Grand Rounds, St. Vincent's Health East and Ascension Hospitals

Treatment of Obesity as a Disease

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Has no financial relationships with ACCME defined commercial interests

Obesity is a Disease: American Association of Clinical Endocrinologists Position Statement[1]

1. "It is the strong contention of AACE that the view of obesity as a behav

2. "..

3. "..

in increased morbidity and mortality."

The American Medical Association designates obesity as a disease.

June 18, 2013, AMA House of Delegates

[1] Mechanick JI, Garber AJ, Handelsman Y, Garvey WT. *Endocr Pract*. 2012;18:642-8.

AACE Designates Obesity as a Chronic Disease* based on AMA Criteria

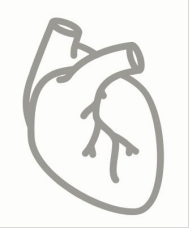
***involves interactions among genetic, environmental, and behavioral factors**

Characteristic signs or symptoms

✔ **BMI**

Results in harm or morbidity

✔ Cardiometabolic and biomechanical complications



Impairment in the normal functioning of some aspect of the body

✔ Satiety hormone regulation of energy intake

✔ Adipose tissue dysfunction

Criteria established by the American Medical Association (AMA), Report 4 of the Council on Scientific Affairs (A-05). Recommendations for Physician and Community Collaboration on the Management of Obesity (Resolution 421, A-04), 2005

Mechanick JI, Garber AJ, Handelsman Y, Garvey WT. *Endocr Pract*. 2012;18:642-8

Assessing Weight: BMI and Waist Circumference

BMI = weight (kg)/height (m^2)*	
Normal weight	BMI 18.5-24.9
Overweight	BMI 25.0-29.9
Obesity class 1	BMI 30.0-34.9
Obesity class 2	BMI 35.0-39.9
Obesity class 3 (severe)	BMI ≥40.0

Waist Circumference (Increase Risk)

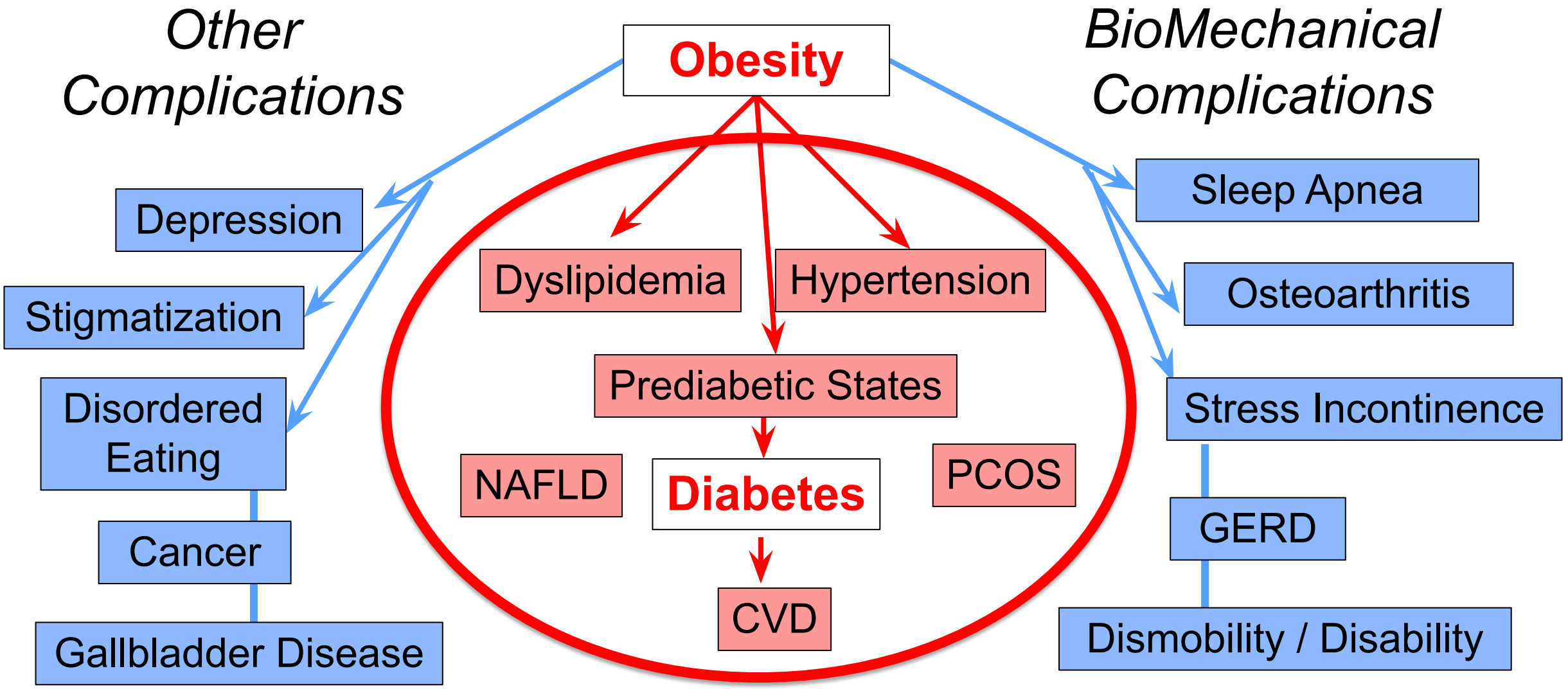
Men
>102 cm (40 in.)

Women
>88 cm (35 in.)

*World Health Organization defines overweight as BMI ≥25 kg/m^2 and obese as BMI ≥30 kg/m^2.

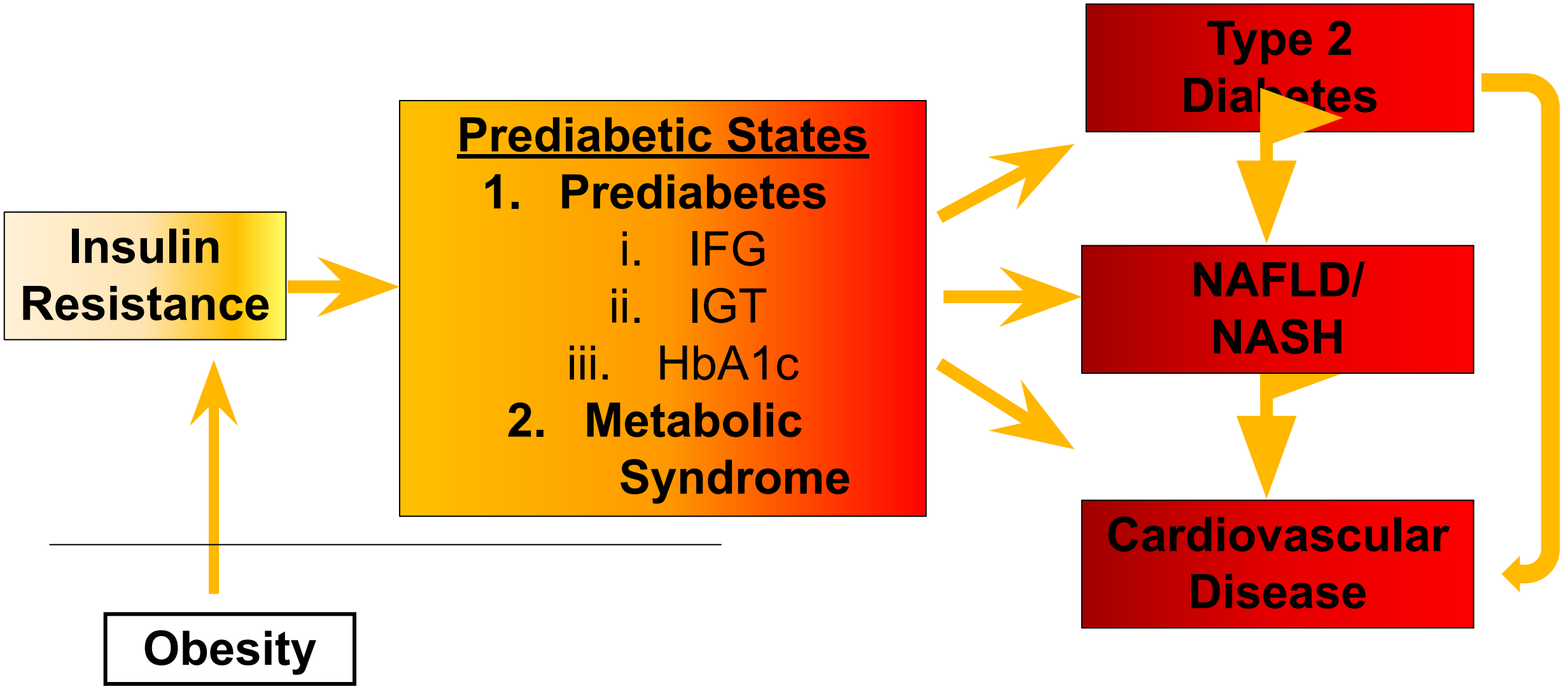
http://www.who.int/mediacentre/factsheets/fs311/en/. Accessed August 20, 2015.

Medical Complications of Obesity



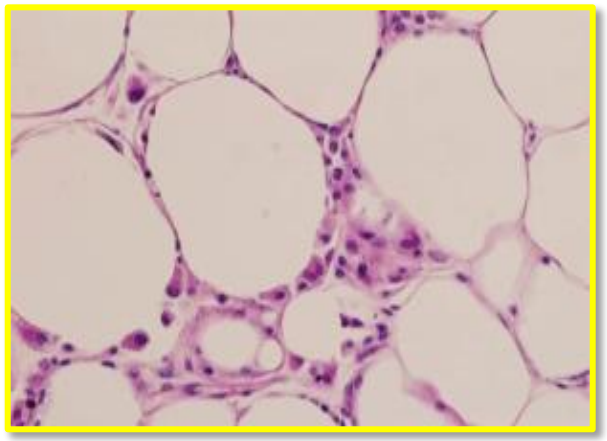
Daniel S, Soleymani T, Garvey WT. Curr Opin Endocrinol Diabetes Obes, 20:377-388, 2013

The Spectrum of Cardiometabolic Disease



Abnormal Adipose Tissue Function in Obesity Pathogenesis of Cardiometabolic Disease

Adipose Tissue Inflammation



Ventral Adiposity

Dysregulated Secretion of Adipocyte Factors

Lipoproteins:
DYSLIPIDEMIA
Increased large VLDL
Increased small LDL
Increased LDL particles
Decreased large HDL

Blood Vessel:
ENDOTHELIAL DYSFUNCTION
Vascular Reactivity
Dysfibrinolysis
Inflammation
Foam Cell
Hypertension

Muscle:
INSULIN RESISTANCE
Glucose Intolerance

Secreted Adipocyte Factors

Insulin Resistance/Adipocyte Size

- Free Fatty Acids
- Leptin
- Adiponectin
- Resistin

Vascular Reactivity

- Free Fatty Acids
- Angiotensinogen (RAAS)
- Inflammation

Dysfibrinolysis

- PAI-1
- Platelet reactivity

Lipids/Lipoproteins

- Acylation Stimulation Protein
- Cholesterol Ester Transfer Protein
- Phospholipid Transfer Protein

Inflammation

- TNF alpha
- IL-1, IL-6, IL-8, IL-10
- MCP-1
- MIF

RAAS, renin–angiotensin–aldosterone system; TNF, tumor necrosis factor; IL, interleukin; MCP-1, monocyte chemotactic protein-1; MIF, macrophage migration inhibiting factor.

Metabolic Syndrome Trait Cluster

Metabolic Syndrome Criteria

- Impaired glucose tolerance
- High waist circumference
- Elevated blood pressures
- Hypertriglyceridemia
- Low HDL

HDL, high-density lipoprotein; LDL, low-density lipoprotein;
PAI-1, plasminogen activator inhibitor-1;
NAFLD, non-alcoholic fatty liver disease

- Small dense LDL
- NAFLD
- Positive family history
- Dysfibrinolysis (high PAI-1)
- Vascular reactivity/ endothelial dysfunction
- Inflammation

