HFpEF herkennen bij obesitas

Je gaat 't pas zien als je het doorhebt

Prof. dr. Rudolf de Boer

HFpEF herkennen bij obesitas.
Je gaat ‘t pas zien als je het doorhebt

Erasmus MC
Universitair Medisch Centrum Rotterdam

WCN Congres, 28/29 November 2024
Novotel Amsterdam Schiphol Airport

Erasmus MC

Disclosures Rudolf de Boer

Memberships/leaderships

- President, Dutch Cardiac Society (2023-2025)
- Review coordinator of the 2021and 2023 update ESC Heart Failure Guidelines
- Task Force member: ESC guidelines Cardio-oncology (2022) and ESC guidelines Cardiomyopathies (2023)
- Co-chair, HFA working group on dilated cardiomyopathy
- Executive Committee of the Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure (DELIVER) trial, sponsored by AstraZeneca
- Study group of the Dapagliflozin Effect on Exercise Capacity Using a 6-minute Walk Test in Patients With Heart Failure With Reduced Ejection Fraction and Preserved Ejection Fraction (DETERMINE Reduced & Preserved) trials, sponsored by AstraZeneca
- National Lead of the Research Study to Look at How Ziltivekimab Works Compared to Placebo in People With Heart Failure and Inflammation (HERMES) trial, sponsored by NovoNordisk
- Executive Committee of the Study to Assess Efficacy and Safety of CDR132L in Patients With Reduced Left Ventricular Ejection Fraction After Myocardial Infarction (HF-REVERT) trial, sponsored by Cardior GmbH

Research grants (paid to the institution):

- Netherlands Heart Foundation (CVON grants 2017-21, 2017-11, 2018-30 & 2020B005)
- leDucq Foundation (CURE-PLaN)
- European Research Council (ERC Consolidator grant 818715, SECRETE-HF)
- Research grants/chemicals/study/analytical help/drugs from: Alnylam, Abbott, AstraZeneca, Boehringer Ingelheim, Cardior GmbH, Ionis Pharmaceuticals Inc., Novartis, Novo Nordisk, and Roche

Speaker personal speaker fees:

- AstraZeneca, Abbott, Bayer, Bristol-Myers Squibb, Cardior GmbH, NovoNordisk, and Roche

Travel support:

- Abbott, Cardior Pharmaceuticals GmbH, and NovoNordisk

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MISS P., 53 YEARS

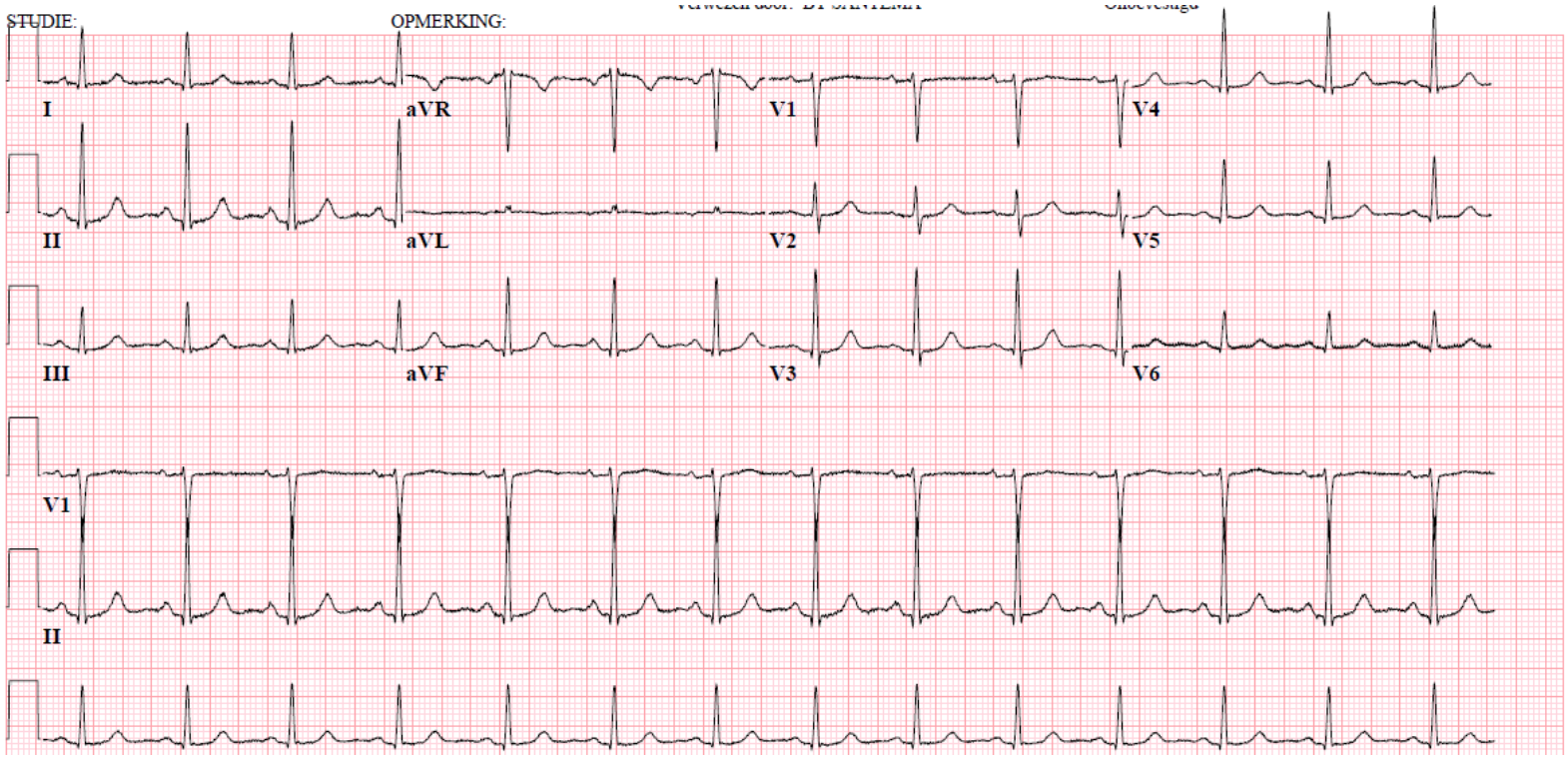
- **Medical history:**
- 2009 arterial hypertension
- 2020 paroxysmal atrial fibrillation
- **Medication:**
- spironolacton 12.5 mg oid
- rivaroxaban 20 mg oid
- metoprolol 100mg oid
- furosemide 40mg oid
- **Clinical presentation & complaints:** Exertional dyspnea, already present during minimal exertion. No dyspnea at rest. Dyspnea is limiting: it prevents her in daily activities, from travelling, and from enjoying life
- **Clinical presentation:** Non-dyspneic at rest.
- Length: 164cm. Weight: 87 kg. **BMI 32,4 kg/m2.**
- RR 130/80 mm Hg. HR: 85 (irregular).
- Minimally swollen ankles. Normal heart and lung sounds.

MISS P., 83 YEARS

Laboratory measurements:

Hemoglobin: 9.2 mmol/l, Creatinin: 86 umol/l, estimated GFR (CKD-EPI): 74 ml/mn/1.73m2, NT-ProBNP: 210 ng/l

ECG:



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ECHO

LVEF: >55%
LAVI: 52,1 ml/m2
LVEDD: 3,9 cm
RWT: 0.53
RV peak pressure: 32.8 mmHg
E/e: 13
Septal E': 6.8 cm/sec
Lateral E': 10.9 cm/sec

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The HFA-PEFF SCORE

Step **E**: **E**cho and natriuretic peptide (Cardiologist)

	Functional	Morphological	Biomarker (SR)	Biomarker (AF)
Major	septal e' < 7 cm/s or lateral e' < 10 cm/s or Average E/e' ≥ 15 or TR velocity > 2.8 m/s (PASP > 35 mmHg)	LAVI > 34 ml/m² or LVMI ≥ 149/122 g/m² (m/w) and RWT > 0,42 #	NT-proBNP > 220 pg/ml or BNP > 80 pg/ml	NT-proBNP > 660 pg/ml or BNP > 240 pg/ml
Minor	Average E/e' 9 -14 or GLS < 16 %	LAVI 29-34 ml/m² or LVMI > 115/95 g/m² (m/w) or RWT > 0,42 or LV wall thickness ≥ 12 mm	NT-proBNP 125-220 pg/ml or BNP 35-80 pg/ml	NT-proBNP 365-660 pg/ml or BNP 105-240 pg/ml

Major Criteria: 2 points	**> 5 points; HFpEF**
Minor Criteria: 1 point	**2-4 points: Diastolic Stress Test or Invasive Haemodynamic Measurements**

Pieske B, et al. *Eur Heart J.* 2019; **40**:3297-3317

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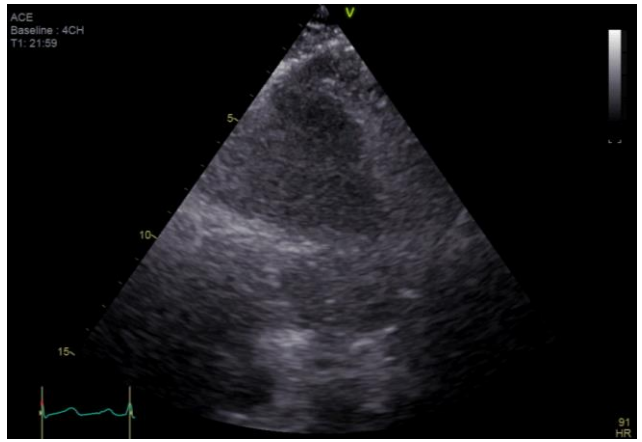
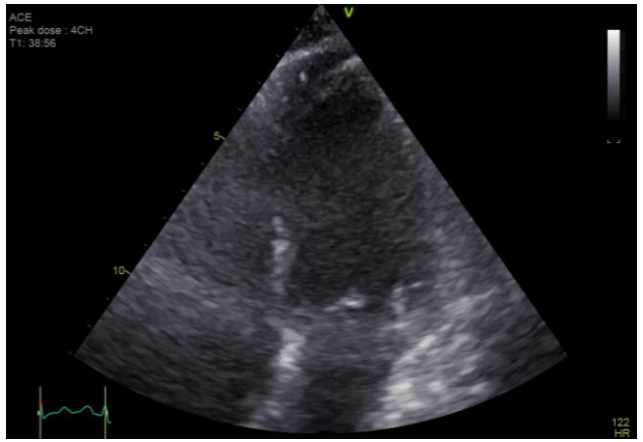
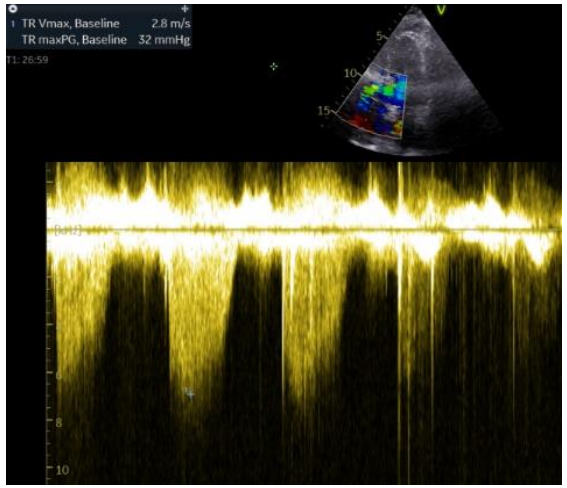
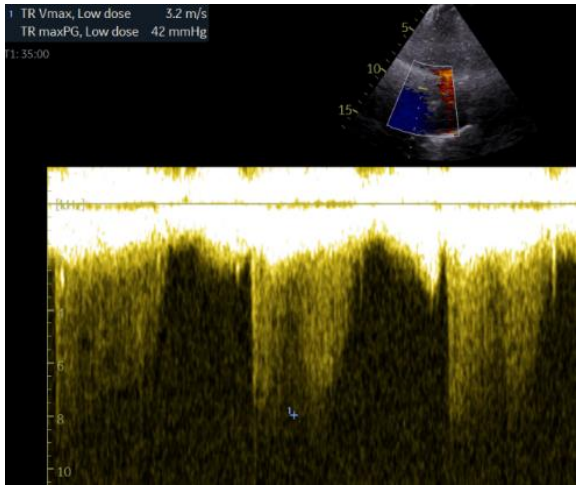
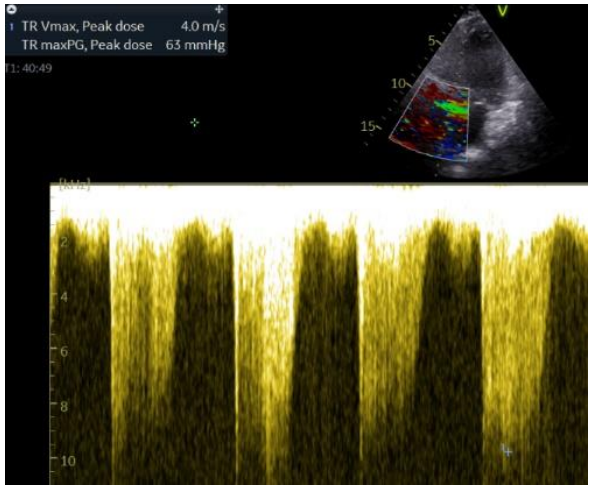
Advanced work-up: exercise echo

