Semaglutide e eventi cardiovascolari

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UOC Diabetologia Territoriale

AUSL Ferrara

Società Medico Chirurgica di Ferrara dal 1846

RENDICONTO DELLE ADUNANZE DELLA 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

SERVIZIO SANITARIO REGIONALE EMILIA-ROMAGNA Azienda Unità Sanitaria Locale di Ferrara

Società Italiana Endocrinologia

Ordine dei Medici Chirurghi e degli Odontoiatri della provincia di FERRARA

Obesità: fenotipizzazione e risvolti terapeutici

Sabato 19 ottobre 2024

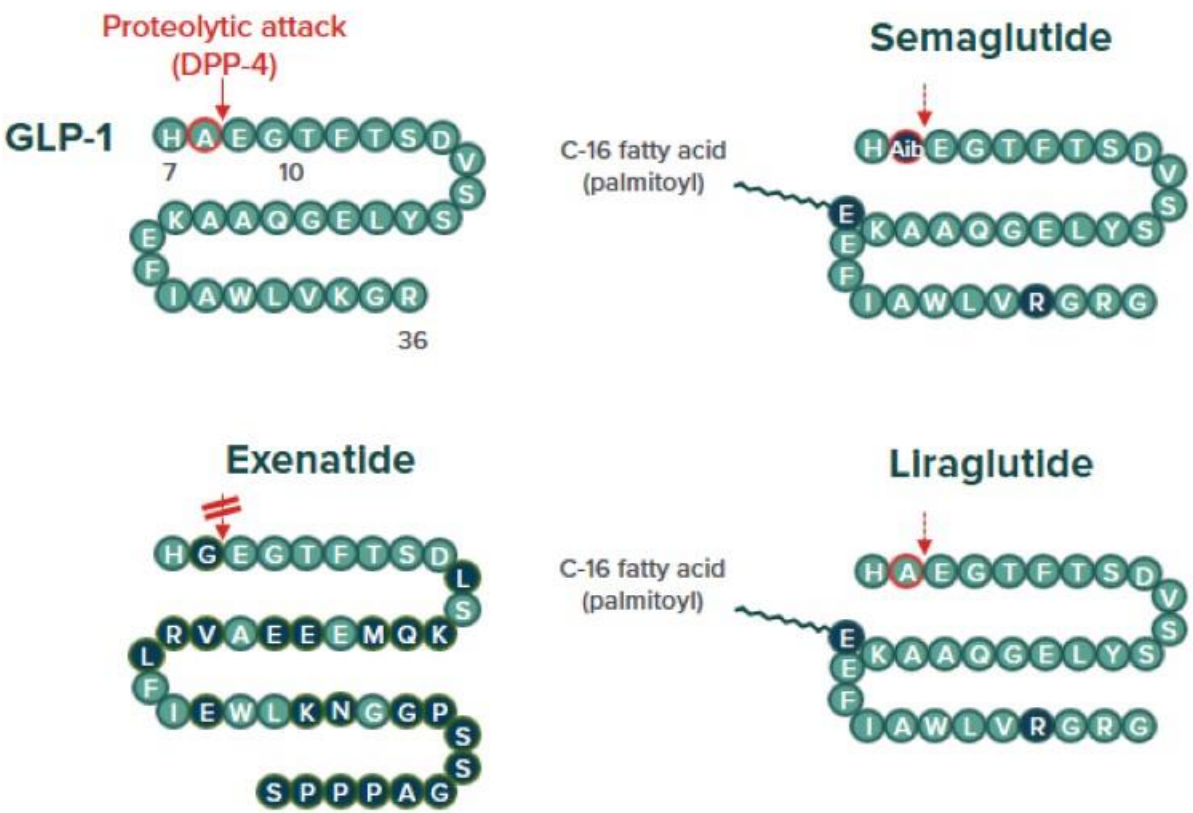
Aula Magna Nuovo Arcispedale S. Anna

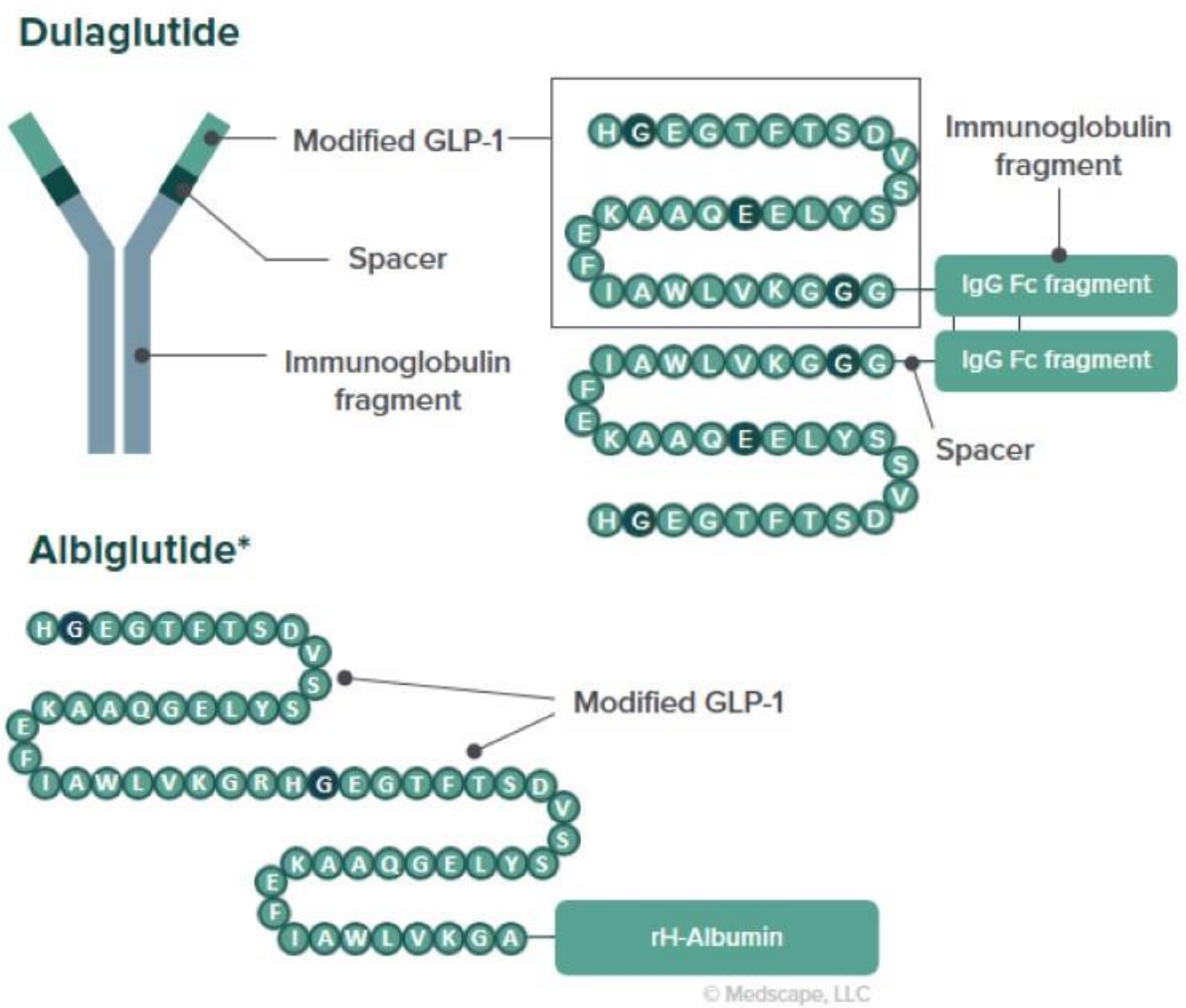
Cona, Ferrara

Il Segretario
Dott. M. Vason

Il Presidente
Dott. R. Zoppellari

Contemporary Management of Diabetes
Incretin Agonists: GLP-1 Agonism

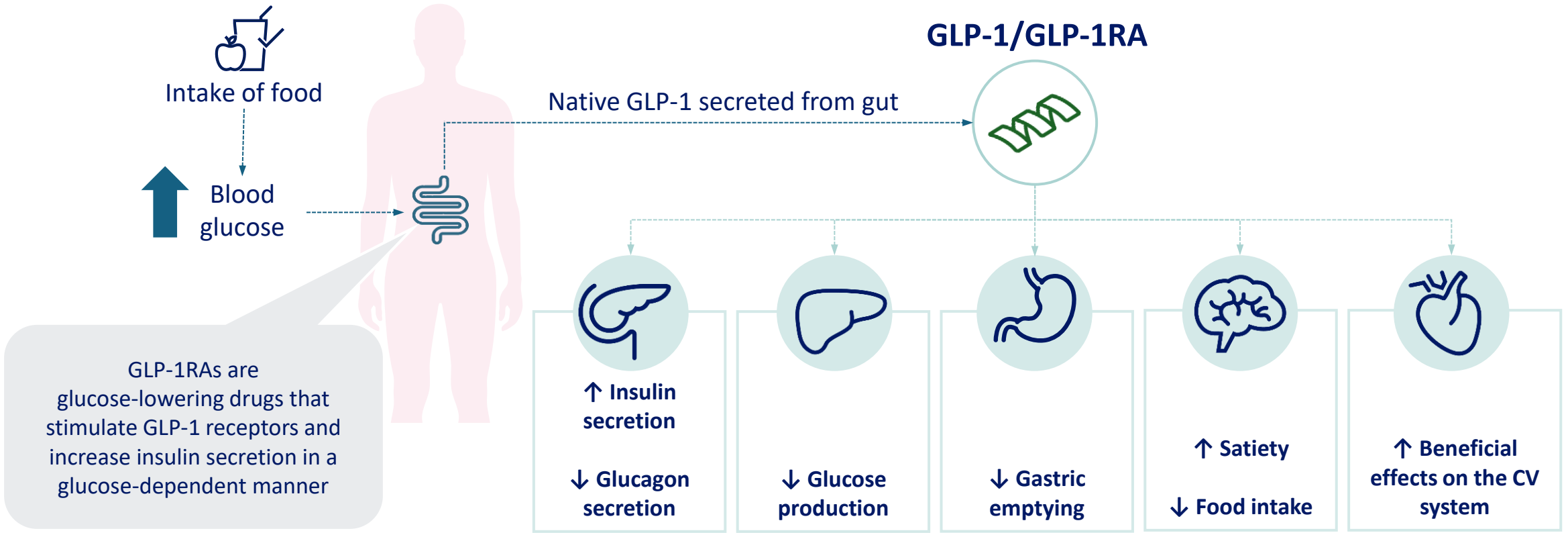




*Withdrawn in 2018 for economic reasons.
DDP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide 1.
Nauck MA, Meier JJ. Eur J Endocrinol. 2019;181:R211-R234.

Purpose of GLP-1 in the body

GLP-1 is an endogenous incretin hormone secreted in the gut in response to food intake

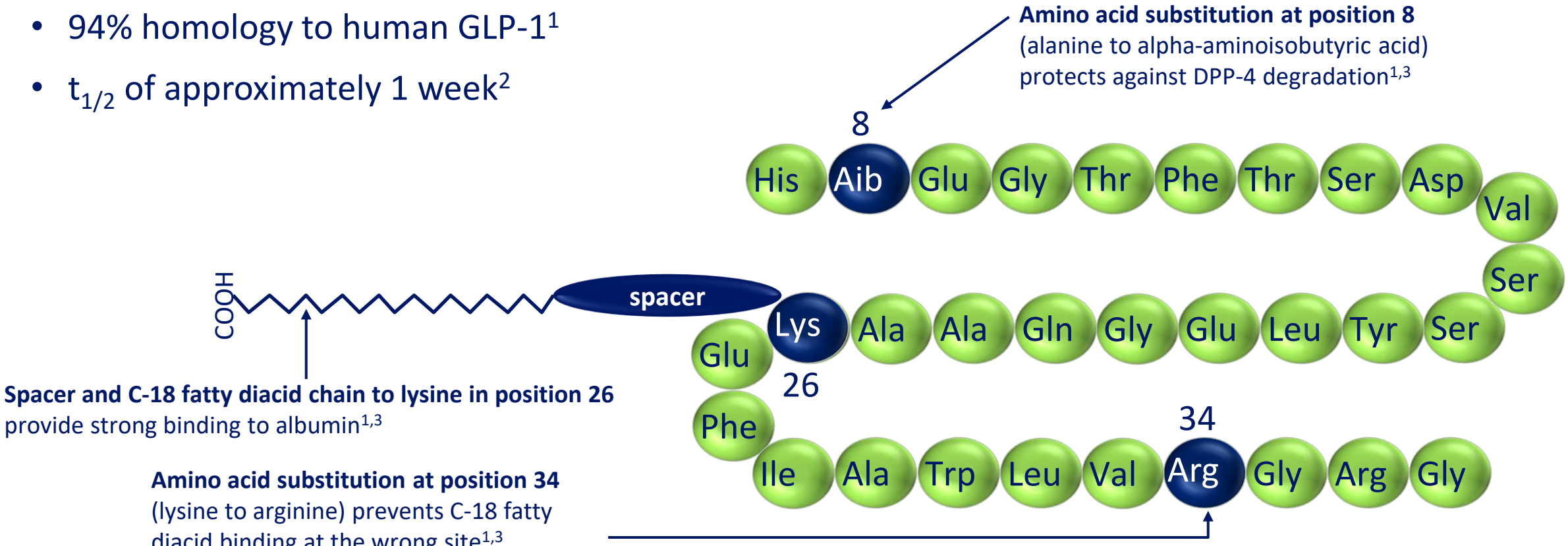


CV, cardiovascular; GLP-1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonist.

1. Vilsbøll T et al. Diabetologia 2002;45:1111–9; 2. Wajchenberg BL. Endocr Rev 2007;28:187–218; 3. Baggio LL, Drucker DJ. Gastroenterology 2007;132:2131–57.

Semaglutide is a human GLP-1 analogue

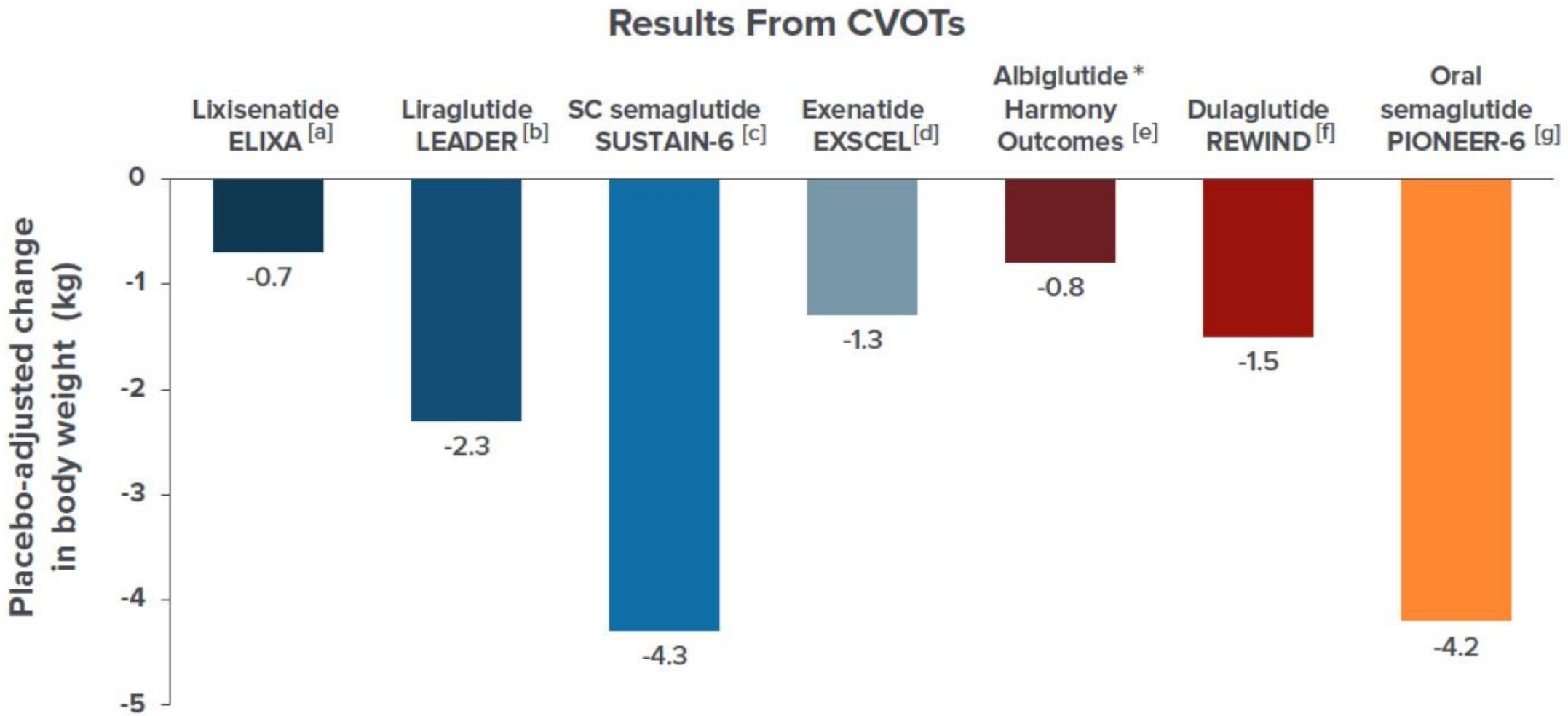
- 94% homology to human GLP-1[1]
- $t_{1/2}$ of approximately 1 week[2]



DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; $t_{1/2}$, half-life.

1. Lau J et al. J Med Chem 2015;58:7370–80; 2. Kapitza C et al. J Clin Pharmacol 2015;55:497–504; 3. Lund A et al. Eur J Intern Med 2014;25:407–14.

GLP-1 RAs Have Demonstrated Efficacy in Weight Reduction

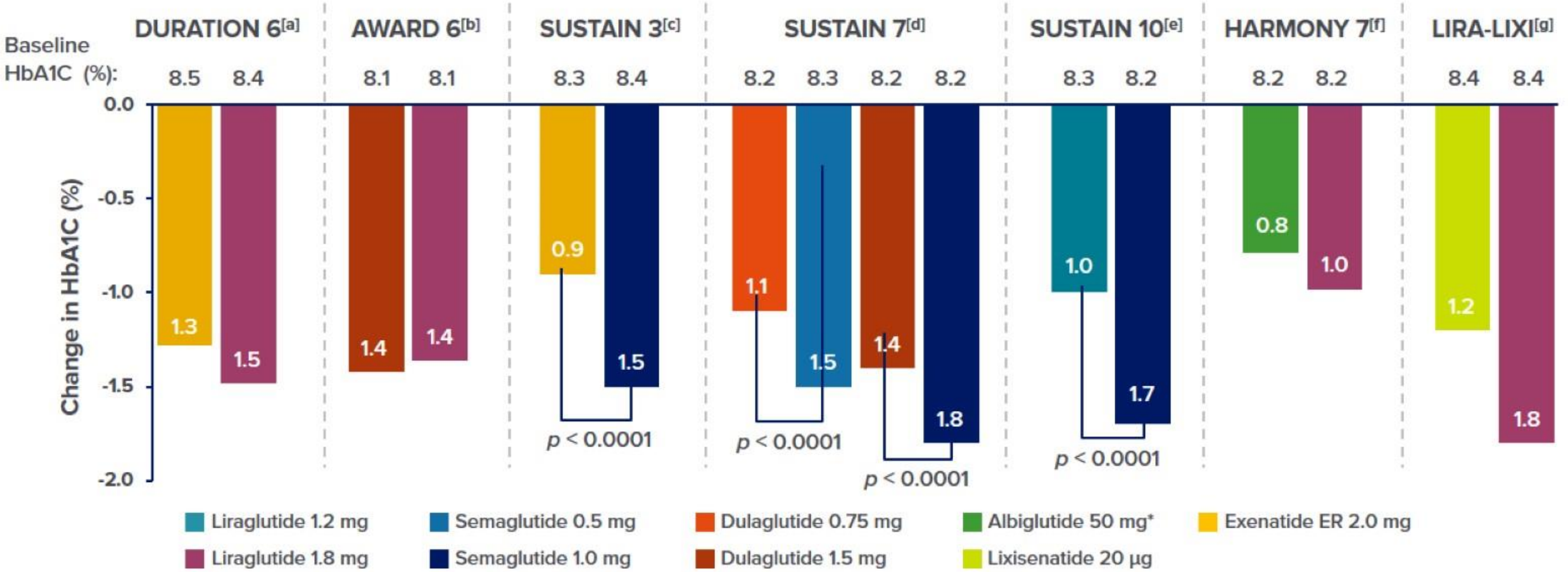


*Albiglutide was withdrawn from the worldwide market in 2018.

a. Pfeffer MA, et al. N Engl J Med. 2015;373:2247-225; b. Marso SP, et al. N Engl J Med. 2016;375:311-322; c. Marso SP, et al. N Engl J Med. 2016;375:1834-1844; d. Holman RR, et al. N Engl J Med. 2017;377:1228-1239; e. Hernandez AF, et al. Lancet. 2018;392:1519-1529; f. Gerstein HC, et al. Lancet. 2019;394:121-130; g. Husain M, et al. N Engl J Med. 2019;381:841-851.

