Obésité, troubles respiratoires du sommeil, insuffisance cardiaque : de nouveaux traitements

60 % des européens sont en surpoids (IMC entre 25 et 29,9 kg/m² ou obèses (IMC ≥ 30 kg/m²)

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Service de Cardiologie
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2025

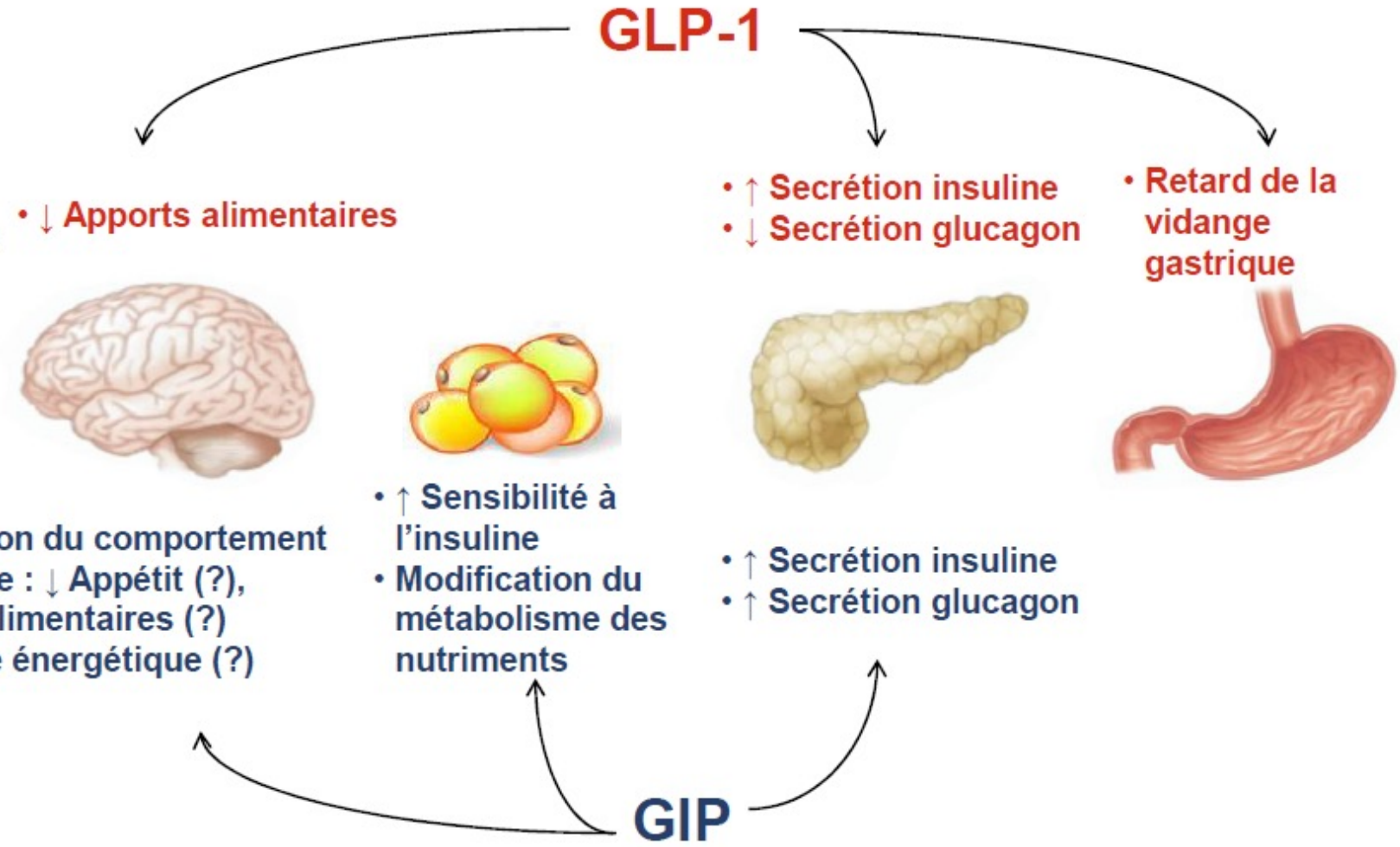
Obésité et troubles respiratoires du sommeil

- La prévalence du SAS obstructif augmente proportionnellement à l'IMC
- 58 % des obèses ont un SAS osbtructif
- Au moins 50 % des patients atteints de SAS obstructif sont obèses
- Les graisses accumulées au niveau du cou, du pharynx et de la ceinture abdominale favorisent l'apparition d'un SAS obstructif
- Les nuit perturbées modifient les mécanismes hormonaux (↑ sécrétion de ghréline et ↓ sécrétion de leptine) régulant la faim et la satiété, modifiant les comportements alimentaires et favorisant la prise de poids
- Après chirurgie bariatrique : amélioration ou guérison des symptômes du SAS obstructif dans 79 à 99 % des cas

Traitement médical du SAS obstructif - Tirzépatide

Intérêt d'un double agonisme des récepteurs du GIP et GLP-1

- Le GLP-1 semble avoir des effets directs sur le SNC, les ilôts pancréatiques et l'estomac[1,2]
- Le GIP a une action potentielle sur le SNC, le tissu adipeux et les ilôts pancréatiques (travaux en cours)[2,3,4]



1. Müller TD, et al. *Mol Metab*. 2019;30:72-130. 2. Seino Y, et al. *J Diabetes Investig*. 2010;1)1-2):8-23. 3. Fukuda M. *Diabetes*. 2021;70(8):dbi210001. 4. Nauck MA, et al. *Diabetes Obes Metab*. 2021 (Ahead of Print). DOI: 10.1111/dom.14496. 5. Samms RJ, et al. *Trends Endocrinol. Metab*. 2020;31(6):410-421. 6. Bastin M, et al. *Diabetes Metab Syndr Obes*. 2019;12:1973-1985.
SNC = système nerveux central; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1.

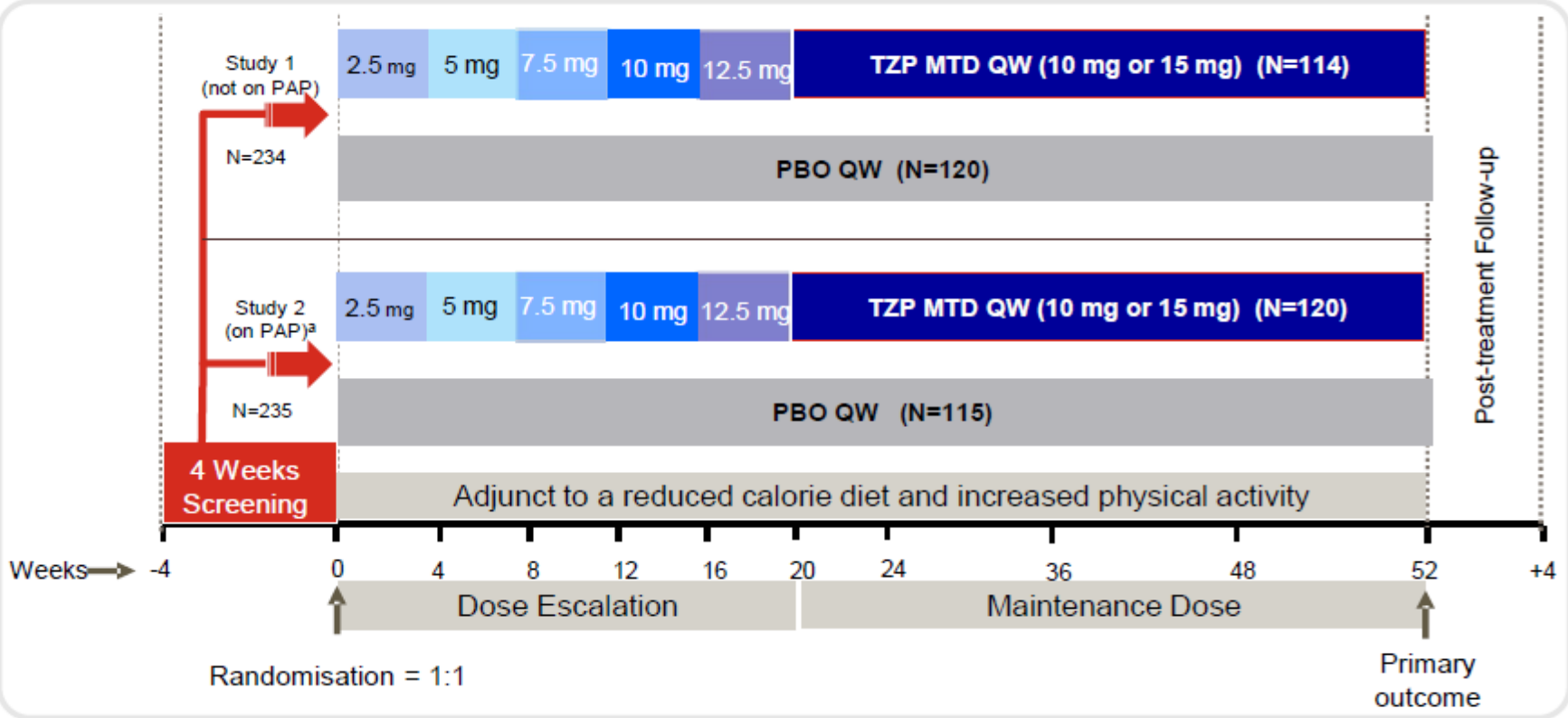
SURMOUNT-OSA Trial : study design

Phase 3, 52-week, randomised, double-blind, placebo-controlled master protocol to evaluate the efficacy and safety of TZP at the MTD (10 or 15 mg) vs. placebo as an adjunct to diet and exercise in participants with moderate-to-severe OSA (AHI ≥15 events/hour) and obesity (BMI ≥30 kg/m^2) without T2D[1-3]

Hypothesis:

TZP in people with OSA and obesity will yield important improvements in OSA severity as assessed by the AHI[1,2]

US, Australia, Brazil, China, Czechia, Germany, Japan, Mexico and Taiwan[3]



[a]Participants in Study 2 were instructed to suspend PAP therapy for 7 days prior to PSG and PRO assessments at baseline, week 20, and week 52.

