L'obesità e il rischio cardiovascolare: nuove opportunità terapeutiche?

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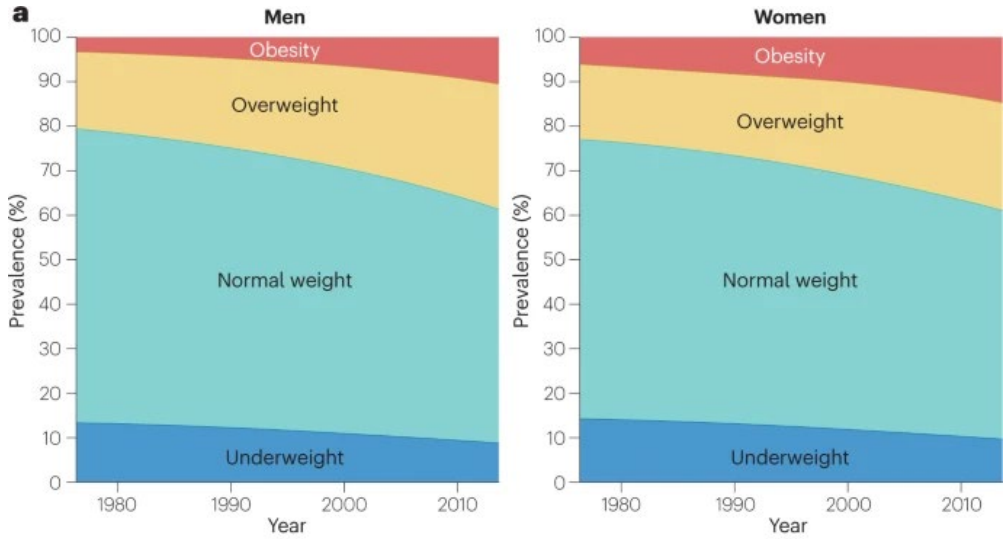
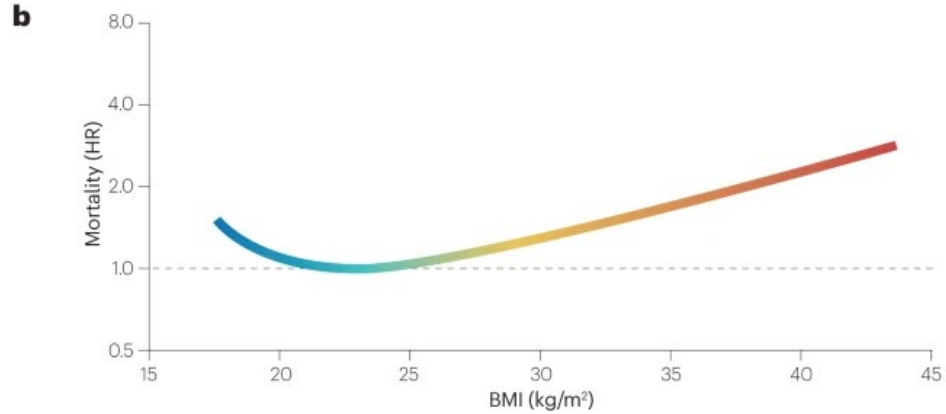
All-cause mortality increases with increasing BMI

NCD Risk Factor Collaboration Trends (N=19,2 million persons)

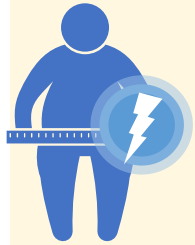
Global trends in BMI categories from 1975 to 2014[1]



Association between BMI and all-cause mortality[2,3]



3x Obesity rates have **nearly tripled** since 1975[5]

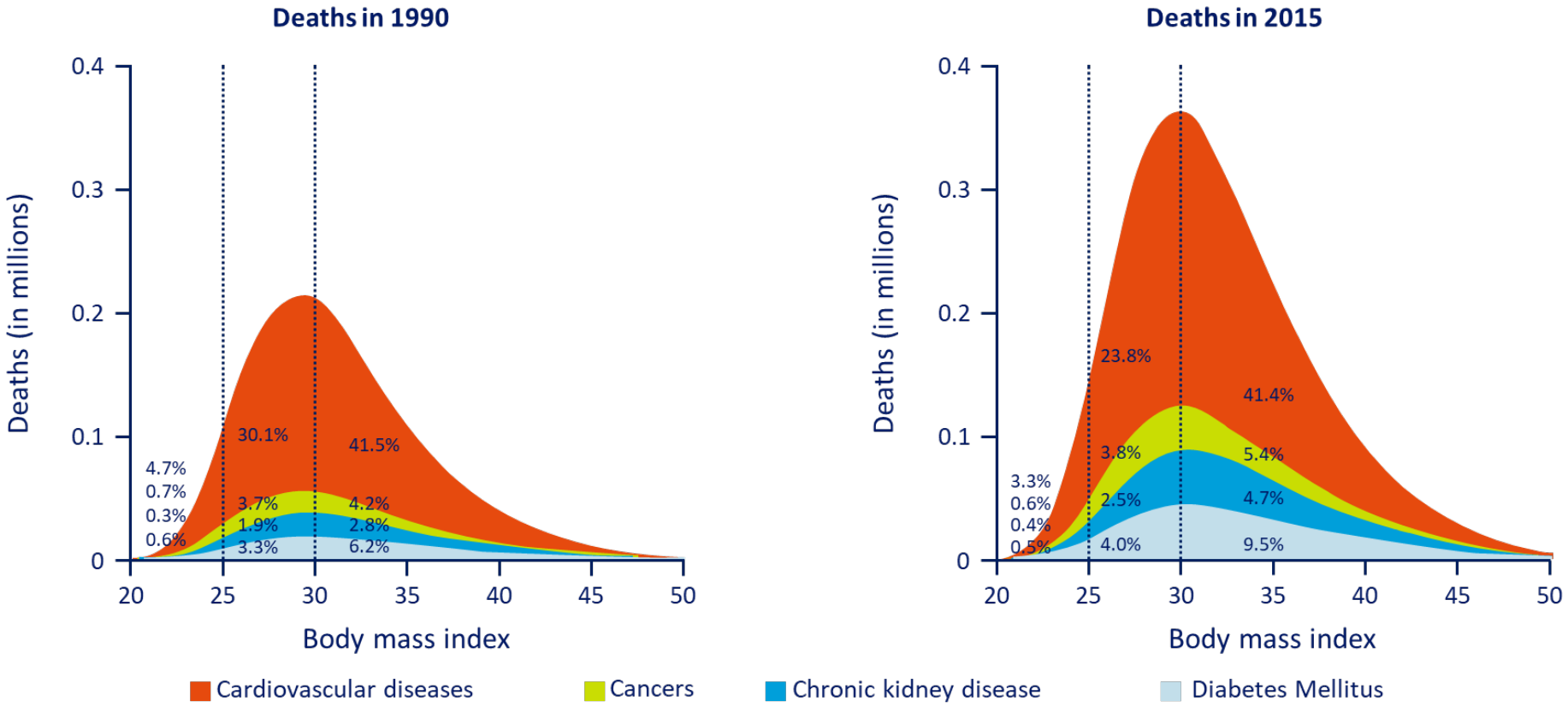


About 878 million people, globally, have obesity[4]

[1]NCD Risk Factor Collaboration Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet 387, 1377–1396 (2016).[2]Global BMI Mortality Collaboration. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet 388, 776–786 (2016). [3]Henning RJ. Obesity and obesity-induced inflammatory disease contribute to atherosclerosis: a review of the pathophysiology and treatment of obesity. Am J Cardiovasc Dis. 2021 Aug 15;11(4):504-529. [54]NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults. Lancet. 2024 Mar 16;403(10431):1027-1050. doi: 10.1016/S0140-6736(23)02750-2. Epub 2024 Feb 29. PMID: 38432237. [5]World Obesity Federation. World obesity atlas 2022. Available at: https://www.worldobesity.org/resources/resource-library/world-obesity-atlas-2022;

CV death contributes to the majority of deaths associated with high BMI

Global Burden of Disease Study (N=68.5 million persons)



~2 million

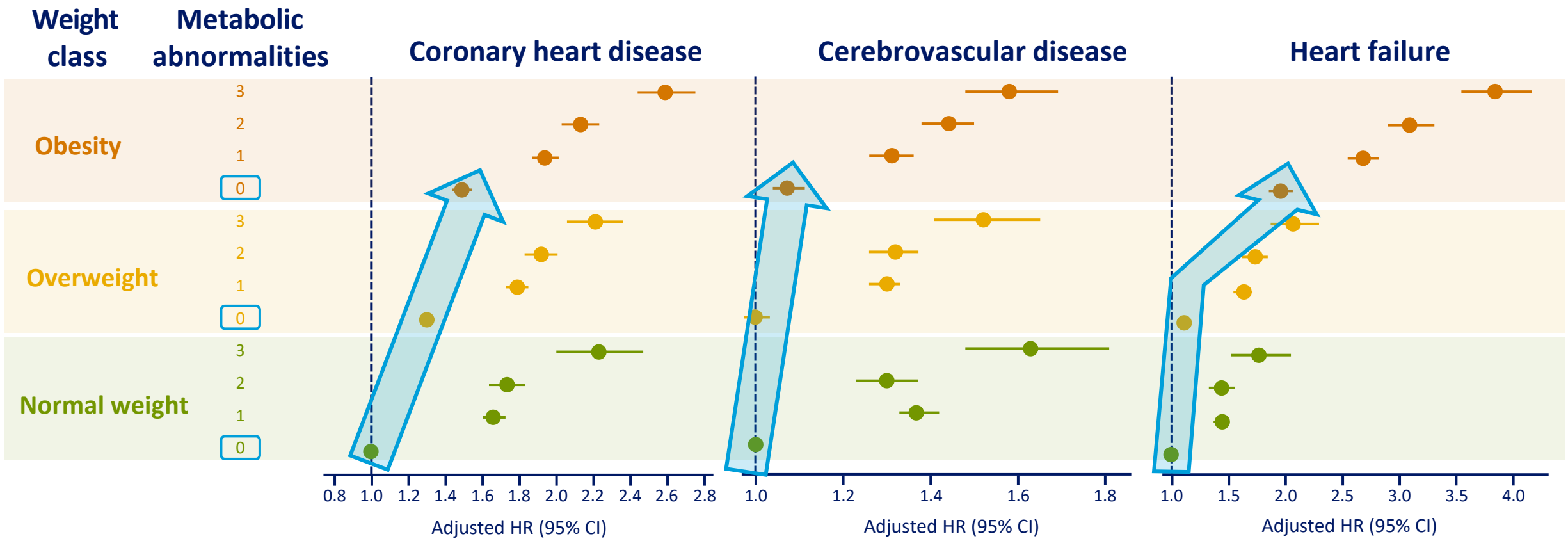
CV-related deaths are attributed to **obesity**

Deaths Associated with a High Body-Mass Index (1990–2015)

GBD 2015 Obesity Collaborators. Health Effects of Overweight and Obesity in 195 Countries over 25 Years N Engl J Med 2017;377:13–27

Overweight or obesity increase the risk of CVE even in the absence of other metabolic abnormalities

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



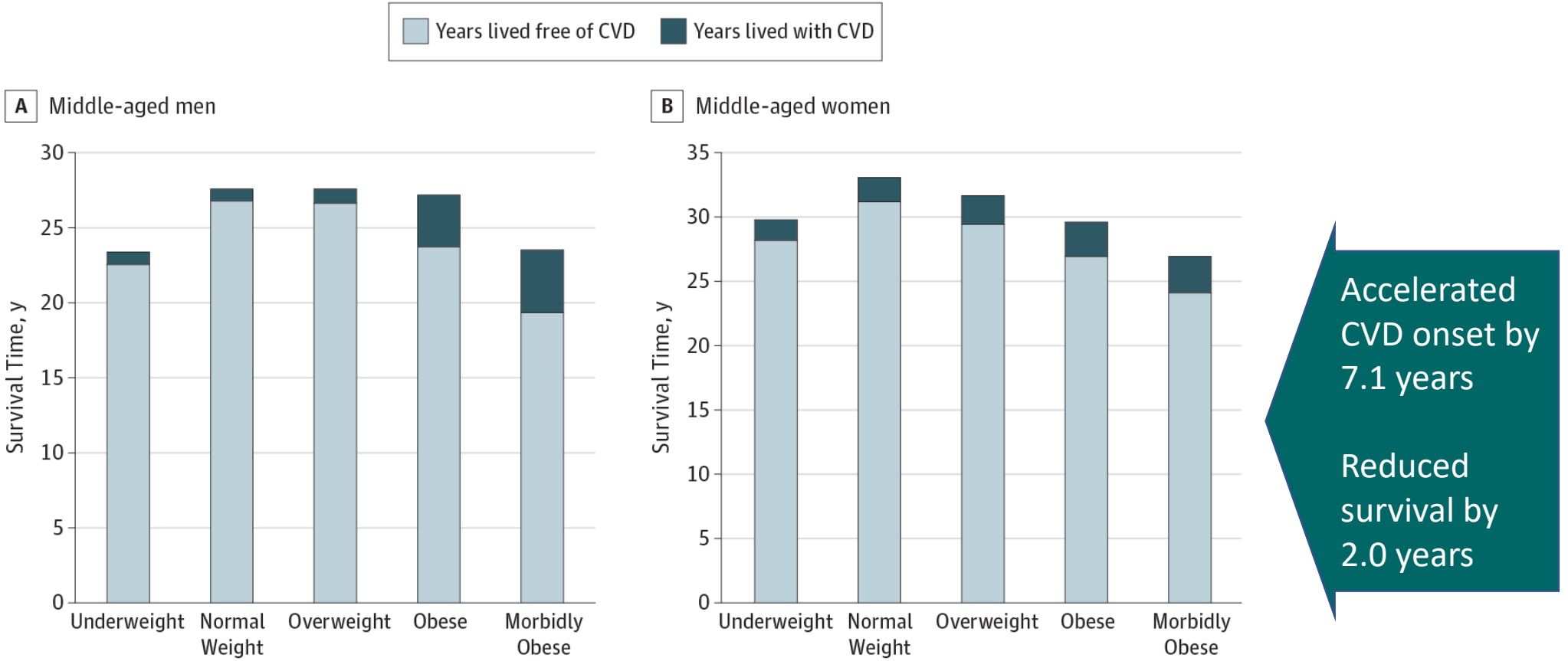
*The three metabolic abnormalities (diabetes, hypertension and hyperlipidaemia) were summed to create ametabolic abnormalities score (0, 1, 2, and 3). †Analyses adjusted for age, sex, smoking status, and social deprivation. The reference category is normal weight, no metabolic abnormalities. CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease; HR, hazard ratio; PVD, peripheral vascular disease; UK, United Kingdom.

