Società Italiana dell'Ipertensione Arteriosa
Lega Italiana contro l'Ipertensione Arteriosa

EVENTO FORMATIVO INTERREGIONALE SIIA
PIEMONTE | LIGURIA | VALLE D'AOSTA
Torino, 12 ottobre 2024

«Obesità e rischio cardiovascolare: nuove opzioni terapeutiche»

Dr. Fabio Dario Merlo
Responsabile Degenza Ordinaria
SC Dietetica e Nutrizione Clinica
AOU Città della Salute e della Scienza

Agenda

1. Evidences of obesity as CV risk
2. Semaglutide
3. Tirzepatide
4. New frontiers
5. Conclusions

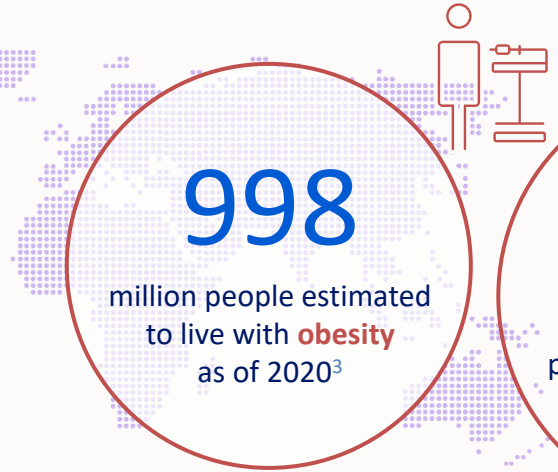
EVIDENCES OF OBESITY AS CV RISK

There is an unmet need for therapies that reduce CV events and support weight management

523 million people had **CVD** in 2019 (globally)[1]

49% of global **CV deaths** are due to **CHD**[1]

32% of all global **deaths** are from **CVD**[2]



998 million people estimated to live with **obesity** as of 2020[3]

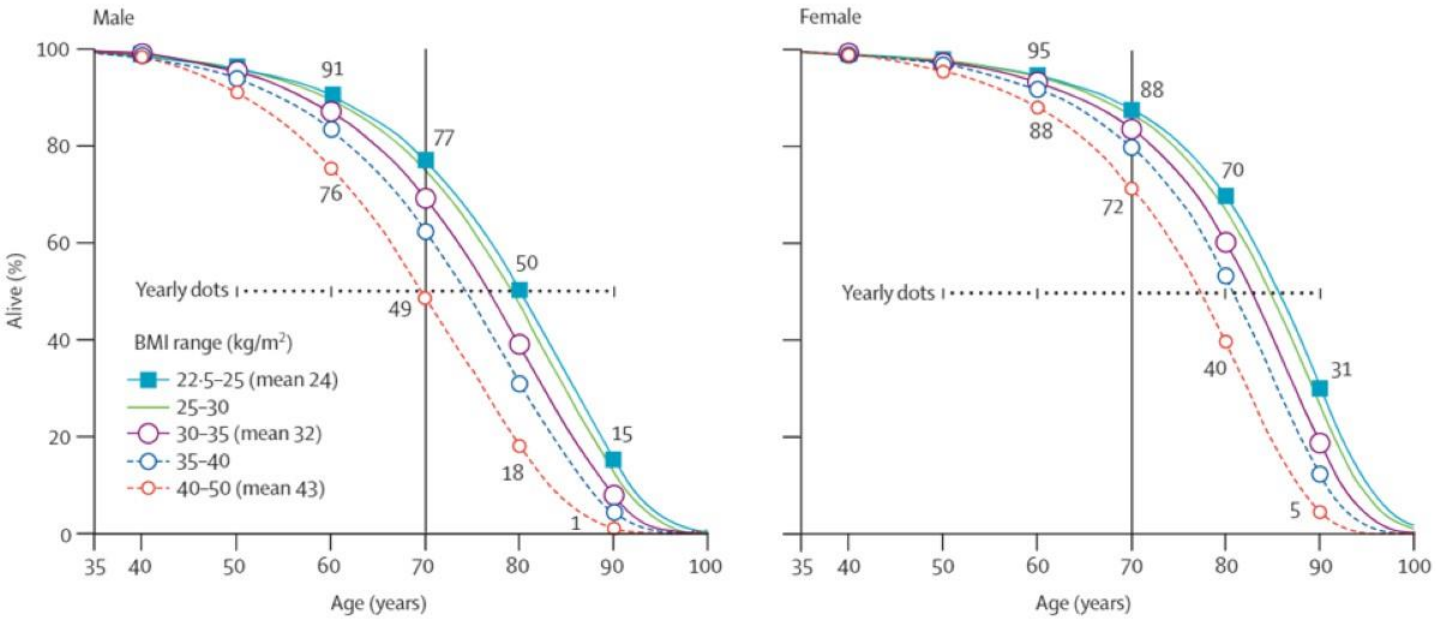
1,556 million people predicted to have **obesity** by 2030[3]

Effective interventions that lower CV events & death in this population are greatly needed![4]

Conditions included in CVD definition may vary. CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease.

1. Roth GA et al. J Am Coll Cardiol 2020;76:2982–3021; 2. WHO. Fact sheet – CVDs. Available at: https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds). Accessed January 2023; 3. World Obesity Federation. World obesity atlas 2023. Available at: https://www.worldobesity.org/resources/resource-library/world-obesity-atlas-2023. Accessed August 2023; 4. GBD 2015 Obesity Collaborators. N Engl J Med 2017;377:13–27.

Life Expectancy Decreases as BMI Increases

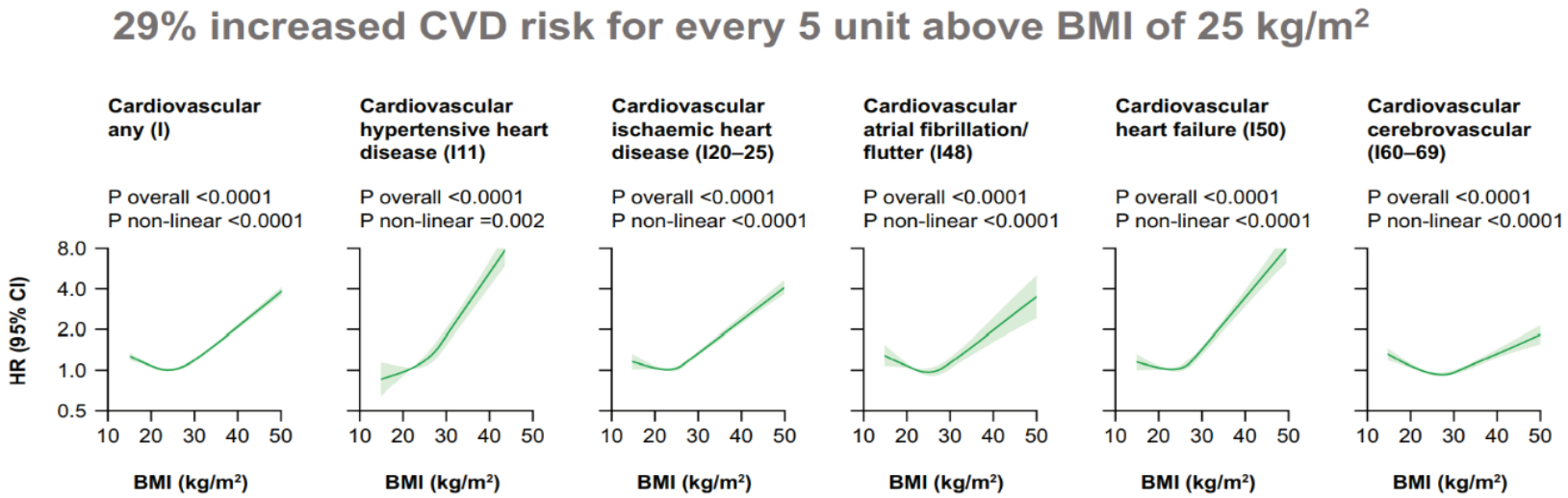


At BMI 30 to 35 kg/m², median survival is reduced by 2 to 4 y
At 40 to 45 kg/m², median survival is reduced by 8 to 10 y*

*Comparable with the effects of smoking.

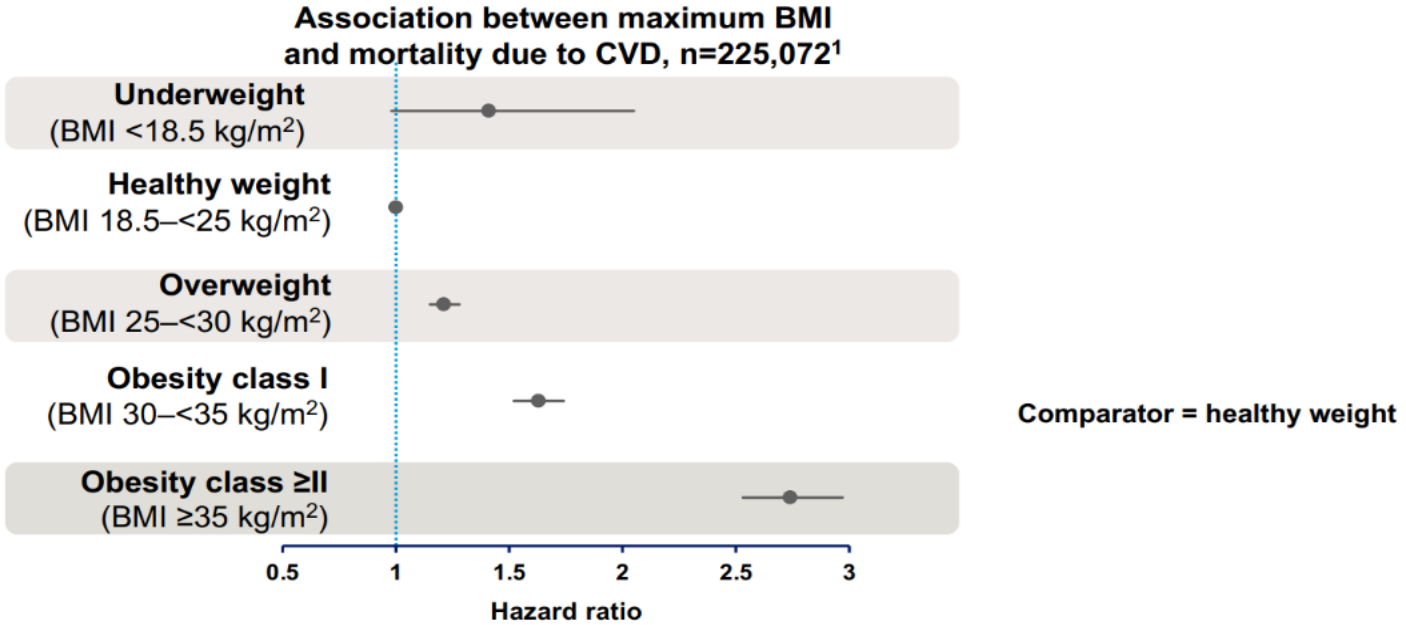
Prospective Studies Collaboration, Whitlock G, et al. Lancet. 2009;373:1083-1096.

Risk of CVD increases as BMI increases



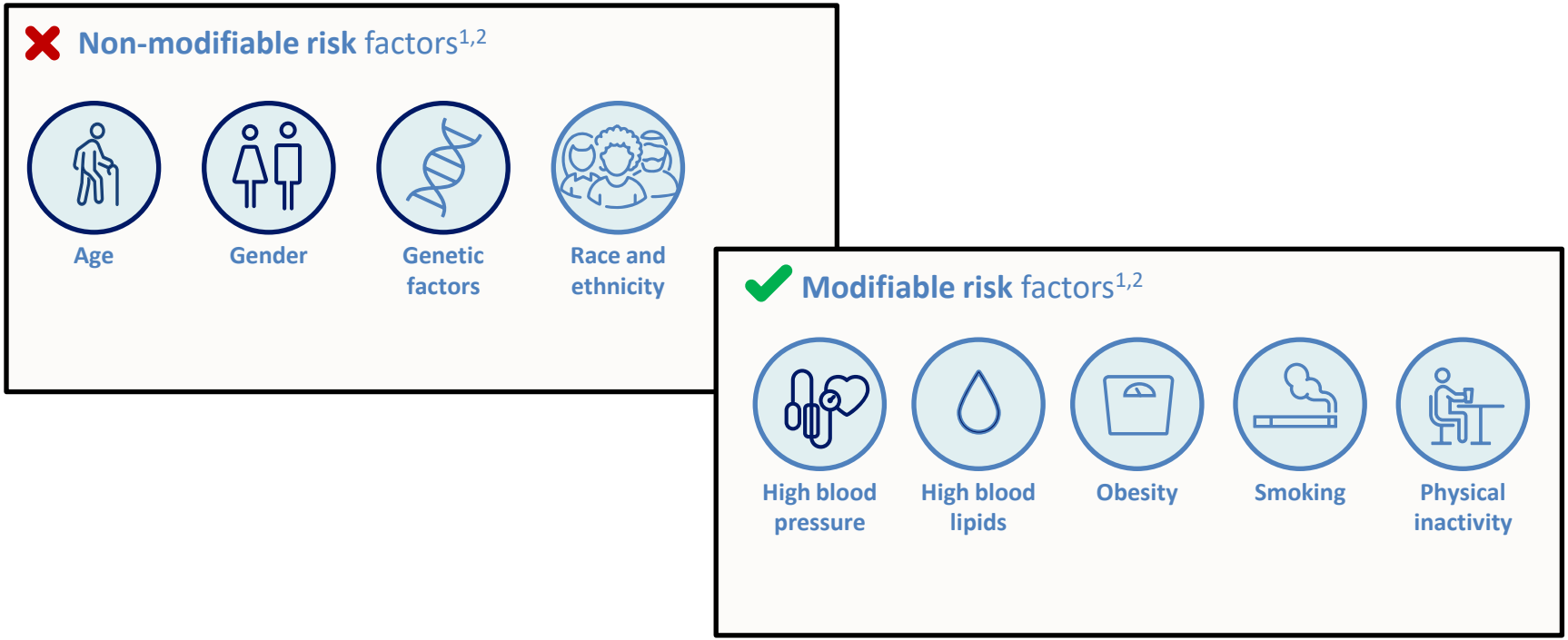
Krishnan Bhaskaran, Lancet Diabetes Endocrinol 2018

CVD is the main cause of death in people with obesity



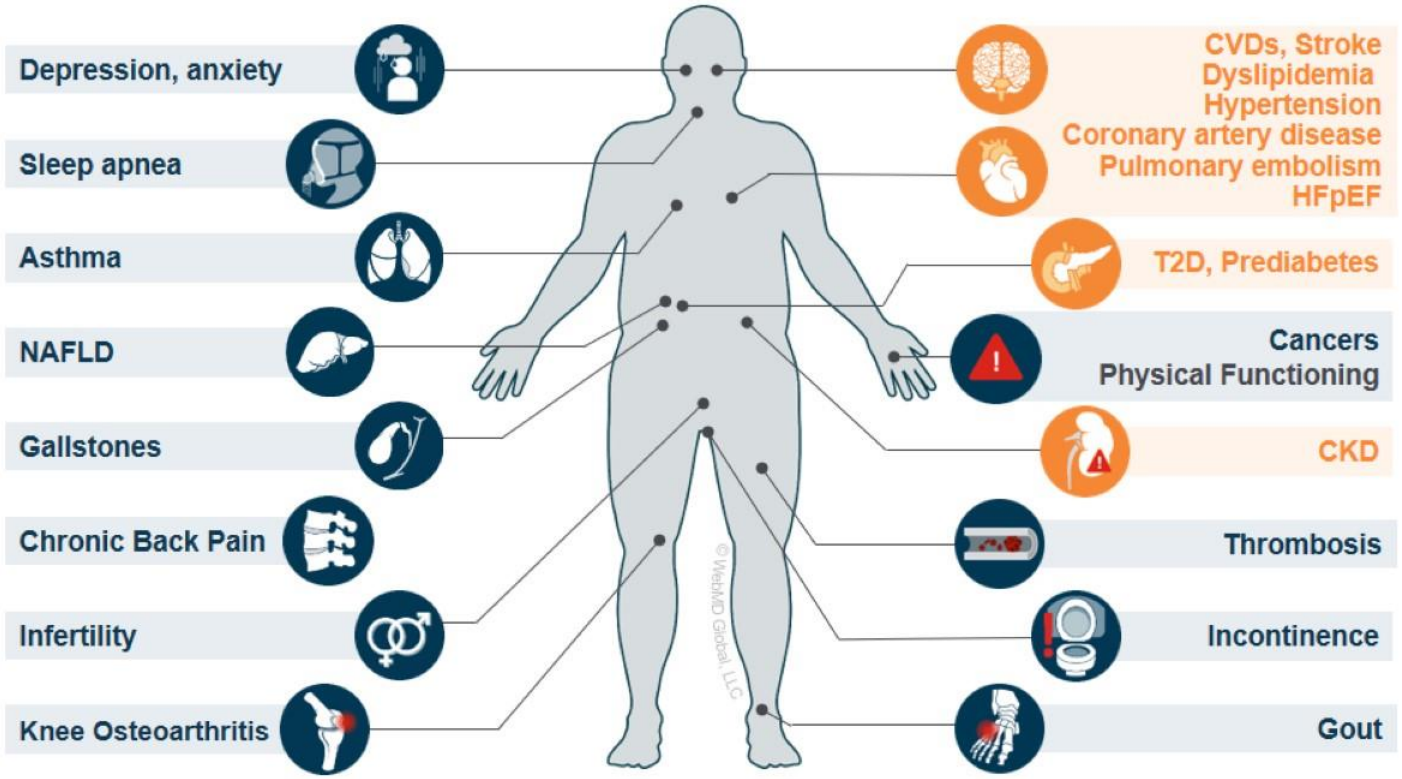
YU et al. Ann Intern Med.2017; 166:613-620

Main risk factors for CVD



CVD, cardiovascular disease.
1. Graham I et al. Eur Heart J 2007;28:2375–414; 2. Piepoli MF et al. Eur Heart J 2016;37:2315–81.

Obesity Is Associated With Multiple Complications

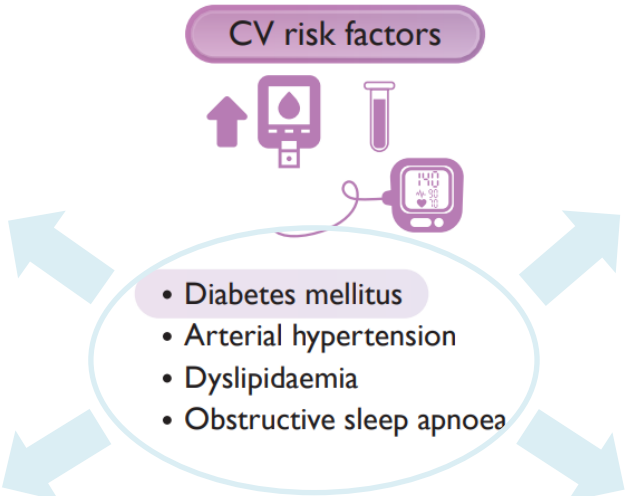


CKD, chronic kidney disease; CVD, cardiovascular disease; HFpEF, heart failure with preserved ejection fraction; NAFLD, nonalcoholic fatty liver disease; T2D, type 2 diabetes.

Sharma AM. Obes Rev. 2010;11:808-809; Guh DP, et al. BMC Public Health. 2009;9:88; Luppino FS, et al. Arch Gen Psychiatry. 2010;67:220-229; Simon et al. Arch Gen Psychiatry. 2006;63:824-830; Church TS, et al. Gastroenterology. 2006;130:2023-2030; Li C, et al. Prev Med. 2010;51:18-23; Hosler AS. Prev Chronic Dis. 2009;6:A48.

Main cardiovascular consequences of obesity.

Diabetes
Insulin resistance, a key factor in T2DM development manifesting long before the onset of diabetes, is also a major feature of obesity. Insulin resistance predicts the risk of developing CVD, even in the absence of diabetes, and promotes atheroma plaque formation.



Dyslipidaemia
Obesity is associated with an atherogenic lipoprotein phenotype including elevation of both fasting and post-prandial triglycerides, Apolipoprotein B (ApoB), and small dense LDL particles, and low high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A1 (ApoA1) levels.
High levels of very-low-density lipoproteins (VLDL) that vehicle plasma triglycerides were found to explain 40% of the excess risk of myocardial infarction associated with higher BMI

Hypertension
Increased BMI, from overweight to all classes of obesity is linearly related to the prevalence of hypertension.

Obstructive sleep apnoea
OSA per se is a risk factor implicated in the development of hypertension and the progression of HF, pulmonary hypertension, and AF overall reflecting how obesity exerts multiple direct and indirect deleterious CV effects.

