Use of GLP-1RA agonist therapy in management of obstructive sleep apnea (OSA)

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Disclosures

- There are no relevant financial conflicts to report
- Off-label medication use will not be discussed

Learning objectives

After this lecture, you should be able to:

Understand common pathophysiology between obesity and sleep apnea

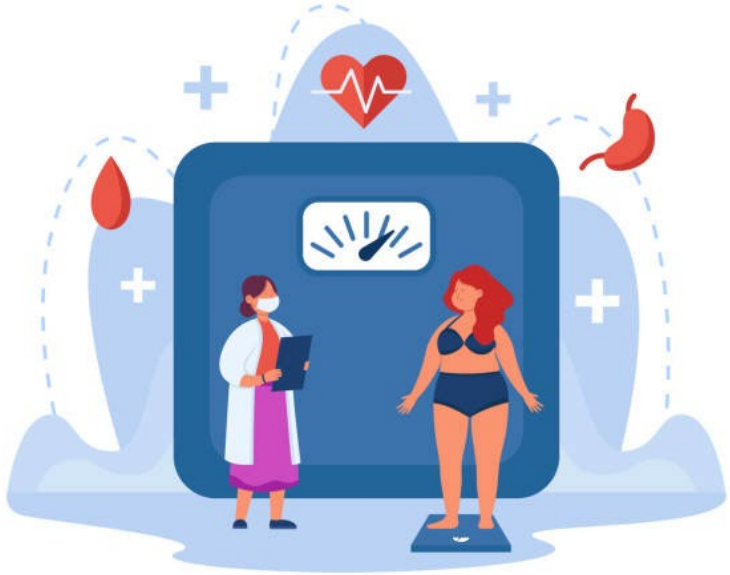
Explain the role of weight loss in management of sleep-disordered breathing

Recognize FDA-approved anti-obesity pharmacotherapy, and rationale for prioritizing use of GLP-1RA medications in OSA

Describe the findings of Surmount-OSA RCT, which demonstrated superiority of tirzepatide for OSA

Background:

Obesity definitions and pathophysiology



Defining obesity: excess and ectopic fat mass

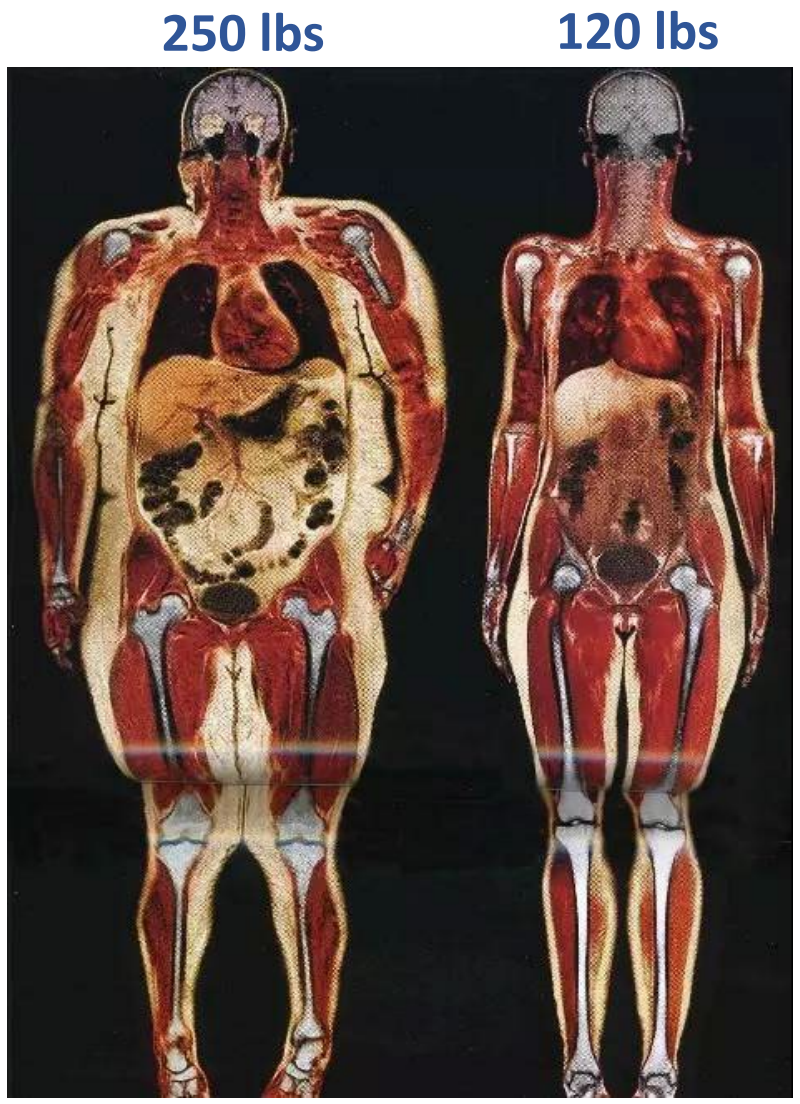
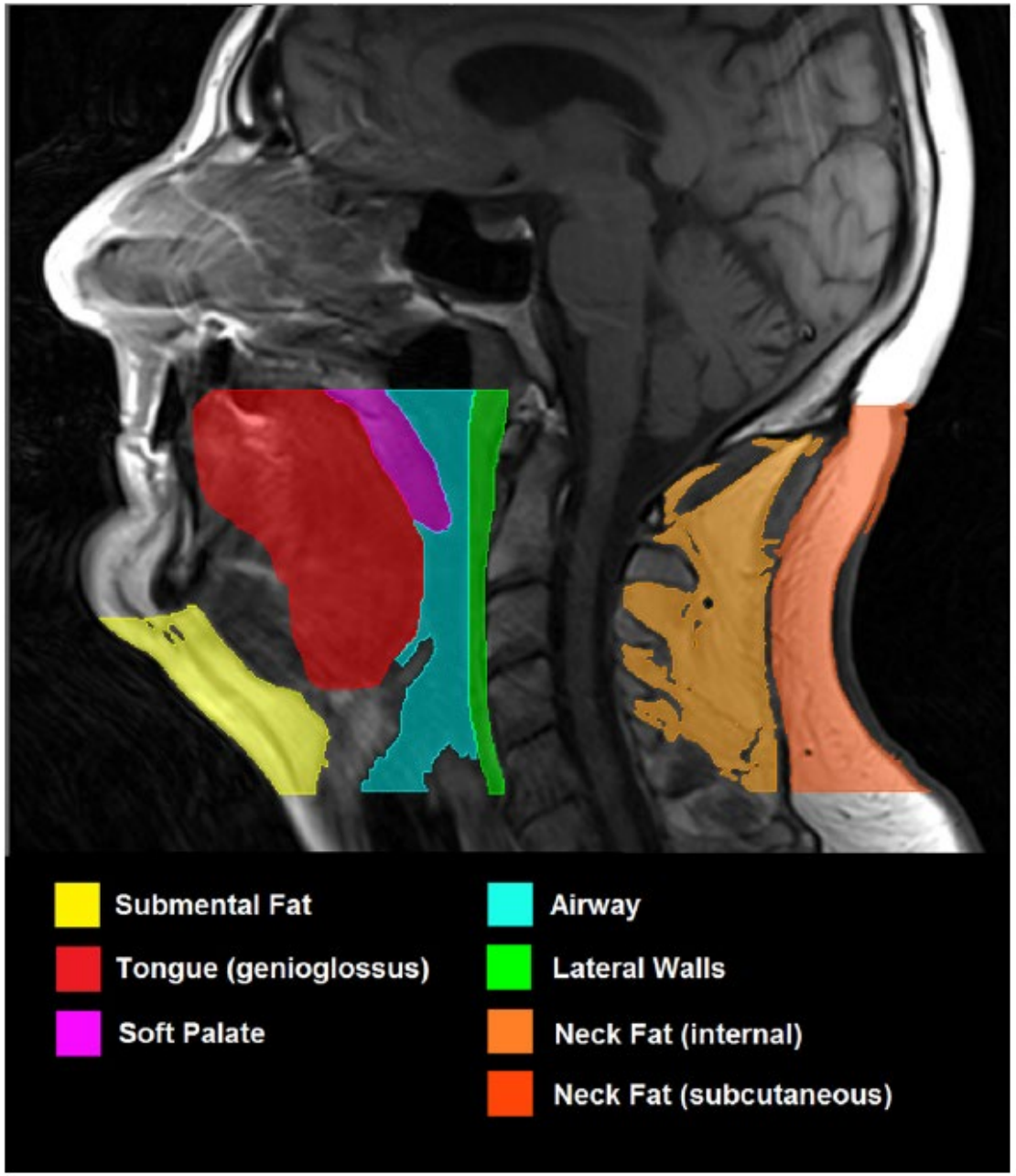


Image source: National Geographic (2004)

- ✓ As subcutaneous depot reaches limits of expandability, fat accumulates in ectopic tissues, notably:
  - Viscera / intrabdominal
  - Tongue and oropharynx
  - Chest wall and thorax
  - Liver, pancreas and organs
- ✓ Ectopic fat accumulation promotes inflammation, insulin resistance, and ***increased cardiometabolic risk***



Ectopic fat depot sites in the neck and oropharynx relevant to airway obstruction

Sprung VS, et al. BMJ Open (2020)

Defining obesity: Body Mass Index (BMI)

BMI classification (age ≥ 18)

$$BMI = \frac{\text{Weight (kg)}}{\text{Height}^2\text{ (m)}} = \frac{\text{Weight (lbs)} \times 703}{\text{Height}^2\text{ (in)}}$$

BMI ≥ 30 kg/m²

Advantages

- Inexpensive
- Highly reproducible
- Adequate screening tool for most patients and epidemiologic studies[1,2]

Disadvantages

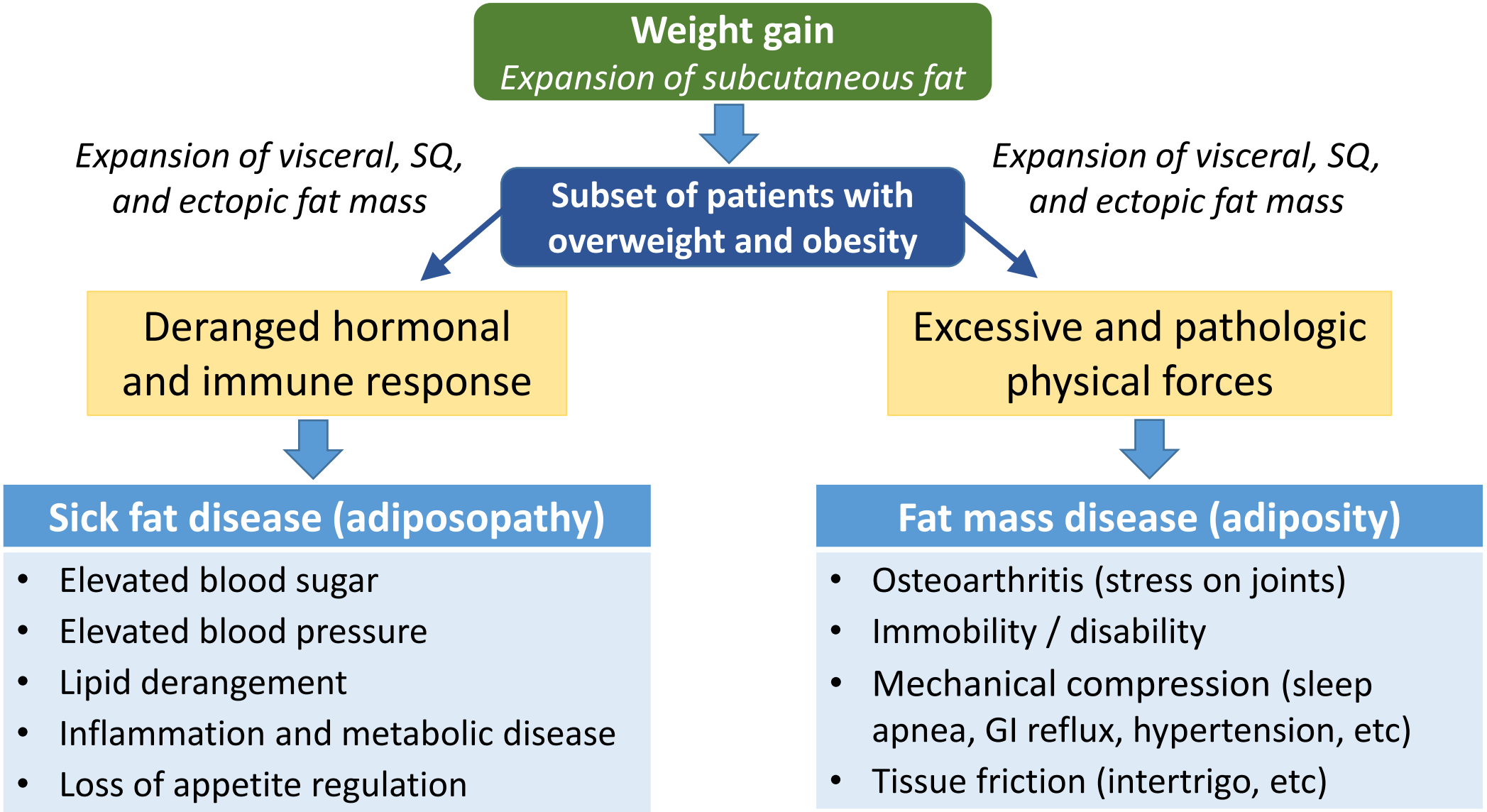
- Does not account for muscle mass or gender-specific differences in body composition
- May not correlate with disease risk[2]
- Requires adjustment for certain racial and ethnic groups[3,4]

1. Jensen MD, et al. J Am Coll Cardiol, 2013.
2. Flegal KM, et al. Am J Clin Nutr 2009.
3. Rahman M, Berenson AB. Obstet Gyn 2010.
4. Chiu M, et al. Diabetes Care 2011

Defining obesity: other methods

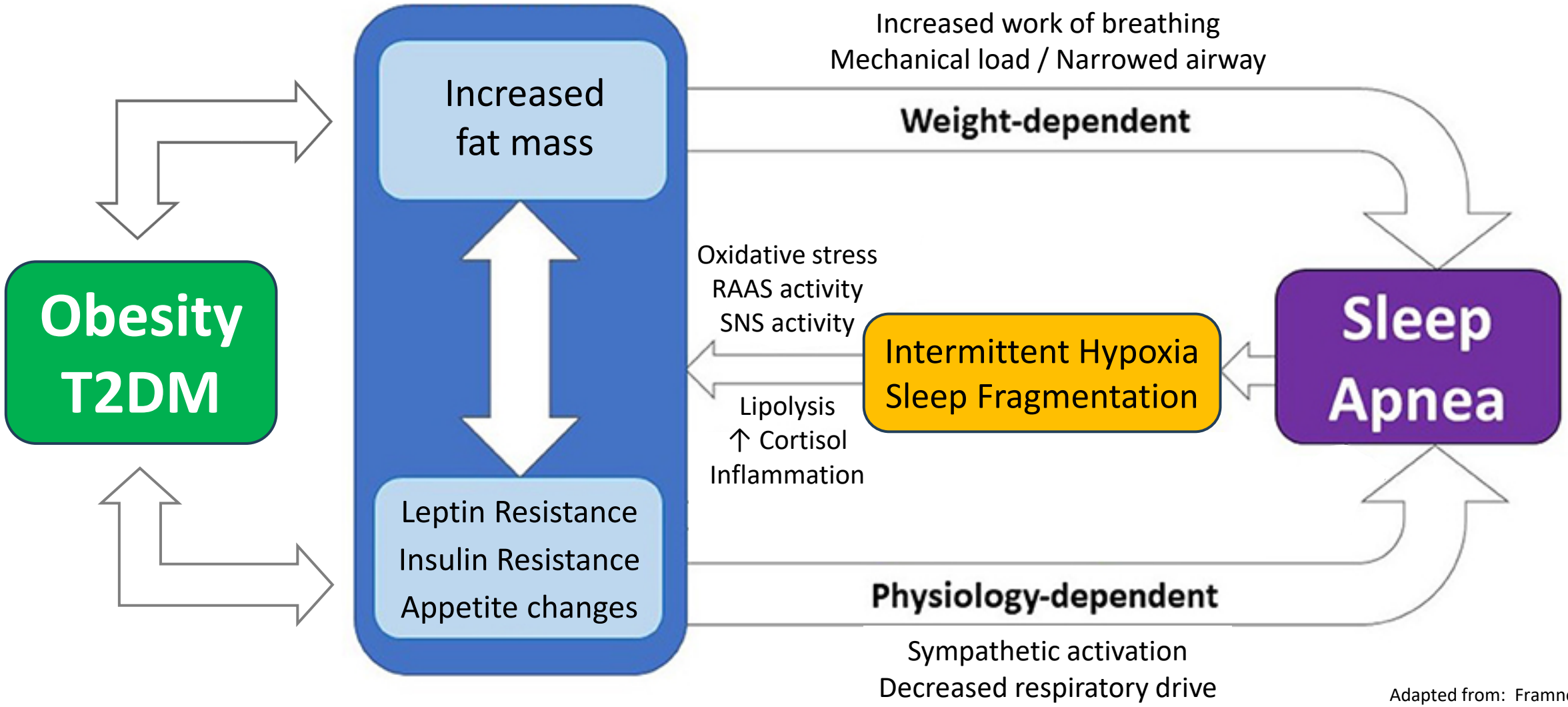
- **Waist circumference (WC)**
  - ✓ US: Men ≤ 40 in, Women ≤ 35 in
- **Waist-to-hip ratio (WHR)**
  - ✓ Men ≥ 0.9, Women ≥ 0.8, High risk (any) > 1.0
- **Waist-to-height ratio (WHtR)**
  - ✓ Normal 0.4 – 0.49, Borderline > 0.5, High > 0.6
- **Body roundness index (BRI)**
  - ✓ Includes height, waist & hip, High risk > 3.5
- **Body composition**
  - ✓ US: Men ≥ 25%, Women ≥ 32% body fat

Obesity as a disease



Adapted from: OMA algorithm, Source: obesitymedicine.org

Bidirectional relationship between OSA, obesity and T2DM



Adapted from: Framnes, SN. *Front. Endocrinol* (2018)

Obesity and sleep apnea:

