News 3. Semaglutide 2.4: novità nel diabete e nell’obesità

Mikiko Watanabe M.D. Ph.D.

Disclosure

Funding from the following companies:

For providing educational sessions

-Novo Nordisk, Eli Lilly, Theras Lifetech

Institutional research grant support or funding for clinical trials

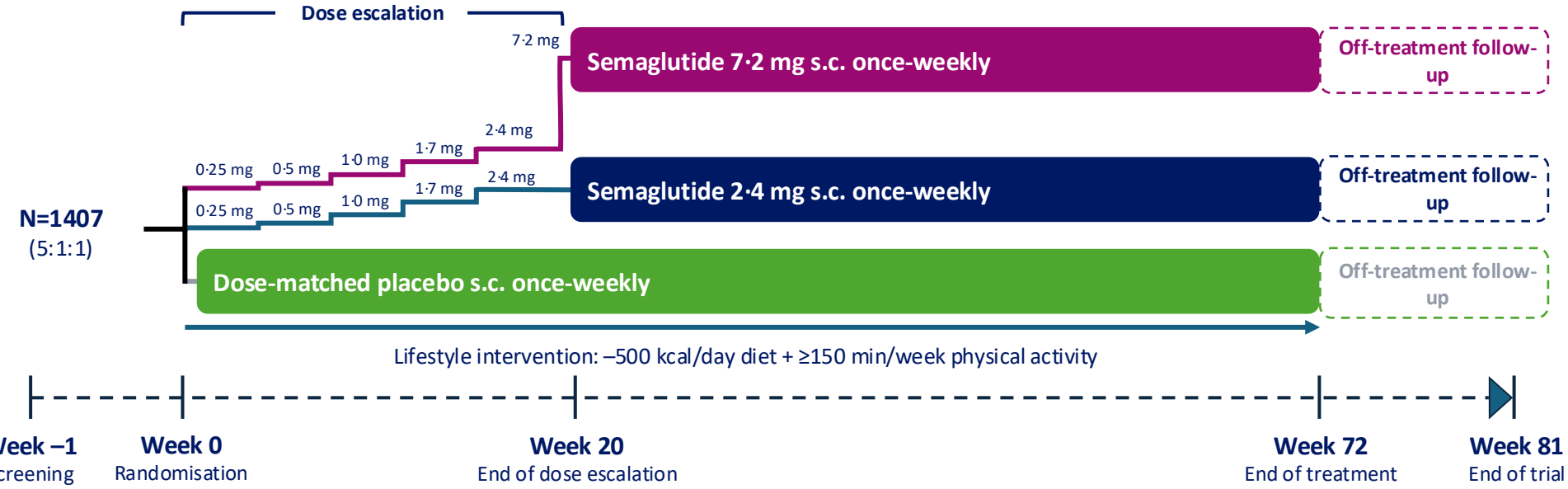
-Novo Nordisk and Boehringer Ingelheim

Institutional Scientific Board and/or consulting

- Novo Nordisk, Eli Lilly

STEP UP trial design

Randomised, double-blind, placebo- and active-controlled, multinational trial



Population

- Adults (≥18 years)
- BMI ≥30 kg/m^2
- ≥1 self-reported unsuccessful dietary effort to lose weight
- Without T2D (HbA_{1c} <6·5%)

Coprimary endpoints*

- Change in bodyweight (%)
- Achieving ≥5% WL

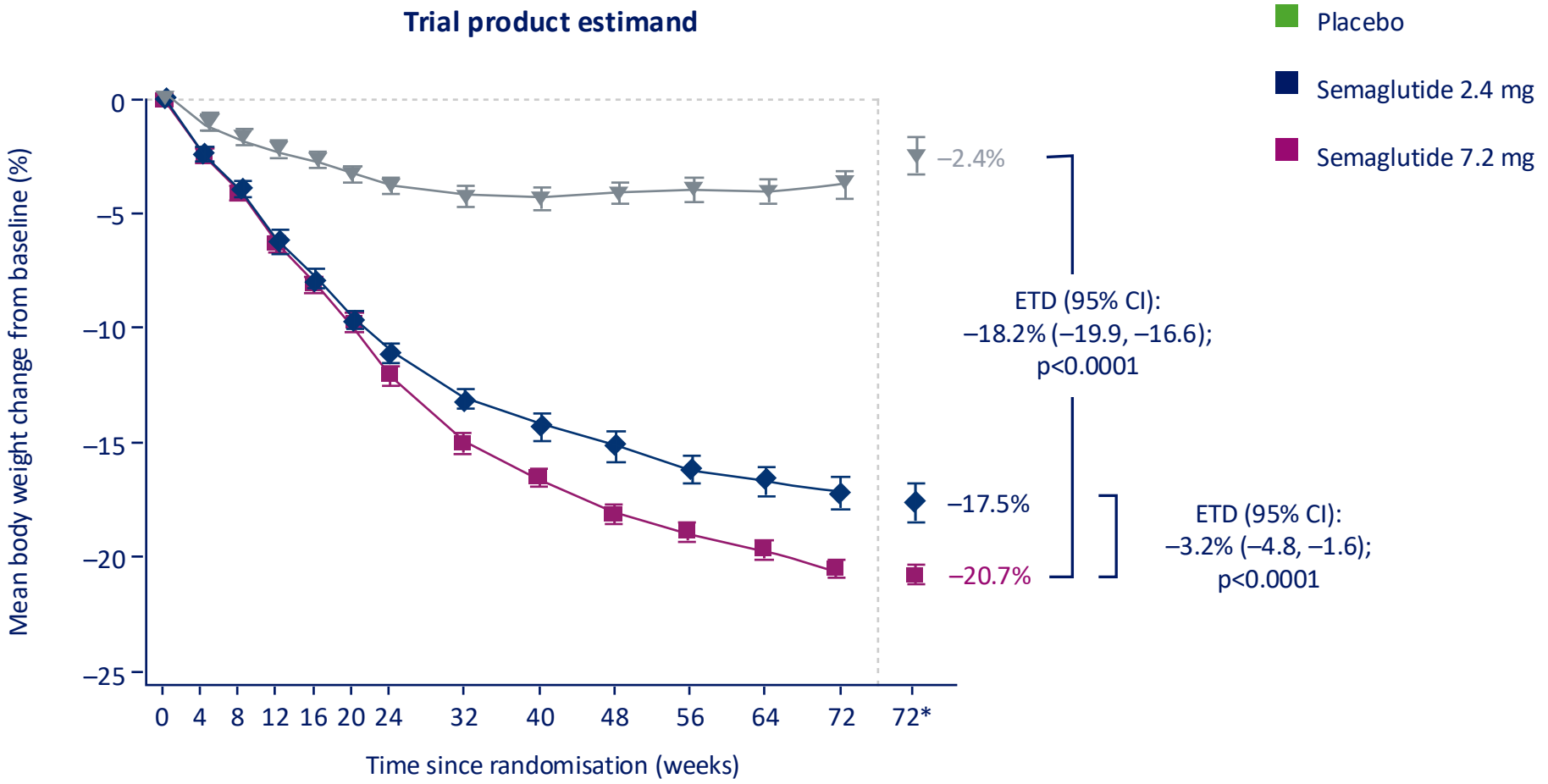
Confirmatory secondary endpoints

- Achieving ≥10%, ≥15%, ≥20%, and ≥25% WL*
- Change in waist circumference (cm)*
- Change in bodyweight (%)†
- Achieving ≥20% and ≥25% WL†

**Semaglutide s.c. 7·2 mg versus placebo. †Semaglutide s.c. 7·2 mg versus 2·4 mg.*
BMI=body mass index. HbA_{1c}=glycated haemoglobin. s.c.=subcutaneous. T2D=type 2 diabetes. WL=weight loss. Additional details included in the speaker notes.
Adapted from Supplementary Figure 1: Trial design.

Change in body weight (%)

STEP UP

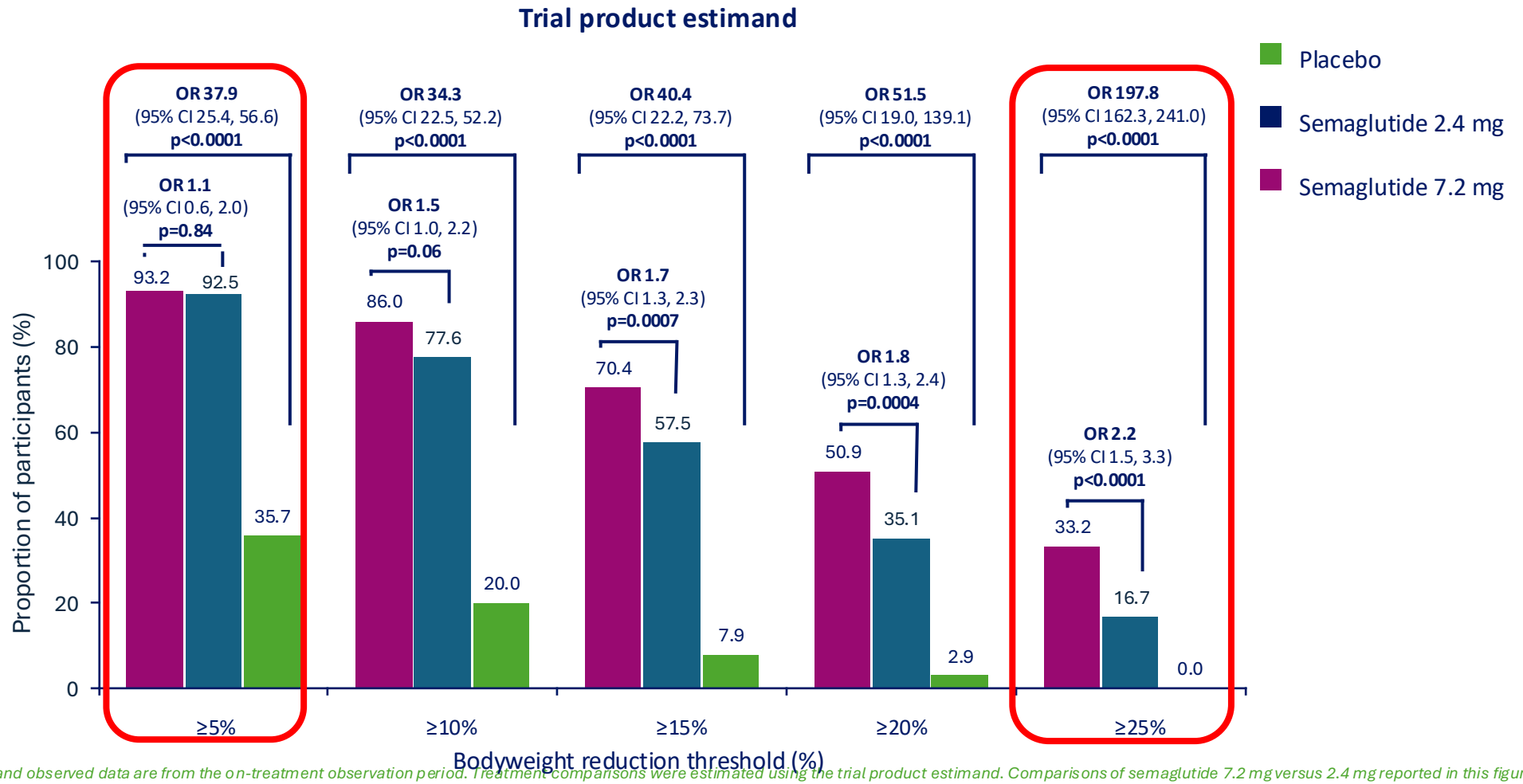


*Data are for the full analysis set, and observed data are from the on-treatment observation period. Treatment comparisons were estimated using the trial product estimand. Error bars are 95% CIs. *Estimated mean change at week 72. CI, confidence interval; ETD, estimated treatment difference.*

Wharton S et al. Lancet Diabetes Endocrinol 2025; DOI: 10.1016/S2213-8587(25)00226-8.

Categorical body weight loss

STEP UP

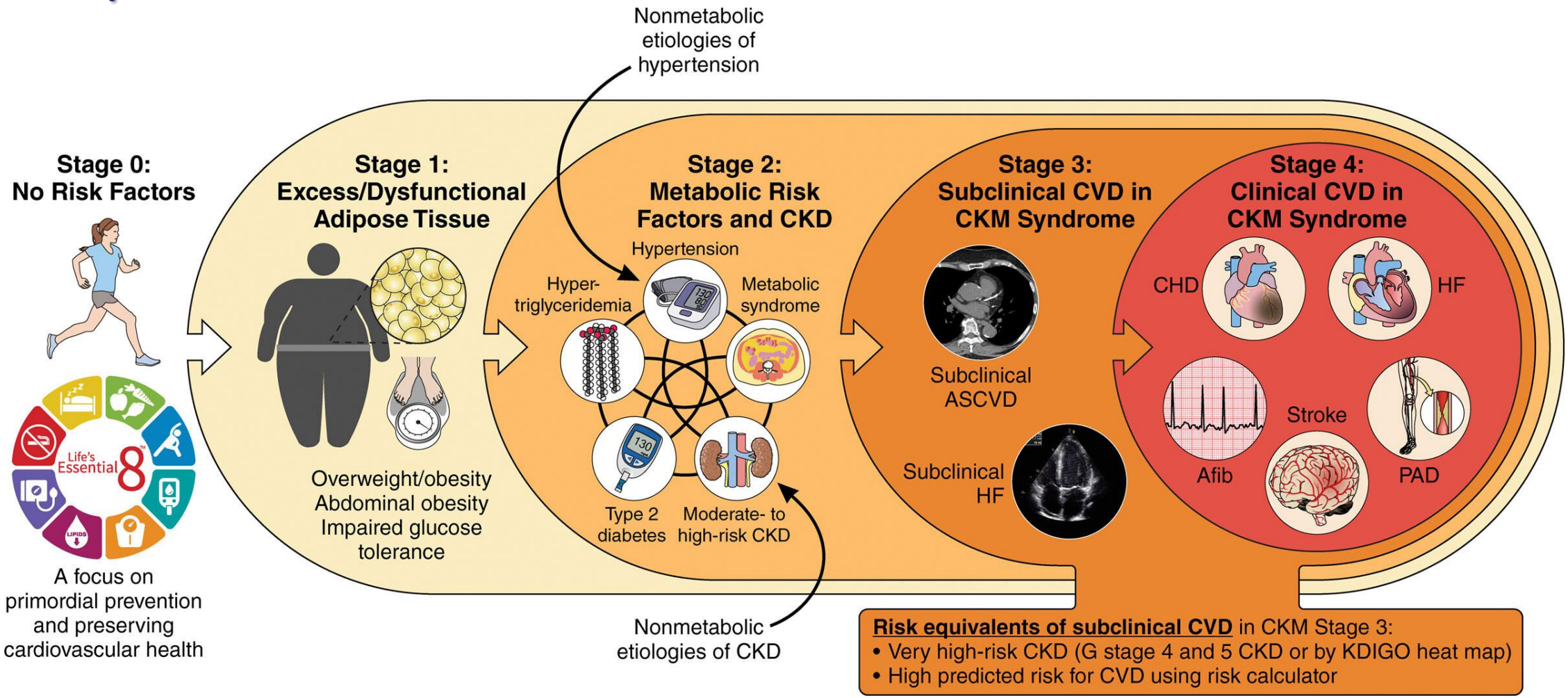


Data are for the full analysis set, and observed data are from the on-treatment observation period. Treatment comparisons were estimated using the trial product estimand. Comparisons of semaglutide 7.2 mg versus 2.4 mg reported in this figure for the proportion of participants with body weight reductions of 5% or greater, 10% or greater, and 15% or greater were conducted in a post-hoc manner. Post hoc analyses were not controlled for multiplicity, and findings for these endpoints should not be used to infer definitive treatment effects.

CI, confidence interval; OR, odds ratio.

Wharton S et al. Lancet Diabetes Endocrinol 2025; DOI: 10.1016/S2213-8587(25)00226-8.

Obesity is a disease that leads to cardio-renal-metabolic complications



Ndumele CE et al. Circulation 2023

OBESITY TREATMENT BASED ON PATIENT PHENOTYPING

FIRST-LINE THERAPY IS LIFESTYLE MODIFICATION (MEDICAL NUTRITIONAL APPROACH AND IMPLEMENTATION OF PHYSICAL ACTIVITY and BEHAVIOUR AL THERAPY)*

EXCLUDE ENDOCRINE FORMS OF OBESITY, if suspected, investigate MONOGENIC FORMS

ASSESSMENT OF THE PRESENCE OF COMPLICATIONS AND PATIENT PHENOTYPING

OBESITY TREATMENT BASED ON PATIENT COMPLICATIONS AND PHENOTYPING

METABOLIC CARDIO RENAL COMPLICATIONS

+ASCVD

Cardiovascular disease was defined as a previous myocardial infarction, previous stroke, or symptomatic peripheral arterial disease in people who are≥ 45 years of age, with a BMI ≥ 27 kg/m².