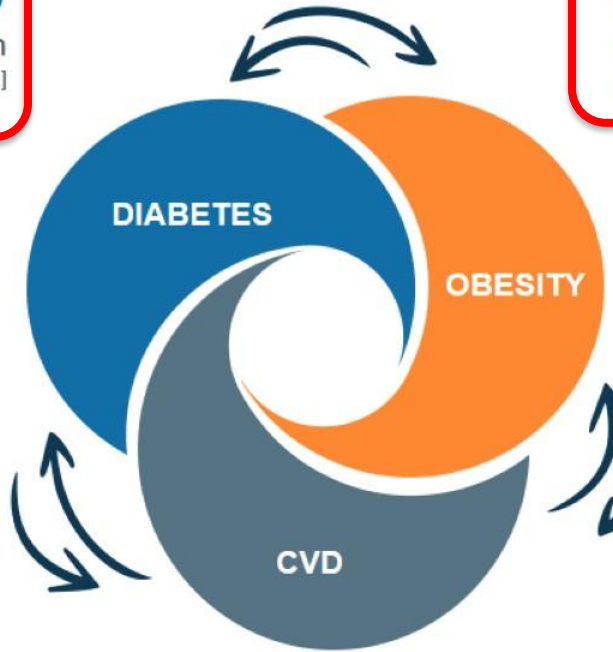
Koskinas KC. Obesity and cardiovascular disease: an ESC clinical consensus statement. European Heart Journal (2024) 00, 1–36

The Epidemiological Link Between Diabetes, Obesity, and CVD

86%
of people with diabetes live with overweight or obesity[1]

31%
of people living with obesity have diabetes[2]

32%
of people with diabetes have CVD[3]



> 2/3
of deaths related to a high BMI are due to CV causes[5]

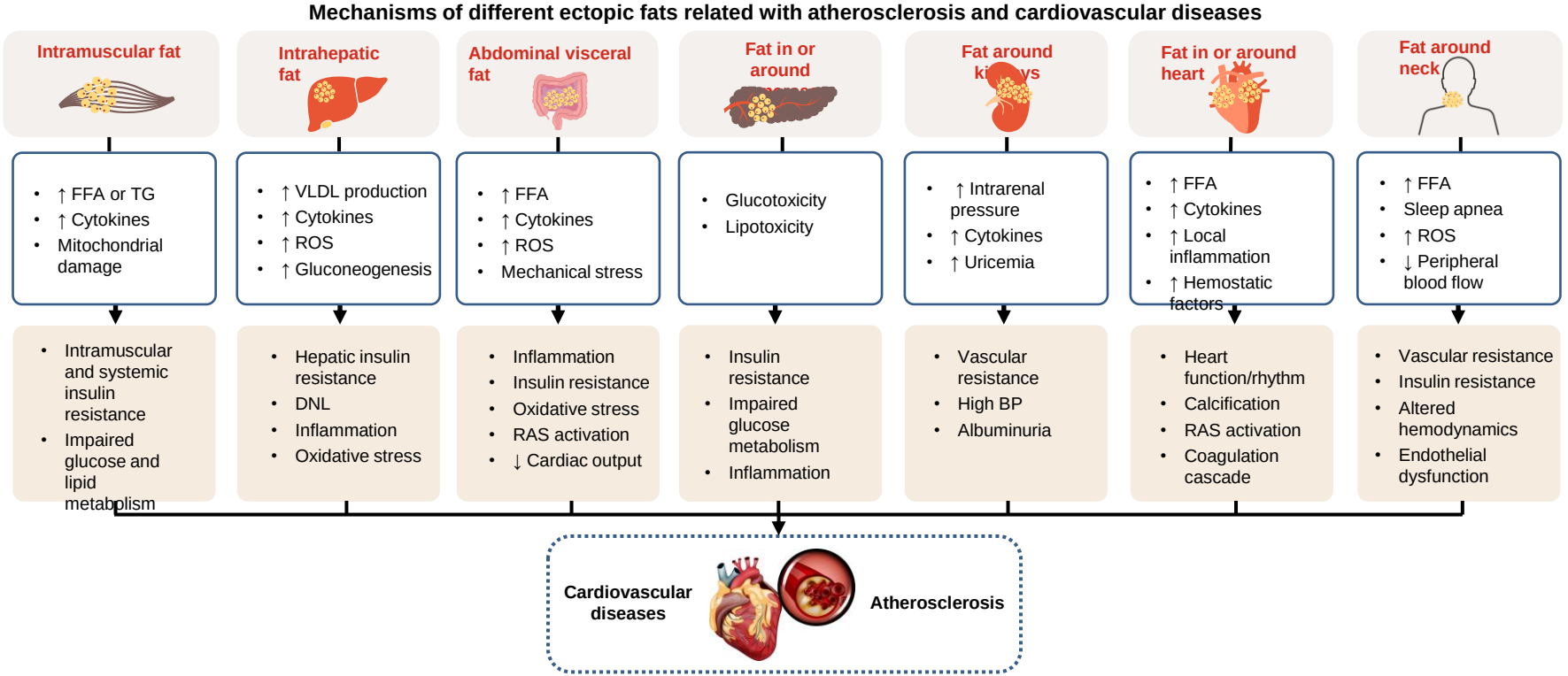
~50%
of deaths related to T2D are due to CV causes[3]

29%
of people with CAD have diabetes[4]

> 80%
of people with CHD live with overweight or obesity[6]

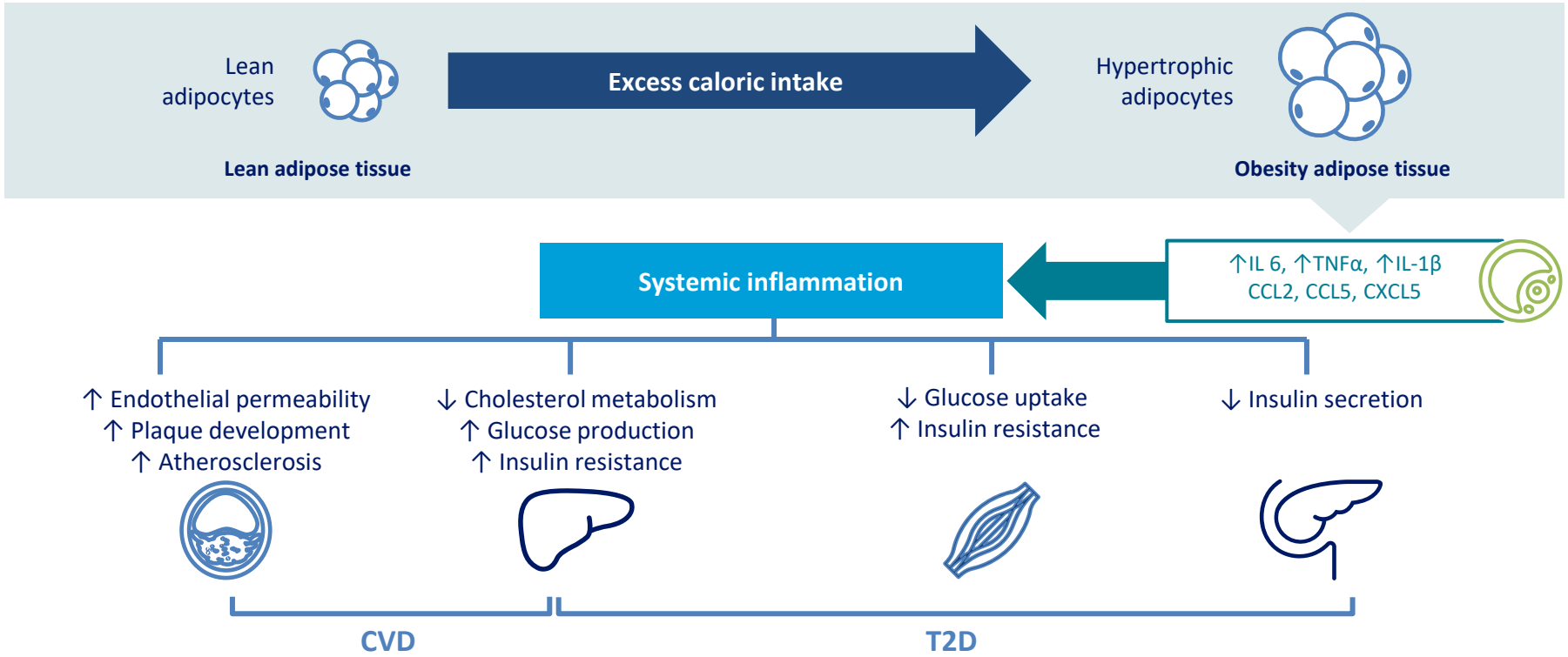
BMI, body mass index; CAD, coronary artery disease; CHD, coronary heart disease; CVD, cardiovascular disease; T2D, type 2 diabetes.
Image courtesy of Nikolaus Marx, MD, FESC, FAHA. Adapted from 1. Daousi C, et al. Postgrad Med J. 2006;82:280-284; 2. Fountain D, et al. Br J Diabetes. 2019;19:8-13; 3. Einarson TR, et al. Cardiovasc Diabetol. 2018;17:83; 4. Mak KH. Eur J Prev Cardiol. 2022;28:1795-1806; 5. GBD Obesity Collaborators. N Engl J Med. 2017;377:13-27; 6. Ades PA, et al. Prev Med. 2017;104:117-119.

Linking Ectopic Fat Deposition and Cardiovascular Disease



BP=Blood Pressure; DNL=De Novo Lipogenesis; FFA=Free Fatty Acid; RAS=Renin-Angiotensin System; ROS=Reactive Oxygen Species; TG=Triglyceride; VLDL=Very Low-density Lipoprotein.
Data from Lim S, Meigs JB. *Arterioscler Thromb Vasc Biol*. 2014;34(9):1820-1826.

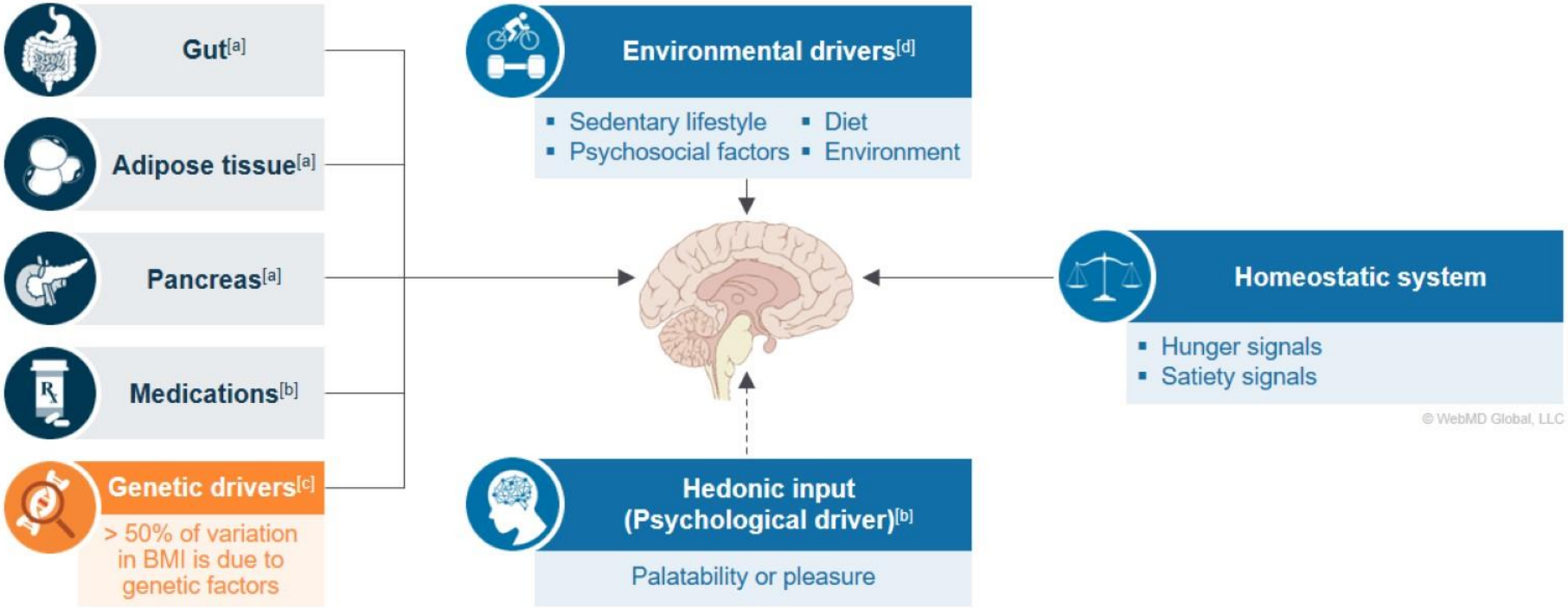
Systemic inflammation increases risk of CVD and T2D



CCL, chemokine (C-C motif) ligand; CVD, cardiovascular disease; CXCL5, chemokine (C-X-C motif) ligand 5; IL, interleukin; T2D, type 2 diabetes; TNFα, tumour necrosis factor alpha.
Yao L et al. J Immunol Res 2014;2014:181450.

Obesity Is a Complex and Multifactorial Disease

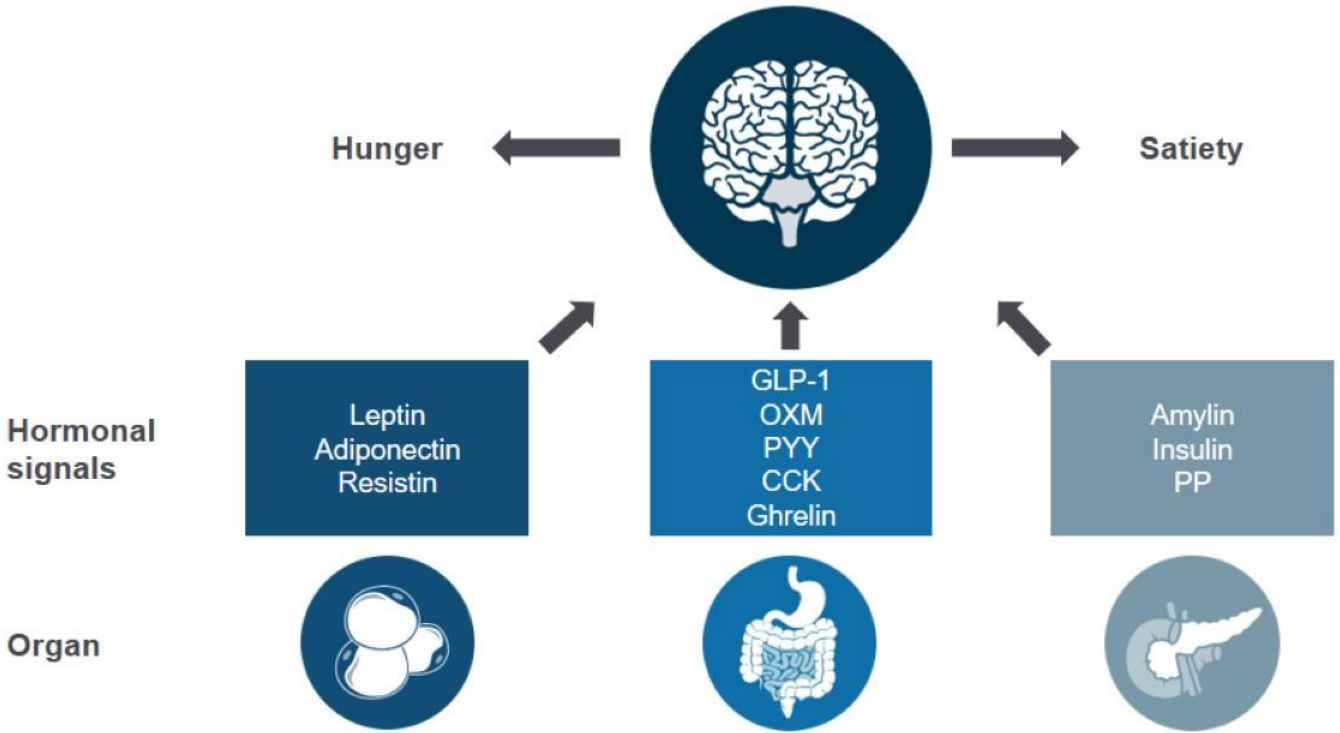
Energy balance is regulated by the brain through various sources of input



a. Klok MD, et al. Obes Rev 2007;8:21-34. b. Berridge KC, et al. Brain Res. 2010;1350:43-64. c. Albuquerque D, et al. Br Med Bull. 2017;123:159-173. d. Flores-Dorantes MT, et al. Front Neurosci. 2020;14:863.

Multiple Hormonal Signals Influence Appetite

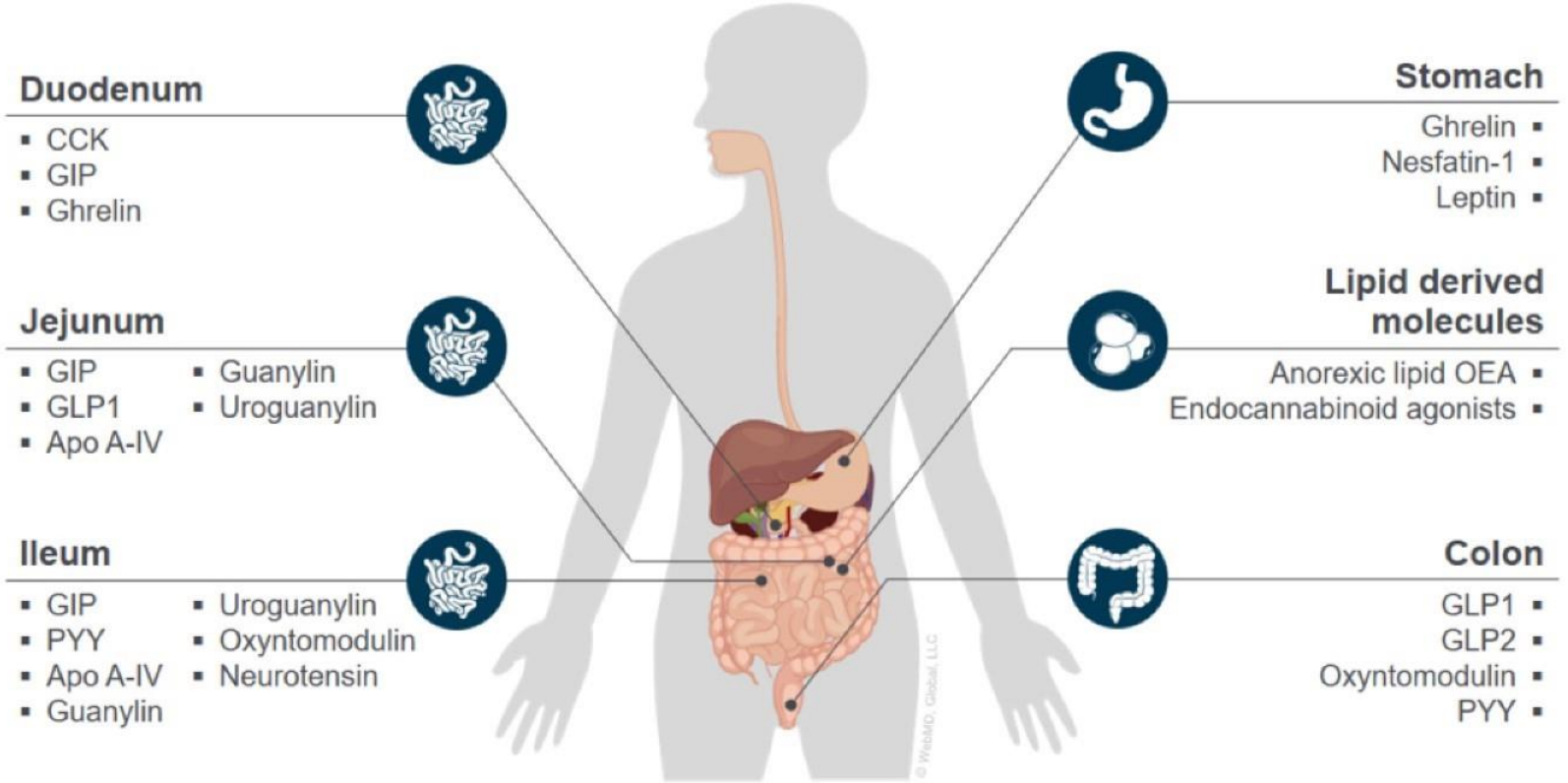
These signals are processed by the brain into feelings of satiety or hunger



CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; OXM, oxyntomodulin; PP, pancreatic polypeptide; PYY, peptide-YY.

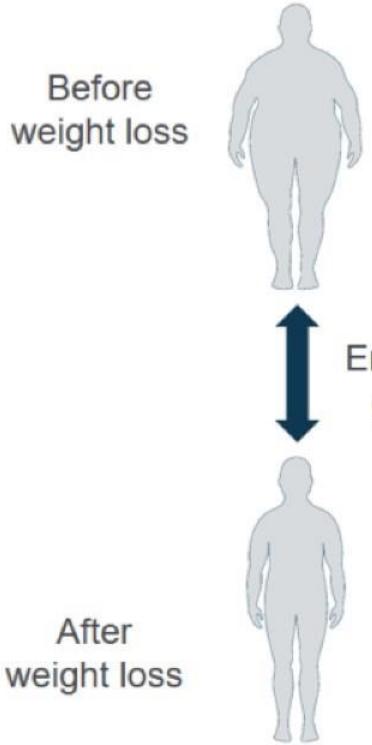
Woods SC, et al. Int J Obes Relat Metab Disord. 2002;26:S8-10; Badman MK, et al. Science. 2005;307:1909-1914.

Energy Regulation and Glucose Homeostasis
Central Role of the Gut



Apo A-IV, apolipoprotein A-IV; ENS, enteric nervous system; OEA, oleoylethanolamide.
Monteiro MP, et al. Gastroenterology. 2017;152:1707-1717.e2.

Weight Loss Alters the Body's Homoeostatic System
Favoring Weight Regain



- ↑ **Hunger**[a]
  - Preference for calorie-dense foods
- ↓ **Energy expenditure**[a]
  - **Metabolism**:
    - ↓ Fat oxidation[b]
    - ↑ Cortisol[b]

Hormone levels[a,c,d]

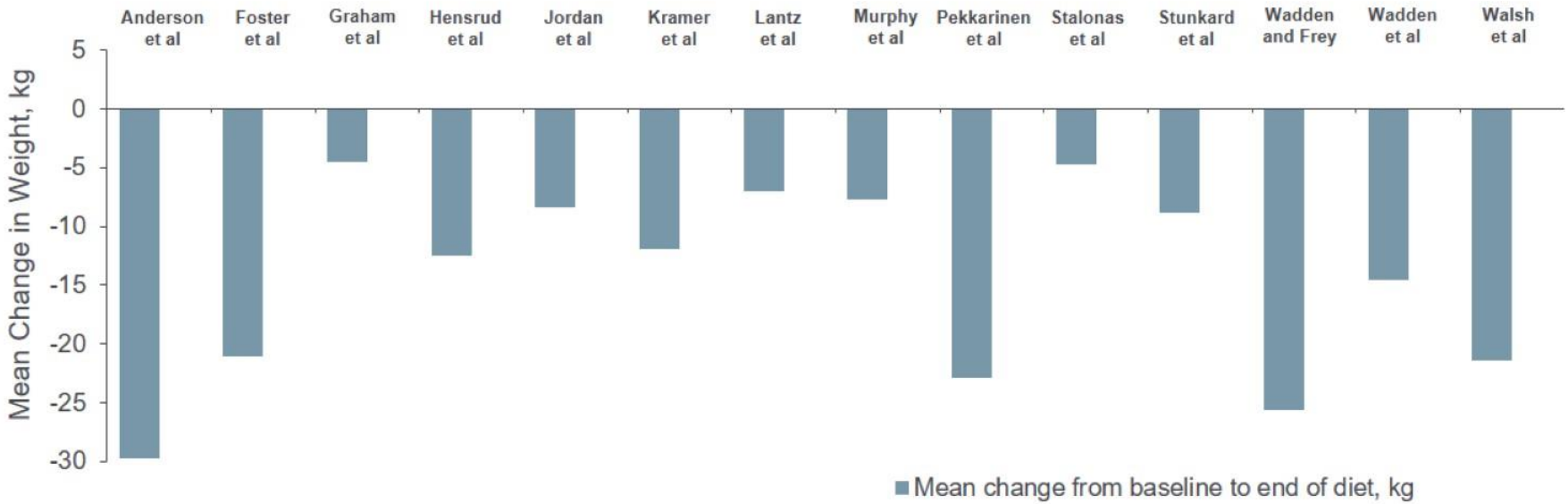
- ↓ **Satiety hormones** (leptin, PYY, GLP-1, CCK)
- ↑ **Hunger hormones** (ghrelin, GIP, NPY, AgRP)

- ↓ **Nervous system activity**[a]
- ↓ **Body mass**[a]
- ↓ **Leptin**[a]
- ↑ **Energy efficiency**[a]

AgRP, agouti-related peptide; CCK, cholecystokinin; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; NPY, neuropeptide Y; PYY, peptide YY.

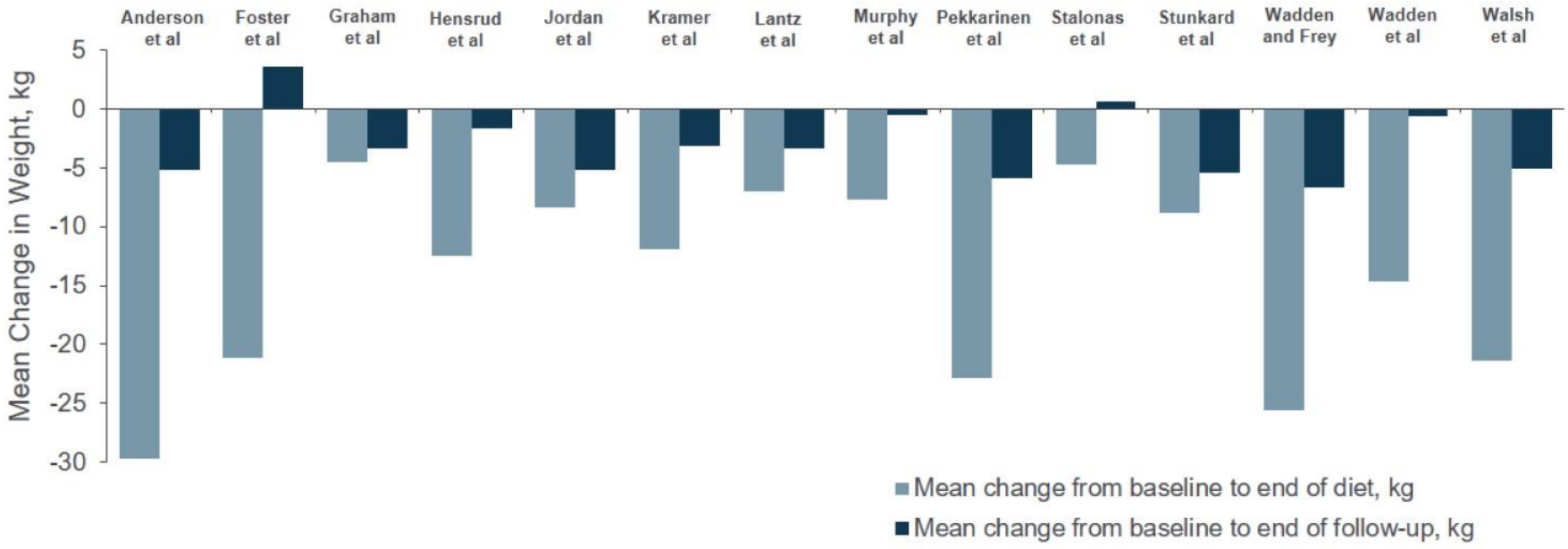
a. Melby CL, et al. Nutrients. 2017;9:468; b. Sumithran P, et al. Clin Sci (Lond). 2013;124:231-241; c. Huang Y. Front Cell Dev Biol. 2021;9:695623; d. Sumithran P, et al. N Engl J Med. 2011;365:1597-1604.

