Scompenso cardiaco: la frazione d'eiezione come guida e obiettivo della terapia?

Lezioni dagli HFpEF trials

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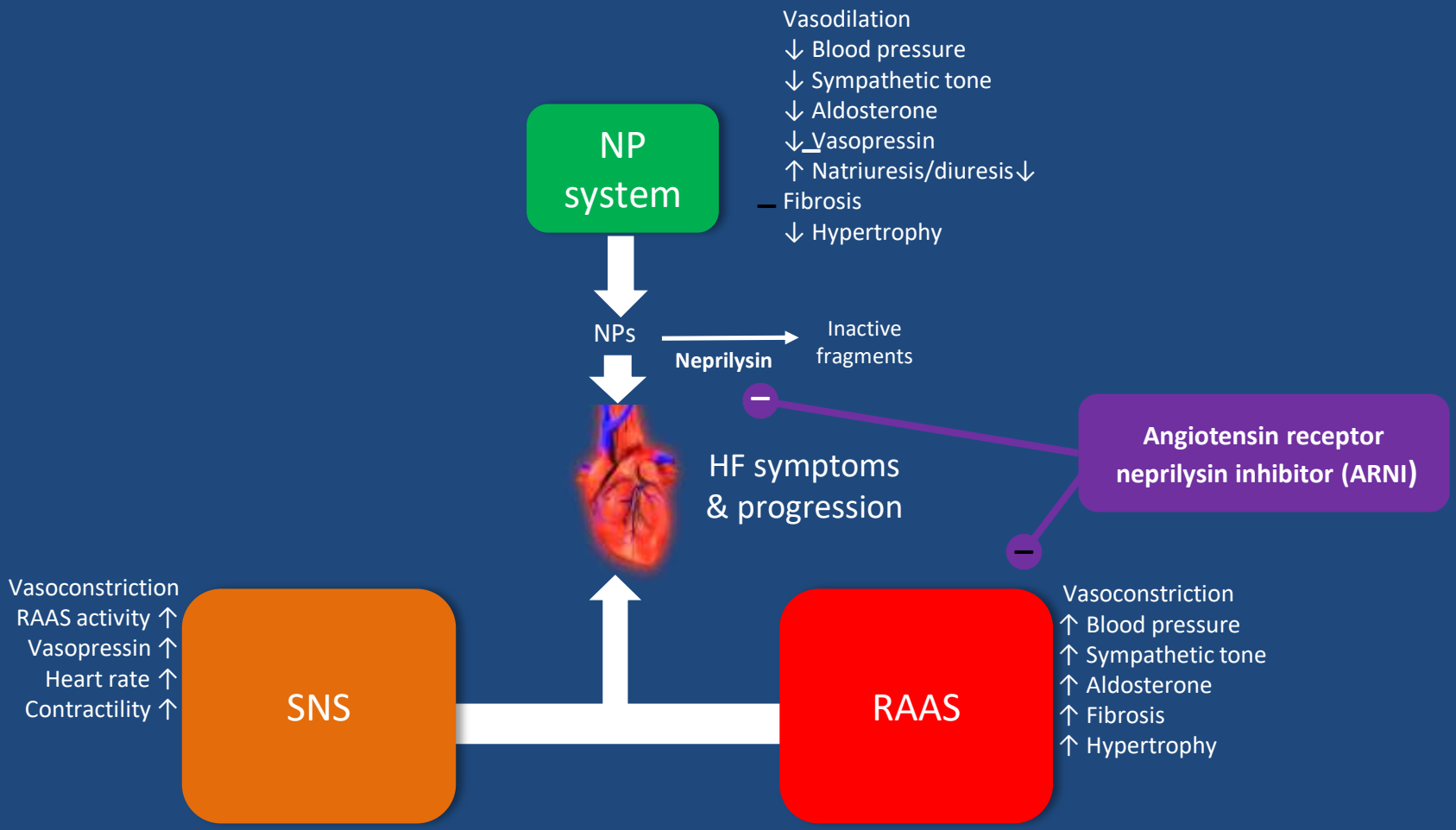
Restoring neurohormonal balance between NP system, SNS, and RAAS may offer therapeutic potential for CHF



CHF=chronic heart failure; NP=natriuretic peptide; RAAS=renin angiotensin aldosterone system; SNS=sympathetic nervous system

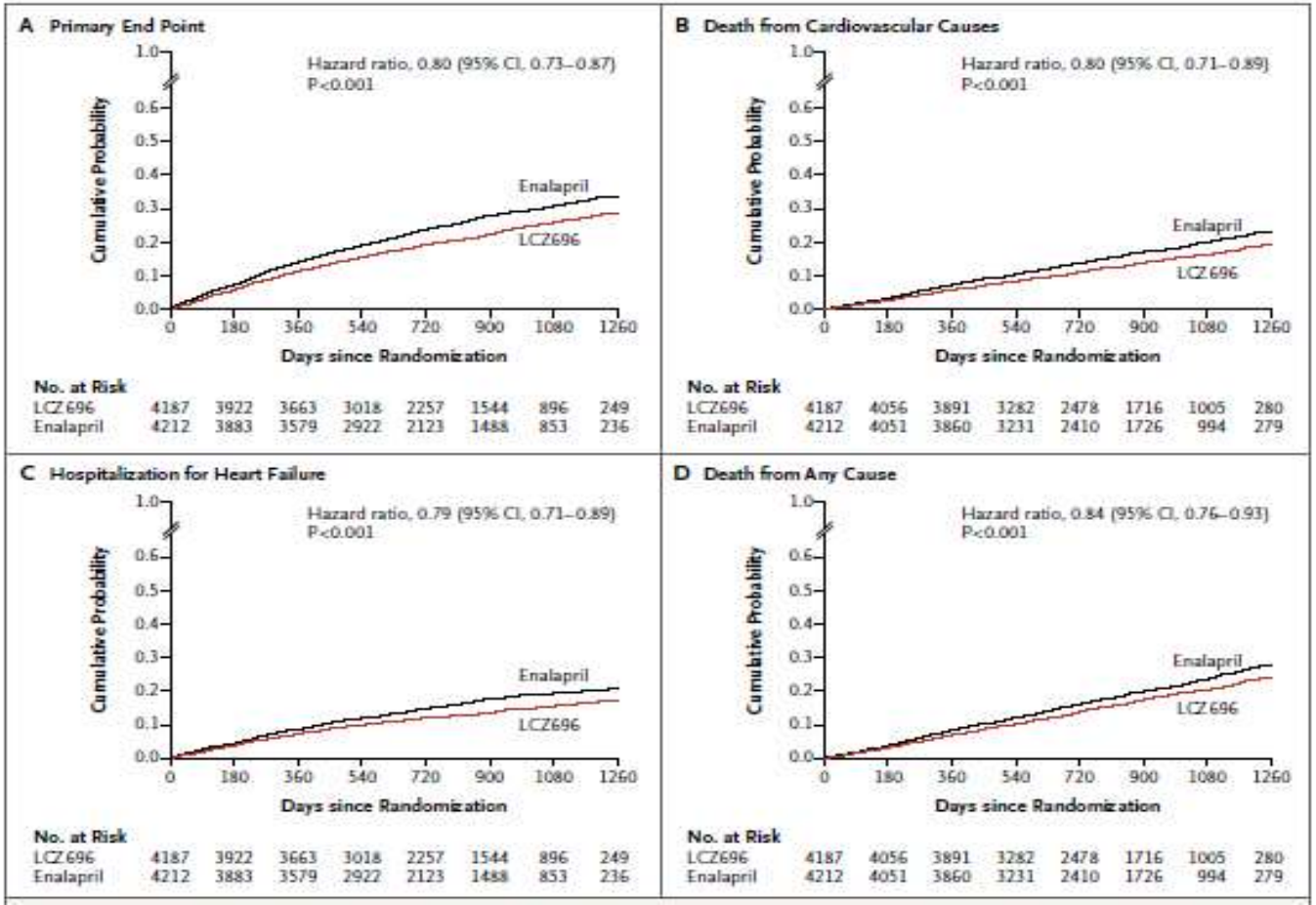
Kemp & Conte. Cardiovascular Pathology 2012;365–371; Schrier & Abraham N Engl J Med 2009;341:577–585
Langenickel & Dole. Drug Discovery Today: Therapeutic Strategies 2012;9:e131–9

ARNi vs Enalapril for the treatment of heart failure (PARADIGM-HF)

