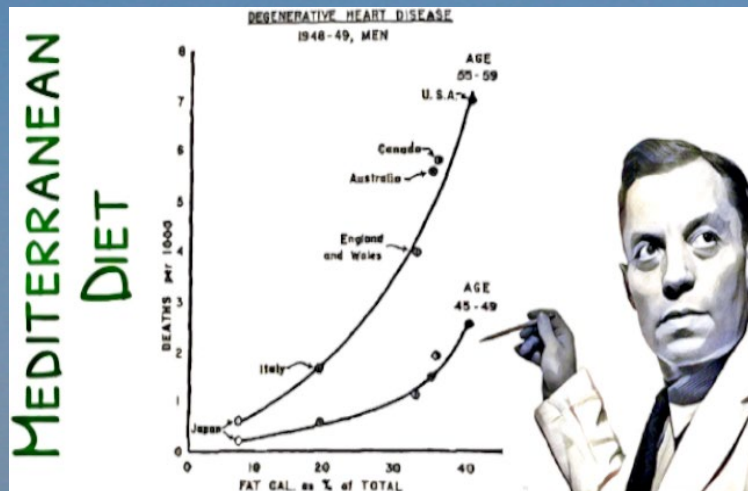




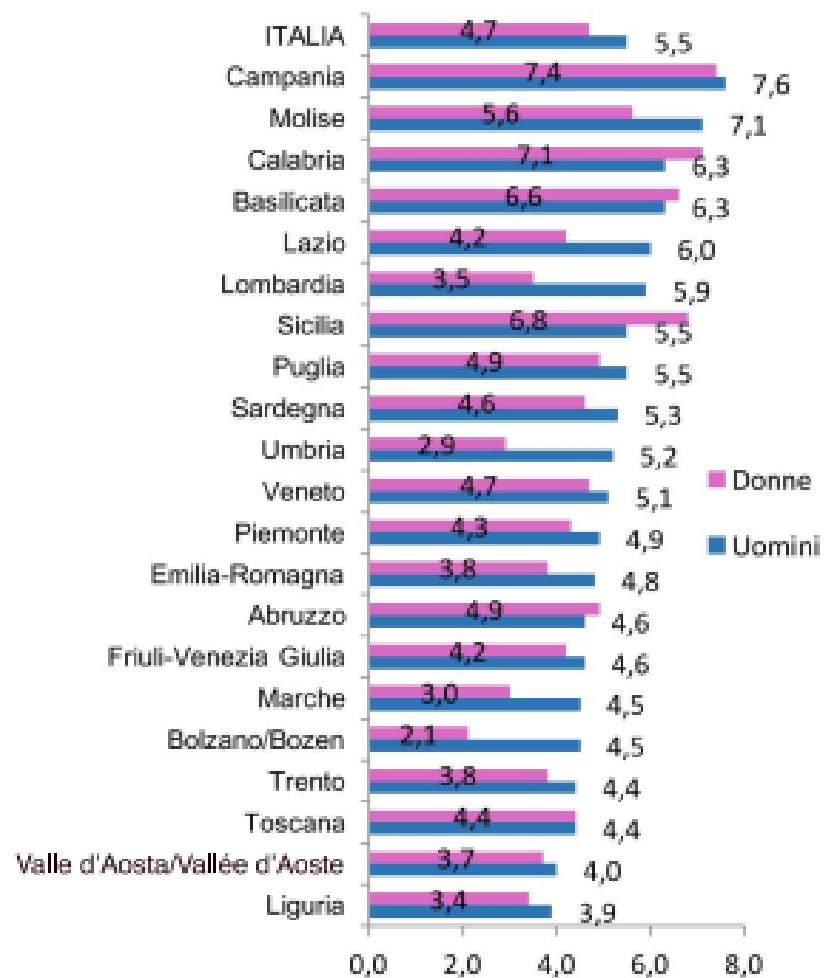
la prevenzione del Diabete

Dr Raffaele Mancini

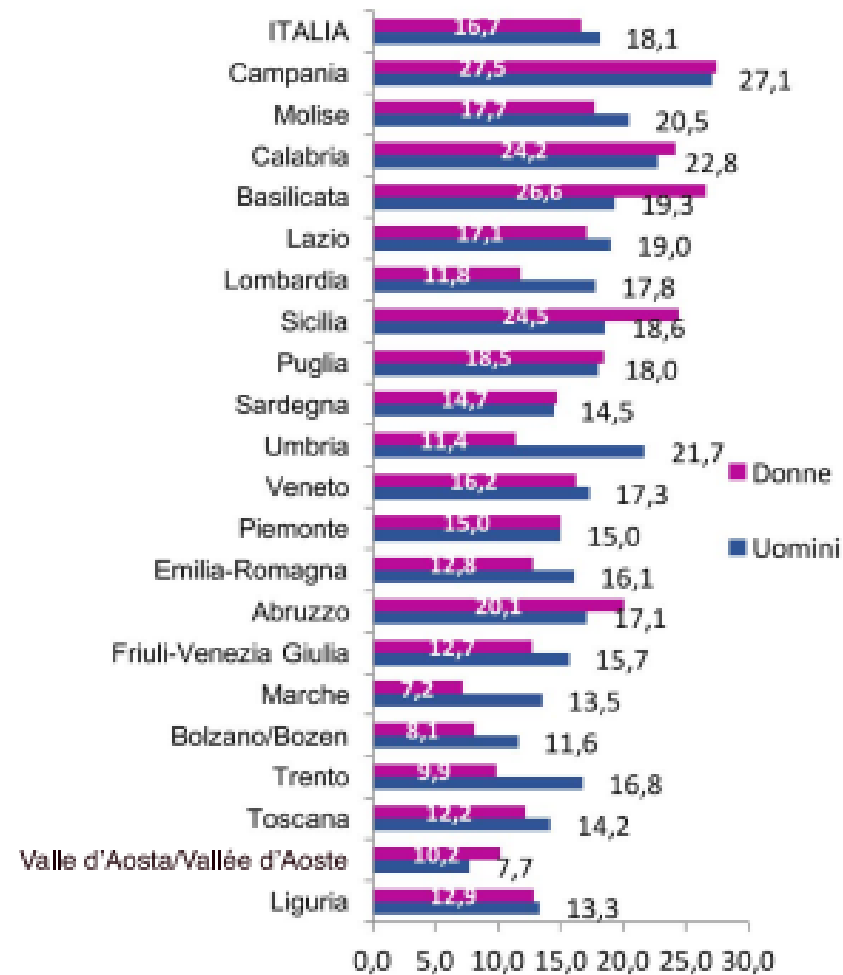


Il Diabete in Italia

Popolazione

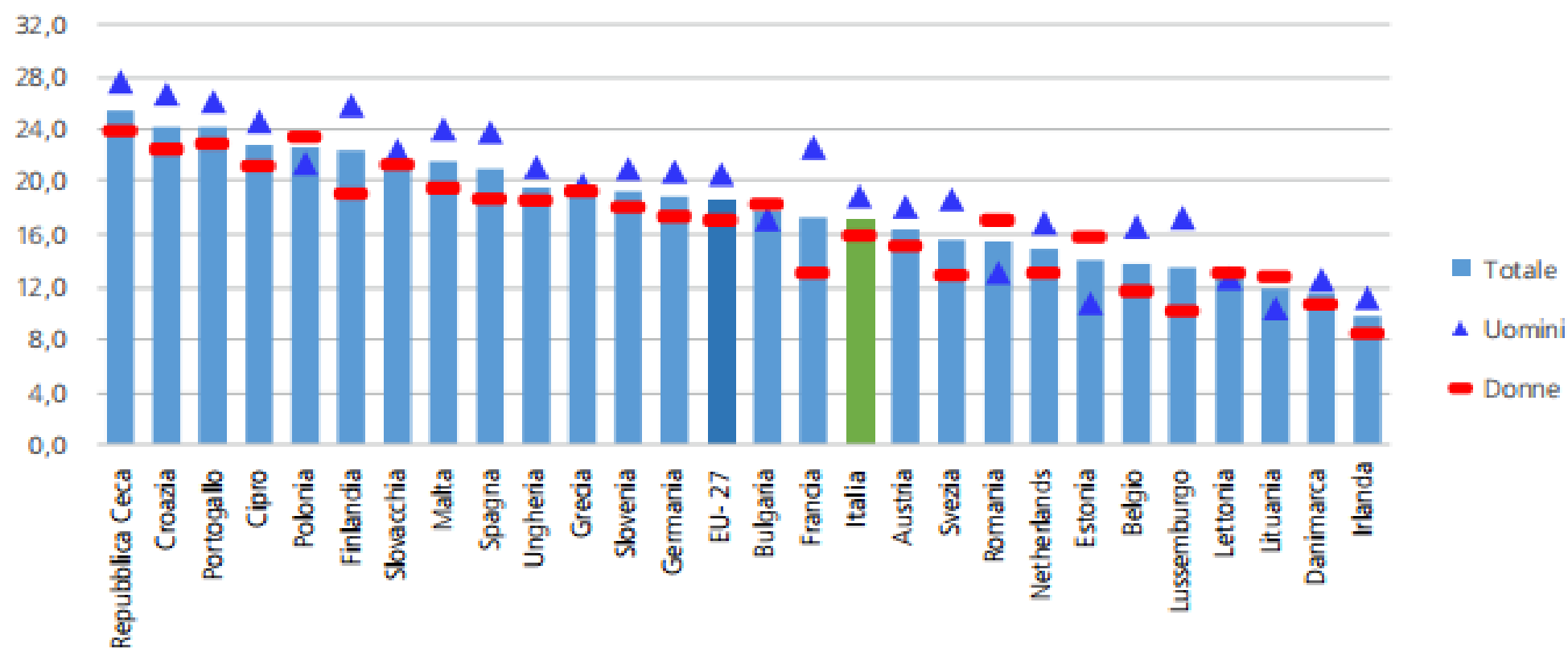


Persone di 65 anni e oltre



Il diabete in Europa

Figura 4. Paesi europei a confronto per la prevalenza del diabete nella popolazione di 65 anni e più, per genere. Anno 2019. Tassi per 100 persone.



Screening and Diagnosis of Prediabetes

Conventional Glycemic Markers



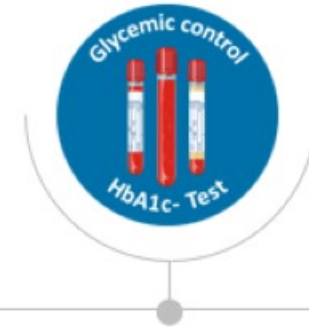
Fasting plasma glucose

100 to 125 mg/dL
(5.6-6.9 mmol/L)



2-Hour 75-g OGTT

140 to 199 mg/dL
(7.8-11.0 mmol/L)



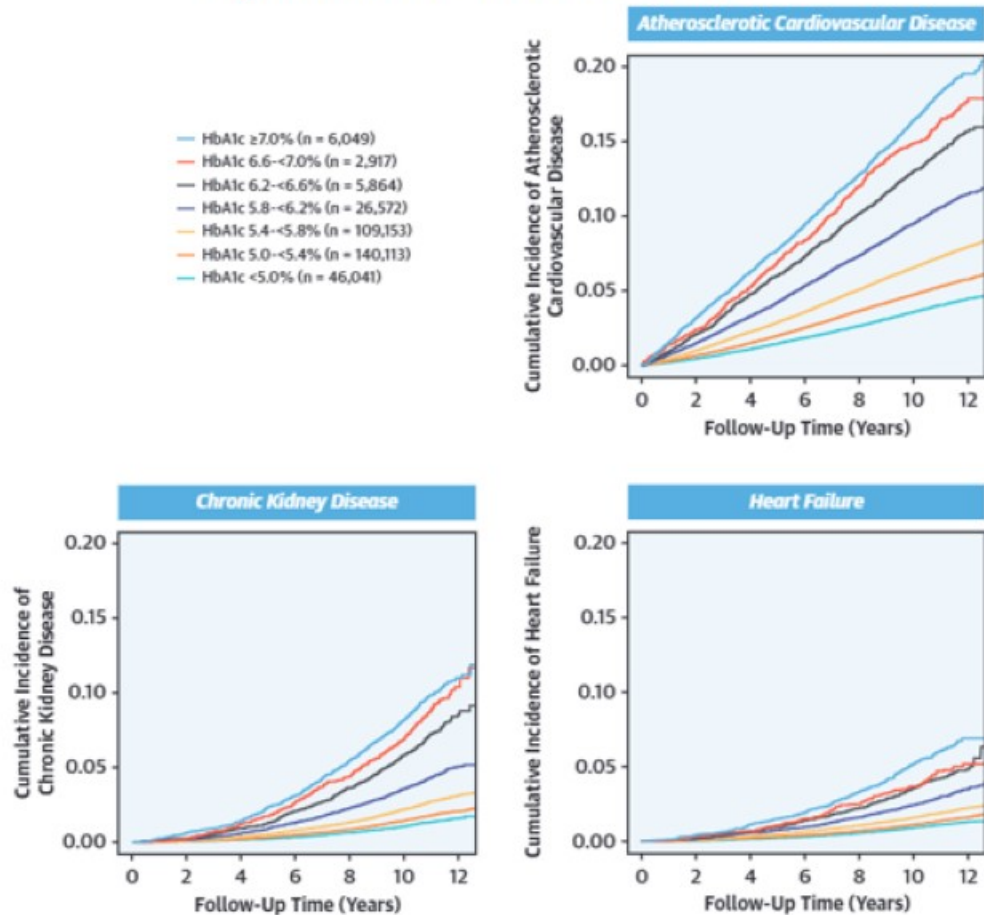
HbA1c

5.7% to 6.4%
(39-47 mmol/mol)

UK Biobank

Prevention of Cardiovascular and Kidney Outcomes

Incidents of ASCVD, Heart Failure, and Chronic Kidney Disease by Baseline HbA1c Level



- 6589 of 46,911 (14.0%) individuals with prediabetes progressed to T2D during the follow-up period
- Among 6476 individuals with prediabetes who developed 1 or more incident outcome:
 - 1930 (29.8%) progressed to T2D during follow-up
 - Only 802 (12.4%) developed T2D prior to an incident diagnosis

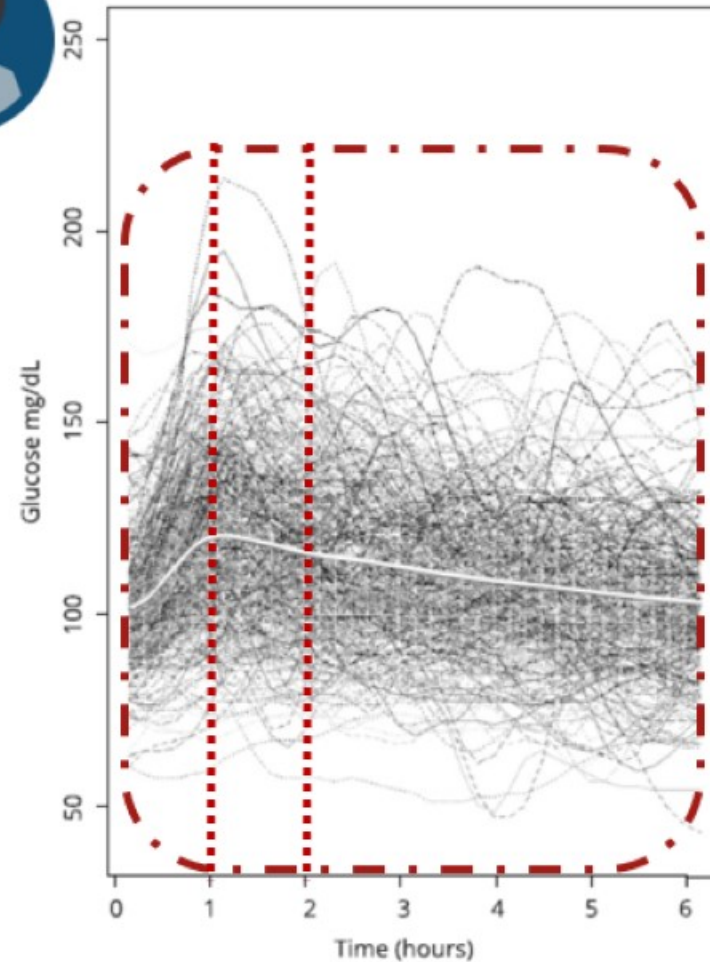
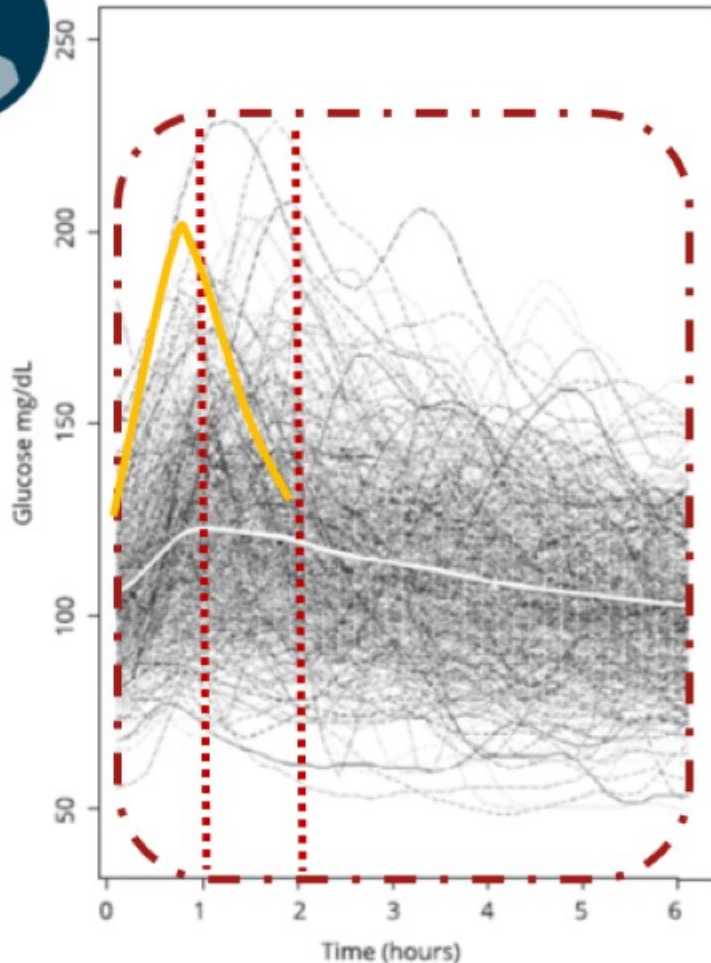
A 3- to 4-fold gradient of cardiovascular and kidney disease risks was observed between HbA1c $> 7.0\%$ and HbA1c $< 5.0\%$. T2D, type 2 diabetes.

Honigberg MC, et al. J Am Coll Cardiol. 2021;78:453-464.

Postprandial Glycemic Response in Adults Without Diabetes

Change of Paradigm

Glycemic patterns of the total number of participants



Results

- 148 patients (51% women)
- Men had higher intake
- Macronutrient distribution was similar in both sexes
- There were no significant differences in the amount of fiber between men and women (5.5 g vs 4.5 g)
- Percentage of values over the range of normal glycemia (> 140 mg/g)
 - 9.7% vs 7.1% in women and men, respectively



American
Diabetes
Association.

Diabetes Care

Oltre un quarto delle persone di età superiore ai 65 anni ha il diabete e la metà degli anziani ha il prediabete

Gli anziani con diabete:

hanno tassi più elevati di morte prematura, disabilità funzionale, perdita muscolare accelerata e malattie coesistenti, come ipertensione, malattie coronariche e ictus, rispetto a quelli senza diabete.

sono anche a maggior rischio rispetto ad altri anziani per diverse sindromi geriatriche comuni, come la politerapia, il deterioramento cognitivo, la depressione, l'incontinenza urinaria, le cadute dannose e il dolore persistente

Queste condizioni possono avere un impatto sulle capacità di autogestione del diabete degli anziani e sulla qualità della vita se non trattate

What Is Prediabetes and Why Is It Important to Manage It?

Prediabetes

**90
million**



90 million people, more than
1 out of 3 adults, have prediabetes

More than 80%



Don't know they have prediabetes

If you have prediabetes, losing weight by

Being more active



Eating healthy



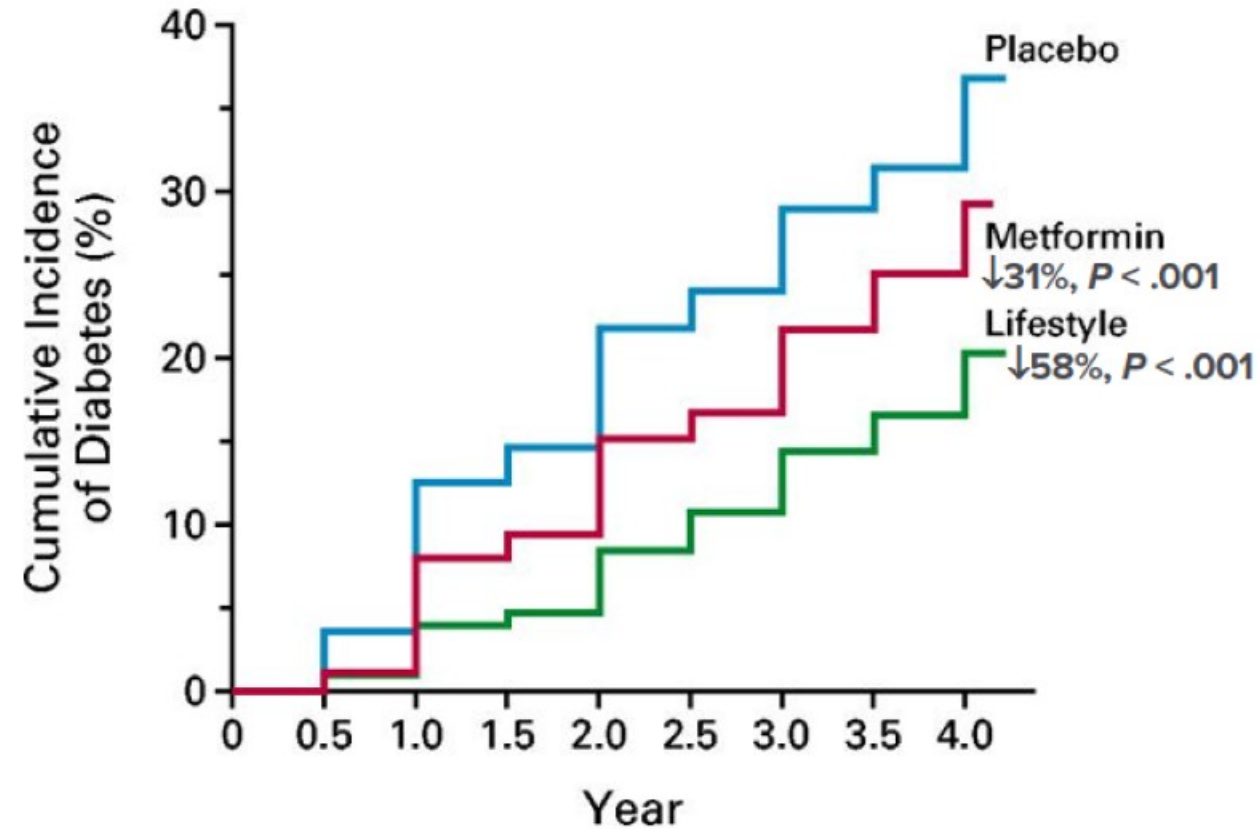
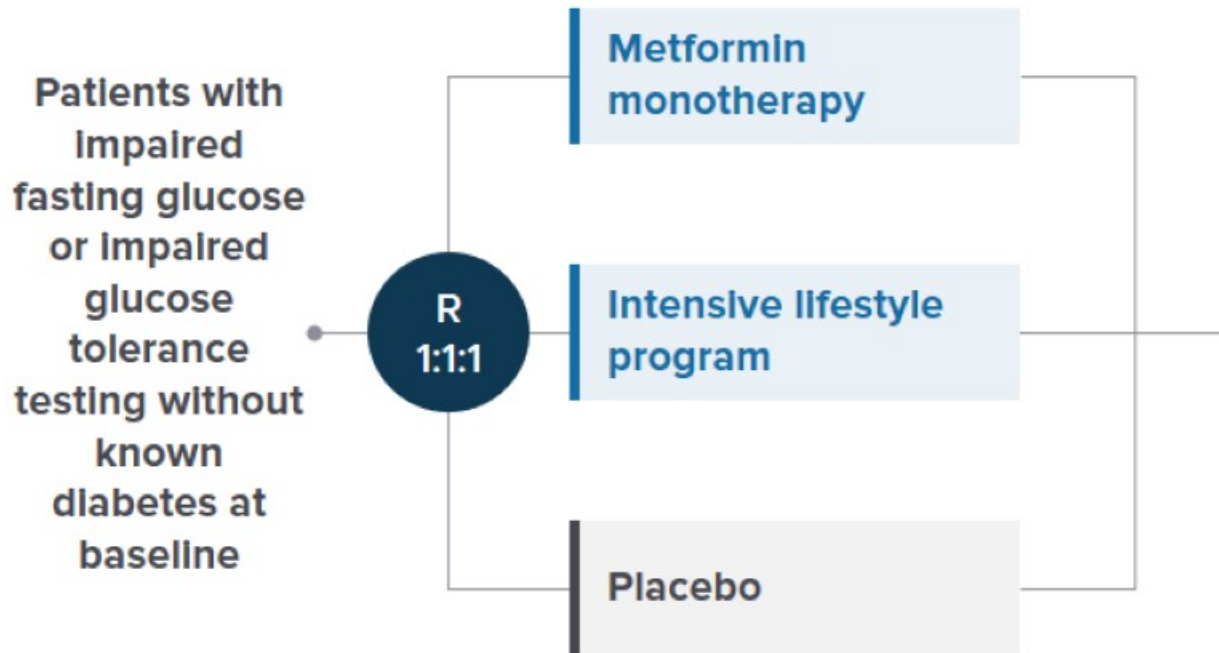
can cut your risk of getting type 2 diabetes

----- **in half** -----

©Medscape, LLC

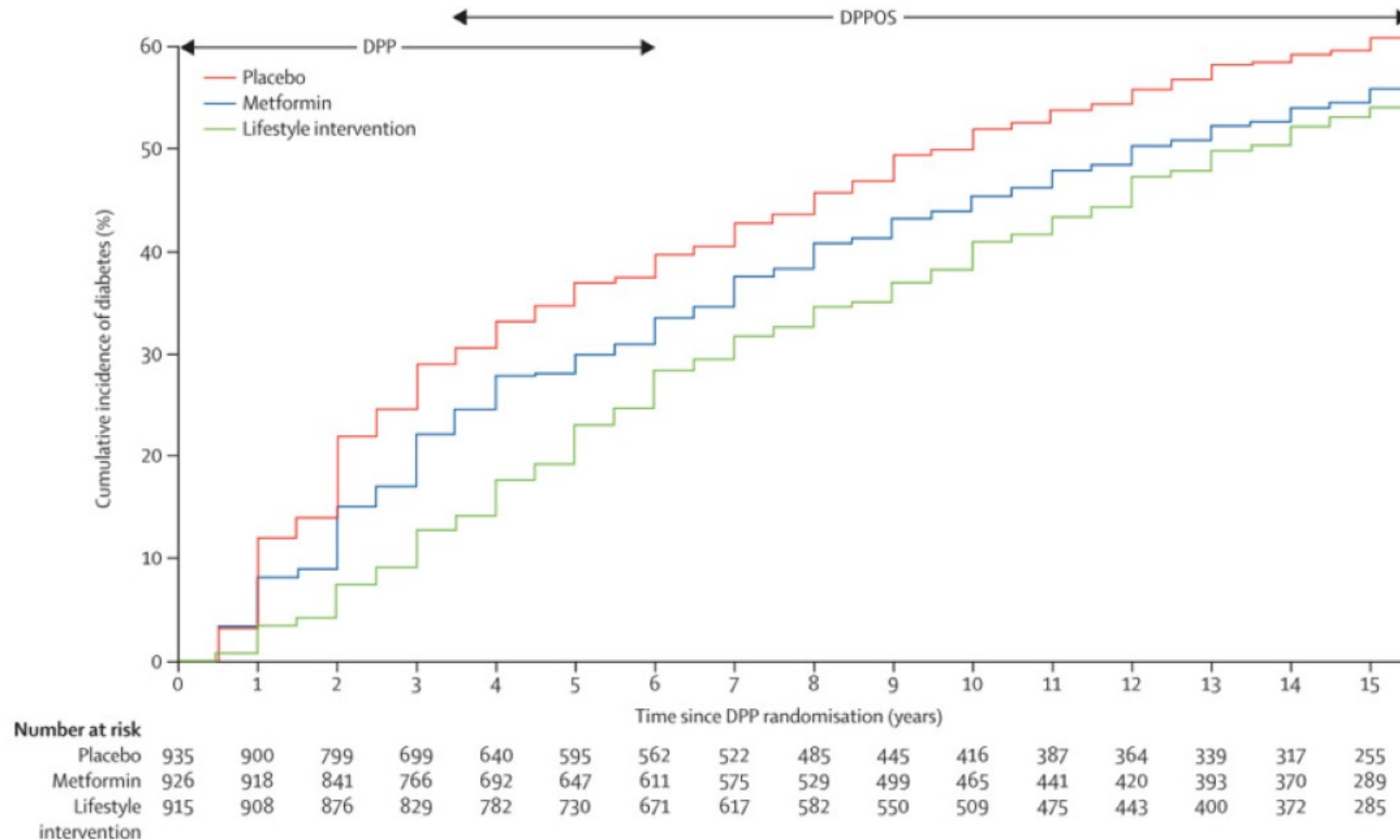
The Diabetes Prevention Program

DPP launched about 2 decades ago and evaluated the benefit of diet plus exercise or metformin on diabetes prevention in patients at risk



DPP

15-Year Follow-Up



Prediabetes Risk Factors

Criteria for Screening for Diabetes of Prediabetes in Asymptomatic Adults

1. Testing should be considered in adults with **overweight or obesity** ($\text{BMI} \geq 25 \text{ kg/m}^2$ or $\geq 23 \text{ kg/m}^2$ in Asian Americans) who have 1 or more of the following risk factors:

- **First-degree relative** with diabetes
- **High-risk race/ethnicity** (eg, African American, Latino, Native American, Asian American, Pacific Islander)
- History of **CVD**, **hypertension** ($\geq 140/90 \text{ mm Hg}$ or on therapy for hypertension)
- **HDL-cholesterol** level $< 35 \text{ mg/dL}$ (0.90 mmol/L) and/or a **triglyceride** level $> 250 \text{ mg/dL}$ (2.82 mmol/L)
- Women with polycystic ovary syndrome
- Physical inactivity
- Other clinical conditions associated with insulin resistance (eg, severe obesity, acanthosis nigricans)

