IMPACT OF OBESITY MEDICATIONS ON MODERN MEDICINE

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NOVEMBER 17,2024

UNIVERSITY of VIRGINIA

Disclosures

- Advisory Board, Eli Lilly
  - Ended

- I have noted brand names, in parentheses, where no generic options exist of medications to delineate the multiple FDA-approved uses of the same generic compound.

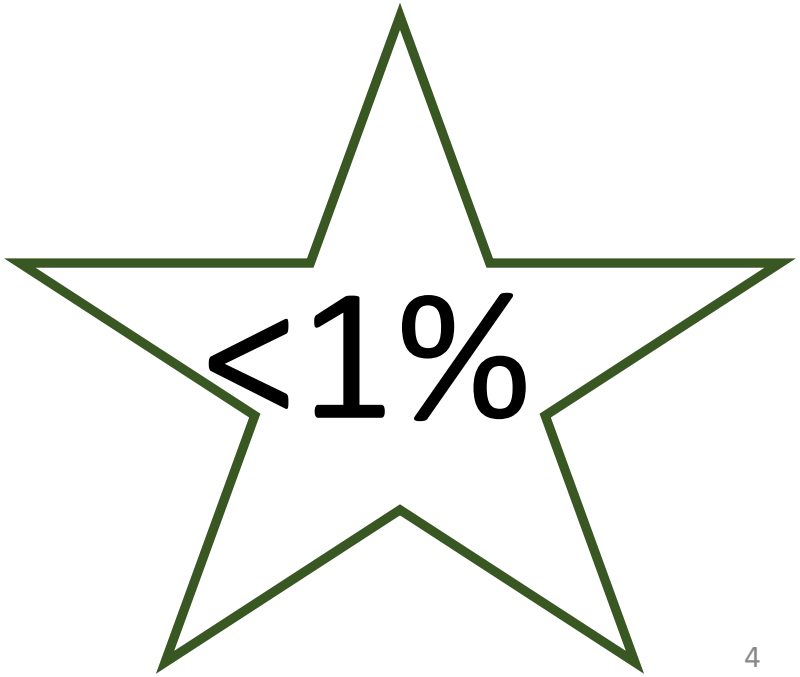
Objectives/Overview

1. State the impact that obesity has on patients and benefits of treating and preventing obesity.
2. Recognize barriers that exist in your patient population to treating overweight and obesity.
3. List 5 aspects of obesity treatment that healthcare providers should consider when tailoring a weight management intervention.

Obesity Specialists[1]

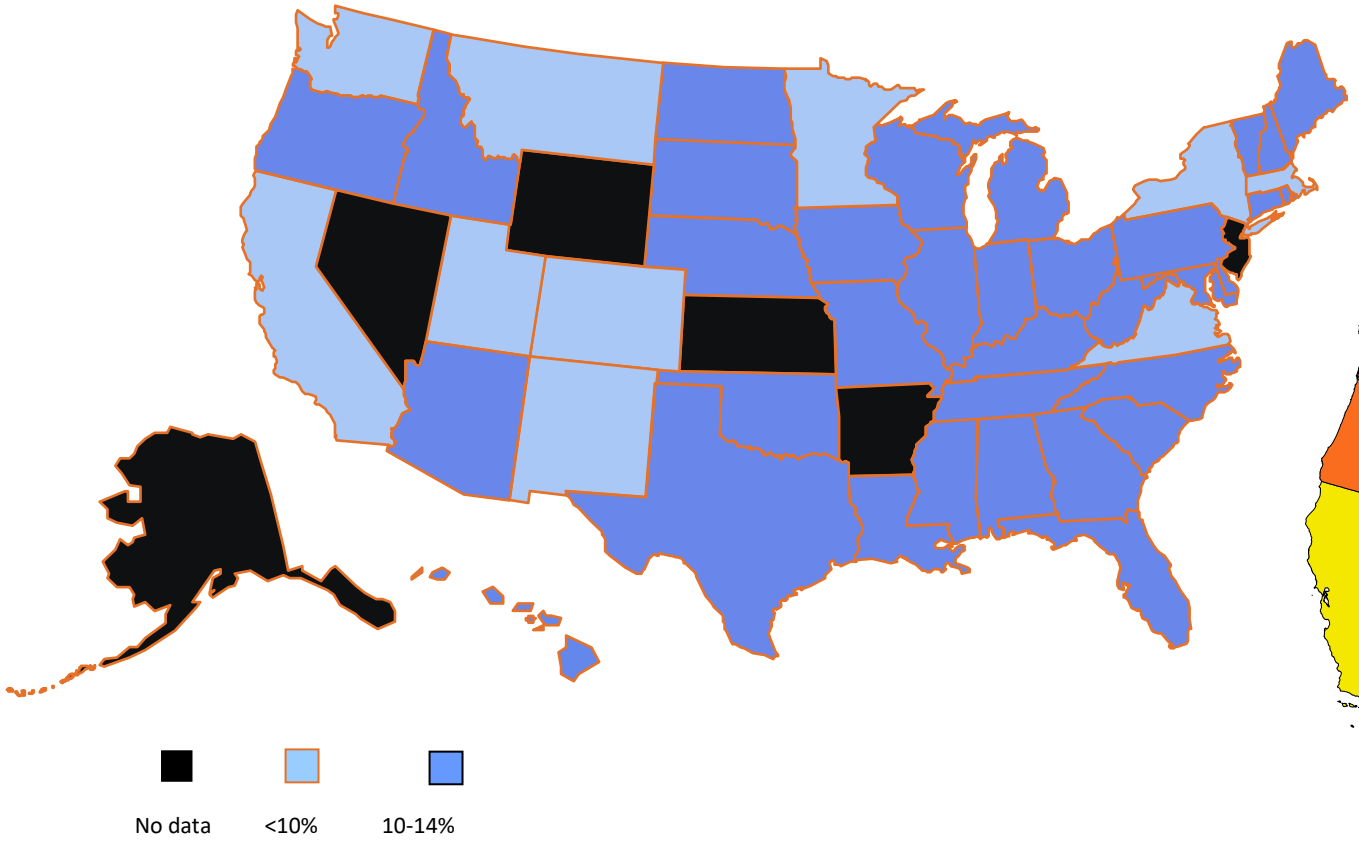
YEAR	ABOM DIPLOMATES
• 2024	8,263
• 2023	6,729
• 2022	5,880
• 2021	5,242
• 2020	4,102
• 2019	3,377
• 2018	2,656
• 2017	2,073

AMERICAN BOARD of OBESITY MEDICINE

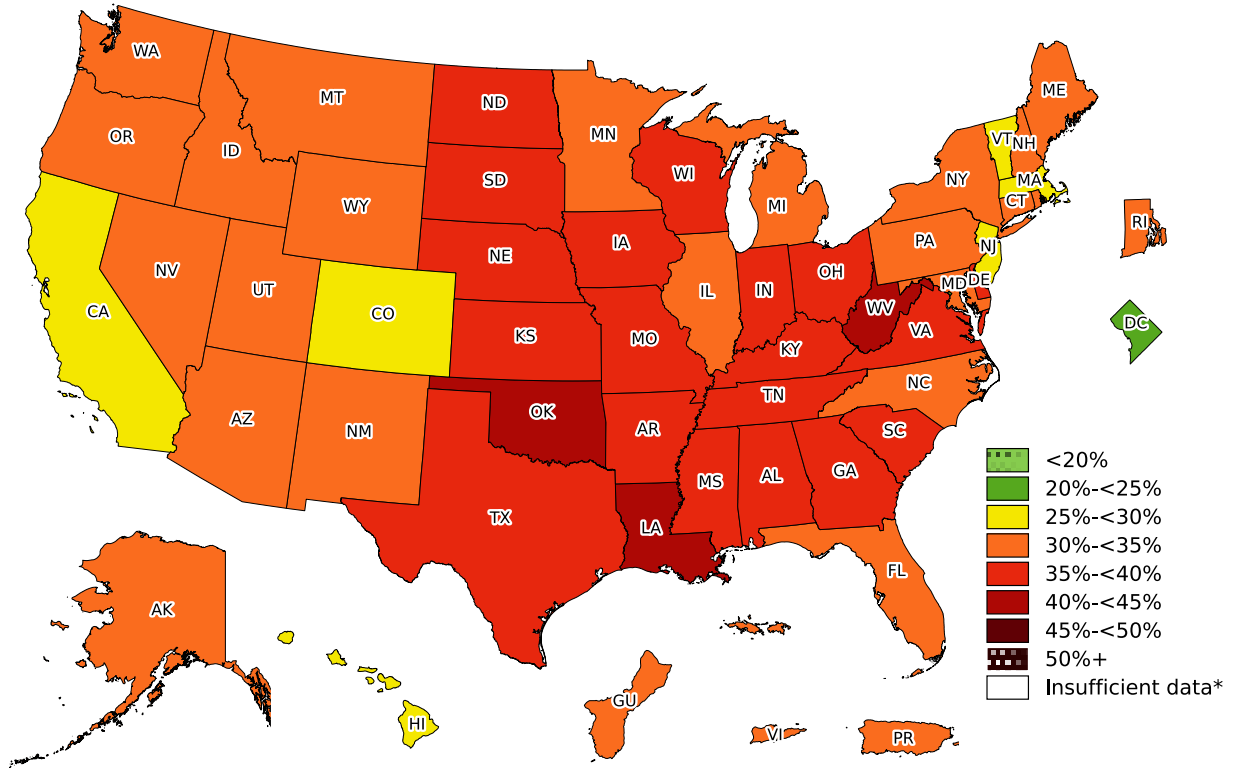


Obesity Trends in US Adults[2]