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

The time spent with CVD is associated with BMI

Cardiovascular Disease Lifetime Risk Pooling Project (N=190,672)

Years lived free of and with CVD in middle-aged (index age, 40-59 years) men (A) and women (B)



Accelerated CVD onset by 7.5 years

Reduced survival by 5.6 years

Accelerated CVD onset by 7.1 years

Reduced survival by 2.0 years

Khan SS, Ning H, Wilkins JT, Allen N, Carnethon M, Berry JD, Sweis RN, Lloyd-Jones DM. Association of Body Mass Index With Lifetime Risk of Cardiovascular Disease and Compression of Morbidity. JAMA Cardiol. 2018 Apr 1;3(4):280-287.

Obesity-related glomerulopathy

Pathologic and clinical characteristics

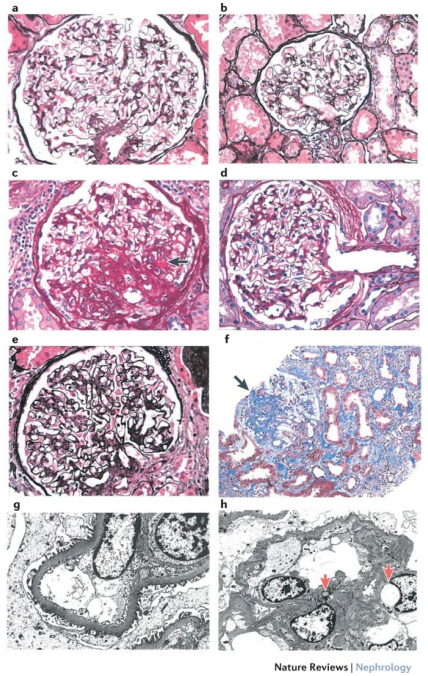
Pathology: glomerulomegaly, focal segmental glomerulosclerosis

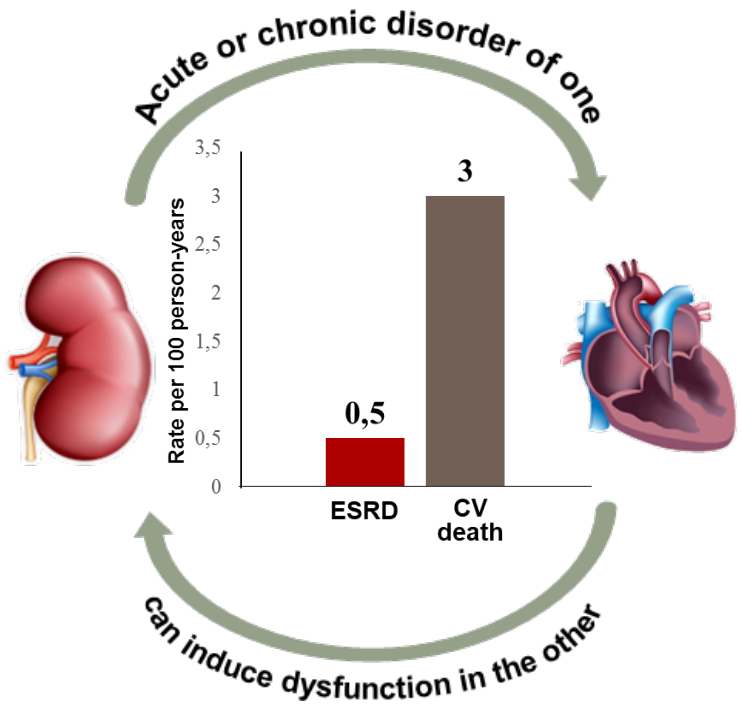
Manifestations: subnephrotic proteinuria, nephrotic-range proteinuria, progressive loss of renal function.

Hemodynamics: increased glomerular filtration rate, renal plasma flow, filtration fraction and tubular reabsorption of sodium.

Adiposity: meta-inflammation, maladaptive responses to hyperfiltration, podocyte depletion, proteinuria, glomerulosclerosis, interstitial fibrosis.

CARDIORENAL METABOLIC SYNDROME





D'Agati VD, Chagnac A, de Vries AP, Levi M, Porrini E, Herman-Edelstein M, Praga M. Obesity-related glomerulopathy: clinical and pathologic characteristics and pathogenesis. Nat Rev Nephrol. 2016 Aug;12(8):453-71
Ronco C et al. J Am Coll Cardiol. 2008; Dalrymple L et al. J Gen Intern Med. 2011

Adipose tissue dysfunction contributes to ectopic fat storage and related complications

Adiposopathy

Healthy Adipose Tissue

Normal adipocyte size
Healthy ECM distribution
M2 resident macrophage

Hyperglycemia/
hyperinsulinemia

Hypertrophy

Inflammation

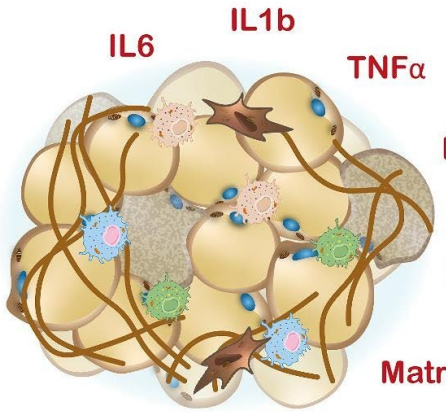
Macrophage polarization

Oxidative stress

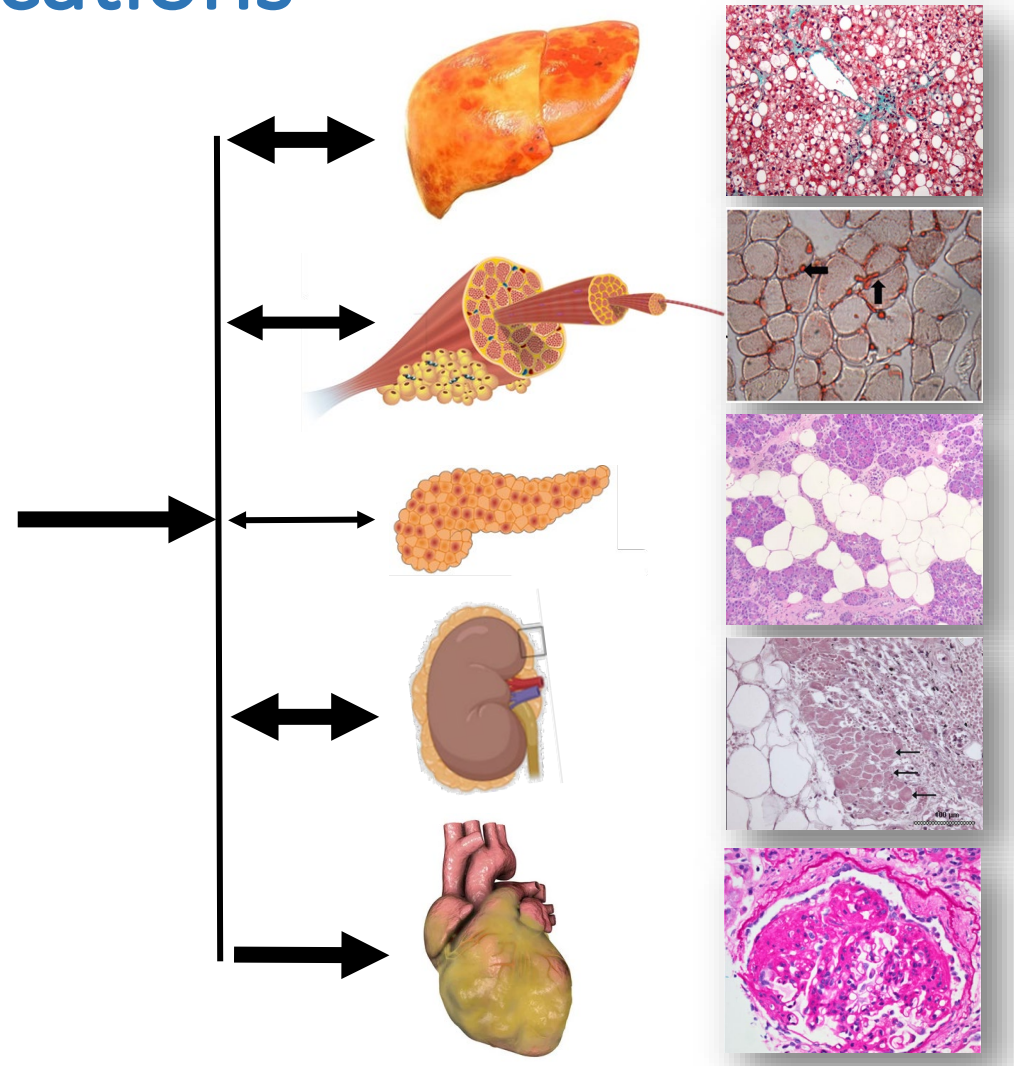
Lipid overload

Fibrosis

Unhealthy Adipose Tissue

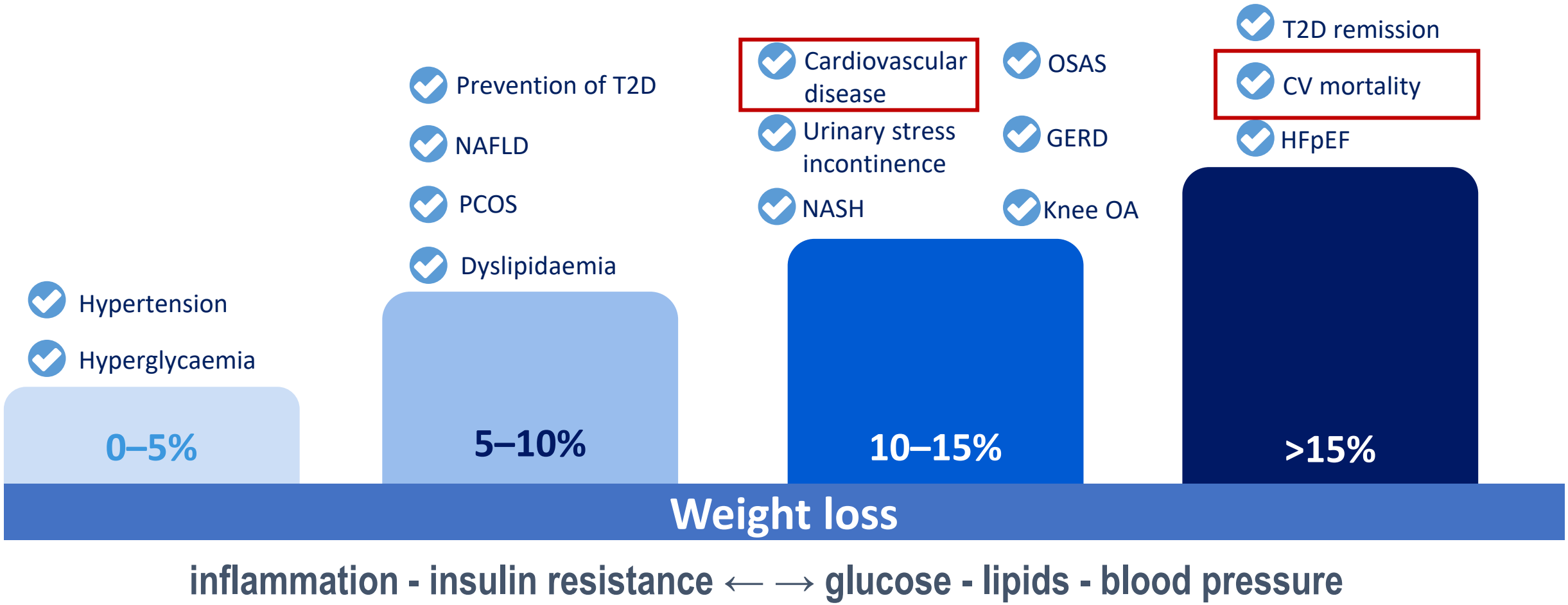


Hypertrophic adipocytes
Necrotic adipocytes
Fibroblast and myofibroblast activation
ECM deposition
Macrophage infiltration
Alternative macrophage activation (Mme, Mox, ...)