Clinical features of heart failure		
Ischemic cardiomyopathy — no. (%)	2506 (59.9)	2530 (60.1)
Left ventricular ejection fraction — %	29.6±6.1	29.4±6.3
Median B-type natriuretic peptide (IQR) — pg/ml	255 (155–474)	251 (153–465)
Median N-terminal pro–B-type natriuretic peptide (IQR) — pg/ml	1631 (885–3154)	1594 (886–3305)
NYHA functional class — no. (%)¶		
I	180 (4.3)	209 (5.0)
II	2998 (71.6)	2921 (69.3)
III	969 (23.1)	1049 (24.9)
IV	33 (0.8)	27 (0.6)
Missing data	7 (0.2)	6 (0.1)
Medical history — no. (%)		
Hypertension	2969 (70.9)	2971 (70.5)
Diabetes	1451 (34.7)	1456 (34.6)
Atrial fibrillation	1517 (36.2)	1574 (37.4)
Hospitalization for heart failure	2607 (62.3)	2667 (63.3)
Myocardial infarction	1818 (43.4)	1816 (43.1)
Stroke	355 (8.5)	370 (8.8)
Pretrial use of ACE inhibitor‖	3266 (78.0)	3266 (77.5)
Pretrial use of ARB‖	929 (22.2)	963 (22.9)

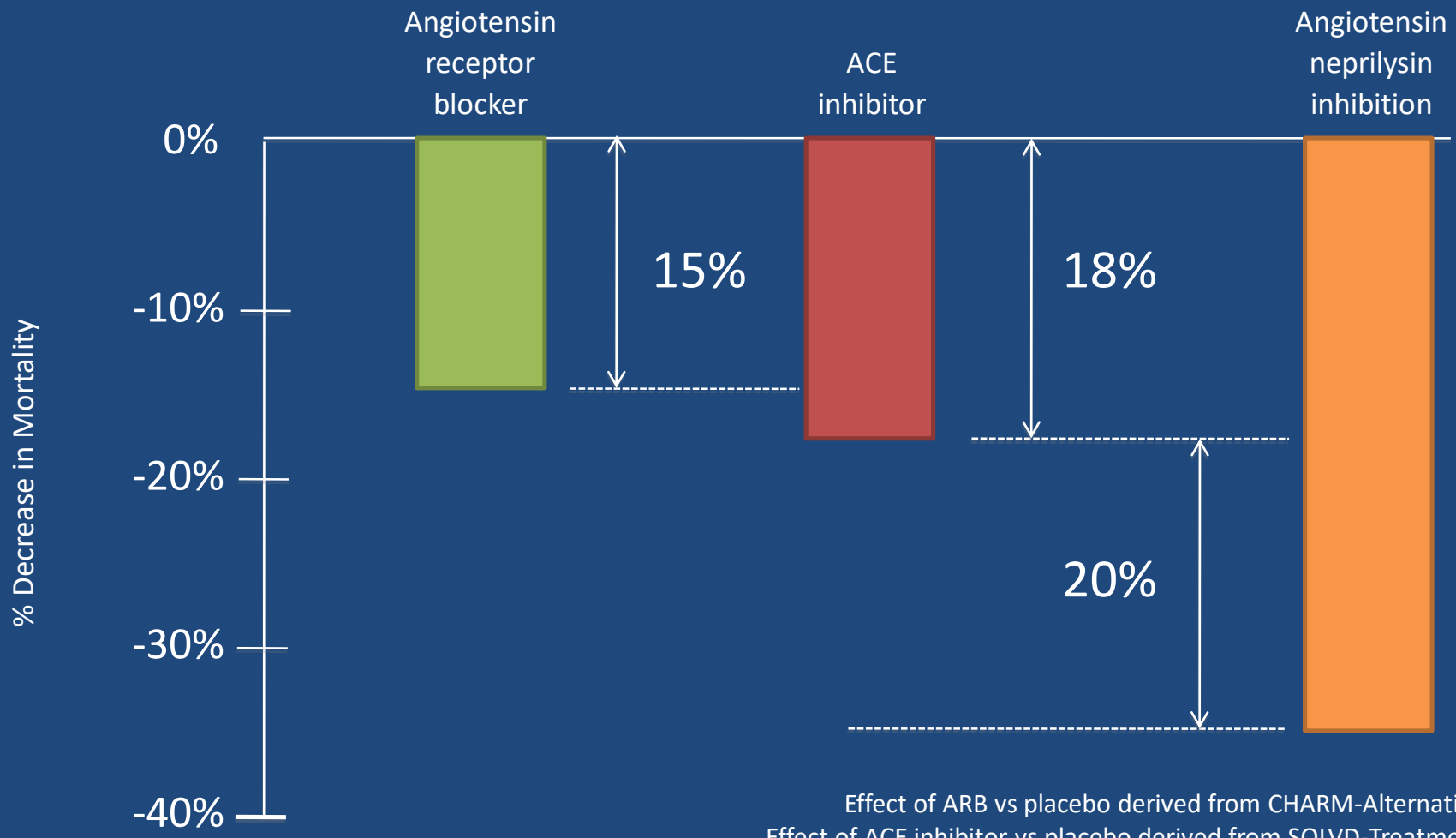
ARNi vs Enalapril for the treatment of heart failure (PARADIGM-HF)

The NEW ENGLAND JOURNAL of MEDICINE



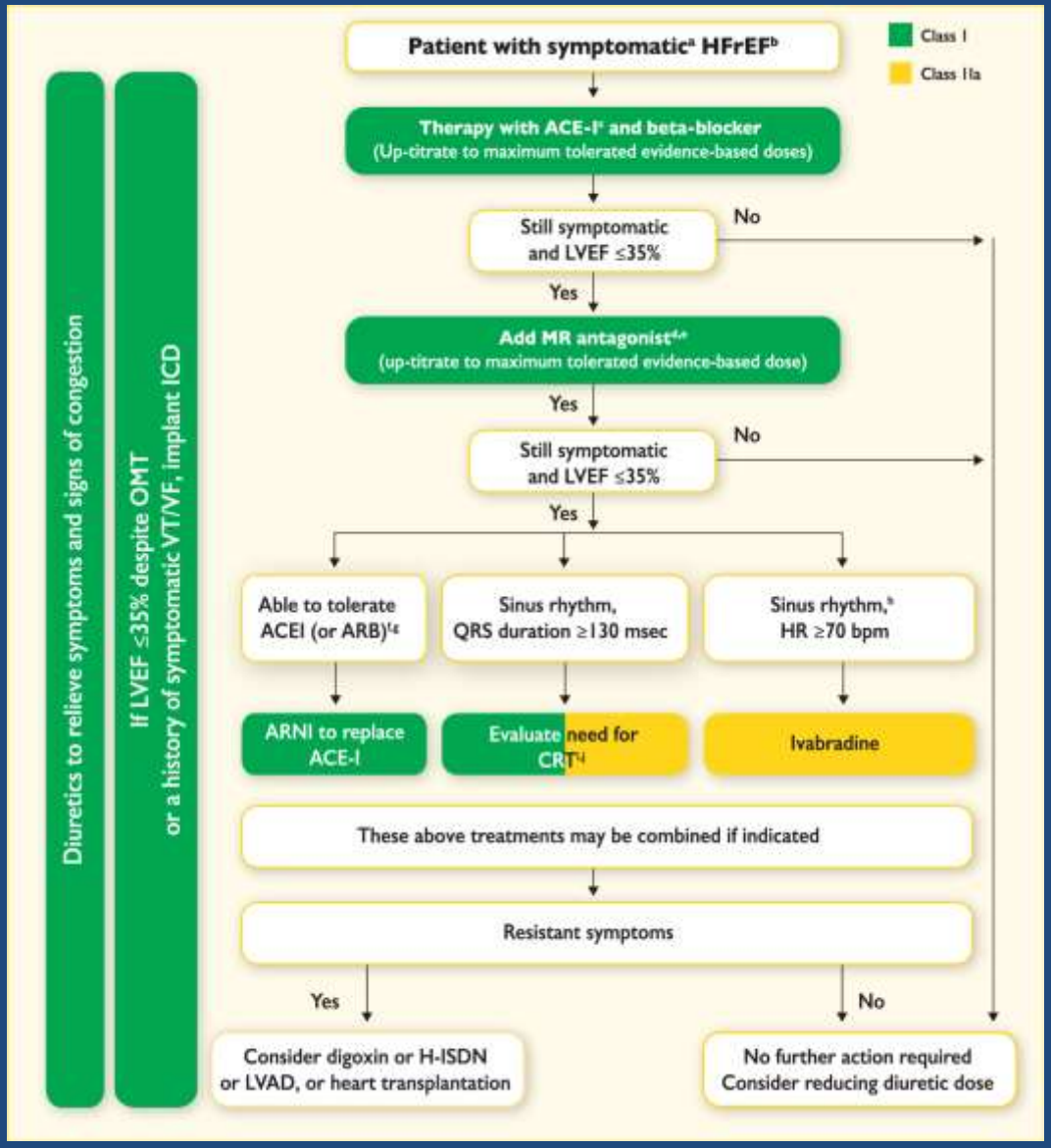
McMurray J et al. 2014

Angiotensin Neprilysin Inhibition With LCZ696 Doubles Effect on CV Death of Current Inhibitors of RAS in the proof-of-concept study Paradigm HF



