

Emerging therapies, where do they fit in?

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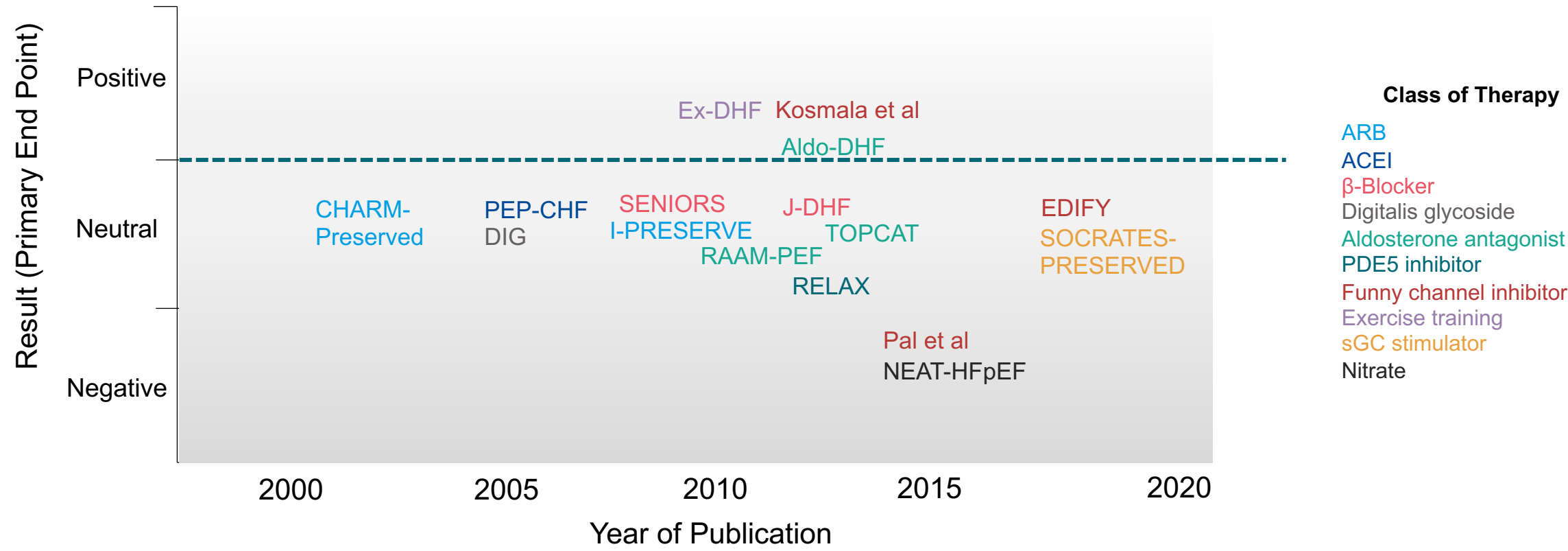


@javedbutler1

Disclosures: Abbott, Adrenomed, Amgen, Array, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, CVRx, G3 Pharmaceutical, Impulse Dynamics, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, Novo Nordisk, Roche, and Vifor

Clinical Trials of Therapies for HFrEF Have Failed To Demonstrate Comparable Benefit in HFpEF

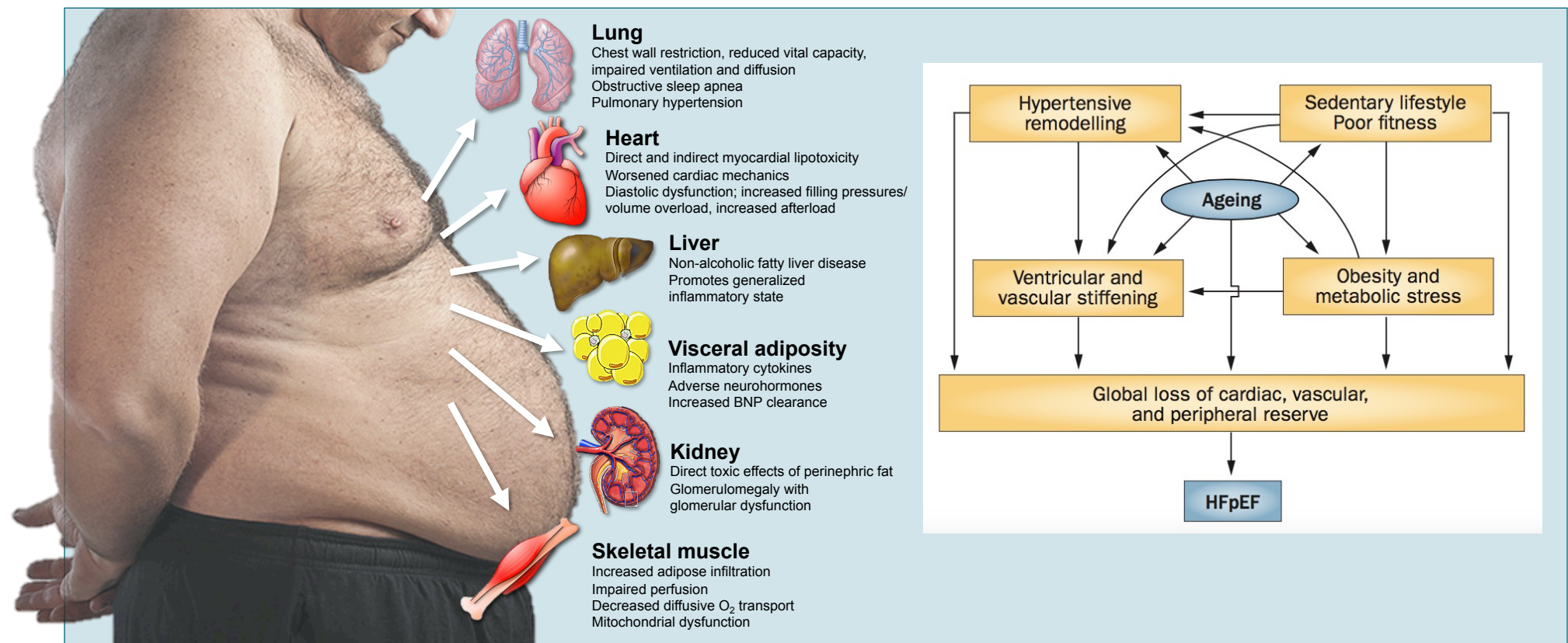
Overview of Major Published HFpEF Randomized Clinical Trials (Phase 2–3)¹⁻¹⁷



