New SELECTions and Guideline Standards in Secondary Prevention of ASCVD

Dr Kim A Connelly MBBS PhD FCCC FSCMR
St Michael's Hospital
Division head, cardiology
Executive Director: Keenan Research centre for Biomedical Science
Associate Professor of Medicine

Faculty/Presenter Disclosure

- **Faculty: Kim Connelly**
- **Relationships with financial sponsors:**
  - **Any direct financial relationships including receipt of honoraria:** Merck, Astra Zeneca, Boehringer Ingelheim, Janssen, Servier, Eli Lilly and Novo Nordisk
  - **Memberships on advisory boards or speakers' bureau:** Merck, Astra Zeneca, Boehringer Ingelheim, Janssen, Servier, Eli Lilly and Novo Nordisk
  - **Patents for drugs or devices**: Boehringer Ingelheim - linaglitpin
  - **Other: financial relationships/investments**

Objectives

Discuss guideline approach to treatment of “residual risk”

Review new data on the link between obesity, semaglutide and CV outcomes

“Semaglutide 2.4 mg has only been approved by the US FDA for chronic weight management. Semaglutide 2.4 mg is still under regulatory review in the EU and other countries. Semaglutide is not approved in any other dose for chronic weight management. Please refer to the SmpC approved by the authorities in your country.“
CV, cardiovascular; EU, European Union; FDA, Food and Drug Administration; SMPC, summary of product characteristics.

Case Vignette: John

- 65-year-old man with prior MI who is new to your practice
- He has come in to have his medications renewed, and asks the question – what else can be done to reduce my future risk of heart disease???

History:

- Hypertension
- Myocardial Infarction 11 months ago

- *Lifestyle:* non-smoker; sedentary job but walks for 20 min per day, but has osteoarthritis of the knee

Physical exam:

- BMI 34 kg/m^2
- BP 126/74 mm/Hg

Laboratory:

- A1C 5.9 %
- eGFR 65 mL/min
- LDL-C 1.4 mmol/L
- ACR 1.7 mg/mmol
- hsCRP: 2.6

Medications:

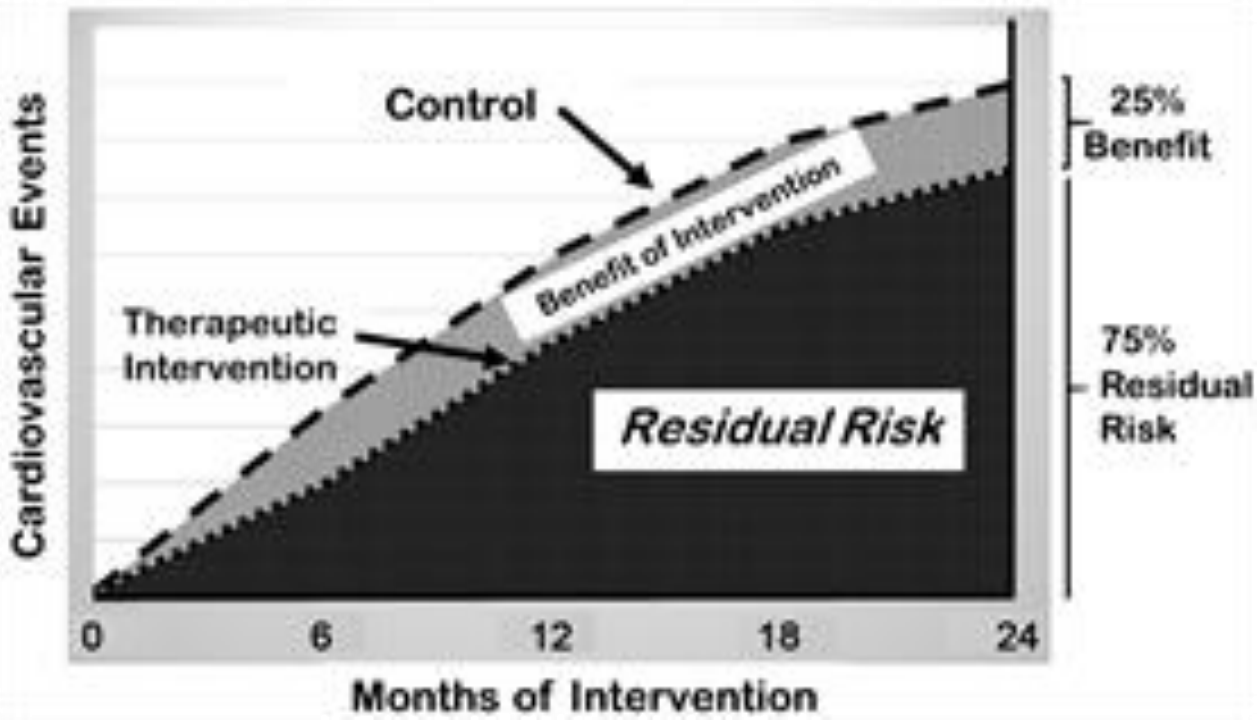
- ASA 81 mg daily /ticagrelor 90mg BID
- Bisoprolol 5 mg daily
- Perindopril 8 mg daily
- Atorvastatin 40 mg qhs

MI: myocardial infarction; ACEi: angiotensin-converting-enzyme inhibitor; BMI: body mass index; BP: blood pressure; A1C: glycated hemoglobin; eGFR: estimated glomerular filtration rate; LDL-C: low-density lipoprotein cholesterol; ACR: albumin to creatinine ratio; ASA: acetylsalicylic acid; DPP4i: dipeptidyl peptidase 4 inhibitor

Poll question #1: Which options have been proven to reduce MACE in John

- A: Icosapent ethyl
- B: Colchicine
- C: S/C semaglutide
- D: PCSK9
- E: SGLT2i

Concept of residual risk and ASCVD



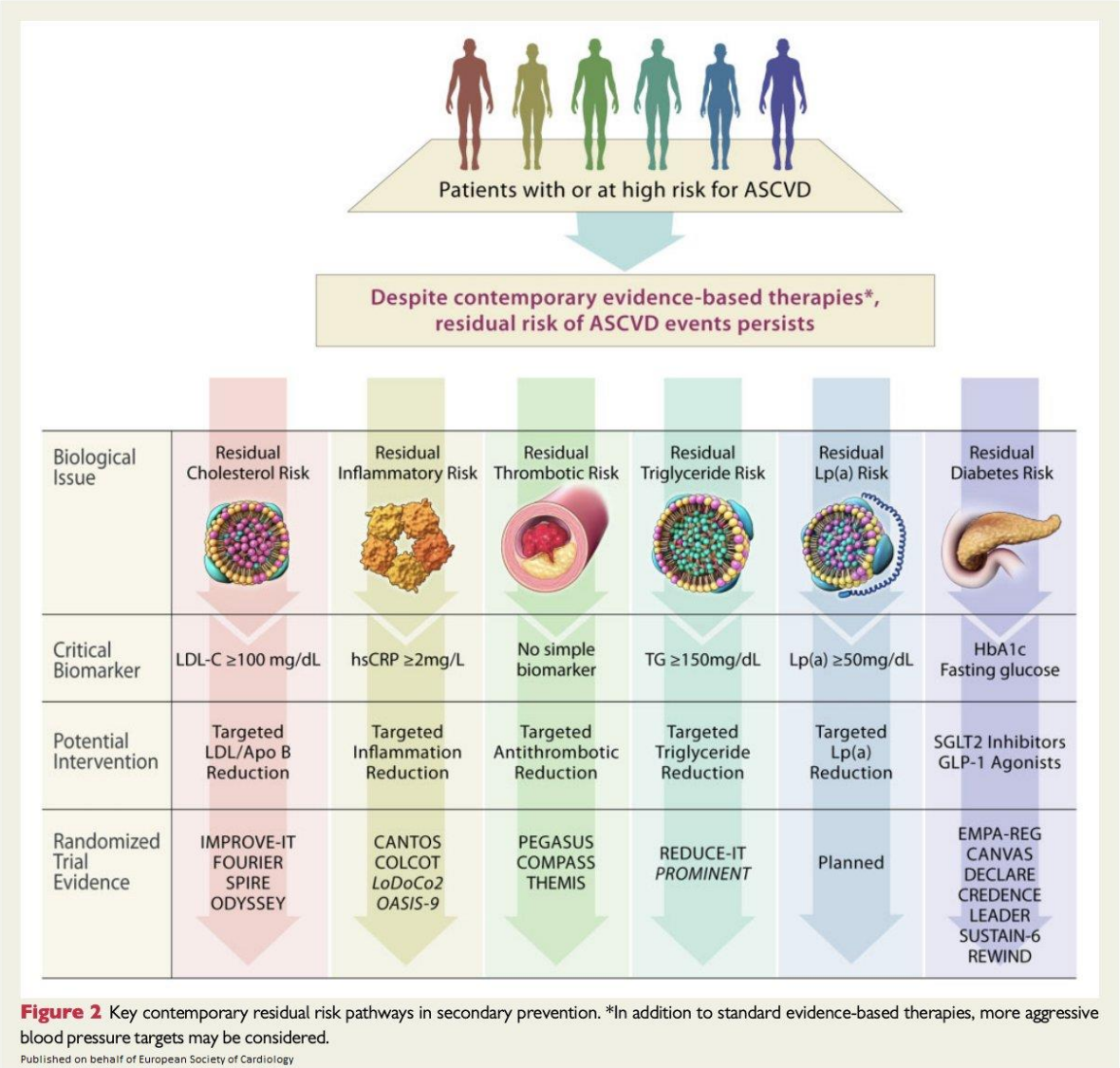


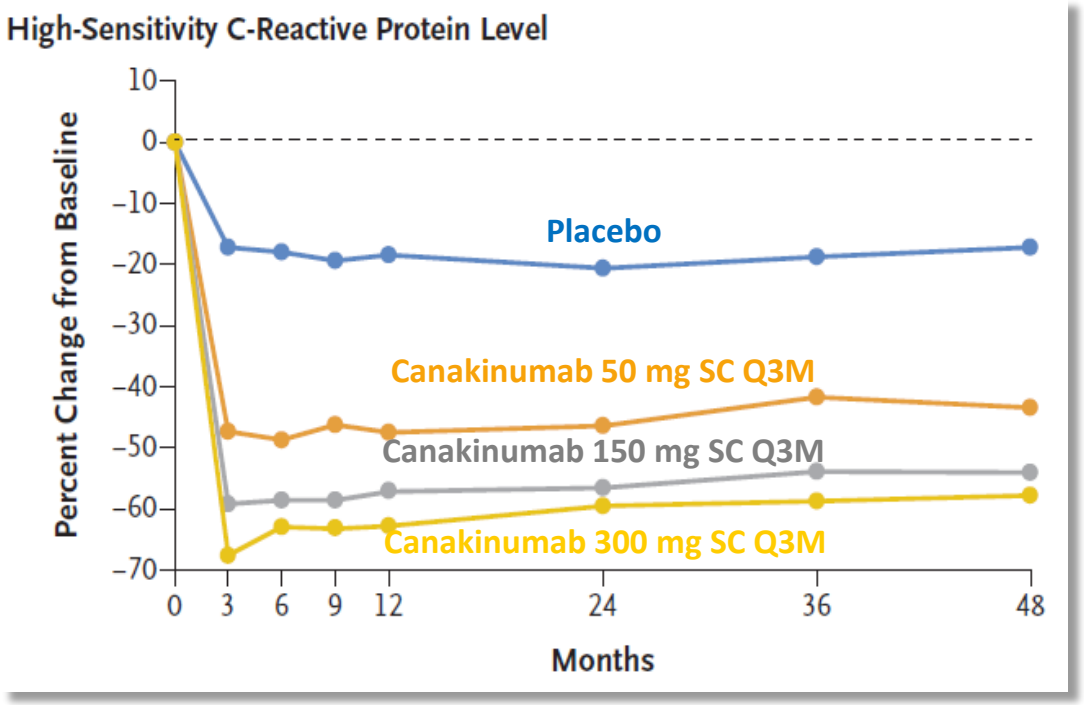
Figure 2 Key contemporary residual risk pathways in secondary prevention. *In addition to standard evidence-based therapies, more aggressive blood pressure targets may be considered.

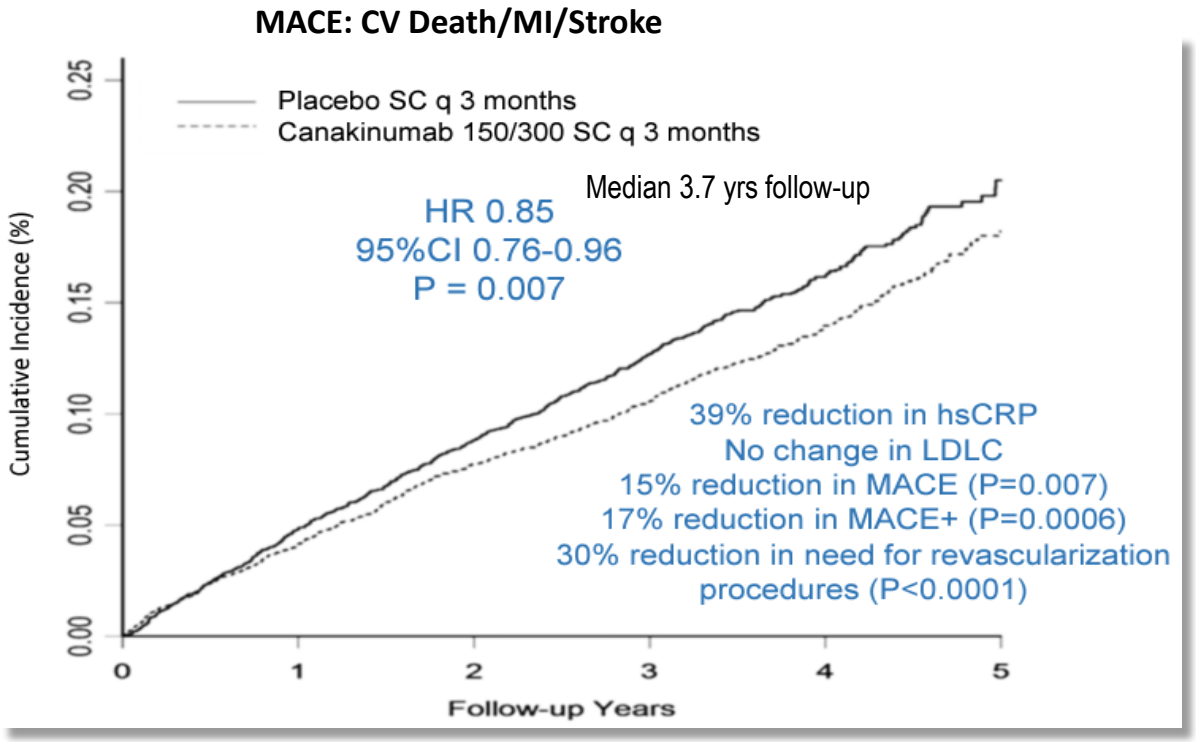
Published on behalf of European Society of Cardiology