Environment

Genetics

↑Energy Intake

↓Energy Expenditure

Excess fat storage

INSULIN SENSITIVE
increased fat mass

INSULIN RESISTANT
Inflammation in Fat

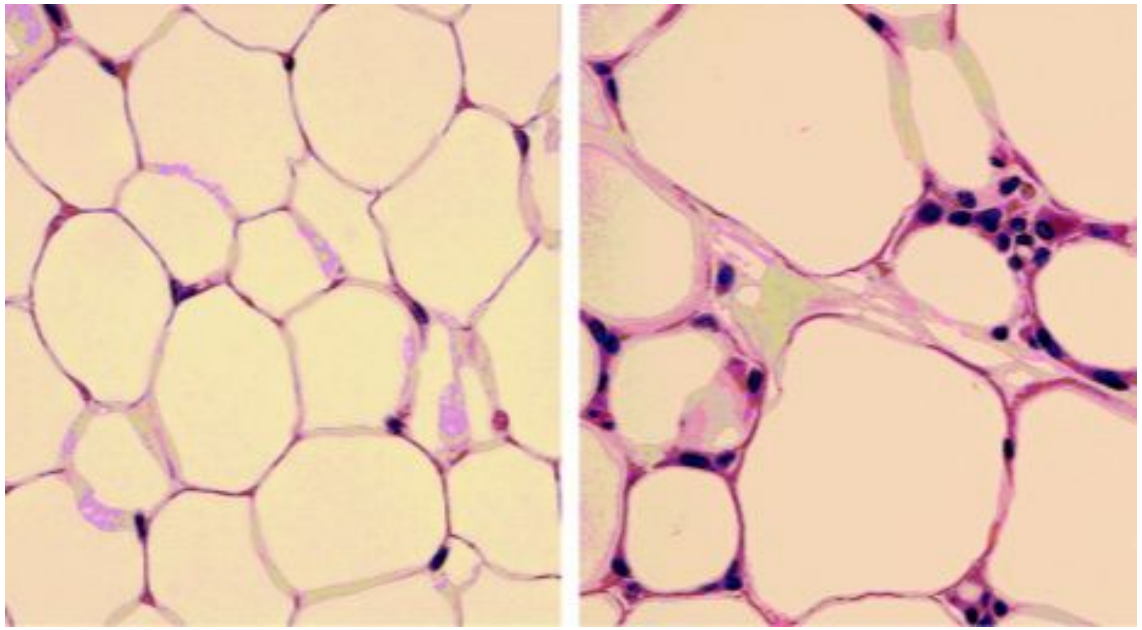
Osteo-ar thritis

Sleep Apnea

Disability

GERD

Urinary Incontinence



Diabetes

Metabolic Syndrome

Prediabetes

NAFLD

HTN

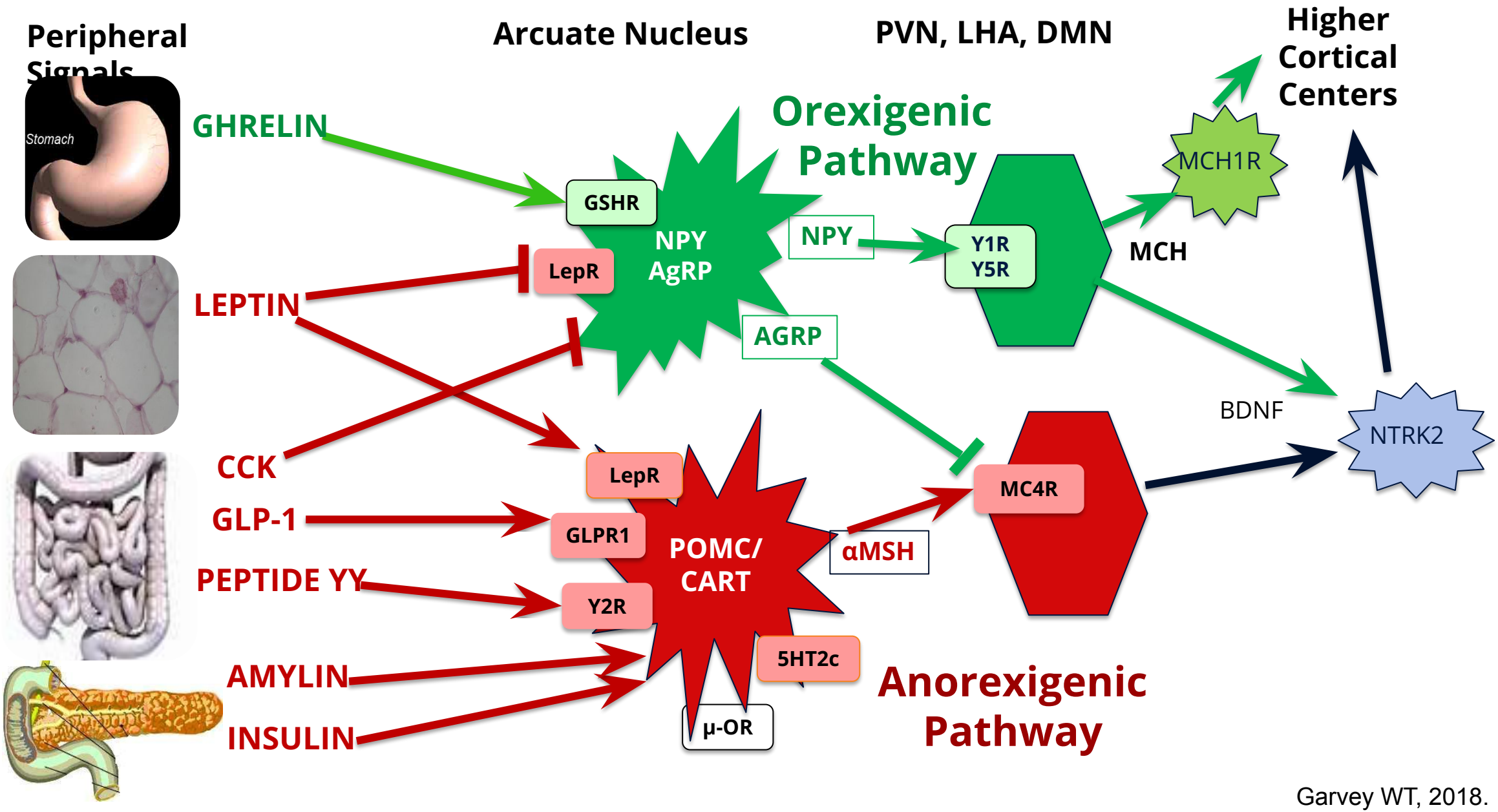
CVD

BIOMECHANICAL Complications

CARDIOMETABOLIC Complications

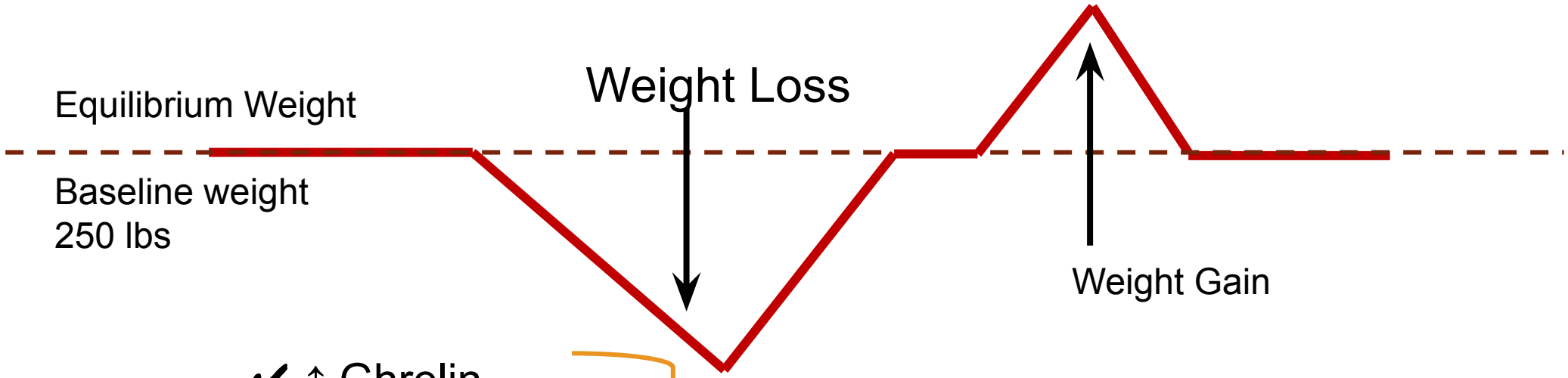
Adapted from Bray GA. *Obesity (Silver Spring)*. 2013;21:893-9.
Domenica M. Rubino, MD.

Regulation of Energy Intake



Garvey WT, 2018.

In Obesity, maladaptive responses protect against weight loss and maintain a high body weight



- ✔ ↑ Ghrelin
- ✔ ↓ Leptin, PYY, CCK, Amylin

→ Increased Appetite

- ✔ ↓ Resting energy expenditure

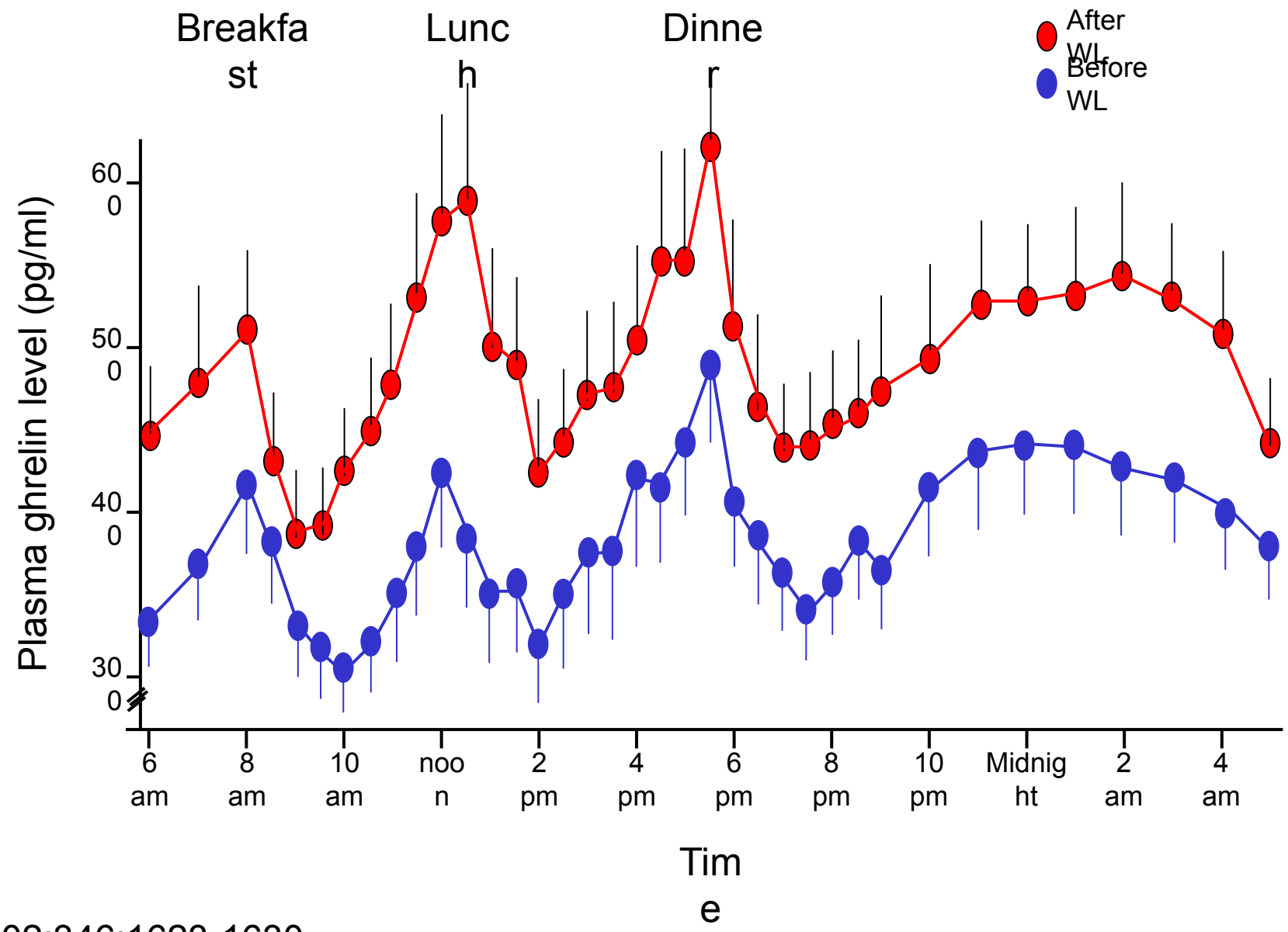
→ Decreased Energy Out

- ✔ ↑ Hunger
- ✔ ↑ Calorie-dense food preferences

→ Increased Energy In

Garvey WT, 2014

24-Hour Plasma Ghrelin Profiles in Obese Subjects before and after Diet-Induced Weight Loss



Cummings, D. et al. N Engl J Med 2002;346:1623-1630

Maladaptations to Weight Loss:

Obesity Protects Obesity

↑ **Orexigenic Hormones**
Ghrelin

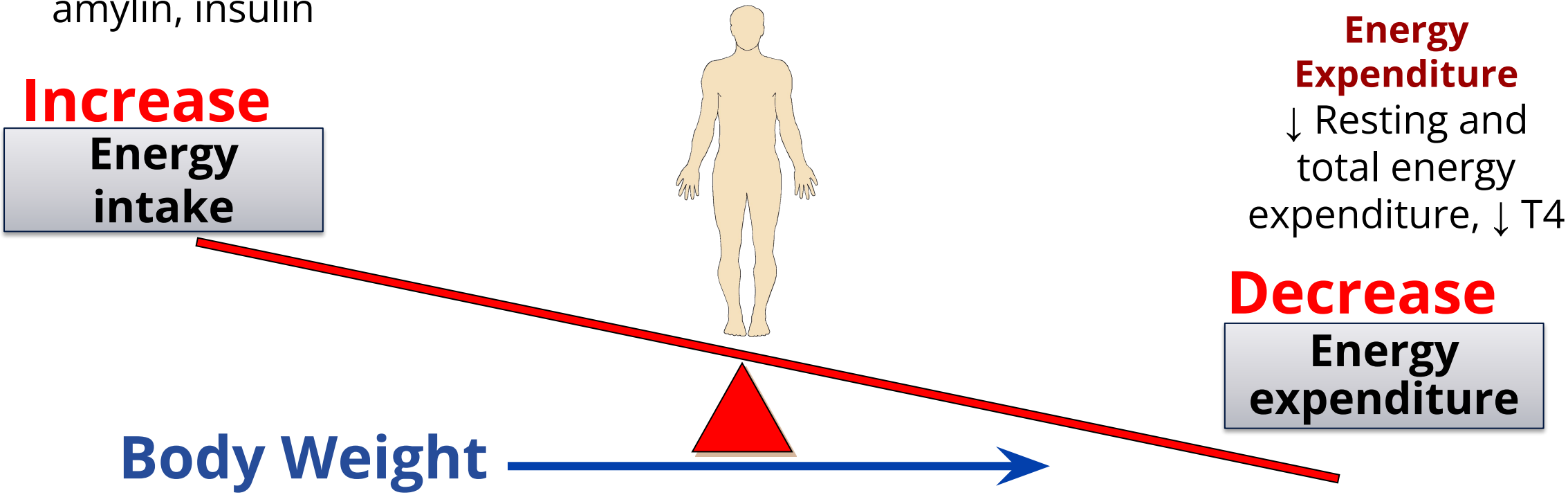
↓ **Anorexigenic Hormones**
Leptin, PYY, CCK, GLP-1, amylin, insulin

Eating Behavior
↑ Hunger, Prefer calorie dense foods

Metabolism
↓ Fat oxidation
↑ Cortisol

Nervous System
↓ SNS activity, ↑ mesolimbic reward center activity

Energy Expenditure
↓ Resting and total energy expenditure, ↓ T4



AACE/EASO New Medical Diagnostic Term for the Disease of Obesity

Adiposity-Based Chronic Disease

Abnormalities in Adipose Tissue

- Mass
- Distribution
- Function

Lifelong disease with complications that impair health

Mechanick J, Hurley D, and Garvey WT. Endocrine Practice, 23(3):372-378, 2017

AACE Obesity Guidelines

AACE Complications-Centric Principles

Treatment of Patients with ABCD

We treat obesity to improve the health of the patient

The prevention and treatment of obesity complications

- Cardiometabolic
- Biomechanical
- Quality of Life

The prevention and treatment of complications is the goal and end-point of therapy, not the loss of a given amount of kilograms per se