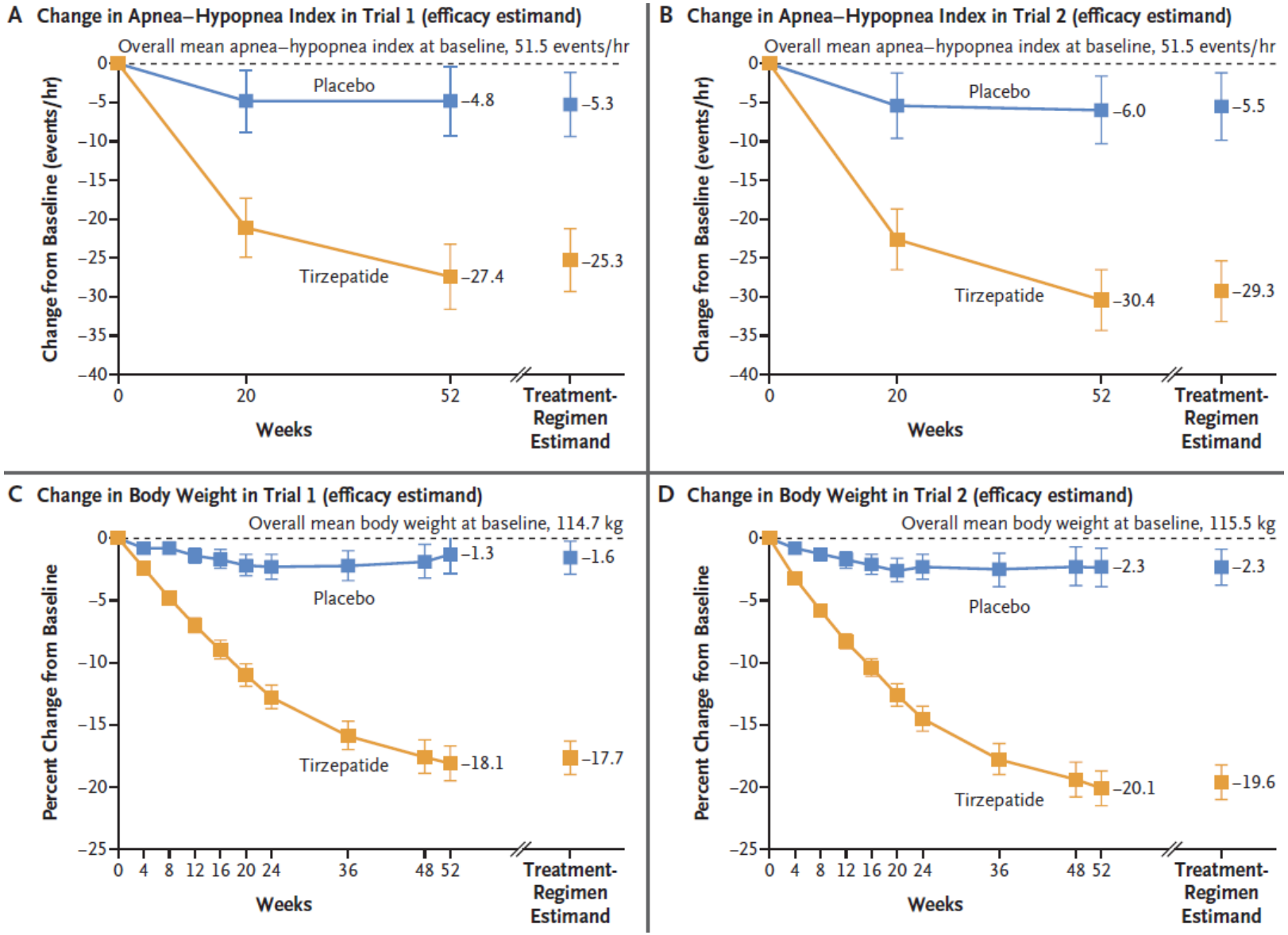
AHI=Apnoea-Hypopnoea Index; BMI=Body Mass Index; MTD=Maximum Tolerated Dose; OSA=Obstructive Sleep Apnoea; PAP=Positive Airway Pressure; PBO=Placebo; PRO=Patient Reported Outcomes; PSG=Polysomnography; QW=Once Weekly; R=Randomization; T2D=Type 2 Diabetes; TZP=Tirzepatide.

1. Malhotra A, et al. 2024;141:107516. 2. https://clinicaltrials.gov/study/NCT05412004 (Accessed April 15, 2024). 3. Malhotra A, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2404881 (Ahead of Print).

Tirzepatide for treatment of obstructive sleep apnea and obesity : SURMOUNT-OSA trial

Patients without PAP

Patients with PAP



Malhotra A, et al. N Engl J Med 2024;391(13):1193-1205

SURMOUNT-OSA Summary

SURMOUNT-OSA

- **SURMOUNT-OSA included two Phase 3 double-blind, randomised, placebo-controlled studies: Study 1 - participants not on PAP therapy; n=234; Study 2 - participants on PAP therapy; n=235**
- **Adults with moderate-to-severe OSA and obesity demonstrated a significant and clinically relevant[a] decrease in AHI with TZP treatment compared to PBO**
- **TZP demonstrated significant improvement in AHI, BW, sleep-related patient-reported outcomes[b], hsCRP, SBP and SASHB in participants with moderate-severe OSA and obesity**
- **The safety and tolerability profile of TZP in participants with moderate-to-severe OSA and obesity was consistent with the safety profile of TZP reported in previous trials**
- **The most frequent adverse events were gastrointestinal-related and were mild to moderate**

[a]According to the AASM, a clinically significant threshold for AHI is defined as ≥15 events/hour.
[b]Includes pooled analysis of PROMIS Sleep-Related Impairment and PROMIS Sleep Disturbance.
AASM=American Academy of Sleep Medicine;AHI=Apnoea-Hypopnoea Index; BW=Body Weight; hsCRP=High-Sensitivity C-reactive Protein; OSA=Obstructive Sleep Apnoea; PAP=Positive Airway Pressure; SASHB=Sleep Apnoea Specific Hypoxic Burden; SBP=Systolic Blood Pressure; TZP=Tirzepatide.
Malhotra A, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2404881 (Ahead of Print).

GLP-1R and GIP agonist in heart failure with preserved EF and obesity

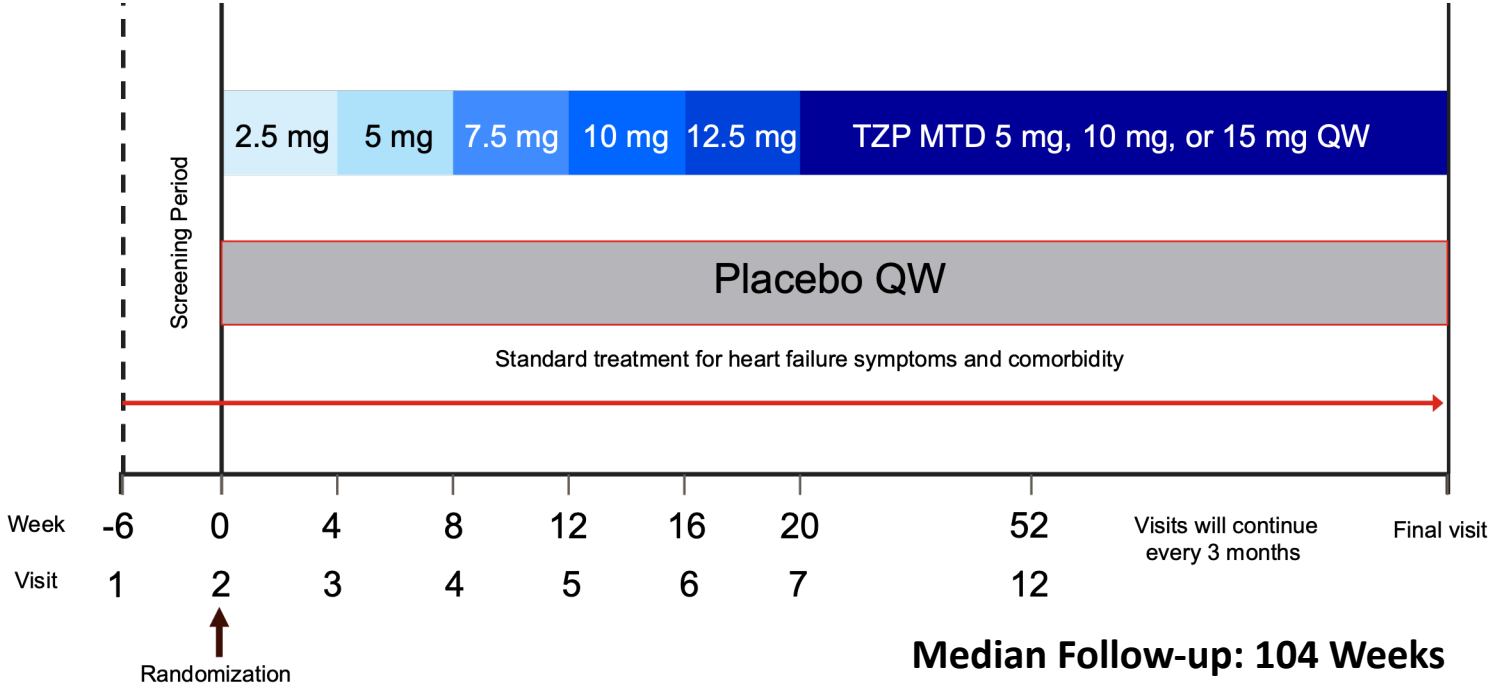
SUMMIT Trial Design

SUMMIT is a multicentre, randomised, double-blind, parallel, placebo-controlled Phase 3 study. It aimed to determine the efficacy and safety of once-weekly tirzepatide in participants with HFpEF and obesity, with or without type 2 diabetes[a].