CANTOS
Canakinumab Anti-inflammatory Thrombosis Outcomes Study

Antiinflammatory Therapy with Canakinumab

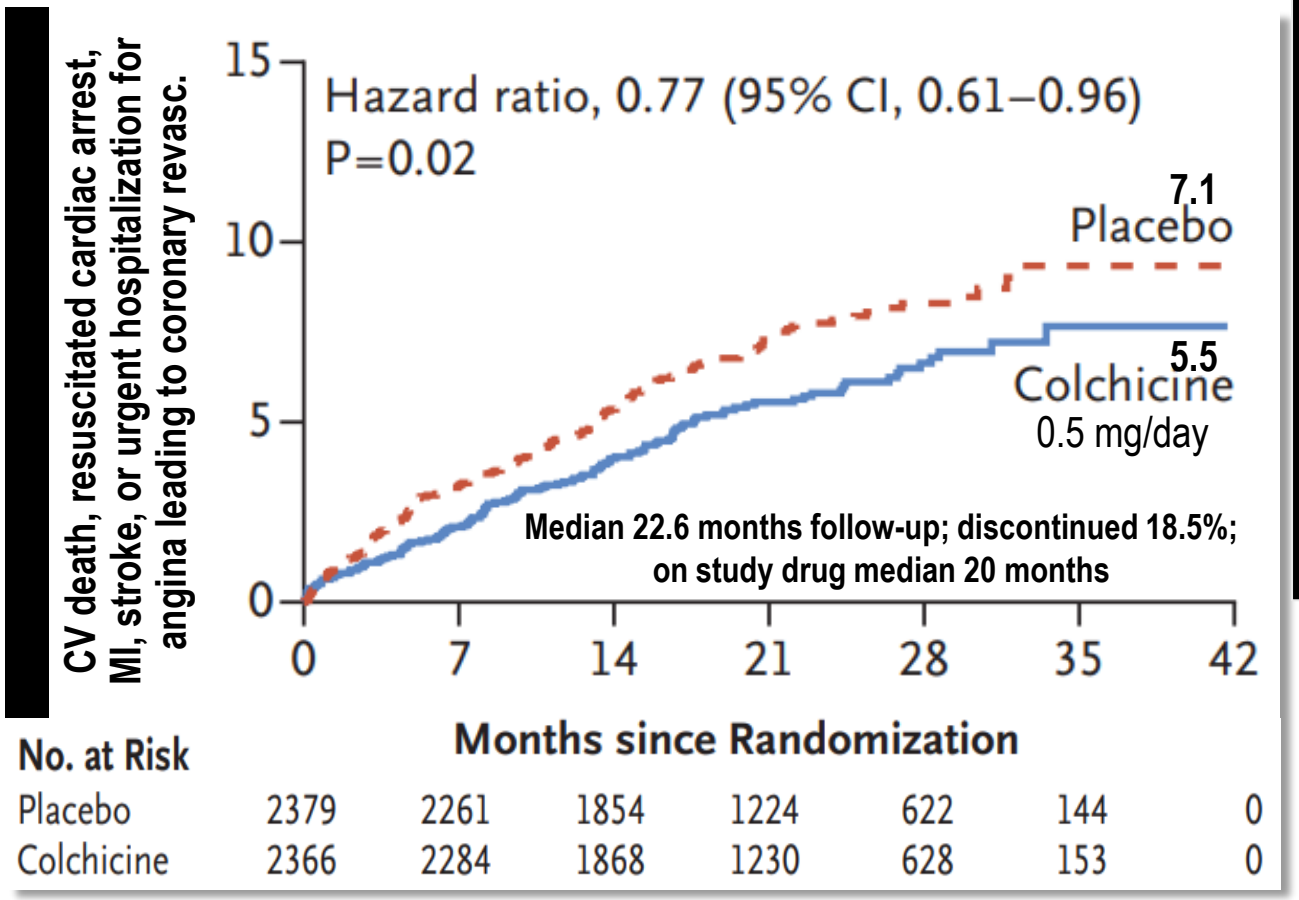
Stable, post-MI (n=10,061), mean 61 yrs old, 26% women, 40% diabetes; prior PCI (67%), CABG 14%; on antithrombotic (95%), lipid-lowering (93%), RAAS inhibitors (80%) with persistent elevation of hsCRP (> 2 mg/L) randomized to canakinumab (50 mg, 150 mg, 300 mg)* or placebo SC Q3months





Ridker et al N Engl J Med 2017;377:1119-31; Lancet 2017;390:1833-42; Lancet 2018;391:319-28

Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction

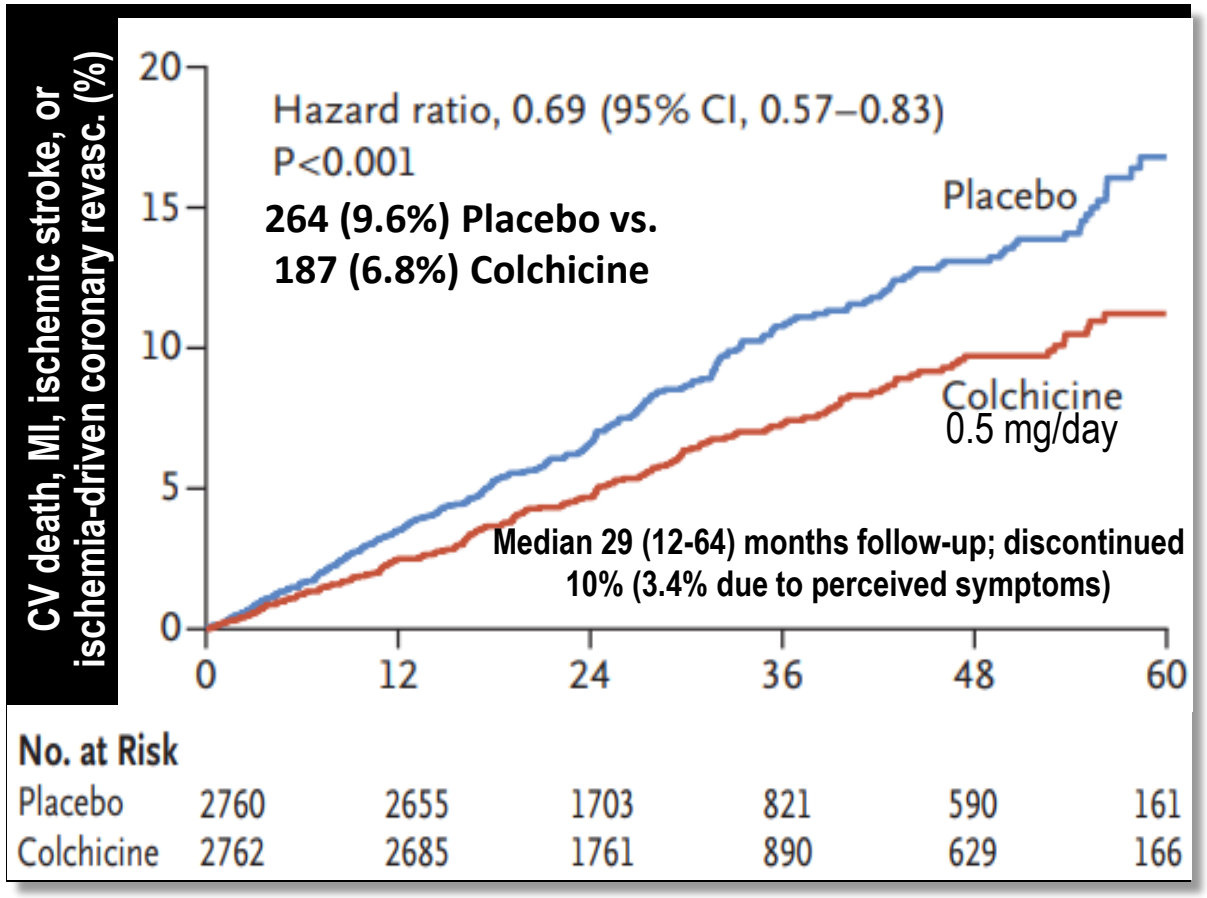


Any adverse event: 16% vs. 15.8%, p=0.89
GI: 17.5% vs. 17.6%, p=0.90
Diarrhea: 9.7% vs. 8.9%, p=0.35
Nausea: 1.8% vs. 1%, p=0.02
Flatulence.: 0.6% vs. 0.2%, p=0.02
Anemia: 0.6% vs. 0.4%, p=0.40
Leukopenia: 0.1% vs. 0.1%, p=0.66
Serious adverse event: 16.4% vs. 17.2%, p=0.47
Infection: 2.2% vs. 1.6%, p=0.15
Pneumonia: 0.9% vs. 0.4%, p=0.03

Tardif et al *N Engl J Med* 2019;381:2497-505

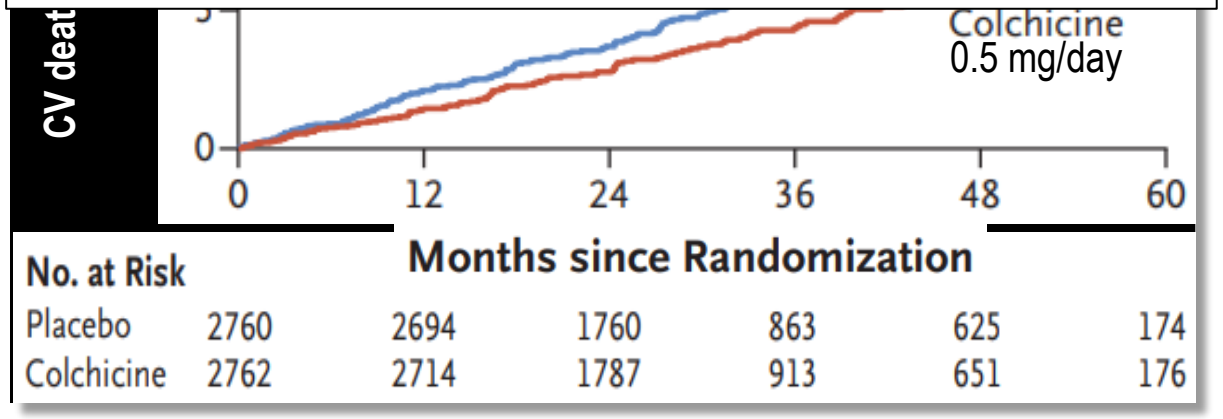
Efficacy and Safety of Low-Dose Colchicine in Chronic Coronary Disease

Primary Endpoint



Secondary Endpoint

Non-CV Death: 1.9% vs. 1.3%
New Cancer: 4.3% vs. 4.4%
Hosp. for infection: 5.0% vs. 5.2%
Hosp. for GI reason: 1.9% vs. 1.8%
Neutropenia: 0.1% vs. 0.1%
Myotoxicity: 0.1% vs. 0.1%



Nidorf et al *N Engl J Med* 2020;383:1838-47

Review

Colchicine for Prevention of Atherothrombotic Events in Patients With Coronary Artery Disease: Review and Practical Approach for Clinicians

Guillaume Marquis-Gravel, MD, MSc,[a] Shaun G. Goodman, MD, MSc,[b,c,d] Todd J. Anderson, MD,[e] Alan D. Bell, MD,[f] David Bewick, MD,[g] Jafna Cox, BA, MD,[h] Jean C. Grégoire, MD,[a] Anil Gupta, MD,[i] Thao Huynh, MD, MSc, PhD,[j] Heather Kertland, PharmD,[b] Simon Kouz, MD,[k] Philippe L. L'Allier, MD,[a] Mina Madan, MD,[l] G. B. John Mancini, MD,[m] Ruth McPherson, MD, PhD,[n] Derek Y.F. So, MD, MSc,[n] Robert C. Welsh, MD,[o] Graham Wong, MD, MPH,[p] and Jean-Claude Tardif, MD[a]

[a] Montréal Heart Institute, Université de Montréal, Montréal, Québec, Canada; [b] St. Michael's Hospital, University of Toronto, Ontario, Canada; [c] Canadian Heart Research Centre, Toronto, Ontario, Canada; [d] Canadian VIGOUR Centre, University of Alberta, Edmonton, Alberta, Canada; [e] Libin Cardiovascular Institute, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada; [f] University of Toronto, Toronto, Ontario, Canada; [g] New Brunswick Heart Center, Saint John, New Brunswick, Canada; [h] Dalhousie University, Capital Health, and Division of Cardiology, Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada; [i] Trillium Health Centre, Mississauga, Ontario, Canada; [j] Division of Cardiology, McGill University Health Center, Montréal, Québec, Canada; [k] Centre Intégré de Santé et de Services Sociaux de Lanaudière—Centre Hospitalier de Lanaudière, Joliette, Québec, Canada; [l] Schulich Heart Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada; [m] University of British Columbia, Department of Medicine, Division of Cardiology, Vancouver, British Columbia, Canada; [n] University of Ottawa Heart Institute, Ottawa, Ontario, Canada; [o] Mazankowski Alberta Heart Institute and University of Alberta, Edmonton, Alberta, Canada; [p] Vancouver General Hospital, University of British Columbia, Vancouver, British Columbia, Canada