Garvey WT et al. Endocrine Practice 22(Suppl 3):1-203, 2016

Basic Principles of the AACE Obesity Guidelines

Diagnosis: two components

- **Anthropometric**: BMI
- **Clinical**: Presence and Severity of Complications

Staging & Treatment

Complications	AACE Stage	Goal	Suggested therapy
No Complications	Stage 0	• Weight Loss or prevent further weight gain • Prevent complications	Lifestyle intervention
Mild-Moderate Complications	Stage 1	Weight loss sufficient to treat complications	• Lifestyle • Consider medication
Severe Complication	Stage 2		• Lifestyle • Medication • Consider surgery

Outcome Goal

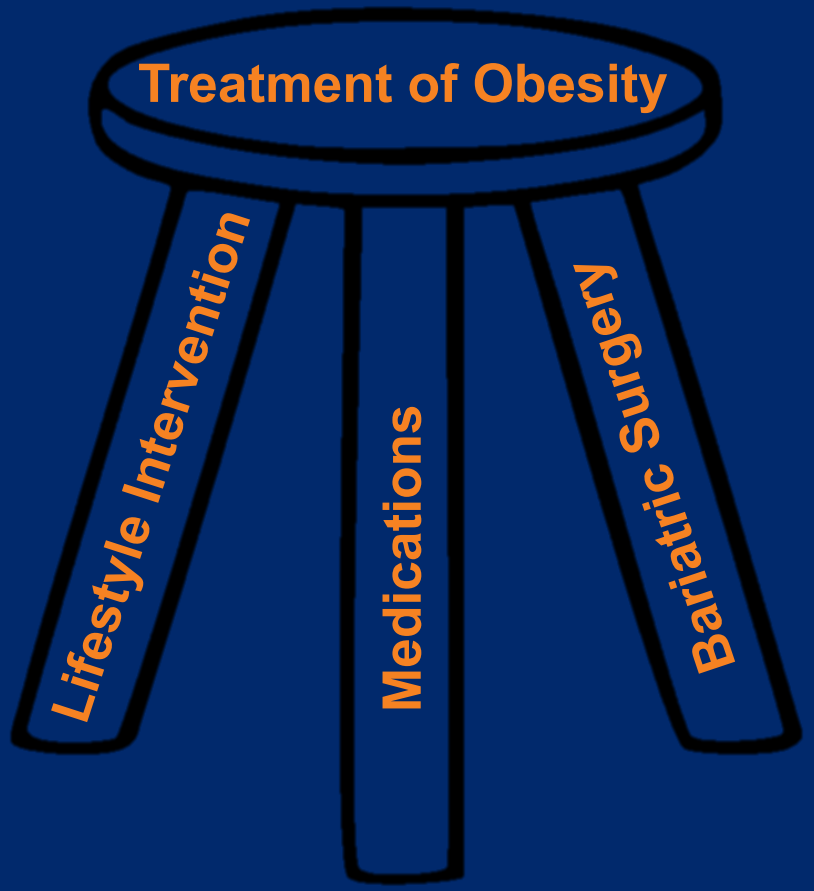
Prevent or treat complications to target

Garvey WT et al. Endocrine Practice 22(Suppl 3):1-203, 2016

% Weight Loss Needed to Reduce Complications

COMPLICATION	% weight loss	Notes	References
Diabetes Prevention	7% to 10%	Maximum benefit 10%	DPP (Lancet, 2009) SEQUEL (Garvey et al, 2013)
Hypertension	5% to >15%	BP still decreasing >15%	Look AHEAD (Wing, 2011)
Dyslipidemia	5% to >15%	TG still decreasing at >15%	Look AHEAD (Wing, 2011)
HbA1c	5% to >15%	HbA1c still decreasing at >15%	Look AHEAD (Wing, 2011)
NAFLD	>10%	Improves steatosis, inflammation, mild fibrosis	Assy et al, 2007; Dixon et at, 2004; Anish et al, 2009
Sleep Apnea (AHI)	10%	Little benefit at ≤ 5%	Sleep AHEAD (Foster, 2009) Winslow et al, 2012
Osteoarthritis	5-10%	Improves symptoms and joint stress mechanics	Christensen et al, 2007 Felson et al, 1992; Aaboe et al, 2011
Stress Incontinence	5-10%		Burgio et al, 2007 Leslee et al, 2009
GERD	5-10%		Singh et al, 2013 Tutujian R, 2011
PCOS	5-15%	Lowers androgens, improves ovulation, increases insulin sensitivity	Panidis D et al, 2008 Norman et al, 2002 Moran et al, 2013

Treatment Modalities
Patients with ABCD with Overweight and Obesity



Lifestyle Therapy for ABCD/Obesity Management

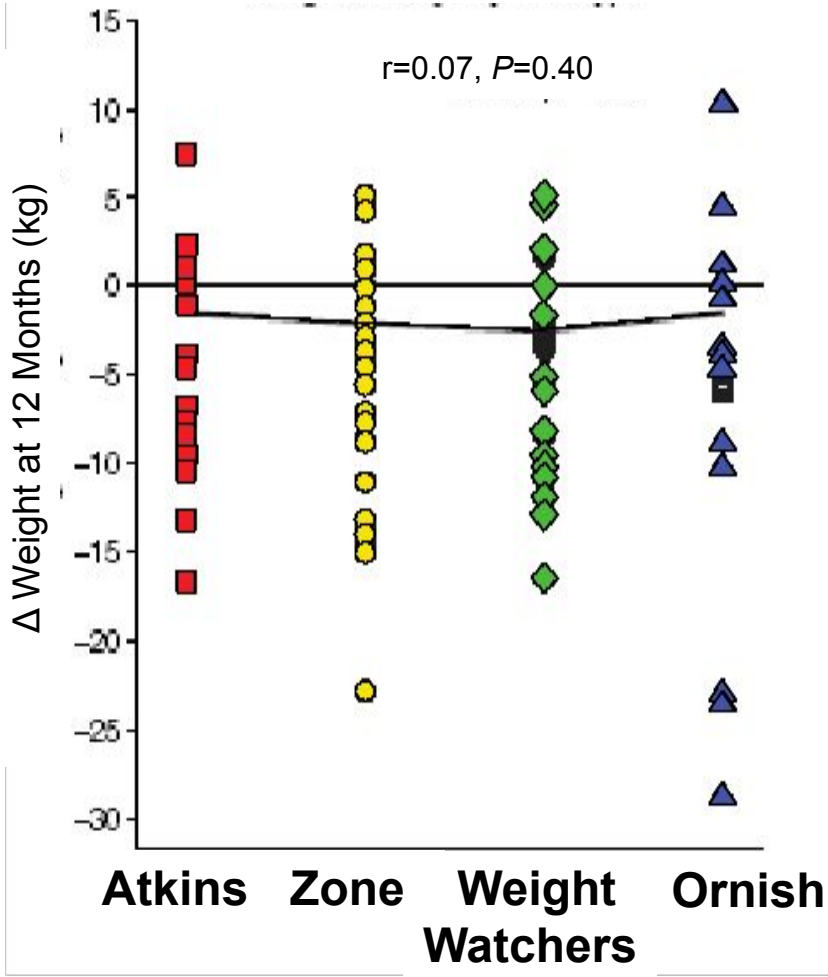
- **Healthy meal plan** (low-fat, low-CHO, DASH, Mediterranean, vegetarian, etc)
  - Reduce energy intake by 500-1,000 kcal/d
  - Reduce portion size
  - Meal replacements
- **Physical Activity**
  - ≥150 min/wk (DPP)
  - Aerobic plus resistance exercise
  - BUT, anything is better than nothing
- **Behavioral interventions**: record food intake, physical activity, and weight; education, psychological factors, motivational interviewing

Diabetes Prevention Program Research Group. *N Engl J Med*. 2002;346:393-403. Look AHEAD Research Group. *Obesity*. 2006;14:737-752.

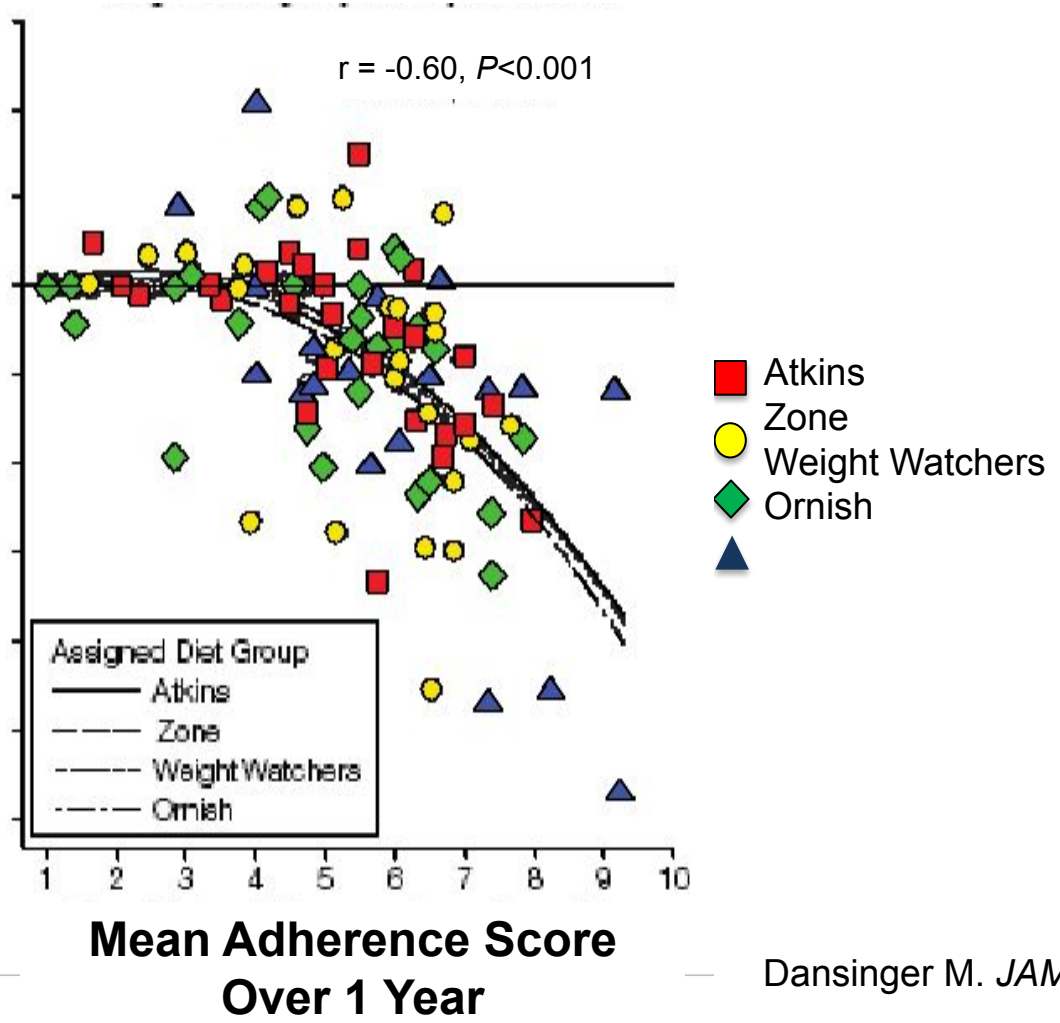
Garvey WT et al. AACE Obesity Guidelines. Endocrine Practice 22(Suppl 3):1-203, 2016

Adherence Is More Important Than Diet Type for Weight Loss Success

Weight Change by Diet Type



Weight Change by Dietary Adherence



Dansinger M. *JAMA*. 2005;293:43-53.

What if there was a treatment for T2D that:

1 Reduc edications

2

3

4

5

6 a

7

8

9

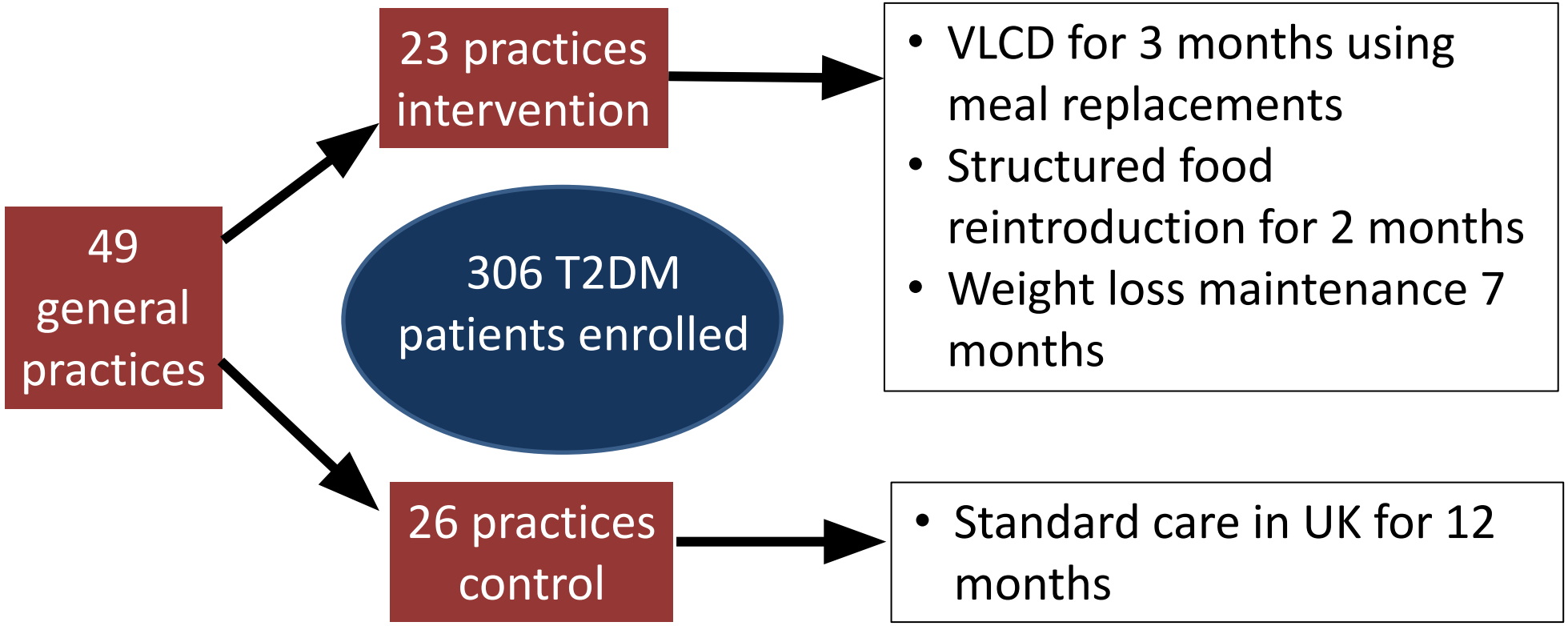
10

This is the therapeutic profile of weight loss in T2D

Look AHEAD study references. Phase 3 trials for weight loss meds
1. Look Ahead Research Group. *Diabetes Care* 2007;30:1374–83; 2. Look Ahead Research Group. *N Engl J Med* 2013;369:145–54;
3. Lean M et al. *Lancet* 2018;391:541–51; 4. Davies MJ *et al. JAMA* 2015;314:687–99

Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial

Lean ME et al. Lancet 391(10120):541-551, 2018



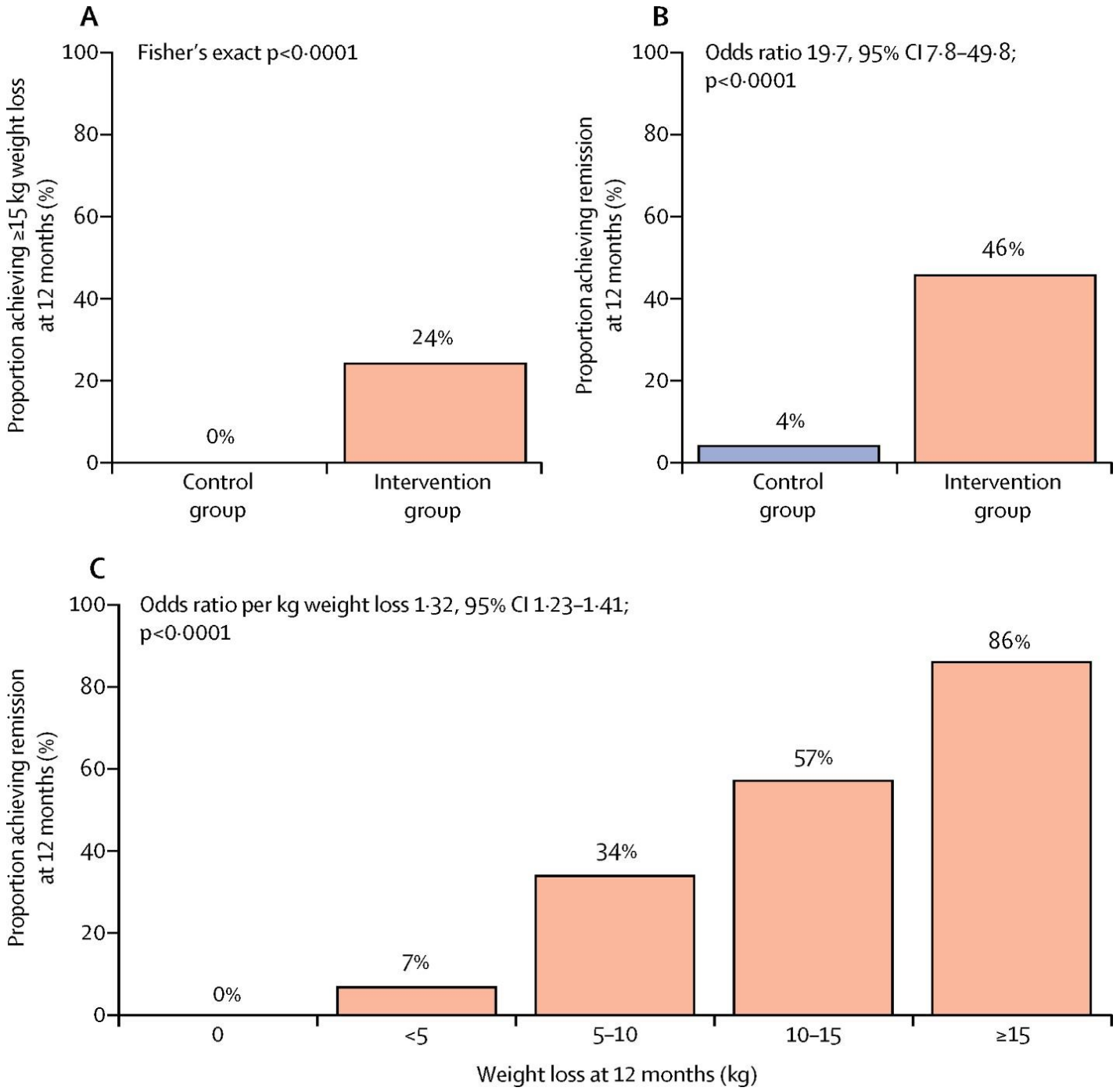
DIRECT Study: Results

Parameter/Outcome	Intervention Group	Control Group
Weight	↓ 10.0 kg	↓ 1.0 kg
HbA1c	↓ 0.9%	↑ 0.1%
Number Diabetes Medications	↓ 0.8	↑ 0.2
Number Blood Pressure Medications	↓ 0.6	↑ 0.1
Triglycerides	↓ 0.31 mmol/L	↑ 0.09 mmol/L
Quality of Life	↑ 7.2	↓ 2.9

Lean ME et al. Lancet 391(10120):541-551, 2018

DIRECT Study:

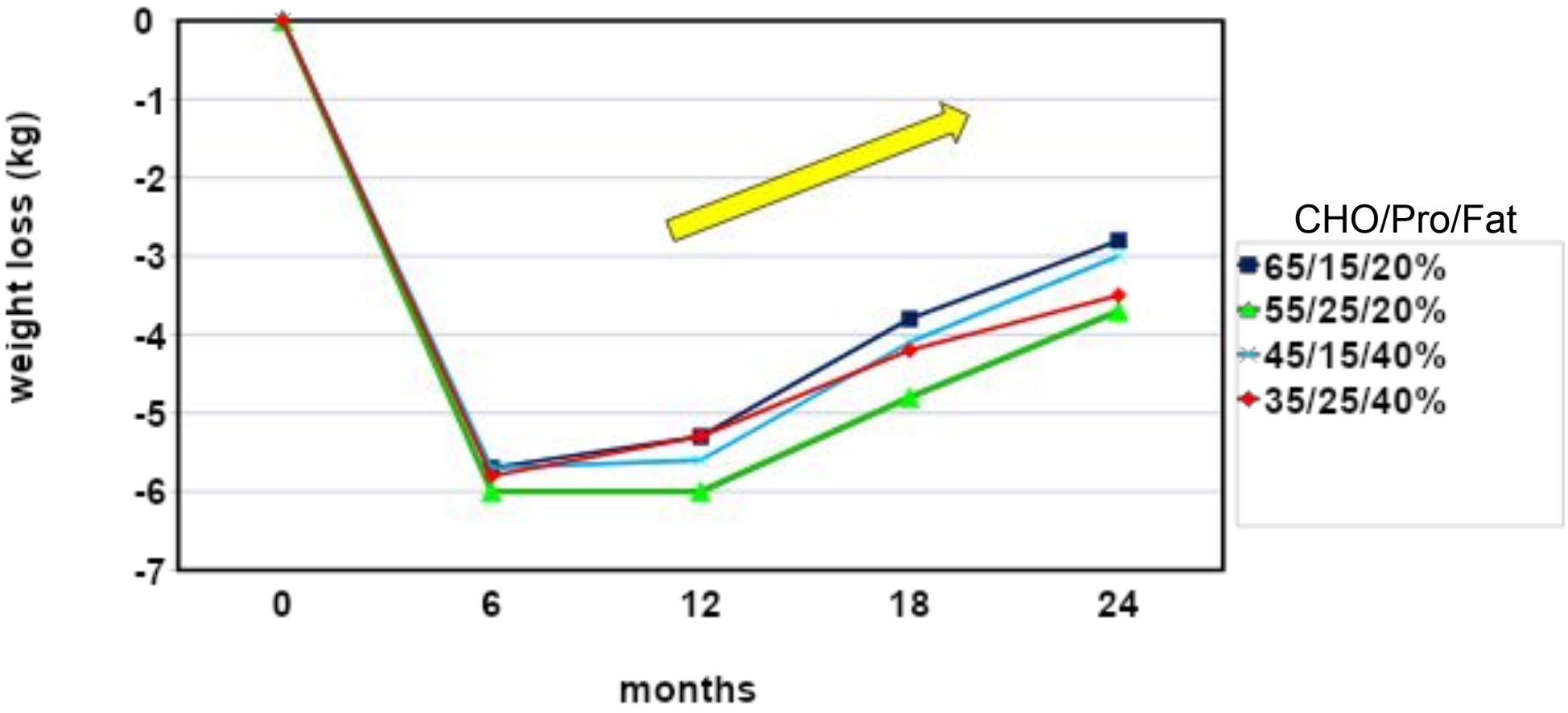
Weight loss and diabetes remission in primary care practices



Lean ME et al. Lancet 391(10120):541-551, 2018

Remember the Pathophysiology of Obesity: mechanisms protecting against weight loss

It is difficult for patients to maintain their weight loss over time.



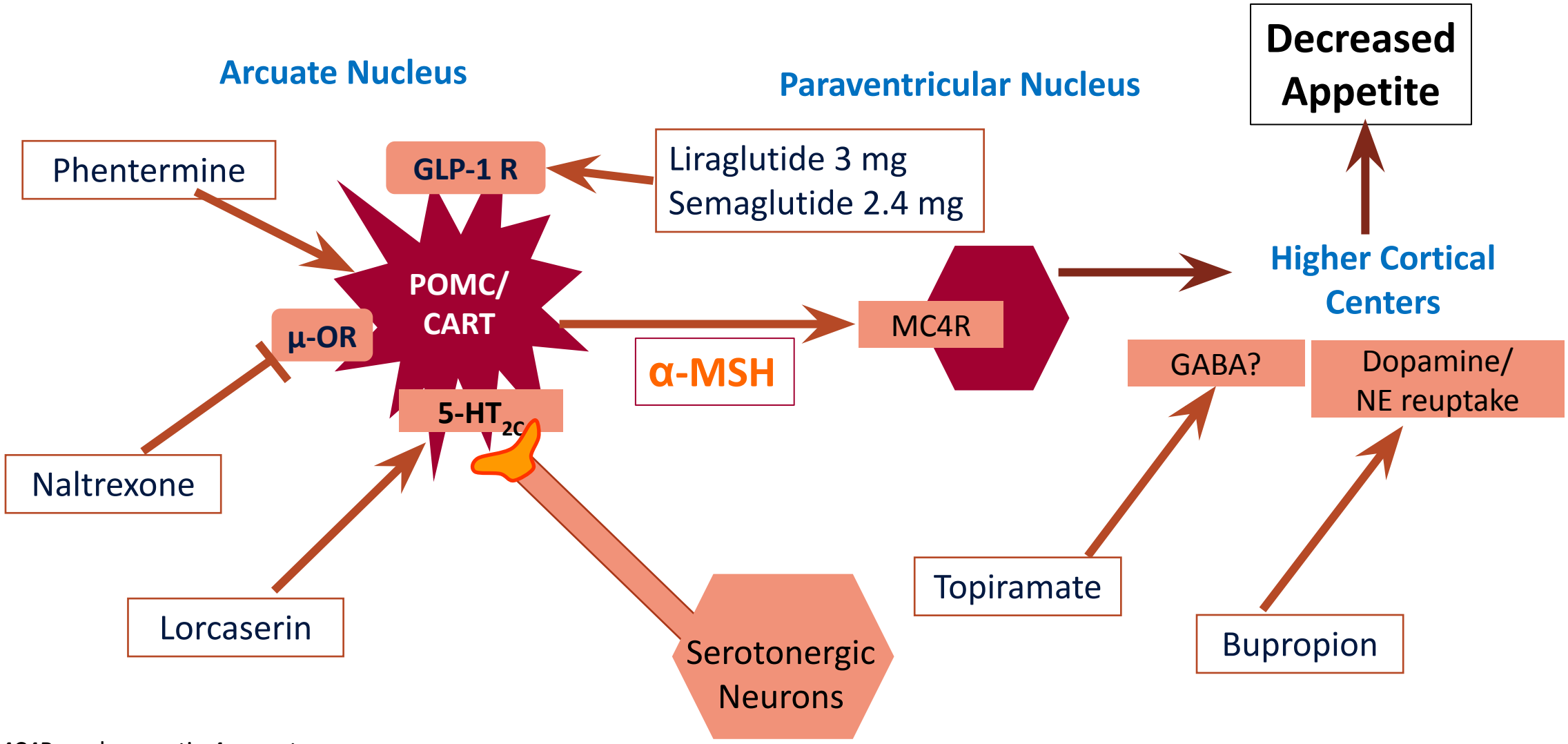
Sacks FS. et al. *NEJM* 2009;360(9) 859-873.

Obesity Pharmacotherapy

Agents	Action	Approval
Previously available		
Phentermine	• Sympathomimetic	• 1959
Orlistat	• GI lipase inhibitor	• 1997
Recently Approved		
Phentermine/ Topiramate ER	• Sympathomimetic/Anticonvulsant (GABA receptor modulation?)	• Approved, Summer 2012
Naltrexone ER/ Bupropion ER	• Dopamine/noradrenaline reuptake inhibitor/Opioid receptor antagonist	• Approved, September 2014
Liraglutide 3 mg	• GLP-1 receptor agonist	• Approved, December 2014
Semaglutide 2.4 mg/week	• GLP-1 receptor agonist	• Approved, June, 2021

US FDA. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA.

