XI Reunión. Estado del Arte en
INSUFICIENCIA CARDIACA
PRÁCTICA CLÍNICA Y MODELOS ORGANIZATIVOS
Sede: Hotel Meliá MaríaPita, A Coruña
A CORUÑA 27-28 SEPTIEMBRE 2024

XI Meeting. State of the Art in
HEART FAILURE
CLINICAL PRACTICE AND ORGANIZATIONAL MODELS
Venue: Hotel Meliá MaríaPita, A Coruña
ACoruñaHF2024
A CORUÑA 27-28 SEPTEMBER 2024

GLP-1 agonists. Is obesity a therapeutic target in HF?

Beatriz Díaz Molina | *Hospital Universitario Central de Asturias*

World Health Organization | Health Topics | Countries | Newsroom | Emergencies | Data | About WHO

العربية | 中文 | Français | Русский | Español

Obesity and overweight

Obesity is **a chronic** complex disease defined by excessive **fat deposits** that can impair health.

(body fat > 25 % ♂ and > 33 % ♀).

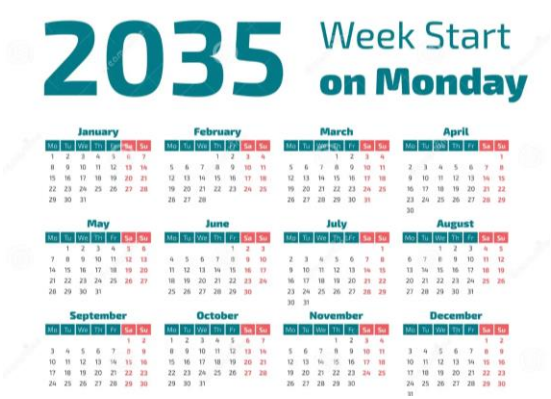
- ✓ The **body mass index is a surrogate marker of fatness.** For adults, WHO defines overweight and obesity as follows:
  - ✓ overweight is a BMI greater than or equal to 25; and
  - ✓ obesity is a **BMI** greater than or equal to **30.**
- ✓ Additional measurements, such as the **waist circumference**, (> 102 cm ♂ y > 88 cm ♀) can help the diagnosis of obesity.

The worldwide prevalence of obesity more than **doubled between 1990 and 2022.** About **16%** of adults aged 18 years and older worldwide were obese in 2022.

ESC European Society of Cardiology
European Heart Journal (2024) **00**, 1–44
https://doi.org/10.1093/eurheartj/ehae466
SPECIAL ARTICLE
Epidemiology, prevention, and health care policies

European Society of Cardiology: the 2023 Atlas of Cardiovascular Disease Statistics

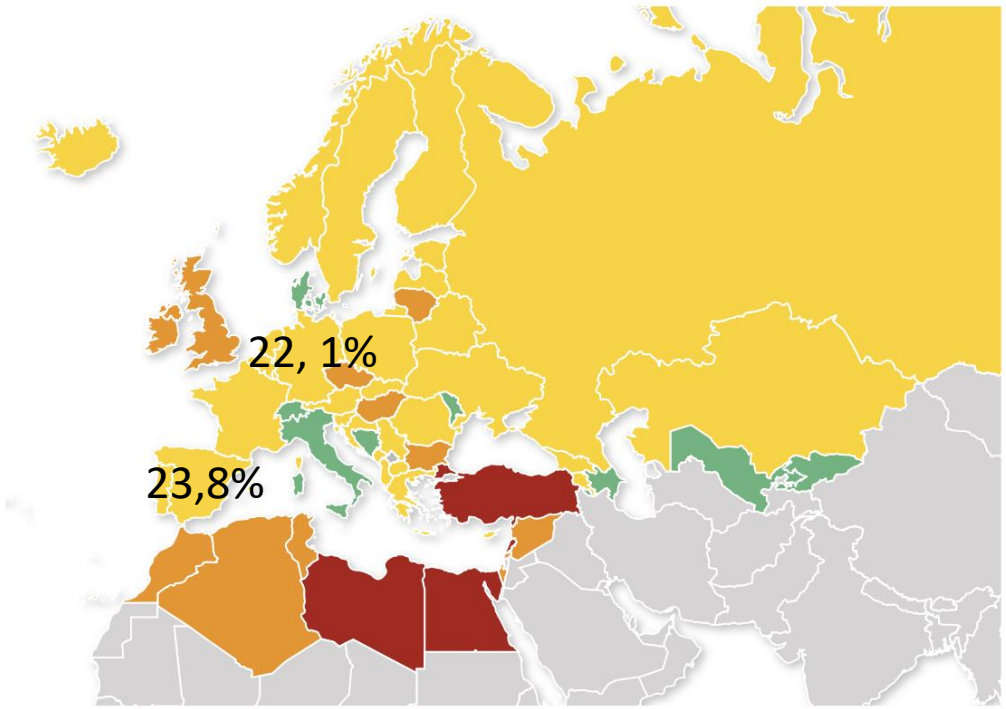
In 2019, 54.8% (IQR 49.6%–56.7%) of people in ESC member countries were overweight and **17.0%** (IQR 15%–20%) obese.



it is estimated that **over half** the world population will be overweight by 2035 and nearly a **quarter** will be obese.

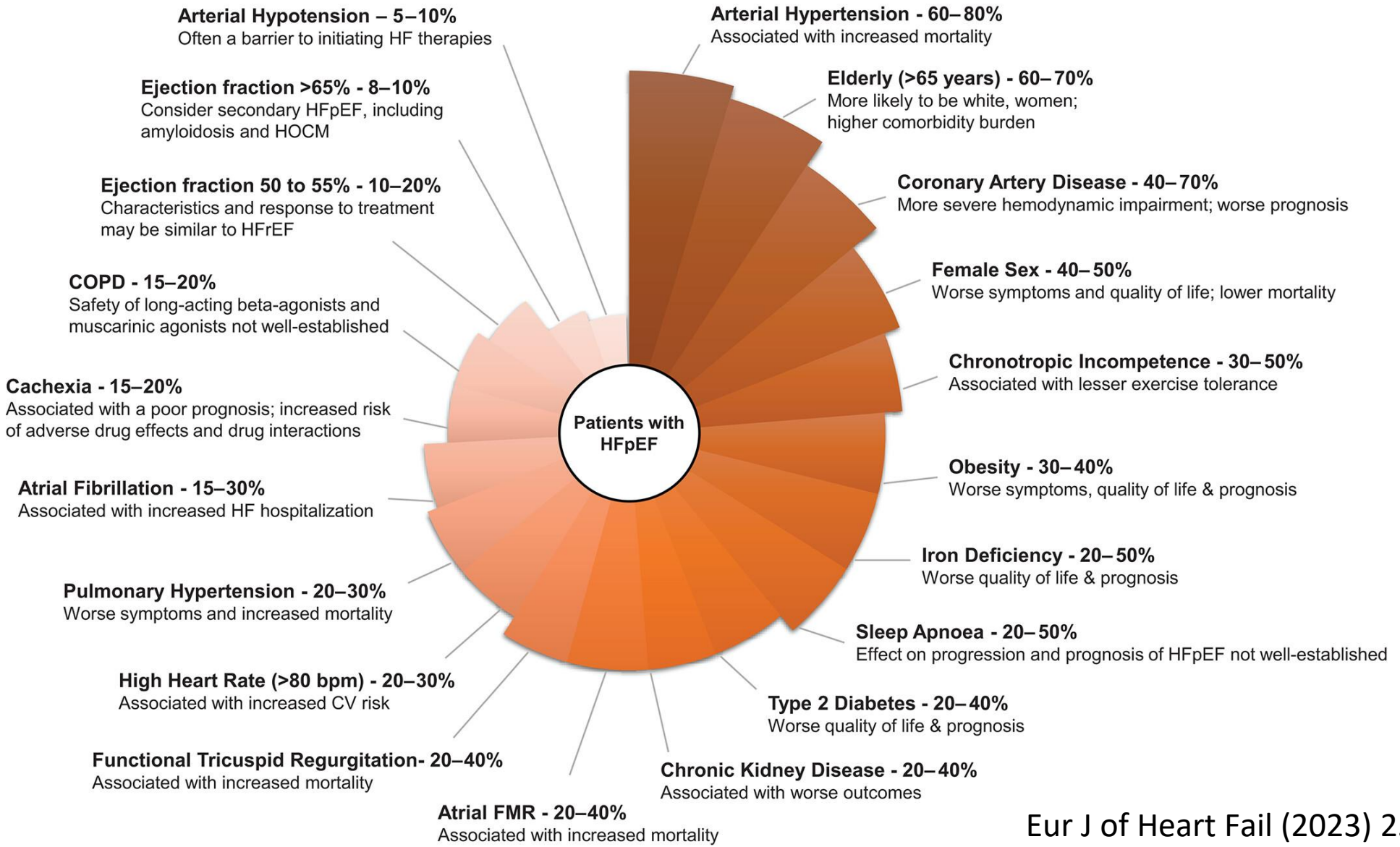
European Heart Journal (2024) **00**, 1–44

Prevalence of obesity (BMI ≥30 kg/m$_2$) across ESC member countries in 2019. Adapted from Timmis *et al.*



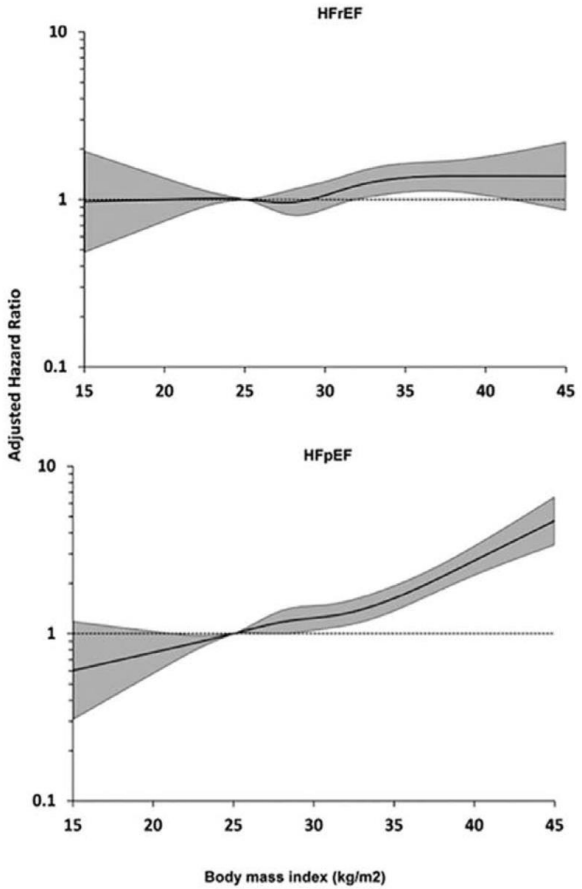
European Heart Journal (2024) **00**, 1–36

The estimated prevalence of important phenotypes of primary heart failure with preserved ejection fraction (HFpEF)

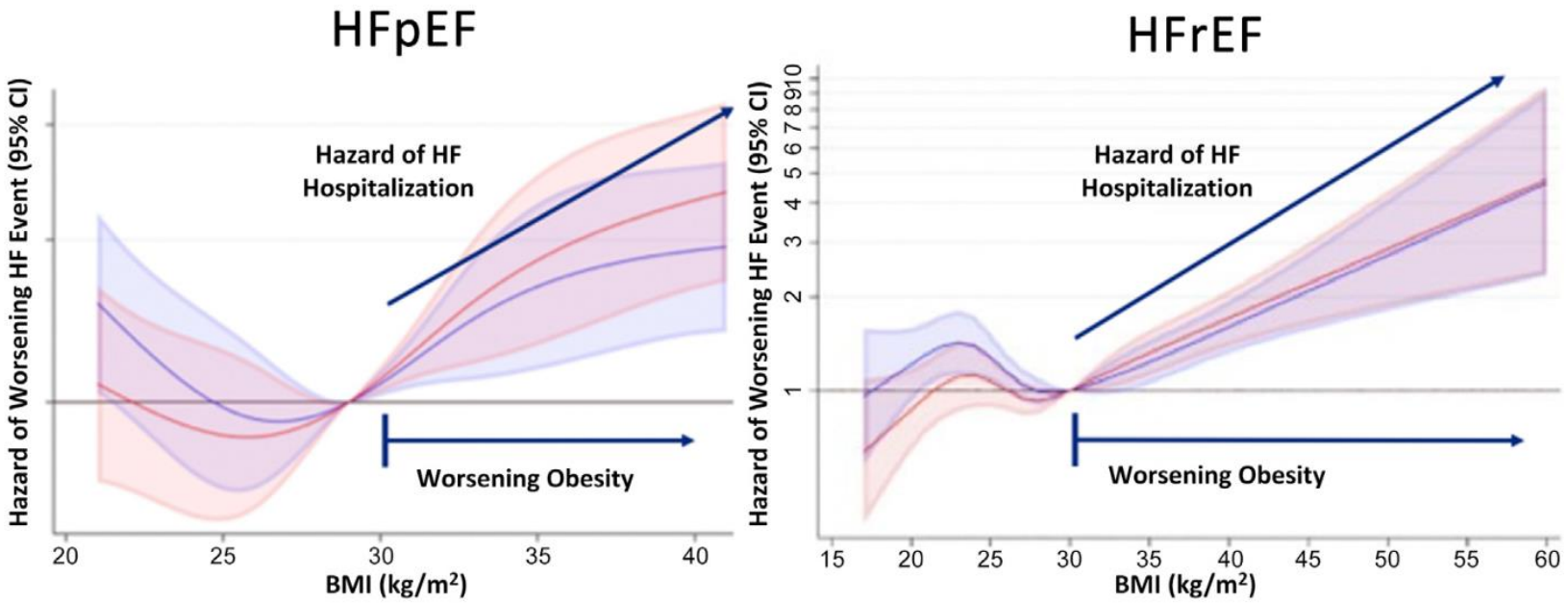


Eur J of Heart Fail (2023) 25, 936–955

Association between body mass index and risk of heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF).



JACC Heart Fail. 2018;6:975–982.



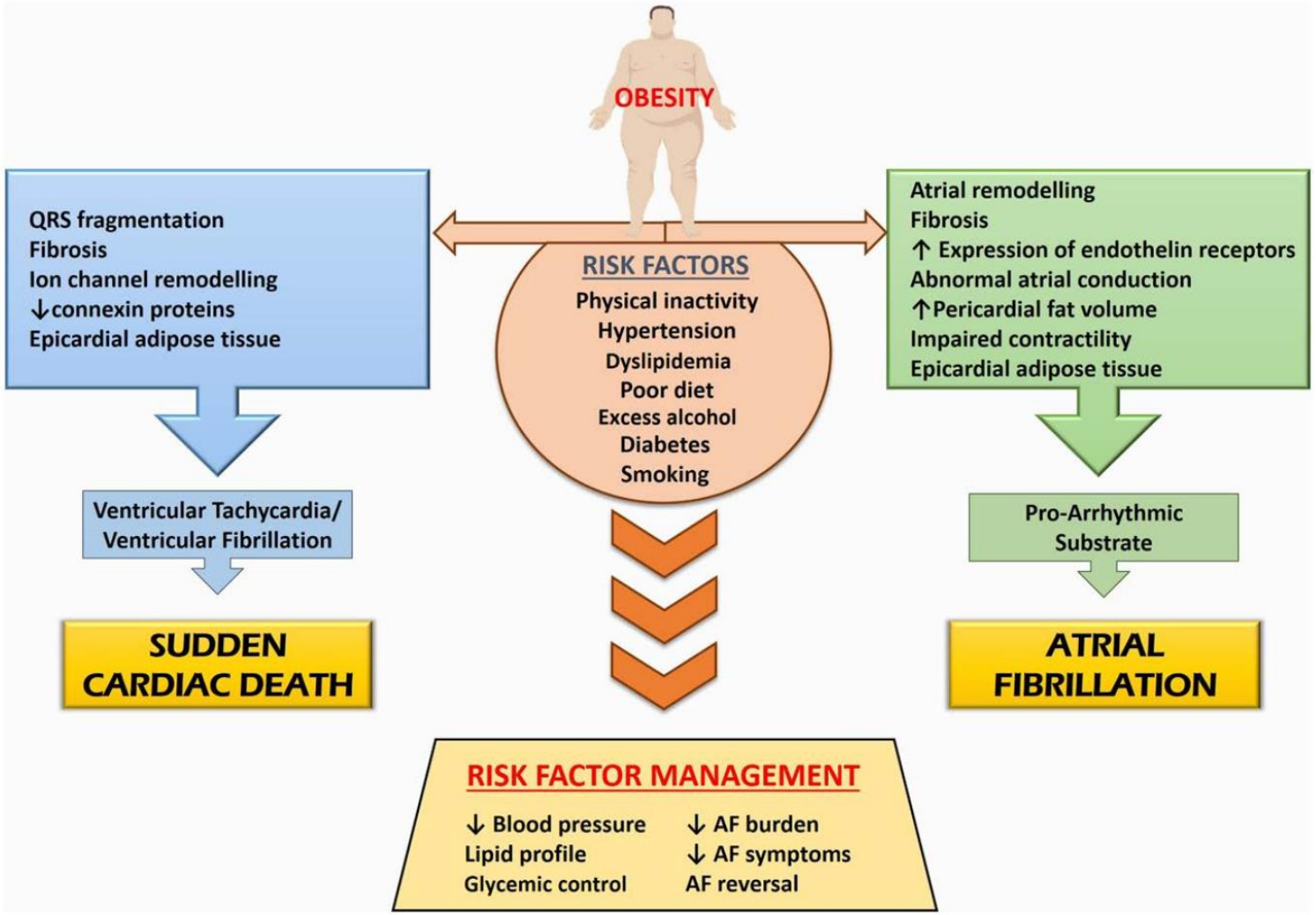
J Am Coll Cardiol HF 2024;12:28–34

Obesity is associated with **cardiovascuar risk factors** such as hypertension, diabetes and dyslipidemia, which have a **deleterious impact** on heart function.

