WEIGHING IN ON HFpEF

A Review of the Clinical Evidence and Emerging Therapies for HFpEF

WEIGHING IN ON HFpEF

A Review of the Clinical Evidence and Emerging Therapies for HFpEF

Welcome & Introduction

Stephanie Poon
MD, MSc, FRCPC

Accreditation

This event is an Accredited Group Learning Activity (Section 1) as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada, and approved by the Canadian Cardiovascular Society. You may claim a maximum of 1 hour (credits are automatically calculated).

Faculty

Chair:

- Stephanie Poon, MD, MSc, FRCPC

Presenters:

- Grace Chua, MD, FRCPC, FACC
- Justin Ezekowitz, MBBCh MSc
- Anique Ducharme, MD, MSc, FRCP, FACC, FCCS, FHSA (h)

Disclosures

	Dr. Stephanie Poon
Any direct financial payments including receipt of honoraria	No disclosures
Membership on advisory boards or speakers' bureaus	Servier, Bayer, Boehringer Ingelheim
Funded grants or clinical trials	Boehringer Ingelheim
All other investments or relationships that could be seen by a reasonable, well-informed participant as having the potential to influence the content of the educational activity	No disclosures

This program has received an educational grant from Novo Nordisk Canada. This program was developed by the Canadian Heart Failure Society and was planned to achieve scientific integrity, objectivity and balance.

Learning Objectives

1. Discuss the interconnectivity between overweight/obesity and cardiovascular diseases such as HFpEF
2. Assess the clinical evidence around management of HFpEF
3. Review the emerging therapies in managing HFpEF, including GLP1RAs

Symposium Agenda

4 mins	Welcome and Introductions Dr. Stephanie Poon
13 mins	Beyond the Scale: Appraising the impact of obesity and the increased risk for cardiovascular disease and HFpEF Dr. Grace Chua
13 mins	Tipping the Balance: A review of obesity management strategies in patients with HFpEF Dr. Justin Ezekowitz
13 mins	Heartwise: An appraisal of the emerging therapies in managing HFpEF and metabolic syndrome Dr. Anique Ducharme
15 mins	Q&A Period All panelists
2 mins	Conclusion Dr. Stephanie Poon

Housekeeping

- To collect your MOC Section 1 credits, please remember to complete both the session evaluation and the congress evaluation
- The evaluation QR code can be found on your tables and will be displayed on the screen after the presentation

WEIGHING IN ON HFpEF

A Review of the Clinical Evidence and Emerging Therapies for HFpEF

Beyond the Scale: Appraising the impact of obesity and the increased risk for cardiovascular disease and HFpEF

Grace L. Chua MD, FRCPC, FACC
Cardiologist, Mackenzie Health

Disclosures

- Grace Chua, MD, FRCPC, FACC
  Cardiologist, Mackenzie Health

CONSULTING FEES/ ADVISORY BOARD MEMBER:	Amgen, Astra Zeneca, Bayer, Boehringer Ingelheim-Eli Lilly Alliance, Bristol Myers Squibb, HLS Therapeutics, Novartis, Novo Nordisk, Pfizer, GSK, Servier, CPD Network, Canadian Collaborative Research Network, University of Toronto, CHEP PLUS
SPEAKERS BUREAU/HONORARIA:	CPD Network Association, Canadian Cardiovascular Society, Canadian Heart Failure Society, Canadian Society of Endocrinology, Canadian Society of Nephrology, EOCI Pharmacomm, LiV Medical Agency, Meducom Health Inc, Medscape, University of Toronto Heart and Stroke Richard Lewar Center of Excellence, Canadian Medical and Surgical Knowledge Translation Research Group
GRANTS/RESEARCH SUPPORT:	Bayer, Novartis
OTHER:	Amgen, Astra Zeneca, Bayer, Novartis, Pfizer, Sanofi, Merck, Bristol Myers Squibb, Moderna, Takeda, Gilead, Regeneron, Glaxo Smith Kline, Vertex Pharmaceuticals Abvie, Biontech, Pfizer, Eli Lilly

Learning objective

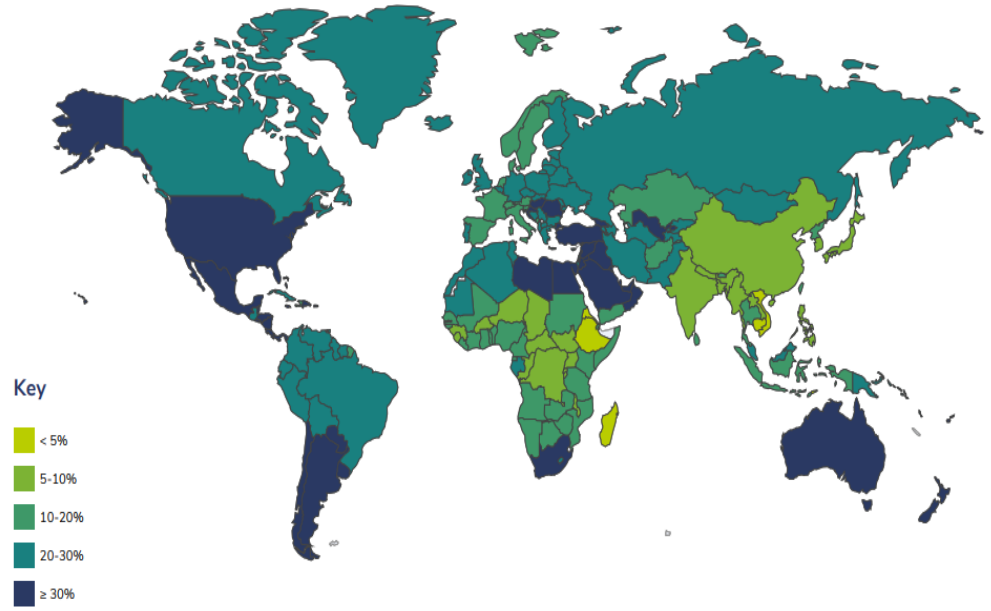
- Discuss the interconnectivity between obesity and cardiovascular diseases such as HFpEF

THE WORLD

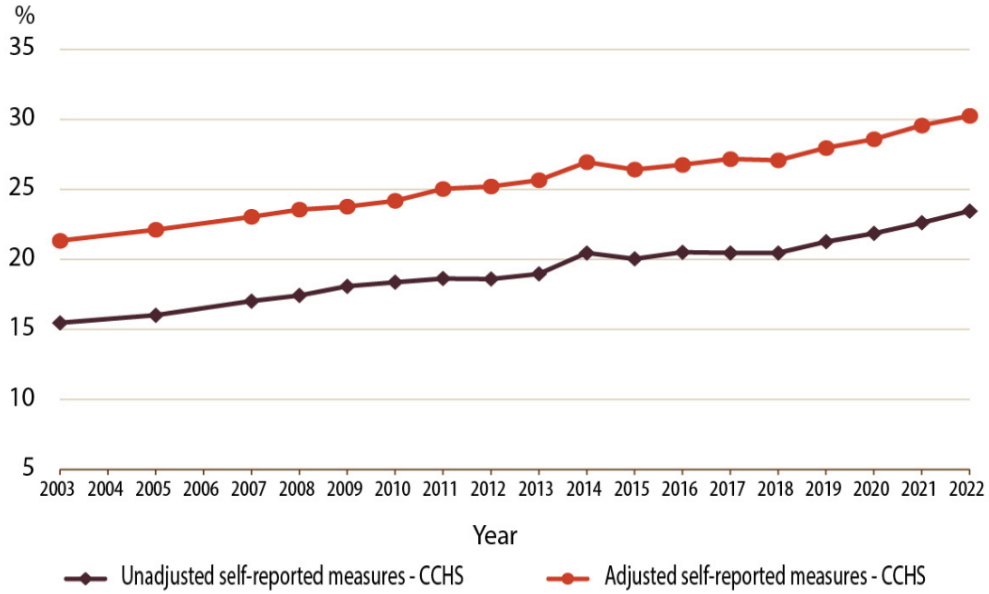
CANADA

Estimates of prevalence of obesity in adults

Obesity BMI ≥ 30 kg/m²



Prevalence of obesity by type of body mass index (BMI) estimate among Canadians aged 18 to 79



Source(s): Canadian Community Health Survey 2003 to 2022.

- 2003 prevalence was 1 in 5 (21%) rising to 1 in 3 (30%) in 2022

Age Groups
Age 18 to 34 (25%)
Age 50-64 (34% peak)
Age 65-70 (29%)

Provinces:
British Columbia (26%)
New Brunswick (43%),
Saskatchewan (38%),
Nova Scotia (36%)
Ontario (30%)
Quebec (29%)
Newfoundland and Labrador (42%)
Prince Edward Island (36%)
Manitoba (34%)
Alberta (31%).

https://data.worldobesity.org/maps/?area=maps

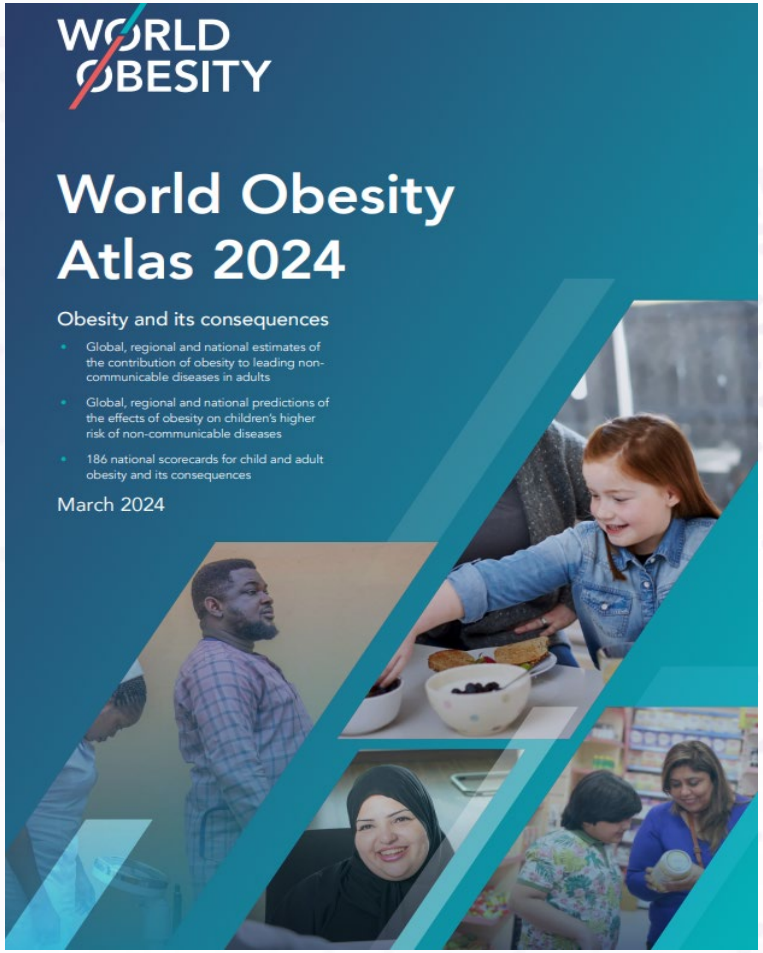


Table 1.1: Global estimate (2020) and projected number of adults (2025-2035) with high BMI

	2020	2025	2030	2035
Adults with overweight (BMI ≥25 to 30 kg/m²)	1.39bn	1.52bn	1.65bn	1.77bn
Adults with obesity (BMI ≥30 kg/m²)	0.81bn	1.01bn	1.25bn	1.53bn
Adults with overweight or obesity as a proportion of all adults globally	42%	46%	50%	54%

Source: World Obesity Federation, 2023b

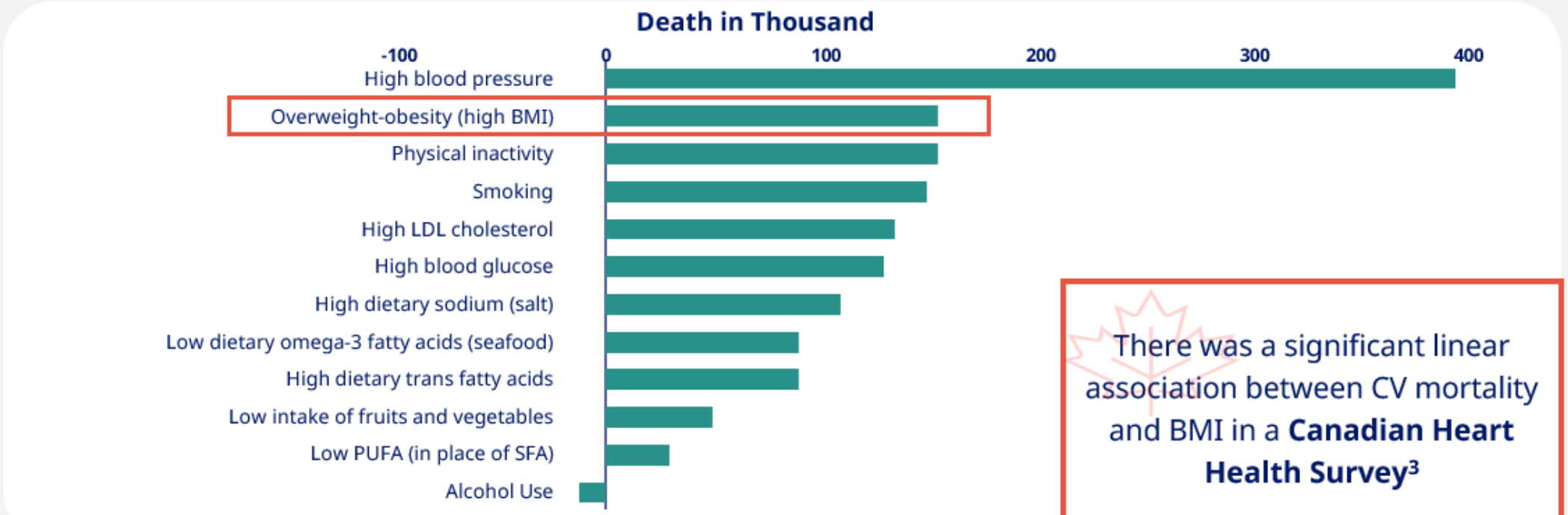
Table 1.2: Top 20 countries for the highest proportion of adult men and women living with high BMI 2020

	Proportion of men with high BMI		Proportion of women with high BMI
Tonga	80%	Tonga	87%
Samoa	79%	Samoa	86%
United States	79%	Kuwait	79%
Malta	78%	Jordan	78%
Kuwait	77%	Saudi Arabia	78%
New Zealand	76%	Qatar	77%
Australia	76%	Turkey	76%
Israel	76%	Libya	75%
Qatar	76%	Lebanon	75%
Canada	76%	Oman	74%
Saudi Arabia	75%	United Arab Emirates	74%
Spain	74%	Egypt	74%
United Kingdom	74%	Bahamas	73%
Jordan	74%	Fiji	73%
Czechia	74%	Iraq	73%
Greece	74%	Algeria	73%
Bulgaria	73%	Tunisia	72%
Lebanon	73%	Bahrain	72%
Iceland	73%	Iran	72%
Montenegro	73%	Mexico	71%

Source: World Obesity Federation, 2023b

Obesity is the 2nd most impactful factor to treat for cardiovascular death prevention

Preventable deaths by treating CV risk factors[1]



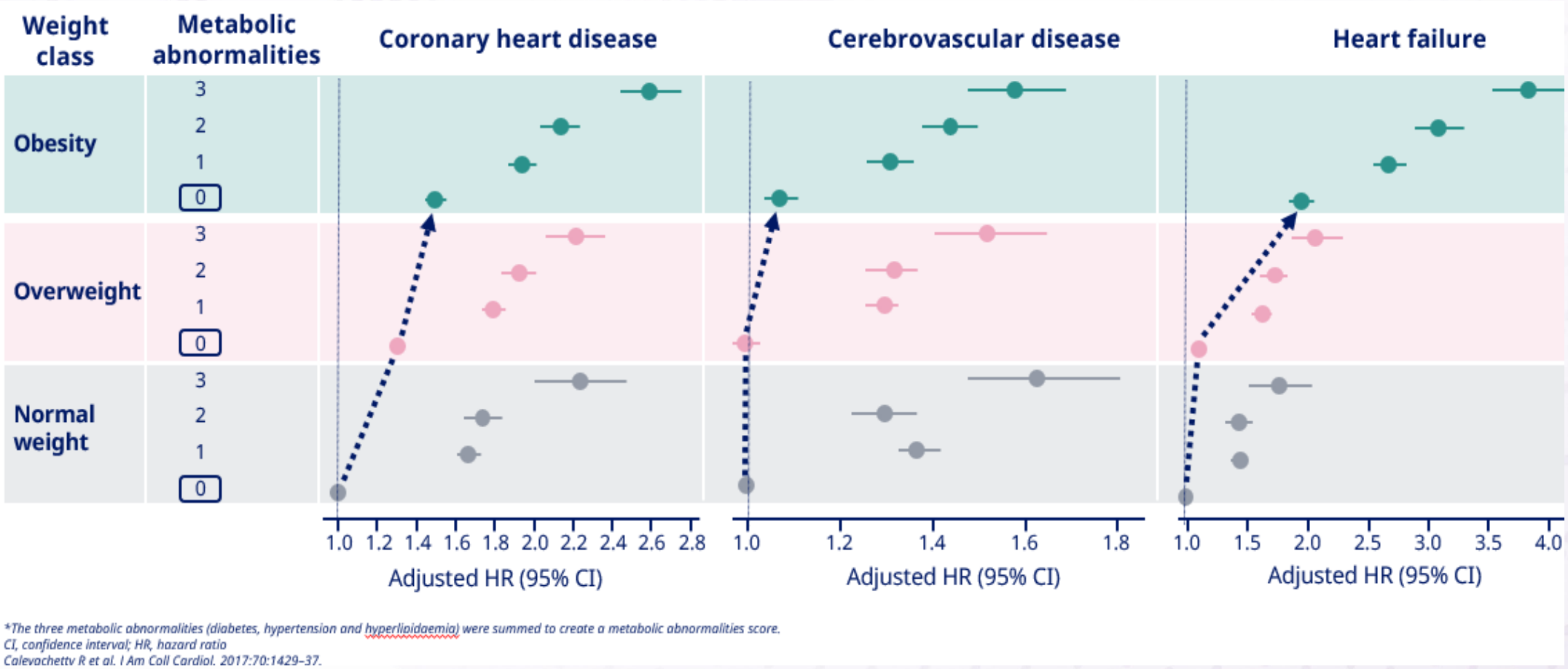
There was a significant linear association between CV mortality and BMI in a **Canadian Heart Health Survey**[3]

In 1 year, cardiovascular disease accounted for 2.7 million deaths related to high BMI[2]

BMI, body mass index; CV, cardiovascular; LDL, low density lipoprotein; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid

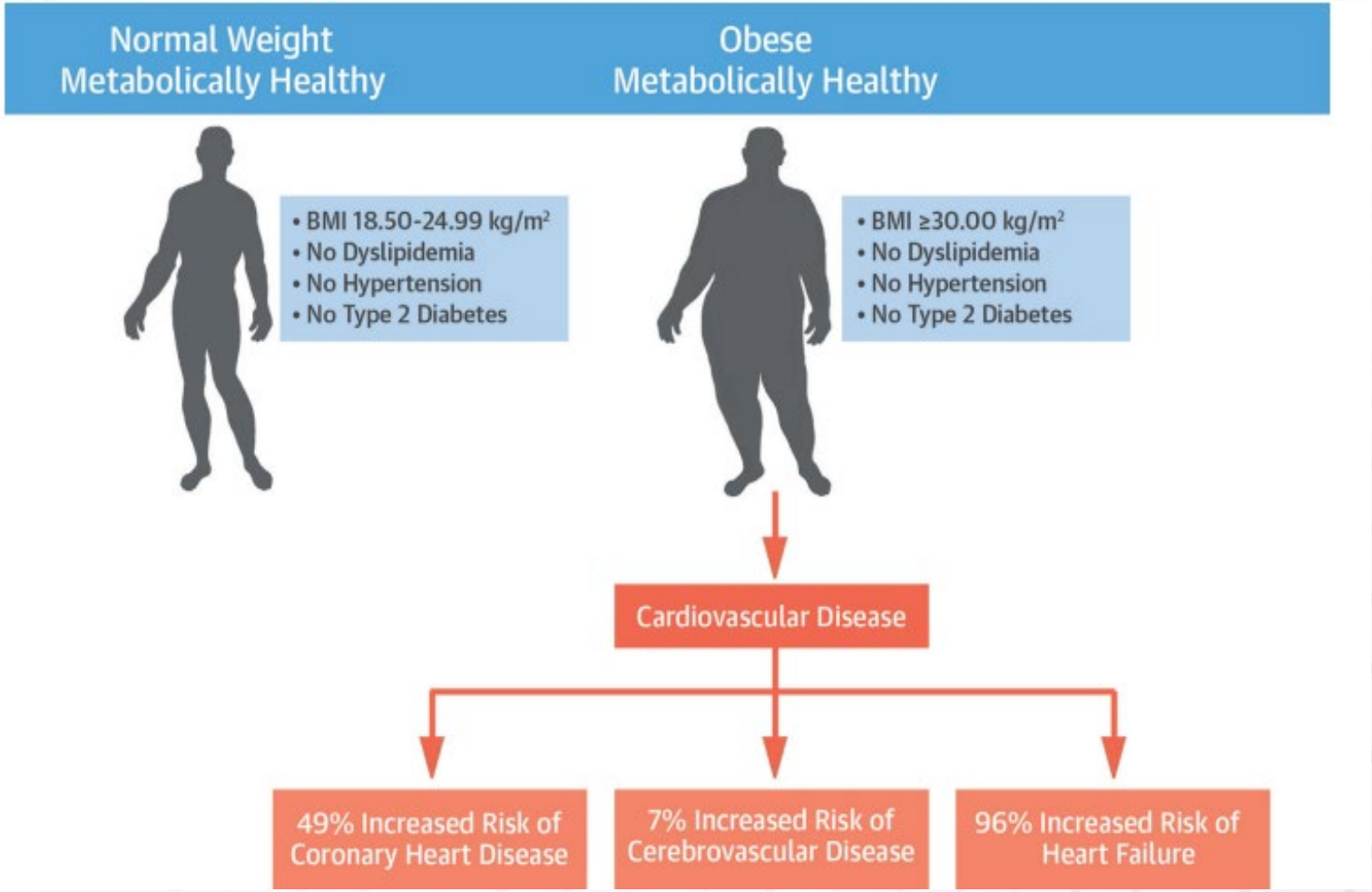
1. Call to Action: Urgent Challenges in Cardiovascular Disease, American Heart Association, 2019. 2. Eur Heart J Qual Care Clin Outcomes. 2019 Jul; 5(3): 225–232. Eur J Prev Cardiol. 2019 May;26(8):824-835. Circulation Research. 2017;120:617–619. GBD 2015 Obesity Collaborators. N Engl J Med. 2017;377:13–27 3. Katzmarzyk, Peter T., et al. "Body mass index and risk of cardiovascular disease, cancer and all-cause mortality." Canadian Journal of Public Health 103 (2012): 147-151

The risk of cardiovascular events increases in both the overweight or obesity groups, even in the absence of other metabolic abnormalities



*The three metabolic abnormalities (diabetes, hypertension and hyperlipidaemia) were summed to create a metabolic abnormalities score.
CI, confidence interval; HR, hazard ratio
Calevachetty R et al. J Am Coll Cardiol. 2017;70:1429–37.

CV risk of obesity in patients without risk factors



Caleyachetty, R. et al. *J Am Coll Cardiol*. 2017;70(12):1429-37.

Obesity paradox?