GLP-1 RAs Have Demonstrated Efficacy in HbA1c Reduction

Results From Head-to-Head Trials

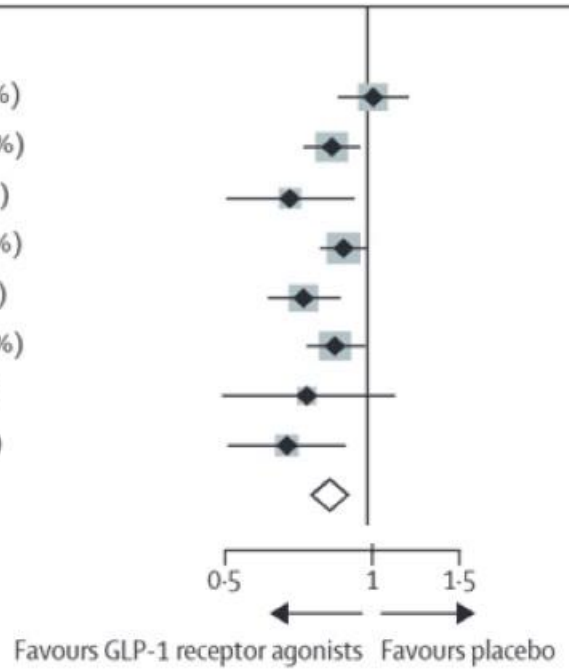


Direct comparisons should not be made between trials. Numerical values for bars may appear the same due to rounding.
*Albiglutide has been withdrawn from the worldwide market in July 2018.
ER, extended release.

a. Buse JB, et al. Lancet. 2013;381:117-124; b. Dungan KM, et al. Lancet. 2014;384:1349-1357; c. Ahmann AJ, et al. Diabetes Care. 2018;41:258-266; d. Pratley RE, et al. Lancet Diabetes Endocrinol. 2018;6:275-286; e. Capehorn MS, et al. Diabetes Metab. 2020;46:100-109; f. Pratley RE, et al. Lancet Diabetes Endocrinol. 2014;2:289-297; g. Nauck M, et al. Diabetes Care. 2016;39:1501-1509.

GLP-1 RAs and MACE in CVOTs
Meta-Analysis

	GLP-1 receptor agonist, n/N (%)	Placebo, n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
Three-point MACE					
ELIXA	400/3034 (13%)	392/3034 (13%)	1·02 (0·89–1·17)		0·78
LEADER	608/4668 (13%)	694/4672 (15%)	0·87 (0·78–0·97)		0·01
SUSTAIN-6	108/1648 (7%)	146/1649 (9%)	0·74 (0·58–0·95)		0·016
EXSCEL	839/7356 (11%)	905/7396 (12%)	0·91 (0·83–1·00)		0·061
Harmony Outcomes	338/4731 (7%)	428/4732 (9%)	0·78 (0·68–0·90)		0·0006
REWIND	594/4949 (12%)	663/4952 (13%)	0·88 (0·79–0·99)		0·026
PIONEER 6	61/1591 (4%)	76/1592 (5%)	0·79 (0·57–1·11)		0·17
AMPLITUDE-O	189/2717 (7%)	125/1359 (9%)	0·73 (0·58–0·92)		0·0069
Subtotal (I^2=44·5%, p=0·082)			0·86 (0·80–0·93)	65 (45–130)	<0·0001

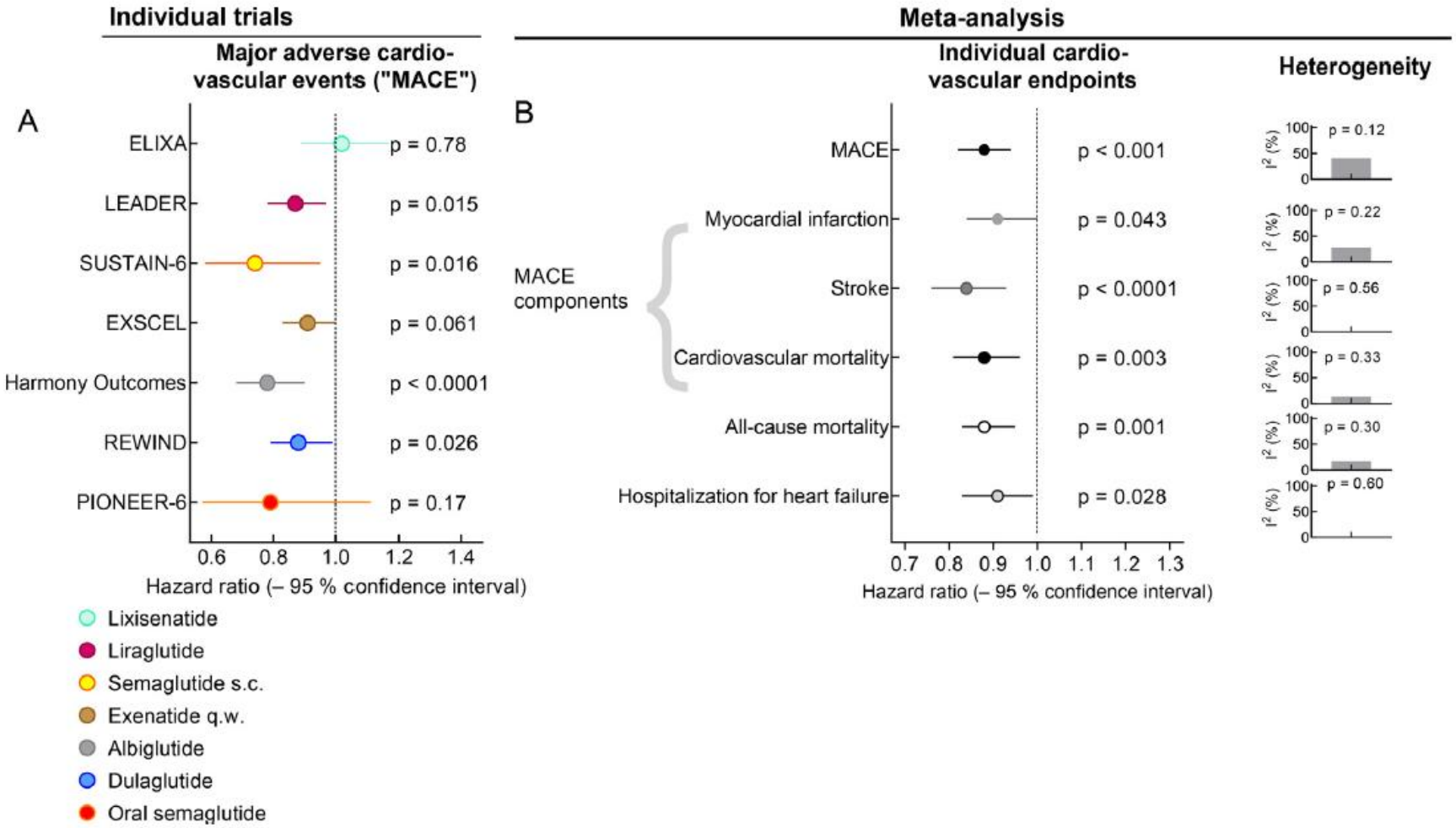


14% reduction in risk of MACE

CVOT, cardiovascular outcome trial; GLP-1 RA, glucagon-like peptide 1 receptor agonist; MACE, major adverse cardiac events.

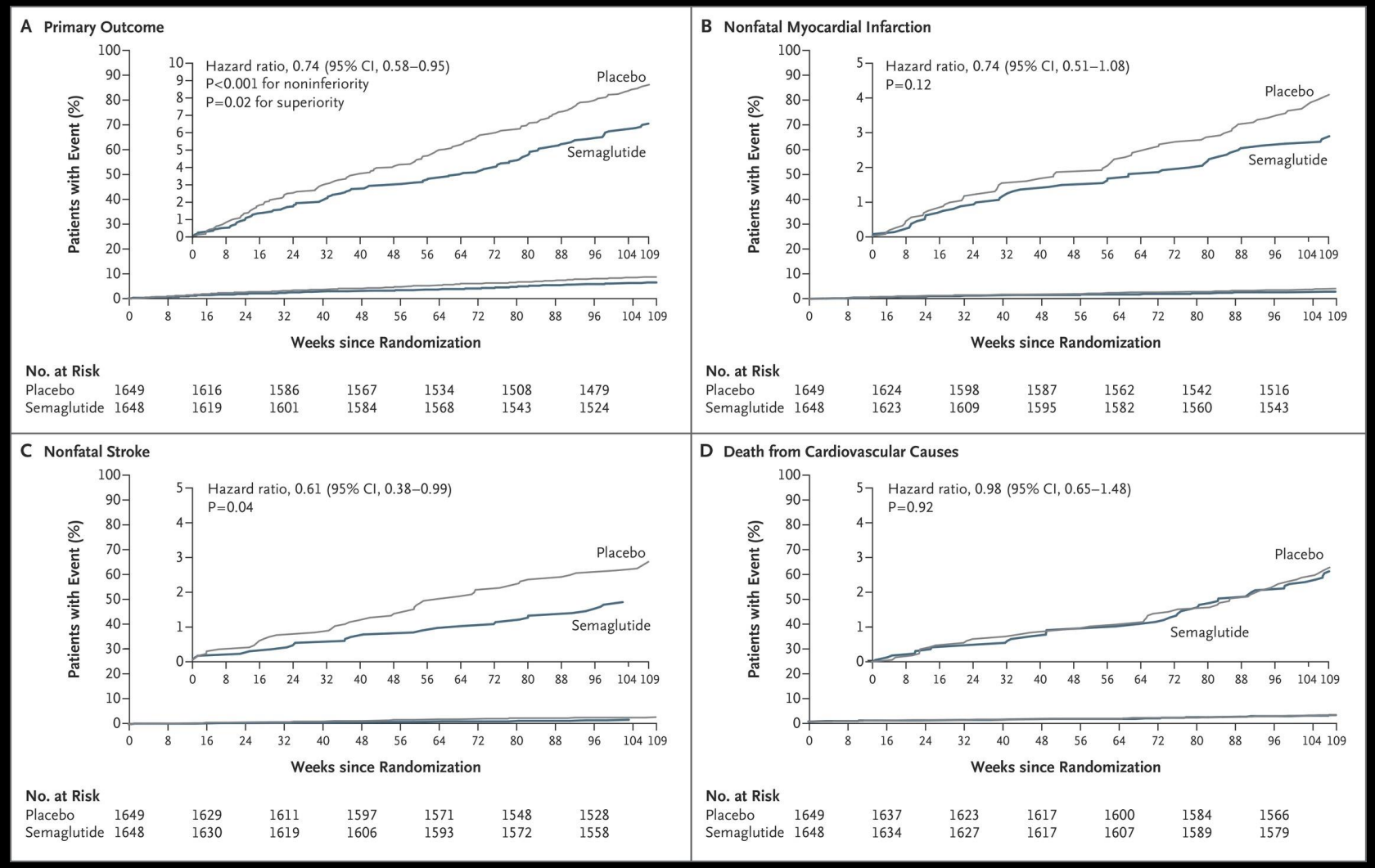
Adapted from Sattar N, et al. Lancet Diabetes Endocrinol. 2021;S2213-8587(21)00203-5.

Efficacia dei GLP-1 RAs su tutti i componenti dell'end point cardiovascolare



Nauck M et al. Molecular Metabolism 2020

SUSTAIN 6 Cardiovascular Outcomes.

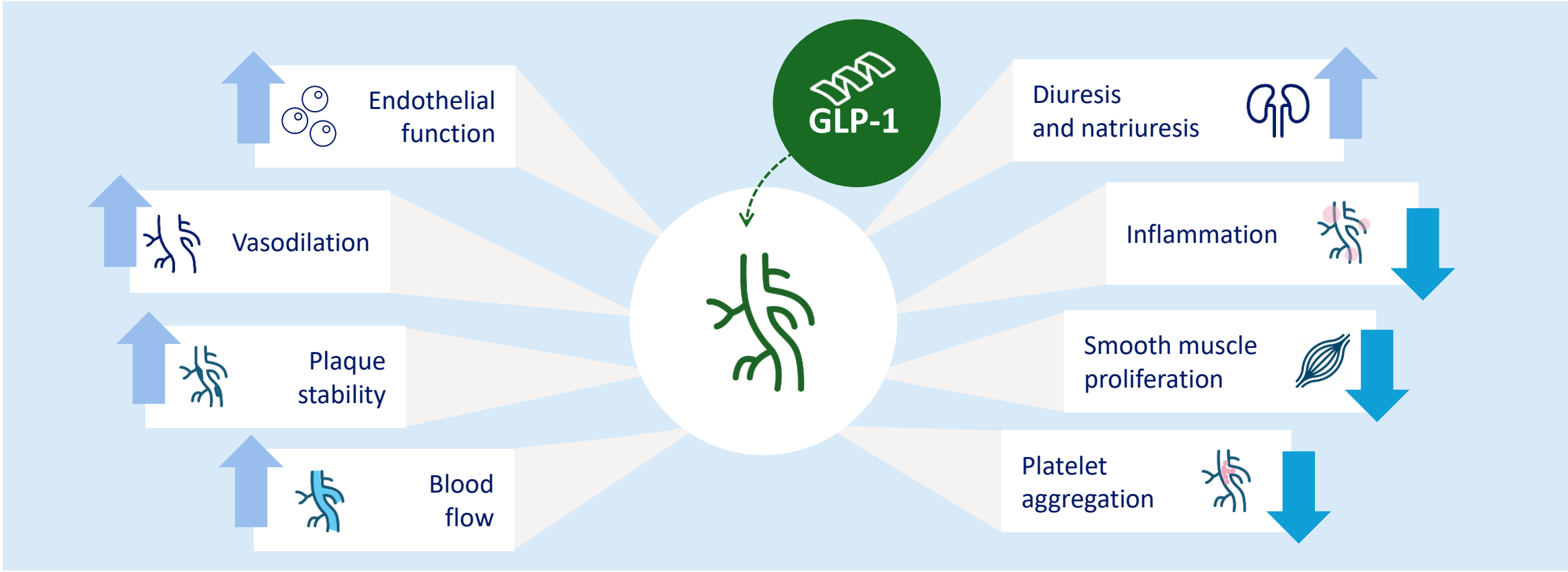


Marso SP et al. N Engl J Med 2016;375:1834-1844

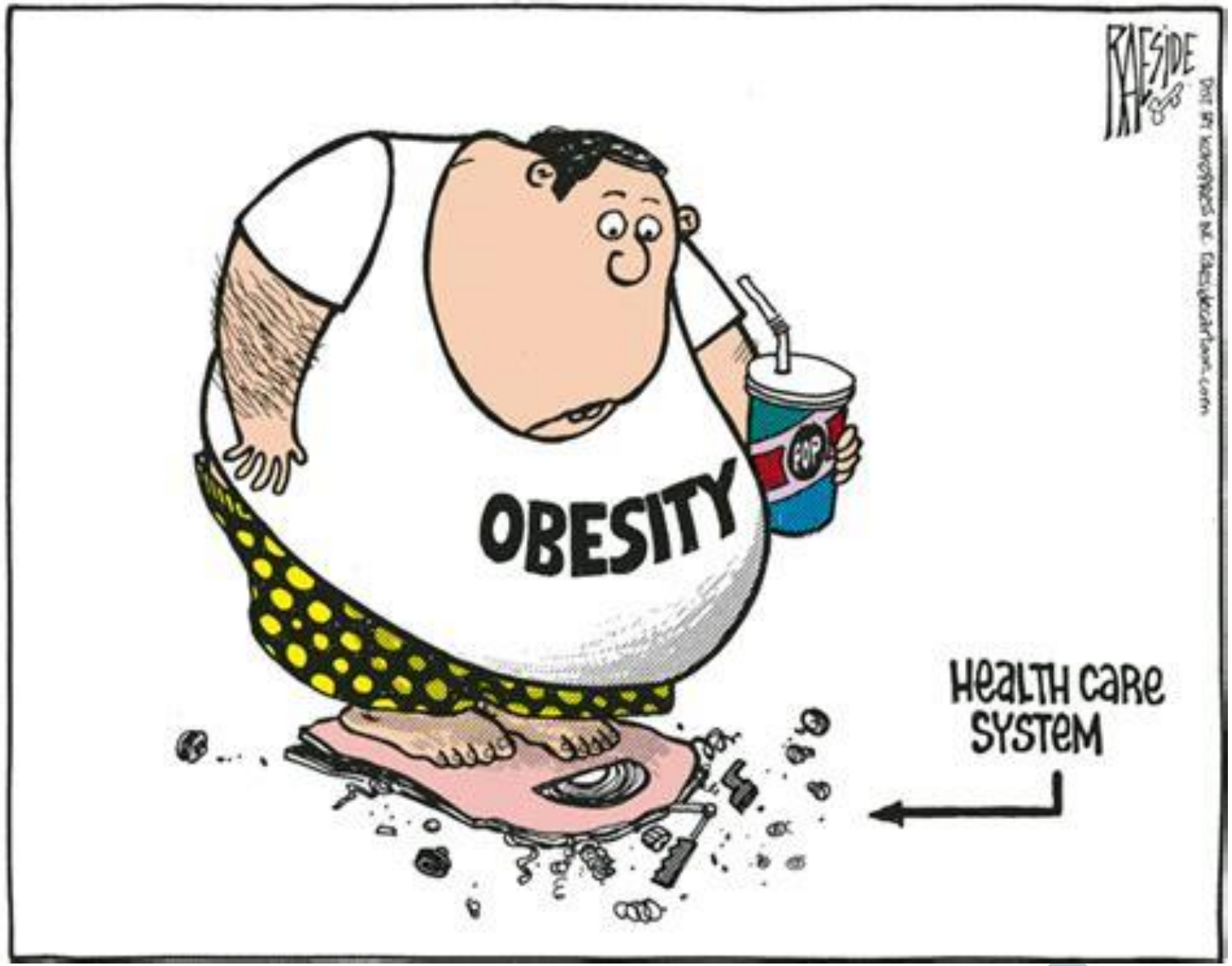
The NEW ENGLAND JOURNAL of MEDICINE

Purpose of GLP-1 in the body

Potential mechanism of the beneficial actions of GLP-1 in the cardiovascular system



GLP-1, glucagon-like peptide-1.
Adapted from Drucker DJ. Cell Metab 2016;24:15–30; Muskiet MHA et al. Nat Rev Nephrol 2017;13:605–28.


