Addressing Weight Management in Cardiovascular Care

Preparing Clinicians to Guide the Weight Loss Journey

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Disclosures: Abbott, American Regent, Amgen, Applied Therapeutic, AskBio, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cardiac Dimension, Cardiocell, Cardior, CSL Bearing, CVRx, Cytokinetics, Daxor, Edwards, Element Science, Faraday, Foundry, G3P, Innolife, Impulse Dynamics, Imbria, Inventiva, Ionis, Lexicon, Lilly, LivaNova, Janssen, Medtronics, Merck, Occlutech, Owkin, Novartis, Novo Nordisk, Pfizer, Pharmacosmos, Pharmain, Prolaio, Regeneron, Renibus, Roche, Salamandra, Sanofi, SC Pharma, Secretome, Sequana, SQ Innovation, Tenex, Tricog, Ultromics, Vifor, and Zoll

ESC European Society of Cardiology

European Heart Journal (2023) **00**, 1–13
https://doi.org/10.1093/eurheartj/ehad664

STATE OF THE ART REVIEW

Diabetes and metabolic disorders

The cardiovascular effects of novel weight loss therapies

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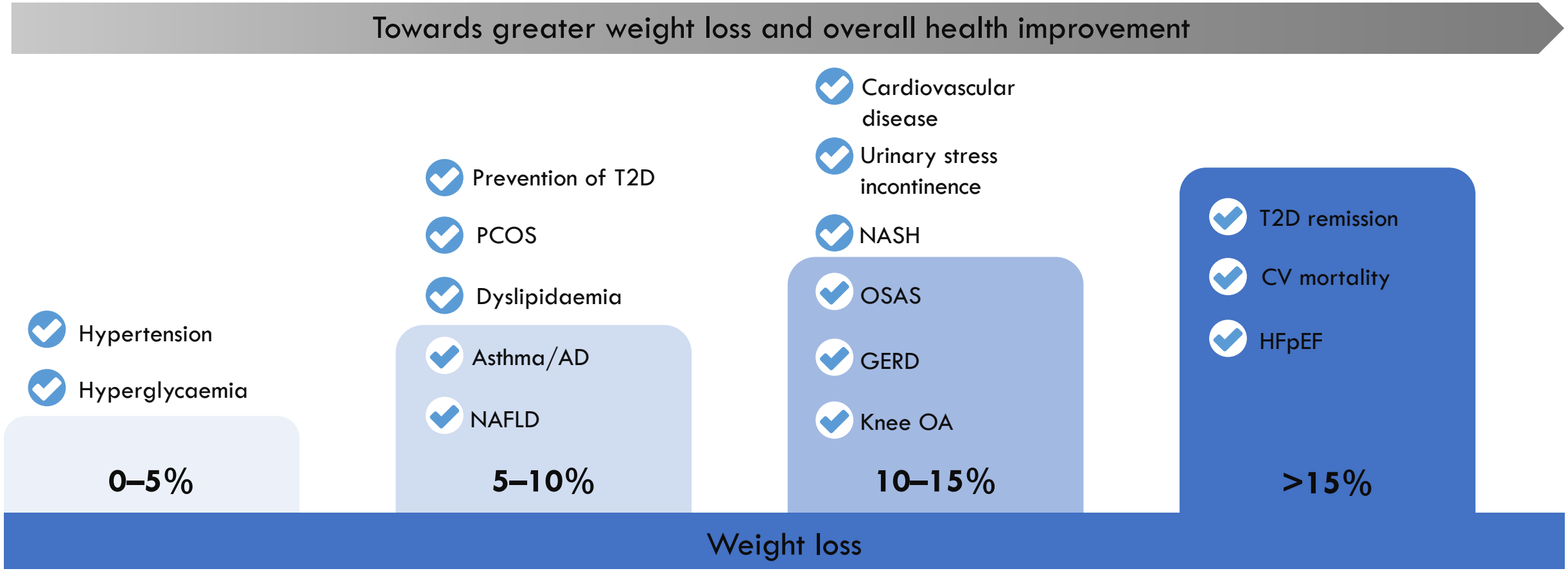
Received 1 June 2022; revised 3 August 2023; accepted 26 September 2023

The effect of weight loss on comorbidities



CV, cardiovascular; GERD, gastroesophageal reflux disease; HFpEF, heart failure with preserved ejection fraction; NAFLD, non-alcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OA, osteoarthritis; OSAS, obstructive sleep apnoea syndrome; T2D, type 2 diabetes; PCOS, polycystic ovary syndrome;

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

Pillars of obesity management

Psychological Intervention

1. Implement multicomponent behaviour modification
2. Manage sleep, time, and stress
3. Cognitive behavioural therapy and/or acceptance and commitment therapy should be provided for patients if appropriate

Pharmacological Therapy

1. Liraglutide
2. Naltrexone/bupropion (in a combination tablet)
3. Orlistat

Criteria
BMI ≥30 kg/m^2 or
BMI ≥27 kg/m^2 with obesity (adiposity) related complications

Bariatric Surgery

Procedure should be decided by surgeon in discussion with patient

1. Sleeve gastrectomy
2. Roux-en-Y gastric bypass
3. Biliopancreatic diversion with/without duodenal switch

Criteria
BMI ≥40 kg/m^2 or
BMI ≥35–40 kg/m^2 with obesity (adiposity) related complications or
BMI ≥30 kg/m^2 with poorly controlled T2D

BMI, body mass index. These medications may not be approved outside of Canada.

Wharton, S. et al. Canadian Medical Association Journal 2020; 192: E875-891.

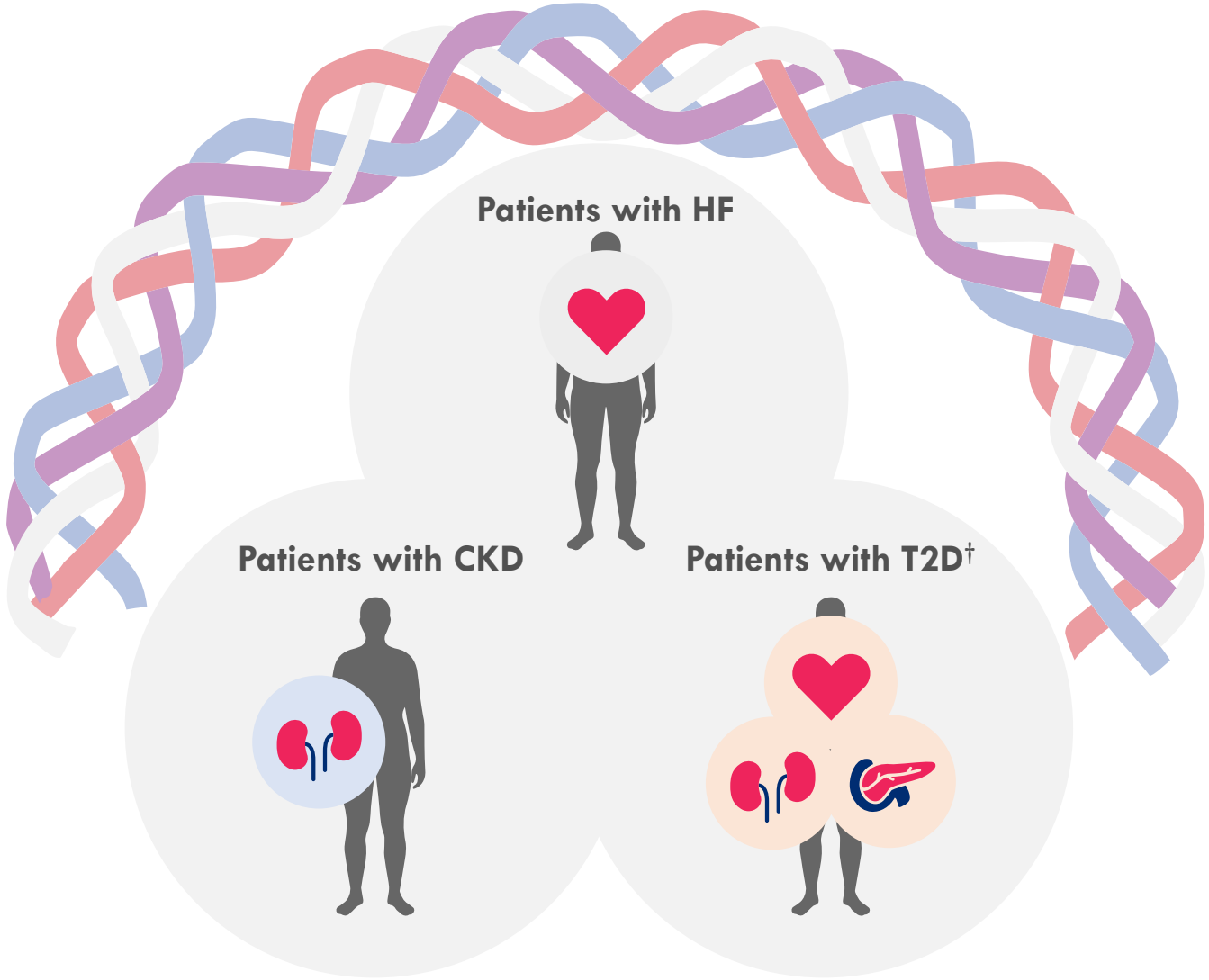
Issues to contend

- Accepting is the a ‘disease’, risk factor that needs treatment
- Accepting that it is an issue for all specialties
- About weight loss vs. specific drugs (for now)
- Diet and exercise
  - Heart failure experience
- Bariatric
- Team and infrastructure

