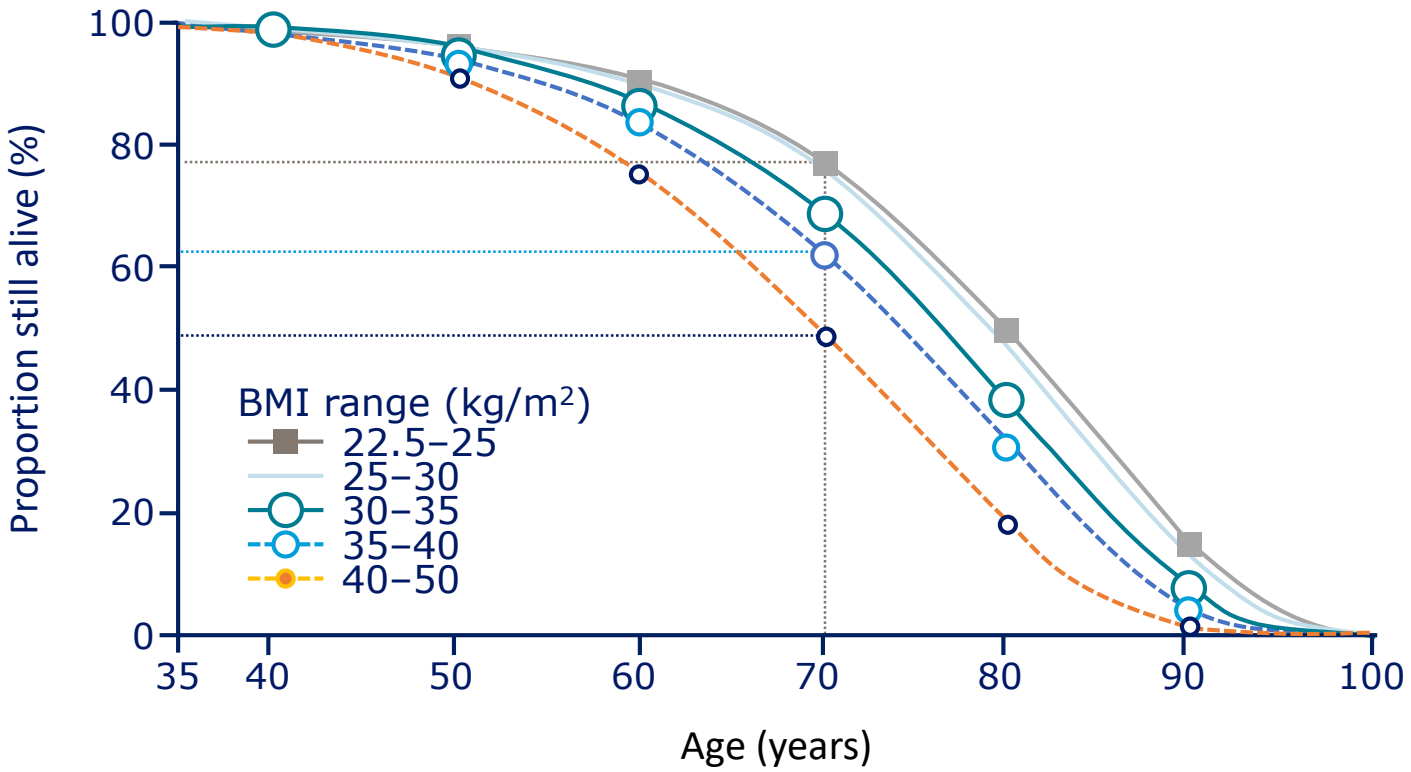
INCRETINE E PROTEZIONE CARDIOVASCOLARE: ULTIME EVIDENZE

Giancarlo Marenzi

Centro Cardiologico Monzino

Life expectancy decreases as BMI increases



Normal BMI =
almost 80% chance
of reaching age 70

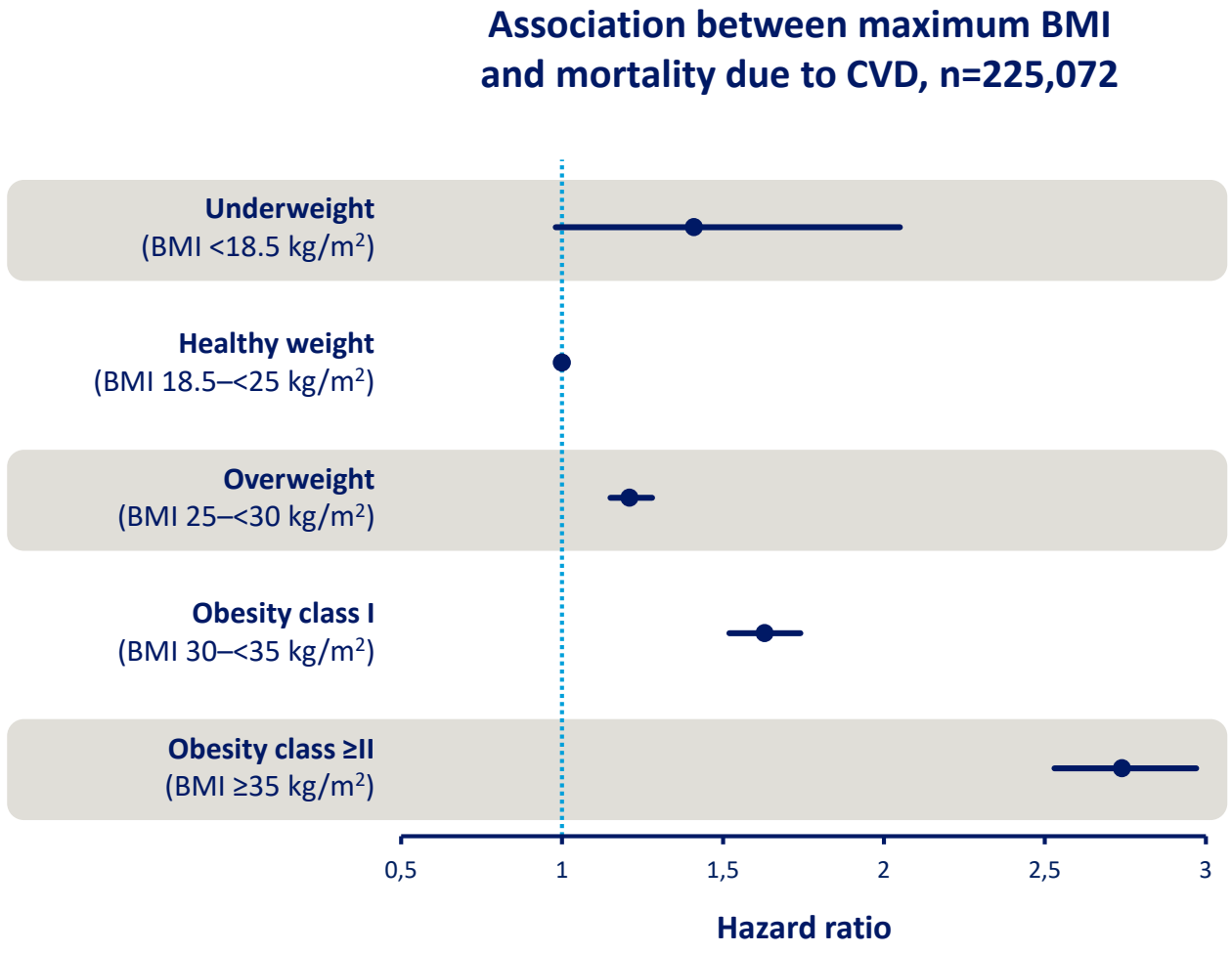
BMI 35–40 =
~60% chance of reaching age 70

BMI 40–50 =
~50% chance of reaching age 70

Data are based on male subjects; n=541,452

Prospective Studies Collaboration. Lancet 2009

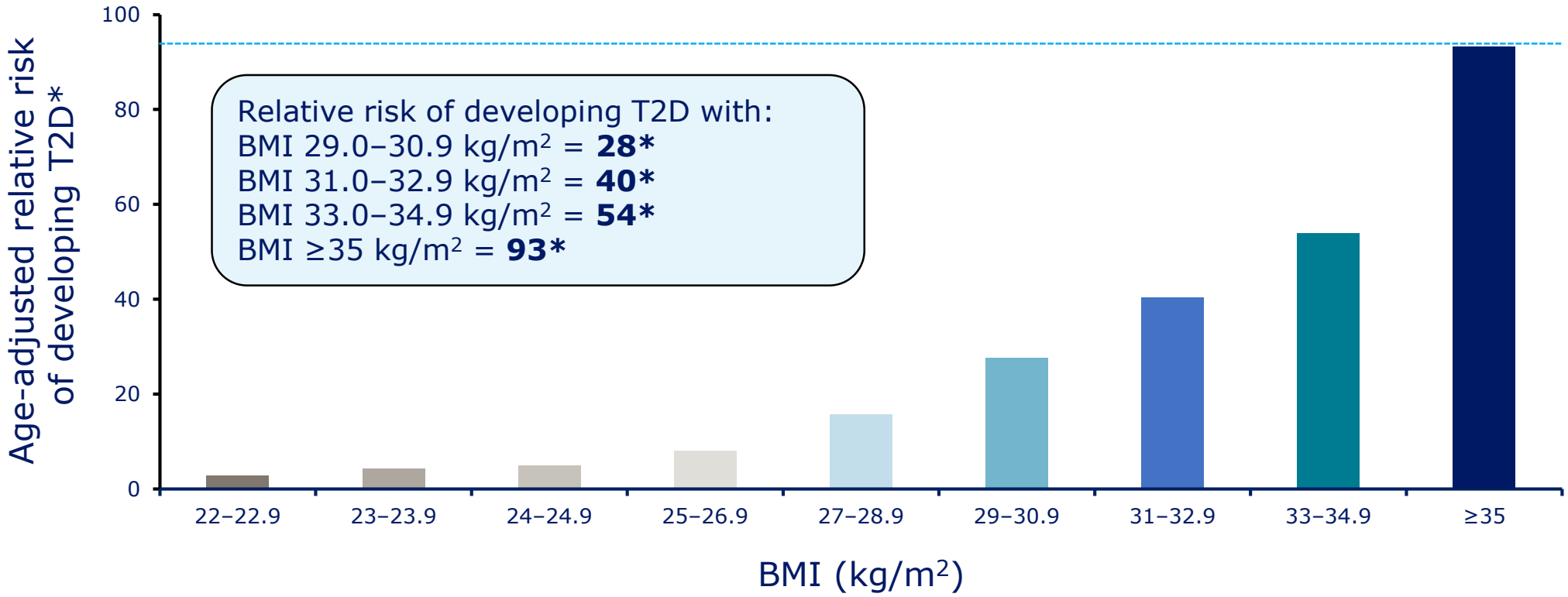
CVD is the primary cause of mortality in obesity



Comparator = healthy weight

Yu et al. Ann Intern Med 2017

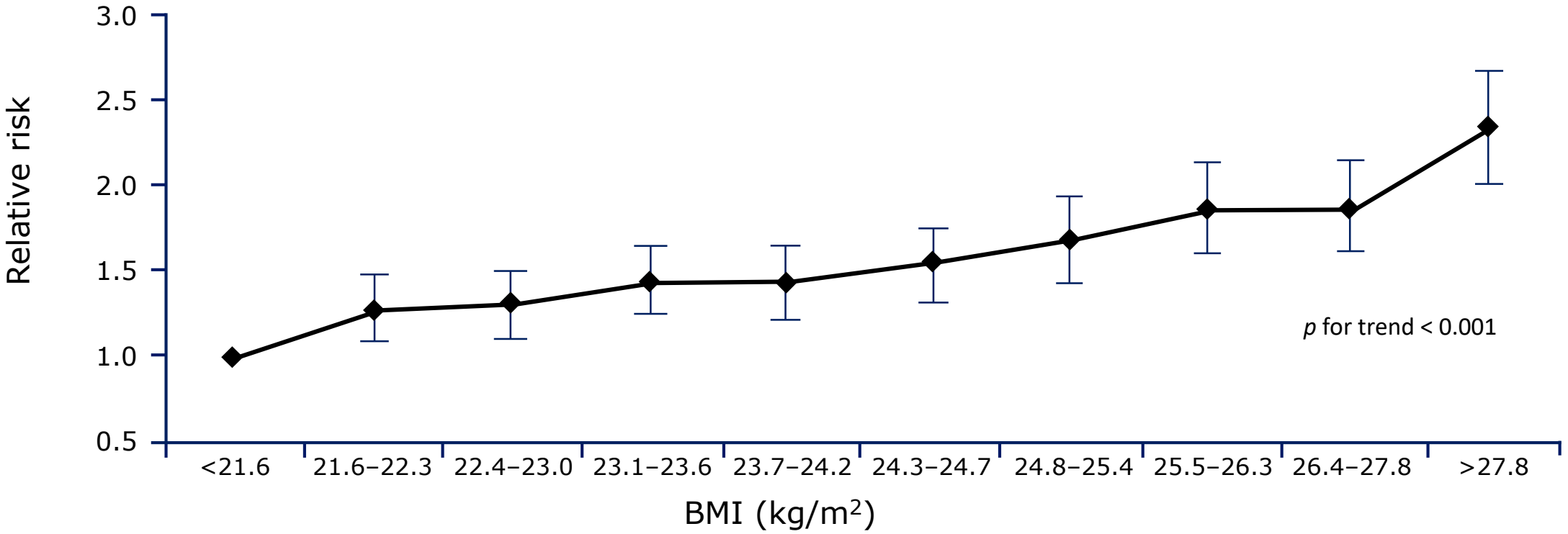
Greater risk of developing T2D with higher BMI



*vs. BMI <22 kg/m²;

