Contemporary Management of HFpEF

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Patient Case

This is a 65-year old lady who presented to the ER with increasing dyspnea and easy fatigability after 8 to 10-meter of level walking. She reported PNDs and occasional orthopnea. Denies chest pain, palpitations, dizziness or syncope.

Risk factors: current 40-pack years of cigarette smoking, HTN, uncontrolled DM, obesity, and dyslipidemia.

Past Medical History: Triple vessel CABG 10 years ago.

Patient Case

Medications: ASA, Atorvastatin, HCTZ, Spironolactone, Bisoprolol, Lisinopril, Insulin, and Metformin.

Pertinent PE: Obese, comfortable at rest, elevated JVP, regular rhythm, rate of 84 bpm, no murmurs, crackles on both bases, 1+ pitting edema.

Investigations: Serum creatinine 1.2 mg/dl, NT-ProBNP of 1480 pg/ml.
ECG showed NSR with voltage criteria for LVH.
Echocardiogram showed biatrial enlargement, eccentric LVH with LVEF of 52%, grade 2 diastolic dysfunction, and mild pulmonary hypertension.

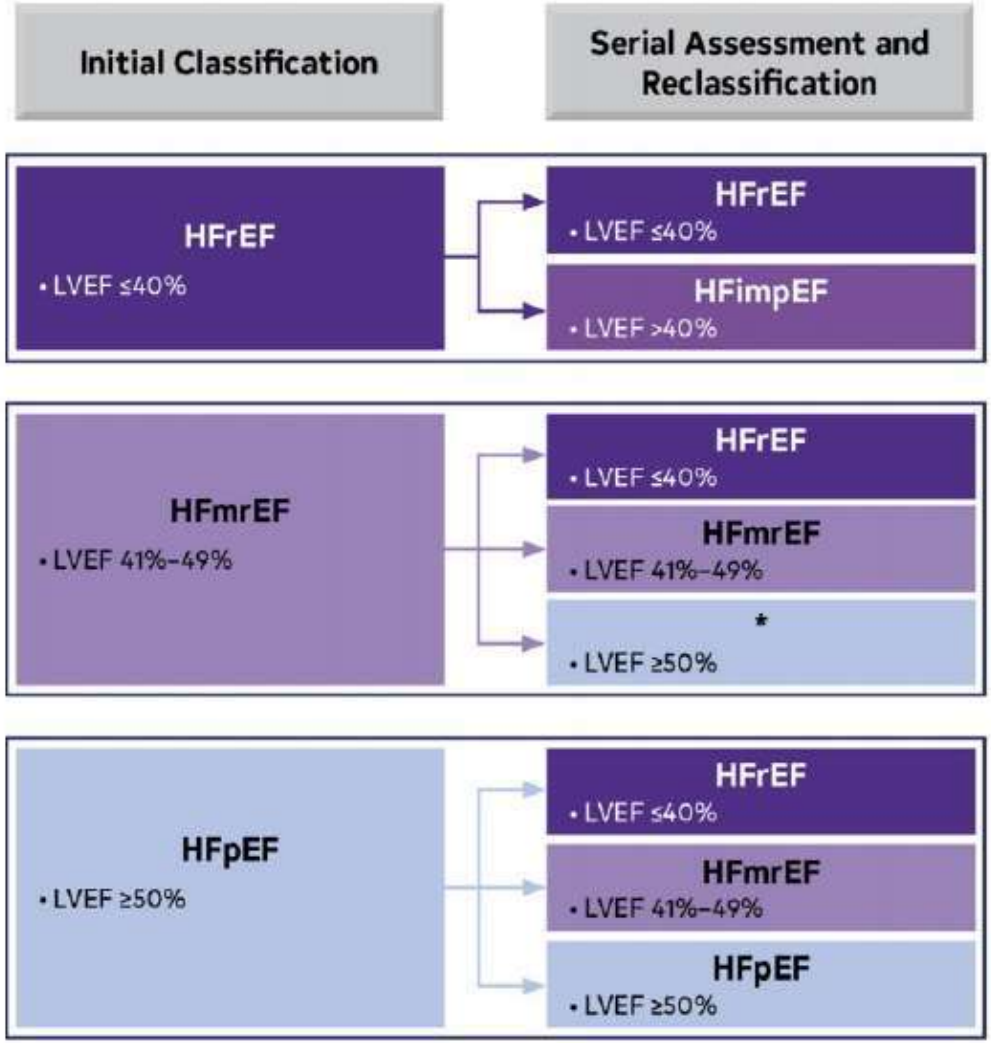
Historic Variability in Definition

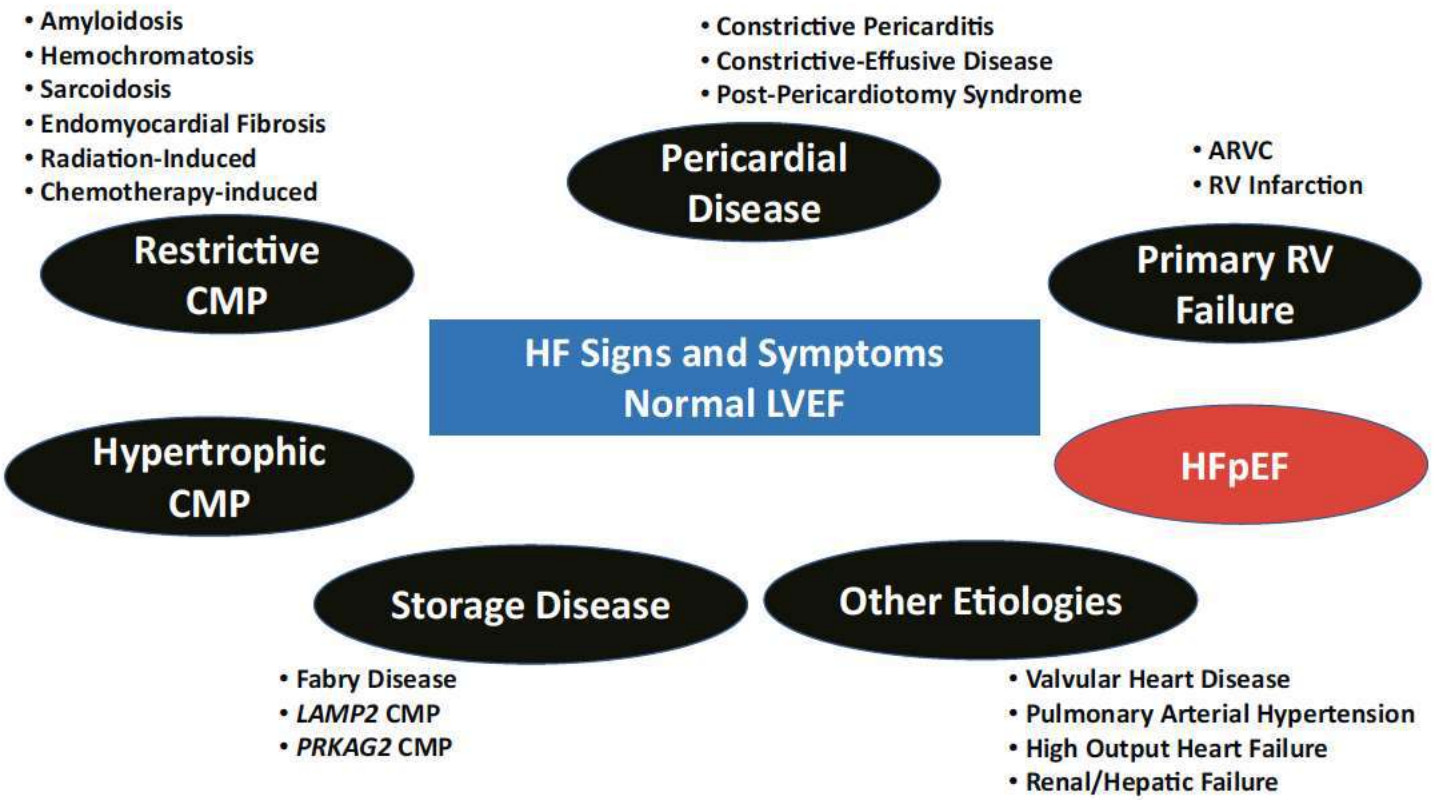
Trial Name	Age, NYHA functional Class	LVEF (%)	Natriuretic Peptides	HF Hospitalization
TOPCAT [99]	Age ≥50 years NYHA functional class II-IV	LVEF ≥45%	BNP ≥100 pg/mL or NT-proBNP ≥360 pg/mL	Within previous 12 months, with management of HF a major component
PARAGON-HF [100]	Age≥50 years NYHA functional class II-IV	LVEF ≥45% and LAE LVH	If NSR, NT-proBNP >200 pg/mL If AF: >600 pg/mL Or if no previous hospitalization and If NSR: NT-proBNP >300 pg/mL, if AF: NT-proBNP >900 pg/mL	Within previous 9 months
EMPEROR-Preserved [106]	Age≥18 years NYHA functional class II-IV (≥3 months)	LVEF >40% (no prior history of LVEF ≤40%)	NT-proBNP >300 pg/mL in NSR or >900 pg/mL in AF	Within 12 months OR evidence of structural changes (LAE or increased LVM) on echo
DELIVER [107]	Age≥40 years NYHA functional class II-IV	(LVEF >40% and evidence of structural heart disease (ie, LAE or LVH)	Elevated natriuretic peptides	Medical history of HF ≥6 weeks before enrolment with at least intermittent need for diuretic treatment

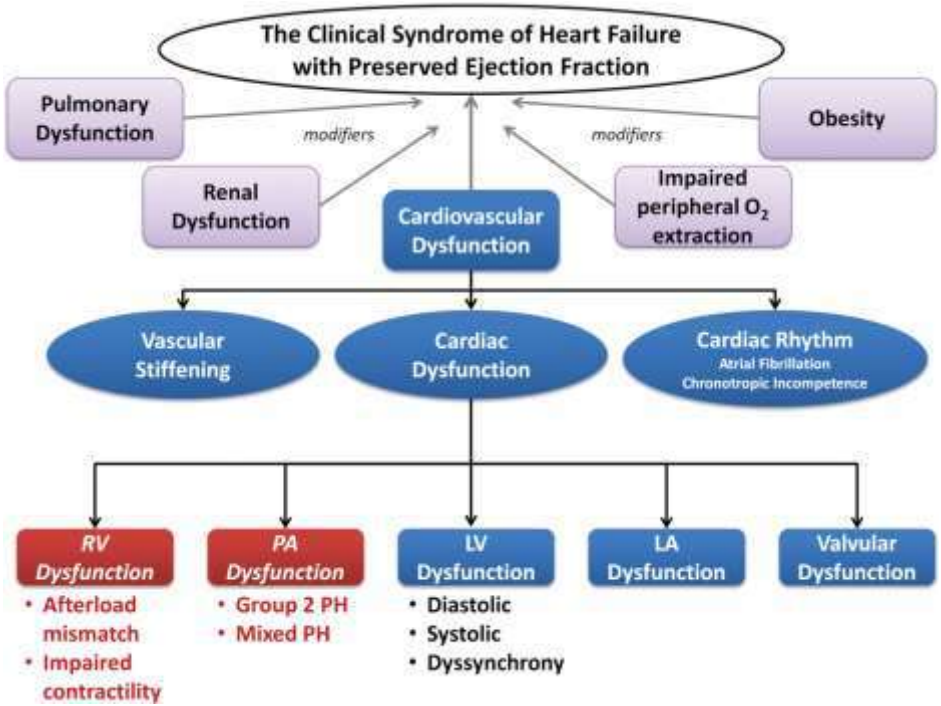
Bozkurt B, et al. JCF 2021; 27 (4)

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines



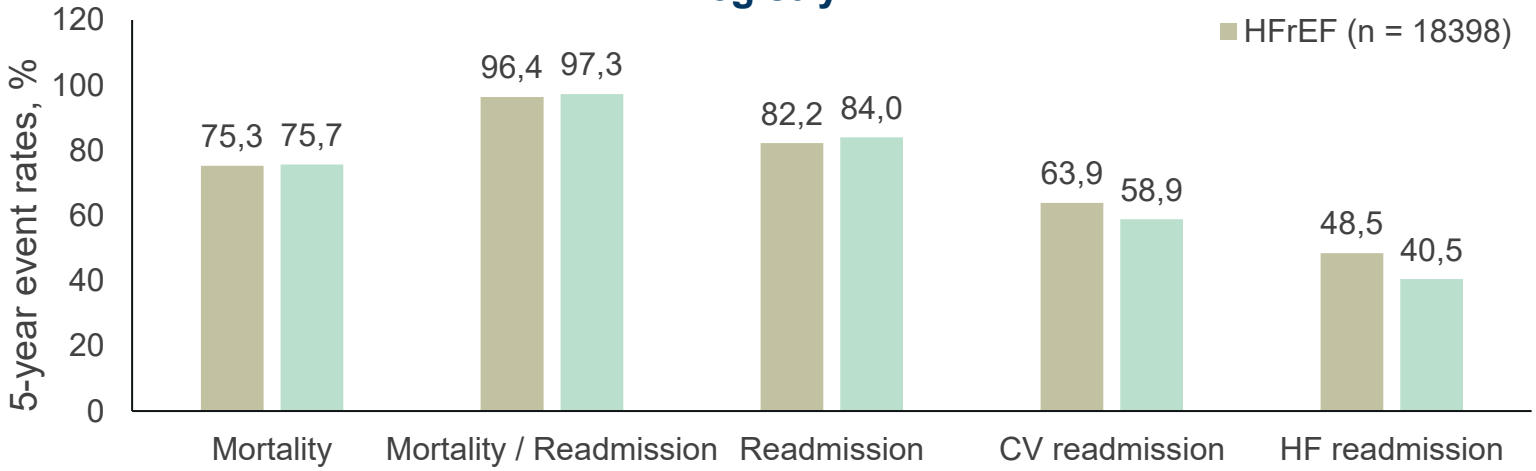

• Amyloidosis
• Hemochromatosis
• Sarcoidosis
• Endomyocardial Fibrosis
• Radiation-Induced
• Chemotherapy-induced
Restrictive CMP
• Constrictive Pericarditis
• Constrictive-Effusive Disease
• Post-Pericardiotomy Syndrome
Pericardial Disease
• ARVC
• RV Infarction
Primary RV Failure
HF Signs and Symptoms
Normal LVEF
Hypertrophic CMP
HFpEF
Storage Disease
• Fabry Disease
• LAMP2 CMP
• PRKAG2 CMP
Other Etiologies
• Valvular Heart Disease
• Pulmonary Arterial Hypertension
• High Output Heart Failure
• Renal/Hepatic Failure



European Heart Journal, Volume 35, Issue 48, 21 December 2014, Pages 3410–3412, https://doi.org/10.1093/eurheartj/ehu212

Mortality and Readmission Rates are Similarly High in HFrEF and HFpEF Following Hospitalization for HF

Five-year outcomes in patients hospitalized with HF in the GWTG-HF Registry*



In a separate analysis, patients with HFmrEF (LVEF 41%-49%) make up 8%-12% of all patients with HF, and have a similar mortality rate to those with HFrEF and HFpEF.[1,2]

CV, cardiovascular; GWTG-HF, Get With the Guidelines–Heart Failure; HF, heart failure; HFmrEF, HF with mid-range ejection fraction; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; LVEF, left ventricular ejection fraction.

*Data from 39,982 patients aged ≥65 years with HF hospitalizations in the GWTG-HF registry, of whom 45.8% had HFpEF and 46.0% had HFrEF. GWTG-HF registry data were combined with US Centers for Medicare and Medicaid Services claims made between January 1, 2005, and December 30, 2009, with 5 years of follow-up through December 2014.