→ Semaglutide 2.4 mg

Naltrexone/ Bupropion (not recommended)[15]

Indicators of High CV Risk:

Definitions vary; most comprise ≥ 40 years of age, BMI ≥ 27 kg/m², male gender, high blood pressure, atherogenic dyslipidemia, smoking, prediabetes, ASCVD risks (ACC/AHA).

→ Tirzepatide 15 mg [2,10]
Semaglutide 2.4 mg [3,4]
Liraglutide 3 mg [12]

Naltrexone/ Bupropion (not recommended)[15]

HF

Clinical heart failure (NYHA II–IV) with LVEF ≥50% (**tirzepatide**) or ≥45% (**semaglutide**), BMI ≥30 kg/m²), reduced functional capacity (KCCQ-CSS <80 or <90), 6-minute walk ≥100 m, and elevated filling pressures (NT-proBNP, echocardiographic criteria, or recent HF hospitalization). T2D was allied in the tirzepatide trial.

→ Tirzepatide 15 mg [11]
Semaglutide 2.4 mg [5]

Naltrexone/ Bupropion (not recommended) [15]

CKD

eGFR < 60 ml/ min per 1.73 m² OR albuminuria (ACR ≥ 3.0 mg/mmol (30mg/g)

→ Semaglutide 2.4 mg[5]
[11,19]

(use if eGFR>30 ml/min;
If eGFR <30 use with caution due to limited data)

Orlistat (caution in obesity due to risks of nephrolithiasis or AKI)[18]

Naltrexone/ Bupropion (not recommended) [15]

GLYCEMIC CONTROL

PREDIABETES

(**HbA1c** ≥ 5.7% and < 6.5%, FPG > 100 ng/dl < 126 mg/dl, OGTT 120 min glucose ≥ 140 mg/dl < 200 mg/dl)

Semaglutide 2.4 mg [22]
Orlistat 120 mg [14]

Metformin: off-label; may reduce diabetes incidence [24].

TYPE 2 DIABETES

(**HbA1c** ≥ 6.5% and < 6.5, FPG > 100 ng/dl < 126 mg/dl, OGTT 120 min glucose ≥ 140 mg/dl < 200 mg/dl)

Semaglutide 2.4 m[29]
Liraglutide 3 mg

SGLT2is support weight loss [37,38,39,40,41], If glycemic control allows, insulin[44,45], thiazolidinediones, and sulfonylureas should be avoided [203]

TYPE 1 DIABETES

(OFF-LABEL only for weight loss purposes)

Semaglutide 2.4 m[51]

MASH/MASLD

Adults with biopsy-confirmed MASH, fibrosis stage (F2–F3) for **semaglutide** 2.4 and **tirzepatide** 15 mg, F0-F3 for **liraglutide** 3 mg , BMI ≥25 kg/m² for **semaglutide** 2.4 mg and **liraglutide** 3 mg . BMI ≥27 kg/m² for **tirzepatide** 15 mg; with or without type 2 diabetes but not for semaglutide 2.4.

→ Semaglutide 2.4 mg
Tirzepatide 15 mg [56]
Liraglutide 3 mg OD[57]

MECHANICAL COMPLICATIONS

OSTEOARTRITIS

Adults ≥18 years with BMI ≥30 kg/m², clinically and radiographically confirmed knee osteoarthritis (ACR criteria; Kellgren–Lawrence grade 2–3), and baseline knee pain ≥40/100 on the WOMAC pain scale.

→ Semaglutide 2.4
Tirzepatide 15 mg (NCT01985165)
Orlistat 120 mg [14]
Naltrexone/bupr opione[64]
Phentiramine/To piramate[26]

OSAS

Adults ≥18 years, BMI ≥30 kg/m², with moderate-to-severe obstructive sleep apnea (AHI ≥15 events/hour); CPAP use allowed (tirzepatide) or excluded (liraglutide); no diagnosis of T2D.

→ Tirzepatide 15 mg [68]
Liraglutide 3 mg [69]
Phentiramine/ Topiramate[70]

WEIGHT LOSS TARGETS /OWCMC**

Set individualized weight management goals

5-10% WL

Orlistat[14]
Liraglutide 3 mg[74]
Naltrexone/ Bupropion[27]
Phentermine/Topira mate (low-mid doses)[60]

10-20% WL

Tirzepatide 5 mg[2]
Semaglutide 2.4mg[3]
Phentermine/Topiramat

>20% WL

Tirzepatide 15mg[2]
Semaglutide 7.2 mg[77]
(not available yet)
Cagrisema[78]
(not available yet)

AGE

≥ 2 y.o. [104]
Setmelanotide (rare genetic obesity)
Metreleptin (rare genetic obesity)

6-12 y.o.
Liraglutide 3mg [109]
(EMA only)

12-18 y.o.
Semaglutide 2.4mg[113]
[115] only)
Orlistat 120 mg[114] (FDA only)

18-65 y.o.
Ph ecision :
Tirzepatide 15 mg
Semaglutide 2.4 m
Naltrexone/Bupropion[27,28]
Phentermine/Topiramate[26]
Orlistat[14]

>65 y.o
Semaglutide 2.4 mg[3] (Us e; no dose adjustment nee d)
Tirzepatide 15 mg (Usable; monitor sensitivity in elderly)
Liraglutide 3 mg[12,74] (Usable; limited data >75 yrs)
Naltrexone/Bupropion[27] (Caution; limited data ≥65 yrs)
Phentermine/Topiramate[26] (Caution; monitor CNS/renal)
Orlistat[14] (Usable; limited efficacy data)

Sarcopenic obesity
Supervised Resistance Training + Protein Intake ≥1.2–1.5 g/kg/day [118]
Liraglutide 3 mg is preferred for gradual weight loss with lean mass preservation and proven cardiovascular safety[33]

EATING BEHAVIOUR

EMOTIONAL EATING

Bupropion / Naltrexon[28]
Tirzepatide 15
Semaglutide 2.4 mg[125]

BINGE EATING

Not AOMs approved explicitly for binge eating disorder.

Liraglutide 3.0 mg[123]
Phentermine/ Topiramate[128]
Naltrexone/B upropion[28]
Orlistat 120 mg[129]
Semaglutide 2.4 mg[125]
Tirzepatide 15 mg[128,134]

SPECIAL POPULATIONS

CANCER safety

No risk from obesity related RCT
Semaglutide 2.4 mg
Tirzepatide 15 mg[145]
Evidence from meta-analysis suggests long-term GLP-1 RA use may increase thyroid cancer risk in mixed T2D populations.[145]
No evidence of increased cancer risk (for other AOMs: **Orlistat, Phentermine/Topiramate, Bupropion/Naltrexone**

Familial Partial Lipodystrophy 1-3 (FPLD1-3)
Acquired Partial Lipodystrophy (Barraquer-Simons)
HIV-Associated Lipodystrophy

Semaglutide 2.4 mg[152]

MONOGENIC OR SYNDROMIC OBESITY

Congenital leptin deficiency
Metreleptin[153]

(biallelic POMC, PCSK1, or LEPR deficiency and for BBS)
Setmelanotide 3 mg[154]

ACQUIRED HYPOTALAMIC

Setmelanotide 3 mg
Semaglutide 2.4 mg

PREGNANCY/WILLINGNESS TO CONCEIVE

AOMs are either contraindicated or advised against during pregnancy due to insufficient safety data and potential risks to the fetus

Stop **Liraglutide 3 mg/Semaglutide 2.4 mg** at least 2 months before

Stop **Tirzepatide 15 mg** at least 1 month before

COSTS /QALY

BS
176, 177

If additional weight loss and reduction of weight-related complications are needed

Bariatric Surgery[177]

If insufficient weight loss or weight regain after BS consider: Tirzepatide[197], **Semaglutide**[194], **Liraglutide**[195,196]

*This framework promotes a phenotype-based, individualized approach to obesity care, prioritizing complications and patient preferences over rigid treatment hierarchies, with patient-HCP shared decision-making considering goals, tolerability, contraindications, and cost. **OWCMC, obesity without clinically manifest complications

Tuccinardi D, et al. *J Endocrinol Invest* **48**, 2761–2798 (2025)

OBESITY TREATMENT BASED ON PATIENT PHENOTYPING

FIRST-LINE THERAPY IS LIFESTYLE MODIFICATION (MEDICAL NUTRITIONAL APPROACH AND IMPLEMENTATION OF PHYSICAL ACTIVITY and BEHAVIOURAL THERAPY)*

EXCLUDE ENDOCRINE FORMS OF OBESITY AND, WHEN CLINICALLY SUSPECTED, INVESTIGATE POTENTIAL MONOGENIC ETIOLOGIES

ASSESSMENT OF COMPLICATIONS AND CLINICAL PHENOTYPE CLASSIFICATION

OBESITY TREATMENT BASED ON PATIENT COMPLICATIONS AND PHENOTYPING

METABOLIC CARDIO RENAL COMPLICATIONS

+ASCVD

Cardiovascular disease was defined as prior myocardial infarction, prior stroke, or clinically symptomatic peripheral arterial disease in individuals aged ≥45 years and with a BMI ≥27 kg/m²

- **Semaglutide 2.4 mg** [4]

Naltrexone/ Buproprion (not recommended)[15]

Indicators of High CV Risk:

Definitions vary; however, most include age ≥40 years, BMI ≥27 kg/m², male sex, hypertension, atherogenic dyslipidemia, smoking, prediabetes, and elevated ASCVD risk (per ACC/AHA criteria)

- **Tirzepatide 15 mg** [2,10]
- **Semaglutide 2.4 mg** [3,4]
- **Liraglutide 3 mg** [12]

Naltrexone/ Buproprion (not recommended)[15]

HF

Clinical heart failure (NYHA II–IV) with preserved or mildly reduced ejection fraction (LVEF ≥50% for **tirzepatide**, ≥45% for **semaglutide**), BMI ≥30 kg/m², impaired functional capacity (KCCQ-CSS <80–90), 6MWT distance ≥100 m, and elevated filling pressures (e.g., NT-proBNP, echocardiographic abnormalities, or recent HF hospitalization). Type 2 diabetes was an inclusion criterion in the tirzepatide trial.

- **Tirzepatide 15 mg** [11]
- **Semaglutide 2.4 mg** [5]

Naltrexone/ Buproprion (not recommended) [15]

CKD

eGFR <60 mL/min/1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [≥30 mg/g])

- **Semaglutide 2.4 mg**[5]
- **Tirzepatide 15 mg** [11,19]

Use if eGFR >30 mL/min/1.73 m²; exercise caution when eGFR <30 mL/min/1.73 m² due to limited data.

Orlistat (caution in obesity due to risks of nephrolithiasis or AKI)[18]

Naltrexone/ Buproprion (not recommended) [15]

GLYCEMIC CONTROL

PREDIABETES

HbA1c 5.7–6.4%, fasting plasma glucose 100–125 mg/dL, or 2-hours OGTT glucose 140–199 mg/dL

- **Tirzepatide 15 mg** [2]
- **Semaglutide 2.4 mg** [22]
- **Liraglutide 3 mg** [12,74]
- **Orlistat 120 mg** [14]

Metformin: off-label use; may reduce the incidence of type 2 diabetes[24].

TYPE 2 DIABETES

HbA1c ≥ 6.5%, fasting plasma glucose ≥ 126 mg/dL, or 2-hours OGTT plasma glucose ≥ 200 mg/dL

- **Tirzepatide 15 mg** [31]
- **Semaglutide 2.4 mg** [29]
- **Liraglutide 3 mg** [33]

SGLT2 inhibitors support weight loss [37,38,39,40,41], If glycemic control allows, insulin[44,45], thiazolidinediones, and sulfonylureas should be avoided due to their propensity to induce weight gain.[203]

TYPE 1 DIABETES

(OFF-LABEL only for weight loss purposes)

- **Tirzepatide 15 mg** [52]
- **Semaglutide 2.4 mg** [51]

MASLD/ MASH

Adults with biopsy-confirmed MASH, fibrosis stage F2–F3 for **semaglutide** 2.4 mg and **tirzepatide** 15 mg; F0–F3 for **liraglutide 3 mg**. BMI ≥25 kg/m² for **semaglutide** 2.4 mg and **liraglutide** 3 mg; BMI ≥27 kg/m² for **tirzepatide** 15 mg, with or without type 2 diabetes; BMI not restricted, and ,with or without type 2 diabetes, for **semaglutide** 2.4.

- **Semaglutide 2.4 mg** [54]
- **Tirzepatide 15 mg** [56]
- **Liraglutide 3 mg OD**[57]

MECHANICAL COMPLICATIONS

OSTEOARTRITIS

Adults ≥18 years with BMI ≥30 kg/m², clinically and radiographically confirmed knee osteoarthritis (ACR criteria; Kellgren–Lawrence grade 2–3), and baseline knee pain ≥40/100 on the WOMAC pain scale

- **Semaglutide 2.4 mg**[63]
- **Tirzepatide 15 mg** (NCT01985165)
- **Orlistat 120 mg** [14]
- **Naltrexone/ bupropione**[64]
- **Phentiramine/ Topiramate**[26]

OSA

Adults ≥18 years, BMI ≥30 kg/m², with moderate-to-severe obstructive sleep apnea (AHI ≥15 events/h); CPAP use allowed (tirzepatide) or excluded (liraglutide); no diagnosis of T2D.

- **Tirzepatide 15 mg** [68]
- **Liraglutide 3 mg** [69]
- **Phentiramine/ Topiramate**[70]

WEIGHT LOSS TARGETS /OWCMC**

Set individualized weight management goals

5-10% WL

- **Orlistat**[14]
- **Liraglutide 3 mg**[74]
- **Naltrexone/ Bupropion**[27]
- **Phentermine/Topiramate (low-mid doses)**[60]

10-20% WL

- **Tirzepatide 5 mg**[2]
- **Semaglutide 2.4mg**[3]
- **Phentermine/ Topiramate (low-mid doses)**[16]

>20% WL

- **Tirzepatide 15mg**[2]
- **Semaglutide 7.2 mg**[77] (not available yet)
- **Cagrisema**[78] (not available yet)

AGE

≥ 2 y.o. [104]
Setmelanotide (rare genetic obesity)
Metreleptin (rare genetic obesity)

6-12 y.o.
Liraglutide 3 mg [109] (EMA only)

12-18 y.o.
Liraglutide 3 mg[112]
Semaglutide 2.4 mg[113]
Phentermine/Topiramate[115] (FDA only)
Orlistat 120 mg[114] (FDA only)

18-65 y.o.
Phenotype-driven tailored decision:
Tirzepatide 15 mg[2]
Semaglutide 2.4 mg[3]
Liraglutide 3 mg[12]
Naltrexone/Bupropion[27,28]
Phentermine/Topiramate[26]
Orlistat[14]

>65 y.o.
Semaglutide 2.4 mg[3] (Usable; no dose adjustment needed)
Tirzepatide 15 mg[2] (Usable; monitor sensitivity in elderly)
Liraglutide 3 mg[12,74] (Usable; limited data >75 yrs)
Naltrexone/Bupropion[27] (Caution; limited data ≥65 yrs)
Phentermine/Topiramate[26] (Caution; monitor CNS/renal)
Orlistat[14] (Usable; limited efficacy data)

Sarcopenic obesity
Supervised Resistance Training + Protein Intake ≥1.2–1.5 g/kg/day [118]
Liraglutide 3 mg is preferred for gradual weight loss with lean mass preservation and proven cardiovascular safety[33]

EATING BEHAVIOUR

EMOTIONAL EATING

- **Bupropion / Naltrexon**[28]
- **Tirzepatide 15 mg**[136]
- **Semaglutide 2.4 mg**[125]

BINGE EATING

Not AOMs approved explicitly for binge eating disorder.

- **Liraglutide 3 mg**[123]
- **Phentermine/ Topiramate**[128]
- **Naltrexone/ Bupropion**[28]
- **Orlistat 120 mg**[129]
- **Semaglutide 2.4 mg**[125]
- **Tirzepatide 15 mg**[128,134]

SPECIAL POPULATIONS

CANCER safety

No significant increase in thyroid cancer risk from obesity related RCT
Semaglutide 2.4 mg[146]
Tirzepatide 15 mg[147]

Evidence from meta-analysis suggests long-term GLP-1 RA use may increase thyroid cancer risk in mixed T2D populations[145].