Participants Enrolled: 731 Participants

Participating Countries

United States, Argentina, Brazil, China, India, Israel, Mexico, Puerto Rico, Russia, and Taiwan[3]



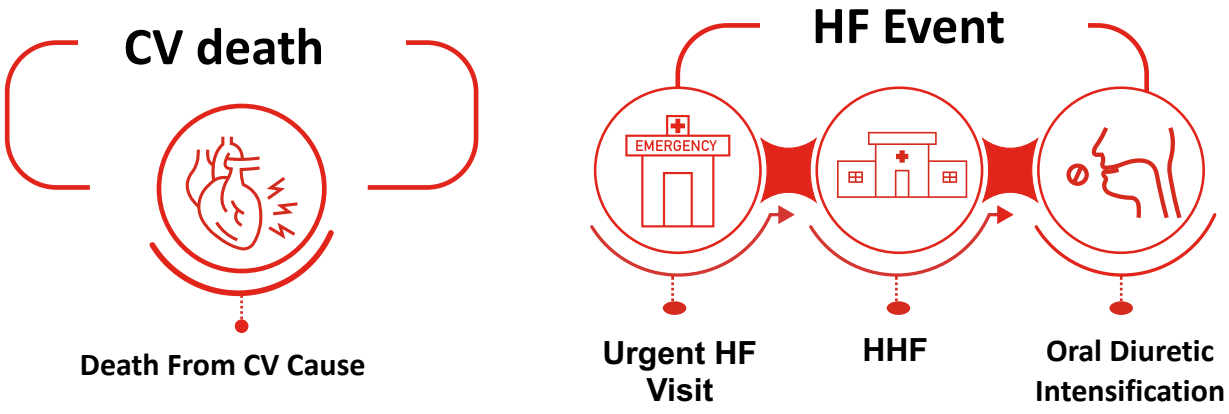
Median Follow-up: 104 Weeks

- [a]Participants with HbA1c <9.5%.
- HbA1c=Glycated Haemoglobin; HFpEF=Heart Failure With Preserved Ejection Fraction; MTD=Maximum Tolerated Dose; QW=Once Weekly; TZP=Tirzepatide.
- https://clinicaltrials.gov/ct2/show/NCT04847557 (Accessed July 07, 2024).

SUMMIT results : dual primary endpoints

Time to First Occurrence of HF Outcomes

Composite Endpoint



Occurrence of the Composite Event of CV Death and/or HF Event During the Study

Results

↓ 38% RR

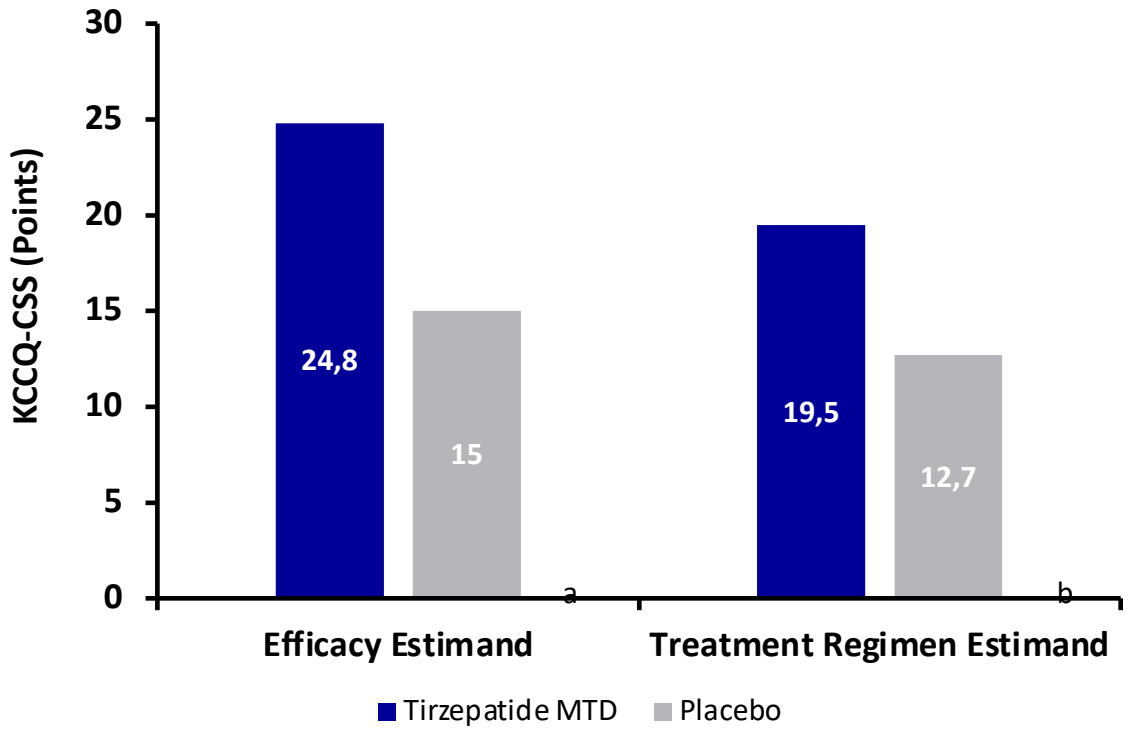
Time-to-first occurrence of HF outcomes
(median follow-up of 104 weeks)

Hazard Ratio=0.62
95% CI: 0.41-0.95; *P*=.026

- CI=Confidence Interval; CV=Cardiovascular; HF=Heart Failure; HHF=Hospitalisation for Heart Failure; RR=Relative Risk Reduction.
- https://investor.lilly.com/news-releases/news-release-details/lillys-tirzepatide-successful-phase-3-study-showing-benefit (Accessed August 01, 2024).

SUMMIT results : dual primary endpoints

Change in KCCQ-CSS from baseline to week 52



Treatment with tirzepatide significantly improved heart failure symptoms and physical limitations.

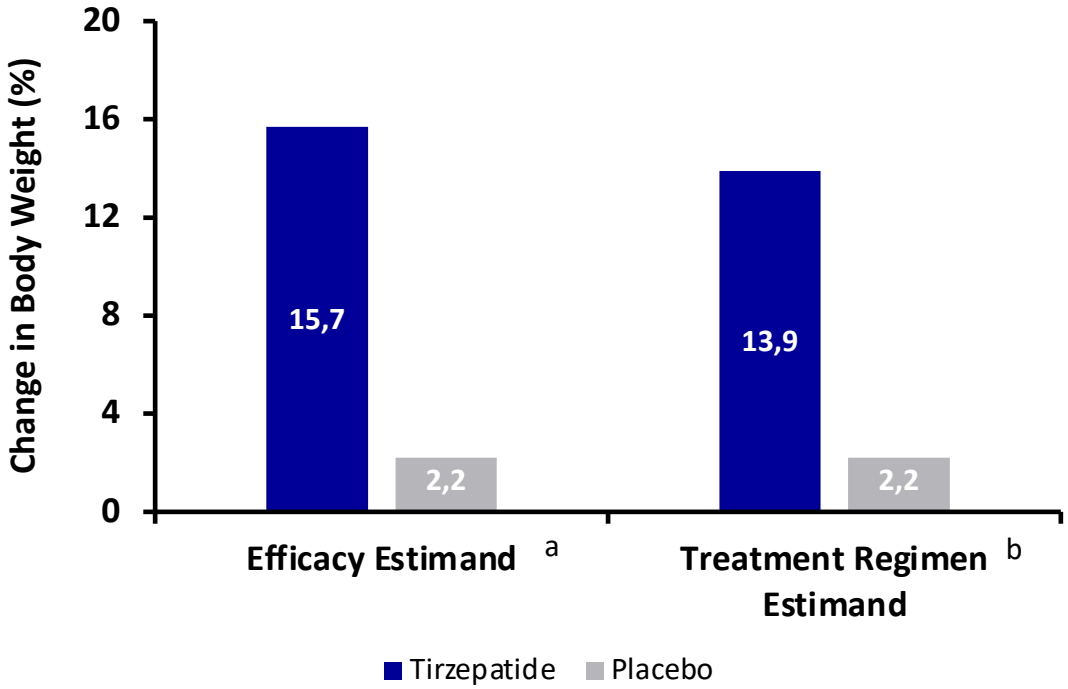
- [a]The efficacy estimand represents efficacy prior to discontinuation of the study drug. [b]The treatment-regimen estimand represents the estimated average treatment effect regardless of treatment discontinuation.
- KCCQ-CSS=Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score; MTD=Maximum Tolerated Dose.
- https://investor.lilly.com/news-releases/news-release-details/lillys-tirzepatide-successful-phase-3-study-showing-benefit (Accessed August 01, 2024).

SUMMIT results

Overview of key secondary endpoints

All Key Secondary Endpoints Were Met

- Exercise capacity was improved, as measured by the 6MWD test, from baseline to Week 52
- Inflammation marker hsCRP was reduced from baseline to Week 52
- Mean body weight was reduced from baseline to Week 52



The most frequently reported adverse events were gastrointestinal, diarrhea, nausea, constipation, vomiting, mild to moderate in severity

- [a]The efficacy estimand represents efficacy prior to discontinuation of the study drug. [b]The treatment-regimen estimand represents the estimated average treatment effect regardless of treatment discontinuation.
- hsCRP=High-Sensitivity C-Reactive Protein; MTD=Maximum Tolerated Dose; 6MWD=Six-Minute Walk Distance.
- https://investor.lilly.com/news-releases/news-release-details/lillys-tirzepatide-successful-phase-3-study-showing-benefit (Accessed August 01, 2024).