1. Shah KS et al. *J Am Coll Cardiol*. 2017;70(20):2476–2486; 2. Kumar V et al. *J Card Fail*. 2023;29(2):124-134.

Neurohormonal blockades for HFpEF

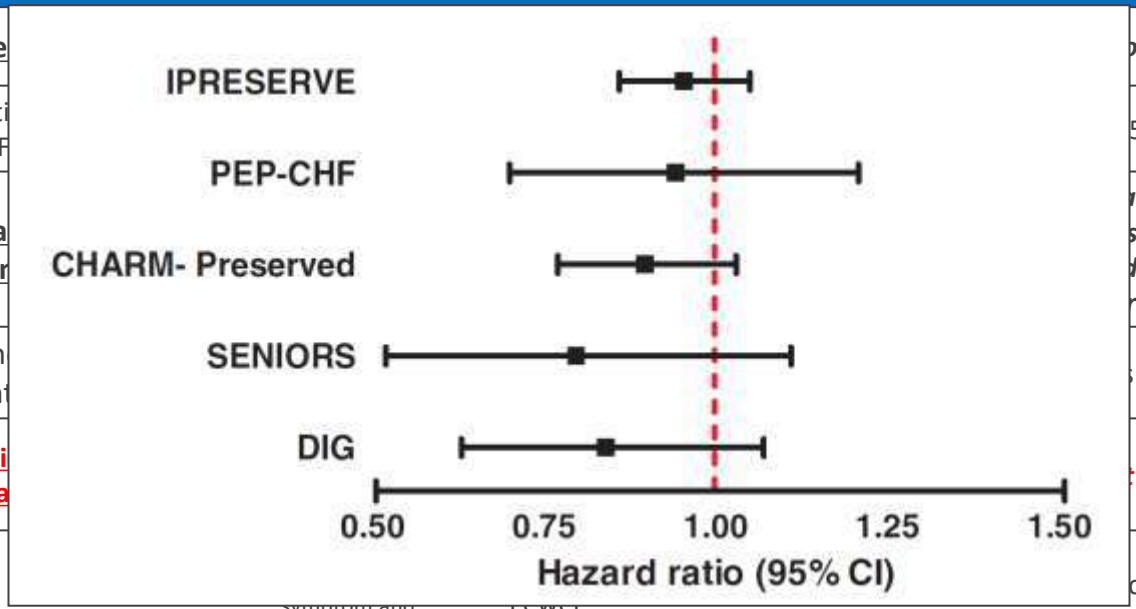
- Digoxin, ACEI, ARBs, BB and spironolactone were tested

	DIG	PEP-CHF	CHARM-Preserved	I-Preserve	SENIORS	TOPCAT
Treatment	***Digoxin***	***Perindopril***	***Candesartan***	***Irbesartan***	***Nebivolol***	***Spironolactone***
Definition (LVEF)	>45%	40-50%	>40%	≥45%	≥35%,	≥45%,
Primary outcome	***HF admission + HF mortality***	***all-cause mortality + HF admission***	***CV death + HF admission***	***All-cause mortality + CV admission***	***All-cause mortality + CV admission***	***CV death + HF admission + aborted cardiac arrest***
Treatment vs. control	21 vs. 24%	HR 0.692	HR 0.86	HR 0.95	HR 0.81	18.6 vs. 20.4%
Statistical significance	***Not sig.***	***Not sig.***	***Not sig.***	***Not sig.***	***Not sig.***	***Not sig.***
		Improved symptom and fewer hospitalization	Fewer hospitalization			Interaction in subgroup analysis

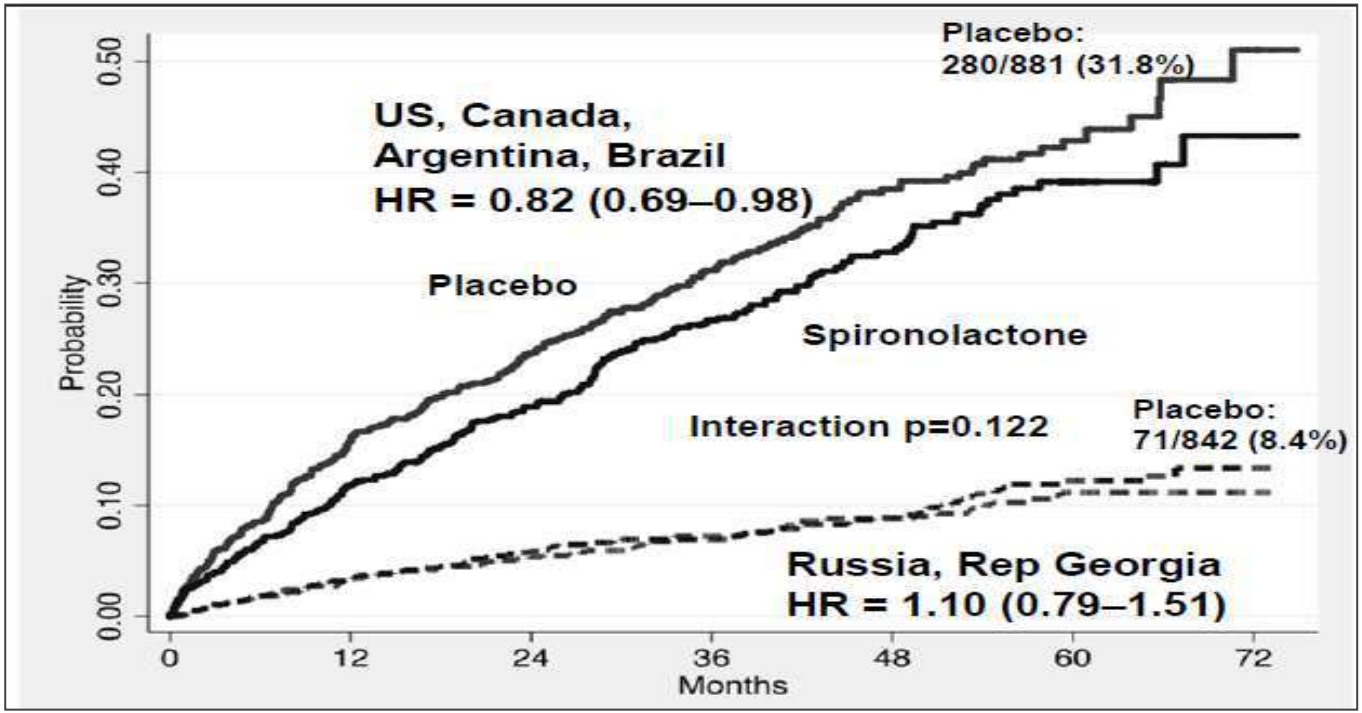
Neurohormonal blockades for HFpEF

- No significant benefit observed from six large HFpEF clinical trials

	DIG	PEP-CHF	CHARM-Preserved	I-Preserve	SENIORS	TOPCAT
Treatme						*olactone*
Definiti (LVEF						5%,
Prima outcor						*th + HF ssion + l cardiac rest*
Treatm vs. cont						. 20.4%
Statisti significa						*t sig.*
		symptom and fewer hospitalization	Fewer hospitalization			ction in subgroup analysis



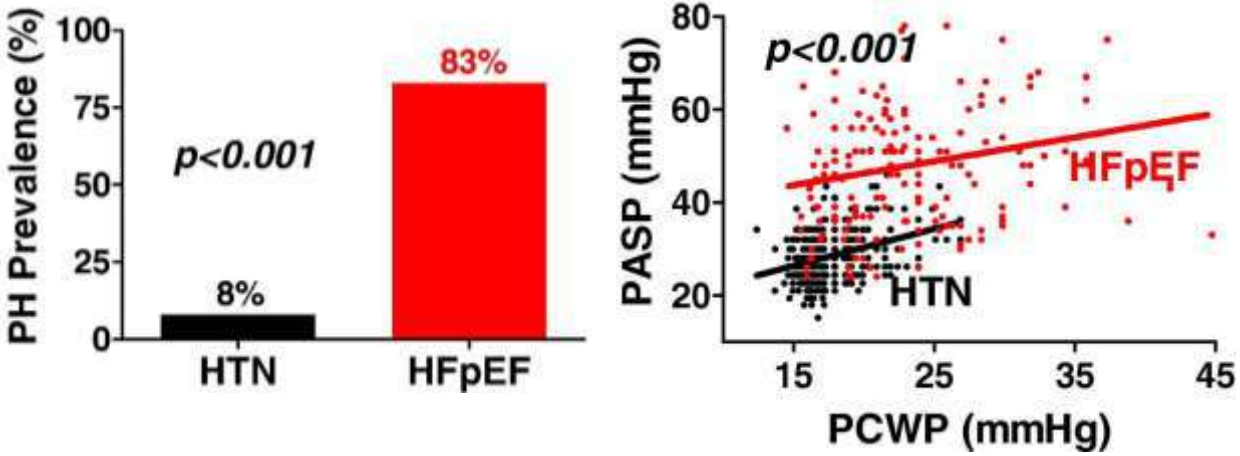
Spironolactone for Heart Failure with Preserved Ejection Fraction (TOPCAT Trial)



Pfeffer MA. Circulation 2015;131:34-42.

PH and RV dysfunction in HFpEF

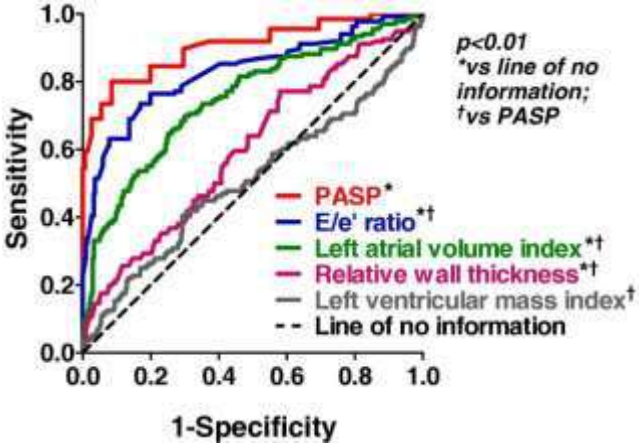
- PH is **highly prevalent** and often **severe** in HFpEF
- Pulmonary venous HTN does not fully account for PH severity, suggesting that **a component of PAH** also contributes to PH in HFpEF
- The PASP **distinguishes HFpEF from HTN** with better diagnostic performance than other parameters.

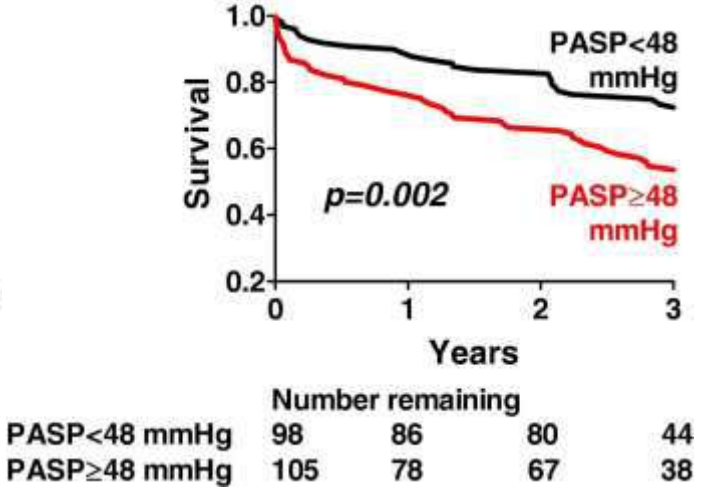


Lam CS et al. J Am Coll Cardiol 2009

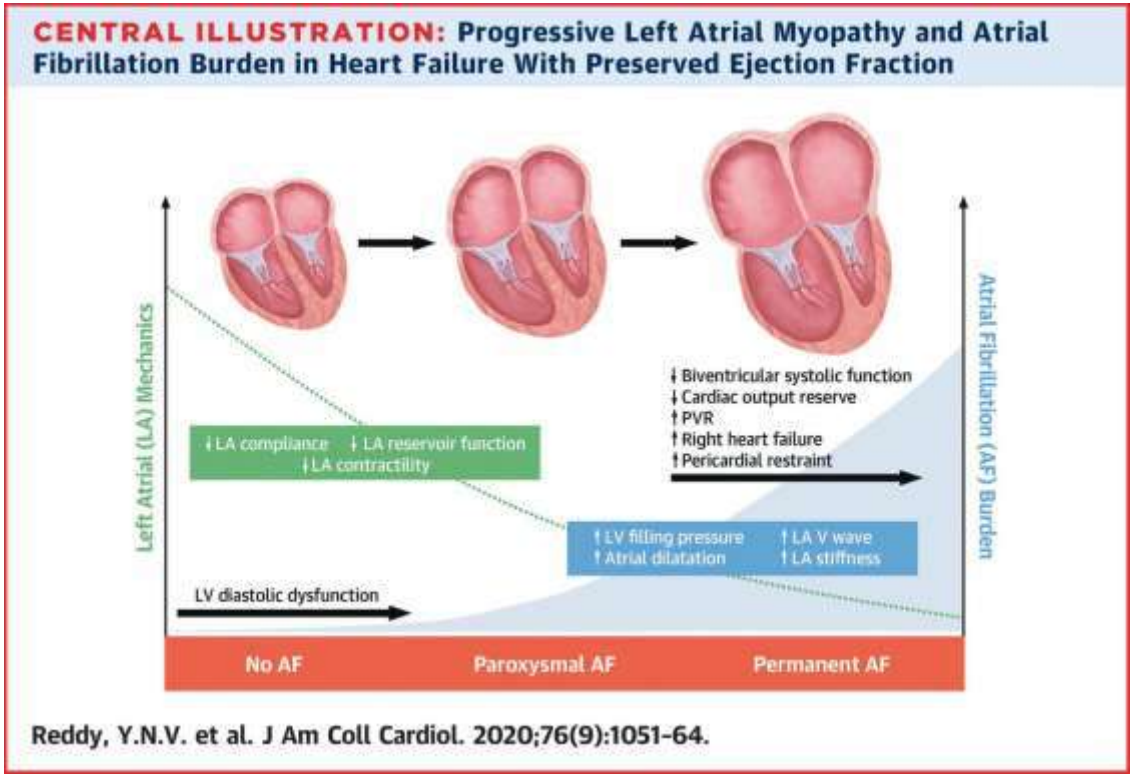
PH and RV dysfunction in HFpEF

- PASP is independently ***associated with mortality*** in HFpEF





Lam CS et al. J Am Coll Cardiol 2009



Yogesh N.V. Reddy et al. J Am Coll Cardiol 2020;76:1051-1064

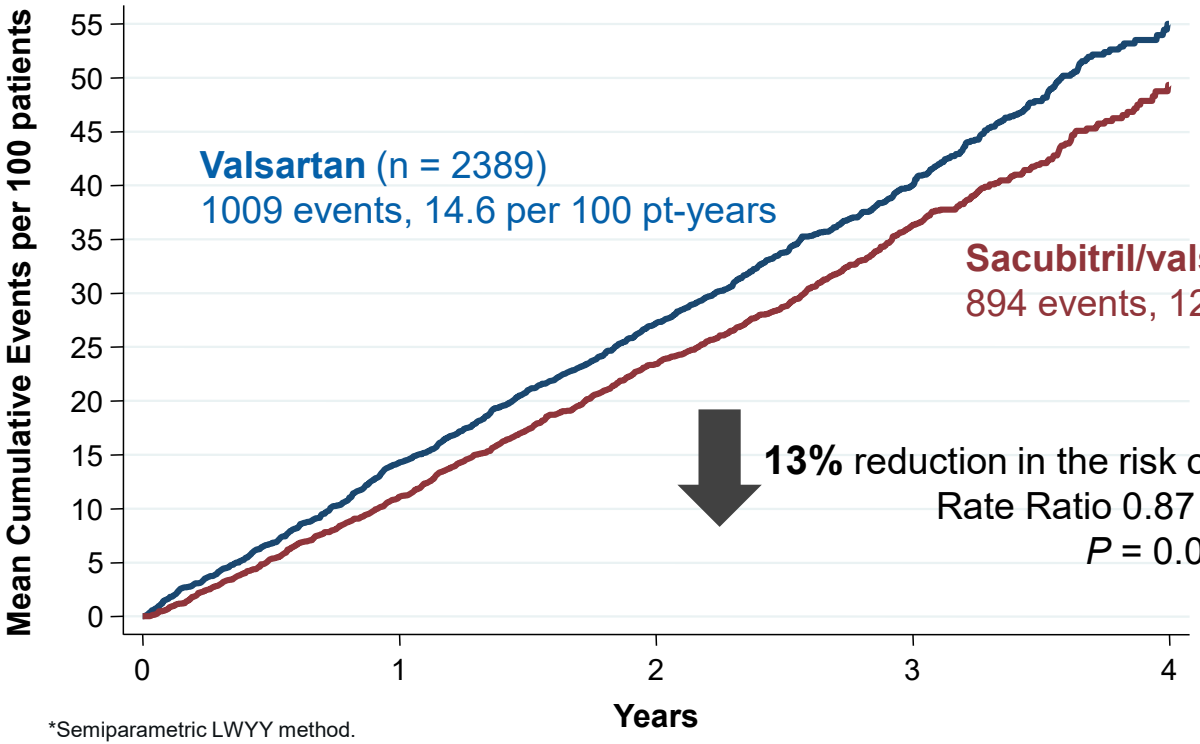
PARAGON-HF

Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction

S.D. Solomon, J.J.V. McMurray, I.S. Anand, J. Ge, C.S.P. Lam, A.P. Maggioni, F. Martinez, M. Packer, M.A. Pfeffer, B. Pieske, M.M. Redfield, J.L. Rouleau, D.J. van Veldhuisen, F. Zannad, M.R. Zile, A.S. Desai, B. Claggett, P.S. Jhund, S.A. Boytsov, J. Comin-Colet, J. Cleland, H.-D. Düngen, E. Goncalvesova, T. Katova, J.F. Kerr Saraiva, M. Lelonek, B. Merkely, M. Senni, S.J. Shah, J. Zhou, A.R. Rizkala, J. Gong, V.C. Shi, and M.P. Lefkowitz, for the PARAGON-HF Investigators and Committees

An International multicenter, randomized , double-blind, parallel group, active –controlled, event driven trial comparing the long-term efficacy and safety of valsartan vs sacubitril/valsartan in patients with chronic HFpEF (LVEF > 45%)

Primary endpoint: Recurrent event analysis of total HF hospitalizations and CV death*



If urgent HF visits were included:
RR = 0.861 (0.747 – 0.993)
P value = 0.040

*Semiparametric LWYY method.