SGLT2 inhibitors: from glucose control to organ-protection

SGLT2 inhibitors have demonstrated…

- **Phase III trials** — Metabolic benefits in patients **with T2D**[1–4]
- **CVOTs** — CV and kidney benefits in patients **with T2D** and CVD[5–14]
- **HF trials** — CV benefits in patients **with HF**, independent of T2D*[15–17]
- **CKD trials** — Kidney benefits in patients **with CKD**, independent of T2D*[18]



Only dapagliflozin is indicated in patients with CKD. *At baseline; †SGLT2 inhibitors may also be used in patients with T2D and ASCVD or high risk of ASCVD.[19] CKD, chronic kidney disease; CVD, cardiovascular disease; CVOT, cardiovascular outcome trial; HF, heart failure; SGLT2, sodium-glucose co-transporter-2; T2D, type 2 diabetes. See slide notes for references

Weight Interventions: Question of CV Benefit?

	Look AHEAD[1]	SOS[2]*	SCOUT[3]	CRESCENDO[4]	LIGHT[5]	CONVENE[6]	CAMELLIA-TIMI[7]	AQCLAIM[8]
Intervention	**Lifestyle +/- orlistat**	***Surgery***	**Sibutramine**	**Rimonabant**	**Naltrexone/ Buproprion**	**Naltrexone/ Bupropion**	**Lorcaserin**	**Phentermine/ Topiramate**
Date started	June 2001	*Jan 1987*	Jan 2003	Dec 2005	Jun 2012	Dec 2015	Jan 2014	Oct 2013
Date ended or ending	Sept 2012	*Nov 2005*	Mar 2009	Apr 2009	Aug 2015	Apr 2016	Sep 2018	Apr 2020
Patients planned or enrolled	5100 (5145)	*4047*	10777	18695	9810>8900 (8910)	8800 (67)	12000	16000
Design **Event rate** **Risk reduction** **Discontinues**	Superior 3.125% 18% 2% pa	*Registry*	Superior 7% 11.4% 30%	Superior 3% 15% 10%	Non-inferior 1.5% HR:<1.4 1.2% pa	? ? ? ?	Non-inferior 1.5% HR:<1.4 5%	? ? ? ?
Primary Outcome	3P-MACE + hospitalisation	*Overall mortality*	3P-MACE + resuscitated cardiac arrest	3P-MACE + hospitalisation	3P-MACE + angina needing hospitalisation	3P-MACE	1. 3P-MACE 2. T2D 3. MACE+	MACE
Results	**Stopped for futility**	***Benefit***	**Harm**	**Terminated**	**Terminated**	**Terminated**	**Non-inferiority established**	**Not started**

*Not a randomised controlled trial

3P, 3-point; HR, hazard ratio; MACE, major adverse cardiac event; T2D, type 2 diabetes

1. Look AHEAD Research Group. *Controlled Clinical Trials*. 2003;24:610-28; 2. Sjöström *et al. JAMA*. 2012;307:56-65; 3. James *et al. N Engl J Med*. 2010;363:905-917; 4. Topol *et al. The Lancet*. 2010,376:517-523; 5. Nissen *et al. JAMA*. 2016;315:990-1004; 6. https://clinicaltrials.gov/ct2/show/NCT02638129 7. https://clinicaltrials.gov/ct2/show/NCT02019264; 8. EU clinical trial register. https://www.clinicaltrialsregister.eu/ctr-search/trial/2012-003946-34/GB

GLP-1 RAs Reduce CV Risk in T2D

	Lixisenatide (ELIXA)[1]	Liraglutide (LEADER)[2]	SC Semaglutide (SUSTAIN 6)[3]	Exenatide ER (EXSCEL)[4]	Dulaglutide (REWIND)[5]	Oral Semaglutide (PIONEER 6)[6]	Efpeglenatide (AMPLITUDE-O)[7]
MACE	↑2%	**↓13%**	**↓26%**	↓9%	**↓12%**	↓21%	**↓27%**
CV death	↓2%	**↓22%**	↓2%	↓12%	↓9%	**↓51%**	↓28%
HF hosp.	↓4%	↓13%	↑11%	↓6%	↓7%	↓14%	N/A
All-cause death	↓6%	**↓15%**	↑5%	↓14%	↓10%	**↓49%**	↓22%
Non-fatal stroke	↑12%	↓11%	**↓39%**	NA	**↓24%**	↓26%	↓20%

CVOT, cardiovascular outcome trial; MACE, major adverse cardiovascular event; SC, subcutaneous

1) Pfeffer M. *N Engl J Med*. 2015;373(23):2247-2257. 2) Marso SP. *N Engl J Med*. 2016;375:311-322. 3) Marso SP et al. *N Engl J Med*. 2016;375(19):1834-1844. 4) Holman RR et al. *N Engl J Med.* 2017;377(13):1228-1239. 5) Gerstein HC et al. *Lancet.* 2019;394(10193):121-130. 6) Husain M et al. *N Engl J Med*. 2019;381(9):841-851. 7. Gerstein HC et al. *N Engl J Med*. 2021;10.1056/NEJMoa2108269.

STEP programme at a glance

Global phase 3a

STEP 1
Weight management (N=1,961)

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

STEP 3
WM with IBT (N=611)

STEP 4
Sustained WM (N=803)

STEP TEENS
WM in adolescents (N=200)

STEP Young
WM in children and adolescents (N=210)

STEP HFpEF
Semaglutide in obesity (N=516)

STEP HFpEF
Semaglutide in T2D (N=610)

Regional phase 3a

STEP 6
East Asian trial (N=400)

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

Phase 3b

STEP 5
Long-term WM (N=300)

STEP 8
H2H vs liraglutide (N=336)

STEP 9
Semaglutide in knee OA (N=375)

STEP 10
Reversal of pre-diabetes (N=375)

SELECT
CVOT (N=17,500)

STEP 11
Korea/ Thailand trial (N=195)