And also to **pathologies that favor the appearance of HF** such as Chronic Kidney Disease and Obstructive Sleep Apnea.

Circulation. 2021;143:e984–e1010.

Relationships between obesity and cardiac arrhythmias.



Ectopic fat is defined as storage of TG in tissues other than adipose tissue, that normally contain only small amounts of fat, such as the liver, skeletal muscle, heart, and pancreas.

Int J Endocrinol 2012; 983814

Obesity and epicardial adiposity are associated with haemodynamic signs of **pericardial constraint** in patients with HFpEF.

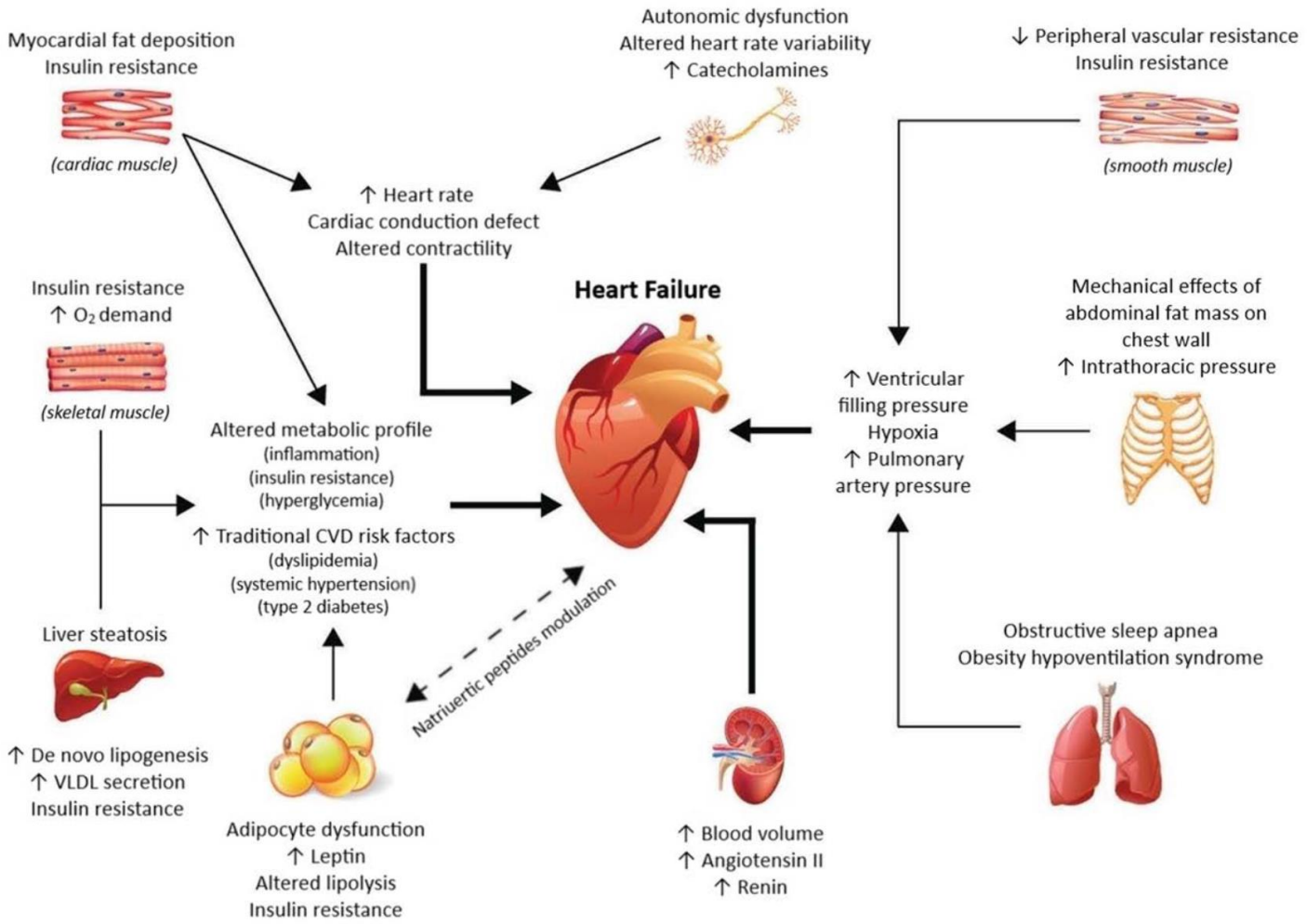
ESC HF 2024;11: 1698-1706

Visceral adipose tissue as **a source of inflammation** and promoter of aterosclerosis.

Atherosclerosis 2014; 233: 104-112

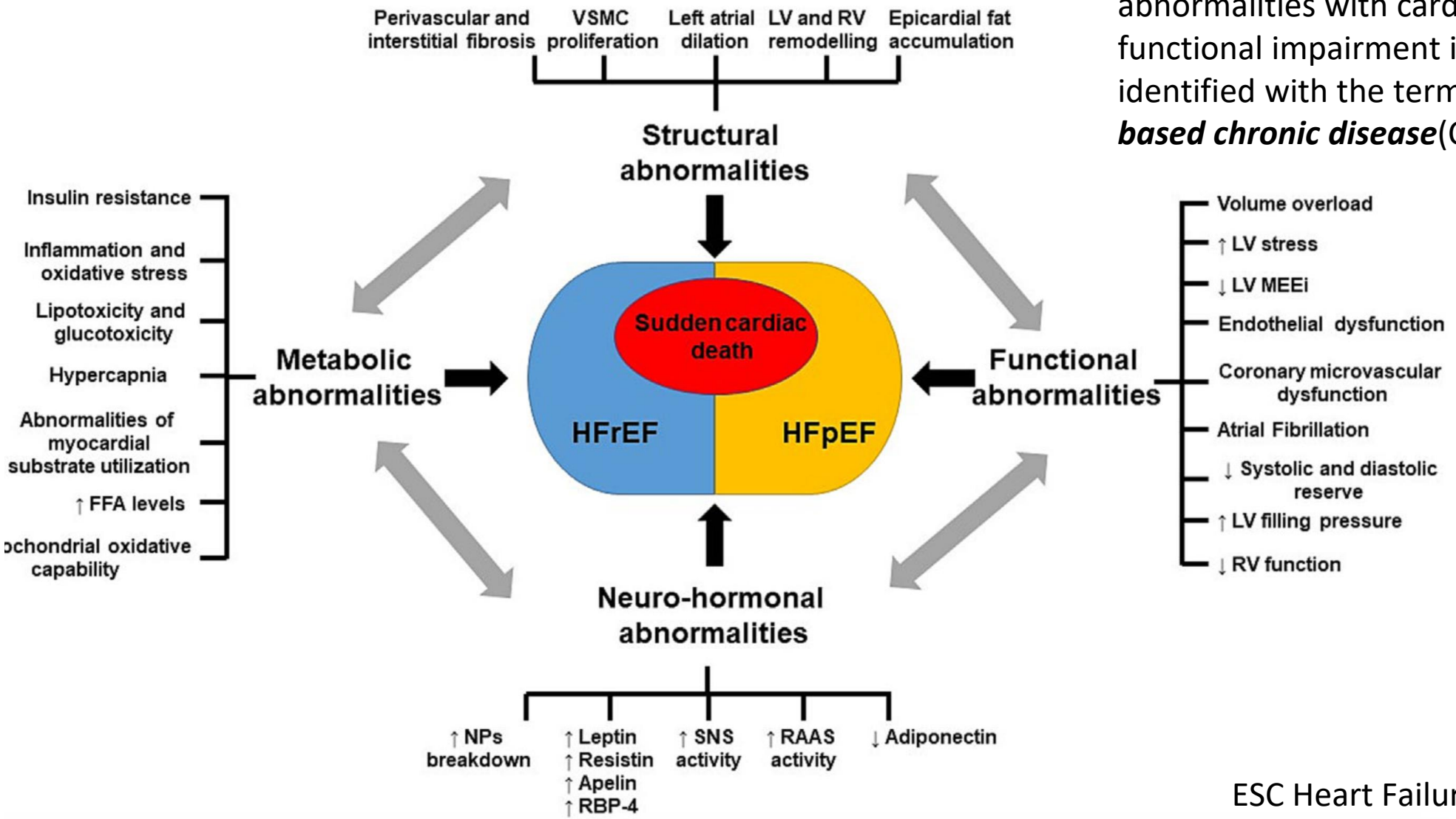
Epicardial cells express CA125, which is positively associated with **inflammatory and fibroblast markers in epicardial adipose tissue.**

J Transl Med 2024 Jul 3;22(1):619.



Circulation. 2021;143:e984–e1010.

Obesity: the perfect storm for heart failure

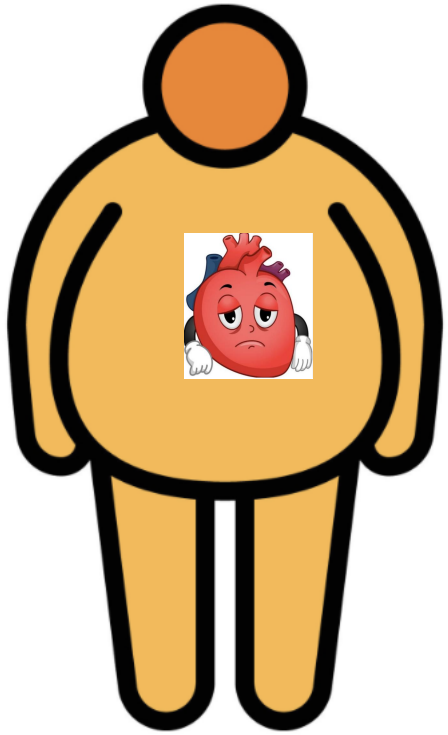


The combination of metabolic abnormalities with cardiac structural and functional impairment is currently identified with the term ***cardiometabolic-based chronic disease***(CMBCD).

ESC Heart Failure 2024

Is obesity a therapeutic target in HF?

YES!



GLP-1 agonists.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 21, 2023 VOL. 389 NO. 12

Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity

M.N. Kosiborod, S.Z. Abildstrøm, B.A. Borlaug, J. Butler, S. Rasmussen, M. Davies, G.K. Hovingh, D.W. Kitzman, M.L. Lindegaard, D.V. Møller, S.J. Shah, M.B. Treppendahl, S. Verma, W. Abhayaratna, F.Z. Ahmed, V. Chopra, J. Ezekowitz, M. Fu, H. Ito, M. Lelonek, V. Melenovsky, B. Merkely, J. Núñez, E. Perna, M. Schou, M. Senni, K. Sharma, P. Van der Meer, D. von Lewinski, D. Wolf, and M.C Petrie, for the STEP-HFpEF Trial Committees and Investigators*

ORIGINAL ARTICLE

Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes

M.N. Kosiborod, M.C. Petrie, B.A. Borlaug, J. Butler, M.J. Davies, G.K. Hovingh, D.W. Kitzman, D.V. Møller, M.B. Treppendahl, S. Verma, T.J. Jensen, K. Liisberg, M.L. Lindegaard, W. Abhayaratna, F.Z. Ahmed, T. Ben-Gal, V. Chopra, J.A. Ezekowitz, M. Fu, H. Ito, M. Lelonek, V. Melenovský, B. Merkely, J. Núñez, E. Perna, M. Schou, M. Senni, K. Sharma, P. van der Meer, D. Von Lewinski, D. Wolf, and S.J. Shah, for the STEP-HFpEF DM Trial Committees and Investigators*

INCLUSION:

BMI> 30 kg/m^2

LVEF > 45

NYHA III, III, IV

KCCQ < 90

Test 6 min > 100 mts

HF:

⬆ LV filling presssures

⬆ natriuretic peptides + echo or hospitalization < 12 months

EXCLUSION:

Change in body weight > 5 kg en < 3 months

DM:

Hb A1c ≥ 6,5%

History os diabetes

Randomization

n= 529 patients

March 2021- March 2022

Semaglutide 2,4 mg/week vs pl.

Follow-up 1 year

STEP-HFpEF

Median body weight (IQR) — kg	104.7 (92.4–120.1)	105.3 (92.4–122.0)	105.1 (92.4–120.8)
Median BMI (IQR)	37.2 (33.9–41.1)	36.9 (33.3–41.6)	37.0 (33.7–41.4)
BMI stratum — no. (%)			
30 to <35	89 (33.8)	91 (34.2)	180 (34.0)
≥35	174 (66.2)	175 (65.8)	349 (66.0)
Median waist circumference (IQR) — cm	119.0 (110.5–127.1)	120.0 (110.5–129.0)	119.4 (110.5–128.0)
Median systolic blood pressure (IQR) — mm Hg	133 (122–145)	132 (120–142)	133 (121–144)
Median NT-proBNP level (IQR) — pg/ml	414.4 (229.2–1014.0)	499.8 (204.7–1025.0)	450.8 (218.2–1015.0)
Median CRP level (IQR) — mg/liter	3.8 (1.9–7.0)	3.9 (2.0–8.4)	3.8 (1.9–7.7)
Median LVEF (IQR) — %	57.0 (50.0–60.0)	57.0 (50.0–60.0)	57.0 (50.0–60.0)
LVEF stratum — no. (%)			
45 to <50%‡	37 (14.1)	48 (18.0)	85 (16.1)
50 to 59%	113 (43.0)	102 (38.3)	215 (40.6)
≥60%	113 (43.0)	116 (43.6)	229 (43.3)
Median KCCQ-CSS (IQR) — points§	59.4 (42.7–72.9)	58.3 (40.5–72.9)	58.9 (41.7–72.9)
Median 6-minute walk distance (IQR) — m	316.0 (251.0–386.0)	325.8 (232.4–392.0)	320.0 (240.0–389.0)
Hospitalization for heart failure within 1 year — no. (%)	42 (16.0)	39 (14.7)	81 (15.3)
Coexisting conditions at screening — no. (%)			
Atrial fibrillation	135 (51.3)	140 (52.6)	275 (52.0)
Hypertension	216 (82.1)	217 (81.6)	433 (81.9)
Coronary artery disease	53 (20.2)	45 (16.9)	98 (18.5)
NYHA functional class — no. (%)			
II	183 (69.6)	167 (62.8)	350 (66.2)
III or IV	80 (30.4)	99 (37.2)	179 (33.8)
Concomitant medication — no. (%)			
Diuretic	207 (78.7)	220 (82.7)	427 (80.7)
Loop diuretic	158 (60.1)	171 (64.3)	329 (62.2)
Thiazide	40 (15.2)	50 (18.8)	90 (17.0)
MRA	89 (33.8)	95 (35.7)	184 (34.8)
ACEI, ARB, or ARNI	210 (79.8)	214 (80.5)	424 (80.2)
Beta-blocker	201 (76.4)	217 (81.6)	418 (79.0)
SGLT2 inhibitor	8 (3.0)	11 (4.1)	19 (3.6)

INCLUSION:

BMI> 30 kg/m^2

LVEF > 45

NYHA III, III, IV

KCCQ < 90

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HF:

⬆ LV filling presssures

⬆ natriuretic peptides + echo or hospitalization < 12 months

EXCLUSION:

Change in body weight > 5 kg en < 3 months

DM:

Hb A1c ≥ 6,5%

History os diabetes

Randomization

n= 529 patients

March 2021- March 2022

Semaglutide 2,4 mg/week vs pl.

