השמנה – טיפול תרופתי בהשוואה לניתוחים בריאטריים

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Obesity: a global pandemic requiring treatment

Prevalence of obesity

Obesity is a chronic, relapsing, progressive disease

650 million people live with obesity

Life expectancy decreases as BMI increases

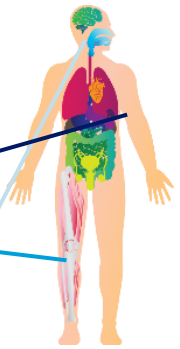
Normal BMI	BMI 35–40	BMI 40–50
80%	**60%**	**50%**

chance of reaching age 70

Obesity complications

Obesity is associated with multiple complications

- Metabolic
- Mechanical
- Mental



Progressive weight loss has biological effects

Greater weight loss gives **greater health benefits**

Metabolic adaptation following weight loss

Weight loss

Adaptations that resist weight loss:

Hormone levels
↓ satiety hormones
↑ hunger hormones

Metabolism
↓ energy expenditure

Weight regain

Obesity management

BMI (kg/m²)

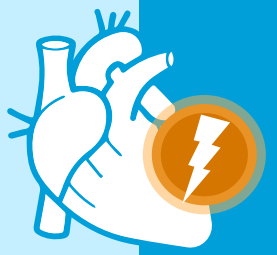
BMI (kg/m²)	
≥40	Surgery
35–39.9	With co-morbidity
30–34.9	Pharmacotherapy
27–29.9	With co-morbidity
25–26.9	Diet, activity & behaviour

There is an unmet need for therapies that reduce CV events and support weight management

422.7
million people had **CVD** in 2015 (globally)

42%
of global **CV deaths** are due to **CHD**

31%
of all global **deaths** are from **CVD**



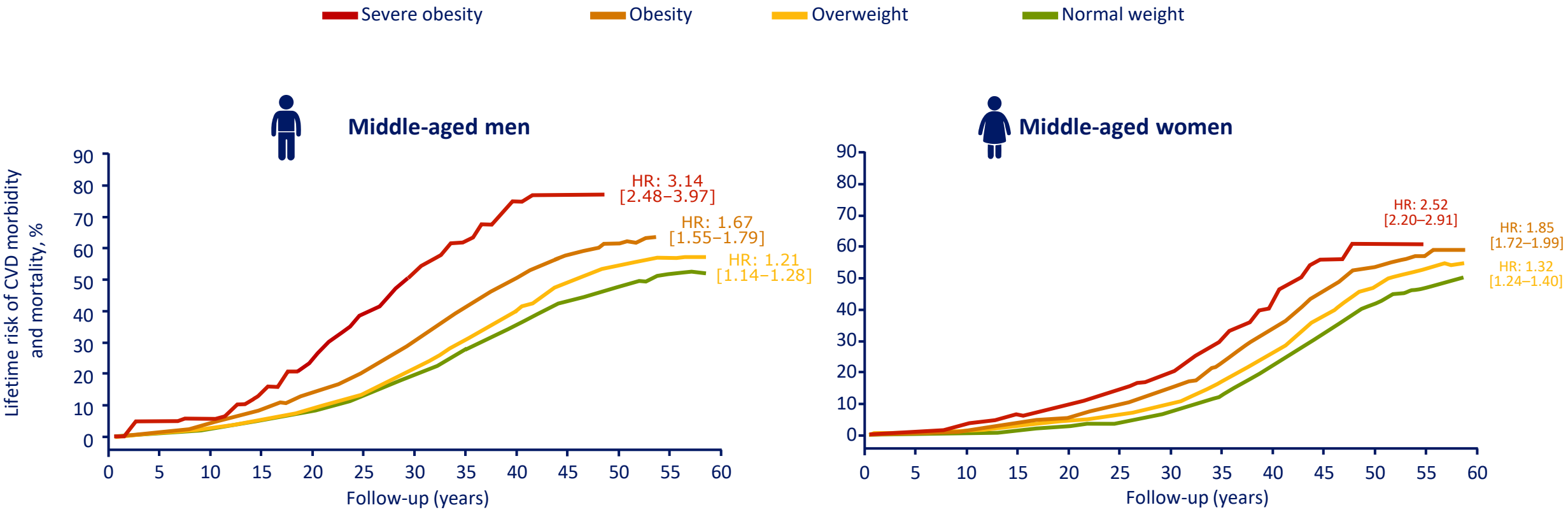
650
million people live with **obesity** as of 2020

Effective interventions that lower CV events & death in this population are greatly needed!

Conditions included in CVD definition may vary. CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease.
WHO Fact sheet – CVDs. Available at: http://www.who.int/mediacentre/factsheets/fs317/en/; Roth GA et al. J Am Coll Cardiol 2017;70:1–25;
WHO, Obesity & Overweight. 2020. Available from https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed November 2020;
GBD 2015 Obesity Collaborators. N Engl J Med, 2017;377:13–27.

Increased risk of CV events with increasing BMI

Cardiovascular Disease Lifetime Risk Pooling Project (N=190,672)



Under bracket numbers indicate 95% CI. Remaining cumulative lifetime risk estimates for total CVD events (adjusted for competing risk of non-cardiovascular death) in middle-aged men and women stratified by BMI groups; HRs are for CVD incidence, compared with normal weight.
BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.
Adapted from Khan SS et al. JAMA Cardiol 2018;3(4):280–7.

Obesity is increasingly recognised as a disease and global health issue

"…obesity is a primary disease, and the full force of our medical knowledge should be brought to bear on the prevention and treatment of obesity as a primary disease entity…"[1]

"Obesity is a chronic disease, prevalent in both developed and developing countries, and affecting children as well as adults."[3]

"Recognizing obesity as a disease will help change the way the medical community tackles this complex issue that affects approximately one in three Americans."[2]

"FDA agrees with these comments that obesity is a disease…Being overweight, i.e., being more than one's ideal weight but less than obese, however, is not a disease." [3]

May 2018

"Obesity is a disease *that will not pass by itself. PwO should benefit from modern medicine"*

"Obesity is a recurring chronic disease due to dysfunction of physiological-genetic mechanisms and is not due to behavioural failure".

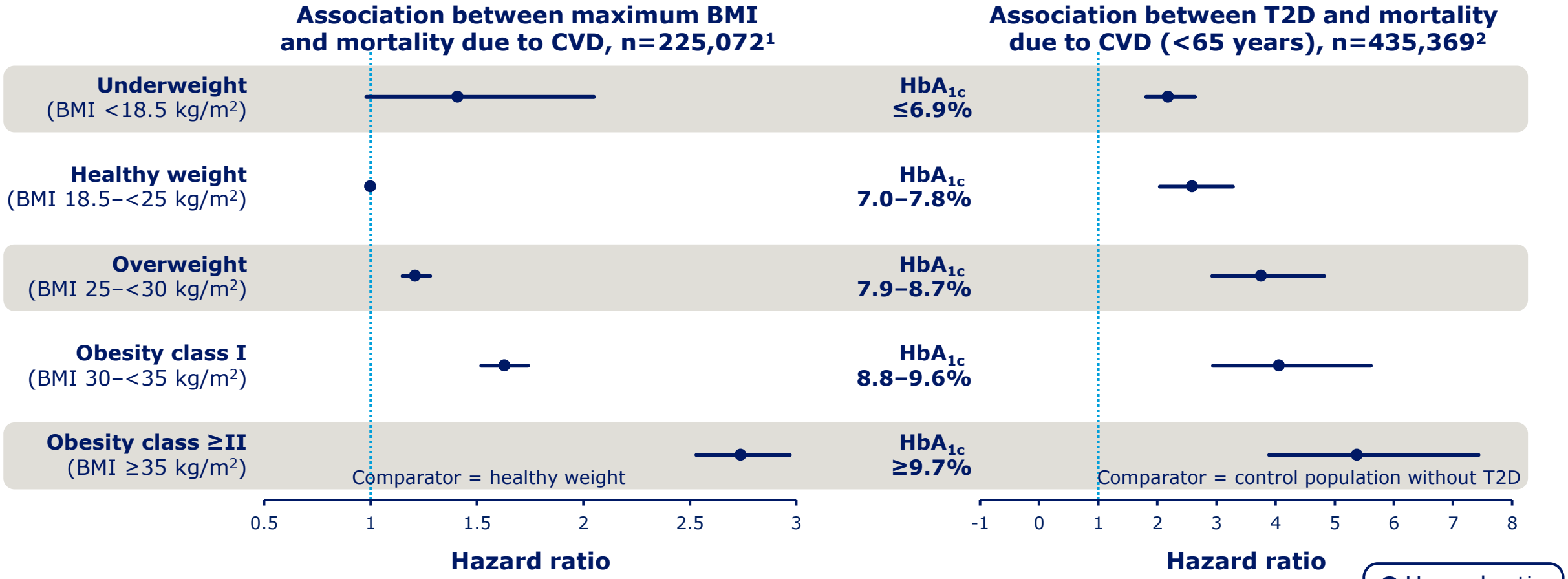
1. Mechanick *et al. Endocr Pract*. 2012;18:642-8; 2. AMA position statement. Available at: http://www.ama-assn.org/; 3. TOS Obesity as a Disease Writing Group. Obesity 2008;16:1161–1177.