Actions of Recently Approved Weight-Loss Medications



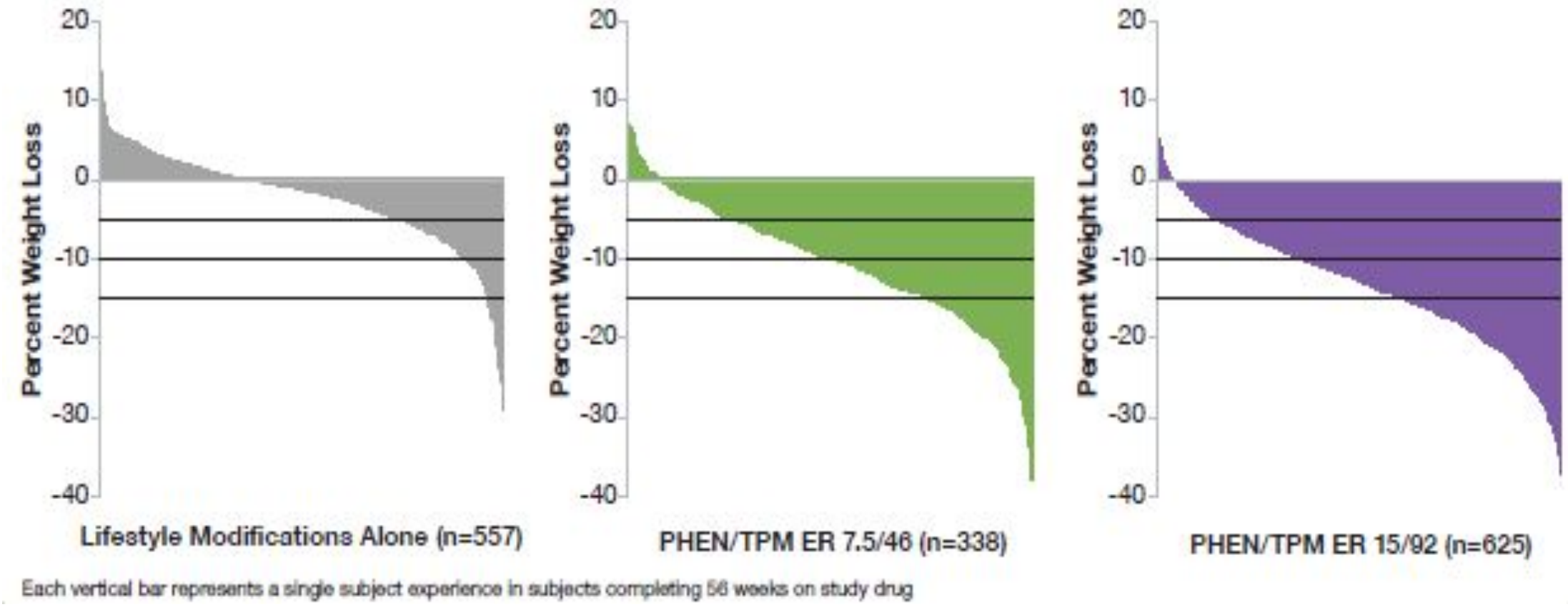
MC4R, melanocortin 4 receptor.
GABA, gamma-aminobutyric acid.
POMC/CART, pro-opiomelanocortin/cocaine- and-amphetamine-regulated transcript.

Courtesy of Dr. W. Timothy Garvey, 2021.

Important Aspects of Obesity Pharmacotherapy

1. Use as an adjunct to a lifestyle intervention program if BMI ≥30 or 27-29.9 with at least one complication.
2. All guidelines advise use to improve health risk, not for cosmetic reasons.
3. Addition of a weight-loss medication consistently achieves greater weight loss than that lifestyle alone, and helps sustain weight loss longer.
4. Consider efficacy, mechanism, side effect profile, warnings, obesity complications, concurrent diseases for optimal selection of medication
5. Therapeutic efficacy is lost once the medication is discontinued. Obesity is a life-long disease and requires long-term treatment and follow-up.
6. There is a large individual variation in the degree of weight loss with any intervention

There is a Variable Response to Weight Loss Therapy: It looks like this.



McCullough PA, et al. Poster AANP 2013.

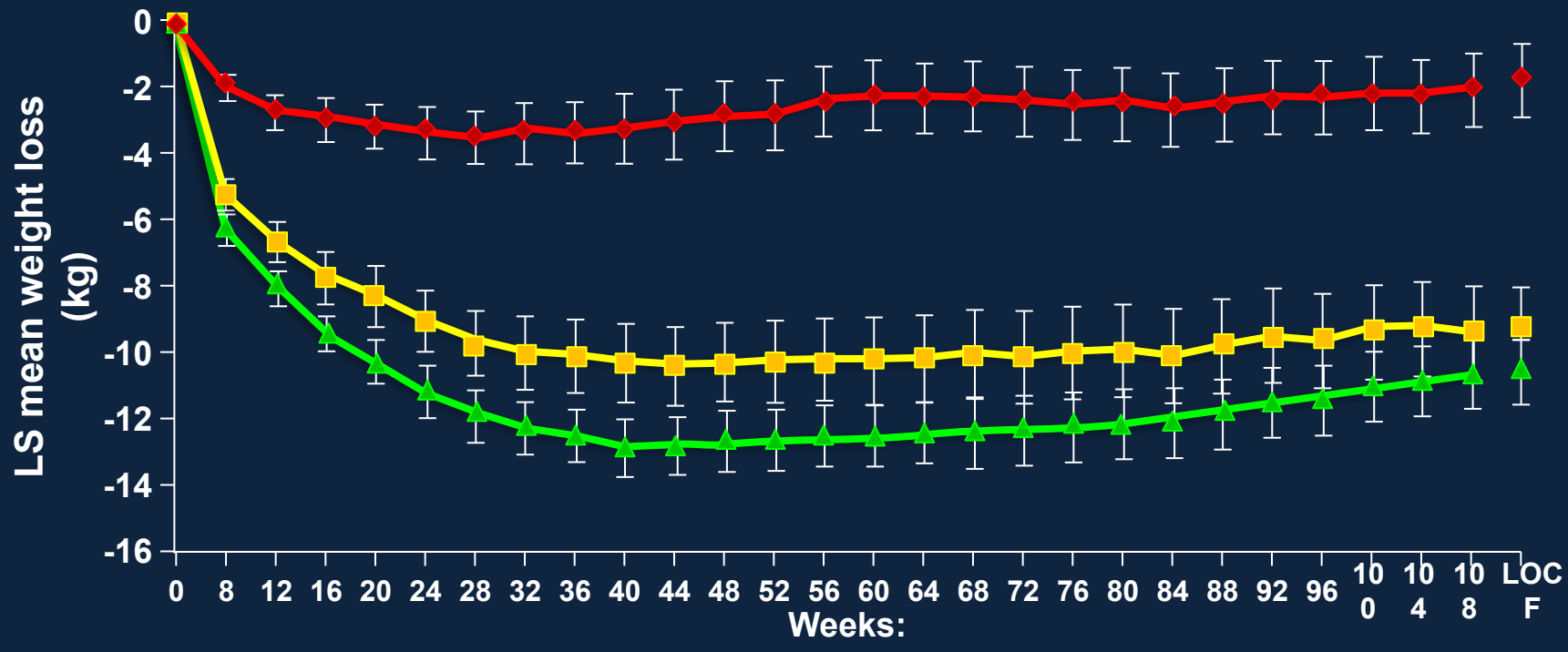
FDA “Off-Ramp” for Obesity Pharmacotherapy

If patient has not lost at least 5 % of baseline weight by week 12 on the maintenance dose, then discontinue medication; need to alter therapy

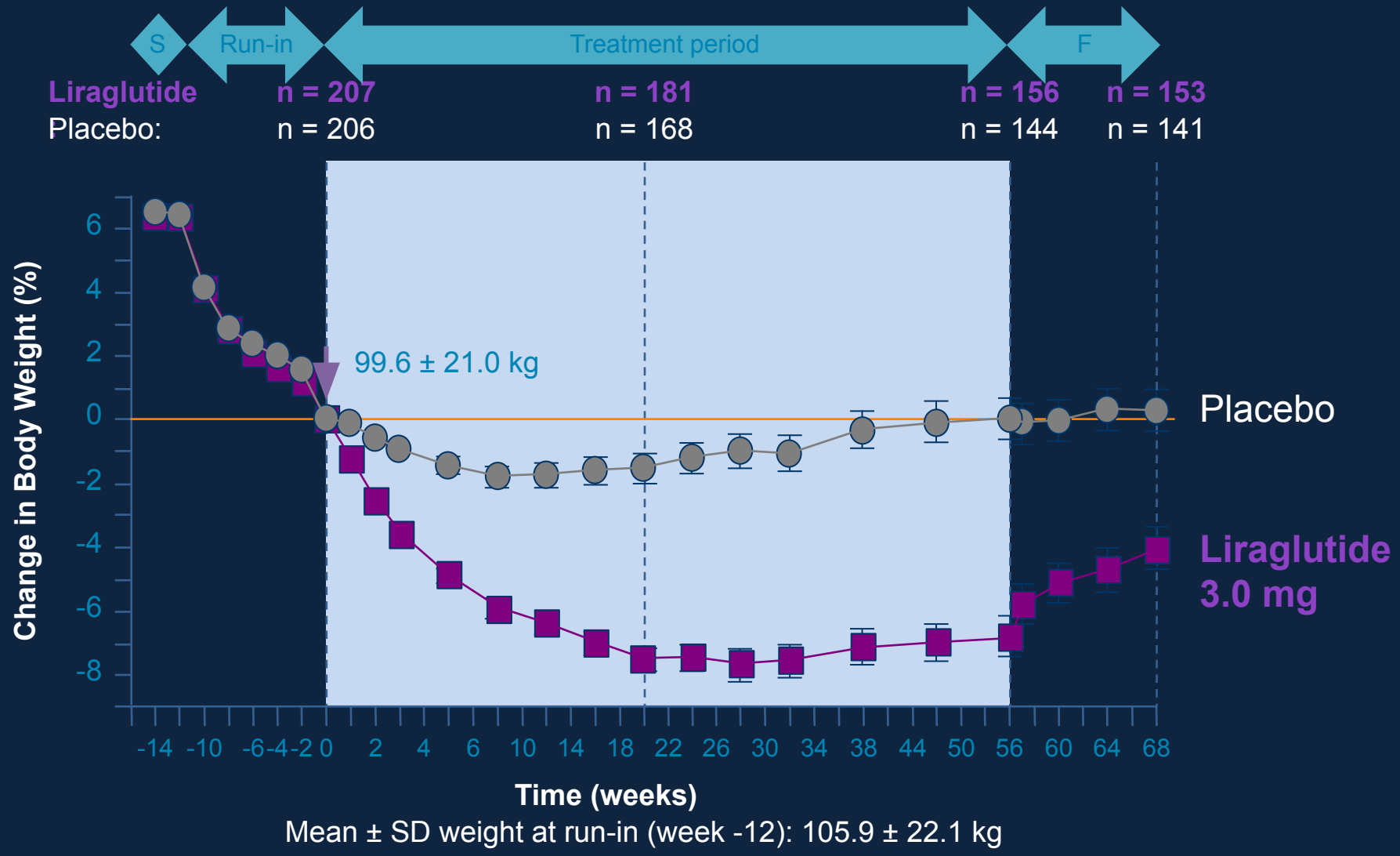
- Naltrexone ER/bupropion ER: Begin one pill 8 mg/90 mg po q AM for week 1, then one bid for week 2, two q AM one q PM week 3, and 2 po bid week 4
- Phentermine/topiramate ER: one pill 3.75 mg/23 mg po q AM for 2 weeks, then treatment dose 7.5 mg/46 mg po q AM. If <3% weight loss at 12 weeks , proceed to top dose 15 mg/92 mg q AM
- Liraglutide 3 mg: Begin at 0.6 mg q day SQ for 1 week than increase by 0.6 mg q day each week until taking 3 mg q day. [off ramp is <4% weight loss at 16 weeks]

Effect of Phentermine/Topiramate ER on Weight Loss in Obese Adults Over 2 Years: SEQUEL Study

Garvey WT et al. *Am J Clin Nutr*. 2012;95(2):297-308.



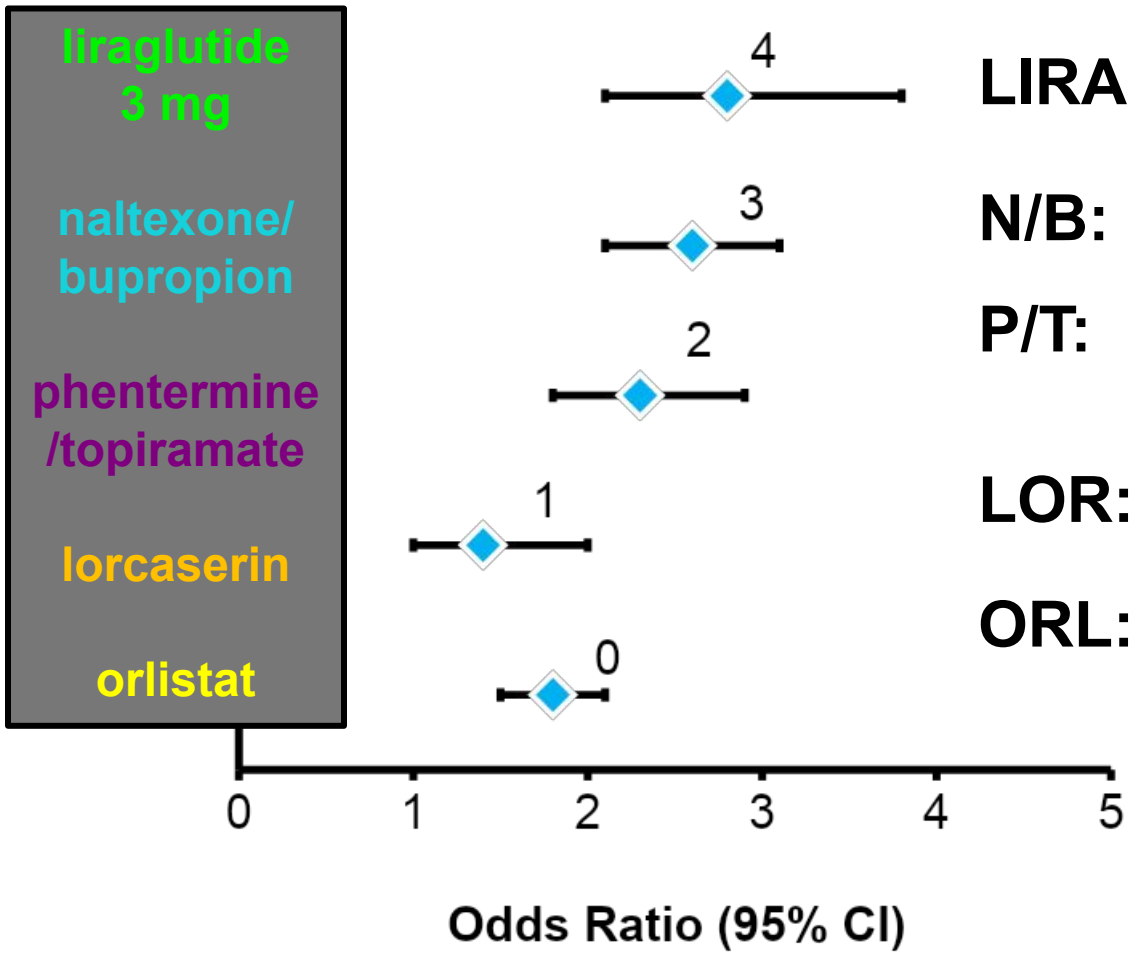
Ability of Liraglutide 3 mg to Maintain and Promote Additional Weight Loss After Low-calorie Diet: SCALE Maintenance Study



Mean ± SD weight at run-in (week -12): 105.9 ± 22.1 kg

Wadden TA et al. *Int J Obes (Lond)*. 2013;37(11):1443–1451.

