Pharmacotherapy for Obesity

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Disclosures

I have relevant relationships with ineligible companies to disclose within the past 24 months.

- Advisory Board for Novo Nordisk and WW
- Consultant for Pfizer, Altimmune, Lilli
- Research for Epitomee

Educational Objectives

At the conclusion of this session, participants should be able to:

- Define obesity as a disease
- Explain the rationale for pharmacotherapy
- List currently available anti-obesity medications
- Discuss emerging therapies

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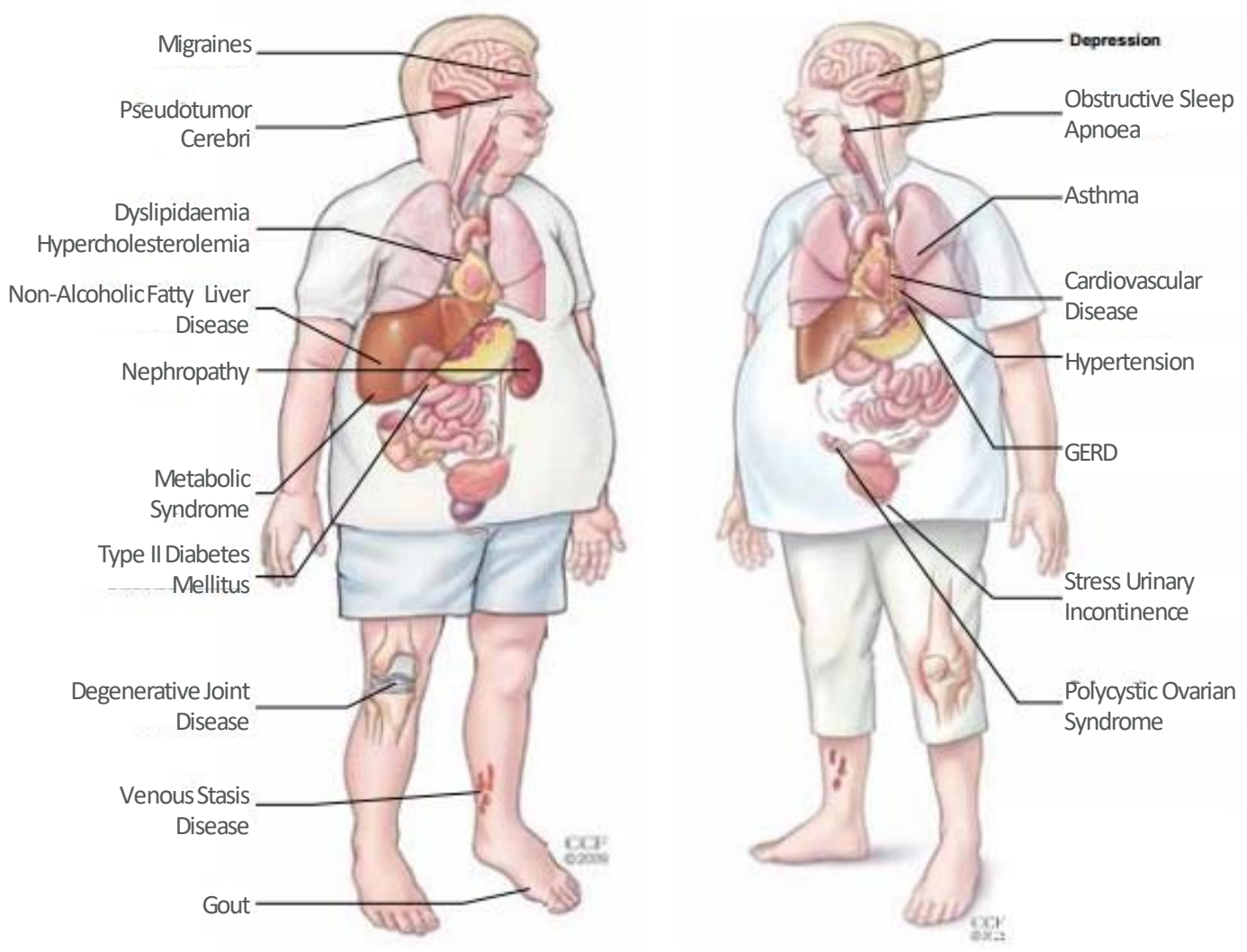
Photo Credit Source: U Conn Rudd Center for Food Policy & Obesity

Obesity affects every organ system



Need to change the paradigm from treating separate medical problems to addressing the underlying cause of multiple medical problems

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GERD, gastroesophageal reflux disorder

Image courtesy: Adapted from Cleveland clinic (available here)

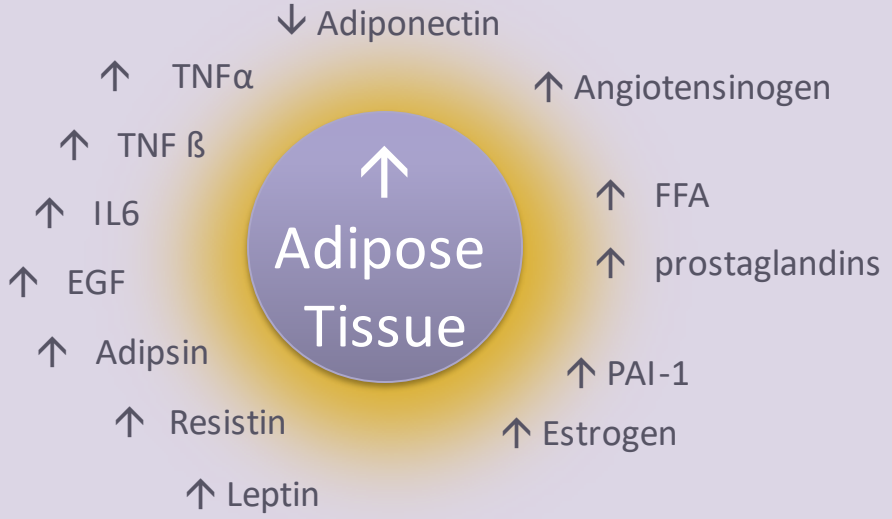
The Pathology of Obesity

Energy Balance Dysregulation

Energy intake

Energy expenditure

Organ System Impairment



LIPOTOXICITY

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Energy Balance Dysregulation

Energy intake

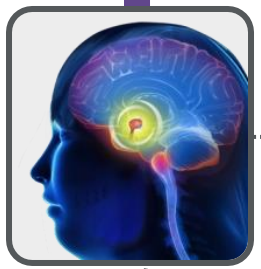
Energy expenditure

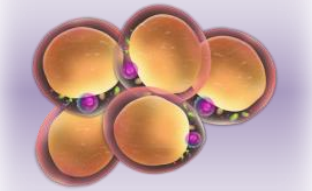
Hedonic input

Heightened palatability or pleasure from food

Environment

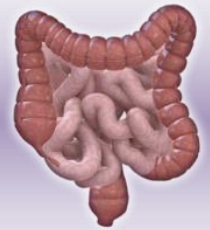
Inactive lifestyle, psychosocial factors, sleep deprivation, etc.



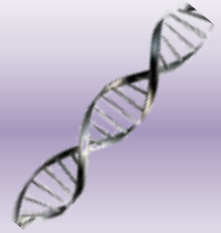


Adipose tissue

Pancreas



Gut



Genetics

Medications

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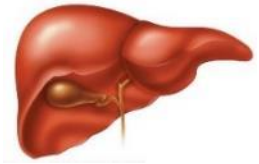
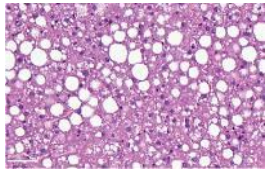
1. Badman, Flier. *Science* 2005;307:1909–14; 2. US Department of Health and Human Services, 1998. NIH Publication No. 98-4083

Weight loss improves obesity-related metabolic dysfunction

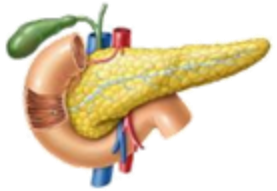
Benefits of Weight Loss



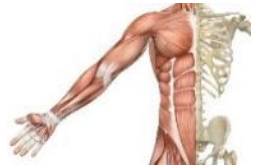
Liver insulin sensitivity



Liver triglycerides

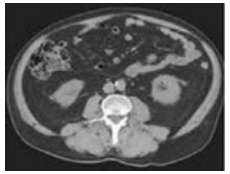


β-cell function

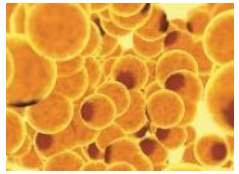


Muscle insulin sensitivity

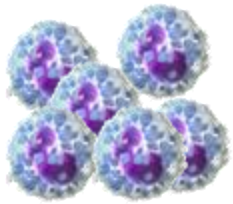
Gene expression in SC adipose



Abdominal adipose tissue



Adipose insulin sensitivity



Inflammatory markers

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Magkos et al. *Cell Metabolism.* 2016;23:591-601.

Weight loss improves obesity related comorbidities

Benefits of 5–10% weight loss

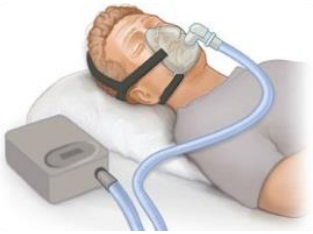
- Reduction in risk of type 2 diabetes[1]

- Reduction in CV mortality[2]

- Improvements in blood lipid profile[3]

- Improvements in blood pressure[4]

- Improvements in severity of obstructive sleep aponea[5,6]



- Improvements in health-related quality of life[7,8]

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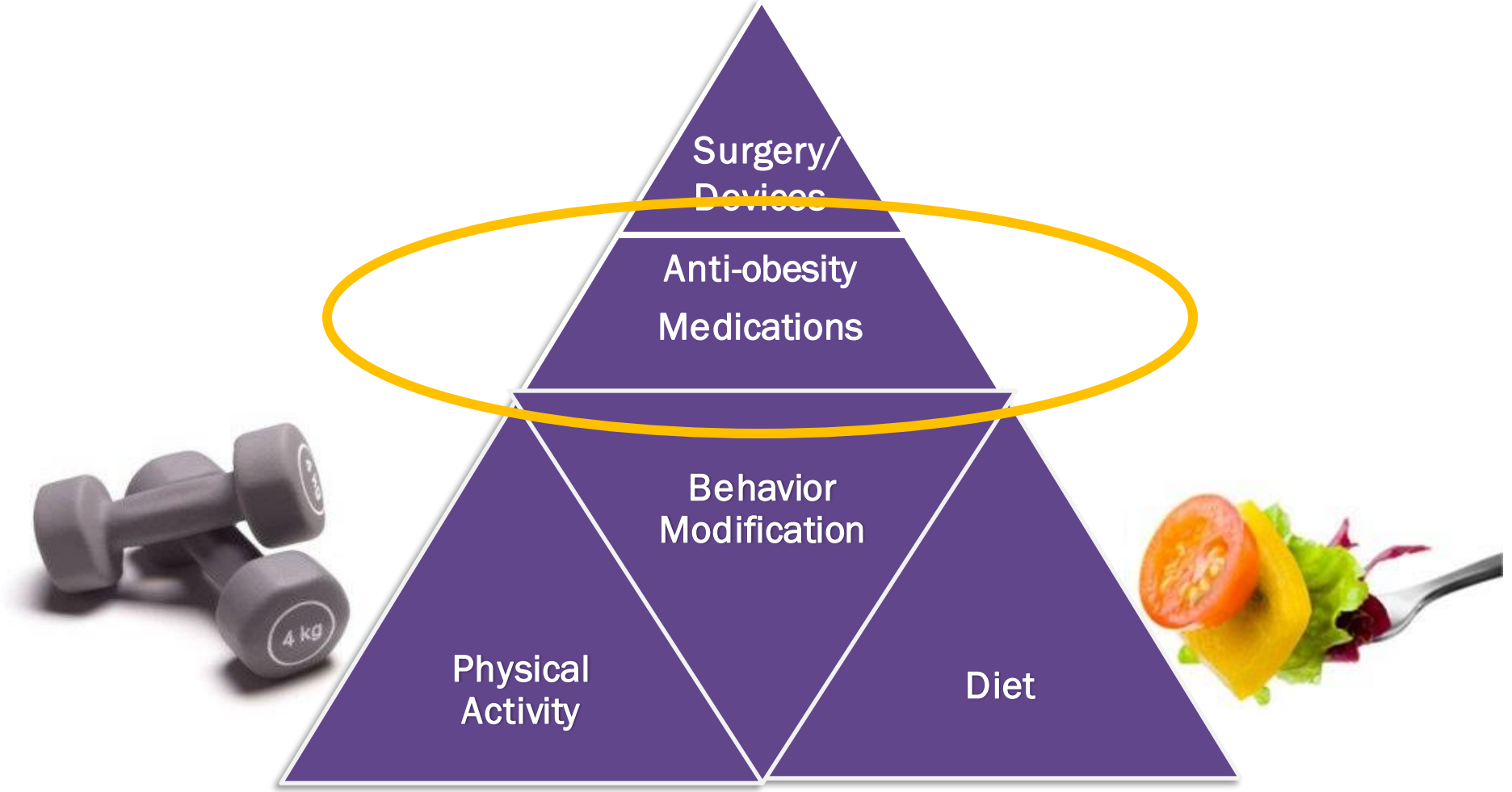
1. Knowler *et al. N Engl J Med* 2002;346:393–403; 2. Li *et al. Lancet Diabetes Endocrinol* 2014;2:474–80; 3. Datillo *et al. Am J Clin Nutr* 1992;56:320–8; 4. Wing *et al. Diabetes Care* 2011;34:1481–6; 5. Foster *et al. Arch Intern Med* 2009;169:1619–26; 6. Kuna *et al. Sleep* 2013;36:641–9; 7. Warkentin *et al. Obes Rev* 2014;15:169–82; 8. Wright *et al. J Health Psychol* 2013;18:574–86

Components of an Effective Obesity Management Program



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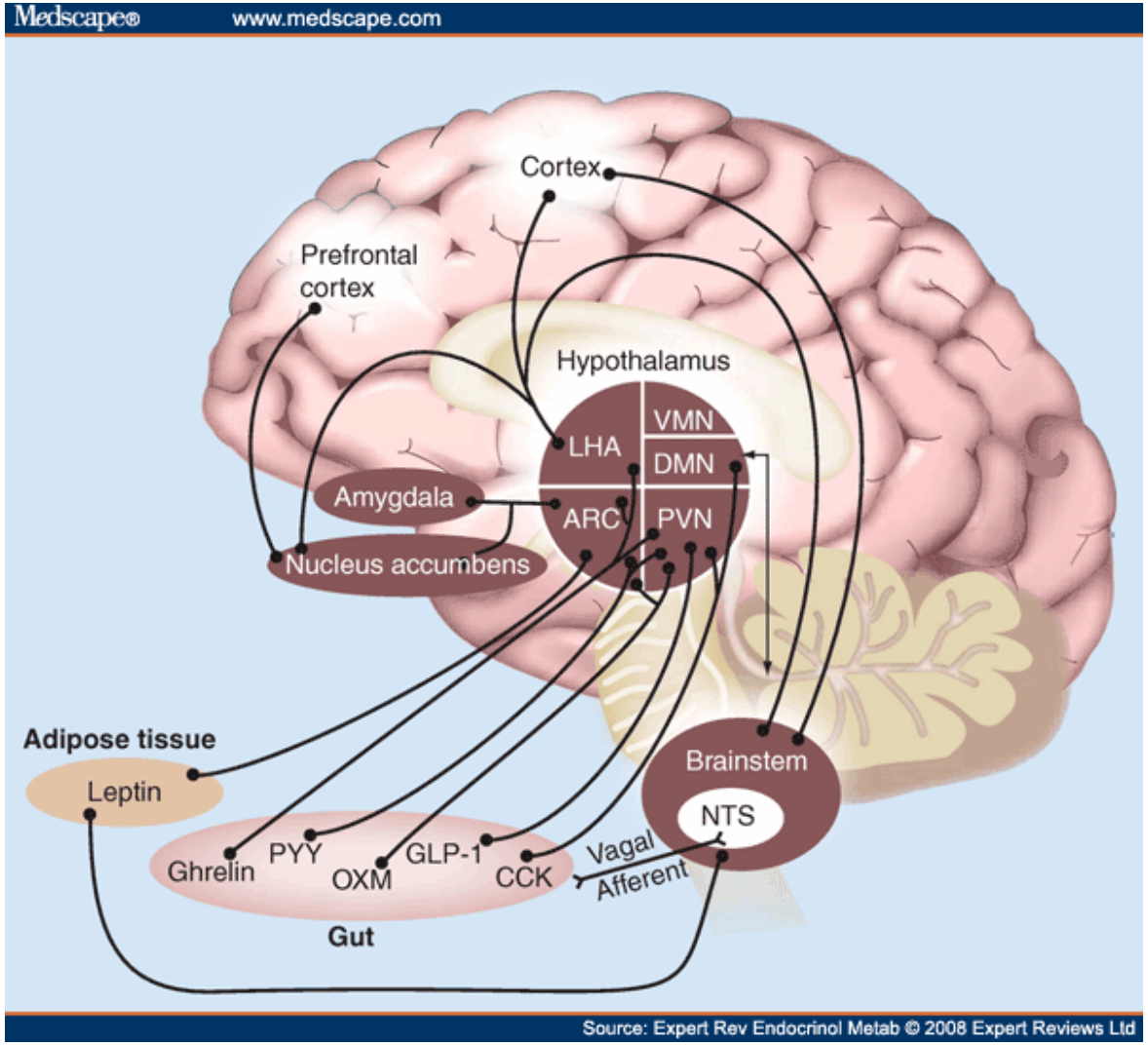
Appetite regulation and the gut-brain axis



GUT

PYY= peptide YY

GLP-1 = Glucagon-like peptide 1

OXM = Oxyntomodulin

CCK = Cholecystokinin

BRAIN

LHA = lateral hypothalamic area

ARC = arcuate nucleus

VMN = ventromedial hypothalamus

DMN = dorsomedial hypothalamic nucleus

PVN = paraventricular nucleus

NTS = nucleus tractus solitarius

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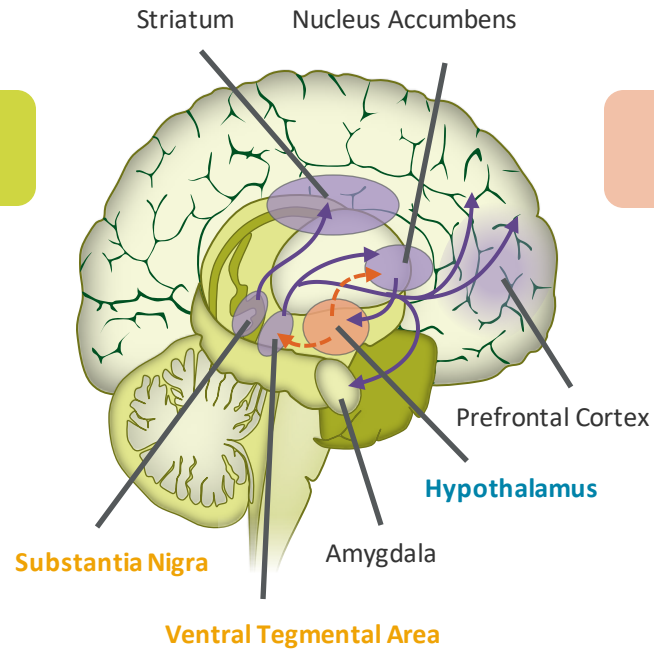
Two CNS Pathways Play a Key Role in Regulating Eating Behavior, Appetite, Cravings, and Weight

Homeostatic System
Hunger / Satiety

- Primarily driven by the arcuate nucleus of the **hypothalamus**
- Detection and integration of energy state information
  - Glucose, leptin, insulin
- Lateral hypothalamus projects to the VTA, and receives input from the nucleus accumbens



Hedonic or Reward System

- Dopaminergic pathways from the **VTA or substantia nigra** to regions such as:
  - Striatum (movement, reward salience)
  - Nucleus accumbens (reward, addiction)
  - Prefrontal cortex (decision making, executive function)
  - Amygdala (memory, emotion)

CNS=central nervous system; VTA=ventral tegmental area.

