STEP-HF$_p$EF

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

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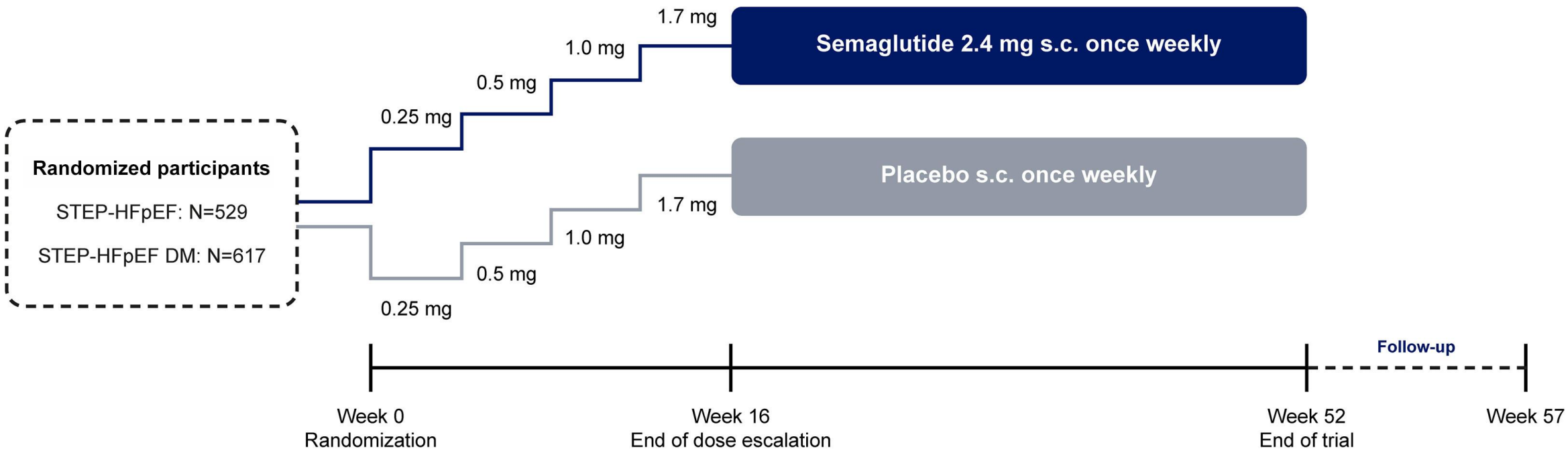
STREP-HFpEF Design



Inclusion criteria
• Male or female, age ≥18 years
• BMI ≥30.0 kg/m^2
• NYHA class II-IV
• LVEF ≥45% at screening
• No hospitalizations due to HF between screening and randomization
• Able to perform the 6MWT at screening with a minimum distance of 100 metres
• KCCQ clinical summary score <90 at screening
• At least one of the following
○ Mean PWP ≥15 mm Hg or LVEDP ≥25 mm Hg documented during catheterization at rest or PA diastolic pressure measured by implantable monitor ≥15 mmHg or PWP or LVEDP ≥25 mm Hg documented during catheterization at exercise
○ Elevated NT-proBNP[a, b] at screening combined with ≥1 of the following: (i) septal é <7 cm/sec or lateral é < 10 cm/sec or average E/é ≥15; (ii) PA systolic pressure >35 mm Hg, (iii) LA enlargement[c], (iv) LV hypertrophy with septal thickness or posterior wall thickness ≥1.2 cm
○ Hospitalization with a primary diagnosis of decompensated HF requiring IV loop diuretic treatment with the previous 12 months combined with ≥2 of the following: (i) septal é <7 cm/sec or lateral é < 10 cm/sec or average E/é ≥15; (ii) PA systolic pressure >35 mm Hg, (iii) LA enlargement[c], (iv) LV hypertrophy with septal thickness or posterior wall thickness ≥1.2 cm, (v) ongoing use of diuretic therapy for ≥30 days before screening
• Diagnosed with T2D ≥90 days prior to screening (STEP HFpEF DM only)
• Treated with diet, exercise and/or glucose lowering treatment[d] according to local label (stable dosing) for ≥30 days prior to screening (STEP HFpEF DM only)
• HbA1C ≤10.0% at the screening visit (STEP HFpEF DM only)