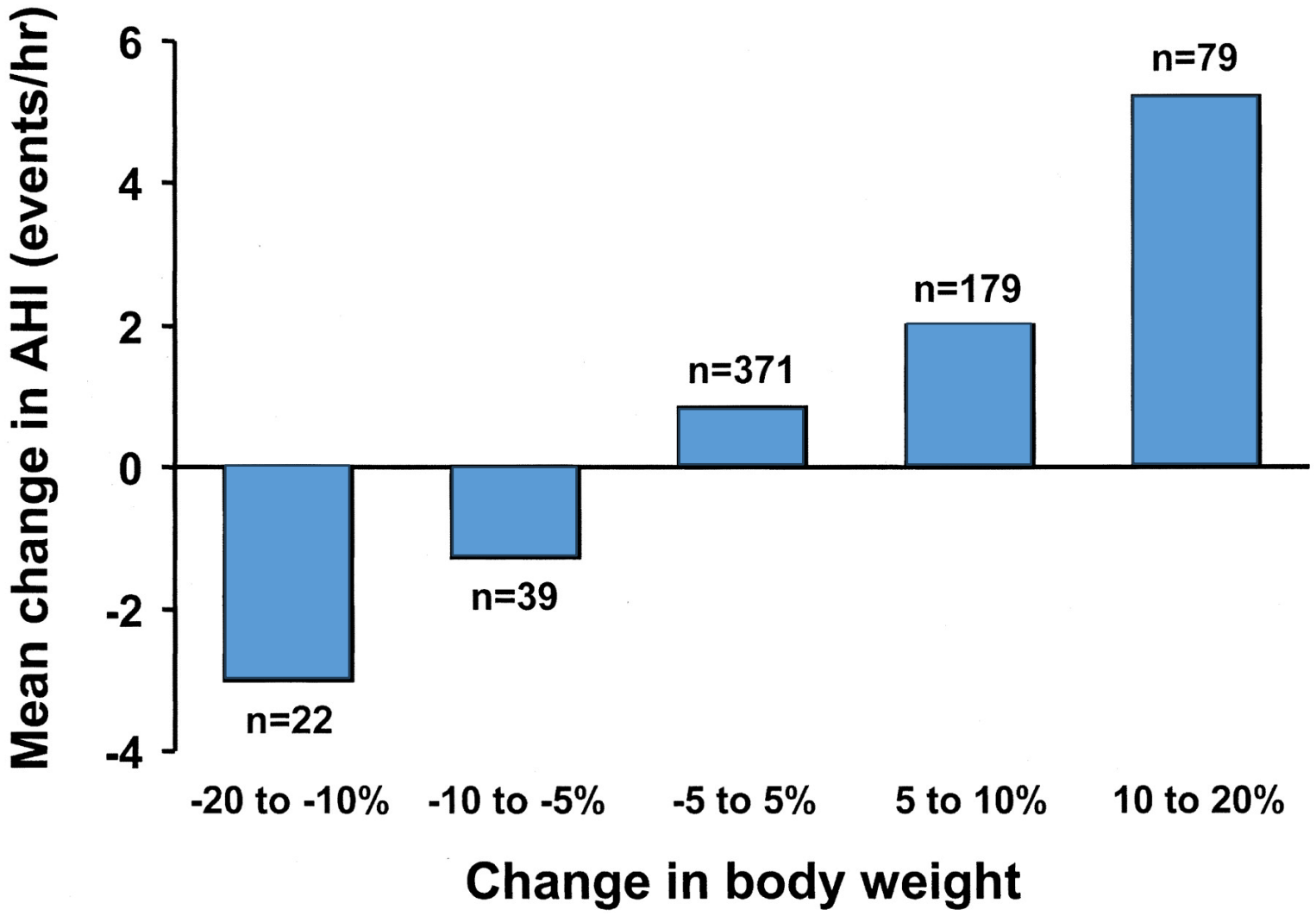
Epidemiology and rationale for weight loss

Obesity and Obstructive Sleep Apnea (OSA)

- High prevalence of **OSA in people with obesity** → about **40%**
- High prevalence of **obesity in people with OSA** → about **70%**
- Increasing body mass index (BMI) is a risk for OSA severity:
  - ❑ **BMI ≥ 30 kg/m²**: 60% with AHI > 5, 26% with AHI > 15
  - ❑ **BMI ≥ 40 kg/m²**: 98% with AHI > 5, 33% with AHI > 15
- About 78% of pts referred for bariatric surgery have OSA

Wolk R, et al. HTN (2003); Sareli AE. Obes Surg (2011)
Valencia-Flores, et al. Obesity (2000)

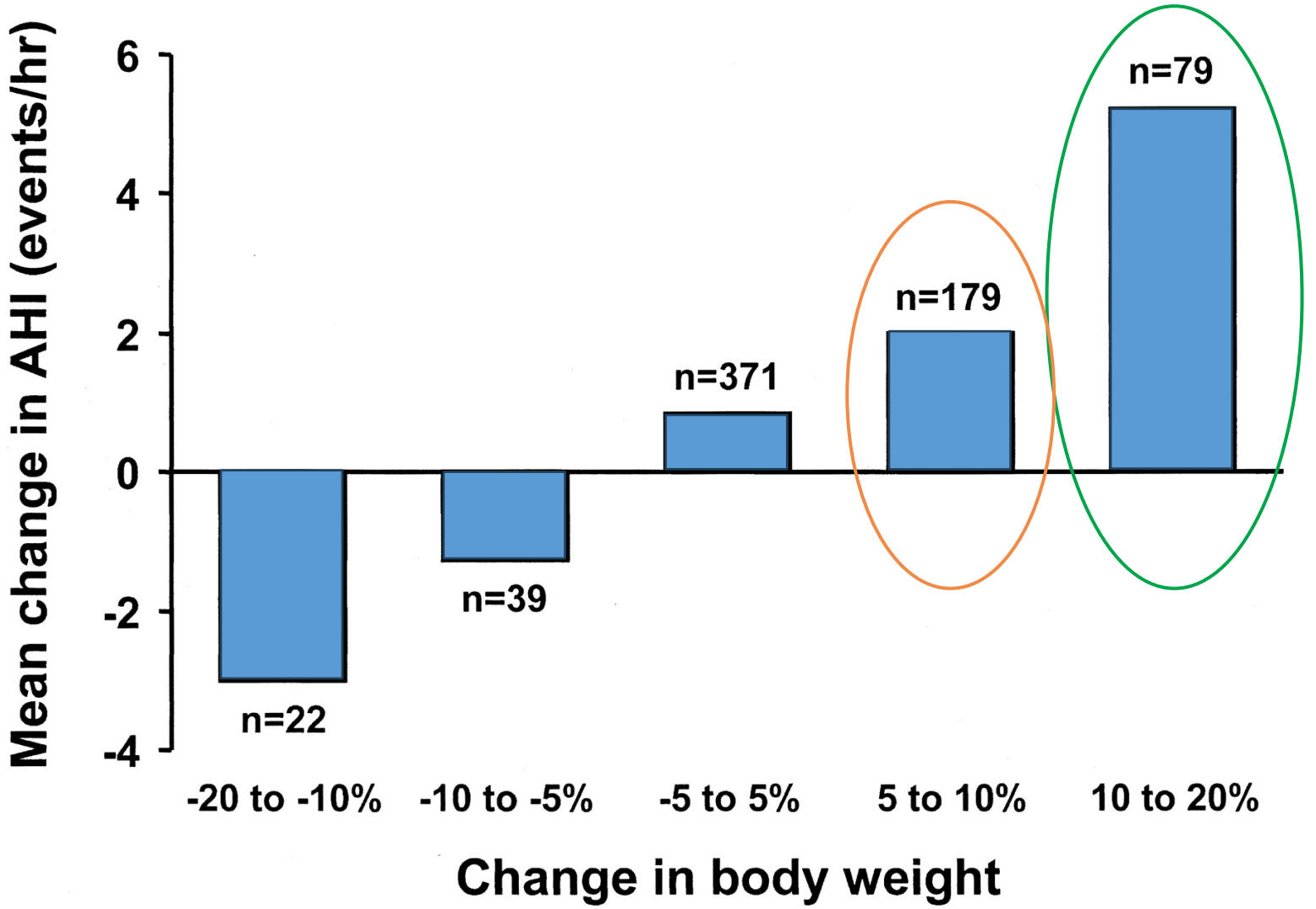
Wisconsin Sleep Cohort Study: 4-year observational weight change and risk of developing sleep apnea (n=690)



Wolk R, et al. Hypertension (2003)
Peppard PE, et al. JAMA (2000)

Wisconsin Sleep Cohort Study: 4-year observational weight change and risk of developing sleep apnea (n=690)

6.0
Odds ratio
AHI ≥ 15



36.6
Odds ratio
adjusted for smoking
AHI ≥ 15

Wolk R, et al. Hypertension (2003)
Peppard PE, et al. JAMA (2000)

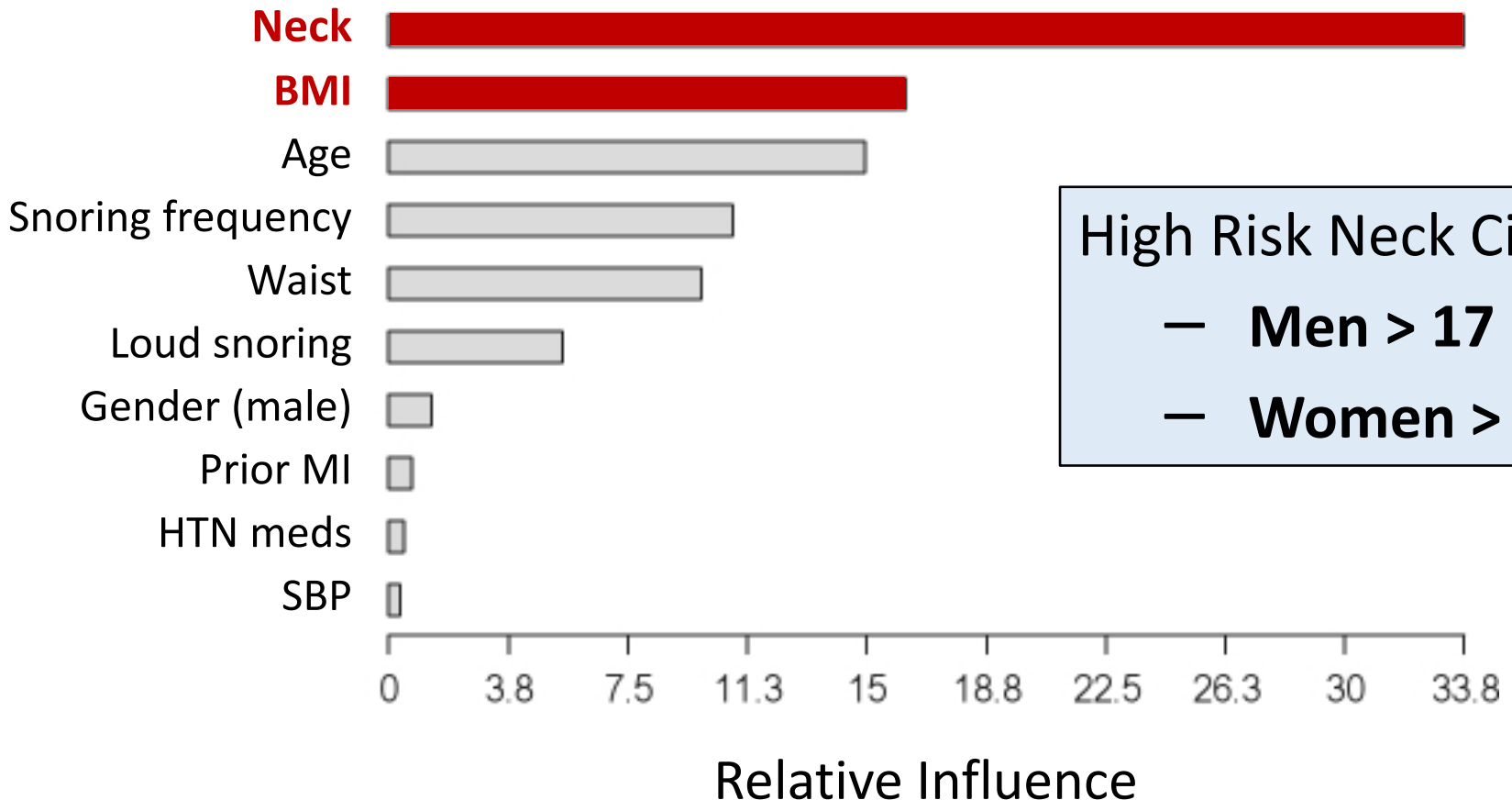
Wisconsin Sleep Cohort Study: 4-year change in weight vs % change AHI highlights importance of primary prevention

Percent Change in Weight (vs No Change)	Estimated Percent Change in AHI (95% Confidence Interval)
−20	−48 (−58 to −35)
−10	−26 (−34 to −18)
−5	−14 (−18 to −9)
+5	+15 (+10 to +21)
+10	+32 (+20 to +45)
+20	+70 (+42 to +104)

Dose response: For every 1% increase/decrease in body weight there is a 3% increase/decrease in AHI

Peppard PE, et al. JAMA (2000)

Sleep Heart Health Study: Neck circumference is the strongest predictor of sleep apnea risk

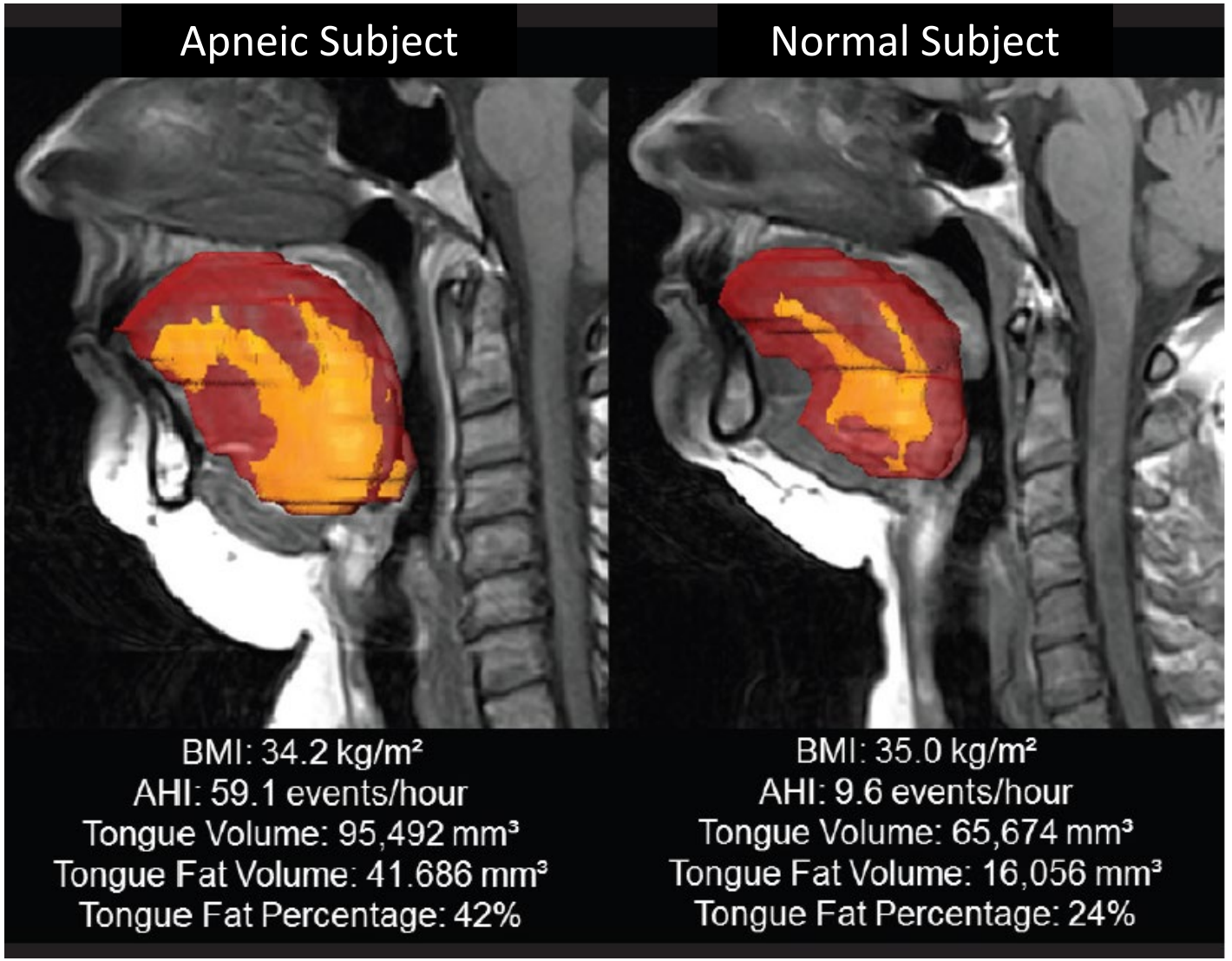


High Risk Neck Circumference:

- **Men > 17** inches
- **Women > 15** inches

Adapted from: Caffo B. Sleep (2010)

Tongue fat predicts OSA risk in obese subjects



After correcting for age, gender and BMI, obese subjects with apnea had significantly more tongue fat than normal controls

Kim AM, et al. Sleep (2014)

Tongue fat volume reduction is primary upper airway mediator of AHI improvement after weight loss