Direct Meta-Analysis: Likelihood of Discontinuation Due to Adverse Events[1]



Common Adverse Events[2-4,a]

LIRA: GI symptoms

N/B: GI symptoms, headache

P/T: insomnia, dry mouth, dizziness, distorted taste, paresthesia

LOR: headache, fatigue

ORL: abdominal discomfort, oily spotting/ stool, fecal urgency

[a] Selected common (defined as incidence > 5%) AEs are noted; refer to medication package inserts and cited references for complete information.

1. Khera R, et al. *JAMA*. 2016;315:2424-2434;
2. Drugs@FDA: FDA approved drug products. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA; 3. Garvey WT, et al. *Endocr Pract*. 2016;22:842-884; 4. ADA. *Diabetes Care.* 2017;40(suppl 1):S57-S63.

Obesity Medications: Contraindications and Precautions[a]

- **Orlistat**
  - Chronic malabsorption syndrome
  - Consider fat soluble vitamins/medications
  - Cholestasis

- **Naltrexone ER/bupropion ER**
  - Uncontrolled hypertension
  - Seizure disorders; anorexia nervosa or bulimia; abrupt discontinuation of some drugs[b]
  - Use of other bupropion-containing products
  - Chronic opioid use (opioid withdrawal)
  - During/within 14 days of MAOI use

- **Phentermine/Topiramate ER**
  - Glaucoma
  - Hyperthyroidism
  - During/within 14 days of MAOI use
  - Topiramate: fetal oral clefts (regular pregnancy testing)

- **Liraglutide 3.0 mg SQ/daily**

- **Semaglutide 2.4 mg SQ/weekly**
  - MEN2, personal/family history of MTC (potential risk of thyroid C-cell tumors—rodent data[c])
  - Acute pancreatitis

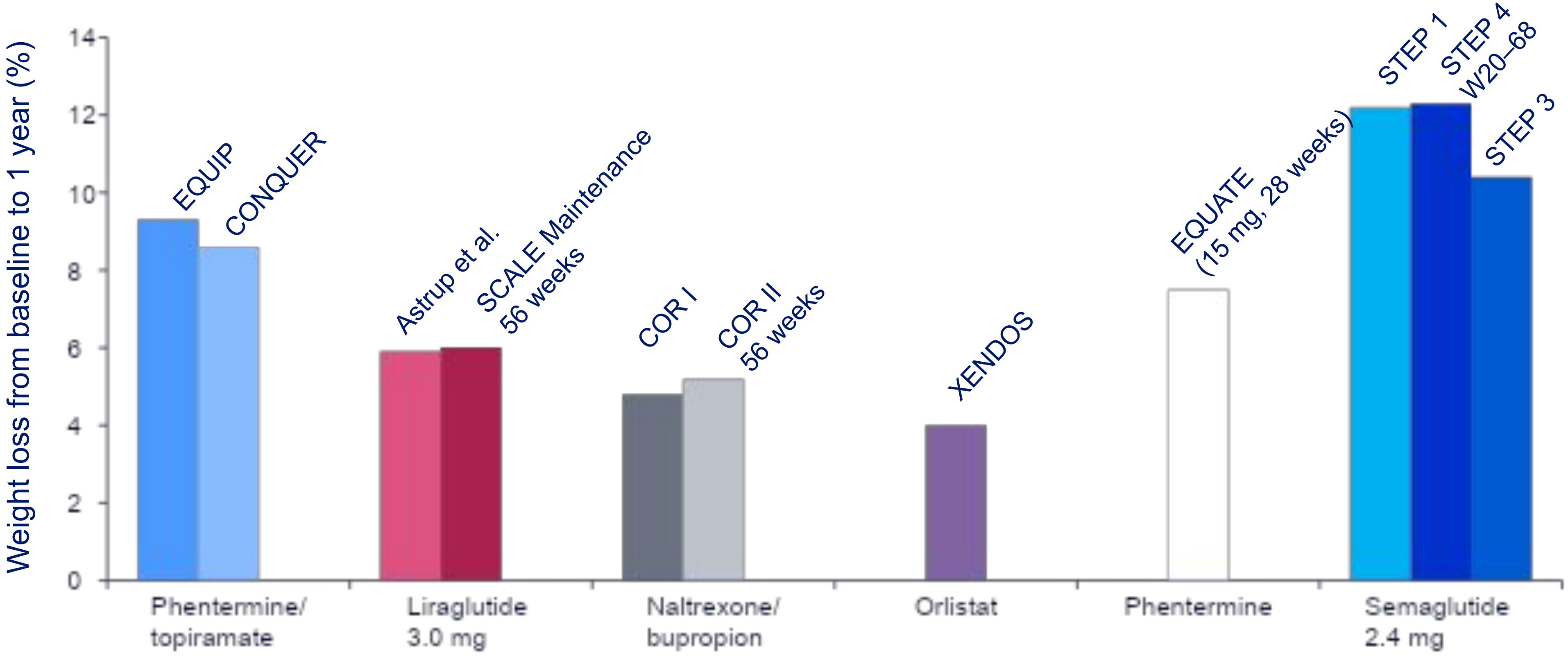
All are contraindicated in pregnancy and generally not recommended for women who are breastfeeding; caution on use of reliable contraception.

US FDA. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA.

[a] For all agents, known hypersensitivity to agent or any component .
[b] Alcohol, benzodiazepines, barbiturates, antiepileptic drugs.
[c] Relevance in humans has not been determined.

Comparative efficacy of obesity medications

All data placebo-subtracted, maximal dose, completers, 1 year, unless otherwise indicated

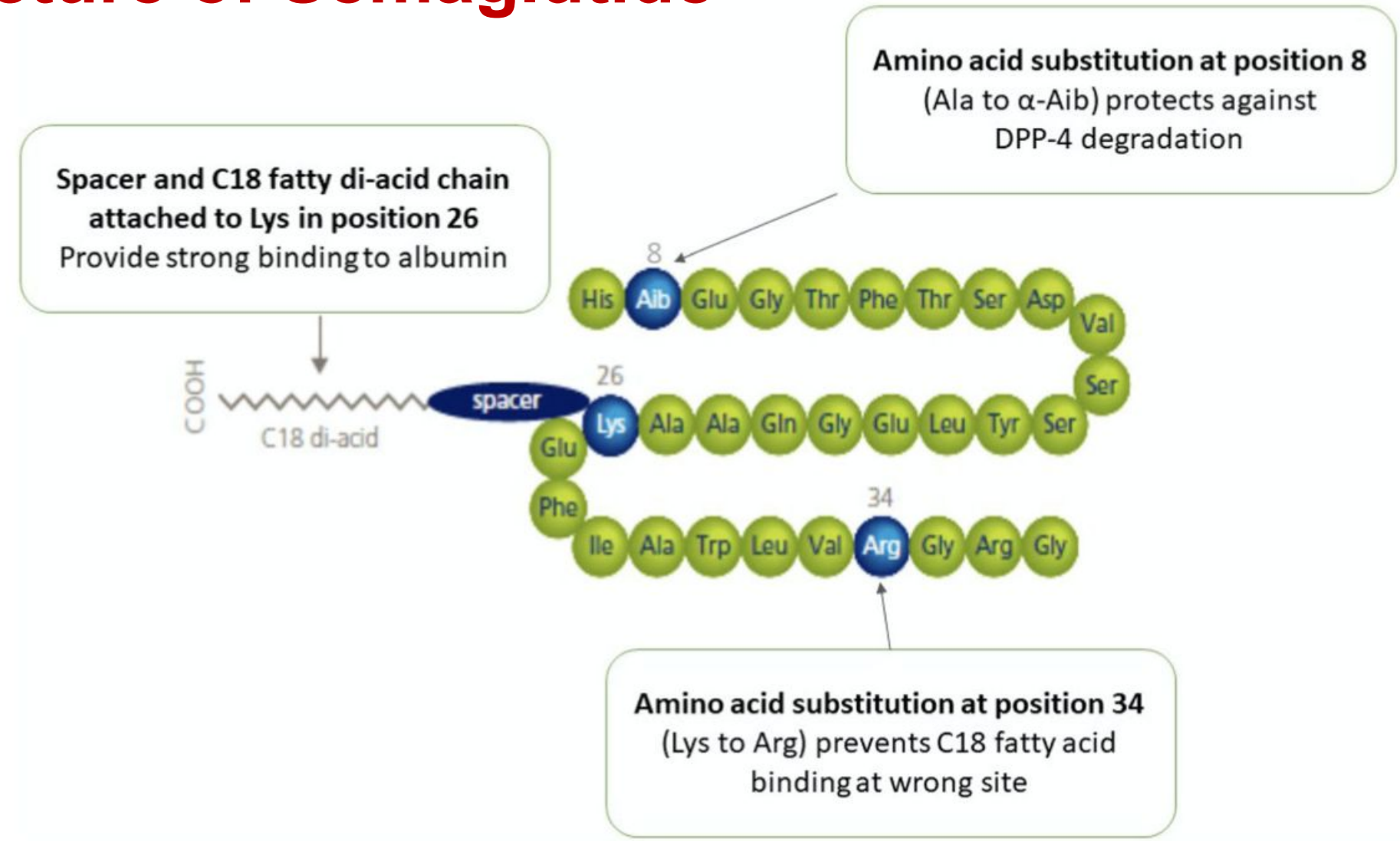


Trial designs, populations and durations for each trial differ, and data are not based on head-to-head trials.

All treatments were used in combination with lifestyle intervention.

Apovian CM et al. Obesity 2013;2... Wadden TA et al. Int J Obes 2013;37:1443–51; Wilding et al. NEJM, 2021; 384(11):989 ; Wadden TA et al. JAMA, 2021; 325(14):1403-1413; Rubino D et al. JAMA, 2021; 32(14)1414-1425

Structure of Semaglutide



Kalra S, Sahay R. A Review on Semaglutide: An Oral Glucagon-Like Peptide 1 Receptor Agonist in Management of Type 2 Diabetes Mellitus. Diabetes Ther. July 28, 2020. https://doi.org/10.1007/s13300-020-00894-y

Completed trials in the phase 3 STEP program[1]

STEP 1 NCT03548935	STEP 2 NCT03552757	STEP 3 NCT03611582	STEP 4 NCT03548987
Weight management	**Weight management in T2D**	**Weight management with IBT**	**Sustained weight management**
Overweight or obesity without T2D	Overweight or obesity with T2D	Overweight or obesity without T2D	Overweight or obesity without T2D
68-week trial plus ongoing extension	68-week trial	68-week trial	68-week trial
Semaglutide 2.4 mg vs placebo	Semaglutide 2.4 mg vs placebo and vs semaglutide 1.0 mg	Semaglutide 2.4 mg vs placebo, both with IBT (diet*, increased physical activity, and counseling sessions)	20-week semaglutide run-in for all participants, then continued semaglutide 2.4 mg vs switch to placebo

In STEP 1, 3, and 4, participants were required to have a baseline BMI ≥27 kg/m^2 with ≥1 weight-related comorbidity (not T2D), or a baseline BMI ≥30 kg/m^2. In STEP 2, participants were required to have a baseline BMI ≥27 kg/m^2 and T2D. All treatment was given subcutaneously once weekly as adjunct to lifestyle intervention.
*A low-calorie, meal-replacement diet for the first 8 weeks, followed by a reduced calorie diet for the rest of the trial.
BMI, body mass index; IBT, intensive behavioral therapy; STEP, Semaglutide Treatment Effect in People with obesity; T2D, type 2 diabetes.