	Rust	Low dose (25 W)	Peak dose (36 W)
4k			
PAPs			
	RV peak 32 mmHg	RV peak 42 mmHg	RV peak 63 mmHg

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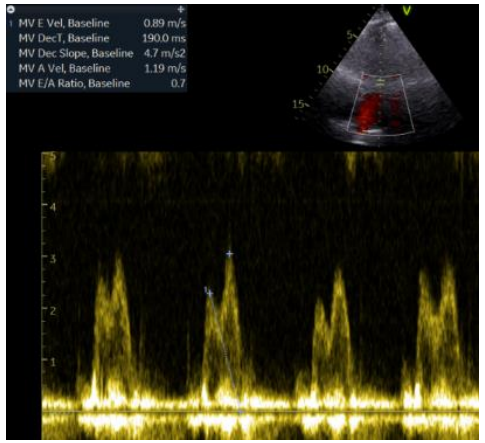
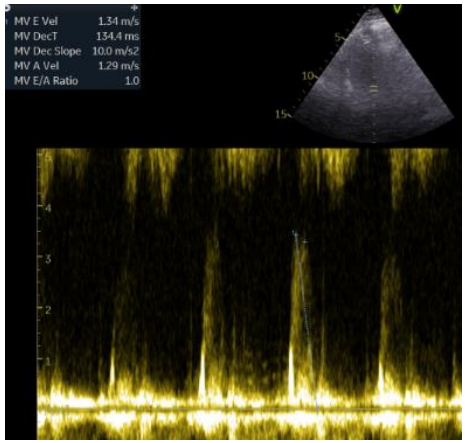
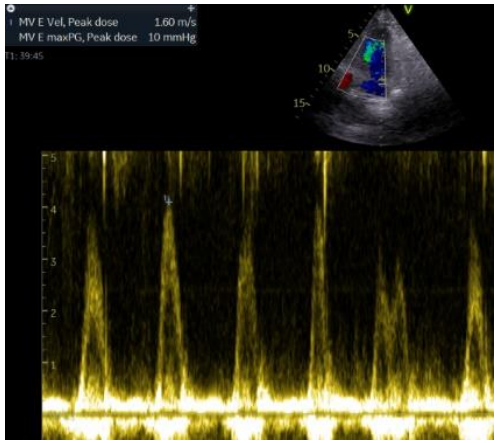
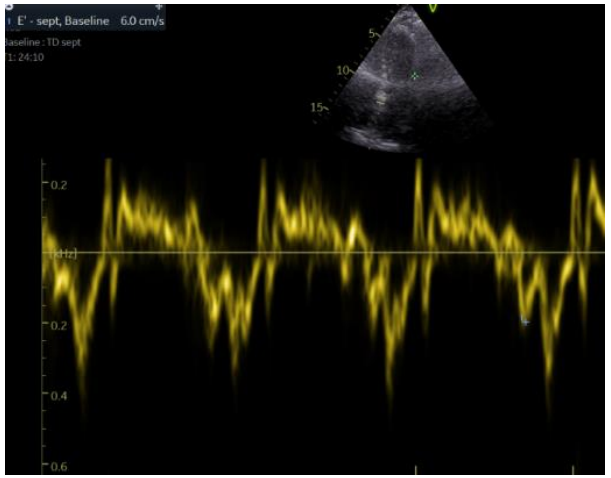
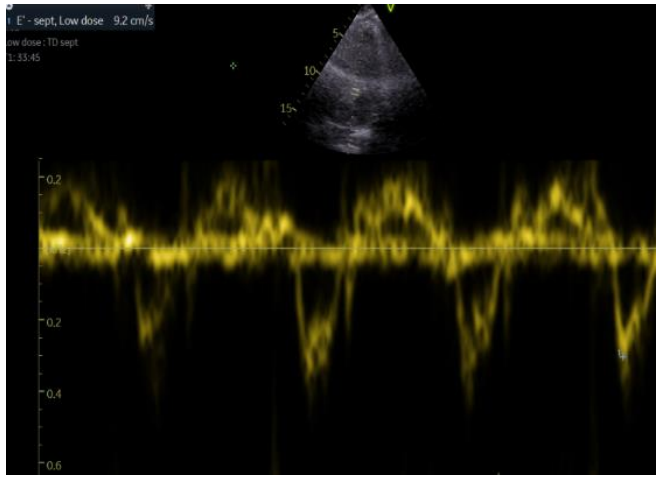
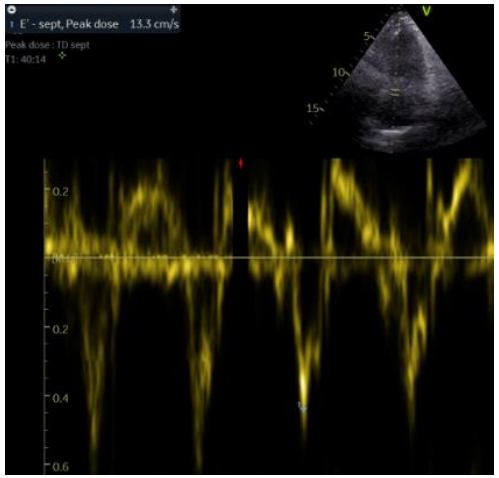
Advanced work-up: exercise echo

	Rest	Low dose (25 W)	Peak dose (36 W)
E/A			
e’			
	E/e’ mean 13,3	E/e’ mean 16,1	E/e’ mean 17,1

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The HFA-PEFF SCORE

Step **E**: **E**cho and natriuretic peptide (Cardiologist)

	Functional	Morphological	Biomarker (SR)	Biomarker (AF)
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Pieske B, et al. *Eur Heart J.* 2019; **40**:3297-3317

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The HFA-PEFF SCORE

Step **F**(2): **F**inal aetiology

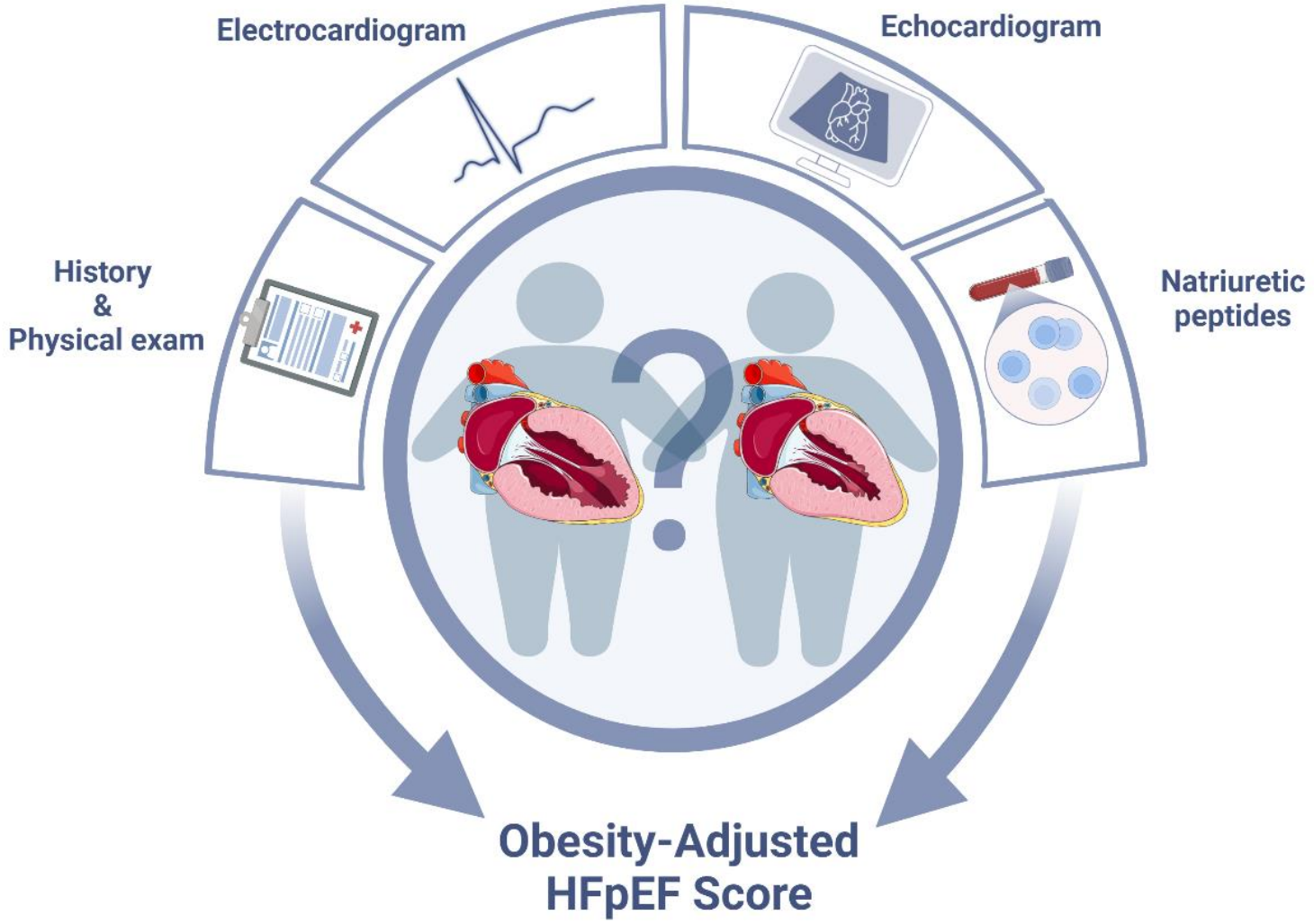
Pieske B, et al. *Eur Heart J.* 2019; **40**:3297-3317

Table 2 **Potential specific aetiologies underlying heart failure with preserved ejection fraction-like syndromes in Step 4 (F_2)**

Abnormalities of the myocardium		
Ischaemic		Myocardial post-infarction/scar[49] Myocardial stunning[50] Epicardial coronary artery disease[51] Microvascular and endothelial dysfunction[52,53–55]
Toxic	Recreational substance abuse	Such as alcohol,[56] cocaine,[57] and anabolic steroids[58]
	Heavy metals	Such as iron,[59] lead,[60] cadmium,[60] cobalt,[61] copper (M. Wilson)[62]
	Medications	Such as chloroquine,[63] ergotamine,[64] cytostatic drugs (e.g. anthracyclines),[64] immunomodulating drugs (e.g. interferons monoclonal antibodies such as trastuzumab, cetuximab)[64]
	Radiation	Mean cardiac radiation doses > 3 Gy[65,66]
Immune and inflammatory	Related to infection	Such as cardiotropic viruses,[67,68] HIV,[69–71] hepatitis,[72] helminths,[73] parasites (e.g. Chagas' disease[74])
	Not related to infection	Lymphocytic myocarditis,[75–79] autoimmune diseases (e.g. rheumatoid arthritis,[80] connective tissue disorders like scleroderma,[81] M. Raynaud,[55] systemic lupus erythematosus,[82] dermato/polymyositis,[83] and hypersensitivity and eosinophilic myocarditis[73,84–87]
Infiltrative	Related to malignancy	Direct infiltrations and metastases[88–90]
	Not related to malignancy	Amyloidosis,[19,91] sarcoidosis,[92,93] primarily and secondary haemochromatosis,[94–96] storage diseases[97] (e.g. Fabry disease,[98,99] Danon disease,[100–102] Pompe disease,[99,102] PRKAG2 deficiency,[99] Gaucher's disease[99])[103,104,105,106]
Metabolic	Hormonal	Such as thyroid diseases,[107,108] parathyroid diseases,[109] acromegaly,[110] GH deficiency,[111] Cushing disease,[112] Conn's disease,[113] Addison disease,[114] phaeochromocytoma,[115] pathologies related to pregnancy and peripartum[116,117]
	Nutritional	Such as deficiencies in thiamine,[118] L-carnitine,[119] selenium,[120] (functional) iron,[121,122] complex malnutrition (e.g. AIDS, infections,[73] anorexia nervosa[73,123,124])
Genetic	Diverse forms	Such as HCM,[97,125,126] restrictive cardiomyopathies,[103,104,106] hypertrophic form of non-compaction cardiomyopathy,[127,128] early forms of muscular dystrophies (Duchenne/Becker disease[129]).
Endomyocardial		HES,[84] EMF,[71,127] endocardial fibroelastosis,[128] carcinoid,[130,131] endocardial calcification (Paget's disease[132])
Abnormalities of loading conditions		
Hypertension		Primary and secondary forms of hypertension[112,113,115,130,131]
Valvular and structural defects	Acquired	Heart valve diseases[133,134]
Valvular and structural defects	Congenital	Septal defects[132,135,136]
Pericardial and endomyocardial pathologies	Pericardial	Constrictive pericarditis and pericardial effusion[137,138]
	Endomyocardial	HES,[86] EMF,[73,139] endocardial fibroelastosis,[140] carcinoid,[141,142] endocardial calcification (Paget's disease[143])
High output states		Severe anaemia,[144] sepsis,[145] thyrotoxicosis,[105] arteriovenous fistula,[146] and pregnancy[147]
Volume overload		Renal failure and fluid overload[148,149,150]
Abnormalities of the cardiac rhythm		
Rhythm disorders		Atrial/ventricular arrhythmias, pacing, conduction disorders[38,151–153]

EMF, endomyocardial fibrosis; GH, growth hormone; HCM, hypertrophic cardiomyopathy; HES, hypereosinophilic syndrome (formerly known as Löffler's endocarditis); HIV/AIDS, human immunodeficiency virus/acquired immune deficiency; LV, left ventricular; PRKAG2, protein kinase AMP-activated non-catalytic subunit gamma 2.

