Novel Strategies for the Medical Management of Obesity

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1

Disclosure

Advisory Board: Lilly; Novo Nordisk; Weight Watchers

Consultant: altimmune; Boehringer Ingelheim; Pfizer; Regeneron; Structure

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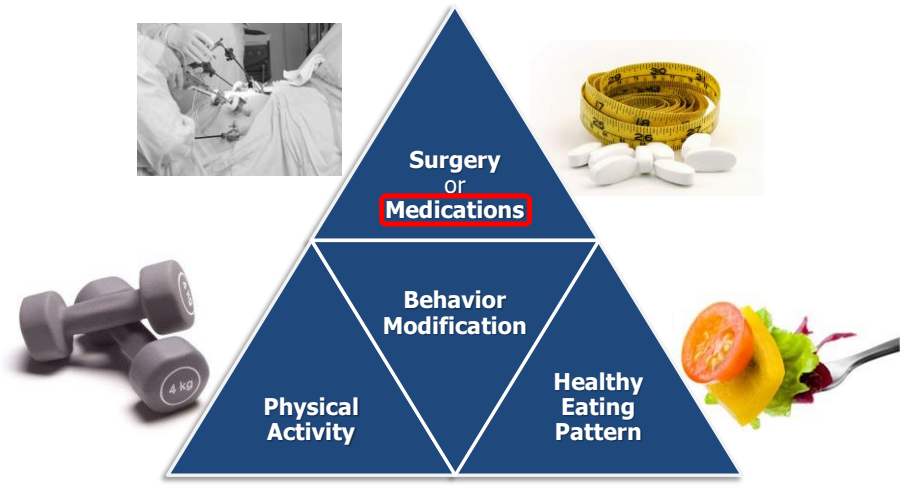
2

Learning Objectives

- Explain the mechanism of action of obesity medications
- Define the effectiveness of obesity medications and general principles of their use
- Discuss the role and use of glucagon like peptide-1 receptor agonists (GLP-1 RA) and GLP-1/ GIP dual agonists in chronic weight management

3

Components of an Effective Obesity Management Program

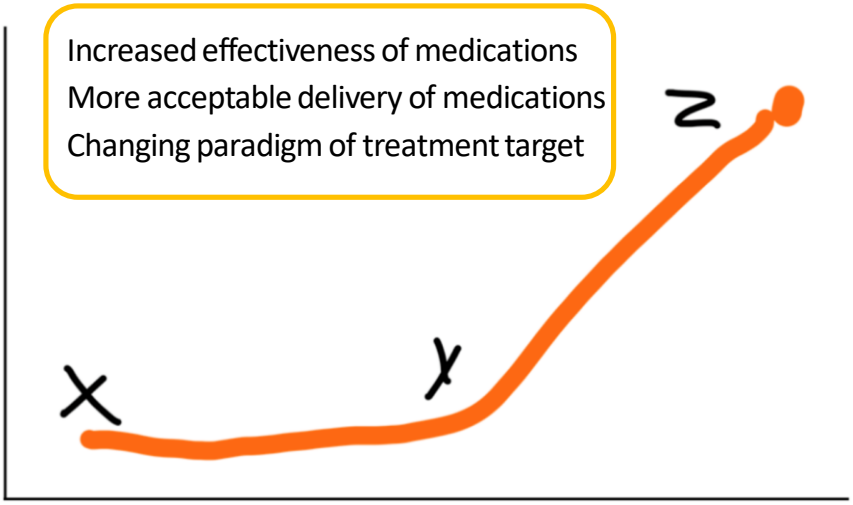


Wadden TA, et al. *Med Clin North Am*. 2000;84(2):441-461; Stumbo P, et al. *Surg Clin North Am*. 2005;85(4):703-723.

4

Inflection Point

Increased effectiveness of medications
More acceptable delivery of medications
Changing paradigm of treatment target



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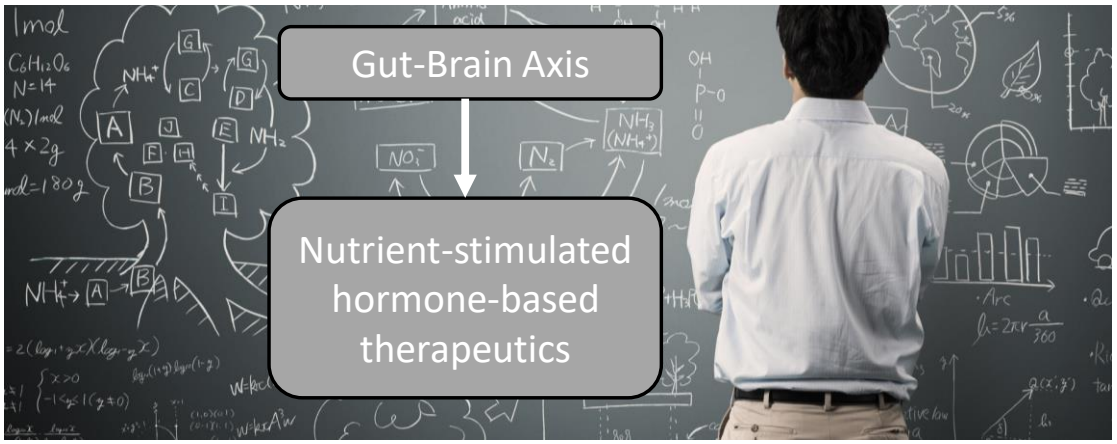
A Paradigm Shift



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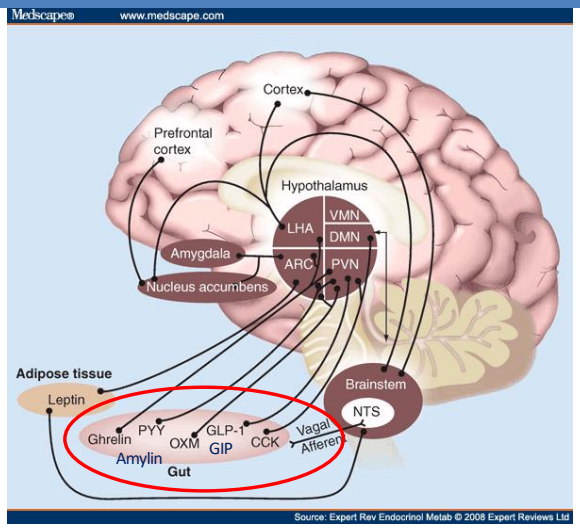
Understanding the Role of Obesity Medications: Appetite Regulation and the Gut-brain Axis

Nutrient-Stimulated Hormones



GUT

PYY= peptide YY

GLP-1 = Glucagon-like peptide 1

GIP = glucose dependent insulinotropic polypeptide

OXM=Oxyntomodulin

CCK=Cholecystokinin

BRAIN

LHA = lateral hypothalamic area

ARC = arcuate nucleus

VMN = ventromedial hypothalamus

DMN = dorsomedial hypothalamic nucleus

PVN = paraventricular nucleus

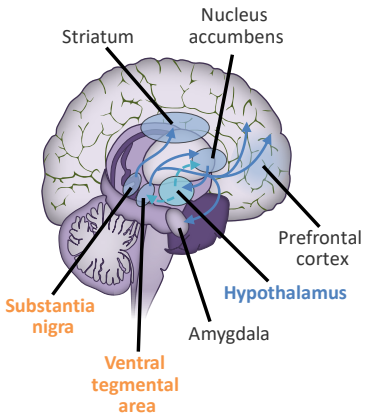
NTS = nucleus tractus solitarius

7

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

Homeostatic System
Hunger / Satiety

- Primarily driven by the arcuate nucleus of the **hypothalamus**
- Detection and integration of energy state information
  - 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.