Marquis-Gravel, Goodman et al *Can J Card* 2021;37:1837-45

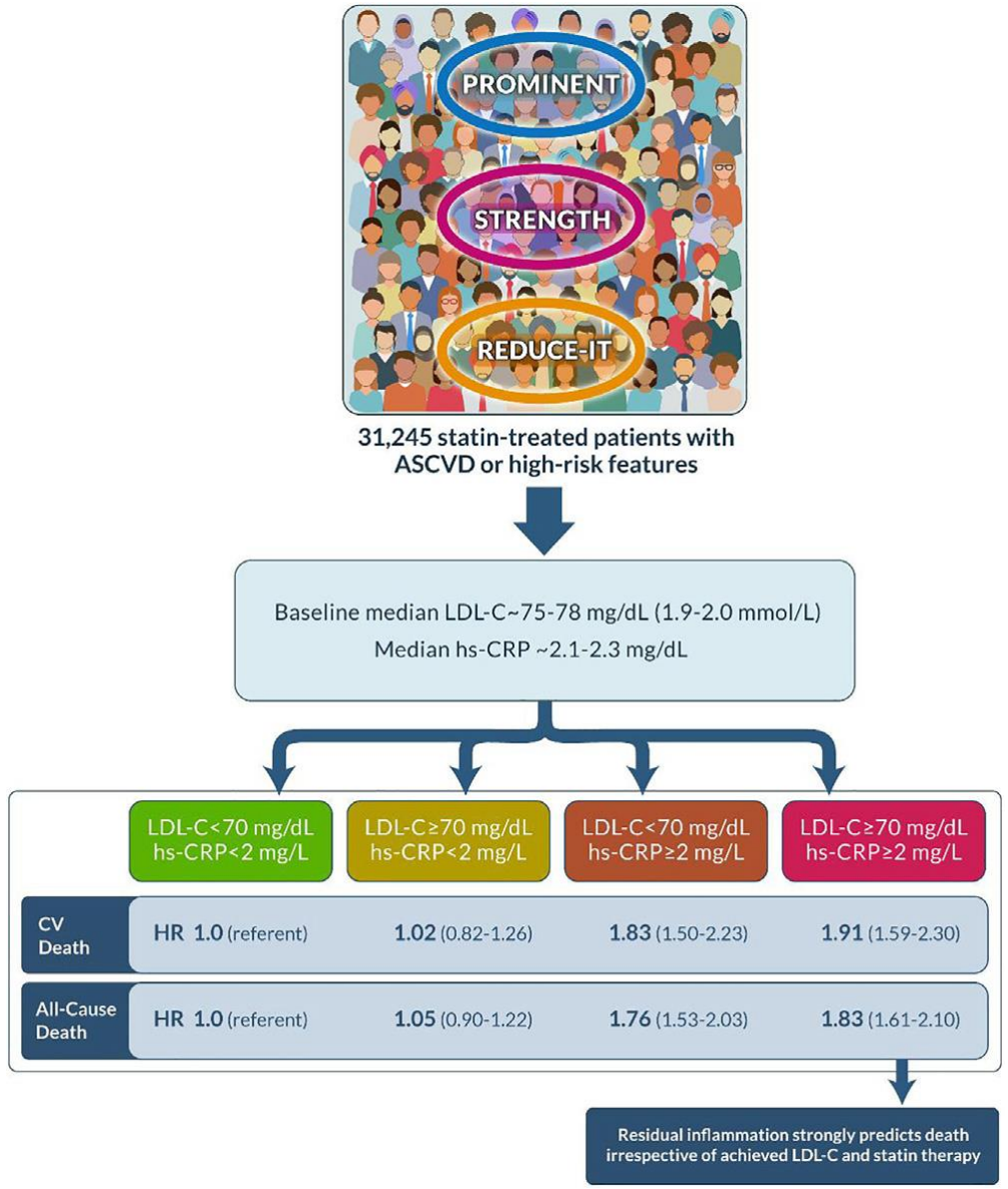
Colchicine in Coronary Artery Disease

- low-dose (e.g., 0.5 mg once daily) should be considered in patients with a recent MI ≤30 days (ideally ≤3 days) or with stable CAD to improve CV outcomes (but not mortality)
- can be administered at any time of the day, without regard to meals, but should be administered with a beverage
- should not be used in patients with severe renal (eGFR<30 mL/min) or hepatic disease because of the risk of severe toxicity
- metabolized by CYP3A4/substrate for P-glycoprotein
  - should *not* be used with CYP3A4 inhibitors (e.g., grapefruit, ritonavir, itraconazole, ketoconazole) or P-glycoprotein inhibitors (e.g., clarithromycin)
- dose should be reduced in patients receiving moderate-to-high doses of diltiazem or verapamil

Marquis-Gravel, Goodman, et al *Can J Card* 2021;37:1837-45

Inflammation and cholesterol at the crossroads of vascular risk

Subodh Verma,[1,2,*] C. David Mazer,[3,4] and Kim A. Connelly[5,6]



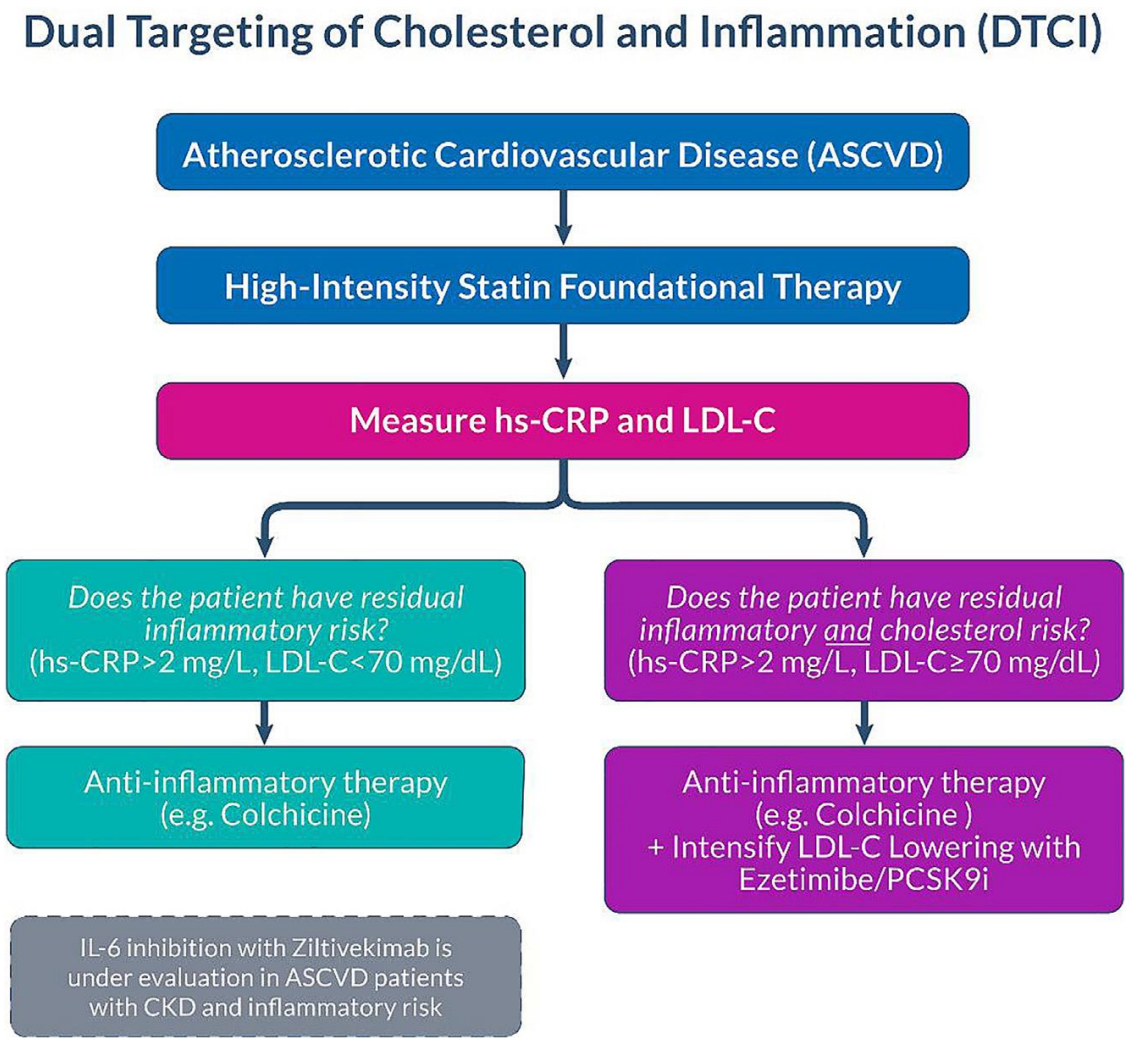


Figure 2. Suggested approach for integrating therapy to manage residual cholesterol and residual inflammatory risk in patients with atherosclerotic cardiovascular disease

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; PCSK9i, proprotein convertase subtilisin/kexin type 9 serine protease inhibitors.

Global prevalence of obesity

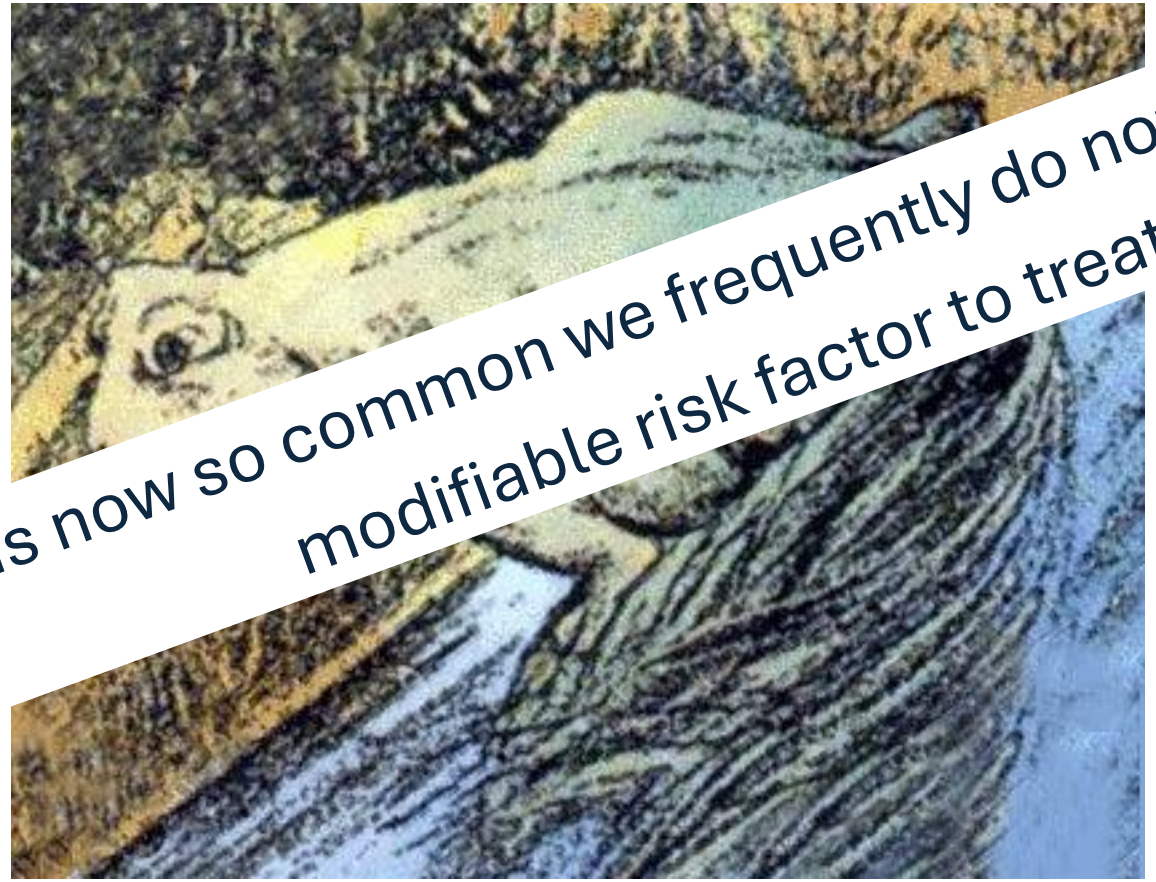
Table 1.0: Estimated global prevalence and numbers of adults living with obesity in 2010–2030

	2010		2025		2030	
Adult obesity prevalence	% adults	number	% adults	number	% adults	number
Obesity (Class I, II and III) BMI ≥30kg/m^2	11.4%	511m	16.1%	892m	17.5%	1,025m
of which, severe obesity (Class II and III) BMI ≥35kg/m^2	3.2%%	143m	5.1%	284m	5.7%	333m
and of these, severe obesity (Class III) BMI ≥40kg/m^2	0.9%	42m	1.7%	93m	1.9%	111m

Source: NCD Risk Factor Collaboration (2017), UN Population Division and World Obesity Federation projections

Conditions included in CVD definition may vary.
CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease.
WHO Fact sheet – CVDs. Available at: http://www.who.int/mediacentre/factsheets/fs317/en/; Roth GA et al. J Am Coll Cardiol 2017;70(1):1–25;
WHO, Obesity & Overweight. 2020. Available from https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed November 2020;
GBD 2015 Obesity Collaborators. N Engl J Med 2017; 377(1):13–27.

Which do you see first? Frog or horse?



Obesity is now so common we frequently do not consider it as a modifiable risk factor to treat

Canadian Journal of Cardiology 38 (2022) 1153–1167

Society Guidelines

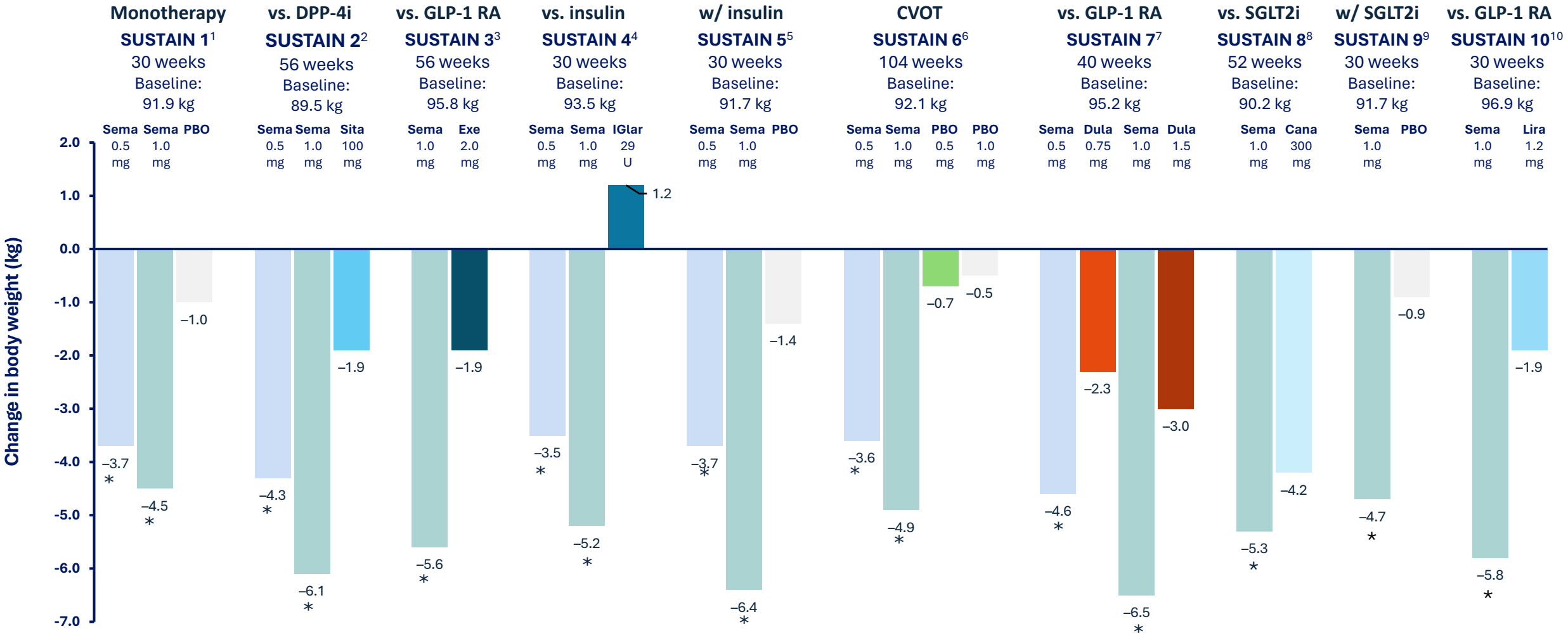
2022 Canadian Cardiovascular Society Guideline for Use of GLP-1 Receptor Agonists and SGLT2 Inhibitors for Cardiorenal Risk Reduction in Adults