2. Patients with prediabetes ($\text{HbA1c} \geq 5.7\%$ [39 mmol/mol], IGT, or IFG) should be tested yearly

3. Women who were diagnosed with GDM should have lifelong testing at least every 3 years

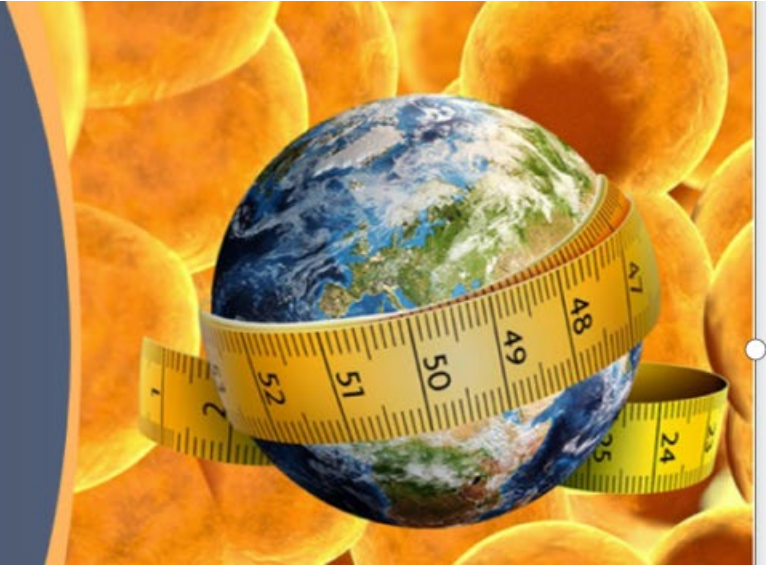
4. For all other patients, testing should begin at the age of 35 years

5. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status

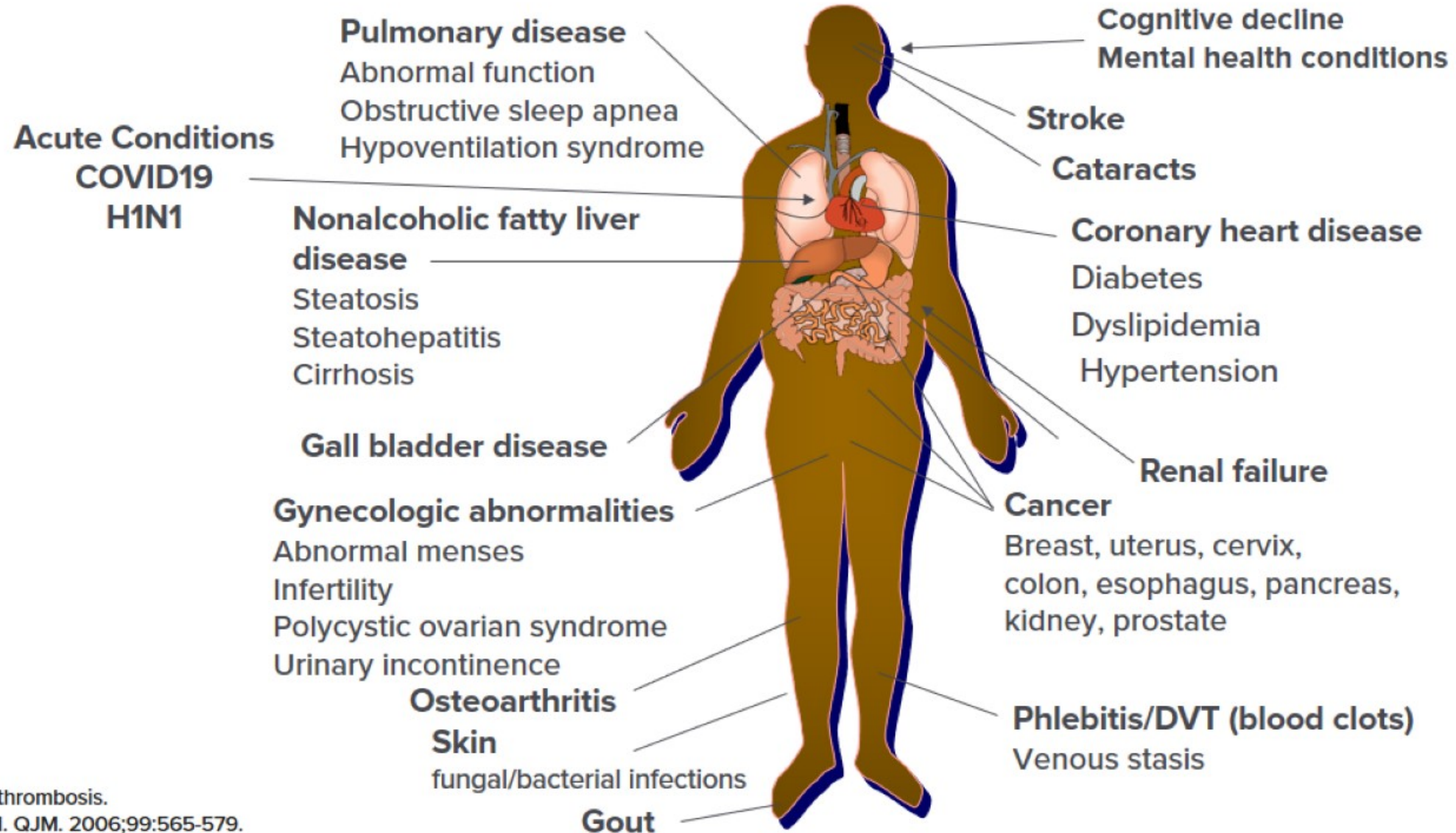
6. People with HIV

Obesity

The Root Cause of Multiple
Morbidities



Medical Complications of Increased Weight

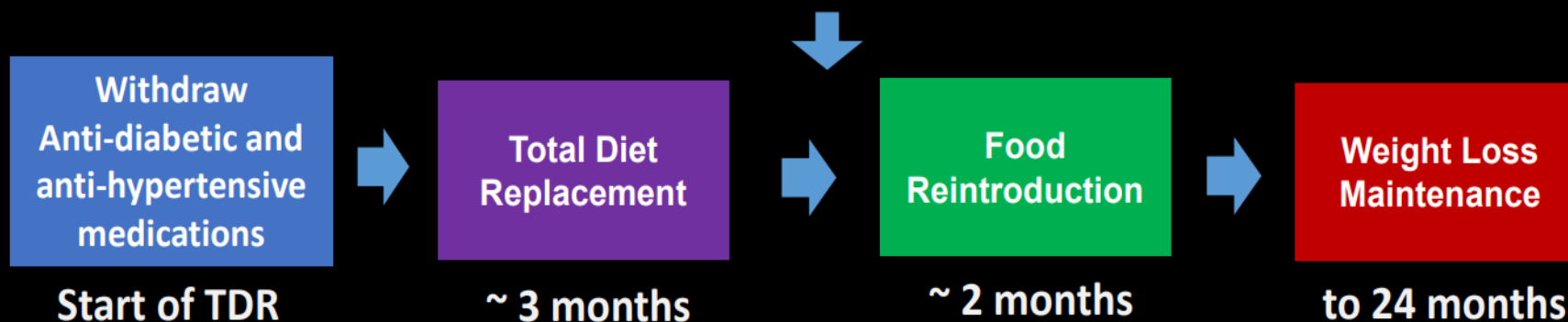


DVT, deep vein thrombosis.
Malnick SD, et al. QJM. 2006;99:565-579.

Structured Programme in Primary Care Setting



Practice nurse/dietitian programme delivery



During year 2, average number of 'monthly' appointments was 7.7

Study design (1)

Main inclusion criteria

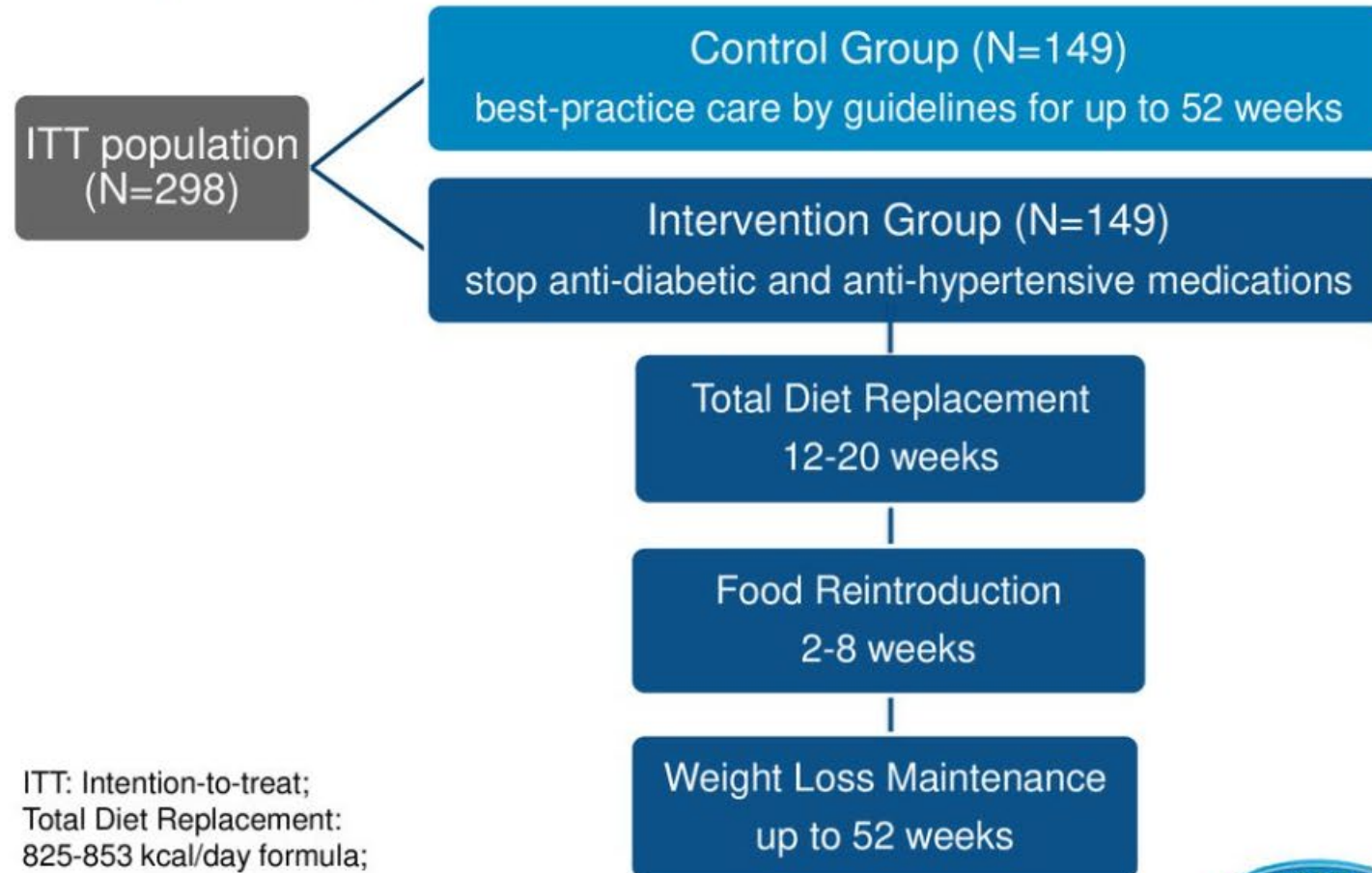
- T2DM diagnosis within the previous 6 years(*)
- age 20–65 years
- BMI: 27 - 45 kg/m²

Endpoint at 12 months

- Weight loss ≥ 15 kg
- DM remission defined as HbA1c $< 6.5\%$ (< 48 mmol/mol) after 2 months without antidiabetic medications

(*) most recent HbA1c value $> 6.0\%$, if HbA1c $< 6.5\%$ antidiabetic medication was continued

Study design (2)



Lean MEJ, et al. Lancet 2017



Co-Primary Outcomes

Weight loss $\geq 15\text{kg}$

Remission T2DM
HbA1c $< 48\text{mmol/mol}$ on no diabetes medications

ITT 12-month Primary Outcome Results

1st Co-Primary Outcome: ≥ 15 kg weight loss

Intervention	36/149 (24%)	$p < 0.0001$
Control	0/149	

2nd Co-Primary Outcome: Remission of diabetes*

Intervention	68/149 (46%)	$p < 0.0001$
Control	6/149 (4%)	

* HbA1c < 48 mmol/mol ($< 6.5\%$)
off all anti-diabetes medication for at least 2 months

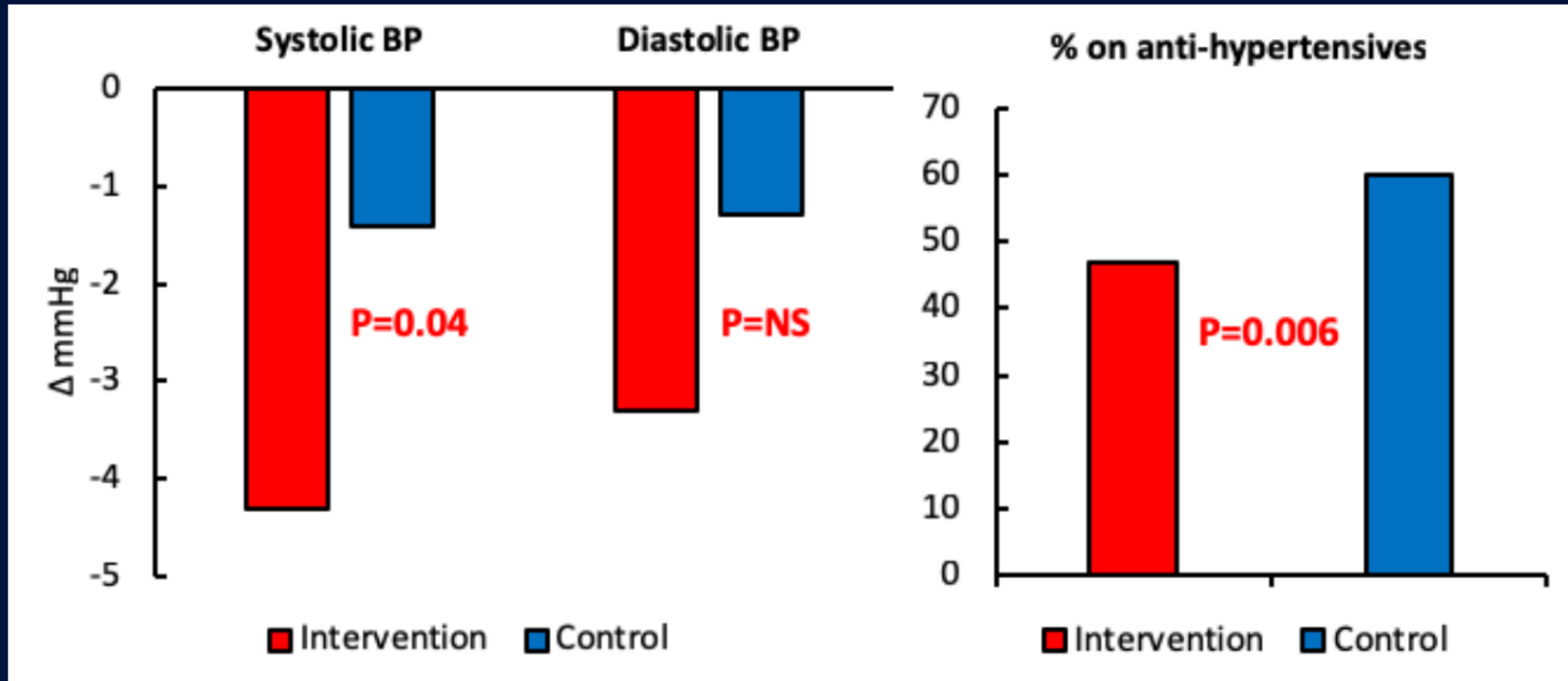
Conclusions

- **T2DM of up to 6 years' duration can be reversed by weight loss with help of an evidence-based structured weight management program delivered in a community setting, by routine primary care staff.**
- **Almost a quarter of participants who followed the intervention achieved at least 15 kg of weight loss at 12 months.**
- **Almost half of patients in the intervention group showed remission of diabetes, and were off antidiabetic medication.**

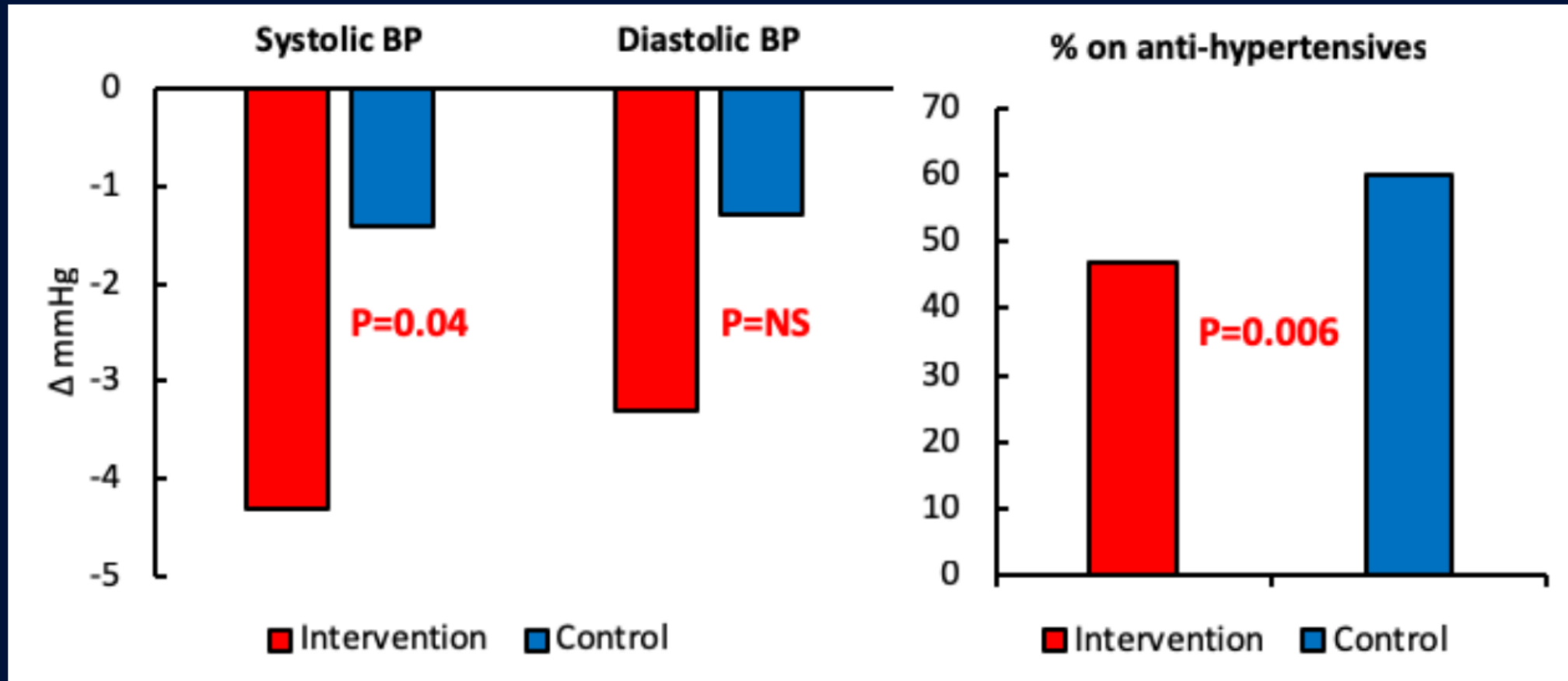
Secondary outcomes at 24 months (ITT)

- Blood pressure
- Serum lipids
- Adverse events
- Quality of life

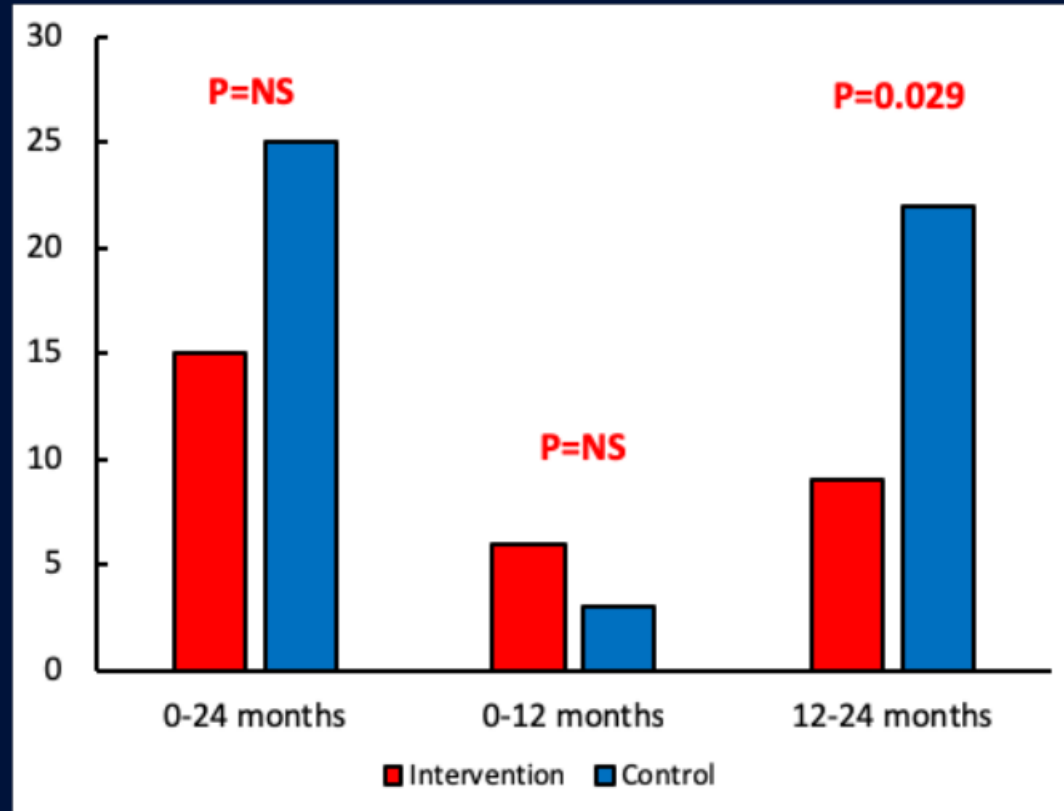
DiRECT: BP falls, with fewer drugs



DiRECT: BP falls, with fewer drugs



DiRECT: Fewer serious adverse events 12-24m



CV & cancer events (post-hoc analysis):

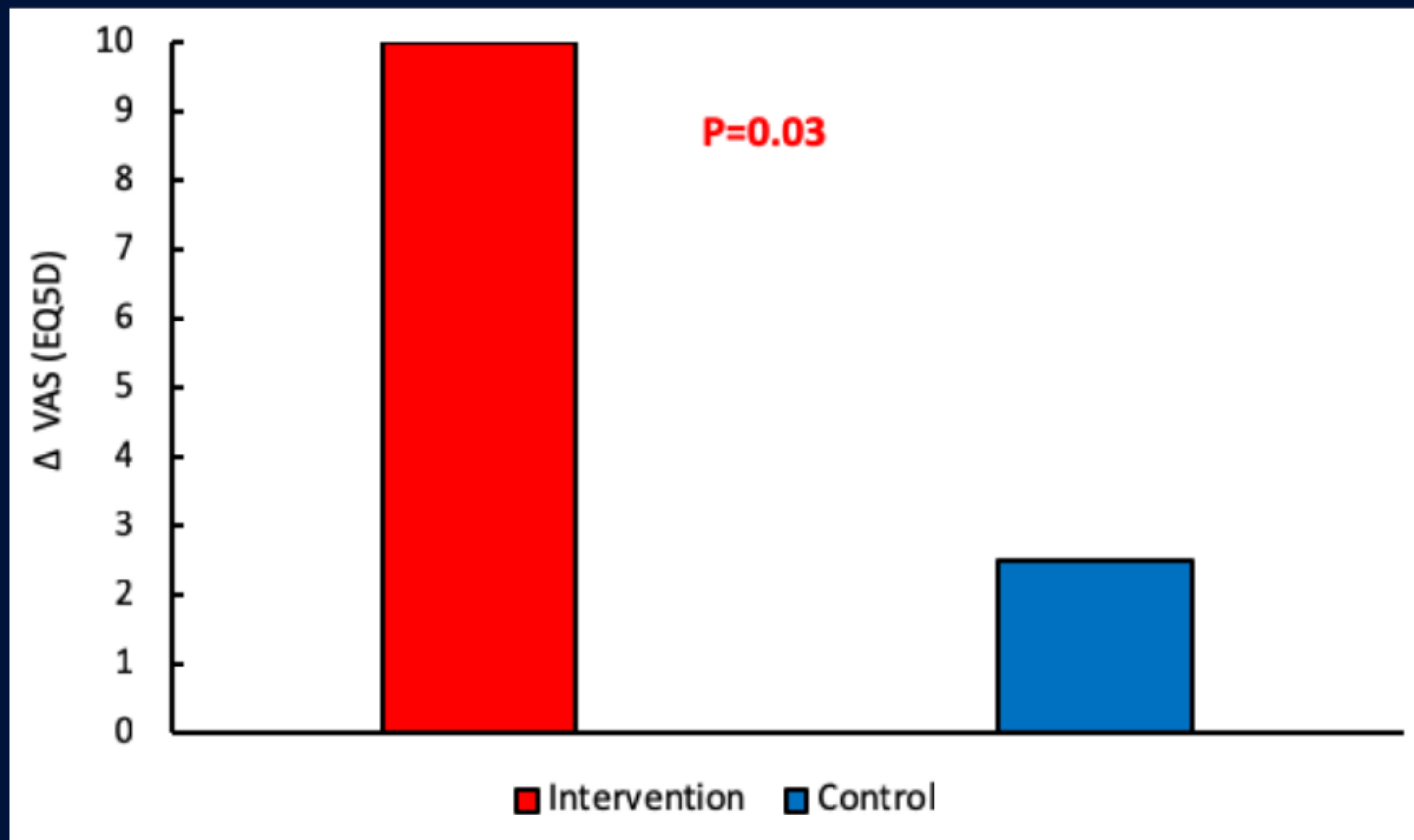
Intervention

- 1 Non-fatal MI, 1 coronary artery disease

Control

- 1 Sudden death, 2 CVA, 1 aortic aneurysm rupture, 1 toe amputation
- 5 cancers: 2 colon, 1 bladder, 1 renal, 1 prostate

DiRECT: Quality of life improves 😊



Scale: 0 – 100

Worst imaginable
to
Best imaginable

Summary:

Intervention group secondary outcomes

- Blood pressure: ↓ Systolic BP, ↓ medications
- Serum lipids: ↓ Triglycerides
- Quality of life ↑ 😊
- Adverse events ↓ SAEs in 12-24 months

LE UCCP IN CALABRIA con presenza del diabetologo

-Le UCCP In Calabria, con presenza di Diabetologo e dietista ,forniti dall'UOSD di diabetologia dell'ASP di Catanzaro:

CZ Nord, CZ Centro



popolazione assistita:

Circa 30.000 pazienti

Cartella informatica

Millewin

-Le UCCP In Calabria senza presenza di diabetologo al loro interno:

UCCP Cz Lido,

Popolazione assistita

Circa 15.000 pazienti

Cartella informatica

CGC

Soverato



circa 15.000 pazienti

Millewin

UCCP Decollatura

Circa 15.000 pazienti

CGC

Lamezia Terme



circa 18.000 pazienti

CGC

San Pietro a Maida;



circa 15.000 pazienti

CGC

Approved Drugs in Europe for Obesity

**Orlistat 60/120 mg
3 times daily**

**Naltrexone 32 mg/
Bupropion 360 mg PR**

Liraglutide 3 mg daily

**Metreleptin
Once daily**

**Semaglutide 2.4 mg
Weekly**

**Setmelanotide
1-3 mg once daily**

Metreleptin – only for leptin deficiency; Semaglutide – UK only; setmelanotide – only for POMC deficiency, LEPR, MC4R genetic causes. PR, prolonged release.

Orlistat [PI]. EMA. Published May 4, 2009. Updated May 7, 2020.

Naltrexone/bupropion [PI]. EMA. Published April 15, 2015. Updated May 19, 2022.

Liraglutide [PI]. EMA. Published April 16, 2015. Updated January 10, 2022.

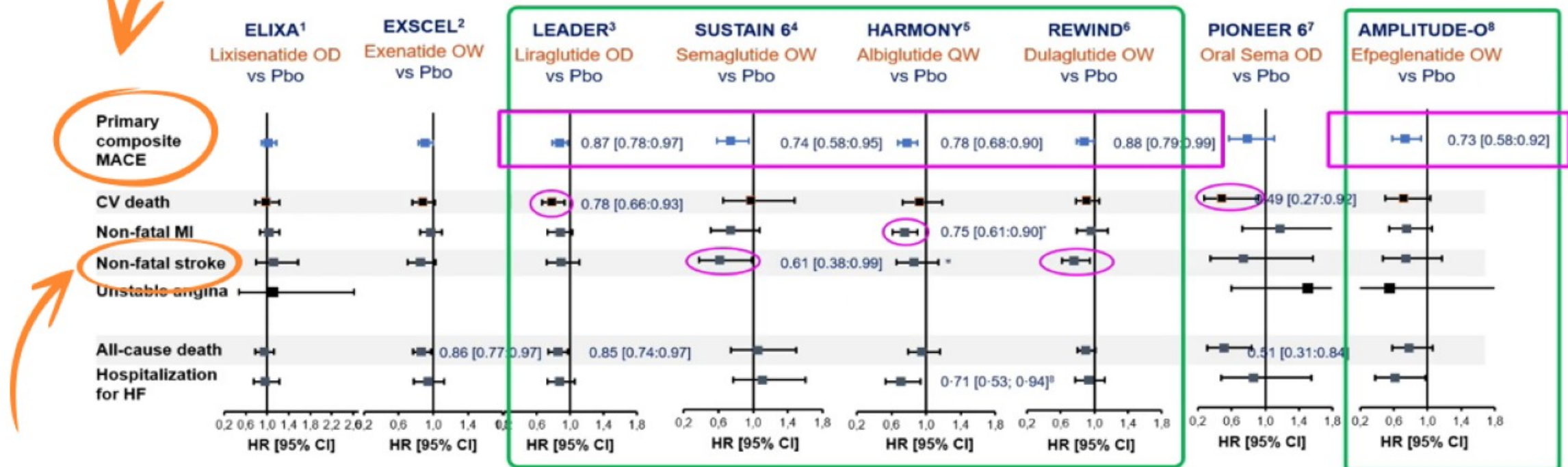
Metreleptin [PI]. EMA. Published August 6, 2018. Updated December 10, 2021.