No evidence of increased cancer risk (for other AOMs: **Orlistat, Phentermine/Topiramate, Bupropion/Naltrexone**

Familial Partial Lipodystrophy 1 -3 (FPLD1-3)
Acquired Partial Lipodystrophy (Barraquer-Simons)
HIV-Associated Lipodystrophy
- **Semaglutide 2.4 mg**[152]

MONOGENIC OR SYNDROMIC OBESITY
Congenital leptin deficiency
- **Metreleptin**[153]

(biallelic POMC, PCSK1, or LEPR deficiency and for BBS)
- **Setmelanotide 3 mg**[154]

ACQUIRED HYPOTALAMIC OBESITY
- **Setmelanotide 3 mg**[154]
- **Semaglutide 2.4 mg**[155]

PREGNANCY/WILLINGNESS TO CONCEIVE

AOMs are either contraindicated or advised against during pregnancy due to insufficient safety data and potential risks to the fetus

Stop **Liraglutide 3 mg/Semaglutide 2.4 mg** at least 2 months before

Stop **Tirzepatide 15 mg** at least 1 month before

COSTS /QALY

BS
176,177

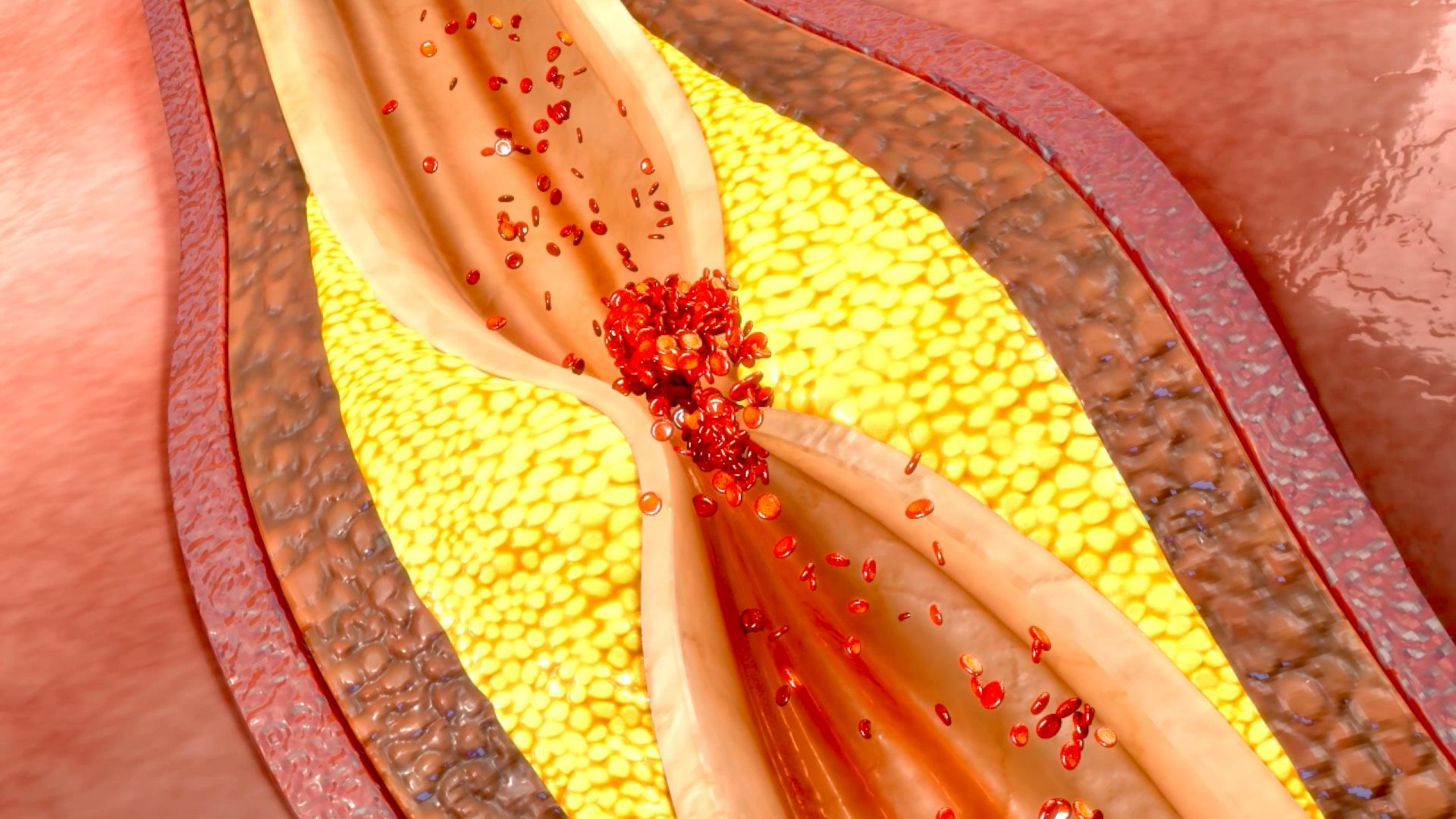
If additional weight loss and reduction of weight-related complications are needed

Bariatric Surgery[177]

If insufficient weight loss or weight regain after BS consider: Tirzepatide[197], Semaglutide[194], Liraglutide[195,196]

*This framework promotes a phenotype-based, individualized approach to obesity care, prioritizing complications and patient preferences over rigid treatment hierarchies, with patient-HCPs shared decision-making considering goals, tolerability, contraindications, and costs. **OWCMC, Obesity Without Clinically Manifest Complications

Tuccinardi D, et al. *J Endocrinol Invest* **48**, 2761–2798 (2025)



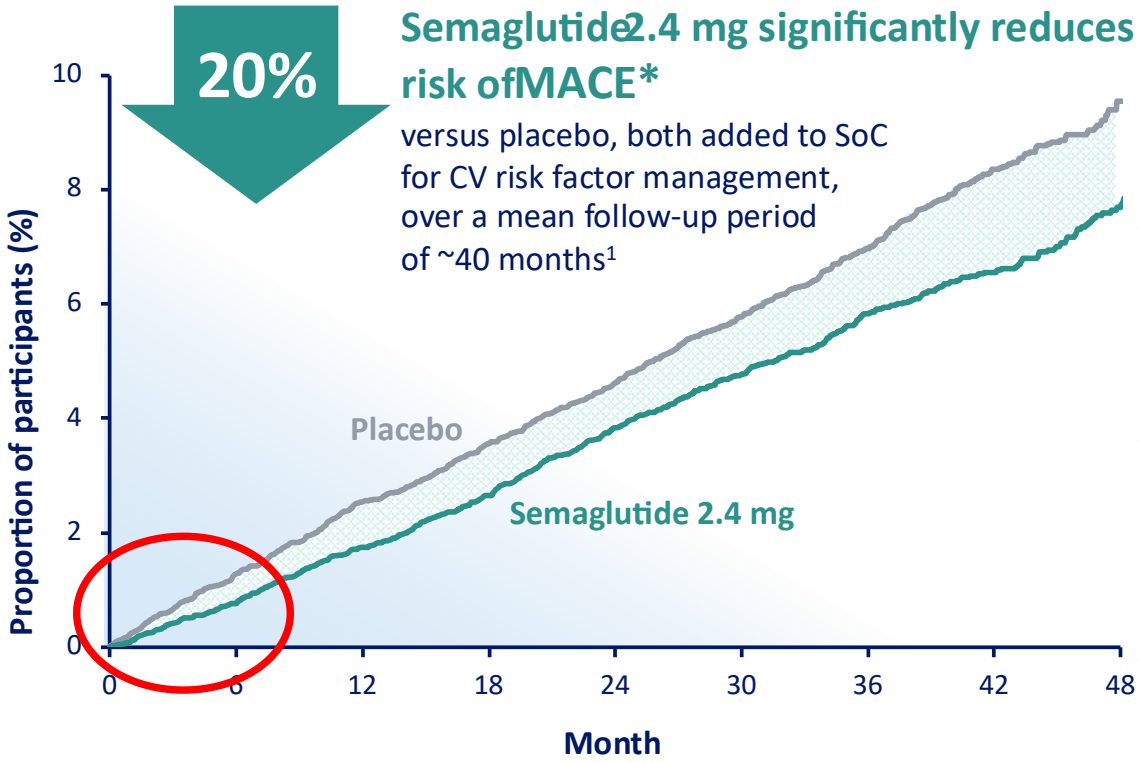
+ASCVD

Cardiovascular disease was defined as prior myocardial infarction, prior stroke, or clinically symptomatic peripheral arterial disease in individuals aged ≥45 years and with a BMI ≥27 kg/m²

Semaglutide 2.4 mg [4]

Naltrexone/ Bupropion (not recommended)[15]

Semaglutide 2.4 mg has shown significant MACE reduction, as well as wider CKM benefits, in people with overweight or obesity and CVD, without diabetes



Semaglutide 2.4 mg significantly reduces risk of MACE*

versus placebo, both added to SoC for CV risk factor management, over a mean follow-up period of ~40 months[1]

The SELECT trial showed further benefits with semaglutide 2.4 mg vs placebo:[1]

19% REDUCTION in risk of **all-cause death**[1†]

73% REDUCTION in risk of **developing diabetes**[1†‡]

22% REDUCTION in risk of **developing kidney disease** or **renal death**[1†§]

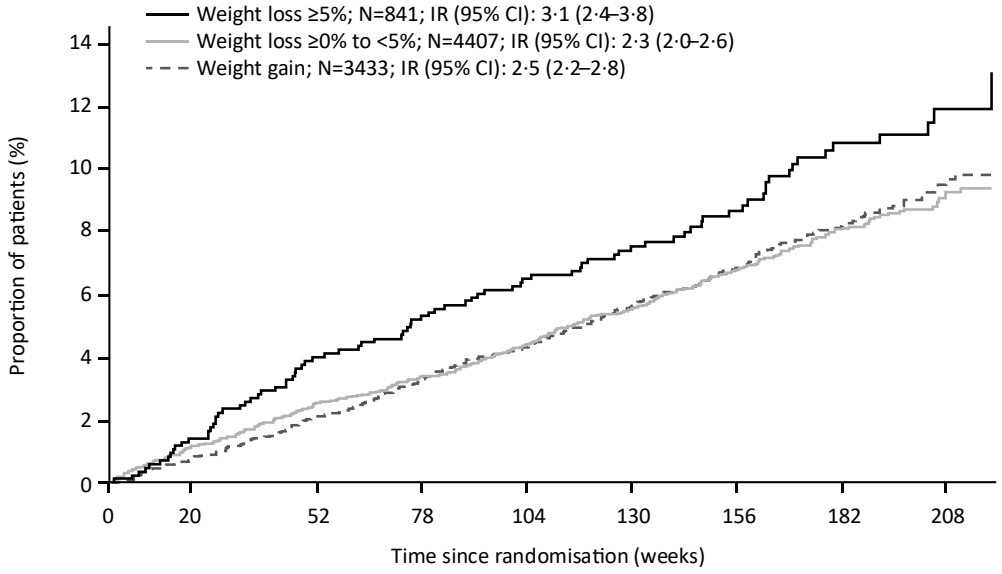
1. Lincoff AM, et al. N Engl J Med. 2023;DOI:10.1056/NEJMoa2307563.

+ASCVD

Cardiovascular disease was defined as prior myocardial infarction, prior stroke, or clinically symptomatic peripheral arterial disease in individuals aged ≥45 years and with a BMI ≥27 kg/m²

Semaglutide 2.4 mg [4]

Naltrexone/ Buproprion (not recommended)[15]



Patients at risk (censored)

Placebo									
Weight loss ≥5%	853 (0)	841 (12)	807 (34)	792 (45)	775 (55)	650 (63)	509 (70)	378 (81)	186 (84)
Weight loss ≥0% to <5%	4478 (0)	4407 (51)	4321 (114)	4245 (151)	4166 (195)	3625 (244)	2916 (287)	2067 (324)	932 (341)
Weight gain	3470 (0)	3433 (27)	3363 (75)	3291 (116)	3228 (152)	2868 (193)	2263 (225)	1639 (254)	609 (271)

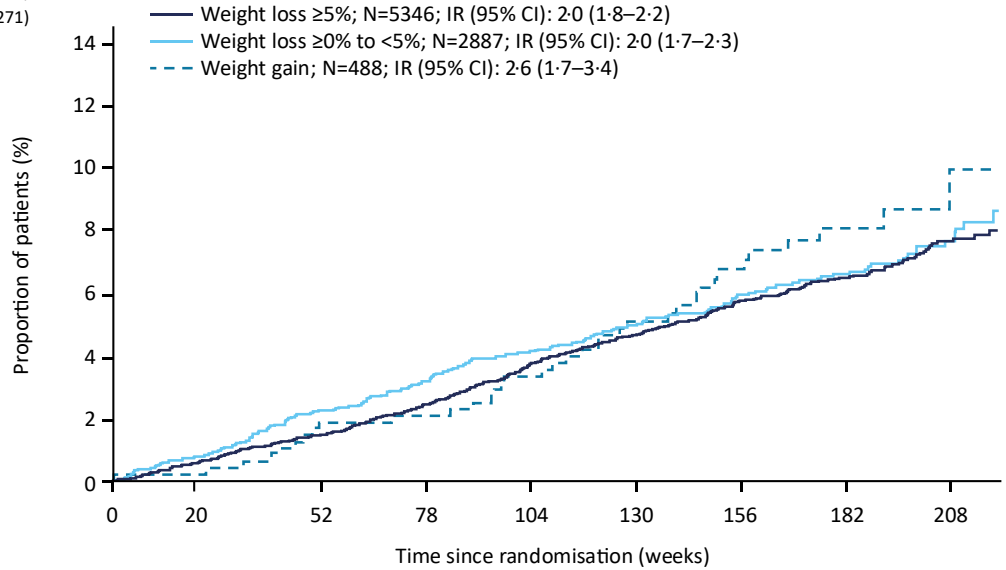
Time from randomisation to first MACE by body weight loss at week 20

In the placebo arm

Time from randomisation to first MACE by body weight loss at week 20

In the semaglutide arm

MACE risk reduction with semaglutide was independent of weight loss



Patients at risk (censored)

Semaglutide									
Weight loss ≥5%	5392 (0)	5346 (30)	5265 (79)	5181 (130)	5074 (199)	4454 (245)	3569 (291)	2655 (316)	1197 (339)
Weight loss ≥0% to <5%	2921 (0)	2887 (21)	2825 (65)	2781 (92)	2726 (119)	2413 (142)	1924 (164)	1340 (176)	517 (186)
Weight gain	490 (0)	488 (1)	472 (9)	468 (10)	459 (16)	404 (24)	306 (30)	203 (34)	71 (36)

Deanfield J et al. *Lancet* 2025;doi:10.1016/S0140-6736(25)01375-3.

+ASCVD

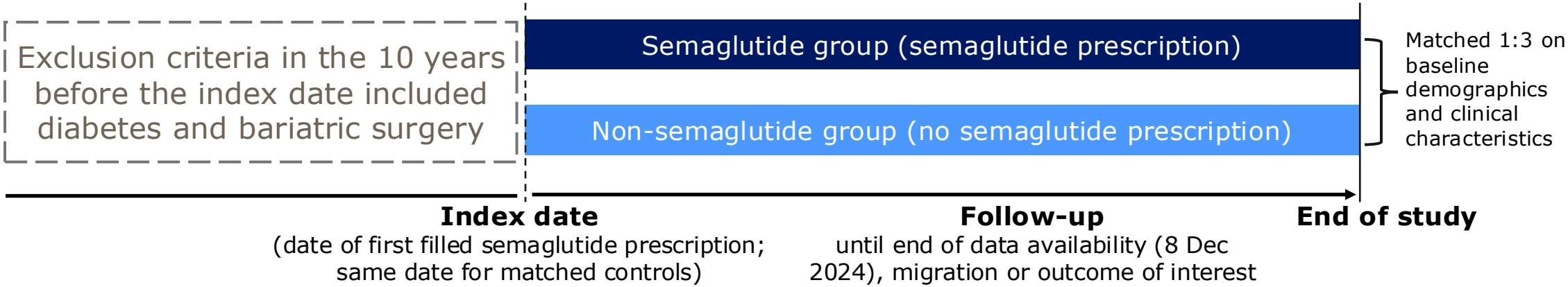
Cardiovascular disease was defined as prior myocardial infarction, prior stroke, or clinically symptomatic peripheral arterial disease in individuals aged ≥45 years and with a BMI ≥27 kg/m²

Semaglutide 2.4 mg [4]

Naltrexone/ Buproprion (not recommended)[15]

HOPE Study Design

Danish hospital records



Inclusion criteria

Aged ≥45 years

Hospital diagnosis of overweight or obesity (BMI ≥25 kg/m²) in the Danish National Patient Register during index period (1 Jan 2012–31 Dec 2022)

For the semaglutide group, ≥1 prescription for once-weekly semaglutide for weight management in Danish Prescription Register (12 Dec 2022–31 Oct 2024)

Outcomes

- Time to 5P-MACE[b]
- Time to 3P-MACE[c]

Statistics

Kaplan-Meier analysis to generate survival curves and Cox proportional hazards model to generate HRs and 95% CIs

[a]Matching was based on date of birth, sex, region of residence, educational level (highest attained), obesity category, time between overweight/obesity diagnosis and index date, comorbidities (HF, MI, stroke), predicted CVD risk score and history of ASCVD. [b]5P-MACE was a composite of MI, stroke, hospitalization for HF, coronary revascularization and all-cause mortality. [c]3P-MACE was a composite of MI, stroke and all-cause mortality. *3P-MACE, 3-point major adverse cardiovascular events; 5P-MACE, 5-point major adverse cardiovascular events; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.*

Presented at the 61st Annual Meeting of the European Association for the Study of Diabetes, September 15–19, 2025, Vienna, Austria. Presentation number: 148