Dahdah N, Tercero-Alcázar C, Malagón MM, Garcia-Roves PM, Guzmán-Ruiz R. Interrelation of adipose tissue macrophages and fibrosis in obesity. Biochem Pharmacol. 2024 May 28;225:116324. Goossens GH. The role of adipose tissue dysfunction in the pathogenesis of obesity-related insulin resistance. Physiol Behav. 2008 May 23;94(2):206-18. Goossens GH, Blaak EE. Adipose tissue dysfunction and impaired metabolic health in human obesity: a matter of oxygen? Front Endocrinol (Lausanne). 2015 Apr 24;6:55.

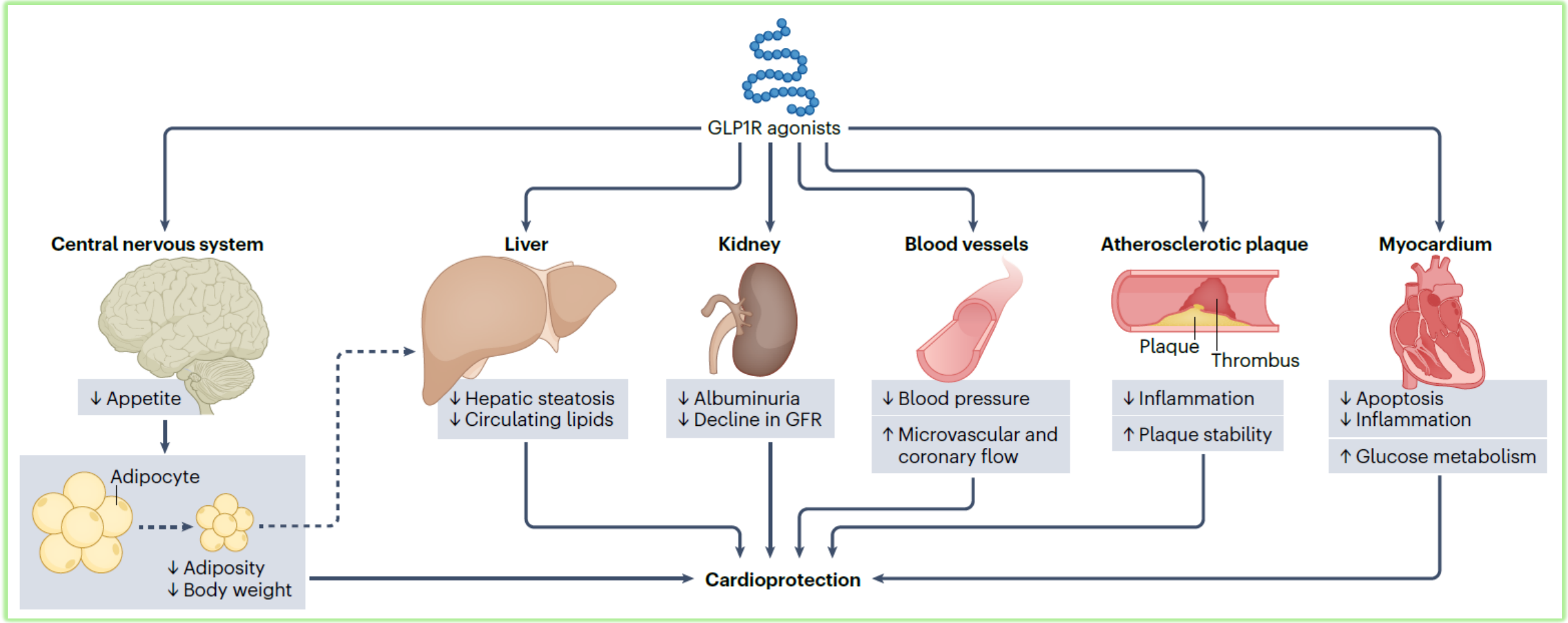
Greater weight loss leads to improved health outcomes in patients with obesity



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

1. Garvey WT et al. Endocr Pract 2016;22(Suppl. 3):1–203; Look AHEAD Research Group; 2. Lancet Diabetes Endocrinol 2016;4:913–21; 3. Lean ME et al. Lancet 2018;391:541–51; 4. Benraoune F and Litwin SE. Curr Opin Cardiol 2011;26:555–61; 5. Sundström J et al. Circulation 2017;135:1577–85.

Cardioprotection mediated by direct and indirect actions of GLP1 RA



Ussher JR, Drucker DJ. Nat Rev Cardiol. 2023 Mar 28.

Overview of status and key observations from obesity CVOTs and registries

	SCOUT[1]	CRESCENDO[2]	LIGHT[3]	CONVENE[4]	CAMELLIA-TIMI[5]	SELECT[6]	SURMOUNT-MMO[7]
Intervention	Sibutramine*	Rimonabant*	Naltrexone/ bupropion	Naltrexone/ bupropion	Lorcaserin*	Once-weekly semaglutide	Tirzepatide
Primary outcome	3P-MACE + resuscitated cardiac arrest	3P-MACE	3P-MACE	3P-MACE	1. 3P-MACE (safety outcome) 2. MACE+ (efficacy outcome)	3P-MACE	5P-MACE
Trial status	**Completed**	**Terminated prematurely** *(Safety concerns)*	**Terminated prematurely** *(Study integrity compromised)*	**Terminated prematurely** *(Selling of US rights)*	**Completed**	**Completed**	**Ongoing**
HR (95% CI) for primary outcome	1.16 (1.03; 1.31); p=0.02	0.97 (0.84; 1.12); p=0.68	50% interim analysis: 0.88 (0.57; 1.34)	No data available	MACE+: 0.97 (0.87; 1.07); p=0.55	0.80 (0.72; 0.90); p<0.001	N/A
Safety/ outcome results	Not safe/Harm†	Not safe‡/Neutral	Safe/Neutral *(integrity compromised)*	No data available	Safe/Neutral	Safe/Benefits (3P-MACE)	N/A
Weight change§	–1.7 kg (vs +0.7 kg) at 12 months	N/A	–3.6% (vs –1.1%) at trial end	No data available	–4.0 kg (vs –2.1 kg) at 40 months	–9.4% (vs –0.9%) at 24 months	N/A

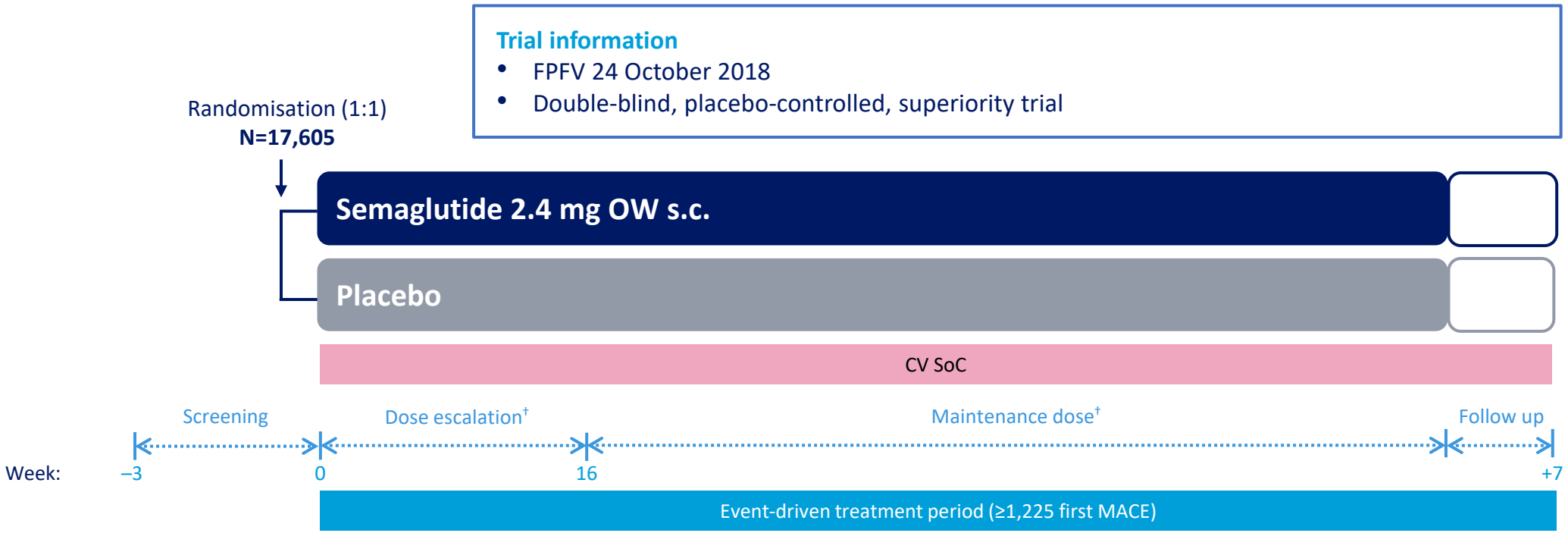
3P-MACE, composite of CV death, non-fatal MI and non-fatal stroke; 5P-MACE, composite of all-cause death, non-fatal MI, non-fatal stroke, coronary revascularisation or HF events; MACE+, composite of MI, stroke, CV death, and hospitalisation due to unstable angina, HF or any coronary revascularisation.
CI, confidence interval; CV, cardiovascular; CVOT, cardiovascular outcome trial; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction; T2D, type 2 diabetes.
See slide notes for footnotes and references.

**The following drugs have been withdrawn by the FDA: rimonabant (2008), sibutramine (2010) and lorcaserin (2020).*
†Increased MACE events with sibutramine vs placebo.
‡Increased neuropsychiatric, serious psychiatric and GI effects with rimonabant vs placebo.
§vs weight loss in control group.

1. James WPT et al. N Engl J Med 2010;363:905-17;
2. Topol EJ et al. Lancet 2010;376:517–23;
3. Nissen SE et al. JAMA 2016;315:990–1004;
4. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02638129. Accessed October 2023;
5. Bohula EA et al. N Engl J Med 2018;379:1107–17;
6. Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563;
7. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT05556512. Accessed October 2023.

Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity - SELECT

Trial design (N=17,604)



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.

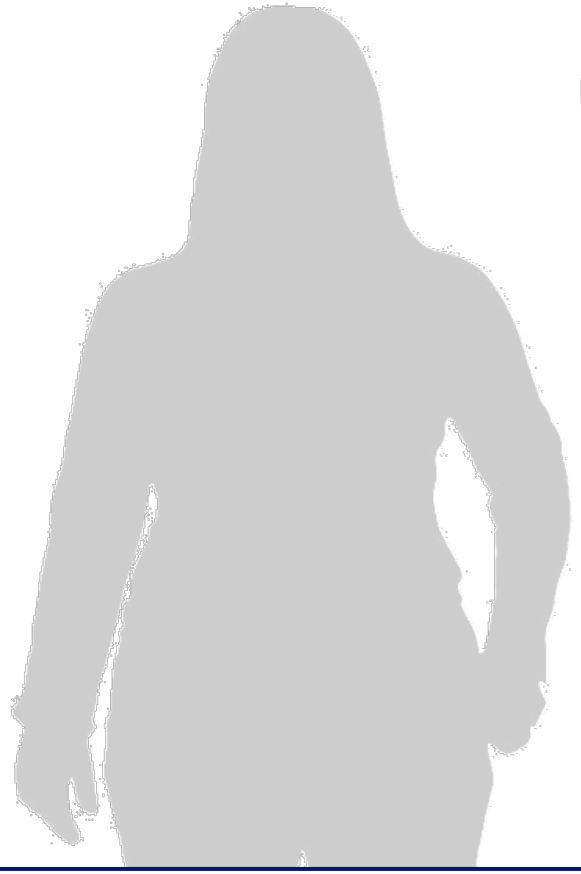
Main inclusion / exclusion criteria of SELECT

Key inclusion criteria[1,2]

Prior MI / stroke*
Symptomatic PAD†

Male or female
≥45 years of age

BMI: ≥27 kg/m^2



Key exclusion criteria[1,2]

HbA_{1c} ≥6.5%

History of type 1
or type 2 diabetes‡

Treatment with glucose
lowering agents within the
last 90 days

Presently classified
as being in 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; 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.