DIAGNOSIS OF HFPEF IN THE OBESE



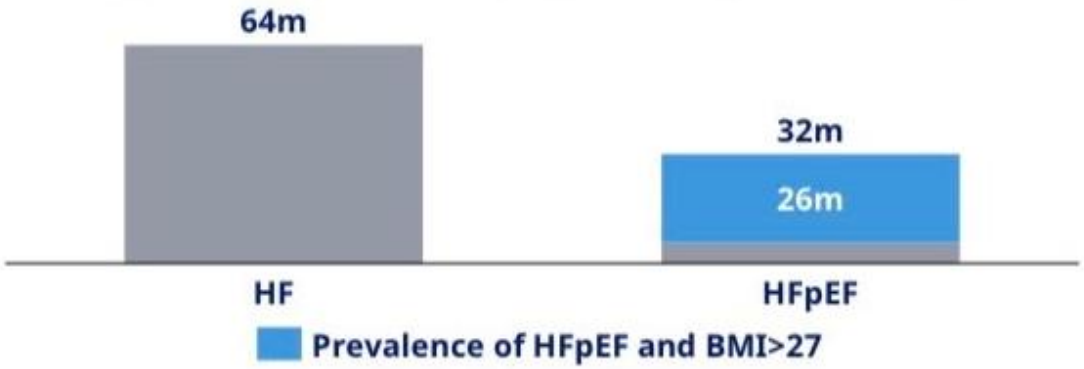
Van Dalen B, et al. *Cardiovasc Diabet.* 2025; submitted

HFpEF compromises ~50% of all HF cases, and ~80% of HFpEF patients live with overweight or obesity

Heart failure with preserved ejection fraction

- Impaired filling capacity
- Stiff and thick ventricle
- LVEF ≥50%

Approximately 26 million people have HFpEF and BMI>27[1,2]



Patients with HFpEF are under a great burden[3]

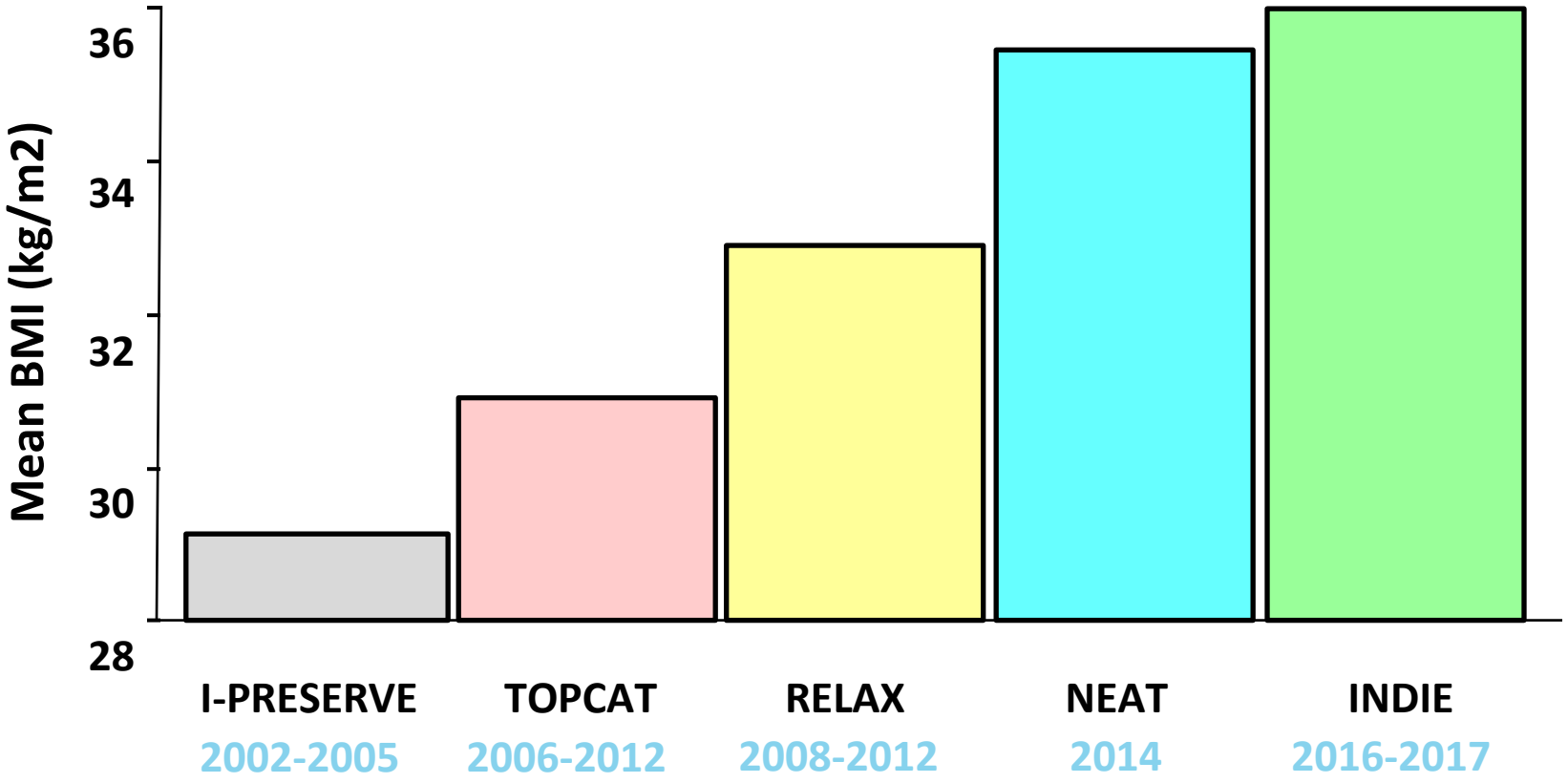
- Higher mortality rate
- Higher risk of hospitalisation
- Higher burden of debilitating symptoms, physical limitations and poor quality of life

The key goals of therapy[3]

- Prolong survival
- Reduce hospitalisations
- Reduce symptoms; improve quality of life and functional status

1. Groenewegen A et al. Eur J Heart Fail 2020;22:1342–13561; Gurwitz JH et al. Am J Med 2013;126:393–400; 2. Haass M et al. Circulation 2011;4:324–331; Kitzman DW, et al. J Am Coll Cardiol 2016;68:200–203 3. Ponikowski P et al. Eur J Heart Fail 2016;18:891–975
LVEF: Left ventricular ejection fraction; HF: Heart failure; HFpEF: Heart Failure with preserved ejection fraction

Obesity is becoming more of a problem in HFpEF



INDIE: 75% obese, 95% overweight or obese

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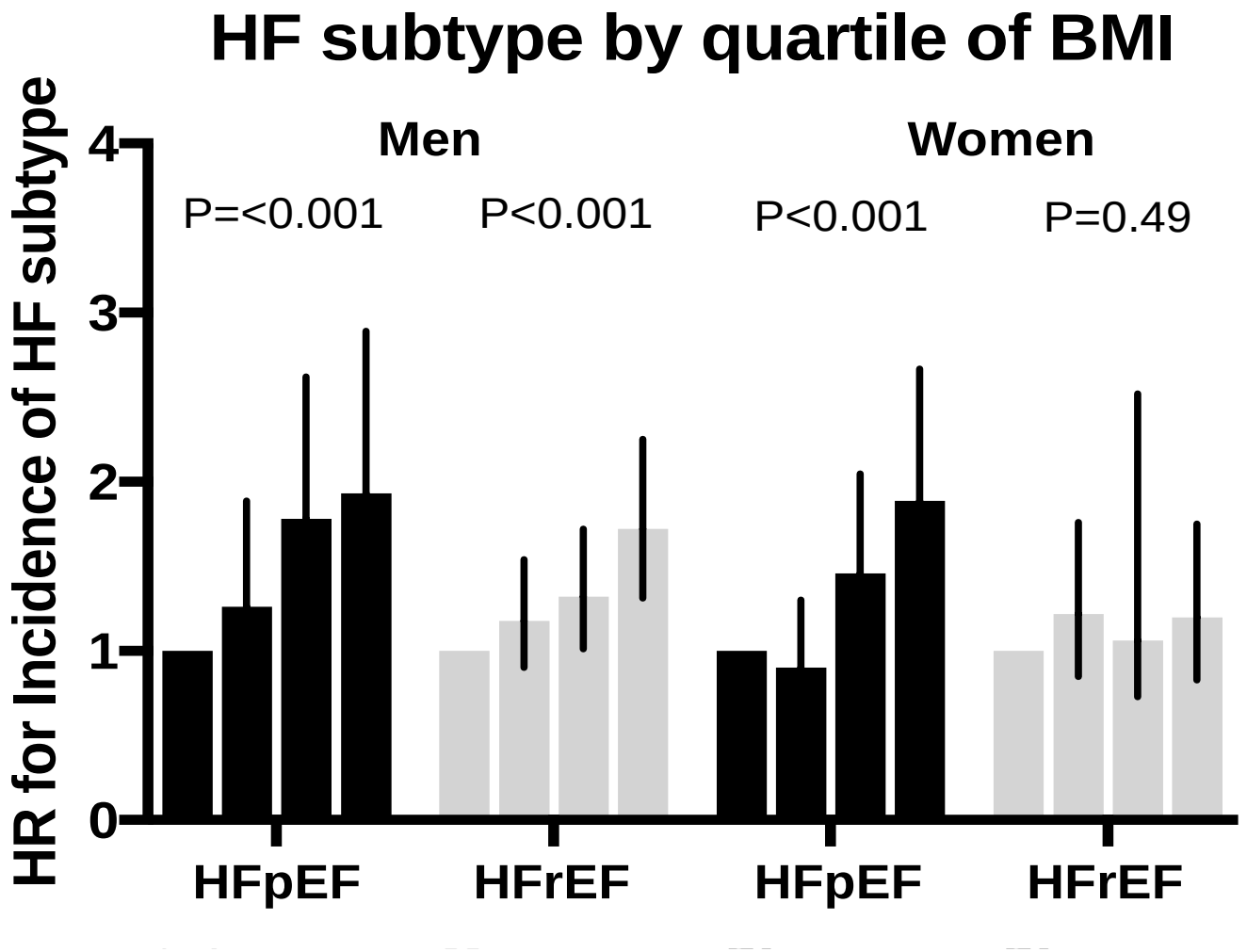
BMI STRONGER PREDICTOR FOR HFPEF THAN FOR HFREF



