2024 RACHMIEL LEVINE-ARTHUR RIGGS

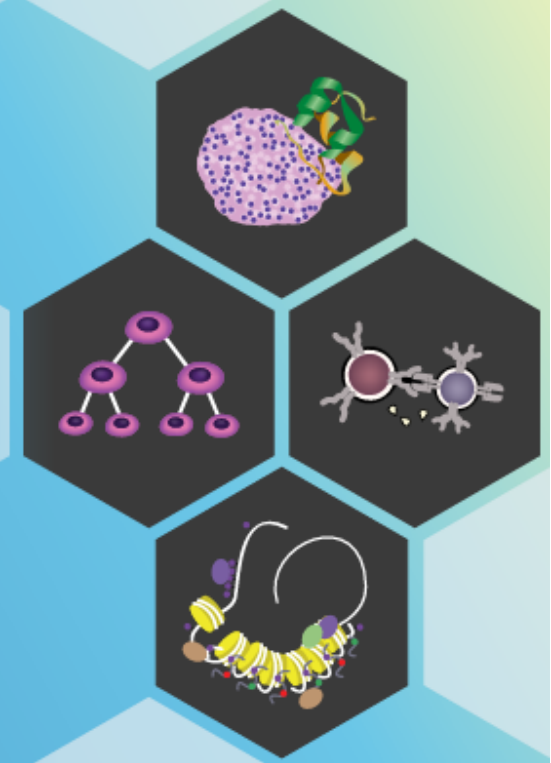
Diabetes Research Symposium

Debate: Weight Loss in Obesity: It is Time for Metabolic Surgery to Move Over?

Donna Ryan, MD

Professor Emerita

Pennington Biomedical Research Center



Disclaimer

This is a Non-CME Accredited Presentation.

Disclosures

- *Scientific Advisor*: Altimmune, Amgen, Astra Zeneca, Biohaven, Boehringer Ingelheim, Calibrate, Carmot/Roche, CinRx, Currax, Epitomee, Fractyl, Gila, Lilly, Nestle, Novo Nordisk, Regeneron, Scientific Intake, Structure Therapeutics, Wondr Health, Zealand

- *Speaker's Bureau:* Novo Nordisk, Lilly

- *Stock Options:* Epitomee, Calibrate, Roman, Scientific Intake, Xeno

- *DSMB:* IQVIA(Rhythm); Llly; CinRx

Objectives

Goal for end of talk:

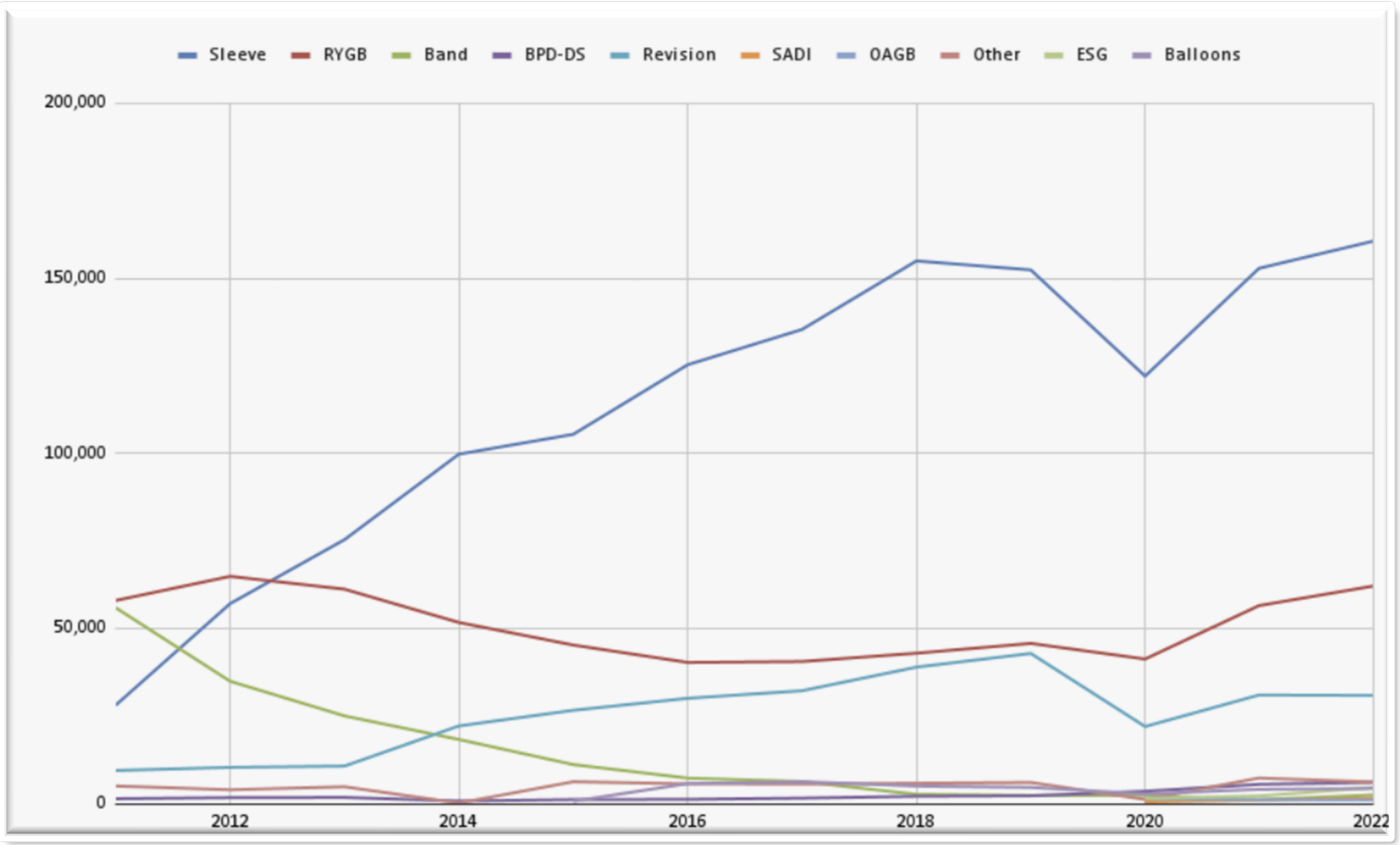
Based on review of the latest evidence for bariatric surgery and high intensity obesity pharmacotherapy, attendees will be able to describe the

- changing landscape in obesity medications, with more robust weight loss and more evidence of disease modifications;
- changing landscape in metabolic and bariatric surgery procedures with SADI and endoscopic gastroplasty emerging as options; and
- pros and cons of endoscopic surgery and medications.

As a result will be able to discuss the best ways to personalized approaches using both treatments, together, for obesity and diabetes management.

SADI-S = single-anastomosis duodeno-ileostomy with sleeve

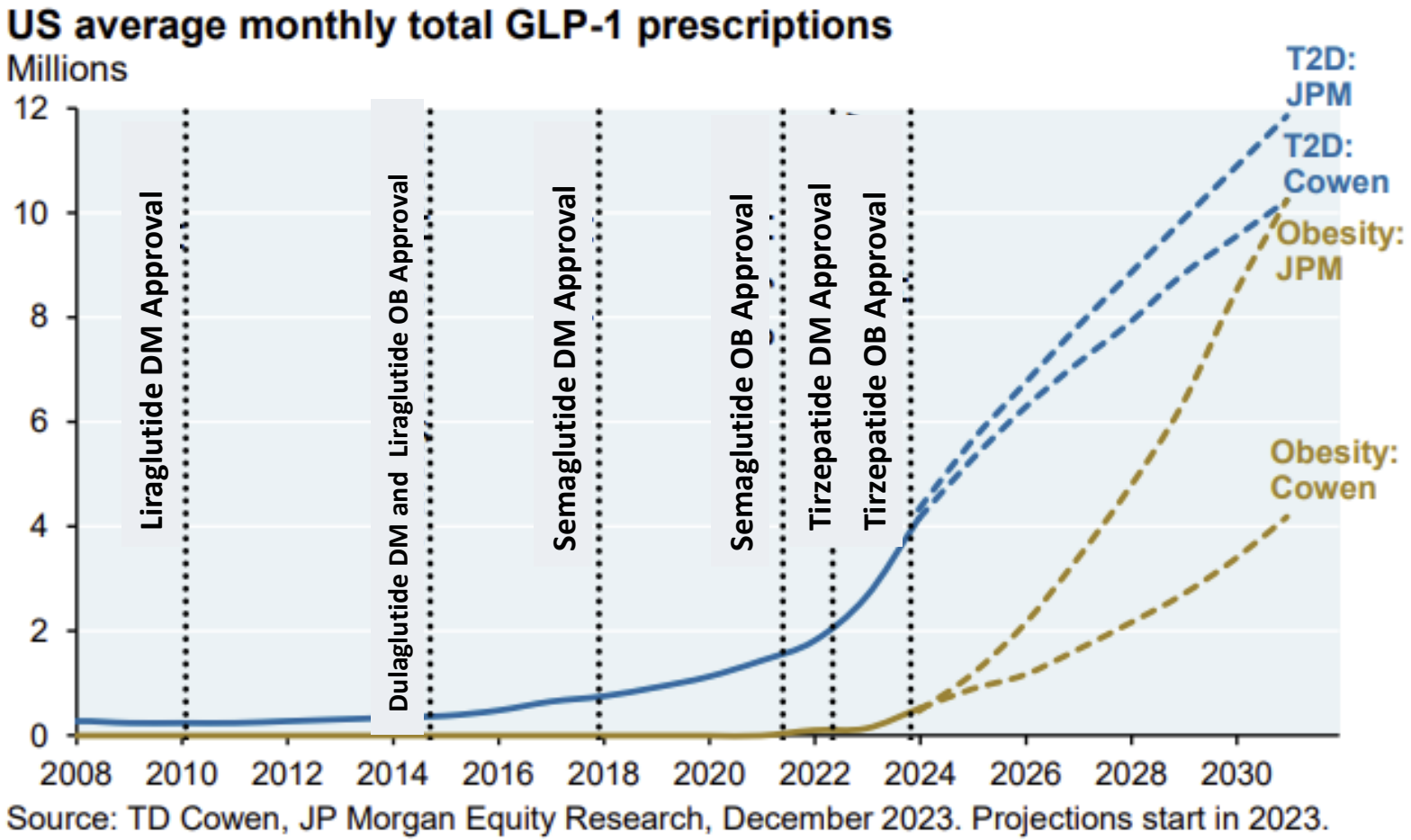
Trends in Bariatric Surgery Procedures 2022-2022
Dramatic shifts and Emergence of New Procedures