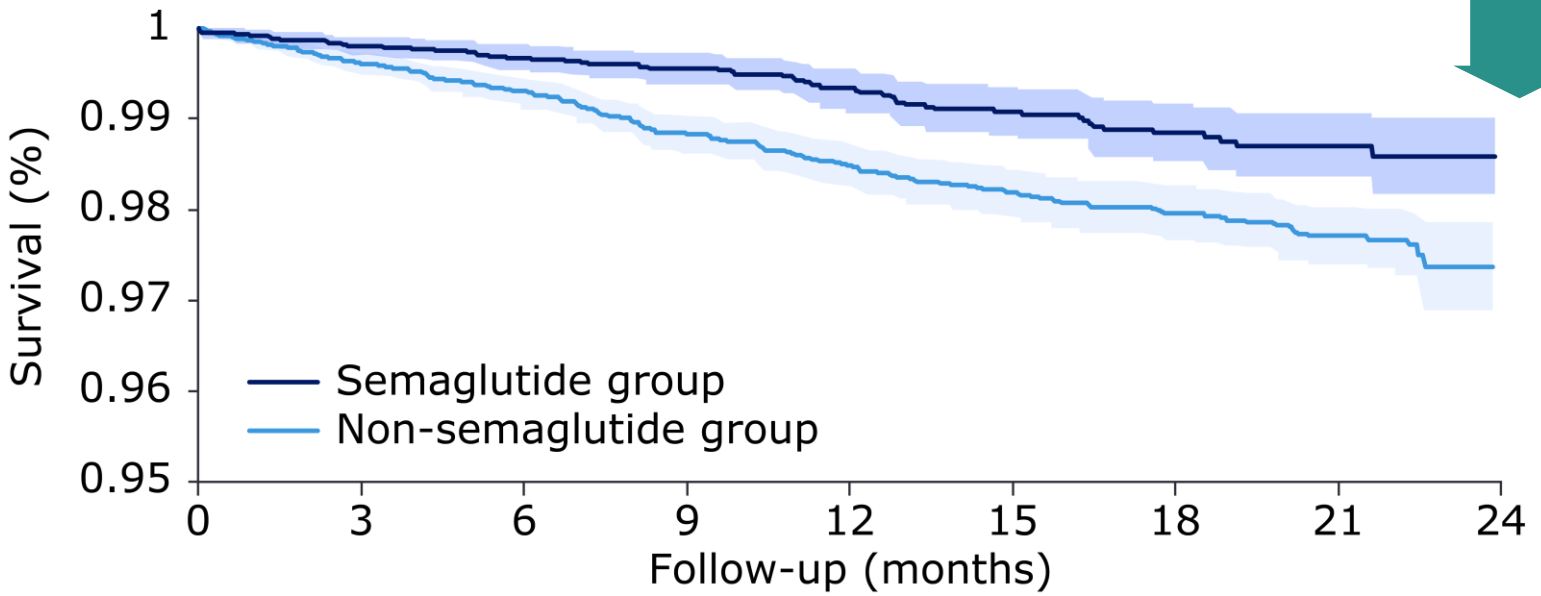
+ASCVD

Cardiovascular disease was defined as prior myocardial infarction, prior stroke, or clinically symptomatic peripheral arterial disease in individuals aged ≥45 years and with a BMI ≥27 kg/m²

Semaglutide 2.4 mg [4]

Naltrexone/ Bupropion (not recommended)[15]

Semaglutide treatment was associated with relatively lower risk of 3P-MACE[a]



47%

Event rate
Semaglutide group: 0.8%
Non-semaglutide group: 1.6%
HR: 0.53 (0.40–0.70)

Incidence of 3P-MACE per 1000 person-years	
Semaglutide	7.4
Non-semaglutide	14.0
Absolute risk reduction	6.6

Individuals at risk (event rate [%])

Semaglutide group	7113 (–)	6580 (0.20)	5728 (0.31)	4873 (0.39)	4151 (0.53)	3383 (0.67)	2506 (0.77)	1178 (–)
Non-semaglutide group	21,339 (–)	19,704 (0.39)	17,127 (0.65)	14,495 (1.00)	12,333 (1.22)	10,059 (1.38)	7472 (1.48)	3528 (–)

Maximum follow-up was 23.5 months

Shaded areas represent the 95% CIs.[a]3P-MACE was a composite of MI, stroke and all-cause mortality.
3P-MACE, 3-point major adverse cardiovascular events; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.

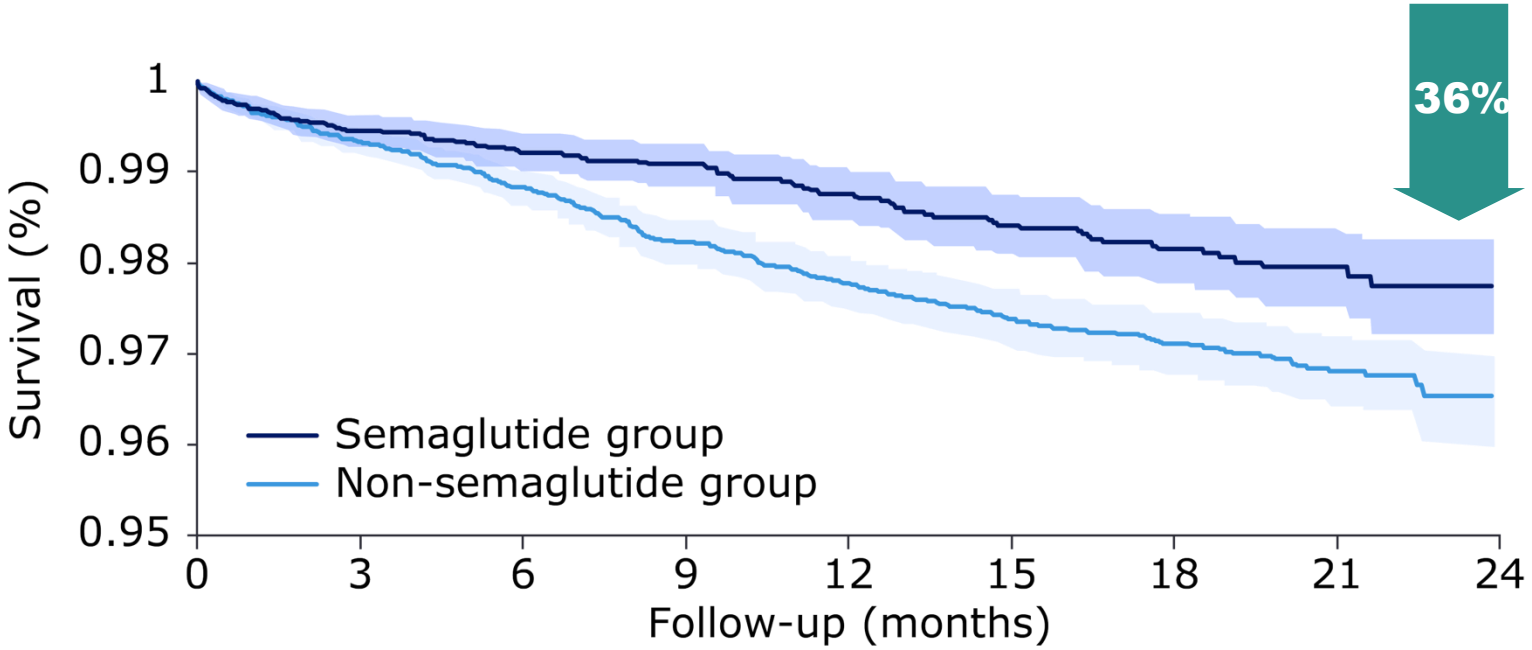
+ASCVD

Cardiovascular disease was defined as prior myocardial infarction, prior stroke, or clinically symptomatic peripheral arterial disease in individuals aged ≥45 years and with a BMI ≥27 kg/m²

Semaglutide 2.4 mg [4]

Naltrexone/ Bupropion (not recommended)[15]

Semaglutide treatment was associated with relatively lower risk of 5P-MACE[a]



Event rate
Semaglutide group: 1.4%
Non-semaglutide group: 2.3%
HR: 0.64 (0.51–0.79)

Incidence of 5P-MACE per 1000 person-years	
Semaglutide	12.8
Non-semaglutide	20.2
Absolute risk reduction	7.4

Individuals at risk (event rate [%])

Semaglutide group	7113 (–)	6557 (0.55)	5705 (0.75)	4856 (0.84)	4133 (1.05)	3365 (1.24)	2490 (1.35)	1169 (–)
Non-semaglutide group	21,339 (0.04)	19,654 (0.67)	17,052 (1.09)	14,410 (1.54)	12,246 (1.83)	9986 (2.04)	7416 (2.15)	3502 (–)

Maximum follow-up was 23.5 months

Shaded areas represent the 95% CIs. [a]5P-MACE was a composite of MI, stroke, hospitalization for HF, coronary revascularization and all-cause mortality.
5P-MACE, 5-point major adverse cardiovascular events; CI, confidence interval; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

+ASCVD

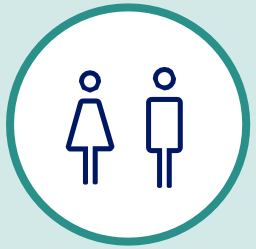
Cardiovascular disease was defined as prior myocardial infarction, prior stroke, or clinically symptomatic peripheral arterial disease in individuals aged ≥45 years and with a BMI ≥27 kg/m²

Semaglutide 2.4 mg [4]

Naltrexone/ Bupropion (not recommended)[15]

STEER Study Design

US Komodo Research Database



Study population

- ≥45 years of age
- Overweight/obesity*
- Established ASCVD†
- Without diabetes
- Initiated semaglutide or tirzepatide on or after May 13, 2022

The propensity score model matched semaglutide and tirzepatide patients 1:1

Primary outcome measures:

- **Revised 3-point MACE:** Myocardial infarction, stroke, and all-cause mortality
- **Revised 5-point MACE:** Myocardial infarction, stroke, hospitalization for heart failure, coronary revascularization, and all-cause mortality

**Defined as body mass index ≥27 kg/m². †Defined as a diagnosis of myocardial infarction or ischemic stroke and/or evidence of peripheral artery disease. ‡End of follow-up for each patient was defined as the earliest of the end of the study period (Jan 31, 2025), end of continuous enrolment, initiation of a non-index GLP-1 or GLP-1/GIP receptor agonist, bariatric surgery, or death.*
ASCVD, atherosclerotic cardiovascular disease; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; MACE, major adverse cardiovascular event.

Wilson L, et al. Presented at the European Society of Cardiology (ESC) Congress together with World Congress of Cardiology; Madrid, Spain; August 29 - September 1, 2025.

+ASCVD

Cardiovascular disease was defined as prior myocardial infarction, prior stroke, or clinically symptomatic peripheral arterial disease in individuals aged ≥45 years and with a BMI ≥27 kg/m²

Semaglutide 2.4 mg [4]

Naltrexone/ Bupropion (not recommended)[15]

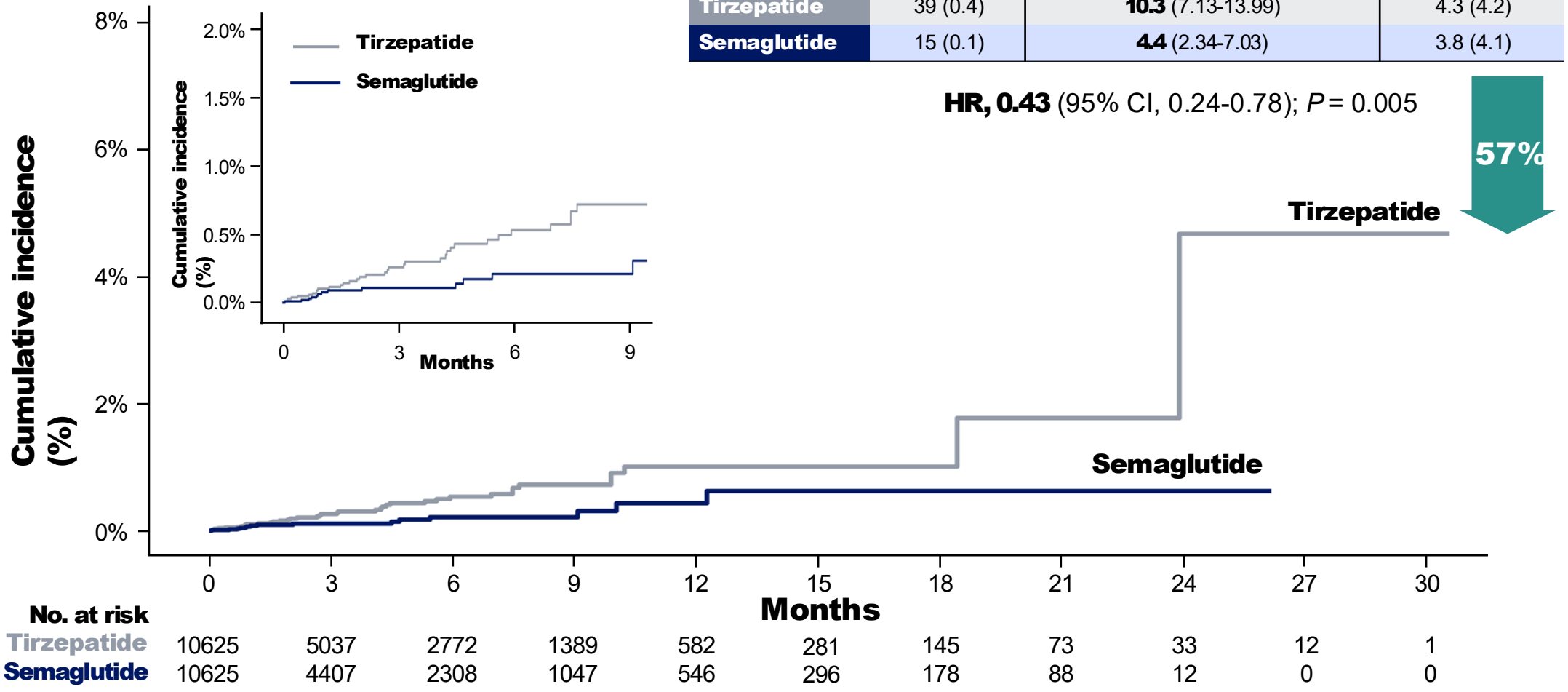
Revised 3-Point MACE*

(Per-Protocol Analysis)

Per-protocol sensitivity analysis censored patients at treatment discontinuation (gap in therapy >30 days)

	Events, n (%)	Incidence rate per 1000 patient-years (95% CI)	Mean (SD) follow-up
Tirzepatide	39 (0.4)	**10.3** (7.13-13.99)	4.3 (4.2)
Semaglutide	15 (0.1)	**4.4** (2.34-7.03)	3.8 (4.1)

HR, 0.43 (95% CI, 0.24-0.78); *P* = 0.005



*Revised 3-pont MACE includes myocardial infarction, stroke, and all-cause mortality.
CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event; SD, standard deviation.

Wilson L, et al. Presented at the European Society of Cardiology (ESC) Congress together with World Congress of Cardiology; Madrid, Spain; August 29 - September 1, 2025.

+ASCVD

Cardiovascular disease was defined as prior myocardial infarction, prior stroke, or clinically symptomatic peripheral arterial disease in individuals aged ≥45 years and with a BMI ≥27 kg/m²

Semaglutide 2.4 mg [4]

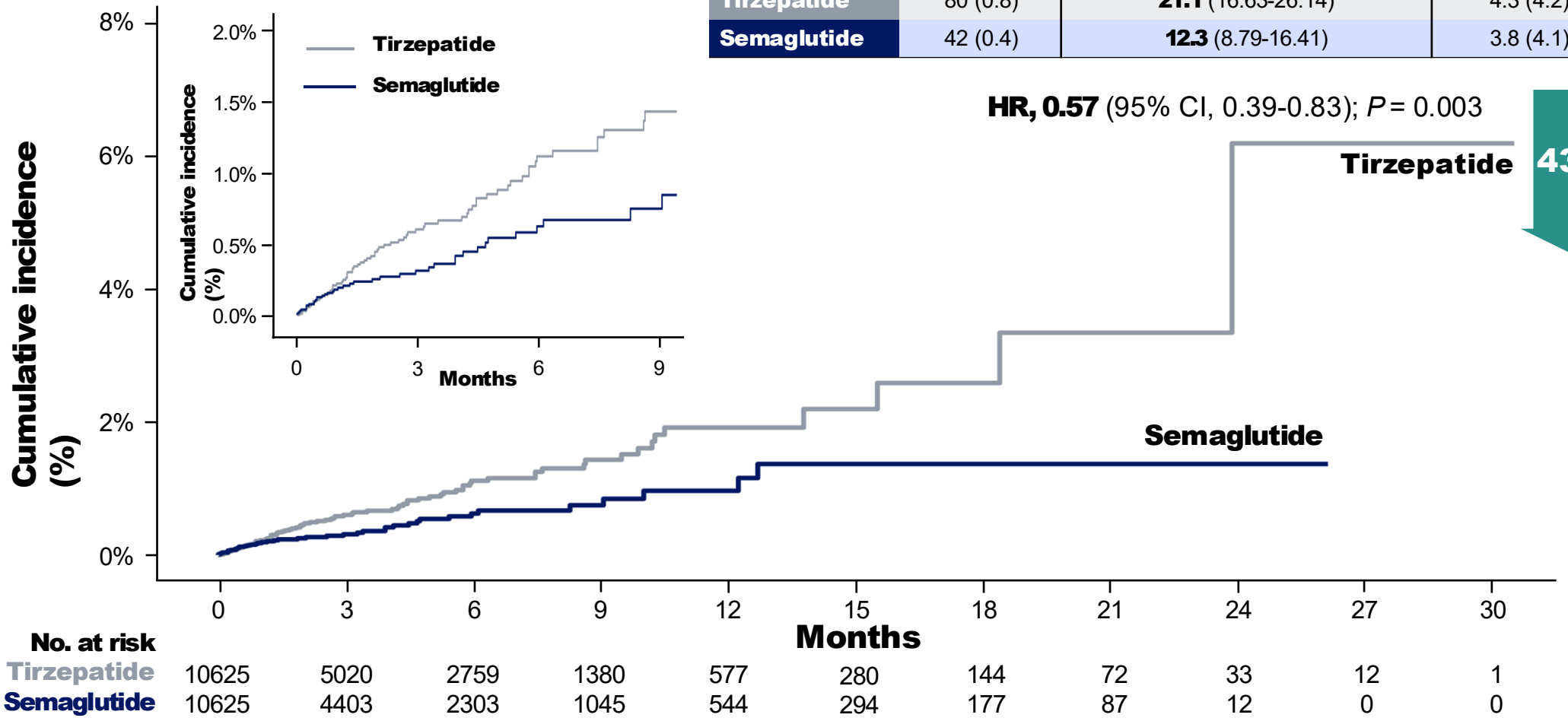
Naltrexone/ Bupropion (not recommended)[15]

Revised 5-Point MACE*

(Per-Protocol Analysis)

Per-protocol sensitivity analysis censored patients at treatment discontinuation (gap in therapy >30 days)

	Events, n (%)	Incidence rate per 1000 patient-years (95% CI)	Mean (SD) follow-up
Tirzepatide	80 (0.8)	**21.1** (16.63-26.14)	4.3 (4.2)
Semaglutide	42 (0.4)	**12.3** (8.79-16.41)	3.8 (4.1)



*Revised 5-pont MACE includes myocardial infarction, stroke, hospitalization for heart failure, coronary revascularization, and all-cause mortality.
CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event; SD, standard deviation.