GLP-1R agonist in heart failure with preserved EF and obesity

STEP-HFpEF trial design

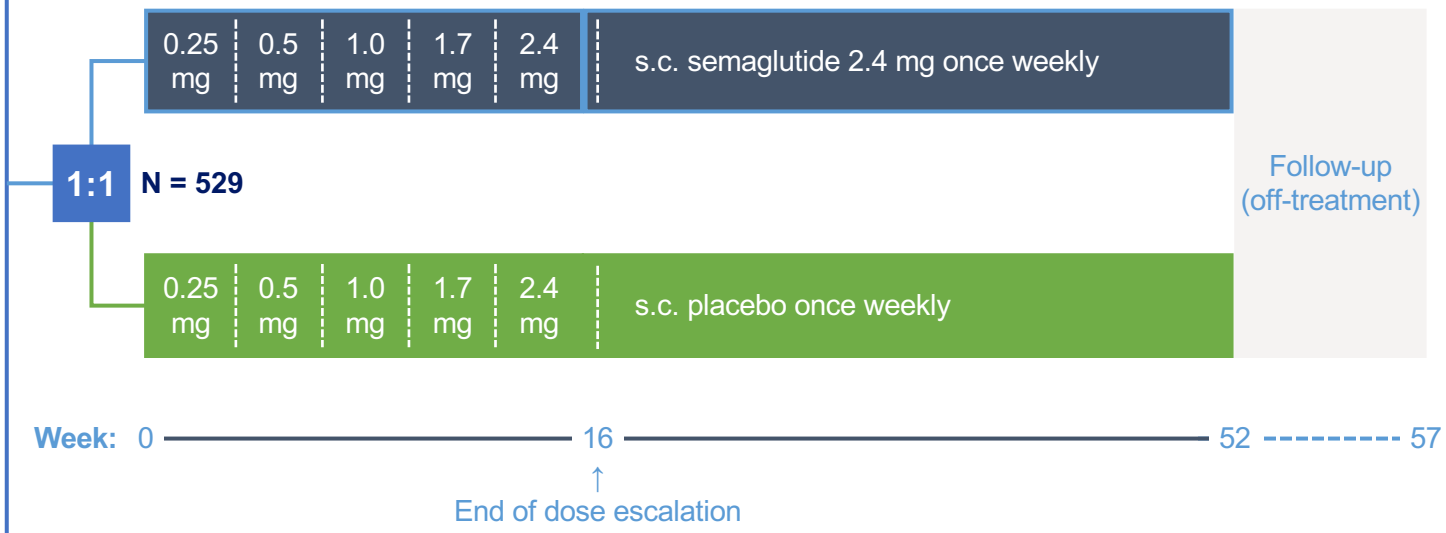
Key inclusion criteria

- Age ≥18 years old, LVEF ≥45%, BMI ≥30 kg/m^2, NYHA FC II-IV symptoms, KCCQ-CSS <90 points, 6MWD ≥100 m
- Evidence of HFpEF based on ≥1 of the following:
  - Elevated LV filling pressures;
  - Elevated natriuretic peptide levels plus echocardiographic abnormalities;
  - HF hospitalization (12 months prior to screening)
  - Ongoing diuretic therapy or echocardiographic abnormalities

Key exclusion criteria

- HbA_{1c} ≥6.5% and self-reported change in body weight >5 kg within 90 days of screening

529 pts, mean age 69 yrs, 56% women, mean BMI 37 (105 kg), without diabetes

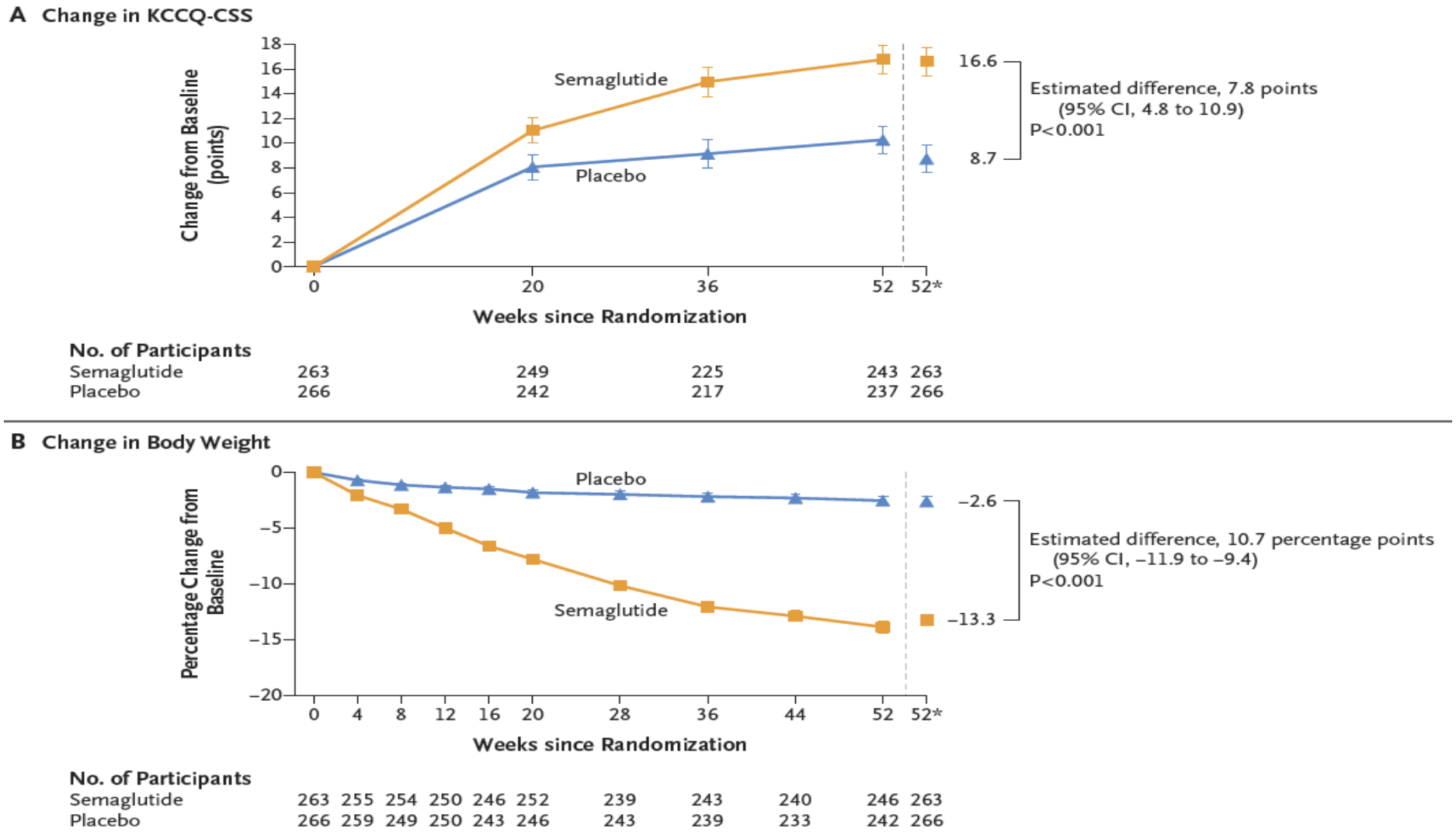


Trial information

- 52-week, randomized, double-blind, placebo-controlled, trial conducted at 83 sites in 13 countries in Asia, Europe, North and South America
- Once-weekly s.c. semaglutide was initiated at 0.25 mg and escalated to 2.4 mg (maintenance dose) by week 16
- A sample size of 516 provided a marginal power of 90% to detect a difference of 4.1 points for change in KCCQ-CSS and 99% to detect a difference of 9.9% for change in body weight between semaglutide and placebo (alpha level of 4% and 1%, respectively)

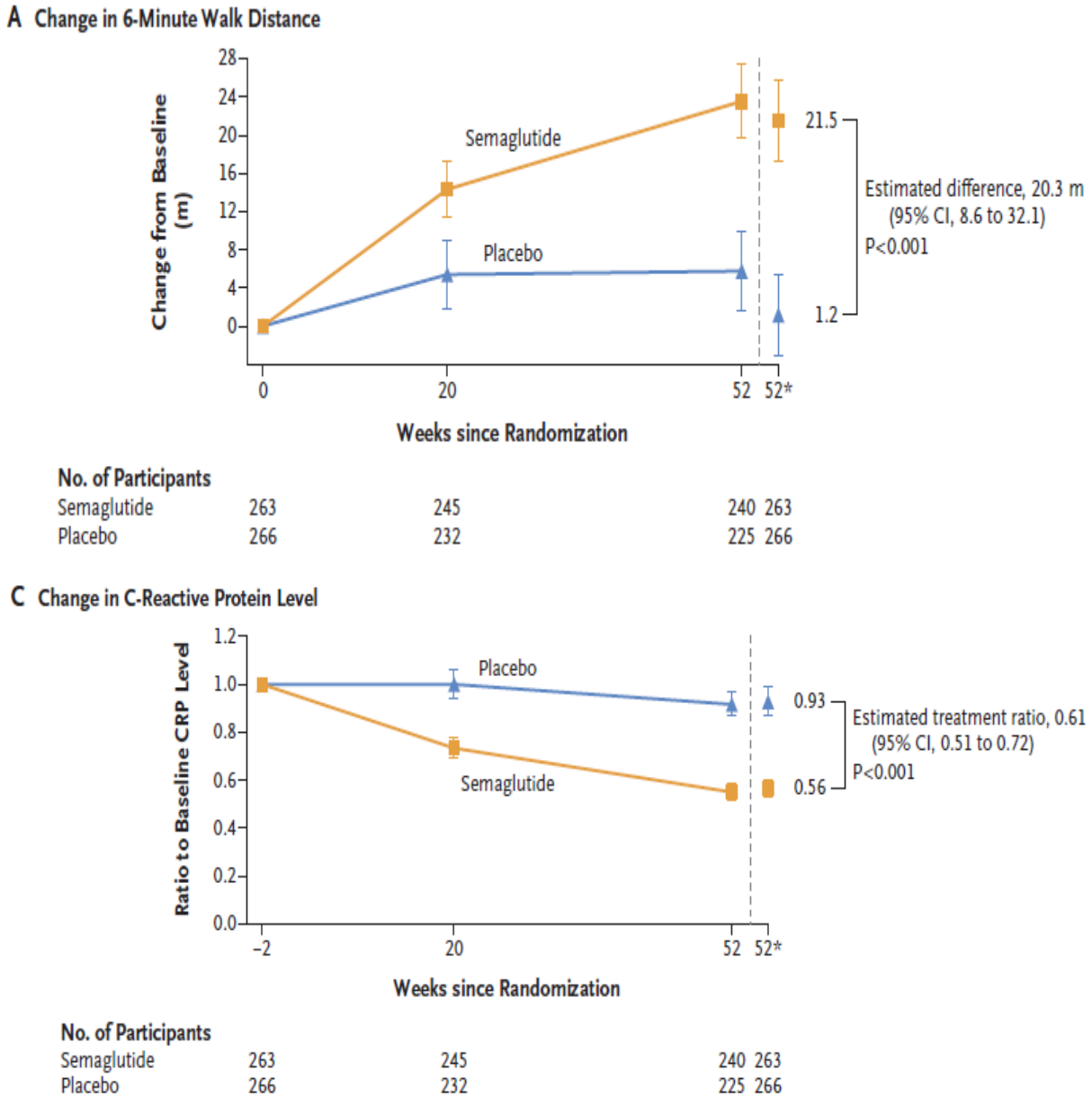
6MWD, 6-minute walk distance; BMI, body mass index; HbA1c, glycated hemoglobin; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; LV, left ventricle; LVEF, left ventricular ejection fraction; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire – clinical summary score; NYHA FC, New York Health Association Functional Class; s.c., subcutaneous.

