Società Medico Chirurgica di Ferrara

dal 1846


REMDICONTO
DELLE ADUNANZE
MEDICO-CHIRURGICA
DI FERRARA

Con il Patrocinio di:

Azienda Ospedaliero Universitaria di Ferrara

Università degli Studi di Ferrara

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara

Ordine dei Medici Chirurghi e degli Odontoiatri della provincia di FERRARA

Obesità: inquadramento clinico e innovazioni terapeutiche

Sabato 21 ottobre 2023

Aula Magna Nuovo Arcispedale S. Anna
Cona, Ferrara

Semaglutide ed eventi cardiovascolari

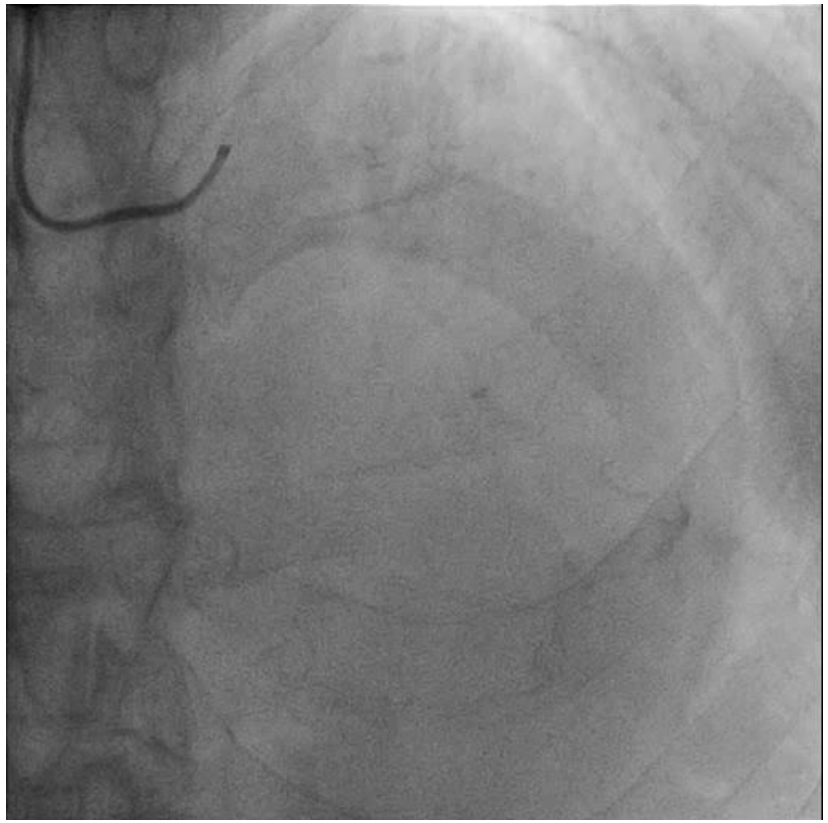
Alessandro Fucili
Centro Scompenso
Cardiologia

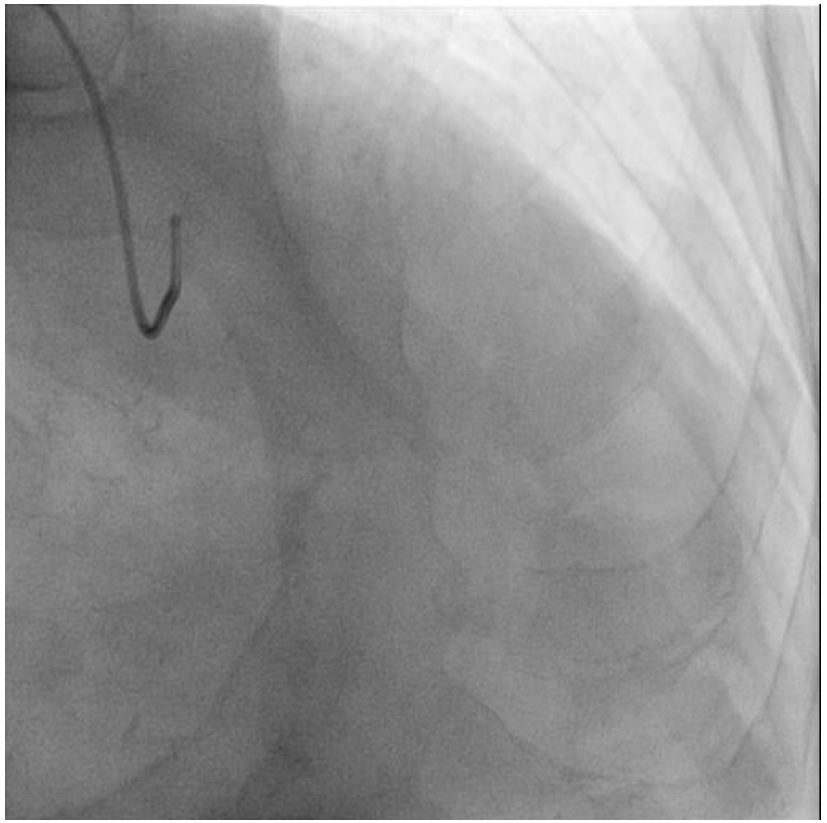
La rapida progressione della Patologia Coronarica

Inferior MI

Successful primary PCI

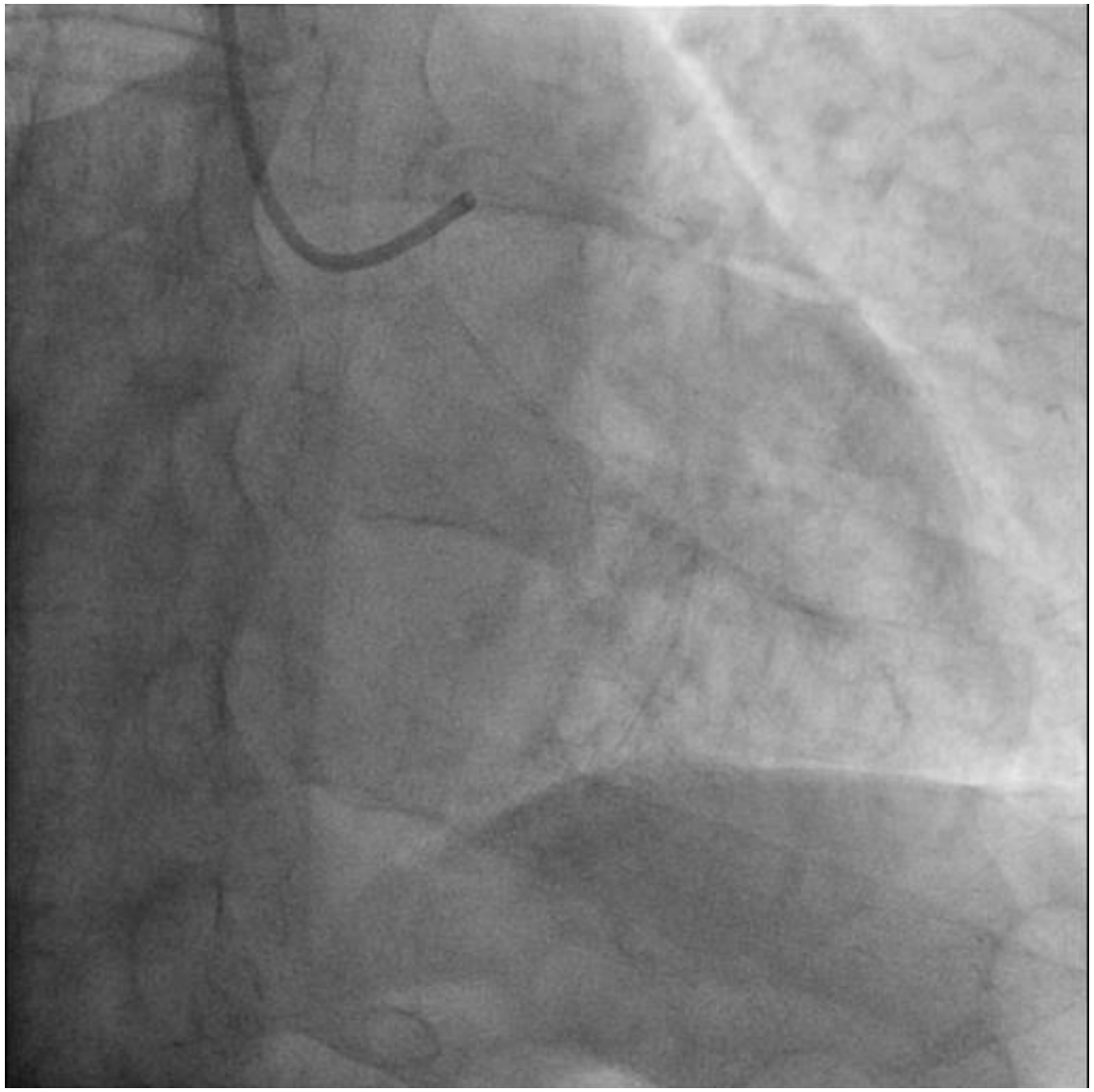
NCL on LAD



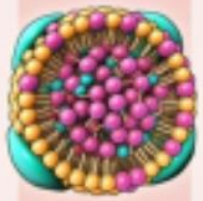
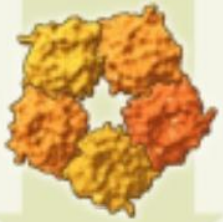
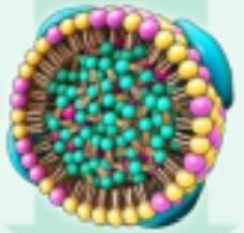
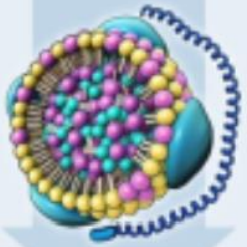
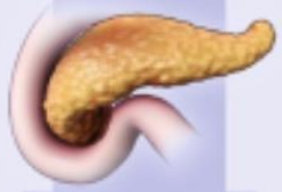


La rapida progressione della Patologia Coronarica “Dopo 1 anno”

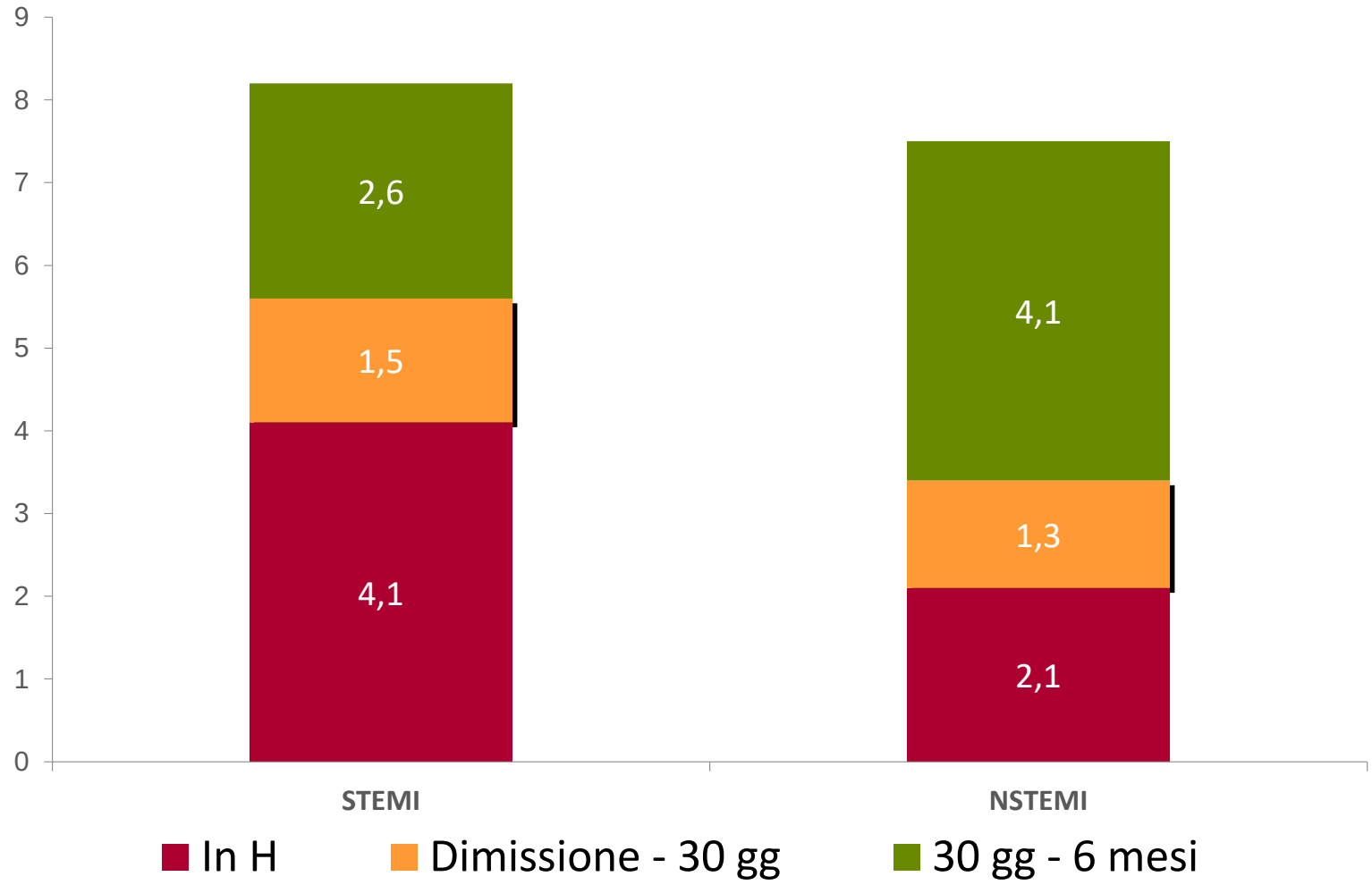
Smoking
LDL over the target
High hsCRP
Sedentary



Rischio Residuo

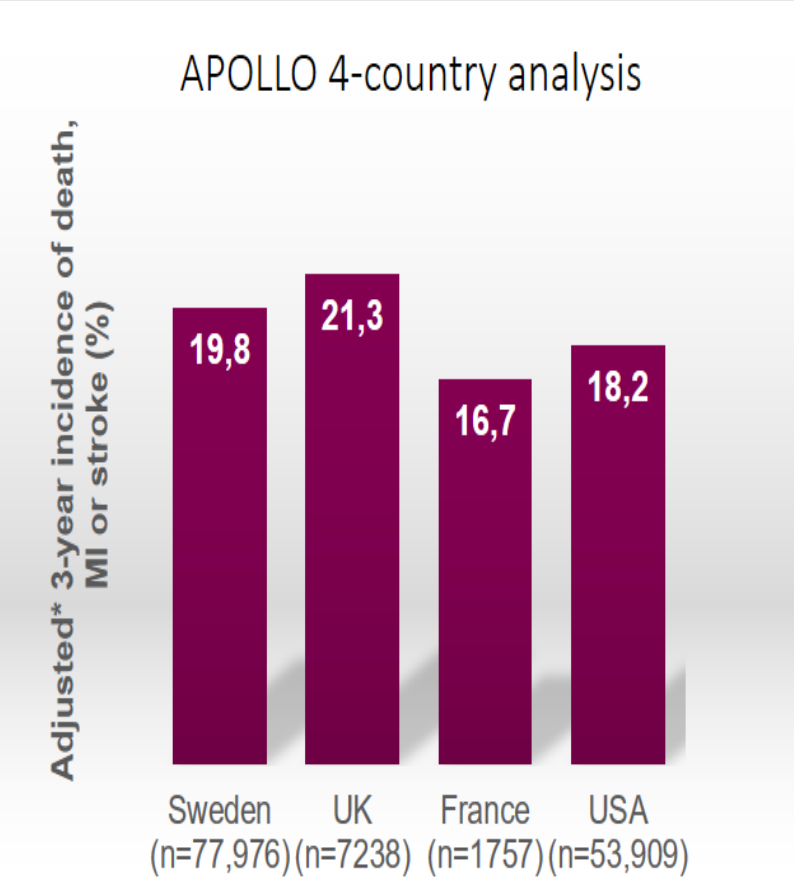
Biological Issue	Residual Cholesterol Risk	Residual Inflammatory Risk	Residual Thrombotic Risk	Residual Triglyceride Risk	Residual Lp(a) Risk	Residual Diabetes Risk
						
Critical Biomarker	LDL-C ≥100 mg/dL	hsCRP ≥2mg/L	No simple biomarker	TG ≥150mg/dL	Lp(a) ≥50mg/dL	HbA1c Fasting glucose
Potential Intervention	Targeted LDL/Apo B Reduction	Targeted Inflammation Reduction	Targeted Antithrombotic Reduction	Targeted Triglyceride Reduction	Targeted Lp(a) Reduction	SGLT2 Inhibitors GLP-1 Agonists

Mortalità a 6 mesi

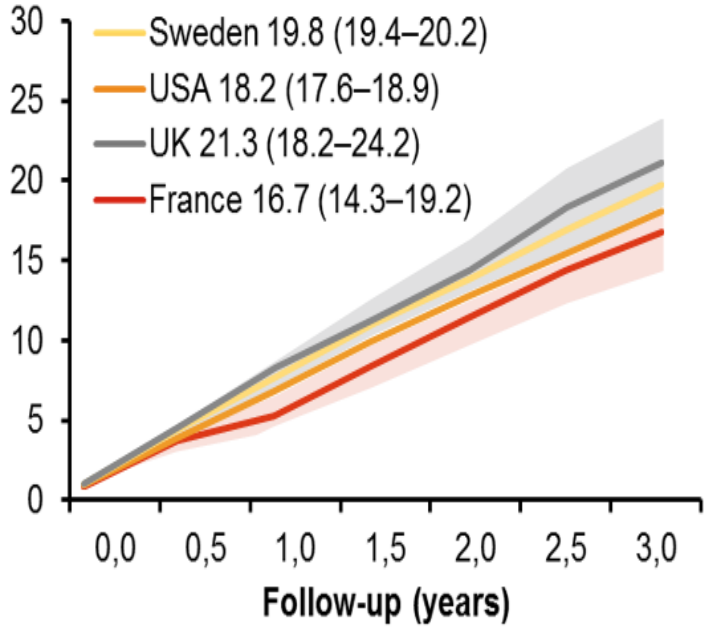


Residual risk

~1 in 5 patients who were event-free for the first year post-MI suffered an MI, stroke or CV death within 3 years

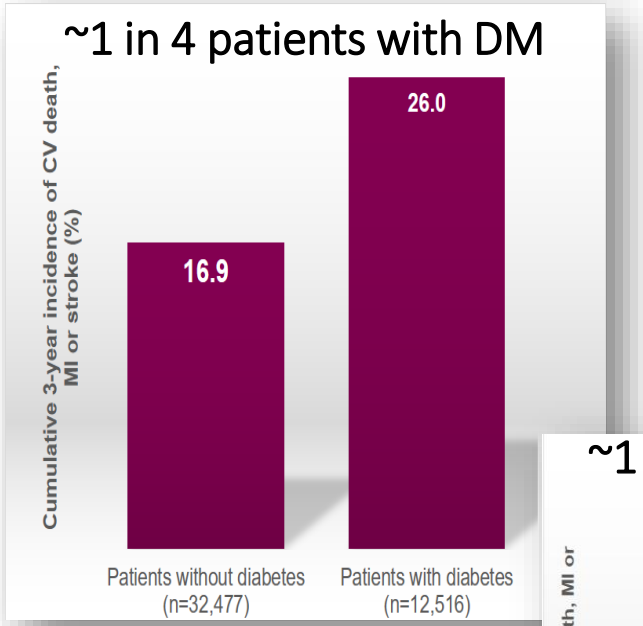


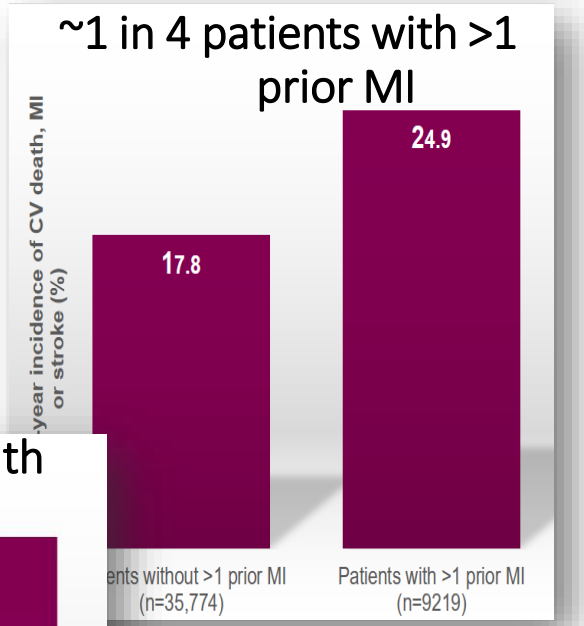
3 years absolute cumulative risk
MI, stroke, CV death

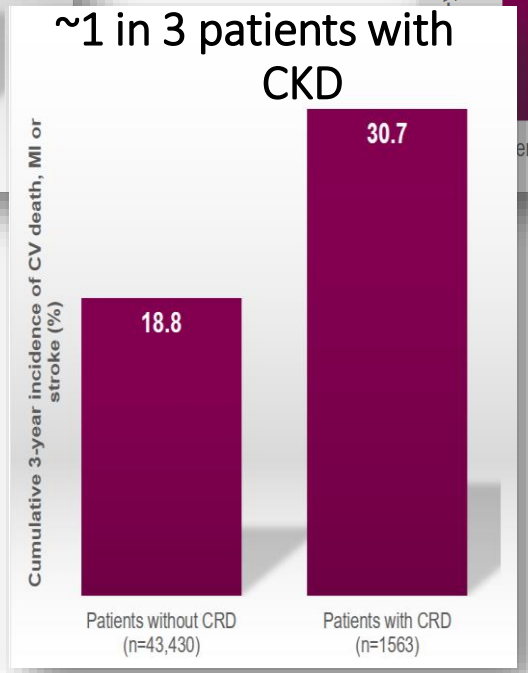


[1]Rapsomaniki E, et al. ESC Late Breaking Registry abstract 2014: In press; [2] DeVore S, et al. ISPOR poster 2014;
[3]Jernberg T, et al. Eur Heart J 2015;36:1163–1170; [4]Blin P, et al. Eur Heart J 2014;35:(Suppl 1)150 (Abstract P790)

Incidence of MI, stroke or CV death within 3 years in event-free patents for 1 year post-MI[1]

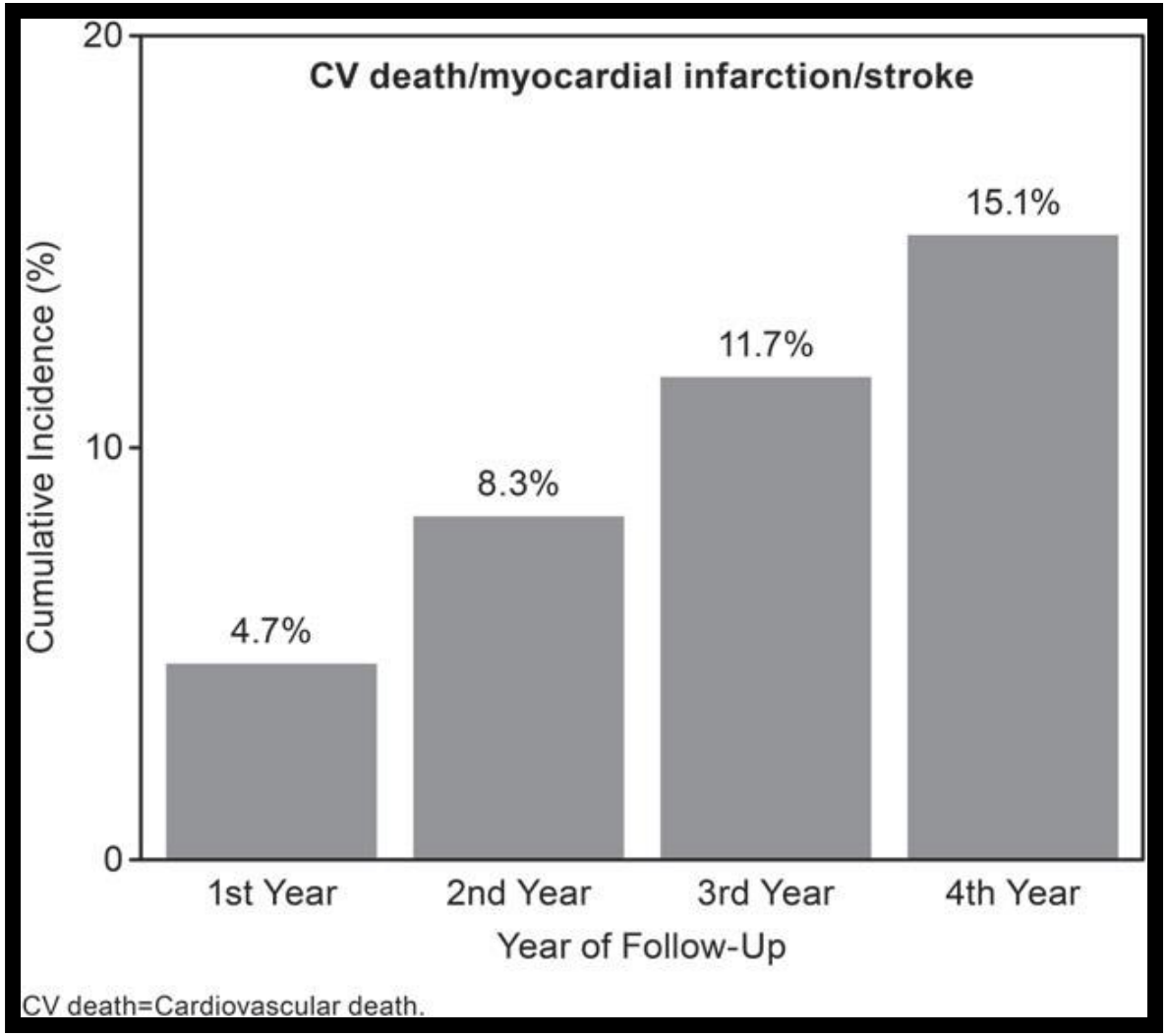






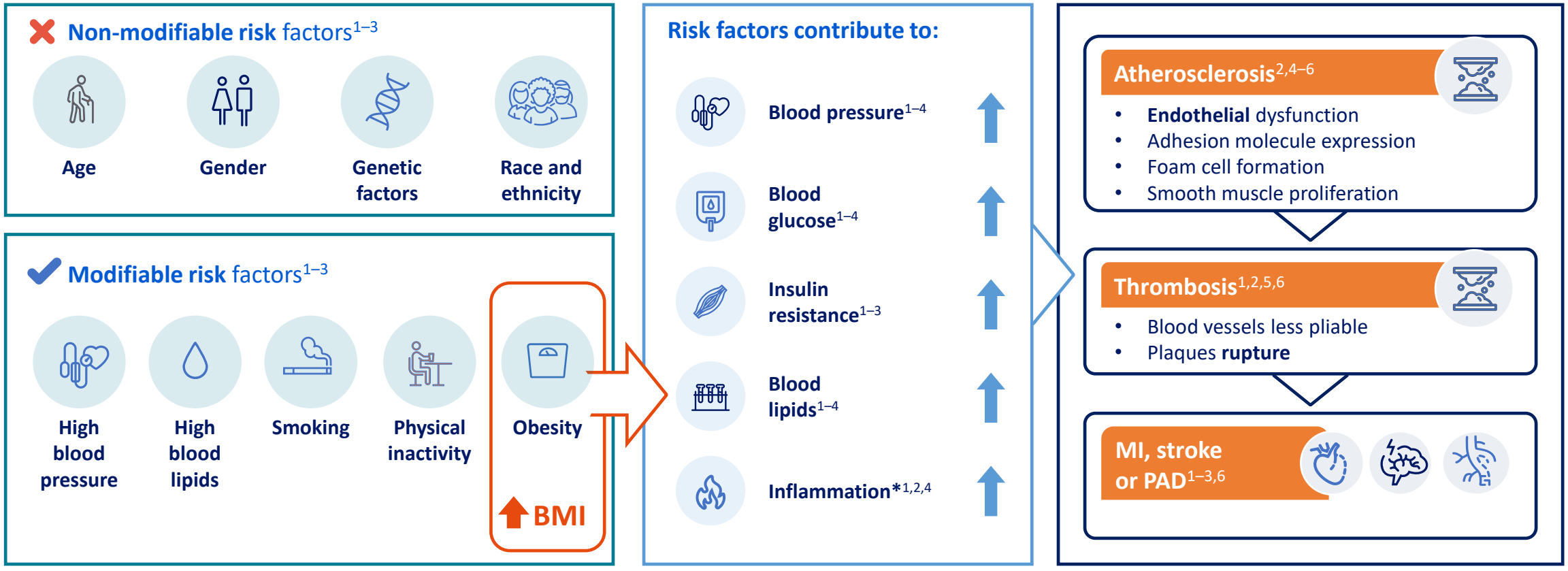
[1] Timmis A, et al. BMJ 2016;353:i3163

Residual Ischemic Risk and Its Determinants in Patients With Previous Myocardial Infarction and Without Prior Stroke or TIA: Insights From the REACH Registry



