Beyond the Scale:
Harnessing Anti-Obesity Medications to Treat Obesity and Its Complications

Diane Thiara, MD, dABOM
Assistant Clinical Professor of Medicine
University of California, San Francisco
Director, UCSF Weight Management Programs
Program Director
Obesity Medicine Subspecialty Fellowship
San Francisco, CA

CONTINUING EDUCATION COMPANY

1

Disclosure

Consultant: Protagonist Therapeutics

Stockholder: Eli Lilly; Novo Nordisk; Viking Therapeutics; Zura

CONTINUING EDUCATION COMPANY

2

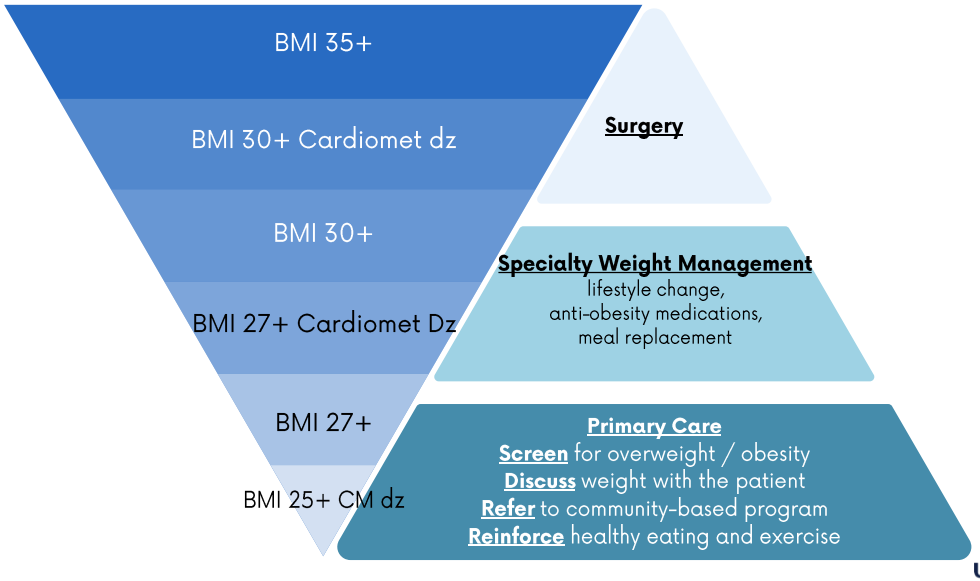
Objectives

- Describe treatment paradigm for obesity
- Know FDA approved AOM for long term use
- Explain pharmacology of GLP1-RA backbone drugs
- Explore role of GLP1-RA backbone drugs in treating obesity and various comorbidities

UCSF Health

3

TREATMENT PYRAMID



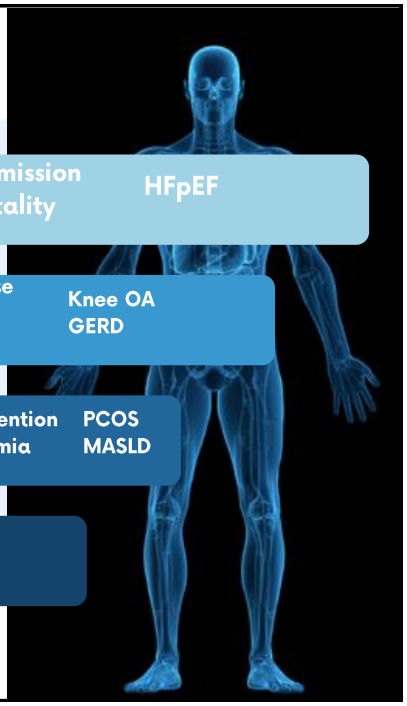
UCSF Health

4

Treating Obesity

What Is the Goal?