- Obesity paradoxically protects against adverse outcomes in patients with established HFpEF, despite being a well-established risk factor incident HFpEF
- May be secondary to bias: findings come from cross-sectional studies limited by
  1) Survival bias (i.e. sicker obese patients die prior to assessment)
  2) Reverse causation (patients with the most severe HF have weight loss due to cachexia)
  3) Measurement bias (measuring BMI instead of visceral fat)

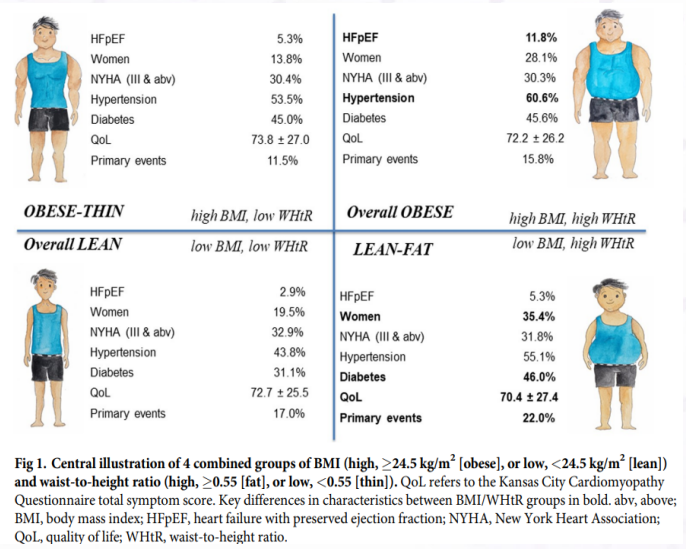
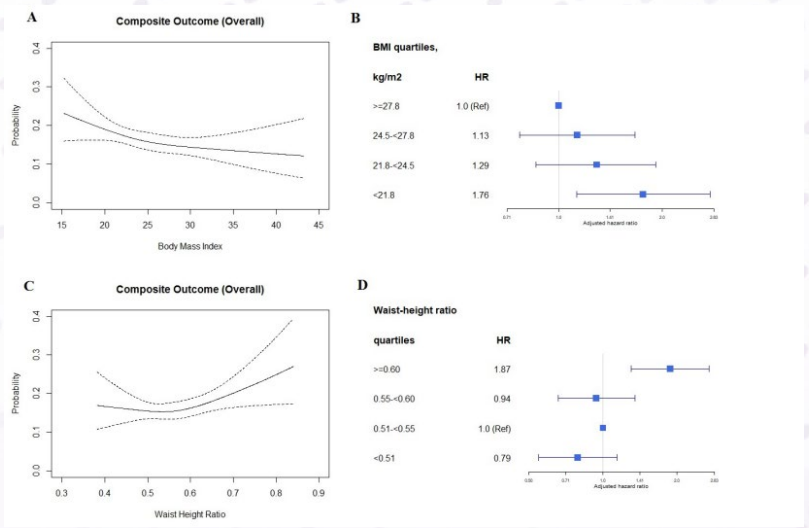
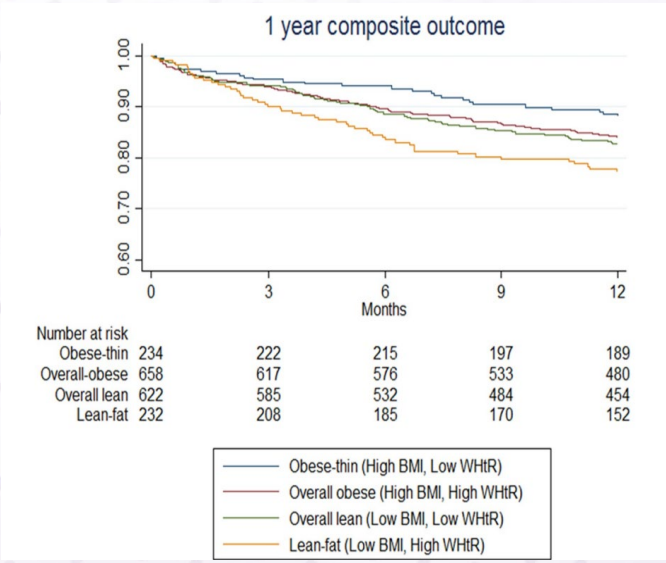


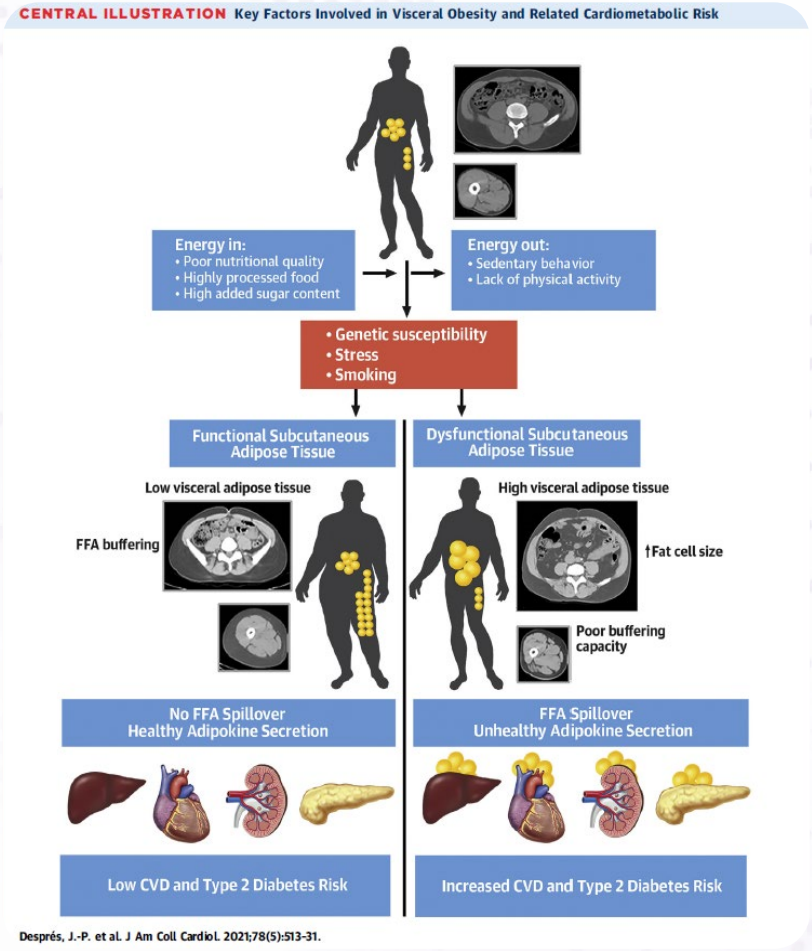
Fig 1. Central illustration of 4 combined groups of BMI (high, ≥24.5 kg/m² [obese], or low, <24.5 kg/m² [lean]) and waist-to-height ratio (high, ≥0.55 [fat], or low, <0.55 [thin]). QoL refers to the Kansas City Cardiomyopathy Questionnaire total symptom score. Key differences in characteristics between BMI/WHtR groups in bold. abv, above; BMI, body mass index; HFpEF, heart failure with preserved ejection fraction; NYHA, New York Heart Association; QoL, quality of life; WHtR, waist-to-height ratio.

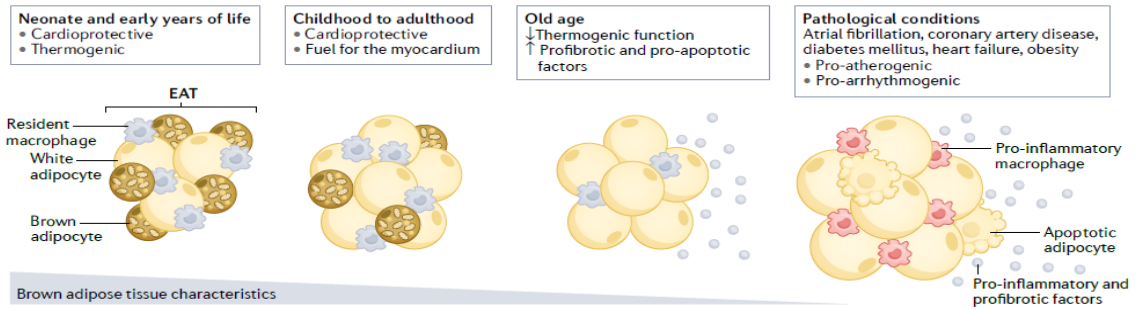


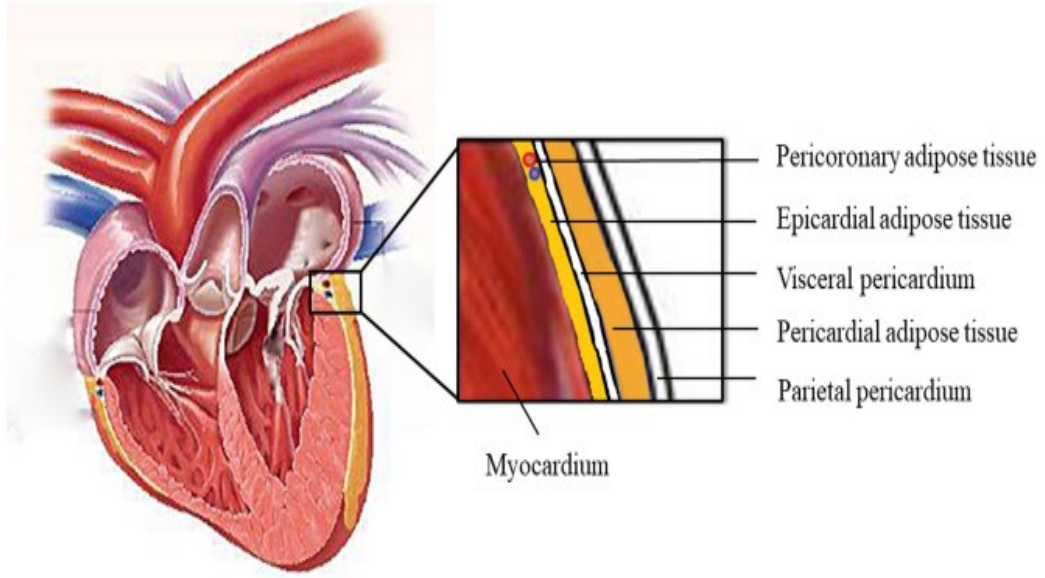


Borlaug, B. et al. *Cardiovascular Research.* 2022.
Chandramouli, C et al. *PLoS Med.* 2019.

Not all fat is created equal: the type of fat and location matter







Iacobellis G. *Nature Reviews Cardiology*. 2022
Li, C. et al. *Front Endocrinol*. 2023.

Epicardial adipose tissue

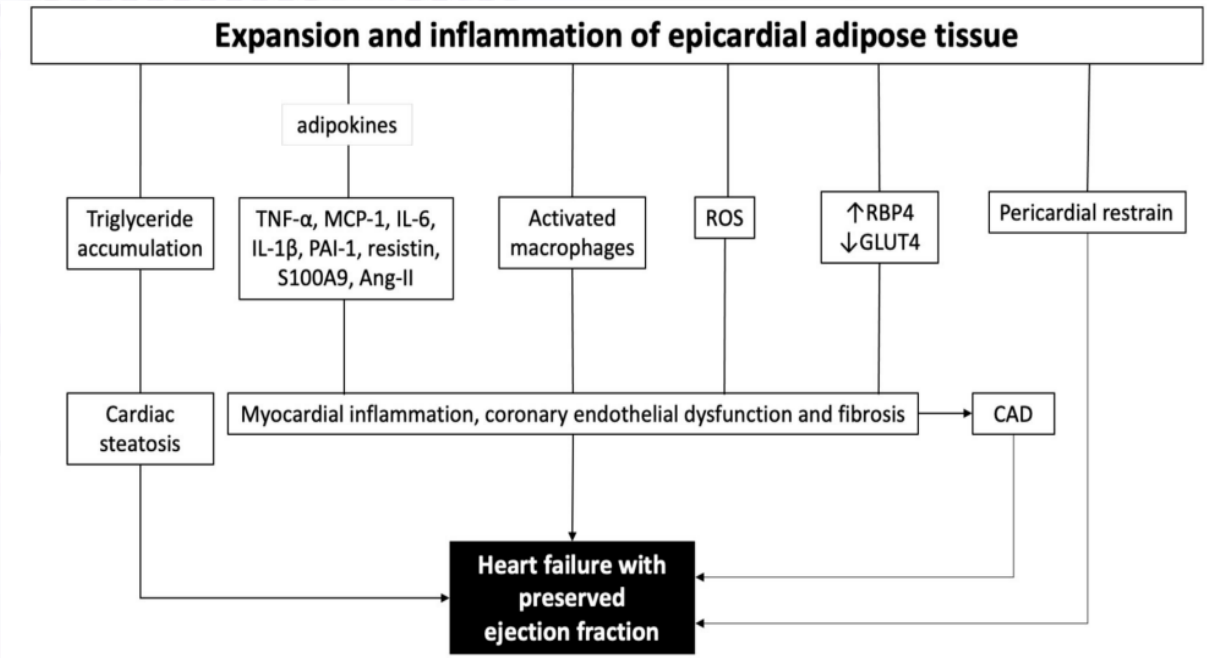
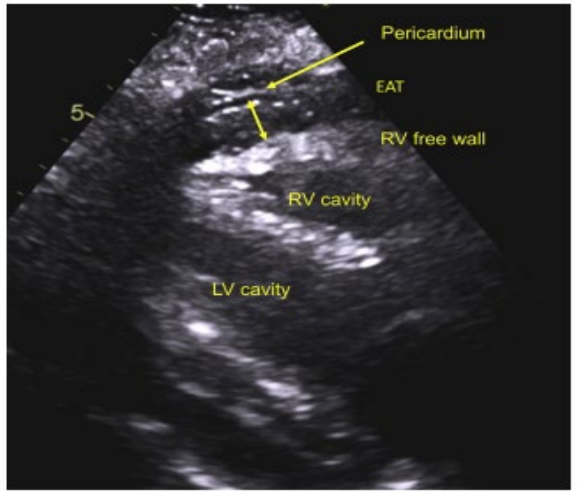
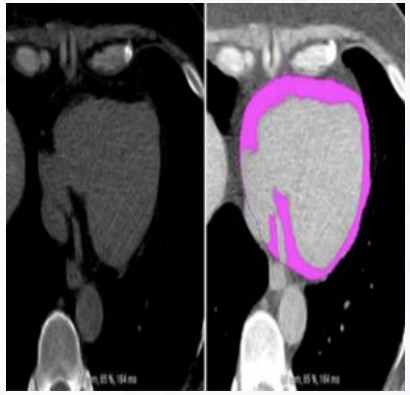


FIGURE 1 | The role of epicardial adipose tissue in the pathogenesis of heart failure with preserved ejection fraction. ROS, reactive oxygen species; TNF-α, tumor necrosis factor alpha; MCP-1, monocyte chemoattractant protein 1; IL-6, interleukin 6; IL-1b, interleukin 1b; PAI-1, plasminogen activator inhibitor-1; Ang-II, angiotensin II; ROS, reactive oxygen species; RBP4, renitol-binding protein 4; GLUT4, glucose transporter-4; CAD, coronary artery disease.





Example with landmarks taken from the parasternal long-axis view. EAT = epicardial adipose tissue; LV = left ventricle;

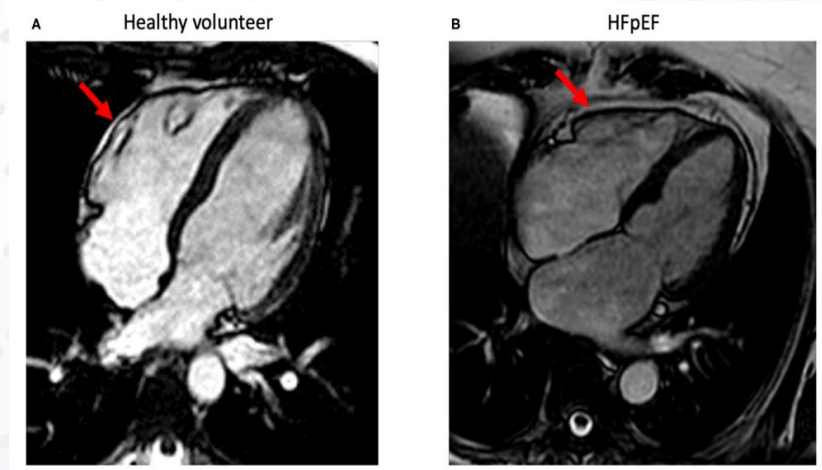
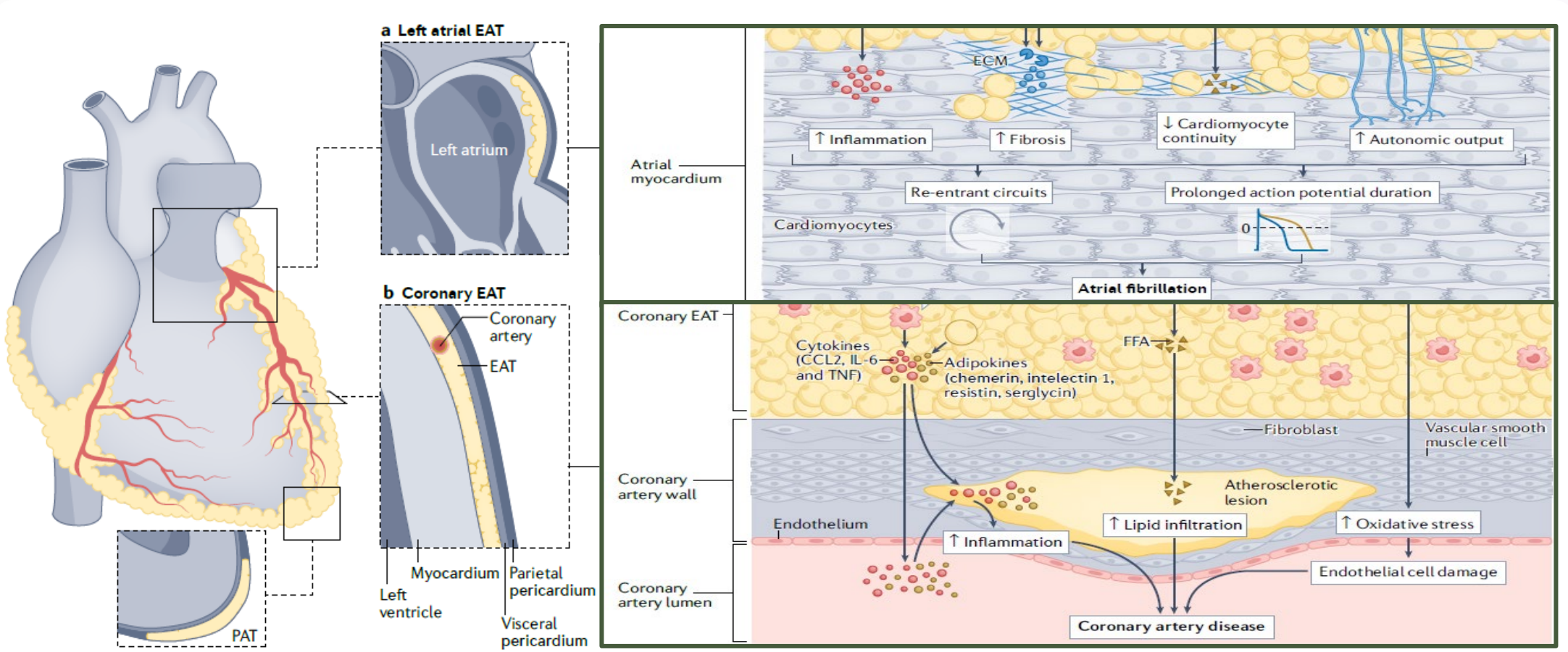


FIGURE 2 | Standard-4-chamber orientations acquired using standard steady-state free precession-cardiac magnetic imaging sequences. The images demonstrate epicardial fat (red arrow) with a minimal (normal) amount in a healthy volunteer **(A)** and in a patient with HFpEF **(B)** with increased epicardial fat surrounding the whole heart.

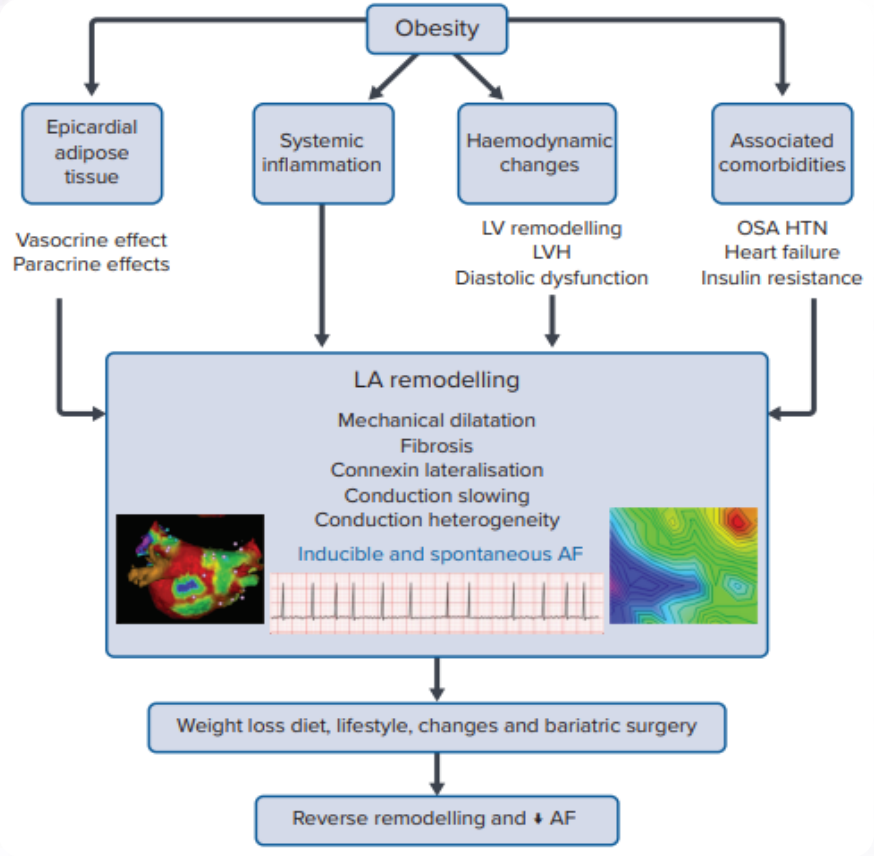
Elsanhoury, A. et al. *Front Cardiovasc Med*. 2021.
Koepp, K et al. *J Am Coll Cardiol HF*. 2020.
Bertaso et al. *Arq Bras Cardiol.* 2013.

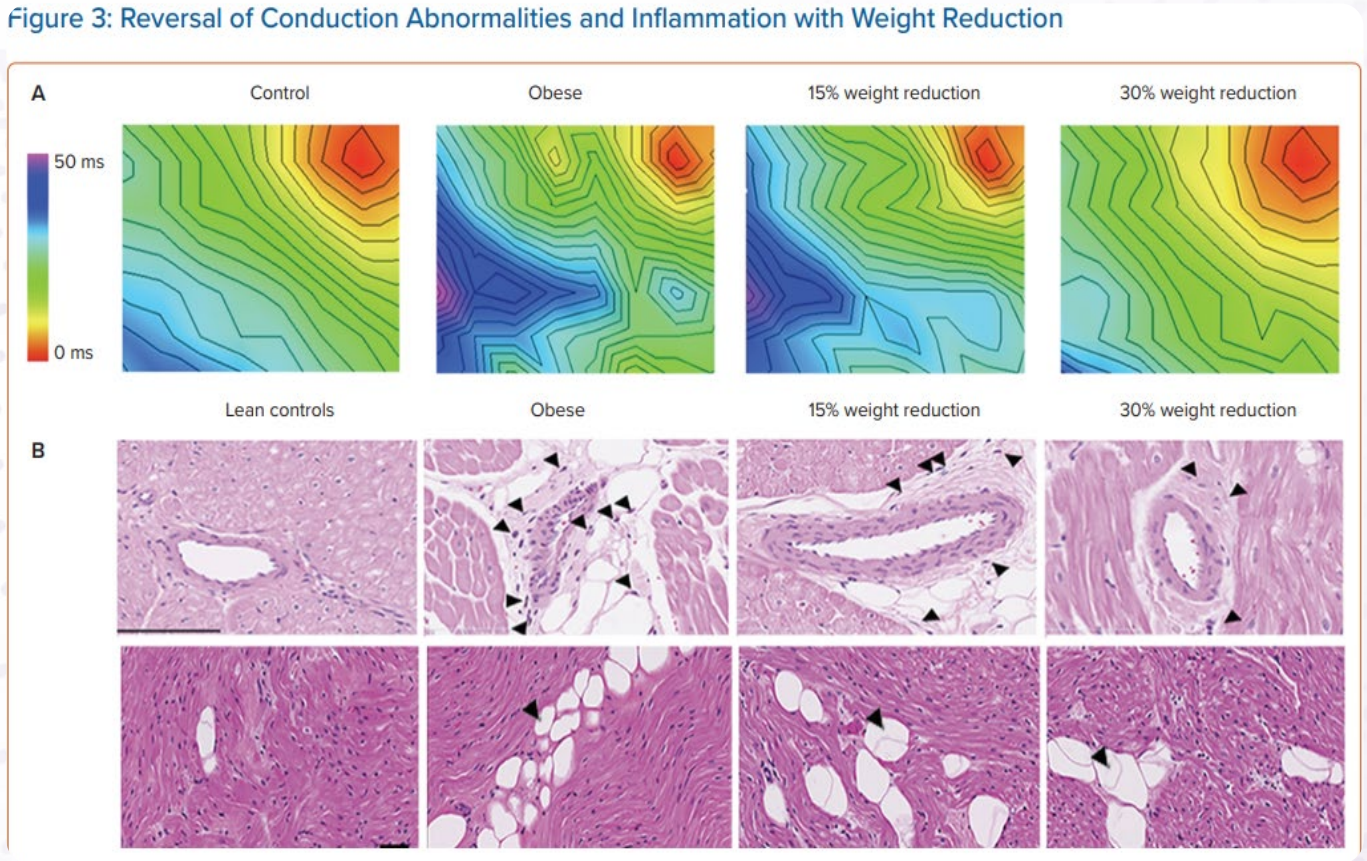
Epicardial fat may be independent of BMI



Adapted from Iacobellis G. *Nature Reviews Cardiology*. 2022.