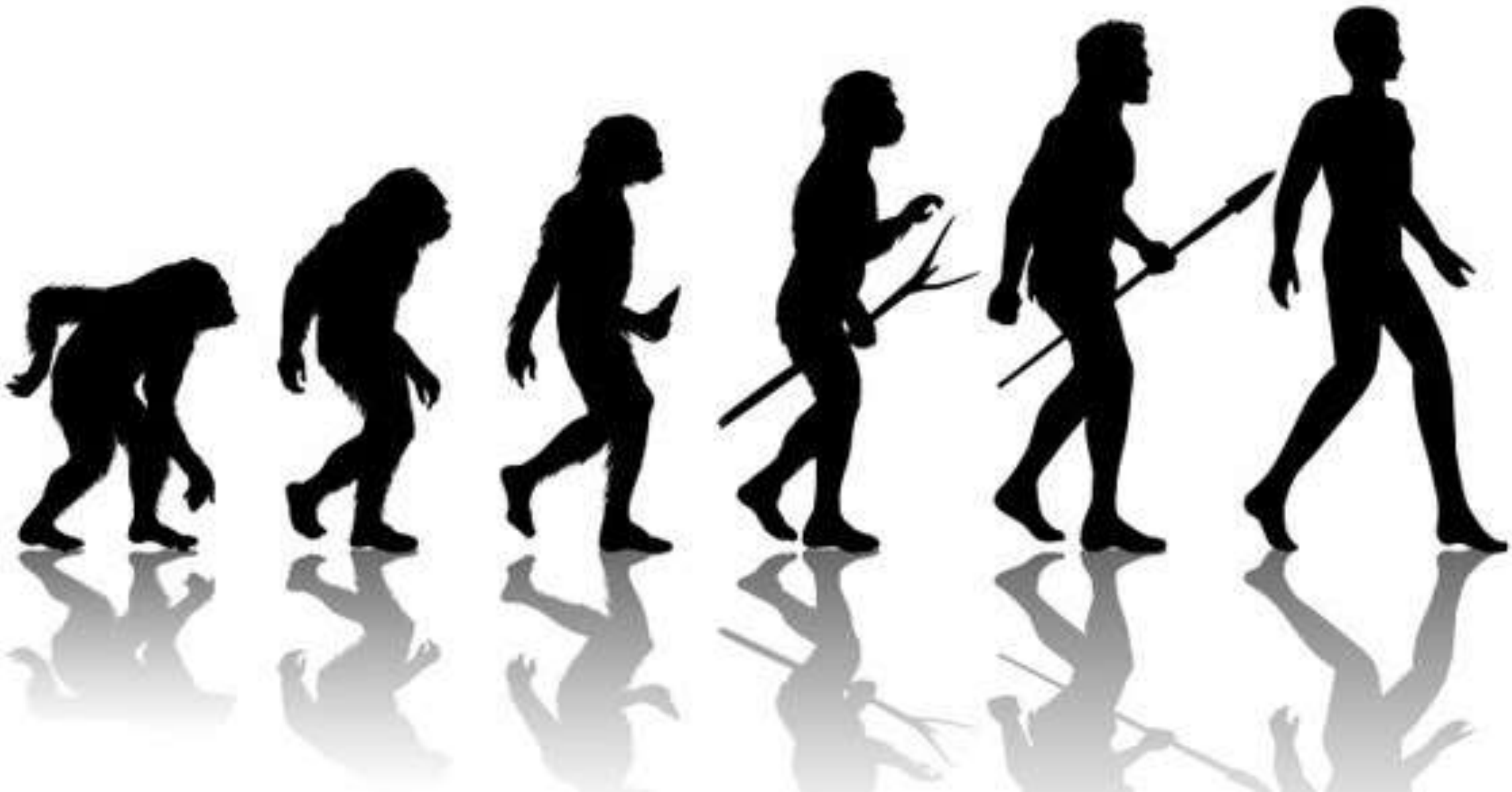
1990



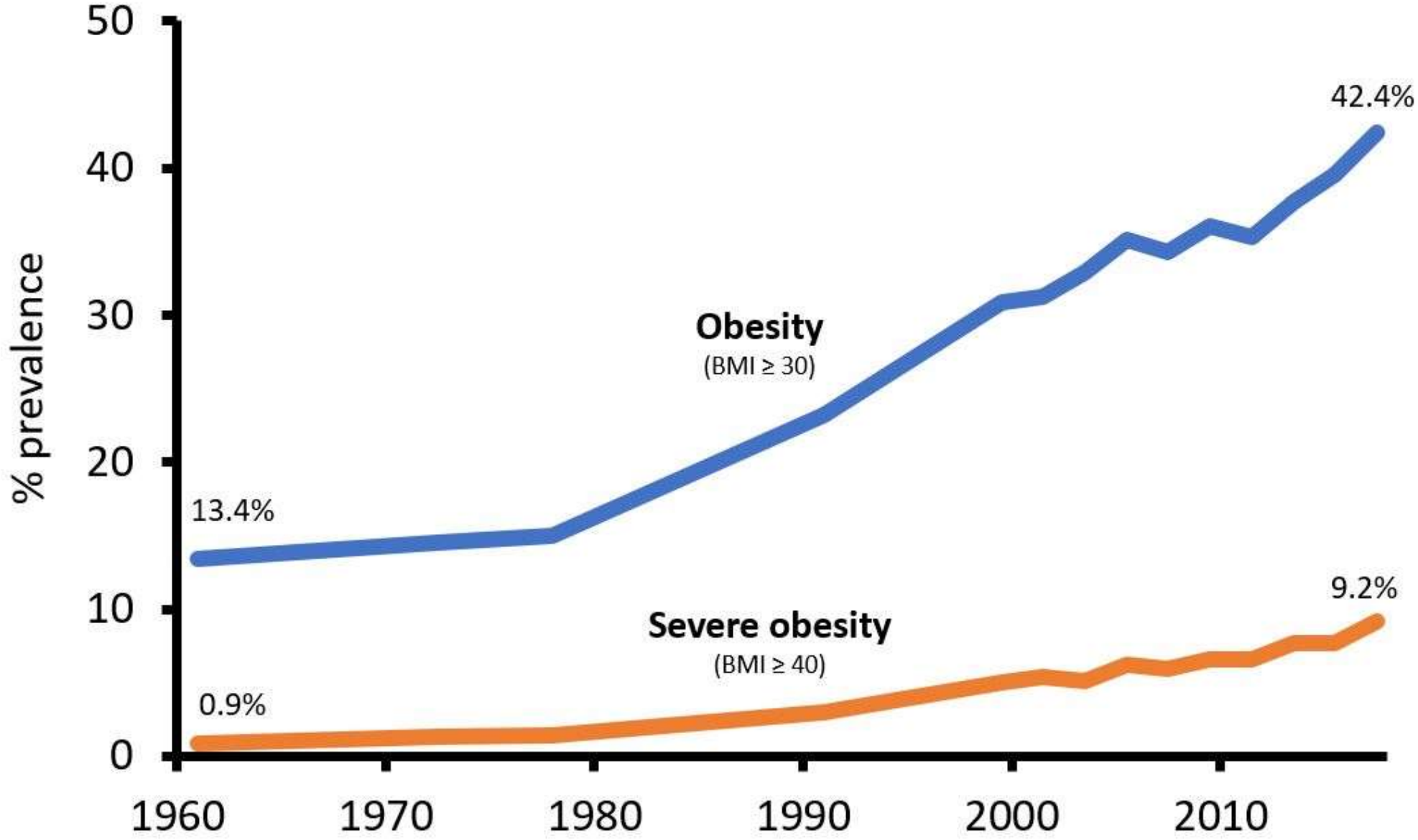
2022



CDC. Behavioral Risk Factor Surveillance System Survey, 2022.



Obesity prevalence in US adults, 1960-2018



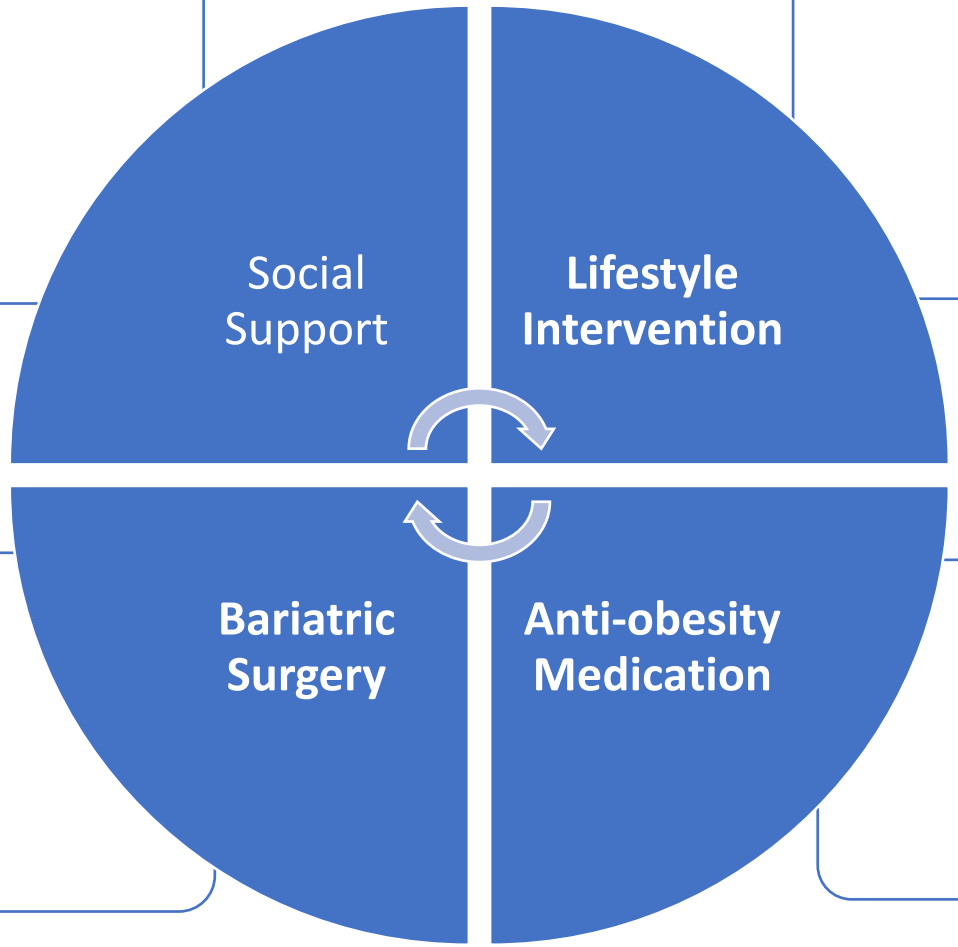
Prepared by Stephan J. Guyenet

Source: CDC, including https://www.cdc.gov/nchs/data/databriefs/db360-h.pdf

University of Virginia

- LCSW
- Monthly support meetings

- Registered Dieticians
- Community Based Exercise Programs



- First bariatric surgery in 1980s
- 300/year

- October 2021
- 550/year

Clinical Evidence of Disease

- 236 diseases
- 13 cancers

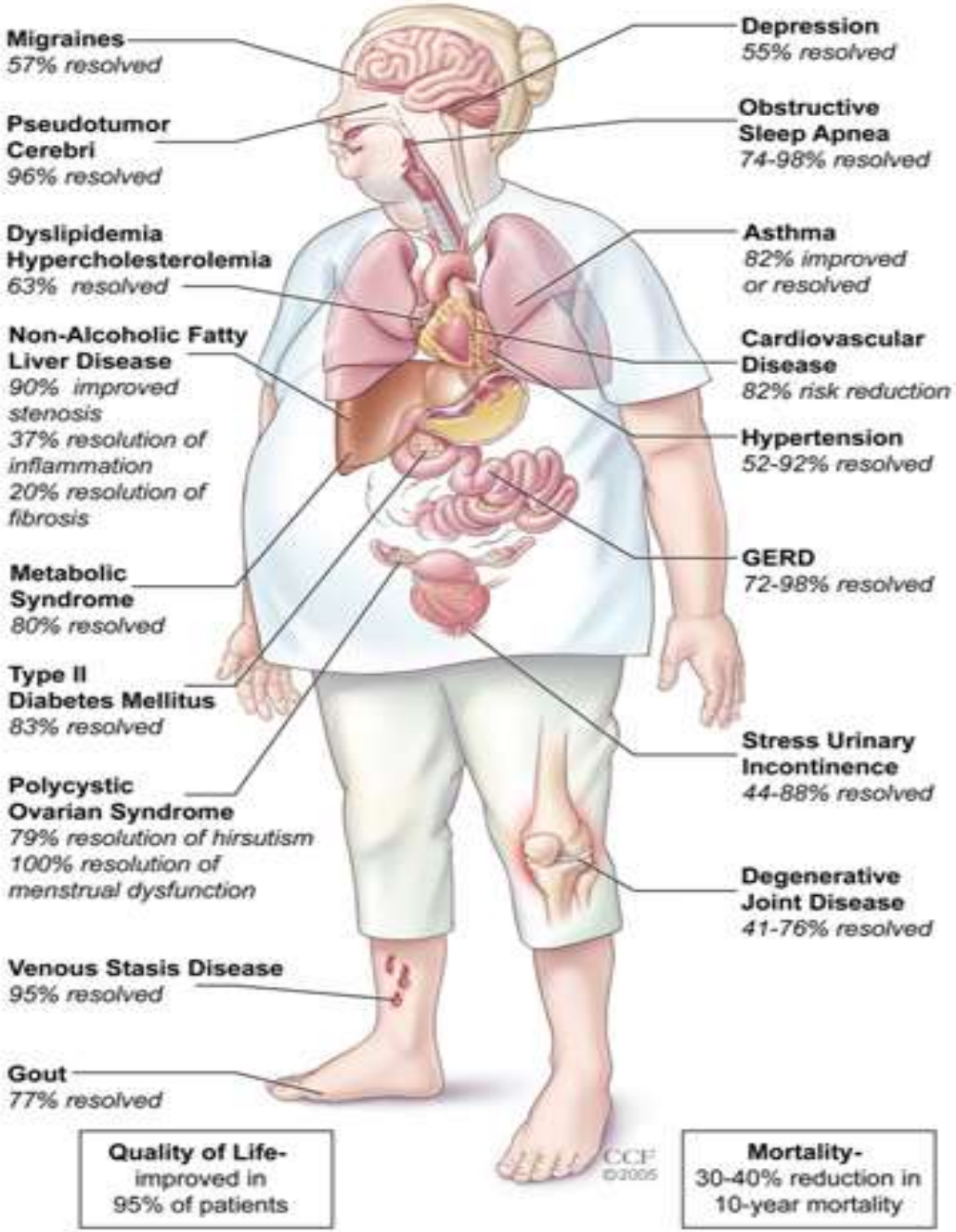


Photo source: Emory Healthcare

5-M Approach

Meals

10% vegetable intake[3]

Movement

46.9%[4]

Mind

Depression: 58% higher risk[5]

OSA: 2-3 fold risk of cardiometabolic disease[6]