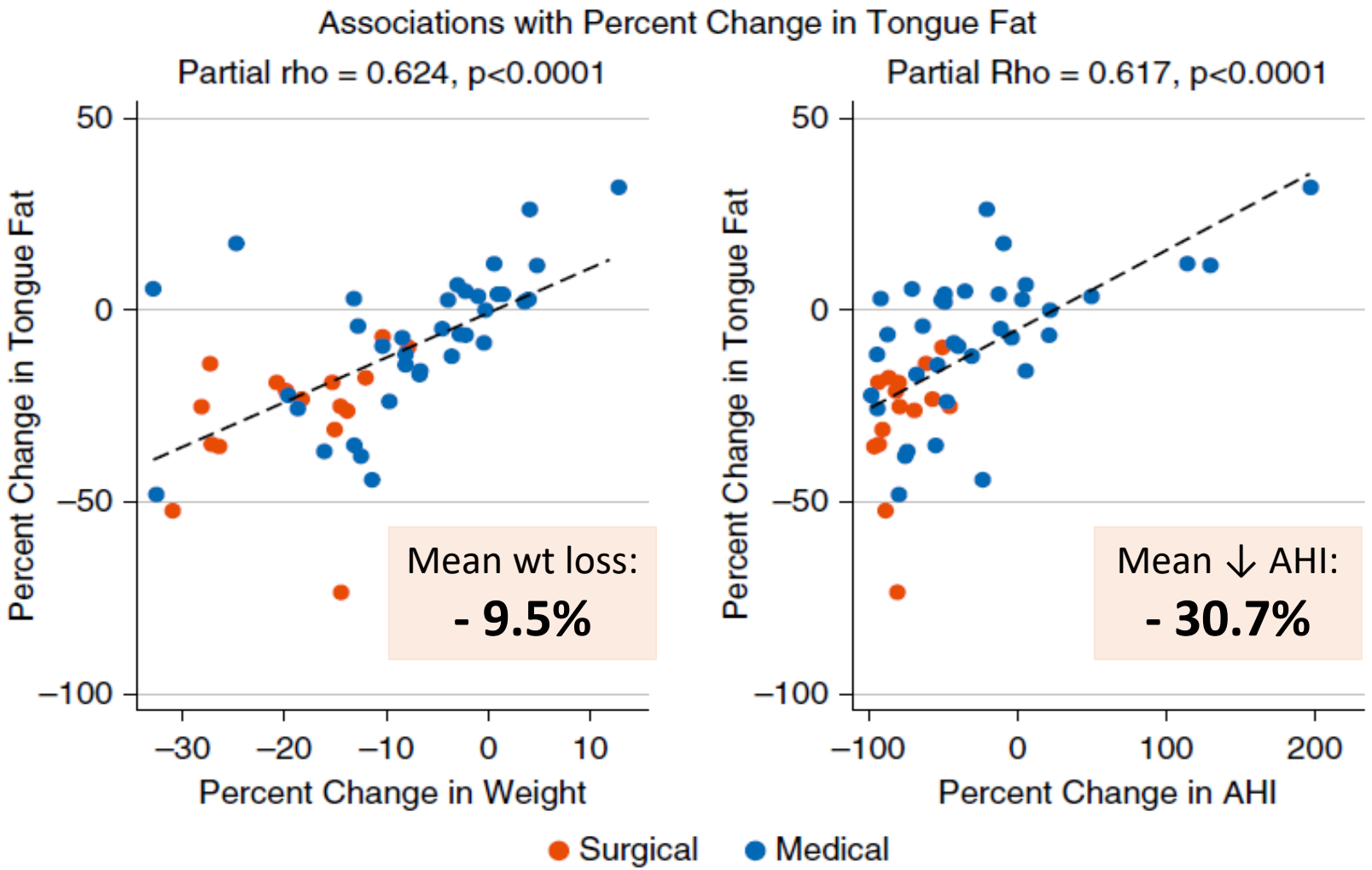
Intensive WL or bariatric surgery (n=67)

AHI ≥ 10 event/hr

Age: 49.4 yrs

Sex: 40% male
60% female

BMI: 42.6 kg/m^2



Wang SH. Am J Resp Crit Care Med (2020)

Tongue fat volume reduction is primary upper airway mediator of AHI improvement after weight loss

Intensive WL or bariatric surgery (n=67)

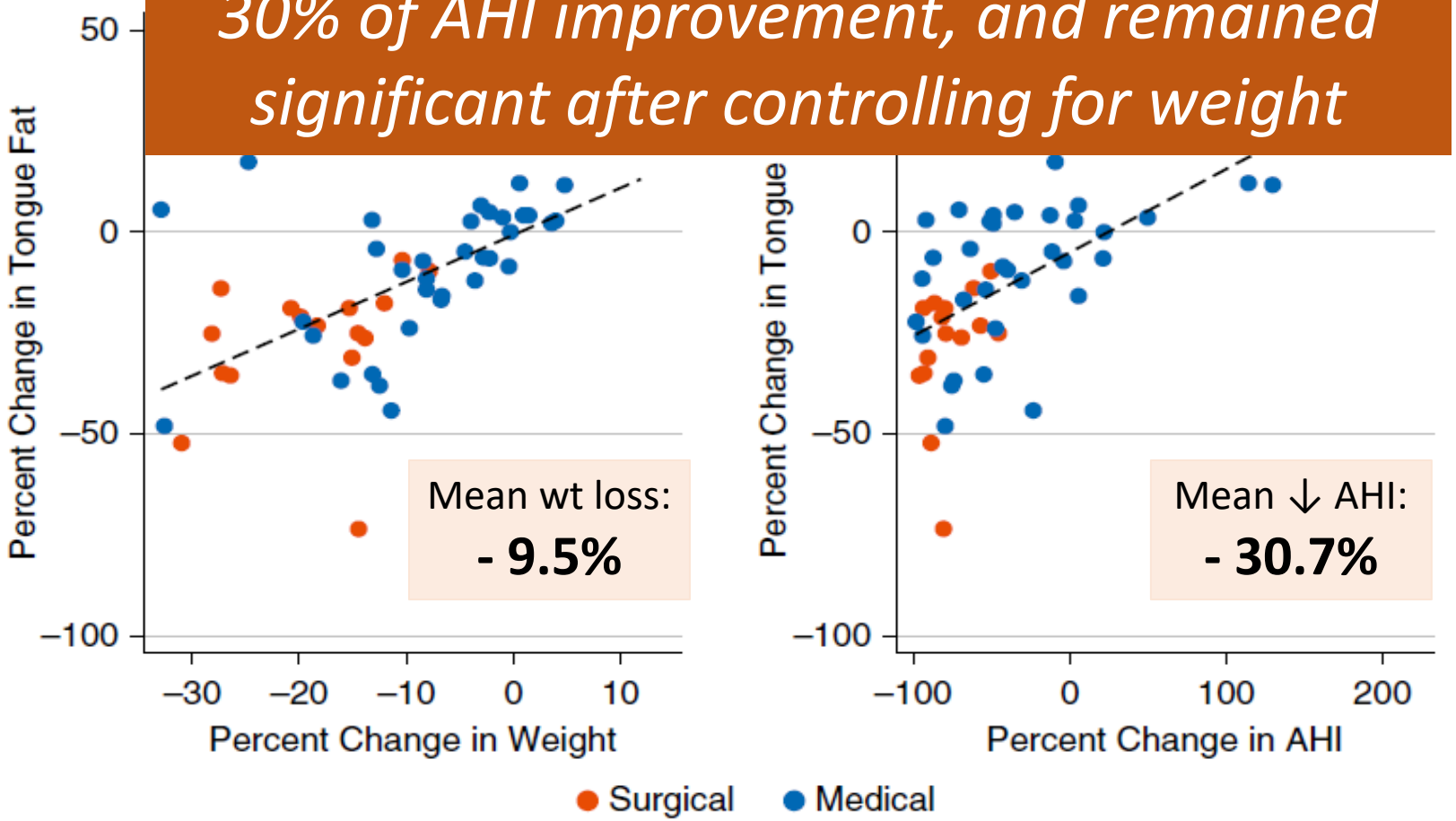
AHI ≥ 10 event/hr

Age: 49.4 yrs

Sex: 40% male
60% female

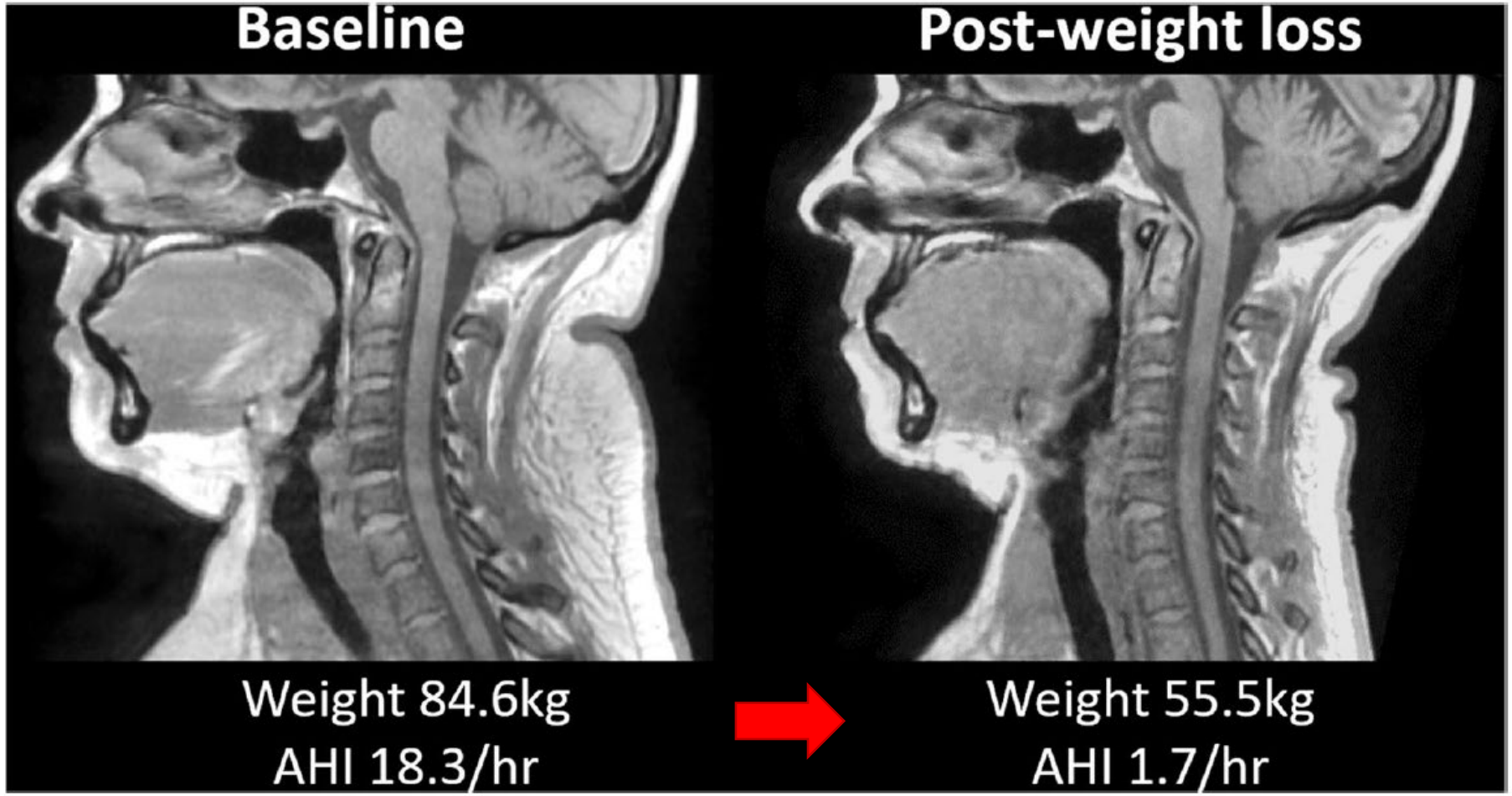
BMI: 42.6 kg/m^2

Tongue fat reduction accounted for about 30% of AHI improvement, and remained significant after controlling for weight



Wang SH. Am J Resp Crit Care Med (2020)

Surgical weight loss dramatically improves upper airway fat

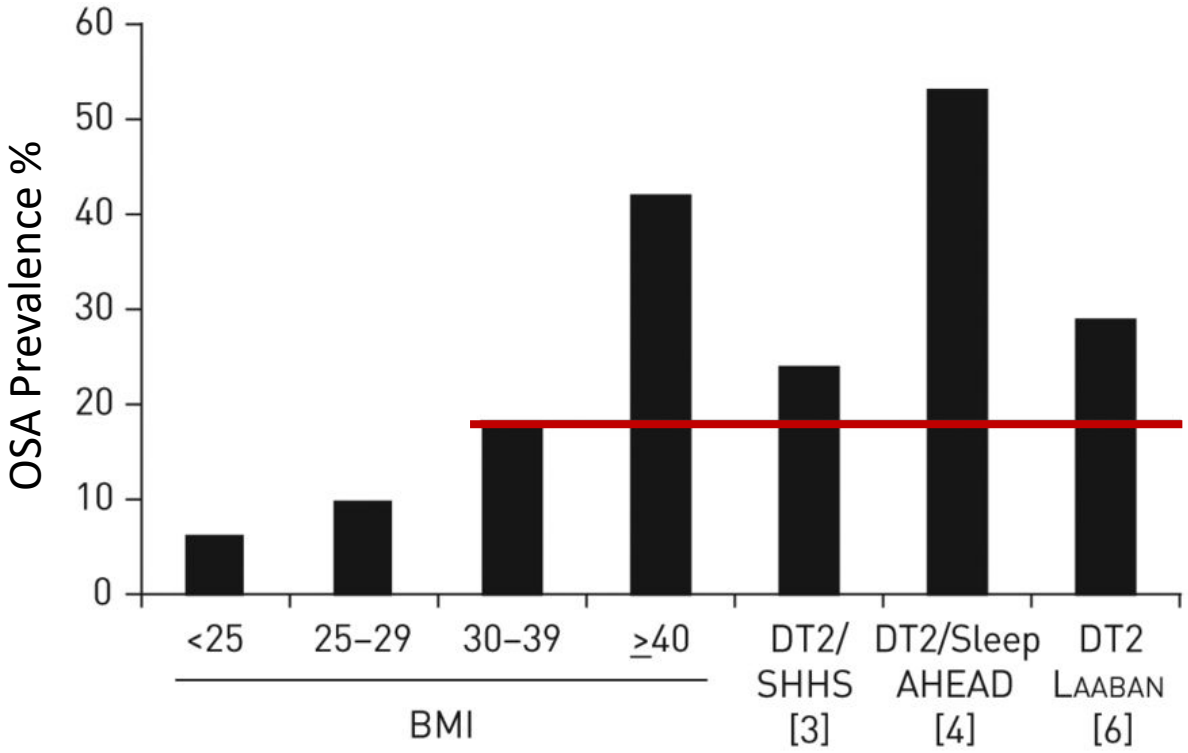


- 34.4% wt loss

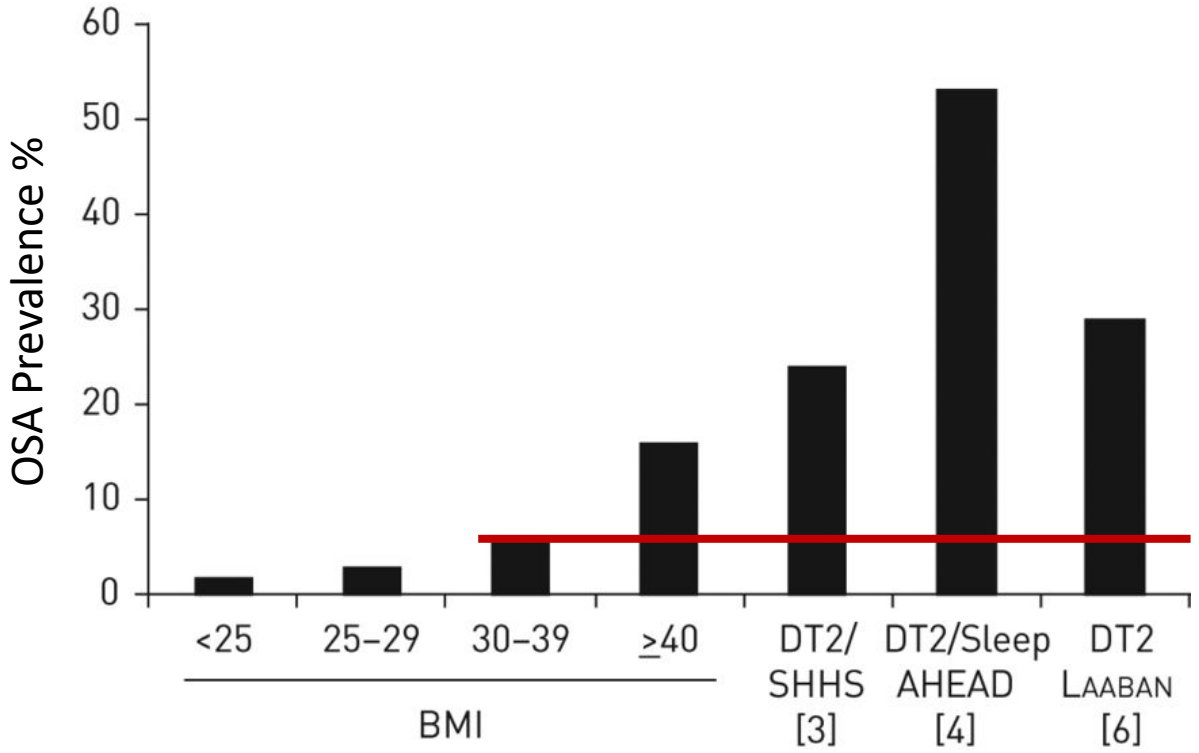
Sutherland K, et al. Sleep and Breathing (2023)

Prevalence of OSA is higher in people with diabetes after accounting for age and BMI

Men, aged 50-69 yrs



Women, aged 50-69 yrs



Bonsignore MR. Eur Resp Rev (2013)

Primary prevention: Weight loss reduces incidence of T2DM in subjects with IGT

	Type 2 DM Risk Reduction
Da Qing IGT and Diabetes Study[1] (Diet and exercise)	**42%**
US Diabetes Prevention Program[2] (Diet and exercise)	**58%**
Semaglutide 10-yr *post hoc* (STEP-1, STEP-4)[3] (Medication)	**60%**
UK Population-based Matched Cohort Study[4] (Surgery)	**80%**
Swedish Obese Subjects Study[5] (Surgery)	**78%**

[1] Pan XR, et al. *Diabetes Care.* 1997;20:537-44.
[2] The DPP Research Group. *N Eng J Med.* 2002;346:393-403.
[3] Garvey WT, et al. *Diabetes* June 2022; 71: Suppl 1.
[4] Booth H, et al. Lancet Diab Endocri (2014)
[5] Caarlson LMS, et al. NEJM Aug 23 2012; 367:8.