- Improving health, NOT for size conformity
  - Should NOT assume excess weight = unhealthy
- Modest weight loss can improve health
- Don't fixate on BMI targets for treatment
- Chronic disease management



Garvey WT et al. Endocr Pract 2016;22(Suppl. 3):1–203; 2
Look AHEAD Research Group. Lancet Diabetes Endocrinol 2016;4:913–21;
Lean ME et al. Lancet 2018;391:541–51; 4. Benraoune F and Litwin SE. Curr Opin Cardiol 2011;26:555–61.

5

TREATMENT PYRAMID

BMI 35+

BMI 30+ Cardiomet dz

Surgery

Taking a medication won't teach someone how to eat healthier foods or exercise more – lifestyle change still matters!

BMI 27+

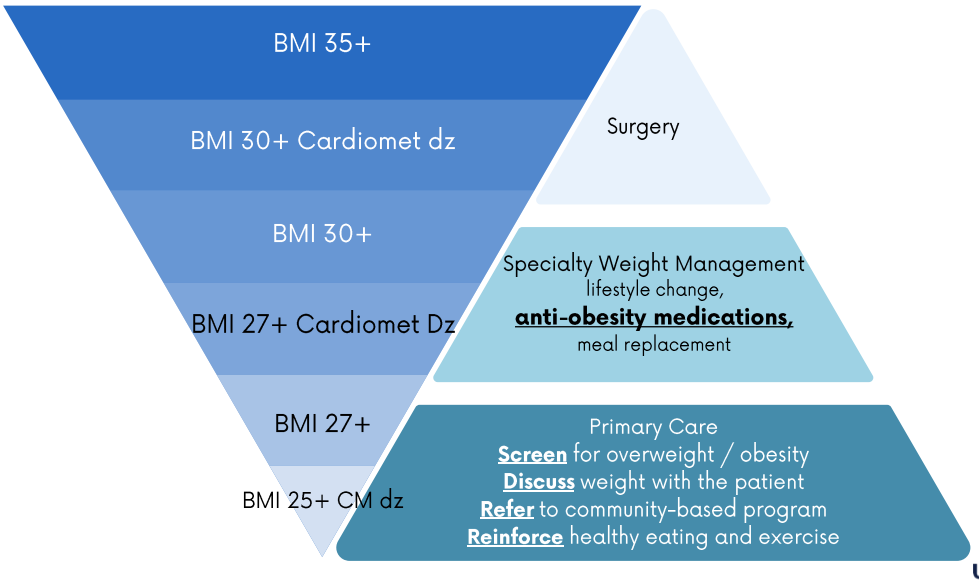
BMI 25+ CM dz

Primary Care
Screen for overweight / obesity
Discuss weight with the patient
Refer to community-based program
Reinforce healthy eating and exercise

UCSF Health

6

TREATMENT PYRAMID

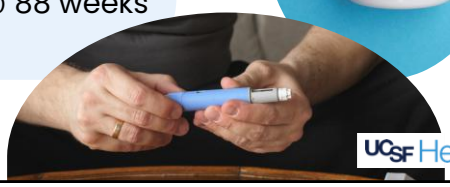


UCSF Health

7

FDA Approved Anti-Obesity Meds

1. ORLISTAT: 3%
2. CONTRAVE: 5-8%; 3-5% @ 2 years
3. SAXENDA: 5-10%; 6% @ 2 years
4. QSYMIA: 9-14%; 10% @ 2 years
5. WEGOVY: 12.5%; 12.6% @ 2 years
6. ZEPBOUND: 17.8%; 25.3% @ 88 weeks



Chakhtoura M, et al. Pharmacotherapy of obesity: an update on the available medications and drugs under investigation. eClinicalMedicine. 2023;58:101882.