Medication

<2%

Metabolic Surgery

<1%

5-M Approach

Meals

Tailored nutritional plan

Adequate protein intake

5 veggies>>fruits/d

Movement

150-420 minutes/week

Strengthening 3 d/week

Mind

Sleep hygiene

CBT

Meditation

Optimized medicine

Social network

Medication

FDA approved AOM therapy

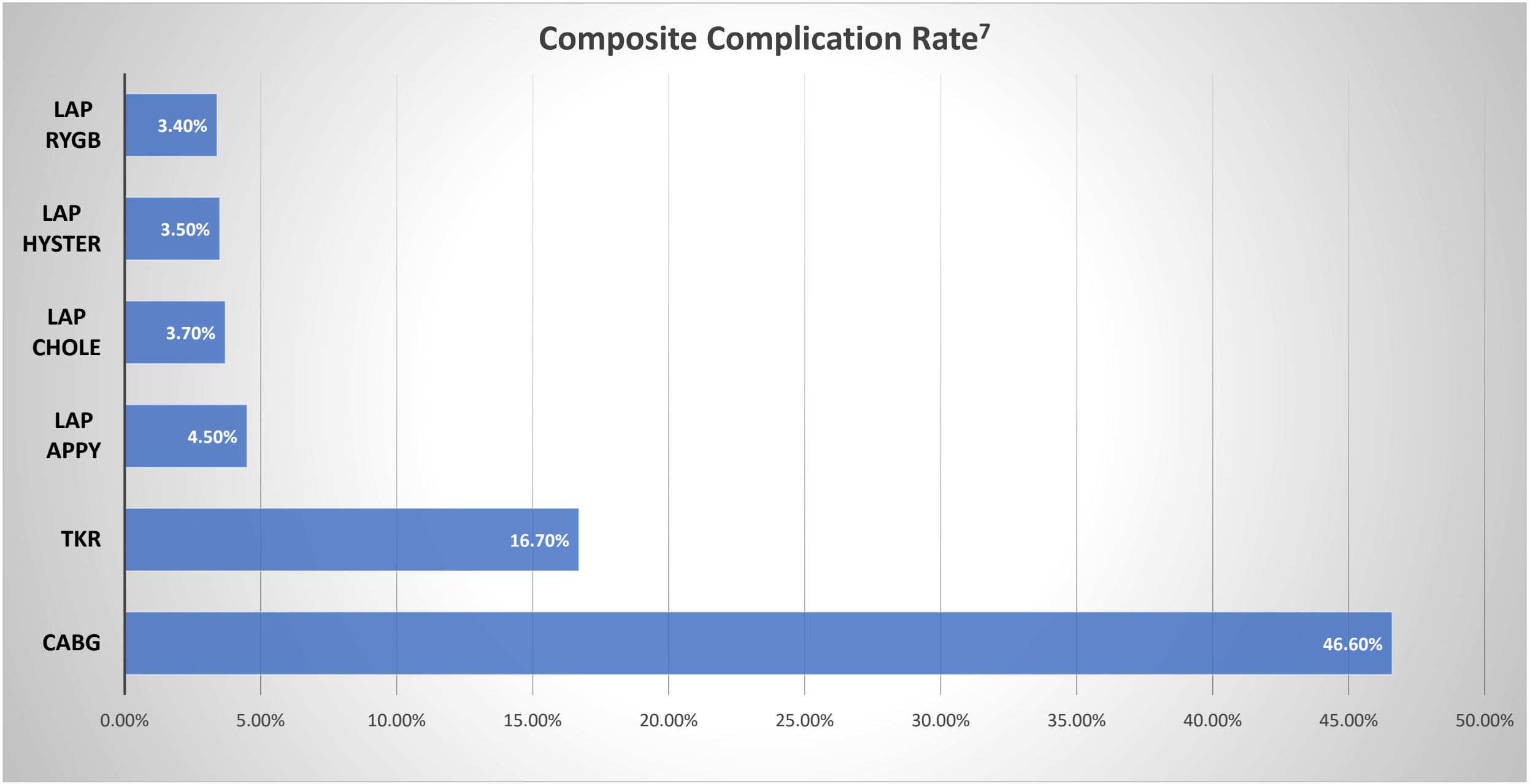
Metabolic Surgery

Sleeve gastrectomy

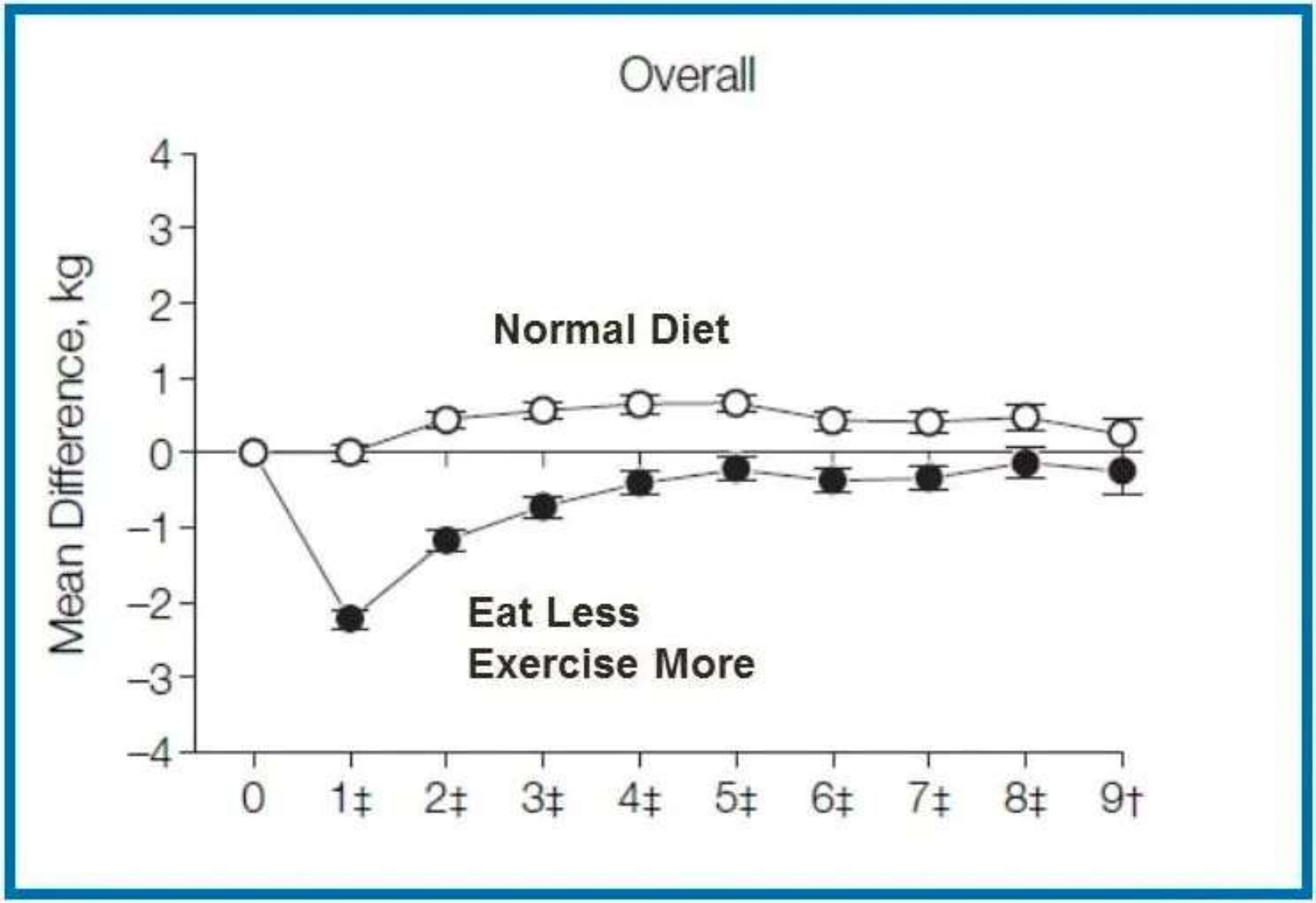
Roux-en-Y bypass

4-M Approach…& then there was the 5th M

- Metabolic Surgery
  - Vastly underutilized
  - Most effective long-term treatment
  - SAFE

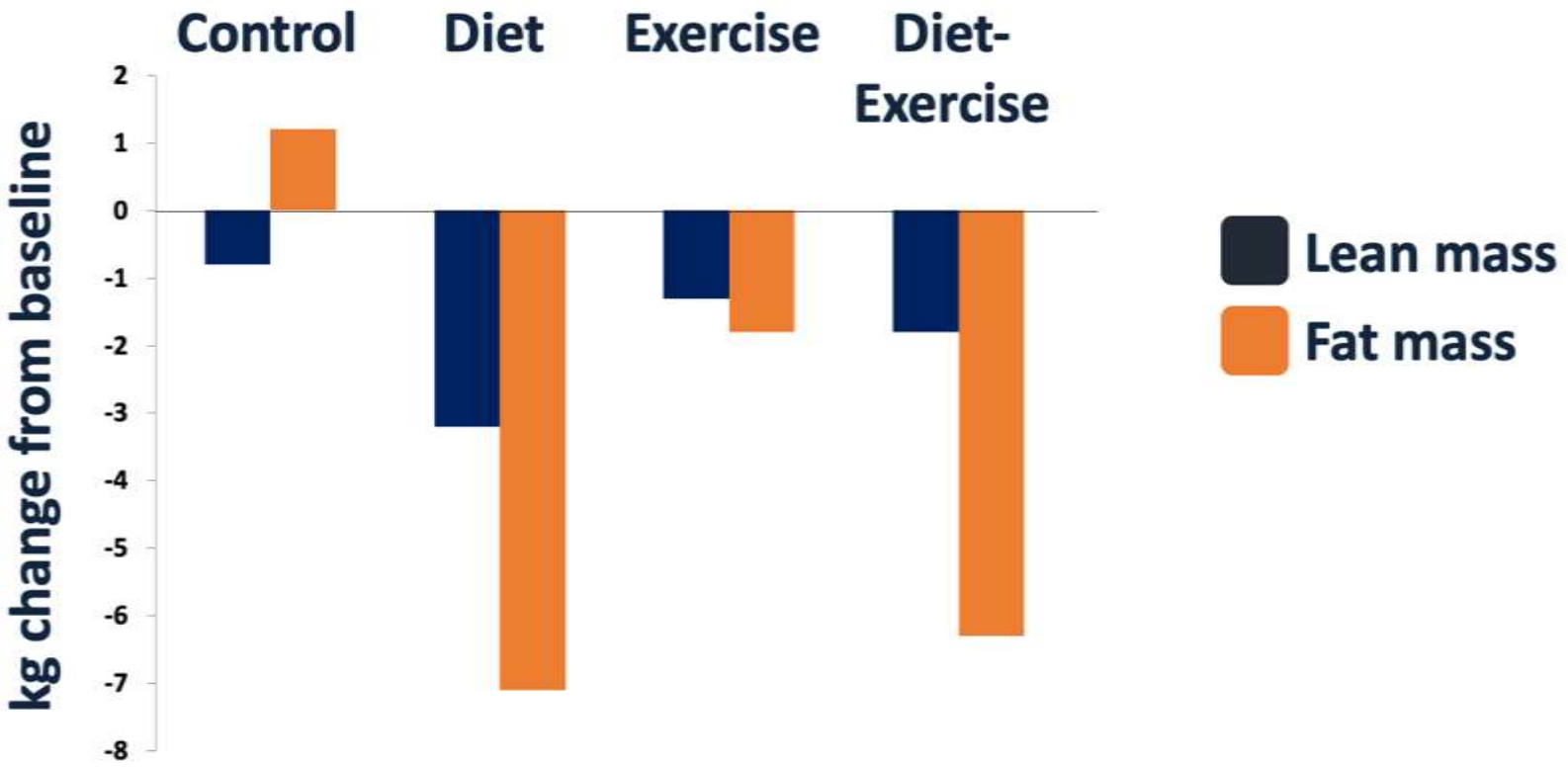

Composite Complication Rate[7]
LAP RYGB
3.40%
LAP HYSTER
3.50%
LAP CHOLE
3.70%
LAP APPY
4.50%
TKR
16.70%
CABG
46.60%
0.00%
5.00%
10.00%
15.00%
20.00%
25.00%
30.00%
35.00%
40.00%
45.00%
50.00%

Ineffective monotherapy



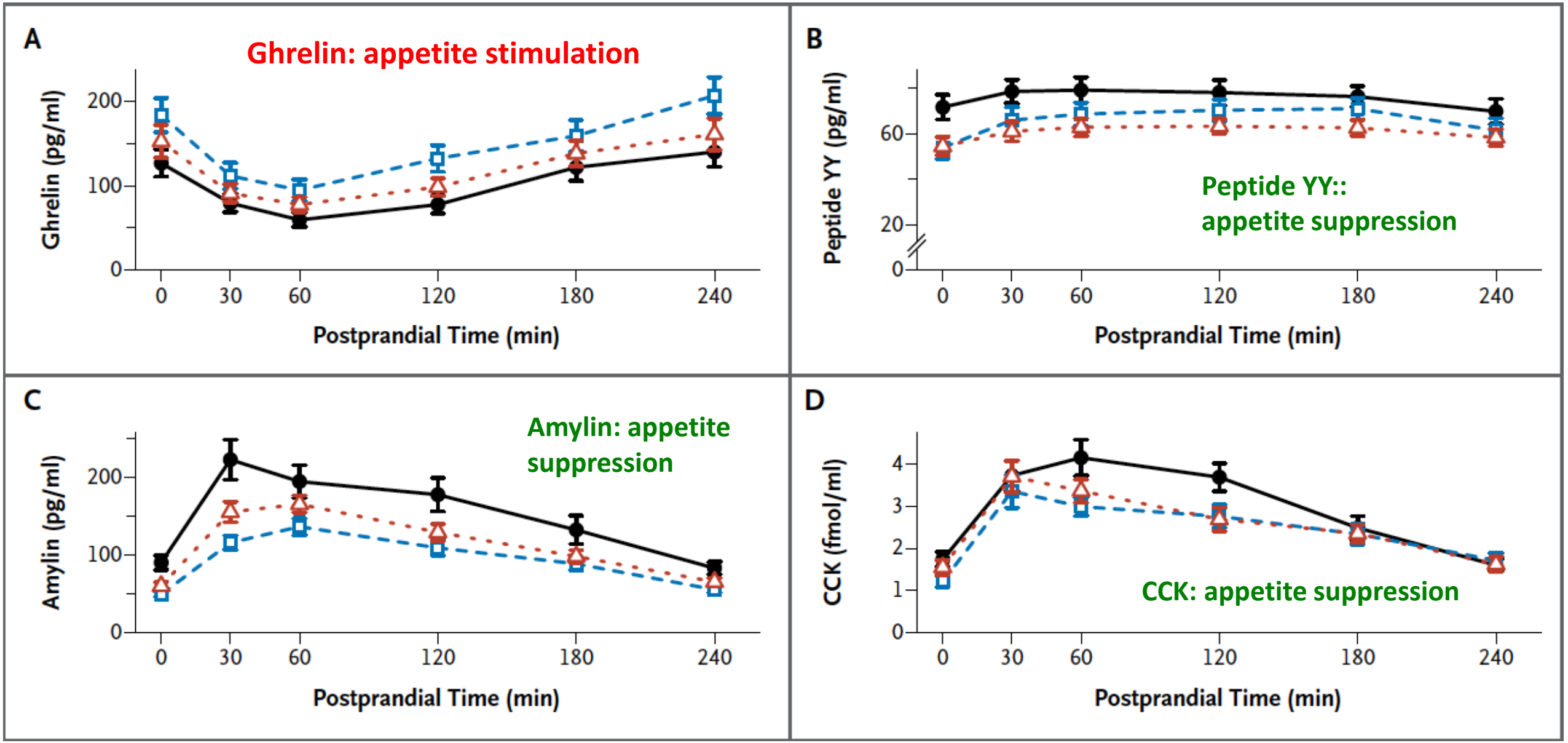
Howard BV et al. JAMA. 2006.[8]

Exercise does little for weight loss[10], but…



Adapted from Villreal et al (2011) *NEJM* 364:1218-29

REGULATION OF BODY MASS



Current FDA Approved AOMs

Short Term Use

- Phentermine
- Phendimetrazine
- Diethylpropion
- Benzphetamine

Long Term Use

- Orlistat
- Phentermine/Topiramate ER (Qsymia®)
- Naltrexone/Bupropion ER (Contrave®)
- Liraglutide (Saxenda®)
- Semaglutide (Wegovy®)
- Tirzepatide (Zepbound®)

What do they do?