Prevalence of complications in people with obesity

	Major depression	Diabetes	Congestive HF	MI	Stroke	Hypertension	Ischaemic heart disease	NAFLD	PCOS	GERD symptoms*	Knee osteoarthritis	OSAS
	Prevalence (%)											
BMI ≥30	**19**	**21**	**3.5**	**21**	**3**	**51**	**8**	**29**	**9**	**35**	**52**	**~40**

*Weekly heartburn and regurgitation.
BMI, body mass index; GERD, gastroesophageal reflux disease; HF, heart failure; MI, myocardial infarction; NAFLD, nonalcoholic fatty liver disease; OSAS, obstructive sleep apnoea syndrome; PCOS, polycystic ovary syndrome.
Simon et al. *Arch Gen Psychiatry* 2006;63:824–30; Su et al. *J Med Economics* 2015;18:886–97; López-Velázquez et al. *Ann Hepatol* 2014;13:166–78; Yildiz et al. *J Clin Endocrinol Metab*. 2008;93:162–68; El-Serag et al. *Am J Gastroenterol.* 2005;100:1243–50; Prieto-Alhambra et al. *Ann Rheum Dis* 2014;73:1659–64; Modena et al. *Rev Assoc Med Bras* 2017;63:852–8.

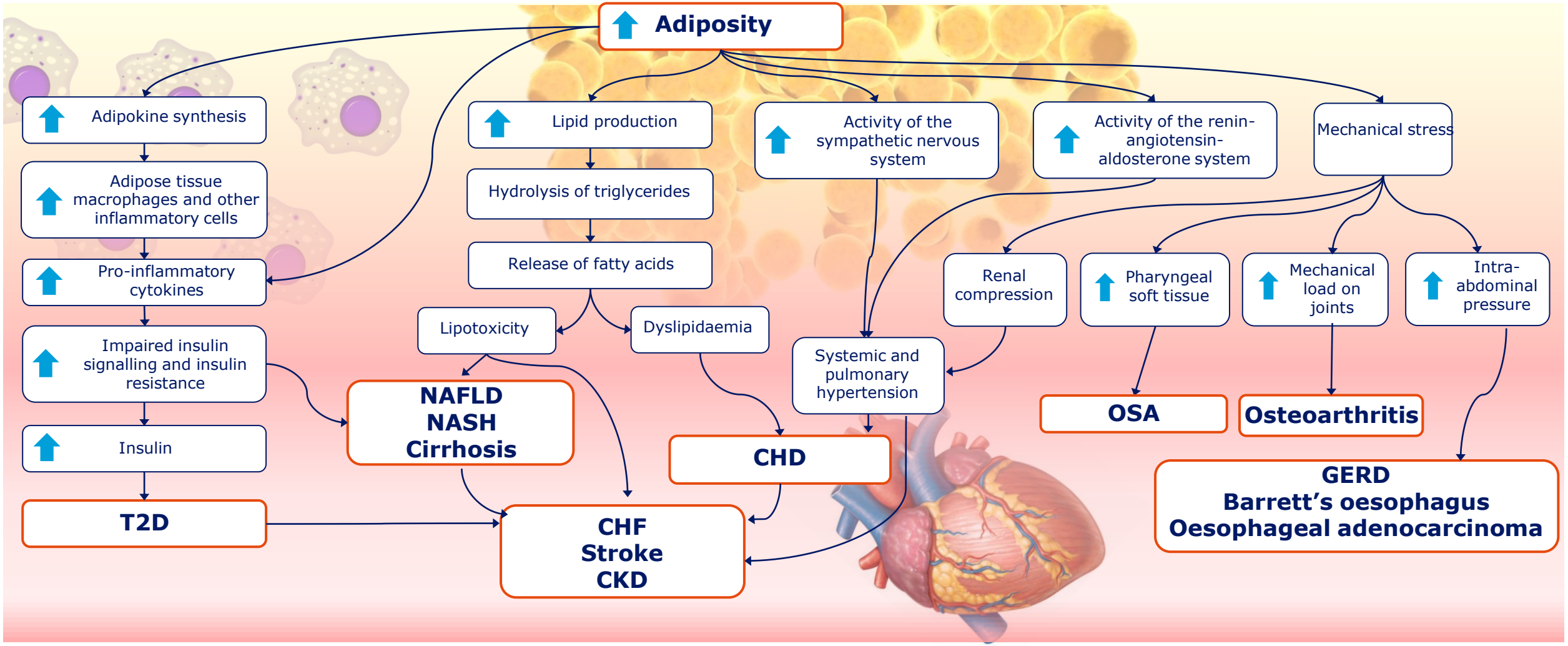
Greater risk of CVD mortality with increased BMI and HbA_{1c}



Left, pooled data from the Nurses Health Study, Nurses Health Study II and Health Professionals Follow-Up Study
Right, individuals with T2D from the Swedish National Diabetes Register and controls without T2D matched for age, sex and county
Multivariate analyses, adjusting for various CVD risk factors. CI, confidence interval; CVD, cardiovascular disease