Effect of ARB vs placebo derived from CHARM-Alternative trial
Effect of ACE inhibitor vs placebo derived from SOLVD-Treatment trial
Effect of LCZ696 vs ACE inhibitor derived from PARADIGM-HF trial

ESC guidelines for heart failure 2016



The PARAGON Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

PARAGON-HF: Key Inclusion and Exclusion Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• ≥ 50 years of age and LVEF ≥ 45% • Heart failure signs/symptoms (NYHA Class II–IV) requiring treatment with diuretic(s) for at least 30 days prior to enrollment • Structural heart disease (LAE or LVH by echocardiography) • Elevation in natriuretic peptides • NT-proBNP >200 pg/ml if hospitalized for HF within 9 months, and >300 pg/ml if not hospitalized; 3-fold increase for patients in AF at enrollment	• Any prior measurement of LVEF < 40% • Current acute decompensated heart failure • Alternative reason for signs and symptoms • SBP < 110 or ≥ 180 mm Hg (or > 150 mm Hg if patient not taking 3 or more antihypertensive medications)

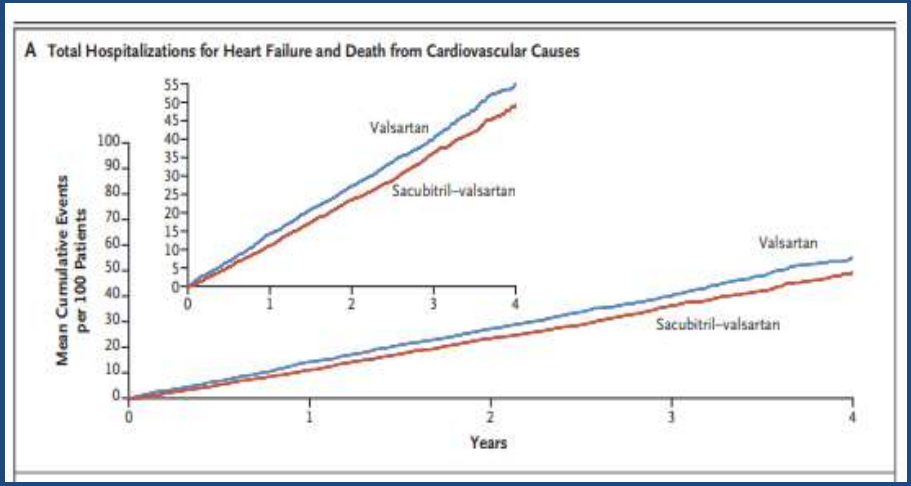
Solomon SD, et al. *JACC-Heart Fail* 2017;5:471-482

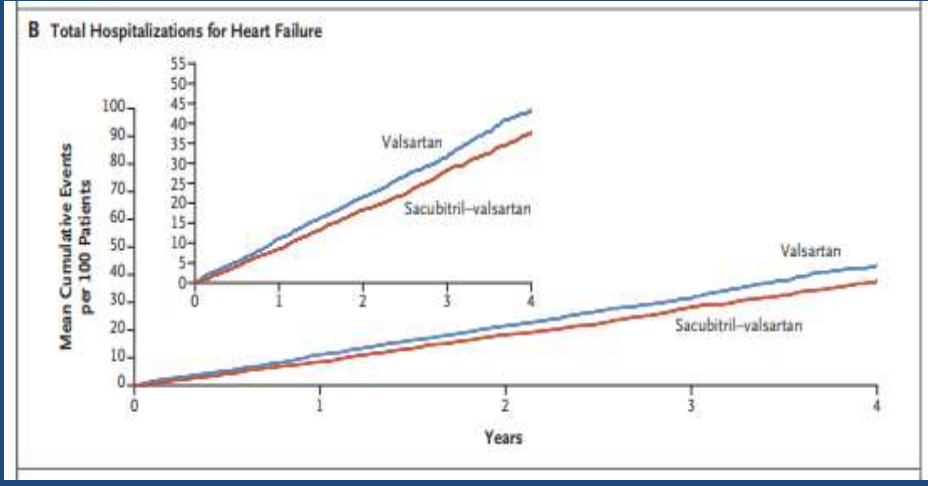
Baseline characteristics

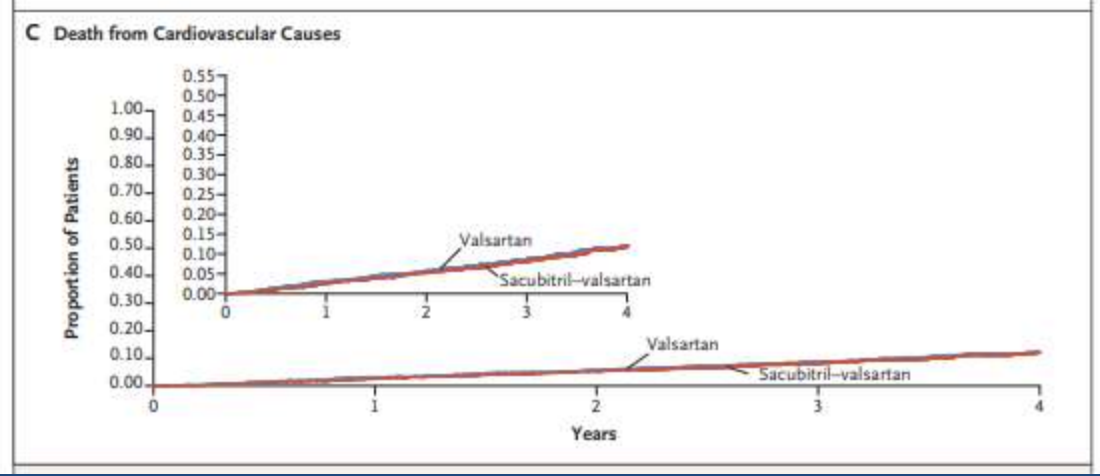
Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Sacubitril–Valsartan (N = 2407)	Valsartan (N = 2389)
Age — yr	72.7±8.3	72.8±8.5
Female sex — no. (%)	1241 (51.6)	1238 (51.8)
Race — no. (%)†		
White	1963 (81.6)	1944 (81.4)
Black	52 (2.2)	50 (2.1)
Asian	297 (12.3)	310 (13.0)
Other	95 (4.0)	85 (3.6)
Geographic region — no. (%)		
North America	288 (12.0)	271 (11.3)
Latin America	191 (7.9)	179 (7.5)
Western Europe	699 (29.0)	691 (28.9)
Central Europe	856 (35.6)	859 (36.0)
Asia–Pacific or other	373 (15.5)	389 (16.3)
Systolic blood pressure — mm Hg‡	130.5±15.6	130.6±15.3
Heart rate — beats/min‡	70.6±12.3	70.3±12.2
Body-mass index§	30.2±4.9	30.3±5.1
Serum creatinine — mg/dl‡	1.1±0.3	1.1±0.3
Estimated GFR — ml/min/1.73 m^2	63±19	62±19
Clinical features of heart failure		
Ischemic cause — no. (%)	899 (37.4)	824 (34.5)
Left ventricular ejection fraction — %	57.6±7.8	57.5±8.0
Median NT-proBNP (interquartile range) — pg/ml	904 (475–1596)	915 (453–1625)