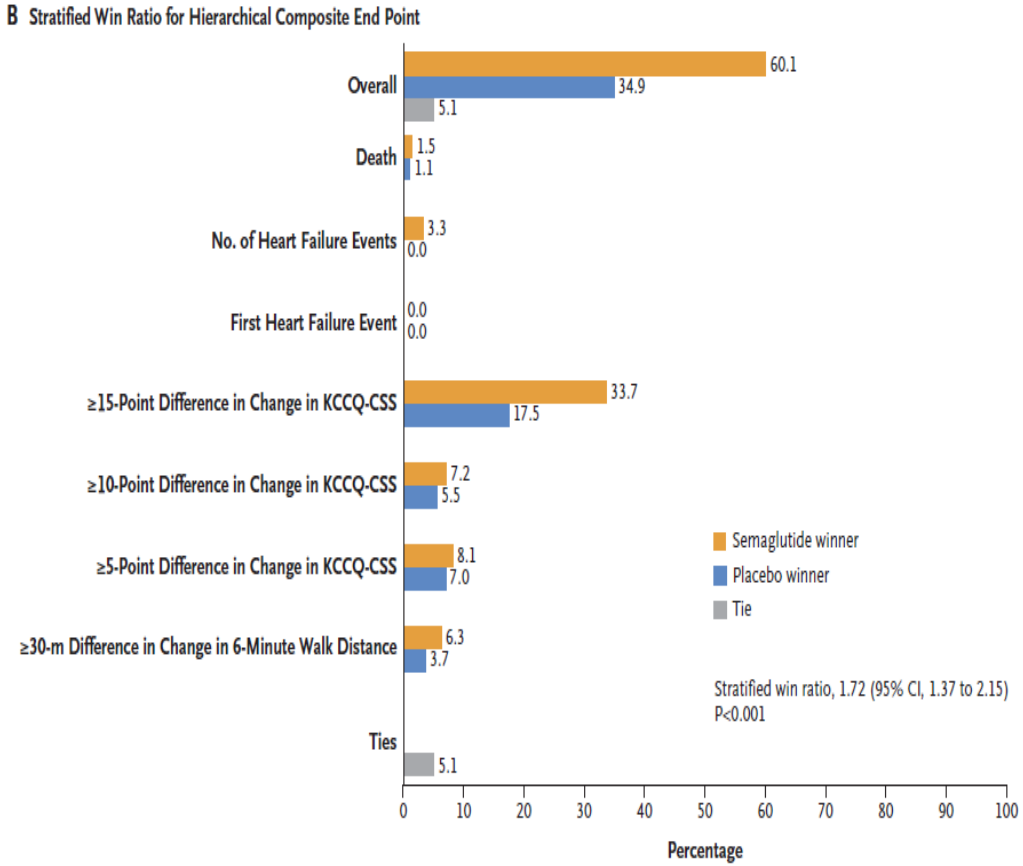
STEP-HFpEF Results : dual primary endpoint



Kosiborod MN, et al. N Engl J Med 2023;389(12):1069-1084

STEP-HFpEF Results : secondary endpoints





% reduction in NT-proBNP from baseline to week 52 :
HR = 0,84; 95 % CI = 0,71-0,98

Kosiborod MN, et al. N Engl J Med 2023;389(12):1069-1084

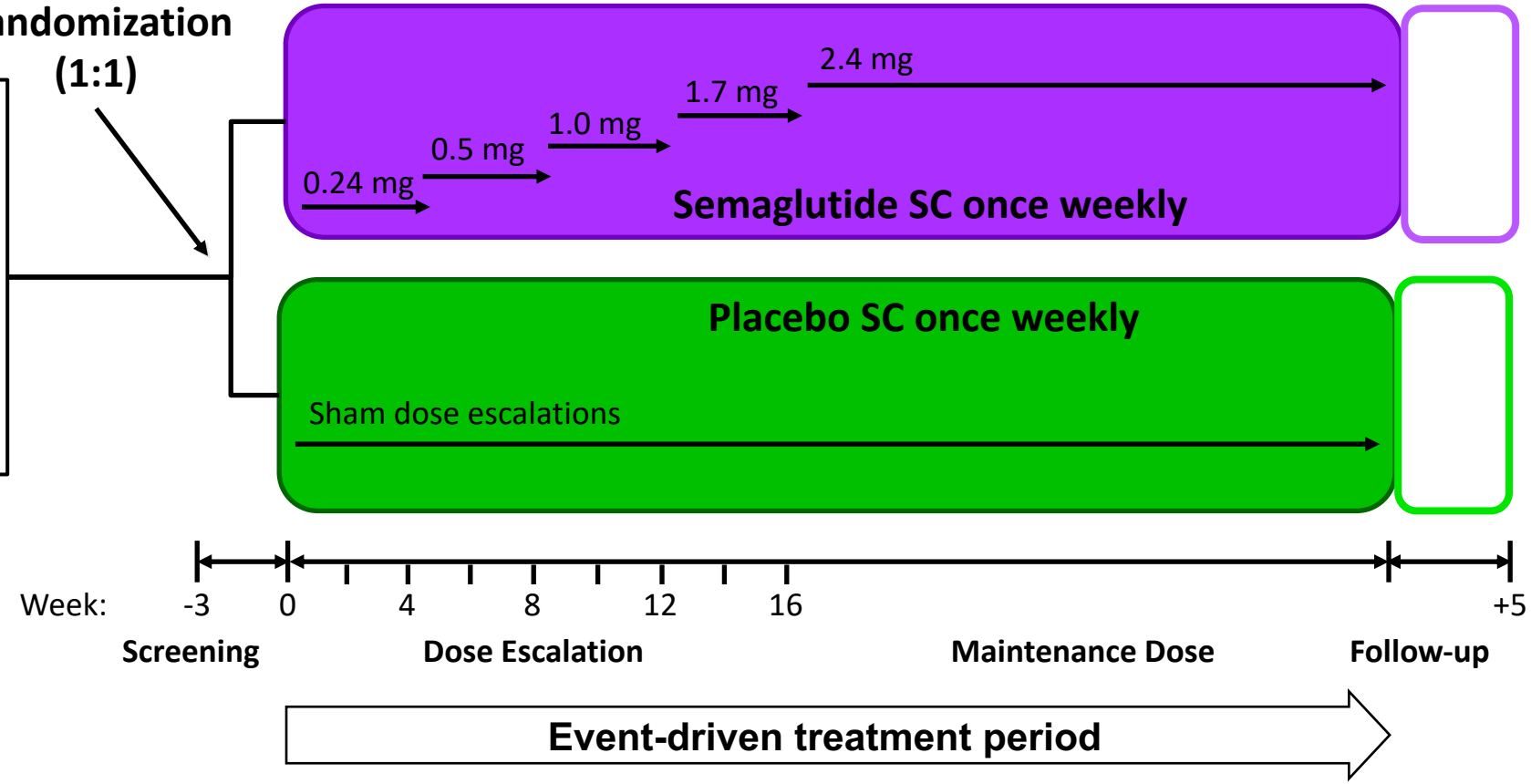
GLP-1R agonist in patients with overweight or obesity and cardiovascular disease without diabetes

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

SELECT Trial Design

- Overweight or obesity
  BMI ≥ 27 kg/m^2
- Established CVD
- No prior diabetes
  HbA_{1c} < 6.5%
- Age ≥ 45 yrs

Randomization (1:1)