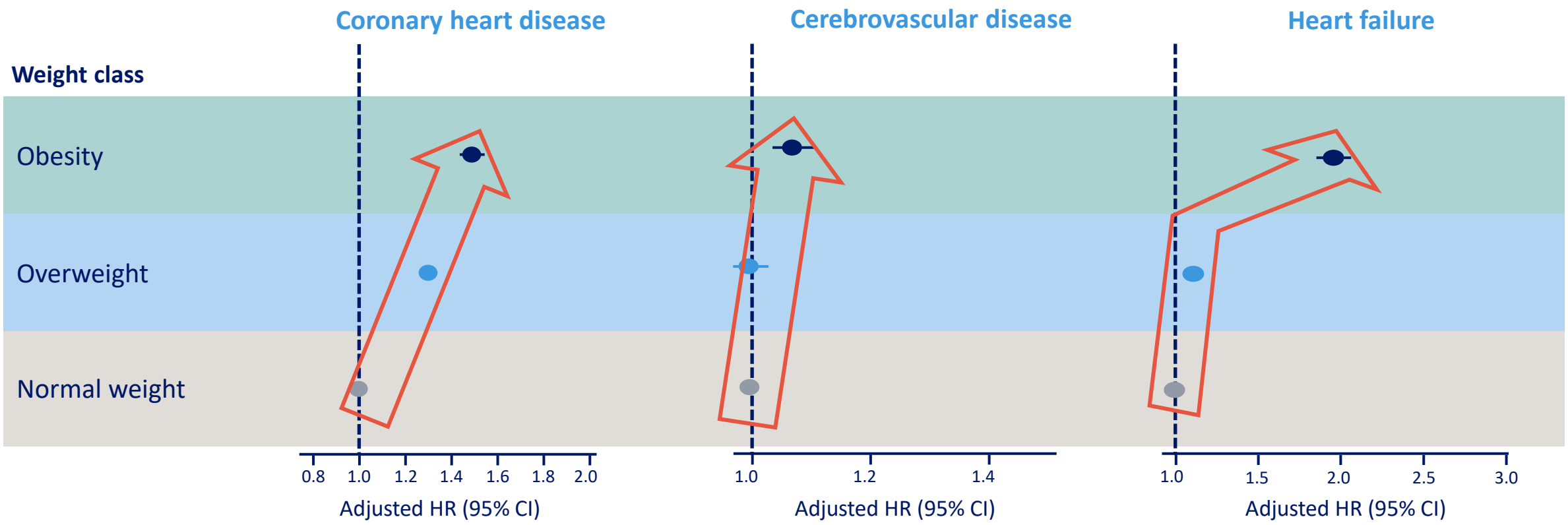
1. Yu et al. Ann Intern Med 2017;166:613-620; 2. Tancredi et al. N Engl J Med 2015;373:1720–32

Excess adiposity leads to major risk factors and common chronic diseases



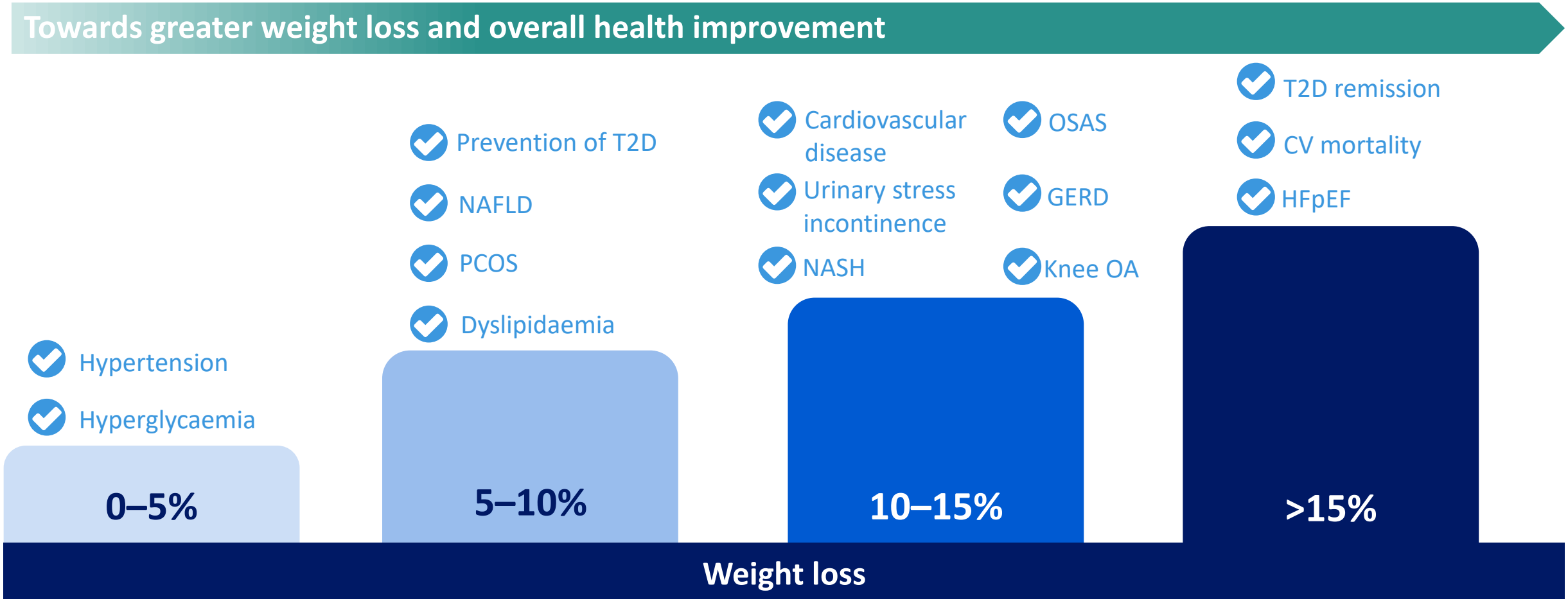
CHD, coronary heart disease; CHF, coronary heart failure; CKD, chronic kidney disease; GERD, gastroesophageal reflux disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic stereohepatitis; OSA, obstructive sleep apnea; T2D, type 2 diabetes. Heymsfield SB, Wadden TA. *NEJM* 2017;376:254–66

Overweight and obesity increase the risk of CVD even in the absence of metabolic abnormalities



Body size, metabolic status and CVD events in 3.5 million UK adults. Analyses adjusted for age, sex, smoking status, and social deprivation. The reference category is normal weight, no metabolic abnormalities.
CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.
Caleyachetty R et al. J Am Coll Cardiol 2017;70:1429–37.

The effect of weight loss on complications



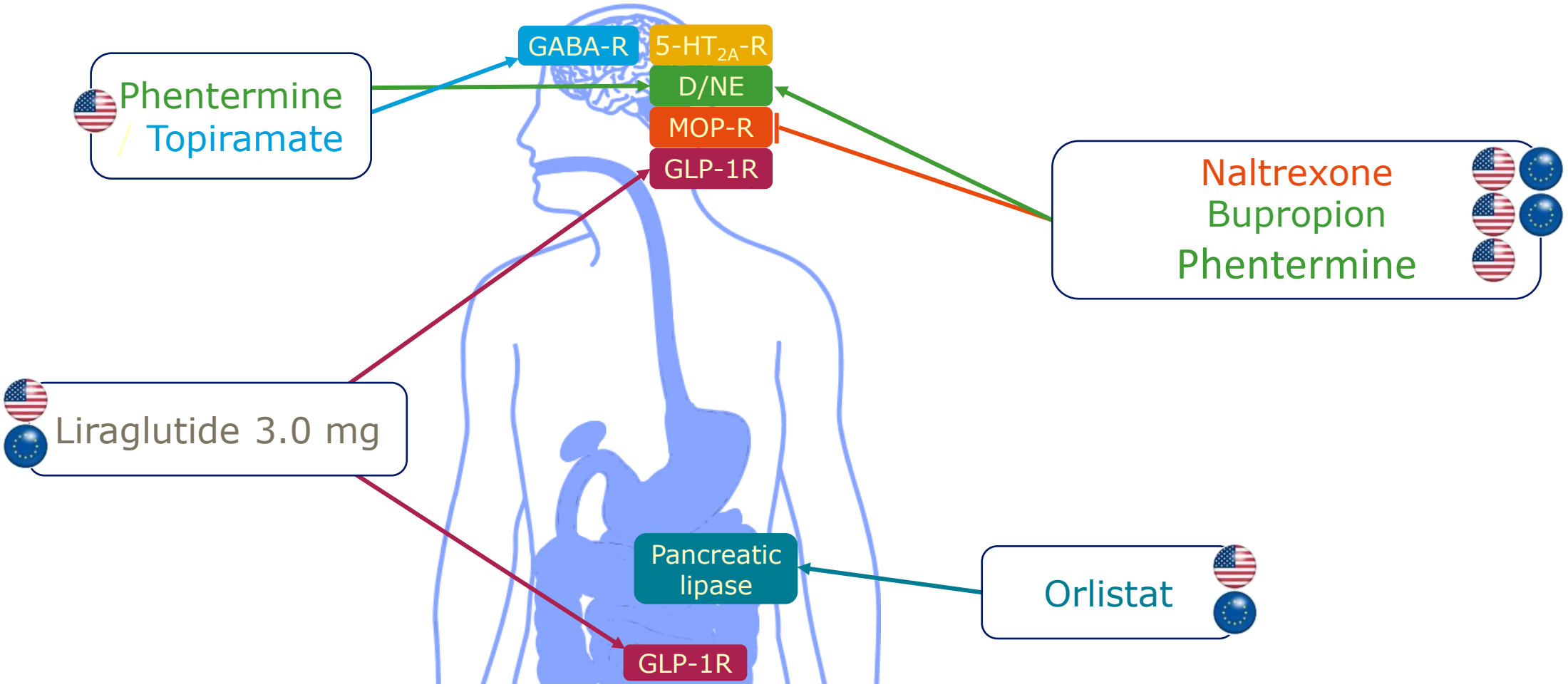
CV, cardiovascular; GERD, gastro-oesophageal reflux disease; HFpEF, heart failure with preserved ejection fraction; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OA, osteoarthritis; OSAS, obstructive sleep apnoea syndrome; PCOS, polycystic ovary syndrome; TG, triglycerides.