Primary Panel: G.B. John Mancini, MD (Co-chair),[a] Eileen O'Meara, MD (Co-chair),[b] Shelley Zieroth, MD,[c] Mathieu Bernier, MD,[d] Alice Y.Y. Cheng, MD,[e] David Z.I. Cherney, MD, PhD,[f] Kim A. Connelly, MD,[g] Justin Ezekowitz, MBBCh, MSc,[h] Ronald M. Goldenberg, MD,[i] Lawrence A. Leiter, MD,[j] Gihad Nesrallah, MD, MSc,[j,k] Breay W. Paty, MD,[l] Marie-Eve Piché, MD, PhD,[d] Peter Senior, MBBS, PhD,[m] Abhinav Sharma, MD,[n] Subodh Verma, MD, PhD,[o] Vincent Woo, MD,[c] **Secondary Panel:** Pol Darras, MD,[l] Jean Grégoire, MD,[b] Eva Lonn, MD,[p] James A. Stone, MD, PhD,[q] Jean-François Yale, MD,[r] Colin Yeung, MD, MPH,[s] and Deborah Zimmerman, MD, MSc[t]

	Practice Statement	Strength of Recommendation	Quality of Evidence
	CV specialists are encouraged to assess kidney and glycemic status through measurement of eGFR, UACR, and A1c and to document LVEF when evaluating symptoms of HF.	–	–
	Recommendations		
Treatment of HF	In adults with HF and LVEF ≤ 40%, we recommend use of SGLT2i to reduce all-cause and CV mortality, hospitalization for HF, and the composite end point of significant decline in eGFR, progression to end-stage kidney disease or death due to kidney disease.	Strong	Moderate
	In adults with HF and LVEF > 40%, we recommend use of SGLT2i to reduce hospitalization for HF.	Strong	Moderate
Treatment of CKD	In adults with CKD (UACR > 20 mg/mmol, eGFR ≥ 25 mL/min/1.73m^2), we recommend use of SGLT2i to reduce the composite of significant decline in eGFR, progression to end-stage kidney disease or death due to kidney disease, all-cause and CV mortality, nonfatal MI, and hospitalization for HF.	Strong	Moderate
Prevention of cardiorenal events in adults with either T2D and ASCVD or multiple risk factors for ASCVD	In adults with T2D and either ASCVD or multiple risk factors for ASCVD, we recommend use of:		
	A. GLP-1RA or SGLT2i to reduce the risk of all-cause, or CV mortality or MACE;	Strong	Moderate
	B. SGLT2i to reduce the risk of hospitalization for HF or the composite of significant decline in eGFR, progression to end-stage kidney disease or death due to kidney disease;	Strong	Moderate
	C. GLP-1RA to reduce the risk of nonfatal stroke.	Strong	Moderate

Mancini et al. Can J Cardiol 2022;38:1153-67

SUSTAIN: Subcutaneous semaglutide demonstrated statistically significant weight loss across clinical trials



** p<0.0001 vs comparator. Dula, dulaglutide; Cana, canagliflozin; Exe, exenatide extended release; IGlar, insulin glargine; Lira, liraglutide; PBO, placebo; Sema, semaglutide; Sita, sitagliptin. 1. Sorli C et al. Lancet Diabetes Endocrinol 2017;5:251–60; 2. Ahrén B et al. Lancet Diabetes Endocrinol 2017;5:341–54; 3. Ahmann AJ et al. Diabetes Care 2018;41:258–66; 4. Aroda VR et al. Lancet Diabetes Endocrinol 2017;5:355–66; 5. Rodbard HW et al. J Clin Endocrinol Metab 2018;103:2291–301; 6. Marso SP et al. N Engl J Med 2016;375:1834–44; 7. Pratley RE et al. Lancet Diabetes Endocrinol 2018;6:275–86; 8. Lingvay I, et al. The Lancet Diabetes & Endocrinology. 2019 Nov;7(11):834-844; 9. Zinman B et al. Lancet Diabetes Endocrinol. 2019 May;7(5):356-367. 10. Capehorn M, et al. Diabetes & Metabolism. 2020 Apr;46(2):100-109.*

The STEP program investigated semaglutide for weight management in people with overweight or obesity

GLOBAL PHASE 3A[1–7]

STEP 1[1]
WM
(N = 1,961)

STEP 2[2]
WM in T2D
(N = 1,210)

STEP 3[3]
WM with IBT
(N = 611)

STEP 4[4]
Sustained WM
(N = 803)

STEP HFpEF[5]
Semaglutide in obesity
(N = 516)

STEP HFpEF DM[6]
Semaglutide in T2D (N = 610)

STEP TEENS[7]
WM in adolescents
(N = 201)

REGIONAL PHASE 3A[8,9]

STEP 6[8]
East Asian trial
(N = 401)

STEP 7[9]
China, Brazil, Korea, Hong Kong MRCT
(N = 375)

PHASE 3B[10–15]

STEP 5[10]
Long-term WM
(N = 304)

STEP 8[11]
H2H vs liraglutide
(N = 338)

STEP 9[12]
Semaglutide in knee OA
(N = 375)

STEP 10[13]
Reversal of pre-diabetes
(N = 201)

SELECT[14]
CVOT
(N = 17,605)

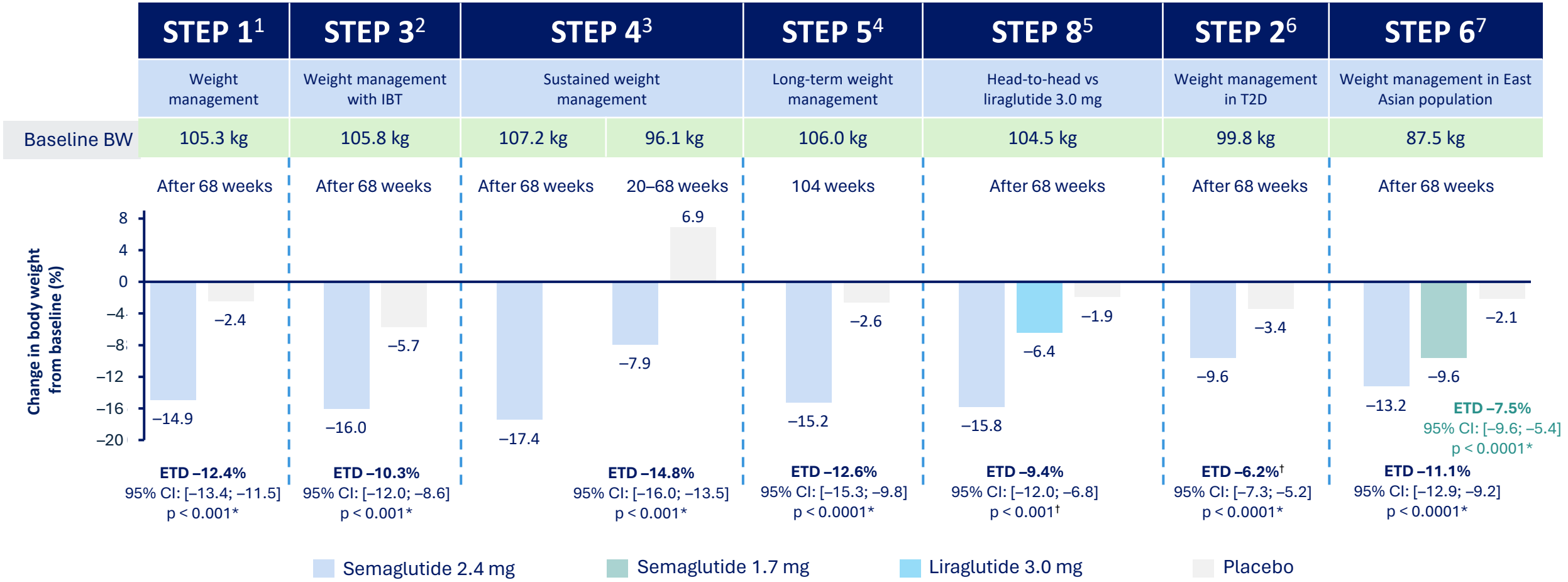
STEP 11[15]
Korea / Thailand trial
(N = 150)

Completed trials and published results

On-going trials

See slide notes for references. STEP 7: China, Brazil, Korea, Hong Kong (left to right) multi-regional clinical trial; Novo Nordisk. Data on file.
CVOT, cardiovascular outcomes trial; DM, diabetes mellitus; H2H, head-to-head; HFpEF, heart failure with preserved ejection fraction; IBT, intensive behavioural therapy; MRCT, multi-regional clinical trial (including China and ≥1 additional East Asian country); OA, osteoarthritis; T2D, type 2 diabetes; WM, weight management.

Weight loss with semaglutide across STEP trials



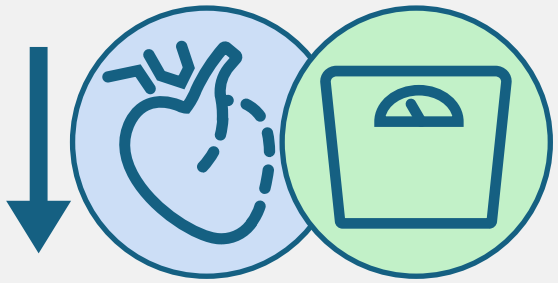
Estimated for the treatment policy estimand (treatment effect regardless of trial product discontinuation and use of rescue medication).
**Statistically significant vs placebo. †Statistically significant vs liraglutide 3.0 mg.*
BW, body weight; ETD, estimated treatment difference; IBT, intensive behavioural 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.

Poll question #2: Semaglutide s/c 2.4mg has been shown to improve outcomes in obese patients with diabetes only

- A: True
- B: False

SELECT Trial: Primary objective

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



Three-component MACE consisted of non-fatal myocardial infarction, non-fatal stroke, CV death.
Established CV disease included ≥1 prior myocardial infarction, ischemic/haemorrhagic stroke, symptomatic peripheral arterial disease, peripheral arterial revascularisation procedure or amputation due to atherosclerotic disease.
CV, cardiovascular; MACE, major adverse cardiovascular event; s.c., subcutaneous.

Why was the SELECT trial conducted?

Few medical treatments for long-term overweight and obesity management **are currently available** and **none are indicated to reduce CV risk.**[1]

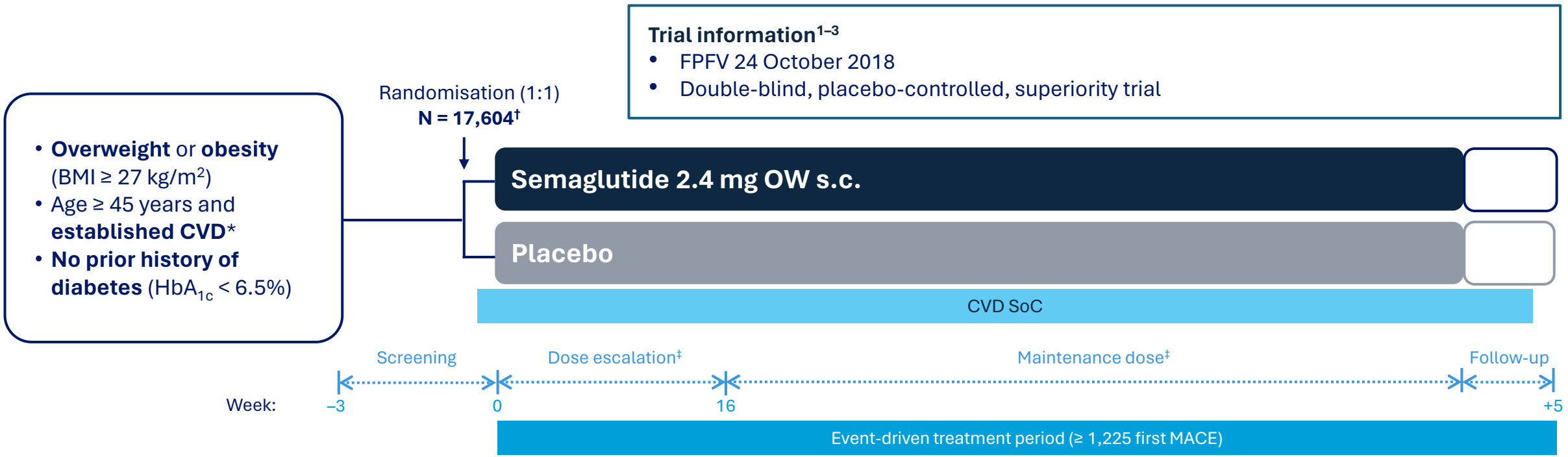
Over the past 30 years, the prevalence of **obesity** has reached **epidemic** proportions.[2]

Individuals with overweight or obesity are at high risk of developing CVD, and this is a predominant cause of death in this group.[2]

Despite improvements in SoC therapies*, **CVD resulted in ~17.9 million deaths globally in 2019.**[3]

Such as anti-hypertensive and lipid-lowering drugs.
CV, cardiovascular, CVD, cardiovascular disease; SoC, standard of care.
1. Powell-Wiley TM et al. Circulation 2021;143:e984–1010; 2. GBD 2015 Obesity Collaborators. N Engl J Med 2017;377:13–27; 3. WHO. Cardiovascular diseases. Available at: https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds). Accessed October 2023.

SELECT Trial design



Three-component MACE consisted of non-fatal MI, non-fatal stroke and CV death.
**Established CVD: MI ≥60 days prior to screening, stroke ≥60 days prior to screening or symptomatic PAD; NYHA class IV excluded. †Number of enrolled participants differs from number reported in baseline publication (17,605) as one participant was randomised twice in error and subsequently removed for the primary analysis. ‡Dose escalation is from week 4 to 16 with intervals of 4 weeks, and maintenance dose is event-driven to end of treatment period.*
BMI, body mass index; CV, cardiovascular; CVD, cardiovascular disease; FPFV, first patient first visit; HbA_{1c}, glycated haemoglobin; MACE, major adverse cardiovascular event; MI, myocardial infarction; NYHA, New York Heart Association;
OW, once weekly; PAD, peripheral artery disease; s.c., subcutaneous; SoC, standard of care.
1. Ryan DH et al. Am Heart J 2020;229:61–9; 2. Lingvay I et al. Obesity (Silver Spring) 2023;31:111–22; 3. Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

Main inclusion/exclusion criteria

Key inclusion criteria[1–3]

Prior MI*
Prior stroke*
Symptomatic PAD†

Male or female individuals aged ≥ 45 years

BMI ≥ 27 kg/m^2

Key exclusion criteria[1–3]

HbA_{1c} ≥ 6.5%

History of type 1 or type 2 diabetes‡

Treatment with glucose-lowering agents within the past 90 days

Presently classified as having NYHA class IV heart failure

>60 days prior to the day of screening. †Symptomatic PAD evidenced by intermittent claudication with ankle-brachial index less than 0.85 (at rest), or peripheral arterial revascularisation procedure or amputation due to atherosclerotic disease. ‡Gestational diabetes was allowed.

