

Cardiovascular Outcome with Semaglutide in Patients with Obesity without Diabetes: The SELECT Trial.

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Obesity and CVD

4 billion

people worldwide
(51% of the population
over 5 years old)
predicted to have
overweight or obesity
by 2035¹

In 2015,
4 million

deaths were attributed
to high BMI, with
2/3rd due to
CVD²

¹World Obesity Atlas 2023.

²GBD 2015 Obesity Collaborators. NEJM 2017;377:13.

Obesity and CV Disease

Multiple Mechanisms Link Obesity with CVD

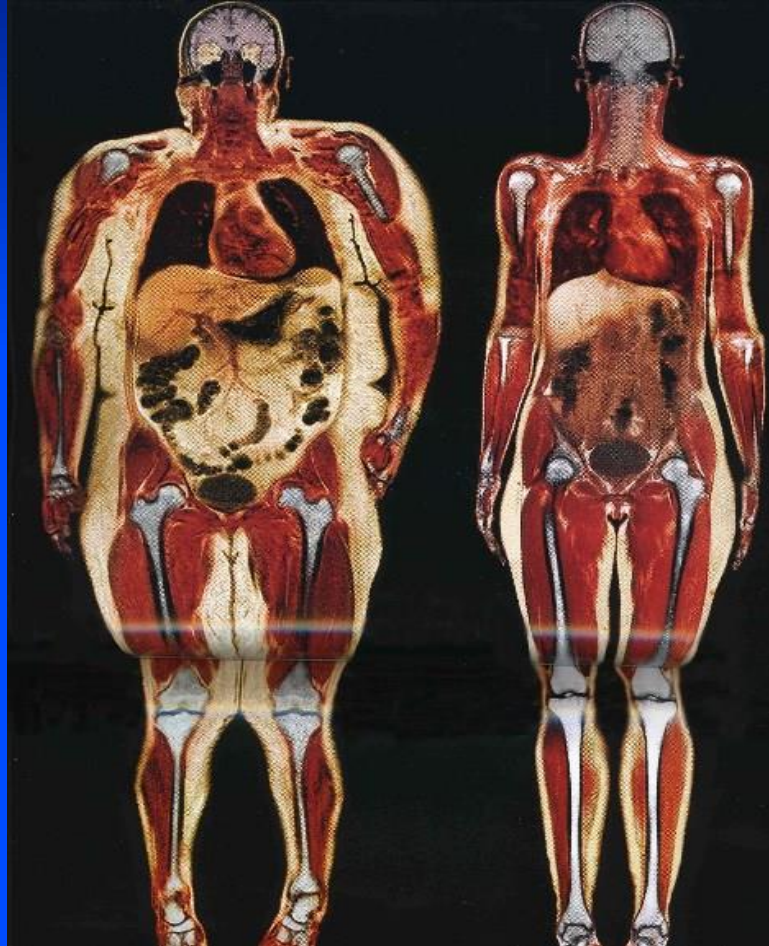
Obesity increases risk of CV risk factors

Dyslipidemia

Hyperglycemia

Hypertension

OSA



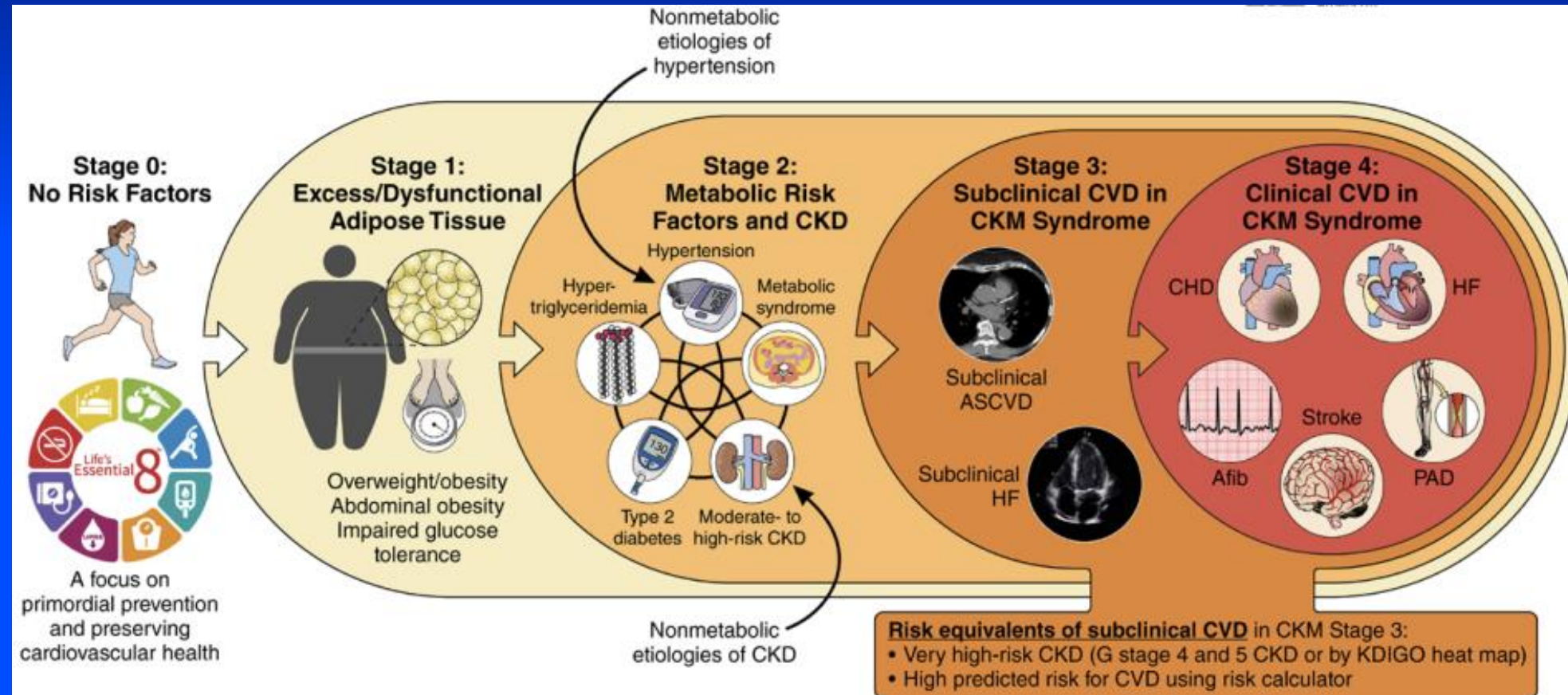
Visceral and ectopic fat mass is a major cardiometabolic risk factor

Production of adipokines

Production of pro-inflammatory cytokines

AHA Presidential Advisory 2023

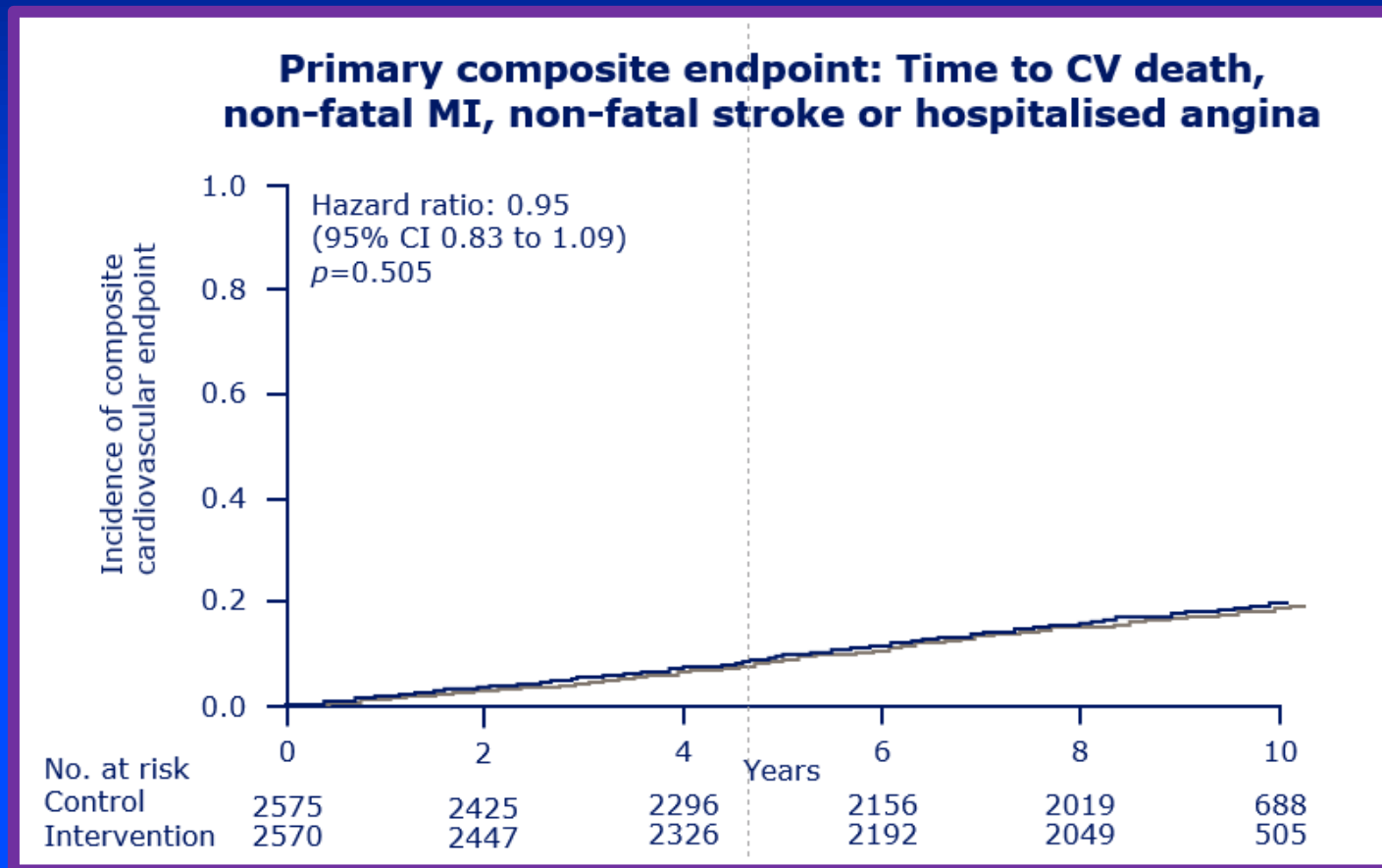
Excess / Dysfunctional Adipose Tissue is a Root Cause of Cardiovascular Disease, Mediated Through CKM Syndrome



Ndumele CE, et al. Circulation 2023;148:1606.

Look AHEAD

CVOT of Lifestyle Intervention in Subjects with T2D



Look AHEAD

CVOT of Lifestyle Intervention in Subjects with T2D Post-Hoc Analysis in Responders

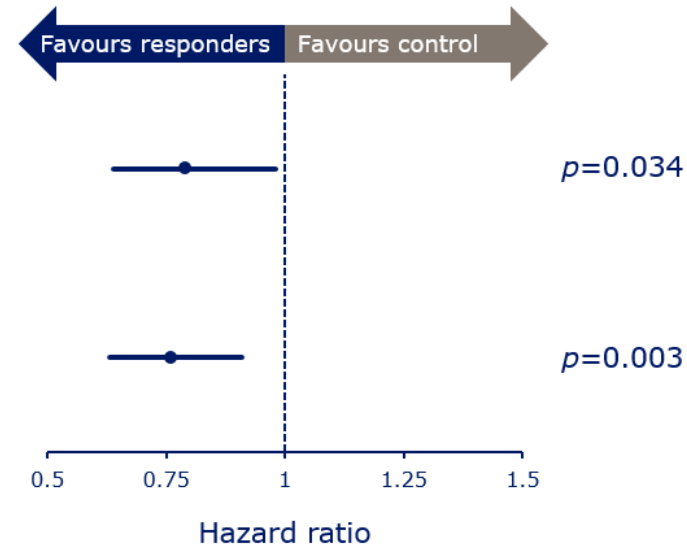
Responder: lost at least 10% of their body weight in the first year of the study

Primary outcome – 21% lower

CV death, non-fatal acute MI, non-fatal stroke, or admission to hospital for angina

Secondary outcome – 24% lower

As above plus CABG, carotid endarterectomy, PCI, hospitalisation for CHF, peripheral vascular disease, or total mortality



Look AHEAD Research Group. Lancet Diabetes Endocrinol. 2016;4:913-921; Koster-Rasmussen R, et al. PloS One. 2016;11:e0146889.