SELECT: Primary and confirmatory secondary endpoints

Primary endpoint[1–3]

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

- Cardiovascular death
- Non-fatal myocardial infarction
- Non-fatal stroke

Confirmatory secondary endpoints[1–3]

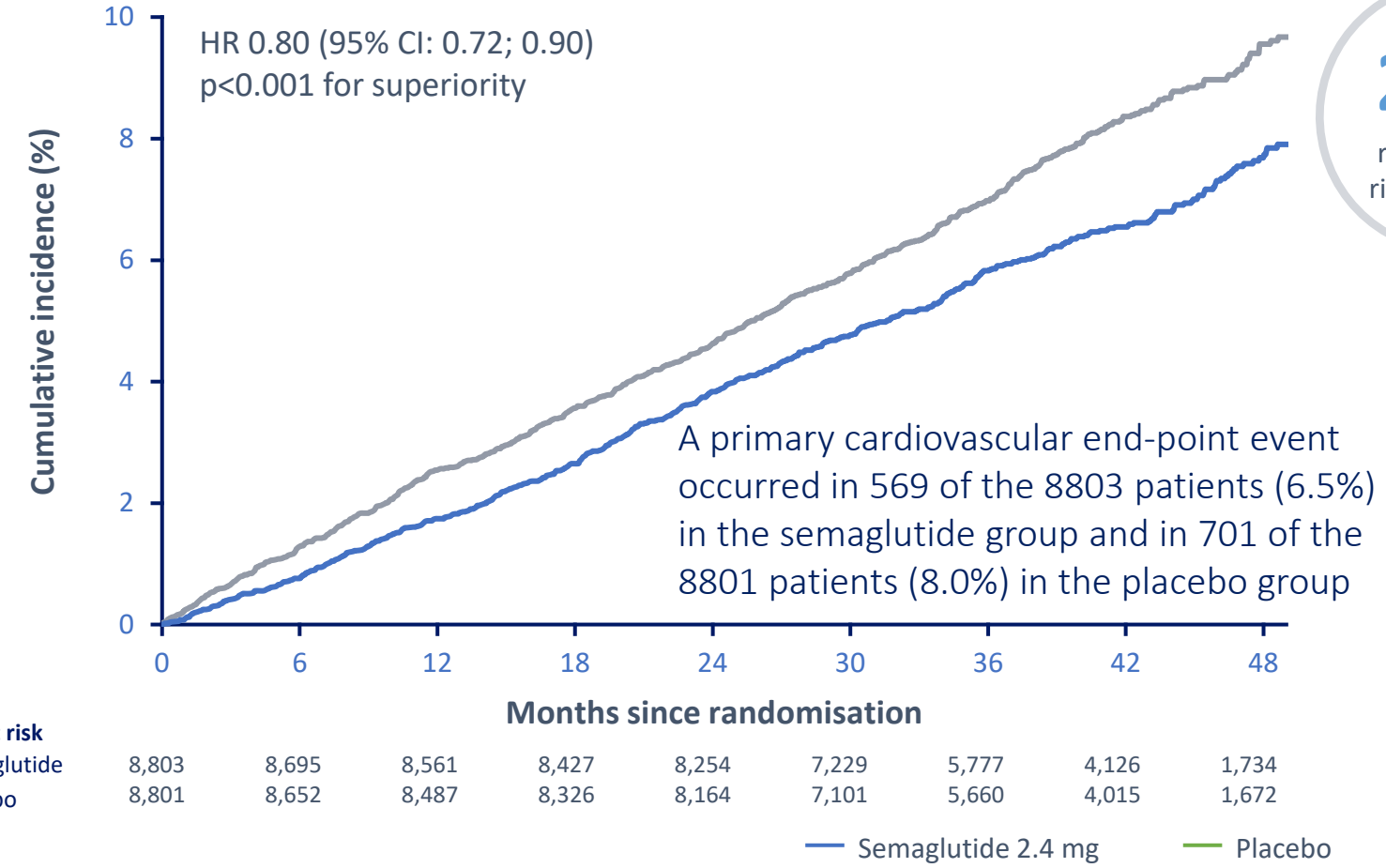
Time from randomisation to occurrence of:

- Cardiovascular death
- Composite heart failure endpoint (HF hospitalisation, urgent HF visit or CV death)
- All-cause death

A hierarchical testing procedure required statistical significance to be established for the primary endpoint before confirmatory secondary and supportive secondary endpoints could be tested.
CV, cardiovascular; HF, heart failure; MI, myocardial infarction.
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.

SELECT: Cumulative incidence of MACE

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]

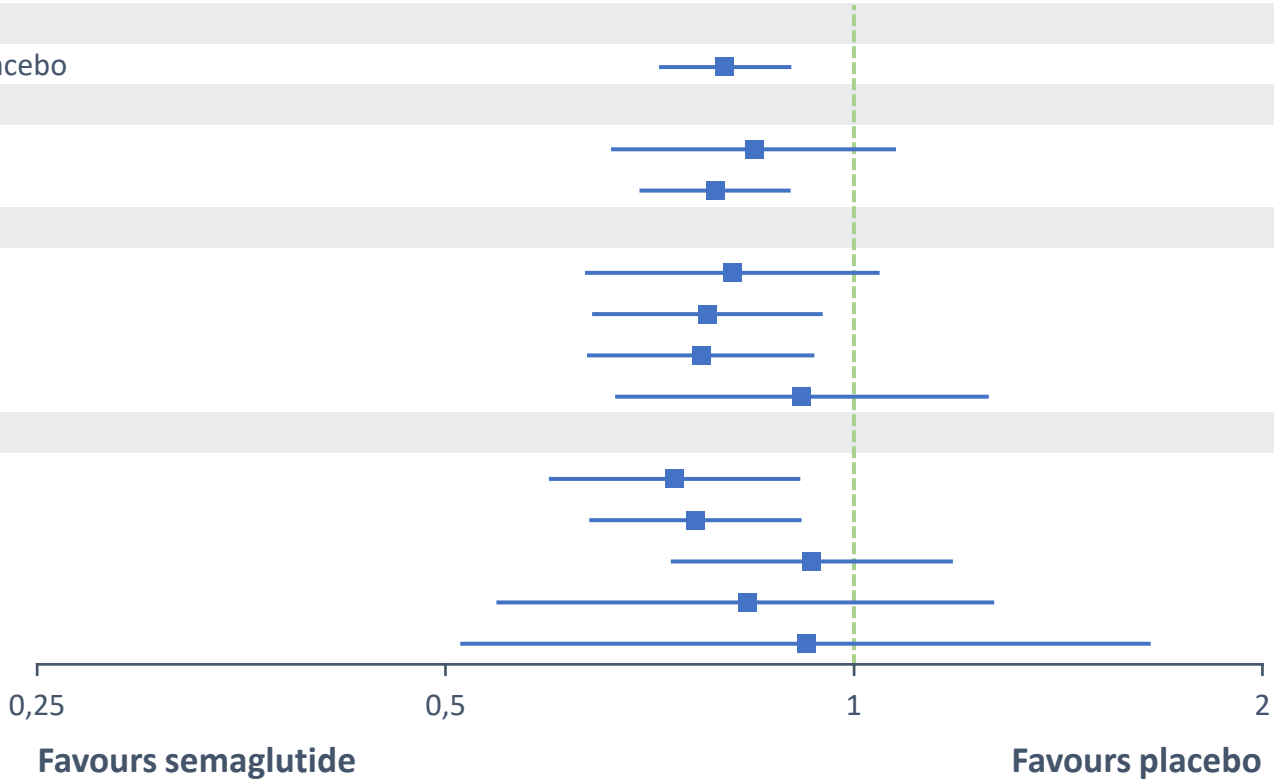
All three components (death from CV causes, non-fatal MI and non-fatal stroke) contributed to MACE risk reduction

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

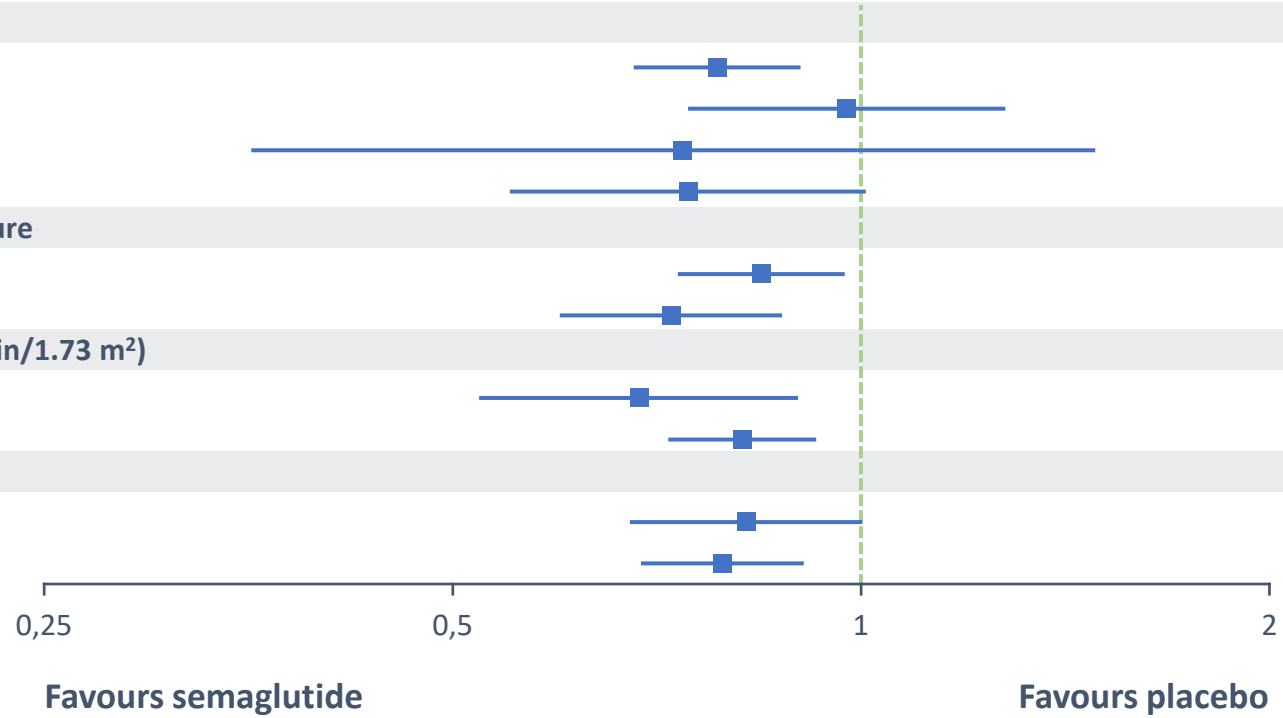
SELECT: Subgroup analysis of MACE (1)



	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/m²)		
<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.

SELECT: Subgroup analysis of MACE (2)

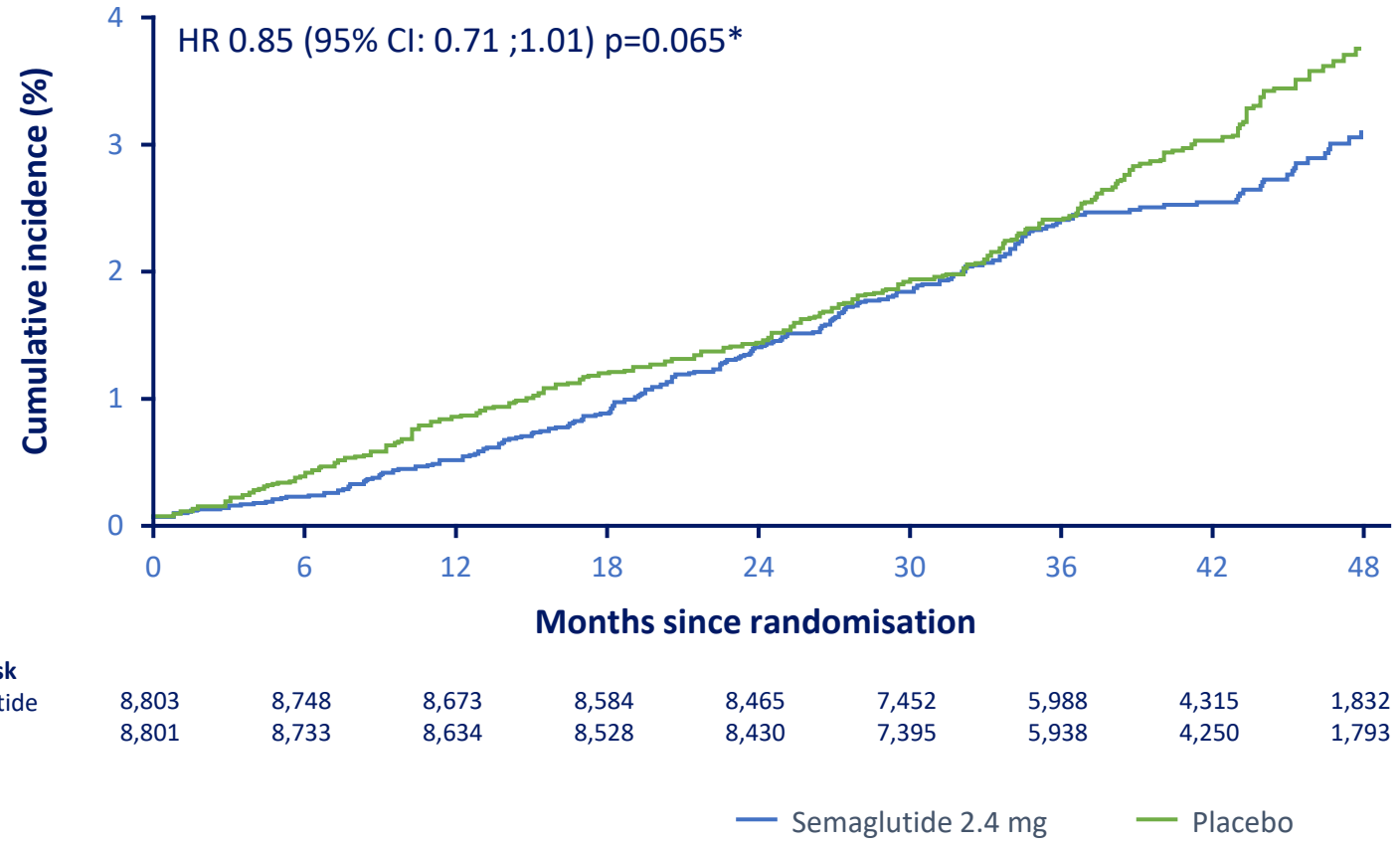


	HR (95% CI)	No. of events / analysed participants (semaglutide; placebo)
CVD		
Only MI	0.78 (0.68; 0.90)	362 / 5,962; 455 / 5,944
Only stroke	0.98 (0.75; 1.27)	109 / 1,578; 109 / 1,556
Only PAD	0.74 (0.36; 1.48)	13 / 376; 19 / 401
≥2 CVDs	0.75 (0.55; 1.00)	76 / 718; 100 / 719
Chronic heart failure		
No	0.84 (0.74; 0.97)	372 / 6,647; 438 / 6,667
Yes	0.72 (0.60; 0.87)	197 / 2,155; 262 / 2,131
eGFR level (mL/min/1.73 m^2)		
<60	0.69 (0.52; 0.90)	94 / 963; 127 / 935
≥60	0.82 (0.72; 0.92)	469 / 7,761; 572 / 7,807
HbA_{1c} level (%)		
<5.7	0.82 (0.68; 1.00)	186 / 2,925; 228 / 2,980
≥5.7	0.79 (0.69; 0.90)	383 / 5,877; 473 / 5,819

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.