UCSF Health

8

GLP-1RA: Semaglutide (Wegovy)
GLP1/GIP RA: Tirzepatide (Zepbound)

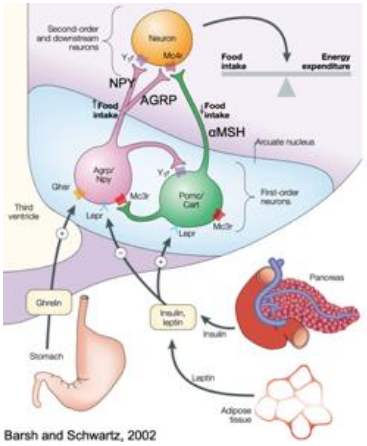
Mechanism of Action

GLP1 RA

- Decrease gastric emptying - Stomach
- Promote satiety – via POMC/CART
- Increase insulin secretion – via pancreas
- Improve insulin sensitivity – via liver

GIP

- GIP – Increase lipolysis and FA synthesis



Barsh and Schwartz, 2002

Drucker DJ, Mechanisms of Action and Therapeutic Application of Glucagon-like Peptide-1, Cell Metabolism,2018, 27 (4), 740-7
Seino Y, et al. GIP and GLP-1, the two incretin hormones: Similarities and differences. J Diabetes Investig. 2010 Apr 22;1(1-2):8-23.

UCSF Health

9

GLP1-RA Backbone Drugs

Side Effects
N/V, dizziness, abdominal pain, diarrhea, headache, fatigue, pancreatitis, cholecystitis, suicidal ideation

Contraindications
Personal or Family hx of Medullary Thyroid Cancer, Pregnancy

Results
Semaglutide: 12.6% BWL @ 68 wks; 35% >/=20% BWL
Tirzepatide: 17.85% BWL @ 68 wks; 35% >/= 25% BWL

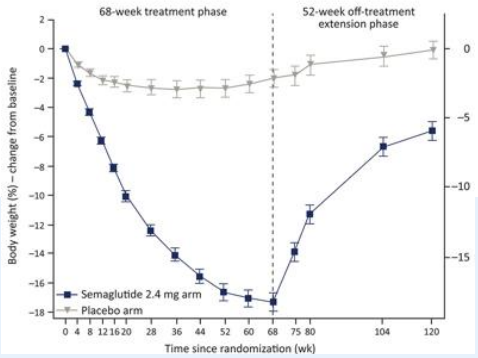
Dosing Guidelines
Weekly injections, effective dose in 5 months

UCSF Health

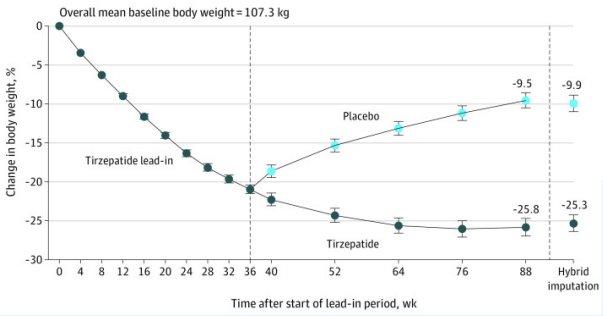
10

Weight Maintenance

Semaglutide 2.4 mg



Tirzepatide 15 mg



STEP 1 Extension[1]
+ 11.6% Body Weight -> Regained 2/3 body weight that was lost

