OBESITY MANAGEMENT MEDICATION:
IS THERE A ROLE PREOP?

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Disclosures

- Advisory Board: Abbott Nutrition, DKSH (rep Eli Lilly), Novo Nordisk
- Speaker's fees: Eurodrug Laboratories, iNova, Novo Nordisk
- Travel support: Novo Nordisk

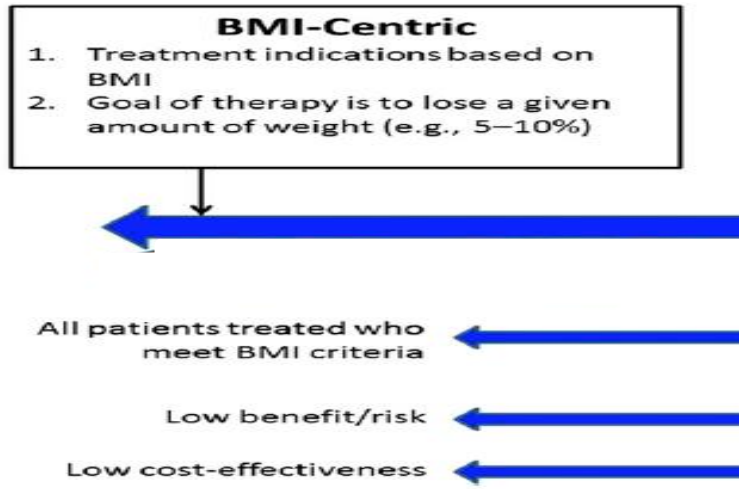
Use of Obesity Management Medications (OMM) Prior to MBS

- *MBS: the obesity intervention which results in one of the greatest weight loss to-date*
- *Patients presenting for MBS: more severe obesity and/or very high BMIs i.e. patients at-risk for mortality and peri-op complications*
- *What are we treating?*
  - *Weight vs Obesity as a Disease*
- *How and What to Use?*
  - *Overview of currently approved OMM*
  - *Evidence for use prior to MBS*
  - *Exclusive vs Adjunctive*
  - *Special patient populations who will benefit from OMM*

Considerations for OMM Use Prior to MBS

1) **Pre-op Weight Loss:**
   - Reduction in peri-op mortality and complications?
   - Greater long-term weight loss?
   - Is this for everyone?

Weight (BMI)-Centric Treatment Approach



Cefalu, W.T., et al., Diabetes Care 2015; AACE/ACE Obesity CPG. Endocr Pact. 2016

What is the Consensus?

ASMBS-IFSO 2022: Indications for Surgery

While there has been initial enthusiasm for weight loss prior to surgery, there are no data to support the practice of insurance-mandated preoperative weight loss; this practice is understood to be discriminatory, arbitrary, and scientifically unfounded, contributing to patient attrition, unnecessary delay of lifesaving treatment, and progression of life-threatening co-morbid conditions . A multidisciplinary team can help assess and manage the patient's modifiable risk factors with a goal of reducing risk of perioperative complications and improving outcomes; the decision for surgical readiness should be primarily determined by the surgeon. "

Eisenberg D, et al. SOARD 2022;18: 1345

IFSO 2024: Consensus on Definitions and CPG

Salminen P, et al. Obes Surg 2024;34:30

Obesity Management Medications (OMM)

Approved for Short-term Use

Phentermine
1959

Approved for Long-term Use

Orlistat
1999

Phentermine + Topiramate (Qsymia)
2012

Naltrexone + Bupropion (Contrave)
2014

Liraglutide (Saxenda)
2014

Semaglutide 2.4mg (Wegovy)
2021

Tirzepatide (Zepbound)
2023

Ozempic 2017

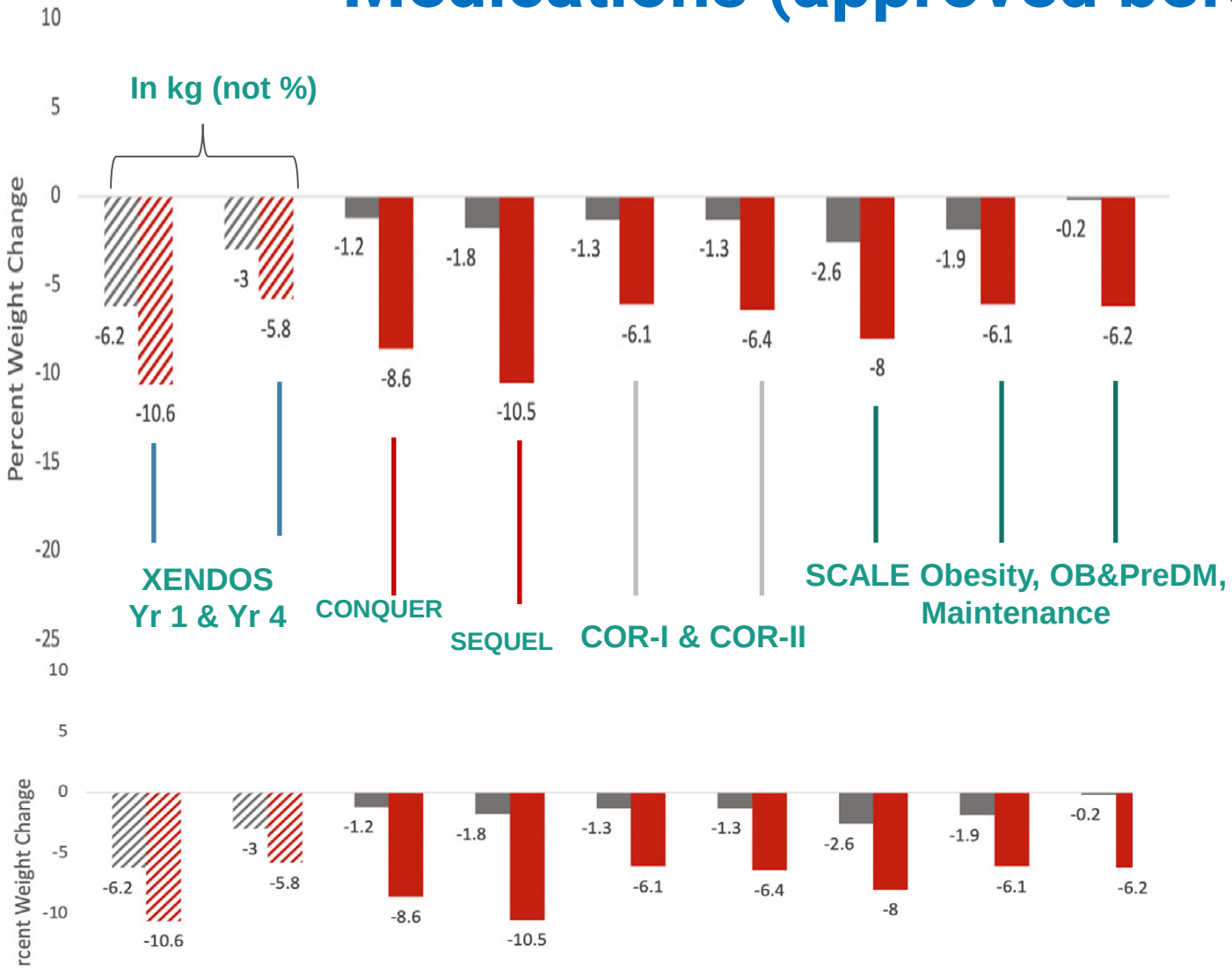
WITHDRAWN
Sibutramine: 1997 → 2010
Rimonabant: 2006 → 2009
Lorcaserin: 2012 → 2020

SHORT-TERM / OFF-LABEL

lisdexamfetamine	Bupropion
Zonisamide	Topiramate
Metformin	Phentermine>3 mths

Year stated is year of FDA approval.

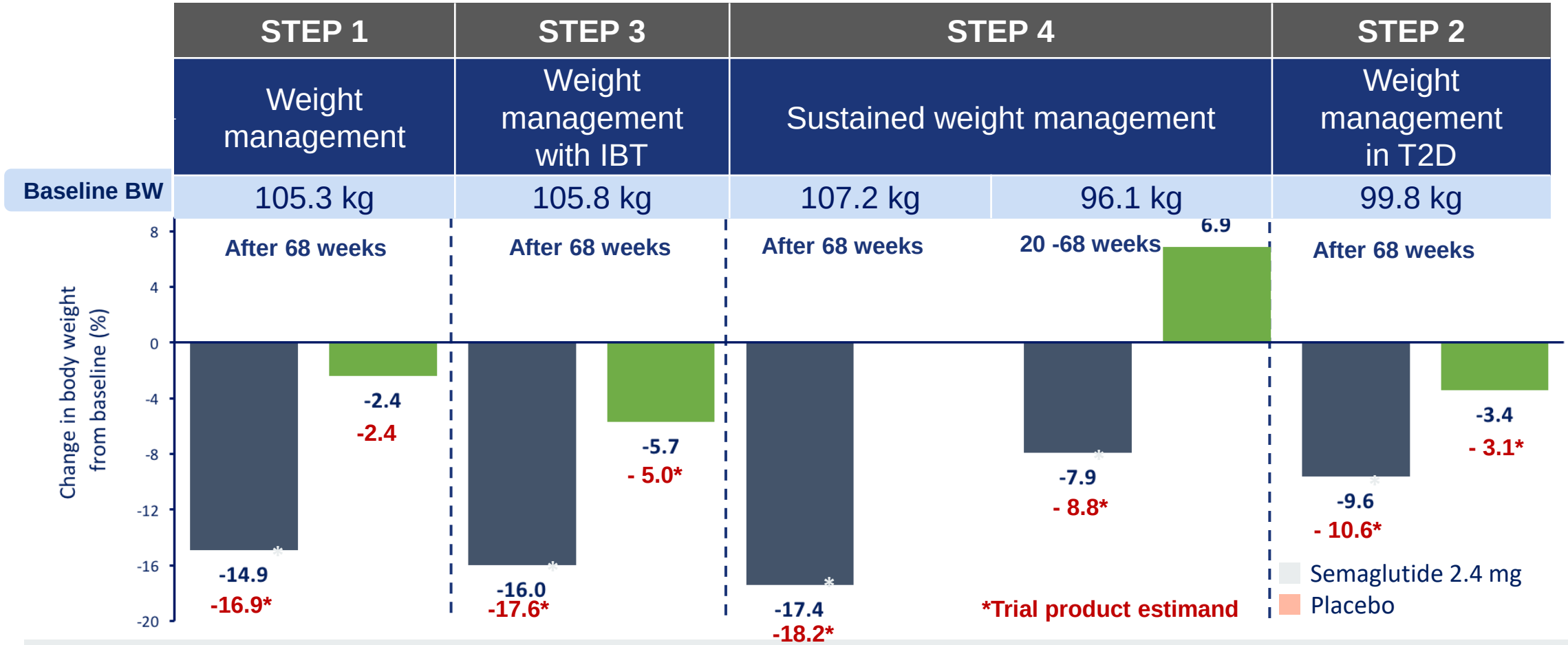
Weight Loss Efficacy of Obesity Management Medications (approved before 2017)



- Orlistat: 5.8-10.6%
- Phentermine: 4-6kg
- Phentermine-Topiramate: 8.6-10.5%
- Naltrexone/Bupropion: 6.1-6.4%
- Liraglutide: 6.1 – 8%

Chakhtoura *M, et al.* eClinicalMedicine 2023;58: 101882

STEP 1 – 7 Semaglutide 2.4 mg once-weekly for obesity treatment: Total Weight Loss 10.6 – 18.2%



Treatment policy estimand: Evaluates the treatment effect regardless of trial product discontinuation and use of rescue medication

*Statistically significant vs placebo. BW, body weight; IBT, intensive behavioural therapy.

Wilding et al. N Engl J Med 2021;384; Davies et al. Lancet 2021;397:971; *Wadden et al. JAMA 2021;325:1403-13*; Rubino et al. JAMA. 2021;325:1414.