SELECT: Cumulative incidence of death from CV causes

First confirmatory secondary endpoint



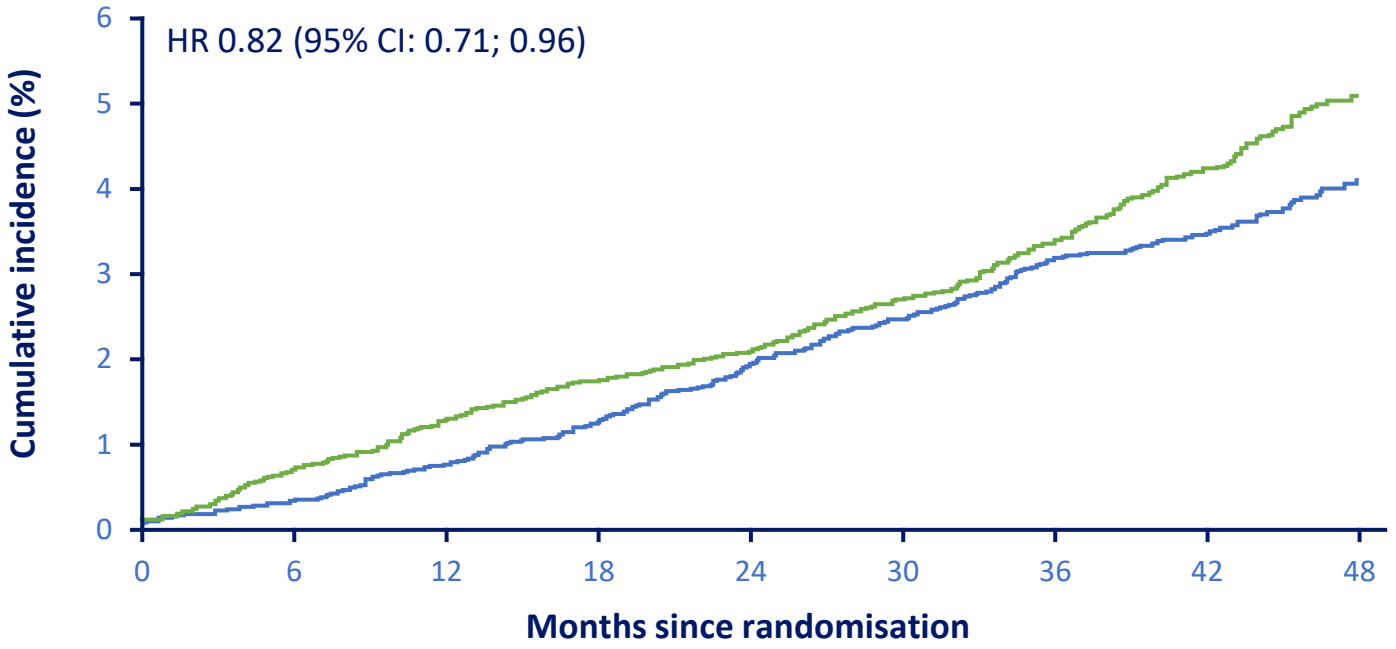
Semaglutide 2.4 mg reduced the risk of death from CV causes by 15% compared with placebo

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.

SELECT: Cumulative incidence of composite heart failure events

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.

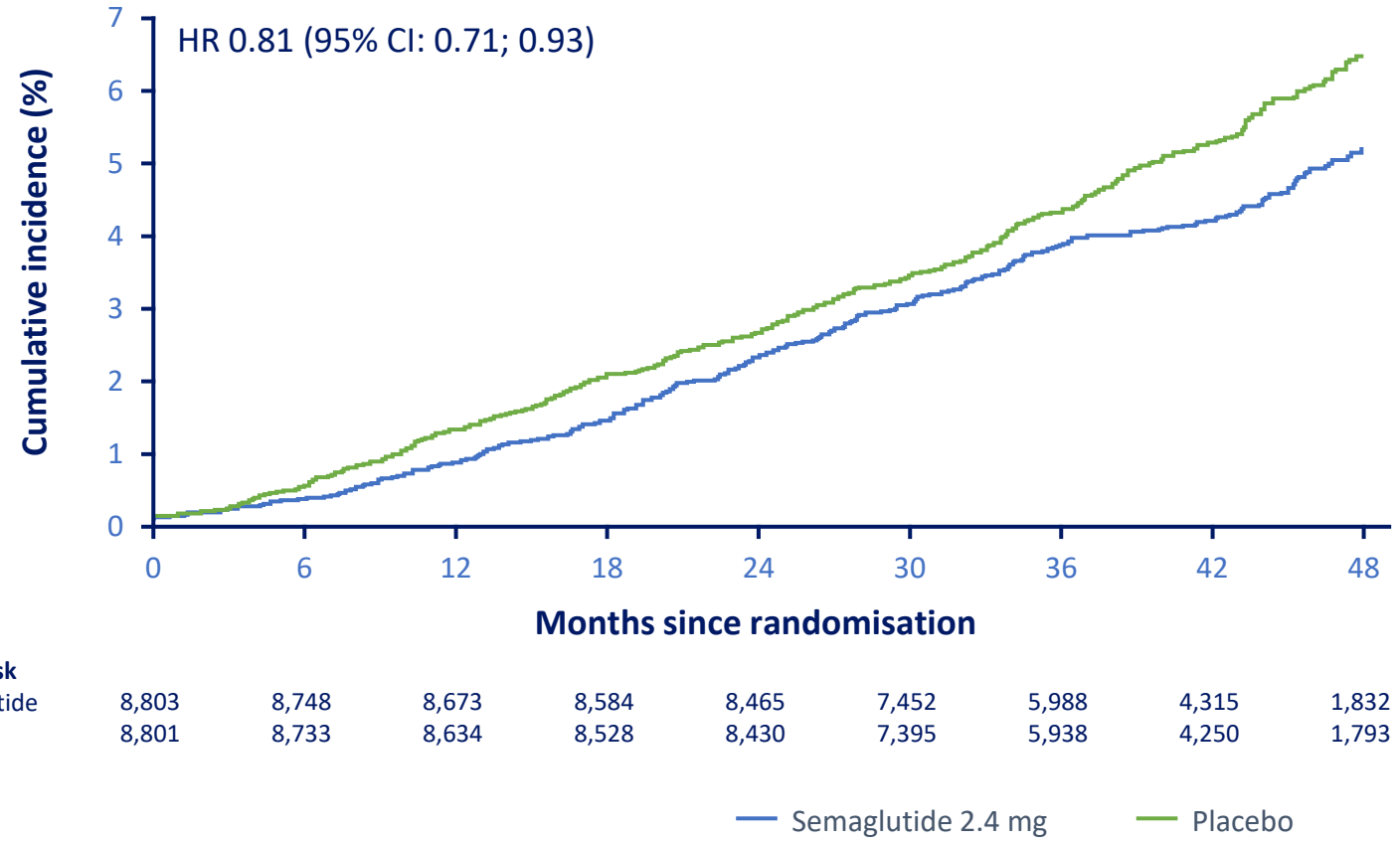
*The difference in the risk of death from CV causes did not meet the required p value for hierarchical testing, so superiority testing for the remaining confirmatory secondary endpoints was not performed.

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

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

SELECT: Cumulative incidence of death from any cause

Third confirmatory secondary endpoint



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.

nature medicine

Article

https://doi.org/10.1038/s41591-024-02996-7

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

Received: 1 March 2024

Accepted: 12 April 2024

Published online: 13 May 2024

Check for updates

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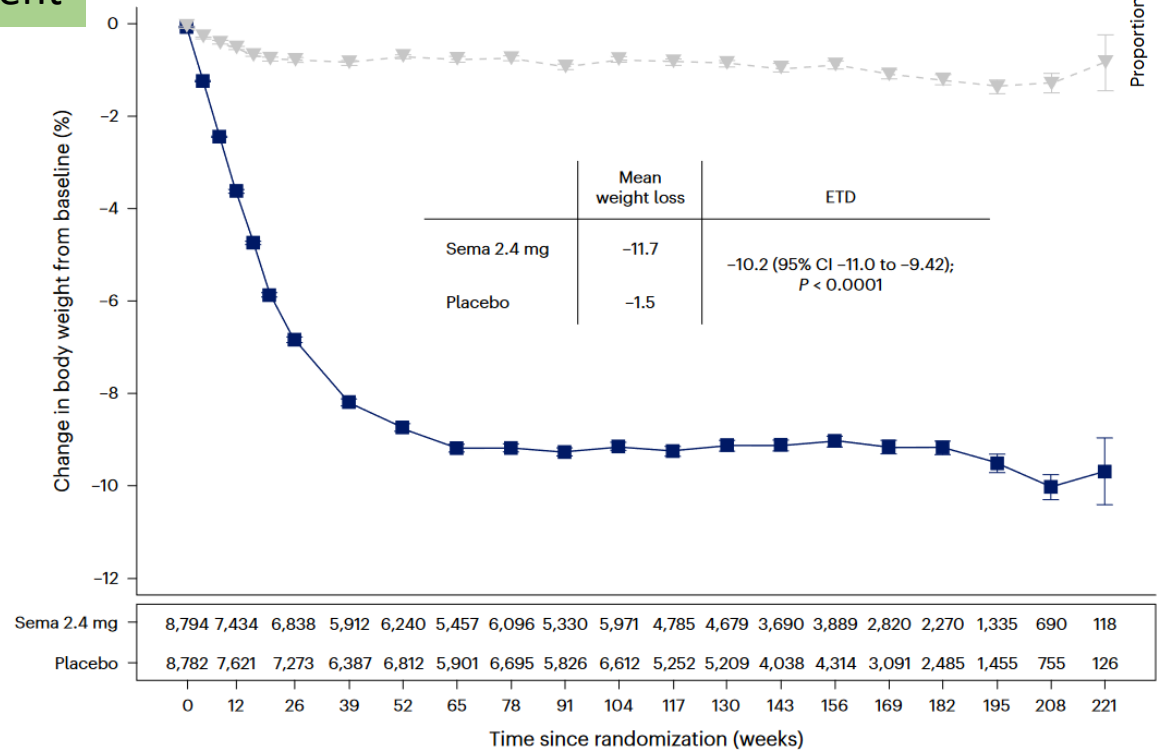
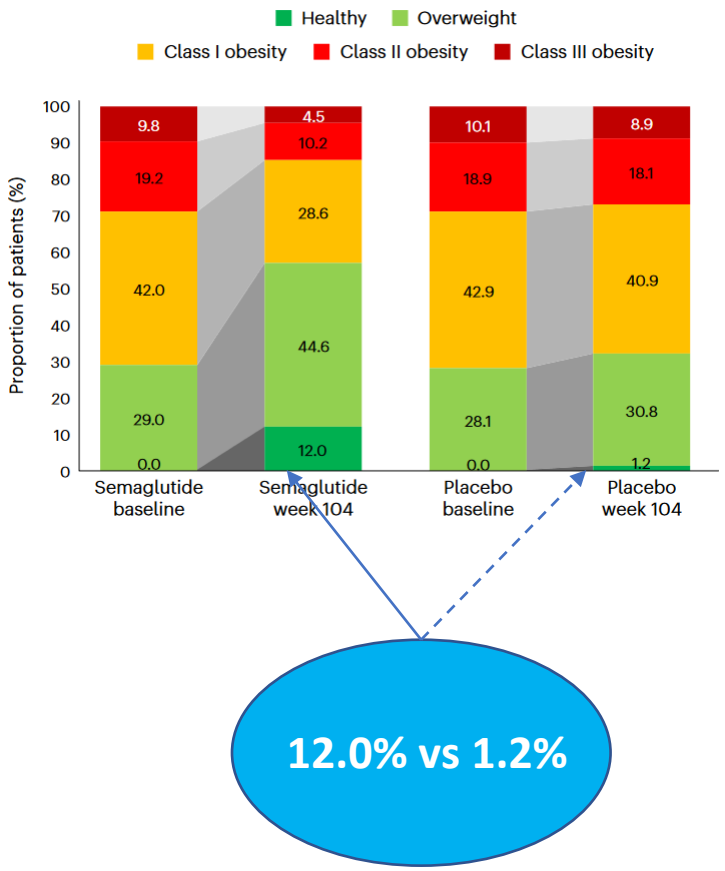
first on-treatment

Women lost more weight on average than men (−11.1% versus −7.5% treatment difference from placebo);

Asian patients lost less weight than patients of other races.



