Super “PEF”: Understanding EF over 60%

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CHFS HF Update 2022 Meeting

Disclosures

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- Amgen

Advisory Board/Consultant:

- AstraZeneca, Bayer, Bristol Myers Squibb, Boehringer-Ingelheim, Cytokinetics, Janssen, Novartis, NovoNordisk

Objectives

- Definitions of HFpEF
- Lessons from recent clinical trials
- LVEF and outcomes
- Mechanistic differences in supra-normal v normal EF
- Future Directions

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Definitions of HFpEF

- ACC/AHA 2013 Guidelines:
  - Signs and symptoms of HF
  - LVEF ≥ 50%
  - Presence of diastolic dysfunction, but lacks specifics
- ESC 2016

Table 3.1 Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).

Yancy et al. 2013 *Circulation*. 62:e147-239
Ponikowski P, et al. EHJ 2016;37:2129-200.

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2022 Classification of HF by EF

- 2013 ACC/AHA Guidelines for HFpEF classification:
  - Signs and symptoms of HF
  - LVEF ≥ 50%
  - Presence of diastolic dysfunction, but lacks specifics
- 2022 AHA/ACC/HFSA Classification of HF by LVEF:

TABLE 4 Classification of HF by LVEF

Type of HF According to LVEF	Criteria
HFrEF (HF with reduced EF)	■ LVEF ≤40%
HFimpEF (HF with improved EF)	■ Previous LVEF ≤40% and a follow-up measurement of LVEF >40%
HFmrEF (HF with mildly reduced EF)	■ LVEF 41%–49% ■ Evidence of spontaneous or provokable increased LV filling pressures (e.g., elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)
HFpEF (HF with preserved EF)	■ LVEF ≥50% ■ Evidence of spontaneous or provokable increased LV filling pressures (e.g., elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)

Please see Appendix 3 for suggested thresholds for structural heart disease and evidence of increased filling pressures.
HF indicates heart failure; LV, left ventricular; and LVEF, left ventricular ejection fraction.

Yancy et al. 2013 *Circulation*. 62:e147-239
Paul A. Heidenreich et al. *J Am Coll Cardiol* 2022; 79:e263-e421.

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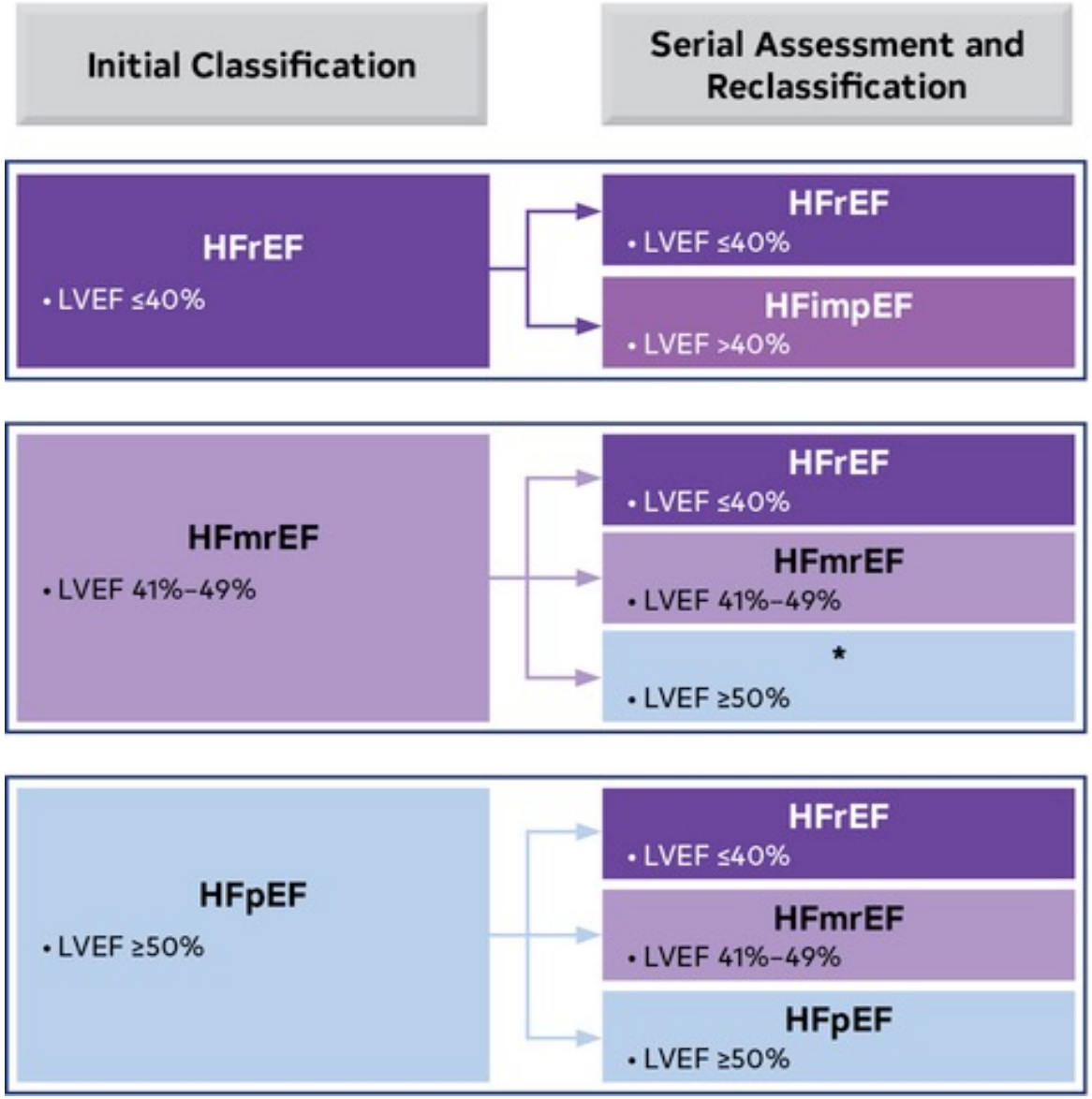

Paul A. Heidenreich et al. *J Am Coll Cardiol* 2022; 79:e263-e421.

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HFpEF Phenotyping Approaches

- Co-morbidities
  - Hypertensive, CAD, PH, CKD, obesity
- Clinical Presentation
  - Congestion, chronotropic incompetence, skeletal muscle weakness, AFib
- Hemodynamics
  - PH, RV failure
- Biomarkers
  - NTproBNP, inflammation, fibrosis
- Tissue/biological based phenotyping

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In 1985… HFpEF-HTN

HYPERTENSIVE HYPERTROPHIC CARDIOMYOPATHY OF THE ELDERLY

ERIC J. TOPOL, M.D., THOMAS A. TRAILL, M.R.C.P., AND NICHOLAS J. FORTUIN, M.D.

Abstract Using echocardiography, we identified 21 patients with a syndrome that included severe concentric cardiac hypertrophy, a small left ventricular cavity, and supernormal indexes of systolic function without concurrent medical illness or ischemic heart disease. Thirteen of the patients presented with dyspnea or chest pain. All patients studied had a history of hypertension and were compared with normotensive controls matched for age and sex. The patients were elderly (mean age, 73.3 years), predominantly female (16 patients), and mostly black (15 patients). Their cardiac function was characterized by excessive left ventricular emptying (ejection fraction on two-dimensional echocardiography [patients vs. controls], 79±4 vs. 59±5 per cent, $P<0.001$) and abnormal diastolic function as manifested by a prolonged early diastolic filling period (279±25 vs. 160±45 msec, $P<0.001$) and reduced peak diastolic dimension increase (11±4 vs. 16±5 cm per second, $P<0.05$). In spite of the clinical presentation of heart failure, all of 9 patients receiving either beta-receptor antagonists or calcium-channel blocking agents obtained symptomatic relief, whereas 6 of 12 patients receiving vasodilator medications had severe hypotensive reactions, including one death. We conclude that this unique subset of hypertensive patients has a clinical syndrome that warrants recognition and tailored management. (N Engl J Med 1985; 312:277-83.)