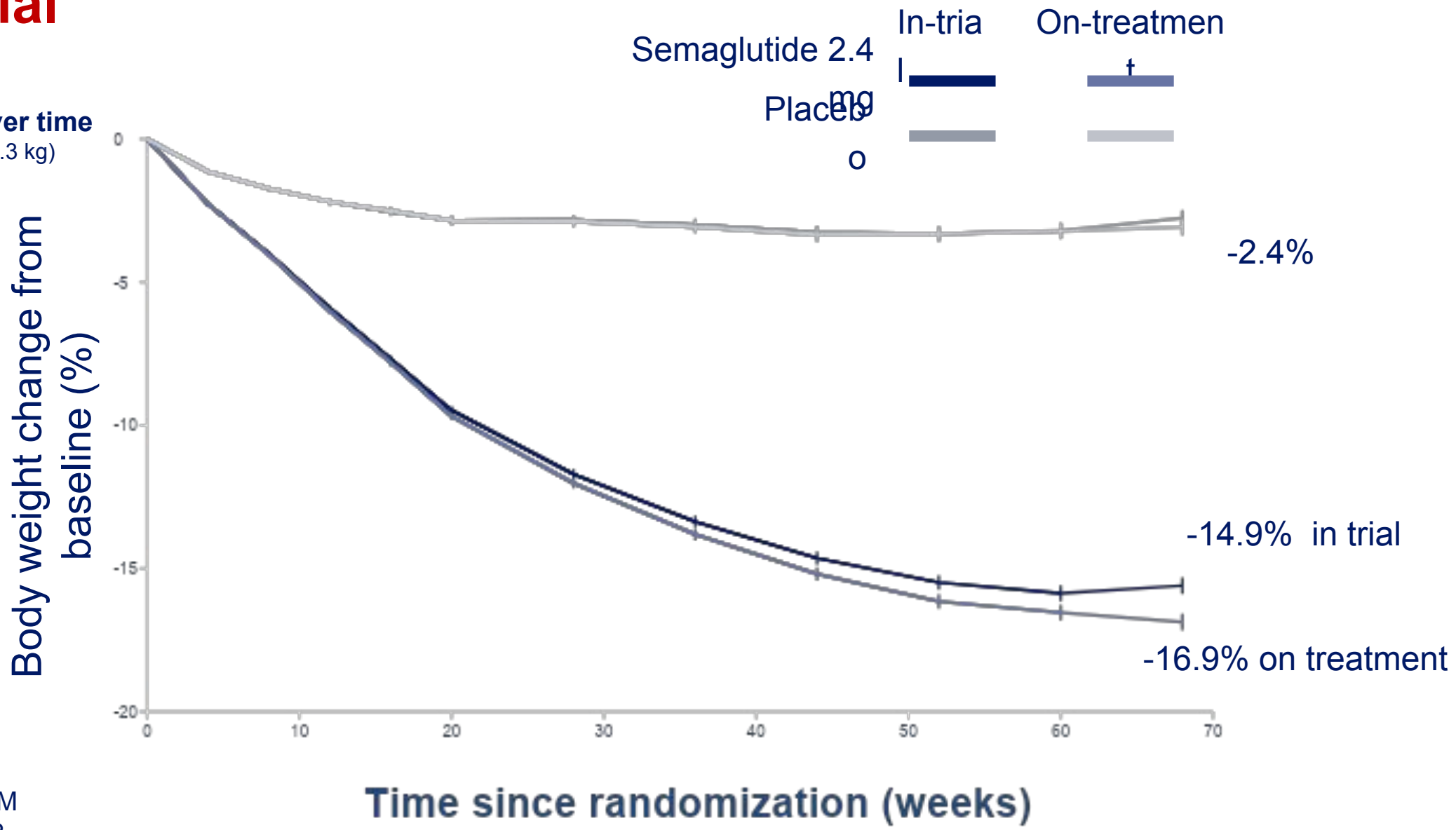
1. Kushner RF, et al. Obesity 2020;28:1050–61.

Davies M, et al. presented at the Endocrine Society (ENDO) virtual meeting, March 20-23, 2021

NEJM, 2021; 384(11):989
Lancet, 2021; 397(10278):971-984
JAMA, 2021; 325(14):1403-1413
JAMA, 2021; 32(14)1414-1425

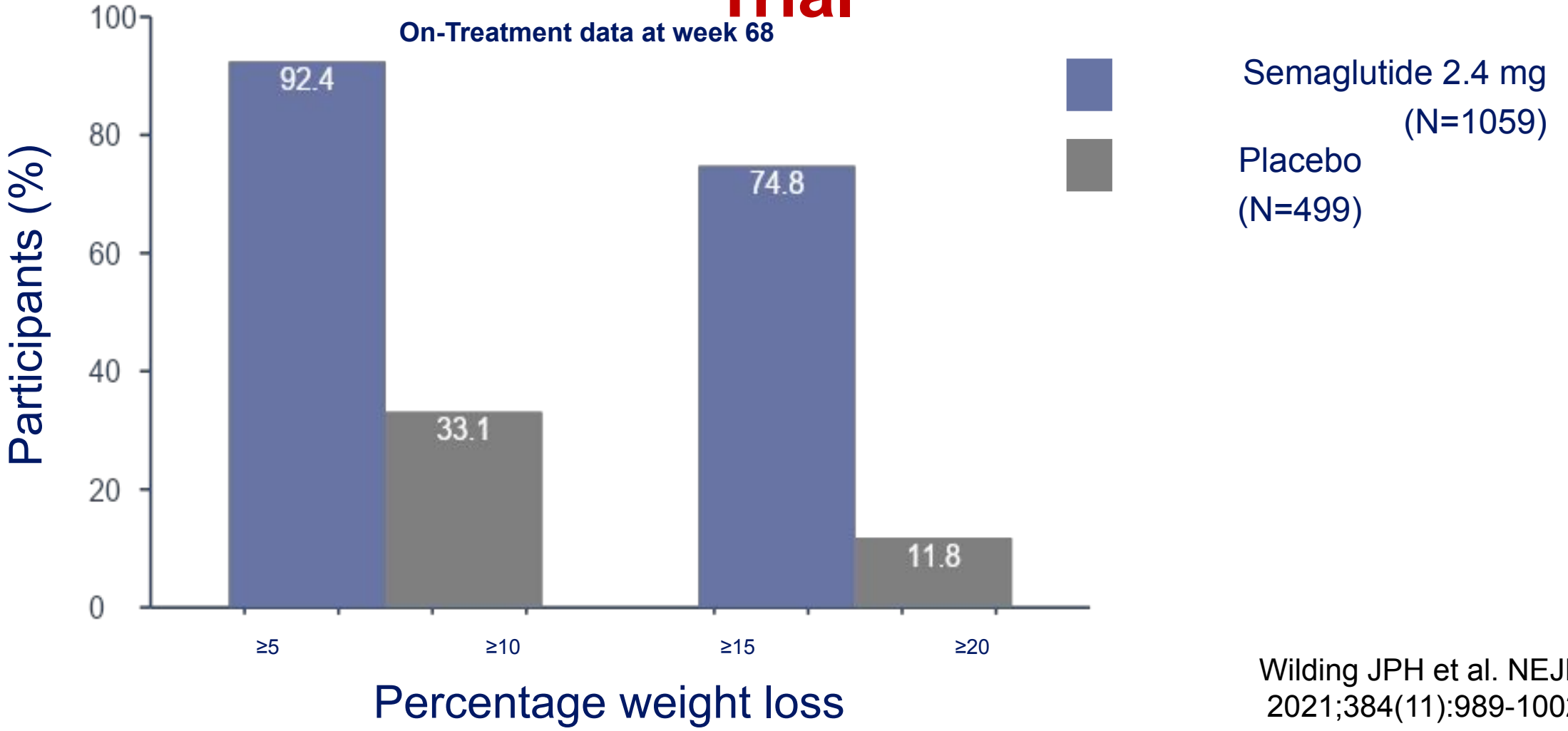
Efficacy of Semaglutide 2.4 mg in Patients with Obesity in the STEP 1 Trial

Observed change over time
(Mean at baseline: 105.3 kg)



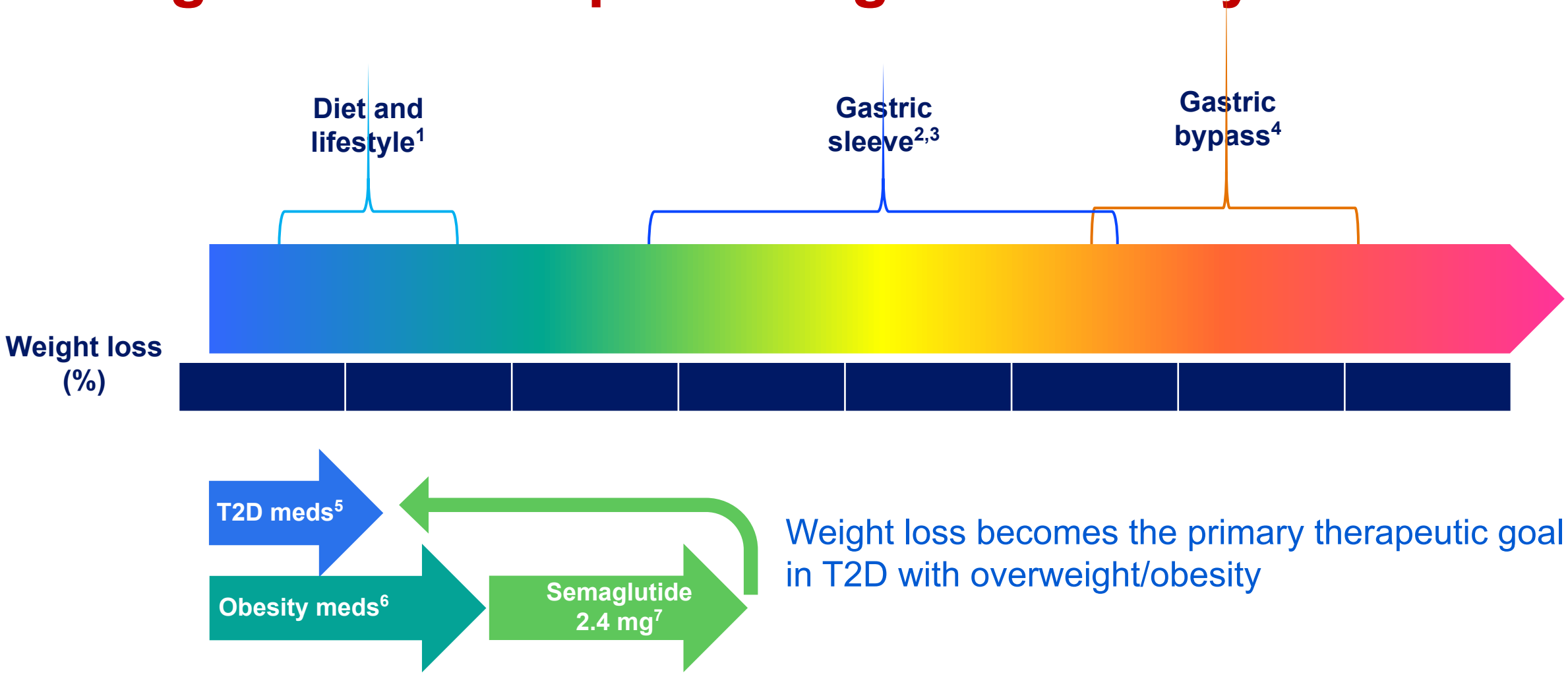
Wilding JPH et al. NEJM 2021;384(11):989-1002

Semaglutide 2.4 mg: Achievement of categorical body weight reductions at week 68 in the STEP 1 Trial



Wilding JPH et al. NEJM 2021;384(11):989-1002

Weight-loss therapies: range of efficacy



Weight loss becomes the primary therapeutic goal in T2D with overweight/obesity

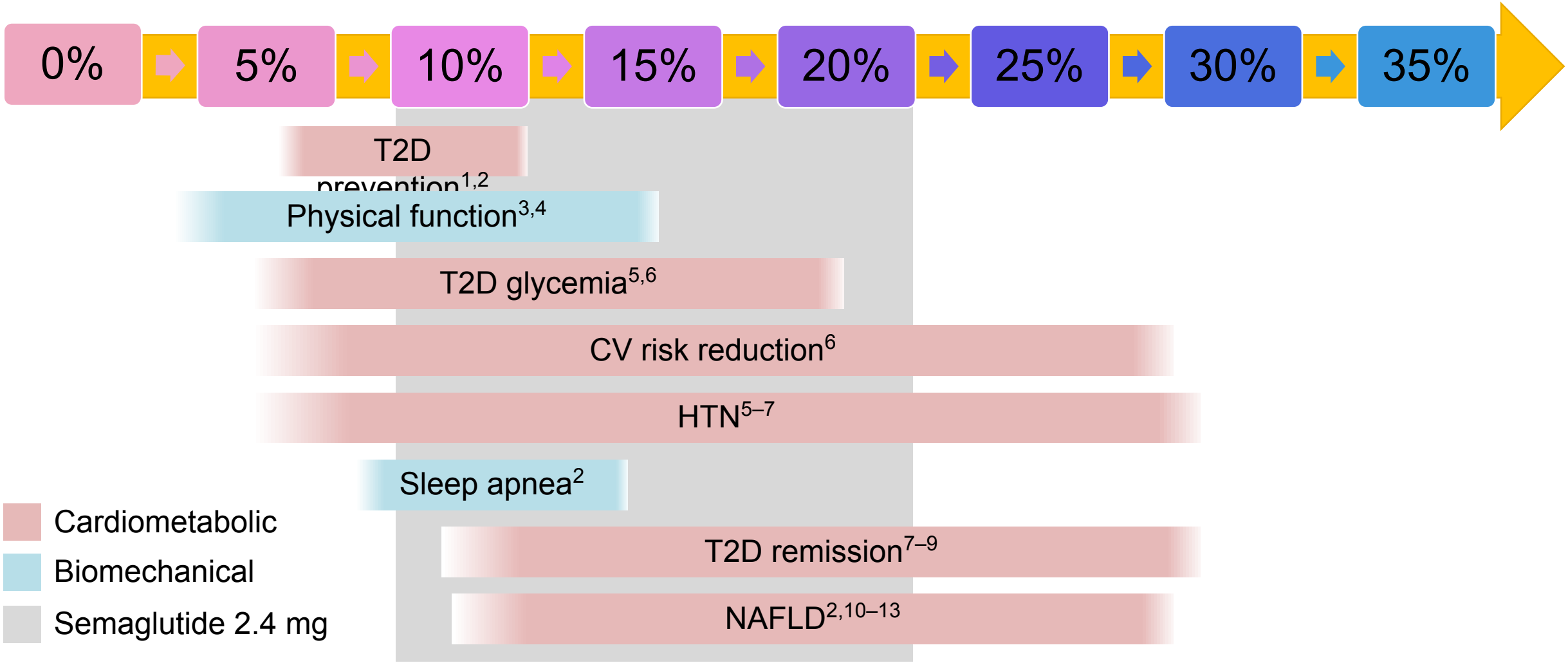
1. Jensen MD et al. Circulation 2014;129:S102–38; 2. Salminen P et al. JAMA 2018;319:241–54; 3. Berry MA et al. Obes Surg 2018;28:649–55; 4. Courcoulas AP et al. JAMA 2013;310:2416–25; 5. Lazzaroni E et al. Pharmacol Res 2021 DOI 10.1016/j.phrs.2021.105782 [Epub]; 6. Garvey WT. Endocr Pract 2013;19:864–74; 7. Wilding JPH et al. N Engl J Med 2021;384:989.