Semaglutide [PI]. EMA. Published March 10, 2022.

Setmelanotide [PI]. EMA. Published July 22, 2021. Revised March 31, 2022.

CV Risk Reduction With Long-Acting GLP-1 RAs

Reduction in MACE = class effect for long-acting GLP-1 RAs



Reduction in stroke risk in the SUSTAIN 6 and REWIND trials

MACE, major adverse cardiovascular events; MI, myocardial infarction; Pbo, placebo.

Melbin L. Presented at: ESC Congress 2021: The Digital Experience; August 27-30, 2021.

GLP-1 RAs and Risk of Cancer

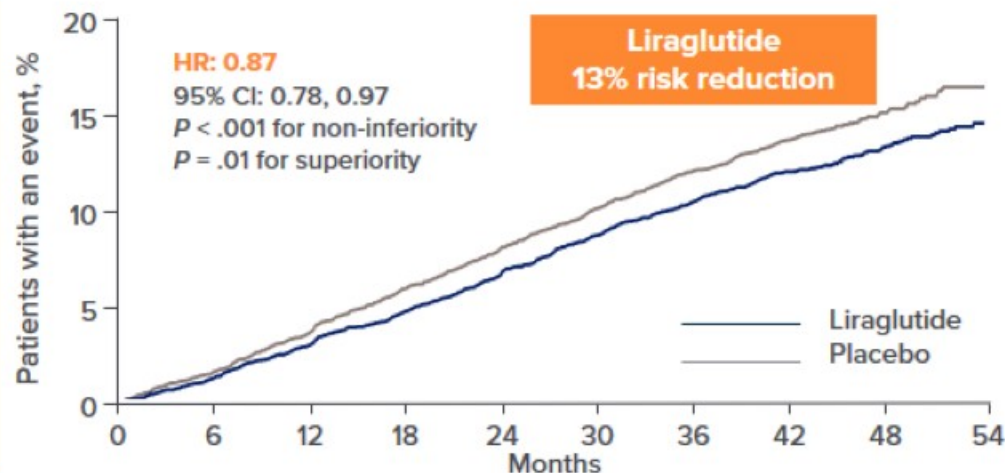
**No significant
increase of
pancreatic cancer
or medullary
thyroid cancer vs
placebo**

Is there a risk of cancer with
GLP-1 RAs?

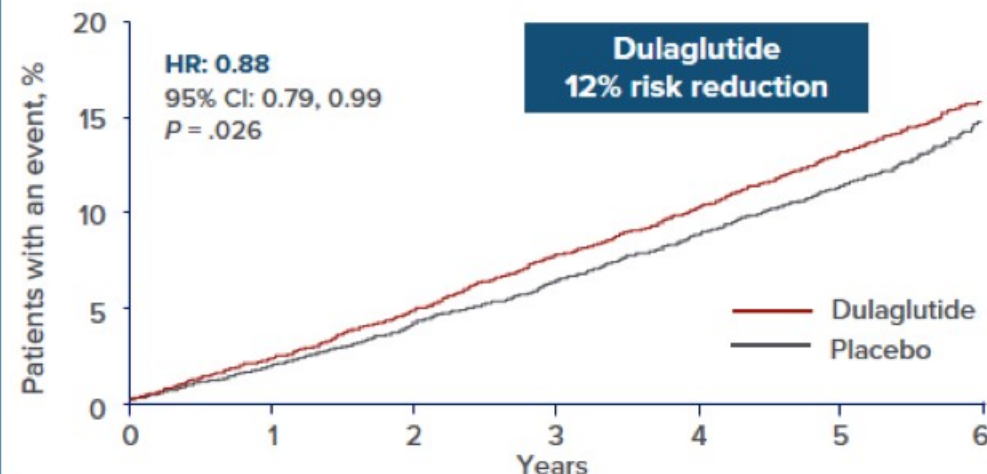
GLP-1 RAs With a Proven CV Benefit

Three-point MACE: nonfatal MI, nonfatal stroke, CV death

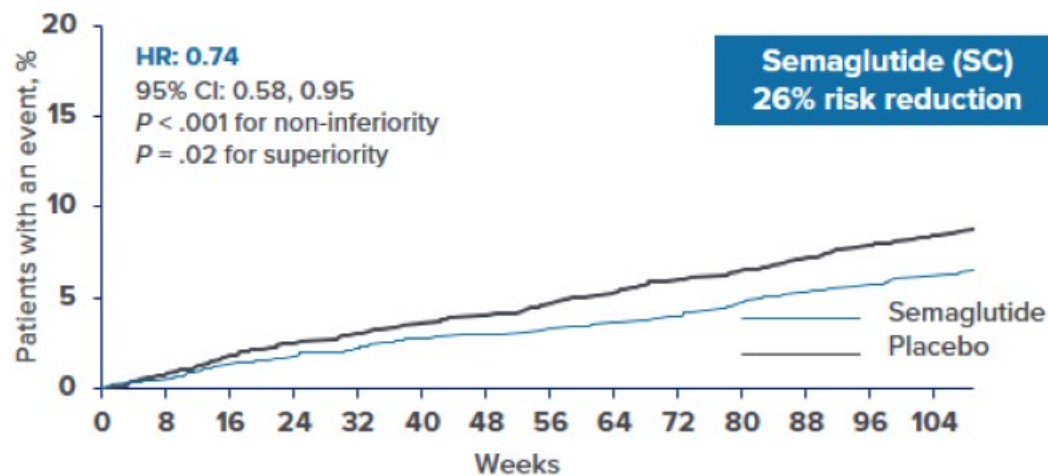
LEADER^[a]



REWIND^[b]



SUSTAIN 6^[c]

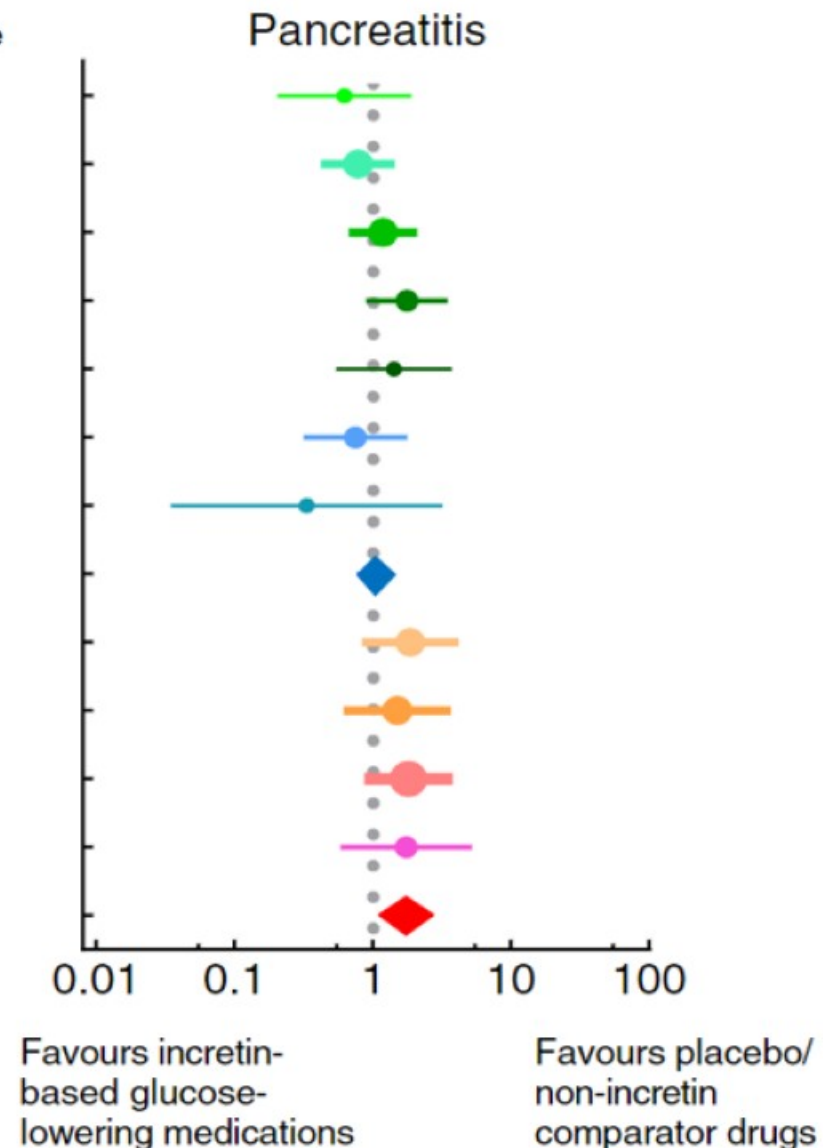


MI, myocardial infarction; SC, subcutaneous.

a. Marso SP, et al. N Engl J Med. 2016;375:311-322; b. Gerstein HC, et al. Lancet. 2019;S0140-6736:31149-31153; c. Marso SP, et al. N Engl J Med. 2016;375:1834-1844.

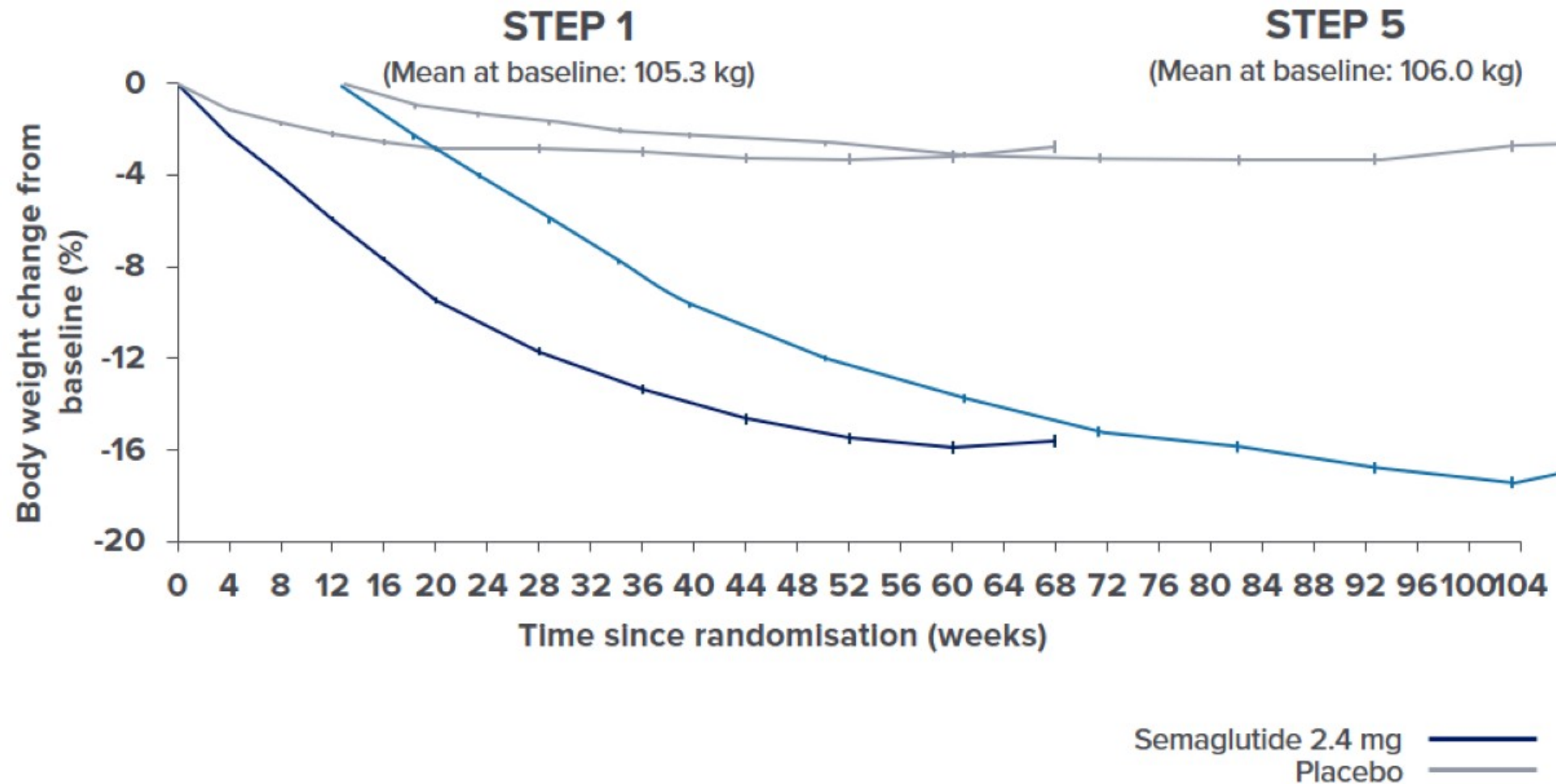
Rates of Pancreatitis – Incretin CVOTs

Study	Compound	Rate ratio (95 % CI)	Z-value	p-value
Pfeffer et al. 2015	Lixisenatide	0.63 (0.20-1.91)	- 0.82	0.41
Marso et al. 2016 a	Liraglutide	0.78 (0.42-1.45)	- 0.78	0.44
Holman et al. 2017	Exenatide q.w.	1.20 (0.67-2.10)	0.60	0.55
Gerstein et al. 2019	Dulaglutide	1.77 (0.90-3.49)	1.65	0.10
Hernandez et al. 2018	Albiglutide	1.43 (0.54-3.80)	0.72	0.50
Marso et al. 2016	Semaglutide s.c.	0.75 (0.32-1.78)	- 0.65	0.52
Husain et al. 2019	Semaglutide oral	0.33 (0.04-3.21)	- 0.95	0.34
All GLP-1 RAs		1.05 (0.78-1.41)	0.31	0.75
Scirica et al. 2013	Saxagliptin	1.88 (0.84-4.21)	1.53	0.13
White et al. 2013	Alogliptin	1.51 (0.62-3.80)	0.91	0.36
Green et al. 2015	Sitagliptin	1.82 (0.87-3.80)	1.60	0.11
Rosenstock et al. 2019	Linagliptin	1.75 (0.60-5.23)	1.01	0.31
All DPP-4 Is		1.75 (1.14-2.70)	2.56	0.01



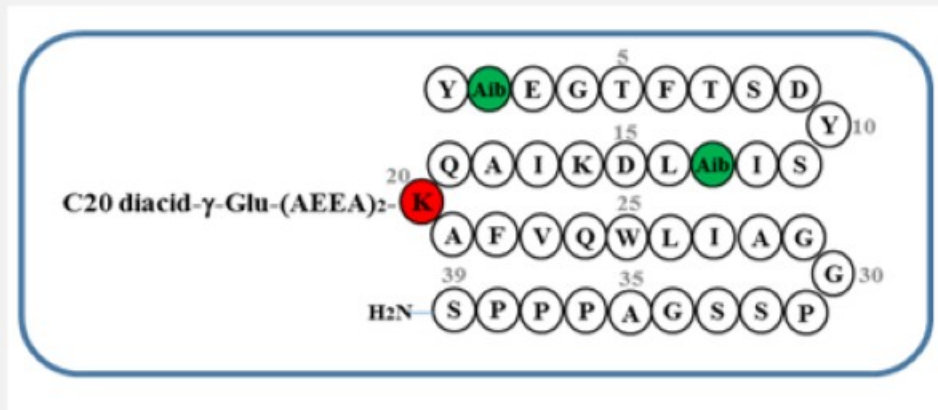
Change in Body Weight Over Time

STEP 1 vs STEP 5



Tirzepatide

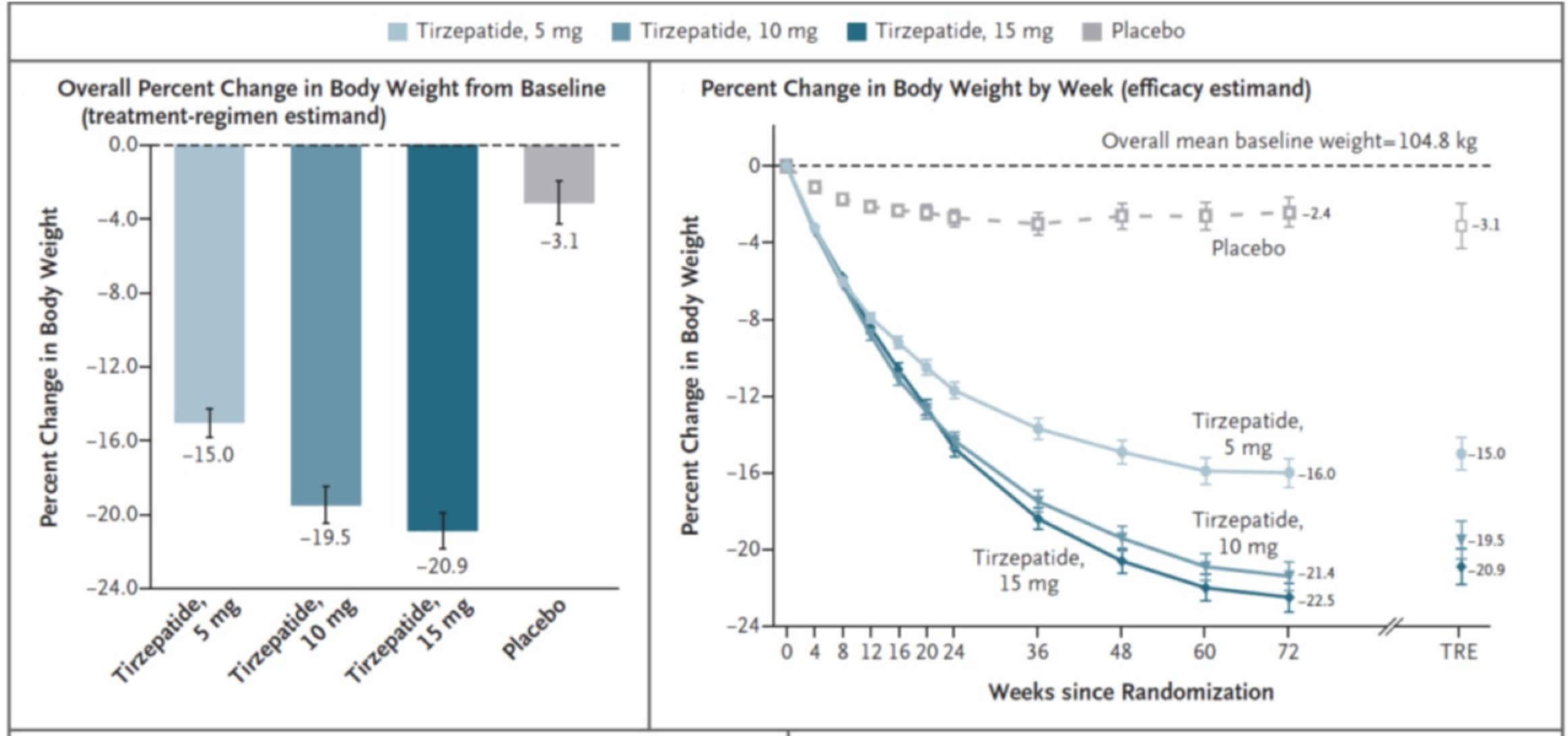
GLP-1/GIP Receptor Dual Agonist



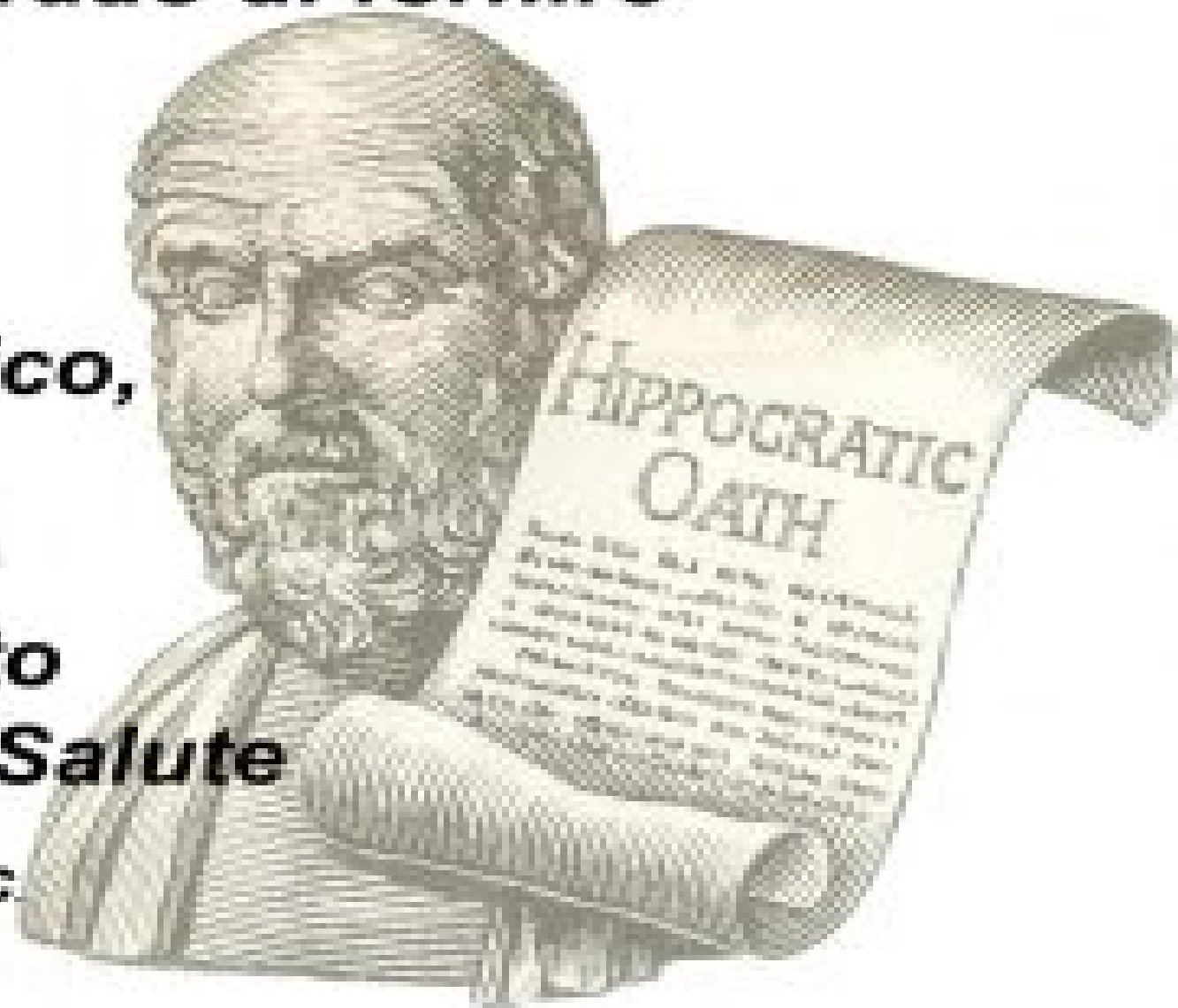
Multi-functional peptide based on the native **GIP and modified to bind to both **GIP** and **GLP-1** receptors**

Tirzepatide

SURMOUNT 1 Study in People With Obesity Without Diabetes



***Se fossimo in grado di fornire
a ciascuno
la giusta dose
di nutrimento
ed esercizio fisico,
ne' in eccesso
ne' in difetto,
avremmo trovato
la strada per la Salute***
Ippocrate, 460-377a.c.



Pathology of Obesity

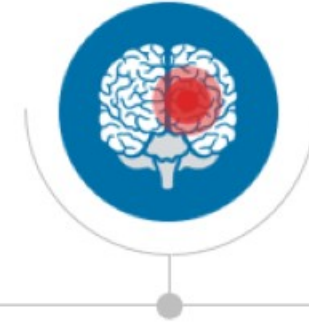


Adipose tissue
dysfunction^[a]

(Inability to store
excess calories,
inflammation,
adipokines, cellular
hypoxia)



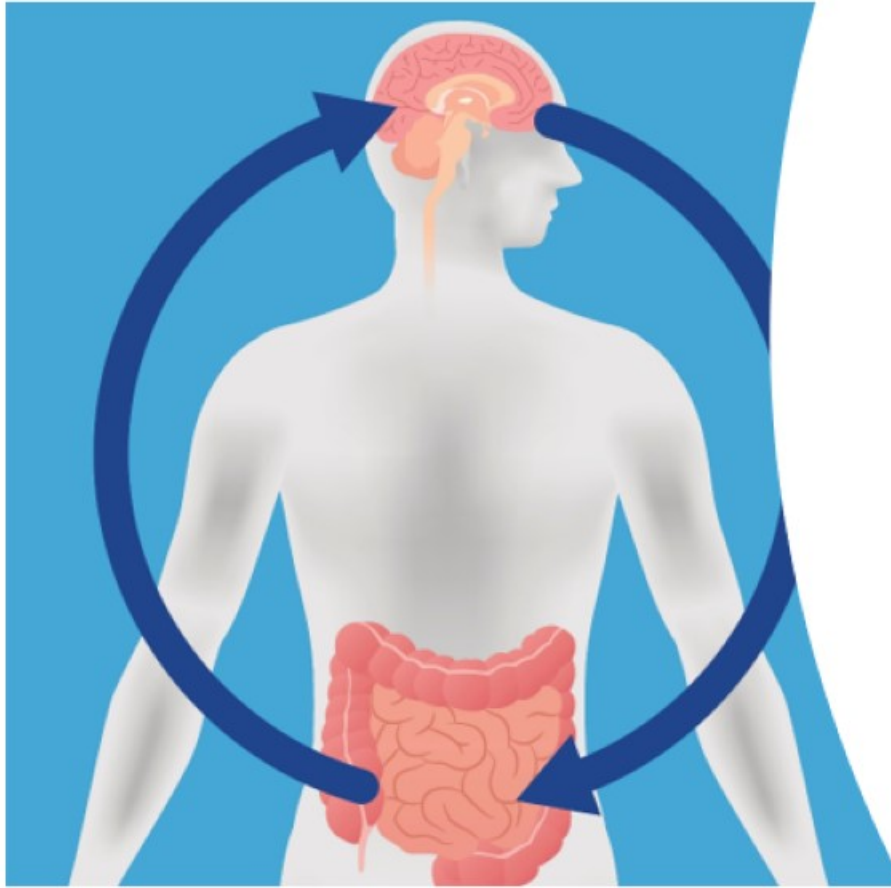
> 140 genetic regions
are now known to
influence obesity
traits^[b]



Neuropathology
associated with
obesity^[c]

The mesolimbic, the
hypothalamus and the
frontal lobe are
primarily evolved to
protect against weight
loss

Gut–Brain Connection

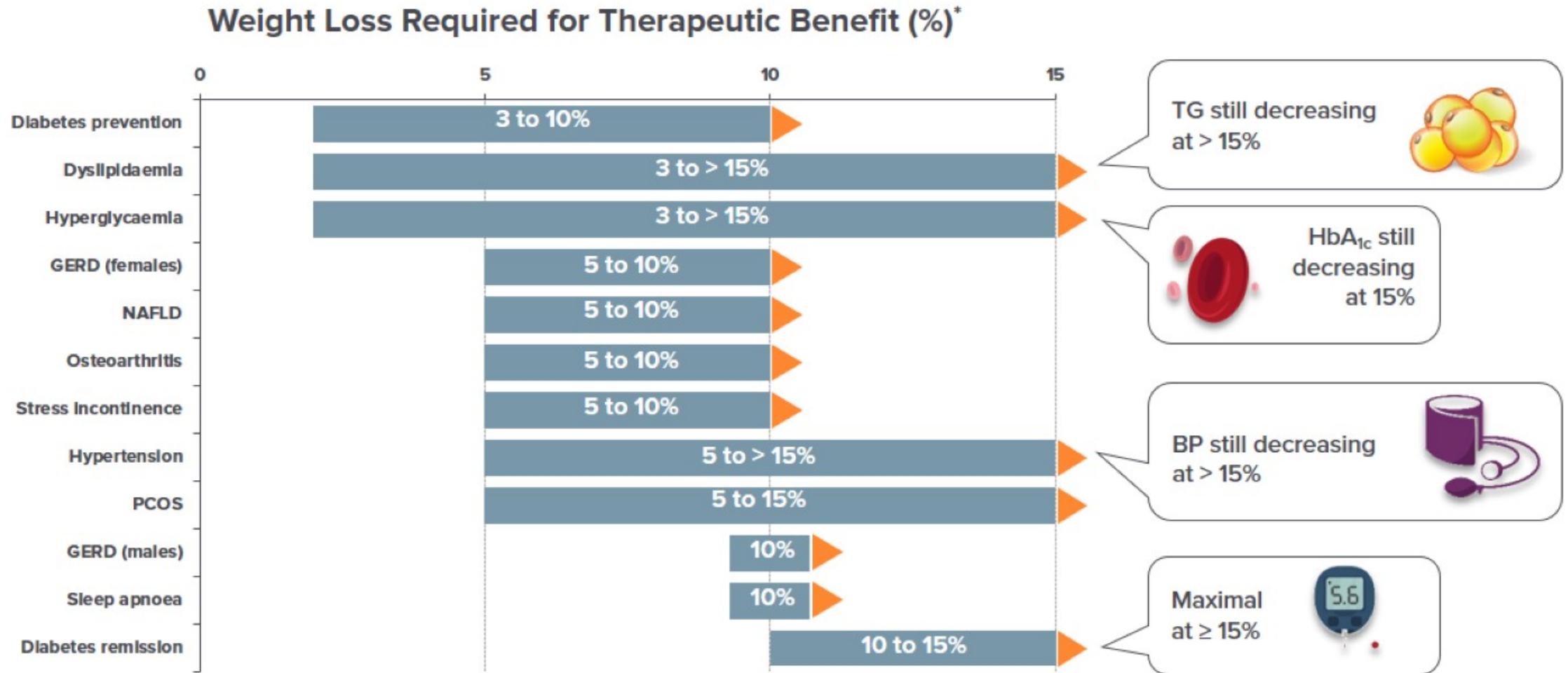


Hormones such as

- GLP-1
- PYY
- Leptin
- Ghrelin

Nutrient-regulated hormones that impact the brain and regulation of weight

How Much Weight Loss Is Needed to Improve Obesity-Related Complications?

