Obesity Medications: Beyond the Hype

Evaluating the Evidence and Barriers to Use

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OHSU CPD

Disclosures

- None
- OSU Drug Use Research & Management
- Oregon Prescription Drug Affordability Board (PDAB)

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Objectives

- Review data supporting efficacy and safety of medications used for treatment of obesity, with a focus on the GLP-1 agonists
- Explore differences and similarities between FDA approved medications for obesity
- Identify cost and insurance coverage trends limiting widespread implementation of newer medications

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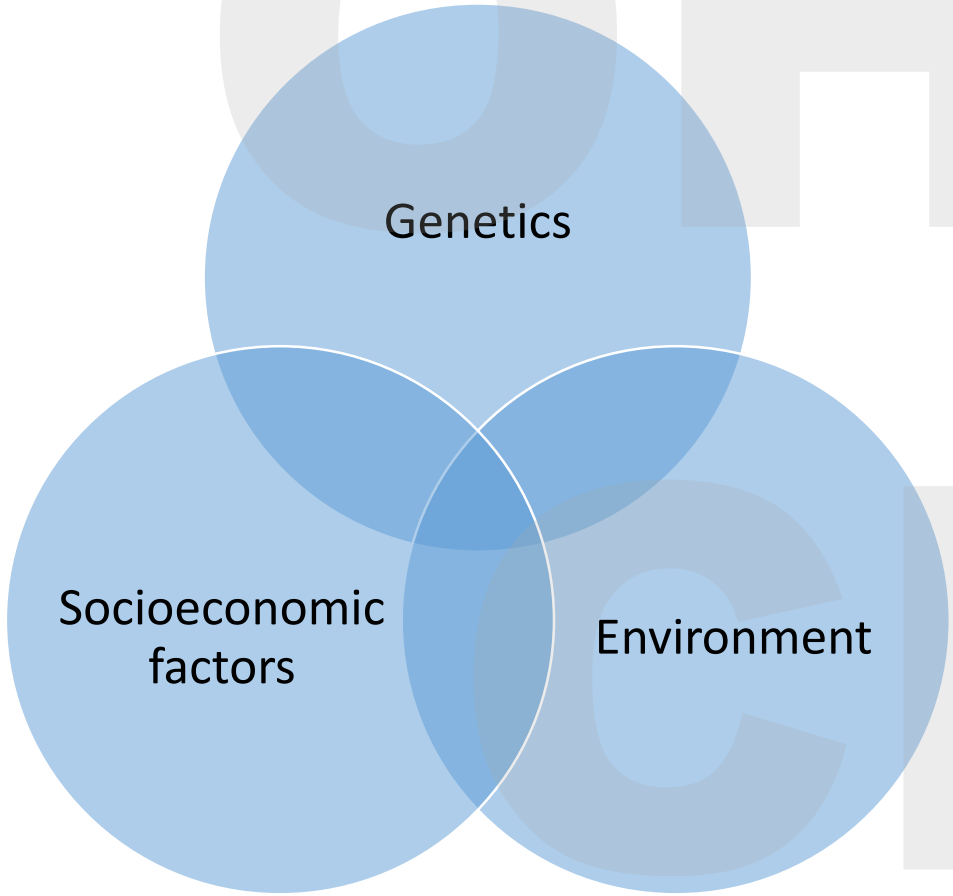
Overweight and Obesity



- Low-income
- People who identify as:
  - Black (black women with highest prevalence 56.9%)
  - Latinx or Hispanic
  - American Indian or Alaska Native
- Medicaid enrollees

People covered by Medicaid are 27% more likely to be obese compared to those with commercial insurance

Urban Institute: Obesity Across America

Businessweek | Feature

Jimmy Kimmel joked about Ozempic at the Oscars. We need to actually talk about it.

1:14 AM · Sep 10, 2023 · **104.4K** Views

weight loss, and could create a market worth $150 billion a year.

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2012

Phentermine/ topiramate (Qsymia) FDA approved

2013

Obesity recognized as a disease

2014

Liraglutide (Saxenda) FDA approved

2014

Naltrexone/ bupropion (Contrave) FDA approved

2020

Lorcaserin (Belviq) removed from market due to safety concerns

2021

Semaglutide (Wegovy) FDA approved

2021

ADA guidelines recommend GLP-1 agonists as first line agents with compelling indication

2023

Tirzepatide (Zepbound) FDA approved

2023

American Academy of Pediatrics recommends pharmacological agents

FDA APPROVED FOR CHRONIC WEIGHT MANAGEMENT

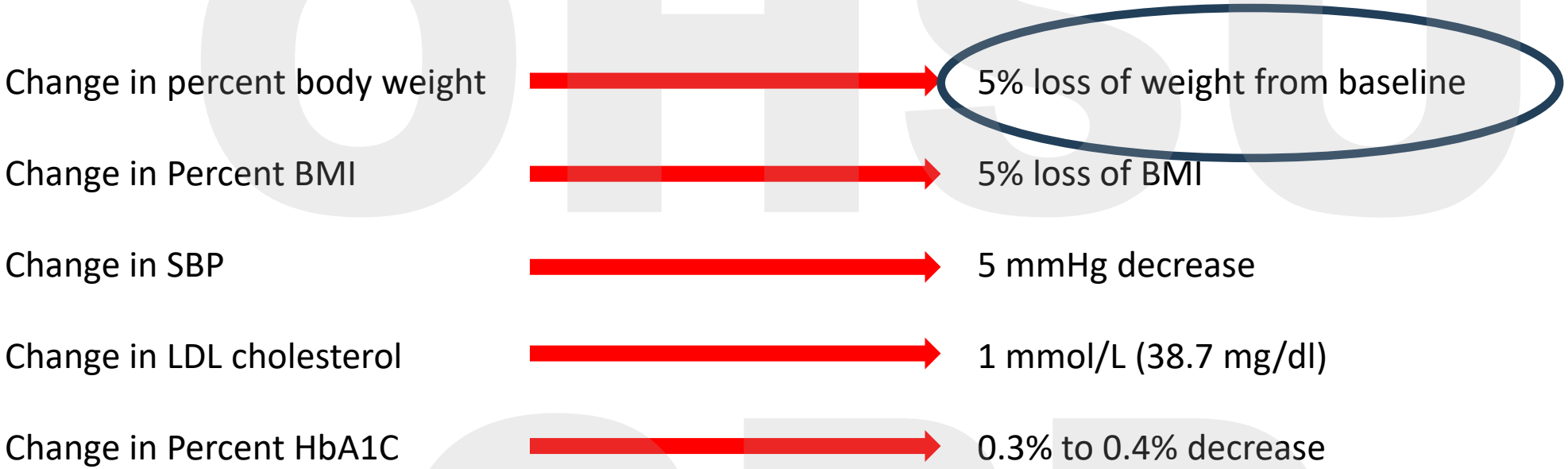
Generic (Brand)	Drug Class	Dose	Route of Admin	Date of FDA approval
Tirzepatide (Zepbound)	GIP/GLP-1 agonist	5 mg weekly	Injection	Nov 8th, 2023
Semaglutide (Wegovy)	GLP-1 agonist	2.4 mg weekly	Injection	June 4th, 2021
Liraglutide (Saxenda)	GLP-1 agonist	3.0 mg daily	Injection	Dec 23rd, 2014
Naltrexone + bupropion (Contrave)	Norepinephrine/ dopamine reuptake inhibitor + opioid antagonist	32 mg + 360 mg (4 tabs daily)	Oral	September 10th, 2014
Phentermine + topiramate (Qysmia)	Sympathomimetic amine + antiepileptic	15 mg + 92 mg (4 capsules daily)	Oral	July 17th, 2012

