THE UNIVERSITY OF KANSAS HEALTH SYSTEM

New Aims in Obesity Pharmacotherapy

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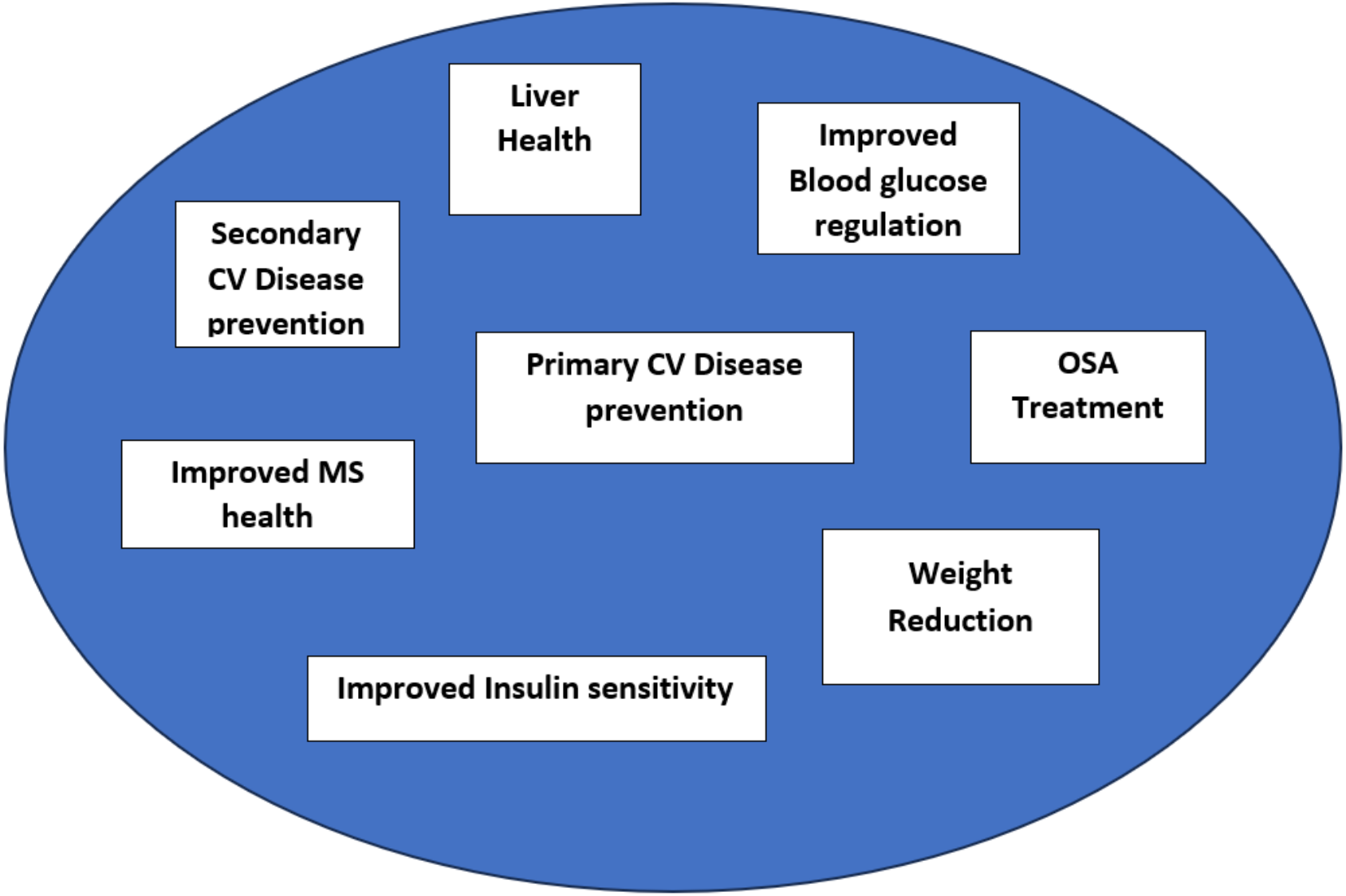
Assistant Professor Internal Medicine