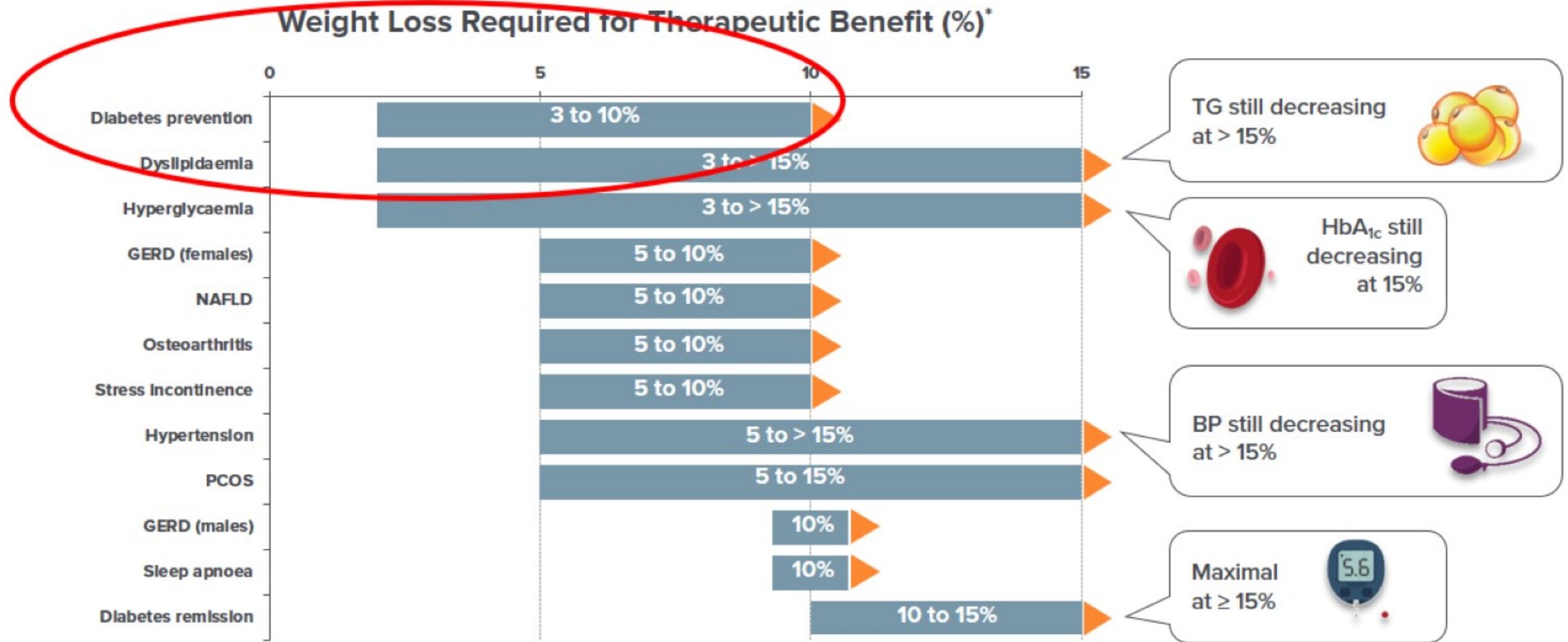


*Figure displays weight loss ranges examined in the studies (impact of >10% weight on NAFLD, and sleep apnea symptoms was not reported).

BP, blood pressure; GERD, gastroesophageal reflux disease; NAFLD, non-alcoholic fatty liver disease; PCOS, polycystic ovary syndrome; TG, triglycerides.

Garvey WT, et al. Endocr Pract. 2016;22(Suppl 3):1-203; Cefalu WT, et al. Diabetes Care. 2015;38:1567-1582; Lean ME, et al. Lancet. 2018;391:541-551; Hannah WN Jr, et al. Clin Liver Dis. 2016;20:339-350.

How Much Weight Loss Is Needed to Improve Obesity-Related Complications?

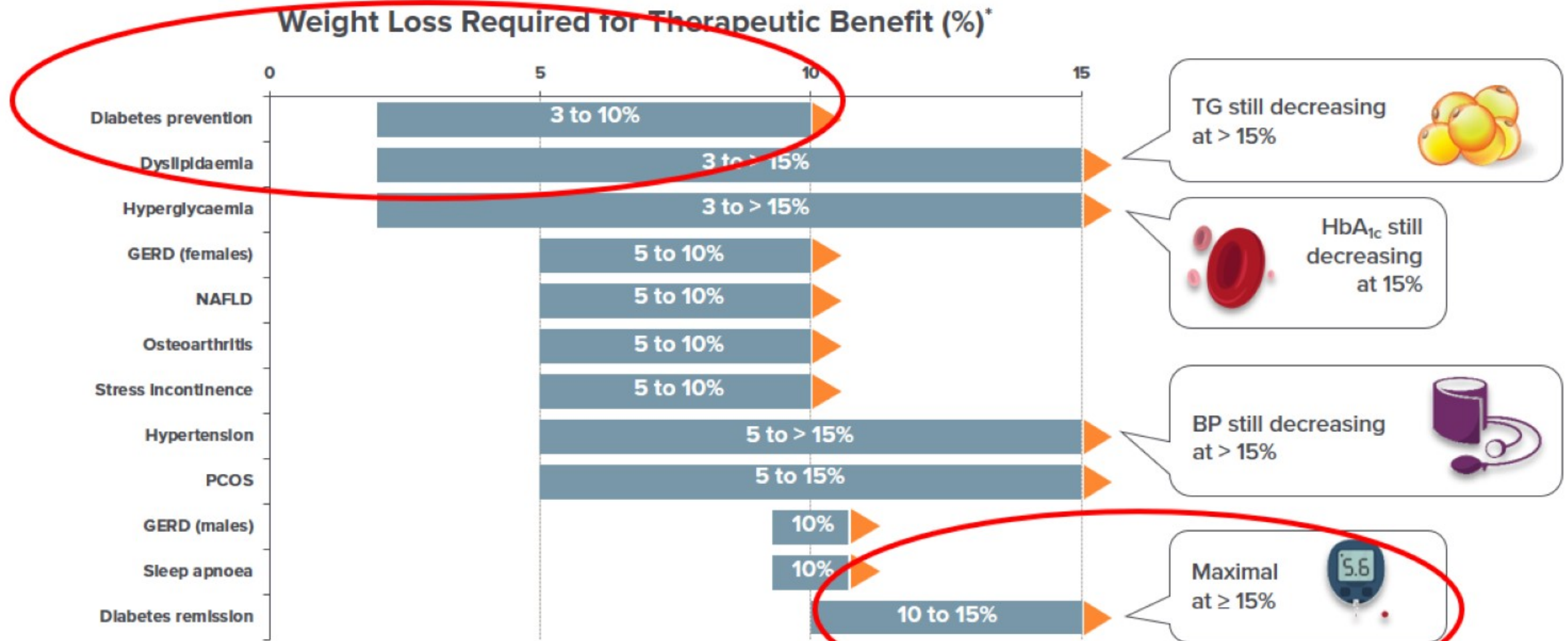


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How Much Weight Loss Is Needed to Improve Obesity-Related Complications?



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Understanding the Biology Leads to Effective Treatment



CBT, cognitive behavioural therapy.
Wharton S, et al. CMAJ. 2020;192:E875-E891.

Approved Drugs in Europe/UK

Orlistat 60/120 mg
three times a day^[a]

Naltrexone 32 mg/
Bupropion 360 mg
prolonged release^[b]

Liraglutide 3 mg daily^[c]

**Metreleptin
once daily^[d]**

**Semaglutide 2.4 mg
weekly^[e]**

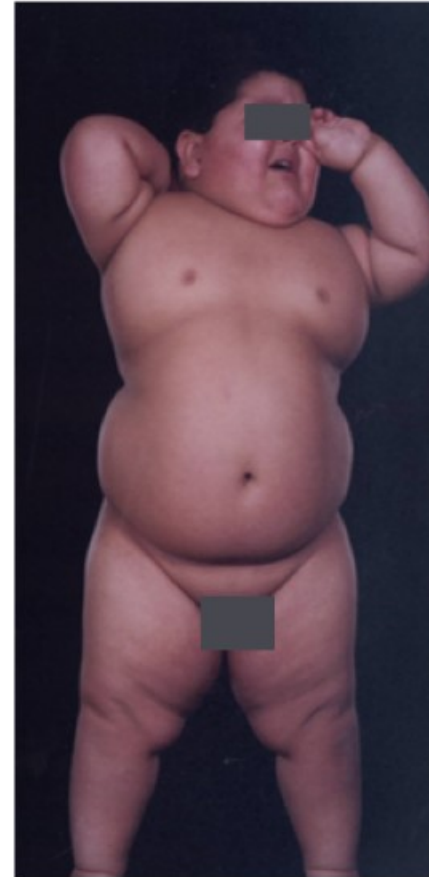
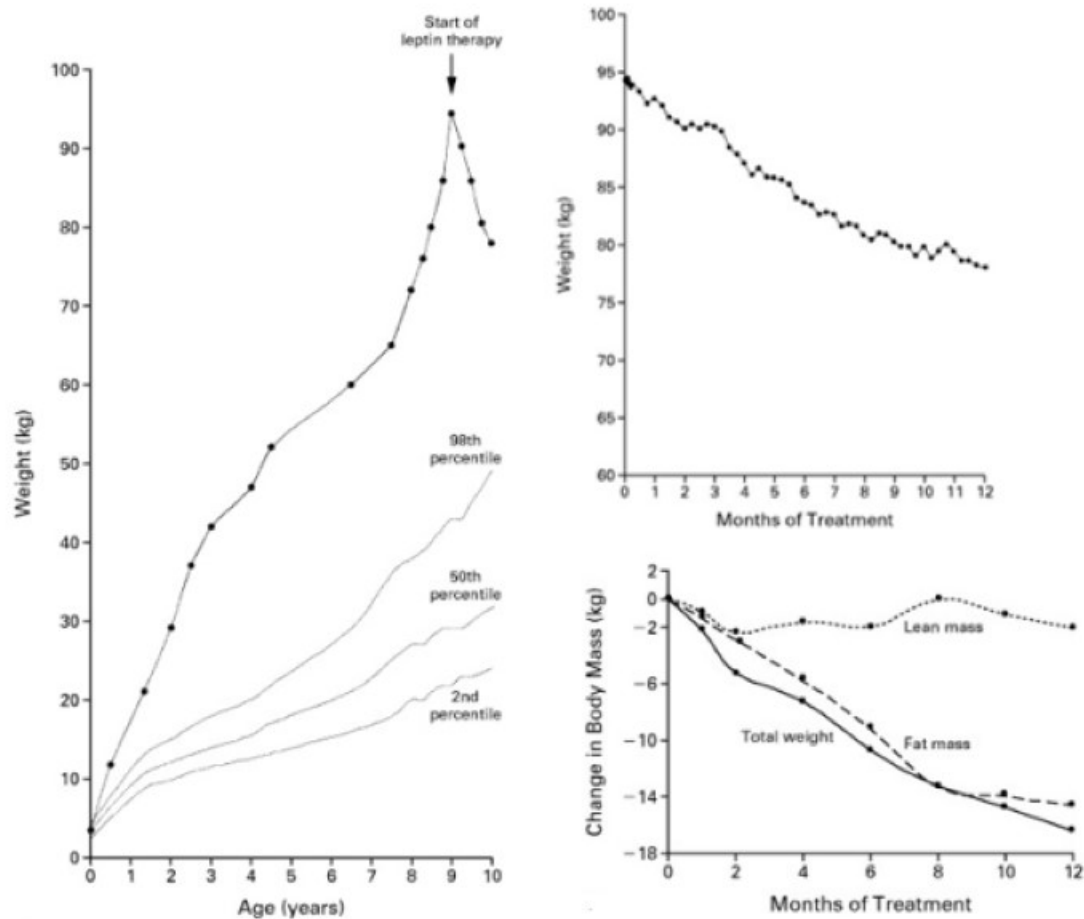
**Setmelanotide
1-3 mg once daily^[f]**

Metreleptin – only for leptin deficiency; Semaglutide – UK only; Setmelanotide – only for POMC deficiency, LEPR – MC4R genetic causes.

a. Orlistat [PI]. EMA. Published November 13, 2008. Updated May 7, 2020; b. Naltrexone/bupropion [PI]. EMA. Published April 15, 2014. Updated May 30, 2022; c. Liraglutide [PI]. EMA. Published April 16, 2015. Updated June 2, 2021; e. Semaglutide [PI]. EMA. Published March 10, 2022; f. Setmelanotide [PI]. EMA. Published July 22, 2021. Updated March 31, 2022.

Effect of Leptin Treatment in Congenital Leptin Deficiency

Effect on Weight and Body Mass



3 yr old
weighing 42 kg

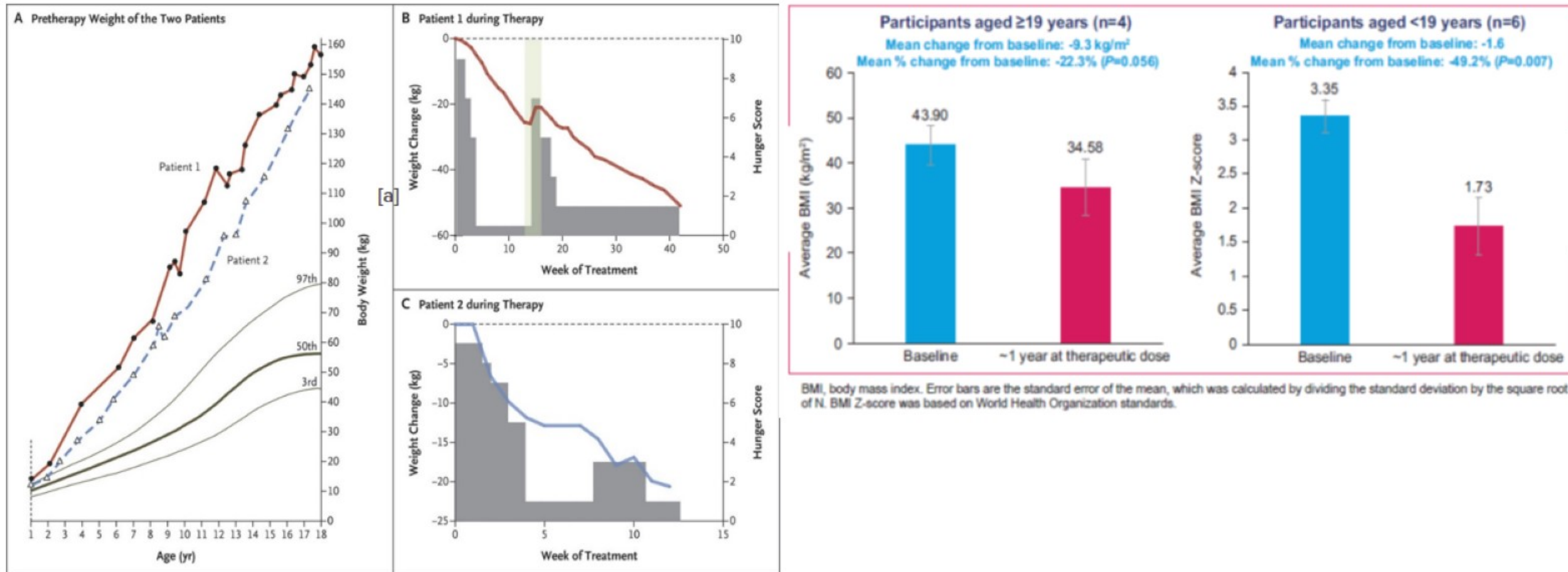


7 yr old
weighing 32 kg

Image courtesy of John Wilding, DM, FRCP.
Farooqi IS, et al. N Engl J Med. 1999;341:879-884.

Setmelanotide Effect on Weight

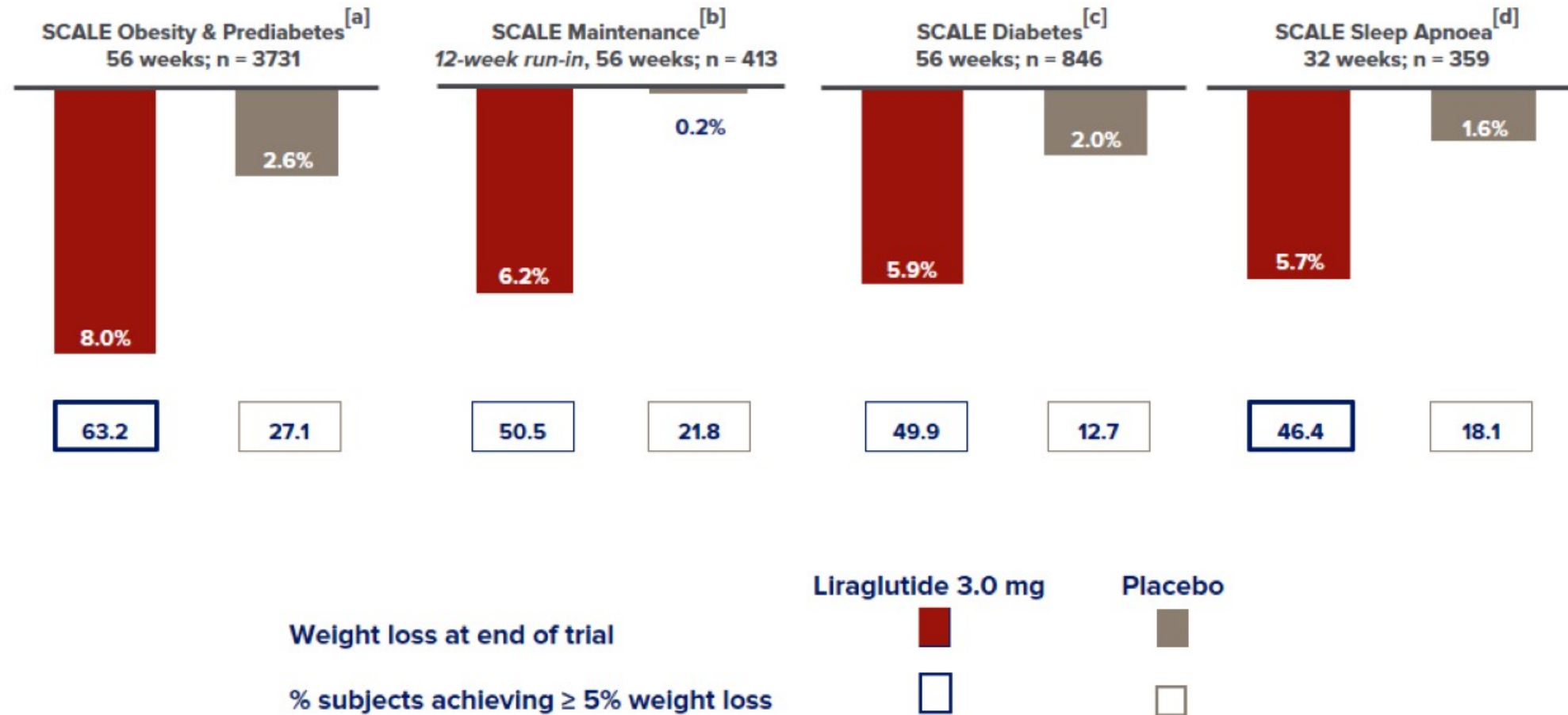
Setmelanotide in MC4R Deficiency: Pretherapy Weight and Changes in Weight and Hunger Scores during Therapy^[a] **Setmelanotide in POMC Deficiency: Change in BMI^[b,c]**



BMI, body mass index; POMC, proopiomelanocortin.

a. Kühnen P, et al. *N Engl J Med* 2016;375:240-246; b. Clément K, et al. *Lancet Diabetes Endocrinol.* 2020;8:960-970; Clément K, et al. Presented at: ObesityWeek® 2019; November 3–7, 2019; Las Vegas, NV.

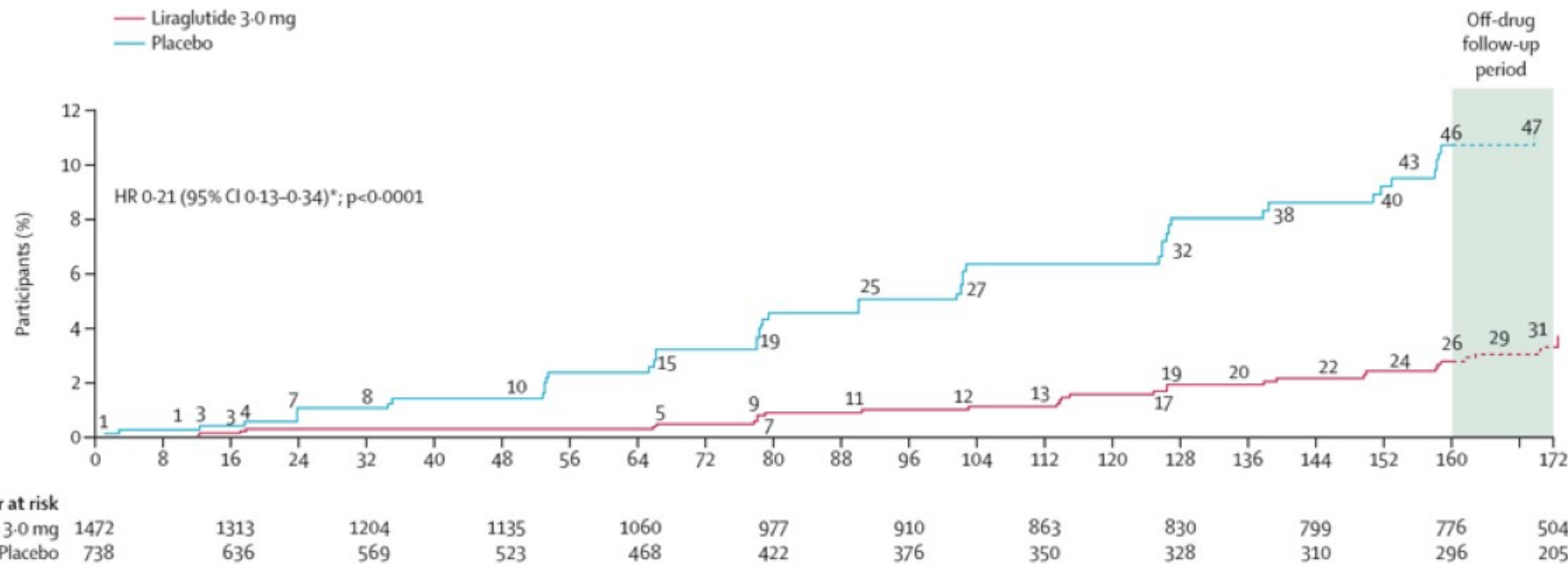
Liraglutide – All SCALE Trials: Effects on Weight Loss



a. Pi-Sunyer X, et al. N Engl J Med. 2015;373;11-22; b. Wadden TA, et al. Int J Obes (Lond) 2013;37:1443-1451; c. Davies MJ, et al. JAMA 2015;314:687-699; d. Blackman A, et al. Diabetologia. 2014;57:Abstract 184—OR.

SCALE: Obesity and Prediabetes 3-Year Data

Individuals Diagnosed With T2D Over Time



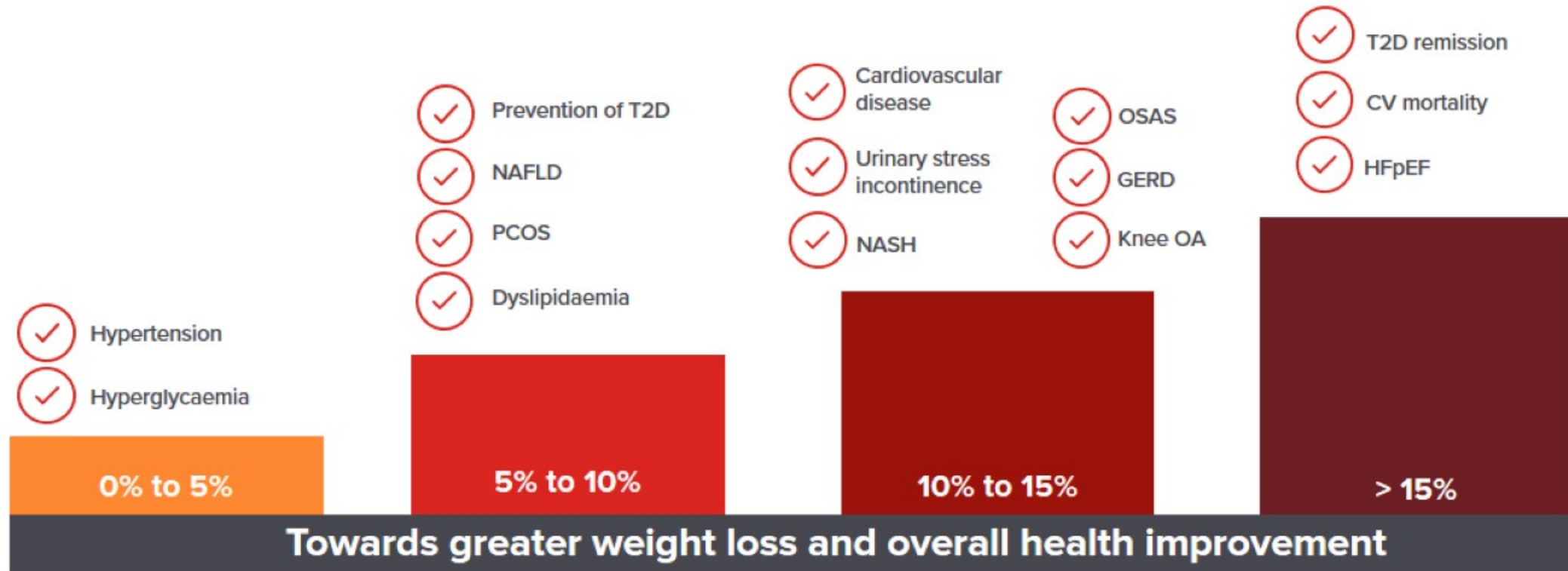
Study Findings

- Treatment with liraglutide 3.0 mg for 3 years was associated with a reduced risk of T2D, weight loss and improvements in glycemic control in individuals with prediabetes
- The treatment was well tolerated and without new safety signals

T2D, type 2 diabetes.
le Roux CW, et al. Lancet. 2017;389:1399-1409.

Importance of Weight Loss and Benefit

Overall Health Improvements



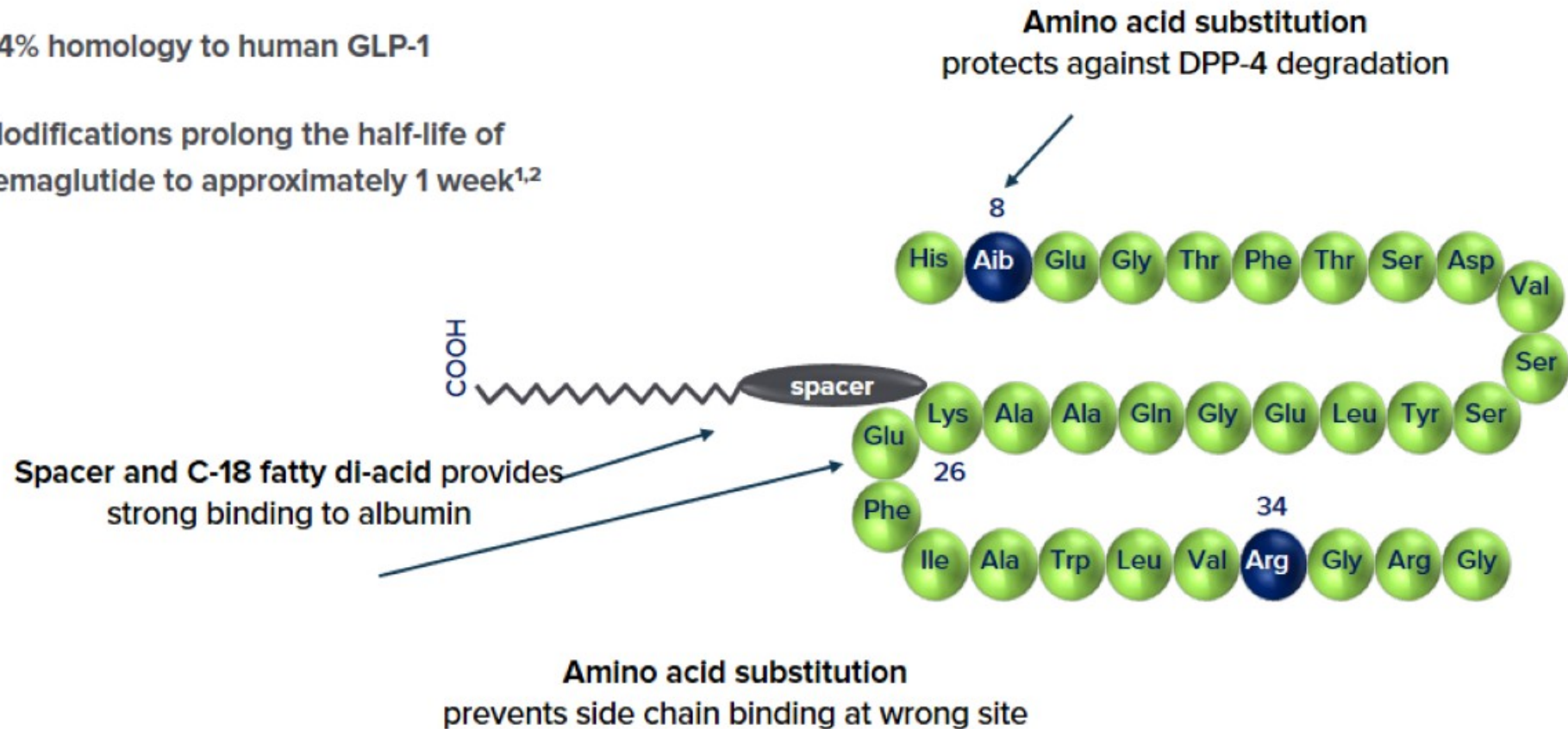
CV, cardiovascular; GERD, gastro-oesophageal reflux disease; HFpEF, heart failure with preserved ejection fraction; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OA: osteoarthritis; OSAS, obstructive sleep apnoea syndrome.

Garvey WT, et al. Endocr Pract. 2016;22(Suppl. 3):1-203; Look AHEAD Research Group. Lancet Diabetes Endocrinol. 2016;4:913-921; Lean ME, et al. Lancet. 2018;391:541-551; Benraoune F, et al. Curr Opin Cardiol. 2011;26:555-561; Sundström J, et al. Circulation. 2017;135:1577-85.