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

8

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)

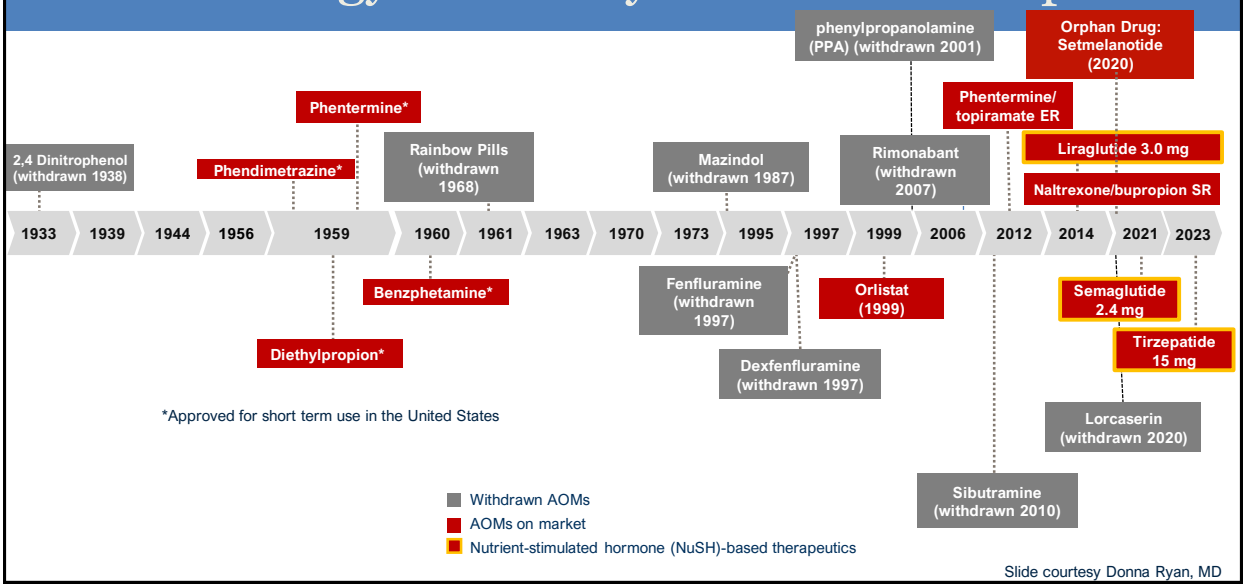
Liking (hedonic)
Sensory pleasure elicited by contact with food

Prospective food consumption
How much an individual feels they would like to eat

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

9

Chronology of Obesity Pharmacotherapies



10

What Is the Primary Purpose of Adjunctive Medications Used in the Treatment of Obesity?

The primary purpose of obesity medications

- Impact the appetite dysregulation of the disease,
- Support adherence to lifestyle interventions by helpin calorie diet and changing their relationship with food,
- Facilitate weight loss and improvements in health

Indicated as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management

BMI of ≥30 or ≥27 with a weight-related complication or comorbidity

11

FDA Approved Obesity Medications

Agents	Mechanism of Action	Effect	Approval Date
Phentermine	▪ Modified amphetamine	Appetite regulation	1959
Orlistat	▪ Blocks the GI lipase enzymes that absorbs fat	Reduces fat absorption	1999
Phentermine/topiramate ER	▪ Modified amphetamine ▪ Anticonvulsant medication already approved for prevention of migraine headaches and for seizure disorder	Appetite regulation	2012
Naltrexone/bupropion SR	▪ Opioid receptor blocker ▪ Increases dopamine/noradrenaline in the brain (already approved for depression and smoking cessation)	Appetite regulation	2014
Liraglutide	▪ Mimics action of GLP-1 gut hormone	Appetite regulation	2014
Setmelanotide	▪ Activates a specific neuro pathway (MC4R) in the brain (indication: obesity due to rare monogenetic forms of obesity)	Appetite regulation	2020
Semaglutide	▪ Mimics action of GLP-1 gut hormone	Appetite regulation	2021
Tirzepatide	▪ Mimics action of GLP-1/GIP gut hormones	Appetite regulation	2023

12

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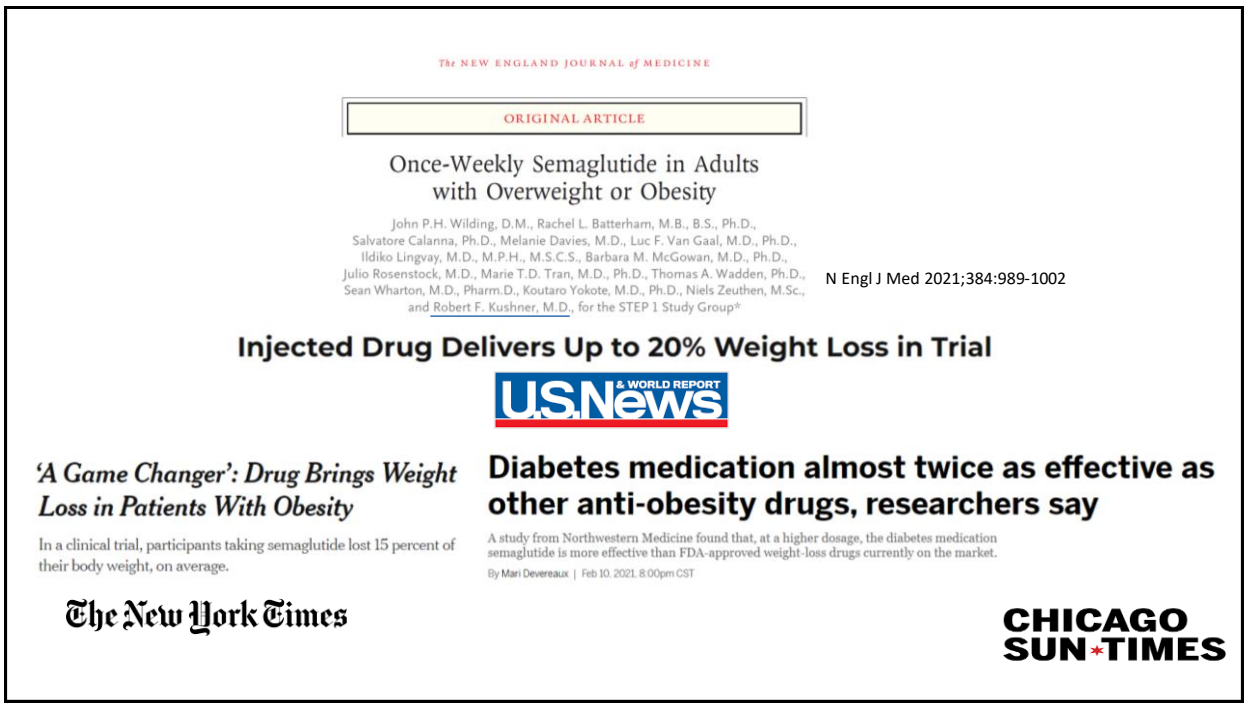
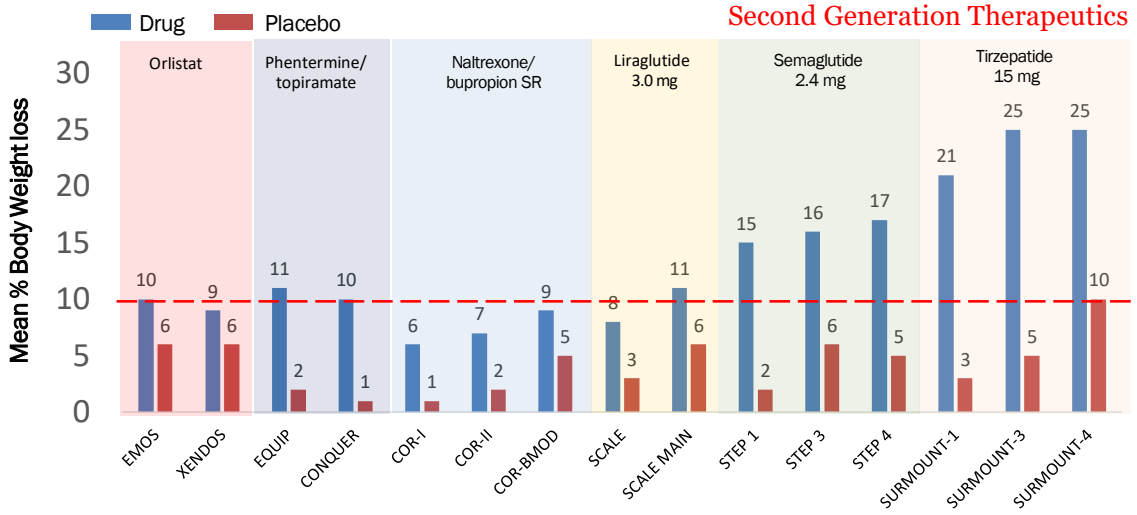
13