RYGB = Roux-en-Y gastric bypass
BPD-DS = biliopancreatic diversion-duodenal switch
SADI-S = single-anastomosis duodeno-ileostomy with sleeve
OAGB = one-anastomosis gastric bypass
ESG = endoscopic sleeve gastroplasty

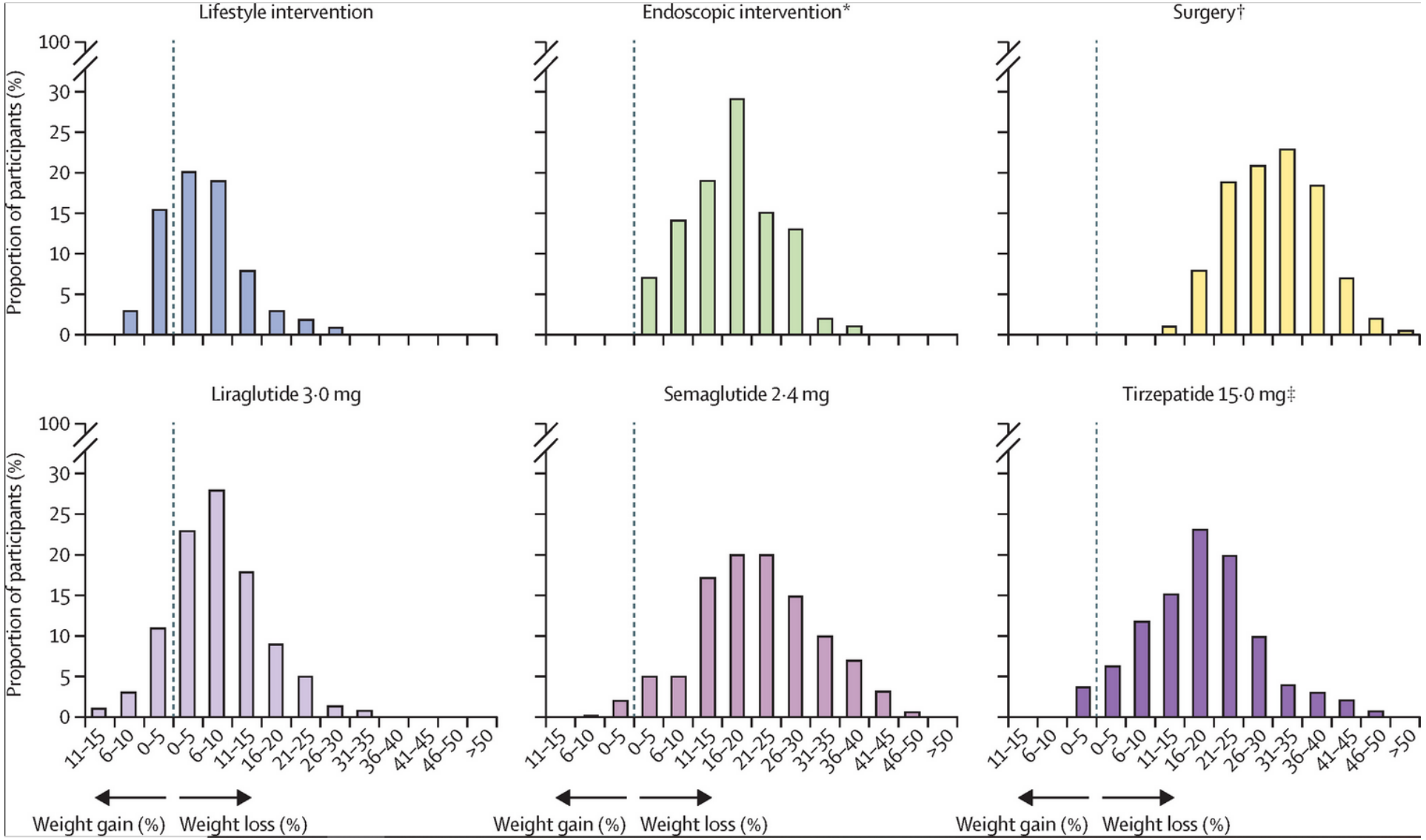
https://asmbs.org/resources/estimate-of-bariatric-surgery-numbers/

Trends in Obesity Medications: Dramatic increase in Prescribing



Benefits
Who is the winner?

First, Let's recognize the heterogeneous response to obesity treatments…



Perdomo CM, et al. Lancet 401:1116-113, 2023.

Second, Let's recognize that historically, surgery has had the upper hand…

www.nature.com/scientificreports

scientific reports

Check for updates

OPEN

Surgery is associated with better long-term outcomes than pharmacological treatment for obesity: a systematic review and meta-analysis

Leonardo Zumerkorn Pipek[1], Walter Augusto Fabio Moraes[2], Rodrigo Massato Nobetani[2], Vitor Santos Cortez[2], Alberto Santos Condi[2], João Victor Taba[2], Rafaela Farias Vidigal Nascimento[3], Milena Oliveira Suzuki[2], Fernanda Sayuri do Nascimento[2], Vitoria Carneiro de Mattos[2], Leandro Ryuchi Iuamoto[4], Wu Tu Hsing[4], Luiz Augusto Carneiro-D'Albuquerque[5], Alberto Meyer[5]✉ & Wellington Andraus[5]

"Surgery was superior for

- weight loss (− 22.05 kg [− 28.86; − 15.23),
- total cholesterol (− 0.88 [− 1.59; − 0.17]),
- triglycerides (− 0.70 [− 0.82; − 0.59]),
- HDL (0.12 [0.02; 0.23]),
- systolic pressure (− 4.49 [− 7.65; − 1.33]), diastolic pressure (− 2.28 [− 4.25; − 0.31]),
- Hb glycated (− 0.97 [− 1.31; − 0.62]), HOMA IR (− 2.94; [− 3.52; − 2.35],) and
- cardiovascular risk (−0.08; [− 0.10; − 0.05])."