Phase 4

US employer
US employer trial

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

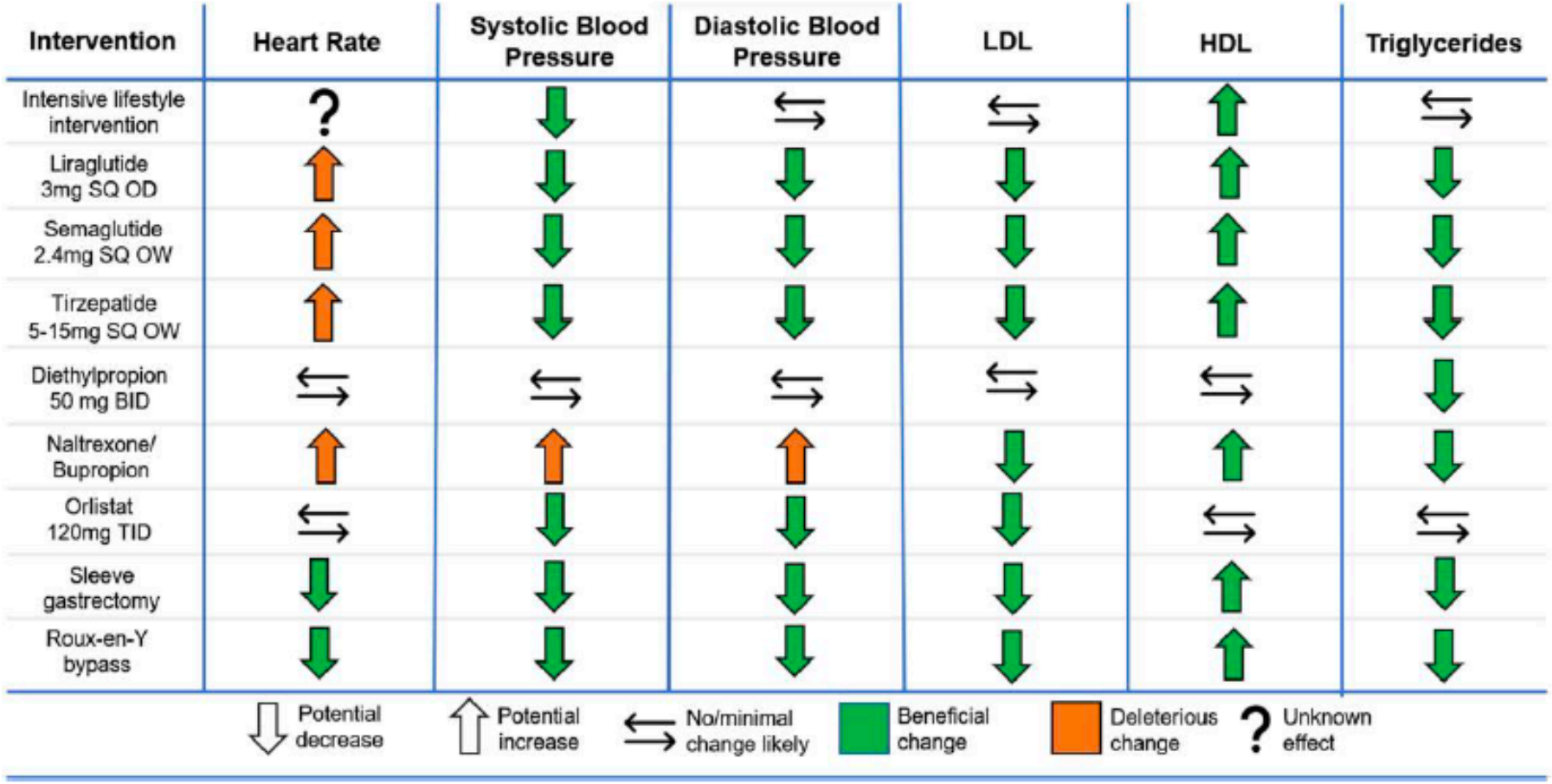
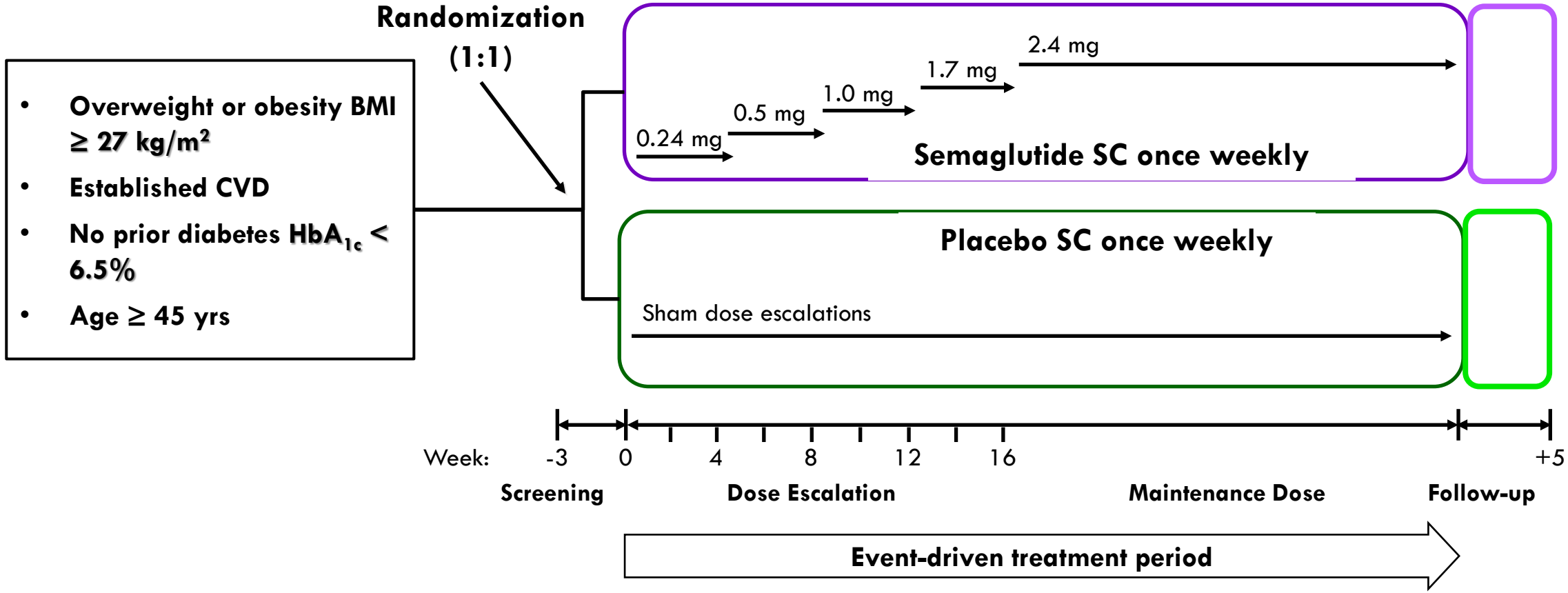


Figure 1 Expected effects of weight loss interventions on cardiovascular risk factors

Usman S, …..Butler J et al, EHJ 2023

Select - Trial Design

SELECT
semaglutide | effects on cardiovascular outcomes in people with overweight or obesity



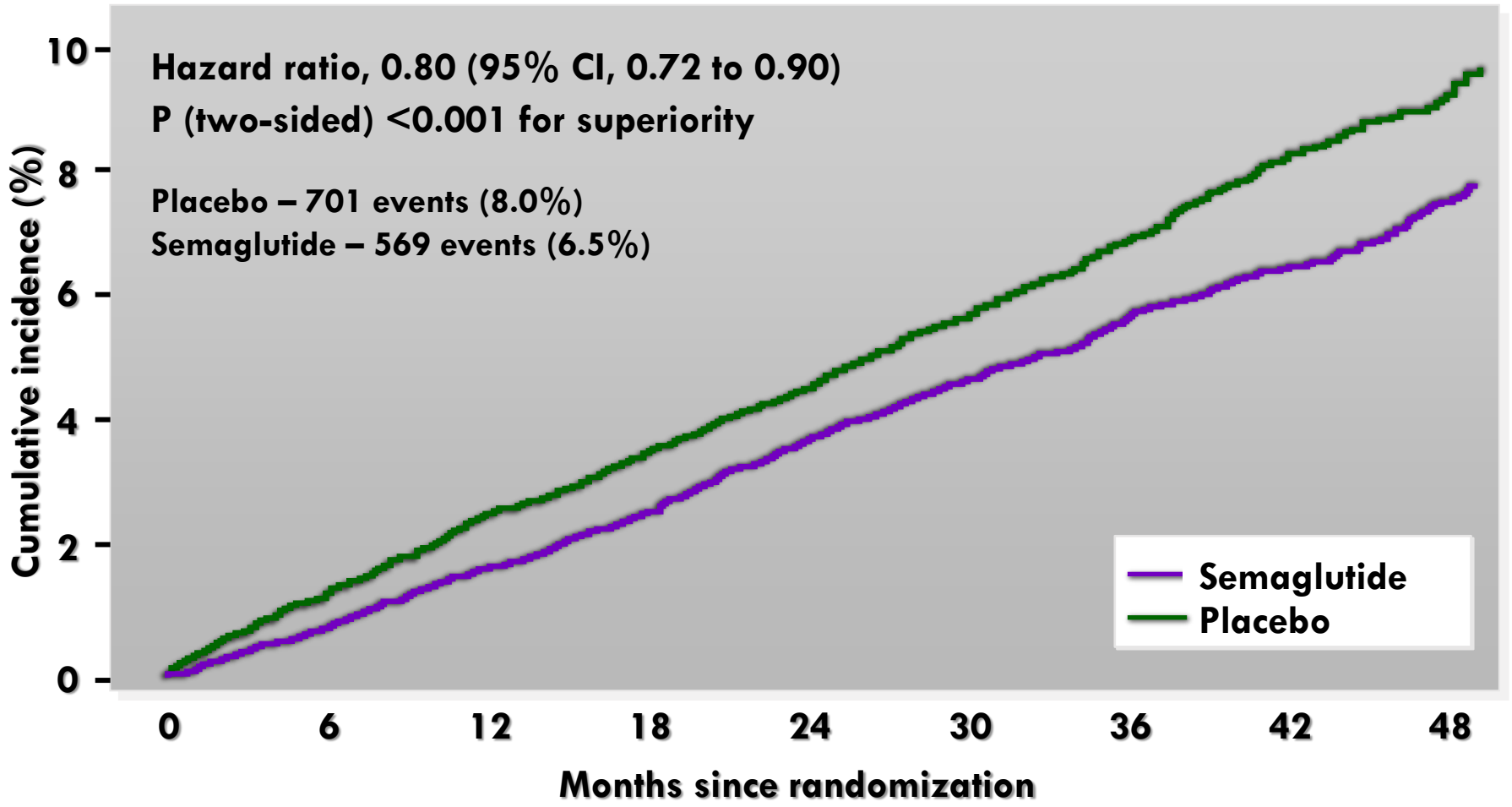
- Semaglutide added to standard of care for CV disease
- Dose reductions or treatment pauses permitted
- Rx for pts who developed diabetes per investigator, except open label GLP-1RA
- No specific, ongoing additional weight interventions