14

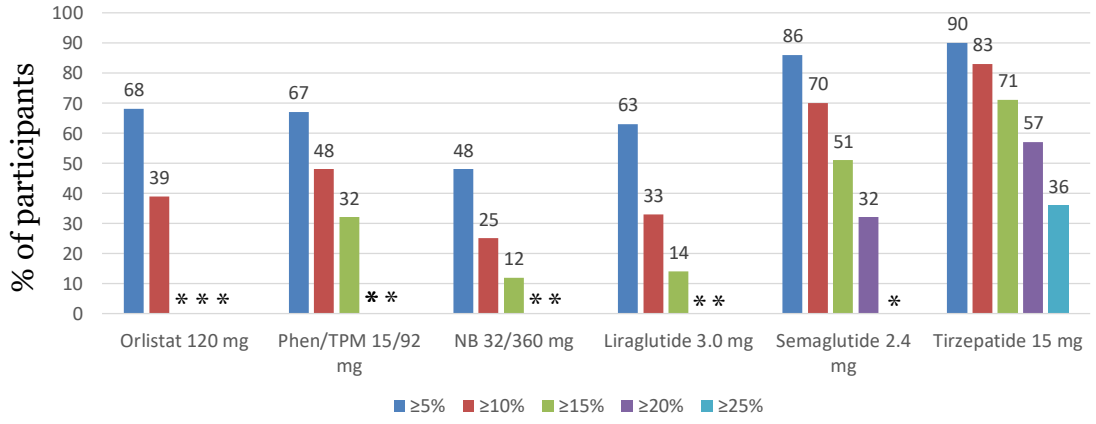
Percent Weight Loss (Drug vs Placebo), Non-Diabetes



Sjöstrom L, et al. *Lancet*. 1998;352(9123):167-172; Davidson MH, et al. *JAMA*. 1999;281(3):235-242; Allison DB, et al. *Obesity (Silver Spring)*. 2012;20(2):330-342; Gadde KM, et al. *Lancet*. 2011;377(9774):1341-1352; Greenway FL, et al. *Lancet*. 2010;376(9741):595-605; Apovian CM, et al. *Obesity (Silver Spring)*. 2013;21(5):935-943; Wadden TA, et al. *Obesity (Silver Spring)*. 2011;19(1):110-120; Pi-Sunyer X, et al. *N Engl J Med*. 2015;373:11-22; Wadden TA, et al. *Int J Obes (Lond)*. 2013;37(11):1443-1451; Wilding JPH, et al. *N Engl J Med*. 2021;384(11):989-1002; Wadden TA, et al. *JAMA*. 2021;325(14):140–1413; Rubino D, et al. *JAMA*. 2021;325(14):1414-1425; Jastreboff AM, et al. *N Engl J Med*. 2022;387(3):205-216; Wadden TA, et al. *Nat Med*. 2023;29(11):2909-2918.

15

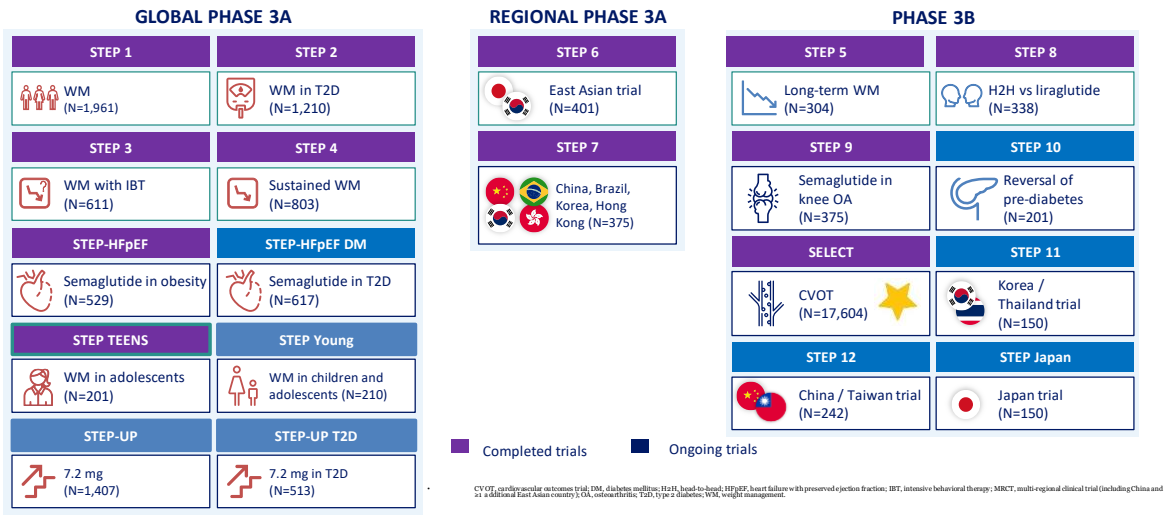
Categorical Weight Loss



16

The STEP Program

Phase 3 Clinical Trial Program of Semaglutide 2.4 mg (S.C. Once Weekly)

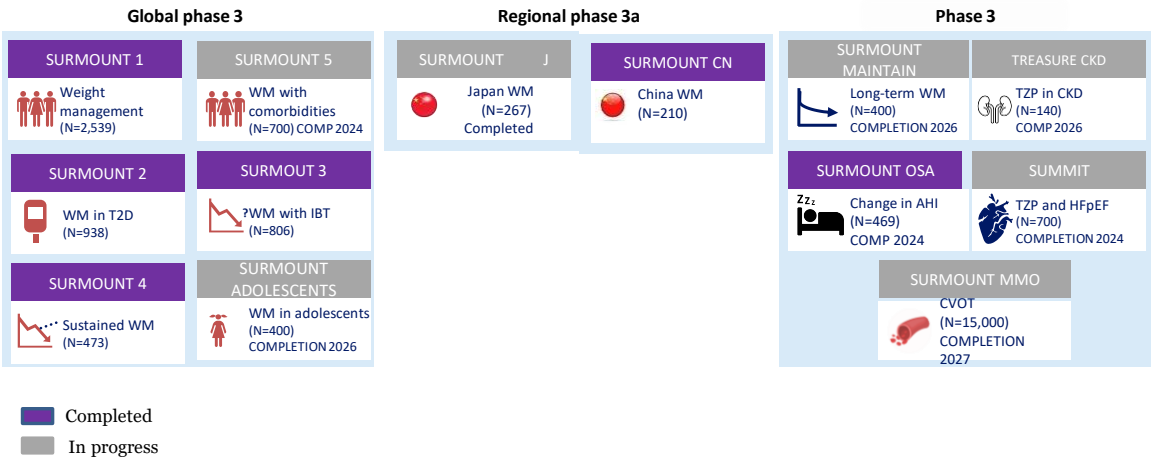


CVOT, cardiovascular outcomes trial; DM, diabetes mellitus; H2H, head-to-head; HFpEF, heart failure with preserved ejection fraction; IBT, intensive behavioral therapy; MRCT, multi-regional clinical trial (including China and ≥1 additional East Asian country); OA, osteoarthritis; T2D, type 2 diabetes; WM, weight management.

