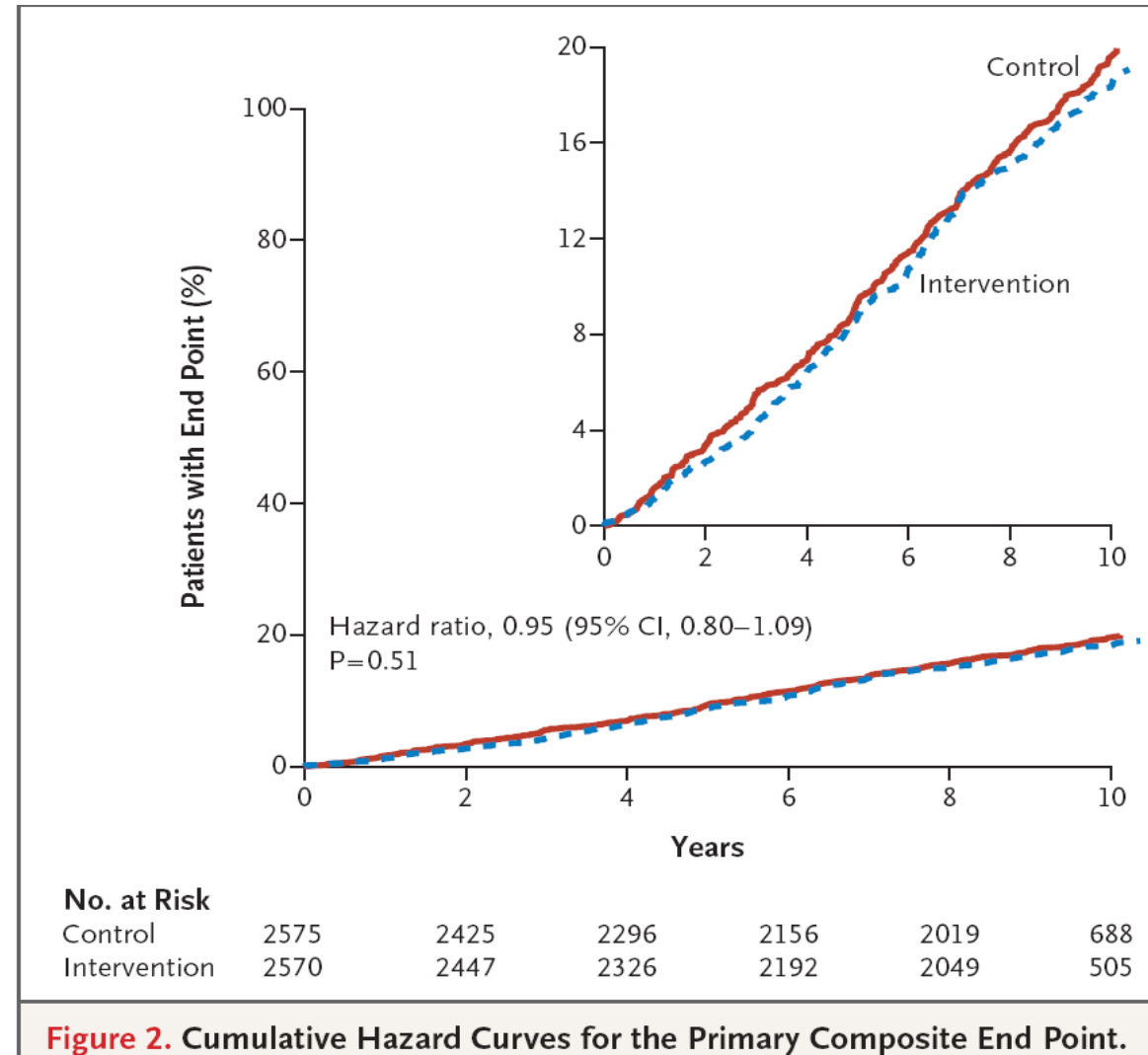CV, cardiovascular; NAFLD, non-alcoholic fatty liver disease
1. Van Gaal L et al. *Int J Obes* 1989;13 Suppl 2:47–9; 2. Knowler WC et al. *N Engl J Med* 2002;346:393–403; 3. Dattilo AM & Kris-Etherton PM. *Am J Clin Nutr* 1992;56:320–8; 4. Wing RR et al. *Diabetes Care* 2011;34:1481–6; 5. Dixon JB et al. *Hepatology* 2004;39:1647-54; 6. Patel AA et al. *J Clin Gastroenterol* 2009;43:970-4; 7. Warkentin LM et al. *Obes Rev* 2014;15:169–82; 8. Wright F et al. *J Health Psychol* 2013;18:574–86; 9. Foster GD et al. *Arch Intern Med* 2009;169:1619–26; 10. Kuna ST et al. *Sleep* 2013;36:641–9; 11. Li G et al. *Lancet Diabetes Endocrinol* 2014;2:474–80

Intensive lifestyle intervention, focused on weight loss, did not improve CV risk in T2D
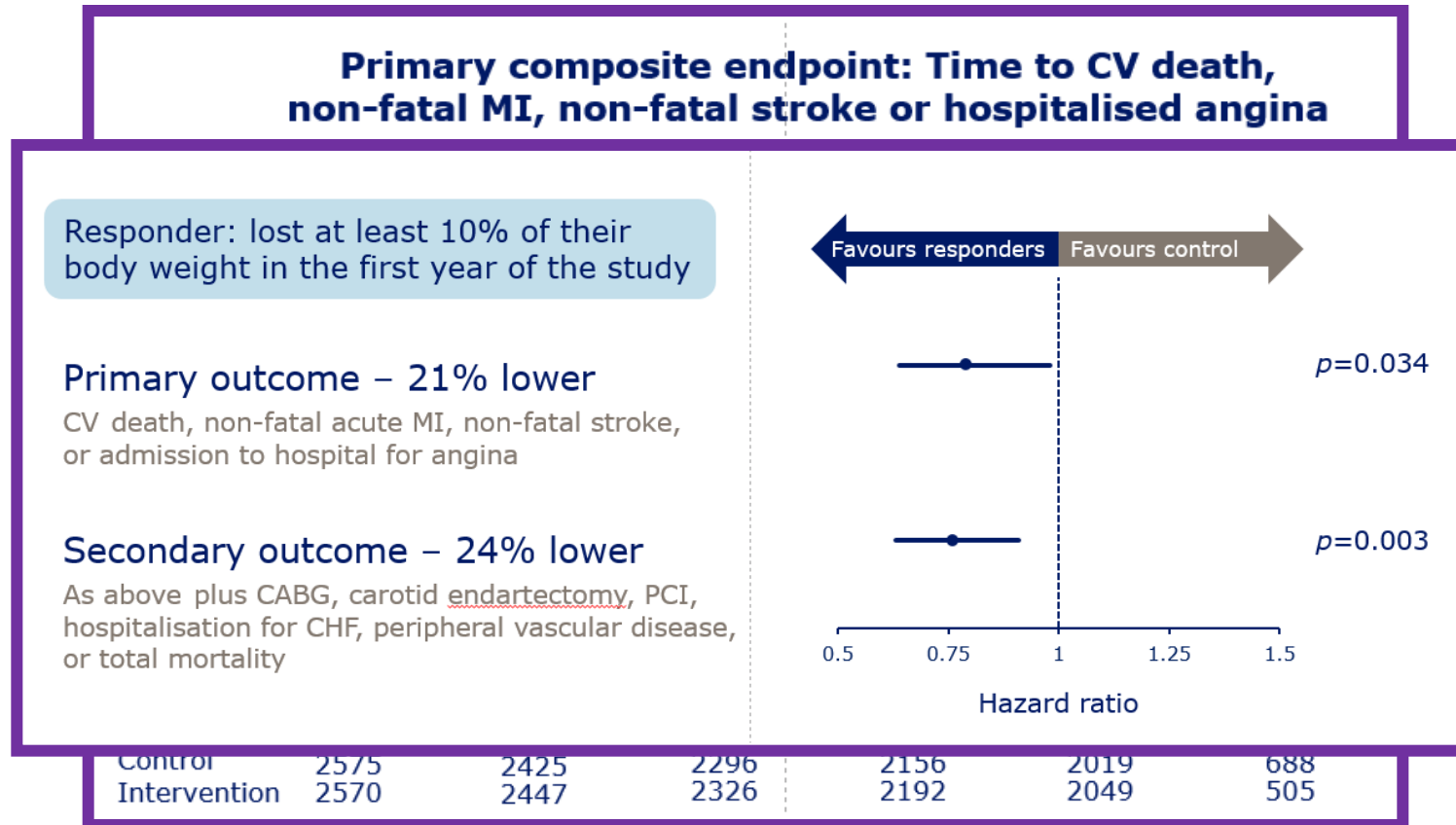
- - - Intervention   —— Control

HR, 0.95;
95% CI 0.80, 1.09

Weight loss

Main effect: -4 (95% CI -5, -3) *p<0.001

No. at risk						
Control	2575	2425	2296	2156	2019	688
Intervention	2570	2447	2326	2192	2049	505

Endpoint: Composite of CV death, non-fatal MI, non-fatal stroke and hospitalisation for angina

Look AHEAD Research Group. *N Engl J Med* 2013;369:145

Look AHEAD: NO cardiovascular benefit

Figure 2. Cumulative Hazard Curves for the Primary Composite End Point.

Look AHEAD Outcome according to weight

CVOT of Lifestyle Intervention in Subjects with T2D

Primary composite endpoint: Time to CV death, non-fatal MI, non-fatal stroke or hospitalised angina

Responder: lost at least 10% of their body weight in the first year of the study

Favours responders   Favours control

Primary outcome – 21% lower
CV death, non-fatal acute MI, non-fatal stroke, or admission to hospital for angina

p=0.034

Secondary outcome – 24% lower
As above plus CABG, carotid endartectomy, PCI, hospitalisation for CHF, peripheral vascular disease, or total mortality

p=0.003

0.5	0.75	1	1.25	1.5	

Hazard ratio

Control	2575	2425	2296	2156	2019	688
Intervention	2570	2447	2326	2192	2049	505

Look AHEAD Research Group. Lancet Diabetes Endocrinol 2016;4:913–21.

Koster-Rasmussen et al. PloS One 2016;11:e0146889.

Approved Drugs in Europe for Obesity

Orlistat 60/120 mg TDS	Naltrexone 32 mg/ Bupropion 360 mg PR	**Liraglutide 3.0 mg daily**
Metreleptin od	**Semaglutide 2.4 mg Weekly**	**Setmelanotide 1-3 mg od**

Metreleptin – only for leptin deficiency; Semaglutide – UK only; setmelanotide – only for POMC deficiency, LEPR, MC4R genetic causes
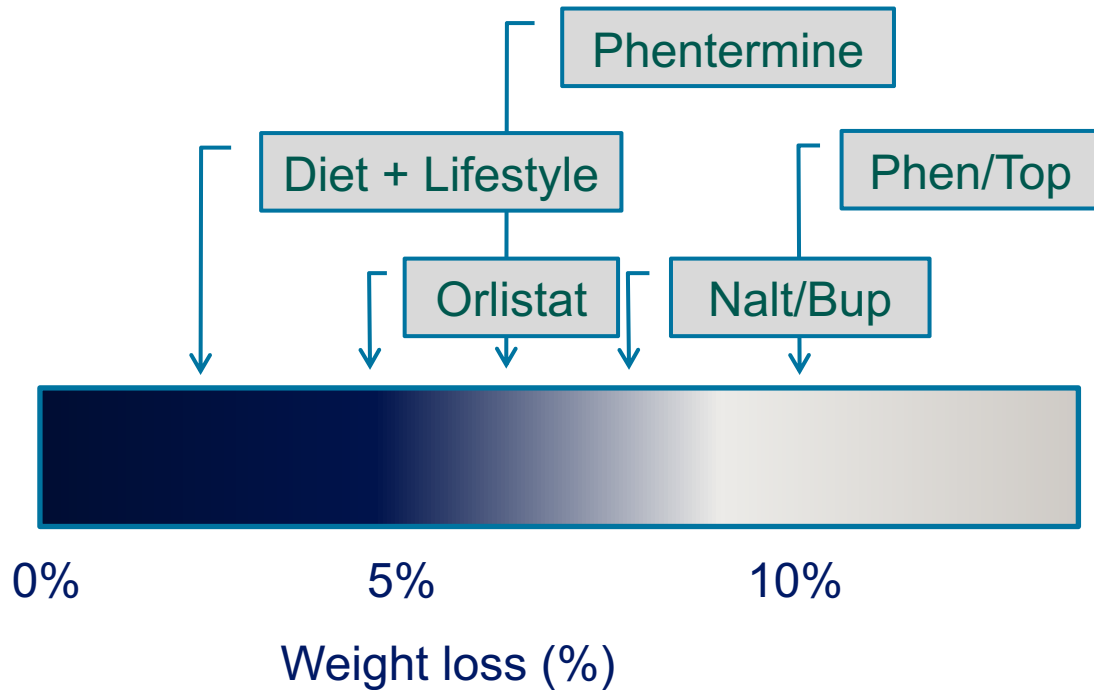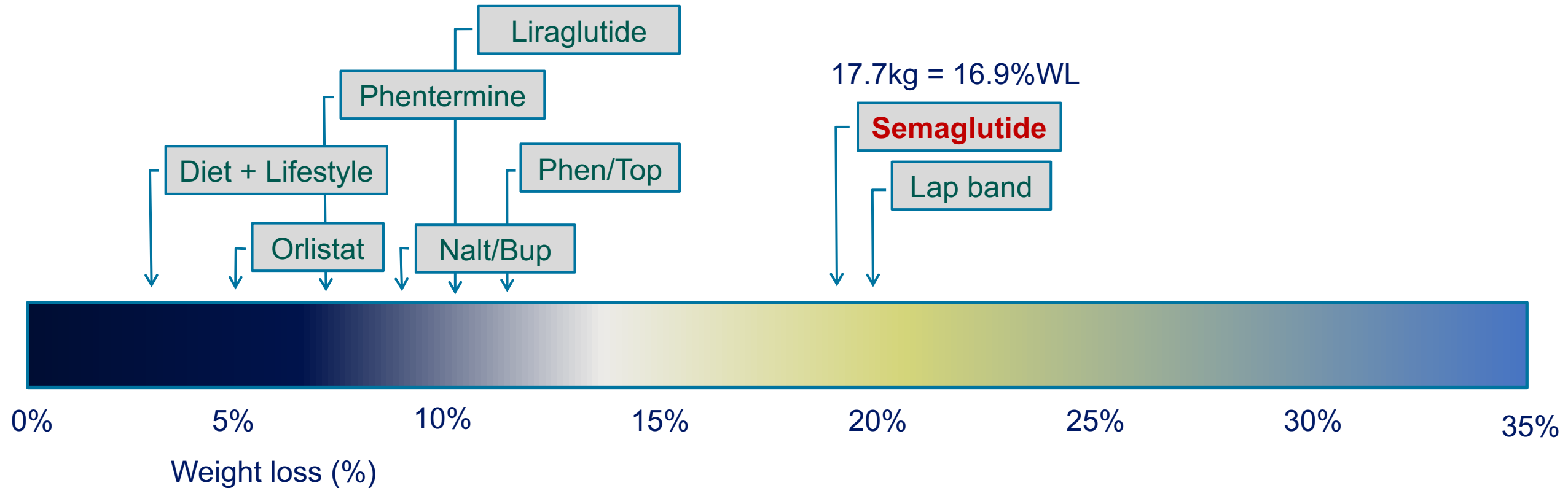https://www.ema.europa.eu/en/medicines/human/EPAR/Xenical
https://www.ema.europa.eu/en/medicines/human/EPAR/mysimba
https://www.ema.europa.eu/en/medicines/human/EPAR/saxenda
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https://www.ema.europa.eu/en/medicines/human/EPAR/wegovy
https://www.ema.europa.eu/en/medicines/human/EPAR/imcivree

Results with approved drugs

New drugs and devices can reduce weight and weight-related comorbidities

Phentermine

Diet + Lifestyle

Phen/Top

Orlistat

Nalt/Bup

0%   5%   10%

Weight loss (%)

Results with actual treatment approaches

Liraglutide

Phentermine

17.7kg = 16.9%WL

Semaglutide

Diet + Lifestyle

Phen/Top

Lap band

Orlistat

Nalt/Bup

0%   5%   10%   15%   20%   25%   30%   35%

Weight loss (%)

Adapted after Aronne L. FDA VI-0521 EMDAC 2010.

