

Efficacia dei nuovi
trattamenti farmacologici
specifici per l'obesità e loro
ricadute dirette sulla
prevenzione
cardiovascolare

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International Obesity Collaborative **CONSENSUS STATEMENT**

Body Mass Index (BMI)



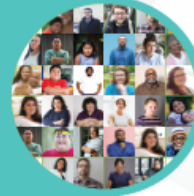
Body mass index (BMI) is a measure used to screen for obesity that neither defines the disease nor replaces clinical judgment. Social determinants, race, ethnicity, and age can modify the risk associated with a given BMI. Successful obesity management should be measured by the health and quality-of-life goals established through shared decision making by the patient and their healthcare provider rather than changes in BMI alone.

International Obesity Collaborative Members



International Obesity Collaborative **CONSENSUS STATEMENT**

Obesity Care vs. Weight Loss



Obesity care and weight loss are not the same.

Obesity care delivered by qualified clinicians consists of evidence-based options that address comorbidities of obesity (diabetes, hypertension, hyperlipidemia, etc.) and improve well-being. Obesity care is about health, not weight. Weight loss is just one outcome of obesity care.

Obesity is a serious, relapsing chronic disease that requires long term care, just like any other chronic disease. Safe and effective evidence-based obesity treatments that improve patient health are available.

Evidence-based methods for obesity and severe obesity may include: nutrition and behavior modification, physical activity, medications, approved devices, and metabolic/bariatric surgery. In decisions shared with patients, clinicians utilize one or more of these modalities to treat obesity.

Globally, medical coverage limits access to effective obesity care, to the detriment of patient health. National statutes and medical insurance coverage have not kept pace with evidence and advances in clinical science. Like other serious chronic diseases, support for obesity care must be incorporated into national public health strategies and include standard benefits and coverage for obesity across the lifespan.

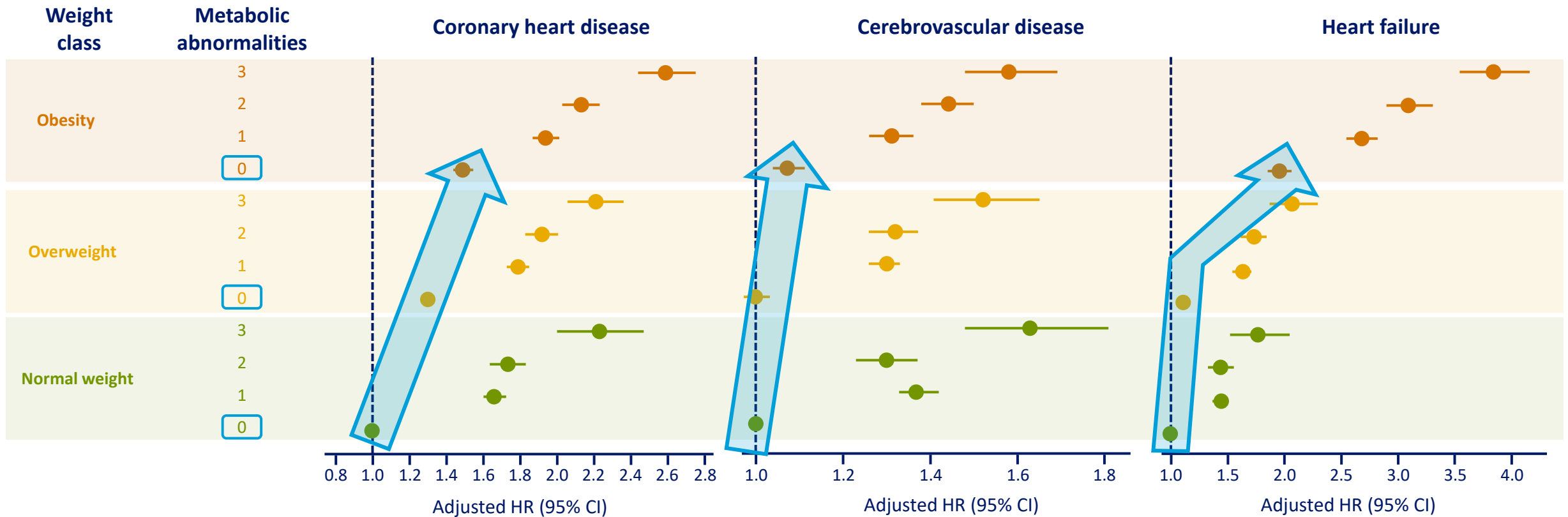
People with obesity deserve care, free from stigma and shame.

International Obesity Collaborative Members



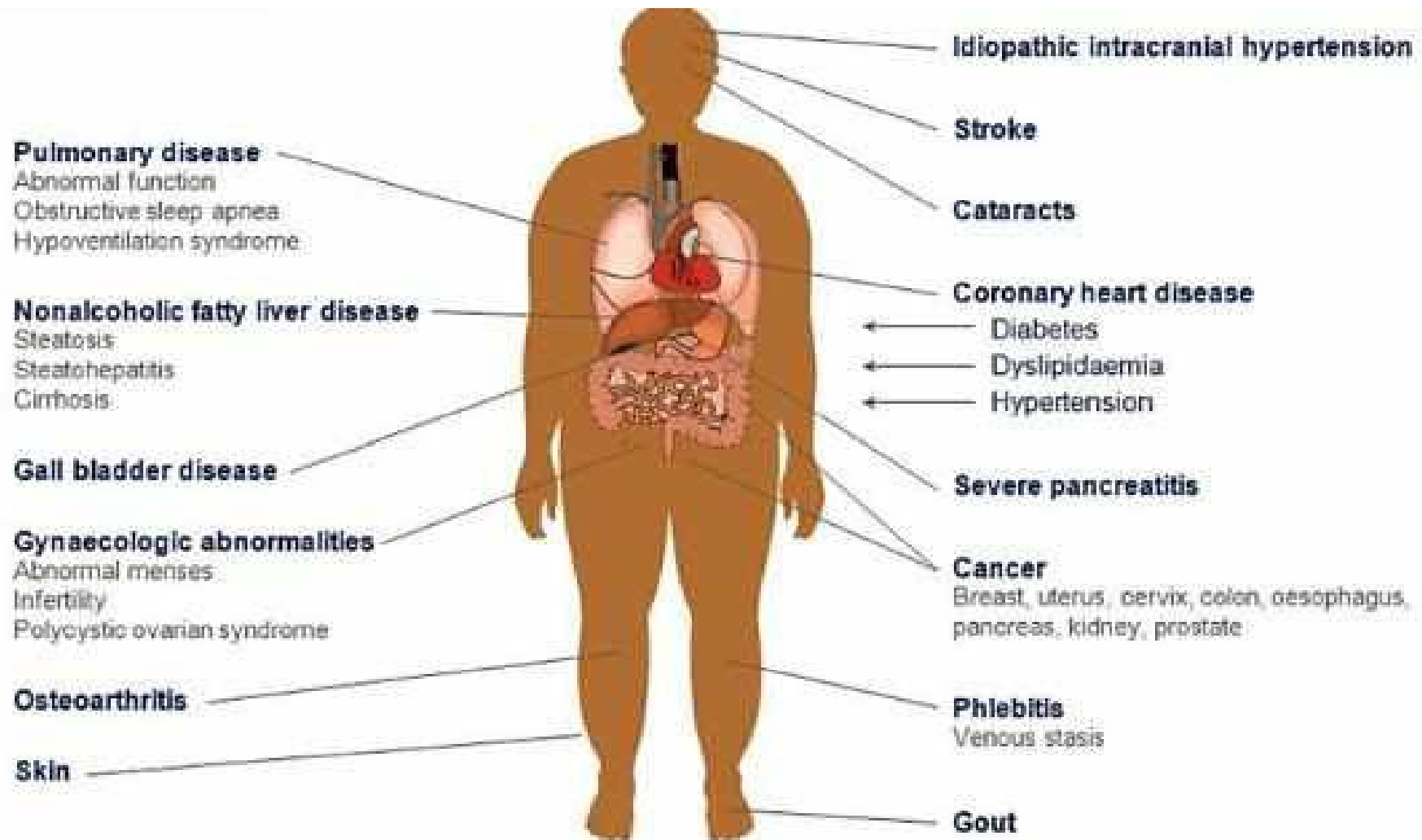
Overweight or obesity increases the risk of CV events even in the absence of other metabolic abnormalities*

Body size, metabolic status and CVD events in 3.5 million UK adults†



*The three metabolic abnormalities (diabetes, hypertension and hyperlipidaemia) were summed to create a metabolic abnormalities score (0, 1, 2, and 3). †Analyses adjusted for age, sex, smoking status, and social deprivation. The reference category is normal weight, no metabolic abnormalities. CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease; HR, hazard ratio; PVD, peripheral vascular disease; UK, United Kingdom. Caleyachetty R et al. J Am Coll Cardiol. 2017;70:1429–37.

Complicanze associate all'Obesità



Obesity meets common criteria of a disease

Definition of Health

"a state of complete physical, mental and social **well-being** and **not merely the absence** of disease or infirmity"

AMA

- An impairment of the normal functioning of some aspect of the body
- Characteristic signs or symptoms
- Harm or morbidity



- Appetite dysregulation
- Abnormal energy balance
- Endocrine dysfunction
- Infertility
- NAFLD
- Dyslipidaemia

Obesity



- Increased body fat
- Symptoms associated with increased body fat including:
 - Joint pain
 - Altered metabolism
 - Sleep apnoea

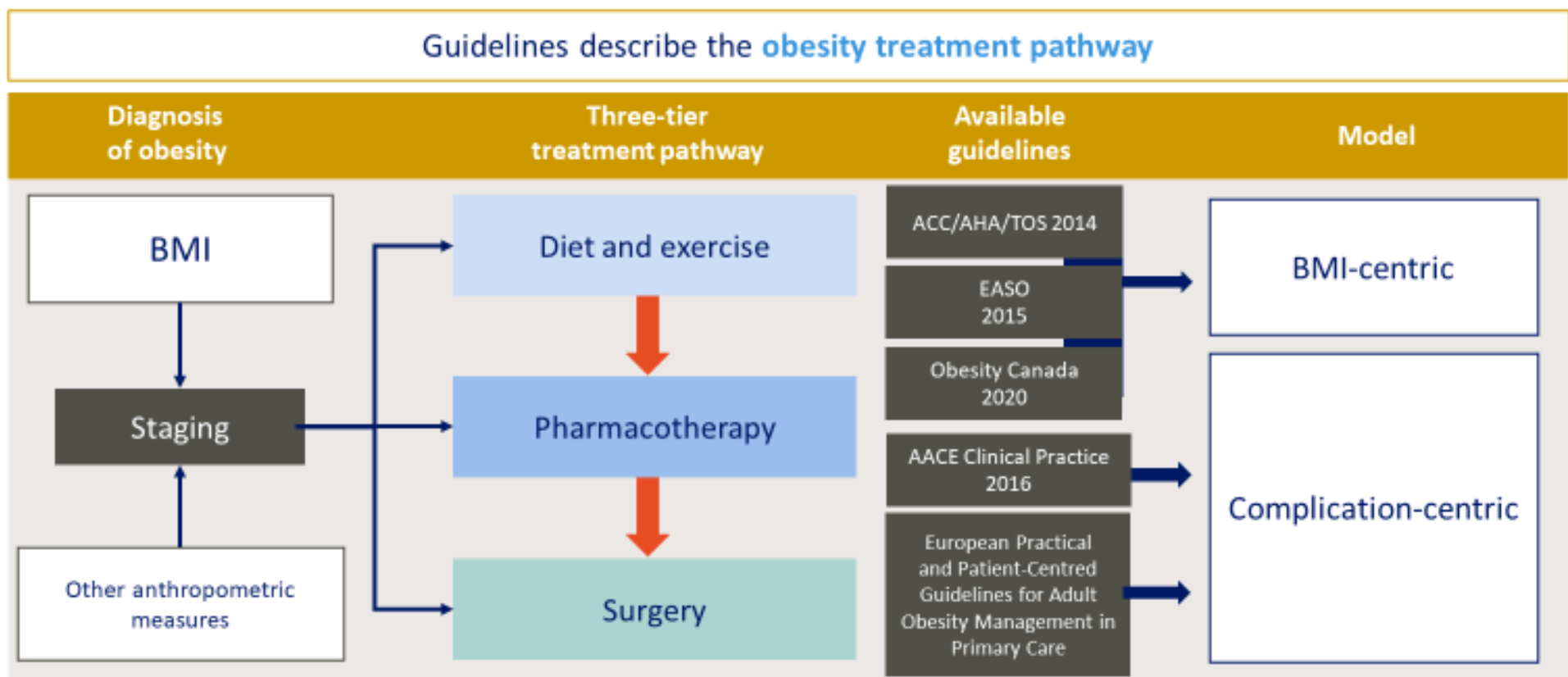


- T2D
- Cardiovascular disease
- Cancer
- Osteoporosis
- Polycystic ovary syndrome