Semaglutide

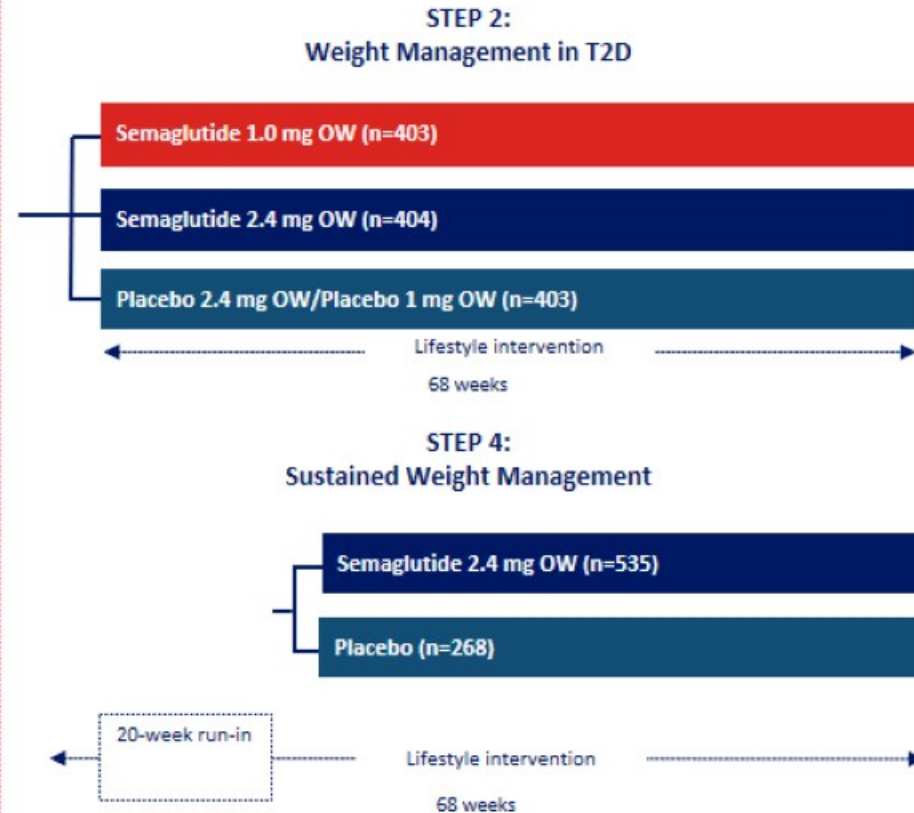
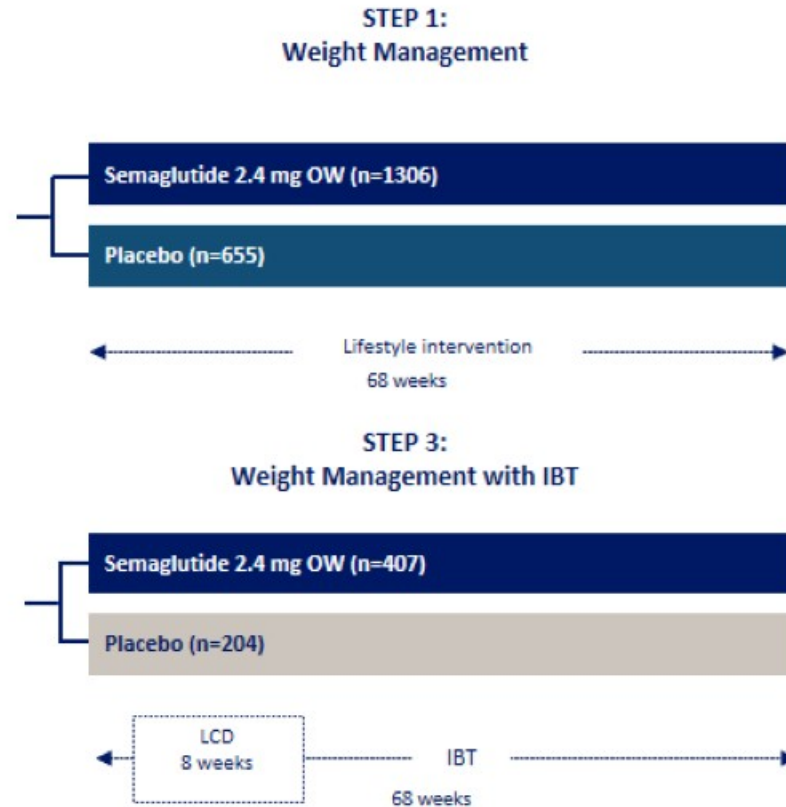
94% homology to human GLP-1

Modifications prolong the half-life of semaglutide to approximately 1 week^{1,2}



DDP-4, dipeptidyl peptidase-4; IBT, Intensive behavioral therapy; LCD, low-calorie diet; OW, once weekly. Kapitza C, et al. J Clin Pharmacol. 2015;55:497-504; Kushner RF, et al. Obesity (Silver Spring). 2020;28:1050-1061; Wilding JPH, et al. N Engl J Med. 2021;384:989.

STEP Program

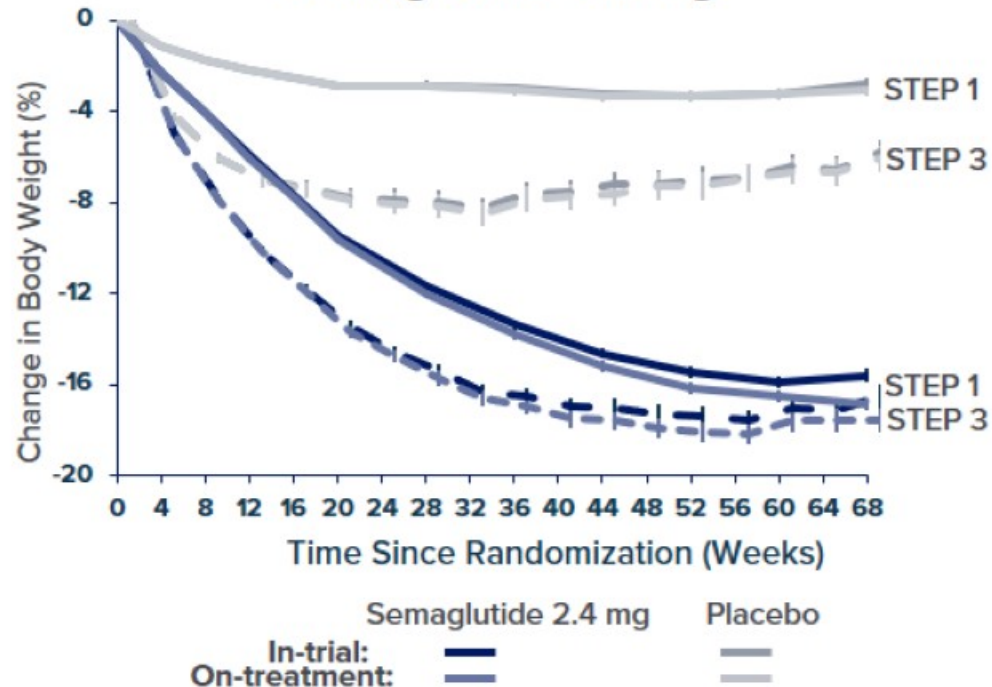


DDP-4, dipeptidyl peptidase-4; IBT, Intensive behavioral therapy;
LCD, low-calorie diet; OW, once weekly.

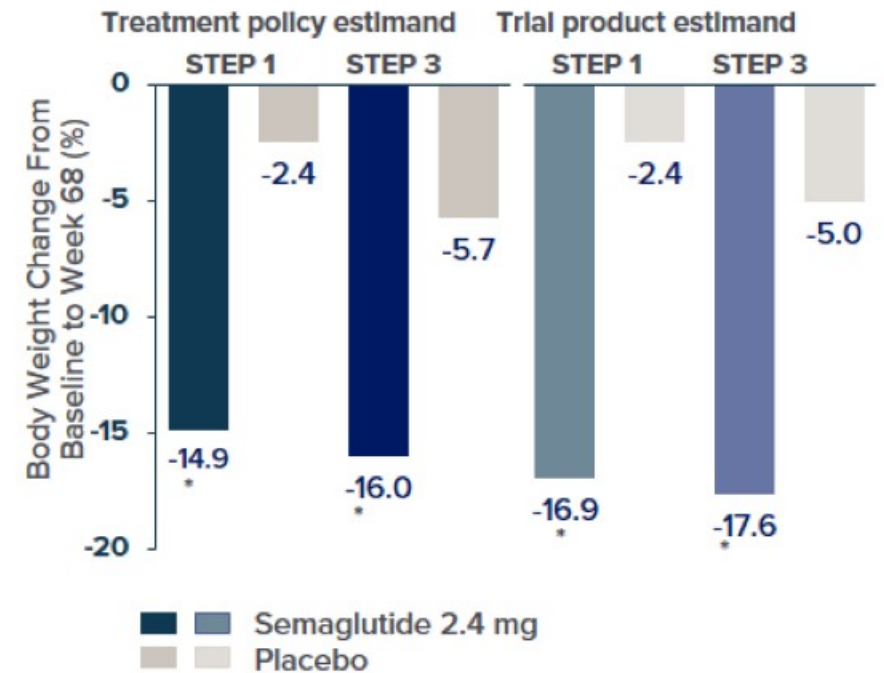
Kapitza C, et al. J Clin Pharmacol. 2015;55:497-504; Kushner RF, et al. Obesity (Silver Spring). 2020;28:1050-1061; Wilding JPH, et al. N Engl J Med. 2021;384:989.

STEP 1 and 3: Body Weight Change

LCD and IBT Appear to Accelerate Initial Weight Loss Achieved with Semaglutide 2.4 mg[†]



Estimated Change from Baseline to Week 68

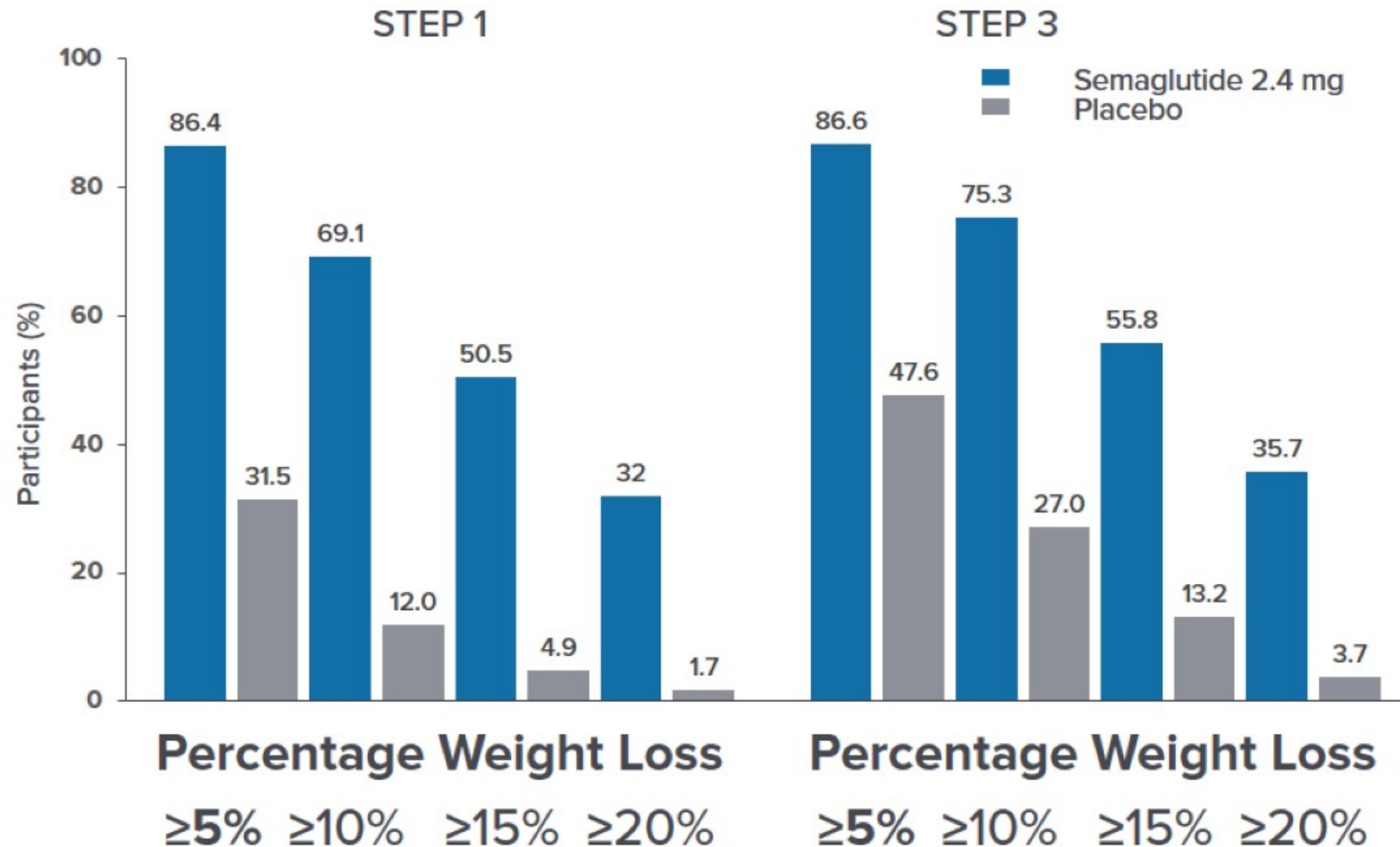


*Statistically significant vs placebo; [†]Observed on-treatment data.

IBT, intensive behavior therapy; LCD, low-calorie diet.

a. Wadden TA, et al. JAMA. 2021;325:1403-1413; b. Wilding JPH, et al. N Engl J Med. 2021;384:989.

STEP 1 and 3: Categorical Weight Loss at Week 68

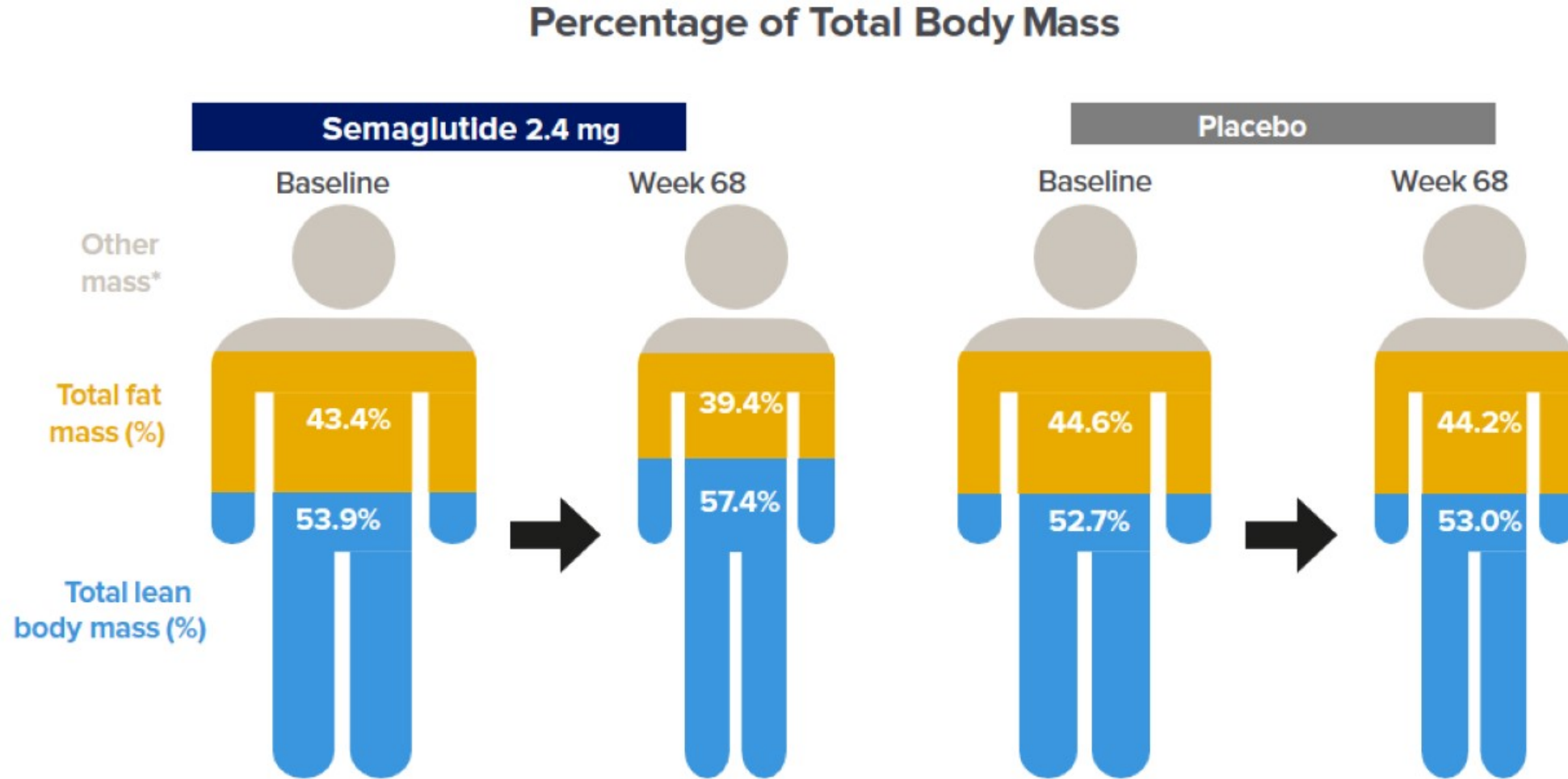


Study Findings

- Data suggest that semaglutide with monthly brief lifestyle counselling alone is sufficient to produce a mean weight loss of 15%
- Addition of LCD and IBT appears to accelerate initial weight loss but does not provide additive weight loss at week 68
- Further research is needed on potential benefits of sequencing LCD and semaglutide 2.4 mg to increase long-term weight loss

a. Wilding JPH, et al. N Engl J Med 2021;384:989; b. Wadden TA, et al. JAMA 2021;e211831.

STEP 1: Body Composition at Baseline and Week 68



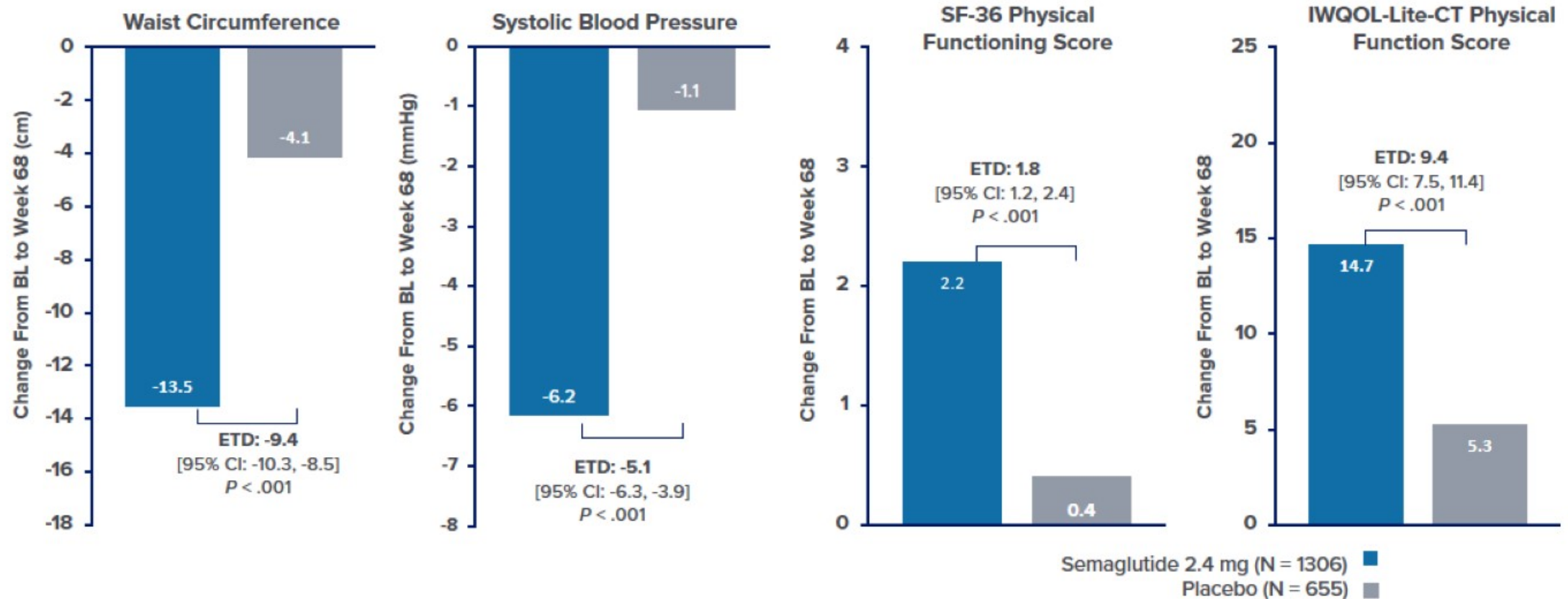
Courtesy of Dr John Wilding, DM, FRCP.
Observed data.

*Includes bone mass.

Wilding JPH, et al. Presented at: ENDO 2021; March 20-23, 2021; Virtual.

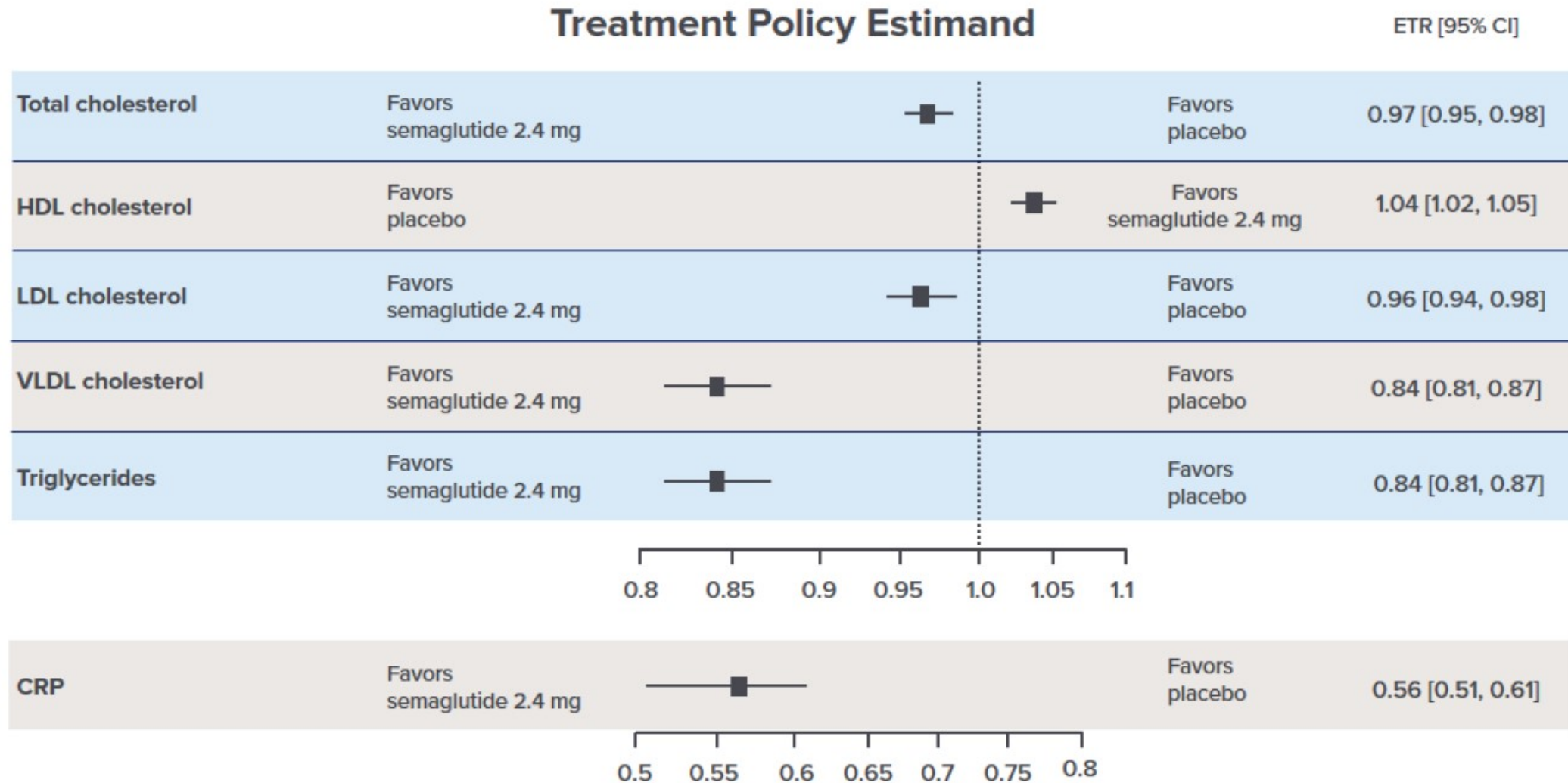
STEP 1: Selected Confirmatory Secondary Endpoints

Treatment Policy Estimand



BL, baseline; ETD, estimated treatment difference; IWQOL-Lite-CT, Impact of Weight on Quality of Life-Lite Clinical Trials Version; SF-36, Short Form36v2® Health Survey, Acute Version
Wilding JPH, et al. N Engl J Med. 2021;384:989-1002

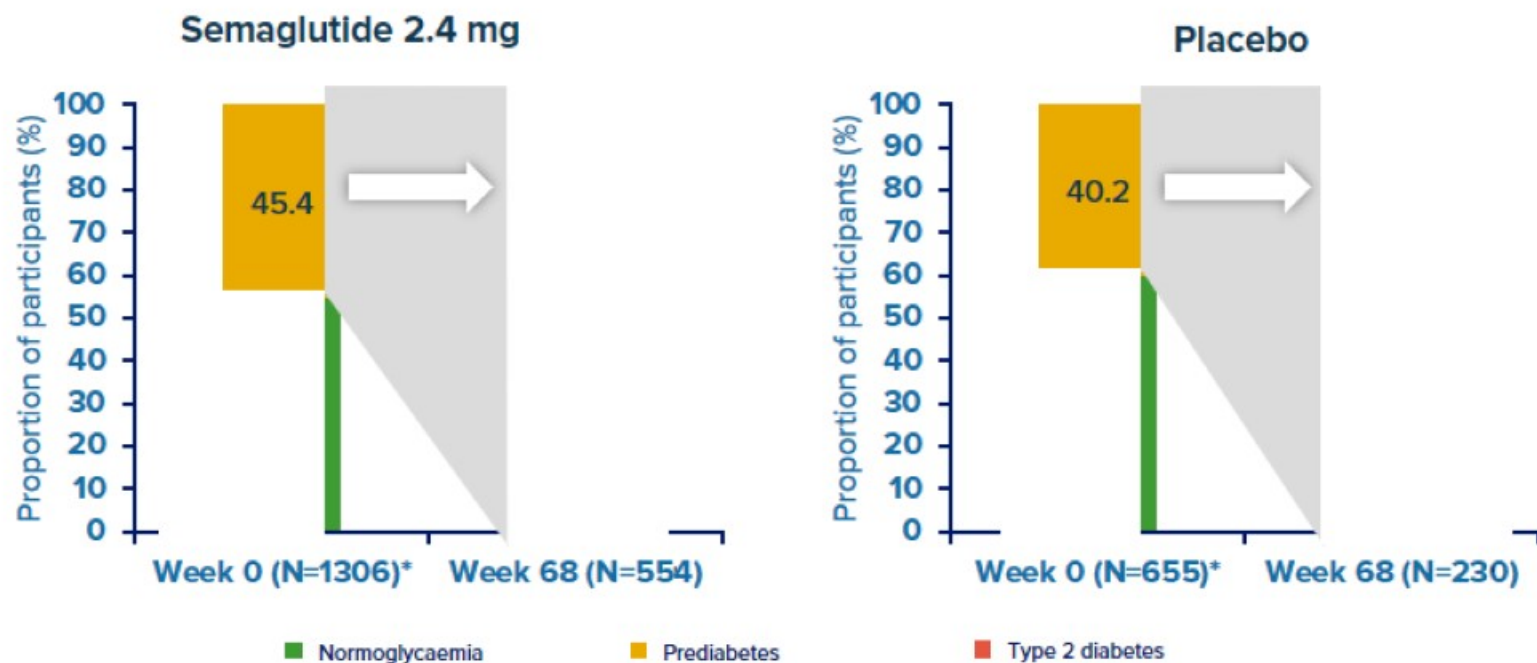
STEP 1: Cardiometabolic Parameters



CRP, C-reactive protein; ETR, estimated treatment ratio; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.
Wilding JPH, et al. N Engl J Med. 2021;384:989-1002.

STEP 1: Regression to Normoglycaemia

Participants with prediabetes at baseline



*Number of participants in overall population; †number of participants with prediabetes at baseline and evaluable data at Week 68

Perreault L et al. Presented at the ADA virtual meeting, June 25–29, 2021.