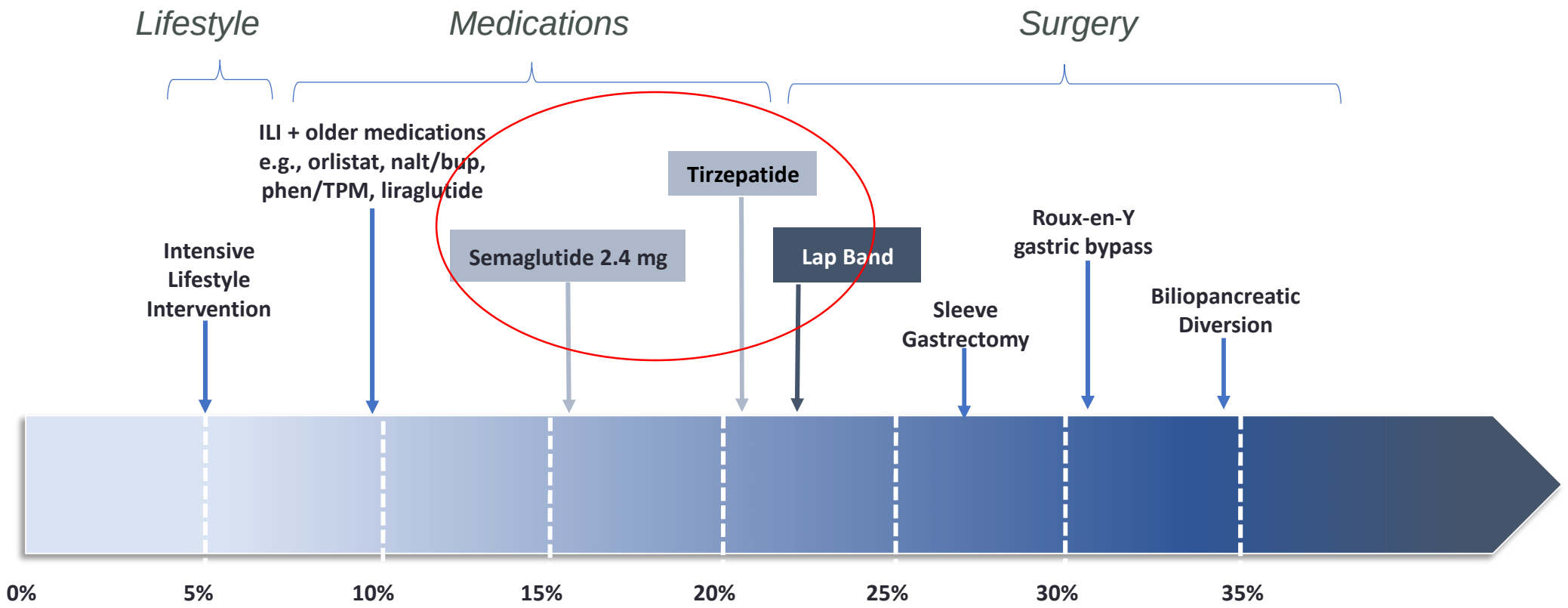
Pipek, L.Z., et al.. Sci Rep 14, 9521 (2024). https://doi.org/10.1038/s41598-024-57724-5

Let's acknowledge the lack of up-to-date data… Studies in the meta-analysis

Author, Year	Study type	Period of randomization	Country	Patient initial BMI	follow-up
Cheng 2022	RCT	03/2014–12/2020	Singapore	27–32 kg/m	5 years
Mingrone 2021	RCT	04/2009–10/2011	Italy	≥ 35	10 years
Schauer 2017	RCT	03/2007–01/2011	USA	27–43	5 years
Crawford 2018	RCT	Period not disclosed	USA	27–43	5 years
Mingrone 2015	RCT	04/2009–10/2009	Italy	≥ 35	5 years
O'Brien 2013	RCT	06/2000–11/2000	Australia	30–35	10 years

Pipek, L.Z., et al.. Sci Rep 14, 9521 (2024). https://doi.org/10.1038/s41598-024-57724-5

Let's acknowledge the lack of up-to-date data… Advances in obesity pharmacotherapy



nal/bup, naltrexone/bupropion; phen/TPM, phentermine/topiramate

Allison DB, et al. *Obesity*. 2012;20(2):330-342. [EQUIP]; Gadde KM, et al. *Lancet*. 2011;37:1341-1352. [CONQER]; Greenway FL, et al. *Lancet.* 2010;376:595-605. [COR-I]; Apovian CM, et al. *Obesity.* 2013;21:935-943 [COR-II]; Wadden TA, et al. *Obesity*. 2011;19(1):110-120. [COR-BMOD]; Pi-Sunyer X, et al. *N Engl J Med*. 2015;373(1):11-22. [SCALE]; Wadden TA, et al. *In J Obes*. 2013;37:1443-1451. [SCALE MAIN]; Enebo LB, et al. Wilding JPH, et al. *N Engl J Med*. 2021;384(11):989. [STEP 1]; Wadden TA, et al. *JAMA*. 2021;325(14):1403-1413. [STEP 3]; Rubino D, et al. *JAMA*. 2021;325(14):1414-1425. [STEP 4]; Ryan D. *Lancet Diabetes Endocrinol*. 2021;9(5):252-254. [STEP]; Sjöström L, et al. *N Engl J Med*. 2007;357:741-52. [Surgery].

96.3% ≥5% loss

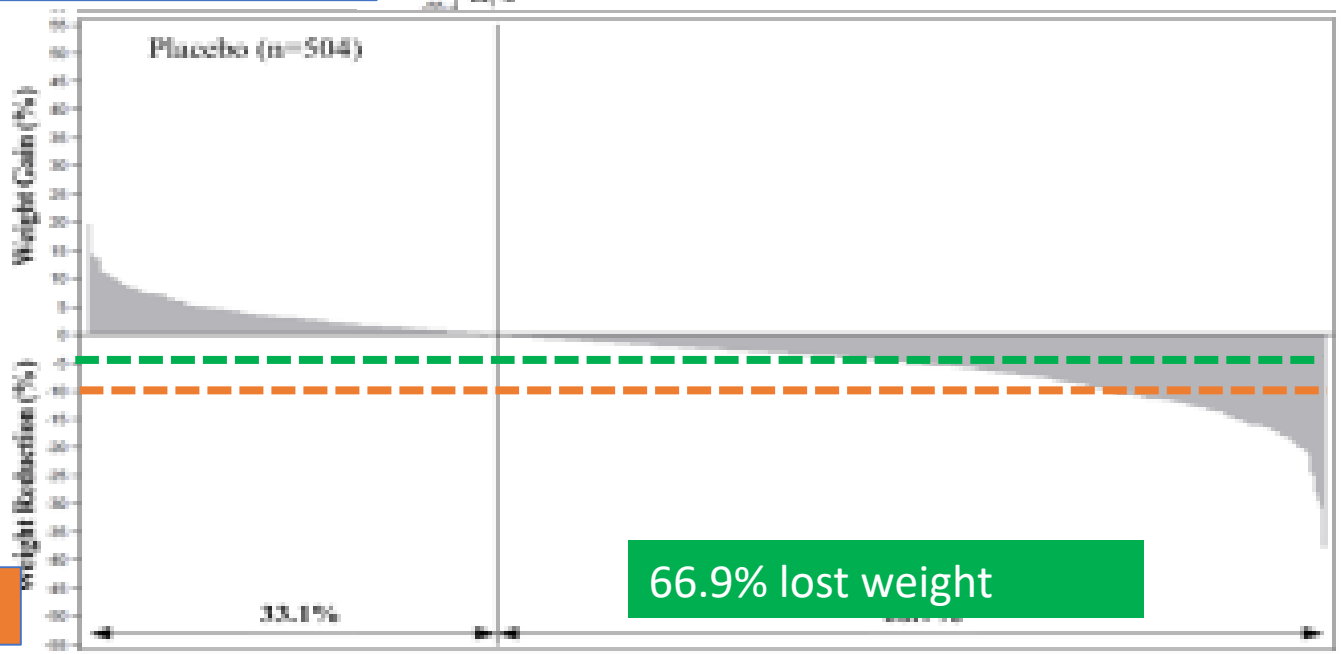
90.1% ≥10% loss

2.3% gained weight

97.7% lost weight

27.9% ≥5% loss

13.5% ≥10% loss



33.1% gained weight

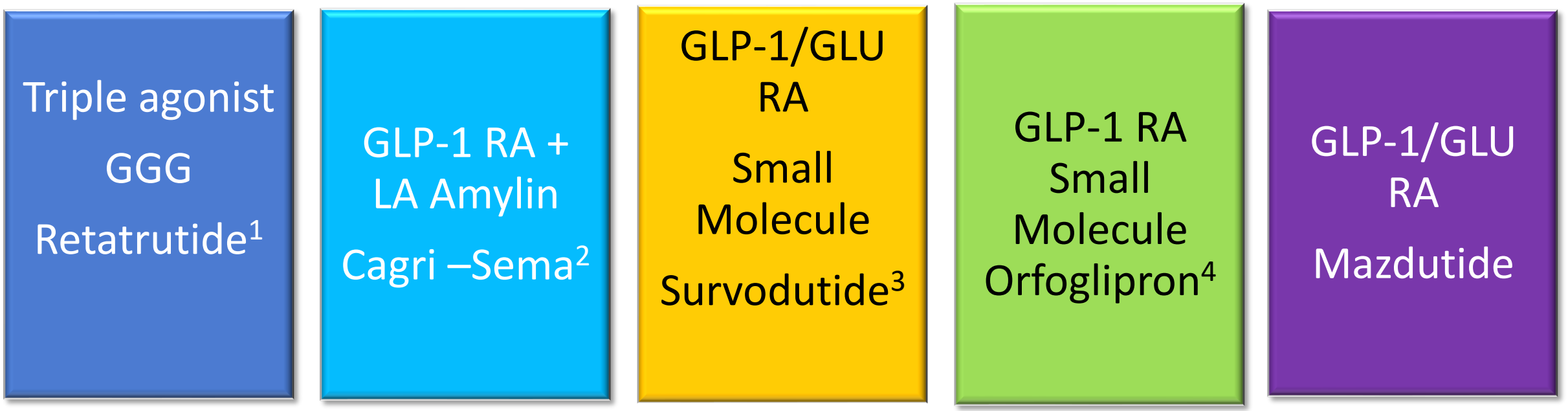
66.9% lost weight

Jastreboff AM, et al. N Engl J Med 2022;387:205-16.