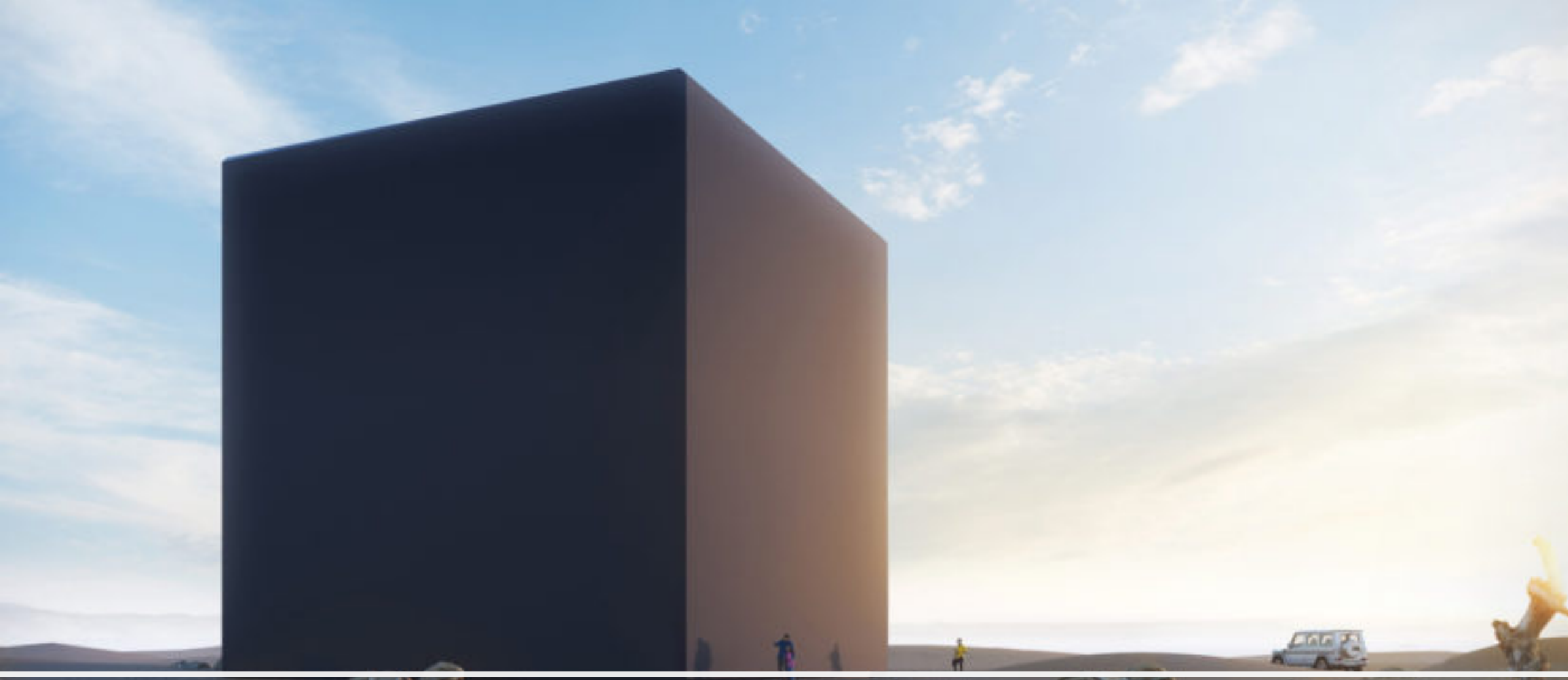
PDE5, phosphodiesterase 5; sGC, soluble guanylate cyclase.

1. Parikh KS et al. *JACC Heart Fail.* 2018;6(8):619-632. 2. Yusuf S et al. *Lancet.* 2003;362(9386):777-781. 3. Massie BM et al. *N Engl J Med.* 2008;359(23):2456-2467. 4. Cleland JG et al. *Eur Heart J.* 2006;27(19):2338-2345. 5. van Veldhuisen DJ et al. *J Am Coll Cardiol.* 2009;53(23):2150-2158. 6. Ahmed A et al. *Circulation.* 2006;114(5):397-403. 7. Pitt B et al. *N Engl J Med.* 2014;370(15):1383-1392. 8. Yamamoto K et al. *Eur J Heart Fail.* 2013;15(1):110-118. 9. Edelmann F et al. *JAMA.* 2013;309(8):781-791. 10. Deswal A et al. *J Card Fail.* 2011;17(8):634-642. 11. Redfield MM et al. *JAMA.* 2013;309(12):1268-1277. 12. Kosmala et al. *J Am Coll Cardiol.* 2013;62(15):1330-1338. 13. Pal N et al. *Circulation.* 2015;132(18):1719-1725. 14. Komajda N et al. *Eur J Heart Fail.* 2017;19(11):1495-1503. 15. Edelmann F et al. *J Am Coll Cardiol.* 2011;58(17):1780-1791. 16. Pieske B et al. *Eur Heart J.* 2017;38(15):1119-1127. 17. Redfield MM et al. *N Engl J Med.* 2015;373(24):2314-2324.

HFpEF : A systemic syndrome



Kitzman D, Shah SJ. *JACC* 2016; Borlaug B. *Nat Rev Cardiol* 2014



HFpEF Monolith



The three Ws of

Why ... is it important?

Effects of undersupply:



Anemia



Digestive disorders



Impaired vision



Fatigue,



Nervousness,

B12

Where

...can I find it?

Who ...needs more?

Groups with an increased risk of an undersupply:



Elderly people



Stressed people



Pregnant and nursing women



Cereal

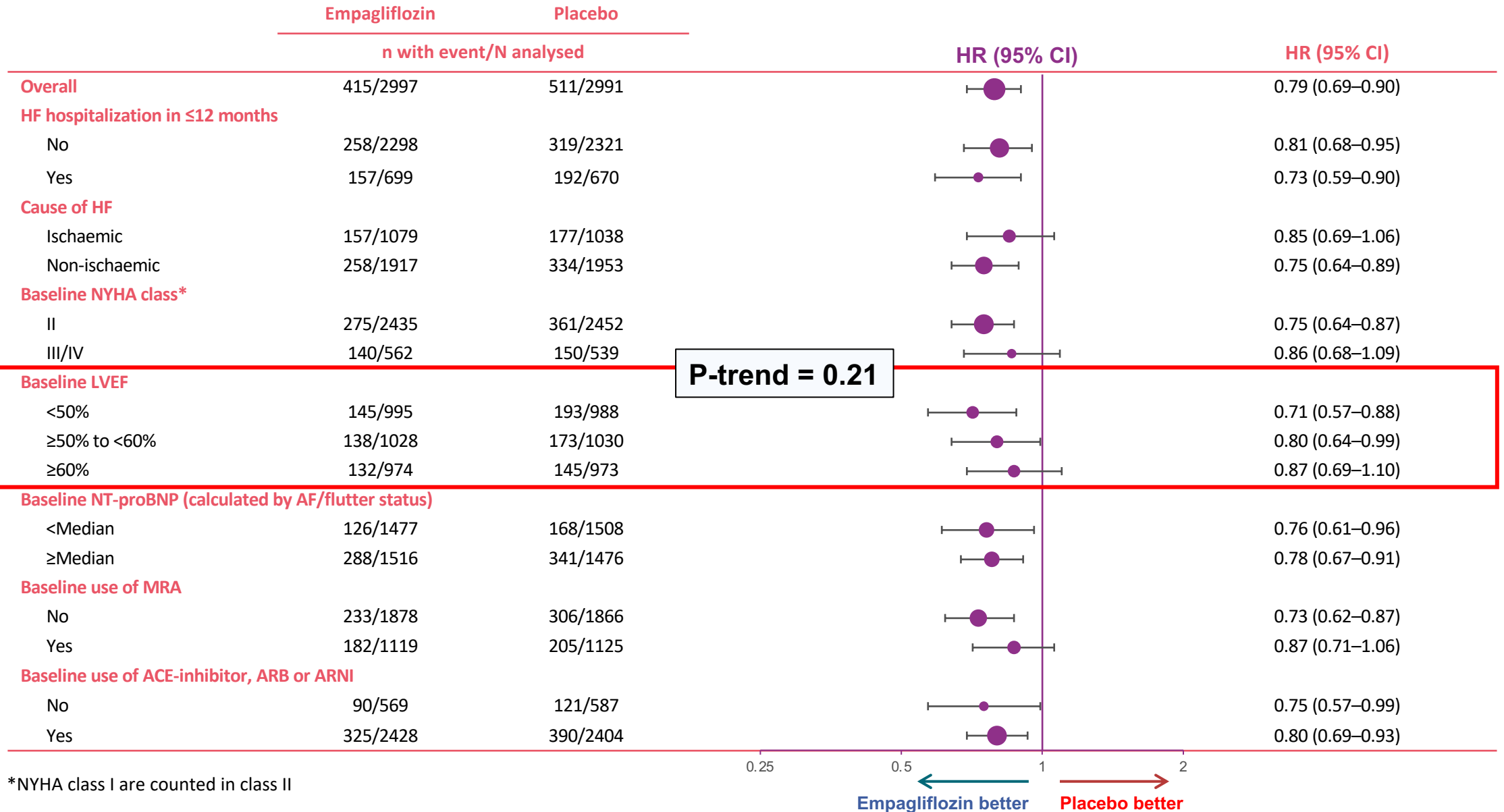


Juices

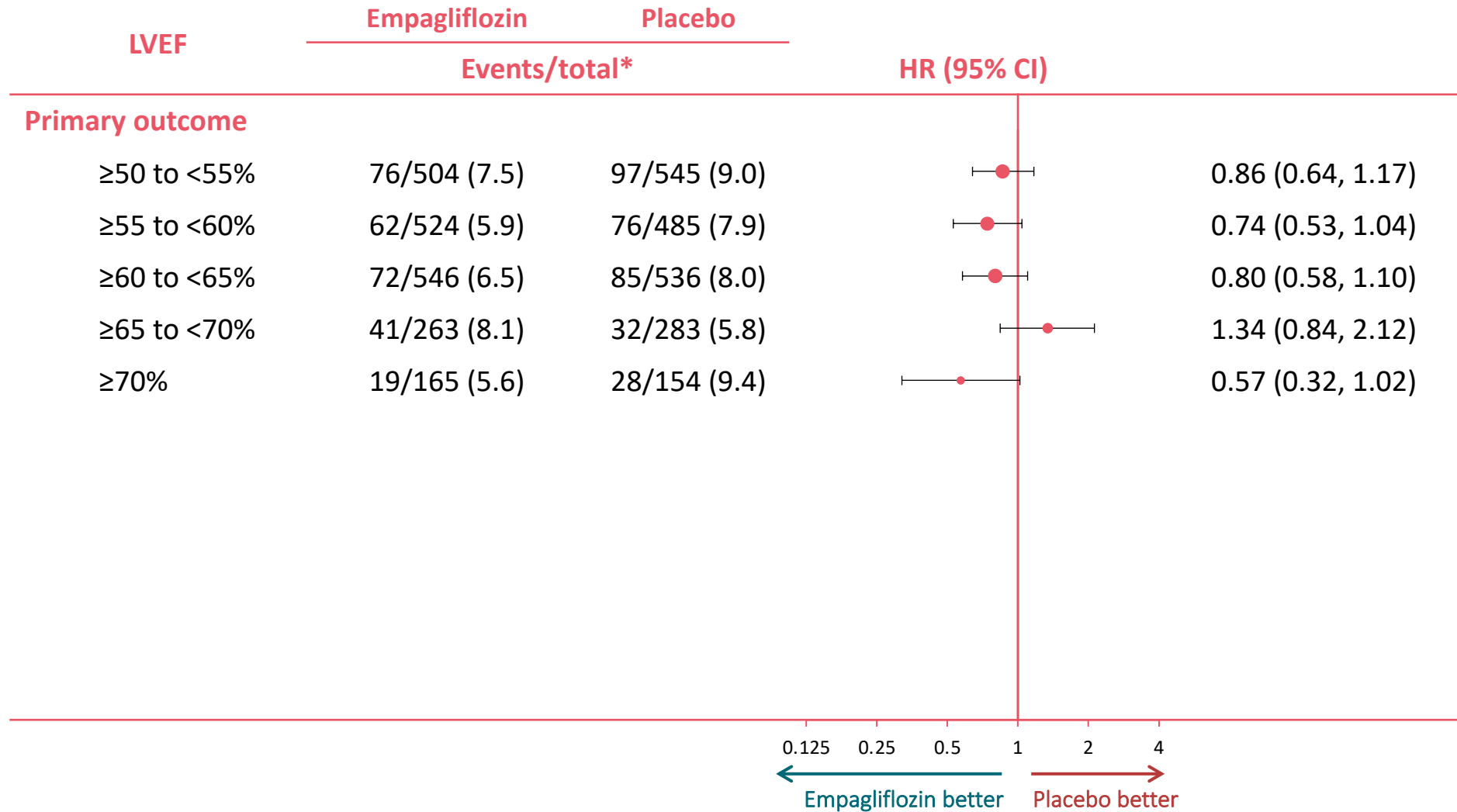


Baby food

EMPEROR Preserved

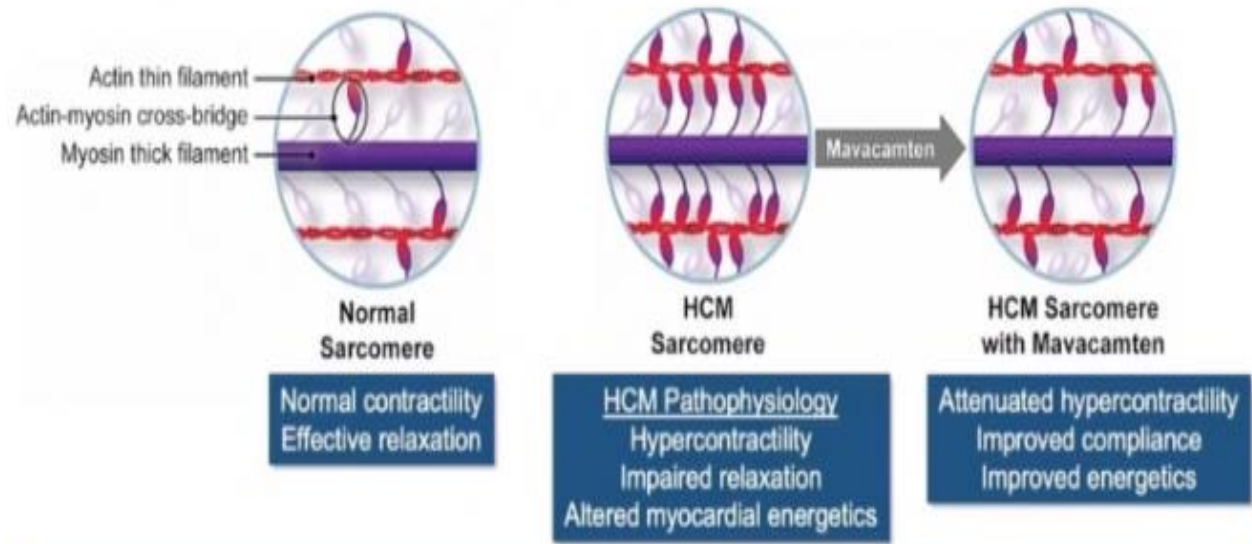