Clinical Cardiology 2016; **39(11)**:670–677

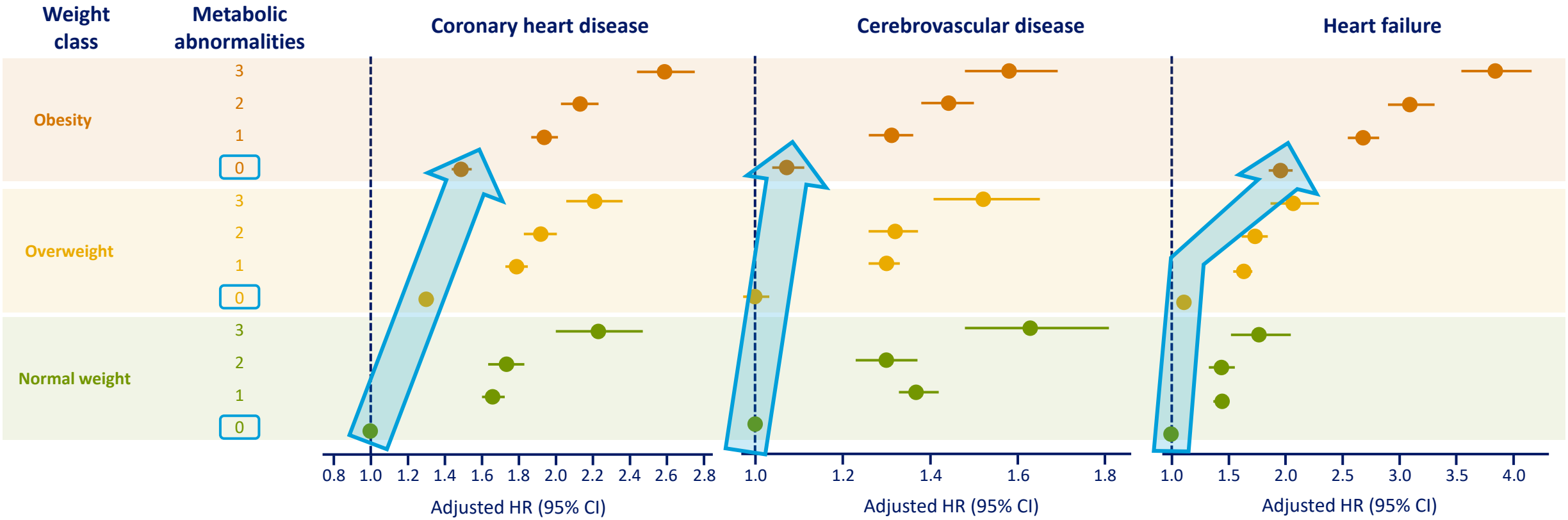
L'Obesità è un Fattore di Rischio Cardiovascolare Prioritario
perchè clasterizza diversi altri Risk Factors



1. Graham I, et al. Eur Heart J 2007;28:2375–414;
2. Piepoli MF, et al. Eur Heart J 2016;37:2315–81; 3.
3. WHO. Global Atlas on Cardiovascular Disease Prevention and Control. 2011. Available at: https://www.who.int/publications/i/item/9789241564373. Accessed January 2023;
4. Burke GL, et al. Arch Intern Med 2008;168:928–35;
5. Ayer J, et al. Eur Heart J 2015;36:1371–6;
6. Ross R. Am Heart J 1999;138(5 Pt 2):S419–20.

Il Sovrappeso e l'Obesità aumenta il rischio di Eventi CV anche in assenza di altre alterazioni metaboliche

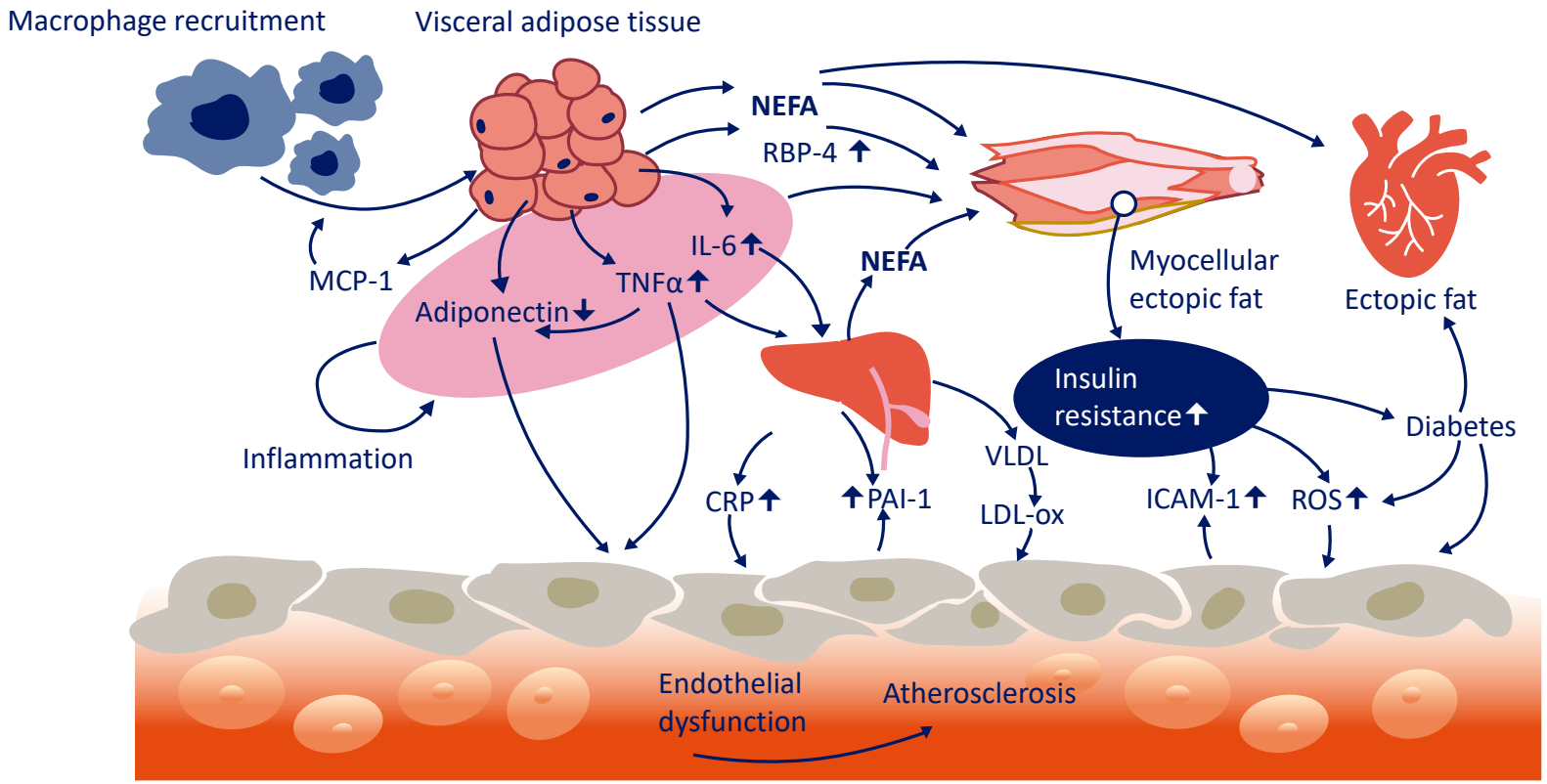
Peso Corporeo, Stato Metabolico ed Eventi CV in 3.5 million di adulti UK



Caleyachetty R et al. J Am Coll Cardiol. 2017;70:1429–37.

L'Infiammazione come Link tra Obesità e CVD

Both abdominal (visceral fat) and insulin resistance may contribute to CVD in obesity



Both abdominal (visceral fat) and insulin resistance may contribute to CVD in obesity

Visceral fat contributes to endothelial dysfunction through activation of inflammatory pathways

Van Gaal LF et al. Nature 2006;444:875–80.

L’infiammazione svolge un ruolo Fisiopatologico Importante ?

1) Cardiopatia Ischemica

2) Scompenso Cardiaco

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1) Cardiopatia Ischemica

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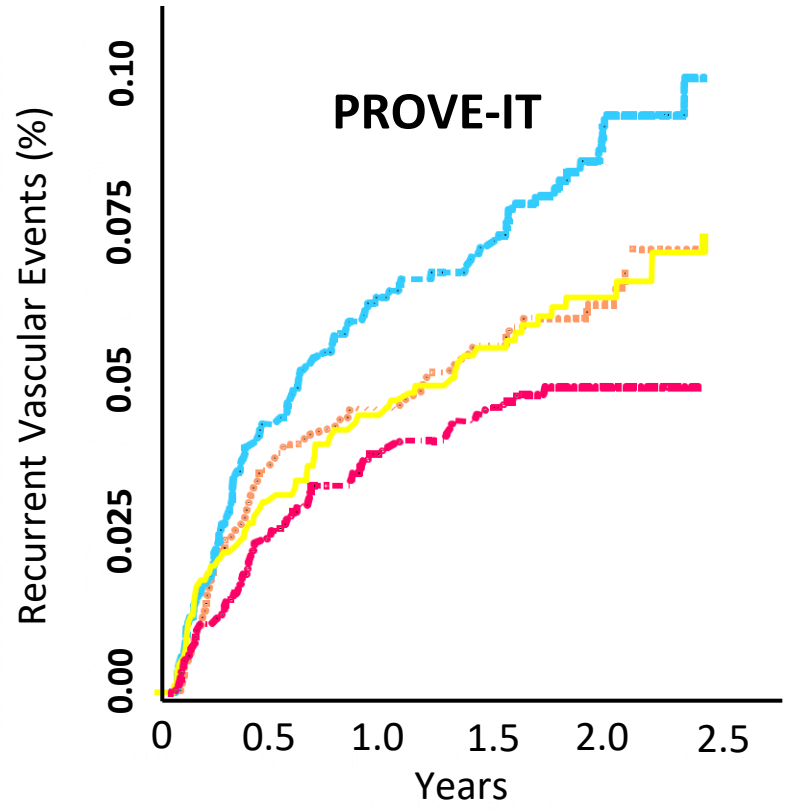
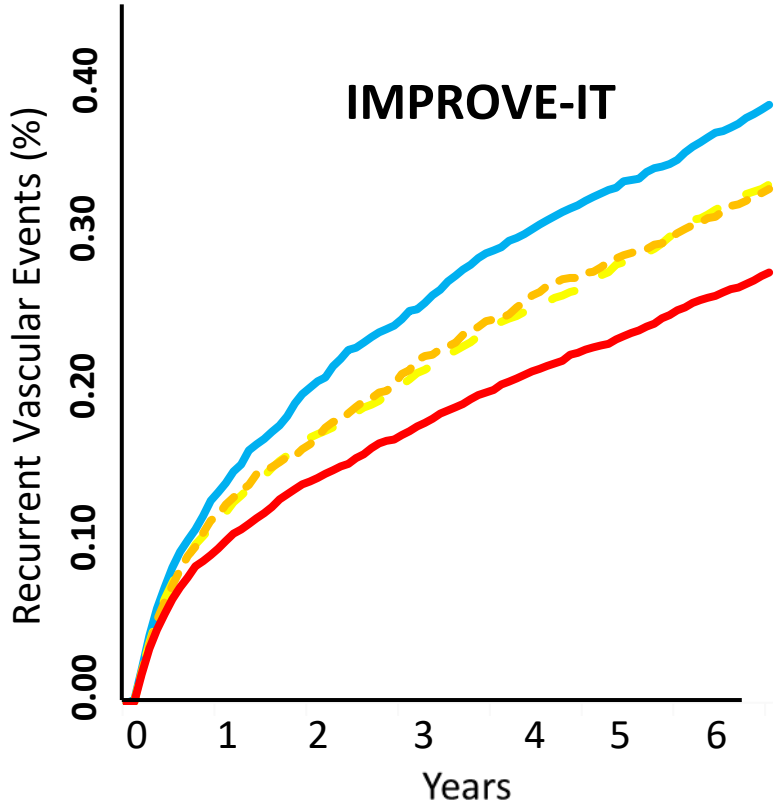
Un Rischio Infiammatorio Residuo che pondera e completa l'effetto benefico delle Statine



Ridker et al, NEJM 2005;352:20-8



Bohula et al, Circulation 2015;132:1224-33

LDL >70 mg/dL
hsCRP > 2mg/L
Neither Goal Achieved

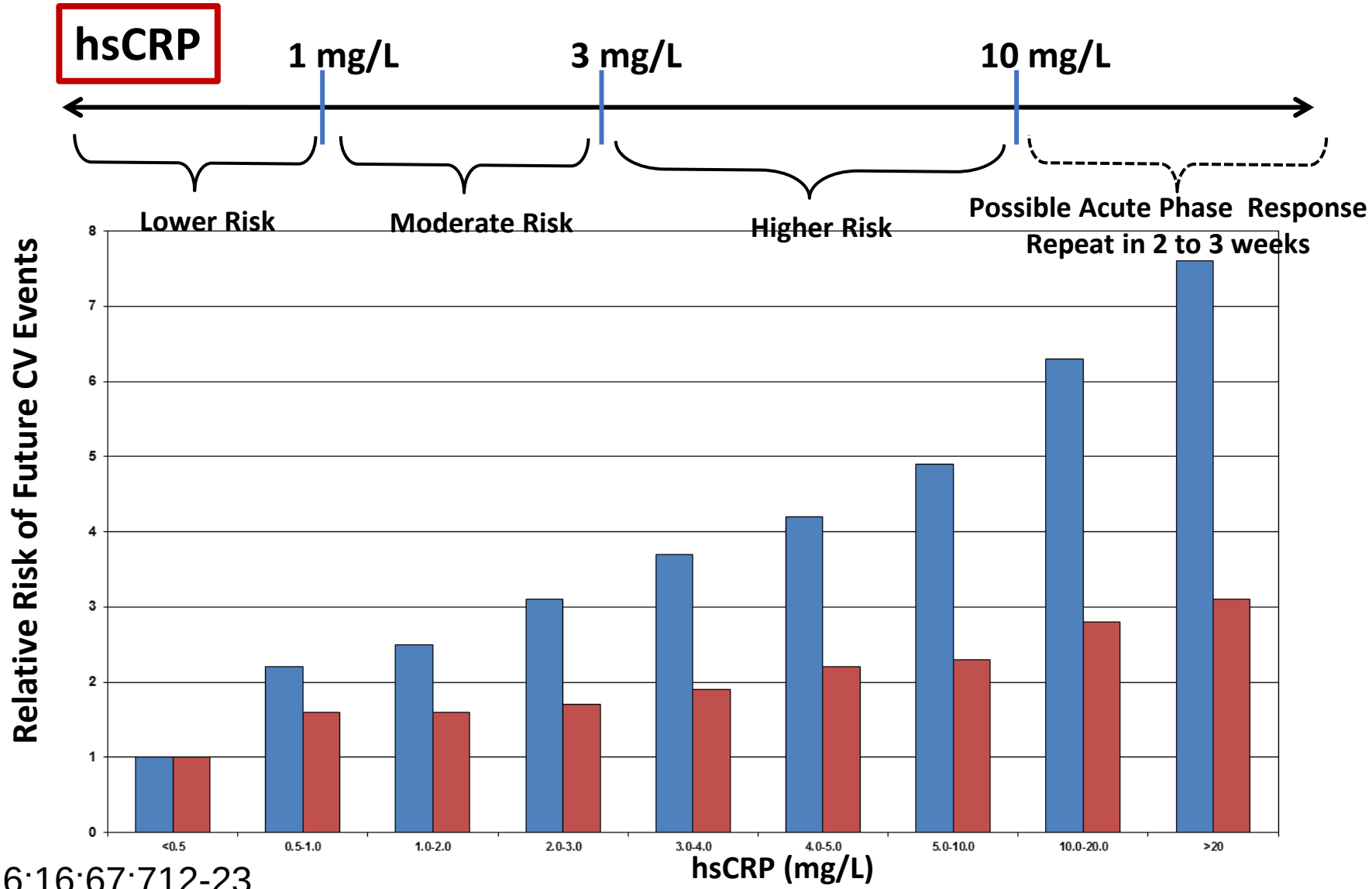
LDL <70 mg/dL
hsCRP > 2mg/L
LDL Goal Achieved

LDL > 70 mg/dL
hsCRP < 2mg/L
hsCRP Goal Achieved

LDL <70 mg/dL
hsCRP < 2mg/L
Dual Goals Achieved

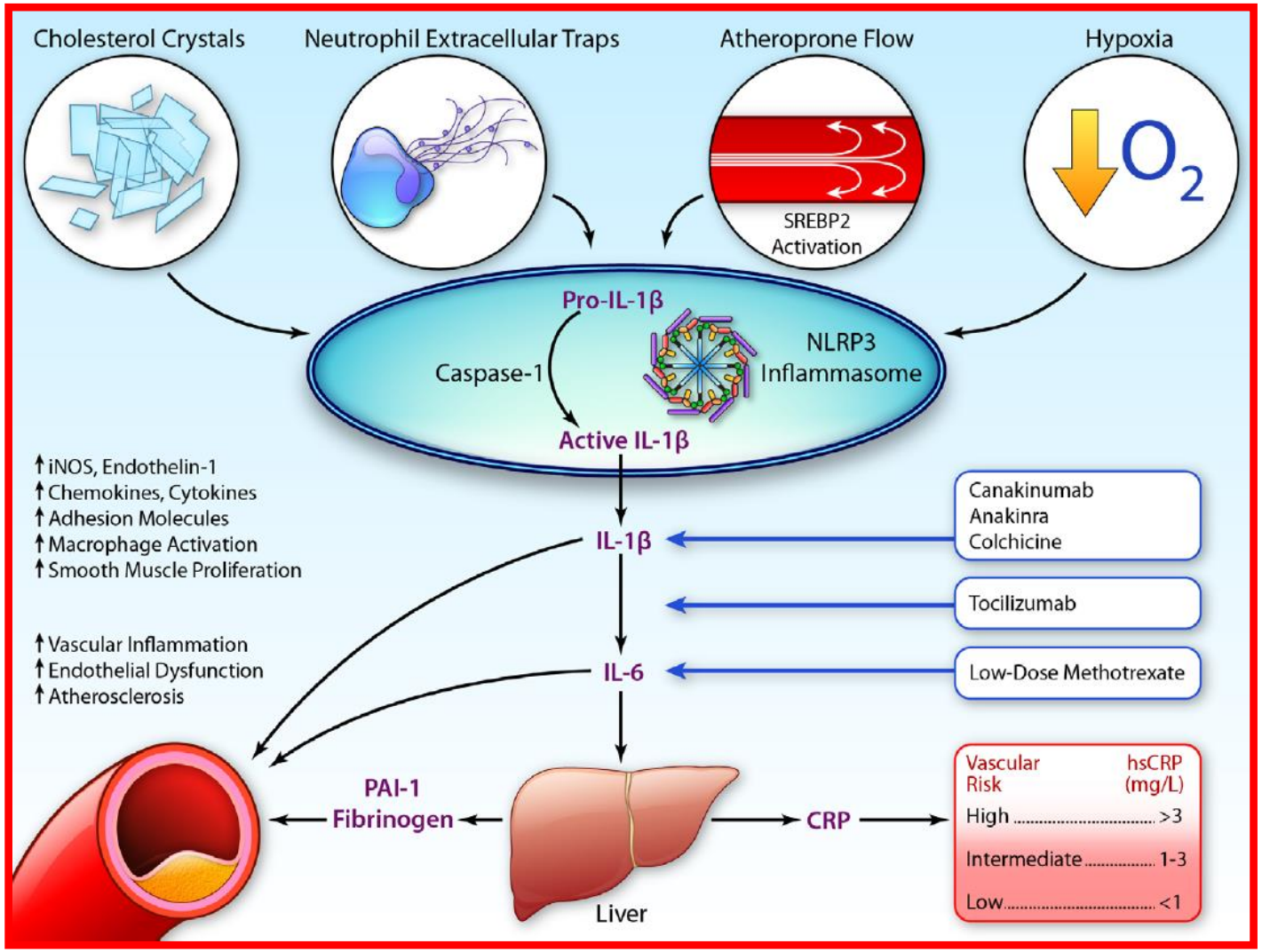
Ridker et al, Eur Heart J 2016;37:1729-22

Un facile Test per identificare i pazienti a rischio: High Sensitivity C-Reactive Protein (hsCRP)



Ridker PM. JACC 2016;16:67:712-23

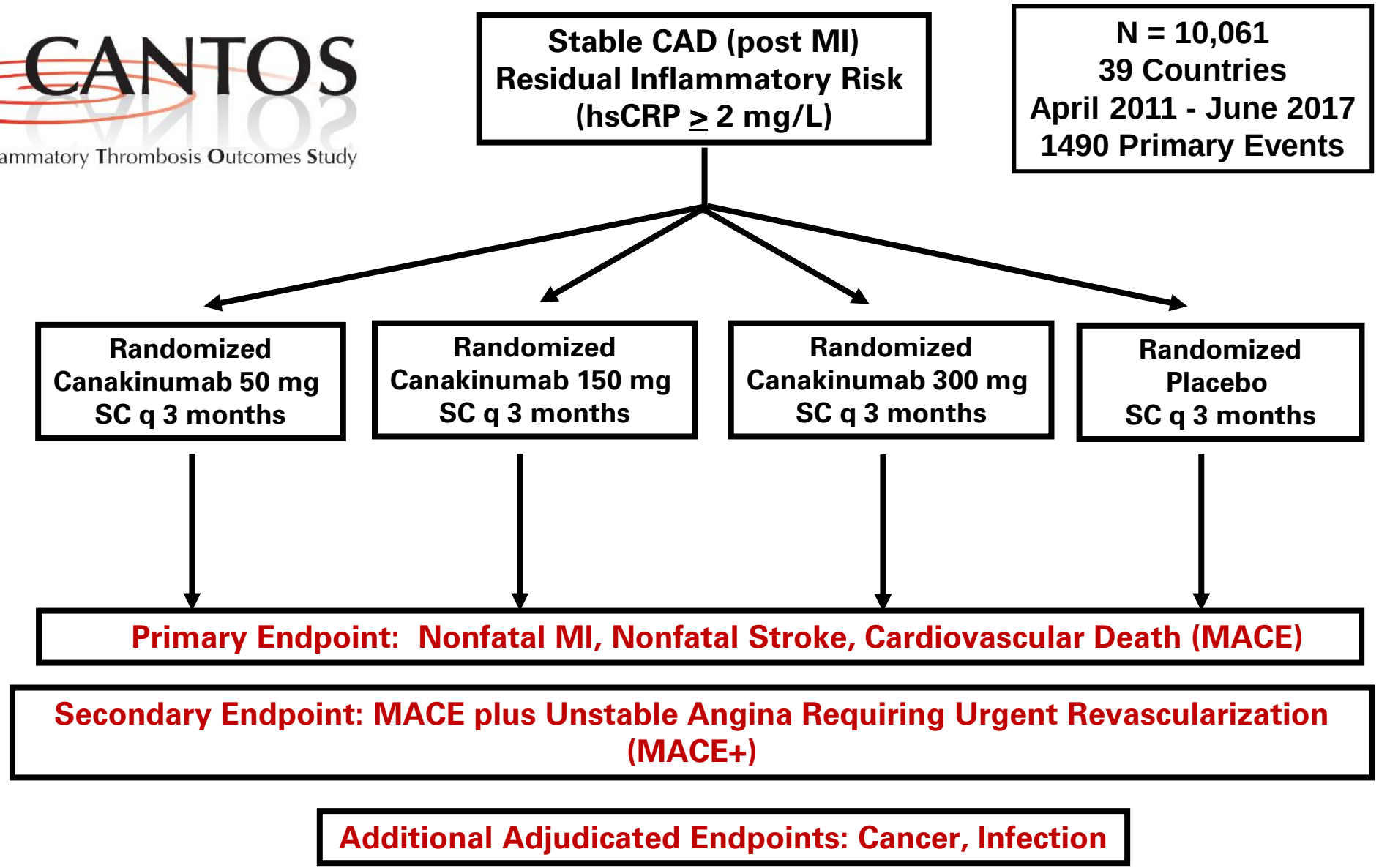
Dalla PCR all' **IL-6** e **IL-1**: Risalendo la cascata infiammatoria identificando i **NUOVI target di protezione aterosclerotica**



Ridker PM. Circ Res 2016;118:145-156.

Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

CANTOS
Canakinumab Anti-inflammatory Thrombosis Outcomes Study

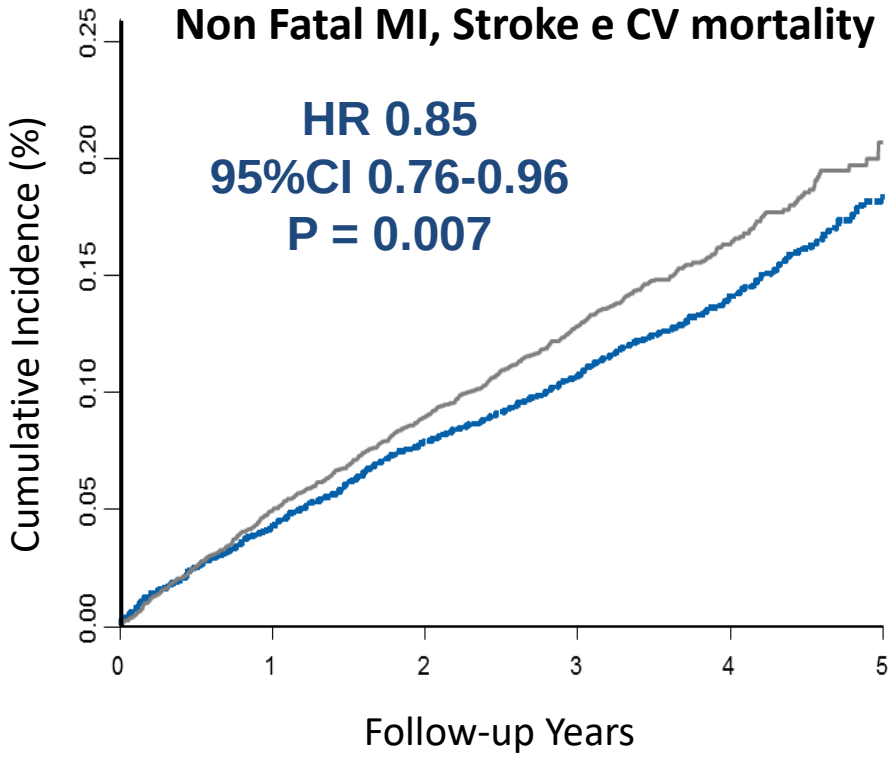


Ridker PM et al. N Engl J Med. 2017;377:1119-31

CANTOS: Primary Cardiovascular Endpoints

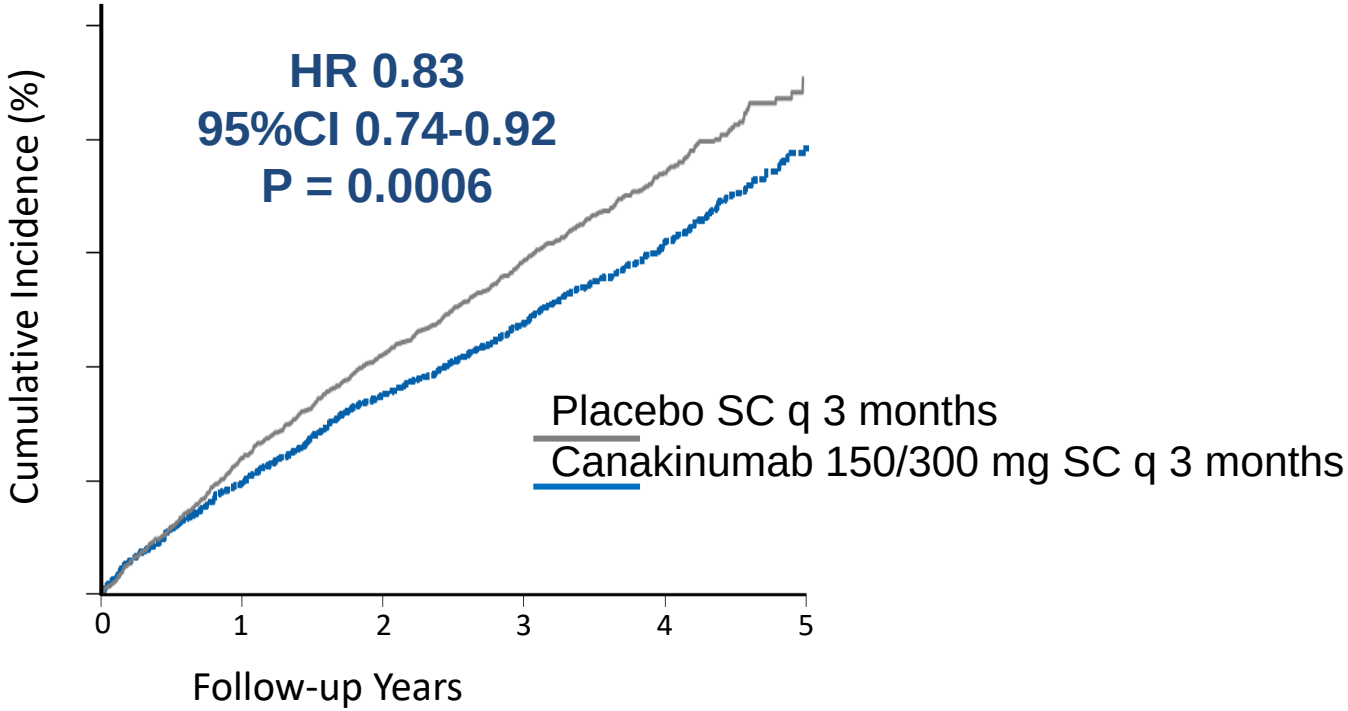
MACE

Non Fatal MI, Stroke e CV mortality



MACE – Plus

(+ rivascolarizzazione)



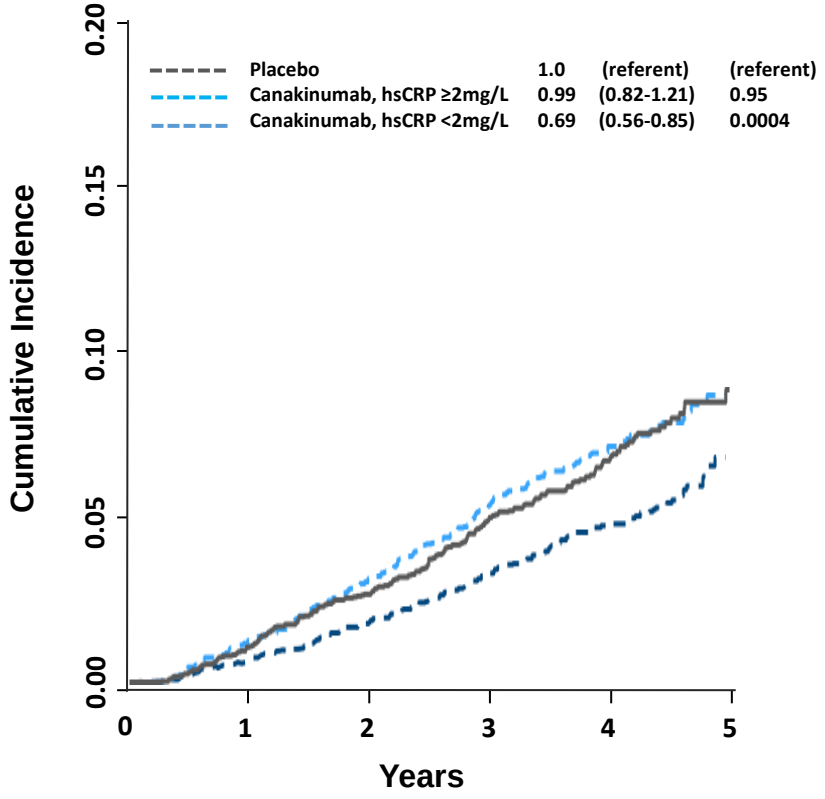
35 - 40% reductions in hsCRP and IL-6
No change in LDLC

Ridker PM et al. N Engl J Med. 2017;377:1119-31

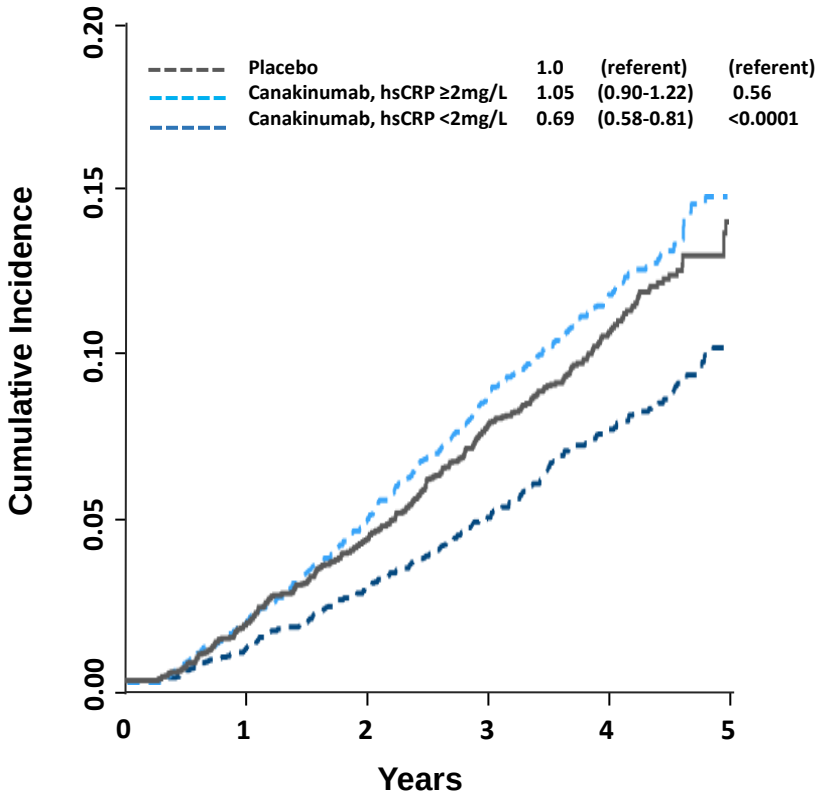
CANTOS : 31% Reduction in Cardiovascular Mortality and All-Cause Mortality

Among Participants with Robust Inhibition of the Inflammatory Response

CANTOS - Cardiovascular Mortality



CANTOS - All Cause Mortality



35 - 40% reductions in hsCRP and IL-6
No change in LDLC

Ridker PM Circulation (in press)

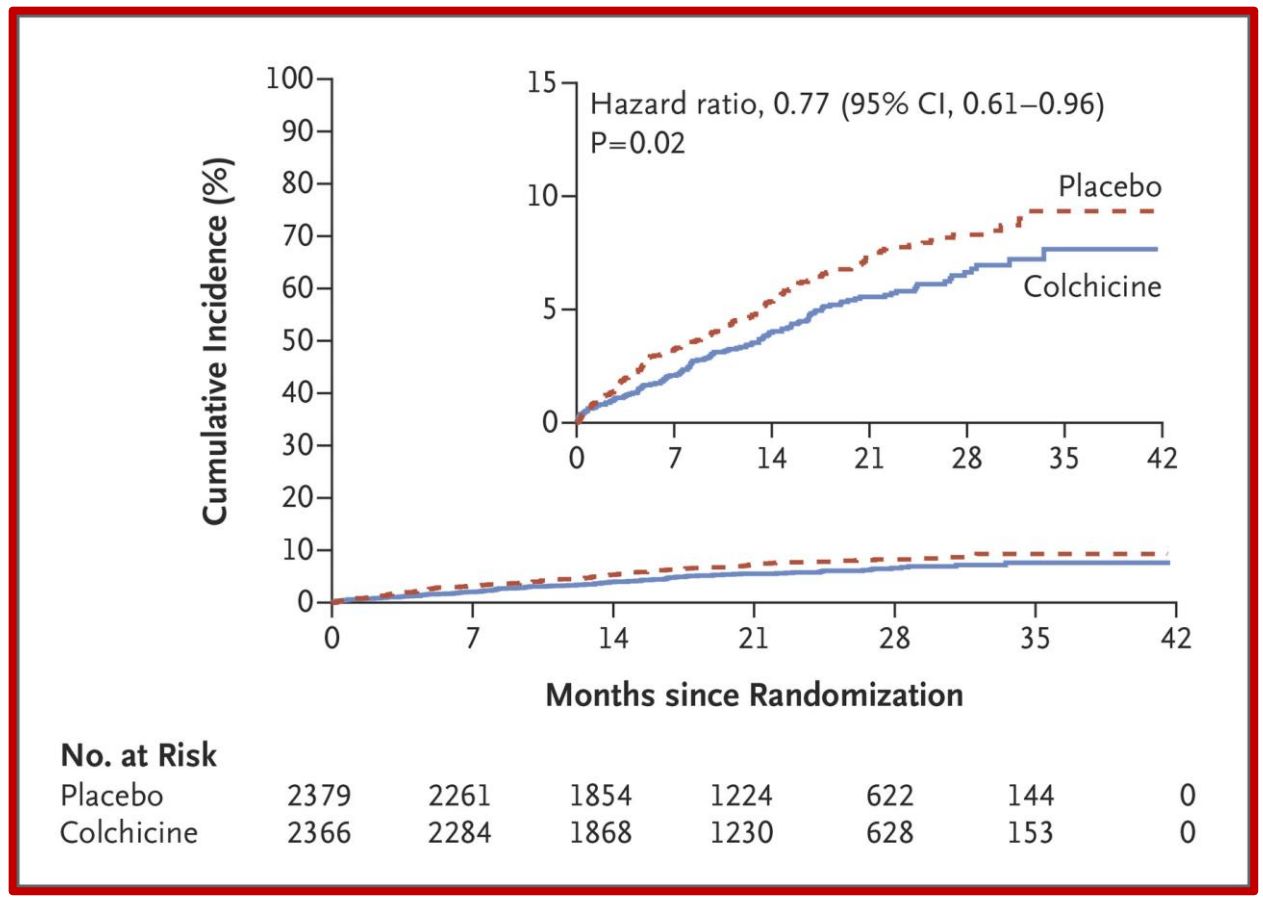
Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction

Jean-Claude Tardif, M.D., Simon Kouz, M.D., David D. Waters, M.D., Olivier F. Bertrand, M.D., Ph.D., et al.

Table 1. Characteristics of the Patients.*

Characteristic	Colchicine (N=2366)	Placebo (N=2379)
Age — yr	60.6±10.7	60.5±10.6
Female sex — no. (%)	472 (19.9)	437 (18.4)
White race — no./total no. (%)†	1350/1850 (73.0)	1329/1844 (72.1)
Body-mass index	28.2±4.8	28.4±4.7
Current smoking — no./total no. (%)	708/2366 (29.9)	708/2377 (29.8)
Hypertension — no. (%)	1185 (50.1)	1236 (52.0)
Diabetes — no. (%)	462 (19.5)	497 (20.9)
History of myocardial infarction — no. (%)	370 (15.6)	397 (16.7)
History of PCI — no. (%)	392 (16.6)	406 (17.1)
History of CABG — no. (%)	69 (2.9)	81 (3.4)
History of heart failure — no. (%)	48 (2.0)	42 (1.8)
History of stroke or TIA — no. (%)	55 (2.3)	67 (2.8)
Time from index myocardial infarction to randomization — days	13.4±10.2	13.5±10.1
PCI for index myocardial infarction — no./total no. (%)	2192/2364 (92.7)	2216/2375 (93.3)
Medication use — no. (%)		
Aspirin	2334 (98.6)	2352 (98.9)
Other antiplatelet agent	2310 (97.6)	2337 (98.2)
Statin	2339 (98.9)	2357 (99.1)
Beta-blocker	2116 (89.4)	2101 (88.3)

* Plus–minus values are means ±SD. Data were missing on the following characteristics: age (assessed according to date of birth; see below) for 435 patients (215 in the colchicine group and 220 in the placebo group), body-mass index (the weight in kilograms divided by the square of the height in meters) for 5 (1 and 4 patients, respectively), and information about the index myocardial infarction for 6 (2 and 4 patients, respectively). Date of birth and race were not required fields because both were considered in some countries to be sensitive data that could allow for the identification of patients. For statistical reporting, missing information regarding the day of birth was replaced by 15, and missing information regarding the month and day of birth was replaced by July 1. CABG denotes coronary-artery bypass graft surgery, PCI percutaneous coronary intervention, and TIA transient ischemic attack.
† Race was reported by the patient.



L’infiammazione svolge un ruolo Fisiopatologico Importante

1) Cardiopatia Ischemica

2) Scompenso Cardiaco

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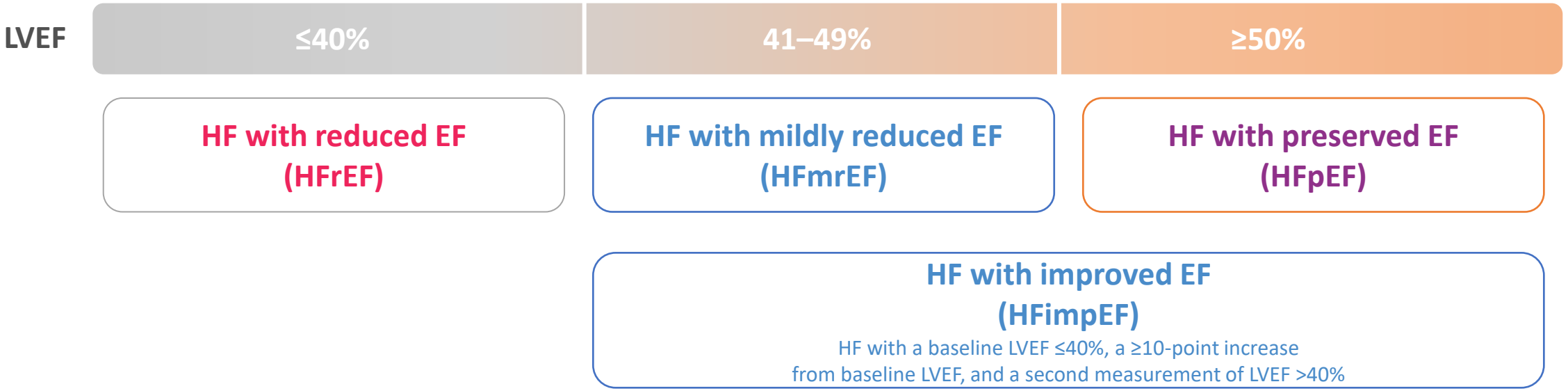
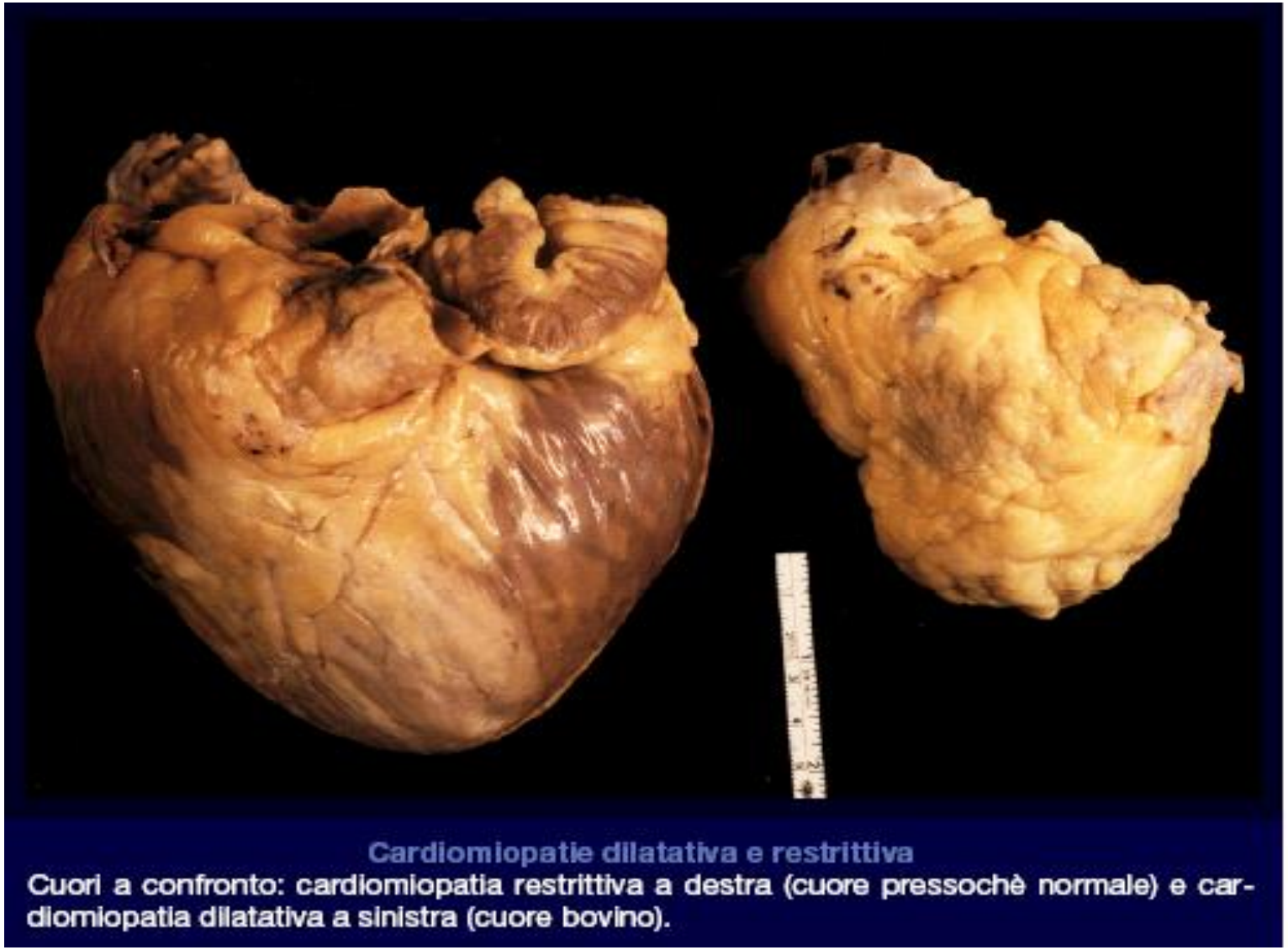
La nuova Classificazione dello Scompenso Cardiaco

ESC
European Society
of Cardiology



EF, ejection fraction; HF, heart failure; LVEF, left ventricular ejection fraction.
Bozkurt B *et al*. *Eur J Heart Fail.* 2021;23:352.

HFrEF vs HFpEF



Cardiomiopatie dilatativa e restrittiva

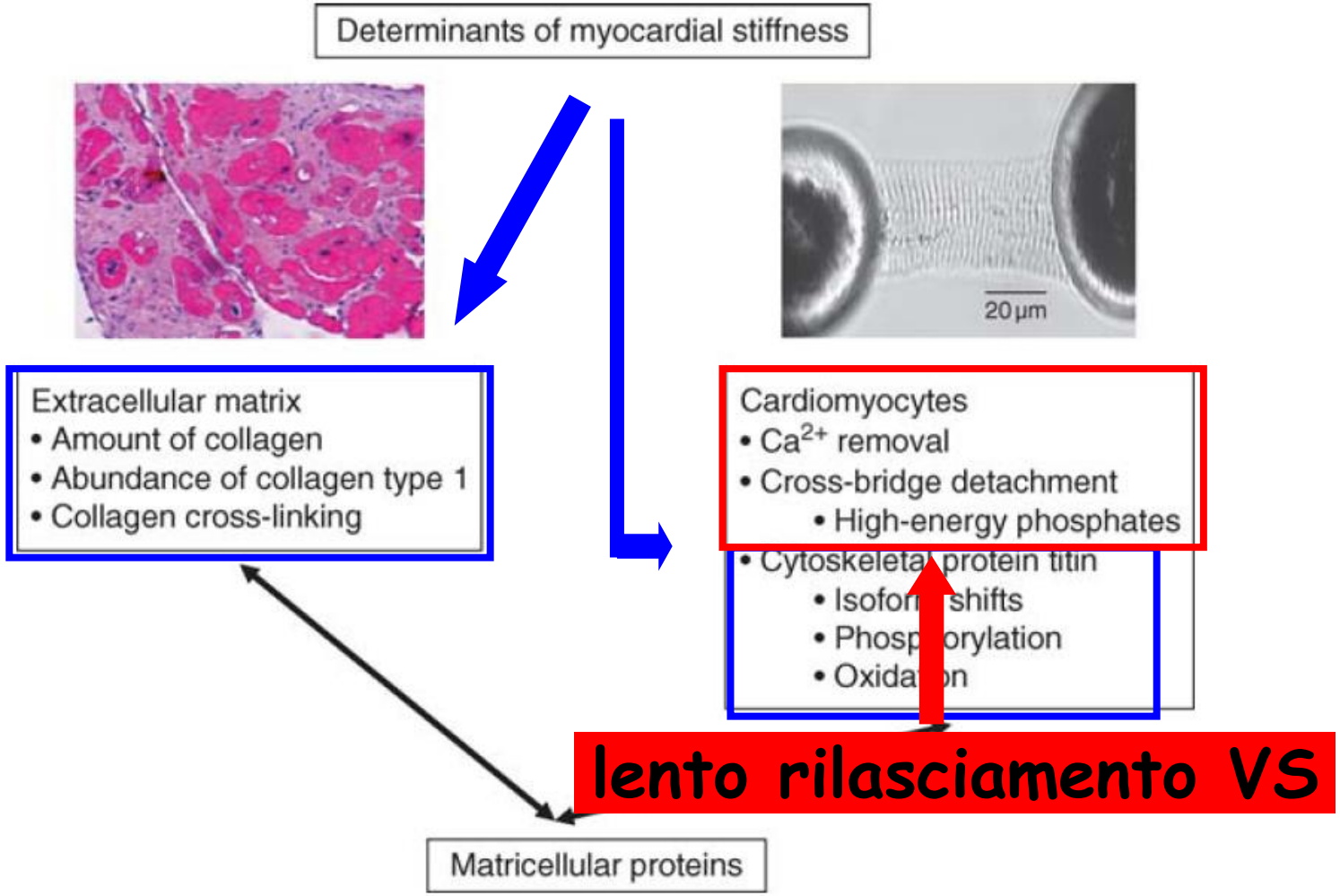
Cuori a confronto: cardiomiopatia restrittiva a destra (cuore pressochè normale) e cardiomiopatia dilatativa a sinistra (cuore bovino).