Maintaining Weight Loss Is Challenging



Follow-up range, 4 to 7 y.
Adapted from Mann T, et al. Am Psychol. 2007;62:220-233.

Maintaining Weight Loss Is Challenging



Follow-up range, 4 to 7 y.
Adapted from Mann T, et al. Am Psychol. 2007;62:220-233.

Weight loss and improved health

Towards greater weight loss and overall health improvement[1–5]

0–5%	5–10%	10–15%	≥15%
Hypertension[1]	Urinary stress incontinence[1]	MASH[1]	Cardiovascular[1] disease
Hyperglycaemia[1]	Prevention of T2D[1]	OSA[1]	MASH[1]
	PCOS[1]	GERD[1]	T2D remission[1,3,5]
	Dyslipidaemia[1]	Knee OA[1]	CV mortality[1,4]
	Asthma/Airway disease[1]		HFpEF[1,4,5]
	NAFLD[1]		

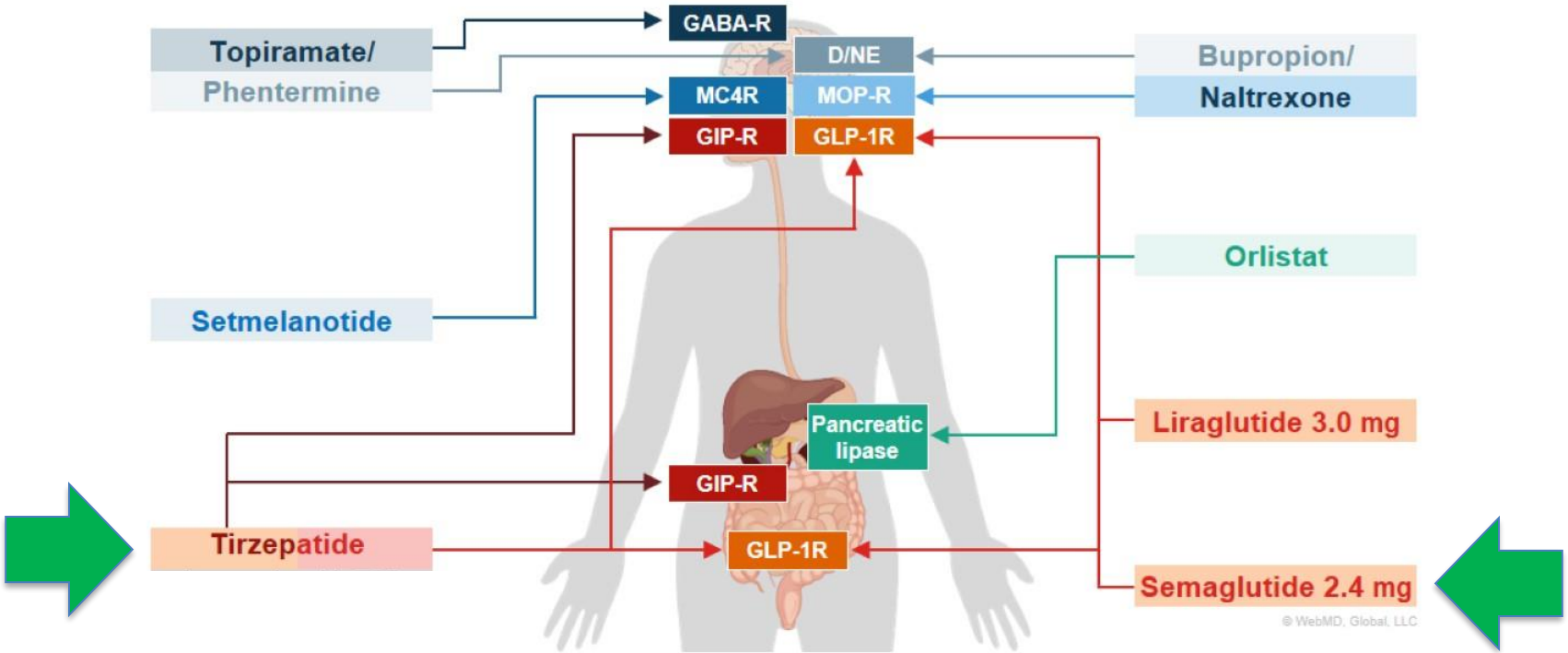
Weight loss

CV, cardiovascular; GERD, gastroesophageal reflux disease; HFpEF, heart failure with preserved ejection fraction; NAFLD, non-alcoholic fatty liver disease; MASH, metabolic associated steatohepatitis NASH, non-alcoholic steatohepatitis; OA, osteoarthritis; OSAS, obstructive sleep apnoea syndrome; PCOS, polycystic ovary syndrome

1. Garvey WT, et al. Endocr Pract 2016;22(Suppl. 3): 1–203; 2. Look AHEAD Research Group. Lancet Diabetes Endocrinol. 2016;4(11): 913–921; 3. Lean ME, et al. Lancet. 2018;391(10120): 541–551; 4. Benraoune F and Litwin SE. Curr Opin Cardiol. 2011;26(6): 555–561; 5. Sundström J, et al. Circulation. 2017;135(17): 1577–1585.

Anti-Obesity Medications

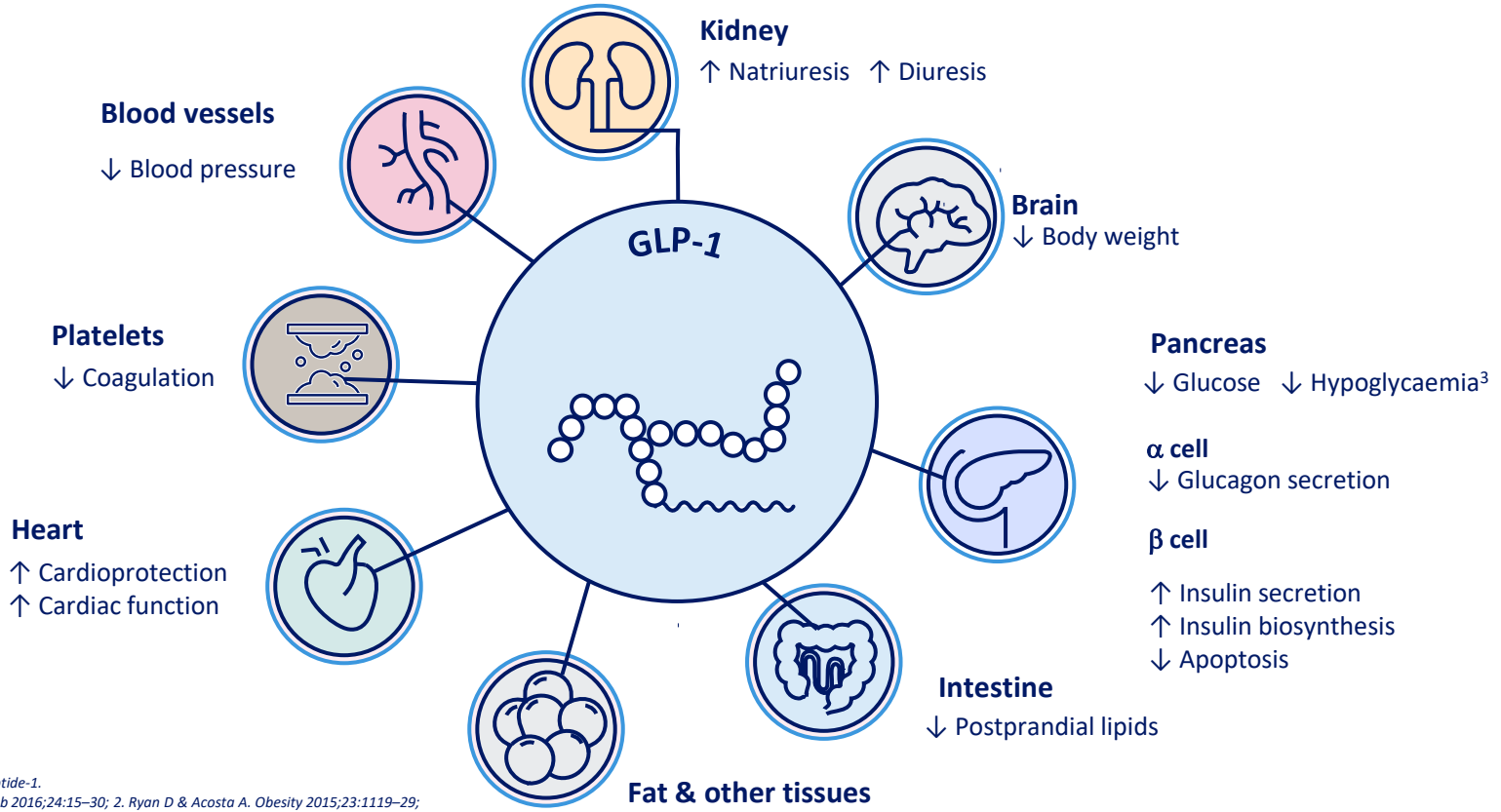
Adjunct to lifestyle changes



D/NE, dopamine/norepinephrine; GABA-R, γ-aminobutyric acid receptor; GIP-1R, GIP-1 receptor; GLP-1R, GLP-1 receptor; MC4R, melanocortin 4 receptor; MOP-R, mu opioid receptor.
Image courtesy of Rachel L. Batterham, OBE, MBBS, PhD. Accessed January 25, 2023. https://www.mayoclinic.org/healthy-lifestyle/weight-loss/in-depth/weight-loss-drugs/art-20044832;
Müller TD, et al. Nat Rev Drug Discov. 2022;21:201-223.

SEMAGLUTIDE

Pleiotropic local and systemic actions of GLP-1[1,2]

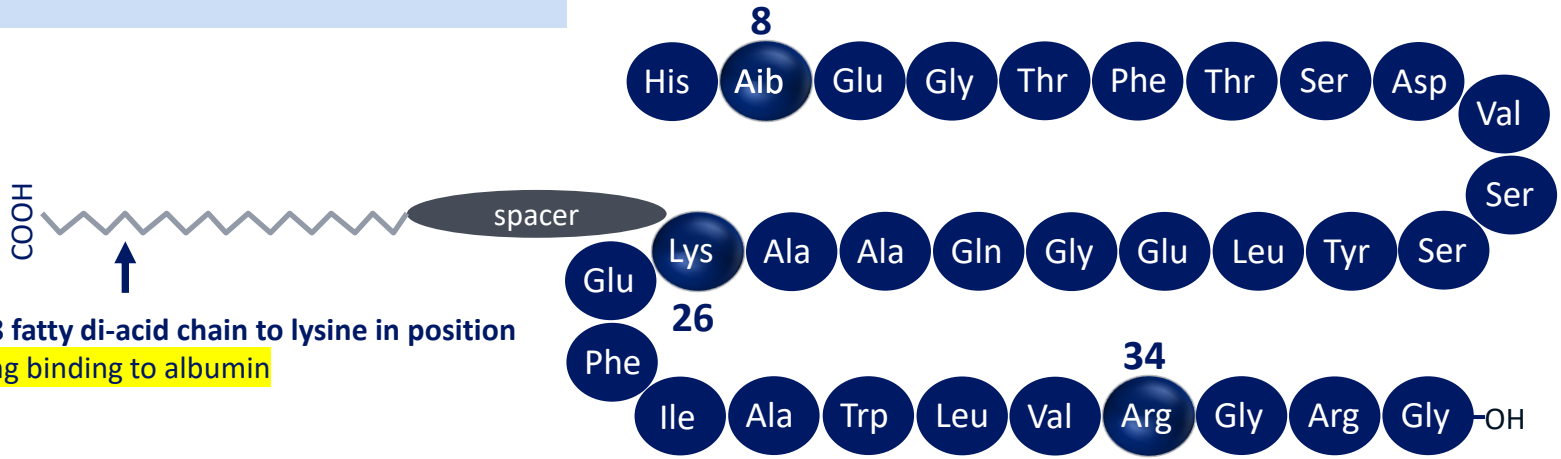


GLP-1, glucagon-like peptide-1.
1. Drucker DD. Cell Metab 2016;24:15–30; 2. Ryan D & Acosta A. Obesity 2015;23:1119–29;
3. Nauck MA et al. Am J Physiol 1997;273:E981–8.

Semaglutide is a human GLP-1 analogue[1,2]

- **94%** homology to human GLP-1
- $t_{½}$ of approximately **1 week**

Amino acid substitution at position 8
(alanine to alpha-aminoisobutyric acid)
protects against DPP-4 degradation



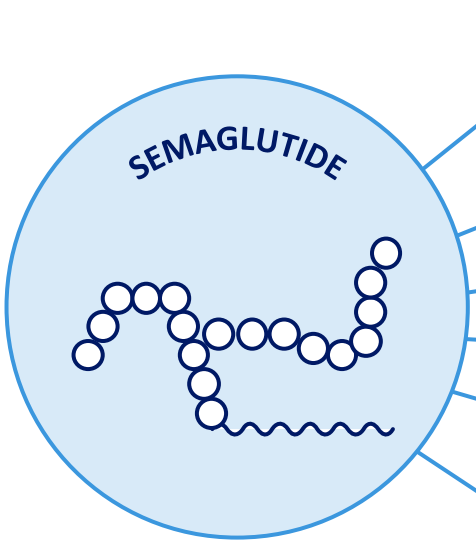
Spacer and C-18 fatty di-acid chain to lysine in position 26 provide strong binding to albumin

Amino acid substitution at position 34
(lysine to arginine) prevents C-18 fatty di-acid binding at the wrong site

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; t½, half-life.
1. Granhall C et al. Clin Pharmacokinet 2019;58:781–91; 2. Lau et al. J Med Chem 2015;58:7370–80.

Semaglutide modifies risk factors for CV complications

Semaglutide has pleiotropic effects on CV risk factors & reduces MACE risk in T2D[1–7]

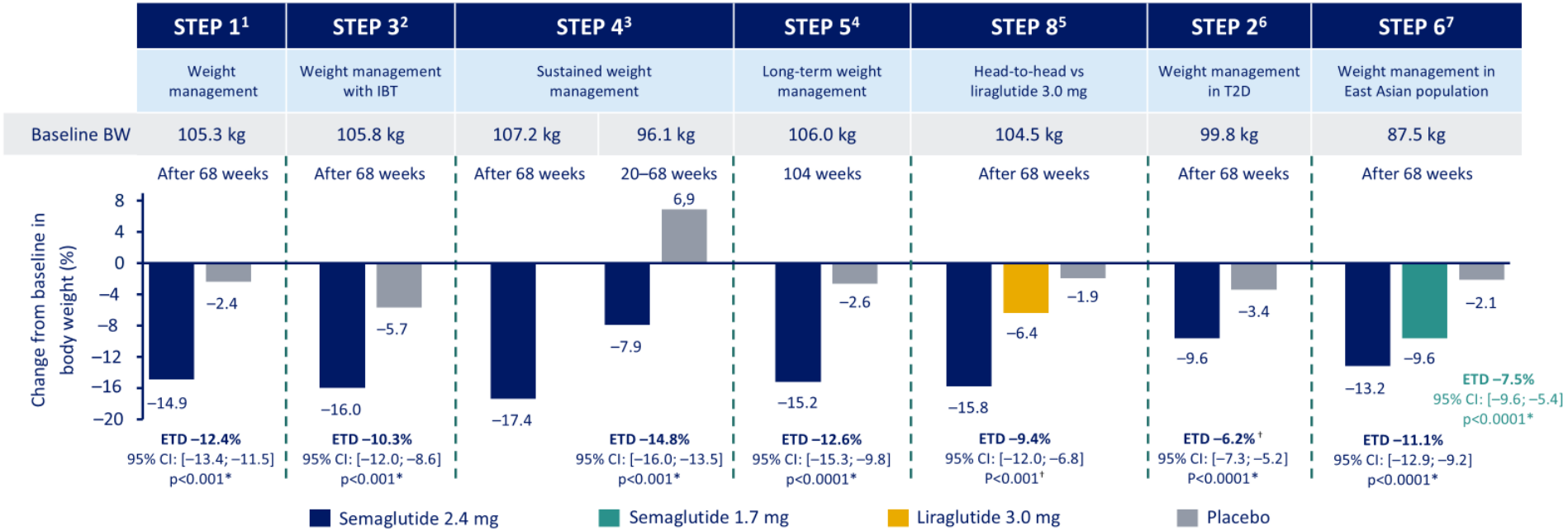


- Improves **glucose** metabolism[1]
- Reduces **body weight**[1–3]
- Reduces **risk of MACE** in patients with T2D at high CV risk[3–5]
- Reduces **inflammation**[1,6]
- Improves **lipid** profile and reduces **blood pressure**[1,2]
- Shown to have **anti-atherosclerotic** effects in mouse models[7]

CV, cardiovascular; MACE, major adverse cardiovascular events; T2D, type 2 diabetes.

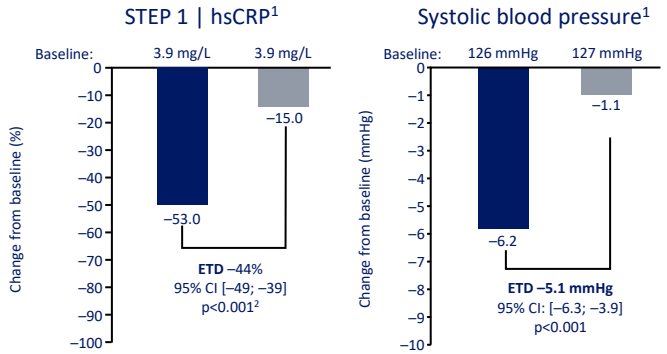
1. Wilding JPH et al. N Engl J Med 2021;384:989; 2. Aroda VR et al. Diabetes Metab 2019;45:409–18; 3. Marso SP et al. N Engl J Med 2016;375:1834–44; 4. Husain M et al. N Engl J Med 2019;381:841–51; 5. Husain M et al. Diabetes Obes Metab 2020;22(3):442–51; 6. Knudsen LB & Lau J. Front Endocrinol (Lausanne) 2019;10:155; 7. Rakipovski G et al. JACC Basic Transl Sci 2018;3:844–57.

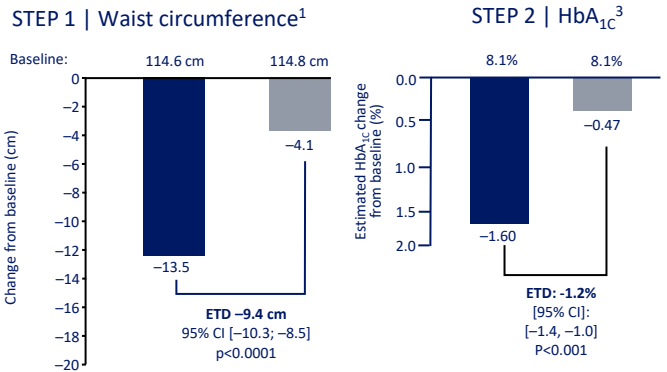
Weight loss was observed with semaglutide across the STEP trials

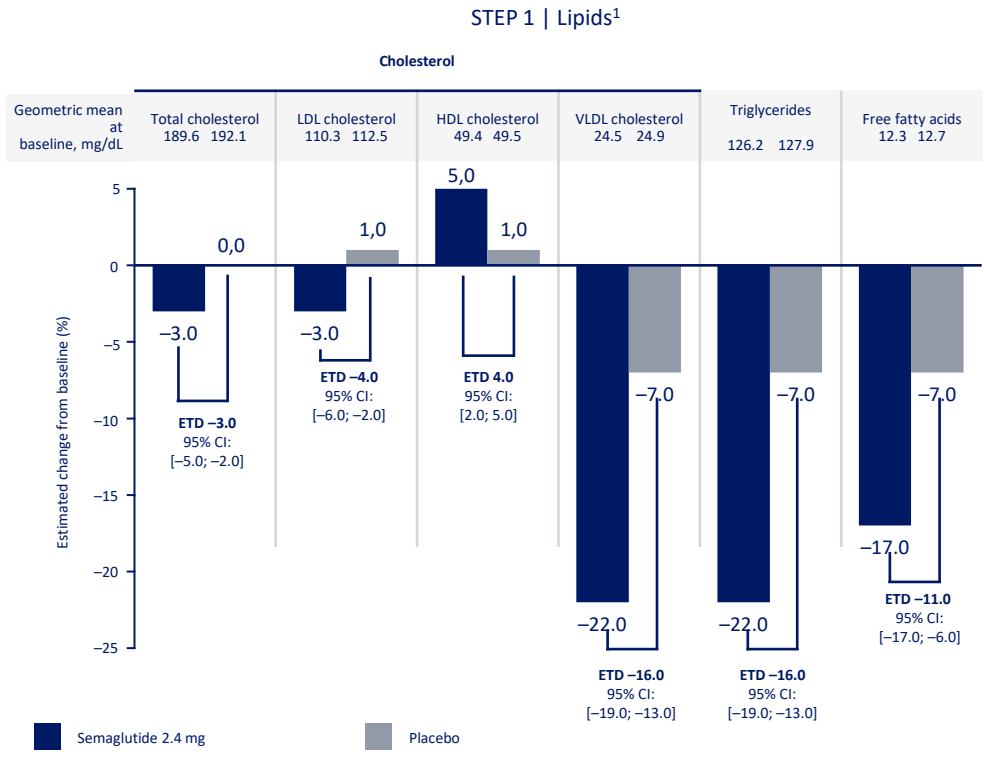


Data shown for the treatment policy estimand (treatment effect regardless of trial product discontinuation and use of rescue medication).
**Statistically significant vs placebo. †Statistically significant vs liraglutide 3.0 mg.*
BW, body weight; CI, confidence interval; ETD, estimated treatment difference; IBT, intensive behavioural therapy; T2D, type 2 diabetes.
1. Wilding JPH et al. N Engl J Med 2021;384:989–1002; 2. Wadden TA et al. JAMA 2021;325:1403–13; 3. Rubino D et al. JAMA 2021;325:1414–25; 4. Garvey WT et al. Nat Med 2022;28:2083–91; 5. Rubino DM et al. JAMA 2022;327:138–50; 6. Davies M et al. Lancet 2021;397:971–84; 7. Kadowaki T et al. Lancet Diabetes Endocrinol 2022;10:193–206.