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

EFFICACY

Generic (Brand)	% weight loss	≥ 5% weight loss (vs. placebo)	≥ 10% weight loss	N
Tirzepatide (Zepbound)	-15.37% (95% CI -16.68 to -14.06)	88.3% vs. 34.5% RR 2.6 (2.3 to 2.9)	76.7% vs. 18.8% RR 4.1 (3.5 to 4.8)	2,539
Semaglutide (Wegovy)	-11.59% (95% CI -14.09 to -9.09)	83.8% vs. 35% RR 2.3 (95% CI 1.9 to 2.8)	67.8% vs. 14% RR 4.7 (95% CI 3.5 to 6.3)	4,786
Phentermine + topiramate (Qysmia)	-8.56% (95% CI -9.93 to -7.19)	67.2% vs. 19.6% RR 3.5 (2.9 to 4.1)	44.9% vs. 7.8% RR 6.1 (5.1 to 7.4)	3,444
Liraglutide (Saxenda)	-4.61% (95% CI -5.44 to -3.78)	58.5% vs. 26.2% RR 2.0 (95% CI 1.6 to 2.6)	29.8% vs. 10.3% RR 2.7 (95% CI 2.0 to 3.5)	5,817
Naltrexone + bupropion (Contrave)	-4.25% (95% CI -5.07 to -3.42)	50.4% vs. 20.8% RR 2.3 (1.7 to 3.2)	27.6% vs. 8.5% RR 3.1 (2.1 to 4.7)	3,710

Outcomes in Clinical Trials: Clinical Differences



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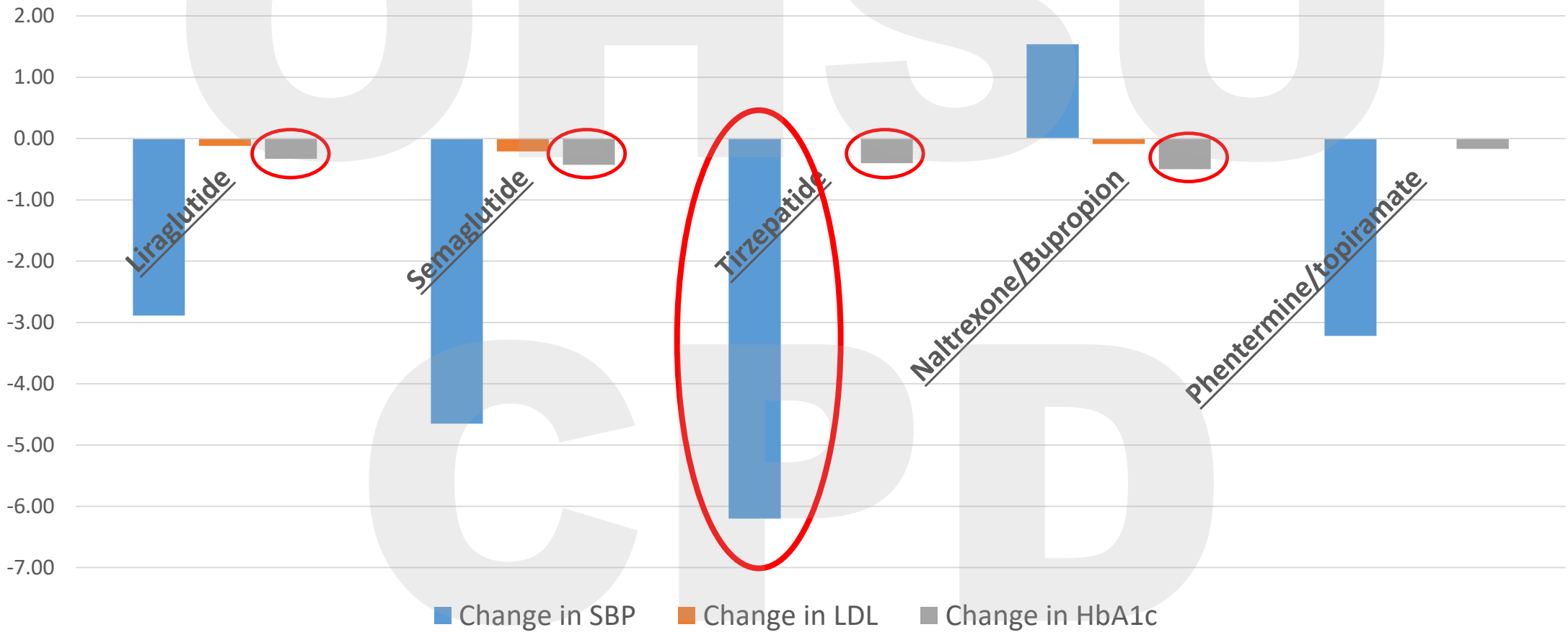
Change in Comorbidity Biomarkers



Head-to-Head Evidence

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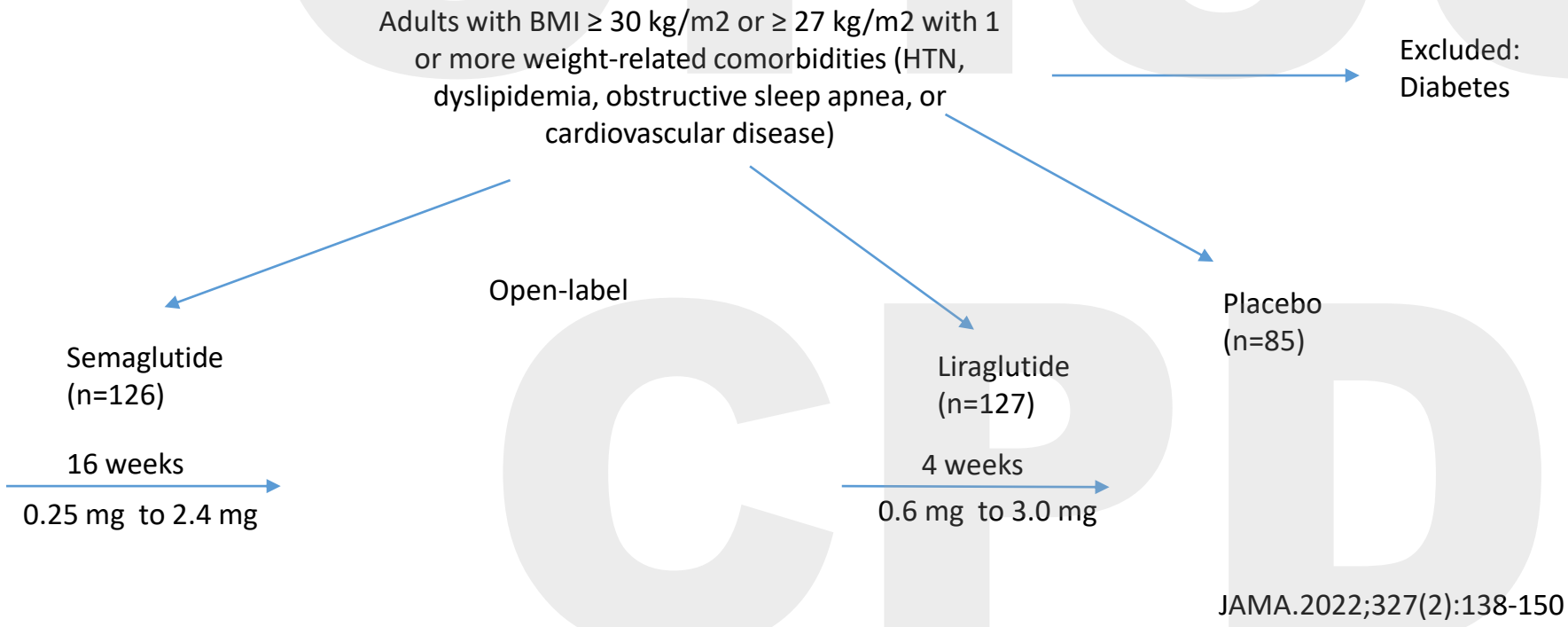
JAMA | Original Investigation

Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes

The STEP 8 Randomized Clinical Trial



JAMA.2022;327(2):138-150

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Semaglutide vs. Liraglutide:

The STEP 8 Randomized Clinical Trial

Table 2. Change in Efficacy Outcomes From Baseline to Week 68 (Treatment Policy Estimand; Full Analysis Set)[a,b]

	Estimated mean change (95% CI) [No.]		Difference for semaglutide, 2.4 mg, vs liraglutide, 3.0 mg (95% CI)[c]	*P* value
	Semaglutide, 2.4 mg (n = 126)	Liraglutide, 3.0 mg (n = 127)		
Primary end point				
Body weight, % change	-15.8 (-17.6 to -13.9) [117]	-6.4 (-8.2 to -4.6) [117]	-9.4 (-12.0 to -6.8)	<.001
Confirmatory secondary end points				
Weight loss at week 68, No. (%)[d]				
Participants with ≥10%	83/117 (70.9)	30/117 (25.6)	Odds ratio: 6.3 (3.5 to 11.2)	<.001
Participants with ≥15%	65/117 (55.6)	14/117 (12.0)	Odds ratio: 7.9 (4.1 to 15.4)	<.001
Participants with ≥20%	45/117 (38.5)	7/117 (6.0)	Odds ratio: 8.2 (3.5 to 19.1)	<.001
Supportive secondary end points				

- ***Possible differences in ability to lower energy intake and mechanisms of energy intake regulation.***
- ***Structural differences?***

JAMA.2022;327(2):138-150

Semaglutide vs. Liraglutide: Withdrawals due to adverse events

- Participants randomized to semaglutide were significantly less likely to withdraw due to an AE compared to those randomized to liraglutide
- 3.2% with semaglutide vs. 12.6% with liraglutide (RR 0.25; 95% CI 0.09 to 0.73)

	Semaglutide, 2.4 mg (n = 126)		Liraglutide, 3.0 mg (n = 127)	
	Participants, No. (%)	Events, No.	Participants, No. (%)	Events, No.
Nausea	77 (61.1)	130	75 (59.1)	102
Constipation	49 (38.9)	80	40 (31.5)	52
Diarrhea	35 (27.8)	51	23 (18.1)	37
Vomiting	32 (25.4)	50	26 (20.5)	34
Headache	20 (15.9)	46	18 (14.2)	20
Eructation	17 (13.5)	20	5 (3.9)	5
Decreased appetite	15 (11.9)	15	16 (12.6)	18

JAMA.2022;327(2):138-150

Dose Titration

Study Methods: *response to poor tolerance of the maintenance dose differed; semaglutide was administered at a lower dose, whereas liraglutide was discontinued and had to be reescalated if restarted.*

Semaglutide

Week 1 through week 4: 0.25 mg once weekly.

Week 5 through week 8: 0.5 mg once weekly.

Week 9 through week 12: 1 mg once weekly.

Week 13 through week 16: 1.7 mg once weekly.

Week 17 and thereafter (maintenance dosage): 2.4 mg once weekly

Half-life: ~1 week

Liraglutide

Week 1: 0.6 mg once daily

Week 2: 1.2 mg once daily

Week 3: 1.8 mg once daily

Week 4: 2.4 mg once daily

Week 5: 3.0 mg once daily

Half-life: ~13 hours

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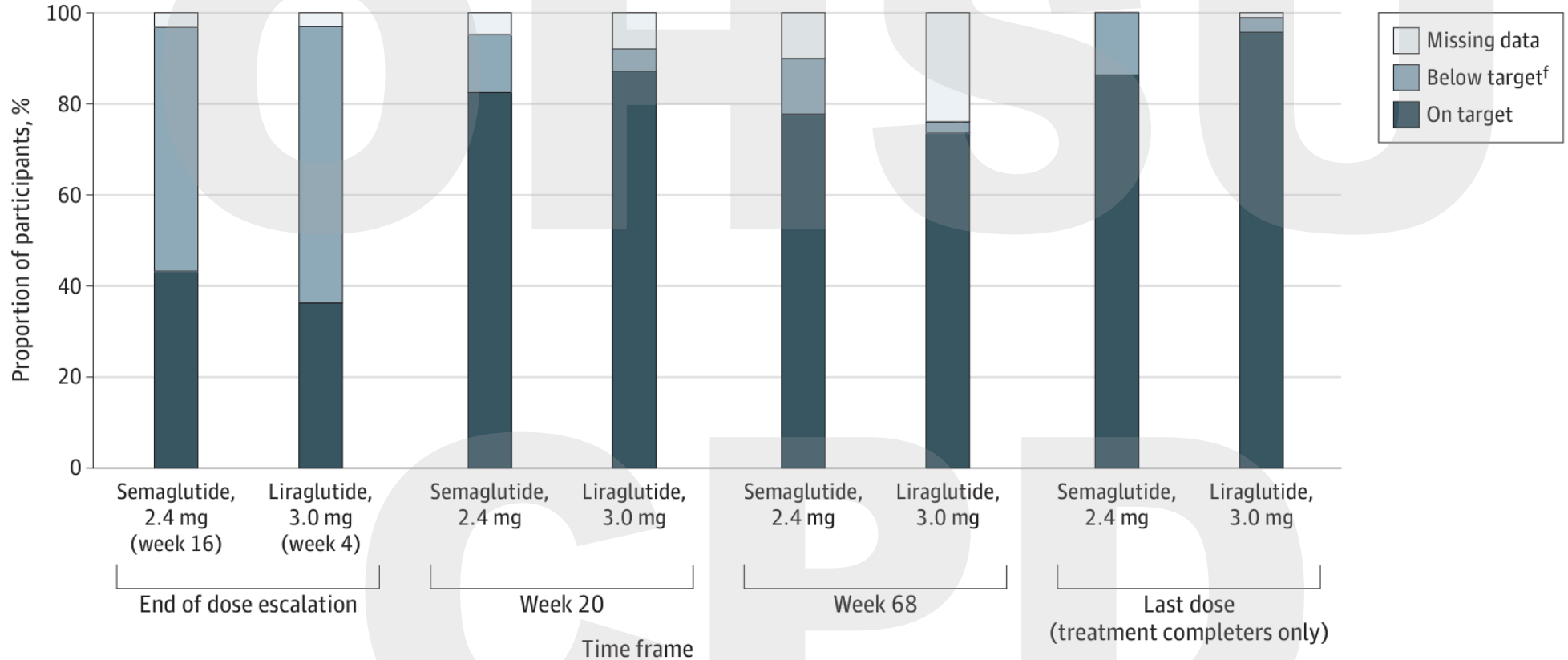
B Participants on or below the target dose during the trial (observed in-trial data)



No. of participants	125	127	125	125	121	121	109	92

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JAMA.2022;327(2):138-150

Table 3.11. NMA Results of Medications for the Management of Obesity, Mean Percentage Weight Loss from Baseline at One Year (95% CI)

Semaglutide				
-4.6 (-2.4 to -7.2)	Phentermine/ Topiramate*			
-8.7 (-7.3 to -10.4)	**-4.1 (-1.9 to -6.3)**	Liraglutide		
-9.1 (-7.2 to -11.5)	**-4.5 (-2.2 to -6.9)**	-0.4 (-2.3 to +1.3)	Bupropion/ Naltrexone	
-13.7 (-12.6 to -15.1)	**-9.1 (-7.1 to -11)**	**-5.0 (-3.9 to -6.1)**	**-4.6 (-3.0 to -6.0)**	Placebo

Legend: Each cell represents estimated absolute differences in percentage weight loss and 95% credible interval for the combined direct and indirect comparisons between two medications or one medication and placebo. Estimates in bold indicate the 95% credible interval does not contain 1.

*High dose.