Colditz et al. Ann Intern Med 1995

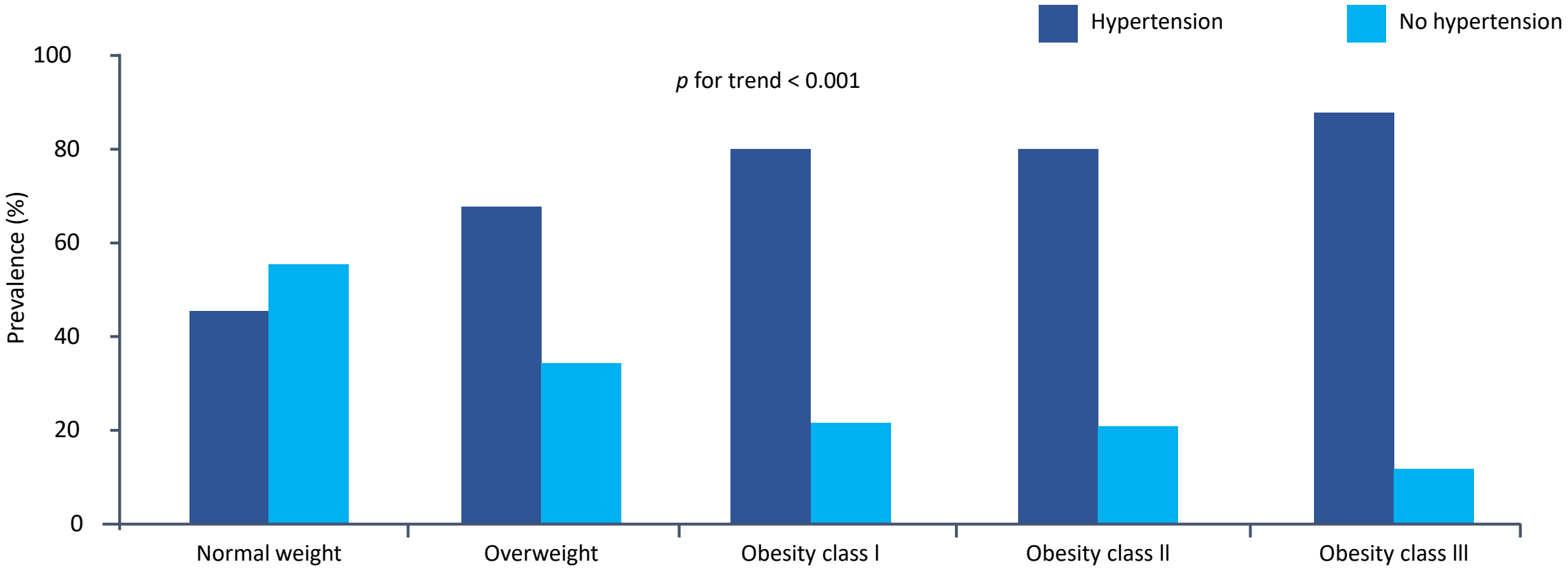
Individuals with high BMI are more likely to develop hypertension than healthy subjects



adjusted for baseline age, cigarette smoking, alcohol intake, exercise, parental history of MI, history of DM and elevated cholesterol

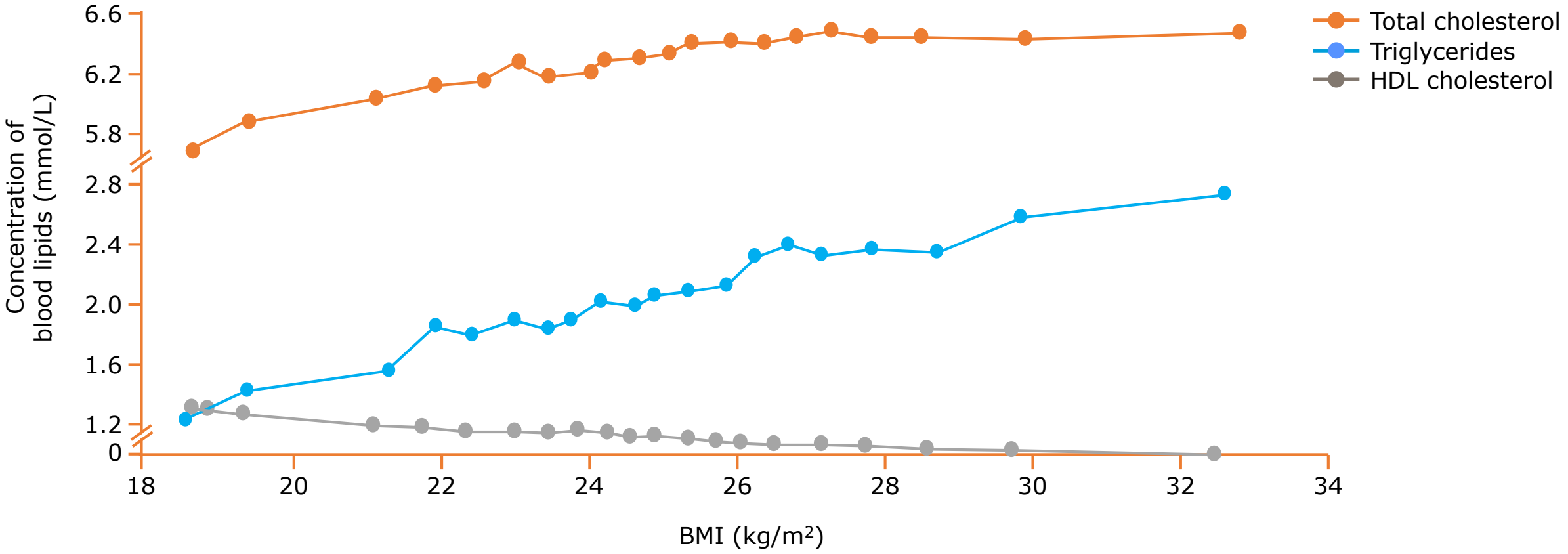
Gelber et al. Am J Hypertens 2007

The prevalence of hypertension increases with increasing BMI



Landi et al. Nutrients 2018

Progressive rise of the total cholesterol and triglycerides with increasing BMI

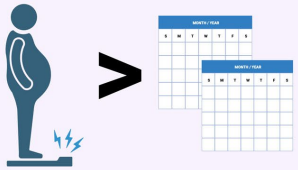


Data are based on UK males aged 40–59 year

James et al. Comparative Quantification of Health Risks. WHO 2004

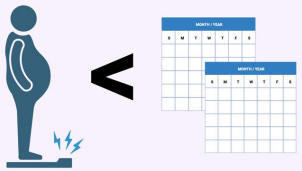
Role of Obesity Duration and Severity in Cardiometabolic Disease Development

Hypertension



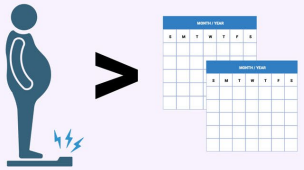
Evidence suggests that **obesity severity** has a greater influence than obesity duration

Type 2 Diabetes Mellitus



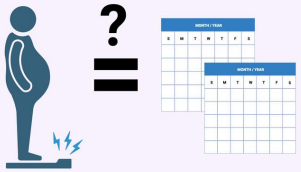
Evidence suggests that **obesity duration** has a greater influence than obesity severity

Dyslipidemia



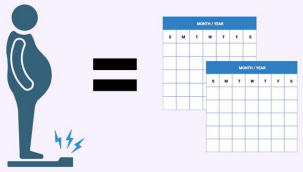
Evidence suggests that **obesity severity** has a greater influence than obesity duration

Cardiovascular/ All-Cause Mortality, Cardiomyopathy



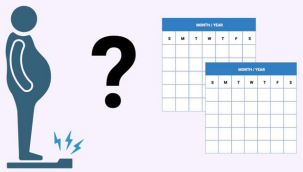
Obesity duration and obesity severity both important, but not fully explored

ASCVD



Obesity severity and obesity duration both important

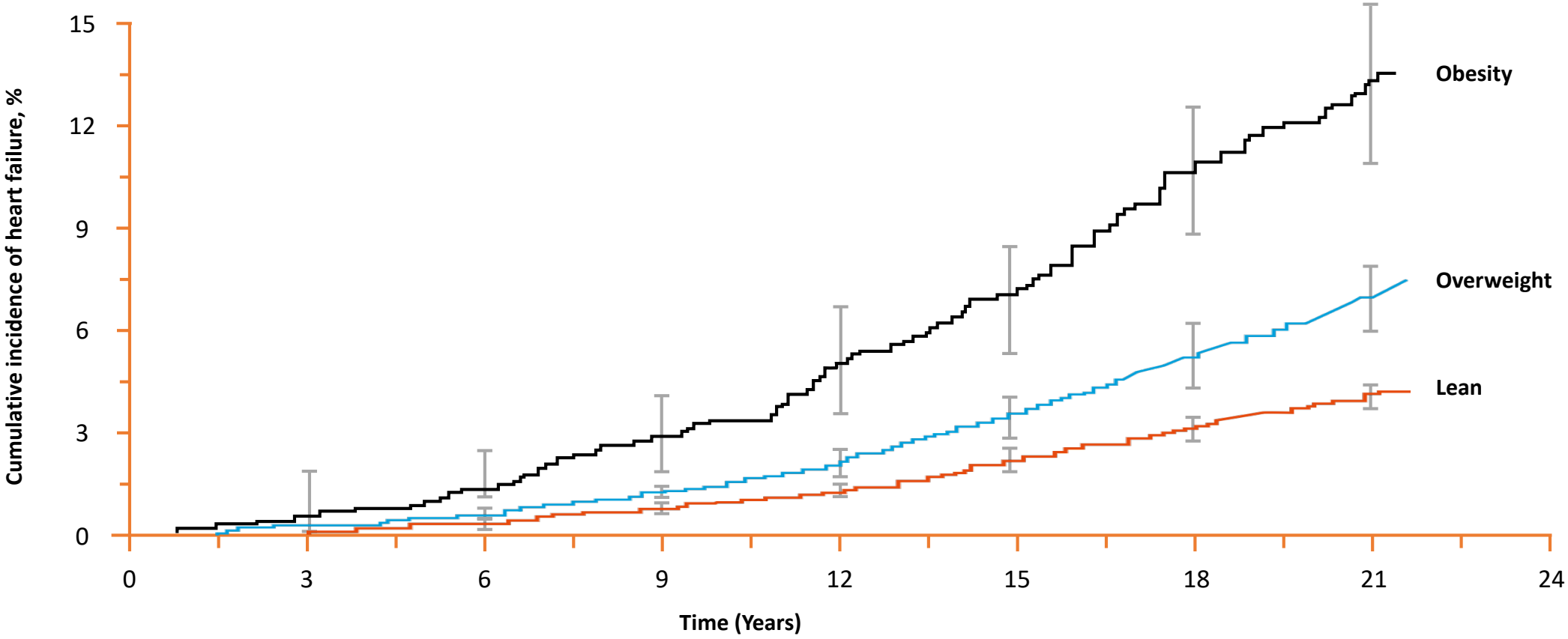
Calcific Aortic Stenosis



No study has examined the impact of obesity duration

Sharnendra K et al. ATVB 2023

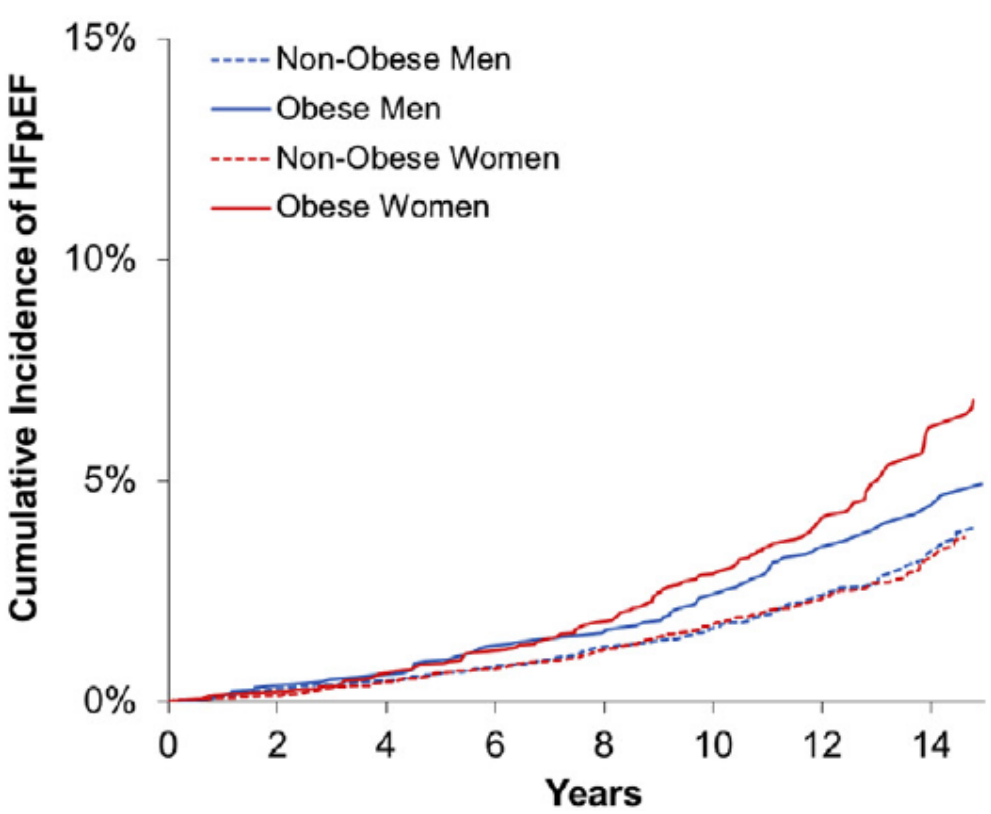
Incidence of Heart Failure over time according to body weight