Stepped approach to obesity management

	BMI 25–26.9 kg/m²	BMI 27–29.9 kg/m²	BMI 30–34.9 kg/m²	BMI 35–39.9 kg/m²	BMI ≥40 kg/m²
Surgery 			When optimal medical and behavioural management has been insufficient	With adiposity-related complications	+
Pharmacotherapy 		With adiposity-related complications	+	+	+
Behavioural modification 	+	+	+	+	+
	All individuals, regardless of body size or composition, benefit from a healthy, well-balanced eating pattern and regular physical activity				

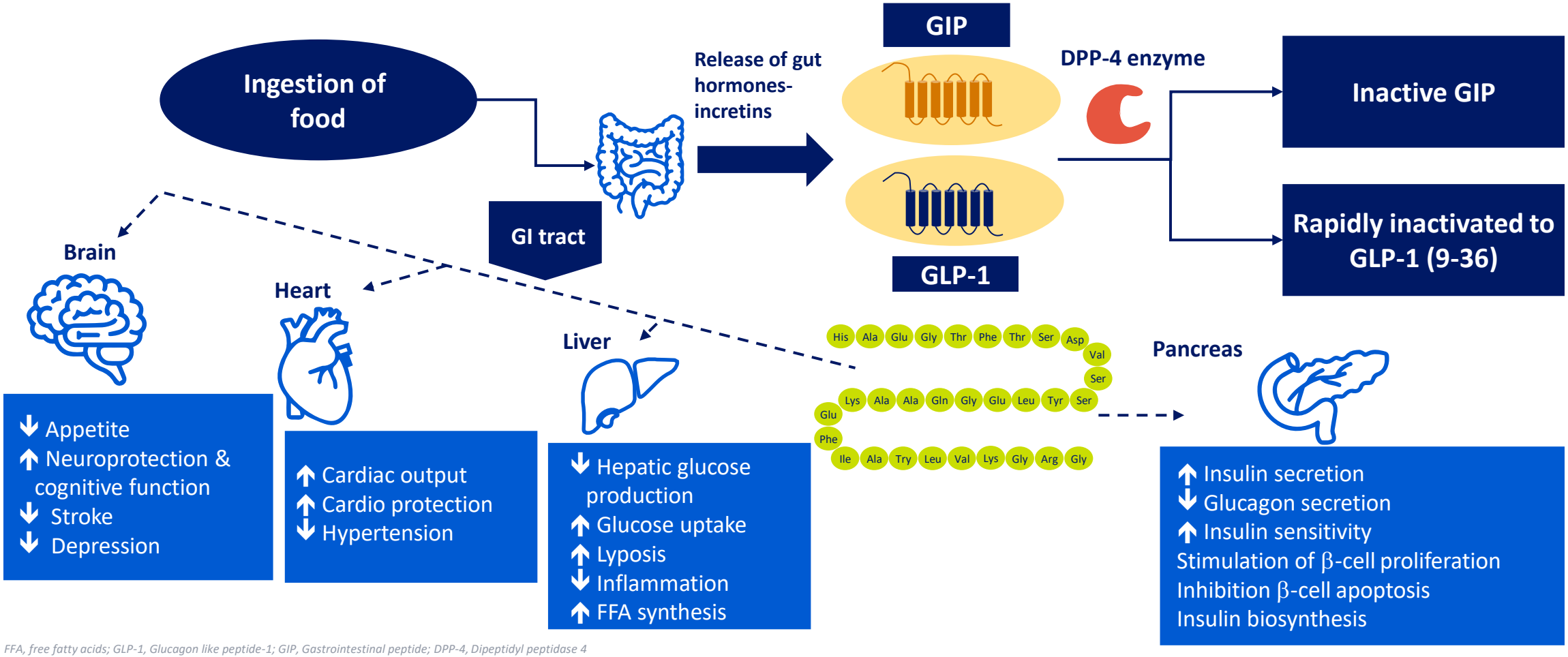
BMI, body mass index.
Wharton S et al. CMAJ 2020;192:E875–91.

Current anti-obesity medications



Lorcaserin and phentermine/topiramate are not approved for weight management in the EU.
5-HT2A-R, 5-hydroxytryptamine 2A receptor; D, dopamine; GABA-R, gamma-aminobutyric acid receptor; GLP-1R, glucagon-like peptide-1 receptor; MOP-R, mu opioid receptor; NE, norepinephrine; WL, weight loss.
Patel. *Metabolism* 2015;64:1376–85; FDA approved drugs available at: http://www.fda.gov/Drugs/default.htm. Last accessed August 2019; EMA approved drugs. Available at: http://www.ema.europa.eu/. Last accessed August 2019.

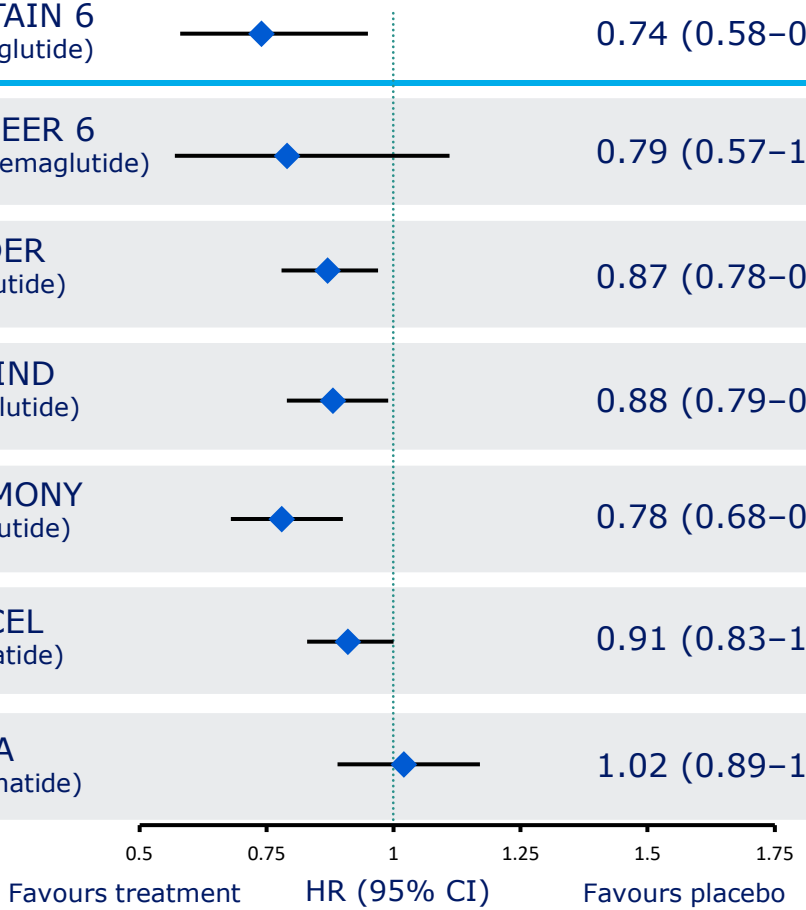
GLP-1 synthesis, release, metabolism and effects in physiology