Ipertrofia di grado non severo

The left ventricle is markedly thickened in this patient with severe hypertension that was untreated for many years. The myocardial fibers have undergone hypertrophy

Meccanismi dello Scompenso HFpEF

ridotta compliance diastolica



lento rilasciamento VS

Borlaug B and Paulus WJ, 2010, Eur Heart J

Numerosi e differenti Fattori di Rischio sono associati all'HFpEF

Overweight/obesity **80%**

Hypertension **60–80%**

Type 2 diabetes **20–40%**

Atrial fibrillation

Chronic kidney disease

Coronary artery disease

Advanced age

COPD

Anaemia

Female sex

Sleep disorders

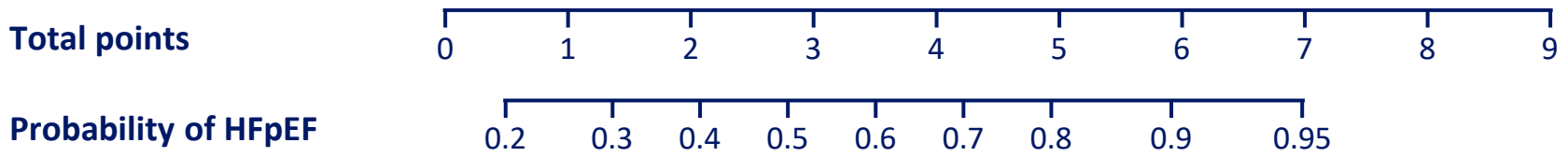
*COPD, chronic obstructive pulmonary disease; **HFpEF, heart failure with preserved ejection fraction***

1. Upadhya B et al. Curr Heart Fail Rep 2015;12:205–214; 2. Shah SJ et al. Circulation 2016;134:73–90; 3. Gomberg-Maitland M et al. JACC Heart Fail 2016;4:325–328; 4. Ho JE et al. Circ Heart Fail 2013;6:279–286;
5. Haykowsky MJ et al. JACC Heart Fail 2018;6:640–649

Diagnosi di HFpEF

The H_2FpEF score

	Clinical variable	Values	Points
H_2	**H**eavy **H**ypertensive	BMI >30 kg/m^2 Use of ≥2 antihypertensive medications	2 1
F	Atrial **f**ibrillation	Paroxysmal or persistent	3
P	**P**ulmonary hypertension	Defined as pulmonary artery systolic pressure >35 mmHg	1
E	**E**lder	Age >60 years	1
F	**F**illing pressure	Doppler echocardiographic E/e' >9	1
H_2FpEF score			Sum (0–9)



Obesity

+

Hypertension

+

Atrial fibrillation

+

Elderly

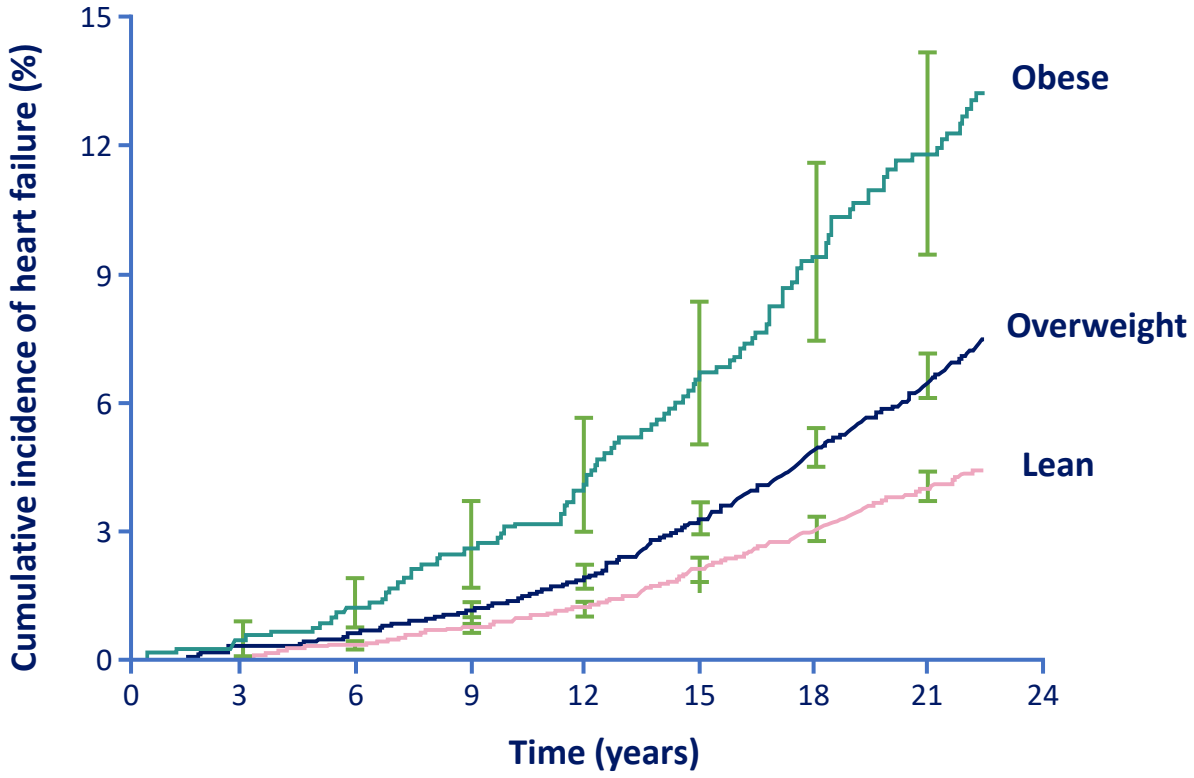
↓

90% probability

BMI, body mass index; HFpEF, heart failure with preserved ejection fraction; E/e', mitral annular early diastolic velocity

Reddy YNV et al. Circulation 2018;138:861–870

L'Obesità comporta un aumento di incidenza di HFpEF



Association of Obesity-Related Traits With HF Subtypes in Sex-Pooled Analyses		
		Multivariable-adjusted
Predictor	Outcome	HR (95% CI)*
BMI	Incident HFpEF	1.34 (1.24; 1.45)
	Incident HFrEF	1.18 (1.10; 1.27)
Waist circumference	Incident HFpEF	1.32 (1.22; 1.44)
	Incident HFrEF	1.19 (1.10; 1.29)

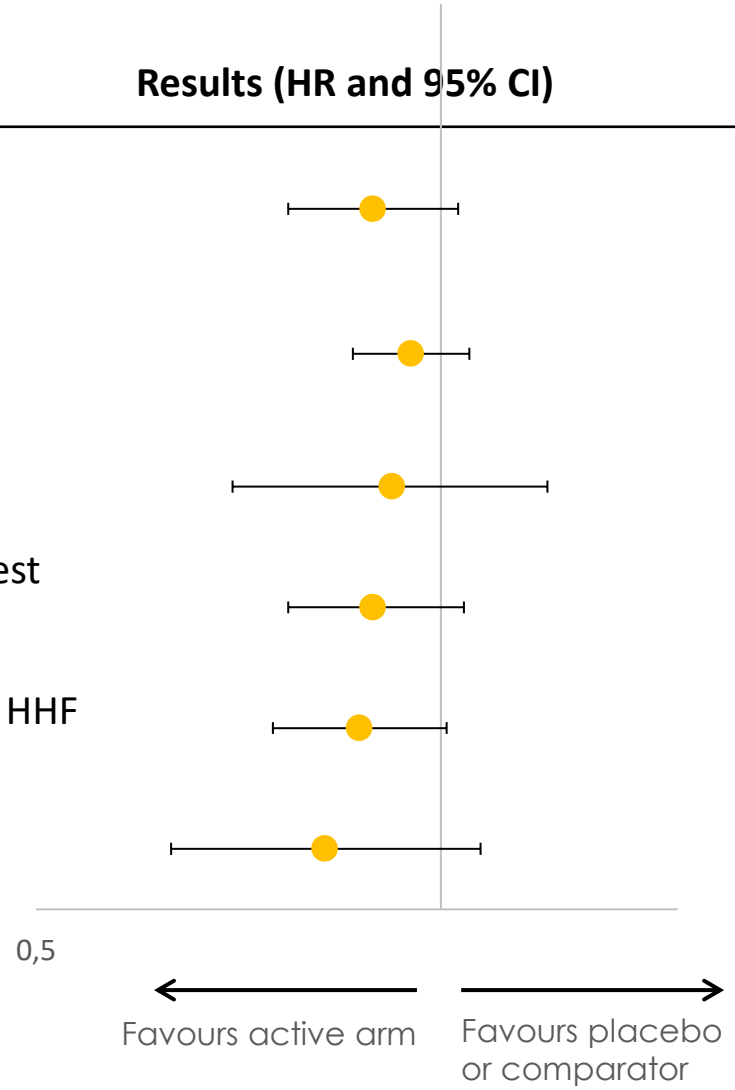
Kenchaiah S et al. Circulation 2009;119:44–52;

Kenchaiah S et al. N Engl J Med 2002;347:305–313;

Savji N et al. JACC Heart Fail 2018;6;701–709

Nessuno studio ha raggiunto la riduzione del Primary Endpoint (Morte CV + Ospedalizzazione per HF)

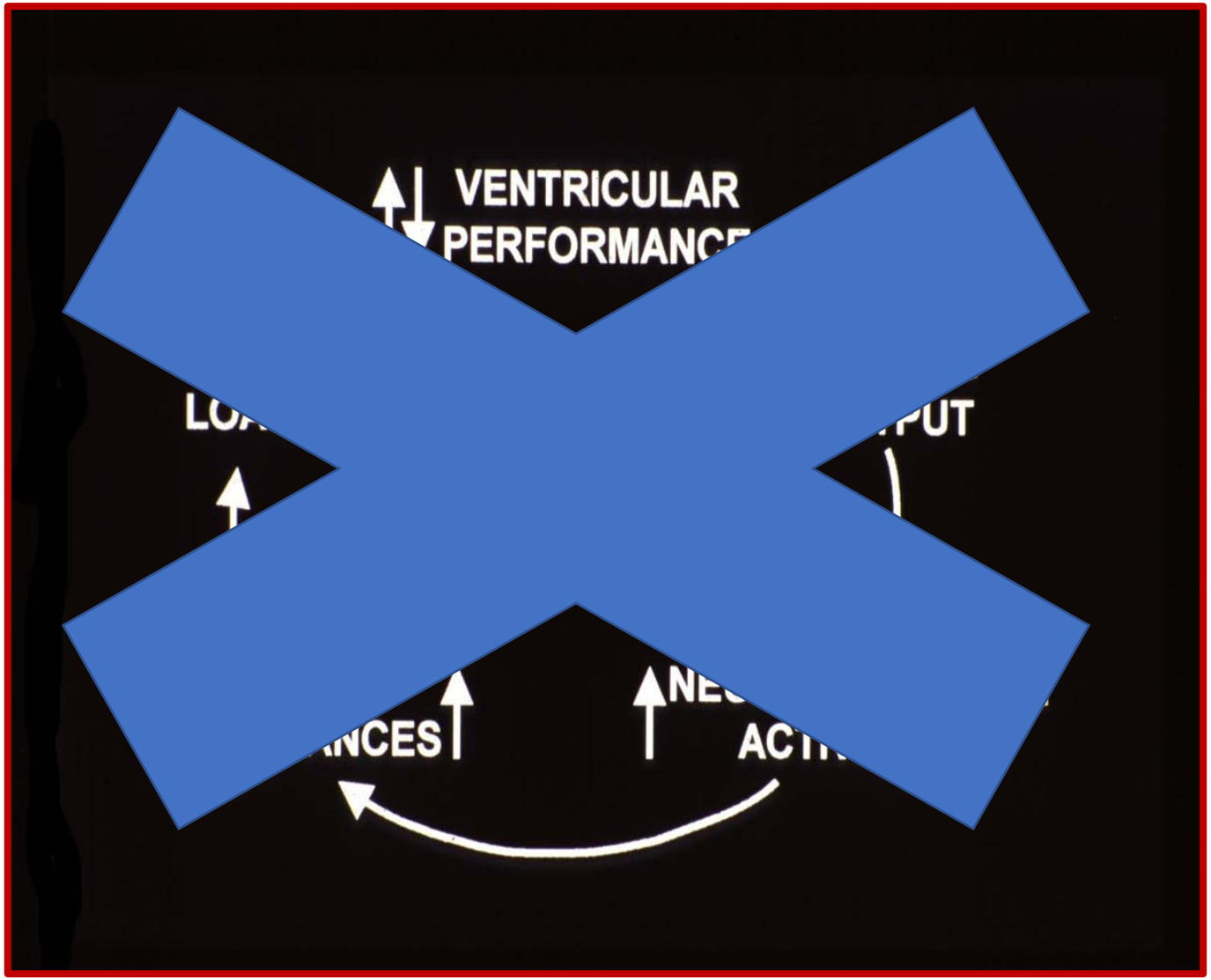
Trial	Treatment arms	Primary endpoint definition
CHARM-Preserved[2]	**Candesartan** vs placebo	HHF+CV death
I-PRESERVE[3]	**Irbesartan** vs placebo	Hospitalization for CV cause+ all-cause mortality
PEP-CHF[4]	**Perindopril** vs placebo	All-cause mortality+HHF
TOPCAT[5]	**Spironolactone** vs placebo	HHF+CV death+aborted cardiac arrest
PARAGON-HF[6]	**Sacubitril/valsartan** vs valsartan	CV death+total (first and recurrent) HHF
DIG-PEF[7]	**Digoxin** vs placebo	HHF+HF mortality



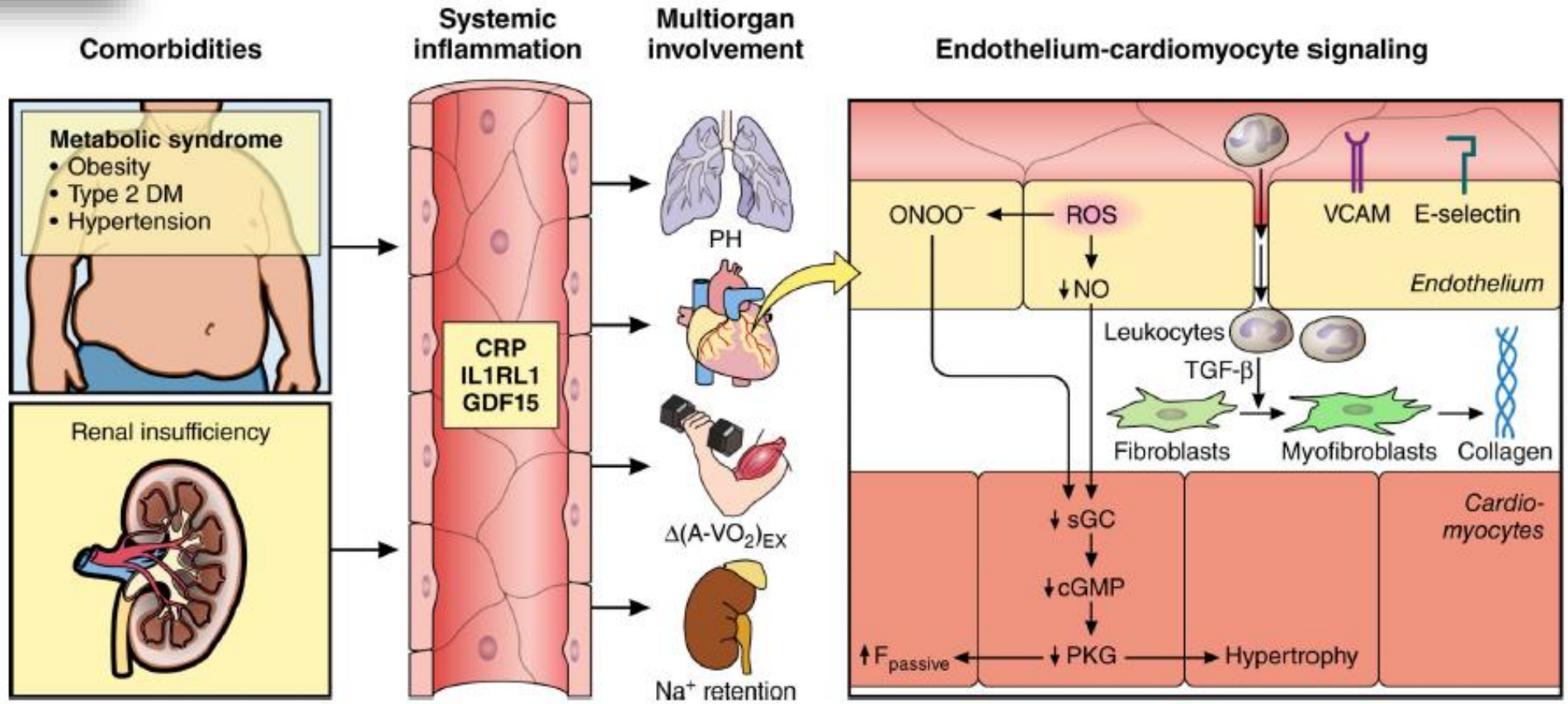
CI, confidence interval; CV, cardiovascular; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HHF, hospitalization for heart failure; HR, hazard ratio. See slide notes for references.

Meccanismo fisiopatologico prevalente

circolo vizioso di attivazione neuroendocrina



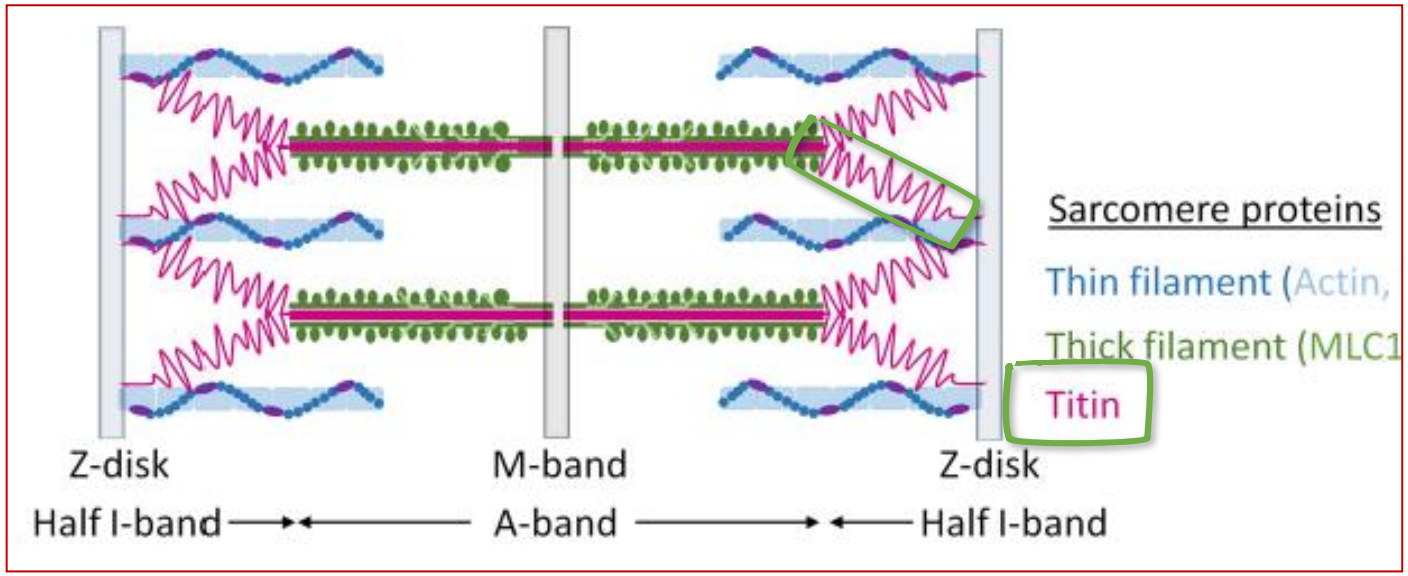
Abbiamo un meccanismo fisiopatologico noto che ha come **mandante** tutte queste comorbidità; come **spietato sicario** l'Infiammazione e come **danno arrecato** il blocco del segnale intracellulare NO dipendente

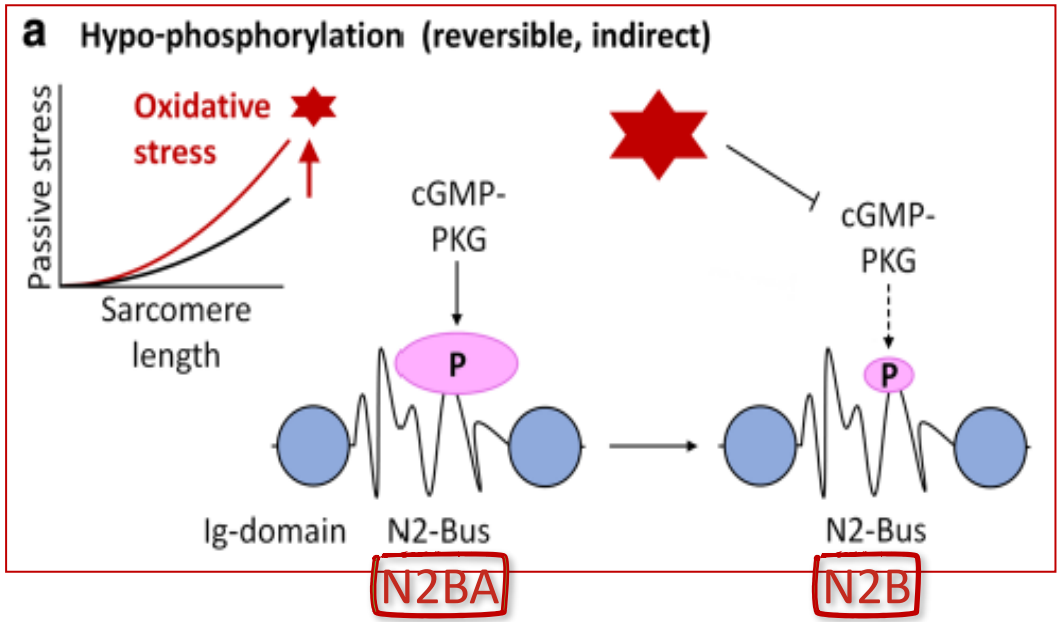


Shah JS et al, Circulation. 2016

Aumentata Compliance Ventricolare

Titina: una proteina sarcomerica con profilo di complianza variabile in base allo stato di fosforillazione





The giant protein Titin functions as a molecular spring:

- is extended during diastolic stretch
- recoils elastically during systoleTwo isoforms: **N2B (>stiff)** and **N2BA (>elastic)**

Titin is responsible for most of the passive tension of myocardium

Beckendorf L, Linke WA. *J Muscle Res Cell Motil* 2015;36:25–36

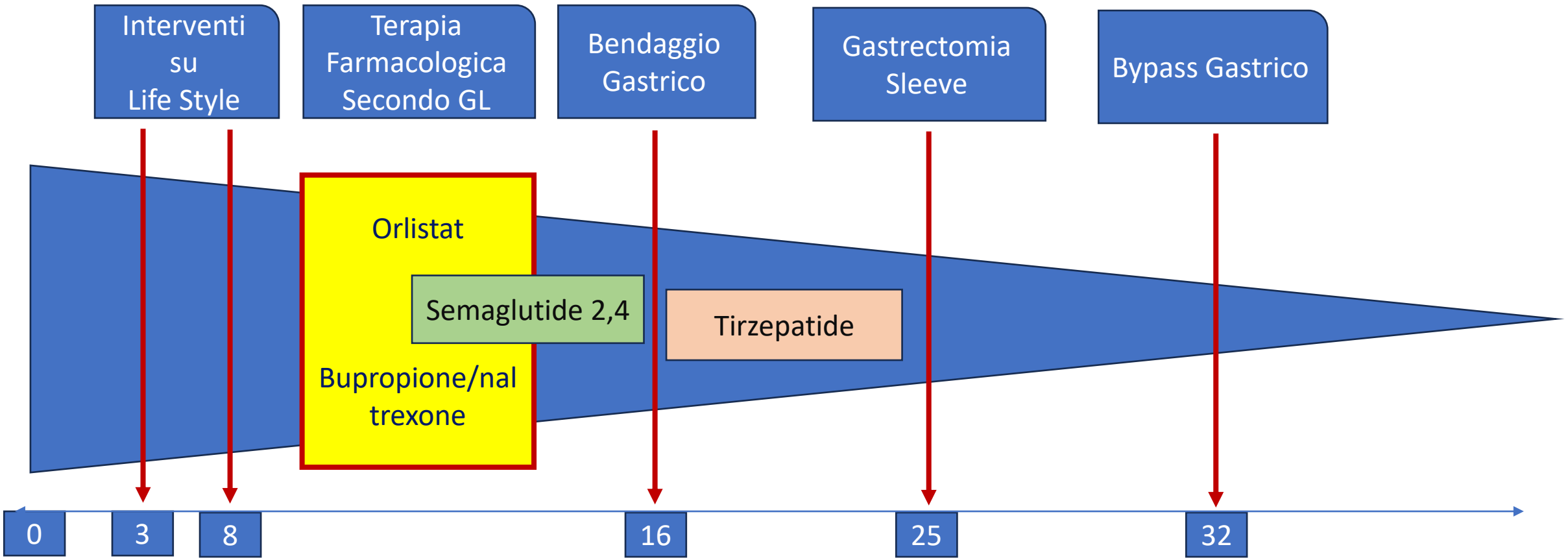
Come trattiamo l’Obesità/Sovrappeso e quindi l’Infiammazione come sua conseguenza nei nostri pazienti?