Savji, et al. *JACC Heart Fail.* 2018; **6**:701-709

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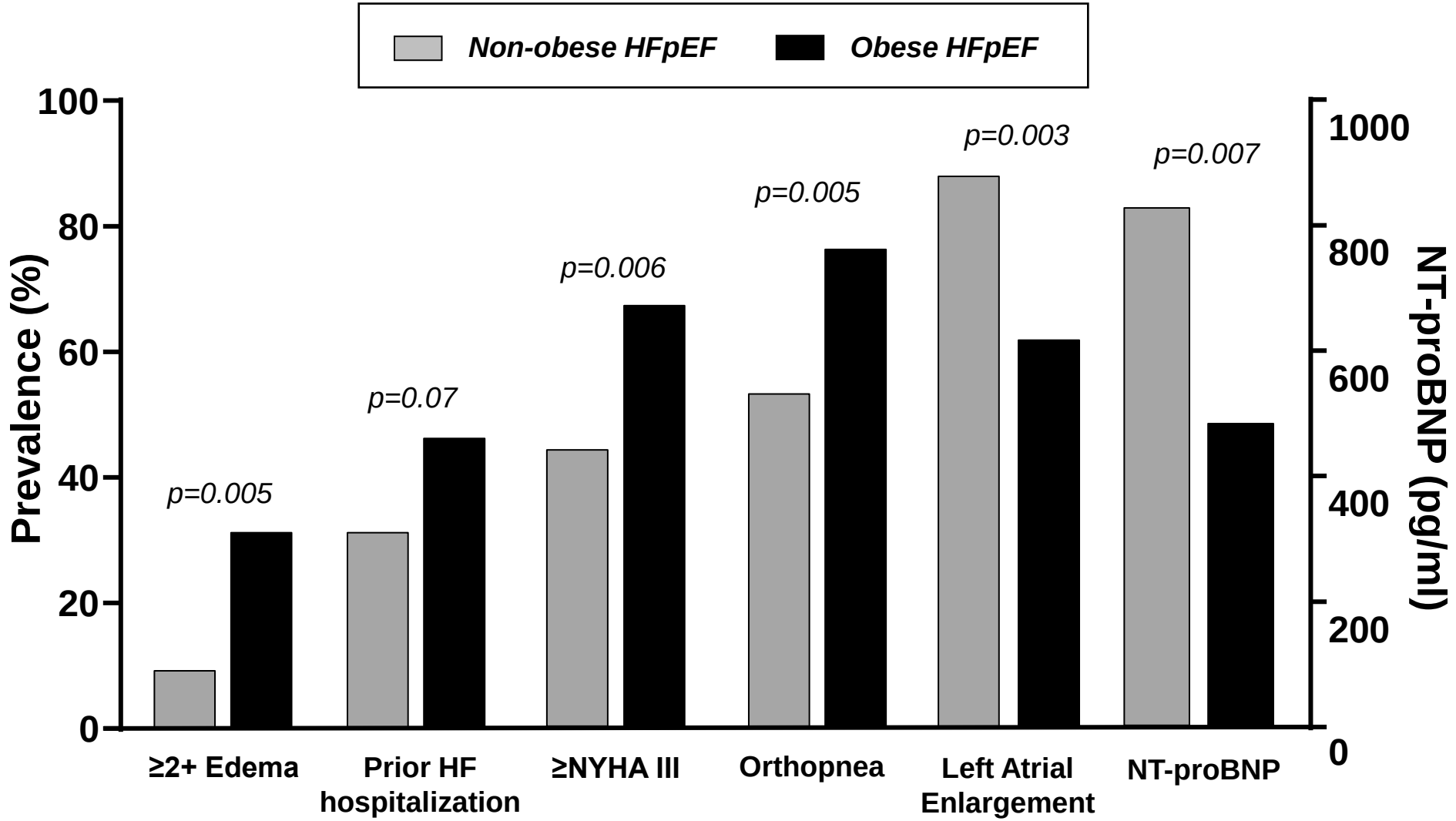
Measures of HF severity are worse in obese HFpEF



Reddy, Borlaug *Mayo Clin Proc* 2019

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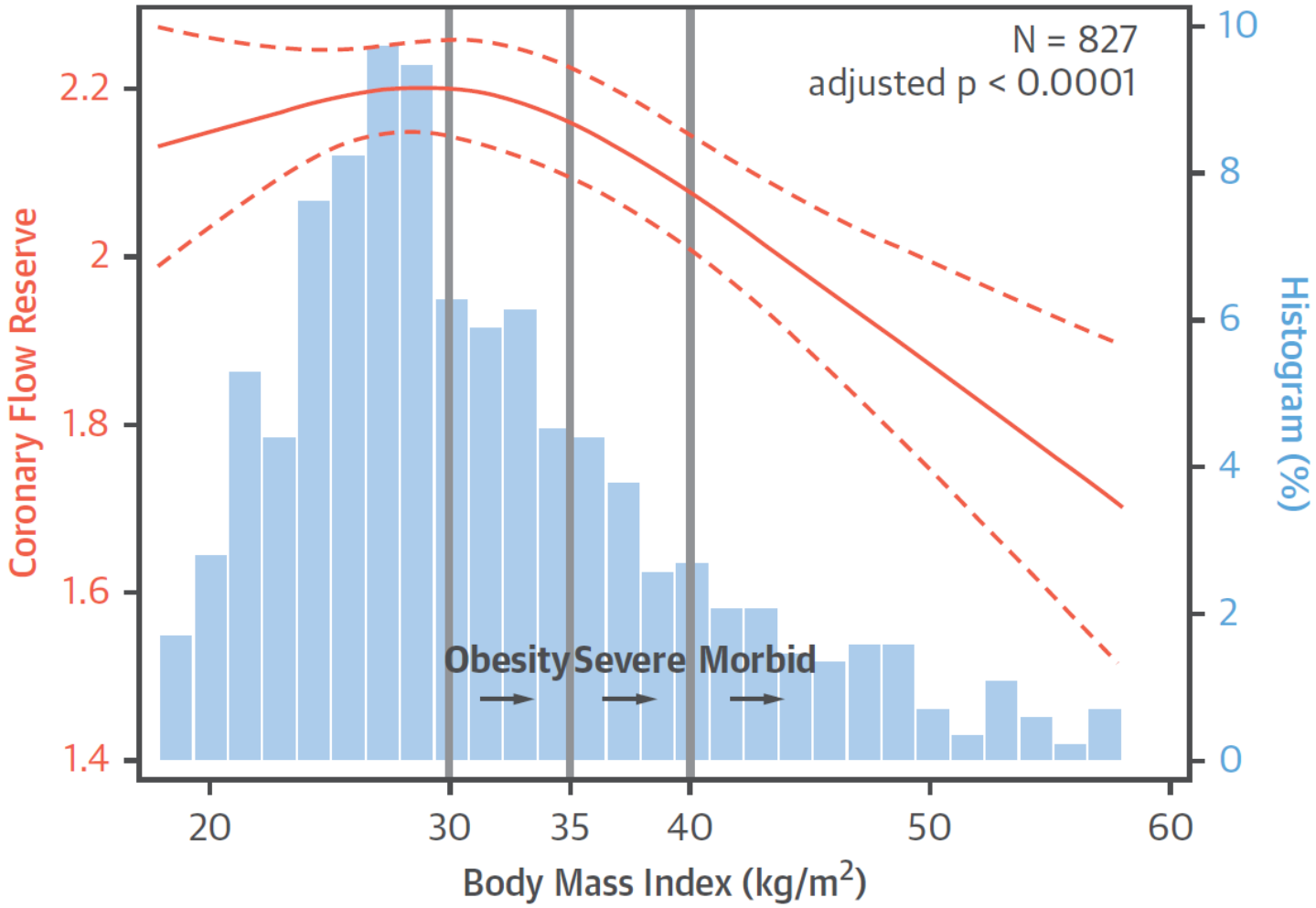
Obesity & Coronary Microvascular Dysfunction



Bajaj, Taqueti *J Am Coll Cardiol* 2018

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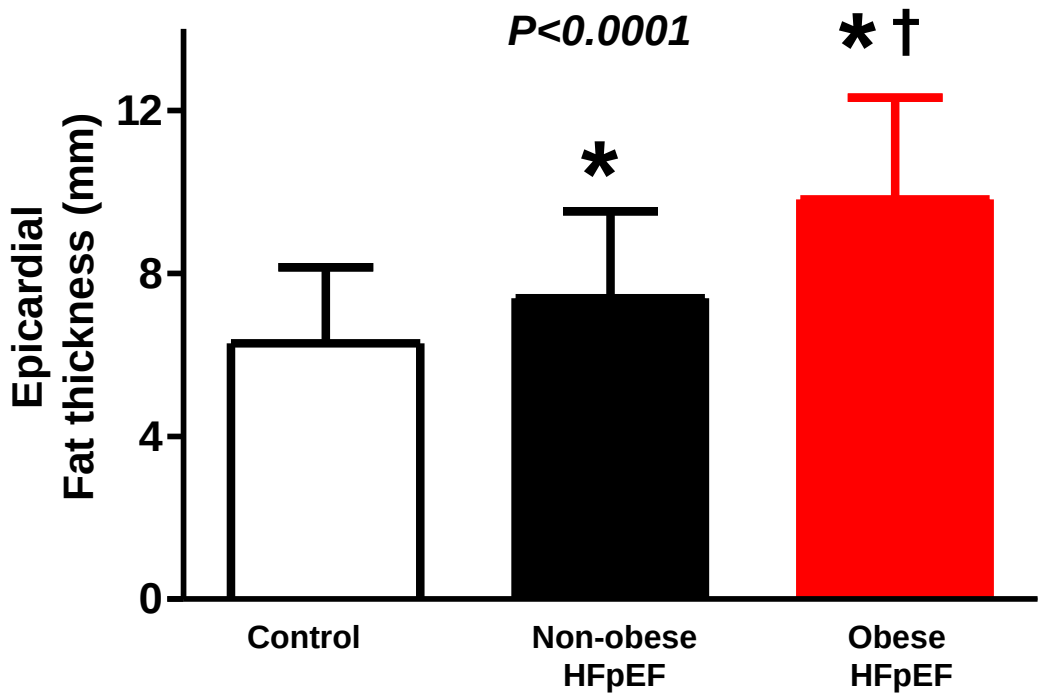
↑Epicardial Fat in Obese HFpEF



Why is this important?

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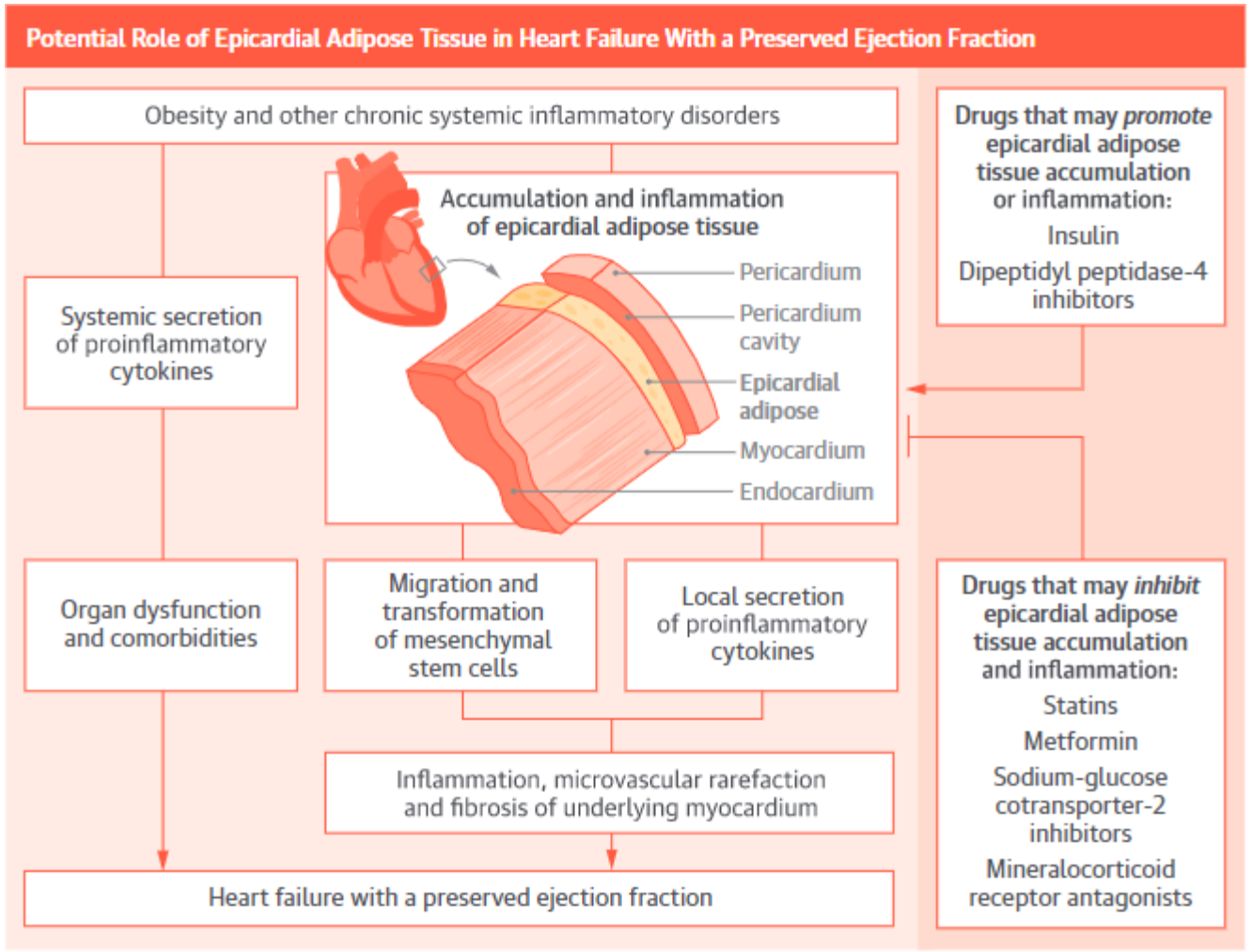