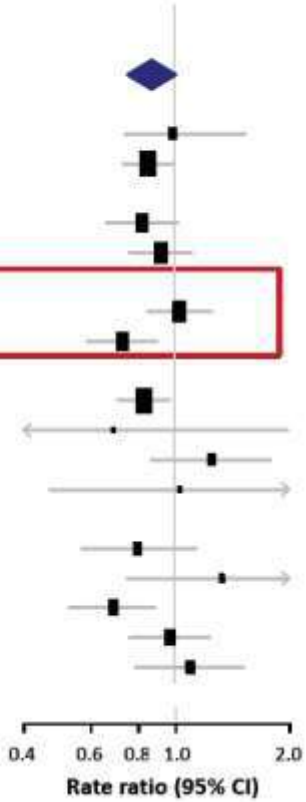
CV, cardiovascular; HF, heart failure

Solomon S, et al. N Engl J Med. 2019 (In press)

Pre-specified subgroups for primary endpoint

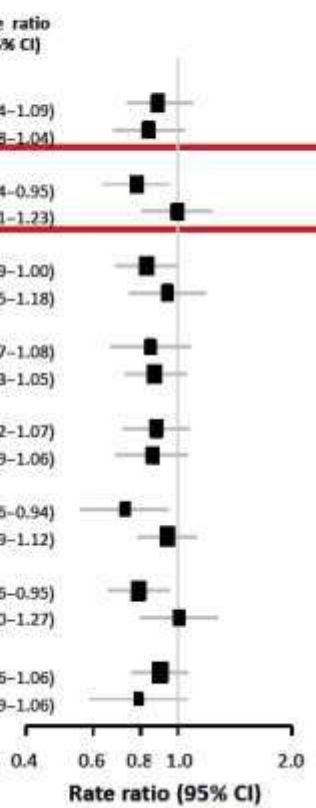
Evidence for overall heterogeneity

Subgroup	No. of events /patients	Rate ratio (95% CI)
Overall	**1903/4796**	**0.87 (0.75–1.01)**
Age (years)		
Less than 65 years	276/825	0.99 (0.64–1.53)
65 years or older	1627/3971	0.85 (0.73–0.99)
Age (years)		
Less than 75 years	938/2597	0.82 (0.66–1.02)
75 years or older	965/2199	0.92 (0.76–1.11)
Sex*		
Male	980/2317	1.03 (0.85–1.25)
Female	923/2479	0.73 (0.59–0.90)
Race		
Caucasian	1542/3907	0.83 (0.71–0.97)
Black	89/102	0.69 (0.24–1.99)
Asian	237/607	1.25 (0.87–1.79)
Other	35/180	1.03 (0.47–2.28)
Region		
North America	478/559	0.80 (0.57–1.14)
Latin America	83/370	1.33 (0.75–2.36)
Western Europe	544/1390	0.69 (0.53–0.89)
Central Europe	466/1715	0.97 (0.76–1.24)
Asia/Pacific	332/762	1.10 (0.79–1.52)



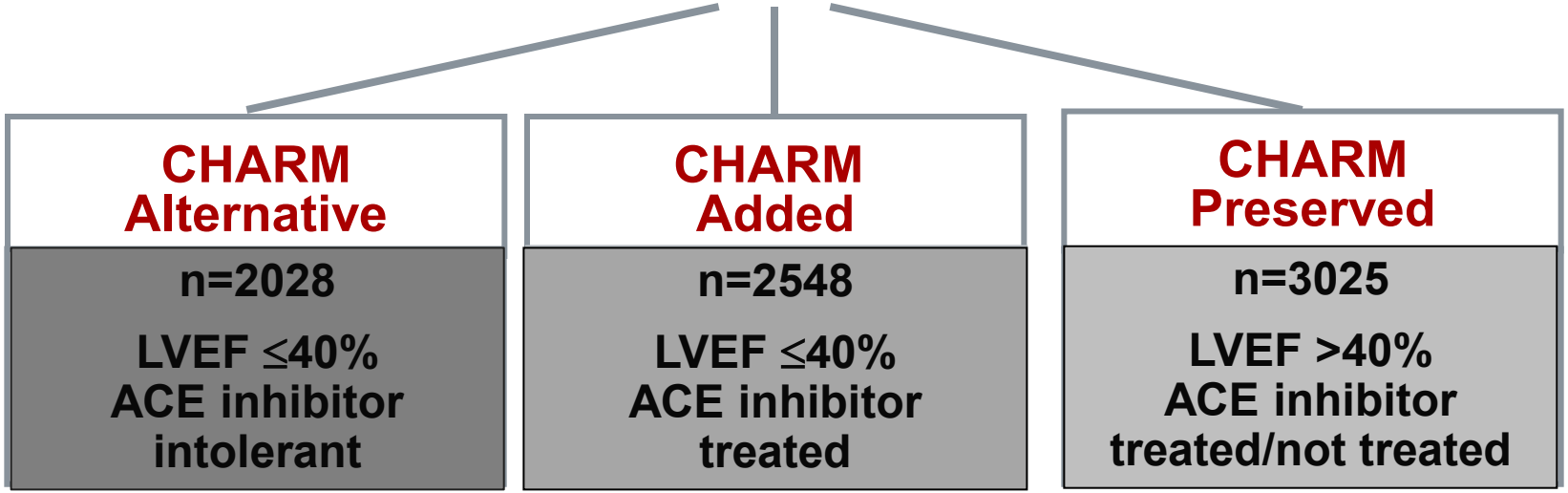
Multivariate interaction p < 0.05.

Subgroup	No. of events /patients	Rate ratio (95% CI)
Diabetic		
Yes	1041/2069	0.89 (0.74–1.09)
No	862/2727	0.84 (0.68–1.04)
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)
History of AF		
Yes	1140/2521	0.83 (0.69–1.00)
No	763/2275	0.94 (0.75–1.18)
Screening NT-proBNP		
at or below median (911 pg/mL)	708/2379	0.85 (0.67–1.08)
above median (911 pg/mL)	1183/2378	0.87 (0.73–1.05)
Screening SBP		
at or below median (137 mmHg)	984/2450	0.88 (0.72–1.07)
above median (137 mmHg)	919/2344	0.86 (0.69–1.06)
MRA use		
Yes	543/1238	0.73 (0.56–0.94)
No	1360/3558	0.94 (0.79–1.12)
Baseline eGFR		
<60 mL/min/1.73m^2	1115/2341	0.79 (0.66–0.95)
>=60 mL/min/1.73m^2	787/2454	1.01 (0.80–1.27)
NYHA class		
I/II	1402/3843	0.90 (0.76–1.06)
III/IV	499/951	0.79 (0.59–1.06)



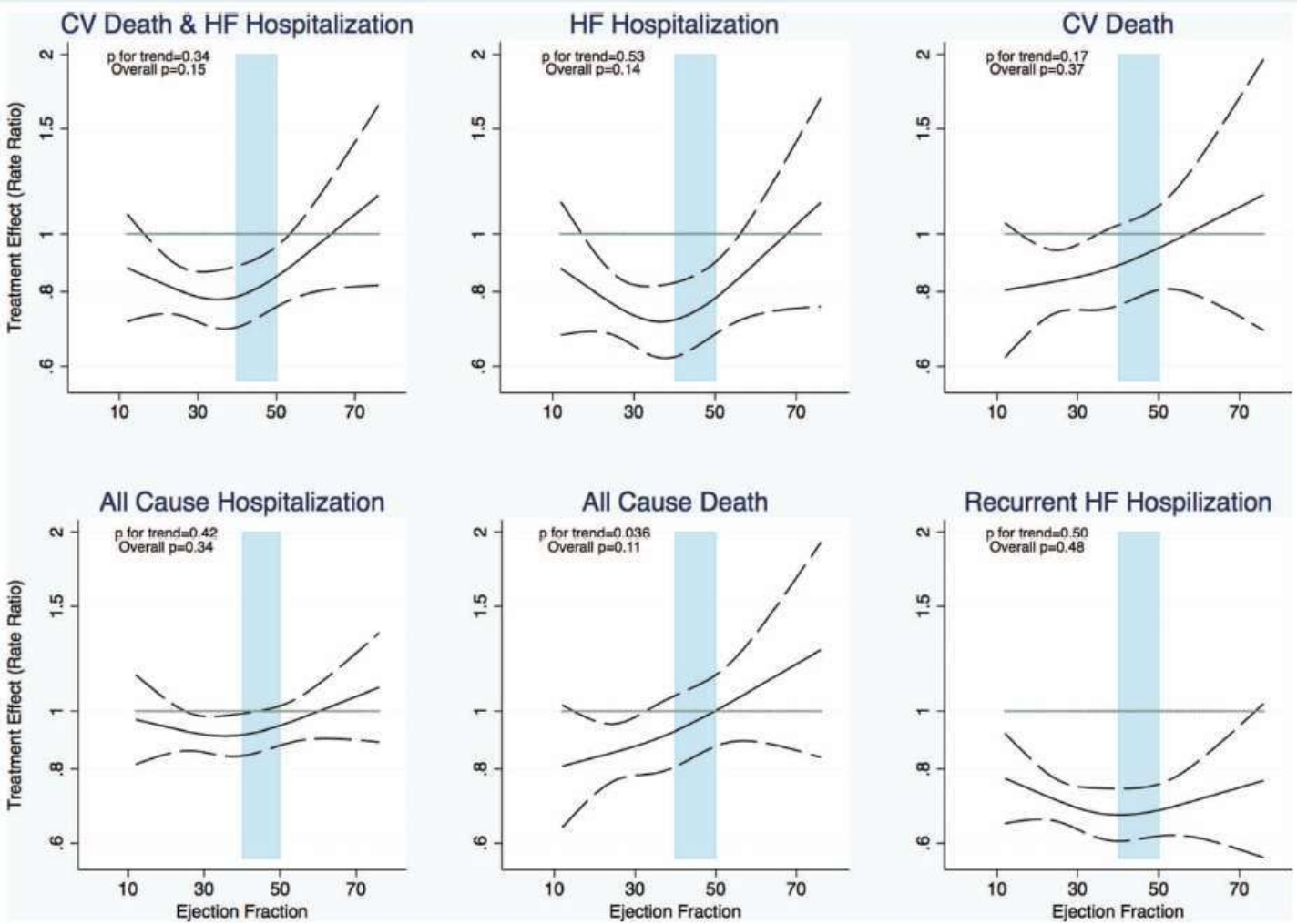
CHARM Program

3 component trials comparing candesartan to placebo in patients with symptomatic heart failure



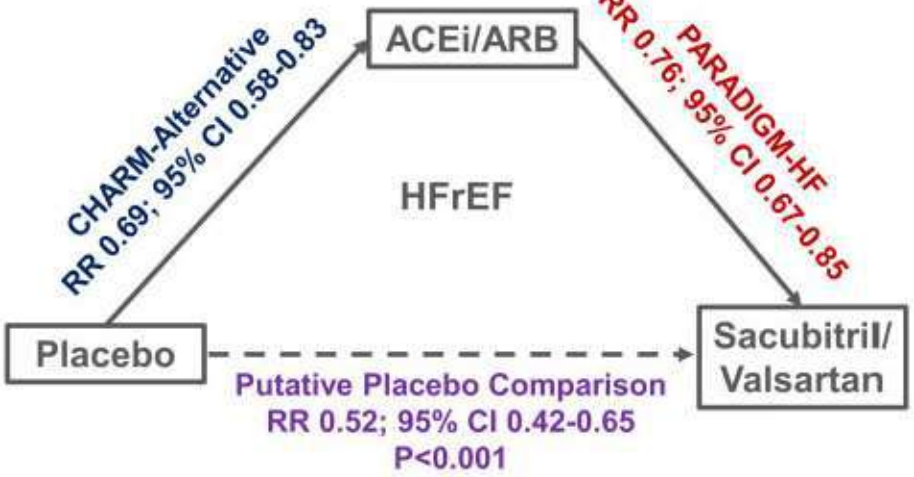
Primary outcome for each trial: CV death or CHF hospitalisation

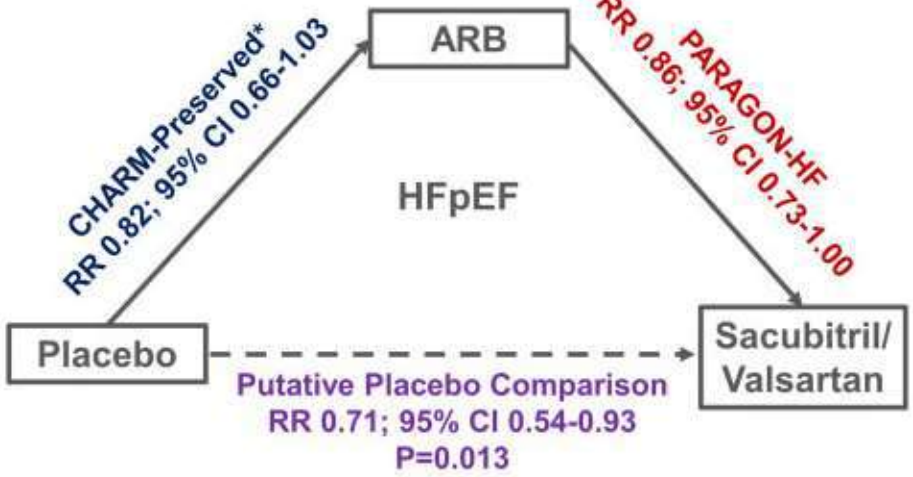
Primary outcome for Overall Program: All-cause death


CV Death & HF Hospitalization
p for trend=0.34
Overall p=0.15
HF Hospitalization
p for trend=0.53
Overall p=0.14
CV Death
p for trend=0.17
Overall p=0.37
All Cause Hospitalization
p for trend=0.42
Overall p=0.34
All Cause Death
p for trend=0.036
Overall p=0.11
Recurrent HF Hospilization
p for trend=0.50
Overall p=0.48
Treatment Effect (Rate Ratio)
.6
.8
1
1.5
2
10
30
50
70
Ejection Fraction

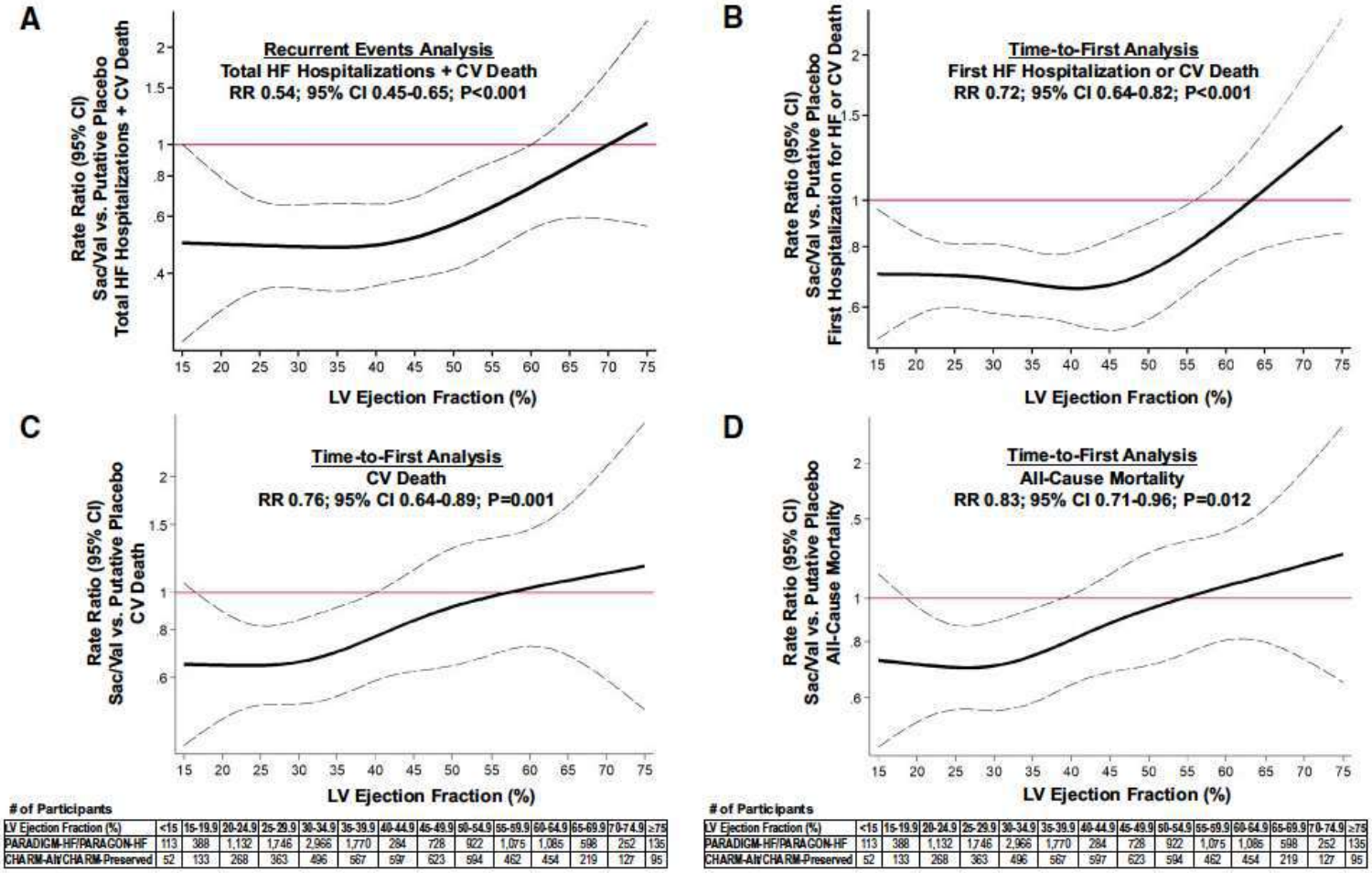
A putative placebo analysis of the effects of sacubitril/valsartan in heart failure across the full range of ejection fraction

Muthiah Vaduganathan [1], Pardeep S. Jhund [2], Brian L. Claggett[1], Milton Packer [3,4], Jiri Widimský [5], Petar Seferovic [6], Adel Rizkala[7], Martin Lefkowitz[7], Victor Shi[7], John J.V. McMurray [2], and Scott D. Solomon[1]*





European Heart Journal (2020) **41**, 2356–2362



# of Participants

LV Ejection Fraction (%)	<15	15-19.9	20-24.9	25-29.9	30-34.9	35-39.9	40-44.9	45-49.9	50-54.9	55-59.9	60-64.9	65-69.9	70-74.9	≥75
PARADIGM-HF/PARAGON-HF	113	388	1,132	1,746	2,966	1,770	284	728	922	1,075	1,086	598	252	135
CHARM-Alt/CHARM-Preserved	52	133	268	363	496	567	597	623	594	462	454	219	127	95