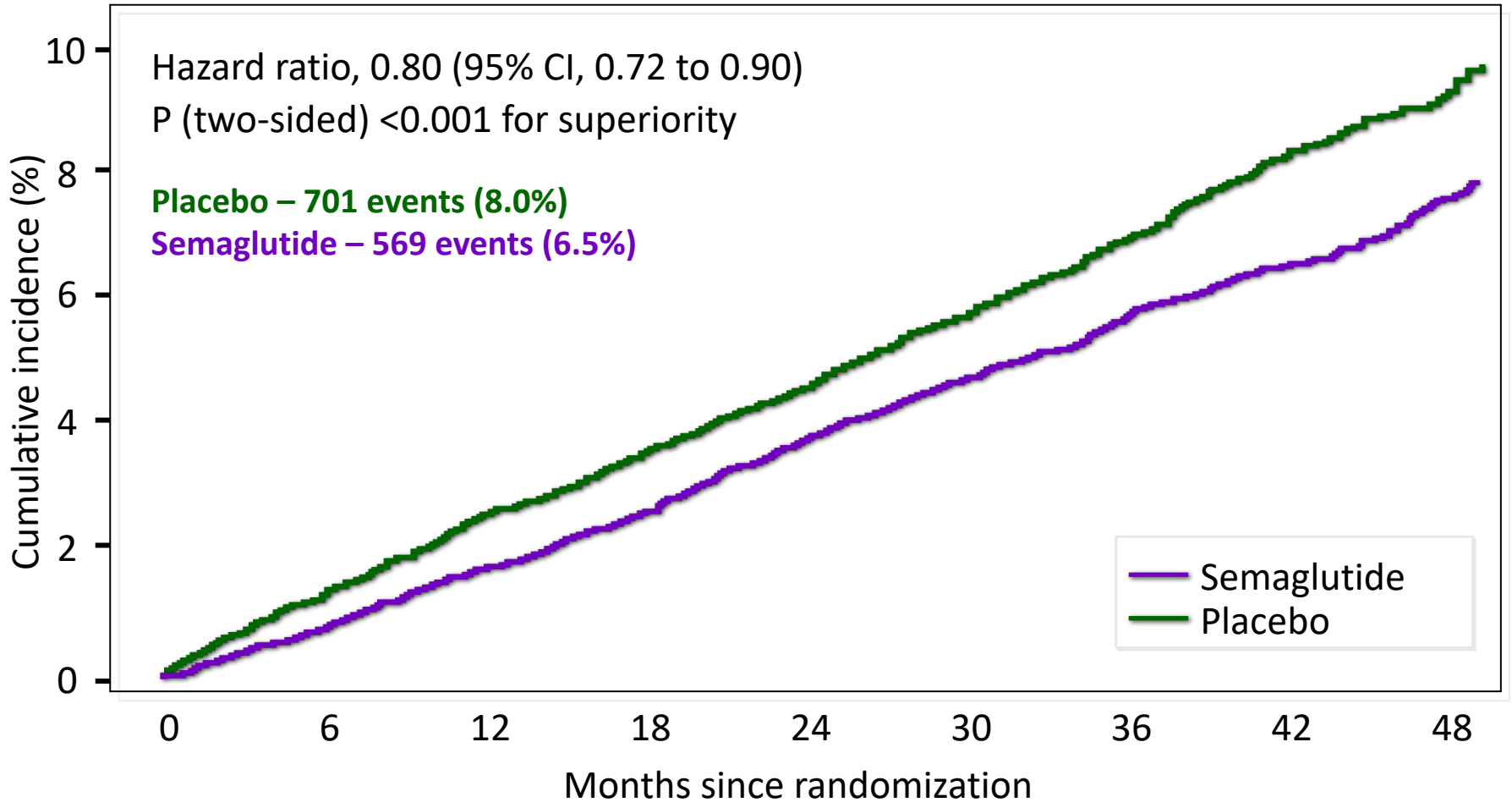
17604 pts, mean age 62 yrs, 28% women, mean BMI 33,3, prior MI 77,3 %, prior HF 24,4 %

- Trial product added to standard of care for underlying CV disease
- Dose reductions or treatment pauses permitted
- Rx for pts who developed diabetes per investigator, except open label GLP-1RA

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

CV Death, Nonfatal MI, or Nonfatal Stroke

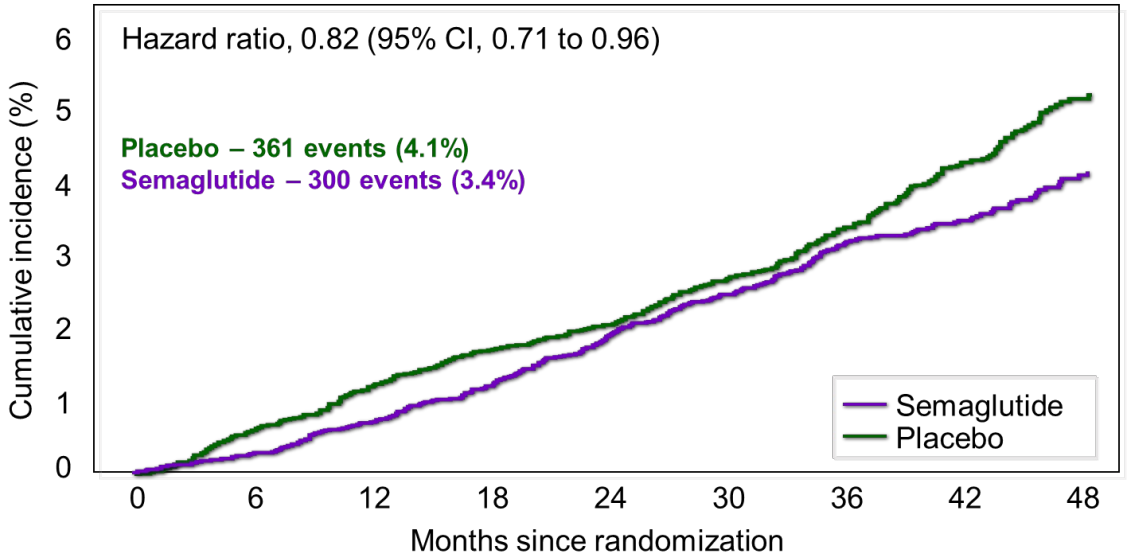
Primary Cardiovascular Composite Endpoint