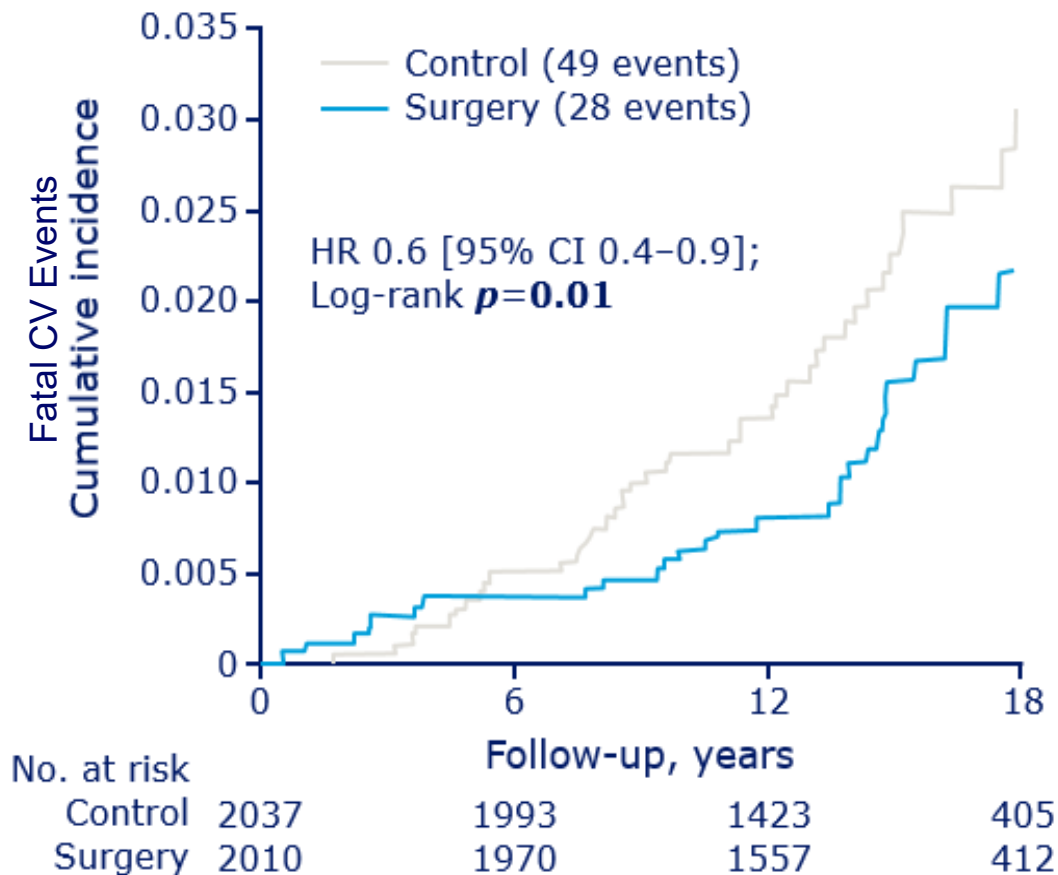
Prior CVOT's of Drugs in Obesity

	SCOUT	CRESCENDO	LIGHT	CONVENE	CAMELLIA-TIMI
Intervention	Sibutramine	Rimonabant	Naltrexone/ Bupropion	Naltrexone/ Bupropion	Lorcaserin
Date started	Jan 2003	Dec 2005	Jun 2012	Dec 2015	Jan 2014
Date ended	Mar 2009	Apr 2009	Aug 2015	Apr 2016	Sep 2018
Patients planned (enrolled)	10777	18695	9810>8900 (8910)	8800 (67)	12000
Design	Superior	Superior	Non-inferior	?	Non-inferior
Event rate	7%	3%	1.5%	?	1.5%
Risk reduction	11.4%	15%	HR:<1.4	?	HR:<1.4
Discontinued	30%	10%	1.2%	?	5%
Primary Outcome	3P-MACE + resuscitated cardiac arrest	3P-MACE + hospitalisation	3P-MACE + angina needing hospitalisation	3P-MACE	1. 3P-MACE 2. T2D 3. MACE+
Results	Harm	Terminated	Terminated	Terminated	Non-inferiority established

James et al. N Engl J Med 2010;363:905–17; Topol et al. Lancet 2010;376:517–23; Nissen et al. JAMA 2016;315:990–1004;
ClinicalTrials.gov (NCT02638129); Bohula et al. N Engl J Med 2018; 379:1107-1117

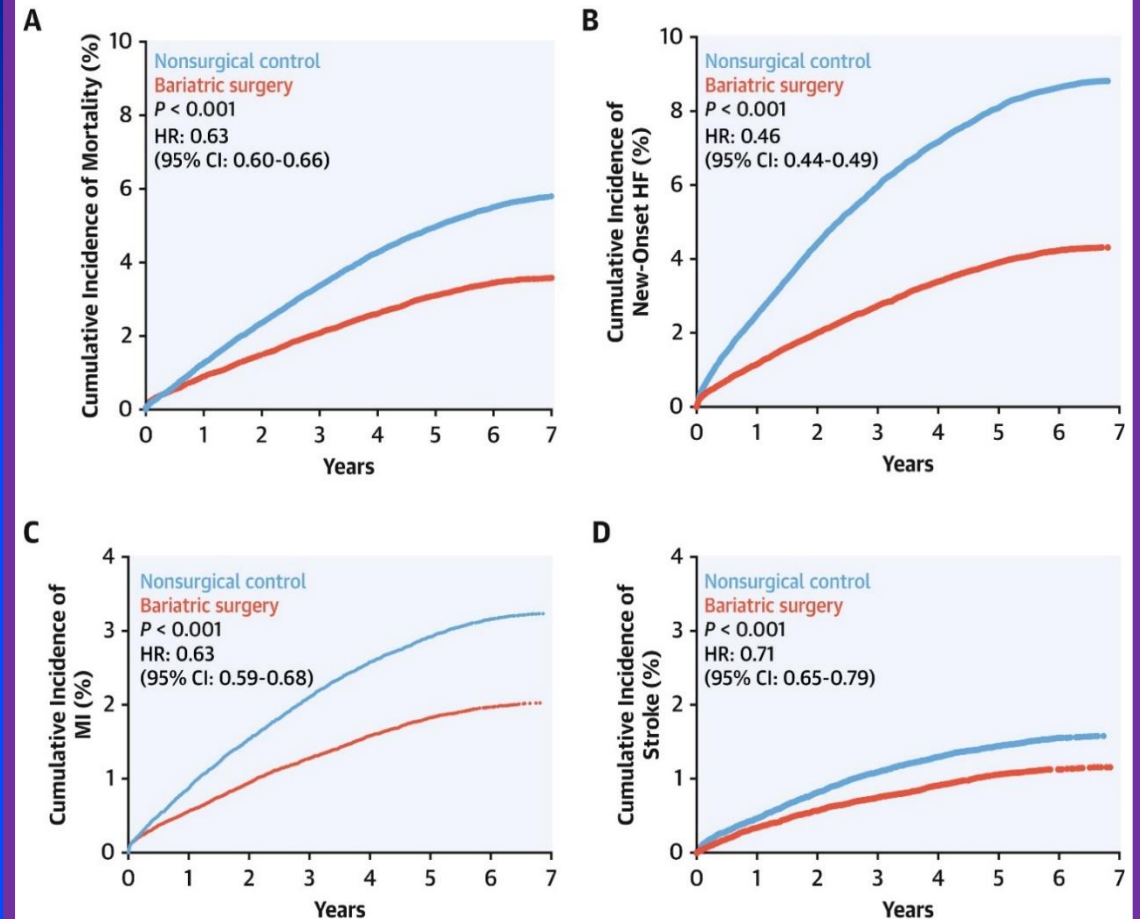
Bariatric Surgery and CV Outcome

SOS Study – Nonrandomized



Sjostrom L, et al. JAMA. 2012;307:56.

Medicare Registry Study 94,885 Matched Pairs

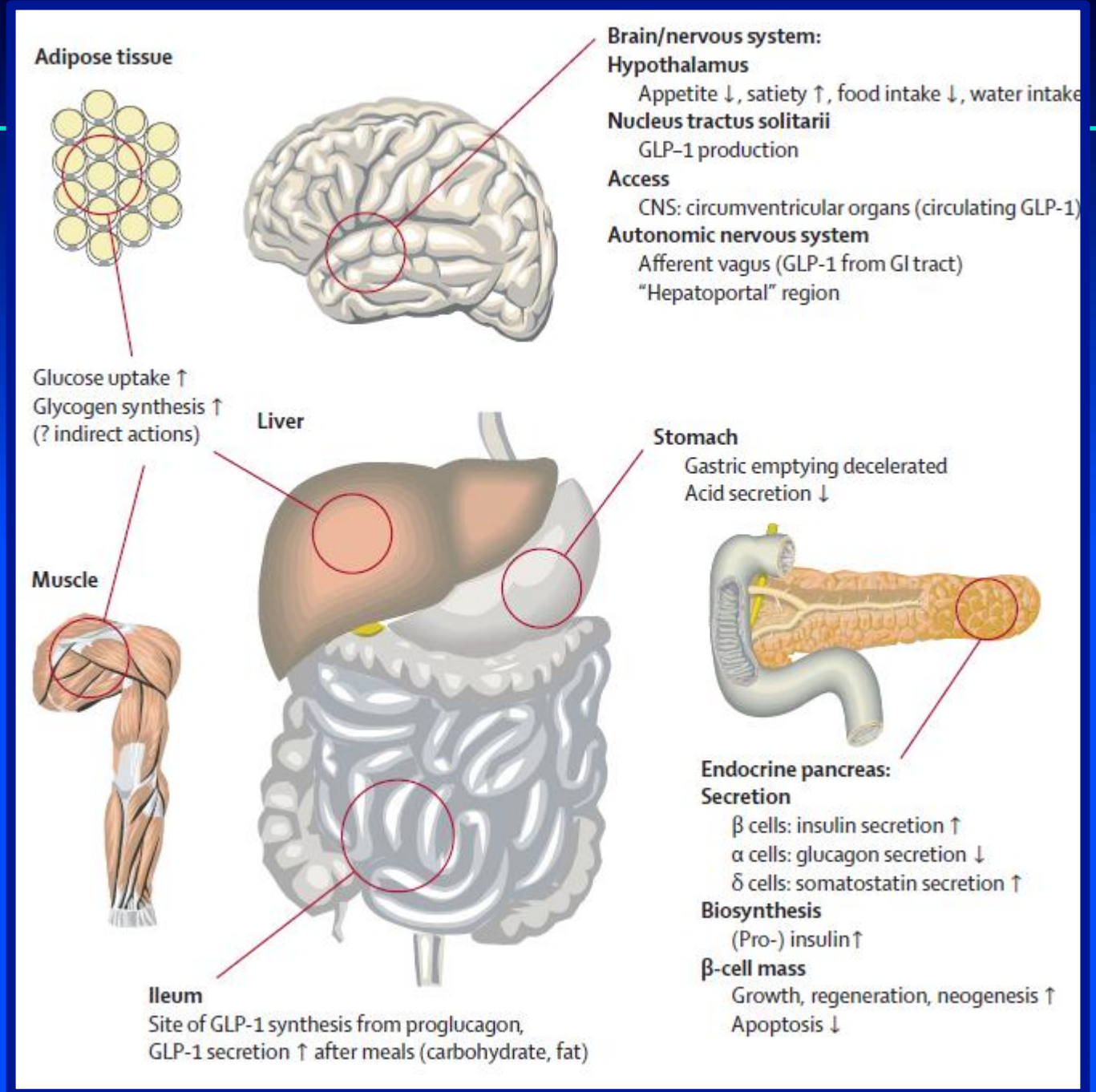


Mentias A, et al. JACC 2022;79:1429.

Physiology of GLP-1

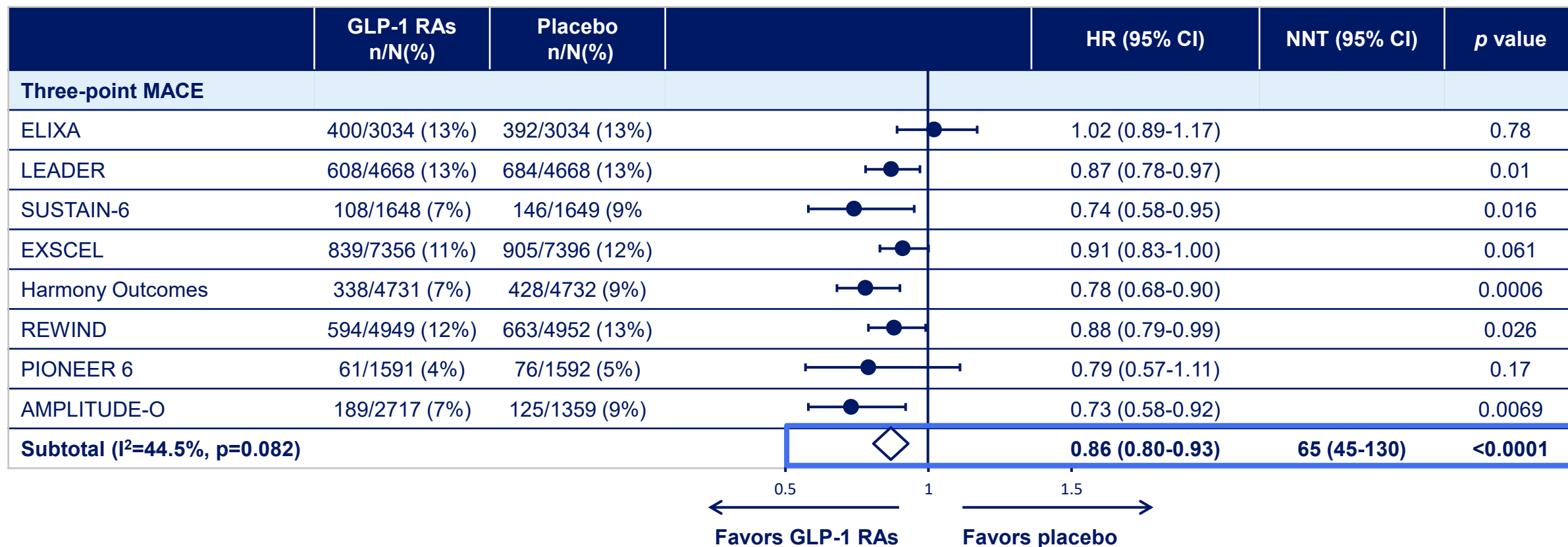
Secretion and Action on Receptors in Different Organs and Tissues

Drucker DJ and Nauck MA.
Lancet 2006; 368: 1696.