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Institute for Clinical and Economic Review, 2022

Clinical Outcomes

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 14, 2023 VOL. 389 NO. 24

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

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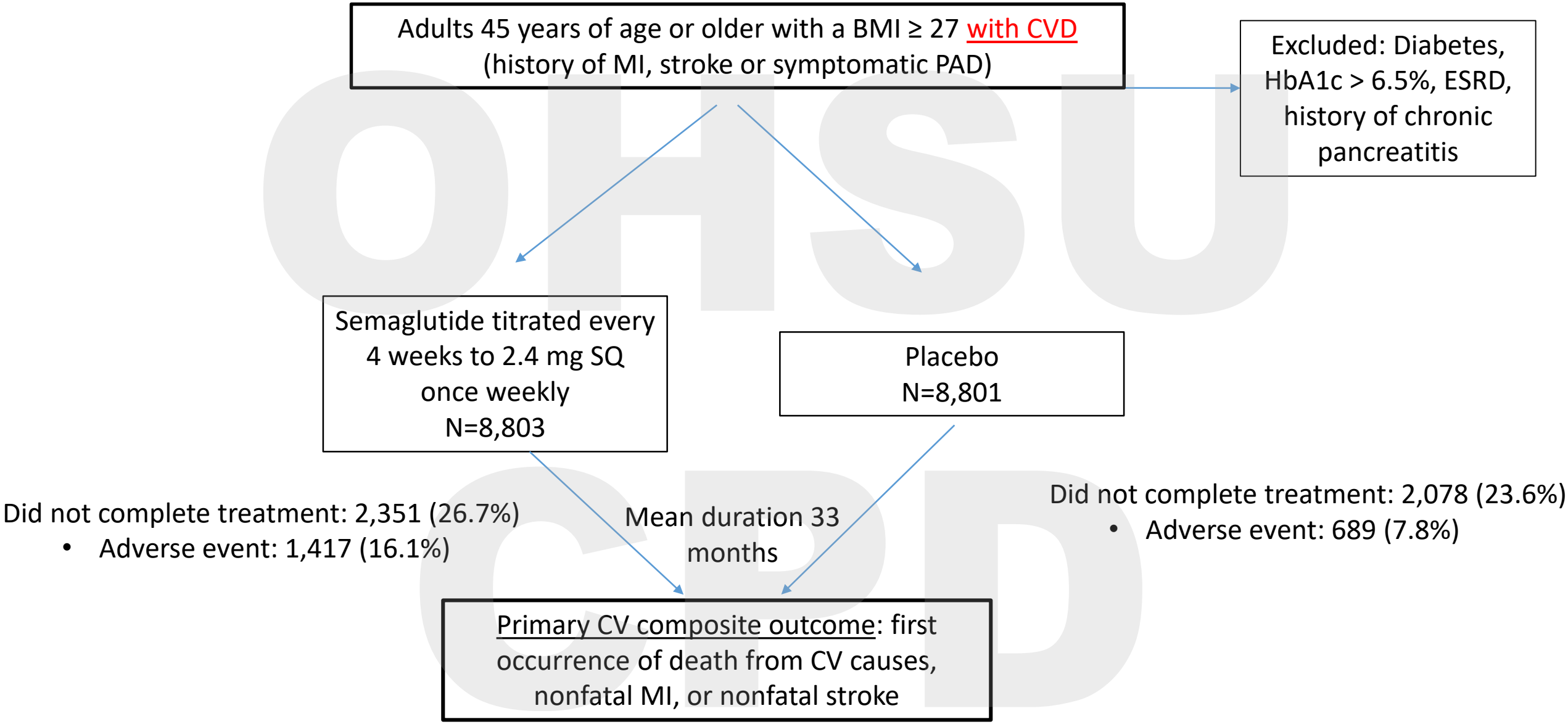
N Engl J Med 2023; 389:2221-2232



N Engl J Med 2023; 389:2221-2232

70% with obesity ★

82% with CHD ★

Aspirin Use 78%
Statin Use 87%
Beta Blocker: 70%
ACE/ARB: 75%

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Semaglutide (N=8803)	Placebo (N=8801)
Age — yr	61.6±8.9	61.6±8.8
Male sex — no. (%)	6355 (72.2)	6377 (72.5)
Race or ethnic group — no. (%)†		
White	7387 (83.9)	7404 (84.1)
Asian	720 (8.2)	727 (8.3)
Black	348 (4.0)	323 (3.7)
Other	253 (2.9)	273 (3.1)
Hispanic or Latino	914 (10.4)	908 (10.3)
Body weight — kg	96.5±17.5	96.8±17.8
BMI‡	33.3±5.0	33.4±5.0
Waist circumference — cm	111.3±13.1	111.4±13.1
Glycated hemoglobin level — %	5.78±0.34	5.78±0.33
Distribution — no. (%)		
<5.7%	2925 (33.2)	2980 (33.9)
≥5.7%	5877 (66.8)	5819 (66.1)
Median high-sensitivity CRP level (IQR) — mg/liter	1.87 (0.89–4.18)	1.80 (0.86–4.06)
Cardiovascular inclusion criteria — no. (%)		
Myocardial infarction only	5962 (67.7)	5944 (67.5)
Stroke only	1578 (17.9)	1556 (17.7)
Peripheral arterial disease only	376 (4.3)	401 (4.6)
Two or more inclusion criteria	718 (8.2)	719 (8.2)
Other§	169 (1.9)	181 (2.1)
eGFR — ml/min/1.73 m²	82.4±17.5	82.5±17.3
Median lipid level (IQR) — mg/dl		
Total cholesterol	153 (131–182)	153 (131–183)
HDL cholesterol	44 (37–52)	44 (37–52)
LDL cholesterol	78 (61–102)	78 (61–102)
Triglycerides	134 (99–188)	135 (100–190)
Systolic blood pressure — mm Hg	131.0±15.6	130.9±15.3
Diastolic blood pressure — mm Hg	79.4±10.0	79.2±9.9
Pulse — beats/min	68.9±10.6	68.6±10.7
EQ-5D-5L index score¶	0.88±0.15	0.88±0.15
EQ-5D-VAS score¶	77.15±15.63	77.15±15.73