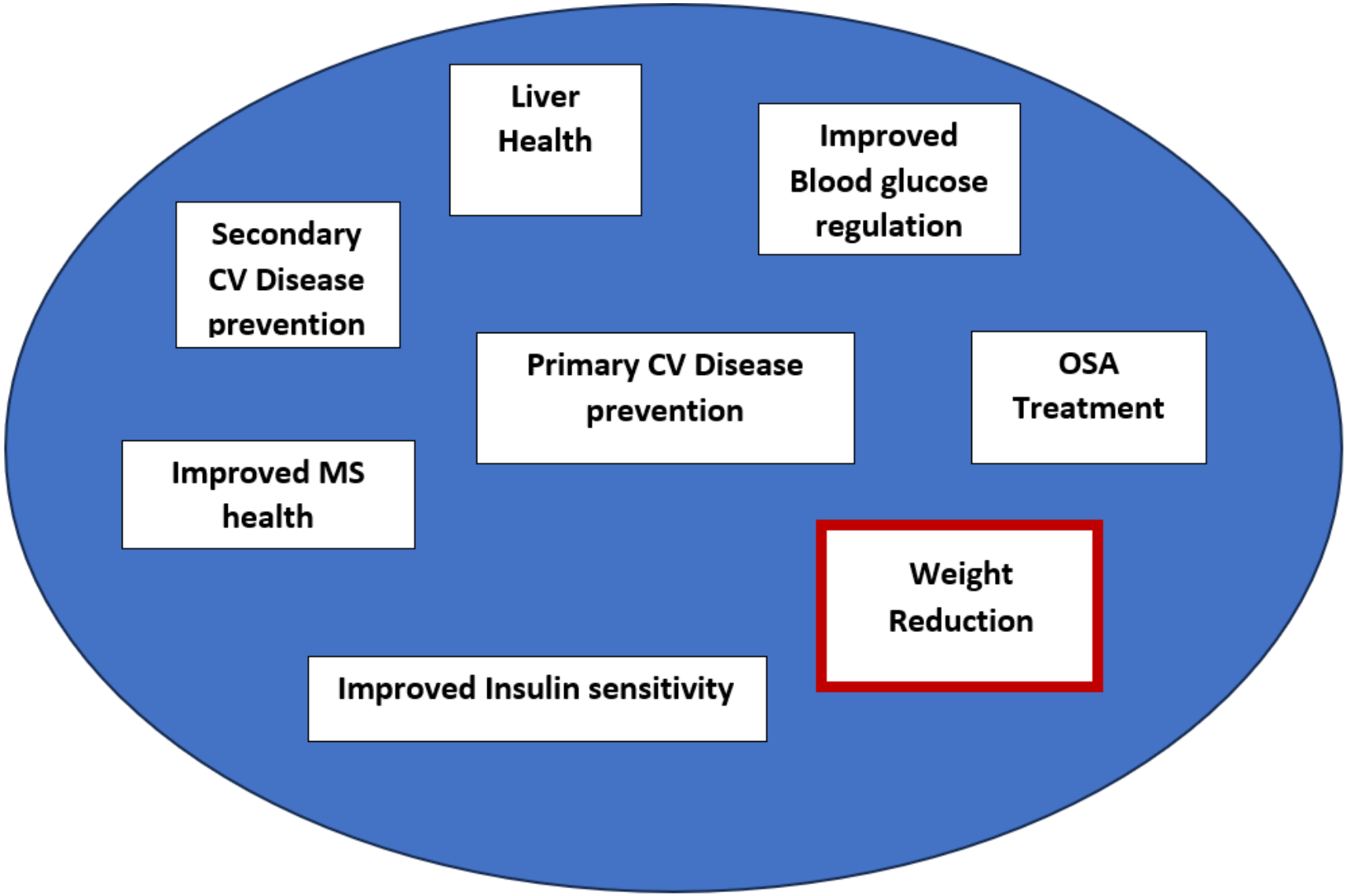
Disclosures

- No financial disclosures

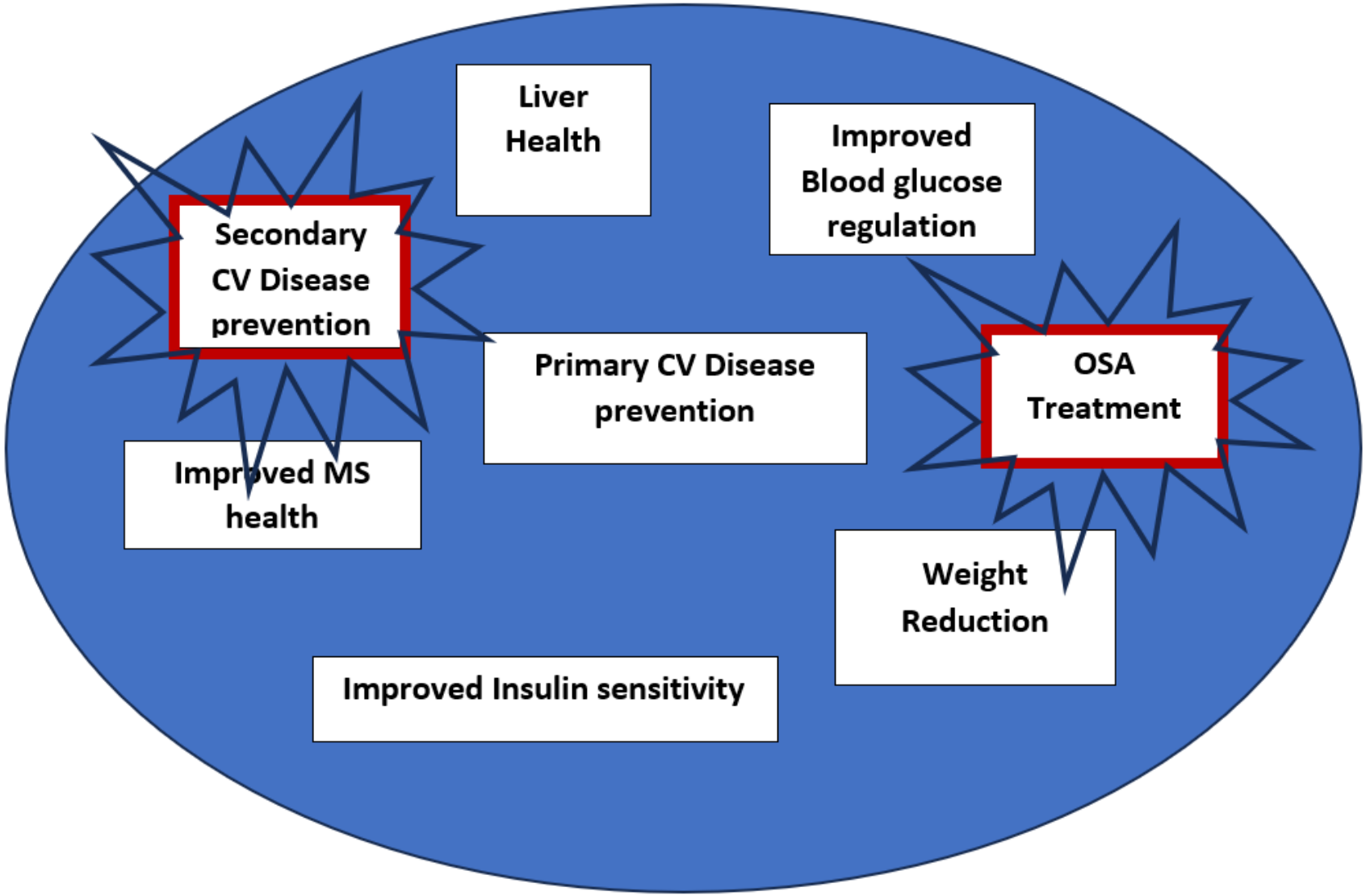
Traditional Aims in Obesity Management



Traditional Aims in Obesity Management



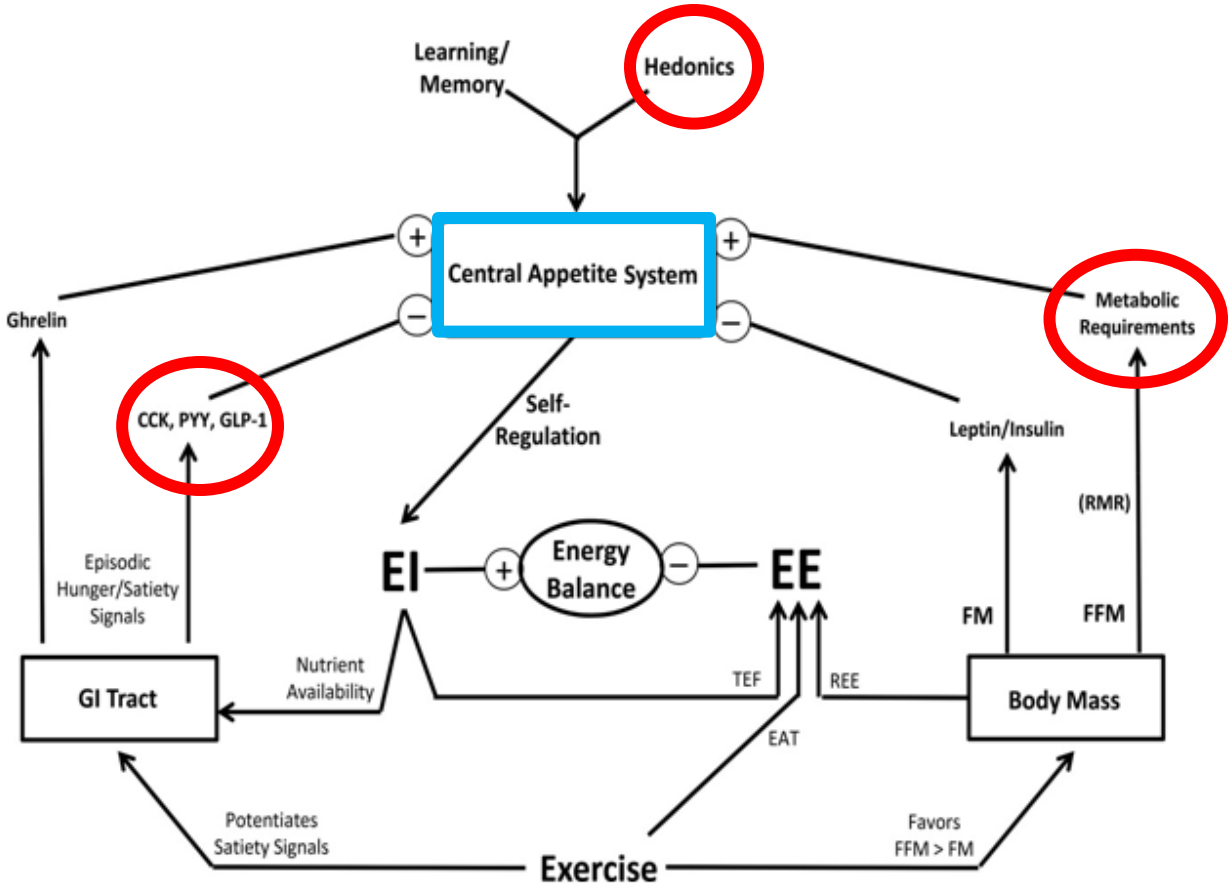
New Aims in Obesity Management



Overview of Obesity Targets/ Tools

- Overview of Appetite Regulation
- Current FDA Approved Anti-obesity Medications

Appetite Regulation/ Targets



Obesity, Volume: 25, Issue: S1, Pages: S8-S16, First published: 23 February 2017, DOI: (10.1002/oby.21771)

FDA Approved Pharmacotherapy for obesity management

FDA Approved Medications for Obesity

- Phentermine/ Diethylpropion
- Orlistat
- Bupropion/ Naltrexone
- Topiramate/ phentermine
- Liraglutide
- Semaglutide
- Tirzepatide

FDA Approved Pharmacotherapy for obesity treatment

FDA Approved Medications for Obesity

- Phentermine/ Diethylpropion
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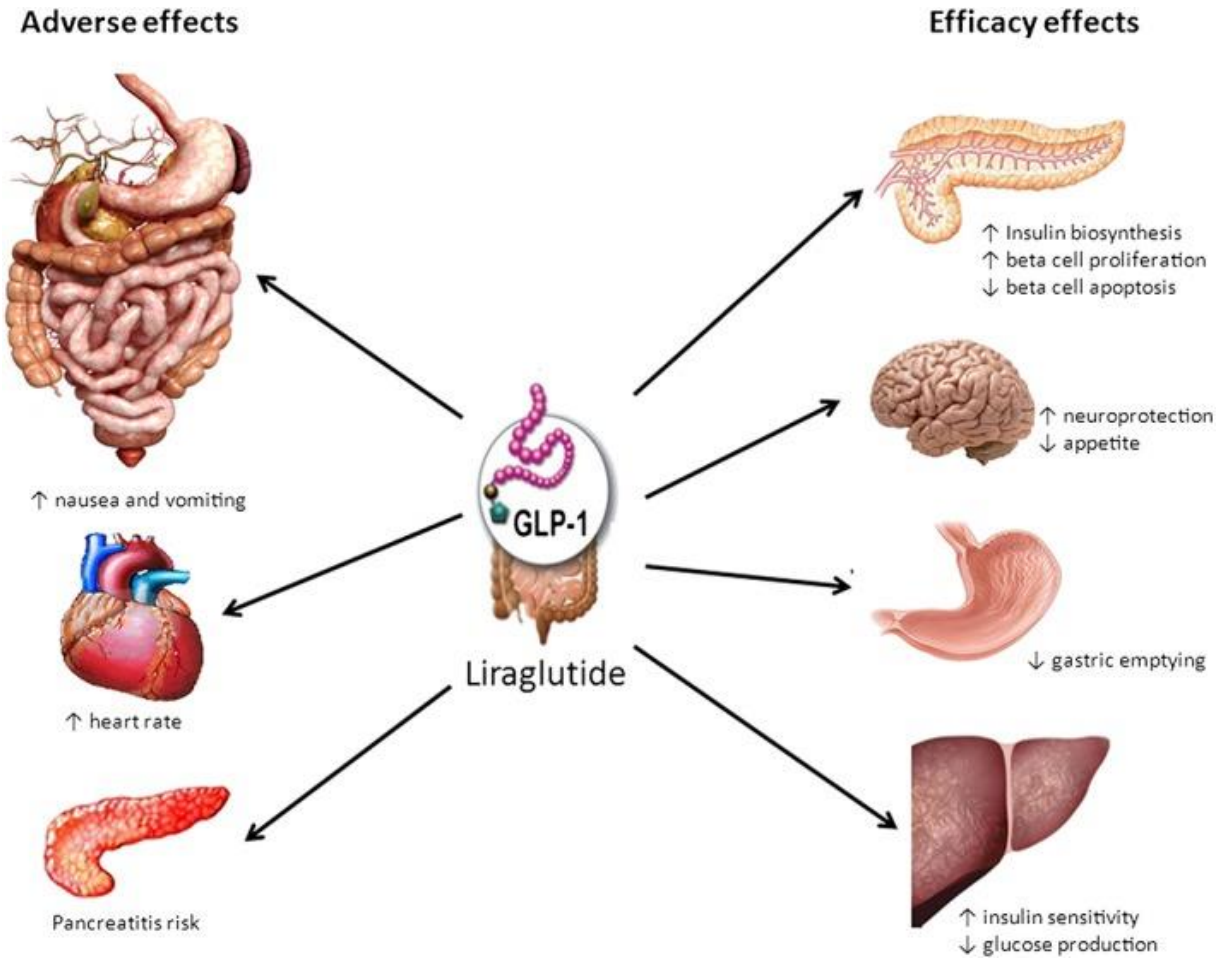
- Liraglutide
- Semaglutide
- Tirzepatide

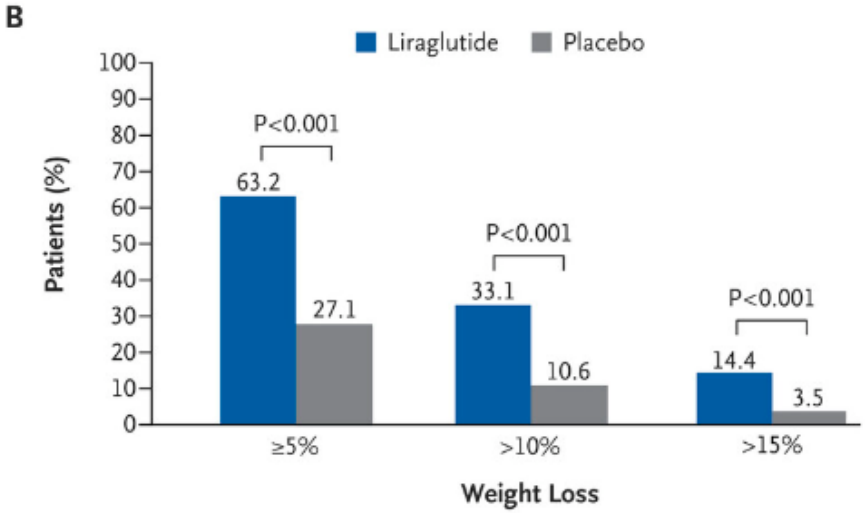
Specific Effects of Incretin Based therapy