Primary Outcome and its components





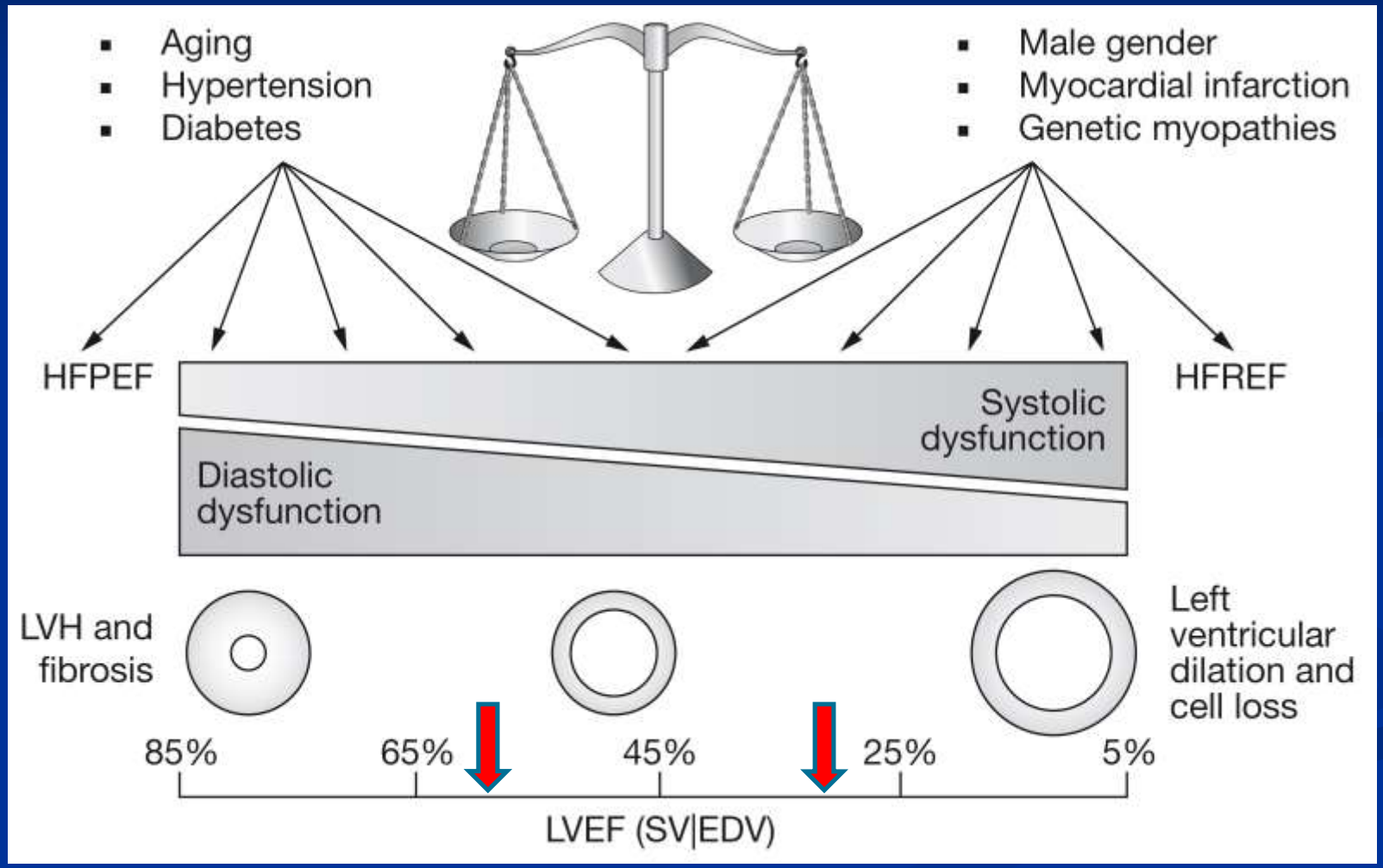


Primary and secondary outcomes

Outcome	Sacubitril–Valsartan (N = 2407)	Valsartan (N = 2389)	Ratio or Difference (95% CI)
Primary composite outcome and components			
Total hospitalizations for heart failure and death from cardiovascular causes†			RR, 0.87 (0.75–1.01)
Total no. of events	894	1009	
Rate per 100 patient-yr	12.8	14.6	
Total no. of hospitalizations for heart failure	690	797	RR, 0.85 (0.72–1.00)
Death from cardiovascular causes — no. (%)	204 (8.5)	212 (8.9)	HR, 0.95 (0.79–1.16)
Secondary outcomes			
Change in NYHA class from baseline to 8 mo — no./total no. (%)			OR, 1.45 (1.13–1.86)
Improved	347/2316 (15.0)	289/2302 (12.6)	
Unchanged	1767/2316 (76.3)	1792/2302 (77.8)	
Worsened	202/2316 (8.7)	221/2302 (9.6)	
Change in KCCQ clinical summary score at 8 mo‡	−1.6±0.4	−2.6±0.4	Difference, 1.0 (0.0–2.1)
Renal composite outcome — no. (%)§	33 (1.4)	64 (2.7)	HR, 0.50 (0.33–0.77)
Death from any cause — no. (%)	342 (14.2)	349 (14.6)	HR, 0.97 (0.84–1.13)

Is it biologically reasonable to classify patients with heart failure only on the basis of EF?

The spectrum of Heart Failure: From Preserved (HF-PEF) to Reduced Ejection Fraction (HF-REF)



Ouzounian et al. Nat Clin Pract Cardiovasc Med 2008;5:375-86

Changing Understanding of EF Categories: Should We Go Back to Reduced vs Normal?

1980s: HF with normal systolic function

Intact Systolic Left Ventricular Function in Clinical Congestive Heart Failure

ROBERT SOUFER, MD, DANIEL WOHLGELERNTER, MD, NESTOR A. VITA, MD, MARCOS AMUCHESTEGUI, MD, H. DIRK SOSTMAN, MD, HARVEY J. BERGER, MD, and BARRY L. ZARET, MD

Congestive Heart Failure with Normal Systolic Function

ANNE HAMILTON DOUGHERTY, MD, GERALD V. NACCARELLI, MD, ELAYNE L. GRAY, BSN, CHARLES H. HICKS, MD, and RICHARD A. GOLDSTEIN, MD

→ Then focus on diastolic dysfunction

ORIGINAL ARTICLE

Diastolic Heart Failure — Abnormalities in Active Relaxation and Passive Stiffness of the Left Ventricle

Michael R. Zile, M.D., Catalin F. Baicu, Ph.D., and William H. Gaasch, M.D.

→ Then diagnostic criteria: signs, symptoms, NPs, echo structure/function

European Journal of Heart Failure (2016) 18, 891–975
doi:10.1002/ejhf.592

ESC GUIDELINES

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

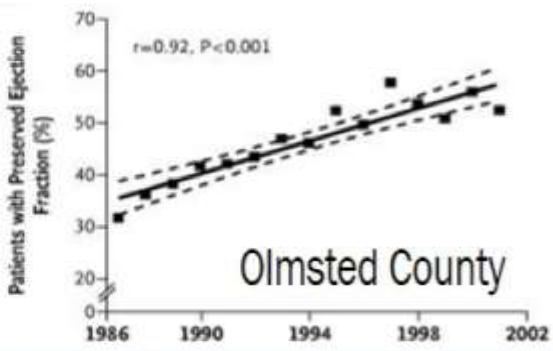
Type of HF	HFrEF	HFmrEF	HFpEF
Criteria 1*			
Criteria 2	LVEF < 40%	LVEF 40-49%	LVEF ≥50%
Criteria 3			

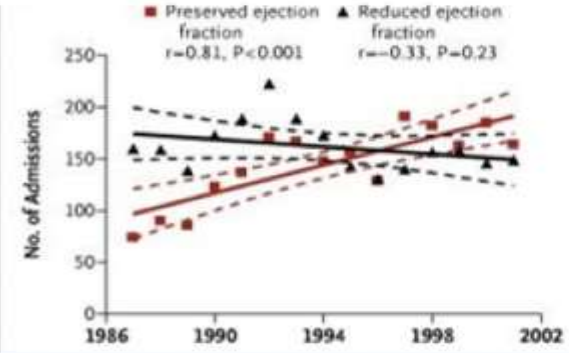
* Symptoms ± Signs

Soufer R, et al. *Am J Cardiol*. 1985;55:1032-1036; Zile MR, et al. *N Engl J Med*. 2004;350:1953-1959; Ponikowski P, et al. *Eur J Heart Fail*.2016;18:891-975.

