



# To the Moun!(jaro)

Updates in Pharmacotherapy and Metabolic  
Surgery for the treatment of obesity

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# Objectives

- 1) Understand treatment in context of chronic disease
- 2) Appreciate the patient's and physician's challenge with metabolic adaptation
- 3) Learn treatment expectations
- 4) Current and future anti-obesity medications
- 5) Learn co-treatment based on comorbidities
- 6) Become comfortable with who should be referred for surgery
- 7) Compare outcomes with medications and surgery for obesity and diabetes

# Chronic Disease

2013 American Medical Association: “recognize obesity as a disease state with **multiple pathophysiological aspects** requiring a **range of interventions to advance obesity treatment and prevention.**”

Notably, it’s also progressive and recurring.

# Indications - Meds and Surgery

## Pharmacotherapy

- 1) BMI  $\geq$  27 + comorbidities
- 2) BMI > 30

## Metabolic Bariatric Surgery

- 1) Class 2 obesity BMI >35 + comorbidities
- 2) Class 3 obesity BMI > 40

## WEIGHT LOSS



CALORIES



ACTIVITY



## WEIGHT GAIN



METABOLISM



HUNGER  
HORMONE



FULLNESS  
HORMONES



# Yeah, yeah, yeah, how do I treat this?!

Must know treatment expectations (as should your patients)

- 1) ILI (Intensive lifestyle intervention)
  - a) 5% total body weight loss (TBWL) on average
  - b) 250lb to 225lb
- 2) Pharmacotherapy
  - a) Historically - 5-10% TBWL
  - b) Now - 15-20% AVERAGE for semaglutide and tirzepatide
- 3) Metabolic/Bariatric Surgery
  - a) 25-40% average TBWL
  - b) Best option for comorbidity/disease remission

# FDA-approved Anti-Obesity Medications (AOM)

**Phentermine**

**Semaglutide (Wegovy)**

**Phentermine/Topiramate (Qsymia)**

**Bupropion/Naltrexone (Contrave)**

**Liraglutide (Saxenda)**

**Diethylpropion**

**Phendimetrazine**

**Orlistat**

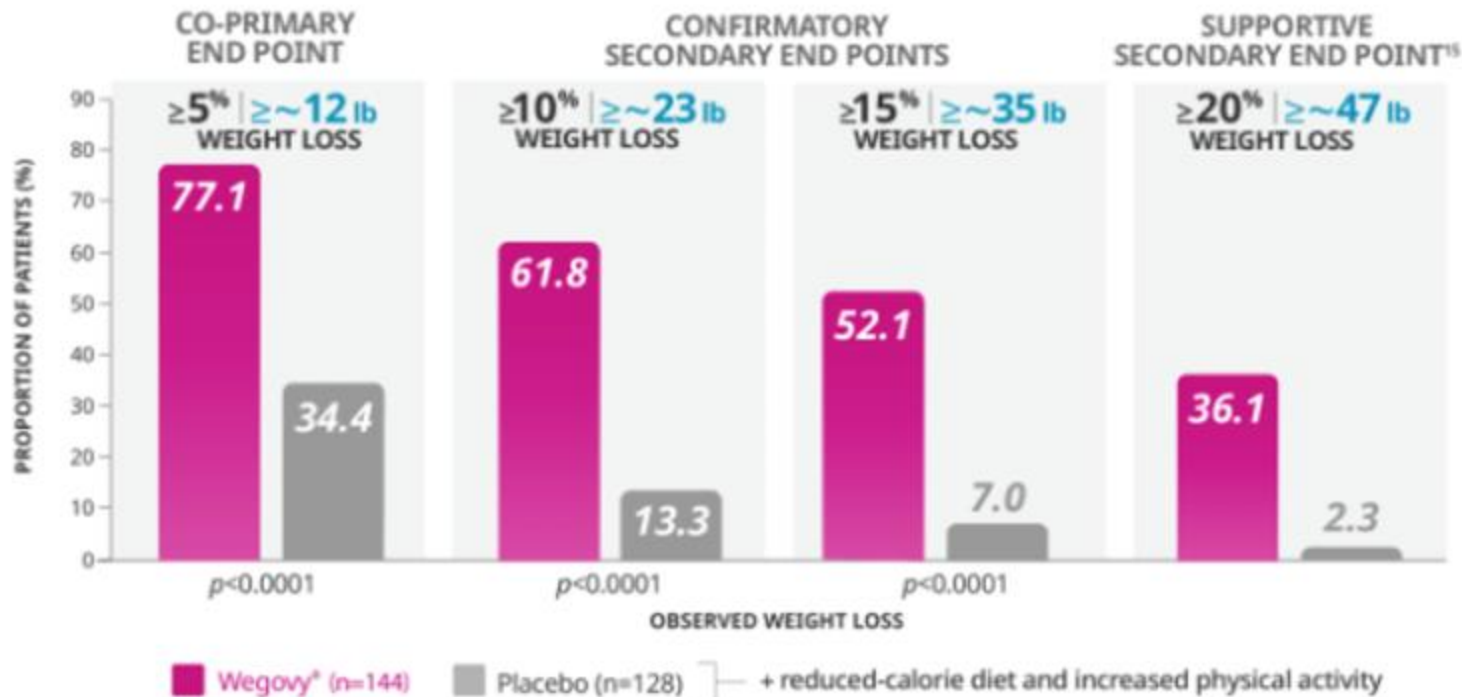
**Setmelanotide (Imcivree) (MC4R agonist - monogenic syndromes)**