EXCLUSION CRITERIA

- **MI, stroke, hospitalization for HF, unstable angina pectoris, or TIA within 30 days prior to the day of screening**
- **SBP > 160 mm Hg at screening**
- **Planned coronary, carotid or peripheral artery revascularization**
- **Any other condition judged by the investigator to be the primary cause of dyspnea**
- **Bariatric surgery prior to screening or planned within the trial time course**
- **Self-reported changed in body weight >5 kg (11 lbs) within 90 days before screening**
- **HbA1c ≥6.5 % (48 mmol/mol) based on latest available value from medical records, no older than 3 months or if unavailable at local measurement at screening**
- **History of T1D or T2D (history of gestational diabetes is allowed) (for STEP HFpEF)**
- **History of T1D (history of gestational diabetes is allowed) (for STEP HFpEF DM)**
- **Treatment with any GLP-1 RA within 90 days prior to the day of screening**
- **Uncontrolled and potentially unstable diabetic retinopathy or maculopathy[e] (STEP HFpEF DM only)**
- **Recurrent severe hypoglycaemic episodes within the last year as judged by the investigator (STEP HFpEF DM only)**
- **Treatment with continuous subcutaneous insulin infusion (STEP HFpEF DM only)**
- **Personal or first-degree relative(s) history of MEN2 or MTC**
- **Acute pancreatitis within the last 180 days prior to screening or history or presence of chronic pancreatitis**
- **End-stage renal disease or chronic or intermittent haemodialysis or peritoneal dialysis**
- **Presence or history of malignant neoplasm within 5 years prior to the day of screening. Basal and squamous cell cancer and any carcinoma in-situ are allowed**
- **Known or suspected hypersensitivity to trial product(s) or related products**
- **Participation in any clinical trial of an approved or non-approved device for the treatment of HF or obesity within 30 days before screening**
- **Receipt of any investigational medicinal product within 30 days before screening**
- **Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using a highly effective contraceptive method**
- **Major surgery scheduled for the duration of the trial, affecting walking ability in the opinion of the investigator**
- **Any disorder, including severe psychiatric disorder, suicidal behaviour within 90 days before screening, and suspected drug abuse, which in the investigator´s opinion might jeopardise subject´s safety or compliance with the protocol.**

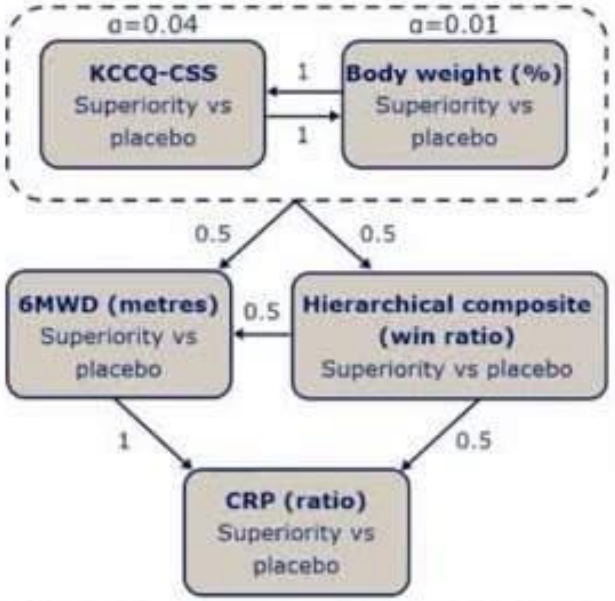
Table 1. Baseline Demographic and Clinical Characteristics of the Participants.*