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Billes SK, et al. Pharmacol Res. 2014;84:1-11.

Components of appetite

Hunger

Drive to consume

Satiety

End state of satisfaction

(between-meal inhibition)

Fullness

Physical feeling experienced in the gut

Wanting

Motivation to consume a specific food (craving)

Satiation

Negative feedback, leading to meal termination (within-meal inhibition)

Liking (hedonic)

Sensory pleasure elicited by contact with food

Prospective food consumption

How much an individual feels they would like to eat

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Blundell *et al. Obes Rev* 2010;11:251–270; van Can *et al. Int J Obes* 2014;38:784–93

What is the Primary Purpose of Adjunctive Medications used in Obesity Treatment?

"The rationale for use of medications is to help patients adhere to a lower calorie diet more consistently in order to achieve more sufficient weight loss and health improvements when combined with increased physical activity."

Jensen MD, et al. *Circulation*. 2014;129(25 Suppl 2):S102-38.

Indicated for patients with a BMI ≥30 kg/m^2 or a BMI ≥27 kg/m^2 associated with a co-morbidity

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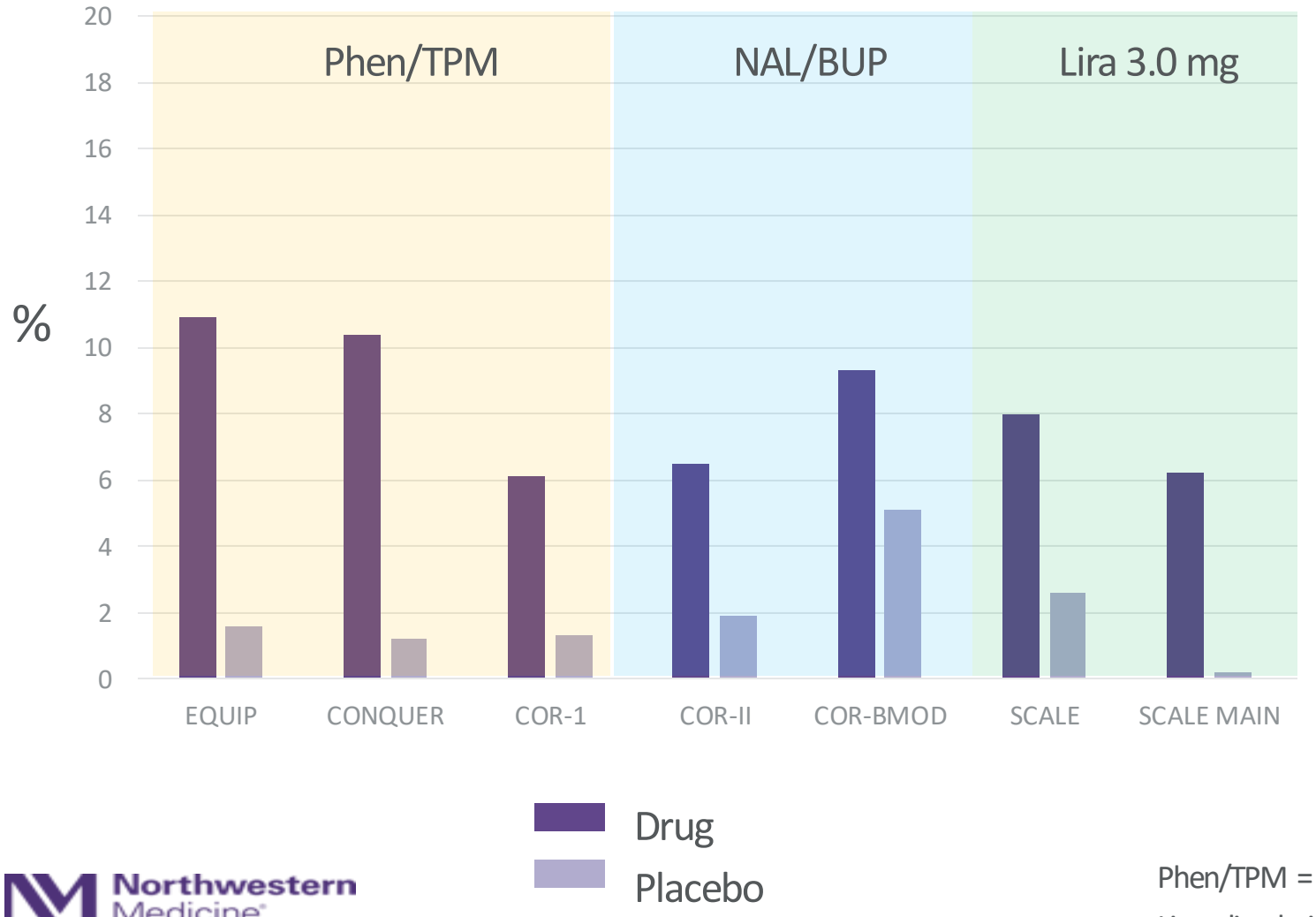
FDA Approved Medications for Chronic Weight Management

Agents	Mechanism of Action	Effect	Approval Date
Orlistat (Xenical® or Alli®)	• Pancreatic lipase inhibition	• Reduces fat absorption	• 1999
Phentermine	• Sympathomimetic	• Appetite regulation	• 1959
Phentermine/topiramate ER (Qsymia®)	• Sympathomimetic • Anticonvulsant (GABA receptor modulation, carbonic anhydrase inhibition, glutamate antagonism)	• Appetite regulation	• 2012
Naltrexone/bupropion SR (Contrave®)	• Opioid receptor antagonist • Dopamine/noradrenaline reuptake inhibitor	• Appetite regulation	• 2014
Liraglutide (Saxenda®)	• GLP-1 receptor agonist	• Appetite regulation	• 2014
Semaglutide (Wegovy™)	• GLP-1 receptor agonist	• Appetite regulation	• 2021

Percent Weight Loss (Drug versus Placebo)



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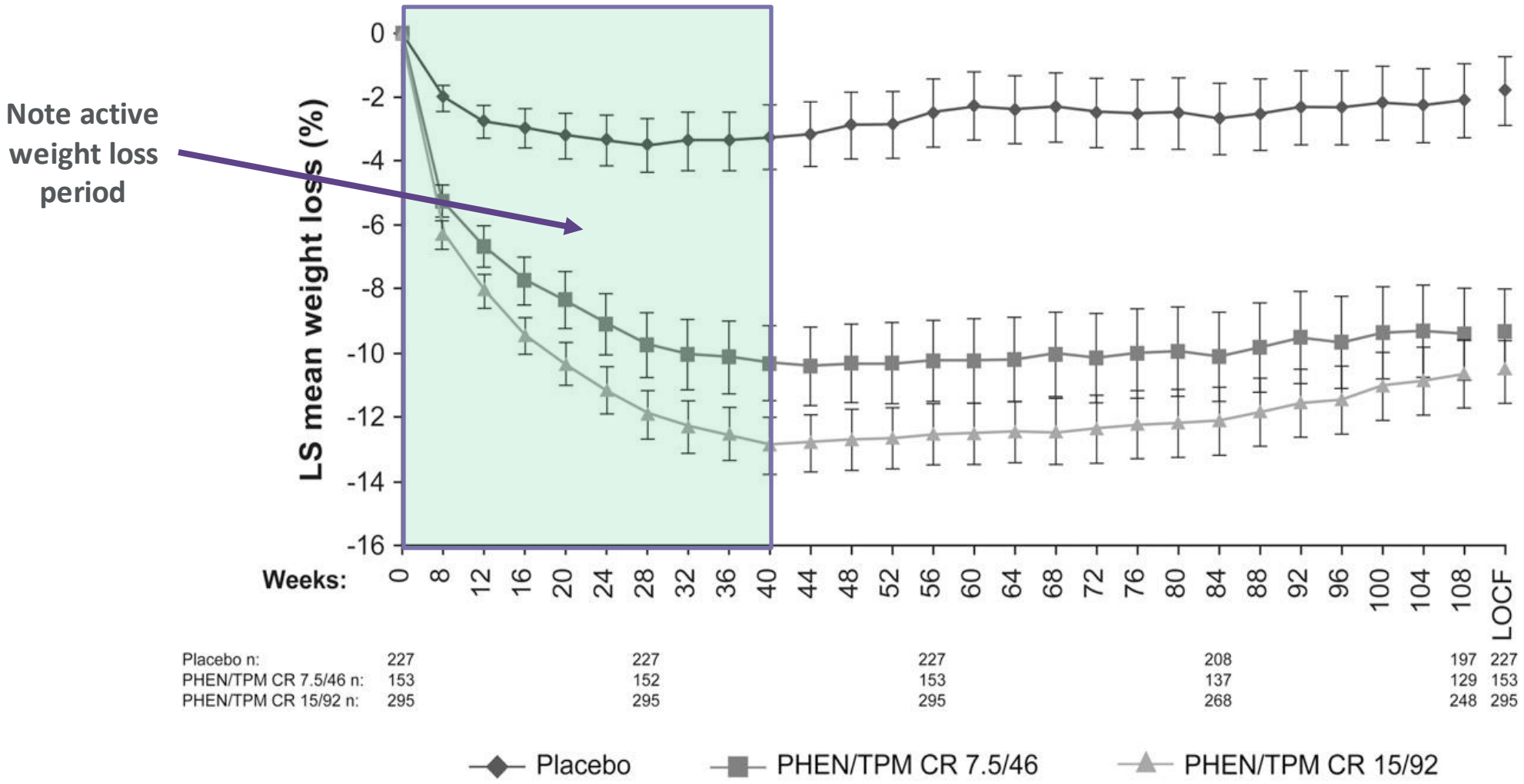
Phen/TPM = phentermine + topiramate; NAL/BUP = naltrexone + bupropion
Lira = liraglutide; Sema = semaglutide

Long-term Outcomes

2 Years Phentermine/Topiramate: Note Early Response



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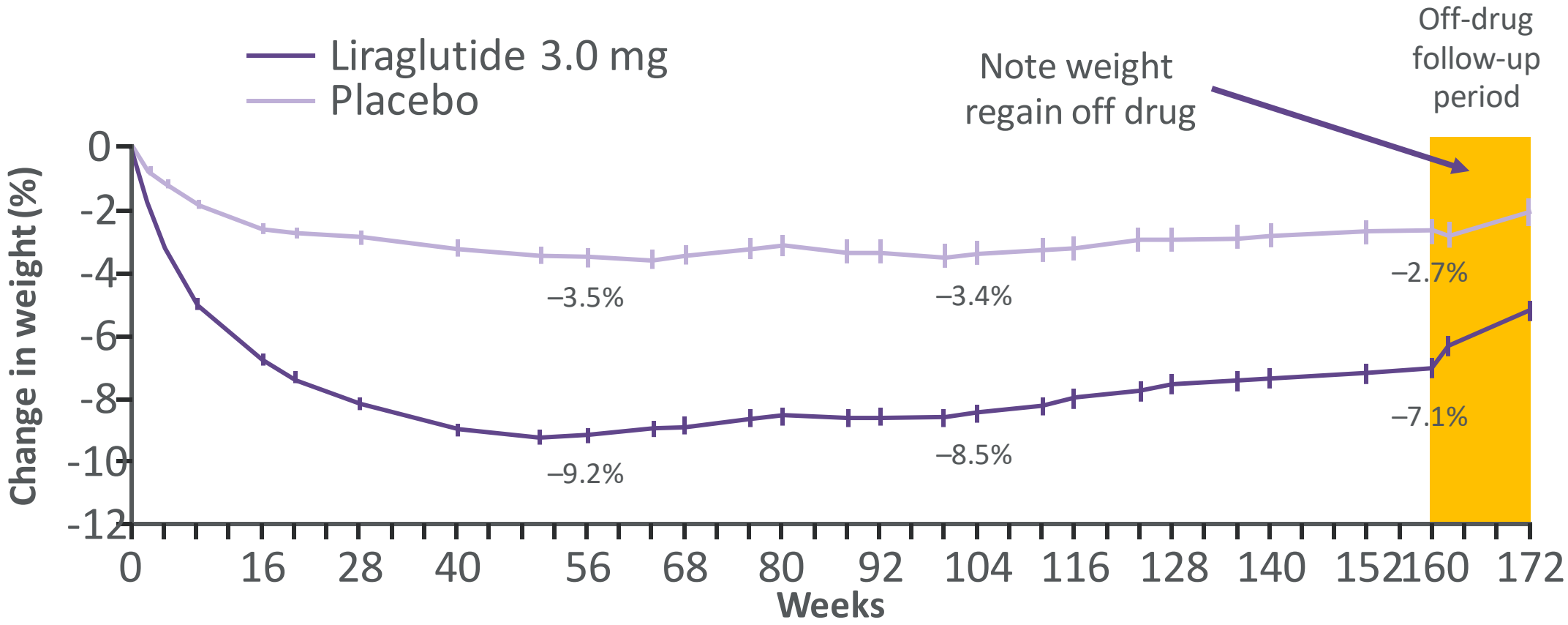
Garvey WT, et al. *Am J Clin Nutr.* 2012;95:297-308.

Three Years of Liraglutide vs Placebo



2254 patients with prediabetes and a BMI of ≥ 30 kg/m^2 or ≥ 27 kg/m^2 and comorbidities

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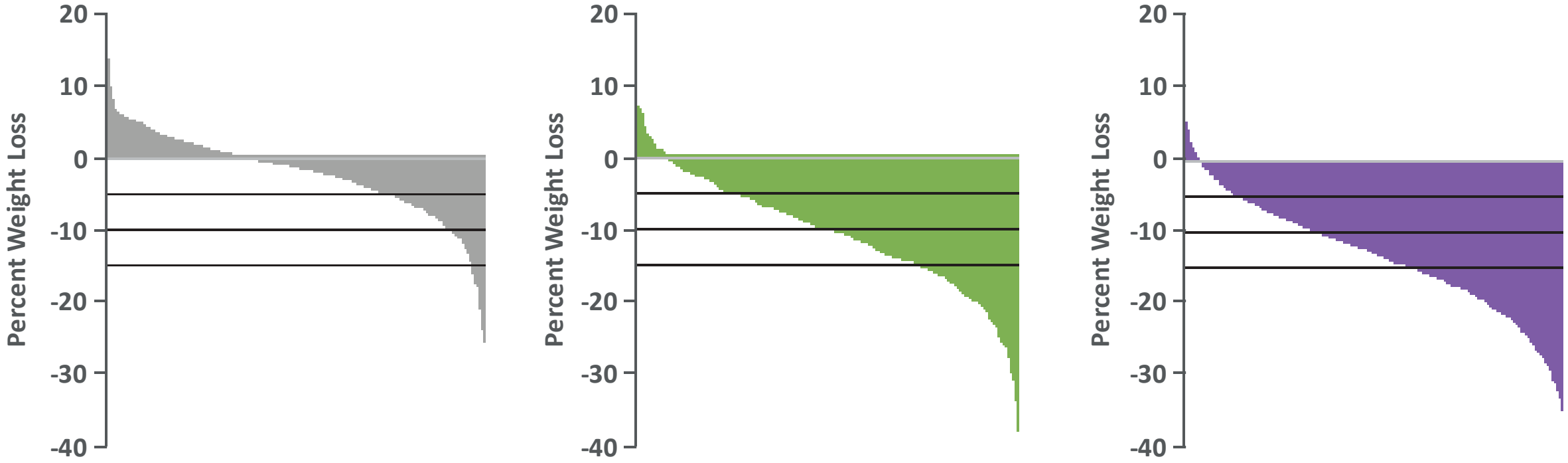
le Roux CW, et al. *Lancet*. 2017;389:1399-1409.

Variable Response to All Weight Loss Therapies *Waterfall Plots Showing Heterogeneity of Treatment Effect*



Each vertical bar represents a single subject experience in subjects completing 56 weeks on study drug

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McCullough PA, Chow DT, Day WW. Weight Loss With Phentermine and Topiramate Extended-Release in Obese and Overweight Subjects Over 1 Year. Presented at the 28th National Conference of the American Association of Nurse Practitioners. June 19-23, 2013.

Improvements in Risk Factors and Comorbidities

	Orlistat	Lorcaserin	Phentermine/ topiramate ER	Naltrexone/ bupropion SR	Liraglutide 3.0 mg	Semaglutide 2.4 mg
WC	↓	↓	↓	↓	↓	↓
BP	↓	↓	↓	↑	↓	↓
LDL	↓↓	↓	↓	↓	↓	↓
HDL	↑	↑	↑	↑	↑	↑
TG	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓
A1C	↓	↓↓	↓	↓	↓↓↓	↓↓↓
HR	↓	↓	-	↑	↑	↑
Diabetes	↓↓	↓↓	↓↓	↓	↓↓↓	↓↓↓

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BP = blood pressure; HDL = high-density lipoprotein; HR = heart rate; LDL = low-density lipoprotein; TG = triglycerides; WC = waste circumference.
Adipex-P (phentermine) prescribing information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/088023s037lbl.pdf; Xenical (orlistat) prescribing information. http://www.gene.com/download/pdf/xenical_prescribing.pdf; Qsymia (phentermine/topiramate ER) prescribing information. https://qsymia.com/pdf/prescribing-information.pdf; Belviq (lorcaserin) prescribing information. www.belviq.com/documents/Belviq_Prescribing_information.pdf; Contrave (naltrexone SR/bupropion SR) prescribing information. http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/200063s000lbl.pdf; Saxenda (liraglutide 3.0 mg) prescribing information. http://novo-pi.nnittest.com/saxenda.pdf.