# Historical results

|                                  | Phentermine | Orlistat                 | Phentermine/Topiramate ER (Qsymia)                                     | Naltrexone SR/Bupropion SR (Contrave)      | Liraglutide 3.0mg (Saxenda)             |
|----------------------------------|-------------|--------------------------|--|--|---|
| Estimated wt loss (vs. placebo)  | 5.1% @ 28wk | 3.1% at 1yr<br>120mg TID | 6.6% at 1yr 7.5/46mg daily<br><b>8.7% at 2yr (high dose-15mg/92mg)</b> | <b>4.8% at 56wk</b><br><b>16/160mg BID</b> | <b>5.6% at 56wk</b><br><b>3mg daily</b> |
| Long-term?                       | No          | Yes                      | Yes  | Yes  | Yes                                     |
| Schedule IV Controlled Substance | Yes         |                          | Yes  |  |   |



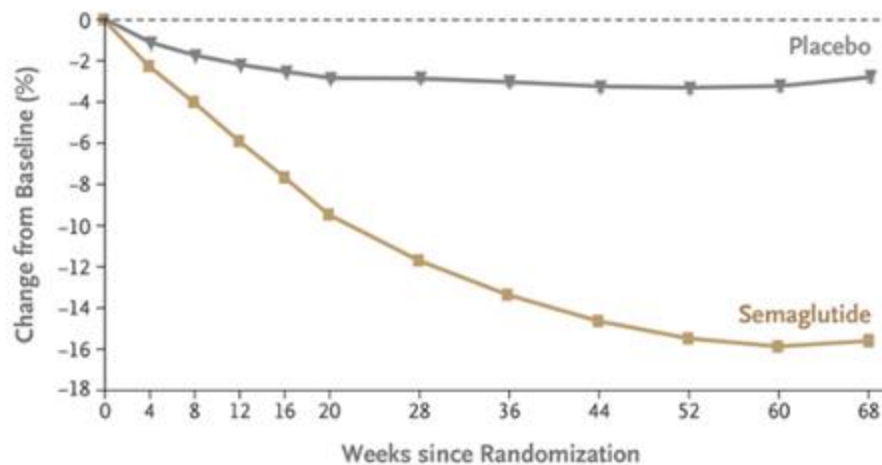
# Semaglutide



# Semaglutide

15% mean TBWL at 1 yr

Body Weight Change from Baseline by Week, Observed In-Trial Data



No. at Risk

|             |      |      |      |      |      |      |      |      |      |      |      |      |
|-------------|------|------|------|------|------|------|------|------|------|------|------|------|
| Placebo     | 655  | 649  | 641  | 619  | 615  | 603  | 592  | 571  | 554  | 549  | 540  | 577  |
| Semaglutide | 1306 | 1290 | 1281 | 1262 | 1252 | 1248 | 1232 | 1228 | 1207 | 1203 | 1190 | 1212 |

Horizon is looking beautiful





■ Tirzepatide 15mg     
 ■ Wegovy<sup>®</sup> (n=144)     
 ■ Placebo (n=128)     
 } + reduced-calorie diet and increased physical activity

# pipeline

All in Phase 3 or pending FDA approval:

Tirzepatide - GLP1 + GIP (gastric inhibitory peptide)