Semaglutide 2.4 mg has benefits on CV risk factors







CI, confidence interval; CV, cardiovascular; ETD, estimated treatment difference; ETR, estimated treatment ratio; HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

1. *Wilding et al. N Engl J Med 2021;384:989-1002; 2. Kosoribod M et al. Poster presented at the American College of Cardiology (ACC) conference, May 15–17 2021, virtual meeting; 3. Davies M et al. Lancet 2021;397:971–84.*

SELECT TRIAL

Semaglutide | effects on cardiovascular outcomes in people with overweight or obesity

SELECT: trial overview

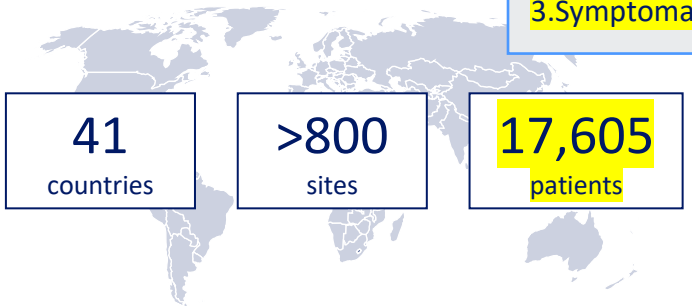
Three-component MACE:
1.non-fatal myocardial infarction
2.non-fatal stroke
3.CV death

Primary objective[1]

To demonstrate that s.c. semaglutide 2.4 mg/once week lowers the incidence of MACE (major adverse cardiovascular event)
versus placebo, both added to Standard of Care, in people with established CVD and overweight or obesity

1.Prior MI
2.Prior stroke
3.Symptomatic PAD

Key trial numbers[1]



41	>800	17,605
countries	sites	patients

Trial design[1,2]

- **Overweight or obesity (BMI ≥ 27)**
- **Established CVD***
- **No prior history of diabetes (HbA1c <6.5%)**

Semaglutide 2.4 mg OW

Placebo

Event-driven (≥1,225 first MACE)
~5 years

SELECT-LIFE[3]

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

*Established CVD: MI ≥60 days ago, stroke ≥60 days ago, or symptomatic PAD, NYHA class IV excluded.
CV, cardiovascular; CVD, CV 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. Ryan DH et al. Am Heart J 2020;229:61–9; 3. ClinicalTrials.gov. SELECT-LIFE. Available at: https://clinicaltrials.gov/ct2/show/NCT04972721. Accessed January 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.

Baseline characteristics of trial participants (2/3)

SELECT: N=17,604

Clinical characteristics

Mean HbA_{1c}[1]

5.8%

With prediabetes[1]

66.4%

Mean BMI[1]

33.3 kg/m²

Distribution (kg/m^2)[1]

<30 | 30–<35 | 35–<40 | 40–<45 | ≥45

28.5 | 42.5 | 19.0 | 6.7 | 3.3%

Mean eGFR

82.5 mL/min/1.73 m

Chronic heart failure[1]

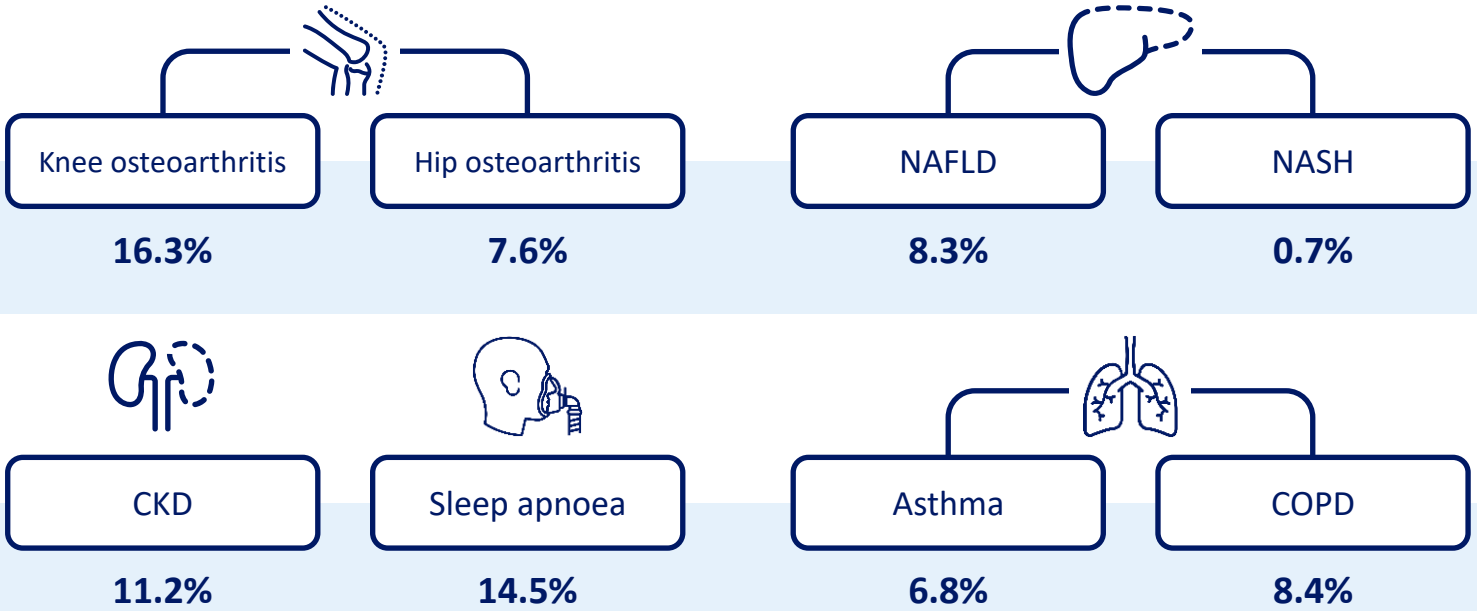
24.3%

- 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.
- BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association.
- 1. supplementary of Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563

Baseline characteristics of trial participants (3/3)

SELECT: N=17,604

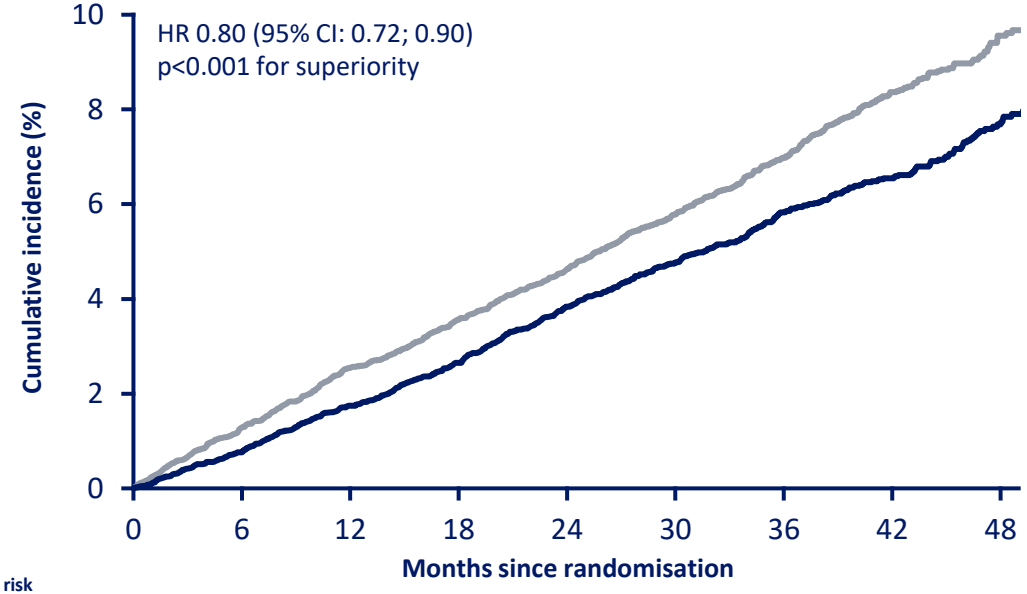
Obesity-related comorbidities



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.
CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.
Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563

Cumulative incidence of MACE

SELECT: Primary cardiovascular composite endpoint



No. at risk									
Semaglutide	8,803	8,695	8,561	8,427	8,254	7,229	5,777	4,126	1,734
Placebo	8,801	8,652	8,487	8,326	8,164	7,101	5,660	4,015	1,672

Semaglutide 2.4 mg — Placebo

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]

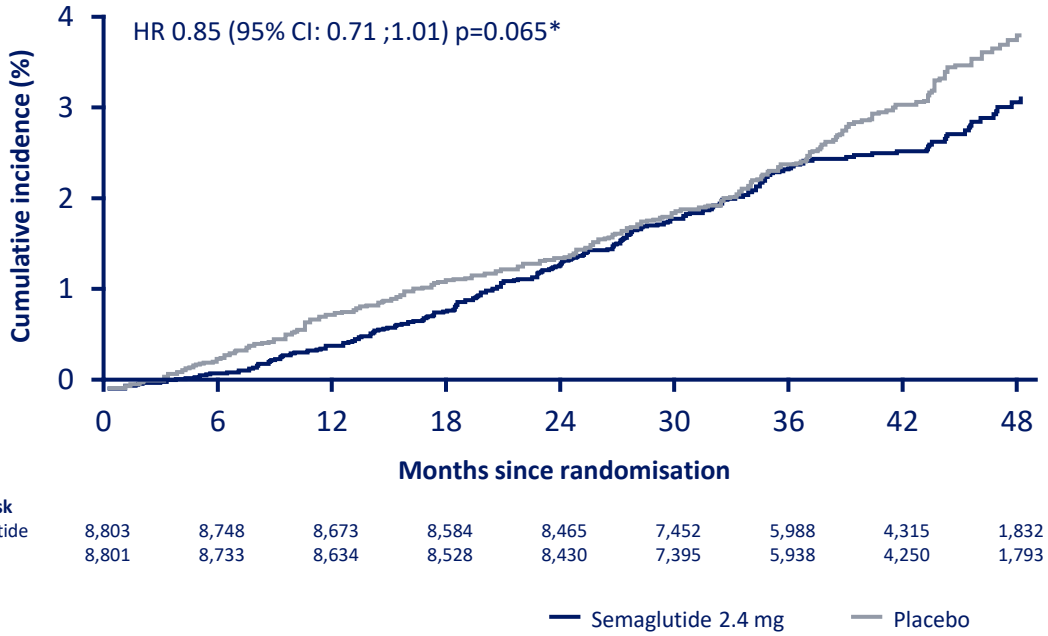
All three components (death from CV causes, non-fatal MI and non-fatal stroke) contributed to MACE risk reduction

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

Cumulative incidence of death from CV causes

SELECT: First confirmatory secondary endpoint



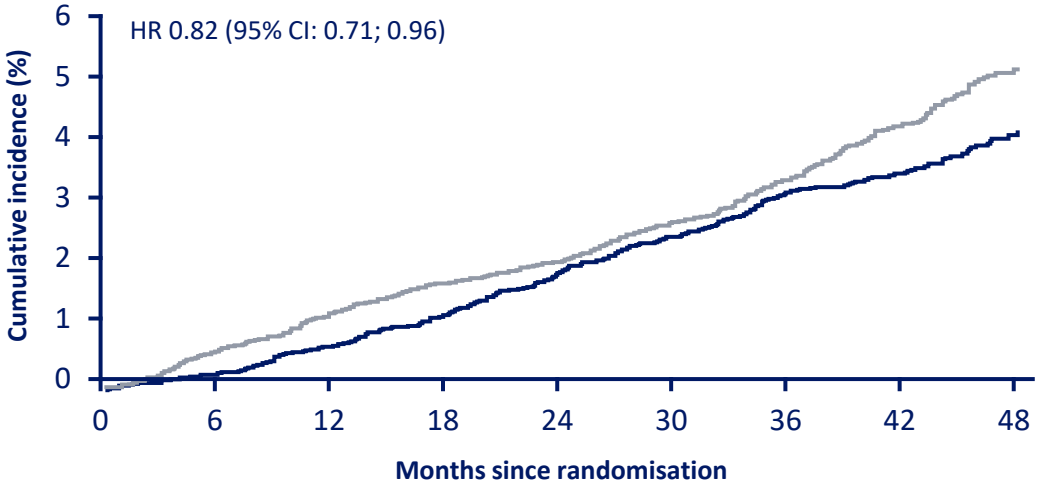
Semaglutide 2.4 mg reduced
the risk of death from CV causes by 15%
compared with placebo

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.

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

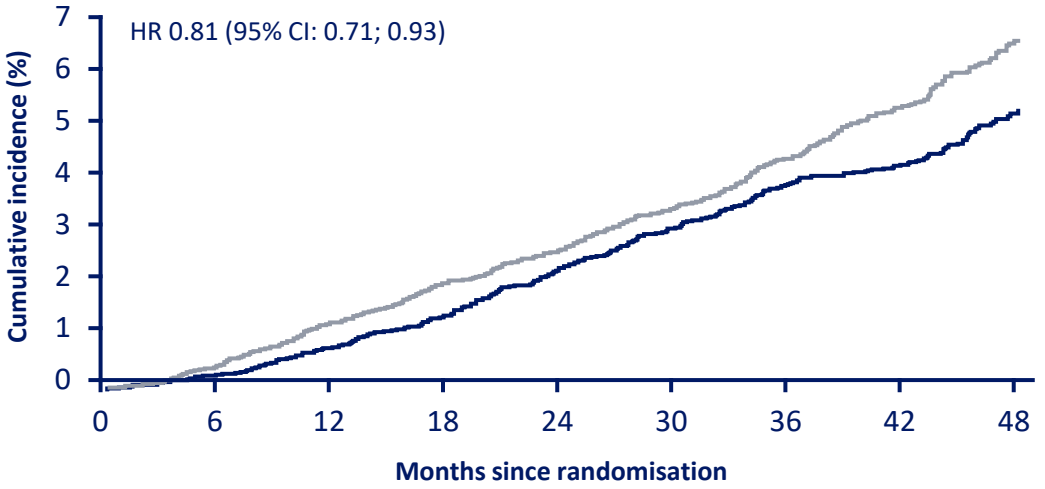
Semaglutide 2.4 mg reduced
the risk of composite HF events by 18%
compared with placebo

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

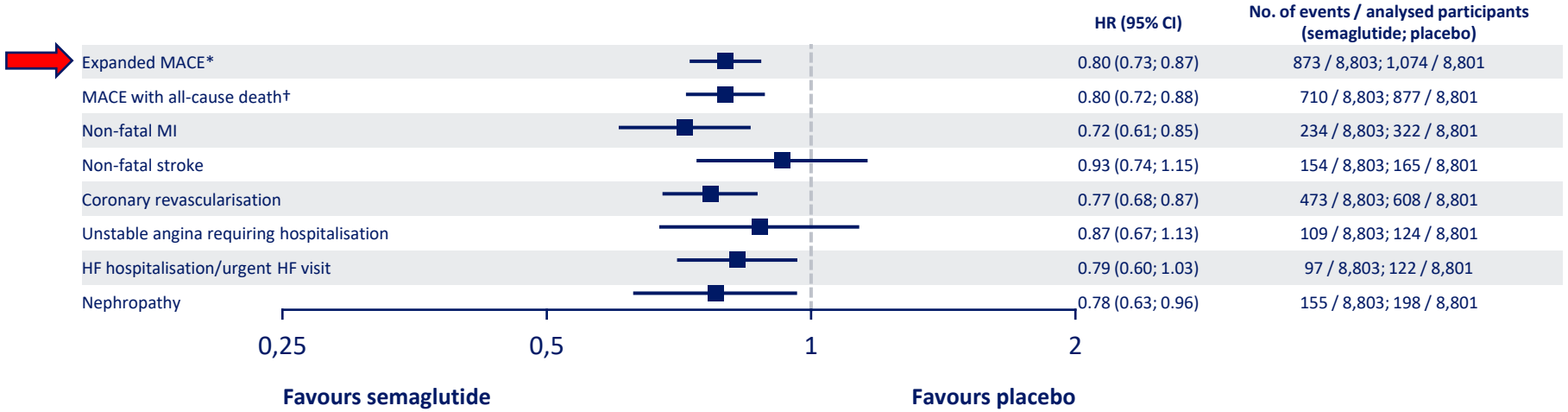
Although the 95% CI was <1, superiority testing was not performed per the hierarchical testing procedure*

*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.

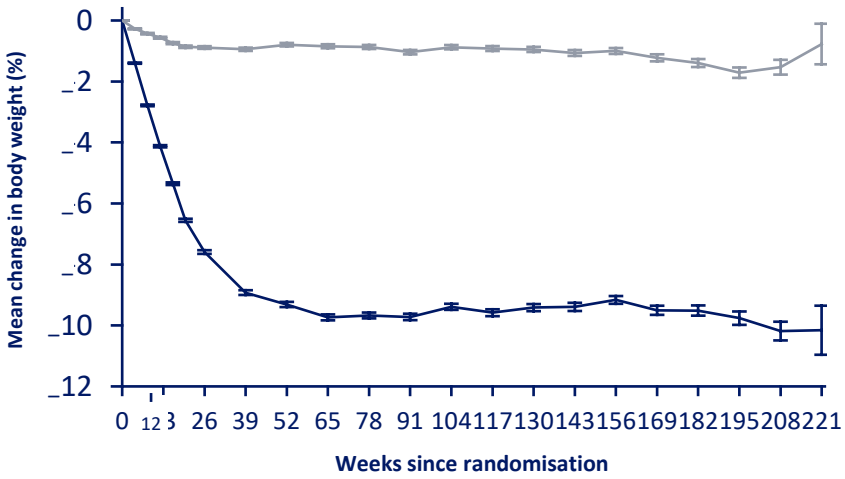
Change in body weight (%)

SELECT

Observed change from baseline over time

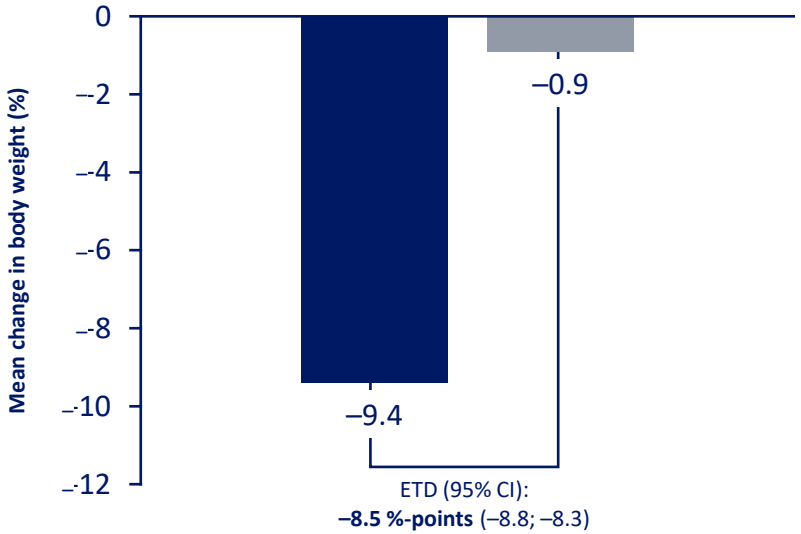
Mean baseline body weight, kg:

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.

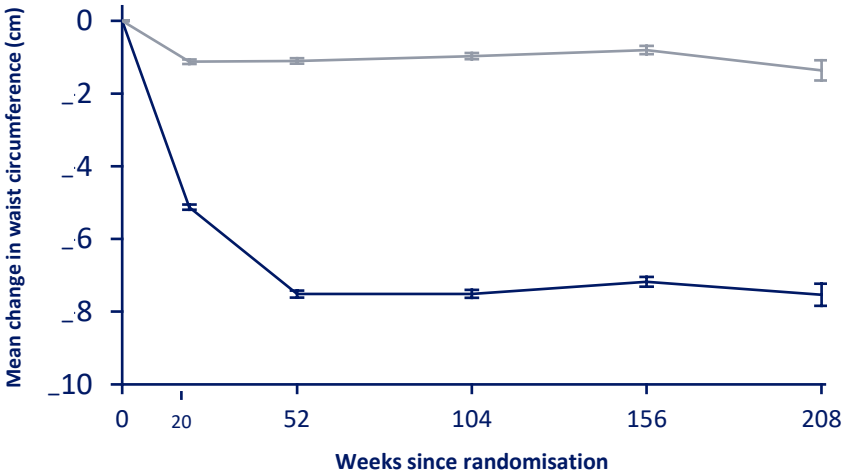
Change in waist circumference

SELECT

Observed change from baseline over time

Mean (SD) baseline waist circumference, cm:

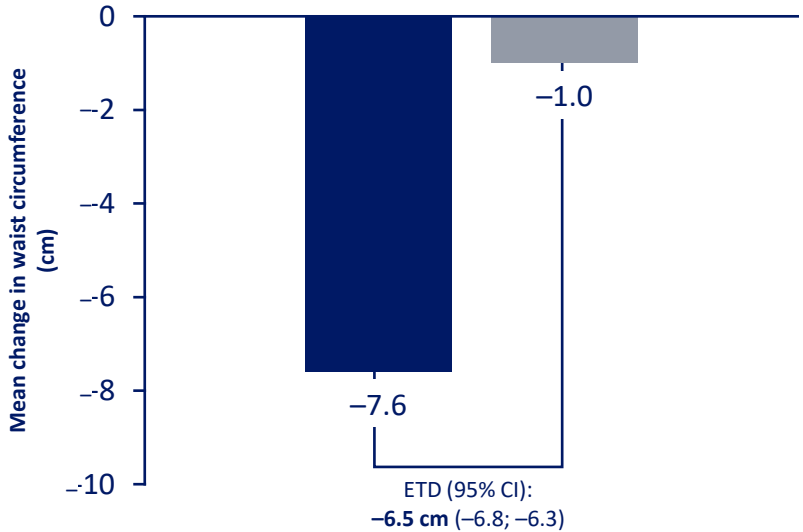
Semaglutide 2.4 mg: 111.3 (13.1) Placebo: 111.4 (13.1)