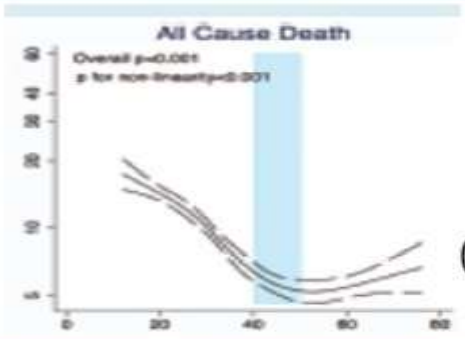
HFpEF Differences vs HFrEF

HFpEF is increasing in incidence and prevalence





HFpEF in registries similar mortality; in trials lower mortality

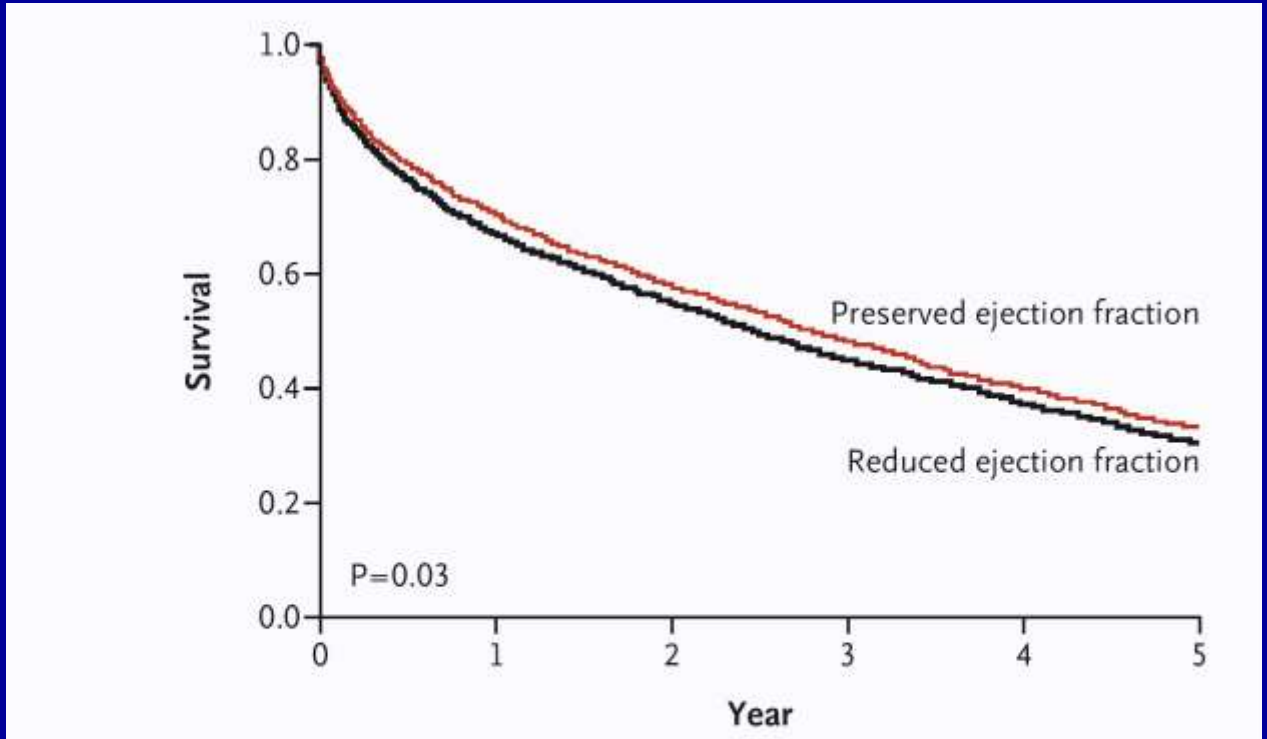


CHARM

HFpEF lower CV risk and higher non-CV risk

Owan TE, et al. *N Engl J Med*. 2006;355:251-259; Chioncel O, et al. *Eur J Heart Fail*. 2017;19: 1574-1585; Lund LH, et al. *Eur J Heart Fail*. 2018;20: 1230-1239.

Prognosis of Patients with Preserved and Reduced Ejection Fraction

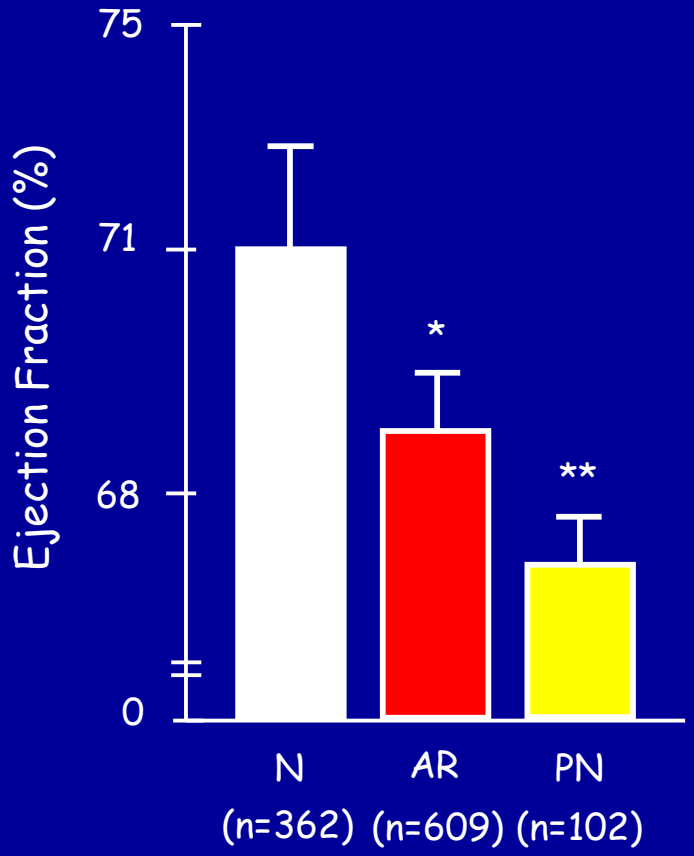


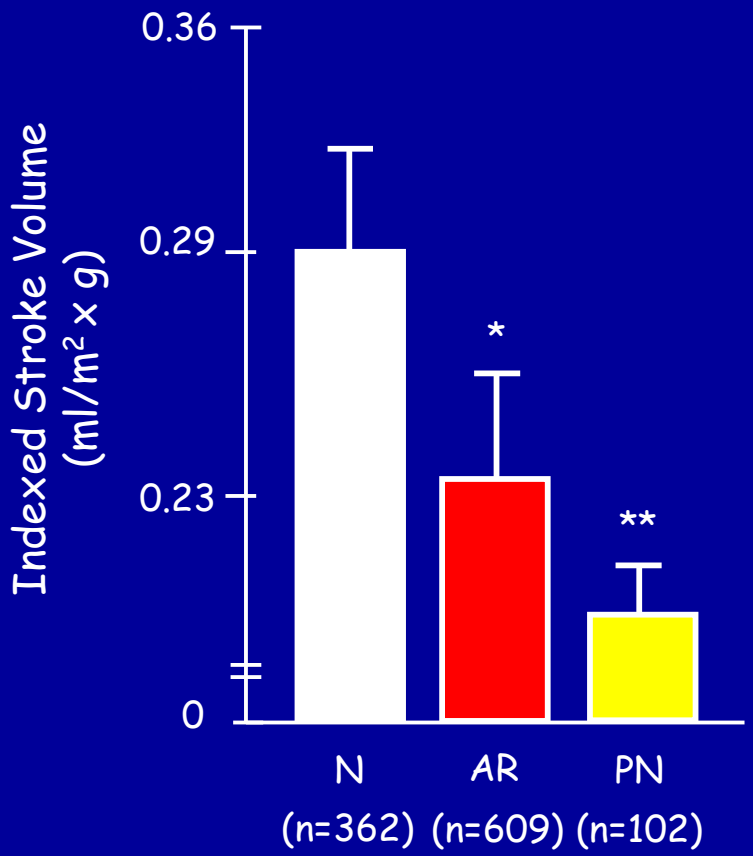
No. at Risk

Reduced ejection fraction	2424	1637	1350	1049	813	604
Preserved ejection fraction	2166	1539	1270	1001	758	574

Owan et al. NEJM 2006; 355:251-9

Diastolic and Systolic Dysfunction Often Coexist in Hypertensive Patients with Preserved EF