Choosing Between Medication Options

Drug factors

- Contraindications
- Dual benefits
- Studied populations

Patient factors

- Patient preferences
- Adverse events
- Prior experiences
- Access

Physician factors

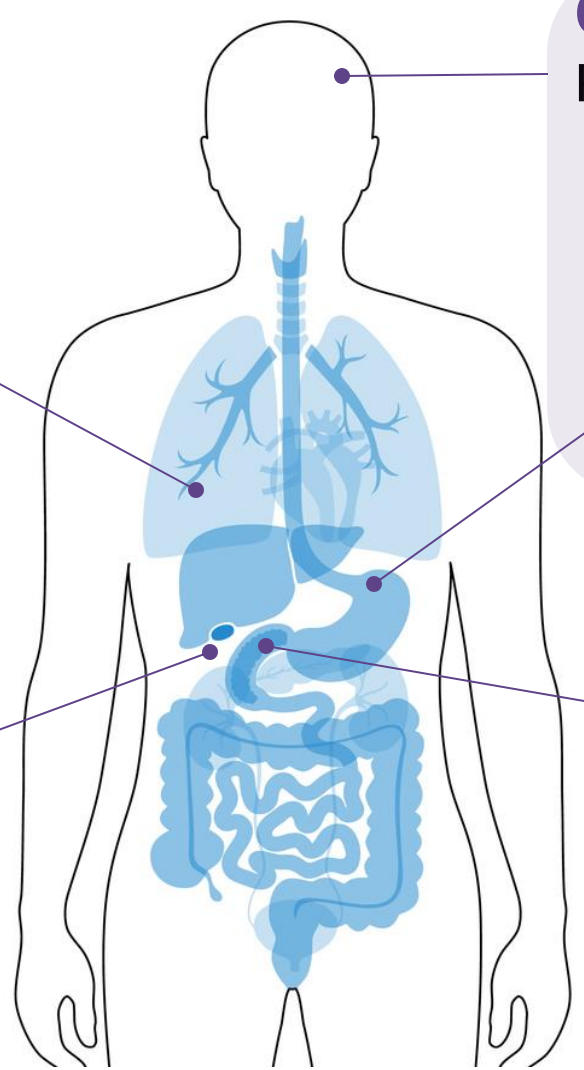
- Provider knowledge/comfort

Emerging Anti-Obesity Pharmacological Therapies

Category	Mechanism	Drug	Stage of Development
Hormonal	GLP-1 receptor agonist	Semaglutide	Approved 2021*
	GLP-1/GIP receptor agonist	Tirzepatide	Phase 3
	GLP-1/glucagon receptor agonist		Phase 2
	GLP-1/GIP/glucagon		Phase 2
	Amylin analogue	Cagrilintide	Phase 2
	GLP-1/amylin analogue		Phase 1
	Ghrelin antagonist		Phase 1
	PYY analogue		Phase 1
	GLP-1 small molecule receptor agonist	Danuglipron	Phase 1
Neuropeptide	Melanocortin-4 receptor agonist	Setmelanotide	Approved 2020 for rare genetic conditions*
Enzyme inhibition	Sodium-glucose transporter-1 and 2 (SGLT1, SGLT2 inhibitor)	Licoglifloxin	Phase 2
Monoamine receptor uptake inhibition	Noradrenaline, dopamine, serotonin update inhibitor	Tesofensine	Phase 3
Monoclonal antibody	Activin type II receptor antagonist	Bimagrumab	Phase 2

*selected approval according to local regulatory agencies

GLP-1: An Incretin Hormone



Central nervous system
Promotes appetite control

Stomach
Decrease gastric emptying

Liver
↓ glucagon reduces hepatic glucose output

Alpha-cells
↓ glucagon secretion post-meal

Beta-cells
Enhances glucose-dependent insulin secretion and beta-cell functional mass

GLP-1: An Incretin Therapy

Targets the incretin pathway = "**incretins**"

GLP-1 RAs (glucagon like peptide-1 receptor agonists)

- Dulaglutide
- Exenatide
- Liraglutide
- Lixisenatide
- Semaglutide

DPP-4 inhibitors (dipeptidyl peptidase-4 inhibitors)

- Alogliptin
- Linagliptin
- Saxagliptin
- Sitagliptin

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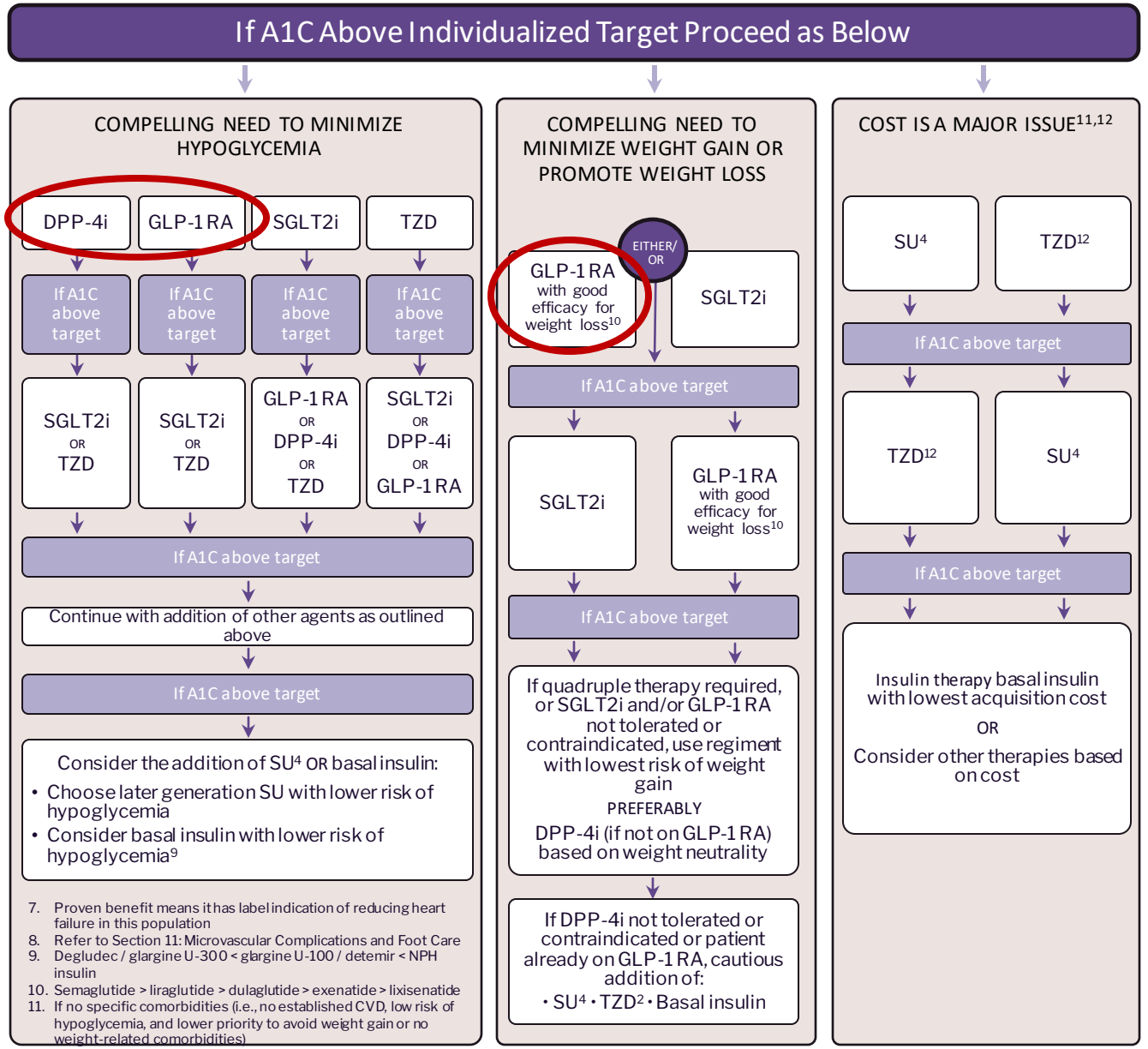
https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed July 15, 2020.

Use of Incretin-based Medications in T2DM

- For glycemic control
- After metformin
- To minimize risk hypoglycemia
- For weight management (GLP-1 RA)
- To reduce major adverse cardiovascular event (MACE) risk



7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)

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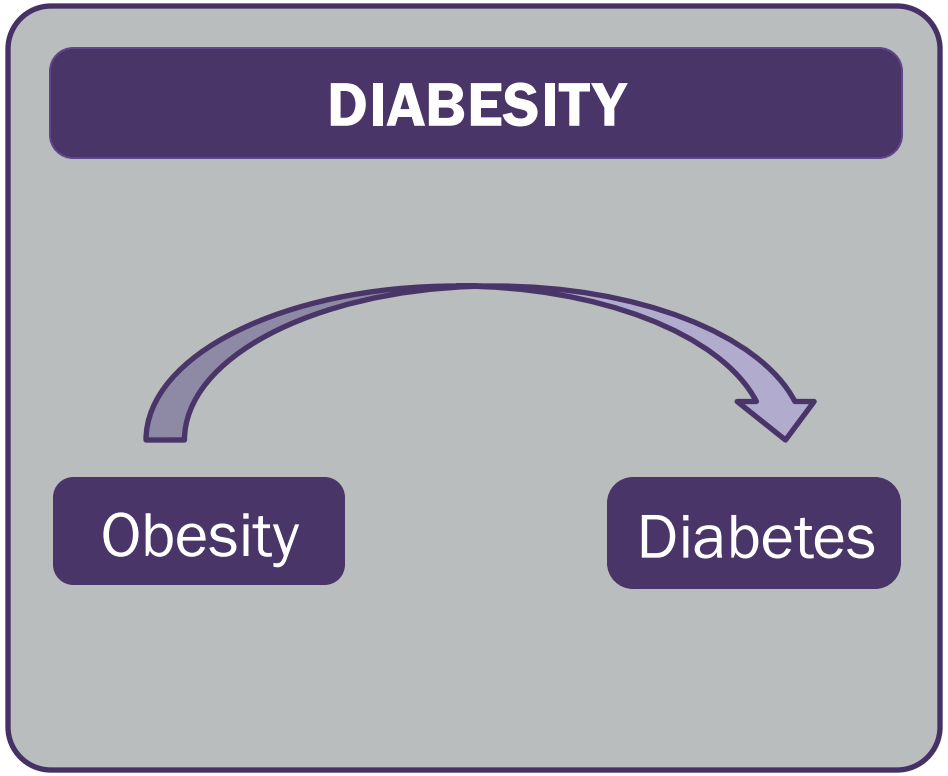
Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes 2021. *Diabetes Care.* 2021;44(Suppl. 1):S111–S124.

Syndemic

[syn-dem-ic] noun

A syndemic or synergistic epidemic involves the clustering of 2 or more diseases within a population; the biological, social, and psychological interaction of those diseases; and the large-scale social forces that precipitate disease clustering in the first place.



https://iaphs.org/syndemics-population-health-qa-anthropologist-emily-mendenhall/syndemic-inforgraphic/

Semaglutide Effect in People with Obesity (STEP) Phase 3a Program

STEP 1

The NEW ENGLAND JOURNAL of MEDICINE

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 18, 2021 VOL. 384 NO. 11

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*

ABSTRACT

BACKGROUND

Obesity is a global health challenge with few pharmacologic options. Whether adults with obesity can achieve weight loss with once-weekly semaglutide at a dose of 2.4 mg as an adjunct to lifestyle intervention has not been confirmed.

METHODS

In this double-blind trial, we enrolled 1961 adults with a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or greater (≥27 in persons with ≥1 weight-related coexisting condition), who did not have diabetes, and randomly assigned them, in a 2:1 ratio, to 68 weeks of treatment with once-weekly subcutaneous semaglutide (at a dose of 2.4 mg) or placebo, plus lifestyle intervention. The coprimary end points were the percentage change in body weight and weight reduction of at least 5%. The primary estimand (a precise description of the treatment effect reflecting the objective of the clinical trial) assessed effects regardless of treatment discontinuation or rescue interventions.

RESULTS

The mean change in body weight from baseline to week 68 was −14.9% in the semaglutide group as compared with −2.4% with placebo, for an estimated treatment difference of −12.4 percentage points (95% confidence interval [CI], −13.4 to −11.5; P<0.001). More participants in the semaglutide group than in the placebo group achieved weight reductions of 5% or more (1047 participants [86.4%] vs. 182 [31.5%]), 10% or more (808 [69.1%] vs. 69 [12.0%]), and 15% or more (612 [50.5%] vs. 28 [4.9%]) at week 68 (P<0.001 for all three comparisons of odds). The change in body weight from baseline to week 68 was −15.3 kg in the semaglutide group as compared with −2.6 kg in the placebo group (estimated treatment difference, −12.7 kg; 95% CI, −13.7 to −11.7). Participants who received semaglutide had a greater improvement with respect to cardiometabolic risk factors and a greater increase in participant-reported physical functioning from baseline than those who received placebo. Nausea and diarrhea were the most common adverse events with semaglutide; they were typically transient and mild-to-moderate in severity and subsided with time. More participants in the semaglutide group than in the placebo group discontinued treatment owing to gastrointestinal events (59 [4.5%] vs. 5 [0.8%]).

CONCLUSIONS

In participants with overweight or obesity, 2.4 mg of semaglutide once weekly plus lifestyle intervention was associated with sustained, clinically relevant reduction in body weight. (Funded by Novo Nordisk; STEP 1 ClinicalTrials.gov number, NCT03548935).

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Kushner at Northwestern University Feinberg School of Medicine, 645 N. Michigan Ave., Suite 530, Chicago, IL 60611, or at rkushner@northwestern.edu.

A complete list of investigators in the STEP 1 trial is provided in the Supplementary Appendix, available at NEJM.org.

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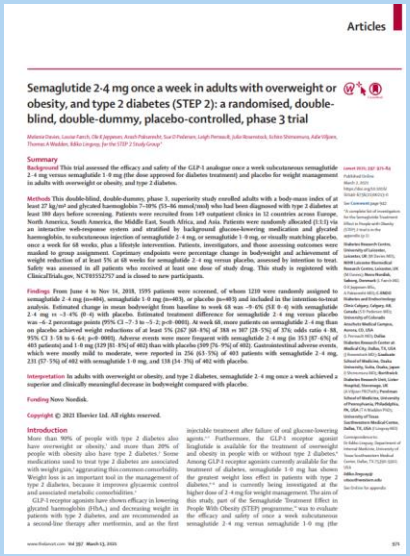
STEP 2

THE LANCET



Articles

Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial

Melanie Davies, Louise Færch, Ole K Jeppesen, Arash Pakseresht, Sue D Pedersen, Leigh Perreault, Julio Rosenstock, Ildiko Shimanoura, Adie Viljoen, Thomas A Wadden, Ildiko Lingvay, *for the STEP 2 Study Group†*

Summary

Background This trial assessed the efficacy and safety of the GLP-1 analogue once a week subcutaneous semaglutide 2·4 mg versus semaglutide 1·0 mg (the dose approved for diabetes treatment) and placebo for weight management in adults with overweight or obesity, and type 2 diabetes.

Methods This double-blind, double-dummy, phase 3, superiority study enrolled adults with a body-mass index of at least 27 kg/m² and glycated haemoglobin 7·0%–10·5% (53–91 mmol/mol) who had been diagnosed with type 2 diabetes at least 180 days before screening. Patients were recruited from 149 outpatient clinics in 12 countries across Europe, North America, South America, the Middle East, South Africa, and Asia. Patients were randomly allocated (1:1:1) via an interactive web-response system and stratified by background glucose-lowering medication and glycated haemoglobin, to subcutaneous injection of semaglutide 2·4 mg, or semaglutide 1·0 mg, or visually matching placebo, once a week for 68 weeks, plus a lifestyle intervention. Patients, investigators, and those assessing outcomes were masked to group assignment. Coprimary endpoints were percentage change in bodyweight and achievement of weight reduction of at least 5% at 68 weeks for semaglutide 2·4 mg versus placebo, assessed by intention to treat. Safety was assessed in all patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, NCT03552757 and is closed to new participants.

Findings From June 4 to Nov 14, 2018, 1595 patients were screened, of whom 1210 were randomly assigned to semaglutide 2·4 mg (n=404), semaglutide 1·0 mg (n=403), or placebo (n=403) and included in the intention-to-treat analysis. Estimated change in mean bodyweight from baseline to week 68 was −9·6% (SE 0·4) with semaglutide 2·4 mg vs −3·4% (0·4) with placebo. Estimated treatment difference for semaglutide 2·4 mg versus placebo was −6·2 percentage points (95% CI −7·3 to −5·2; p<0·0001). At week 68, more patients on semaglutide 2·4 mg than on placebo achieved weight reductions of at least 5% (267 [68·8%] of 388 vs 307 [28·5%] of 376; odds ratio 6·88, 95% CI 5·19 to 9·14; p<0·0001). Adverse events were more frequent with semaglutide 2·4 mg (in 353 [87·4%] of 403 patients) and 1·0 mg (339 [84·1%] of 403) than with placebo (309 [76·9%] of 402). Gastrointestinal adverse events, which were mostly mild to moderate, were reported in 256 (63·5%) of 403 patients with semaglutide 2·4 mg, 235 (57·5%) of 462 with semaglutide 1·0 mg, and 138 (34·3%) of 402 with placebo.

Interpretation In adults with overweight or obesity, and type 2 diabetes, semaglutide 2·4 mg once a week achieved a superior and clinically meaningful decrease in bodyweight compared with placebo.

Funding Novo Nordisk.

Introduction

More than 90% of people with type 2 diabetes also have overweight or obesity,[1] and more than 20% of people with obesity also have type 2 diabetes.[2] Some medications used to treat type 2 diabetes are associated with weight gain,[3] aggravating this common comorbidity. Weight loss is an important tool in the management of type 2 diabetes, because it improves glycaemic control and associated metabolic comorbidities.[4]

GLP-1 receptor agonists have shown efficacy in lowering glycated haemoglobin (HbA_{1c}) and decreasing weight in patients with type 2 diabetes, and are recommended as a second-line therapy after metformin, and as the first injectable treatment after failure of oral glucose-lowering agents.[5,6] Furthermore, the GLP-1 receptor agonist liraglutide is available for the treatment of overweight and obesity in people with or without type 2 diabetes.[7] Among GLP-1 receptor agonists currently available for the treatment of diabetes, semaglutide 1·0 mg has shown the greatest weight loss effect in patients with type 2 diabetes,[8,9] and is currently being investigated at the higher dose of 2·4 mg for weight management. The aim of this study, part of the Semaglutide Treatment Effect in People With Obesity (STEP) programme,[10] was to evaluate the efficacy and safety of once a week subcutaneous semaglutide 2·4 mg versus semaglutide 1·0 mg (the

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STEP 3

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Research

JAMA | Original Investigation

Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults With Overweight or Obesity
The STEP 3 Randomized Clinical Trial

Thomas A. Wadden, PhD; Timothy S. Bailey, MD; Lena K. Billings, MD, MMSc; Melanie Davies, MD; Juan P. Frias, MD; Anna Koroleva, MD; Ildiko Lingvay, MD, MPH, MSCS; Patrick M. O'Neil, PhD; Domenica M. Rubino, MD; Dorthe Skovgaard, MD, PhD; Signe D. K. Wallenstein, MSc; W. Timothy Garvey, MD; for the STEP 3 Investigators

Visual Abstract
Supplemental content

IMPORTANCE Weight loss improves cardiometabolic risk factors in people with overweight or obesity. Intensive lifestyle intervention and pharmacotherapy are the most effective noninvasive weight loss approaches.

OBJECTIVE To compare the effects of once-weekly subcutaneous semaglutide, 2.4 mg vs placebo for weight management as an adjunct to intensive behavioral therapy with initial low-calorie diet in adults with overweight or obesity.

DESIGN, SETTING, AND PARTICIPANTS Randomized, double-blind, parallel-group, 68-week, phase 3a study (STEP 3) conducted at 41 sites in the US from August 2018 to April 2020 in adults without diabetes (N = 611) and with either overweight (body mass index ≥ 27) plus at least 1 comorbidity or obesity (body mass index ≥ 30).

INTERVENTIONS Participants were randomized (2:1) to semaglutide, 2.4 mg (n = 407) or placebo (n = 204), both combined with a low-calorie diet for the first 8 weeks and intensive behavioral therapy (ie, 30 counseling visits) during 68 weeks.

MAIN OUTCOMES AND MEASURES The co-primary end points were percentage change in body weight and the loss of 5% or more of baseline weight by week 68. Confirmatory secondary end points included losses of at least 10% or 15% of baseline weight.

RESULTS Of 611 randomized participants (495 women [81.0%]; mean age 46 years [SD, 11]; body weight 105.8 kg [SD, 22.9], and body mass index 38.0 [SD, 6.7]), 567 (92.8%) completed the trial, and 505 (82.7%) were receiving treatment at trial end. At week 68, the estimated mean body weight change from baseline was −16.0% for semaglutide vs −5.7% for placebo (difference, −10.3 percentage points [95% CI, −12.0 to −8.6]; P < .001). More participants treated with semaglutide vs placebo lost at least 5% of baseline body weight (86.6% vs 43.9%, respectively; P < .001). A higher proportion of participants in the semaglutide vs placebo group achieved weight losses of at least 10% or 15% (75.3% vs 27.0% and 55.8% vs 13.2%, respectively; P < .001). Gastrointestinal adverse events were more frequent with semaglutide (82.8%) vs placebo (63.2%). Treatment was discontinued owing to these events in 3.4% of semaglutide participants vs 0% of placebo participants.

CONCLUSIONS AND RELEVANCE Among adults with overweight or obesity, once-weekly subcutaneous semaglutide compared with placebo, used as an adjunct to intensive behavioral therapy and initial low-calorie diet, resulted in significantly greater weight loss during 68 weeks. Further research is needed to assess the durability of these findings.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03548532

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: A list of the STEP 3 investigators appears in eAppendix 1 in Supplement 1.

Corresponding Author: Thomas A. Wadden, PhD, Perelman School of Medicine at the University of Pennsylvania, 3535 Market St, Ste 3027, Philadelphia, PA 19104 (twadden@pennmedicine.upenn.edu).