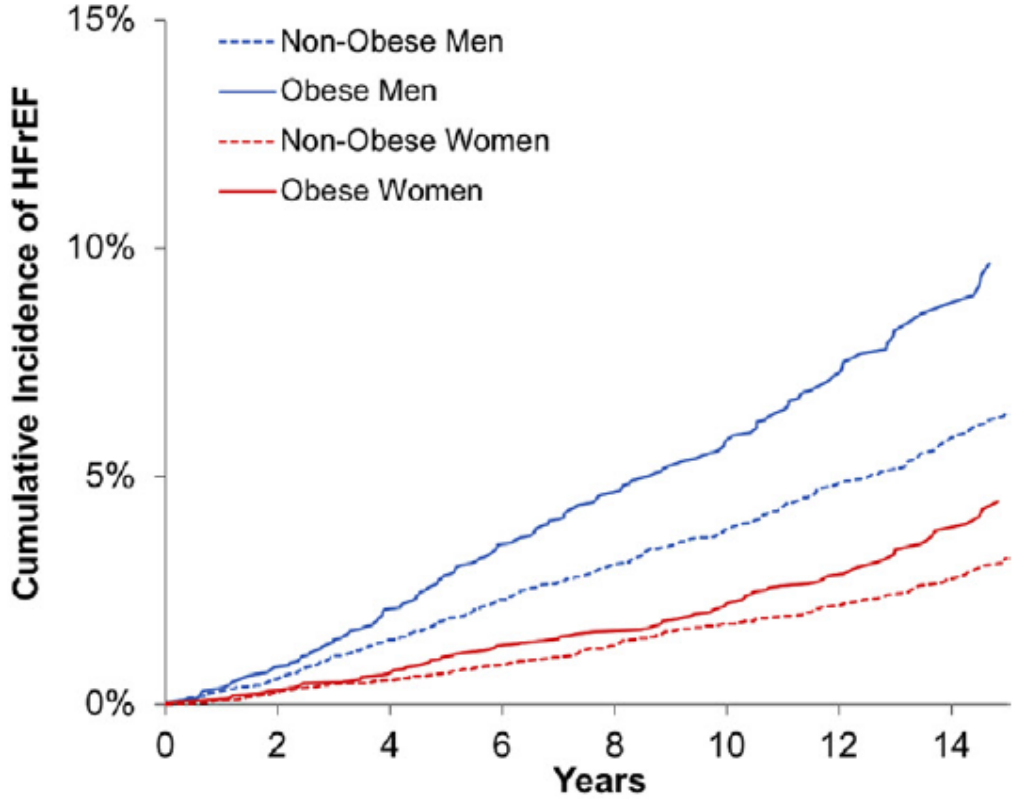


This study was done in a prospective cohort of 21,094 men (mean age, 53 years) without known coronary heart disease at baseline in the Physicians' Health Study

Kenchaiah et al. Circulation 2009

The Association of Obesity and Cardiometabolic Traits With Incident HFpEF and HFrEF

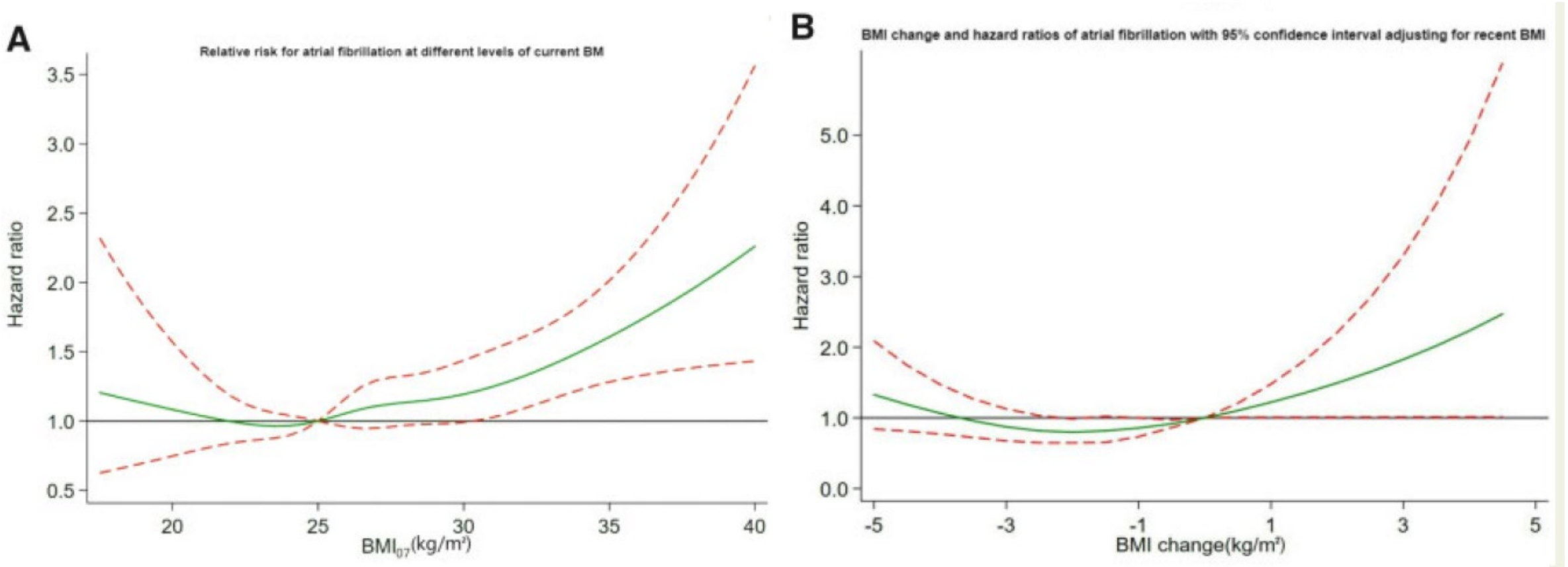




Savji N et al. JACC: Heart Fail 2018

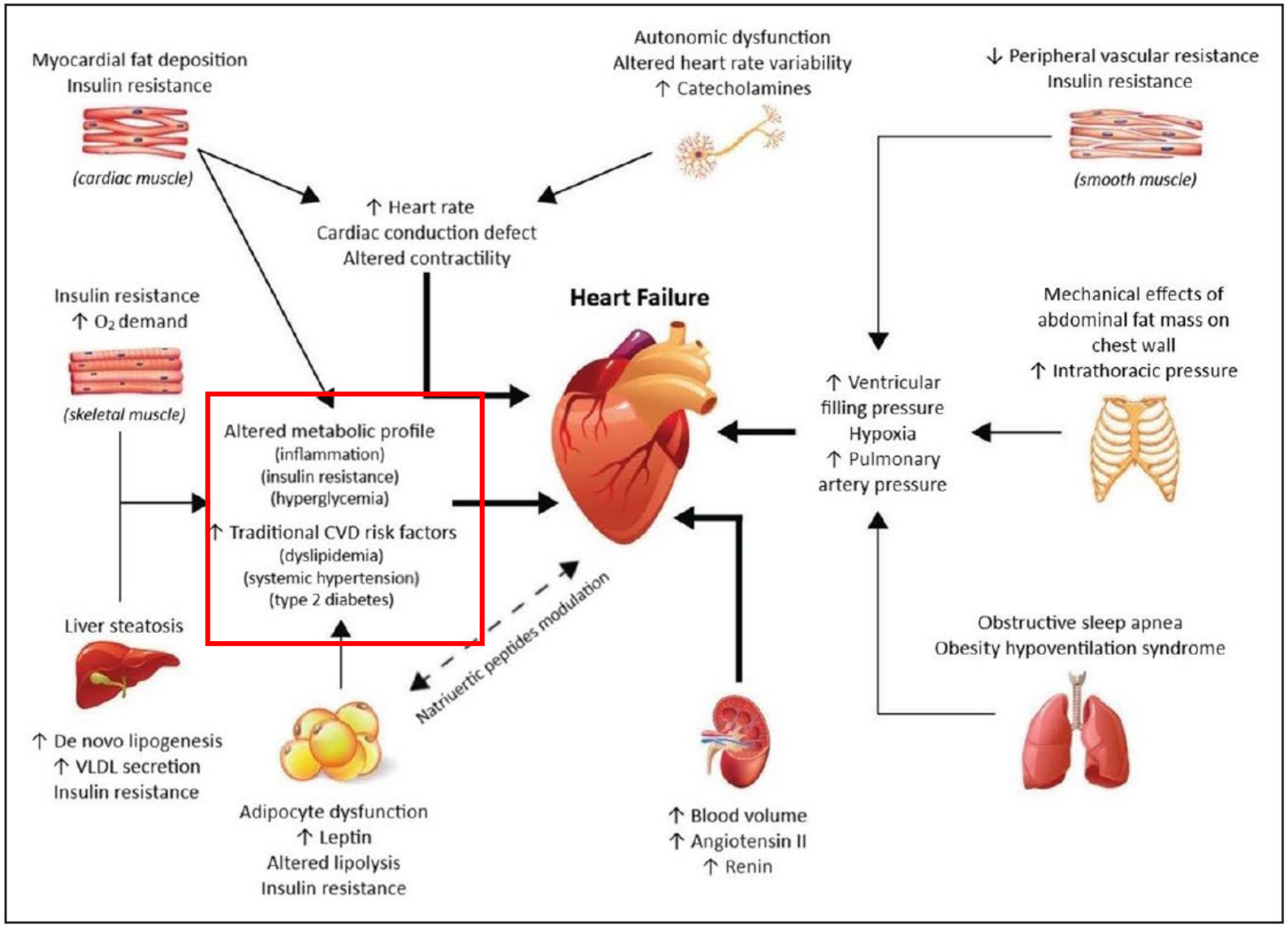
Weight and weight change and risk of atrial fibrillation: the HUNT study

HR adjusted for sex, age, height, smoking status, level of education, marital status, physical activity, and alcohol consumption

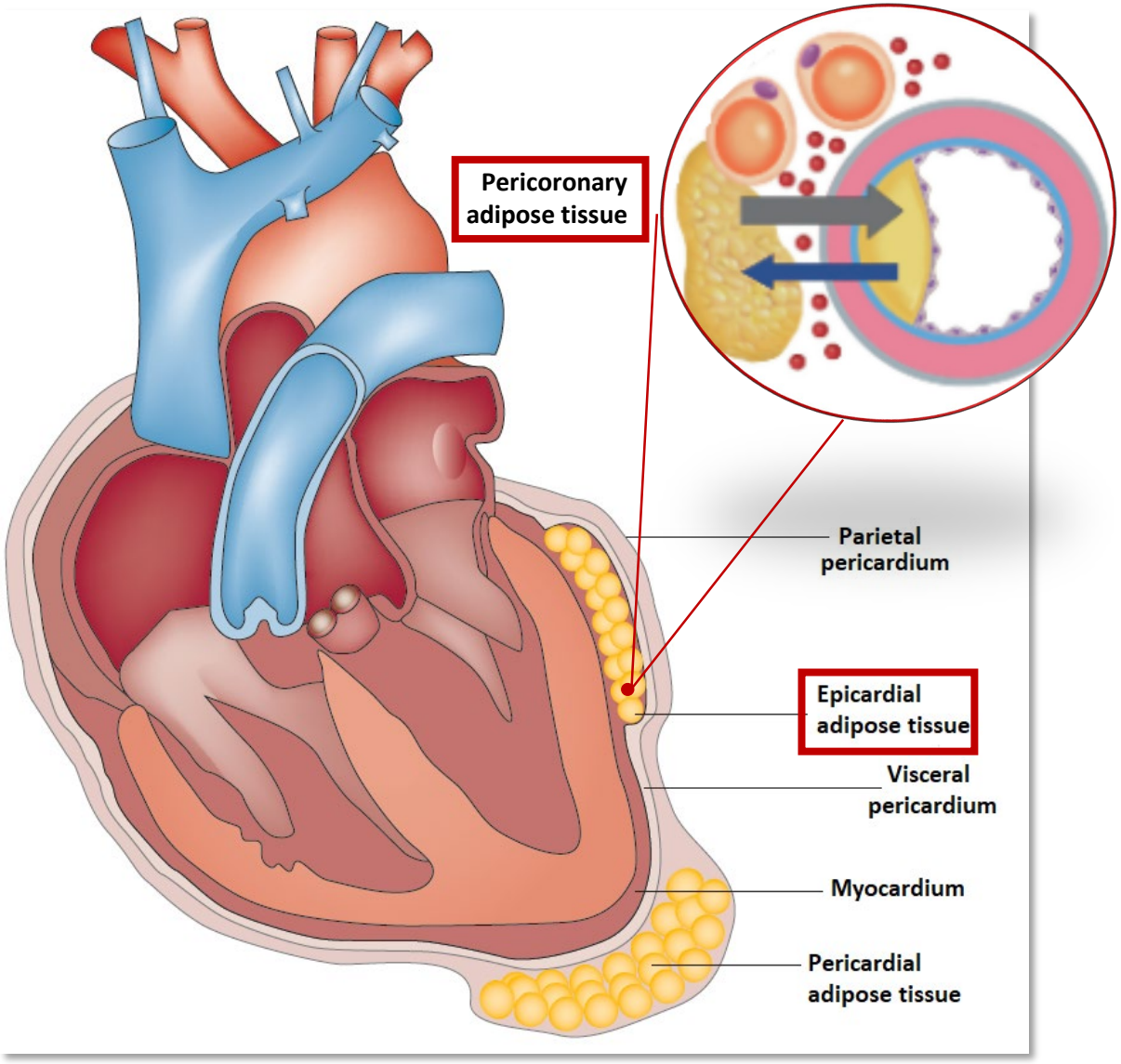


Feng T et al. Circulation 2023

Obesity and Cardiovascular Disease



Powell-Wiley TM et al. Circulation 2021



- **Epicardial adipose tissue (EAT)** is the layer of AT located between the visceral layer of the pericardium and the myocardium, without an intervening fascial plane, supplied by branches of the coronary arteries.
- The layer of EAT directly encompassing the coronary arteries represents the **pericoronary adipose tissue (PCAT)**, being an integral part of the vascular wall itself.
- The **lack of an anatomical barrier** allows **crosstalk** between EAT and the contiguous myocardium and coronary arteries.