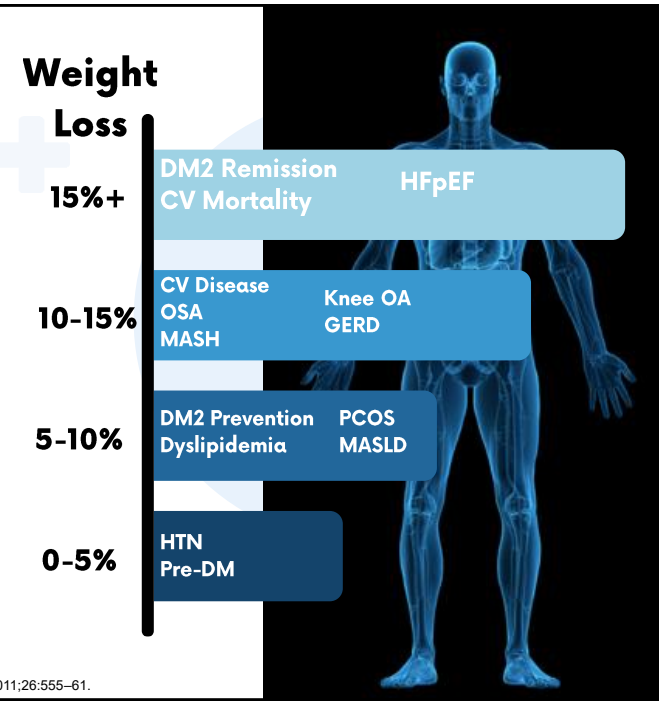
SURMOUNT 4[2]
+11% Body Weight Gain vs additional -4.4% Body Weight Loss

1. Wilding JPH, et al; STEP 1 Study Group. Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension. Diabetes Obes Metab. 2022 Aug;24(8):1553-1564.
2. Aronne L, et al. Continued Treatment With Tirzepatide for Maintenance of Weight Reduction in Adults With Obesity: The SURMOUNT-4 Randomized Clinical Trial. JAMA. 2023;330(22):2011-2023.

UCSF Health

11

Treating Obesity to Treat Other Cardiometabolic and Mechanical Diseases



Garvey WT et al. Endocr Pract 2016;22(Suppl. 3):1–203; 2
Look AHEAD Research Group. Lancet Diabetes Endocrinol 2016;4:913–21;
Lean ME et al. Lancet 2018;391:541–51; 4. Benraoune F and Litwin SE. Curr Opin Cardiol 2011;26:555–61.

12

Cardiovascular Disease

SELECT TRIAL:

Phase 3, Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity

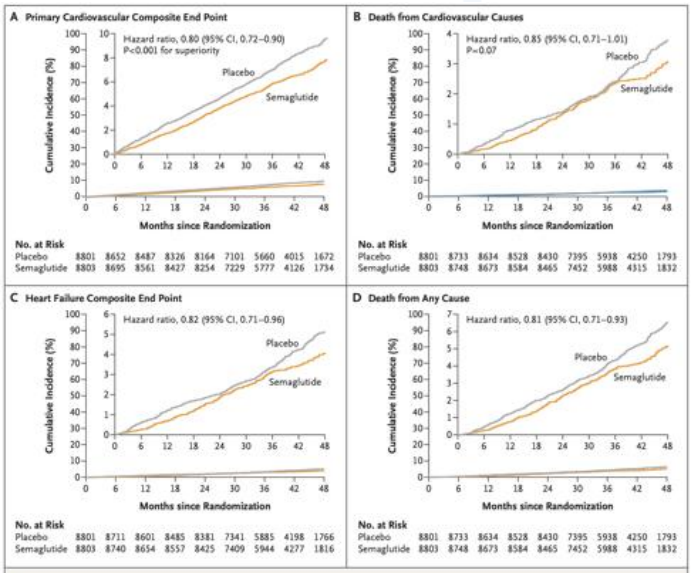
- **Inclusion: BMI 27 + & Known ASCVD (MI, Stroke, PAD)**
- **Exclusion: DM**
- **39.8±9.4 months follow-up**
- **~17,500 participants enrolled -> ½ semaglutide, ½ placebo**
- **~70% male, starting age: 61 yo**

Lincoff AM, et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. N Engl J Med. 2023;389(24):2221-2232

UCSF Health

13

Cardiovascular Disease: SELECT TRIAL



Lincoff AM, et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. N Engl J Med. 2023;389(24):2221-2232

UCSF Health

14

Cardiovascular Disease

SELECT TRIAL:

FDA Approval for Wegovy in people with BMI 27+ and ASCVD

- Expands coverage to people with Medicare

SURMOUNT-MMO

Phase 3, Tirzepatide on the Reduction on Morbidity and Mortality in Adults With Obesity