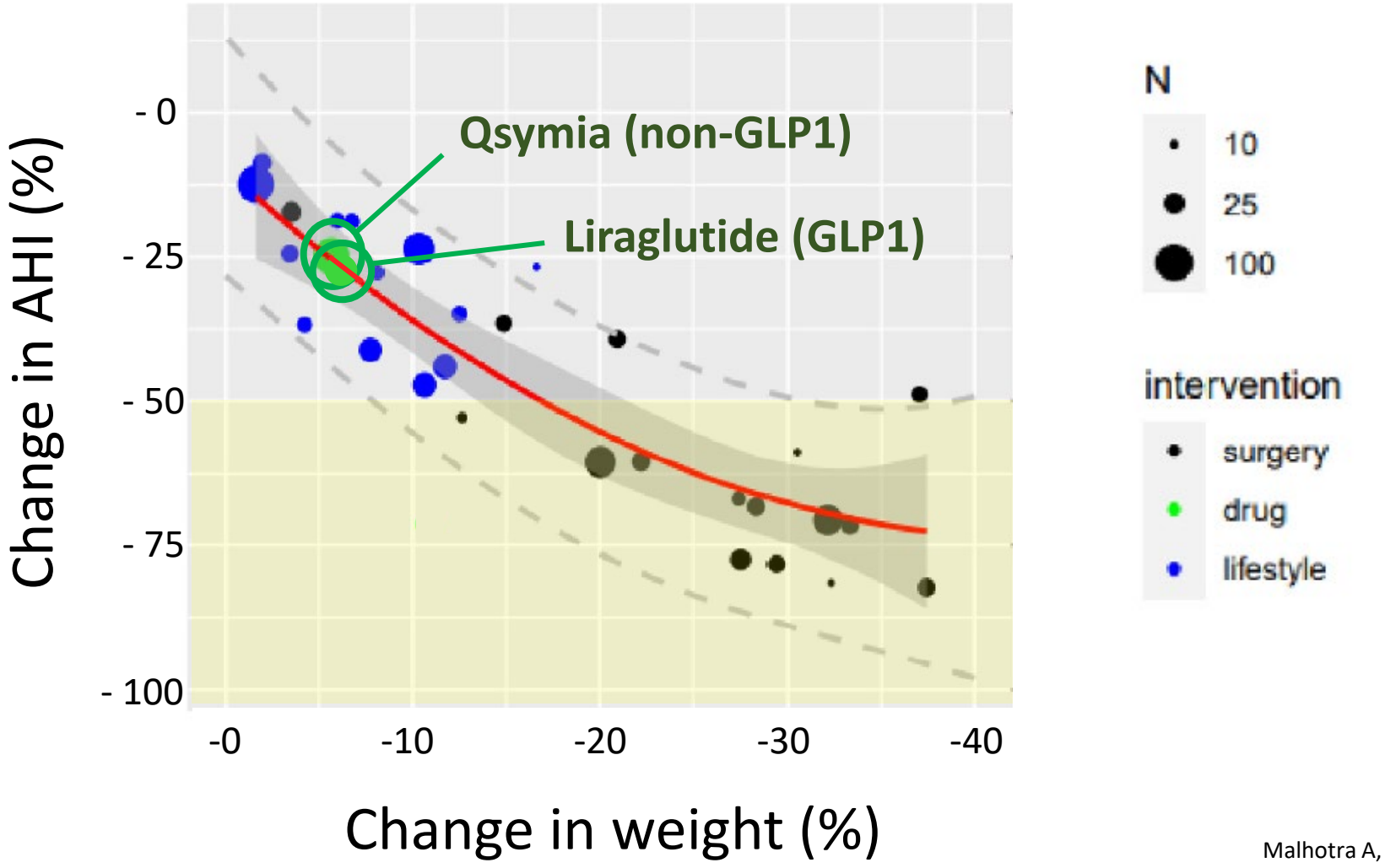
Secondary prevention: obesity-related comorbidities (ORCs) improve at varied weight loss thresholds

Co-morbidity	Improves with weight loss?	Clinical benefit threshold	Reduction after bariatric surgery
MAFLD- Steatosis	Yes	≥ 5%	90%
Prediabetes	Yes	5 to ≥ 10%	80%
Type 2 diabetes	Yes	5 to ≥ 15%	70-85%
Hypertension	Yes	5 to ≥ 15%	40-92%
Dyslipidemia	Yes	5 to ≥ 15%	63%
Obstructive sleep apnea	Yes	≥ 10%	78-98%
NASH- Steatohepatitis	Variable	10 to 40%	20-37%

Apovian C, et al. JCEM (2015) 100; 342-362
Ryan DH, Yackey SR. Curr Obes Rep (2017)
AACE/ACE Obesity CPG, Endocrine Pract (2016)
Look AHEAD Study group. Wing et al, 2011.
Brthauer SA. Clev Clin J Med (2006).
Zhang N. Surg Endosc (2013).

Meta-analysis (27 studies): Intentional weight reduction improves apnea-hypopnea index (AHI)

Only surgical interventions were able to achieve reduction in AHI > 50%



Malhotra A, et al. Sleep Med (2024)

Summary: Obesity and OSA

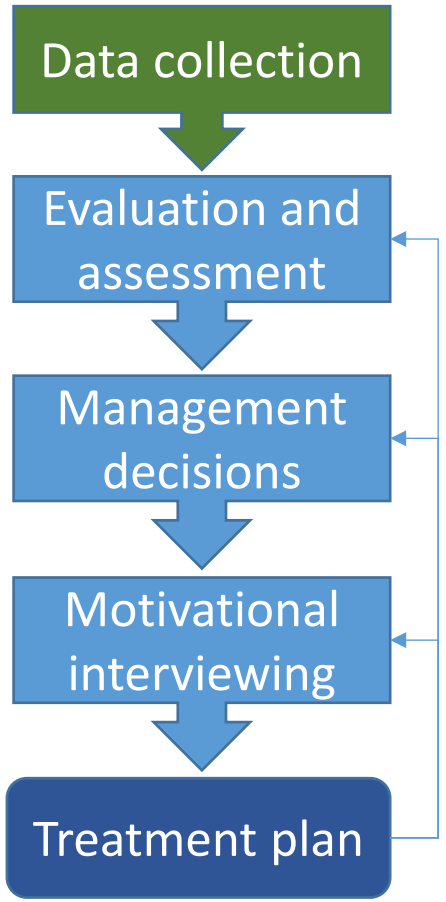
- Nearly all people with class 3 obesity (BMI ≥ 40) have mild sleep apnea, and about 1 in 3 have moderate-to-severe disease (AHI ≥ 15)
- ***Neck circumference*** and ***tongue fat*** are the strongest predictors of OSA risk in people with obesity
- Having ***diabetes increases risk of OSA***, and vice-versa
- As little as 5-10% weight loss can improve OSA, but ***weight loss of 18% or more*** is typically needed to achieve a significant reduction in AHI > 50%

Obesity Management:

Formulating a treatment plan

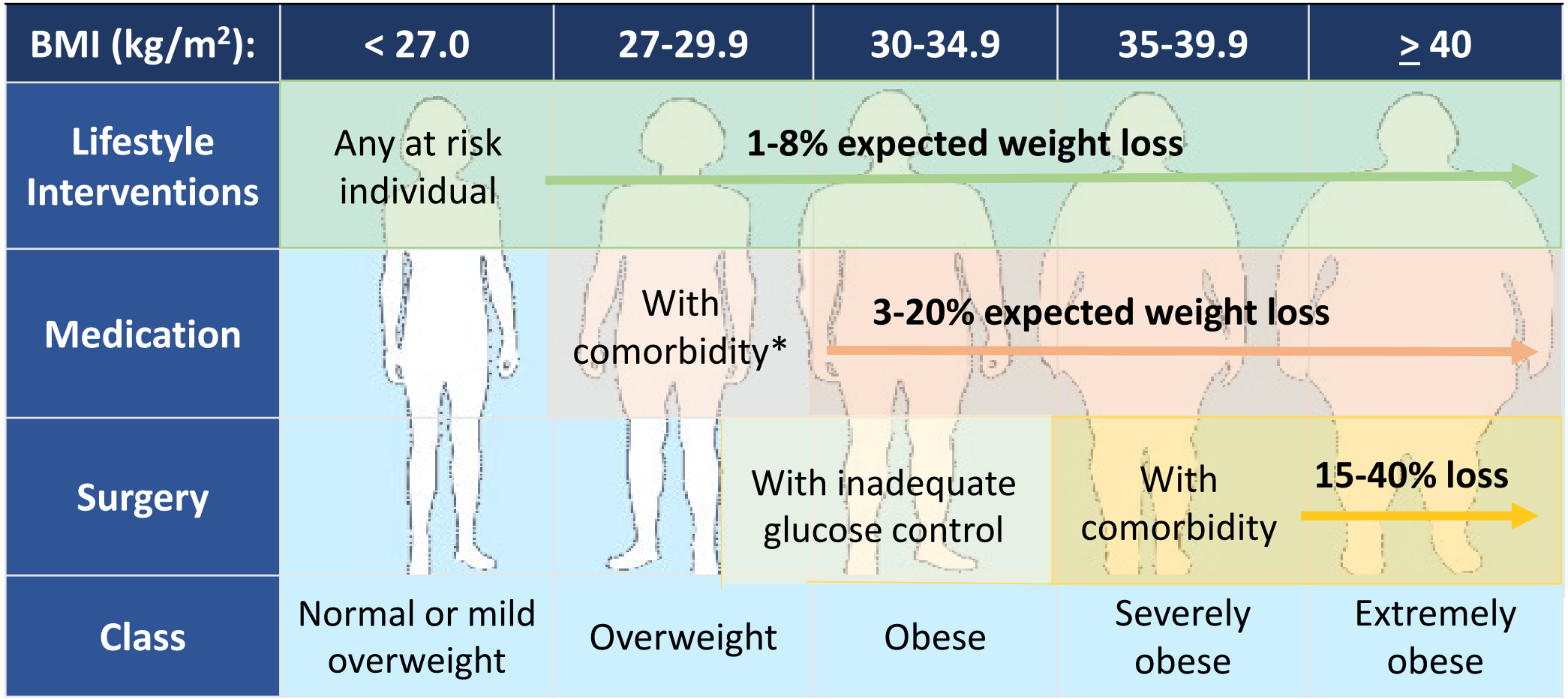
Obesity management overview

1. **Screening and diagnosis**
   - Anthropometric analysis
   - Clinical assessment → history and physical exam
   - Assess for weight-related comorbidities
2. **Treatment plan: Goals and Considerations**
   - Lifestyle modification
   - Pharmacotherapy
   - Referral to weight management specialist
   - Metabolic (bariatric) surgery
3. **Follow-up and maintenance**



AACE/ACE Obesity CPG, Endocrine Pract (2016)
OMA Obesity Algorithm (2020)

Guide for selecting obesity treatment



* Comorbidities include any metabolic risk factor such as diabetes, HTN, or dyslipidemia

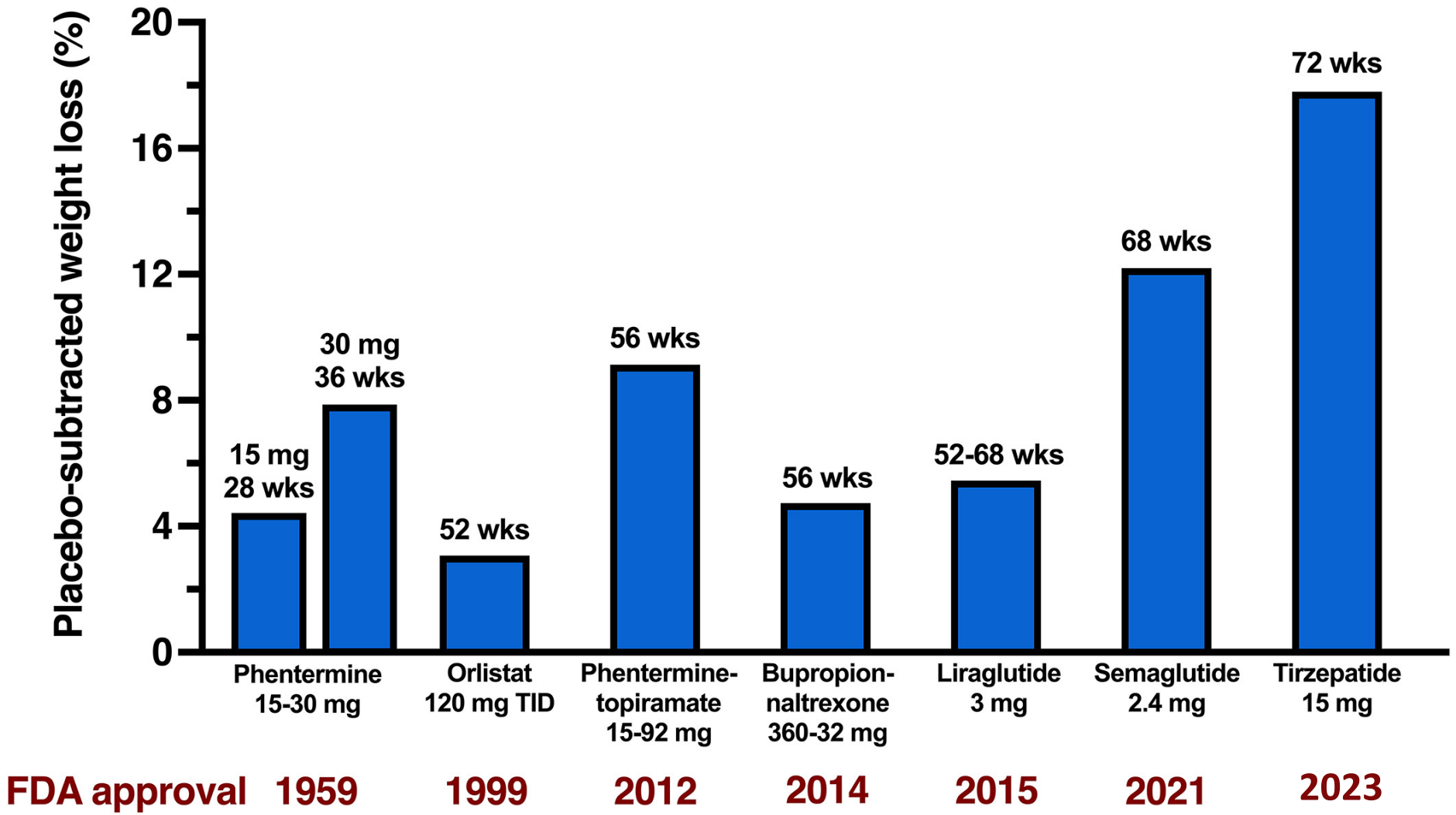
Adapted from: ADA Standards. *Diabetes Care* (2022)

FDA approved anti-obesity medications (AOM)

- **Anorexiants**
  - Phentermine / Topiramate (Qsymia)[1]
  - Naltrexone / Bupropion (Contrave)
- **GLP-1R agonist**
  - Liraglutide (Saxenda)[1]
  - Semaglutide (Wegovy)[1]
- **GIP / GLP-1R agonist**
  - Tirzepatide (Zepbound)
- **Fat-calorie Malabsorption**
  - Orlistat (Alli)[1]
- **CNS stimulants (amphetamines)**
  - Phentermine[2]
  - Mazindol
  - Diethylpropion
  - Benzphetamine
  - Phendimetrazine
- **MC4R agonist**
  - Setmelanotide (Imcivree)[3]
- **Mechanical**
  - Plenity (hydrogel)

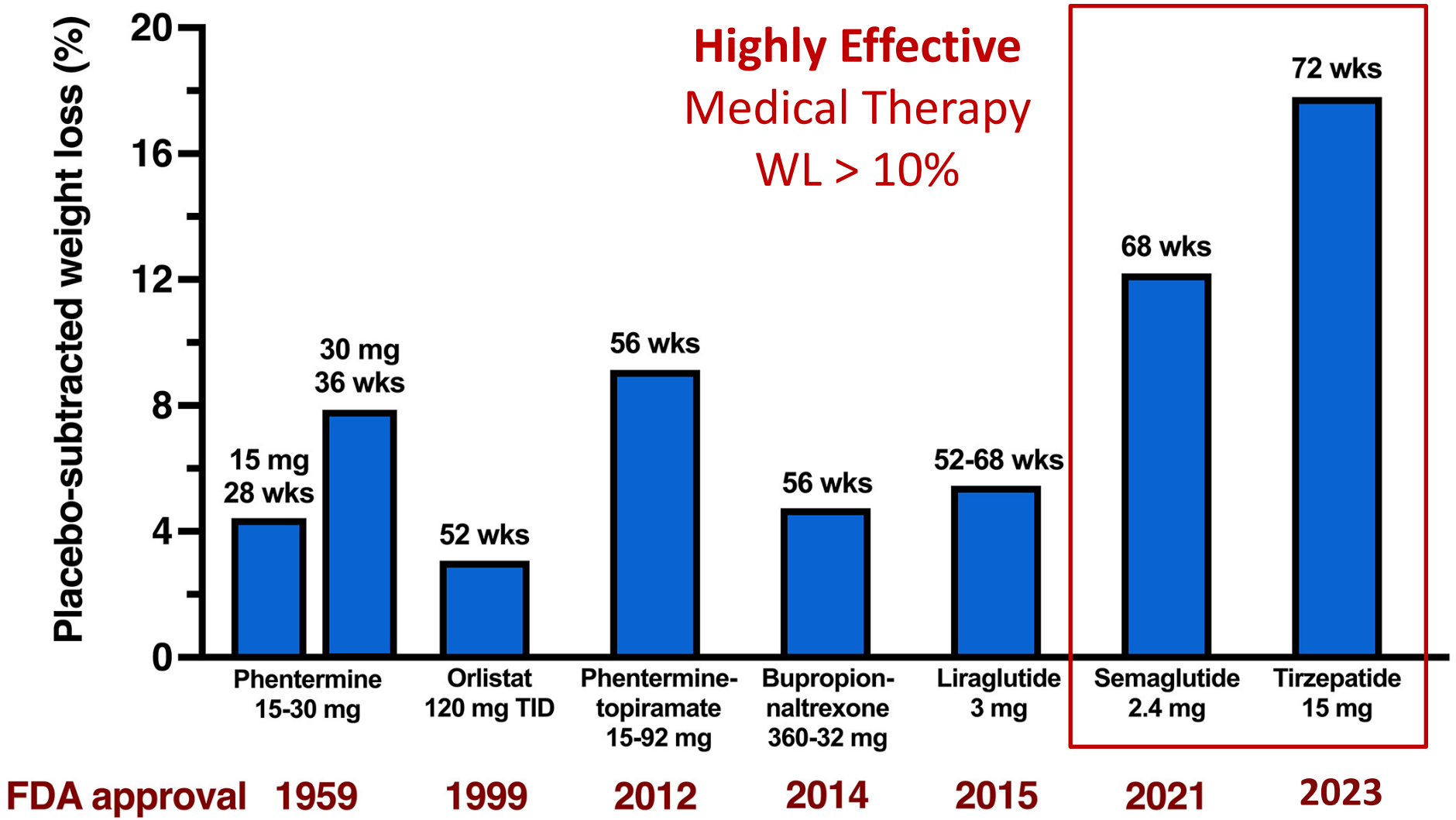
1. FDA approved age > 12 years
2. Age > 16 years
3. Select patients > 6 years