Characteristic	Semaglutide (N=263)	Placebo (N=266)	Total (N=529)
Female sex — no. (%)	149 (56.7)	148 (55.6)	297 (56.1)
Median age (IQR) — yr	70 (62–75)	69 (62–75)	69 (62–75)
Ethnic group — no. (%)†			
Hispanic or Latino	15 (5.7)	21 (7.9)	36 (6.8)
Not Hispanic or Latino	248 (94.3)	245 (92.1)	493 (93.2)
Race — no. (%)†			
Black	8 (3.0)	13 (4.9)	21 (4.0)
White	255 (97.0)	252 (94.7)	507 (95.8)
Other	0	1 (0.4)	1 (0.2)
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)

Primary and confirmatory secondary endpoints and tests for superiority

Dual primary endpoints

- Change in KCCQ-CSS from baseline to week 52
- Change in body weight from baseline to week 52



Confirmatory secondary endpoints

- Change in 6MWD and change in CRP from baseline to week 52
- Hierarchical composite endpoint comprising:
  - Time to all-cause death
  - Number of HF events requiring hospitalisation or urgent HF visit
  - Time to first HF event requiring hospitalisation or urgent HF visit
  - Differences of at least 15, 10 and 5 points in KCCQ-CSS change between baseline and week 52
  - Difference of at least 30 metres in 6MWD change between baseline and week 52

For the dual primary endpoints, the alpha will be split with 1% allocation for weight change and 4% for change in KCCQ-CSS. If one of the two endpoints is superior then the full alpha can be recycled for the other endpoint, and hence the remaining primary endpoint will be tested at the 5% significance level (two-sided). If superiority is confirmed for both primary endpoints, then the confirmatory secondary endpoint will be tested. The 5% alpha will be split between 6MWD and the hierarchical composite endpoint, so that the hierarchical composite endpoint will be tested at 2.5% significance level, and if superiority is confirmed, the 6MWD will be tested at 2.75% significance level. If superiority is not confirmed for the hierarchical composite endpoint, the 6MWD will be tested at 2.5% significance level. If superiority is confirmed for both 6MWD and the hierarchical composite endpoint, CRP will be tested at 5% significance level. If only 6MWD is confirmed, CRP will be tested at 2.5% significance level. If only the hierarchical composite is confirmed, CRP will be tested at 2.25% significance level.

6MWD, 6-minute walk distance; CRP, C-reactive protein; HF, heart failure; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score.

1. Buroson CF, S.C. Stat Med. 2009;28(3):739–761.

Kosiborod M, et al. Presented at the annual meeting of the Heart Failure Association (HFA), European Society of Cardiology (ESC) congress, 20–23 May 2023, virtual and in person (Prague – Czechia) meeting