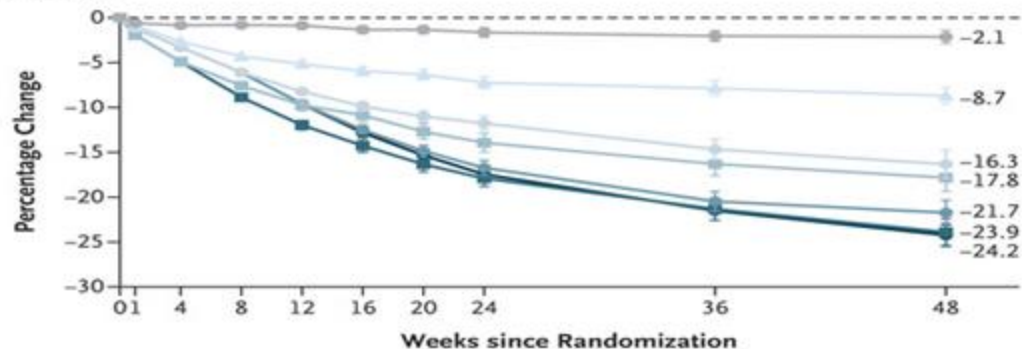
Retatrutide - GLP1 + GIP + glucagon

Methylphenidate

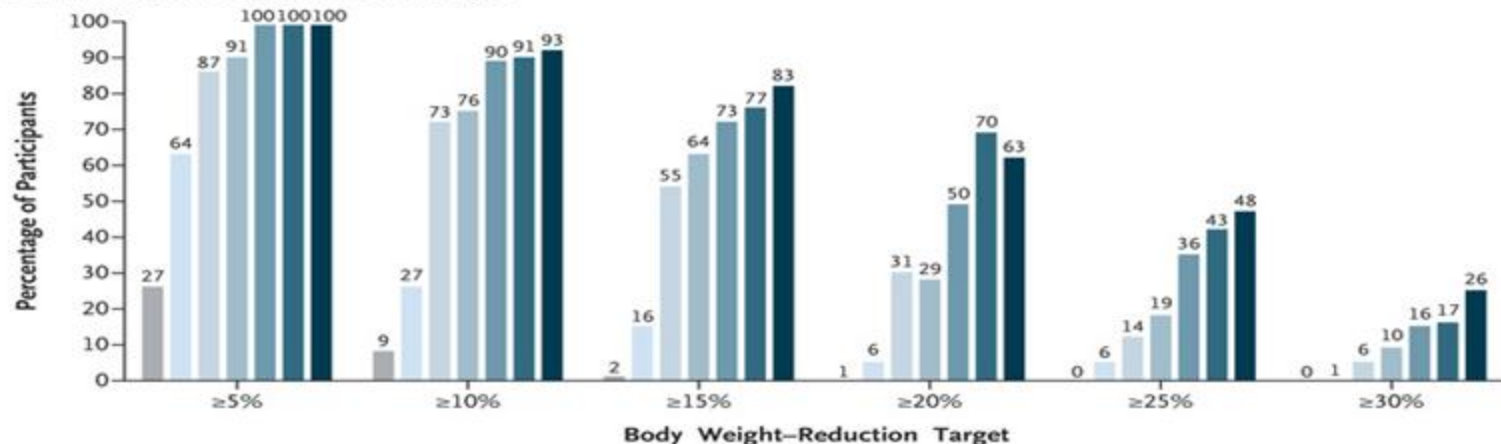
Dapagliflozin + metformin

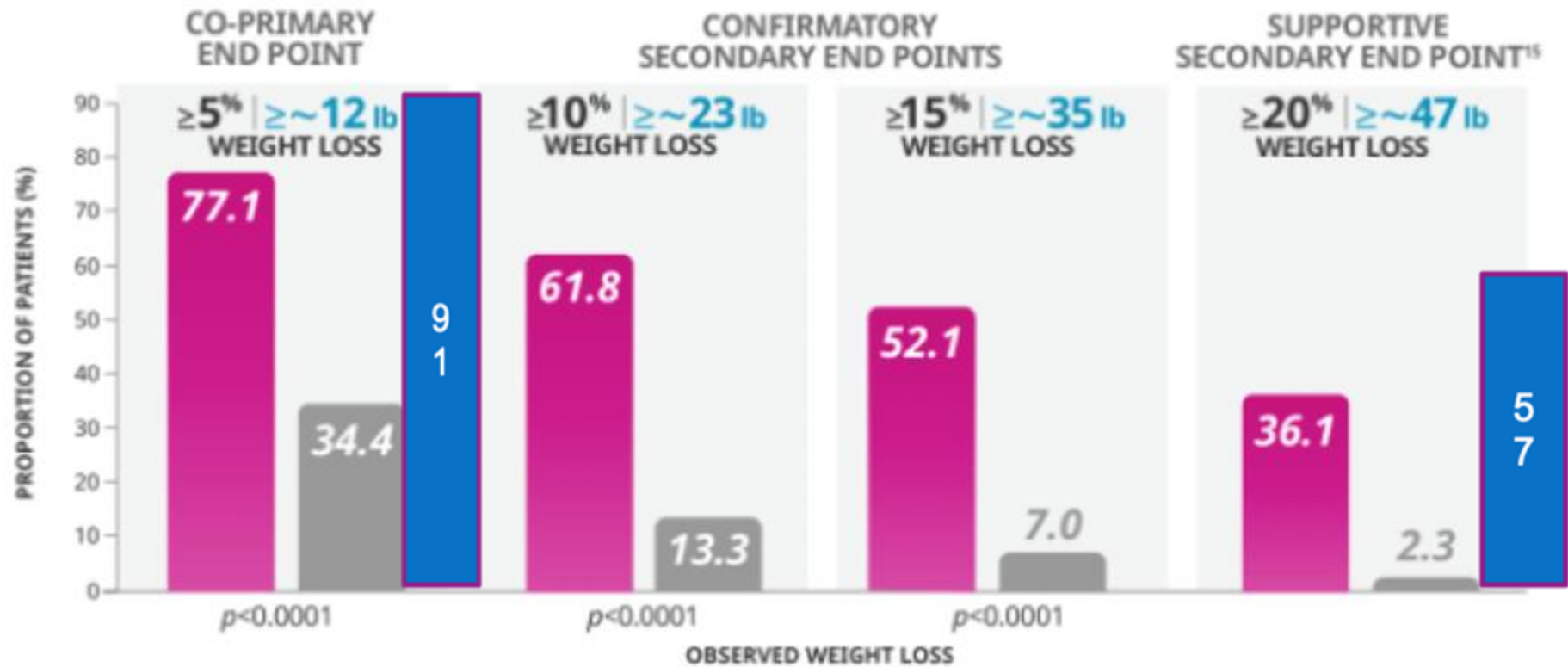
Placebo
  Retatrutide, 1 mg
  Retatrutide, 4 mg (ID, 2 mg)
  Retatrutide, 4 mg (ID, 4 mg)
  Retatrutide, 8 mg (ID, 2 mg)
  Retatrutide, 8 mg (ID, 4 mg)
  Retatrutide, 12 mg (ID, 2 mg)

### A Changes in Body Weight



### B Attainment of Weight-Reduction Targets





■ Tirzepatide 15mg
 ■ Wegovy® (n=144)
 ■ Placebo (n=128)
 } + reduced-calorie diet and increased physical activity