RAFESIDE
OBESITY
POP
HEALTH CARE SYSTEM

Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies

*Prospective Studies Collaboration**

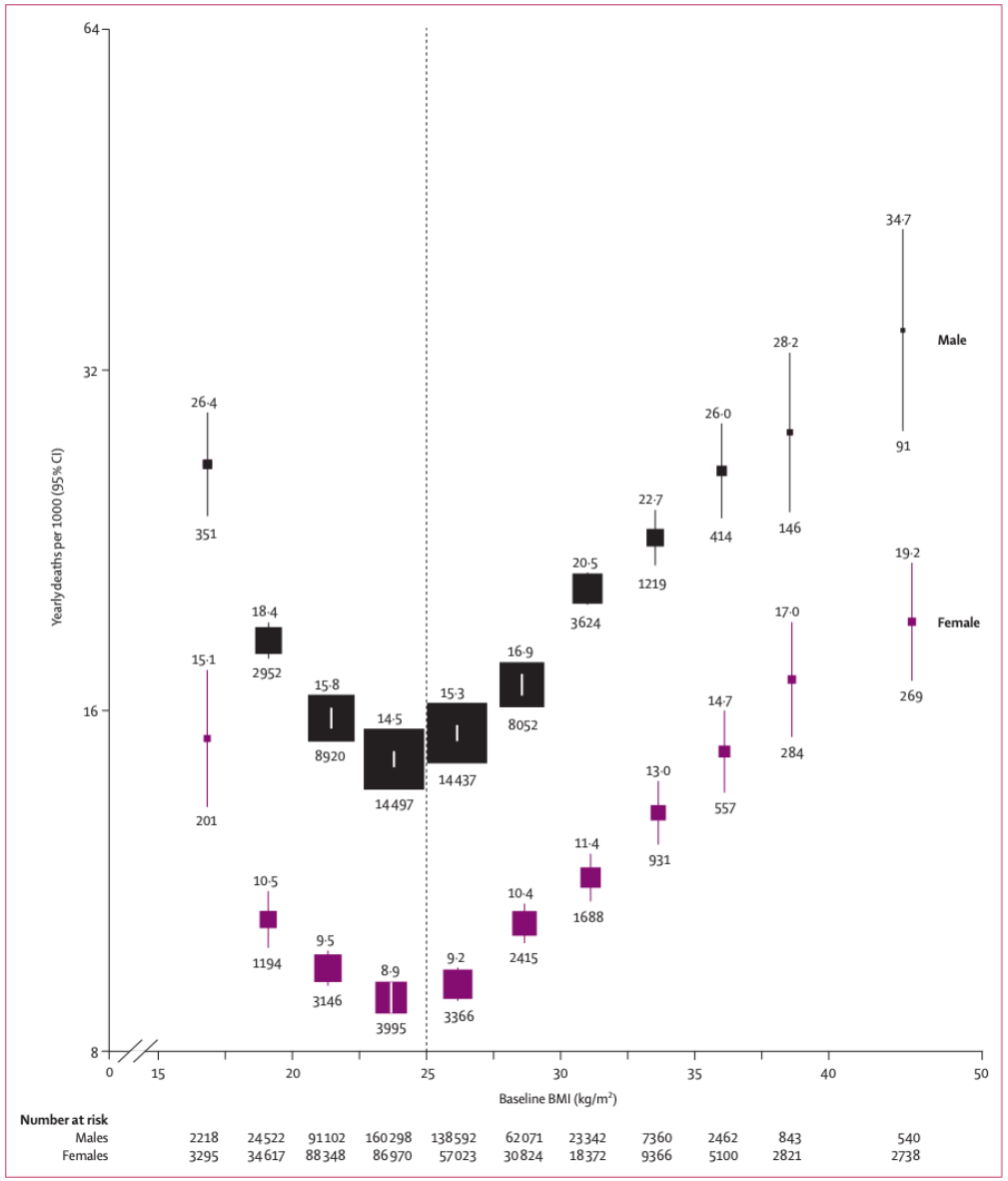


Figure 2: All-cause mortality versus BMI for each sex in the range 15–50 kg/m² (excluding the first 5 years of follow-up)

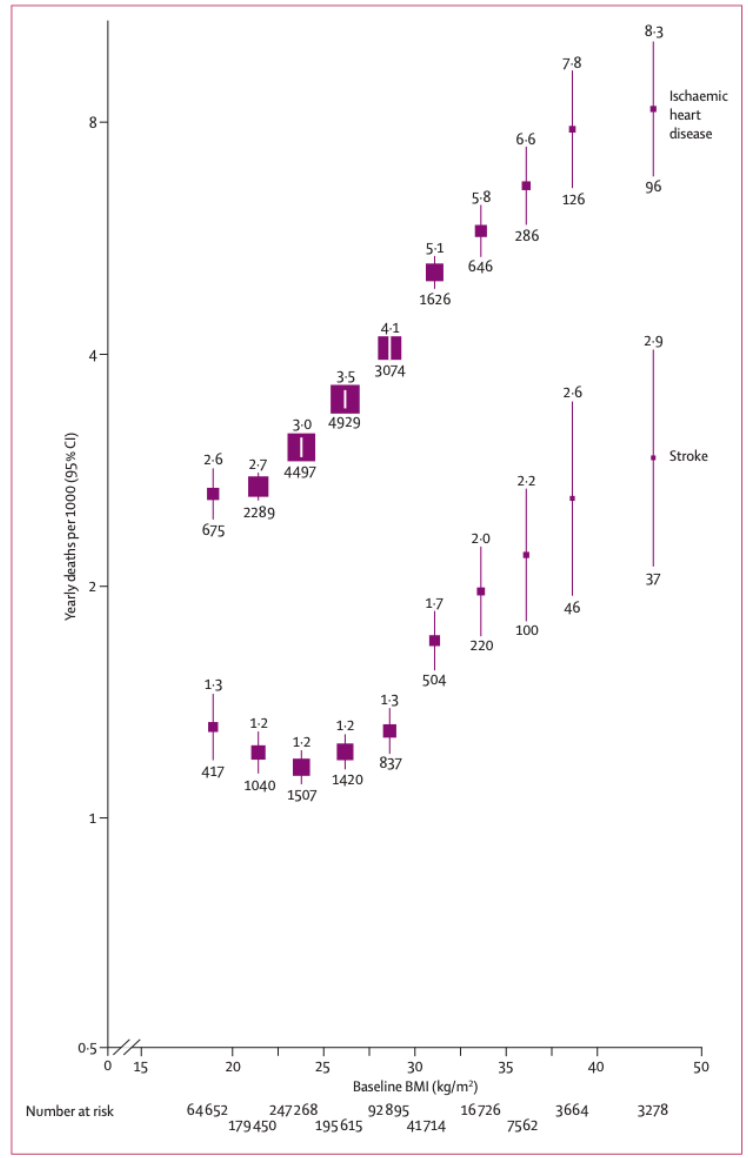


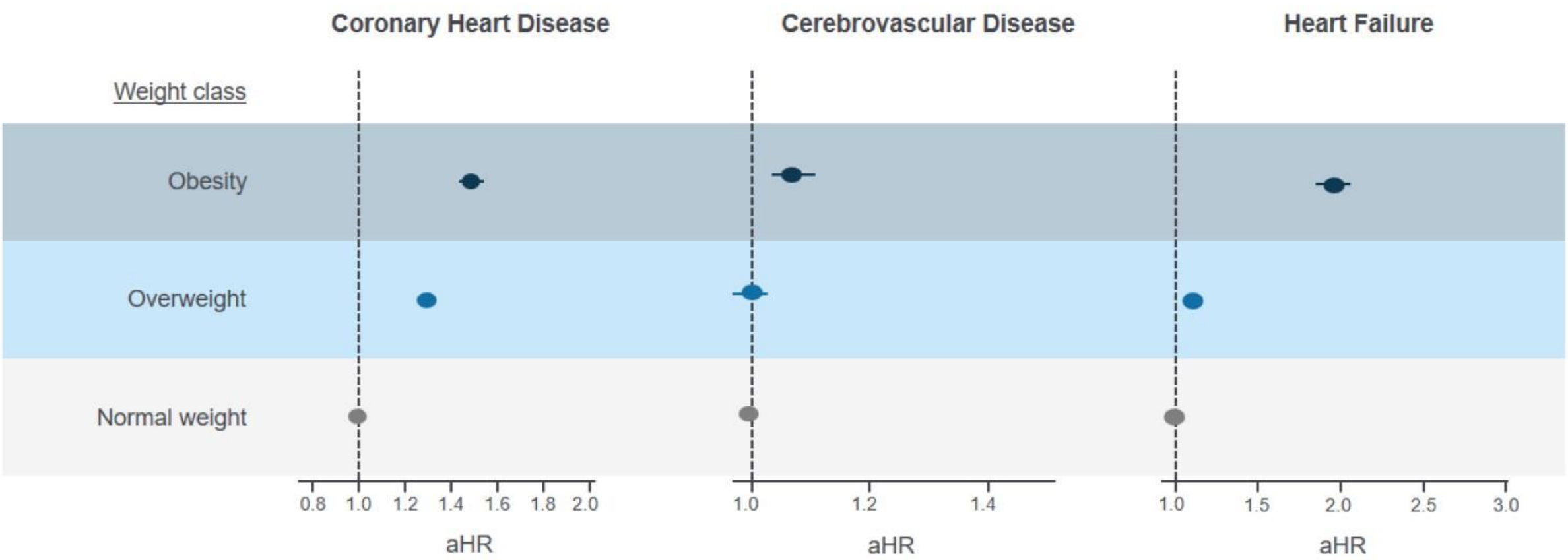
Figure 3: Ischaemic heart disease and stroke mortality versus BMI in the range 15–50 kg/m² (excluding the first 5 years of follow-up)

For every 5-unit increase in body mass index (BMI) above 25 kg/m2, vascular mortality increases by 41% and overall mortality increases by 29%

Lancet 2009; 373: 1083–96

Overweight and Obesity Increase the Risk for CVD
Even in the Absence of Metabolic Abnormalities

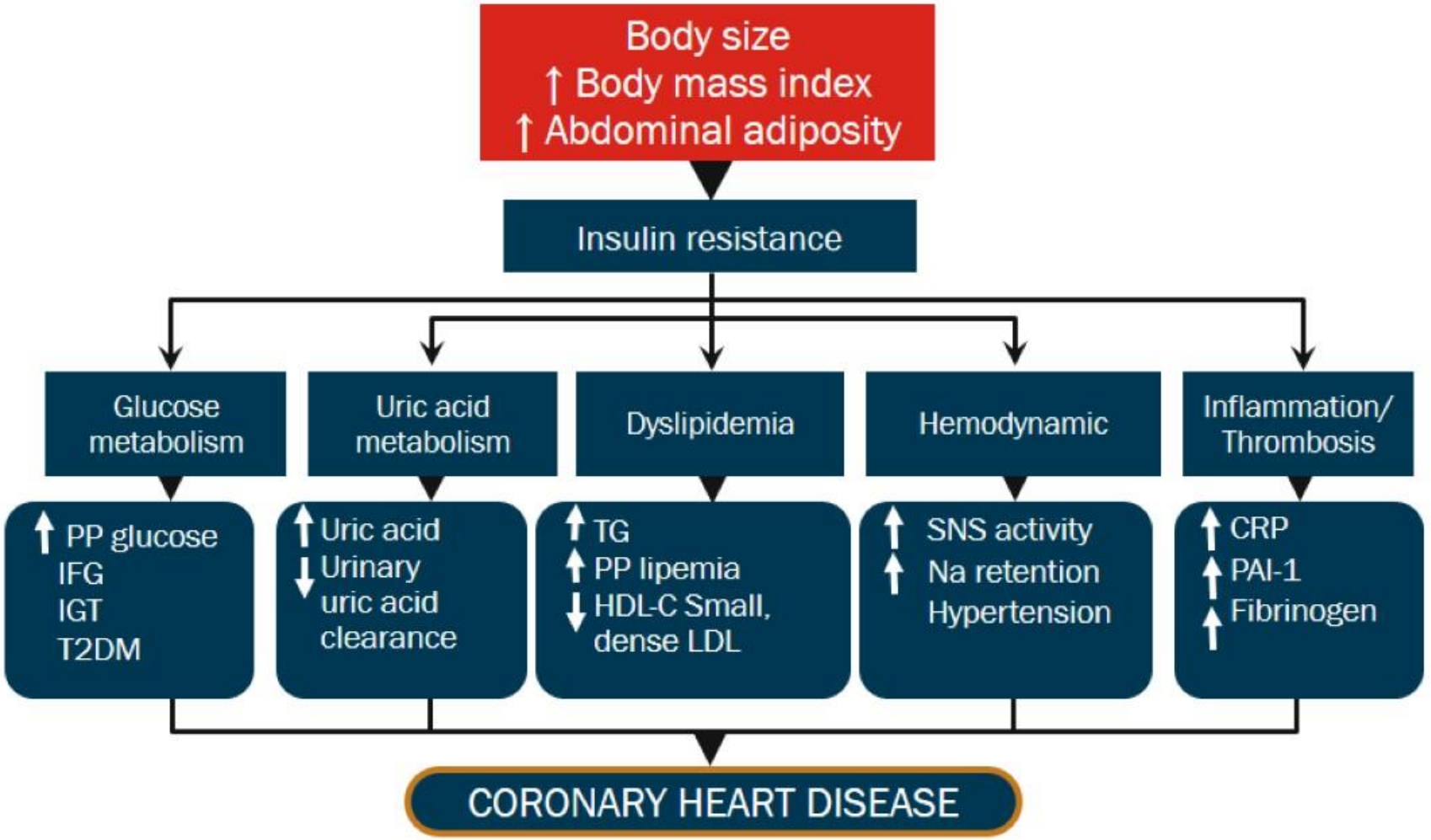
Body Size, Metabolic Status, and CVD Events in 3.5 M UK Adults



aHR, adjusted hazard ratio.

Caleyachetty R, et al. J Am Coll Cardiol. 2017;70:1429-1437.

Leading Drivers of Cardiometabolic Risk



Reaven GM. *Diabetes*. 1988;37:1595-1607; Reaven GM. *Drugs*. 1999;58(suppl):19-20.

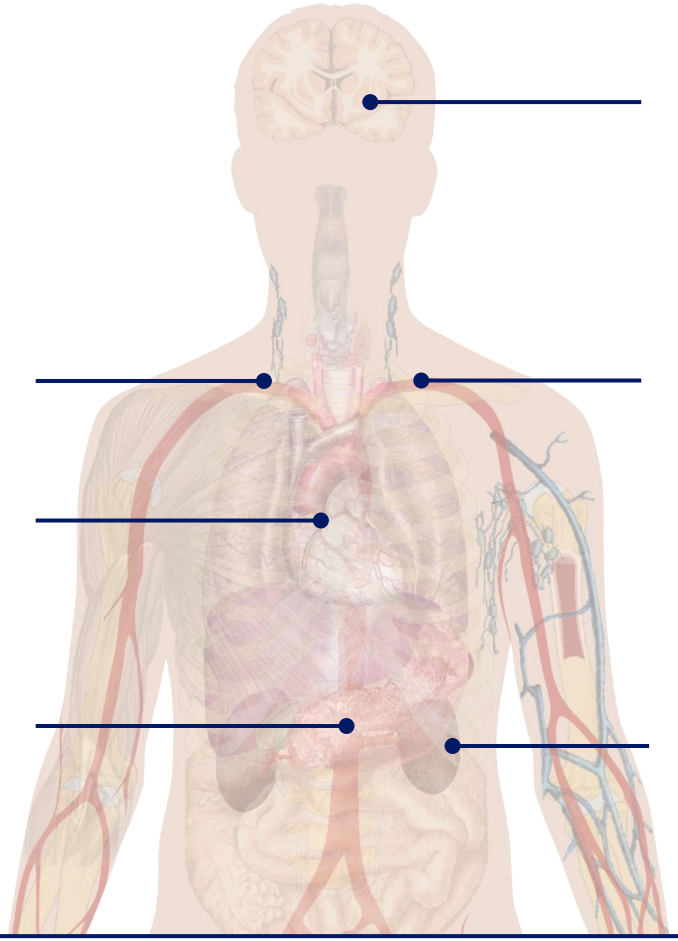
Sustained weight loss can make a big difference in reducing risk of ASCVD

Reduction in:

- Hypertension
- Dyslipidaemia
- Glycaemic control
- Kidney function

↓

ASCVD risk reduction



Improved measures of **sleep quality** and **mood** (i.e. depression)[4]

Improvements in **blood pressure**[1]

Improvements in **lipid profile**[5]

Reduction in **CV mortality**[2]

Reduction in **hyperglycaemia**[3]

Improvements in **proteinuria**, **albuminuria** and **GFR normalisation**[6]

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; GFR, glomerular filtration rate.

1. Wing RR et al. Diabetes Care 2011;34:1481–1486; 2. Li G et al. Lancet Diabetes Endocrinol 2014; 2:474–480; 3. Cefalu WT et al. Diabetes Care 2015;38:1567–1582; 4. Alfaris N et al. Obesity (Silver Spring) 2015;23:558–565; 5. Datillo AM, Kris-Etherton PM. Am J Clin Nutr 1992;56:320–328; 6. Bolignano D, Zoccali C. Nephrol Dial Transplant 2013;28(Suppl 4):iv82–98.

Once-Weekly Semaglutide in Adults with Overweight or Obesity

Wilding JPH. et al. DOI: 10.1056/NEJMoa2032183

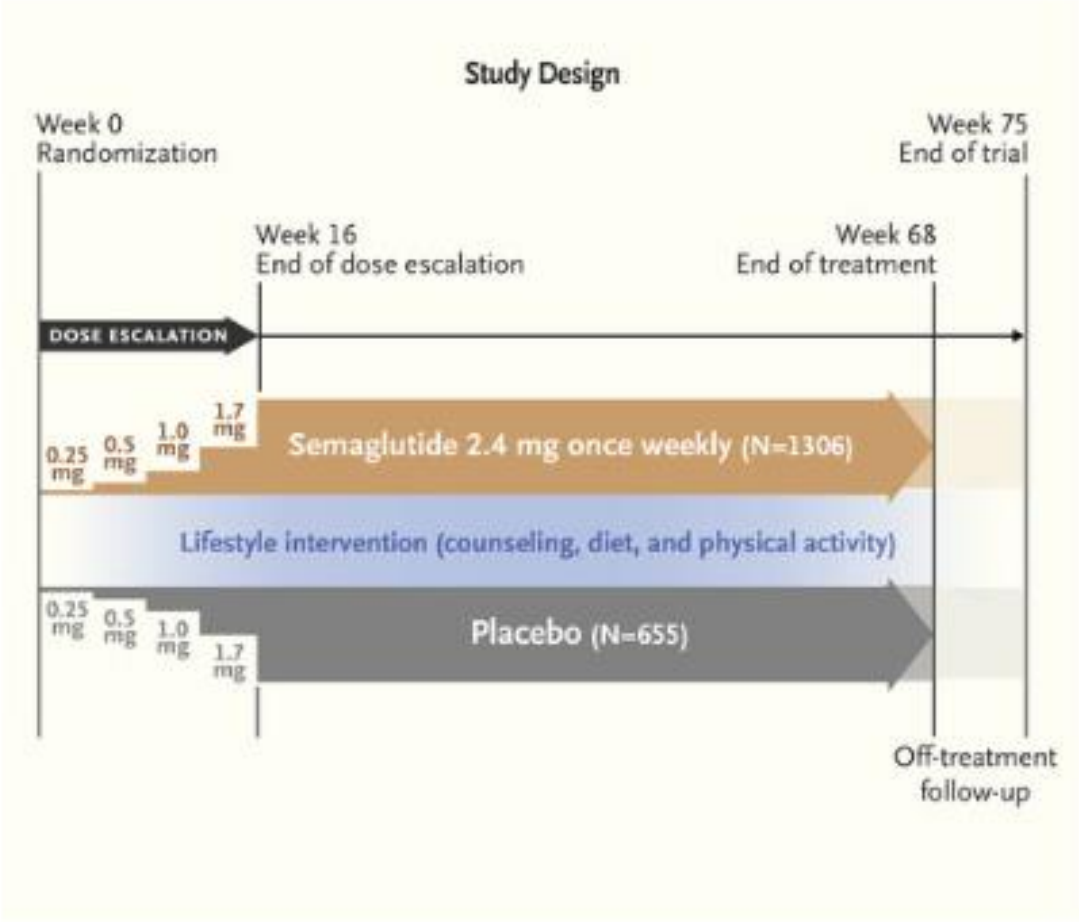
CLINICAL PROBLEM

Clinical guidelines suggest pharmacologic intervention in addition to diet and exercise to promote weight loss among adults with BMI ≥30 (or ≥27 in those with coexisting conditions). Barriers to medication use include limited efficacy, adverse effects, and cost. Subcutaneous semaglutide, a glucagon-like peptide-1 analogue FDA-approved to treat type 2 diabetes in adults, has been accompanied by weight loss in previous clinical trials.