Table 2. Efficacy End Points.*

End Point	Semaglutide (N=263)	Placebo (N=266)	Estimated Difference or Ratio (95% CI)	P Value
Dual primary end points				
Change in KCCQ-CSS from baseline to week 52 — points	16.6	8.7	7.8 (4.8 to 10.9)†	<0.001
Percentage change in body weight from baseline to week 52	−13.3	−2.6	−10.7 (−11.9 to −9.4)†	<0.001
Confirmatory secondary end points				
Change from baseline to week 52 in 6-minute walk distance — m	21.5	1.2	20.3 (8.6 to 32.1)†	<0.001
Change from baseline to week 52 in CRP level — %	−43.5	−7.3	0.61 (0.51 to 0.72) ‡§	<0.001
Hierarchical composite end point — crude percentage of wins¶	60.1	34.9	1.72 (1.37 to 2.15)‖	<0.001
Supportive secondary end points				
Change from baseline to week 52 in systolic blood pressure — mm Hg	−4.9	−2.0	−2.9 (−5.8 to 0.1)†	—
Change from baseline to week 52 in waist circumference — cm	−11.7	−2.7	−9.1 (−10.6 to −7.5)†	—
Change from baseline to week 52 in KCCQ-OSS — points**	16.6	9.1	7.5 (4.4 to 10.6)†	—
Percentage reduction in body weight at week 52 — % of participants				
≥10% reduction	65.9	9.5	15.5 (9.4 to 25.4)‖	—
≥15% reduction	43.9	2.1	30.6 (12.2 to 76.6)‖	—
≥20% reduction	23.6	0.4	56.0 (7.8 to 400.8)‖	—
Increase in KCCQ-CSS at week 52 — % of participants				
≥5-point increase	75.3	63.7	1.9 (1.3 to 2.8)‖	—
≥10-point increase	63.4	48.5	2.1 (1.4 to 3.1)‖	—
Attainment of anchor-based threshold for change in KCCQ-CSS — % of participants††	43.2	32.5	1.9 (1.3 to 2.9)‖	—
Attainment of anchor-based threshold for change in 6-minute walk distance — % of participants‡‡	42.5	28.0	2.0 (1.4 to 3.0)‖	—
Exploratory end points assessed in the overall population				
Percentage reduction from baseline to week 52 in NT-proBNP level	−20.9	−5.3	0.84 (0.71 to 0.98)‡§§	—
≥15-point improvement in KCCQ-CSS at week 52 — no. of participants (%)	123 (50.6)	85 (35.9)	2.2 (1.5 to 3.2)‖	—
Adjudicated heart failure event (hospitalization or urgent visit for heart failure), time-to-event analysis — no. of events	1	12	0.08 (0.00 to 0.42)¶¶	—