Epicardial fat and atrial fibrillation





Al-Kaisey, A et al. *Arrhythmia and Electrophysiology Review*. 2021.

Epicardial fat and atrial fibrillation

Lifestyle and risk factors

2020 CCS AF Guidelines:

Alcohol and Tobacco

Limit to ≤ 1 standard drink[1] per day. Complete abstinence from alcohol may be preferred in selected patients.

Target complete abstinence from tobacco-related products

Sleep Apnea

CPAP for moderate-severe OSA (AHI ≥ 15/hour)
Regular assessment of CPAP adherence

Weight Loss

Target a weight loss of ≥ 10% to a BMI of less than 27 kg/m^2

Diabetes

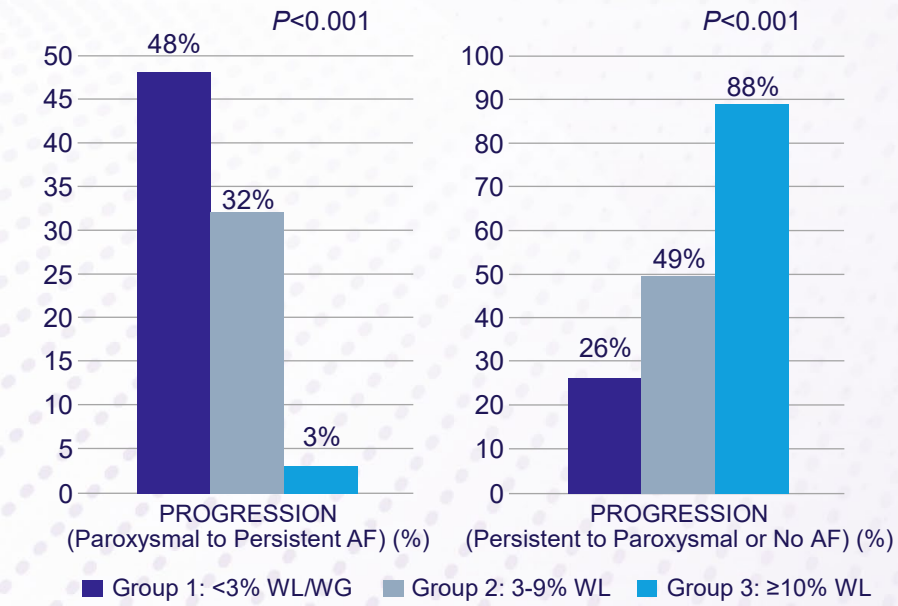
Target a HbA1c of ≤ 7.0%

Exercise

1. Moderate intensity aerobic exercise ≥ 30 minutes a day at least 2-5 days per week (target ≥ 200 minutes weekly).
2. Resistance exercise 2-3 days per week.
3. Flexibility exercises at least 10 minutes per day at least 2 days per week in those > 65 years of age.

Blood Pressure

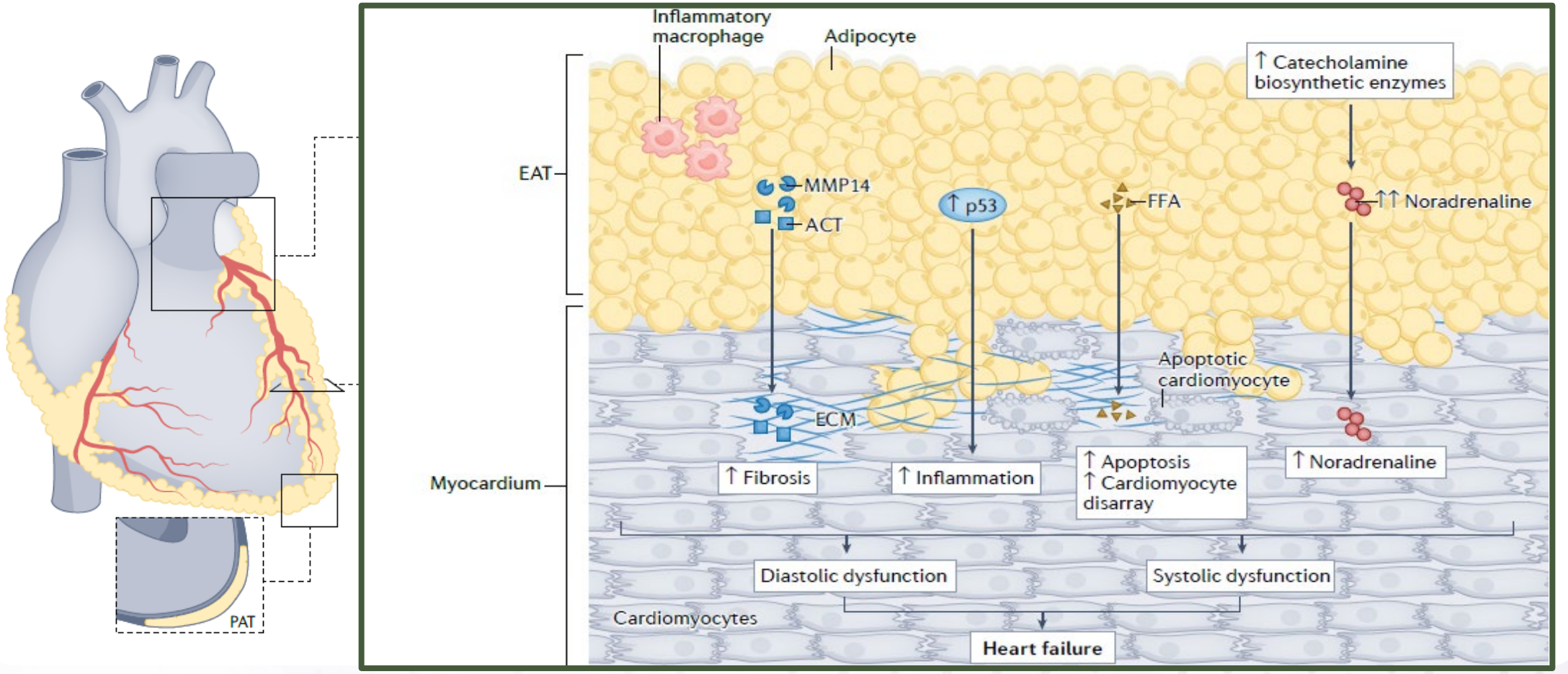
Target ≤ 130/80 mmHg at rest and ≤ 200/100 mmHg at peak exercise. ACE-I or ARB may be preferred.



REVERSE-AF
Middeldorp, M. et al.
Europace (2018) 20, 1929-1935

Andrade J et al. *Can J Cardiol.* 2020.

Epicardial fat may be independent of BMI



Adapted from Iacobellis G. *Nature Reviews Cardiology*. 2022.

Changes seen in obesity HFpEF

Vessel Wall/Other Organs

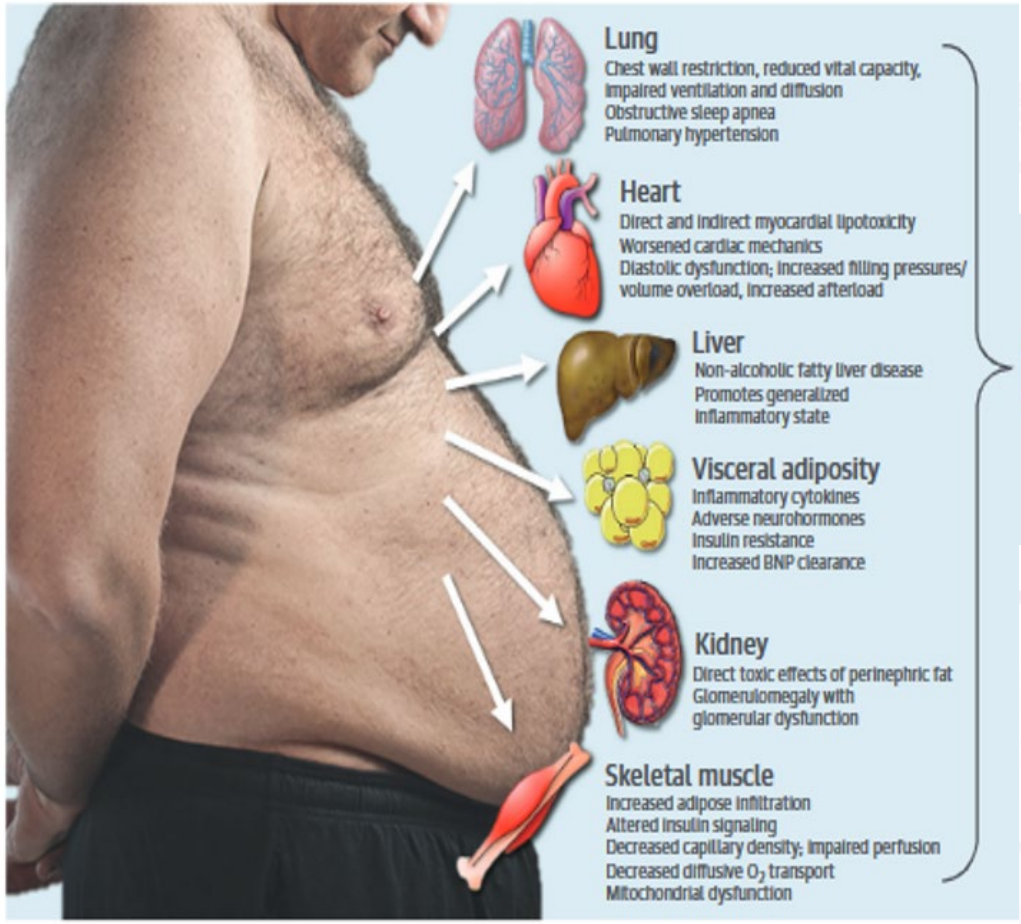
- Volume expansion (secondary to systemic vasodilation and sodium retention)
- Neurohormonal activation (both SNS, RAAS via adipokines)—hypertension and HF
- Systemic inflammation
- VAT/EAT expansion
- Liver fat promotes inflammation, dyslipidemia and insulin resistance
- Perinephric fat leads to mechanical compression of kidneys and obesity related glomerulopathy, hyperfiltration, microvascular proliferation
- Changes in skeletal muscle including adipose infiltration, capillary rarefaction, mitochondrial dysfunction that lead to exercise intolerance

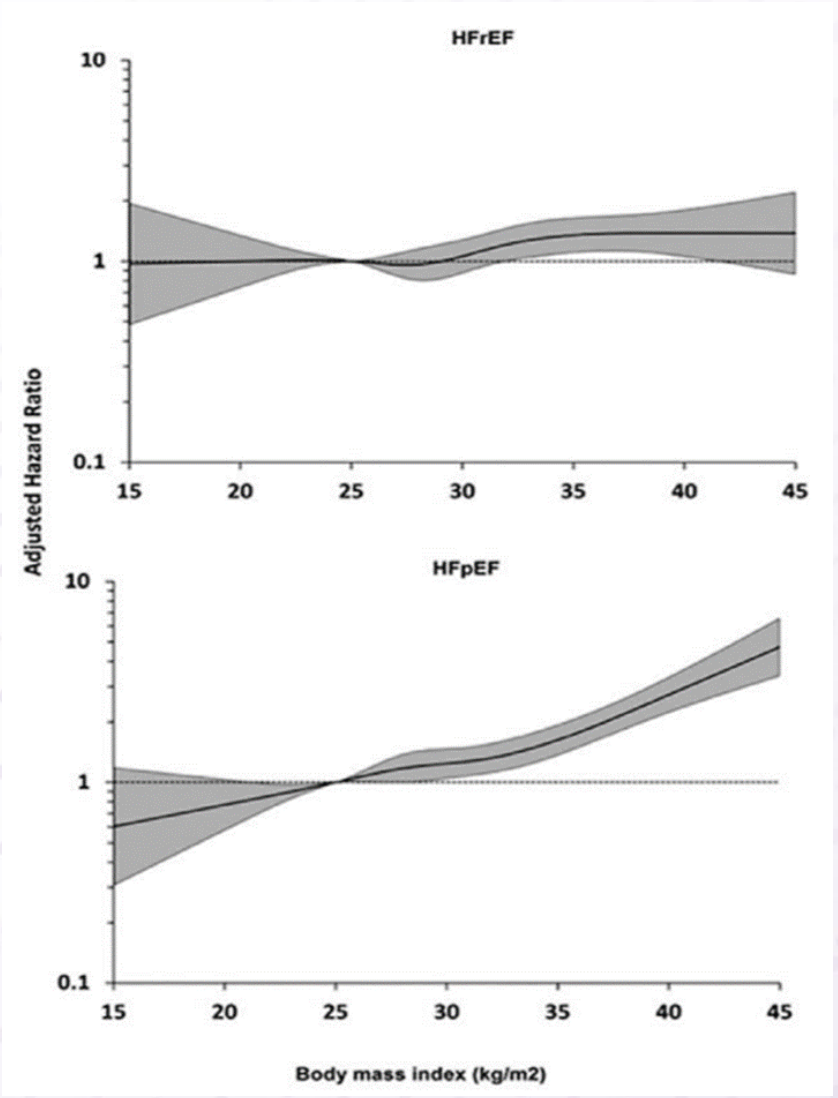
Cardiac

- LV cavity dilatation
- Eccentric hypertrophy and concentric remodelling
- Increase in diastolic chamber stiffness
- Severe impairments in systolic and diastolic reserve, particularly with exercise
- LA remodelling and dysfunction, AF
- EAT causes ventricular interdependence, RV-PA coupling abnormalities
- Increase in cardiac FFA uptake and oxidation and decreased glucose oxidation
- Increase in PVR and pulmonary hypertension leading to RV dysfunction
- Cardiac fibrosis

Borlaug B et al. *Cardiovascular Research. 2022.*

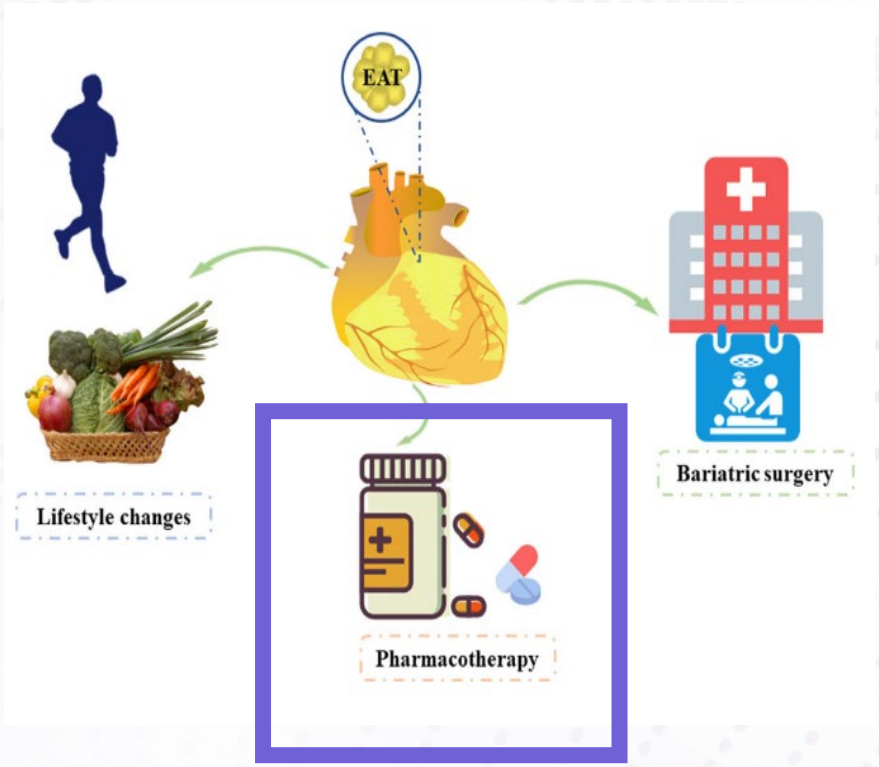
Pathophysiology of heart failure in obesity





Adapted from Kitzman D et al. *JACC*. 2016.

Treatment of epicardial adipose tissue (EAT)



Weight loss leads to improved health outcomes

Towards greater weight loss and overall health improvement

Benefits of 0–5%	Benefits of 5–10%	Benefits of 10–15%	Benefits of >15%
Hypertension	Prevention of T2D	CVD	T2D remission
Hyperglycemia	PCOS	Urinary stress incontinence	CV mortality
	Dyslipidemia	NASH	HFpEF
	Asthma/AD	OSAS	
	NAFLD	GERD	
	OSA severity	Knee OA	
	Disability & HRQoL		

Weight loss

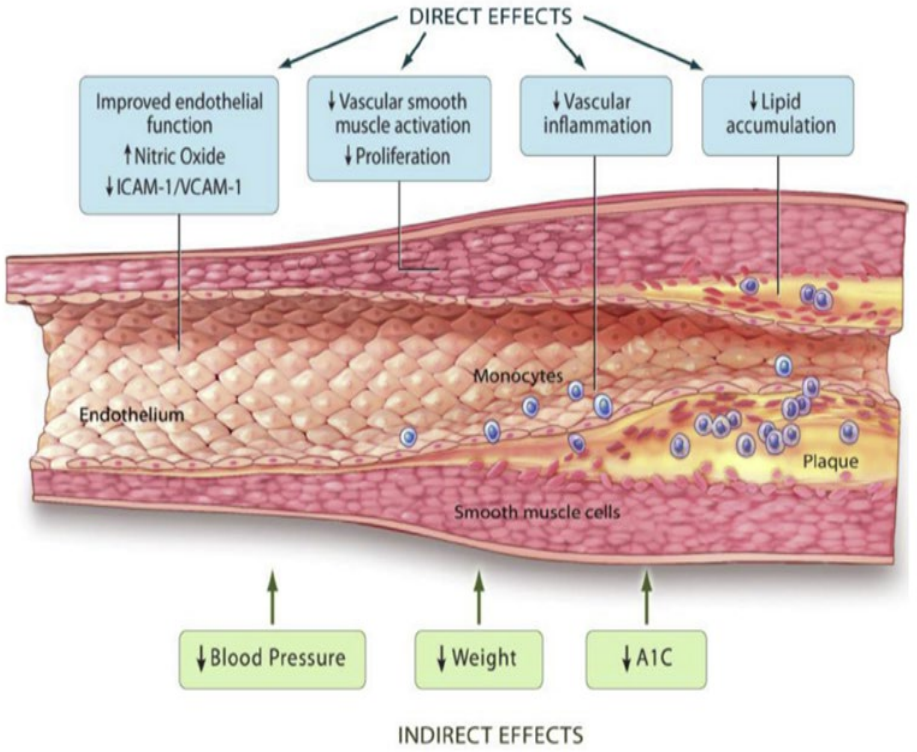
AD, airway disease; CVD, cardiovascular disease; Disability (pain & physical function); GERD, gastresophageal reflux disease; HFpEF, heart failure with preserved ejection fraction; HRQoL, health-related quality of life; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OSA, obstructive sleep apnea; OSAS, OSA syndrome; PCOS, polycystic ovary syndrome; TG, triglycerides; T2D, type 2 diabetes mellitus.

Garvey WT et al. Endocr Pract 2016;22(Suppl. 3):1–203; Look AHEAD Research Group. Lancet Diabetes Endocrinol 2016;4:913–921; Lean ME et al. Lancet 2018;391:541–551; Benraoune F and Litwin SE. Curr Opin Cardiol 2011;26:555–561; Sundström J et al. Circulation 2017;135:1577–1585; Foster et al. Arch Intern Med 2009;169:1619–26; Kuna et al. Sleep 2013;36:641–9; Warkentin et al. Obes Rev 2014;15:169–82; Wright et al. J Health Psychol 2013;18:574–86; Christensen et al. Ann Rheum Dis. 2007;66:433-9; Diabetes Prevention Program Research Group. Lancet. 2009;374:1677-86.

Li C et al. *Front Endocrinol*. 2023.

Mechanisms of action: GLP-1 RA

Extracardiac



Sharma A., Verma S. *Can J Diabetes.* 2020.

Epicardial Fat

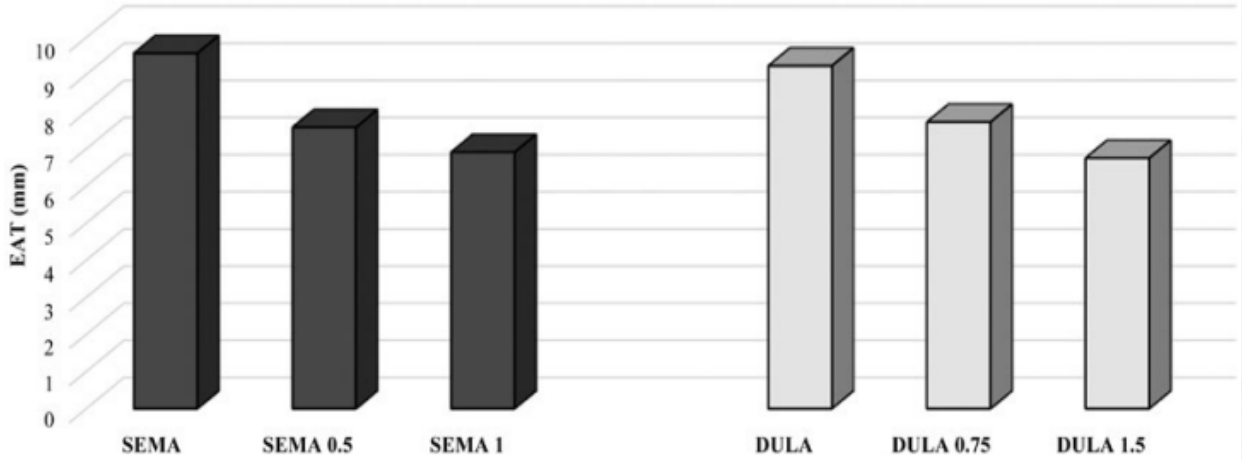
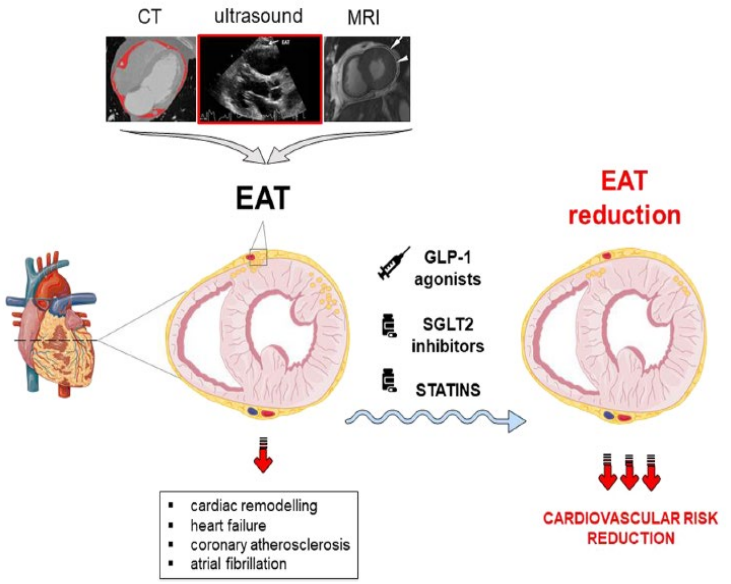


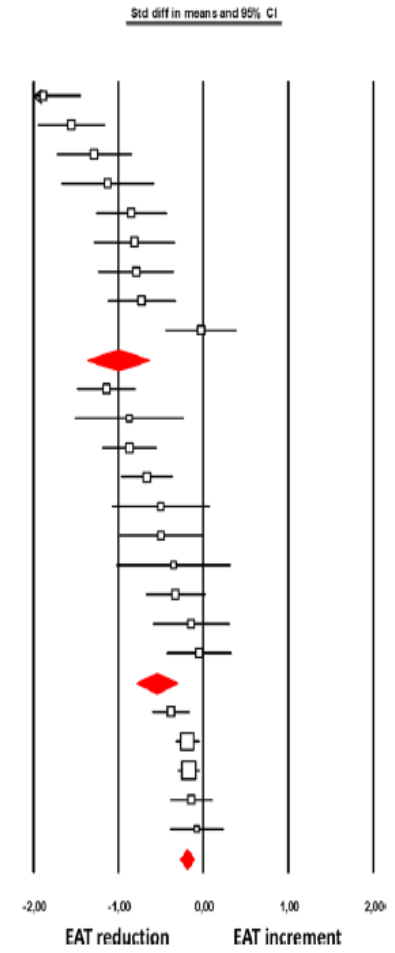
Figure 1. EAT reduction in the semaglutide and dulaglutide groups after 12 weeks, according to the medication dosage. Legend: EAT (epicardial fat thickness); SEMA (semaglutide) and DULA (dulaglutide) bars indicate baseline EAT. SEMA 0.5 and DULA 0.75 bars indicate EAT after 12-week treatment with semaglutide, 0.5 mg, and dulaglutide, 0.75 mg, once weekly, respectively. SEMA 1 and DULA 1.5 bars indicate EAT after 12-week treatment with semaglutide, 1 mg, and dulaglutide, 1.5 mg, once weekly, respectively.