Gestione Cardiologica attuale della problematica Obesità:

«mi raccomando mangi di meno e cammini di più»

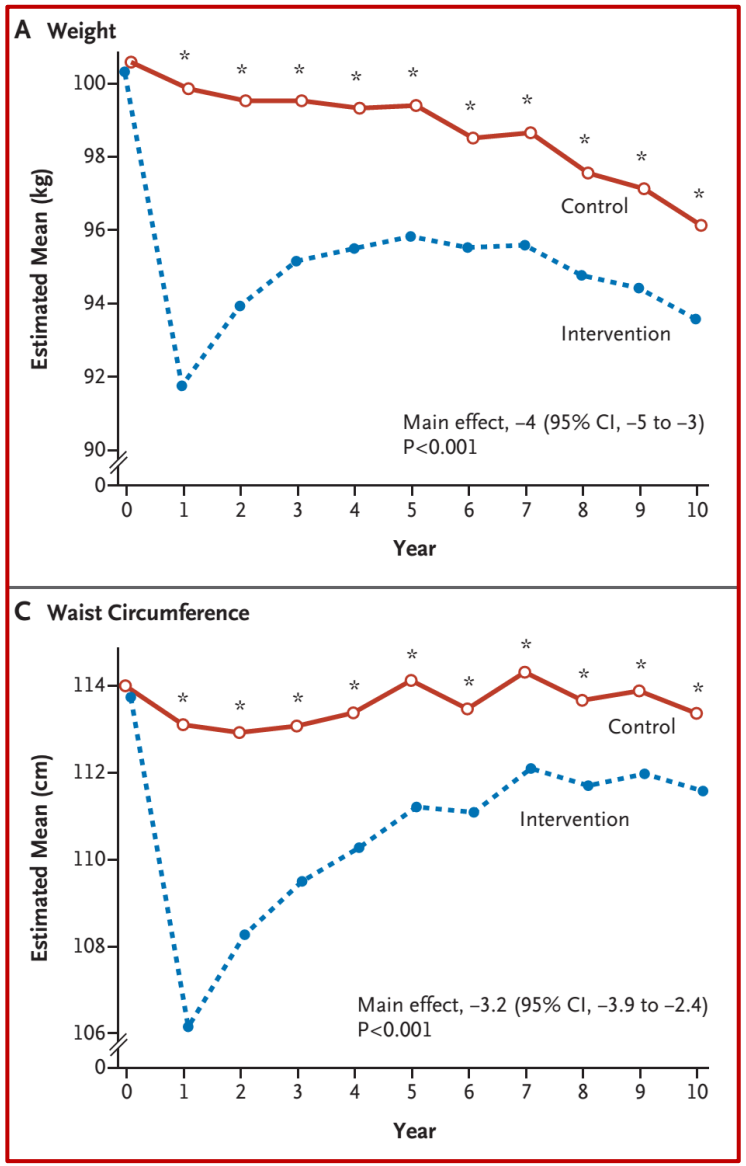
poco prima di aprire la porta dell'ambulatorio

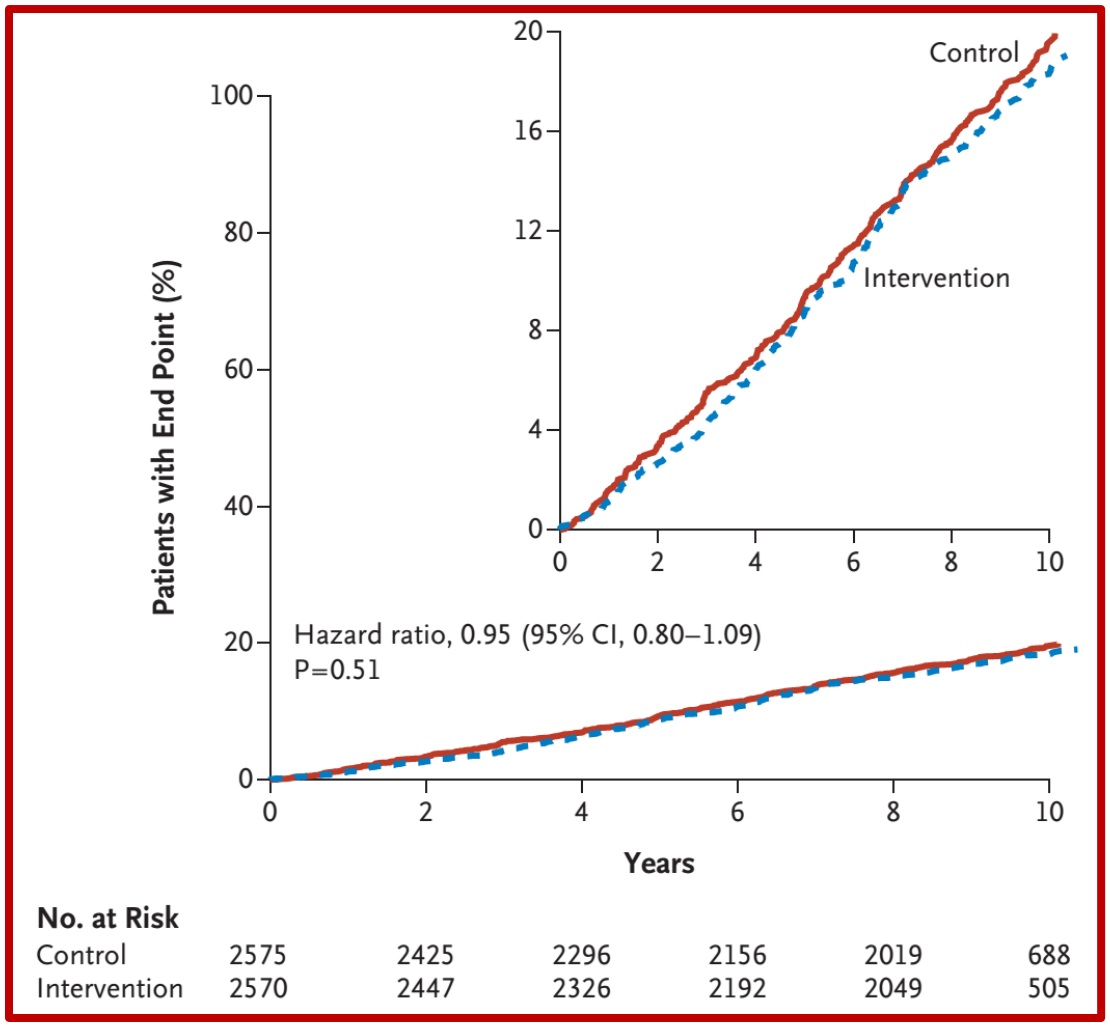
Risultati di riduzione di Peso con diverse Terapie



Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

The Look AHEAD Research Group*

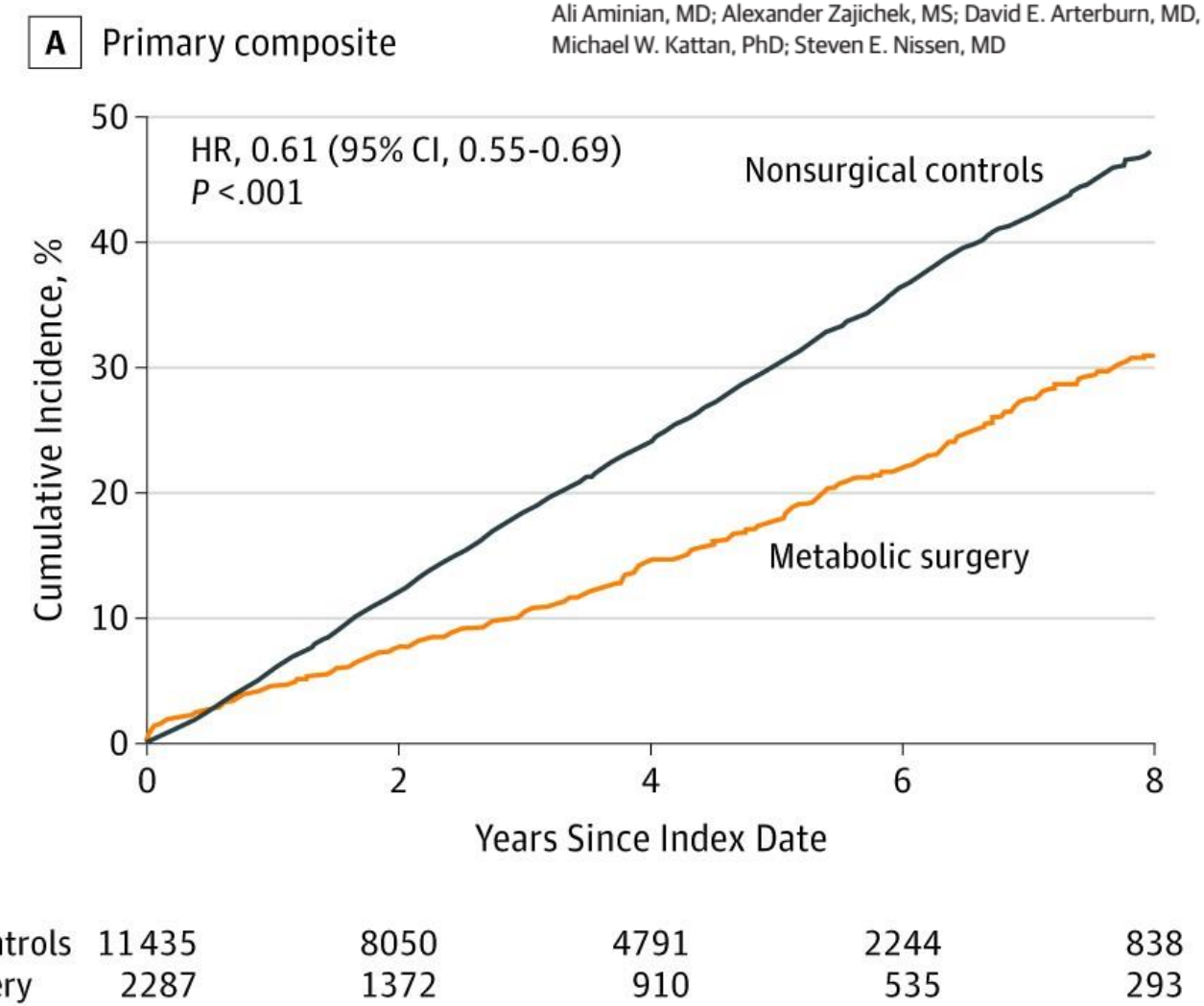




JAMA | Original Investigation

Association of Metabolic Surgery With Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes and Obesity

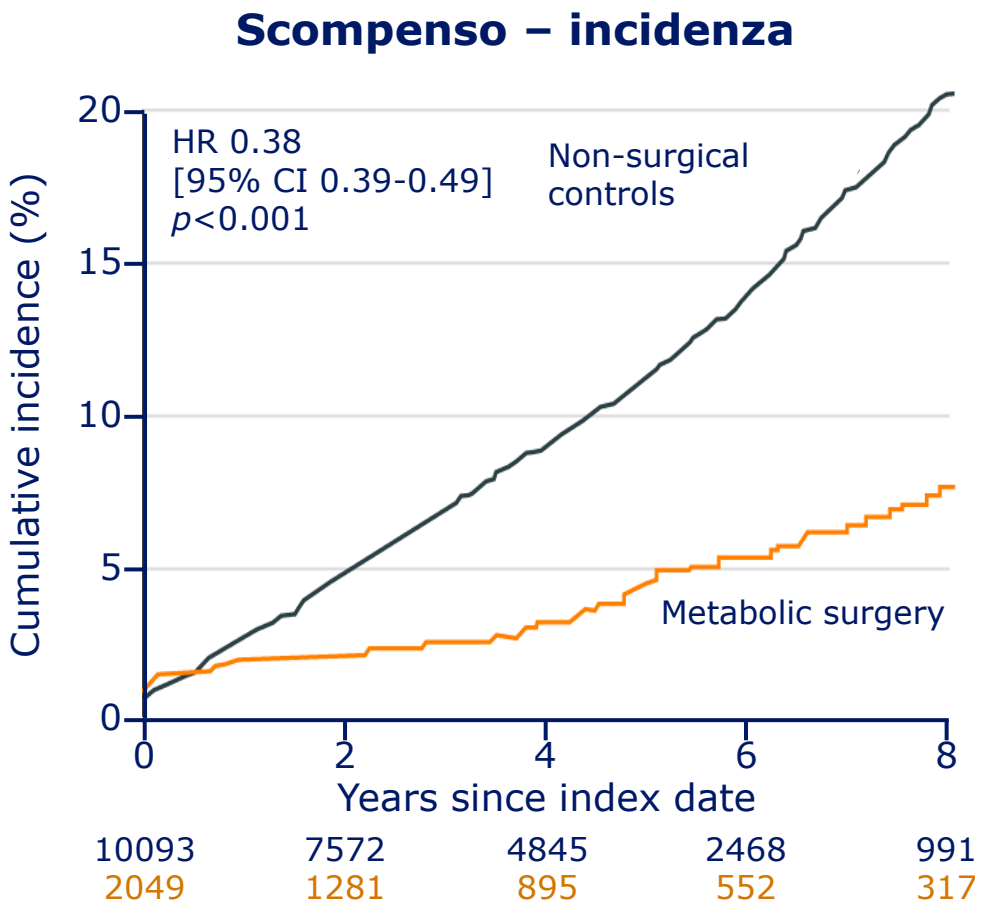
Ali Aminian, MD; Alexander Zajichek, MS; David E. Arterburn, MD, MPH; Kathy E. Wolski, MPH; Stacy A. Brethauer, MD; Philip R. Schauer, MD; Michael W. Kattan, PhD; Steven E. Nissen, MD



The primary end point, first occurrence of

1) coronary artery events,
2) cerebrovascular events,
3) heart failure,
4) atrial fibrillation,
5) nephropathy,
6) all-cause mortality,

Riduzione Incidenza HF con Chirurgia Metabolica

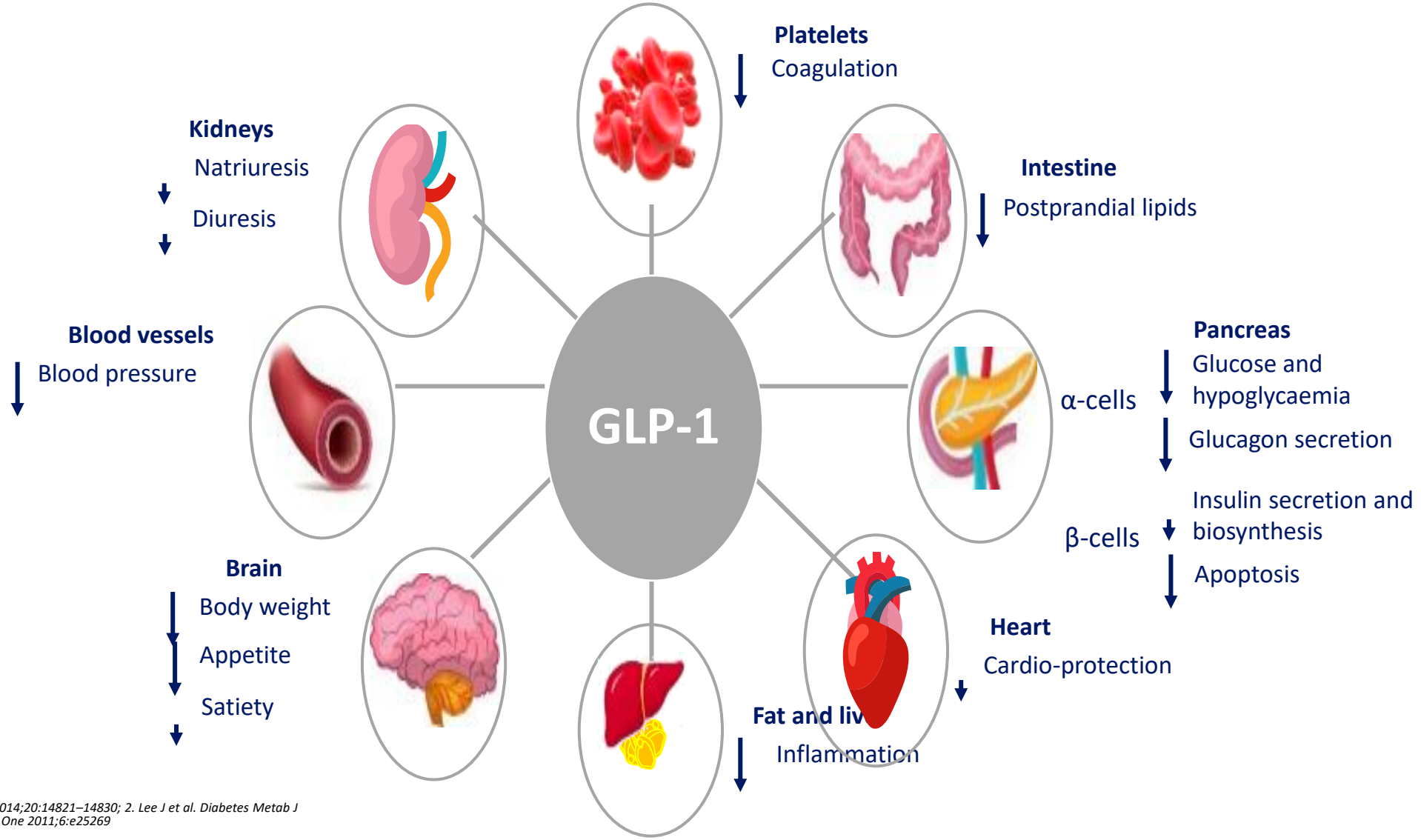


Aminian *et al. JAMA* 2019;322:1271–1282

CI, confidence interval; HR, hazard ratio. Number represent number of patients

Agonisti GLP-1

Classe di farmaci ipoglicemizzanti e con effetti documentati di prevenzione cardiovascolare primaria e secondaria nel DM

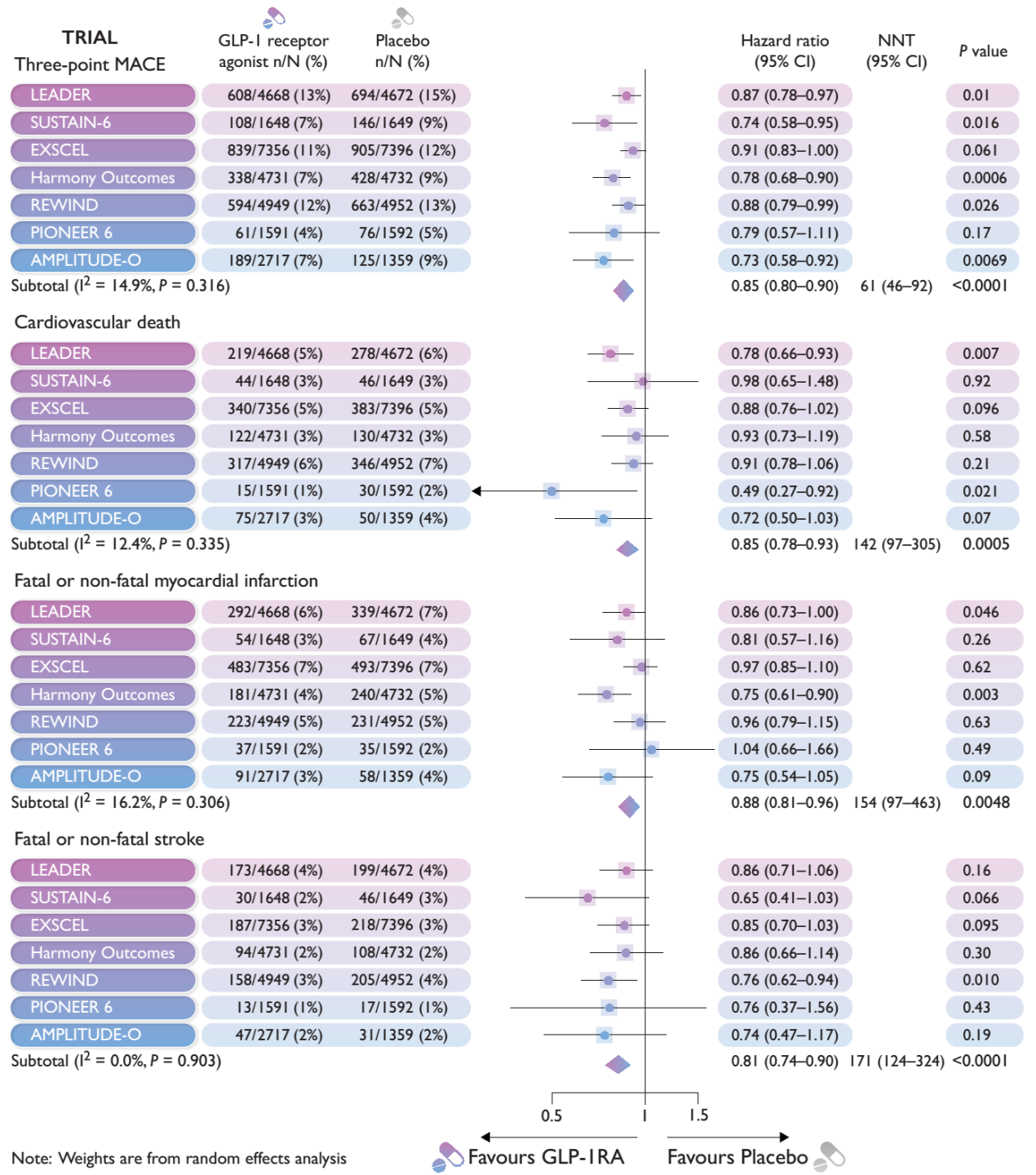


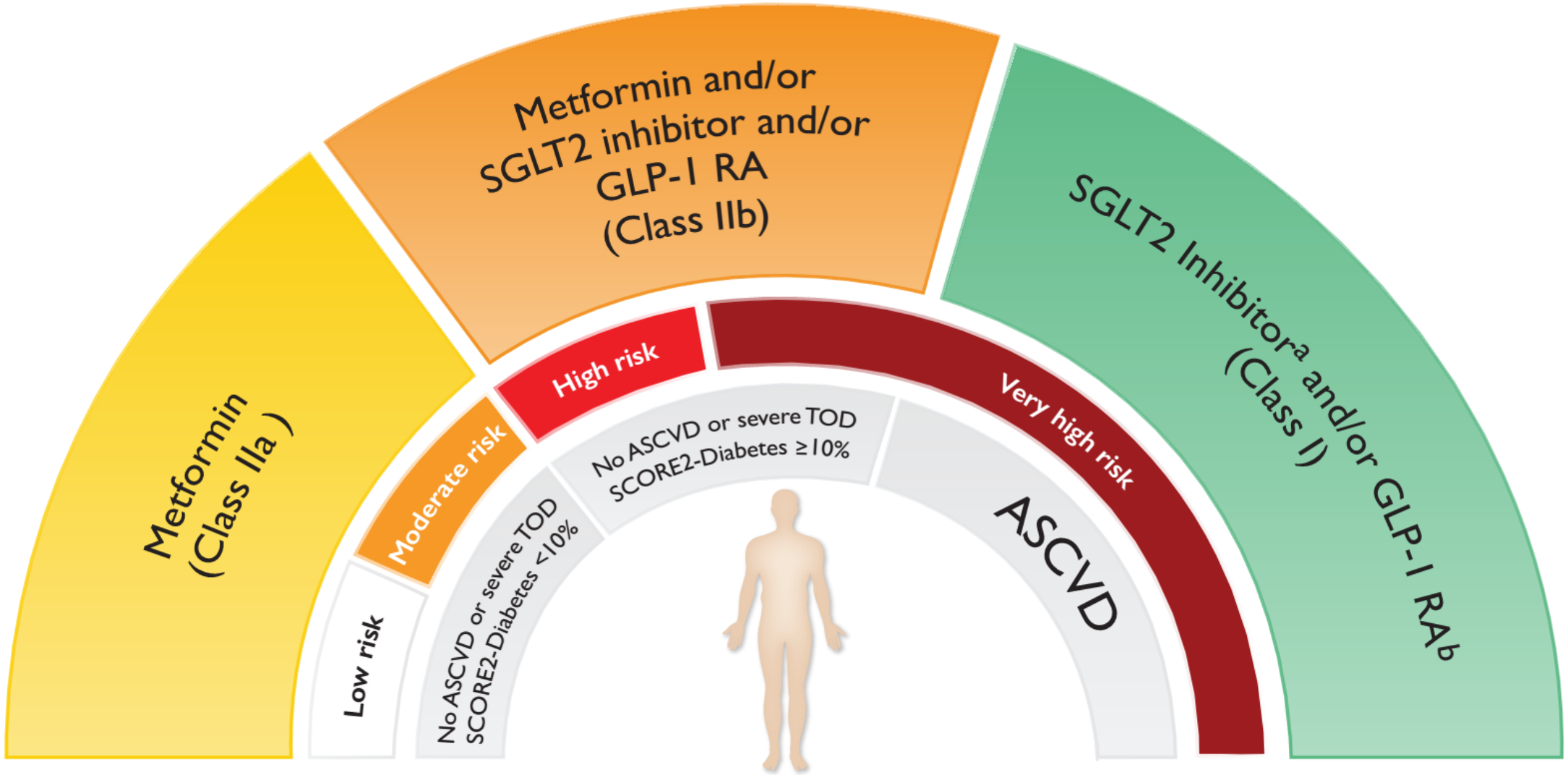
GLP-1, glucagon-like peptide

1. Wang XC et al. World J Gastroenterol 2014;20:14821–14830; 2. Lee J et al. Diabetes Metab J 2012;36:262–267; 3. Sharma S et al. PLoS One 2011;6:e25269

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes

ESC
European Society of Cardiology





Risk assessment for patients with type 2 diabetes based on the presence of ASCVD/severe TOD and 10-year CVD risk estimation via SCORE2-Diabetes

Trial design: SCALE Obesity and Prediabetes

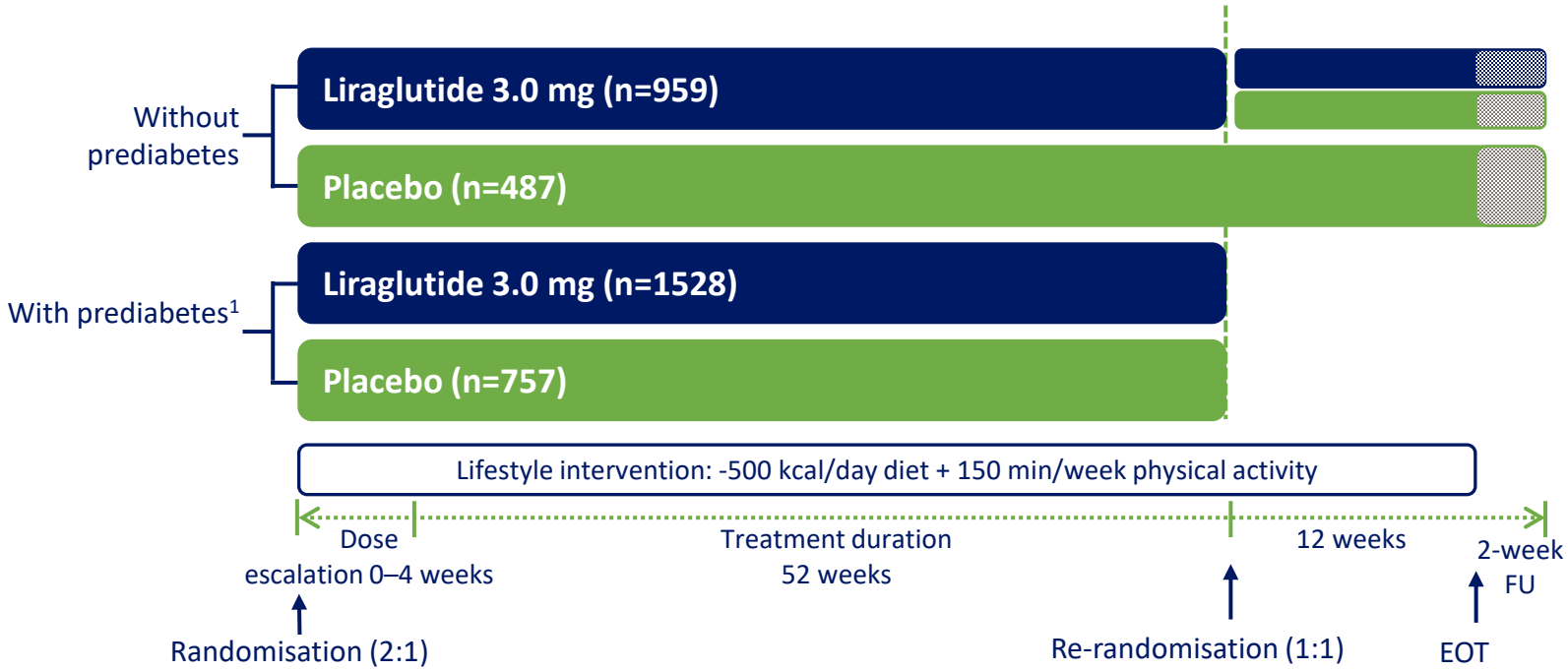
Liraglutide 3.0 mg for weight management (56 weeks)