Follow-up 1 year

STEP-HFpEF

PATIENTS:

56 % ♀, age 69 years

BMI 37

LVEF 57 %

NTproBNP 451 pg/ml

KCCQ 58.9

Test 6 min 320 mts

HF:

⬆ LV filling pressures: 14 %

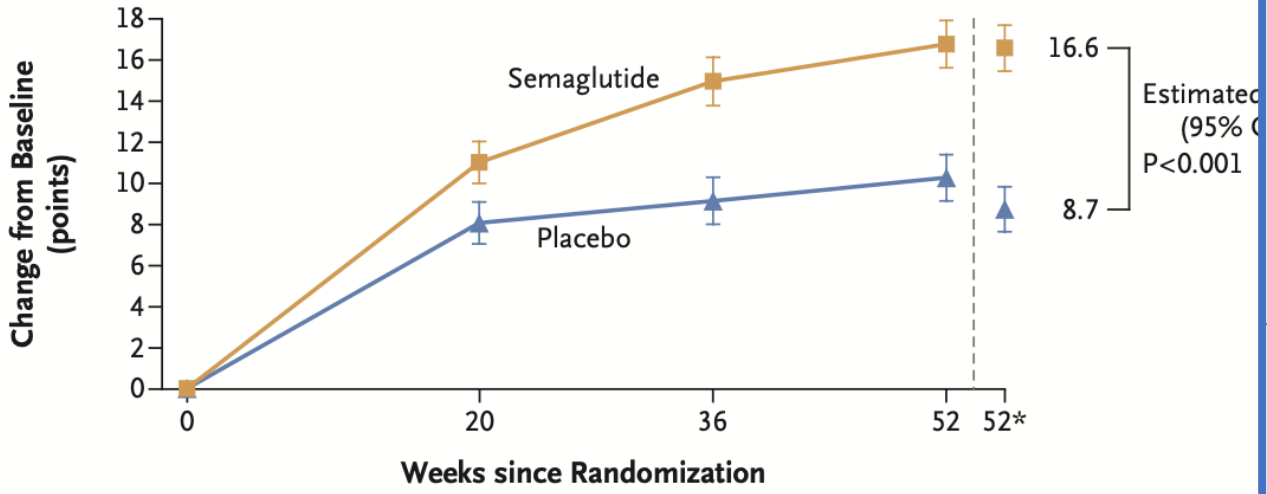
⬆ **NP + echo** 72%

Hospitalization < 12 months 13.4 %

SGLT2i 3,6%

STEP-HFpEF

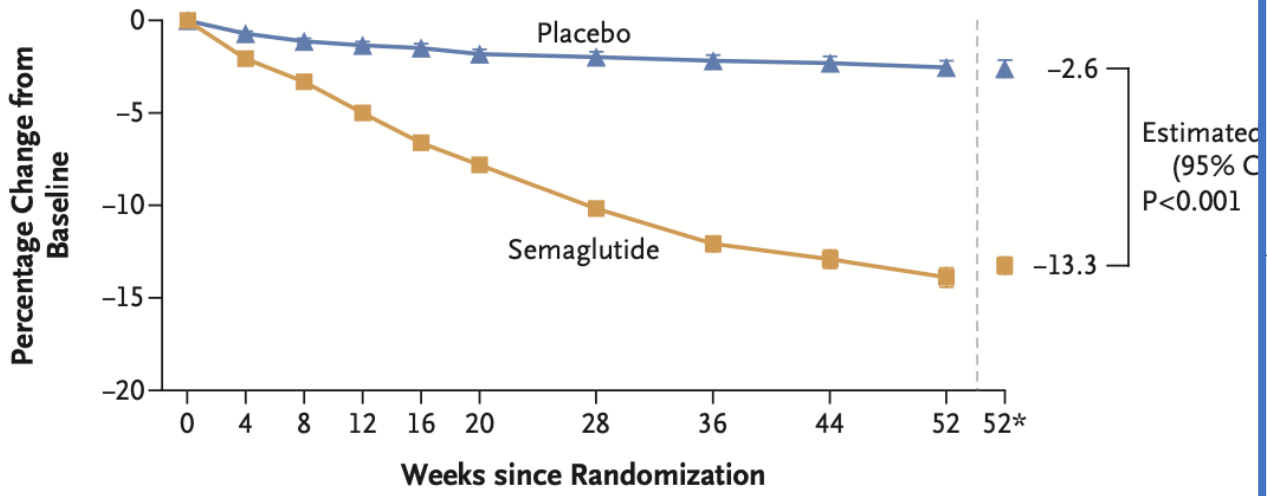
A Change in KCCQ-CSS



No. of Participants

Semaglutide	263	249	225	243	263
Placebo	266	242	217	237	266

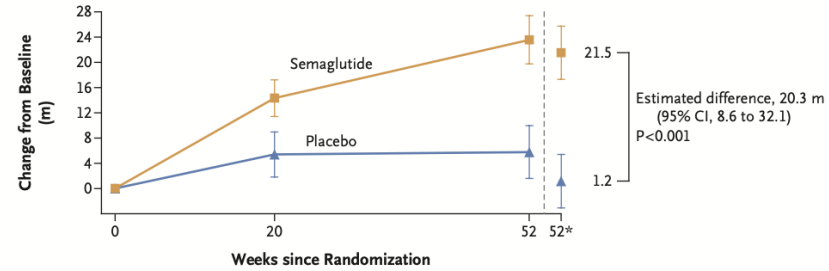
B Change in Body Weight



No. of Participants

Semaglutide	263	255	254	250	246	252	239	243	240	246	263
Placebo	266	259	249	250	243	246	243	239	233	242	266

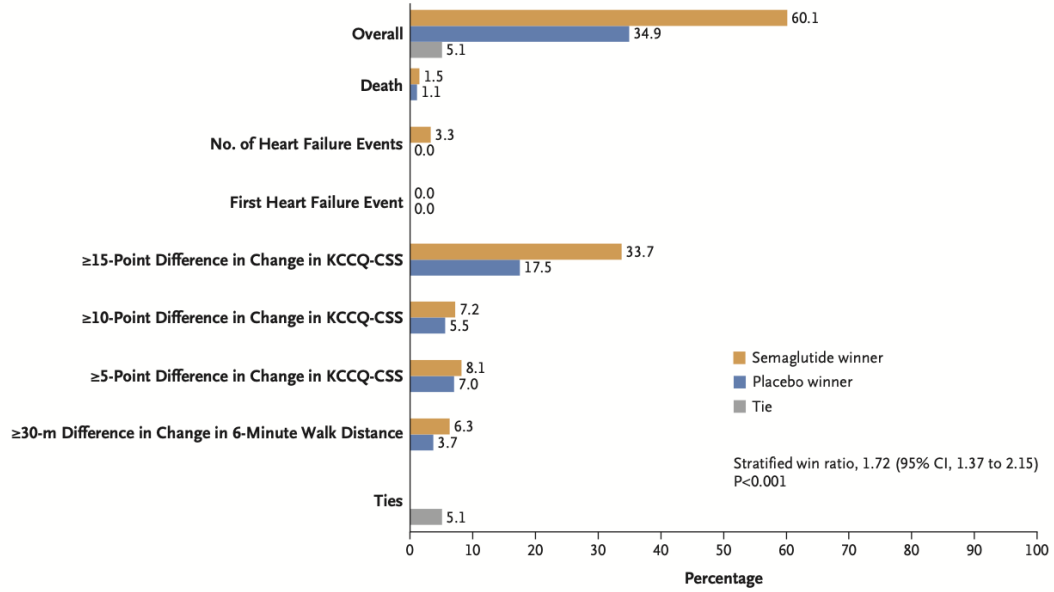
A Change in 6-Minute Walk Distance



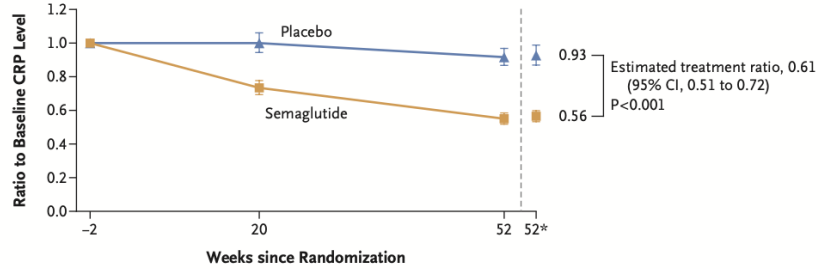
No. of Participants

Semaglutide	263	245	240	263
Placebo	266	232	225	266

B Stratified Win Ratio for Hierarchical Composite End Point



C Change in C-Reactive Protein Level



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Placebo	266	232	225	266

INCLUSION:

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NYHA III, III, IV

KCCQ < 90

Test 6 min > 100 mts

HF:

⬆ LV filling pressures

⬆ natriuretic peptides + echo or hospitalization < 12 months

DM tipo 2 > 90 days

EXCLUSION:

Change in body weight> 5 kg < 3 months

DM type 1

Hb A1c ≥ 10 %

Uncontralled retinopathy

Randomization

N= 616

June 2021- August 2022

Semaglutide 2,4 mg/sem vs pl.

Follow up 1 year

STEP-HFpEF DM

Median BMI (IQR)	36.9 (33.6–41.5)	36.9 (33.5–41.1)
Median NT-proBNP level (IQR) — pg/ml	477.8 (251.2–969.2)	502.3 (240.2–1114.6)
Median CRP level (IQR) — mg/liter	3.7 (1.8–8.4)	3.3 (1.6–8.4)
Median duration of diabetes (IQR) — yr	8.0 (3.6–14.3)	8.0 (4.1–15.2)
Median glycated hemoglobin level (IQR) — %	6.7 (6.2–7.4)	6.9 (6.2–7.7)
Median LVEF (IQR) — %	57.0 (50.0–61.0)	55.0 (50.0–60.0)
Median KCCQ-CSS (IQR) — points‡	60.4 (44.8–72.9)	58.3 (41.1–70.8)
Median 6-minute walk distance (IQR) — m	280.0 (205.1–357.6)	280.0 (200.0–345.0)
Hospitalization for heart failure within 1 year — no. (%)	49 (15.8)	63 (20.6)
Coexisting conditions at screening — no. (%)		
Atrial fibrillation	117 (37.7)	126 (41.2)
Hypertension	255 (82.3)	271 (88.6)
Coronary artery disease	79 (25.5)	69 (22.5)
Obstructive sleep apnea	25 (8.1)	28 (9.2)
NYHA functional class — no. (%)		
II	223 (71.9)	212 (69.3)
III or IV	87 (28.1)	94 (30.7)
Concomitant medication — no. (%)		
Diuretic	246 (79.4)	252 (82.4)
Loop diuretic	186 (60.0)	187 (61.1)
Thiazide	42 (13.5)	43 (14.1)
MRA	105 (33.9)	95 (31.0)
ACEI, ARB, or ARNI	249 (80.3)	253 (82.7)
Beta-blocker	257 (82.9)	253 (82.7)
SGLT2 inhibitor	107 (34.5)	95 (31.0)

INCLUSION:

BMI > 30 kg/m^2

LVEF > 45

NYHA III, III, IV

KCCQ < 90

Test 6 min > 100 mts

HF:

⬆ LV filling pressures

⬆ natriuretic peptides + echo or hospitalization < 12 months

DM tipo 2 > 90 days

EXCLUSION:

Change in body weight> 5 kg < 3 months

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Hb A1c ≥ 10 %

Uncontralled retinopathy

Randomization

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June 2021- August 2022

Semaglutide 2,4 mg/sem vs pl.

Follow up 1 year

Median BMI (IQR)

STEP-HFpEF DM

PATIENTS:

56 % ♂, 69 years

BMI 36.9

LVEF 57 %

NTproBNP 493 pg/ml

KCCQ 59.4

Test 6 min 280 mts

HB A1c 6.8%

HF:

⬆ LV filling pressures: 8,3 %

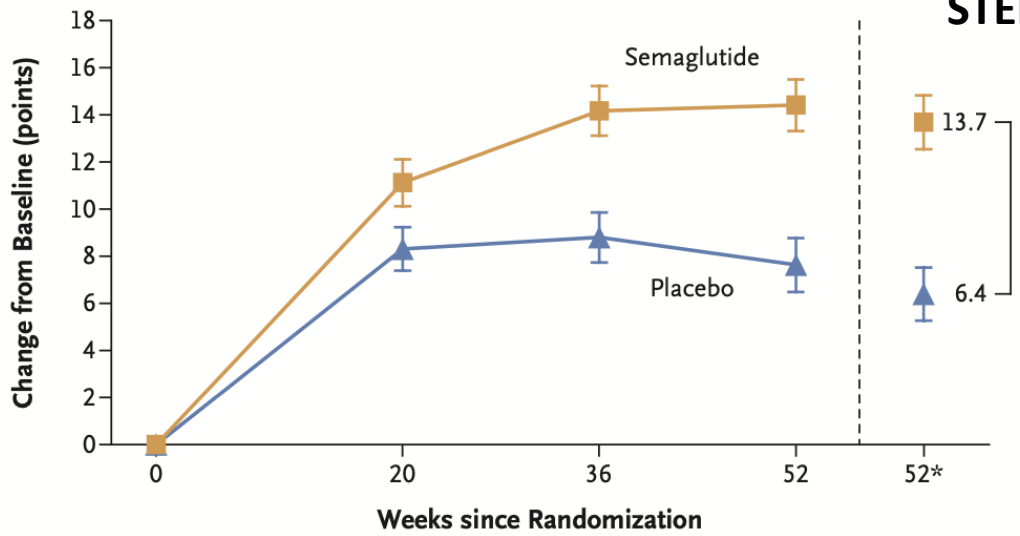
⬆ **NP + echo** 74,4 %

Hospitalization < 12 months 17.4 %

SGLT2i 34,5 %. /31 %

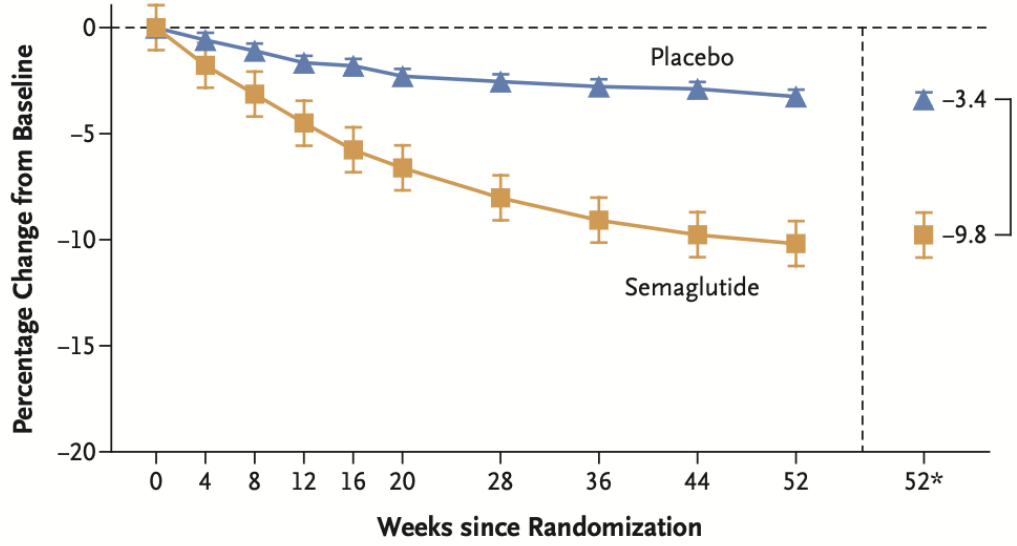
STEP-HFpEF DM

A Change in KCCQ-CSS



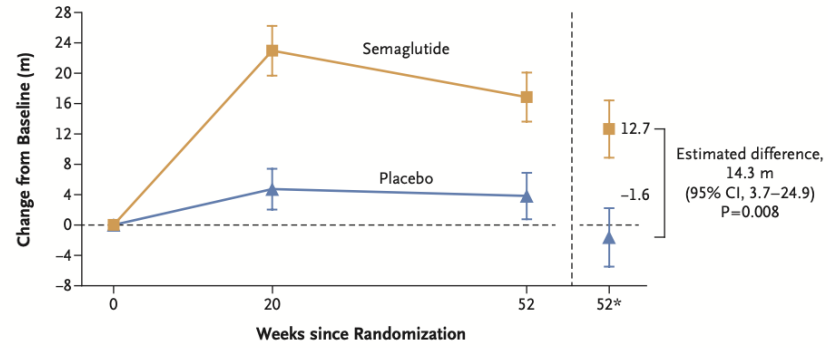
No. of Participants					
Semaglutide	310	289	274	281	310
Placebo	306	284	270	272	306

B Change in Body Weight



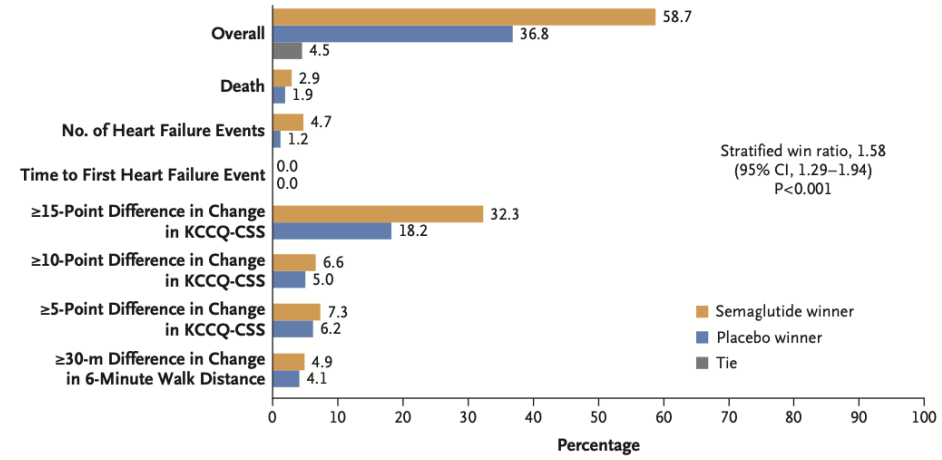
No. of Participants											
Semaglutide	310	307	297	299	290	292	283	286	282	286	310
Placebo	306	300	298	287	292	289	282	278	273	278	306