Change in BMI category

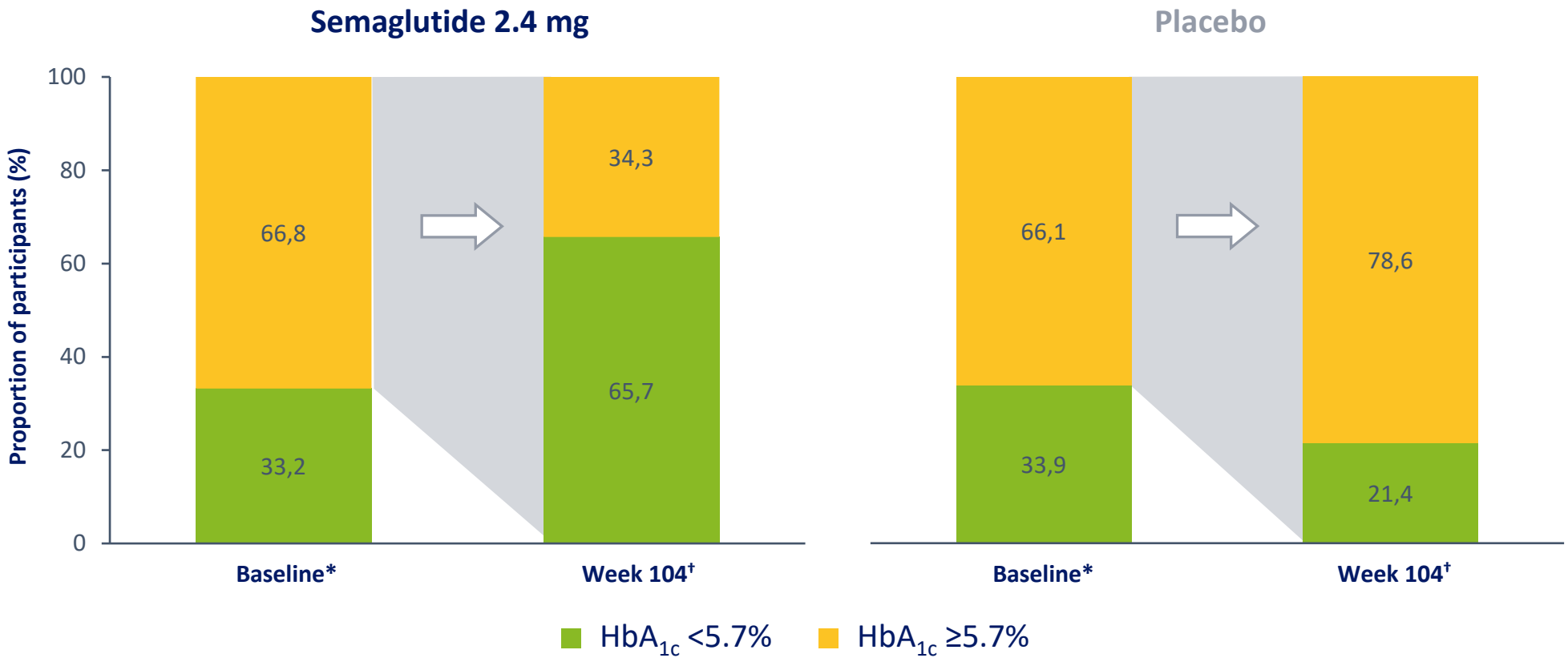


12.0% vs 1.2%

P values are two-sided and are not adjusted for multiplicity.
ETD, estimated treatment difference; sema, semaglutide.

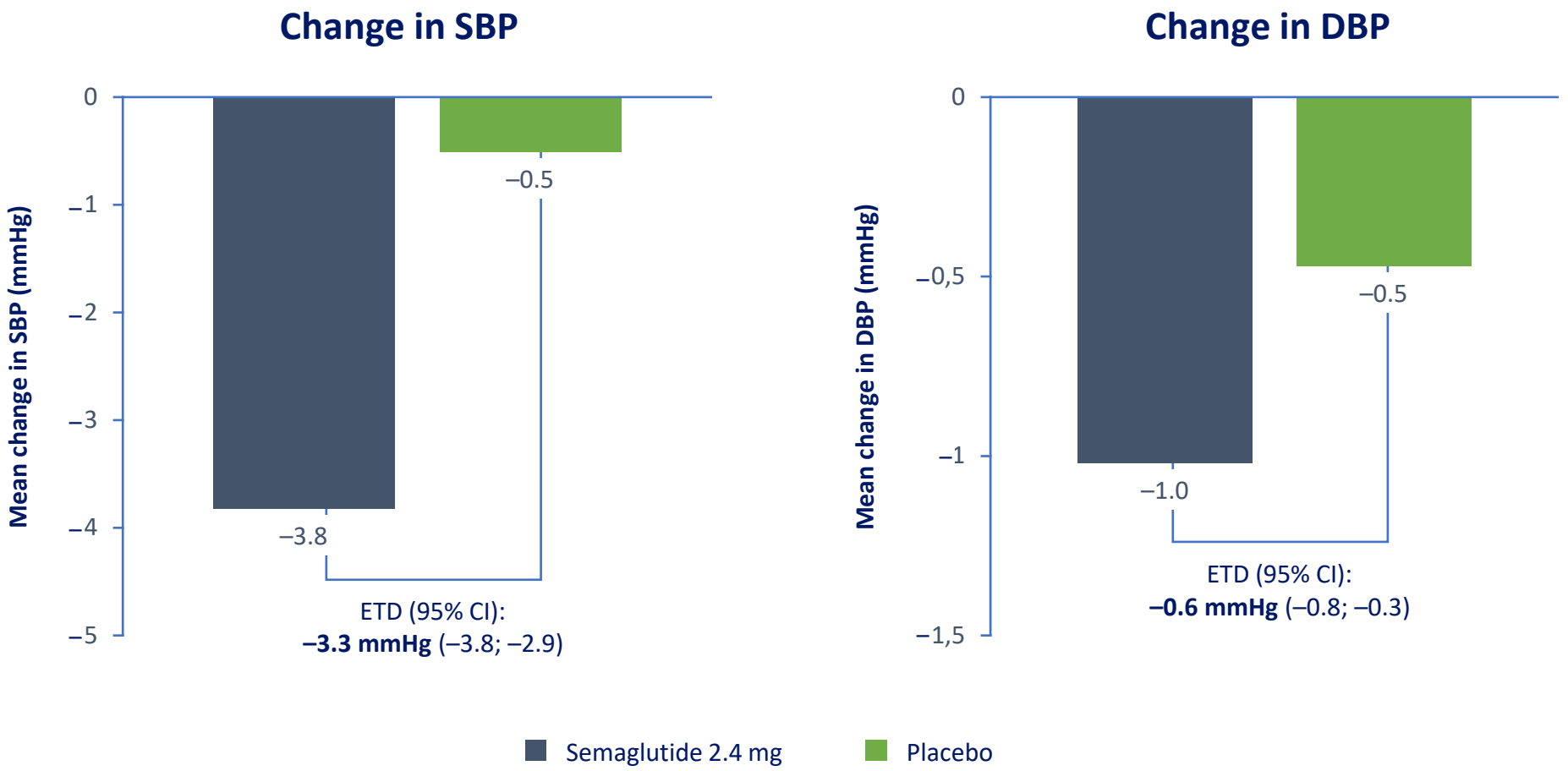
SELECT: Change in HbA_{1c}

Participants with baseline HbA_{1c} ≥5.7%



- Proportions estimated using logistic regression with treatment as factor and baseline HbA_{1c} as a covariate. *Number of participants with HbA_{1c} ≥5.7% at baseline was 5,877 for semaglutide and 5,819 for placebo. †Number of participants with HbA_{1c} ≥5.7% at baseline and evaluable data (assessment or imputation) at week 104 was 5,750 for semaglutide and 5,663 for placebo.
- CI, confidence interval; ETD, estimated treatment difference; HbA_{1c}, glycated haemoglobin.
- Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

SELECT: Change in blood pressure (mmHg)



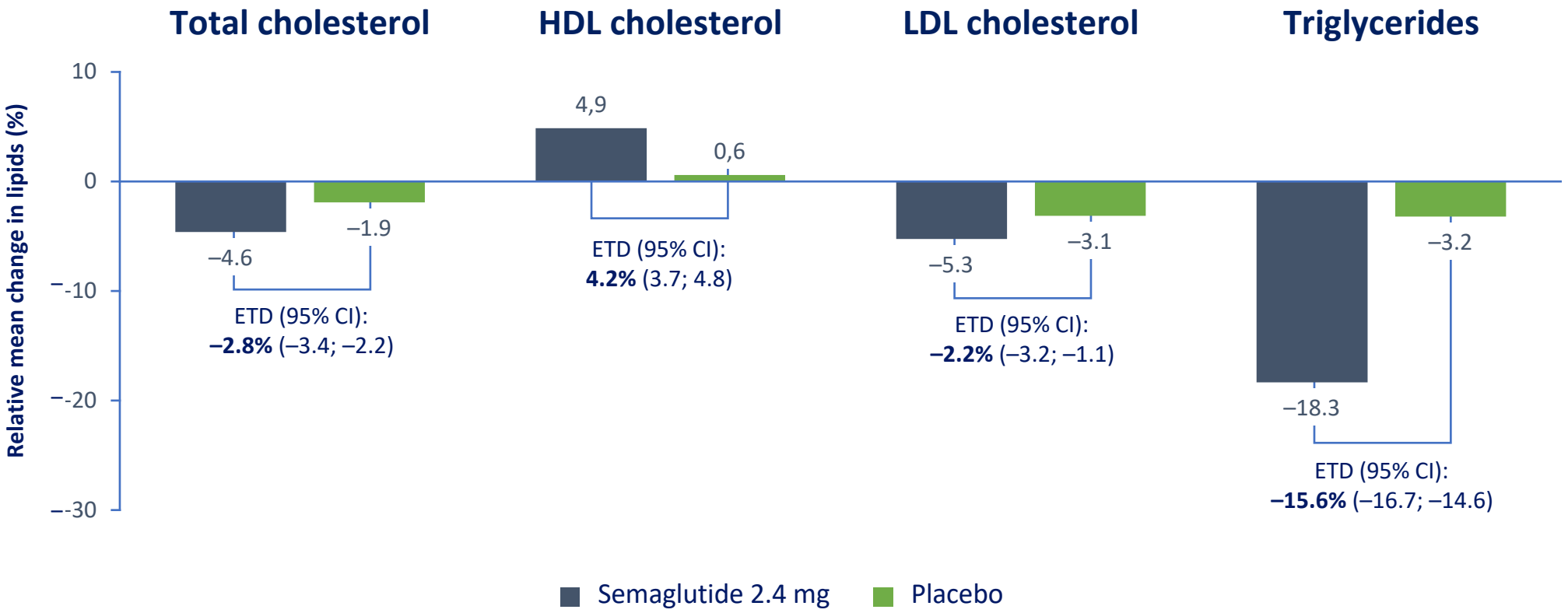
Change from baseline to week 104, estimated using ANCOVA with treatment as factor and the baseline value as covariate. CIs have not been adjusted for multiplicity.
ANCOVA, analysis of covariance; CI, confidence interval; DBP, diastolic blood pressure; ETD, estimated treatment difference; SBP, systolic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

SELECT: Change in lipids (%)

High-sensitivity CRP level

SEMAGLUTIDE	PLACEBO
–39.12%	**–2.08%**

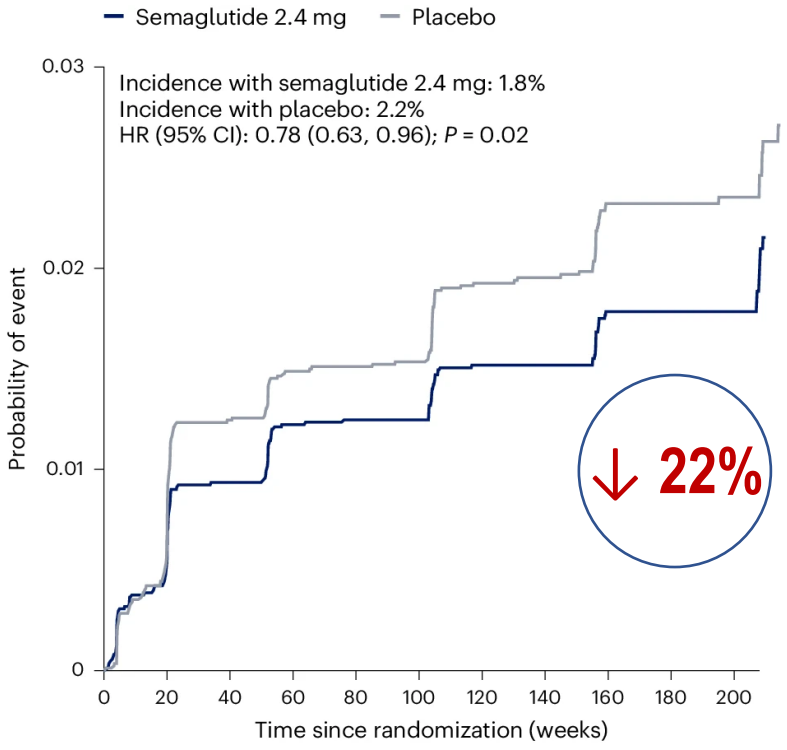
(–37.82%, –39.70 to –35.90)



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.