Comparative efficacy of weight loss meds



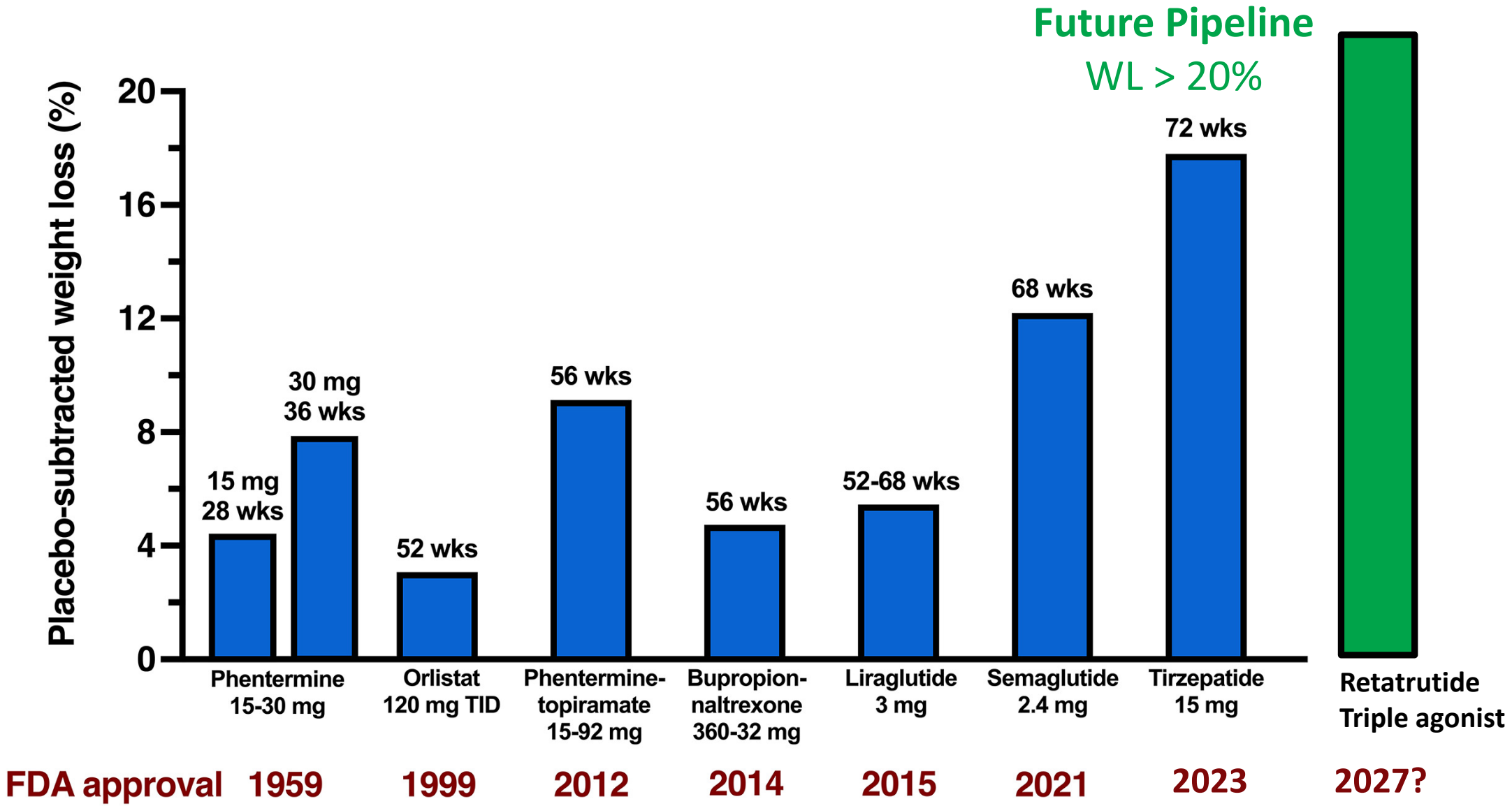
Malik IO, et al. Obes (2022)

Comparative efficacy of weight loss meds



Malik IO, et al. Obes (2022)

Comparative efficacy of weight loss meds



Malik IO, et al. Obes (2022)

Obesity Management:

GLP-1RA therapy in comorbid OSA

Therapeutic benefits of GLP1RA which may impact OSA

Adapted from: Ryan DH. AHJ (2020)

Available FDA-approved GLP-1RA therapies

FDA-approved for *both* weight loss and T2D management

FDA-approved only for T2DM

Exenetide


Byetta 2x SC daily pen
Bydureon Weekly SC pen

Dulaglutide


Trulicity SC Weekly auto-injector pen

Lisixenetide


Adylixin SC daily pen
Insulin combo 100/33 SC daily

GLP-1RA

Liraglutide

Victoza


Diabetes only, SC daily pen

Saxenda


Weight loss only, SC daily pen

Degludec/lira


Diabetes only
Xultophy insulin combo 100/3.6 SC daily pen

GLP-1RA

Semaglutide

Ozempic


Diabetes only, SC weekly pen

Wegovy


Weight loss only
SC weekly auto-injector pen

Rybelsus


Diabetes only
Once daily oral pill

Dual GIP/GLP-1RA

Tirzepatide

Mounjaro


Diabetes only
SC Weekly auto-injector pen

Zepbound
Weight loss only
SC weekly auto-injector pen
SC weekly vial with syringe

GLP-1RA: Liraglutide

Mechanism of action	Delays gastric emptying, enhances glucose-dependent insulin release, ↑ satiety via hypothalamic POMC activation
Dosing	• ***Saxenda (weight loss)***: Begin 0.6 mg SQ daily, then increase every 1-2 weeks, 0.6 > 1.2 > 1.8 > 2.4 > 3.0 mg/day • ***Victoza (diabetes)***: Begin 0.6 mg SQ daily, then increase every 1-2 weeks, 0.6 > 1.2 > 1.8 mg/day
Benefits	Weight loss, cardiorenal protective effect, 15% ↓MACE
HbA1c lowering	1.0 – 1.6 %
Contraindications	Medullary thyroid cancer or MEN-2 (personal/family), pregnancy or breastfeeding
Side effects	Nausea/vomiting, diarrhea, tachycardia, fertility/OCP Rare (< 1%): pancreatitis, gallstones, mood/SI

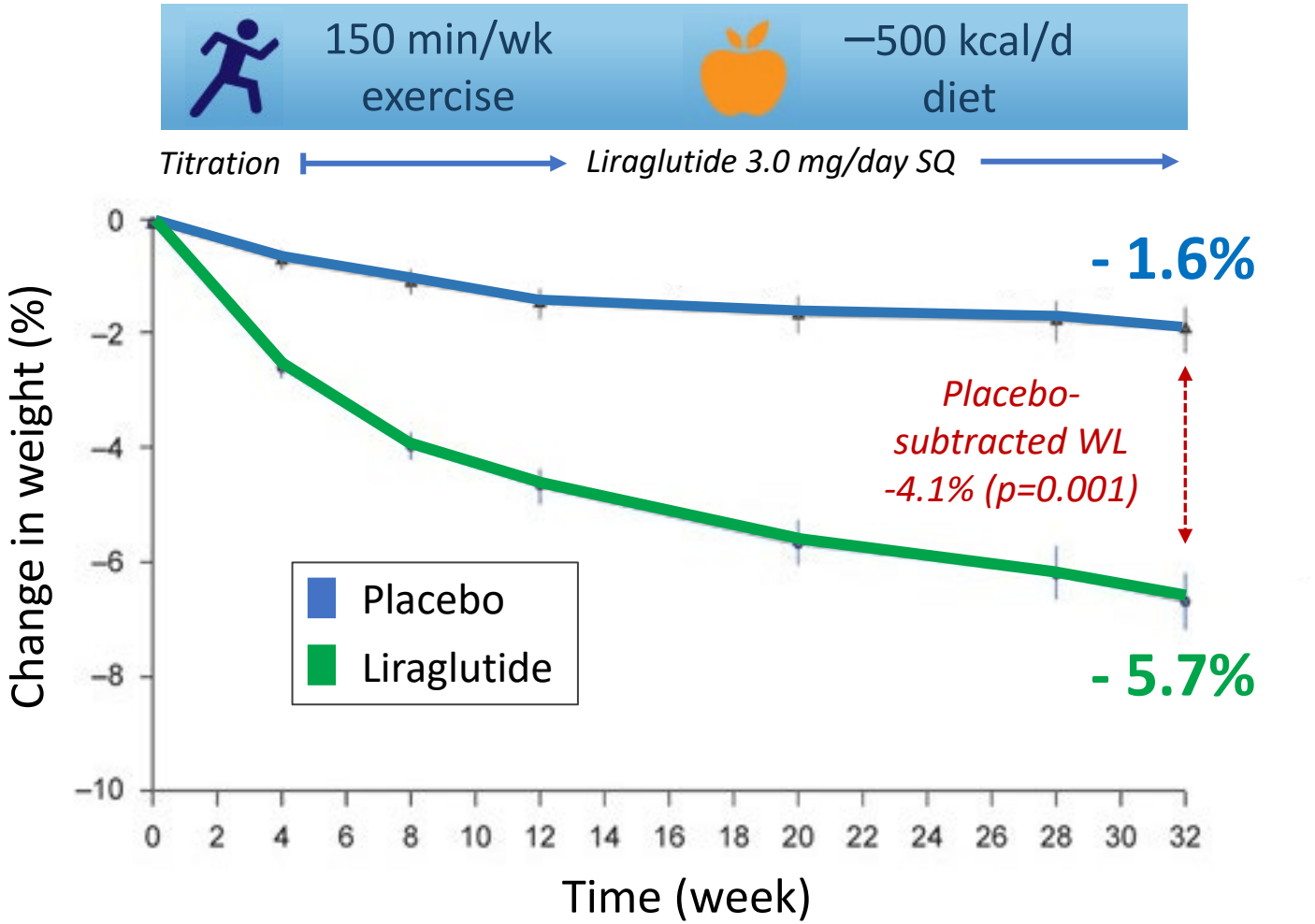
SCALE trial: Effect of liraglutide 3.0 mg in people with obesity and moderate to severe OSA

Key Inclusion Criteria

- Age 18 – 64 years
- Body mass index ≥ 30 kg/m^2 and weight stable for at least 3 months
- Apnea-hypopnea index (AHI) ≥ 15 events/hour
- Unable or unwilling to use CPAP

Key Exclusion Criteria

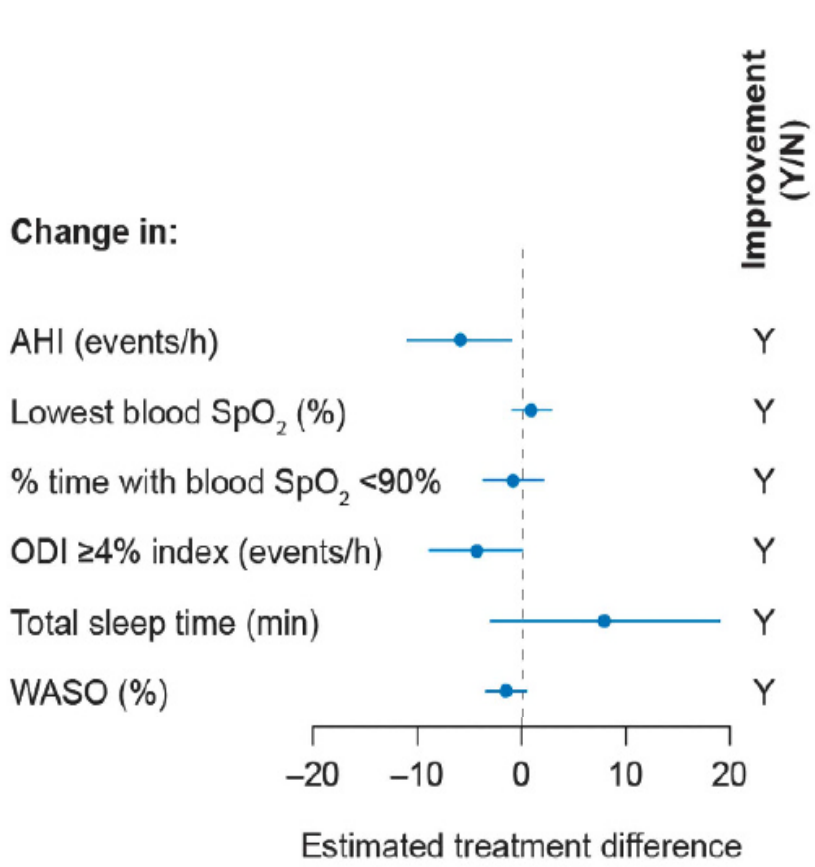
- Central sleep apnea
- Diabetes (any type)



Blackman A, et al. Int J Obes (2016)

SCALE trial: Effect of liraglutide 3.0 mg in people with obesity and moderate to severe OSA

<u>No</u> significant difference in Epworth, FOSQ, or SF-36 symptom scores between groups



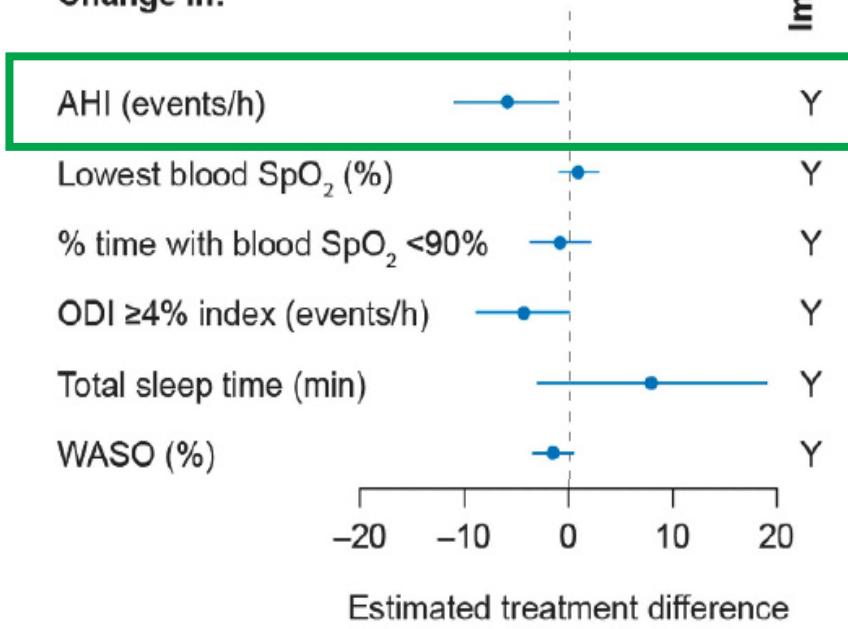
	Baseline		Observed mean ± SE change from baseline at week 32 (LOCF)		Estimated treatment difference (95% CI)	P value
	Liraglutide 3.0 mg N=180	Placebo N=179	Liraglutide 3.0 mg N=168	Placebo N=166		
AHI (events/h)	49.0±27.5	49.3±27.5	–12.2±1.8	–6.1±2.0	–6.1 (–11.0 to –1.2)	0.015
Lowest blood SpO_2 (%)	74.2±10.5	74.7±10.4	1.6±0.7	0.8±0.7	0.8 (–1.0 to 2.5)	0.40
% time with blood SpO_2 <90%	14.9±18.2	14.4±18.9	–2.3±1.1	–1.3±1.2	–0.9 (–3.7 to 1.8)	0.51
ODI ≥4% index (events/h)	43.7±26.1	44.1±26.1	–9.5±1.7	–5.2±1.9	–4.4 (–8.9 to 0.2)	0.06
Total sleep time (min)	356.3±62.3	348.4±63.7	20.7±4.6	18.5±4.8	7.7 (–3.1 to 18.6)	0.16
WASO (%)	20.4±11.7	22.3±12.3	–4.0±0.9	–3.7±0.9	–1.7 (–3.6 to 0.3)	0.10

Blackman A, et al. Int J Obes (2016)

SCALE trial: Effect of liraglutide 3.0 mg in people with obesity and moderate to severe OSA

<u>No</u> significant difference in Epworth, FOSQ, or SF-36 symptom scores between groups

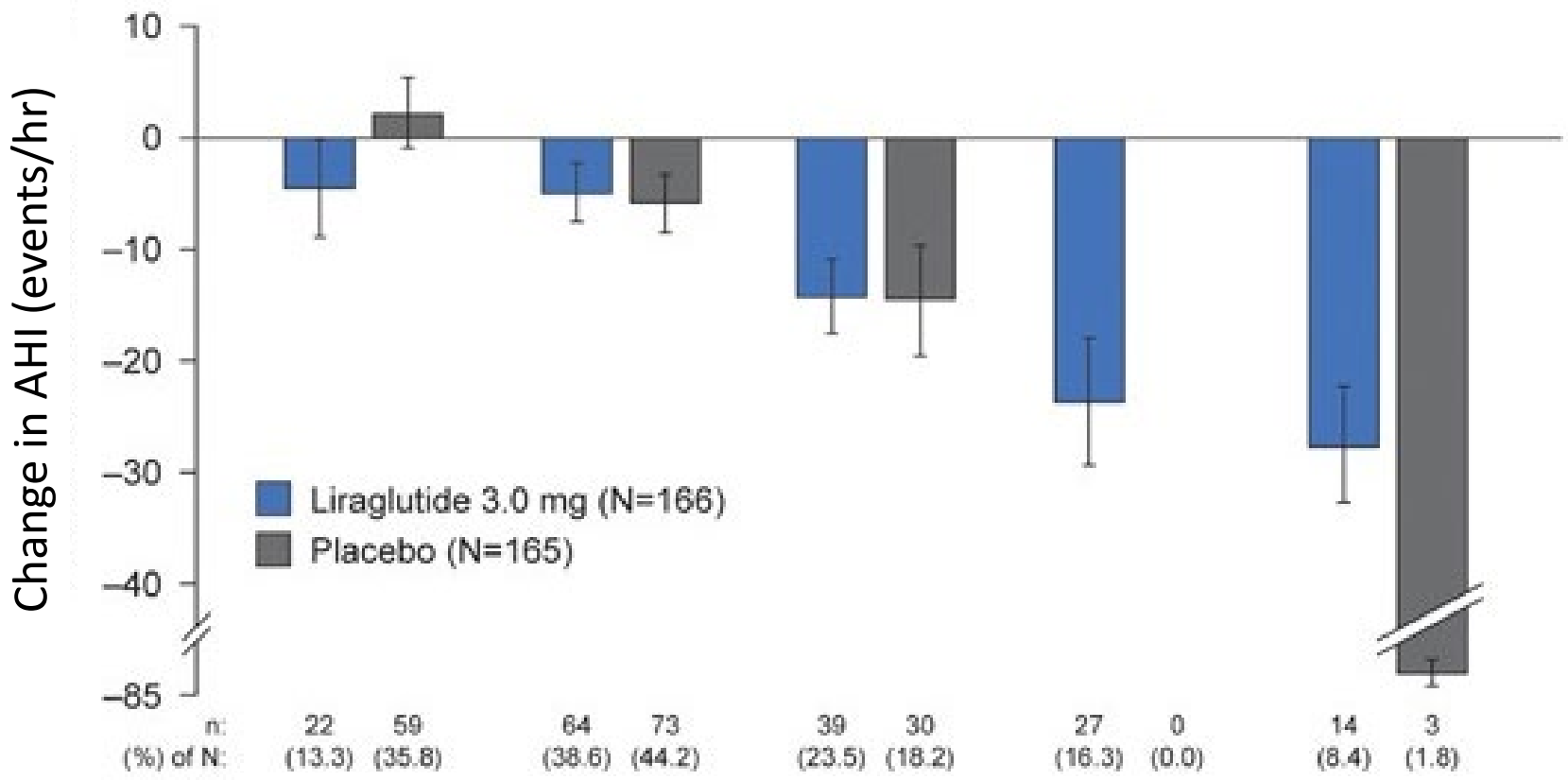
AHI ↓ 24.9% with Liraglutide vs 12.4% with placebo