Effect of Empagliflozin vs Placebo: Primary Outcome and Total HHF by LVEF at Baseline



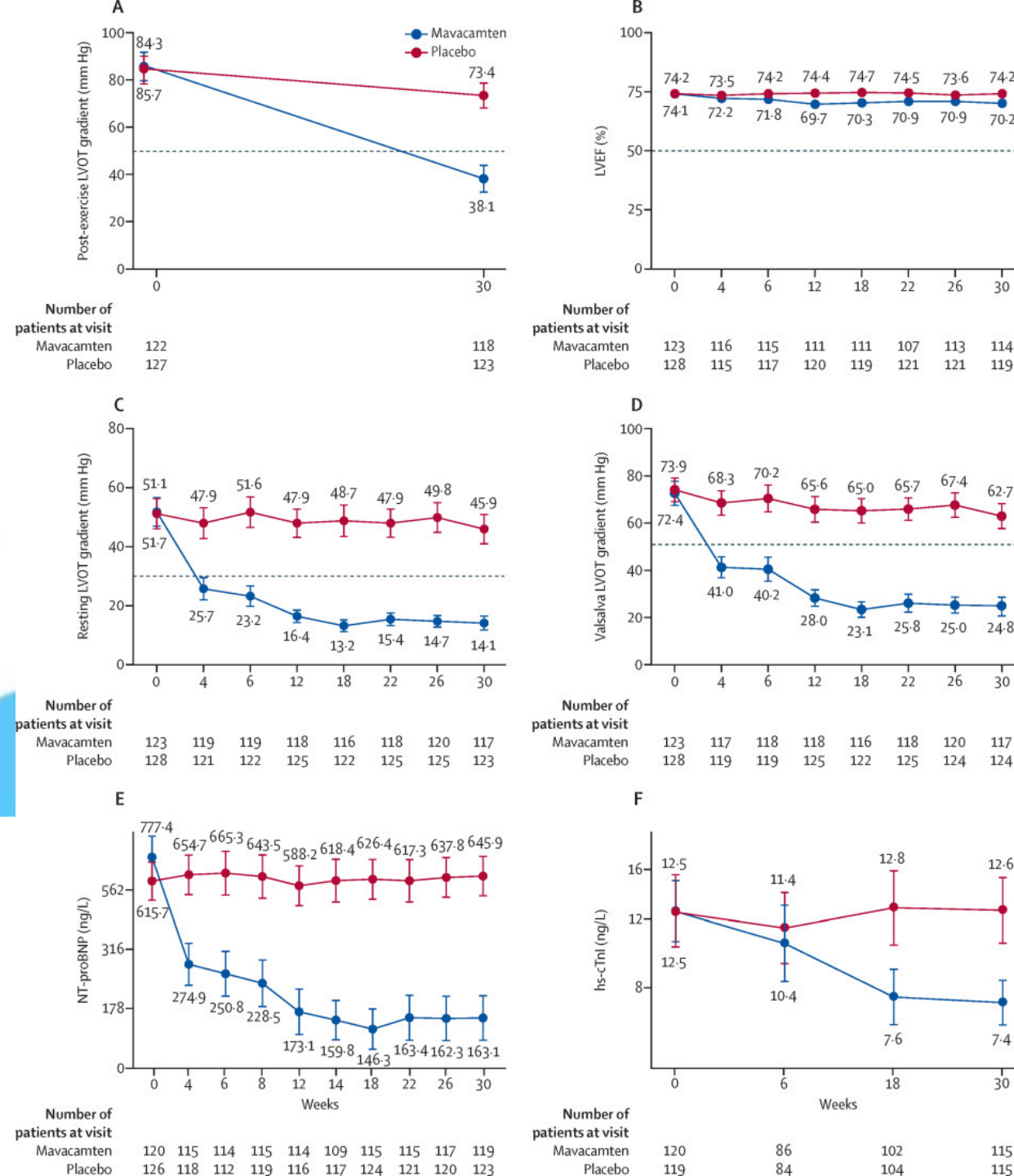
*For the primary outcome, the events/100 patient-years are reported in parentheses. These data are not reportable for total HHF.