Trial objective

Efficacy and safety of liraglutide 3.0 mg, as adjunct to D&E, in participants with obesity or overweight plus comorbidities, without diabetes

Inclusion criteria

- ≥18 years
- Stable BW
- BMI ≥30 kg/m^2 or ≥27 kg/m^2 + comorbidities



Trial information

- June 2011 to March 2013
- Randomised controlled double-blind study
- 191 sites in 27 countries
- Duration: 56 weeks (with prediabetes), 68 weeks (without prediabetes)

1. ADA. Diabetes Care 2010;33(Suppl. 1):S11–61
BW, body weight; D&E, diet and exercise; EOT, end of treatment; FU, follow-up; HRQoL, health-related quality of life; WC, waist circumference

Pi-Sunyer et al. N Engl J Med 2015;373:11–22

Co-primary End-Point

Change in body weight (%)

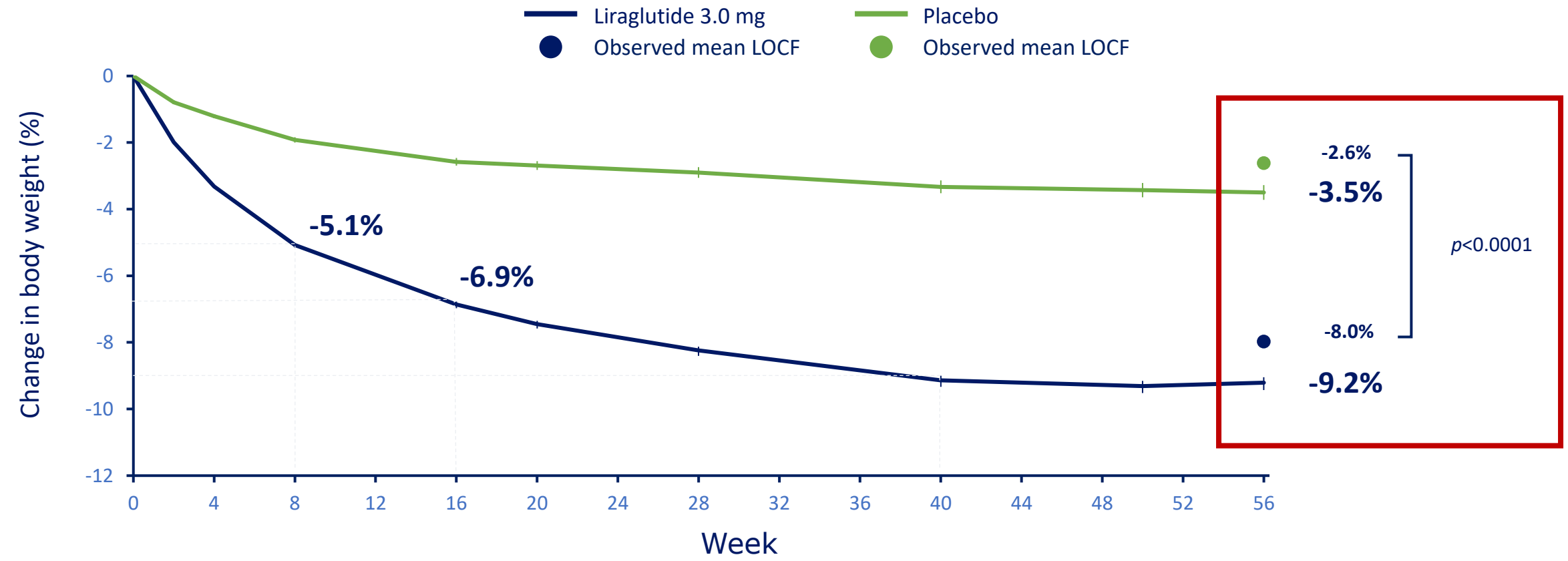
SCALE Obesity and Prediabetes: 0-56 weeks

The NEW ENGLAND JOURNAL of MEDICINE

JULY 2, 2015

A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management

Mean baseline weight: 106 kg



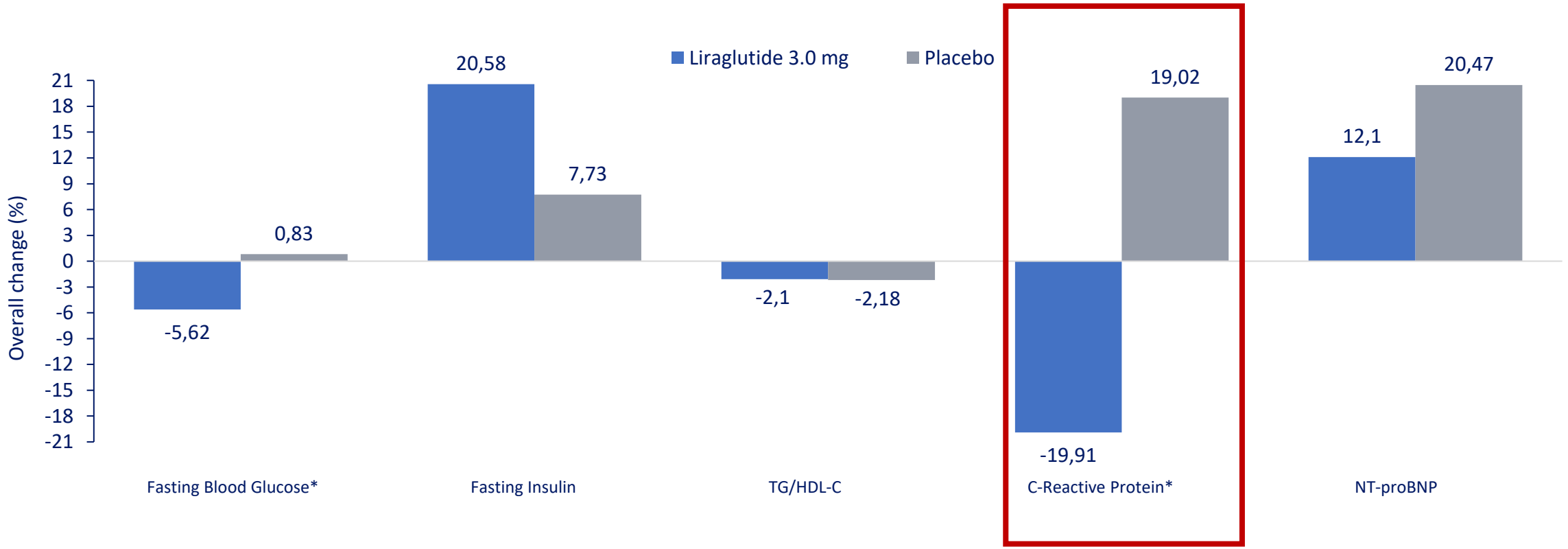
FAS, fasting visit data only. Line graphs are observed means (±SE). Statistical analysis is ANCOVA.
FAS, full analysis set; LOCF, last observation carried forward; SE, standard error

Lifestyle intervention: -500 kcal/day diet + 150 min/week physical activity

Effetto su Parametri Metabolici

Effects of liraglutide on visceral and ectopic fat in adults with overweight and obesity at high cardiovascular risk: a randomised, double-blind, placebo-controlled, clinical trial

Ian J Neeland, Steven P Marso, Colby R Ayers, Bienka Lewis, Robert Oslica, Wynona Francis, Susan Rodder, Ambarish Pandey, Parag H Joshi



Values are estimated means. Estimated treatment differences are calculated using analysis of covariance from the modified intention-to-treat (mITT) population without imputation.
p-value, Fasting Blood Glucose (%), 0.005; Fasting Insulin (%), 0.41; TG/HDL-C (%), 0.99; C-Reactive Protein (%), 0.03; NT-proBNP (%), 0.38
**Statistically significant, p < 0.005*
HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; NT-proBNP, N-terminal prohormone of brain natriuretic peptide
Neeland et al. The Lancet Diabetes & Endocrinology 2021; 9(9): 595-605

Received: 28 May 2022 | Revised: 25 August 2022 | Accepted: 26 August 2022

DOI: 10.1002/oby.23596

ORIGINAL ARTICLE

Clinical Trials and Investigation

Obesity THE OBESITY SOCIETY WILEY

Marked weight loss on liraglutide 3.0 mg: Real-life experience of a Swiss cohort with obesity

Sara Santini[1] | Nathalie Vionnet[1] | Jérôme Pasquier[2] | Elena Gonzalez-Rodriguez[3,4] | Montserrat Fraga[5] | Nelly Pitteloud[1,4] | Lucie Favre[1,4]

TABLE 1 Anthropometric data at baseline, after 4 months, and after 10 months of liraglutide treatment

	Baseline	After 4 months	After 10 months
Age (y)	43.6 ± 11.6	–	–
Female	35/54 (65%)	35/54 (68%)	33/49 (67%)
Weight (kg)	115.2 ± 19.6	106.1 ± 18.2*	101.0 ± 18.5§
BMI (kg/m^2)	40.8 ± 5.7	37.5 ± 5.4*	35.8 ± 5.4§
Waist circumference (cm)	116.3 ± 17.5	107.0 ± 15.7*	106.6 ± 22.1§
Weight loss (kg)	–	−10 ± 3.7	−14.1 ± 6.6
Weight loss (%)	–	−8.7 ± 3.1	−12.4 ± 5.5

Note: Data expressed as mean ± SD.

*$p < 0.05$ between baseline and 4 months.

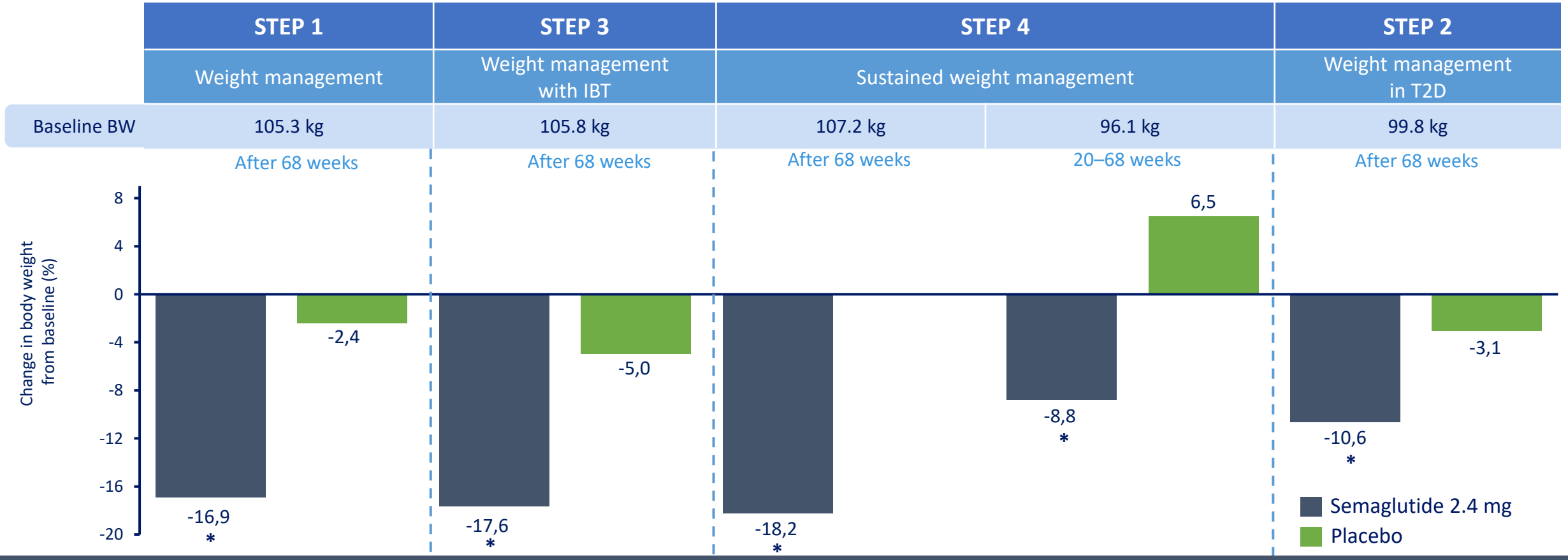
§$p < 0.05$, between baseline and 10 months.

TABLE 2 Clinical outcomes after 10 months of liraglutide treatment

	n	Baseline	After 10 months
Metabolic comorbidities			
Hypertension	48	20/48 (42%)	18/48 (37%)
Dyslipidemia	47	24/47 (51%)	16/47 (34%)
Prediabetes	48	30/48 (62%)	4/48 (8%)*
Hepatic steatosis	20	20/20 (100%)	12/20 (60%)*
Metabolic parameters			
Glucose (mmol/L)	43	5.8 ± 0.8	5.2 ± 0.4*
HbA_{1C} (%)	45	5.5 ± 0.4	5.2 ± 0.3*
Insulin (mU/L)	32	31.1 ± 22.3	19.8 ± 11.8*
HOMA-IR	32	8.5 ± 7.4	4.6 ± 3.0*
Total cholesterol (mmol/L)	45	4.6 ± 0.8	4.5 ± 0.7
HDL (mmol/L)	44	1.3 ± 0.4	1.3 ± 0.2
Triglycerides (mmol/L)	45	1.6 ± 1.0	1.3 ± 0.7*
LDL (mmol/L)	44	2.7 ± 0.6	2.6 ± 0.7
hsCRP (mg/dL)	33	7.6 ± 5.3	4.6 ± 4.4*
AST (U/L)	44	23.4 ± 11.1	19.7 ± 7.7*
ALT (U/L)	44	33.2 ± 20.7	26.1 ± 18.4*
γ-GT (U/L)	43	37.2 ± 27.2	26.5 ± 18.5*
NAFLD fibrosis score	26	−1.5 ± 1.0	−2.33 ± 1.1*
Body composition			
Fat mass (%)	36	49.6 ± 6.1	46.3 ± 6.4*
Fat mass (kg)	36	54.4 ± 11.8	44.0 ± 10.6*
VAT (g)	36	2247 ± 1157	1717 ± 1002*
Lean mass (%)	36	49.3 ± 6.0	51.8 ± 7.2*
Lean mass (kg)	36	55.0 ± 10.6	51.7 ± 11.3*
FMI (kg/m^2)	36	19.6 ± 4.5	16.1 ± 3.8*
ALMI (kg/m^2)	36	9.5 ± 1.3	9.0 ± 1.1*

Perdita di Peso ottenuta negli Studi STEP di fase 3

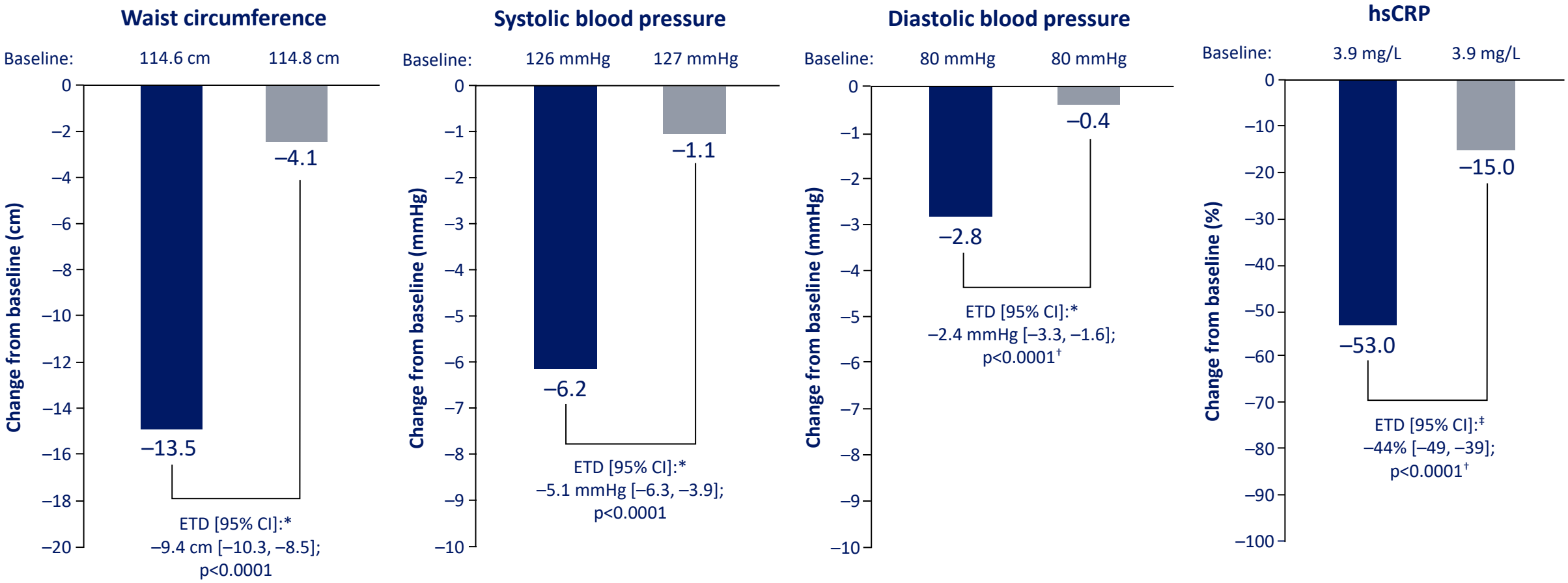
Semaglutide 2.4 mg settimanale in partecipanti in sovrappeso o obesi



Trial product estimand: Evaluates the treatment effect under the assumption that the trial product is taken as intended

**Statistically significant vs placebo.*
BW, body weight; IBT, intensive behavioural therapy.
Wilding et al. N Engl J Med 2021;384:989-1002; Davies et al. Lancet 2021;397:971-84.; Wadden et al. JAMA 2021;325:1403-13; Rubino et al. JAMA. 2021;325:1414-25.

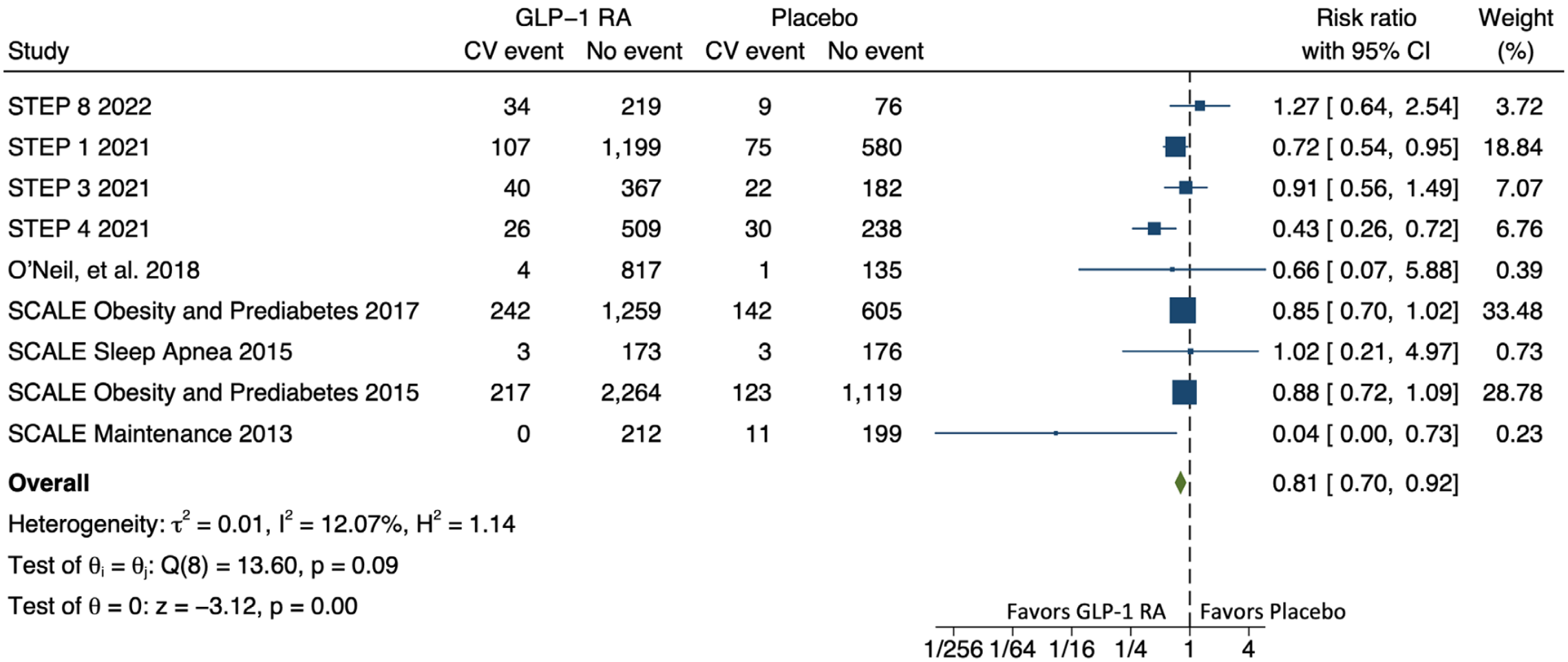
Cambiamento del profilo di rischio CV dal basale alla settimana 68



**Expressed as estimated absolute difference between groups. †Not adjusted for multiplicity. ‡Expressed as estimated relative percentage difference between groups.*
Data are for the in-trial period and the treatment policy estimand.
CI, confidence interval; CV, cardiovascular; ETD, estimated treatment difference; hsCRP, high-sensitivity C-reactive protein.
Garvey et al. Presented at the European and International Congress on Obesity (ECO) virtual meeting. May 10–13, 2021.

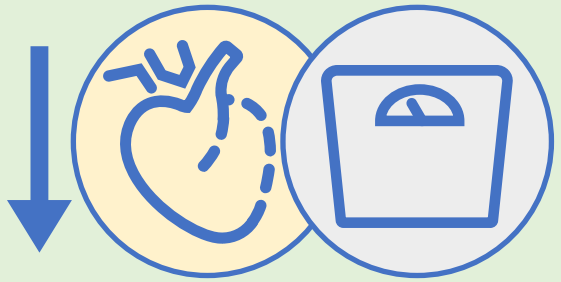
Effect of glucagon-like peptide-1 receptor agonists on cardiovascular events in overweight or obese adults without diabetes: A meta-analysis of placebo-controlled randomized trials

11430 pazienti



The primary objective of SELECT

To demonstrate that once weekly s.c. **semaglutide 2.4 mg** lowers the incidence of **MACE** versus semaglutide **placebo,** both added to standard of care in participants with **established CV disease** and **overweight or obesity**



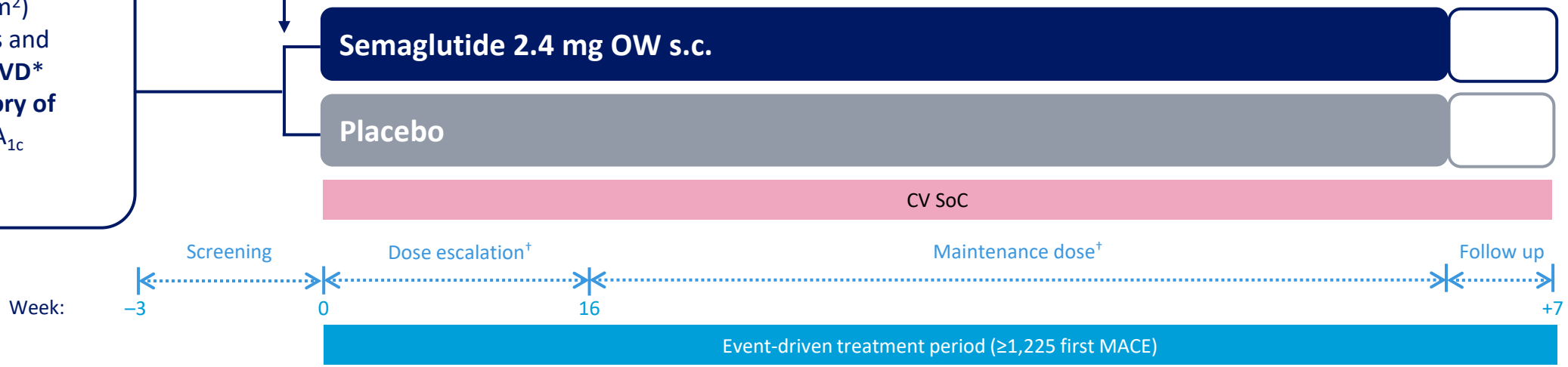
Three-component MACE consisted of non-fatal myocardial infarction, non-fatal stroke, CV death.
CV, cardiovascular; MACE, major adverse cardiac event; SELECT, semaglutide effects on cardiovascular outcomes in people with overweight or obesity; s.c., subcutaneous.

SELECT Trial

- **Overweight** or **obesity** (BMI ≥27 kg/m^2)
- Age ≥45 years and **established CVD***
- **No prior history of diabetes** (HbA_{1c} <6.5%)

Randomisation (1:1)
N=17,605

Trial information
- FPFV 24 October 2018
- Double-blind, placebo-controlled, superiority trial



Three-component MACE consisted of non-fatal MI, non-fatal stroke, CV death.
**Established CVD: MI ≥60 days ago, stroke ≥60 days ago, or symptomatic PAD, NYHA class IV excluded.*
†Dose escalation is from week 4 to 16 with intervals of 4 weeks, and maintenance dose is event-driven to end of treatment period.
BMI, body mass index; CV, cardiovascular; CVD, cardiovascular disease; FPFV, first patient first visit; HbA_{1c}, glycated haemoglobin; MACE, major adverse cardiovascular event; MI, myocardial infarction; NYHA, New York Heart Association; OW, once weekly; PAD, peripheral artery disease; s.c., subcutaneous; SELECT, semaglutide effects on cardiovascular outcomes in people with overweight or obesity; SoC, standard of care.
Ryan DH et al. Am Heart J 2020;229:61–9; Lingvay I et al. Obesity (Silver Spring) 2023;31:111–22.

Baseline characteristics of SELECT trial participants

N=17,605

MI only

n=11,908

67.6%

Stroke only

n=3,135

17.8%

PAD only

n=777

4.4%

≥2 CV inclusion criteria: n=1,433, 8.1%

CV, cardiovascular; MI, myocardial infarction; SELECT, semaglutide effects on cardiovascular outcomes in people with overweight or obesity.
Lingvay I et al. Obesity (Silver Spring) 2023;31:111–22.