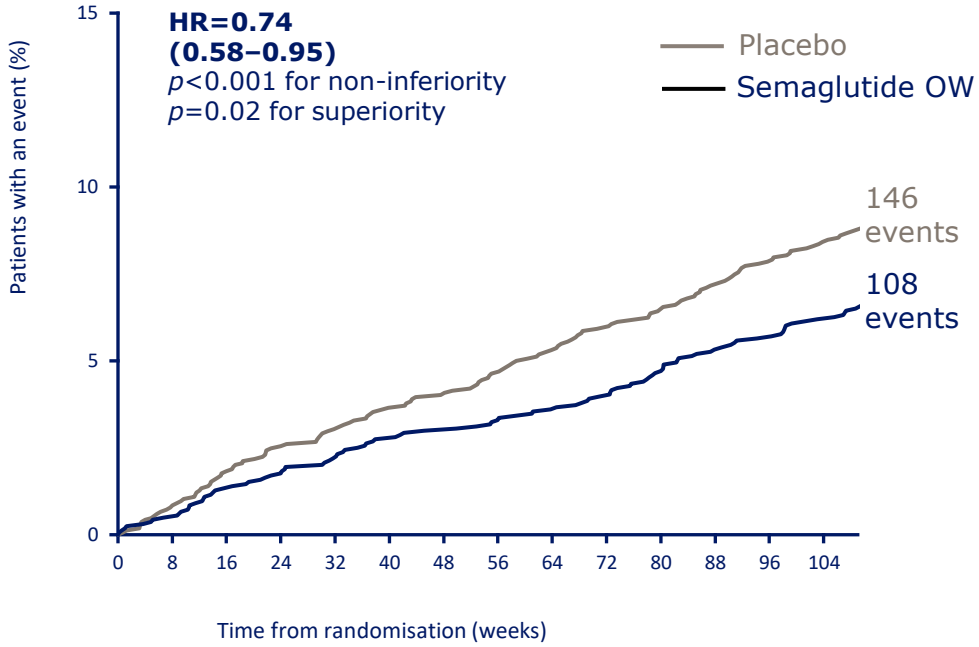
FFA, free fatty acids; GLP-1, Glucagon like peptide-1; GIP, Gastrointestinal peptide; DPP-4, Dipeptidyl peptidase 4
Sharma et al. Biomed Pharmacother. 2018;108:952-962

GLP-1RAs are associated with CV benefits in T2D

CVOT	HR (95% CI)	Trial size (N)	*p*-value*
SUSTAIN 6 (semaglutide)	0.74 (0.58–0.95)	3,297	0.02
PIONEER 6 (oral semaglutide)	0.79 (0.57–1.11)	3,183	0.17
LEADER (liraglutide)	0.87 (0.78–0.97)	9,340	0.01
REWIND (dulaglutide)	0.88 (0.79–0.99)	9,901	0.026
HARMONY (albiglutide)	0.78 (0.68–0.90)	9,463	<0.01
EXSCEL (exenatide)	0.91 (0.83–1.00)	14,742	0.06
ELIXA (lixisenatide)	1.02 (0.89–1.17)	6,068	0.81

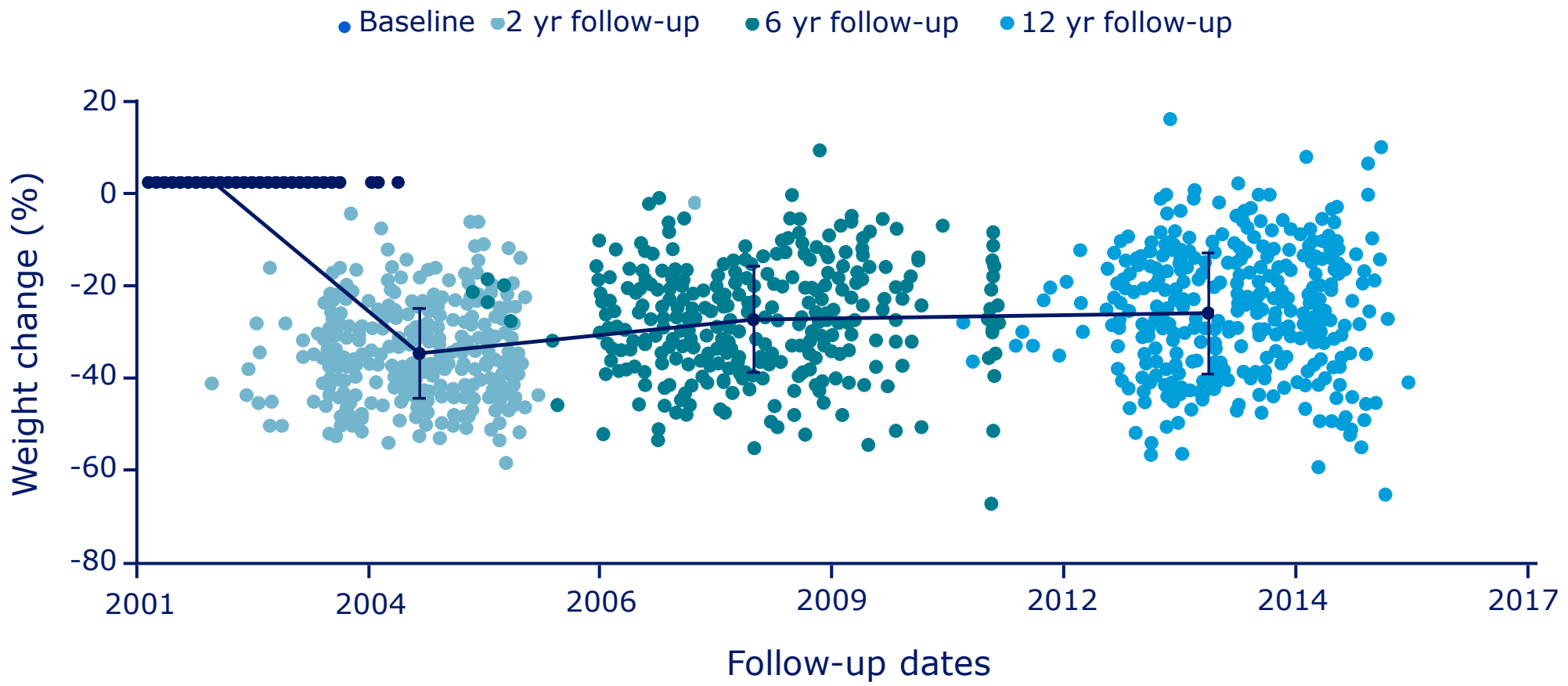


SUSTAIN 6: primary endpoint



All trials used 3-point MACE endpoints except ELIXA, which used a 4-point MACE endpoint. **p*-value for superiority. CI, confidence interval; CV, cardiovascular; CVOT, cardiovascular outcomes trial; GLP-1, glucagon-like peptide-1; HR, hazard ratio; MACE, major adverse cardiac event; OW, once weekly. Adapted from Singh and Sing *Indian J Endocrinol Metab* 2017;21:4–10; Holman et al. *N Engl J Med* 2017;377:1228–39;
Neal et al. *N Engl J Med* 2017;377:644–57; Hernandez et al. *Lancet* 2018;392:1519–29; Marso et al. *N Engl J Med* 2016;375:311–22; Marso et al. *N Engl J Med* 2016;375:1834–44;
Husain et al. *N Engl J Med* 2019;381:841–51; Gerstein et al. *Lancet* 2019;394:121–30.