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*



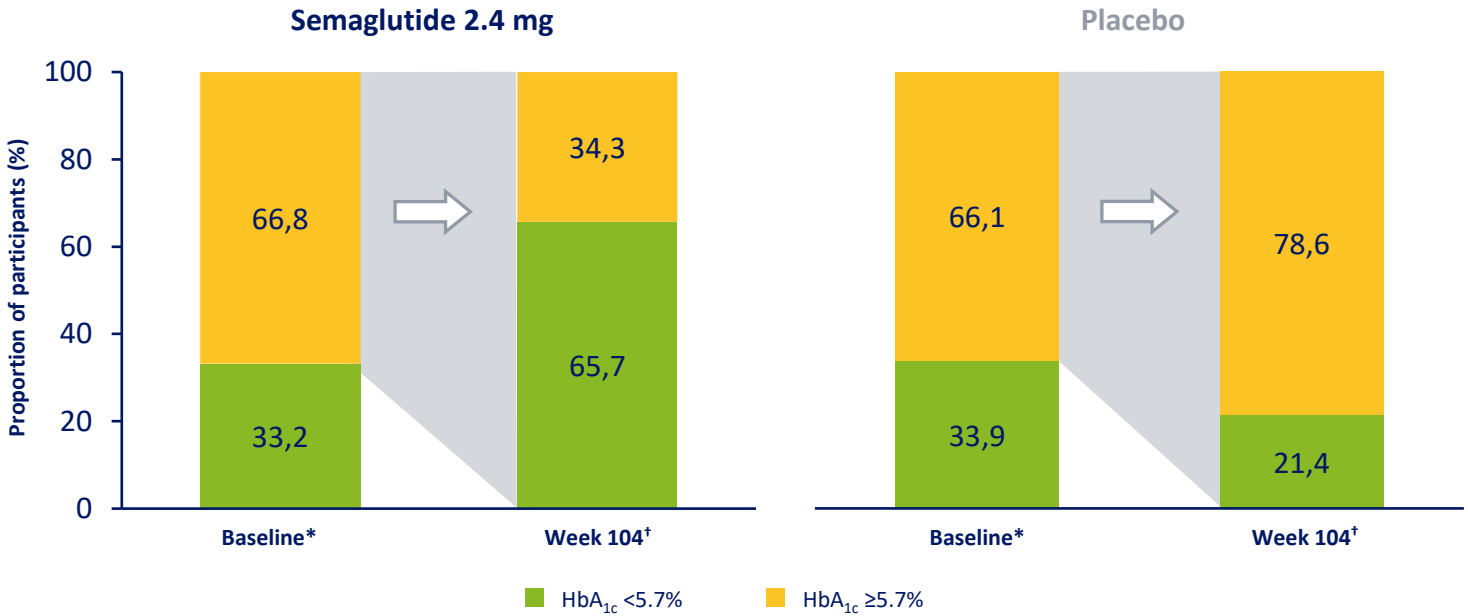
Semaglutide 2.4 mg Placebo

*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 HbA_{1c}

SELECT: Participants with baseline HbA_{1c} ≥5.7%



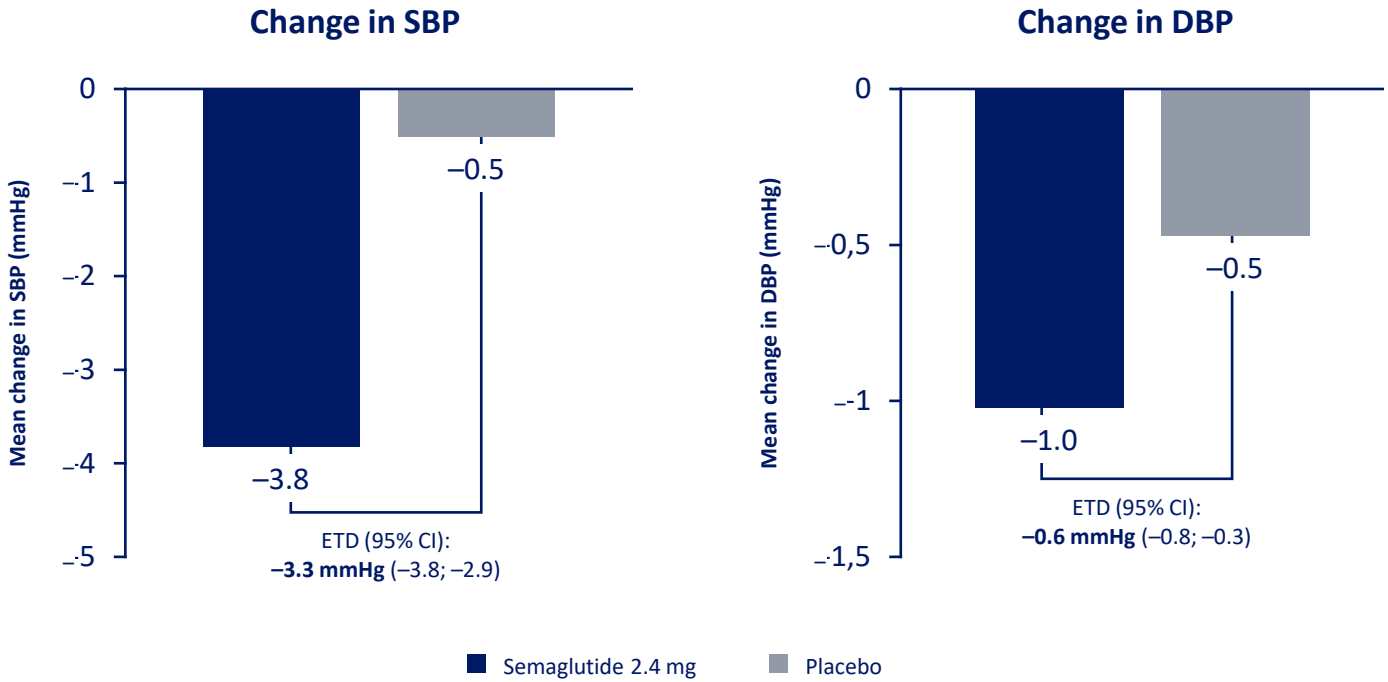
*Proportions estimated using logistic regression with treatment as factor and baseline HbA_{1c} as a covariate. *Number of participants with HbA_{1c} ≥5.7% at baseline was 5,877 for semaglutide and 5,819 for placebo. †Number of participants with HbA_{1c} ≥5.7% at baseline and evaluable data (assessment 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.

Change in blood pressure (mmHg)

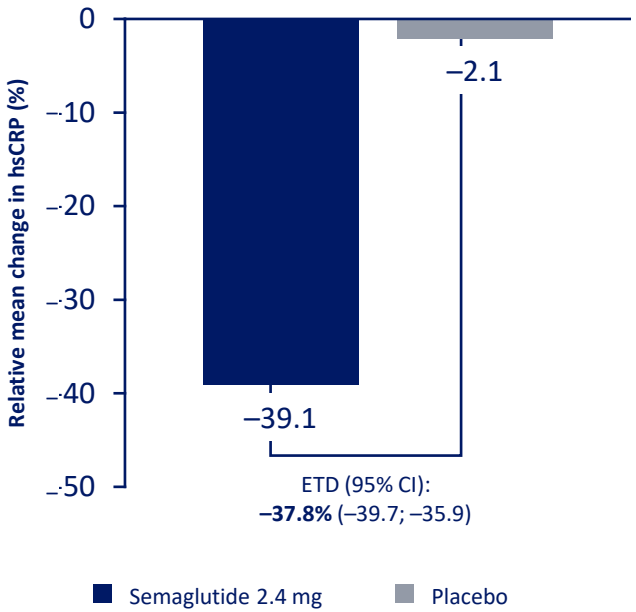
SELECT



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 hsCRP (%)

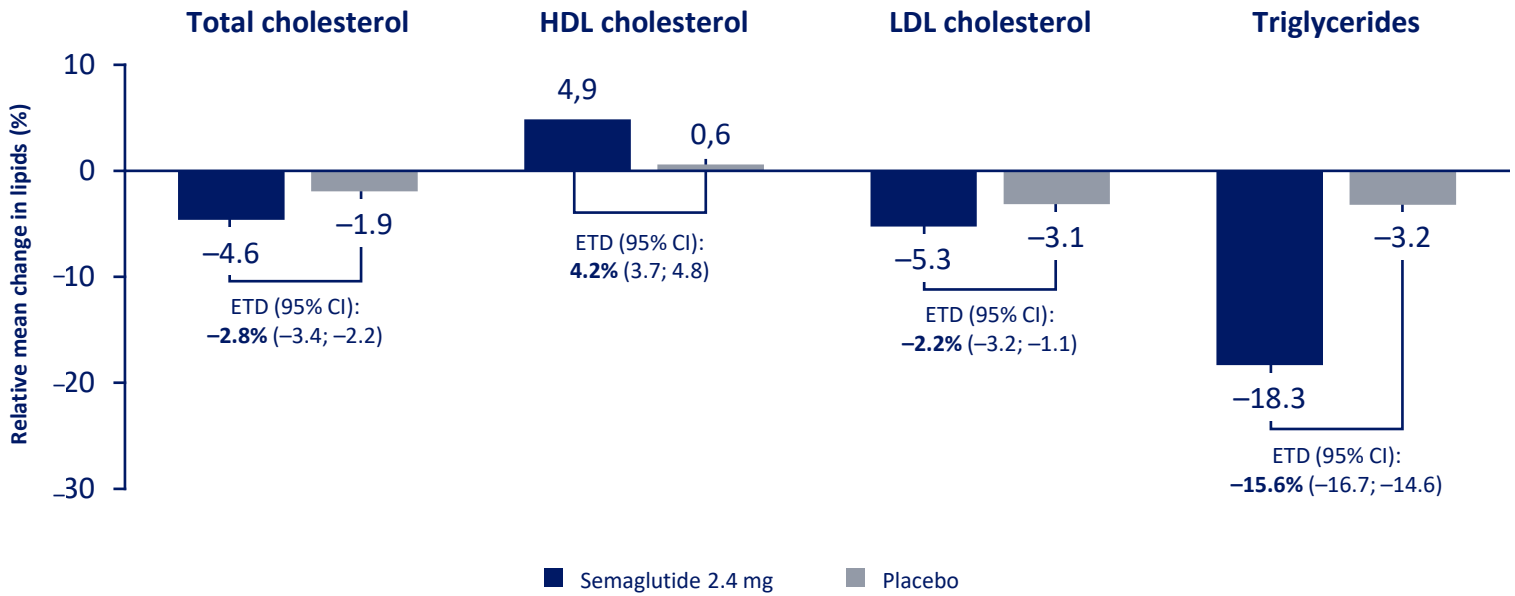
SELECT



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.

Change in lipids (%)

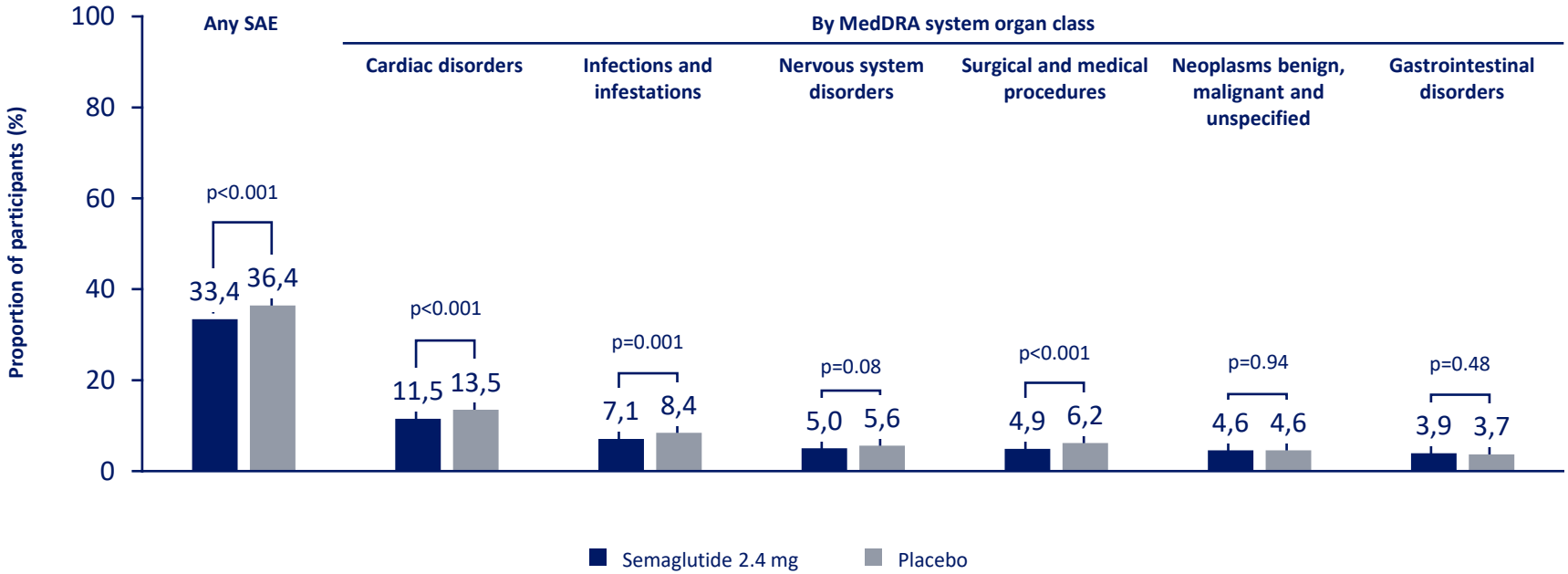
SELECT



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.

Serious adverse events

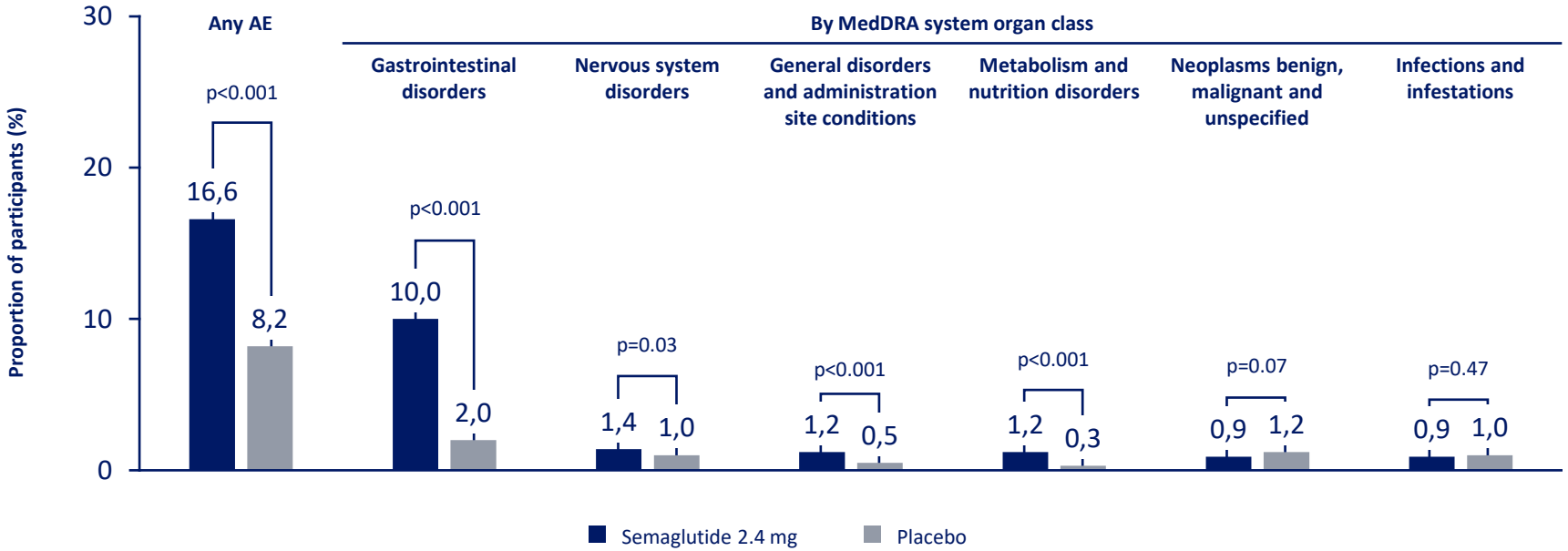
SELECT



Two-sided p-values from Fisher's exact test for test of no difference.
MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event.
Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

Permanent discontinuations due to adverse events

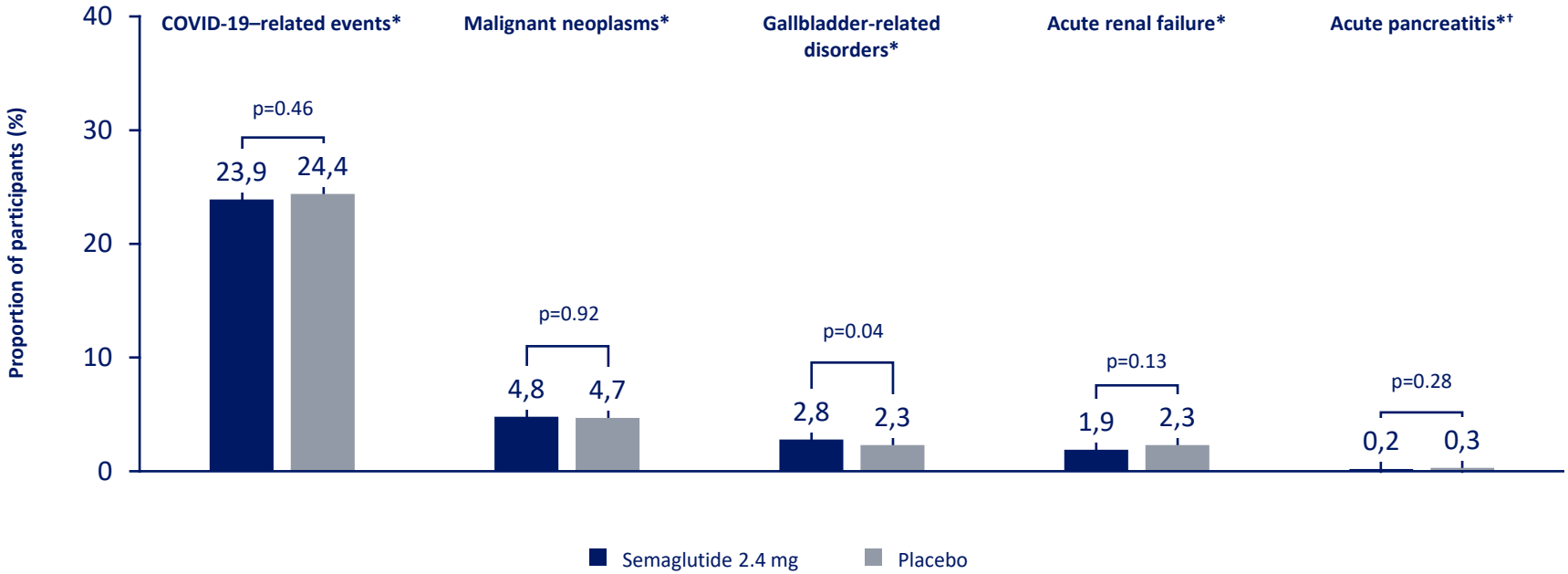
SELECT



Two-sided p-values from Fisher's exact test for test of no difference.
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.
Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

Prespecified adverse events of special interest

SELECT



**Based on prespecified MedDRA queries. †Confirmed by the EAC. Investigators reported pancreatitis (acute or other type) events in 29 participants (0.3%) in the semaglutide group and 30 participants (0.3%) in the placebo group.*
AE, adverse event; EAC, Events Adjudication Committee; MedDRA, Medical Dictionary for Regulatory Activities.
Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

Conclusions from SELECT

Semaglutide 2.4 mg significantly reduced risk of MACE by 20% vs placebo in people with established CVD and overweight or obesity without T2D, with consistent effects across participant subgroups[1,2]

Semaglutide 2.4 mg had consistent beneficial effects across measured CV endpoints[1]

Results suggest a benefit with semaglutide on the risk of CV death, HF composite endpoints and all-cause death (risk reduction for CV-related death did not reach statistical significance and other endpoints were not tested)[1]

Semaglutide 2.4 mg improved multiple modifiable risk factors known to drive CV events, such as body weight, waist circumference, blood pressure, lipids and hsCRP[1]

SELECT safety findings were consistent with previous trials with semaglutide[1–3]

This is the first time a weight management medication has shown a reduction in CV events in people with established CVD and overweight or obesity, without T2D[1]

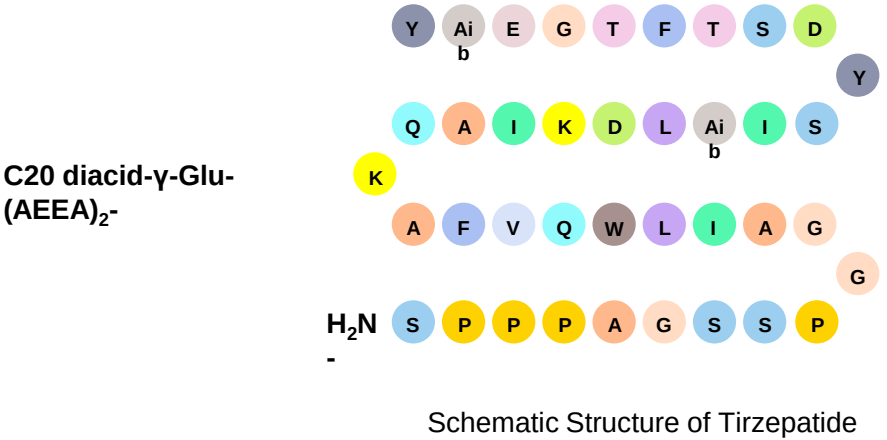
CV, cardiovascular; CVD, cardiovascular disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; hsCRP, high-sensitivity C-reactive protein; MACE, major adverse cardiovascular events; T2D, type 2 diabetes.

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; 3. Bergman NC et al. Diabetes Obes Metab 2023;25:18–35.

TIRZEPATIDE

Tirzepatide: A Brief Description

- Tirzepatide is a long-acting GIP receptor and GLP-1 receptor agonist[1]
- It is an amino acid sequence including a C20 fatty diacid moiety that enables albumin binding and prolongs the half-life[1]
- Mean half-life of approximately 5 days (116.7 h), enabling once-weekly dosing[1]
- Its plasma concentrations in patients with renal and hepatic impairment do not differ from those in healthy people[2]



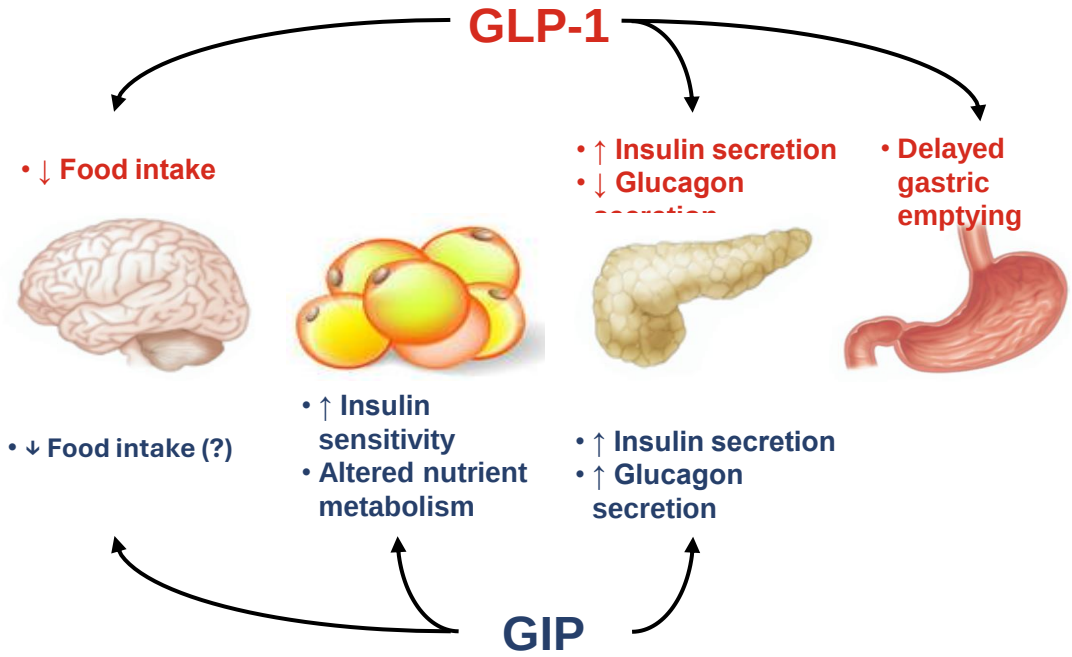
Schematic Structure of Tirzepatide

GIP=Glucose-Dependent Insulinotropic Polypeptide; GIPR=Glucose-Dependent Insulinotropic Polypeptide Receptor; GLP-1R=Glucagon-Like Peptide-1 Receptor.

1. Coskun T, et al. *Mol Metab*. 2018;18:3-14. 2. Urva S, et al. *Diabetes*. 2020;69(1):Abstract 971-P.

GIP and GLP-1 Receptor Agonist: Potential Mechanism of Action

- GLP-1 has suggested direct actions in the CNS, islets, and stomach[1,2]
- GIP has shown potential actions in research in the CNS (preclinical), adipose tissue (clinical and preclinical), and islets (clinical and preclinical)[2-4]
- A single-molecule GIP/GLP-1 receptor agonist may enable therapeutic actions that are improved over the sum of GIP and GLP-1 single-receptor agonism[5,6]



CNS=central nervous system; GIP=glucose-dependent insulinotropic polypeptide; GLP-1=glucagon-like peptide-1.

1. Müller TD, et al. *Mol Metab*. 2019;30:72-130. 2. Seino Y, et al. *J Diabetes Investig*. 2010;1(1-2):8-23. 3. Fukuda M. *Diabetes*. 2021;70(8):dbi210001. 4. Nauck MA, et al. *Diabetes Obes Metab*. 2021;23(3):5-29. 5. Samms RJ, et al. *Trends Endocrinol Metab*. 2020;31(6):410-421. 6. Bastin M, et al. *Diabetes Metab Syndr Obes*. 2019;12:1973-1985.