Iacobellis G., Villasante Fricke, A. Journal of the Endocrine Society 2020,4(4):1-9

Treatment of epicardial adipose tissue (EAT)

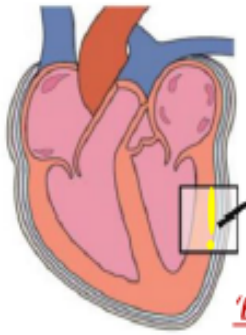


Study name	Study type	Measure unit	Drug class	Drug type	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Iaccobellis 2017_2	RCT	mm	GLP-1 RA	Liraglutide	-1,886	0,227	0,051	-2,331	-1,441	-8,314	0,000
Iaccobellis 2017_1	RCT	mm	GLP-1 RA	Liraglutide	-1,553	0,202	0,041	-1,949	-1,157	-7,684	0,000
Li 2020	SAS	mm	GLP-1 RA	Liraglutide	-1,286	0,225	0,051	-1,727	-0,844	-5,708	0,000
Zhao 2021	SAS	mm	GLP-1 RA	Liraglutide	-1,126	0,279	0,078	-1,673	-0,579	-4,036	0,000
Iaccobellis 2020_1	RCT	mm	GLP-1 RA	Semaglutide	-0,848	0,213	0,045	-1,265	-0,431	-3,984	0,000
Dutour 2016	RCT	mL	GLP-1 RA	Exenatide	-0,814	0,246	0,061	-1,296	-0,332	-3,310	0,001
Moreno 2015	SAS	mm	GLP-1 RA	Exenatide/Liraglutide	-0,791	0,229	0,053	-1,241	-0,342	-3,453	0,001
Iaccobellis 2020_2	RCT	mm	GLP-1 RA	Dulaglutide	-0,727	0,205	0,042	-1,130	-0,325	-3,542	0,000
Van Eyk 2019	RCT	cm2	GLP-1 RA	Liraglutide	-0,027	0,213	0,045	-0,445	0,391	-0,127	0,899
Overall			**GLP-1 RA**		-1,005	0,165	0,034	-1,368	-0,642	-5,421	0,000
Braha 2019	SAS	cm3	SGLT2-i	Dapagliflozin	-1,141	0,177	0,031	-1,487	-0,795	-6,466	0,000
Yagi 2017_2	SAS	mm	SGLT2-i	Canagliflozin	-0,873	0,326	0,106	-1,512	-0,234	-2,678	0,007
Iaccobellis 2020_4	RCT	mm	SGLT2-i	Dapagliflozin	-0,871	0,166	0,028	-1,196	-0,545	-5,244	0,000
Iaccobellis 2020_3	RCT	mm	SGLT2-i	Dapagliflozin	-0,664	0,155	0,024	-0,971	-0,358	-4,252	0,000
Yagi 2017_1	SAS	mm	SGLT2-i	Canagliflozin	-0,499	0,294	0,086	-1,075	0,078	-1,696	0,090
Sato 2020	SAS	cm3	SGLT2-i	Dapagliflozin	-0,497	0,250	0,062	-0,987	-0,008	-1,990	0,047
Fukuda 2017	SAS	cm3	SGLT2-i	Ipragliflozin	-0,354	0,344	0,118	-1,027	0,320	-1,029	0,303
Requena-Ibanez 2021	RCT	mL	SGLT2-i	Empagliflozin	-0,329	0,179	0,032	-0,679	0,021	-1,840	0,066
Bouchi 2017	SAS	cm3	SGLT2-i	Luseogliflozin	-0,144	0,231	0,053	-0,596	0,308	-0,624	0,533
Gaborit 2021	RCT	mL	SGLT2-i	Empagliflozin	-0,050	0,196	0,039	-0,435	0,334	-0,256	0,798
Overall			**SGLT2-i**		-0,552	0,120	0,014	-0,787	-0,316	-4,592	0,000
Park 2010_1	SAS	mm	statin	Atorvastatin	-0,381	0,114	0,013	-0,605	-0,157	-3,333	0,001
Raggi 2019_1	SAS	mL	statin	Atorvastatin	-0,187	0,072	0,005	-0,329	-0,045	-2,579	0,010
Raggi 2019_2	SAS	mL	statin	Pravastatin	-0,173	0,067	0,004	-0,304	-0,041	-2,579	0,010
Park 2010_2	SAS	mm	statin	Simvastatin	-0,143	0,127	0,016	-0,391	0,105	-1,128	0,259
Soucek 2015	RCT	cm3	statin	Atorvastatin	-0,078	0,162	0,026	-0,396	0,241	-0,478	0,632
Overall			**statin**		-0,195	0,041	0,002	-0,276	-0,114	-4,738	0,000



Mayasoedova, V et al. *Cardiovascular Diabetology*. 2023.

Epicardial fat paradox and effects of GLP-1R agonists HFpEF vs. HFrEF



'Epicardial fat paradox'

HFpEF ↑ **Epicardial fat** → ↑ CRP, Trop-T, myocardial fibrosis markers
↑ Heart failure Hospitalizations/CV deaths

Mechanism: EAT dysfunction → inflammation, myocardial fibrosis,
Excess FFA release → intramyocardial lipids, mechanical effects

HFrEF ↓ **Epicardial fat** → ↑ CRP, natriuretic peptides, Trop-T
↑ Hospitalizations for heart failure(HHF)/CV deaths

Mechanism: EAT may act as a metabolic reservoir in this setting
(substantial EAT thinning reflects cardiac cachexia in advanced HF)

GLP-1 receptor agonists

- **No HF** → May prevent new onset HF
- **Inflammatory Metabolic HFpEF** → May Prevent HHF and atrial fibrillation/flutter events via:
  - Qualitative changes (reversal of EAT dysfunction, anti-inflammatory effects, increase in FFA oxidation)
  - Quantitative changes (reduction in EAT)
- **Advanced HFrEF** → May increase HF hospitalizations/deaths
  - EAT GLP-1R modulation and further reduction may interfere with FFA release under high energy demand

Harmony Outcomes: Albiglutide

STEP-HFpEF: Semaglutide
STEP-HFpEF-DM

Improvement in HF outcomes

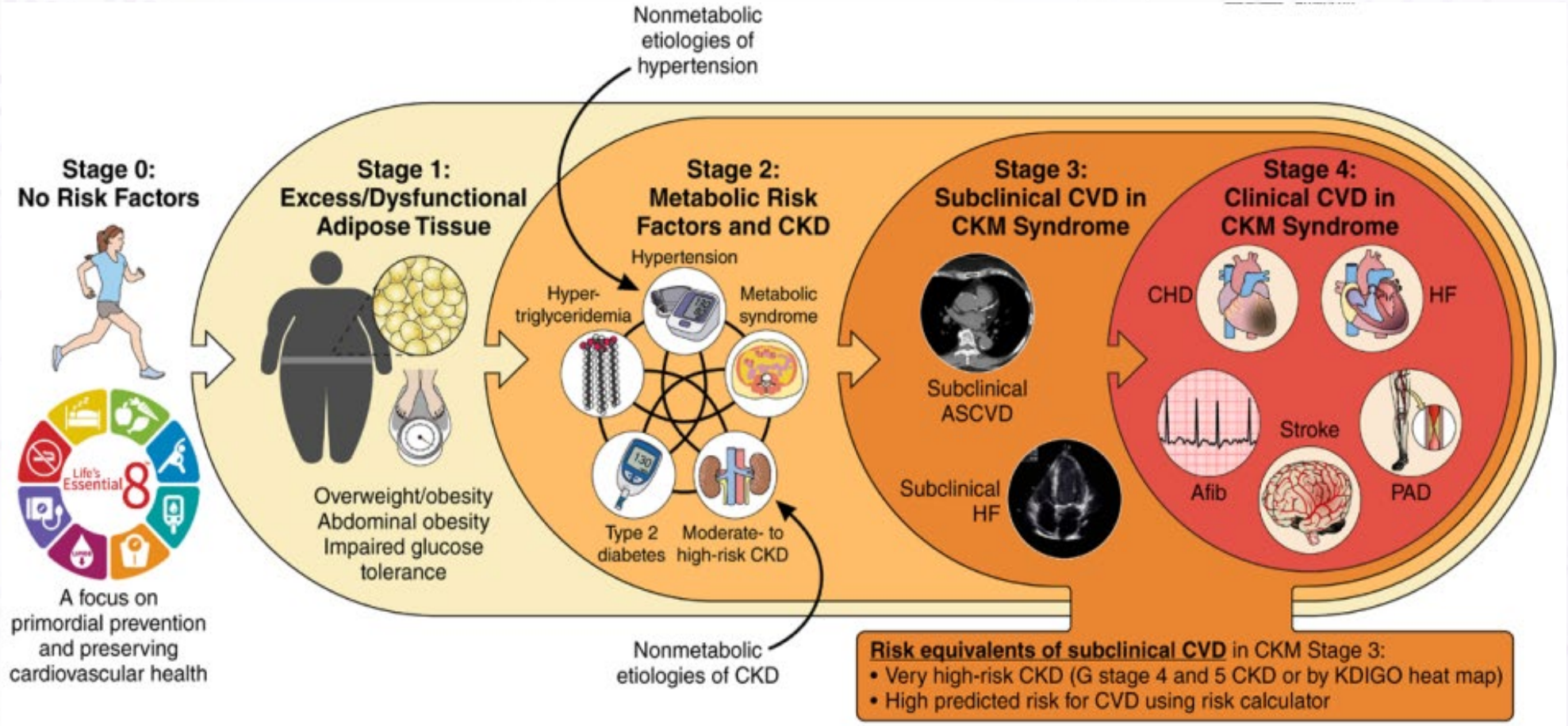
EXSCEL trial
(Exenatide Study of Cardiovascular Event Lowering)

FIGHT trial (Functional Impact of GLP-1 for Heart Failure Treatment) (Liraglutide)

Both showed an increased risk of hospitalization for HFrEF

Adapted from Banerjee M. *Circ Heart Fail*. 2023.

Stages of Cardiovascular-Kidney-Metabolic Syndrome



Ndumele et al. Circulation 2023;148

Take home messages

- Obesity rates and prevalence are rising
  - It's becoming a worldwide epidemic
- Patients with obesity are at higher risk for cardiovascular morbidity and mortality and this may be independent of BMI or other risk factors
- Visceral or more specifically Epicardial Adipose Tissue (EAT) gives stronger correlation to CV disease than BMI but is poorly measured without standardization
- EAT can explain mechanisms for atrial fibrillation, coronary artery disease and HFpEF in metabolically active patients with excess visceral fat
- Certain cardiometabolic therapies (SGLT2i and GLP1RA) offer better EAT reduction and may offer an explanation to superior reductions seen in ASCVD and HFpEF events, particularly in obese patients

WEIGHING IN ON HFpEF

A Review of the Clinical Evidence and Emerging Therapies for HFpEF

Tipping the Balance: A review of obesity management strategies in patients with HFpEF

Justin Ezekowitz MB, BCH, MSc, FRCPC, FACC, FAHA, FESC
Professor of Medicine, University of Alberta
Cardiologist, Mazankowski Alberta Heart Institute

Disclosures

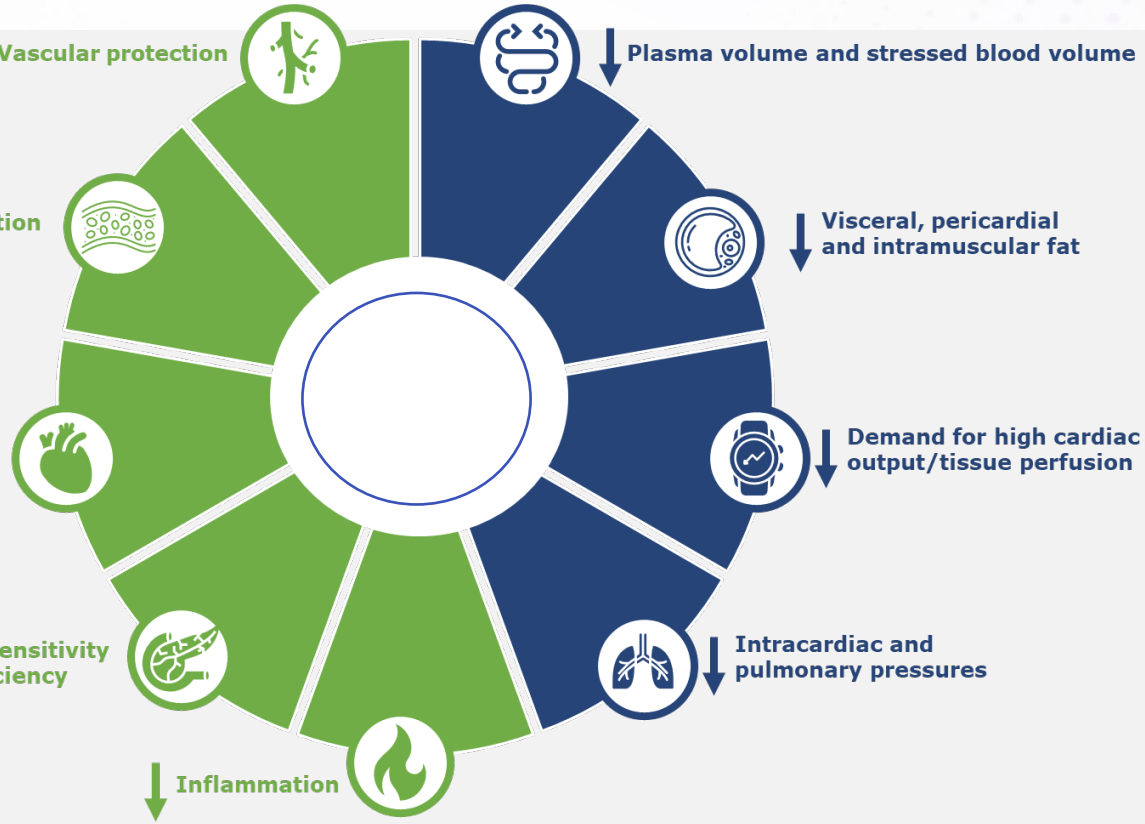
	Dr. Justin Ezekowitz
Any direct financial payments including receipt of honoraria	AstraZeneca, Bayer, Boehringer Ingelheim, Novartis, Novo Nordisk, Otsuka; serves as an advisor to US2.ai.
Membership on advisory boards or speakers' bureaus	No disclosures
Funded grants or clinical trials	American Regent, Applied Therapeutics, AstraZeneca, Bayer, Cytokinetics, Merck & Co, Novo Nordisk, Otsuka; CIHR, Heart and Stroke Foundation, NIH, PCORI
All other investments or relationships that could be seen by a reasonable, well-informed participant as having the potential to influence the content of the educational activity	CCS, CHFS, AHA, ESC, ACC, HFSA, AHS, UofA, CVC

A REVIEW OF OBESITY MANAGEMENT STRATEGIES IN PATIENTS WITH HFpEF

- Some slides courtesy of Drs. Haykowsky, Lee and others

THE OBESITY PHENOTYPE OF HFpEF

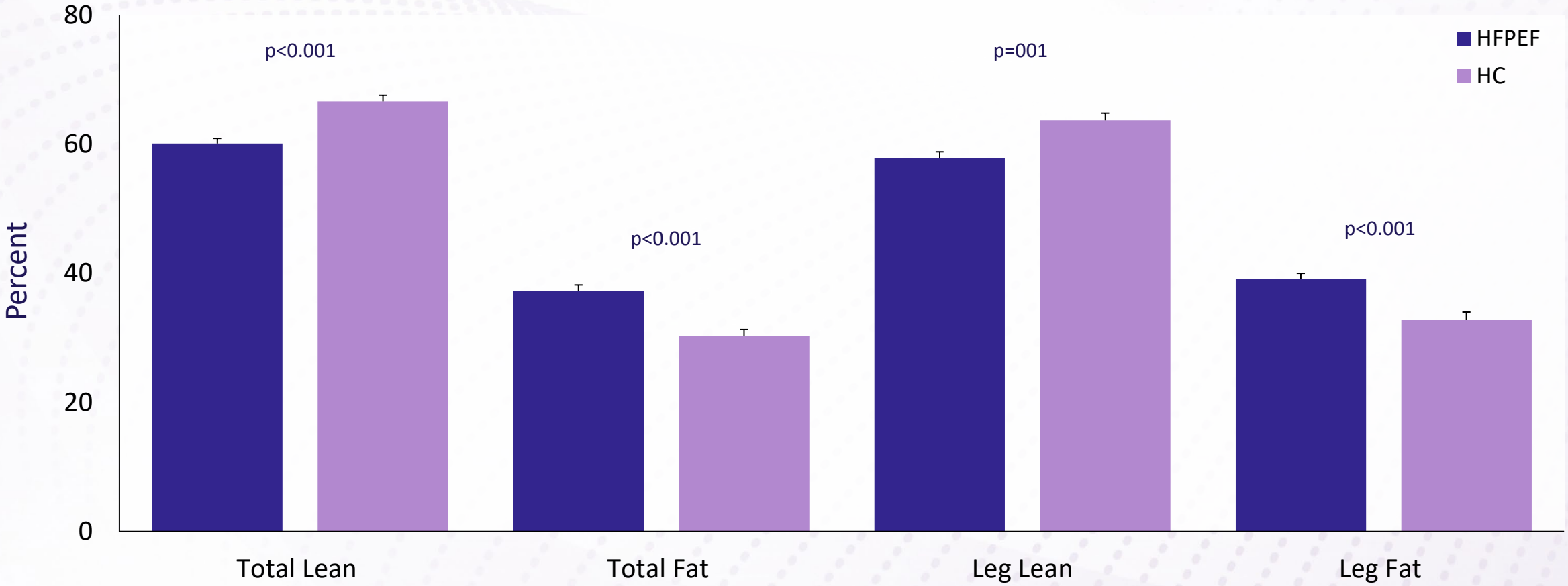
Mechanisms of action



Patient impact

- Weight loss
- Improved symptoms
- Reduced physical limitations
- Increased exercise capacity

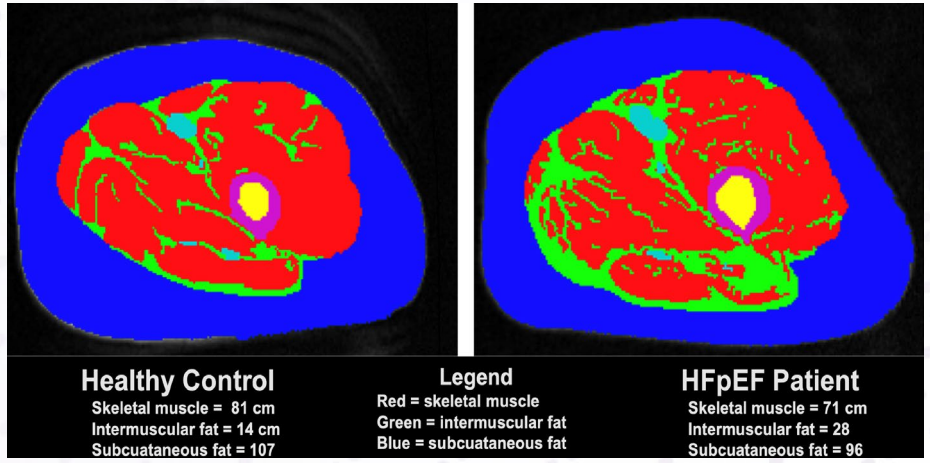
LEAN AND FAT MASS IN HFpEF AND AGE-MATCHED HEALTHY CONTROLS



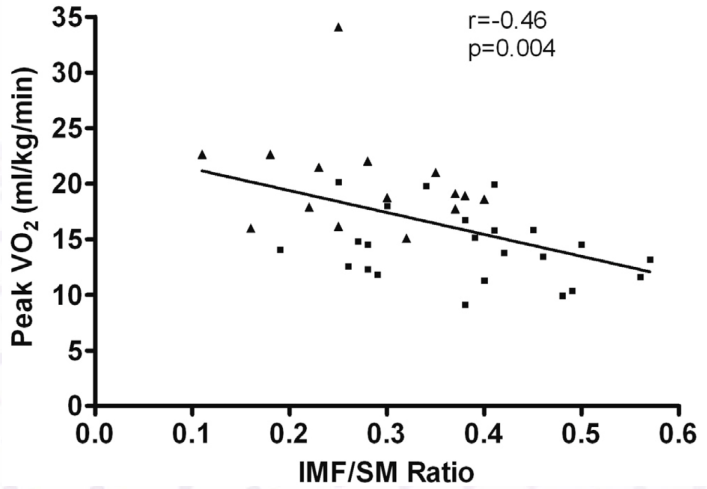
HFpEF, n=60, mean age: 70 yr; HC, healthy control, n=40, mean age: 69 yr; data adjusted for age and gender, mean ± SE.