GLP-1 RA – Meta-Analysis in T2D

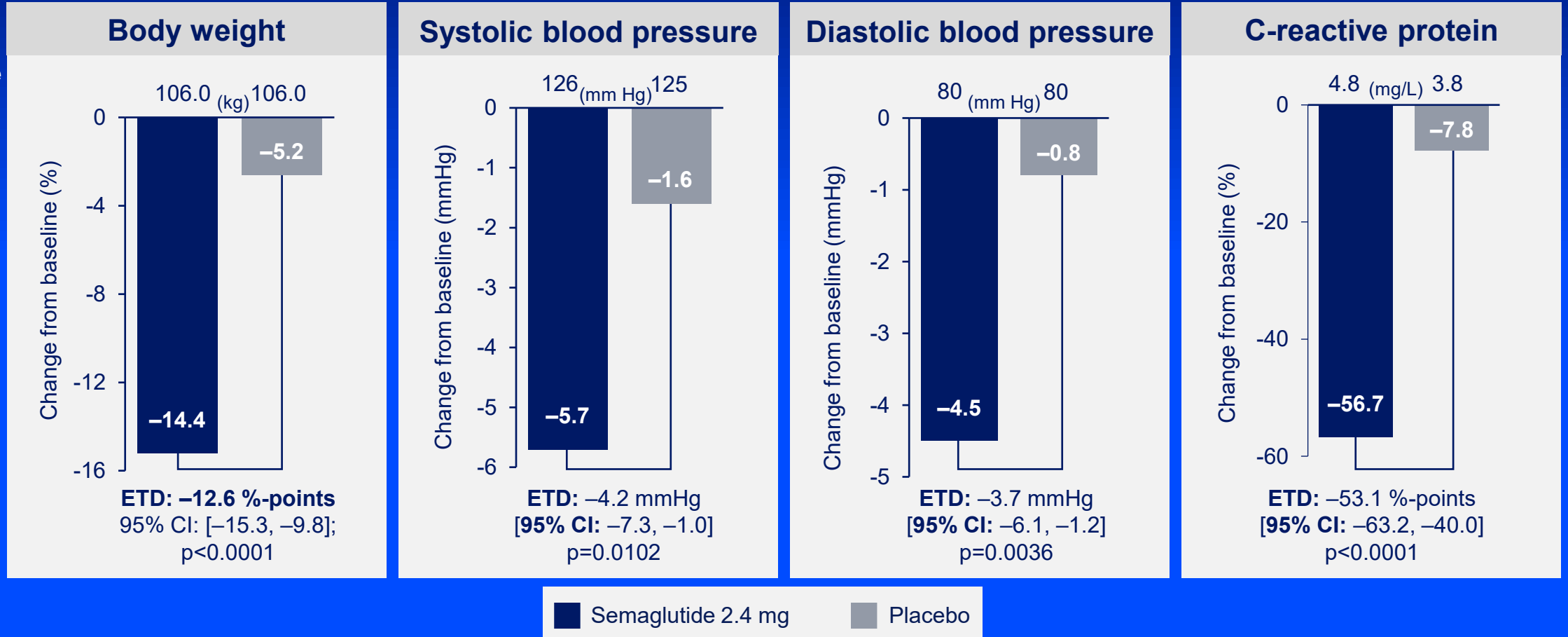
MACE – CV Death, MI, Stroke



Semaglutide 2.4 mg SC Weekly

Effect on CV Risk Factors after 2 Years – STEP 5 trial

Mean
baseline
value:



Garvey W et al. Nature Medicine 2022;28:2083.

Semaglutide for CV Risk Reduction in Patients With Overweight or Obesity and CVD Without Diabetes CV Outcome Superiority Trial

- Overweight or obesity
BMI ≥ 27 kg/m²
- Established CVD
- No prior diabetes
HbA_{1c} < 6.5%
- Age ≥ 45 yrs

Randomization (1:1)

Semaglutide SC 2.4 mg once-weekly

Placebo SC once-weekly

Event-driven, powered for 17% RRR, 1225 first MACE

Enrolled 17,604 patients

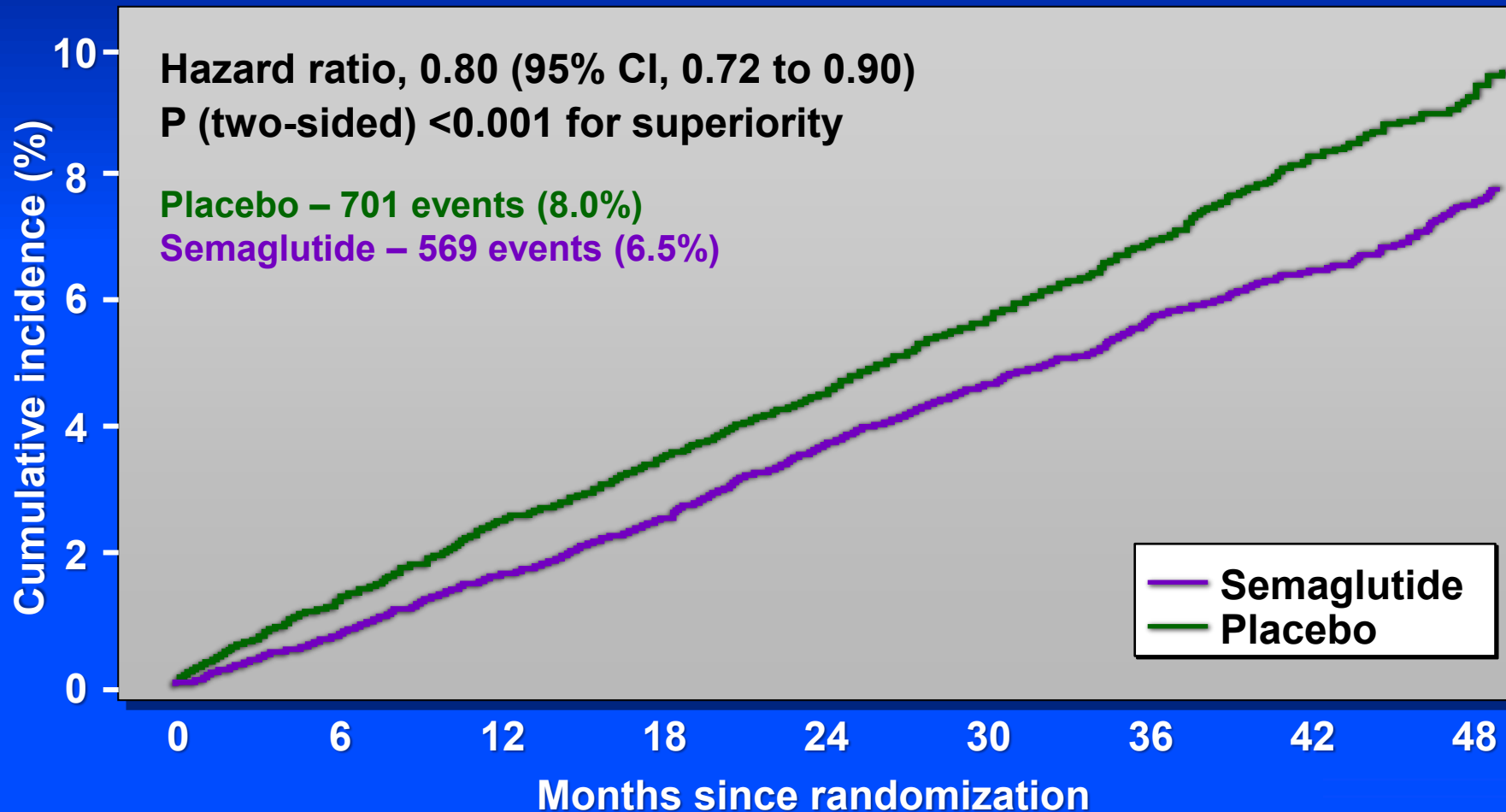
804 sites in 41 countries

Mean Follow-up – 39.8 months

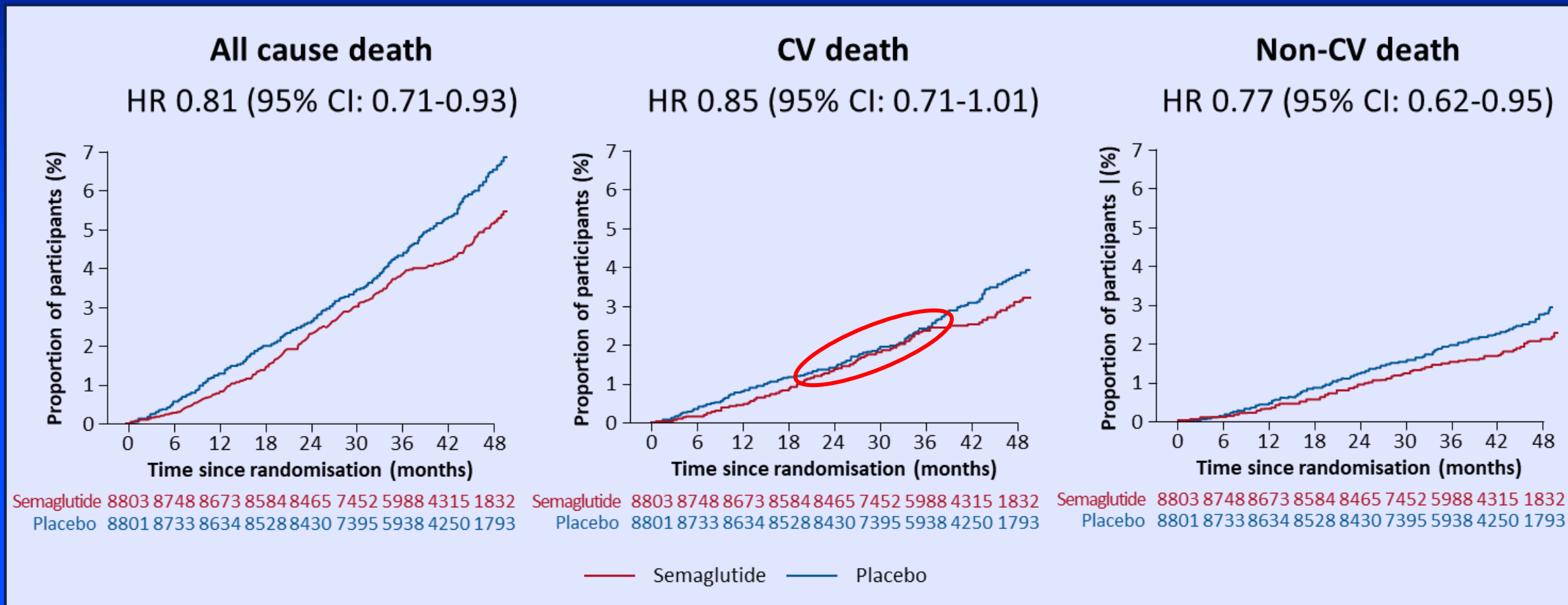
Primary endpoint:

MACE (CV death, nonfatal MI, nonfatal stroke) in time-to-first-event analysis

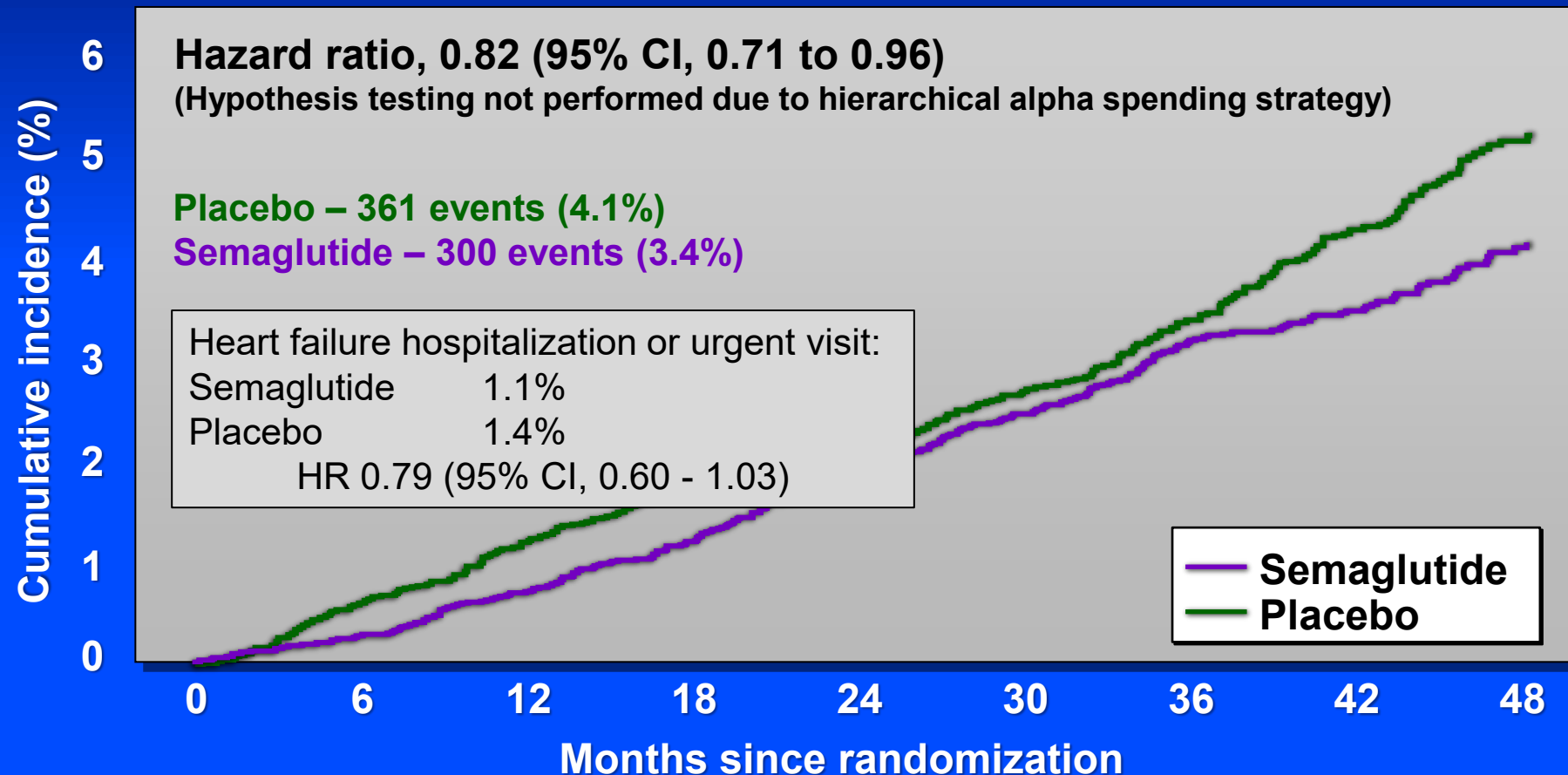
CV Death, Nonfatal MI, or Nonfatal Stroke Primary Cardiovascular Composite Endpoint



Death by Treatment Group



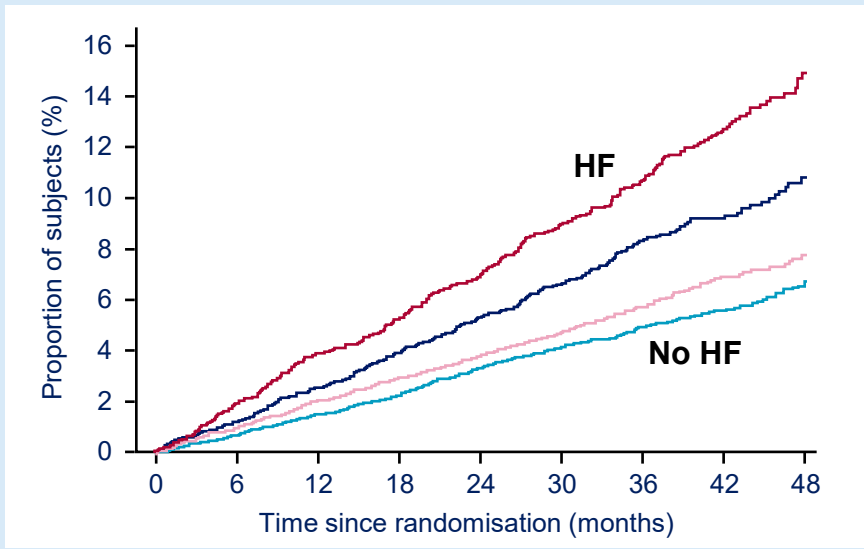
Heart Failure Composite CV death or hospitalization or urgent visit for heart failure



Outcomes in Heart Failure

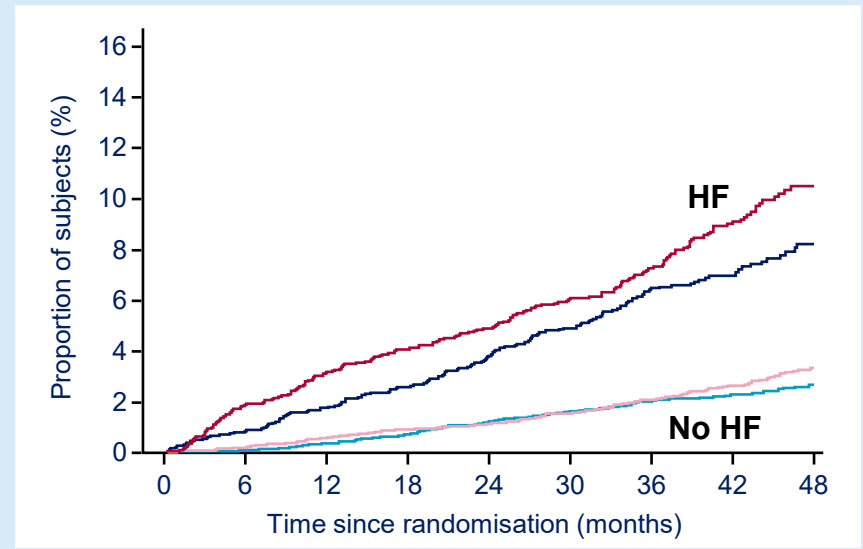
4286 Patients with History of HF at Enrollment

MACE



Semaglutide 2.4 mg vs. placebo	HR (95% CI)	Interaction p-value
HF	0.72 (0.60–0.87)	
No HF	0.84 (0.74–0.97)	0.1934

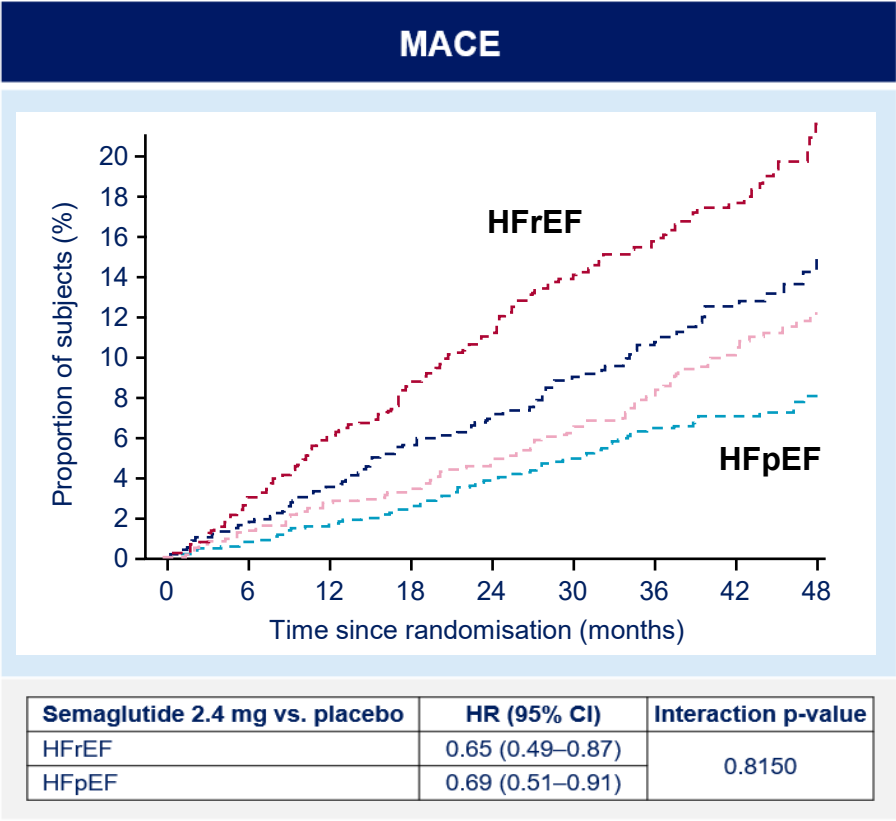
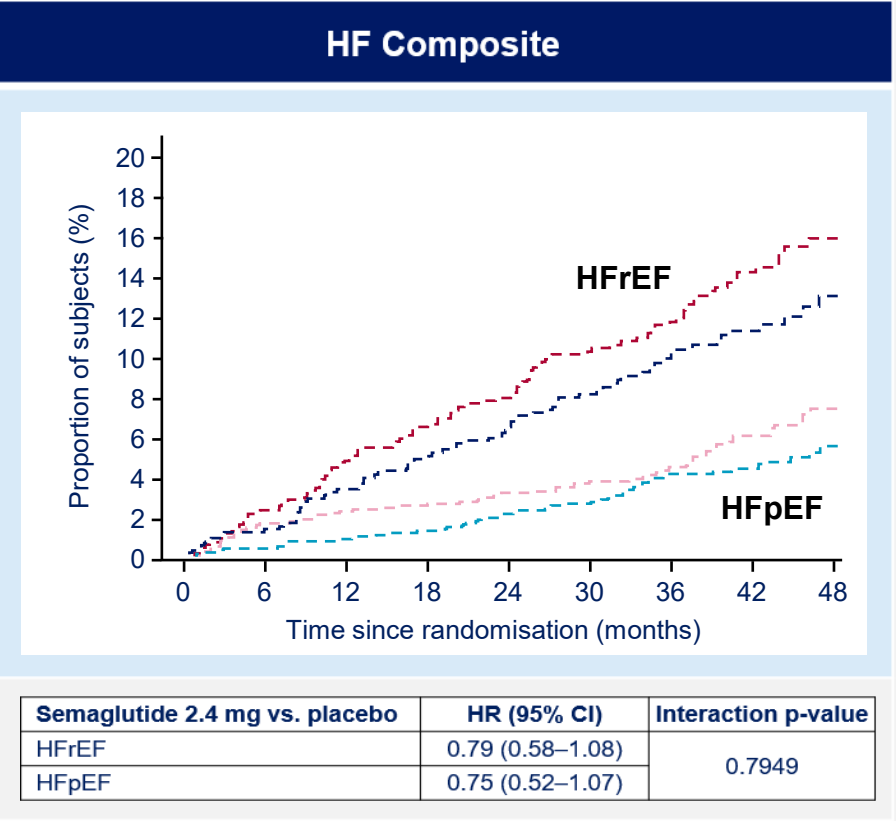
HF Composite



Semaglutide 2.4 mg vs. placebo	HR (95% CI)	Interaction p-value
HF	0.79 (0.64–0.98)	
No HF	0.85 (0.68–1.06)	0.6383

— Placebo HF — Placebo no HF — Semaglutide HF — Semaglutide no HF

Outcome by Heart Failure Subtype at Enrollment



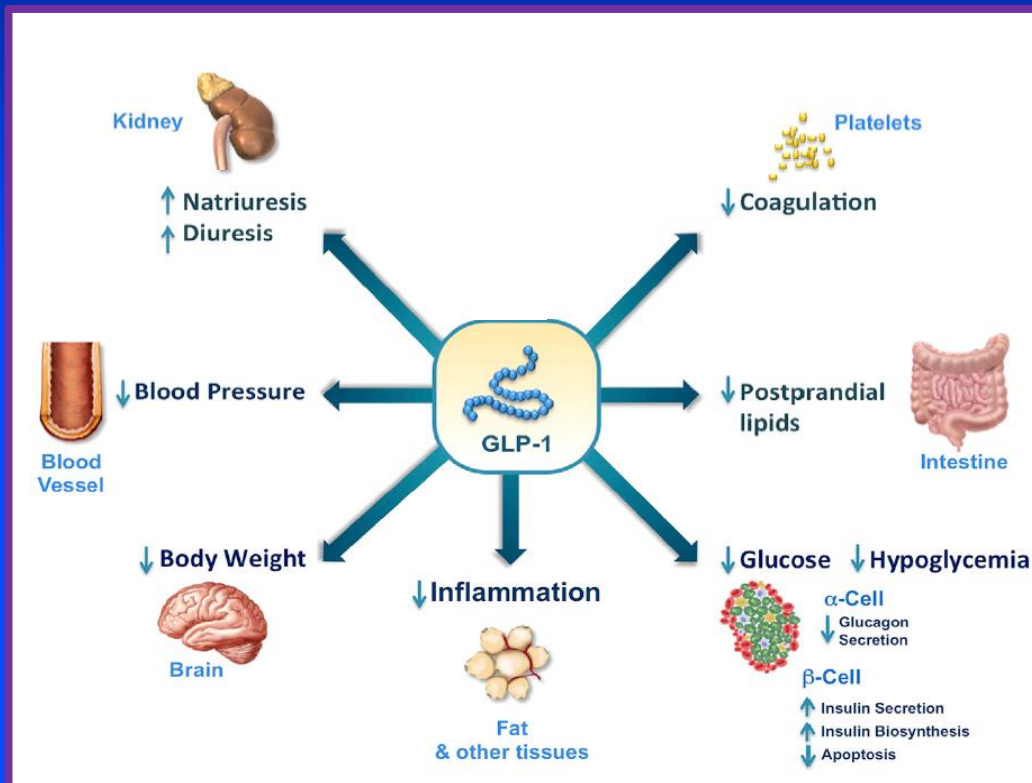
--- Placebo HFrEF --- Placebo HFpEF --- Semaglutide HFrEF --- Semaglutide HFpEF