Wilson L, et al. Presented at the European Society of Cardiology (ESC) Congress together with World Congress of Cardiology; Madrid, Spain; August 29 - September 1, 2025.

HF

Clinical heart failure (NYHA II–IV) with preserved or mildly reduced ejection fraction (LVEF ≥50% for **tirzepatide**, ≥45% for **semaglutide**), BMI ≥30 kg/m², impaired functional capacity (KCCQ-CSS <80–90), 6MWT distance ≥100 m, and elevated filling pressures (e.g., NT-proBNP, echocardiographic abnormalities, or recent HF hospitalization). Type 2 diabetes was an inclusion criterion in the tirzepatide trial.

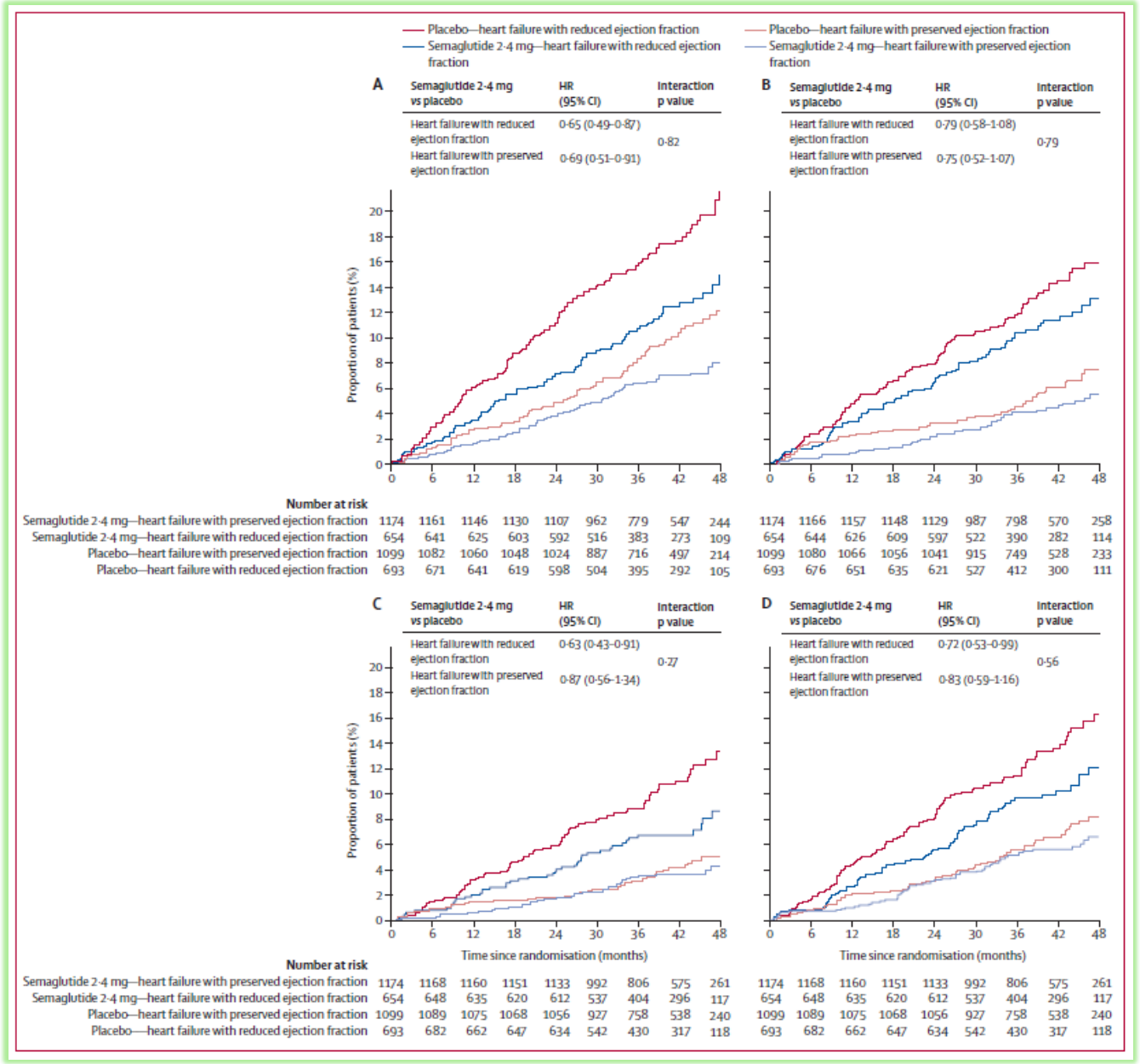
Tirzepatide 15 mg [11]

Semaglutide 2.4 mg [5]

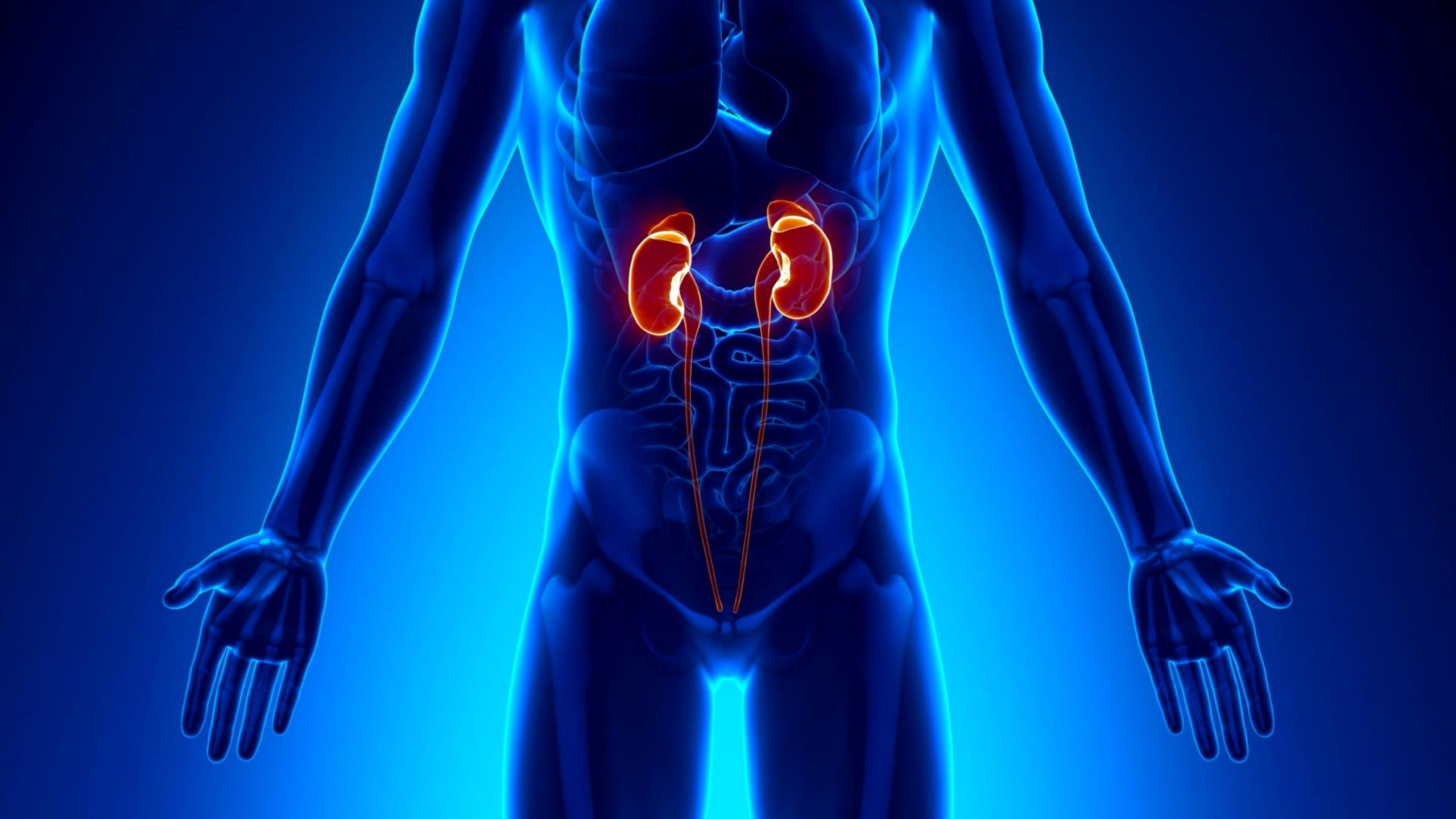
Naltrexone/ Buproprion (not recommended) [15]

MACE (A), HF composite (B), CV death (C), All-cause death (D) by HF subtype

- Semaglutide reduced MACE in both subtypes: **HR 0.65 (HFrEF)** and **0.69 (HFpEF)**; no interaction (p = 0.97).
- Semaglutide lowered the **HF composite endpoint** regardless of ejection-fraction category.
- Reductions in CV death and all-cause mortality were **directionally similar**, with a numerically greater absolute benefit in HFrEF due to higher baseline risk.



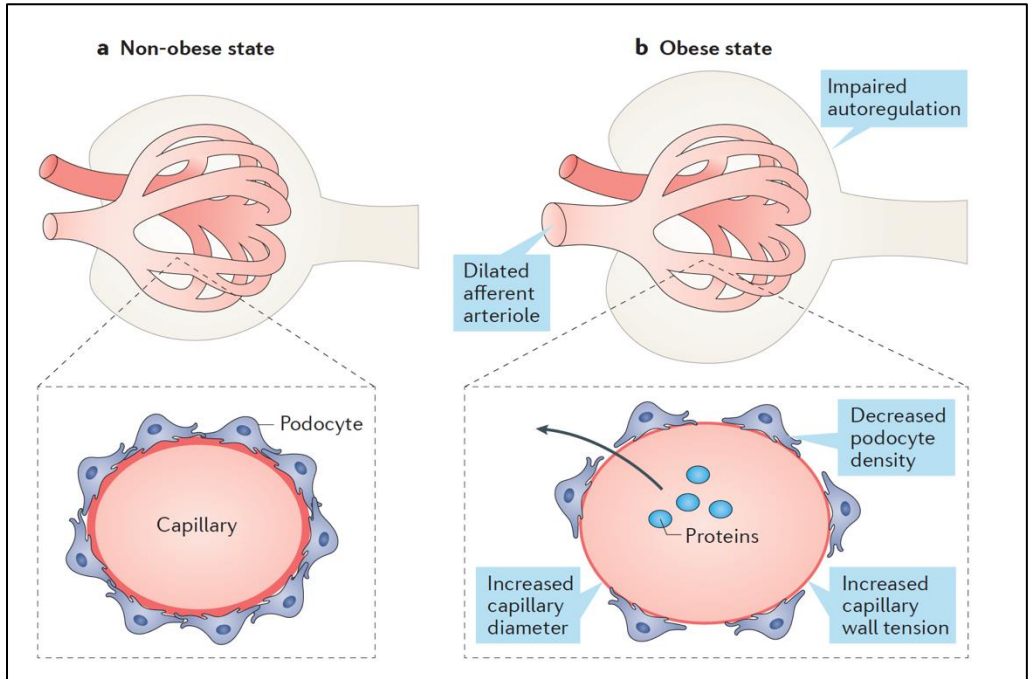
Cumulative incidence curves showing the risk of MACE comparing semaglutide with placebo according to presence or absence of HF. The cumulative incidence rate is calculated using the Aalen–Johansen method. CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events.
Deanfield J, et al. Lancet. 2024;404(10454):773–786.

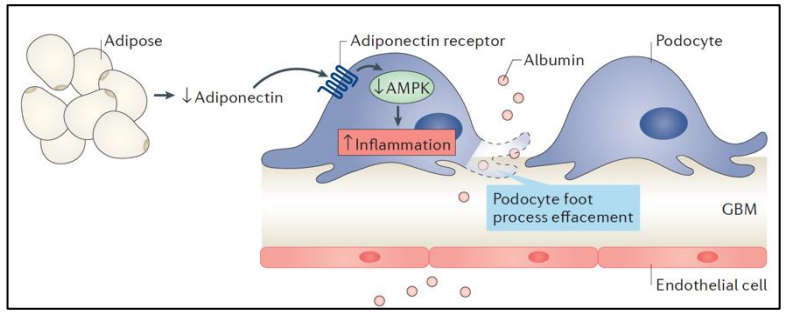


Hyperfiltration and Obesity-Related Glomerulopathy

↑ plasma flow → afferent vasodilation + efferent vasoconstriction → ↑ intraglomerular pressure
↑ sodium reabsorption → impaired tubulo-glomerular feedback
↑ RAAS & sympathetic activation (leptin), ↓ adiponectin, inflammation,

Lean → Obesity → **Obesity-related glomerulopathy (ORG)** → **Proteinuria** (~ 90% subnephrotic, ~10% nephrotic) / eGFR decline (~ 10% ESRD)





Yau K. Nat Rev Endocrinol. 2024
D'Agati VD et al. *Nat Rev Nephrol.* 2016;12:453–471

CKD

eGFR <60 mL/min/1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [≥30 mg/g])

↓

Semaglutide 2.4 mg[5]

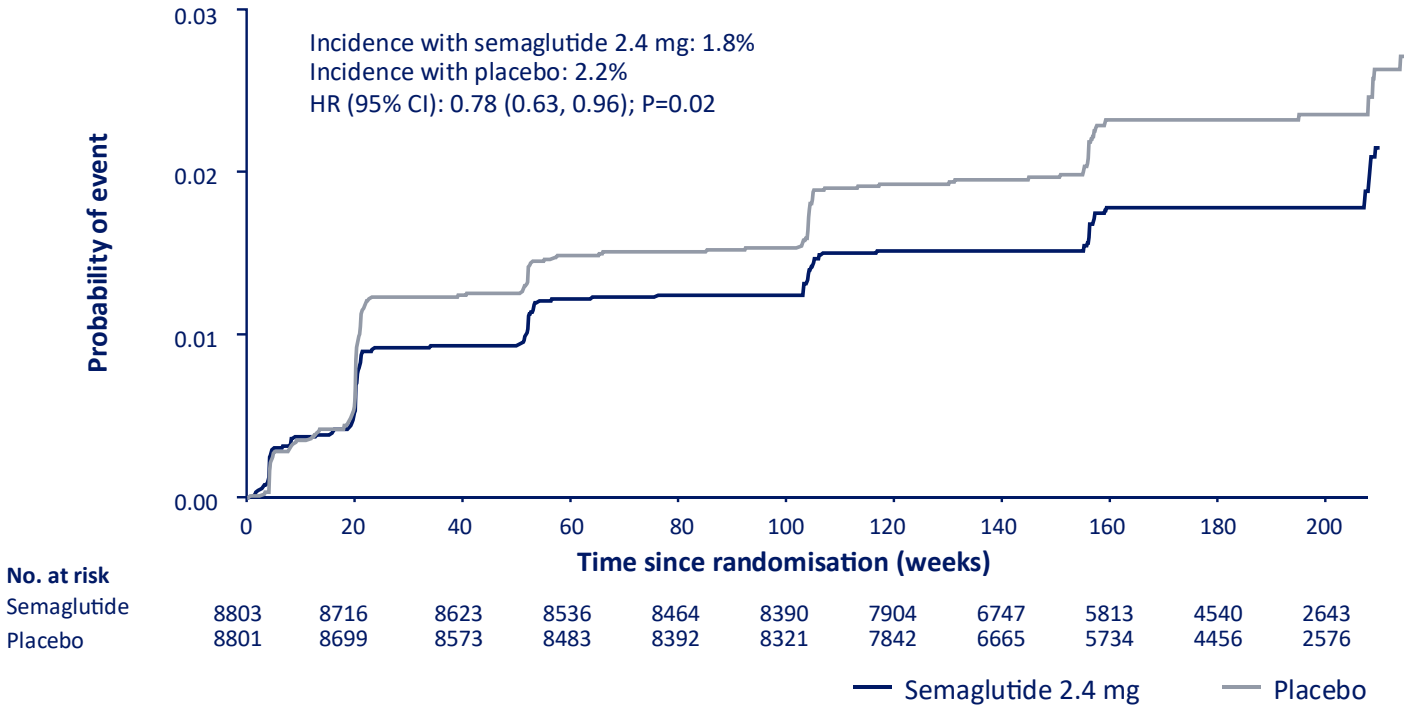
Tirzepatide 15 mg
[11,19]

Use if eGFR >30 mL/min/1.73 m²; exercise caution when eGFR <30 mL/min/1.73 m² due to limited data.