Haykowsky, Kitzman. *J Gerontol A Biol Sci Med Sci*. 2013

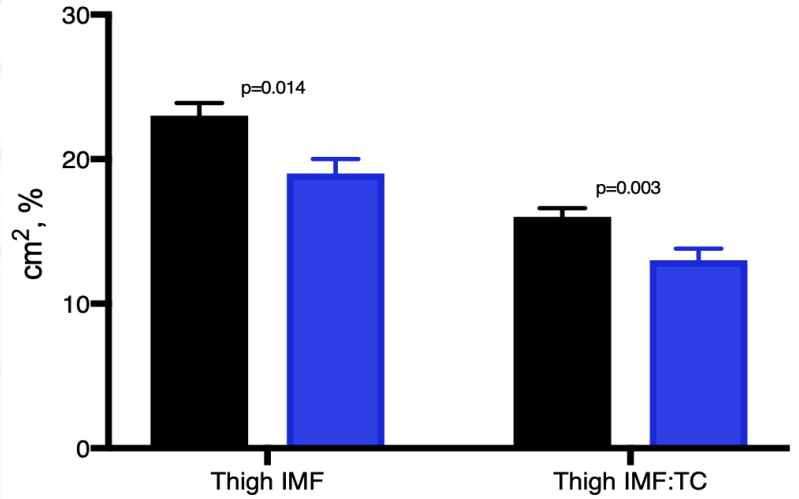
THIGH MUSCLE COMPOSITION: REDUCED VO_{2peak} IN HFpEF

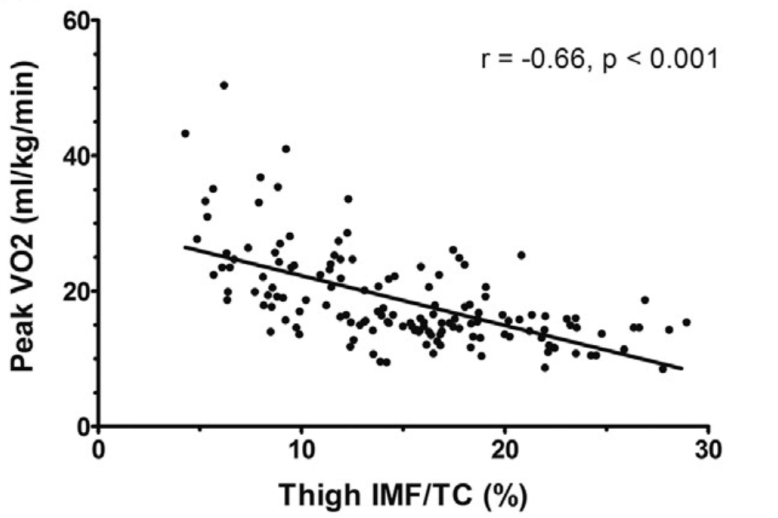


HFpEF, n=23, mean age: 69 yr HC, n=15, mean age: 70 yr



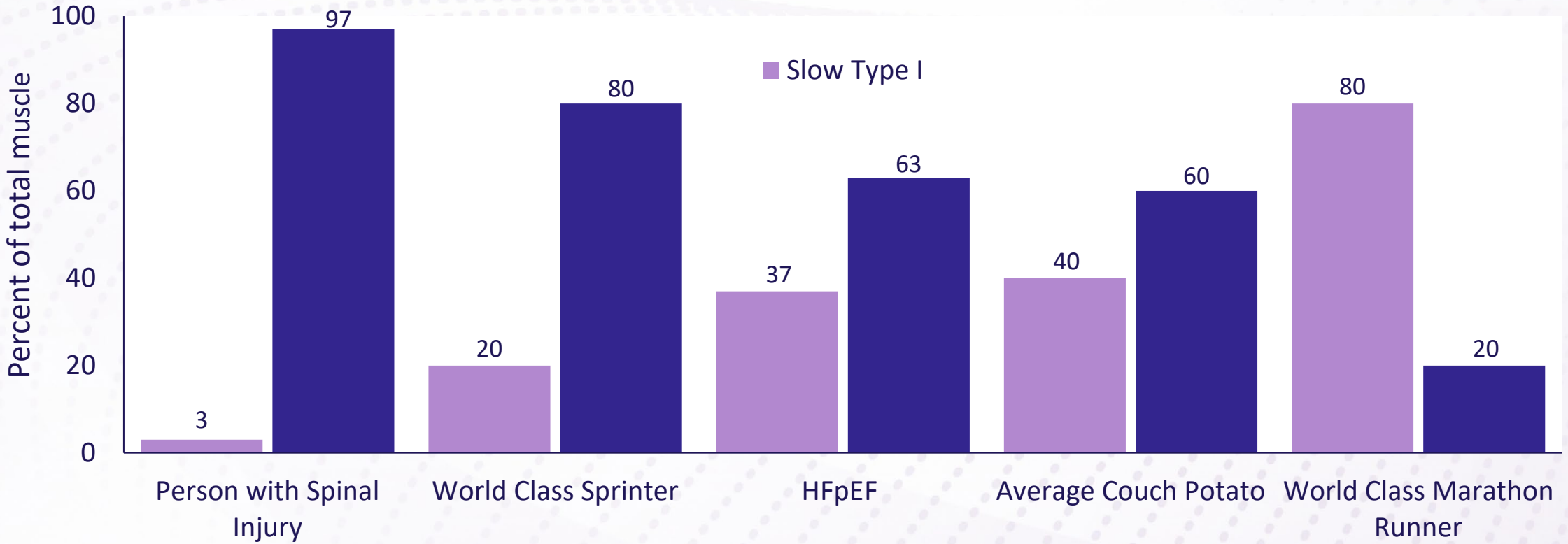
Haykowsky, Kitzman. *Am J Cardiol*. 2014





Haykowsky et al. *J Am Coll Cardiol HF*. 2018

MUSCLE FIBER TYPE DISTRIBUTION



HFpEF data from Kitzman et al. *Am J Physiol Heart Circ Physiol*. 2014; All other data adapted from Andersen et al. *Scientific American*. 2000

DO WEIGHT MANAGEMENT STRATEGIES CHANGE OUTCOMES FOR PATIENTS WITH HFpEF?

maybe

SUMMARY OF NON-DRUG TRIALS IN HFpEF FOR WEIGHT LOSS

- 4 RCTs (only 1 trial in HFpEF)
  - 2 diet and exercise, 1 diet alone, 1 orlistat
  - 3 reported significant weight loss
  - 2 reported improvement in exe capacity & QoL
  - 1 reported improvement in NYHA in HFpEF

McDowell K, et al. Obes Rev 2018;19:1189-1204

DOES DIET WORK WEIGHT LOSS?

- Exercise / pills / injections / surgery may be inappropriate / unacceptable / unavailable
- ~10 kg weight loss possible in 12 weeks (DiRECT)
- Flexible / tailored
- Empowers patients / behavioral change
- Mechanistic data on weight loss (not drug-related)

Lean MEJ, et al. DiRECT trial. Lancet 2017;391:541-551
Haag L, et al. ReDIRECT trial. NIHR Open Res 2023;2:57

WHAT WORKS FOR WEIGHT LOSS?

- Caloric restriction e.g., portion control, balanced low-energy diets
  - very low-calorie diets (VLCD) <800 kcal/day
  - low-calorie diets (LCD) 800-1200 kcal/day
- Restrict energy intake for specified time periods
  - intermittent fasting, time-restricted eating
- Specific e.g., plant-based, hypocaloric Mediterranean
  - modified to local food availability/preferences
- Modified macronutrients
  - very low/low/mod carb, low-fat
- High-protein
  - to preserve lean muscle mass and enhance satiety
- Focus on specific food groups
  - e.g., ↑ fruit/veg, avoid refined sugars

Visseren FLJ, Mach, F, et al. EHJ 2021;42:3227-3337

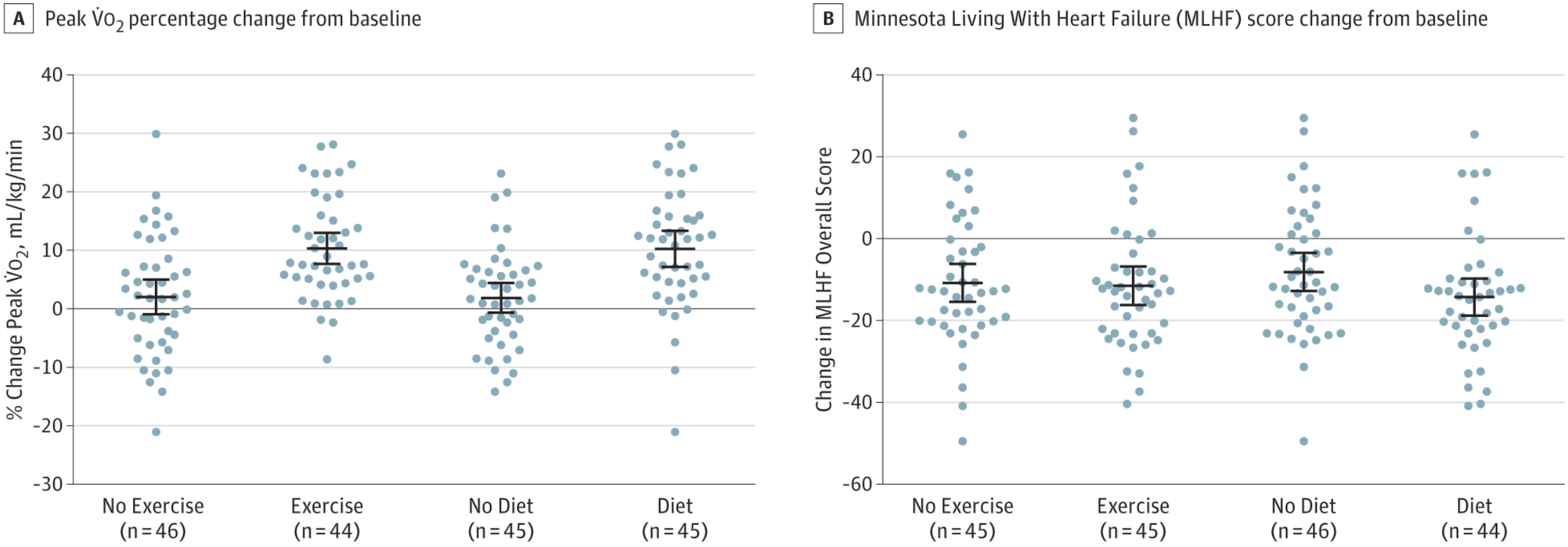
CALORIC RESTRICTION + EXERCISE IN HFpEF

Effect of Caloric Restriction or Aerobic Exercise Training on Peak Oxygen Consumption and Quality of Life in Obese Older Patients With Heart Failure With Preserved Ejection Fraction: A Randomized Clinical Trial

- 20 weeks of diet, exercise, or both; attention control consisted of telephone calls every 2 weeks.
- Prescribed calorie intake deficits were ~ 400 kcal/d
- but not less than 1000 kcal/d.
- Body weight decreased by:
  - 7% (7 kg [SD, 1]) in the diet group,
  - 3% (4 kg [SD, 1]) in the exercise group,
  - 10% (11 kg [SD, 1] in the exercise + diet group
  - 1% (1 kg [SD, 1]) in the control group

JAMA. 2016;315(1):36-46. doi:10.1001/jama.2015.17346

Effect of Caloric Restriction or Aerobic Exercise Training on Peak Oxygen Consumption and Quality of Life in Obese Older Patients With Heart Failure With Preserved Ejection Fraction: A Randomized Clinical Trial

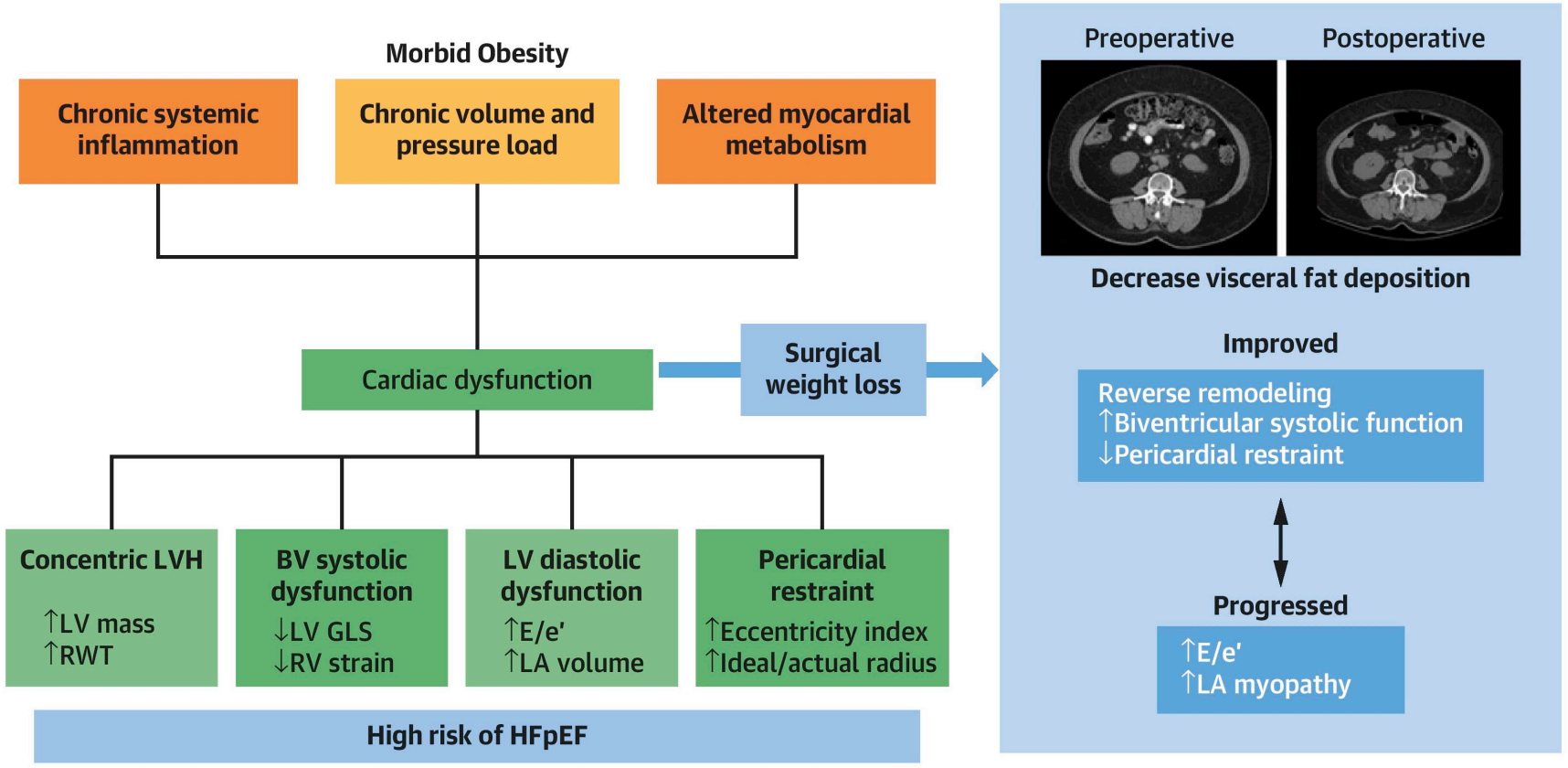


Adjusted Individual Changes of Primary Study Outcomes From Baseline to 20-Week Follow-up by Factorial GroupMLHF score has a range from 0 to 105; a higher score indicates worse heart failure–related quality of life. The P values represent comparison of least squares means of the outcome measure following adjustment for baseline values, sex, and β-blocker use. The P values in panel A were <.001 for each group (exercise vs no exercise; diet vs no diet); in panel B, .70 for the exercise group vs no exercise group and .08 for the diet group vs no diet group. By factorial group, peak $\dot{V}o_2$ data are missing in 4 cases: 2 in the exercise group (due to gas leak and injury), 1 in the diet group (due to injury), and 1 in the no diet group (due to gas leak). By factorial group, MLHF data are missing in 4 cases: 2 in the diet group, 1 in the exercise group, and 1 in the no exercise group (all due to patient errors). Error bars indicate 95% CI and the horizontal bar indicates the mean.

JAMA. 2016;315(1):36-46. doi:10.1001/jama.2015.17346

BARIATRIC SURGERY

CENTRAL ILLUSTRATION: Cardiac Dysfunction in Obesity and Effect of Surgical Weight Loss

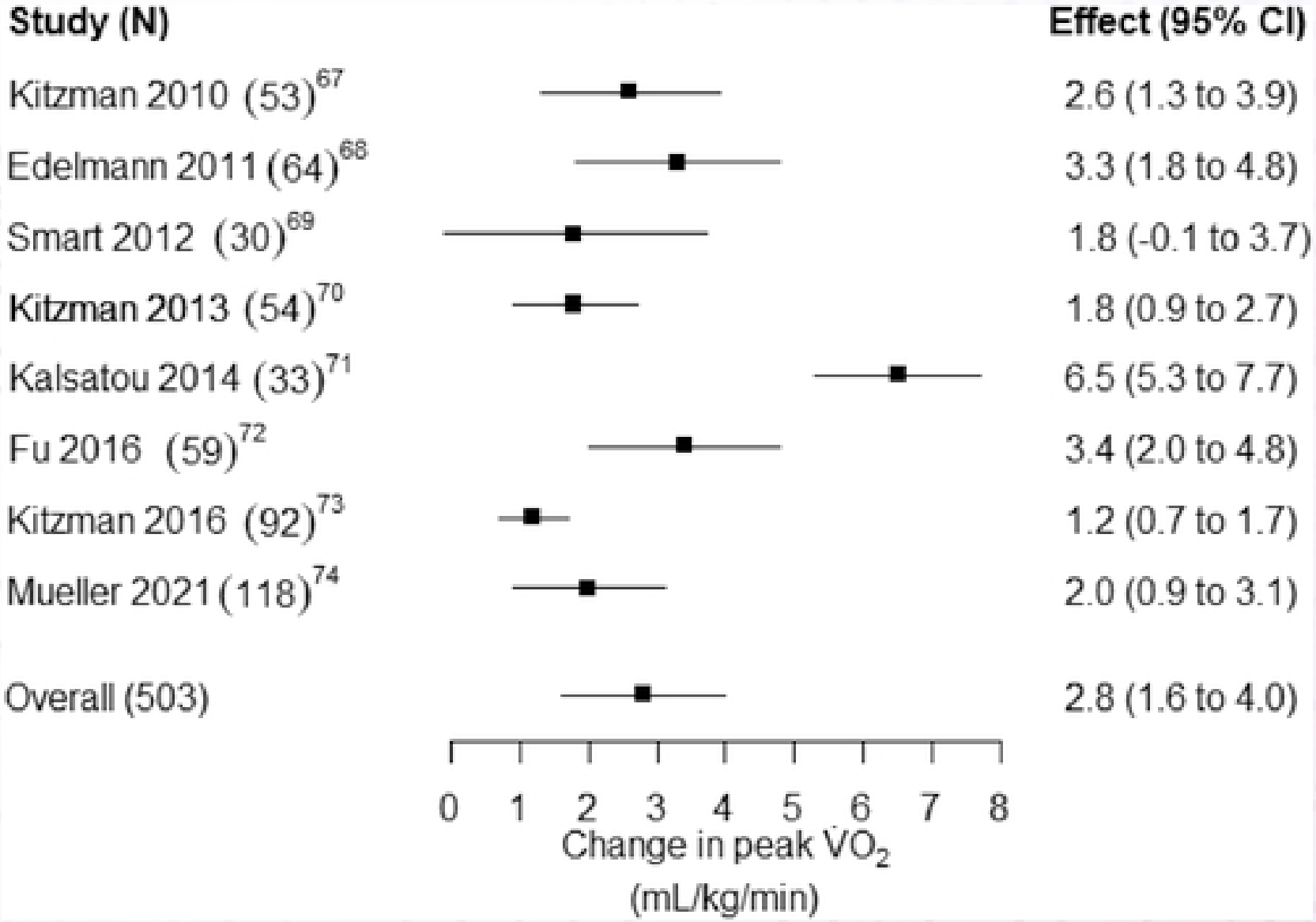


Sorimachi H, et al. J Am Coll Cardiol. 2022;80(16):1501-1512.

EVIDENCE BASE FOR BARIATRIC SURGERY IN HFpEF

EXERCISE

Forest Plot of Peak VO2 Increase in Randomized Exercise Training trials in Chronic HFpEF



Sachdev et al. *J Am Coll Cardiol* 2023; 81:1524-1542.

Trial, country, estimated completion	N	Population	Intervention	Duration	Primary outcome	Other outcomes
REHAB-HFpEF US ~2028 (NCT05525663)	880	Acute HFpEF, age ≥60y	Tailored, progressive, multi-domain physical rehab	6mo	All-cause Rehospitalization and death	Prevalence of major mobility disability (6MWT <160m), All-cause rehosp, All-cause death, CV rehosp & death, SPPB, 6MWT, KCCQ
REACH-HFpEF UK ~2024 (NIHR130487)	520	HFpEF patients & caregivers	Tailored programmes of exercise-based cardiac rehab	52wks	Change in KCCQ-CSS, body weight (%)	6MWD, time to all-cause death, no. of HF events, time to first HF event, KCCQ-CSS, CRP, ≥10/15/20% weight loss, SBP, WC
AMEND Preserved UK ~2024/5? (IRAS ID 317281)	102	HFpEF Multi-ethnic	12-week diet vs health advice	12wks		Heart function, symptoms, ability to exercise, participants' views on changing diet and how impacted symptoms

CONCLUSIONS

- An approach to weight loss focused on non-pharmacologic methods has limited evidence base that it alters clinical outcomes
  - Diet = modest effect on weight loss and possible surrogate outcomes
    - Caloric restriction = ~7% BW (short term)
  - Bariatric Surgery = zero evidence of benefit, potential risks
  - Exercise = modest effect on weight loss and possible surrogate outcomes
    - Exercise = ~3% BW (short term)

WEIGHING IN ON HFpEF

A Review of the Clinical Evidence and Emerging Therapies for HFpEF

Heartwise: An appraisal of the emerging therapies in managing HFpEF and metabolic syndrome

Anique Ducharme MD, MSc, FRCPC, FCCS, FHFSA(h)
Canadian Heart Failure Society – Immediate Past President
Director, Heart Failure Clinic, Montreal Heart Institute,
Professor of Medicine, University of Montreal
Chairholder, University of Montreal, Fondation Marcelle et Jean Coutu, Cal et Janine Moisan for Better Practices in Advanced Heart Failure

DISCLOSURES – ANIQUE DUCHARME

- Speaker Bureau/Advisory Board
  - Abbott, Astra-Zeneca, Bayer (past), Boehringer-Ingelheim, Novartis, NovoNordisk.
- Research Support/Grants:
  - Abbott, Astra-Zeneca, Bayer, BioBridge, Merck, Novartis, NovoNordisk.
  - Steering comittee: GUIDE-HF (Abbott), HERMES (NovoNordisk), SYMPHONY (AstraZeneca)
  - National Lead: Merck (VICTOR)

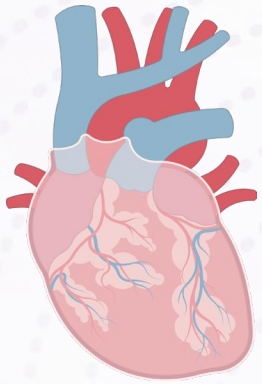
*NT-proBNP ≥1000 pg/mL or BNP ≥250 pg/mL for patients without AF; elevated NT-proBNP ≥2000 pg/mL or BNP ≥500 pg/mL for patients with AF AF, atrial fibrillation; BNP, B-type natriuretic peptide; CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide Colorado Prevention Center. NCT06008197. Available at: https://clinicaltrials.gov/study/NCT06008197 (accessed April 2024)

LEARNING OBJECTIVE

- **Review the emerging therapies in managing HFpEF and metabolic syndrome**

*NT-proBNP ≥1000 pg/mL or BNP ≥250 pg/mL for patients without AF; elevated NT-proBNP ≥2000 pg/mL or BNP ≥500 pg/mL for patients with AF AF, atrial fibrillation; BNP, B-type natriuretic peptide; CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide Colorado Prevention Center. NCT06008197. Available at: https://clinicaltrials.gov/study/NCT06008197 (accessed April 2024)