Mavacamten: Mechanism of Action



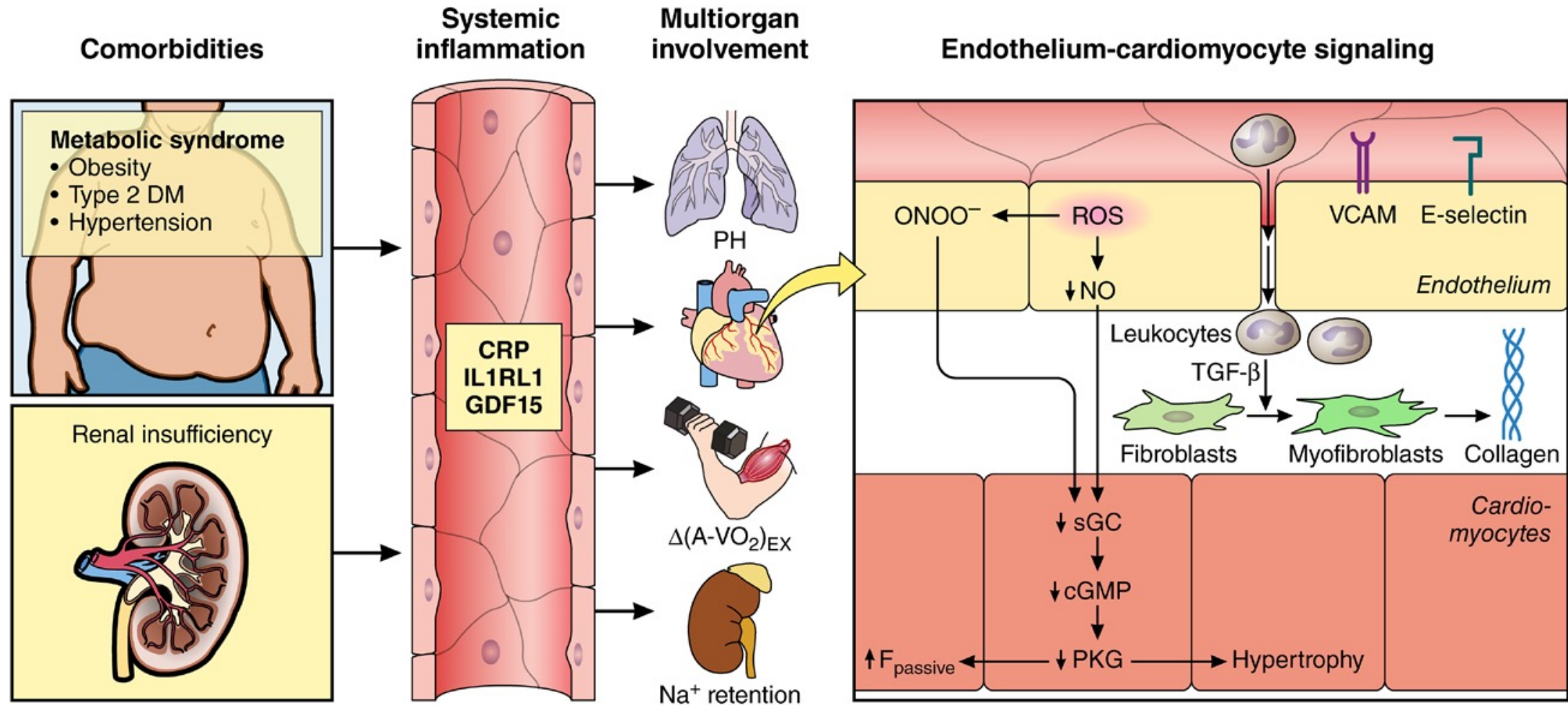
Mavacamten is a targeted inhibitor of cardiac myosin that reduces the number of myosin-actin cross-bridges and decreases contractility

ACC.21



A Study of Mavacamten in Participants With HFpEF and Elevation of NT-proBNP With or Without Elevation of cTnT (EMBARK-HFpEF)

A systemic syndrome



VITALITY

Phase IIb - HFpEF



≥45%

Design similarities

- Randomization within 6 months after HF event
- Elevated NT-proBNP / BNP
- 2-week titration intervals, repeated titration options

VITALITY-HFpEF

KCCQ-PLS
3 arms / 10 + 15 mg

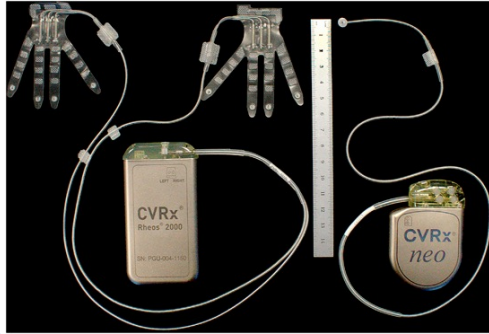
Ancillary studies: Genetics / BMx / Accelerometry