Orlistat (caution in obesity due to risks of nephrolithiasis or AKI)[18]

Naltrexone/ Buproprion (not recommended)[15]

Time to first occurrence of the main 5-component kidney composite endpoint†



Semaglutide 2.4 mg reduced the risk of the main kidney composite endpoint by 22% compared with placebo

Data are the observed (i.e. as measured) probability of patients experiencing their first occurrence of the main 5-component kidney composite endpoint during the in-trial period, analysed using the Kaplan–Meier method, and the estimated HR, analysed using a Cox regression model. Tied events were handled using the Exact method, if possible, or Efron's method, if not. Numbers below the graph are the number of patients at risk. p values are two-sided and not adjusted for multiplicity

†The main 5-component kidney composite endpoint included death from kidney causes, initiation of chronic kidney replacement thera py (dialysis or transplantation), onset of persistent eGFR <15 mL/min/1.73 m², persistent ≥50% reduction in eGFR compared with baseline or onset of persistent macroalbuminuria. CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, ha zard ratio.

Colhoun HM et al. Nat Med 2024;30:2058–2066.

CKD

eGFR <60 mL/min/1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [≥30 mg/g])

↓

Semaglutide 2.4 mg[5]

Tirzepatide 15 mg[11,19]

Use if eGFR >30 mL/min/1.73 m²; exercise caution when eGFR <30 mL/min/1.73 m² due to limited data.

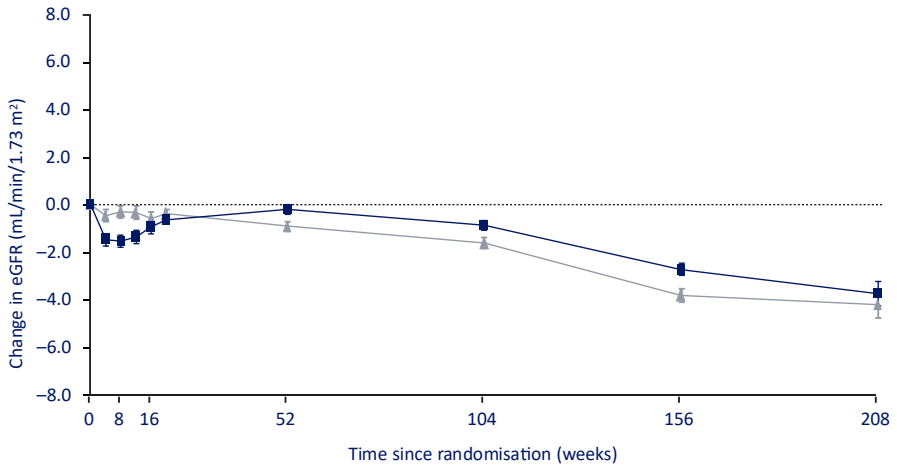
Orlistat (caution in obesity due to risks of nephrolithiasis or AKI)[18]

Naltrexone/ Bupropion (not recommended)[15]

Changes in eGFR over time

In the overall population

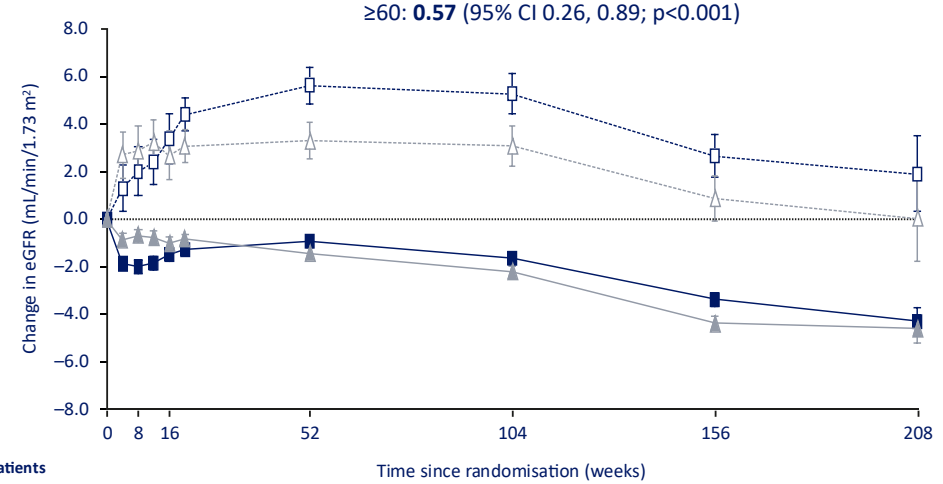
Treatment effect at 104 weeks: **0.75 mL/min/1.73 m²** (95% CI 0.43, 1.06; p<0.001)



Number of patients							
Semaglutide 2.4 mg	8803	2681	2563	7726	7513	5032	889†
Placebo	8801	2692	2607	7731	7431	4986	862†

By subgroup

Treatment effect at 104 weeks (by eGFR subgroups, mL/min/1.73 m ²):
<60: **2.19** (95% CI 1.00, 3.38; p<0.001)
≥60: **0.57** (95% CI 0.26, 0.89; p<0.001)



Number of patients						
eGFR <60 mL/min/1.73 m²						
Semaglutide 2.4 mg	243	226	832	801	539	115†
Placebo	237	229	788	750	493	88†
eGFR ≥60 mL/min/1.73 m²						
Semaglutide 2.4 mg	2430	2330	6872	6691	4479	771†
Placebo	2443	2367	6921	6662	4485	774†

eGFR (mL/min/1.73 m²): <60 ≥60
Semaglutide 2.4 mg
Placebo

Data are estimated mean (CI) changes from the estimated baseline value in eGFR, analysed using a mixed model for repeated mea surements.
Numbers below the graphs are the number of patients contributing to the analysis.
p values are two-sided and not adjusted for multiplicity. Darker lines are used for the larger subgroups.
†Given gradual entry to the trial across the enrolment period and variable follow -up duration, data at 156 and 208 weeks are sparser compared with prior time points.
CI, confidence interval; eGFR, estimated glomerular filtration rate.
Colhoun HM et al. Nat Med 2024;30:2058–2066.

CKD

eGFR <60 mL/min/1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [≥30 mg/g])

↓

Semaglutide 2.4 mg[5]

Tirzepatide 15 mg[11,19]

Use if eGFR >30 mL/min/1.73 m²; exercise caution when eGFR <30 mL/min/1.73 m² due to limited data.

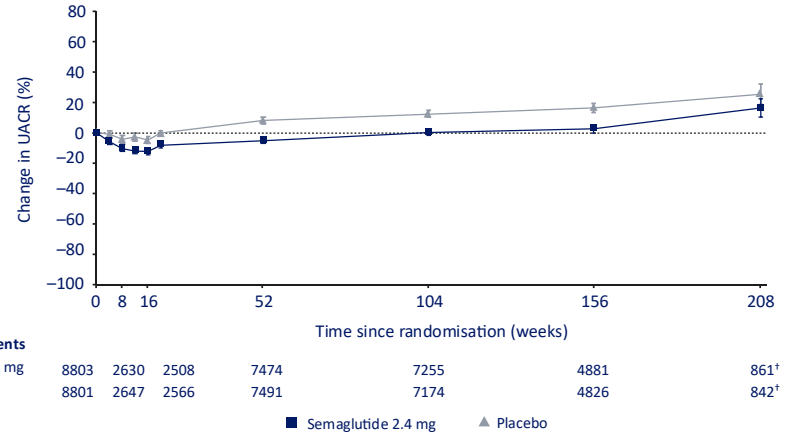
Orlistat (caution in obesity due to risks of nephrolithiasis or AKI)[18]

Naltrexone/ Buproprion (not recommended)[15]

Changes in UACR over time

In the overall population

Treatment effect at 104 weeks: **–10.7%** (95% CI –13.2, –8.2; p<0.001)



Number of patients							
Semaglutide 2.4 mg	8803	2630	2508	7474	7255	4881	861†
Placebo	8801	2647	2566	7491	7174	4826	842†

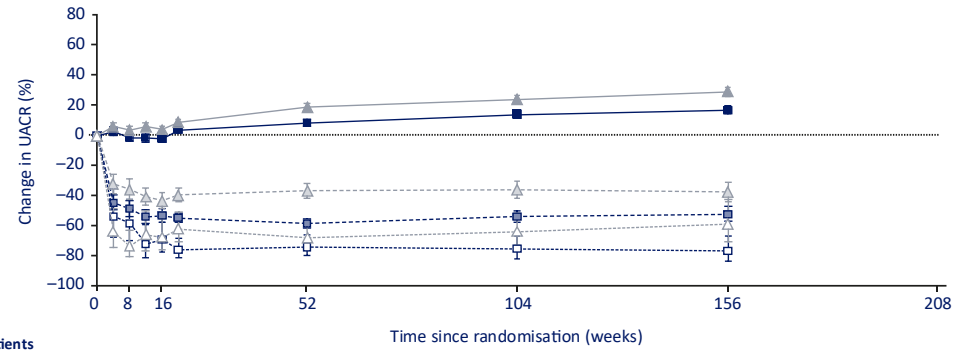
By subgroup

Treatment effect at 104 weeks (by UACR subgroups, mg/g)

<30: **–8.1%** (95% CI –10.6, –5.6; p<0.001)

30 to <300: **–27.2%** (95% CI –35.3, –18.1; p<0.001)

≥300: **–31.4%** (95% CI –54.9, 4.3; p=0.08)



Number of patients						
UACR <30 mg/g						
Semaglutide 2.4 mg	2249	2151	6315	6161	4174	743†
Placebo	2300	2225	6412	6188	4166	716†
UACR 30 to <300 mg/g						
Semaglutide 2.4 mg	271	252	861	823	529	88†
Placebo	240	232	781	725	493	100†
UACR ≥300 mg/g						
Semaglutide 2.4 mg	39	38	137	117	75	12†
Placebo	34	35	132	118	81	12†

UACR (mg/g): <30, 30 to <300, ≥300

Semaglutide 2.4 mg

Placebo

Data are estimated mean (CI) changes from the estimated baseline value in UACR, analysed using a mixed model for repeated mea surements. The change in UACR was analysed as the estimated mean ratio to baseline; for ease of interpretation, these ratios have been c onverted to relative percentage changes from baseline using the formula (estimated ratio – 1) × 100. Numbers below the graphs are the number of patients contributing to the analysis. p values are two-sided and not adjusted for multiplicity. Darker lines are used for the larger subgroups.

†Given gradual entry to the trial across the enrolment period and variable follow -up duration, data at 156 and 208 weeks are sparser compared with prior time points. CI, confidence interval; UACR, urinary albumin -to-creatinine ratio.

Colhoun HM et al. Nat Med 2024;30:2058–2066.


98
mg
dL

GLYCEMIC CONTROL

PREDIABETES

HbA1c 5.7–6.4%, fasting plasma glucose 100–125 mg/dL, or 2-hours OGTT glucose 140–199 mg/dL

- Tirzepatide 15 mg [2]
- Semaglutide 2.4 mg [22]
- Liraglutide 3 mg [12,74]
- Orlistat 120 mg [14]

Metformin: off-label use; may reduce the incidence of type 2 diabetes[24].

TYPE 2 DIABETES

HbA1c ≥ 6.5%, fasting plasma glucose ≥ 126 mg/dL, or 2-hours OGTT plasma glucose ≥ 200 mg/dL

- Tirzepatide 15 mg [31]
- Semaglutide 2.4 mg [29]
- Liraglutide 3 mg [33]

SGLT2 inhibitors support weight loss [37,38,39,40,41], If glycemic control allows, insulin[44,45], thiazolidinediones, and sulfonylureas should be avoided due to their propensity to induce weight gain.[203]

TYPE 1 DIABETES

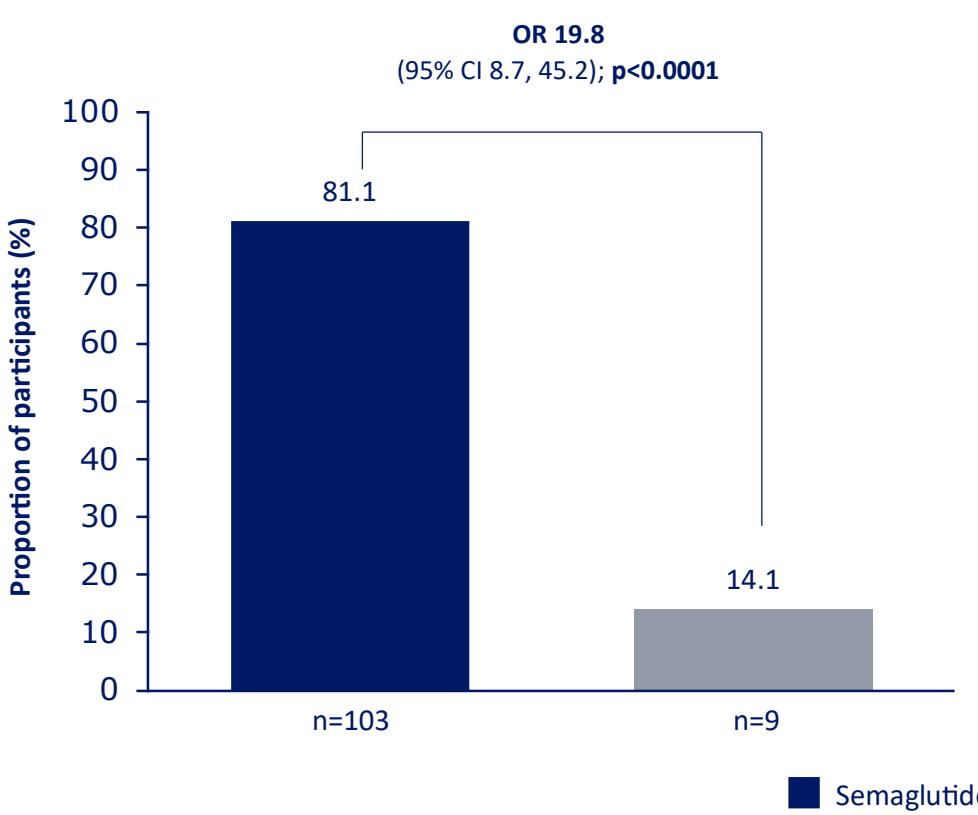
(OFF-LABEL only for weight loss purposes)

- Tirzepatide 15 mg [52]
- Semaglutide 2.4 mg [51]

Reversion to normoglycaemia

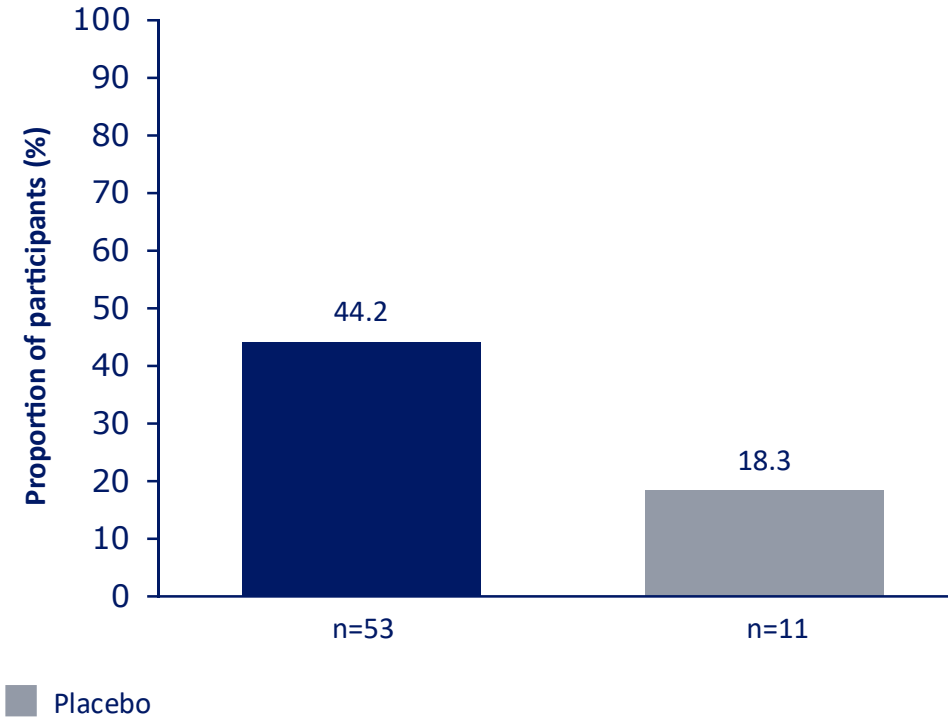
Primary endpoint (week 52) and exploratory endpoint (week 80)

Reversion to normoglycaemia at week 52



Reversion to normoglycaemia at week 80

Off treatment



Semaglutide 2.4 mg Placebo

Normoglycaemia was defined as having both HbA $_{1c}$ <6.0% and FPG <5.5 mmol/L. Observed proportions of participants, during the in-trial observation period in the FAS. ORs are for the treatment policy estimand. CI, confidence interval; FAS, full analysis set; FPG, fasting plasma glucose; HbA $_{1c}$, glycated haemoglobin; OR, odds ratio.
McGowan, B et al. Obes Facts 2024;17(suppl 1):72

McGowan BM et al. *Lancet Diabetes Endocrinol*. 2024;12(9):631-642

GLYCEMIC CONTROL

PREDIABETES

HbA1c 5.7–6.4%, fasting plasma glucose 100–125 mg/dL, or 2-hours OGTT glucose 140–199 mg/dL

- Tirzepatide 15 mg [2]
- Semaglutide 2.4 mg [22]
- Liraglutide 3 mg [12,74]
- Orlistat 120 mg [14]

Metformin: off-label use; may reduce the incidence of type 2 diabetes[24].