On Treatment Analysis

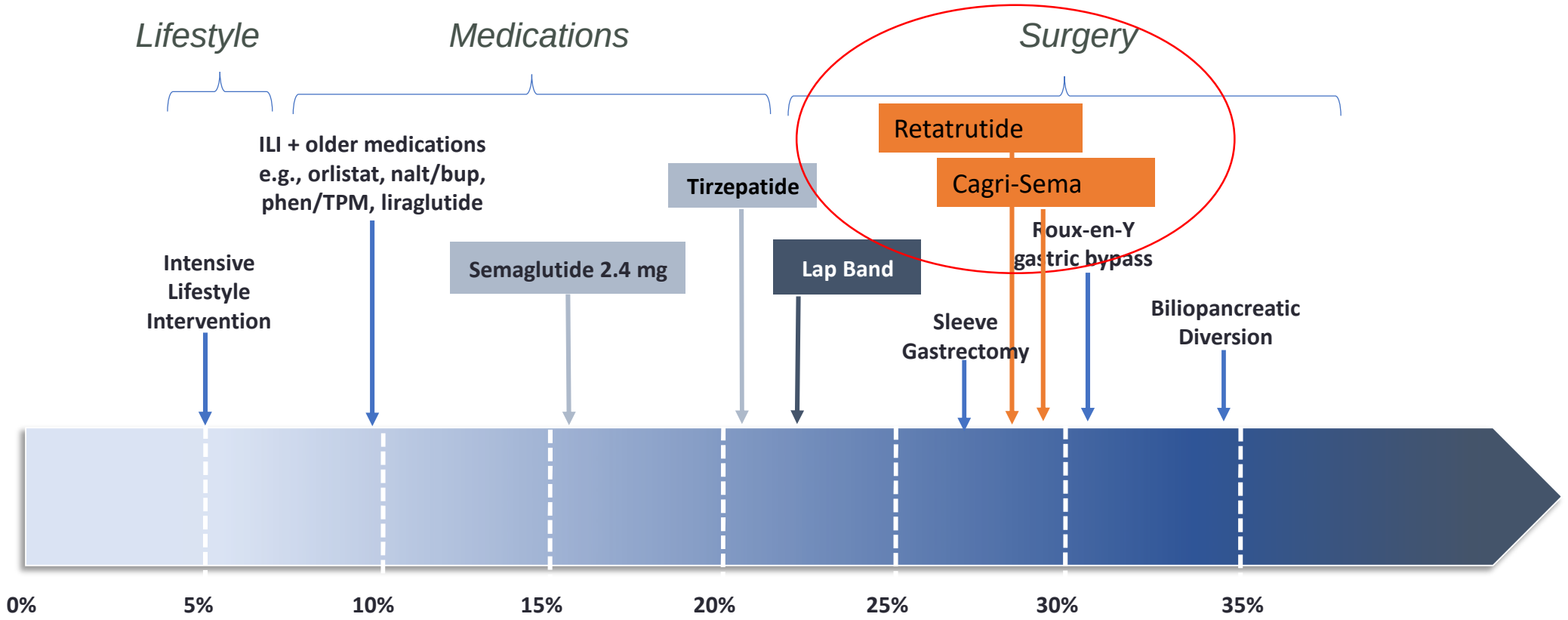
Semaglutide and Tirzepatide are the Beginning

Obesity Medicines in Phase 3



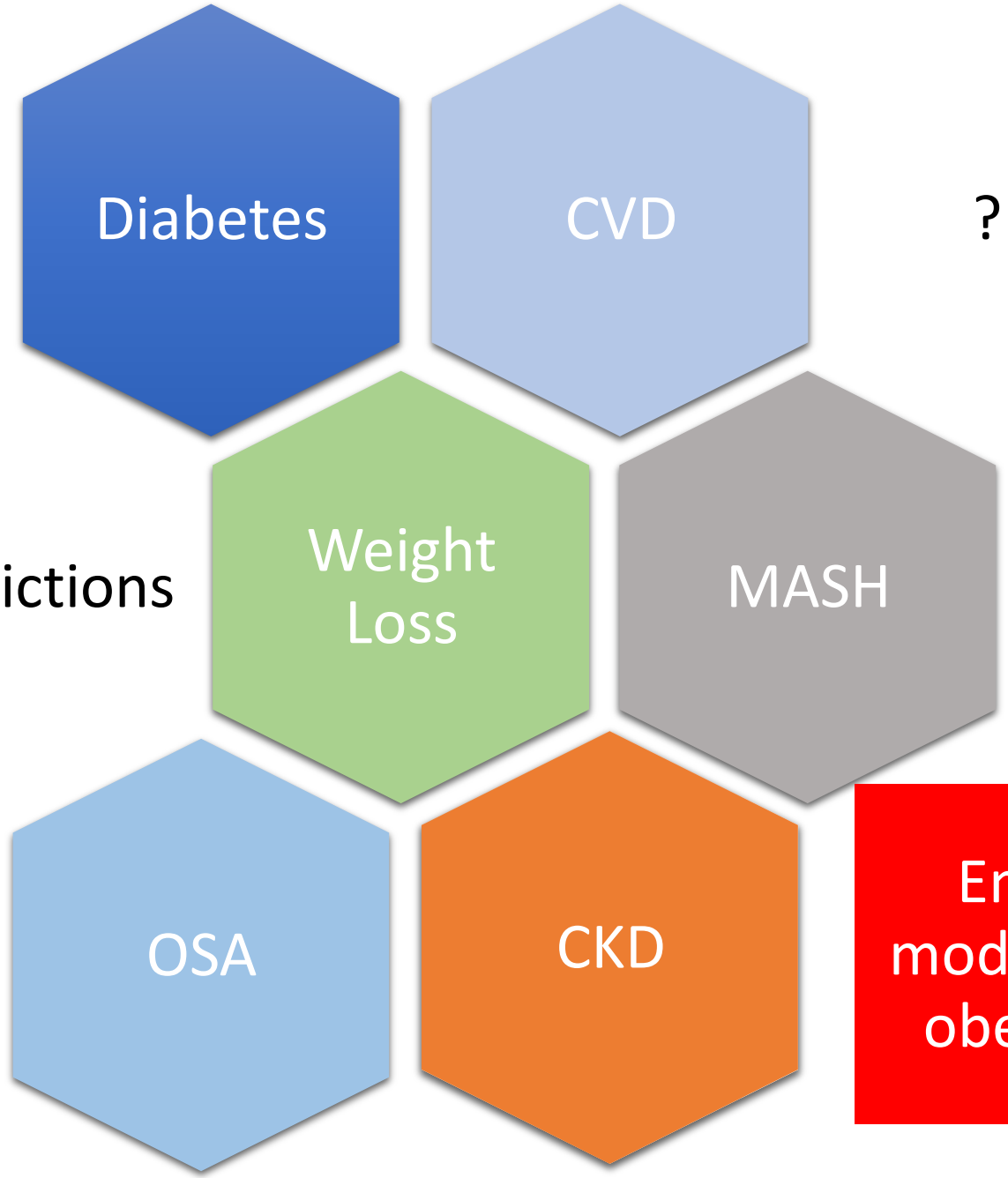
1. Jastreboff A, et al. N Engl J Med 2023;389:514-526. 2. Enebo LB, et al. Lancet. 2021 May 8;397(10286):1736-1748. 3. le Roux CW, et al. Lancet Diabetes Endocrinol. 2024 Mar;12(3):162-173. 4. Wharton S et al. N Engl J Med. 2023 Sep 7;389(10):877-888. 5. Ji, L., Jiang, H., Cheng, Z. et al. Nat Commun 14, 8289 (2023).

Pipeline Medications Rival Surgery in Weight Loss



nal/bup, naltrexone/bupropion; phen/TPM, phentermine/topiramate

Allison DB, et al. *Obesity*. 2012;20(2):330-342. [EQUIP]; Gadde KM, et al. *Lancet*. 2011;37:1341-1352. [CONQER]; Greenway FL, et al. *Lancet.* 2010;376:595-605. [COR-I]; Apovian CM, et al. *Obesity.* 2013;21:935-943 [COR-II]; Wadden TA, et al. *Obesity*. 2011;19(1):110-120. [COR-BMOD]; Pi-Sunyer X, et al. *N Engl J Med*. 2015;373(1):11-22. [SCALE]; Wadden TA, et al. *In J Obes*. 2013;37:1443-1451. [SCALE MAIN]; Enebo LB, et al. Wilding JPH, et al. *N Engl J Med*. 2021;384(11):989. [STEP 1]; Wadden TA, et al. *JAMA*. 2021;325(14):1403-1413. [STEP 3]; Rubino D, et al. *JAMA*. 2021;325(14):1414-1425. [STEP 4]; Ryan D. *Lancet Diabetes Endocrinol*. 2021;9(5):252-254. [STEP]; Sjöström L, et al. *N Engl J Med*. 2007;357:741-52. [Surgery].