Bariatric surgery is associated with variable weight loss outcomes

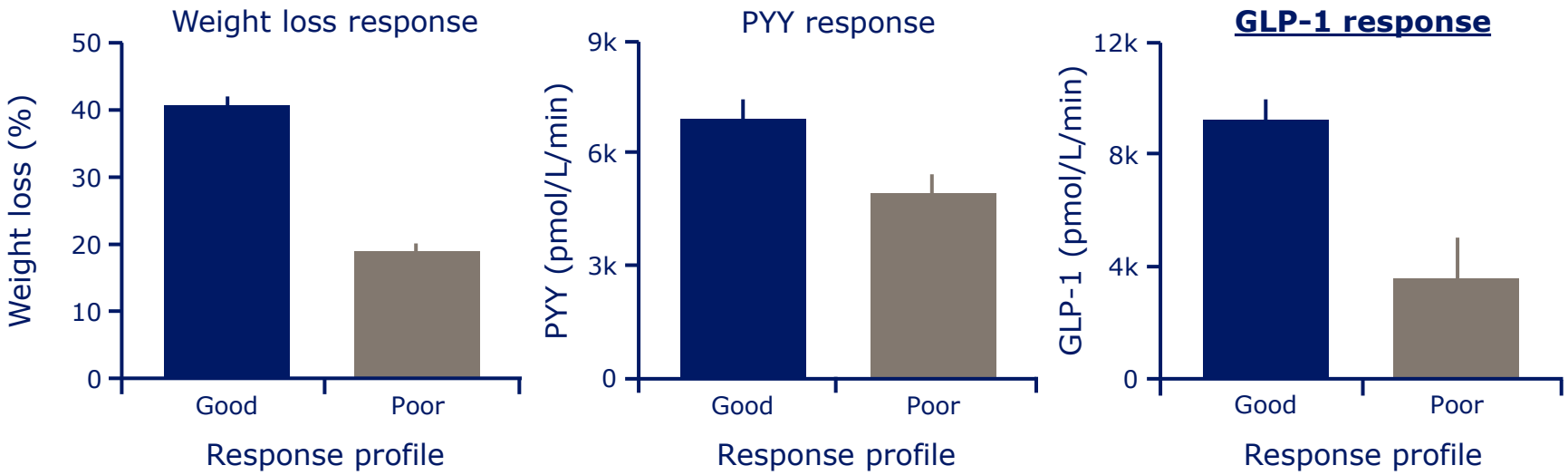


Data are mean change in body weight from baseline to follow-up years 2, 6 and 12. n= 418 patients who sought and underwent Roux-en-Y gastric bypass; blue line indicates mean percent change .

Adams *et al. NEJM* 2017;377:1143-1155

GLP-1 and PYY linked to surgical weight loss

- **Patients who experienced a good weight loss response following bariatric surgery also had higher levels of PYY and GLP-1[1–3]**



GLP-1, glucagon-like peptide-1; PYY, peptide YY

1. Santo *et al. Obes Surg.* 2016;26:919-25; 2. le Roux *et al. Ann Surg* 2006;243:108–14; 3. le Roux *et al. Ann Surg* 2007;246:780–5

מדוע מתרחשת העליה במשקל לאחר ניתוח בריאטרי?

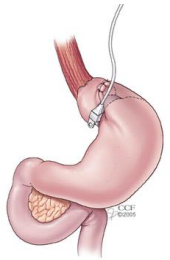
Etiology of Weight Regain after Bariatric Surgery

Patient-Specific Factors	Surgery-Specific Factors
Amount of physical activity	Dilation of gastrojejunal stoma
Mental health issues	Gastro-gastric fistula
Nutritional compliance	Gastric pouch length
Follow-Up	Greater residual gastric volume
Preoperative variables	Dilation of gastric sleeve
Hormonal imbalance	Retained fundus
Support group attendance	
Control of food urges/ emotional eating	

Karmali et al, Weight Recidivism Post-Bariatric Surgery: A Systematic Review OBES SURG (2013) 23:1922–1933

השפעה של נתוחים בריאטרים על הורמוני המעי/קיבה

Adjustable gastric banding[1,3]



Ghrelin ↑
PYY (no change)
GLP-1 (no change)
Oxyntomodulin (no change)
Glicentin (no change)

Excess weight loss:[2*†]
48%

Sleeve gastrectomy[1,3]

Ghrelin ↓
PYY ↑
GLP-1 ↑
Oxyntomodulin ↑
Glicentin ↑

Excess weight loss:[2*†]
62%

Roux-en-Y gastric bypass[1,3]

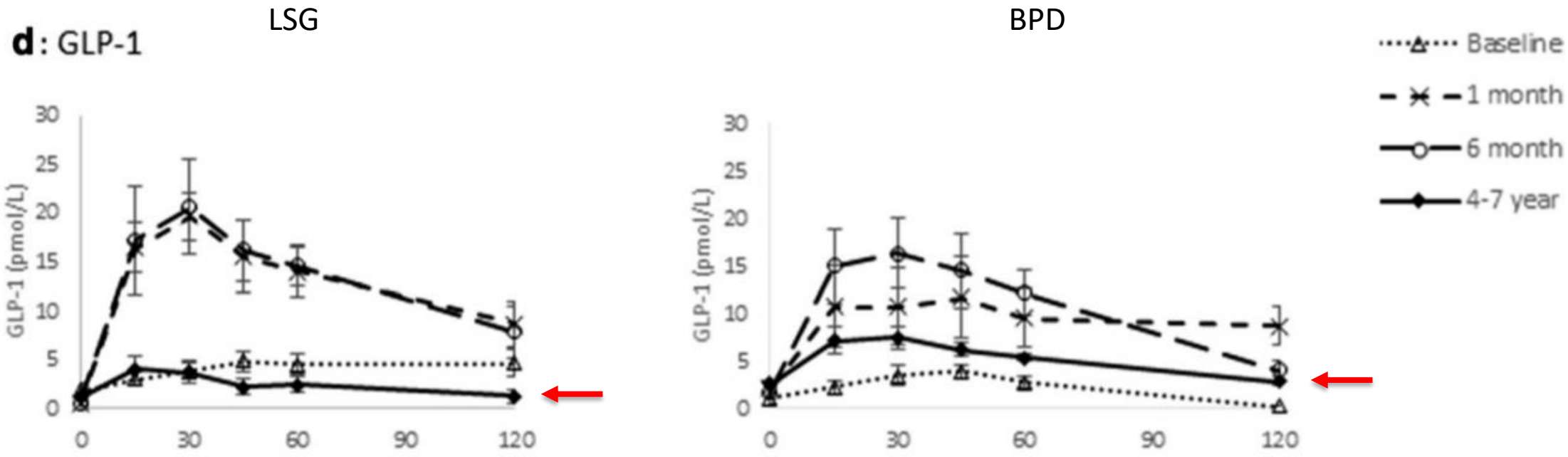
Ghrelin ↑ or (no change)
PYY ↑↑
GLP-1 ↑↑
Oxyntomodulin ↑↑
Glicentin ↑

Excess weight loss:[2*†]
87%

*Excess weight loss = change in weight from preoperative over excess body weight (based on ideal goal weight with BMI of 27 kg/m^2).
†All percentages are rounded and data is from 24 months post-surgery
GLP-1, glucagon-like peptide-1; PYY, peptide YY
** Including One Anastomosis Gastric Bypass

1. Field *et al. Nat Rev Endocrinol* 2010;6:444–53; 2. Lodhia *et al. Int J Obes* 2012;2:S47–50 3. Perakakis N Metabolism 2019 101: 153997

Long term follow up post bariatric surgery shows a decrease in OGTT induced GLP-1 levels



Changes in GLP-1 and GIP during the OGTT before and 1 month, 6 months and 4–7 years after LSG and BPD. Value represents mean ± standard error. GLP1, glucagon-like peptide-1; LSG, laparoscopic sleeve gastrectomy; BPD, biliopancreatic diversion.