Focus Areas for Tirzepatide Clinical MoA Research

Tirzepatide

Glycemic control

- Beta-cell function
- Insulin sensitivity
- Glucagon secretion

Weight reduction

- Body Composition
- Food intake
- Appetite Regulation
- Modified lipid oxidation

Lipid metabolism

- Plasma lipid control

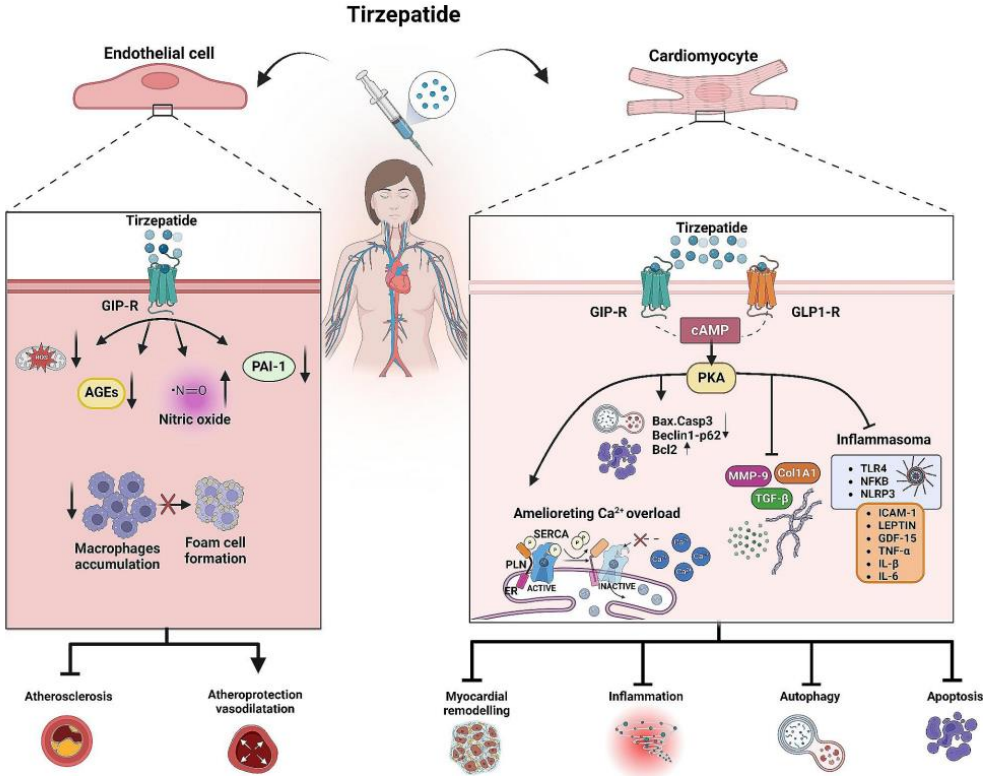
Cardiorenal Effects

- Heart Rate
- Blood Pressure
- Renal Function

MoA=mechanism of action.

1. Heise T, et al. Oral presentation at: *ADA 2022*. Abstract 338-OR. 2. Heise T, et al. *Lancet Diabetes Endocrinol*. 2022;10(6):418-429. 3. Gastaldelli A, et al. *Lancet Diabetes Endocrinol*. 2022;10(6):393-406. 4. Samms RJ, et al. *Trends Endocrinol Metab*. 2020;31(6):410-421.

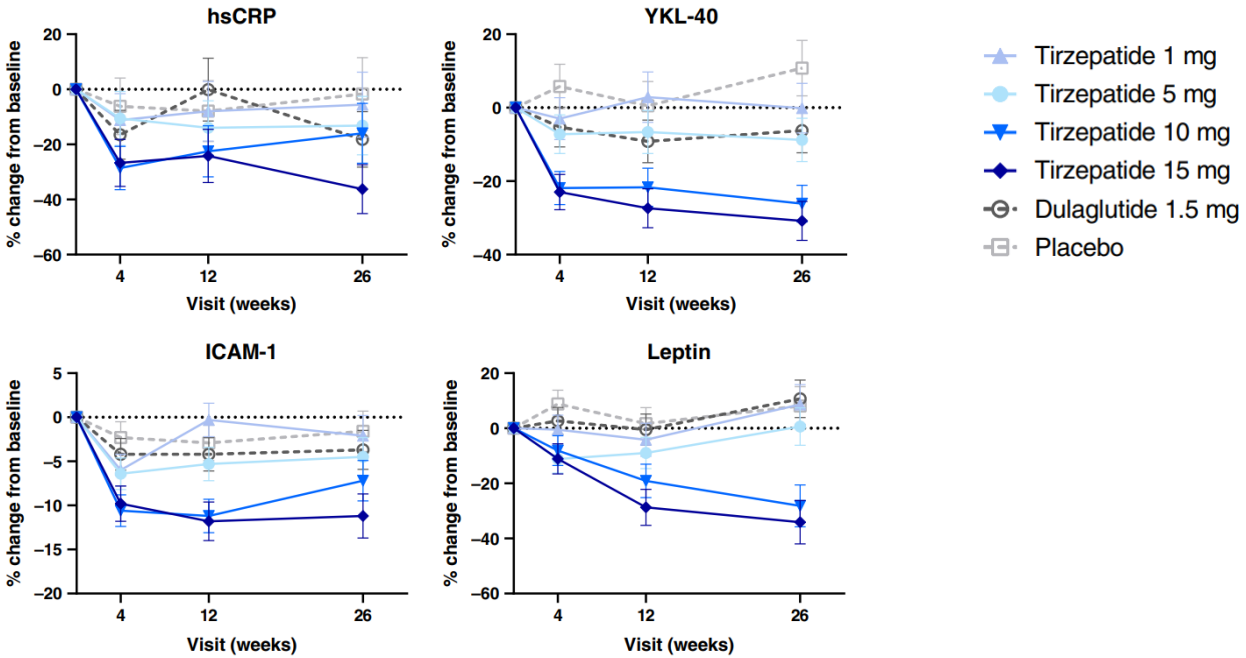
Comprehensive picture of molecular and cellular interaction relevant to beneficial effect of tirzepatide in metabolic and cardiovascular disorders



Taktaz F. Bridging the gap between GLP1-receptor agonists and cardiovascular outcomes: evidence for the role of tirzepatide. Cardiovascular Diabetology (2024) 23:242

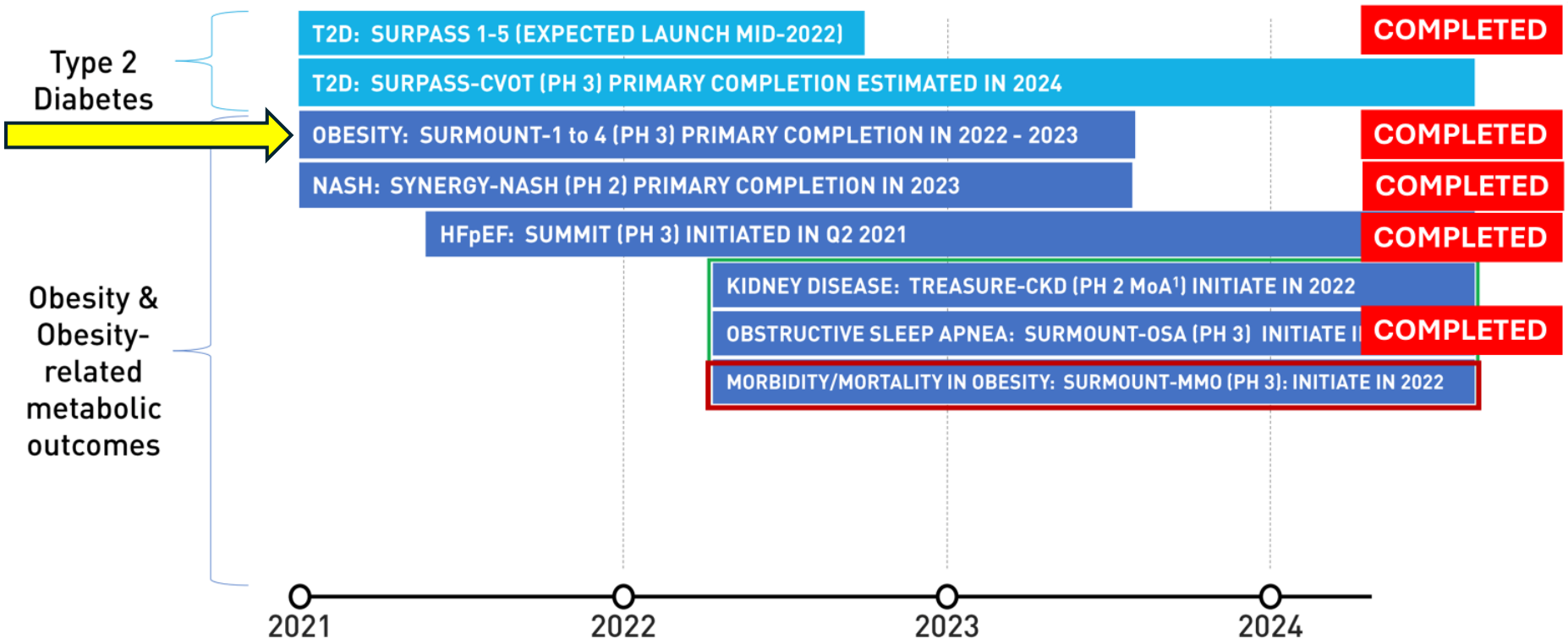
Tirzepatide decreased several biomarkers that have been associated with cardiovascular risk.

Percentage change from baseline over time in hsCRP, YKL-40, ICAM-1, and leptin



Jonathan M. Wilson. The dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist tirzepatide improves cardiovascular risk biomarkers in patients with type 2 diabetes: A post hoc analysis. Diabetes Obes Metab. 2022;24:148–153

Tirzepatide Clinical Development Program

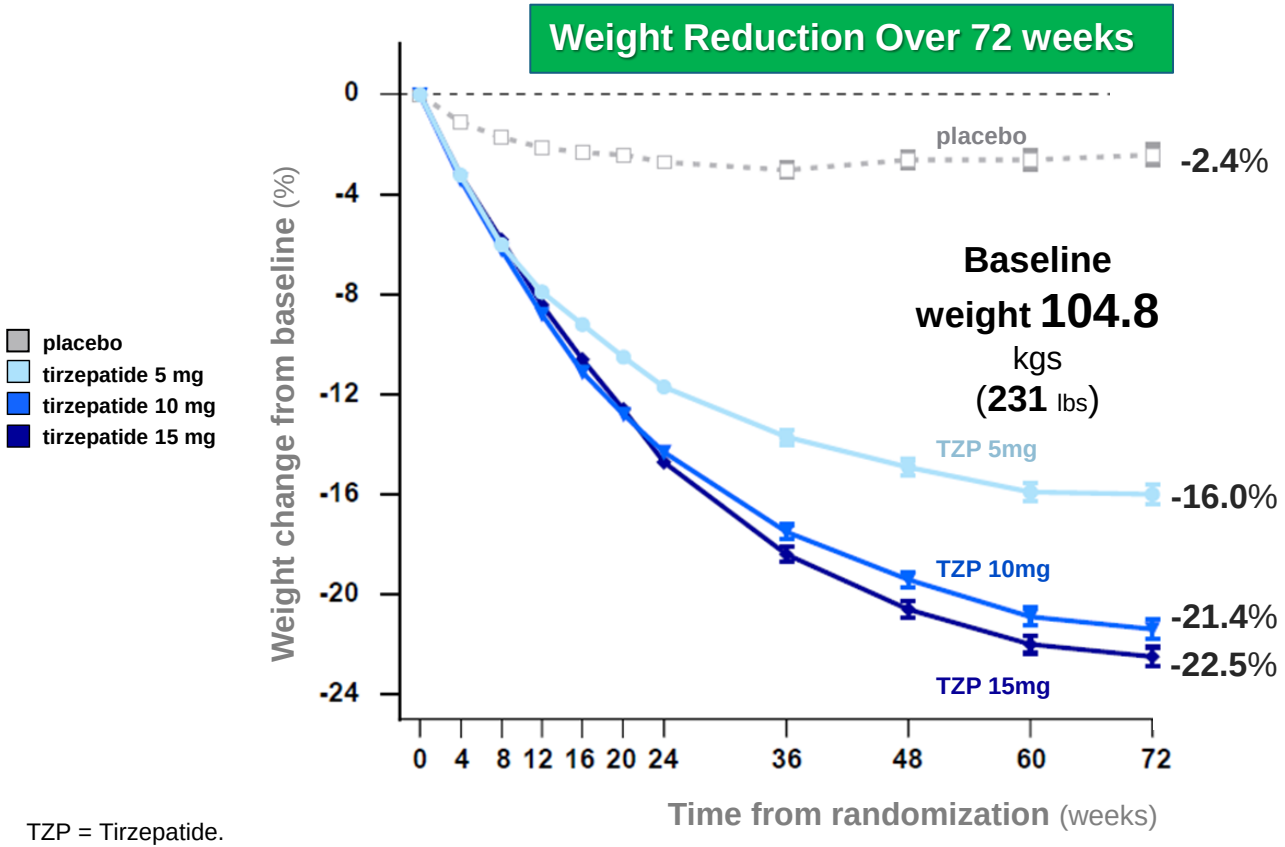


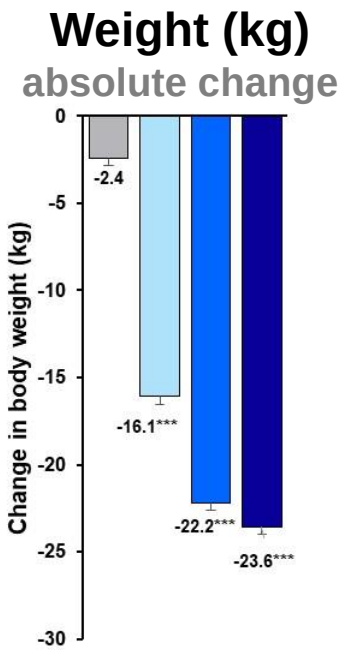
[1]Not an outcomes study;
CKD/DKD = Chronic Kidney Disease/Diabetic Kidney Disease; CVOT = Cardiovascular Outcomes; HFpEF = Heart Failure with Preserved Ejection Fraction; MoA = Mechanism of Action; NASH = Non-Alcoholic Steatohepatitis; OSA = Obstructive Sleep Apnea; T2D = Type 2 Diabetes.

LeRoux, Jastreboff, Nissen SURMOUNT Symposium presented at the 2022 EASD annual meeting

SURMOUNT 1: Study in people with Obesity without Diabetes

SURMOUNT 1: Study in people with Obesity without Diabetes



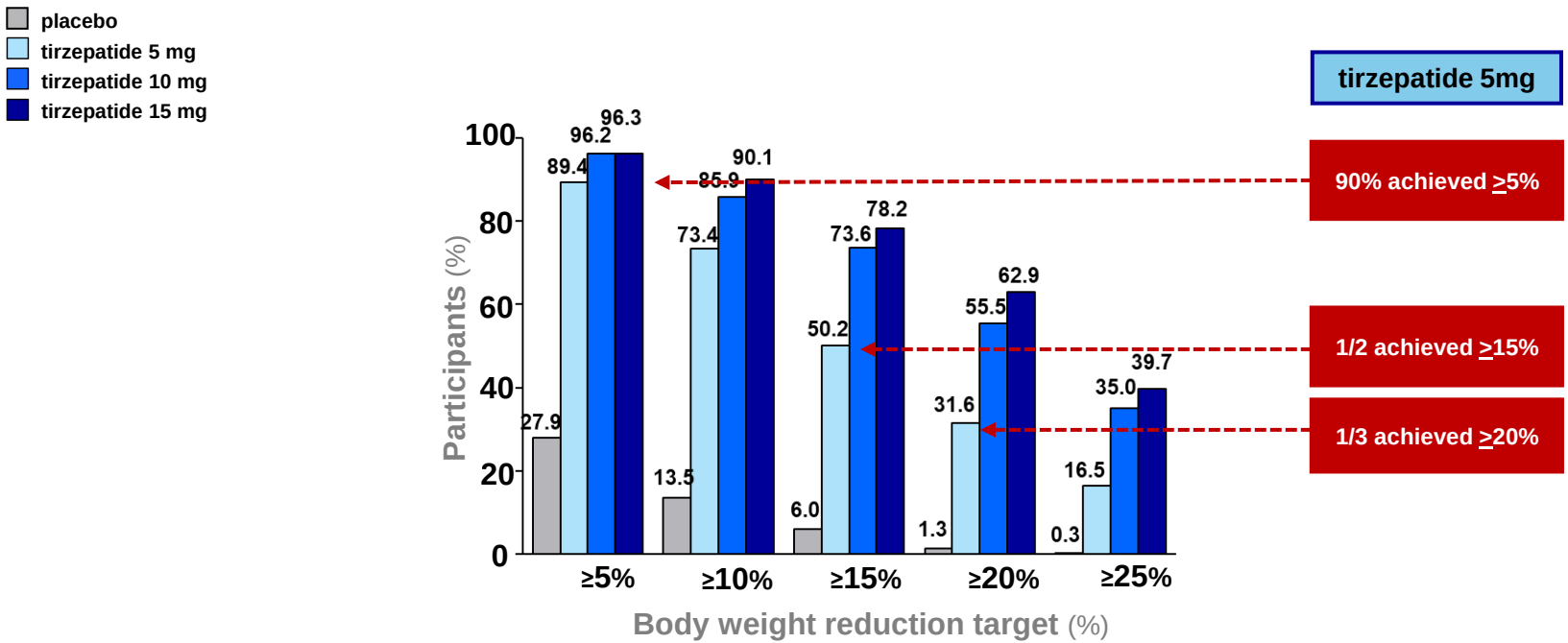


Average Weight Reduction 16-24 kg (35-52 lbs)

TZP = Tirzepatide.

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

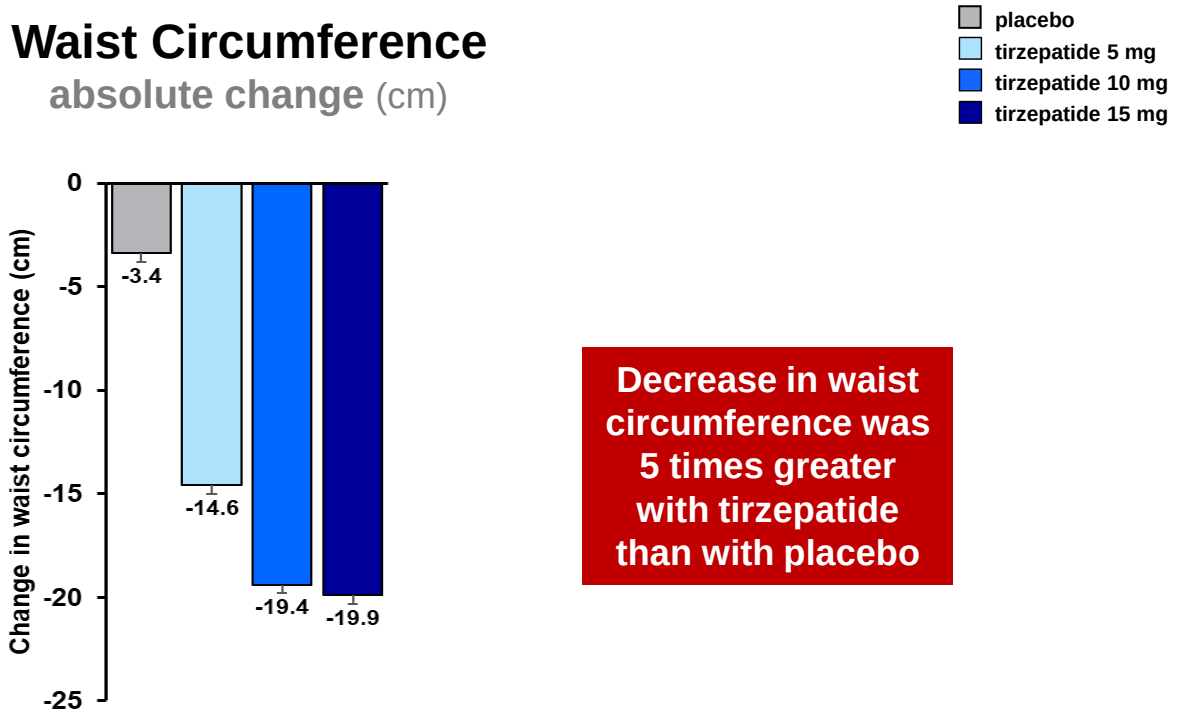
Percent of Participant Reaching Weight-Reduction Targets



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

Change in Waist Circumference

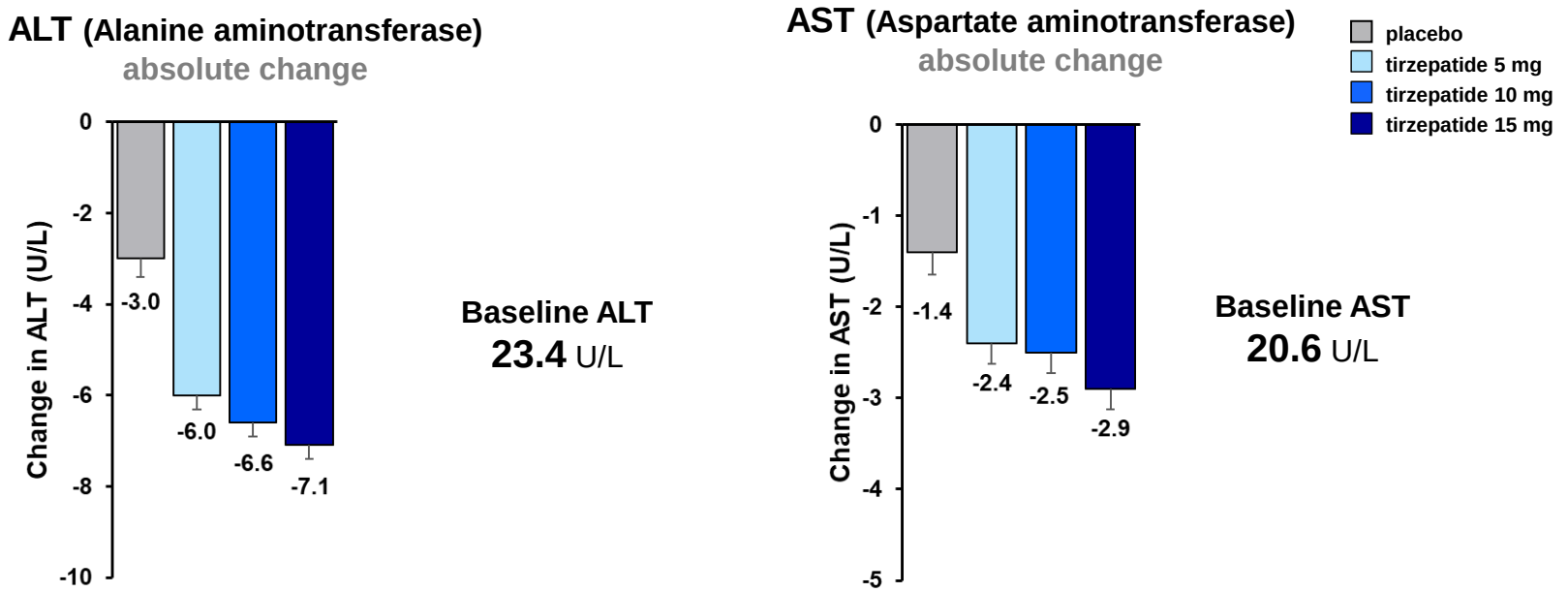
Baseline waist circumference 114.1 cm



Decrease in waist circumference was 5 times greater with tirzepatide than with placebo