17

SURMOUNT Program at a Glance

Phase 3 Clinical Trial Program of Tirzepatide 10-15 mg (S.C. Once Weekly)



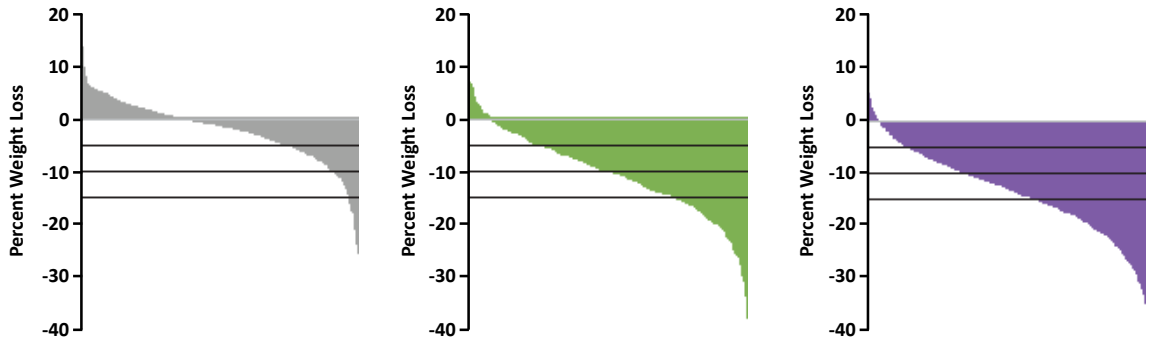
18

Key Points to Know About Obesity Medications

1. Heterogeneity of Treatment Effect (THE)
2. Look for Early Response
3. Note Withdrawal Response
4. Benefits of Continued Use
5. Improved Metabolic Risk Factors
6. Affect on Appetite
7. GLP-1 has Pleotropic Effects – CV Risk Reduction
8. Dose Escalation

19

1. Heterogeneity of Treatment Effect

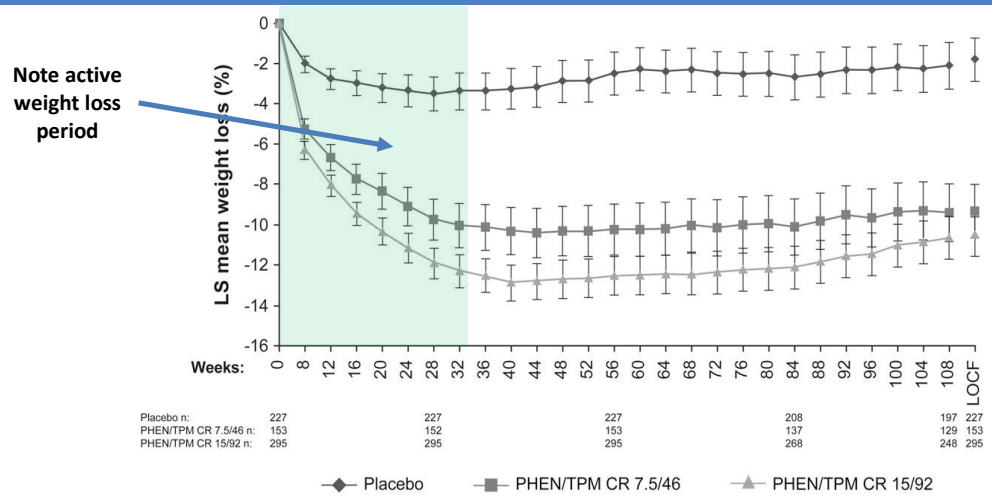


Each vertical bar represents a single subject experience in subjects completing 56 weeks on study drug

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.

20

2. Look for Early Response

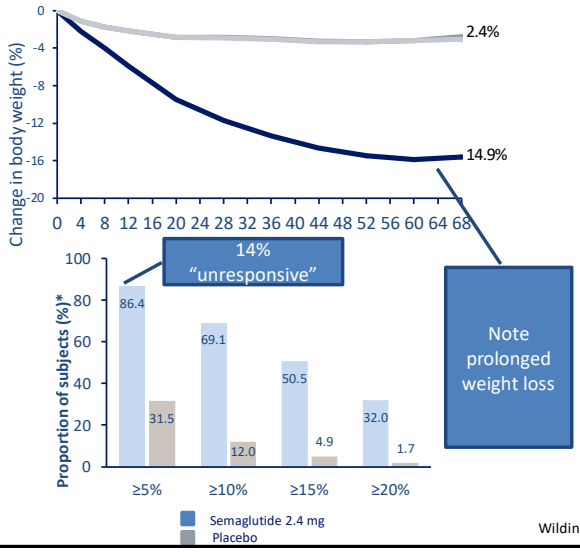


Garvey WT, et al. *Am J Clin Nutr.* 2012;95:297-308.

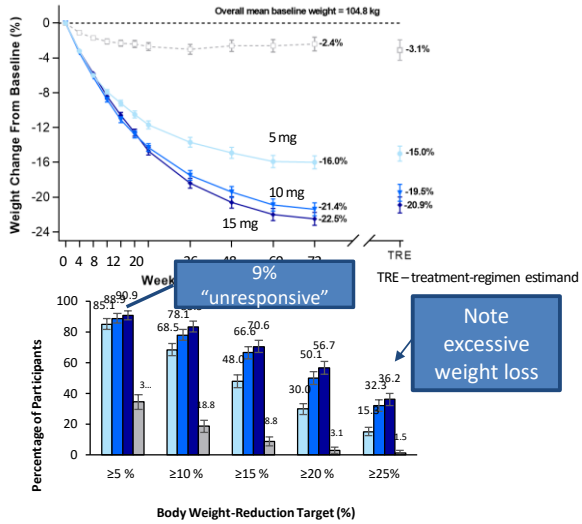
21

STEP 1 and SURMOUNT 1

Semaglutide



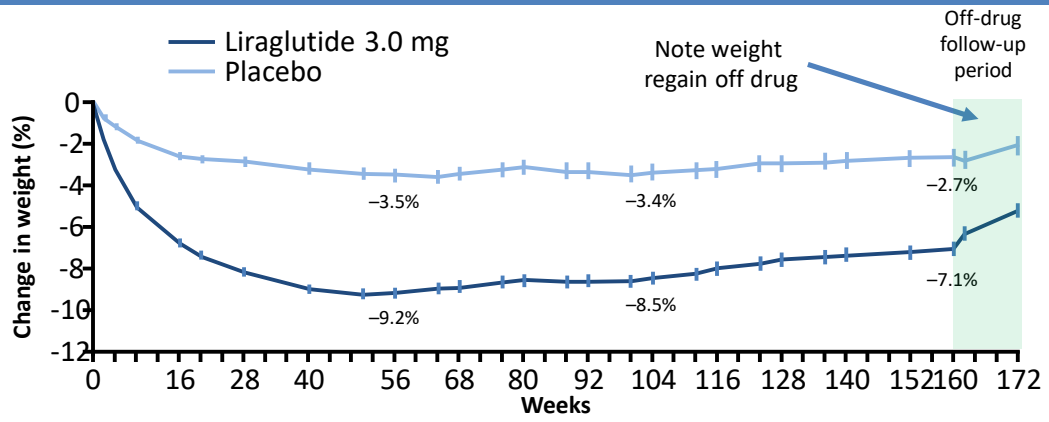
Tirzepatide



Wilding JPH, et al. N Engl J Med 2021;384:989-100; Jastreboff AM, et al N Engl J Med 2022;387:205-216