# Precision Medicine

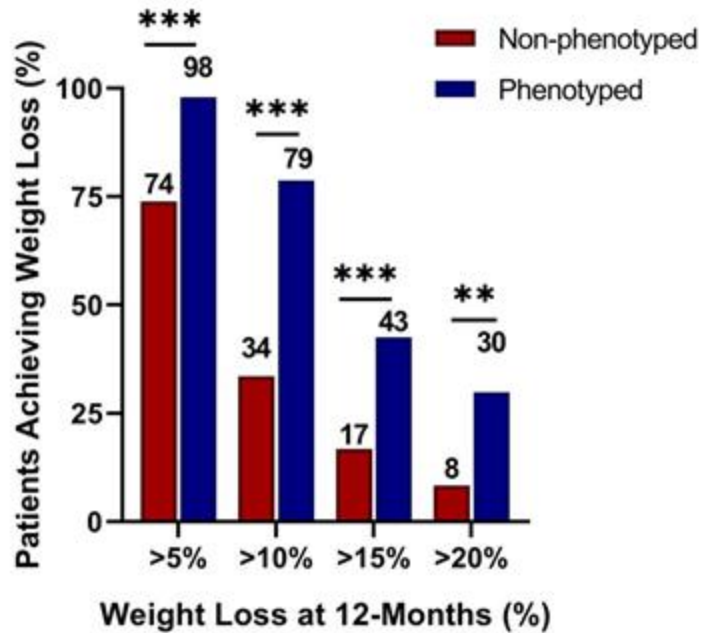
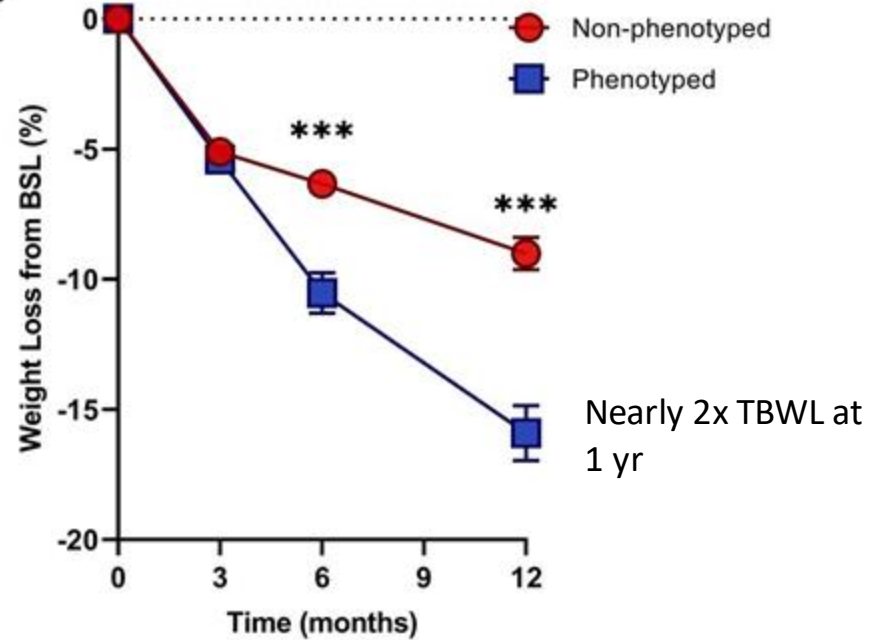
## Phenotype-guided pharmacotherapy

- A) Hungry Brain - abnormal satiation
  - a) Phentermine-Topiramate ER 7.5mg/46mg daily
  - b) Or Lorcaserin (removed from market)
- B) Emotional Hunger - abnormal hedonic eating
  - a) Naltrexone-Bupropion SR
- C) Hungry Gut - abnormal satiety
  - a) Liraglutide 3mg
- D) Slow Burn - low predicted energy expenditure
  - a) Phentermine 15mg + resistance training

## Trial Medications

- Naltrexone-Bupropion SR
- Liraglutide
- Lorcaserin
- Phentermine
- Phentermine-Topiramate ER



**A****B**

PG pharmacotherapy for obesity management improves weight loss outcomes.

(A) Percentage of patients achieving levels of weight loss after 1 year of either non-PG (n = 228) or PG (n = 84) treatment.

(B) The average percentage of total body weight loss from BSL in non-PG (red circles) and PG (blue squares) treatment at 3, 6, and 12 months. \*\*P < 0.01, \*\*\*P < 0.001. BSL, baseline; PG, phenotype guided.