Topol E. NEJM 1985;321:27-283

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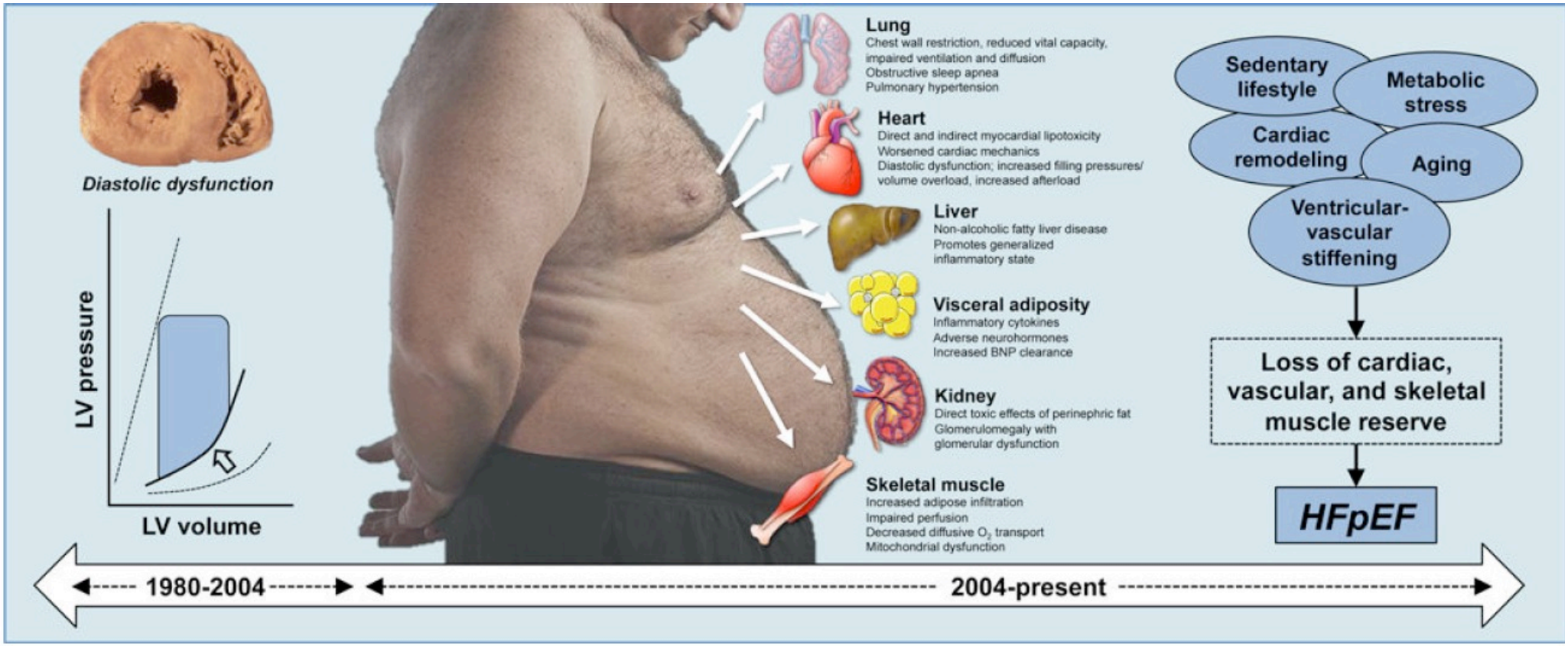
Evolving Phenotype of HFpEF



Shah S. J CV Translational Res. 2017;10(3): 233–244 .

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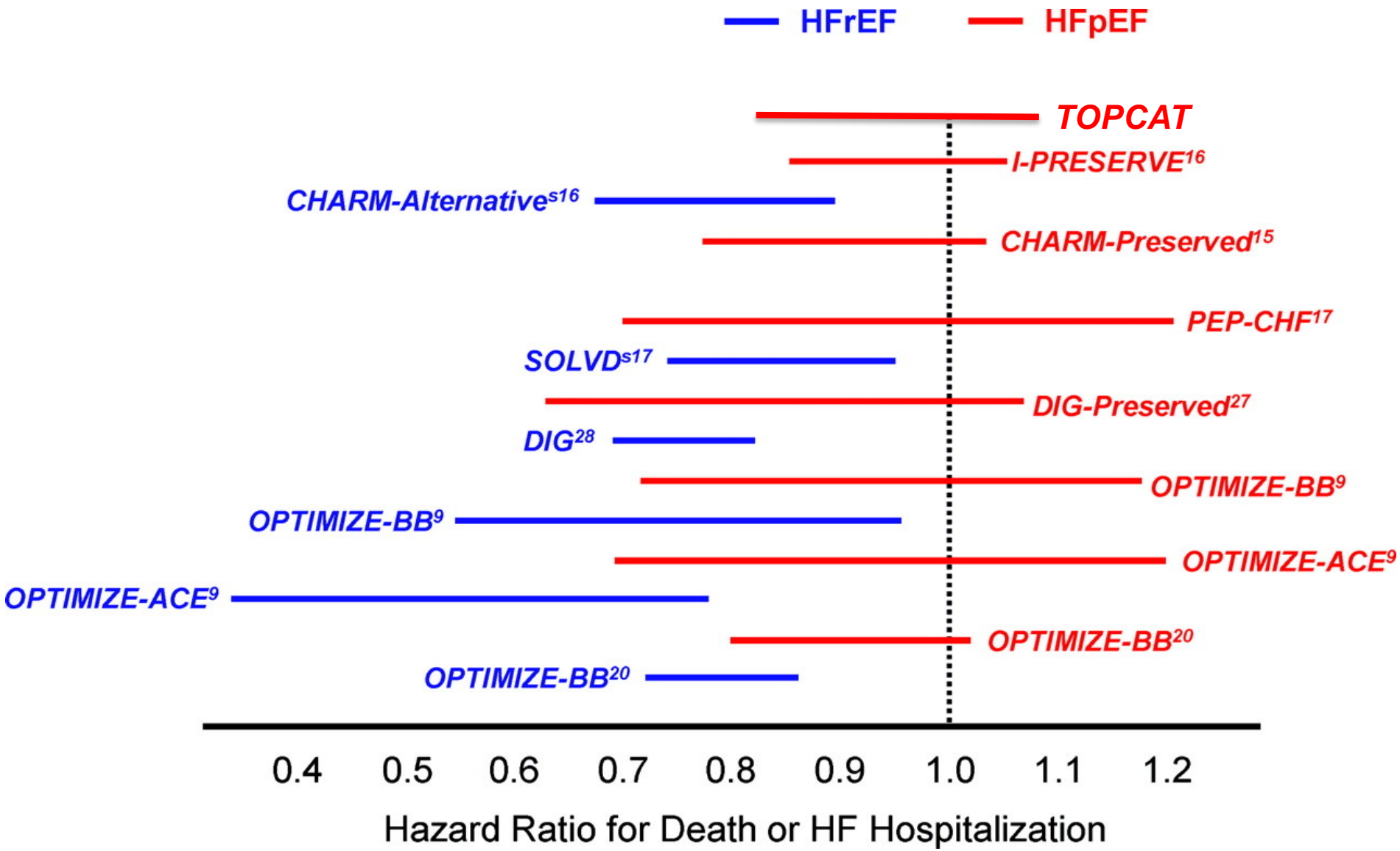
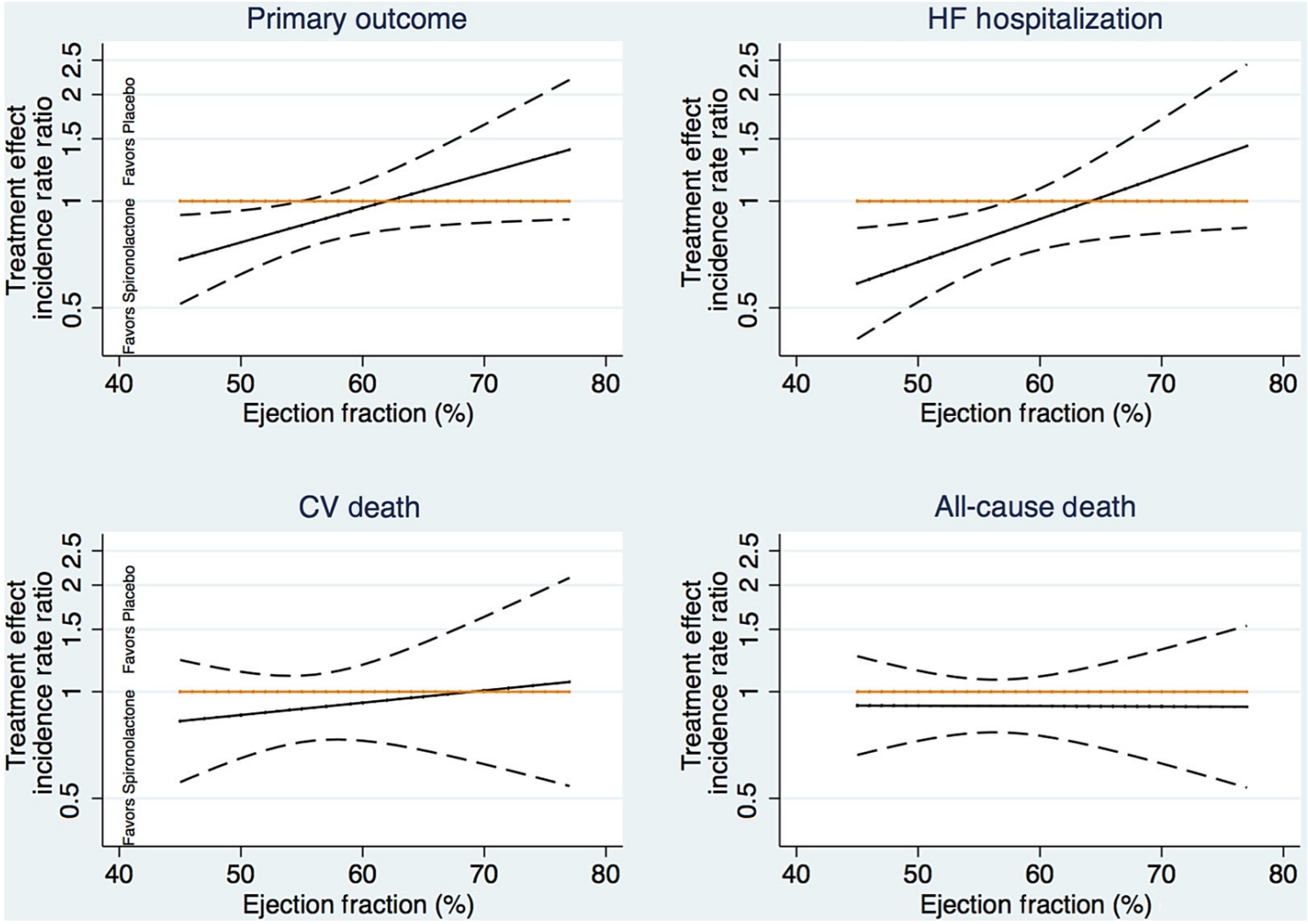
Treatments Trials Until Recently…