Liraglutide 3.0 mg (Saxenda©) for Weight Loss and Remission of Pre-Diabetes. Real-World Clinical Evaluation of Effectiveness among Patients Awaiting Bariatric Surgery

% Weight loss at 6 & **12** months

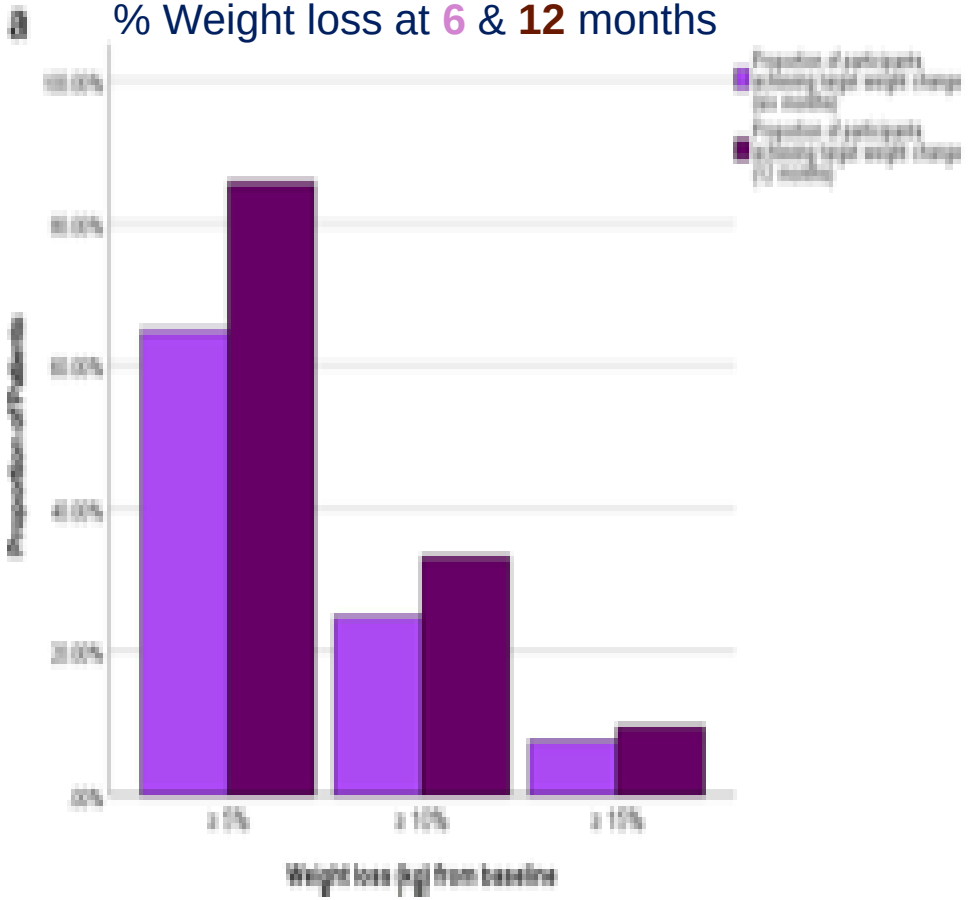


Table 1 Baseline characteristics of cohort

Characteristics	N	Mean
Age (years)	50	46.2
Baseline weight (kg)	50	153.8
Body mass Index (kg/m^2)	50	54.1

	WEIGHT (kg)				Body mass Index (kg/m^2)			HbA1c (mmol/mol)		
	Mean difference		SD	*P*-value	Mean difference	SD	*p*-value	Median	IQR	P-value
0 v 6 wks	-4.82		5.7	<0.001*	-1.56	2.6	<0.001*			
0 v 12 wks	-7.36	**4.8%**	23.9	0.043	-2.54	3.4	<0.001*	3.0	4.0	0.002*
0 v 26 wks	-10.9	**7.1%**	9.1	<0.001*	-3.67	3.5	<0.001*	4.7	4.5	<0.001*
0 v 52 wks	-14.0	**9%**	9.2	<0.001*	-4.64	4.0	<0.001*	5.5	4.95	0.009*

Remission of pre-diabetes at 6 & 12 month:
92.3% and 72.2% respectively.

Use of Semaglutide 1mg (DM) & Liraglutide 3mg (non-DM) for 1 year While on Wait List for MBS

Retrospective; N = 102, estimated time in wait list > 12 months; Mean Age 53 and Mean BMI ~43; Females ~70%

Weight Loss at 26 and 52 weeks by BMI categories

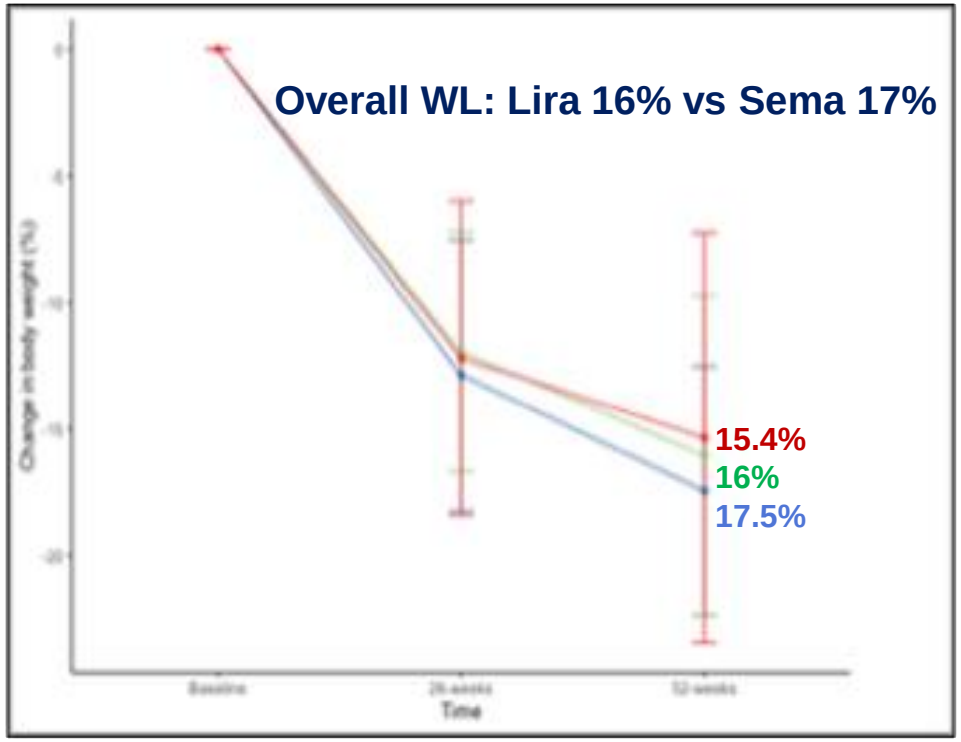
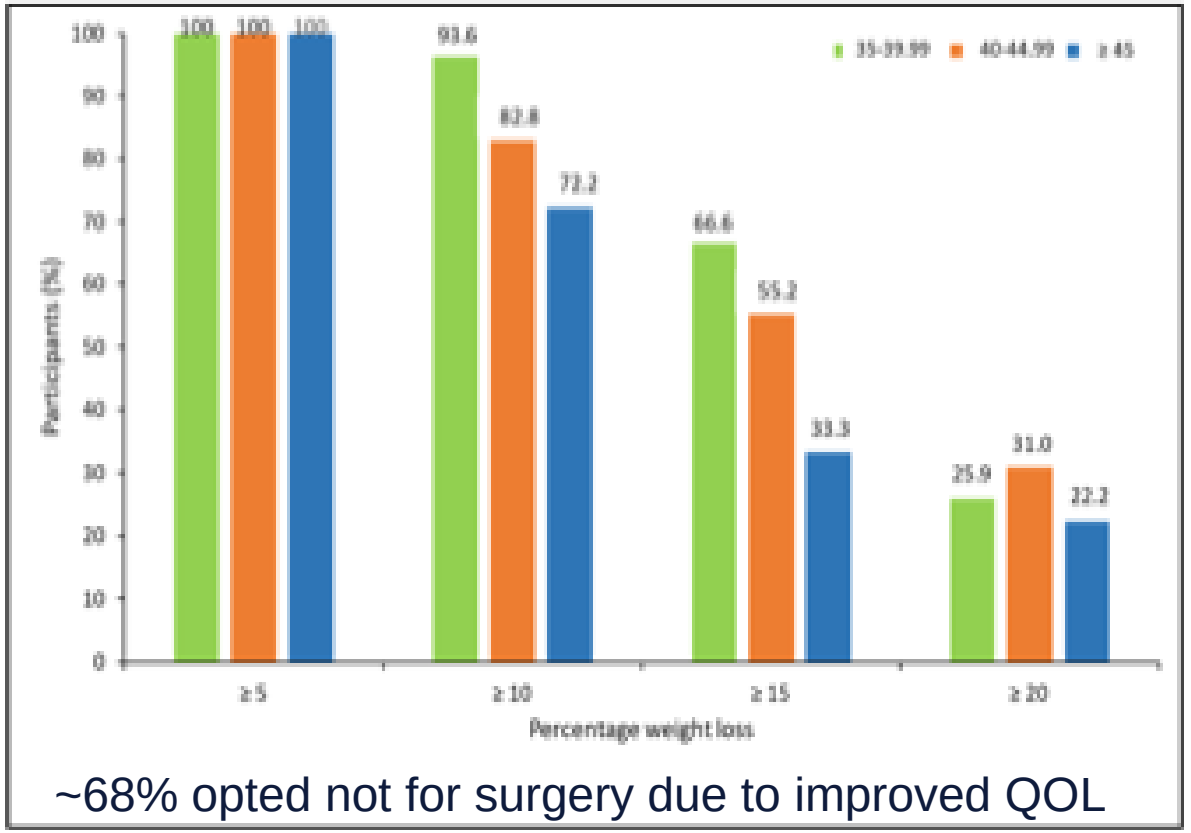


Figure 3. Changes in in percentage of weight loss at 26 and 52 weeks according to BMI range: 35–39.99 kg/m^2 (blue), 40–44.99 kg/m^2 (green), and >45 kg/m^2 (red).