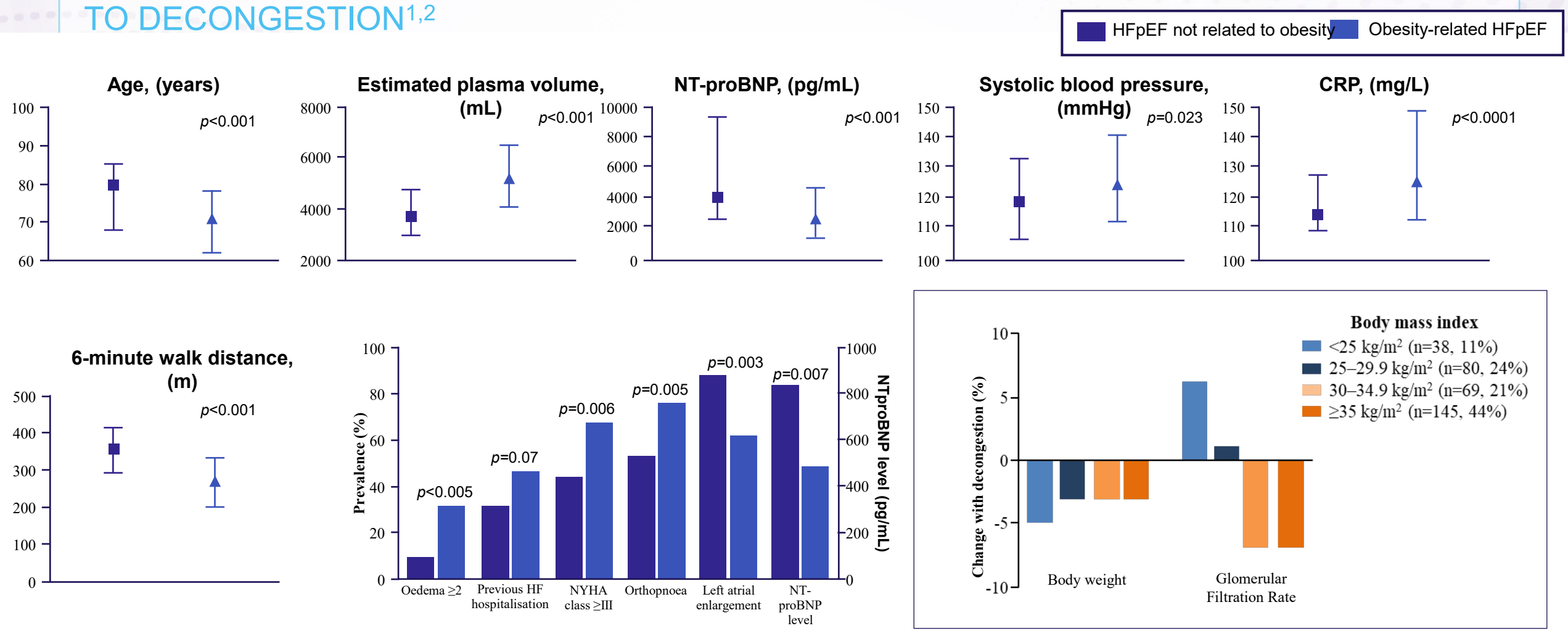
NUMEROUS PHENOTYPES ARE FREQUENTLY ENCOUNTERED IN HFpEF



HFpEF with pulmonary hypertension	HFpEF is a common cause of pulmonary hypertension, occurring in 31–88% of HFpEF patients[1–5]
Ageing-related HFpEF	HFpEF is the most common form of HF in elderly populations.[6] Among elderly women, HFpEF comprises almost 90% of incident HF cases[7]
CAD-related HFpEF	The prevalence of CAD-related HFpEF ranges from 35–53%, with patients experiencing a poorer prognosis than those with CAD-unrelated HFpEF[1]
Obesity phenotype of HFpEF	**Approximately 80% of the total HFpEF population are living with overweight or obesity[8]**
Pro-inflammatory phenotype of HFpEF	**A new understanding of the phenotypic heterogeneity of HFpEF includes the proposal of a proinflammatory phenotype driven by comorbidities such as obesity and T2D[9,10]**

*NT-proBNP ≥1000 pg/mL or BNP ≥250 pg/mL for patients without AF; elevated NT-proBNP ≥2000 pg/mL or BNP ≥500 pg/mL for patients with AF AF, atrial fibrillation; BNP, B-type natriuretic peptide; CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide Colorado Prevention Center. NCT06008197. Available at: https://clinicaltrials.gov/study/NCT06008197 (accessed April 2024)

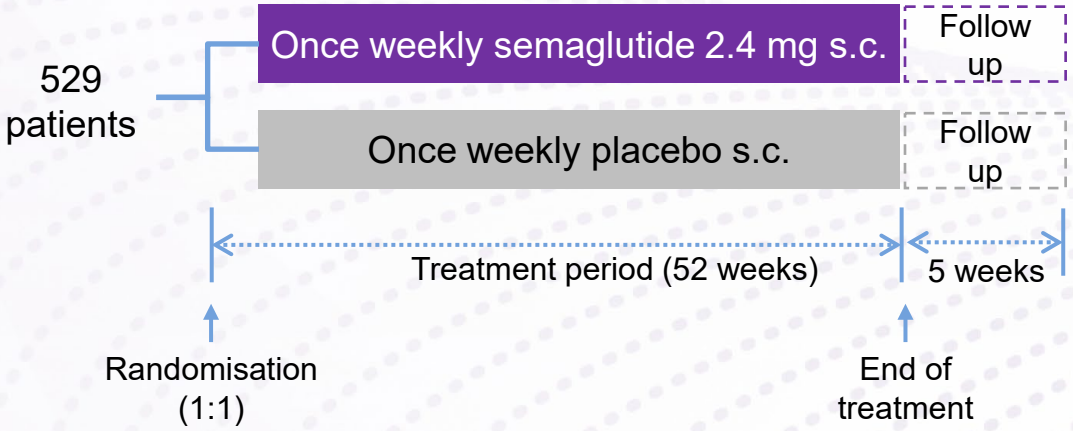
OBESITY-RELATED HFpEF: YOUNGER, EXPANDED VOLUME, LOWER NT-proBNP, MORE INFLAMMATION, WORSE SYMPTOMS AND FUNCTION, IMPAIRED RESPONSE TO DECONGESTION[1,2]



*NT-proBNP ≥1000 pg/mL or BNP ≥250 pg/mL for patients without AF; elevated NT-proBNP ≥2000 pg/mL or BNP ≥500 pg/mL for patients with AF AF, atrial fibrillation; BNP, B-type natriuretic peptide; CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide
Colorado Prevention Center. NCT06008197. Available at: https://clinicaltrials.gov/study/NCT06008197 (accessed April 2024)

COMPLETED TRIALS

STEP-HFpEF[1]



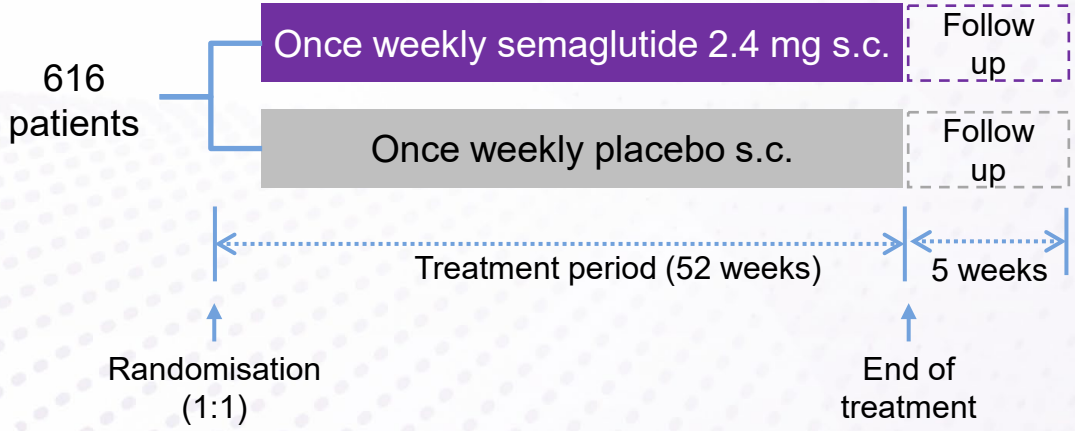
Primary objective:

- To investigate the effects of semaglutide 2.4 mg s.c. once weekly on physical function, symptoms and body weight compared with placebo, both added to SoC, in people with the obesity phenotype of HFpEF and no T2D

Dual primary endpoint:

- Change from baseline to Week 52 in KCCQ-CSS and body weight

STEP-HFpEF-DM[2]



Primary objective:

- To investigate the effects of semaglutide 2.4 mg s.c. once weekly on physical function, symptoms and body weight compared with placebo, both added to SoC, in people with the obesity phenotype of HFpEF and T2D

Dual primary endpoint:

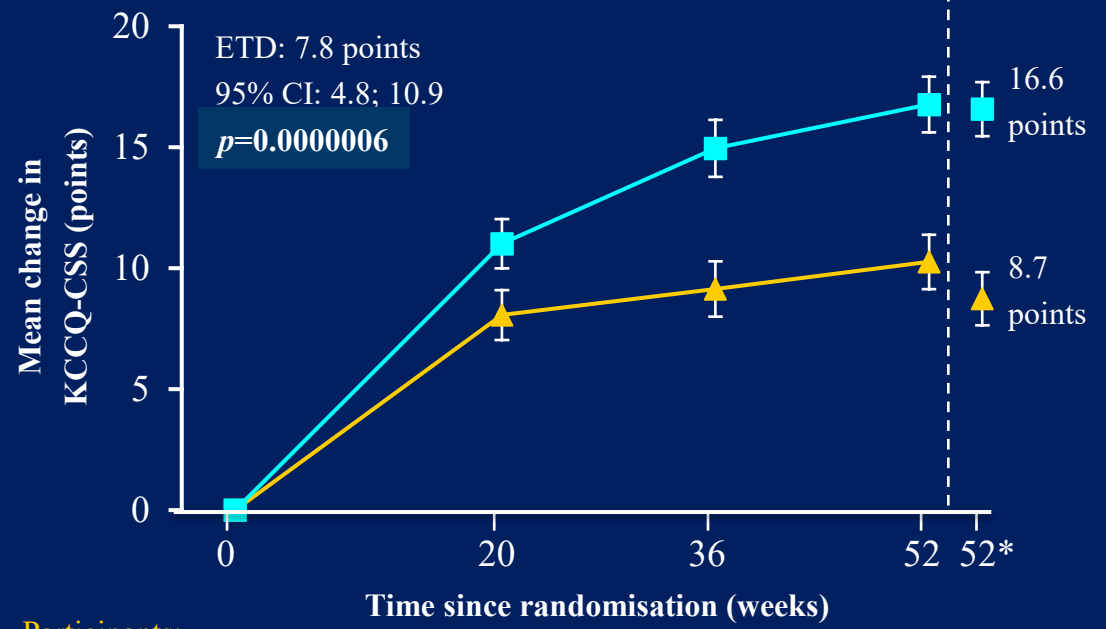
- Change from baseline to Week 52 in KCCQ-CSS and body weight

*NT-proBNP ≥1000 pg/mL or BNP ≥250 pg/mL for patients without AF; elevated NT-proBNP ≥2000 pg/mL or BNP ≥500 pg/mL for patients with AF AF, atrial fibrillation; BNP, B-type natriuretic peptide; CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide Colorado Prevention Center. NCT06008197. Available at: https://clinicaltrials.gov/study/NCT06008197 (accessed April 2024)

CHANGE FROM BASELINE TO WEEK 52 IN KCCQ-CSS

DUAL PRIMARY ENDPOINTS

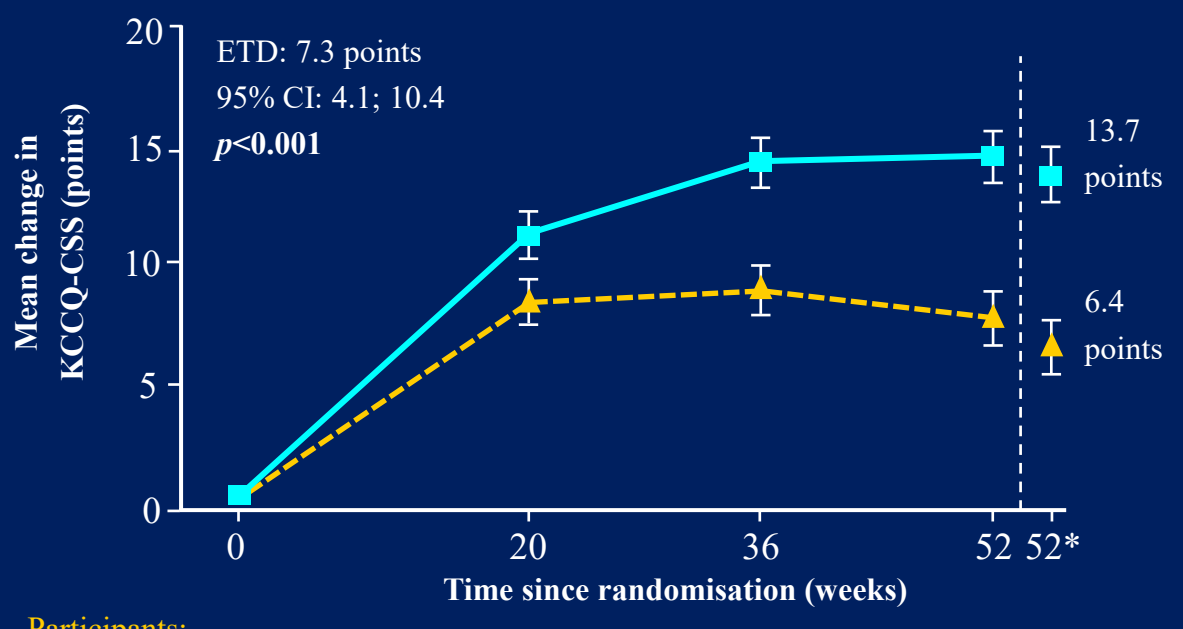
STEP-HFpEF[1]



Participants:					
Sema 2.4 mg	263	249	225	243	263
Placebo	266	242	217	237	266

Overall mean baseline KCCQ-CSS (points) 56.7

STEP-HFpEF-DM[2]



Participants:					
Sema 2.4 mg	310	289	274	281	310
Placebo	306	284	270	272	306

Overall median baseline KCCQ-CSS (points) 59.4

Semaglutide 2.4 mg
Placebo

*NT-proBNP ≥1000 pg/mL or BNP ≥250 pg/mL for patients without AF; elevated NT-proBNP ≥2000 pg/mL or BNP ≥500 pg/mL for patients with AF AF, atrial fibrillation; BNP, B-type natriuretic peptide; CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide Colorado Prevention Center. NCT06008197. Available at: https://clinicaltrials.gov/study/NCT06008197 (accessed April 2024)

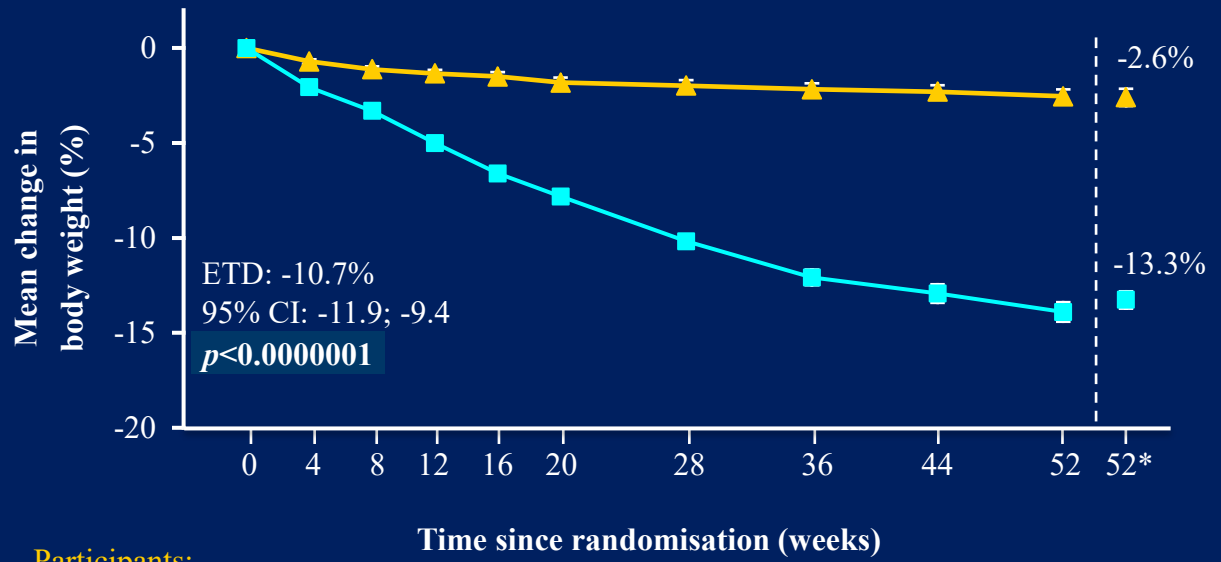
Data are for the treatment policy estimand; *Data are estimated mean changes from baseline to Week 52 for the treatment policy estimand using ANCOVA and an imputation approach for missing data
ANCOVA, analysis of covariance; CI, confidence interval; DM, diabetes mellitus; ETD, estimated treatment difference; HFpEF, heart failure with preserved ejection fraction; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score; sema, semaglutide

1. Kosiborod MN et al. *N Engl J Med* 2023;389:1069–1084; 2. Kosiborod MN et al. *N Engl J Med* 2024 (Epub ahead of print)

CHANGE FROM BASELINE TO WEEK 52 IN BODY WEIGHT

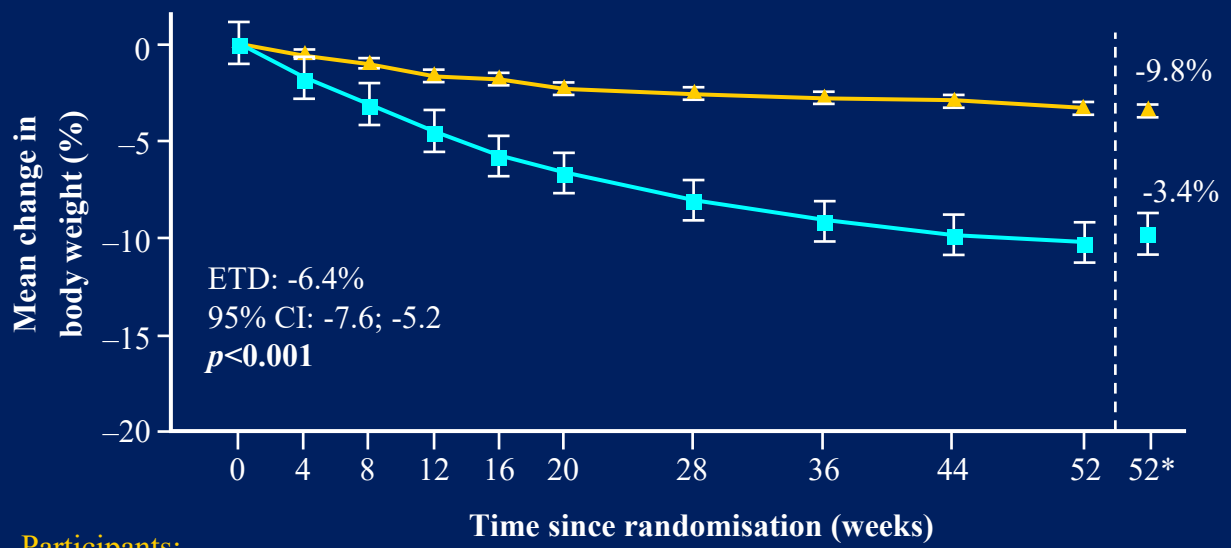
DUAL PRIMARY ENDPOINTS

STEP-HFpEF[1]



Participants:											
Sema 2.4 mg	263	255	254	250	246	252	239	243	240	246	263
Placebo	266	259	249	250	243	246	243	239	233	242	266

STEP-HFpEF-DM[2]



Participants:											
Sema 2.4 mg	310	307	297	299	290	292	283	286	282	286	310
Placebo	306	300	298	287	292	289	282	278	273	278	306

Semaglutide 2.4 mg

Placebo

Overall mean baseline body weight (kg) 108.4

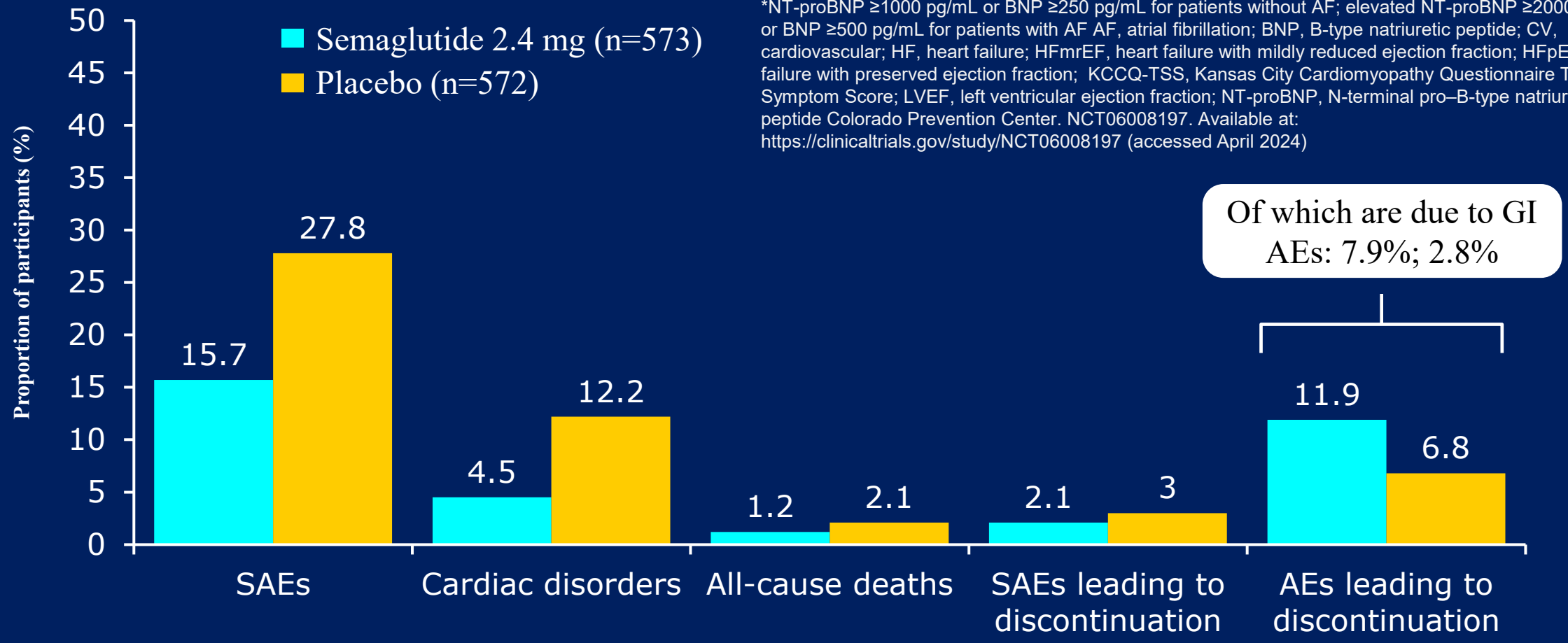
Overall median baseline body weight (kg) 102.7

*NT-proBNP ≥1000 pg/mL or BNP ≥250 pg/mL for patients without AF; elevated NT-proBNP ≥2000 pg/mL or BNP ≥500 pg/mL for patients with AF AF, atrial fibrillation; BNP, B-type natriuretic peptide; CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide Colorado Prevention Center. NCT06008197. Available at: https://clinicaltrials.gov/study/NCT06008197 (accessed April 2024)

Data are for the treatment policy estimand. *Data are estimated mean changes from baseline to Week 52 for the treatment policy estimand using ANCOVA and an imputation approach for missing data
ANCOVA, analysis of covariance; CI, confidence interval; DM, diabetes mellitus; ETD, estimated treatment difference; HFpEF, heart failure with preserved ejection fraction; sema, semaglutide
1. Kosiborod MN et al. *N Engl J Med* 2023;389:1069–1084; 2. Kosiborod MN et al. *N Engl J Med* 2024 (Epub ahead of print)

SAFETY OVERVIEW: POOLED ANALYSIS

ON-TREATMENT PERIOD



*NT-proBNP ≥1000 pg/mL or BNP ≥250 pg/mL for patients without AF; elevated NT-proBNP ≥2000 pg/mL or BNP ≥500 pg/mL for patients with AF AF, atrial fibrillation; BNP, B-type natriuretic peptide; CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide Colorado Prevention Center. NCT06008197. Available at: https://clinicaltrials.gov/study/NCT06008197 (accessed April 2024)

The overall comparison of SAEs, as well as the most frequently reported SAEs between the two treatment groups was performed post-hoc using Fisher's exact test and reported using unadjusted two-sided *p*-values (*p*-values are only shown for SAE groups with a frequency above 5% in either treatment group). AE, adverse event; GI, gastrointestinal; SAE, serious adverse event

Kosiborod MN et al. *N Engl J Med* 2023;389:1069–1084

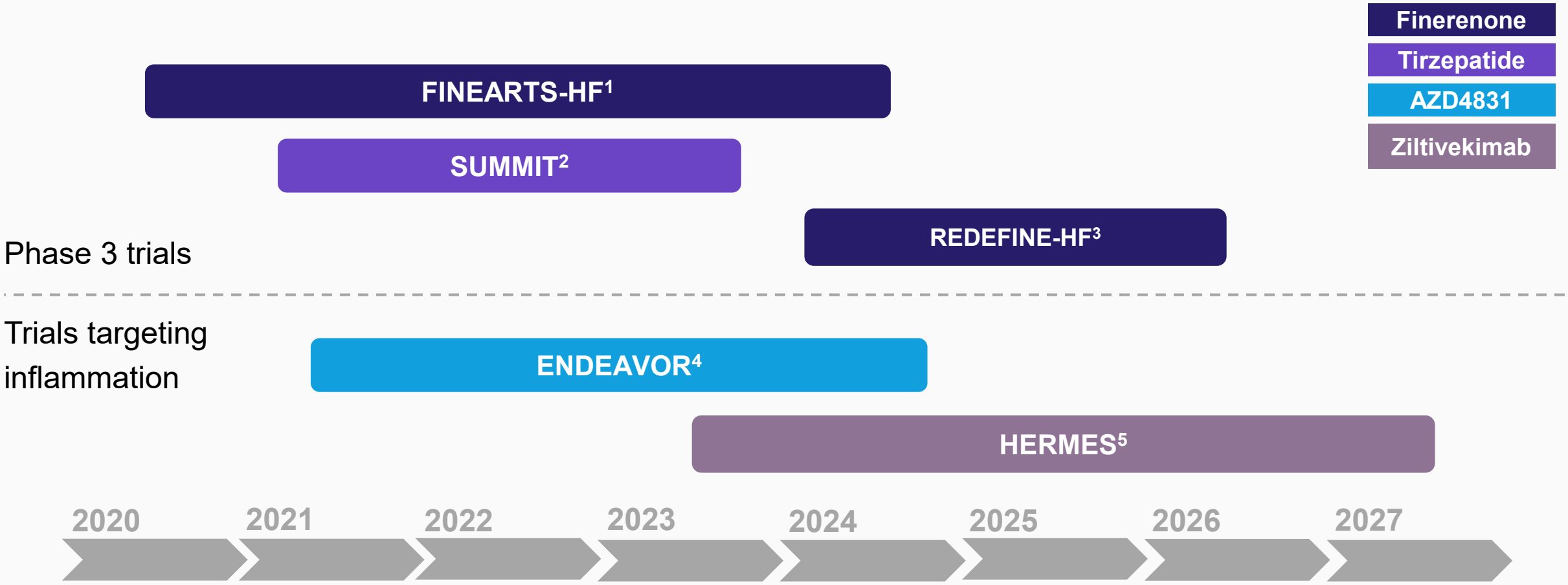
WEIGHING IN ON HFpEF

A Review of the Clinical Evidence and Emerging Therapies for HFpEF

What's next in HFpEF?