Primary and confirmatory secondary endpoints
SELECT

Primary endpoint[1,2]

Time from randomisation to first occurrence of composite endpoint consisting of:

- CV death
- Non-fatal MI
- Non-fatal stroke

Confirmatory secondary endpoints[1,2]

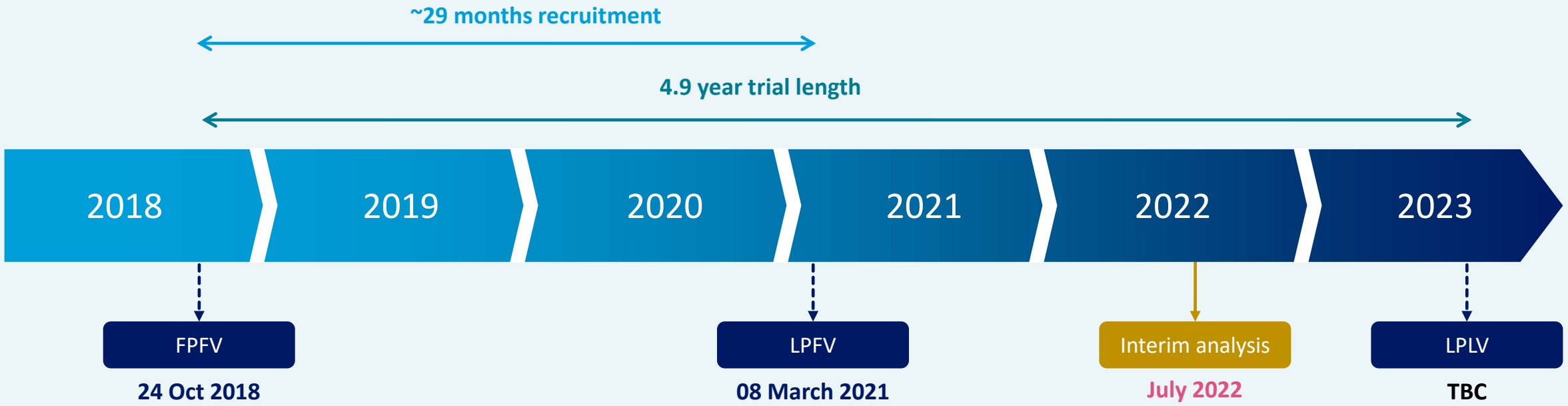
Time from randomisation to occurrence of:

- CV death
- Composite HF endpoint consisting of HF hospitalisation, urgent HF visit or CV death
- All-cause death

CV, cardiovascular; HF, heart failure; MI, myocardial infarction; SELECT, semaglutide effects on cardiovascular outcomes in people with overweight or obesity.

1. Ryan DH et al. Am Heart J 2020;229:61–9; 2. Lingvay I et al. Obesity (Silver Spring) 2023;31:111–22.

Timelines for SELECT



As the SELECT trial is event driven, timelines are dependent on the event rates

FPFV, first patient first visit; LPFV, last patient first visit; LPLV, last patient last visit; SELECT, semaglutide effects on cardiovascular outcomes in people with overweight or obesity.

Results: Baseline characteristics in the overall population and by baseline HbA_{1c} value

(1 of 5)

Characteristic	Overall (N = 17,605)	HbA_{1c} <5.7% (N = 5,904)	HbA_{1c} ≥5.7% to <6.0% (N = 6,087)	HbA_{1c} ≥6.0% to <6.5% (N = 5,609)
CV inclusion criteria, n (%)*				
MI only	11,908 (67.6)	3,861 (65.4)	4,198 (69.0)	3,846 (68.6)
Stroke only	3,135 (17.8)	1,199 (20.3)	1,049 (17.2)	886 (15.8)
PAD only	777 (4.4)	254 (4.3)	254 (4.2)	269 (4.8)
≥2 CV inclusion criteria	1,433 (8.1)	470 (8.0)	469 (7.7)	493 (8.8)
Demographics				
Age (years), mean (SD)	61.6 (8.9)	61.0 (9.1)	61.7 (8.8)	62.1 (8.6)
Age group (years), n (%)				
45 to <55	4,150 (23.6)	1,599 (27.1)	1,400 (23.0)	1,150 (20.5)
55 to <65	6,727 (38.2)	2,149 (36.4)	2,365 (38.9)	2,211 (39.4)
65 to <75	5,362 (30.5)	1,707 (28.9)	1,848 (30.4)	1,806 (32.2)
75 to <85	1,318 (7.5)	435 (7.4)	458 (7.5)	424 (7.6)
≥85	48 (0.3)	14 (0.2)	16 (0.3)	18 (0.3)
Male, n (%)	12,733 (72.3)	4,274 (72.4)	4,409 (72.4)	4,046 (72.1)
Region, n (%)				
North America	4,401 (25.0)	1,717 (29.1)	1,423 (23.4)	1,259 (22.4)
South America	1,152 (6.5)	494 (8.4)	385 (6.3)	273 (4.9)
Europe	6,507 (37.0)	1,834 (31.1)	2,380 (39.1)	2,291 (40.8)
Africa	845 (4.8)	273 (4.6)	280 (4.6)	292 (5.2)
Asia	2,201 (12.5)	722 (12.2)	757 (12.4)	722 (12.9)
Other	2,499 (14.2)	864 (14.6)	862 (14.2)	772 (13.8)

Results: Baseline characteristics in the overall population and by baseline HbA_{1c} value
(2 of 5)

Characteristic	Overall (N = 17,605)	HbA_{1c} <5.7% (N = 5,904)	HbA_{1c} ≥5.7% to <6.0% (N = 6,087)	HbA_{1c} ≥6.0% to <6.5% (N = 5,609)
Race, n (%)[†]				
Asian	1,447 (8.2)	446 (7.6)	501 (8.2)	500 (8.9)
Black	671 (3.8)	228 (3.9)	214 (3.5)	228 (4.1)
White	14,791 (84.0)	5,033 (85.2)	5,120 (84.1)	4,634 (82.6)
Other[‡]	527 (3.0)	160 (2.7)	191 (3.1)	176 (3.1)
Ethnicity, n (%)[§]				
Hispanic or Latino	1,822 (10.3)	755 (12.8)	594 (9.8)	473 (8.4)
Not Hispanic or Latino	15,612 (88.7)	5,111 (86.6)	5,431 (89.2)	5,065 (90.3)
Tobacco use, n (%)				
Current smoker	2,950 (16.8)	834 (14.1)	1,069 (17.6)	1,046 (18.6)
Never smoked	6,123 (34.8)	2,275 (38.5)	2,048 (33.6)	1,800 (32.1)
Previous smoker	8,530 (48.5)	2,794 (47.3)	2,970 (48.8)	2,762 (49.2)
Body measurements				
Body mass index (kg/m^2), mean (SD)	33.34 (5.04)	32.84 (4.83)	33.23 (4.94)	33.97 (5.29)
Body mass index (kg/m^2), n (%)				
<30	5,024 (28.5)	1,895 (32.1)	1,747 (28.7)	1,382 (24.6)
30 to <35	7,475 (42.5)	2,521 (42.7)	2,638 (43.3)	2,314 (41.3)
35 to <40	3,346 (19.0)	1,002 (17.0)	1,117 (18.4)	1,225 (21.8)
40 to <45	1,174 (6.7)	330 (5.6)	403 (6.6)	440 (7.8)
≥45	586 (3.3)	156 (2.6)	182 (3.0)	248 (4.4)

Adapted from Table 1
Baseline is defined as the assessment from the randomization visit (or the screening visit if the assessment from the randomization visit was not available). Data for all variables were not obtained for the entire population. Smoking is defined as at least one cigarette or equivalent daily.
[†]Race was not reported for some participants (overall population: n = 169; 1.0%). [‡]The category "Other" for race includes participants whose race was recorded as "American Indian or Alaska Native", "Native Hawaiian or Pacific Islander", or "Other". [§]Ethnicity was not reported for some participants (overall population: n = 171; 1.0%).
HbA_{1c}, glycated hemoglobin; SD, standard deviation.

Results: Baseline characteristics in the overall population and by baseline HbA_{1c} value
(4 of 5)

Characteristic	Overall (N = 17,605)	HbA_{1c} <5.7% (N = 5,904)	HbA_{1c} ≥5.7% to <6.0% (N = 6,087)	HbA_{1c} ≥6.0% to <6.5% (N = 5,609)
Renal variables				
eGFR (mL/min/1.73 m^2), mean (SD)	82.5 (17.4)	83.2 (17.6)	82.1 (17.5)	82.2 (17.1)
Renal function, eGFR (mL/min/1.73 m^2), n (%)				
Normal ≥90	6,990 (39.7)	2,459 (41.6)	2,363 (38.8)	2,167 (38.6)
Mild RI 60 to <90	8,577 (48.7)	2,791 (47.3)	2,994 (49.2)	2,790 (49.7)
Moderate RI 30 to <60	1,826 (10.4)	575 (9.7)	655 (10.8)	595 (10.6)
Severe RI 15 to <30	69 (0.4)	29 (0.5)	23 (0.4)	17 (0.3)
End-stage renal disease <15	2 (<0.1)	2 (<0.1)	0	0
Albumin/creatinine ratio (mg/g), median (IQR)‖	7.37 (4.46–15.39)	7.15 (4.32–14.80)	7.26 (4.44–14.67)	7.79 (4.65–16.56)
Albuminuria (mg/g), n (%)				
Normoalbuminuria (<30)	14,846 (84.3)	4,991 (84.5)	5,165 (84.9)	4,687 (83.6)
Microalbuminuria (30 to <300)	1,968 (11.2)	634 (10.7)	668 (11.0)	666 (11.9)
Macroalbuminuria (≥300)	325 (1.8)	117 (2.0)	91 (1.5)	117 (2.1)
eGFR <60 mL/min/1.73 m^2 or UACR ≥30 mg/g, n (%)	3,697 (21.0)	1,197 (20.3)	1,270 (20.9)	1,229 (21.9)
Lipid and C-reactive protein levels				
High-sensitivity C-reactive protein (mg/L), median (IQR)	1.83 (0.87–4.12)	1.66 (0.81–3.72)	1.80 (0.85–4.01)	2.08 (0.96–4.54)
Total cholesterol (mmol/L), median (IQR)	3.97 (3.39–4.73)	4.02 (3.39–4.79)	3.96 (3.39–4.70)	3.93 (3.39–4.67)

Adapted from Table 1
Baseline is defined as the assessment from the randomization visit (or the screening visit if the assessment from the randomization visit was not available). Data for all variables were not obtained for the entire population. The eGFR was estimated using the CKD-EPI formula; the renal function categories are based on the eGFR as per CKD-EPI. ‖To convert albumin/creatinine ratio from mg/g to mg/mmol, divide the mg/g value by 8.849557522.
CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; IQR, interquartile range; RI, renal impairment; SD, standard deviation; UACR, urinary albumin to creatinine ratio.

Results: Baseline characteristics in the overall population and by baseline HbA_{1c} value
(5 of 5)

Characteristic	Overall (N = 17,605)	HbA_{1c} <5.7% (N = 5,904)	HbA_{1c} ≥5.7% to <6.0% (N = 6,087)	HbA_{1c} ≥6.0% to <6.5% (N = 5,609)
LDL-C (mmol/L), median (IQR)	2.02 (1.57–2.64)	2.05 (1.59–2.69)	2.02 (1.58–2.63)	2.00 (1.56–2.60)
HDL-C (mmol/L), median (IQR)	1.13 (0.96–1.34)	1.17 (0.99–1.40)	1.13 (0.97–1.34)	1.09 (0.94–1.29)
Triglycerides (mmol/L), median (IQR)	1.52 (1.11–2.12)	1.43 (1.05–2.02)	1.52 (1.11–2.10)	1.60 (1.19–2.24)
Free fatty acids (mmol/L), median (IQR)	0.30 (0.17–0.48)	0.30 (0.16–0.48)	0.29 (0.16–0.47)	0.31 (0.18–0.48)
VLDL-C (mmol/L), median (IQR)	0.68 (0.50–0.95)	0.64 (0.47–0.91)	0.68 (0.50–0.95)	0.72 (0.54–1.01)
Blood pressure and heart rate				
Systolic blood pressure (mmHg), mean (SD)	131.0 (15.4)	130.4 (15.4)	131.0 (15.5)	131.6 (15.4)
Diastolic blood pressure (mmHg), mean (SD)	79.3 (10.0)	79.3 (10.0)	79.4 (10.0)	79.2 (9.9)
Pulse (beats/min), mean (SD)	68.8 (10.7)	68.5 (10.7)	68.5 (10.6)	69.4 (10.7)
Patient-reported outcomes				
EQ-VAS score, mean (SD)	77.15 (15.68)	77.83 (15.68)	77.08 (15.60)	76.49 (15.73)
EQ-5D index score, mean (SD)	0.88 (0.15)	0.88 (0.15)	0.88 (0.15)	0.88 (0.14)
WRSS total score, mean (SD)	1.13 (0.77)	1.08 (0.77)	1.13 (0.77)	1.16 (0.77)

Adapted from Table 1
Baseline is defined as the assessment from the randomization visit (or the screening visit if the assessment from the randomization visit was not available). Data for all variables were not obtained for the entire population.
EQ-5D, EuroQoL 5 Dimensions; EQ-VAS, EuroQoL Visual Analog Scale; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; IQR, interquartile range; SD, standard deviation; VLDL-C, very-low-density lipoprotein cholesterol; WRSS, weight-related sign and symptom.

Results: CV history at randomization in the overall population and by baseline HbA_{1c} value
(1of 2)

Characteristic	Overall (N = 17,605)	HbA_{1c} <5.7% (N = 5,904)	HbA_{1c} ≥5.7% to <6.0% (N = 6,087)	HbA_{1c} ≥6.0% to <6.5% (N = 5,609)
Coronary heart disease, n (%)	14,453 (82.1)	4,730 (80.1)	5,025 (82.6)	4,694 (83.7)
Myocardial infarction, n (%)	13,439 (76.3)	4,376 (74.1)	4,687 (77.0)	4,372 (77.9)
Non-ST-segment elevation	4,443 (25.2)	1,412 (23.9)	1,616 (26.5)	1,414 (25.2)
ST-segment elevation	5,414 (30.8)	1,724 (29.2)	1,875 (30.8)	1,813 (32.3)
Unknown	2,991 (17.0)	1,046 (17.7)	1,002 (16.5)	942 (16.8)
Coronary artery stenosis ≥50%, n (%)*	9,692 (55.1)	3,037 (51.6)	3,436 (56.4)	3,206 (57.2)
Coronary revascularization, n (%)	11,849 (67.3)	3,763 (63.7)	4,162 (68.4)	3,920 (69.9)
Percutaneous coronary intervention	10,337 (58.7)	3,272 (55.4)	3,637 (59.8)	3,424 (61.0)
Coronary artery bypass graft	2,057 (11.7)	652 (11.0)	719 (11.8)	685 (12.2)
Stroke, n (%)	4,108 (23.3)	1,537 (26.0)	1,376 (22.6)	1,193 (21.3)
Ischemic stroke	2,983 (16.9)	1,086 (18.4)	1,032 (17.0)	865 (15.4)
Hemorrhagic stroke	329 (1.9)	153 (2.6)	102 (1.7)	73 (1.3)
Undetermined stroke	517 (2.9)	203 (3.4)	154 (2.5)	159 (2.8)
Transient ischemic attack, n (%)	761 (4.3)	289 (4.9)	261 (4.3)	210 (3.7)
Carotid artery stenosis ≥50%, n (%)*	807 (4.6)	253 (4.3)	285 (4.7)	269 (4.8)
Carotid revascularization, n (%)	421 (2.4)	129 (2.2)	151 (2.5)	141 (2.5)

Adapted from Table 2
CV history was based on the participant's medical records and the investigator's discretion. For CV history, the sub-classifications listed may not total the full number of patients with the relevant CV history, as investigators were not required to provide information about the relevant sub-classification; furthermore, for coronary revascularization, stroke, and myocardial infarction, the electronic case report form was designed to only collect the sub-classifications for the most recent event.
**NoR <90%; % is calculated using N for the relevant (sub-)population. For coronary artery stenosis, carotid artery stenosis, and peripheral artery stenosis, NoR was ≥80% of the total population.*
CV, cardiovascular; HbA_{1c}, glycated hemoglobin; NoR, number of responses; SD, standard deviation.

novo nordisk®

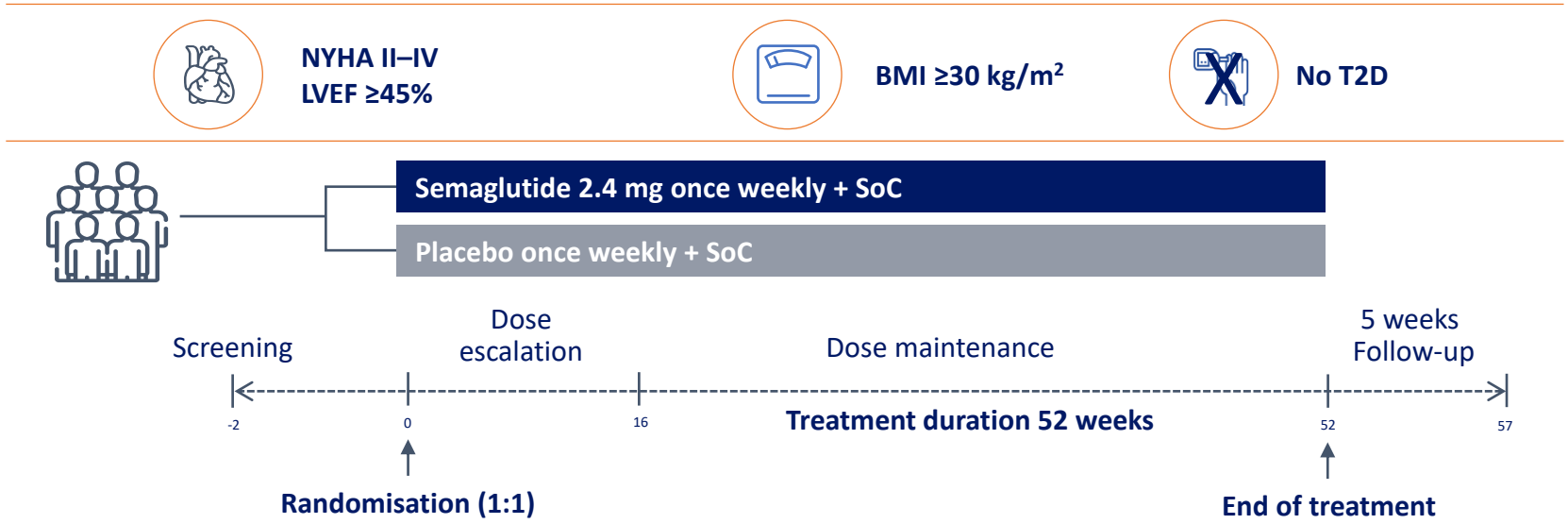
company announcement

Semaglutide 2.4 mg reduces the risk of major adverse cardiovascular events by 20% in adults with overweight or obesity in the SELECT trial

The trial achieved its primary objective by demonstrating a statistically significant and superior reduction in MACE of 20% for people treated with semaglutide 2.4 mg compared to placebo[1]. The primary endpoint of the study was defined as the composite outcome of the first occurrence of MACE defined as cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. All three components of the primary endpoint contributed to the superior MACE reduction demonstrated by semaglutide 2.4 mg. 1,270 first MACEs were accrued.

STEP-HFpEF trial design

N=529



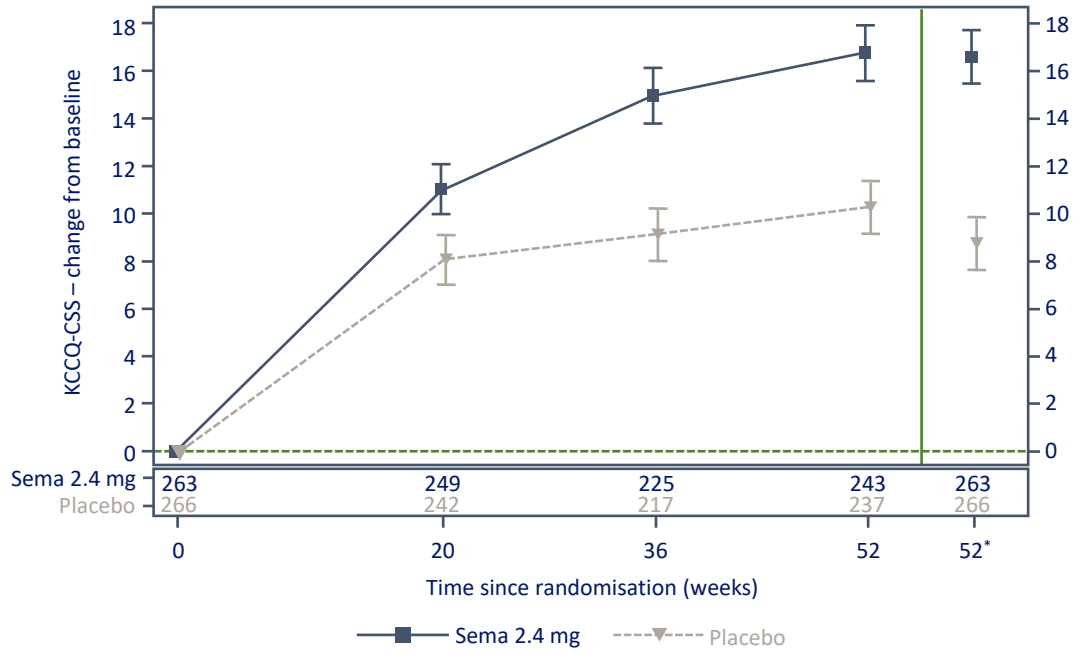
Primary objective	Key endpoints
To investigate the effects of semaglutide 2.4 mg s.c. once weekly on **physical function, symptoms** and **body weight** compared with placebo, both added to SoC, in people with the obesity phenotype of HFpEF and no T2D	**Dual primary endpoints:** KCCQ-CSS and body weight **Confirmatory secondary endpoints**: 6MWD, hierarchical composite endpoint*, CRP **Key exploratory endpoints**: loop diuretic medication, NT-proBNP, NYHA class, time to first HF event (hospitalisation or urgent visit)

**Comprising time to all-cause death, time to and number of HF events, changes in KCCQ-CSS and 6MWD*
6MWD, 6-minute walk distance; BMI, body mass index; CRP, C-reactive protein; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; s.c., subcutaneous; SoC, standard of care; T2D, type 2 diabetes
Novo Nordisk A/S. NCT04788511. Available at: https://clinicaltrials.gov/ct2/show/NCT04788511 (accessed August 2023); Kosiborod MN et al. JACC HF 2023;11(8_Part_1):1000–1010

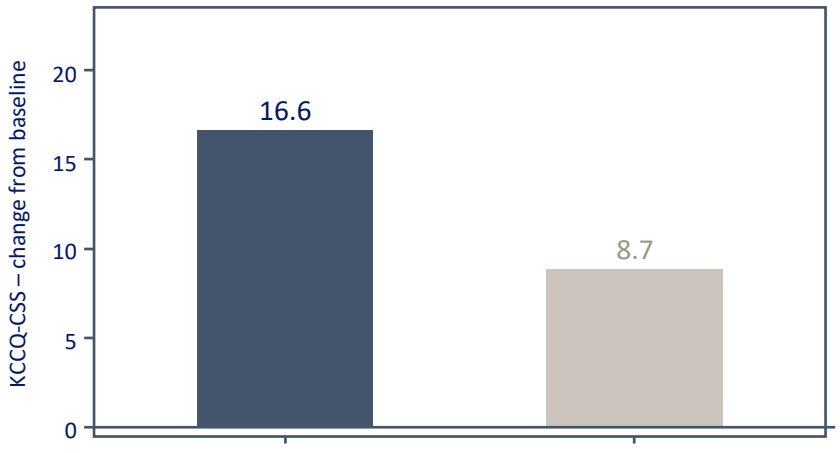
Significant improvement in mean KCCQ-CSS

Primary endpoint (treatment policy estimand)

Observed mean change



Treatment policy estimand (week 52)



Analysis at week 52	ETD	95% CI	*p*-value
Sema 2.4 mg vs placebo	7.8 points	4.8; 10.9	<0.001

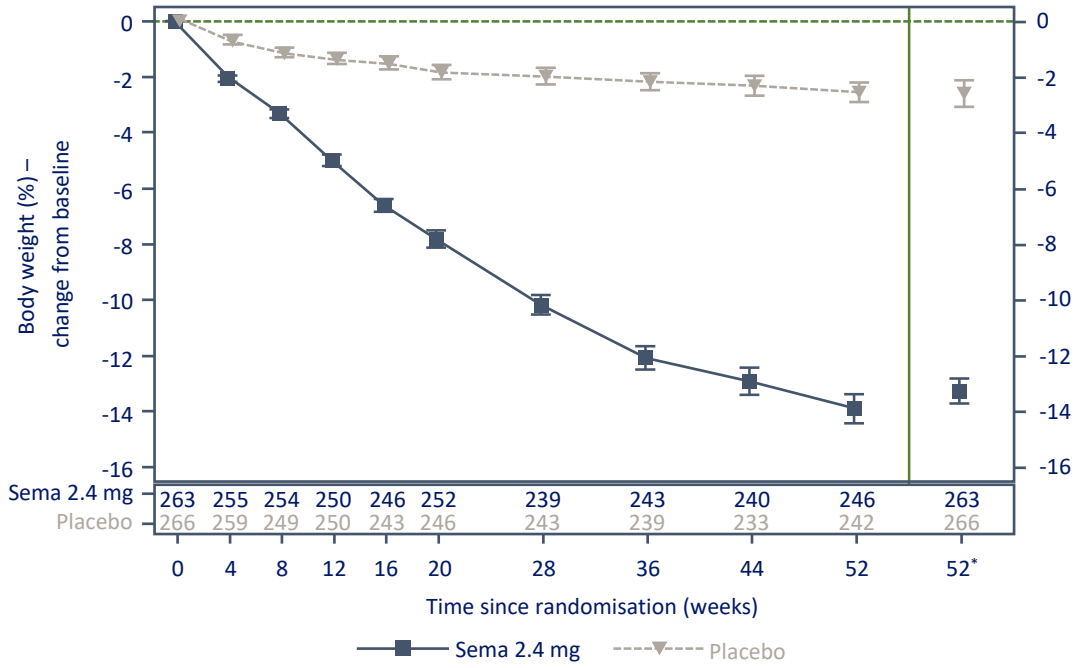
Baseline median KCCQ-CSS: 58.9 points

In the left figure, error bars are ± standard error of the mean. Numbers shown in the lower panel are numbers of patients contributing to the mean
**Estimated means*
CI, confidence interval; ETD, estimated treatment difference; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; sema, semaglutide
Kosiborod MN et al. N Engl J Med 2023; DOI: 10.1056/NEJMoa2306963 (soon to be published)