**Jun
2018**

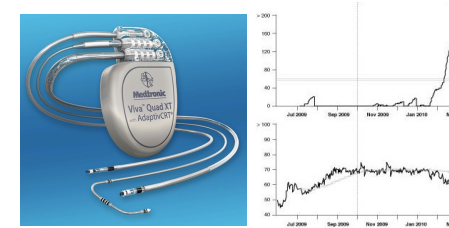
**750
enrolled**

DEVICES FOR HFpEF

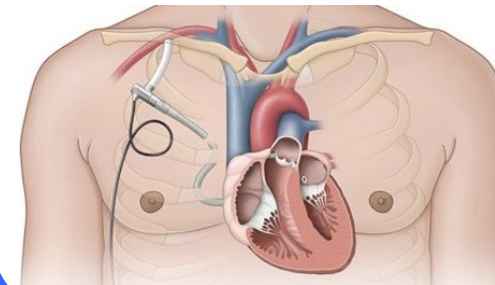
CAROTID BARORECEPTOR STIMULATOR



PACEMAKER DEVICES



LEFT ATRIAL ASSIST DEVICE



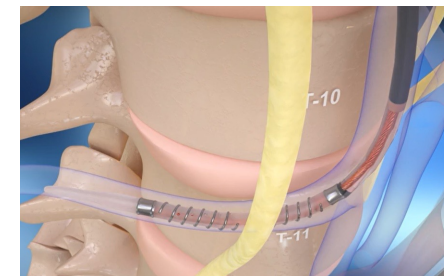
IMPLANTABLE HEMODYNAMIC SENSOR



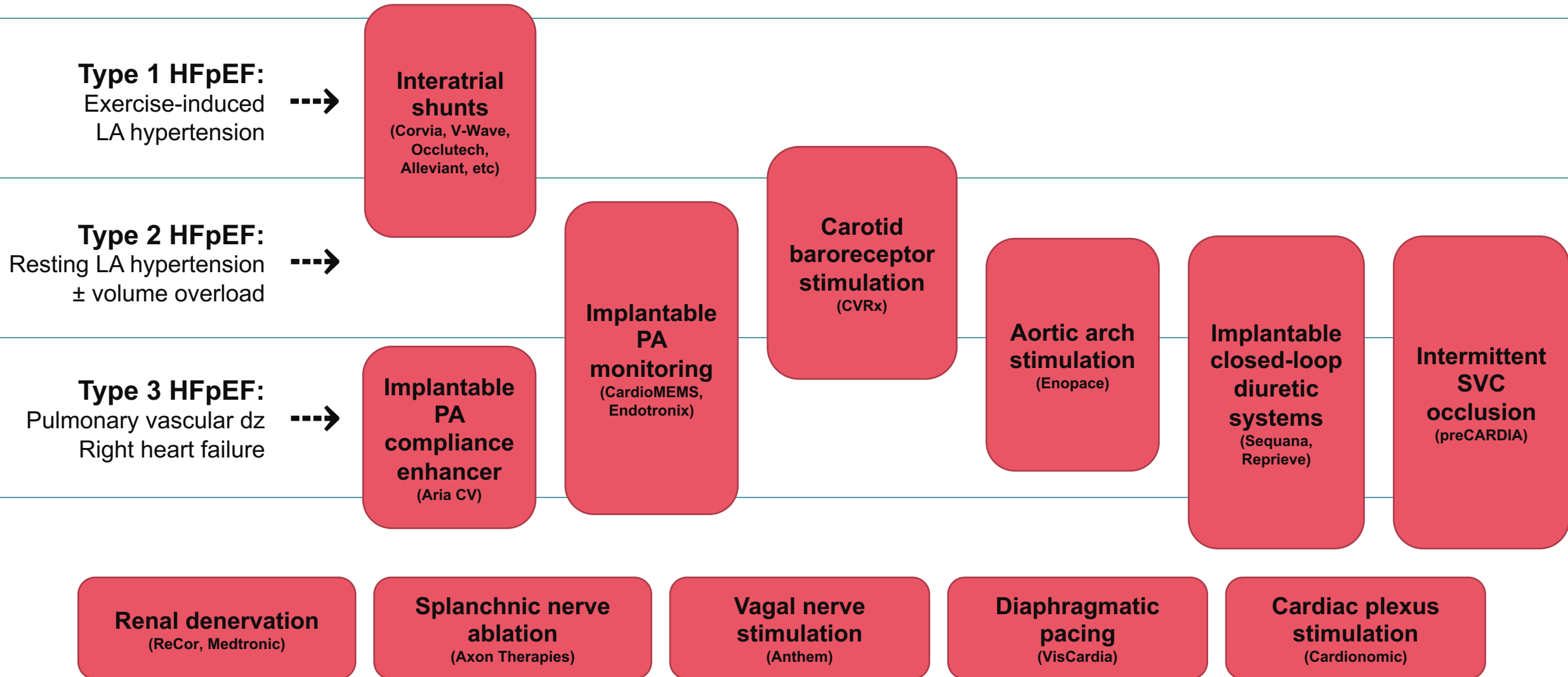
INTERATRIAL SHUNT DEVICE



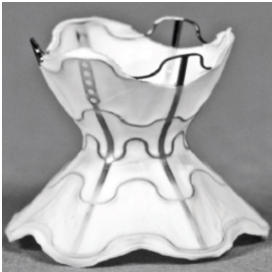
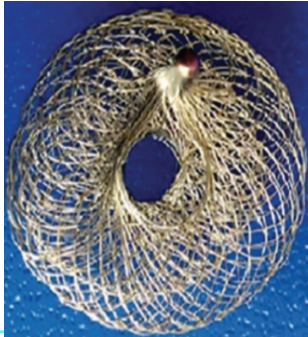
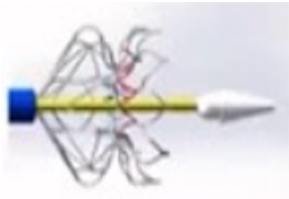
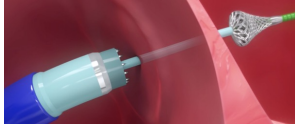
GSN ABLATION



Device-based therapeutics for HFpEF



Interatrial shunt devices/procedures

Device							
Type	Implant	Implant	Implant	Implant	Procedure	Procedure	Procedure
Description	Nitinol stent	Nitinol/PTFE hourglass	Nitinol braid with central orifice	Tubular nitinol device with retention arms	Coring catheter	RF catheter	Cutting catheter
Shunt flow	LA → RA	LA → RA	LA → RA	LA → CS	LA → RA	LA → RA	LA → RA
Shunt size	8 mm	5.1 mm	4, 6, 8, 10 mm	7 mm	6 mm	4-12 mm	4 mm
Development stage	Phase 3 RCT	Phase 3 RCT	Open-label studies	FIH complete	Animal studies	FIH complete	FIH complete

*CS = coronary sinus; FIH = first in human

HeartShare

Retrospective (Y1-2)

Existing datasets
(cohort studies, trials)



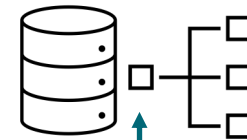
Data aggregation, harmonization
Image repository
Additional omics analyses



Advanced analytics (e.g.,
multi-omics, ML) for
HFpEF sub-classification

Prospective (Y1-5)

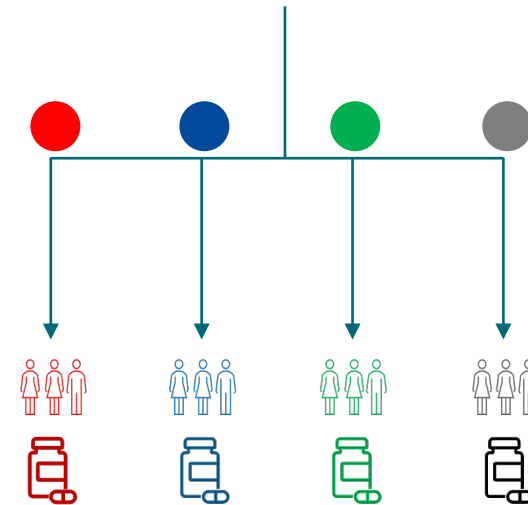
Existing datasets
(cohort studies, trials)



Learnings from
retrospective component

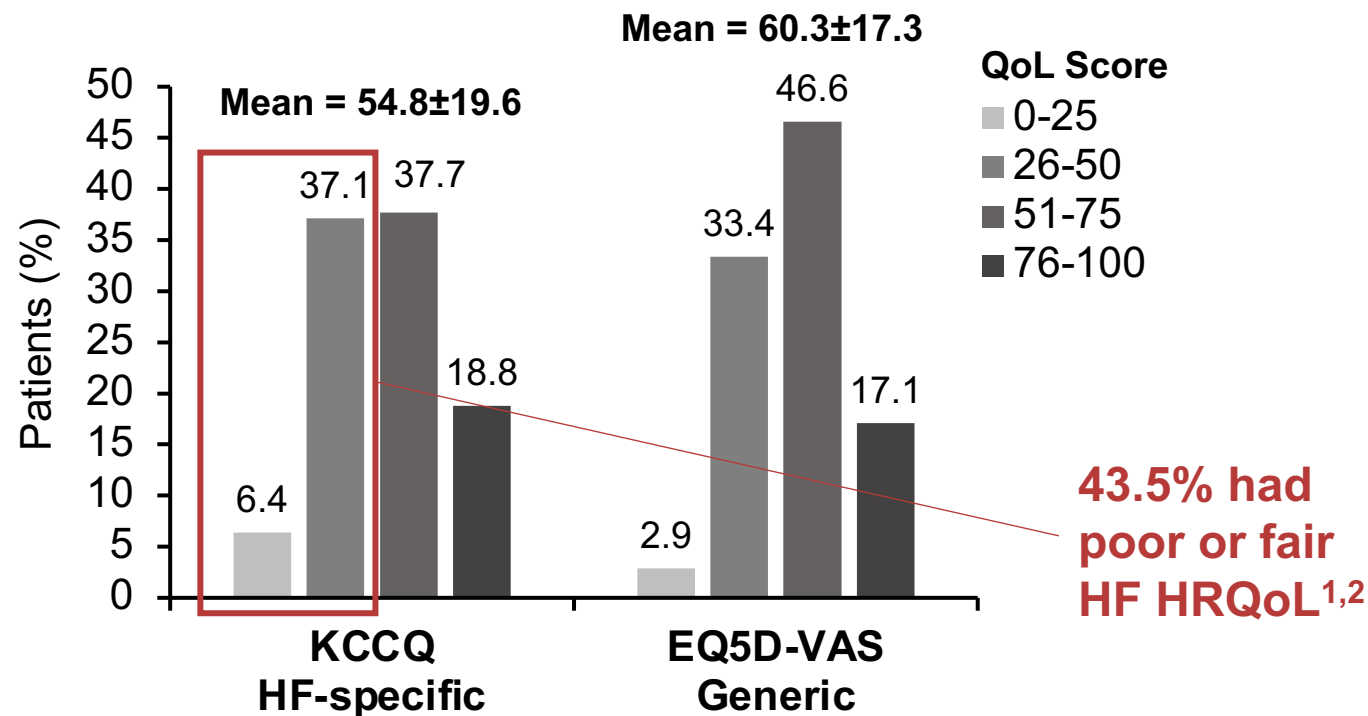
Future (Y5+)