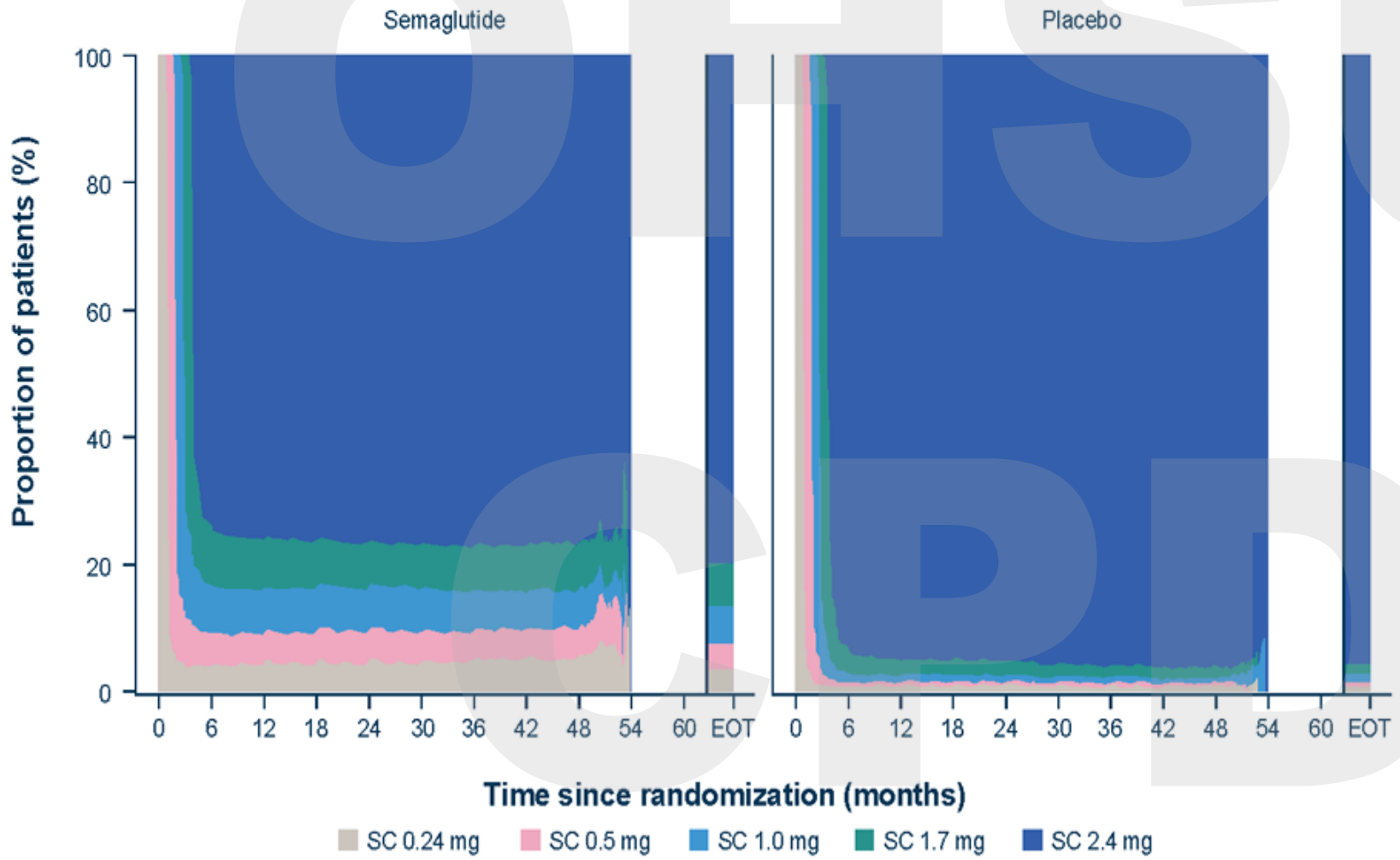
ARR 1.5%/NNT 67

Mean change in % body weight: -9.39% vs. -0.88% (Difference -8.51%; 95% CI -8.75 to -8.27)

Table 2. Primary and Secondary Time-to-First-Event Efficacy End Points.*

End Point	Semaglutide (N=8803)	Placebo (N=8801)	Hazard Ratio (95% CI)	P Value
	number of patients (percent)			
Primary cardiovascular composite end point†	569 (6.5)	701 (8.0)	0.80 (0.72 to 0.90)	<0.001
Confirmatory secondary end points‡				
Death from cardiovascular causes	223 (2.5)	262 (3.0)	0.85 (0.71 to 1.01)	0.07
Heart failure composite end point§	300 (3.4)	361 (4.1)	0.82 (0.71 to 0.96)	NA
Death from any cause	375 (4.3)	458 (5.2)	0.81 (0.71 to 0.93)	NA
Supportive secondary end points¶				
Cardiovascular expanded composite end point‖	873 (9.9)	1074 (12.2)	0.80 (0.73 to 0.87)	NA
Cardiovascular composite end point with death from any cause**	710 (8.1)	877 (10.0)	0.80 (0.72 to 0.88)	NA
Nonfatal myocardial infarction	234 (2.7)	322 (3.7)	0.72 (0.61 to 0.85)	NA
Nonfatal stroke	154 (1.7)	165 (1.9)	0.93 (0.74 to 1.15)	NA
Hospitalization or urgent medical visit for heart failure	97 (1.1)	122 (1.4)	0.79 (0.60 to 1.03)	NA
Coronary revascularization	473 (5.4)	608 (6.9)	0.77 (0.68 to 0.87)	NA
Unstable angina leading to hospitalization	109 (1.2)	124 (1.4)	0.87 (0.67 to 1.13)	NA
Glycated hemoglobin level ≥6.5%††	306 (3.5)	1059 (12.0)	0.27 (0.24 to 0.31)	NA
Nephropathy composite end point‡‡	155 (1.8)	198 (2.2)	0.78 (0.63 to 0.96)	NA
Glycated hemoglobin level ≥5.7% among patients with baseline glycated hemoglobin <5.7%§§	623 (21.3)	1501 (50.4)	0.33 (0.30 to 0.36)	NA

Figure S3. Dosing of Semaglutide and Placebo over the Course of the Trial.



D/C due to AE's:
16.6% vs. 8.2%; p<0.001
Discontinuations due to GI Disorders:
10% vs. 2%; p<0.001

Efficacy Conclusions

- Compared to placebo or usual care, all FDA approved drugs are effective at reducing body weight
- Tirzepatide (15.4%), semaglutide (11.6%) and phentermine + topirimate (8.6%) resulted in clinically meaningful weight loss (≥ 5% weight loss)
- In the only head-to-head study, semaglutide resulted in a significant difference in weight loss of 9.4% compared to semaglutide
- Only tirzepatide had a clinically meaningful reduction in systolic blood pressure (≥ 5 mmHg) of -6.2 mmHg
- No drugs reduced LDL-C by meaningful levels
- Tirzepatide, semaglutide and liraglutide are all FDA approved for T2DM and resulted in clinically meaningful improvements in HbA1c (≥ 0.3%)

Evidence Limitations

- Few head-to-head data
- No comparisons with surgery or intensive lifestyle therapy
- Limited long-term studies and analysis of off-treatment effects
- Significant conflicts of interest and funding by industry

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Safety

Generic (Brand)	Common AEs	Withdrawals due to AE	Other Safety Concerns
Tirzepatide (Zepbound)	Nausea, constipation, diarrhea, vomiting	RR 2.21	• AE's triggered by rapid weight loss (cholecystitis, cholelithiasis) • DC if pancreatitis is suspected • Contraindicated if personal or family history of medullary thyroid cancer or patients with multiple endocrine neoplasia type 2 • Monitor for depression and suicidal ideation.
Semaglutide (Wegovy)		RR 1.81	
Liraglutide (Saxenda)		RR 2.20	
Naltrexone + bupropion (Contrave)	Nausea, constipation, headaches, dizziness, dry mouth	RR 1.92	• Avoid with opioids • CYP drug interactions • Monitor for increases in BP, HR
Phentermine + topiramate	Paresthesia, dry. Mouth, constipation, disordered taste insomnia, dizziness	RR 1.88	• Monitor for pregnancy • Cognitive impairment • Monitor for mood, behavior, or sleep changes; suicidal ideation/behaviors

Barriers to implementation

- Potential side effects
- Long-term safety
- Durability of treatment effect
- Shortages
- Cost
- Insurance coverage
- Inequities in treatment access

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Duration and Stopping Criteria

- Liraglutide study - weight loss as maintained out to 3 years (-5.4% at 56 weeks and -4.2% at 160 weeks).
- Semaglutide – Weight loss maintained out to 4 years
- Stopping Criteria: If at least 5% weight loss is not achieved after 12 weeks at maximum tolerated dose, they should be discontinued.
- Weight regain is common after stopping treatment and long-term use may be needed to maintain weight loss (2/3 of prior weight loss)