Categorical Weight Loss at 52 weeks by BMI categories



~68% opted not for surgery due to improved QOL

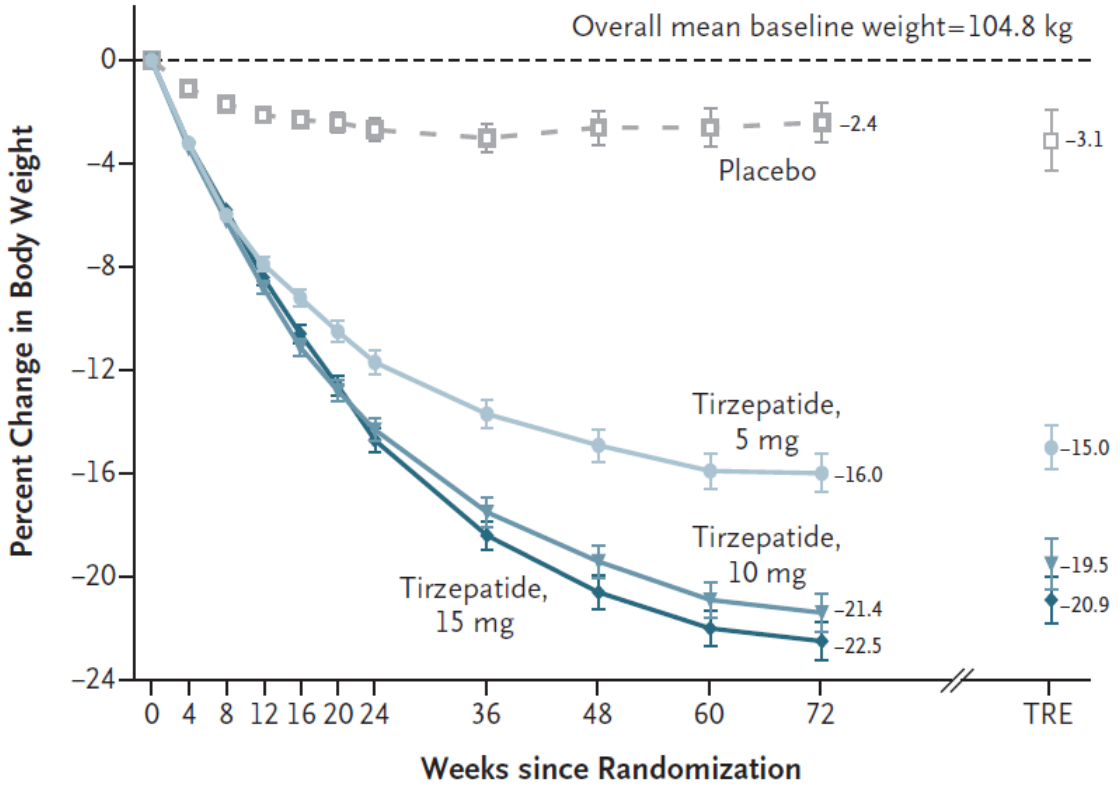
ORIGINAL ARTICLE

SURMOUNT-1

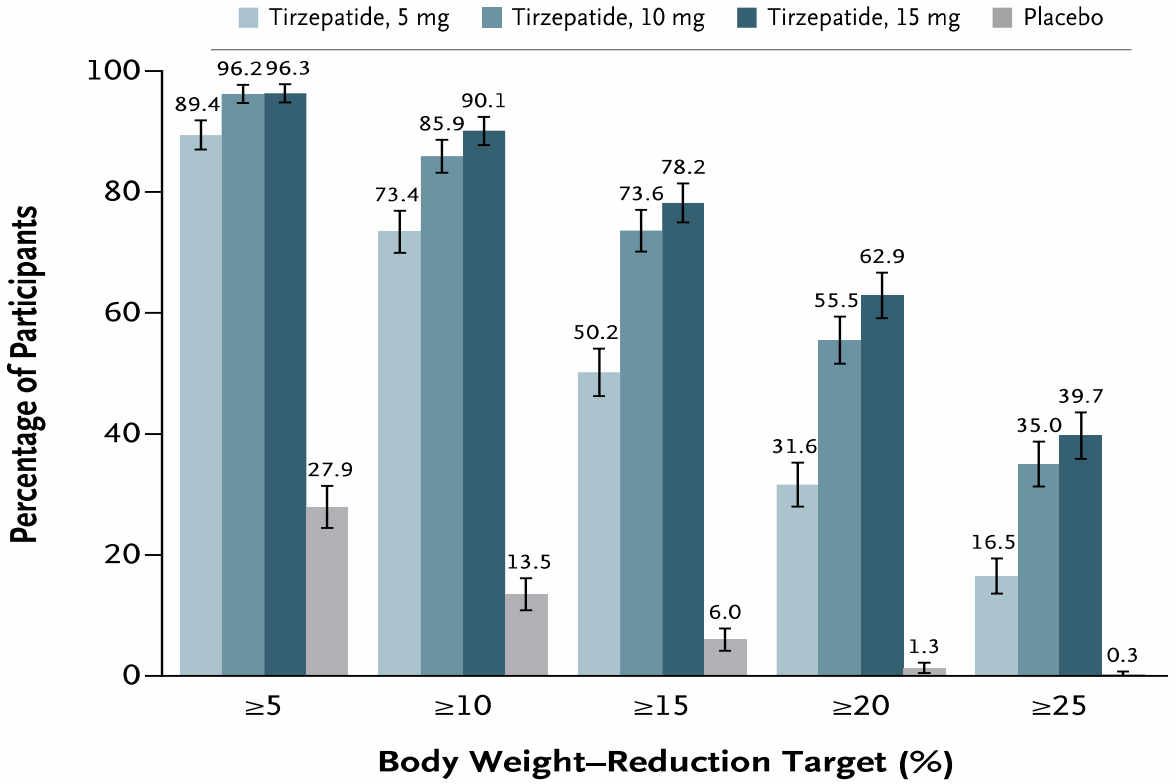
Tirzepatide Once Weekly for the Treatment of Obesity

USA,Argentina,Brazil,China,India, Japan, Mexico, Russia and Taiwan

B Percent Change in Body Weight by Week (efficacy estimand)



D Participants Who Met Weight-Reduction Targets (efficacy estimand)



Jastreboff A.M. et al. NEJM Online 4June2022; DOI: 10.1056/NEJMoa2206038

Use of phentermine-topiramate extended release in combination with sleeve gastrectomy in patients with BMI 50 kg/m^2 or more

Jamy D. Ard, M.D.[a,b,*], Daniel P. Beavers, Ph.D.[c], Erica Hale, M.S.[b], Gary Miller, Ph.D.[b,d], Stephen McNatt, M.D.[b,e], Adolfo Fernandez, M.D.[b,e]

- N = 25; BMI > 50kg/m^2; planned to undergo LSG
- Phentermine-Topiramate (PHN-Top, 7.5/46–15/92 mg/d) started at 3 months pre-op and continued for 2 years post-LSG

- Outcomes: Weight loss, BMI changes, and odds for achieving BMI 40 with PHN-Top vs Controls (BMI>50 and underwent LSG, without PHN-Top)

Ard JD, et al. Surg Obes Relat Dis 2019;15:1039

Use of Phentermine-Topiramate Pre-LSG in PwO with Mean BMI 61: ~16% weight loss pre-op achieved

Baseline characteristics of the study sample

Description	LSG alone (n = 40) mean ± SD or n (%)	LSG + phen/top (n = 15) mean ± SD or n (%)	Overall (n = 55) mean ± SD or n (%)
Age (yr)	45.0 ± 10.8	43.4 ± 7.3	44.6 ± 10.0
Female (%)	33 (82.5)	12 (80.0)	45 (81.8)
Initial weight (kg)	159.5 ± 21.0	178.9 ± 31.1	164.8 ± 25.4
Excess weight (kg)	89.5 ± 17.6	106.0 ± 26.3	94.0 ± 21.4
Preop weight (kg)	147.2 ± 17.4	150.8 ± 25.1	148.2 ± 19.6
Weight change, initial to preop (kg)	−12.3 ± 12.5 **7.7%**	-28.1 ± 12.8 **15.7%**	−16.6 ± 14.3
Initial BMI (kg/m^2)	57.0 ± 5.6	61.2 ± 7.1	58.1 ± 6.3
Preop BMI (kg/m^2)	52.7 ± 5.3	51.7 ± 6.2	52.4 ± 5.5
Operative time (min)	87.2 ± 22.2	100.4 ± 23.6	90.8 ± 23.1
Length of stay (d)	1.2 ± .4	1.3 ± .5	1.3 ± .4
Hiatal hernia repair (count)	7	5	12
30-d complication (count)	6	1	6

LSG = laparoscopic sleeve gastrectomy; SD = standard deviation; BMI = body mass index

Ard JD, et al. Surg Obes Relat Dis 2019;15:1039

Use of Phentermine-Topiramate Pre-LSG in PwO BMI>50 resulted in greater weight loss post-op and higher odds for achieving BMI<40 at 2 years

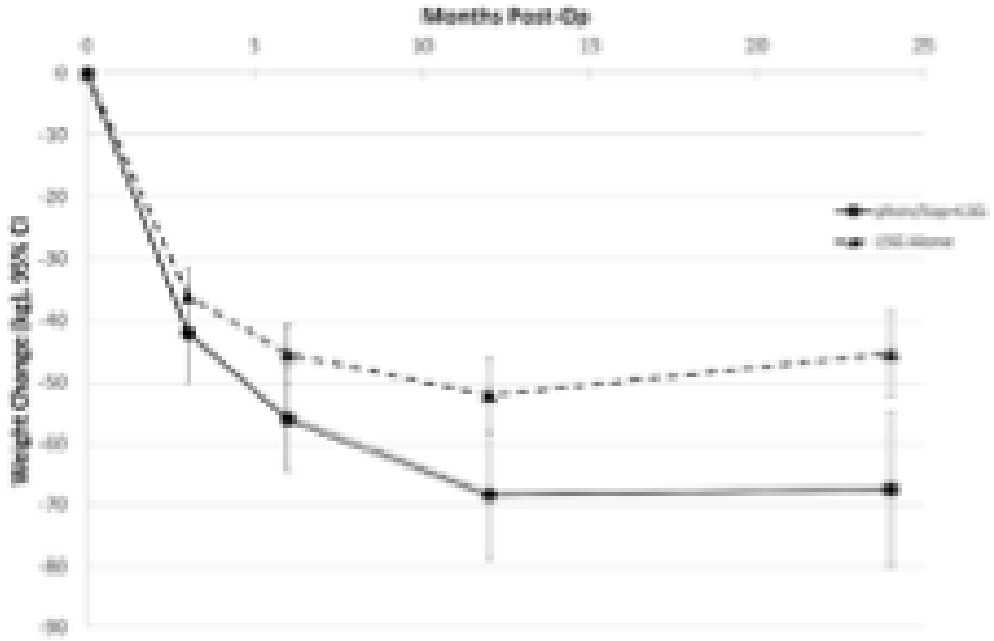


Fig. 1. Change in weight (kg) after laparoscopic sleeve gastrectomy (LSG) for those treated with phentermine and topiramate extended release (phen/top) + LSG versus LSG alone

- %TWL at 12 months: 39.3% (phen/top+LSG) vs –31.4% (control) (p=0.018)
- %TWL at 24 months: phen/top+LSG 11.2% greater initial weight loss (p=0.007).
- The odds ratio for achieving BMI <40 at 2 years was 4.1 (Phen/Top vs Controls)

Ard JD, et al. Surg Obes Relat Dis 2019;15:1039

OMM Use Prior to MBS

- **For Routine Pre-Operative Weight Loss to Reduce Post-op complications & Mortality**
  - Not routinely recommended
  - Pre-op weight loss does not correlate with post-op weight loss at 1 year
  - May benefit those with an anticipated long waiting time for MBS / Those unsure of MBS
  - Otherwise, case-by-case basis
- **As Adjunctive Therapy for those with very high BMI: Started Pre-Operatively and Continued Post-operatively**
  - For pre-op weight loss and greater (sustained) post-op weight loss akin to staged intervention
  - Patients with more severe obesity (i.e. obesity-related complications/comorbidities)
- **Choice of OMM**
  - Considerations as per any non-surgical patient with obesity

Considerations for OMM Use Prior to MBS

1) **Pre-op Weight Loss:**
   - Reduction in peri-op mortality and complications?
   - Greater long-term weight loss and outcomes?

2) Pre-op metabolic control especially T2D

Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures – 2019 update: cosponsored by American Association of Clinical Endocrinologists/American College of Endocrinology, The Obesity Society, American Society for Metabolic & Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists

R12. (2013)

- **Pre-procedure weight loss can reduce liver volume and may help improve the technical aspects of surgery in patients with an enlarged liver or fatty liver disease and therefore may be recommended before a bariatric procedure (Grade B; BEL 1; downgraded due to inconsistent evidence).**
- **Pre-procedure weight loss or medical nutritional therapy may be recommended to patients in selected cases to improve co-morbidities, such as pre-procedure glycemic targets (Grade D).**

R14. (2019*).

- **Pre-procedure glycemic control must be optimized using a diabetes comprehensive care plan, including healthy low-calorie dietary patterns, medical nutrition therapy, physical activity, *and, as needed, pharmacotherapy* (Grade A; BEL 1).**

Mechanick JI, et al. Surg Obes Relat Dis 2020;16:175

Pre-operative Glycemic Control as a Predictor of Diabetes Remission

- N=245 patients with diabetes pre-RYGB, 6-month intensive medical management to with goal of A1C<7%.
  - Patients who achieved a 1% decrease in A1C were 68% more likely to achieve diabetes remission at 1 year after surgery. (English et al. Obes Surg 2015)

- de Oliveira et al. (Obes Surg 2015): patients with A1C <7% were more likely to achieve postoperative diabetes remission than those with higher A1C (OR 2.43, 10%).