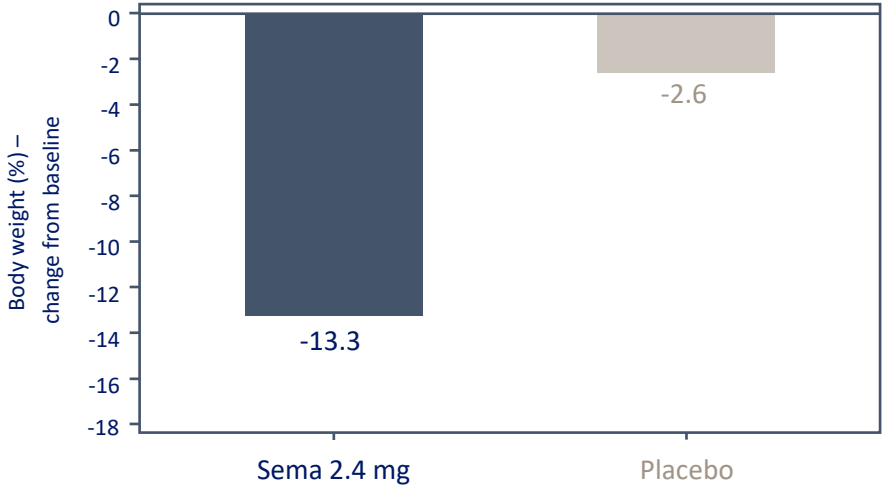
Significant decrease in mean body weight

Primary endpoint (treatment policy estimand)

Observed mean change



Treatment policy estimand (week 52)



Analysis at week 52	ETD	95% CI	*p*-value
Sema 2.4 mg vs placebo	-10.7%	-11.9; -9.4	<0.001

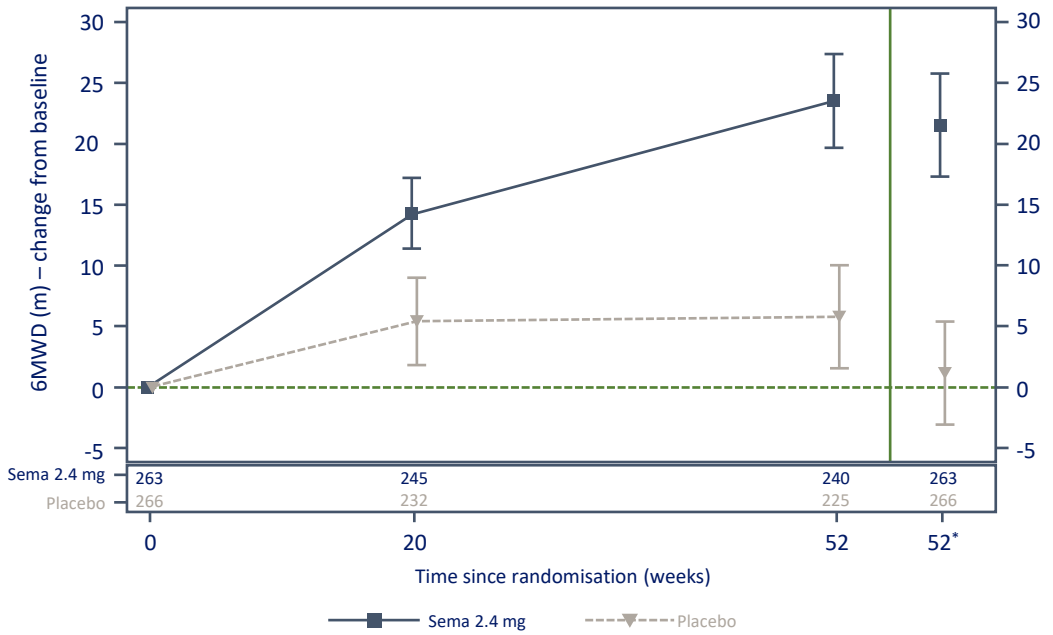
Baseline median body weight: 105.1 kg

In the left figure, error bars are ± standard error of the mean. Numbers shown in the lower panel are numbers of patients contributing to the mean
**Estimated means*
CI, confidence interval; ETD, estimated treatment difference; sema, semaglutide
Kosiborod MN et al. N Engl J Med 2023; DOI: 10.1056/NEJMoa2306963 (soon to be published)

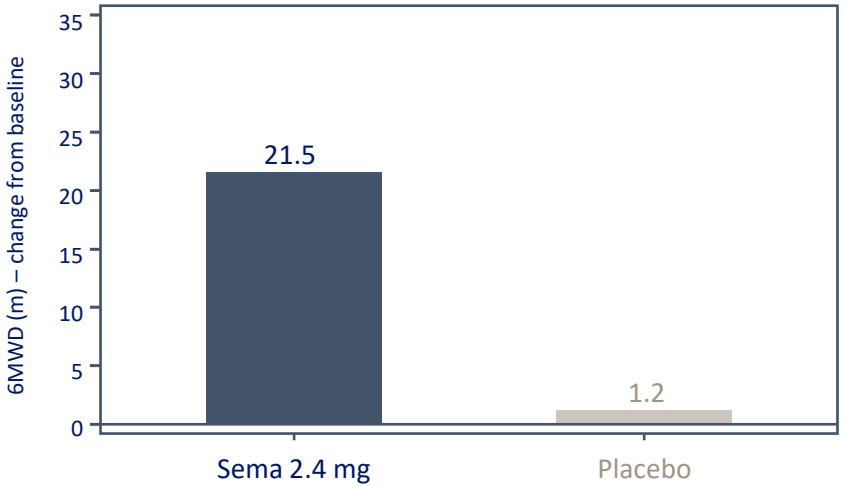
Significant increase in mean 6MWD

Confirmatory secondary endpoint (treatment policy estimand)

Observed mean change



Treatment policy estimand (week 52)



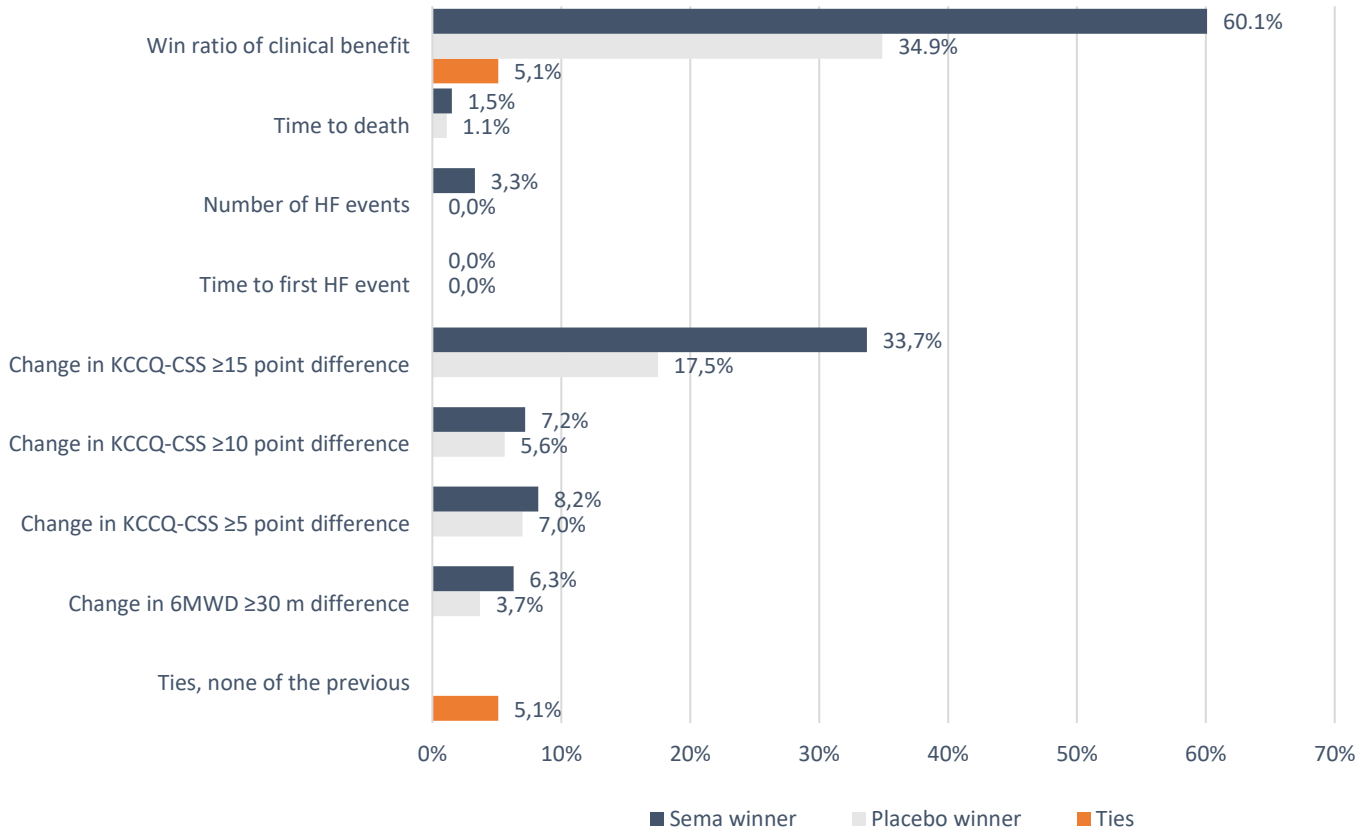
Analysis at week 52	ETD	95% CI	*p*-value
Sema 2.4 mg vs placebo	20.3 m	8.6; 32.1	0.001

Baseline 6MWD: 320.0 m

In the left figure, error bars are ± standard error of the mean. Numbers shown in the lower panel are numbers of patients contributing to the mean
**Estimated means*
6MWD, 6-minute walk distance; CI, confidence interval; ETD, estimated treatment difference; sema, semaglutide
Kosiborod MN et al. N Engl J Med 2023; DOI: 10.1056/NEJMoa2306963 (soon to be published)

Win ratio for composite hierarchical endpoint

Confirmatory secondary endpoint (treatment policy estimand)



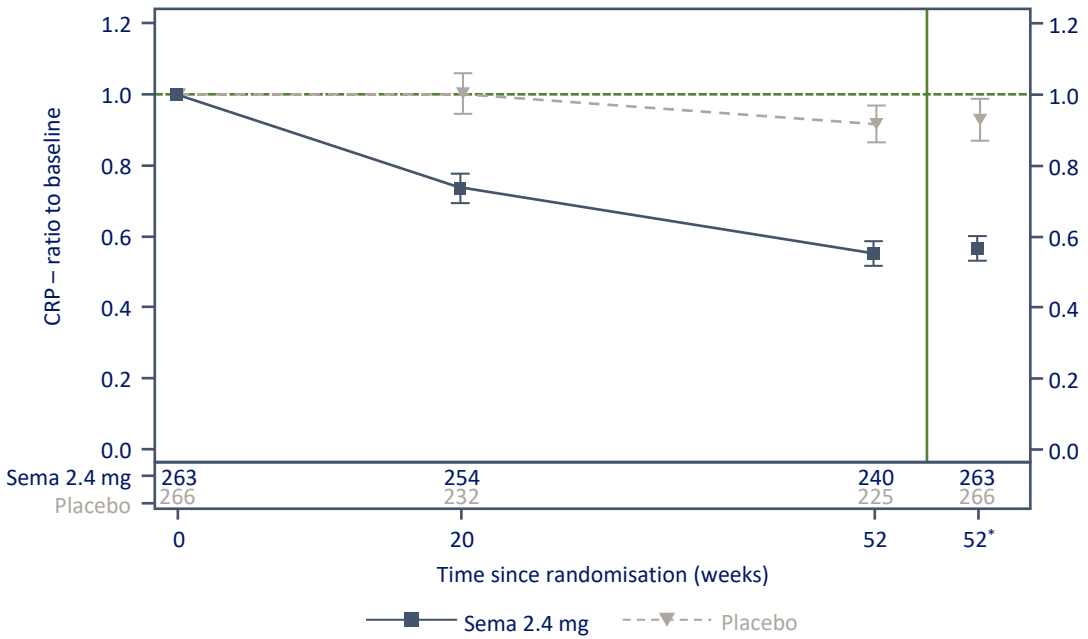
Analysis at week 52	Stratified WR	95% CI	*p*-value
Sema 2.4 mg / placebo	1.72	1.37; 2.15	<0.001

There are 72% more wins with sema 2.4 mg versus placebo or if considering an untied pair, the odds that a patient receiving sema 2.4 mg is the winner is 1.72 (versus placebo)
6MWD, 6-minute walk distance; CI, confidence interval; HF, heart failure; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; WR, win ratio
Kosiborod MN et al. N Engl J Med 2023; DOI: 10.1056/NEJMoa2306963 (soon to be published)

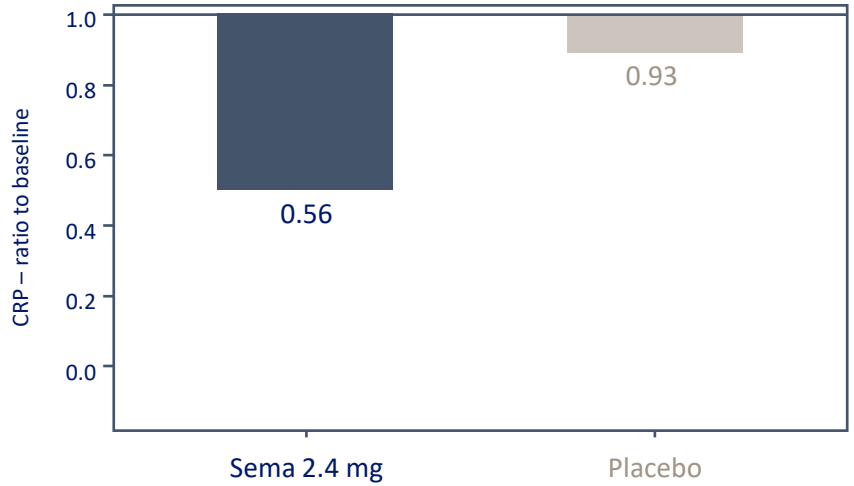
Significant decrease in CRP levels

Confirmatory secondary endpoint (treatment policy estimand)

Observed mean ratio*



Treatment policy estimand (week 52)

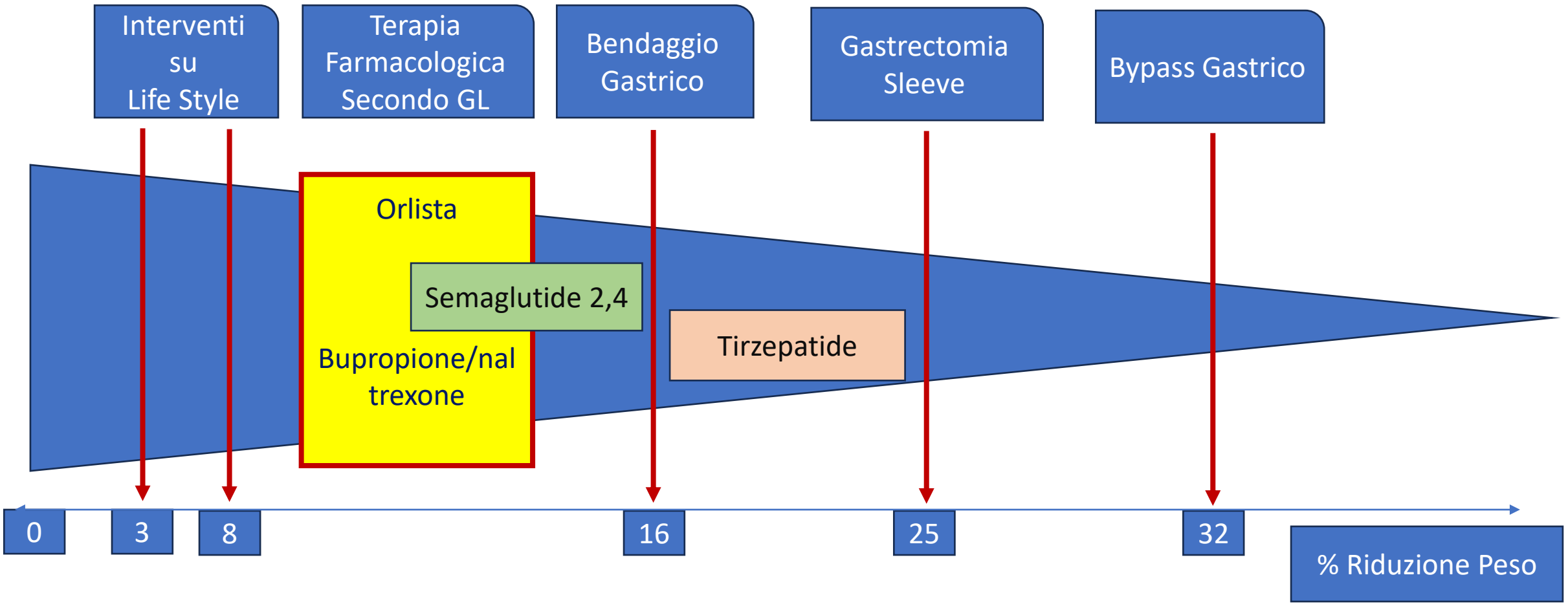


Analysis at week 52	ETR	95% CI	*p*-value
Sema 2.4 mg vs placebo	0.61	0.51; 0.72	<0.001

Baseline CRP levels: 3.8 mg/L

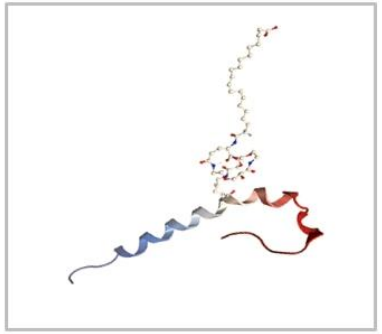
*Observed proportions of CRP below 2 mg/L: 50% vs 28.4% for sema 2.4 mg vs placebo, respectively. *Ratios above 1 indicate increased and ratios below 1 express decreased CRP levels with sema 2.4 mg vs placebo. In the left figure, error bars are ± standard error of the mean calculated on a logarithmic scale and back-transformed to a linear scale*
CI, confidence interval; CRP, C-reactive protein; ETR, estimated treatment ratio; sema, semaglutide
Kosiborod MN et al. N Engl J Med 2023; DOI: 10.1056/NEJMoa2306963 (soon to be published)

Risultati di riduzione di Peso con diverse Terapie



Background and Rationale

- Tirzepatide is a multi-functional peptide based on the native GIP peptide sequence, modified to bind to GIP or GLP-1 receptors[1]
- Tirzepatide has shown superior glycaemic control and weight loss compared to selective GLP-1 receptor agonists in preclinical and clinical studies, with an acceptable safety and tolerability profile[1-3]
- Tirzepatide is a 39 amino acid linear peptide and includes a C20 fatty diacid moiety. The fatty acid component can bind to albumin
- Mean half-life of ~5 days, enabling once-weekly dosing
- Albumin concentrations in hepatic impaired subjects can be lower than that in control, and hence there could be, in theory, an impact of hepatic impairment on tirzepatide PK



Abbreviations: GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1

1. Coskun et al. Mol Metab. 2018;18:3-14
2. Frias et al. Lancet. 2018;392:2180-93
3. Frias et al. New Engl J Med. 2021;385(6):503-515.

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Tirzepatide Once Weekly for the Treatment of Obesity

Jastreboff AM et al. DOI: 10.1056/NEJMoa2206038

CLINICAL PROBLEM

Several clinical guidelines recommend pharmacotherapy for obesity. Tirzepatide — a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist recently approved in the United States to treat type 2 diabetes — induced clinically relevant weight reduction in phase 2 studies of people with diabetes. However, its efficacy for weight reduction in those without diabetes is unknown.

CLINICAL TRIAL

Design: An international, phase 3, double-blind, randomized, placebo-controlled trial examined the efficacy and safety of tirzepatide in adults with obesity or overweight who did not have diabetes.

Intervention: 2539 adults with a body-mass index of 30 or higher, or 27 or higher with at least one weight-related complication, were assigned to once-weekly subcutaneous tirzepatide at one of three doses (5 mg, 10 mg, or 15 mg) or placebo, in addition to lifestyle intervention. Treatment included a dose-escalation phase and lasted for 72 weeks. The coprimary end points were the percentage change in weight from baseline to week 72 and weight reduction of at least 5% by week 72.

RESULTS

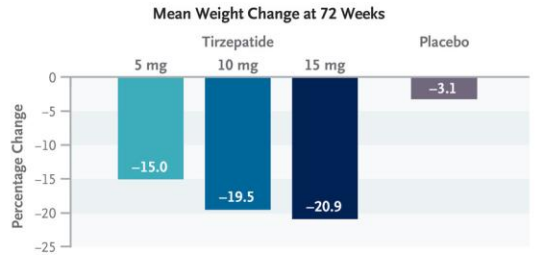
Efficacy: Both the percentage change in weight and the percentage of participants with at least 5% weight reduction were significantly greater with all three doses of tirzepatide than with placebo.

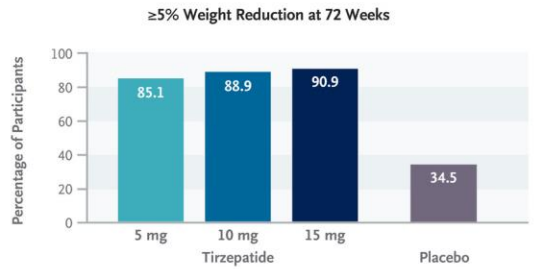
Safety: Gastrointestinal events, including nausea, diarrhea, and constipation, were the most common adverse events seen with tirzepatide; the majority of events were transient and mild to moderate in severity.

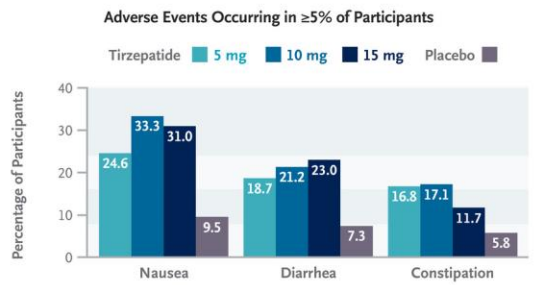
LIMITATIONS AND REMAINING QUESTIONS

- Enrolled participants may have been more committed to weight management than many people with obesity.
- Cardiometabolic variables (e.g., blood pressure and lipid levels) were relatively normal at baseline, so the ability to show a potential improvement within the time frame of this study was limited.
- The number of participants with overweight plus at least one weight-related complication was small (140 of the 2539 participants; 5.5%), which prevented definitive conclusions in this subgroup.

Links: Full Article | NEJM Quick Take | Editorial







CONCLUSIONS

All three doses of once-weekly subcutaneous tirzepatide led to clinically meaningful and sustained weight reduction in obese adults who did not have diabetes.

Effects of Tirzepatide Versus Insulin Glargine on Cystatin C–Based Kidney Function: A SURPASS-4 Post Hoc Analysis

Hiddo J.L. Heerspink, Naveed Sattar, Imre Pavo, Axel Haupt, Kevin L. Duffin, Zhengyu Yang, Russell J. Wiese, Jonathan M. Wilson, Andrea Hemmingway, David Z.I. Cherney, Katherine R. Tuttle

Tirzepatide slowed the cystatin C–based eGFR decline rate compared with insulin glargine

Context

Tirzepatide reduces body weight and eGFR-creatinine compared with insulin glargine

However, eGFR-creatinine may be influenced by muscle mass changes

Aim

Examine effects of tirzepatide on kidney function assessed by eGFR-cystatin C, which is not affected by muscle mass changes

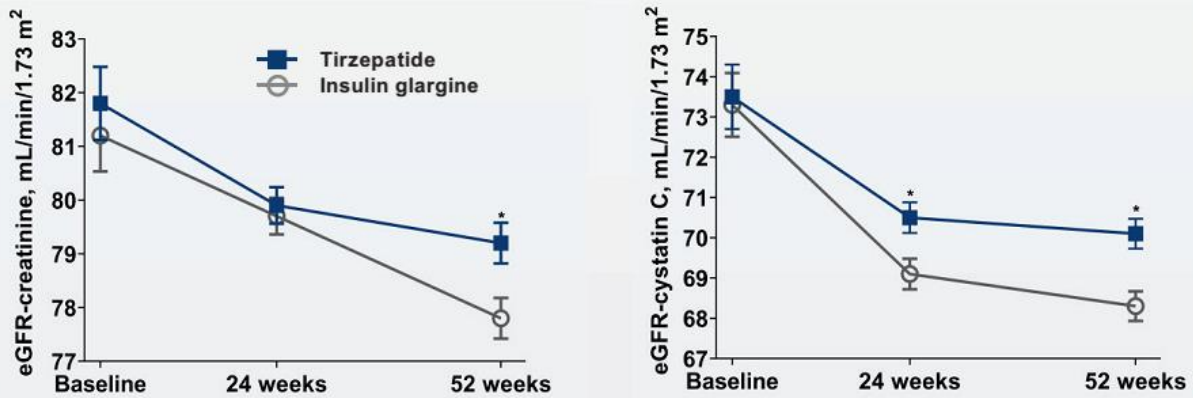
Population

Type 2 diabetes
High cardiovascular risk

n = 995	*n* = 1,000
Tirzepatide 5, 10, 15 mg (pooled for analysis)	Titrated insulin glargine 100 U/mL

Key Result

Tirzepatide slowed the eGFR decline rate when assessed by both creatinine– and cystatin C–based eGFR



*$P < 0.05$ for tirzepatide vs. insulin glargine

Effects on eGFR-cystatin C were consistent across subgroups defined by demographics, and by baseline glycemic control, SGLT2 inhibitor use, body weight, albuminuria status, and eGFR

Correlation Analyses

Baseline, 1-year, and 1-year change from baseline values correlated between eGFR-creatinine and -cystatin C

There were no significant correlations between changes in either eGFR measure and body weight changes

SURMOUNT-MMO: Population

Primary Prevention Population (Target: 40% of total)

BMI ≥27 kg/m²

N=~15,000 Follow-up 3.5 years
TZP MTD vs placebo
Key exclusion criteria: T2D/T1D

Secondary Prevention Population (Target: 60% of total)

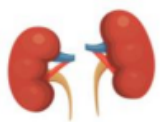
Primary Composite Endpoint

CV Composite:

1. All-cause Death
2. Non-fatal MI
3. Non-fatal Stroke
4. Coronary Revascularization
5. HF events that result in hospitalization or urgent visits

Key Secondary Endpoints

T2D Diagnosis



Improving renal outcomes

MACE-3

Improvement in Physical Functioning

Secondary/Tertiary Endpoints

- Change in body weight
- All-Cause Hospitalization
- Major Adverse Liver Outcomes (MALO)
- PROs
- Obesity-Related Malignancy
- Afib hospitalizations, ablation or cardioversion
- Additional Biomarkers

Risultati

- La riduzione del Peso come strategia terapeutica per il controllo del rischio residuo è un obbiettivo complesso da raggiungere
- L’intervento sul life style è di lieve entità e difficile da mantenere e comunque non associato ad una riduzione degli eventi CV
- I nuovi trattamenti possono determinare riduzioni significative e persistenti
- L’impiego di tali farmaci ha comportato una riduzione degli eventi CV e pertanto rappresenta una nuova strategia di gestione del Rischio Residuo