Treat disease

GLP-1/GIP RA

Improve BG, prevent glucagon release, appropriate insulin response

Remission of disease through weight loss

Alter Behavior

Phentermine

Suppress appetite

GLP-1/GIP RA

Regulates appetite

Increase satiety

Change physiology

Bupropion

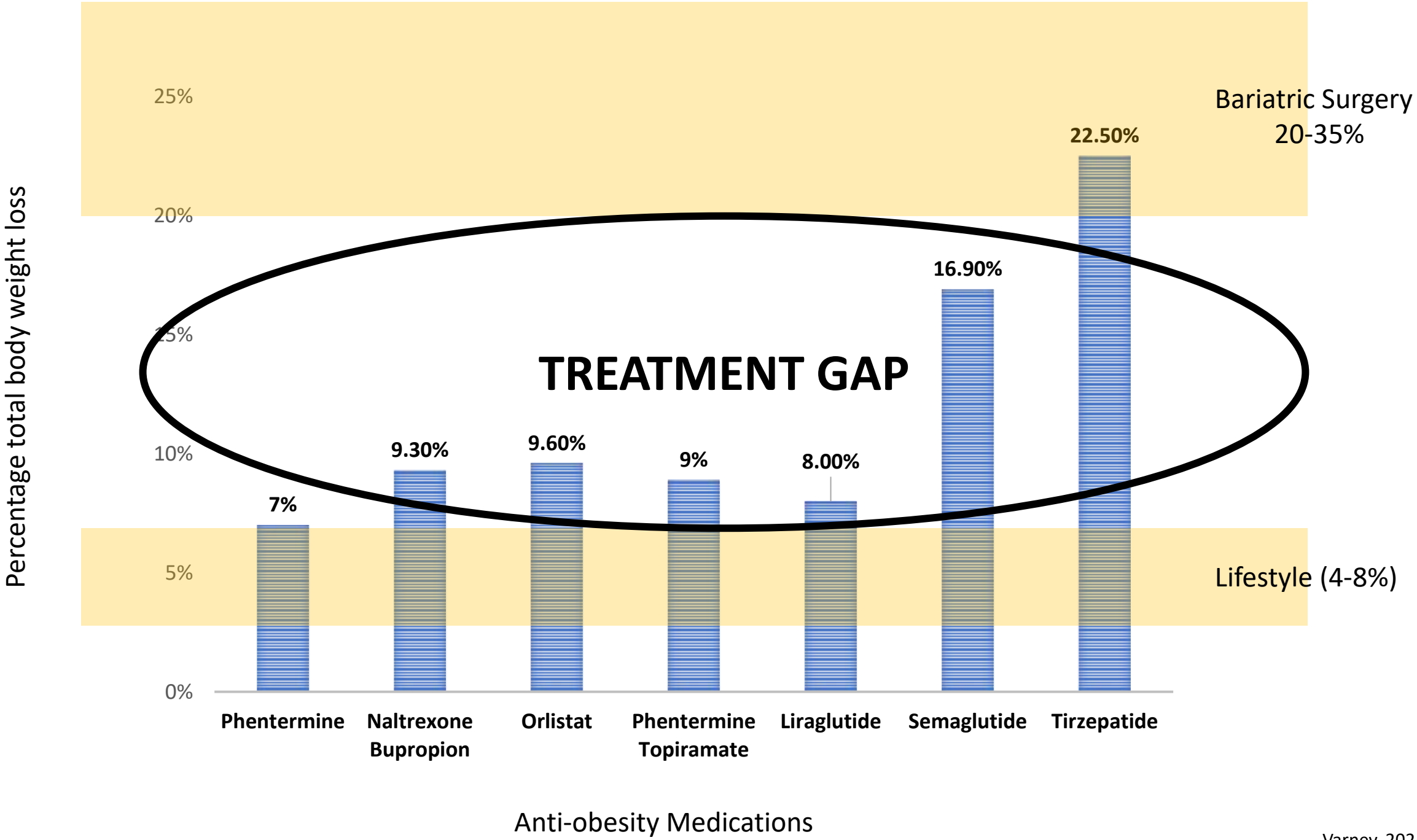
Increase of dopamine

Naltrexone

Blocks opioid receptors at POMC neurons

GLP-1/GIP RA

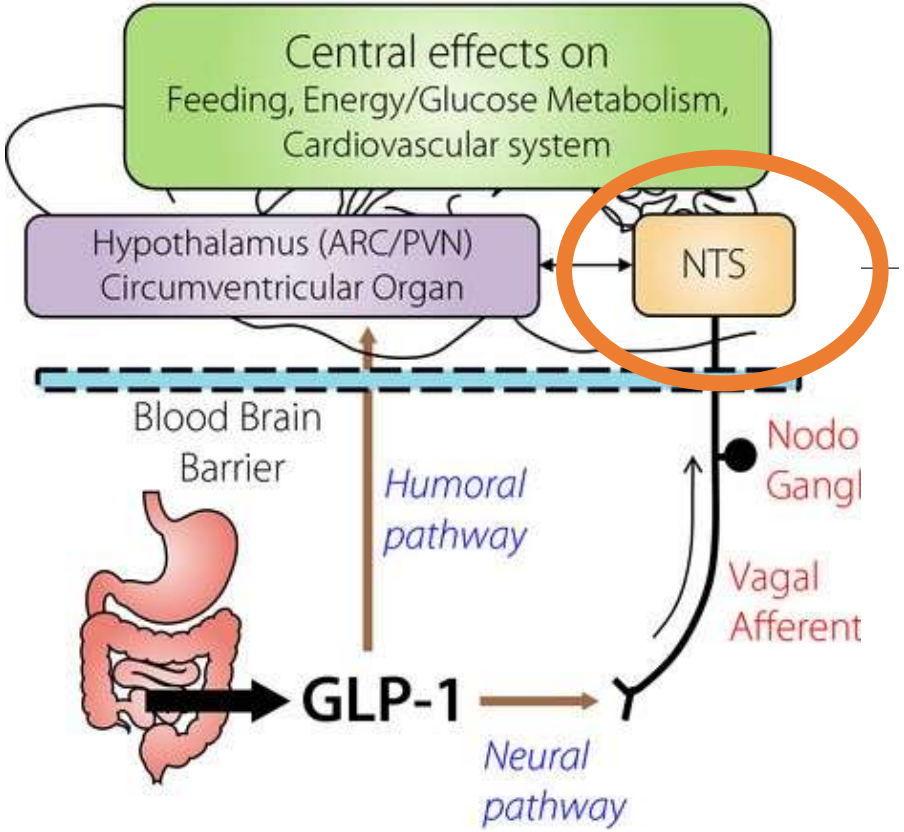
Slow GI motility (a little)

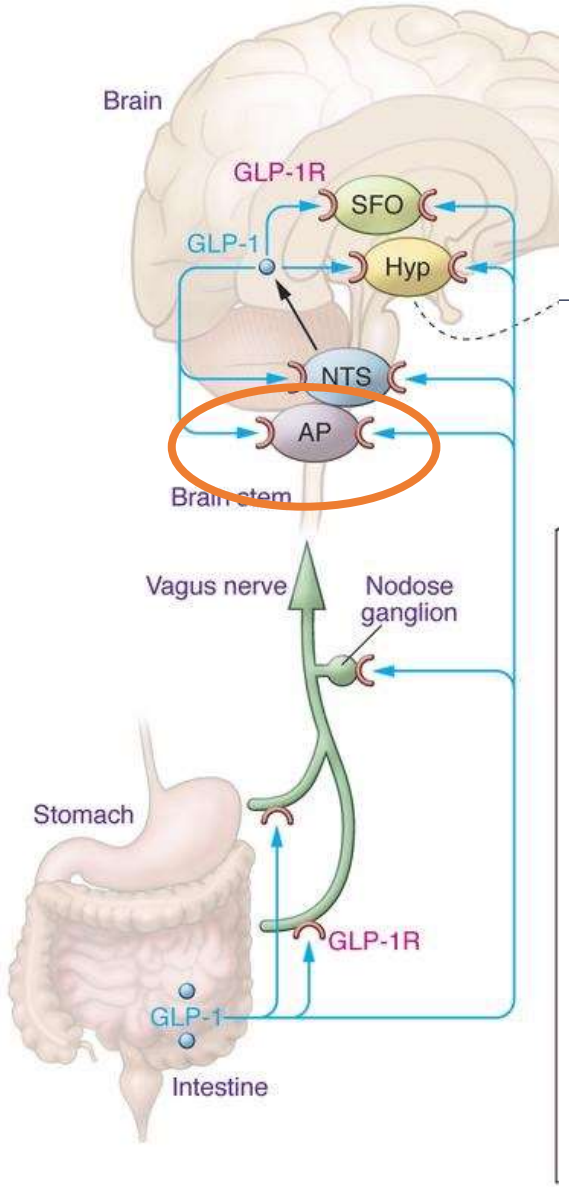

Percentage total body weight loss
25%
20%
15%
10%
5%
0%
Bariatric Surgery
20-35%
Lifestyle (4-8%)
TREATMENT GAP
7%
9.30%
9.60%
9%
8.00%
16.90%
22.50%
Phentermine
Naltrexone Bupropion
Orlistat
Phentermine Topiramate
Liraglutide
Semaglutide
Tirzepatide
Anti-obesity Medications

Varney, 2024

GLP-1/GIP RA

- FDA approval
  - 2005 (Exenatide) for DM2
  - 2014 (liraglutide/Saxenda®) for obesity
  - 2017 (semaglutide/Ozempic®) for DM2
  - 2021 (semaglutide/Wegovy®) for obesity
  - May 13, 2022 (tirzepatide/Mounjaro®) for DM2
  - November 8, 2023 (tirzepatide/Zepbound®) for obesity
- Epic success (and failure) for obesity
  - Shortages
  - Access
  - Media and societal (and healthcare?) bias





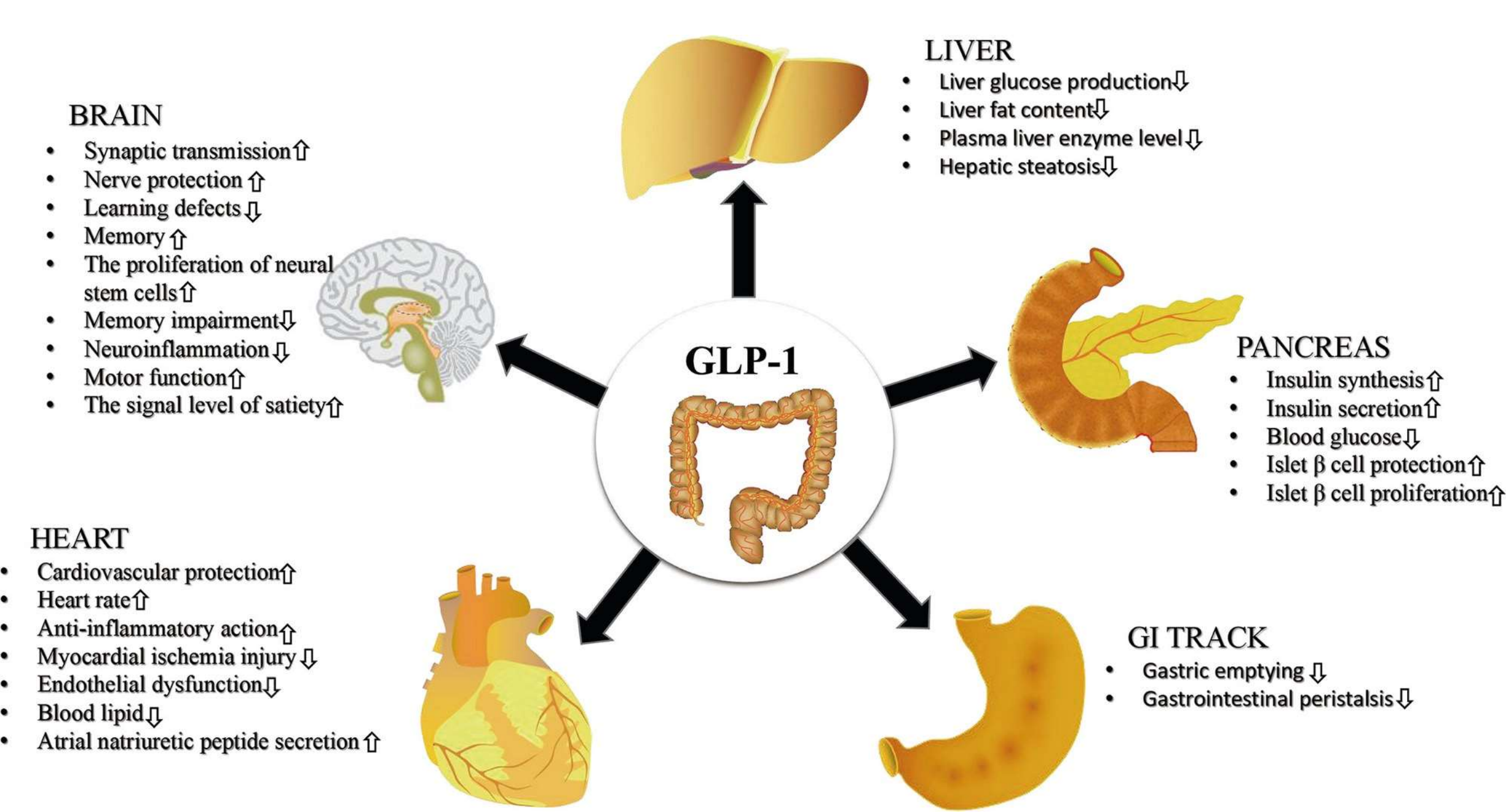
BREAKING NEWS![9]

- BUT HOW do they work???