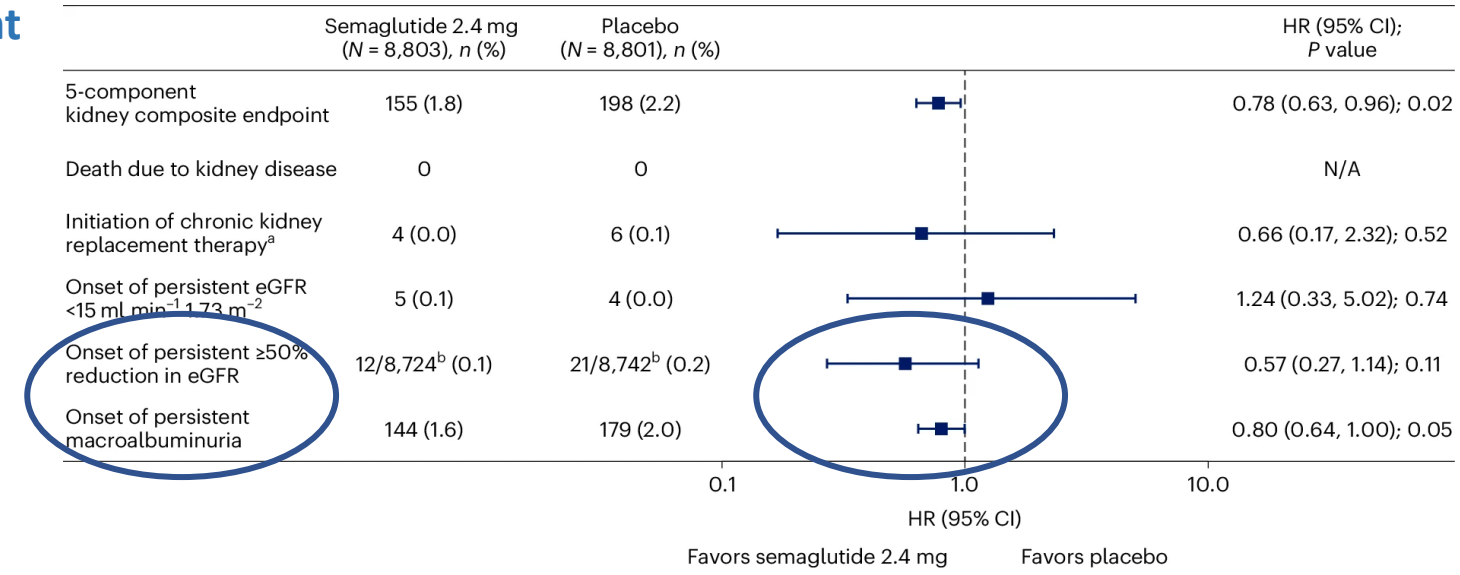
SELECT: Long-term kidney outcomes

Main 5-component kidney composite endpoint



Patients at risk

Semaglutide 2.4 mg	8,803	8,716	8,623	8,536	8,464	8,390	7,904	6,747	5,813	4,540	2,643
Placebo	8,801	8,699	8,573	8,483	8,392	8,321	7,842	6,665	5,734	4,456	2,576



Effect of semaglutide 2.4 mg on continuous kidney endpoints

eGFR at 104 weeks
↑ 0.75 ml/min

Annual eGFR slope
↑ 0.39 ml/min

UACR
↓ 10.7%

Other pre-specified kidney endpoints
HR 0.82
(0.69, 0.97; *P*=0.02)

Colhoun HM, Lingvay I, Brown PM, Deanfield J, Brown-Frandsen K, Kahn SE, Plutzky J, Node K, Parkhomenko A, Rydén L, Wilding JPH, Mann JFE, Tuttle KR, Idorn T, Rathor N, Lincoff AM. Long-term kidney outcomes of semaglutide in obesity and cardiovascular disease in the SELECT trial. Nat Med. 2024 May 25.

Potential Actions of GIP and GLP-1 Based on Preclinical and Clinical Research

GLP-1 Receptor Agonism

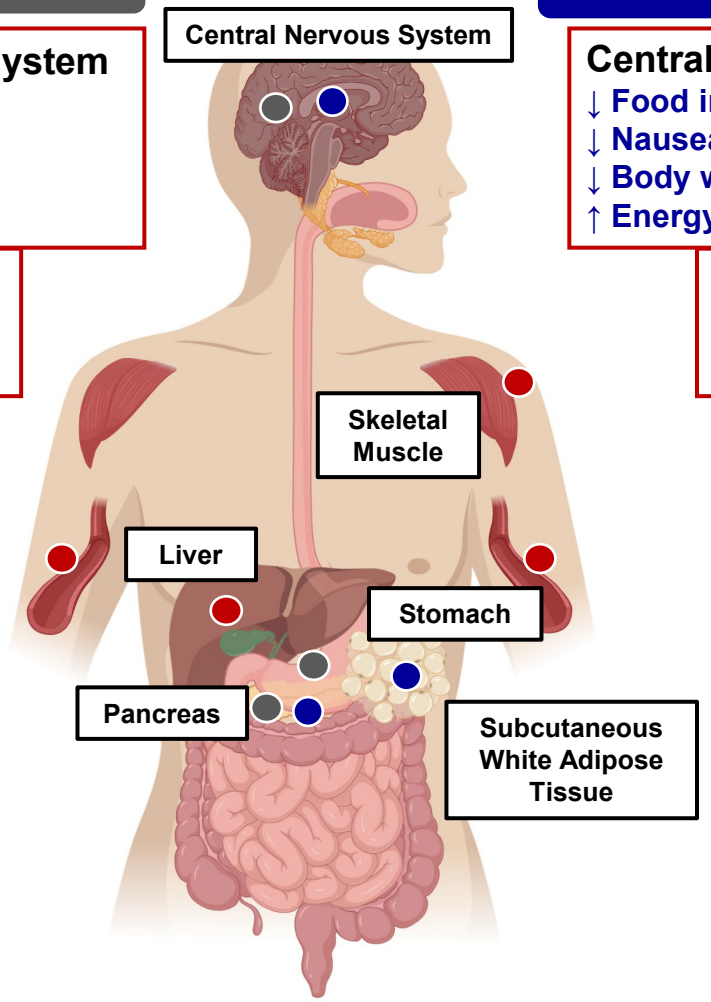
Central Nervous System
↑ Satiety
↓ Food Intake
↑ Nausea
↓ Body Weight

Pancreas
↑ Insulin
↓ Glucagon

Stomach
↓ Gastric Emptying

Systemic
↓ Hyperglycaemia

Liver
↑ Insulin Sensitivity
↓ Hepatic Glucose Production
↓ Ectopic Lipid Accumulation



- GLP-1 Receptor Agonism
- GIP Receptor Agonism
- Indirect Action

GIP Receptor Agonism

Central Nervous System
↓ Food intake
↓ Nausea
↓ Body weight
↑ Energy expenditure

Pancreas
↑ Insulin
↑ Glucagon (glucose dependent)

Subcutaneous White Adipose Tissue
↑ Insulin Sensitivity
↑ Lipid Buffering Capacity
↑ Blood Flow
↑ Storage Capacity
↓ Proinflammatory Immune Cell Infiltration

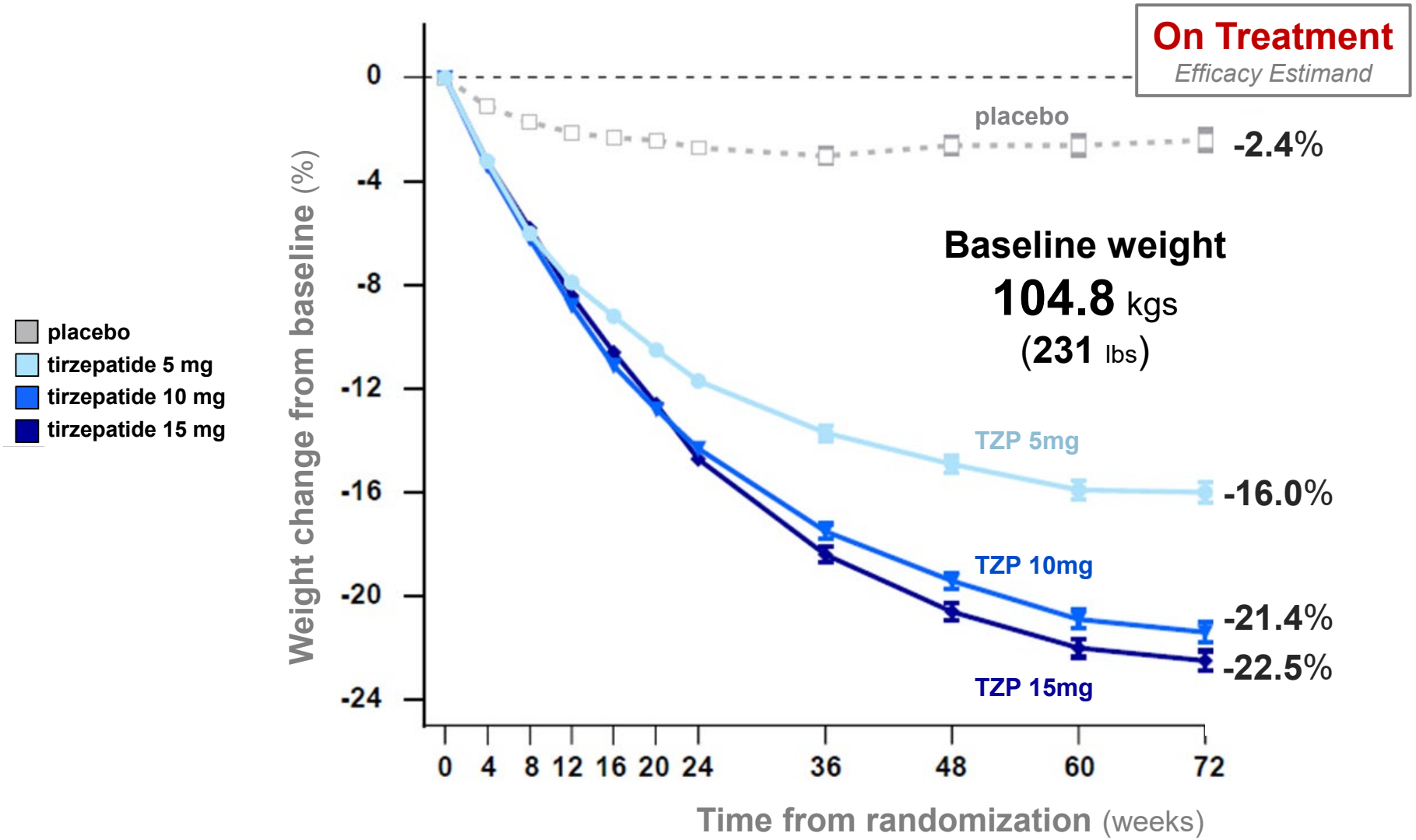
Systemic
↓ Hyperglycaemia, Dietary Triglyceride

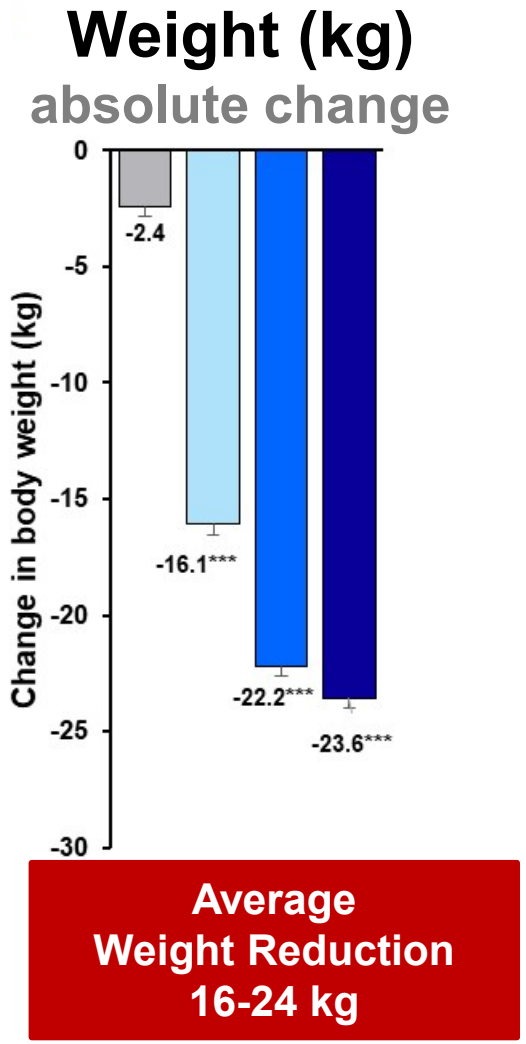
Skeletal Muscle
↑ Insulin Sensitivity
↑ Metabolic Flexibility
↓ Ectopic Lipid Accumulation

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

Adapted from: Samms RJ, et al. Trends Endocrinol Metab. 2020;31(6):410-421

SURMOUNT 1: Weight Reduction Over 72 weeks (absolute change)





Average Weight Reduction 16-24 kg

TZP = Tirzepatide.