Selected Adverse Events

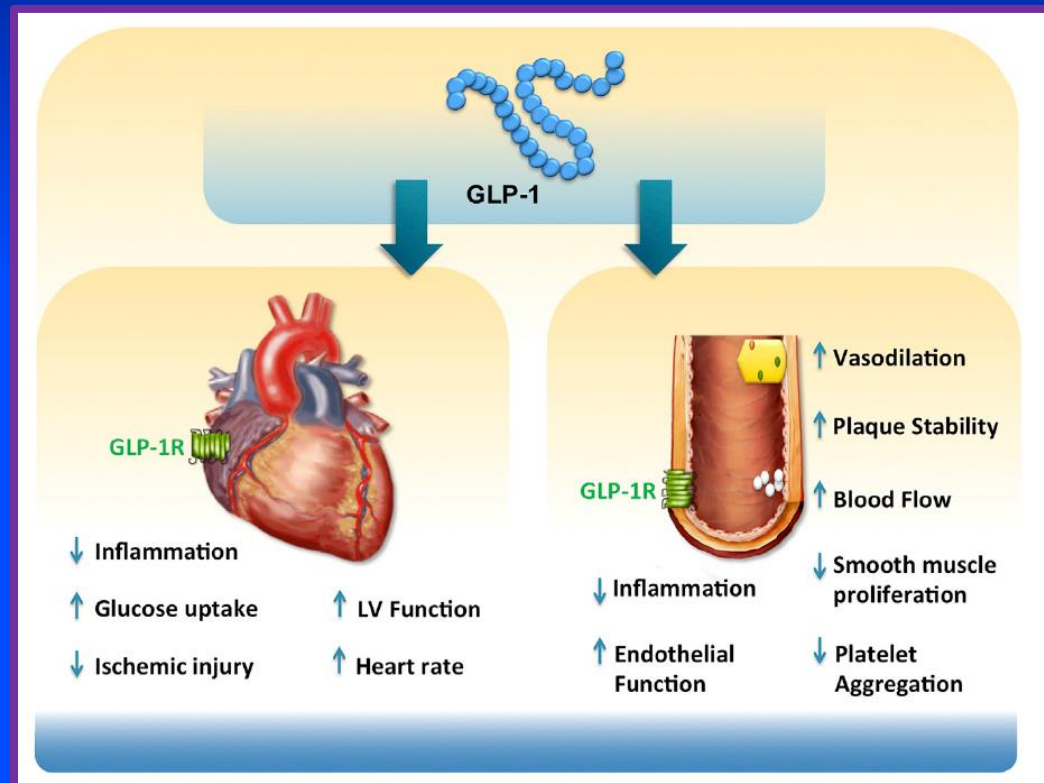
(Percent of patients)	Semaglutide	Placebo	P-Value
Serious adverse event (SAE)	33.4	36.4	<0.001
Cardiac disorders	11.5	13.5	<0.001
Infections / infestations	7.1	8.4	0.001
Nervous system	5.0	5.6	0.08
Gastrointestinal	3.9	3.7	0.48
Adverse event leading to drug D/C	16.6	8.2	<0.001
Gastrointestinal	10.0	2.0	<0.001
Metabolism / nutritional	1.2	0.3	<0.001
Adverse events of special interest			
Acute pancreatitis	0.2	0.3	0.28
Gallbladder-related	2.8	2.3	0.04
COVID-19 related	23.9	24.4	0.46
Malignant neoplasms	4.8	4.7	0.92

GLP-1 RA Effects That May Impact CVD

Indirect Systemic

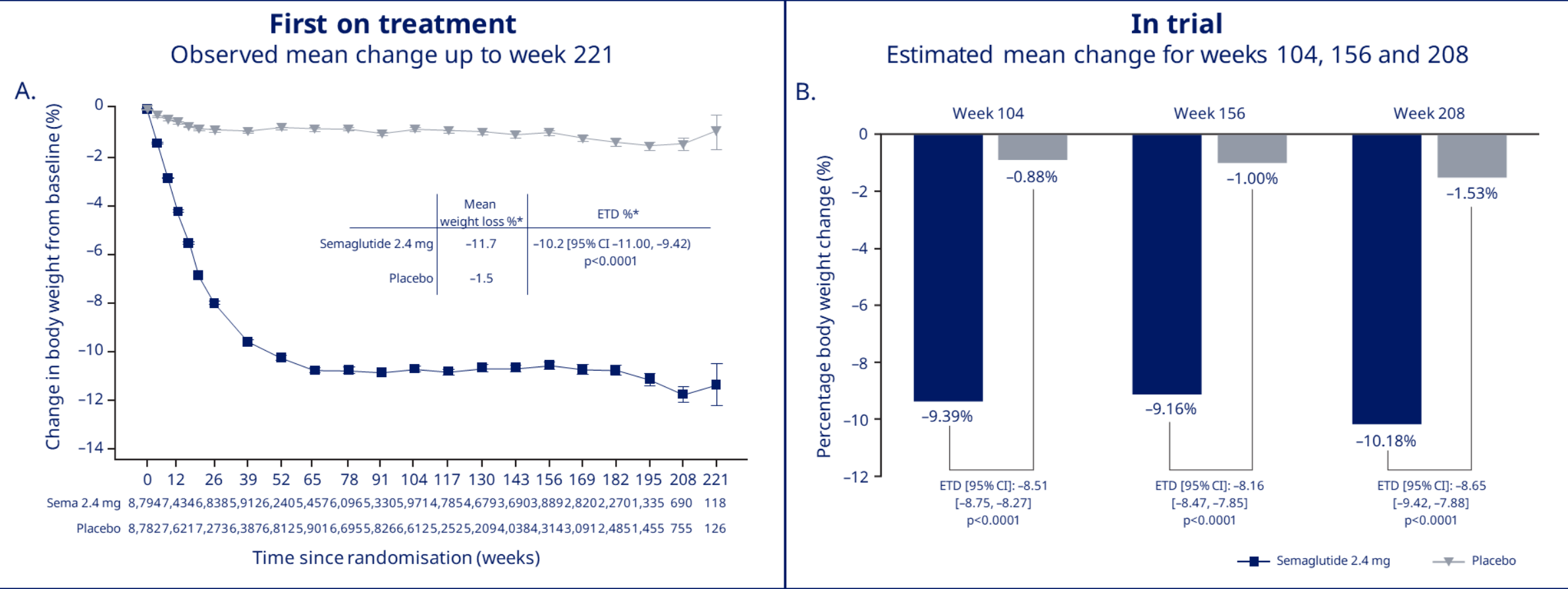


Direct Cardiovascular



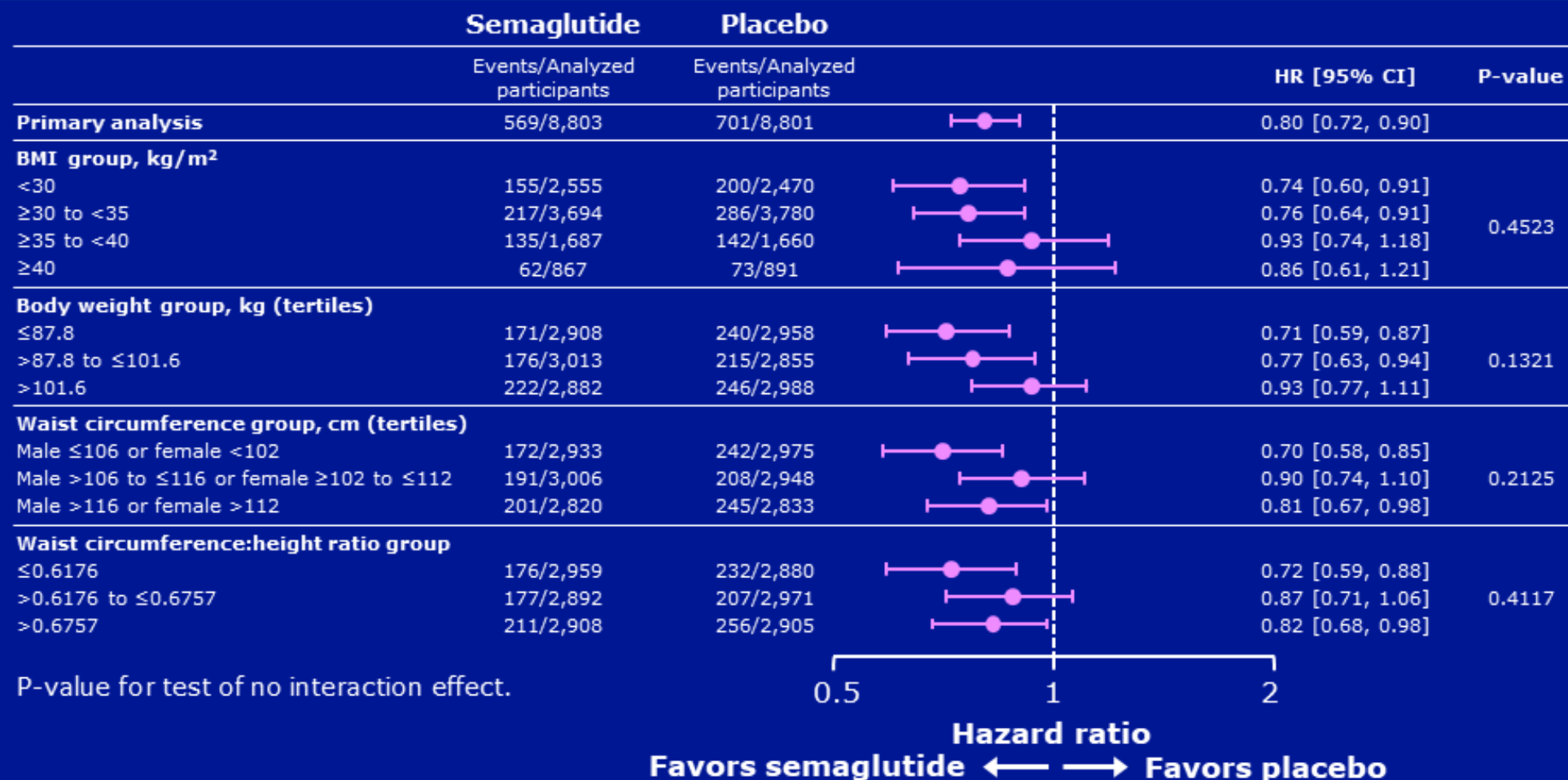
Semaglutide Effect on Weight

Effect of Semaglutide on Change in Weight



MACE Reduction with Semaglutide

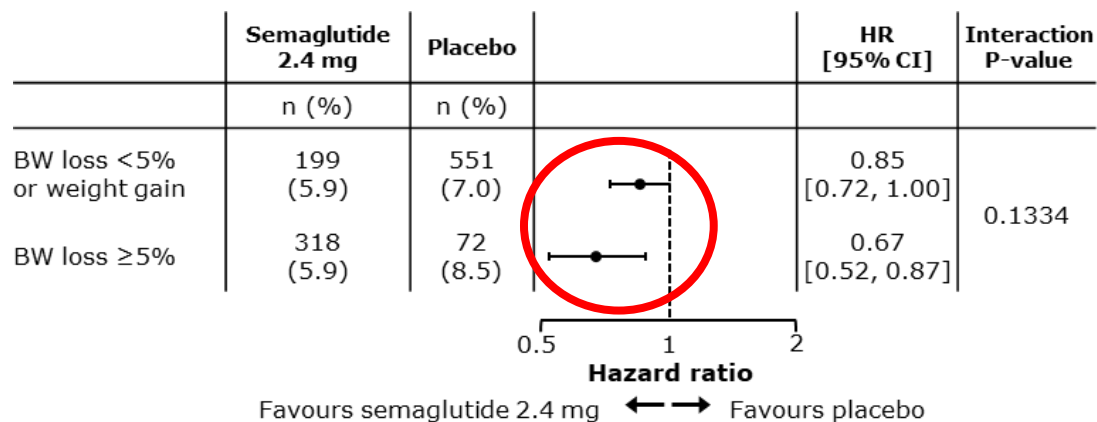
Consistent Effect Regardless of Baseline Adiposity