N = Normal
AR = Altered Relaxation
PN = Pseudonormal

Sciarretta et al. Am J Hypert 2009,22:437-43

Clinical Characteristics of HFPEF

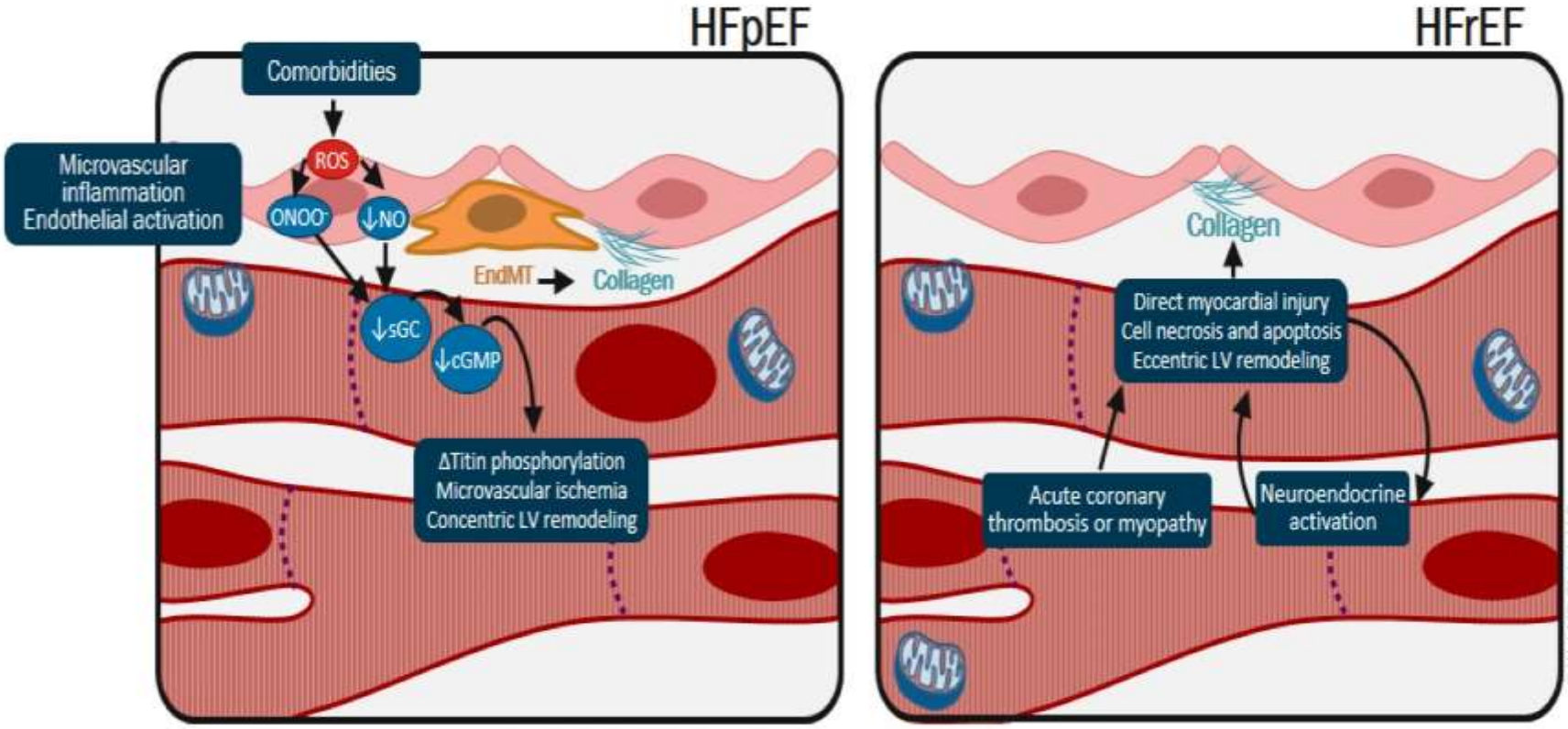
Characteristic	Reduced Ejection Fraction (N=2429)	Preserved Ejection Fraction (N=2167)	P Value	Adjusted P Value†
Age (yr)	71.7±12.1	74.4±14.4	<0.001	NA
Male sex (% of patients)	65.4	44.3	<0.001	<0.001
Body-mass index‡	28.6±7.0	29.7±7.8	0.002	0.17
Obesity (% of patients)‡§	35.5	41.4	0.007	0.002
Serum creatinine on admission (mg/dl)	1.6±1.0	1.6±1.1	0.31	0.30
Hemoglobin on admission (g/dl)	12.5±2.0	11.8±2.1	<0.001	<0.001
Hypertension (% of patients)	48.0	62.7	<0.001	<0.001
Coronary artery disease (% of patients)	63.7	52.9	<0.001	<0.001
Atrial fibrillation (% of patients)	28.5	41.3	<0.001	<0.001
Diabetes (% of patients)	34.3	33.1	0.42	0.61
Substantial valve disease (% of patients)	6.5	2.6	<0.001	0.05
Ejection fraction (%)	29±10	61±7	<0.001	NA

Owan et al. NEJM 2006; 355:251-9

Comorbidity-Driven Inflammation Hypothesis

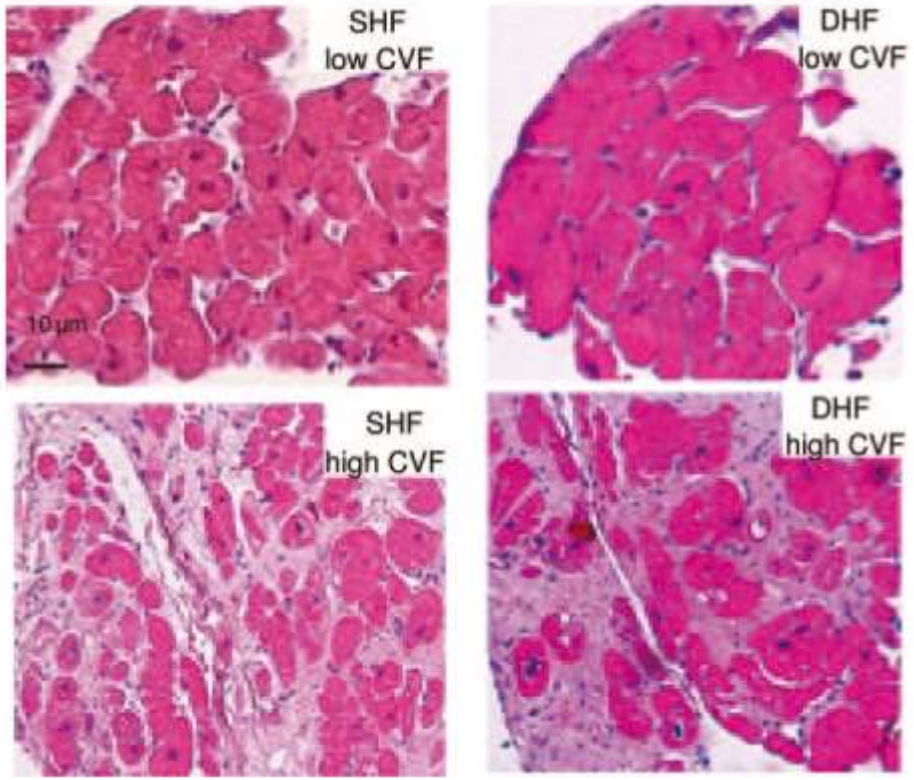
2. Distinct HFpEF syndrome ?

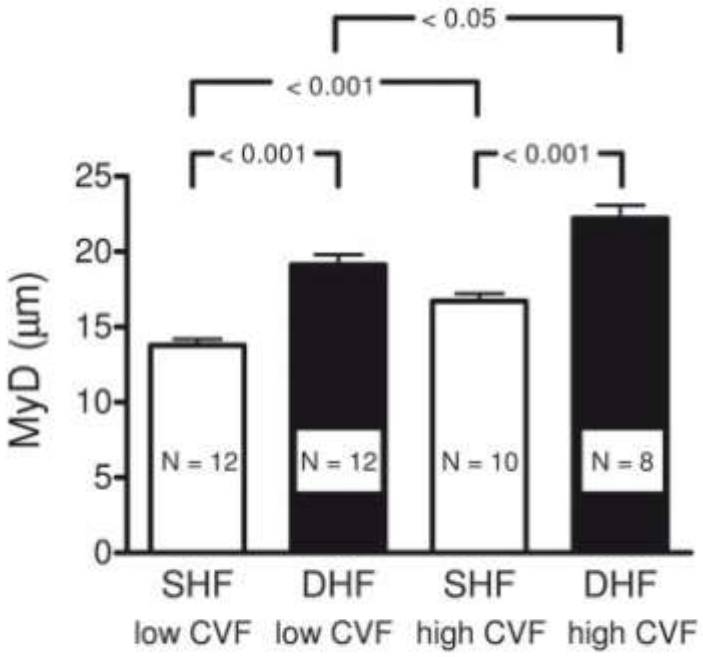
- Completely novel treatment strategies needed?



Lam CSP, Lund LH. *Heart*. 2016;102:257-259. Paulus WJ, et al. *J Am Coll Cardiol*. 2013;62:263-271.