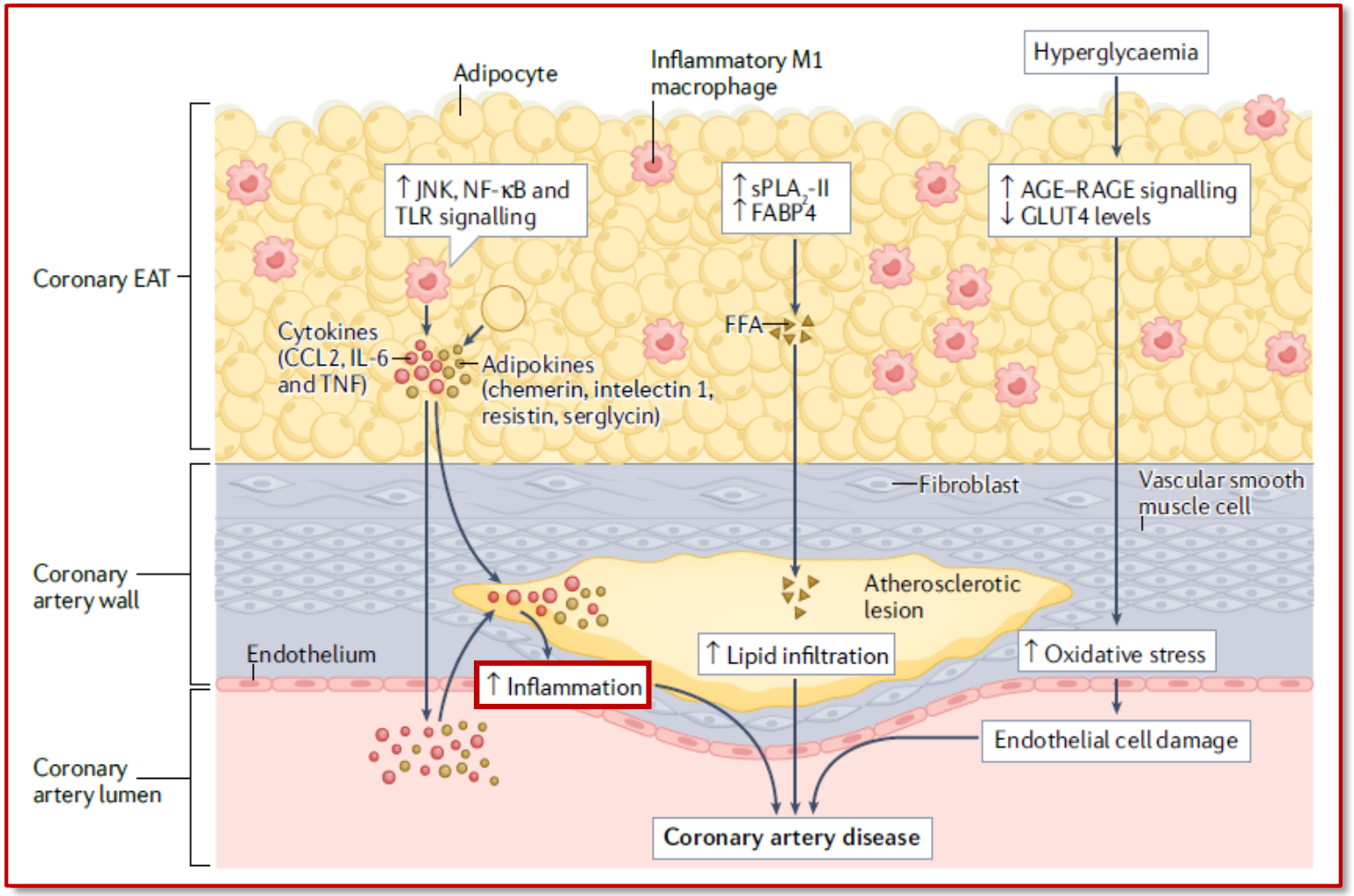
Guglielmo M et al. Atherosclerosis 2021
Iacobellis G et al. Nat Rev Cardiol 2022

Physiopathology of EAT/PCAT

- ✓ EAT functions:
  - ❑ Barrier against pathogens
  - ❑ Mechanical
  - ❑ Thermogenic
  - ❑ Metabolic
  - ❑ Paracrine/vasocrine secretion of numerous bioactive molecules

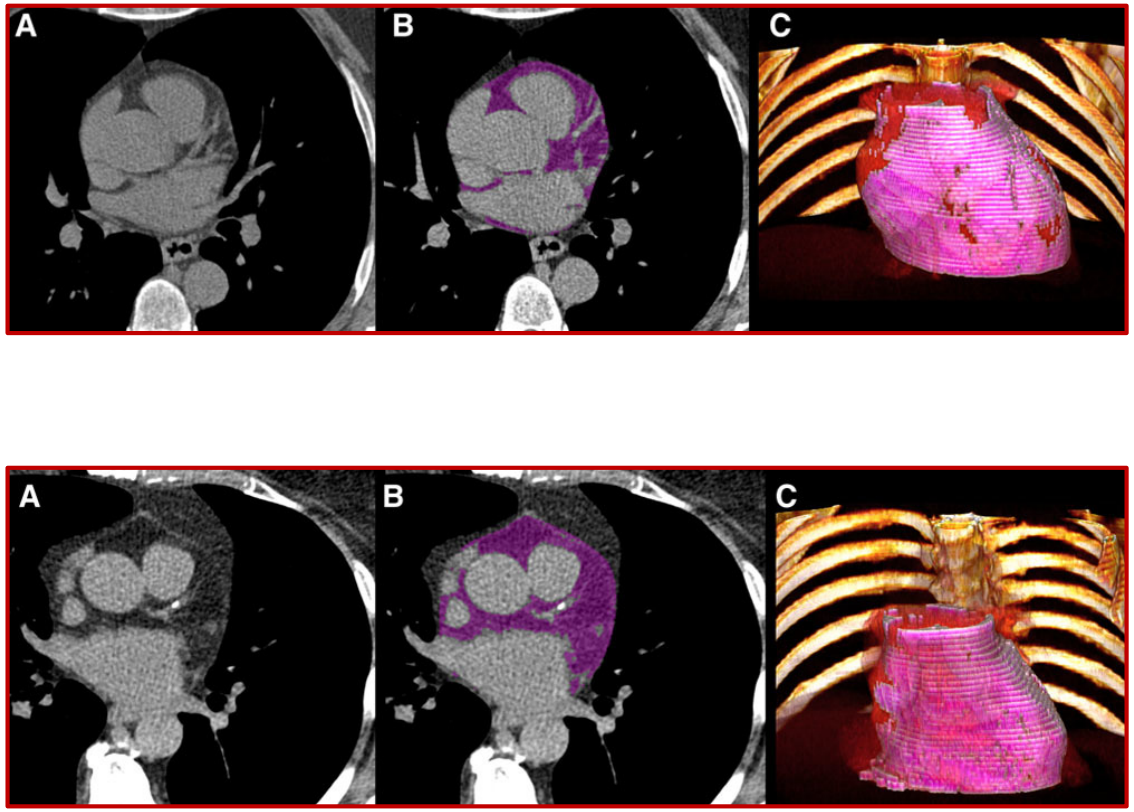
- ✓ Under physiological conditions, EAT exerts a net vasodilatory, anti-oxidant and anti-inflammatory effect on the vasculature.

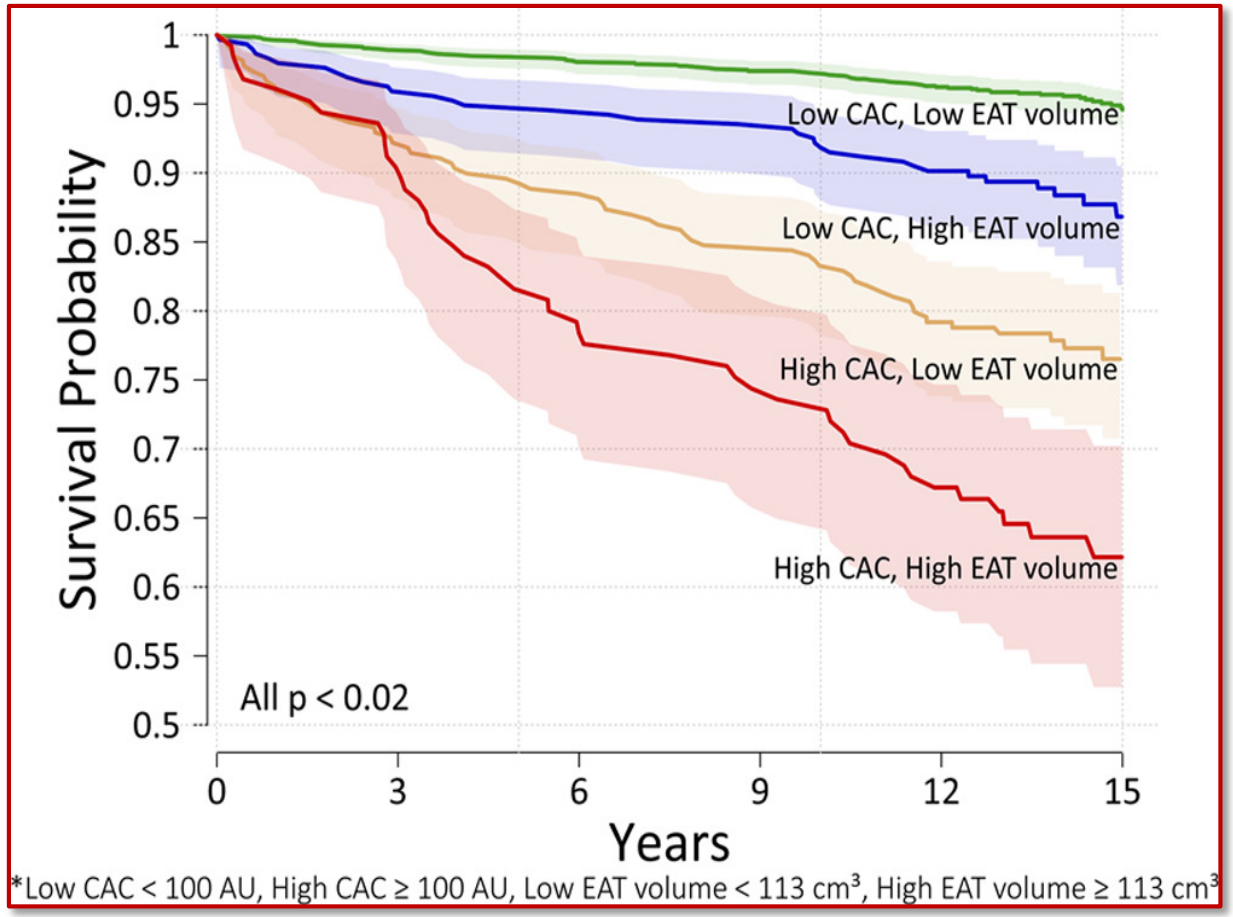
- ✓ Under pathological conditions, there is a shift in the secretome of dysfunctional EAT, with increased production of pro-inflammatory adipokines and cytokines.



M. Guglielmo M et al. Atherosclerosis 2021
Iacobellis G et al. Nat Rev Cardiol 2022

Correlation between epicardial adipose tissue & MACE





CAC = coronary artery calcium

Eisemberg E et al. Circ Cardiovasc Imaging 2020

Effects of weight loss medications on mortality and cardiovascular events: A systematic review of randomized controlled trials in adults with overweight and obesity

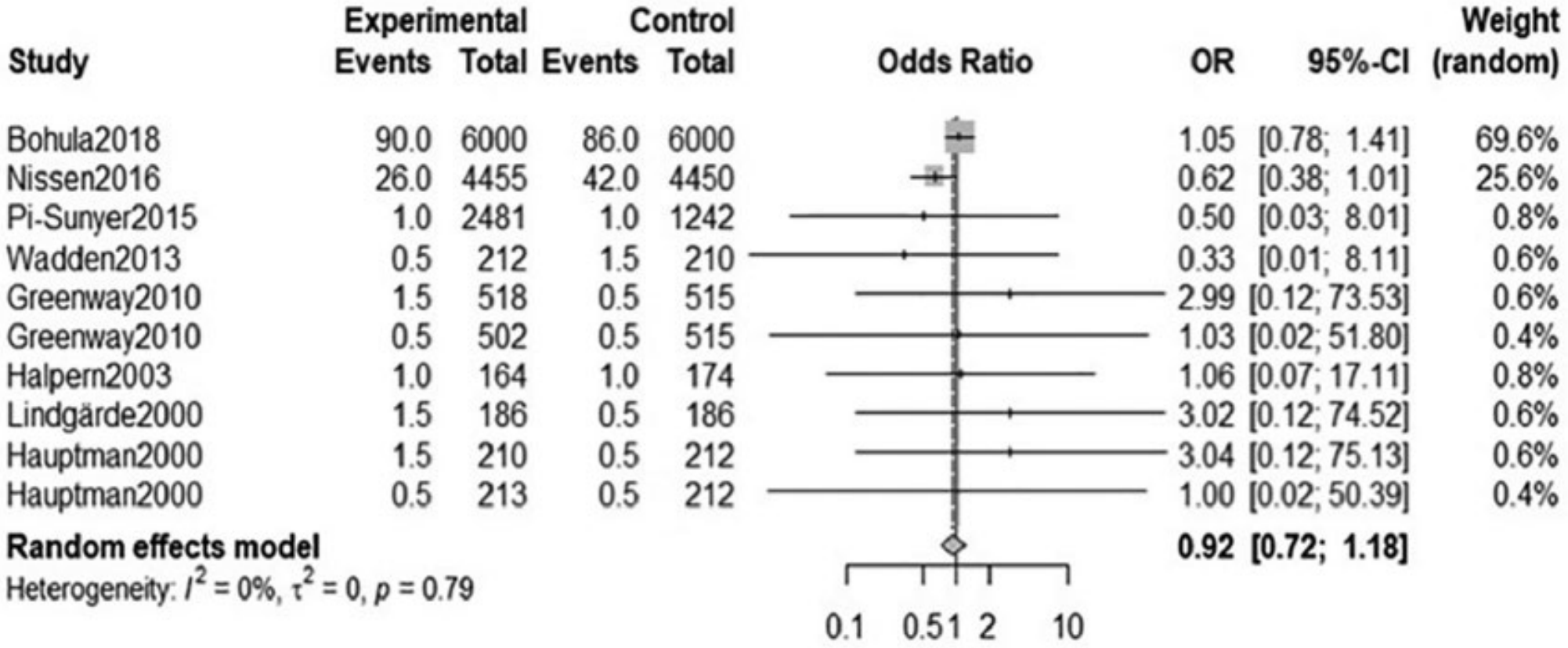


Figure 3 Effect of anti-obesity drugs on cardiovascular mortality.