Cardiovascular Efficacy

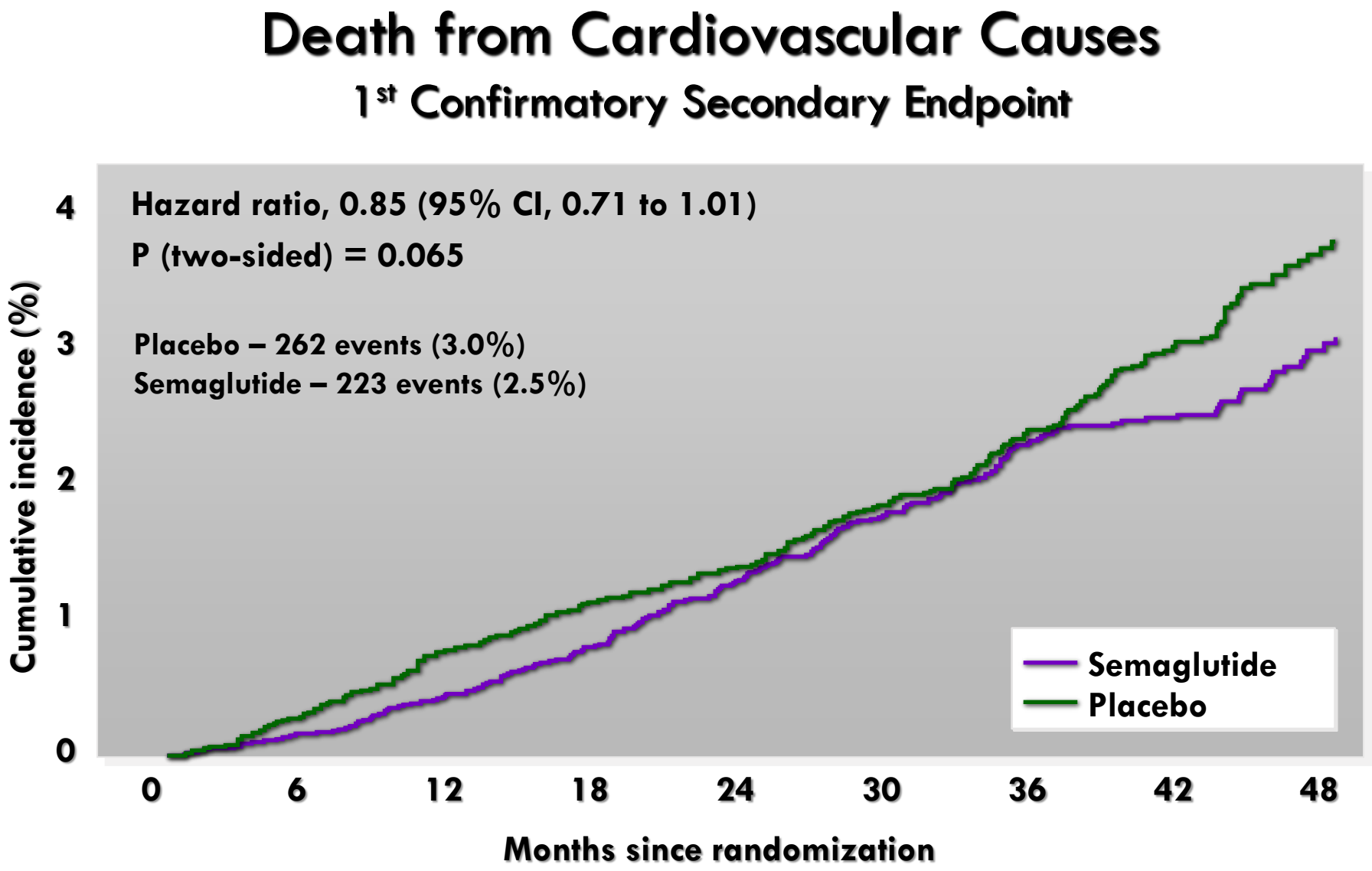
SELECT
semaglutide | effects on cardiovascular outcomes in people with overweight or obesity

CV Death, Nonfatal MI, or Nonfatal Stroke

Primary Cardiovascular Composite Endpoint



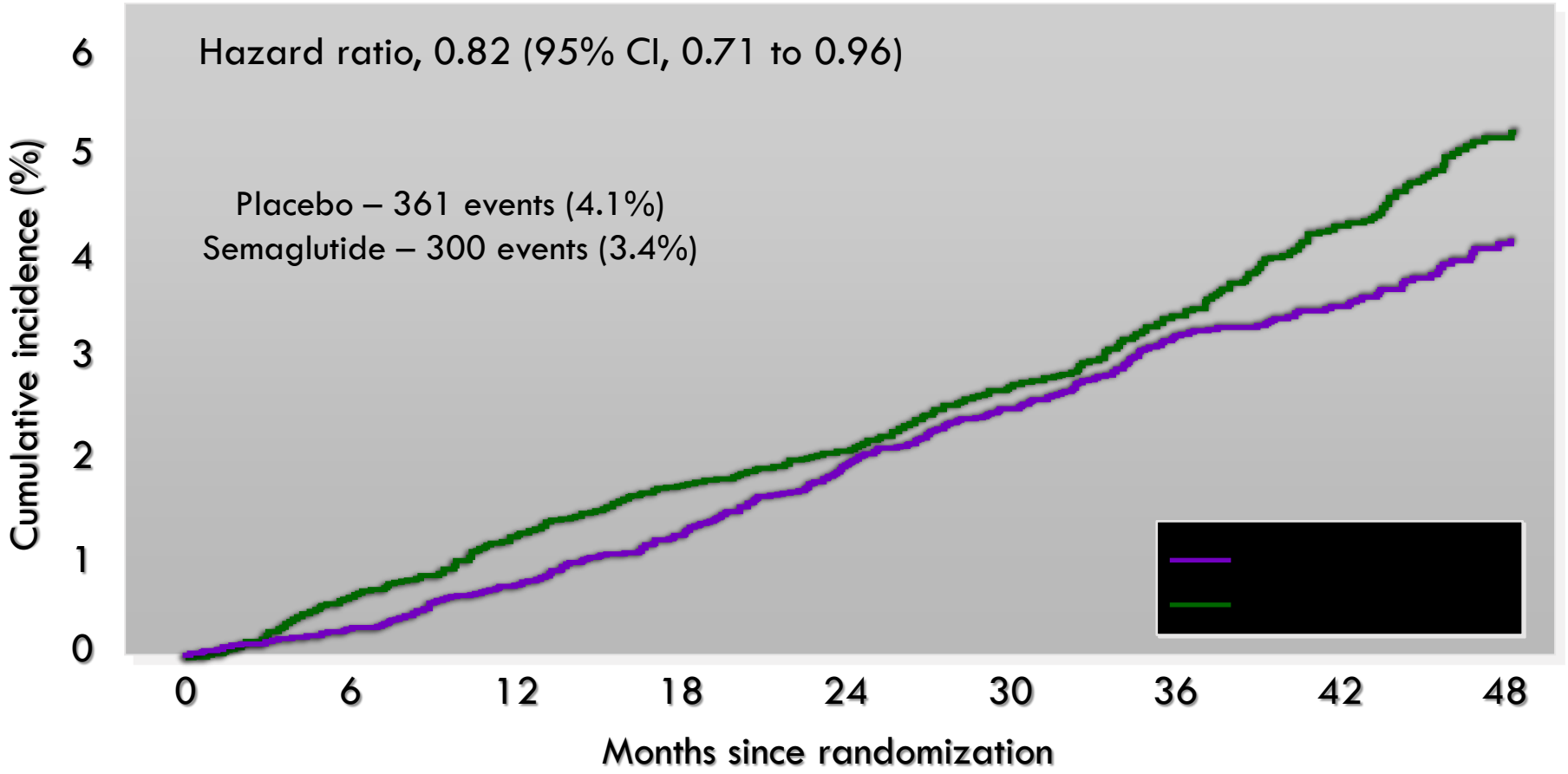
CV Efficacy: Confirmatory Secondary Endpoints