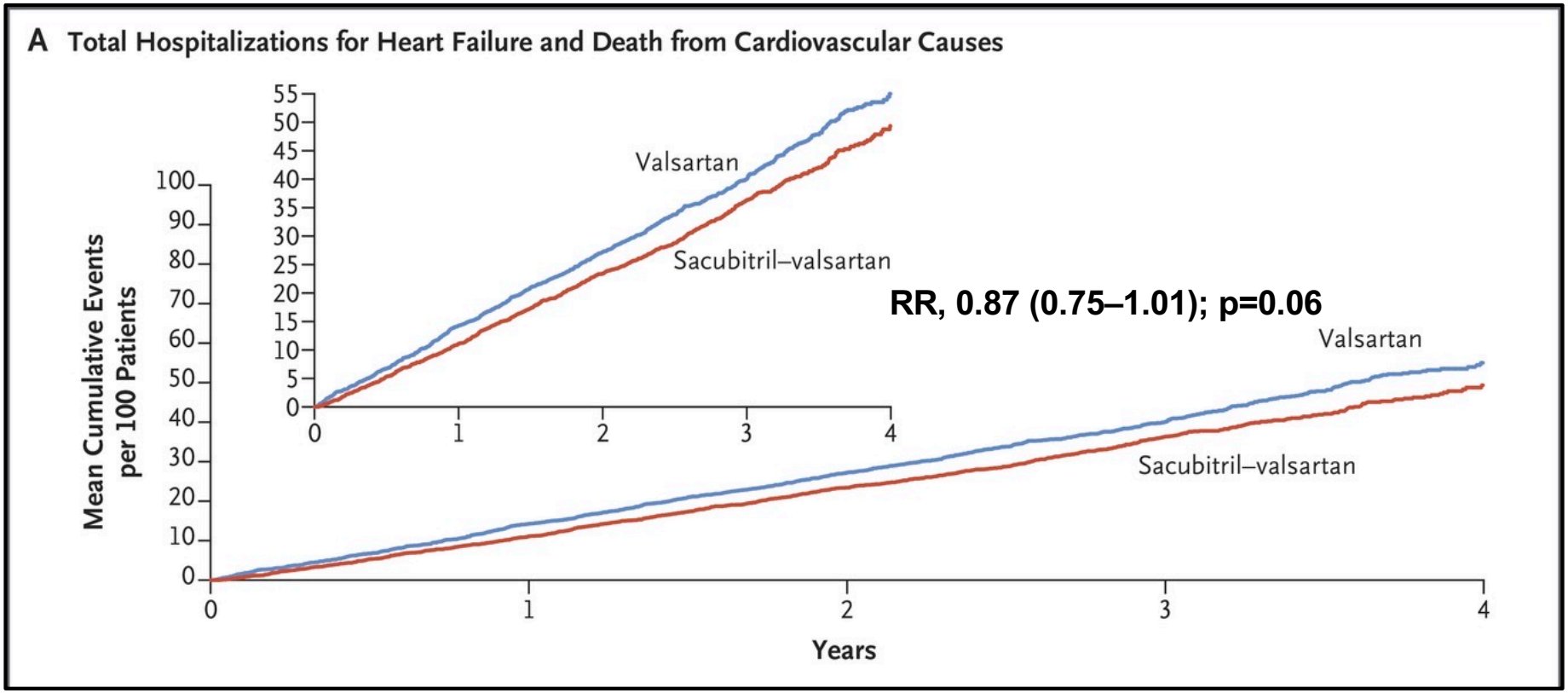
Adapted from Borlaug B, Redfield M. Circ 2011;123:2006-13

TOPCAT: Treatment Effect by EF



Solomon SD et al. Eur Heart J. 2016(37)5:455–462

PARAGON-HF Study



- Sacubitril-valsartan v. valsartan; LVEF > 45%
- At median follow up of 35 months, no statistically significant between-group difference in the composite outcome of total hospitalizations for heart failure or death from cardiovascular causes.

Solomon SD, et al. NEJM 2019; 381:1609-20.