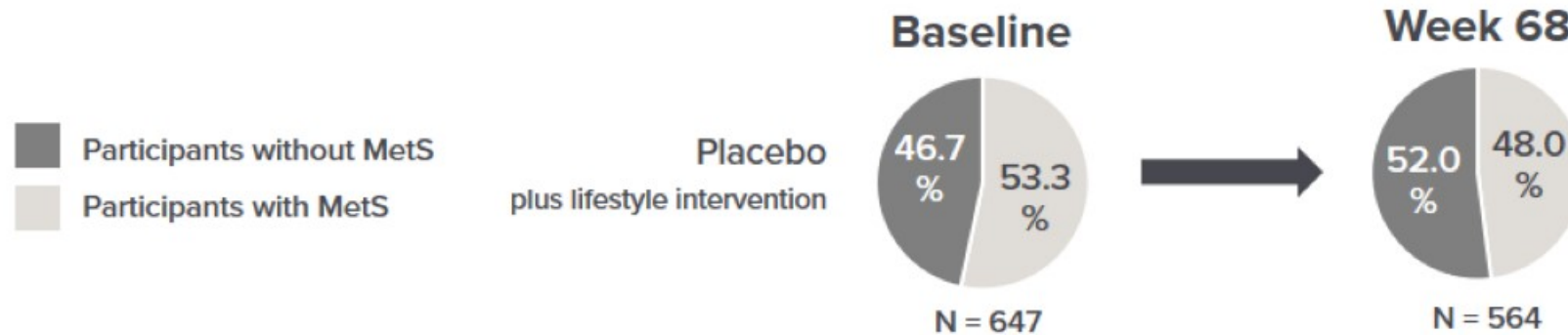
STEP 1: Prevalence of Metabolic Syndrome

Proportion of Participants with MetS at Baseline and at Week 68



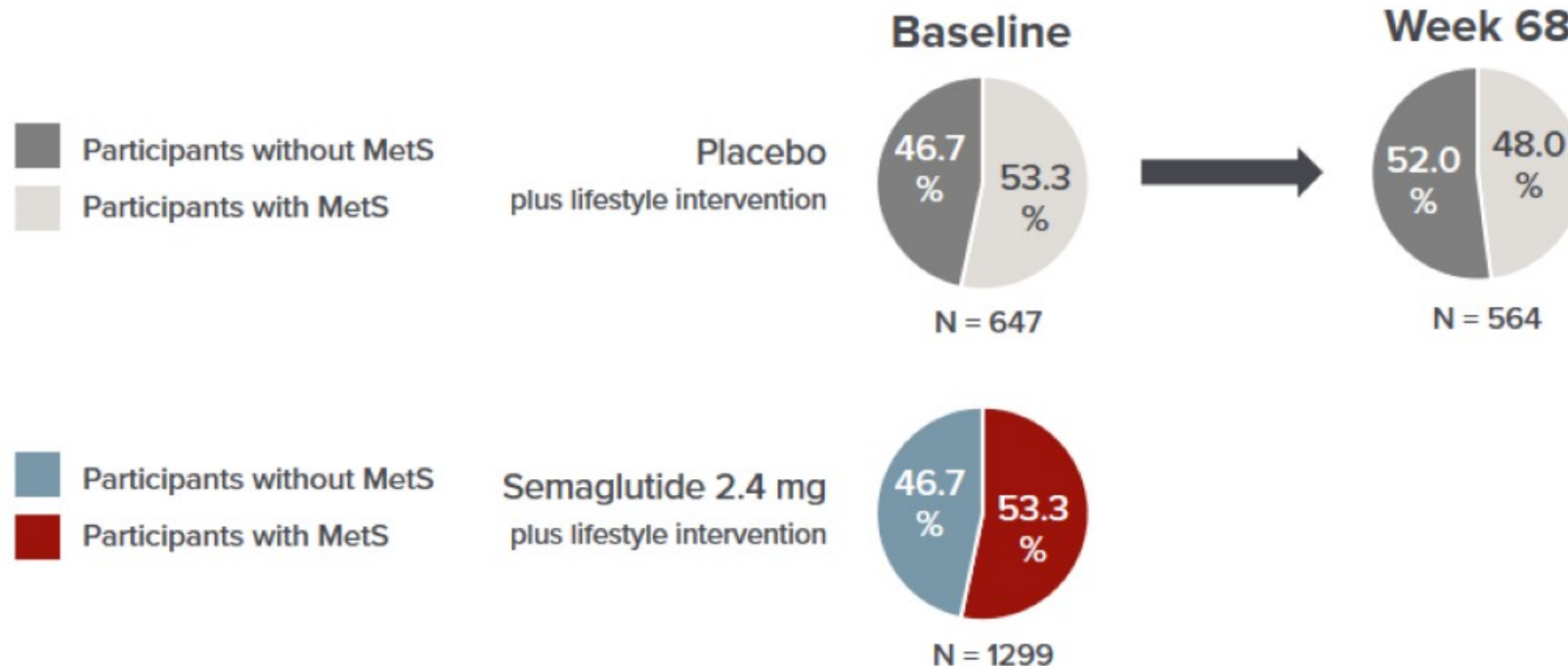
STEP 1: Prevalence of Metabolic Syndrome

Proportion of Participants with MetS at Baseline and at Week 68



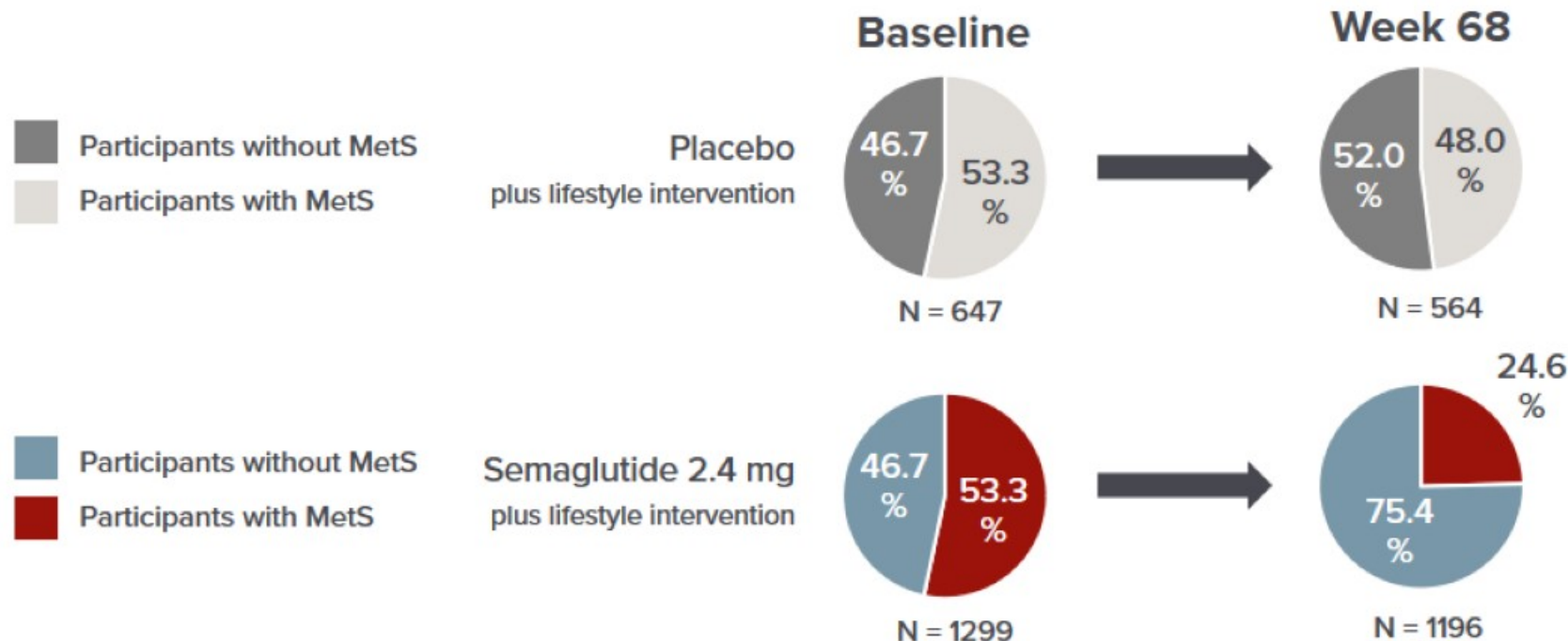
STEP 1: Prevalence of Metabolic Syndrome

Proportion of Participants with MetS at Baseline and at Week 68

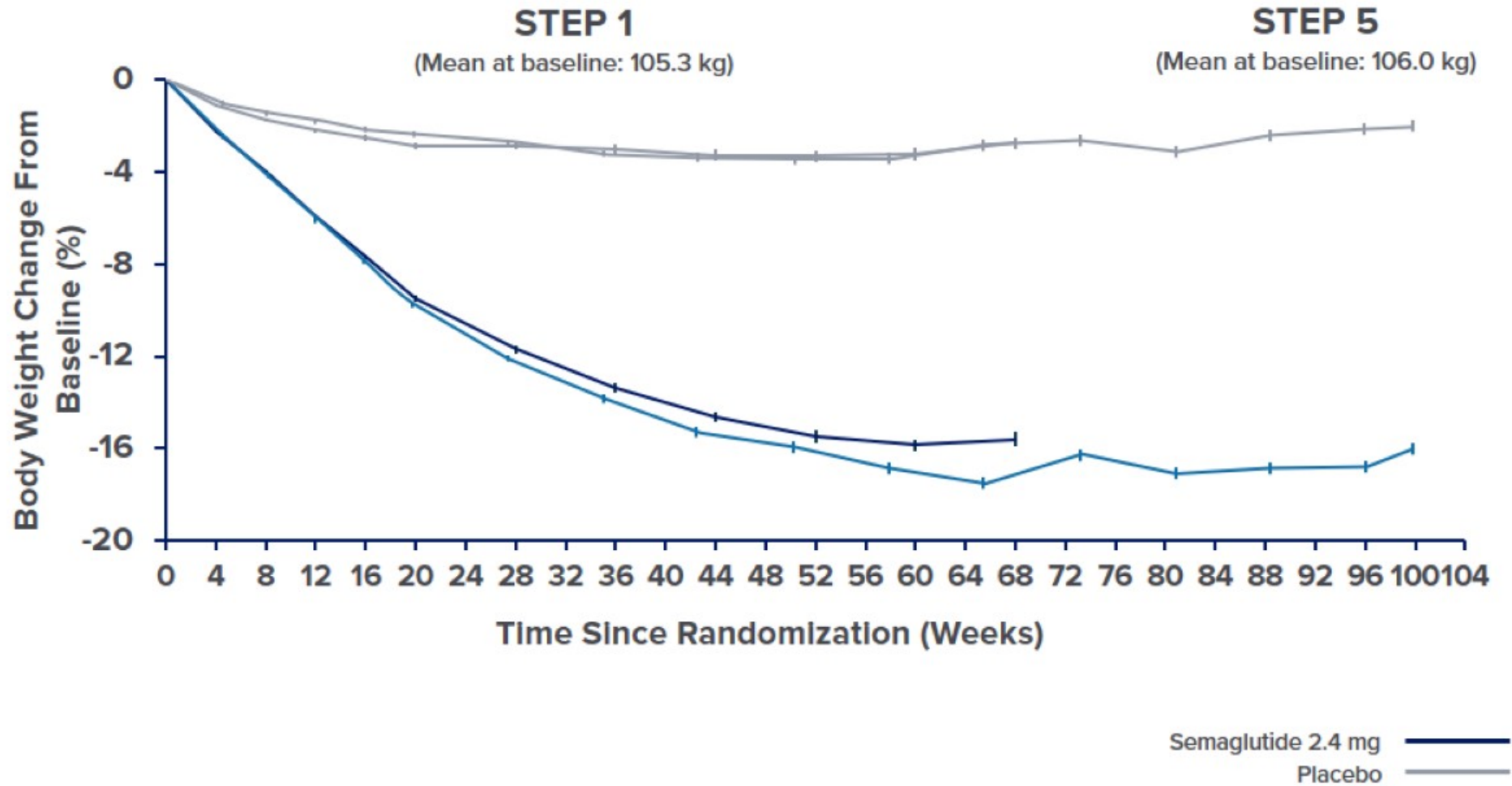


STEP 1: Prevalence of Metabolic Syndrome

Proportion of Participants with MetS at Baseline and at Week 68

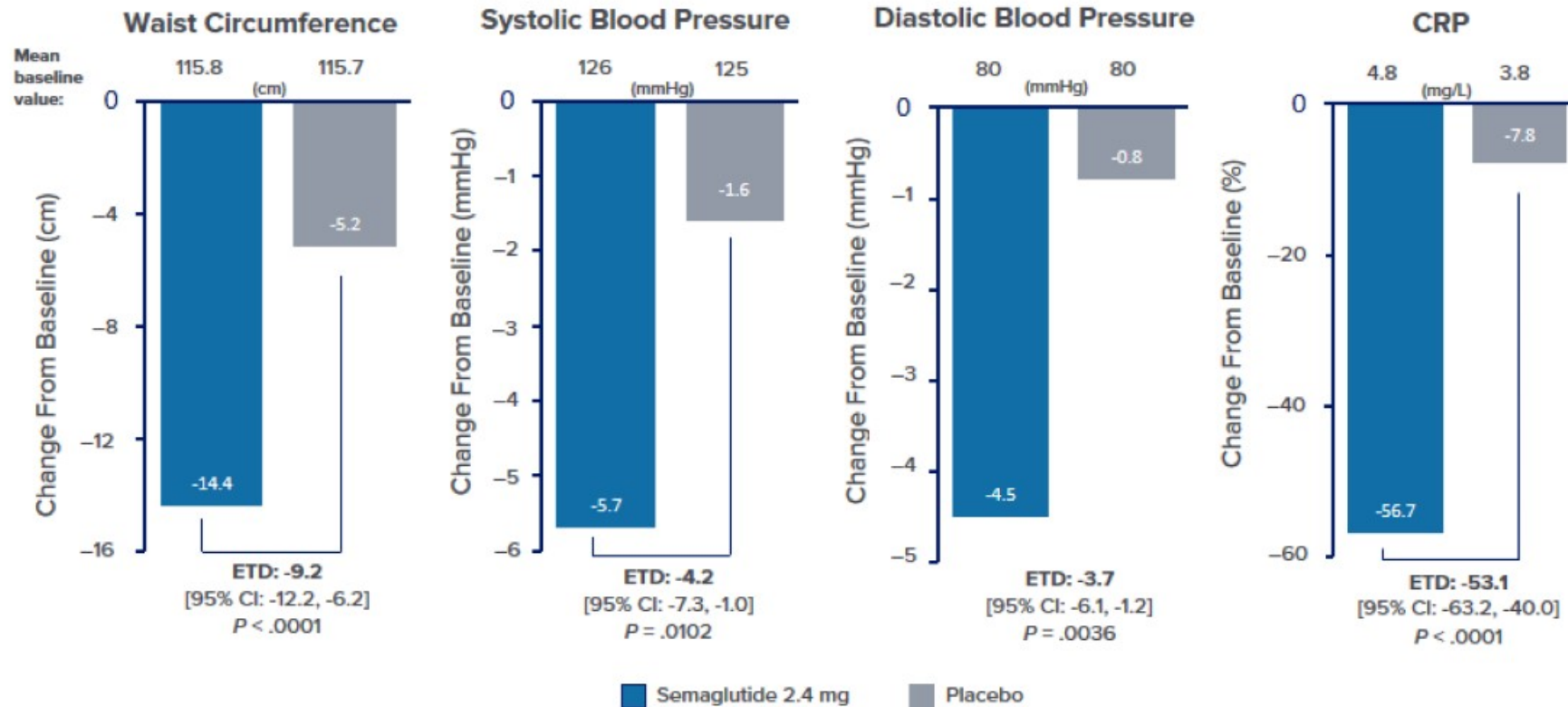


Change in Body Weight Over Time: STEP 1 vs STEP 5



STEP 5: Change in Cardiovascular Risk Factors at Week 104

Treatment Policy Estimand



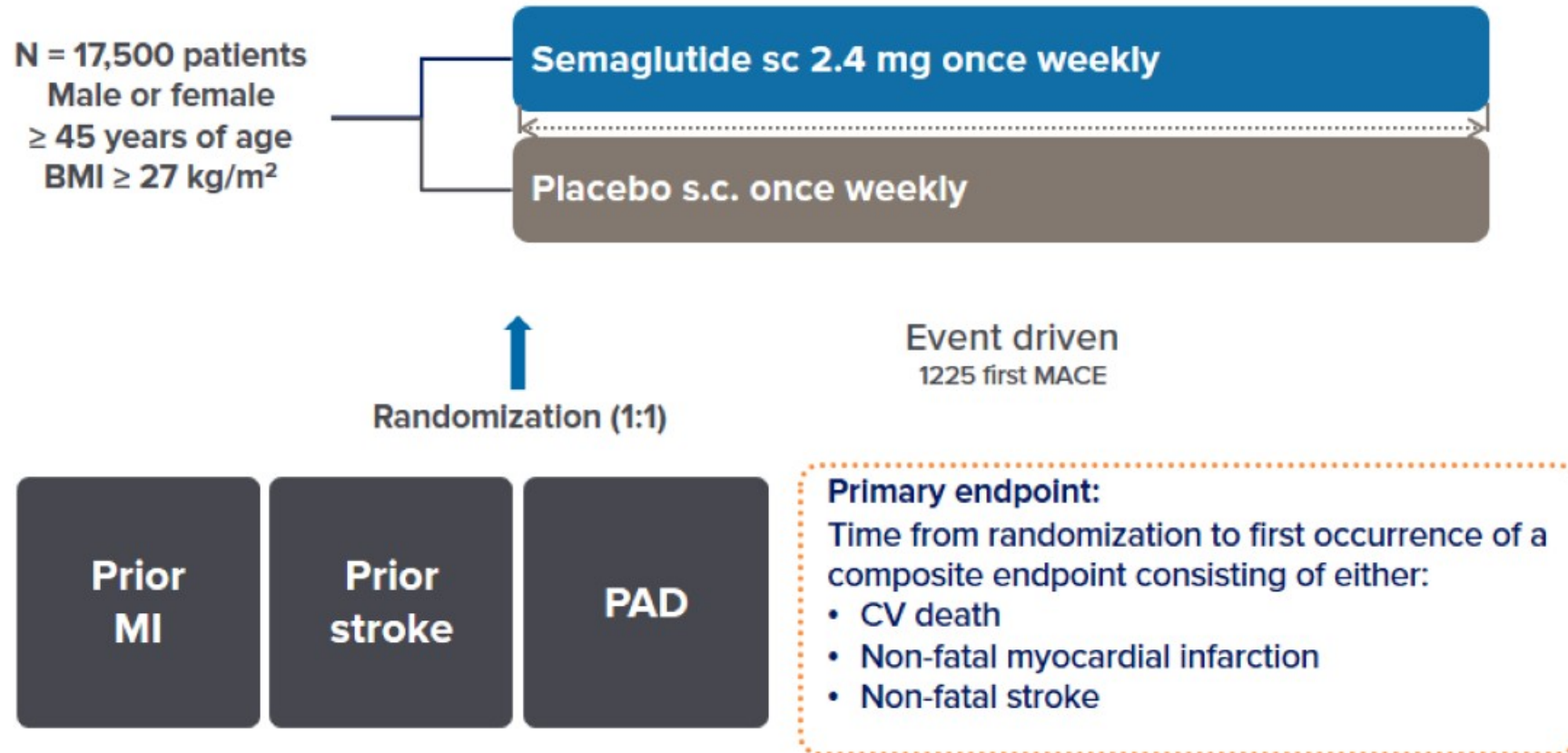
Safety Summary

- Semaglutide 2.4 mg appeared to be well-tolerated and has an established safety profile
- The most common adverse events among people treated with semaglutide 2.4 mg were gastrointestinal events
- Most were transient, and mild or moderate in severity
- Three participants had mild acute pancreatitis and 1 had gallstones in STEP 1

CRP, C-reactive protein

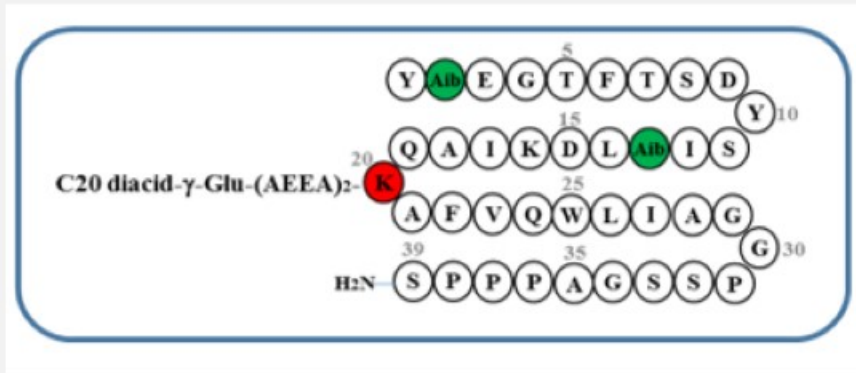
Garvey WT, et al. Presented at: 39th Annual Meeting of The Obesity Society; November 1-5, 2021; Virtual.

SELECT: GLP-1RA in High CVD Risk Overweight Patients Without Diabetes



CV, cardiovascular; MACE, Major adverse cardiovascular event; MI, myocardial infarction; PAD, peripheral artery disease; sc, subcutaneous.
Ryan DH, et al. Am Heart J. 2020;229:61-69.

Tirzepatide: GLP-1/GIP Receptor Dual Agonist

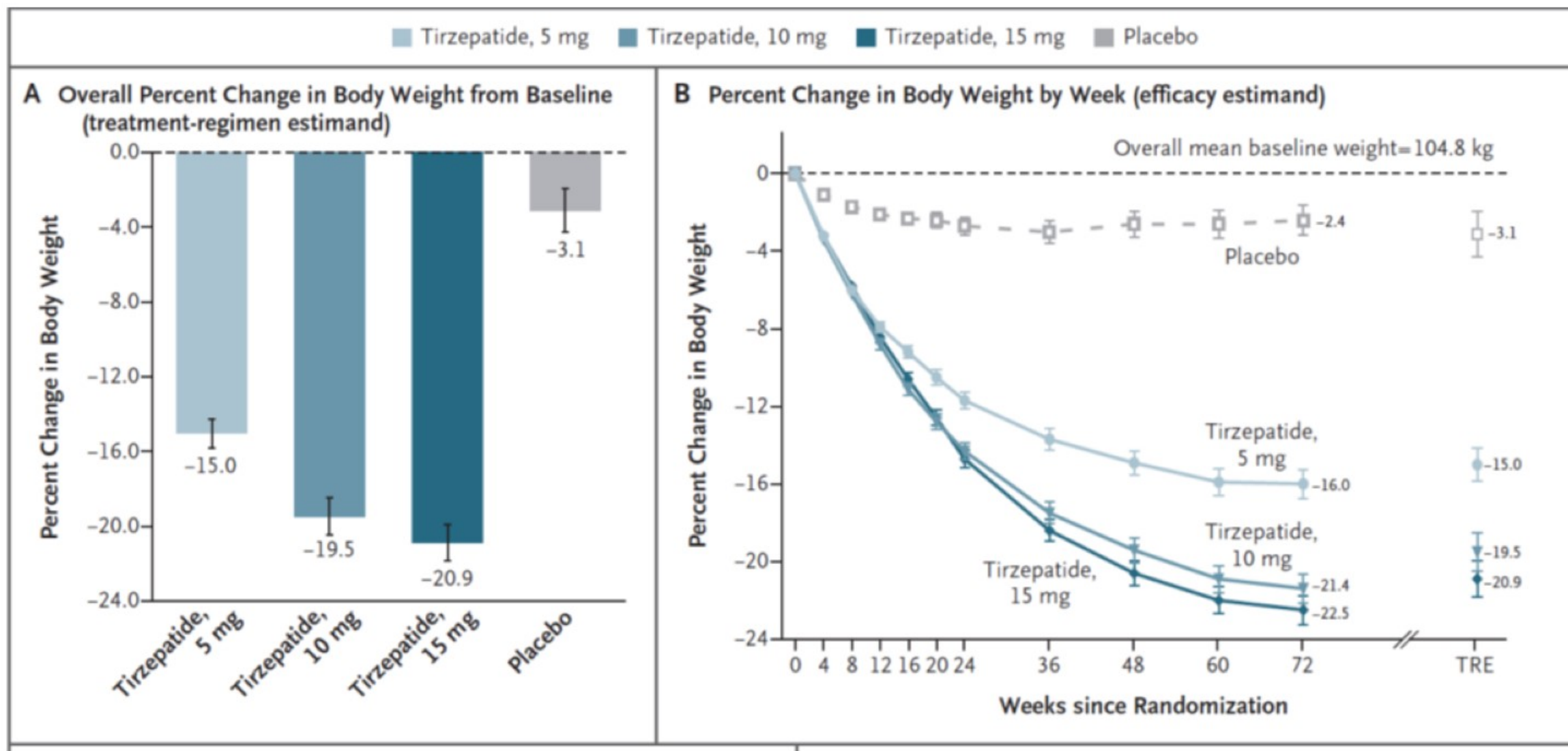


Multifunctional peptide based on the native GIP and modified to bind to both GIP and GLP-1 receptors

Mean half life ~5 days. Once weekly dosing

Trials in T2D and ongoing trials for obesity

Tirzepatide: SURMOUNT 1 Study in People With Obesity Without Diabetes



Tirzepatide: Proportion Meeting Weight Loss Targets in SURMOUNT 1 Phase 3 Trial

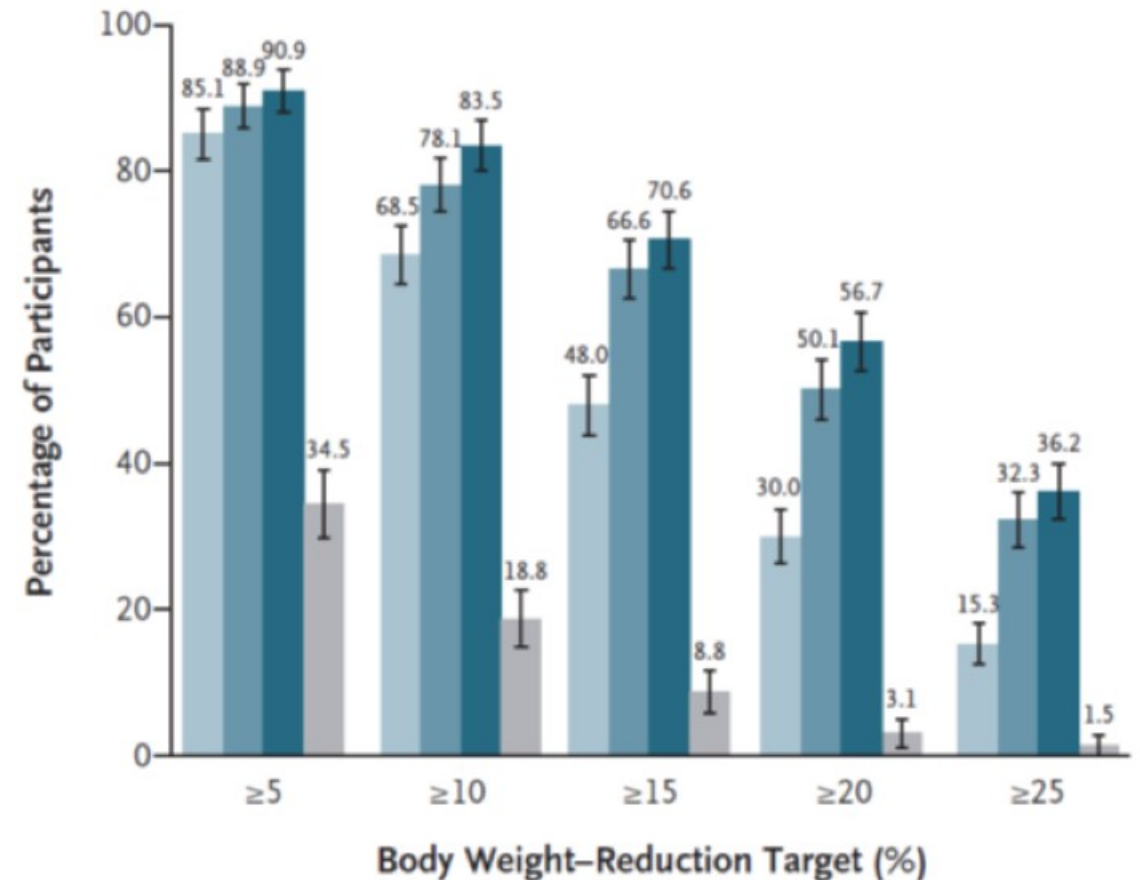
Over 85% of trial participants lost at least 5% body weight at all doses

More than half lost 20% of body weight or more at 10-mg and 15-mg doses

In an exploratory analysis, over 30% lost 25% of weight or more at 10-mg and 15-mg doses

Adverse events were similar to GLP-1 RA and included dose-dependent nausea and vomiting, mainly during dose escalation

Participants Who Met Weight-Reduction Targets (treatment-regimen estimand)

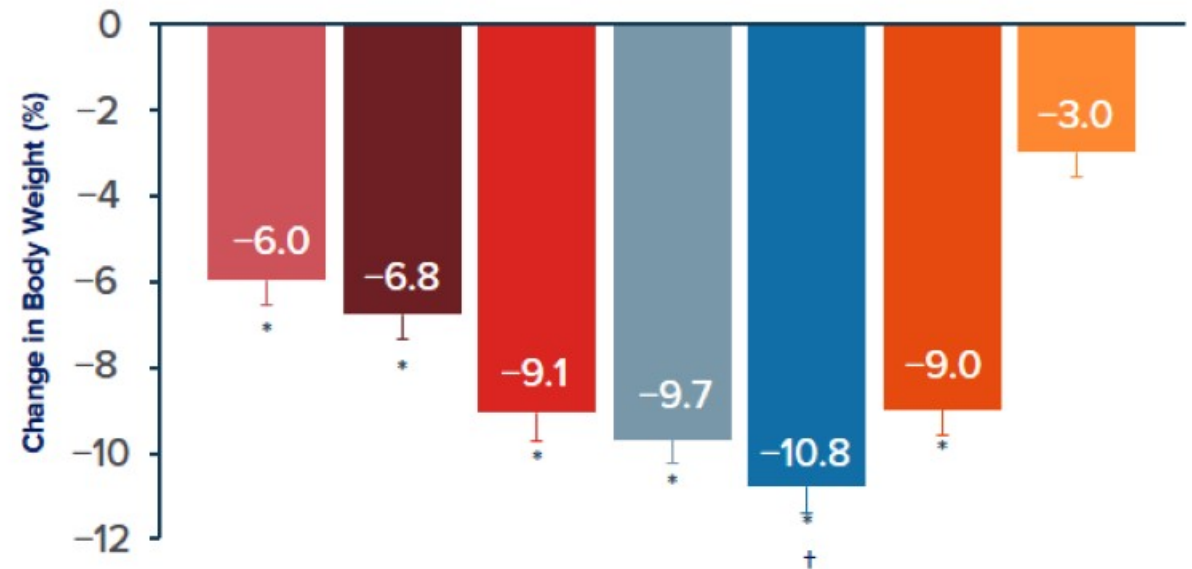
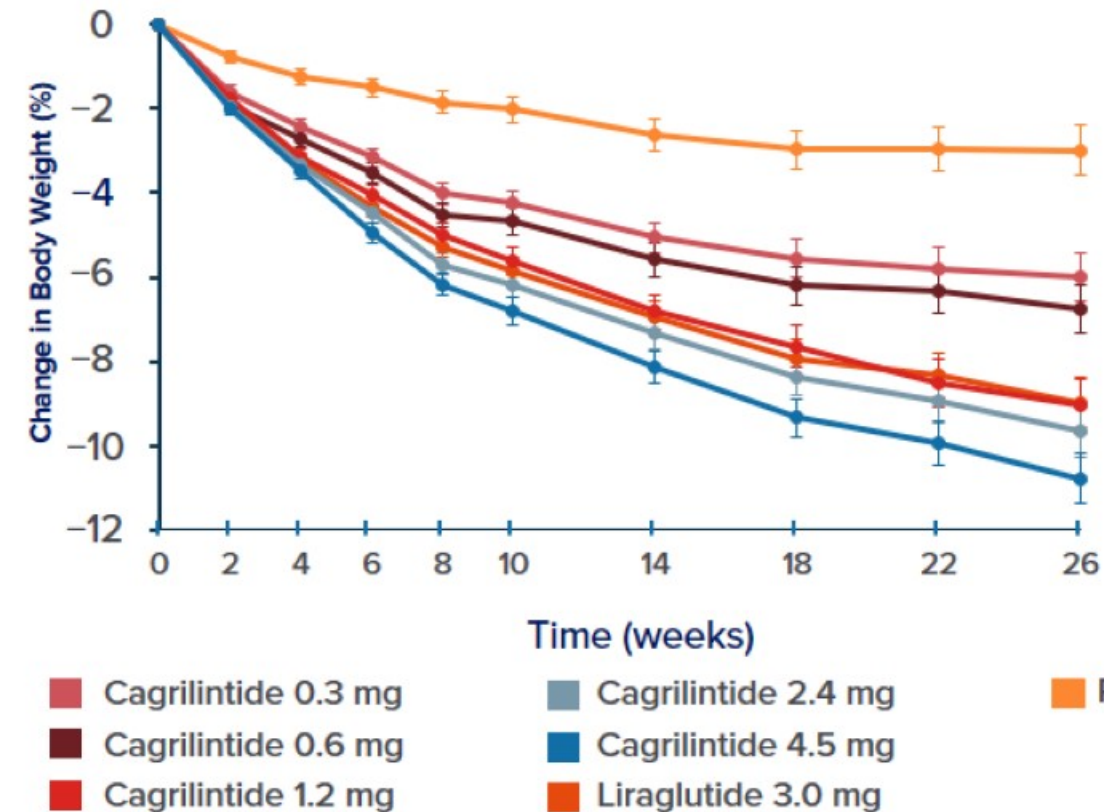


GLP-1 RA, glucagon-like peptide-1 receptor agonist.