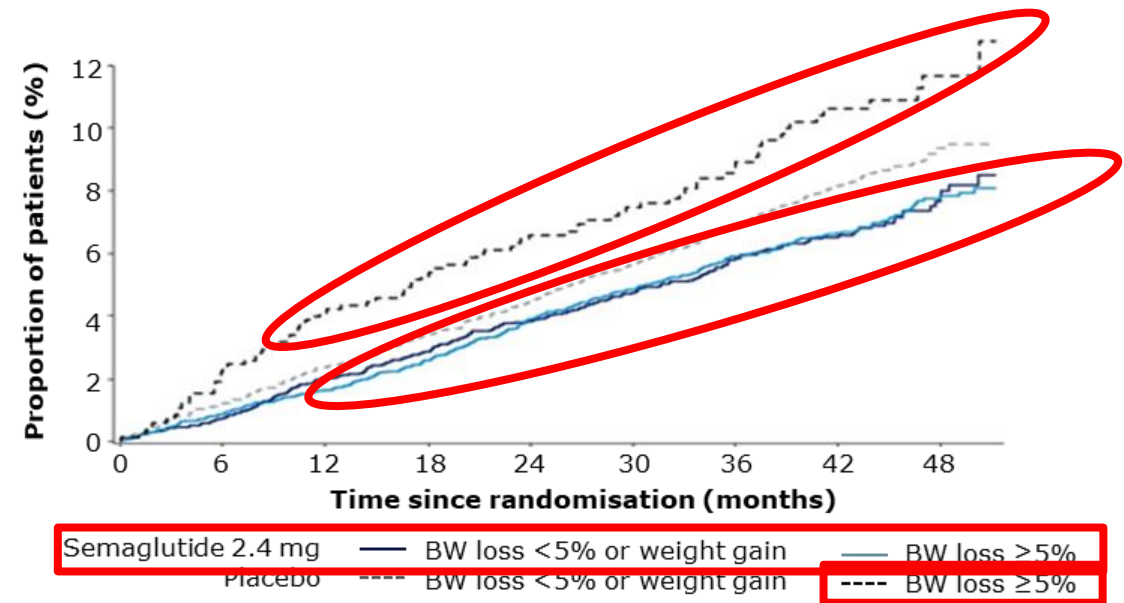
CV Benefit of Semaglutide

Independent of Extent of Weight Loss

MACE after week 20 by percentage change in body weight (baseline to week 20)

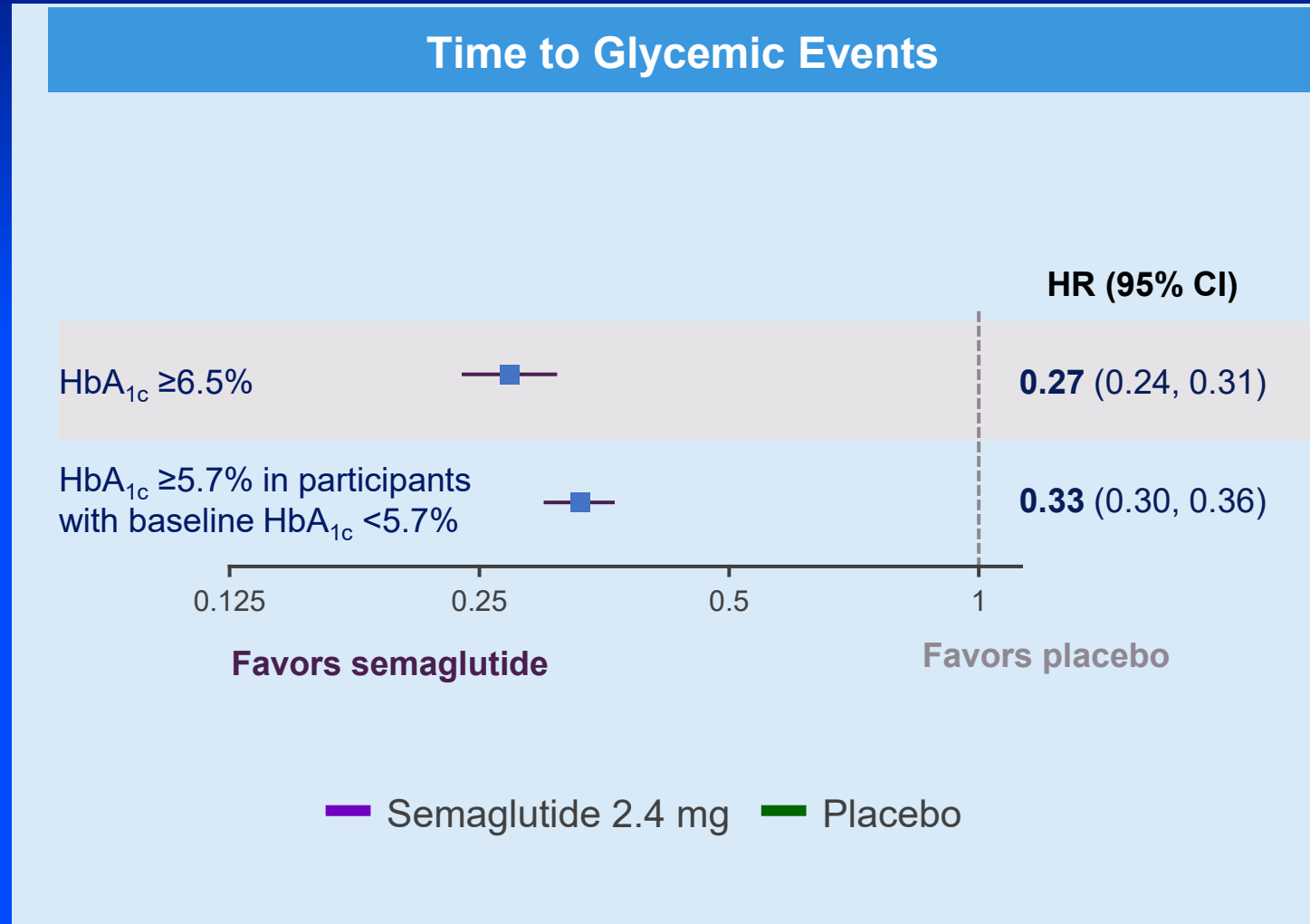


Time to first MACE by percentage change in body weight (baseline to week 20)



Improved Glycemic Control

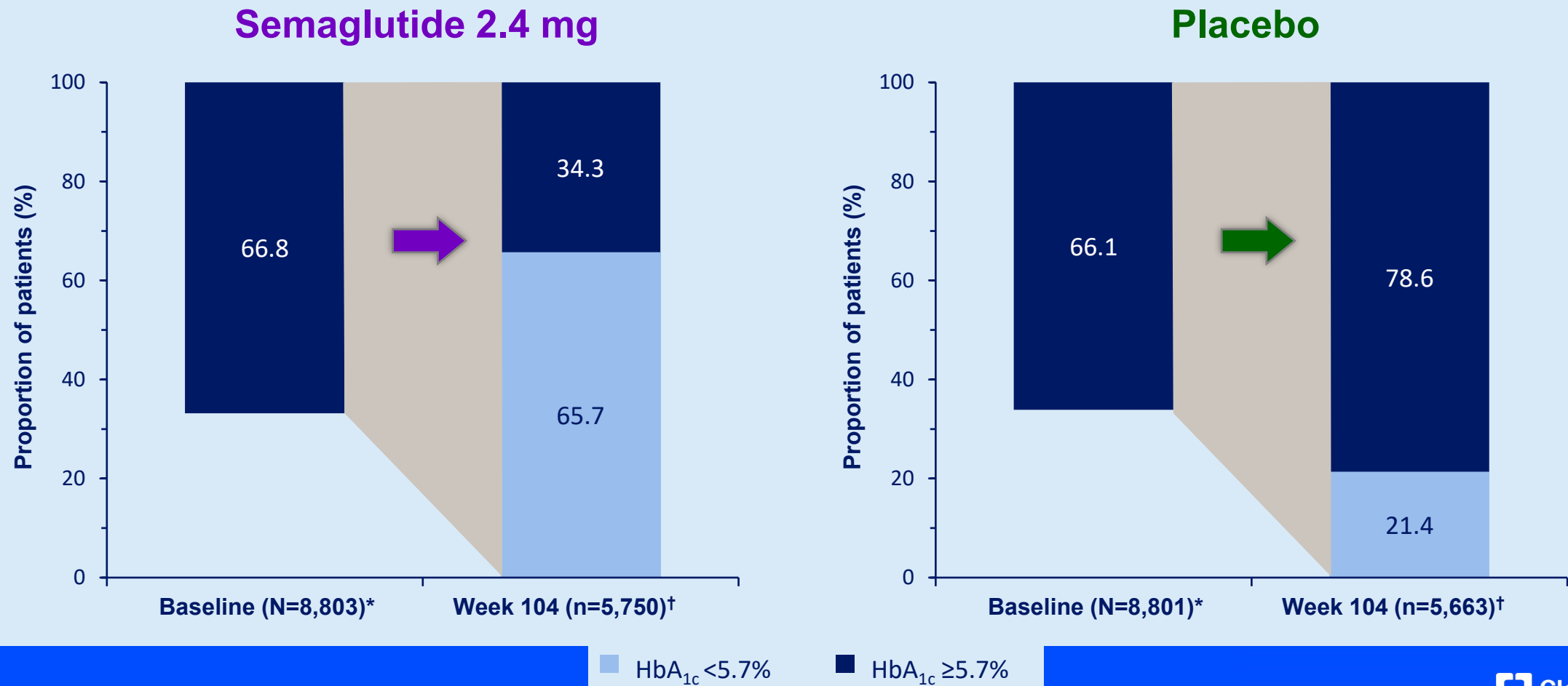
Prevention of Biochemical Diabetes and Prediabetes



Improved Glycemic Control

Biochemical Regression of Prediabetes

Change in HbA_{1c} in patients with HbA_{1c} ≥5.7% at baseline



Glycemic Control and CV Outcome

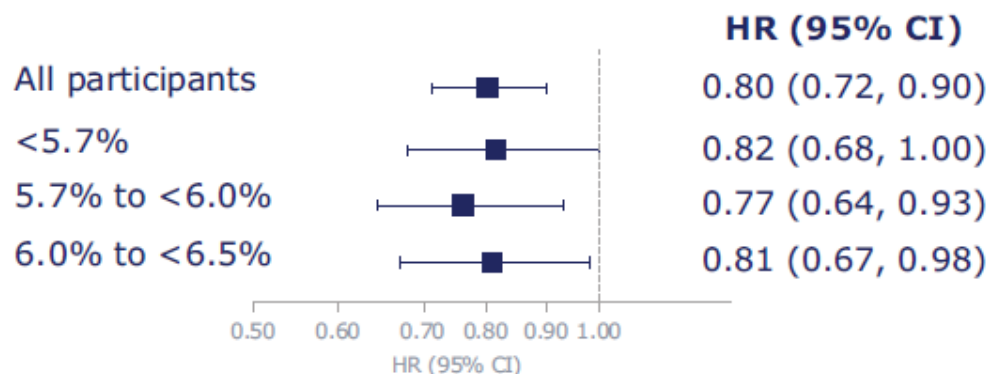
Effect Independent of Baseline or Change in HbA_{1c}

Semaglutide's effect on CV end points
was as follows:



Consistent across baseline HbA_{1c} groups
(<5.7, 5.7 to <6.0, and 6.0 to <6.5%)
for all end points except all-cause mortality*

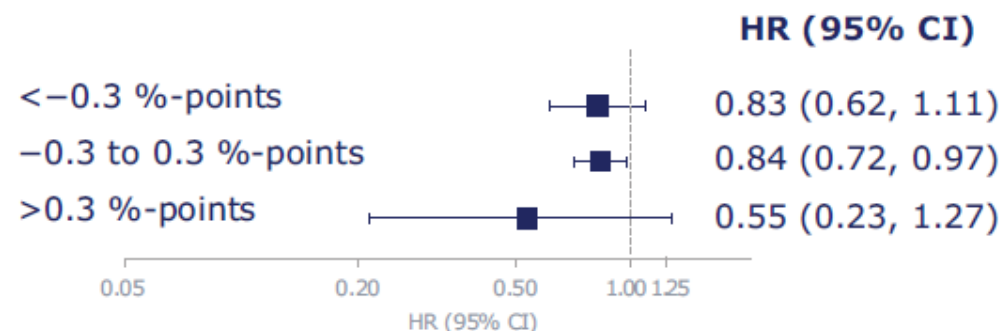
Time to first MACE by baseline HbA_{1c}



Favors **semaglutide 2.4 mg** ← → Favors placebo

Consistent across change from baseline to week 20
HbA_{1c} groups (<-0.3, -0.3 to 0.3, and >0.3 %-points)
for all end points*