AMA, American Medical Association; NAFLD, non-alcoholic fatty liver disease; T2D, type 2 diabetes

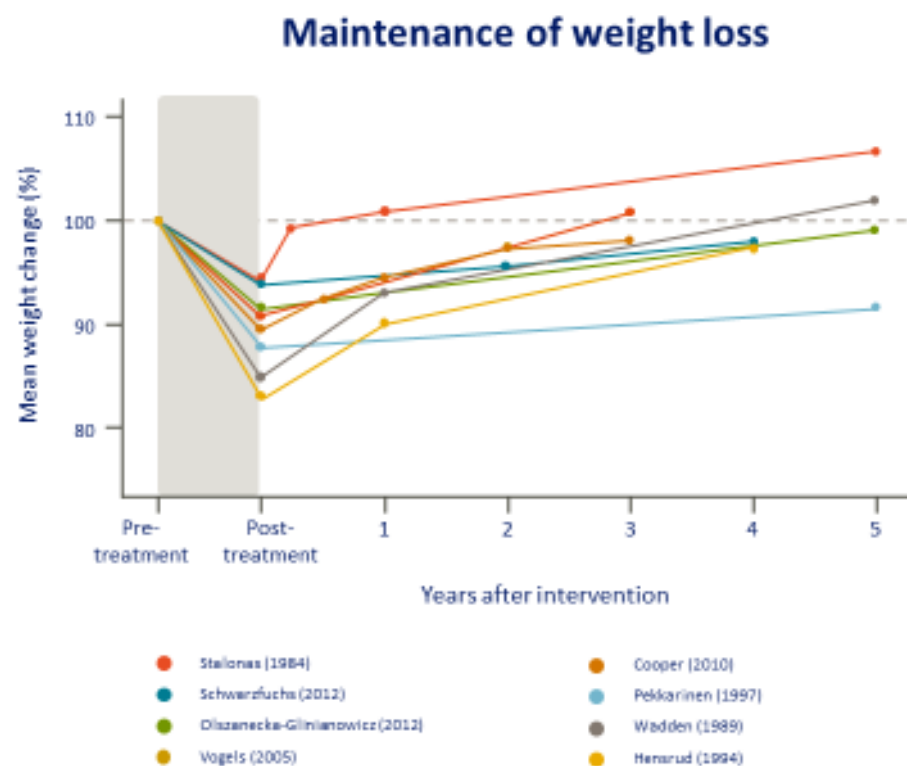
1. Mechanick et al. *Endocr Pract* 2012; 18(5): 642-648; 2. World Health Organization. *Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19-22 June 1946*

Obesity management

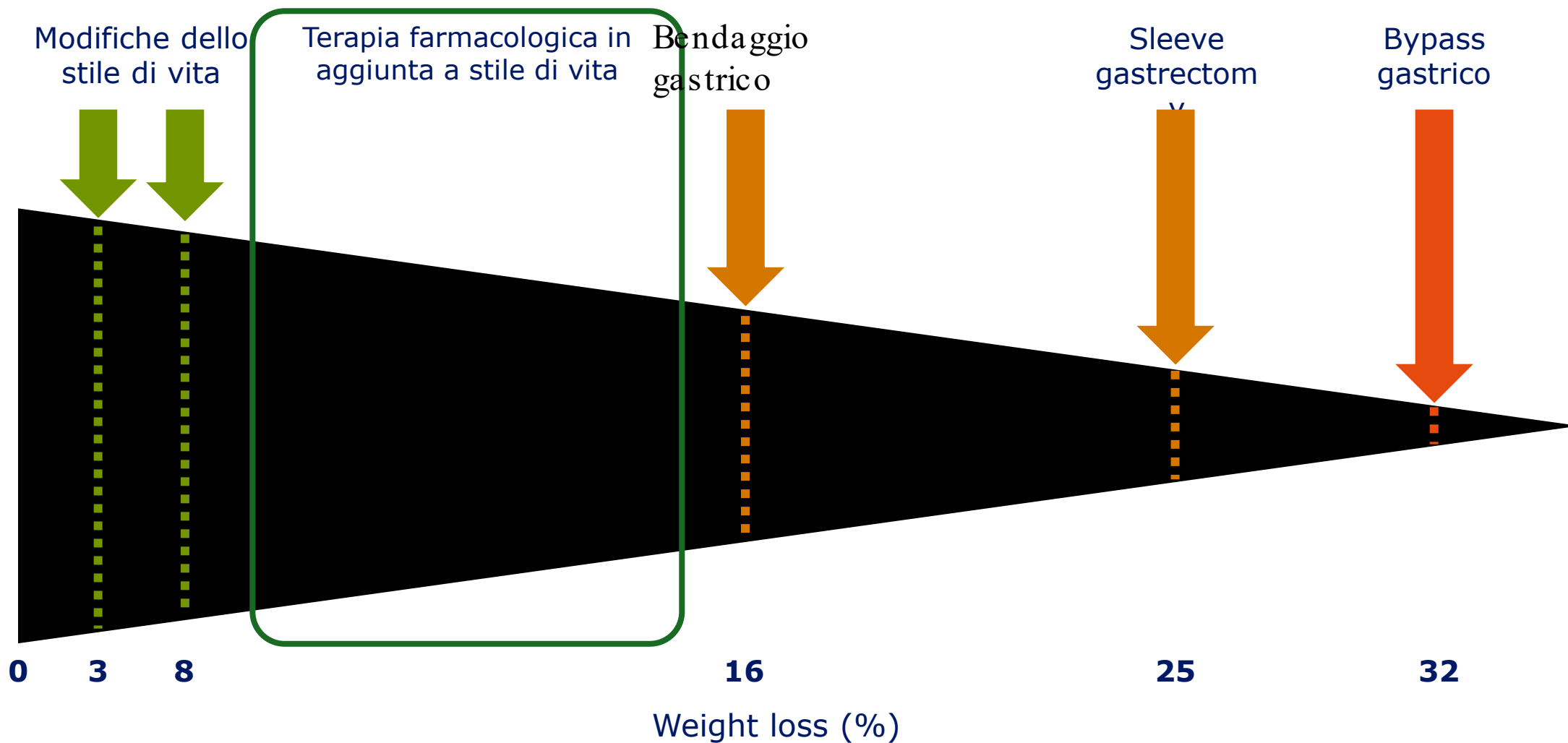


BMI, body mass index.

Long-term weight loss is challenging

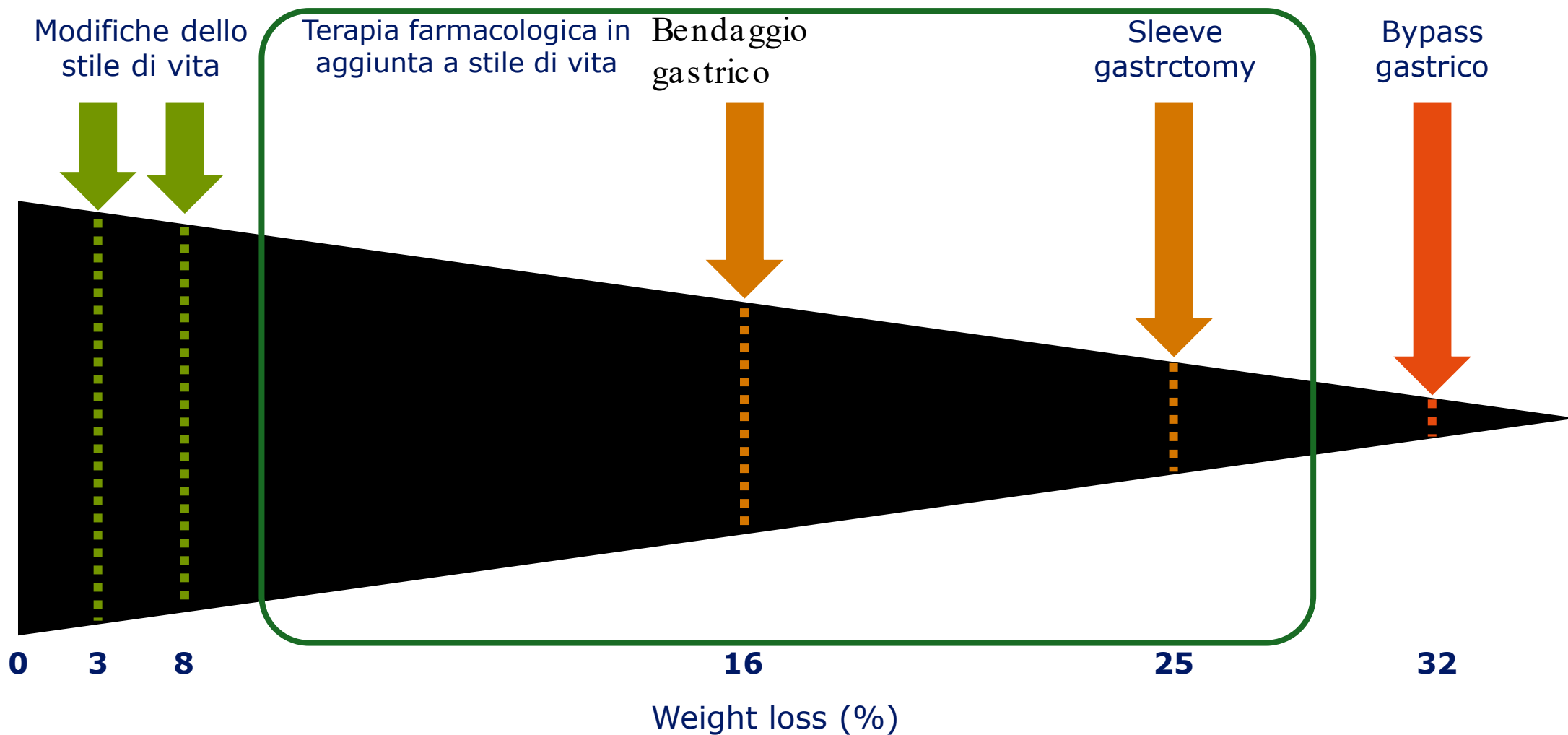


Opzioni di trattamento per pazienti con obesità: target diversi i per livelli di obesità diversi



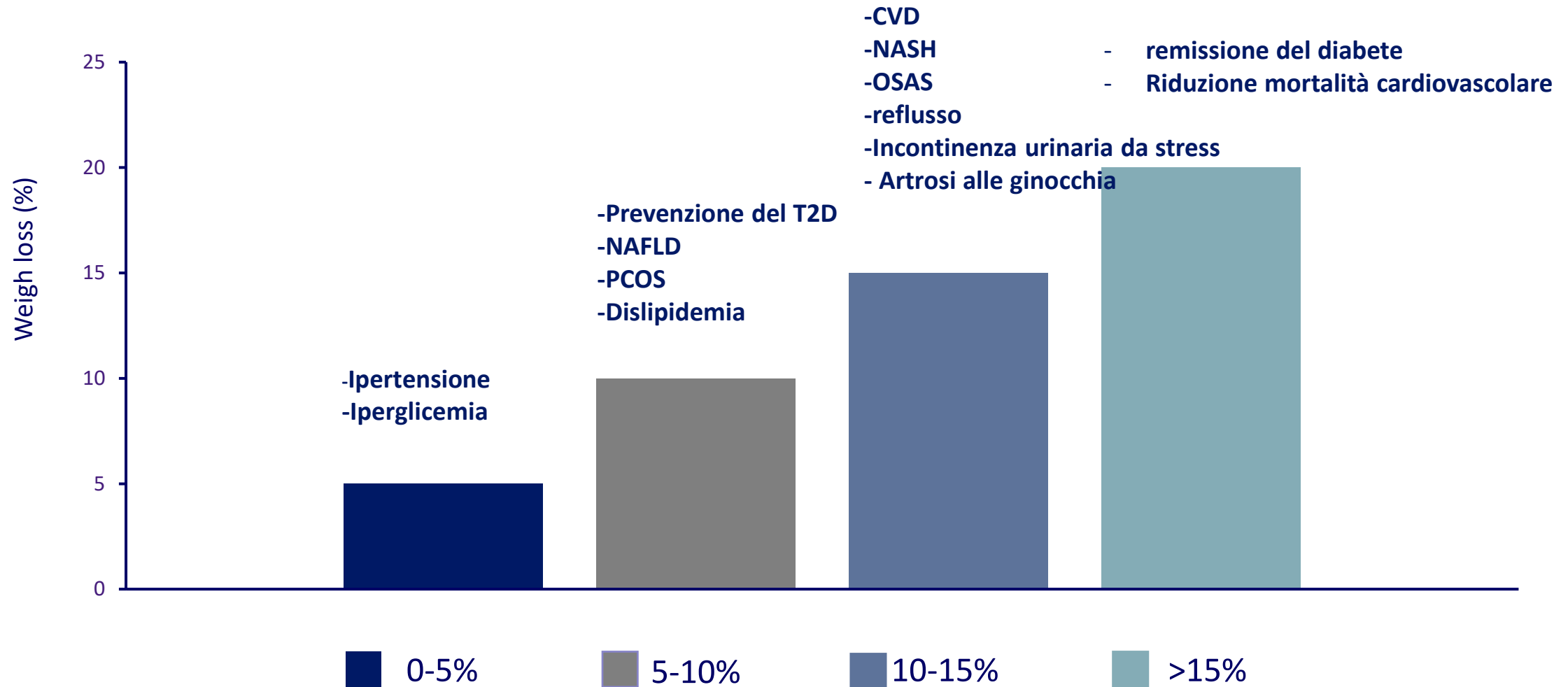
I target devono essere funzionali alle necessità terapeutiche da raggiungere