BMI, body mass index; HbA_{1c}, glycated haemoglobin; MI, myocardial infarction; NYHA, New York Heart Association; PAD, peripheral artery disease.

1. Ryan DH et al. Am Heart J 2020;229:61–9; 2. Lingvay I et al. Obesity (Silver Spring) 2023;31:111–22; 3. Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

Primary and confirmatory secondary endpoints[1-3]

3-point MACE

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

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

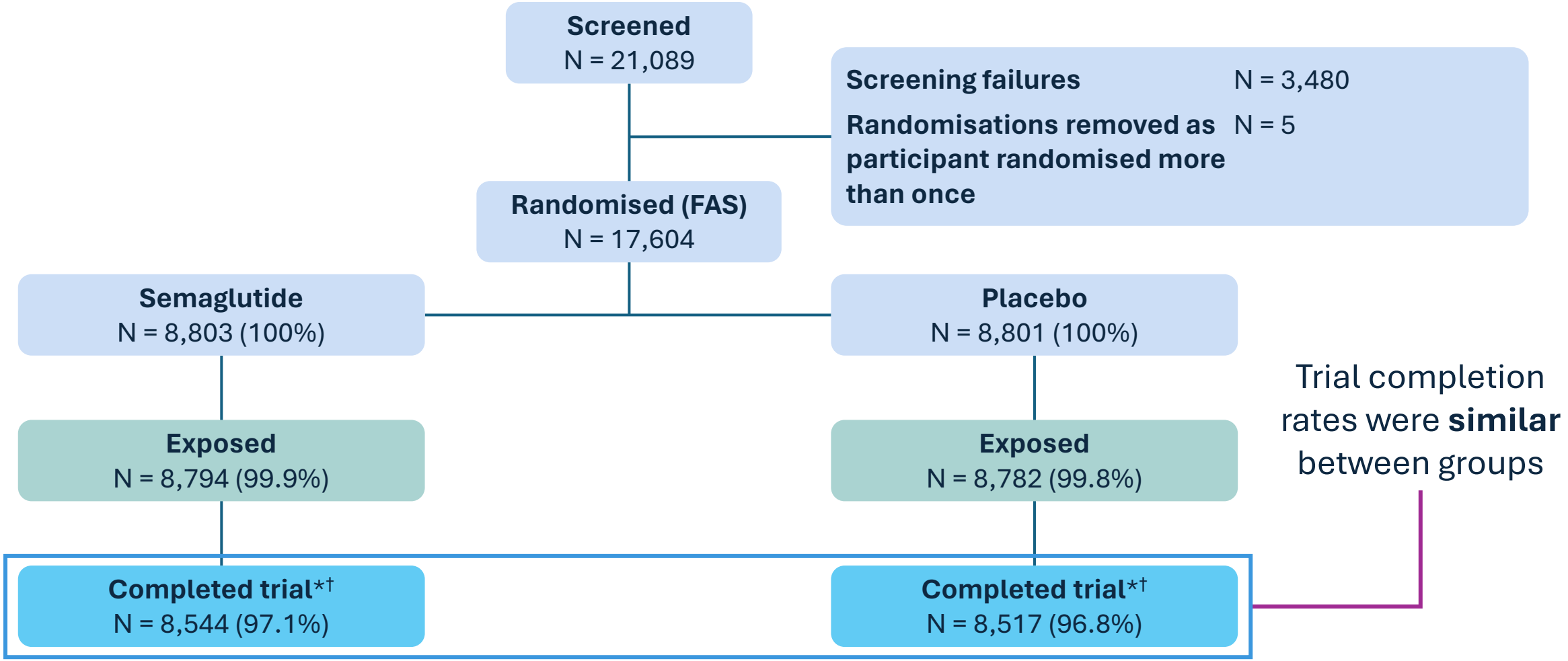
Confirmatory secondary endpoints

Time from randomisation to occurrence of:

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



*Participants who attended the follow-up visit or who died during the trial. †The trial was not completed by 259 (2.9%) participants with semaglutide (participant withdrawal: 67 [0.8%]; lost to follow-up: 192 [2.2%]) and 284 (3.2%) participants with placebo (participant withdrawal: 96 [1.1%]; lost to follow-up: 188 [2.1%]).
FAS, full analysis set.
Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

Baseline characteristics of trial participants

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

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[2]

82.5 mL/min/1.73 m²

Chronic heart failure[1]

24.3%

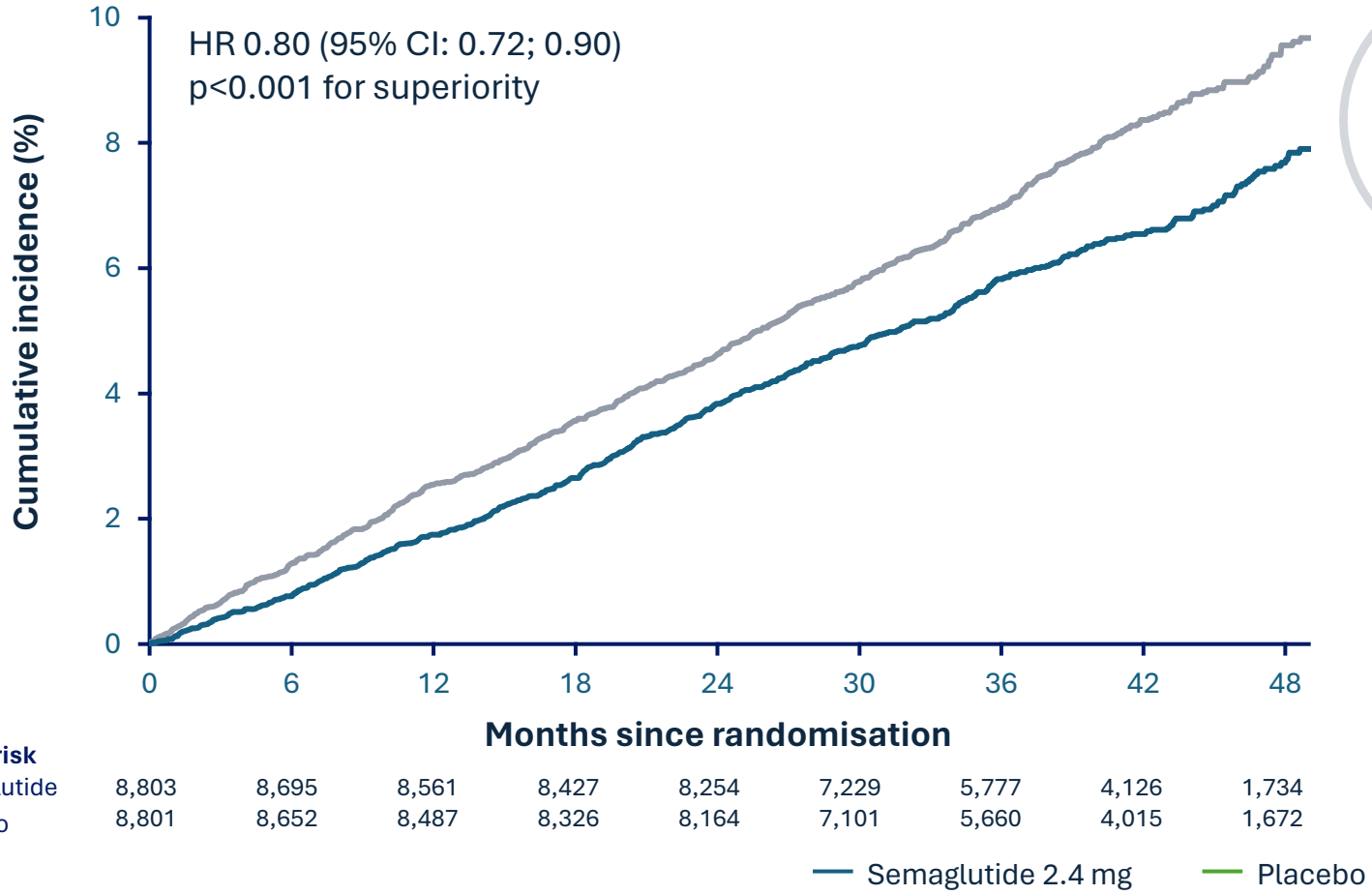
Subclass[2]

HFpEF| HFrEF | Unknown

12.9 | 7.7 | 3.8

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. Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563; 2. Novo Nordisk. Data on file.

Primary endpoint: Cumulative incidence of MACE



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]

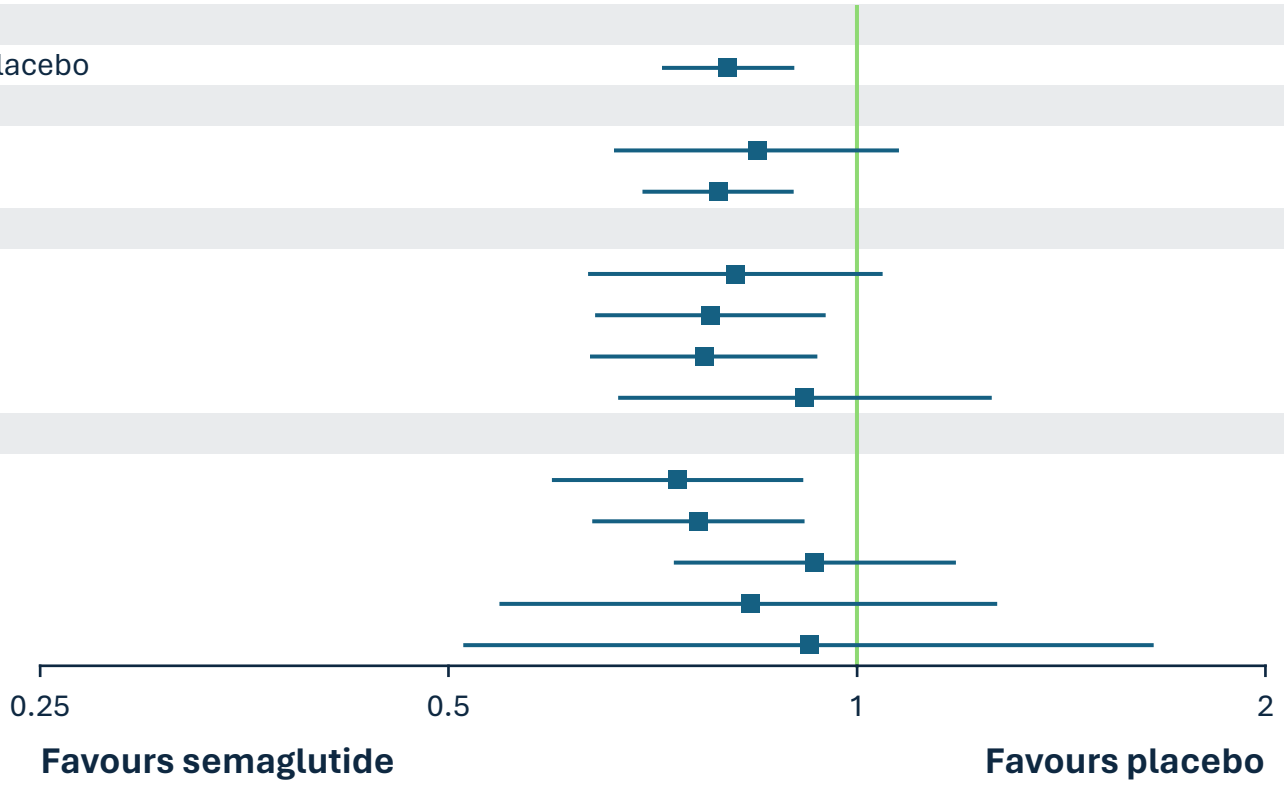
All three components (death from CV causes, non-fatal MI and non-fatal stroke) contributed to MACE risk reduction

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. Novo Nordisk A/S. Company announcement, 8 August 2023. Available at: https://www.novonordisk.com/content/nncorp/global/en/news-and-media/news-and-ir-materials/news-details.html?id=166301. Accessed October 2023.

Semaglutide demonstrated consisted effects across subgroups

Subgroup analyses of three-point MACE

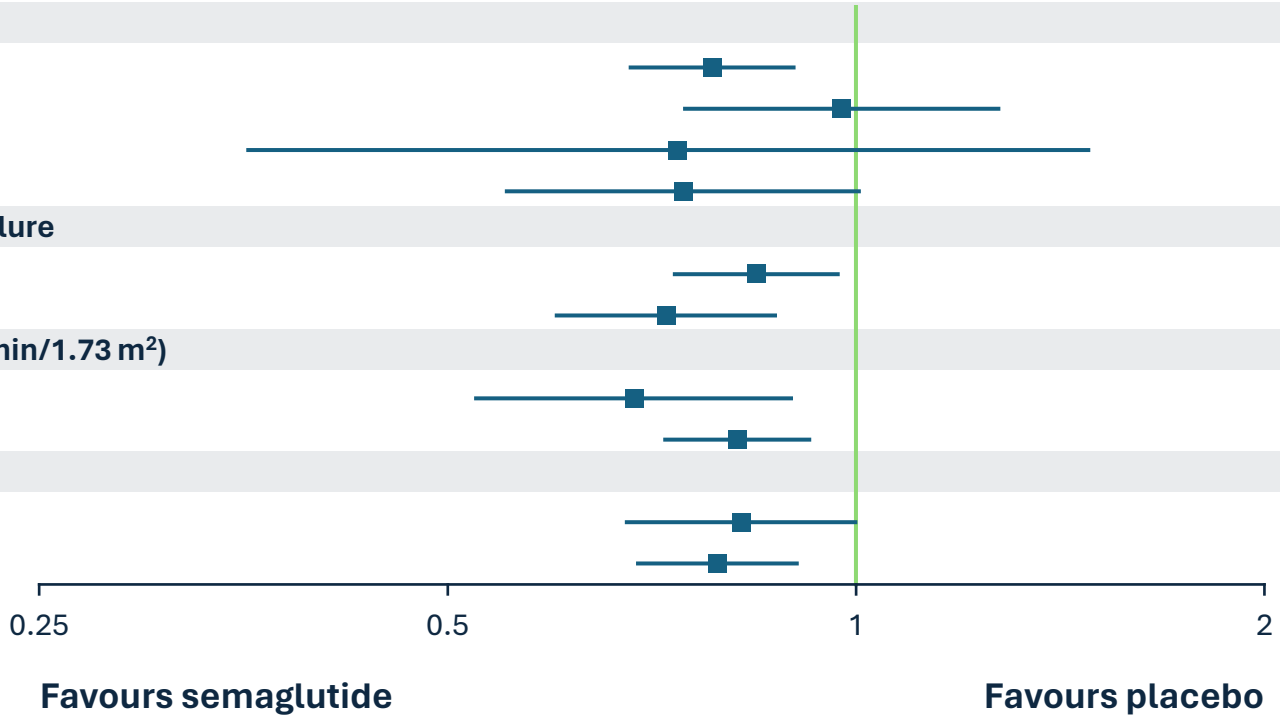


	HR (95% CI)	No. of events / analysed participants (semaglutide; placebo)
Primary analysis		
Semaglutide / placebo	0.80 (0.72; 0.90)	569 / 8,803; 701 / 8,801
Sex		
Female	0.84 (0.66; 1.07)	126 / 2,448; 147 / 2,424
Male	0.79 (0.70; 0.90)	443 / 6,355; 554 / 6,377
Age (years)		
< 55	0.81 (0.64; 1.04)	115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