STREP-HFpEF Primary Endpoints

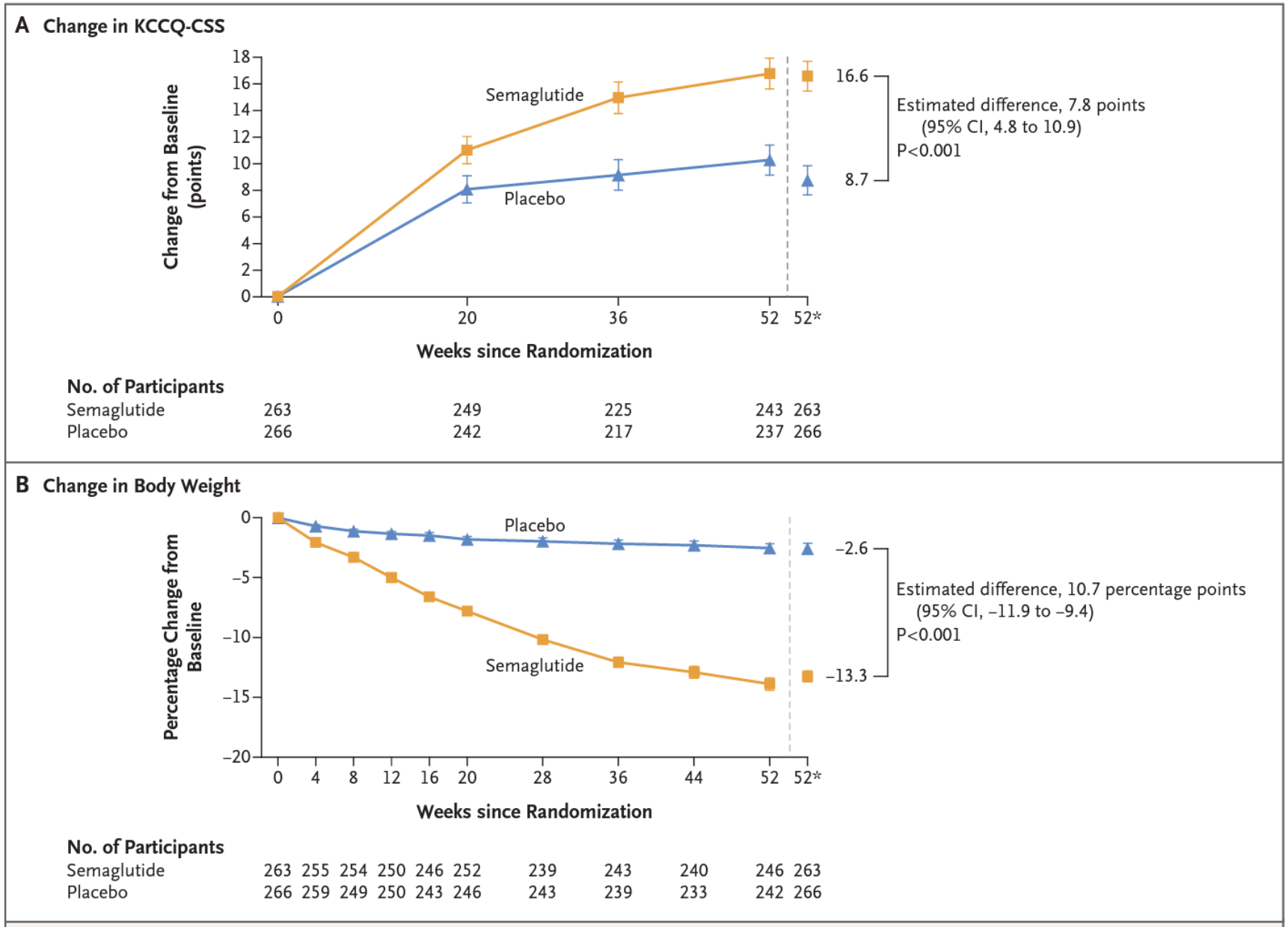