Jastreboff AM, et al. N Engl J Med. 2022. doi: 10.1056/NEJMoa2206038 [Epub ahead of print].

Cagrilintide Effect on Body Weight

Cagrilintide Phase 2 Trial: Change in Body Weight (%)
Baseline to Week 26 – Primary Estimand*



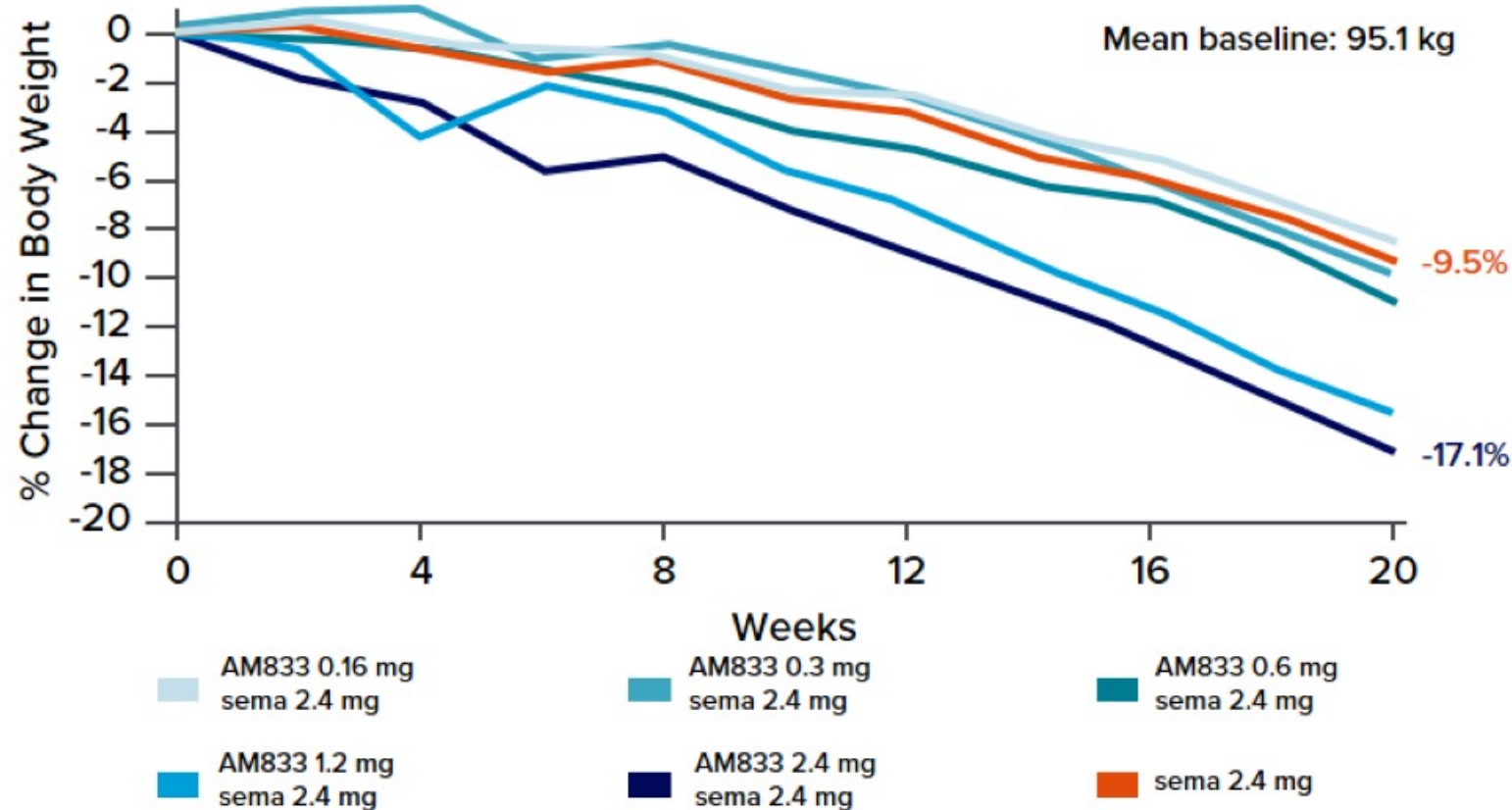
vs placebo
* $P < .001$

vs liraglutide
† $P < .05$ in favour of
cagrilintide

*Primary estimand assumes that all participants were adherent to treatment. Mean (SEM) change from baseline in body weight (%) by treatment week; – MAR-MI – treatment adherent – full analysis set. ANCOVA estimates using the primary analysis.

Courtesy of John Wilding, DM, FRCP; Batterham RL, et al. Presented at: ECO 2021, May 10-13, 2021; Virtual. Poster 0099.

Weight Loss With Semaglutide and Amylin Agonist *Cagrilintide and Semaglutide Phase 1 Trial*



66% of people on
AM833 + semaglutide
2.4 mg achieved > 15%
weight loss in
20 weeks

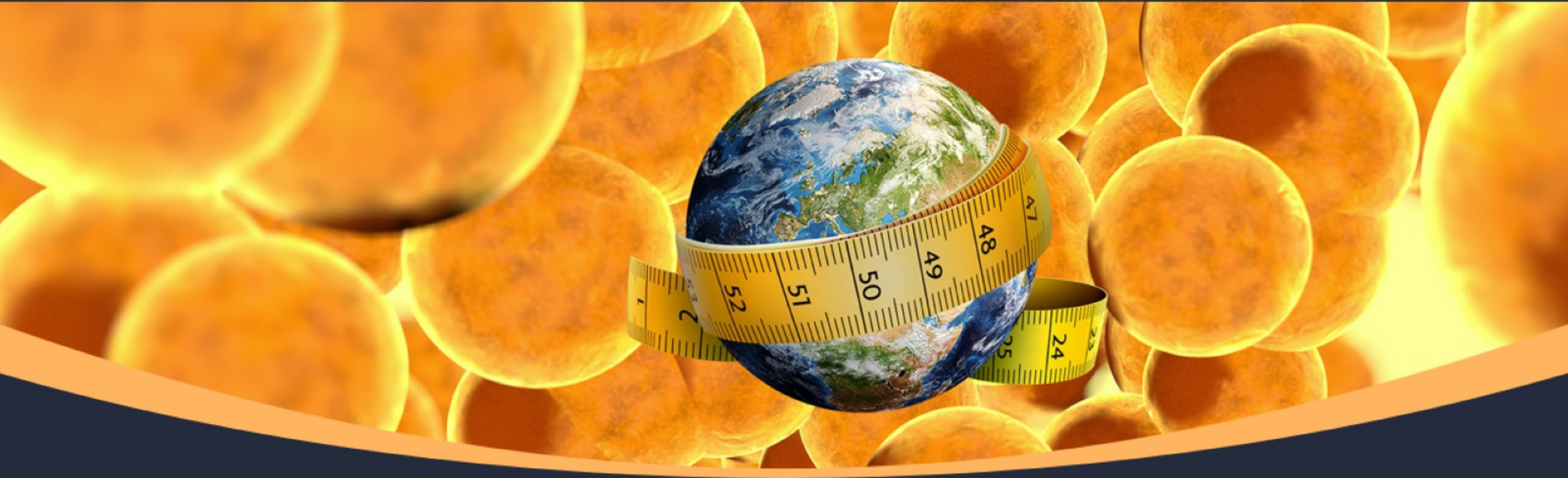
Obesity Treatment: Long-Term Options for Weight Management

Pharmacotherapy combined with lifestyle intervention can provide 15% weight loss for weight management



George Washington University School of Public Health and Health Services. Obesity Drug Outcome Measures: A Consensus Report of Considerations Regarding Pharmacologic Intervention. Accessed June 15th, 2022. <https://publichealth.gwu.edu/pdf/obesitydrugmeasures.pdf>; Jensen MD, et al. Circulation. 2014;129:S102-S138; Salminen P, et al. JAMA. 2018;319:241-254; Berry MA, et al. Obes Surg. 2018;28:649-55; Wilding JPH, et al. N Engl J Med. 2021;384:989-1002.

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Discussion

The Case for Multidisciplinary Obesity Care in Clinical Practice

Case 1

FACULTY

Sean Wharton, MD, PharmD, FRCP(C)



Case Study



Gender: Female

Age: 38 years

History

Single parent with 2 children
Works as housekeeper
Main income earner in her family

Reason for appointment

- Appointment because of her weight
- She has tried lots of diets and would like you to help her to lose weight
- She is frustrated and sad

What Questions Would You Ask Her?

“Regardless of what her measurements are, she is unhappy, and weight is somehow associated with it.”

“We need to ask why she thinks weight loss will help and what she is trying to achieve.”

Assess for Obesity Drivers, Complications, and Barriers

The 4Ms of Obesity



Mental

Cognition
Depression
Attention Deficit
Addiction
Psychosis
Eating Disorder
Trauma
Insomnia



Mechanical

Sleep Apnea
Osteoarthritis
Chronic Pain
Reflux Disease
Incontinence
Thrombosis
Intertrigo
Plantar Fasciitis



Metabolic

Type 2 Diabetes
Dyslipidemia
Hypertension
Gout
Fatty Liver
Gallstones
PCOS
Cancer



Monetary

Education
Employment
Income
Disability
Insurance
Benefits
Bariatric Supplies
Weight-Loss Programs

Case Study (cont)



Gender: Female
Age: 38 years

Class II obesity with comorbidities

Examination

- Height: 170 cm. Weight: 105 kg
- BMI: 36 kg/m²

Past medical history

- Hypothyroidism
- Knee pain
- Treatment: Levothyroxine 100mcg/day

Physical examination

- BP 142/85 mmHg
- Pannus with intertrigo

Blood tests

- A1c 6.2%, LDL 2.5, AST 50 (ULN 40)

Case Study (cont)



Gender: Female

Age: 38 years

“

She is sad, because she wanted to be a schoolteacher but had to keep cleaning houses to support her children, who are in university now.

”

“

She has tough days at work with a colleague that is not nice to her, and she comes home and soothes herself with calorie rich foods.

”

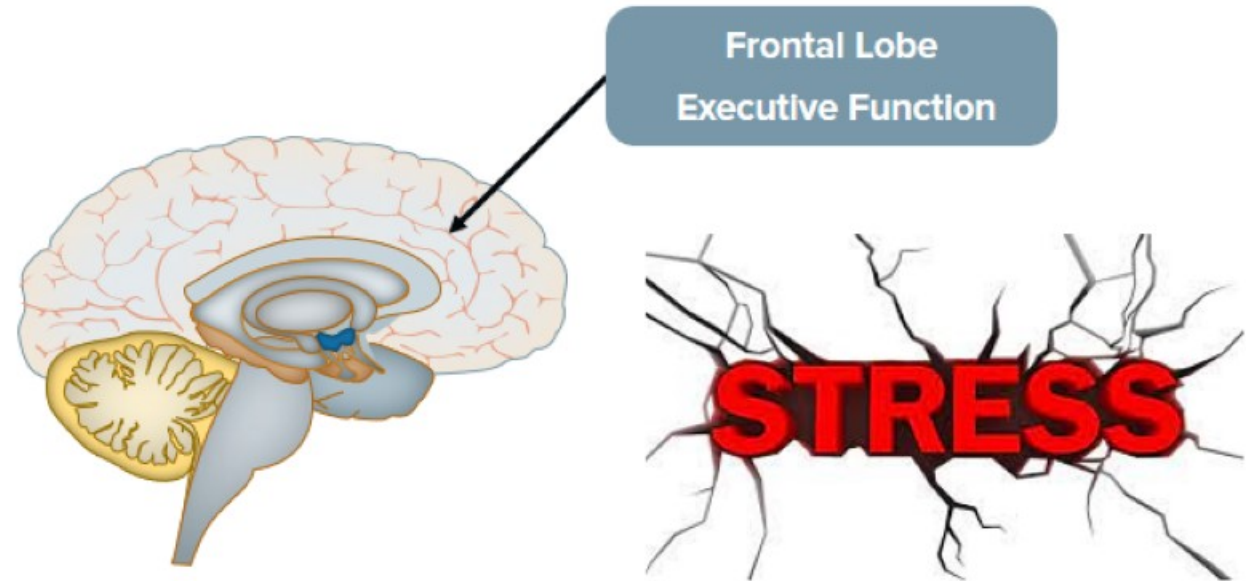
Treatment



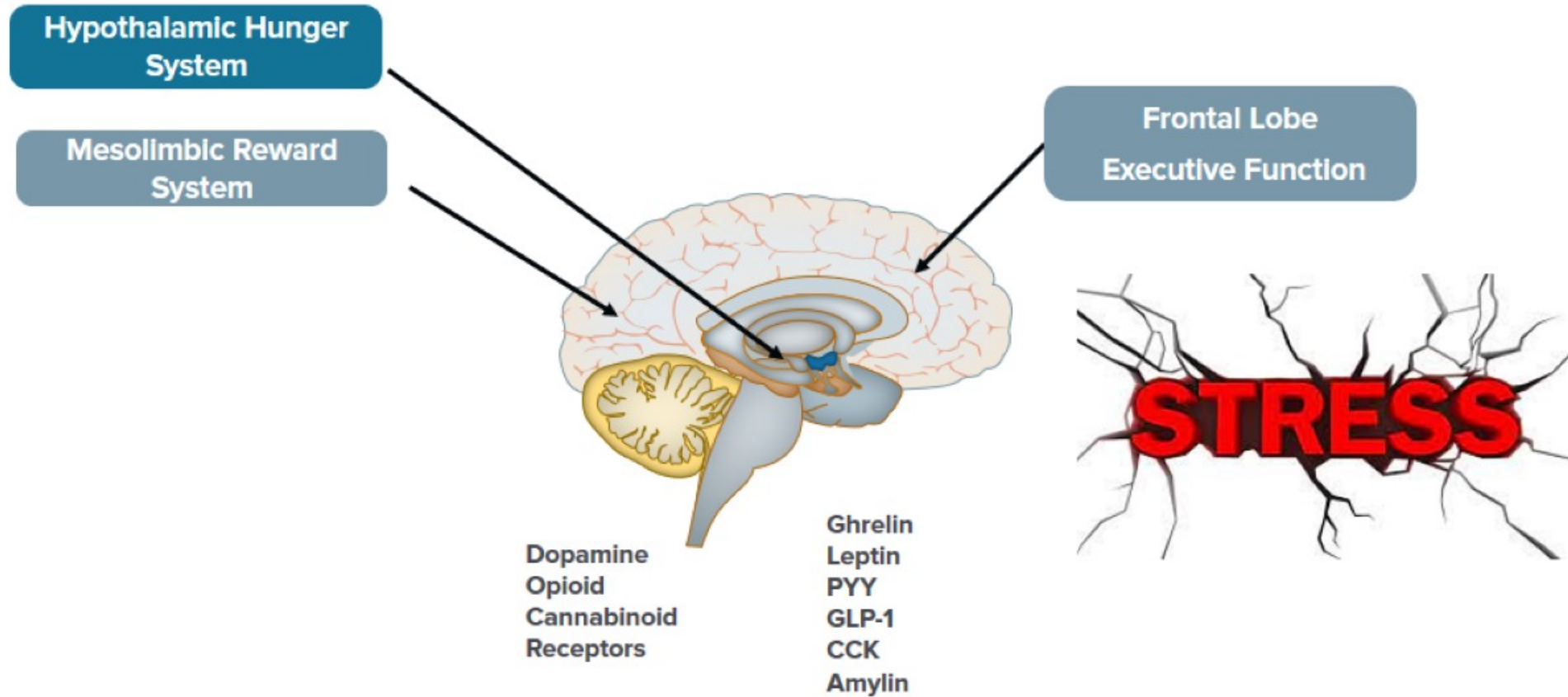
TREATMENT: Education about

- Causes of weight gain
- The neuropathology and that IT IS NOT HER FAULT
- The relationship to emotional stressors