Huang, KP., Acosta, A.A., Ghidewon, M.Y. *et al.* Dissociable hindbrain GLP1R circuits for satiety and aversion. *Nature* **632**, 585–593 (2024).

GLP-1/GIP RA

- **Treat underlying disease**
  - Low/abnormal GLP-1 response in those with obesity
  - Abnormal glucagon signaling
  - Insulin resistance rises with adipose tissue and MASLD
- **Effective with little S/E**
  - Unprecedented weight loss
  - Side effects are tolerable
- **Safe**
  - Pancreatitis
  - Medullary Thyroid Cancer/MEN-2
- **Other benefits**
  - MACE data
  - Multi-organ benefit


LIVER
Liver glucose production⇩
Liver fat content⇩
Plasma liver enzyme level⇩
Hepatic steatosis⇩
BRAIN
Synaptic transmission⇧
Nerve protection ⇧
Learning defects ⇩
Memory ⇧
The proliferation of neural stem cells⇧
Memory impairment⇩
Neuroinflammation ⇩
Motor function⇧
The signal level of satiety⇧
GLP-1
PANCREAS
Insulin synthesis⇧
Insulin secretion⇧
Blood glucose⇩
Islet β cell protection⇧
Islet β cell proliferation⇧
HEART
Cardiovascular protection⇧
Heart rate⇧
Anti-inflammatory action⇧
Myocardial ischemia injury ⇩
Endothelial dysfunction⇩
Blood lipid⇩
Atrial natriuretic peptide secretion ⇧
GI TRACK
Gastric emptying ⇩
Gastrointestinal peristalsis⇩

Zhao et al.[10]

Updates- October 2024

- ”Mounting evidence” for dermatological conditions[11]
  - Psoriasis
  - Hidradenitis Suppurativa
  - Acanthosis Nigricans
  - Hailey-Hailey Disease
  - Diabetic wounds

Updates- October 2024

- Psoriasis
- Hidradenitis Suppurativa
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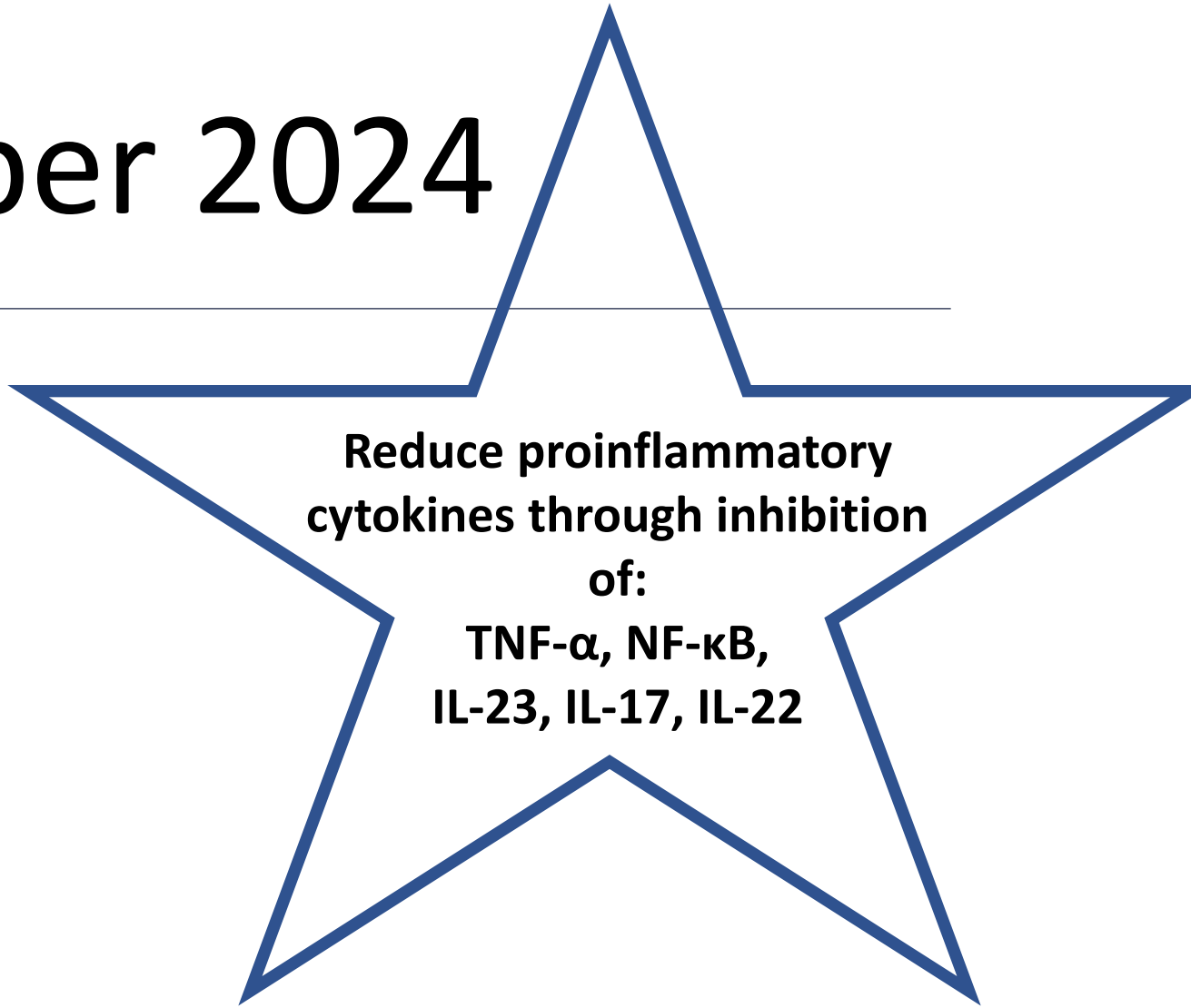
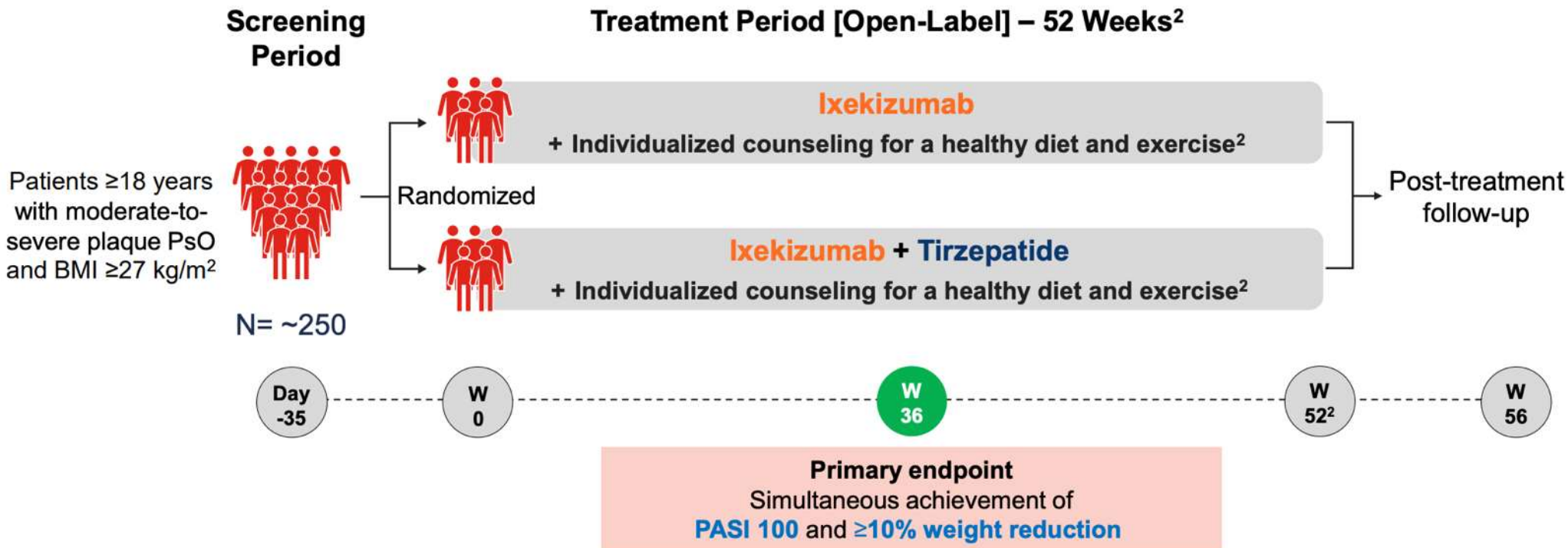


Updates- October 2024

- Ixekizumab + Tirzepatide (TOGETHER-PsO Clinical Trial)
  - Overweight and Obesity
  - Moderate to Severe Plaque Psoriasis
  - Phase 3b/RCT/Multicenter/Open-Label

TOGETHER-PsO Study Design (NCT06588283)[1]

Adult Patients with Moderate-to-Severe Plaque PsO and Obesity with BMI ≥27 kg/m^2



BMI=Body Mass Index; N=Number of Patients in the Analysis Population; PASI 100=100% Improvement in Psoriasis Area and Severity Index; PsO=Psoriasis; W=Week.

1. https://clinicaltrials.gov/study/NCT06588283 (Accessed September 19, 2024). 2. Data on file, Eli Lilly and Company.

Key Inclusion and Exclusion Criteria

Inclusion Criteria

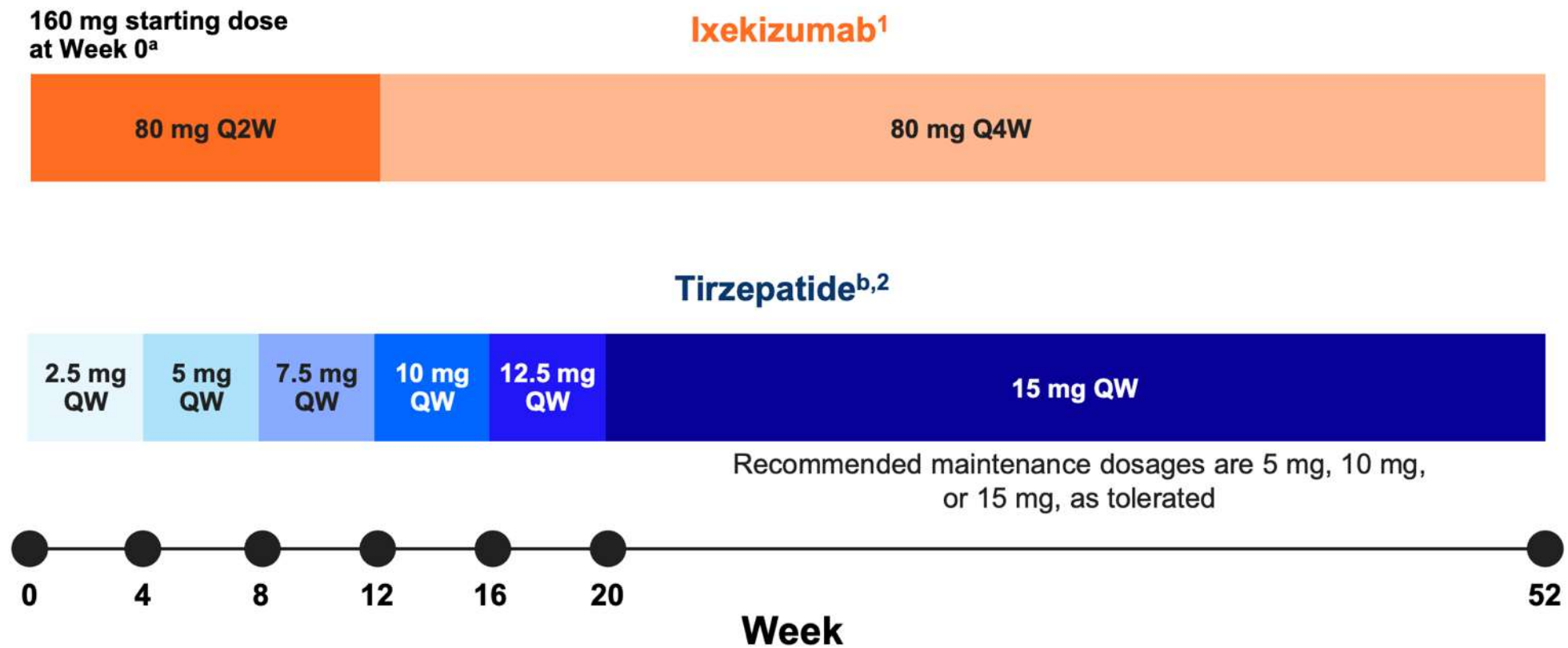
- ≥18 years of age
- Diagnosis of moderate-to-severe plaque PsO for ≥6 months
- sPGA score of ≥3 and PASI score ≥12
- ≥10% BSA involvement
- BMI ≥27 kg/m^2