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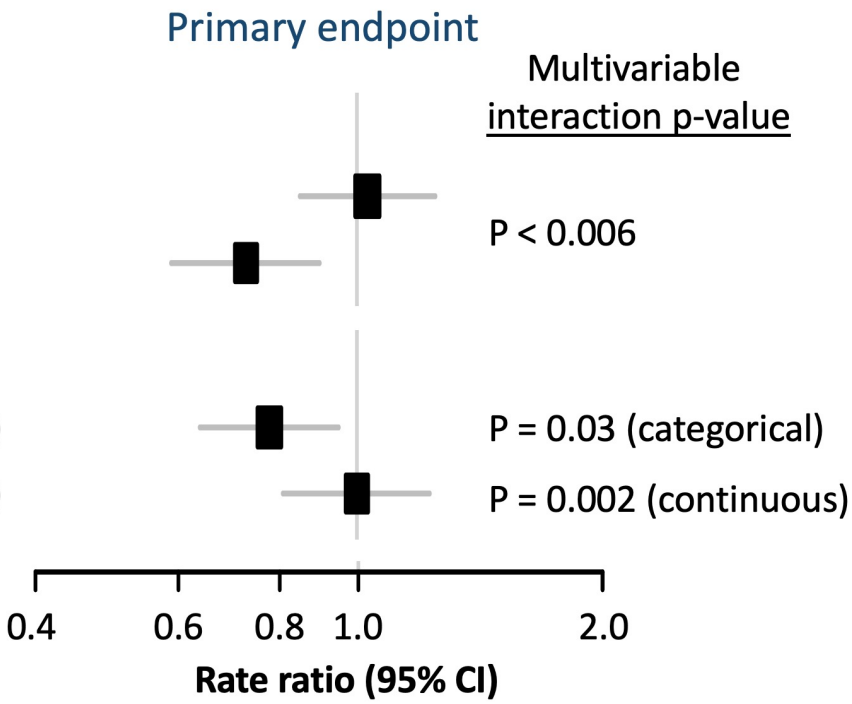
PARAGON-HF Study

Subgroup	No. of events/ patients	Rate ratio (95% CI)
Sex		
Male	980/2317	1.03 (0.85–1.25)
Female	923/2479	0.73 (0.59–0.90)
LVEF		
at or below median (57%)	1048/2495	0.78 (0.64–0.95)
above median (57%)	855/2301	1.00 (0.81–1.23)



Potential ARNI responders:

- LVEF< 55-60%
- Already on MRA treatment
- May work better in women than men

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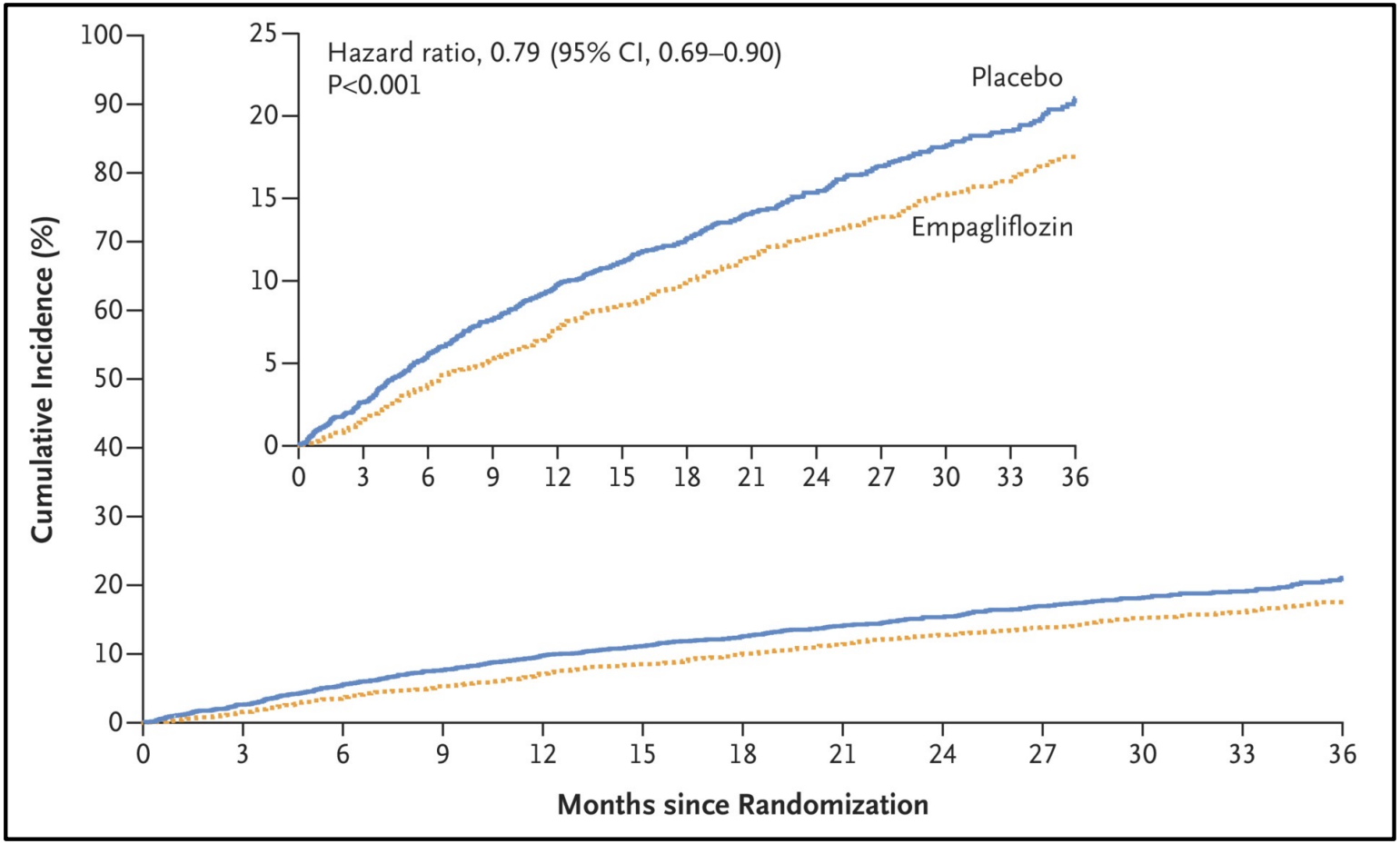
Solomon SD, et al. NEJM 2019; 381:1609-20.

EMPEROR-Preserved

- N=5988
- Empagliflozin vs. placebo
- HF with LVEF > 40%
- 67% with LVEF ≥ 50%
- Primary outcome driven by HF hospitalizations



Anker et al; N Engl J Med 2021; 385:1451-1461

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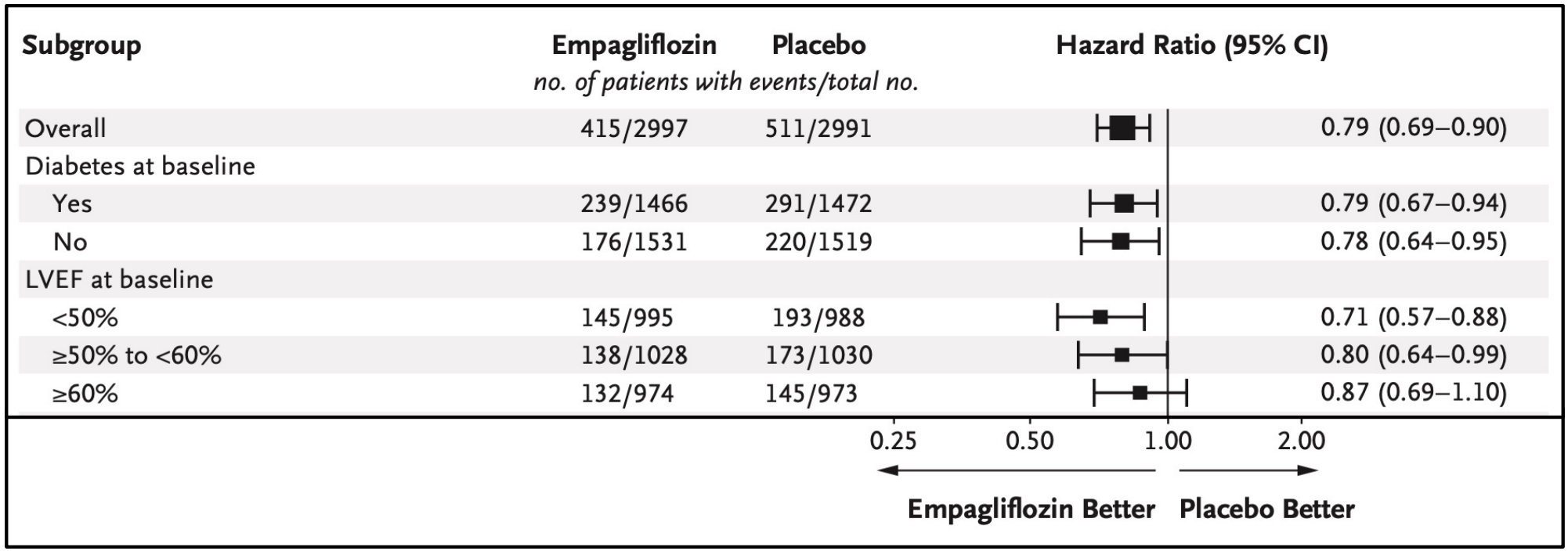
EMPEROR-Preserved