Opzioni di trattamento per pazienti con obesità: target diversi i per livelli di obesità diversi



I target devono essere funzionali alle necessità terapeutiche da raggiungere

Una perdita maggiore di peso garantisce il raggiungimento di obiettivi terapeutici più ambiziosi ¹⁻⁵

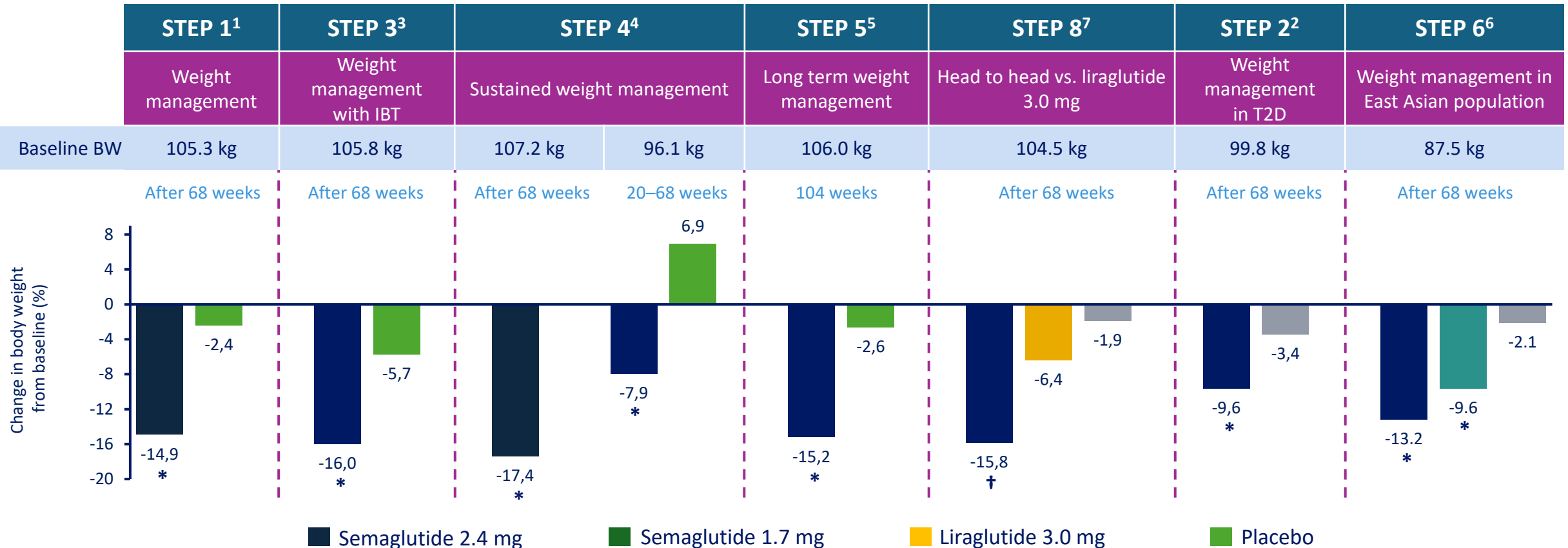


Semaglutide clinical development programme for weight management

STEP summaries

Weight loss across STEP trials

Semaglutide 2.4 mg once-weekly in participants with overweight or obesity



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

*Statistically significant vs. placebo. † Statistically significant vs. liraglutide 3.0 mg
 BW, body weight; IBT, intensive behavioural therapy.
 1. Wilding et al. *N Engl J Med* 2021; doi:10.1056/NEJMoa2032183; 2. Davies et al. *Lancet*, 2021; doi.org/10.1016/S0140-6736(21)00213-0; 3. Wadden et al. *JAMA*. doi:10.1001/jama.2021.1831; 4. Rubino et al. *JAMA*. 2021 Apr 13;325(14):1414-1425. doi: 10.1001/jama.2021.3224.
 5. Garvey et al. *Nat Med* 28, 2083–2091 (2022); 6. Kadowaki et al. *The Lancet Diabetes & Endocrinology* 2022; 7. Rubino et al. *JAMA* 2022; 327(2): 138-150

Semaglutide 2.4 mg effect modifiers with respect to weight loss in the STEP programme



Efficacy was demonstrated regardless of age, sex, race, ethnicity, baseline body weight and BMI, presence of type 2 diabetes, and level of renal function.



Mean weight loss was greater in subgroups of women, people without type 2 diabetes and people with a lower versus higher baseline body weight.



Extensive work has been done on STEP data to identify other baseline variables that affect weight loss, but no clear indications of other effect modifiers of weight loss have been identified.



Individual weight loss varied within all subgroups.



Future biomarker analysis from the STEP biobank will be conducted to explore effect modifiers in obesity

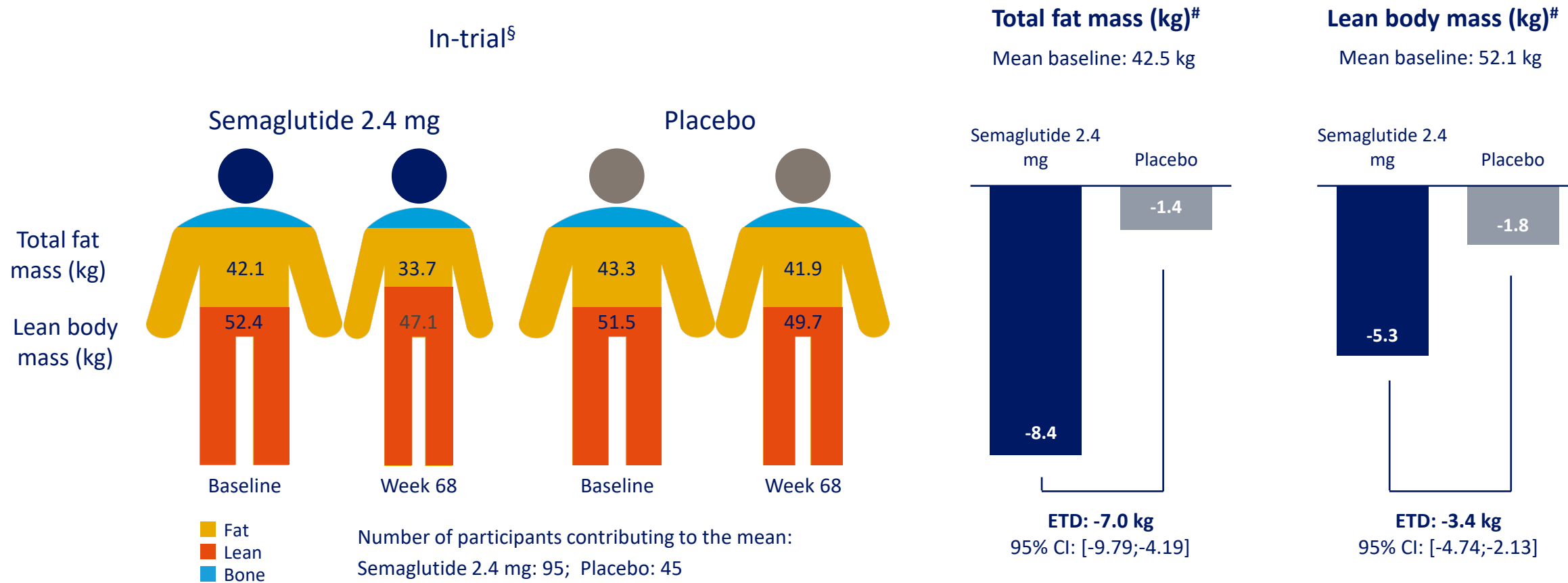
The following documentation is available in the public domain:

FDA summary basis of approval on subgroups:

- Clinical Pharmacology [Review \(fda.gov\)](#) Check pages: 31 – 33
- Statistical review: [Review \(fda.gov\)](#) Check pages 34 - 39

Change in body composition (DXA)

STEP 1



[§] Observed data for the in-trial period; [#] Estimated data for the treatment policy estimand.
CI, confidence interval; DXA, dual energy x-ray absorptiometry; ETD, estimated treatment difference.
Wilding et al. presented at the Endocrine Society (ENDO) virtual meeting, March 20-23, 2021.

Key baseline characteristics

STEP 1–5

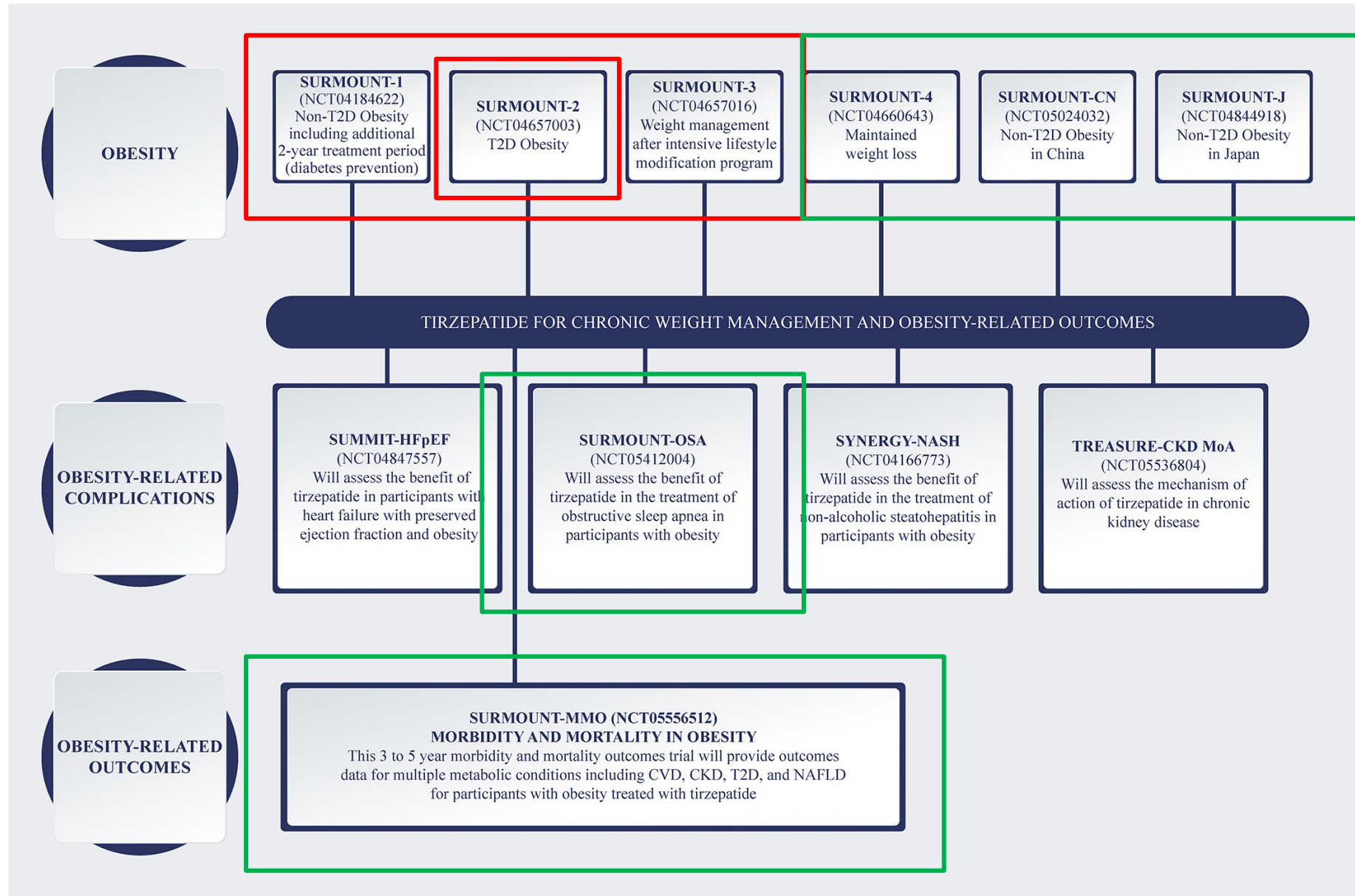
	STEP 1 WM (N=1,961)	STEP 2 WM in T2D (N=1,210)	STEP 3 WM with IBT (N=611)	STEP 4 Sustained WM (N=902)	STEP 5 Long-term WM (N=304)
Sex, female, n (%)	1,453 (74.1)	616 (50.9)	495 (81.0)	717 (79.5)	236 (77.6)
Age, years	46.5 (12.7)	55.3 (10.6)	46.2 (12.7)	46.4 (11.9)	47.3 (11.0)
BMI, kg/m ²	37.9 (6.7)	35.7 (6.3)	38.0 (6.7)	38.3 (7.0)	38.5 (6.9)
Waist circumference, cm	114.7 (14.7)	114.6 (14.1)	113.0 (15.5)	115.1 (15.6)	115.7 (14.8)
HbA _{1c} %	5.7 (0.32)	8.1 (0.8)	5.7 (0.3)	5.7 (0.3)	5.7 (0.3)
Diabetes duration, years	N/A	8.6 (6.2)	N/A	N/A	N/A
Systolic blood pressure, mmHg	126.5 (14.3)	130.0 (13.5)	124.4 (14.8)	126.4 (14.3)	125.5 (14.5)
FPG, mmol/L	5.3 (0.6)	8.6 (2.2)	5.2 (0.5)	5.4 (0.6)	5.3 (0.6)