Structural Myocardial Changes in Heart Failure with Preserved and Reduced Ejection Fraction

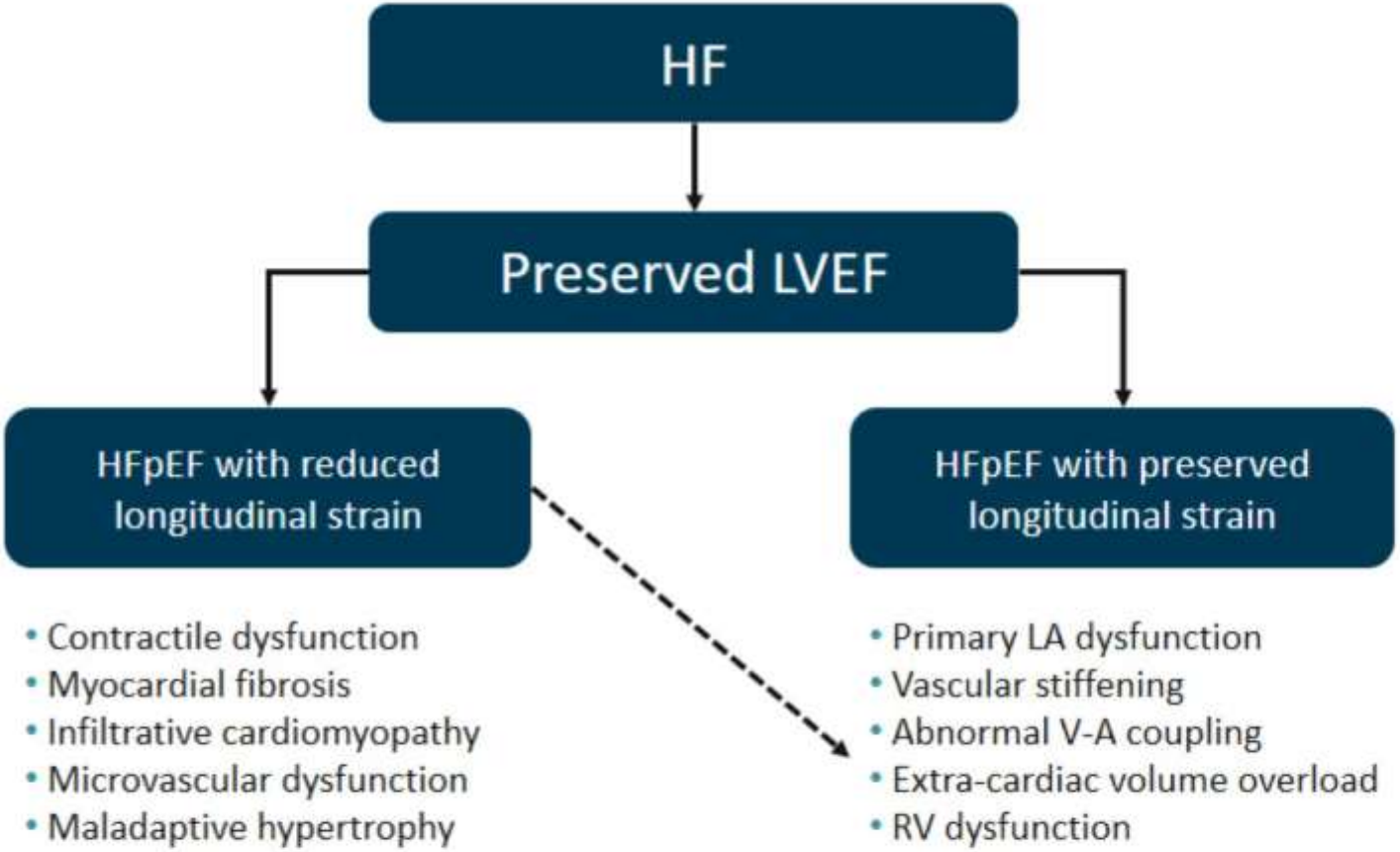




MyD= Cardiomyocite Diameter
CVF= Collagen Volume Fraction

Van Heerebeek et al. Circulation 2006;113:1966-73

Phenotyping HFpEF: Beyond EF (cont)



Omar AMS, et al. *Circ Res*. 2016;119:357-374.

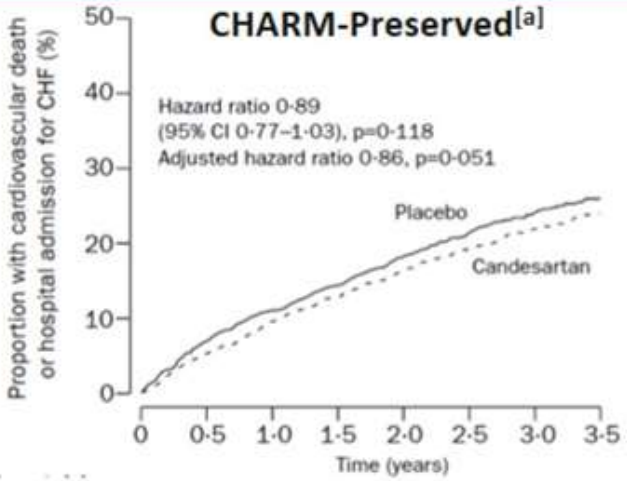
Comorbidities and Non-CV Risk Are Relatively More Important in HFpEF and Vary Among Patients With HFpEF: TOPCAT, CHARM Preserved, I-PRESERVE

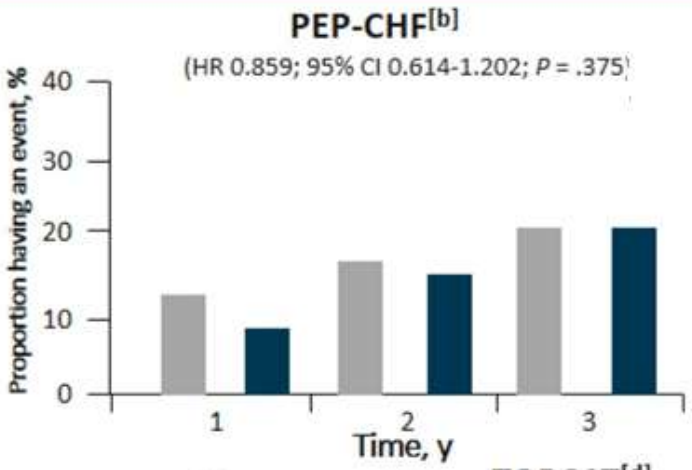
3. "Just" age-related comorbidities ?

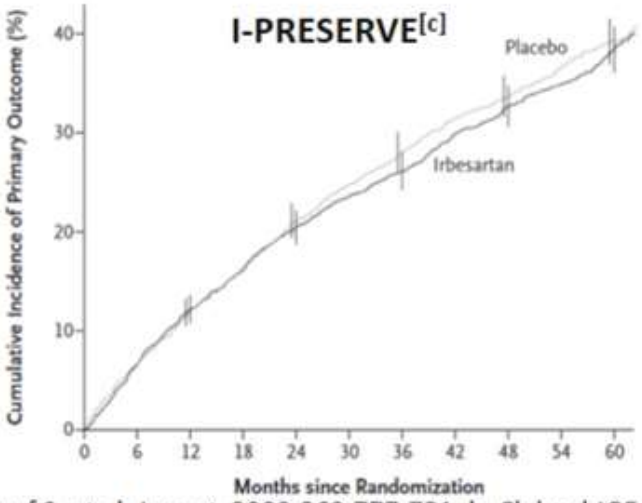
Age related differences in patients with heart failure with preserved ejection fraction	Young heart failure with preserved ejection fraction	Elderly heart failure with preserved ejection fraction
Clinical characteristics	Men ↑ Obese	Women ↑ Atrial fibrillation, hypertension, renal disease
Cardiac structure and function	↑ Concentric hypertrophy ↑ Filling pressure ↑ Left ventricular volume	↑ Left atrial size
Clinical outcomes	↑ Cardiovascular cause of death ↑ Sudden cardiac death	↑ Noncardiovascular cause of death

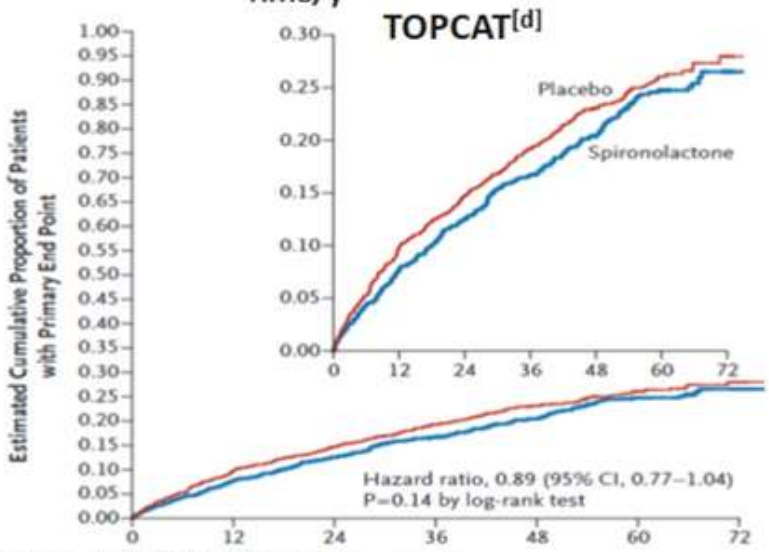
Tromp J, et la. *J Am Coll Cardiol*.2019; 74: 601-612.