- Study completion date: 9/2027

Lincoff AM, et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. N Engl J Med. 2023;389(24):2221-2232

UCSF Health

15

Heart Failure with Preserved Ejection Fraction

Semaglutide 2.4 mg[1]

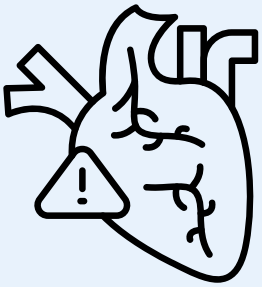
improvements in HF-related symptoms (KCCQ-CSS)

- 7.8 point improvement compared to placebo.

Weight loss: -13.3%

Improved exercise function

- increase of 20.3 meters in the 6-minute walk distance



Tirzepatide 15 mg (SUMMIT Trial)[2]

improvements in HF-related symptoms (KCCQ-CSS)

- 7.8 point improvement compared to placebo.

Less likely to have worsening HF Symptoms @ 2 years

- 8.0% vs 14.2% Placebo (HR: 0.54)

1. Kosiborod MN, et al. Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. N Engl J Med. 2023;389(12):1069-1084.
2. Packer M, Zile MR, Kramer CM, et al. Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity. N Engl J Med. 2025;392(5):427-437.

UCSF Health

16

Obstructive Sleep Apnea

SURMOUNT OSA

Phase 3, Tirzepatide for Treatment of Obstructive Sleep Apnea and Obesity

- Inclusion: BMI 27+ & Mod-Severe OSA
- Exclusion: DM, Central Sleep Apnea, Planned surgery for OSA
- 52 weeks
- 235 participants -> ½ tirzepatide (10 or 15 mg), ½ placebo
- 2 Trial Groups: not on PAP (1), on PAP (2)
- ~77% male, starting age – 52 yo

Malhotra A, et al. Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity. N Engl J Med. 2024;391(13):1193-1205.

UCSF Health

17

OSA: SURMONT OSA

Table 2. Primary and Key Secondary End Points According to Trial Group for the Treatment-Regimen Estimand.*

End Point	Trial 1			Trial 2		
	Tirzepatide N=114	Placebo N=120	Estimated Treatment Difference or Relative Risk (95% CI)†	Tirzepatide N=120	Placebo N=115	Estimated Treatment Difference or Relative Risk (95% CI)†
Primary end point						
Change in AHI (95% CI) — no. of events/hr	−25.3 (−29.3 to −21.2)	−5.3 (−9.4 to −1.1)	−20.0 (−25.8 to −14.2)	−29.3 (−33.2 to −25.4)	−5.5 (−9.9 to −1.2)	−23.8 (−29.6 to −17.9)
Key secondary end points						
Percent change in AHI (95% CI)	−50.7 (−62.3 to −39.1)	−3.0 (−16.9 to 10.9)	−47.7 (−65.8 to −29.6)	−58.7 (−69.1 to −48.4)	−2.5 (−16.2 to 11.2)	−56.2 (−73.7 to −38.7)
Reduction of ≥50% in AHI events at wk 52 — no. (%)	70 (61.2)	23 (19.0)	3.3 (2.1 to 5.1)	86 (72.4)	27 (23.3)	3.1 (2.1 to 4.5)
AHI of <5 or AHI of 5 to 14 with ESS ≤10 at wk 52 — no. (%)	48 (42.2)	19 (15.9)	2.9 (1.8 to 4.8)	60 (50.2)	16 (14.3)	3.3 (2.0 to 5.4)
Percent change in body weight (95% CI)	−17.7 (−19.0 to −16.3)	−1.6 (−2.9 to −0.2)	−16.1 (−18.0 to −14.2)	−19.6 (−21.0 to −18.2)	−2.3 (−3.8 to −0.9)	−17.3 (−19.3 to −15.3)
Change in hsCRP concentration at wk 52 (95% CI) — mg/liter	−1.4 (−1.7 to −1.1)	−0.7 (−1.1 to −0.3)	−0.7 (−1.2 to −0.2)	−1.4 (−1.6 to −1.1)	−0.3 (−0.8 to 0.1)	−1.0 (−1.6 to −0.5)
Change in sleep apnea–specific hypoxic burden at wk 52 (95% CI) — % min/hr	−95.2 (−103.2 to −87.2)	−25.1 (−44.3 to −5.9)	−70.1 (−90.9 to −49.3)	−103.0 (−110.3 to −95.6)	−41.7 (−63.9 to −19.5)	−61.3 (−84.7 to −37.9)
Change in systolic blood pressure at wk 48 (95% CI) — mm Hg	−9.5 (−11.5 to −7.5)	−1.8 (−3.9 to 0.2)	−7.6 (−10.5 to −4.8)	−7.6 (−9.7 to −5.6)	−3.9 (−6.3 to −1.6)	−3.7 (−6.8 to −0.7)
Additional secondary end point‡						
Change in diastolic blood pressure at wk 48 (95% CI) — mm Hg	−4.9 (−6.4 to −3.5)	−2.1 (−3.6 to −0.6)	−2.8 (−5.0 to −0.7)	−3.3 (−4.7 to −1.9)	−2.2 (−3.8 to −0.6)	−1.1 (−3.2 to 1.0)