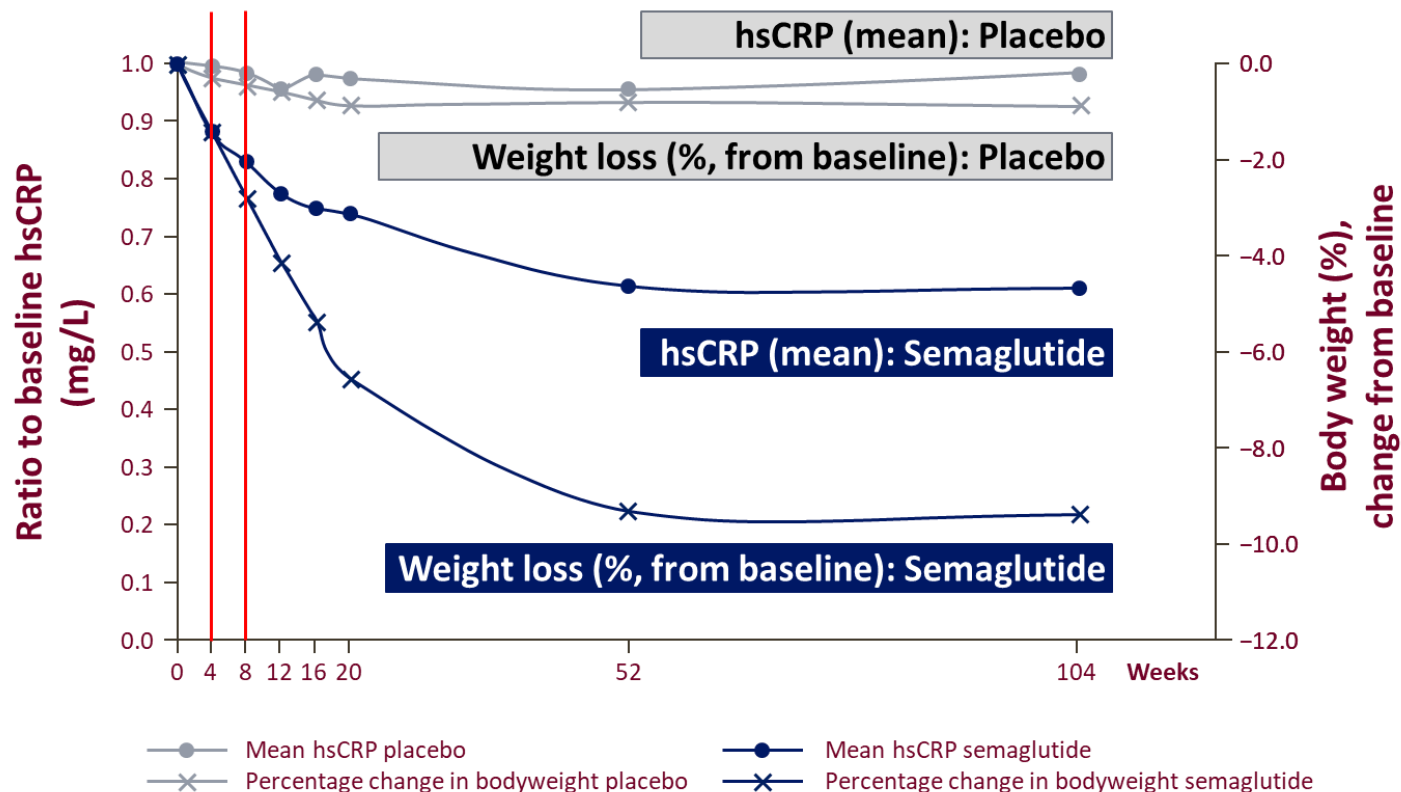
Time to first MACE by HbA_{1c} change from baseline to week 20



Favors **semaglutide 2.4 mg** ← → Favors placebo

*Data are from the in-trial period. End points included MACE, expanded MACE, MACE with all-cause mortality, coronary revascularization, CV death, nonfatal myocardial infarction, nonfatal stroke, all-cause mortality, heart failure composite, heart failure requiring hospitalization or urgent heart failure visit

Time Course of Changes in hsCRP and Body Weight



**Ratio to baseline hsCRP,
Semaglutide**

4 wks: ~12%

8 wks: ~20%

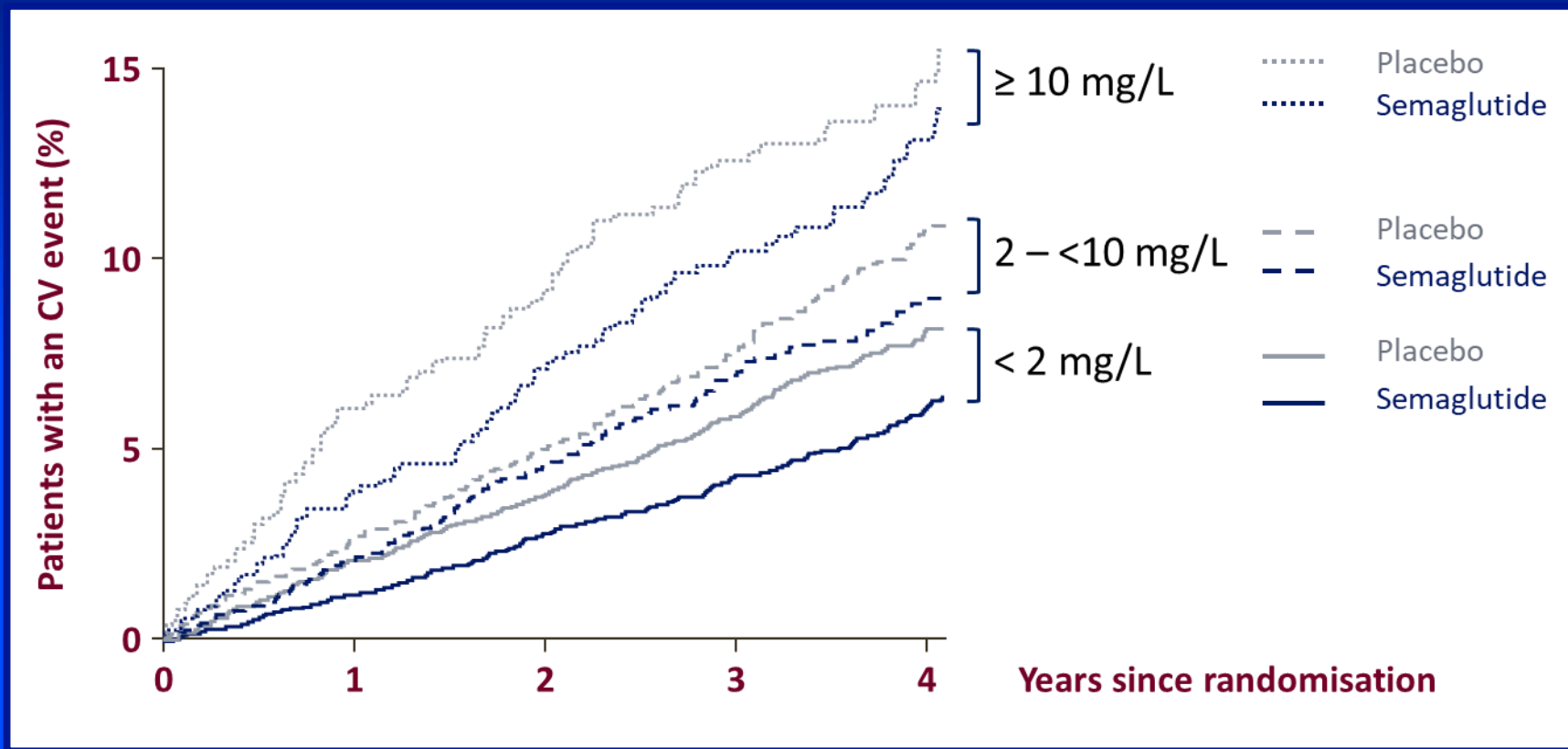
**Weight loss (%),
Semaglutide**

4 wks: ~2%

8 wks: ~3%

Semaglutide effects on hsCRP reduction occurred early - prior to major weight loss

Time to First MACE by hsCRP Cutpoints

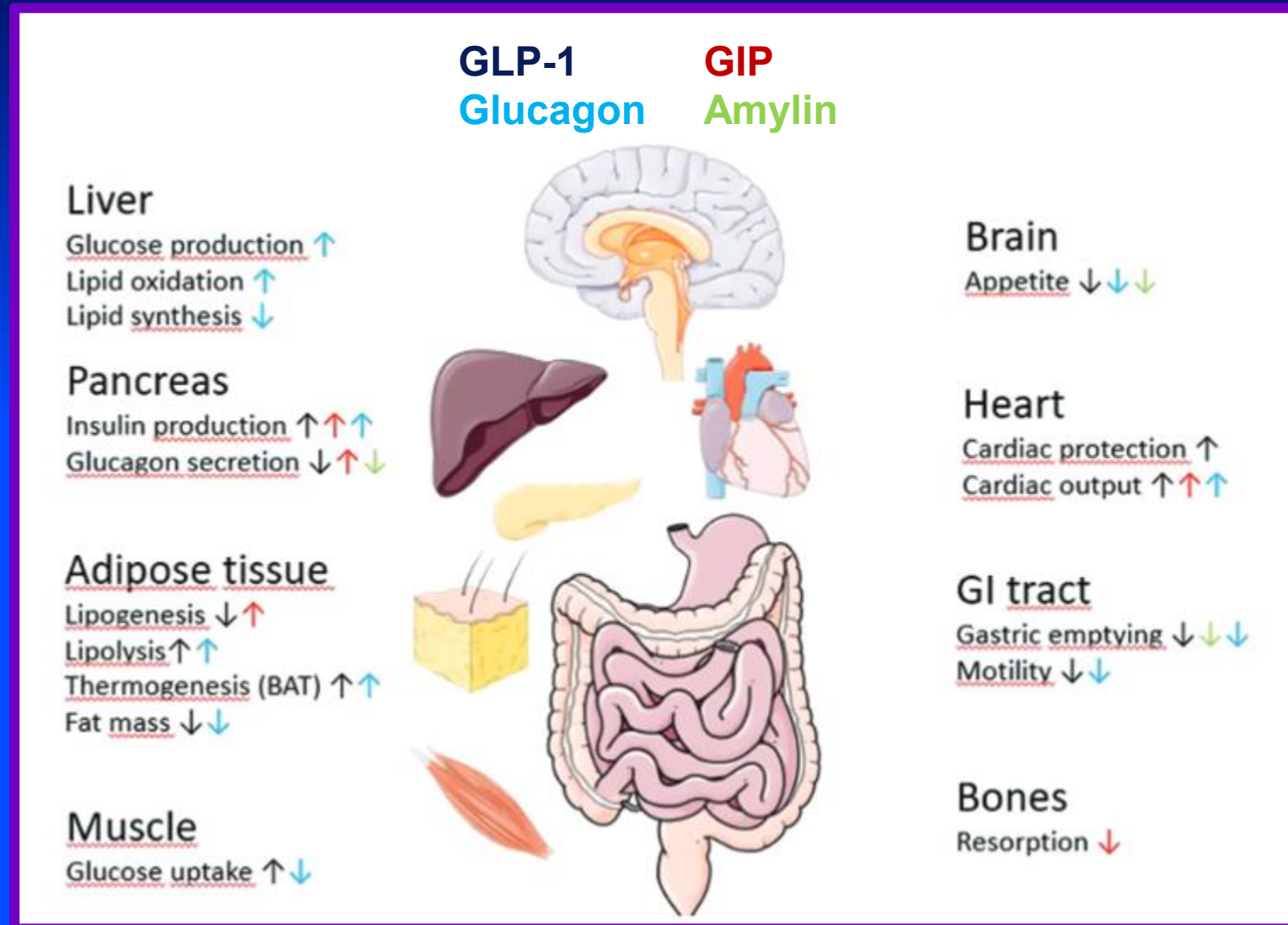


Higher baseline hsCRP values predicted increased risk of MACE, CV Death, All-cause Death
Semaglutide reduced risk of MACE across all hsCRP subgroups

Summary

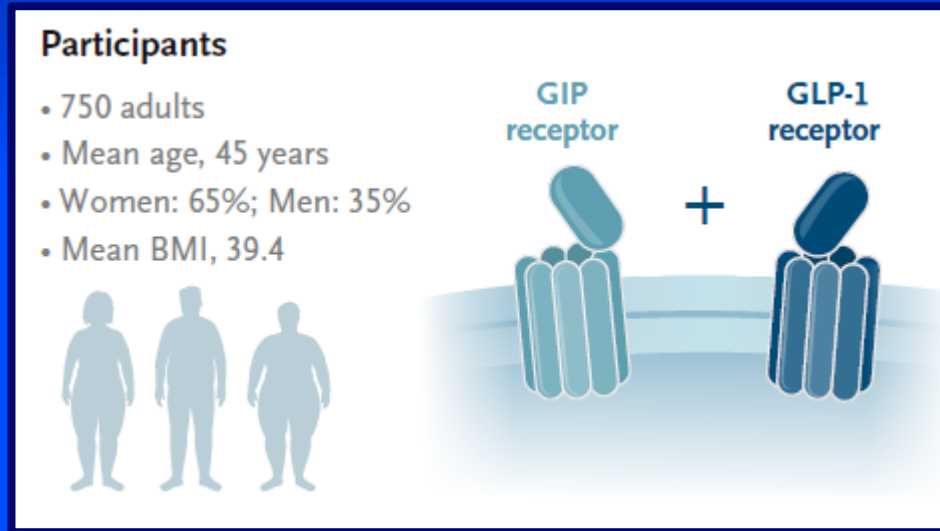
- Among patients with pre-existing CVD and overweight or obesity, but who do not have diabetes, once weekly subcutaneous semaglutide 2.4 mg reduced the risk of CV death, MI, or stroke by 20% (hazard ratio 0.80, 95% CI 0.72 – 0.90).
- Semaglutide reduced all-cause mortality, driven by similar reductions in CV and non-CV death. Non-CV death acted as a competing risk for CV death.
- Semaglutide reduced MACE and the heart failure composite endpoint among patients with baseline heart failure, similarly in those with HFpEF and HFrEF.
- Magnitude of CV benefit was largely independent of baseline levels or therapeutic changes in measures of adiposity, glycemic control, or inflammation.