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

Change in Liver Enzymes

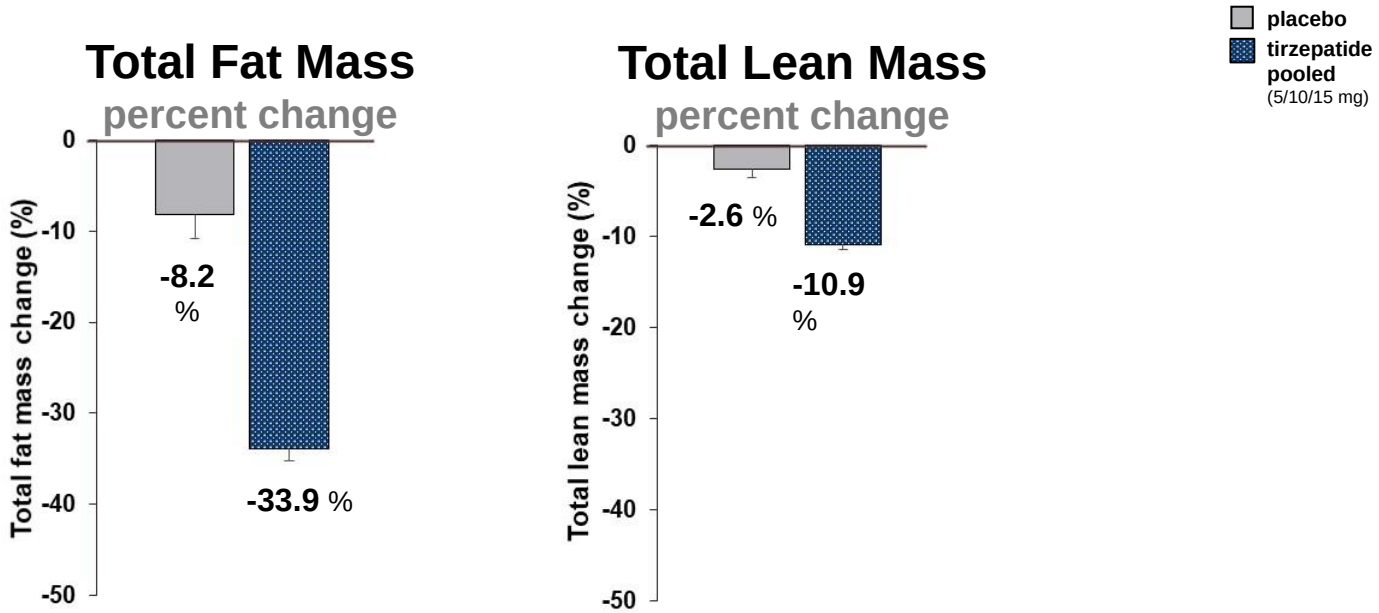


The decrease in liver enzymes activity with tirzepatide needs to be explored further in studies to assess the potential benefit on liver health

ALT = Alanine Transaminase; AST = Aspartate Transaminase.
Jastreboff AM, et al. *N Engl J Med* 2022. Jul 21;387(3):205-216

Change in Body Composition (DXA)

n = 160



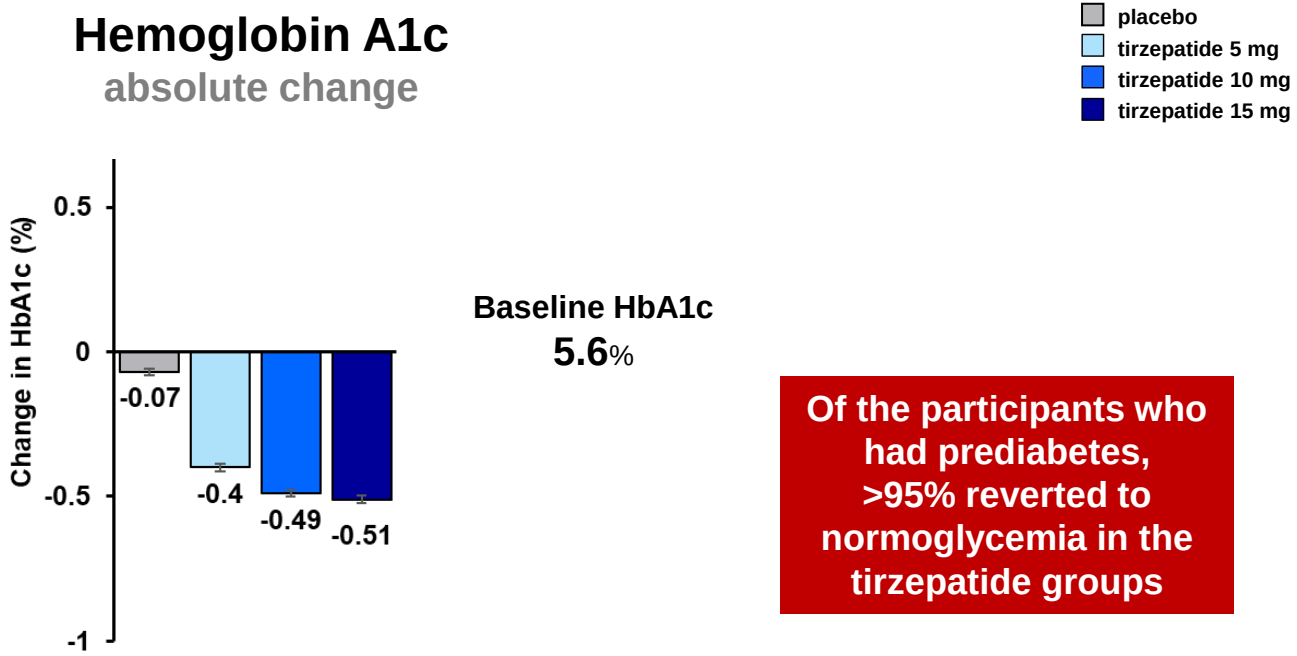
As with lifestyle and surgical treatments, participants on tirzepatide had a ~3 times greater percent reduction in fat mass than lean mass, resulting in an overall improvement in body composition.

Additionally, participants on tirzepatide had significant improvements in visceral fat mass.

DXA = Dual-energy x-ray absorptiometry.

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

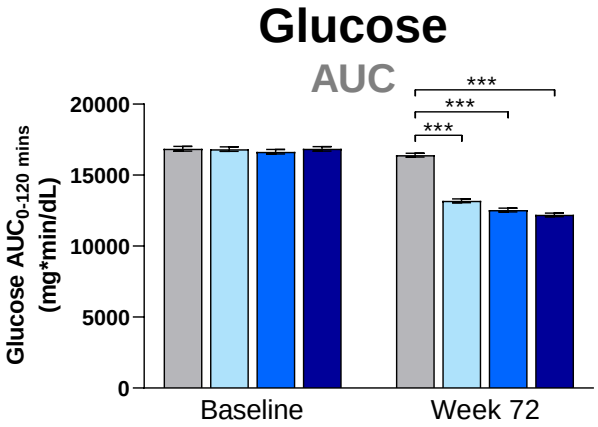
Change **in** HbA1c

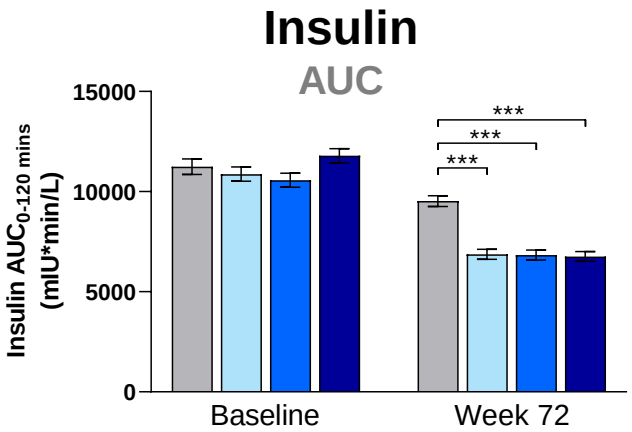


HbA1c = Glycated Hemoglobin.

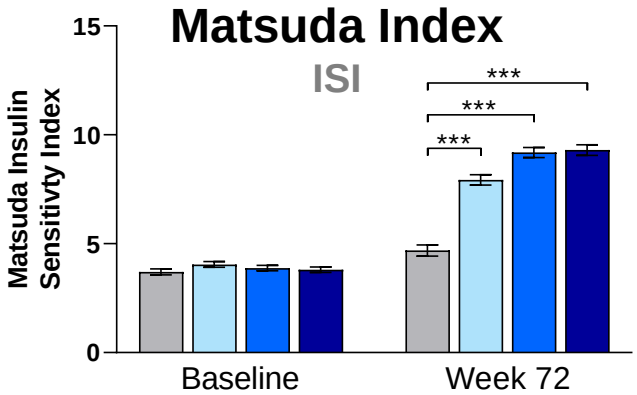
Jastreboff AM, et al. *N Engl J Med* 2022. Jul 21;387(3):205-216

Insulin Sensitivity





placebo
tirzepatide 5 mg
tirzepatide 10 mg
tirzepatide 15 mg

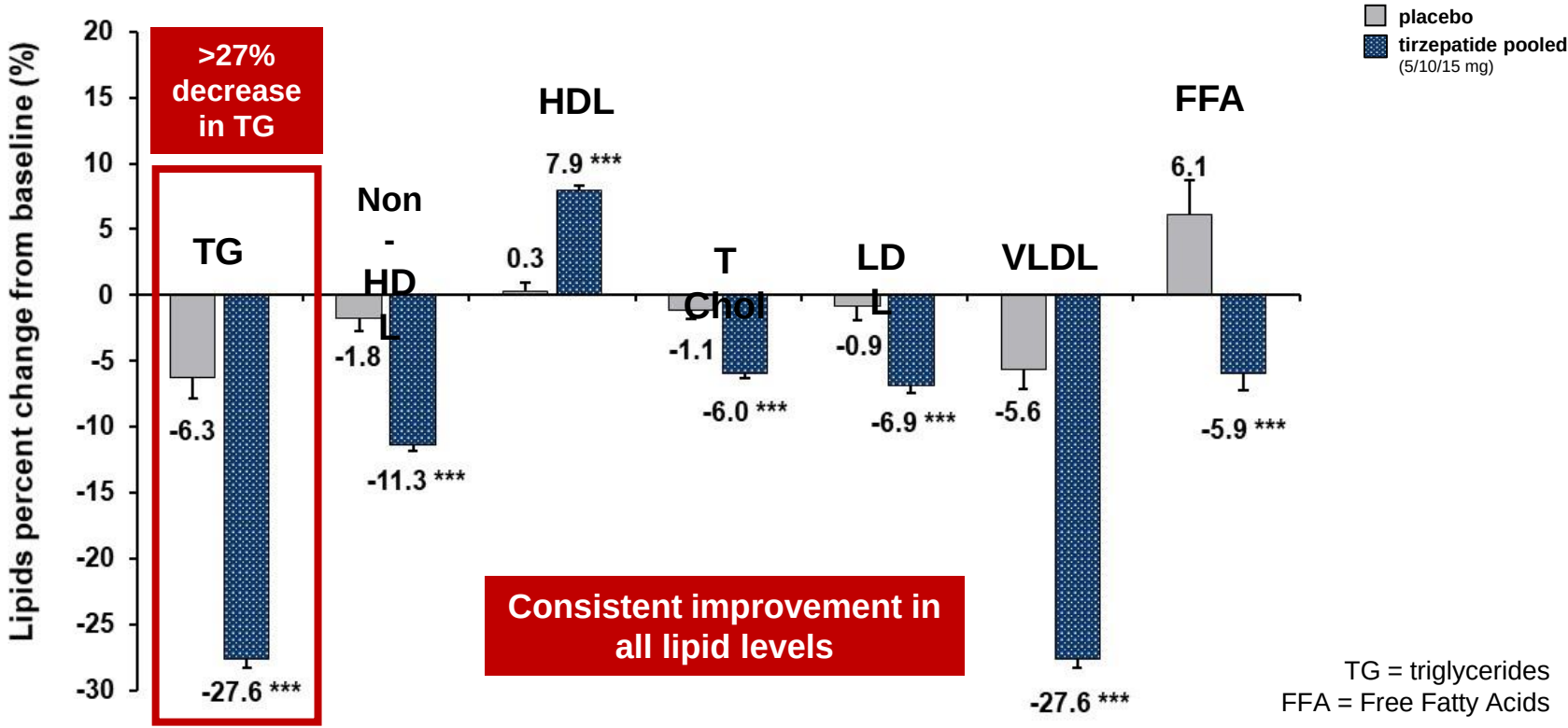


Improvement in insulin sensitivity with all doses of tirzepatide at 72 weeks

AUC = Area under the curve; ISI = Insulin sensitivity index.

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

Change in Lipids



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

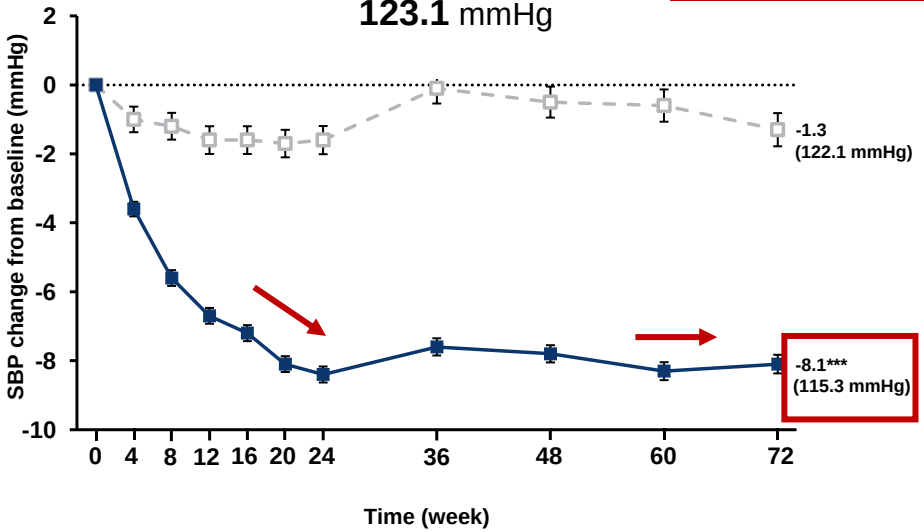
Jastreboff AM, et al. *N Engl J Med* 2022. Jul 21;387(3):205-216

Change in Blood Pressure Over 72 weeks

Systolic Blood Pressure

baseline SBP
123.1 mmHg

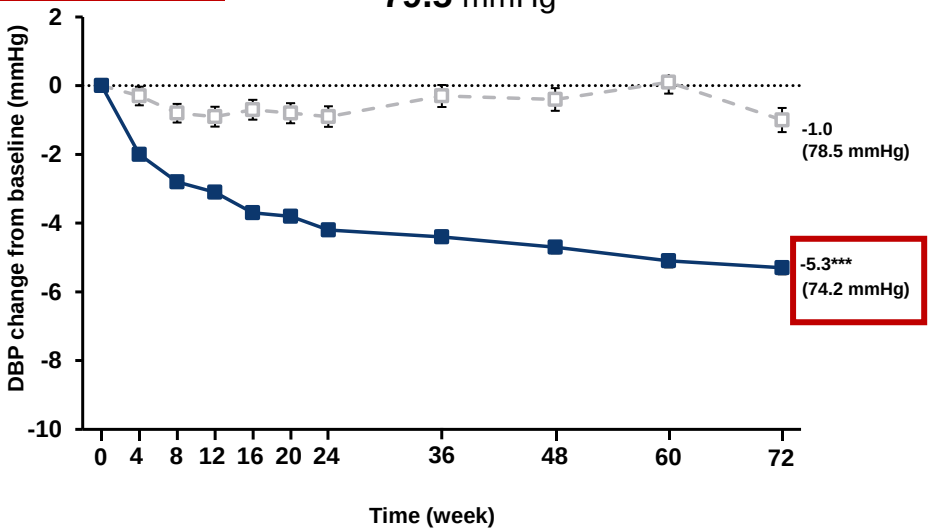
Improvement in blood pressure does not appear to be dependent on the high magnitude of weight reduction



Diastolic Blood Pressure

baseline DBP
79.5 mmHg

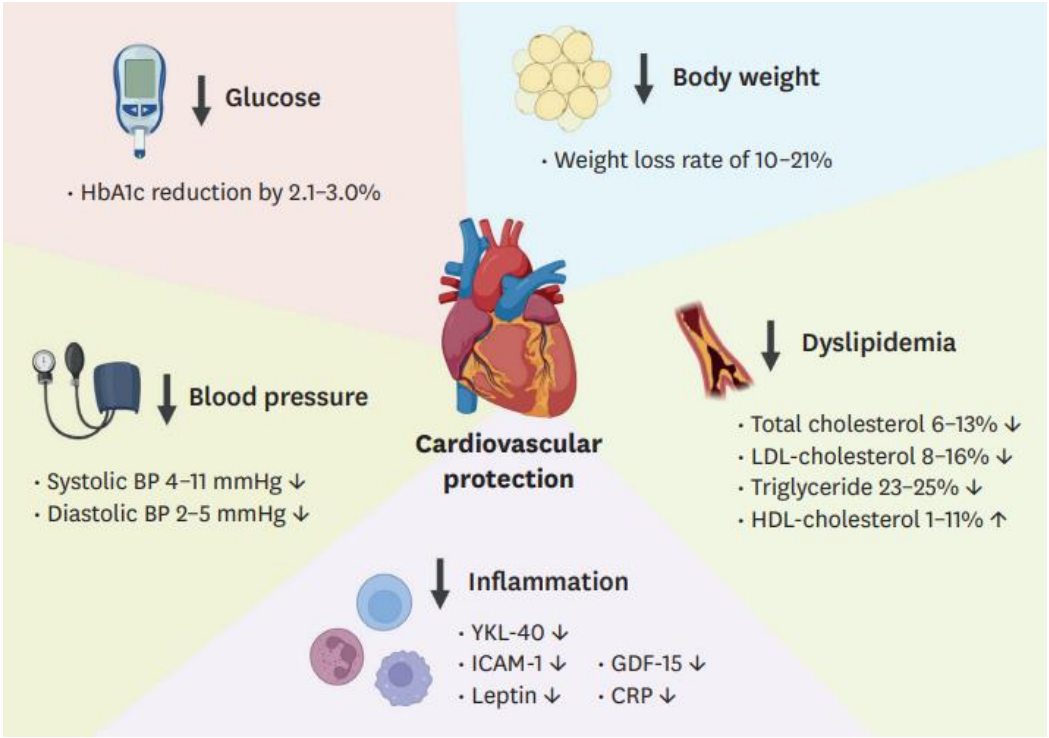
placebo
tirzepatide pooled
(5/10/15 mg)



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

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

Potential mechanisms by which tirzepatide imparts cardiovascular benefits.



Cho YK. The Cardiovascular Effect of Tirzepatide: A Glucagon-Like Peptide-1 and Glucose-Dependent Insulinotropic Polypeptide Dual Agonist. J Lipid Atheroscler. 2023 Sep;12(3):213-222

nature medicine

ANALYSIS

https://doi.org/10.1038/s41591-022-01707-4

Check for updates

OPEN

Tirzepatide cardiovascular event risk assessment: a pre-specified meta-analysis

Naveed Sattar[1,6] ✉, Darren K. McGuire[2], Imre Pavo[3], Govinda J. Weerakkody[4], Hiroshi Nishiyama[4], Russell J. Wiese[4] and Sophia Zoungas[5,6] ✉

Study Design

Randomization

- The meta-analysis included centrally adjudicated MACEs from:
  - One Phase 2 study (26 weeks in duration)
  - Five international Phase 3 studies (40-52 weeks in duration)
  - One regional Phase 3 study (52 weeks in duration)

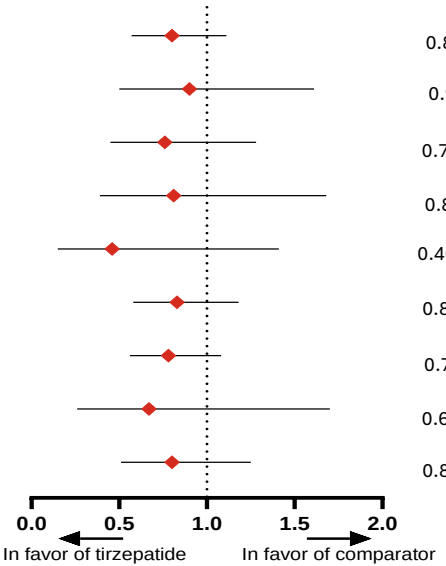
TZP Phase 2 trial	**2:1 to tirzepatide (1 mg, 5 mg, 10 mg, or 15 mg) or comparator (placebo or dulaglutide 1.5 mg)**
TZP Phase 3 trial SURPASS-1 SURPASS-2 SURPASS-3 SURPASS-5 SURPASS J-mono	**3:1 to tirzepatide (5 mg, 10 mg, or 15 mg) or comparator (placebo, semaglutide 1 mg, insulin degludec or dulaglutide 0.75 mg)**
TZP Phase 3 trial SURPASS-4	**1:1 to tirzepatide (5 mg, 10 mg, or 15 mg) or comparator (insulin glargine)**

MACE=Major Adverse Cardiovascular Event; TZP=Tirzepatide.

Sattar N, et al. *Nat Med*. 2022; (Ahead of Print).

Primary and Secondary Cardiovascular Outcomes Confirmed by Centrally Blinded Adjudication

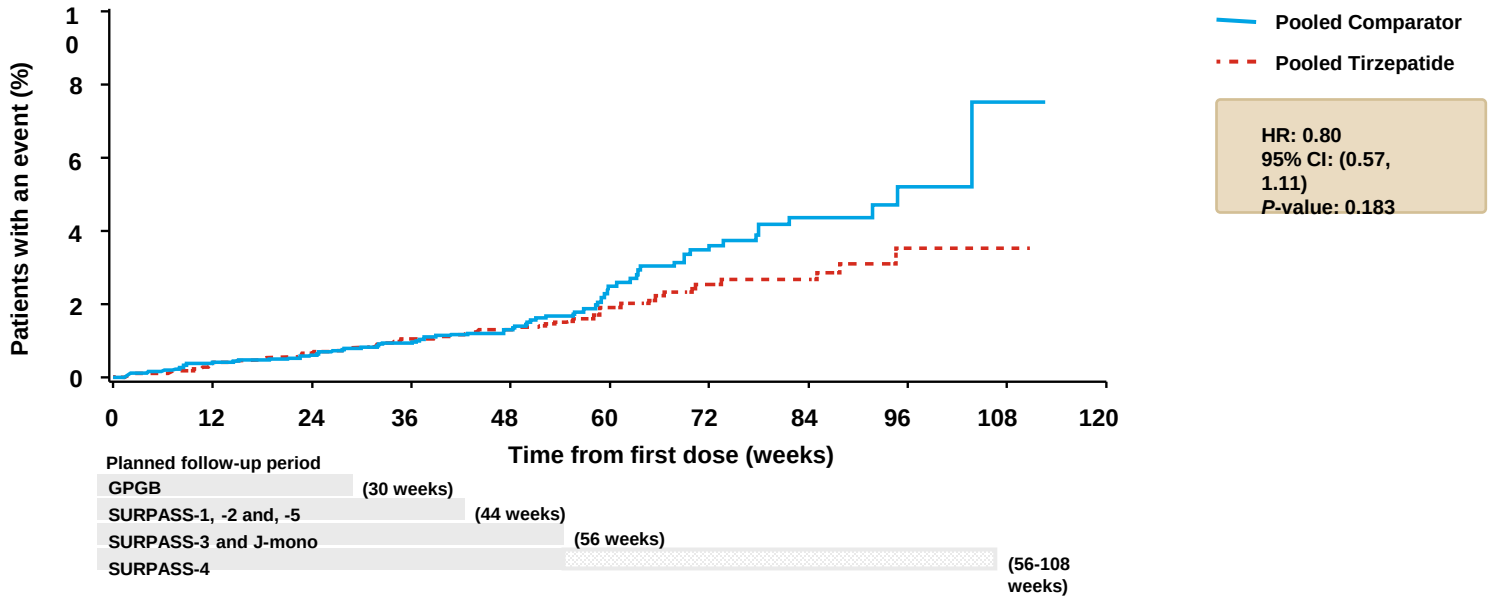
	All Tirzepatide N=4887 n (n/100 Person-Years[a])	All Comparator N=2328 n (n/100 Person-Years[a])	HR With 95% CI	HR (95% CI)	*P* Value
Composite MACE-4	72 (1.35)	70 (1.61)		0.80 (0.57, 1.11)	0.183
Death due to cardiovascular cause[b]	25 (0.46)	22 (0.43)		0.90 (0.50, 1.61)	
Myocardial infarction	30 (0.56)	30 (0.71)		0.76 (0.45, 1.28)	
Stroke	15 (0.27)	15 (0.35)		0.81 (0.39, 1.68)	
Hospitalization for unstable angina	5 (0.09)	9 (0.20)		0.46 (0.15, 1.41)	
Composite MACE-3[c]	67 (1.25)	62 (1.42)		0.83 (0.58, 1.18)	0.306
Composite MACE-3 or hospitalization for heart failure	74 (1.39)	71 (1.71)		0.78 (0.56, 1.08)	0.137
Hospitalization for heart failure	10 (0.19)	9 (0.29)		0.67 (0.26, 1.70)	
All-cause death	41 (0.76)	39 (0.86)		0.80 (0.51, 1.25)	



[a]Strata size adjusted estimate. Strata are defined as trial-level cardiovascular risk (SURPASS-4 forms one stratum, and all other trials form one stratum). [b]Death due to cardiovascular cause includes adjudication-confirmed deaths due to a cardiovascular or undetermined cause. [c]MACE-3 includes death due to cardiovascular or undetermined cause, myocardial infarction, or stroke.
Note: *P* values were based on the Wald Chi-square test. Data are point estimate of HR (illustrated by the diamond symbol) and range of 2-sided 95% CI of the HR.
HR=Hazard Ratio; CI=Confidence Interval; MACE=Major Adverse Cardiovascular Event.
Sattar N, et al. *Nat Med*. 2022; (Ahead of Print).