Change in AHI: ~22 events/hr %BWL ~ -17%

%Change in AHI: ~ - 50%

Malhotra A, et al. Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity. N Engl J Med. 2024;391(13):1193-1205.

UCSF Health

18

Obstructive Sleep Apnea

SURMOUNT OSA

FDA Approval for Zepbound in people with BMI 27+ and Moderate to Severe OSA

- **Expands coverage to people with Medicare**

Malhotra A, et al. Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity. N Engl J Med. 2024;391(13):1193-1205.

UCSF Health

19

Metabolic Dysfunction Associated Steatohepatitis: MASH

Semaglutide 2.4 mg: ESSENCE Trial

Phase 3, Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis

Inclusion: Bx confirmed F2/F3 MASH

Exclusion: Chronic liver disease; A1c >9.5; EtOH (>20 g F, >30 g M); GFR <30

1129->2:1 ratio semaglutide 2.4 mg vs Placebo

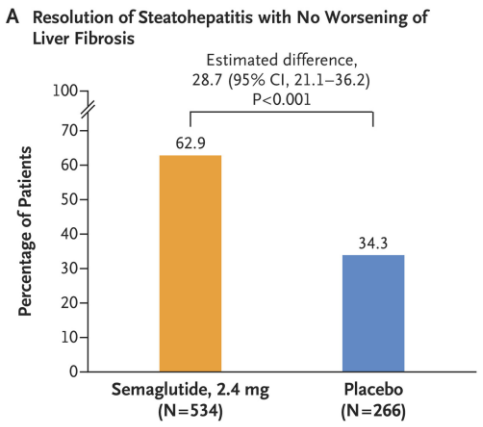
240 weeks; first analysis at 72 weeks (published here)

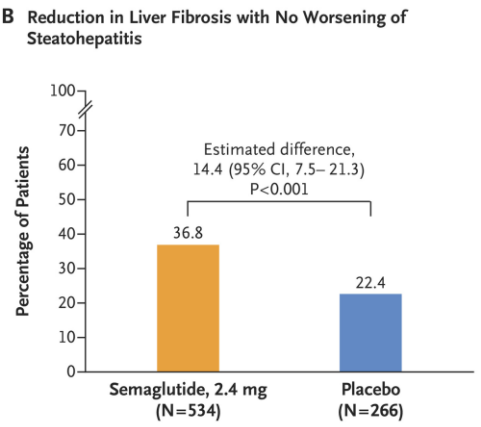
~55% female, starting age – 55 yo, BMI ~34 kg/m2

UCSF Health

20

Semaglutide 2.4 mg - ESSENCE Trial





Primary endpoints:
- Resolution of steatohepatitis with no worsening of fibrosis:
- Improvement in liver fibrosis with no worsening of steatohepatitis:

Secondary endpoints:
- Resolution of steatohepatitis + Improvement in fibrosis: 32.7% sema vs 16.1% placebo
- -8.5% BWL (-10.5% sema vs -2.0% placebo)

Sanyal AJ, et al. Phase 3 trial of semaglutide in metabolic dysfunction-associated steatohepatitis. N Engl J Med. 2025;392(21).