# of Participants

LV Ejection Fraction (%)	<15	15-19.9	20-24.9	25-29.9	30-34.9	35-39.9	40-44.9	45-49.9	50-54.9	55-59.9	60-64.9	65-69.9	70-74.9	≥75
PARADIGM-HF/PARAGON-HF	113	388	1,132	1,746	2,966	1,770	284	728	922	1,075	1,086	598	252	135
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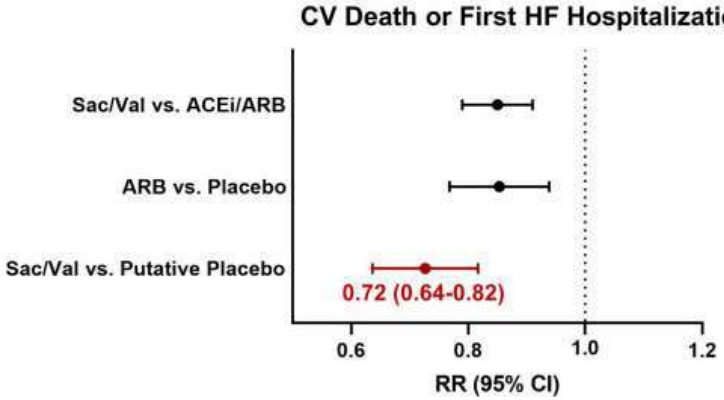
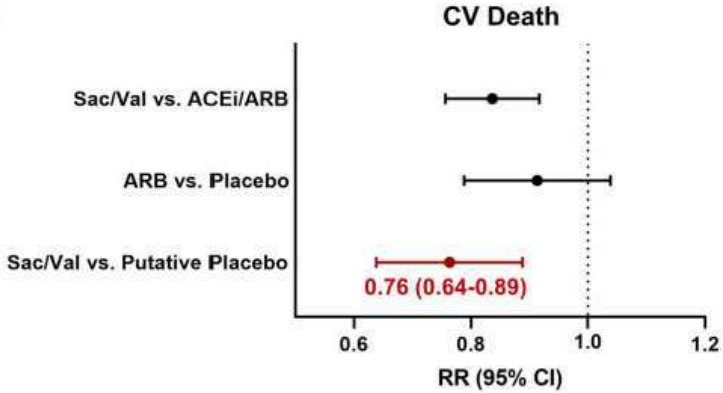
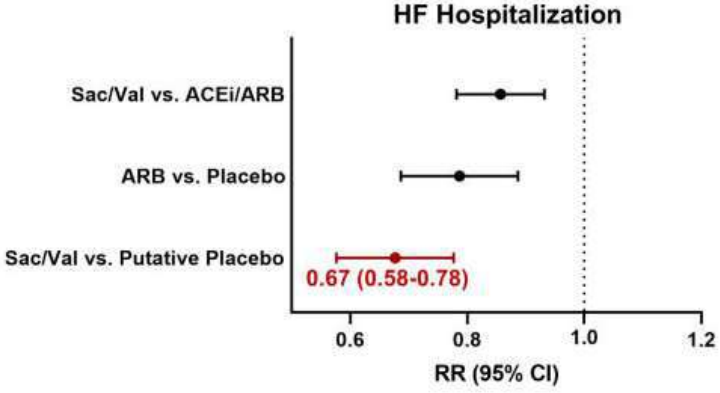
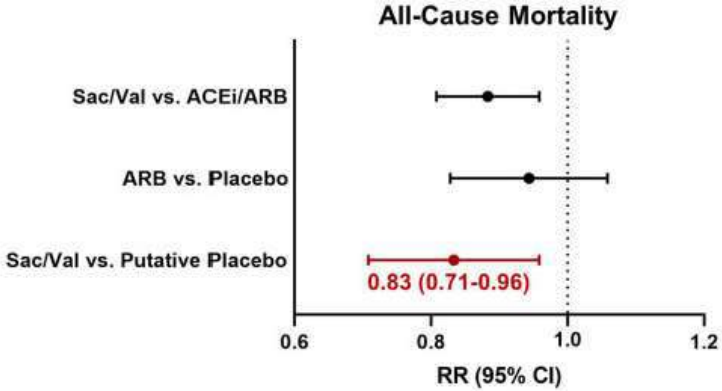


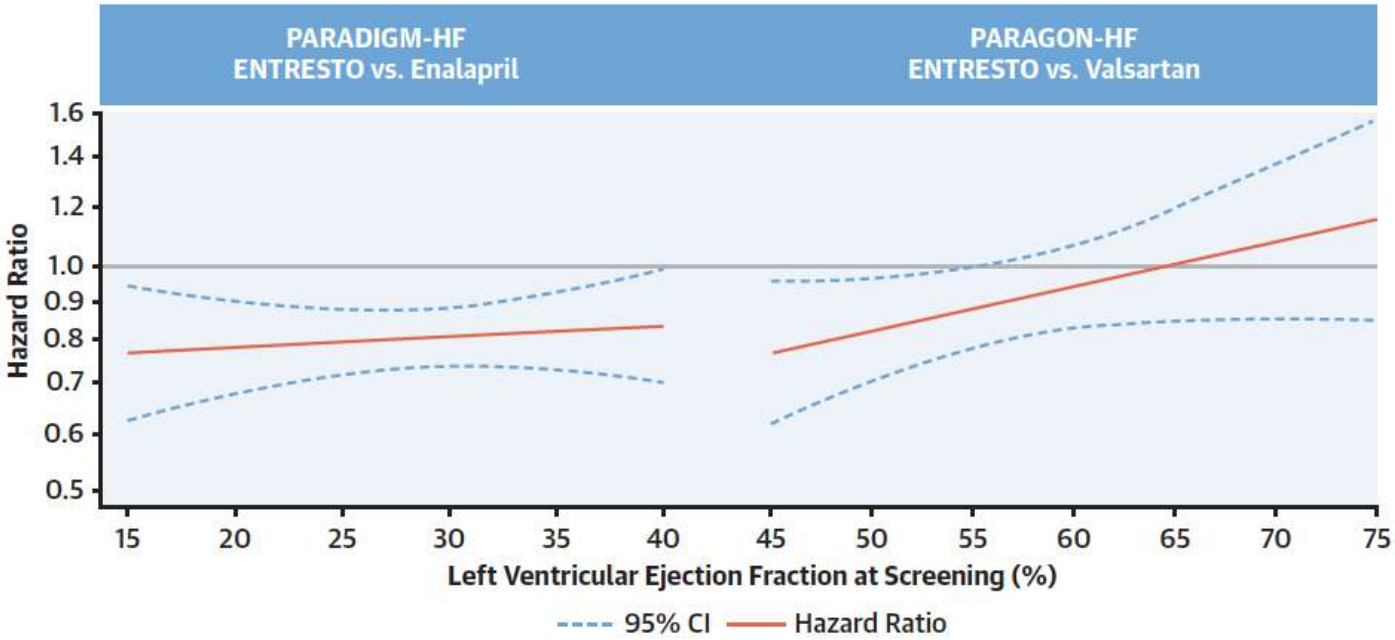




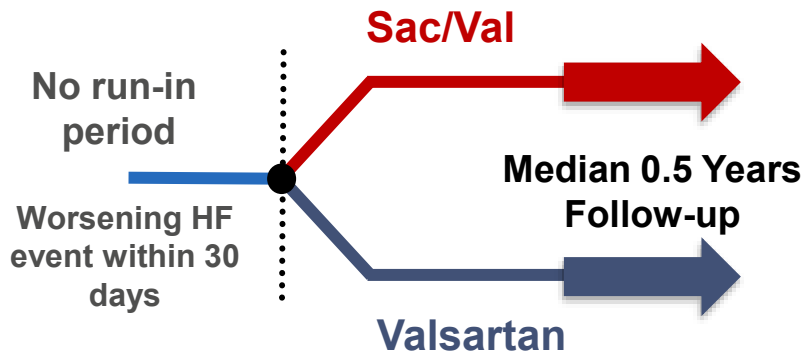
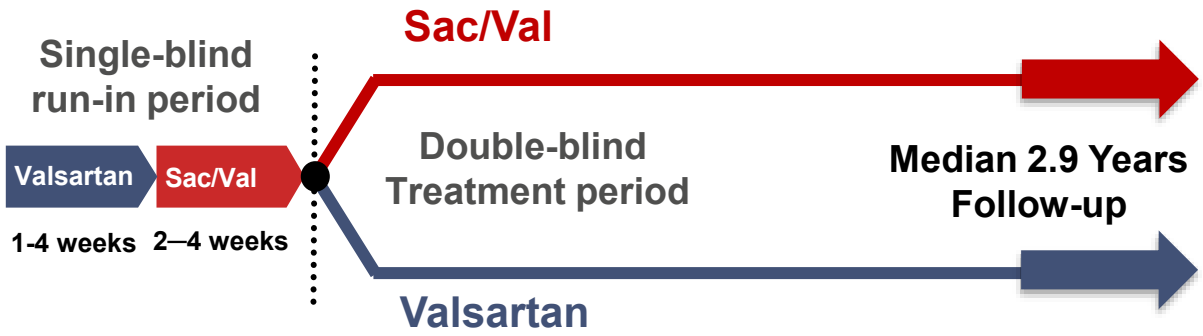


European Heart Journal (2020) **41**, 2356–2362

In both trials, the lower the EF, the greater the reduction in HR

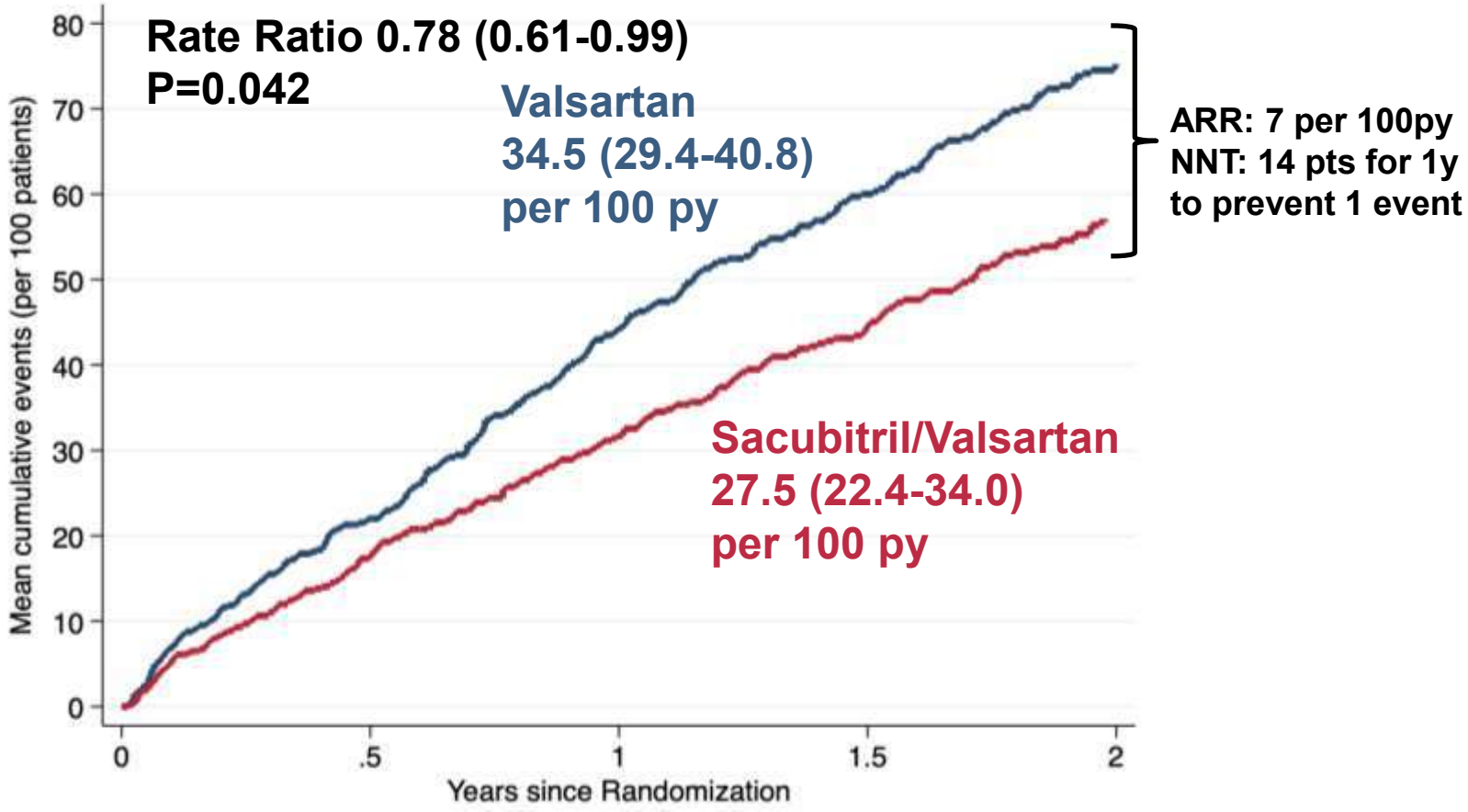


Lam C, Solomon S. JACC 2021; 77 (25)

Entry criteria	Study design
PARAGLIDE-HF (n=466) • Age ≥18 years • HF with LVEF >40% • Current or recent worsening HF event (HF hospitalization, urgent HF visit, or ED stay) • Elevated natriuretic peptides	 Mentz RJ, *et al. J Card Fail* 2023
PARAGON-HF (n=4,796) • Age ≥50 years • HF with LVEF ≥45% • NYHA class II-IV • Elevated natriuretic peptides • Structural heart disease (LVH or LAE)	 Solomon SD, *et al. JACC HF* 2017

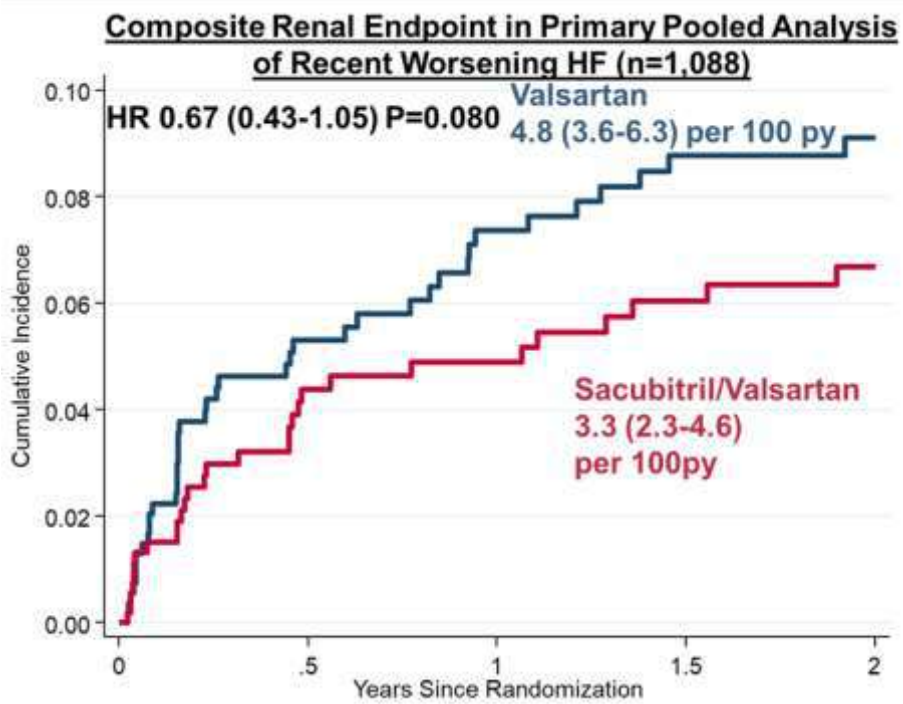
Primary Pooled Analysis (n=1,088)

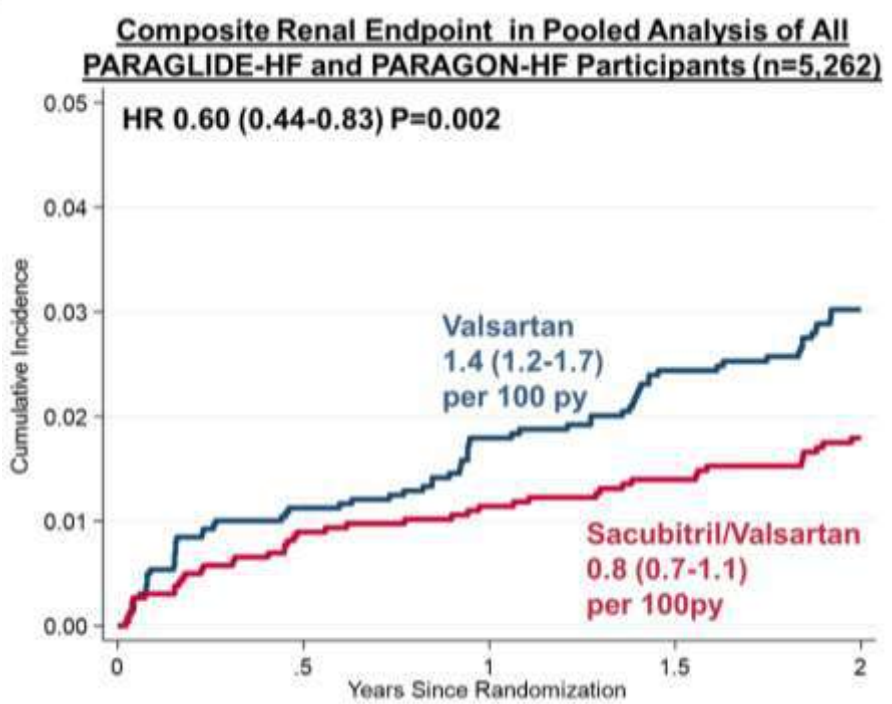
Primary Endpoint: Total Worsening HF Events and CV Death