TYPE 2 DIABETES

HbA1c ≥ 6.5%, fasting plasma glucose ≥ 126 mg/dL, or 2-hours OGTT plasma glucose ≥ 200 mg/dL

- Tirzepatide 15 mg [31]
- Semaglutide 2.4 mg [29]
- Liraglutide 3 mg [33]

SGLT2 inhibitors support weight loss [37,38,39,40,41], If glycemic control allows, insulin[44,45], thiazolidinediones, and sulfonylureas should be avoided due to their propensity to induce weight gain.[203]

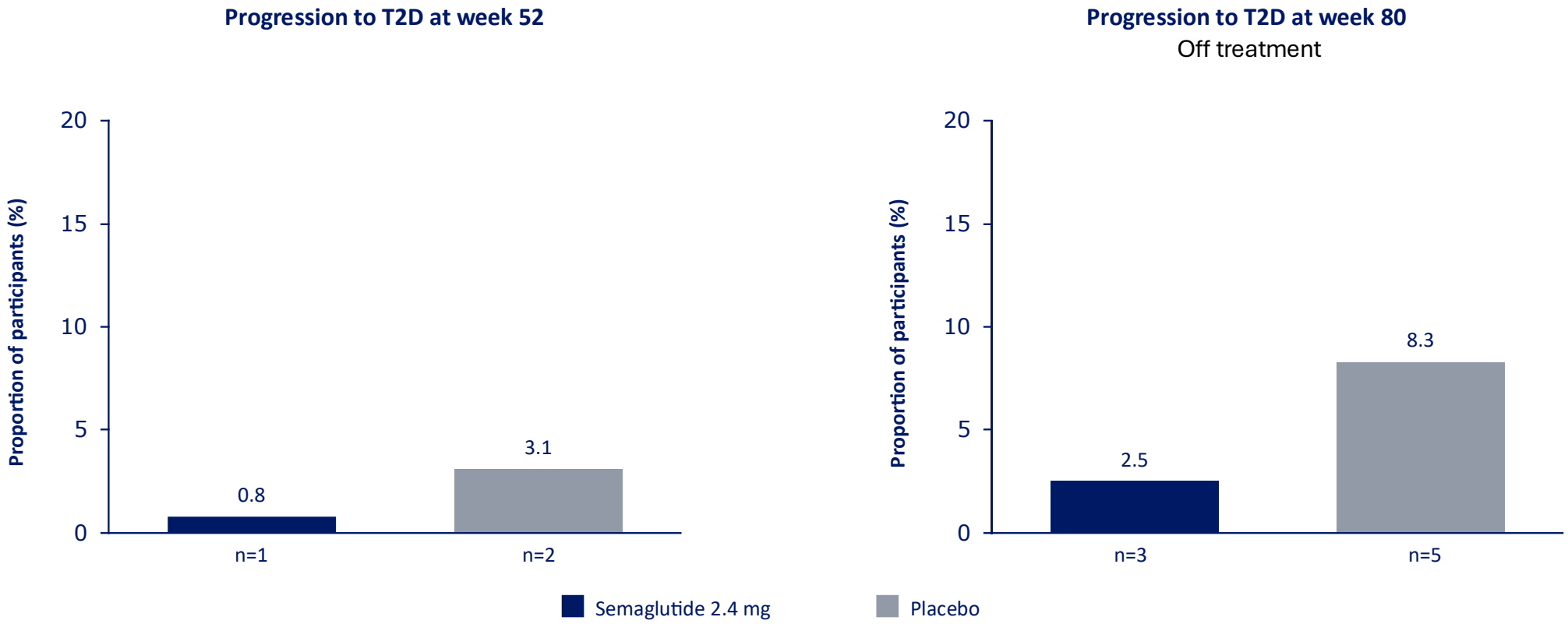
TYPE 1 DIABETES

(OFF-LABEL only for weight loss purposes)

- Tirzepatide 15 mg [52]
- Semaglutide 2.4 mg [51]

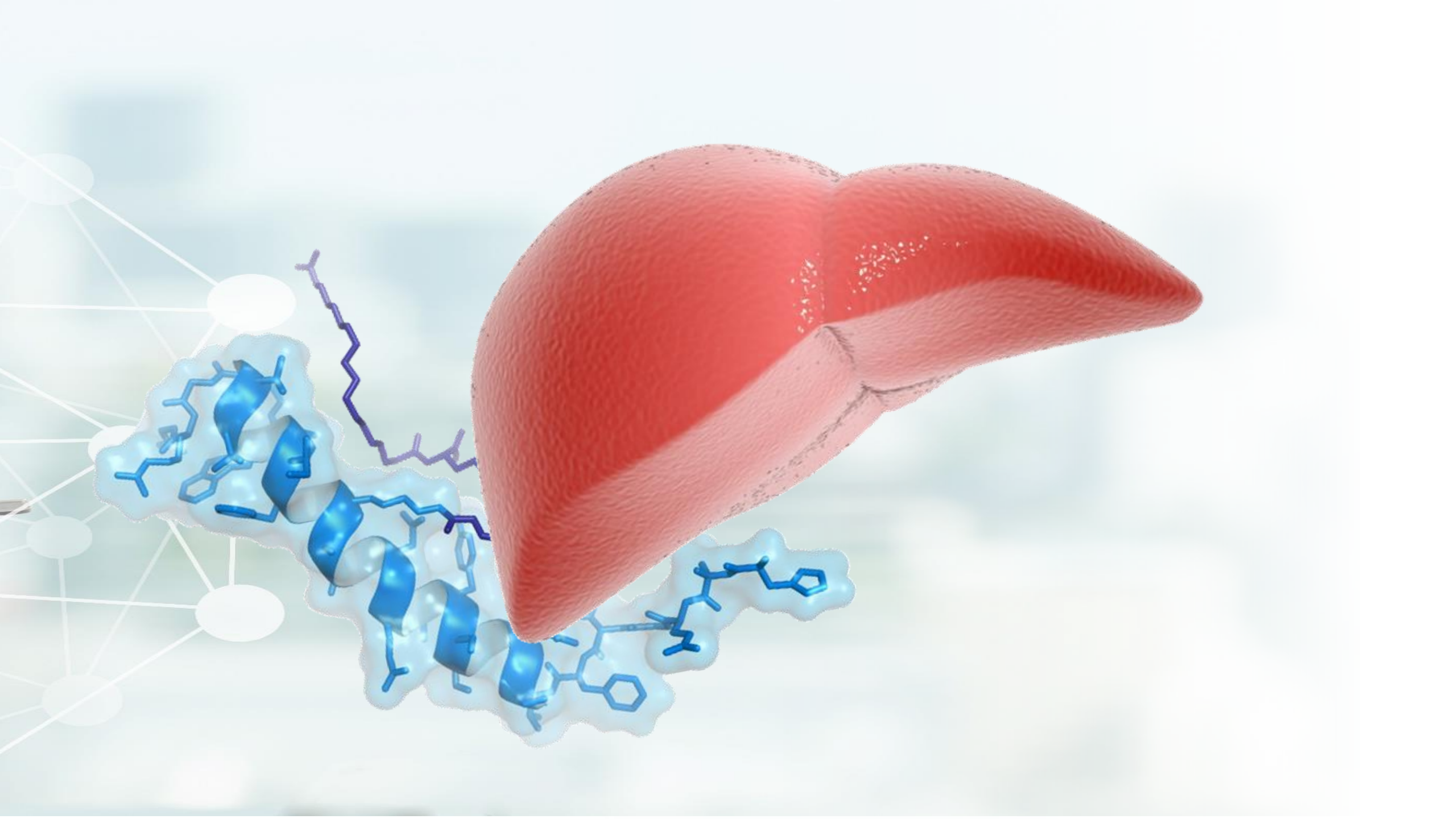
Progression to T2D

Exploratory endpoints

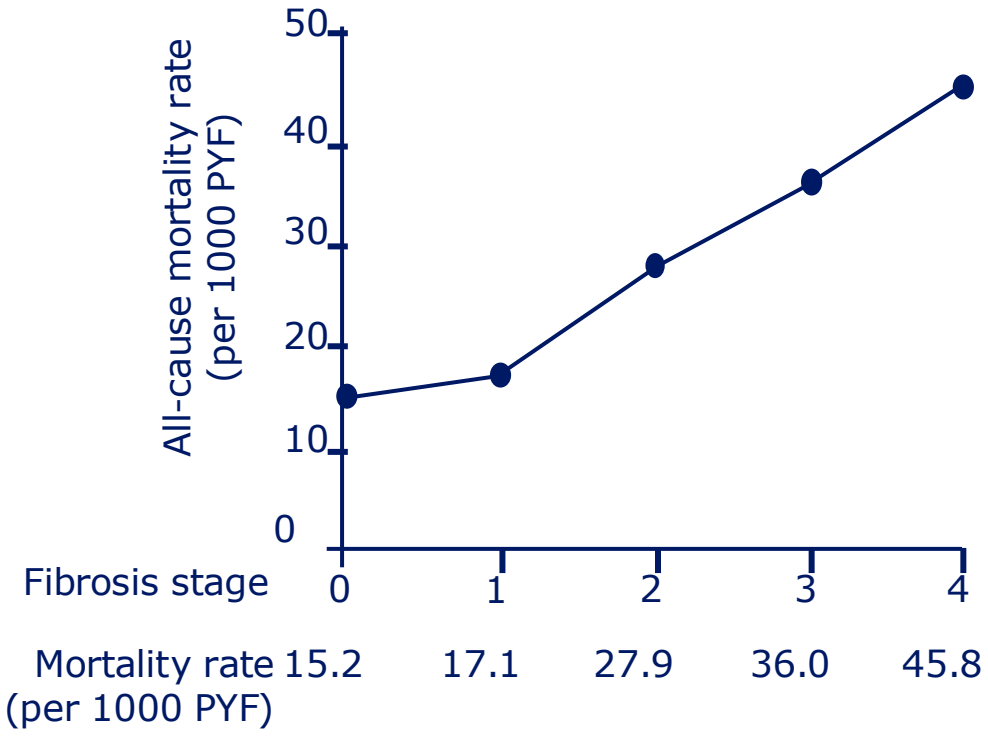


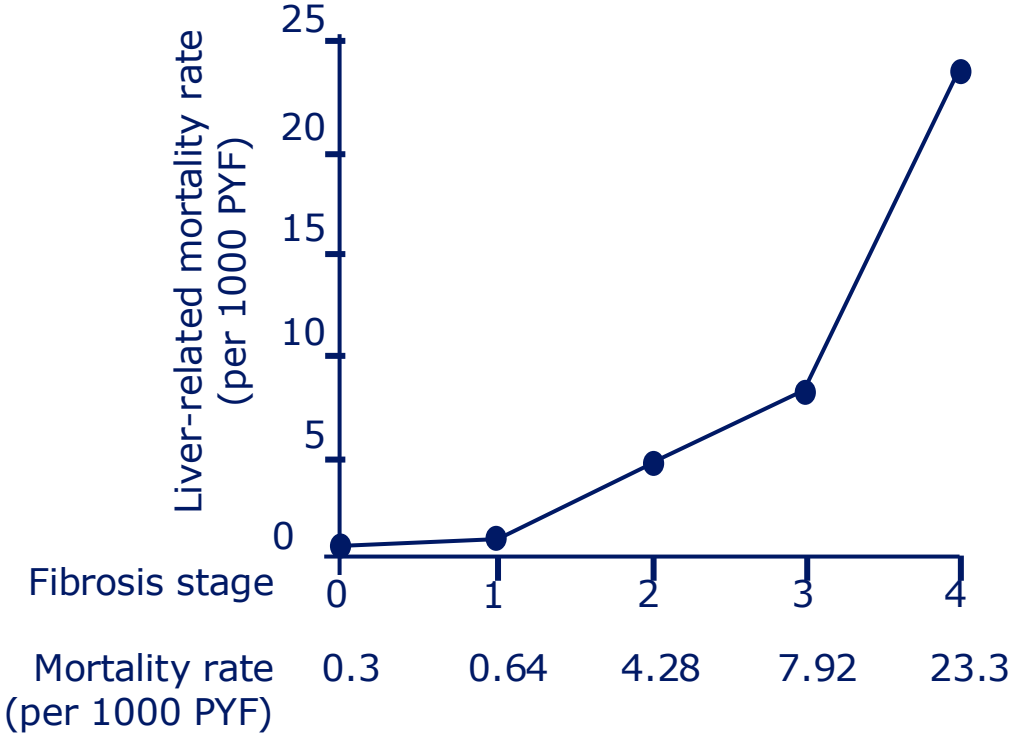
T2D was defined as having HbA_{1c} ≥6.5% and/or FPG ≥7.0 mmol/L verified with a repeated blood sample within 4 weeks. Observed proportions of participants, during the in -trial observation period in the FAS. FAS, full analysis set; FPG, fasting plasma glucose; HbA_{1c} glycated haemoglobin; T2D, type 2 diabetes.
McGowan et al. presented at the 2024 31st European Congress on Obesity, Venice, Italy, 12 –15 May 2024. Abstract AS12.02

McGowan BM et al. *Lancet Diabetes Endocrinol*. 2024;12(9):631-642



Liver fibrosis stage is a predictor of increased mortality





Meta-analysis of 5 studies reporting fibrosis stage-specific mortality, N=1495.
PYF, patient-years of follow-up.
Dulai PS et al. *Hepatology*. 2017;65:1557–65.

MASLD/ MASH

Adults with biopsy-confirmed MASH, fibrosis stage F2–F3 for **semaglutide** 2.4 mg and **tirzepatide** 15 mg; F0–F3 for **liraglutide 3 mg**. BMI ≥25 kg/m² for **semaglutide** 2.4 mg and **liraglutide** 3 mg; BMI ≥27 kg/m² for **tirzepatide** 15 mg, with or without type 2 diabetes; BMI not restricted, and ,with or without type 2 diabetes, for **semaglutide** 2.4.