# Internist vs. AI-created surgeon

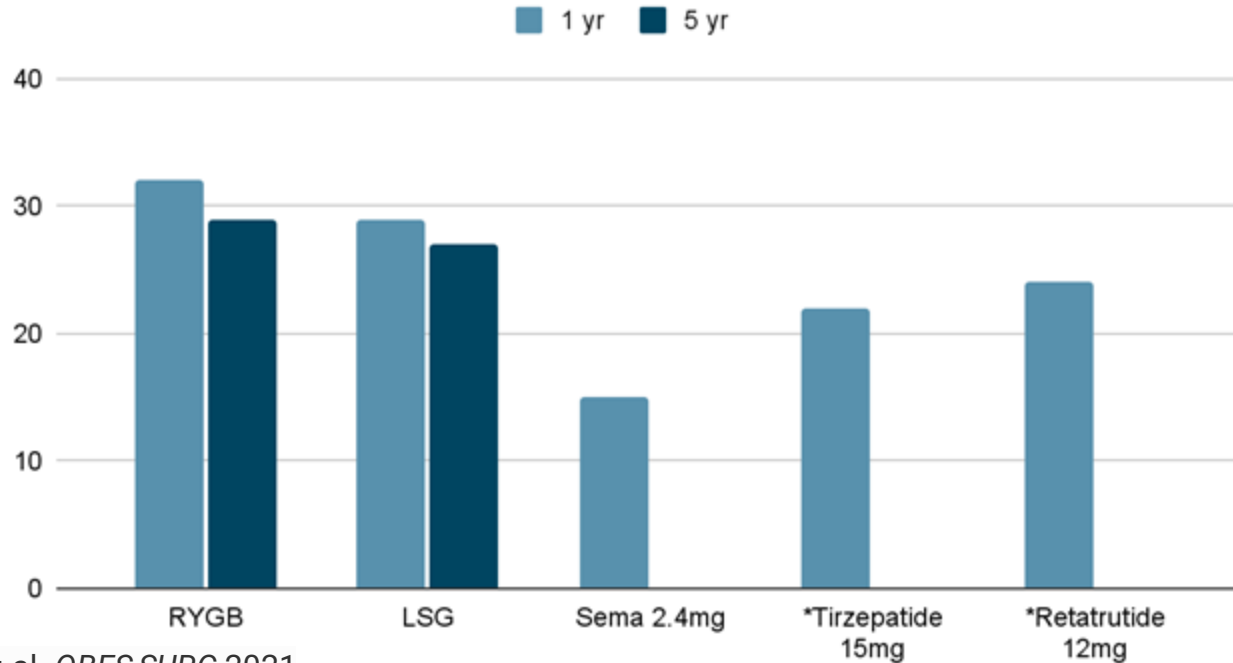
Can we  
compete?



Do I have to  
go back to  
appy's all  
day? Or  
worse yet,  
clinic?!