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

Semaglutide demonstrated consisted effects across subgroups

Subgroup analyses of three-point MACE

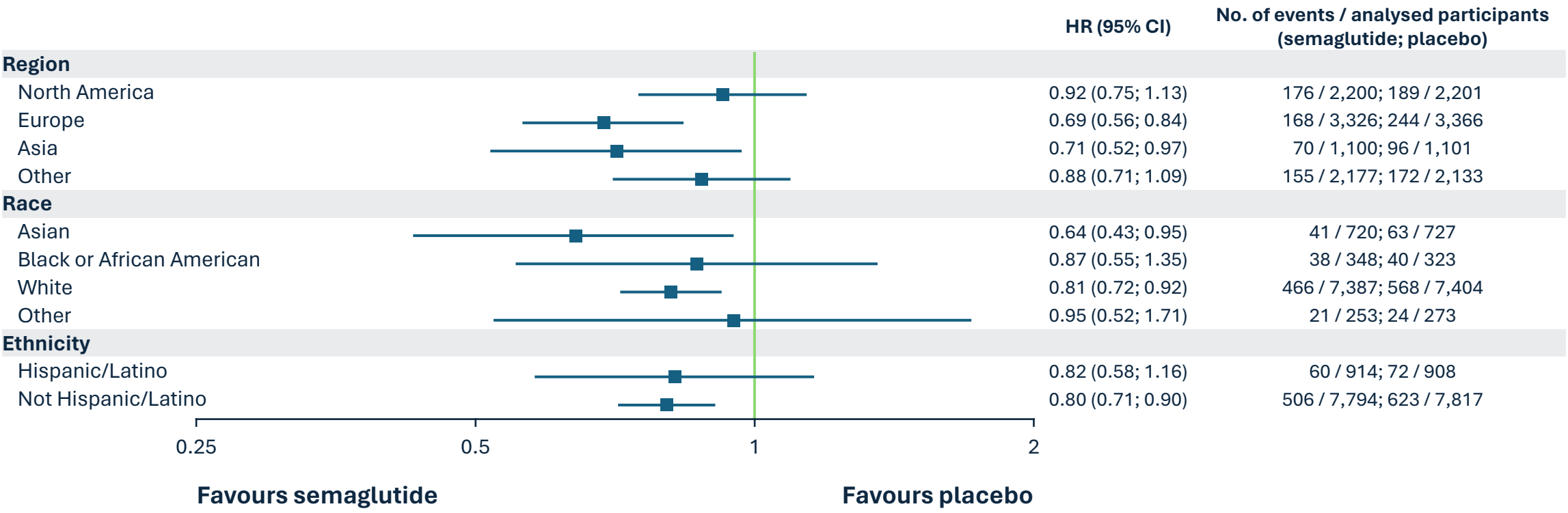


	HR (95% CI)	No. of events / analysed participants (semaglutide; placebo)
CVD		
Only MI	0.78 (0.68; 0.90)	362 / 5,962; 455 / 5,944
Only stroke	0.98 (0.75; 1.27)	109 / 1,578; 109 / 1,556
Only PAD	0.74 (0.36; 1.48)	13 / 376; 19 / 401
≥ 2 CVDs	0.75 (0.55; 1.00)	76 / 718; 100 / 719
Chronic heart failure		
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.

Semaglutide demonstrated consisted effects across subgroups

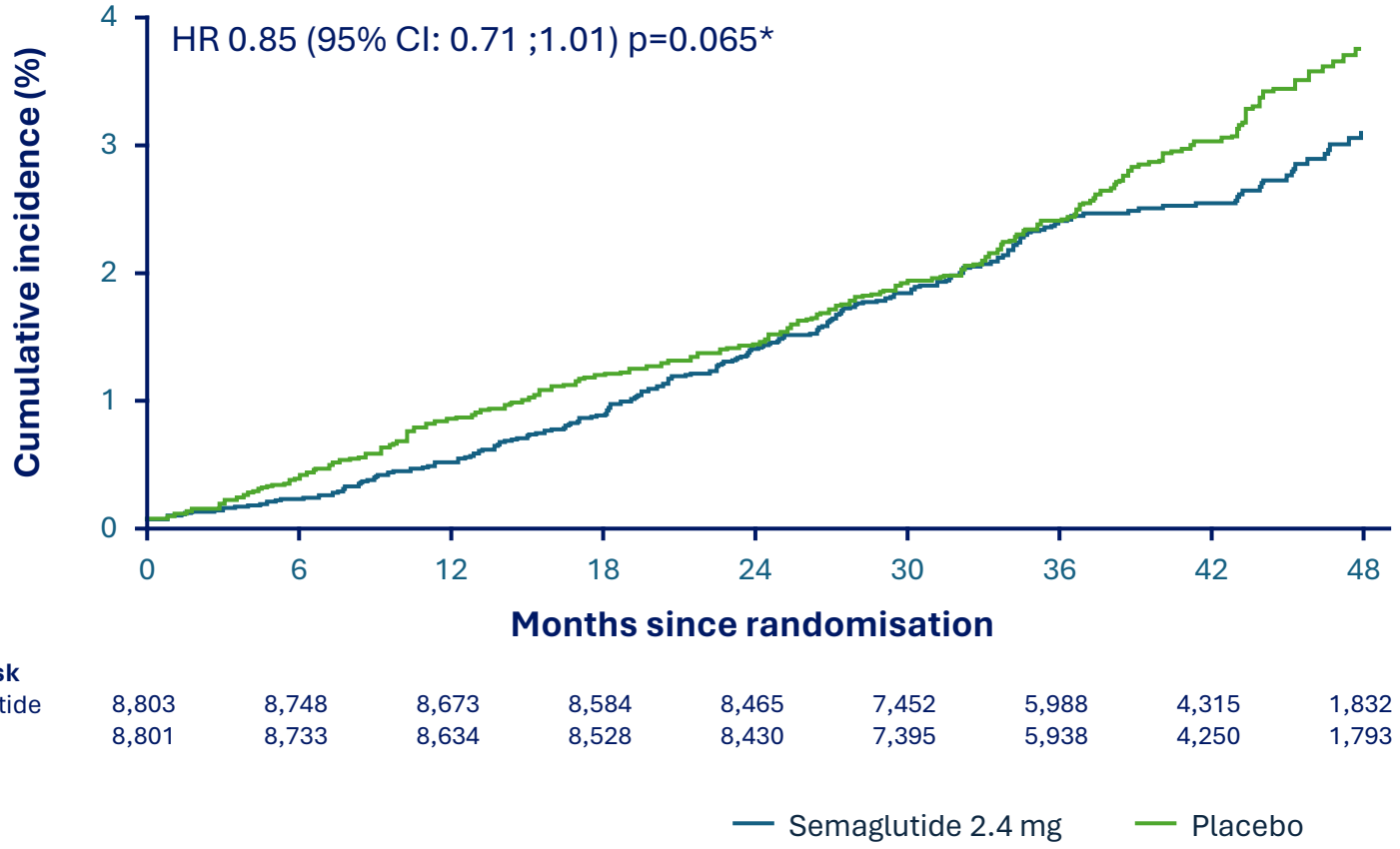
Subgroup analyses of three-point MACE



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; HR, hazard ratio; MACE, major adverse cardiovascular event.
Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

Cumulative incidence of death from CV causes

First confirmatory secondary endpoint



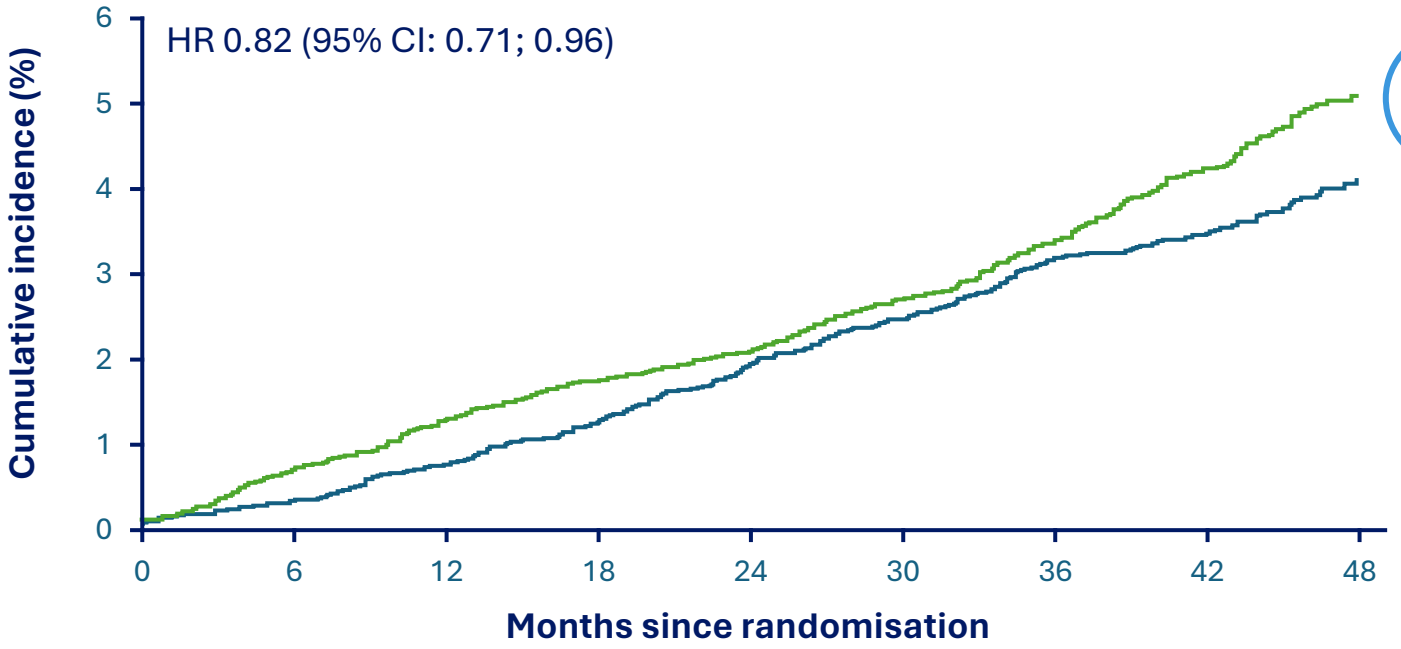
Semaglutide 2.4 mg reduced the risk of death from CV causes by 15%
compared with placebo

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.

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

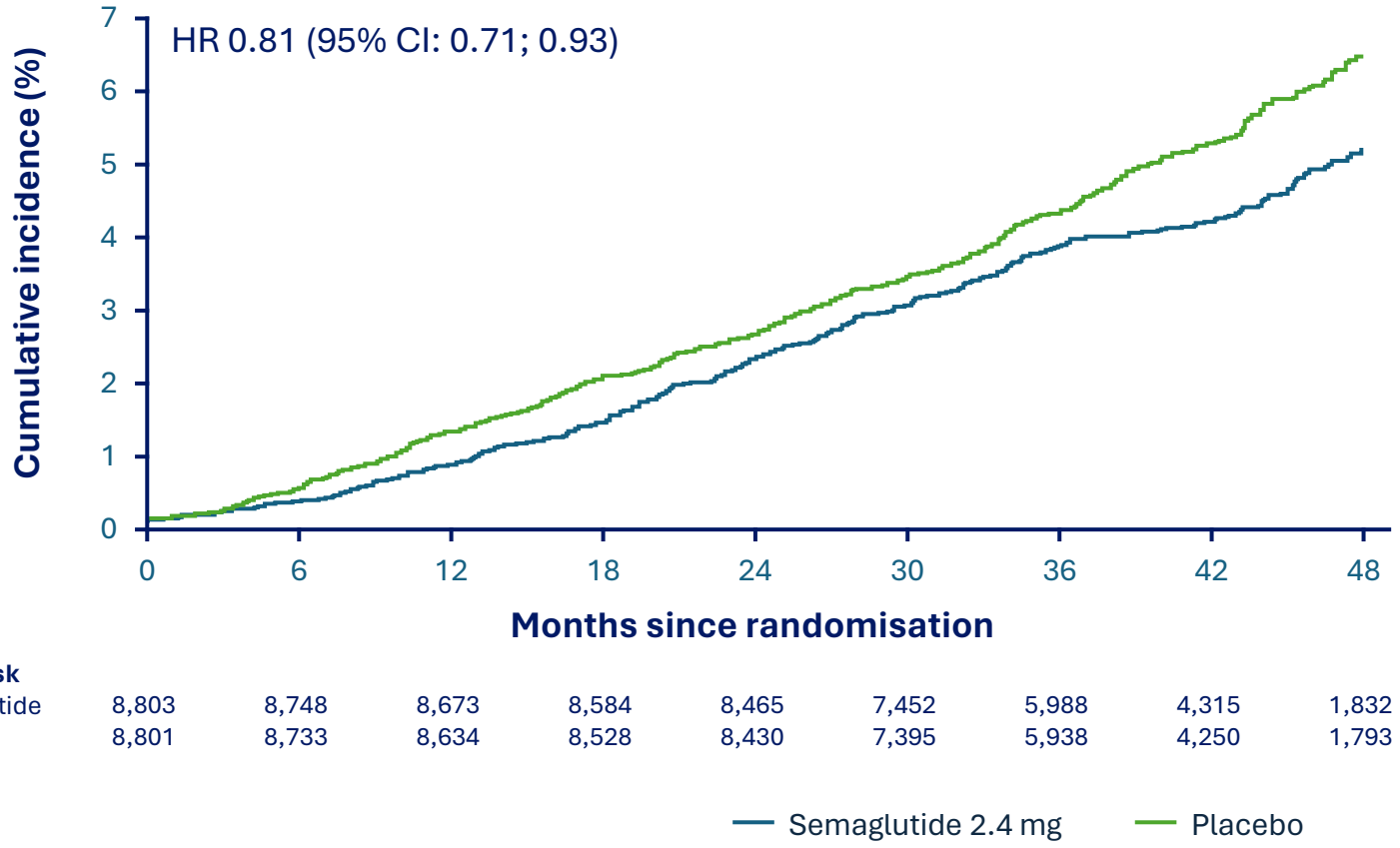
Semaglutide 2.4 mg reduced the risk of composite HF events by 18% compared with placebo

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.