A Change in 6-Minute Walk Distance

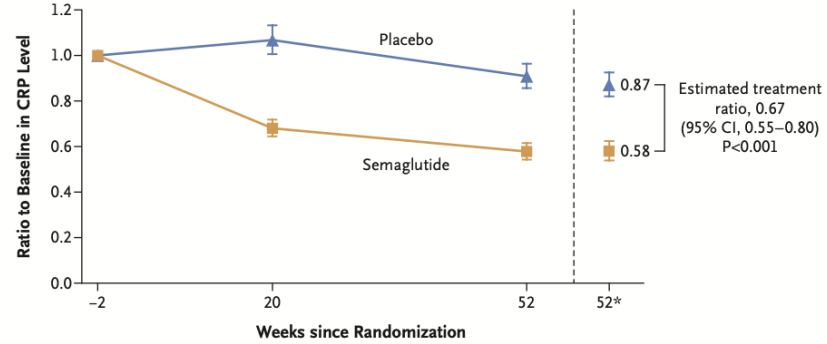


No. of Participants				
Semaglutide	310	284	281	310
Placebo	306	277	265	306

B Stratified Win Ratio for Hierarchical Composite End Point



C Change in C-Reactive Protein Level



No. of Participants				
Semaglutide	310	288	286	310
Placebo	306	285	277	306

ORIGINAL ARTICLE

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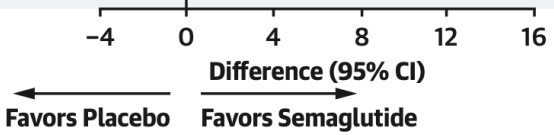
Semaglutide and NYHA Functional Class in Obesity-Related Heart Failure With Preserved Ejection Fraction

STEP

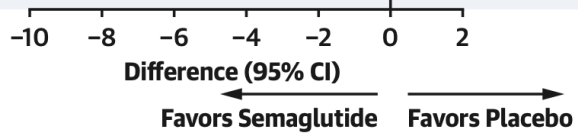
A KCCQ-CSS (Points)

Population	Adjusted Mean Difference (95% CI), Points	*P* Value
Overall	7.5 (5.3-9.8)	<0.001*
NYHA Functional Class		0.061
II	6.0 (3.4-8.6)	
III/IV	10.5 (6.6-14.4)	



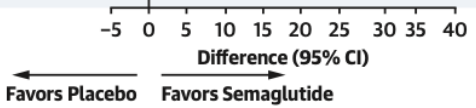
Change in Bodyweight (%)

Population	Adjusted Mean Difference (95% CI), %	*P* Value
Overall	−8.4 (−9.2 to −7.5)	<0.001*
NYHA Functional Class		0.958
II	−8.4 (−9.4 to −7.3)	
III/IV	−8.3 (−9.9 to −6.8)	



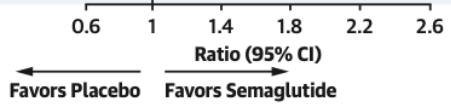
B Change in 6MWD (m)

Population	Adjusted Mean Difference (95% CI), Meters	*P* Value
Overall	17.1 (9.2-25.0)	<0.001*
NYHA Functional Class		0.347
II	14.4 (5.1-23.7)	
III/IV	22.5 (8.3-36.6)	



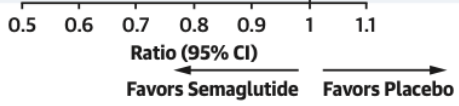
Hierarchical Composite Endpoint (Win Ratio)

Population	Win Ratio (95% CI)	*P* Value
Overall	1.65 (1.42-1.91)	<0.001*
NYHA Functional Class		0.165
II	1.53 (1.27-1.83)	
III/IV	1.95 (1.48-2.58)	



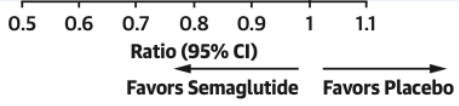
Change in CRP (Ratio to Baseline)

Population	Treatment Ratio (95% CI)	*P* Value
Overall	0.64 (0.56-0.72)	<0.001*
NYHA Functional Class		0.725
II	0.65 (0.56-0.75)	
III/IV	0.62 (0.50-0.77)	



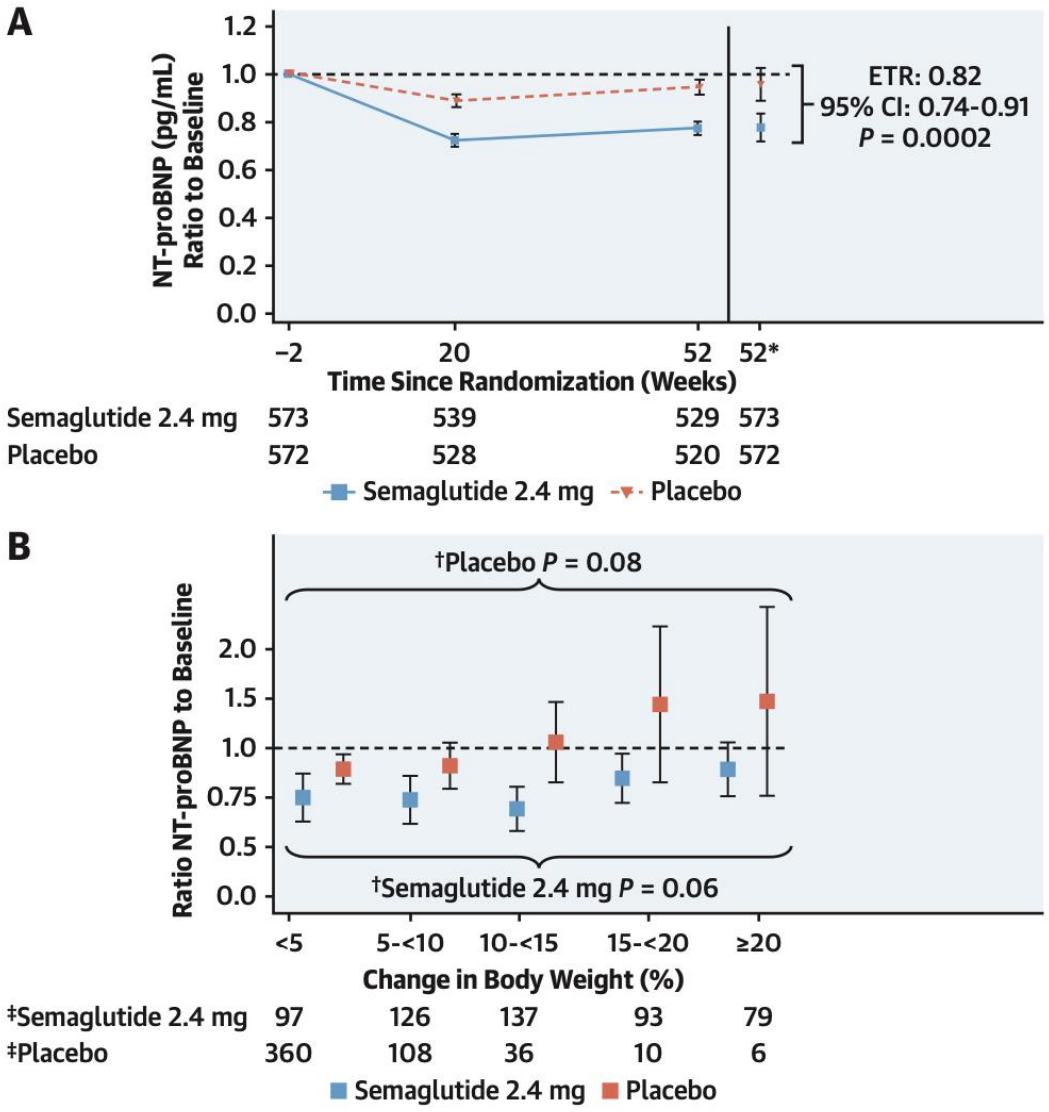
C Change in NT-proBNP (Ratio to Baseline)

Population	Treatment Ratio (95% CI)	*P* Value
Overall	0.82 (0.74-0.91)	<0.001*
NYHA Functional Class		0.250
II	0.86 (0.76-0.97)	
III/IV	0.75 (0.62-0.91)	



J Am Coll Cardiol 2024;84:247–257

Semaglutide and NT-proBNP in Obesity-Related HFpEF



A — Change in KCCQ-CCS

Population	Treatment Difference (95% CI), Points	*P* Value
Overall	7.5 (5.3 to 9.8)	0.02
NT-proBNP <300 pg/mL	4.5 (0.8 to 8.2)	
NT-proBNP 300-810 pg/mL	6.2 (2.4 to 10.0)	
NT-proBNP >810 pg/mL	11.9 (8.1 to 15.7)	

−10 0 10 20

Favors Placebo Favors Semaglutide

B — Change in Body Weight

Population	Treatment Difference (95% CI), %-Points	*P* Value
Overall	−8.4 (−9.2 to −7.5)	0.21
NT-proBNP <300 pg/mL	−9.4 (−10.8 to −7.9)	
NT-proBNP 300-810 pg/mL	−8.3 (−9.7 to −6.8)	
NT-proBNP >810 pg/mL	−7.5 (−9.0 to −6.0)	

−15 −10 −5 0 5

Favors Semaglutide Favors Placebo

C — Change in 6MWD

Population	Treatment Difference (95% CI), m	*P* Value
Overall	17.1 (9.2 to 25.0)	0.32
NT-proBNP <300 pg/mL	17.7 (4.5 to 31.0)	
NT-proBNP 300-810 pg/mL	9.5 (−4.0 to 23.0)	
NT-proBNP >810 pg/mL	23.8 (10.4 to 37.2)	

−10 10 30 50

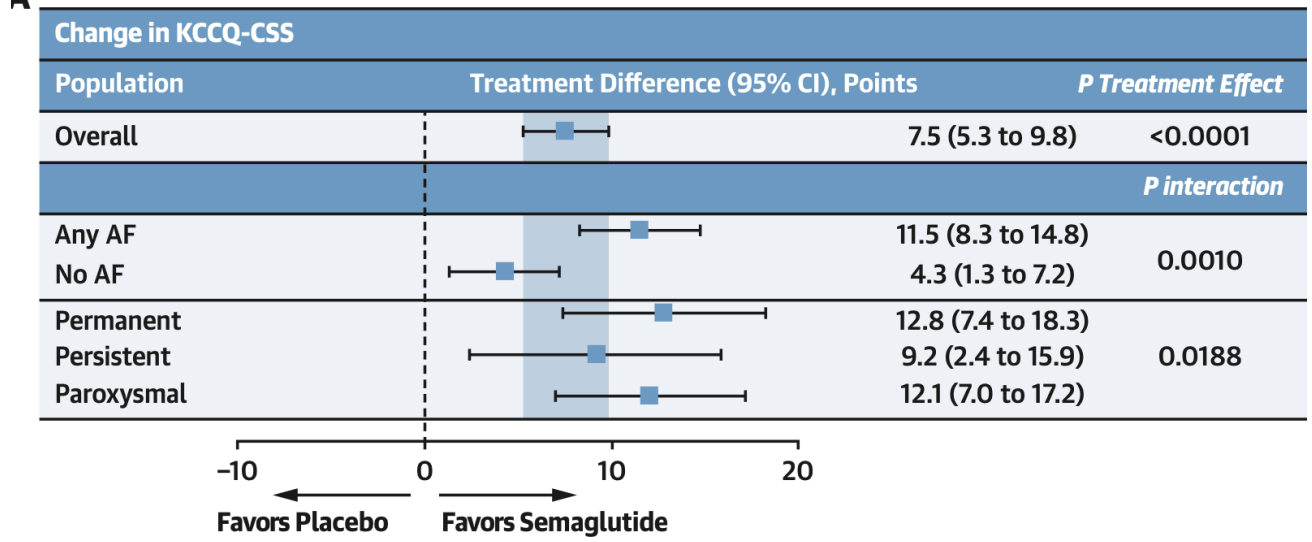
Favors Placebo Favors Semaglutide

J Am Coll Cardiol 2024;84:27–40

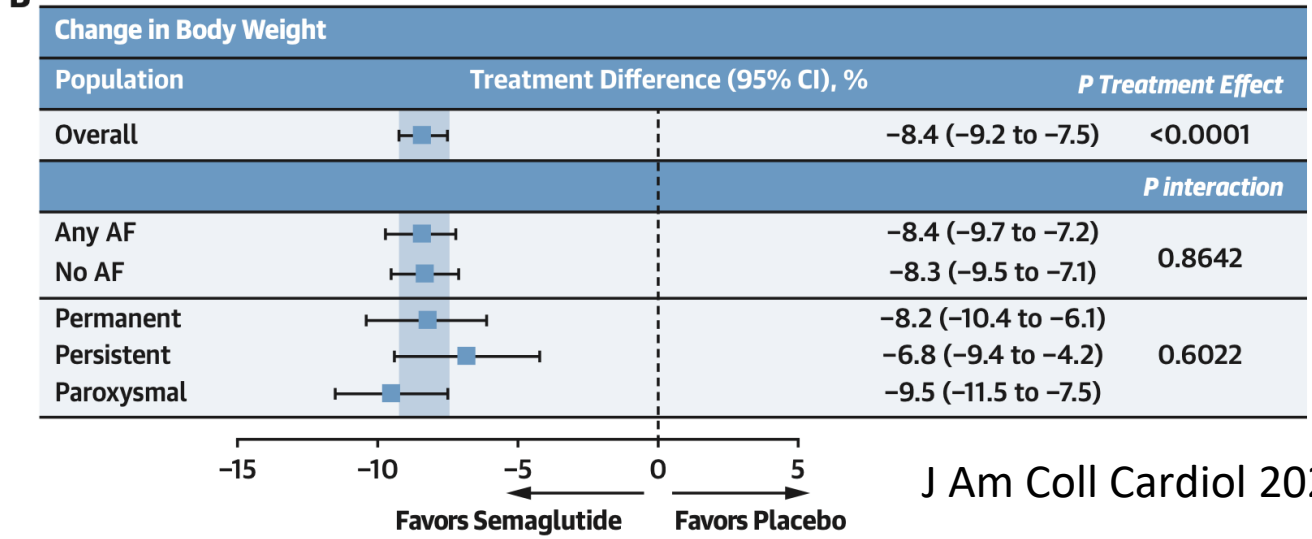
Atrial Fibrillation and Semaglutide Effects in Obesity-Related Heart Failure With Preserved Ejection Fraction

- **518 with AF** and 627 without AF
- Patients with AF
  - Older (72 vs 67 years) and higher natriuretic peptides.
  - Más peso (106.2 vs 101) but BMI similar.