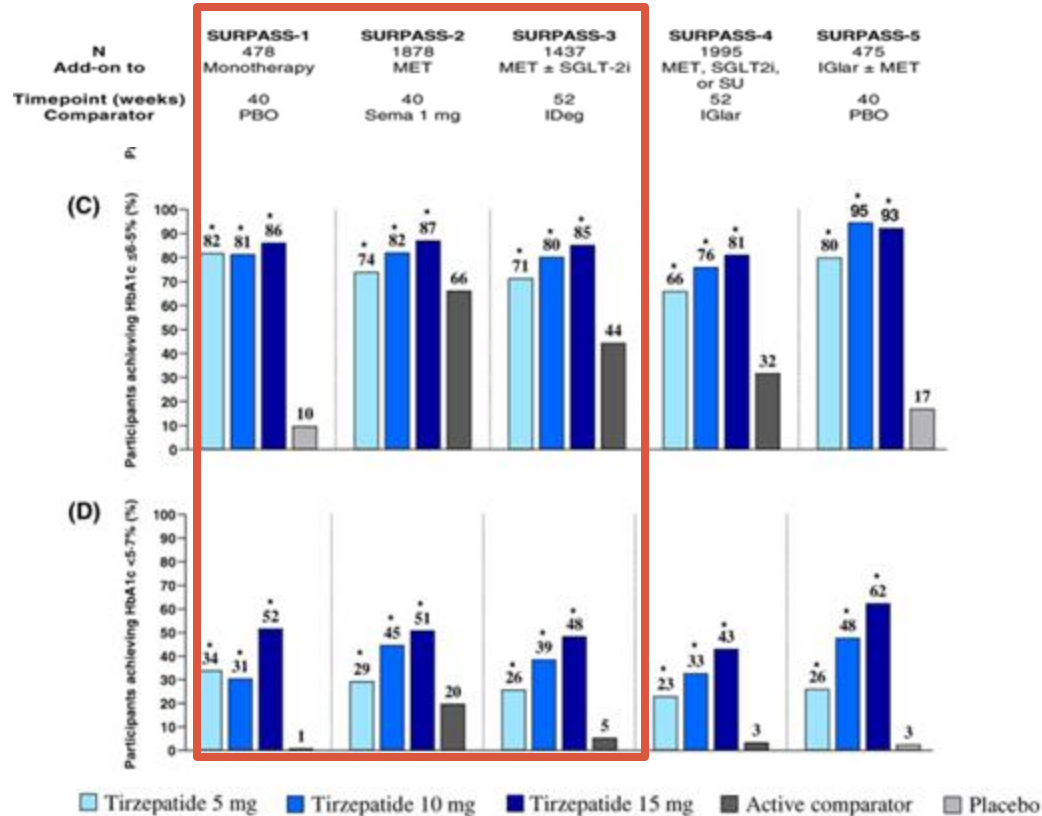
# Weight loss

Percentage of Total Body Weight Loss



van Rijswijk, AS., et al. *OBES SURG* 2021

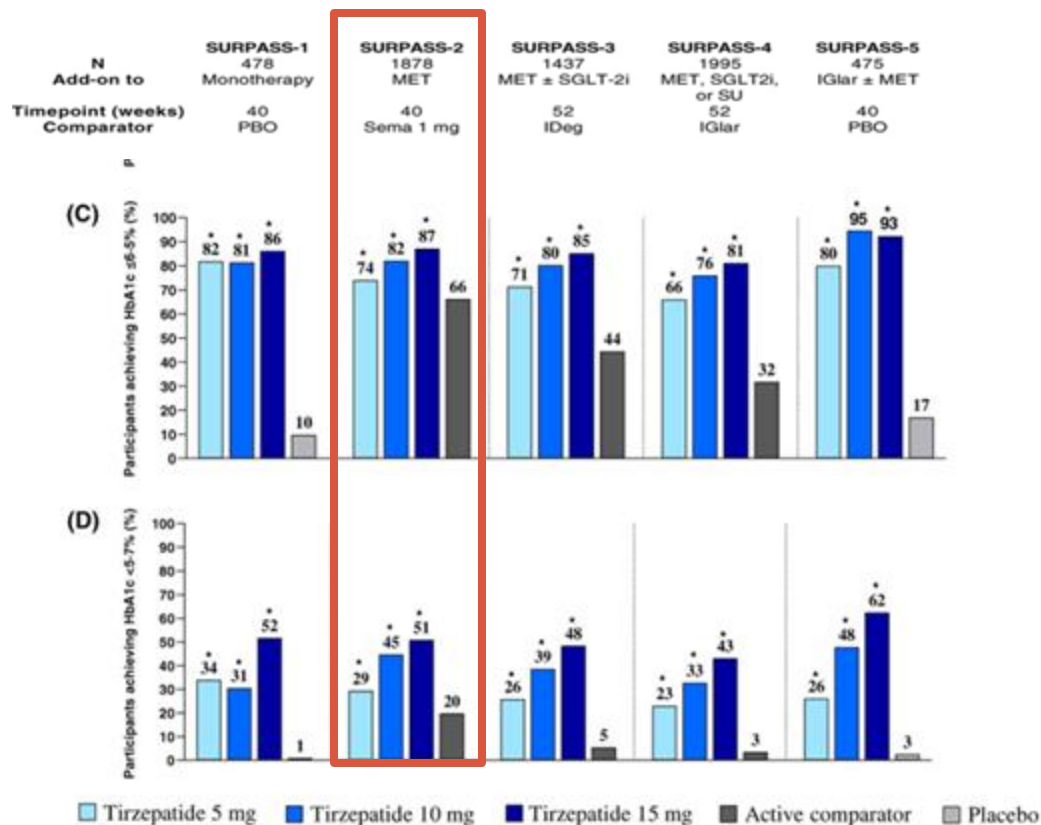
# Tirzepatide, Semaglutide 1mg, and DM2



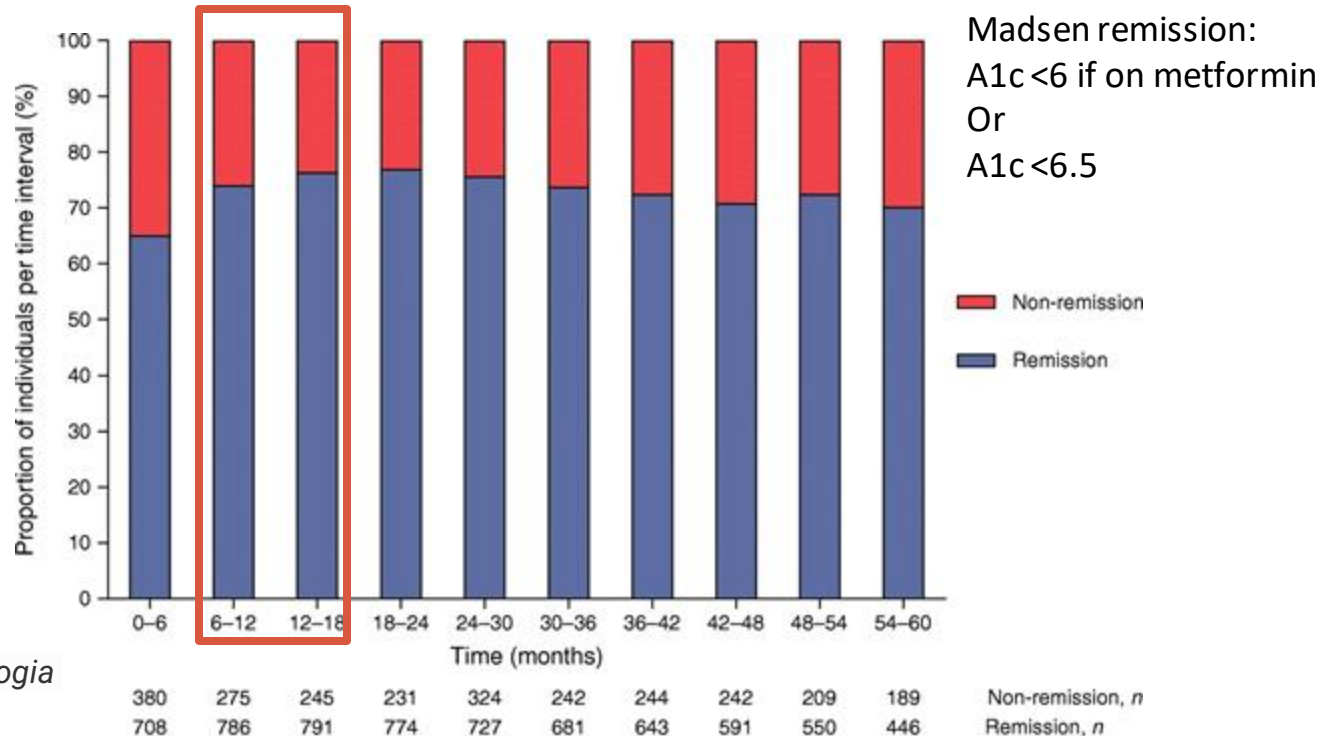
# Tirzepatide vs. Semaglutide 1mg

## Tirzepatide

- 2.5x “remission” rate
- A1c  $\leq$  6.5: 30% improvement



# RYGB for DM2; Danish

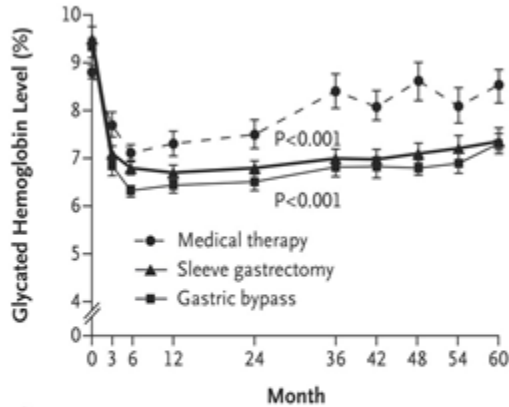


Madsen, et al. *Diabetologia*  
2019

# Stampede Trial LSG & RYGB

# Tirzepatide

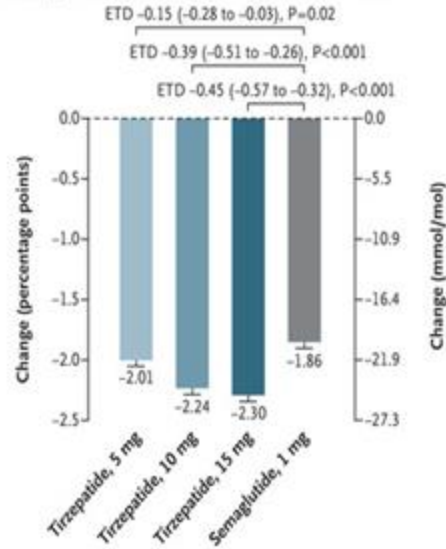
**A Glycated Hemoglobin**



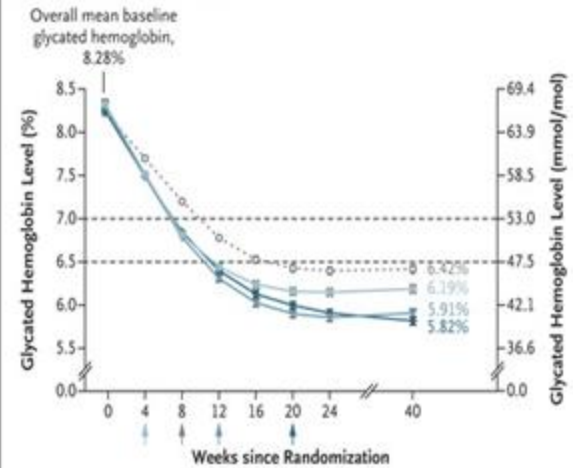
Mean (median)  
Value at Visit

|                         | 0         | 3         | 6         | 12        | 24        | 36        | 42 | 48 | 54 | 60 |
|-------------------------|-----------|-----------|-----------|-----------|-----------|-----------|----|----|----|----|
| Medical therapy         | 8.8 (8.6) | 7.3 (6.8) | 7.5 (7.2) | 8.4 (7.7) | 8.6 (8.2) | 8.5 (8.0) |    |    |    |    |
| Gastric bypass          | 9.3 (9.4) | 6.4 (6.2) | 6.5 (6.4) | 6.8 (6.6) | 6.8 (6.8) | 7.3 (6.9) |    |    |    |    |
| Sleeve gastrec-<br>tomy | 9.5 (8.9) | 6.7 (6.4) | 6.8 (6.8) | 7.0 (6.7) | 7.1 (6.6) | 7.4 (7.2) |    |    |    |    |