1. Thinzar Min et al, Effect of Laparoscopic Sleeve Gastrectomy on Static and Dynamic Measures of Glucose Homeostasis and Incretin Hormone Response 4-Years Post-Operatively Obesity Surgery (2020) 30:46–55

Saxenda post-bariatric

	Suliman et al	Rye et al	Wharton et al	Abrahamsson et al	Muratori et al	Shehadeh et al	Talbot et al	Rigas et al	Creange et al
סוג המחקר	פרוספקטיבי	רטרוספקטיבי	רטרוספקטיבי	רטרוספקטיבי	רטרוספקטיבי	רטרוספקטיבי	רטרוספקטיבי	רטרוספקטיבי	רטרוספקטיבי
מספר משתתפים מנותחים (n)	76	20	117	13	20	25	32	48	25
סוגי הניתוחים שעברו בעבר	SG\ RYGB\ Other	RYGB \ LSG\ VBG\ AGB	RYGB\ AGB\ Gastric sleeve	GBS	LSG\RYGB\LAGB	sleeve gastrectomy\ gastric banding\ gastric bypass\ Last both	Bariatric surgery	LAGB\ LSG\ GBP	LAGB\ RYGB\LSG\LAGB & RYGB
אוכלוסיית המטופלים	טופל במרפאת ICLDC וקיבל סאקסנדה	עליה במשקל של יותר מ 10%\ ירידה של פחות מ 20%\ הגעה לפלאטו ולא מתאימים לקטגוריות הקודמות	טופלו בסאקסנדה במרפאה. עלו בממוצע 58% מהמשקל שאיבדו לאחר הניתוח	פחות מ 50% ירידה במשקל העודף במשך 15- 20 חודשים	עליה ב BMI לאחר הירידה שהושגה בניתוח	מטופלים שעלו חזרה מעל 25% מהמשקל שהשילו לאחר הניתוח ולא הגיבו לשינוי אורחות חיים	העלו 15% מהמשקל שהורידו לאחר הניתוח.	פלאטו בירידה במשקל מוקדם מהצפוי	עברו ניתוח בריאטרי בעבר והתחילו טיפול עם סאקסנדה
משך הזמן בממוצע מהניתוח	4 שנים	6.3 שנים	7.8 שנים	לפחות שנתיים	4.5 שנים	-	1.1 שנים	-	-
משך הטיפול על סאקסנדה	213 יום	28 שבועות	7.6 חודשים	15-20 חודשים	10.9 חודשים	3 חודשים	9 חודשים	7 חודשים	24 שבועות
ירידה במשקל לאחר הניתוח תחת סאקסנדה	**-6.1% -12.2% ERs**	**-9.7%**	**-5.5%**	**-10.4%**	**-5.2 kg\m2**	**-10%**	**-7.2%**	**-13.4%**	**-9.45%**

Rye P, Modi R, Cawsey S, et al. Efficacy of High-Dose liraglutide as an adjunct for weight loss in patients with prior bariatric surgery. OBES SURG. 2018;28(11):3553–3558 \ M Suliman, Buckley A, Al Tikriti A, Tan T, le Roux CW, Lessan N, et al. Routine clinical use of liraglutide 3 mg for the treatment of obesity: outcomes in non-surgical and bariatric surgery patients. Diabetes Obes Metab. 2019;21(6):1498–501. \ Wharton S et al : Liraglutide 3.0 mg for the management of insufficient weight loss or excessive weight regain post-bariatric surgery. Clinical obesity Clinical Obesity. 2019;9:e12323\ Rigas G, Talbot ML, Tam C. The role of adjuvant pharmacotherapy in the management of patients with a partial response to bariatric metabolic surgery-the first Australian experience. Obes Facts. 2018;11(suppl 1):1-358 \ Talbot L LK, Tam C, Rigas T. Liraglutide use in patients who have regained weight after bariatric surgery: the first Australian experience. Abstract O.078 presented at the 22nd World Congress of the International Federation for the Surgery of Obesity Metabolic Disorders, August 29-September 2, 2017, London, UK. 2017, \ Shehadeh N ZW, Zuckerman Levin N, Said W, Zolotov S, Elemy A. Liraglutide treatment in post-bariatric surgery patients who failed to maintain weight reduction. Surg Obes Relat Dis. 2017;13:S144. A5173. \ Muratori F DSG, Pellegrino D, Vignati F. Effectiveness of liraglutide 3.0 mg treatment on weight regain after bariatric surgery in severely obese patients. Obes Facts. 2018;11(Suppl 1):280. T4P117. Abrahamsson N HA. GLP-1 analog treatment in the failed gastric bypass patient. Poster 2233-P presented at: 75th Annual Meeting and Scientific Sessions of the ADA; June 2015; Boston, MA.\ Creange C, Lin E, Ren-Fielding C, et al. Use of liraglutide for weight loss in patients with prior bariatric surgery. Surg Obes Relat Dis. 2016;12(7):S157.

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL USING LIRAGLUTIDE FOR WEIGHT REGAIN AFTER ROUX-EN-Y GASTRIC BYPASS