? Neuroinflammation

? Addictions

Following in the footsteps of bariatric surgery

Emerging disease-modifying traits of new obesity medications.


Do increasing weight loss efficacy and disease modifying effects of obesity medications mean that new medications will replace MBS?

PROs of MBS

- Robust weight loss for most
- Long term weight loss for most
- Proven efficacy for mortality, MACE. cancer, et al.
- Trained work force to standard of care
- Proven safety relative to other procedures
- ROI in 3 years

PROs of Meds

CONs of MBS

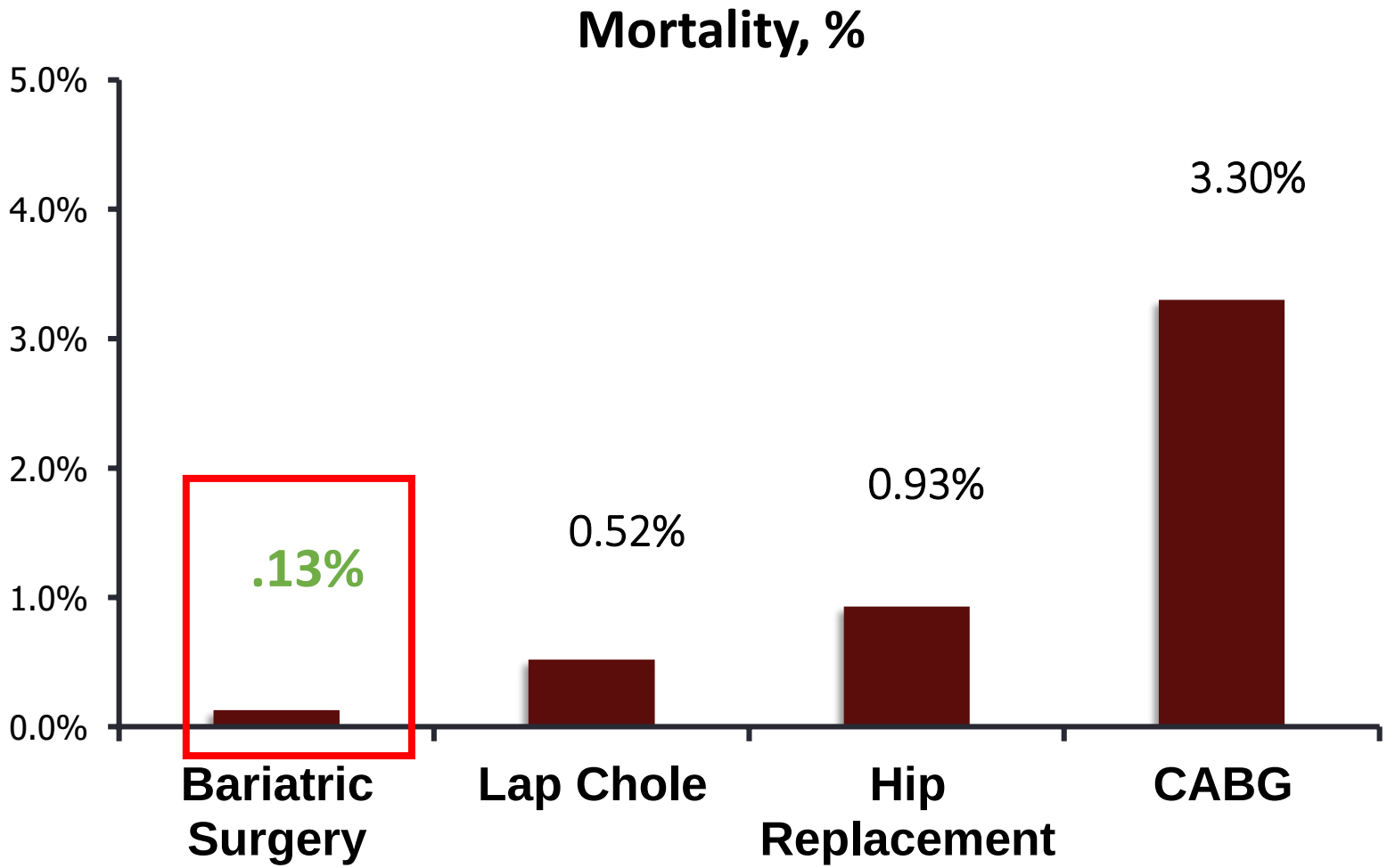
- Although low, complications and mortality occur
- Not everyone responds adequately
- Weight regain is common
- With regain, complications return
- Long term follow-up is needed
- Nutritional support is needed over the long term
- Gall bladder disease and mental health issues occur

CONs of Meds

Bariatric Surgery: Low 90-day Mortality (but relative to other surgeries)

When performed at a bariatric Surgery Center of Excellence

0.13% Mortality; n=5365 Bariatric Surgery Patients From 2012–June 2016



Ballantyne GH, et al. Bariatric surgery: low mortality at a high-volume center. Obes Surg. 2008 Jun;18(6):660-7.

Surgery requires Follow Up Care! General Recommendations

Surgery Follow-up	
	☐ Monitor weight and evidence of complications
	☐ Assess adherence to lifestyle interventions
	☐ Assess cardiovascular fitness, sleep, mood, substance use, social engagement
	☐ Chemistry, CBC/platelets (complete blood count), lipids
	☐ Avoid NSAIDs (nonsteroidal anti-inflammatory drugs)
	☐ Adjust medications as needed (diabetes, HTN)
	☐ Vitamin, trace element supplementation
	☐ Consider support groups

Mechanick J, et al. *Endocr Pract*. 2019;25(Suppl 2):1-75.

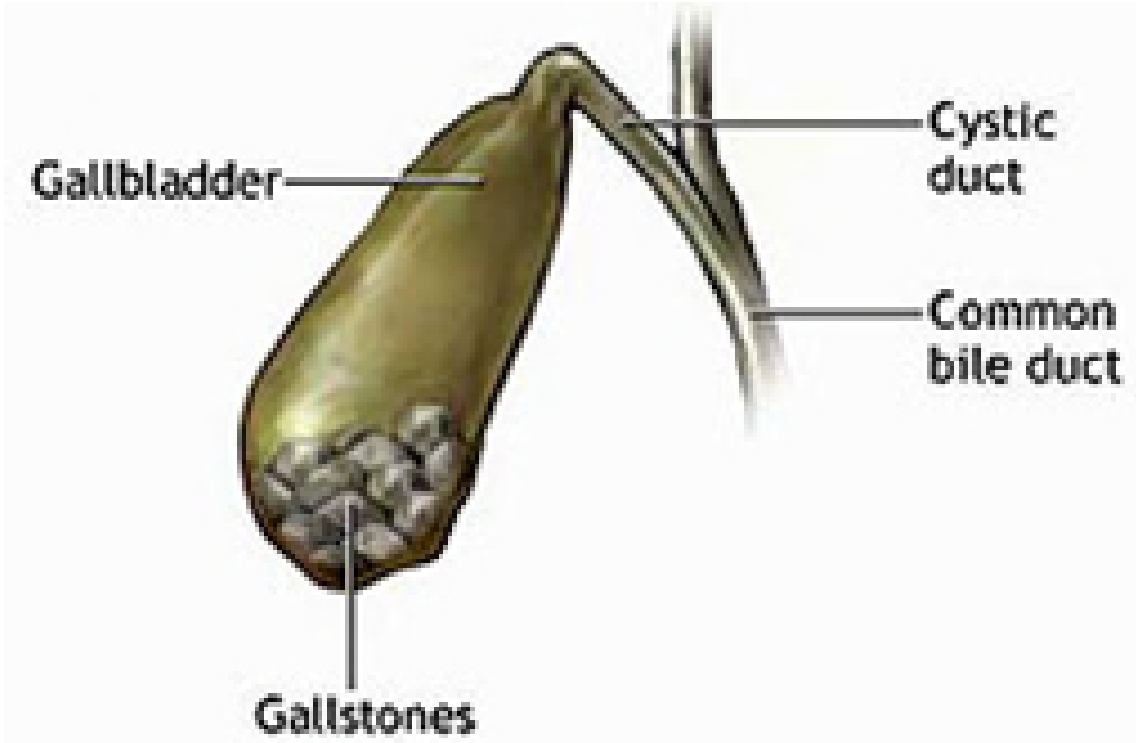
Recommended Follow-up for Nutritional and Metabolic Deficiencies After Bariatric Surgery

Procedure	Initial	Interval Until Stable	Once stable
LABG	1 month	Every 1-2 months	Every 12 months
LSG	1 month	Every 3-6 months	Every 12 months
RYGB	1 month	Every 3 months	Every 6-12 months
BPD/DS *biliopancreatic diversion with duodenal switch*	1 month	Every 3 months	Every 6 months

Mechanick J, et al. *Endocr Pract*. 2019;25(Suppl 2):1-75.