STEP 4

JAMA®
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Research

JAMA | Original Investigation

Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity
The STEP 4 Randomized Clinical Trial

Domenica Rubino, MD; Nicola Abdallah Abrahamsson, MD; Melanie Davies, MD; Dan Hesse, PhD; Frank L. Greenway, MD; Camilla Jensen, MSc; Ildiko Lingvay, MD, MPH, MCSI; Ofri Mosenzon, MD; Julio Rosenstock, MD; Miguel A. Rubio, MD; Gottfried Rudofsky, MD; Sayeh Tadayon, MD; Thomas A. Wadden, PhD; Oren Dicker, MD; for the STEP 4 Investigators

Visual Abstract
Multimedia
Related article
Supplemental content

IMPORTANCE The effect of continuing vs withdrawing treatment with semaglutide, a glucagon-like peptide 1 receptor agonist, on weight loss maintenance in people with overweight or obesity is unknown.

OBJECTIVE To compare continued once-weekly treatment with subcutaneous semaglutide, 2.4 mg, with switch to placebo for weight maintenance (both with lifestyle intervention) in adults with overweight or obesity after a 20-week run-in with subcutaneous semaglutide titrated to 2.4 mg weekly.

DESIGN, SETTING, AND PARTICIPANTS Randomized, double-blind, 68-week phase 3a withdrawal study conducted at 73 sites in 10 countries from June 2018 to March 2020 in adults with body mass index of at least 30 (or ≥27 with ≥1 weight related comorbidity) and without diabetes.

INTERVENTIONS A total of 902 participants received once-weekly subcutaneous semaglutide during run-in. After 20 weeks (16 weeks of dose escalation; 4 weeks of maintenance dose), 803 participants (89.0%) who reached the 2.4-mg/wk semaglutide maintenance dose were randomized (2:1) to 48 weeks of continued subcutaneous semaglutide (n = 535) or switched to placebo (n = 268), plus lifestyle intervention in both groups.

MAIN OUTCOMES AND MEASURES The primary end point was percent change in body weight from week 20 to week 68; confirmatory secondary end points were changes in waist circumference, systolic blood pressure, and physical functioning (assessed using the Short Form-36 Version 2 Health Survey, Acute Version [SF-36]).

RESULTS Among 803 study participants who completed the 20-week run-in period (with a mean weight loss of 10.6%) and were randomized (mean age, 46 [SD, 12] years; 634 [79%] women; mean [SD] body weight, 107.2 kg [SD, 22.7 kg]), 787 participants (98.0%) completed the trial and 741 (92.3%) completed treatment. With continued semaglutide, mean body weight change from week 20 to week 68 was −7.9% vs +6.9% with the switch to placebo (difference, −14.8 [95% CI, −16.0 to −13.5] percentage points; P < .001). Waist circumference (−9.7 cm [95% CI, −10.9 to −8.5 cm]), systolic blood pressure (−3.9 mm Hg [95% CI, −5.8 to −2.0 mm Hg]), and SF-36 physical functioning score (2.5 [95% CI, 1.6-3.3]) also improved with continued subcutaneous semaglutide vs placebo (all P < .001). Gastrointestinal events were reported in 49.9% of participants who continued subcutaneous semaglutide vs 26.9% with placebo; similar proportions discontinued treatment because of adverse events with continued semaglutide (2.4%) and placebo (2.2%).

CONCLUSIONS AND RELEVANCE Among adults with overweight or obesity who completed a 20-week run-in period with subcutaneous semaglutide, 2.4 mg once weekly, maintaining treatment with semaglutide compared with switching to placebo resulted in continued weight loss over the following 48 weeks.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03548987

Author Affiliations: Author affiliations are listed at the end of this article.

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Wilding JPH et al. NEJM 2021; doi: 10.1056/NEJMoa2032183. Online ahead of print; Davies M et al. Lancet 2021; doi: 10.1016/S0 140-6736(21)00213-0. Online ahead of print; Wadden TA et al. JAMA 2021; doi: 10.1001/jama.2021.1831. Online ahead of print; Rubino DM et al. JAMA 2021; doi: 10.1001/jama.2021.3224.

The NEW ENGLAND JOURNAL of MEDICINE

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*

N Engl J Med 2021;384:989-1002

Injected Drug Delivers Up to 20% Weight Loss in Trial

U.S. News & WORLD REPORT

'A Game Changer': Drug Brings Weight Loss in Patients With Obesity

In a clinical trial, participants taking semaglutide lost 15 percent of their body weight, on average.

The New York Times

Diabetes medication almost twice as effective as other anti-obesity drugs, researchers say

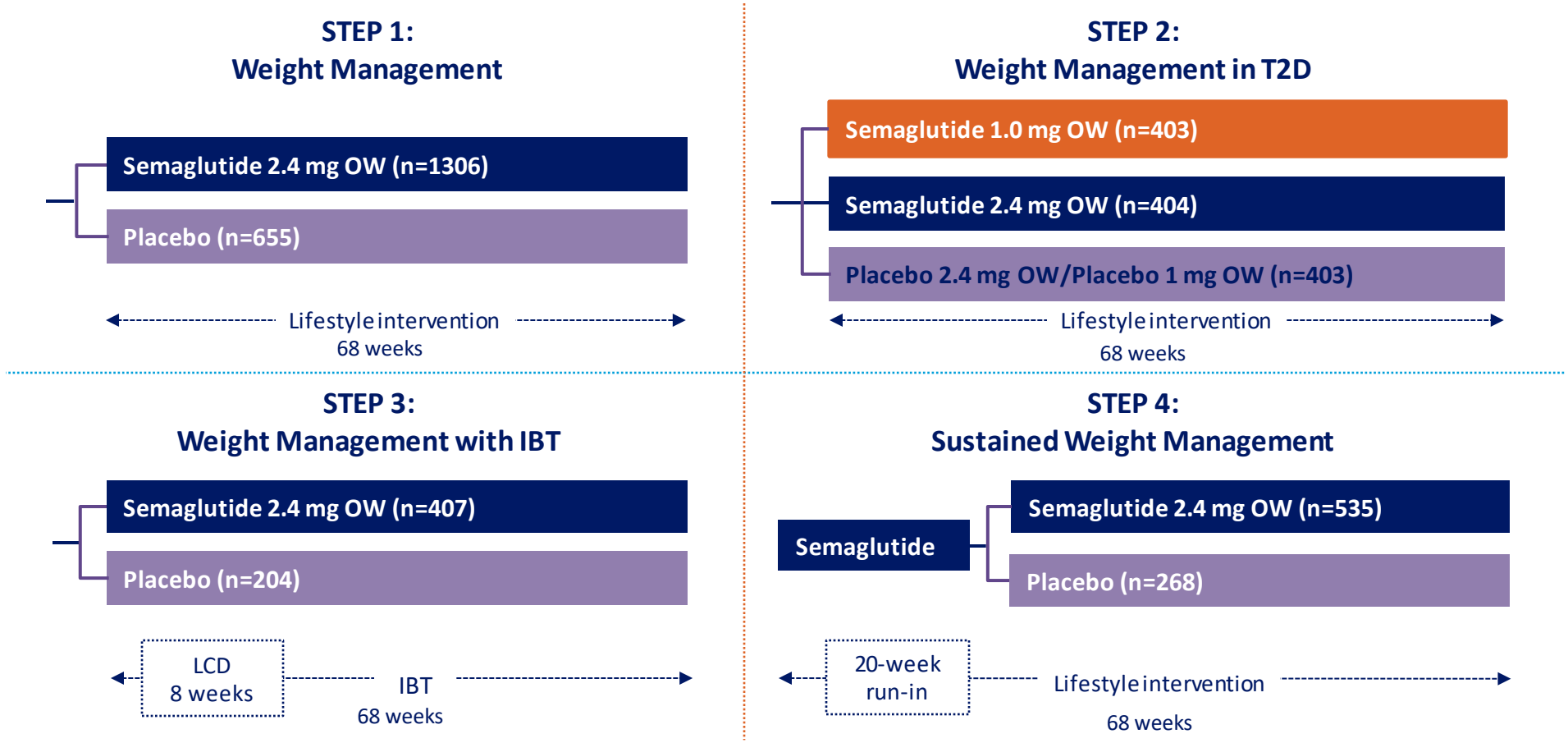
A study from Northwestern Medicine found that, at a higher dosage, the diabetes medication semaglutide is more effective than FDA-approved weight-loss drugs currently on the market.

By Mari Devereaux | Feb 10, 2021, 8:00pm CST

CHICAGO SUN-TIMES

STEP Program: Four Pivotal Trials at a Glance

4700 PATIENTS IN TOTAL



Lifestyle intervention: –500 kcal/day diet + 150 min/week physical activity.
IBT, intensive behavioural therapy; LCD, low-calorie diet; OW, once weekly; STEP, Semaglutide Treatment Effect in People with obesity.
Kushner et al. Obesity (Silver Spring) 2020;28:1050–61.

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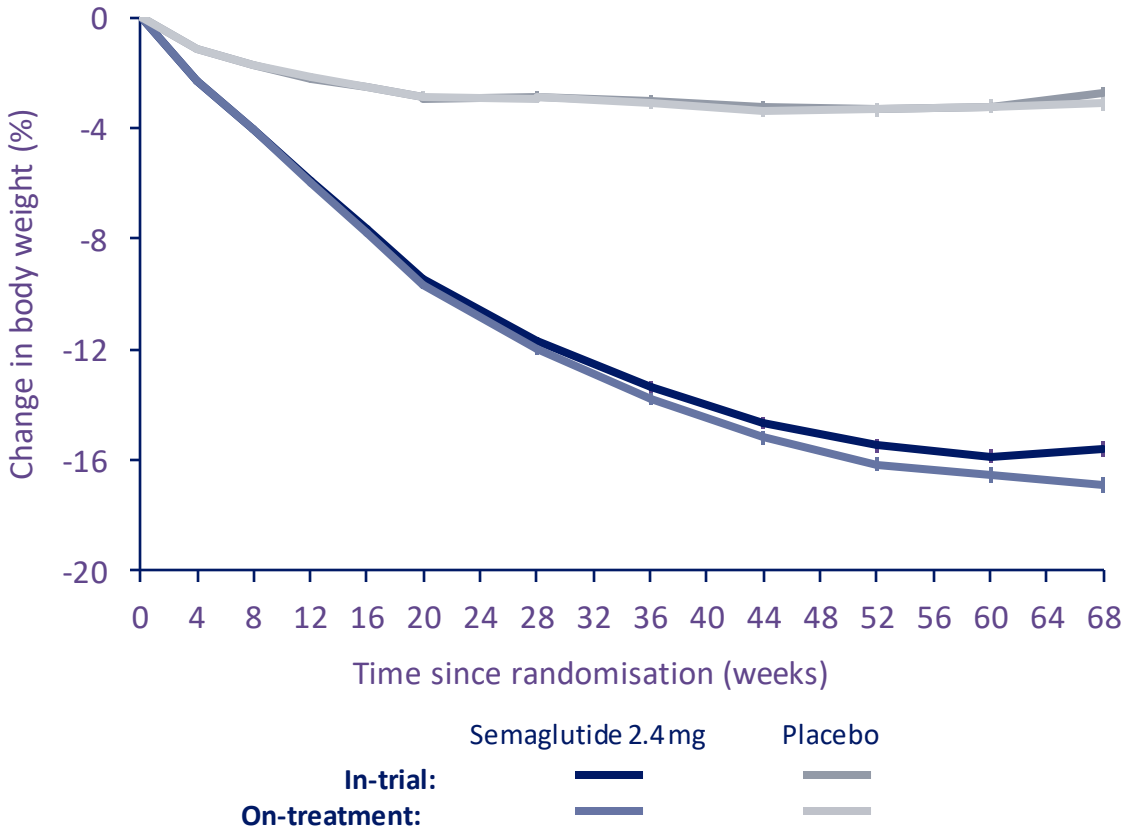
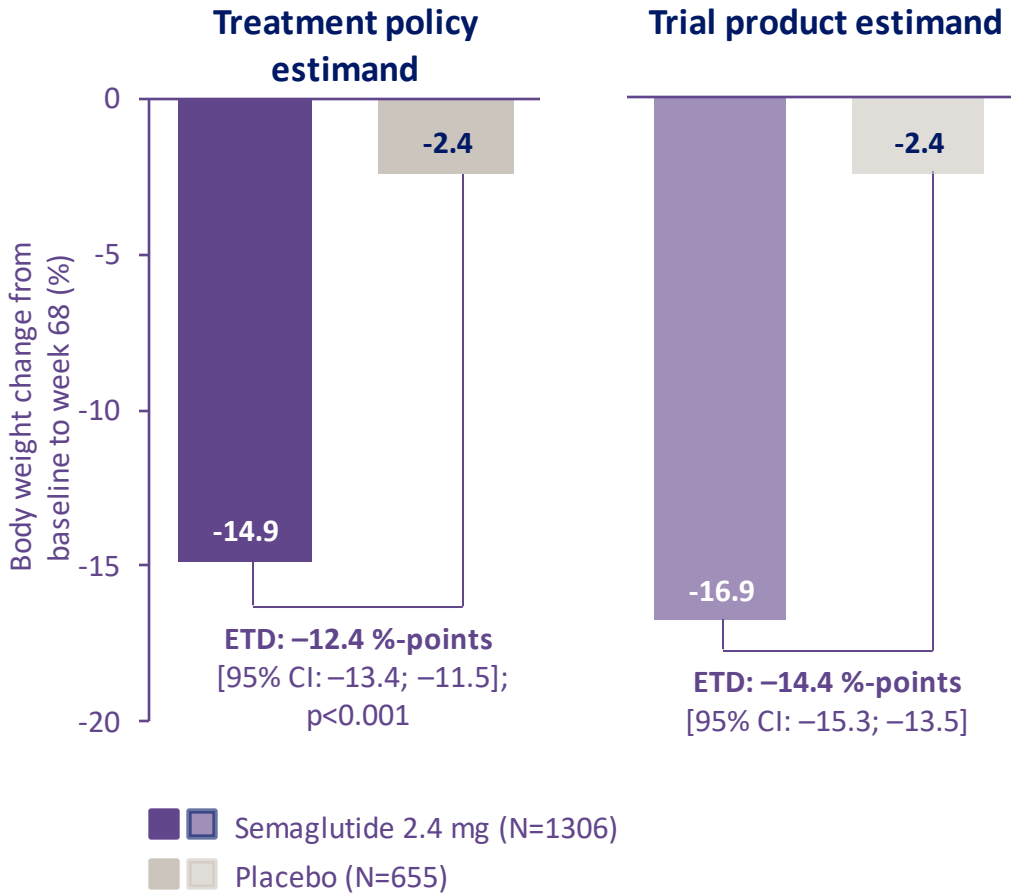
STEP 1: Body Weight Change

Observed body weight change over time



Estimated change from baseline to week 68



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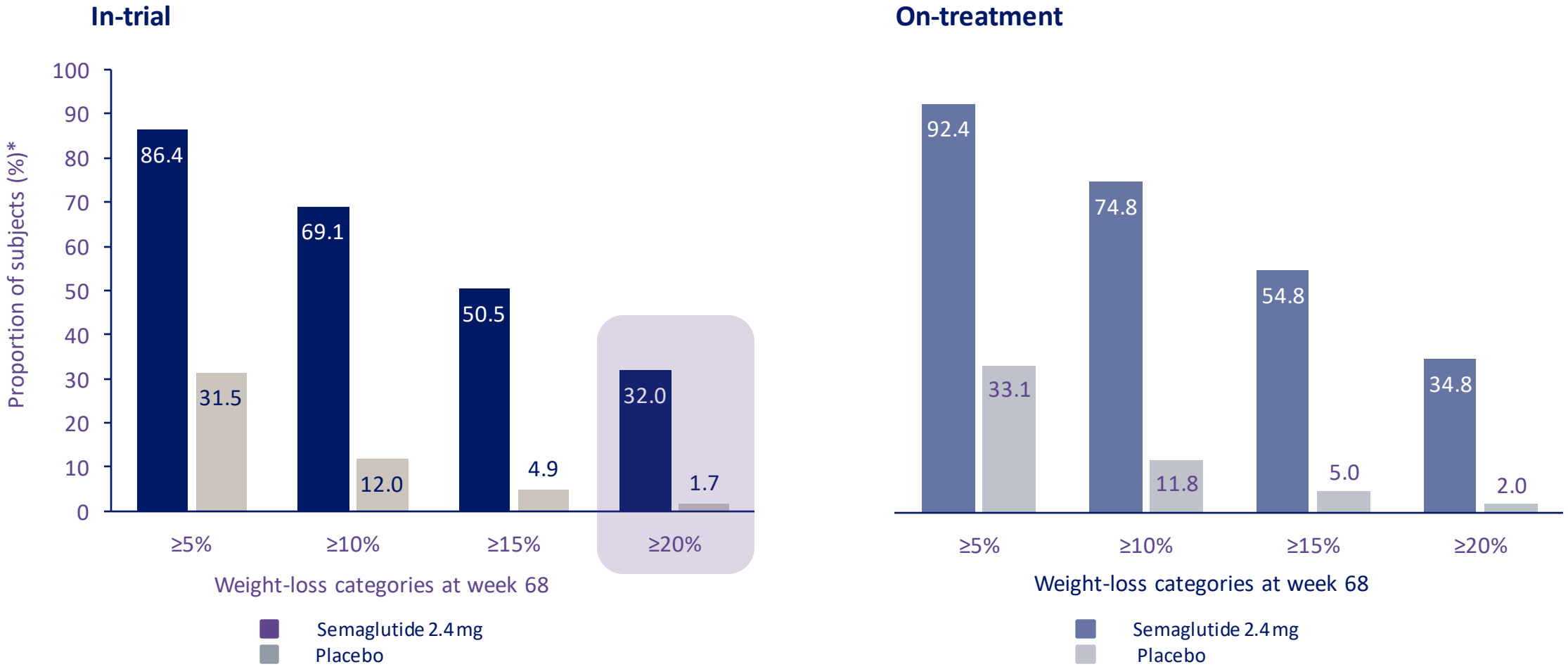
Wilding JPH, et al. N Engl J Med 2021;384:989-1002

STEP 1: Categorical Body Weight Loss



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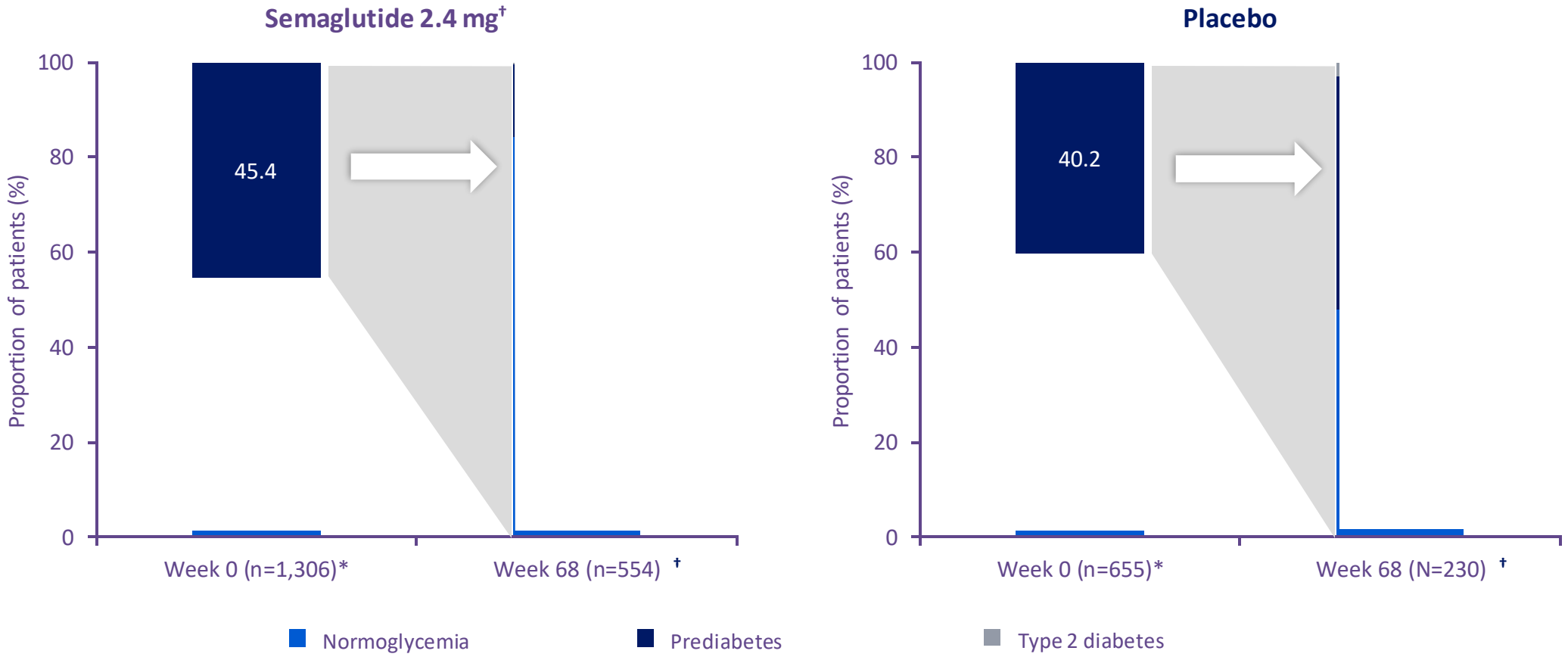
Wilding JPH, et al. N Engl J Med 2021;384:989-1002