ONGOING HFpEF TRIALS

AZD4831 is an investigational agent not approved for HFpEF
Ziltivekimab is an investigational agent not approved for HFpEF



*NT-proBNP ≥1000 pg/mL or BNP ≥250 pg/mL for patients without AF; elevated NT-proBNP ≥2000 pg/mL or BNP ≥500 pg/mL for patients with AF AF, atrial fibrillation; BNP, B-type natriuretic peptide; CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide Colorado Prevention Center. NCT06008197. Available at: https://clinicaltrials.gov/study/NCT06008197 (accessed April 2024)

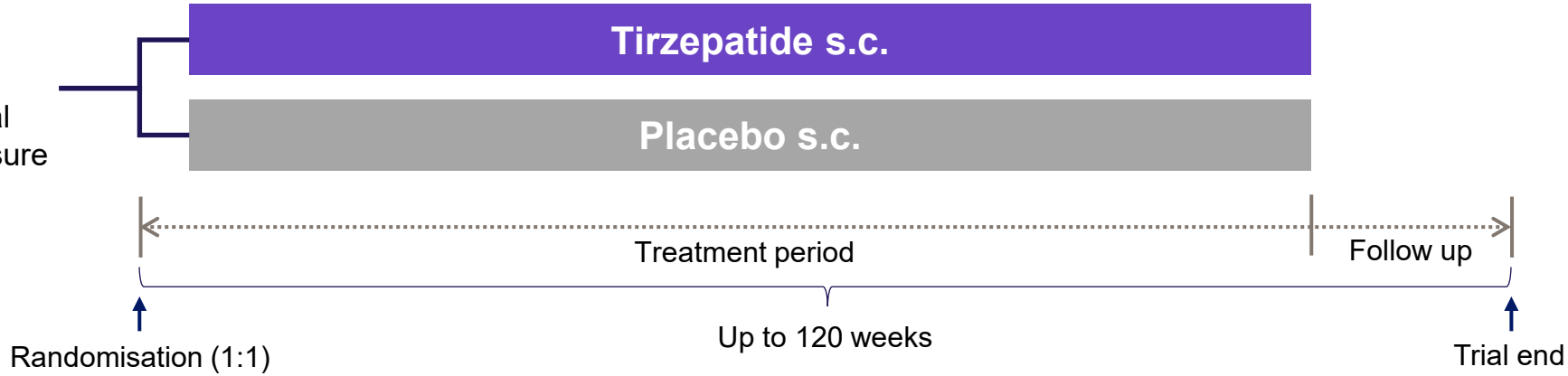
SUMMIT

A Phase 3, randomised, double-blind trial to evaluate tirzepatide in patients with obesity-related HFpEF

Estimated completion date: July 2024

700 patients

- NYHA class II–IV
- LVEF ≥50%
- Elevated NT-proBNP levels, structural heart disease or elevated filling pressure
- BMI ≥30 kg/m^2
- eGFR <70 mL/min/1.73 m^2 or HF decompensation within 12 months of screening



Primary endpoint:

- Hierarchical composite of all-cause mortality, HF events, 6MWD or KCCQ-CSS
- Change from baseline to week 52 in 6MWD

Confirmatory secondary endpoints:

From baseline to week 52:

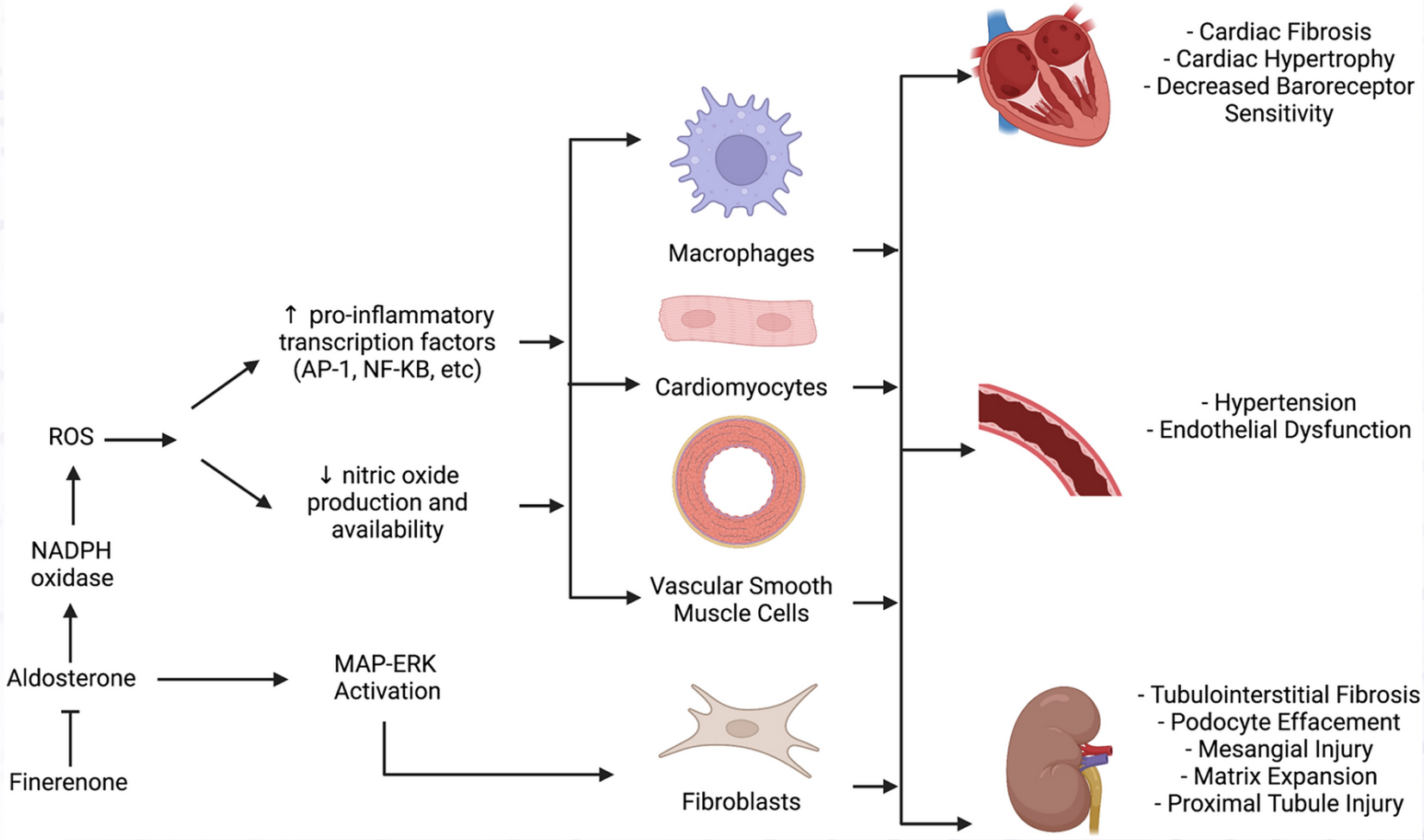
- Change in body weight
- Change in KCCQ-CSS
- Percentage of participants with NYHA class change

From baseline to week 24:

- Change in 6MWD

*NT-proBNP ≥1000 pg/mL or BNP ≥250 pg/mL for patients without AF; elevated NT-proBNP ≥2000 pg/mL or BNP ≥500 pg/mL for patients with AF AF, atrial fibrillation; BNP, B-type natriuretic peptide; CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide Colorado Prevention Center. NCT06008197. Available at: https://clinicaltrials.gov/study/NCT06008197 (accessed April 2024)

FINERENONE, A SELECTIVE MINERALOCORTICOID RECEPTOR ANTAGONIST



*NT-proBNP ≥1000 pg/mL or BNP ≥250 pg/mL for patients without AF; elevated NT-proBNP ≥2000 pg/mL or BNP ≥500 pg/mL for patients with AF AF, atrial fibrillation; BNP, B-type natriuretic peptide; CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide Colorado Prevention Center. NCT06008197. Available at: https://clinicaltrials.gov/study/NCT06008197 (accessed April 2024)

Palanisamy, S. et al. *Cardiol Ther* 11, 337–354 (2022).

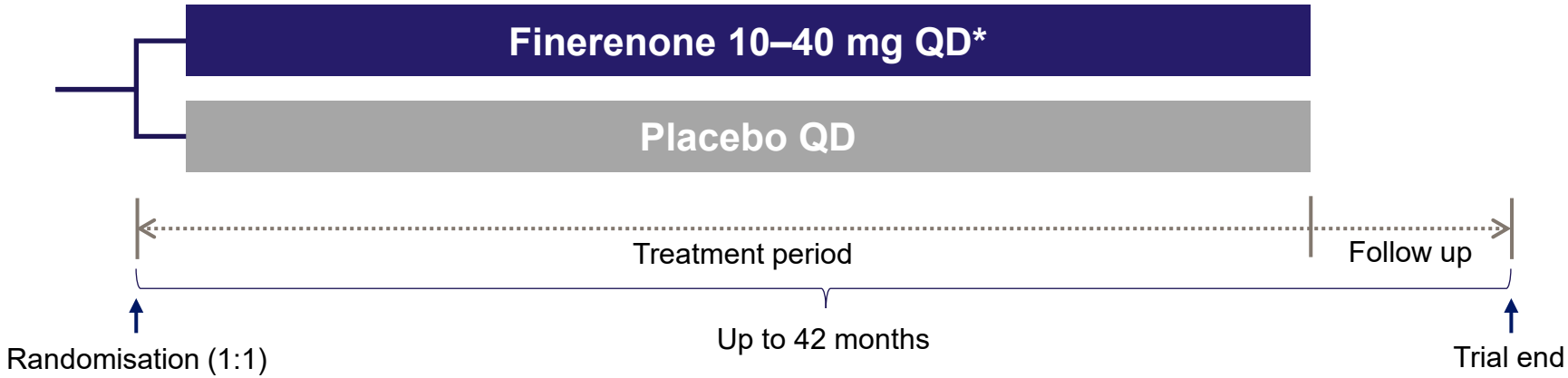
FINEARTS-HF

A Phase 3, randomised, double-blind trial to evaluate finerenone in patients with HFpEF

Estimated completion date: June 2024

6,016 patients

- NYHA class II–IV
- LVEF ≥40%
- Elevated NT-proBNP levels, structural heart disease or elevated filling pressure



Primary endpoint:

- Number of CV deaths from baseline to week 52
- Number of HF events from baseline to week 52

Confirmatory secondary endpoints:

- Time to first occurrence of composite renal endpoints†
- Time to death from any cause
- Change from baseline to week 52 in KCCQ-TSS

*NT-proBNP ≥1000 pg/mL or BNP ≥250 pg/mL for patients without AF; elevated NT-proBNP ≥2000 pg/mL or BNP ≥500 pg/mL for patients with AF AF, atrial fibrillation; BNP, B-type natriuretic peptide; CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide Colorado Prevention Center. NCT06008197. Available at: https://clinicaltrials.gov/study/NCT06008197 (accessed April 2024)

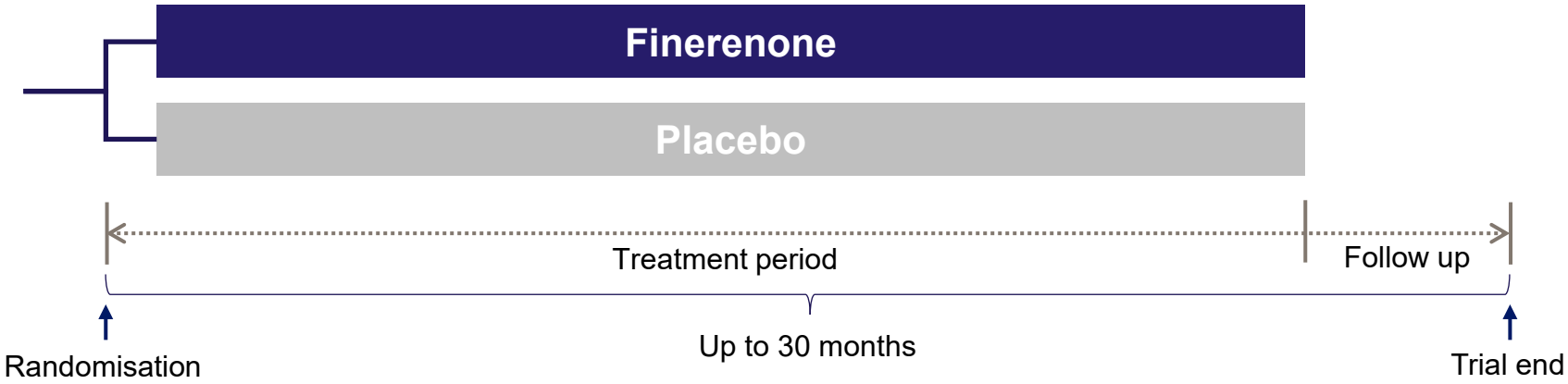
REDEFINE-HF

A Phase 3, randomised, double-blind trial to evaluate finerenone in patients with HFmrEF/HFpEF

Estimated completion date: April 2026

5,200 patients

- LVEF ≥40 (imaging evidence of HFmrEF or HFpEF)
- Current hospitalisation or recently discharged with the primary diagnosis of HF
- HF signs and symptoms at the time of hospital admission
- Elevated NT-proBNP or BNP levels*



Primary endpoints:

- Composite total of HF events and CV death
- Number of serious adverse events
- Number of adverse events leading to discontinuation of study drug

Confirmatory secondary endpoints:

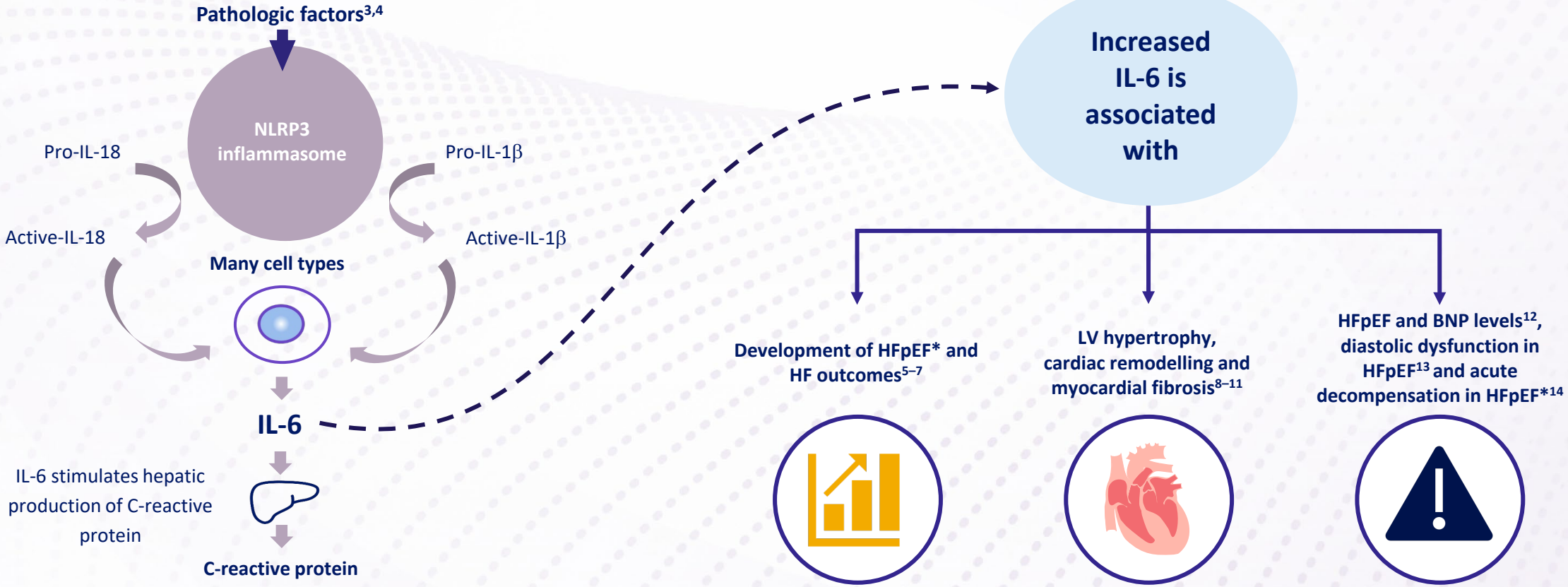
- Time to first occurrence of the composite of CV death of HF event
- Total HF events
- Change from baseline in KCCQ-TSS (at month 6)
- Time to CV death
- Time to all-cause death

*NT-proBNP ≥1000 pg/mL or BNP ≥250 pg/mL for patients without AF; elevated NT-proBNP ≥2000 pg/mL or BNP ≥500 pg/mL for patients with AF

AF, atrial fibrillation; BNP, B-type natriuretic peptide; CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide

Colorado Prevention Center. NCT06008197. Available at: https://clinicaltrials.gov/study/NCT06008197 (accessed April 2024)

NLPR3 INFLAMMASOME ACTIVATION IS THOUGHT TO PLAY A ROLE IN HF[1,2]



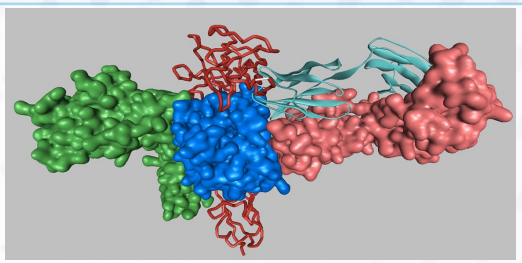
There is no consistency for classification of HFpEF based on ejection fraction in previous research and HFpEF was defined as LVEF>40%, LVEF>45% or LVEF>50% in these different studies

BNP, B-type natriuretic peptide; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; IL-1β, interleukin-1β; IL-6, interleukin-6; IL-18, interleukin-18; LV, left ventricular; LVEF, left ventricular ejection fraction; NLRP3, NOD [nucleotide oligomerization domain]-, LRR [leucine-rich repeat]- and PYD [pyrin domain]-containing protein 3

1. Olsen MB et al. JACC: Bas Transl Sci 2022;7:84–98; 2. Butts B et al. J Card Fail 2015;21:586–593; 3. Ridker PM et al. Circ Res 2016;118:145–156 (Figure adapted); 4. Wu J et al. Front Physiol 2021;12:709703; 5. Kalogeropoulos A et al. J Am Coll Cardiol 2010;55:2129–2137; 6. Chia YC et al. J Am Heart Assoc 2021;10:e018549; 7. Markousis-Mavrogenis G et al. Eur J Heart Fail 2019;21:965–973; 8. Meléndez GC et al. Hypertension 2010;56:225–231; 9. Hirota H et al. Proc Natl Acad Sci 1995;92:4862–4866; 10. Zhao L et al. Circ Res 2016;118:1918–1929; 11. Savvatis K et al. Basic Res Cardiol 2014;109–449; 12. Collier P et al. Eur J Heart Fail 2011;13:1087–1095; 13. Wu CK et al. Crit Care Med 2011;39:984–992; 14. Abernethy A et al. J Am Heart Assoc 2018;7:e007385

*NT-proBNP ≥1000 pg/mL or BNP ≥250 pg/mL for patients without AF; elevated NT-proBNP ≥2000 pg/mL or BNP ≥500 pg/mL for patients with AF AF, atrial fibrillation; BNP, B-type natriuretic peptide; CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide Colorado Prevention Center. NCT06008197. Available at: https://clinicaltrials.gov/study/NCT06008197 (accessed April 2024)

CANAKINUMAB, A HUMAN MONOCLONAL ANTIBODY NEUTRALIZING IL-1B



CANTOS
Canakinumab Anti-inflammatory Thrombosis Outcomes Study

Stable CAD (post MI)
Residual Inflammatory Risk
(hsCRP ≥ 2 mg/L)

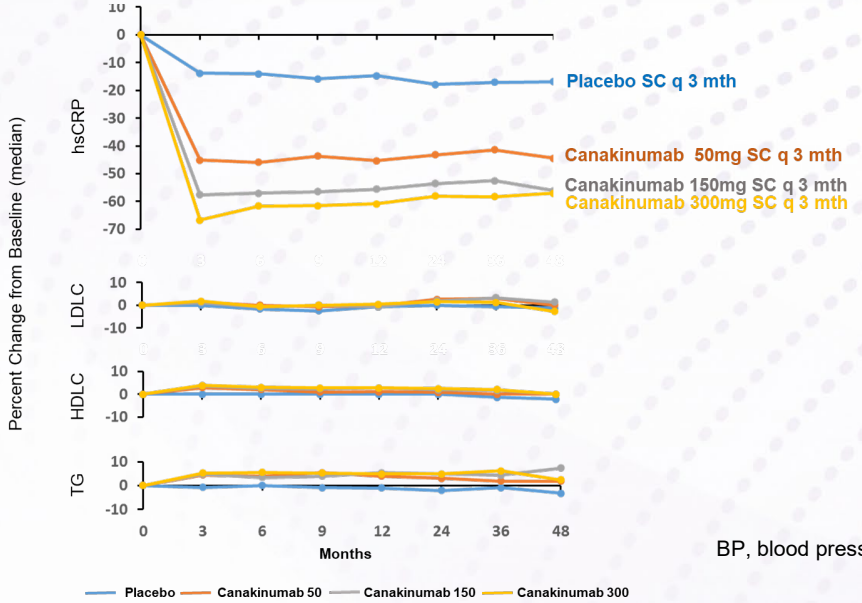
N = 10,061
39 Countries
April 2011 - June 2017
1490 Primary Events