Packer *J Am Coll Cardiol* 2018

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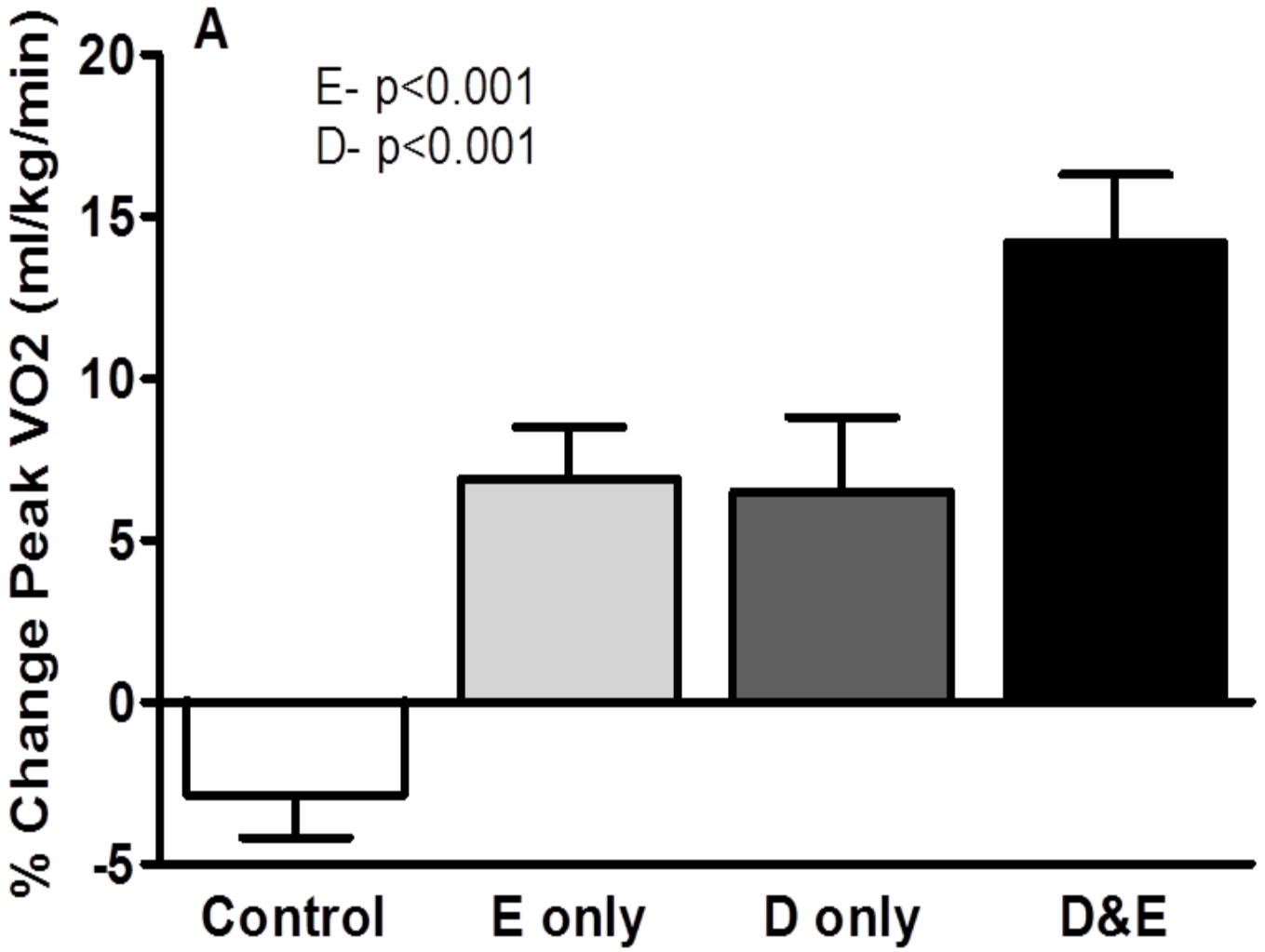
OBESITY IN HFPEF
WHAT CAN WE OFFER ?

- Weight loss + exercise
- Bariatric surgery
- SGLT2 inhibitors
- GLP1-RA
- Newer classes: e.g. tirzepatide

Can weight loss treat HFpEF?



Kitzman D, et al. *JAMA.* 2016; **315**:36-46

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BARIATRIC SURGERY

Obesity

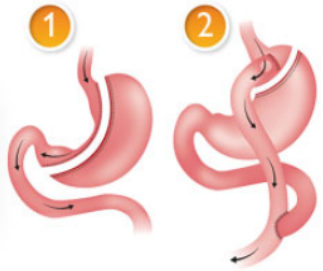
Previous literature has shown that bariatric surgery effectively targets CV risk factors

Cardiovascular risk factors

- Hypertension
- Metabolic syndrome: diabetes – dyslipidaemia
- Increased inflammation

Bariatric surgery

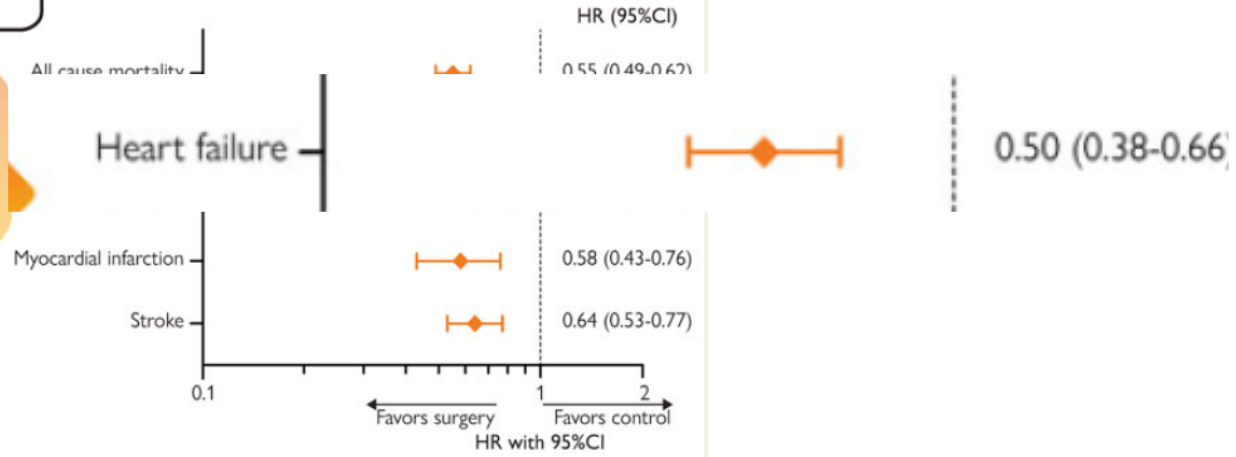
1. Laparoscopic sleeve gastrectomy
2. Laparoscopic Roux-en-Y gastric bypass



Cardiovascular disease

- Heart failure
- Atrial fibrillation
- Coronary artery disease
- Stroke

Pooled analysis showed significant reduced HR for all outcomes, except for AF:



Systematic review &

Meta analysis

26002 HF patients

40657 controls

van Veldhuisen SL, et al. *Eur Heart J.* 2022; **43**:1955-1969

SGLT2 INHIBITORS

- Consistently associated with weight loss (~ 2-5 kg)
- Explained - in part – by diuresis but also by loss of adipose tissue
- Overall effects exceed the effects that may be expected from weight loss

DELIVER TRIAL – DAPAGLIFLOZIN ACROSS THE BMI SPECTRUM

Dapagliflozin for heart failure according to body mass index: A prespecified analysis of the DELIVER trial

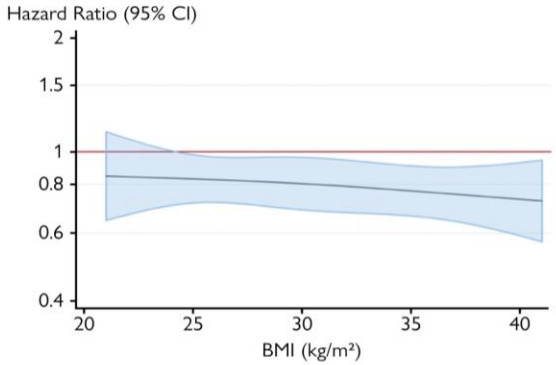
6257 patients in DELIVER trial with a recorded BMI measurement at baseline

- HFpEF or HFmrEF
- Randomized to dapagliflozin or matched placebo

- 45% patients were obese
- 78% were obese or overweight

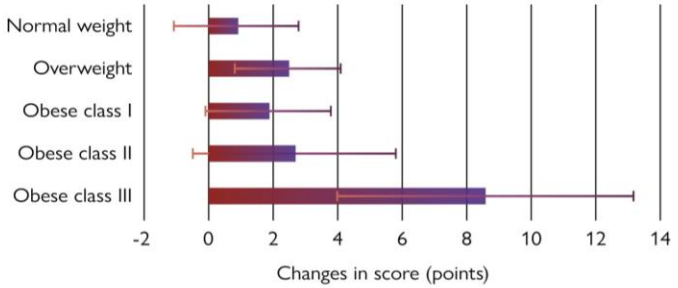
Prespecified analysis by baseline BMI

Primary outcome (worsening HF or CV death)



Dapagliflozin reduced the incidence of primary outcome, regardless of baseline BMI

Mean change in KCCQ-TSS from baseline to 8 months according to BMI category



Larger increases (improvement) in KCCQ-TSS were seen in patients with obesity

Adamson C et al. *Eur Heart J*. 2022; **43**: 4406–4417

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2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Official ESC Guidelines slide set

RECOMMENDATION FOR THE TREATMENT OF PATIENTS WITH SYMPTOMATIC HEART FAILURE WITH PRESERVED EJECTION FRACTION

Recommendations	Class	Level
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFpEF to reduce the risk of HF hospitalization or CV death.	I	A

ESC
European Society of Cardiology

GLP1 RECEPTOR ANALOGUES

novo nordisk®

company announcement

Semaglutide 2.4 mg reduces the risk of major adverse cardiovascular events by 20% in adults with overweight or obesity in the SELECT trial

Bagsværd, Denmark, 8 August 2023 – Novo Nordisk today announced the headline results from the SELECT cardiovascular outcomes trial. The double-blinded trial compared subcutaneous once-weekly semaglutide 2.4 mg with placebo as an adjunct to standard of care for prevention of major adverse cardiovascular events (MACEs) over a period of up to five years. The trial enrolled 17,604 adults aged 45 years or older with overweight or obesity and established cardiovascular disease (CVD) with no prior history of diabetes.

The trial achieved its primary objective by demonstrating a statistically significant and superior reduction in MACE of 20% for people treated with semaglutide 2.4 mg compared to placebo[1]. The primary endpoint of the study was defined as the composite outcome of the first occurrence of MACE defined as cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. All three components of the primary endpoint contributed to the superior MACE reduction demonstrated by semaglutide 2.4 mg. 1,270 first MACEs were accrued.

https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=166301

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STEP – HFPEF TRIAL

- HFpEF, N=529
- BMI>30
- Semaglutide 2.4 mg once weekly
- 52 weeks

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)