Key baseline characteristics

STEP 6-8

	STEP 6 WM in Japanese and Koreans (N=401)	STEP 7 WM in predominantly Asians (N=375)	STEP 8 WM effect v/s lira 3.0 mg (N=338)
Sex, female, n (%)	148 (37)	170 (45.3)	265 (78.4)
Age, years	51 (11)	41	49
BMI, kg/m ²	31.9 (4.3)	34	37.5
Waist circumference, cm	103.2 (10.7)	108	113.3
HbA _{1c} , %	6.4 (1.2)	8.0	5.5
Diabetes duration, years	N/A	N/A	N/A
Systolic blood pressure, mmHg	134 (14)	127.0	N/A
FPG, mmol/L	6.2 (1.5)	N/A	N/A

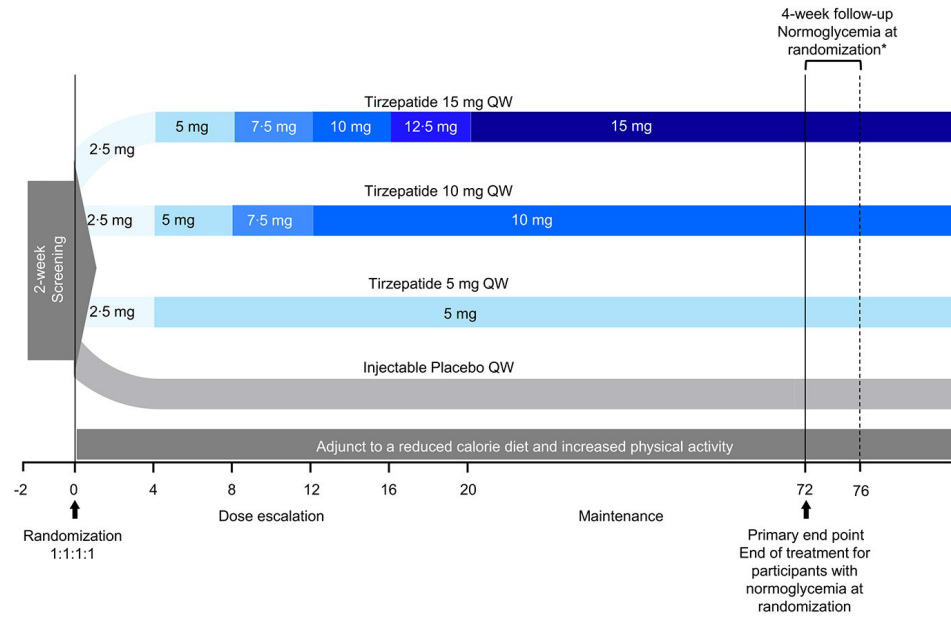
SURMONT Programme



SURMONT 1-3 Study design

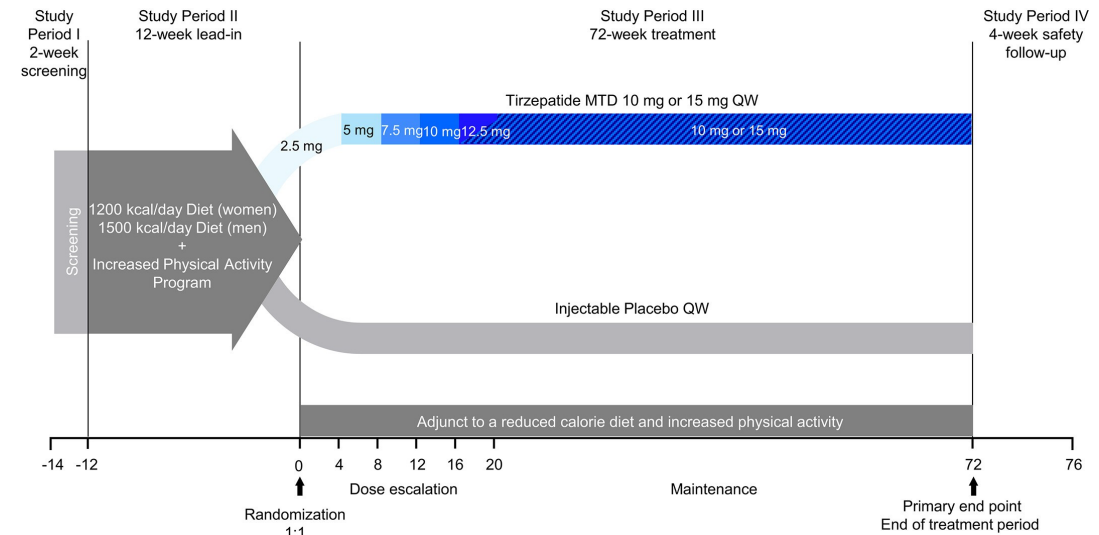
SURMONT 1 Obese no T2D

N=2,539



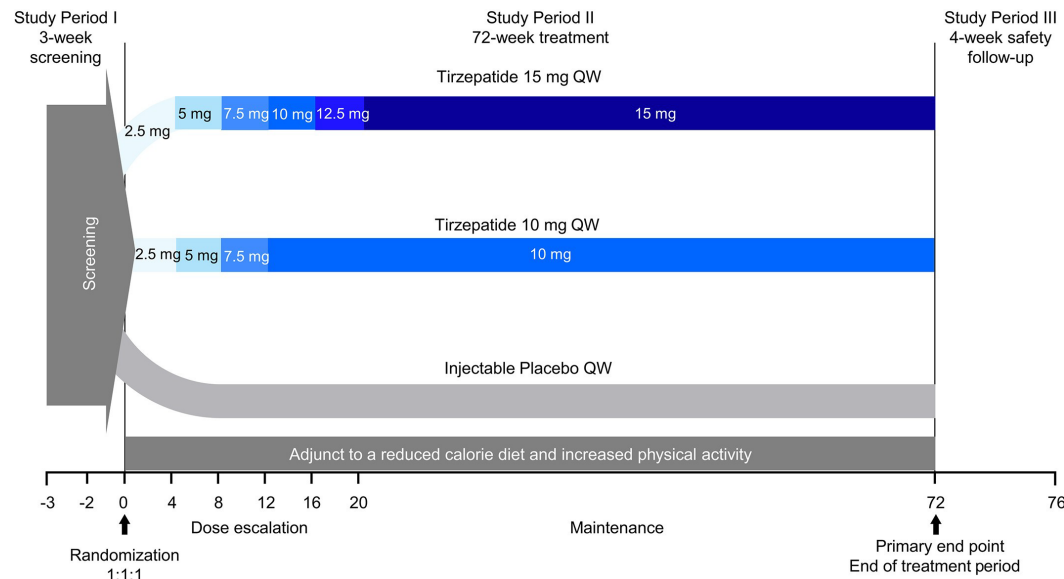
SURMONT-3 Obese no T2D

N=579

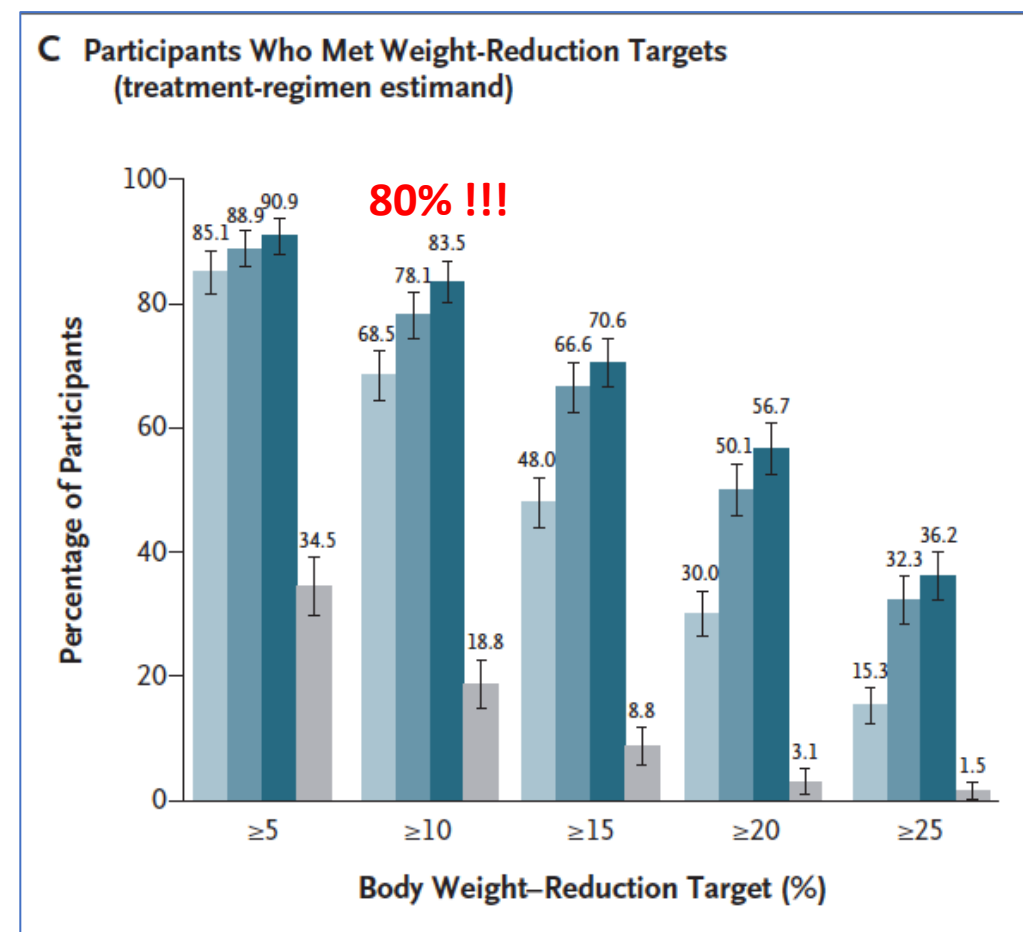
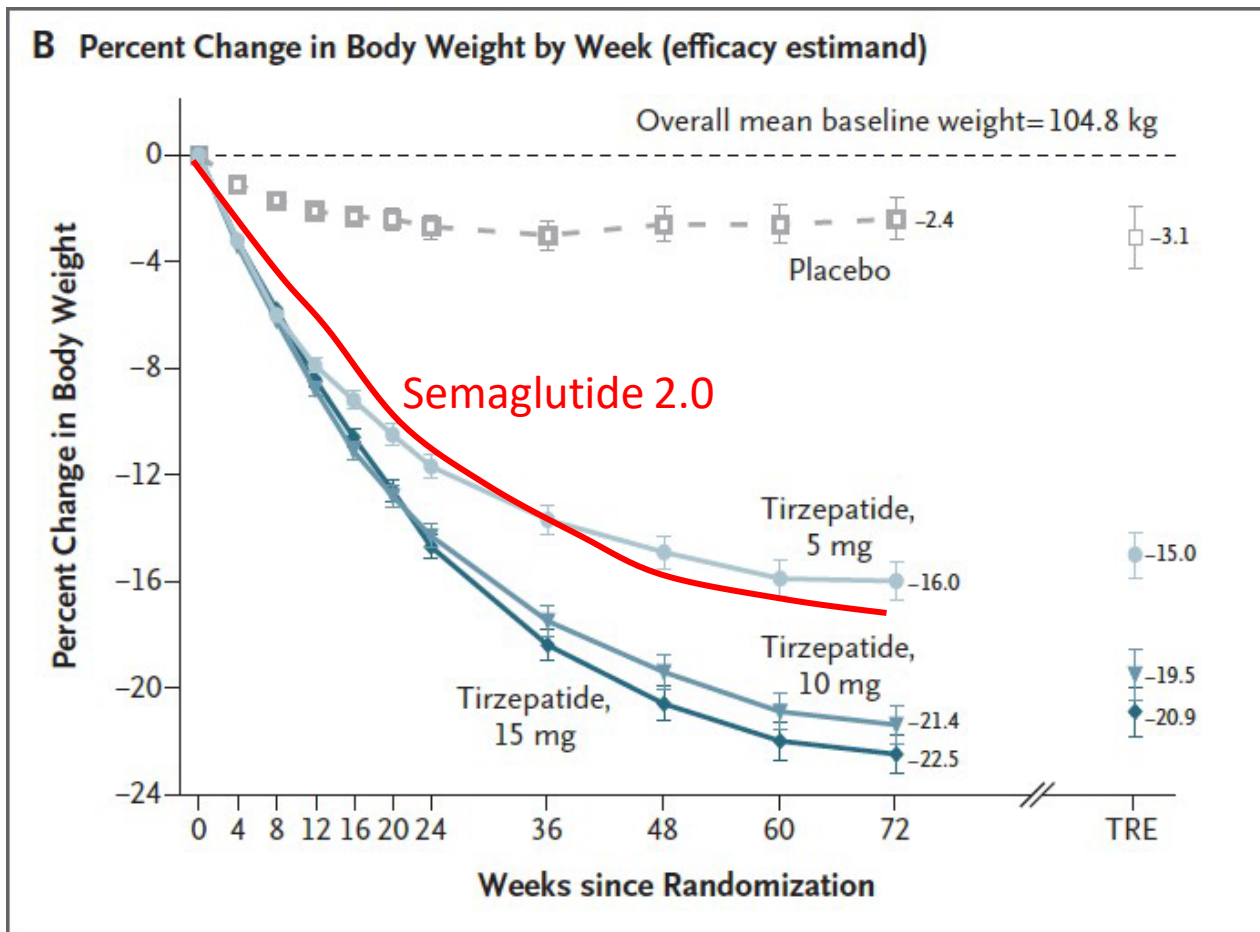