Shift from baseline to week 68 in glycaemic status in patients with prediabetes at baseline



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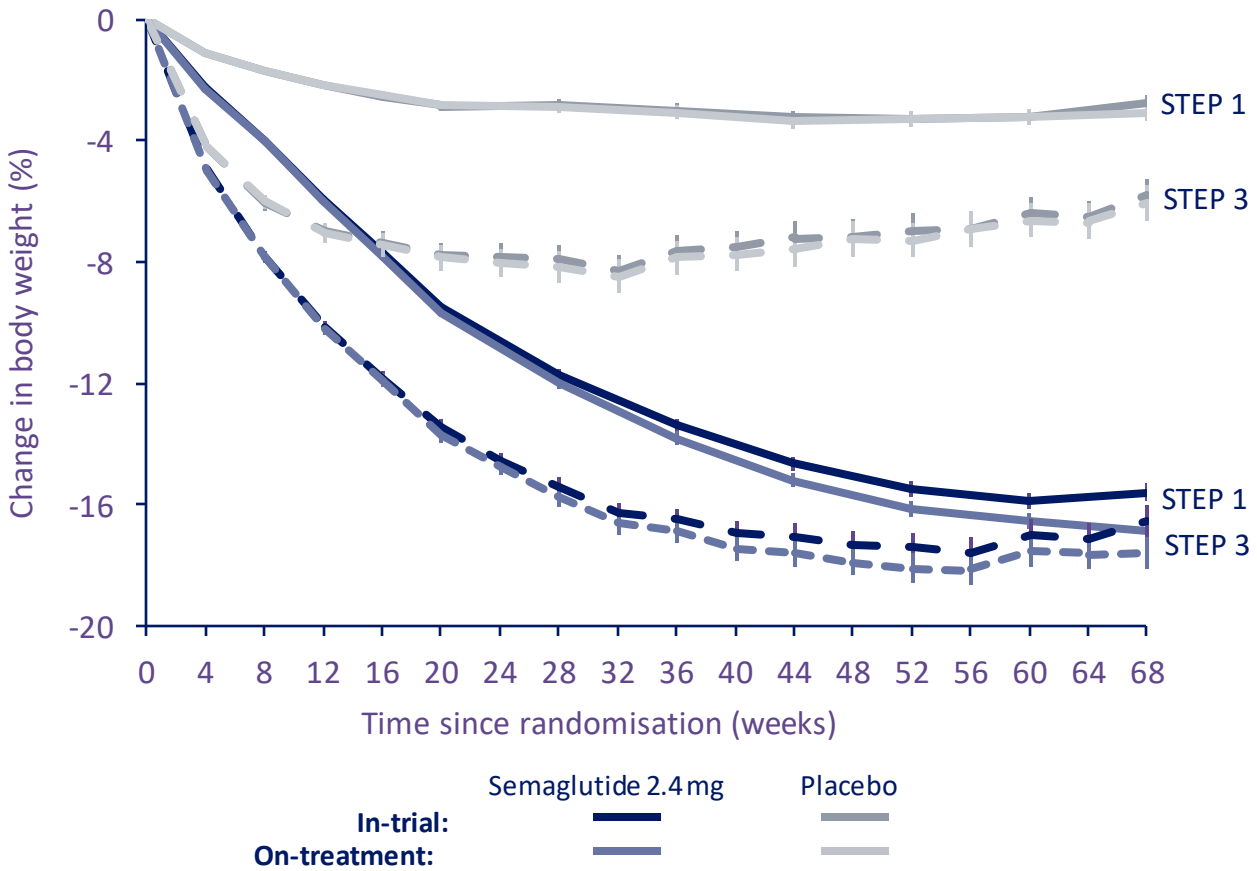
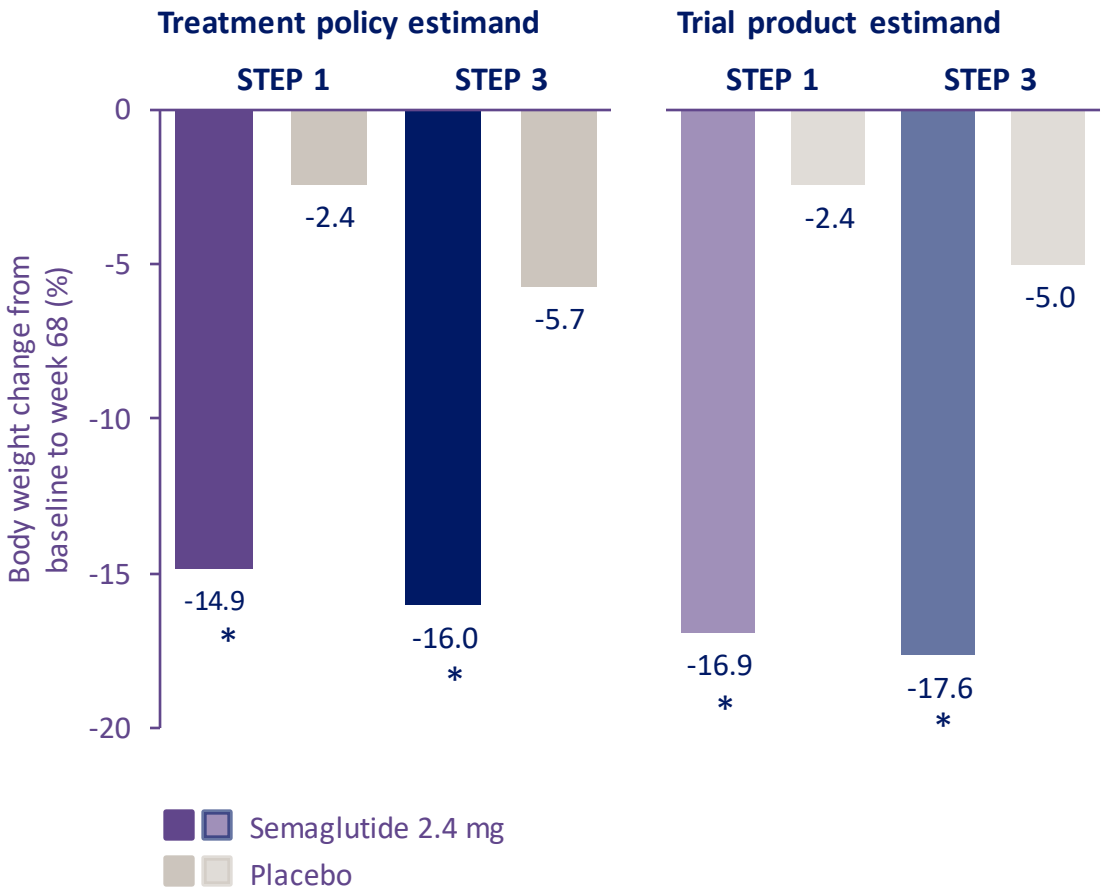
*Adapted from Perreault L, et al. ADA 2021;81-OR

STEP 1 & 3: Body Weight Change

LCD and IBT Appear to Accelerate Initial Weight Loss Achieved with Semaglutide 2.4 mg but does not result in greater percent weight loss at 68 weeks



Estimated change from baseline to week 68



*Statistically significant vs placebo. †Observed on-treatment data.
IBT, intensive behaviour therapy; LCD, low-calorie diet.

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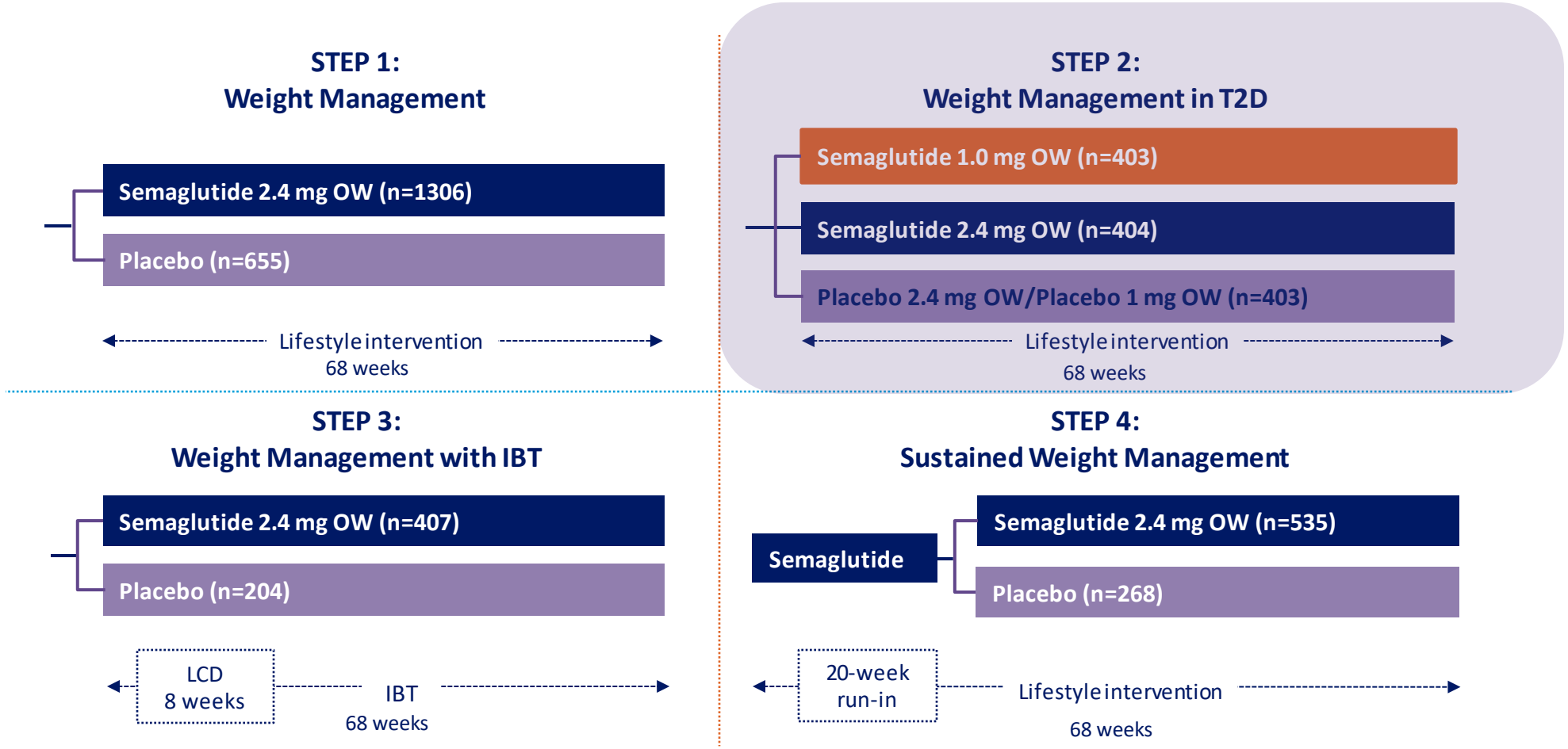
Wadden TA, et al. JAMA 2021;e211831; Wilding JP, et al. N Engl J Med 2021;384:989.

STEP Program: Four Pivotal Trials at a Glance

4700 PATIENTS IN TOTAL



Lifestyle intervention: –500 kcal/day diet + 150 min/week physical activity.
IBT, intensive behavioural therapy; LCD, low-calorie diet; OW, once weekly; STEP, Semaglutide Treatment Effect in People with obesity.
Kushner et al. Obesity (Silver Spring) 2020;28:1050–61.

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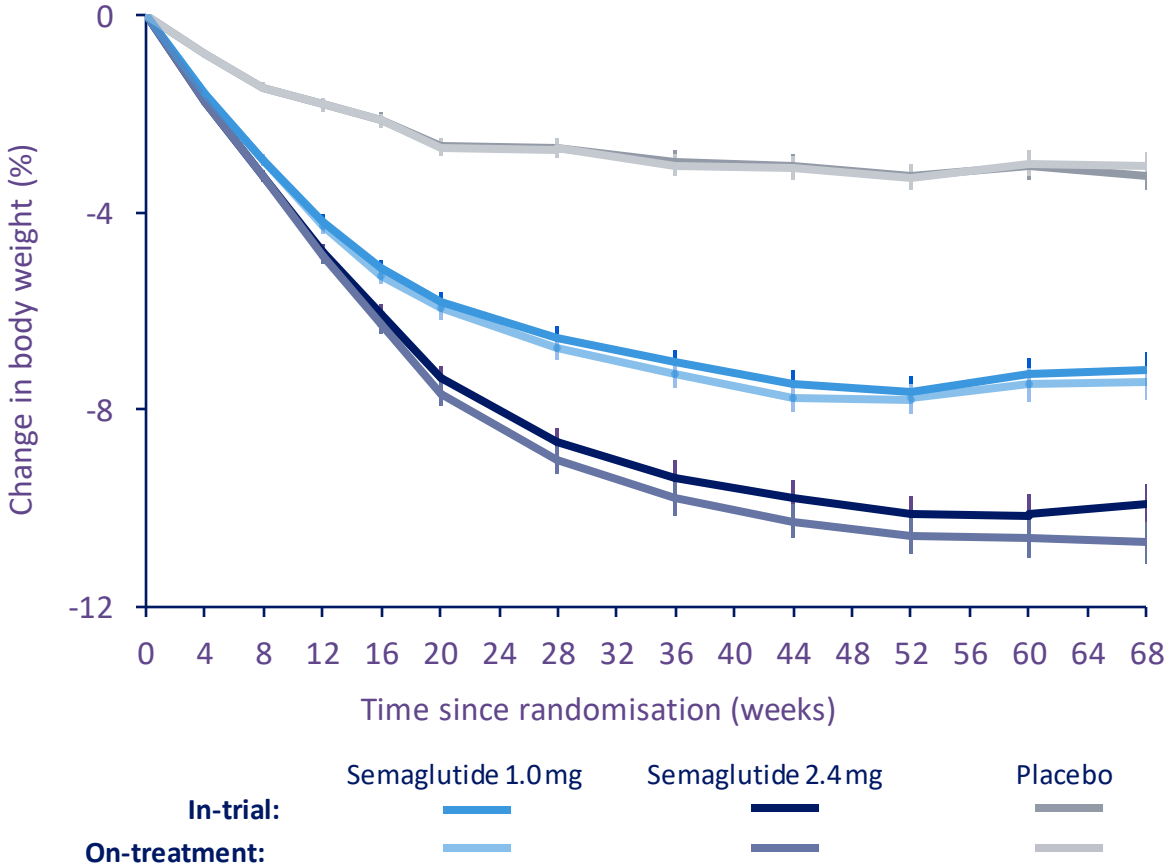
STEP 2: Body Weight Change

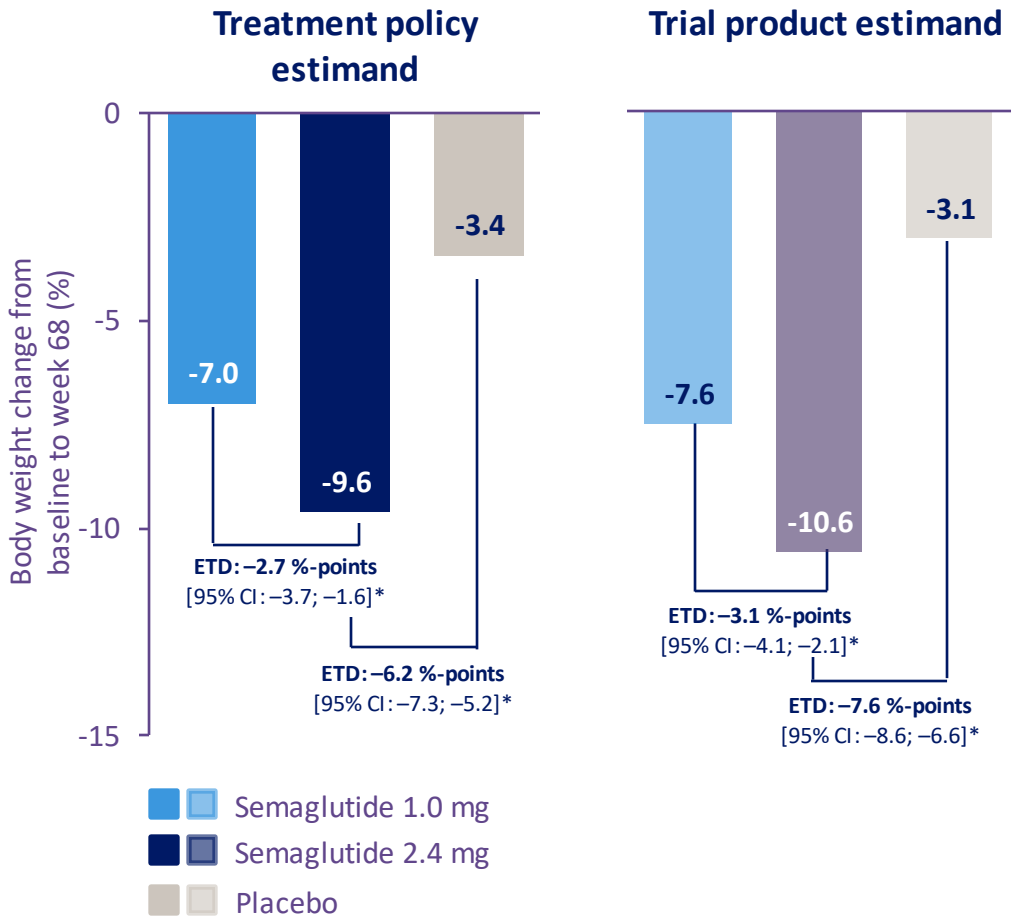
PATIENTS WITH T2D

Observed body weight change over time

(Mean at baseline: 219 lbs.)