Capristo E et al. Nutrition, Metabolism & Cardiovascular Diseases 2021

Effects of weight loss medications on mortality and cardiovascular events: A systematic review of randomized controlled trials in adults with overweight and obesity

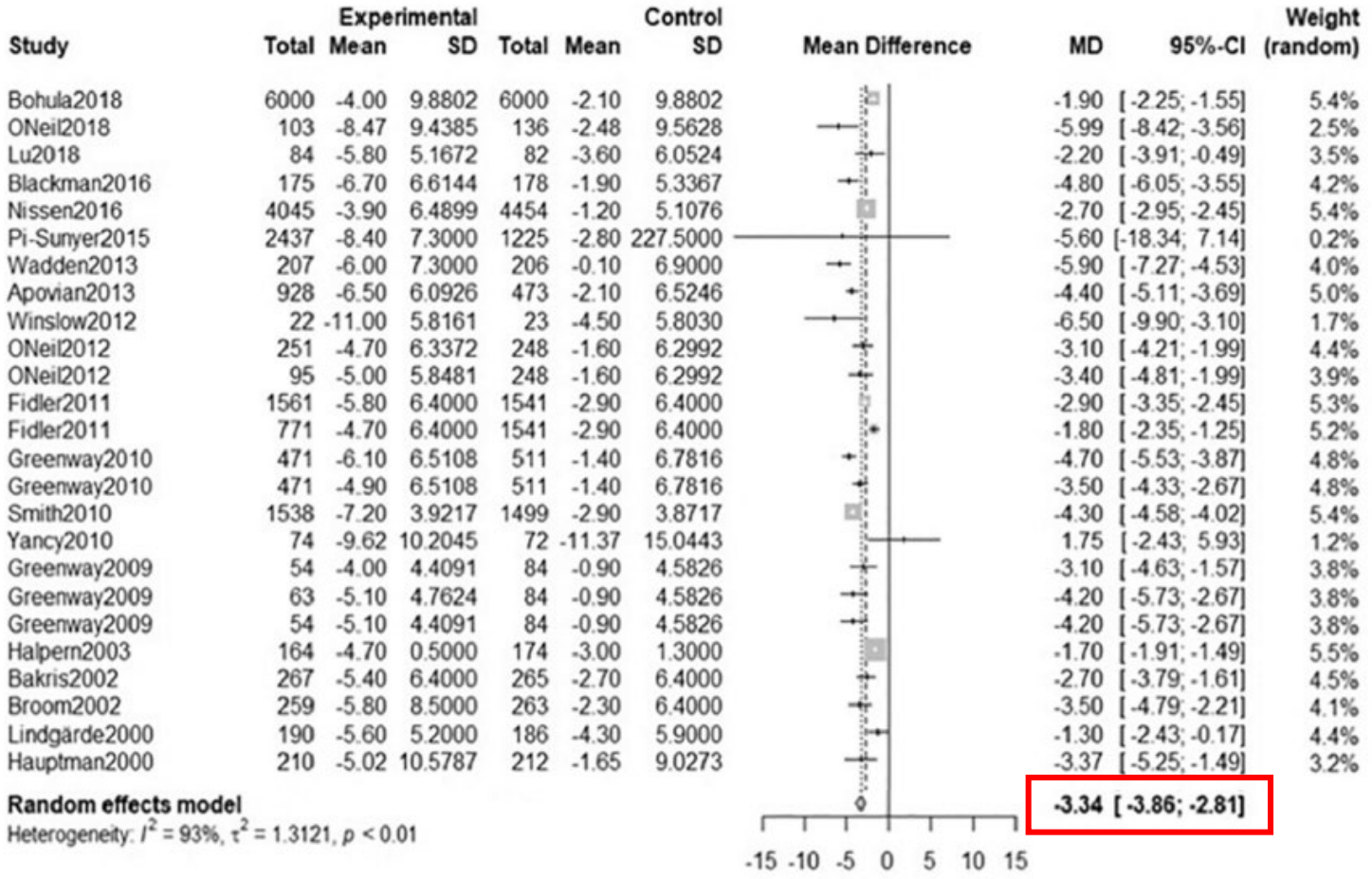
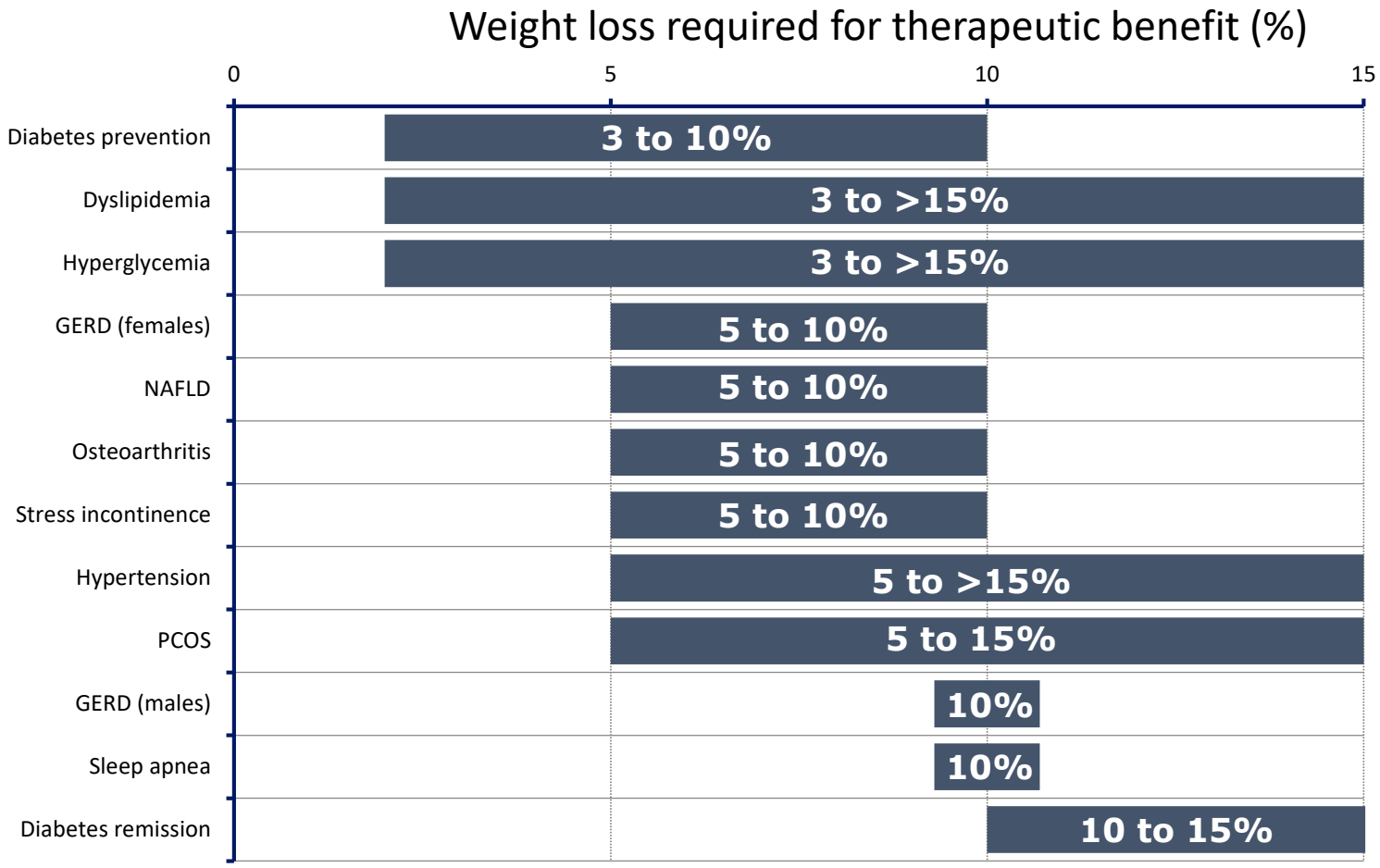


Figure 4 Effect of anti-obesity drugs on weight loss (kg).

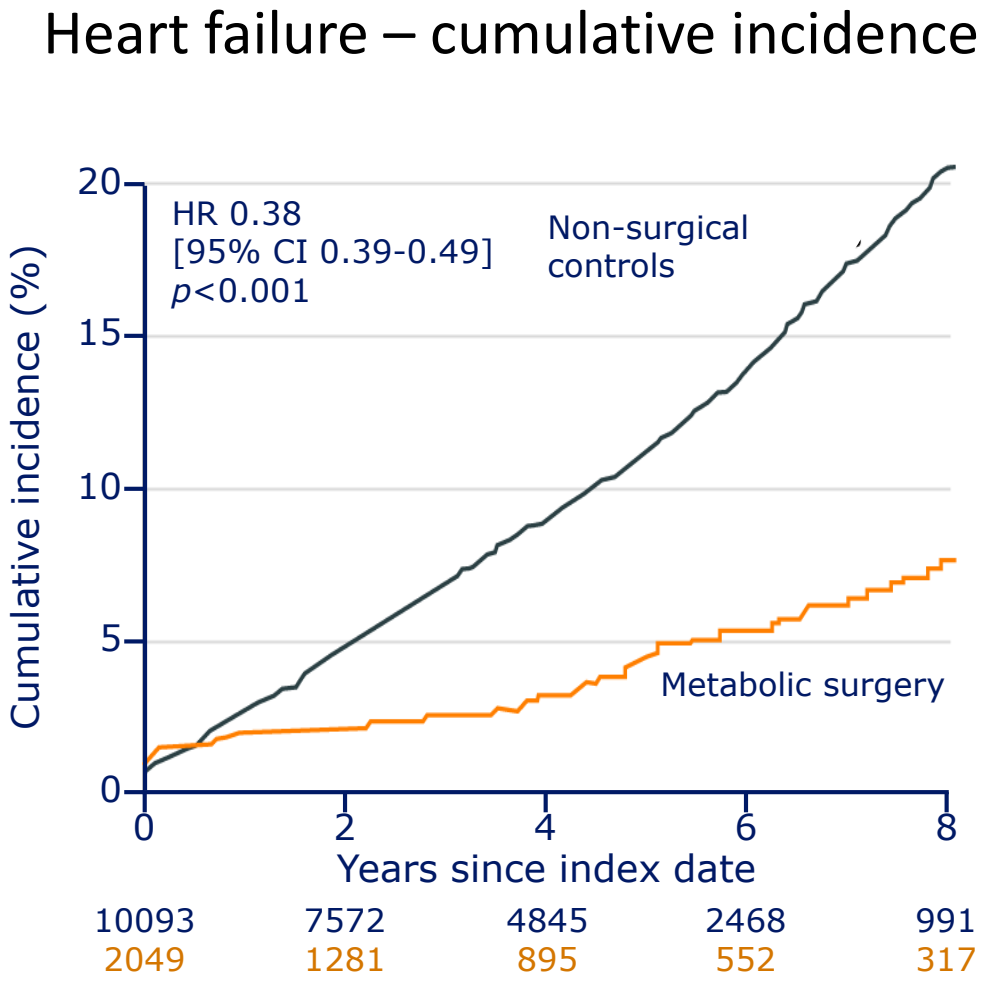
Capristo E et al. Nutrition, Metabolism & Cardiovascular Diseases 2021

How much weight loss is needed to improve obesity-related complications?



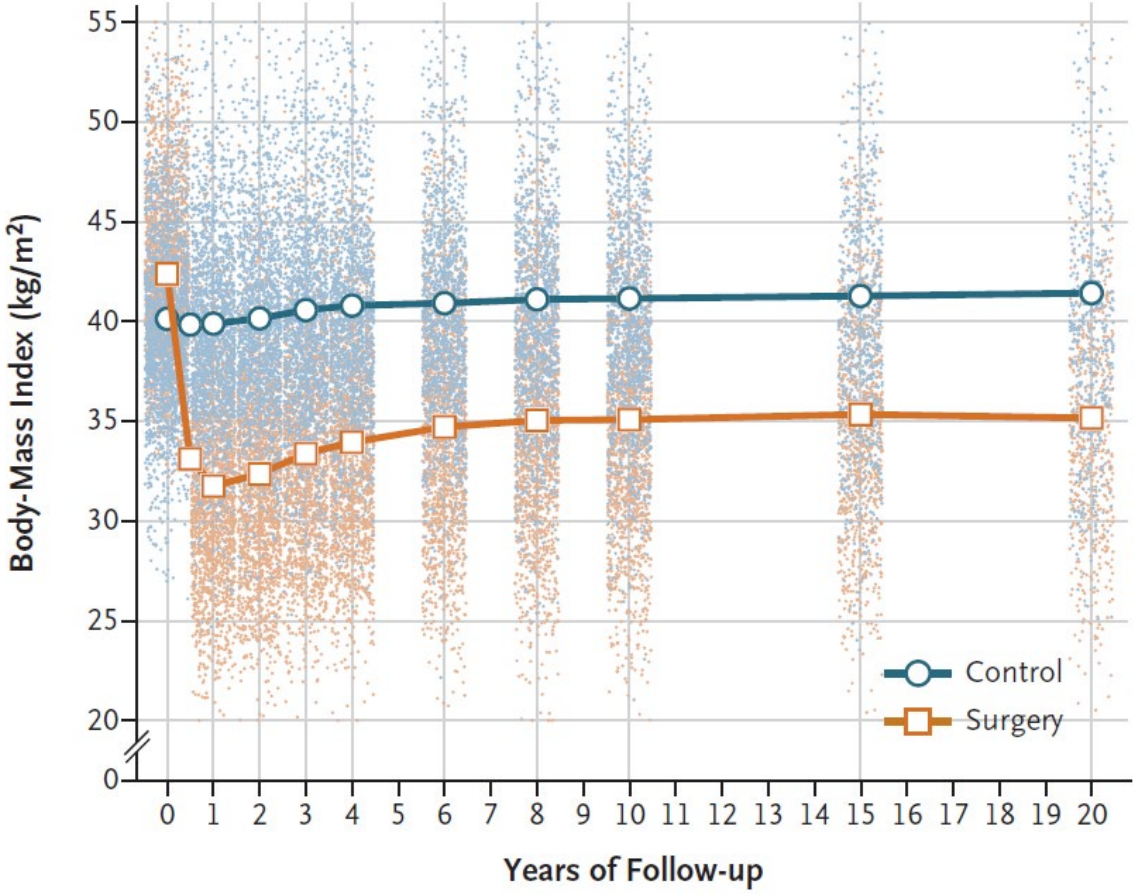
Cefalu et al. Diabetes Care 2015; Lean et al. Lancet 2018 Hannah & Harrison. Clin Liver Dis 2016