SURMONT-2 Obese T2D

N=938



SURMONT-1 - Results



Physical function score: Doubled

PAS: - 6 mmHg
 TH: -20 mg/dl
 HDL: +9 mg/dl

Discontinuation for GI AE: 6 %

Jastreboff AM *NEJM* 2022

SURMONT-2 - Results

BMI: ≥ 27 kg/m²
 HbA1c: 7-10%

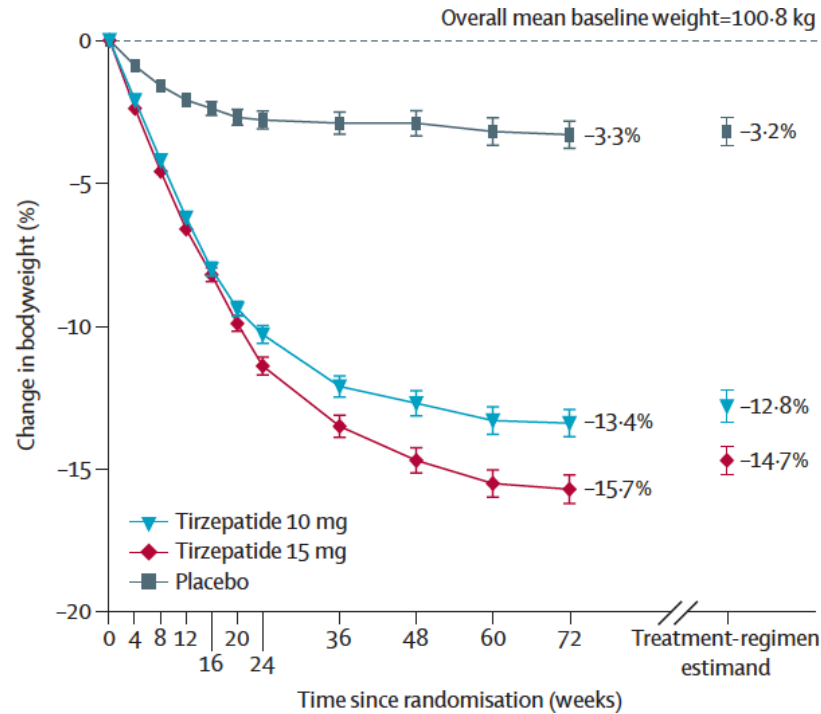
AGE: 55+/-10 yrs
 Female: 50 %
 BMI: 36+/-6 kg/m²
 HbA1c 8+/-1 %

Treatment

Diet only 6 %
 MonoT 55%
 2 drugs 32%
 3 drugs 7%

Metf. 90 %
 SU 20 %
 SGLT-2 20%
 Other 5 %

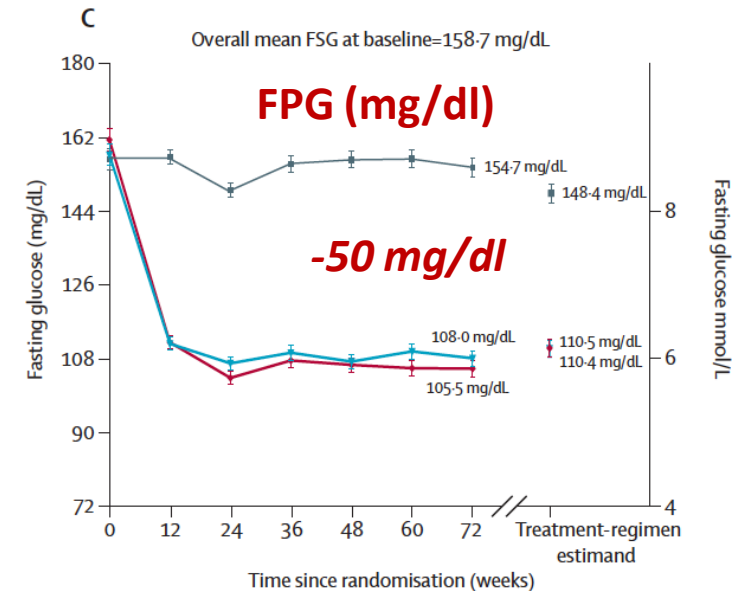
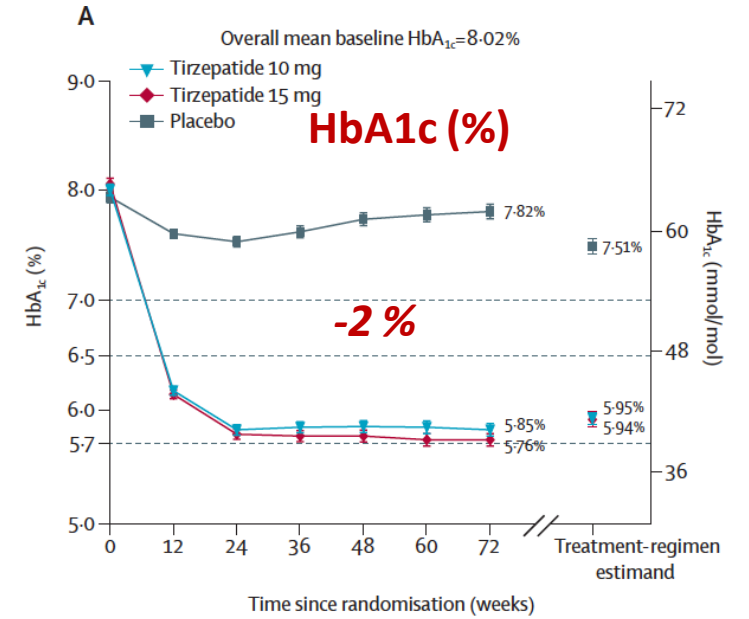
Body weight loss (%)



Discontinuation for GI AE

TIRZ 10: 4 %

TIRZ 15: 7 %



SURMONT-2 (7 points PG profile)