22

3. Note Withdrawal Response

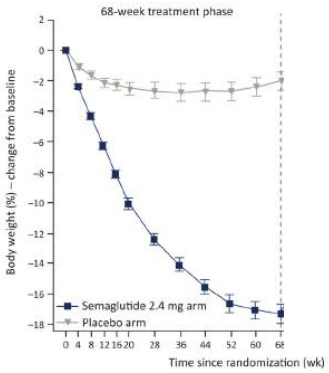


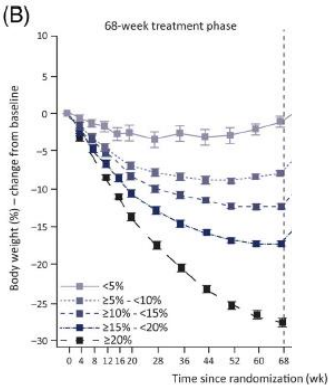
2254 patients with prediabetes and a BMI of ≥ 30 kg/m^2 or ≥ 27 kg/m^2 and comorbidities

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

23

The STEP 1 Trial Extension of Semaglutide 2.4 mg



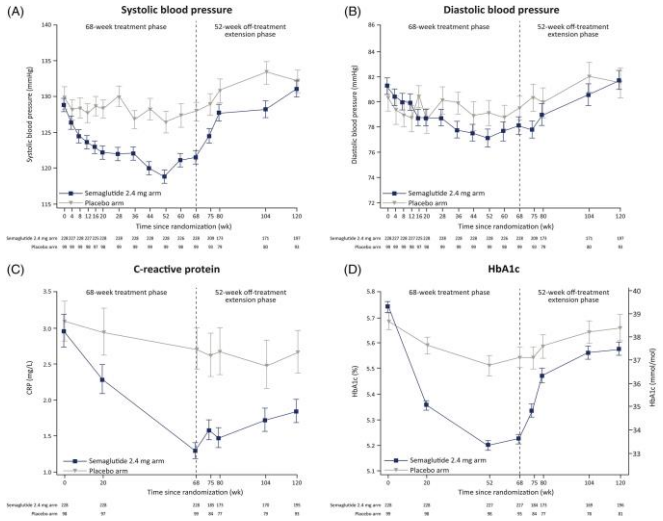


N=327 subject

Wilding JPH et al. Diab Obes Metab 2022:1-12

24

The STEP 1 Trial Extension of Semaglutide 2.4 mg



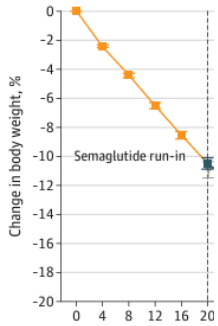
Wilding JPH et al. Diab Obes Metab 2022:1-12

25

What Happens When You "Blindly" Stop the Medication?

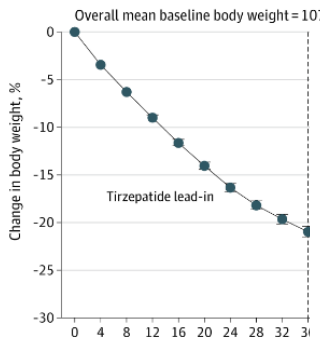
STEP 4 (semaglutide)

Overall mean baseline body weight = 107.2 kg



SURMOUNT-4 (tirzepatide)

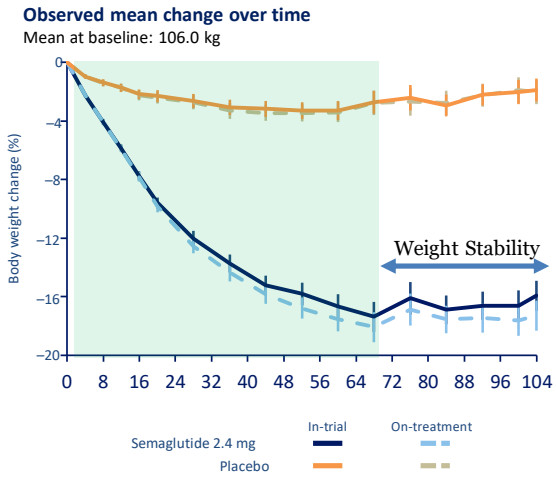
Overall mean baseline body weight = 107.3 kg

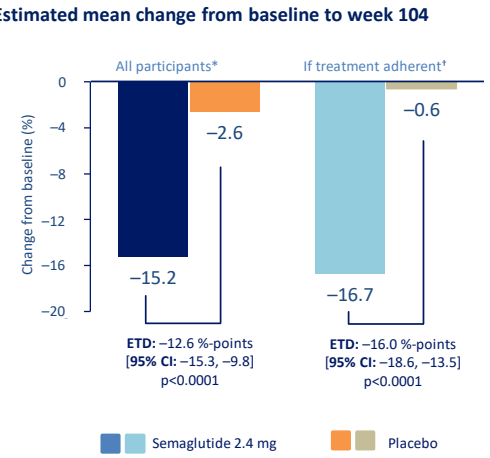


Rubino D et al. JAMA 2021 Apr 13;325(14):1414-1425; Aronne LJ et al. JAMA 2023 (online)