Effect of Pooled Tirzepatide versus Pooled Comparator on Time to First Occurrence of Adjudication-Confirmed MACE-4 (Primary Outcome)

Adjusted Kaplan-Meier Plot



Cumulative number of events: Number of patients at risk

Pooled Tirzepatide:	0:4887	15:4813	28:4726	43:4477	53:2477	62:960	68:832	69:515	72:188	72:19	72:0
Pooled Comparator:	0:2328	13:2292	19:2250	28:2118	36:1438	52:914	62:794	67:496	69:172	70:14	70:0

Note: *P* values are based on the Wald Chi-square test. Gray bars represent the planned follow-up period for trials GPGB (30 weeks), SURPASS-1, SURPASS-2 and SURPASS-5 (44 weeks), SURPASS-3 and SURPASS J-mono (56 weeks), and SURPASS-4 (56-108 weeks).

HR=Hazard Ratio; CI=Confidence Interval; MACE=Major Adverse Cardiovascular Event.

Sattar N, et al. *Nat Med*. 2022;(Ahead of Print).

ESC European Society of Cardiology
European Heart Journal (2024) **00**, 1–123
https://doi.org/10.1093/eurheartj/ehae177

2024 ESC Guidelines for the management of chronic coronary syndromes

Developed by the task force for the management of chronic coronary syndromes of the European Society of Cardiology (ESC)

ESC Guidelines recommendations on GLP-1RAs

- Glucose-lowering medications with effects on weight loss (e.g. GLP-1RAs) should be considered in patients with T2DM with overweight or obesity to reduce weight (Class IIa, level of evidence B).[61]
- GLP-1RAs with proven CV benefit (liraglutide, semaglutide s.c., dulaglutide, efpeglenatide) are recommended in patients with T2DM and atherosclerotic CVD to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication (Class I, level of evidence A).[61]
- The GLP-1 RA semaglutide should be considered in overweight (BMI >27 kg/m^2) or obese chronic coronary syndrome patients without diabetes to reduce CV mortality, MI, or stroke. (Class IIa, level of evidence B).[155]

NEW FRONTIERS

Gut Hormone Monotherapies in Development

FGF-21
FGF-21 analogs (phase 1, 2)[a-c]

Ghrelin/GOAT
GOAT inhibitor (phase 2)[d]

GDF-15
LA-GDF-15 (phase 1)[e]
GDF-15 agonist (phase 1)[e]

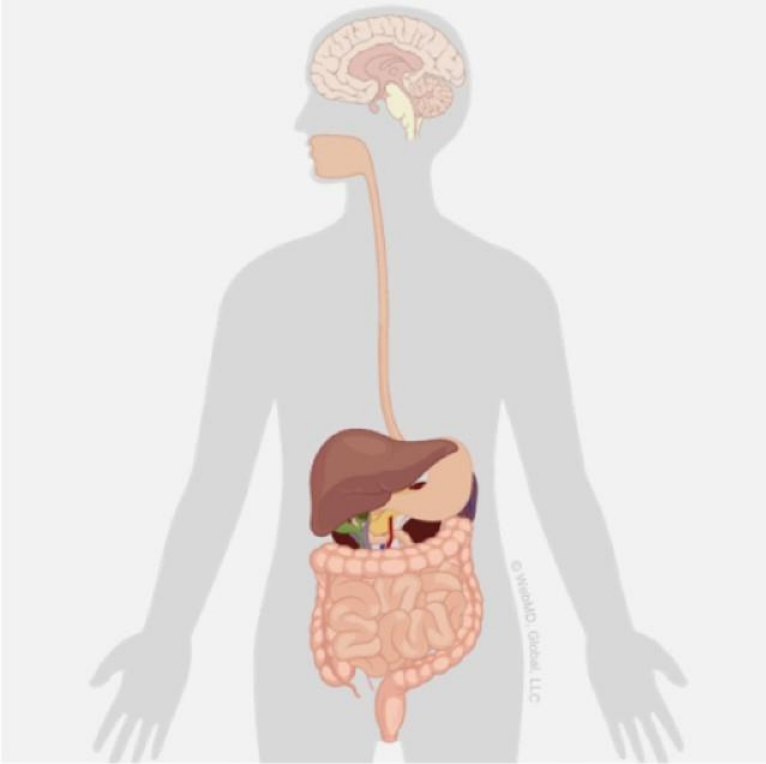
GIP
Long-acting GIPR agonist (phase 1)[e]
GIPR agonist (preclinical)[e]

GLP-1RA
Receptor agonists (phase 1, 2, 3)[e]

GLP-1R and GcgR
Dual agonists (phase 1, 2)[e]

Amylin
Amalyn analogs (preclinical, phase 1, 2)[e,f]

Y2R
PYY analogues (phase 1, 2)[e]



FGF, fibroblast growth factor; GDF-15, growth differentiation factor 15; GcgR, glucagon receptor; GOAT, ghrelin O-acyltransferase; RA, receptor agonist.; Y2R, neuropeptide Y receptor type 2.

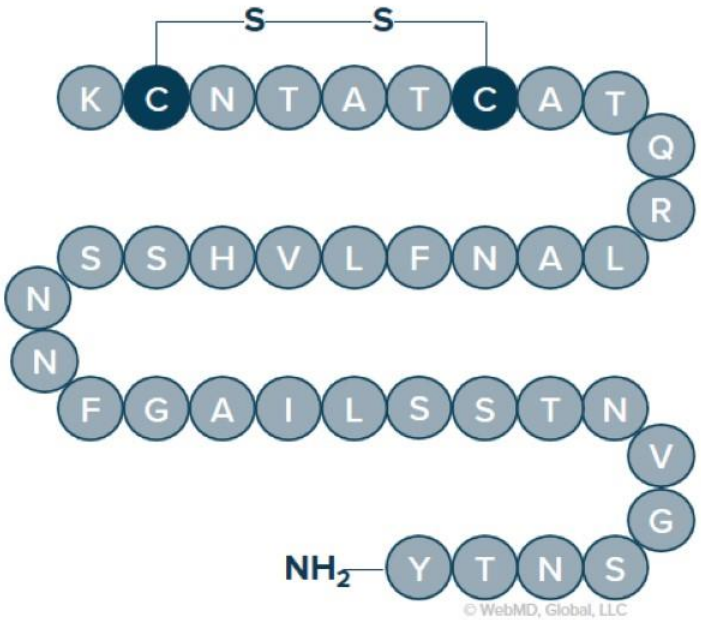
a. Verzijl CRC et al. Expert Opin Investig Drugs. 2020;29:125-133. b. Gaich G, et al. Cell Metab. 2013;18:333-40. c. Yan J, et al. Front Cardiovasc Med. 2021;8:655575. d. Miller JL, et al. J Clin Endocrinol Metab. 2022;107:e2373-e2380. e. Müller TD, et al. Nat Rev Drug Discov. 2022 Mar;21:201-223. f. Mathiesen DS, et al. Curr Opin Endocrinol Diabetes Obes. 2022;29:183-190.

Cagrilintide (AM833): Human Amylin Analogue

Amylin: A Neuroendocrine Peptide

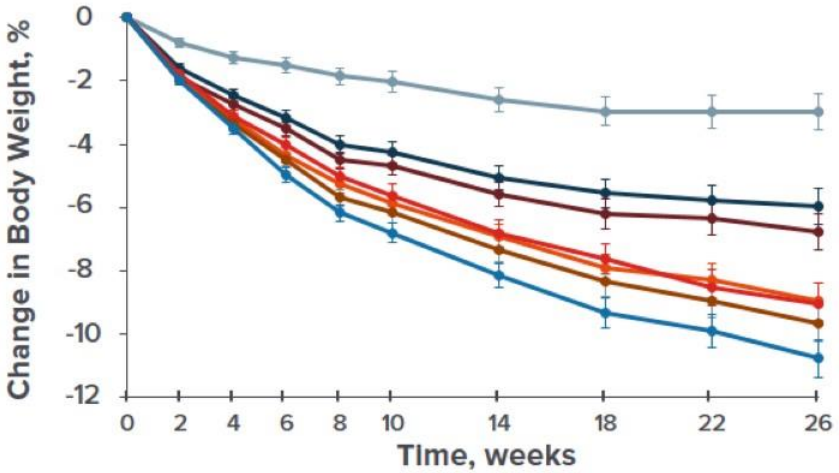
- Co-secreted with insulin from pancreatic β-cells in response to food intake
- Acts as a satiety signal, slows gastric emptying, suppresses the postprandial glucagon response

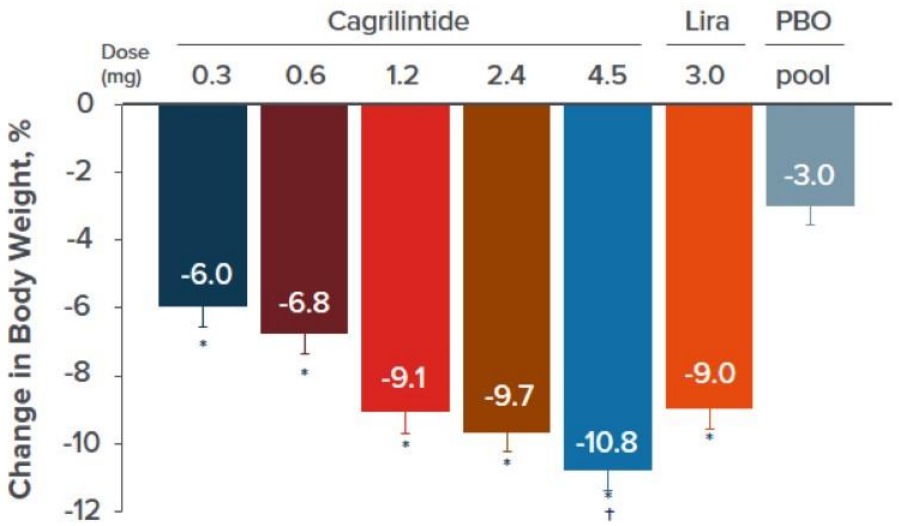
Native human amylin



Boyle CN, et al. Mol Metab. 2018;8:203-210; Zakariassen HL, et al. Basic Clin Pharmacol Toxicol. 2020;127:163-177; Hay DL et al. Pharmacol Rev. 2015;67:564-600.

Cagrilintide (AM833) vs Liraglutide and Placebo
Change in Body Weight to Week 26





Cagrilintide 0.3 mg
Cagrilintide 0.6 mg
Cagrilintide 1.2 mg
Cagrilintide 2.4 mg
Cagrilintide 4.5 mg
Liraglutide 3.0 mg
Placebo pool

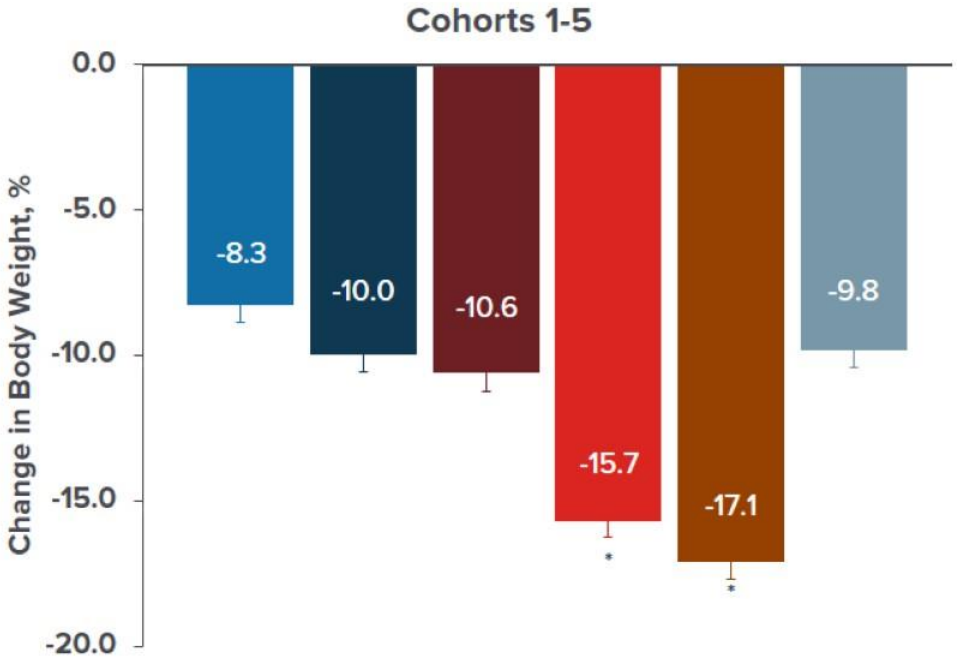
vs placebo
*$P < .001$

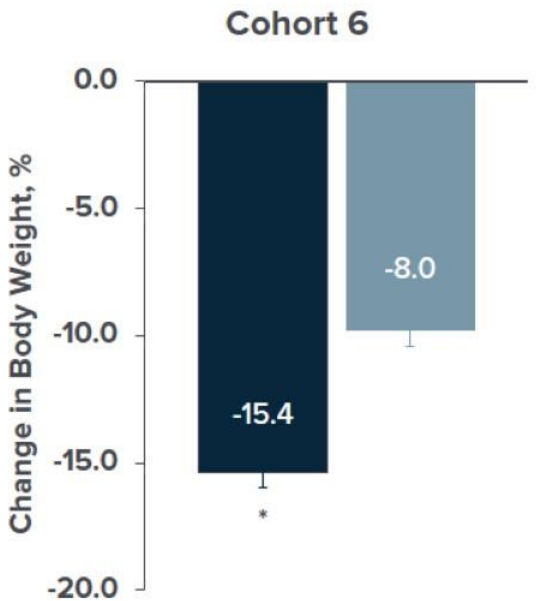
vs liraglutide
†$P < .05$

Mean (SEM) change from baseline in body weight (%) by treatment week.
Rubino D. Presented at: Obesity Week 2021; virtual; November 1-5, 2021.

Cagrilintide (AM833) and Semaglutide

Estimated Change in Body Weight to Week 20





Cagrilintide 0.16 mg + semaglutide 2.4 mg
Cagrilintide 0.3 mg + semaglutide 2.4 mg
Cagrilintide 0.6 mg + semaglutide 2.4 mg
Cagrilintide 1.2 mg + semaglutide 2.4 mg
Cagrilintide 2.4 mg + semaglutide 2.4 mg
Placebo pool + semaglutide 2.4 mg
Cagrilintide 4.5 mg + semaglutide 2.4 mg
Matched placebo + semaglutide 2.4 mg

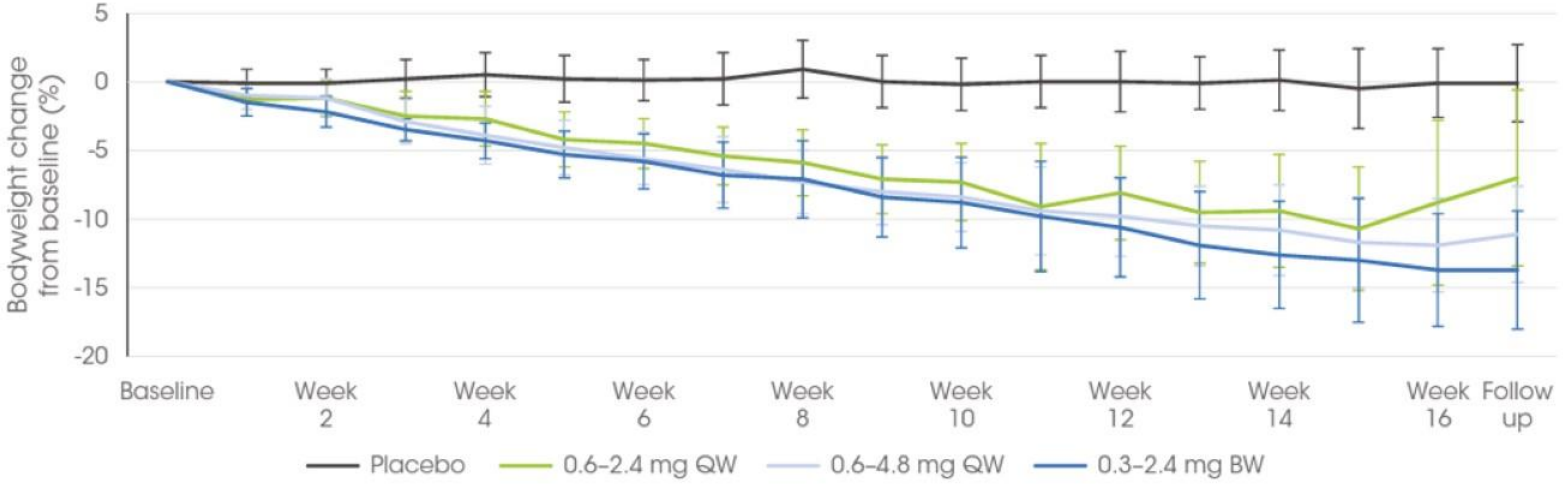
*P < .01 vs pooled or matched placebo.

a. Rubino D, et al. Presented at: Obesity Week 2021 ; virtual; November 1-5, 2021; b. Enebo LB, et al. Lancet. 2021;397:1736-1748.

Dual GLP-1R and GCGR Agonism in Obesity

- BI 456906 is a novel, subcutaneous dual GLP-1R/GCGR agonist
- Phase 1 study, multiple rising doses were generally well tolerated, with no unexpected safety signals
- AEs led to withdrawal from dose escalation in 36.3% of patients in Part A and 17.8% of patients in Part B, where dose escalation was more gradual

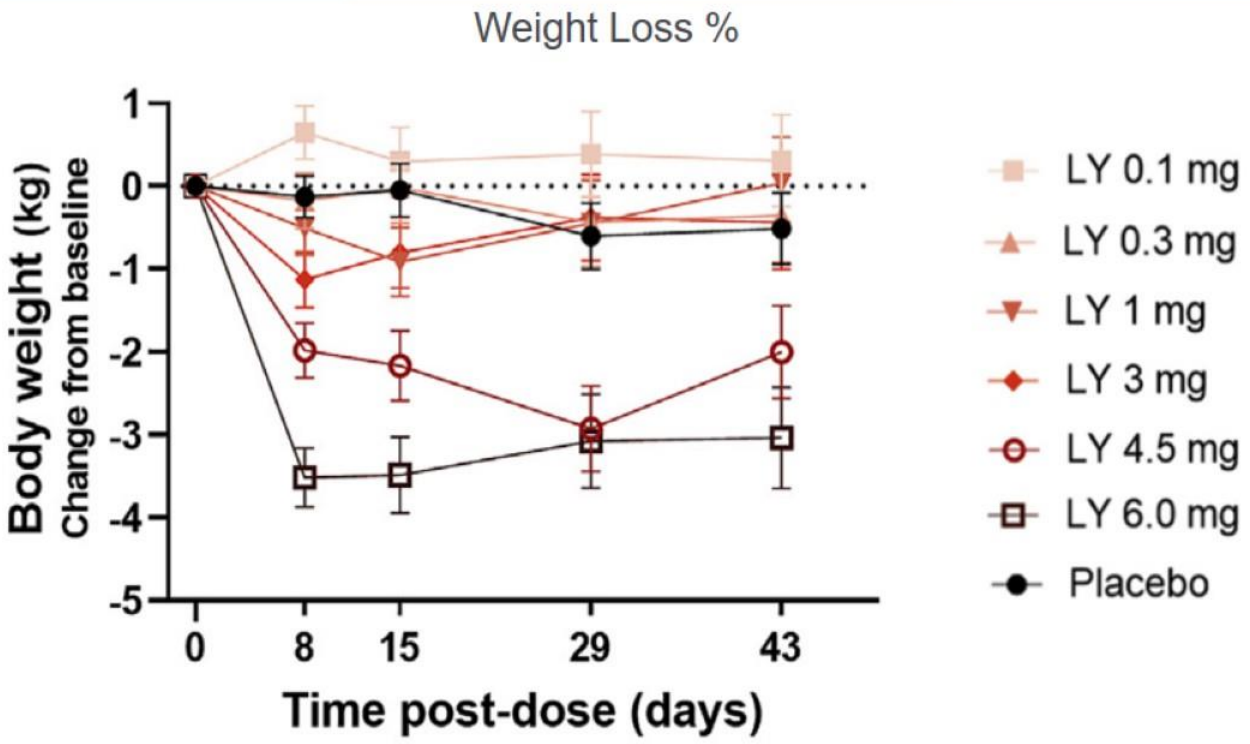
BI 456906 resulted in bodyweight reductions of up to 13.7% at Week 16 in part B



BW, biweekly; GLP-1R, glucagon-like peptide-1 receptor; GCGR, glucagon receptor; QW, once weekly.
Arrubla J, et al. Presented at: Obesity Week 2021; virtual; November 1-5, 2021.

Triple Agonist: LY3437943
Phase 1 Single Ascending Dose Study

GLP-1R | **GIP-R** | **Glucagon-R**



Coskun T, et al. Cell Metab. 2022;34:1234-1247.e9.

Conclusions

- **Obesity** is a chronic, complex, progressive, and relapsing disease
- Obesity in strongly associated with the **risk of developing CVD**
- There is an unmet need for **therapies** that can reduce CV risk and support successful weight management
- **Semaglutide** has proven to be safe and effective in significantly reducing risk of MACE by 20% vs placebo
- **Semaglutide** had consistent beneficial effects across CV outcomes and participant subgroups
- **Tirzepatide** has proven to be safe and effective in reducing body weight and the main cardiovascular consequences of obesity. Data about risk of MACE reduction in patients without diabetes, are not yet disposable
- According to the **2024 ESC Guidelines** the use of semaglutide should be considered in overweight or obese chronic coronary syndrome patients to reduce CV mortality, MI or stroke (IIa, B)
- **High costs** of the therapies could surely be a limitation, especially if not reimbursed by National Health System

GRAZIE DELL'ATTENZIONE !!