A



B



J Am Coll Cardiol 2024

Semaglutide and diuretic use in obesity-related heart failure with preserved ejection fraction: a pooled analysis of the STEP-HFpEF and STEP-HFpEF-DM trials

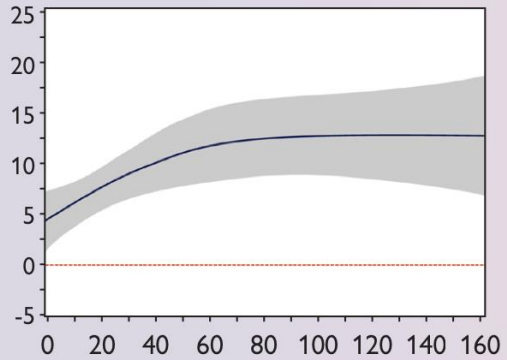
Semaglutide was effective and safe regardless of baseline diuretic use, but KCCQ-CSS improvements were magnified at ↑ loop diuretic doses

Totally daily dose of loop diuretics increased in the placebo arm and decreased in the semaglutide arm during follow-up

Semaglutide reduced new initiation of loop diuretics by 71% and resulted in a 2.7-fold ↑ likelihood of loop diuretic discontinuations (P=0.02)

Primary outcome: KCCQ-CSS

52-week treatment difference (semaglutide-placebo)

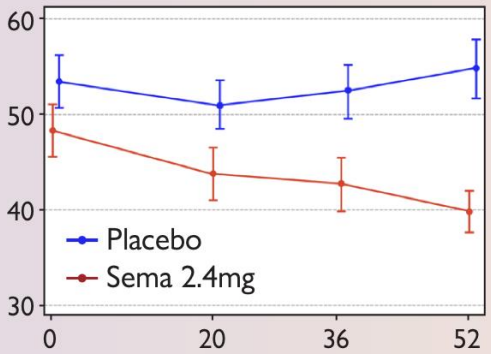


Baseline loop diuretic dose (mg/day furosemide equivalents)

P-interaction = 0.011

Loop diuretic dose changes

Loop diuretic dose changes (mg/day furosemide equivalents)

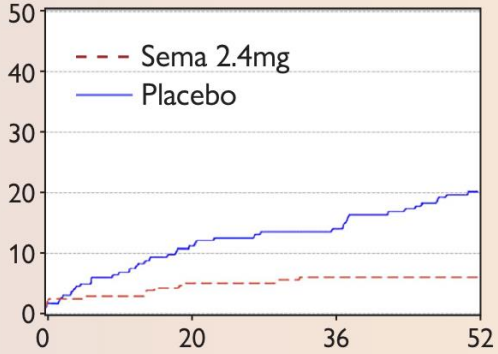


Time since randomization (weeks)

Estimated treatment difference over 52 weeks: -11.8 mg/day (95% CI -16.8; -6.8); P<0.0001

New loop diuretic initiation

Cumulative incidence of new loop diuretic initiations

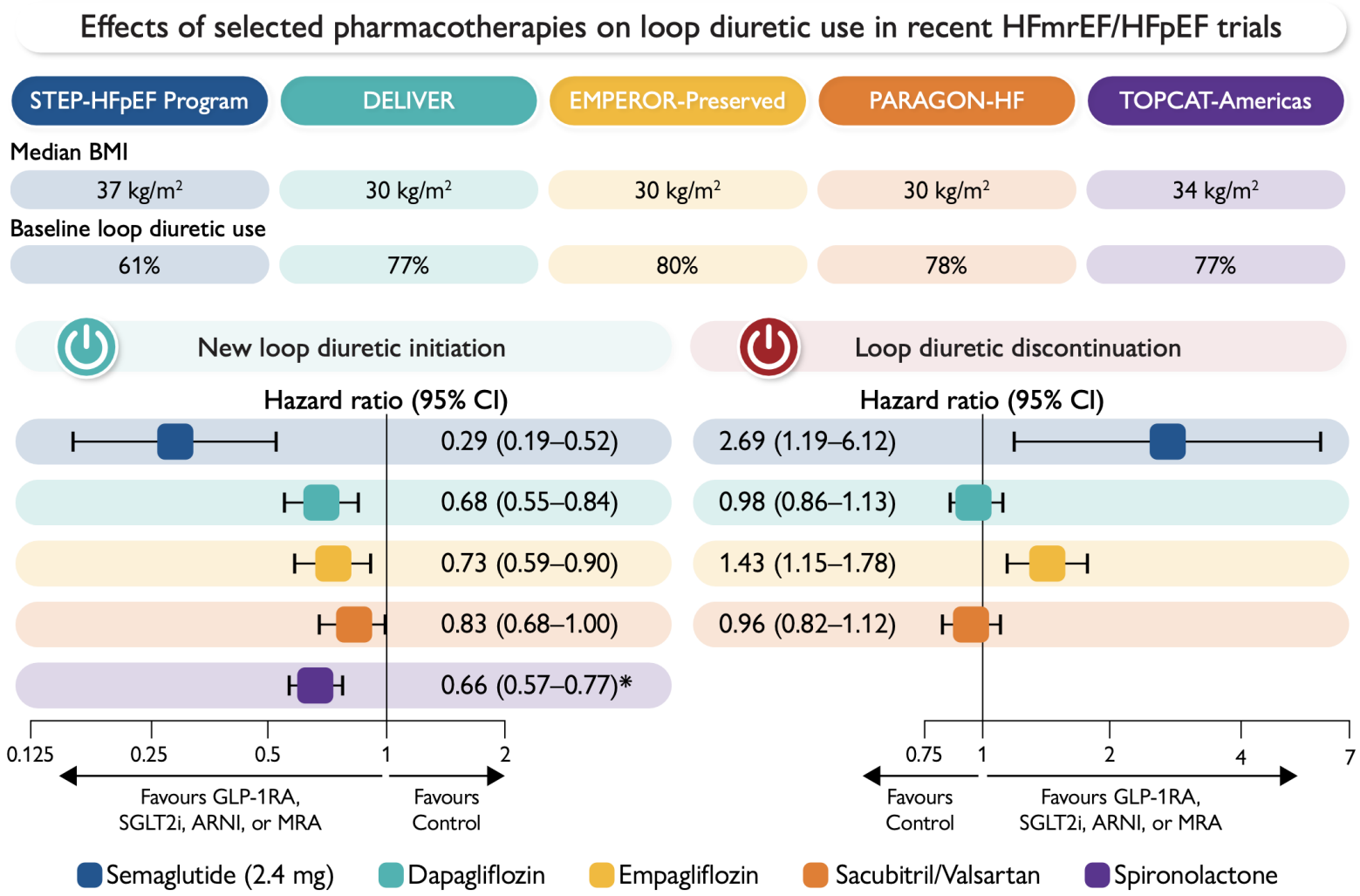


Time since randomization (weeks)

HR 0.29 (95% CI 0.16, 0.52); P<0.0001

European Heart Journal (2024) **00**, 1–16

STEPping down diuretic therapy with semaglutide in obesity-related heart failure with preserved ejection fraction: decongestion or disease modification?

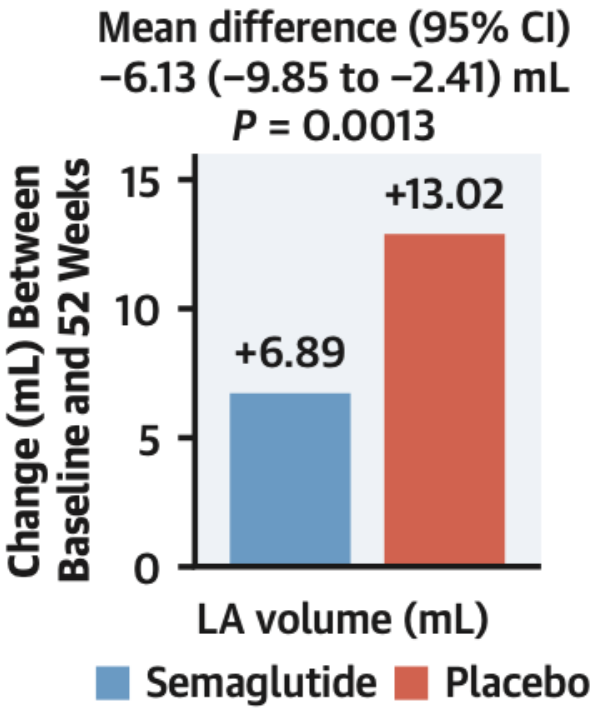


- ❑ Enhance afferent renal arteriolar vaso ⬆, renal Flow and natriuresis.
- ❑ Attenuate reflex renal vaso ⬇ renal in response to loop diuretic.
- ❑ ⬇ kidney inflammation.
- ❑ Preserve kidney structure and function (FLOW).
- ❑ ⬇ adiposity, pericardial restraint and adverse ventricular interaction.

European Heart Journal (2024) **00**, 1–4

Effect of Semaglutide on Cardiac Structure and Function in Patients With Obesity-Related Heart Failure

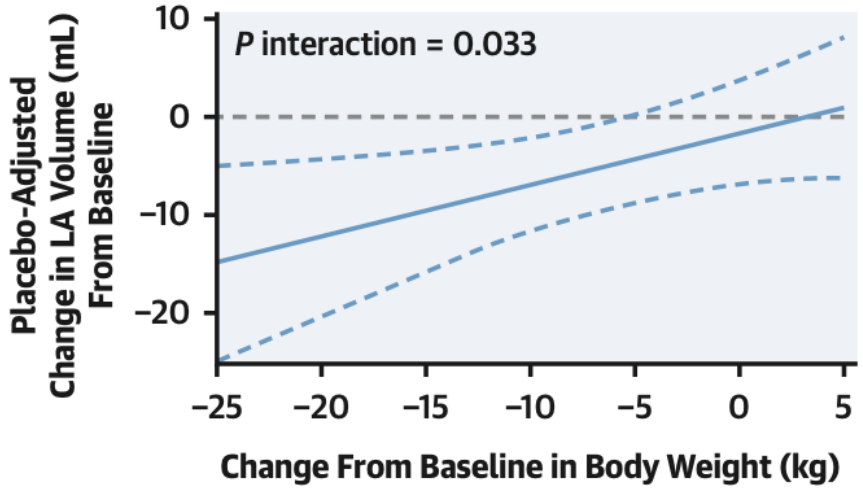
Treatment Effects of Semaglutide on LA Volume and Other Parameters



Benefits of semaglutide on LA remodeling were consistent irrespective of age, sex, BMI, NT-proBNP, hsCRP, diabetes status, AF status, LVEF, and background pharmacotherapy

Semaglutide also improved E wave velocity, E/A ratio, E/e' average, and RV remodeling compared with placebo, but did not impact LV mass, LV mechanics, or LA strain

Benefits of Semaglutide on LA Volume Related to Magnitude of Weight Loss



However, benefits of semaglutide on E wave velocity, E/e' average, and RV end-diastolic area were not associated with weight change between baseline and 52 weeks

J Am Coll Cardiol 2024

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 14, 2023 VOL. 389 NO. 24

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

A. Michael Lincoff, M.D., Kirstine Brown-Frandsen, M.D., Helen M. Colhoun, M.D., John Deanfield, M.D., Scott S. Emerson, M.D., Ph.D., Sille Esbjerg, M.Sc., Søren Hardt-Lindberg, M.D., Ph.D., G. Kees Hovingh, M.D., Ph.D., Steven E. Kahn, M.B., Ch.B., Robert F. Kushner, M.D., Ildiko Lingvay, M.D., M.P.H., Tugce K. Oral, M.D., Marie M. Michelsen, M.D., Ph.D., Jorge Plutzky, M.D., Christoffer W. Tornøe, Ph.D., and Donna H. Ryan, M.D., for the SELECT Trial Investigators*

N Engl J Med 2023;389:2221-32.

INCLUSION CRITERIA:

BMI> 27 kg/m^2

CV disease

- Previous MI
- Previous stroke
- Peripheral arterial disease

EXCLUSION CRITERIA:

Previous DM

Hb A1c > 6,5%

Previous treatment with aGLP-1

NYHA class IV HF

End-stage kidney disease / dialysis

CV or neurolgic event < 60 d

Planned revascularization

Randomization

N= 17604

October 2018 -Marzch 2021

Semaglutida 2,4 mg/sem vs pl.

Follow-up 39,8 months

SELECT

Characteristic	Semaglutide (N=8803)	Placebo (N=8801)
Age — yr	61.6±8.9	61.6±8.8
Male sex — no. (%)	6355 (72.2)	6377 (72.5)
Race or ethnic group — no. (%)†		
White	7387 (83.9)	7404 (84.1)
Asian	720 (8.2)	727 (8.3)
Black	348 (4.0)	323 (3.7)
Other	253 (2.9)	273 (3.1)
Hispanic or Latino	914 (10.4)	908 (10.3)
Body weight — kg	96.5±17.5	96.8±17.8
BMI‡	33.3±5.0	33.4±5.0
Waist circumference — cm	111.3±13.1	111.4±13.1
Glycated hemoglobin level — %	5.78±0.34	5.78±0.33
Distribution — no. (%)		
<5.7%	2925 (33.2)	2980 (33.9)
≥5.7%	5877 (66.8)	5819 (66.1)
Median high-sensitivity CRP level (IQR) — mg/liter	1.87 (0.89–4.18)	1.80 (0.86–4.06)
Cardiovascular inclusion criteria — no. (%)		
Myocardial infarction only	5962 (67.7)	5944 (67.5)
Stroke only	1578 (17.9)	1556 (17.7)
Peripheral arterial disease only	376 (4.3)	401 (4.6)
Two or more inclusion criteria	718 (8.2)	719 (8.2)
Other§	169 (1.9)	181 (2.1)
eGFR — ml/min/1.73 m^2	82.4±17.5	82.5±17.3

N Engl J Med 2023;389:2221-32.

INCLUSION CRITERIA:

BMI> 27 kg/m^2

CV disease

- Previous MI
- Previous stroke
- Peripheral arterial disease

EXCLUSION CRITERIA:

Previous DM

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Previous treatment with aGLP-1

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End-stage kidney disease / dialysis

CV or neurolgic event < 60 d

Planned revascularization

Randomization

N= 17604

October 2018 -Marzch 2021

Semaglutida 2,4 mg/sem vs pl.

Follow-up 39,8 months

PATIENTS:

72.3 % ♂, mean age 61.69 years

BMI 33.3

- **MI 67.7%**
- Stroke 17.9%
- Peripheral arterial disease 4.3%
- 2 or more 8.2%

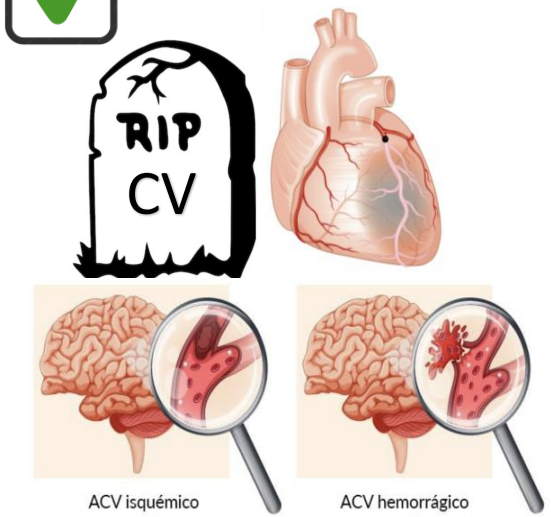
Nearly ¼ Chronic Heart Failure

0 patients with ISGLT2.

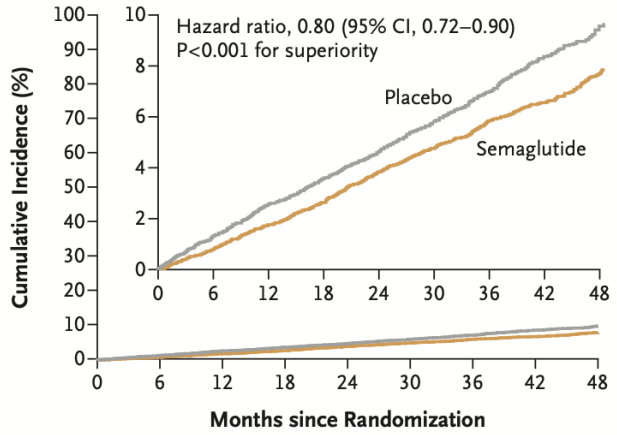
213/ 8803 semaglutide
332 /8801 placebo
} 3,1%

N Engl J Med 2023;389:2221-32.