CLINICAL TRIAL

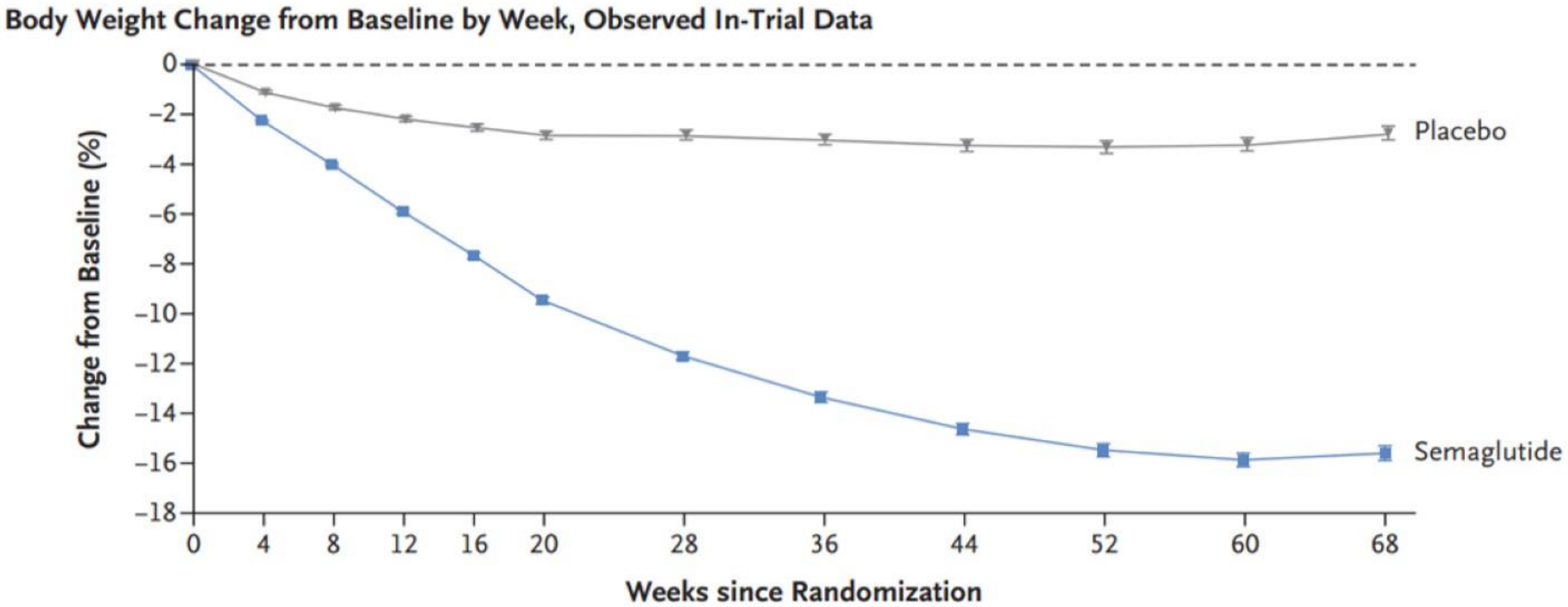
A phase 3, double-blind, randomized, controlled trial comparing semaglutide with placebo, plus lifestyle changes, in overweight or obese adults without diabetes.

1961 participants were assigned to receive 2.4 mg of subcutaneous semaglutide (with gradual increase to the 2.4 mg dose) or placebo weekly for 68 weeks; both groups received a counseling intervention involving diet and exercise. Coprimary end points were percentage change in body weight and weight reduction ≥5%.



Effect of Semaglutide 2.4 mg vs Placebo on Body Weight
STEP 1 Trial

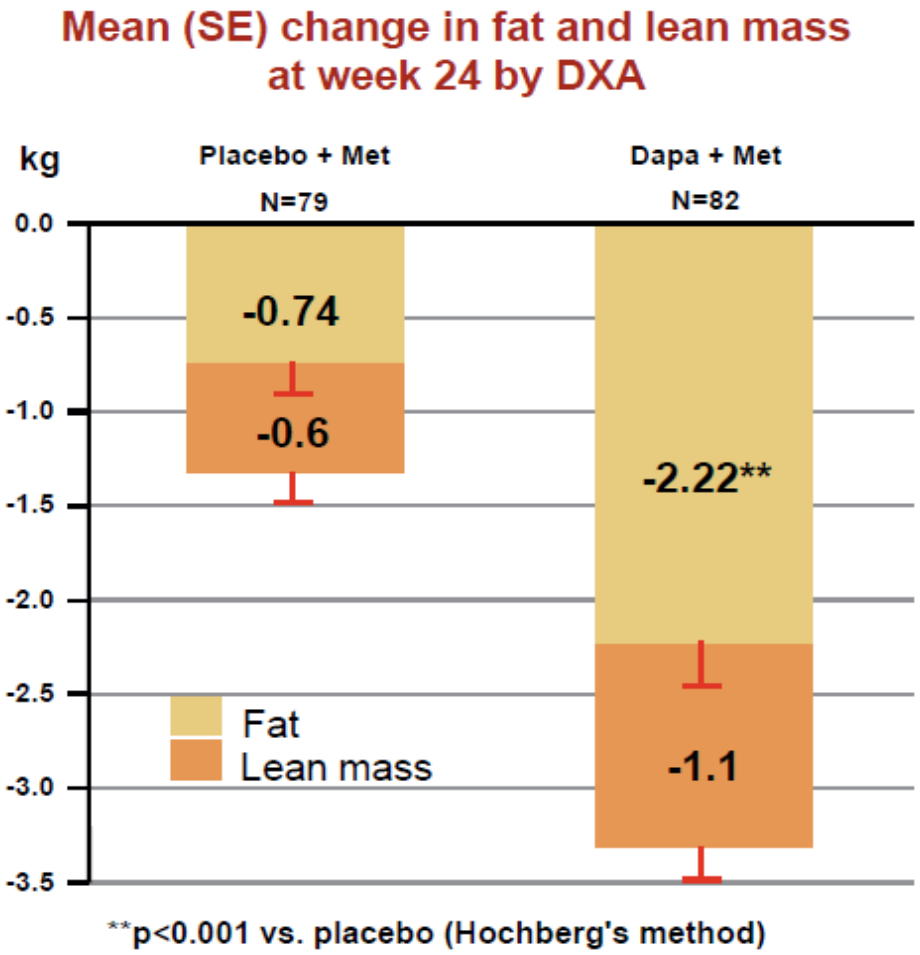
1961 Adults With BMI ≥ 30, no T2D

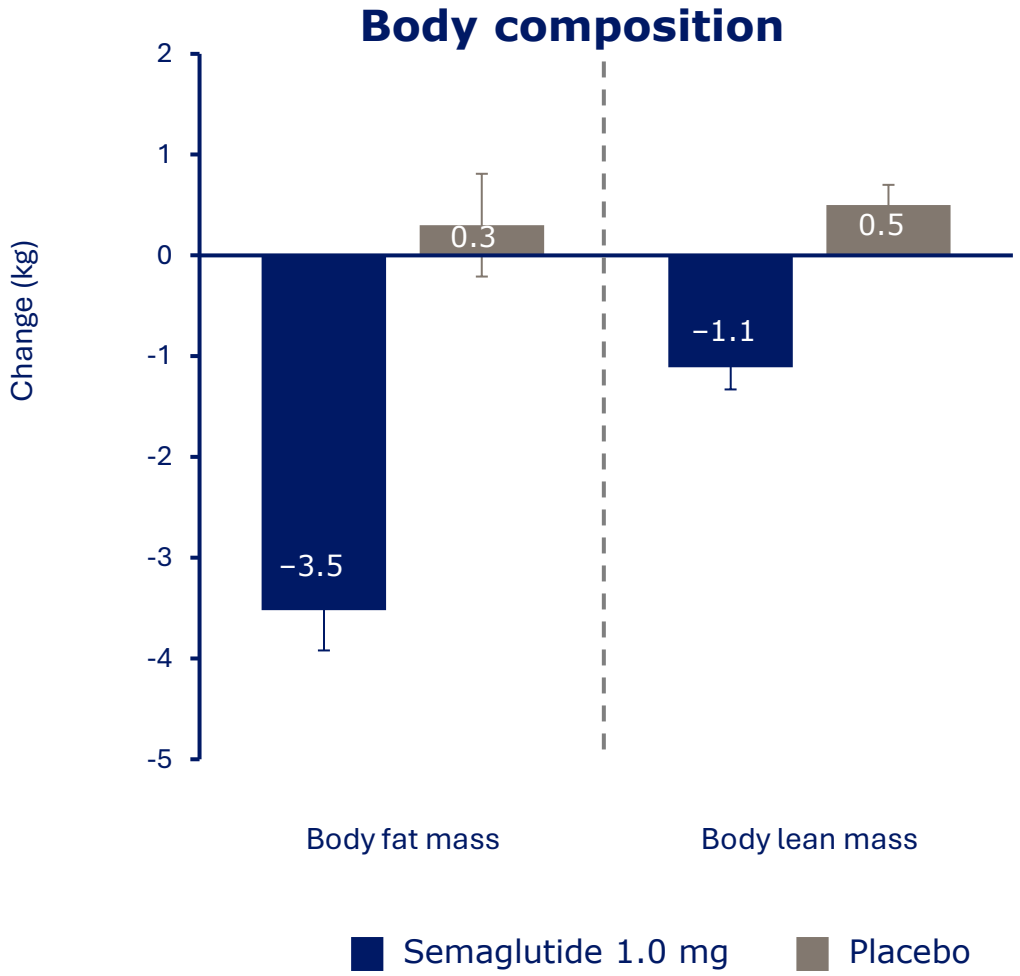


Wilding JPH, et al. N Engl J Med 2021;384:989-1002.

Semaglutide reduces fat mass

PRIMARY MECHANISM OF WEIGHT LOSS

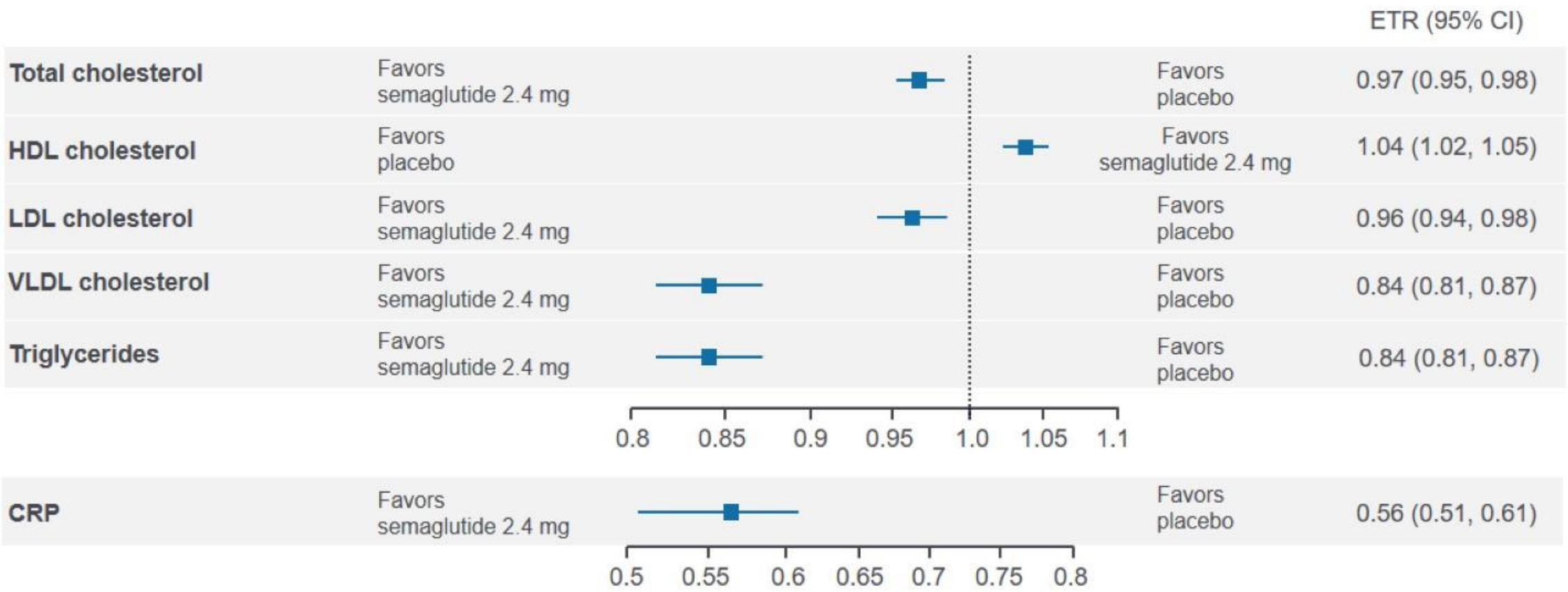




Measurements of body weight and body composition were performed on different days. Data are presented as mean (standard error).
Blundell J et al. *Diabetes Obes Metab* 2017;19:1242–51.

STEP 1: Cardiometabolic Parameters

Treatment Policy Estimand



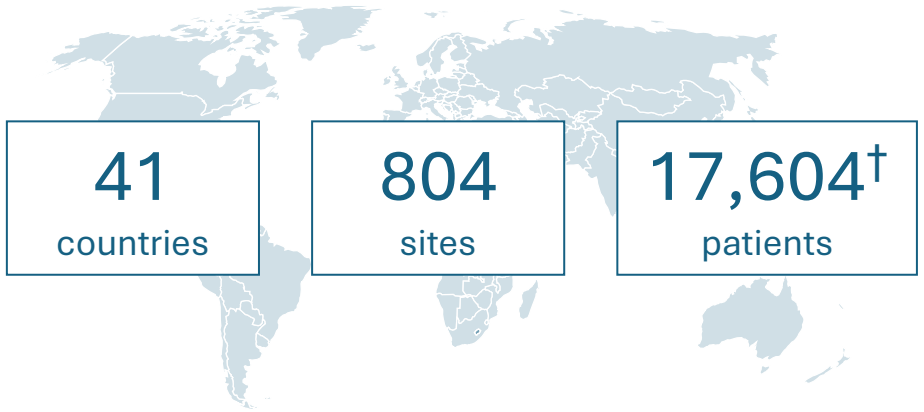
CRP, C-reactive protein; ETR, estimated treatment ratio; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.
Slide courtesy of John Wilding, DM, FRCP. Wilding JPH, et al. N Engl J Med 2021;384:989-1002.

SELECT: Trial overview

Primary objective[1,2]

To demonstrate that s.c. semaglutide 2.4 mg OW lowers the incidence of MACE versus placebo, both added to SoC, in people with established CVD and overweight or obesity

Key trial numbers[2]



Trial design[1–3]

- **Overweight or obesity**
- **Established CVD***
- **No prior history of diabetes**

Semaglutide 2.4 mg OW

Placebo

Event driven
Mean follow-up: 39.8 months

SELECT-LIFE[4]

10-year post-trial observational follow-up to assess potential long-term effects of anti-obesity medication

**Established CVD: MI ≥60 days prior to screening, stroke ≥60 days prior to screening or symptomatic PAD; NYHA class IV excluded. †Differs from number reported in baseline publication (17,605) as one patient was randomised twice in error and subsequently removed for the primary analysis.*
CVD, cardiovascular disease; MACE, major adverse cardiovascular event; MI, myocardial infarction; NYHA, New York Heart Association; OW, once weekly; PAD, peripheral artery disease; s.c. subcutaneous; SoC, standard of care.
1. Lingvay I et al. Obesity (Silver Spring) 2023;31:111–22; 2. Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563; 3. Ryan DH et al. Am Heart J 2020;229:61–9; 4. ClinicalTrials.gov. SELECT-LIFE. Available at: https://clinicaltrials.gov/ct2/show/NCT04972721. Accessed October 2023.

Main inclusion/exclusion criteria

SELECT

Key inclusion criteria[1–3]

Prior MI*
Prior stroke*
Symptomatic PAD†

Male or female individuals aged ≥45 years

BMI ≥27 kg/m^2

Key exclusion criteria[1–3]

HbA_{1c} ≥6.5%

History of type 1 or type 2 diabetes‡

Treatment with glucose-lowering agents within the past 90 days

Presently classified as having NYHA class IV heart failure

*>60 days prior to the day of screening. †Symptomatic PAD evidenced by intermittent claudication with ankle-brachial index less than 0.85 (at rest), or peripheral arterial revascularisation procedure or amputation due to atherosclerotic disease. ‡Gestational diabetes was allowed.
BMI, body mass index; HbA_{1c}, glycated haemoglobin; MI, myocardial infarction; NYHA, New York Heart Association; PAD, peripheral artery disease.
1. Ryan DH et al. Am Heart J 2020;229:61–9; 2. Lingvay I et al. Obesity (Silver Spring) 2023;31:111–22; 3. Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

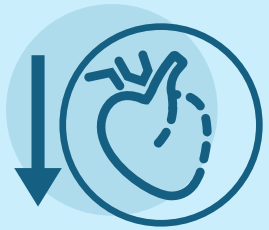
Trial objectives

SELECT

Added to SoC in people with established CVD and overweight or obesity

Primary[1–3]

Demonstrate that semaglutide 2.4 mg lowers the incidence of 3-point MACE vs placebo



Secondary[1–3]

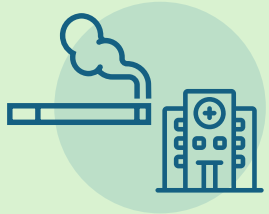
Compare the effect of semaglutide 2.4 mg vs placebo on:

- Mortality
- CV risk factors
- Glucose metabolism
- Body weight
- Renal function

Exploratory[4]

Compare the effect of semaglutide 2.4 mg vs placebo on:

- Smoking status
- Hospitalisations



Three-component MACE consisted of non-fatal myocardial infarction, non-fatal stroke and CV death.
CV, cardiovascular; CVD, cardiovascular disease; MACE, major adverse cardiovascular event; SoC, standard of care.
1. Ryan DH et al. Am Heart J 2020;229:61–9; 2. Lingvay I et al. Obesity (Silver Spring) 2023;31:111–22; 3. Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563; 4. ClinicalTrials.gov. SELECT. Available at: https://clinicaltrials.gov/ct2/show/NCT03574597. Accessed October 2023.