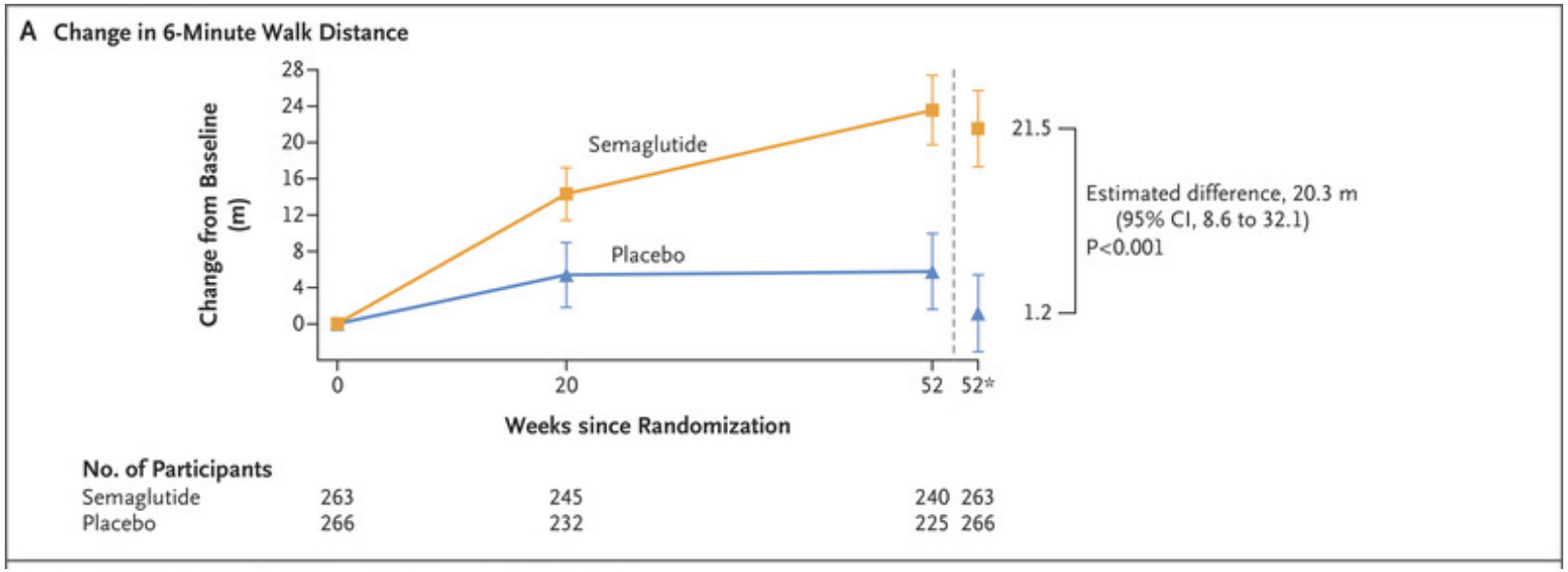
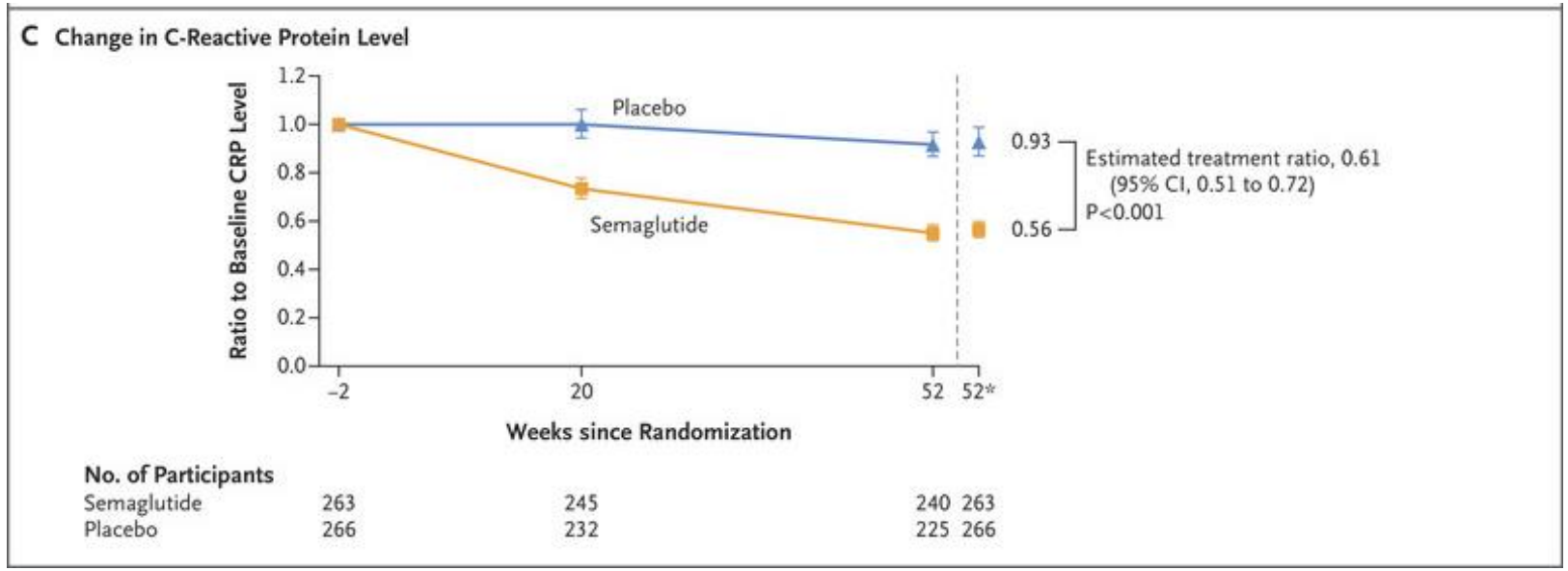