SELECT

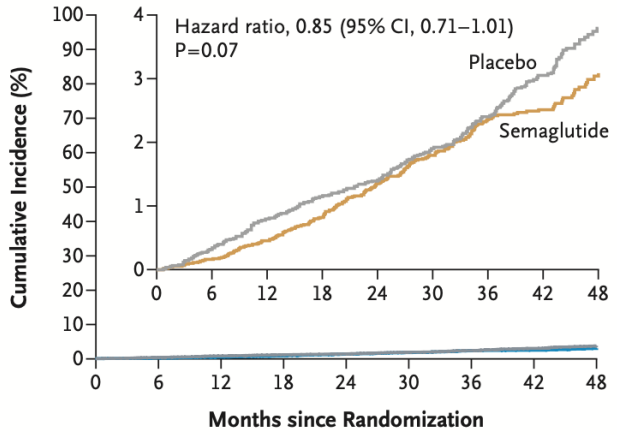


A Primary Cardiovascular Composite End Point



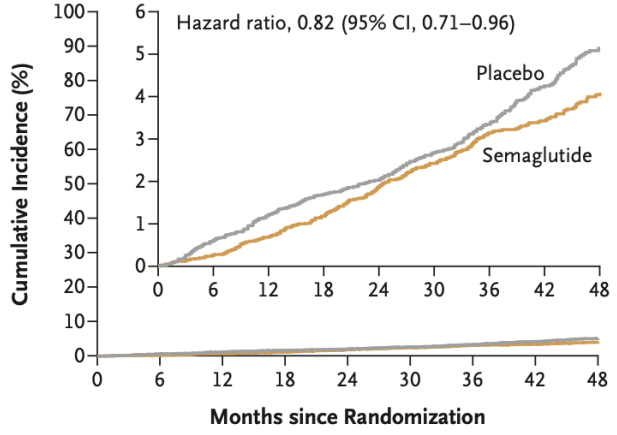
No. at Risk									
Placebo	8801	8652	8487	8326	8164	7101	5660	4015	1672
Semaglutide	8803	8695	8561	8427	8254	7229	5777	4126	1734

B Death from Cardiovascular Causes



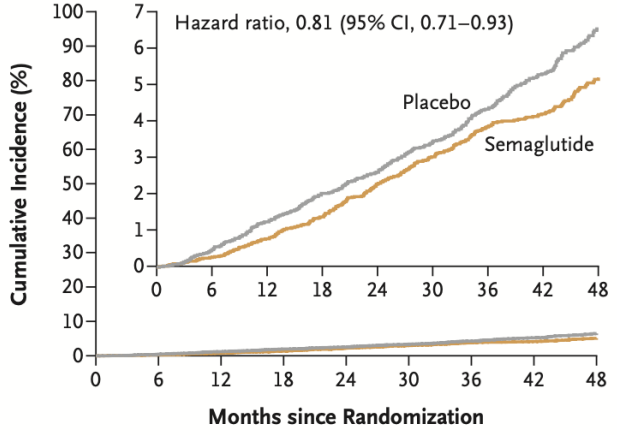
No. at Risk									
Placebo	8801	8733	8634	8528	8430	7395	5938	4250	1793
Semaglutide	8803	8748	8673	8584	8465	7452	5988	4315	1832

C Heart Failure Composite End Point



No. at Risk									
Placebo	8801	8711	8601	8485	8381	7341	5885	4198	1766
Semaglutide	8803	8740	8654	8557	8425	7409	5944	4277	1816

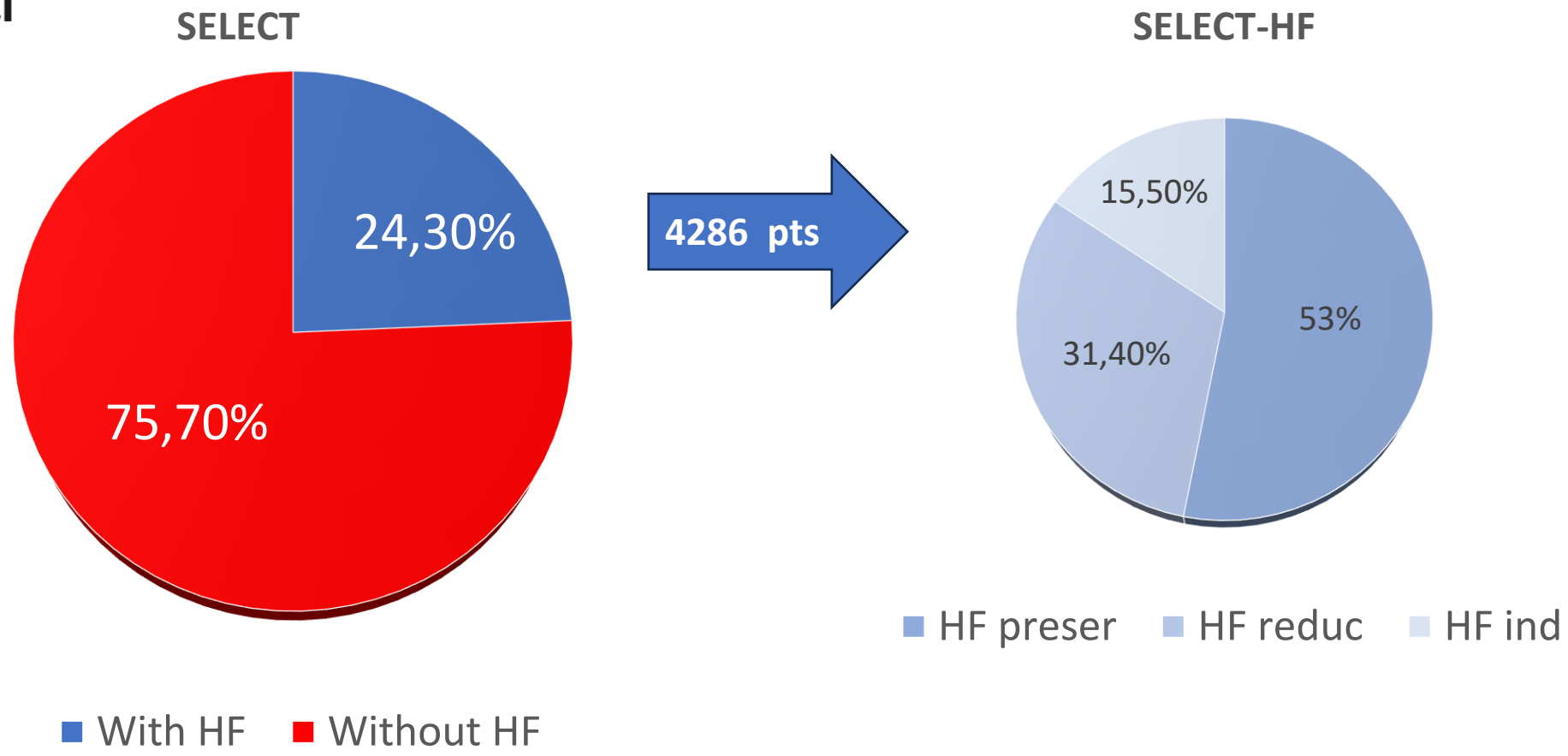
D Death from Any Cause



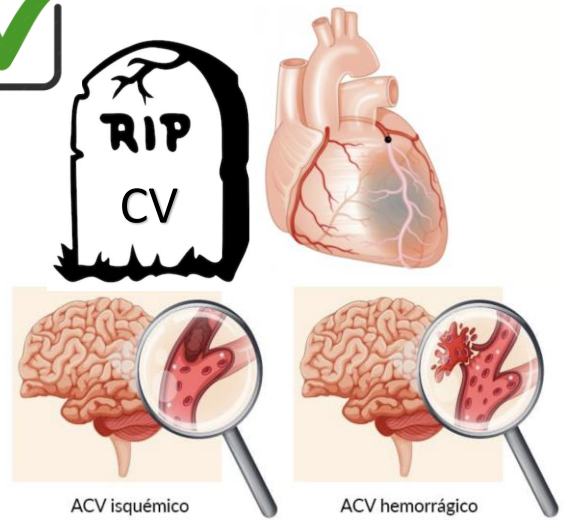
No. at Risk									
Placebo	8801	8733	8634	8528	8430	7395	5938	4250	1793
Semaglutide	8803	8748	8673	8584	8465	7452	5988	4315	1832

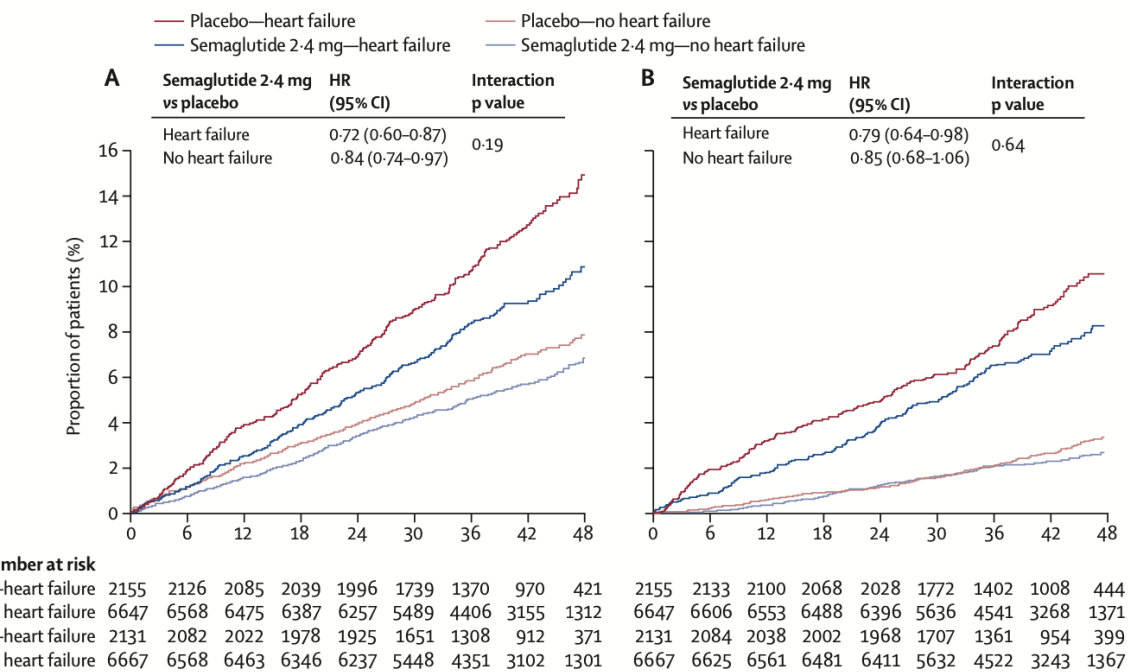
N Engl J Med 2023;389:2221-32.

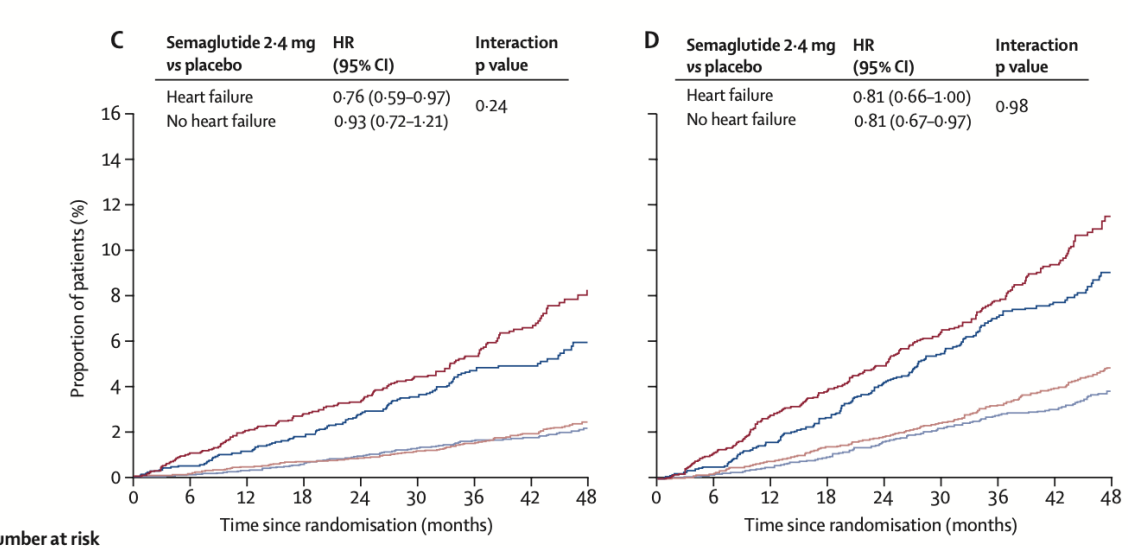
Semaglutide and cardiovascular outcomes in patients with obesity and prevalent heart failure: a prespecified analysis of the SELECT trial



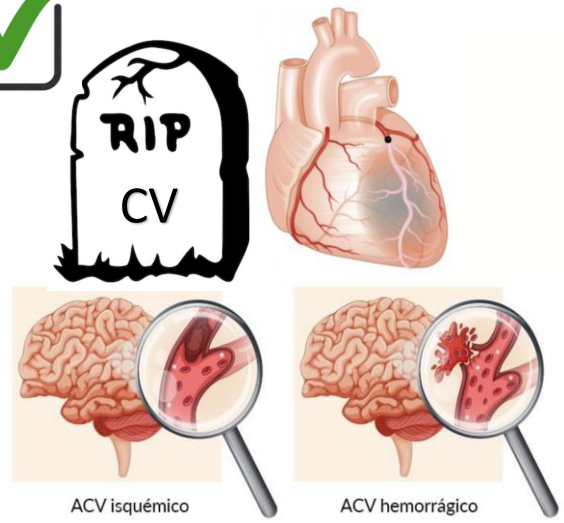
Lancet 2024; 404: 773–86

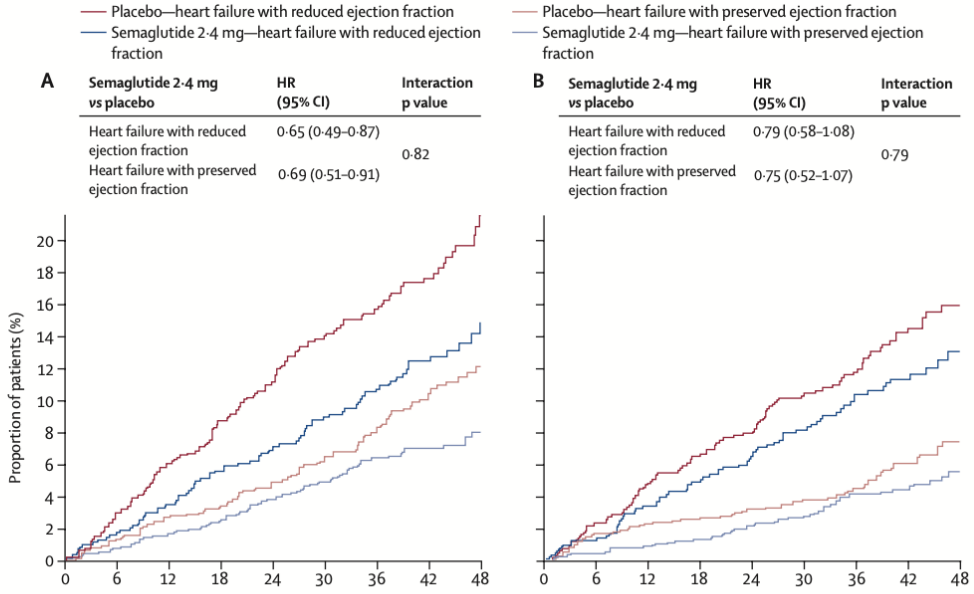






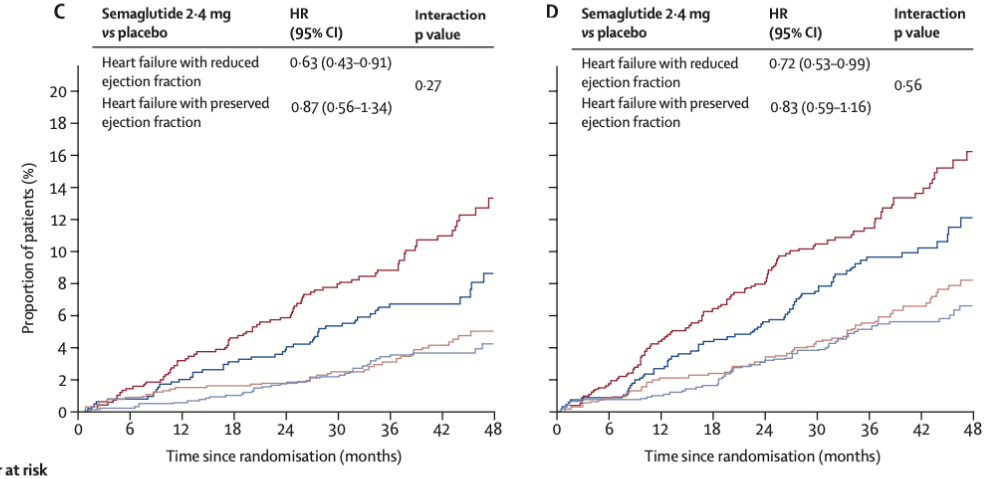
Lancet 2024; 404: 773–86





Number at risk

Semaglutide 2·4 mg—heart failure with preserved ejection fraction	1174	1161	1146	1130	1107	962	779	547	244	1174	1166	1157	1148	1129	987	798	570	258
Semaglutide 2·4 mg—heart failure with reduced ejection fraction	654	641	625	603	592	516	383	273	109	654	644	626	609	597	522	390	282	114
Placebo—heart failure with preserved ejection fraction	1099	1082	1060	1048	1024	887	716	497	214	1099	1080	1066	1056	1041	915	749	528	233
Placebo—heart failure with reduced ejection fraction	693	671	641	619	598	504	395	292	105	693	676	651	635	621	527	412	300	111



Number at risk

Semaglutide 2·4 mg—heart failure with preserved ejection fraction	1174	1168	1160	1151	1133	992	806	575	261	1174	1168	1160	1151	1133	992	806	575	261
Semaglutide 2·4 mg—heart failure with reduced ejection fraction	654	648	635	620	612	537	404	296	117	654	648	635	620	612	537	404	296	117
Placebo—heart failure with preserved ejection fraction	1099	1089	1075	1068	1056	927	758	538	240	1099	1089	1075	1068	1056	927	758	538	240
Placebo—heart failure with reduced ejection fraction	693	682	662	647	634	542	430	317	118	693	682	662	647	634	542	430	317	118

Lancet 2024; 404: 773–86

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 11, 2024 VOL. 391 NO. 2

Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes

Vlado Perkovic, M.B., B.S., Ph.D., Katherine R. Tuttle, M.D., Peter Rossing, M.D., D.M.Sc., Kenneth W. Mahaffey, M.D., Johannes F.E. Mann, M.D., George Bakris, M.D., Florian M.M. Baeres, M.D., Thomas Idorn, M.D., Ph.D., Heidrun Bosch-Traberg, M.D., Nanna Leonora Lausvig, M.Sc., and Richard Pratley, M.D., for the FLOW Trial Committees and Investigators*

N Engl J Med 2024;391:109-21.