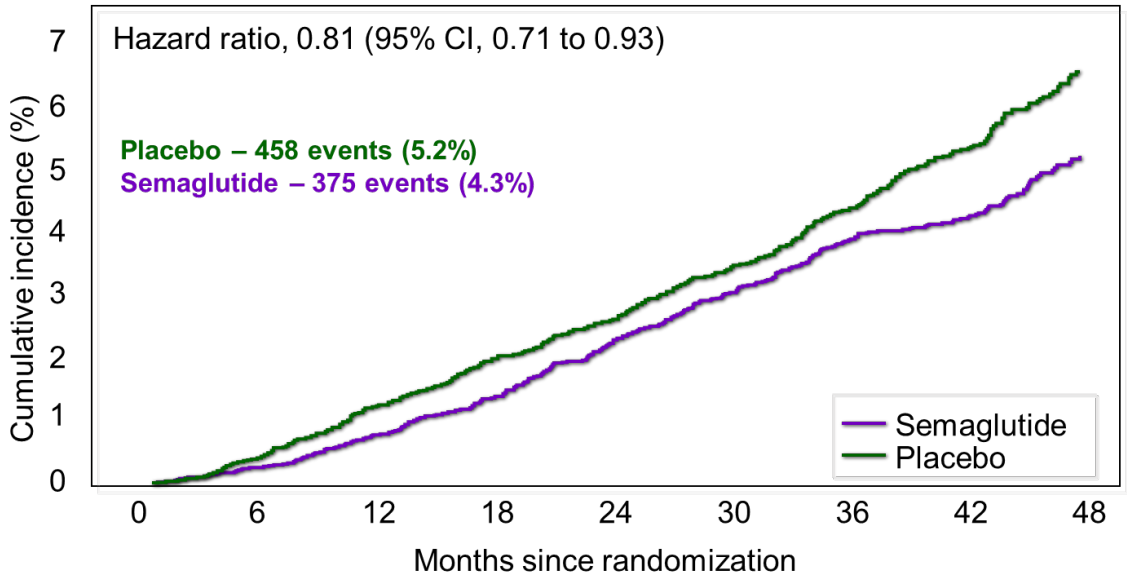
SELECT Trial – Cardiovascular Efficacy

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

Heart Failure Composite*
2nd Confirmatory Secondary Endpoint



Death from Any Cause
3rd Confirmatory Secondary Endpoint



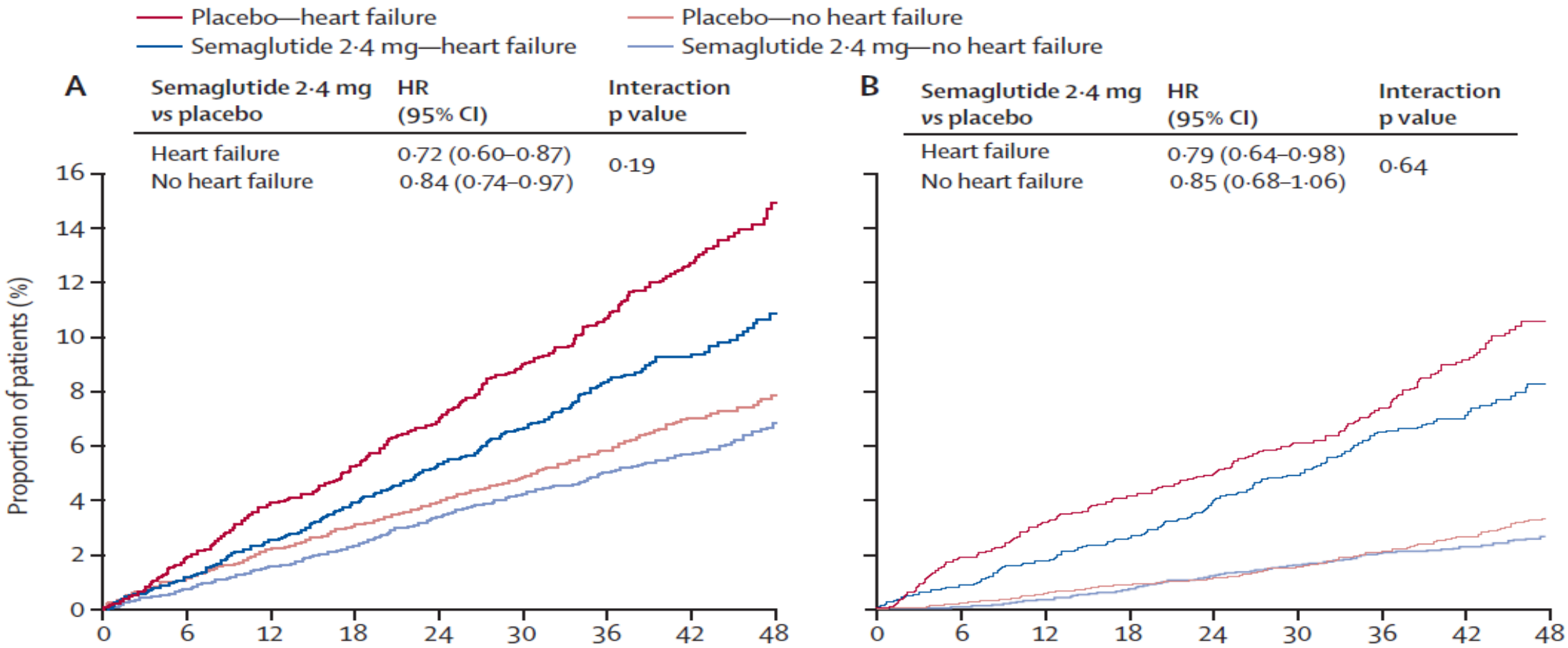
* Heart Failure Composite : CV death or hospitalization or urgent visit for heart failure

Change in body weight by 104 weeks : -8.5 % (95 % CI = -8.8 to -8.3)
Change in hs C-reactive protein : -37.8 % (-39.7 to -39.9)

Prespecified analysis of SELECT trial : patients with (4286) or without (13318) heart failure

Cxvx death, non fatal MI and stroke

Cxvx death, hospitalization or urgent visit for HF



In patients with atherosclerotic cxvx disease and overweight or obesity, semaglutide 2,4 mg reduce MACE and composite HF endpoint in patient with or without an history of HF

Deanfield J, et al. Lancet 2024;404:773-86

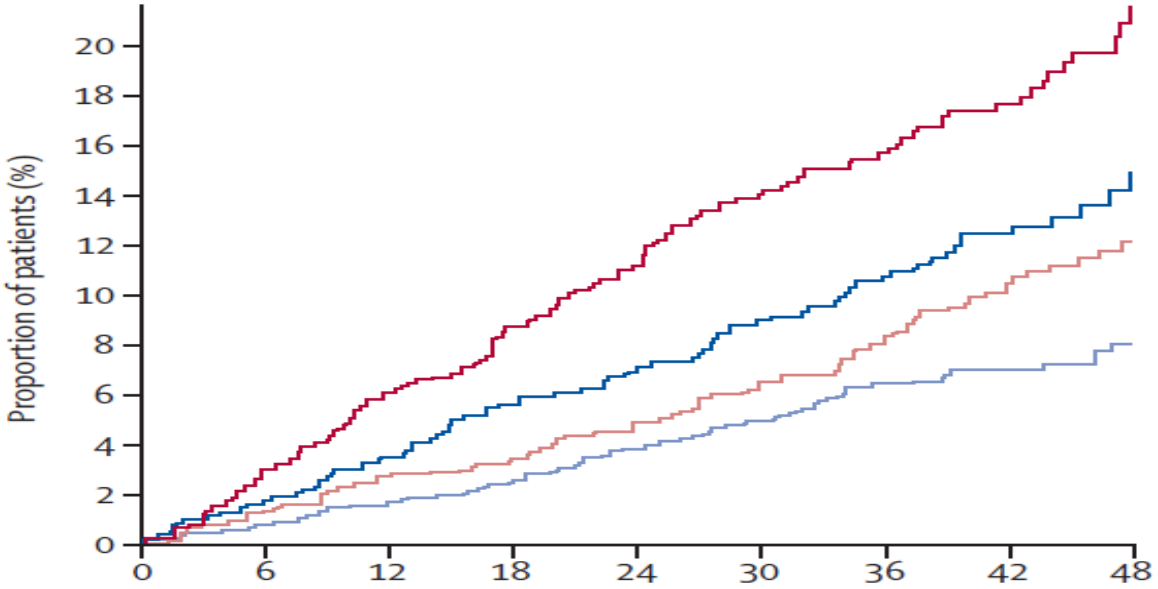
Prespecified analysis of SELECT trial : patients with HFrEF (1347) or HFpEF (2273)

Cxvx death, non fatal MI and stroke

Placebo—heart failure with reduced ejection fraction
Semaglutide 2·4 mg—heart failure with reduced ejection fraction

A

Semaglutide 2·4 mg vs placebo	HR (95% CI)	Interaction p value
Heart failure with reduced ejection fraction	0·65 (0·49–0·87)	0·82
Heart failure with preserved ejection fraction	0·69 (0·51–0·91)	

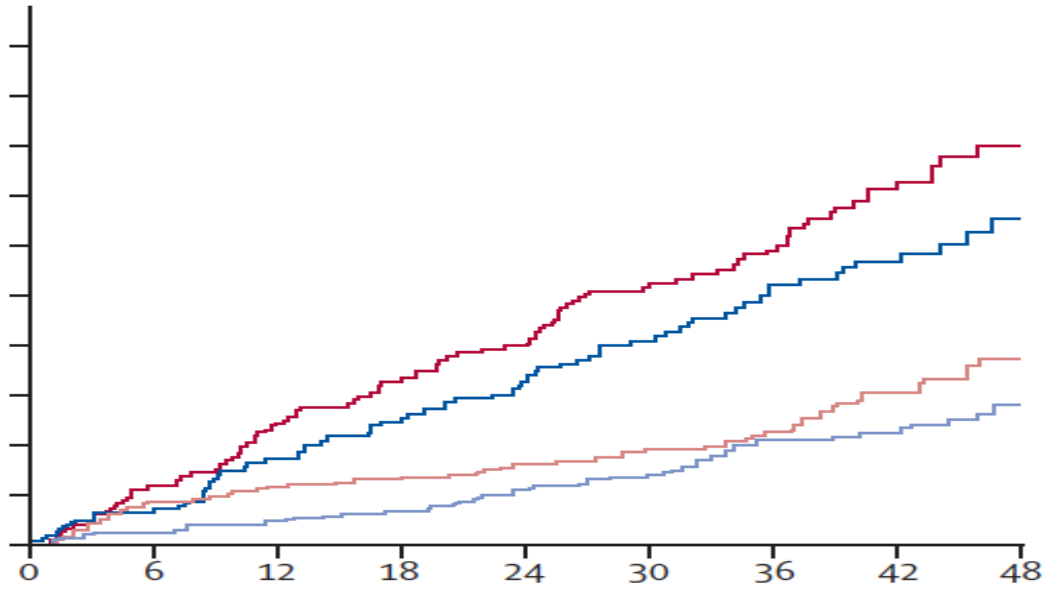


Cxvx death, hospitalization or urgent visit for HF

Placebo—heart failure with preserved ejection fraction
Semaglutide 2·4 mg—heart failure with preserved ejection fraction

B

Semaglutide 2·4 mg vs placebo	HR (95% CI)	Interaction p value
Heart failure with reduced ejection fraction	0·79 (0·58–1·08)	0·79
Heart failure with preserved ejection fraction	0·75 (0·52–1·07)	