26

4. Benefit of Continued Use
STEP 5 Trial

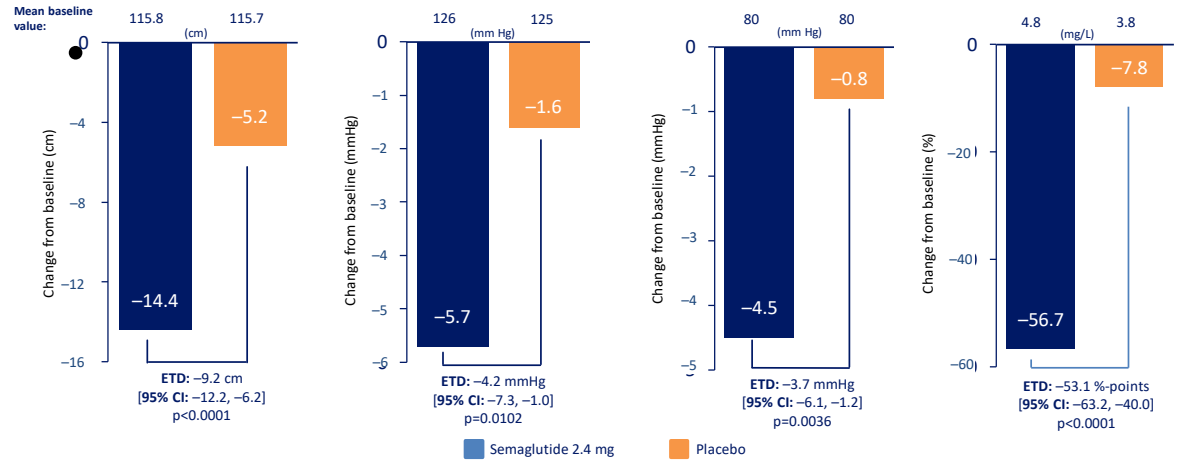




Garvey WT et al. Nature Medicine 2022;28:2083-2091

27

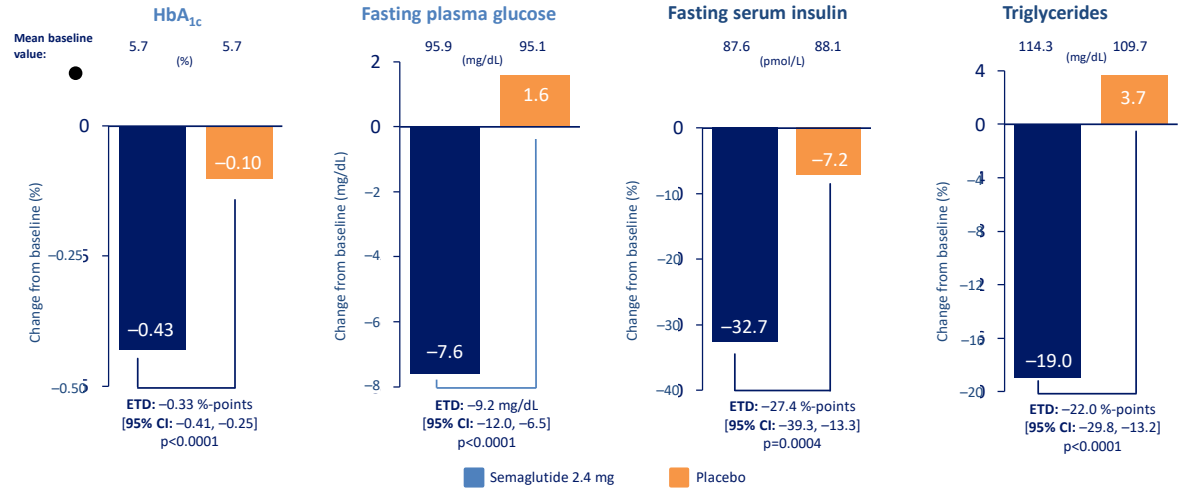
5. Improved Cardiovascular Risk Factors
STEP 5 Trial



Garvey WT, et al. *Nat Med.* 2022;28(10);2083-2091.

28

5. Improved Metabolic Risk Factors STEP 5 Trial



Garvey WT, et al. *Nat Med*. 2022;28(10);2083-2091.

29

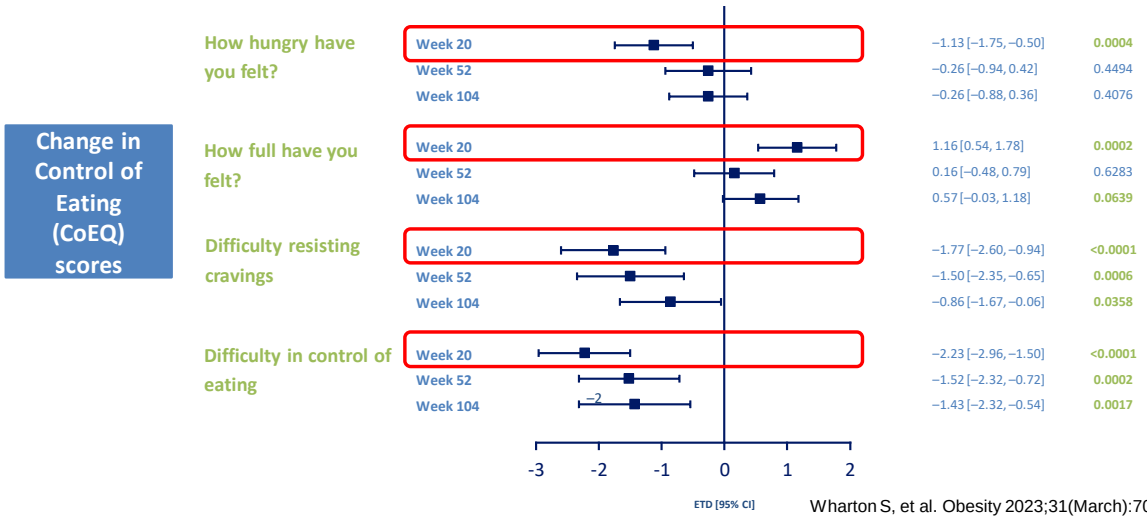
5. Improved Metabolic Risk Factors Across Drugs

	Orlistat	Phentermine/ topiramate ER	Naltrexone/ bupropion SR	Liraglutide 3.0 mg	Semaglutide 2.4 mg	Tirzepatide 15 mg
WC	↓	↓	↓	↓	↓	↓
BP	↓	↓	↑	↓	↓	↓
LDL	↓↓	↓	↓	↓	↓	↓
HDL	↑	↑	↑	↑	↑	↑
TG	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓
A1C	↓	↓	↓	↓↓↓	↓↓↓	↓↓↓
HR	↓	-	↑	↑	↑	↑
Diabetes	↓↓	↓↓	↓	↓↓↓	↓↓↓	↓↓↓

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.

30

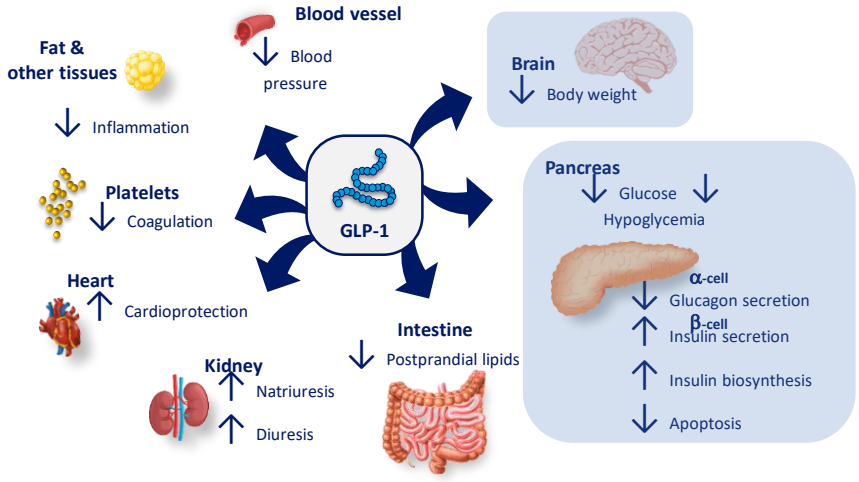
6. Effect on Appetite STEP 5 Trial



Wharton S, et al. Obesity 2023;31(March):703-715

31

7. GLP-1 Has Pleotropic Effects – CV Risk Reduction



Ryan DH, et al. *Am Heart J.* 2020;229:61-69.

32

Overview of Status & Key Results from Obesity Studies: CVOTs & Registries

	SCOUT[1]	CRESCENDO[2]	LIGHT[3]	CONVENE[4]	CAMELLIA-TIMI[5]
Intervention	Sibutramine*	Rimonabant*	Naltrexone/ bupropion	Naltrexone/ bupropion	Lorcaserin*
Primary outcome	3P-MACE + resuscitated cardiac arrest	3P-MACE	3P-MACE	3P-MACE	1. 3P-MACE (safety outcome) 2. MACE+ (efficacy outcome)
Trial status	Completed	Terminated prematurely *(Safety concerns)*	Terminated prematurely *(Study integrity compromised)*	Terminated prematurely *(Selling of US rights)*	Completed
HR (95% CI) for primary outcome	1.16 (1.03; 1.31); p=0.02	0.97 (0.84; 1.12); p=0.68	50% interim analysis: 0.88 (0.57; 1.34)	No data available	MACE+: 0.97 (0.87; 1.07); p=0.55
Safety/ outcome results	Not safe/Harm†	Not safe‡/Neutral	Safe/Neutral *(integrity compromised)*	No data available	Safe/Neutral
Weight change§	–1.7 kg (vs +0.7 kg) at 12 months	N/A	–3.6% (vs –1.1%) at trial end	No data available	–4.0 kg (vs –2.1 kg) at 40 months

Trial terminated/Not safe
Neutral
Trial completed

* withdrawn

3P-MACE, composite of CV death, non-fatal MI and non-fatal stroke; 5P-MACE, composite of all-cause death, non-fatal MI, non-fatal stroke, coronary revascularisation or HF events; MACE+, composite of MI, stroke, CV death, and hospitalisation due to unstable angina, HF or any coronary revascularisation.
CI, confidence interval; CV, cardiovascular; CVOT, cardiovascular outcome trial; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction; T2D, type 2 diabetes.
See slide notes for footnotes and references.