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Medical News & Perspectives

November 15, 2023

As Semaglutide's Popularity Soars, Rare but Serious Adverse Effects Are Emerging

Kate Ruder, MSJ

JAMA. 2023;330(22):2140-2142. doi:10.1001/jama.2023.16620

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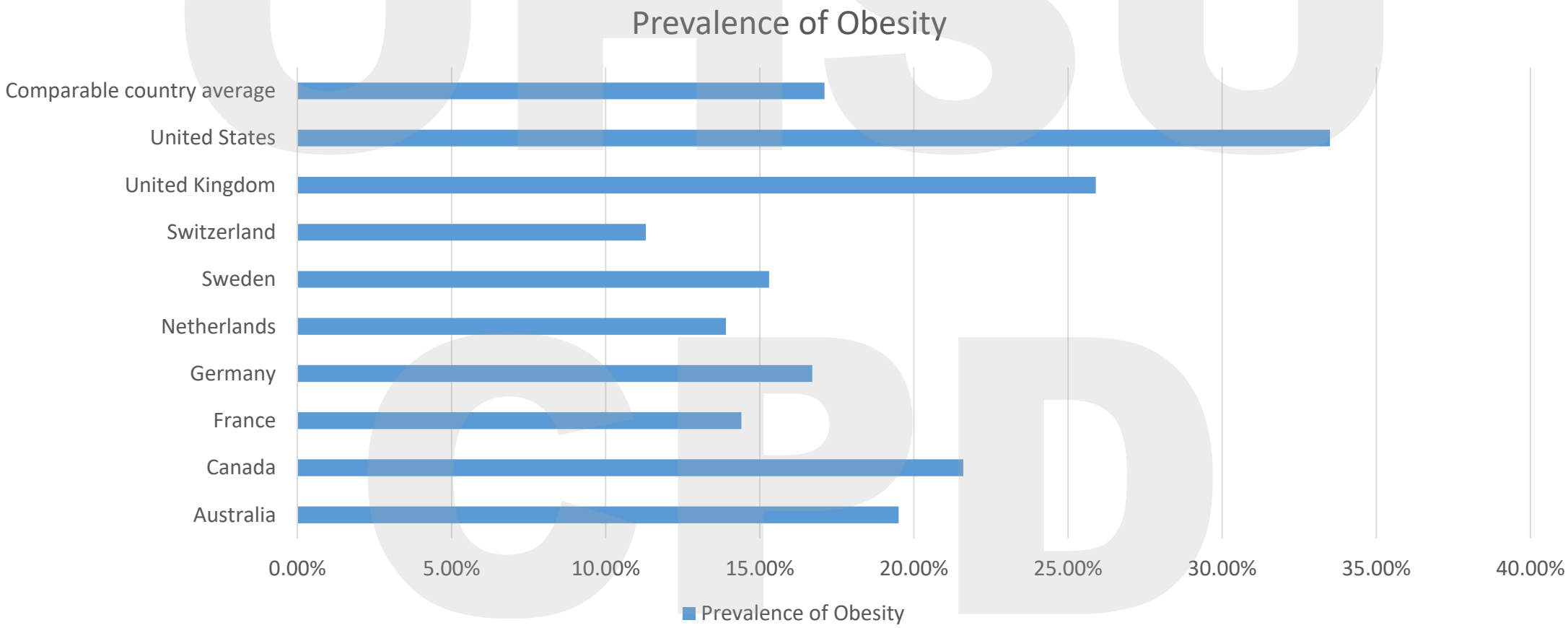
- Hold before elective surgery due to safety concerns of vomiting while under anesthesia
- Increase risk of GI adverse events (pancreatitis, bowel obstruction, gastroparesis) compared to bupropion-naltrexone
  - Absolute risk ≤ 1%
- FDA review of reports of suicidal ideation/behaviors
- Long-term risks?

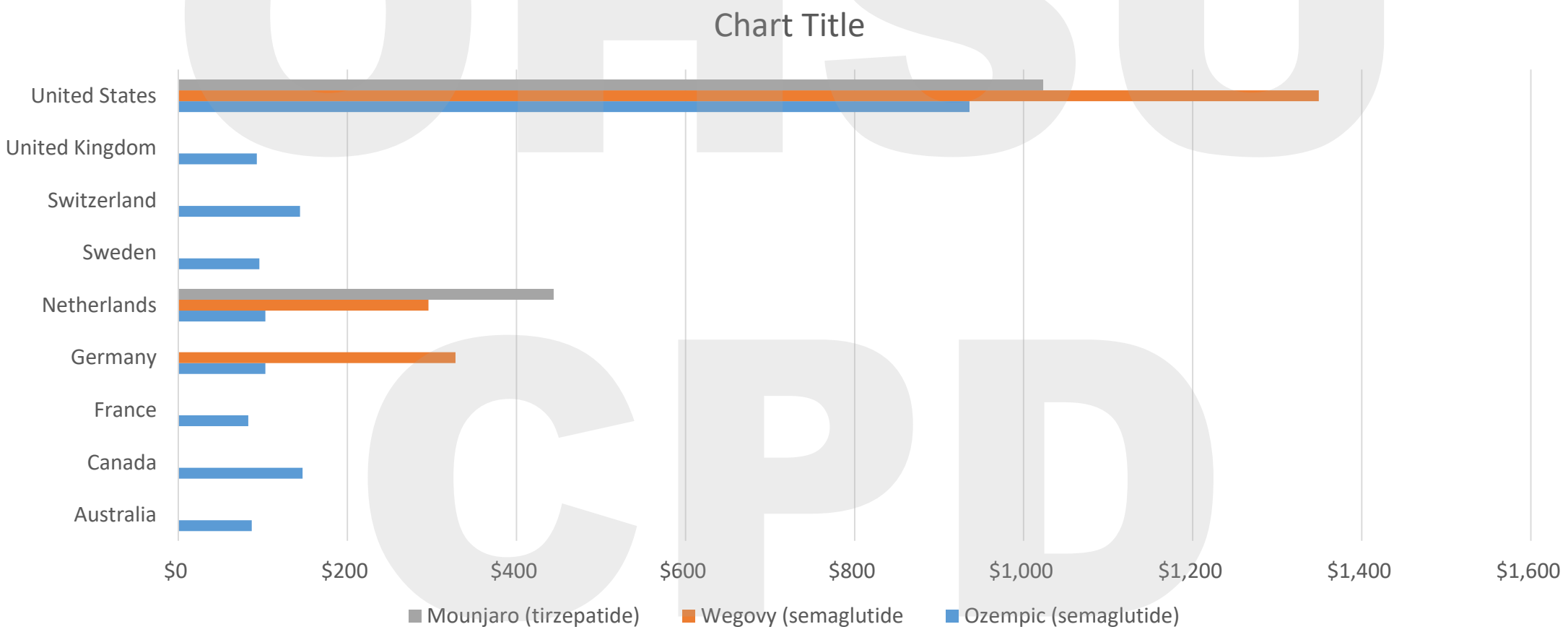
JAMA. 2023;330(18):1795-1797.

Prevalence of Obesity by Country



KFF Analysis

Cost of One Month Supply By Country



KFF Analysis

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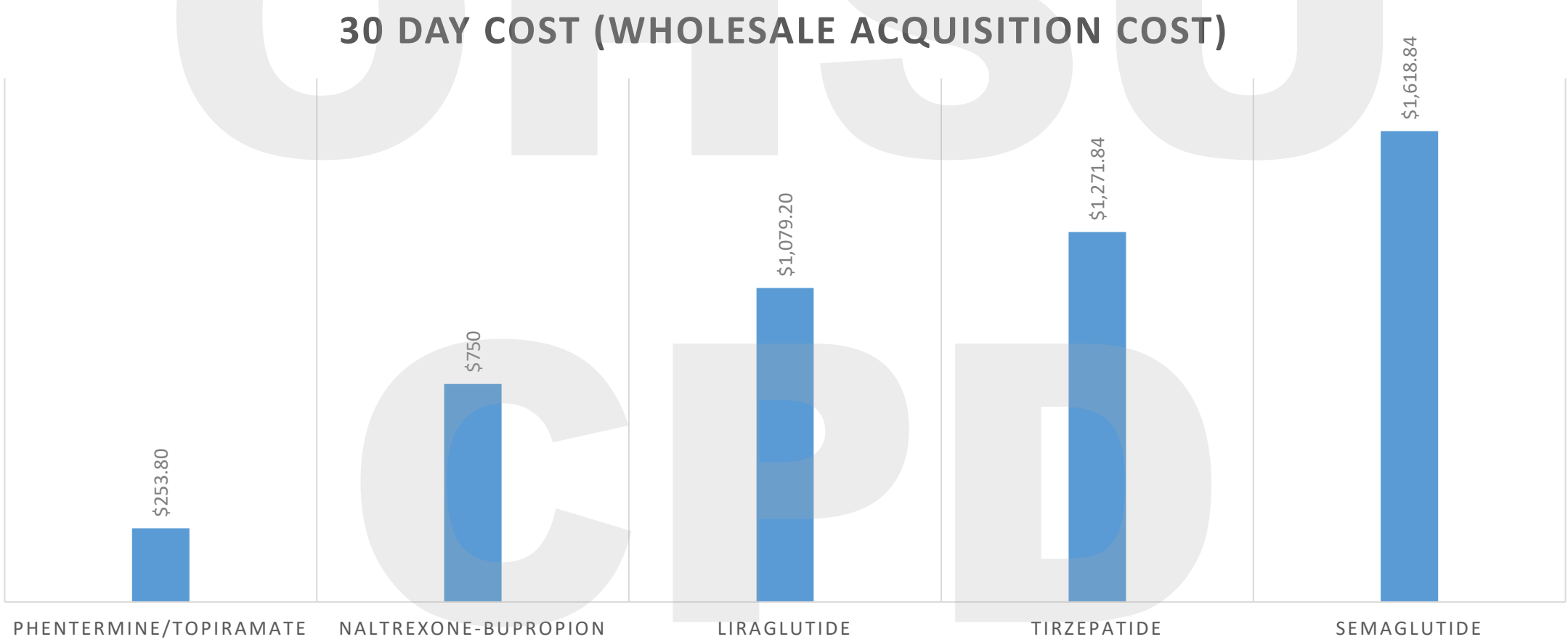
Cost is a barrier