- Randomized Canakinumab 50 mg SC q 3 months
- Randomized Canakinumab 150 mg SC q 3 months
- Randomized Canakinumab 300 mg SC q 3 months
- Randomized Placebo SC q 3 months

Primary Endpoint: Nonfatal MI, Nonfatal Stroke, Cardiovascular Death (MACE)

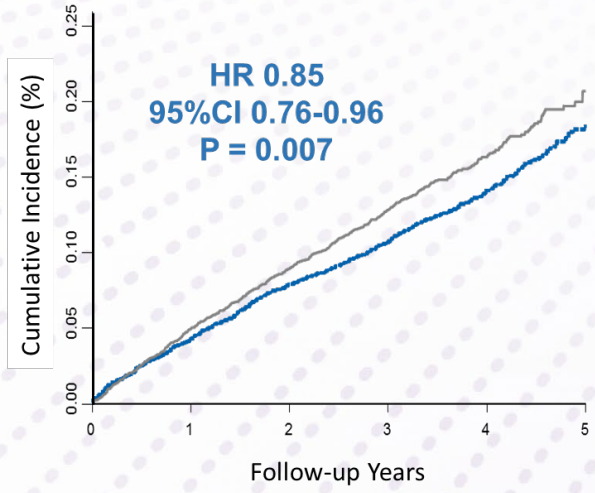
Secondary Endpoint: MACE plus Unstable Angina Requiring Urgent Revascularization (MACE+)

Additional Adjudicated Endpoints: Cancer, Infection

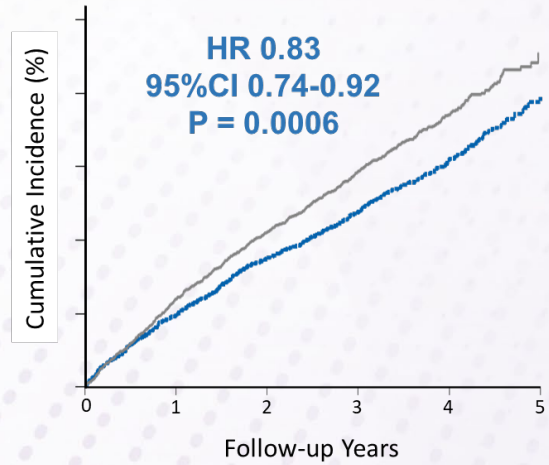


Placebo SC q 3 months
Canakinumab 150/300 mg SC q 3 months

MACE



MACE - Plus



35 - 40% reductions in hsCRP and IL-6
No change in LDLC
No change in BP

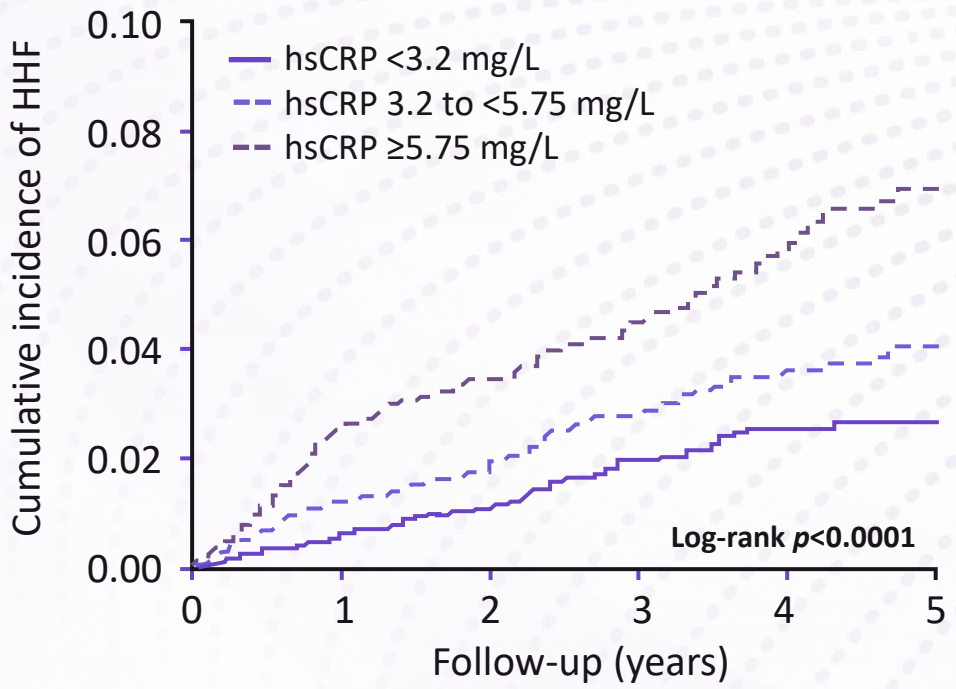
BP, blood pressure; CAD, coronary artery disease; HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; LDLC, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; MI, myocardial infarction; SC, subcutaneous

*NT-proBNP ≥1000 pg/mL or BNP ≥250 pg/mL for patients without AF; elevated NT-proBNP ≥2000 pg/mL or BNP ≥500 pg/mL for patients with AF AF, atrial fibrillation; BNP, B-type natriuretic peptide; CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide Colorado Prevention Center. NCT06008197. Available at: https://clinicaltrials.gov/study/NCT06008197 (accessed April 2024)

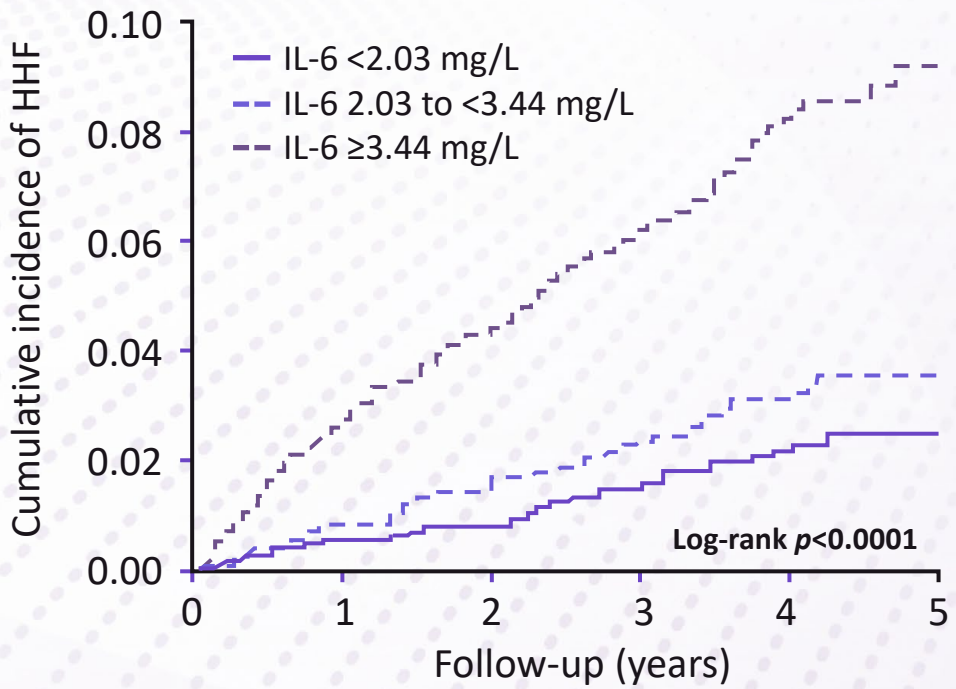
Ridker PM et al. *NEJM* 2017;377:1119-31

PRESPECIFIED EXPLORATORY ANALYSIS OF CANTOS TRIAL: BASELINE hsCRP AND IL-6 LEVELS PREDICTED HHF

Incident HHF by hsCRP levels



Incident HHF by IL-6 levels

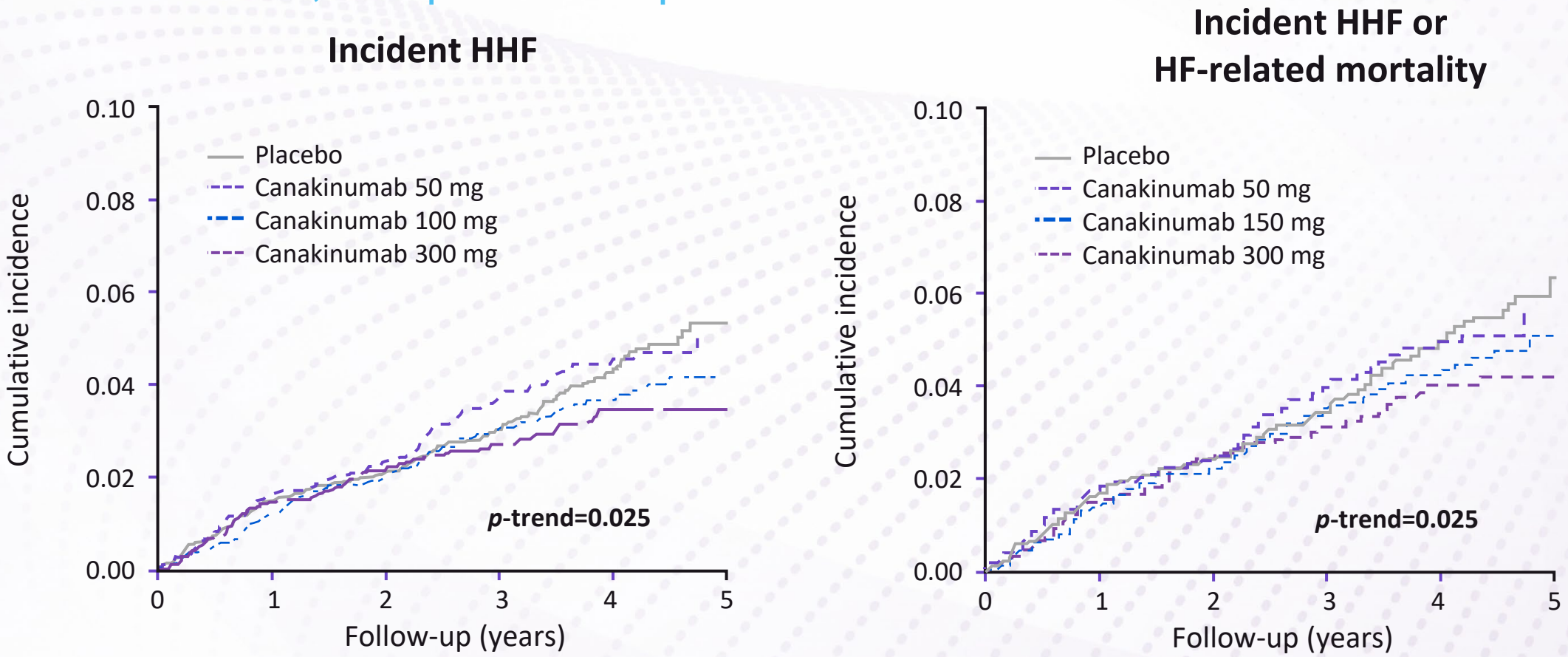


*NT-proBNP ≥1000 pg/mL or BNP ≥250 pg/mL for patients without AF; elevated NT-proBNP ≥2000 pg/mL or BNP ≥500 pg/mL for patients with AF AF, atrial fibrillation; BNP, B-type natriuretic peptide; CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide Colorado Prevention Center. NCT06008197. Available at: https://clinicaltrials.gov/study/NCT06008197 (accessed April 2024)

HHF, hospitalisation for heart failure; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6
Everett BM et al. Circulation 2019;139:1289–1299

PRESPECIFIED EXPLORATORY ANALYSIS OF CANTOS TRIAL:

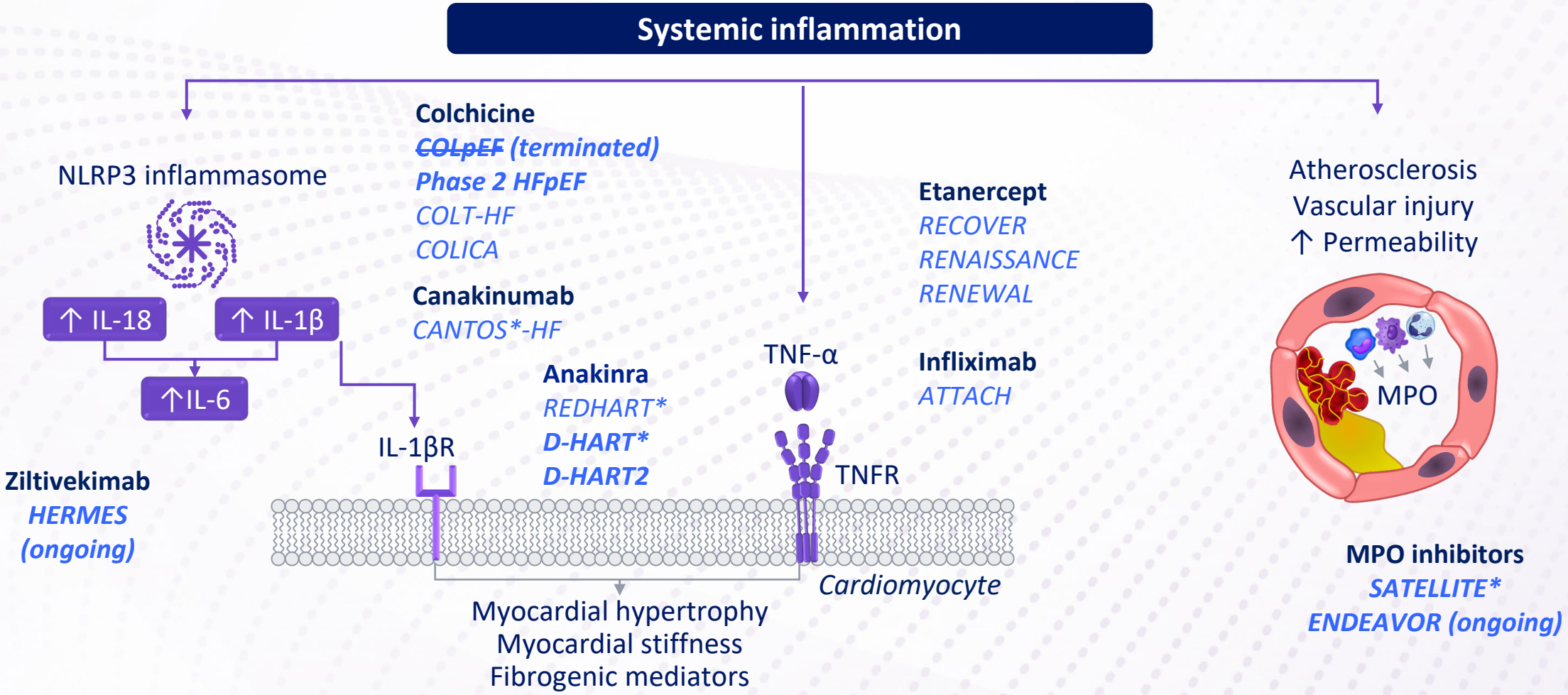
Modest but statistically significant dose-dependent benefit of IL-1β inhibition on incident HHF, compared with placebo



*NT-proBNP ≥1000 pg/mL or BNP ≥250 pg/mL for patients without AF; elevated NT-proBNP ≥2000 pg/mL or BNP ≥500 pg/mL for patients with AF AF, atrial fibrillation; BNP, B-type natriuretic peptide; CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide Colorado Prevention Center. NCT06008197. Available at: https://clinicaltrials.gov/study/NCT06008197 (accessed April 2024)

HF, heart failure; HHF, hospitalisation for heart failure; IL-1β, interleukin-1β
Everett BM et al. Circulation 2019;139:1289–1299

CLINICAL TRIALS OF ANTI-INFLAMMATORY THERAPIES FOR HF



*NT-proBNP ≥1000 pg/mL or BNP ≥250 pg/mL for patients without AF; elevated NT-proBNP ≥2000 pg/mL or BNP ≥500 pg/mL for patients with AF AF, atrial fibrillation; BNP, B-type natriuretic peptide; CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide Colorado Prevention Center. NCT06008197. Available at: https://clinicaltrials.gov/study/NCT06008197 (accessed April 2024)

Trials that included patients with HFpEF are highlighted in bold light blue

*Trial met its primary endpoint. HF, heart failure; HFpEF, heart failure with preserved ejection fraction; IL-18, interleukin-18; IL-1β, interleukin-1β; IL-1β-R, interleukin-1β receptor; IL-6, interleukin-6; MPO, myeloperoxidase; NLRP3, NOD [nucleotide oligomerisation domain]-, LRR [leucine-rich repeat]- and PYD [pyrin domain]-containing protein 3; TNFR, tumour necrosis factor receptor; TNF-α, tumour necrosis factor-α

Figure adapted from Pugliese et al. Cardiovasc Res 2022;118:3536–55

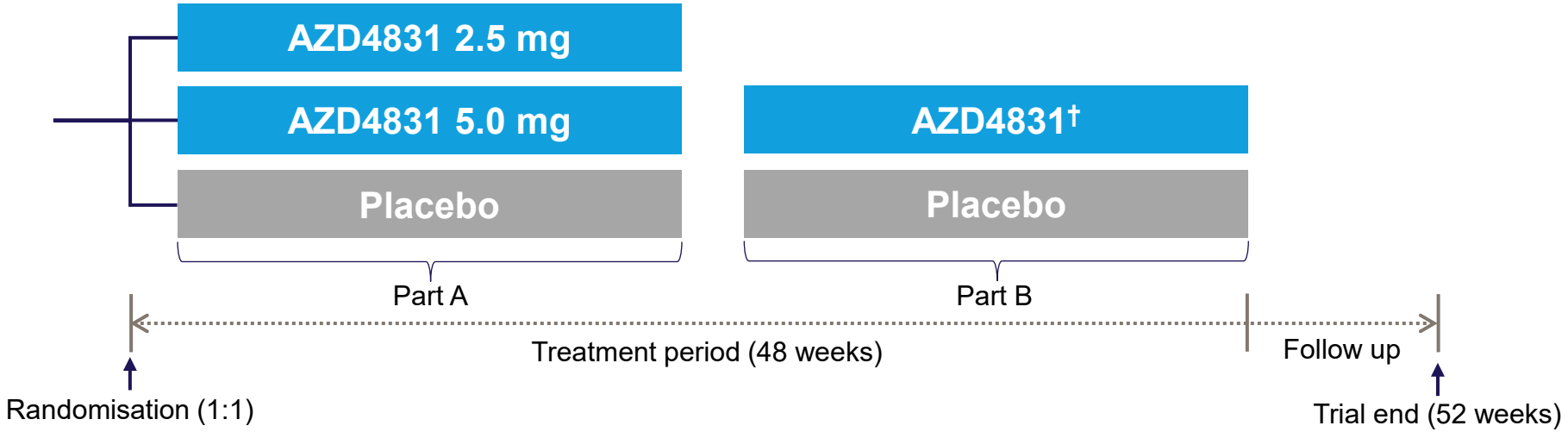
ENDEAVOR

A phase 2b and phase 3, randomised, double-blind, sequential trial to evaluate AZD4831* in patients with HFpEF

Study completion date: March 2024

1,485 patients

- LVEF >40 %
- Documented stable symptomatic HF
- 6MWD 30–400 m
- KCCQ-TSS ≤90



Primary endpoint:

Change from baseline to 16 and 24 weeks:

- KCCQ–TSS
- 6MWD

Confirmatory secondary endpoints:

- Change from baseline to 24 and 48 weeks in the KCCQ-TSS and 6MWD
- Change from baseline to 16 and 24 weeks in LV-GLS, LAVI and LVMI
- Change from baseline to 16, 24 and 48 weeks in NT-proBNP levels

*NT-proBNP ≥1000 pg/mL or BNP ≥250 pg/mL for patients without AF; elevated NT-proBNP ≥2000 pg/mL or BNP ≥500 pg/mL for patients with AF AF, atrial fibrillation; BNP, B-type natriuretic peptide; CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide Colorado Prevention Center. NCT06008197. Available at: https://clinicaltrials.gov/study/NCT06008197 (accessed April 2024)

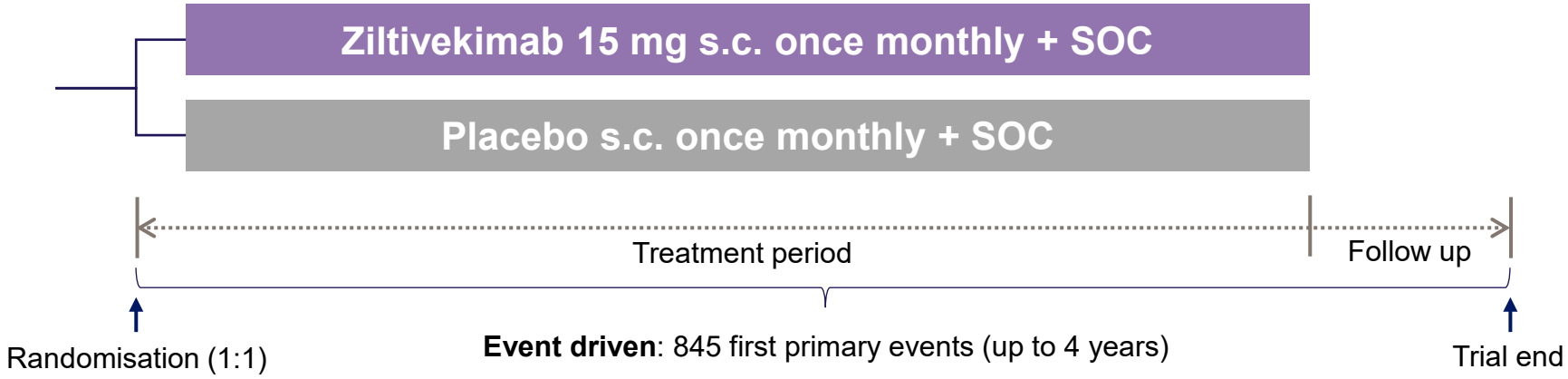
HERMES[1,2]

A Phase 3, randomised, double-blind, cardiovascular outcomes trial

Estimated completion date: July 2027

5,600 patients

- Elevated hsCRP ≥2 mg/L
- NYHA class II–IV
- LVEF >40 %
- Elevated NT-proBNP levels
- Echocardiographic signs of HFmrEF or HFpEF



Primary endpoint:

Time to the first occurrence of:

- CV death
- HHF
- Urgent HF visit

Confirmatory secondary endpoints:

- Time to the first occurrence of cardiovascular death, HHF or urgent heart failure visit, non-fatal myocardial infarction or non-fatal stroke
- Number of CV death, HHF or urgent heart failure visits (first and recurrent)
- Time to occurrence of CV death
- Time to occurrence of all-cause death

*NT-proBNP ≥1000 pg/mL or BNP ≥250 pg/mL for patients without AF; elevated NT-proBNP ≥2000 pg/mL or BNP ≥500 pg/mL for patients with AF AF, atrial fibrillation; BNP, B-type natriuretic peptide; CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide Colorado Prevention Center. NCT06008197. Available at: https://clinicaltrials.gov/study/NCT06008197 (accessed April 2024)

CV, cardiovascular; HF, heart failure; HFF, hospitalisation for heart failure; HFpEF, heart failure with preserved ejection fraction; hsCRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; s.c., subcutaneous; SOC, standard of care

1. Novo Nordisk A/S.NCT05636176 Available at: https://clinicaltrials.gov/ct2/show/NCT05636176 (accessed April 2024); 2. Novo Nordisk A/S. Data on file

WEIGHING IN ON HFpEF

A Review of the Clinical Evidence and Emerging Therapies for HFpEF

Q&A Period

All panelists

THANK YOU!

WEIGHING IN ON HFpEF

A Review of the Clinical Evidence and Emerging Therapies for HFpEF

Please remember to complete both the session evaluation and congress evaluation

Next Up! Please proceed to the 36th floor for the Workshops. There will be a French workshop offered in the Champlain Ballroom.