Obesity, Weight Loss and Gall Bladder Disease

- Obesity increases risk for gall stones.
- Weight loss, especially rapid weight loss, increases risk for gall stones and acute gall bladder disease.



Gall Bladder Stones

Everhart JE. Contributions of obesity and weight loss to gallstone disease. Ann Intern Med. 1993 Nov 15;119(10):1029-35.

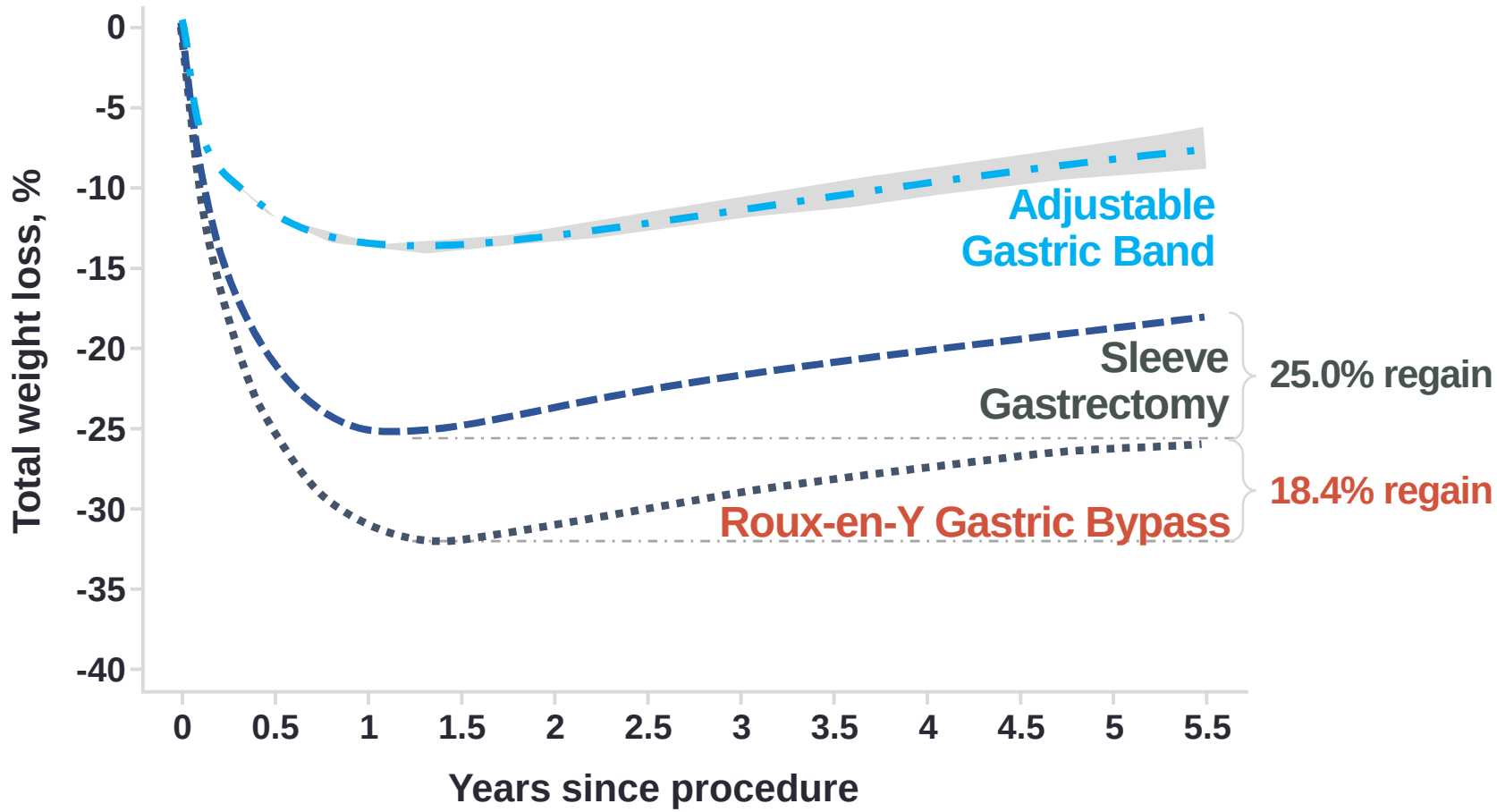
Mental Health Adverse Outcomes with Bariatric Surgery
Review of 32 studies

"Post-bariatric surgery patients had higher self-harm/suicide attempt risk compared to age-, sex-, and BMI-matched controls."

Castaneda D, Popov VB, Wander P, Thompson CC. Risk of Suicide and Self-harm Is Increased After Bariatric Surgery-a Systematic Review and Meta-analysis. Obes Surg. 2019 Jan;29(1):322-333.

Comparative Effectiveness and Weight Regain Between Bariatric Surgery Procedures

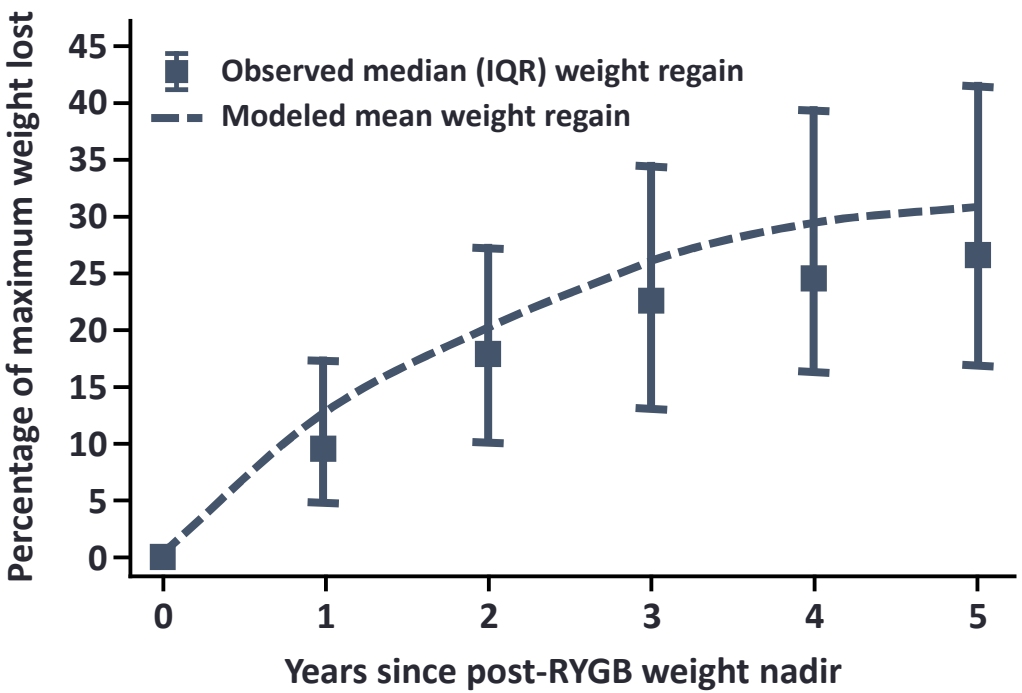
[A PCORnet Cohort Study] N=44,978



Arterburn, et al. *Ann Intern Med*. 2018;169(11):741-750.

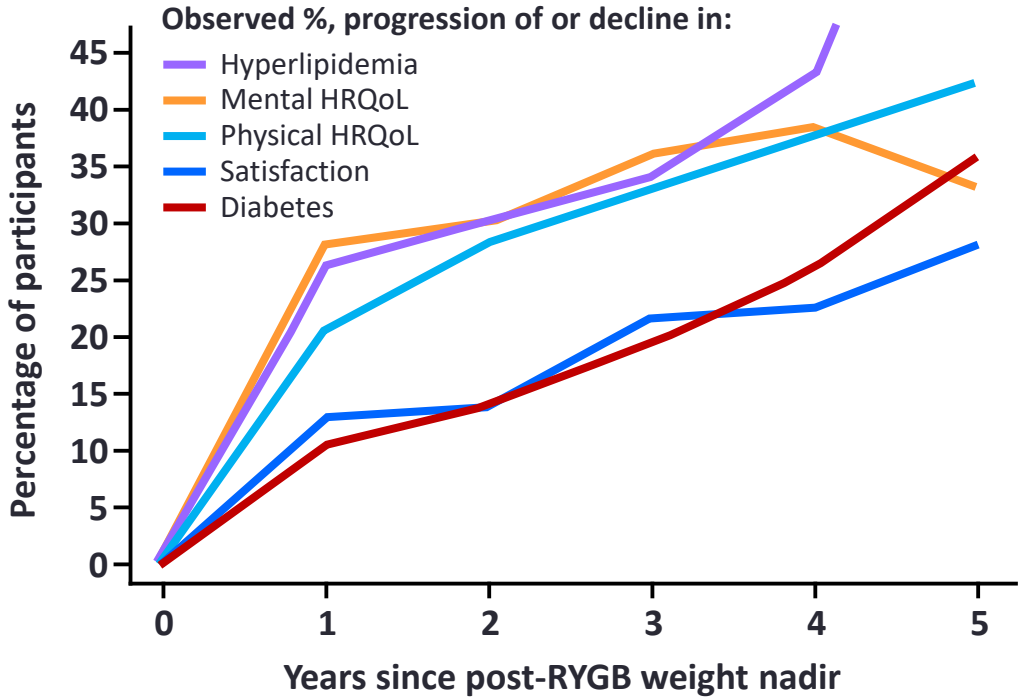
Weight Regain and Return of Selected Comorbidities (LABS-2)

Weight regain, as percentage of maximum weight lost



Median weight regain was 25.2% of maximum weight loss (25th – 75th% = 14% – 39%)

Clinical outcomes associated with weight regain



% of adults with progression—or decline—of selected clinical outcomes by year since weight nadir

HRQoL, health-related quality of life
IQR, interquartile range
RYGB, Roux-en-Y gastric bypass

King, et al. *JAMA*. 2018:320(15):1560-1569.