Exclusion Criteria

- Diagnosis of T1DM
- Insulin-treated T2DM
- Prior or planned surgical treatment for obesity
- Family or personal history of MTC or MEN syndrome type 2
- Active, or history of, IBD
- Diagnosis or history of malignant disease within the 5 years prior to randomization, with the following exceptions: basal cell or squamous epithelial carcinomas of the skin or cervical carcinoma *in situ*
- A serious disorder or illness other than PsO
- History of chronic or acute pancreatitis
- Any prior use of IXE or TZP
- Previous failure or intolerance to an IL-17 inhibitor or GLP-1 RA

BMI=Body Mass Index; BSA=Body Surface Area; IBD=Inflammatory Bowel Disease; GLP-1 RA=Glucagon-like Peptide-1 Receptor Agonist; IL=Interleukin; IXE=Ixekizumab; MEN=Multiple Endocrine Neoplasia; MTC=Medullary Thyroid Carcinoma; PASI=Psoriasis Area and Severity Index; PsO=Psoriasis; sPGA=Static Physician's Global Assessment; T1DM=Type 1 Diabetes Mellitus; T2DM=Type 2 Diabetes Mellitus; TZP=Tirzepatide. https://clinicaltrials.gov/study/NCT06588283 (Accessed September 19, 2024).

On-Label Dosing for Ixekizumab and Tirzepatide



[a]Administered as two 80 mg injections at Week 0. [b]From 5 mg, the dosage may be increased in 2.5 mg increments after at least 4 weeks on the current dose.
QW=Once Weekly; Q2W=Once Every 2 Weeks; Q4W=Once Every 4 Weeks.
1. Taltz [US PI]. Indianapolis, IN, USA: Eli Lilly USA LLC, 2024. 2. Zepbound [US PI]. Indianapolis, IN, USA: Eli Lilly USA LLC, 2024.

Key Primary and Secondary Outcomes

Primary

- Simultaneous achievement of PASI 100 and ≥10% weight reduction

Secondary

- Simultaneous achievement of PASI 75 and ≥5% weight reduction
- Achievement of PASI 100
- Achievement of ≥10% weight reduction

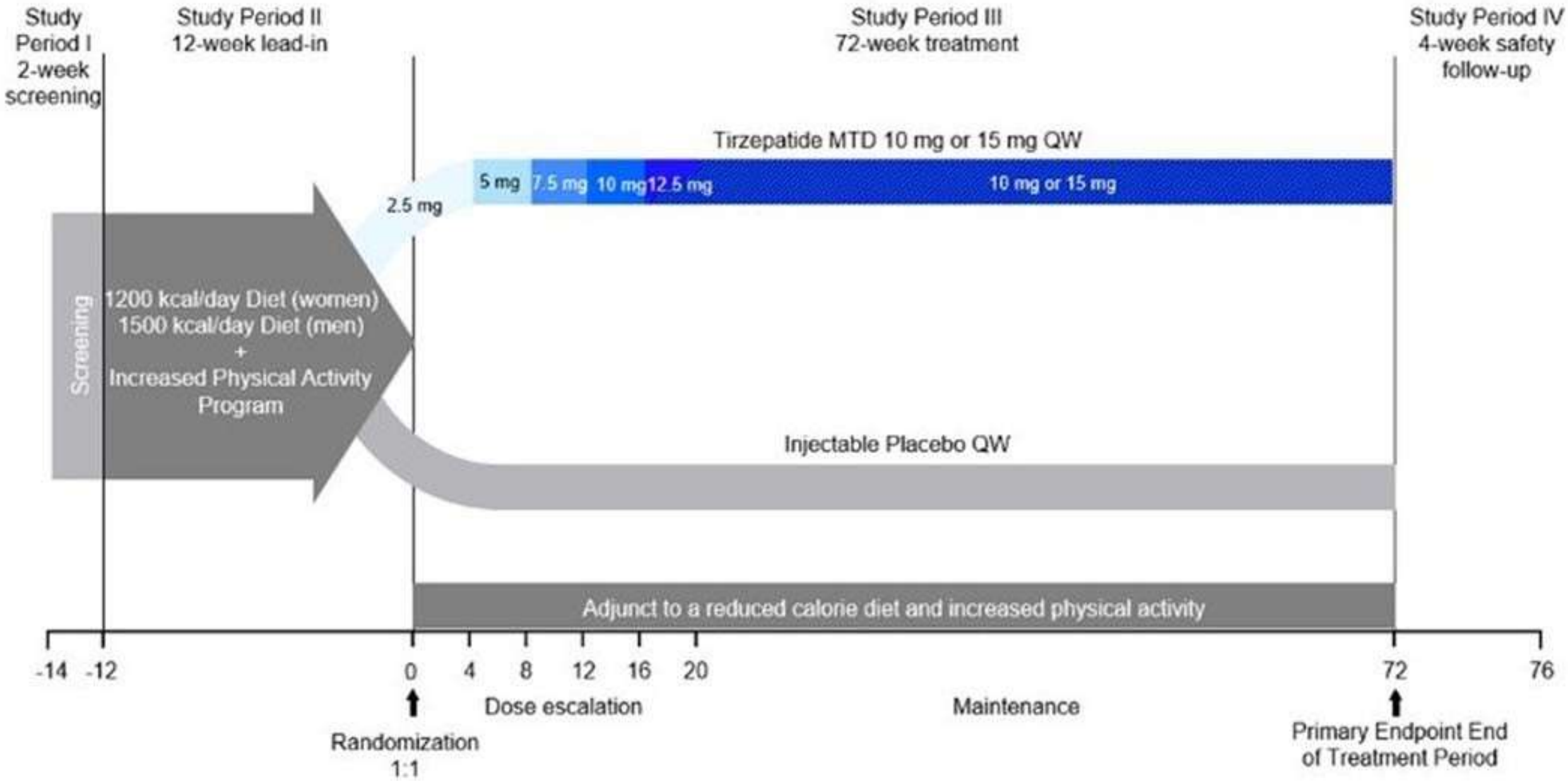
PASI 75=75% Improvement in Psoriasis Activity and Severity Index; PASI 100=100% Improvement in Psoriasis Activity and Severity Index.
https://clinicaltrials.gov/study/NCT06588283 (Accessed September 19, 2024).

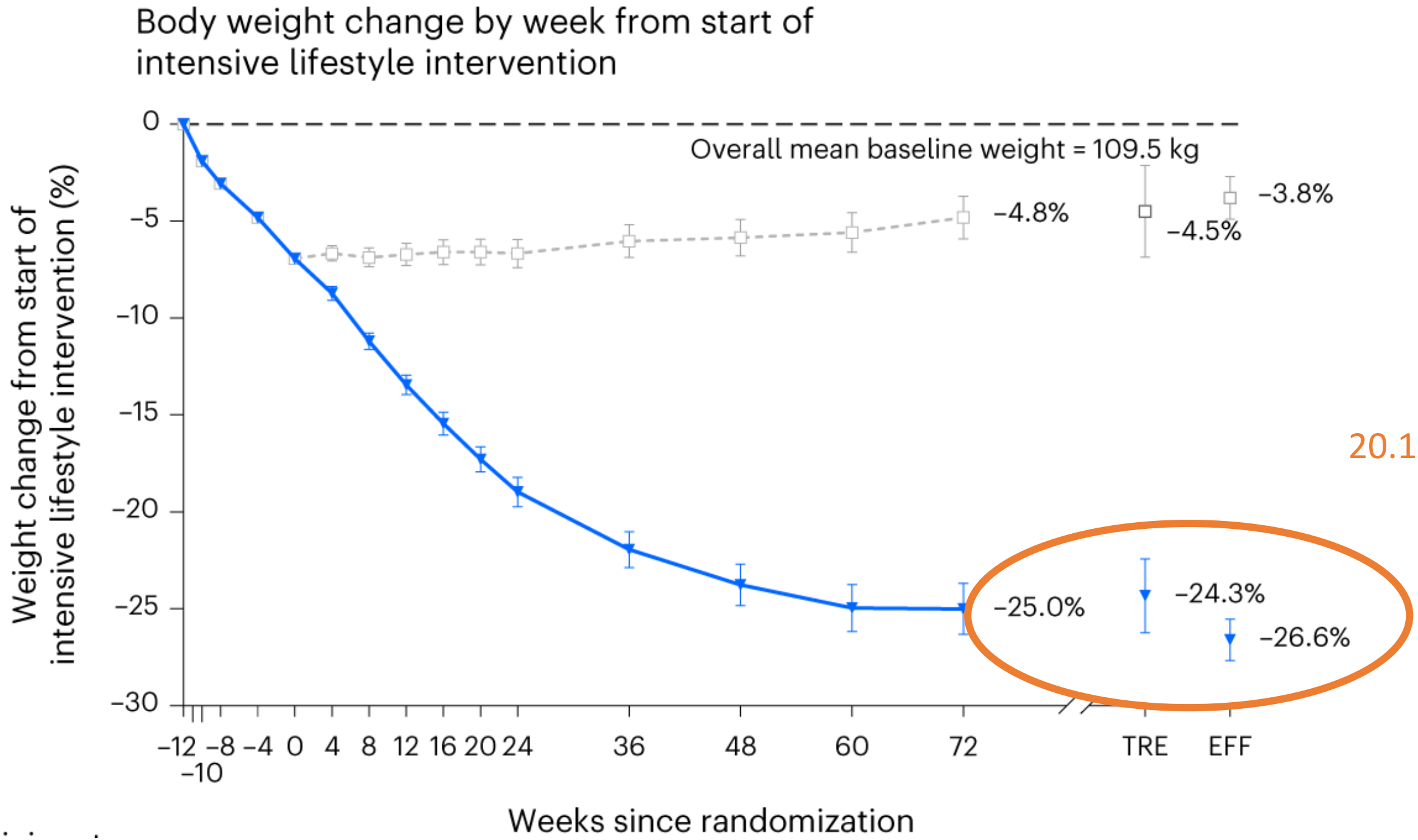
Updates-August 2023

- SELECT Trial, randomized, double-blind[11]
- Semaglutide 2.4 mg
- 17,604 patients
  - Age ≥ 45 years, BMI ≥ 27 kg/m^2
  - 41 countries
  - Established CAD and no DM2 hx
- Primary Endpoints
  - Cardiovascular death, nonfatal MI, nonfatal stroke
  - 20% reduction

Updates-October 2023

- SURMOUNT-3 trial[12]
- Tirzepatide 10 mg or 15 mg
- Double-blind, placebo controlled, 1:1 randomization
  - N=579 patients
  - BMI of ≥30 or ≥27 kg/m^2 with 1 obesity co-morbid condition (excluded DM2)
- 12-week run-in of lifestyle changes only


Study Period I
2-week screening
Study Period II
12-week lead-in
Study Period III
72-week treatment
Study Period IV
4-week safety follow-up
Tirzepatide MTD 10 mg or 15 mg QW
5 mg
2.5 mg
7.5 mg
10 mg
12.5 mg
10 mg or 15 mg
Screening
1200 kcal/day Diet (women)
1500 kcal/day Diet (men)
+
Increased Physical Activity Program
Injectable Placebo QW
Adjunct to a reduced calorie diet and increased physical activity
-14
-12
0
4
8
12
16
20
72
76
Dose escalation
Maintenance
Randomization
1:1
Primary Endpoint End of Treatment Period


Body weight change by week from start of intensive lifestyle intervention
Weight change from start of intensive lifestyle intervention (%)
0
−5
−10
−15
−20
−25
−30
Overall mean baseline weight = 109.5 kg
−4.8%
−4.5%
−3.8%
−25.0%
−24.3%
−26.6%
20.1%
−12 −10
−8
−4
0
4
8
12
16
20
24
36
48
60
72
TRE
EFF
Weeks since randomization

Updates-April 2024

- SURMOUNT-OSA phase 3 clinical trials[13]
- Tirzepatide 10 mg and 15 mg
- Cohort
  - Moderate to severe OSA
  - Obesity
  - Not on PAP therapy (study 1)
  - On and planned to use PAP (study 2)
  - 70% male
- Significant reduction in:
  - AHI (55% and 62.8%)
  - Weight (18.1% and 20.1%)