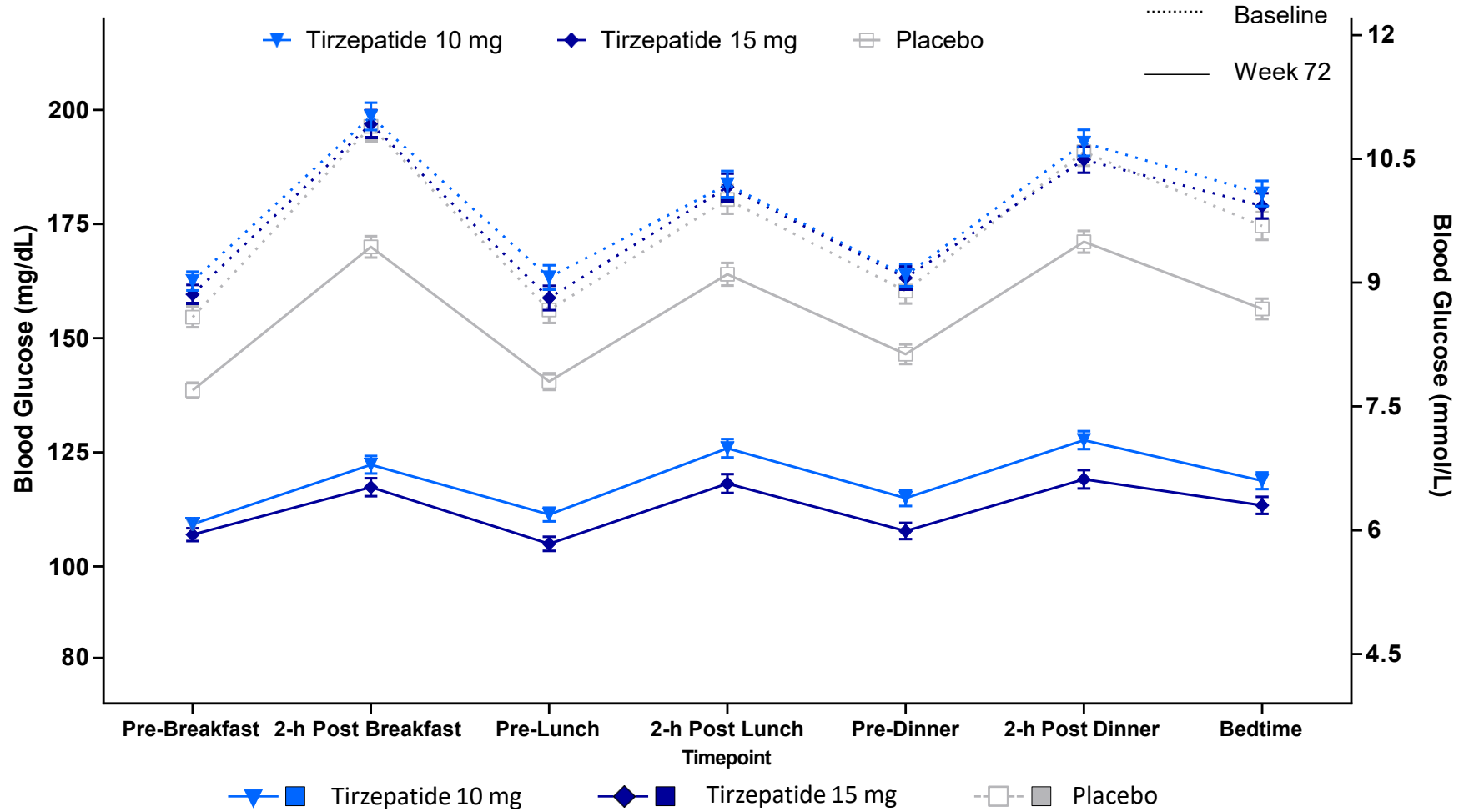
BMI: ≥ 27 kg/m²
HbA1c: 7-10%

AGE: 55+/-10 yrs
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Treatment

Diet only 6 %
MonoT 55%
2 drugs 32%
3 drugs 7%

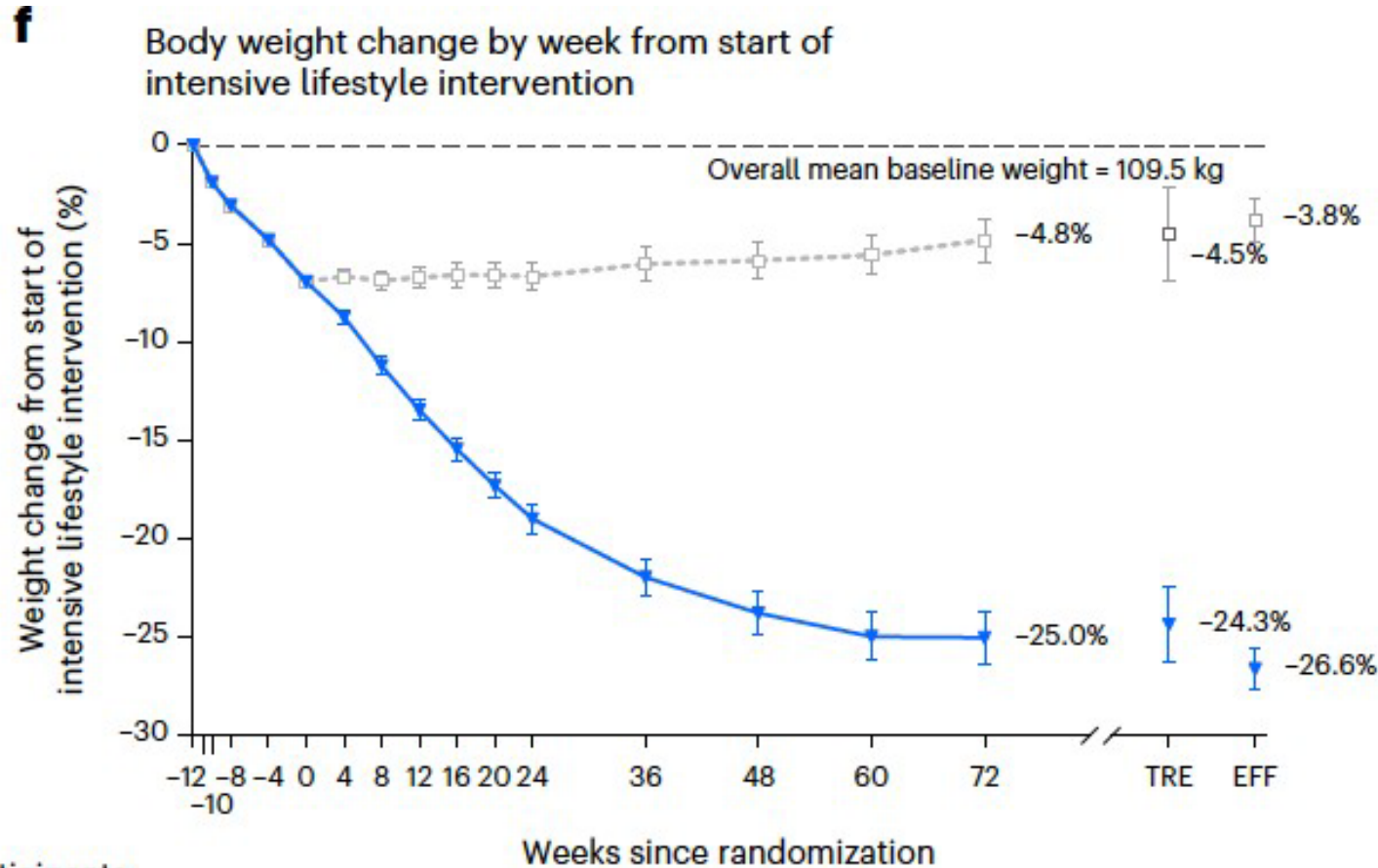
Metf. 90 %
SU 20 %
SGLT-2 20%
Other 5 %



Discontinuation for GI AE **TIRZ 10: 4 %**
TIRZ 15: 7 %

SURMONT-3 (TZP after LS intervention)

Estimated pooled treatments difference



No. of participants

Tirzepatide MTD	287	287	283	279	279	273	266	261	262	287	284
Placebo	292	292	288	268	260	242	228	218	223	292	291

Triglycerides (mg/dl)
-28.0 (-32.3, -23.4)

HDL-C (mg/dl)
11.4 (8.2, 14.7)

SBP (mmHg)
-9.2 (-11.2, -7.2)

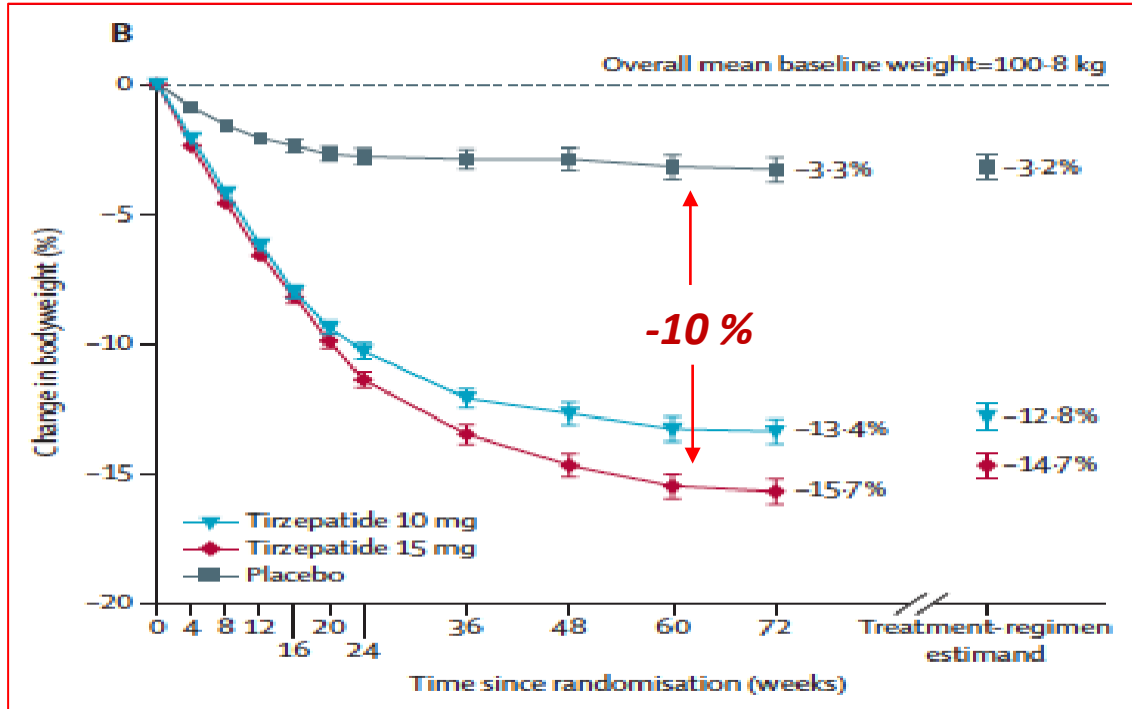
Fast. Glucose (mg/dl)
-11.2 (-13.5, -8.8)

HbA1c (%)
-0.5 (-0.5, -0.4)

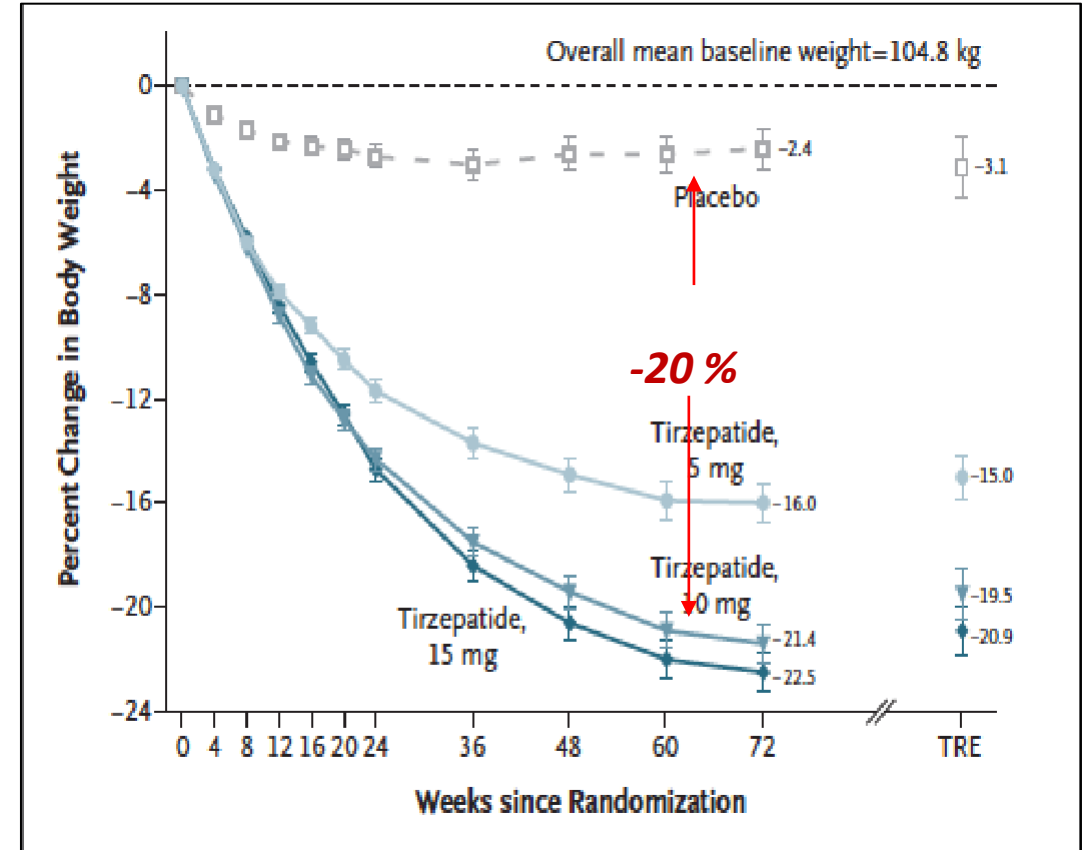
Discontinuation for GI AE: 10 %

In T2D Tirzepatide is less effective on weight loss

SURMONT-2 (T2D, BMI 36)



SURMONT-1 (No T2D, BMI 37)



SURMONT-1 e 2

- Regular lifestyle counseling sessions, delivered by a dietitian or a qualified health care professional**
- Deficit of 500 calories per day**
- At least 150 minutes of PA per week.**

SURMONT-2

To minimise the risk of hypoglycaemia, participants taking sulfonylureas at randomisation had their dose halved (or stopped if already on the lowest dose).

No insulin.