Cumulative incidence of death from any cause

Third confirmatory secondary endpoint



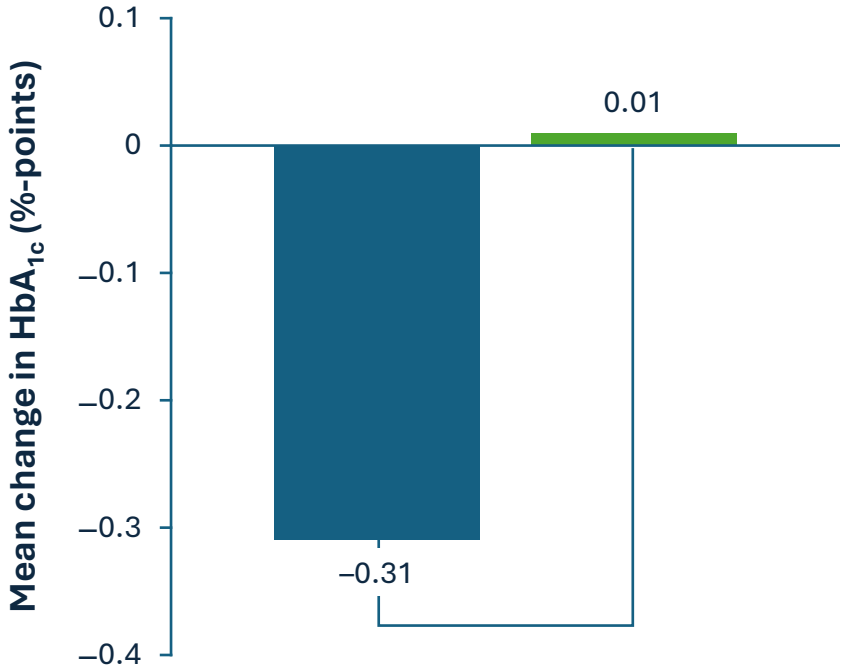
Semaglutide 2.4 mg reduced the risk of death from any cause by 19%
compared with placebo

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.

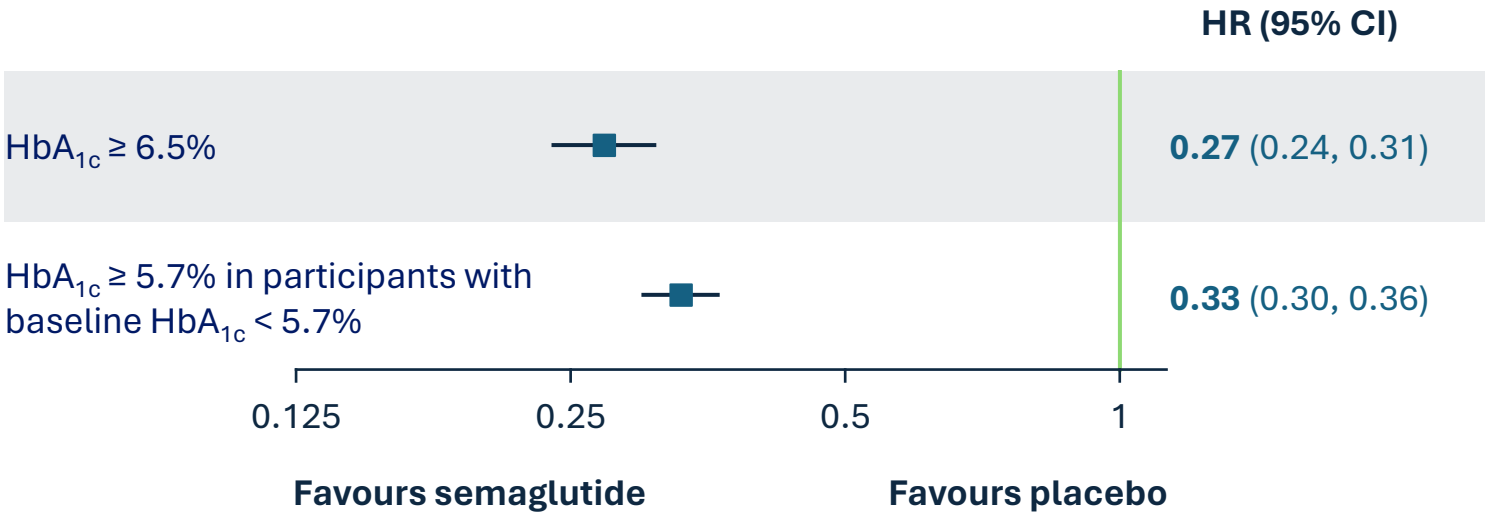
Change in glycaemic status

Change in HbA_{1c}*



ETD (95% CI):
–0.32 %-points (–0.33; –0.31)

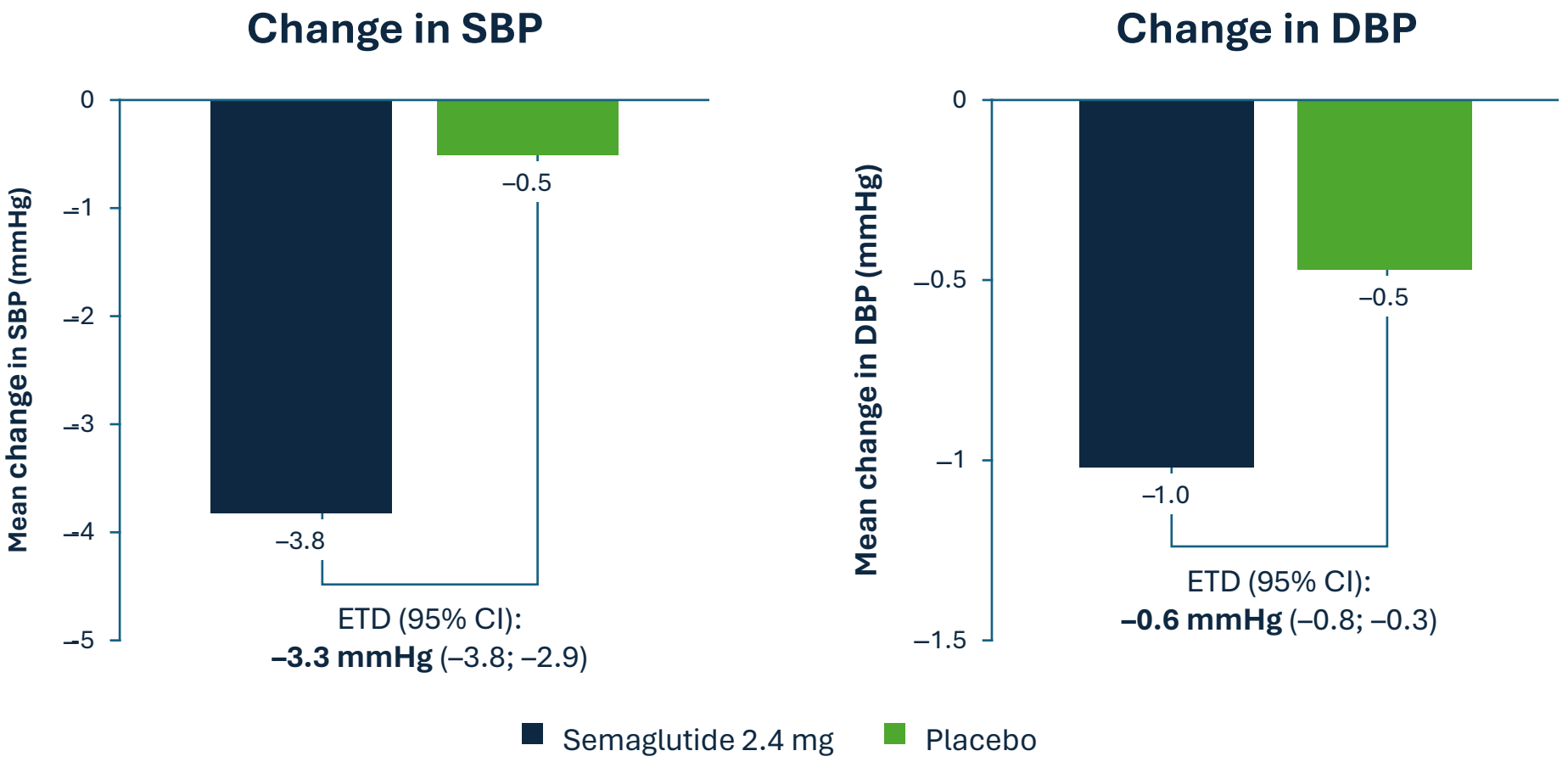
Time to glycaemic events†



Semaglutide 2.4 mg Placebo

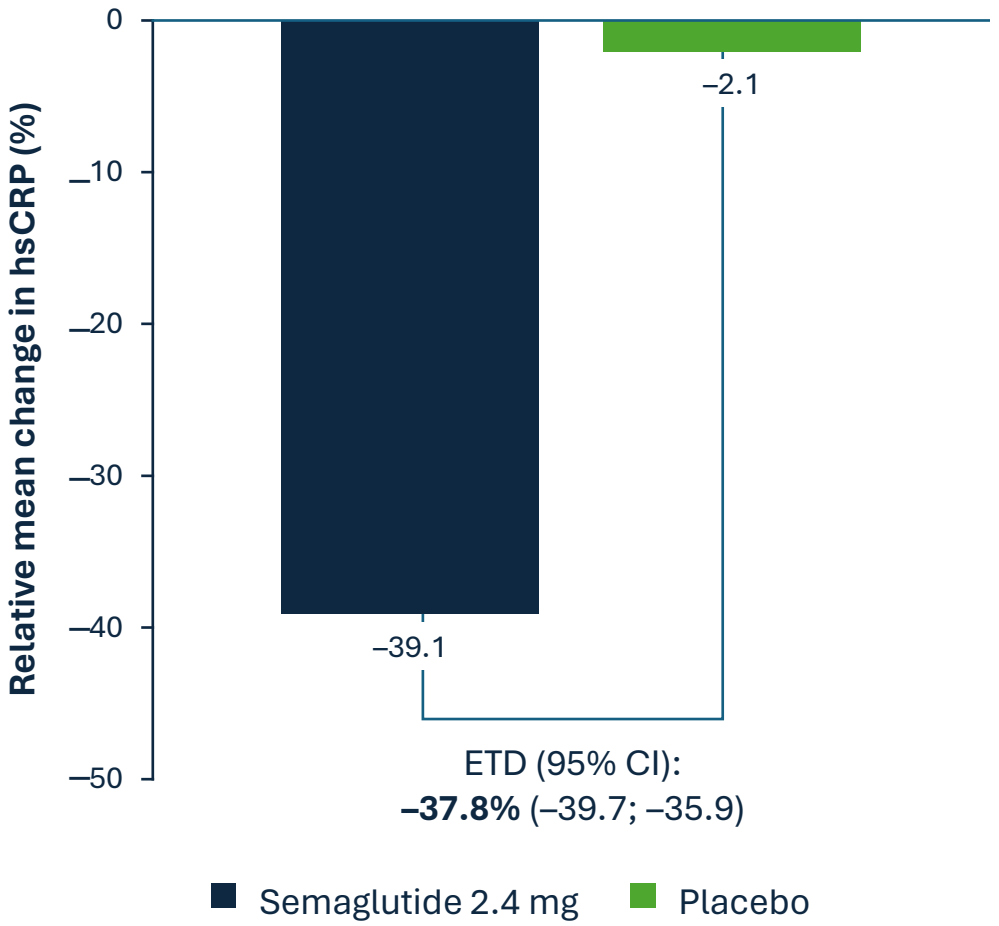
*CIs have not been adjusted for multiplicity. *Change from baseline to week 104, estimated using ANCOVA with treatment as factor and the baseline value as covariate. †HRs were estimated using a Cox proportional hazards regression model. ANCOVA, analysis of covariance; CI, confidence interval; ETD, estimated treatment difference; HbA_{1c}, glycated haemoglobin; HR, hazard ratio.*
Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

Change in blood pressure (mmHg)



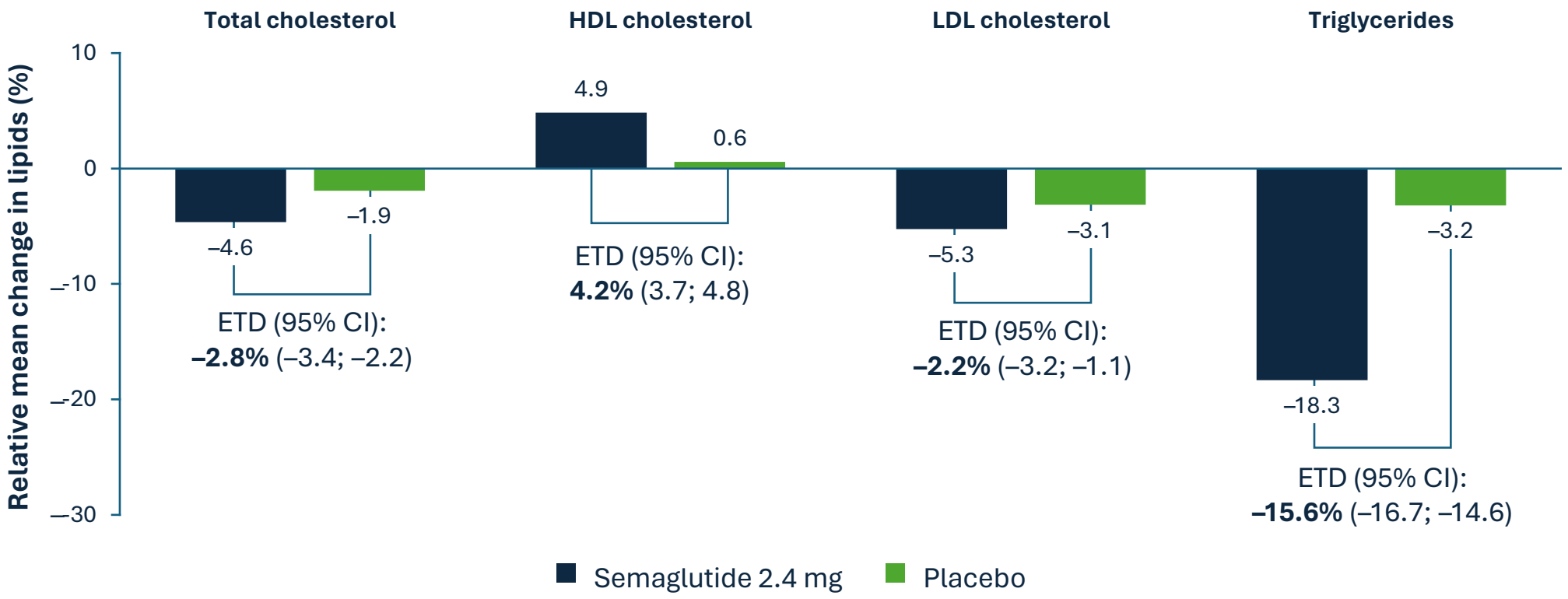
Change from baseline to week 104, estimated using ANCOVA with treatment as factor and the baseline value as covariate. CIs have not been adjusted for multiplicity.
ANCOVA, analysis of covariance; CI, confidence interval; DBP, diastolic blood pressure; ETD, estimated treatment difference; SBP, systolic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