Baseline characteristics of trial participants (1/3)

SELECT: N=17,604

Demographics

Male | Female

72.3 | 27.7%

Mean age

61.6 years

Asian|Black|White|Other

8.2 | 3.8 | 84.0 | 3.0%

Participants by CV inclusion criteria

MI only

67.6%

Stroke only

17.8%

PAD only

4.4%

≥2 CV inclusion criteria

8.2%

Number of enrolled participants differs from number reported in baseline publication (17,605) as one participant was randomised twice in error and subsequently removed for the primary analysis.
CV, cardiovascular; MI, myocardial infarction; PAD, peripheral arterial disease.
Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

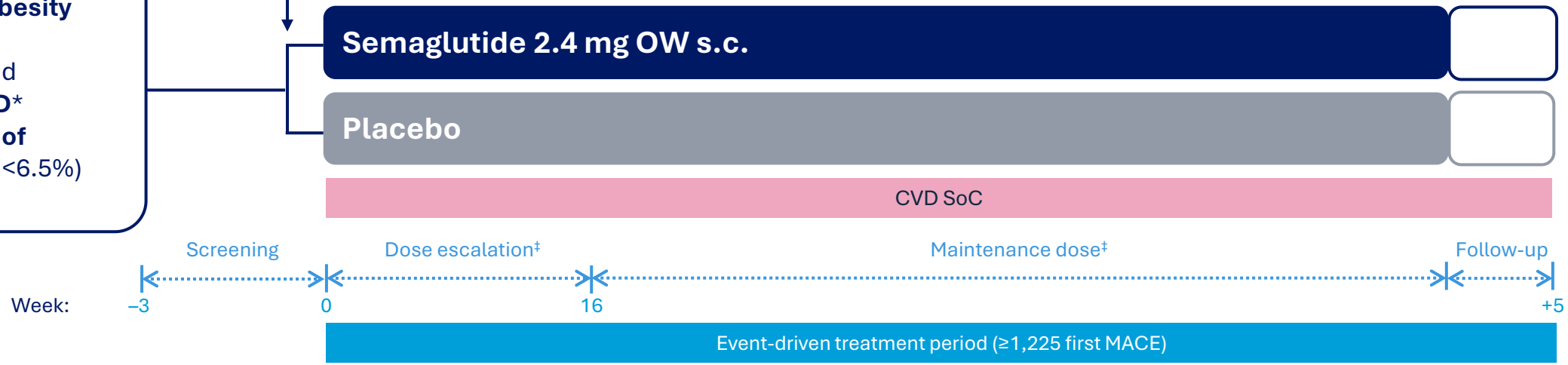
Trial design

SELECT

Trial information[1–3]
- FPFV 24 October 2018
- Double-blind, placebo-controlled, superiority trial

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

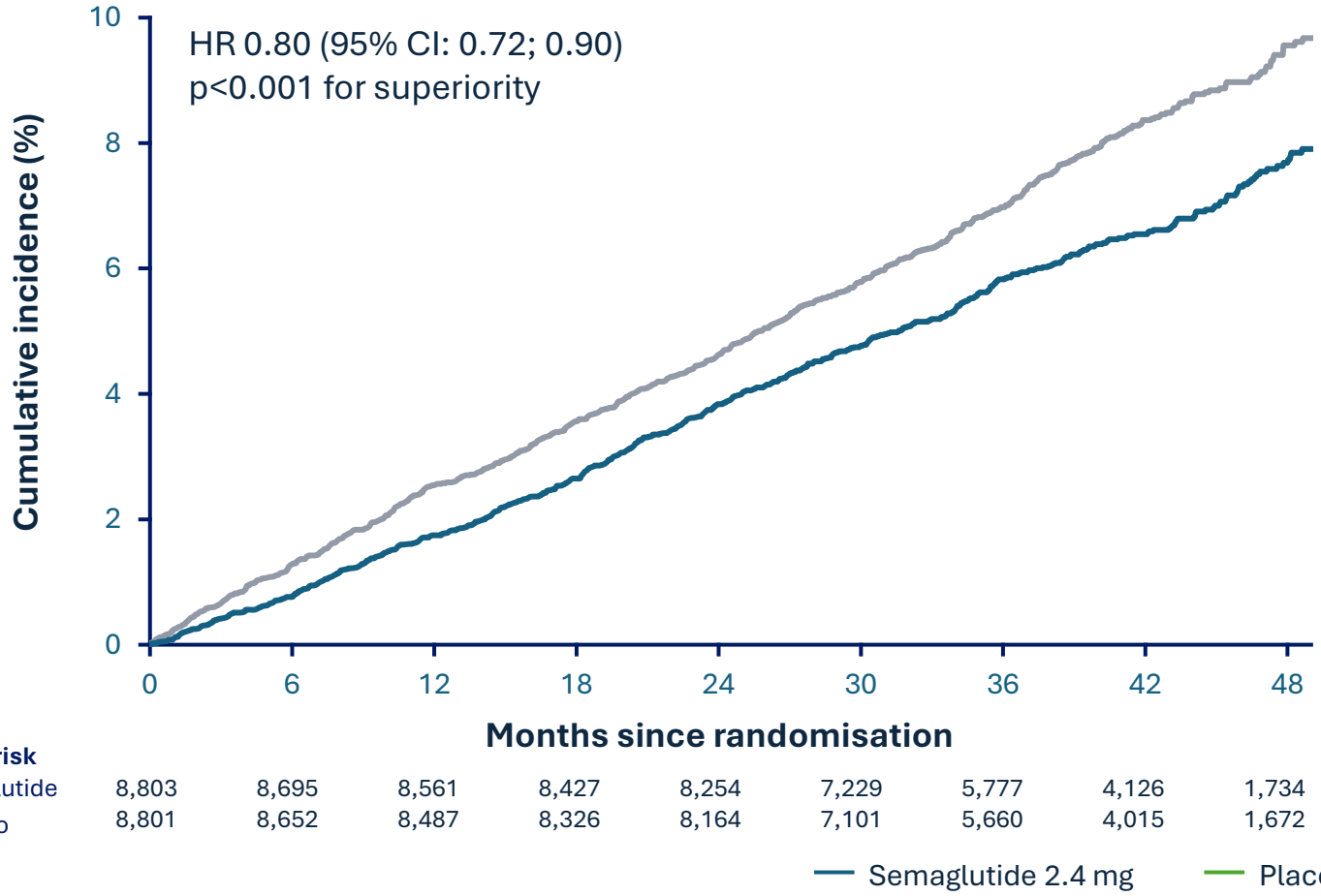
Randomisation (1:1)
N=17,604†



Three-component MACE consisted of non-fatal MI, non-fatal stroke and CV death.
**Established CVD: MI ≥60 days prior to screening, stroke ≥60 days prior to screening or symptomatic PAD; NYHA class IV excluded. †Number of enrolled participants differs from number reported in baseline publication (17,605) as one participant was randomised twice in error and subsequently removed for the primary analysis. ‡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; SoC, standard of care.
1. Ryan DH et al. Am Heart J 2020;229:61–9; 2. Lingvay I et al. Obesity (Silver Spring) 2023;31:111–22; 3. Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

Cumulative incidence of MACE

SELECT: Primary cardiovascular composite endpoint



20%
reduction in risk of MACE*

Semaglutide 2.4 mg significantly reduced
the risk of MACE by 20%
compared with placebo in people with obesity and established CVD, without T2D[1,2]

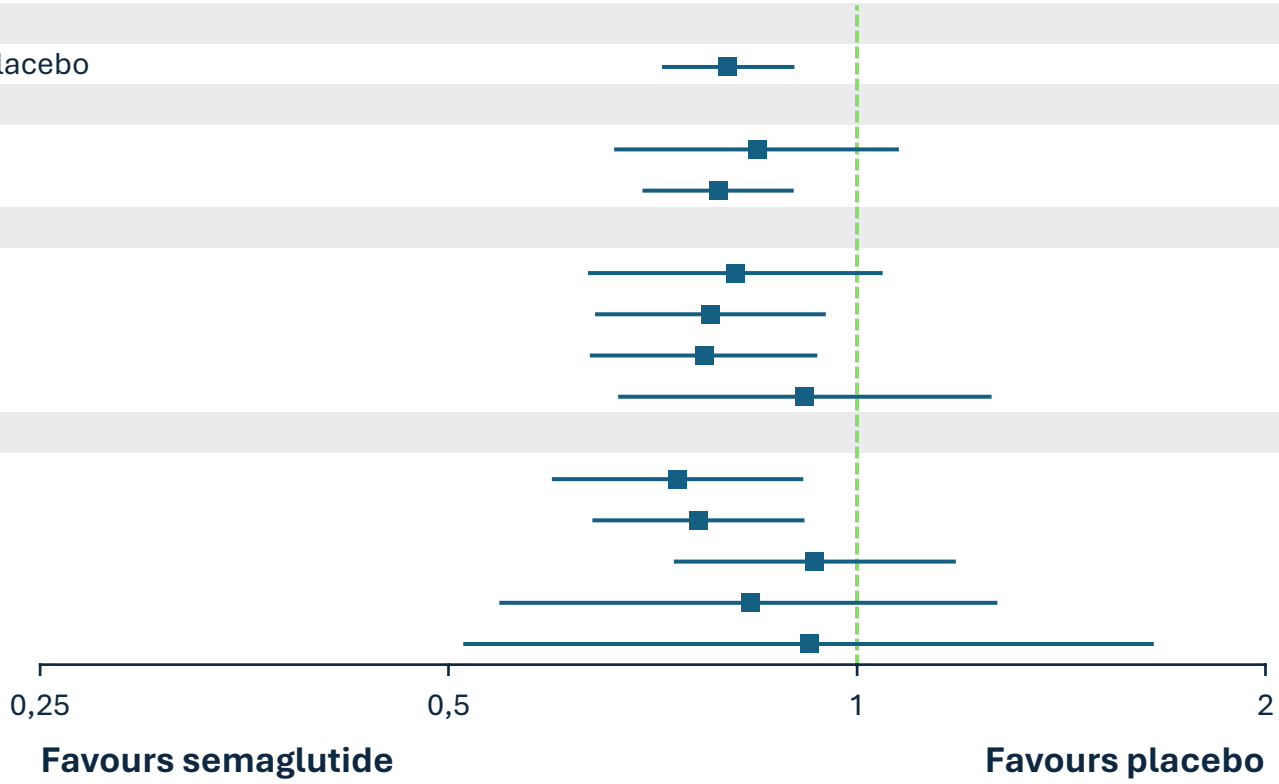
All three components (death from CV causes, non-fatal MI and non-fatal stroke) contributed to MACE risk reduction

Mean follow-up time was 39.8 months

Cumulative incidence (using the Aalen–Johansen method) of the composite MACE primary endpoint. The HR was estimated using a Cox proportional hazards regression model. The proportion of participants with MACE was 6.5% with semaglutide 2.4 mg and 8.0% with placebo. MACE was defined as death from CV causes, non-fatal myocardial infarction, or non-fatal stroke.
CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction.
1. Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563; 2. American College of Cardiology, SELECT: Semaglutide Reduces Risk of MACE in Adults With Overweight or Obesity, Accessed October 2023, https://www.acc.org/Latest-in-Cardiology/Articles/2023/08/10/14/29/SELECT-Semaglutide-Reduces-Risk-of-MACE-in-Adults-With-Overweight-or-Obesity

Subgroup analysis of MACE (1/3)

SELECT

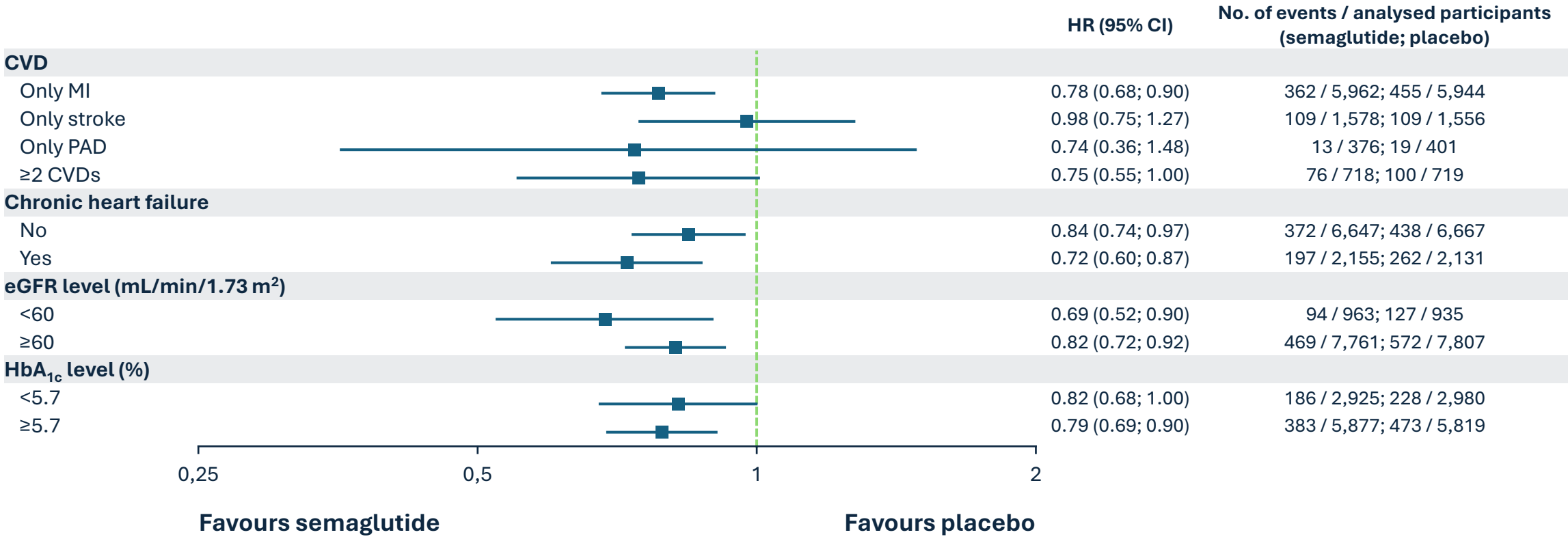


	HR (95% CI)	No. of events / analysed participants (semaglutide; placebo)
Primary analysis		
Semaglutide / placebo	0.80 (0.72; 0.90)	569 / 8,803; 701 / 8,801
Sex		
Female	0.84 (0.66; 1.07)	126 / 2,448; 147 / 2,424
Male	0.79 (0.70; 0.90)	443 / 6,355; 554 / 6,377
Age (years)		
<55	0.81 (0.64; 1.04)	115 / 2,057; 141 / 2,094
≥55 to <65	0.78 (0.64; 0.95)	187 / 3,387; 234 / 3,338
≥65 to <75	0.77 (0.64; 0.93)	189 / 2,656; 247 / 2,706
≥75	0.92 (0.67; 1.25)	78 / 703; 79 / 633
BMI (kg/m^2)		
<30	0.74 (0.60; 0.91)	155 / 2,555; 200 / 2,469
≥30 to <35	0.76 (0.64; 0.91)	217 / 3,693; 286 / 3,781
≥35 to <40	0.93 (0.74; 1.18)	135 / 1,687; 142 / 1,659
≥40 to <45	0.83 (0.55; 1.26)	40 / 579; 49 / 595
≥45	0.92 (0.51; 1.65)	22 / 289; 24 / 297

For the subgroup analyses, HRs were estimated using a Cox proportional hazards regression with interaction between treatment group and the relevant subgroup as fixed factor. Except for the primary analysis, widths of the CIs were not adjusted for multiplicity. MACE was defined as death from CV causes, non-fatal myocardial infarction, or non-fatal stroke.
BMI, body mass index; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular event.
Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

Subgroup analysis of MACE (2/3)

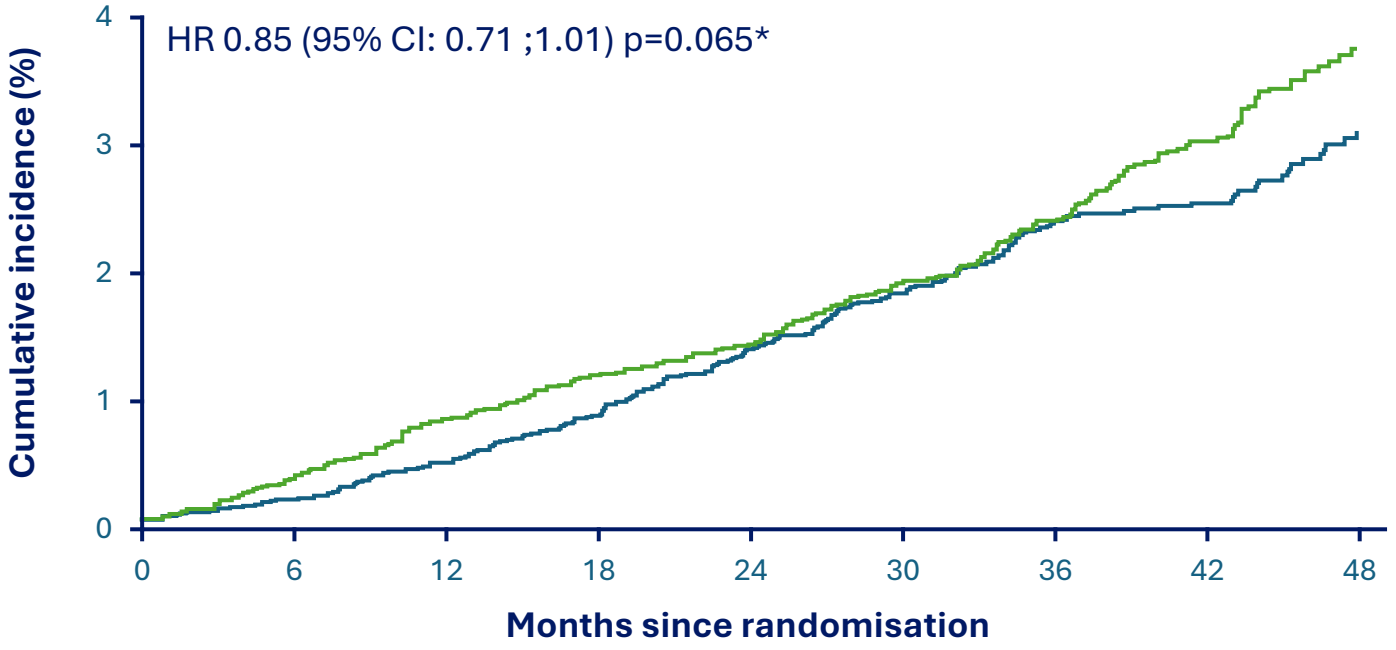
SELECT



For the subgroup analyses, HRs were estimated using a Cox proportional hazards regression with interaction between treatment group and the relevant subgroup as fixed factor.
Except for the primary analysis, widths of the CIs were not adjusted for multiplicity. MACE was defined as death from CV causes, non-fatal myocardial infarction, or non-fatal stroke.
CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction; PAD, peripheral arterial disease.
Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

Cumulative incidence of death from CV causes

SELECT: First confirmatory secondary endpoint



No. at risk									
Semaglutide	8,803	8,748	8,673	8,584	8,465	7,452	5,988	4,315	1,832
Placebo	8,801	8,733	8,634	8,528	8,430	7,395	5,938	4,250	1,793

Semaglutide 2.4 mg Placebo

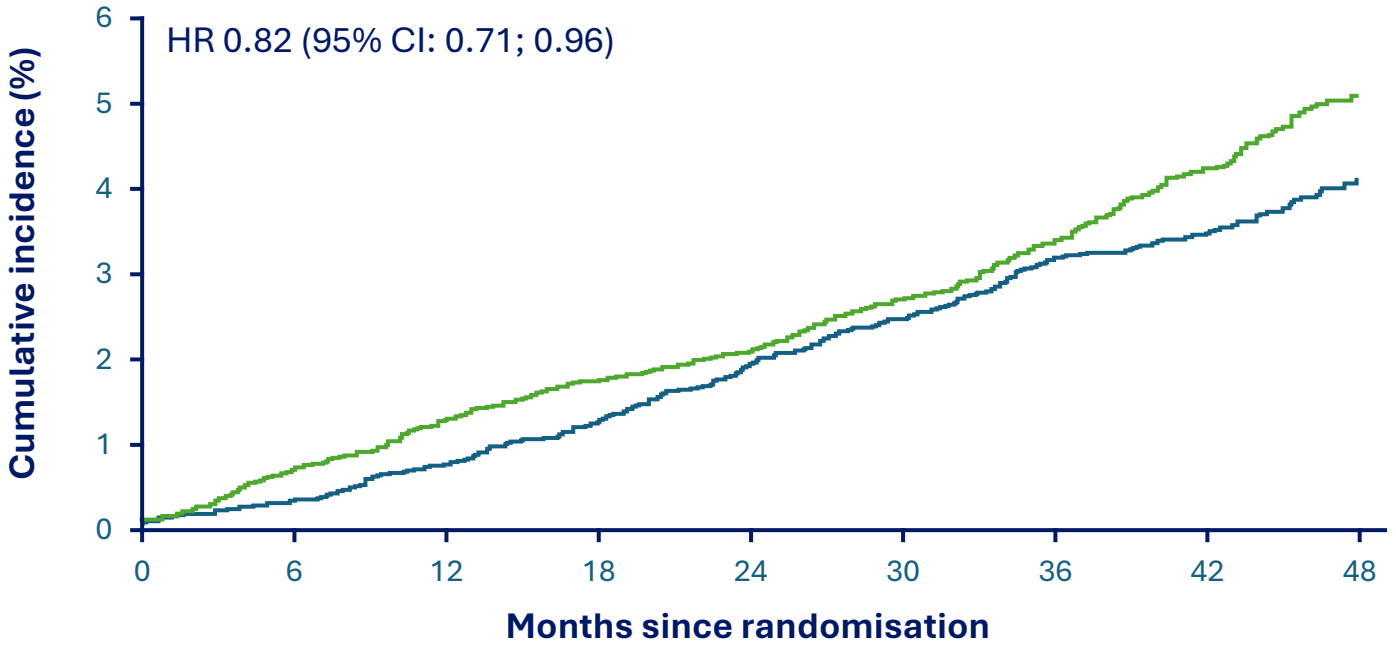
Semaglutide 2.4 mg reduced the risk of death from CV causes by 15% compared with placebo

This result was not statistically significant, but suggests a benefit from semaglutide 2.4 mg

Cumulative incidence (using the Aalen–Johansen method) of the confirmatory secondary endpoints. The HR was estimated using a Cox proportional hazards regression model. The proportion of participants with death from CV causes was 2.5% with semaglutide 2.4 mg and 3.0% with placebo.
**Nominal significance level was 0.046.*
CI, confidence interval; CV, cardiovascular; HR, hazard ratio.
Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

Cumulative incidence of composite heart failure events

SELECT: Second confirmatory secondary endpoint



No. at risk									
Semaglutide	8,803	8,740	8,654	8,557	8,425	7,409	5,944	4,277	1,816
Placebo	8,801	8,711	8,601	8,485	8,381	7,341	5,885	4,198	1,766

Semaglutide 2.4 mg — Placebo

Semaglutide 2.4 mg reduced the risk of composite HF events by 18% compared with placebo

Although the 95% CI was <1, superiority testing was not performed per the hierarchical testing procedure*

Cumulative incidence (using the Aalen–Johansen method) of the confirmatory secondary endpoints. The HR was estimated using a Cox proportional hazards regression model. The proportion of participants with composite heart failure events was 3.4% with semaglutide 2.4 mg and 4.1% with placebo. Composite heart failure events included HF hospitalisation, urgent HF visit or CV-related death.