Secondary Endpoint: Renal Composite

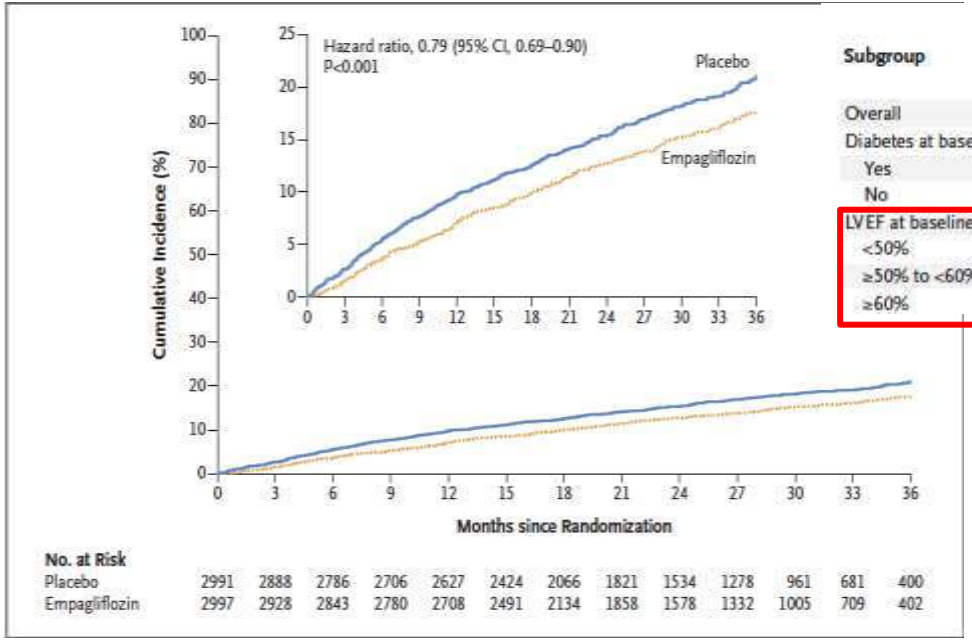
Time to first ≥50% decline in eGFR from baseline, ESRD, or renal death





Empagliflozin in Heart Failure with a Preserved Ejection Fraction

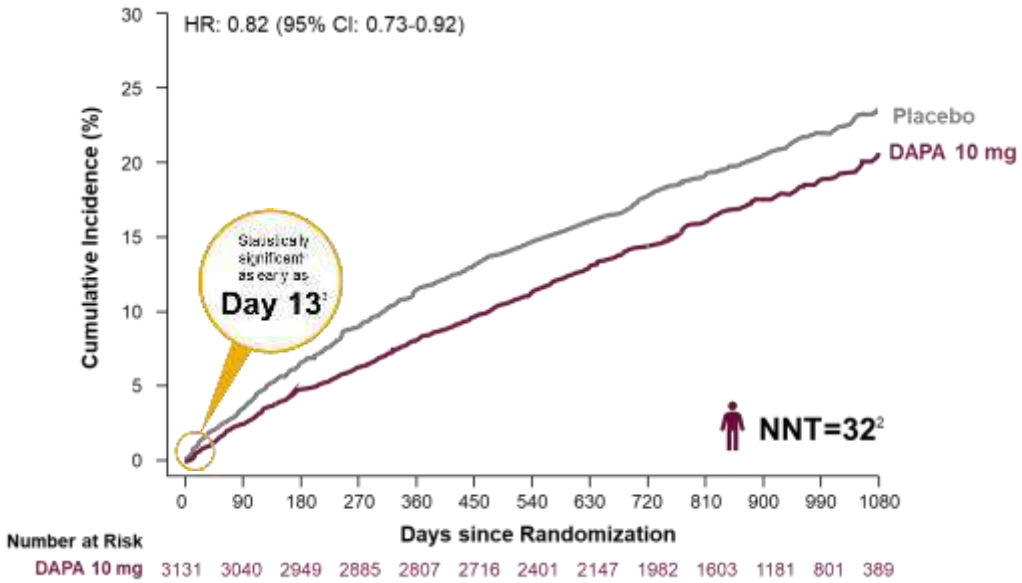
S.D. Anker, J. Butler, G. Filippatos, J.P. Ferreira, E. Bocchi, M. Böhm, H.-P. Brunner–La Rocca, D.-J. Choi, V. Chopra, E. Chuquiure-Valenzuela, N. Giannetti, J.E. Gomez-Mesa, S. Janssens, J.L. Januzzi, J.R. Gonzalez-Juanatey, B. Merkely, S.J. Nicholls, S.V. Perrone, I.L. Piña, P. Ponikowski, M. Senni, D. Sim, J. Spinar, I. Squire, S. Taddei, H. Tsutsui, S. Verma, D. Vinereanu, J. Zhang, P. Carson, C.S.P. Lam, N. Marx, C. Zeller, N. Sattar, W. Jamal, S. Schnaidt, J.M. Schnee, M. Brueckmann, S.J. Pocock, F. Zannad, and M. Packer, for the EMPEROR-Preserved Trial Investigators*



Subgroup	Empagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of patients with events/total no.		
Overall	415/2997	511/2991	0.79 (0.69–0.90)
Diabetes at baseline			
Yes	239/1466	291/1472	0.79 (0.67–0.94)
No	176/1531	220/1519	0.78 (0.64–0.95)
LVEF at baseline			
<50%	145/995	193/988	0.71 (0.57–0.88)
≥50% to <60%	138/1028	173/1030	0.80 (0.64–0.99)
≥60%	132/974	145/973	0.87 (0.69–1.10)

NEJM 2021; DOI: 10.1056/NEJMoa2107038

Dapagliflozin significantly reduced the risk of CV death and worsening HF[a] in patients with HFmrEF and HFpEF[1]



CV Death or Worsening HF[a]
18% RRR
3.1% ARR
p=0.0008

CV death
12% RRR
1% ARR
0.88 (0.74, 1.05)

Worsening HF[a]
21% RRR
3.7% ARR
0.79 (0.69, 0.91)

Consistent benefit in the primary endpoint across key subgroups

All-cause mortality was also reduced in the dapagliflozin group

All-cause mortality
6% RRR
~1% ARR
0.94 (0.83, 1.07)

Quality of life
2.4 Points TSS-KCCQ
P<0.001

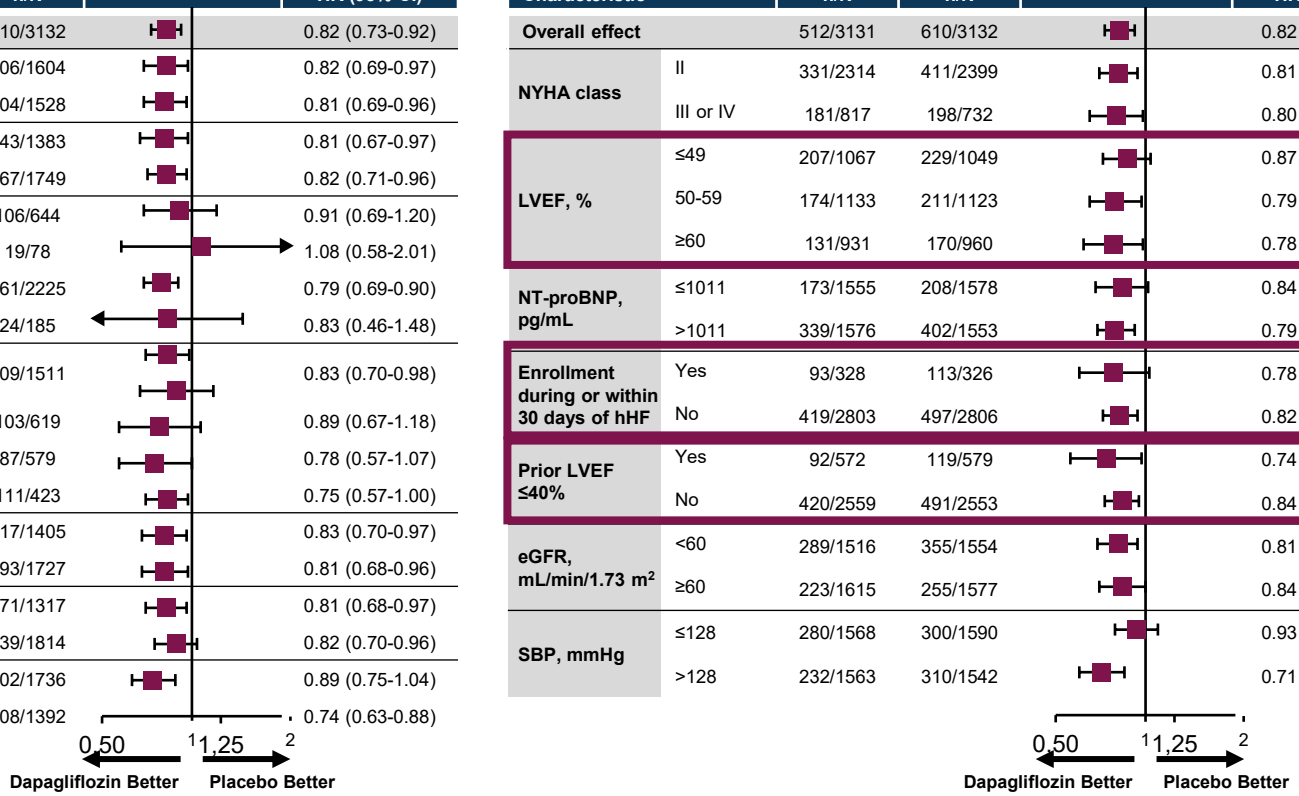
[a]Nominal significance at Day 13 (HR, 0.45; 95% CI, 0.20-0.99; p=0.046), with sustained statistical significance starting at Day 15.

1. Solomon SD et al. *N Engl J Med*. 2022;387(12):1089-1098

Consistent Treatment Benefit Across All Prespecified Subgroups

Characteristic		DAPA n/N	PBO n/N	HR (95% CI)
Overall effect		512/3131	610/3132	0.82 (0.73-0.92)
Age, yr	≤72	247/1545	306/1604	0.82 (0.69-0.97)
	>72	265/1586	304/1528	0.81 (0.69-0.96)
Sex	Female	195/1364	243/1383	0.81 (0.67-0.97)
	Male	317/1767	367/1749	0.82 (0.71-0.96)
Race	Asian	97/630	106/644	0.91 (0.69-1.20)
	Black	21/81	19/78	1.08 (0.58-2.01)
	White	372/2214	461/2225	0.79 (0.69-0.90)
	Other	22/206	24/185	0.83 (0.46-1.48)
Region	Europe/ Saudi Arabia	261/1494	309/1511	0.83 (0.70-0.98)
	Asia	92/607	103/619	0.89 (0.67-1.18)
	Latin America	70/602	87/579	0.78 (0.57-1.07)
	North America	89/428	111/423	0.75 (0.57-1.00)
T2D	Yes	270/1401	317/1405	0.83 (0.70-0.97)
	No	242/1730	293/1727	0.81 (0.68-0.96)
AF/AFL on ECG	Yes	227/1327	271/1317	0.81 (0.68-0.97)
	No	285/1803	339/1814	0.82 (0.70-0.96)
BMI, kg/m²	<30	275/1734	302/1736	0.89 (0.75-1.04)
	≥30	236/1395	308/1392	0.74 (0.63-0.88)

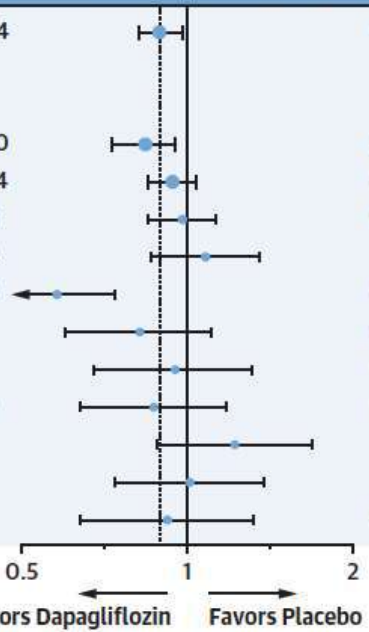
Characteristic		DAPA n/N	PBO n/N	HR (95% CI)
Overall effect		512/3131	610/3132	0.82 (0.73-0.92)
NYHA class	II	331/2314	411/2399	0.81 (0.70-0.94)
	III or IV	181/817	198/732	0.80 (0.65-0.98)
LVEF, %	≤49	207/1067	229/1049	0.87 (0.72-1.04)
	50-59	174/1133	211/1123	0.79 (0.65-0.97)
	≥60	131/931	170/960	0.78 (0.62-0.98)
NT-proBNP, pg/mL	≤1011	173/1555	208/1578	0.84 (0.68-1.02)
	>1011	339/1576	402/1553	0.79 (0.69-0.92)
Enrollment during or within 30 days of hHF	Yes	93/328	113/326	0.78 (0.60-1.03)
	No	419/2803	497/2806	0.82 (0.72-0.94)
Prior LVEF ≤40%	Yes	92/572	119/579	0.74 (0.56-0.97)
	No	420/2559	491/2553	0.84 (0.73-0.95)
eGFR, mL/min/1.73 m²	<60	289/1516	355/1554	0.81 (0.69-0.94)
	≥60	223/1615	255/1577	0.84 (0.70-1.00)
SBP, mmHg	≤128	280/1568	300/1590	0.93 (0.79-1.10)
	>128	232/1563	310/1542	0.71 (0.60-0.85)



Solomon SD et al. Online ahead of print. *N Engl J Med*. 2022.

All Cause Hospitalizations- 11% Reduction

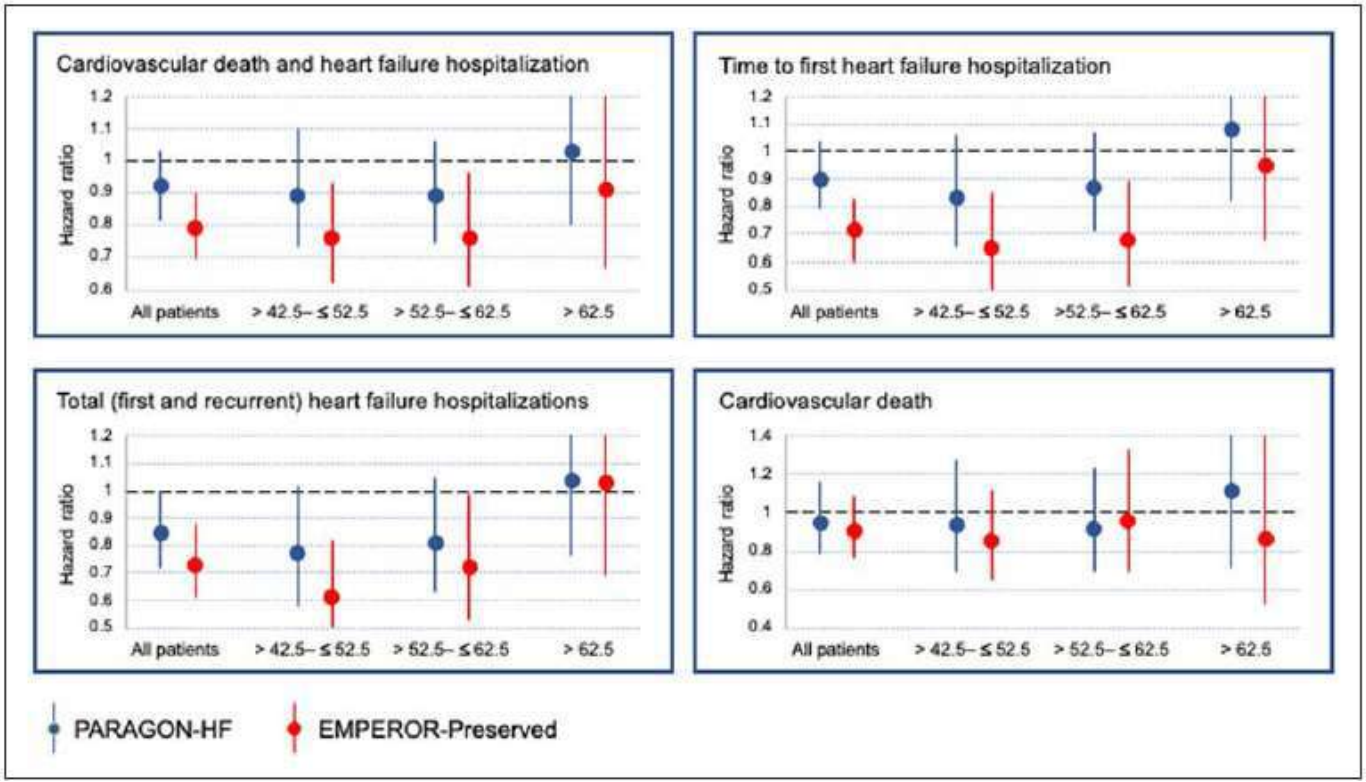
	Total # of Events					
	Dapagliflozin	Placebo	Rate Ratio (95% CI)	Rate Ratio	(95% CI)	*P* Value
All-Cause Hospitalization	2,226	2,484		0.89	(0.82-0.98)	0.015
Top Causes of Hospitalization						
Cardiac	906	1,080		0.84	(0.73-0.95)	0.008
Noncardiac	1,320	1,404		0.94	(0.85-1.04)	0.22
Infectious	524	535		0.98	(0.85-1.13)	0.76
Nervous System	176	162		1.08	(0.86-1.36)	0.49
Gastrointestinal	94	162		0.58	(0.43-0.74)	<0.001
Renal/Urinary	107	131		0.82	(0.60-1.11)	0.20
Respiratory/Thoracic	109	115		0.95	(0.68-1.31)	0.74
Injury, Poisoning, or Procedural	96	110		0.87	(0.64-1.18)	0.38
Vascular	100	82		1.22	(0.88-1.69)	0.24
Cancer	90	89		1.01	(0.74-1.38)	0.95
Metabolism/Nutrition	78	85		0.92	(0.64-1.32)	0.64