CV Efficacy: Confirmatory Secondary Endpoints

Heart Failure Composite*

2nd Confirmatory Secondary Endpoint

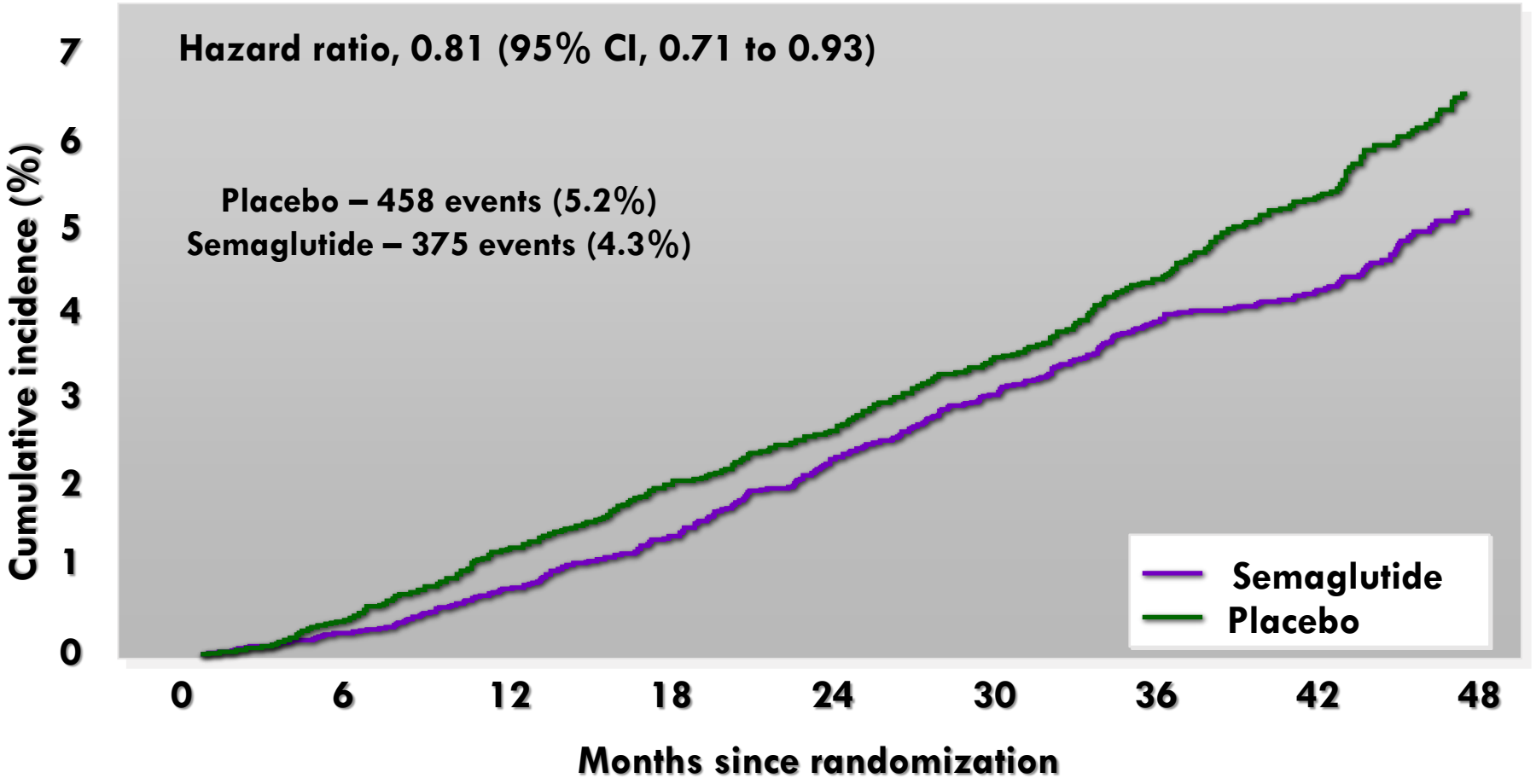


*Heart failure composite - CV death or hospitalization or urgent visit for heart failure

CV Efficacy: Confirmatory Seconday Endpoints

Death from Any Cause

3rd Confirmatory Secondary Endpoint

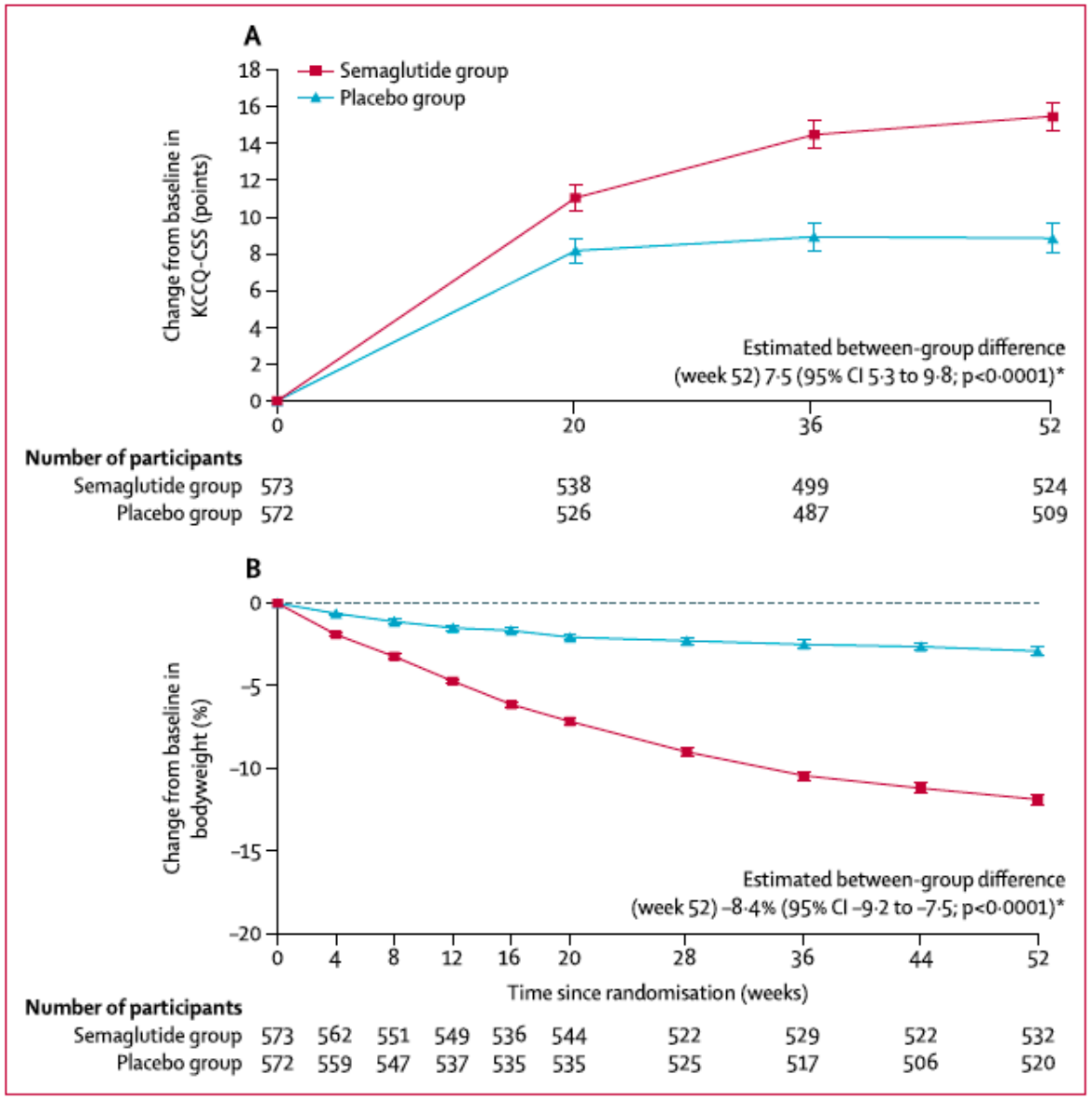


Semaglutide versus placebo in people with obesity-related heart failure with preserved ejection fraction: a pooled analysis of the STEP-HFpEF and STEP-HFpEF DM randomised trials

Javed Butler, Sanjiv J Shah*, Mark C Petrie, Barry A Borlaug, Steen Z Abildstrøm, Melanie J Davies, G Kees Hovingh, Dalane W Kitzman, Daniél Vega Møller, Subodh Verma, Mette Nygaard Einfeldt, Marie L Lindegaard, Søren Rasmussen, Walter Abhayaratna, Fozia Z Ahmed, Tuvia Ben-Gal, Vijay Chopra, Justin A Ezekowitz, Michael Fu, Hiroshi Ito, Małgorzata Lelonek, Vojtěch Melenovský, Bela Merkely, Julio Núñez, Eduardo Perna, Morten Schou, Michele Senni, Kavita Sharma, Peter van der Meer, Dirk Von Lewinski, Dennis Wolf, Mikhail N Kosiborod, for the STEP-HFpEF Trial Committees and Investigators*

www.thelancet.com **Published online April 7, 2024** **https://doi.org/10.1016/S0140-6736(24)00469-0**