Bariatric surgery is not perfect.

PROs of MBS

- Robust weight loss for most
- Long term weight loss for most
- Proven efficacy for mortality, MACE. cancer, MASH, et al.
- Trained work force to standard of care
- Proven safety relative to other procedures
- ROI in 3 years

PROs of Meds

- The weight loss efficacy is rivalling surgery
- Medications have non-weight related benefits on glycemia, CVD, CKD, OSA. and MASH
- Oral and SQ options exist
- The class has been used for 20 years and the safety and tolerability profiles are known

CONs of MBS

- Although low, complications and mortality occur
- Not everyone responds adequately
- Weight regain is common
- With regain, complications return
- Long term follow-up is needed
- Nutritional support is needed over the long term
- Gall bladder disease and mental health issues occur

CONs of Meds

PROs of MBS

- Robust weight loss for most
- Long term weight loss for most
- Proven efficacy for mortality, MACE. cancer, MASH, et al.
- Trained work force to standard of care
- Proven safety relative to other procedures
- ROI in 3 years

PROs of Meds

- The weight loss efficacy is rivalling surgery
- Medications have non-weight related benefits on glycemia, CVD, CKD, OSA. and MASH
- Oral and SQ options exist
- The class has been used for 20 years and the safety and tolerability profiles are known

CONs of MBS

- Although low, complications and mortality occur
- Not everyone responds adequately
- Weight regain is common
- With regain, complications return
- Long term follow-up is needed
- Nutritional support is needed over the long term
- Gall bladder disease and mental health issues occur

CONs of Meds

- The meds are costly
- There are shortages - they are difficult to get
- Most must take them for life
- Not everyone responds adequately
- With stopping, weight and complications return
- Allergic reactions are possible
- Gall bladder disease, delayed gastric emptying occur
- For older individuals, loss of lean mass and frailty and fracture may occur with weight loss.

New obesity medications are not perfect.

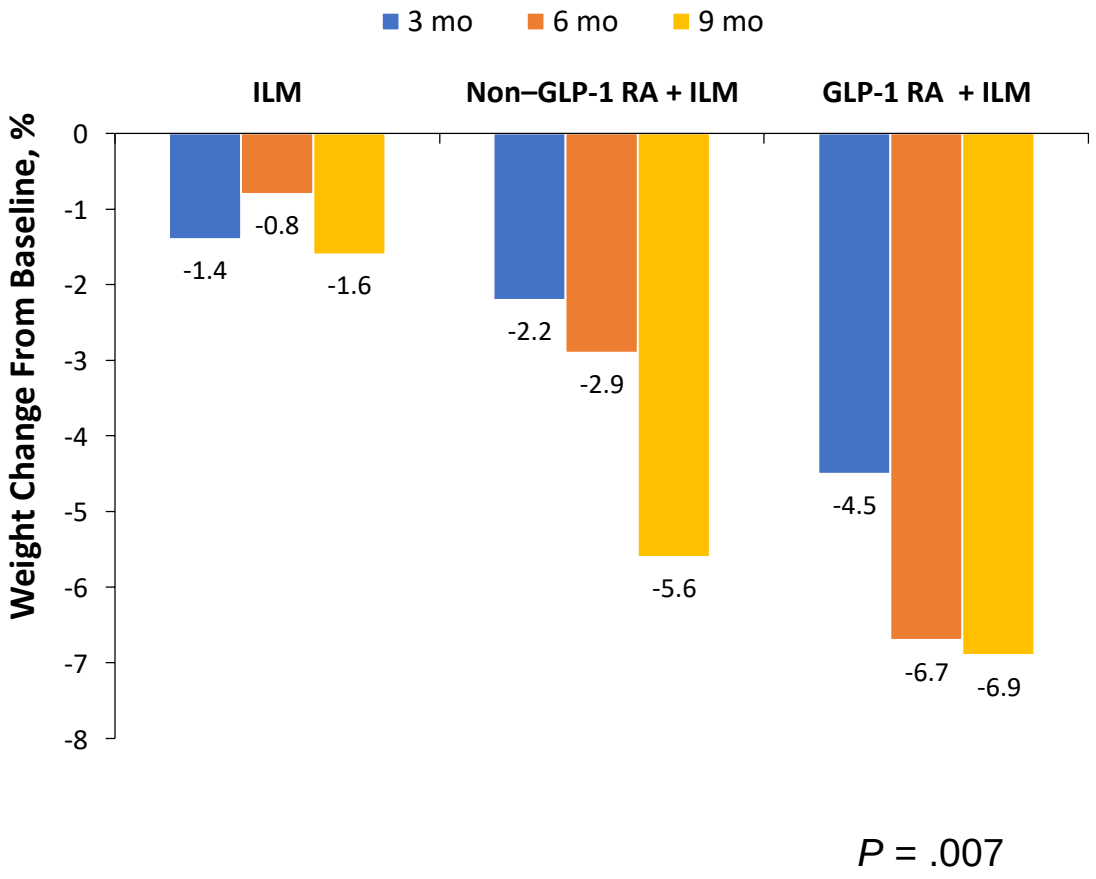
Is it time to compare?

Efficacious modern pharmacotherapy will not replace metabolic surgery.
The two will be used to complement each other.

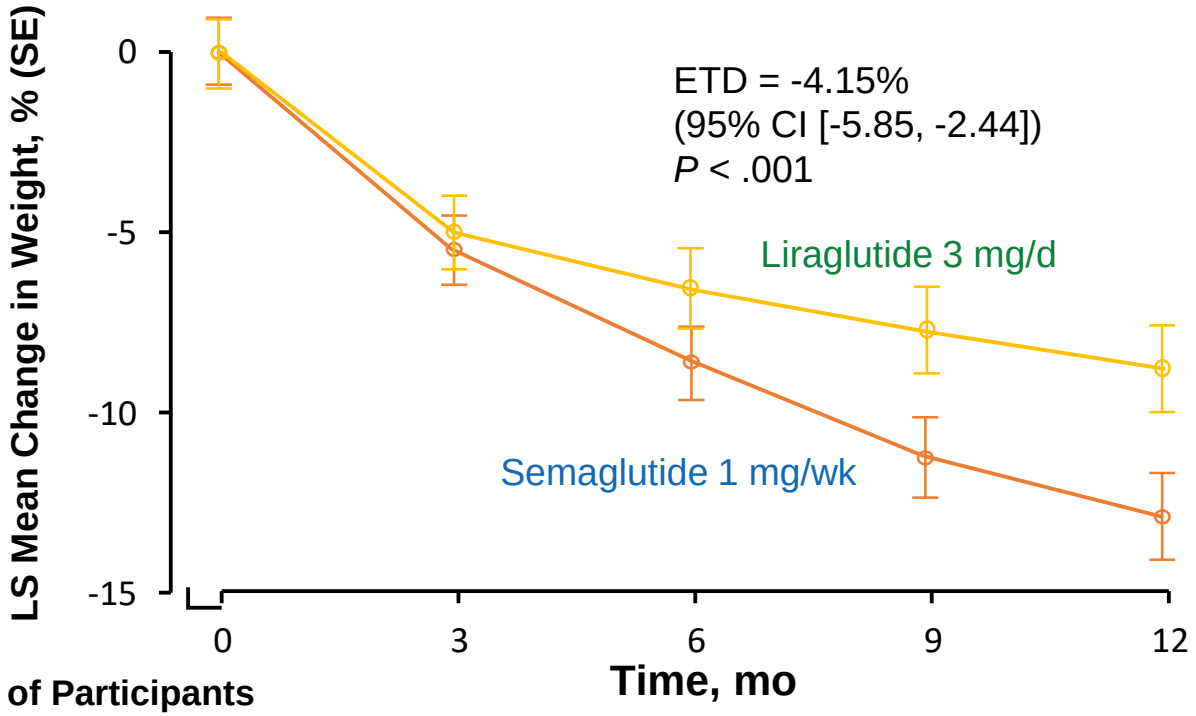
Let’s compare strategies using both!