ORIGINAL ARTICLE

Once-Weekly Semaglutide in Adults with Overweight or Obesity

John P.H. Wilding, D.M., Rachel L. Batterham, M.B., B.S., Ph.D.,
Salvatore Calanna, Ph.D., Melanie Davies, M.D., Luc F. Van Gaal, M.D., Ph.D.,
Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Barbara M. McGowan, M.D., Ph.D.,
Julio Rosenstock, M.D., Marie T.D. Tran, M.D., Ph.D., Thomas A. Wadden, Ph.D.,
Sean Wharton, M.D., Pharm.D., Koutaro Yokote, M.D., Ph.D., Niels Zeuthen, M.Sc.,
and Robert F. Kushner, M.D., for the STEP 1 Study Group*

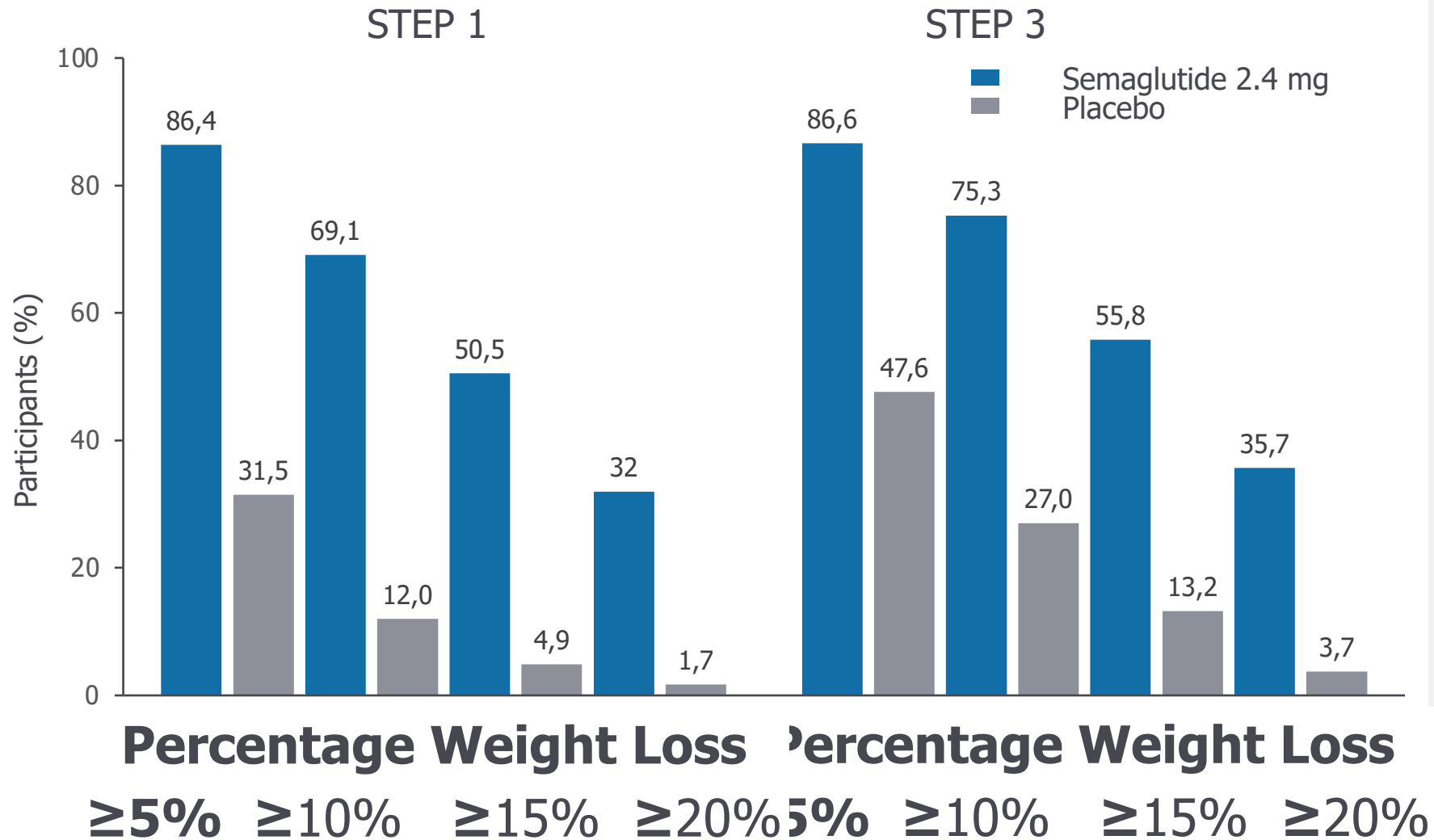# Change in Body Weight Over Time: STEP 1 vs STEP 5

STEP 1
(Mean at baseline: 105.3 kg)

STEP 5
(Mean at baseline: 106.0 kg)

Body Weight Change From Baseline (%)

Time Since Randomization (Weeks)

Semaglutide 2.4 mg
Placebo

Wilding JPH, et al. N Engl J Med 2021;384:989-1002; Garvey WT, et al. Presented at: 39th Annual Meeting of The Obesity Society; November 1-5, 2021; Virtual.
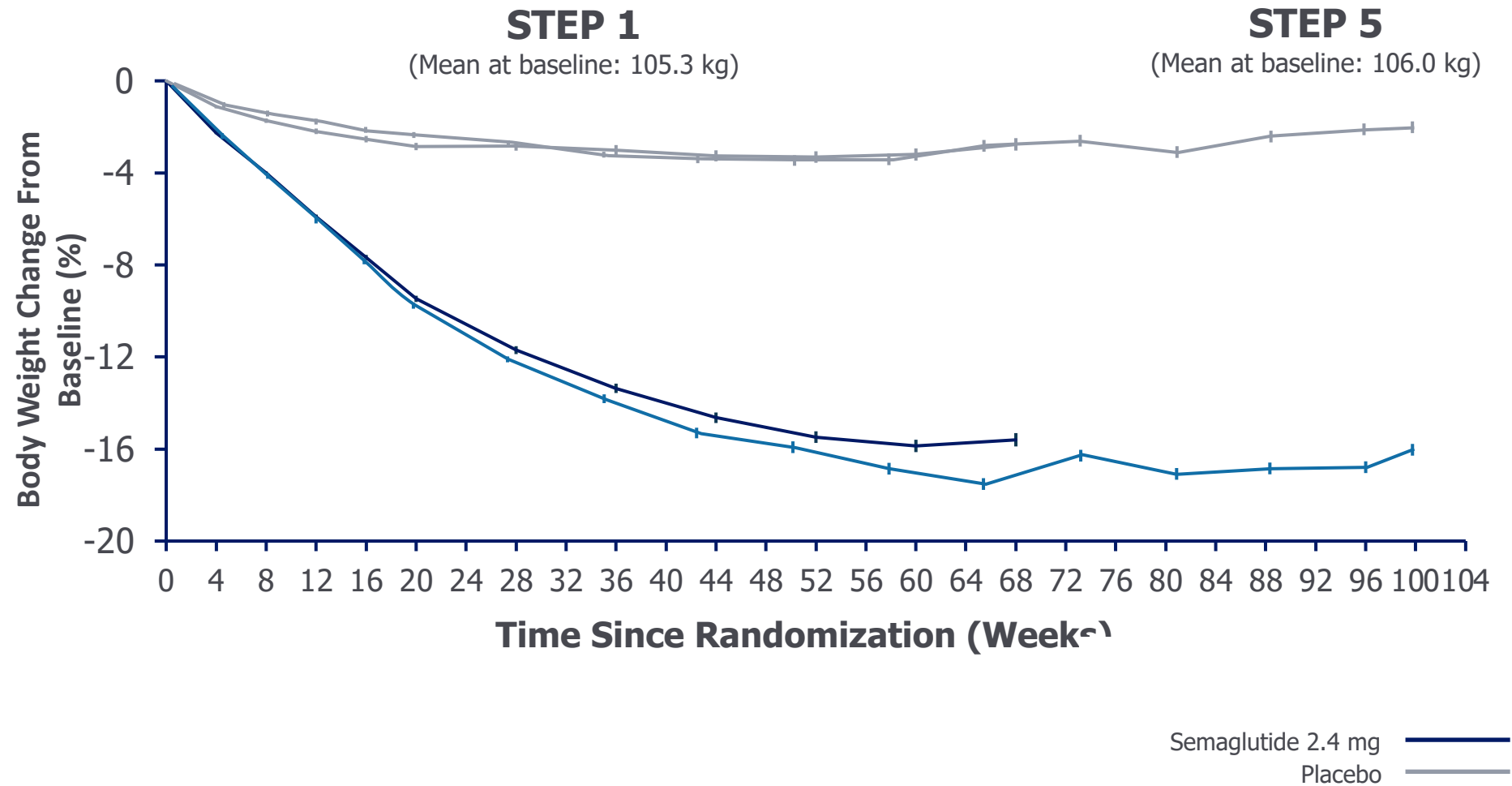
STEP 1 and 3: Body Weight Change

Change in body weight (%)

Estimated Change from Baseline to Week 68
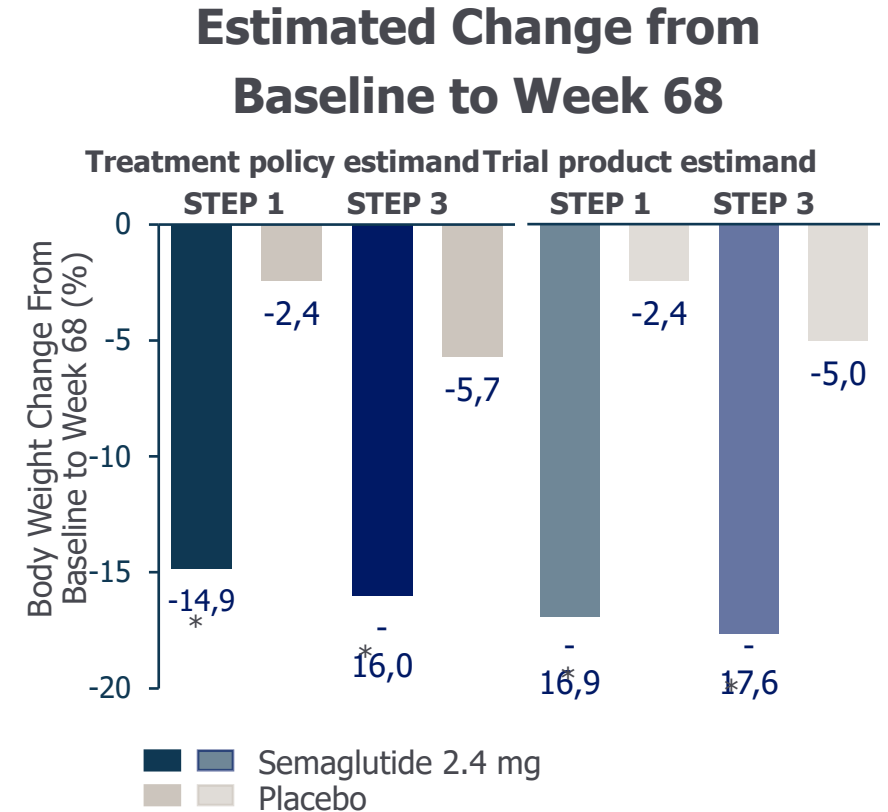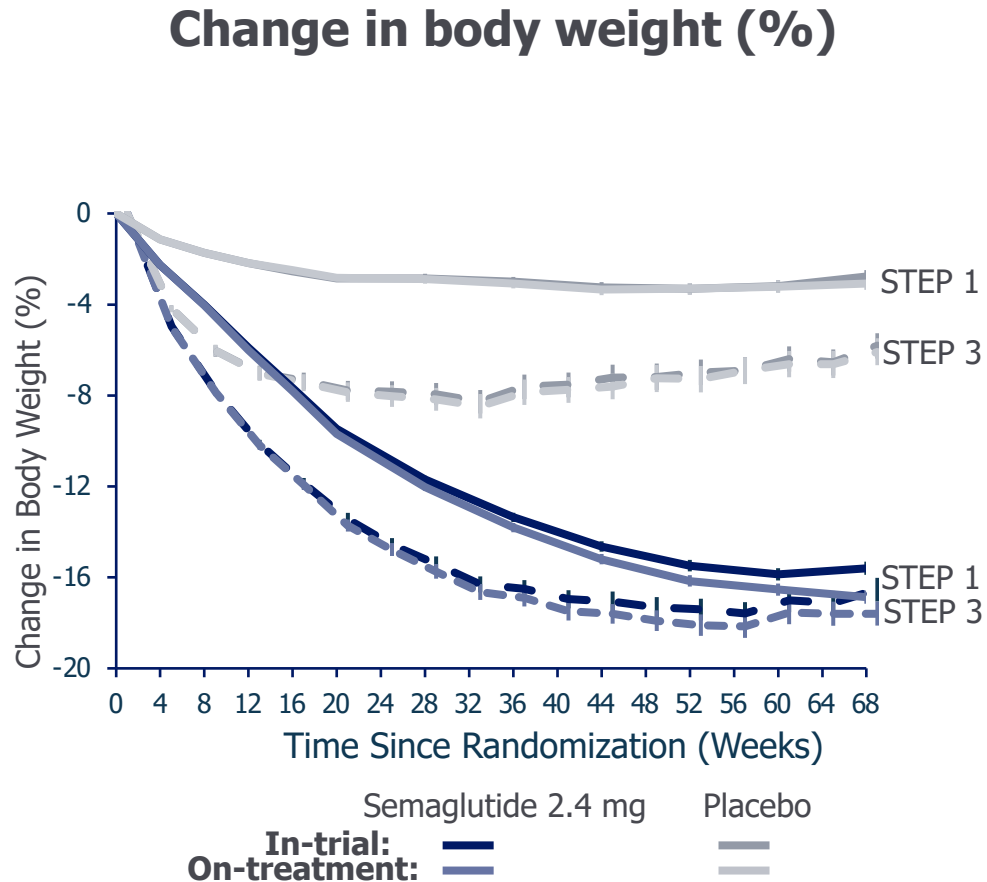
*Statistically significant vs placebo; †Observed on-treatment data.
IBT, intensive behavior therapy; LCD, low-calorie diet.
a. Wadden TA, et al. JAMA. 2021;325:1403-1413; b. Wilding JPH, et al. N Engl J Med. 2021;384:989.

STEP 1 and 3: Categorical Weight Loss at Week 68

STEP 1

STEP 3

Participants (%)

Semaglutide 2.4 mg
Placebo

STEP 1 values: 86,4 · 31,5 · 69,1 · 12,0 · 50,5 · 4,9 · 32 · 1,7

STEP 3 values: 86,6 · 47,6 · 75,3 · 27,0 · 55,8 · 13,2 · 35,7 · 3,7

Percentage Weight Loss

≥5%   ≥10%   ≥15%   ≥20%

Percentage Weight Loss

≥5%   ≥10%   ≥15%   ≥20%

Study Findings

- Data suggest that semaglutide with monthly brief lifestyle counselling alone is sufficient to produce a mean weight loss of 15%

- Further research is needed on potential benefits of sequencing LCD and semaglutide 2.4 mg to increase long-term weight loss

a. Wilding JPH, et al. N Engl J Med 2021;384:989; b. Wadden TA, et al. JAMA 2021;e211831.

STEP 1: Change in C-reactive protein

Mean at baseline (mg/L):   **3.9**   **3.9**

Semaglutide 2.4 mg   Placebo

-15,0

-53,0

ETD: -44.0%
95% CI: -49; -39
p<0.0001
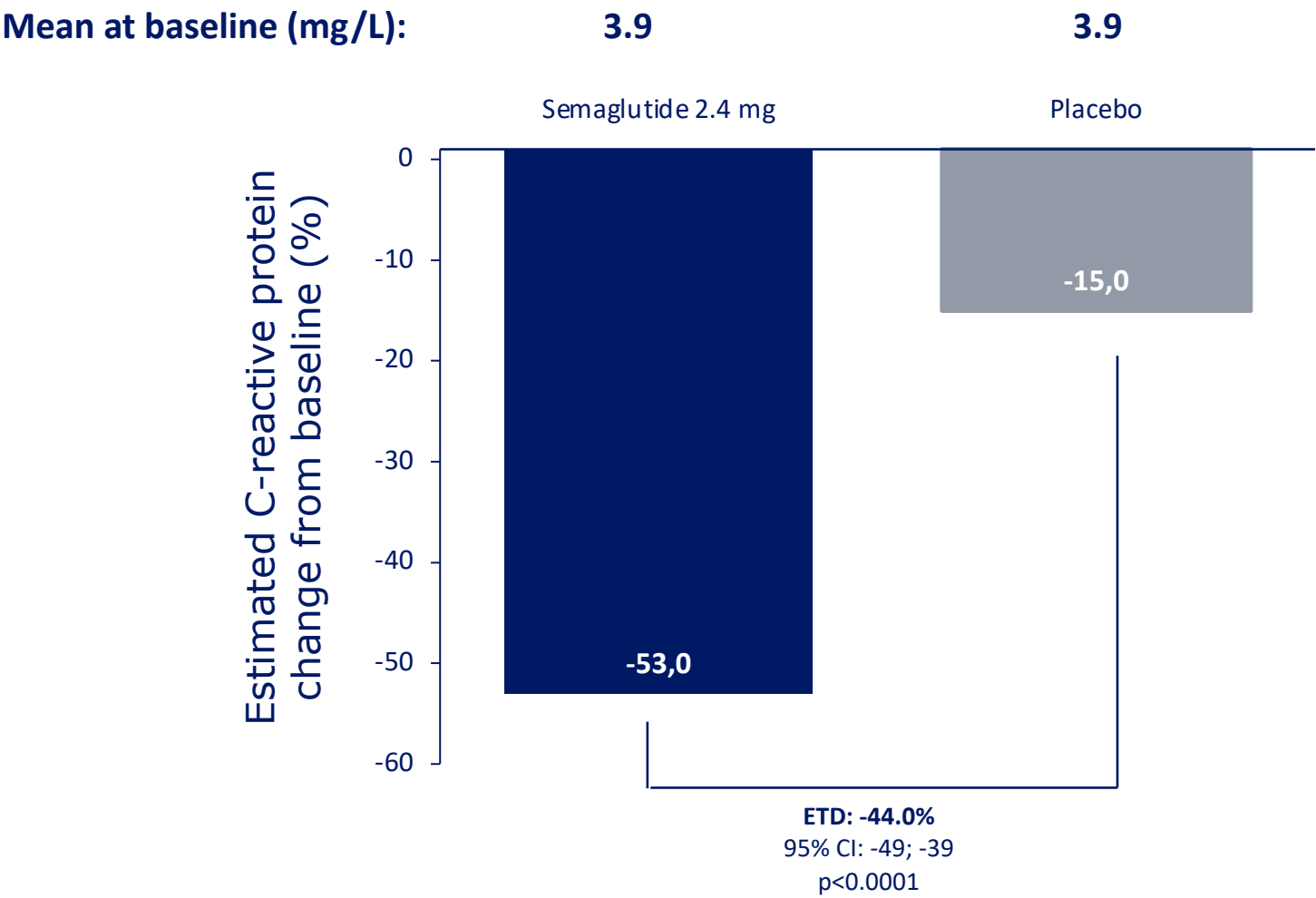
Estimated for the treatment policy estimand.
CI, confidence interval; ETD, estimated treatment difference (for the treatment policy estimand).
Wilding JPH et al. NEJM 2021; doi: 10.1056/NEJMoa2032183. Online ahead of print.
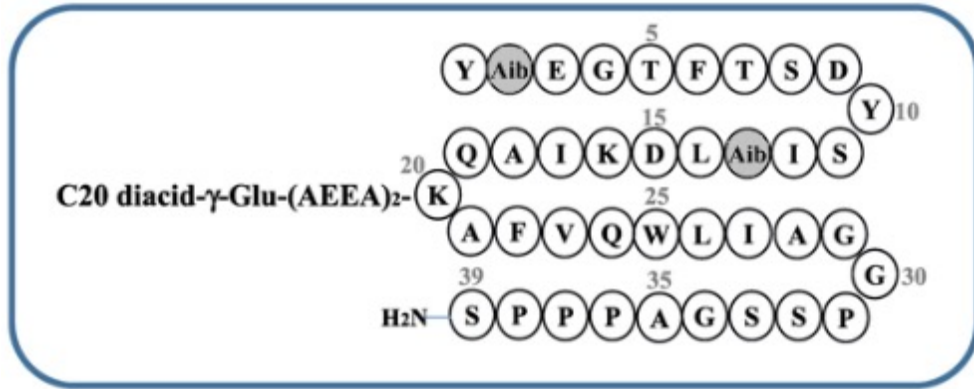
Results with actual treatment approaches