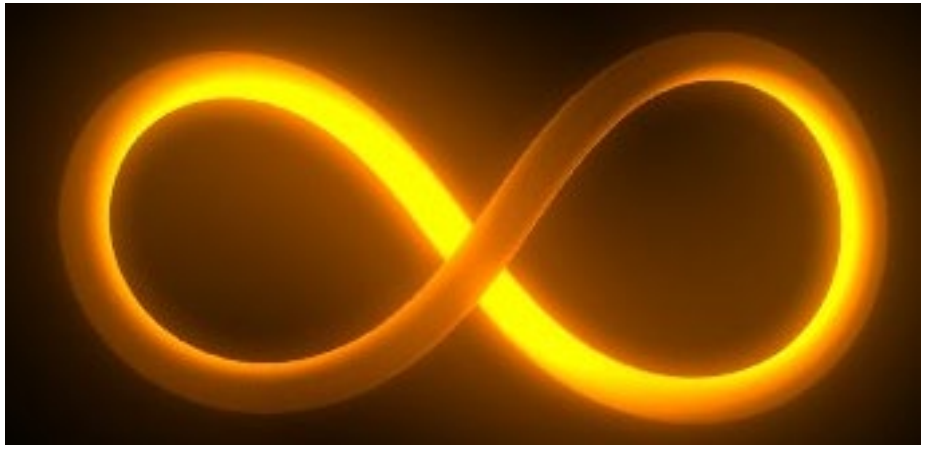
FLOW



To impact cardiac outcomes, weight loss needs to be

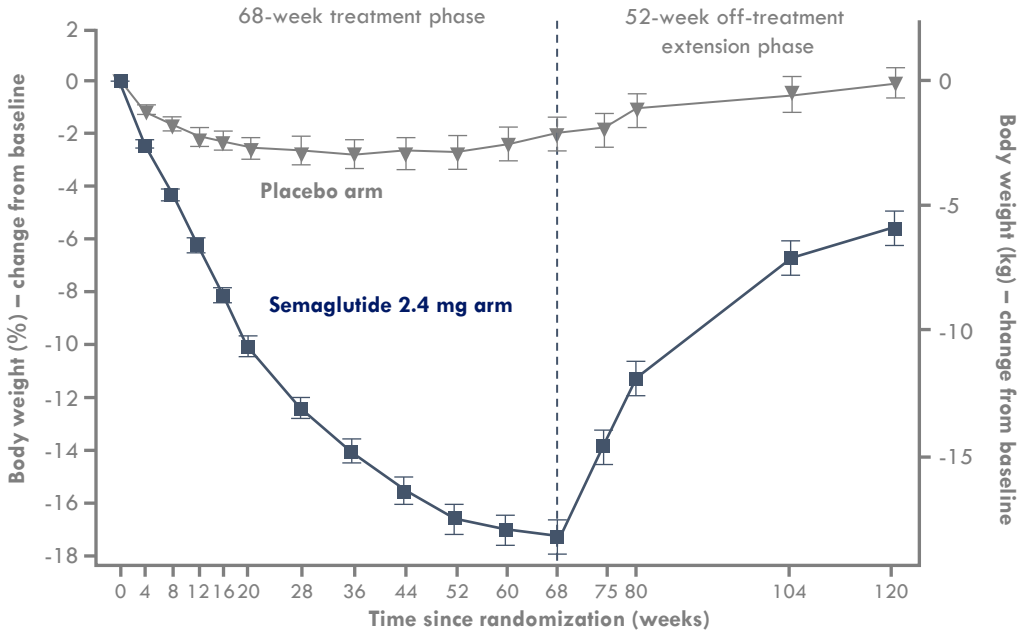
Significant

Sustained



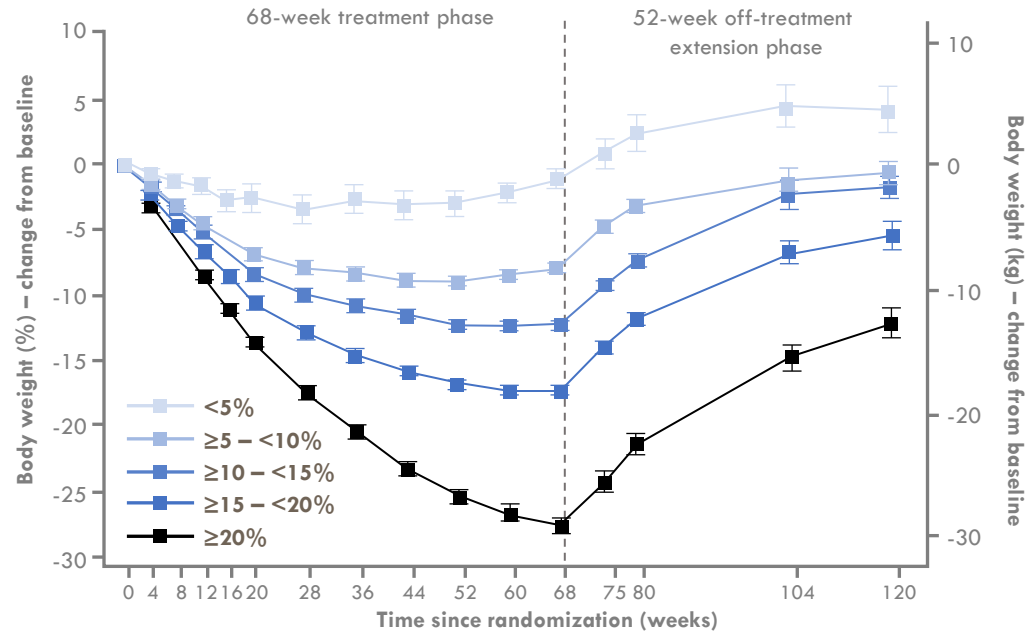
Change in body weight from baseline by week (1 of 2)

All participants in the extension analysis set



Semaglutide 2.4 mg arm	228	226	228	228	225	228	228	228	228	228	227	228	209	174	171	197
Placebo arm	99	99	99	98	97	98	99	99	99	99	99	99	93	79	80	93

Participants in the semaglutide arm, grouped by categorical weight loss from weeks 0–68



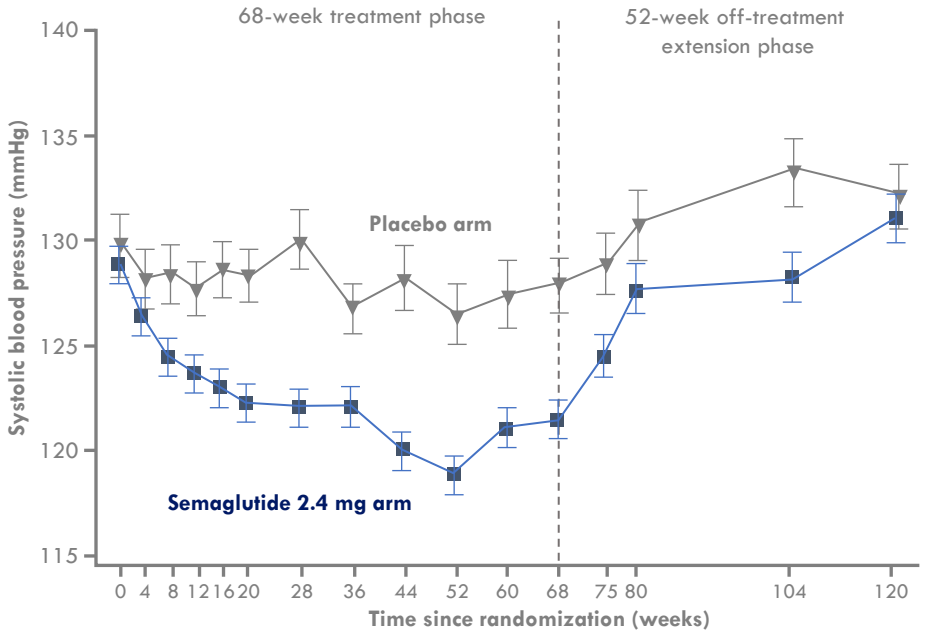
<5%	14	13	14	14	13	14	14	14	14	14	14	14	13	12	11	12
≥5 – <10%	41	40	41	41	40	41	41	41	41	41	41	41	36	32	32	35
≥10 – <15%	45	45	45	45	45	45	45	45	45	45	45	45	44	37	32	37
≥15 – <20%	48	48	48	48	48	48	48	48	48	48	48	48	47	38	41	45
≥20%	80	80	80	80	79	80	80	80	80	80	79	80	69	55	55	68

Adapted from Figure 1. Change from baseline in body weight by week.

Data are observed mean changes from baseline (± standard error) for the extension analysis set from the in-trial period. The dashed vertical line at week 68 indicates the end of the main phase and start of the off-treatment extension phase. Numbers shown in the lower panels are participants contributing to the mean. Extension analysis set (ExAS), included all participants eligible for the extension who attended ≥1 visit on week 75, 80, 104 or 120.