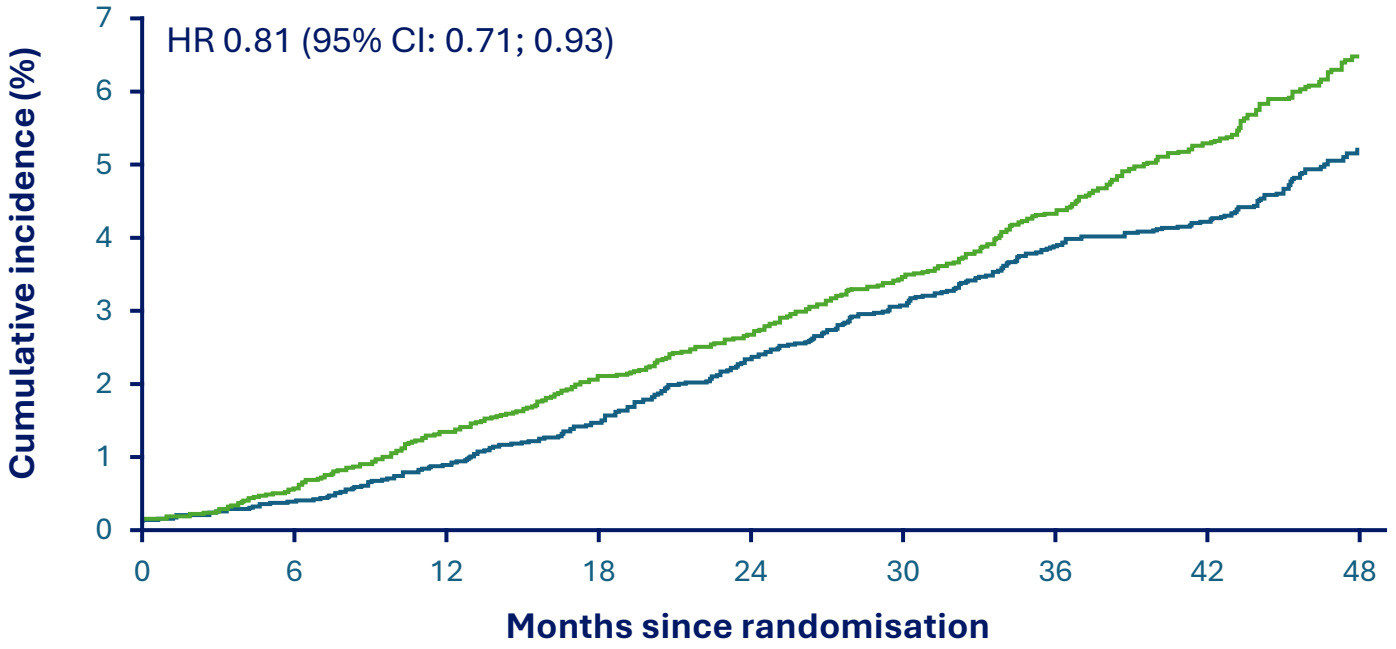
**The difference in the risk of death from CV causes did not meet the required p value for hierarchical testing, so superiority testing for the remaining confirmatory secondary endpoints was not performed.*

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio.

Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

Cumulative incidence of death from any cause

SELECT: Third confirmatory secondary endpoint



No. at risk									
Semaglutide	8,803	8,748	8,673	8,584	8,465	7,452	5,988	4,315	1,832
Placebo	8,801	8,733	8,634	8,528	8,430	7,395	5,938	4,250	1,793

Semaglutide 2.4 mg — Placebo

Semaglutide 2.4 mg reduced the risk of death from any cause by 19% compared with placebo

Although the 95% CI was <1, superiority testing was not performed per the hierarchical testing procedure*

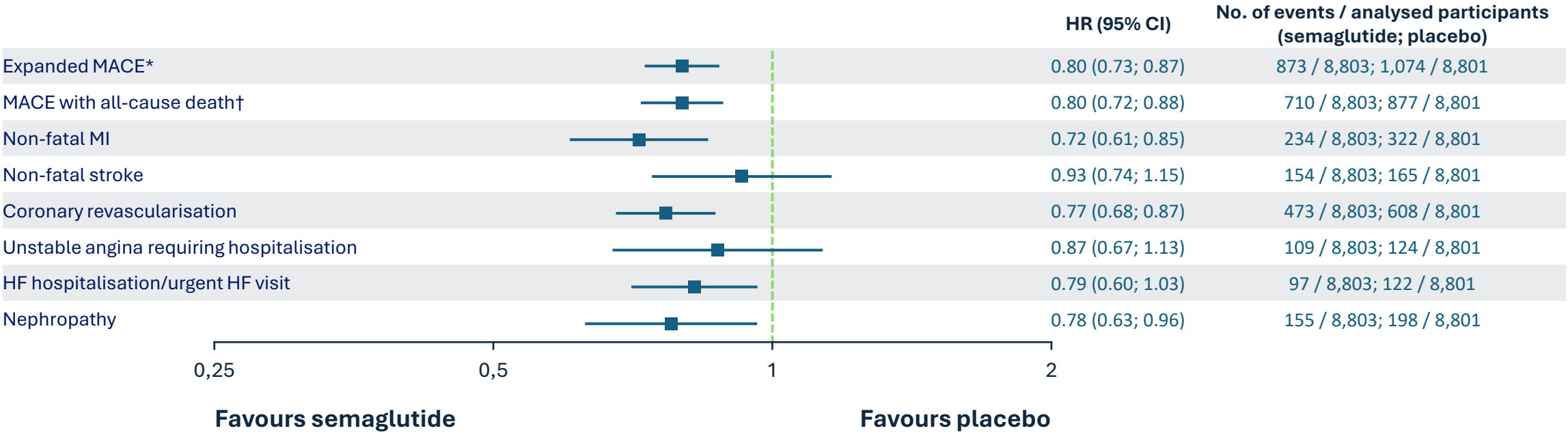
*Cumulative incidence (using the Aalen–Johansen method) of the confirmatory secondary endpoints. The HR was estimated using a Cox proportional hazards regression model. The proportion of participants with death from any cause was 4.3% with semaglutide 2.4 mg and 5.2% with placebo. *The difference in the risk of death from CV causes did not meet the required p value for hierarchical testing, so superiority testing for the remaining confirmatory secondary endpoints was not performed. CI, confidence interval; CV, cardiovascular; HR, hazard ratio.*

Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

Secondary CV endpoints

SELECT

Semaglutide 2.4 mg had **consistent beneficial effects** across measured CV endpoints



HRs were estimated using a Cox proportional hazards regression model. Widths of the CIs have not been adjusted for multiplicity.
**Death from CV causes, non-fatal MI, non-fatal stroke, coronary revascularisation or unstable angina requiring hospitalisation. †All-cause death, non-fatal MI or non-fatal stroke.*
CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction.
Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

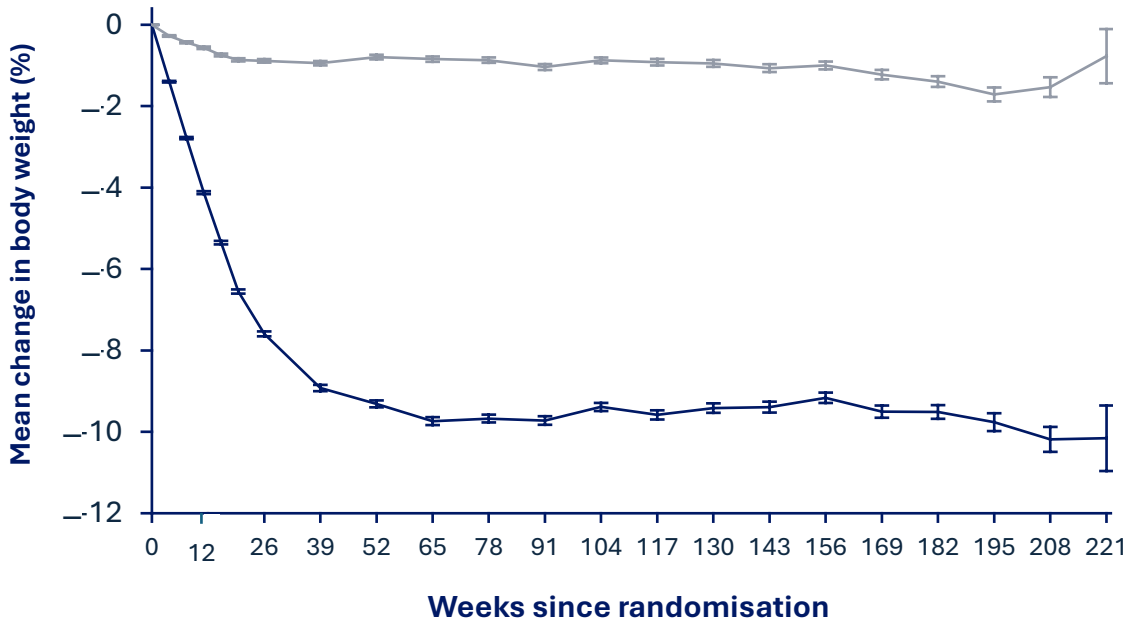
Change in body weight (%)

SELECT

Observed change from baseline over time

Mean baseline body weight, kg:

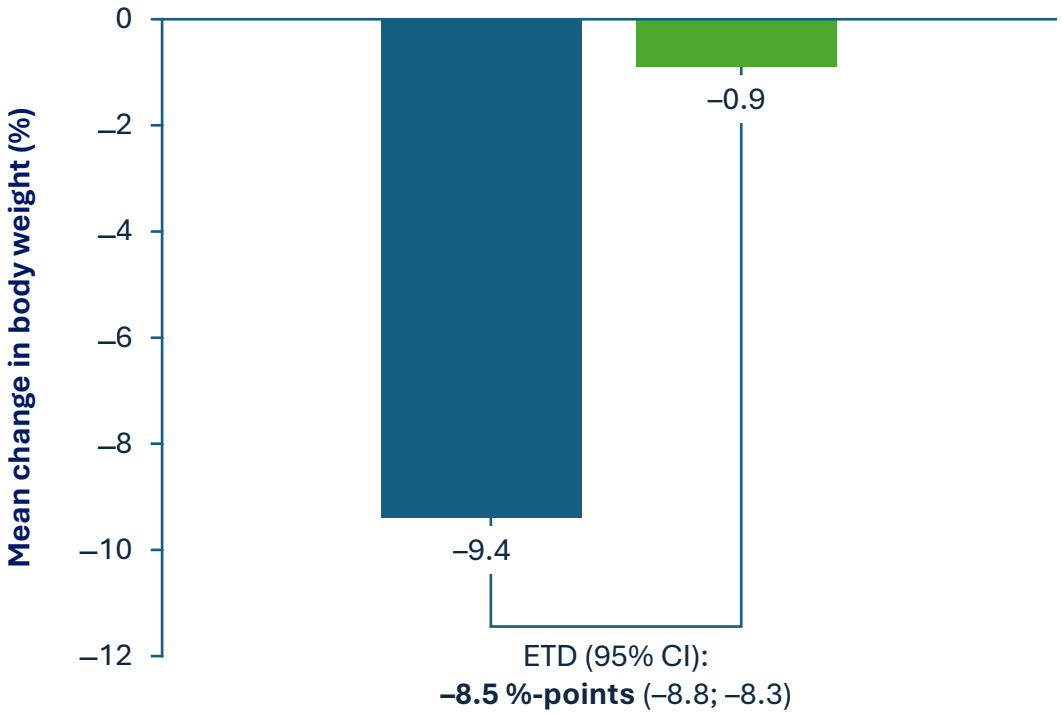
Semaglutide 2.4 mg: 96.5 Placebo: 96.8



No. of participants

Semaglutide	8,803	7,647	7,493	6,690	7,290	6,447	7,282	6,460	7,474	5,991	5,898	4,686	5,085	3,650	2,954	1,737	921	157
Placebo	8,801	7,715	7,516	6,704	7,269	6,340	7,272	6,392	7,378	5,871	5,879	4,583	5,014	3,560	2,890	1,698	898	152

Estimated change from baseline to week 104*



Semaglutide 2.4 mg Placebo

*Error bars in the left-hand figure are 95% CI as calculated by 1.96 times the standard error. *Estimated using an ANCOVA with treatment as factor and the baseline value as covariate, using multiple imputation for missing values under a missing-at-random assumption. CIs have not been adjusted for multiplicity. ANCOVA, analysis of covariance; CI, confidence interval; ETD, estimated treatment difference; SD, standard deviation.*

Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

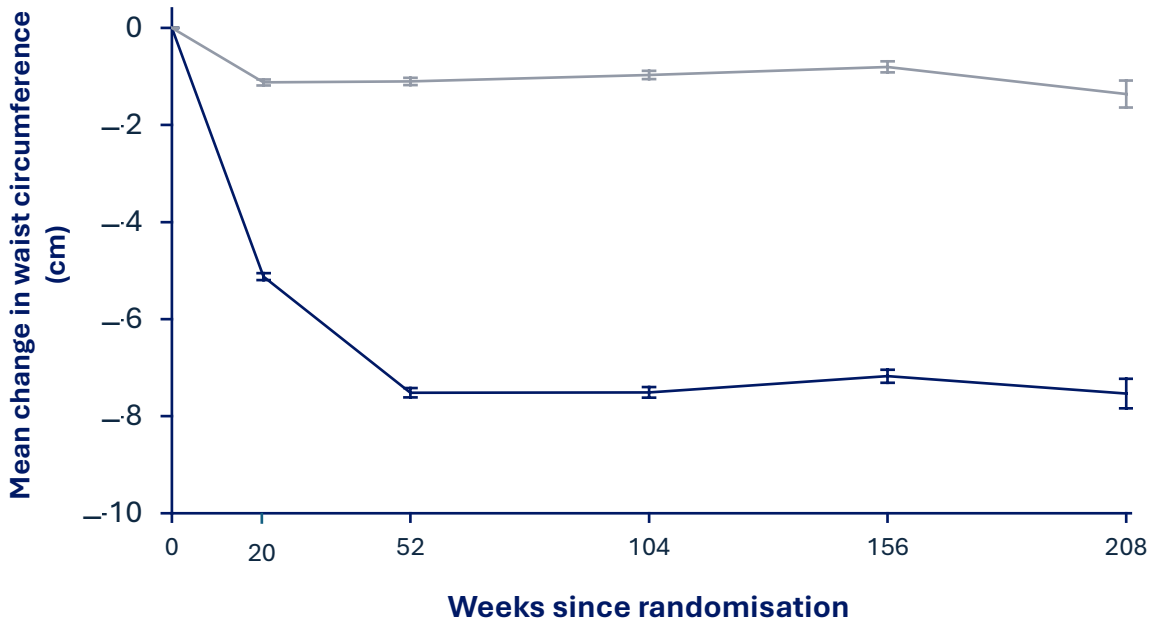
Change in waist circumference

SELECT

Observed change from baseline over time

Mean (SD) baseline waist circumference, cm:

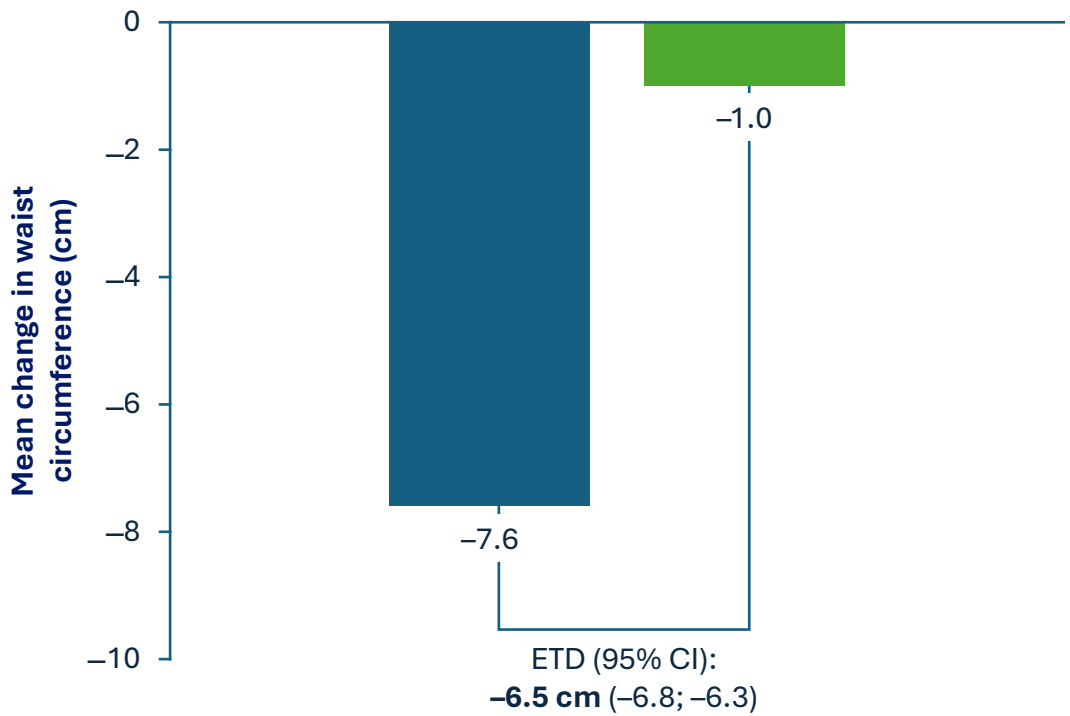
Semaglutide 2.4 mg: 111.3 (13.1) Placebo: 111.4 (13.1)



No. of participants

Semaglutide	8,759	7,507	7,193	7,373	5,013	912
Placebo	8,756	7,533	7,182	7,273	4,950	887

Estimated change from baseline to week 104*



Semaglutide 2.4 mg Placebo

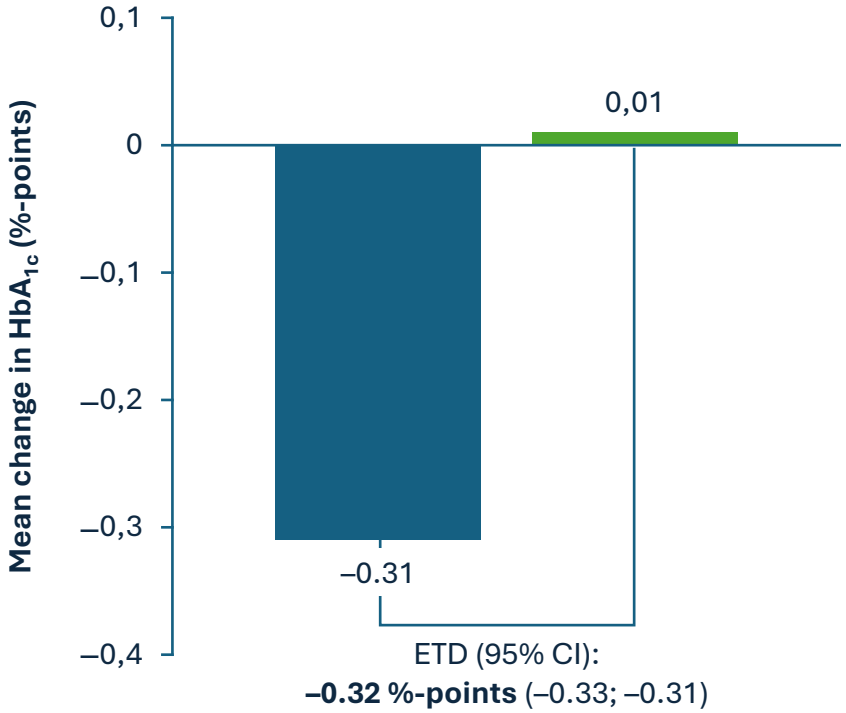
*Error bars in the left-hand figure are 95% CI as calculated by 1.96 times the standard error. *Estimated using an ANCOVA with treatment as factor and the baseline value as covariate, using multiple imputation for missing values under a missing-at-random assumption. CIs have not been adjusted for multiplicity. ANCOVA, analysis of covariance; CI, confidence interval; ETD, estimated treatment difference; SD, standard deviation.*

Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

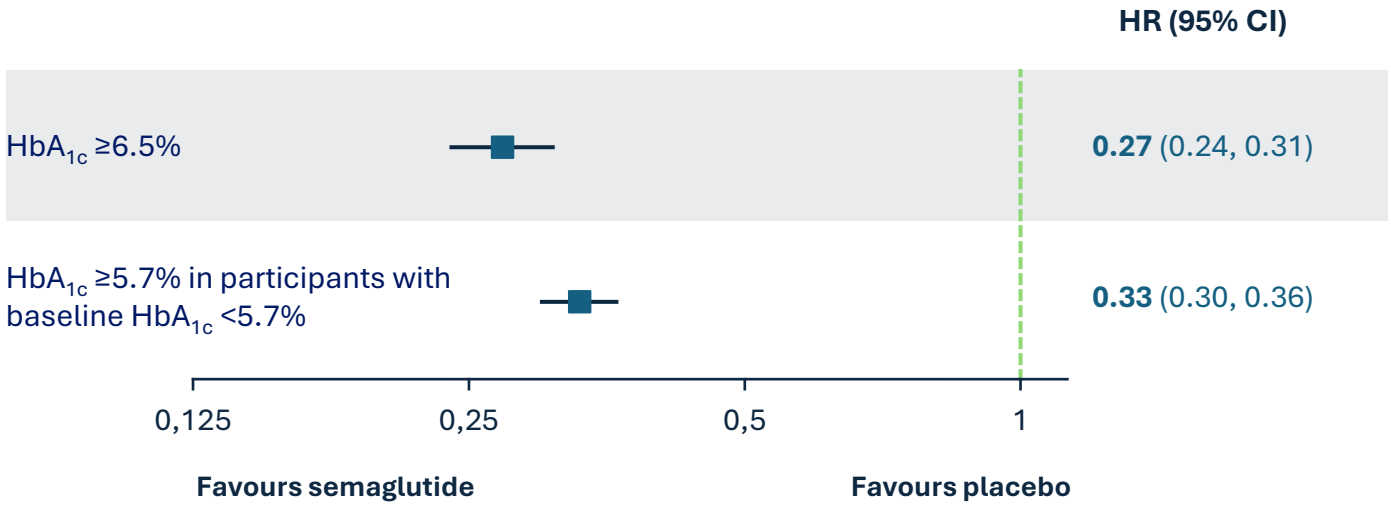
Change in glycaemic status

SELECT

Change in HbA_{1c}*



Time to glycaemic events†



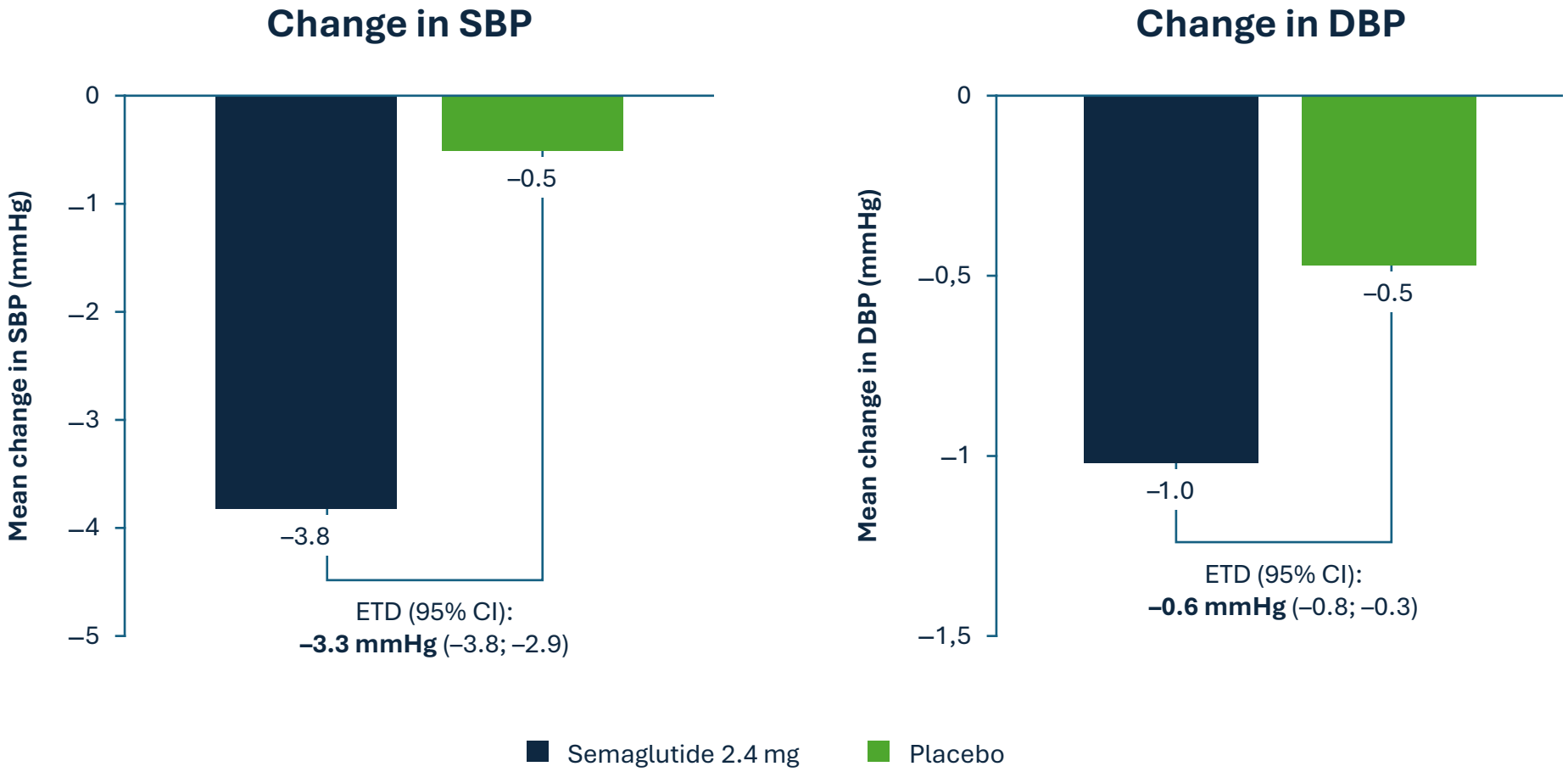
Semaglutide 2.4 mg Placebo

*CIs have not been adjusted for multiplicity. *Change from baseline to week 104, estimated using ANCOVA with treatment as factor and the baseline value as covariate. †HRs were estimated using a Cox proportional hazards regression model. ANCOVA, analysis of covariance; CI, confidence interval; ETD, estimated treatment difference; HbA_{1c}, glycated haemoglobin; HR, hazard ratio.*

Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

Change in blood pressure (mmHg)

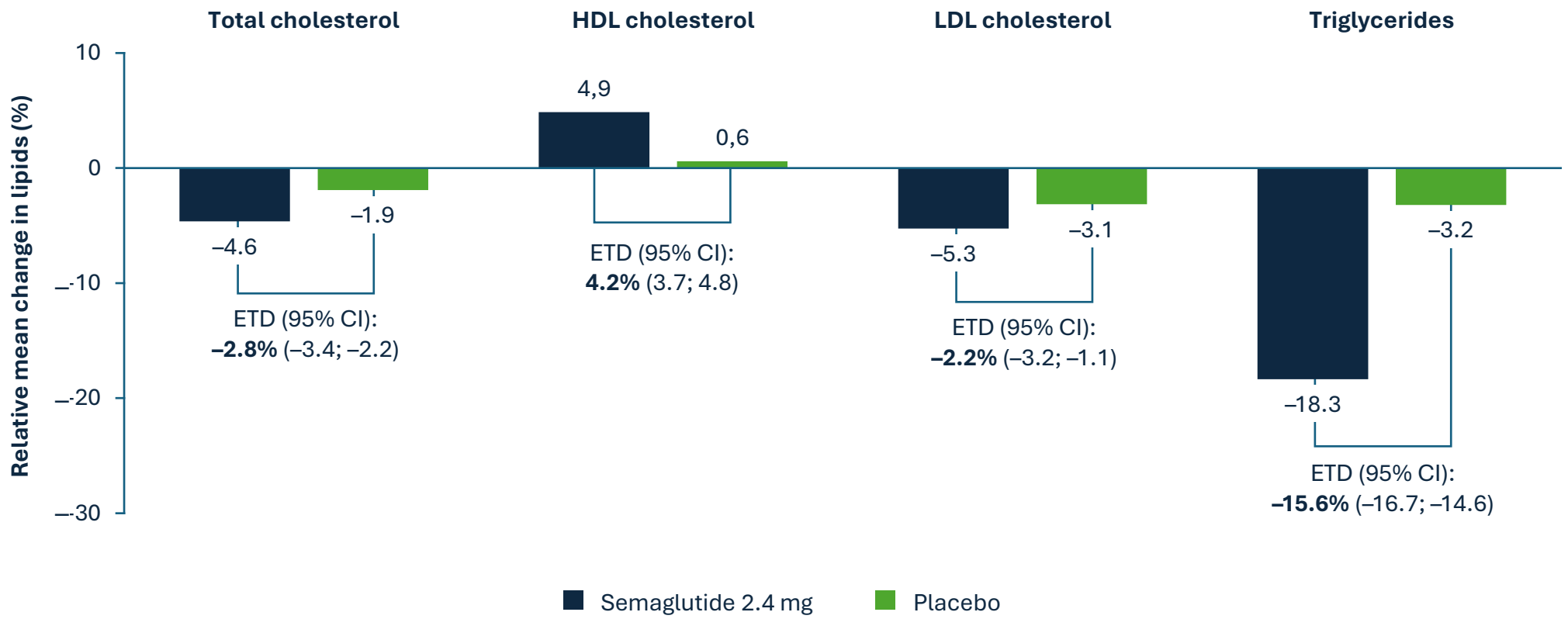
SELECT



Change from baseline to week 104, estimated using ANCOVA with treatment as factor and the baseline value as covariate. CIs have not been adjusted for multiplicity.
ANCOVA, analysis of covariance; CI, confidence interval; DBP, diastolic blood pressure; ETD, estimated treatment difference; SBP, systolic blood pressure.
Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

Change in lipids (%)

SELECT

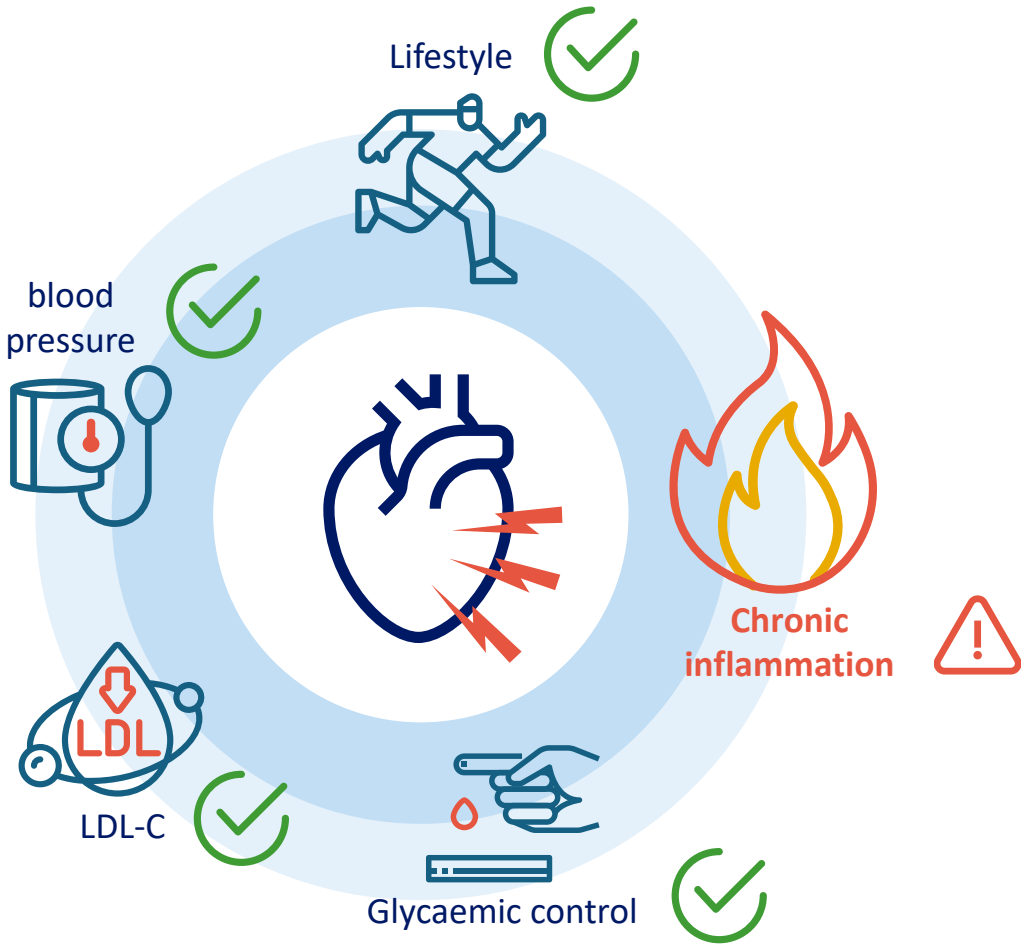


Relative changes from baseline (log-transformed before analysis) to week 104, estimated using ANCOVA with treatment as factor and the baseline value as covariate. CIs have not been adjusted for multiplicity.
ANCOVA, analysis of covariance; CI, confidence interval; ETD, estimated treatment difference; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

The concept of residual inflammatory risk

- Recurrent cardiovascular events occur frequently despite control of conventional risk factors (e.g lifestyle intervention, BP, LDL-C and glycaemic control). This is recognized as **”residual cardiovascular risk”**[1]
- **Ongoing chronic inflammation** is an important contributor to the risk of recurrent cardiovascular event and is mainly driven by the NLRP3 inflammasome pathway[2]
- The most widely used marker of this signalling cascade is **hsCRP**, a convenient barometer of the extent of ongoing inflammation[2]

Residual inflammatory risk (RIR) is classified as levels of high-sensitivity **C-reactive protein (hsCRP) ≥2 mg/L**[3]



BP, blood pressure; LDL-C, low density lipoprotein – cholesterol; NLRP3, NOD [nucleotide oligomerization domain]-, LRR [leucine-rich repeat]- and PYD [pyrin domain]-containing protein 3

1. Vanuzzo Intern Emerg Med 2011; 6 Suppl 1: 45-51; 2. Ridker et al. Circulation 2020;141:787–789; 3. Ridker Eur Heart J 2016; 37(22): 1720-1722

Mosenzon et al. Cardiovascular Diabetology (2022) 21:172
https://doi.org/10.1186/s12933-022-01585-7

Cardiovascular Diabetology

RESEARCH Open Access

Impact of semaglutide on high-sensitivity C-reactive protein: exploratory patient-level analyses of SUSTAIN and PIONEER randomized clinical trials

Ofri Mosenzon[1*], Matthew S. Capehorn[2], Alessandra De Remigis[3], Søren Rasmussen[3], Petra Weimers[3] and Julio Rosenstock[4]

Change in hsCRP by trial	n	Ratio to baseline [95% CI]	p-value vs baseline	Comparisons between treatment arms: ETR [95% CI] to comparator	Comparisons between treatment arms: p-value for ETR
SUSTAIN 3					
S.c. semaglutide 1.0 mg	402	0.55 [0.49;0.61]	<0.0001	0.75 [0.65;0.88]	0.0002
Exenatide ER 2.0 mg	404	0.72 [0.65;0.81]	<0.0001		
PIONEER 1					
Oral semaglutide 7 mg	175	0.72 [0.62;0.82]	<0.0001	0.72 [0.59;0.89]	0.0021
Oral semaglutide 14 mg	174	0.75 [0.65;0.86]	<0.0001	0.76 [0.62;0.93]	0.0089
Placebo	177	0.99 [0.85;1.15]	0.8839		
PIONEER 2					
Oral semaglutide 14 mg	408	0.63 [0.57;0.70]	<0.0001	0.70 [0.61;0.80]	<0.0001
Empagliflozin 25 mg	410	0.91 [0.83;1.00]	0.0443		
PIONEER 5					
Oral semaglutide 14 mg	161	0.82 [0.70;0.95]	0.0105	0.83 [0.67;1.03]	0.0839
Placebo	160	0.99 [0.85;1.15]	0.8919		

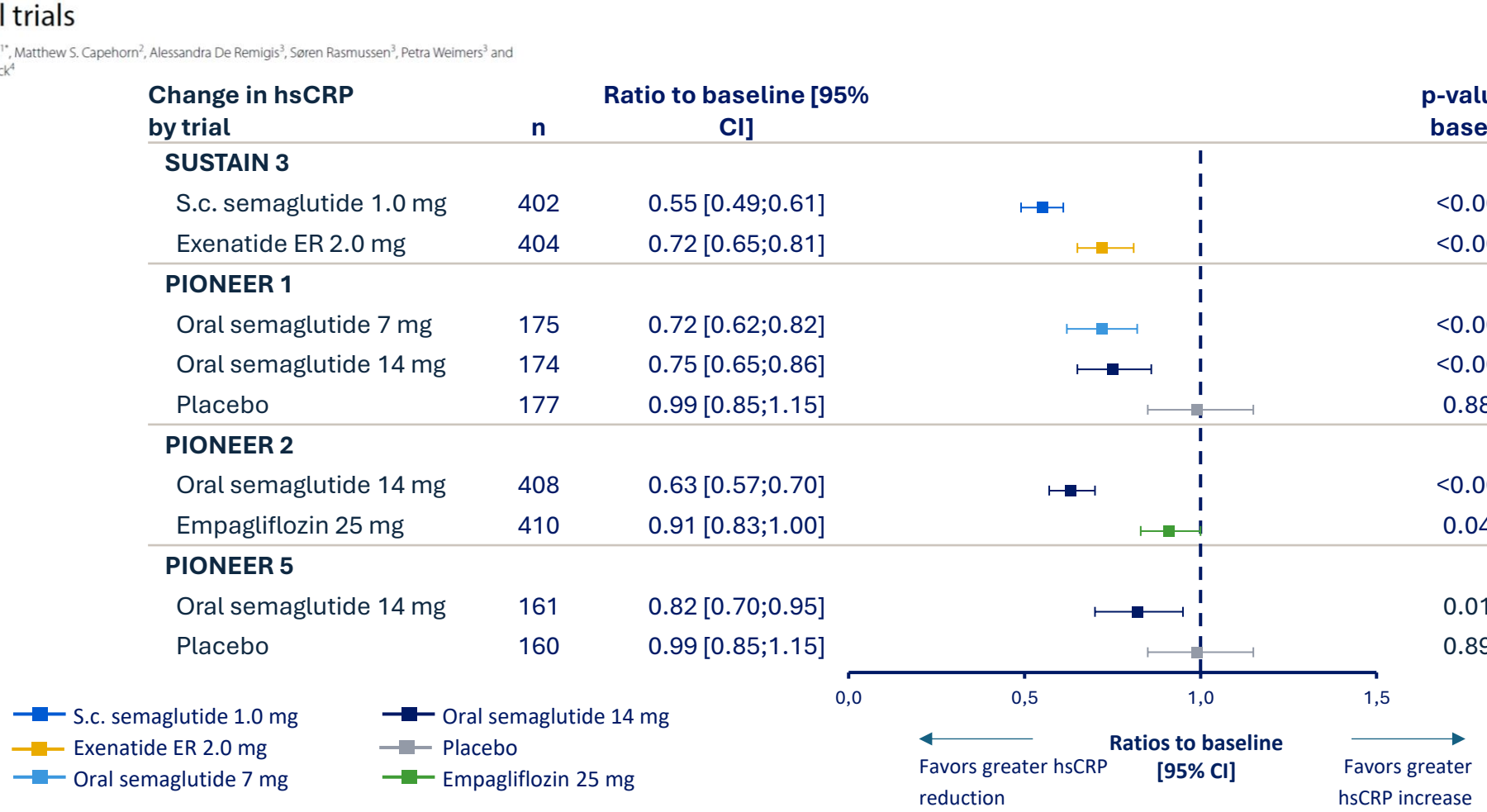
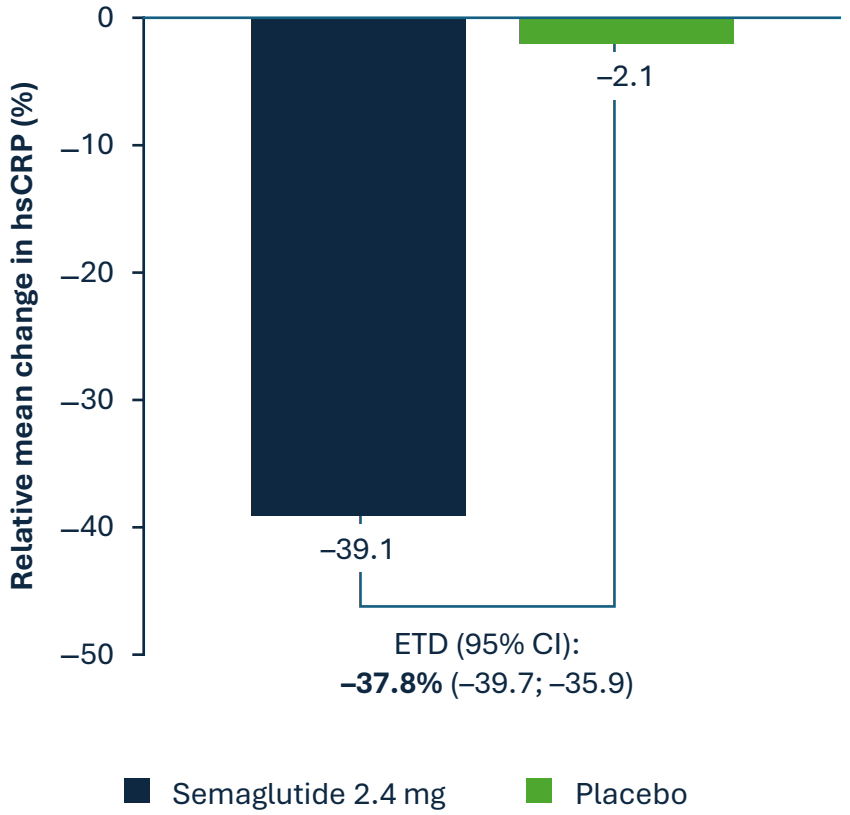


Figure 1. "On-treatment without rescue medication" data from the full analysis set. Changes from baseline and ratios to baseline were analyzed using a mixed model for repeated measurements, with treatment as categorical fixed effect and baseline value as covariate, all nested within visit, and an unstructured residual covariance matrix. The ratio to baseline and the corresponding baseline value were log-transformed prior to analysis. Trial durations: 56 weeks for SUSTAIN 3, 26 weeks for PIONEER 1 and 5, and 52 weeks for PIONEER 2.
CI, confidence interval; ER, extended release; ETR, estimated treatment ratio; hsCRP, high-sensitivity C-reactive protein; n, number of subjects with available hsCRP data; s.c., subcutaneous.