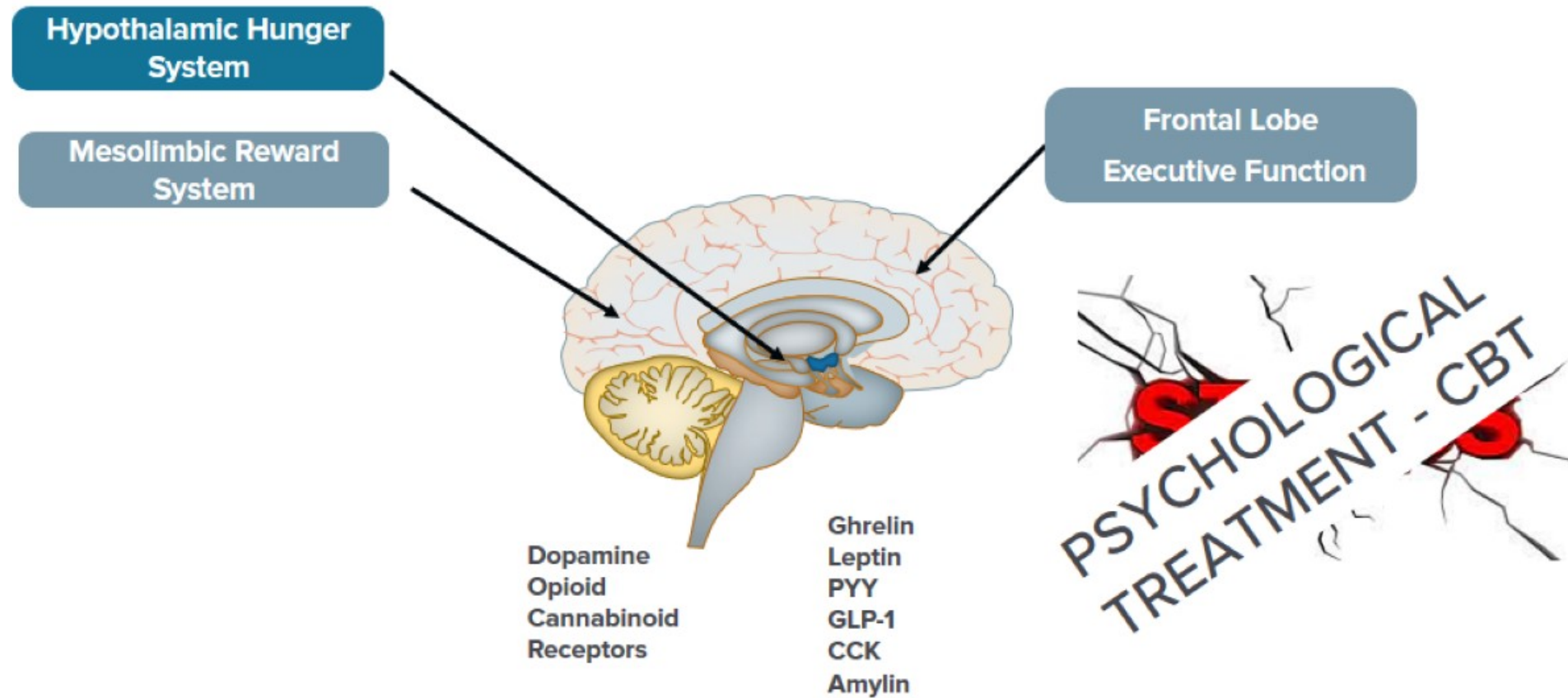
Obesity and the Brain



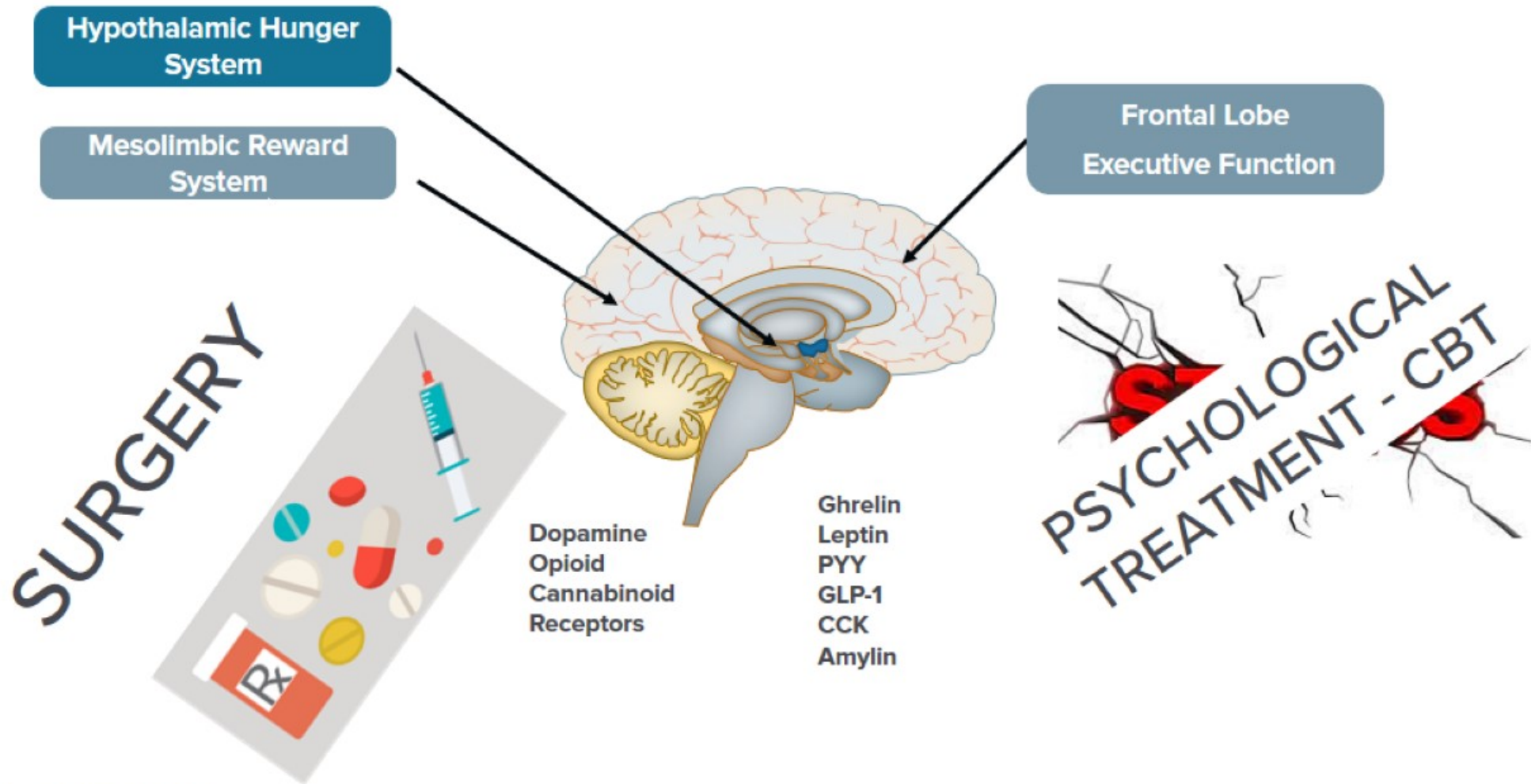
Obesity and the Brain



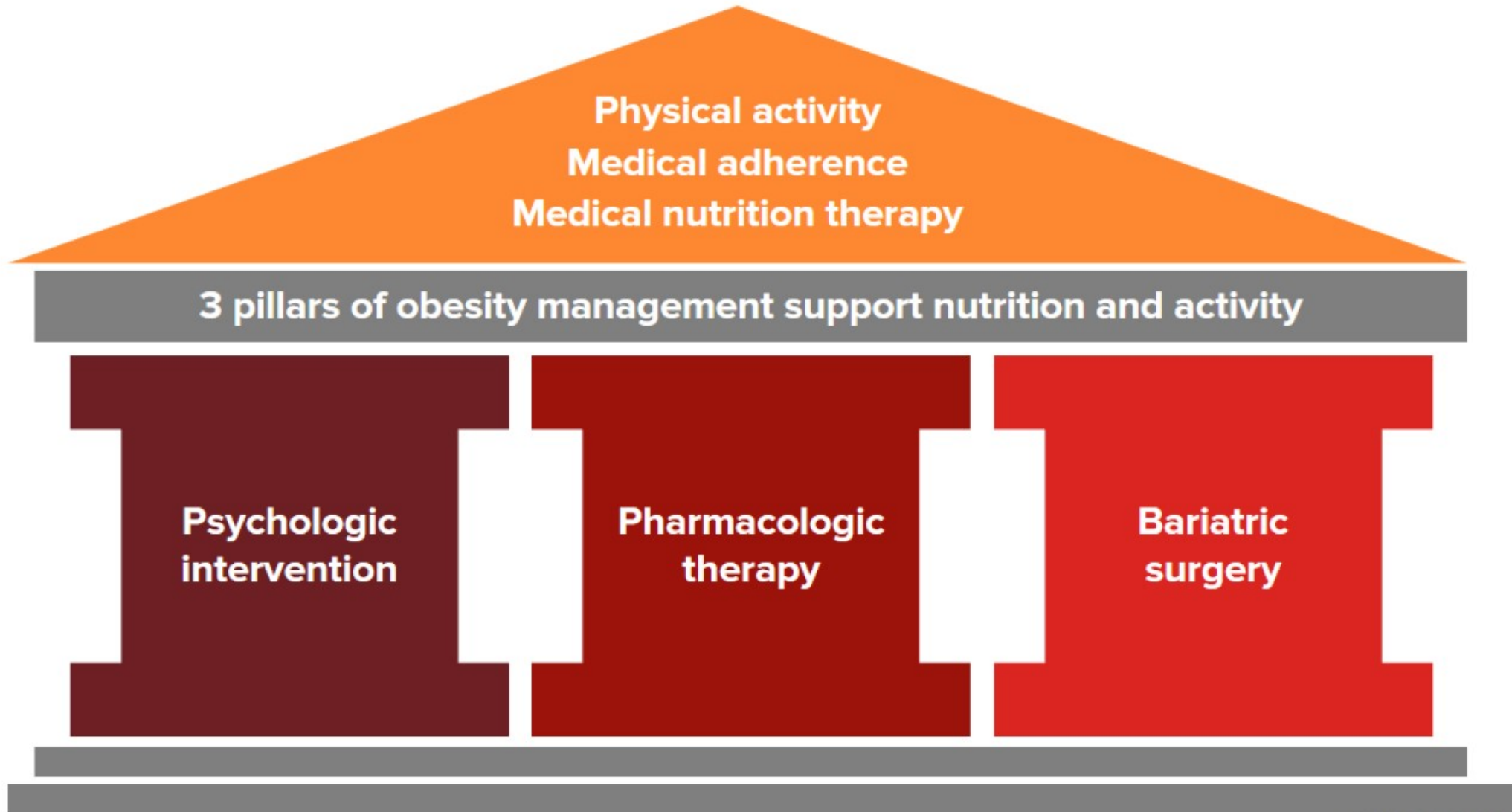
Obesity and the Brain



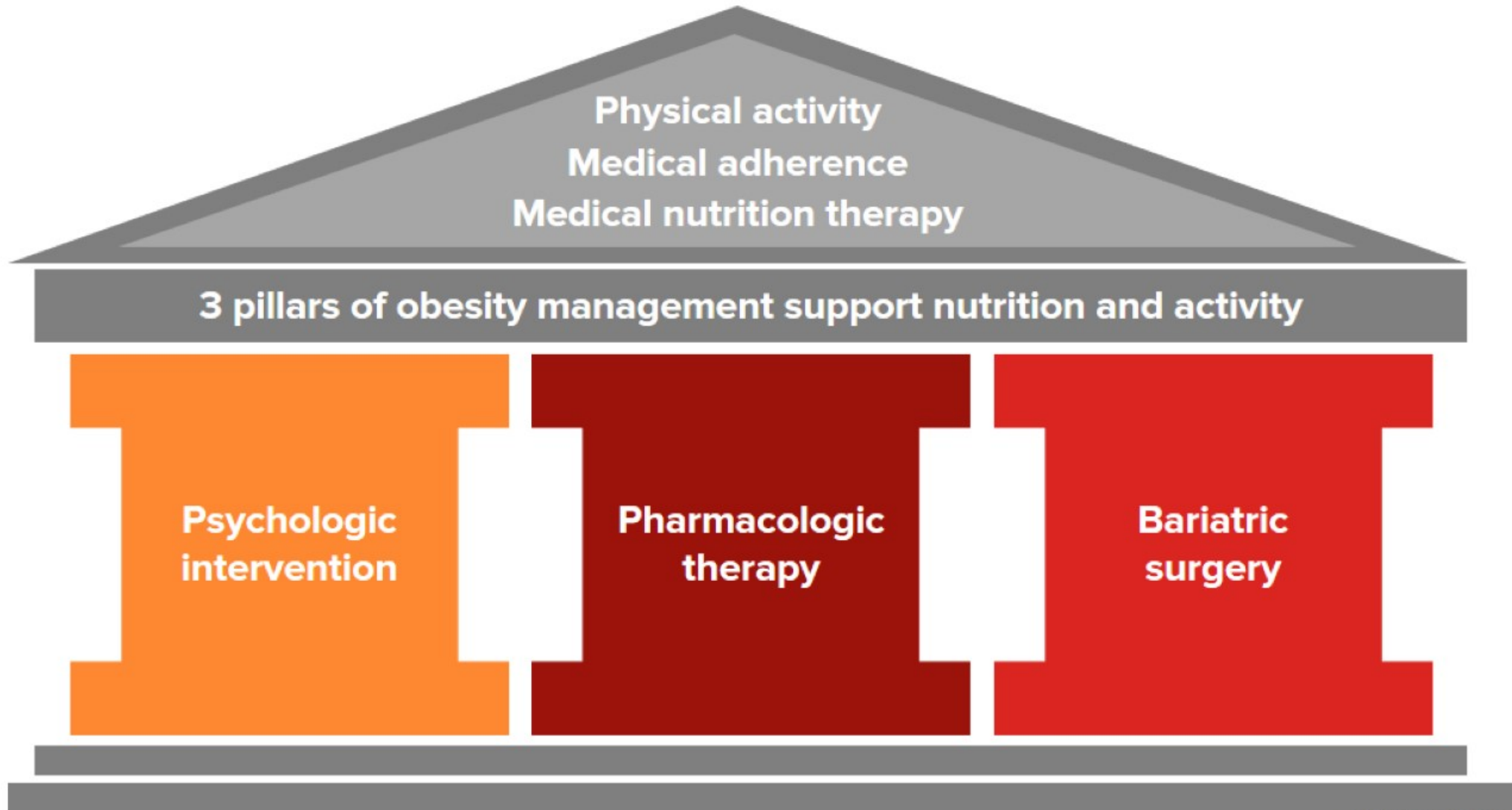
Obesity and the Brain



Overall Treatment Strategy



Overall Treatment Strategy

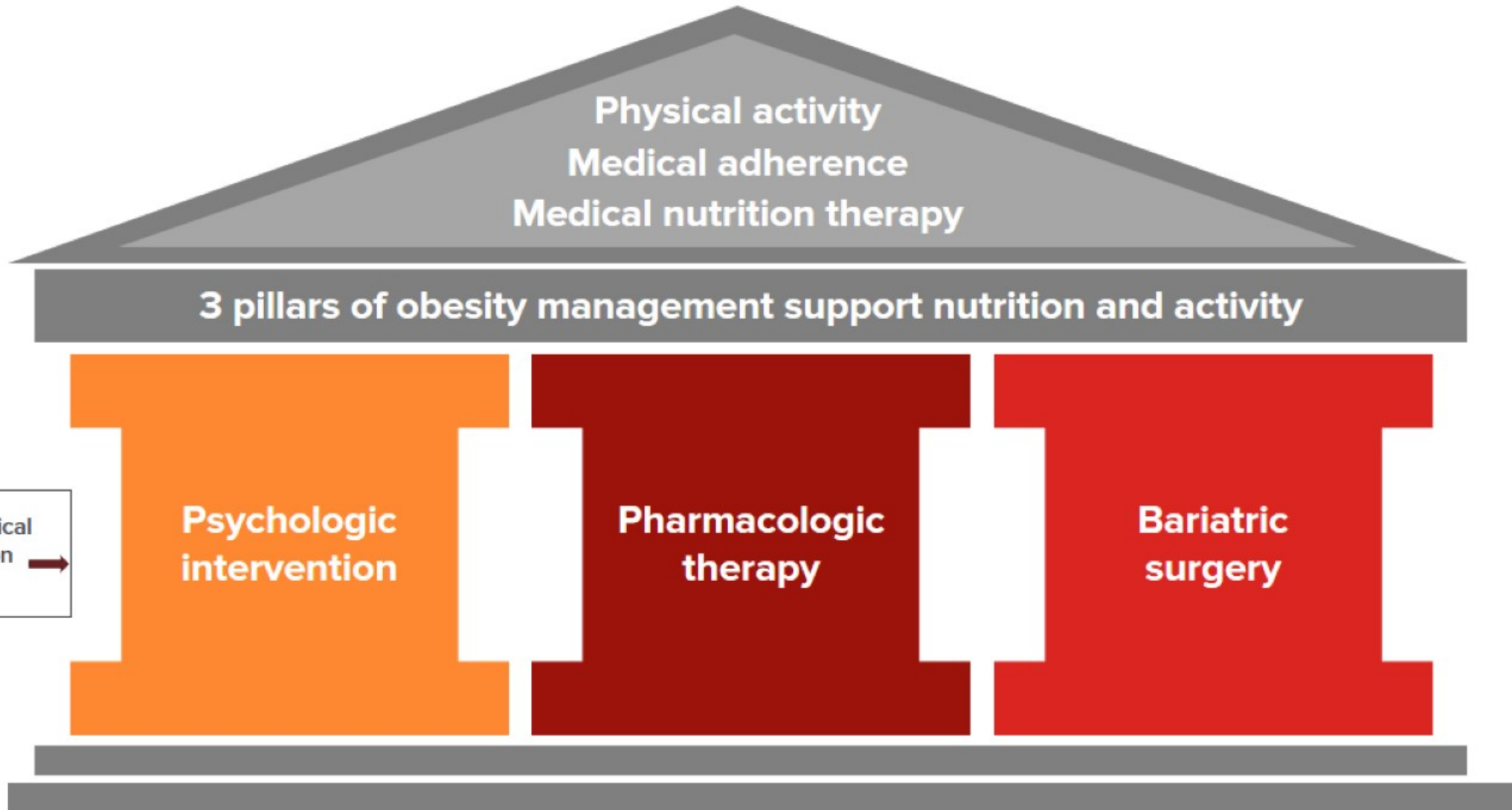


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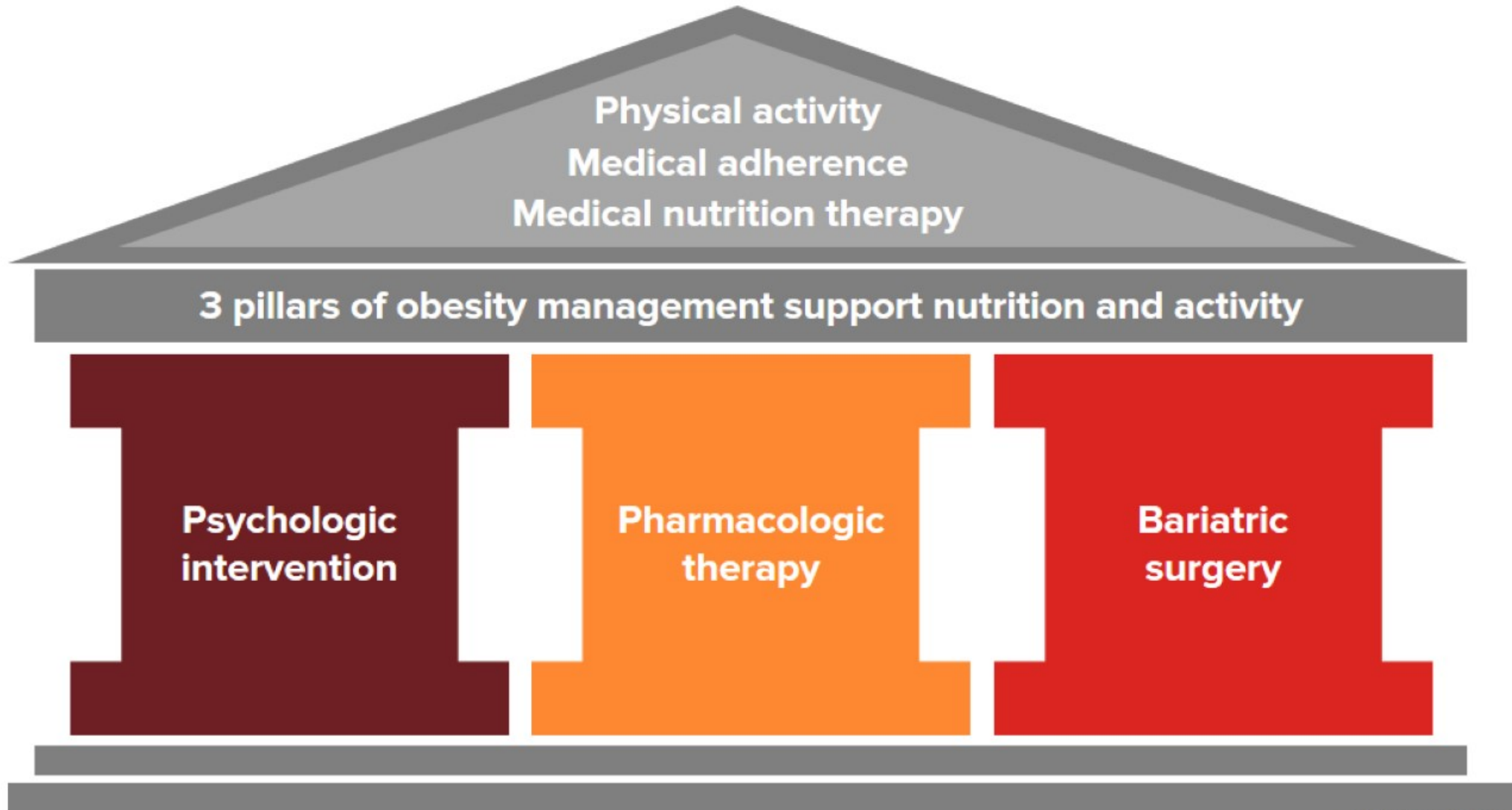
Wharton S, et al. CMAJ. 2020;192:E875-E891.

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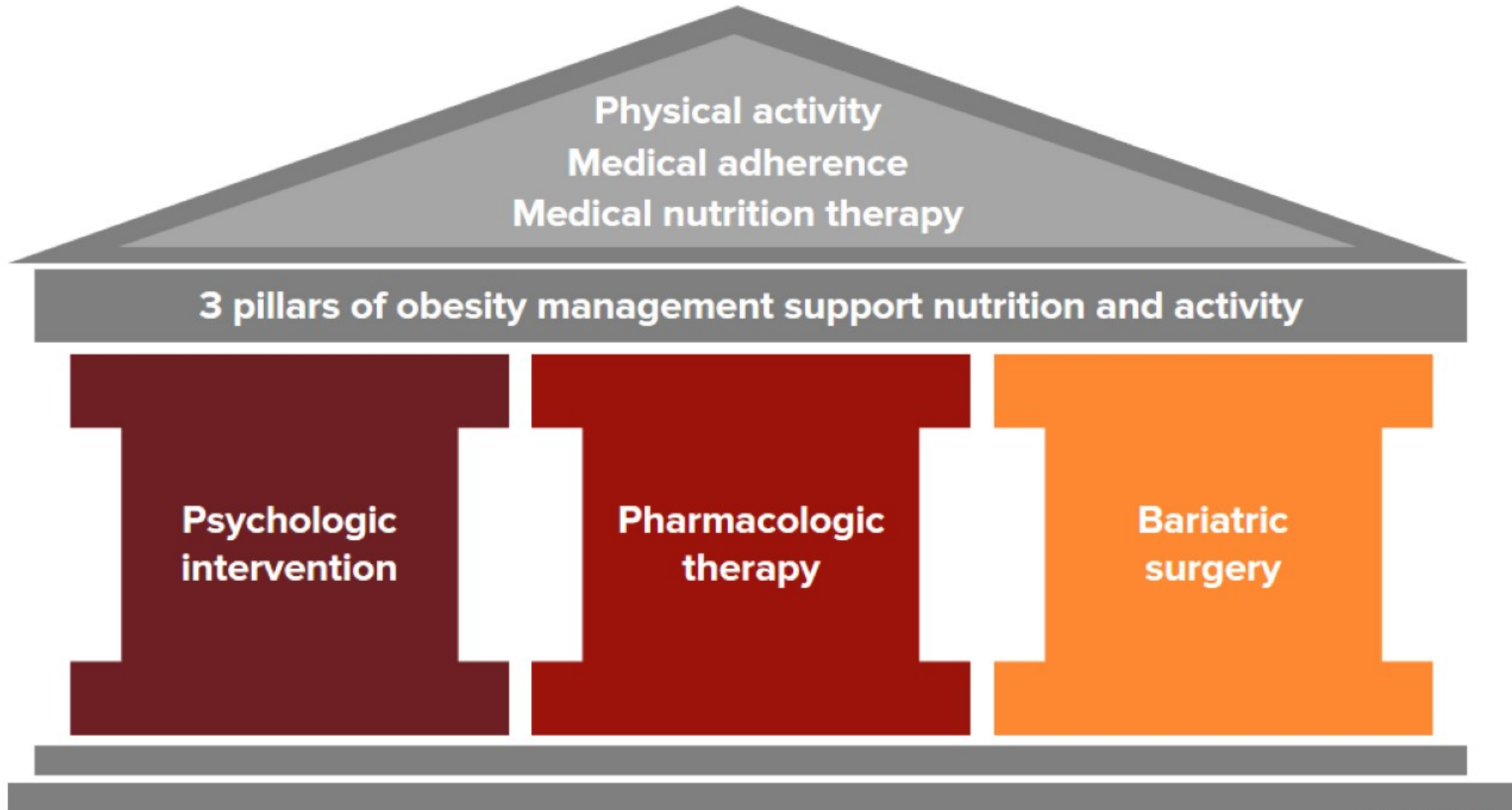
Overall Treatment Strategy



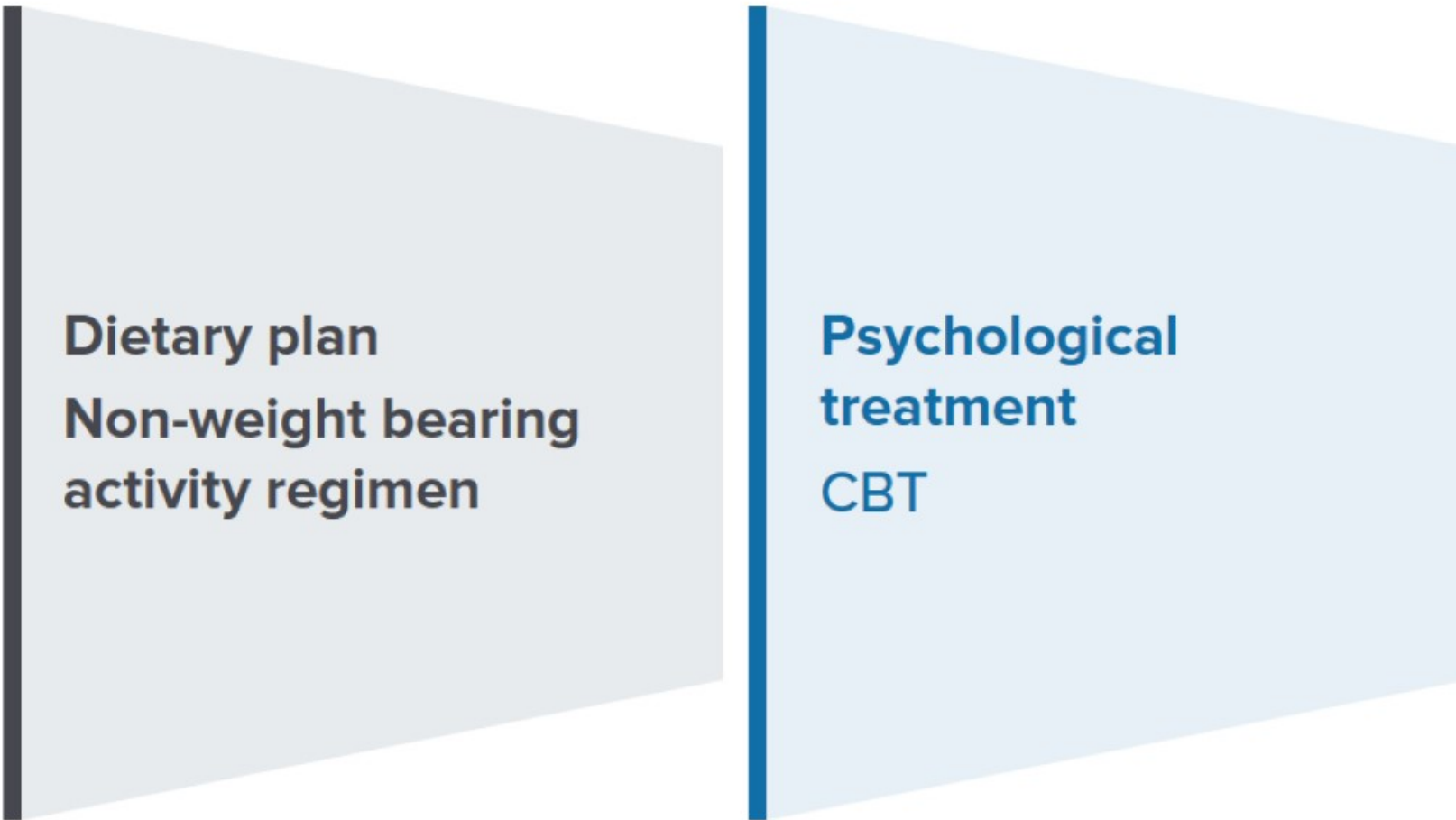
Overall Treatment Strategy



Overall Treatment Strategy



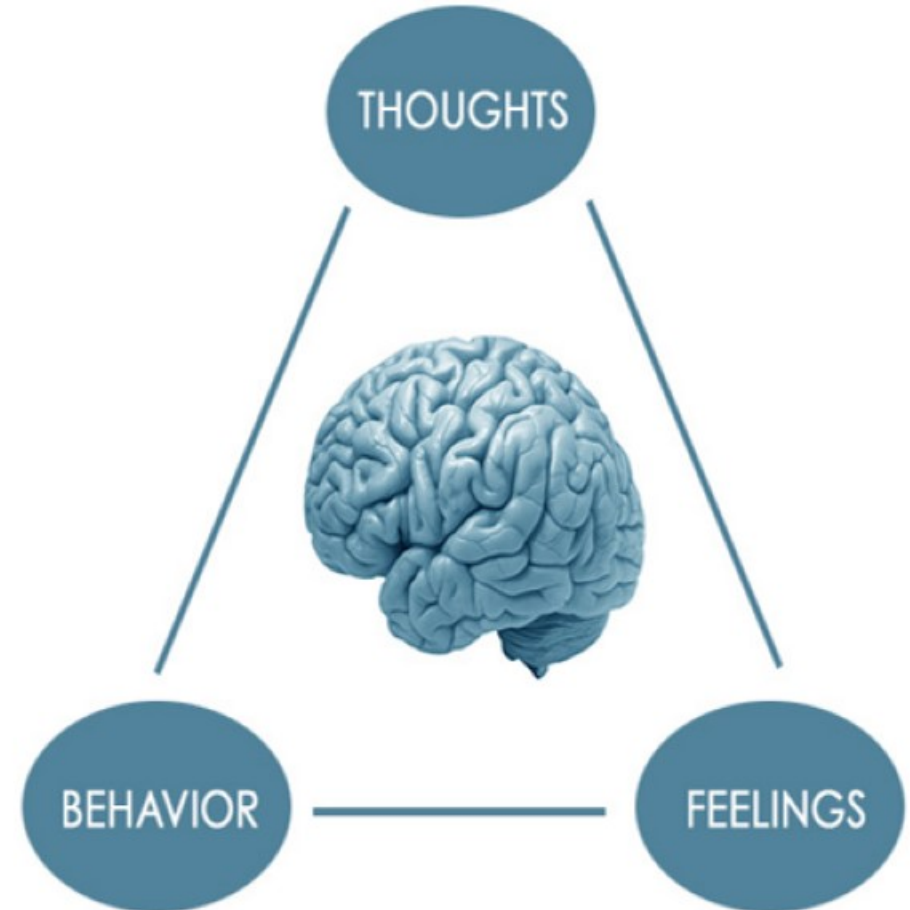
Patient Management



Dietary plan
Non-weight bearing
activity regimen

Psychological
treatment
CBT

CBT for Weight Management



The cognitive behavioral workbook for weight management is a step-by-step program

Patient Management

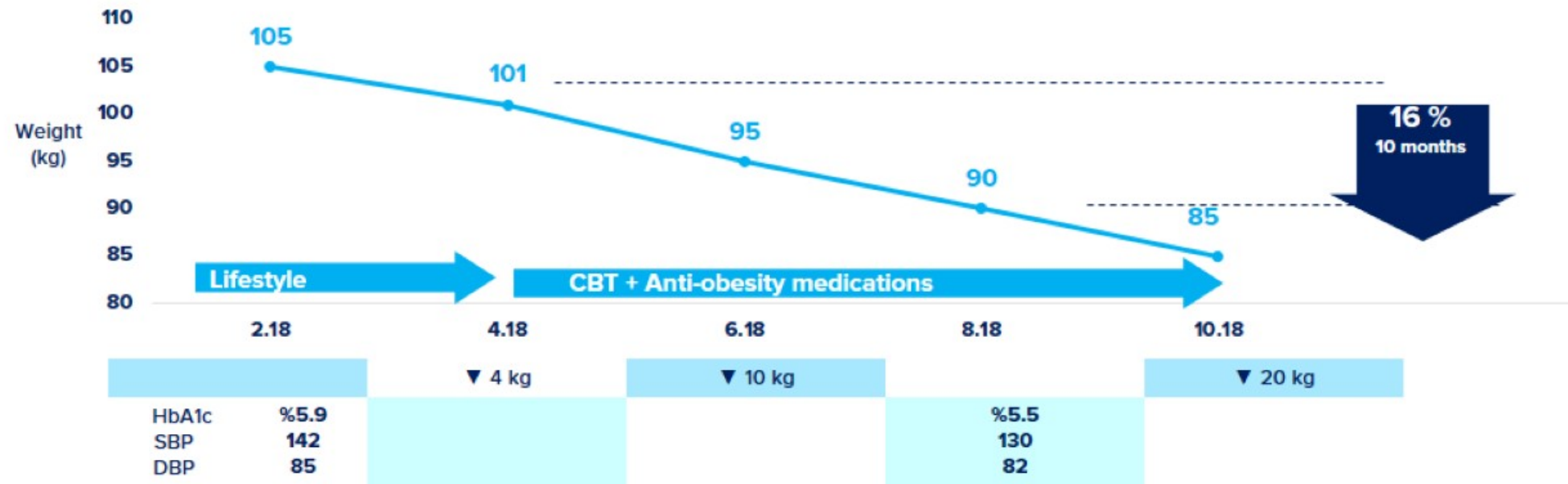


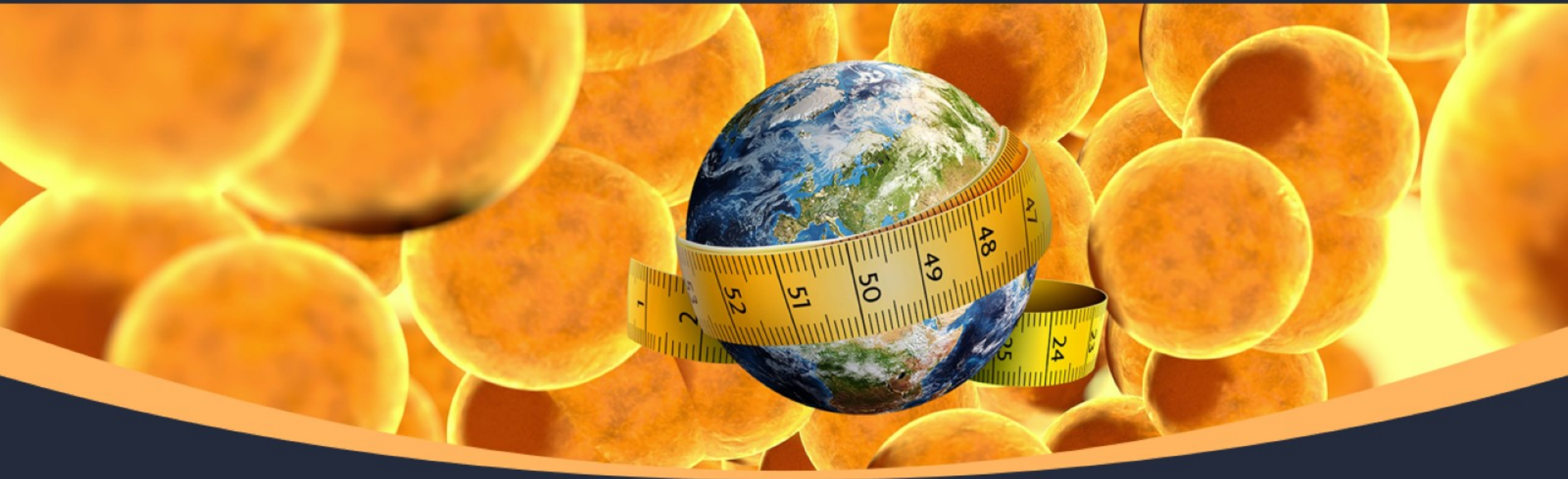
Dietary plan
Non-weight bearing
activity regimen

Psychological
treatment
CBT

Anti-obesity medication

Evolution of Treatment





Discussion

The Case for Multidisciplinary Obesity Care in Clinical Practice

Case 2

FACULTY

John Wilding, DM, FRCP



Case Study



Gender: Female
Age: 47 years

History

Works part-time in a supermarket
Two teenage children at home
Non smoker, rarely drinks alcohol

Medical History

- Asthma (has 2 inhalers)
- PCOS (required fertility treatment)
- Gestational diabetes
- Last recorded weight 105 kg 5 years ago
- Medication: salbutamol and beclomethasone inhalers, OTC analgesics

Not a frequent GP attender (not seen for 2 years)

Case Study (cont)



Gender: Female
Age: 47 years

Symptoms

Fatigue, general aches, pains
More breathless than previously
Reduced exercise tolerance

Examination

- Blood pressure – 150/98 mmHg
- Weight 126 kg
- BMI 42 kg/m²
- No joint inflammation or tenderness
- CV and respiratory examination normal

Questions



- Would you raise the issue of weight with her at this stage?
- What investigations should be done at this point?
- What other conditions might you consider looking for?

Case Study



Gender: Female

Age: 47 years

Biological exams

HbA1c – 46 mmol/mol (6.4%)

**Chol 5.2 mmol/L; HDL 1.0 mmol/L; Ratio 5;
TG 1.9 mmol/L**

**LFTs normal, except ALT 56 UI/L
(normal range 10-42 UI/L)**

24-hr BP confirms hypertension

Next Steps



- **Diet and lifestyle advice**
Referred to Diabetes Prevention Programme
- **Statin?**
Does not wish to take statin at the moment (worried about potential AEs)
- **Antihypertensive medication**
ACE inhibitor added

4 Months Later



- **Diabetes prevention program online:**
She has lost 3 kg in weight
- **BP improved:** 138/78 mmHg on ACE inhibitor
- **HbA1c 6.4%**
- **Unhappy about rate of weight loss,**
still tired and short of breath; asks
about weight loss medication

Pharmacologic Options



Orlistat

Liraglutide

Naltrexone /bupropion

Semaglutide

Evolution

12 Months Later



Gender: Female
Age: 47 years

Evolution

Weight 108 kg
More active, walking dog every day
Breathing is better
BP 128/76 mmHg
HbA1c 38 mmol/mol (5.6%)
Much happier and wants to continue with medication, although no longer losing weight



Discussion

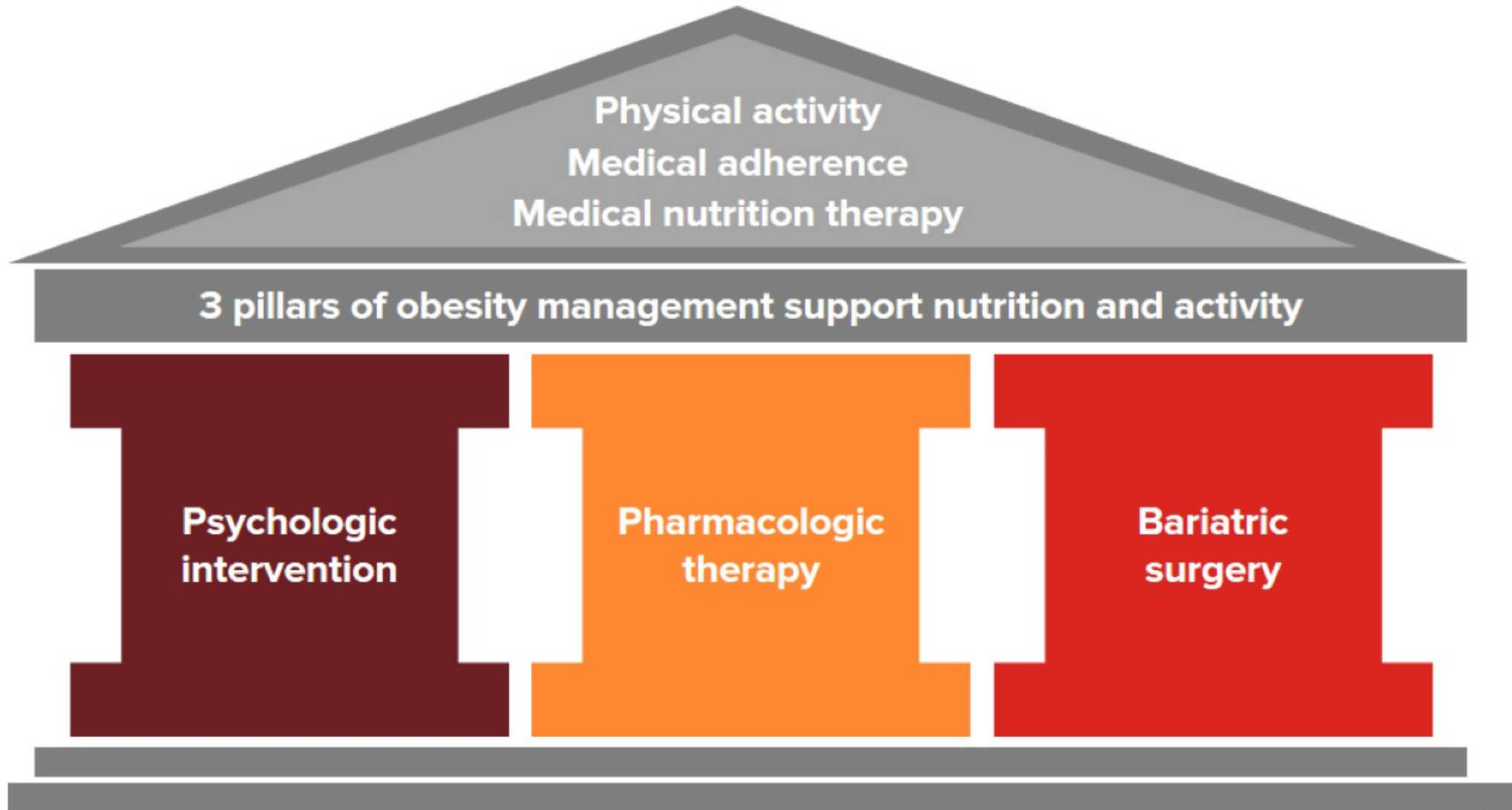
A Concerted Effort to Tackle Obesity Call to Action

FACULTY

Arya M. Sharma, MD, DSc (hon), FRCPC



Overall Treatment Strategy



A Medscape **LIVE!** EVENT

THANK YOU

for participating in
this activity!