33

Rationale for SELECT

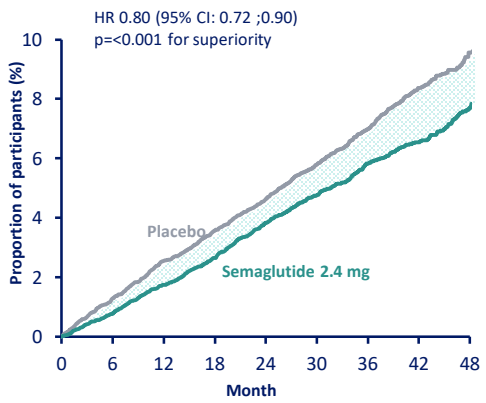
Individuals with overweight or obesity and high cardiovascular risk, but without established diabetes, are candidates for heart disease secondary prevention.

SELECT was not a weight loss study. It was a heart disease prevention study.

Ryan DH et al. Am Heart J 2020;229:61-69.

34

SELECT: Semaglutide 2.4 mg CVOT



20% reduction in MACE*

Semaglutide 2.4 mg significantly reduced MACE* incidence

versus placebo† over a period of up to 5 years[1]

All three components (CV death, non-fatal MI and non-fatal stroke) contributed to this MACE reduction[1]

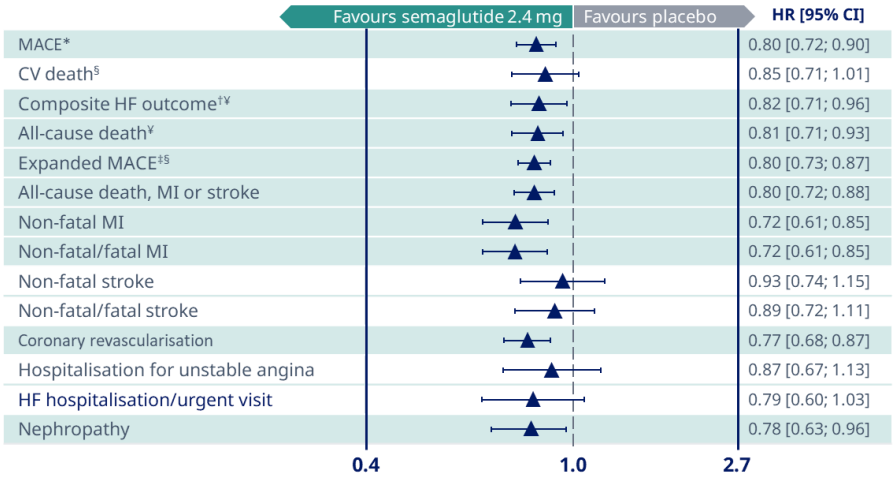
The effect of semaglutide 2.4 mg on MACE* appeared to be **consistent across different patient subgroups**

MACE, major adverse cardiovascular events; MI, myocardial infarction

Lincoff AM, et al. *N Engl J Med*. 2023. doi:10.1056/NEJMoa2307563

35

SELECT: Semaglutide 2.4 mg Showed Consistent Beneficial Effects Across all Measured CV Outcomes

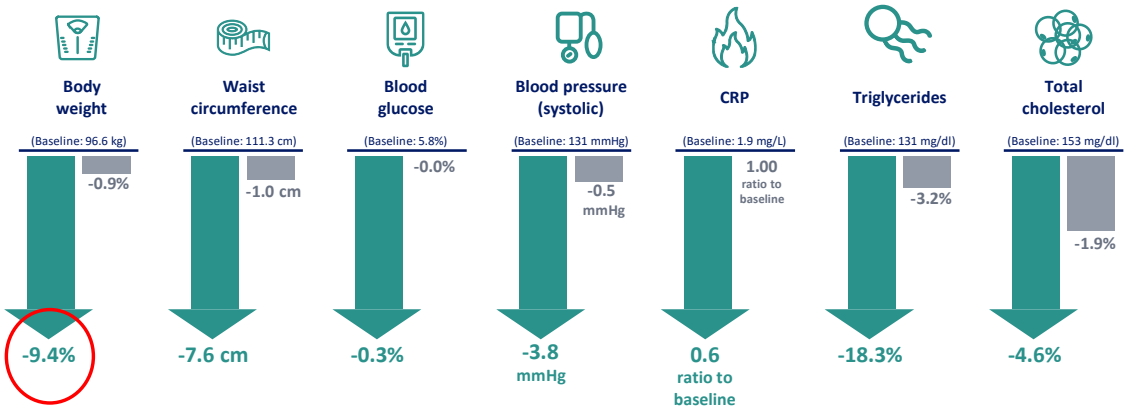


Lincoff AM, et al. *N Engl J Med*. 2023. doi:10.1056/NEJMoa2307563

36

SELECT – Changes in Cardiometabolic Parameters

Change from baseline to Week 104 in semaglutide 2.4 mg and placebo groups[1]



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

37

Overview of Status & Key Results from Obesity Studies: CVOTs & Registries

	SCOUT[1]	CRESCENDO[2]	LIGHT[3]	CONVENE[4]	CAMELLIA-TIMI[5]	SELECT[6]
Intervention	Sibutramine*	Rimonabant*	Naltrexone/ bupropion	Naltrexone/ bupropion	Lorcaserin*	Once-weekly semaglutide
Primary outcome	3P-MACE + resuscitated cardiac arrest	3P-MACE	3P-MACE	3P-MACE	1. 3P-MACE (safety outcome) 2. MACE+ (efficacy outcome)	3P-MACE
Trial status	Completed	Terminated prematurely *(Safety concerns)*	Terminated prematurely *(Study integrity compromised)*	Terminated prematurely *(Selling of US rights)*	Completed	Completed
HR (95% CI) for primary outcome	1.16 (1.03; 1.31); p=0.02	0.97 (0.84; 1.12); p=0.68	50% interim analysis: 0.88 (0.57; 1.34)	No data available	MACE+: 0.97 (0.87; 1.07); p=0.55	0.80 (0.72; 0.90); p<0.001
Safety/ outcome results	Not safe/Harm†	Not safe†/Neutral	Safe/Neutral *(integrity compromised)*	No data available	Safe/Neutral	Safe/Benefits (3P-MACE)
Weight change§	–1.7 kg (vs +0.7 kg) at 12 months	N/A	–3.6% (vs –1.1%) at trial end	No data available	–4.0 kg (vs –2.1 kg) at 40 months	–9.4% (vs –0.9%) at 24 months

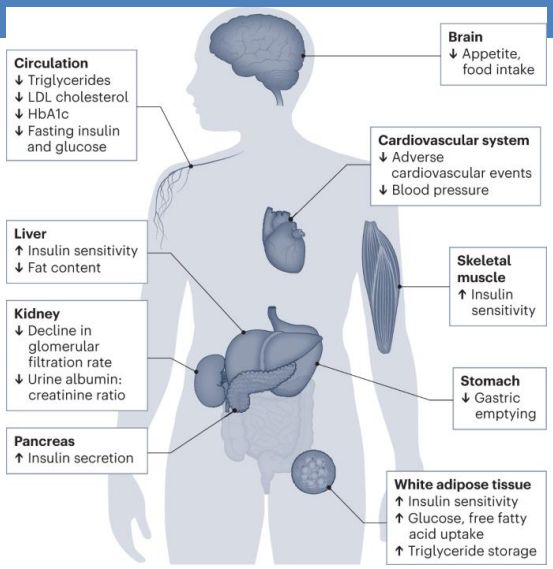
Trial terminated/Not safe
Neutral
Trial completed

* withdrawn

3P-MACE, composite of CV death, non-fatal MI and non-fatal stroke; 5P-MACE, composite of all-cause death, non-fatal MI, non-fatal stroke, coronary revascularisation or HF events; MACE+, composite of MI, stroke, CV death, and hospitalisation due to unstable angina, HF or any coronary revascularisation.
CI, confidence interval; CV, cardiovascular; CVOT, cardiovascular outcome trial; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction; T2D, type 2 diabetes.
See slide notes for footnotes and references.