23 kg = 22.5%WL = 60% EWL

Tirzepatide

17.7kg = 16.9%WL

Liraglutide

Phentermine

Semaglutide

Diet + Lifestyle

Phen/Top

Lap band

Orlistat

Nalt/Bup

0%   5%   10%   15%   20%   25%   30%   35%

Weight loss (%)

Results with actual treatment approaches

23 kg = 22.5%WL = 60% EWL

Tirzepatide

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Phentermine

17.7kg = 16.9%WL

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Gastric bypass

Orlistat

Nalt/Bup

Lap band

Sleeve gastrectomy

0%   5%   10%   15%   20%   25%   30%   35%
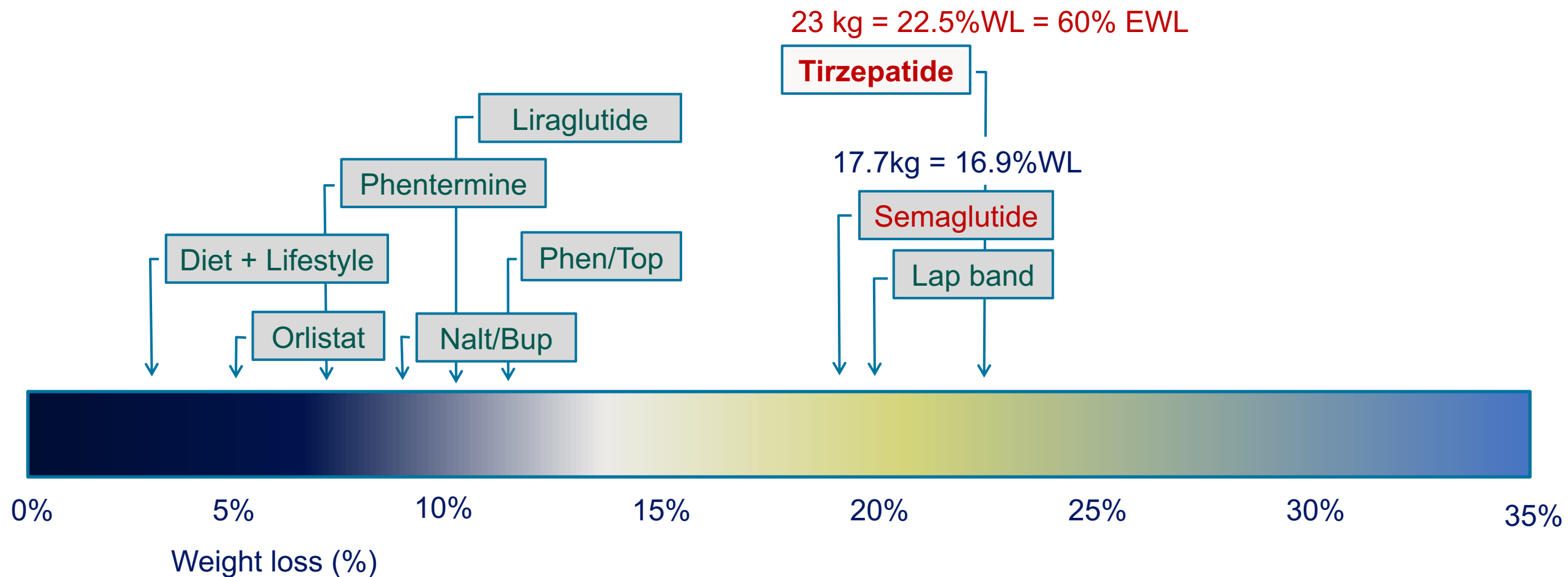
Weight loss (%)
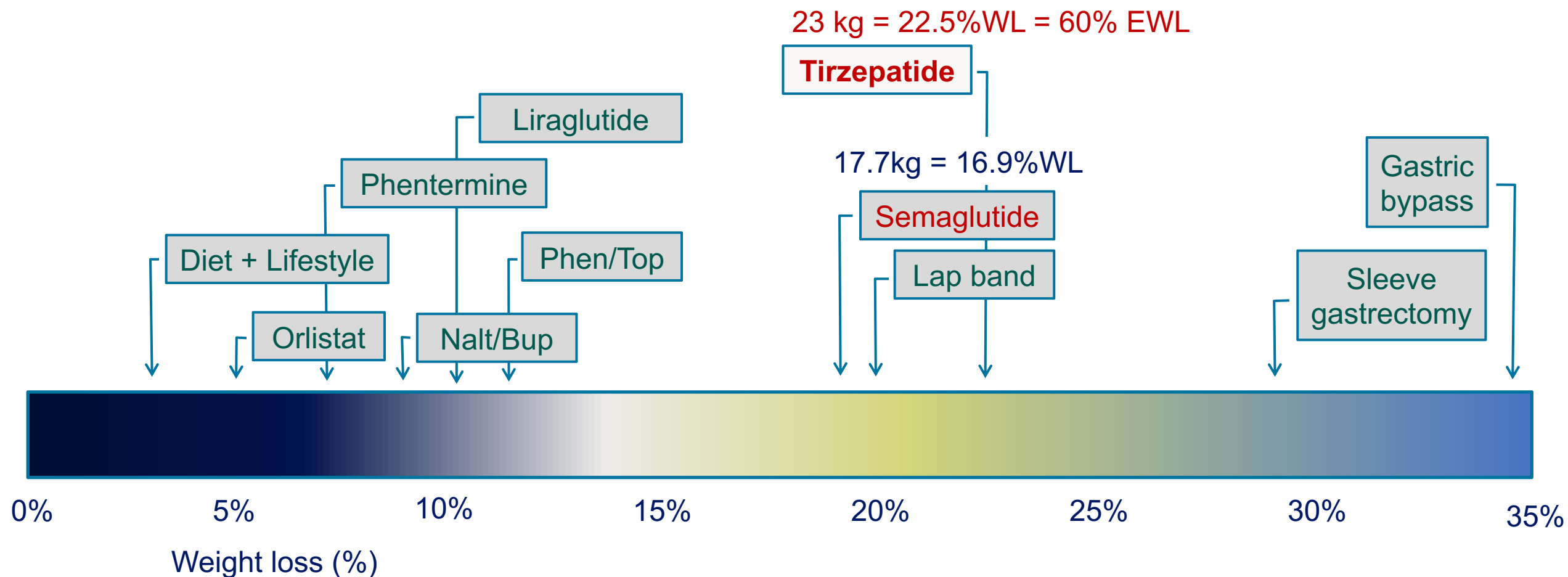
Tirzepatide: A GIP/GLP-1 Receptor Agonist

Tirzepatide molecule structure

C20 diacid-γ-Glu-(AEEA)₂- (K)

Shading indicates non-coded amino acids.

Tirzepatide is a 39-amino acid peptide with a C20 fatty diacid moiety that enables albumin binding and prolongs the half-life

In preclinical models, tirzepatide caused robust body weight loss mainly by significant reduction in food intake[1]

Legend:
- Vehicle (Q3D)
- Semaglutide (30 nmol/kg, Q3D)
- Tirzepatide (10 nmol/kg, Q3D)
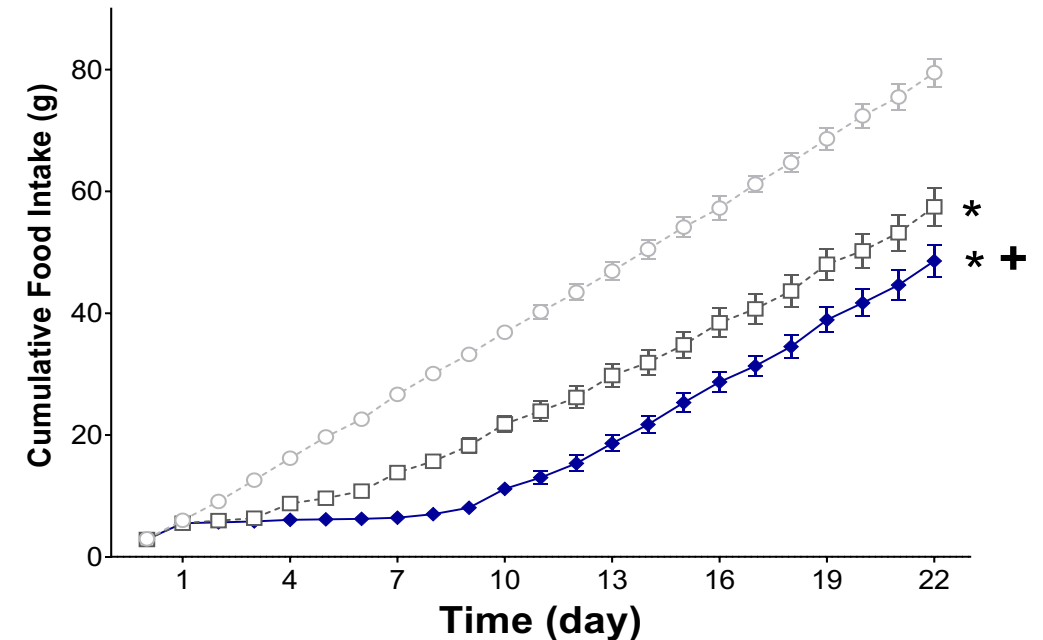
Cumulative food intake in DIO mice. $P < 0.05$ using one-way ANOVA repeated measures vs vehicle (*) or semaglutide (+)

GIP=glucose-dependent insulinotropic polypeptide; GLP-1=glucagon-like peptide-1.
1. Coskun et al. Mol Metab. 2018;18:3-14.

Tirzepatide: A GIP/GLP-1 Receptor Agonist

In humans, tirzepatide demonstrated:

- robust body weight reductions at doses of 5, 10 and 15 mg compared with semaglutide 1 mg in patients with T2D in SURPASS-2 (**Fig. A**)[1]

- improved beta-cell function and insulin sensitivity in a mechanism of action trial (**Fig. B**)[2]

A. Overall mean baseline body weight = 93.8 kg

Body weight, change from baseline (kg) vs Weeks

- Semaglutide 1 mg — -6.2 kg (-6.7%)
- Tirzepatide 5 mg — -7.8 kg (-8.5%)
- Tirzepatide 10 mg — -10.3 kg (-11.0%)
- Tirzepatide 15 mg — -12.4 kg (-13.1%)

B. Clamp Disposition Index (pmol m^{-2} L min^{-2} kg^{-1})

Baseline: Placebo 0.4, Semaglutide 1 mg 0.3, Tirzepatide 15 mg 0.3
Week 28: Placebo 0.3, Semaglutide 1 mg 1.4, Tirzepatide 15 mg 2.3

Proportion of Participants Achieving Weight Loss ≥5%, ≥10%, ≥15%: Treatment-Regimen Estimand

Change in Body Weight was Sustained Up to 2 Years

SURPASS-4
Overall mean baseline weight = 90.3 kg

Insulin Glargine
TZP 5 mg
TZP 10 mg
TZP 15 mg

Mean Change in Weight (kg) [SE]
(% change)

Week

2,3 (2.3%)
-5,8 (-8.6%)
-10,4 (-10.8%)
-11,1 (-12.8%)
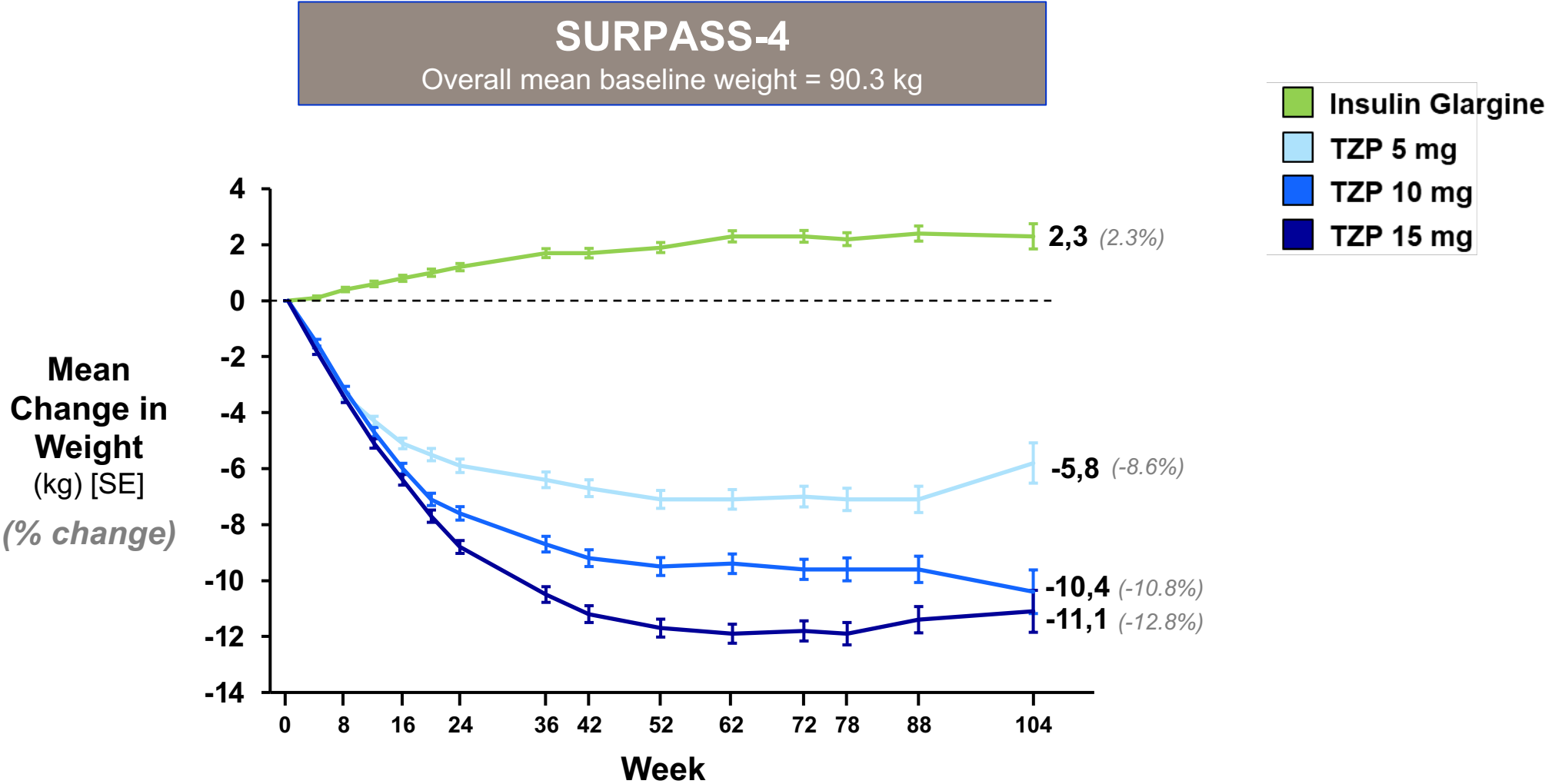
Potential actions of GIP and GLP-1

Central Nervous System
↓ **Food intake**
↓ **Nausea**
↓ **Body weight**
↑ **Energy expenditure**

Subcutaneous White Adipose Tissue
↑ **Insulin Sensitivity**
↑ **Lipid Buffering Capacity**
↑ **Blood Flow**
↑ **Storage Capacity**
↓ **Proinflammatory Immune Cell Infiltration**

Secretion and receptor localization of GIP and GLP-1

K-cells
L-cells

Brain
Fat
Bone
α cell • β cell
Nutrients
secretion
GIP
secretion
GLP-1
Lung
Heart
Kidney
β cell • Acinar cells
Gastrointestinal tract

Incretin action on various organs

	GIP	GLP-1
	Cerebroprotection	Satiety
	Fat accumulation	Lipolysis
		Lung protection
		Cardio protection
	Bone formation	
		Natriuresis Renal protection
	Glucagon secretion Insulin secretion	Glucagon suppression Insulin secretion
		Gastric emptying GI motility ↓

Kaneko S, touchREVIEWS in Endocrinology 2022;18:10-19
Samms RJ, et al. Trends Endocrinol Metab. 2020;31(6):410-421