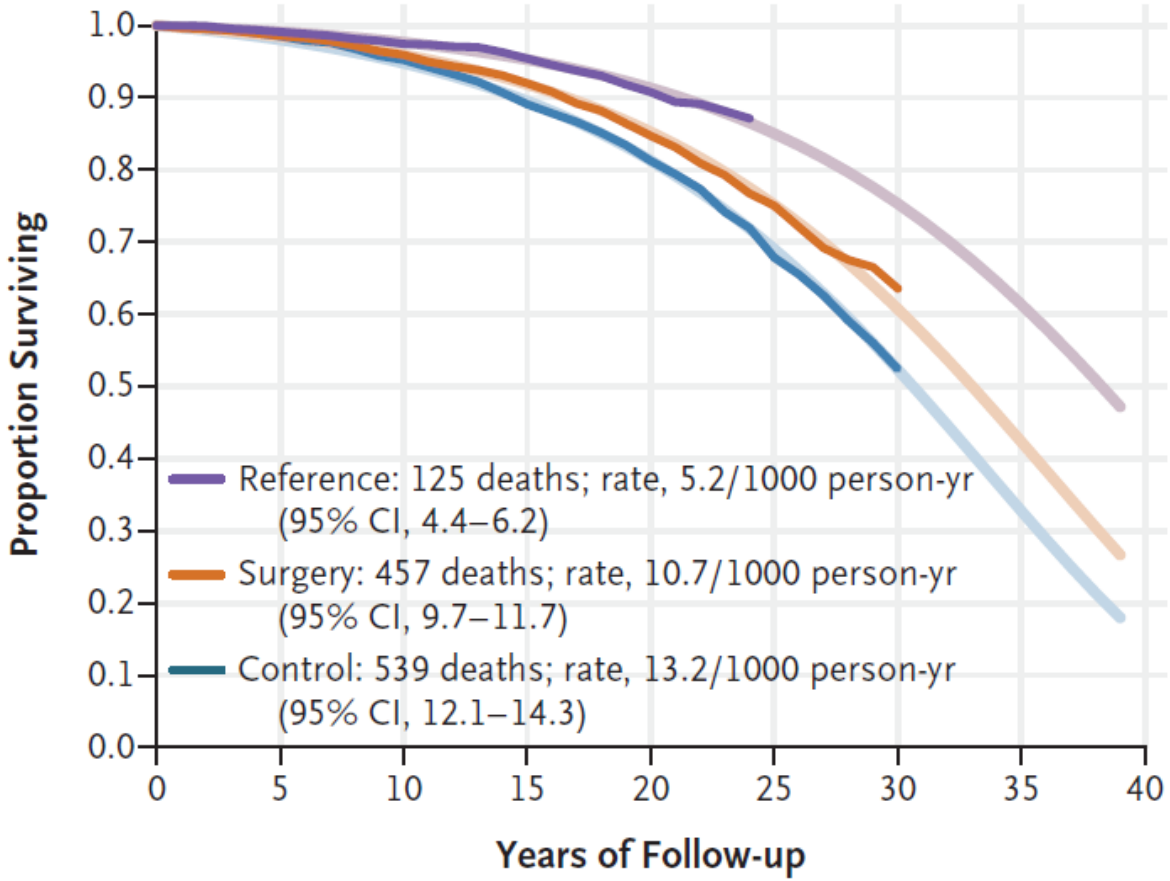
Metabolic surgery is associated with decreased risk of developing heart failure



Aminian et al. JAMA 2019

Life Expectancy after Bariatric Surgery in the Swedish Obese Subjects Study

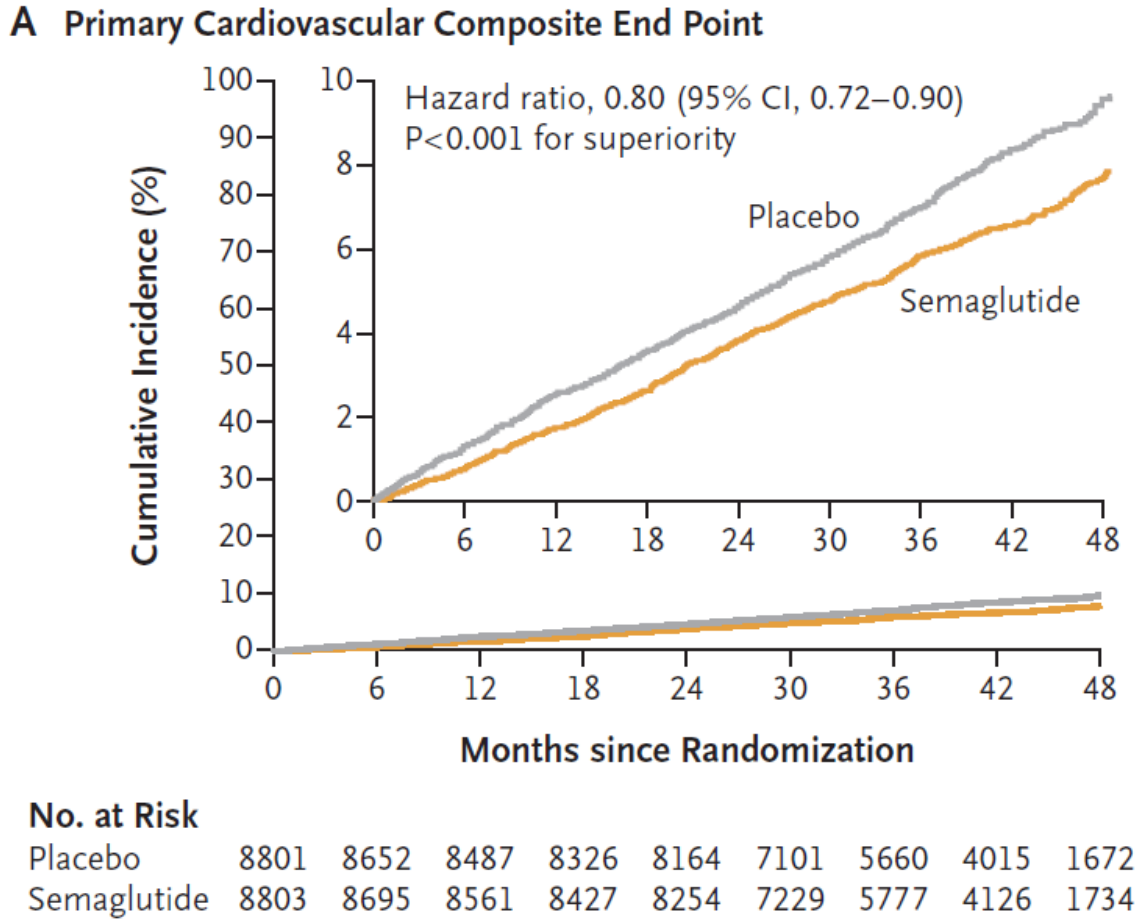




Carlsson LMS et al. NEJM 2020

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

- 17.604 pazienti con precedente malattia CV e BMI $\geq$27 kg/m^2 senza diabete
- Randomizzati a semaglutide 2.4 mg s.c./7 gg
- Endpoint primario: morte cardiovascolare, infarto e ictus non fatali
    - Calo ponderale del 9.4%



Lincoff AM et al. for the SELECT Trial investigators. NEJM 2023

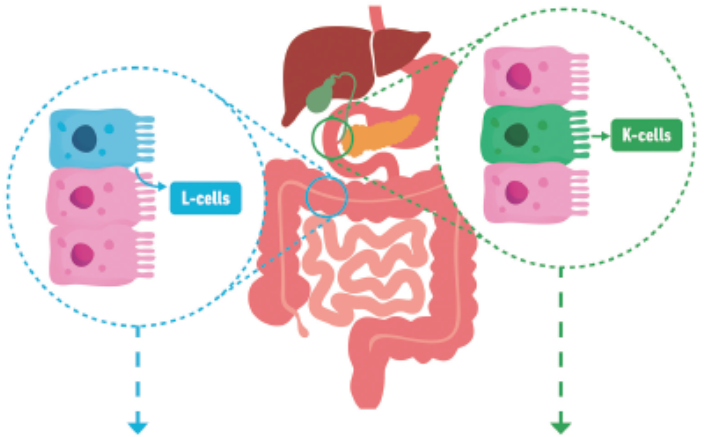
Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

Table 3. Supportive Binary and Continuous Secondary End Points.*

End Point	Semaglutide (N=8803)	Placebo (N=8801)	Difference (95% CI)†
Glycated hemoglobin level of <5.7% among patients with baseline glycated hemoglobin level of ≥5.7% — no./total no. (%)‡			
At week 52	3848/5831 (66.0)	1136/5748 (19.8)	10.15 (9.18 to 11.23)
At week 104	3775/5750 (65.7)	1211/5663 (21.4)	8.74 (7.91 to 9.65)
Mean change from randomization to week 104			
Body weight — %	−9.39±0.09	−0.88±0.08	−8.51 (−8.75 to −8.27)
Waist circumference — cm	−7.56±0.09	−1.03±0.09	−6.53 (−6.79 to −6.27)
Glycated hemoglobin level — percentage points	−0.31±0.00	0.01±0.00	−0.32 (−0.33 to −0.31)
Systolic blood pressure — mm Hg	−3.82±0.16	−0.51±0.16	−3.31 (−3.75 to −2.88)
Diastolic blood pressure — mm Hg	−1.02±0.10	−0.47±0.10	−0.55 (−0.83 to −0.27)
Heart rate — beats/min	3.79±0.11	0.69±0.11	3.10 (2.80 to 3.39)
EQ-5D-5L index score§	0.01±0.00	−0.01±0.00	0.01 (0.01 to 0.02)
EQ-5D-VAS score§	2.52±0.16	0.92±0.16	1.60 (1.16 to 2.04)
High-sensitivity CRP level — %	−39.12	−2.08	−37.82 (−39.70 to −35.90)
Total cholesterol level — %	−4.63	−1.92	−2.77 (−3.37 to −2.16)
HDL cholesterol level — %	4.86	0.59	4.24 (3.70 to 4.79)
LDL cholesterol level — %	−5.25	−3.14	−2.18 (−3.22 to −1.12)
Triglyceride level — %	−18.34	−3.20	−15.64 (−16.68 to −14.58)

Lincoff AM et al. for the SELECT Trial investigators. NEJM 2023

Efficacy and Safety of Tirzepatide in Type 2 Diabetes and Obesity Management

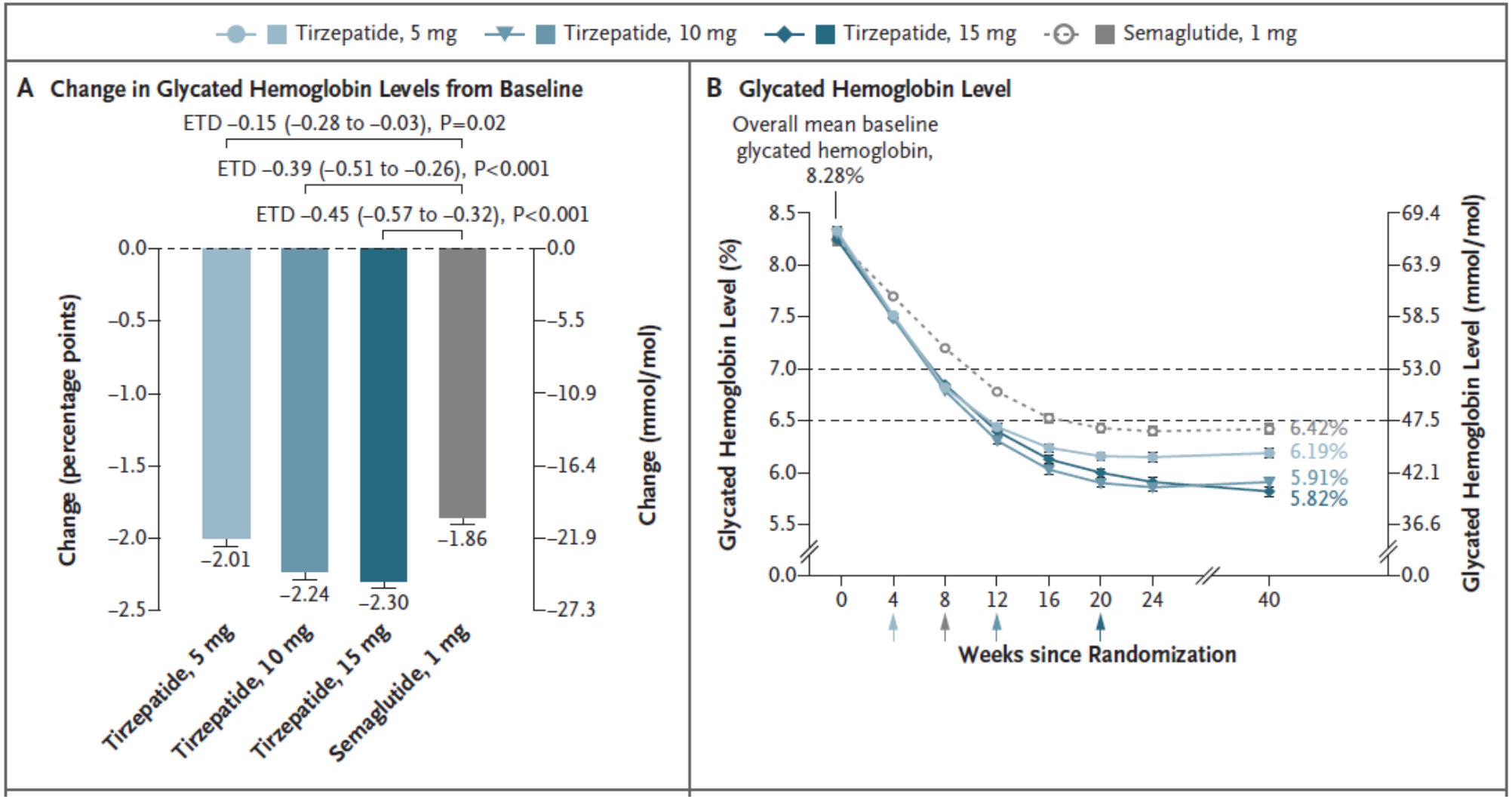


	GLP-1	GIP
Brain	↓ Appetite ↓ Food intake ↑ Nausea	↓ Appetite* ↓ Food intake* ↓ Nausea*
Pancreas	↑ Insulin secretion ↓ Glucagon	↑ Insulin secretion ↑ Glucagon
Stomach	↓ Gastric emptying	↓ Gastric acid secretion
Adipose tissue	↑ Lipolysis	↑ Lipogenesis ↑ Lipid buffering capacity
Bone		↓ Bone resorption
Heart	↑ Cardioprotection	
Kidney	↑ Natriuresis ↑ Diuresis	

Pancreatic and exopancreatic actions of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1).