53% of the US population would meet the treatment criteria according to FDA approved indications



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GLP-1 Costs in Oregon

Drug	Average gross healthcare spend per enrollee per year[38]	Average patient out-of-pocket cost per year[39]
Subject drug Ozempic	$4,439.02	$326.60
Trulicity	$5,060.96	$296.31
Byetta	$4,784.16	$404.50
Victoza	$5,645.41	$299.19
Rybelsus	$2,252.25	$314.99
Average	$4,436.36	$328.32

Ozempic 

2022 Average annual patient out of pocket costs		
Value	APAC Database[31] (commercial plans only)	Data Call[32]
Average Co-Pay	$174.44	$130.49
Average Deductible	$77.12	$52.31
Average Coinsurance	$47.42	$92.36
Average Total Out-of-Pocket Costs for Patients[33]	$298.99	$277.64

Cost Effectiveness

Treatment	Comparator	Cost per Life Year Gained	Cost per QALY Gained
Semaglutide	Lifestyle modification	$624,000	$237,000
Liraglutide	Lifestyle modification	$1,210,000	$483,000
Phentermine/Topiramate	Lifestyle modification	$22,000	$8,000
Bupropion/Naltrexone	Lifestyle modification	$360,000	$123,000

Treatment	Comparator	Cost Effective at $50,000 per QALY Gained	Cost Effective at $100,000 per QALY Gained	Cost Effective at $150,000 per QALY Gained	Cost Effective at $200,000 per QALY Gained
Semaglutide	Lifestyle modification	0.0%	0.0%	1.2%	10.2%
Liraglutide	Lifestyle modification	0.0%	0.0%	0.0%	0.0%
Phentermine/Topiramate	Lifestyle modification	69.0%	87.1%	91.9%	94.2%
Bupropion/Naltrexone	Lifestyle modification	1.0%	14.6%	40.9%	63.4%

Phen/Top

↓

Nal/Bup

↓

Tirzepatide

↓

Semaglutide

↓

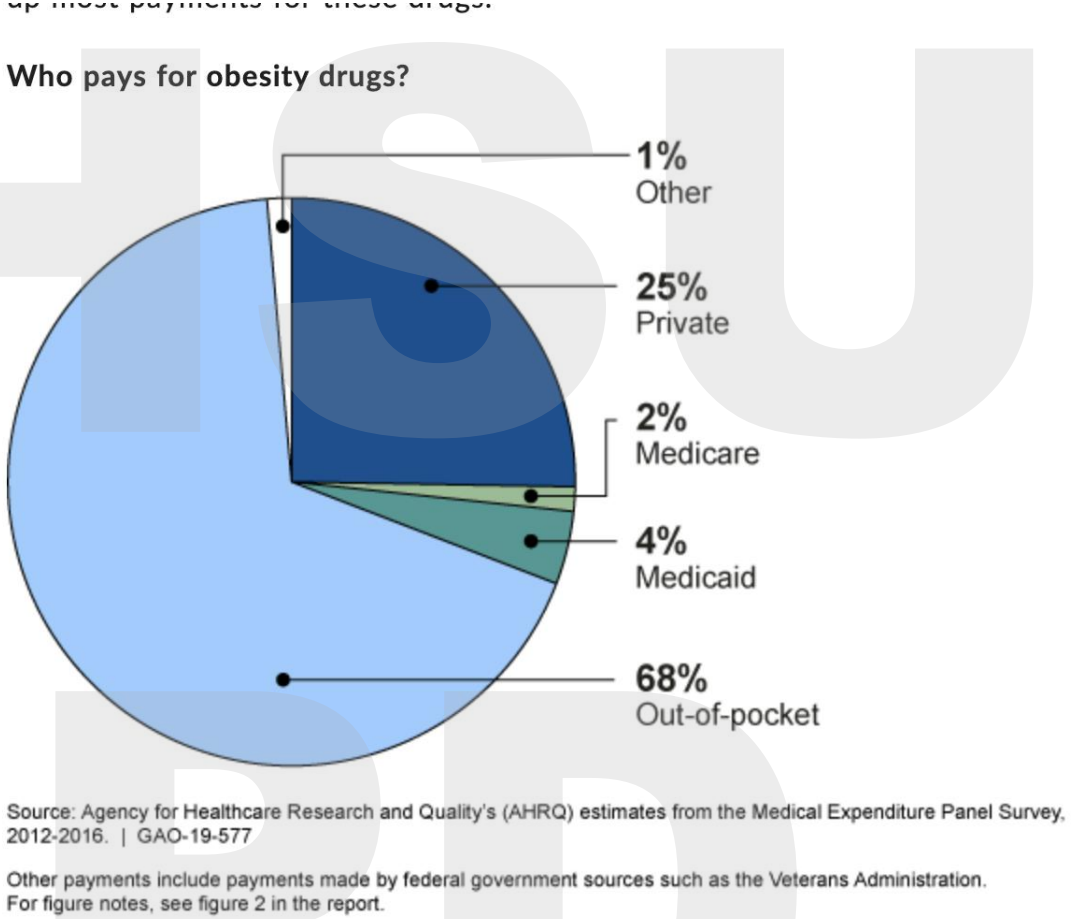
Liraglutide

↓

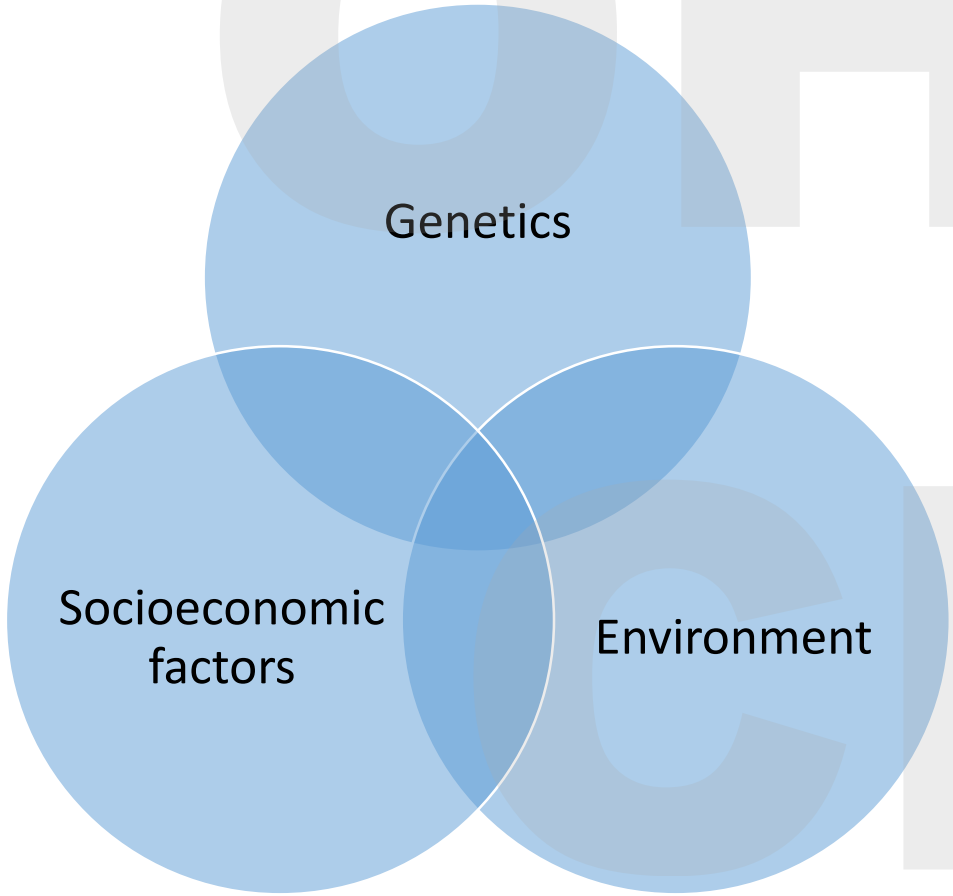
Institute for Clinical and Economic Review, 2022