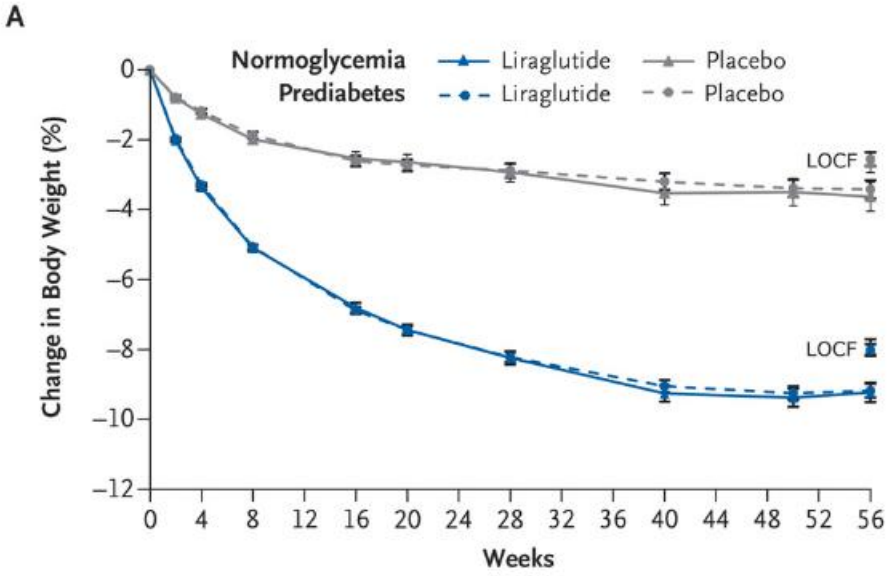


Liraglutide

- FDA approved in 2014
- MOA – GLP-1. Improved insulin sensitivity, slows gastric emptying, reduces central hunger at hypothalamic level
- Side Effects – nausea/ vomiting, constipation, c-cell tumors, pancreatitis
- Special considerations – MEN, disordered eating patterns, injectable

Liraglutide



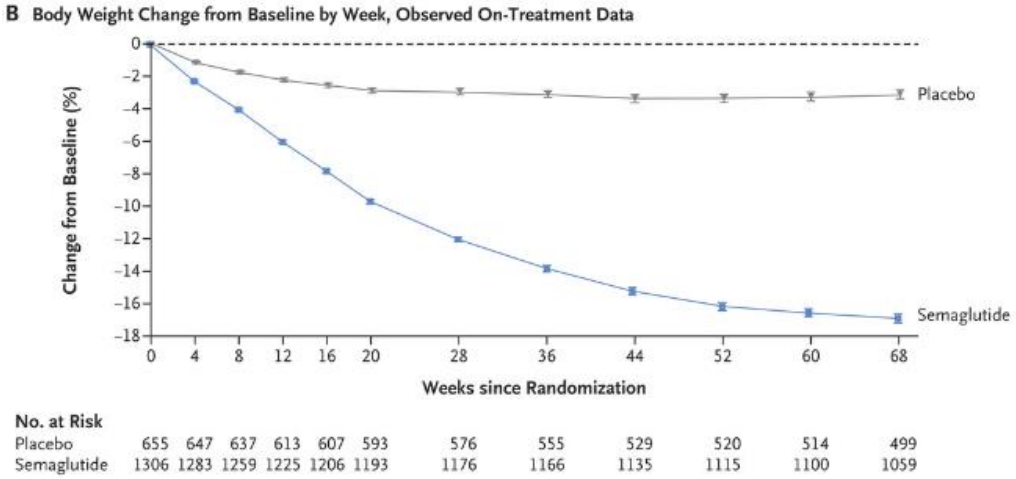


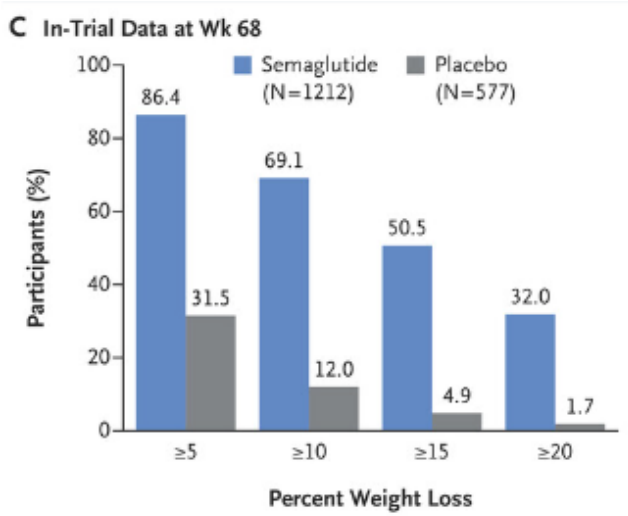
Xavier et al, NEJM. Vol 373, July 2, 2015

Semaglutide

- FDA approved in June 2021
- MOA – GLP-1. Improved insulin sensitivity, slows gastric emptying, reduces central hunger at hypothalamic level
- Side Effects – nausea/ vomiting, constipation, c-cell tumors, pancreatitis
- Special considerations – MEN, disordered eating patterns, injectable (weekly)

Semaglutide





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

1.Davies, Melanie et al.

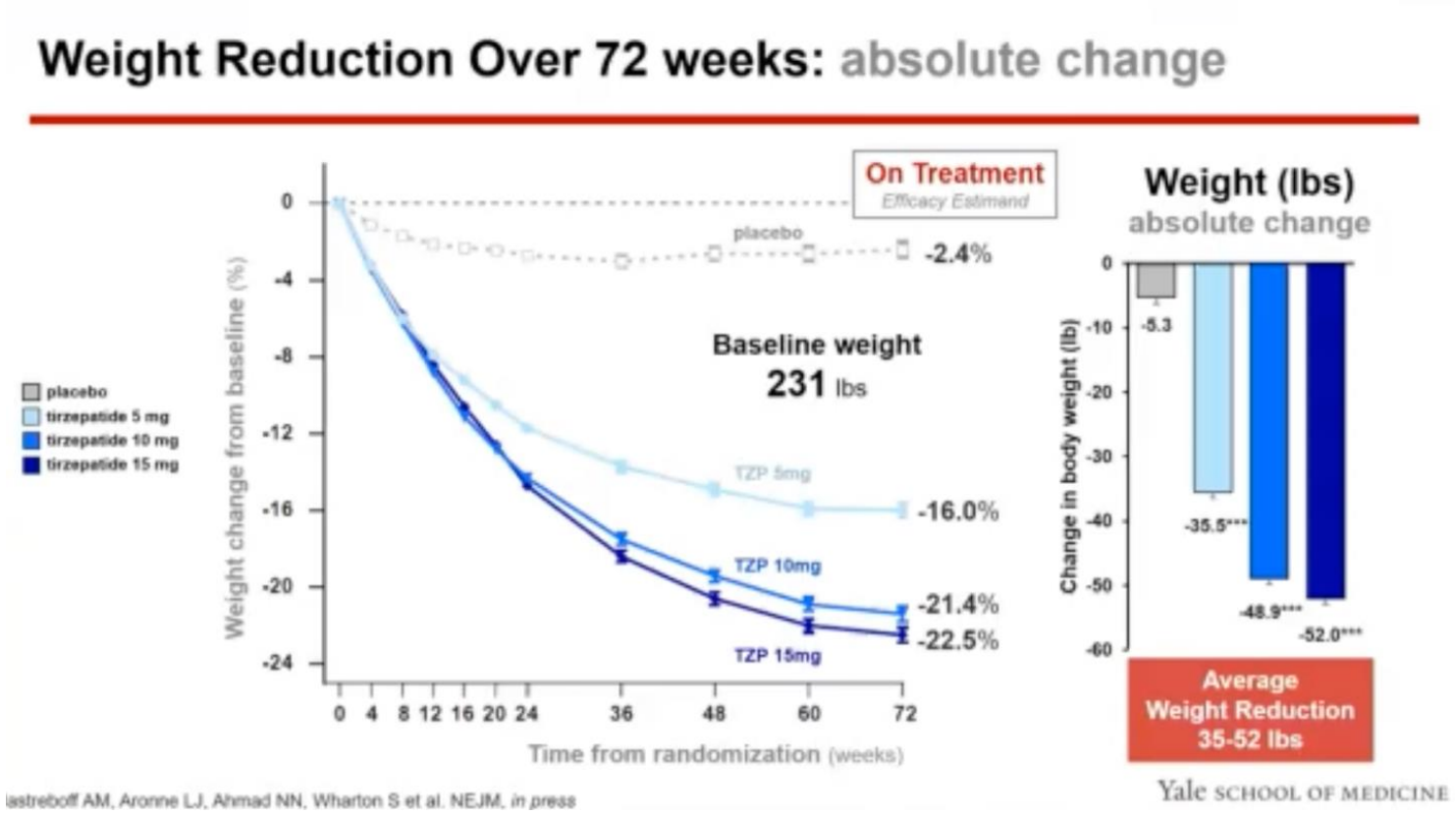
2.The Lancet, Volume 397, Issue 10278, 971 - 984

10/4/2024

Tirzepatide

- FDA approved for Obesity Management Nov 2023
- MOA: GLP-1 and GIP agonist
- Side effects: nausea/ vomiting, constipation, c-cell tumors, pancreatitis
- Special considerations – MEN, disordered eating patterns, injectable (weekly), **OCP alteration**