SURMOUNT-1 *Obesity Management*
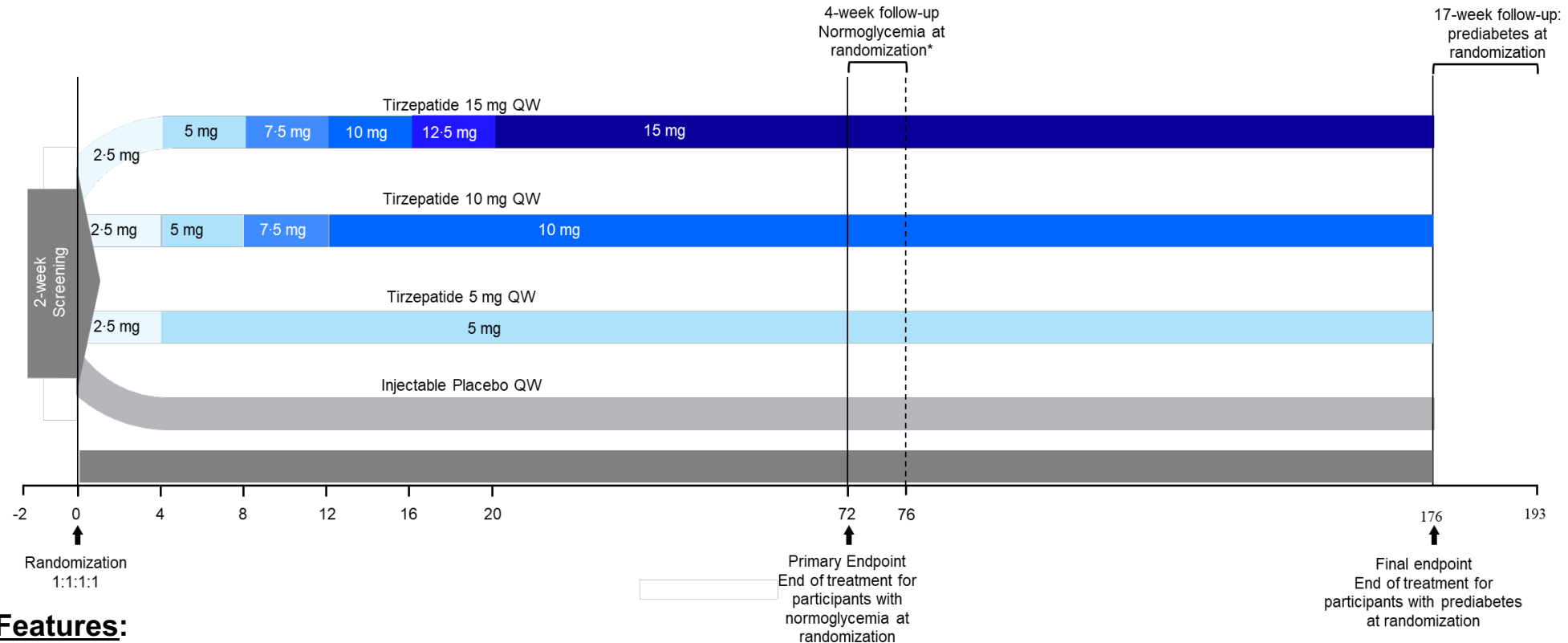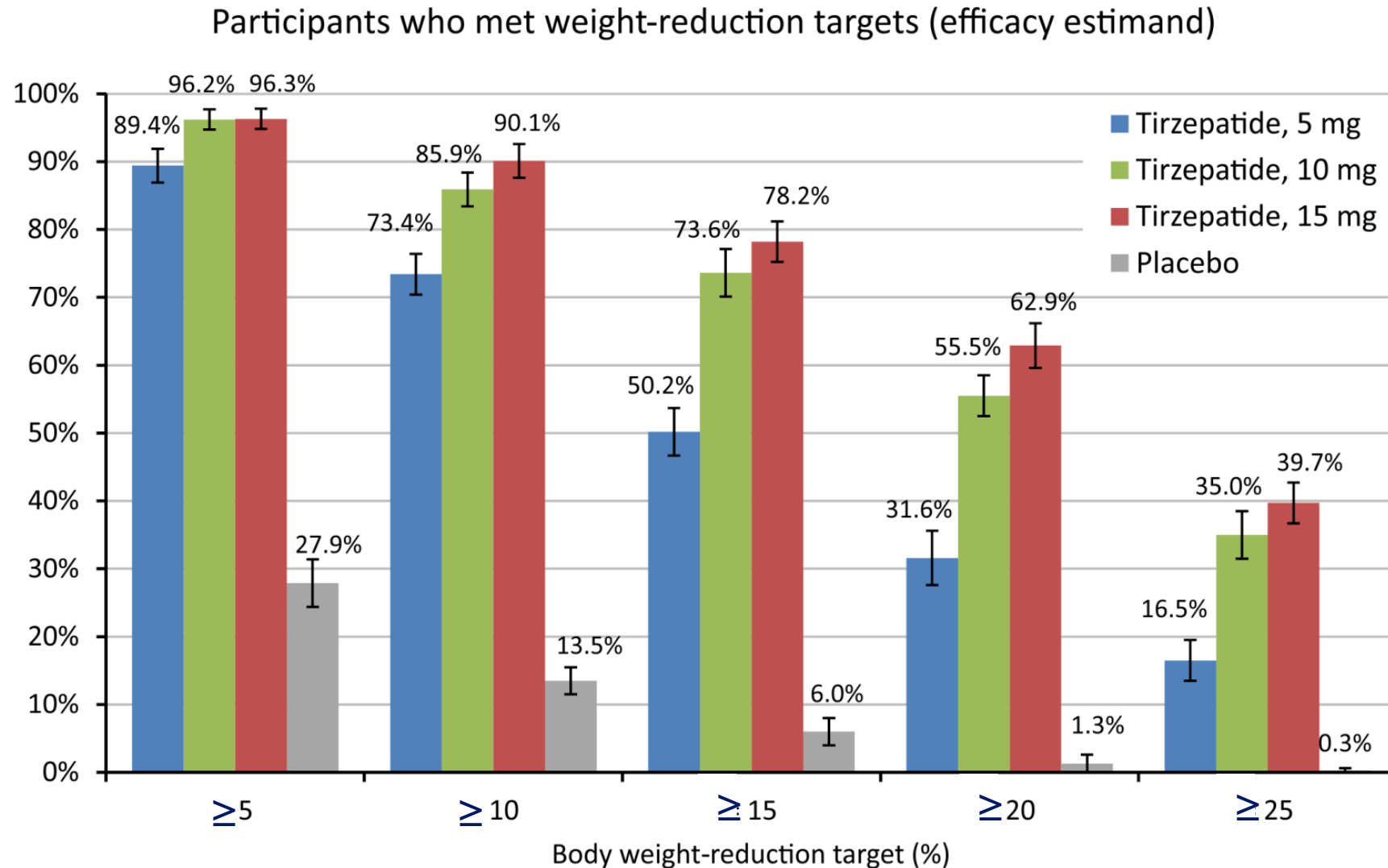

Key Features:

- N=2539

- 4 arms (1:1:1:1 randomization)

- Randomization stratified by country, sex and prediabetes status (yes, no)

- Study duration dependent on pre-diabetes status: 72/176 weeks

- An upper limit of 70% enrollment of women used to ensure a sufficiently large sample of men

- During the first, 72-week period, one study drug dose reduction per participant was permitted to help manage intolerable gastrointestinal symptoms

Weight Reduction: Percent Change and Change in Pounds
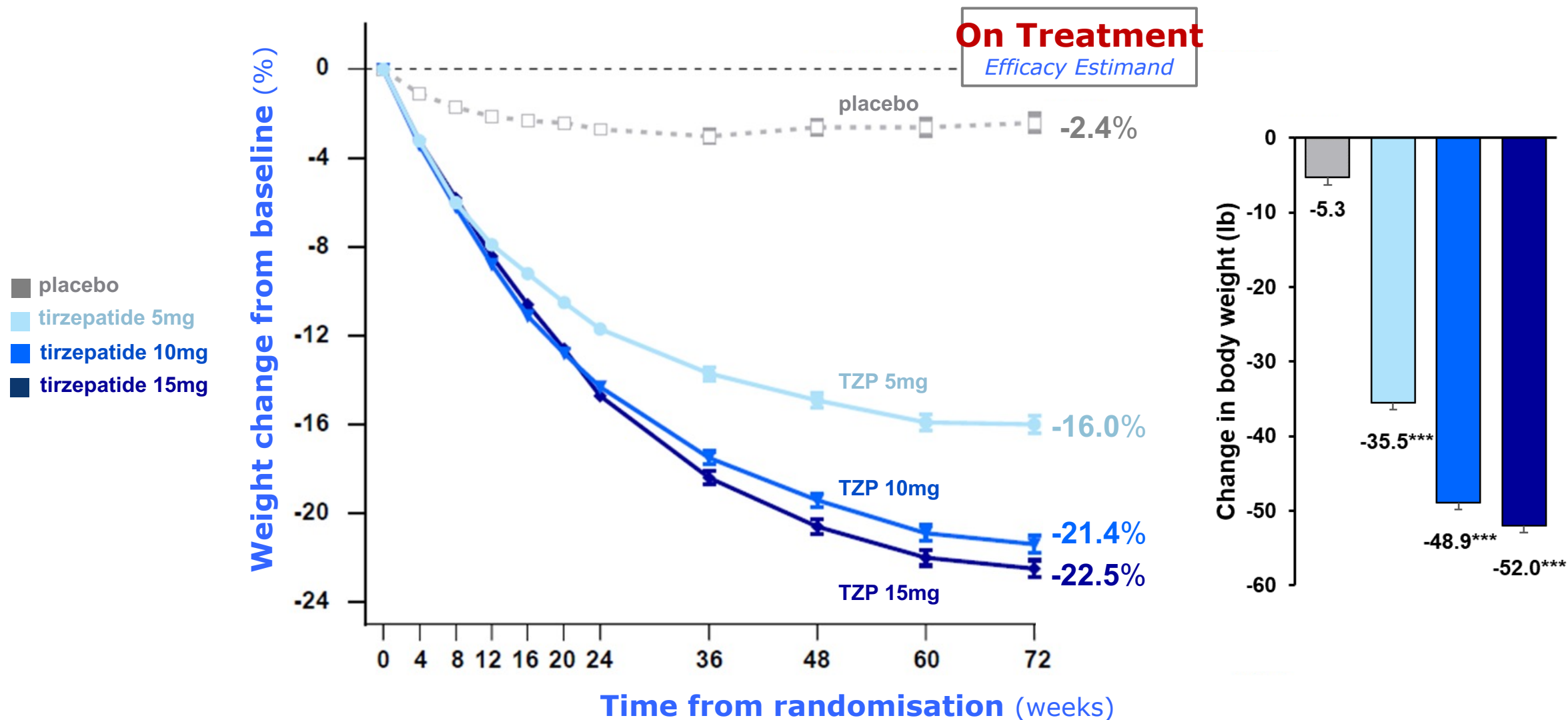
Efficacy estimand: MMRM analysis, mITT population (efficacy analysis set). Data presented over time are least squares means ± standard errors. Tirzepatide vs. placebo at 72 weeks: ***p<0.001.

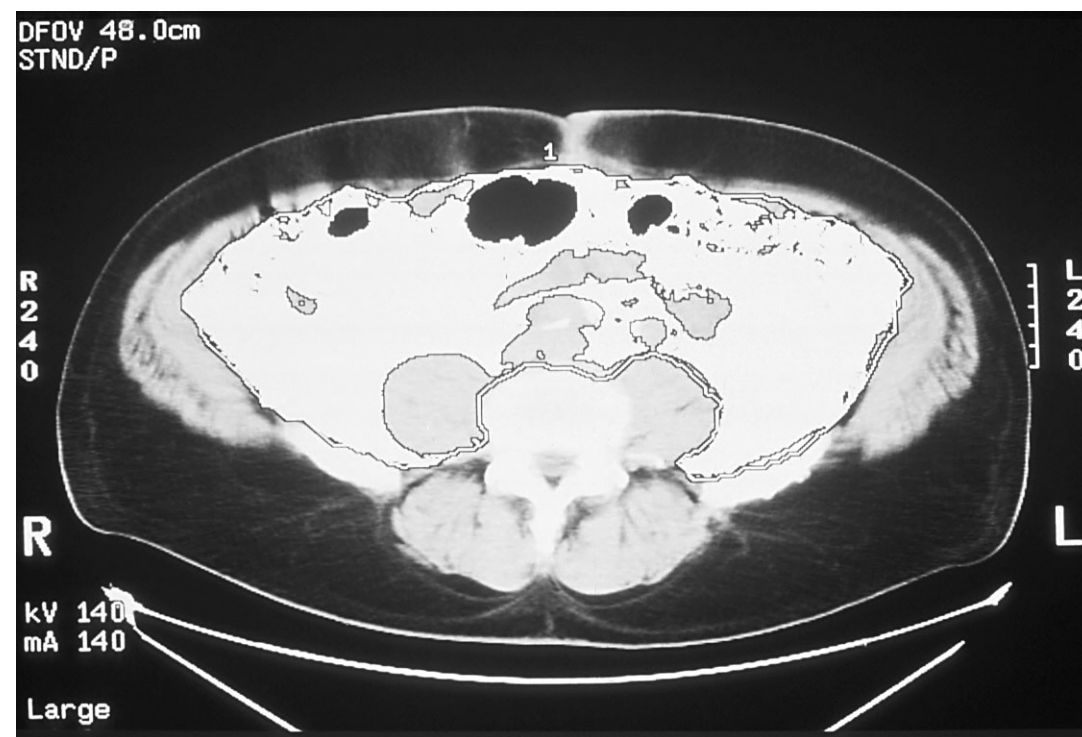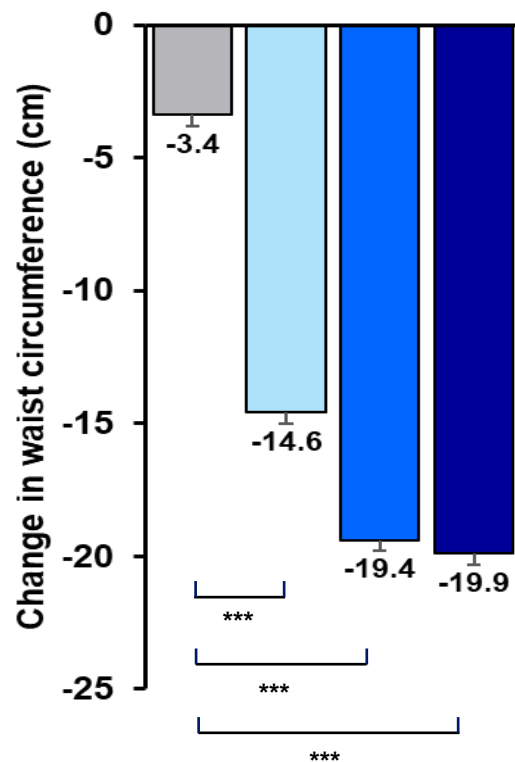# Effect of once-weekly Tirzepatide, as compared with placebo, on body weight

Participants who met weight-reduction targets (efficacy estimand)

Decrease in Waist Circumference

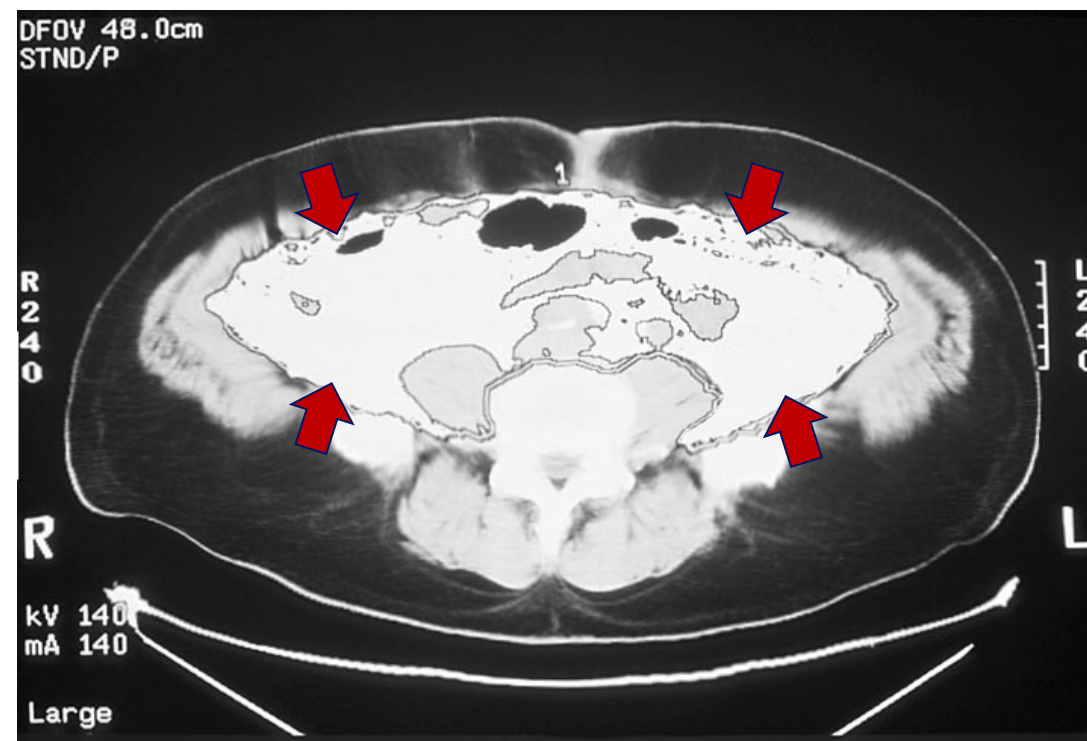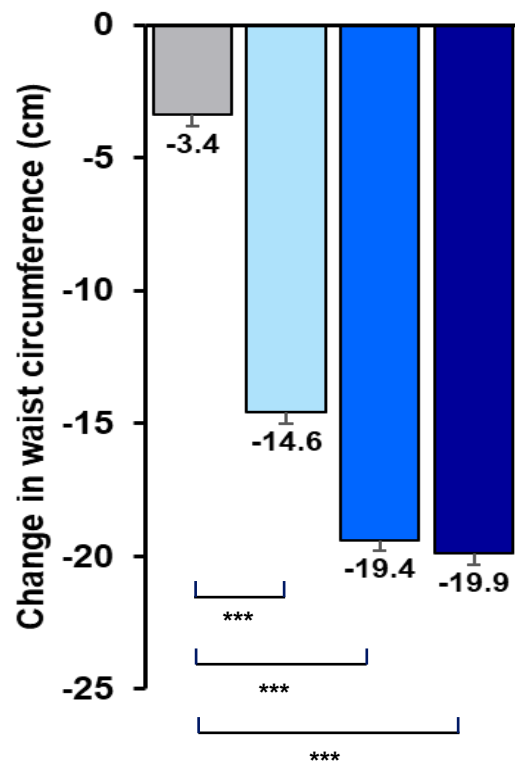**Overall mean waist circumference at baseline = 114.1 cm**

Treatment-regimen estimand: ANCOVA analysis, mITT population (full analysis set). Efficacy estimand: MMRM analysis, mITT population (efficacy analysis set). Data are LS means ± standard errors. Tirzepatide vs. placebo at 72 weeks: ***p<0.001.