	Improvement (Y/N)	Baseline		Observed mean ± SE change from baseline at week 32 (LOCF)		Estimated treatment difference (95% CI)	P value
		Liraglutide 3.0 mg N=180	Placebo N=179	Liraglutide 3.0 mg N=168	Placebo N=166		
AHI (events/h)	Y	49.0±27.5	49.3±27.5	–12.2±1.8	–6.1±2.0	–6.1 (–11.0 to –1.2)	0.015
Lowest blood SpO_2 (%)	Y	74.2±10.5	74.7±10.4	1.6±0.7	0.8±0.7	0.8 (–1.0 to 2.5)	0.40
% time with blood SpO_2 <90%	Y	14.9±18.2	14.4±18.9	–2.3±1.1	–1.3±1.2	–0.9 (–3.7 to 1.8)	0.51
ODI ≥4% index (events/h)	Y	43.7±26.1	44.1±26.1	–9.5±1.7	–5.2±1.9	–4.4 (–8.9 to 0.2)	0.06
Total sleep time (min)	Y	356.3±62.3	348.4±63.7	20.7±4.6	18.5±4.8	7.7 (–3.1 to 18.6)	0.16
WASO (%)	Y	20.4±11.7	22.3±12.3	–4.0±0.9	–3.7±0.9	–1.7 (–3.6 to 0.3)	0.10

Blackman A, et al. Int J Obes (2016)

SCALE trial: Benefit of liraglutide on OSA was attenuated after adjusting for weight loss



Blackman A. Int J Obes (2016)

GLP-1RA: Semaglutide

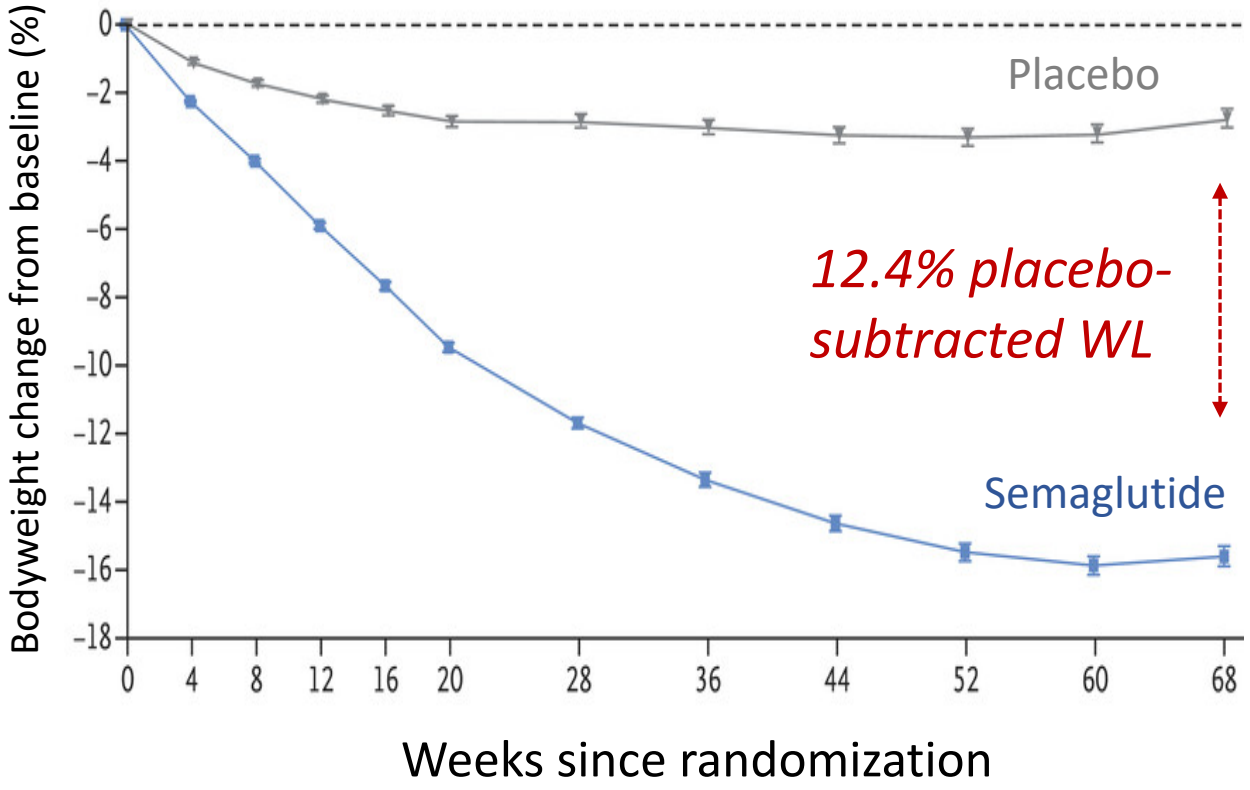
Mechanism of action	Delays gastric emptying, enhances glucose-dependent insulin release, ↑ satiety via hypothalamic POMC activation
Dosing	• ***Wegovy (weight loss or CVD high risk)***: SQ auto-injector pen, increase monthly, 0.25 > 0.5 > 1 > 1.7 > 2.4 mg/week • ***Ozempic (diabetes)***: SQ adjustable pen, max 2 mg/week • ***Rybelsus (diabetes)***: oral pill, 3, 7 or 14 mg PO daily
Benefits	Weight loss, cardiorenal protective, 20% ↓MACE
HbA1c lowering	1.1 – 2.1 %
Contraindications	Medullary thyroid cancer or MEN-2 (personal/family), pregnancy or breastfeeding
Side effects	Nausea/vomiting, diarrhea, tachycardia, fertility/OCP Rare (< 1%): pancreatitis, gallstones, mood/SI, NAION

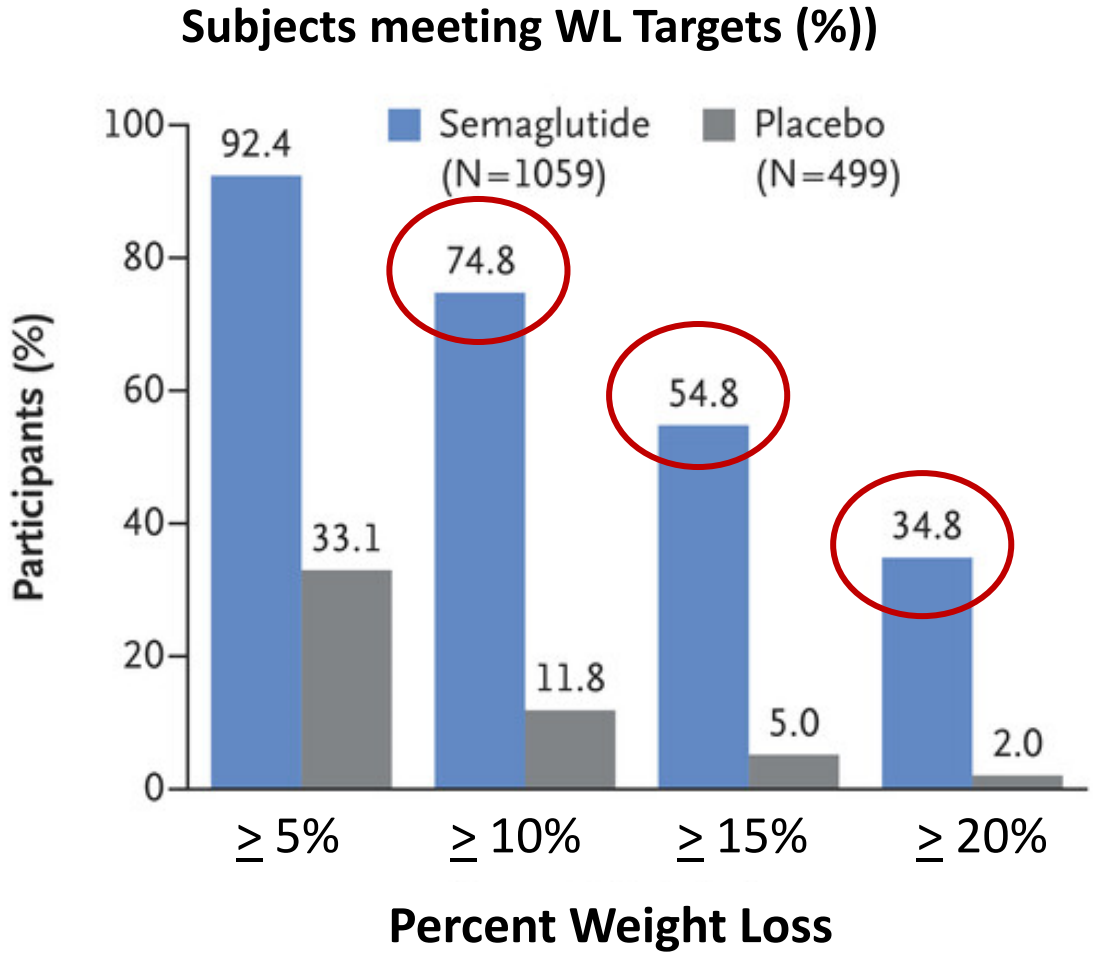
Semaglutide and OSA

1. **There are <u>no</u> ongoing or planned clinical trials**
2. **Potential for post-hoc analysis**
   - STEP trials → semaglutide for weight loss (T2D and non-DM)
   - SUSTAIN trials → semaglutide for diabetes control (T2D only)
   - SELECT trial → cardiovascular outcomes trial in non-diabetics
   - STEP-5 → 2-year study for weight loss in subjects without T2D
     - Semaglutide arm: n=27/152 (17.8%) with known OSA
     - Placebo arm: n=24/152 (15.8%) with known OSA

STEP-1 trial: Semaglutide shows robust weight loss at 68 wks

Baseline: BMI 38, weight 105 kg, T2DM excluded but 40-45% subjects with pre-diabetes (n= 1961)

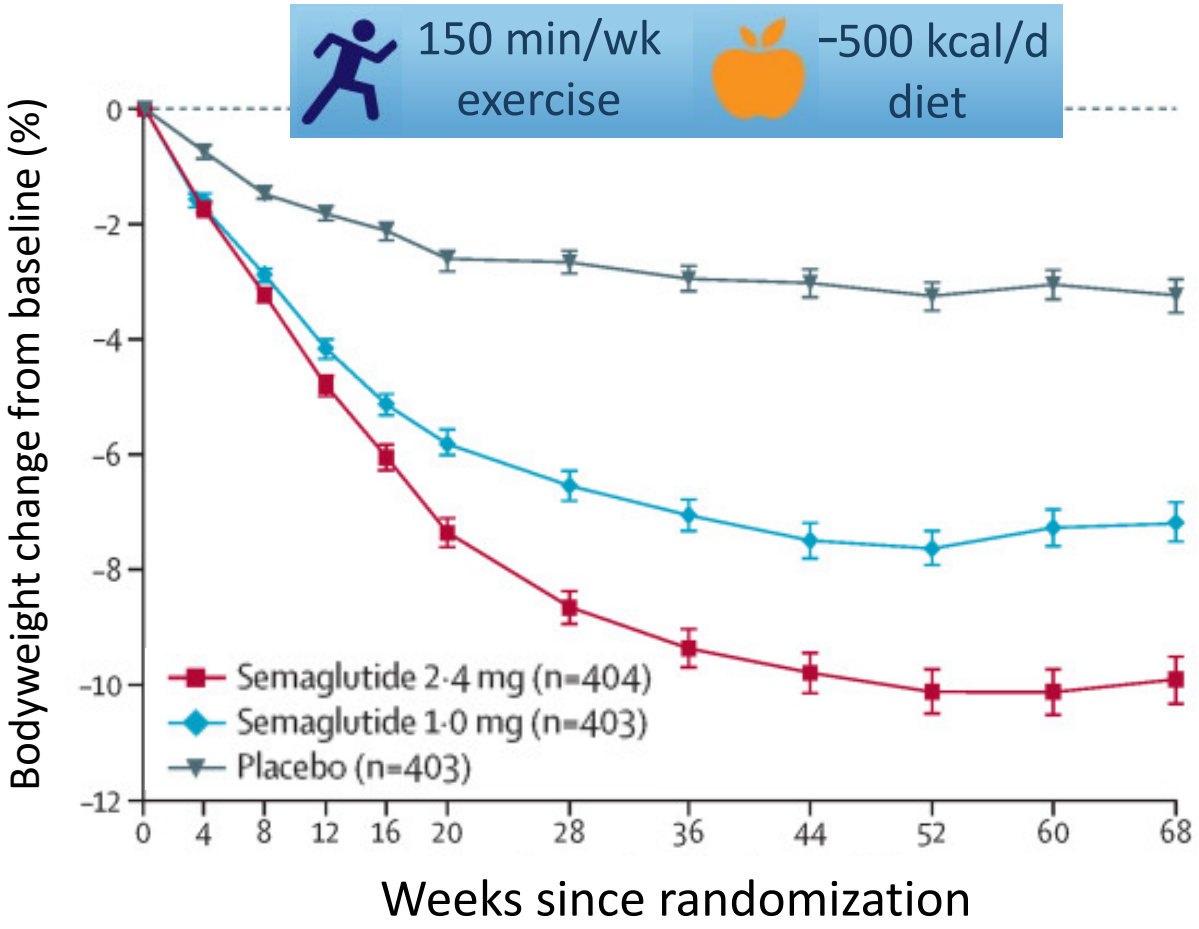


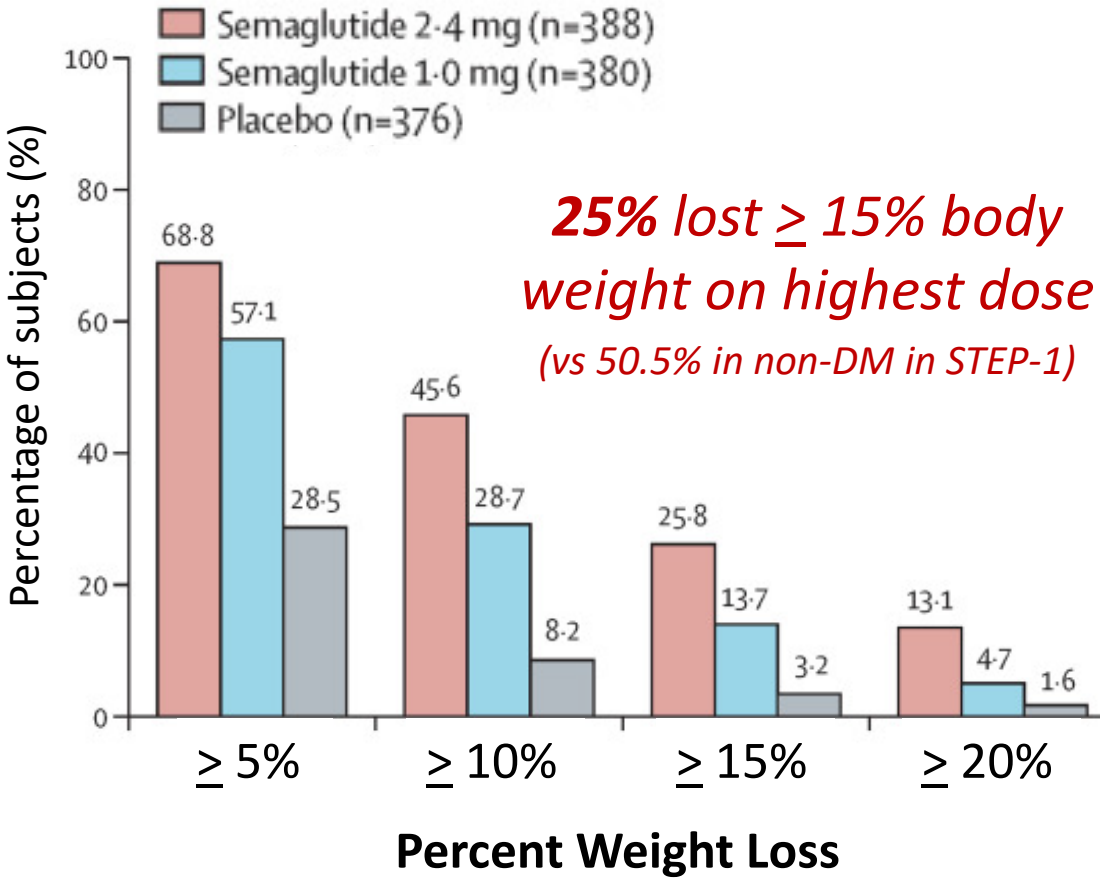


Wilding JPH, et al. NEJM (2021)

STEP-2: Semaglutide 2.4 mg shows robust weight loss in T2DM

Mean baseline A1c 8.1%, weight 99.8 kg, DM duration > 8 years and 0-3 glucose-lowering meds





***25%** lost ≥ 15% body weight on highest dose*

(vs 50.5% in non-DM in STEP-1)