GLP-1 + Bariatric Surgery: Single Site Experience

207 Patients with postsurgical weight recurrence, 2014-2019



P = .007



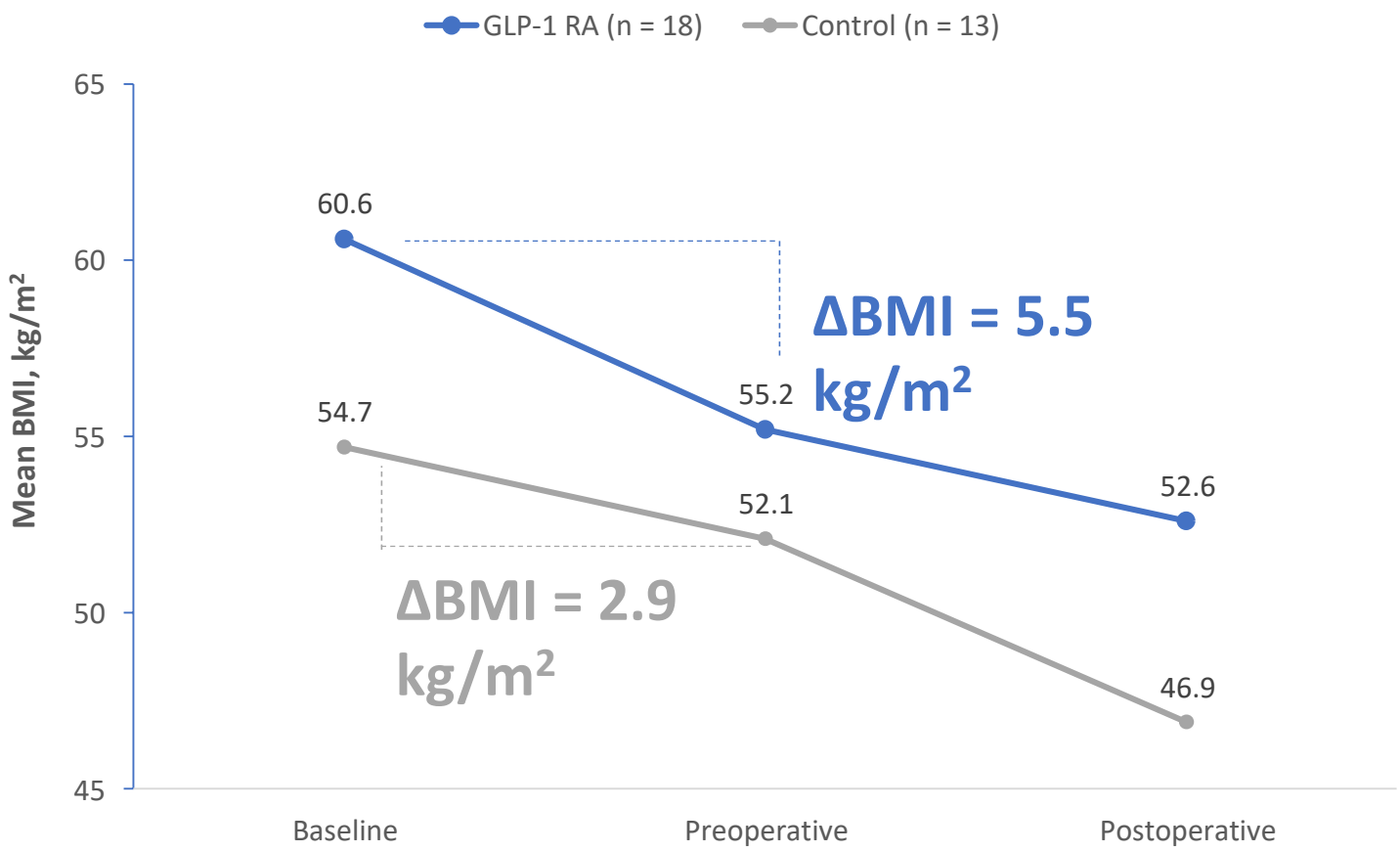
No. of Participants					
Lira 3 mg/d	92	81	72	56	51
Sema 1 mg/wk	115	104	87	63	55

1. Gazda CL et al. *Obesity (Silver Spring).* 2021;29:829-836.

2. Murvelashvili N et al. *Obesity (Silver Spring).* 2023;31:1280-1289.

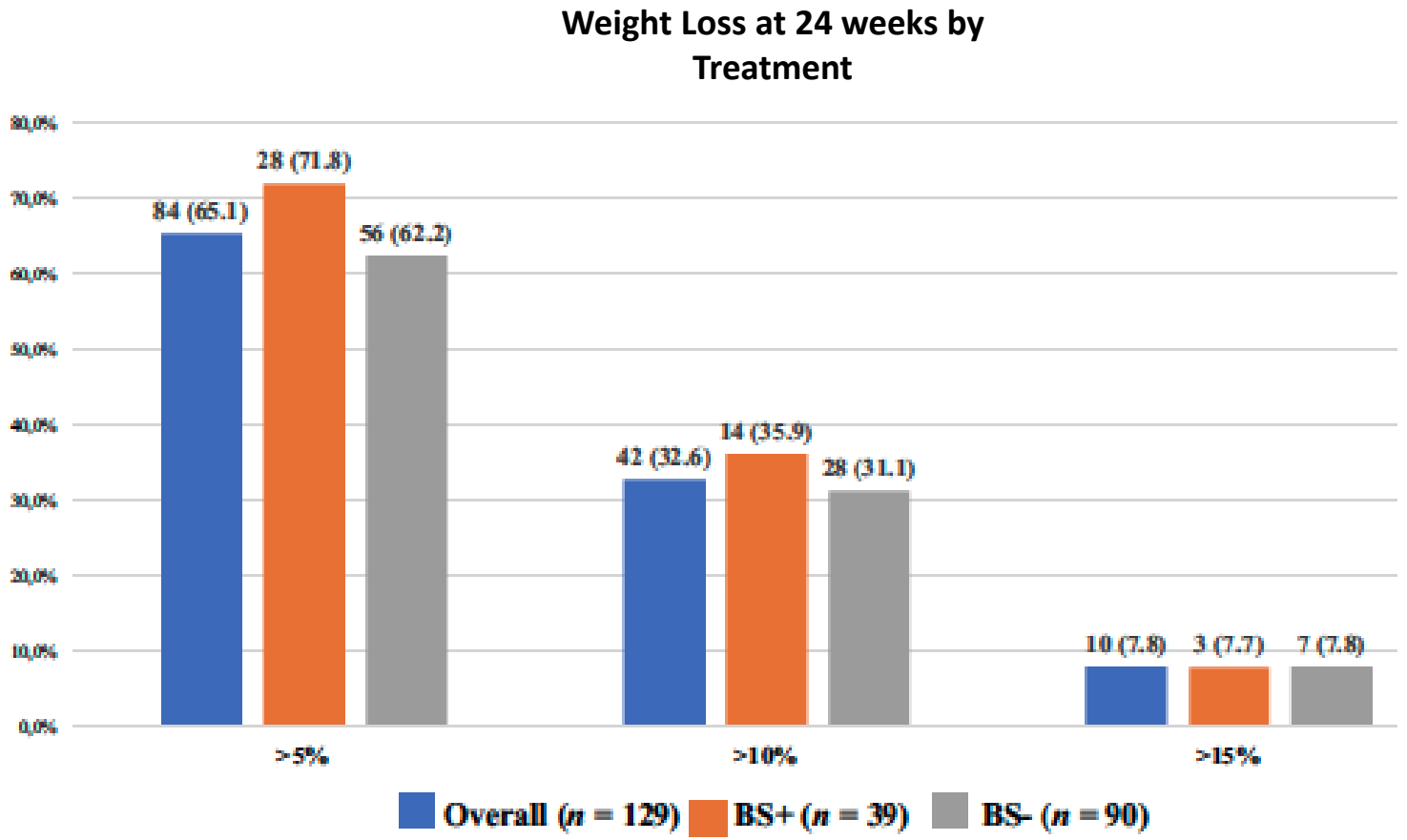
GLP-1s Given Before Bariatric Surgery

- Single-center retrospective cohort
- 31 patients with BMI >50 kg/m2
- Minimally invasive SADI or RYGB
- GLP-1 + counseling vs. counseling alone



Ilanga M, et al. Use of GLP-1 agonists in high risk patients prior to bariatric surgery: a cohort study. Surg Endosc. 2023. 37(12):9509-9513.

Semaglutide has similar effects in patients with and without a history of Bariatric Surgery



- 90 patients recruited for semaglutide 2.4 mg therapy
- 39 patients (historical) bariatric surgery + semaglutide comparators
- No difference in weight loss at 24 weeks

Bonnet J-B et al. *Obesity (Silver Spring).* 2024;32:50-58.

How can we determine the optimal use of all tools in the toolbox?


Thank you!
Let’s be friends!