Decrease in Waist Circumference

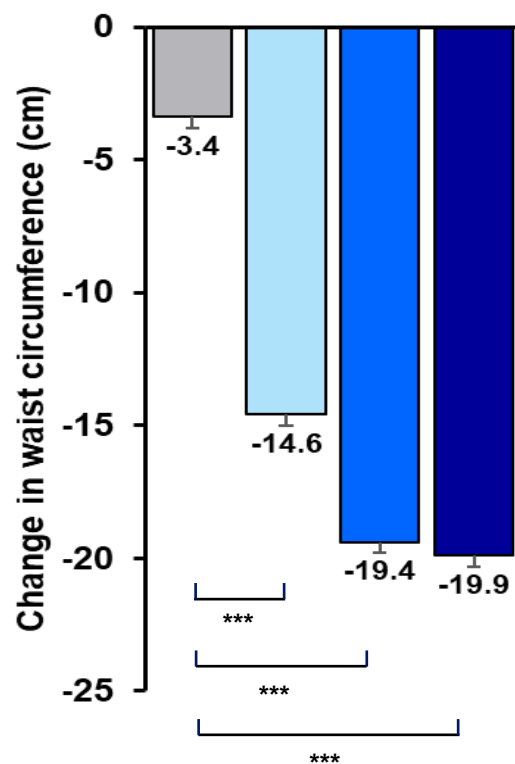**Overall mean waist circumference at baseline = 114.1 cm**

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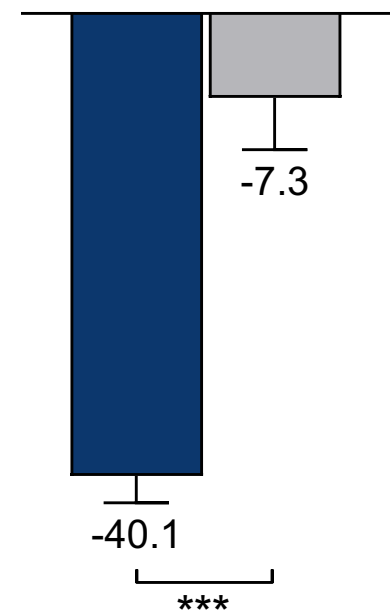
Decrease in Waist Circumference

On Treatment
Efficacy Estimand

□ Placebo □ Tirzepatide 5 mg ■ Tirzepatide 10 mg ■ Tirzepatide 15 mg

Change in waist circumference (cm)

- -3.4
- -14.6
- -19.4
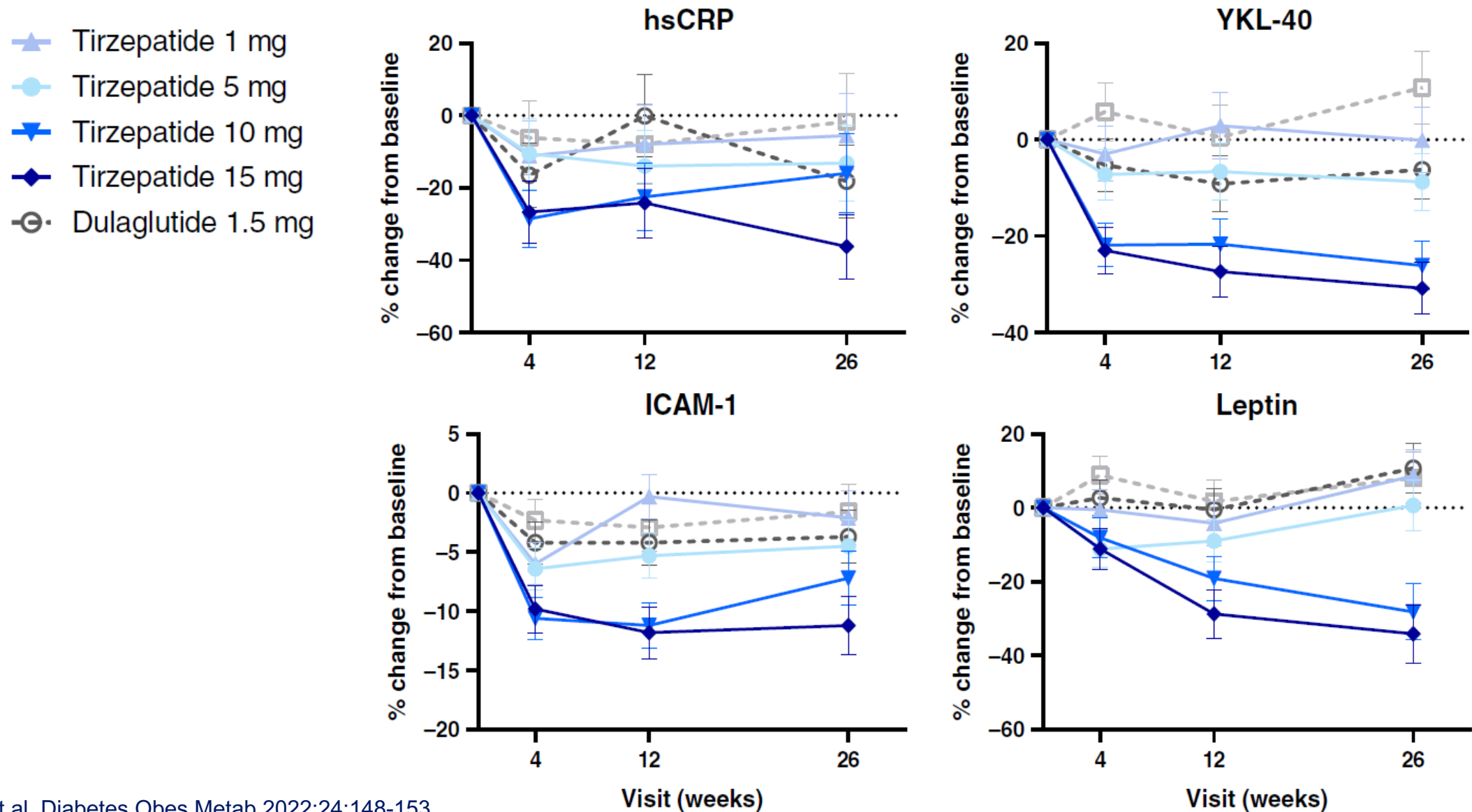- -19.9

***
***
***

Visceral fat mass

- -7.3
- -40.1

***

■ Tirzepatide 5/10/15 mg pooled
□ Placebo

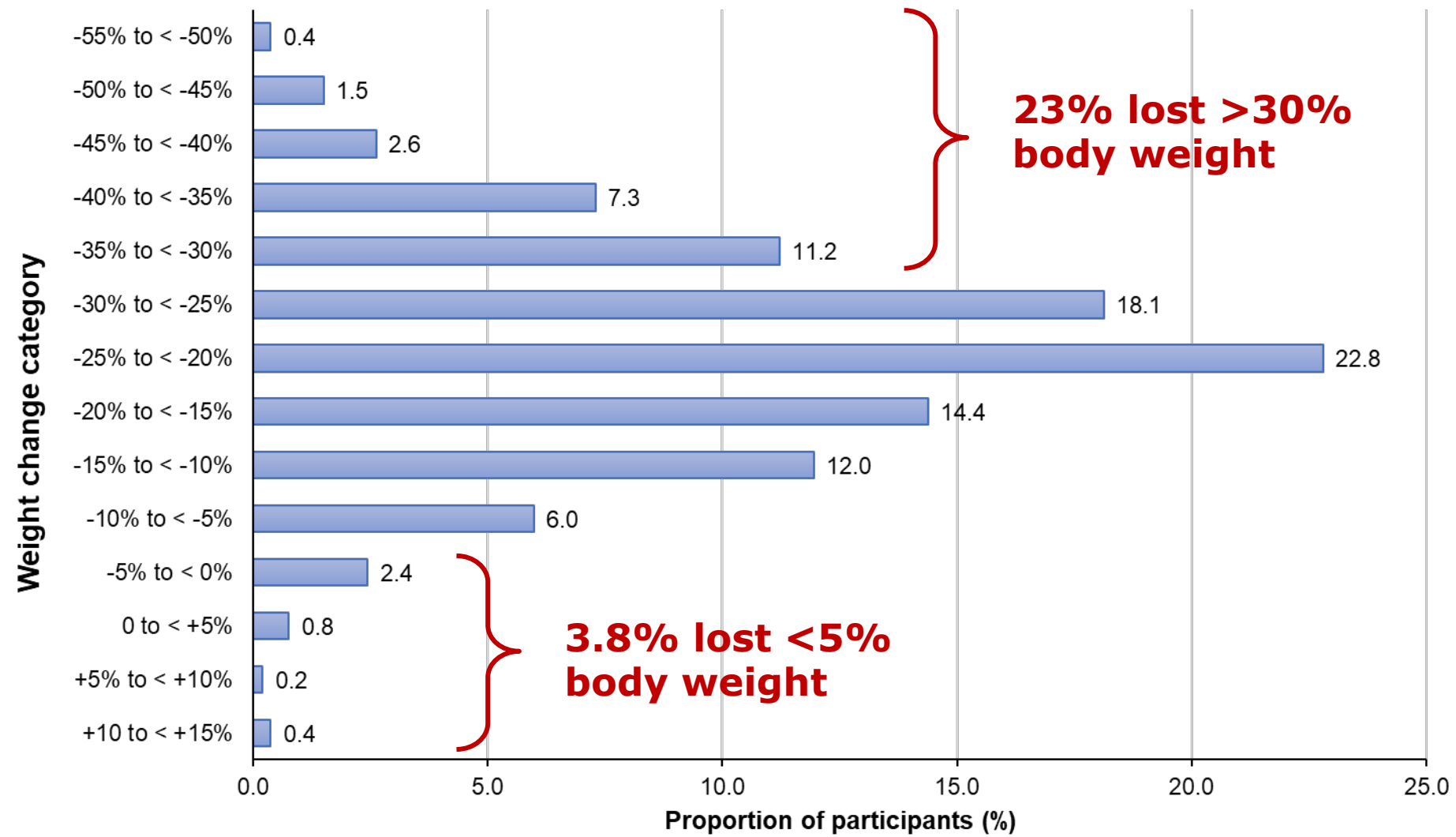Mean percentage change from baseline at week 72

Overall mean waist circumference at baseline = 114.1 cm

Treatment-regimen estimand: ANCOVA analysis, mITT population (full analysis set). Efficacy estimand: MMRM analysis, mITT population (efficacy analysis set). Data are LS means ± standard errors. Tirzepatide vs. placebo at 72 weeks: ***p<0.001.

30

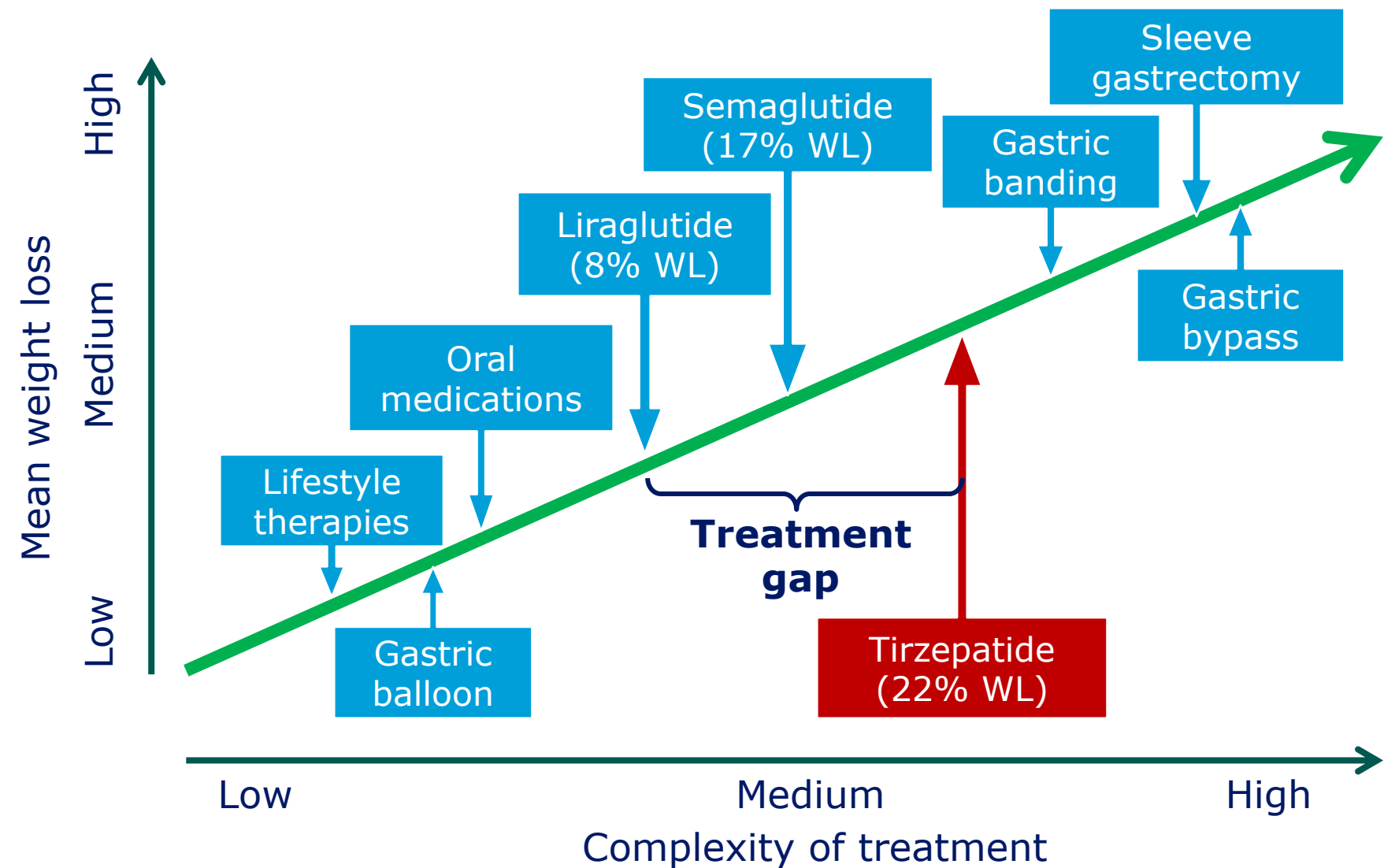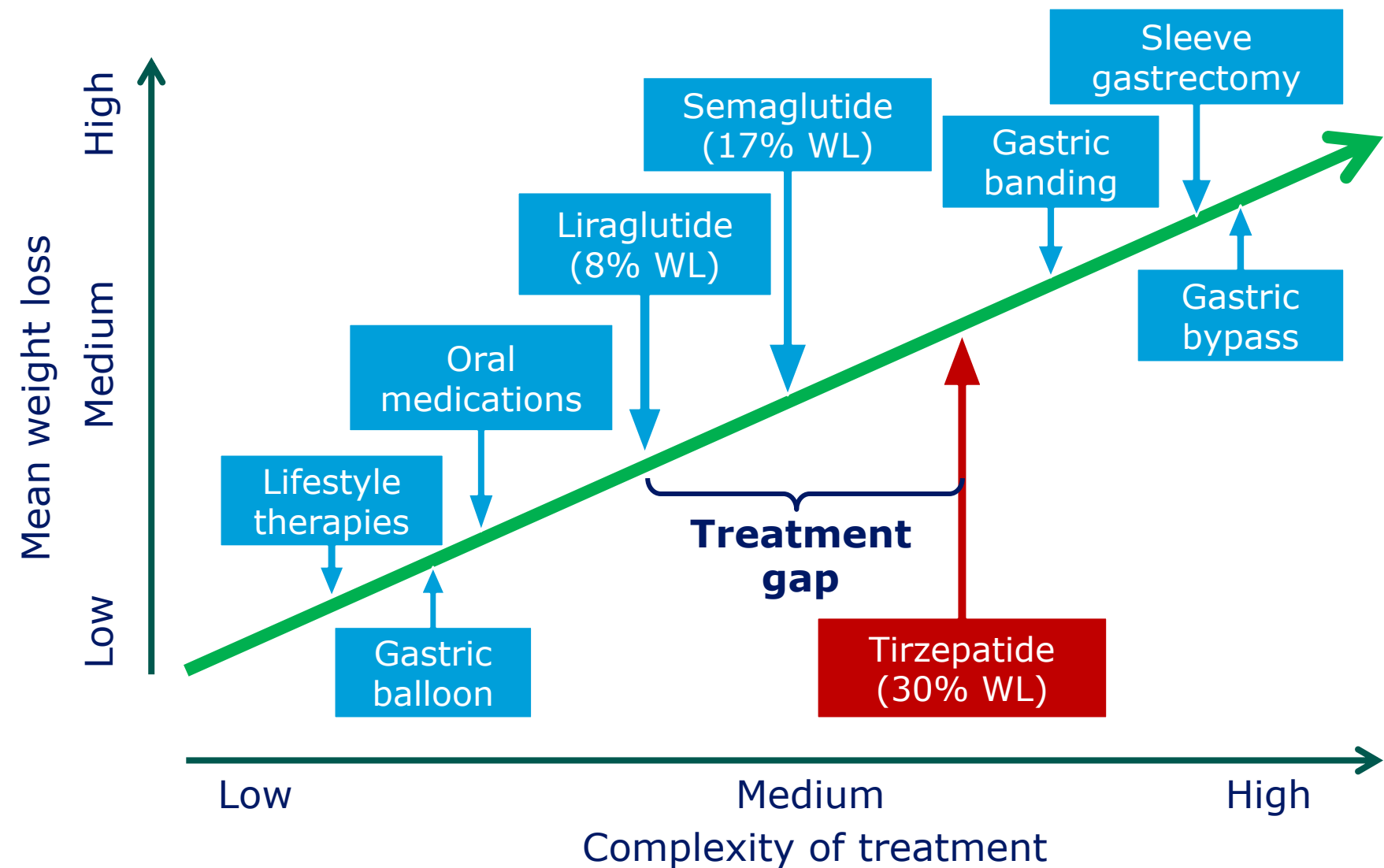# Perspectives on comorbid factors: conventional RF and beyond

Wilson JM et al, Diabetes Obes Metab 2022;24:148-153

Variability of weight loss response with tirze

23% lost >30% body weight

3.8% lost <5% body weight

Data on file, Eli Lilly and Company

Perspectives on weight; closing the GAP

Mean weight loss (Low / Medium / High) vs Complexity of treatment (Low / Medium / High)

- Lifestyle therapies
- Gastric balloon
- Oral medications
- Liraglutide (8% WL)
- Semaglutide (17% WL)
- Gastric banding
- Sleeve gastrectomy
- Gastric bypass
- **Treatment gap**
- Tirzepatide (22% WL)