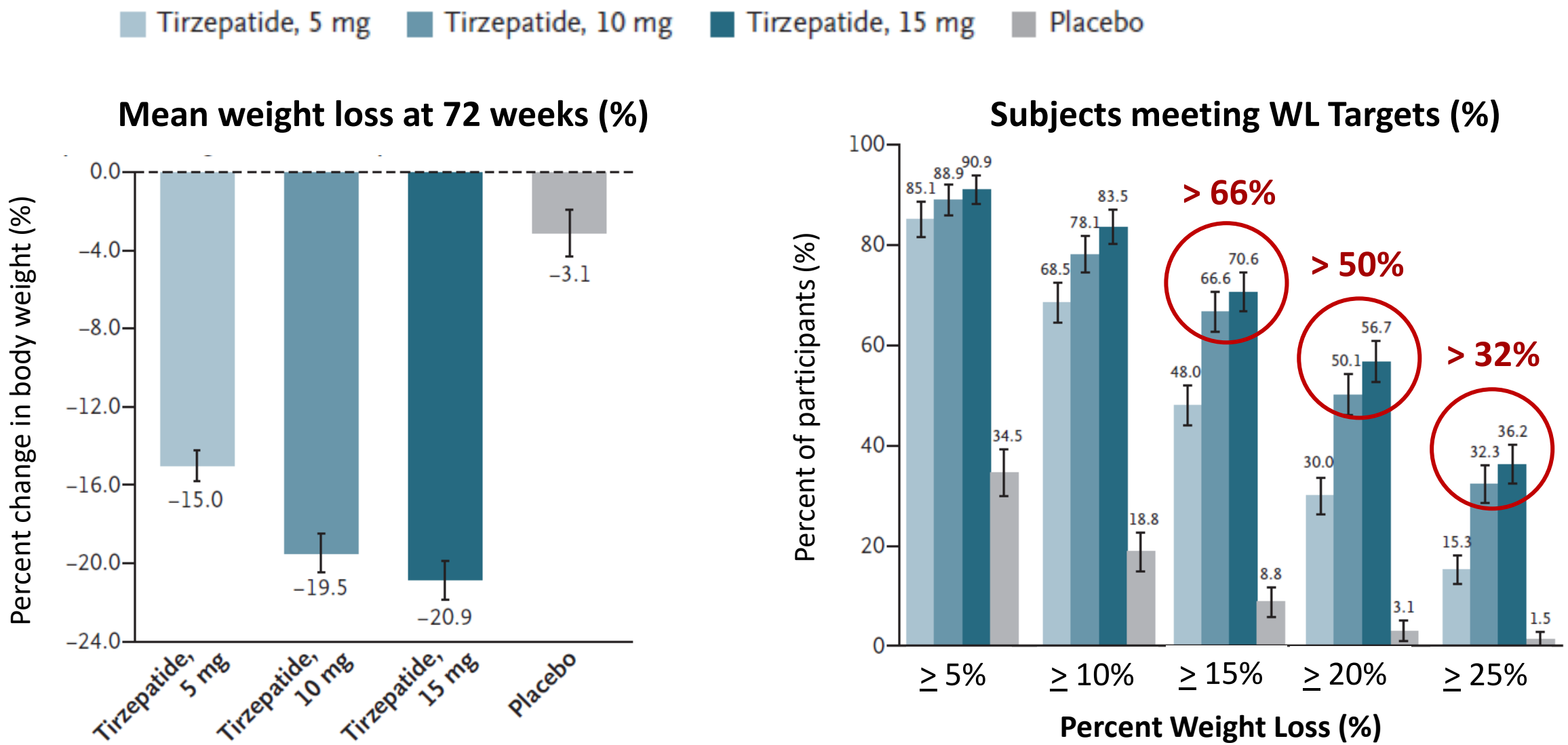
Davies M, et al. Lancet (2021)

GIP/GLP-1R agonist: Tirzepatide

Mechanism of action	• **GLP-1:** delayed gastric emptying, ↑ satiety, ↑ insulin • **GIP:** ↑ glucagon, ↑ lipolysis + glucose uptake, ↑ satiety
Dosing	• ***Single-use pens***: 2.5, 5, 7.5, 10, 12.5 or 15 mg SC weekly • ***Vials***: 2.5 or 5 mg SC weekly
Benefits	Weight loss, robust A1c lowering, OSA improves
HbA1c lowering	1.5 – 2.4 %
Contraindications	Medullary thyroid cancer or MEN-2 (personal/family), pregnancy or breast-feeding
Side effects	Nausea/vomiting, GI issues, fertility/OCP Rare (< 1%): Pancreatitis, cholecystitis, hypoglycemia

SURMOUNT-1 trial: Tirzepatide highly effective for WL

Baseline: BMI 38, weight 105 kg, T2DM excluded but 40% with pre-diabetes (n= 2539)



Jastreboff, A.
NEJM (2022)

SURMOUNT-OSA: Phase 3 trial of Tirzepatide vs placebo for treatment of OSA

Key Inclusion Criteria

- Age ≥ 18 years
- Body mass index ≥ 30 kg/m^2 or ≥ 27 kg/m^2 in Japan
- Moderate to severe sleep apnea, with AHI ≥ 15 events/hour
- History inadequate weight loss with diet and lifestyle modification alone

Key Exclusion Criteria

- Any diabetes history, A1c ≥ 6.5%
- Any treatment for OSA other than positive airway pressure (PAP)
- Central/mixed sleep apnea
- Major craniofacial abnormalities
- Contraindication to tirzepatide use

Malhotra A, et al. Cont Clin Trial (2024)

SURMOUNT-OSA: Primary objective

Double-blind, placebo-controlled trial, powered to demonstrate tirzepatide at maximum tolerated dose (MTD, 10 or 15 mg QW) is superior to placebo for mean decrease in AHI

Primary endpoint:

- Change in AHI from baseline to week 52 (events/h)
- Hypopnea is defined as any abnormal respiratory event lasting > 10s with > 30% reduction in airflow or > 4% oxygen desaturation

Malhotra A, et al. Cont Clin Trial (2024)

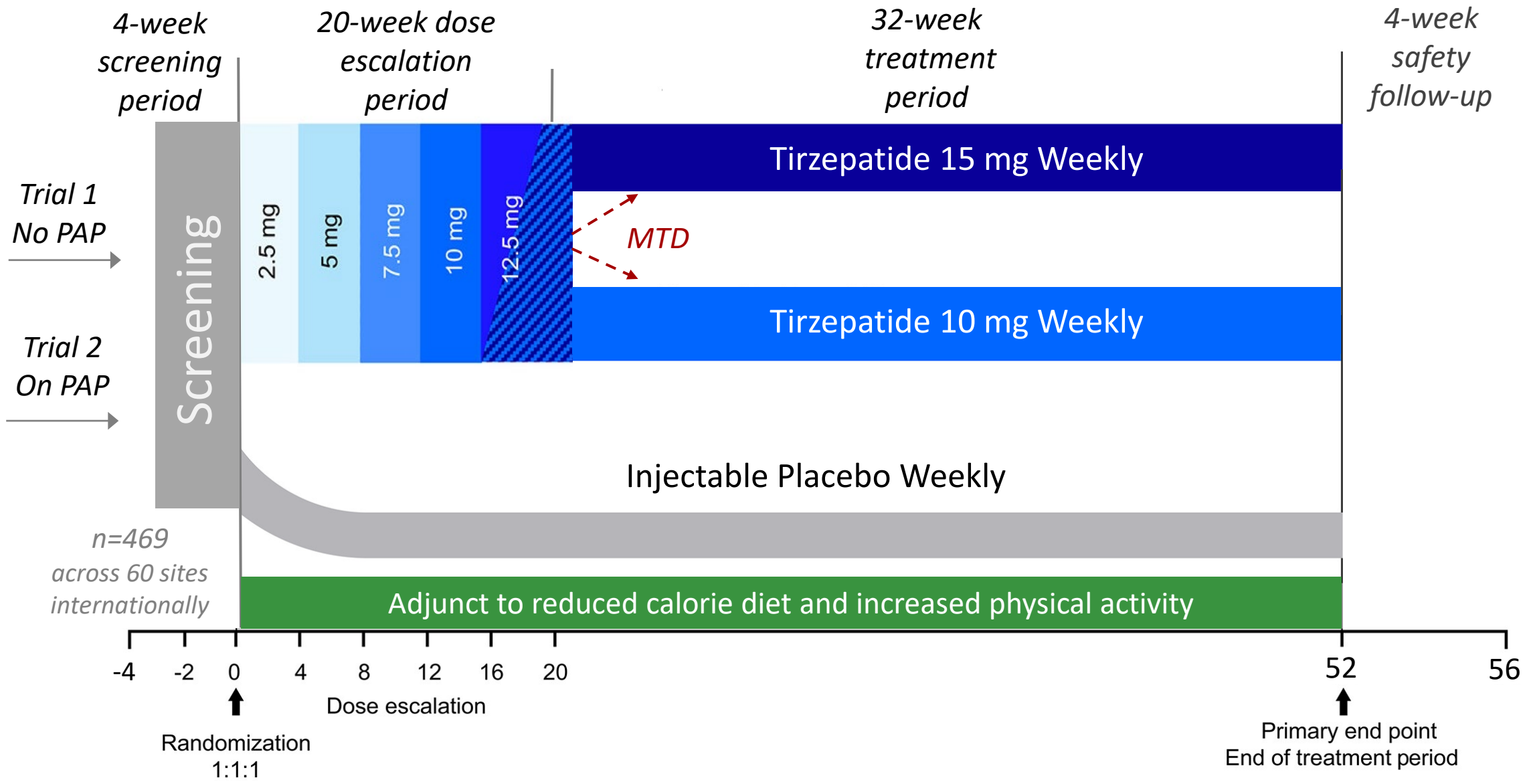
SURMOUNT-OSA: Secondary objectives

Secondary endpoints:

- Percentage of subjects with > 50% reduction in AHI from baseline
- Percentage of subjects with AHI < 5 events/hr or AHI < 14 events/hr and a score of 10 or less on the Epworth Sleepiness Scale (range 0 – 24)
- Percent change in body weight
- Change in OSA-specific hypoxic burden on polysomnography
- Change in Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Impairment and Sleep Disturbance scales
- Change in systolic blood pressure

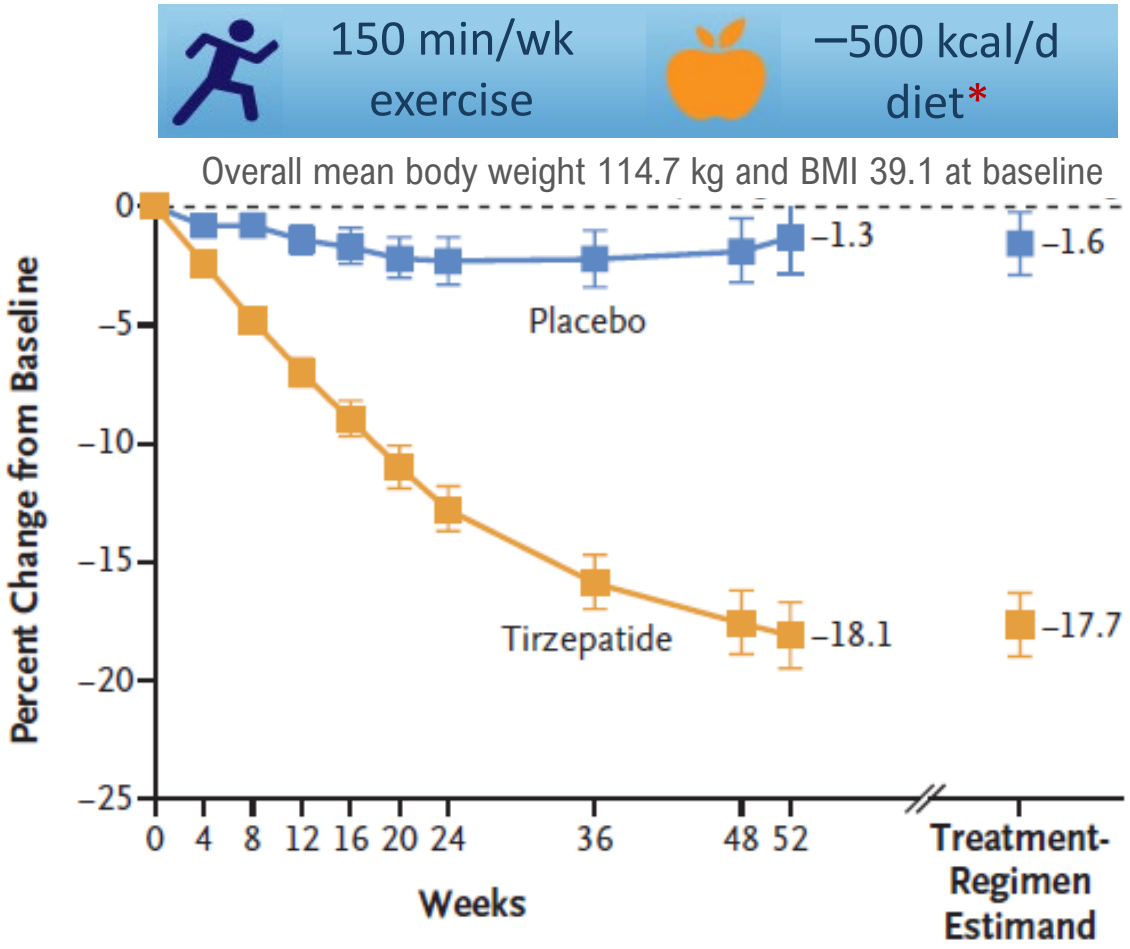
Malhotra A, et al. Cont Clin Trial (2024)

SURMOUNT-OSA: Study Design

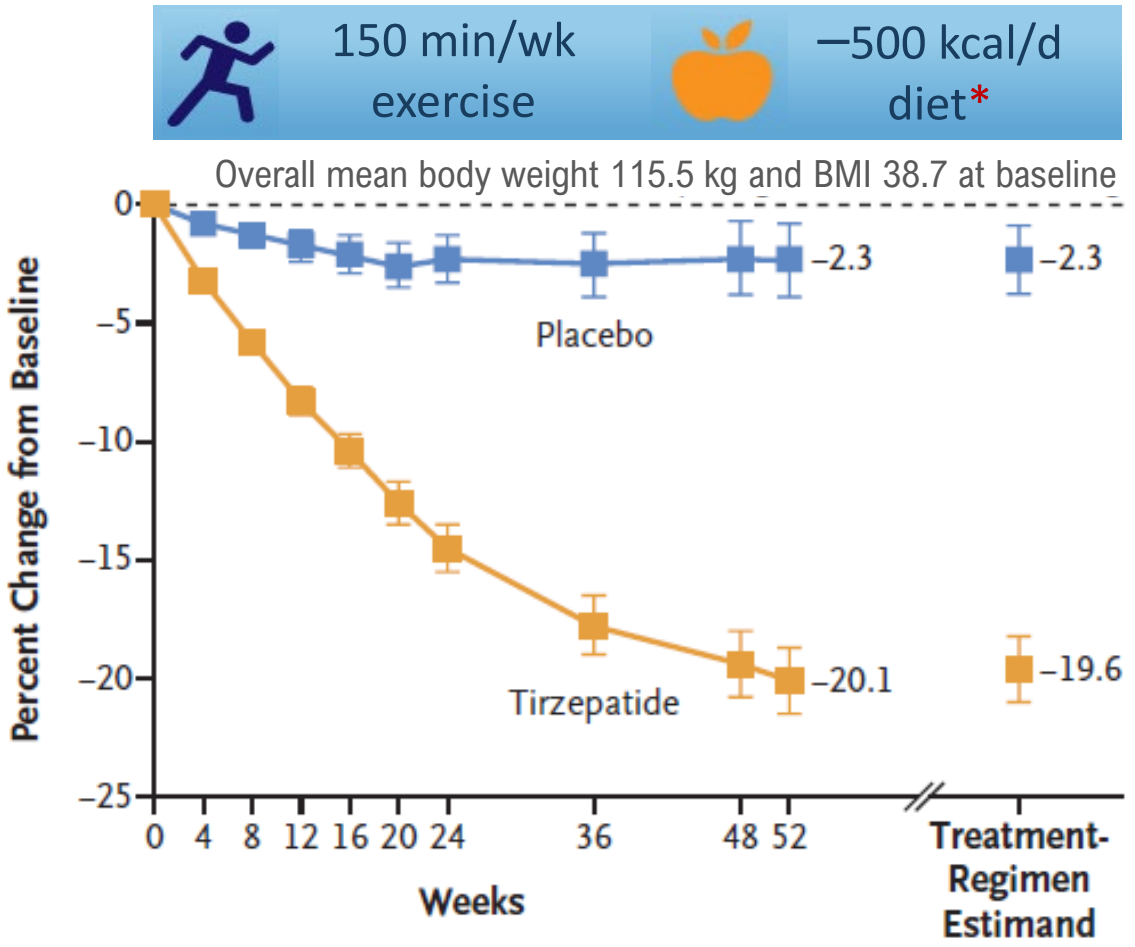


SURMOUNT-OSA: Mean change in body weight

Trial 1: No PAP therapy (n= 234)

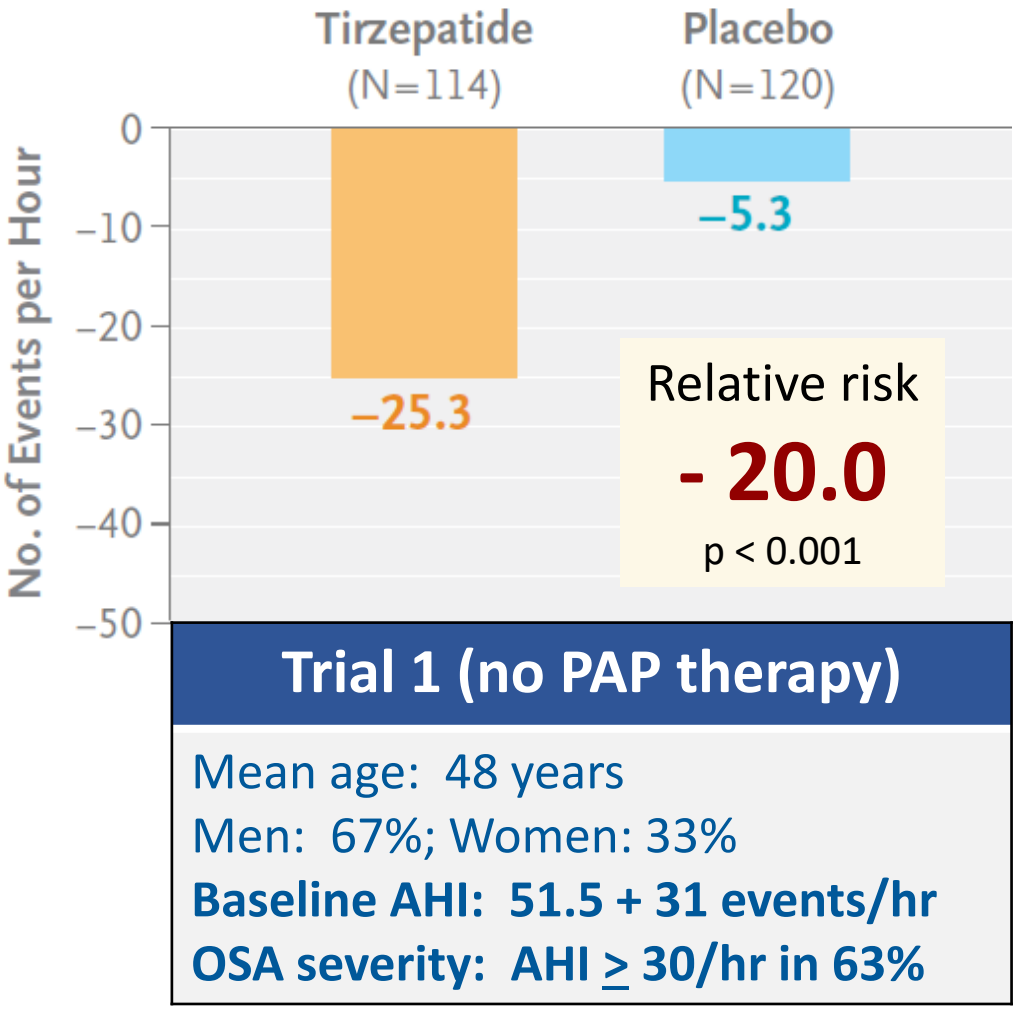


Trial 2: PAP therapy (n= 235)