Change in hsCRP (%)

SELECT



Relative changes from baseline (log-transformed before analysis) to week 104, estimated using ANCOVA with treatment as factor and the baseline value as covariate. CIs have not been adjusted for multiplicity.
ANCOVA, analysis of covariance; CI, confidence interval; ETD, estimated treatment difference; hsCRP, high-sensitivity C-reactive protein.
Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

nature medicine

Article

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Long-term weight loss effects of semaglutide in obesity without diabetes in the SELECT trial

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Check for updates

Donna H. Ryan[1], Ildiko Lingvay[2], John Deanfield[3], Steven E. Kahn[4], Eric Barros[5], Bartolome Burguera[6], Helen M. Colhoun[7], Cintia Cercato[8], Dror Dicker[9], Deborah B. Horn[10], G. Kees Hovingh[5], Ole Kleist Jeppesen[5], Alexander Kokkinos[11], A. Michael Lincoff[12], Sebastian M. Meyhöfer[13], Tugce Kalayci Oral[5], Jorge Plutzky[14], André P. van Beek[15], John P. H. Wilding[16] & Robert F. Kushner[17]

Effetti diretti sul sistema cardiovascolare

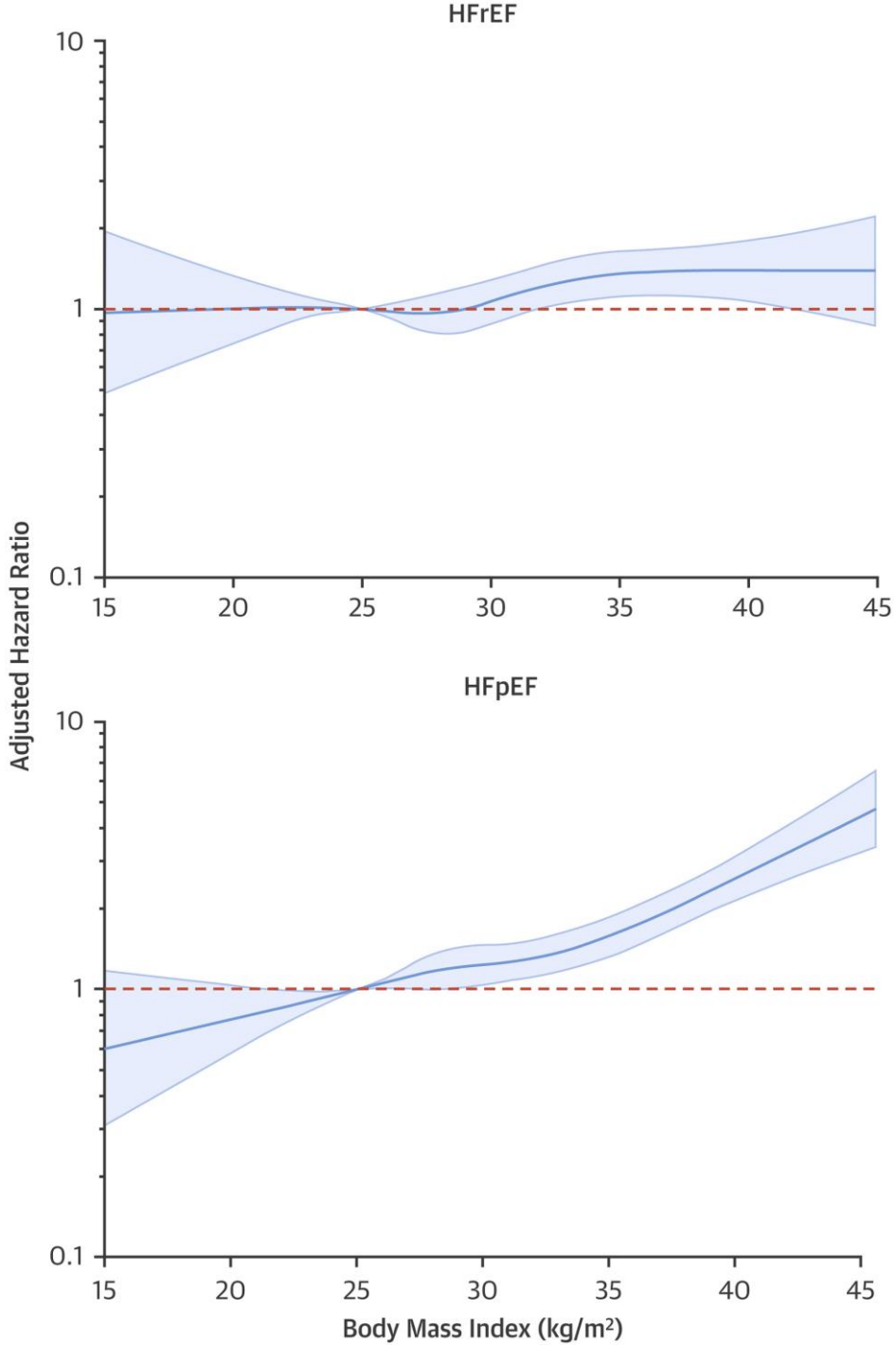
- Miglioramento della funzione endoteliale, con riduzione della rigidità arteriosa.
- Riduzione dell'infiammazione vascolare, con effetti positivi su aterosclerosi e salute vascolare.
- Protezione del miocardio, con riduzione del danno ossidativo.

Riduzione della pressione arteriosa

- Semaglutide contribuisce alla riduzione della pressione sanguigna, migliorando la salute cardiovascolare.
- Questi effetti sono evidenti anche senza una significativa perdita di peso.

Effetti anti-aterosclerotici

- Riduzione della progressione dell'aterosclerosi:
- Riduzione dell'infiammazione
- Miglioramento del profilo lipidico
- Prevenzione dell'accumulo di placche nelle arterie, con riduzione del rischio di eventi cardiaci.



JACC: HEART FAILURE
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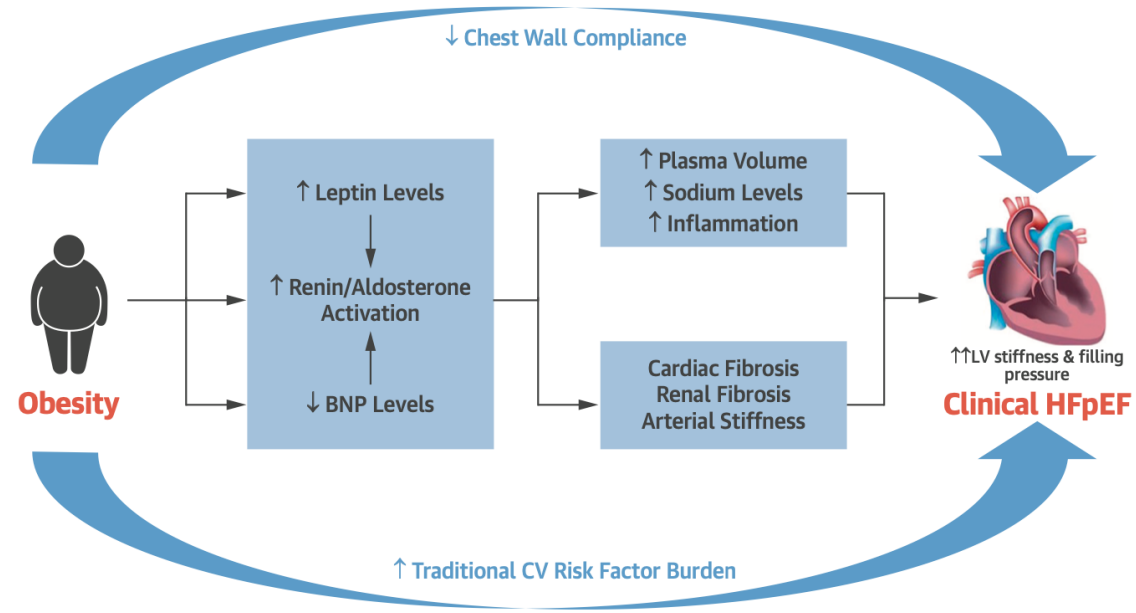
MINI-FOCUS ISSUE: FITNESS AND THE HEART

STATE-OF-THE-ART REVIEW

Physical Activity, Fitness, and Obesity in Heart Failure With Preserved Ejection Fraction

Ambarish Pandey, MD, MSCS,[a] Kershaw V. Patel, MD,[a] Muthiah Vaduganathan, MD, MPH,[b] Satyam Sarma, MD,[a] Mark J. Haykowsky, PhD,[c] Jarett D. Berry, MD, MS,[a,d] Carl J. Lavie, MD[e]

CENTRAL ILLUSTRATION **Mechanisms Through Which Obesity May Contribute to Development and Progression of HFpEF**



Pandey, A. et al. J Am Coll Cardiol HF. 2018;6(12):975–82.

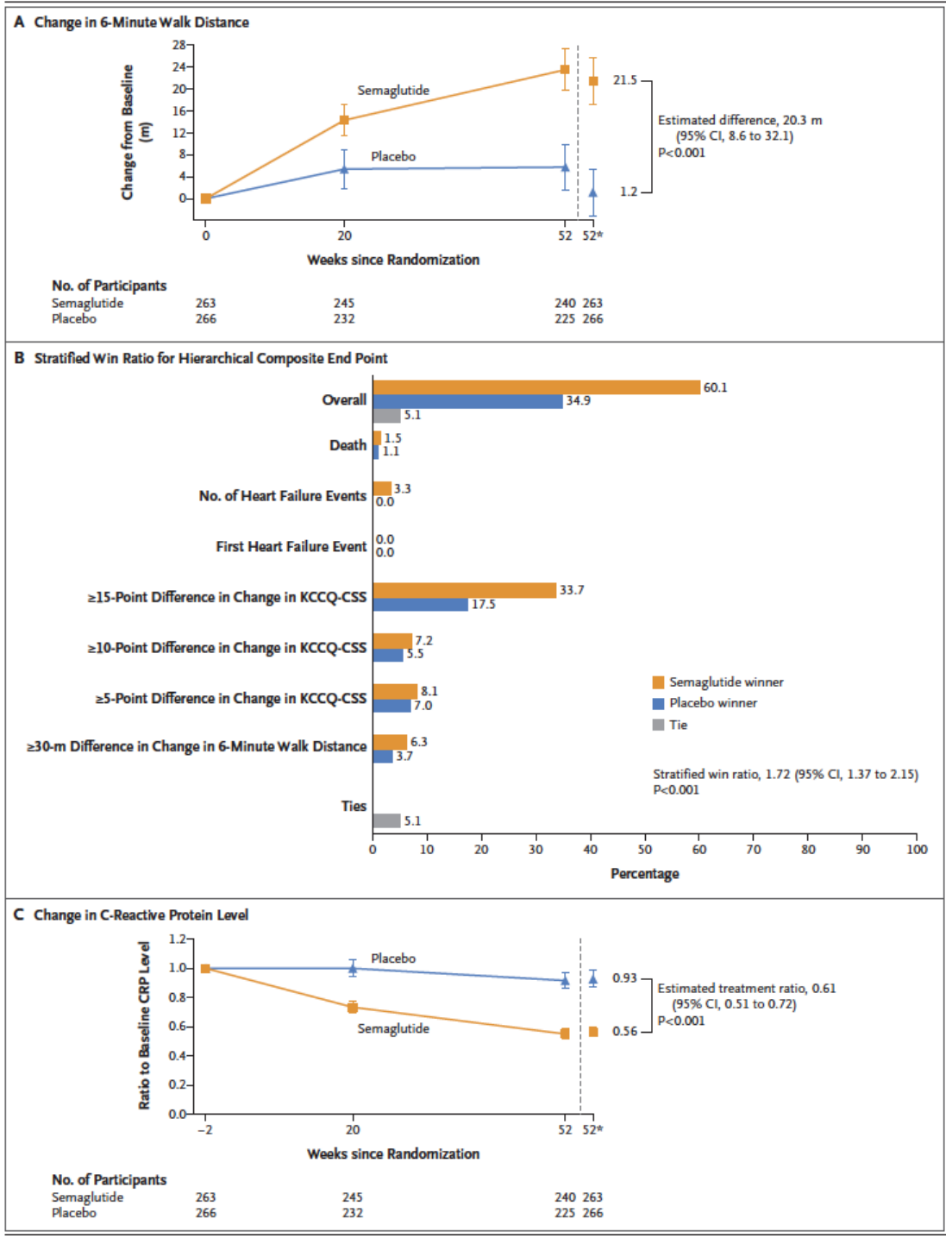
STEP-HFpEF STUDY

The NEW ENGLAND JOURNAL of MEDICINE

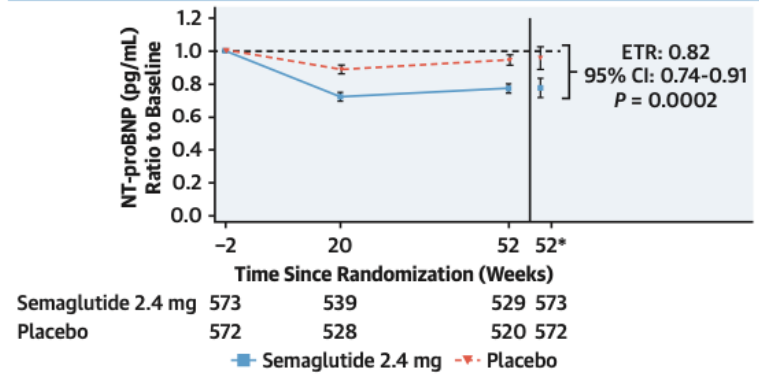
ESTABLISHED IN 1812 SEPTEMBER 21, 2023 VOL. 389 NO. 12

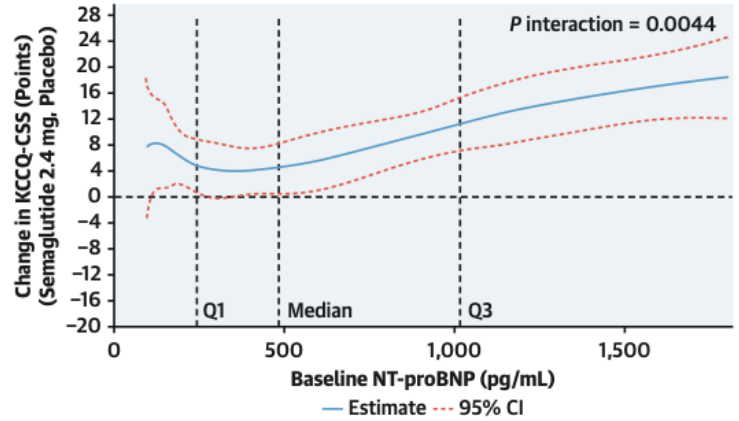
Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity

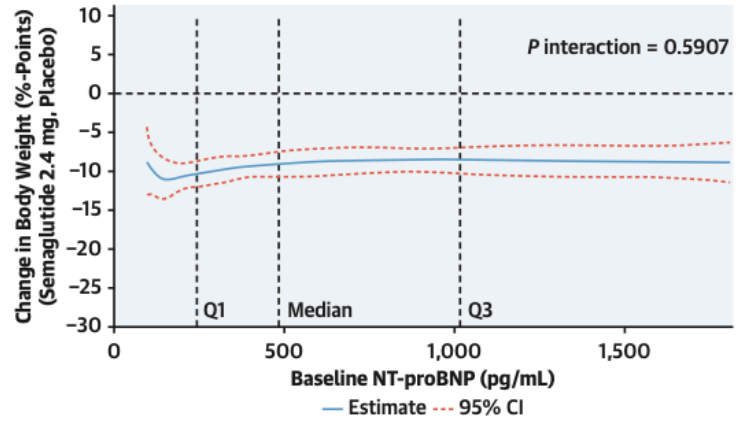
M.N. Kosiborod, S.Z. Abildstrøm, B.A. Borlaug, J. Butler, S. Rasmussen, M. Davies, G.K. Hovingh, D.W. Kitzman, M.L. Lindegaard, D.V. Møller, S.J. Shah, M.B. Treppendahl, S. Verma, W. Abhayaratna, F.Z. Ahmed, V. Chopra, J. Ezekowitz, M. Fu, H. Ito, M. Lelonek, V. Melenovsky, B. Merkely, J. Núñez, E. Perna, M. Schou, M. Senni, K. Sharma, P. Van der Meer, D. von Lewinski, D. Wolf, and M.C Petrie, for the STEP-HFpEF Trial Committees and Investigators*



Semaglutide, compared with placebo, reduced NT-proBNP at 20 and 52 weeks.
Semaglutide improved health status in all patients, with a more pronounced impact in those with higher vs lower baseline NT-proBNP.
Semaglutide reduced body weight consistently across baseline NT-proBNP levels.







Petrie MC, et al. J Am Coll Cardiol. 2024;84(1):27–40.

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Semaglutide and NT-proBNP in Obesity-Related HFpEF

Insights From the STEP-HFpEF Program

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Conclusioni

- **Perdita di peso sostanziale**:

Il trattamento con semaglutide porta a una perdita di peso media del 10-13%, con un impatto più pronunciato nelle donne rispetto agli uomini.

- **Effetti diretti sul sistema cardiovascolare**:

Oltre alla perdita di peso, la semaglutide migliora la funzione endoteliale, riduce l'infiammazione e protegge il cuore dal danno ossidativo.

- **Riduzione dei sintomi dell'insufficienza cardiaca**:

Il trattamento con semaglutide suggerisce un miglioramento dello stress miocardico e della congestione cardiaca, indipendente dalla sola perdita di peso.

- **Impatto globale sul rischio cardiovascolare**:

La semaglutide riduce il 20% degli eventi cardiovascolari maggiori (MACE), confermandosi come una promettente terapia per ridurre il rischio in pazienti con obesità e insufficienza cardiaca.

Grazie per l’attenzione

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Società Medico Chirurgica di Ferrara dal 1846

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Obesità: fenotipizzazione e risvolti terapeutici

Sabato 19 ottobre 2024

Aula Magna Nuovo Arcispedale S. Anna

Cona, Ferrara

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Il Presidente
Dott. R. Zoppellari