US CDC, Decision Resources 2012; Martin *et al. Surg Obes Relat Dis* 2010;6:8–15; GWU. Obesity Drug Outcome Measures: A Consensus Report of Considerations Regarding Pharmacologic Intervention. 2012. http://sphhs.gwu.edu/pdf/releases/obesitydrugmeasures.pdf

Perspectives on weight; closing the GAP

Mean weight loss (y-axis: Low, Medium, High)

Complexity of treatment (x-axis: Low, Medium, High)

- Lifestyle therapies
- Gastric balloon
- Oral medications
- Liraglutide (8% WL)
- Semaglutide (17% WL)
- Gastric banding
- Sleeve gastrectomy
- Gastric bypass
- Tirzepatide (30% WL)
- Treatment gap

US CDC, Decision Resources 2012; Martin *et al. Surg Obes Relat Dis* 2010;6:8–15; GWU. Obesity Drug Outcome Measures: A Consensus Report of Considerations Regarding Pharmacologic Intervention. 2012. http://sphhs.gwu.edu/pdf/releases/obesitydrugmeasures.pdf

Comments and perspectives on safety

	Lira 3.0 SCALE-1	Sema 2.4 STEP-1	Tirze 15 mg SURMOUNT-1
Age	45.2	46.0	44.9
BMI	38.3	37.8	38.1
W Loss %	8.0 (5.4%)	14.8 (12.4)	20.9 (17.8)
Nausea	40.2	44.2	31.0
Vomiting	16.3	24.8	12.2
Diarrhea	20.9	31.5	23.0

Surpass 2	Sema 1 mg	Tirze 10 mg
Nausea	17.9	19.2
All GI events	41.2	46.1

Surpass 2 – Frias J et al, NEJM 2021; 385: 503-515

Perspectives on Outcome: Prior CVOTs of Drugs in Obesity

	SCOUT	CRESCENDO	LIGHT	CONVENE	CAMELLIA-TIMI
Intervention	**Sibutramine**	**Rimonabant**	**Naltrexone/ Buproprion**	**Naltrexone/ Bupropion**	**Lorcaserin**
Date started	Jan 2003	Dec 2005	Jun 2012	Dec 2015	Jan 2014
Date ended	Mar 2009	Apr 2009	Aug 2015	Apr 2016	Sep 2018
Patients planned (enrolled)	10777	18695	9810>8900 (8910)	8800 (67)	12000
Design Event rate Risk reduction Discontinued	Superior 7% 11.4% 30%	Superior 3% 15% 10%	Non-inferior 1.5% HR:<1.4 1.2%	? ? ? ?	Non-inferior 1.5% HR:<1.4 5%
Primary Outcome	3P-MACE + resuscitated cardiac arrest	3P-MACE + hospitalisation	3P-MACE + angina needing hospitalisation	3P-MACE	1. 3P-MACE 2. T2D 3. MACE+
Results	**Harm**	**Terminated**	**Terminated**	**Terminated**	**Non-inferiority established**

Adapted from and by courtesy of dr M. Lincoff, Cleveland Clinic, US
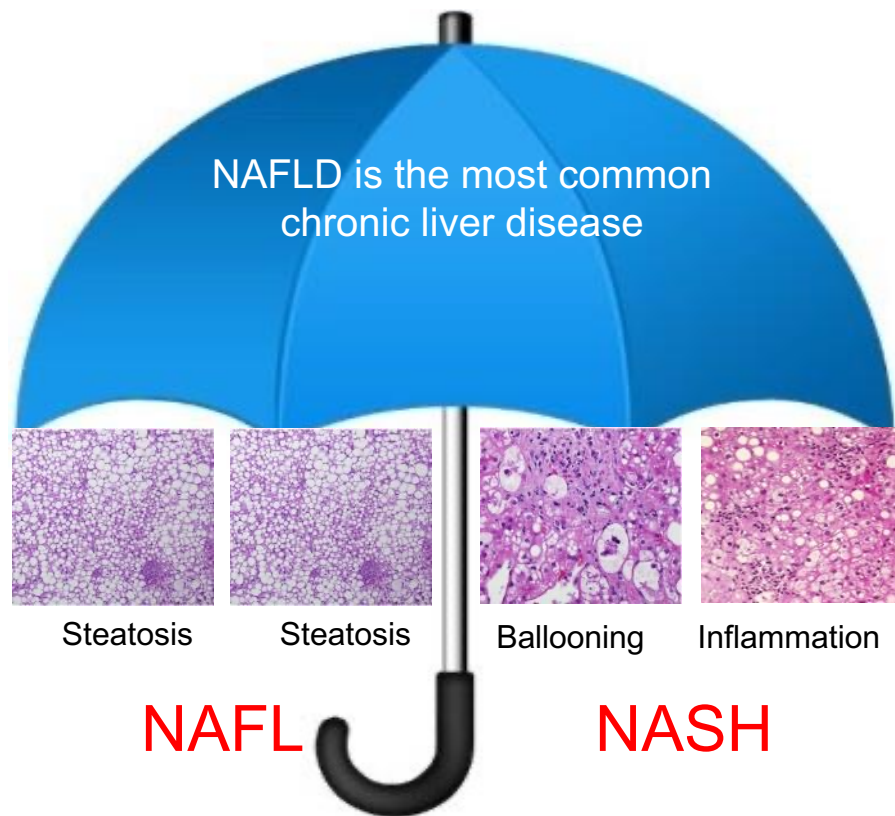
Perspectives on Outcome: Prior CVOTs of Drugs in Obesity

	SCOUT	CRESCENDO	LIGHT	CONVENE	CAMELLIA-TIMI	SELECT
Intervention	**Sibutramine**	**Rimonabant**	**Naltrexone/ Buproprion**	**Naltrexone/ Bupropion**	**Lorcaserin**	**Semaglutide**
Date started	Jan 2003	Dec 2005	Jun 2012	Dec 2015	Jan 2014	Nov 2018
Date ended	Mar 2009	Apr 2009	Aug 2015	Apr 2016	Sep 2018	Q4 2023
Patients planned (enrolled)	10777	18695	9810>8900 (8910)	8800 (67)	12000	17500
Design Event rate Risk reduction Discontinued	Superior 7% 11.4% 30%	Superior 3% 15% 10%	Non-inferior 1.5% HR:<1.4 1.2%	? ? ? ?	Non-inferior 1.5% HR:<1.4 5%	Superiority 2.2% 17% TBD
Primary Outcome	3P-MACE + resuscitated cardiac arrest	3P-MACE + hospitalisation	3P-MACE + angina needing hospitalisation	3P-MACE	1. 3P-MACE 2. T2D 3. MACE+	3P-MACE
Results	**Harm**	**Terminated**	**Terminated**	**Terminated**	**Non-inferiority established**	**Interim analysis**

Prior CVOTs of Drugs in Obesity

	SCOUT	CRESCENDO	LIGHT	CONVENE	CAMELLIA-TIMI	SELECT	SURMOUNT-MMO
Intervention	**Sibutramine**	**Rimonabant**	**Naltrexone/ Buproprion**	**Naltrexone/ Bupropion**	**Lorcaserin**	**Semaglutide**	**Tirzepatide**
Date started	Jan 2003	Dec 2005	Jun 2012	Dec 2015	Jan 2014	Nov 2018	Q4 2022
Date ended	Mar 2009	Apr 2009	Aug 2015	Apr 2016	Sep 2018	Q4 2023	Q4 2027
Patients planned (enrolled)	10777	18695	9810>8900 (8910)	8800 (67)	12000	17500	15000
Design **Event rate** **Risk reduction** **Discontinued**	Superior 7% 11.4% 30%	Superior 3% 15% 10%	Non-inferior 1.5% HR:<1.4 1.2%	? ? ? ?	Non-inferior 1.5% HR:<1.4 5%	Superiority 2.2% 17% TBD	Superiority ER TBA
Primary Outcome	3P-MACE + resuscitated cardiac arrest	3P-MACE + hospitalisation	3P-MACE + angina needing hospitalisation	3P-MACE	1. 3P-MACE 2. T2D 3. MACE+	3P-MACE	Extended 5P-MACE
Results	**Harm**	**Terminated**	**Terminated**	**Terminated**	**Non-inferiority established**	**Interim analysis**	

Perspectives on other outcomes: the umbrella of NAFLD

NAFLD is the most common chronic liver disease

Steatosis   Steatosis   Ballooning   Inflammation

NAFL   NASH

SEMA NASH ongoing
TIRZE NASH ongoing
OTHER COMBO to follow

Chalasani N. et al. Hepatology, 67 (1), 2018

Global prevalence of overweight or obesity

In children and adolescents in 2016

41 million children <5 years
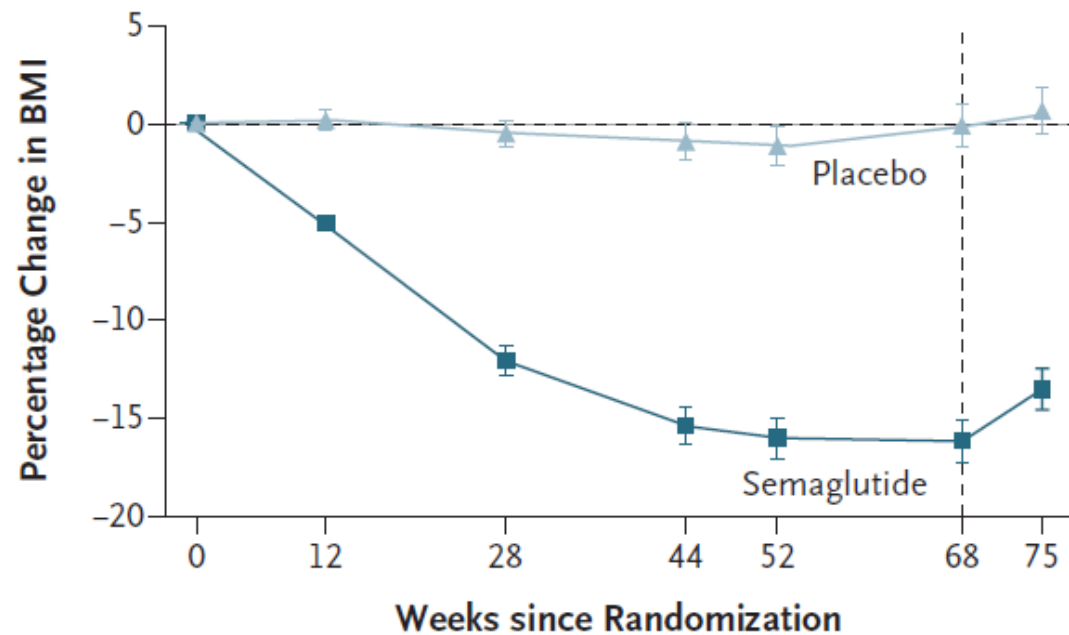
>340 million children and adolescents 5-19 years

Other future perspectives
BMI During Adolescence and Outcome

Predominantly due to Diabetes and BP

Twig G, et al. N Engl J Med. 2016;374:2430-2440.
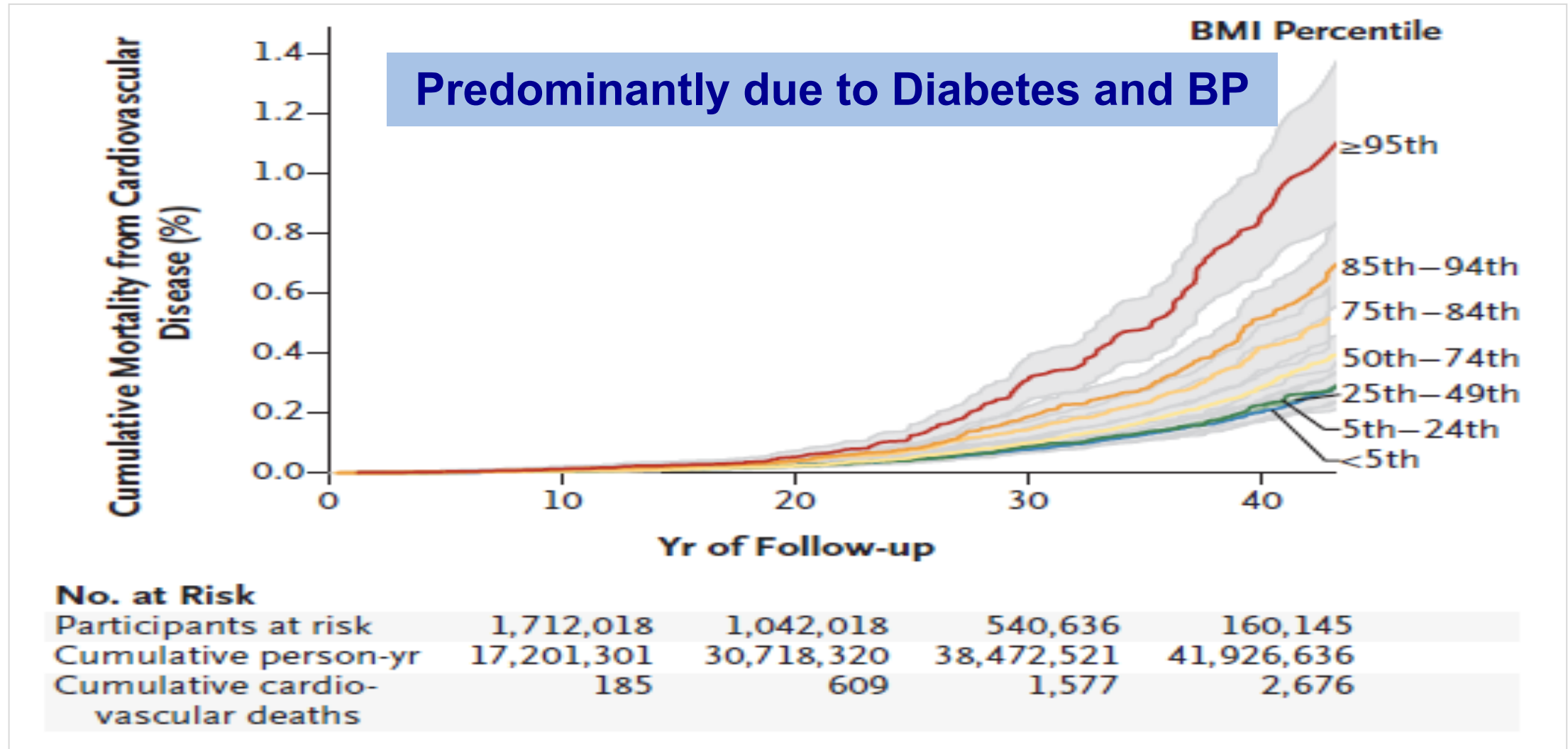
Semaglutide in adolescents