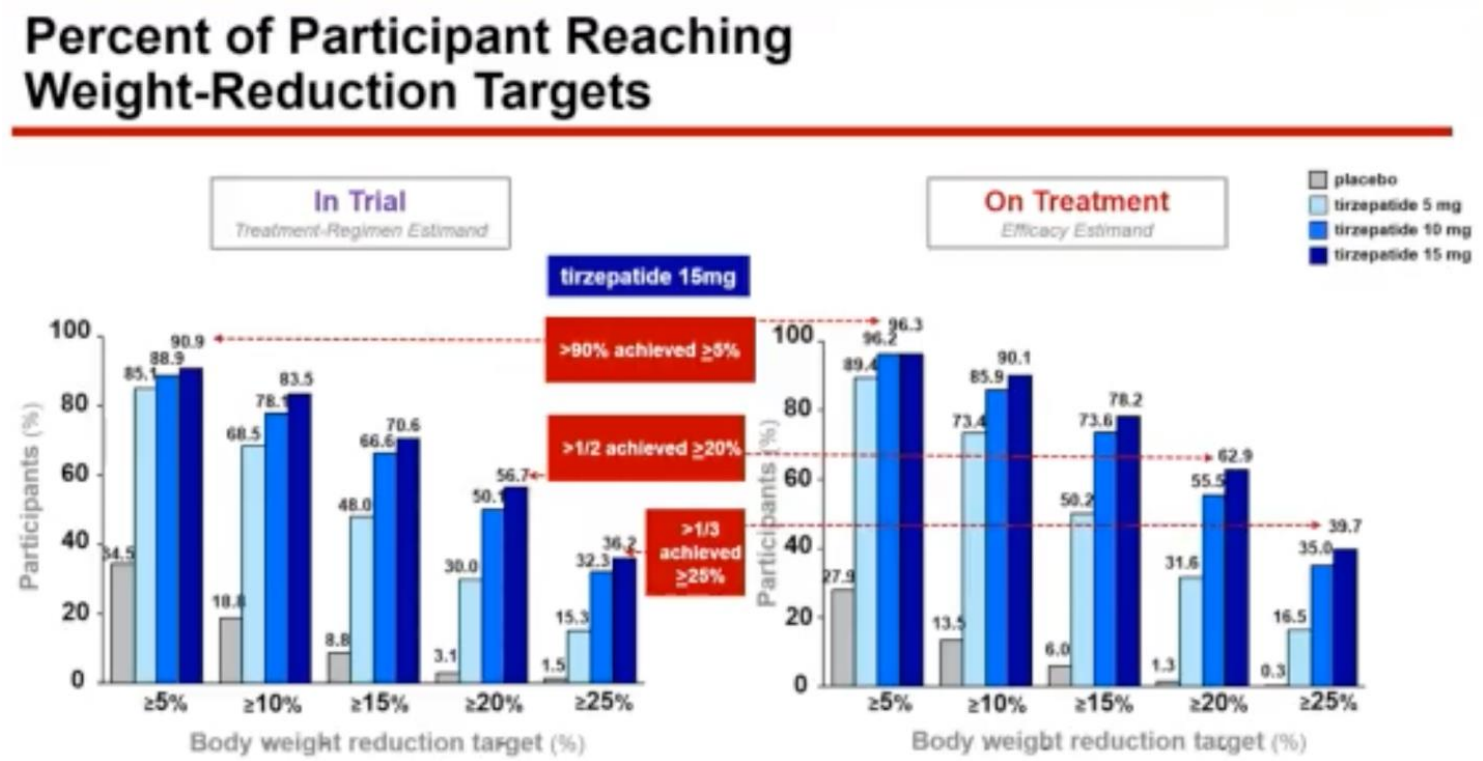
SURMOUNT study



astreboff AM, Aronne LJ, Ahmad NN, Wharton S et al. NEJM, *in press*

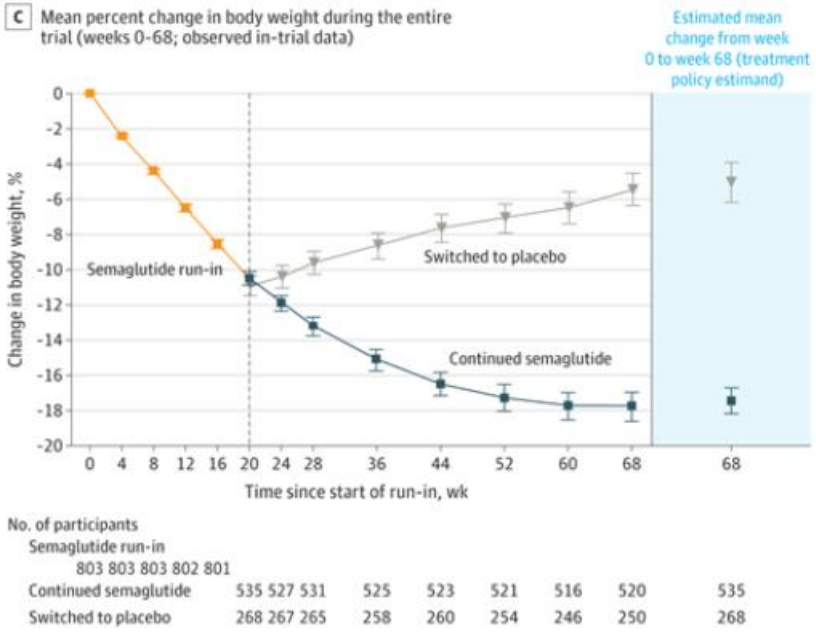
Yale SCHOOL OF MEDICINE

SURMOUNT cont.

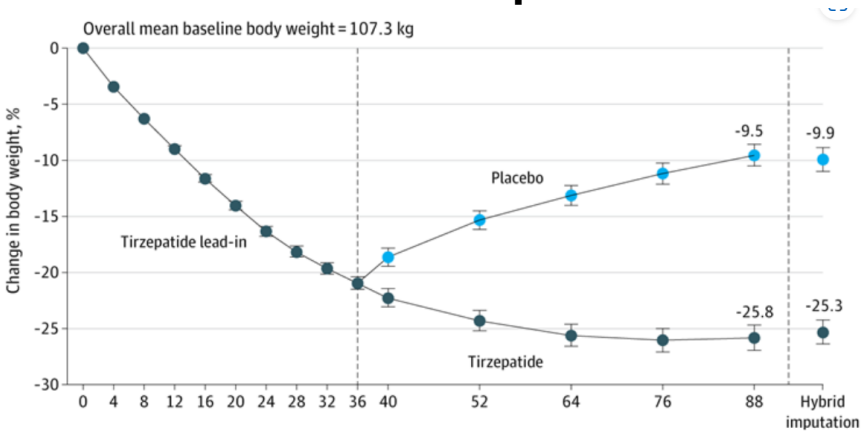


Duration of therapy

STEP 4 - Semaglutide



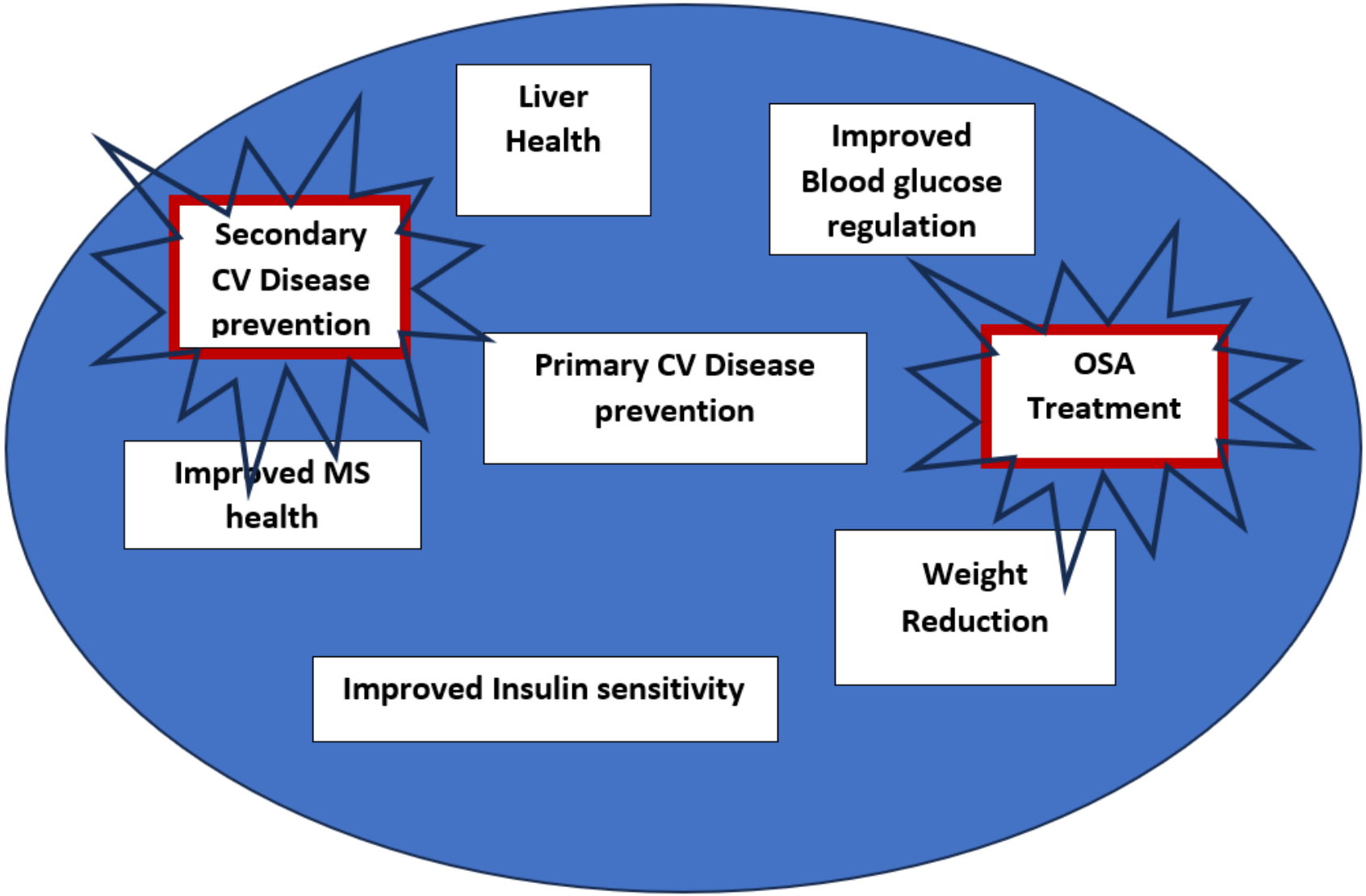
SURMOUNT 4 - Tirzepatitde



Rubino D, Abrahamsson N, Davies M, et al. Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity: The STEP 4 Randomized Clinical Trial. *JAMA.* 2021;325(14):1414–1425. doi:10.1001/jama.2021.3224

Aronne LJ, Sattar N, Horn DB, et al. Continued Treatment With Tirzepatide for Maintenance of Weight Reduction in Adults With Obesity: The SURMOUNT-4 Randomized Clinical Trial. *JAMA.* 2024;331(1):38–48. doi:10.1001/jama.2023.24945

New Aims in Obesity Management



THE UNIVERSITY OF KANSAS HEALTH SYSTEM

SELECT

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

Authors: A. Michael Lincoff, M.D., Kirstine Brown-Frandsen, M.D., Helen M. Colhoun, M.D., John Deanfield, M.D., Scott S. Emerson, M.D., Ph.D., Sille Esbjerg, M.Sc., Søren Hardt-Lindberg, M.D., Ph.D., +9, for the SELECT Trial Investigators* Author Info & Affiliations

Published November 11, 2023 | N Engl J Med 2023;389:2221-2232 | DOI: 10.1056/NEJMoa2307563

VOL. 389 NO. 24

November 2023

Overview

- 17,604 patients, multicenter (>800 in 41 countries)
- Double blinded, randomized (1:1)
- Age >45
- BMI >27
- No DM

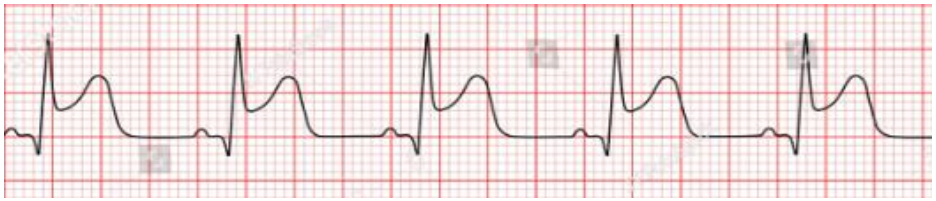
- 72% male
- Avg BMI 33
- Avg A1c 5.8

Population

- All participants had history of:
  - MI (~75%)
  - CVA
  - Symptomatic PVD
  - ~25% carried clinical diagnosis of heart failure