Updates-June 2024

- First QUAD agonist
- NA-931 (phase 2 clinical trials)[18]
- ***ORAL FORMULATION***
  - GLP-1, GIP, Glucagon, IGF-1
    - Insulin-like growth factor-1

Updates-June 2024

- Insulin-like growth factor-1
  - Typically used for growth hormone deficiency
    - Decreases fat mass (lipolysis/lipid oxidation) in those with GH receptor defects
    - Observational studies show deficiencies in IGF-1 with patients with high BMI

Updates-June 2024

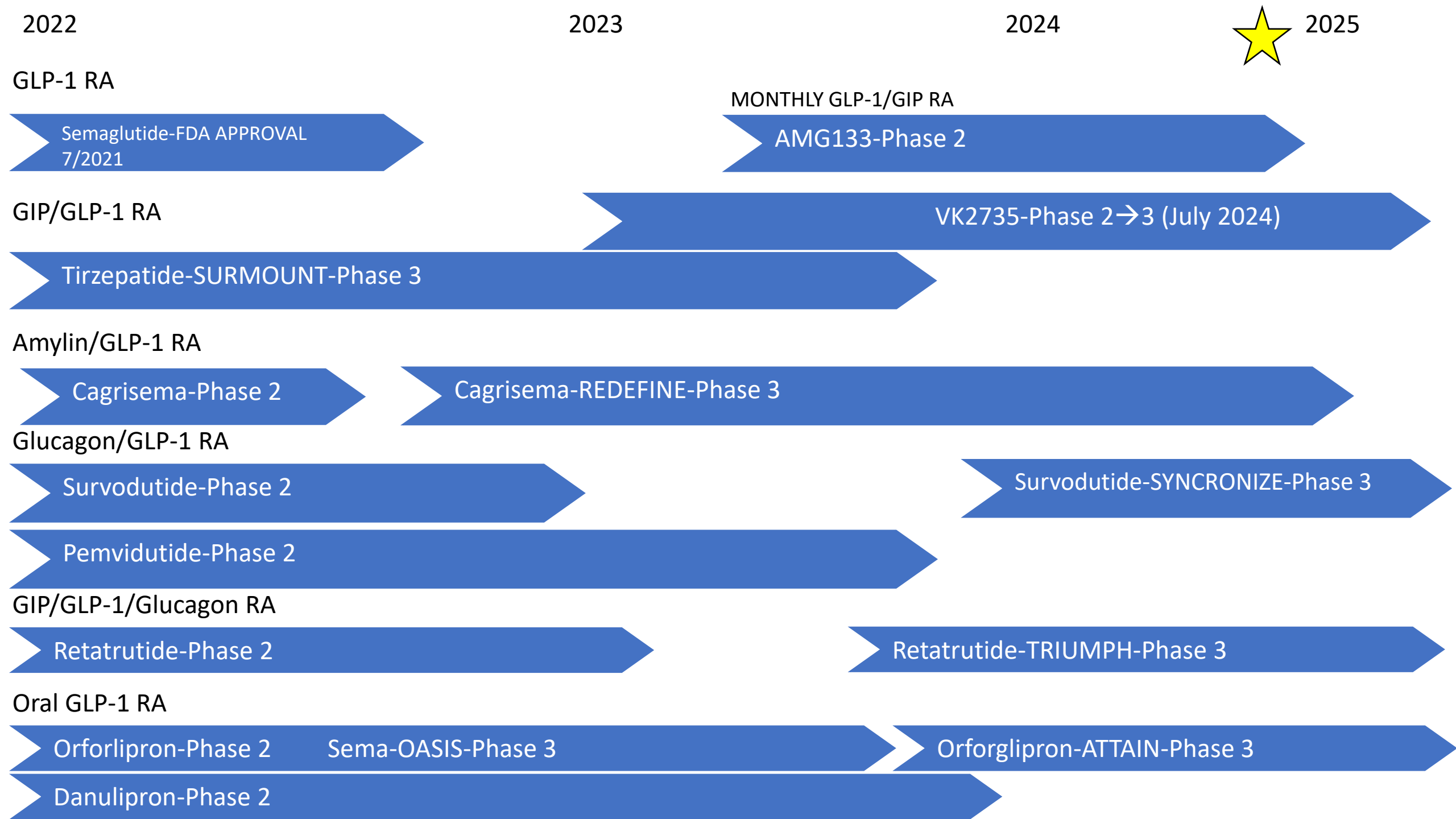
- Insulin-like growth factor-1
  - ***BUILDS muscle mass***
  - Regulates blood sugar
  - Protective in cognitive health
  - Supports kidney function

Updates-June 2024

- NA-931
  - Tested in those with obesity and without DM2
  - Body weight reduction up to ***26% @ 13 weeks***
  - Decrease in plasma glucose levels @ 23%
  - Decrease in triglycerides (34%)
  - **PRESERVES MUSCLE MASS**

Updates-AOM Pipeline

- Nutrient-stimulated hormone (NuSH) based
- Previous AOM
  - 5-11% total body weight loss
- Horizon AOM
  - 14-28% total body weight loss


2022
2023
2024
2025
GLP-1 RA
Semaglutide-FDA APPROVAL 7/2021
MONTHLY GLP-1/GIP RA
AMG133-Phase 2
GIP/GLP-1 RA
VK2735-Phase 2→3 (July 2024)
Tirzepatide-SURMOUNT-Phase 3
Amylin/GLP-1 RA
Cagrisema-Phase 2
Cagrisema-REDEFINE-Phase 3
Glucagon/GLP-1 RA
Survodutide-Phase 2
Survodutide-SYNCRONIZE-Phase 3
Pemvidutide-Phase 2
GIP/GLP-1/Glucagon RA
Retatrutide-Phase 2
Retatrutide-TRIUMPH-Phase 3
Oral GLP-1 RA
Orforlipron-Phase 2
Sema-OASIS-Phase 3
Orforglipron-ATTAIN-Phase 3
Danulipron-Phase 2

Barriers to Care

Cost

Coverage

Supply

Education

Equity

Solutions

- Patient level
  - Adopting one evidence-based guideline/toolkit in specialty clinics
- Provider level
  - Eliminate bias
  - Education and training
  - RX as part of your overall treatment plan
- System level
  - Mandate inclusion into clinic planning
  - Maximize billing and prior authorization process

Obesity Medicine Integration

Location

Central location

Smaller teams within each clinic

Lifestyle

Registered Dietician

Exercise Physiologist/Physical Therapist/Athletic Trainer

LCSW/Psychologist

Medications

Pharmacists

ABOM physicians

OMA Certificate of Advanced Education in Obesity Medicine (NP/PA)

Surgeons

Local partnership

Summary

- Obesity impacts your practice
- Good: Safe, effective and well tolerated medications
- Bad: Access restrictions preventing many from receiving these treatment
- Ugly: Obesity rates will likely get worse before they get better

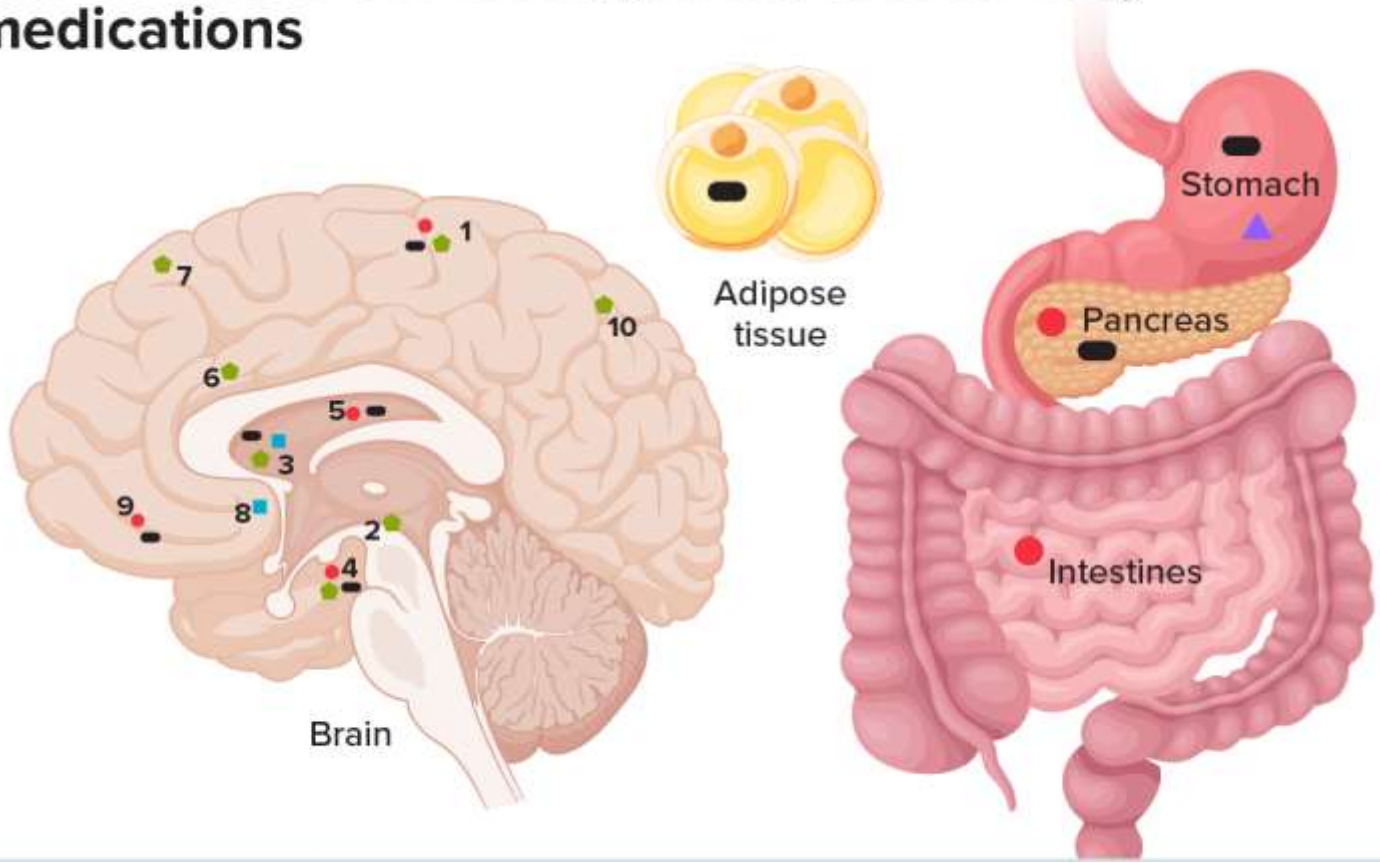
<u>Hope</u>

Obesity will be treated as a chronic disease across all specialties

Additional Resources

AOM	MOA	Dosing	Most common S/E	Kidney/Liver S/E	CKD adjust	Hepatic adjust	Duration
Phentermine	Anorexiant through ↑ NE CNS	Daily Half-life=20 hr	Insomnia, dry mouth,agitation, constipation	↑ of BP/HR, palpitations, cardiac ischemia, PPH	eGFR 15-29: max 15mg /d eGFR <15 and dialysis: avoid	**No**	**Short-term, <3 months**
Phentermine/topiramate-ER	As above plus GABA receptor modulation	Daily Half-life=21 hr	Insomnia, dry mouth,agitation, constipation, dizziness, parasthesia	Nephrolithiasis, metabolic acidosis, ↑ creatinine≥0.3 mg/dl, hypokalemia, ↑ HR, hypotension if on BP meds	eGFR <50: maximum daily dose 7.5mg/46 mg Avoid in dialysis as not studied	**Mild: No** Mod: max daily 7.5 mg/46 mg Avoid in severe, no studies	**Long term**
Orlistat	Pancreatic and gastric lipase inhibitor	TID with meals Half-life=1.5 hr	**GI**	↓ drug concentration cyclosporine, ↓ absorption of fat-soluble vitamins, oxalate stones, pedal edema, Leukocytoclastic vasculitis, liver injury	**No** *admin cyclosporine 3 hours after dose	**No*** *some cases of liver injury	**Long term**
Naltrexone-bupropion	Anorexiant through ↑ dopamine>NE and opioid antagonist	BID Half-life=21 hr	GI, HA, dizziness, dry mouth	↑ of BP/HR, palpitations, ↑ creatinine (OCT2 inhibition?), hepatotoxicity	Mod/severe impairment: max 1 tab BID Avoid in dialysis as not studied	Mod/severe impairment: max 1 tab BID Avoid in severe impairment	**Long term**
Liraglutide	GLP-1 RA; ↑ insulin release*, inhibits glucagon, regulates appetite and GI motility	Daily Half-life=13 hr	**GI**	↑ HR, AKI, use caution with renal impairment & insulin use, gallbladder disease	**No***	**No**	**Long term**
Semaglutide	GLP-1 RA; ↑ insulin release*, inhibits glucagon, regulates appetite and GI motility	Weekly Half-life=7 d	**GI**	As above	**No***	**No**	**Long term**
Tirzepatide	GIP>GLP-1 receptor affinity. As above plus ↑ of adiponectin	Weekly Half-life=5 d	**GI**	As above	**No***	**No**	**Long term**