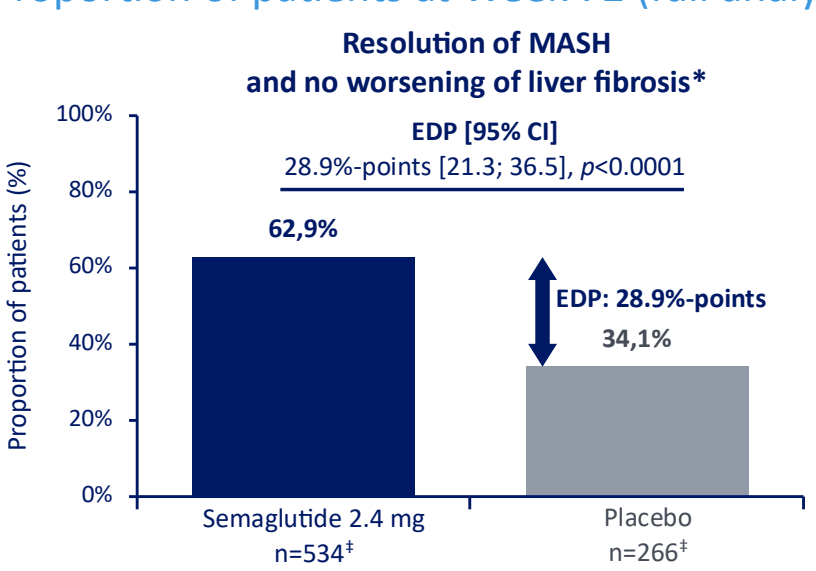
Semaglutide 2.4 mg [54]

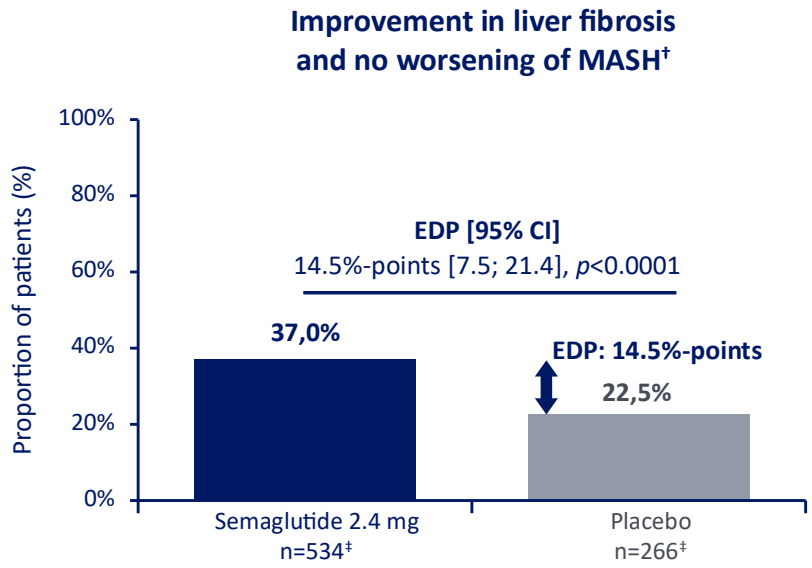
Tirzepatide 15 mg [56]

Liraglutide 3 mg OD[57]

Steatohepatitis resolution and improvement in liver fibrosis

Proportion of patients at Week 72 (full analysis set)





Significantly more patients with MASH F2–F3 treated with semaglutide 2.4 mg achieved **both primary endpoints of MASH resolution (62.9%) and improvement in liver fibrosis (37.0%)** than those treated with placebo **(34.1%, 22.5% respectively)**

*Analysis set: FAS (interim), first 800 randomised subjects. EDP: Estimated difference in responder proportions with 95% confidence interval and two -sided p-value. *Resolution of steatohepatitis is defined as a NAS of 0 -1 for inflammation, 0 for ballooning and any value for steatosis according to NASH CRN. No worsening of liver fibrosis is defined as no increase in fibrosis score. Fibrosis is graded on the NASH CRN fibrosis scale from 0-4. †Improvement in fibrosis is defined as >= 1 grade improvement on the NASH CRN fibrosis scale. No worsening of steat ohepatitis is defined as no increase from baseline in NAS score for ballooning, inflammation or steatosis. The absolute difference between responder proportions, 95% c onfidence interval, P value was generated with the use of Cochran -Mantel-Haenszel (CMH) test stratified by baseline diabetes status (medical history) and fibrosis stage (eligibility read). ‡Missing data were handled by reference -based multiple imputation and Rubin's rule based on the Mantel -Haenszel estimator and Sato's estimate of the standard error (reference) were used to aggregate results. CI, confidence interval; EDP, estimated difference in responder proportions; F, fibrosis stage; MASH, metabolic dysfunction associated steatohepatitis; NASH CRN, Non -Alcoholic Steatohepatitis Clinical Research Network. Newsome PN et al. Oral Presentation at American Association for the Study of the Liver The Liver M eeting; Late Breaker 5018; November 19 2024; San Diego, USA.;*

Sanyal AJ, Newsome PN, Kliers I, et al. Phase 3 Trial of Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis. *N Engl J Med*. 2025;392(21):2089-2099

MASLD/ MASH

Adults with biopsy-confirmed MASH, fibrosis stage F2–F3 for **semaglutide** 2.4 mg and **tirzepatide** 15 mg; F0–F3 for **liraglutide 3 mg**. BMI ≥25 kg/m² for **semaglutide** 2.4 mg and **liraglutide** 3 mg; BMI ≥27 kg/m² for **tirzepatide** 15 mg, with or without type 2 diabetes; BMI not restricted, and ,with or without type 2 diabetes, for **semaglutide** 2.4.

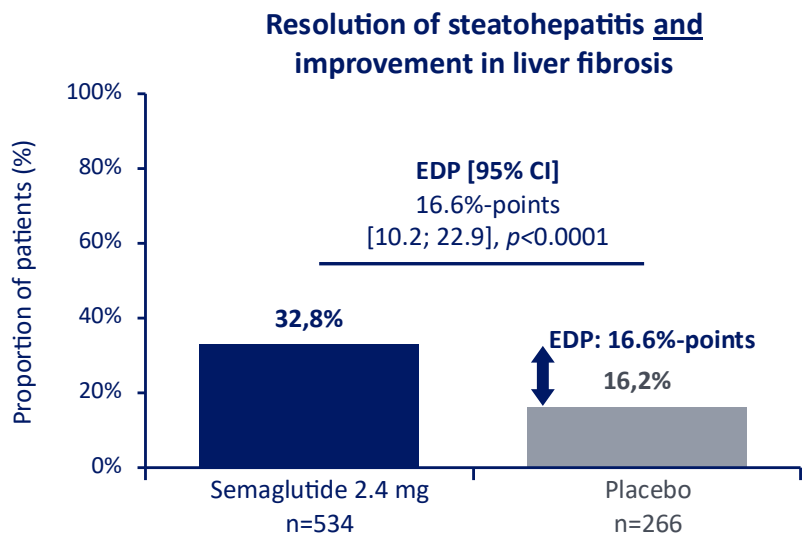
Semaglutide 2.4 mg [54]

Tirzepatide 15 mg [56]

Liraglutide 3 mg OD[57]

FDA Approves Treatment for Serious Liver Disease Known as 'MASH'

Action Will Provide New Therapy for Growing Public Health Issue



Significantly more patients with MASH F2–F3 treated with semaglutide 2.4 mg achieved **resolution of steatohepatitis and improvement in liver fibrosis (32.8%)** than those treated with placebo **(16.2%)**

Analysis set: FAS (interim), first 800 randomised subjects. Metabolic dysfunction-associated steatohepatitis (MASH) was previously known as nonalcoholic steatohepatitis (NASH). EDP: Estimated difference in responder proportions with 95% confidence interval and two -sided p-value. Resolution of steatohepatitis is defined as a NAS of 0 -1 for inflammation, 0 for ballooning and any value for steatosis according to NASH CRN. Improvement in fibrosis is defined as >= 1 grade improvement on the NASH CRN fibrosis scale. NASH CRN: Non -Alcoholic Steatohepatitis Clinical Research Network. The absolute difference between responder proportions, 95% confidence interval, P value was generated with the use of Cochran -Mantel-Haenszel (CMH) test stratified by baseline diabetes status (medical history) and fibrosis stage (eligibility read). Missing d ata were handled by reference-based multiple imputation and Rubin's rule based on the Mantel -Haenszel estimator(reference) and Sato's estimate of the standard error were use d to aggregate results. CI, confidence interval; EDP, estimated difference in responder proportions; F, fibrosis stage; MASH, metabolic dysfunction-associated steatohepatitis; n, number of participants. Newsome PN et al. Oral Presentation at American Association for the Study of the Liver The Liver Meeting; Late Breaker 5018; November 19 2024; San Diego, USA.

Sanyal AJ, Newsome PN, Kliers I, et al. Phase 3 Trial of Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis. *N Engl J Med*. 2025;392(21):2089-2099

OBESITY TREATMENT BASED ON PATIENT PHENOTYPING

FIRST-LINE THERAPY IS LIFESTYLE MODIFICATION (MEDICAL NUTRITIONAL APPROACH AND IMPLEMENTATION OF PHYSICAL ACTIVITY and BEHAVIOUR AL THERAPY)*

EXCLUDE ENDOCRINE FORMS OF OBESITY, if suspected, investigate MONOGENIC FORMS

ASSESSMENT OF THE PRESENCE OF COMPLICATIONS AND PATIENT PHENOTYPING

OBESITY TREATMENT BASED ON PATIENT COMPLICATIONS AND PHENOTYPING

METABOLIC CARDIO RENAL COMPLICATIONS

+ASCVD

Cardiovascular disease was defined as a previous myocardial infarction, previous stroke, or symptomatic peripheral arterial disease in people who are≥ 45 years of age, with a BMI ≥ 27 kg/m².

- Semaglutide 2.4 mg

Naltrexone/ Buproprion (not recommended)[15]

Indicators of High CV Risk:

Definitions vary; most comprise ≥ 40 years of age, BMI ≥ 27 kg/m², male gender, high blood pressure, atherogenic dyslipidemia, smoking, prediabetes, ASCVD risks (ACC/AHA).

- Tirzepatide 15 mg [2,10]
- Semaglutide 2.4 mg [3,4]
- Liraglutide 3 mg [12]

Naltrexone/ Buproprion (not recommended)[15]

HF

Clinical heart failure (NYHA II–IV) with LVEF ≥50% (**tirzepatide**) or ≥45% (**semaglutide**), BMI ≥30 kg/m²), reduced functional capacity (KCCQ-CSS <80 or <90), 6-minute walk ≥100 m, and elevated filling pressures (NT-proBNP, echocardiographic criteria, or recent HF hospitalization). T2D was allied in the tirzepatide trial.

- Tirzepatide 15 mg [11]
- Semaglutide 2.4 mg [5]

Naltrexone/ Buproprion (not recommended) [15]

CKD

eGFR< 60 ml/ min per 1.73 m² OR albuminuria (ACR ≥ 3.0 mg/mmol (30mg/g)

- Semaglutide 2.4 mg[5]
- Tirzepatide 15 mg [11,19]

(use if eGFR>30 ml/min;
If eGFR <30 use with caution due to limited data)

Orlistat (caution in obesity due to risks of nephrolithiasis or AKI)[18]

Naltrexone/ Buproprion (not recommended) [15]

GLYCEMIC CONTROL

PREDIABETES

(**HbA1c** ≥ 5.7% and < 6.5%, FPG > 100 ng/dl < 126 mg/dl, OGTT 120 min glucose ≥ 140 mg/dl < 200 mg/dl)

- Tirzepatide 15 mg [2]
- Semaglutide 2.4 mg [22]
- Liraglutide 3 mg [12,74]
- Orlistat 120 mg [14]

Metformin: off-label; may reduce diabetes incidence [24].

TYPE 2 DIABETES

(**HbA1c** ≥ 6.5% and < 6.5, FPG > 100 ng/dl < 126 mg/dl, OGTT 120 min glucose ≥ 140 mg/dl < 200 mg/dl)

- Tirzepatide 15 mg [11]
- Semaglutide 2.4 mg [29]
- Liraglutide 3 mg [33]

SGLT2is support weight loss [37,38,39,40,41], if glycemic control allows, insulin[44,45], thiazolidinediones, and sulfonylureas should be avoided [203]

TYPE 1 DIABETES

(OFF-LABEL only for weight loss purposes)

- Tirzepatide 15 mg [52]
- Semaglutide 2.4 mg [51]

MASH/MASLD

Adults with biopsy-confirmed MASH, fibrosis stage (F2–F3) for **semaglutide** 2.4 and **tirzepatide** 15 mg, F0-F3 for **liraglutide** 3 mg , BMI ≥25 kg/m² for **semaglutide** 2.4 mg and **liraglutide** 3 mg . BMI ≥27 kg/m² for **tirzepatide** 15 mg; with or without type 2 diabetes but not for semaglutide 2.4.

- Semaglutide 2.4 mg [4]
- Tirzepatide 15 mg [55]
- Liraglutide 3 mg OD [57]

MECHANICAL COMPLICATIONS

OSTEOARTRITIS

Adults ≥18 years with BMI ≥30 kg/m², clinically and radiographically confirmed knee osteoarthritis (ACR criteria; Kellgren–Lawrence grade 2–3), and baseline knee pain ≥40/100 on the WOMAC pain scale.

- Semaglutide 2.4 mg [63]
- Tirzepatide 15 mg (NCT01985165)
- Orlistat 120 mg [14]
- Naltrexone/bupropione[64]
- Phentiramine/Topiramate[26]

OSAS

Adults ≥18 years, BMI ≥30 kg/m², with moderate-to-severe obstructive sleep apnea (AHI ≥15 events/hour); CPAP use allowed (tirzepatide) or excluded (liraglutide); no diagnosis of T2D.

- Tirzepatide 15 mg [68]
- Liraglutide 3 mg [69]
- Phentiramine/Topiramate[70]

WEIGHT LOSS TARGETS /OWCMC**

Set individualized weight management goals

5-10% WL

- Orlistat[14]
- Liraglutide 3 mg[74]
- Naltrexone/ Bupropion[27]
- Phentermine/Topiramate (low-mid doses)[60]

10-20% WL

- Tirzepatide 5 mg[2]
- Semaglutide 2.4mg[3]
- Phentermine/Topiramate (low-mid doses)[26]

>20% WL

- Tirzepatide 15mg[2]
- Semaglutide 7.2 mg[77] (not available yet)
- Cagrisema[78] (not available yet)

AGE

≥ 2 y.o.[104]
Setmelanotide (rare genetic obesity)
Metreleptin (rare genetic obesity)

6-12 y.o.
Liraglutide 3mg[109] (EMA only)

12-18 y.o.
Liraglutide 3mg[112]
Semaglutide 2.4mg[113]
Phentermine/ Topiramate[111] (FDA only)
Orlistat 120 mg[114] (FDA only)

18-65 y.o.
Phenotype-driven tailored decision:
Tirzepatide 15 mg
Semaglutide 2.4 mg
Liraglutide 3 mg
Naltrexone/Bupropion[27,28]
Phentermine/Topiramate[26]
Orlistat[14]

>65 y.o.
Semaglutide 2.4 mg[3] (Usable; no dose adjustment needed)
Tirzepatide 15 mg[2] (Usable; monitor sensitivity in elderly)
Liraglutide 3 mg[12,74] (Usable; limited data >75 yrs)
Naltrexone/Bupropion[27] (Caution; limited data ≥65 yrs)
Phentermine/Topiramate[26] (Caution; monitor CNS/renal)
Orlistat[14] (Usable; limited efficacy data)

Sarcopenic obesity
Supervised Resistance Training + Protein Intake ≥1.2–1.5 g/kg/day [118]
Liraglutide 3 mg is preferred for gradual weight loss with lean mass preservation and proven cardiovascular safety[33]

EATING BEHAVIOUR

EMOTIONAL EATING

- Bupropion / Naltrexon[28]
- Tirzepatide 15 mg
- Semaglutide 2.4 mg[125]

BINGE EATING

Not AOMs approved explicitly for binge eating disorder.

- Liraglutide 3.0 mg[123]
- Phentermine/ Topiramate[128]
- Naltrexone/Bupropion[28]
- Orlistat 120 mg[129]
- Semaglutide 2.4 mg[125]
- Tirzepatide 15 mg[128,134]

SPECIAL POPULATIONS

CANCER safety

No significant increase in thyroid cancer risk from obesity related RCT
Semaglutide 2.4 mg[143]
Tirzepatide 15 mg[143]

Evidence from meta-analysis suggests long-term GLP-1 RA use may increase thyroid cancer risk in mixed T2D populations.[145]

No evidence of increased cancer risk (for other AOMs: **Orlistat, Phentermine/Topiramate, Bupropion/Naltrexone**

Familial Partial Lipodystrophy 1-3 (FPLD1-3)
Acquired Partial Lipodystrophy (Barraquer-Simons)
HIV-Associated Lipodystrophy
Semaglutide 2.4 mg[152]

MONOGENIC OR SYNDROMIC OBESITY
Congenital leptin deficiency
Metreleptin[153]
(biallelic POMC, PCSK1, or LEPR deficiency and for BBS)
Setmelanotide 3 mg[154]

ACQUIRED HYPOTALAMIC OBESITY
Setmelanotide 3 mg[154]
Semaglutide 2.4 mg[155]

PREGNANCY/WILLINGNESS TO CONCEIVE

AOMs are either contraindicated or advised against during pregnancy due to insufficient safety data and potential risks to the fetus

Stop **Liraglutide 3 mg/Semaglutide 2.4 mg** at least 2 months before

Stop **Tirzepatide 15 mg** at least 1 month before

COSTS /QALY

BS
176, 177

If additional weight loss and reduction of weight-related complications are needed

Bariatric Surgery[177]

If insufficient weight loss or weight regain after BS consider: Tirzepatide[197], Semaglutide[194], Liraglutide[195,196]

*This framework promotes a phenotype-based, individualized approach to obesity care, prioritizing complications and patient preferences over rigid treatment hierarchies, with patient-HCP shared decision-making considering goals, tolerability, contraindications, and cost. **OWCMC, obesity without clinically manifest complications

Tuccinardi D, et al. *J Endocrinol Invest* **48**, 2761–2798 (2025)