Obesity Week 2021, ID: oral 001

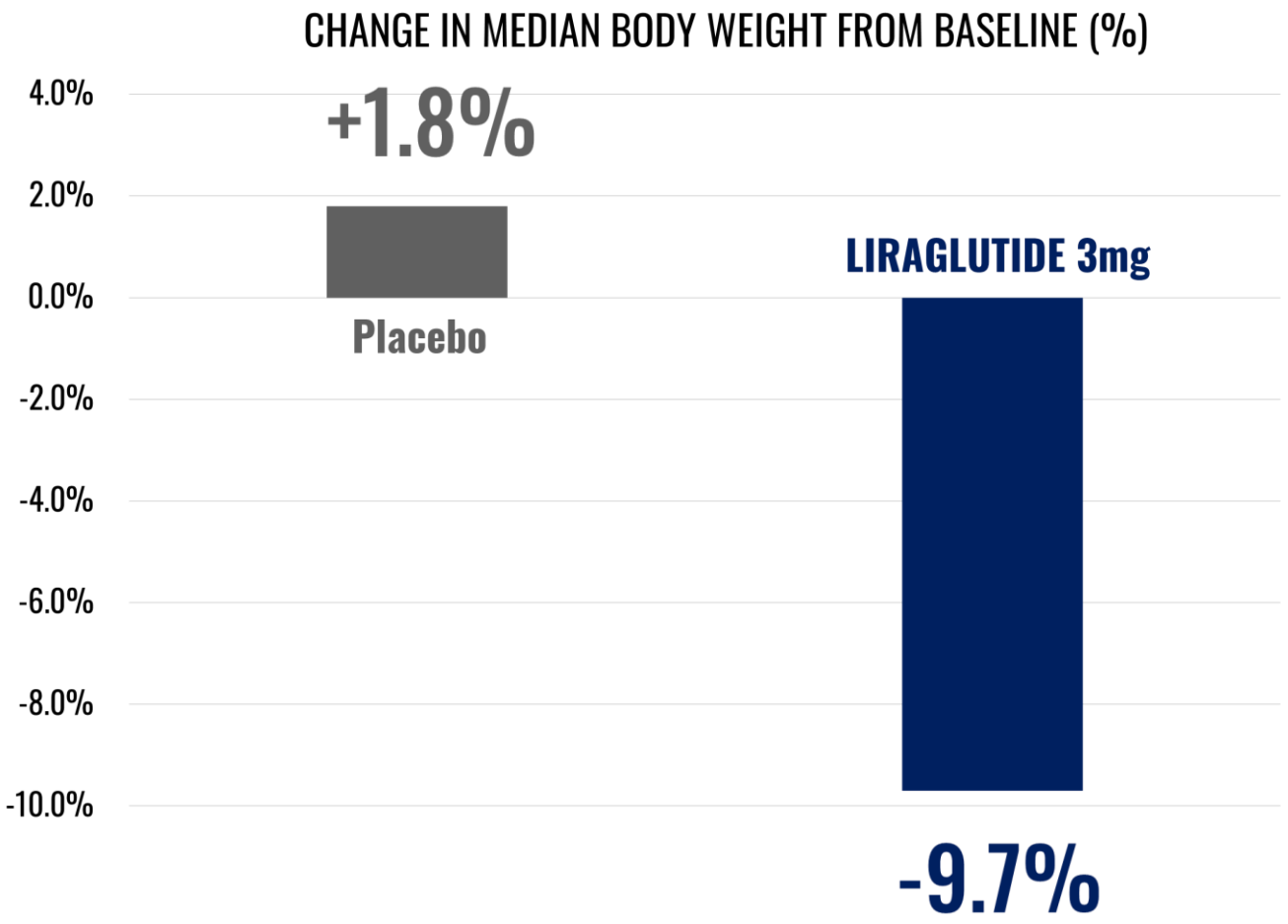
STUDY DESIGN

- **2:1** block randomization method
- Stratified by **gender** and **percent** post-operative total body weight loss (≤ 25 or 25-49.9%) to receive Liraglutide 3.0 mg/day (n=89) OR placebo (n=43)

Patients attended clinics visits every **3 months** from baseline to **56 weeks** and received lifestyle counseling from registered dieticians

Primary Endpoint:
Proportion of patients losing **>5%** of baseline body weight

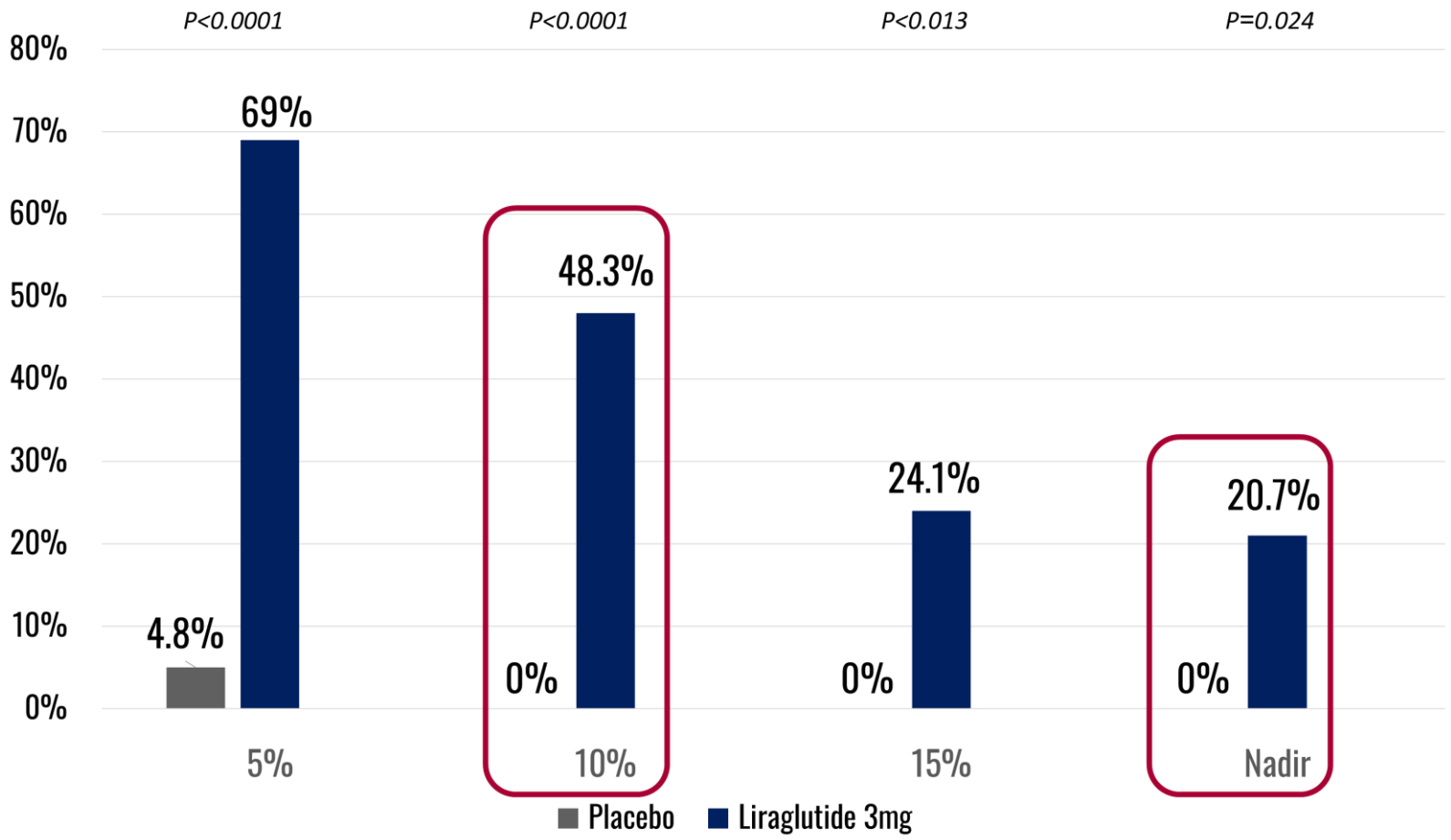
Patients treated with Saxenda had a significant weight loss as compared to placebo treated patients at 12 months



At week 56, the median weight lost from BWL-B was 9.7% (IQR=2.4–15.0) and -1.8% (IQR=-4.2–0.7) in the Liraglutide and placebo arms, respectively (p<0.00001)

Holly F Lofton et al, A Randomized, Double-Blind, Placebo-Controlled Trial Using Liraglutide for Weight Regain after RYGB. Oral presentation, Obesity Week 2021

Proportion of Patients who lost 5%, 10%, 15% or Met/Exceeded Nadir at 12M



Holly F Lofton et al, A Randomized, Double-Blind, Placebo-Controlled Trial Using Liraglutide for Weight Regain after RYGB. Oral presentation, Obesity Week 2021

Conclusions regarding GLP-1RA and Cardiometabolic Risk

What we know from the CVOTs:

- GLP-1RAs reduce atherosclerotic MACE in patients with and without established ASCVD
- GLP-1RAs reduce a broad definition of progression of renal disease, driven by albuminuria
- Guidelines are catching up, but still behind in the literature

What we still need more clarity on :

- More experience in Primary Prevention
- Benefit of “Dual” Agents
- Role of Oral GLP-1RA in CV Risk Reduction
- GLP-1RAs in Patients without Diabetes

Summary

- Anti obesity medication can give better outcomes for patients before and after Bariatric surgery
- Obesity is a chronic disease and should be treated as such for the long term
- The new/future anti-obesity medication have the potential of weigh reduction almost as Bariatric surgeries

- The obesity treatment should be tailored to patients situation

תודה על ההקשבה

ד"ר דובינסקי אנג'לינה

מומחית ברפואה פנימית, סוכרת והשמנה