UCSF Health

21

Metabolic Dysfunction Associated Steatohepatitis: MASH

Semaglutide 2.4 mg: ESSENCE Trial
- **FDA Approval for use 8/2025**

Tirzepatide 5 mg, 10 mg, 15 mg: SYNERGY-NASH

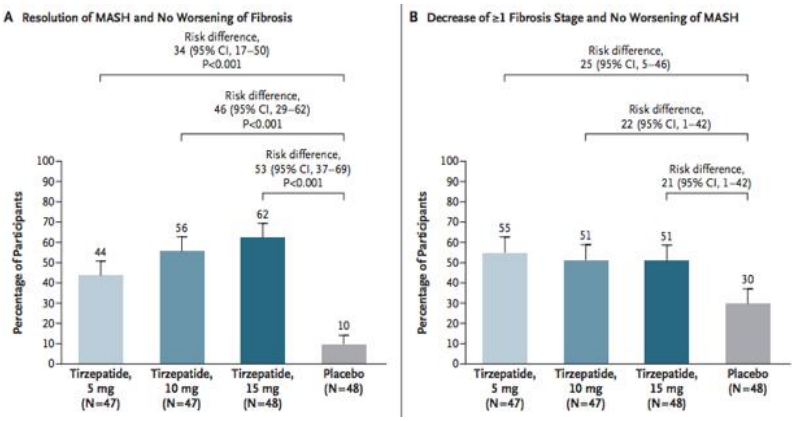
UCSF Health

22

Tirzepatide 5, 10, 15 mg: SYNERGY-NASH

- Phase 2, RCT
- Inclusion: BMI 27+ & bx confirmed MASH + Fibrosis (F2/F3) (w or w/out DM)

- Dose based increase in resolution of MASH with no worsening of fibrosis
- Dose independent decrease in fibrosis stage with no worsening in MASH



Loomba R, et al. Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with Liver Fibrosis. *N Engl J Med*. 2024;391(4):299-310.

UCSF Health

23

Prediabetes

Semaglutide 2.4 mg - STEP 10[1]

- Obesity + Pre-DM, 52 weeks
- 12.2% BWL in semaglutide group
- 84.1% achieved normoglycemia vs to 47.8% placebo group
  - Odds Ratio 19.8

Tirzepatide 5, 10, 15 mg[2]

- Obesity + Pre-DM, 176 weeks
- 18.4% BWL in tirzepatide 15 mg group
- 1.3% of tirzep groups with DM vs. 13.3% placebo group with DM @ 3 yrs
  - Hazard Ratio 0.07

1. Rubino D, et al. Effect of Once-Weekly Semaglutide 2.4 mg on Body Weight in Adults with Obesity: A Randomized, Double-Blind, Placebo-Controlled Study. Lancet Diabetes Endocrinol. 2024;12(5):327-339.
2. Jastreboff AM, le Roux CW, Stefanski A, et al. Tirzepatide for Obesity Treatment and Diabetes Prevention. N Engl J Med. 2025;392(10):958-971.