Kosiborod M, et al. *N Engl J Med.* 2023; **389**:1069-1084

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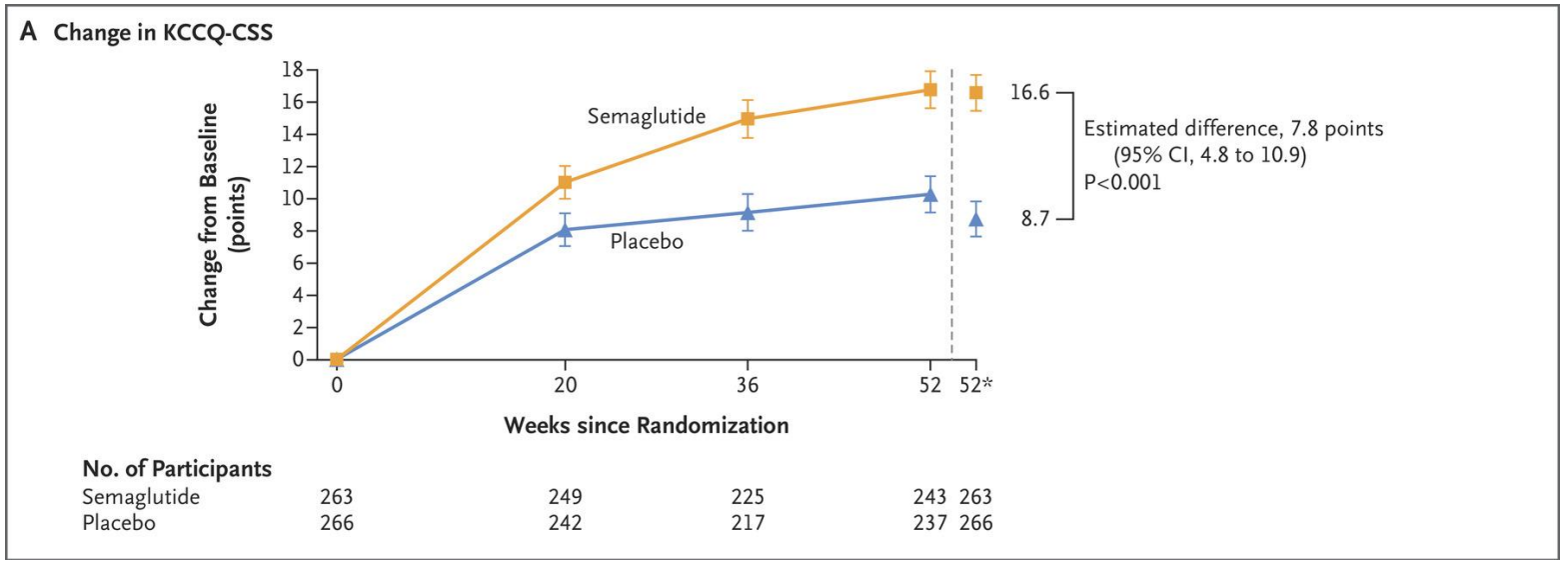
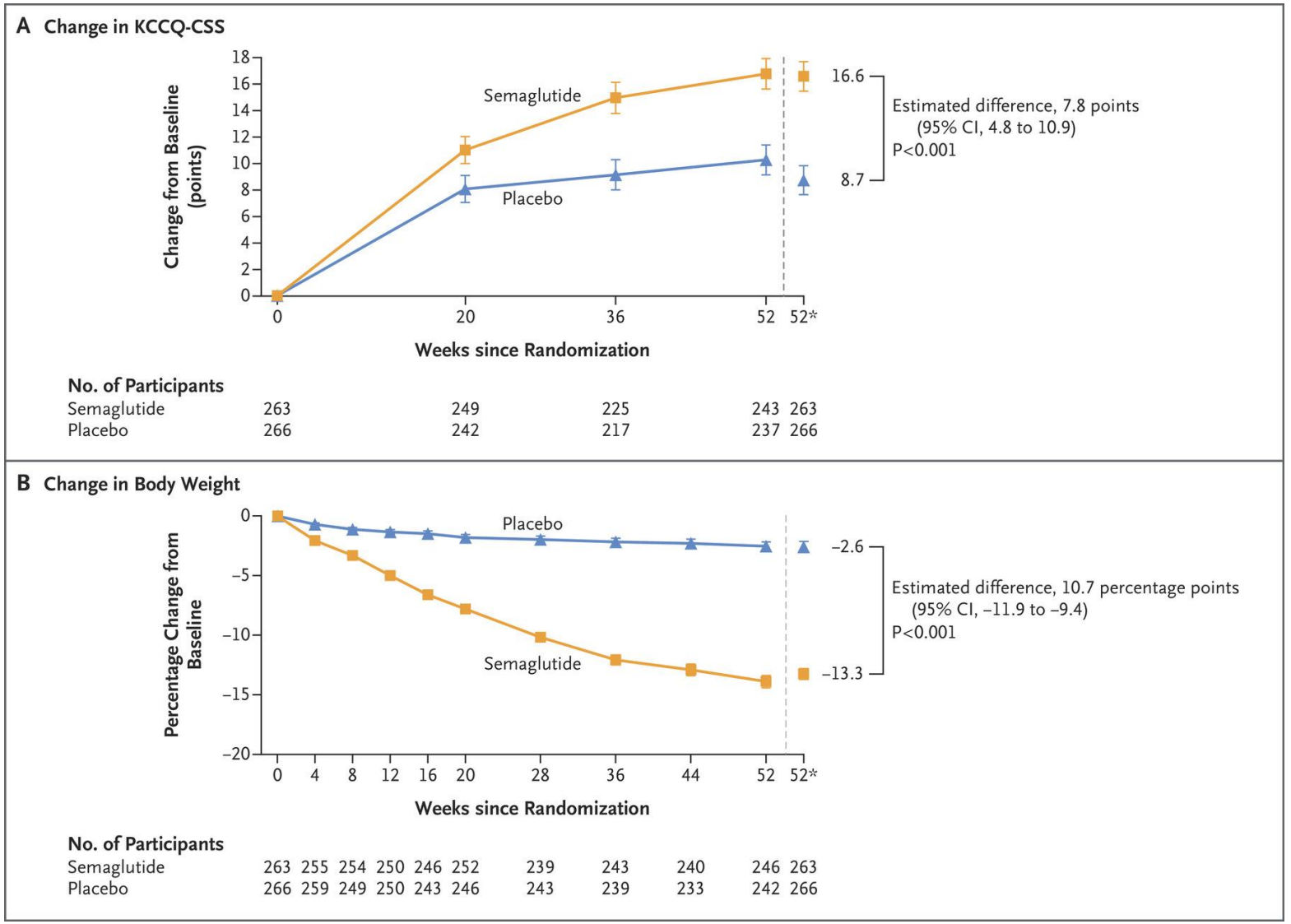
STEP HFPEF - RESULTS



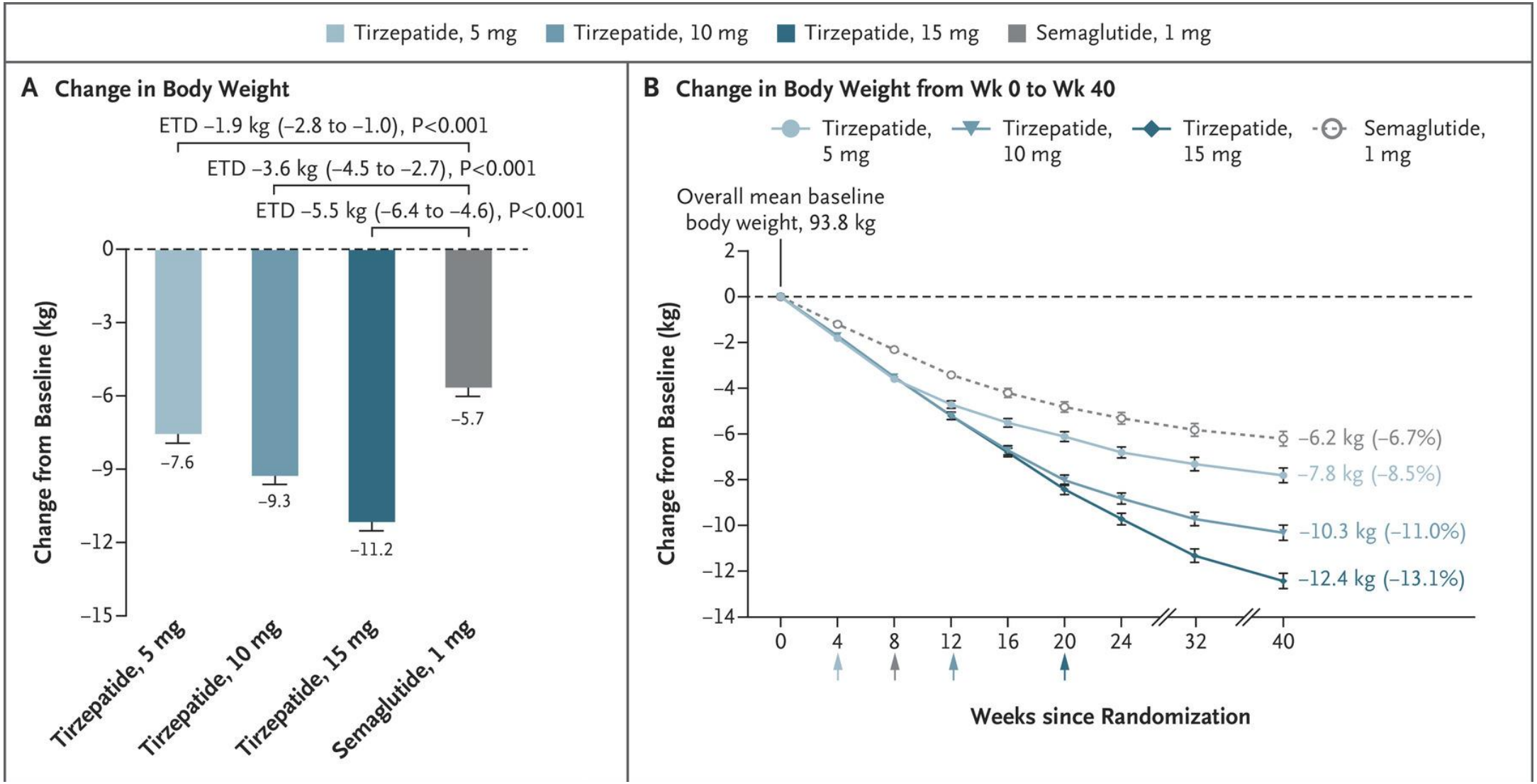
Kosiborod M, et al. *N Engl J Med.* 2023; **389**:1069-1084

STEP HFPEF - RESULTS



Kosiborod M, et al. *N Engl J Med.* 2023; **389**:1069-1084

WHAT TO EXPECT OF OTHER DRUGS?



Frias JP, et al. *N Engl J Med* 2021; **385**:503-515

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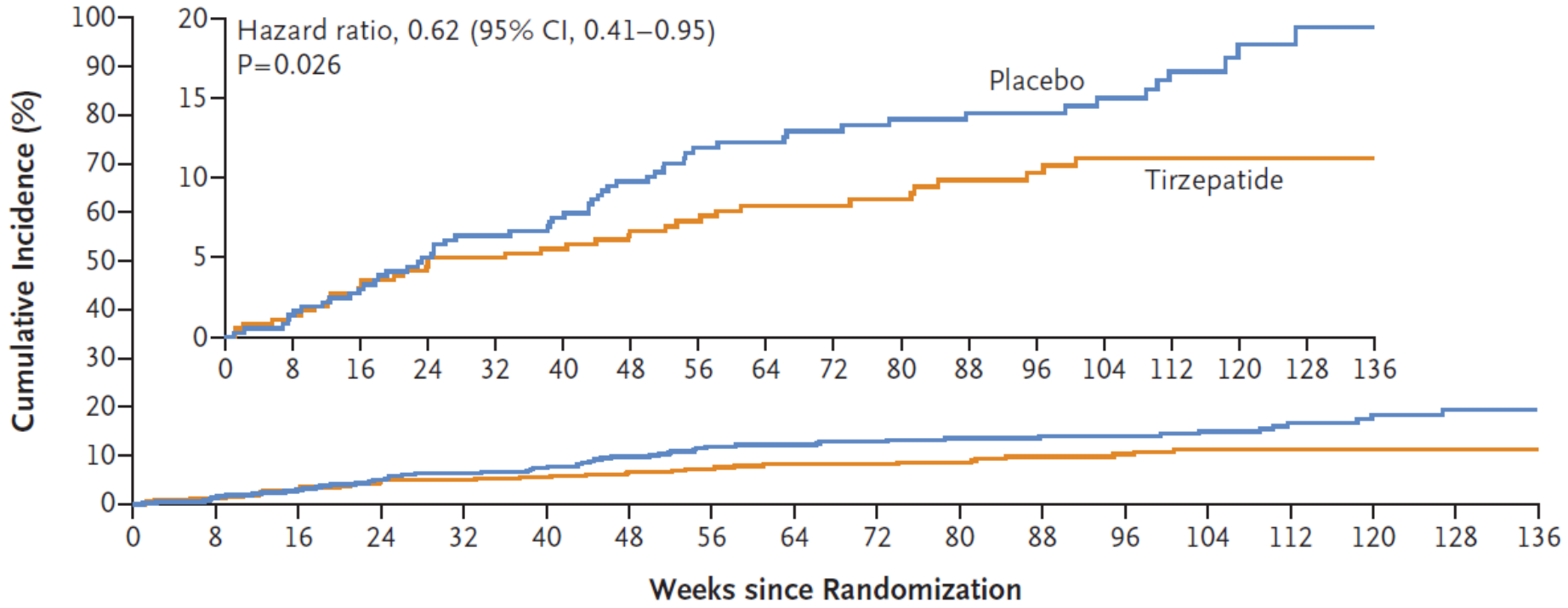
SUMMIT TRIAL

- 1494 patients screened, 731 randomized (364 TIR and 367 PL)
- Mean age 65.2 years, 54% women
- mean BMI 38.3, mean body weight 103 kg, WHR 0.73
- LVEF 61%, 73% NYHA class II
- NTproBNP 180, CRP 5.8

- Median follow-up was 104 weeks (2.0 years)
- 70 pts (19.2%) on TIR and 87 (21.3%) on PL discontinued Tx

Packer M, et al. *N Engl J Med.* 2024 Nov 16 doi: 10.1056/NEJMoa2410027

SUMMIT TRIAL – PRIMARY END POINT



No. at Risk

Placebo	367	361	349	339	332	328	318	268	259	240	219	215	195	165	145	94	73	45
Tirzepatide	364	359	349	344	340	338	333	284	275	251	228	220	196	167	146	105	82	46

Figure 1. Composite of Death from Cardiovascular Causes or a Worsening Heart-Failure Event.

Shown is the cumulative incidence of death from cardiovascular causes or a worsening heart-failure event (the composite primary end point), assessed in a time-to-first-event analysis, among 364 patients who received tirzepatide and 367 patients who received placebo. The inset shows the same data on an expanded y axis.