Master protocol to test
precision Rx in HFpEF

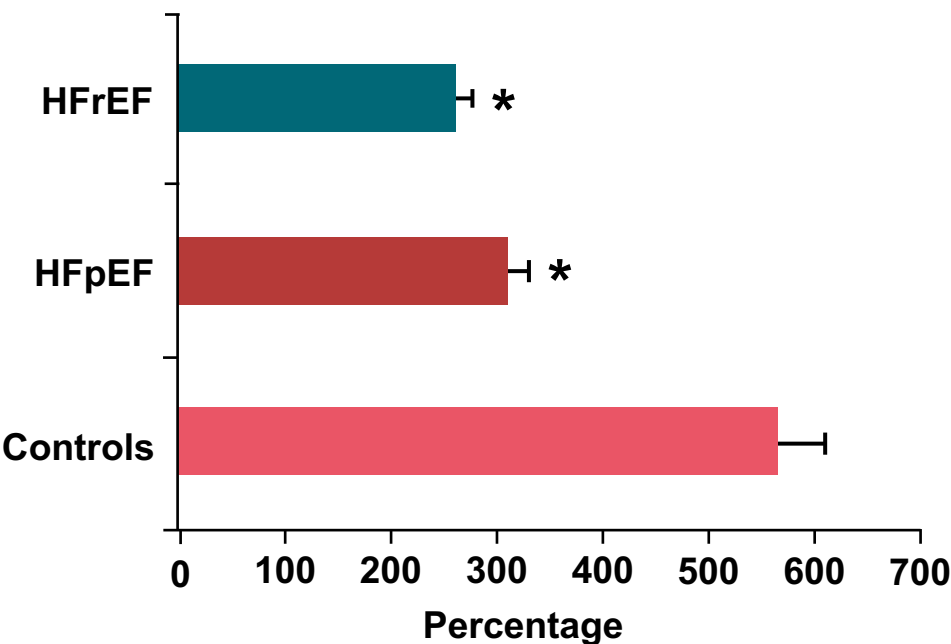


Patients With HFpEF Experience Impairment in QoL and Functional Capacity

Baseline HRQoL in TOPCAT Patients^{1,a}



Percentage Increase in VO₂ With Exercise in Patients With HF Versus Controls^{3,b}



*P<.05.

Lower scores indicate more severe impairment¹

EQ5D-VAS, EQ5D Visual Analogue Scale; HRQoL health-related quality of life; KCCQ, Kansas City Cardiomyopathy Questionnaire; QoL, quality of life; TOPCAT, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial; VO₂, peak oxygen uptake.

^aAmong 3400 patients ≥50 years of age with LVEF ≥45% who were enrolled in TOPCAT. ^bData from control subjects (N = 24), patients with HFpEF defined as chronic NYHA II-IV symptoms with LVEF >50% and PCWP at rest >15 mm Hg (N = 48), and patients with HFrEF defined as NYHA II-IV LV systolic dysfunction with LVEF <45% (N = 56).

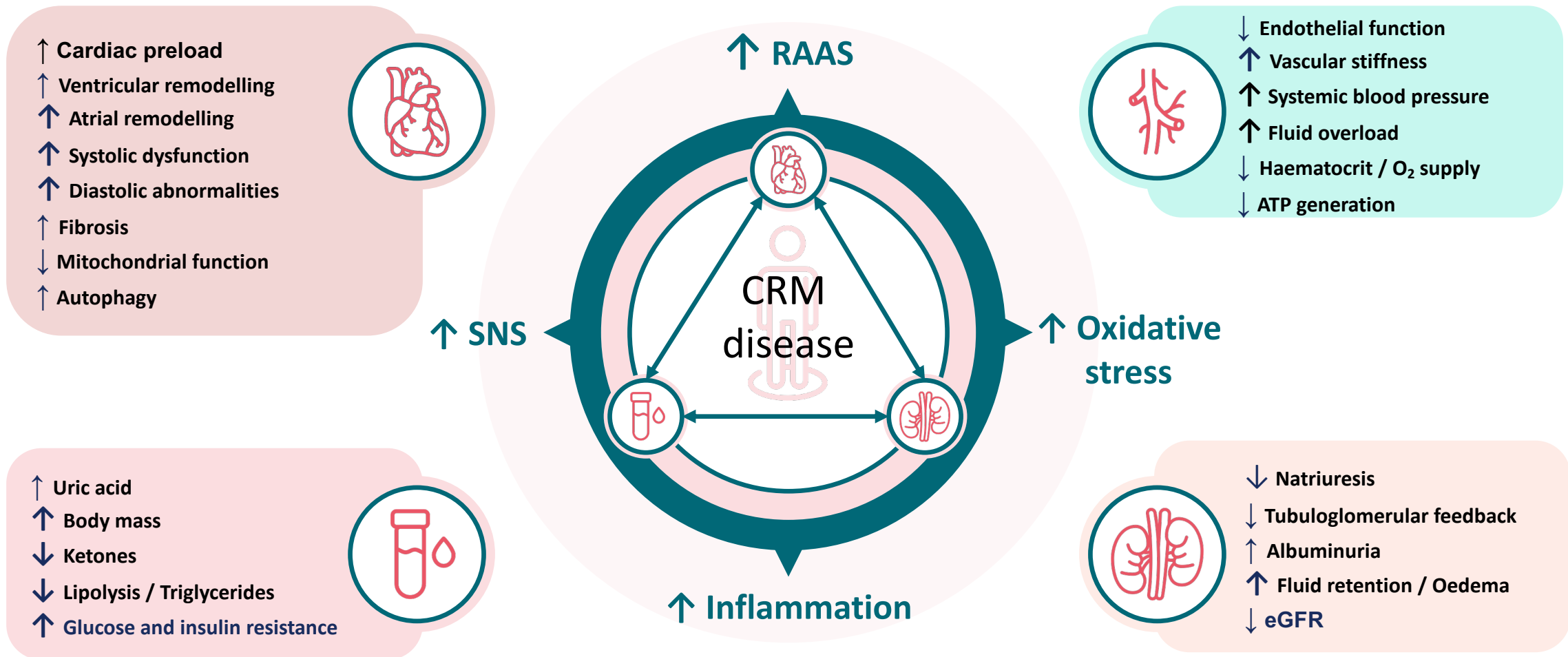
Permission requested from *Circ Heart Fail* for figure use.