**E' vero che i pazienti con diabete
hanno difficoltà a perdere peso ?**

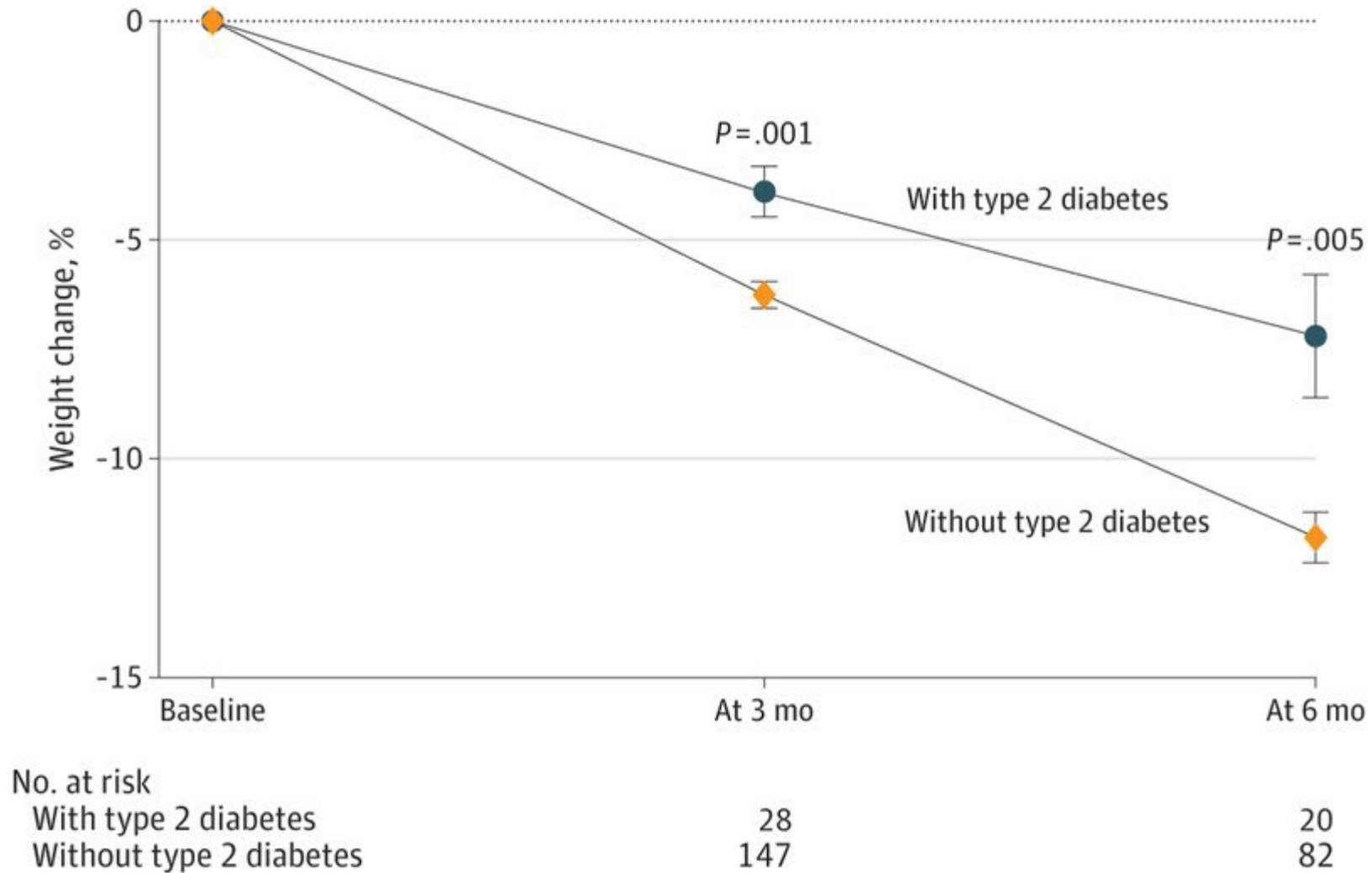
T2D are resistant to WL

Table 1. Weight Change and Effect on A1C From Weight-Loss Interventions in People With Type 2 Diabetes Compared to Weight Change from Similar Interventions in People Without Diabetes

Interventions	Weight Change in Subjects With Type 2 Diabetes (lb)		12-Month A1C Change (%)	12-Month Weight Change in Subjects Without Diabetes (lb)
	6-month	12-month		
Weight-loss diet (n = 532)	-5.3	-5.7	-0.4	-10.1 to -16.7
Orlistat, 120 mg three times a day (n = 574)	-11	-11.2	-0.8	-18
Sibutramine, 15–20 mg (n = 152)	-16.5	-15.8	-0.4	-18
Rimonabant, 20 mg (n = 355)*	-13	-13.2	-0.6	-18.7

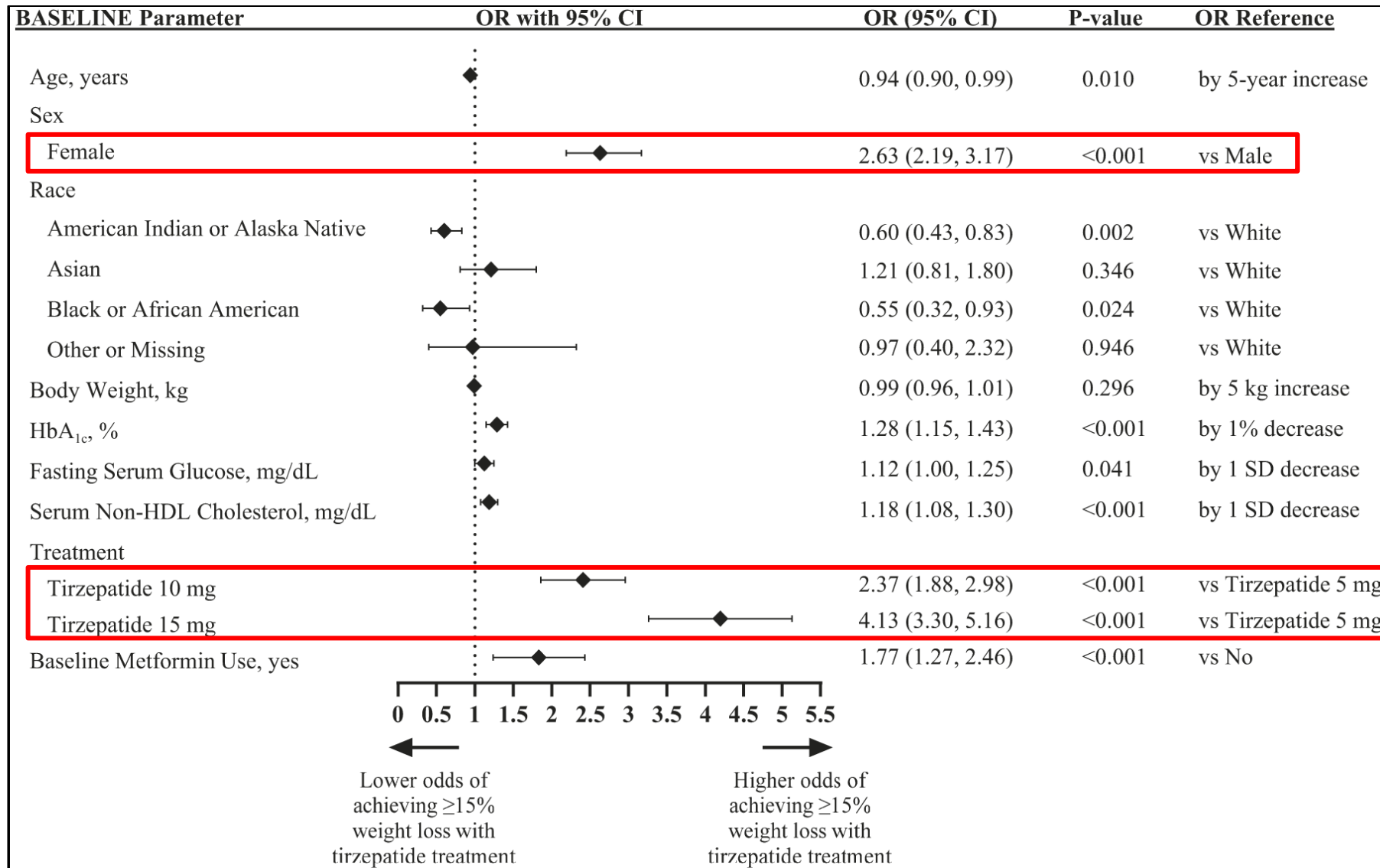
*New drug that blocks endocannabinoid receptors, thus reducing appetite and the brain's craving for flavorful foods and nicotine. Adapted from ref. 16

Real world (Semaglutide)



Perché ?

Predictors of $WL > 15\%$ in T2D (SURPASS 1-4)



Female %

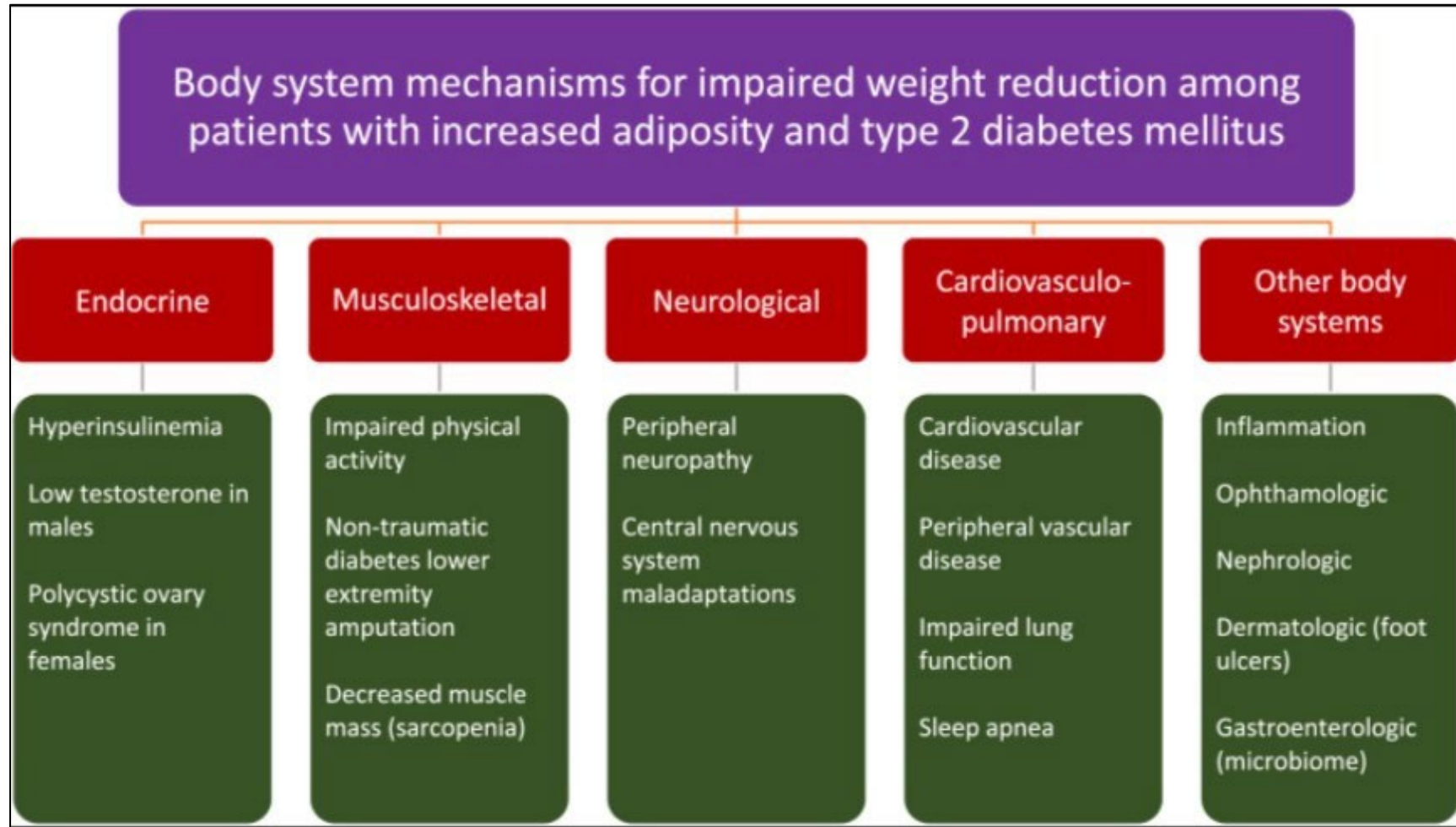
SURMOUNT-1

67%

SURMOUNT-2

51%

Diabete e Resistenza alla perdita di peso



Compliance ?