Treating chronic diseases to target

	T2D	Hypertension	Atherosclerosis	ABCD/obesity
Biomarker target	HbA_{1c}	Blood pressure	LDL cholesterol	BMI
Reason for target	Prevent complications			
Complications	CKD, retinopathy, neuropathy, CVD	CHF, stroke, CKD	MI, stroke, amputation	T2D, HTN, NAFLD/ NASH, sleep apnea, osteoarthritis

ABCD, adiposity-based chronic disease; CHF, congestive heart failure; CVD, cardiovascular disease; HTN, hypertension; LDL, low-density lipoprotein; MI, myocardial infarction; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.
Garvey WT and Mechanick MD. Obesity (Silver Spring). 2020; 28:484–92. Frühbeck G et al. Obes Facts 2019;12:131–6;

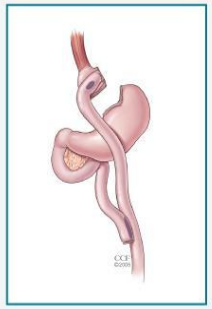
New medications: treating ABCD to target



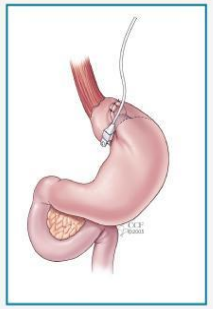
1. Knowler WC et al. N Engl J Med 2002;346:393–403; 2. Cefalu WT et al. Diabetes Care 2015;38:1567–82; 3. Christensen R et al. Osteoarthritis Cartilage 2005;13:20–7; 4. Bliddal H et al. Obes Revs 2014:15:578–86; 5. Wing RR et al. Diabetes Care 2011;34:1481–6; 6. Ooi GJ et al. Int J Obes 2017;41:902–8; 7. Courcoulas AP et al. JAMA Surg. 2018;153:427–34; 8. Lean ME et al. Lancet 2018;391:541–51; 9. Dambha-Miller H et al. Diabet Med. 2020;37:681–8; 10. Vilar Gomez E et al. Gastroenterology 2015;149:367–78; 11. Koutoukidis DA et al. Metabolism 2021;115:154455; 12. Promrat K et al, Hepatology 2010;51:121–9; 13. Liu X et al, Obesity Surgery 2007;17:486–92.

Surgical and Endoscopic Therapies for Treatment of Obesity

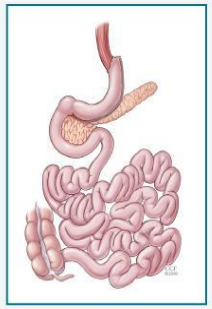
SURGICAL PROCEDURE



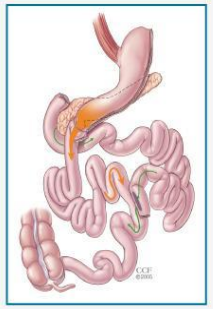
Gastric Bypass



Band



Sleeve

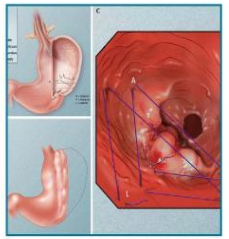


DS

NON-SURGICAL PROCEDURE

Aspire Assist

Ellipse Balloon

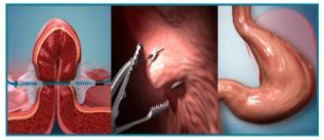


Endoscopic Sleeve Gastoplasy Apollo Device

Obalon Balloon

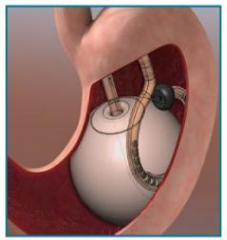
Orbera

Oral Hydrogels

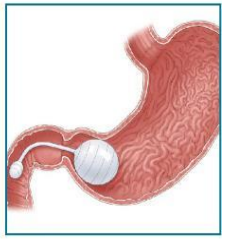


POSE Procedure

Reshape



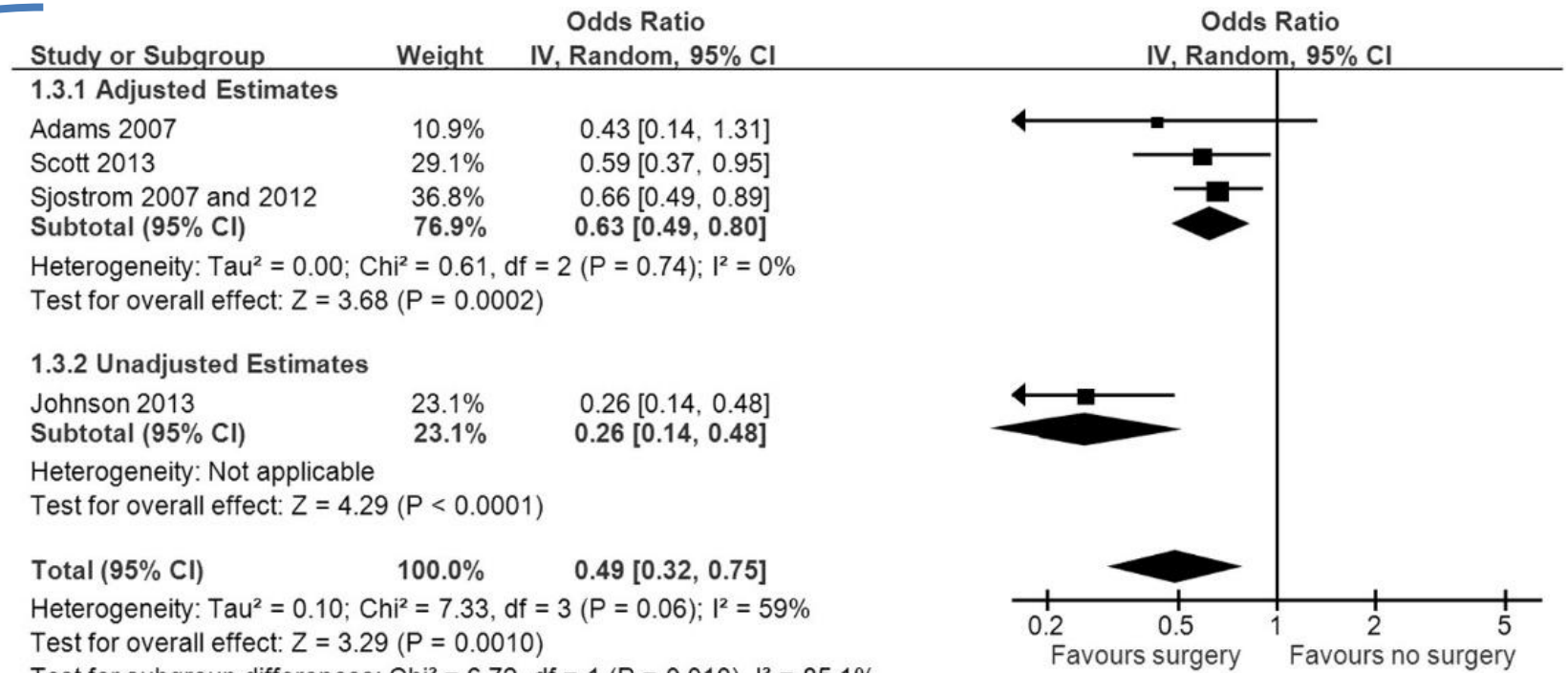
Spatz Balloon



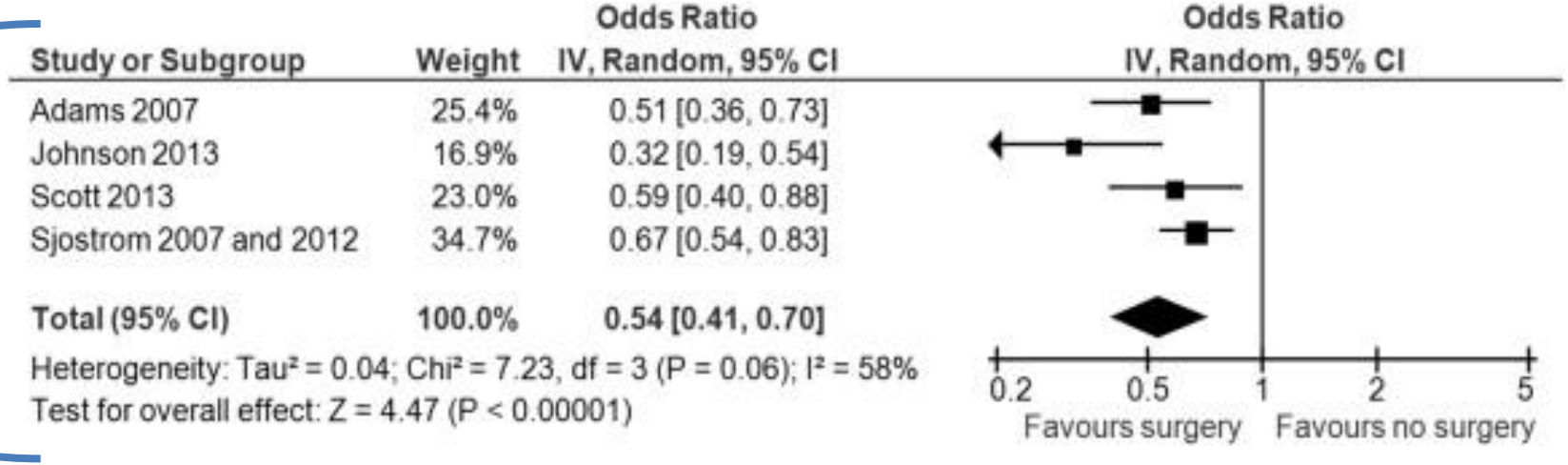
Transpyloric Shuttle

Bariatric Surgery Decreases Risk of MI and MACE Outcomes: a meta-analyses

Myocardial Infarction

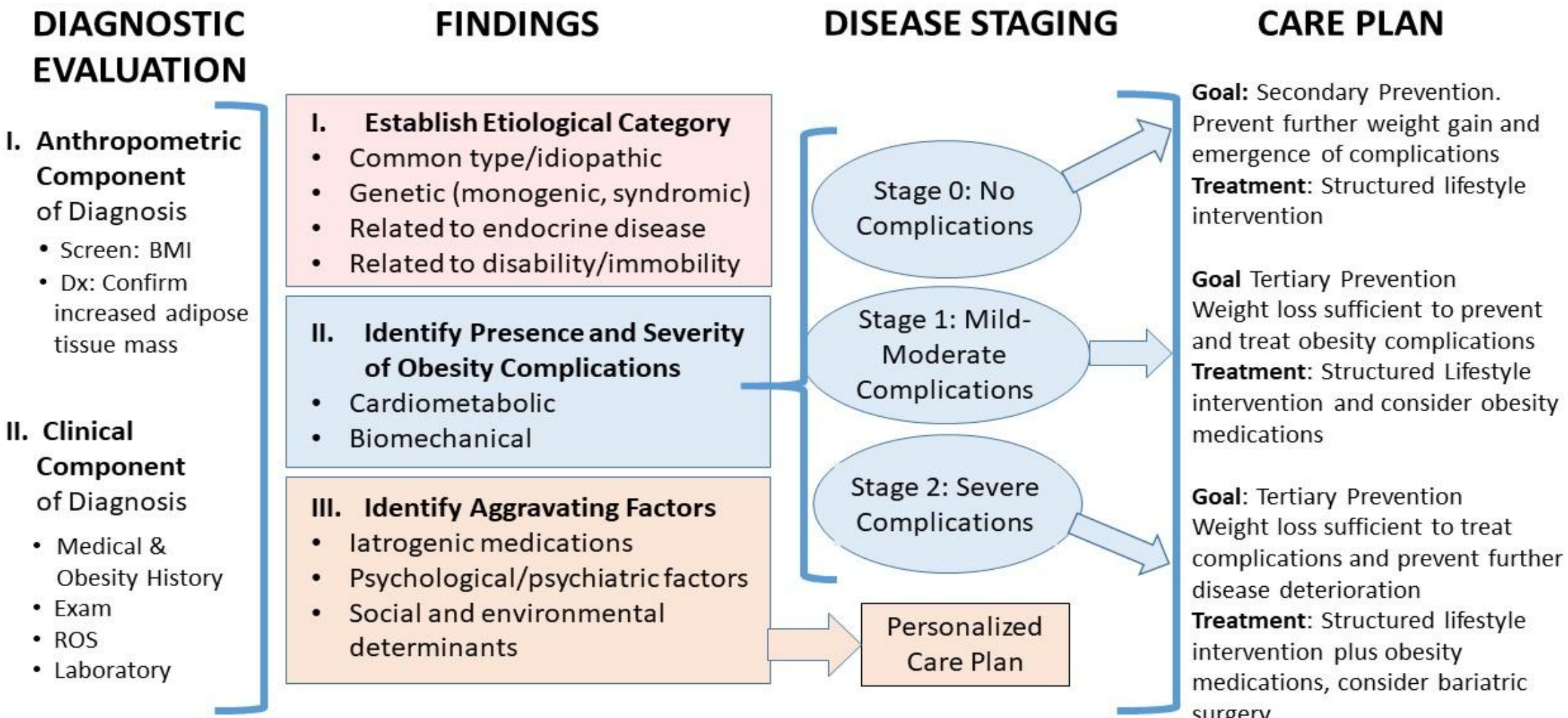


MACE



Kwok CS, et al. Bariatric surgery and its impact on cardiovascular disease and mortality: a systematic review and meta-analysis. Int J Cardiol. 173(1):20-28, 2014

AACE Obesity Guidelines and the Evaluation and Management of High-Risk Patients with Obesity



Garvey WT, Mechanick JI. Proposal for a scientifically correct and medically actionable disease classification system (ICD) for obesity. Obesity. 2020; 28(3):484-492

THANK YOU!