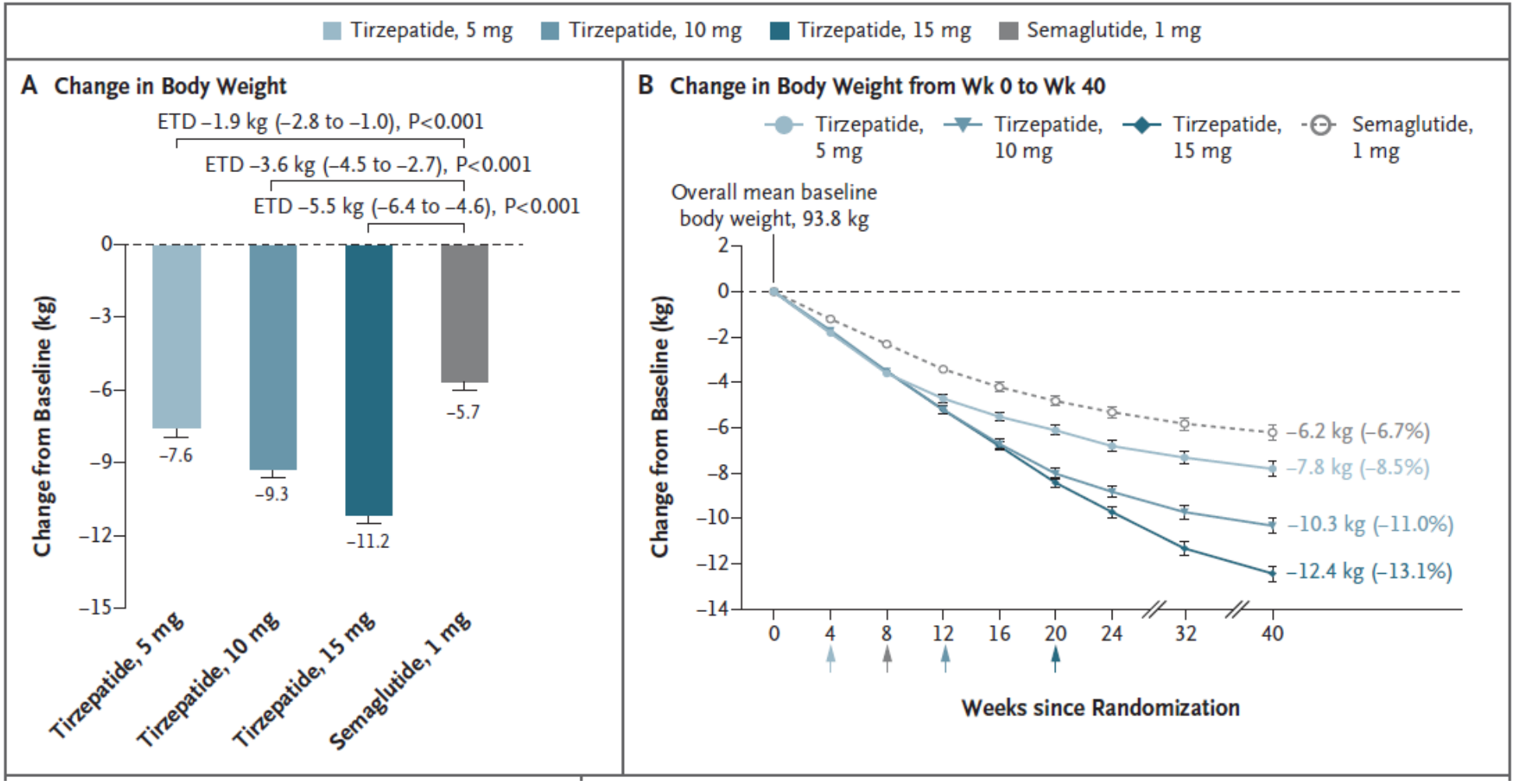
Sinha R et al. Journal of Obesity & Metabolic Syndrome 2023

Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes



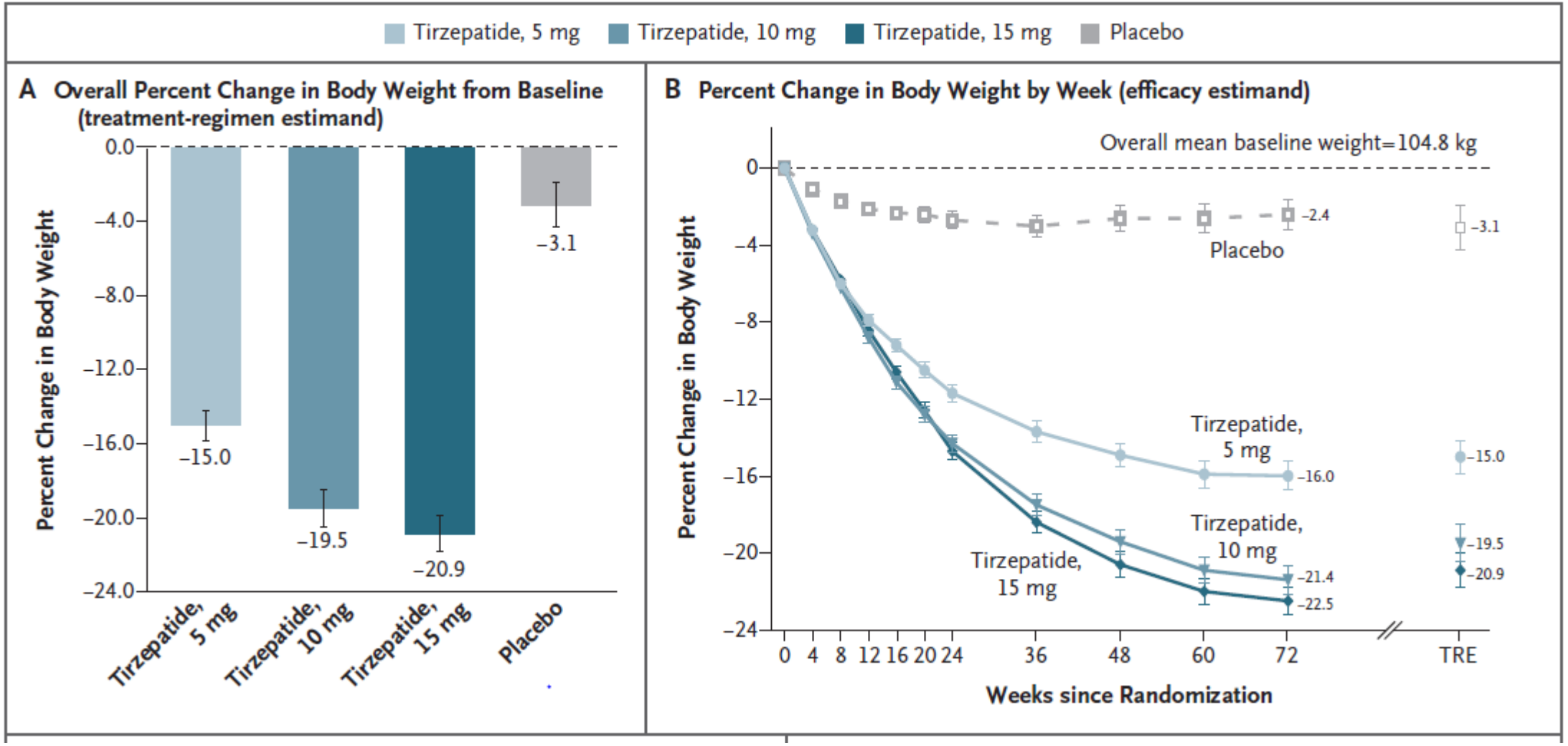
Frias JP et al. for the SURMOUNT-2 Invest. N Engl J Med 2021

Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes



Frias JP et al. for the SURMOUNT-2 Invest. N Engl J Med 2021

Tirzepatide Once Weekly for the Treatment of Obesity



Jastreboff AM et al. for the SURMOUNT-1 Invest. N Engl J Med 2022

Tirzepatide Once Weekly for the Treatment of Obesity

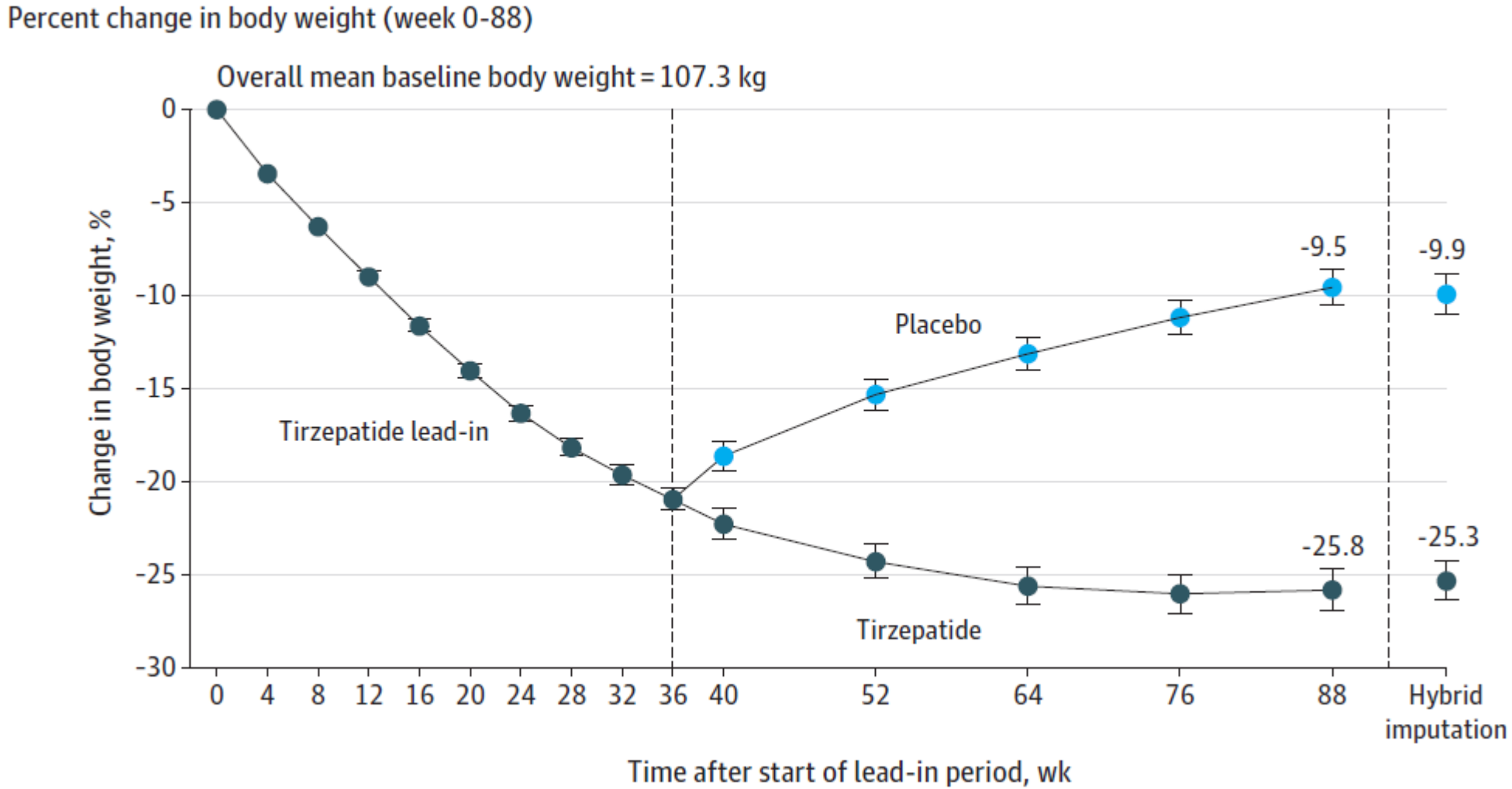
Table 3. Key Secondary and Additional Secondary End Points for Pooled Tirzepatide Dose Groups (Treatment-Regimen Estimand).*