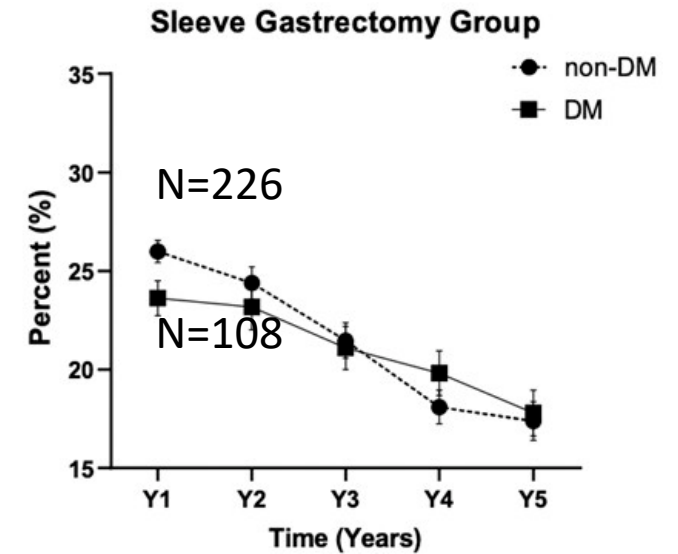
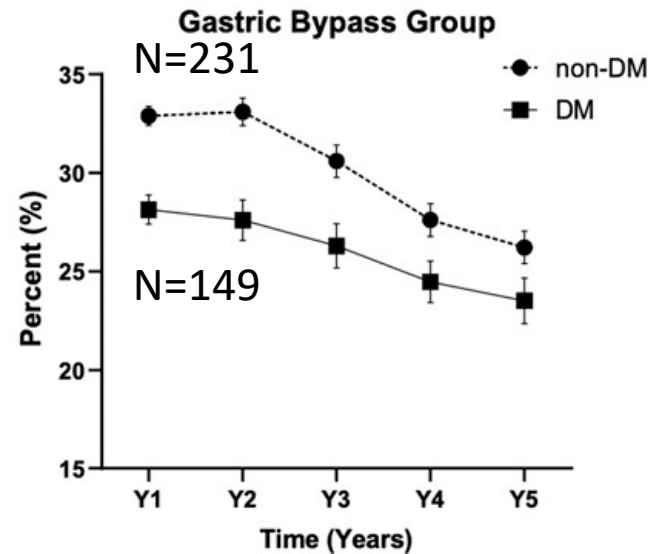
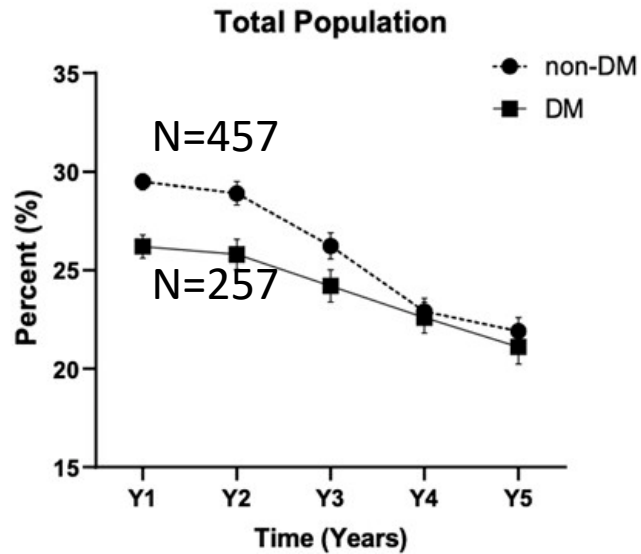
Ho perso peso, ho glicemie ottime quindi finalmente posso mangiare

Bariatric surgery

Michigan Bariatric Surgery Cohort (MI-BASiC)

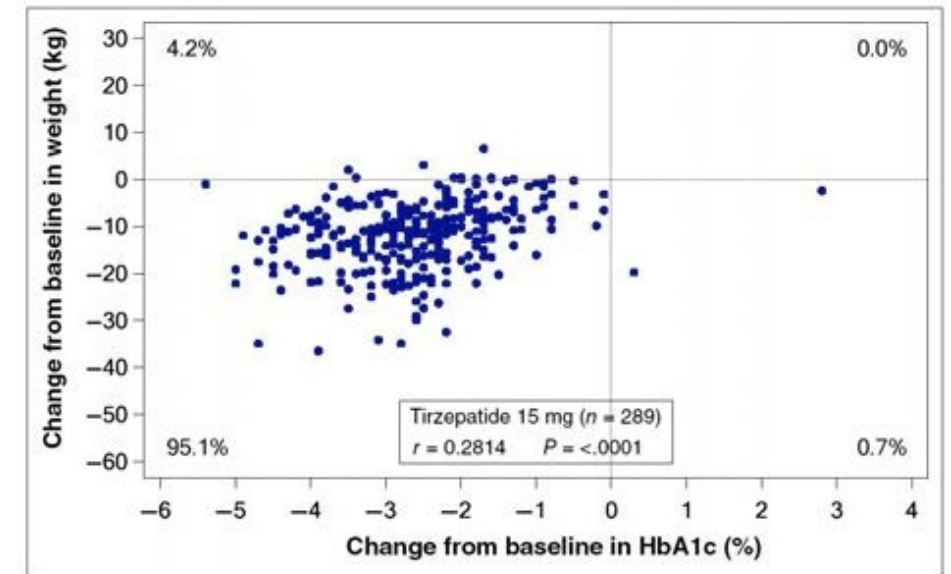
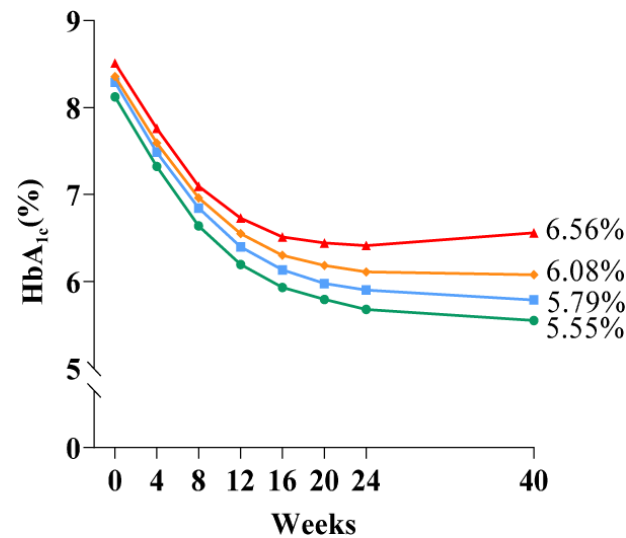
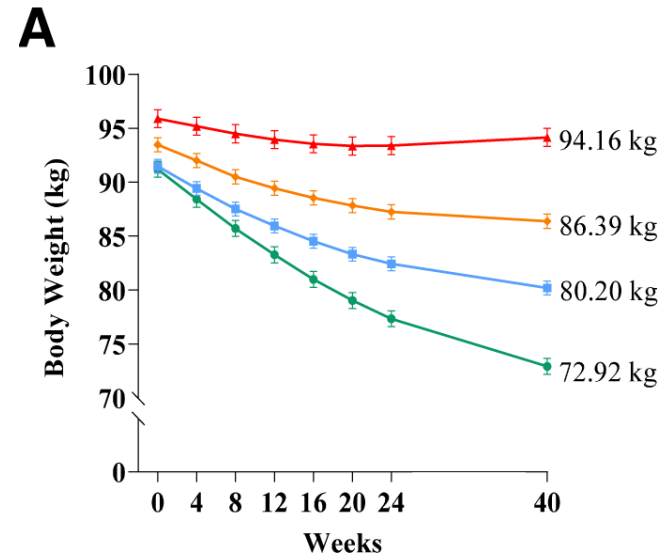
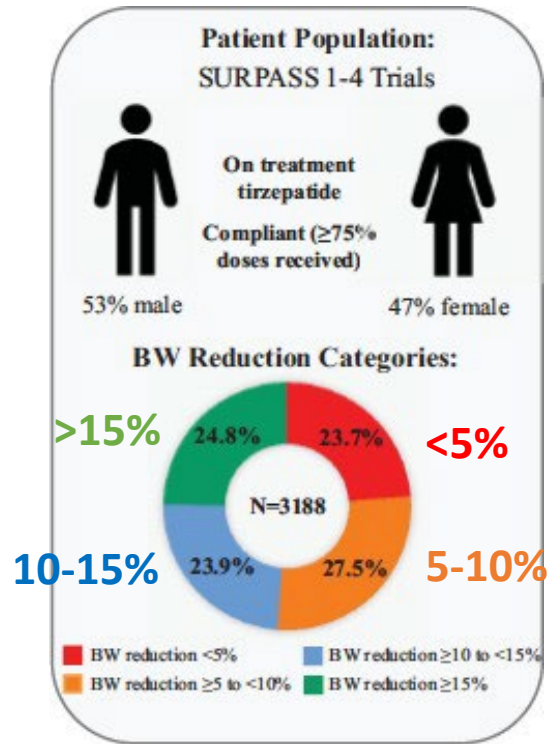
(B)

Percentage of Weight Loss Over 5 Years



Conseguenze ?

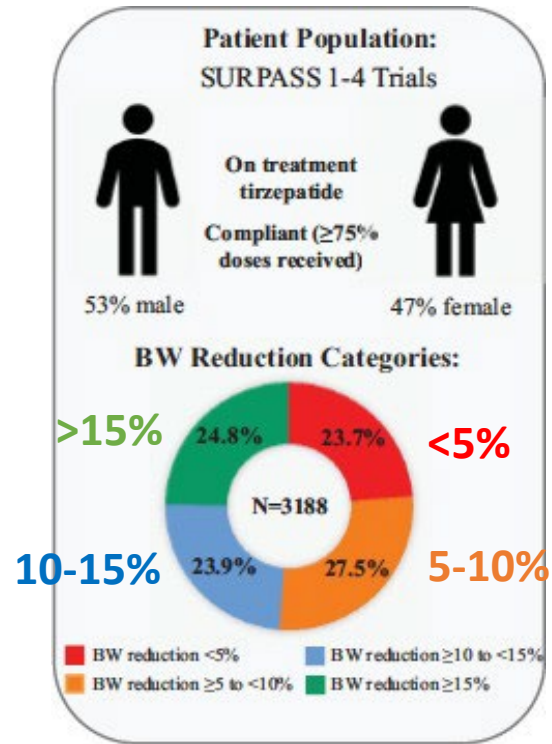
Dissocazione tra HbA1c e FRCV in T2D (SURPASS)



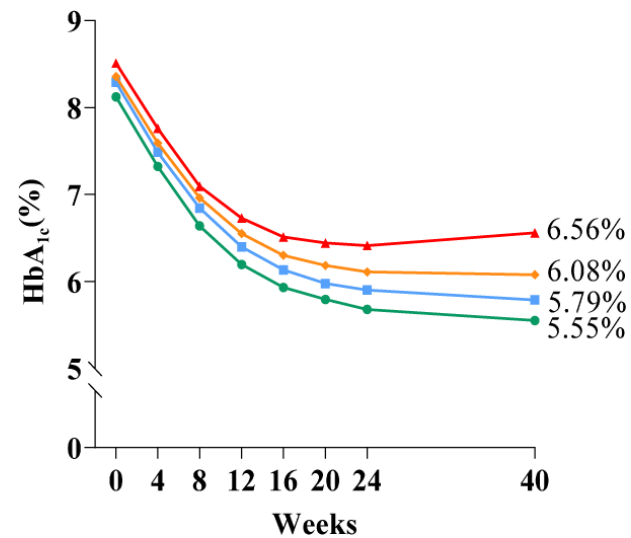
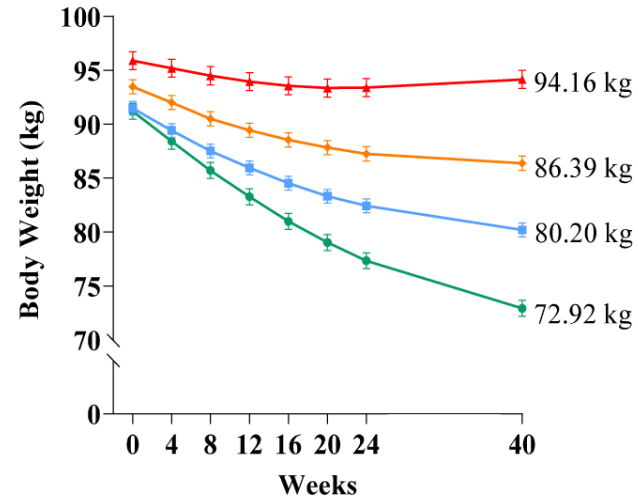
Pedersen SD Diabetes Obes Metab. 2023

Diabetes Care 2023;46:2292–2299

Dissocazione tra HbA1c e FRCV in T2D (SURPASS)



A



Changes in Cardiometabolic Risk Factors by Weight Loss Category:

		Baseline to Week 40/42		
	WC (cm)	1) 111	-2	↓
		2) 109	-6	↓
		3) 109	-9	↓
		4) 109	-15	↓
	SBP (mmHg)	1) 132	-2	↓
		2) 131	-5	↓
		3) 132	-7	↓
		4) 131	-10	↓
	TG (mg/dL)	1) 190	2%	↑
		2) 202	-12%	↓
		3) 185	-18%	↓
		4) 179	-24%	↓
	ALT (IU/L)	1) 30	-4%	↓
		2) 29	-15%	↓
		3) 29	-23%	↓
		4) 28	-22%	↓

Conclusioni

- 1) Tirzepatide è molto efficace nelle 2 malattie**
- 2) I pazienti con diabete di tipo 2 sono resistenti al calo ponderale**
 - Hanno più comorbidità ?
 - Hanno minore compliance ?
- 3) La variabilità del calo ponderale influenza i fattori di rischio CV e, verosimilmente, la qualità di vita, ma non il miglioramento del controllo metabolico (effetto diretto del farmaco sulla β cellula).**

The background features a series of overlapping, wavy, ribbon-like shapes in shades of blue, teal, and purple. These shapes flow across the frame from left to right. The background itself is a smooth gradient, transitioning from a light, almost white color on the left to a dark, muted purple on the right.

Grazie !