UCSF Health

24

Chronic Kidney Disease

Semaglutide 2.4 mg (STEP 1-3 Exploratory Results)[1]

- Improvements in albuminuria @ 68 weeks
- No Change in eGFR
- Mostly people with normal kidney fxn

Tirzepatide (TREASURE CKD)[2]

- Enrolling through Jan 2026
- Obesity+CKD, 1/2 will have DM

1. Hiddo J.L. et al. Effects of Semaglutide on Albuminuria and Kidney Function in People With Overweight or Obesity With or Without Type 2 Diabetes: Exploratory Analysis From the STEP 1, 2, and 3 Trials. *Diabetes Care* 1 April 2023; 46 (4): 801–810.
2. https://trials.lilly.com/en-US/trial/360461

UCSF Health

25

Knee Osteoarthritis

Semaglutide 2.4 mg: STEP 9[1]

- BMI 30+ & moderate + pain & moderate knee OA on imaging
- 10.5% BWL @68 weeks
- Change in WOMAC score: start @ 70.9
  - -41.7 points in sema group and -27.5 points in placebo group
- % Change in SF-36
  - +12.0 points in sema vs. 6.5 points in placebo

Tirzepatide: STOP KNEE-OA[2]

- Enrolling through 2027

1. Bliddal H, Bays H, Czernichow S, et al. Once-Weekly Semaglutide in Persons with Obesity and Knee Osteoarthritis. N Engl J Med. 2024;391(17):1573-1583.
2. https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=22143&isClinicalTrial=True

UCSF Health

26

Other Indications Being Studies

Substance Use Disorder

Alcohol Use Disorder
Opiate Use Disorder
Methamphetamine Use Disorder

Cognitive Disorders

Dementia
Alzheimer's Disease
Parkinson's Disease

Autoimmune Disease

Psoriasis
RA
IBD

Breast Cancer

HS

A Fib

UCSF Health

27

My Patient Should Be on a GLP1-RA Backbone Drug, Now What?

Insurance companies change coverage policies without updating provider

- Requirements for coverage are very opaque
- Easier to get coverage for dual indication usage (ie. Wegovy for CVD + BMI >/= 27, Zepbound for Mod-Severe OSA +Obesity)

Most ALWAYS need a prior authorization that includes:

- Weight, Height, BMI
- Statement that patient has been enrolled in lifestyle change programming that includes discussion of diet, exercise and behavioral change. Despite this work, patient has not lost weight. Many require PROOF – through your notes, through evidence of patient doing something like WW or Noom, insurance-developed ILI

Medicaid covers GLP1RA Backbone Drugs Varies, expect changes in 2026

- although certain counties have higher BMI criteria (40+)
- California, Connecticut, Delaware, Hawaii, Kansas, Louisiana, Michigan, Minnesota, Mississippi, New Hampshire, Pennsylvania, Rhode Island, South Carolina, Texas, Virginia, and Wisconsin
- California to stop covering in 2026

Medicare does NOT cover medications for weight loss – by LAW – Medicare Modernization Act of 2003

- No way to get around this (even with expert prior auths)
- Exceptions: If FDA has approved for DUAL indication – ie. Wegovy for ASCVD + BMI >/= 27 OR MASH, Zepbound for Mod-Severe OSA +Obesity

UCSF Health

28

ON THE HORIZON (aka The Gold Rush)

ORAL GLP1 RA

Other Dual Agonists
- GLP/Amylin
- GLP/Glucagon

Triple Receptor Agonist– RETATRUTIDE
- GIP, GLP, and Glucagon RA

GLPRA/GIP Antagonist– AMG 133.
- Activin Receptor Inhibitors– BIMAGRUMAB

29

Clinical Points

- FDA approved indications for Semaglutide 2.4 mg (Wegovy) and Tirzepatide (Zepbound)
  - Both: Obesity or Overweight with a weight related comorbidity
  - Wegovy: BMI 27+ AND ASCVD
    - Requires proof of MI, Stroke, PAD
  - Wegovy: MASH, details tbd
  - Zepbound: BMI 27+ AND Mod-Severe OSA
    - Requires proof of AHI 15+
- Much more to come in the next several years
- Maintenance of weight loss is key for improvement in morbidity and mortality a/w obesity.

UCSF Health

30