Insurance Coverage

- Across all insurance types, pharmacotherapy is the least-covered treatment options for chronic weight management



Overweight and Obesity



- Low-income
- People who identify as:
  - Black (black women with highest prevalence 56.9%)
  - Latinx or Hispanic
  - American Indian or Alaska Native
- Medicaid enrollees

People covered by Medicaid are 27% more likely to be obese compared to those with commercial insurance

Urban Institute: Obesity Across America

Medicaid Drug Rebate Program (MDRP)

- Created in 1990
- Medicaid programs cover nearly all FDA approved drugs in exchange for rebates
- Drugs that *can be* excluded from coverage:
  - Drugs used for anorexia, weight loss, or weight gain
  - Agents used to promote fertility
  - For cosmetic purposes or hair growth
  - Symptomatic relief of cough and colds
  - Vitamins and minerals
  - Nonprescription drugs
  - For erectile dysfunction

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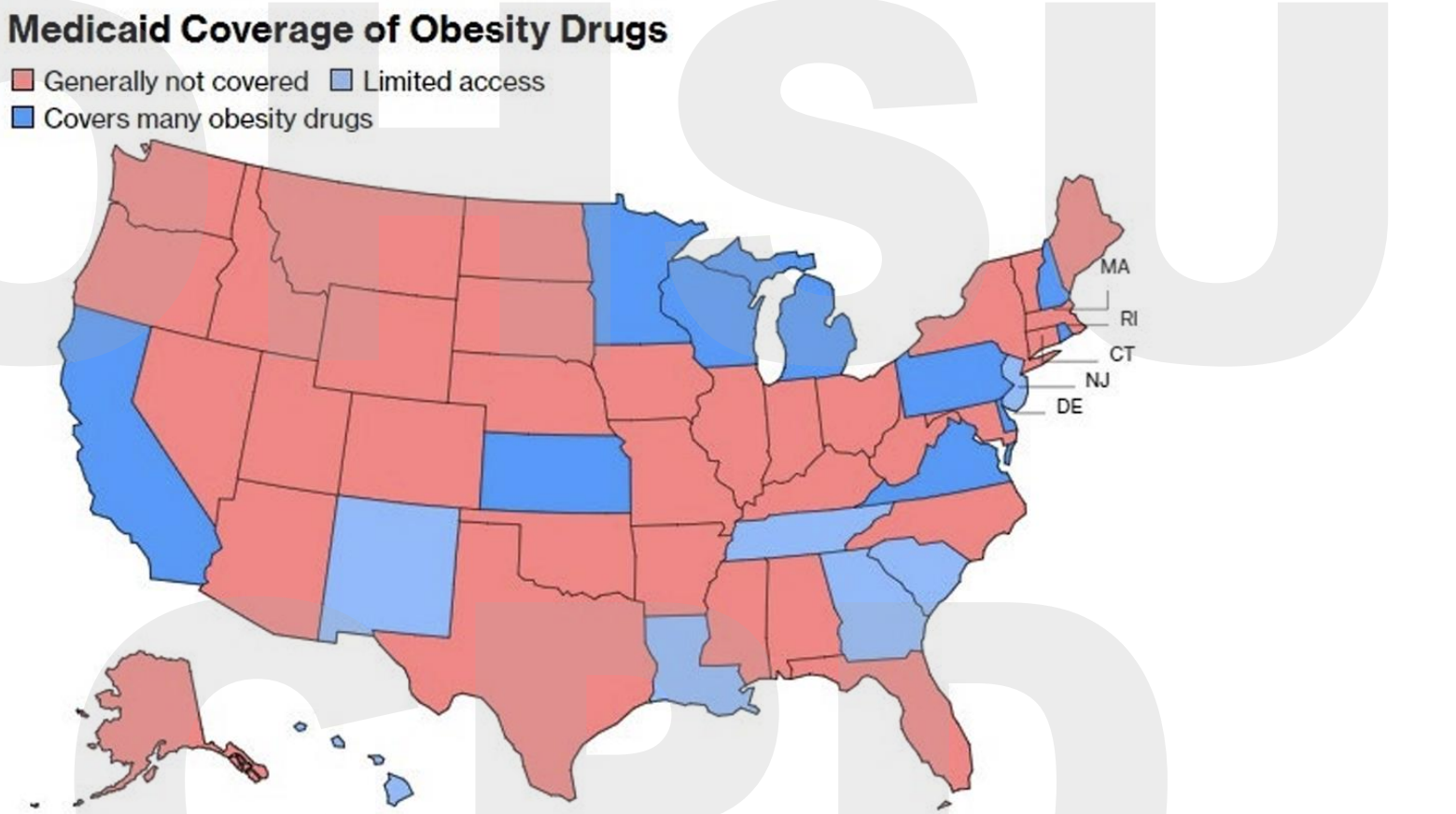

Data: Bloomberg survey of online plan documents and communication with state officials.
Connecticut's Medicaid program plans to start covering obesity drugs in July. Coverage shown as of April 2023.

Source: Court E, Langreth R

Oregon Medicaid

- Treatment coverage limited to intensive nutritional and physical activity counseling
- Bariatric surgery is covered for
  - adults with BMI ≥ 40 kg/m2 or BMI ≥ 30 kg/m2 with T2DM or at least 2 other serious obesity-related comorbidities
  - Adolescents ≥ 13 years old with obesity of significant comorbid conditions
- Pharmacological treatments are not covered under the OHP Prioritized List of health services
- Exceptions are made for specific cases in children and youth under the age of 21 years through the Early and Periodic Screening, Diagnostic and Treatment (EPSDT) Program.
- Oregon Health Plan will begin reviewing coverage policies and guidelines and budgetary analysis of coverage changes for weight management drugs.

Medicare Part D

- Covers only screening and counseling provided by a primary care provider
- Weight loss programs only if part of a treatment plan for a comorbidity
- Drugs for weight loss explicitly excluded from coverage when Part D benefit was constructed

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Utilization Management

- Coverage is inconsistent and constantly changing
- Prior authorization criteria commonly used to ensure use is consistent with FDA approved indications and added to comprehensive weight management program
- Reauthorization criteria may require documented drug tolerance and meeting required weight loss from baseline
- Some plans are tightening PA criteria on GLP-1 agonists to prevent off-label use for weight management

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Conclusions

- Newer agents for chronic weight management, including GLP-1 agonists and GIP/GLP-1 agonists are effective in reducing weight from baseline compared to placebo and standard of care.
- Short term GI side effects need to be managed with careful dose titration
- More data on long term safety and durability of treatment is needed
- Barriers to widespread use include cost, insurance coverage, and drug shortages

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