Weghuber D. et al, N Engl J Med, 2022;387:2245-57

Perspectives on accessibility & reimbursability

US CDC, Decision Resources 2012; Martin *et al. Surg Obes Relat Dis* 2010;6:8–15; GWU. Obesity Drug Outcome Measures: A Consensus Report of Considerations Regarding Pharmacologic Intervention. 2012. http://sphhs.gwu.edu/pdf/releases/obesitydrugmeasures.pdf
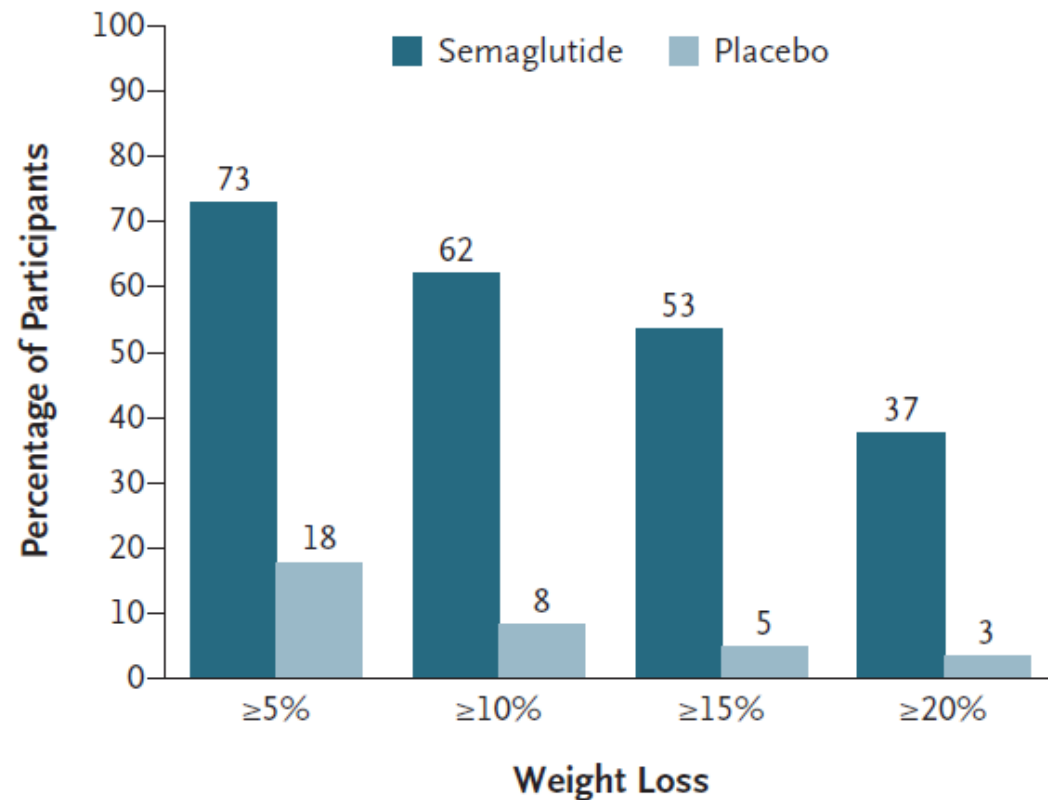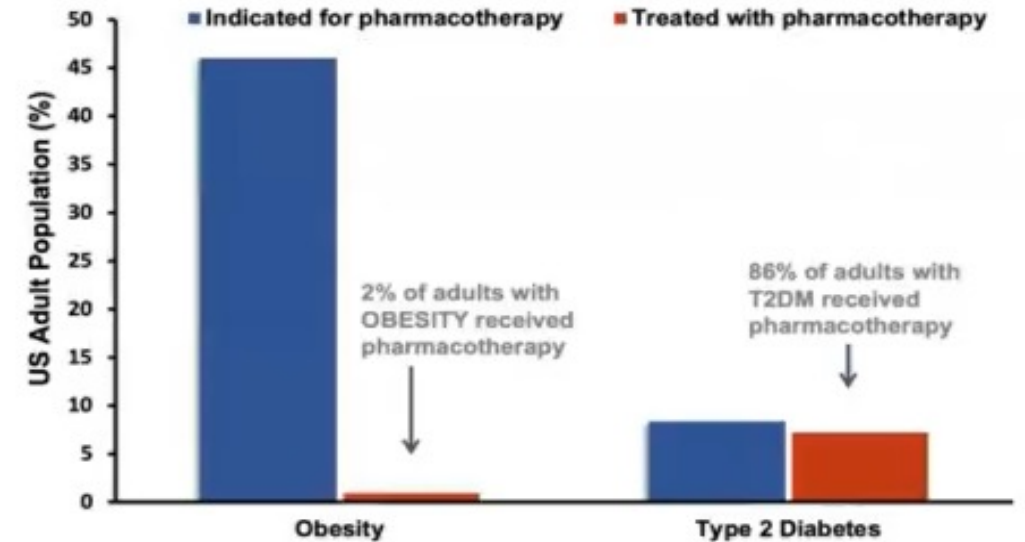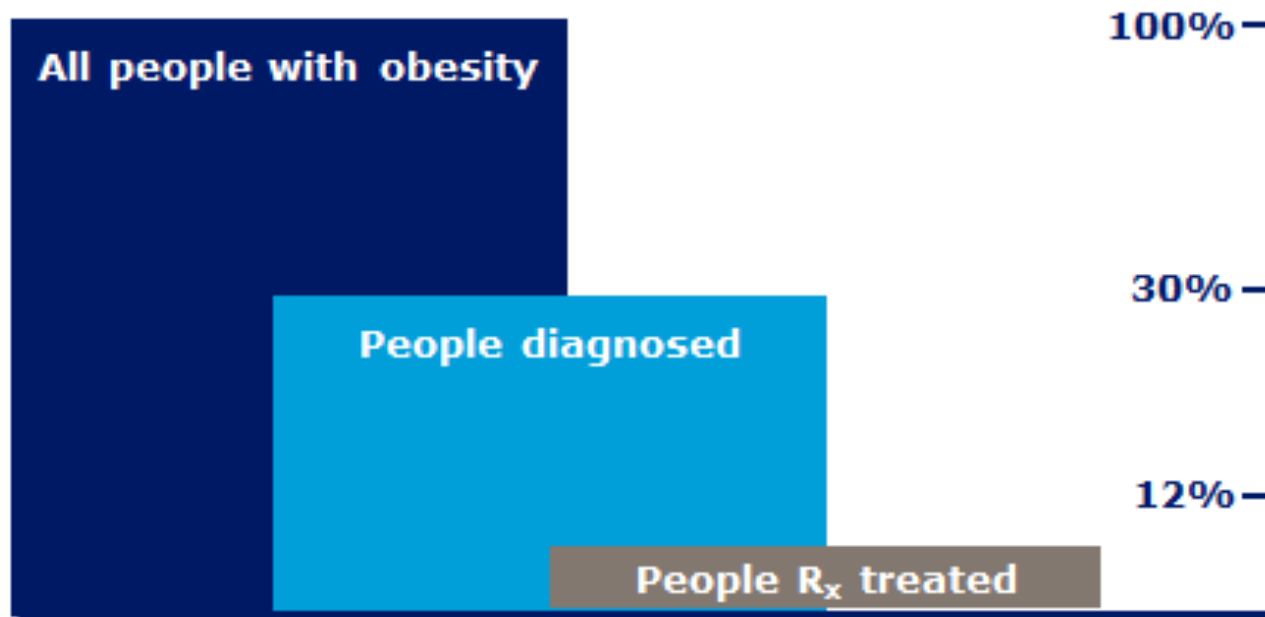
Other future perspectives

- Semaglutide & tirzepatide in adolescent obesity

- Persistent findings – when to stop, how to taper off ?

- Perspectives on 'legacy effect'

- Effect in ageing population: the obesity paradox

- Perspectives on accessibility & reimbursability

- **Still indications for bariatric, metabolic surgery ?**

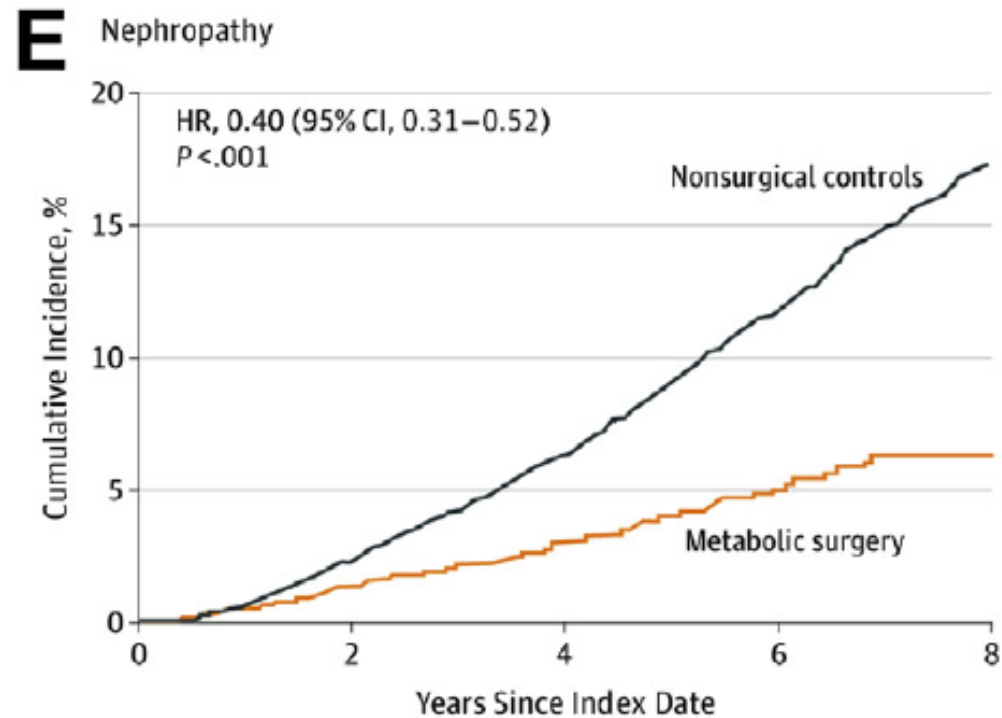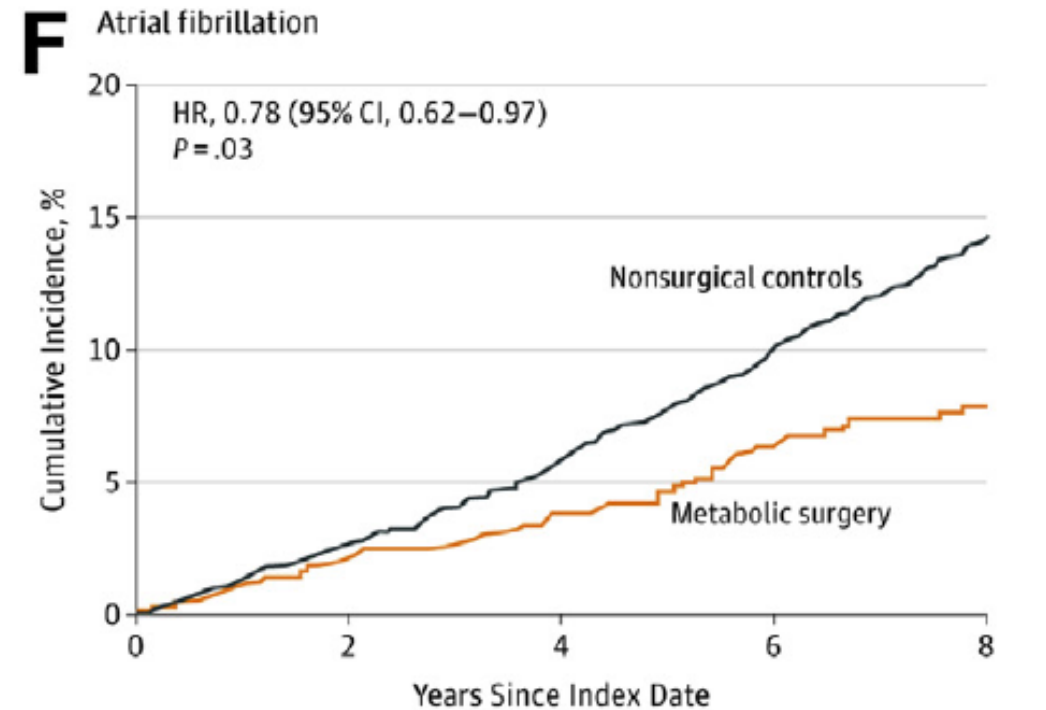94,885 Matched Patients with Obesity

Weight Loss Surgery
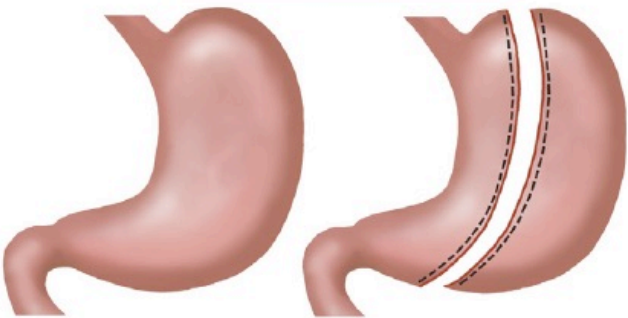
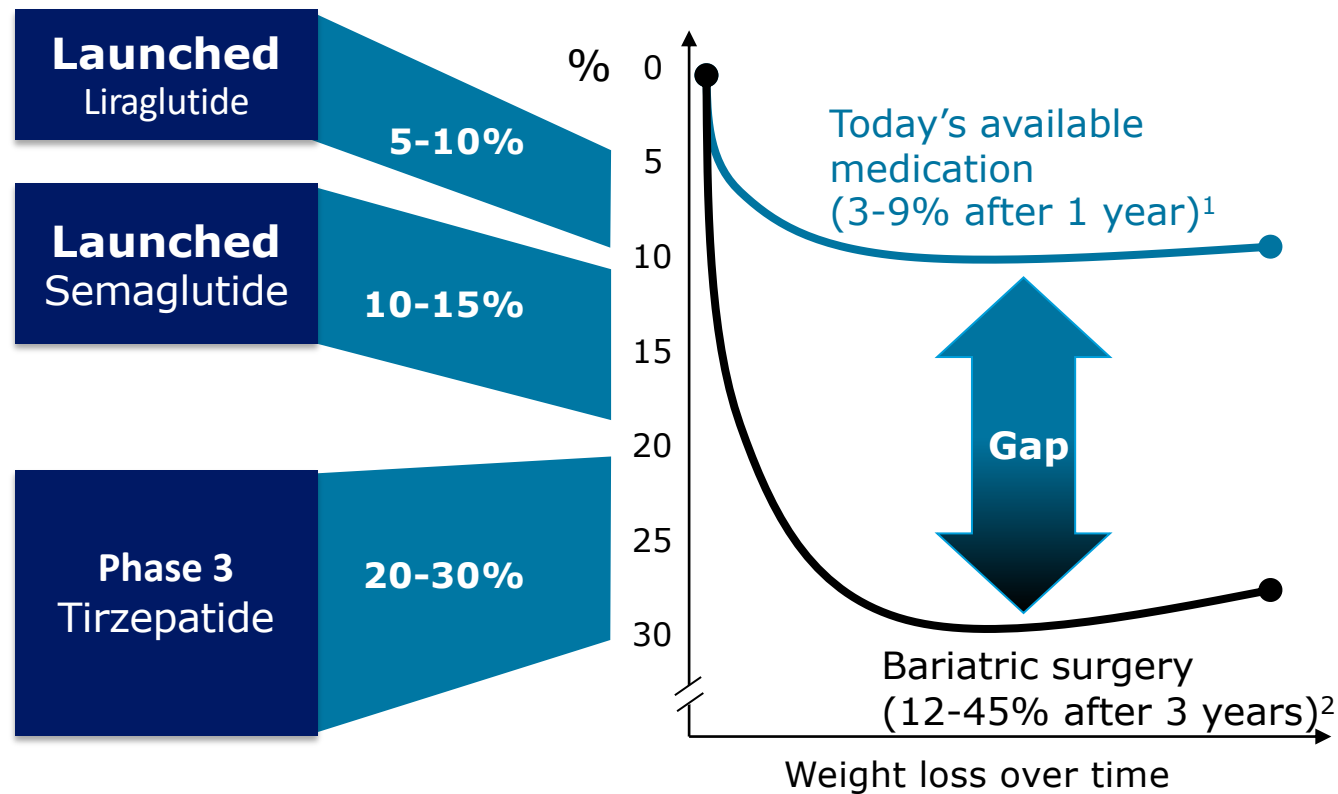After Median Follow-up 4.0 (IQR 2.4-5.7) Years

37% ↓ Risk of Mortality

54% ↓ Risk of New-Onset HF

37% ↓ Risk of MI

29% ↓ Risk of Stroke

Nonsurgical control — Bariatric surgery

Mentias A et al, J Am Coll Cardiol, 2022;79:1429-37
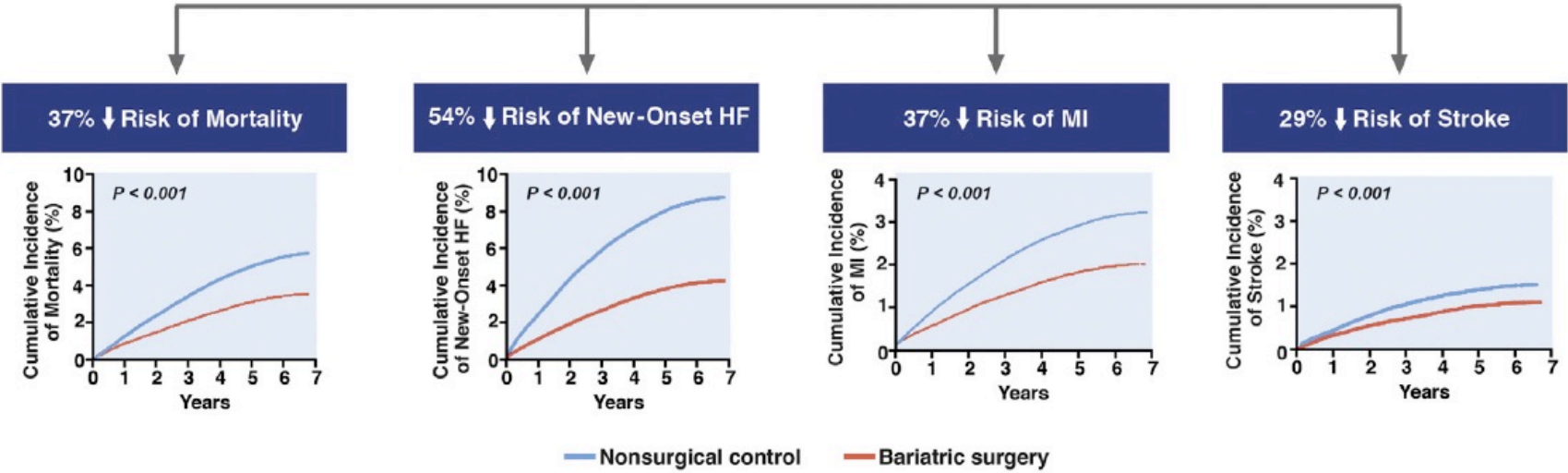
Eight-year cumulative incidence estimates for special endpoints

E Nephropathy

HR, 0.40 (95% CI, 0.31–0.52)
P <.001

Nonsurgical controls

Metabolic surgery

Cumulative Incidence, %

Years Since Index Date

F Atrial fibrillation

HR, 0.78 (95% CI, 0.62–0.97)
P = .03

Nonsurgical controls

Metabolic surgery

Cumulative Incidence, %

Years Since Index Date

No. at risk

Nonsurgical controls	9190	7056	4515	2262	893	10734	8152	5212	2660	1072
Metabolic surgery	1937	1216	838	506	293	2135	1328	915	555	319

Aminian A, et al. JAMA 2019;322:1271-1282

Launched
Liraglutide

5-10%

Launched
Semaglutide

10-15%

Phase 3
Tirzepatide

20-30%

% 0

5

10

15

20

25

30

Today's available
medication
(3-9% after 1 year)[1]

Gap

Bariatric surgery
(12-45% after 3 years)[2]

Weight loss over time

Future targets & options

➢ CagriSema

➢ MC4R agonist

➢ Oral semaglutide

➢ AMG-133

➢ Retatrutide: GIP/GLP1/Glucagon

➢ Mazdutide

➢ Pemvidutide (NASH)

Anti-obesity drug discovery: advances and challenges

Timo D. Müller[ID][1,2✉], Matthias Blüher[3], Matthias H. Tschöp[ID][4,5] and Richard D. DiMarchi[ID][6✉]