- All patient were continued on current therapy that was standard of care for their CV condition:
  - **90%** on lipid lowering agent
  - **86.2%** on platelet aggregation agent
  - **70.2%** on BB therapy
  - **45%** on ACEi
  - **29%** on ARB

No pt on SGLT2 at time of randomization, 500 patients treated by end of study



Endpoints

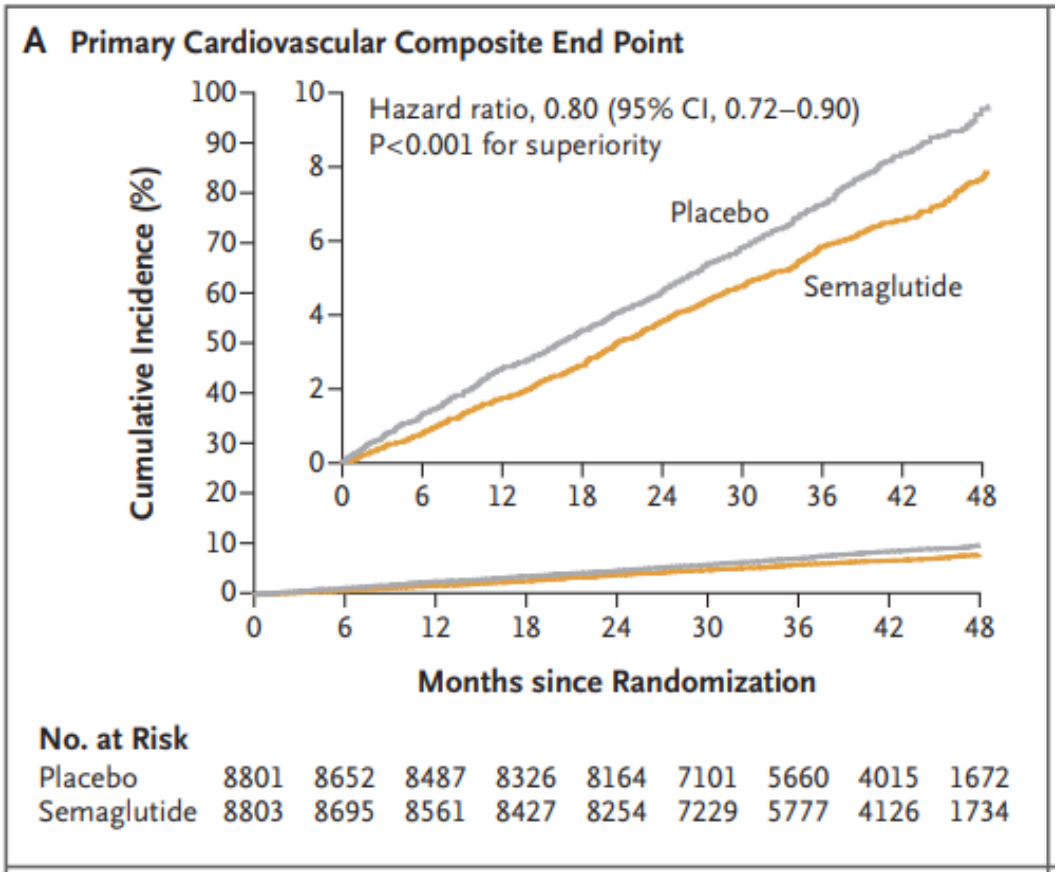
- Primary Endpoints
  - Death from CV disease
  - Nonfatal MI
  - Nonfatal CVA
- Secondary Endpoints
  - A1c change
  - Change in body weight
  - Change in waist circumference
  - Change in BP
  - Heart rate change
  - Change in lipids
  - Change in CRP

Results – Primary Endpoint

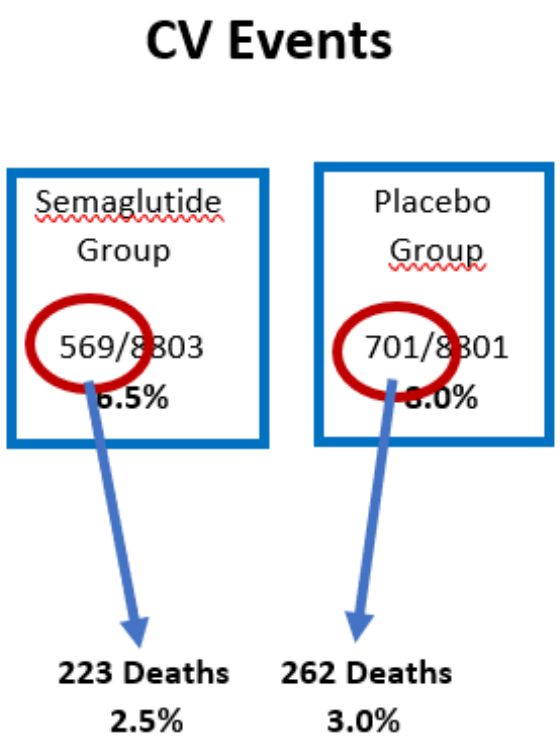
CV Events

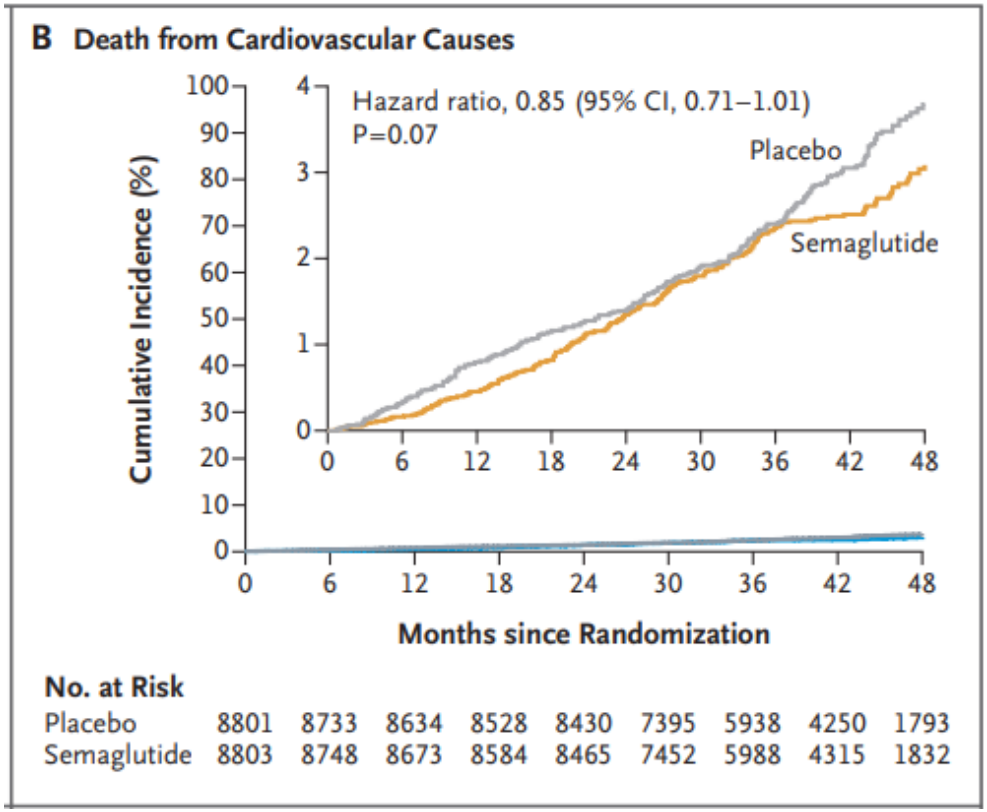
Semaglutide Group	Placebo Group
569/8803	701/8801
6.5%	**8.0%**

HR 0.8 (95% CI, 0.72 to 0.9, p<0.001)



Results – CV Deaths





Results – Composite HF

Death from CV cause

+

Hospitalization from HF

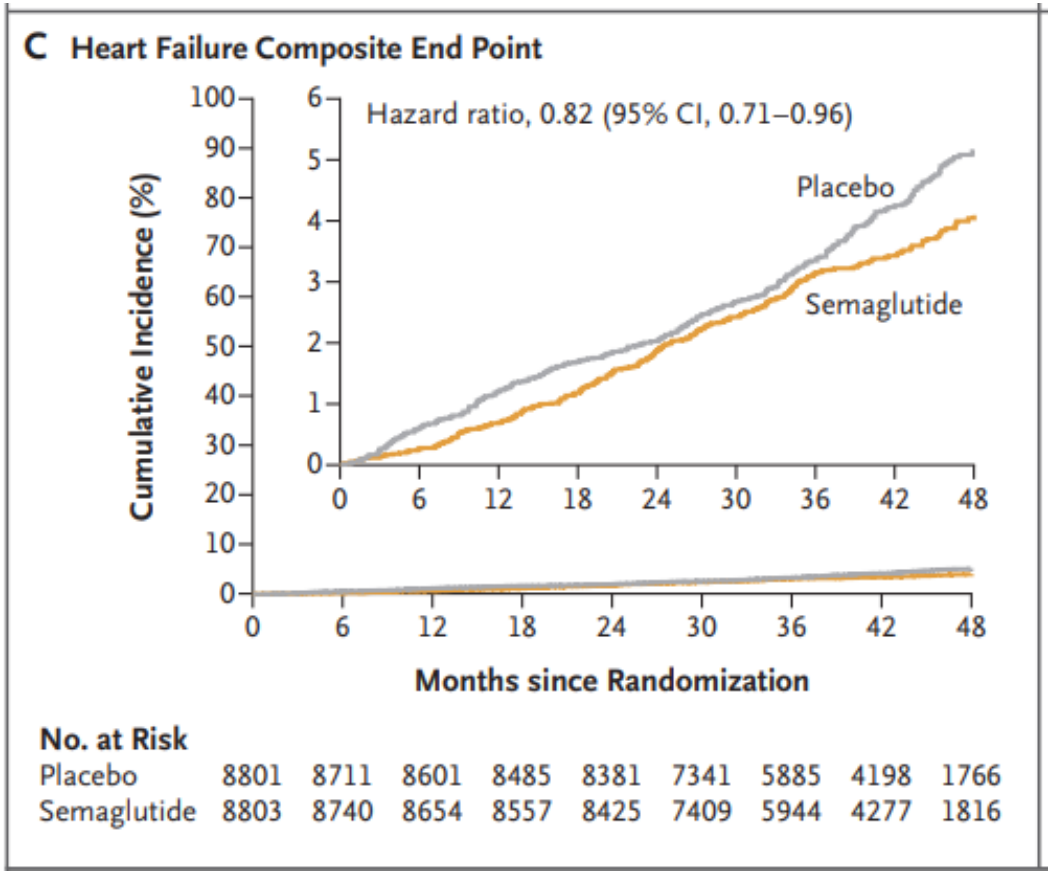
+

Urgent Medical visit for HF

HF Endpoint

Semaglutide Group	Placebo Group
300/8803	261/8801
3.4%	**4.1%**

HR 0.82 (CI 95%, 0.71 to 0.93)