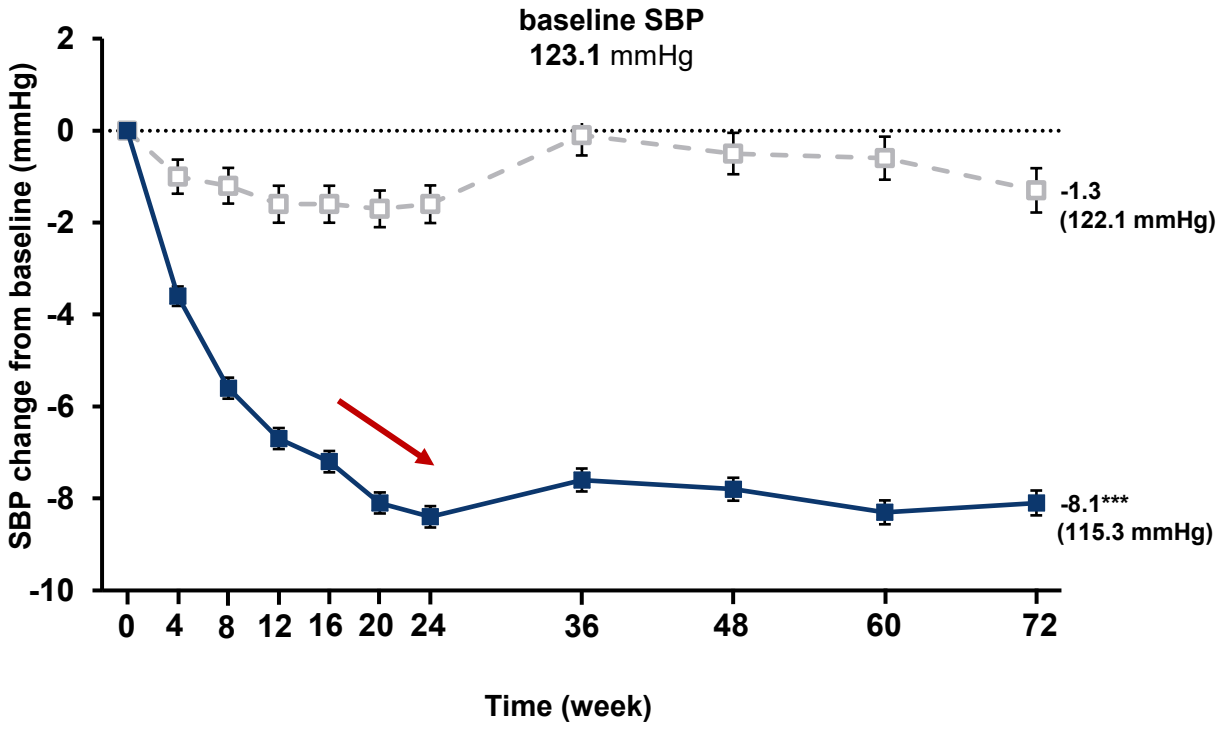
Jastreboff AM et al. N Engl J Med. 2022 Jul 21;387(3):205-216.

SURMOUNT 1:Change in Blood Pressure

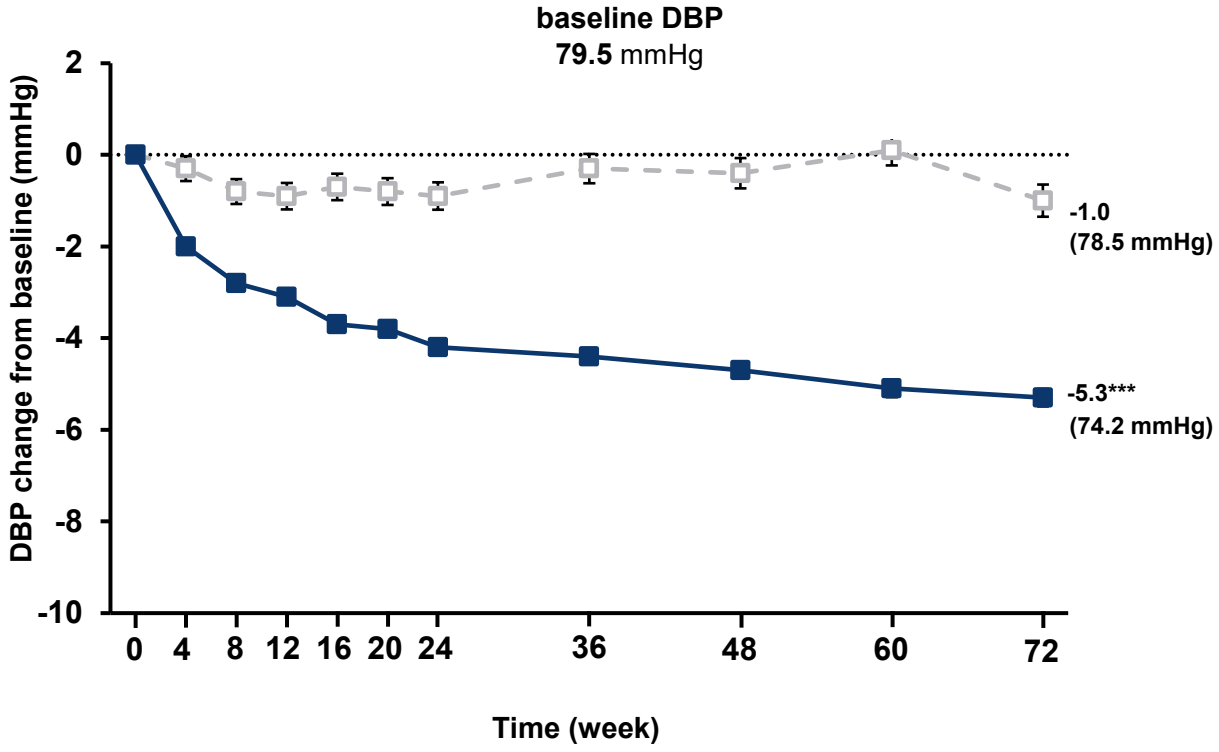
On Treatment
Efficacy Estimand

placebo
tirzepatide pooled (5/10/15 mg)

Systolic Blood Pressure



Diastolic Blood Pressure

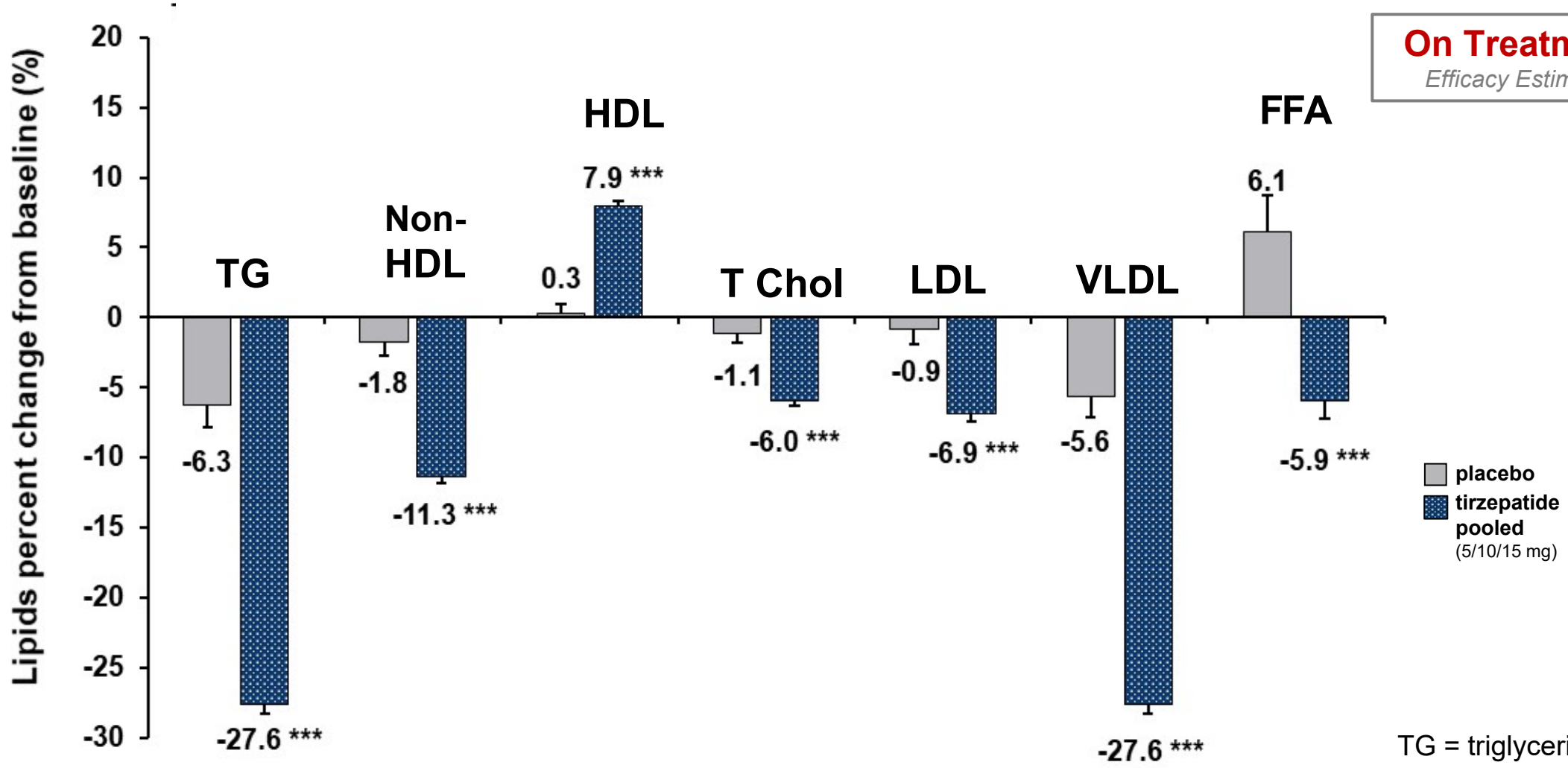


Improvements in blood pressure do not appear to be dependent on the magnitude of weight loss

DBP = Diastolic blood pressure; SBP = Systolic blood pressure.

Jastreboff AM, et al. N Engl J Med 2022. Jul 21;387(3):205-216

SURMOUNT 1: Change in Lipids



TG = triglycerides
FFA = Free Fatty Acids

FFA = Free fatty acids; HDL = High-density lipoprotein; LDL = Low-density lipoprotein; T = Total; TG = Triglycerides; VLDL = Very low-density lipoprotein.

Jastreboff AM, et al. N Engl J Med 2022. Jul 21;387(3):205-216

A Study of Tirzepatide on the Reduction on Morbidity and Mortality in Adults With Obesity

SURMOUNT-MMO

International, randomized, double-blind, placebo controlled phase III trial

Patients with obesity without diabetes; BMI ≥27 kg/m2; with or at high risk for ASCVD (N=15,374)

Tirzepatide sc, tolerated dose escalat.

[Time Frame: Up to 5 Years]

Placebo sc

Estimated Primary Completion Date: October 2027
(Final data collection date for primary outcome measure)

- **Primary outcome**: Time to first occurrence of All-Cause Death, Nonfatal Myocardial Infarction (MI), Nonfatal Stroke, Coronary Revascularization, or Heart Failure Events
- **Select secondary outcomes**: time to T2D onset, composite renal death/ESRD/eGFR decline/HF events/body weight change (hierarchical), time to first occurrence of any component event of MACE-3, SF-36, MACE components, etc.

Summarizing…

- Patients with overweight/obesity and CVD may benefit from similar CVD **protection** under GLP1 RA treatment like the diabetic counterpart.
- The CV protection yielded by Semaglutide 2.4 mg spreads across **subgroups**.
- Indirect evidence on the **potential** benefits of Tirzepatide for CVD exists, data in patients selected for CVD are awaited.
- The mechanisms are likely **composite** (and direct?), yet they remain to be fully elucidated (ectopic fat, CV risk factors, systemic proinflammation, prothrombotic risk, etc)
- Whether this CVD protection applies to those with **lower** CVR is unknown.
- Future guidelines and health policies may (and should) take this into account to grant GLP-1 RA **availability** to patients with obesity prone to CVD.