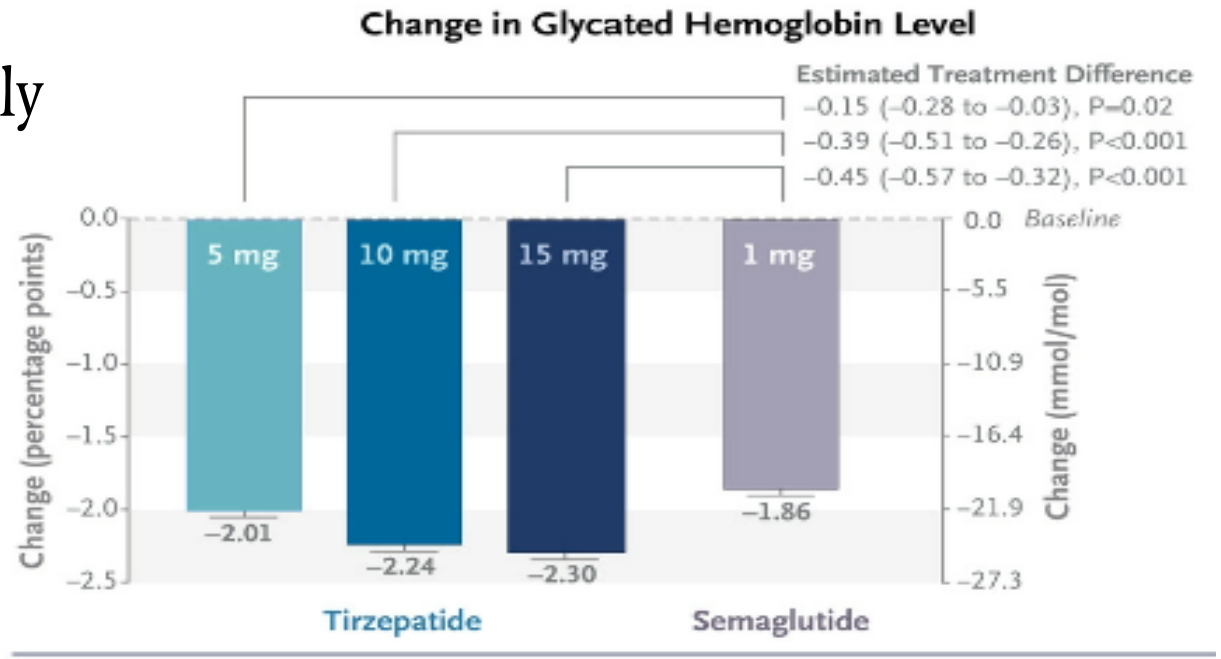
- N=39 with diabetes on insulin pre-RYGB: pre-op LCD for 14 days → reduced insulin doses by half → greater weight loss 1 year post-RYGB, and much higher rates of diabetes remission (72.7% vs 5.9%) (Biro JM et al. J Surg Res 2013)

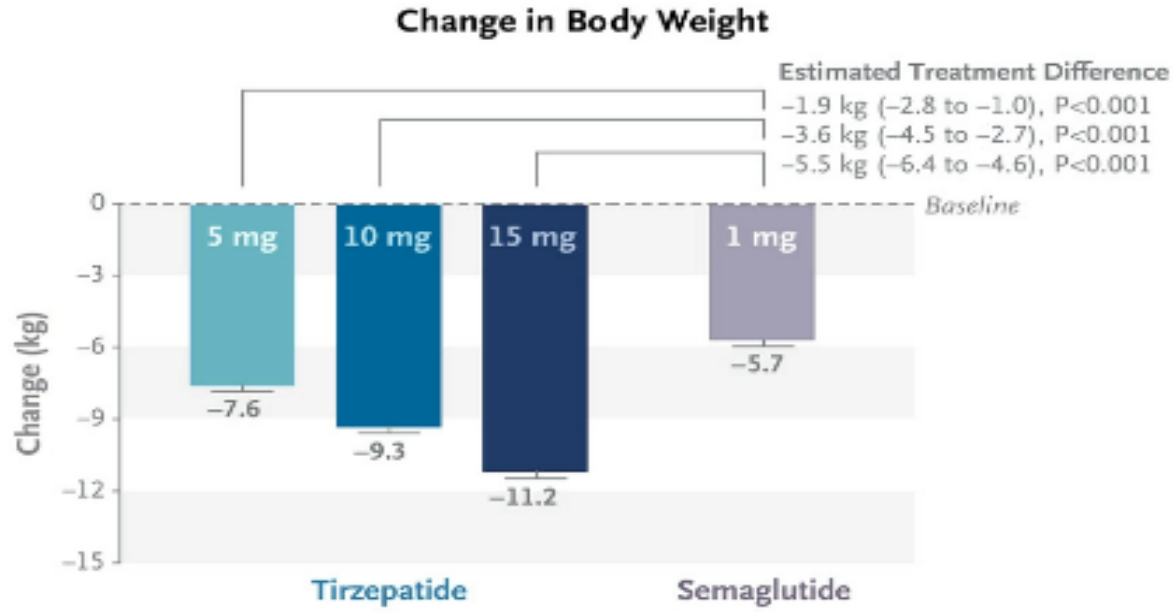
Carter J, et al. Surg Obes Relat Dis 2021; 17(12):1956

SURPASS 2

Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes

- Approved by the FDA as Mounjaro® (tirzepatide) in May 2022 for T2D and Zepbound in Nov 2023 for obesity
- Tirzepatide: 5 mg, 10 mg, or 15 mg vs semaglutide 1 mg QW

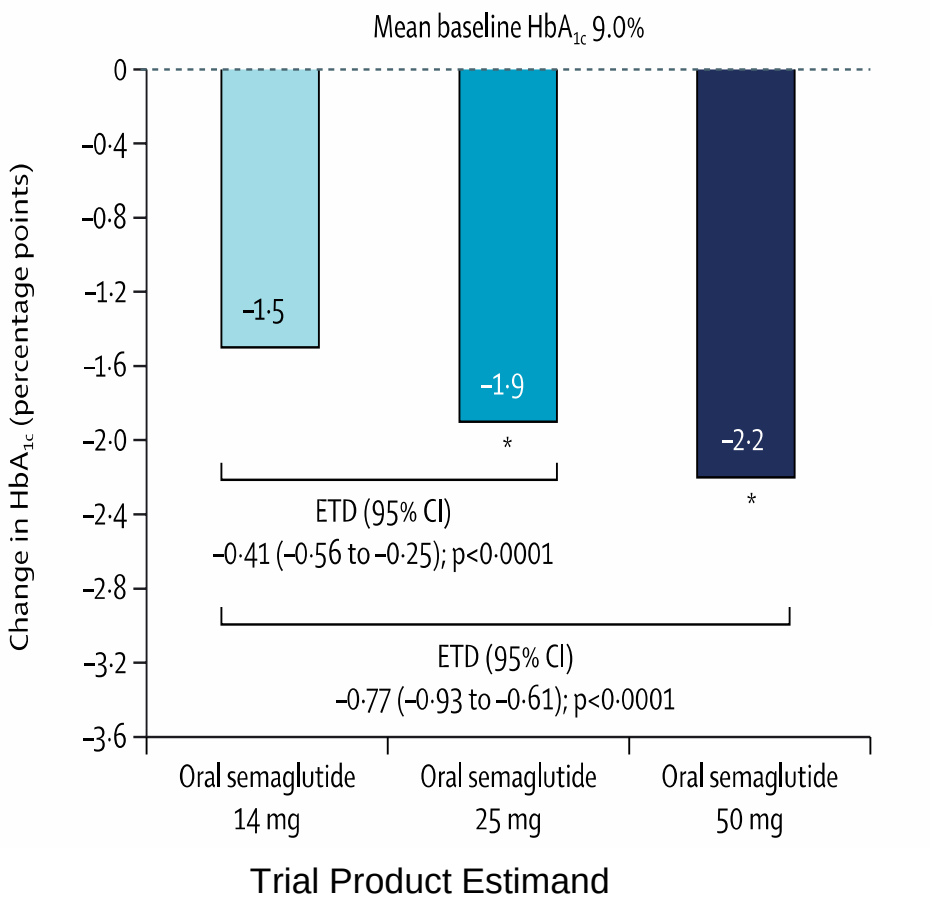


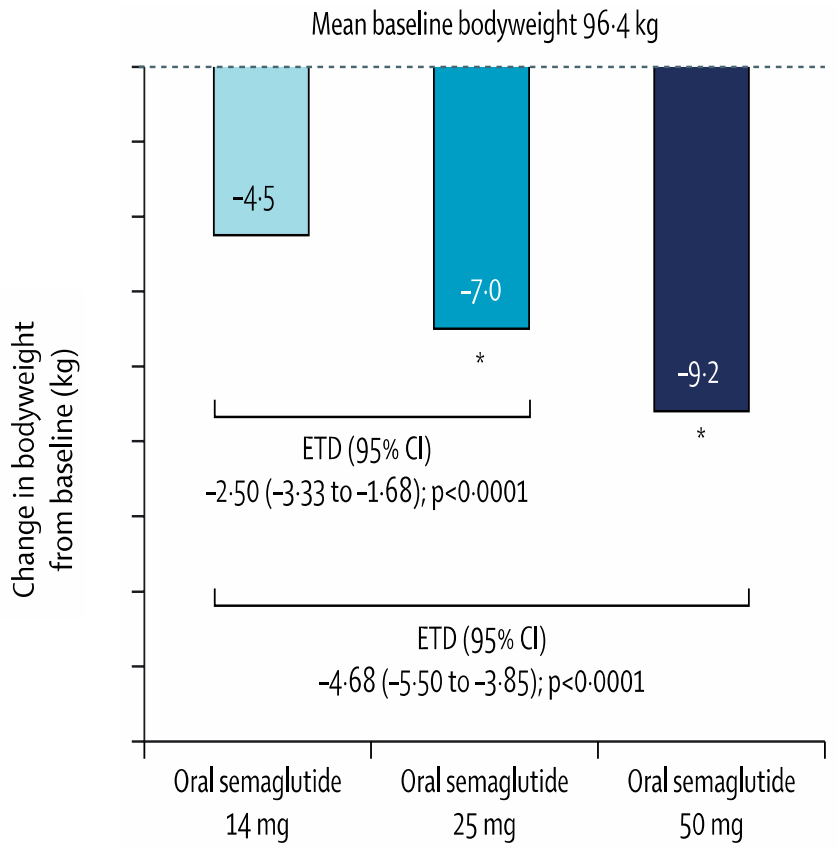


SURMOUNT 2: 15.7%

Efficacy and safety of once-daily oral semaglutide 25 mg and 50 mg compared with 14 mg in adults with type 2 diabetes (PIONEER PLUS): a multicentre, randomised, phase 3b trial

Vanita R Aroda, Jens Aberle, Lars Bardtrum, Erik Christiansen, Filip K Knop, Sanaz Gabery, Sue D Pedersen, John B Buse





- N=1606
- ~20% Asians
- 43% taking at least 1 OHA (1-3 OHAs, no insulin)
- Up to 16/52 titration
- 68-week duration

Lancet June 26, 2023 doi.org/10.1016/ S0140-6736(23)01127-3

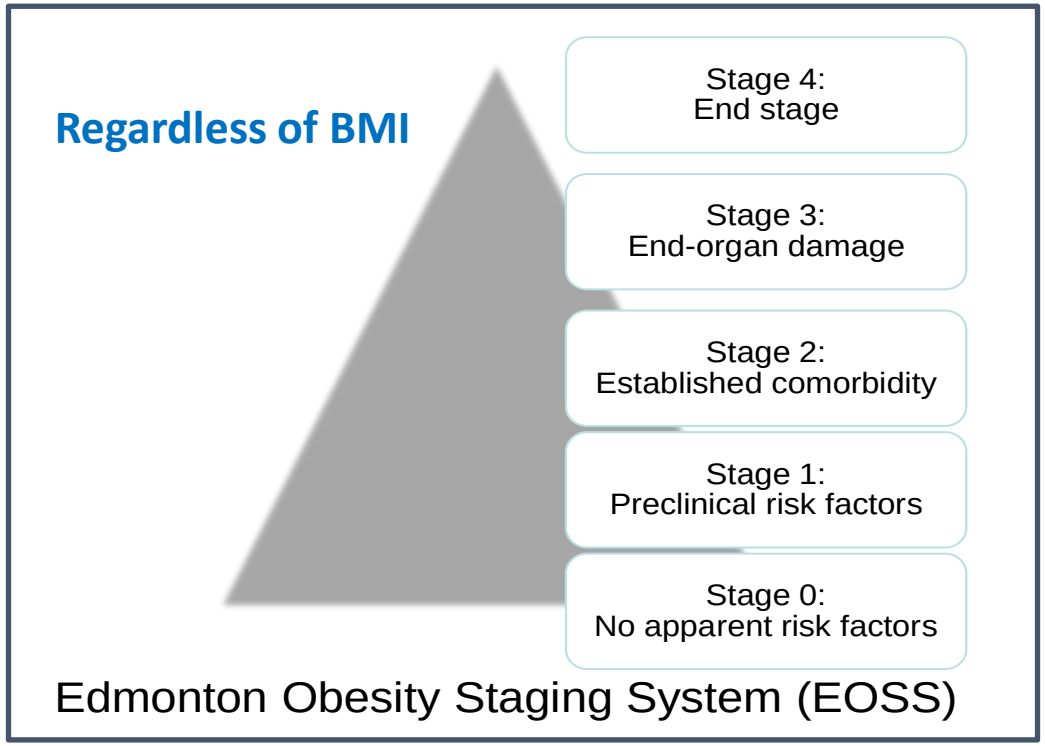
Considerations for OMM Use Prior to MBS

1) **Pre-op Weight Loss:**
   - Reduction in peri-op mortality and complications?
   - Greater long-term weight loss and outcomes?