Gut Hormones and Target Organs



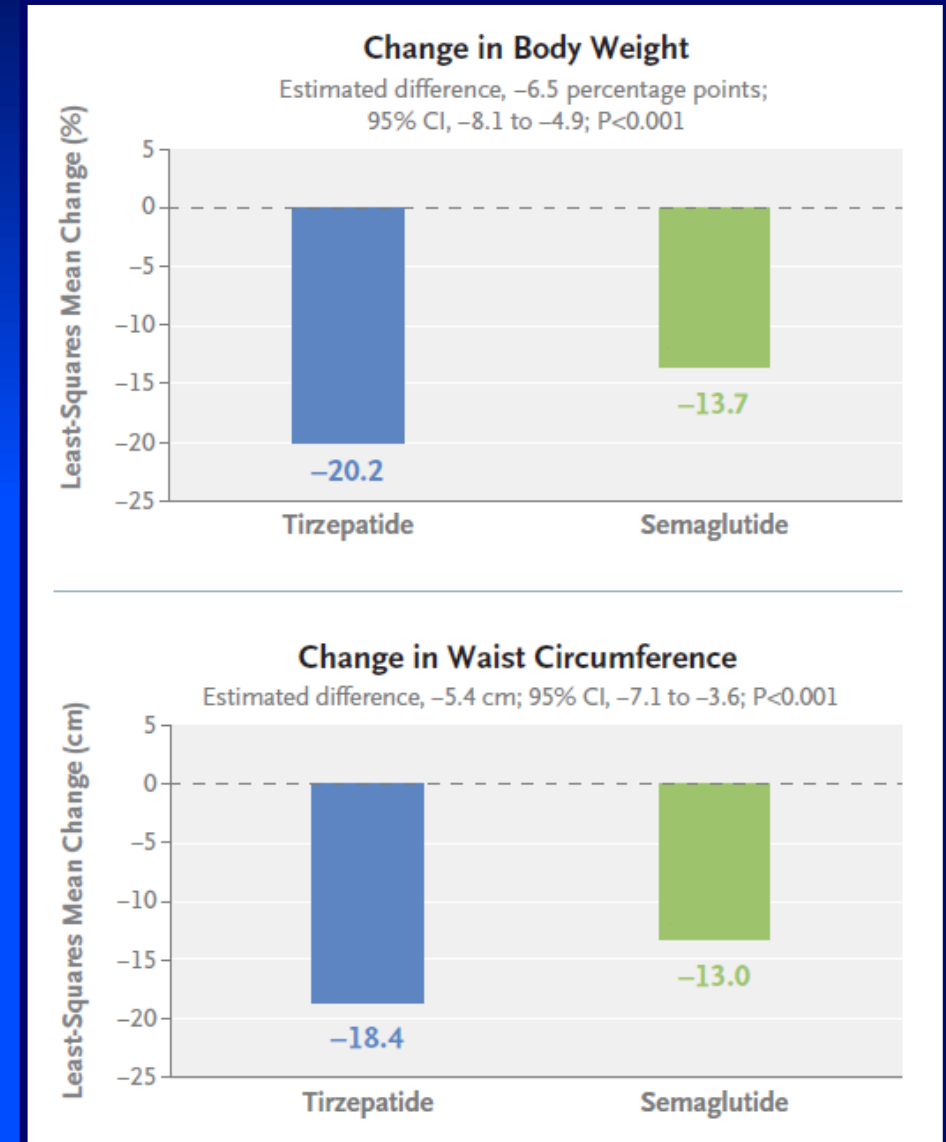
Tirzepatide – Dual GLP-1 / GIP* Agonist

Tirzepatide vs Semaglutide for Obesity Management: SURMOUNT-5 Trial



*GIP - glucose-dependent insulintropic polypeptide

Aronne LJ et al. NEJM 2025;
10.1056/NEJMoa2416394 |



Tirzepatide in Overweight or Obesity – CV Outcome

SURMOUNT MMO: Tirzepatide in Patients with Overweight or Obesity and High ASCVD Risk

- BMI ≥ 27 kg/m²
- 1° Prevention – multiple risk factors*
- 2° Prevention – established CVD (CAD, CVA, or PAD)

Tirzepatide 5, 10, or 15 mg SC once-weekly

Placebo SC once-weekly

Randomization (1:1)
Stratified by 1° or 2° prevention and sex

Event-driven: 1614 first MACE and 800 MACE-3 events
Enrolled 15,374 patients

*Risk factors - age, dyslipidemia, hypertension, kidney disease, prediabetes, tobacco, hsCRP, Lp(a), CAC Score

Endpoints

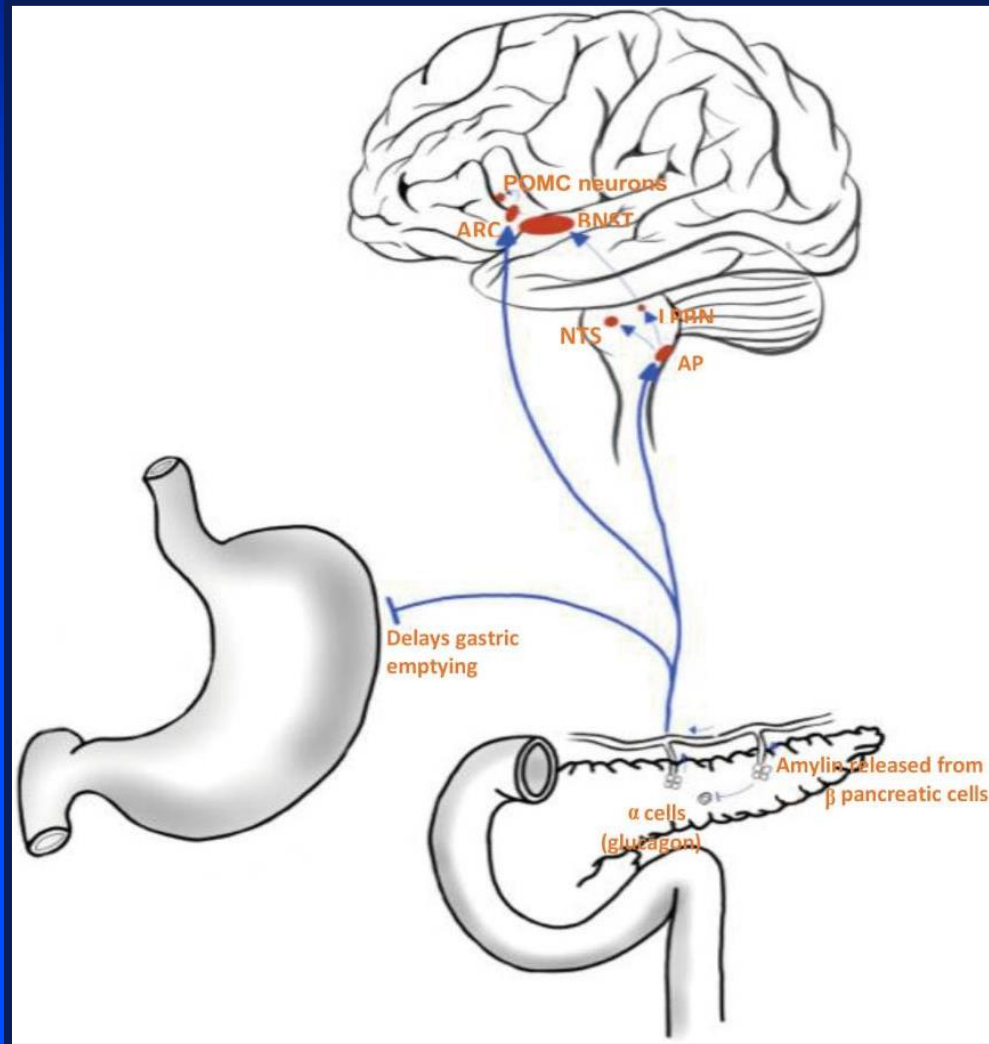
Primary Composite: all-cause death, non-fatal MI, non-fatal stroke, coronary revascularization, HF hospitalization/urgent visit

Key Secondary: MACE-3, T2DM diagnosis, renal outcomes, physical function

NCT05556512: Projected completion 2027

Cagrilintide (Amylin Analogue)

Amylin as Obesity Treatment



- Functions as satiety hormone
- Co-secreted with insulin from β pancreatic cells on nutrient delivery to small intestine
- Binds to receptor in the area postrema and the arcuate nucleus of the hypothalamus
- Synergistic with leptin in hypothalamus
- Native amylin is unstable – fibrillates
- Synthetic analogues stabilized
 - Pramlintide – short half life (20-45 min) requiring TID injection
 - Cagrilintide – long acting (half life 159-195 h) allowing weekly injection.

Dehestani et al. J Obesity and Metabolic Syndrome 2021;30:320.

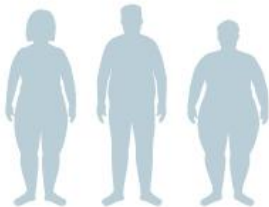
Kruse et al. J Medicinal Chemistry 2021;64:111483.

CagriSema - Combined GLP-1 and Amylin Analogues

Cagrilintide and Semaglutide for Obesity Management: REDEFINE-1 Trial

Participants

- 3417 adults
- Mean age, 47 years
- Women: 68%; Men: 32%



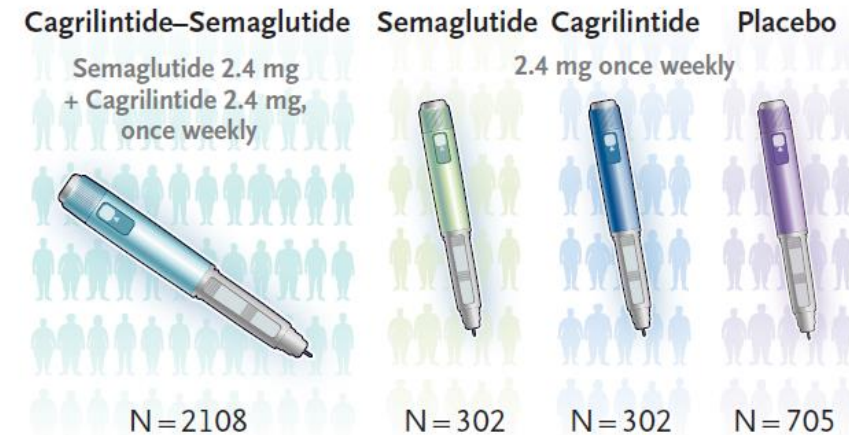
Semaglutide



GLP-1 receptor

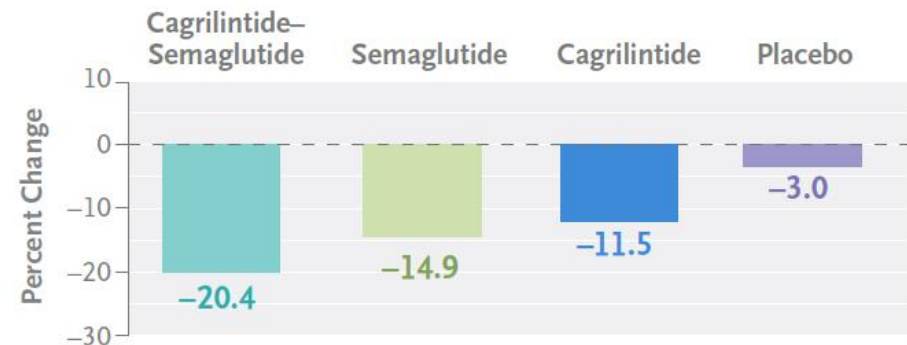


Garvey WT et al. NEJM 2025;
10.1056/NEJMoa2502081



Mean Change in Body Weight

Difference, cagrilintide-semaglutide vs. placebo:
-17.3 percentage points (95% CI, -18.1 to -16.6); $P < 0.001$



Next Generation Incretin Analogues

Category	Name	Target		Company
Dual receptor	CagriSema	GLP-1 / Amylin		Novo Nordisk
Dual receptor	Dapiglutide	GLP-1 / GLP-2		Zealand
Dual receptor	Survodutide	GLP-1 / Glucagon		Zealand/Boehringer
Dual receptor	Maridebart cafraglutide	GLP-1 / GIP antagonist	mAb – monthly	Amgen
Dual receptor	VK-2735	GLP-1 / GIP		Viking Therapeutics
Dual receptor	CT-388	GLP-1 / GIP	daily	Carmot/Roche
Dual receptor	CT-868	GLP-1 / GIP	weekly	Carmot/Roche
Triple receptor	Retatrutide	GLP-1 / GIP / Glucagon		Eli Lilly
Oral	Oral semaglutide	GLP-1		Novo Nordisk
Oral	Orforglipron	GLP-1		Eli Lilly
Oral	Danuglipron	GLP-1	↑GI intolerance	Pfizer
Oral	Ecinoglutide	GLP-1		Sciwind Bioscience
Oral	Amycretin	GLP-1 / Amylin		Novo Nordisk
Myostatin inhibitor	Bimagrumab	Activin receptor	↑lean mass	Versanis/Eli Lilly
Myostatin inhibitor	Taldefgrobep alpha	Myostatin blocker	↑lean mass	Biohaven

Semaglutide 2.4 mg is the first weight management therapy proven in a rigorous RCT to reduce the risk of CV events, establishing overweight or obesity as a modifiable risk factor for cardiovascular disease.

Atherosclerotic Cardiovascular Disease

Modifiable Risk Factors

HTN	Dys-Lipidemia	T2DM	Tobacco Use	Sedentary Lifestyle	Poor Nutrition	Obesity or Overweight
ACE/ARBs Diuretics β -blockers CCBs MRAs DASH Diet	Statins PCSK9i Ezetimibe Bempedoic acid Icosapent ethyl	GLP-1RA SGLT-2i	Smoking cessation	Cardiac Rehab	Mediterranean Diet DASH Diet Plant-Based Diet	GLP-1RA Semaglutide