PRIMARY EP √

HF HOSPITALIZATION √

CV DEATH ✖

AC DEATH ✖

QUALITY OF LIFE √

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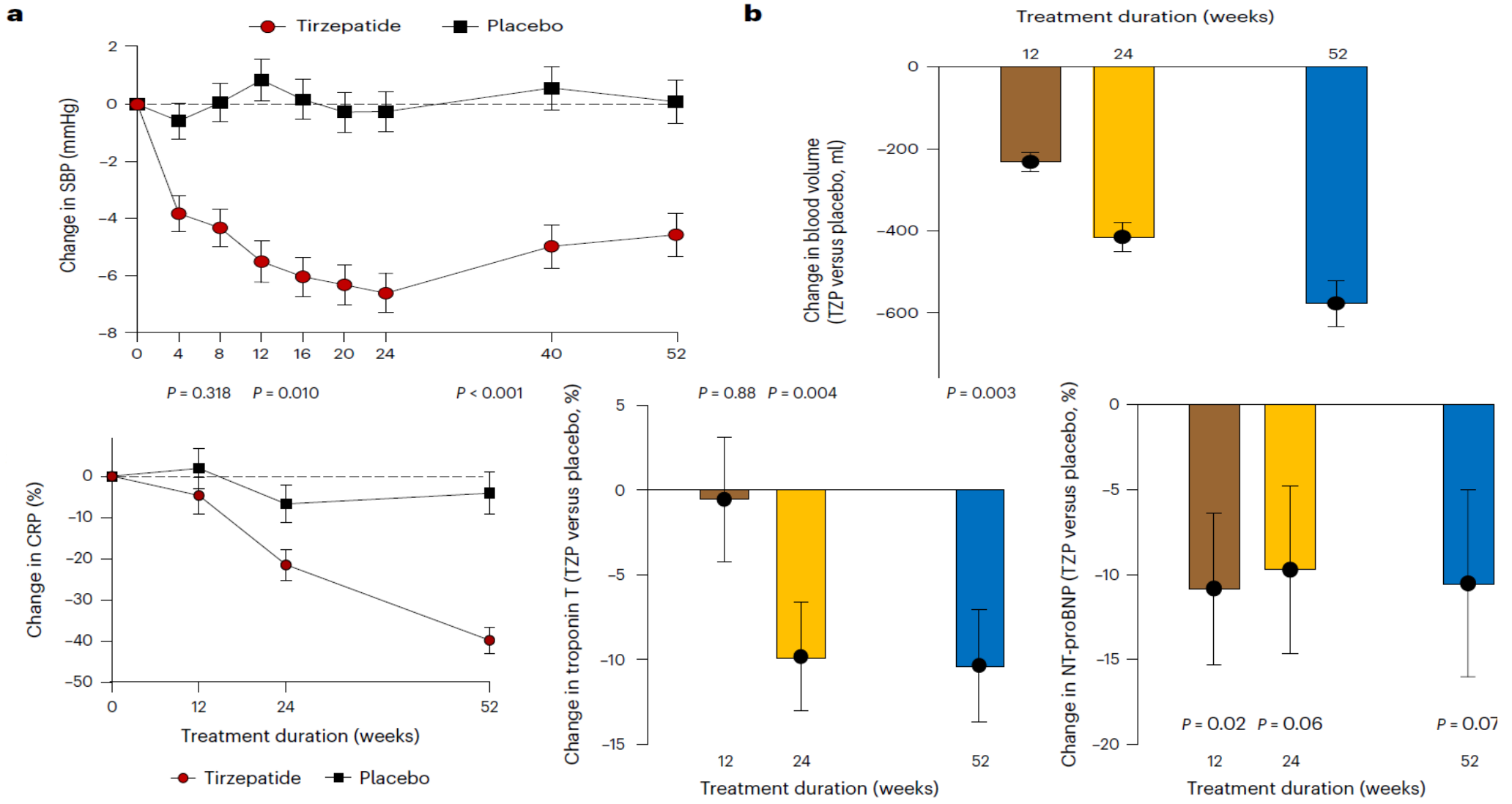
Packer M, et al. *N Engl J Med.* 2024 Nov 16 doi: 10.1056/NEJMoa2410027

SUMMIT – HEMODYNAMIC SUBSTUDY



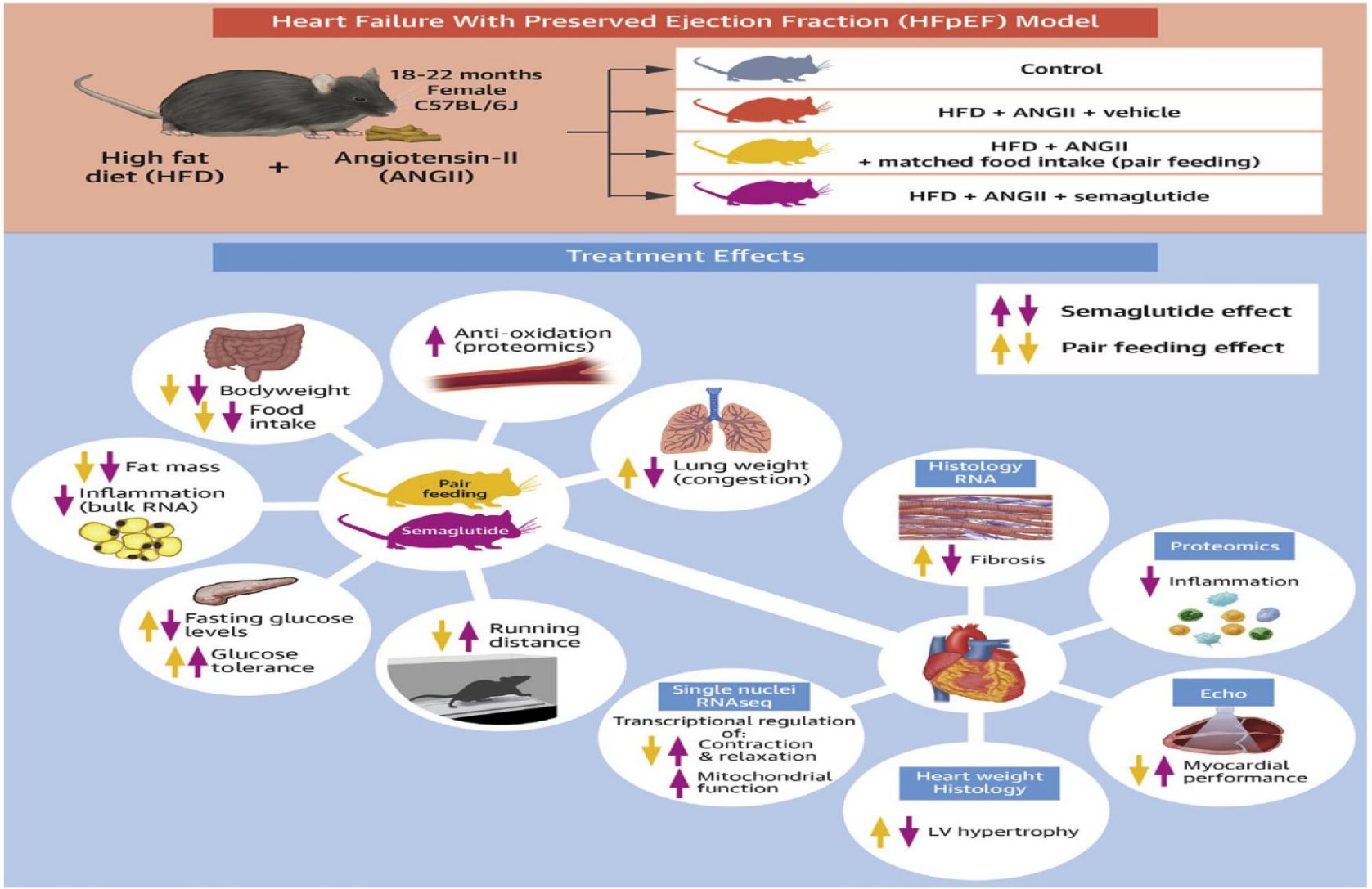
N of participants			
Tirzepatide	332	323	305
Placebo	323	313	298

N of participants			
Tirzepatide	336	329	311
Placebo	336	325	316

N of participants			
Tirzepatide	341	335	317
Placebo	339	331	320

Borlaug B, et al. *Nat Med* 2024 doi.org-10.1038-s41591-024-03374-z

EFFECTS OF SEMAGLUTIDE EXCEED THOSE OF DIETARY RESTRICTION



Withaar C, et al. J Am Coll Cardiol Basic Trans Science. 2023;8(10):1298-314.

Withaar C, et al. *J Am Coll Cardiol Basic Trans Science.* 2023; **8**:1298–1314

SUMMARY

- Obesity is **by far** the most common condition to accompany or precede HFpEF
- Obesity was - until now (?) – not seen as a bona fide Tx target

- Lifestyle remains the cornerstone of weight control!
- We now have **powerful** agents that lower body weight – and may be particularly effective in HFpEF

- Is weight loss driving **everything** ?
- Or drug-specific ancillary effects?

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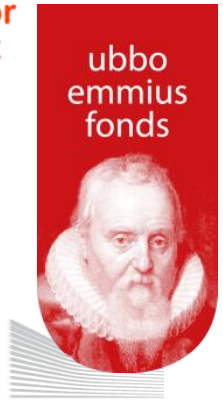

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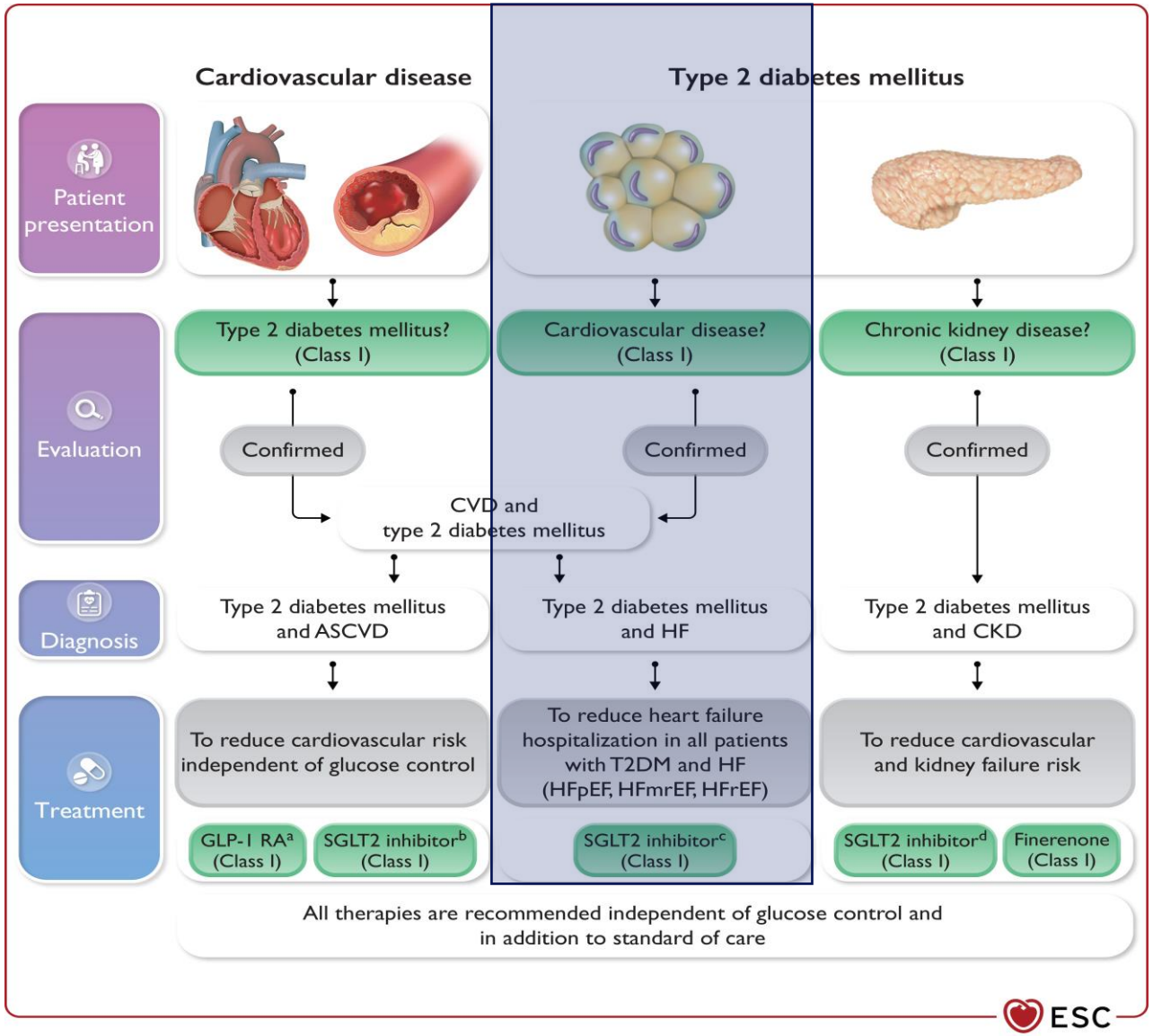
ESC DIABETES GUIDELINES