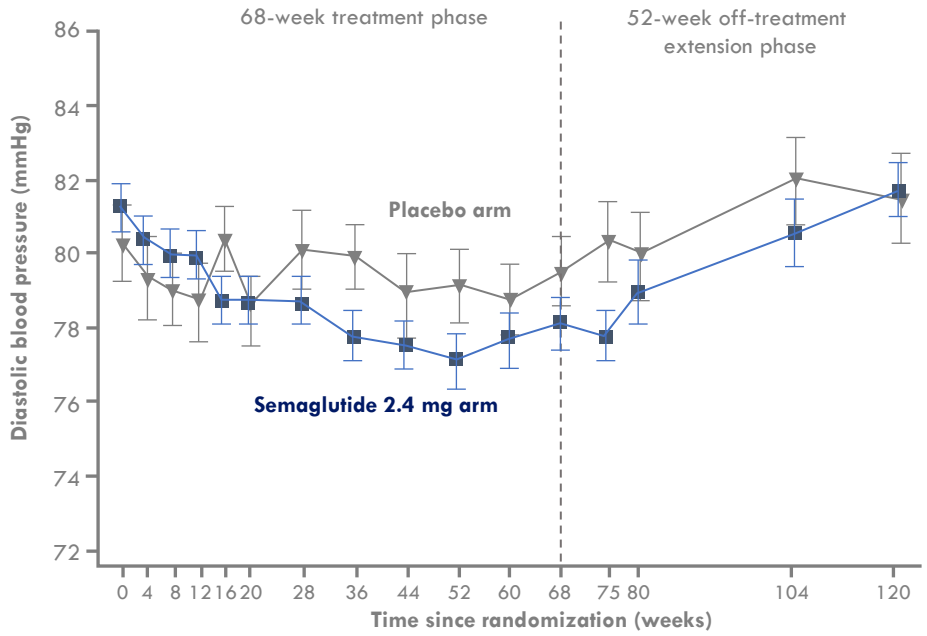
Change in blood pressure from baseline by week

Systolic blood pressure



Semaglutide 2.4 mg arm	228	227	228	227	225	228	228	228	228	228	226	228	209	173	171	197
Placebo arm	99	99	99	98	97	98	99	99	99	99	98	99	93	79	80	93

Diastolic blood pressure



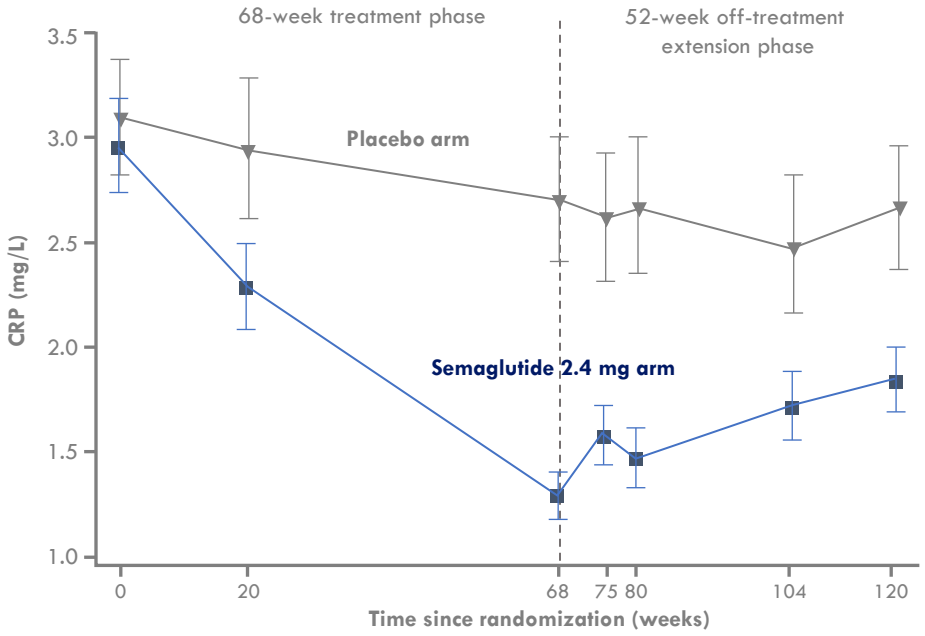
Semaglutide 2.4 mg arm	228	227	228	227	225	228	228	228	228	228	226	228	209	173	171	197
Placebo arm	99	99	99	98	97	98	99	99	99	99	98	99	93	79	80	93

Adapted from Figure 2. Systolic blood pressure, diastolic blood pressure, C-reactive protein and HbA_{1c} by week.

Data are observed mean changes from baseline (± standard error) for the extension analysis set from the in-trial period. The dashed vertical line at week 68 indicates the end of the main phase and start of the off-treatment extension phase. Numbers shown in the lower panels are participants contributing to the mean. Extension analysis set (ExAS), included all participants eligible for the extension who attended ≥1 visit on week 75, 80, 104 or 120. HbA_{1c}, glycated haemoglobin.

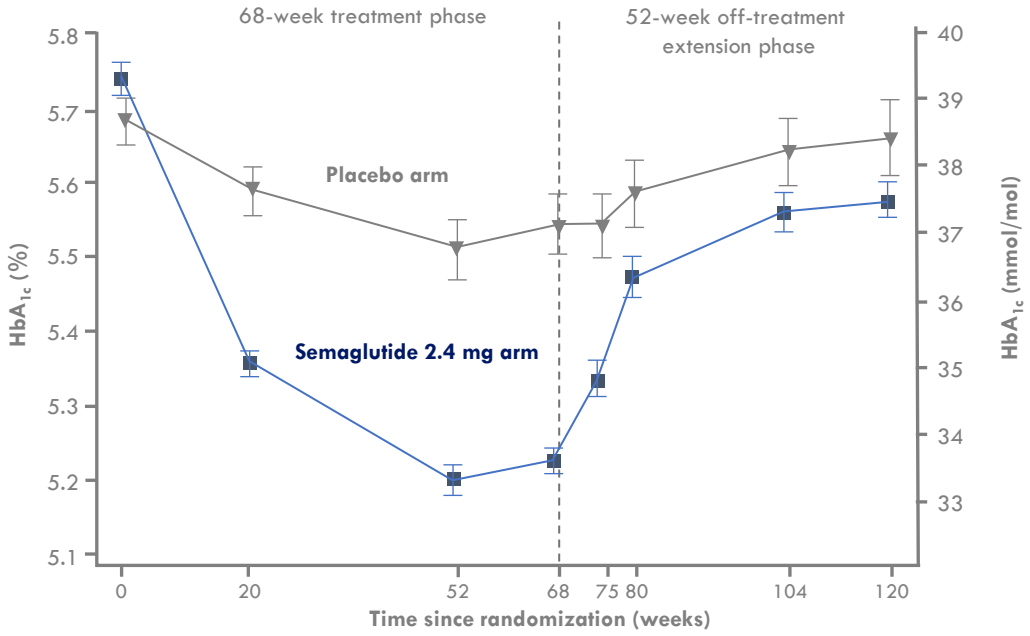
Change in C-reactive protein and HbA_{1c} from baseline by week

C-reactive protein



Semaglutide 2.4 mg arm	228	228	228	185	173	170	195
Placebo arm	98	97	99	84	77	79	93

HbA_{1c}



Semaglutide 2.4 mg arm	228	228	227	227	184	173	169	196
Placebo arm	99	98	98	95	84	77	78	81

Adapted from Figure 2. Systolic blood pressure, diastolic blood pressure, C-reactive protein and HbA_{1c} by week.

Data are observed mean changes from baseline (± standard error) for the extension analysis set from the in-trial period; for C-reactive protein, standard error was calculated on the logarithmic scale and back-transformed to the linear scale. The dashed vertical line at week 68 indicates the end of the main phase and start of the off-treatment extension phase. Numbers shown in the lower panels are participants contributing to the mean. Extension analysis set (EAS), included all participants eligible for the extension who attended a 1-visit on-week 75, 80, 104 or 120.
HbA_{1c}, glycated haemoglobin; CRP, C-reactive protein.

Cardiometabolic Benefits of Blocking Myostatin

Taldefgrobep Pre-clinical and Early Clinical Data

- Currently approved anti-obesity medications achieve total body weight loss off a composite reduction of fat and lean muscle mass
- Blocking myostatin can produce metabolic and body composition changes highly relevant to individuals living with obesity (Figure 1)
- In the clinic, anti-myostatin therapies have demonstrated the ability to reduce fat mass, increase lean mass, and improve metabolic parameters
  - Clinically, taldefgrobep has been generally safe and well-tolerated with low rates of GI and musculoskeletal complaints
  - In healthy adults, taldefgrobep generated significant improvements in body composition relative to placebo (Figure 3)