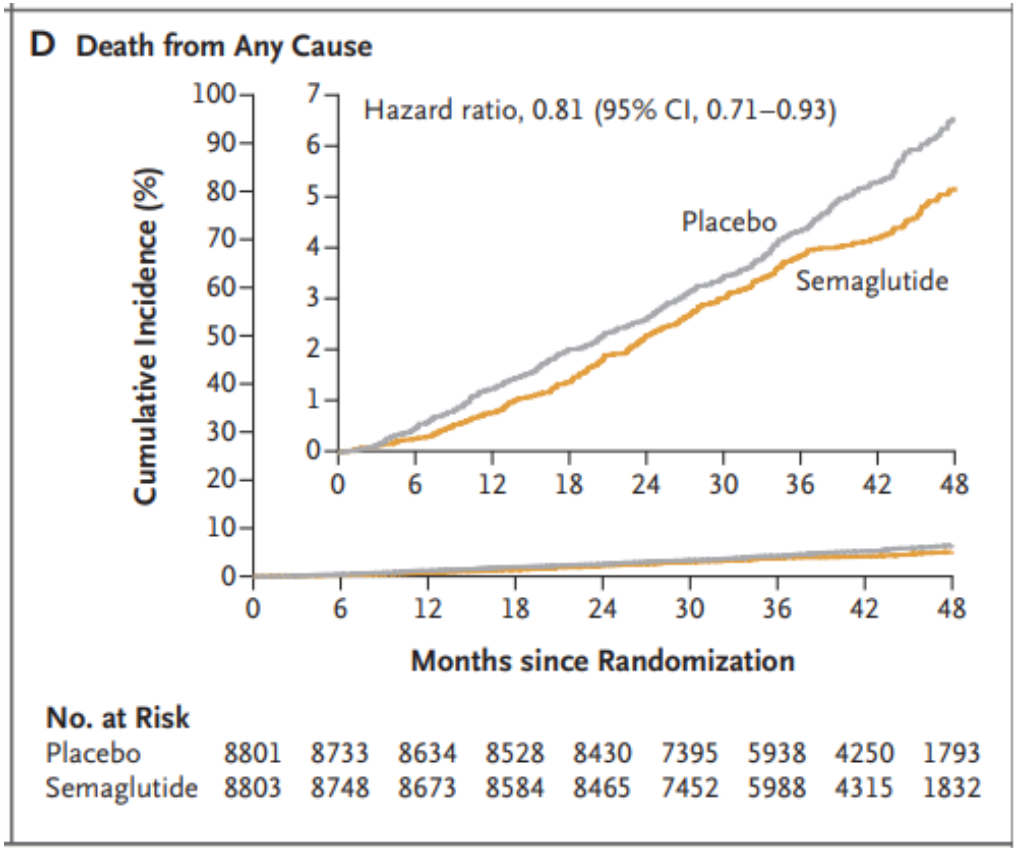


Results – Death Any Cause

All Cause Mortality

Semaglutide Group	Placebo Group
375/8803	458/8801
4.3%	**5.2%**

HR 0.81 (CI 95%, 0.71 to 0.93)



Secondary Endpoints

Table 3. Supportive Binary and Continuous Secondary End Points.*

End Point	Semaglutide (N=8803)	Placebo (N=8801)	Difference (95% CI)†
Glycated hemoglobin level of <5.7% among patients with baseline glycated hemoglobin level of ≥5.7% — no./total no. (%)‡			
At week 52	3848/5831 (66.0)	1136/5748 (19.8)	10.15 (9.18 to 11.23)
At week 104	3775/5750 (65.7)	1211/5663 (21.4)	8.74 (7.91 to 9.65)
Mean change from randomization to week 104			
Body weight — %	−9.39±0.09	−0.88±0.08	−8.51 (−8.75 to −8.27)
Waist circumference — cm	−7.56±0.09	−1.03±0.09	−6.53 (−6.79 to −6.27)
Glycated hemoglobin level — percentage points	−0.31±0.00	0.01±0.00	−0.32 (−0.33 to −0.31)
Systolic blood pressure — mm Hg	−3.82±0.16	−0.51±0.16	−3.31 (−3.75 to −2.88)
Diastolic blood pressure — mm Hg	−1.02±0.10	−0.47±0.10	−0.55 (−0.83 to −0.27)
Heart rate — beats/min	3.79±0.11	0.69±0.11	3.10 (2.80 to 3.39)
EQ-5D-5L index score§	0.01±0.00	−0.01±0.00	0.01 (0.01 to 0.02)
EQ-5D-VAS score§	2.52±0.16	0.92±0.16	1.60 (1.16 to 2.04)
High-sensitivity CRP level — %	−39.12	−2.08	−37.82 (−39.70 to −35.90)
Total cholesterol level — %	−4.63	−1.92	−2.77 (−3.37 to −2.16)
HDL cholesterol level — %	4.86	0.59	4.24 (3.70 to 4.79)
LDL cholesterol level — %	−5.25	−3.14	−2.18 (−3.22 to −1.12)
Triglyceride level — %	−18.34	−3.20	−15.64 (−16.68 to −14.58)

Adverse events

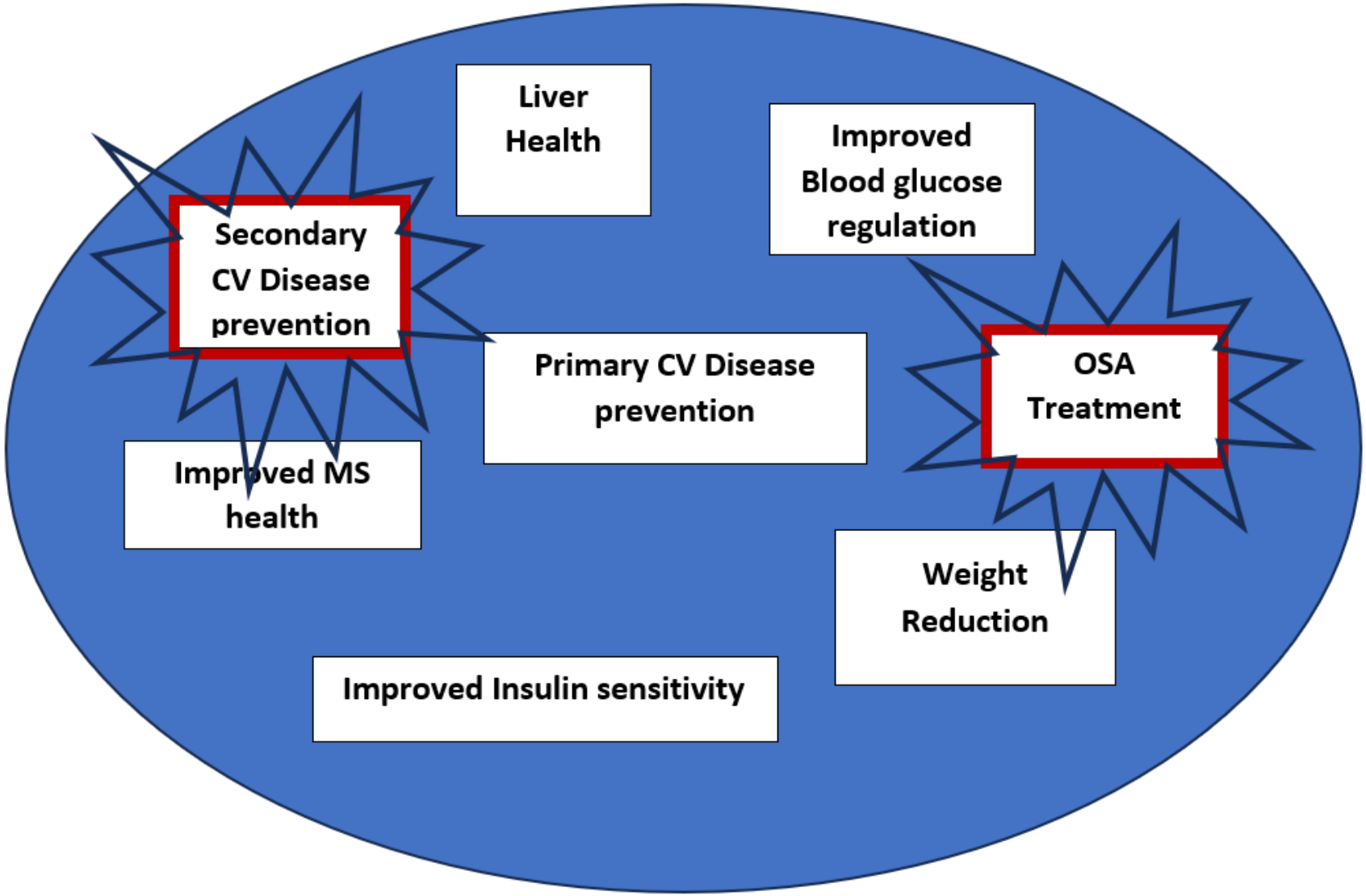
Event	Semaglutide (N=8803)	Placebo (N=8801)	P Value†
	no. of patients (%)		
Serious adverse events‡	2941 (33.4)	3204 (36.4)	<0.001
Cardiac disorders	1008 (11.5)	1184 (13.5)	<0.001
Infections and infestations	624 (7.1)	738 (8.4)	0.001
Nervous system disorders	444 (5.0)	496 (5.6)	0.08
Surgical and medical procedures	433 (4.9)	548 (6.2)	<0.001
Neoplasms benign, malignant, and unspecified	405 (4.6)	402 (4.6)	0.94
Gastrointestinal disorders	342 (3.9)	323 (3.7)	0.48
Adverse events leading to permanent discontinuation of trial product, irrespective of seriousness‡	1461 (16.6)	718 (8.2)	<0.001
Gastrointestinal disorders	880 (10.0)	172 (2.0)	<0.001
Nervous system disorders	124 (1.4)	92 (1.0)	0.03
Metabolism and nutrition disorders	108 (1.2)	27 (0.3)	<0.001
General disorders and administration-site conditions	105 (1.2)	47 (0.5)	<0.001
Neoplasms benign, malignant, and unspecified	80 (0.9)	105 (1.2)	0.07
Infections and infestations	75 (0.9)	84 (1.0)	0.47