1. Lewis EF et al. *Circ Heart Fail*. 2016;9(3):e001937. 2. Green CP et al. *J Am Coll Cardiol*. 2000;35(5):1245-1255. 3. Dhakal BP et al. *Circ Heart Fail*. 2015;8(2):286-294.

Health Status

- What is a win?
- What is the threshold for safety?
- Who will pay?

Compensatory mechanisms and inflammation lead to a cascade of responses in the body



ATP, adenosine triphosphate; CRM, cardiovascular, renal and metabolic; eGFR, estimated glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system; SGLT2, sodium-glucose co-transporter-2; SNS, sympathetic nervous system.

1. Givens RC, Schulze PC. Molecular changes in heart failure. In: Eisen H, ed. Heart Failure: A Comprehensive Guide to Pathophysiology and Clinical Care. London: Springer Verlag; 2017:1–26. 2. Ronco C, et al. J Am Coll Cardiol. 2008;52:1527. 3.

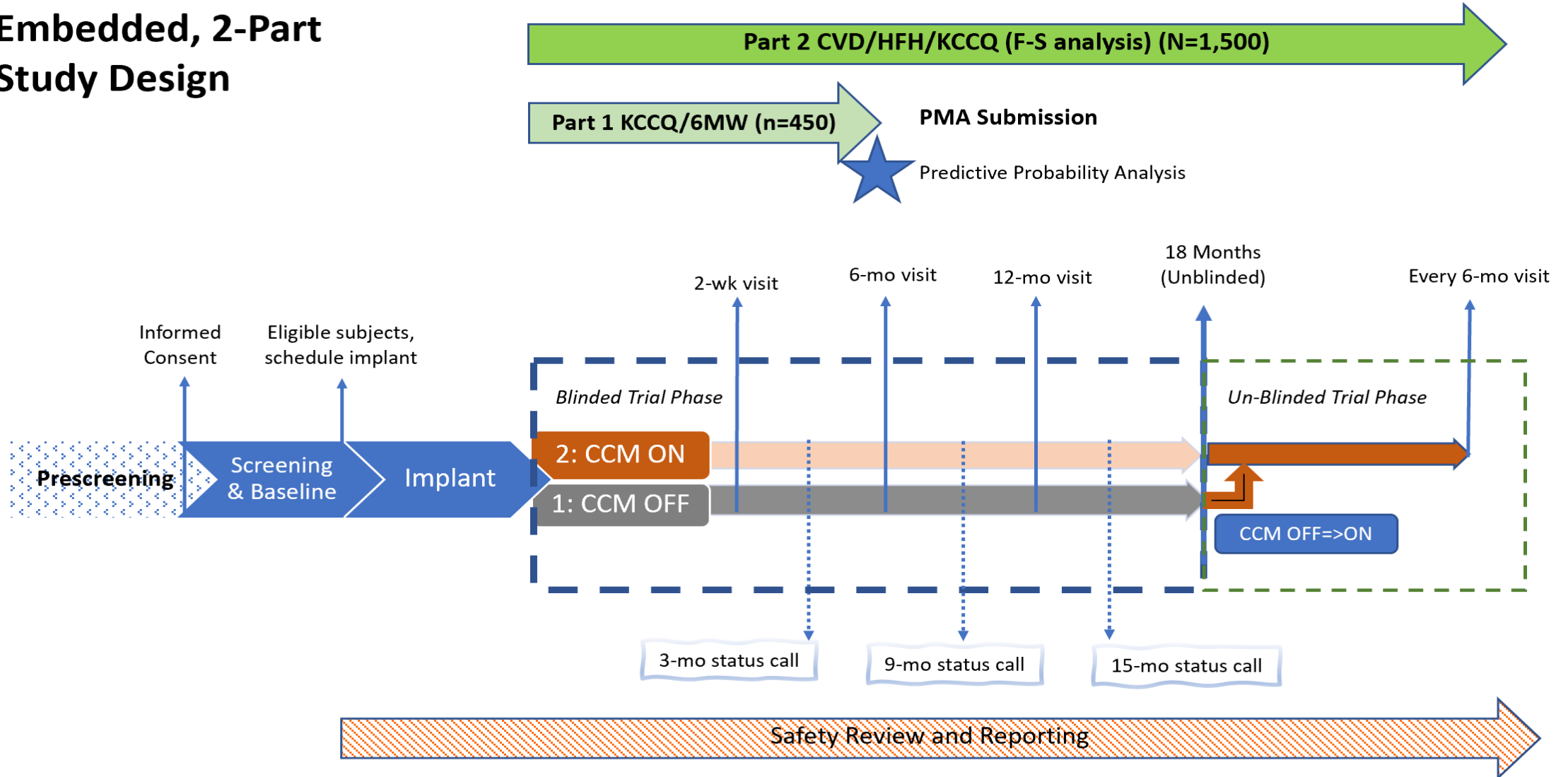
Santos-Ferreira D, et al. Cardiology. 2020;145:311–20.

Summary of the Impact of Cardiac Contractility Modulation in Patients with Heart Failure

Intracellular Ca^{2+} metabolism	↑
Improvement in diastolic Ca^{2+} levels (SERCA2a; phosphorylation of phospholamban)	
Phosphorylation of myofilaments (troponin I, myosin light chain 2, myosin binding protein)	↑
Titin phosphorylation	↑
Titin distensibility	↑
Small heat shock protein (e.g. α B-crystallin)	↑
Oxidative stress	↓
Cardiac fibrosis	↓
Sympathetic nerve activity	↓
Neutral metabolic activity	+
Improvement in LV systolic reserve	+
Improvement in LV diastolic filling (E/E')	+
Improvement in QoL	+

AIM HIGHER Trial

Embedded, 2-Part Study Design



Balloon Angioplasty