Rationale, design and baseline data of FLOW, a kidney outcomes trial with once-weekly semaglutide in DM2 and CKD

Methods

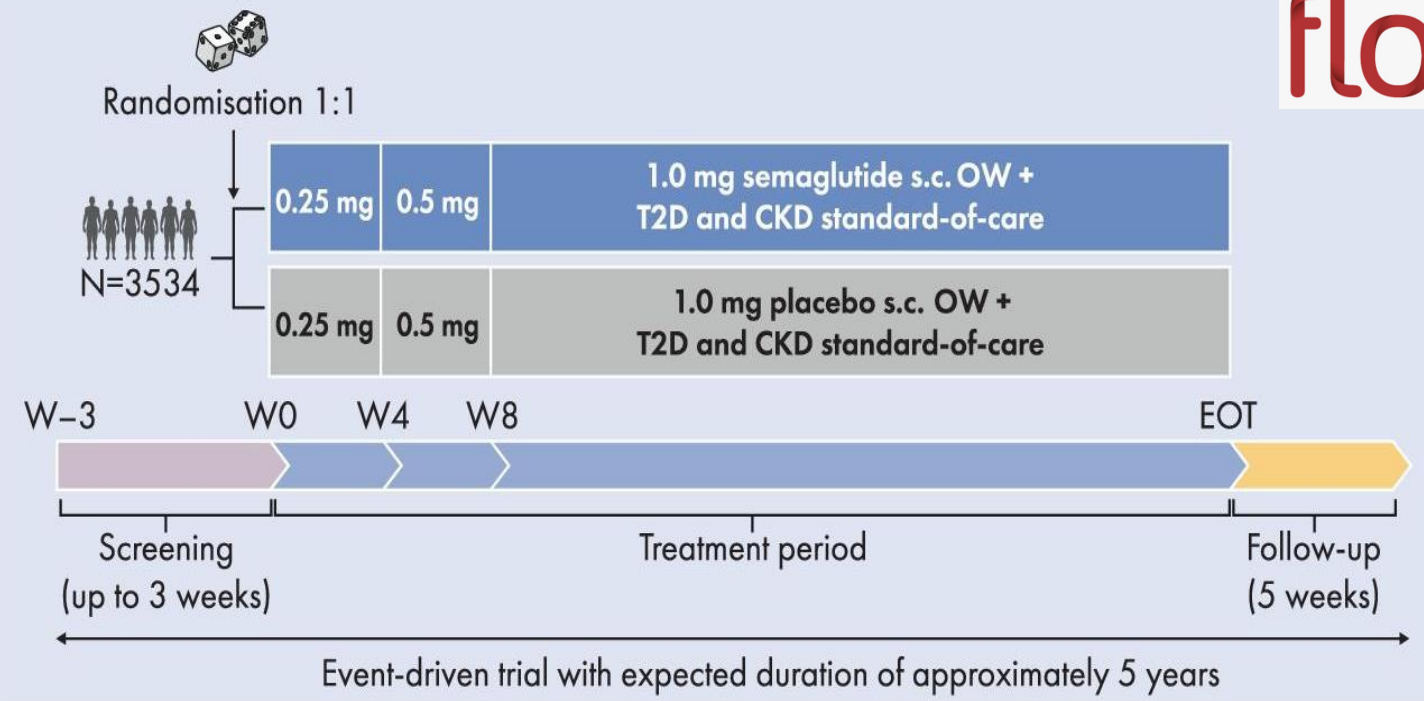
Participants:

- Adults with T2D
- eGFR ≥50 to ≤75 ml/min/1.73 m² and UACR >300 to <5000 mg/g OR
- eGFR ≥25 to <50 ml/min/1.73 m² and UACR >100 to <5000 mg/g

Composite primary endpoint:

Time to first occurrence of:

- Kidney failure (persistent eGFR <15 ml/min/1.73 m² or initiation of CKRT);
- Persistent ≥50% reduction in eGFR; or
- Death from kidney or CV causes



Baseline characteristics

68.2% at very high risk for CKD progression according to KDIGO categorisation, eGFR of 47.0 (15) ml/min/1.73 m²; median UACR of 568 (range: 2–11 852) mg/g

Advanced type 2 diabetes:
Mean age 66.6 years
Mean diabetes duration 17.4 years
Mean HbA_{1c} 7.8%

15.5% receiving SGLT-2is

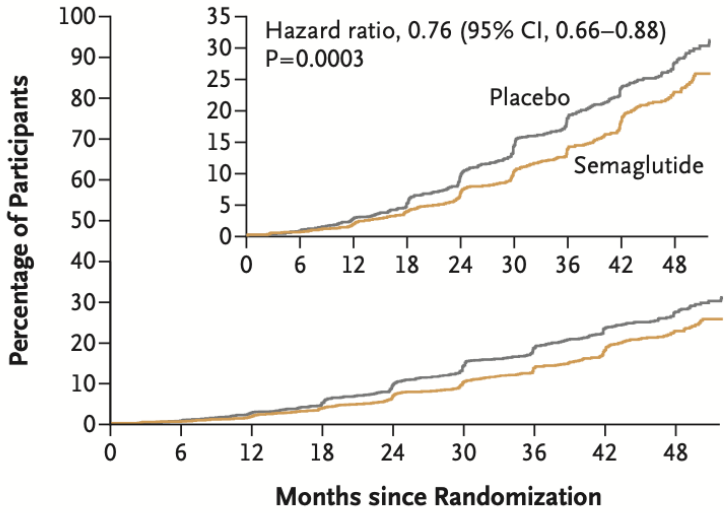
Rossing P, et al NDT 2023

Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes

Vlado Perkovic, M.B., B.S., Ph.D., Katherine R. Tuttle, M.D., Peter Rossing, M.D., D.M.Sc., Kenneth W. Mahaffey, M.D., Johannes F.E. Mann, M.D., George Bakris, M.D., Florian M.M. Baeres, M.D., Thomas Idorn, M.D., Ph.D., Heidrun Bosch-Traberg, M.D., Nanna Leonora Lausvig, M.Sc., and Richard Pratley, M.D., for the FLOW Trial Committees and Investigators*

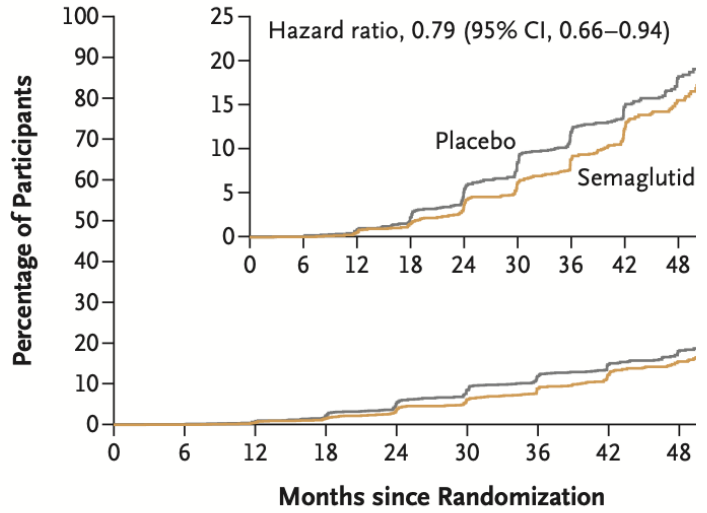
flow

A First Major Kidney Disease Event



No. at Risk									
Placebo	1766	1736	1682	1605	1516	1408	1048	660	354
Semaglutide	1767	1738	1693	1640	1572	1489	1131	742	392

B First Kidney-Specific Component Event



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Placebo	1766	1736	1682	1605	1516	1408	1048	660	354
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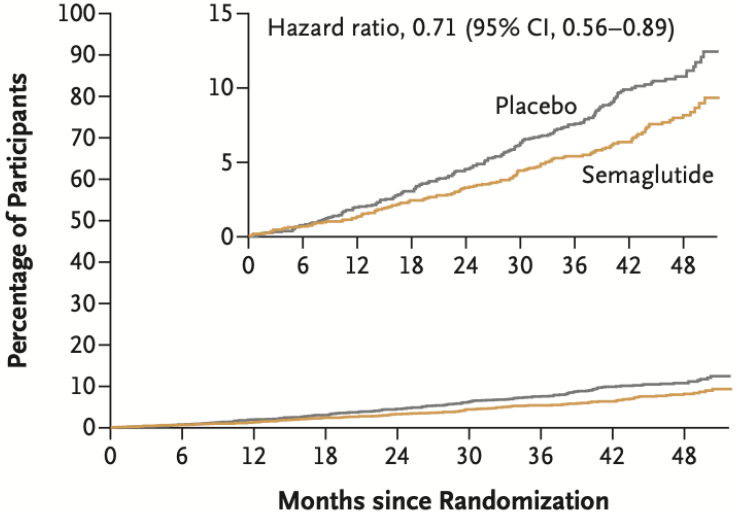
C Death from Cardiovascular Causes

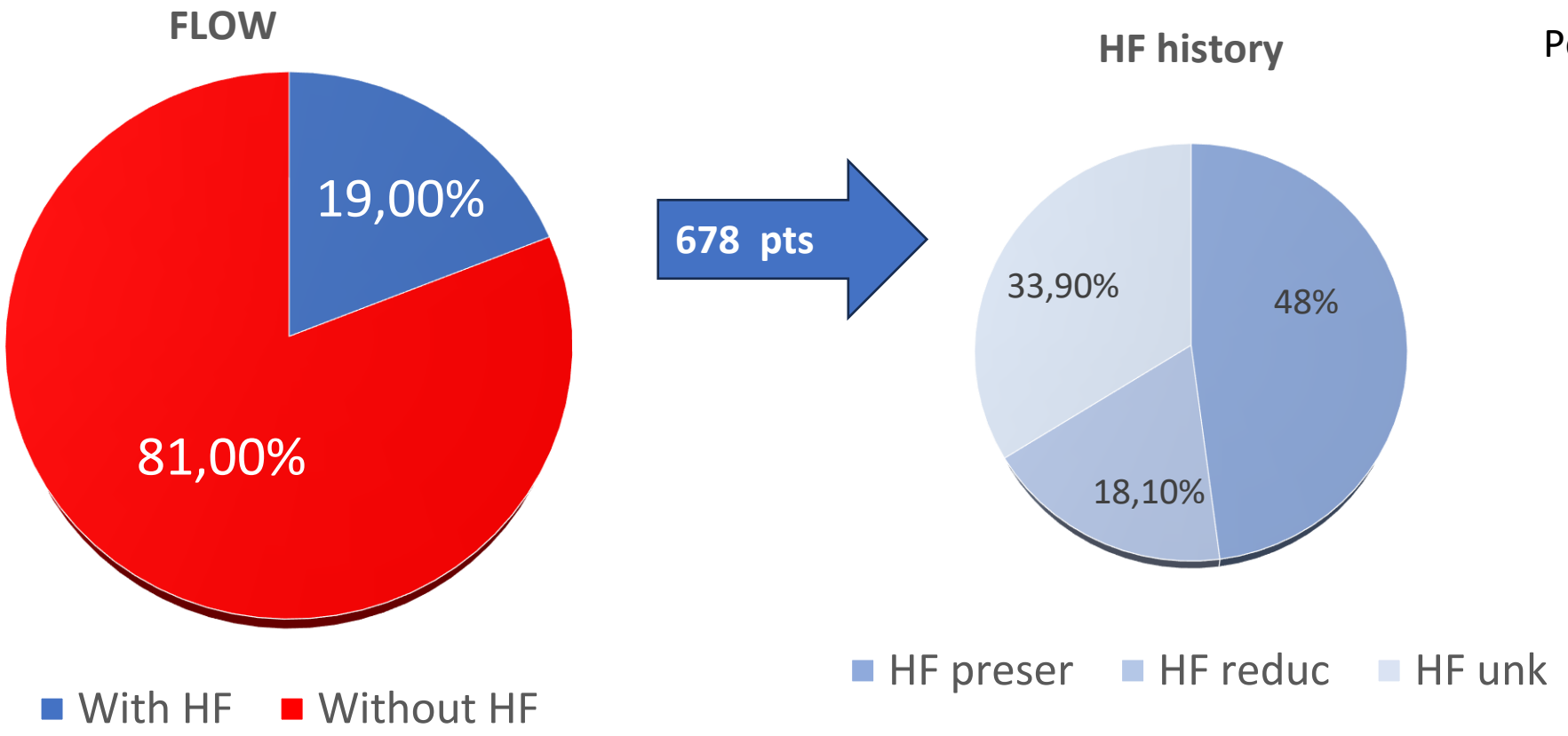


No. at Risk									
Placebo	1766	1737	1697	1641	1601	1544	1185	772	437
Semaglutide	1767	1739	1703	1665	1627	1583	1234	838	460

N Engl J Med 2024;391:109-21.

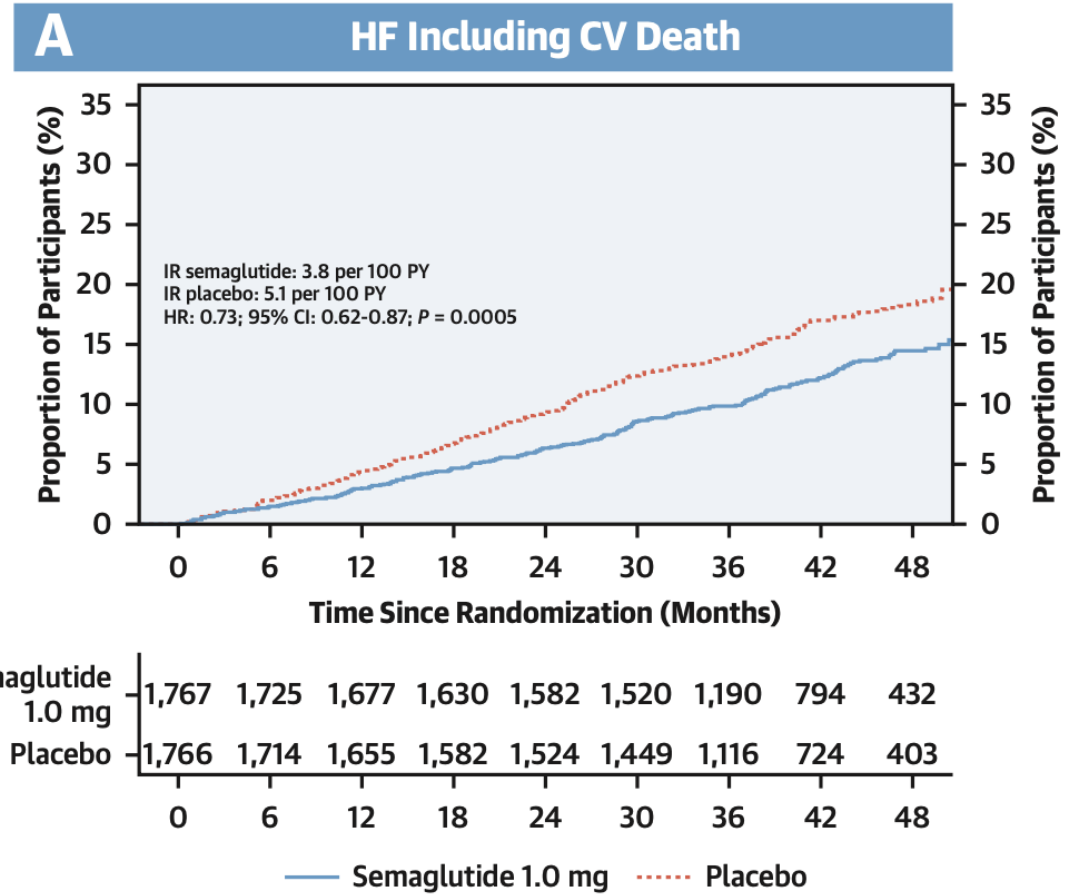
Effects of Semaglutide on Heart Failure Outcomes in Diabetes and Chronic Kidney Disease in the FLOW Trial