JACC 2023; 81 (10): 1004-1006

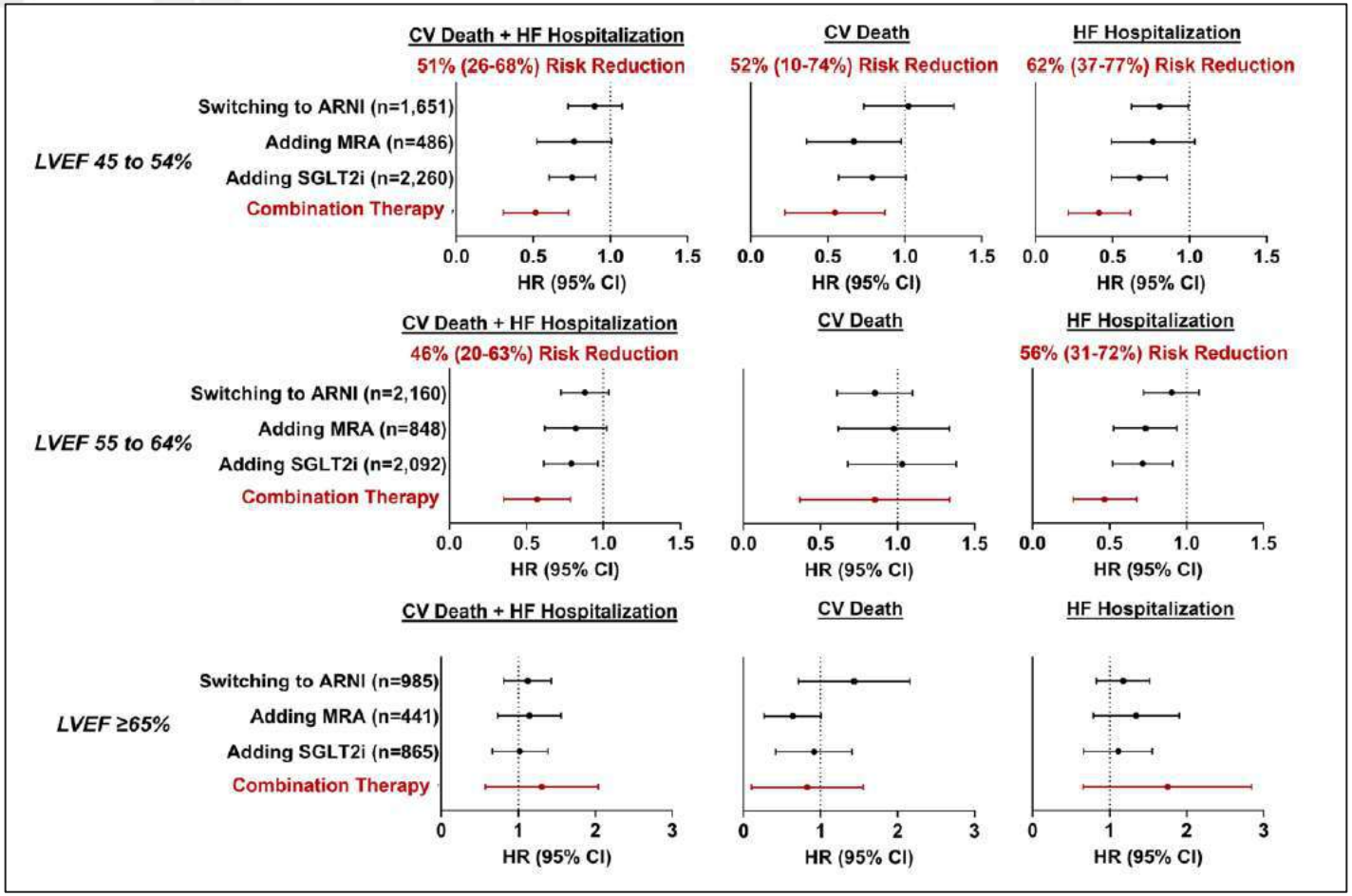
ARNI vs. SGLT2i:PARAGON- HF and EMPEROR-PRESERVED

Similar trends of response to therapy with increasing EF



Circulation. 2021;144:00–00. DOI: 10.1161/CIRCULATIONAHA.121.056657

PARAGON, EMPEROR, and TOPCAT



Circulation. 2022;145:1741–1743.

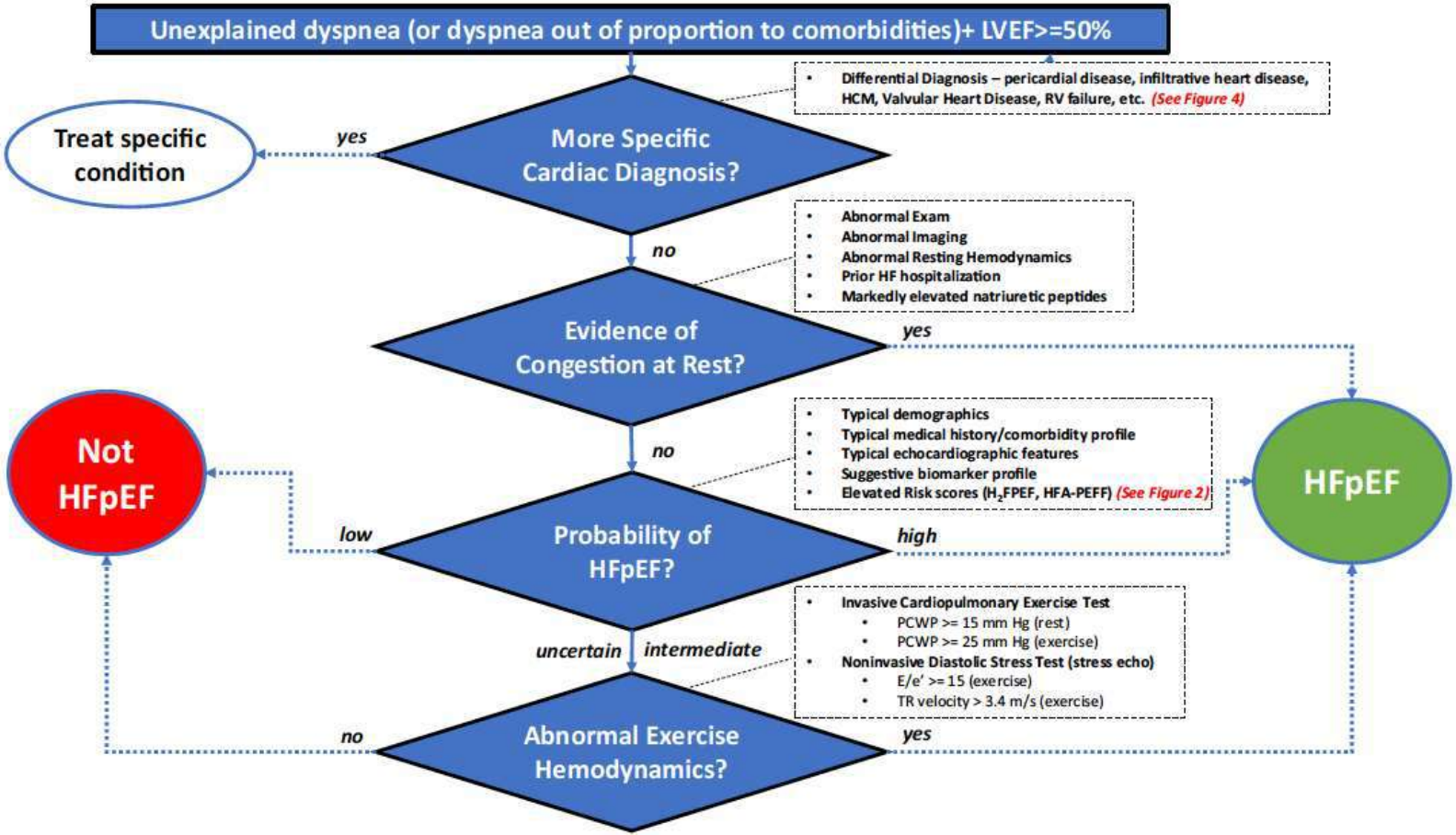
How to Manage Heart Failure With Preserved Ejection Fraction

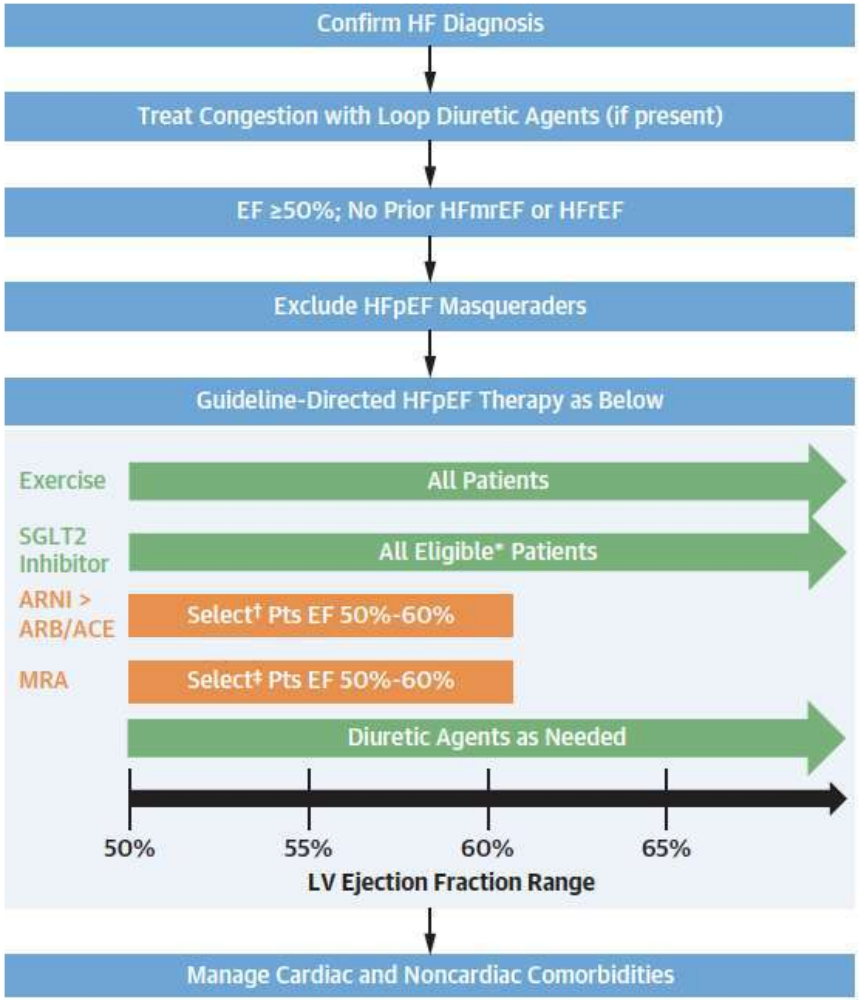
Practical Guidance for Clinicians

Akshay S. Desai, MD, MPH,[a] Carolyn S.P. Lam, MBBS, PhD,[b,c] John J.V. McMurray, MD,[d] Margaret M. Redfield, MD[e]

TABLE 1 Overview of HF Therapy According to LVEF

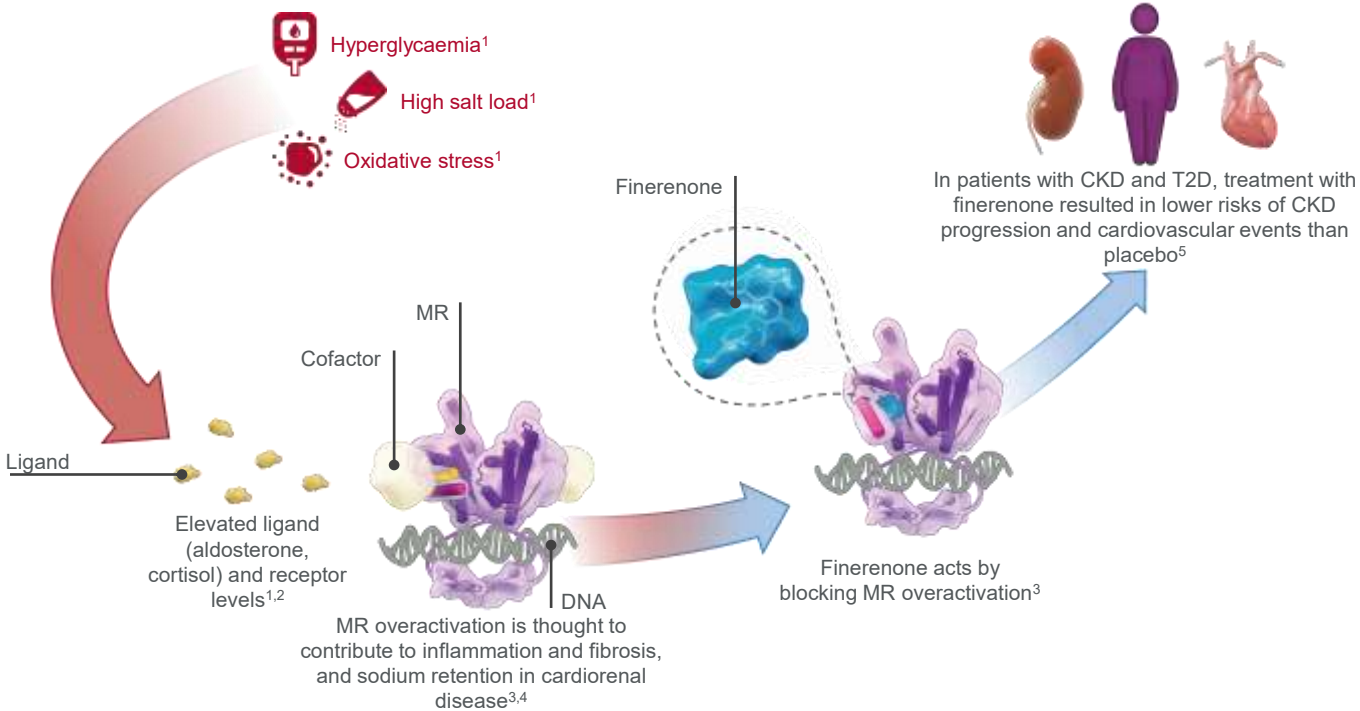
Initial Classification	LVEF, %	Diagnostic Contingencies	Initial Approach	Potential LVEF Trajectories and Treatment Implications
HFpEF	≥50	Symptoms of HF and evidence of elevated filling pressure (congestion) at rest or with exercise[a]	Treat as HFpEF	LVEF may stay stable or decline Treat as HFrEF if LVEF declines <50%
HFmrEF	41-49	Symptoms of HF and evidence of elevated filling pressure (congestion) at rest or with exercise[a]	Treat as HFrEF	LVEF may improve or decline Treat as HFrEF even if LVEF subsequently improves
HFrEF	≤40	Symptoms of HF or asymptomatic	Treat as HFrEF	LVEF may improve to >40% (HFimpEF) Treat as HFrEF even if LVEF subsequently improves


Unexplained dyspnea (or dyspnea out of proportion to comorbidities)+ LVEF>=50%
Differential Diagnosis – pericardial disease, infiltrative heart disease, HCM, Valvular Heart Disease, RV failure, etc. (See Figure 4)
More Specific Cardiac Diagnosis?
yes
Treat specific condition
no
Abnormal Exam
Abnormal Imaging
Abnormal Resting Hemodynamics
Prior HF hospitalization
Markedly elevated natriuretic peptides
Evidence of Congestion at Rest?
yes
no
Typical demographics
Typical medical history/comorbidity profile
Typical echocardiographic features
Suggestive biomarker profile
Elevated Risk scores (H2FPEF, HFA-PEFF) (See Figure 2)
Not HFpEF
low
Probability of HFpEF?
high
HFpEF
uncertain
intermediate
Invasive Cardiopulmonary Exercise Test
PCWP >= 15 mm Hg (rest)
PCWP >= 25 mm Hg (exercise)
Noninvasive Diastolic Stress Test (stress echo)
E/e' >= 15 (exercise)
TR velocity > 3.4 m/s (exercise)
no
Abnormal Exercise Hemodynamics?
yes



Desai AS, et al. J Am Coll Cardiol HF. 2023;11(6):619-636.