**A Change in Glycated Hemoglobin Levels from Baseline**



**B Glycated Hemoglobin Level**



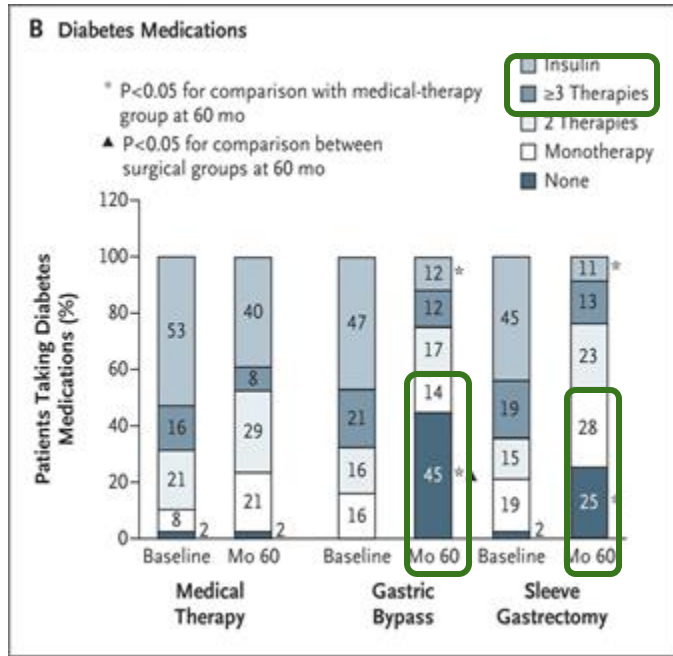


**BUT WAIT**

**THERE'S MORE**



# STAMPEDE or “Endo’s eat your heart out”



Stampede

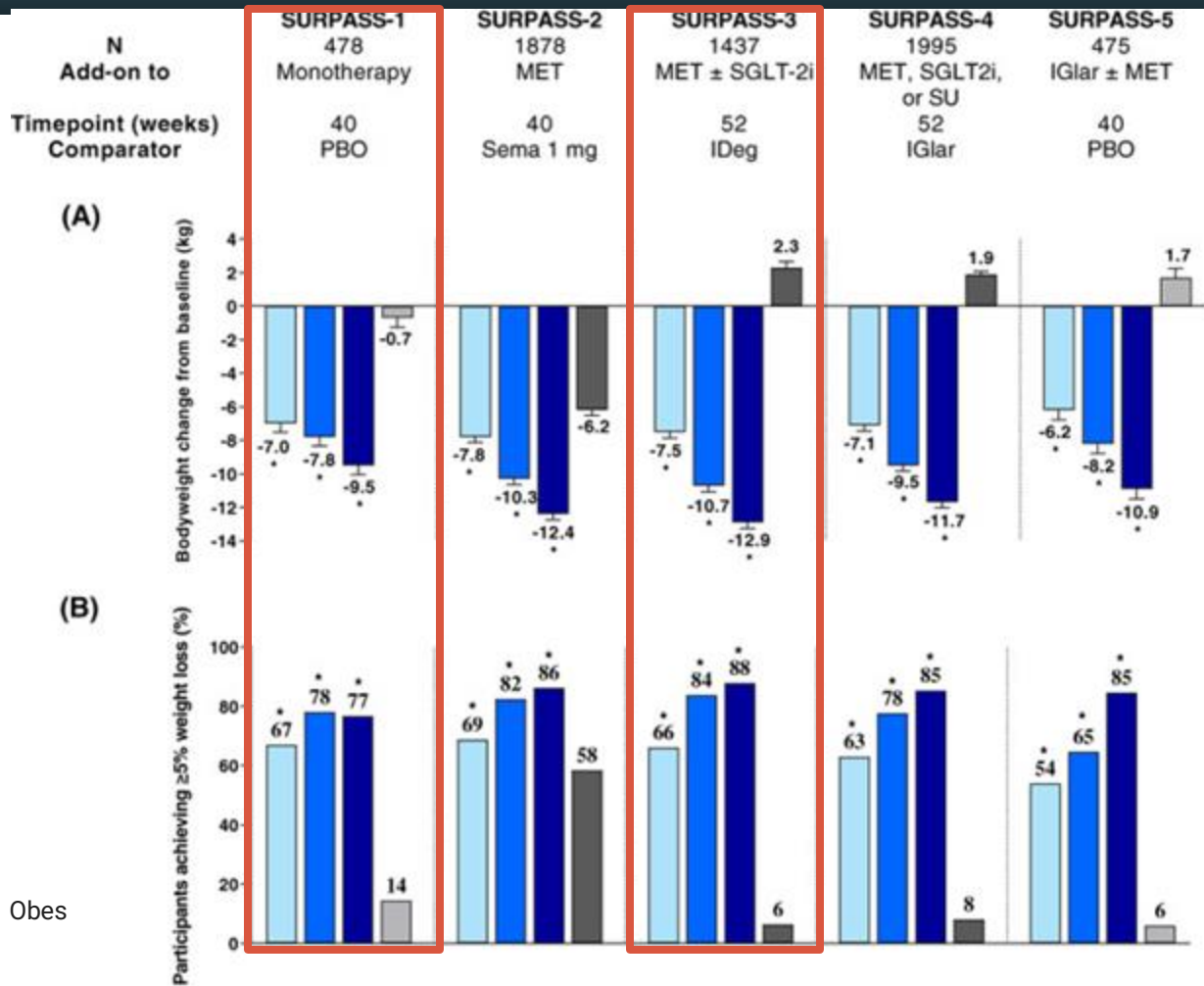
- 2/3 were on insulin or  $\geq 3$  therapies

Surpass-2

- Metformin only

# Limitations

No head to head of premier pharmacotherapy (Sema 2/2.4 or Tirzepatide 15) and surgery



# Primary Prevention of CV Disease

## SELECT Trial (first reported Aug 8 2023)

- Semaglutide 2.4mg + documented CV disease and No DM2
- 20% risk reduction in MACE
- 5 yr follow up

## Swedish Obesity Study

- 44% reduced risk of CV CV death
- 33% reduced risk of MACE (Adjusted for multivariable adjustments for baseline conditions)
- \* Note: reduction without known CV disease

# Postop pharmacotherapy

50% lost >5% of weight

1/3 lost 10% and 15% lost >15%

Phentermine better for 21-30 yr; Liraglutide better for >60 yr

\*\*Semaglutide and Tirzepatide not in trial

# References

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