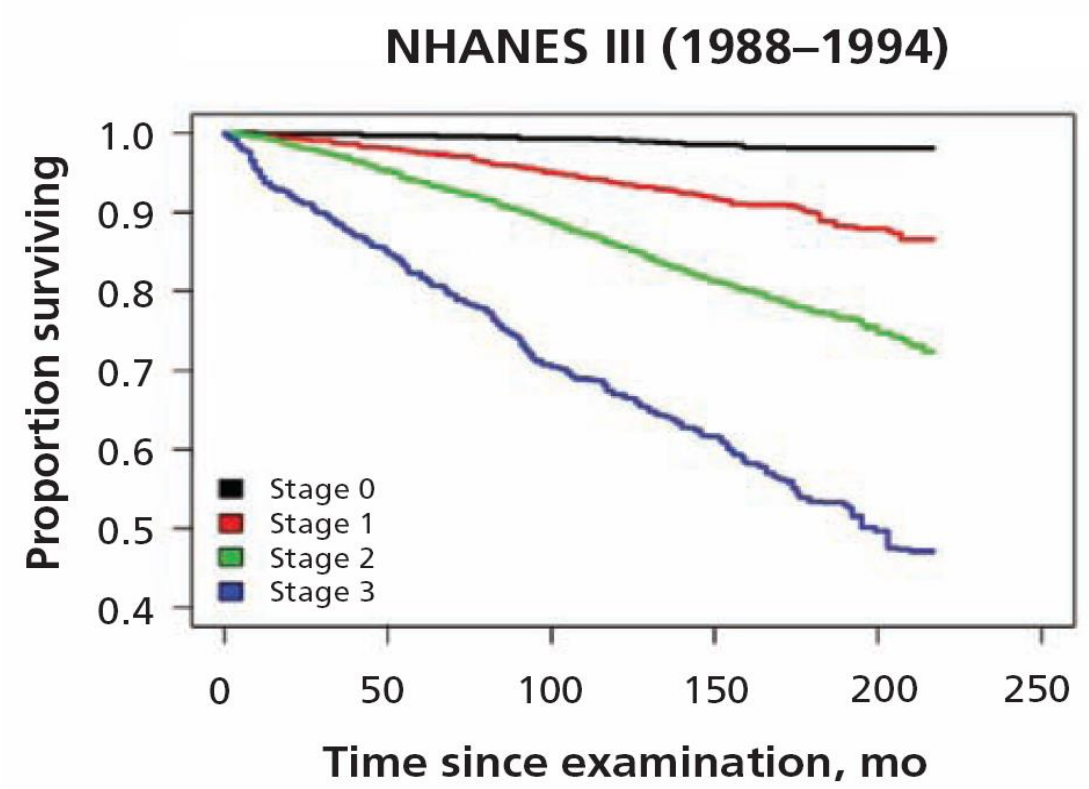
2) Pre-op metabolic control especially T2D

3) Pre-op control of obesity-related complications

Complication (Chronic Disease)-Centric Model of Care: Firstly, assess obesity-related health impact



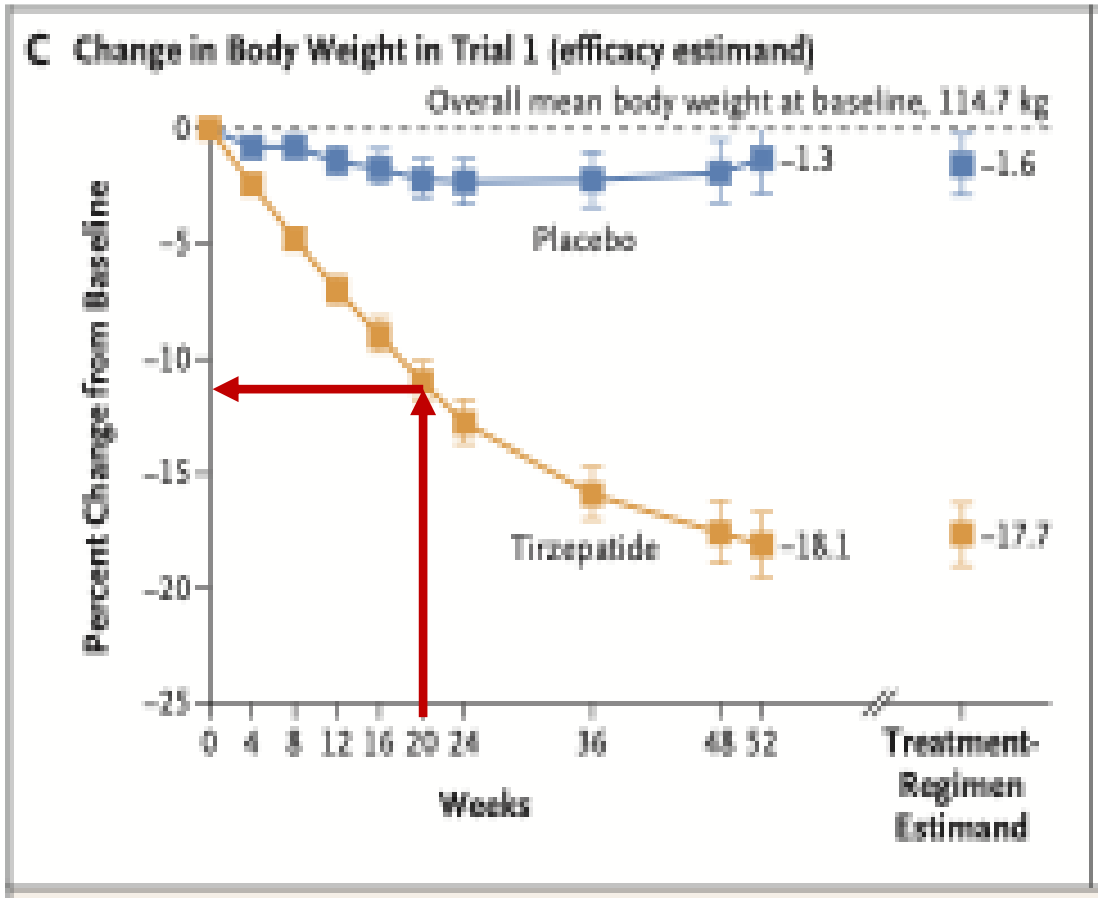
Sharma AM, Kushner RF. *Int J Obes*. 2009;33(3):289

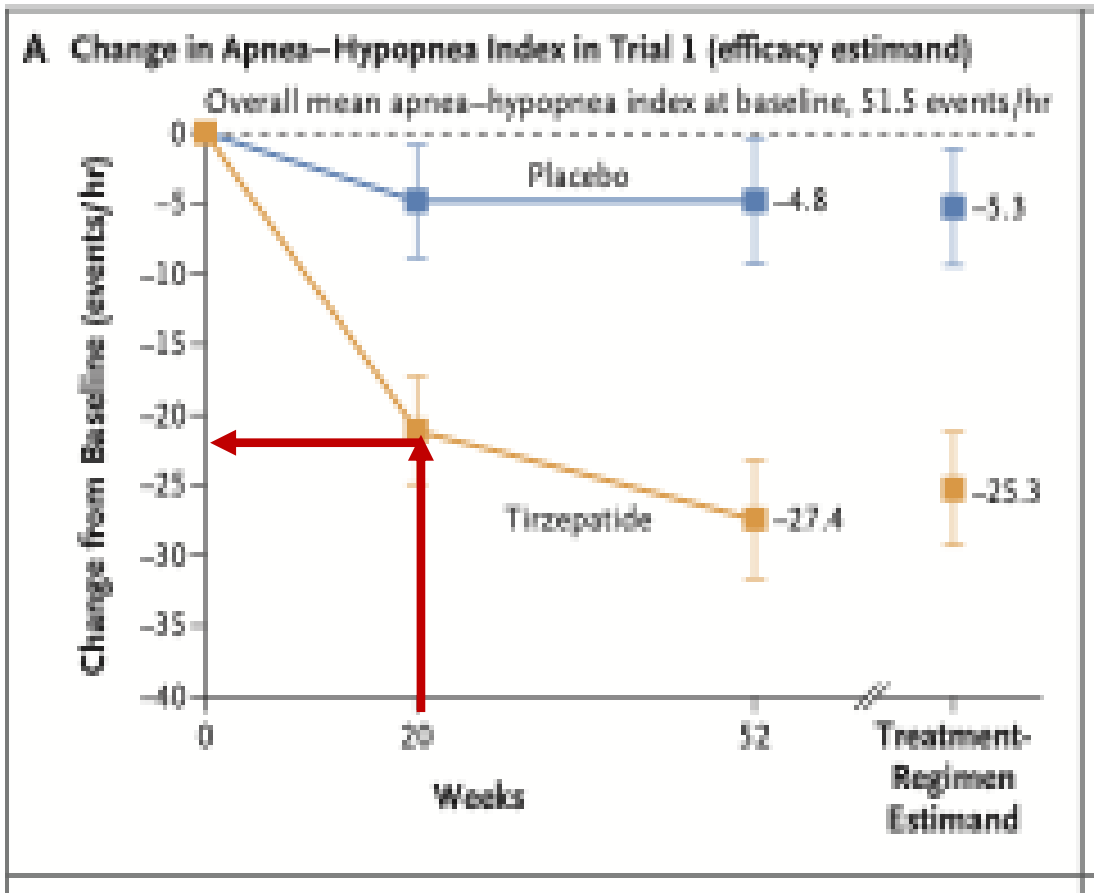


Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity

SURMOUNT-OSA

Not on CPAP





Malhotra A, et al. NEJM Online June 21, 2024. DOI: 10.1056/NEJMoa2404881

RANDOMIZED TRIAL OF EXTENDED-RELEASE PHENTERMINE/TOPIRAMATE FOR OSA

http://dx.doi.org/10.5665/sleep.2204

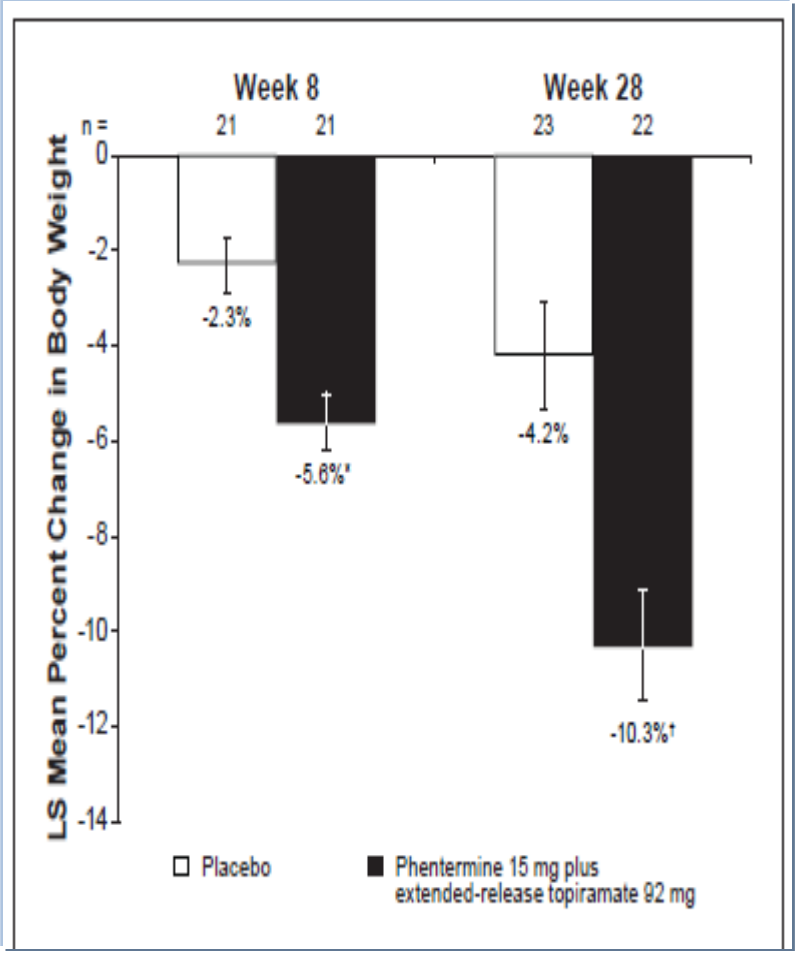
A Randomized, Double-Blind, Placebo-Controlled Study of an Oral, Extended-Release Formulation of Phentermine/Topiramate for the Treatment of Obstructive Sleep Apnea in Obese Adults