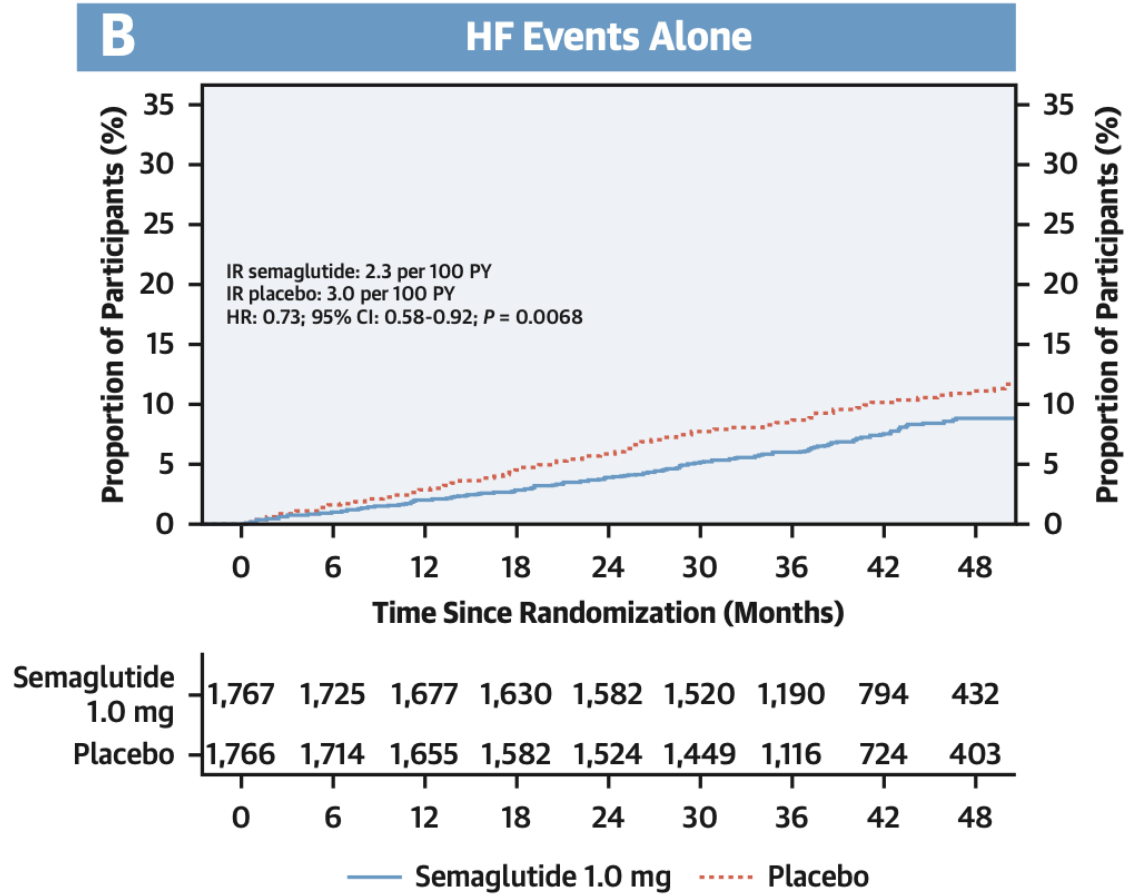
Post-hoc



Pratley et al JACC. 2024;

Effects of Semaglutide on Heart Failure Outcomes in Diabetes and Chronic Kidney Disease in the FLOW Trial





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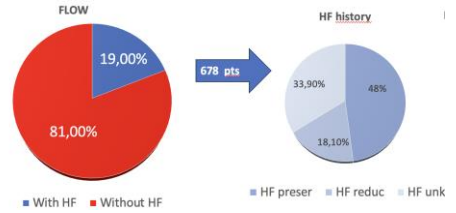
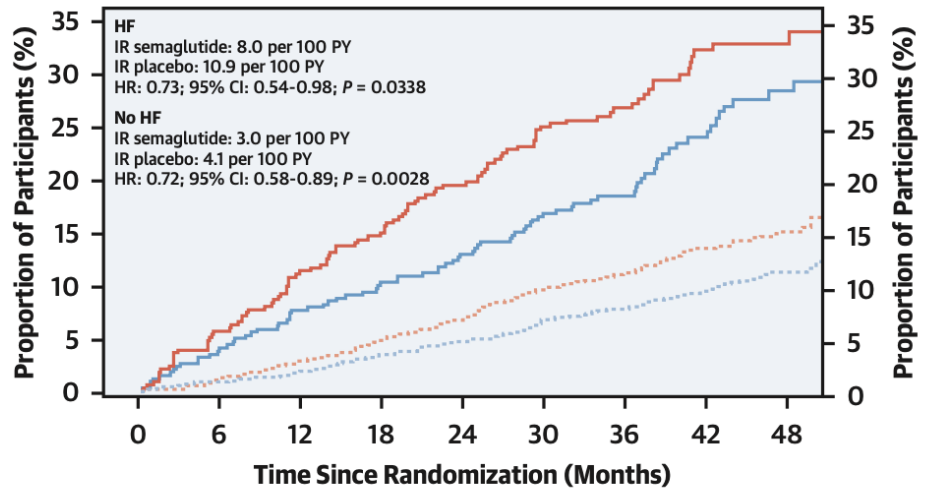


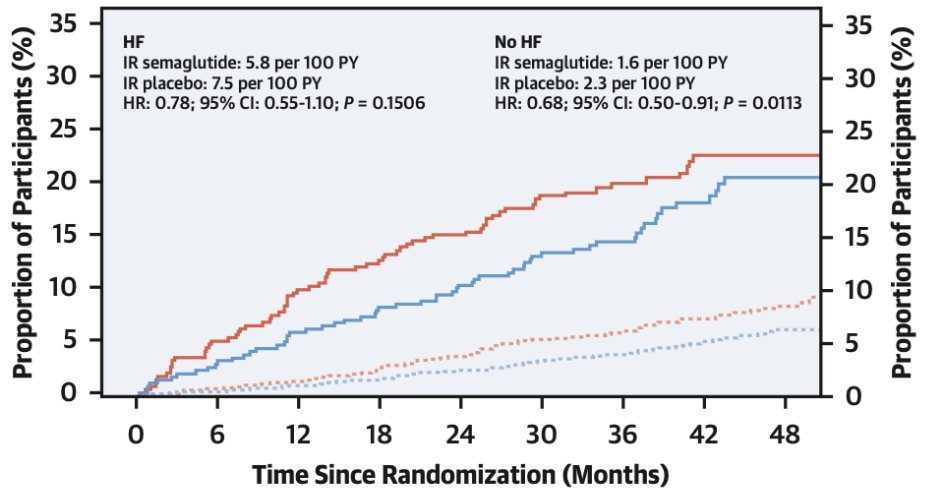
C HF Including CV Death by Baseline HF Status



	0	6	12	18	24	30	36	42	48
Semaglutide 1.0 mg HF	342	325	312	301	286	269	196	124	83
Semaglutide 1.0 mg No HF	1,424	1,399	1,364	1,328	1,295	1,250	994	670	349
Placebo HF	336	313	291	273	251	230	165	103	61
Placebo No HF	1,430	1,401	1,364	1,309	1,273	1,219	951	621	342

Semaglutide 1.0 mg-HF
Semaglutide 1.0 mg-No HF
Placebo-HF
Placebo-No HF

D HF Events Alone by baseline HF status



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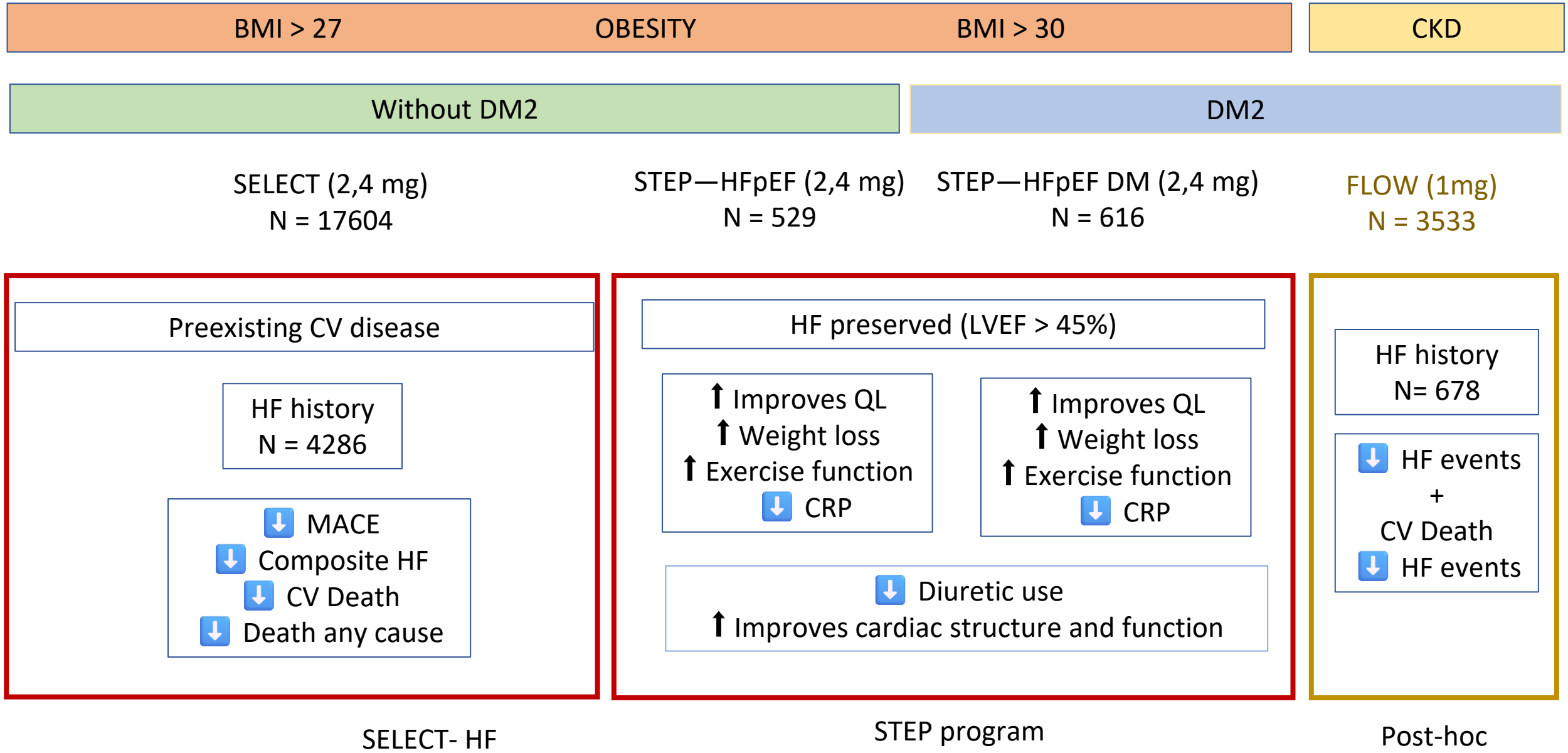

BMI > 27
OBESITY
BMI > 30
CKD
Without DM2
DM2
SELECT (2,4 mg)
N = 17604
STEP—HFpEF (2,4 mg)
N = 529
STEP—HFpEF DM (2,4 mg)
N = 616
FLOW (1mg)
N = 3533
Preexisting CV disease
HF history
N = 4286
MACE
Composite HF
CV Death
Death any cause
HF preserved (LVEF > 45%)
Improves QL
Weight loss
Exercise function
CRP
Improves QL
Weight loss
Exercise function
CRP
Diuretic use
Improves cardiac structure and function
HF history
N= 678
HF events
+
CV Death
HF events
SELECT- HF
STEP program
Post-hoc

BMI > 27 | OBESITY | BMI > 30

CKD

Without DM2

DM2

SELECT (2,4 mg)
N = 17604

STEP—HFpEF (2,4 mg)
N = 529

STEP—HFpEF DM (2,4 mg)
N = 616

FLOW (1mg)
N = 3533

Preexisting CV disease

HF preserved (LVEF > 45%)

HFpEF history
N = 2273

HFpEF
N = 1145

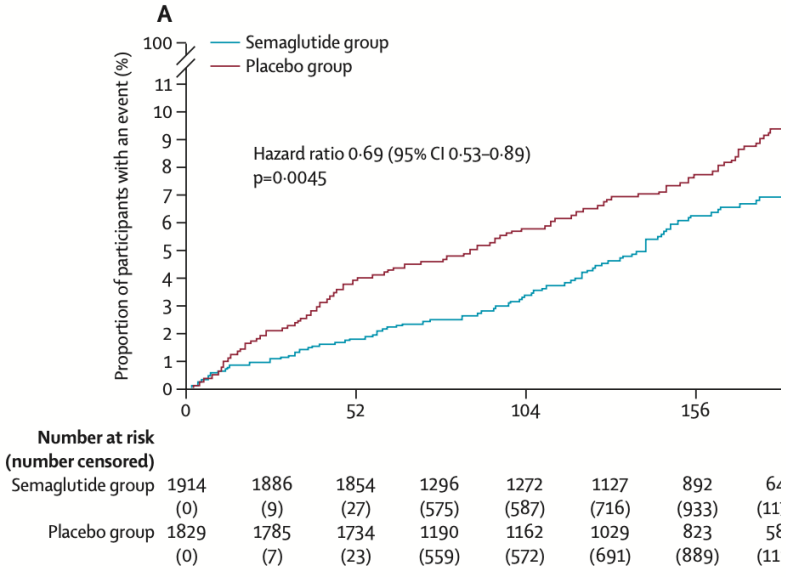
HFpEF history
N = 325

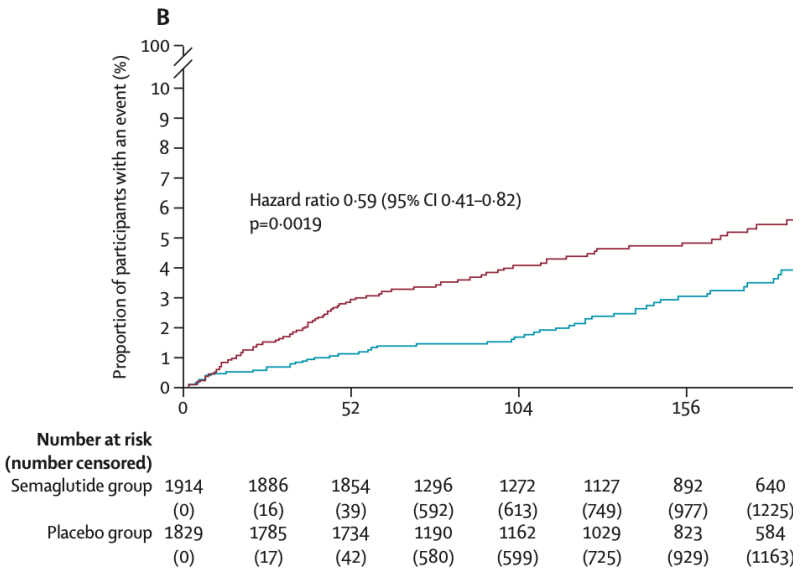
SELECT- HF

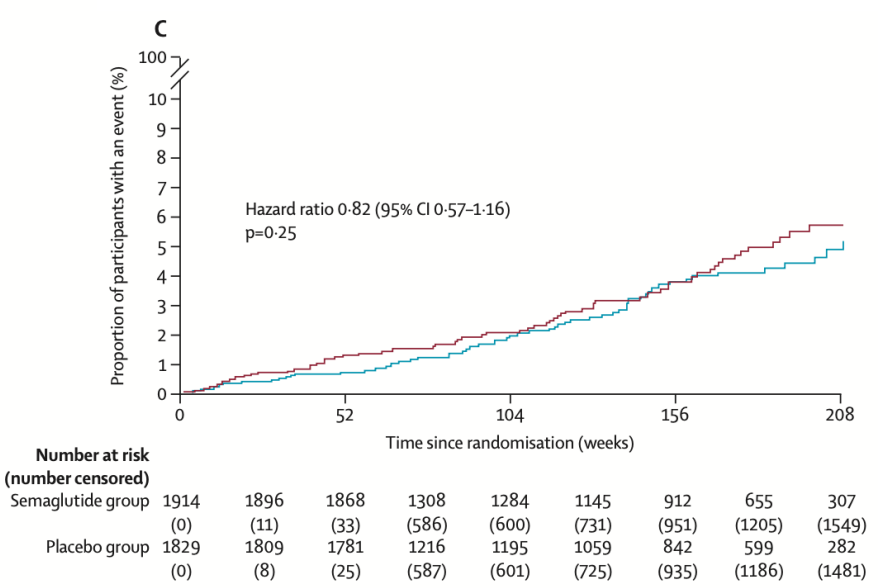
STEP program

Post-hoc

Semaglutide versus placebo in patients with heart failure and mildly reduced or preserved ejection fraction: a pooled analysis of the SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM randomised trials







Combined endpoint of cardiovascular death or worsening heart failure events

Worsening heart failure events

Cardiovascular death

IN SUMMARY

- ✓ **Association** between obesity and **risk of heart failure** with reduced ejection fraction (HFrEF) and heart failure with **preserved ejection fraction** (HFpEF).

- ✓ In patients with **obesity-related HFpEF**, semaglutide **improved heart failure-related symptoms and physical limitations.** Semaglutide also led to a **reduction in loop diuretic** use.

- ✓ Semaglutide appeared to **improve adverse cardiac remodeling** compared with placebo, further suggesting that treatment with semaglutide may be disease modifying among patients with obesity-related HFpEF.

- ✓ In patients **with HFpEF**, semaglutide reduced the risk of the combined endpoint of **cardiovascular death or worsening heart failure** events, and **worsening heart failure events** alone.
- ✓ **AND If Preexisting CV disease**, semaglutide reduces **cardiovascular death/CV any cause**.

- ✓ These data support the use of semaglutide as an efficacious therapy to **reduce the risk of clinical heart failure events in patients with HFpEF**, for whom few treatment options are currently available.

Thank you for your attention