38

GLP-1 and GIP Incretin Hormones: Extended Metabolic Effects



Semaglutide
GLP-1 Receptor Agonist
Ozempic® for diabetes
Wegovy® for obesity

Tirzepatide
GLP-1/GIP Receptor Agonist
Mounjaro® for diabetes
Zepbound® for obesity

GLP-1 = glucagon like peptide-1, GIP = glucose dependent insulinotropic polypeptide

39

The American Diabetes Association (ADA) Includes Weight Management in its Most Recent Guidelines - 2024

Achievement and Maintenance of Weight Management Goals:

Set individualized weight management goals

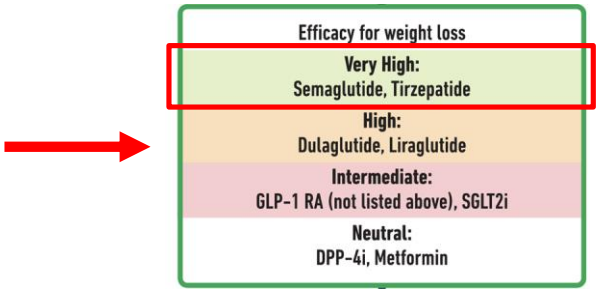
General lifestyle advice: medical nutrition therapy/eating patterns/ physical activity

Intensive evidence-based structured weight management program

Consider medication for weight loss

Consider metabolic surgery

When choosing glucose-lowering therapies:
Consider regimen with high-to-very-high dual glucose and weight efficacy



Data from SUSTAIN and SURPASS Trials

Diabetes Care. 2024.

40

The 5 C's of Choosing an AOM

1	**C**ontraindications and cautions	*Assess the patient's clinical history and risk/benefit of each AOM*
2	**C**omorbidities	*When appropriate, use an AOM that can treat obesity and improve other comorbidities*
3	**C**ues	*Consider patient-described appetite control symptoms, AEs, and mode of delivery*
4	**C**ombinations	*Consider combination therapy with lifestyle interventions, other AOMs, and surgery*
5	**C**ost and coverage	*Consider the medication cost and patient's insurance coverage*

Adapted from Horn. Postgrad Med. 2022;134:359.

41

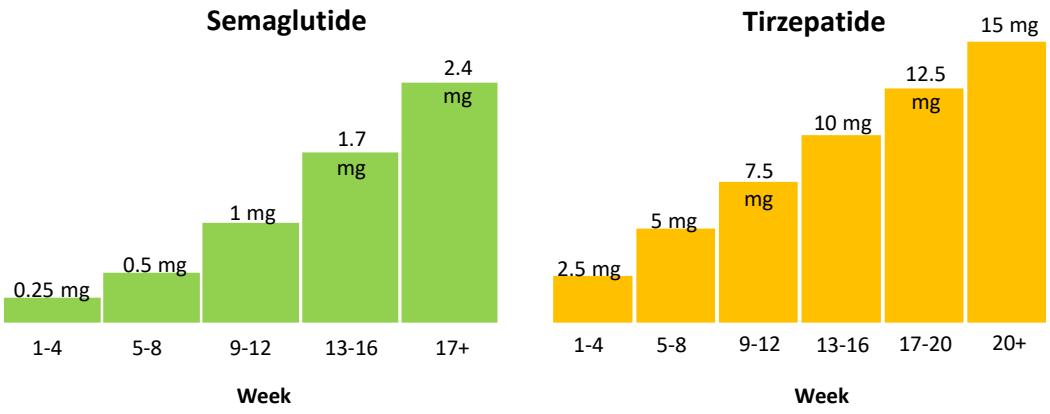
Common Adverse Events with Semaglutide: STEP 1

	Semaglutide (N=1306)	Placebo (N=655)
AE leading to discontinuation	7.0%	3.1%
Nausea	44.2%	17.4%
Diarrhea	31.5%	15.9%
Vomiting	24.8%	6.6%
Constipation	23.4%	9.5%
Nasopharyngitis	21.5%	20.3%
Headache	15.2%	12.2%
Dyspepsia	10.3%	3.5%
Abdominal pain	10.0%	5.5%
Upper respiratory tract infection	8.7%	12.2%

Wilding JPH, et al. *N Engl J Med*. 2021;384(11):989-1002.

42

8. Dose Escalation



FDA Prescribing Information.

43

Patient Consultation and Counseling

- GI side effects are typically mild-moderate, temporary nature
- Will titrate dose up to help with adverse events

Tips to Reduce Side Effects from GLP-RAs and GLP-1/GIP RAs

- Follow a scheduled eating pattern, do not skip meals
- Take the injection with a little food in the stomach

Gorgojo-Martinez JJ, et al. *J Clin Med.* 2023.

44

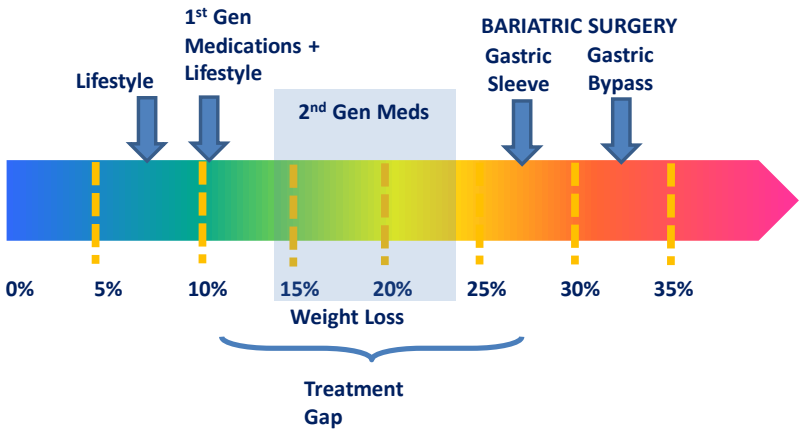
Emerging Anti-obesity Pharmacological Therapies: A New Paradigm

Category	Mechanism	Drug	Route	Development Stage	Weight Loss	Weeks
	GLP-1 RA	Semaglutide	SC	Approved '21	15.2%	104
	GLP-1/GIP RA	Tirzepatide	SC	Approved '23	21%	72
	GLP-1 RA	Semaglutide (SNAC)	Oral	Phase 3	17.4%	68
NuSH- based therapeutics	GLP-1 RA and Amylin RA	Cagri Sema	SC	Phase 3	_	_
	GLP-1/Glucagon RA	Survodutide Pemvidutide Cotadtide efinopegdutide	SC	Phase 2	14.9% - - -	46 - - -
	GLP-1/ GIP/Glucagon RA	Retatrutide	SC	Phase 2	24.2%	48
	GLP-1 small molecule RA	Danuglipron Orforglipron	Oral	Phase 2	- 14.7%	- 36
Monoclonal antibody	Activin type II RA	Bimagrumab	SC	Phase 2	_	_

RA, receptor agonist; SC, subcutaneous

45

Average Effectiveness of Available Treatments



Jensen et al. *Circulation.* 129(25 Suppl 2):S102-38, 2014
LABS consortium. *N Engl J Med.* 2009;361(5):445-54.
Colman E, et al. *N Engl J Med.* 2012;367(17):1577-79.

46

Take Home Points

- Pharmacotherapy is an evidence-based, effective treatment for obesity
- By knowing the expected weight loss trajectories, we can better monitor our patients for effectiveness and responsiveness
- Medications will likely be needed to be used long-term
- Hormonal treatment of obesity (e.g., GLP-1, GIP, amylin, glucagon) represents a new paradigm in obesity therapeutics
- 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

47