Consistent results across diabetes status and lower LVEF at baseline (interaction p value > 0.10)

Anker et al; N Engl J Med 2021; 385:1451-1461

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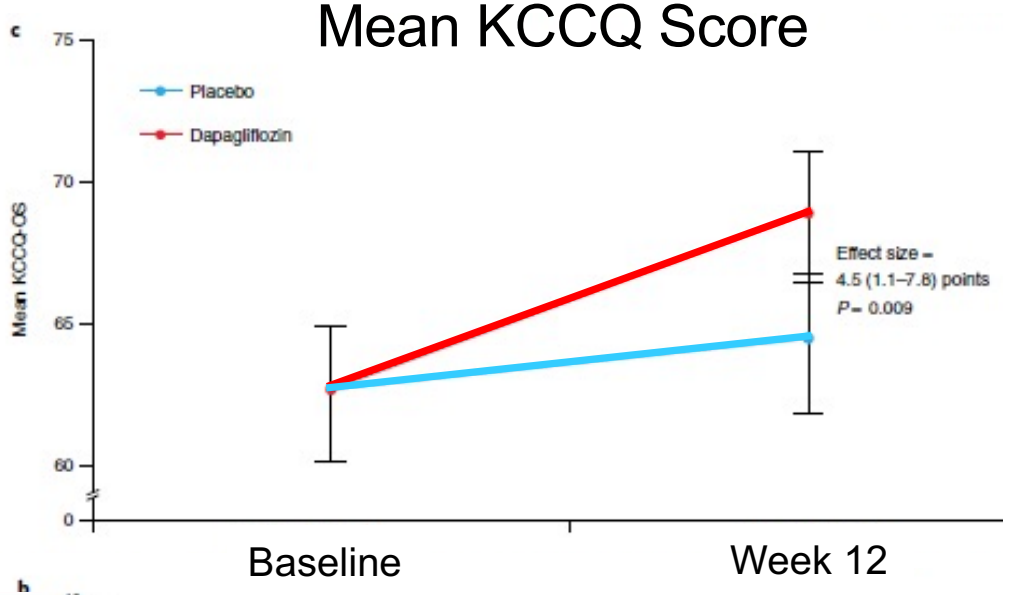
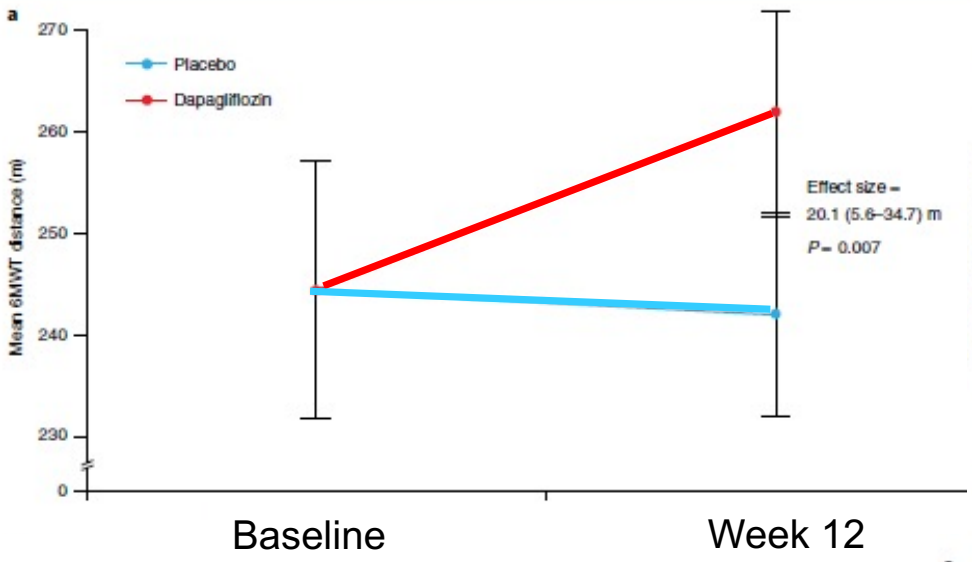
PRESERVED-HF Results

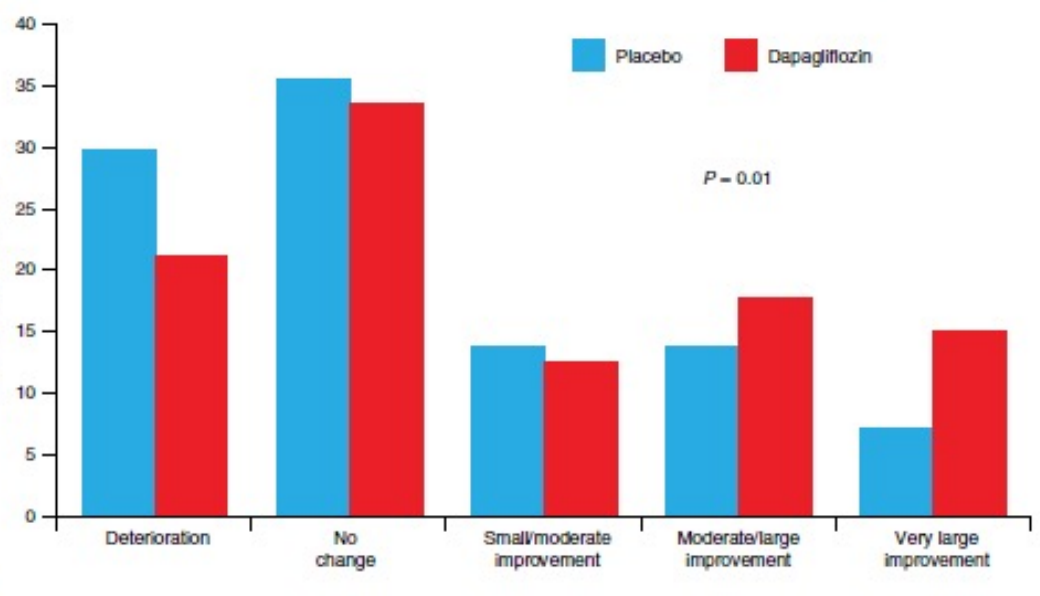
- N=324
- Dapagliflozin vs. placebo
- HF with LVEF ≥ 45%
- +5.8-point improvement in KCCQ vs. placebo