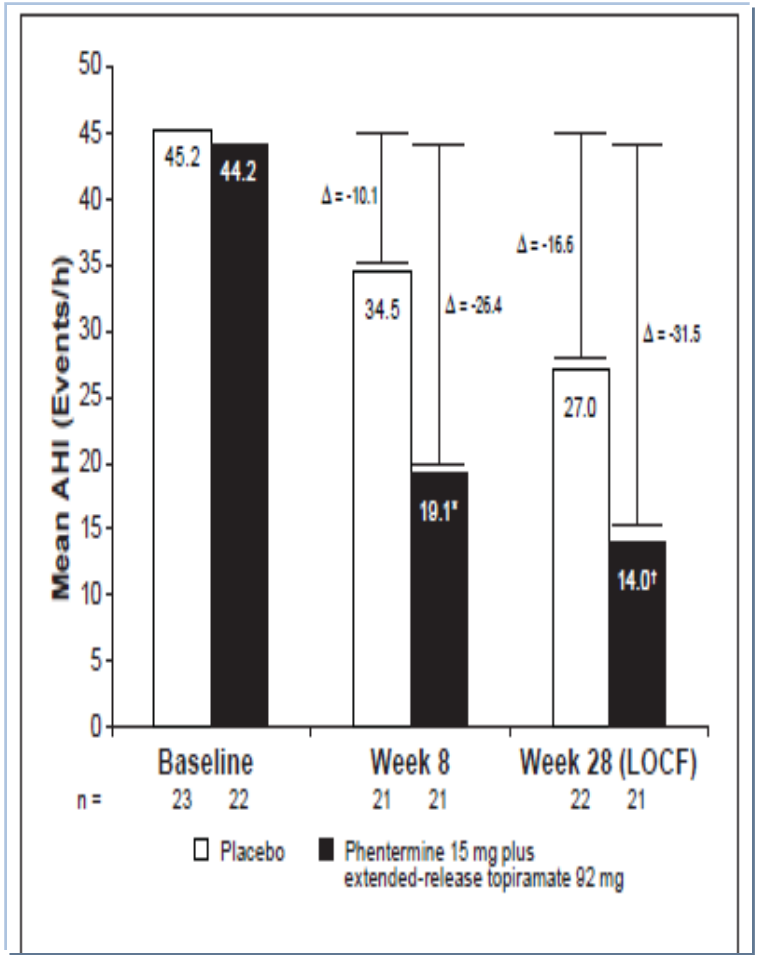
David H. Winslow, MD[1]; Charles H. Bowden, MD[2]; Karen P. DiDonato, RN, MSN[2]; Pamela A. McCullough, PhD[1]

Table 2—Baseline obstructive sleep apnea parameters (collected via overnight PSG; ITT)

Parameter	Placebo (n = 23)	Phentermine 15 mg plus Extended-Release Topiramate 92 mg (n = 22)
AHI, events/h (SD)	45.2 (34.25)	44.2 (22.40)
RDI, events/h (SD)	60.7 (31.78)	58.8 (21.24)
Mean overnight oxygen saturation, % (SD)	93.9 (2.39)	93.4 (1.99)
Minimum overnight oxygen saturation, % (SD)	76.3 (13.88)	77.1 (13.59)
Arousal index, arousals/h (SD)	63.5 (30.49)	61.5 (20.27)
Apnea index, events/h (SD)	16.1 (24.23)	9.4 (15.95)
Hypopnea index, events/h (SD)	29.1 (18.78)	34.8 (18.76)

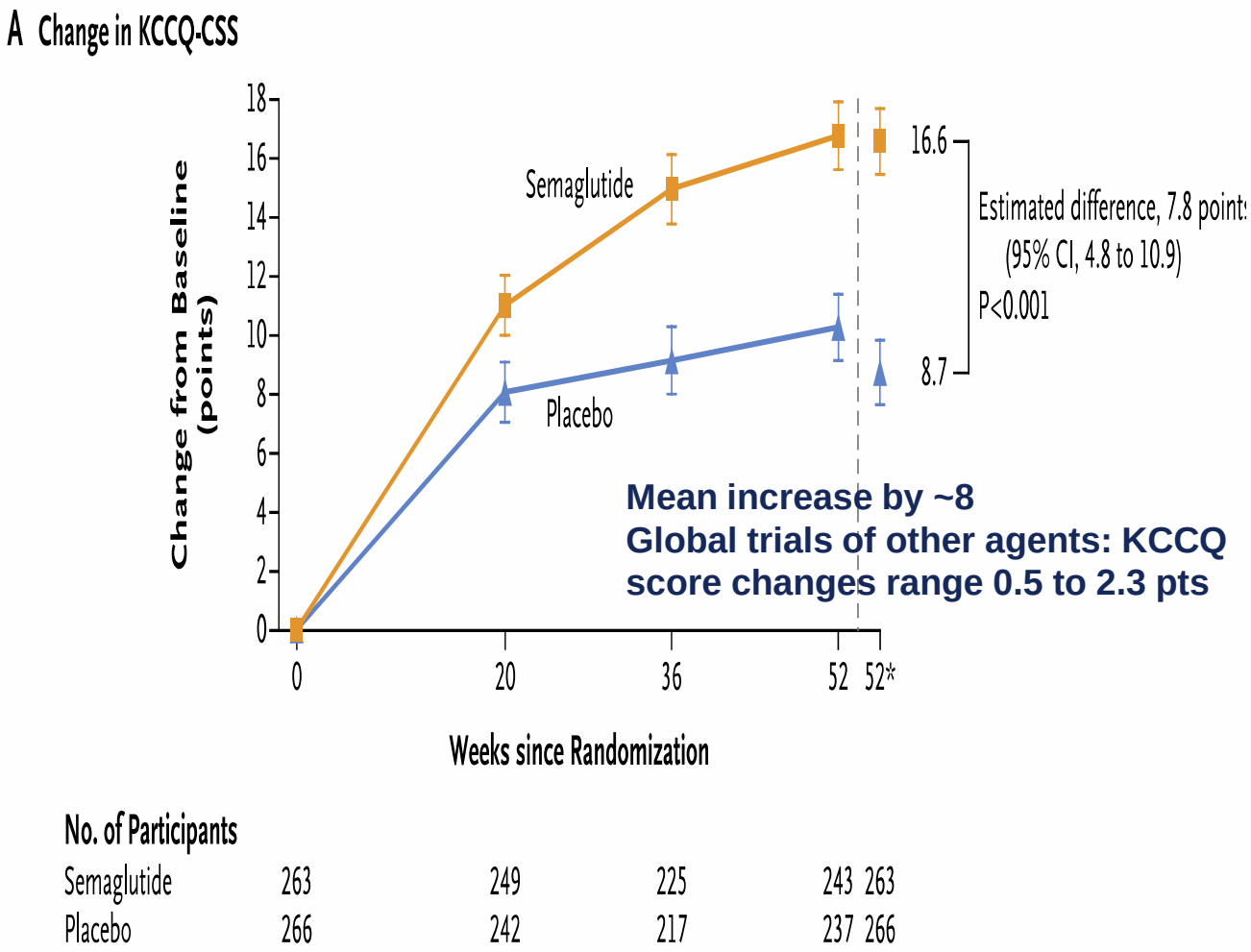
AHI, apnea-hypopnea index; ITT, intent to treat; PSG, polysomnography; RDI, respiratory disturbance index; SD, standard deviation.

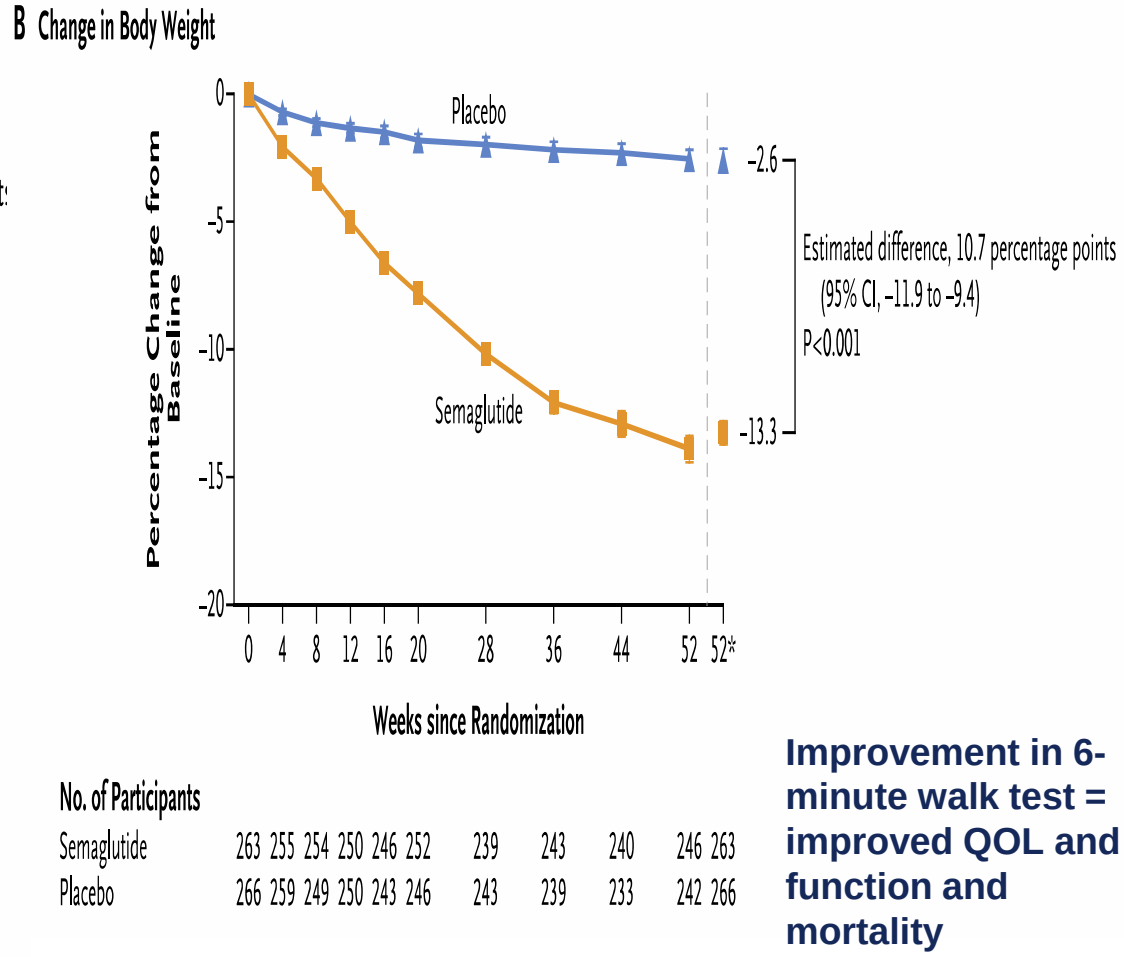




Semaglutide 2.4mg/week in HFpEF (STEP HFpEF): greater reduction in HF symptoms, improvement in physical function