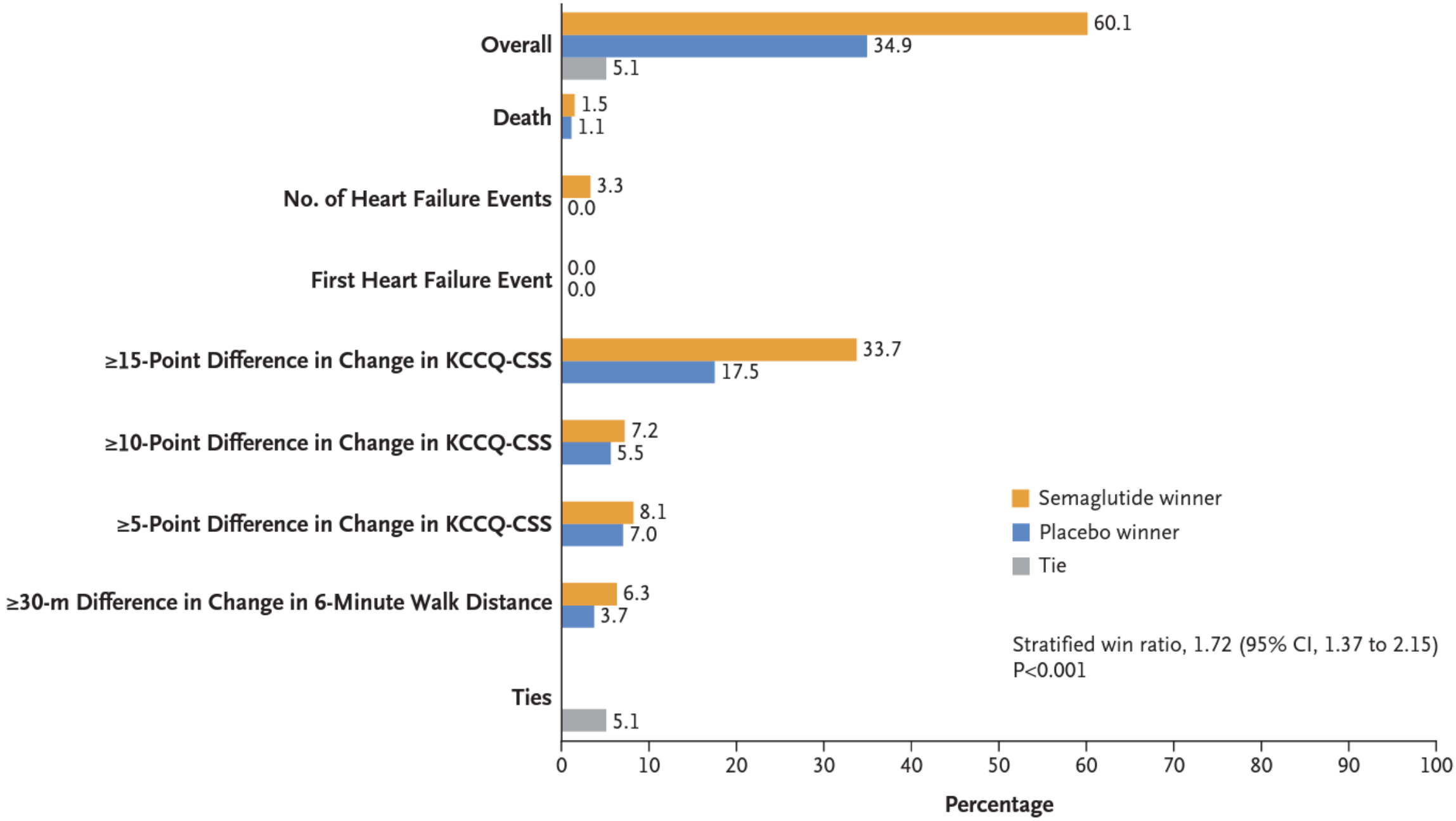
Figure 1. Changes from Baseline to Week 52 in the Dual Primary End Points.