Estimated change from baseline to week 68



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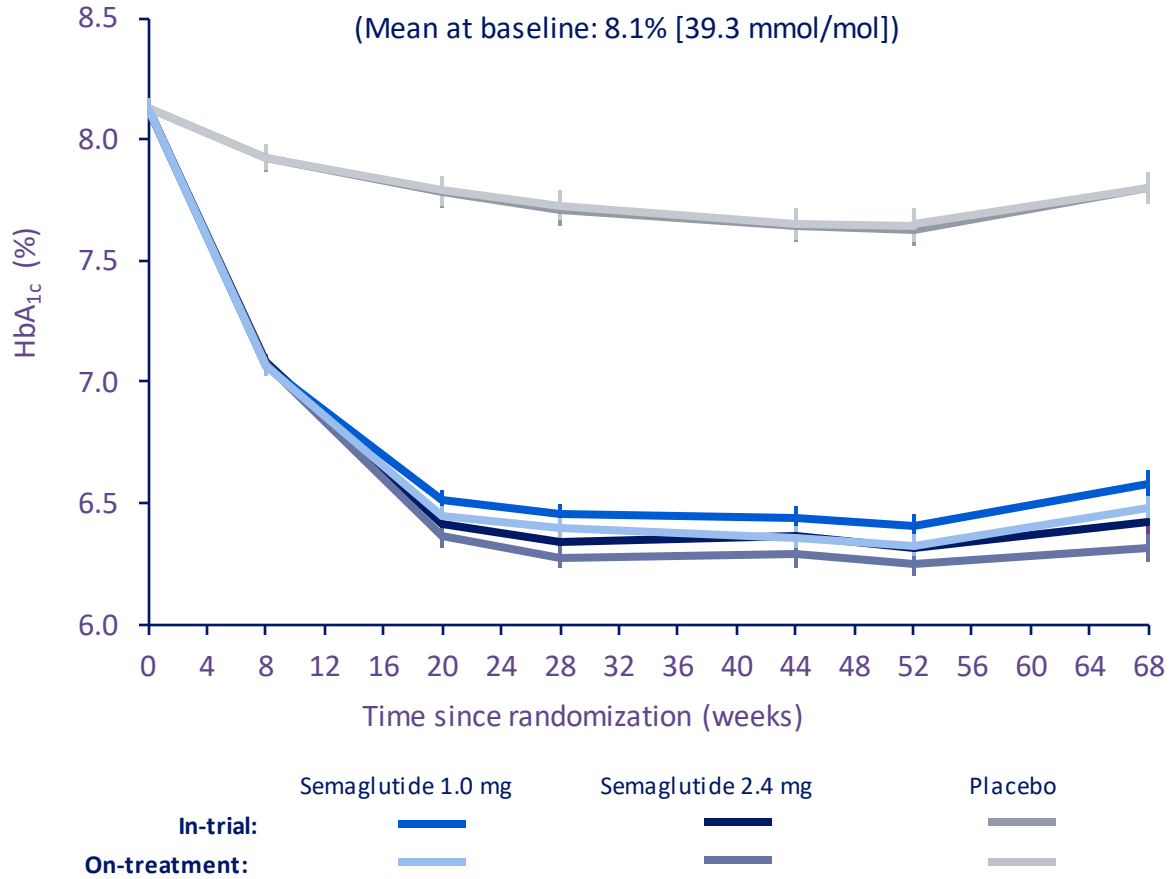
Davies M, et al. Lancet 2021;397:971–84

STEP 2 key results

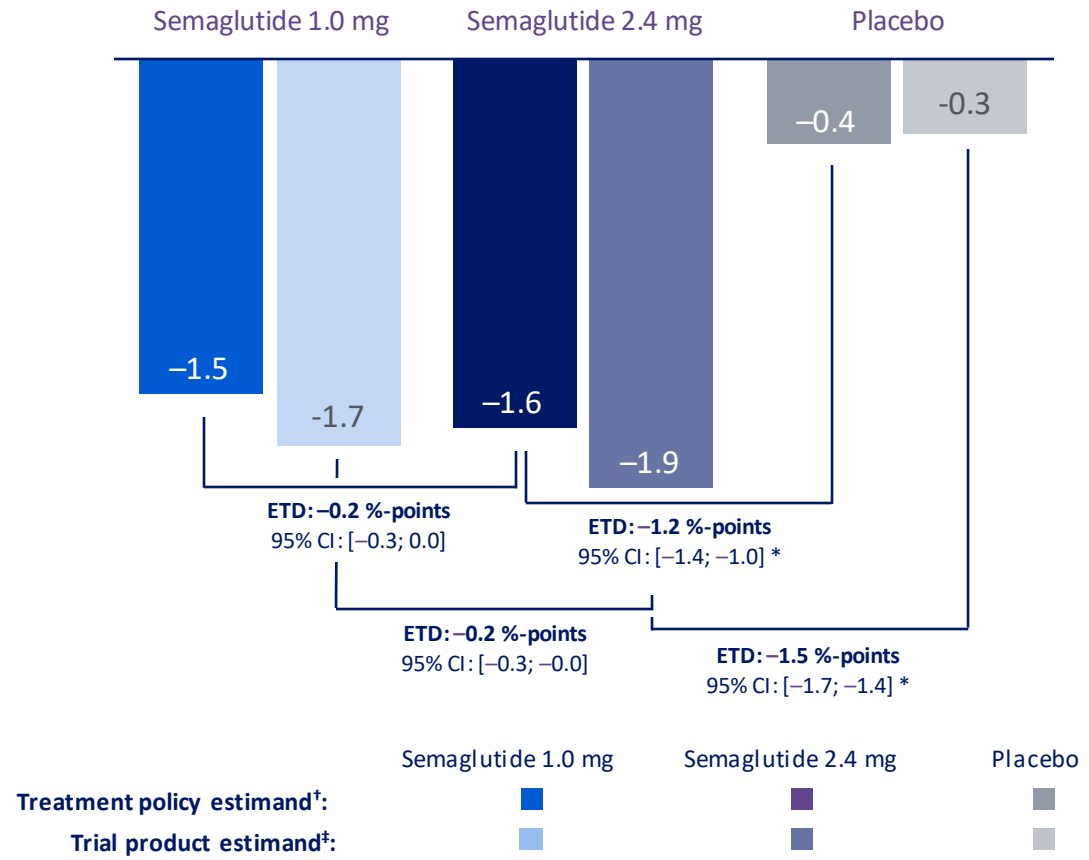
HbA_{1c} (%) from baseline to week 68

Observed mean HbA_{1c} over time

(Mean at baseline: 8.1% [39.3 mmol/mol])



Estimated change from baseline to week 68



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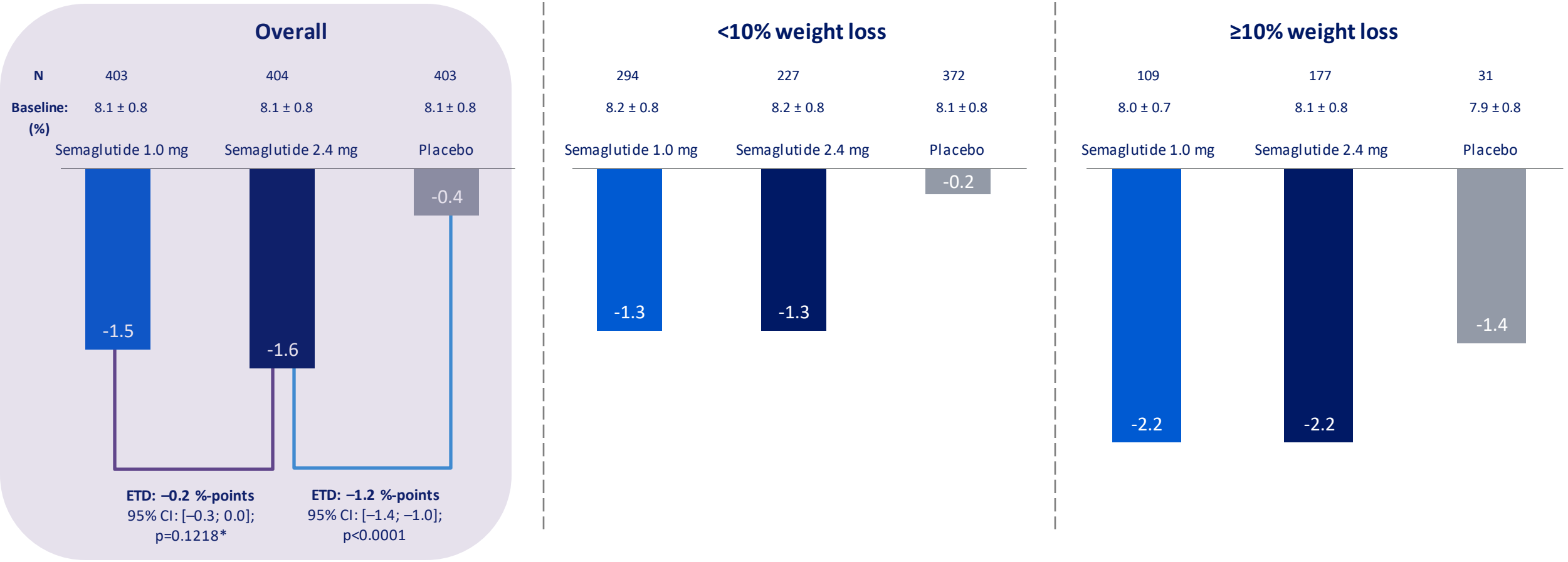
Davies M, et al. *Lancet.* 2021;397(10278):971-984.

HbA_{1c}
Change from baseline (%-points) to Week 68



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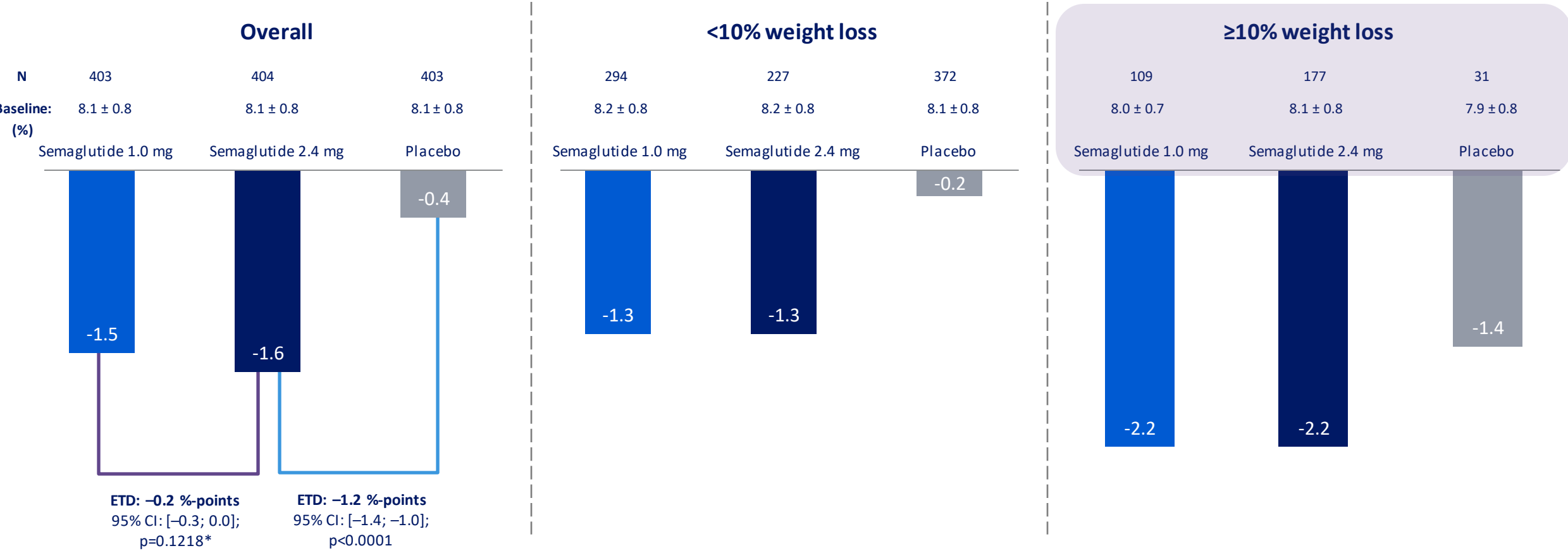
Davies M, et al. Lancet 2021;397:971–84

HbA_{1c}
Change from baseline (%-points) to Week 68



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Davies M, et al. Lancet 2021;397:971–84

HbA_{1c}
Change from baseline (%-points) to Week 68

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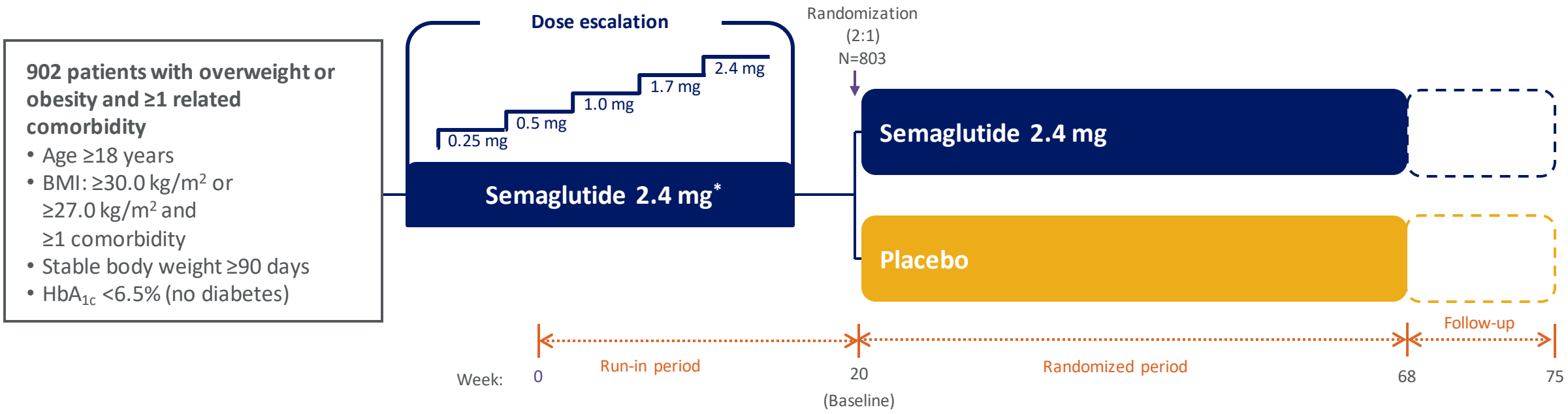
Davies M, et al. Lancet 2021;397:971–84

STEP 4: maintaining weight loss

Trial design: randomized, double-blind, placebo-controlled trial



Trial objective

- To compare the effect of semaglutide on body weight in subjects who have reached the target dose during run-in compared to those switching to placebo
- To generate data to support maintained weight loss in subjects continuing semaglutide treatment

*As an adjunct to lifestyle intervention (-599 kcal/day diet + 150 min/week physical activity).
Abbreviations: BMI, body mass index; OW, once-weekly; s.c., subcutaneous; SF-36, 36-item Short Form Questionnaire.
References: NCT03548987. Available from https://clinicaltrials.gov/ct2/show/NCT03548987?term=semaglutide&recrs=de&cond=Obesity&draw=2&rank=7. Accessed September 2020.

Northwestern Medicine

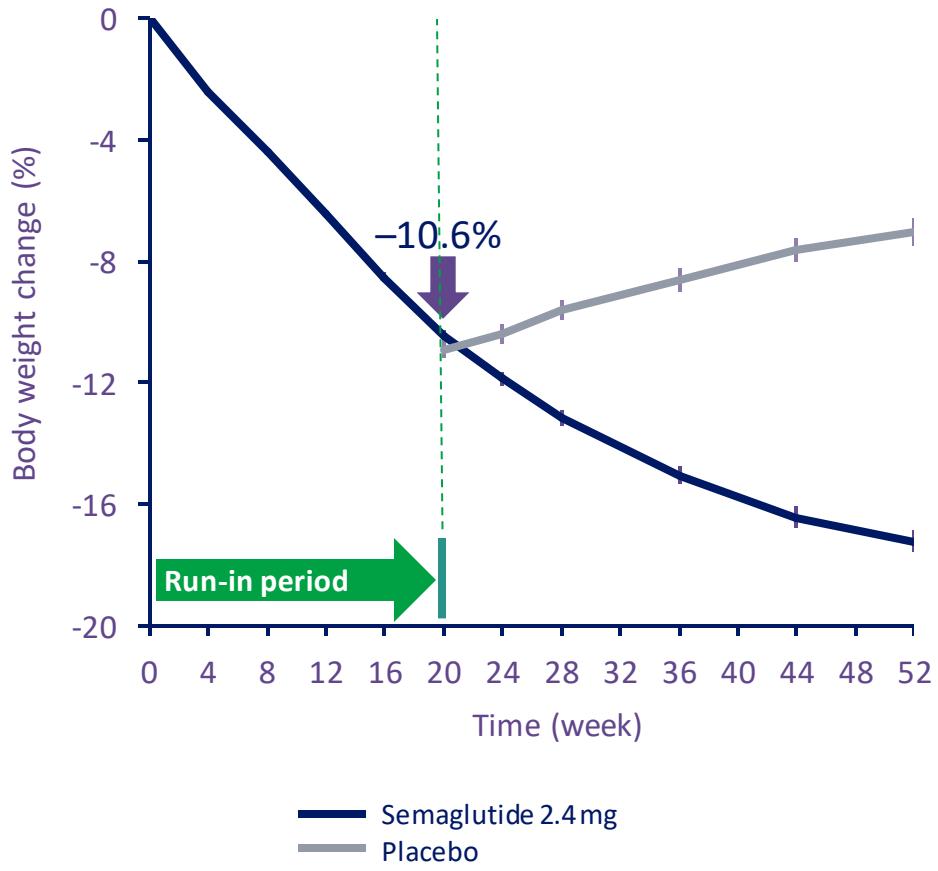
Rubino D, et al. *JAMA.* 2021;325(14):1414-1425

STEP 4: Body Weight Change

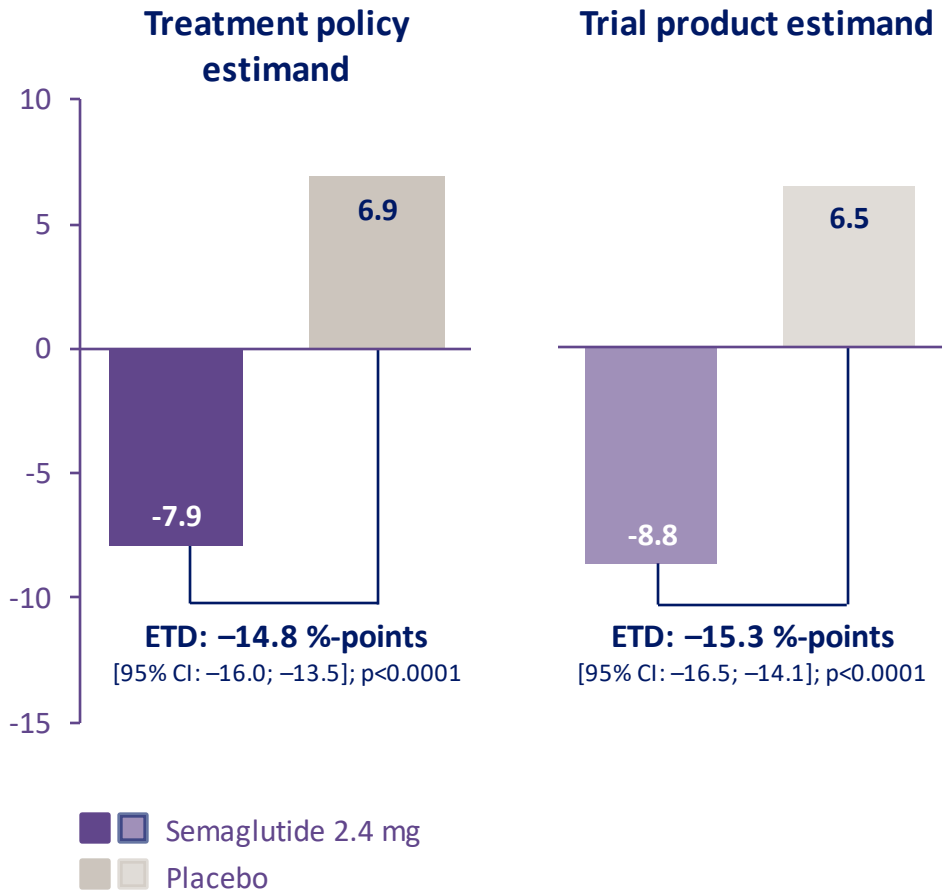
Observed body weight change over time

Mean at week 0: 235 lbs.