FDA Response – March 8, 2024

FDA NEWS RELEASE

FDA Approves First Treatment to Reduce Risk of Serious Heart Problems Specifically in Adults with Obesity or Overweight

New Aims in Obesity Management



Tirzepatide and OSA (SURMOUNT- OSA)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity

Atul Malhotra, M.D., Ronald R. Grunstein, M.D., Ph.D., Ingo Fietze, M.D., Terri E. Weaver, Ph.D., Susan Redline, M.D., M.P.H., Ali Azarbarzin, Ph.D., Scott A. Sands, Ph.D., Richard J. Schwab, M.D., Julia P. Dunn, M.D., Sujatro Chakladar, Ph.D., Mathijs C. Bunck, M.D., Ph.D., and Josef Bednarik, M.D., for the SURMOUNT-OSA Investigators*

June 21, 2024

Backgroud

- At present, no pharmacologic intervention for OSA
- PAP therapy is insufficient to lower risk of CV disease to baseline
- Many individuals with OSA are not compliant with PAP usage (30-60%)
  - NIH 2016 data

Study Overview

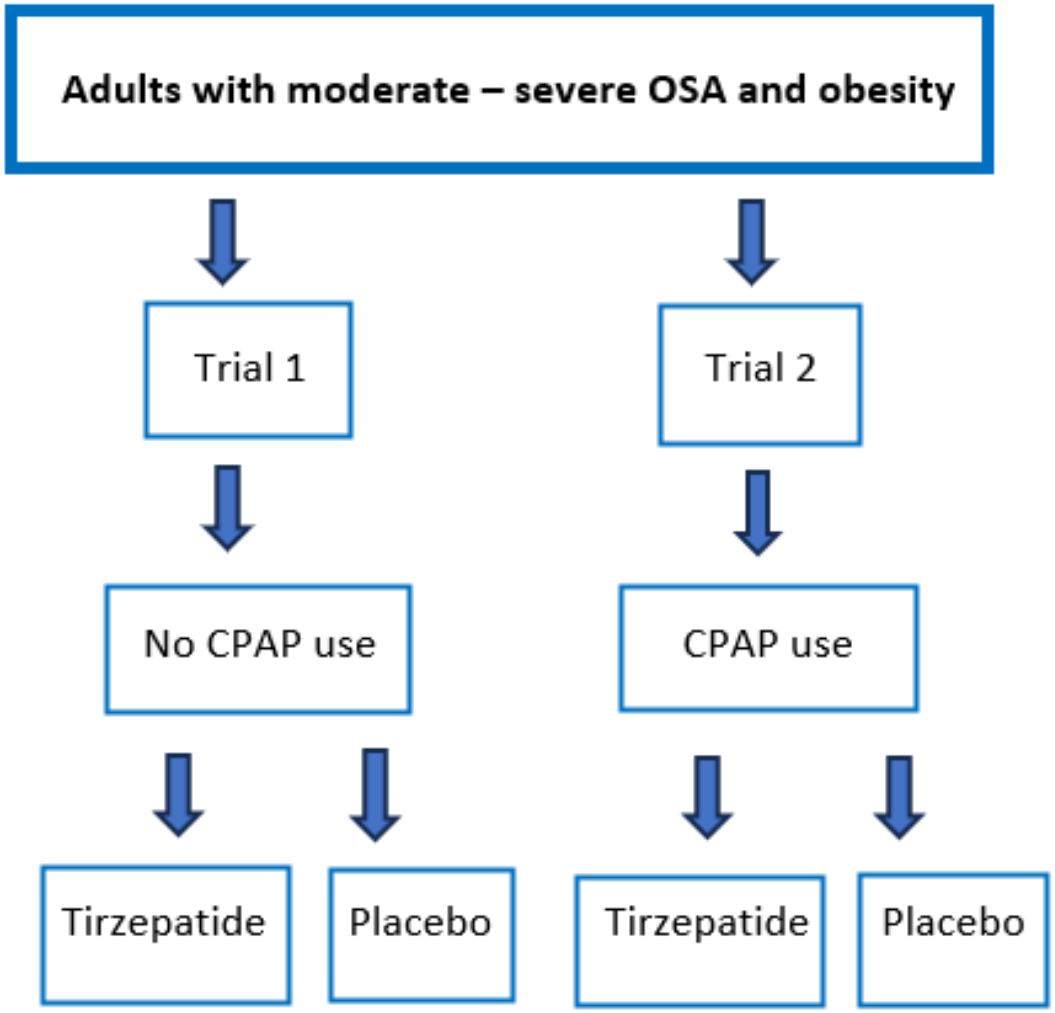
- 52 week, phase 3
- Double blinded
- Multi center (60 sites, 9 countries)
- Inclusion Criteria:
  - Adults with AHI >15 (moderate) and BMI >30
- Exclusion Criteria
  - Diabetes, mixed or central sleep apnea, craniofacial abnormality

- All participants received lifestyle counseling on healthy nutrition with 500kcal per day deficit and >150 min per week of physical activity

Patient Demographics

- 470 patients total
- 1:1:1:1
- ~30% female
- 60-70% white, 30-40% Latino/ Hispanic, ~20% Asian
- ~60% with prediabetes
- ~80% dyslipidemia

Methods


Adults with moderate – severe OSA and obesity
Trial 1
Trial 2
No CPAP use
CPAP use
Tirzepatide
Placebo
Tirzepatide
Placebo

Tirzepatide Titration

- All individuals randomized to tirzepatide group were started on 2.5mg weekly and increased q4 weeks toward a max tolerated treatment dose of **10mg or 15mg weekly** by week 20

- If unable to reach at least 10mg weekly discontinued medication or placebo but remained in the trial

- Data analysis was done with all patients receiving at least 1 dose of medication/placebo
  - Treatment regimen estimand vs. Efficacy estimand