Figure 1: Cardiometabolic Benefits of Blocking MSTN

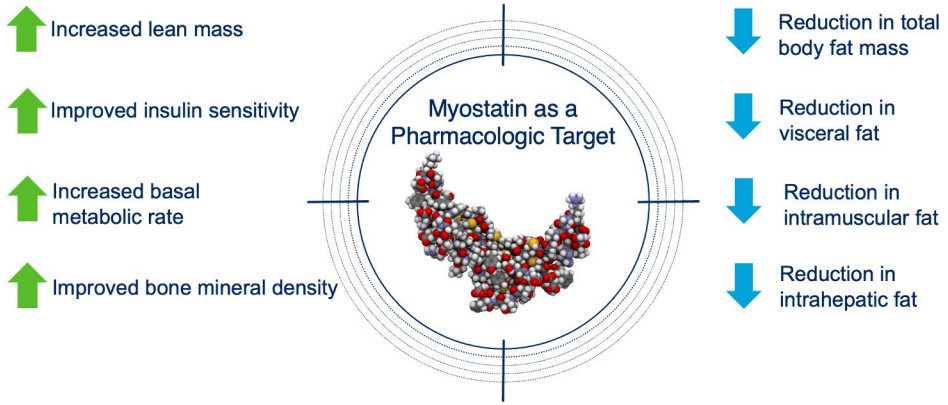
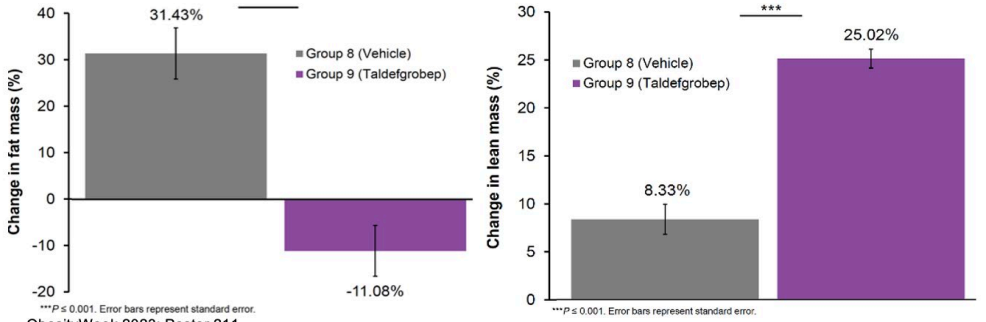
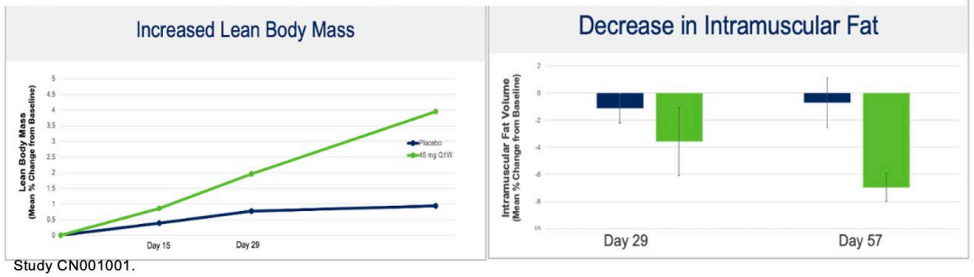


Figure 2. Taldefgrobep Body Composition Changes in DIO Mice



ObesityWeek 2023; Poster 211.

Figure 3. Taldefgrobep Body Composition Changes in Healthy Adults



Study CN001001.

Pipeline for future obesity medications – Phase 1

Name	Dose	Administration	Mechanism of action	Company	Expected completion date	Clinical Trials gov	Other indication(s)
CT-996	NA	PO, OD	GLP-1 RA	Carmot Therapeutics	November-2024	NCT05814107	NA
Long-acting amylin agonist	NA	NA	Amylin RA	Eli Lilly	NA	NA	NA
AZD6234	NA	SC, OW	Amylin RA	AstraZeneca	December 2023	NCT05511025	NA
ZP8396	NA	SC, OW	Amylin RA	Zealand Pharma	May-2024	NCT05613387	NA
HM15136	NA	SC, frequency not stated	Glucagon RA	Hanmi Pharmaceutical	Completed	NCT04032782	NA
NNC0165-1562	NA	SC, OW	PYY RA	Novo Nordisk	Completed	NCT02568306	NA
Y-14	9-36mg	SC, OW/every 2 weeks	PYY RA	Zihipp	Completed	NCT0367311	NA
VK2735	NA	PO, frequency not stated	GLP-1 RA + GIP RA	Viking Therapeutics	NA	NA	Phase 1 – MASH
VK2735	NA	SC, OW	GLP-1 RA + GIP RA	Viking Therapeutics	December-2023	NCT05203237	Phase 1 MASH
SCO-094	NA	PO, frequency not stated	GLP-1 RA + GIP RA	Scohia Pharma	NA	NA	Phase 1 - T2D, MASH
CT-388	5–12 mg	SC, OW	GLP-1 RA + GIP RA	Carmot Therapeutics	Completed	NCT04838405	Phase 1 - T2D
Amycretin (NNC0487-0111)	1 100 mg	PO, OD	GLP-1 RA + Amylin RA	Novo Nordisk	November-2024	NCT05369390	NA
Dacra QW II	NA	NA	Amylin RA + calcitonin RA	Eli Lilly	NA	NA	NA
NNC0165-1562 and	NA	SC, OW	PYY RA + GLP-1RA	Novo Nordisk	Completed	NCT03574584	NA
HM15211	NA	SC, OW	GLP-1 RA + GIP RA + GCG RA	Hanmi Pharmaceutical	Completed	NCT03374241	Phase 2 – MASH
NNC0247-0829	NA	SC, OW	GDF15 analogue	Novo Nordisk	Completed	NCT04010786	NA
JNJ-9090/CIN-109	NA	SC, OW/Twice weekly	GDF15 analogue	CinRx Pharma	NA	NA	NA
SCO-267	NA	PO, OD	G-protein-coupled receptor 40	Scohia Pharma	Completed	JapicCTI-195057	Phase 1 - MASH

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Pipeline for future obesity medications – Phase 2

Name	Dose	Administration	Mechanism of action	Company	Expected completion	Clinical Trials gov	Other indication(s)
Danuglipron	40–200 mg	PO, BD	GLP-1 RA	P fizer	Completed	NCT04707313	NA
Cagrilintide	0.3–4.5 mg	SC, OW	Amylin RA	Novo Nordisk	Completed	NCT03856047	Phase 1 - MASH
PYY 1875	0.03–2.4 mg	SC, NA	PYY RA	Novo Nordisk	Completed	NCT03707990	NA
Efinopegdutide	5–10 mg	SC, OW	GLP-1 RA + GCG RA	Hanmi Pharmaceutical	Completed	NCT03486392	Phase 2 - T2D, MASH, MASLD
Pemvidutide	1.2–2.4 mg	SC, OW	GLP-1 RA + GCG RA	Altimmune	Completed	NCT05295875	Phase 2 - MASH, MASLD Phase 1 – T2D
AMG 133	NA	SC, once monthly	GLP-1 RA + GIP receptor antagonist	Amgen	January-2025	NCT05669599	NA
NNC0165-1875 + Semaglutide	1–2 mg + 2.4 mg	SC, every 2 to 4 weeks	GLP-1 RA + PYY RA	Novo Nordisk	Completed	NCT04969939	NA
Dapiglutide	4–6 mg	SC, OW	GLP-1 RA + GLP2 RA	Zealand Pharma	August-2024	NCT05788601	NA
Bimagrumab + Semaglutide	30 mg/kg + 1–2.4 mg	IV, every 4 weeks (Bimagrumab) + SC, OW	Activin receptor II inhibition + GLP-1 RA	Versanis Bio	September-2025	NCT05616013	NA
S-309309	NA	PO, OD	MGAT2	Shionogi	May-2024	NCT05925114	NA

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Pipeline for future obesity medications – Phase 3

Name	Dose	Administration	Mechanism of action	Company	Expected completion date	Clinical Trials gov	Other indication(s)
Semaglutide*	50 mg	PO, OD	GLP-1 RA	Novo Nordisk	Completed	NCT05035095	Phase 3 - T2D
Orforglipron	NA	PO, OD	GLP-1 RA	Eli Lilly	September-2027	NCT05869903	Phase 3 - T2D, CV outcomes in T2D
Semaglutide	7.2 mg	SC, OW	GLP-1 RA	Novo Nordisk	NA	NA	NA
Tirzepatide*	5–15 mg	SC, OW	GLP-1 RA + GIP RA	Eli Lilly	Completed	NCT04184622	Phase 3 - T2D, HFpEF, OSA, CV outcomes in T2D, morbidity and mortality in obesity Phase 2 - MASH, CKD
CagriSema	2.4 mg/2.4 mg	SC, OW	GLP-1 RA + Amylin RA	Novo Nordisk	October-2026	NCT05567796	Phase 3 - T2D, CV outcomes
Survodutide	3.6 –6 mg	SC, OW	GLP-1 RA + GCG RA	Boehringer Ingelheim	Completed	NCT04667377	Phase 2 - T2D, MASH
Mazdutide	4–6 mg	SC, OW	GLP-1 RA + GCG RA	Innovent Biologics	April-2024	NCT05607680	Phase 3 - T2D Phase 1 CKD
Mazdutide	9 mg	SC, OW	GLP-1 RA + GCG RA	Innovent Biologics	September 2025	NCT06164873	NA
Retatrutide	4–12 mg	SC, OW	GLP-1 RA + GIP RA + GCG RA	Eli Lilly	May-2026	NCT05929066	Phase 3 - T2D, OA Phase 2 - CKD

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Role of Cardiologist

- Hypertension
- Lipids

- DM

- CKD
- Obesity

Role of Team

- Heart failure
- Valvular disease
- SGLT2i - CKM
- Etc.

- Systems of care