Change in hsCRP (%)



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 (%)

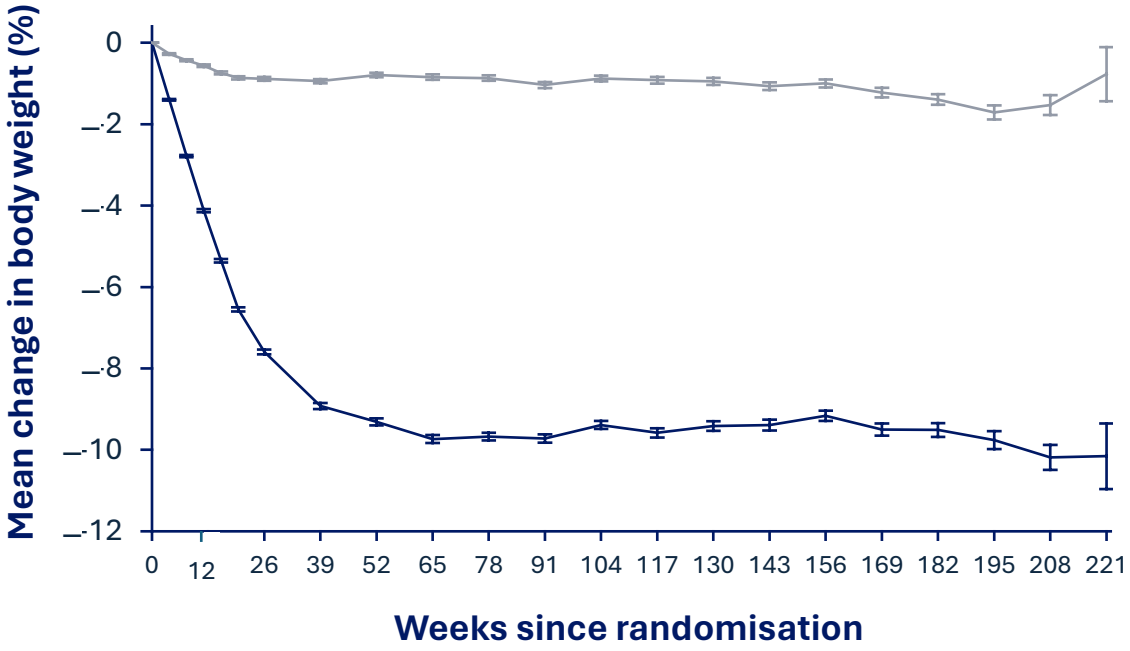


Relative changes from baseline (log-transformed before analysis) to week 104, estimated using ANCOVA with treatment as factor and the baseline value as covariate. CIs have not been adjusted for multiplicity.
ANCOVA, analysis of covariance; CI, confidence interval; ETD, estimated treatment difference;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

Change in body weight (%)

Observed change from baseline over time

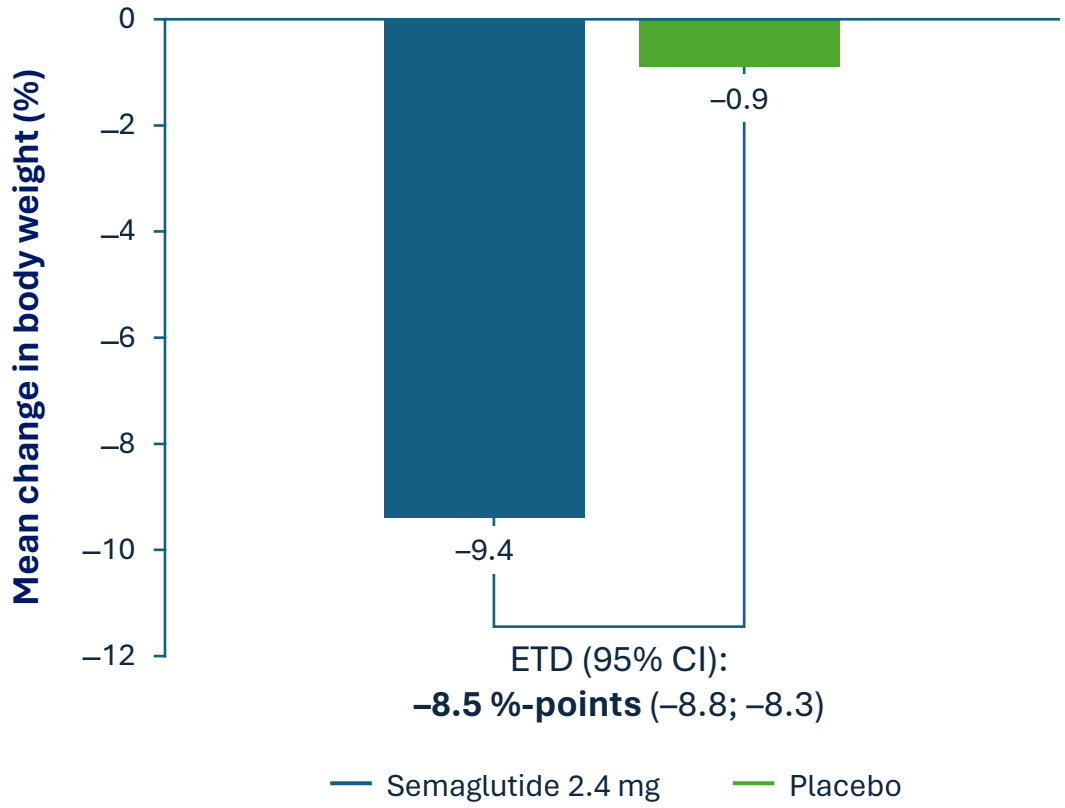
Mean baseline body weight, kg:
Semaglutide 2.4 mg: 96.5 Placebo: 96.8



No. of participants

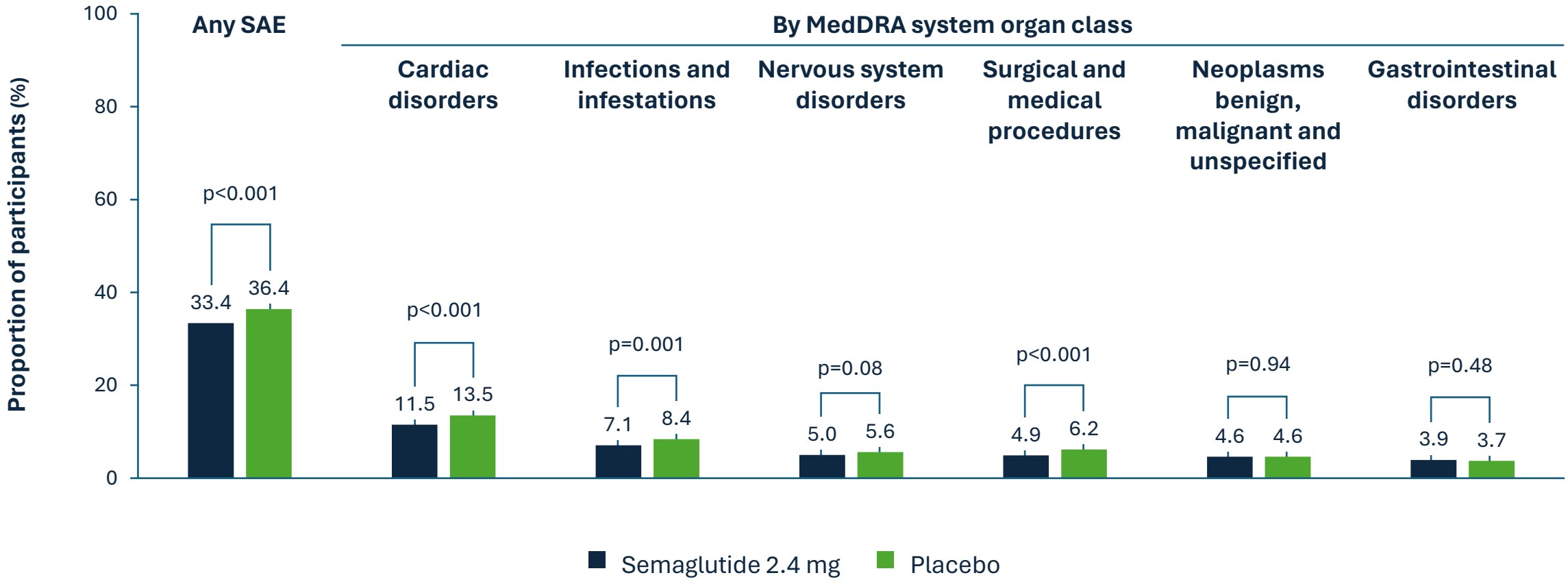
Semaglutide	8,803	7,647	7,493	6,690	7,290	6,447	7,282	6,460	7,474	5,991	5,898	4,686	5,085	3,650	2,954	1,737	921	157
Placebo	8,801	7,715	7,516	6,704	7,269	6,340	7,272	6,392	7,378	5,871	5,879	4,583	5,014	3,560	2,890	1,698	898	152

Estimated change from baseline to week 104*



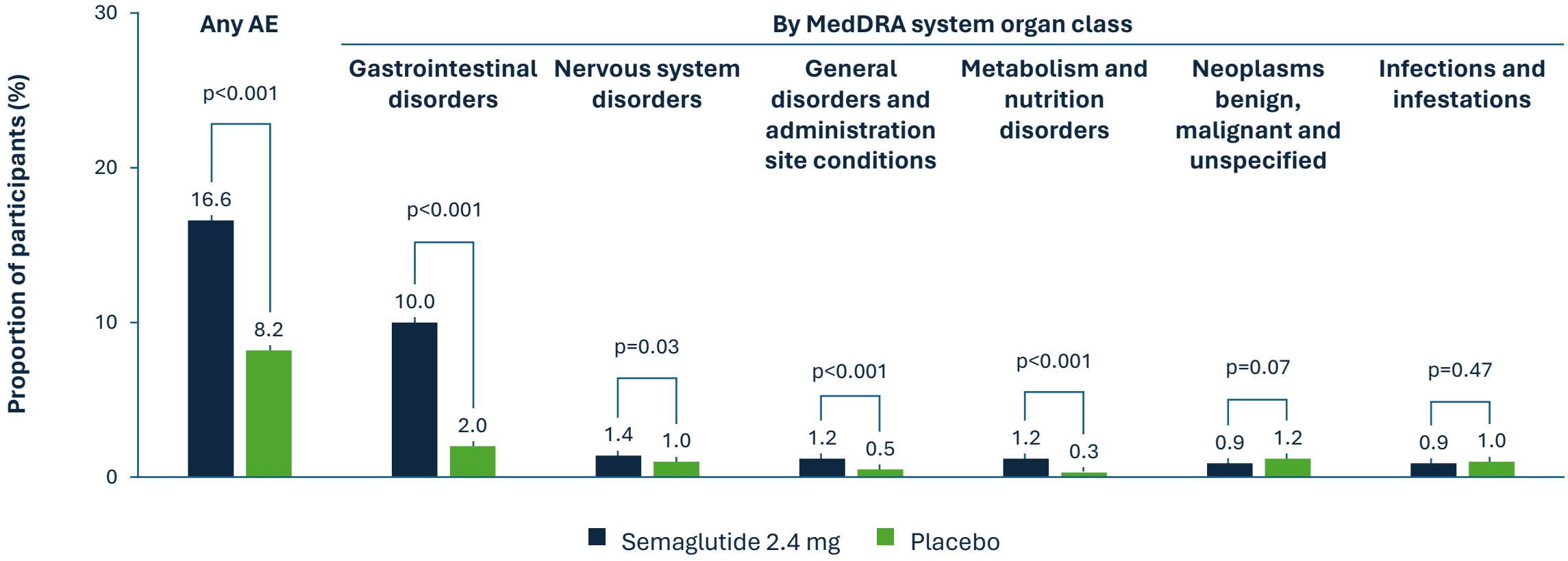
*Error bars in the left-hand figure are 95% CI as calculated by 1.96 times the standard error. *Estimated using an ANCOVA with treatment as factor and the baseline value as covariate, using multiple imputation for missing values under a missing-at-random assumption. CIs have not been adjusted for multiplicity.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

Serious adverse events



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



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.

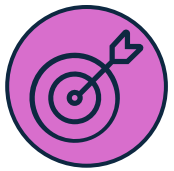
Conclusions from SELECT

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

Semaglutide 2.4 mg had consistent beneficial effects across measured CV endpoints.[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] confirming the well-established safety and tolerability profile of semaglutide 2.4 mg.



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. Novo Nordisk A/S. Company announcement, 8 August 2023. Available at: https://www.novonordisk.com/content/nncorp/global/en/news-and-media/news-and-ir-materials/news-details.html?id=166301. Accessed October 2023; 3. Bergman NC et al. Diabetes Obes Metab 2023;25:18–35.

S/c Semaglutide: Wegovy

1 INDICATIONS

Wegovy® (semaglutide injection) is indicated as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in:

- Adult patients with an initial body mass index (BMI) of
  - 30 kg/m^2 or greater (obesity), or
  - 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity such as hypertension, type 2 diabetes mellitus, dyslipidemia, or obstructive sleep apnea.
- Pediatric patients aged 12 to less than 18 years:
  - with an initial BMI at the 95th percentile or greater for age and sex (obesity; see Table 1), and
  - a body weight above 60 kg (132 lbs), and
  - an inadequate response to reduced calorie diet and physical activity alone.

Back to John

- Diet and lifestyle modification
- Discussed exercise (150 mins per week), ordered ABI – left leg 0.6
- Polyvascular disease: Riva 2.5mg BID and stop ticagrelor at 12 months post PCI (covered by Dr Abramson)
- Discussed S/C semaglutide
- Has elevated CRP – colchicine 0.5mg discussed