Marx N, et al. *Eur Heart J.* 2023 doi.org/10.1093/eurheartj/ehad192

Table 2. Primary and Secondary End Points.*

End Point	Tirzepatide (N=364) Value	Tirzepatide (N=364) Events/100 patient-yr	Placebo (N=367) Value	Placebo (N=367) Events/100 patient-yr	Hazard Ratio or Difference (95% CI)†	P Value
Primary end points and components						
Adjudicated death from cardiovascular causes or a worsening heart-failure event resulting in hospitalization, intravenous drugs in an urgent care setting, or intensification of oral diuretic therapy — no. (%)	36 (9.9)	5.5	56 (15.3)	8.8	0.62 (0.41 to 0.95)	0.026
Adjudicated death from cardiovascular causes — no. (%)	8 (2.2)	1.2	5 (1.4)	0.7	1.58 (0.52 to 4.83)	
Adjudicated death from undetermined cause — no. (%)	2 (0.5)	0.3	0	0	—	
Adjudicated worsening heart-failure event resulting in hospitalization, intravenous drugs in an urgent care setting, or intensification of oral diuretic therapy — no. (%)	29 (8.0)	4.5	52 (14.2)	8.2	0.54 (0.34 to 0.85)	
Adjudicated worsening heart-failure event resulting in hospitalization — no. (%)	12 (3.3)	1.8	26 (7.1)	3.9	0.44 (0.22 to 0.87)	
Adjudicated worsening heart-failure event resulting in intravenous diuretic therapy in an urgent care setting — no. (%)	5 (1.4)	0.7	12 (3.3)	1.8	0.41 (0.14 to 1.16)	
Adjudicated worsening heart-failure event resulting in intensification of oral diuretic therapy in an outpatient setting — no. (%)	17 (4.7)	2.6	21 (5.7)	3.2	0.80 (0.42 to 1.52)	
Death from any cause — no. (%)	19 (5.2)	2.8	15 (4.1)	2.2	1.25 (0.63 to 2.45)	
Change at 52 weeks in KCCQ-CSS	19.5±1.2	—	12.7±1.3	—	6.9 (3.3 to 10.6)‡	<0.001§
Key secondary end points						
Change at 52 weeks in 6-minute walk distance — m	26.0±3.8	—	10.1±3.9	—	18.3 (9.9 to 26.7)‡	<0.001§
Percent change at 52 weeks in body weight — %	−13.9±0.4	—	−2.2±0.5	—	−11.6 (−12.9 to −10.4)	<0.001
Percent change at 52 weeks in high-sensitivity C-reactive protein level — %	−38.8±4.5	—	−5.9±5.3	—	−34.9 (−45.6 to −22.2)¶	<0.001
Adjusted change at 52 weeks in physiological and laboratory measurements						
NT-proBNP — ratio of geometric means‖	0.93±0.04	—	1.04±0.04	—	0.90 (0.79 to 1.01)¶	
Systolic blood pressure — mm Hg	−4.6±0.8	—	0.1±0.8	—	−4.7 (−6.8 to −2.5)	
Heart rate — beats/min	3.0±0.5	—	0.3±0.5	—	2.8 (1.3 to 4.3)	

PRIMARY EP √

CV DEATH ✖

HF HOSPITALIZATION √

AC DEATH ✖

QUALITY OF LIFE √

CRP √

NTPROBNP ✖

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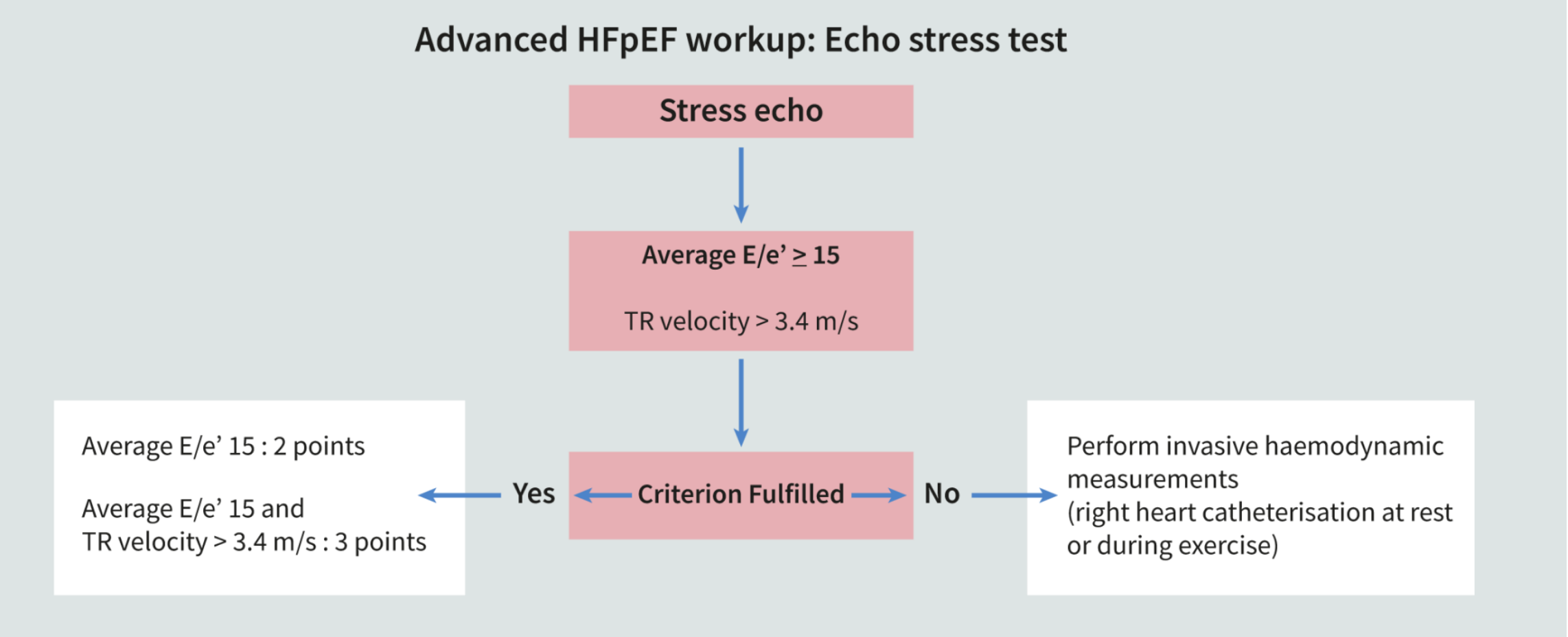
Packer M, et al. *N Engl J Med.* 2024 Nov 16 doi: 10.1056/NEJMoa2410027

The HFA-PEFF SCORE

Step **F**(1): **F**unctional testing



Pieske B, et al. *Eur Heart J.* 2019; **40**:3297-3317

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EXERCISE ECHOCARDIOGRAPHY

Parameters

- VO_2
- CO
- Estimation of intracardiac pressure
  - E/e' (LV end-diastolic pressure)
  - Pulmonary pressure

Calculate

- Peripheral O_2 extraction

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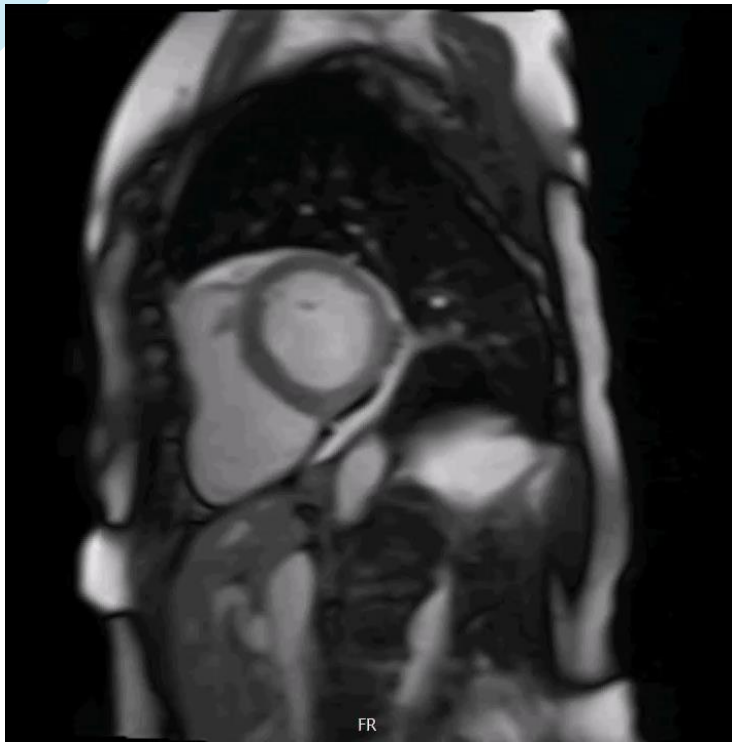
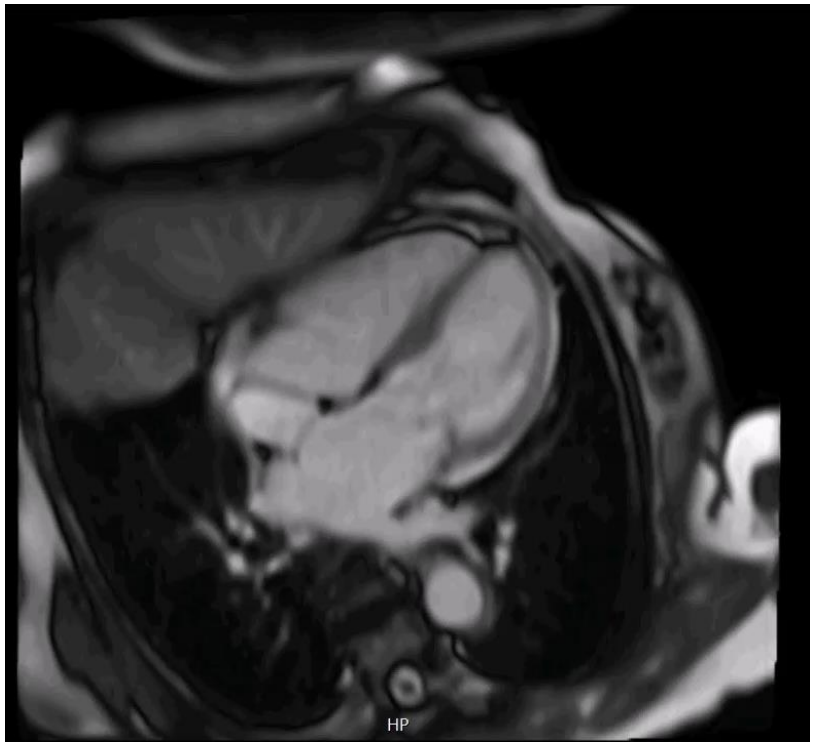
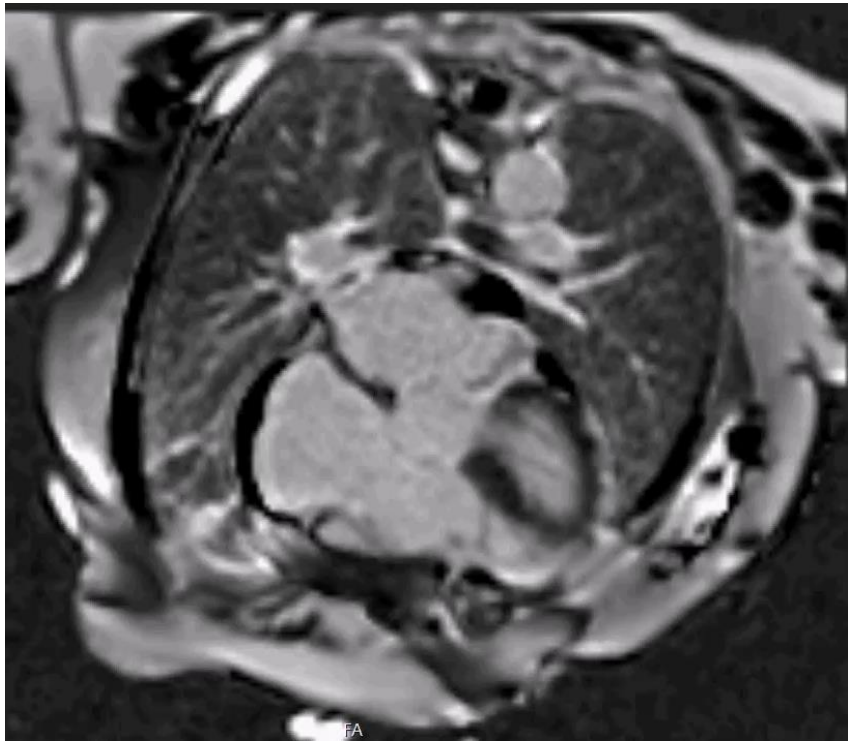
ADVANCED WORK-UP: CARDIAC MR







Normal LV and RV, with normal dimensions and function.

No myocardial fibrosis. No signs of cardiac amyloid.

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