Mean weight at randomization (week 20): 211.8 lbs.



Estimated change from week 20 to week 68



Data for the in-trial observation period. Error bars are ± standard error of the mean. CI, confidence interval; ETD, estimated treatment difference (treatment policy estimand). Rubino D, et al. JAMA 2021. doi:10.1001/jama.2021.3224 [Epub].

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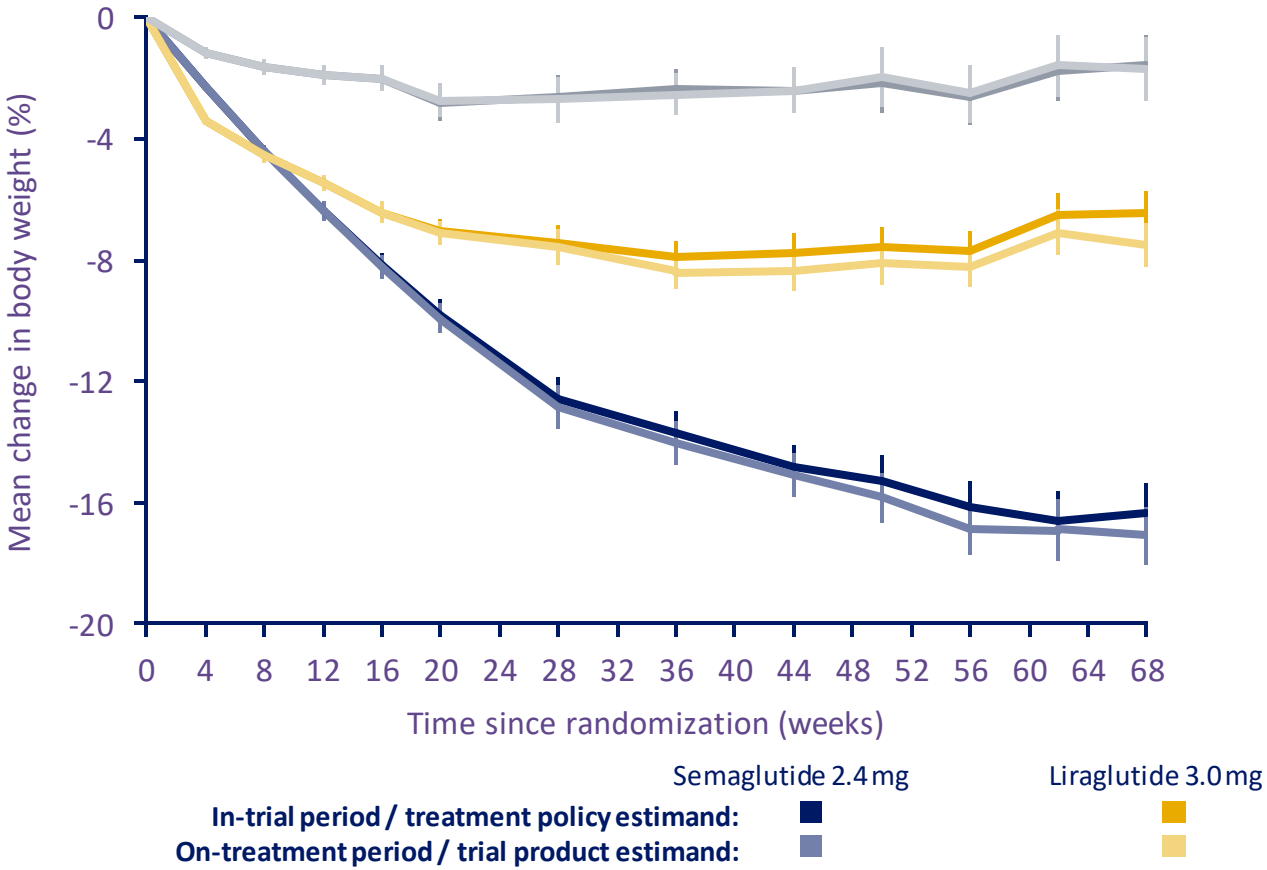
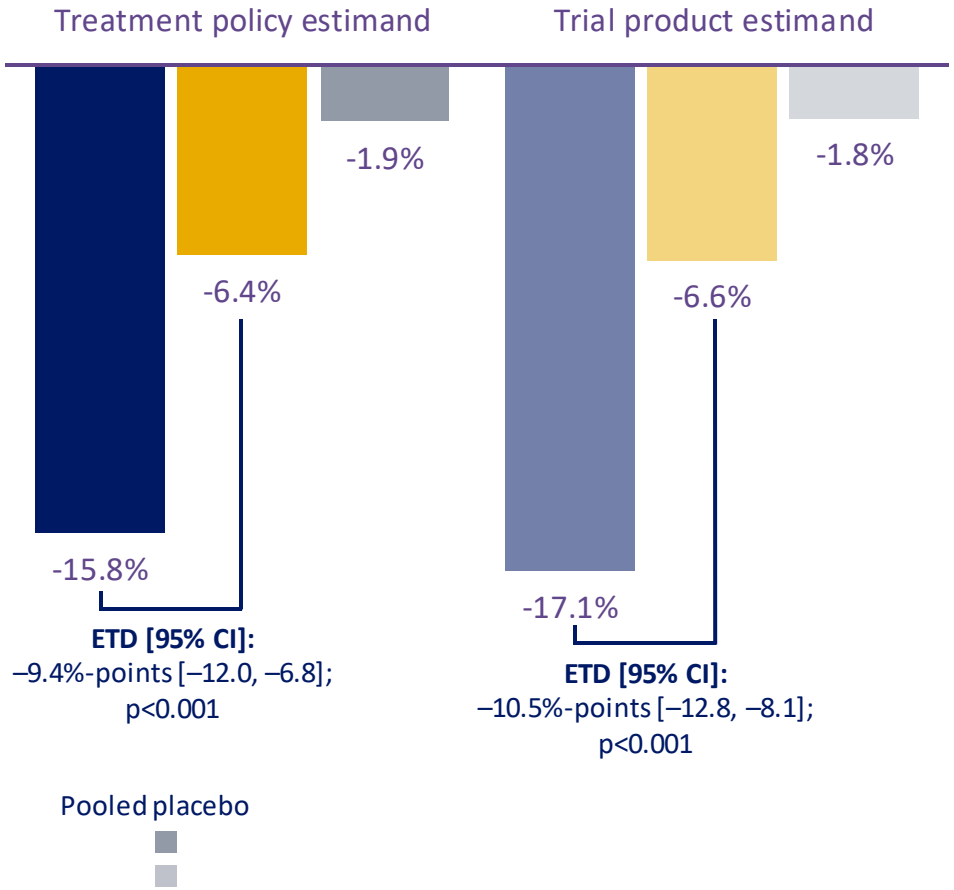
Change in body weight

Observed change from baseline over time*

(Mean at baseline: 104.5 kg)



Estimated change from baseline to week 68†



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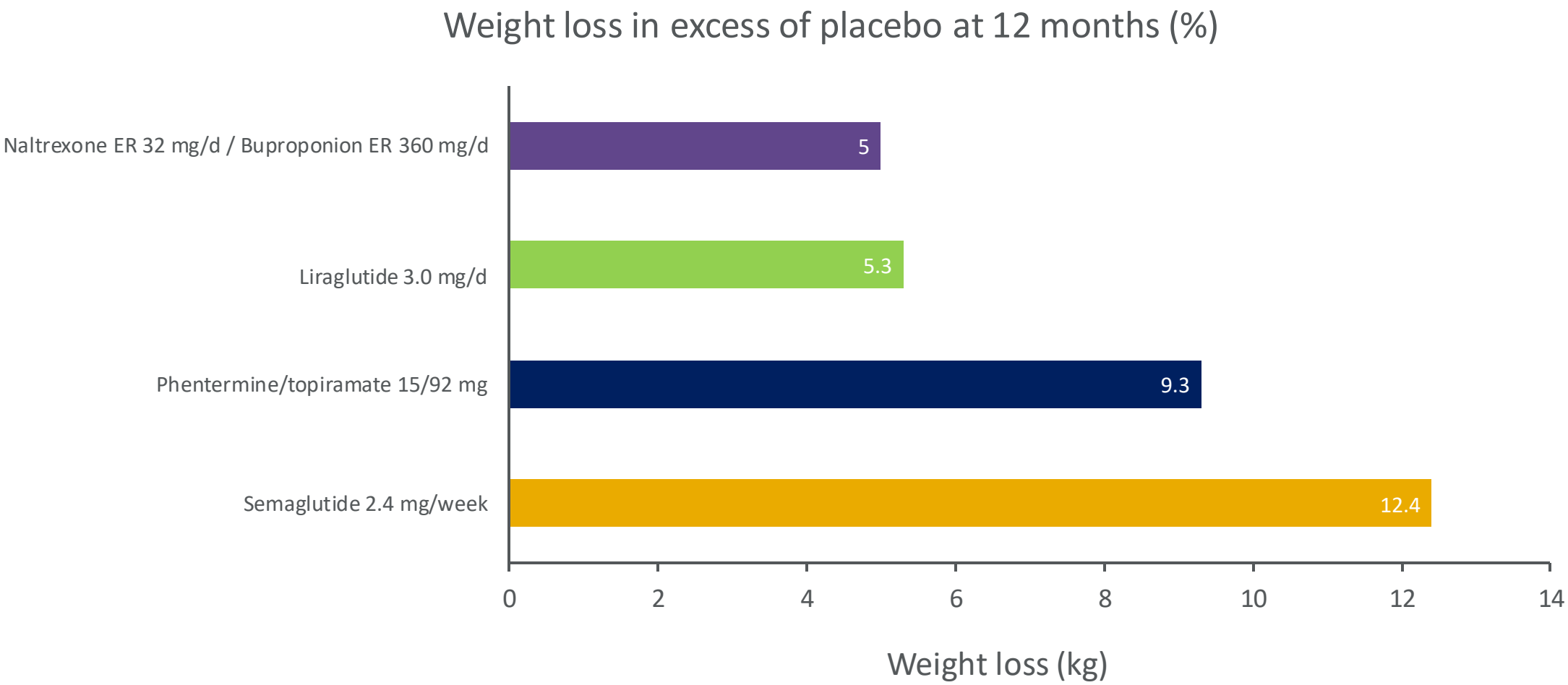
Rubino DM et al. JAMA 2022;327:138-150

Estimated Treatment Difference Drug versus Placebo



ER, extended-release.
Adapted from Khera et al. *JAMA* 2016;315:2424–34.

Courtesy of T Wadden

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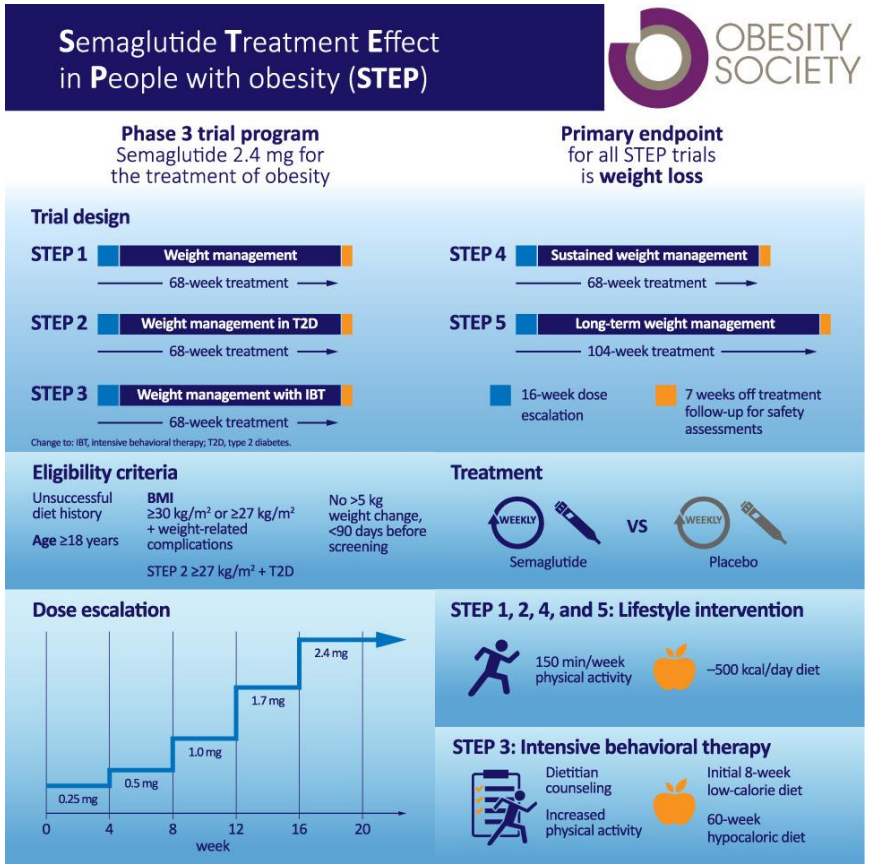
Summary of the STEP trials

What have we learned?

- The long-acting GLP-1 RA semaglutide pushes the weight loss envelope to an average weight loss of 15%, with one-third losing ≥20% (STEP 1)
- Semaglutide 2.4 mg is twice as effective as liraglutide 3.0 mg (STEP 8)
- Adding intensive lifestyle counseling only added 1% more weight loss versus modest lifestyle counseling (STEP 3)
- Stopping medication treatment leads to gradual weight regain – reinforcing the underlying biology of the disease (STEP 4)
- The incretin effect on reducing HbA1c is not improved by increasing dose of semaglutide (STEP 2)



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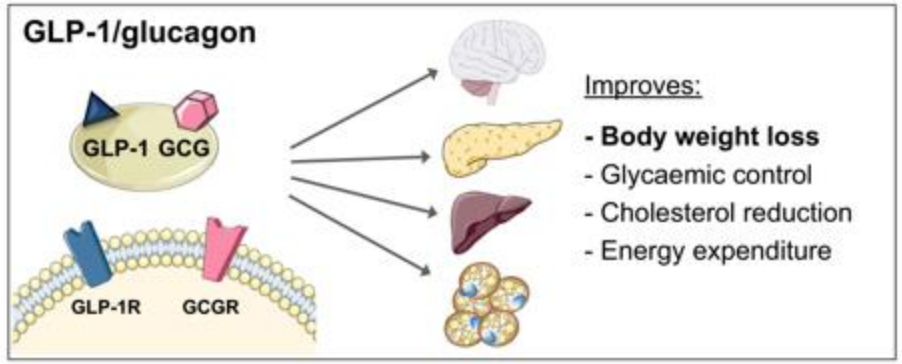
Working principles and target tissues of dual & triple agonists

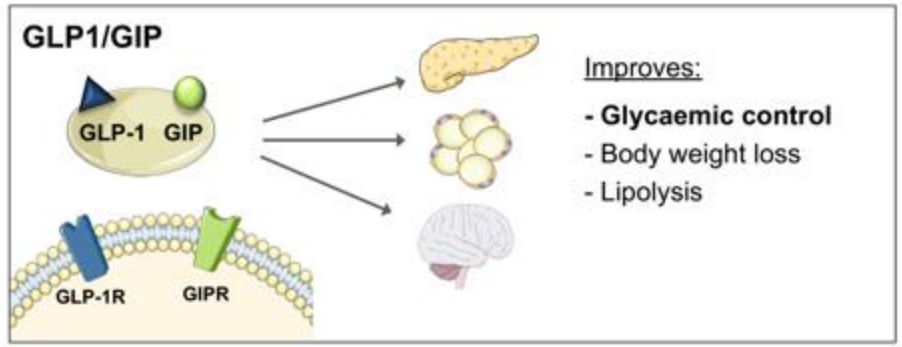
GLP-1/glucagon

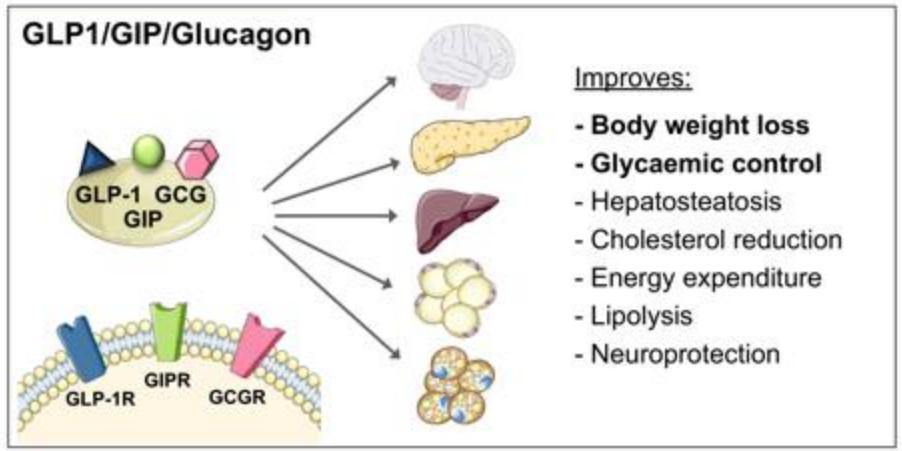
GLP-1/GIP

GLP-1/GIP/glucagon

The most predominant metabolic effects are indicated in bold letters







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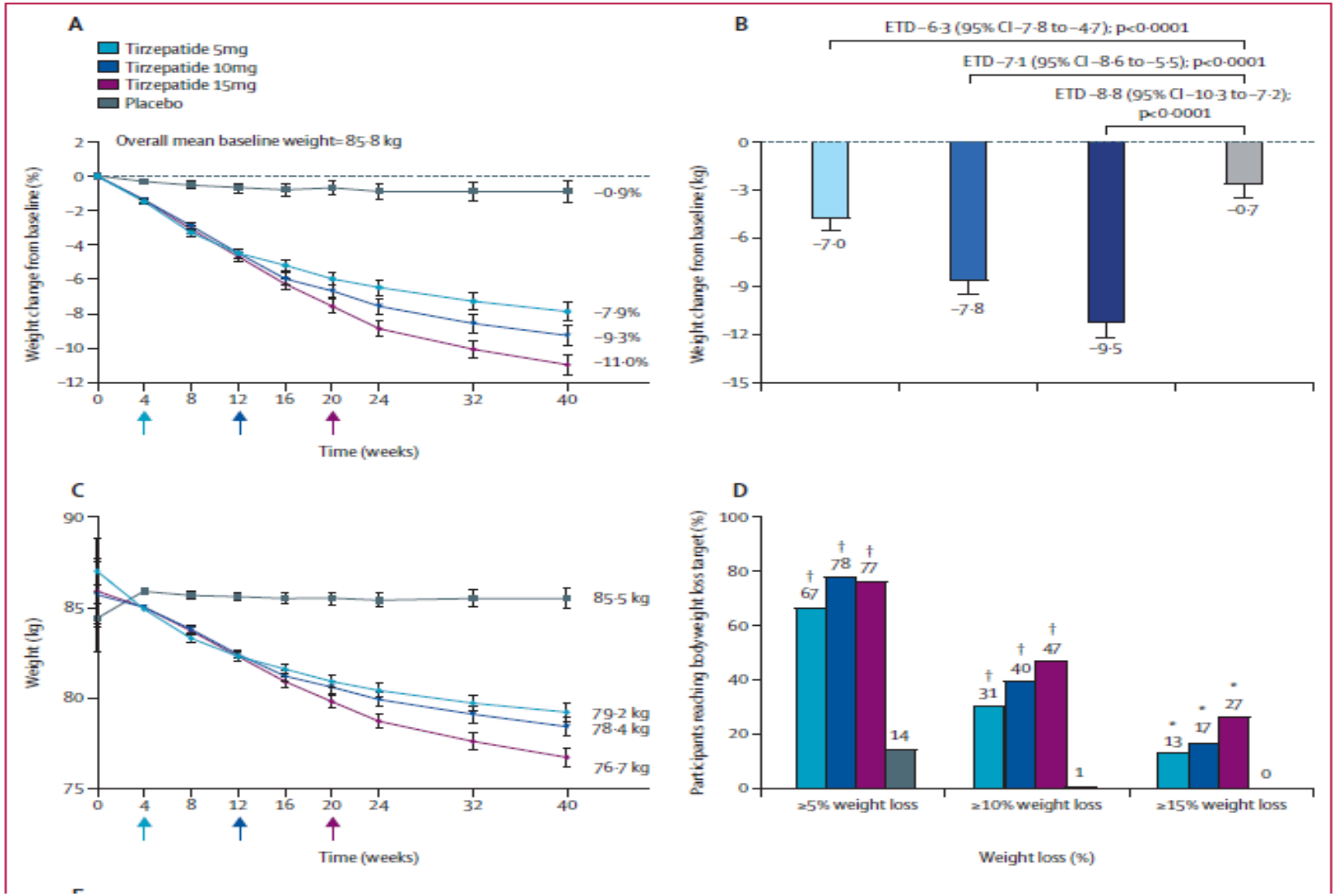
Journal of Internal Medicine, Volume: 284, Issue: 6, Pages: 581-602, First published: 19 September 2018, DOI: (10.1111/joim.12837)