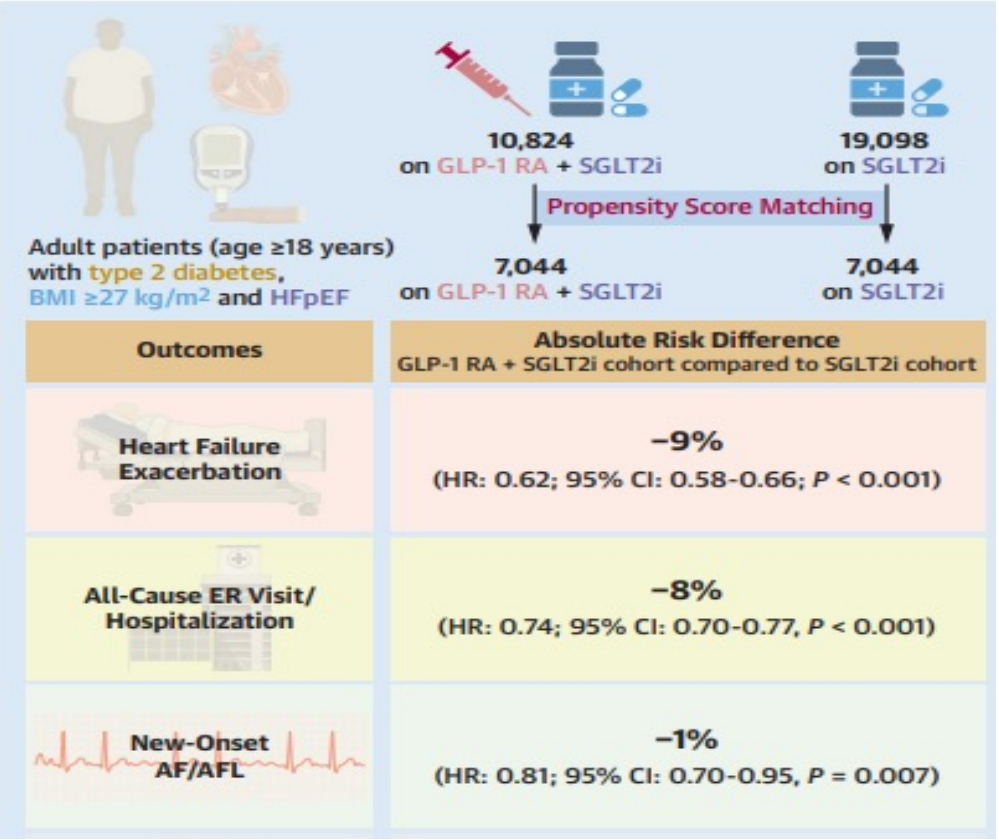


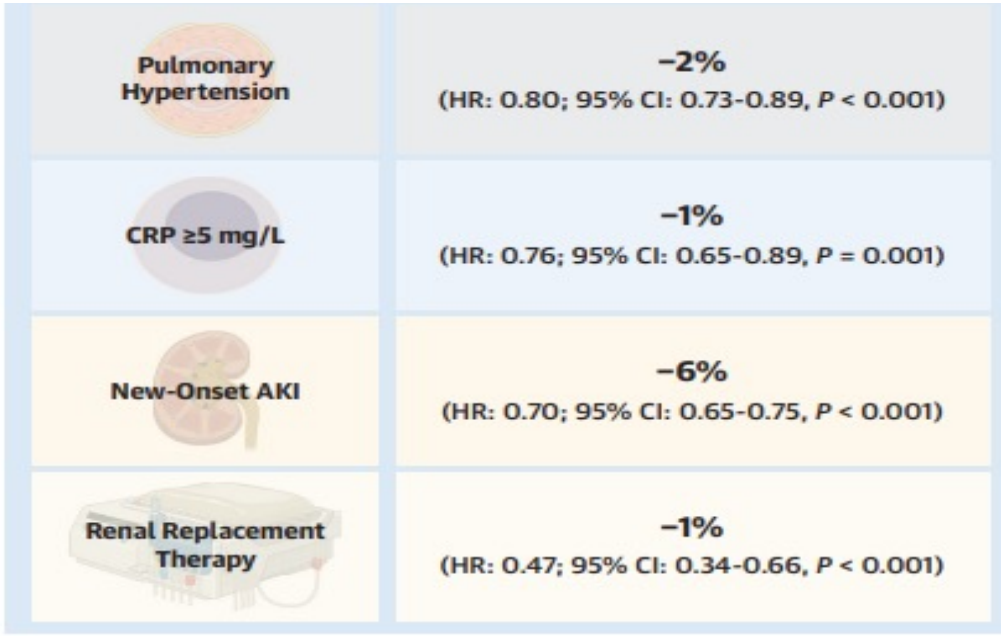
In patients with other atherosclerotic cxvx disease and overweight or obesity, semaglutide 2,4 mg reduce MACE and composite HF endpoint in patients with a history of HF, regardless EF subtype

Deanfield J, et al. Lancet 2024;404:773-86

GLP-1 receptor agonists among patients with overweight or obesity, type 2 diabetes and HFpEF on SGLT2 inhibitors

Retrospective cohort study using the TriNetX research database





GLP-1RA, in addition to SGLT2i, was associated with a significantly lower risk of HF hospitalization, suggesting a potential incremental benefit

Patel R, et al. JACC Heart Fail 2024;12:1814-1826

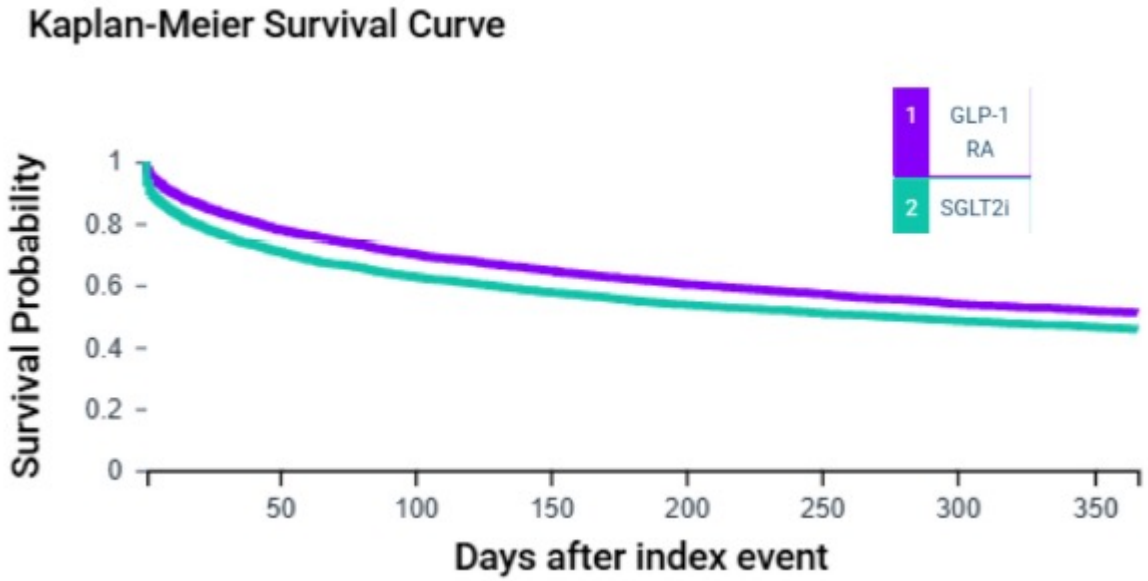
GLP-1 receptor agonists among patients with heart failure and atherosclerotic cardiovascular disease on SGLT2 inhibitors

Retrospective cohort study using the TriNetX research database with propensity score matching using 37 variables including demographics, diagnoses and medications (diabetes mellitus = 91 %)

GLP-1RA + SGLT2i group : 5272 pts

SGLT2i alone group : 5272 pts

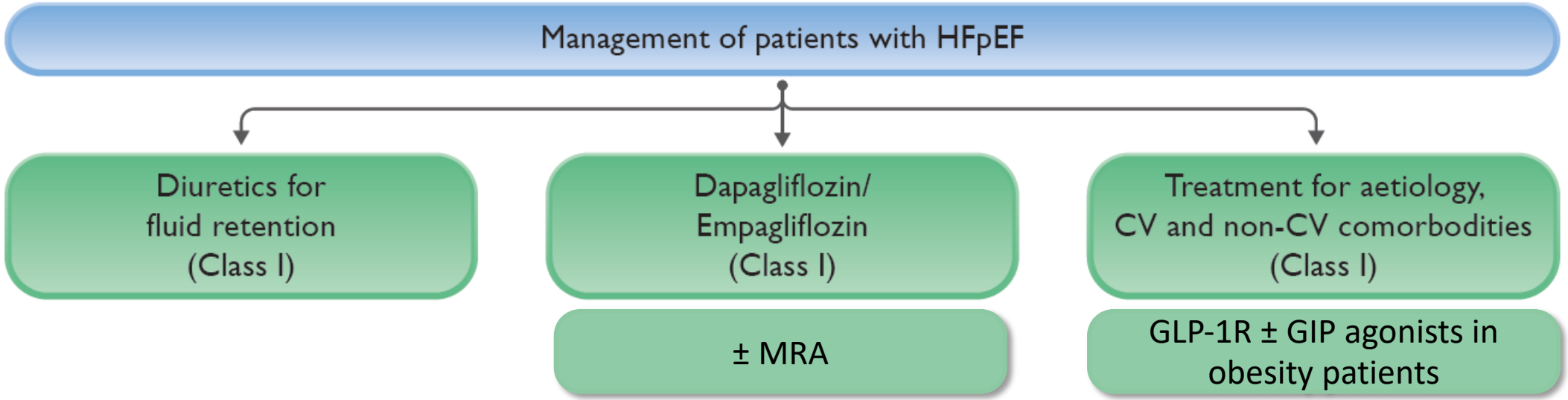
Mortality or hospitalization (primary outcome)



After one-year follow-up, the GLP-1RA + SGLT2i group had a significantly lower risk of mortality or hospitalization (-22%), mortality (-28%), hospitalization (-22%), heart failure exacerbation (-23%) vs the SGLT2i alone group. Subgroup analysis showed consistent benefits in patients with HFpEF, HFrEF, patients diabetes, obesity and CKD

Chen SY, et al. Eur Heart J Cardiovasc Pharmacother 2025 Feb 17:pvaf014. Doi : 10.1093/ehjcvp/pvaf014

Traitement de l'ICFEp (≥ 50%) – Adapté des recommandations ESC 2023



Recommendation	Class[a]	Level[b]
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFpEF to reduce the risk of HF hospitalization or CV death.[c] [6,8]	I	A

McDonagh TA, et al. Eur Heart J 2023;44(37):3627-3639

Effets de la chirurgie bariatrique sur les facteurs de risque des maladies cxvx - Méta-analyse

- Amélioration de l'HTA chez 61,7 % des patients
- Amélioration des hyperlipidémies chez 70 % des patients
- Résolution ou amélioration du diabète chez 86 % des patients
- Résolution du SAS obstructif et du syndrome d'hypoventilation de l'obèse chez 85,7 % de patients
- Diminution masse et index de masse ventriculaire gauche
- Maintien de ces bénéfices à long terme (10 ans)
- Diminution du risque cardiovasculaire de 72 % à 5 ans
- Diminution du risque de mortalité coronaire de 59 % à 15 ans
- Lever de contre-indication relative à greffe cardiaque

Ashrafian H, et al. Circulation 2008;118:2091-2102

Synthèse

- L’obésité est une étiologie majeure du SAS obstructif et de l’insuffisance cardiaque
- L’insuffisance cardiaque à fraction d’éjection préservée est la forme prédominante chez l’obèse
- Le diagnostic de l’insuffisance cardiaque est plus difficile chez les patients obèses
- Les agonistes des récepteurs GLP1 et du GIP paraissent un traitement d’avenir chez les obèses présentant un SAS obstructif et/ou uns insuffisance cardiaque associés aux iSGLT2
- La place respective du traitement médical de l’obésité et de la chirurgie bariatrique reste à déterminer