Abstract | Enormous progress has been made in the last half-century in the management of diseases closely integrated with excess body weight, such as hypertension, adult-onset diabetes and elevated cholesterol. However, the treatment of obesity itself has proven largely resistant to therapy, with anti-obesity medications (AOMs) often delivering insufficient efficacy and dubious safety. Here, we provide an overview of the history of AOM development, focusing on lessons learned and ongoing obstacles. Recent advances, including increased understanding of the molecular gut–brain communication, are inspiring the pursuit of next-generation AOMs that appear capable of safely achieving sizeable and sustained body weight loss.
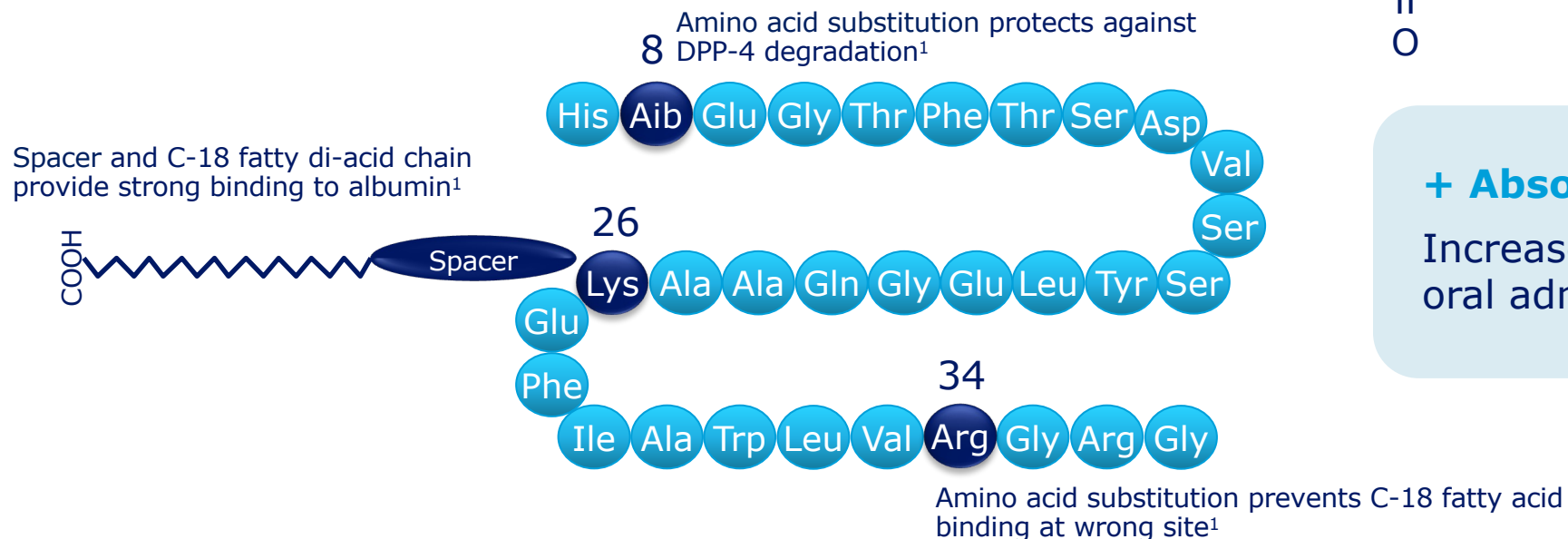
1. Long-term Drug Treatment for Obesity: A Systematic and Clinical Review;
Susan Z. Yanovski, MD; Jack A. Yanovski, MD, PhD JAMA. 2014;311(1):74-86;

2. Treatment of Obesity: Weight Loss and Bariatric Surgery
B M. Wolfe E. Kvach and RH. Eckel   Circulation Research. 2016;118:1844–1855

3. Progress and challenges in anti-obesity pharmacotherapy
Bessesen D & Van Gaal L, The Lancet Diab Endocrinol, 2018; 6(3):237-248

4. Anti-obesity Drug Discovery: advances and challenges
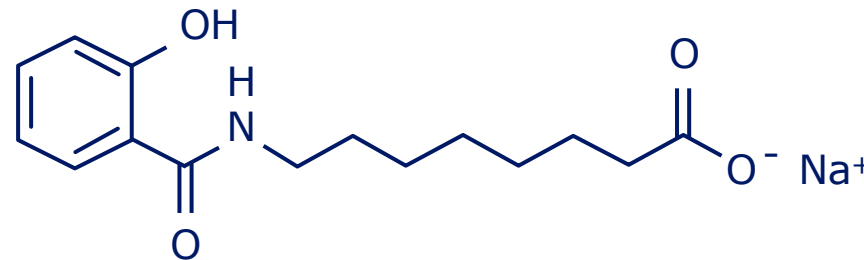Timo D. Muller et al. Nat Rev Drug Discovery. 2022;21: 201-223

Semaglutide in an oral formulation

Semaglutide

94% homology to human GLP-1[1]
$t_{1/2}$ of approximately 1 week[2–4]

Sodium **N**-(8-(2-hydroxybenzoyl) **A**mino) **C**aprylate

Amino acid substitution protects against DPP-4 degradation[1]

8

His · Aib · Glu · Gly · Thr · Phe · Thr · Ser · Asp · Val · Ser

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

COOH — Spacer

26

Lys · Ala · Ala · Gln · Gly · Glu · Leu · Tyr · Ser
Glu
Phe

34

Ile · Ala · Trp · Leu · Val · Arg · Gly · Arg · Gly

Amino acid substitution prevents C-18 fatty acid binding at wrong site[1]

+ Absorption enhancer (SNAC)

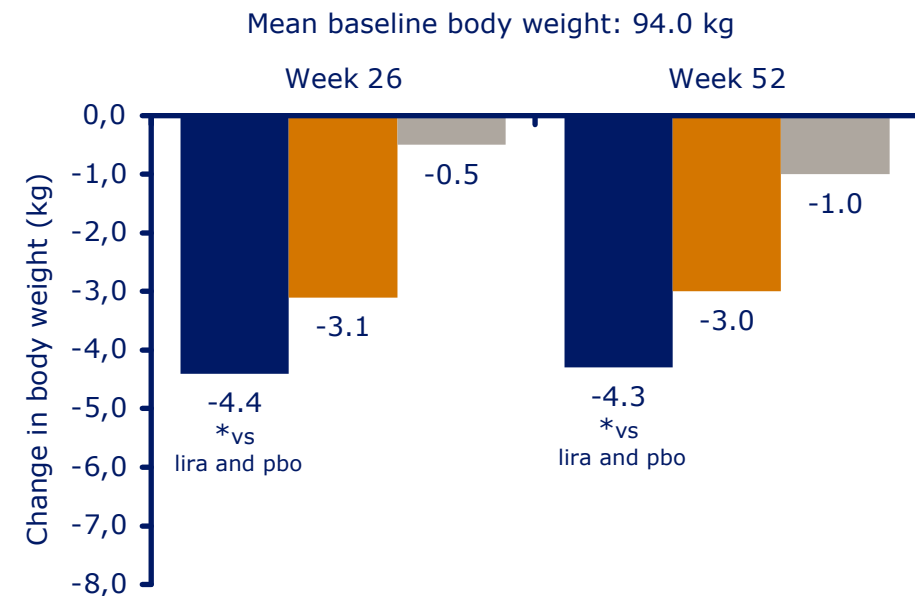Increase bioavailability of oral administration[5]

Oral semaglutide significantly reduced body weight compared with injectable liraglutide and placebo

PIONEER 4 (patients with type 2 diabetes)


Observed change in body weight

Mean baseline body weight: 94.0 kg
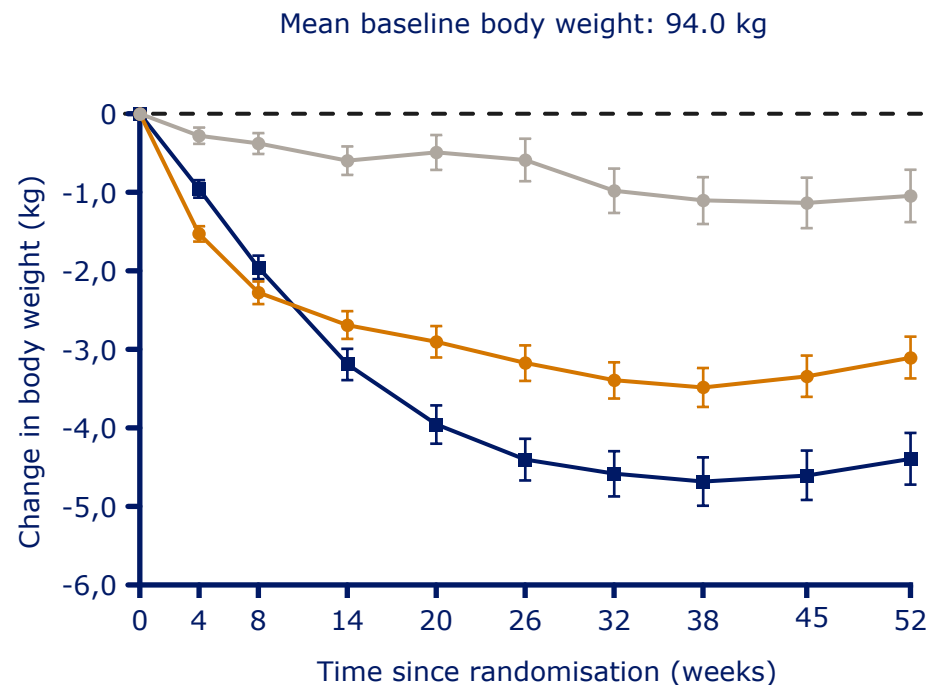
Estimated body weight change from baseline

Mean baseline body weight: 94.0 kg

Week 26 — -4.4 *vs lira and pbo, -3.1, -0.5

Week 52 — -4.3 *vs lira and pbo, -3.0, -1.0

Legend: ■ Oral semaglutide 14 mg ■ Liraglutide 1.8 mg ■ Placebo

# Development of Cagrilintide, a Long-Acting Amylin Analogue

Thomas Kruse,* Jakob Lerche Hansen, Kirsten Dahl, Lauge Schäffer, Ulrich Sensfuss, Christian Poulsen, Morten Schlein, Ann Maria Kruse Hansen, Claus Bekker Jeppesen, Charlotta Dornonville de la Cour, Trine Ryberg Clausen, Eva Johansson, Simone Fulle, Rikke Bjerring Skyggebjerg, and Kirsten Raun
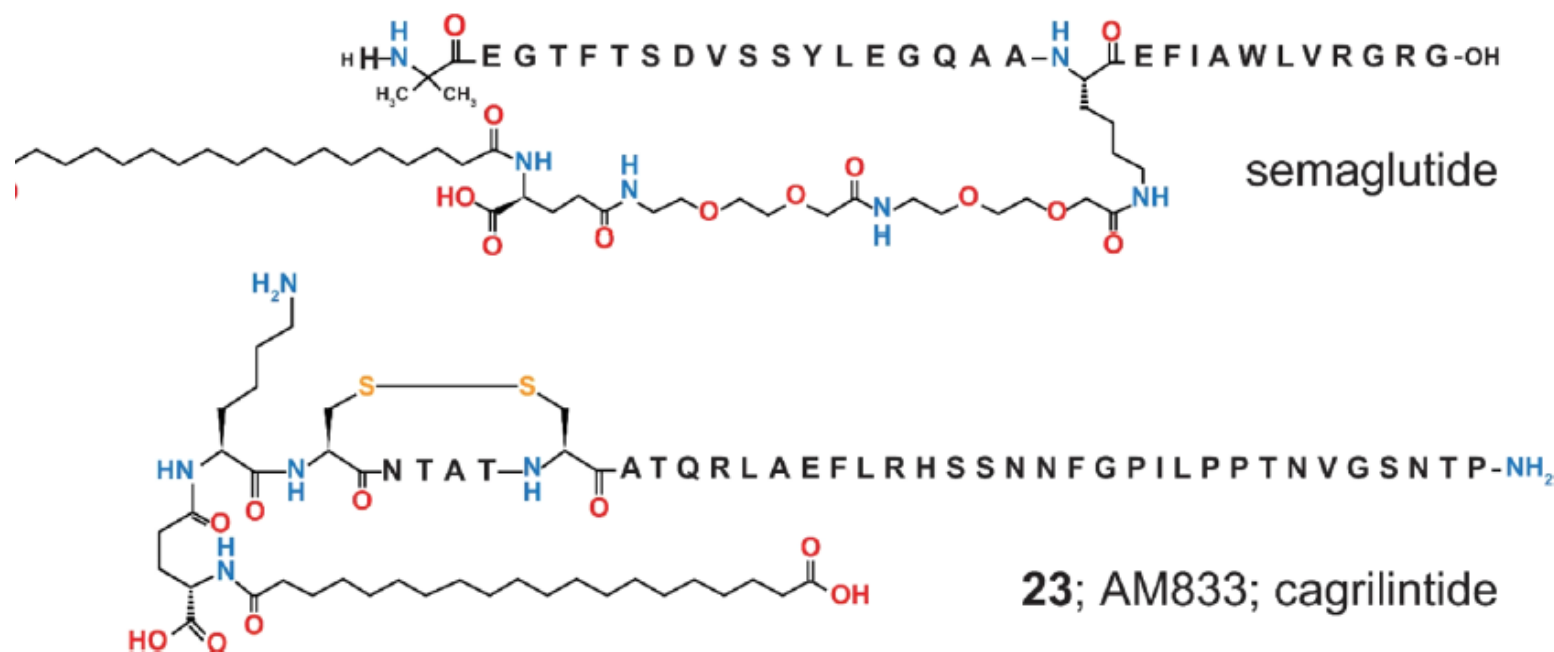
Safety, tolerability, pharmacokinetics, and pharmacodynamics of concomitant administration of multiple doses of cagrilintide with semaglutide 2·4 mg for weight management: a randomised, controlled, phase 1b trial
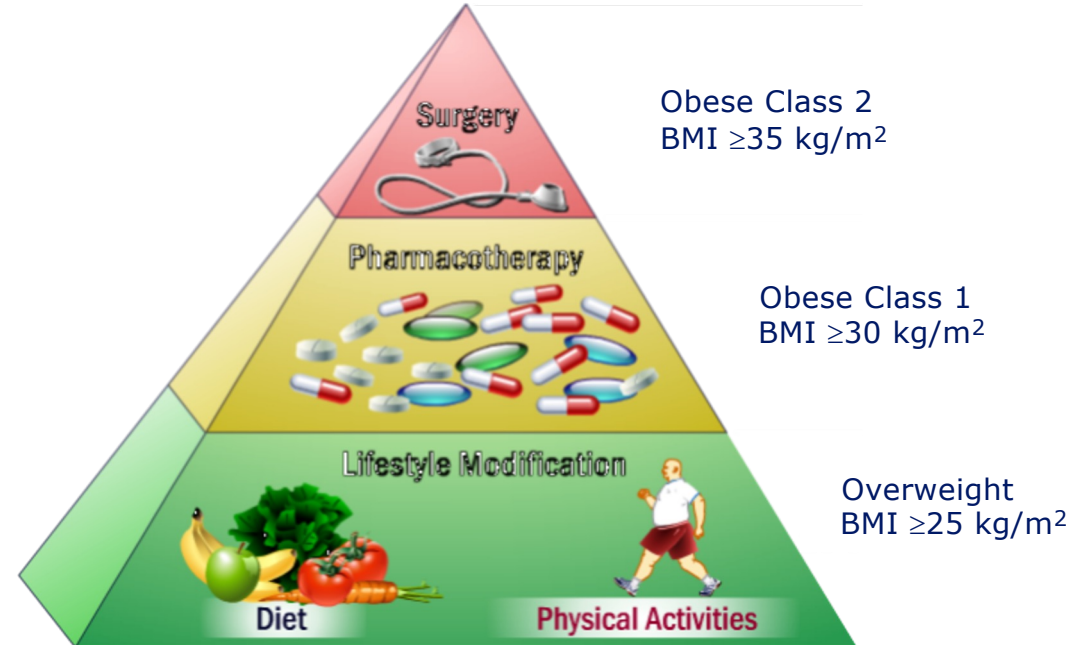
Lone B Enebo, Kasper K Berthelsen, Martin Kankam, Michael T Lund, Domenica M Rubino, Altynai Satylganova, David C W Lau
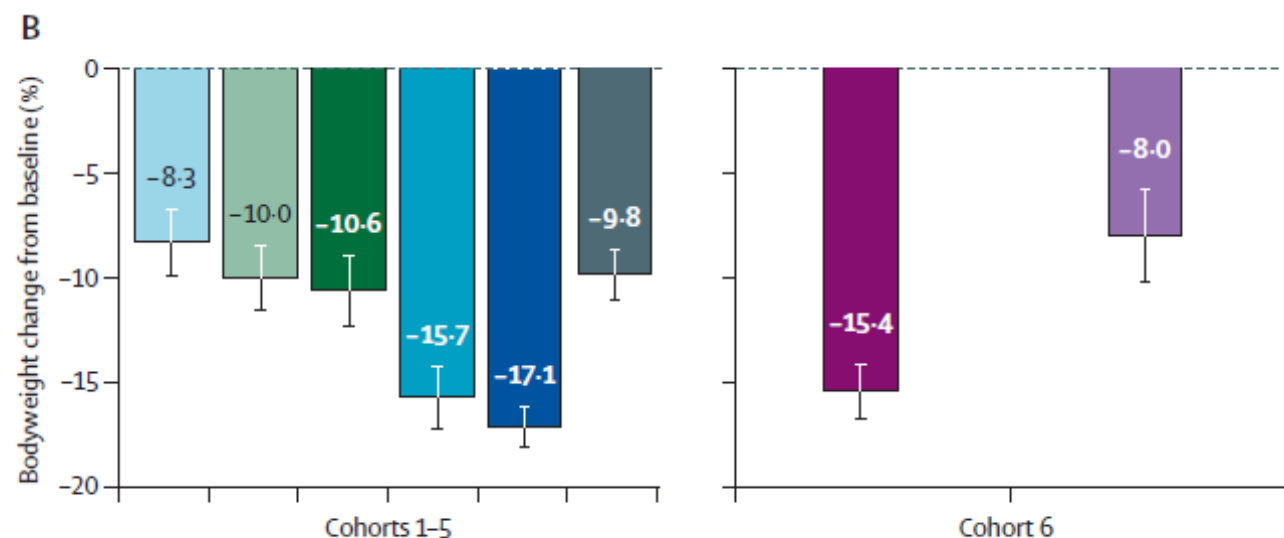
Is TIRZEPATIDE the golden bullet ?
Pharmacotherapy Helps with Adherence to a Lifestyle Change

1. Increase the **number** of patients responding to lifestyle modification

2. Increase the **magnitude** of the response

3. Increase the **duration** of the response

Surgery — Obese Class 2 BMI ≥35 kg/m^2

Pharmacotherapy — Obese Class 1 BMI ≥30 kg/m^2

Lifestyle Modification — Overweight BMI ≥25 kg/m^2

Diet   Physical Activities

Why Should Cardiologists Care About Obesity?

Obesity is a key risk factor for CVD, T2DM and adverse clinical outcomes

Affects a significant and increasing proportion of patients in cardio/diabetes practice

New drugs result in substantial weight loss (> 15% and more) with reduction of CVRFs and potential direct benefits on diabetes control and CVD outcome

Obesity should be prevented and treated early for future gain…

There is a fascinating future perspective for non-surgical obesity treatment

Thank you for your attention