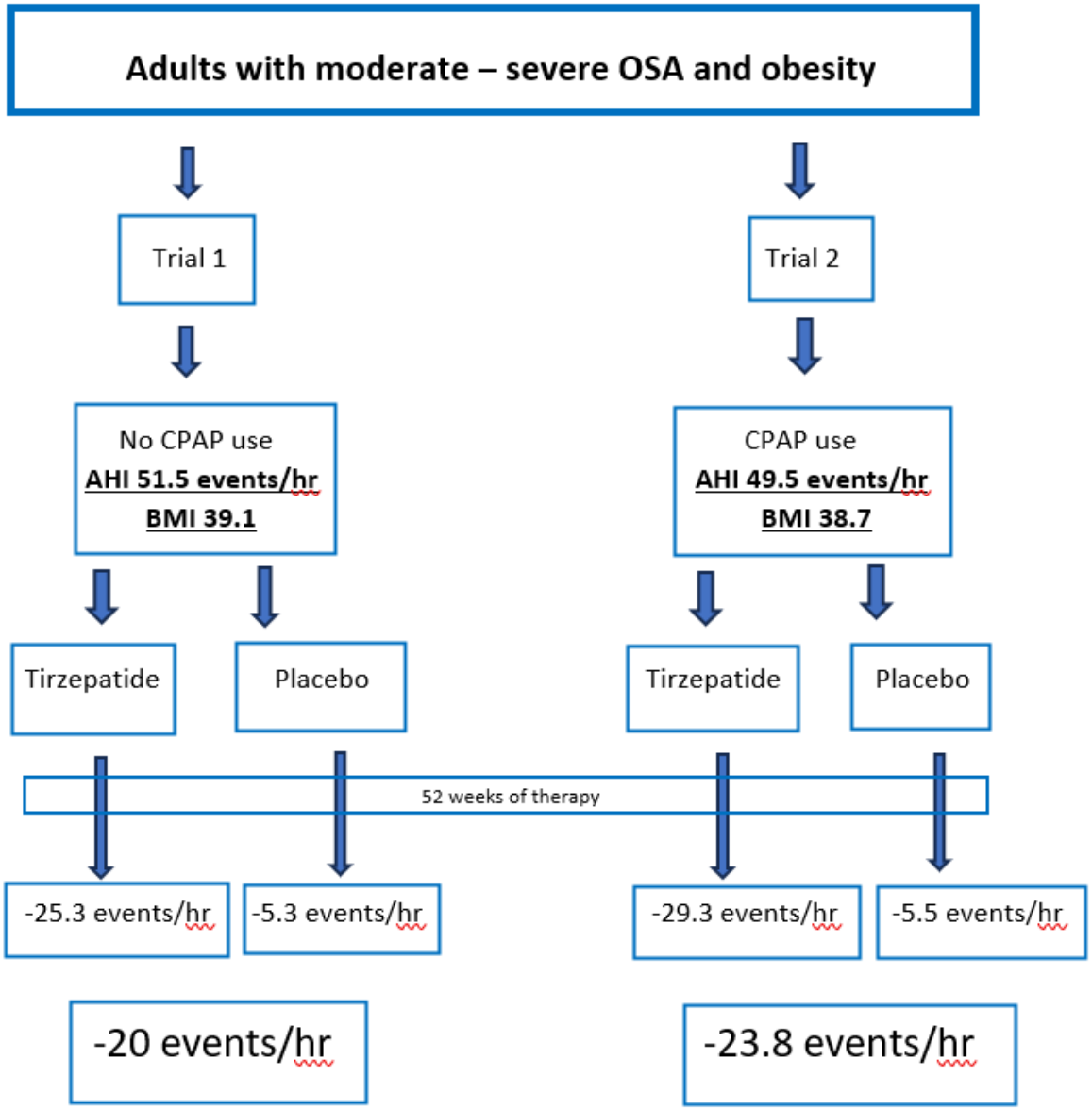
Endpoints

- Change in Apnea-Hypopnea Index (AHI) from baseline

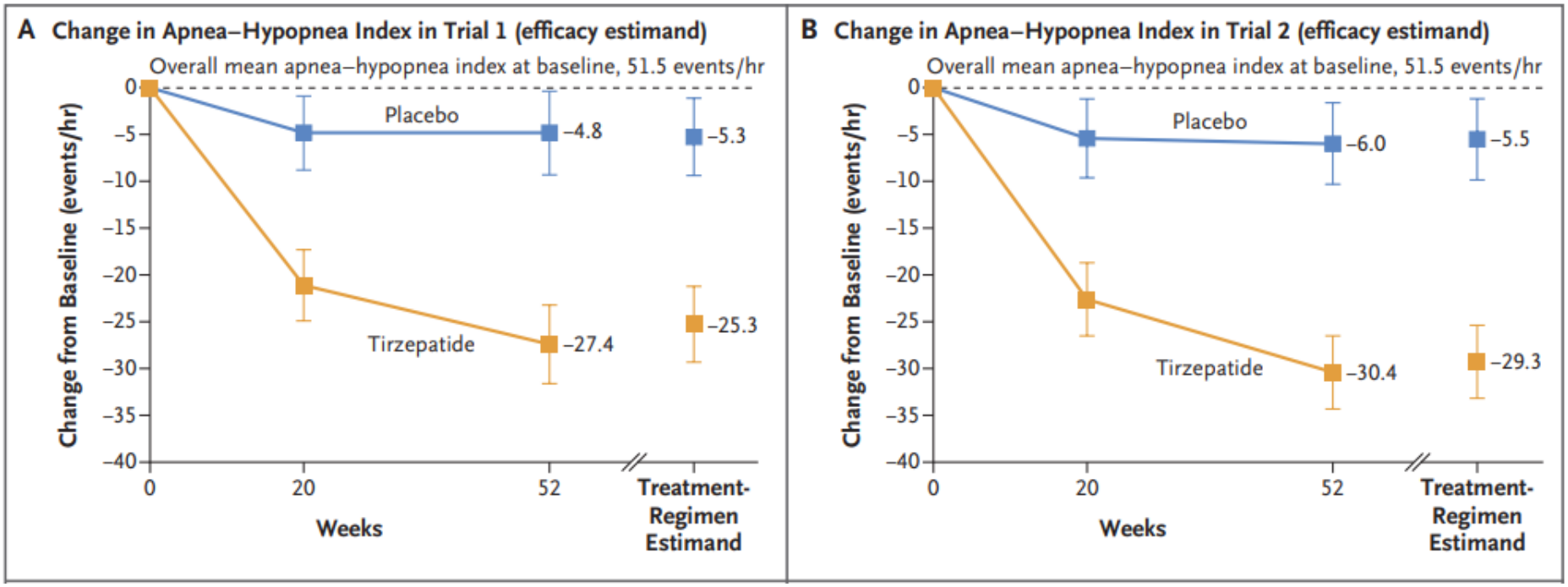
- Percent change in AHI
- AHI reduction of at least 50%
- Percentage of participants with AHI of less than 5 events per hour and score of <11 on Epworth sleepiness scale
- Percentage change in body weight
- Change in hrCRP
- Change in sleep apnea specific hypoxic burden
- Change in scores on the Patient Reported Outcomes Measurement Information System, Short form sleep-related Impairment and PROMIS short form sleep disturbance scale
- Change in systolic BP

Results

Treatment regimen
Estimand



Change in AHI



Primary Endpoint – Change in AHI from baseline

- Trial 1: -47.7% (95% CI -65.8 to -29.6), $p < 0.001$
- Trial 2: -56.2% (95% CI -73.7 to -38.7), $p < 0.001$

Results

- Sleep apnea specific hypoxic burden
  - Trial 1: -47.7% (95% CI -65.8 to -29.6), $p < 0.001$
  - Trial 2: -56.2% (95% CI -73.7 to -38.7), $p < 0.001$

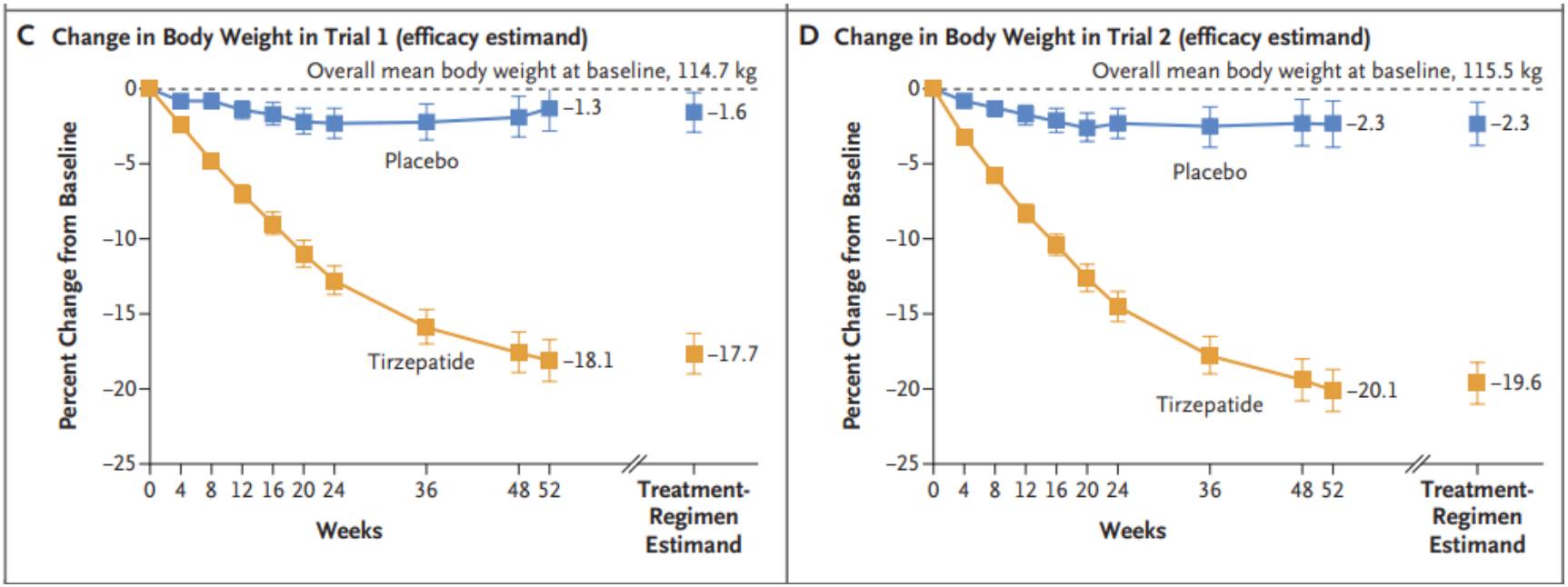
- Percentage of participants who had a reduction in the AHI of at least 50%
  - Trial 1 – 61%
  - Trial 2 - 72%

- Percentage of participants who had AHI <5 events per hour
  - Trial 1 – 42%
  - Trial 2 – 50%

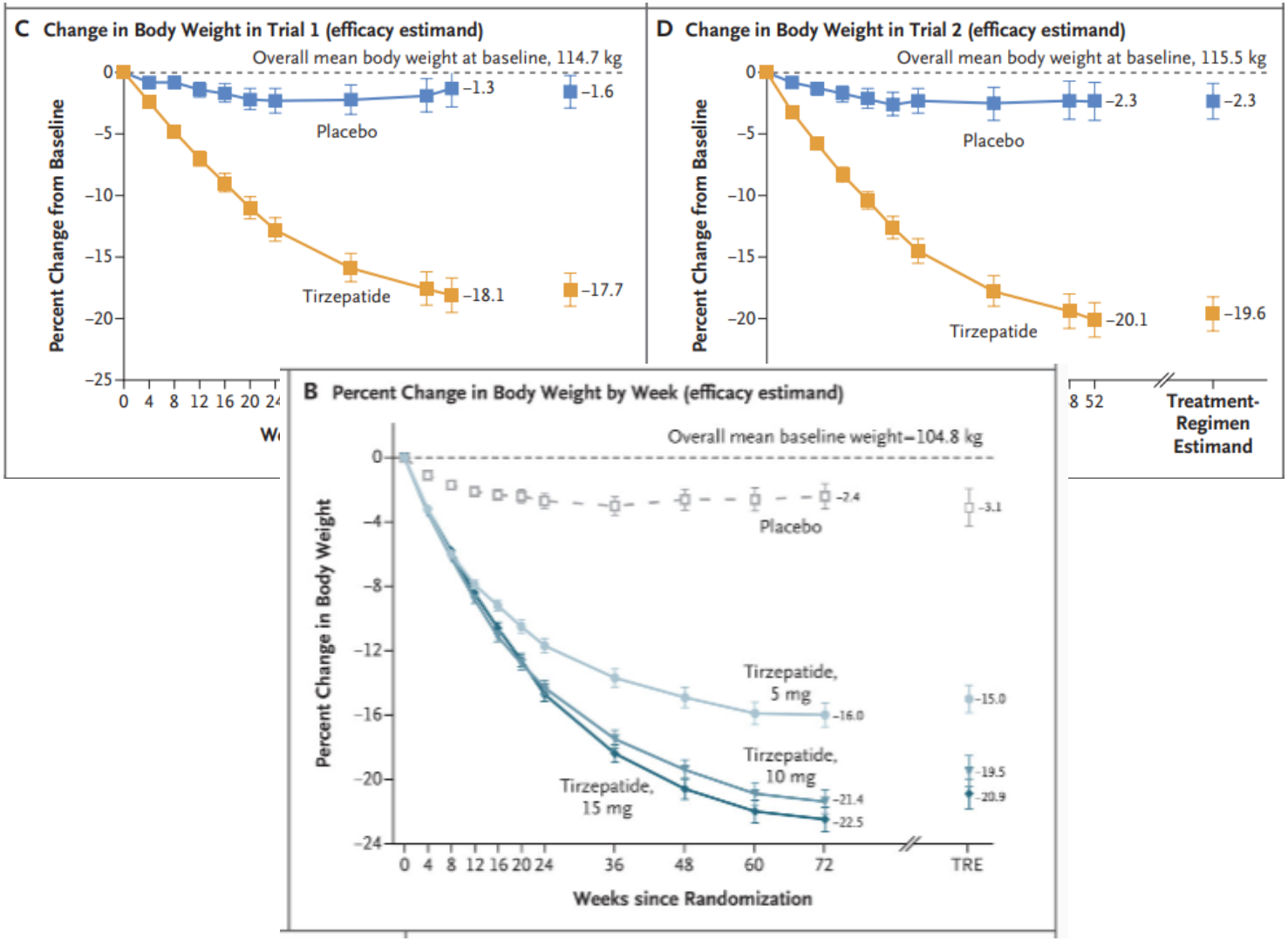
Results

- PROMIS-SRI (Sleep Related Impairment)
  - Trial ½ Pooled - -3.9 (95% CI - -5.7 to -2.2, p<0.001)
- PROMOIS-SD T (Sleep Disturbance)
  - Trial ½ Pooled - -3.1 (95% CI - -4.5 to -1.5, p<0.001)
- Change in Systolic BP
  - Trial 1: -7.6 mm Hg (95% CI -10.5 to -4.8), p < 0.001
  - Trial 2: -3.7 mm Hg (95% CI -6.8 to -0.7), p = 0.02

Change in Body Weight



Change in Body Weight



Adverse Events

Trial 1
78% of tirzepatide group
76.7% placebo group

Trial 2
83.2% tirzepatitde group
72.8% placebo group

Serious Adverse events in 35 participants, 7.5%

- Pancreatitis x2 (tirzepatide)
- No medullary cancer
- 5 cases severe depression disorder (2 tirzepatide, 3 placebo)
- No Deaths

FDA Response

???

HEALTH AND SCIENCE

Eli Lilly expects FDA decision on weight loss drug Zepbound for sleep apnea as early as end of the year

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SHARE

Thank you!

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