Mean KCCQ Score



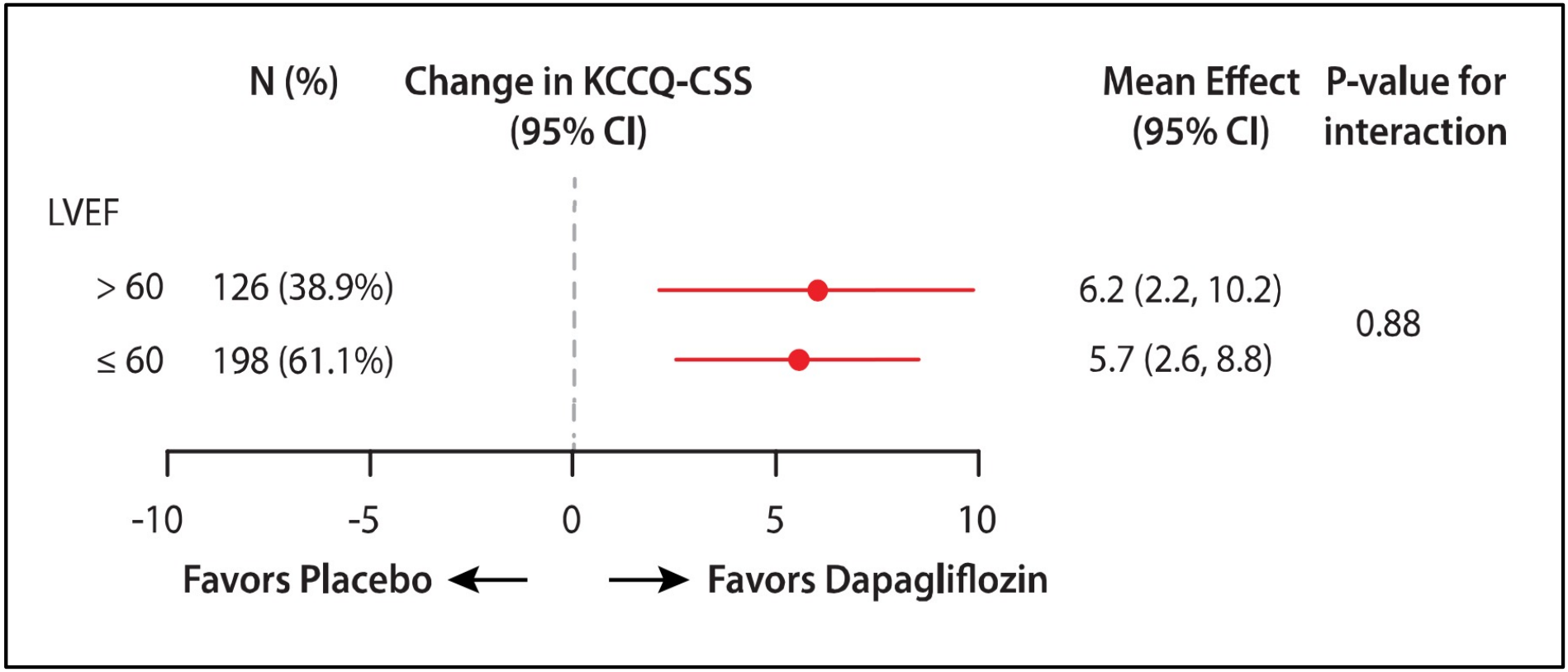
Mean 6MWT





Nassif ME et al. Nature Medicine 2021

PRESERVED-HF Results



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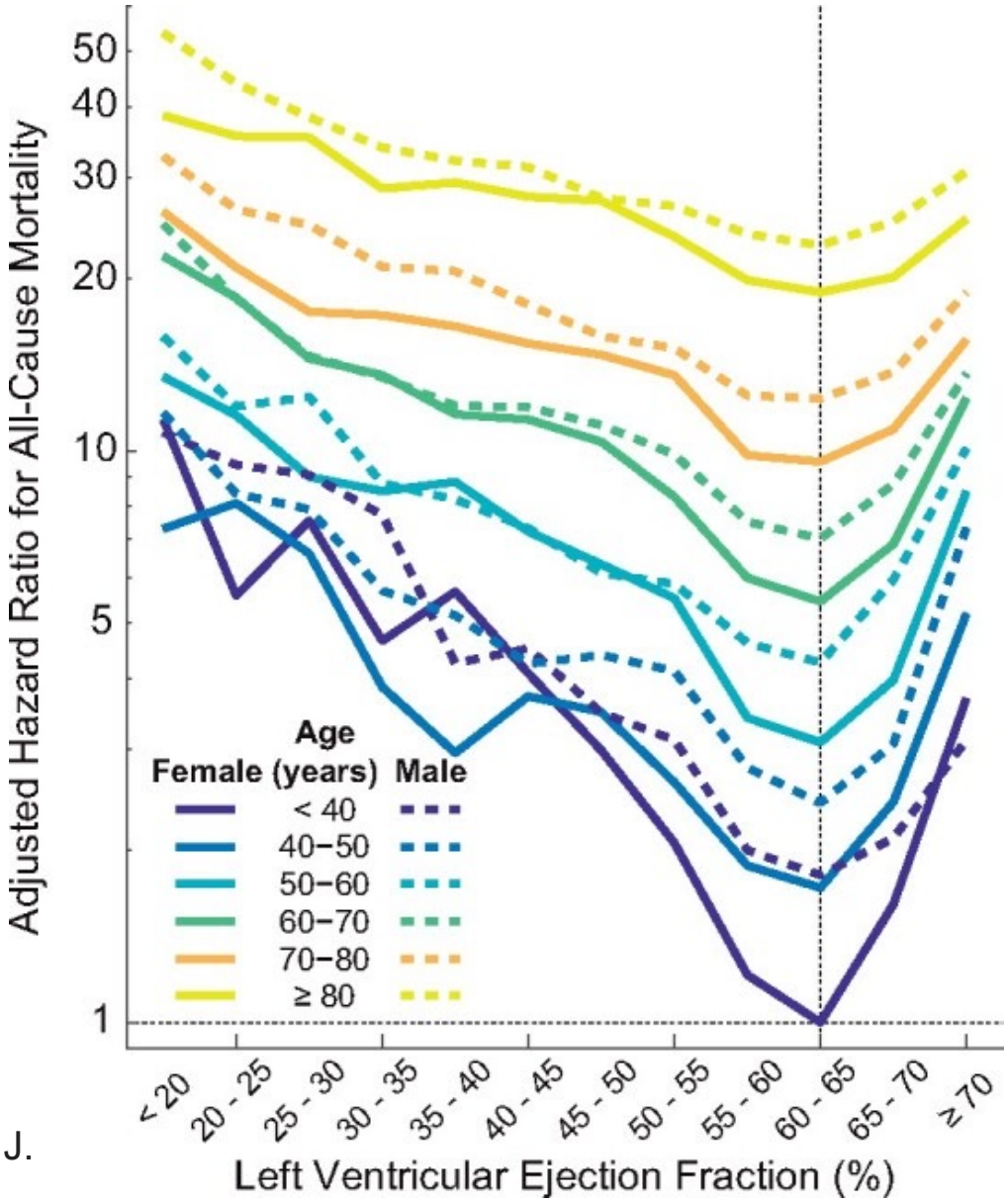
Nassif ME et al. Nature Medicine 2021

LVEF and Mortality – where does the nadir lie?



Wehner GJ, et al. Eur Heart J. 2020;41(12):1249-1257.