Finerenone, a novel, selective, nonsteroidal MRA, blocks MR overactivation



Finerenone is approved by the FDA and is indicated to reduce the risk of sustained eGFR decline, ESKD, CV death, non-fatal MI, and HHF in adult patients with CKD associated with T2D. Finerenone is currently under review by other health authorities, including the EMA

1. Buonafine M, *et al. Am J Hypertens* 2018;31:1165–1174; 2. Buglioni A, *et al. Hypertension* 2015;65:45–53; 3. Agarwal R, *et al. Nephrol Dial Transplant* 2020; doi: 10.1093/ndt/gfaa294;
4. Khan NUA & Movahed A. *Rev Cardiovasc Med* 2004;5:71–81; 5. Bakris GL, *et al. N Engl J Med* 2020;383:2219–2229

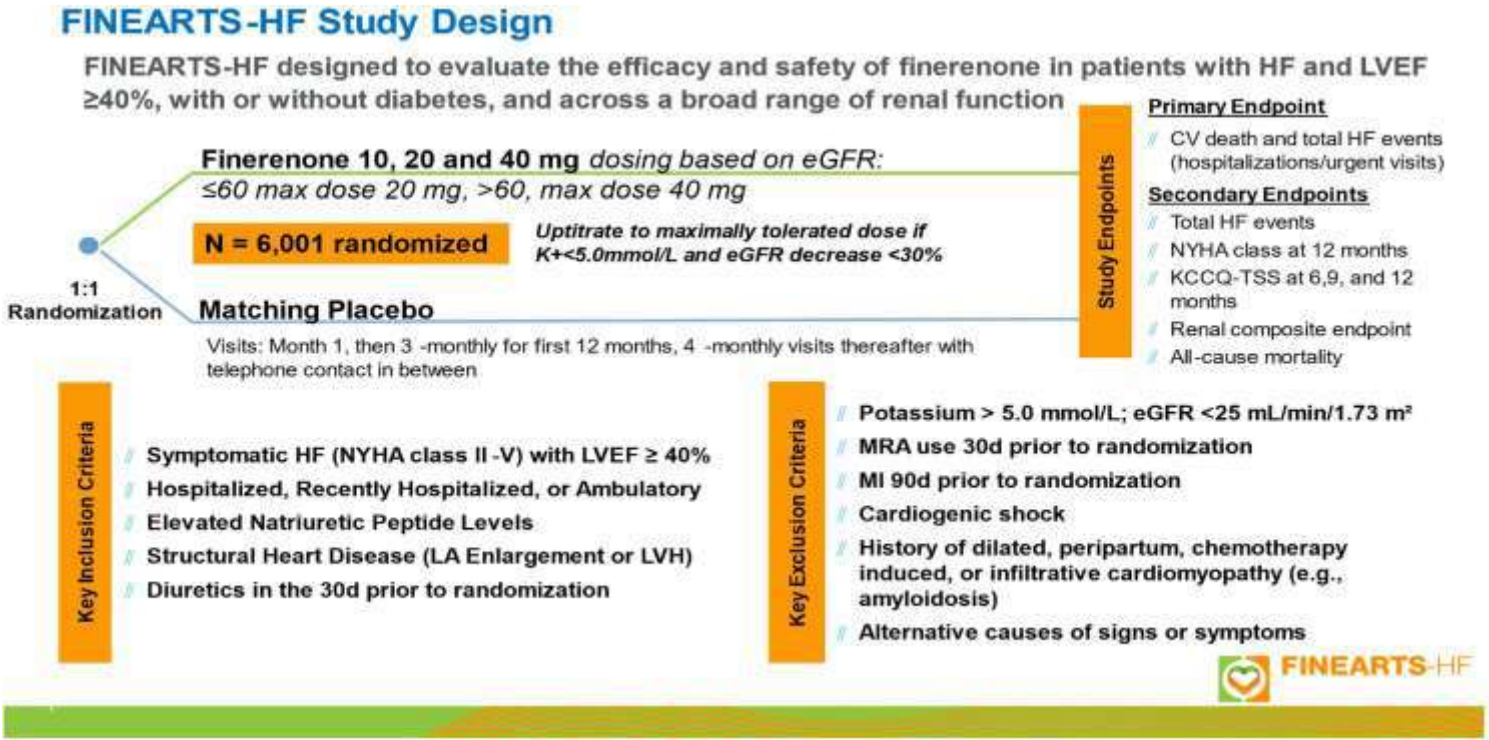
The NEW ENGLAND JOURNAL of MEDICINE

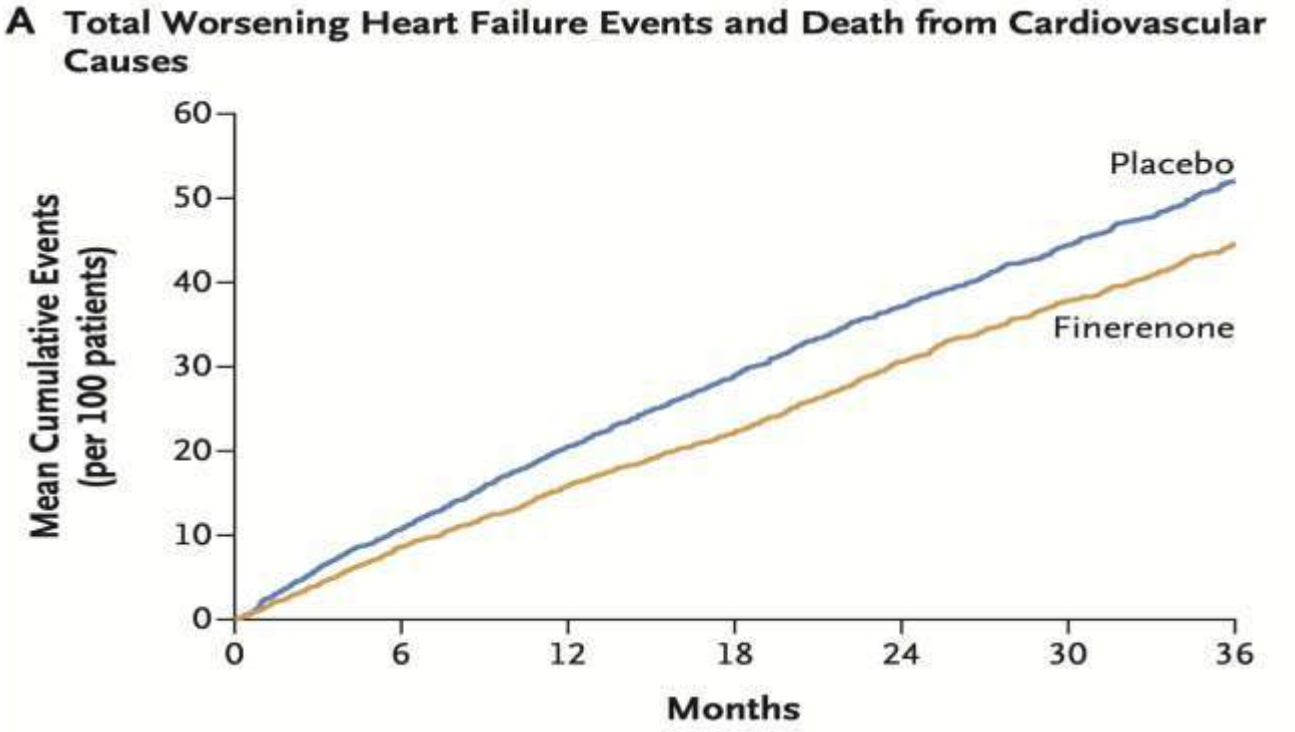
ORIGINAL ARTICLE

Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

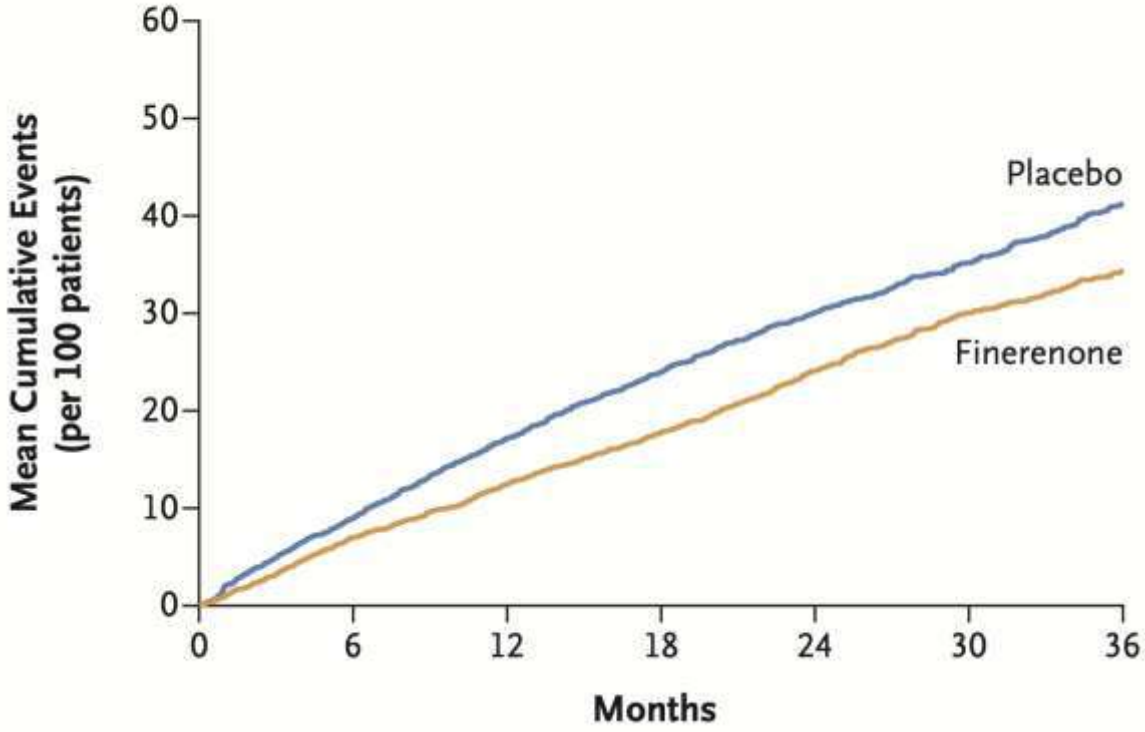
S.D. Solomon, J.J.V. McMurray, M. Vaduganathan, B. Claggett, P.S. Jhund, A.S. Desai, A.D. Henderson, C.S.P. Lam, B. Pitt, M. Senni, S.J. Shah, A.A. Voors, F. Zannad, I.Z. Abidin, M.A. Alcocer-Gamba, J.J. Atherton, J. Bauersachs, M. Chang-Sheng, C.-E. Chiang, O. Chioncel, V. Chopra, J. Comin-Colet, G. Filippatos, C. Fonseca, G. Gajos, S. Goland, E. Goncalvesova, S. Kang, T. Katova, M.N. Kosiborod, G. Latkovskis, A.P.-W. Lee, G.C.M. Linssen, G. Llamas-Esperón, V. Mareev, F.A. Martinez, V. Melenovský, B. Merkely, S. Nodari, M.C. Petrie, C.I. Saldarriaga, J.F.K. Saraiva, N. Sato, M. Schou, K. Sharma, R. Troughton, J.A. Udell, H. Ukkonen, O. Vardeny, S. Verma, D. von Lewinski, L. Voronkov, M.B. Yilmaz, S. Zieroth, J. Lay-Flurrie, I. van Gameren, F. Amarante, P. Kolkhof, and P. Viswanathan, for the FINEARTS-HF Committees and Investigators*

Finerenone in patients with heart failure with mildly reduced or preserved ejection fraction: Rationale and design of the FINEARTS-HF trial

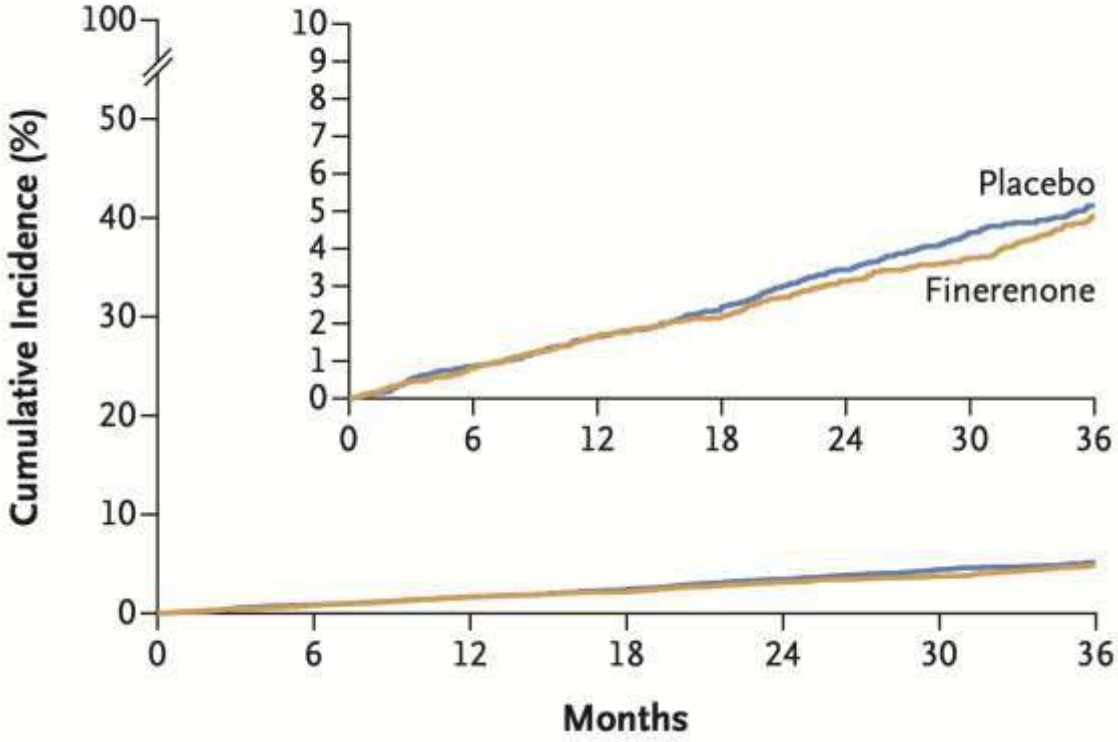



A Total Worsening Heart Failure Events and Death from Cardiovascular Causes
Mean Cumulative Events (per 100 patients)
60
50
40
30
20
10
0
0
6
12
18
24
30
36
Months
Placebo
Finerenone

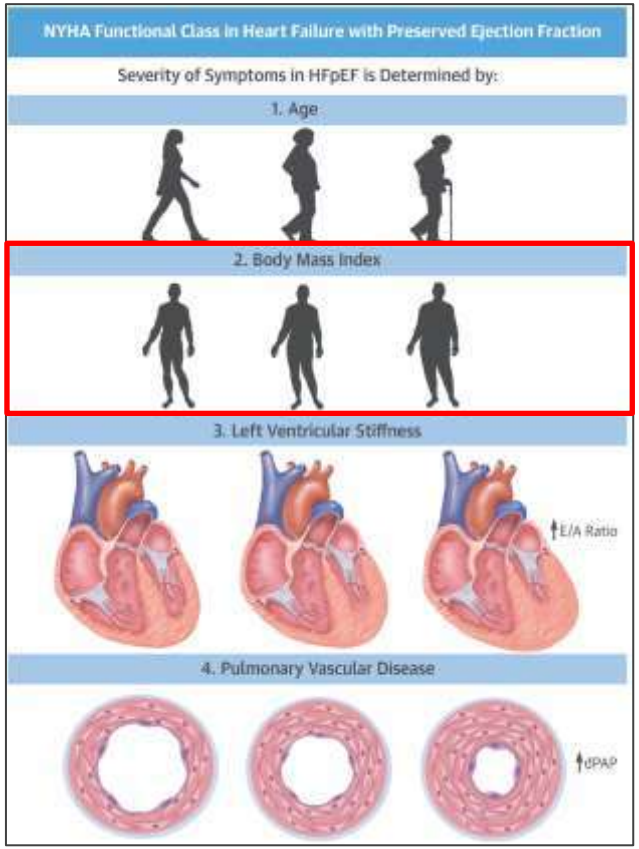
B **Total Worsening Heart Failure Events**



Death from Cardiovascular Causes



Obese phenotypes of HFpEF



Predictor of in-hospital mortality

Variables	Adjusted OR * (95% CI)	p
BMI	3.542 (1.362-9.212)	0.010
SBP < 100mmHg	3.472 (1.602-7.525)	0.002
WBC ≥ 10000/mcL	2.184 (1.135-4.203)	0.019
Na < 135mmol/L	2.628 (1.360-5.079)	0.004
Cr ≥ 2.0mg/dL	2.224 (1.030-4.804)	0.042