Tirzepatide (GLP-1/GIP dual agonist): SURPASS-1 Trial

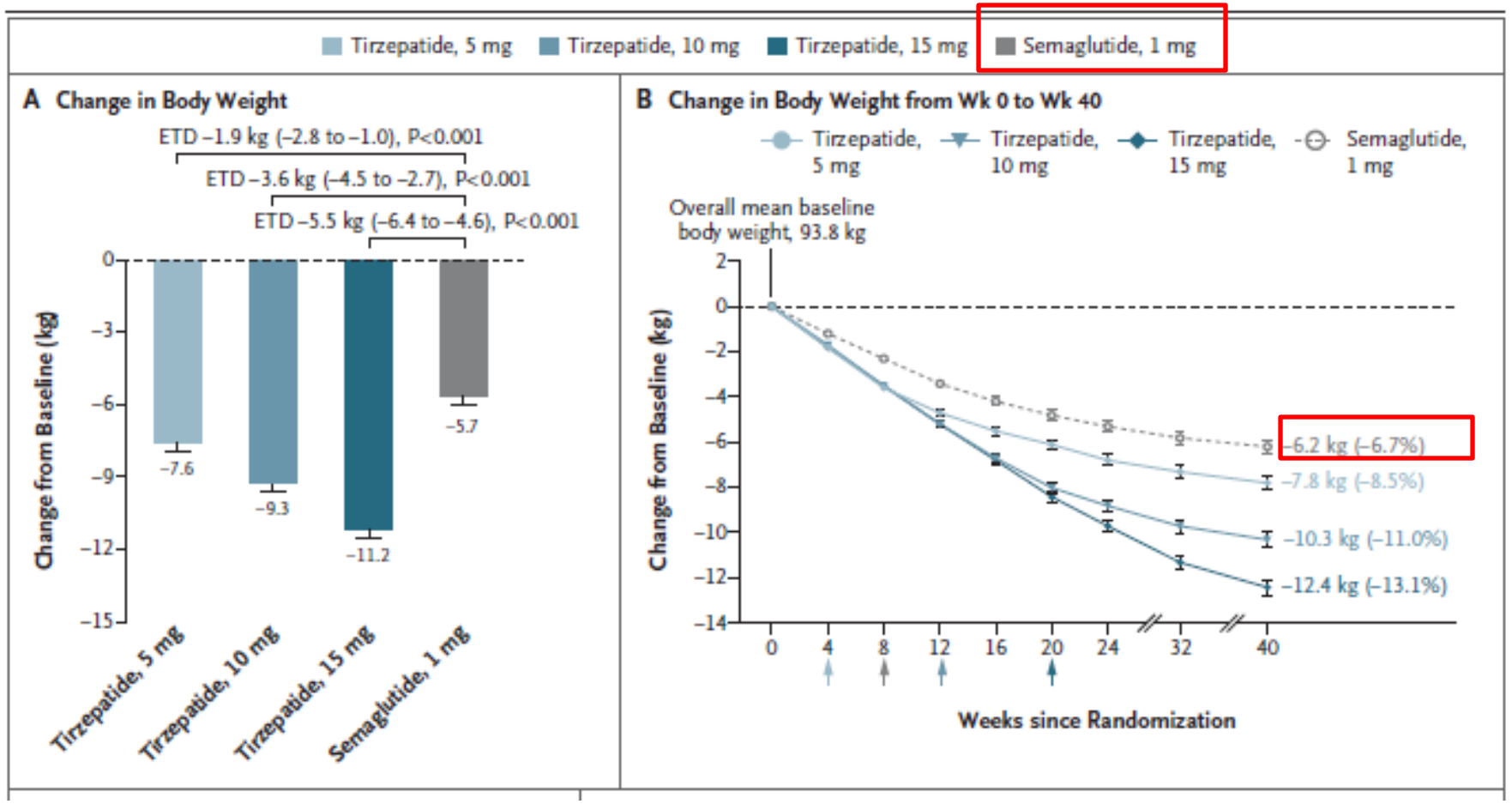
40-week, phase 3 trial
478 subjects with T2DM
Ave HbA1c 7.94%
Ave BMI 31.9 kg/m^2



Rosenstock J et al. Lancet 2021:398:143-155

Tirzepatide (GLP-1/GIP dual agonist): SURPASS-2 Trial

40-week, phase 3 trial
1879 subjects with T2DM
Ave HbA1c 8.3%
Ave BMI 34 kg/m^2



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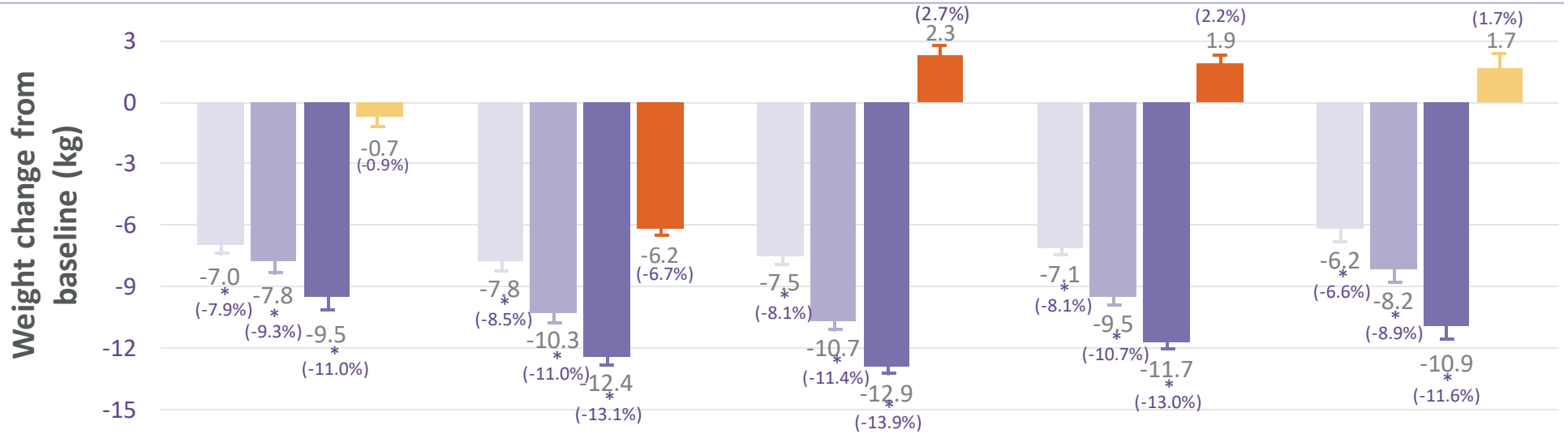
Frias JP et al. NEJM 2021:385:503-515

SURPASS: Body Weight Change from Baseline

Study	SURPASS-1[1]	SURPASS-2[2]	SURPASS-3[3]	SURPASS-4[4]	SURPASS-5[5]
Duration	40 weeks	40 weeks	52 weeks	52 weeks	40 weeks
Baseline Weight (kg)	85.9	93.7	94.3	90.3	95.3



Superiority vs	Placebo	Semaglutide 1 mg	Insulin degludec	Insulin glargine	Placebo
Background therapy	Monotherapy	Add-on to MET	Add-on to MET or MET + SGLT2i	Add-on to MET, SGLT2i, or SU	Add-on to insulin glargine ± MET

*P<0.001 vs placebo or active comparator. Data are LSM (SE); mITT population (efficacy analysis set). MMRM analysis.

1. Rosenstock J et al. *Lancet.* 2021;398(10295):143-155. 2. Frias JP et al. *N Engl J Med.* 2021;385(6):503-515. 3. Ludvik B et al. *Lancet.* 2021;398(10300):583-598. 4. Del Prato S et al. *Lancet.* 2021;(Accepted). 5. Dahl D et al. Poster presented at: *ADA* 2021. Poster LB-20. Graph adapted from Eli Lilly and Company, 2021.

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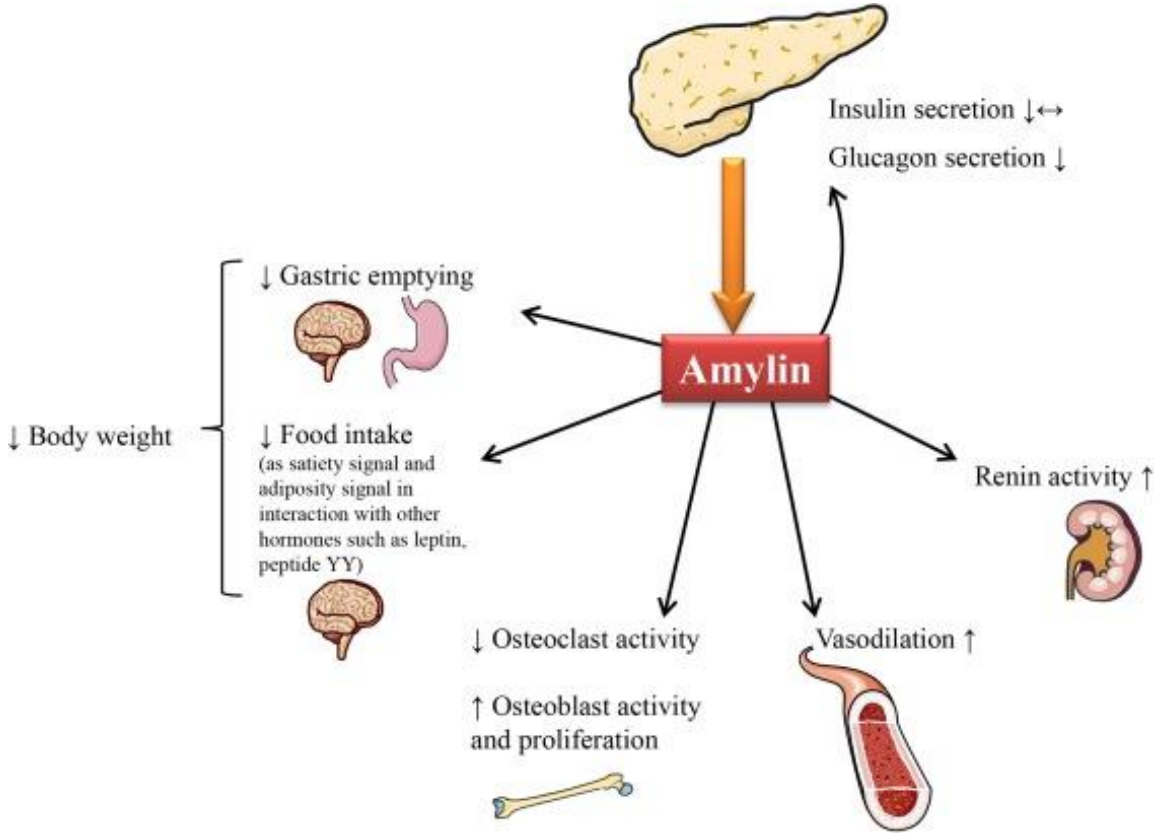
Cagrilinide (long acting amylin)

Native amylin is a glucoregulatory pancreatic hormone co-secreted with insulin that is involved in:

- delay of gastric emptying
- suppression of postprandial glucagon release
- Reduced energy intake through activation of receptors in the area postrema and nucleus of the solitary tract (NST) of the hindbrain



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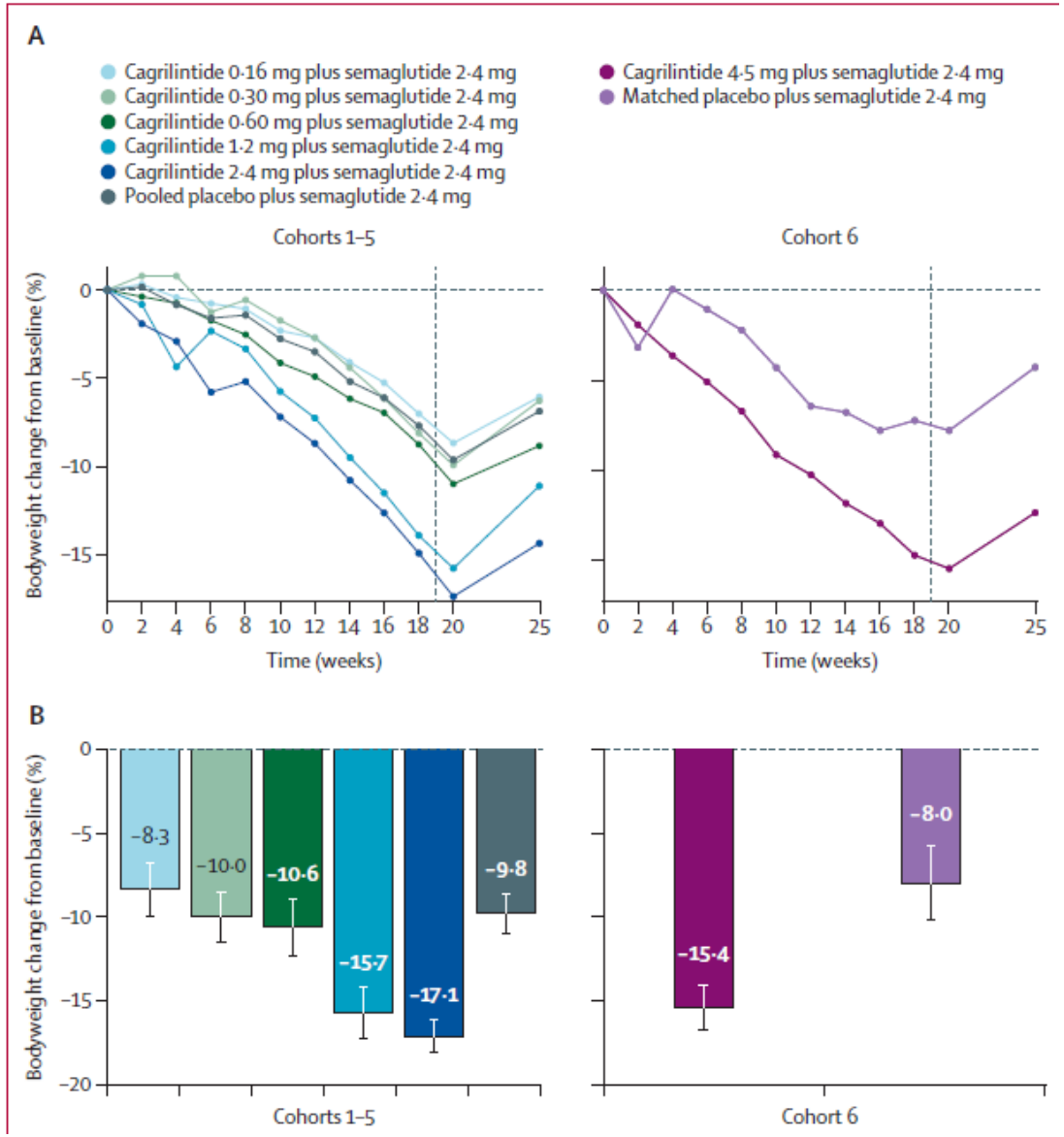
Boyle CN, et al. Mol Metab 2018;8:203-210

Semaglutide 2.4 mg + Cagrilinitide ascending doses

Phase 1b trial



Enebo LB et al. Lancet 2021;397:1736-1748

Take Home Points

- Obesity is a disease of energy balance dysregulation and lipotoxicity
- Pharmacotherapy is an evidence-based, effective treatment
- Hormonal treatment of obesity (e.g., GLP-1, GIP, amylin, glucagon) represents a new paradigm in obesity therapeutics
- By leveraging gut hormones as mono-, dual or tri-agonists or combination agents, average weight loss is expected to reach ≥15% and is associated with improvement in cardiovascular biomarkers
- It is incumbent that you become competent in the use of pharmacotherapy for obesity and consider treatment in selected patients who would benefit

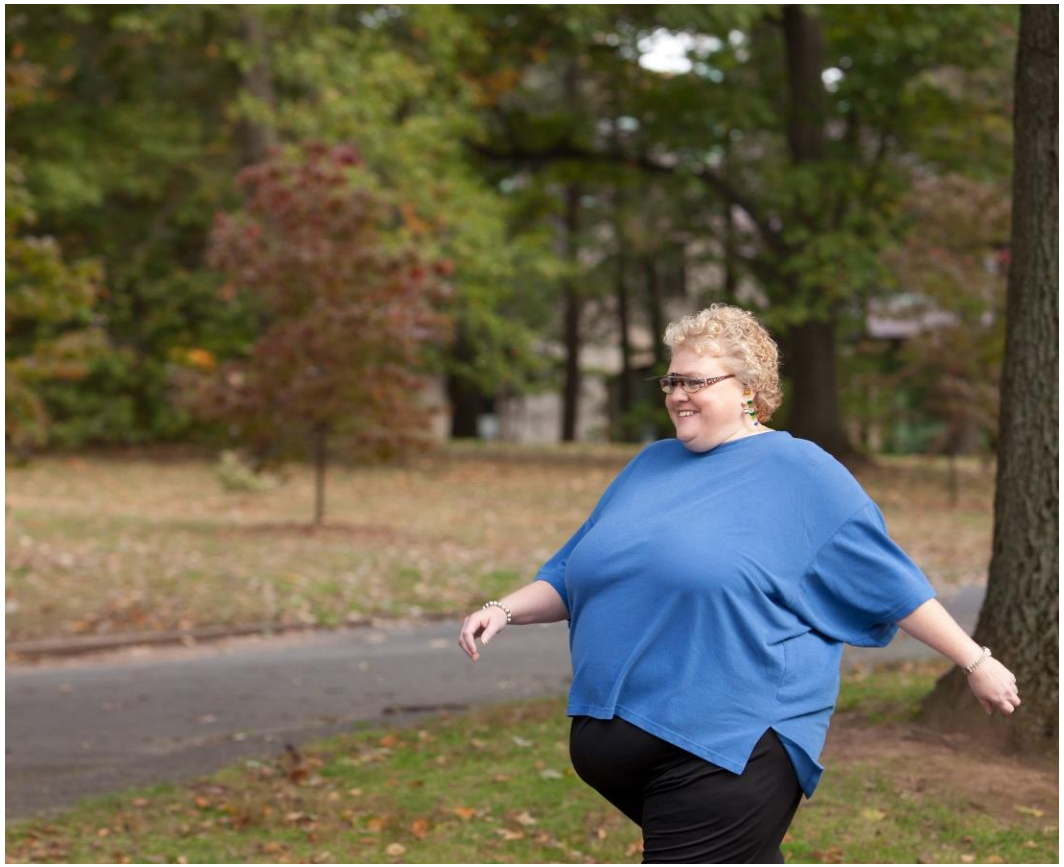


Photo Credit Source: U Conn Rudd Center for Food Policy & Obesity