End Points	Pooled Tirzepatide Groups†	Placebo (N = 643)	Estimated Treatment Difference from Placebo (95% CI)
	least-squares mean (95% CI)		
Key secondary end points‡			
Change from baseline to week 20 in body weight — kg§	−12.8 (−13.1 to −12.5)	−2.7 (−3.2 to −2.2)	−10.1 (−10.7 to −9.6)
Change in measure			
SF-36 physical function score§¶	3.6 (3.2 to 4.0)	1.7 (0.8 to 2.6)	1.9 (1.0 to 2. 9)
Systolic blood pressure — mm Hg	−7.2 (−7.8 to −6.7)	−1.0 (−2.3 to −0.3)	−6.2 (−7.7 to −4.8)
Percentage change in level‖			
Triglycerides — mg/dl	−24.8 (−26.3 to −23.1)	−5.6 (−10.0 to −1.2)	−20.3 (−24.3 to −16.1)
Non-HDL cholesterol — mg/dl	−9.7 (−10.7 to −8.6)	−2.3 (−4.9 to −0.2)	−7.5 (−10.1 to −4.9)
HDL cholesterol — mg/dl	8.0 (6.9 to 9.1)	−0.7 (−2.9 to 1.5)	8.8 (6.1 to 11.5)
Fasting insulin — mIU/liter**	−42.9 (−44.9 to −40.9)	−6.6 (−15.3 to 2.2)	−38.9 (−44.8 to −32.4)
Additional secondary end points††			
Change in diastolic blood pressure — mm Hg	−4.8 (−5.2 to −4.4)	−0.8 (−1.6 to 0.0)	−4.0 (−4.9 to −3.1)
Percentage change in level‖			
Total cholesterol — mg/dl	−4.8 (−5.6 to −4.0)	−1.8 (−3.7 to 0.1)	−3.1 (−5.2 to −1.0)
LDL cholesterol — mg/dl	−5.8 (−6.9 to −4.6)	−1.7 (−4.6 to 1.3)	−4.2 (−7.2 to −1.0)
VLDL cholesterol — mg/dl	−24.4 (−25.9 to −22.9)	−4.8 (−9.2 to −0.4)	−20.6 (−24.6 to −16.4)
Free fatty acids — mmol/liter	−7.5 (−10.7 to −4.3)	9.5 (3.8 to 15.3)	−15.6 (−20.8 to −9.9)

Jastreboff AM et al. for the SURMOUNT-1 Invest. N Engl J Med 2022

Continued Treatment With Tirzepatide for Maintenance of Weight Reduction in Adults With Obesity

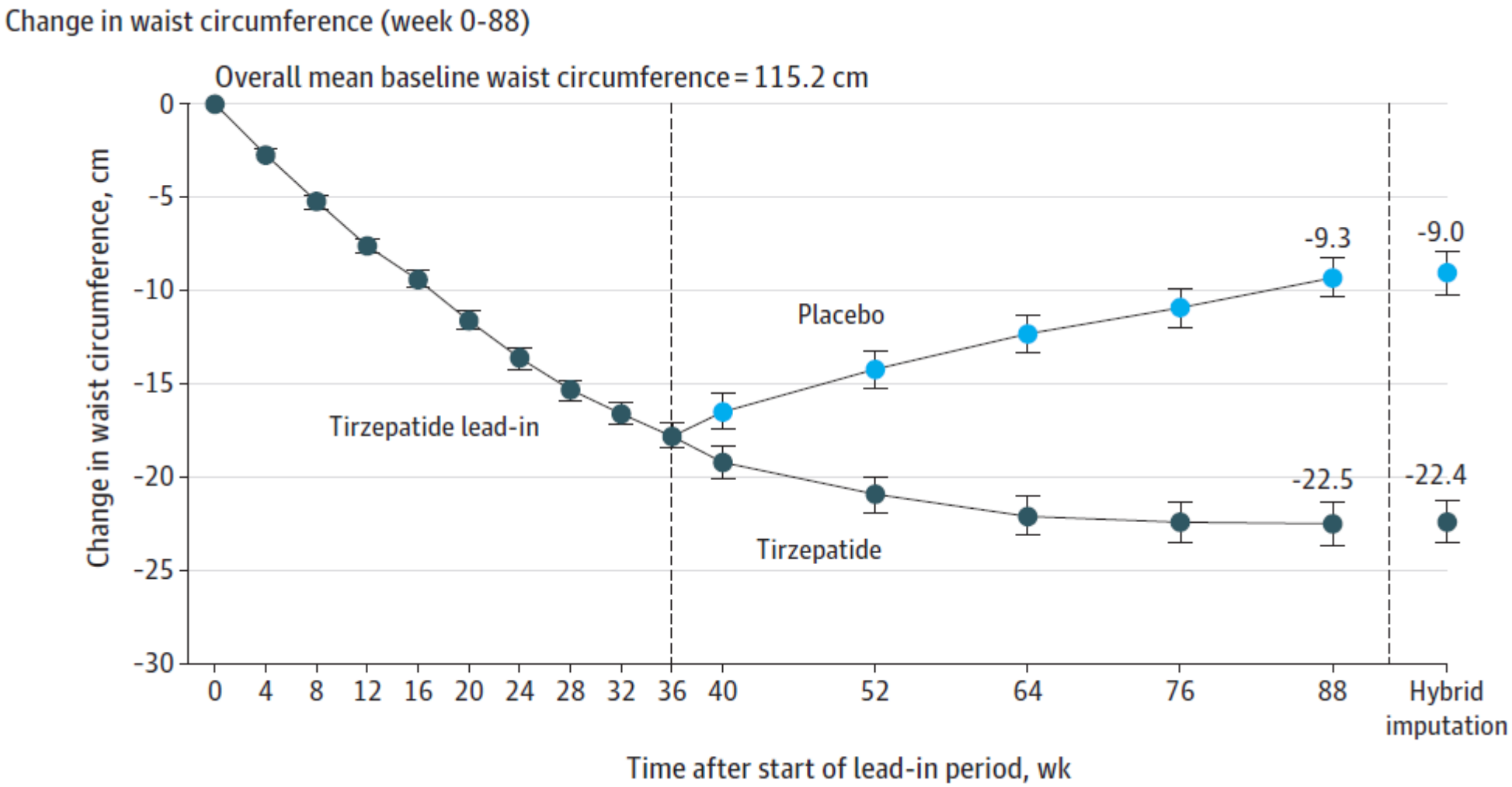
The SURMOUNT-4 Randomized Clinical Trial



Aronne LJ et al. for the SURMOUNT-4 Invest. JAMA 2024

Continued Treatment With Tirzepatide for Maintenance of Weight Reduction in Adults With Obesity

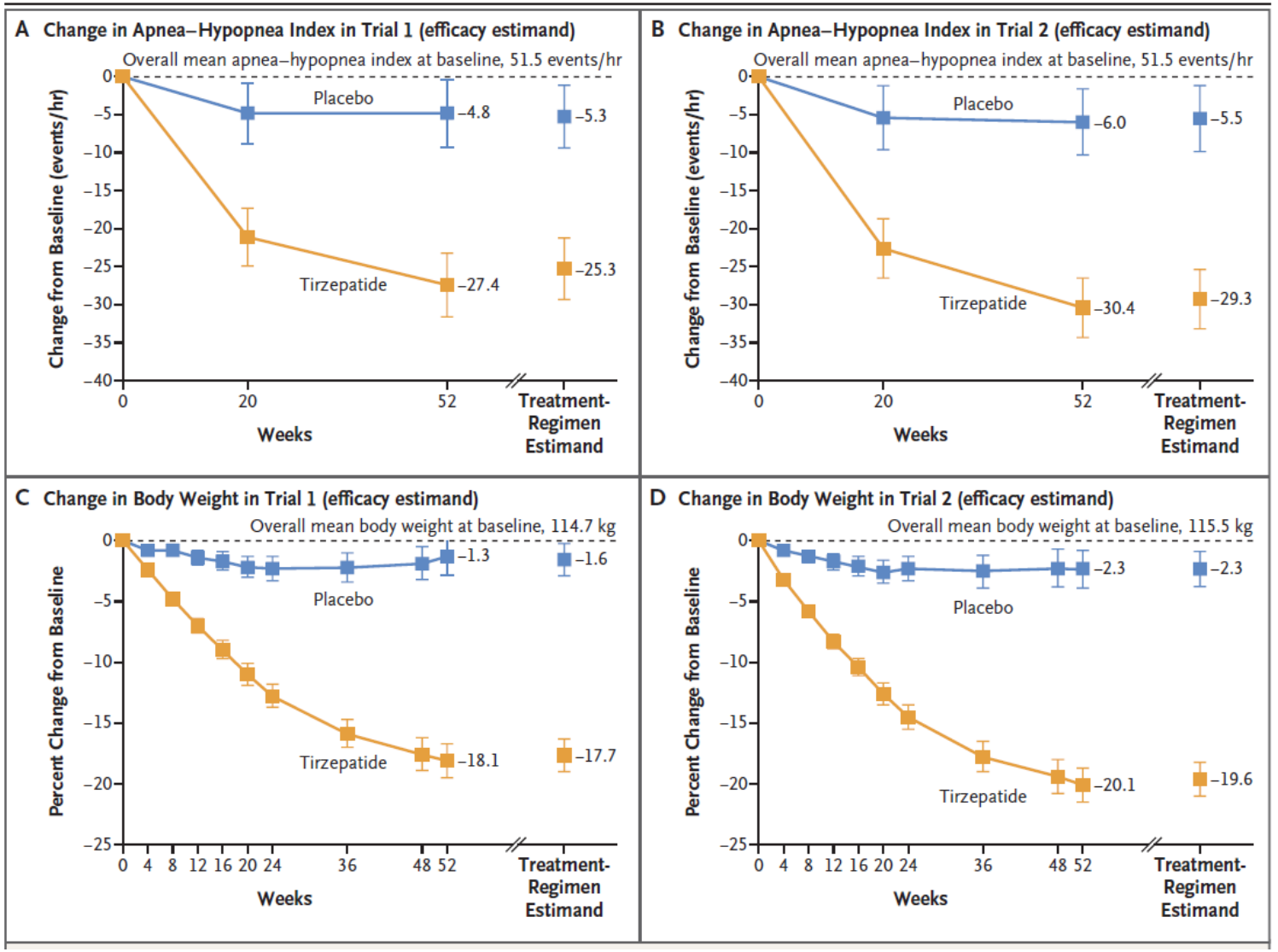
The SURMOUNT-4 Randomized Clinical Trial



Aronne LJ et al. for the SURMOUNT-4 Invest. JAMA 2024

Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity

Trial 1: no CPAP
Trial 2: CPAP



Malhotra A et al. for the SURMOUNT-OSA Invest. N Engl J Med 2024

Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity

Table 2. Primary and Key Secondary End Points According to Trial Group for the Treatment-Regimen Estimand.*

End Point	Trial 1			Trial 2		
	Tirzepatide N=114	Placebo N=120	Estimated Treatment Difference or Relative Risk (95% CI)†	Tirzepatide N=120	Placebo N=115	Estimated Treatment Difference or Relative Risk (95% CI)†
Primary end point						
Change in AHI (95% CI) — no. of events/hr	−25.3 (−29.3 to −21.2)	−5.3 (−9.4 to −1.1)	−20.0 (−25.8 to −14.2)	−29.3 (−33.2 to −25.4)	−5.5 (−9.9 to −1.2)	−23.8 (−29.6 to −17.9)
Key secondary end points						
Percent change in AHI (95% CI)	−50.7 (−62.3 to −39.1)	−3.0 (−16.9 to 10.9)	−47.7 (−65.8 to −29.6)	−58.7 (−69.1 to −48.4)	−2.5 (−16.2 to 11.2)	−56.2 (−73.7 to −38.7)
Reduction of ≥50% in AHI events at wk 52 — no. (%)	70 (61.2)	23 (19.0)	3.3 (2.1 to 5.1)	86 (72.4)	27 (23.3)	3.1 (2.1 to 4.5)
AHI of <5 or AHI of 5 to 14 with ESS ≤10 at wk 52 — no. (%)	48 (42.2)	19 (15.9)	2.9 (1.8 to 4.8)	60 (50.2)	16 (14.3)	3.3 (2.0 to 5.4)
Percent change in body weight (95% CI)	−17.7 (−19.0 to −16.3)	−1.6 (−2.9 to −0.2)	−16.1 (−18.0 to −14.2)	−19.6 (−21.0 to −18.2)	−2.3 (−3.8 to −0.9)	−17.3 (−19.3 to −15.3)
Change in hsCRP concentration at wk 52 (95% CI) — mg/liter	−1.4 (−1.7 to −1.1)	−0.7 (−1.1 to −0.3)	−0.7 (−1.2 to −0.2)	−1.4 (−1.6 to −1.1)	−0.3 (−0.8 to 0.1)	−1.0 (−1.6 to −0.5)
Change in sleep apnea–specific hypoxic burden at wk 52 (95% CI) — % min/hr	−95.2 (−103.2 to −87.2)	−25.1 (−44.3 to −5.9)	−70.1 (−90.9 to −49.3)	−103.0 (−110.3 to −95.6)	−41.7 (−63.9 to −19.5)	−61.3 (−84.7 to −37.9)
Change in systolic blood pressure at wk 48 (95% CI) — mm Hg	−9.5 (−11.5 to −7.5)	−1.8 (−3.9 to 0.2)	−7.6 (−10.5 to −4.8)	−7.6 (−9.7 to −5.6)	−3.9 (−6.3 to −1.6)	−3.7 (−6.8 to −0.7)
Additional secondary end point‡						
Change in diastolic blood pressure at wk 48 (95% CI) — mm Hg	−4.9 (−6.4 to −3.5)	−2.1 (−3.6 to −0.6)	−2.8 (−5.0 to −0.7)	−3.3 (−4.7 to −1.9)	−2.2 (−3.8 to −0.6)	−1.1 (−3.2 to 1.0)

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Conclusioni

- Oltre a numerose conseguenze per la salute, l'obesità contribuisce alle malattie cardiovascolari indirettamente attraverso lo sviluppo di fattori di rischio e direttamente attraverso meccanismi biologici.

- La riduzione/normalizzazione del peso corporeo si associa ad una riduzione del rischio cardiovascolare

- È evidente la necessità di raddoppiare gli sforzi per colpire il rischio cardio-metabolico legato all'obesità come strategia per combattere le malattie cardiovascolari


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