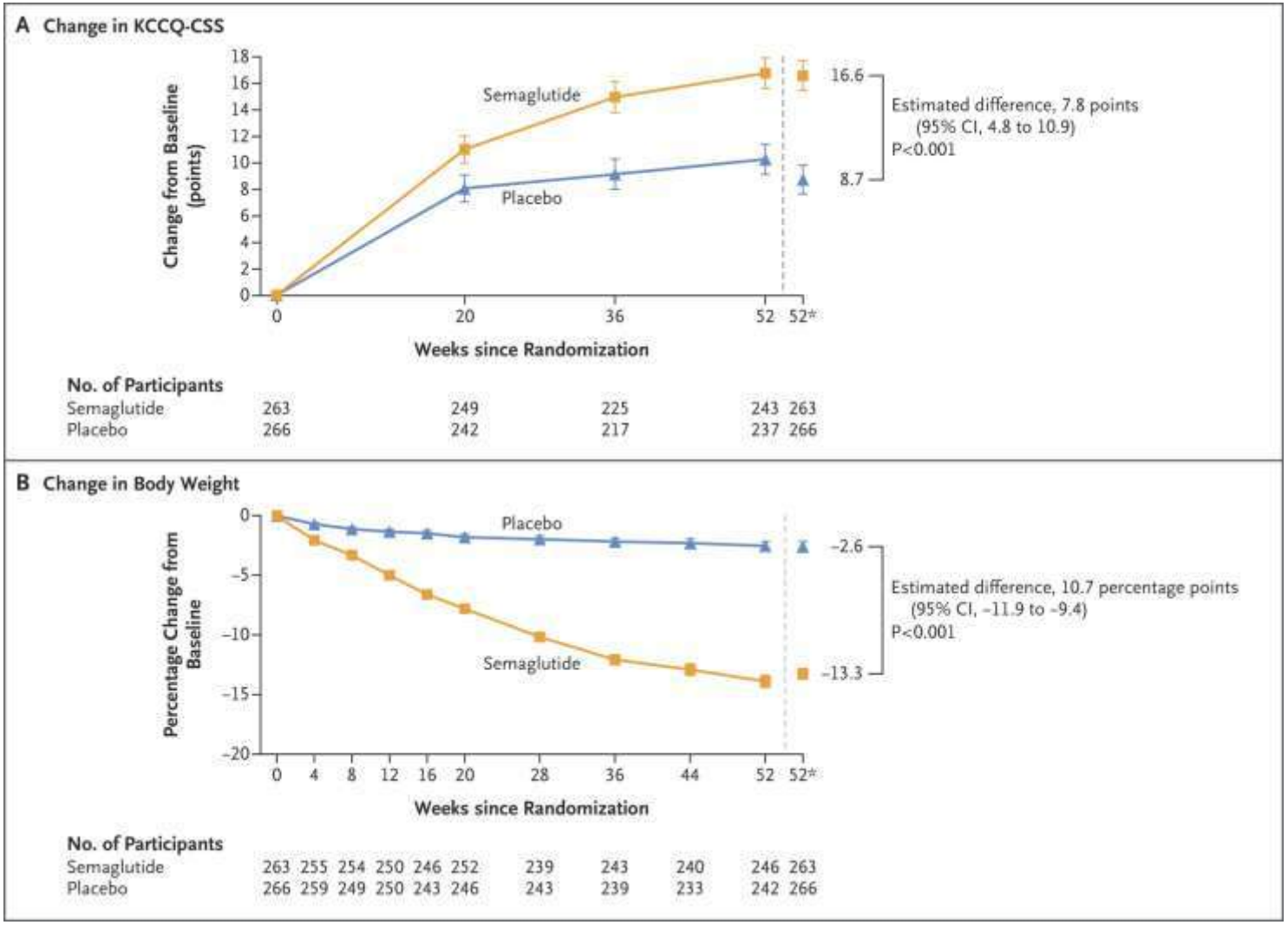
- **Obesity is common in HFpEF**, related with poor functional capacity and clinical outcome

Dalos D, et al. J Am Coll Cardiol. 2016

The NEW ENGLAND JOURNAL of MEDICINE

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

Mikhail N. Kosiborod, M.D., Steen Z. Abildstrøm, Ph.D., Barry A. Borlaug, M.D., Javed Butler, M.D., Søren Rasmussen, Ph.D., Melanie Davies, M.D., G. Kees Hovingh, M.D., Ph.D., Dalane W. Kitzman, M.D., Marie L. Lindegaard, M.D., D.M.Sc., Daniël V. Møller, M.D., Ph.D., Sanjiv J. Shah, M.D., Marianne B. Treppendahl, M.D., Ph.D., et al., for the STEP-HFpEF Trial Committees and Investigators*


A Change in KCCQ-CSS
Change from Baseline (points)
Semaglutide
Placebo
16.6
8.7
Estimated difference, 7.8 points
(95% CI, 4.8 to 10.9)
P<0.001
Weeks since Randomization
No. of Participants
Semaglutide 263 249 225 243 263
Placebo 266 242 217 237 266
B Change in Body Weight
Percentage Change from Baseline
Placebo
Semaglutide
−2.6
−13.3
Estimated difference, 10.7 percentage points
(95% CI, −11.9 to −9.4)
P<0.001
Weeks since Randomization
No. of Participants
Semaglutide 263 255 254 250 246 252 239 243 240 246 263
Placebo 266 259 249 250 243 246 243 239 233 242 266

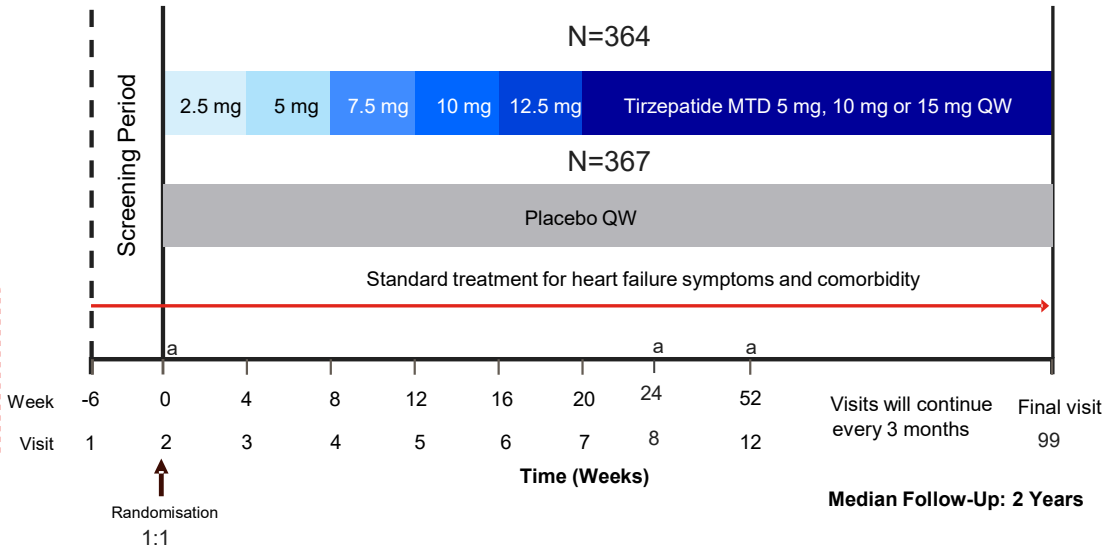
SUMMIT Trial Design

SUMMIT is a randomised, multicentre, international, placebo-controlled, double-blind, parallel-arm Phase 3 study. The study was designed to evaluate the efficacy and safety of once-weekly tirzepatide in participants with HFpEF and obesity.

Participants Enrolled: 731

Participating Countries

United States, Argentina, Brazil, China, India, Israel, Mexico, Russia and Taiwan[3]



[a]KCCQ, 6MWD and hsCRP were measured at baseline and 24 and 52 weeks.

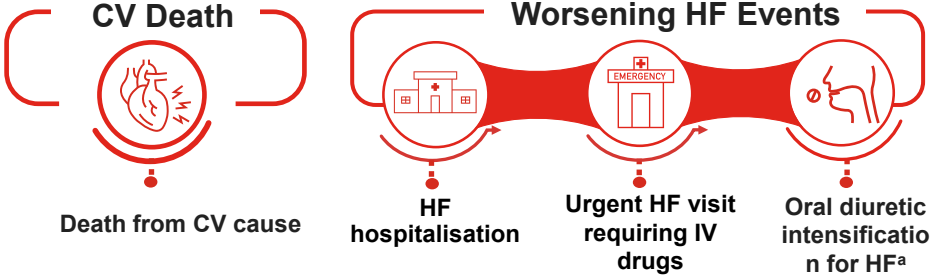
HFpEF=Heart Failure With Preserved Ejection Fraction; hsCRP=High-Sensitivity C-Reactive Protein; KCCQ=Kansas City Cardiomyopathy Questionnaire; MTD=Maximum Tolerated Dose; QW=Once Weekly; 6MWD=6-Minute Walk Distance.

Packer M, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2410027 (Ahead of print).

SUMMIT Trial Endpoints

Dual Primary Endpoints

Time to the first occurrence of the composite endpoint of CV death or worsening HF events



Change in KCCQ-CSS from Baseline to Week 52

Key Secondary Endpoints

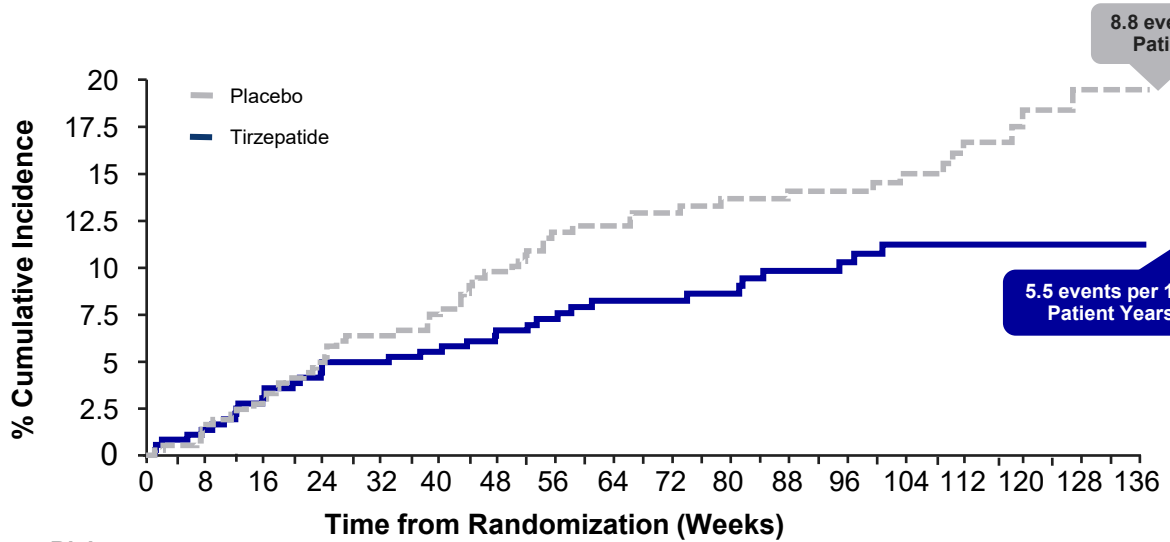
- Change from baseline to Week 52 in 6MWD
- Percent change from baseline to Week 52 in body weight
- Change from baseline to Week 52 in hsCRP

[a]Diuretic intensification in the absence of worsening heart failure was not designated as an event.

CV=Cardiovascular; HF=Heart Failure; hsCRP=High-Sensitivity C-Reactive Protein; IV=Intravenous; KCCQ-CSS=Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; 6MWD=6-Minute Walk Distance.

Packer M, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2410027 (Ahead of print).

SUMMIT Primary Endpoint: Time to First Event for CV Death or Worsening HF Event[a]



HR 0.62
(95% CI 0.41-0.95)
P=.026

RRR 38%

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

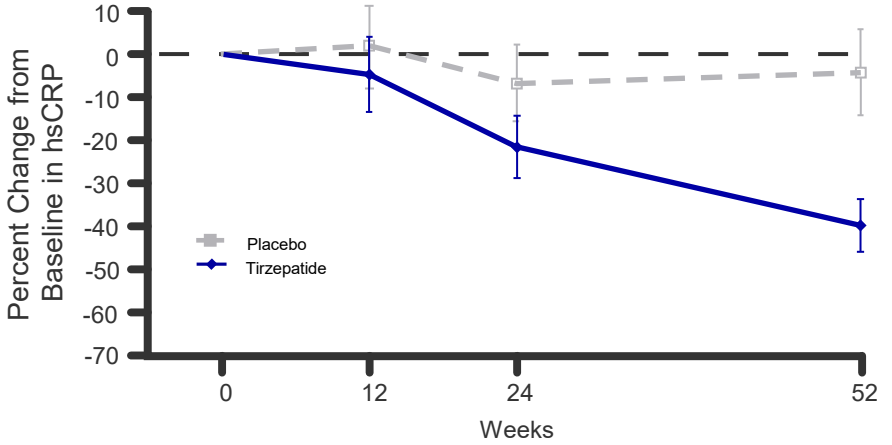
[a]Worsening HF event was defined as heart failure symptoms requiring hospitalization, intravenous drugs for HF in an urgent care setting or intensification of oral diuretics. Changes in oral diuretics without worsening HF was not designated as an event.

CI=Confidence Interval; CV=Cardiovascular; HF=Heart Failure; HR=Hazard Ratio; RRR=Relative Risk Reduction.

Packer M, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2410027 (Ahead of print).

Change From Baseline to Week 52 in hsCRP

Key Secondary Endpoint



No. of Participants				
Placebo	332	323	313	298
Tirzepatide	344	332	323	305

Treatment Regimen Estimand

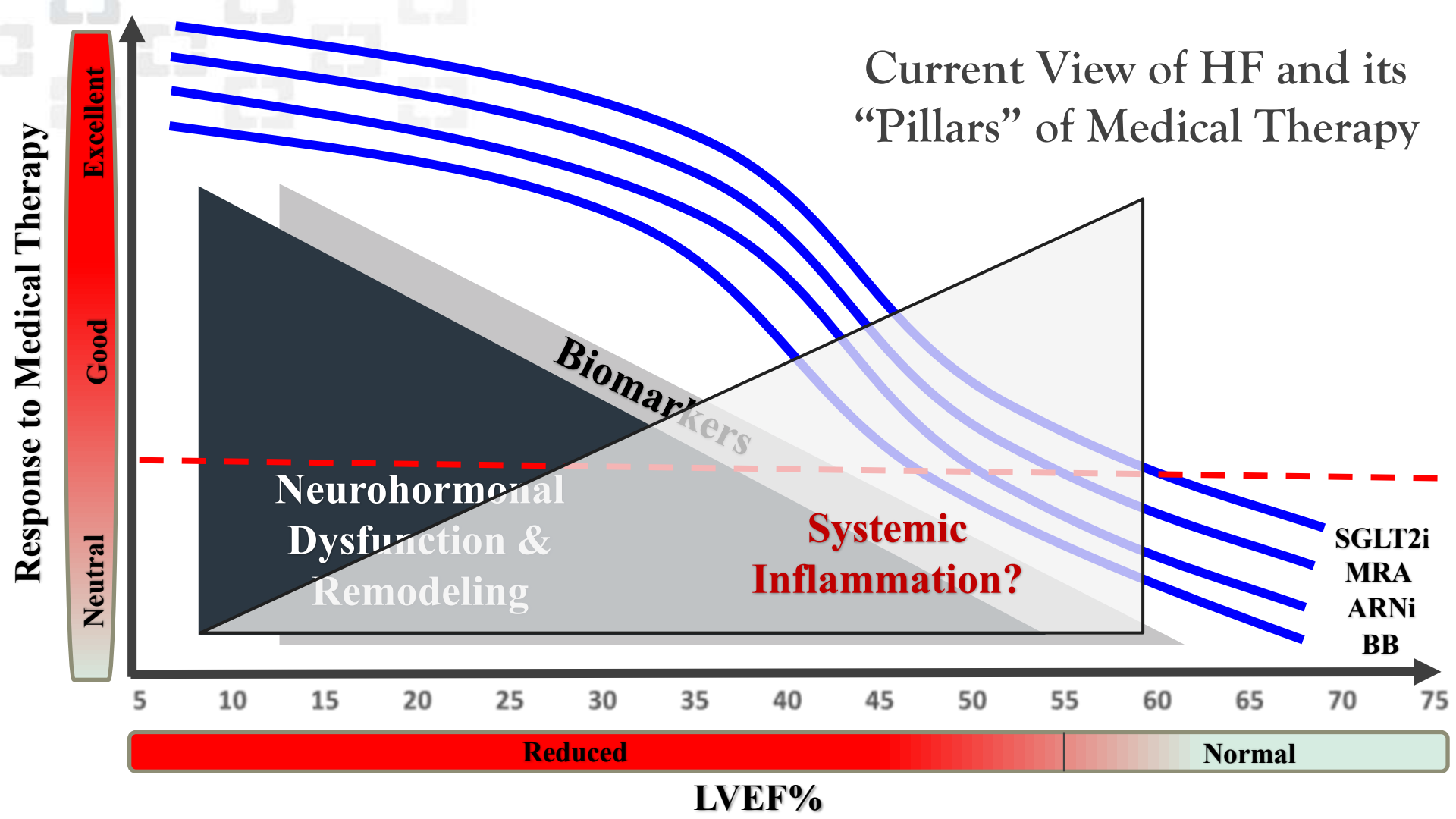
ETD -34.9
(95% CI -45.6 to -22.2)[a]
P<.001

A greater reduction in hsCRP was observed in patients on tirzepatide compared to placebo.

[a]Data were log-transformed before analysis. Tirzepatide vs. placebo: ***P<0.001. Data presented are LSM±SE with 95% CI.

CI=Confidence Interval; ETD=Estimated Treatment Difference; hsCRP=High Sensitivity C-reactive Protein; LSM=Least-Square Mean; MMRM=Mixed Model Repeated Measures; SE=Standard Error; TRE=Treatment Regimen Estimand.

Packer M, et al. *NEJM*. 2024;doi:10.1056/NEJMoa2410027 (Ahead of print).


Current View of HF and its "Pillars" of Medical Therapy
Response to Medical Therapy
Excellent
Good
Neutral
Biomarkers
Neurohormonal Dysfunction & Remodeling
Systemic Inflammation?
SGLT2i
MRA
ARNi
BB
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
Reduced
Normal
LVEF%

Summary

- **Preserved EF is not necessarily Normal EF!**
- **Normal EF proved to be a moving target: 55 is new 40!, perhaps a little higher in women than men based on accumulating evidence.**
- All four "pillars" of HF therapy have evidence to support their use in abnormal EF (reduced or preserved), more so with ARNI and SGLT2i as it gets closer to "normal", and more so on hospitalizations than mortality at that range.
- New targets for medical therapy in HFpEF are being identified.

Submit your abstracts

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