N=529 patients; HFpEF with BMI≥30kg/m^2; Median BMI 37.2kg/m^2 (66% with BMI≥35); 97% white; Median LVEF 57%; NYHA II (66%); 58% with AFib



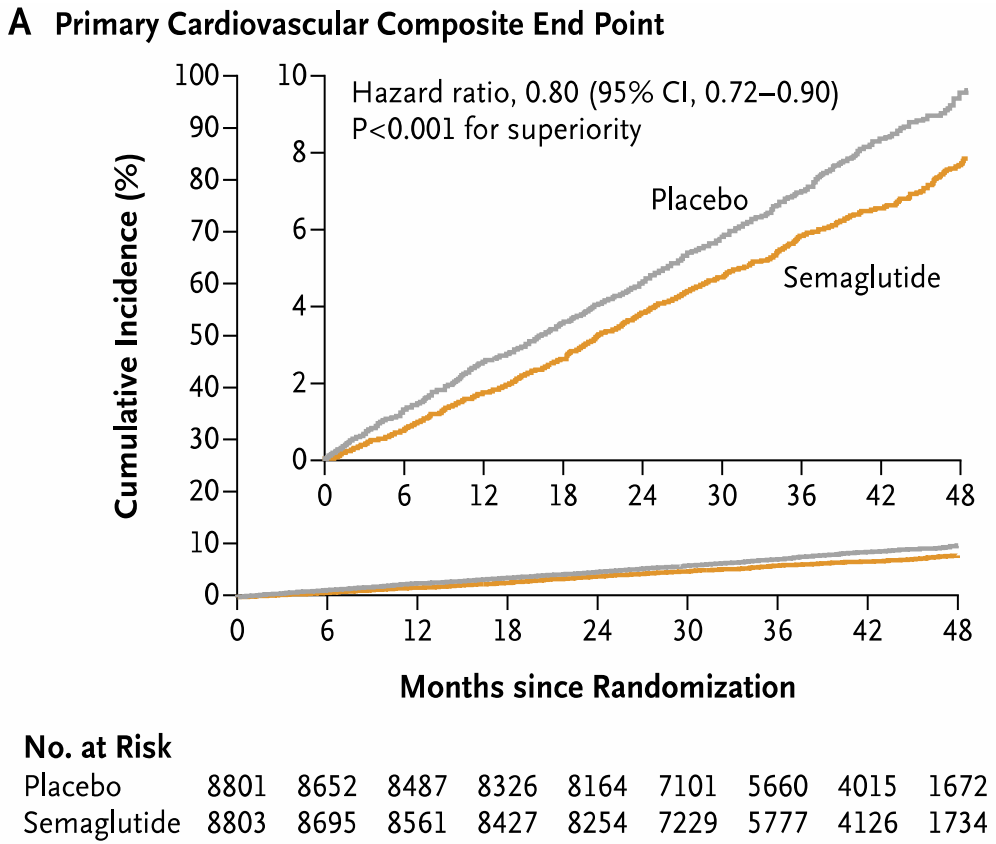


Improvement in 6-minute walk test = improved QOL and function and mortality

Lincoff A.M, et al. N Engl J Med 2023; 389:2221

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes **(SELECT)**

- ✓ N = 17,605, Age≥45 yrs, BMI≥27kg/m^2
- ✓ With pre-existing CVD (MI, stroke, PAD) but without DM.



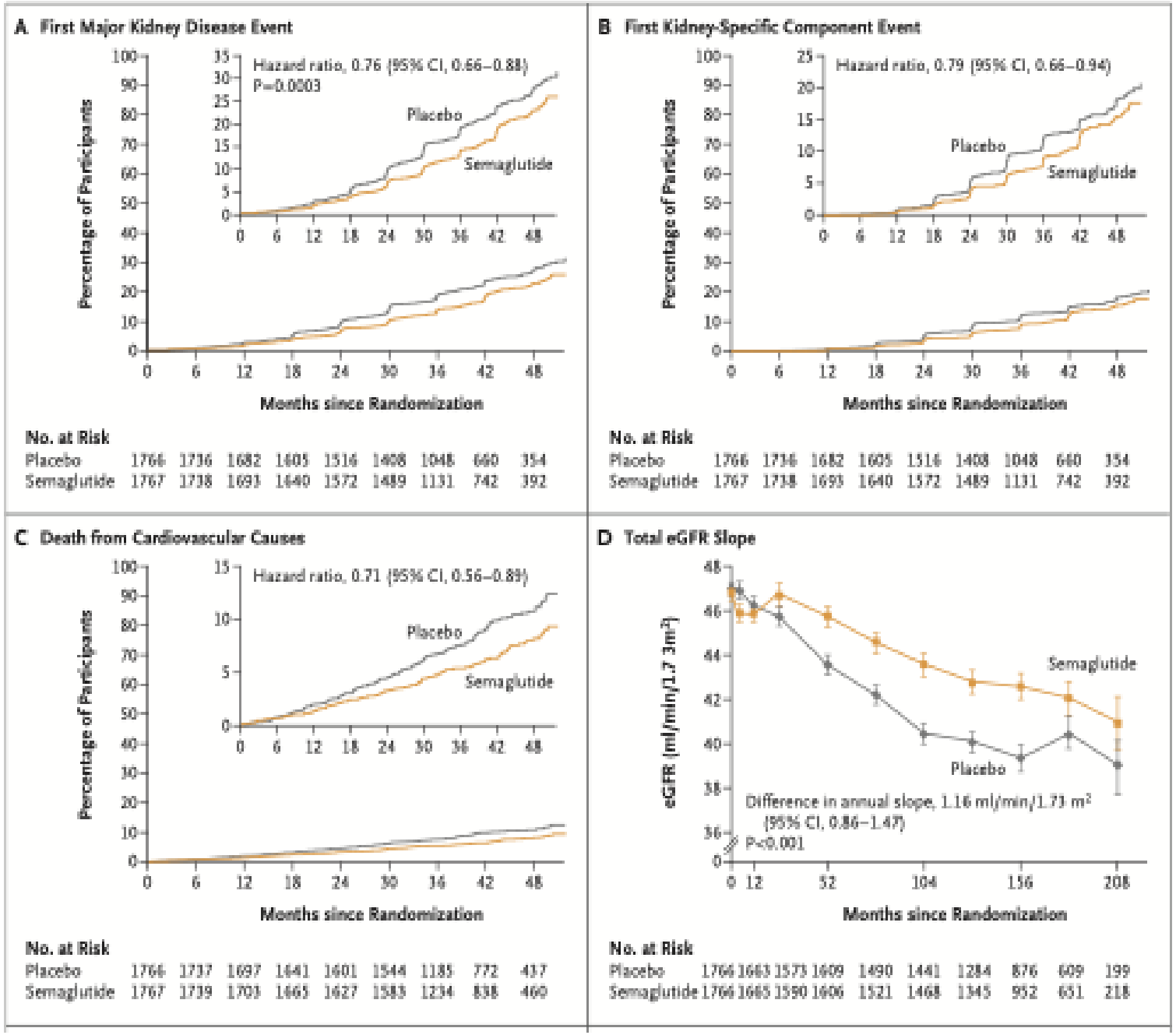
Treatment with semaglutide 2.4mg was associated with a statistically significant **20% reduction in major adverse cardiovascular events (MACE)**, defined as cardiovascular death, nonfatal myocardial infarction or nonfatal stroke compared with placebo, driven mostly by non-fatal MI (HR 0.72).

Wt loss 9.4% (sema) vs 0.9% (placebo) at 108 months

FLOW Trial (Evaluate Renal Function with Semaglutide Once Weekly)

- In 3553 pts with T2D + CKD, semaglutide 1mg was associated with a statistically significant **reduction in renal outcomes (24%),** in cardiovascular death (29%), major CV events (18%) and death from any cause (20%)

- Median follow-up: 3.4 years
- Direct renal effects of GLP1RA



Perkovic V, et al. N Engl J Med published online 24May24; DOI: 10.1056/NEJMoa2403347

OMM Use Prior to MBS

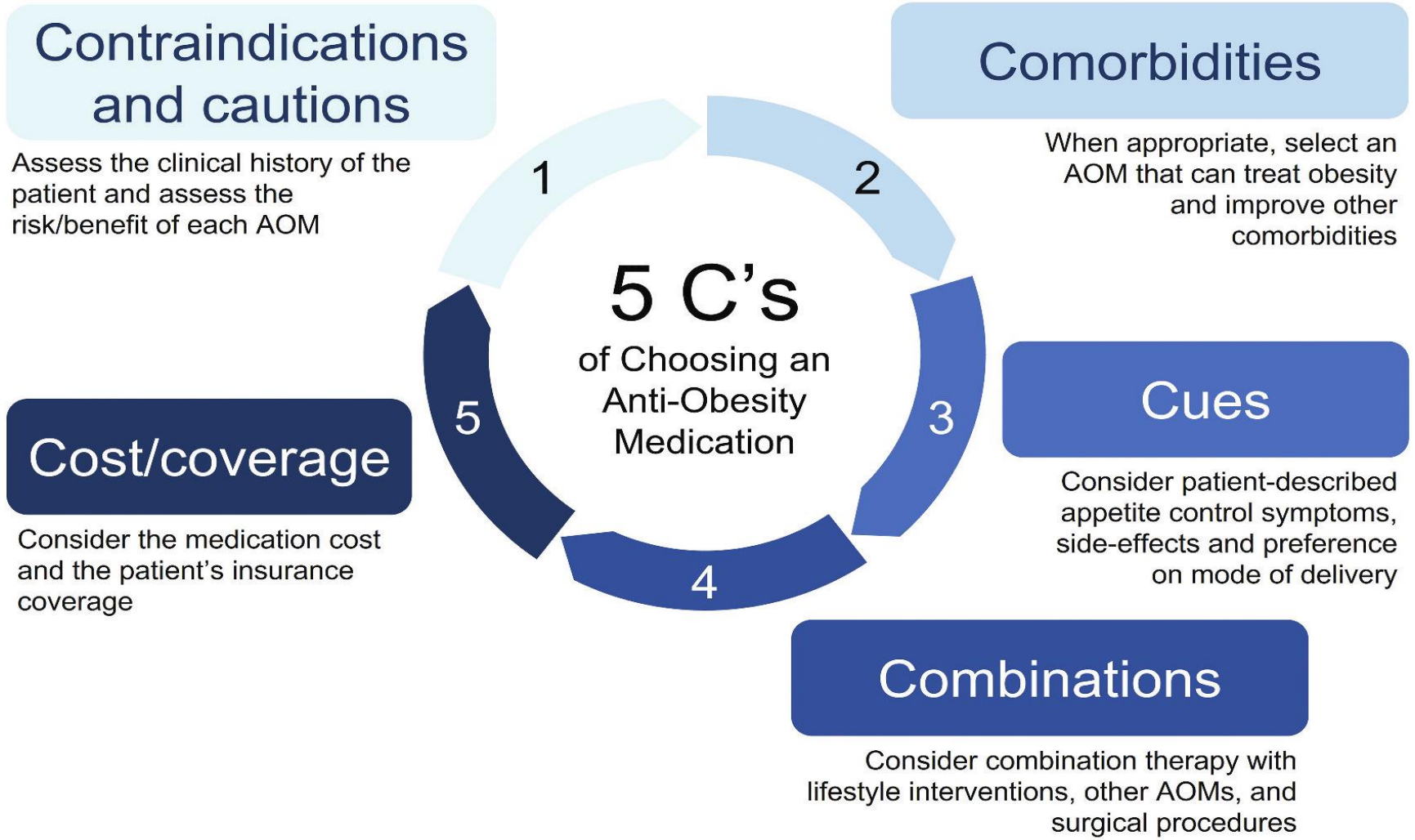
- **For DM control**
  - Strongly recommended with use of meds if needed

- **For Pre-operative Control of Obesity-Related Complications/Comorbidities (ORC):**
  - Patients unable to afford or tolerate CPAP, with severe ORCs which will increase peri-op risk
  - Those with an anticipated long waiting time for MBS: to improve and/or reduce progression of ORC
  - With aim to reduce short- and long-term complications

Considerations for OMM Use Prior to MBS

1) **Pre-op Weight Loss:**
   - Reduction in peri-op mortality and complications?
   - Greater long-term weight loss and outcomes?
2) **Pre-op metabolic control especially T2D**
3) **Pre-op control of obesity-related complications**
4) ***Patient selection: Access and other considerations***

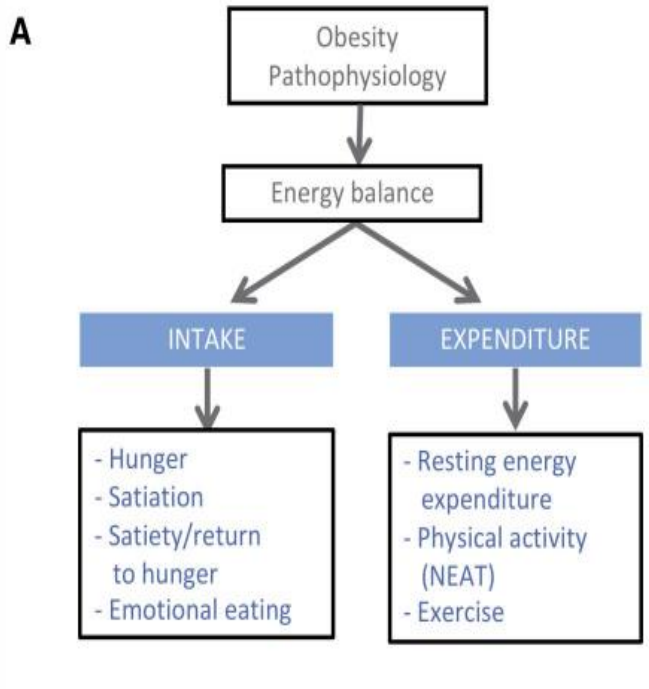
The 5Cs of Choosing an OMM



Horn D.B., et al. Postgraduate Medicine 2022; 134 (4):359.