STREP-HFpEF Secondary Endpoints

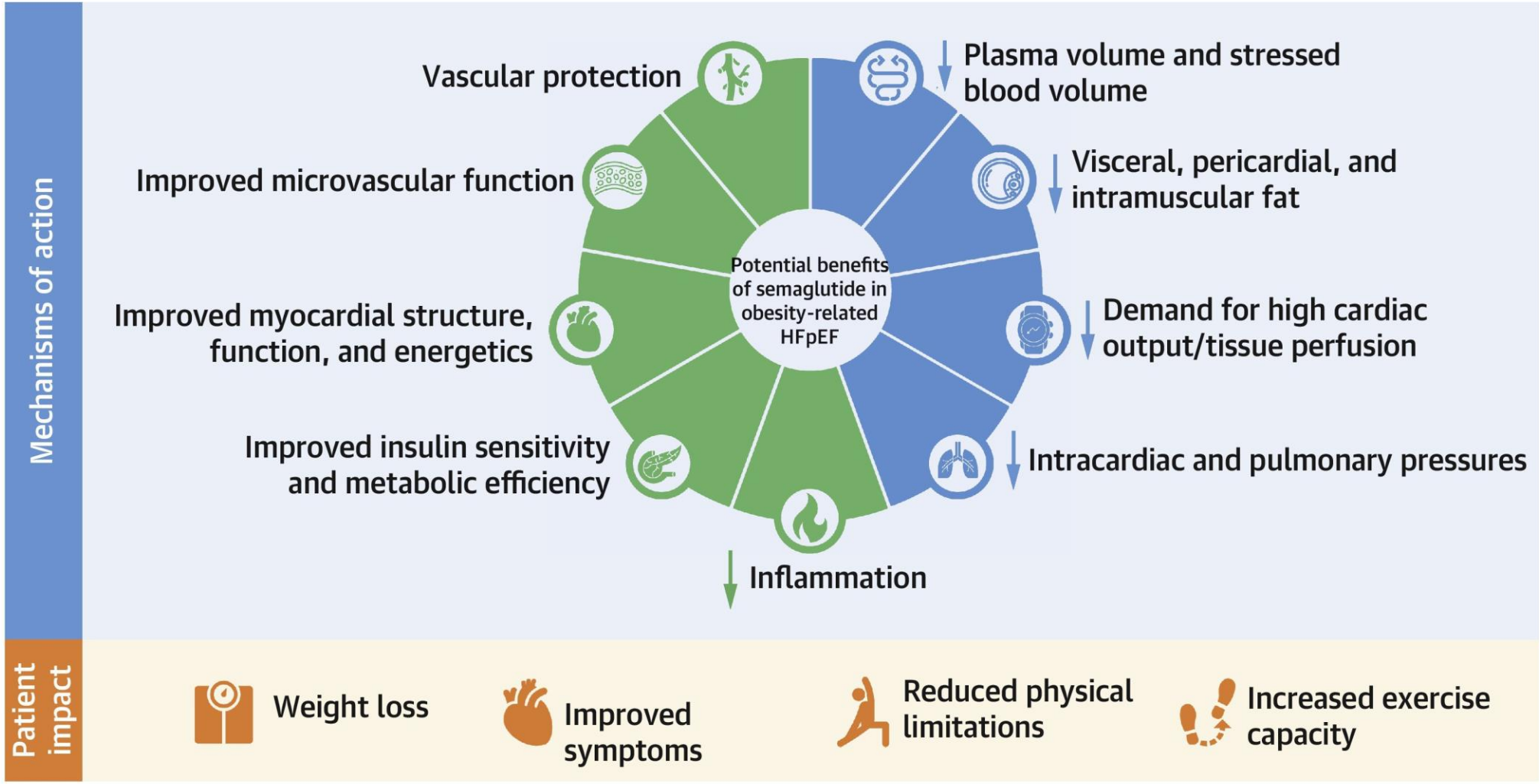




B Stratified Win Ratio for Hierarchical Composite End Point



CENTRAL ILLUSTRATION: Potential Mechanisms of Benefit for Semaglutide in Individuals With the Obesity Phenotype of HFpEF



Kosiborod MN, et al. J Am Coll Cardiol HF. 2023;11(8P1):e009664.