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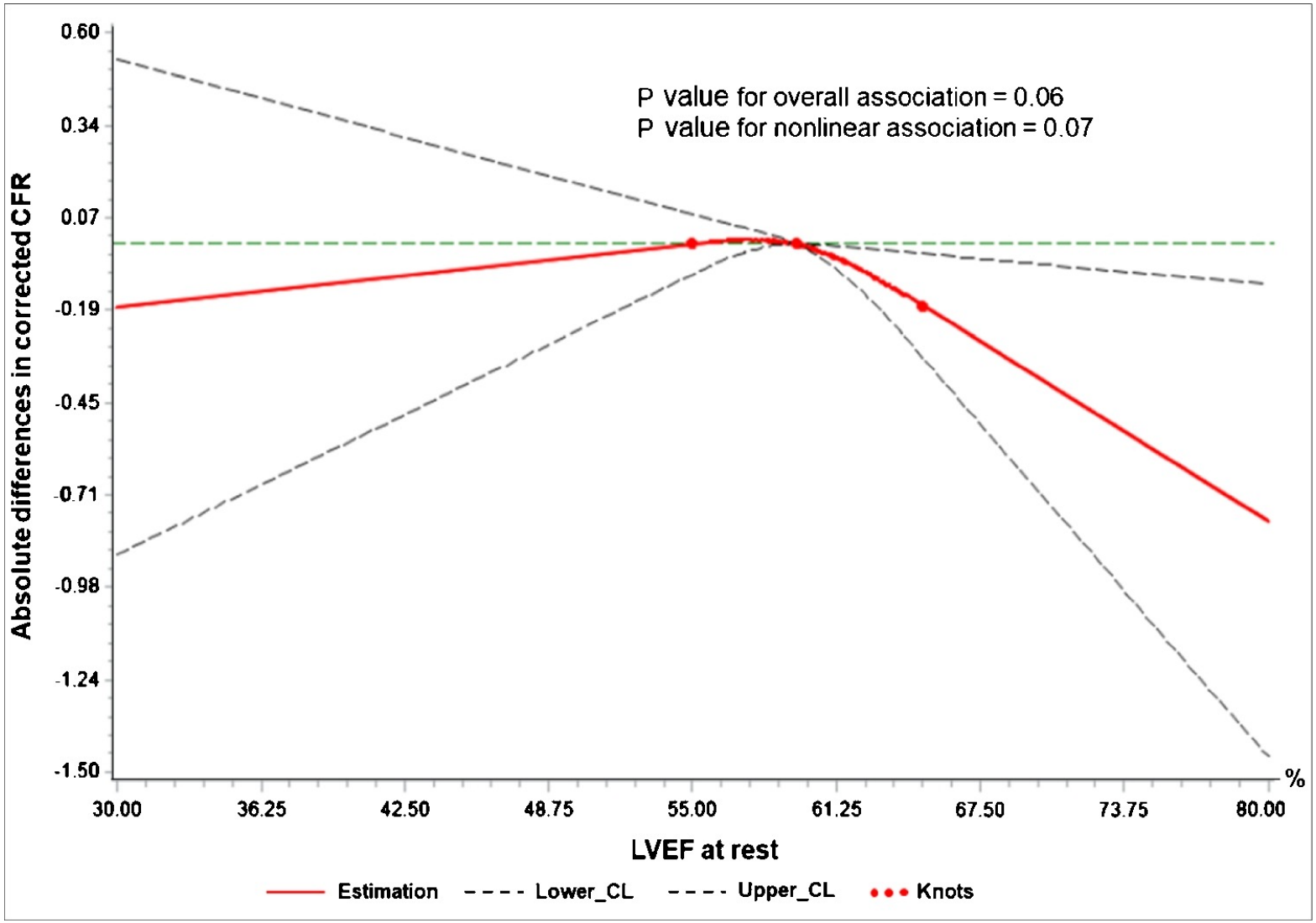
Coronary flow reserve in supra-normal EF



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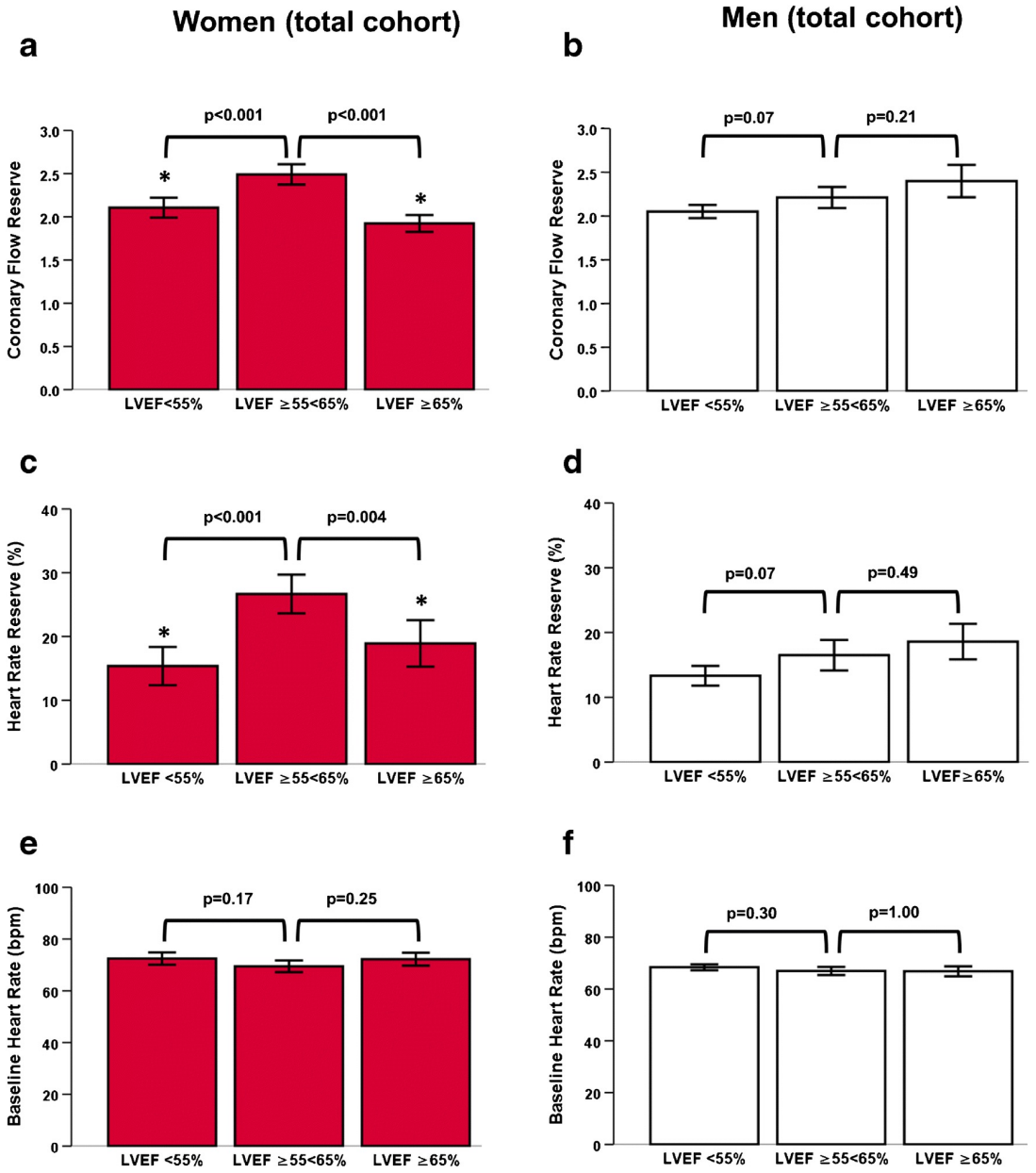
Wu P, et al. Eur J Nucl Med Mol Imaging. 2022. PMID: 34988625.