Selection of Antiobesity Medications Based on Phenotypes Enhances Weight Loss: A Pragmatic Trial in an Obesity Clinic

- N = 312 presenting to Mayo Clinic for obesity management
- Measurements done: used to classify 4 obesity phenotypes



- 85% phenotype found
- 27% ≥ 2 phenotypes found

- Abnormal satiation ("hungry brain"): **phentermine-topiramate** extended release at a dose of 7.5/46 mg daily or lorcaserin at 20 mg daily
- Abnormal hedonic eating ("emotional hunger"): **naltrexone/bupropion** sustained release at a dose of 16/180 mg twice daily
- Abnormal satiety ("hungry gut"): **liraglutide 3 mg** subcutaneous daily
- Low predicted energy expenditure ("slow burn"): phentermine 15 mg daily plus increased resistance training.

Acousta A, et al. Obesity 2021;69:662

Available pharmacotherapy options in South-SouthEast Asia

*Choice and duration of obesity medication should be made with respect to the **individual's clinical characteristics and the country-specific approved labeling** of the available products.*

Pharmacotherapeutic options for managing obesity in South/Southeast Asia *(Aug 2024 Update)*

	Orlistat	Liraglutide 3.0 mg	Phentermine*	Naltrexone ER/ bupropion ER	Semaglutide 2.4mg
Bangladesh	✓	✓			
Brunei Darussalam	✓	✓			
India	✓				
Indonesia	✓	✓			
Malaysia	✓	✓	✓	✓	**Registered**
Philippines	✓	✓†	✓		**Registered**
Singapore	✓†	✓†	✓	✓	**Registered**
Sri Lanka	✓	✓			
Thailand	✓	✓†	✓	✓	**Registered**
Vietnam	✓	✓			

**Phentermine is approved only for short-term use (≤12 weeks) †Approved for use in adolescents ≥12 years old.*

ER, extended-release

† Approved for use in adolescents ≥12 years old.

Tham KW et al. Obesity Reviews. 2023;e13520

OBESITY MANAGEMENT MEDICATION:
IS THERE A ROLE PREOP?

YES but in Selected Patient Populations

- *Those with very high BMI akin to "staged intervention"*
- *Those with anticipated long wait time to MBS*
- *Those with severe obesity / ORC: to control ORC, reduce morbidity*

Choice of OMM needs to take into consideration patient characteristics/phenotype, contraindications, preference, cost, access and those with proven direct benefits

Thank you for your kind attention!

Weight (BMI)-Centric Treatment Approach

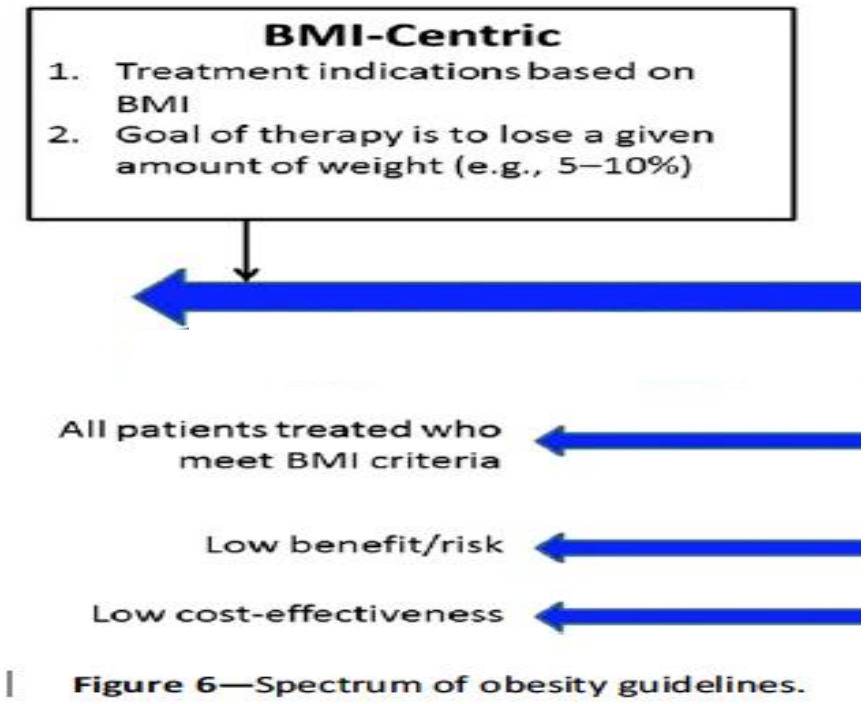
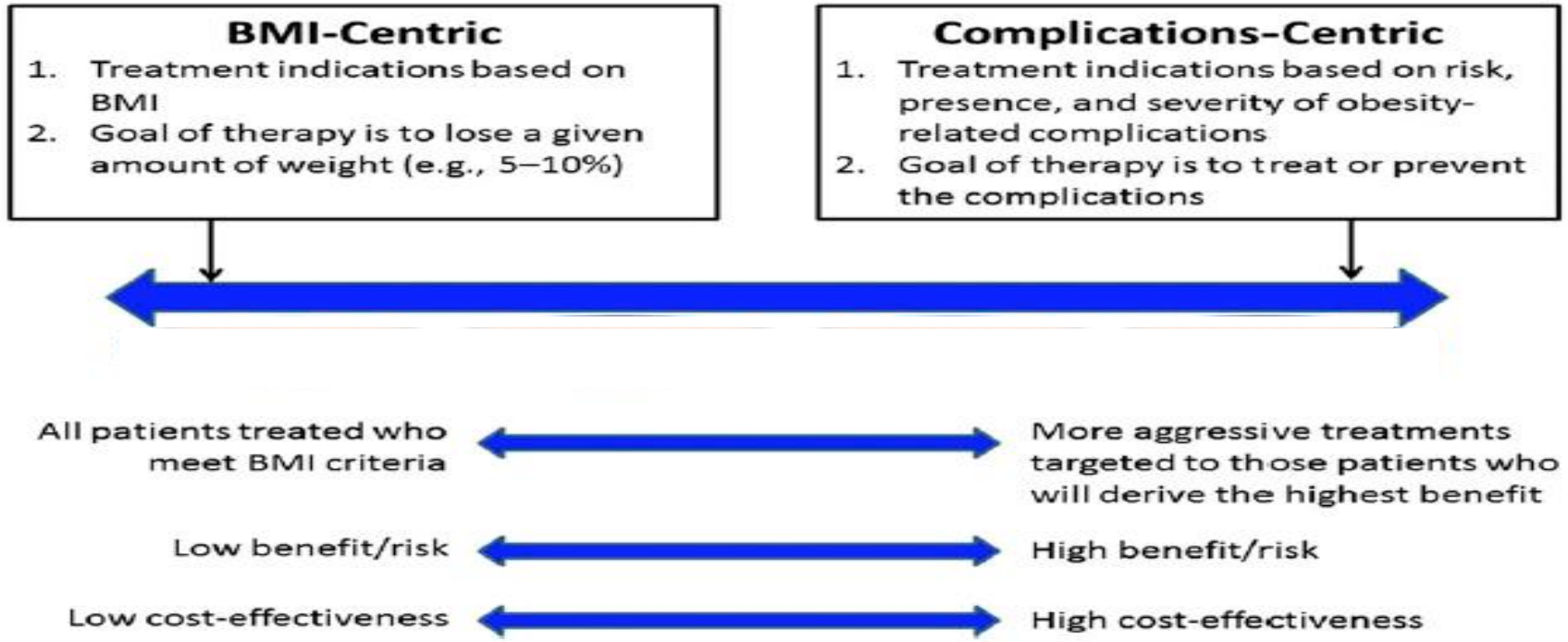


Figure 6—Spectrum of obesity guidelines.

Cefalu, W.T., et al., Diabetes Care 2015; AACE/ACE Obesity CPG. Endocr Pact. 2016

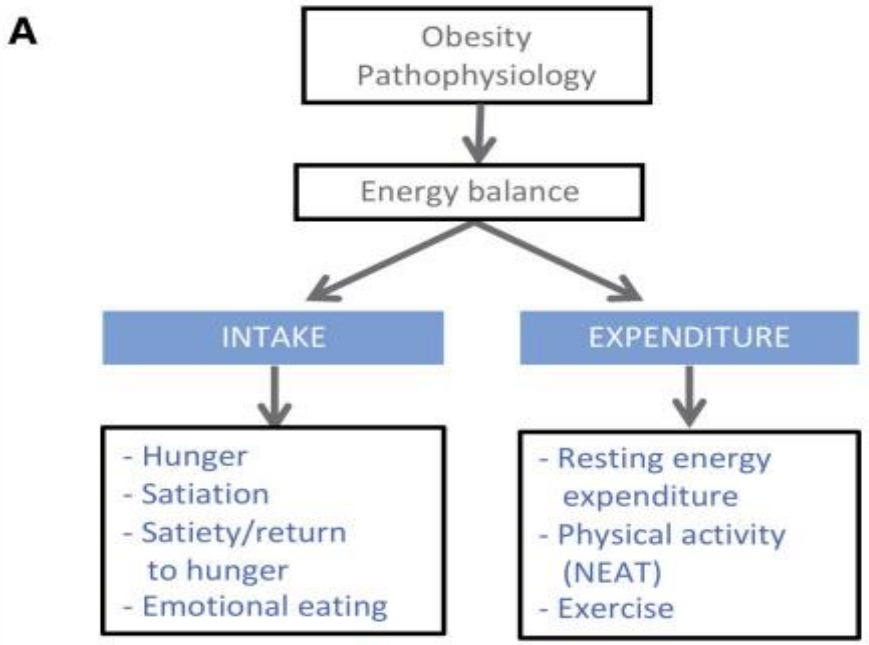
Complication-Centric Approach Risk Stratifies and Prioritizes Those Most Impacted for Treatment



Cefalu, W.T., et al., Diabetes Care 2015; AACE/ACE Obesity CPG. Endocr Pact. 2016

Selection of Antiobesity Medications Based on Phenotypes Enhances Weight Loss: A Pragmatic Trial in an Obesity Clinic

- N = 312 presenting to Mayo Clinic for obesity management
- Measurements done: Body composition, REE, questionnaires on eating behaviour (hedonic), satiety, satiation, affect, PA → used to classify 4 obesity phenotypes



- **Hungry brain = abnormal satiation**
- **Emotional hunger = hedonic eating**
- **Hungry gut = abnormal satiety**
- **Slow burn = decreased metabolic rate**

Singapore General Hospital

Figure 1 Study design. Acousta A, et al. Obesity 2021;69:662