Site of action of FDA-approved anti-obesity medications



MEDICATION	SITE OF ACTION IN THE BRAIN	SITE OF ACTION IN OTHER PARTS OF THE BODY
GLP-1 analogs	1, 3, 4, 5, 9	Gastrointestinal tract
Naltrexone/Bupropion	1, 2, 3, 4, 6, 7, 10	None
Phentermine/Topiramate	2, 3, 8	None
Orlistat	None	Gastrointestinal tract
GIP/GLP-1 dual analogs	1, 3, 4, 5, 9	Adipose tissue, gastrointestinal tract

Phentermine

MOA: **Anorexiant through ↑ NE CNS**

Dosing: Daily

Half-life: 20 hours

Most Common S/E: Insomnia, dry mouth, agitation, constipation

CKD adjust:

eGFR 15-29: max 15mg /d

eGFR <15 and dialysis: avoid

Liver adjust: No

AVERAGE WEIGHT LOSS: 7%

Phentermine/topiramate ER

MOA: Anorexiant through ↑ NE CNS & GABA receptor modulation

Dosing: Daily

Half-life: 21 hours

Most Common S/E: Insomnia, dry mouth, agitation, constipation, dizziness and **paresthesia**

CKD adjust:

- eGFR <50: maximum daily dose 7.5mg/46 mg
- Dialysis: Avoid

Liver adjust:

- **Moderate:** maximum daily dose 7.5mg/46 mg
- Severe: Avoid

AVERAGE WEIGHT LOSS: 9%

Orlistat

MOA: Pancreatic and gastric lipase inhibitor

Dosing: TID with meals

Half-life: 1.5 hours

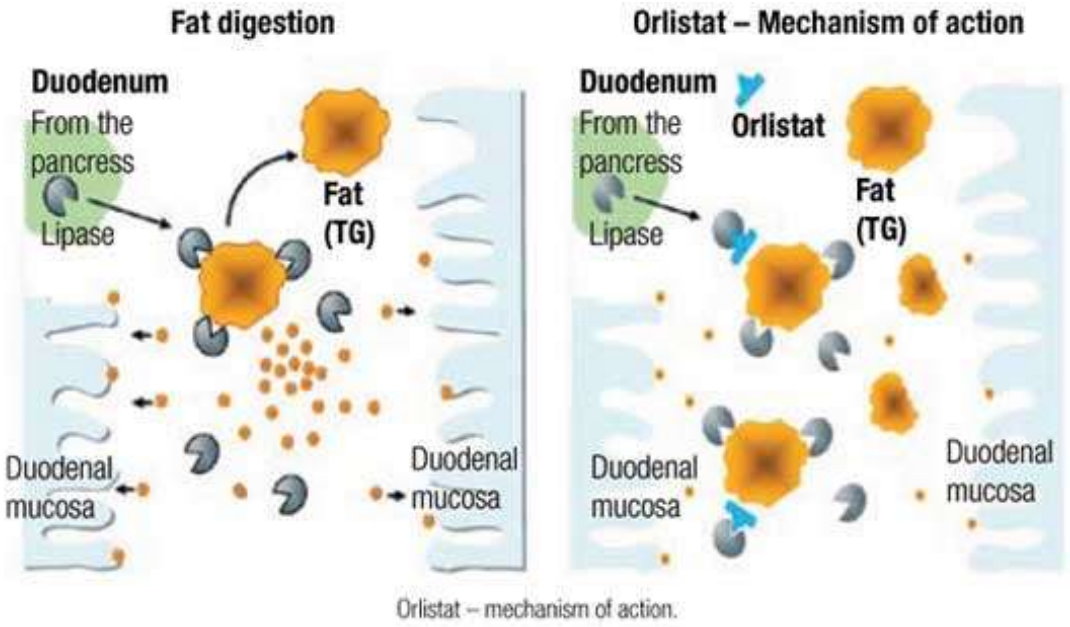
Most Common S/E: GI

CKD adjust: No

Admin cyclosporine 3 hours after dose

Liver adjust: No

Some cases of liver injury



Orlistat – mechanism of action.

Source: MedExpress

AVERAGE WEIGHT LOSS: 9.6%

Naltrexone-bupropion

MOA: Anorexiant through ↑ dopamine>NE and opioid antagonist

Dosing: BID
Half-life: 21 hours
Most Common S/E: GI, HA, dizziness, dry mouth

CKD adjust:
Mod/severe impairment: max 1 tab BID
Dialysis: Avoid

Liver adjust:
Mod/severe impairment: max 1 tab BID
Dialysis: Avoid

AVERAGE WEIGHT LOSS: 9.3%

Liraglutide

MOA: GLP-1 RA; ↑ insulin release*, inhibits glucagon, regulates appetite and GI motility

Dosing: Daily

Half-life: 13 hours

Most Common S/E: GI,

CKD adjust: No*

Liver adjust: No

AVERAGE WEIGHT LOSS: 8%

Semaglutide

MOA: GLP-1 RA; ↑ insulin*, inhibits glucagon, regulates appetite & GI motility

Dosing: weekly

Half-life: 7 days

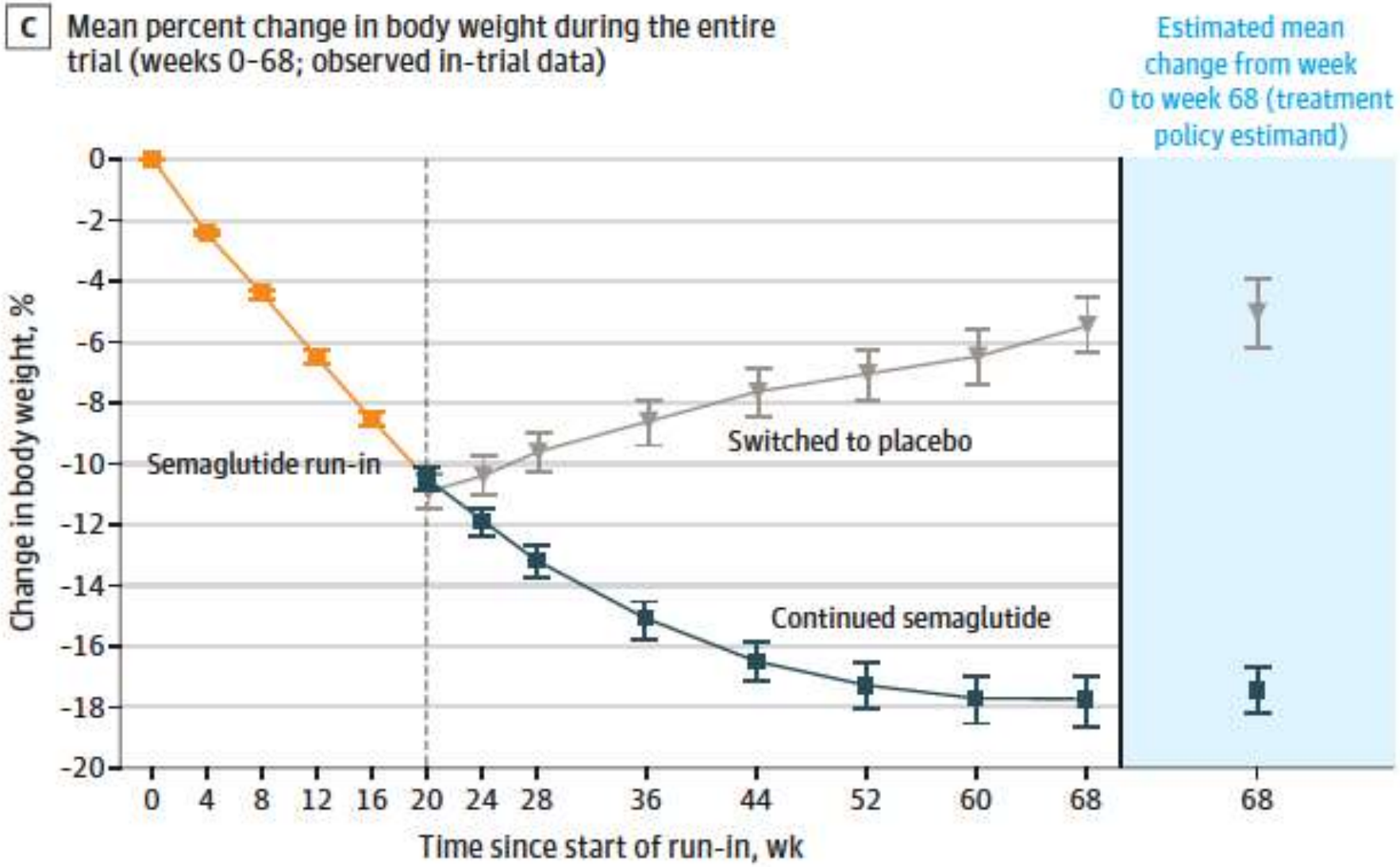
Most Common S/E: GI,

CKD adjust: No*

Liver adjust: No

AVERAGE WEIGHT LOSS: 16.9%

Semaglutide
STEP-4 Trial



Tirzepatide

MOA: GLP-1/GIP RA; ↑ insulin release*, inhibits glucagon, regulates appetite and GI motility & increase of adiponectin

Dosing: weekly

Half-life: 5 days

Most Common S/E: GI,

CKD adjust: No*

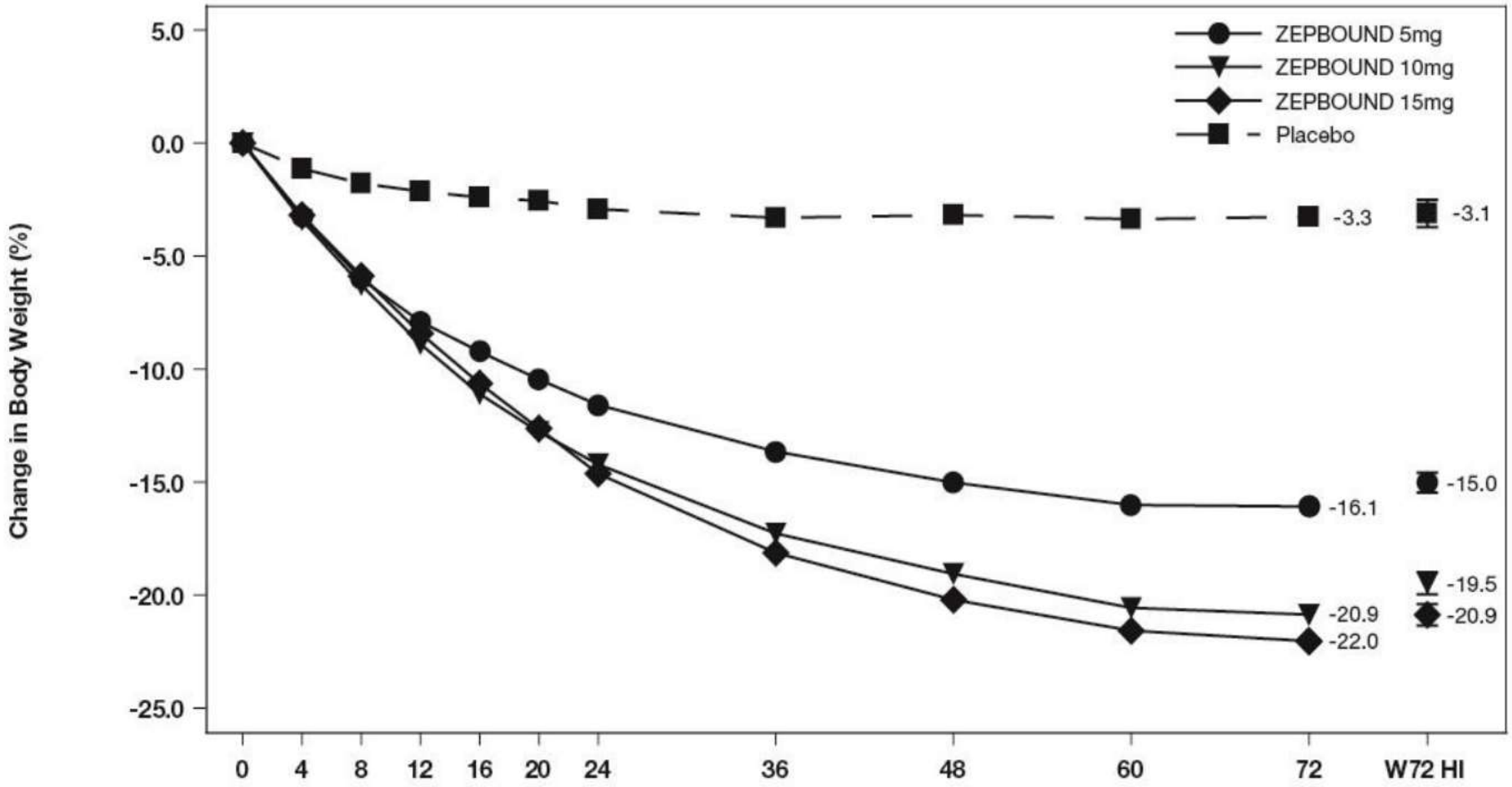
Liver adjust: No

AVERAGE WEIGHT LOSS: 20.9%

SURMOUNT-1

Tirzepatide

Figure 3: Change from Baseline (%) in Body Weight in Study 1



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Questions