Microvascular dysfunction and sympathetic activity in supra-normal EF



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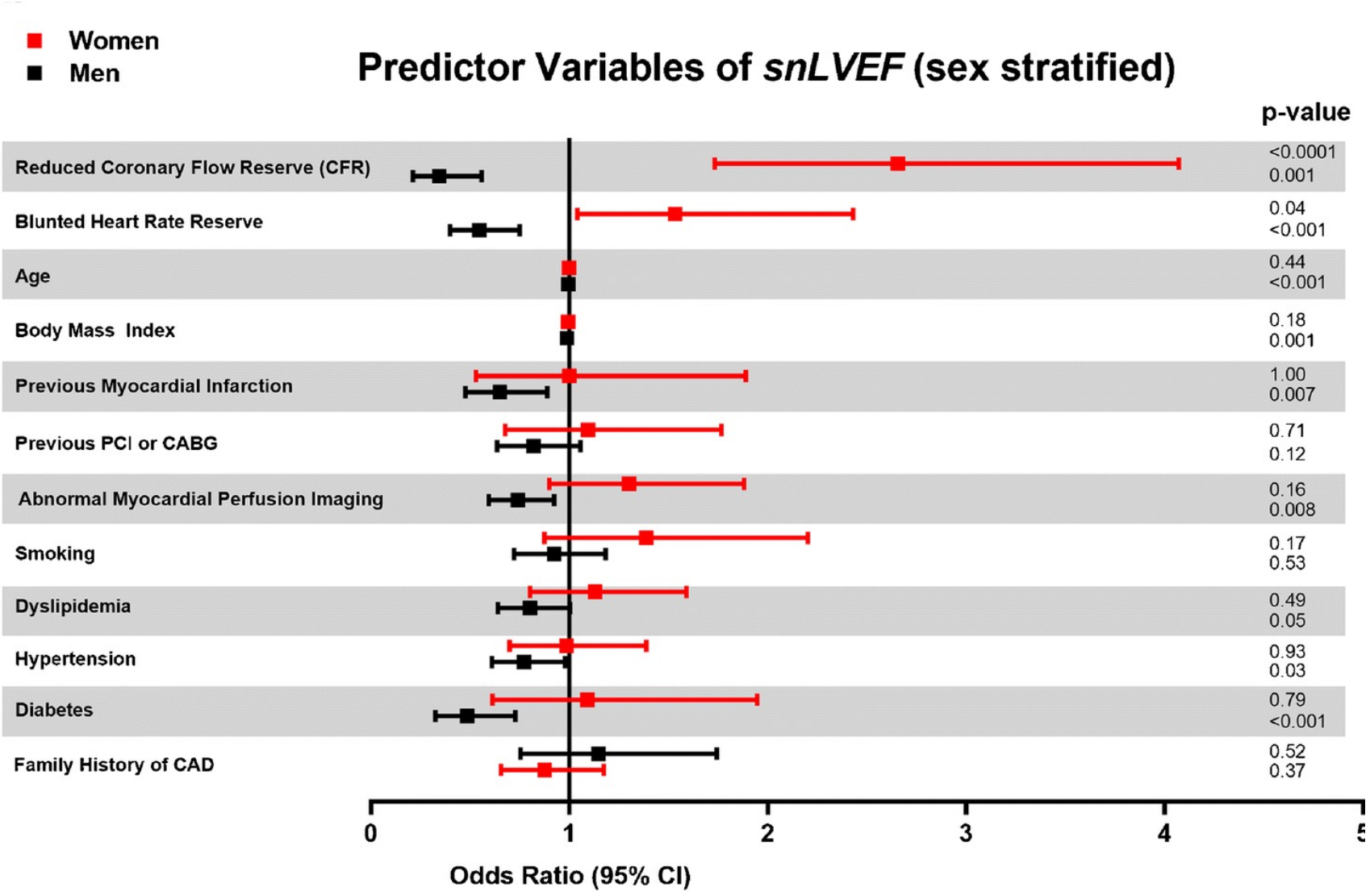
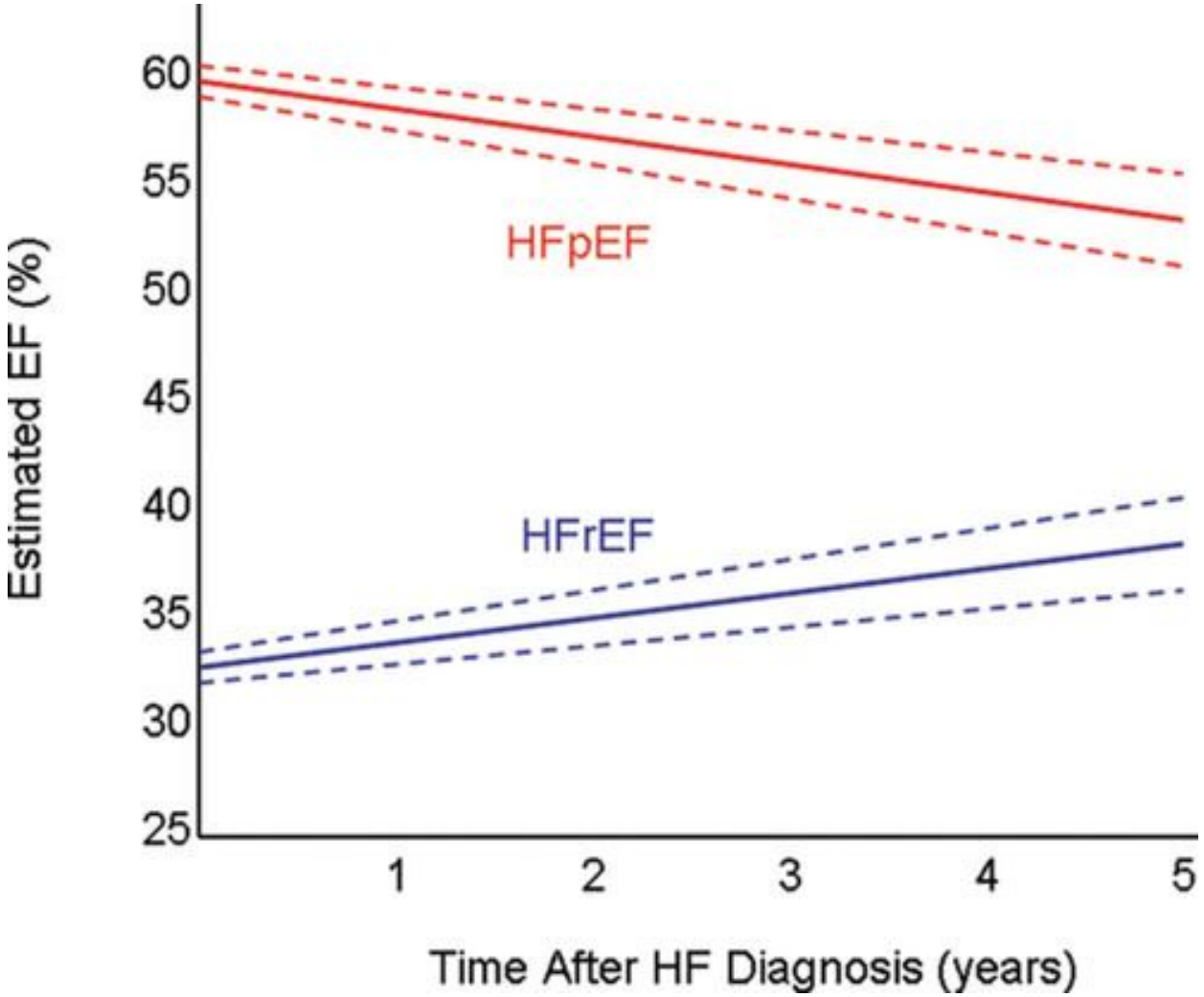

Women
Men
Predictor Variables of snLVEF (sex stratified)
p-value
Reduced Coronary Flow Reserve (CFR)
<0.0001
0.001
Blunted Heart Rate Reserve
0.04
<0.001
Age
0.44
<0.001
Body Mass Index
0.18
0.001
Previous Myocardial Infarction
1.00
0.007
Previous PCI or CABG
0.71
0.12
Abnormal Myocardial Perfusion Imaging
0.16
0.008
Smoking
0.17
0.53
Dyslipidemia
0.49
0.05
Hypertension
0.93
0.03
Diabetes
0.79
<0.001
Family History of CAD
0.52
0.37
0
1
2
3
4
5
Odds Ratio (95% CI)

EF changes over time…



SM Dunlay et al. 2012 Circulation: Heart Failure. 2012:5(6): 720-726.

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Summary

- Patients with supra-normal EF appear to have worse outcomes than LVEF 50-60% patients.
- There appears to be a differential response to HF therapies in those with LVEF > 60% versus 50-60% for some therapies (MRA, ARNI).
- There may be mechanistic differences in supra-normal EF versus normal EF patients related to coronary reserve and microvascular disease.
- Further study is needed to better understand supra-normal EF, mechanistic underpinnings, and therapies this group responds to compared to other groups of HF.

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THANK YOU!

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