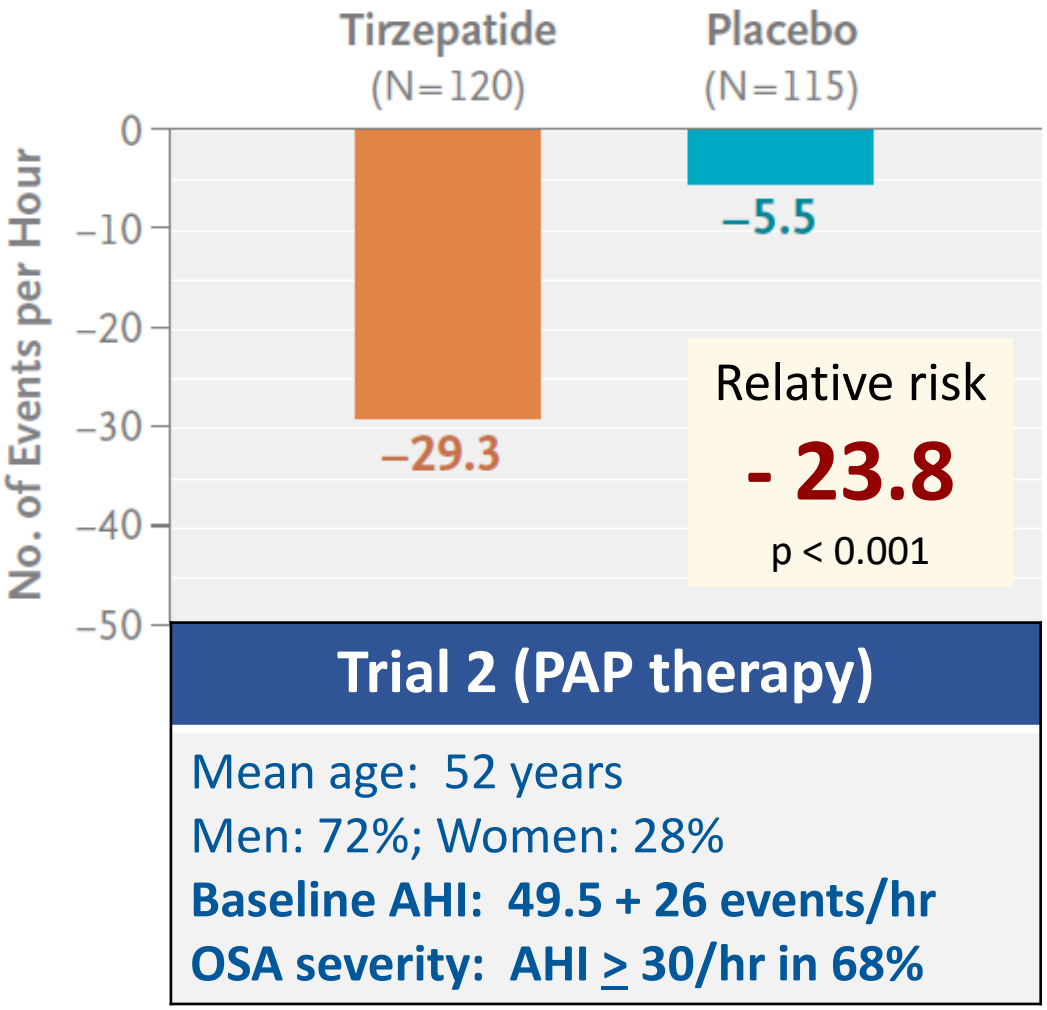
** Energy goals adjusted if BMI < 22 kg/m2 reached*

SURMOUNT-OSA: Primary Outcome, Change in AHI



Trial 1 (no PAP therapy)

Mean age: 48 years
Men: 67%; Women: 33%
Baseline AHI: 51.5 + 31 events/hr
OSA severity: AHI ≥ 30/hr in 63%

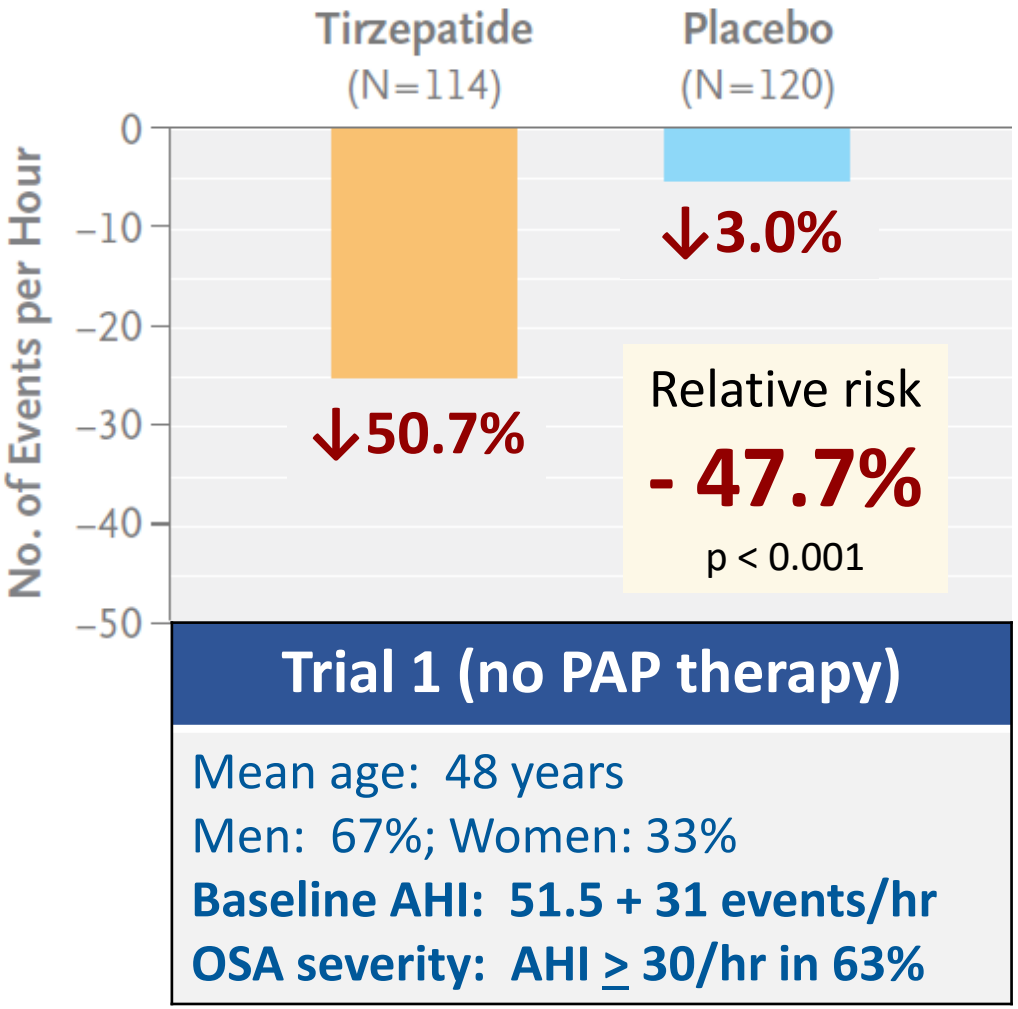


Trial 2 (PAP therapy)

Mean age: 52 years
Men: 72%; Women: 28%
Baseline AHI: 49.5 + 26 events/hr
OSA severity: AHI ≥ 30/hr in 68%

Malhotra A.
NEJM (June 2024)

SURMOUNT-OSA: Secondary Objective, % Change in AHI



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Baseline AHI: 51.5 + 31 events/hr
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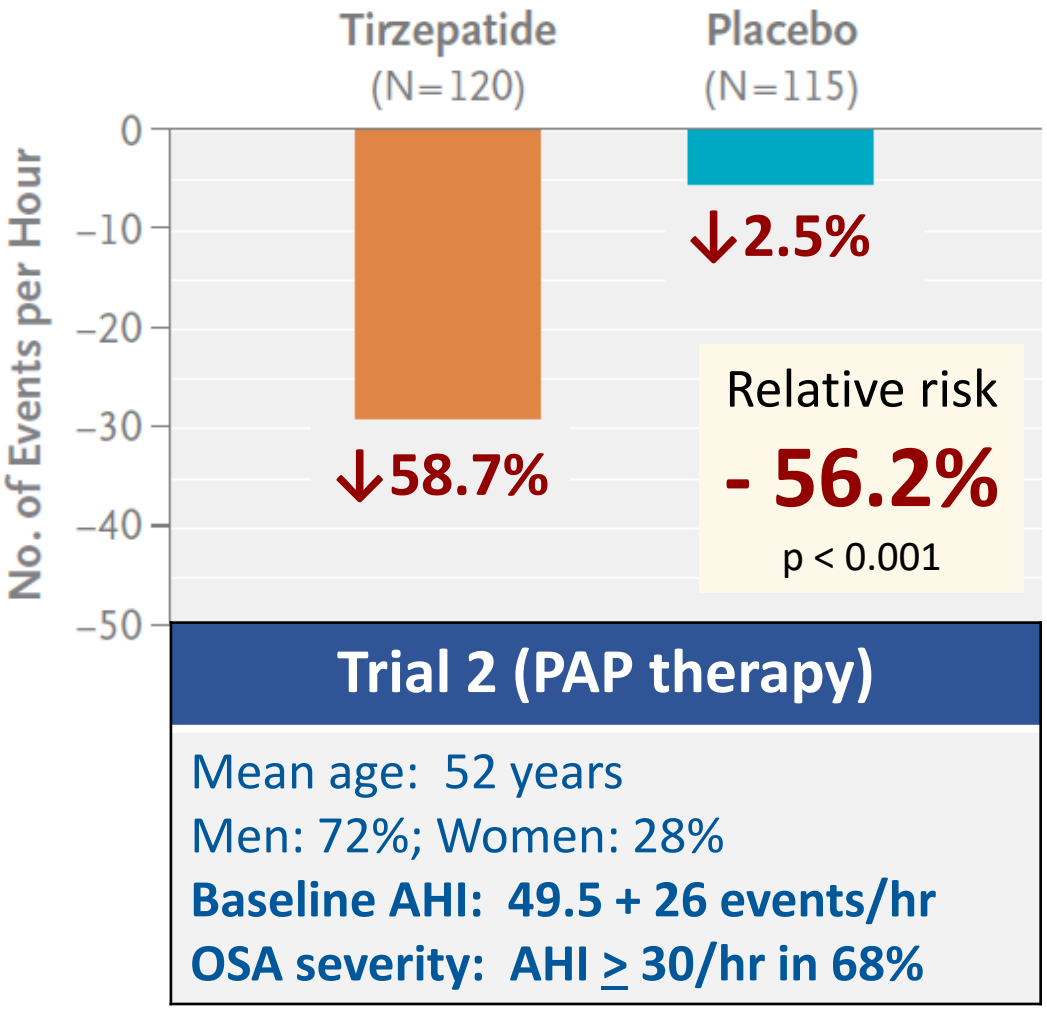


Trial 2 (PAP therapy)

Mean age: 52 years
Men: 72%; Women: 28%
Baseline AHI: 49.5 + 26 events/hr
OSA severity: AHI ≥ 30/hr in 68%

Malhotra A.
NEJM (June 2024)

SURMOUNT-OSA: Secondary outcomes

- **Reduction of ≥ 50% in AHI events ($p < 0.001$):**
  - Trial 1 (no PAP): 61% vs 19% in placebo
  - Trial 2 (PAP): 72% vs 23% in placebo
  - About 3.2x as likely to achieve this with tirzepatide
- **Disease resolution (AHI < 5 or AHI 5-14 + ESS < 10):**
  - Trial 1 (no PAP): 43% vs 16% in placebo
  - Trial 2 (PAP): 51% vs 14% in placebo
  - About 3x as likely to achieve this with tirzepatide

Malhotra A, et al. Cont Clin Trial (2024)

SURMOUNT-OSA: Secondary outcomes

Estimated treatment difference (RR):

- Systolic blood pressure: - 3.7 – 7.6 mmHg
- Diastolic blood pressure: - 1.1 – 2.8 mmHg
- PROMIS-SRI scale (pooled): -3.9 points
- PROMIS-SD scale (pooled): - 3.1 points
- OSA-specific hypoxic burden: - 61.3 – 70.1% min/hr

Tirzepatide is superior to placebo for ALL primary/secondary endpoints

Malhotra A. NEJM (2024)

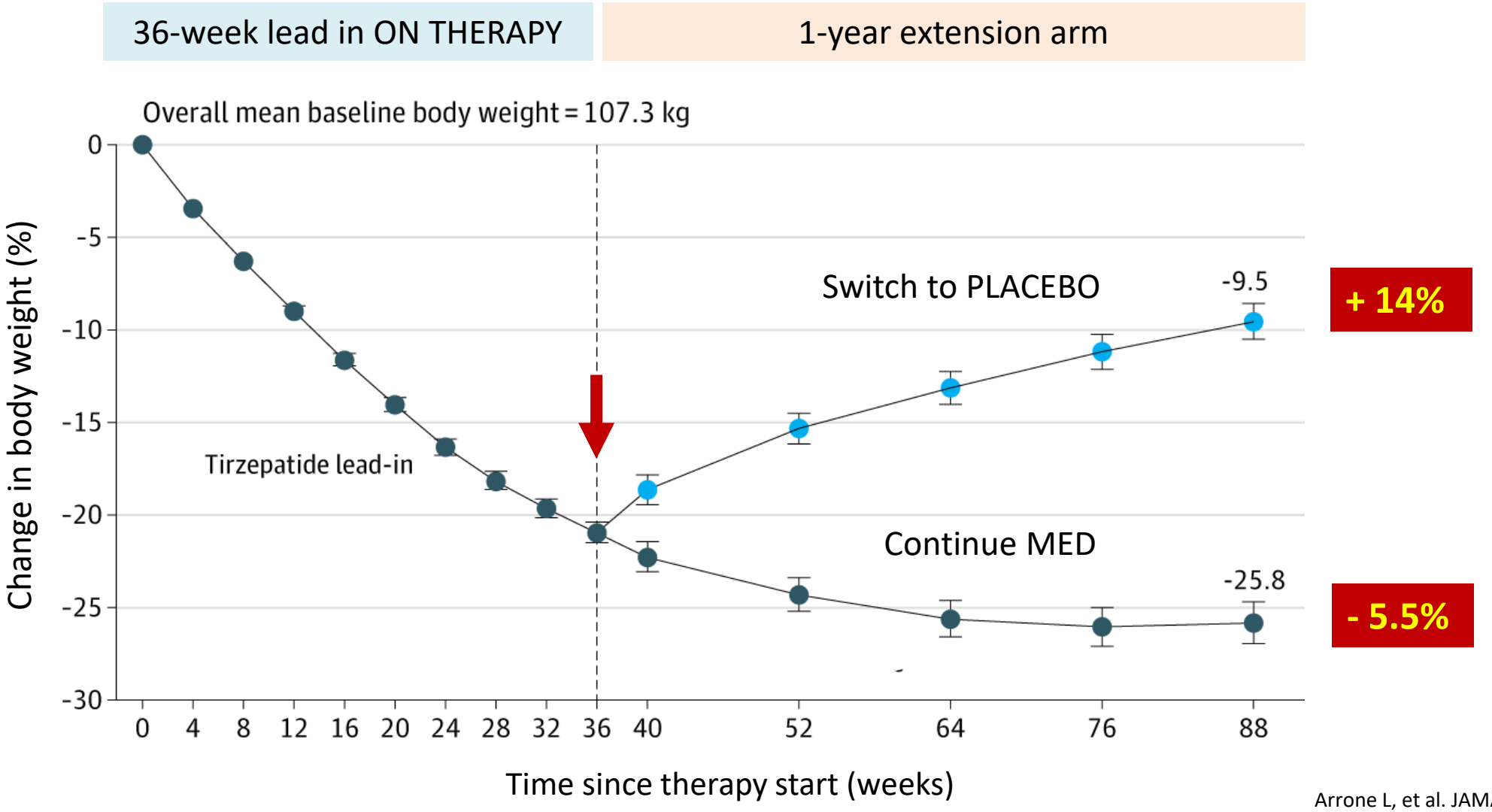
SURMOUNT-OSA: Pooled safety outcomes

Safety outcome	Tirzepatide	Placebo
Adverse event leasing to study drug discontinuation	3.9%	4.3%
Diarrhea	24.0%	10.7%
Nausea	23.6%	7.7%
Acute pancreatitis	0.9%	0%

Less discontinuation on treatment

Malhotra A, et al. Cont Clin Trial (2024)

SURMOUNT-4: Tirzepatide extension trial shows continued weight loss to nadir > 25% after 1 year vs weight regain with discontinuation



Arrone L, et al. JAMA (2024)

Key Points

- Strategies targeting ***primary and secondary prevention*** of obesity and diabetes, including GLP-1RA, reduce OSA disease burden.

- GLP-1RA ***semaglutide and tirzepatide should be prioritized*** in OSA management where weight loss of 15-20% or more is typically needed for disease improvement or remission.

- SURMOUNT-OSA demonstrated superiority of tirzepatide in reducing OSA burden and was well tolerated in phase 3 trials.

Future questions

- How important are weight-independent effects of GLP-1RA in OSA? Would we ever consider using in BMI < 27 kg/m^2?
- Can GLP-1RA improve airway tone or neural pathways related to breathing?
- What is the optimal way to use GLP-1RA therapies in OSA?
  - Monotherapy for mild disease management?
  - Patients unwilling or unable to tolerate device-based therapy?
  - Comorbid disease management, ie diabetes or CVD risk reduction?
- Will tirzepatide or other GLP-1RA gain FDA-approval for OSA indication?

Any questions?