Outcomes Trials in HFpEF









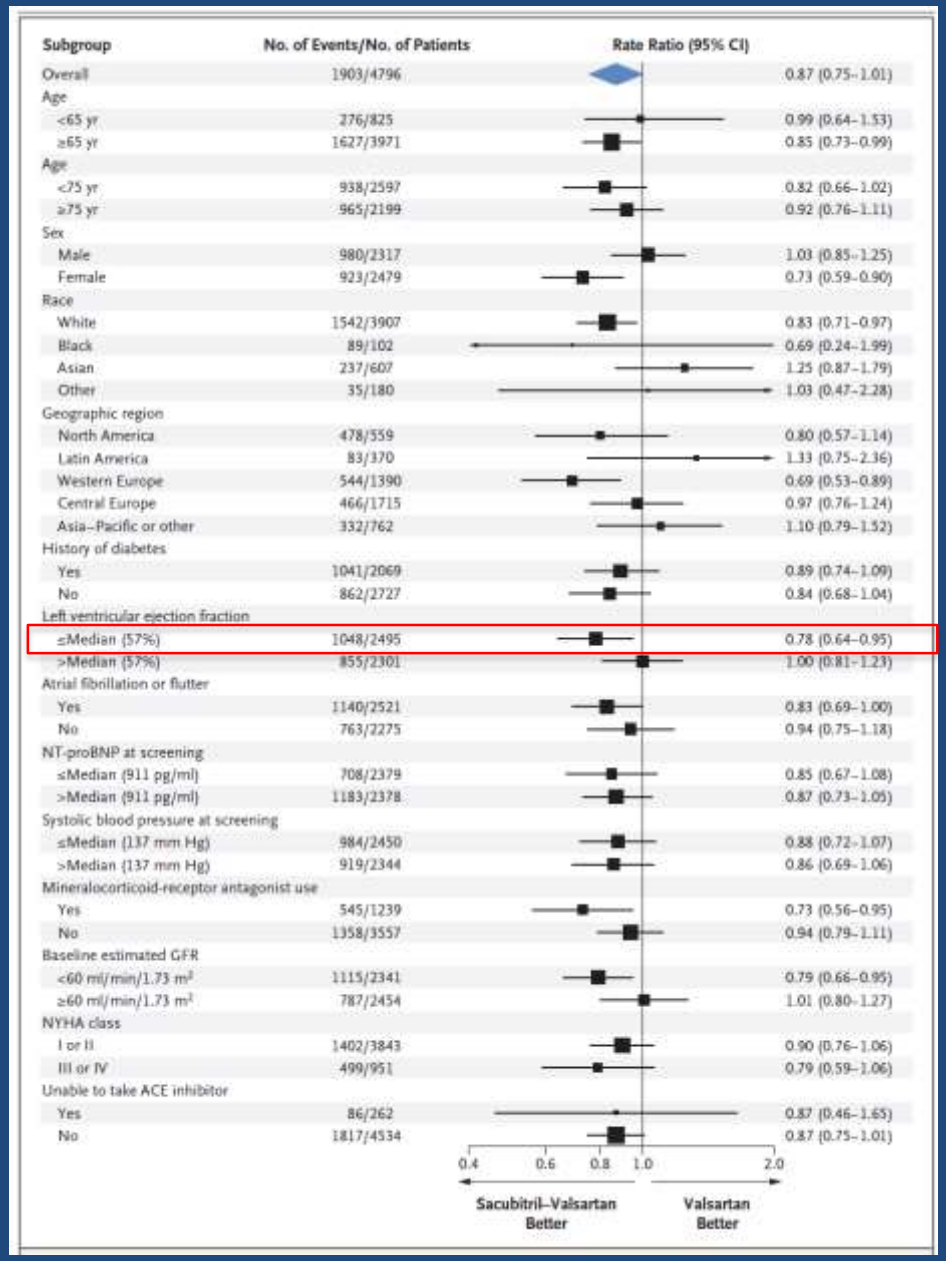
a. Yusuf S, et al. *Lancet*. 2003;363:777-781; b. Cleland JGF, et al. *Eur Heart J*. 2006;27:2338-2345;
c. Massie BM, et al. *N Eng J Med*. 2008;359:2456-2367; d. Pitt B, et al. *N Eng J Med*. 2014;370:1383-1392.

Definition of heart failure according to EF

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).

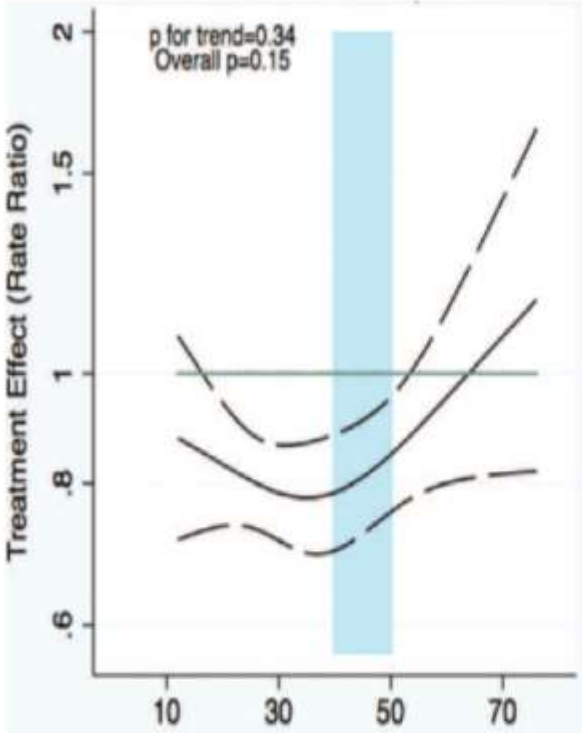
2016 ESC Guidelines on diagnosis and treatment of HF

Primary Outcome in Prespecified Subgroups in PARAGON-HF

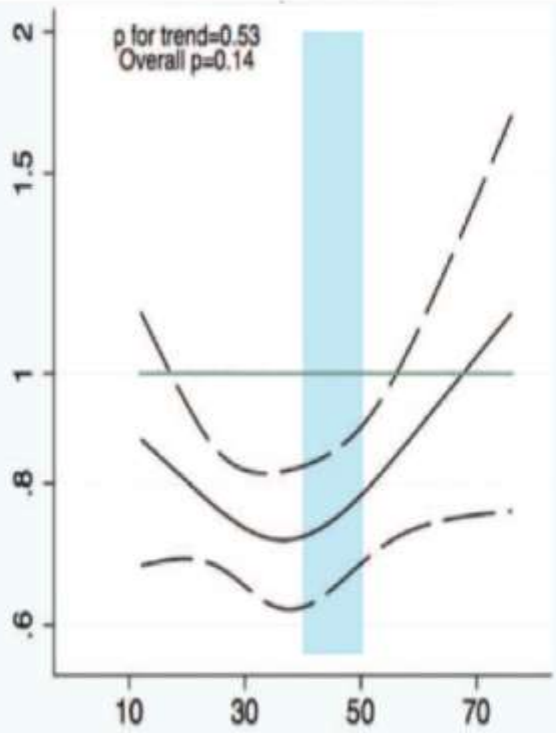


CHARM-Programme: Effect of Candesartan Across the LVEF Spectrum

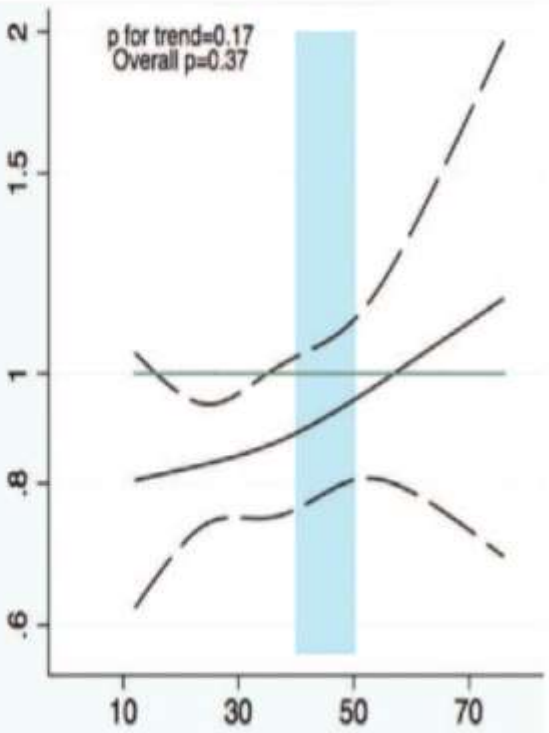
CV Death or HF Hospitalization



HF Hospitalization

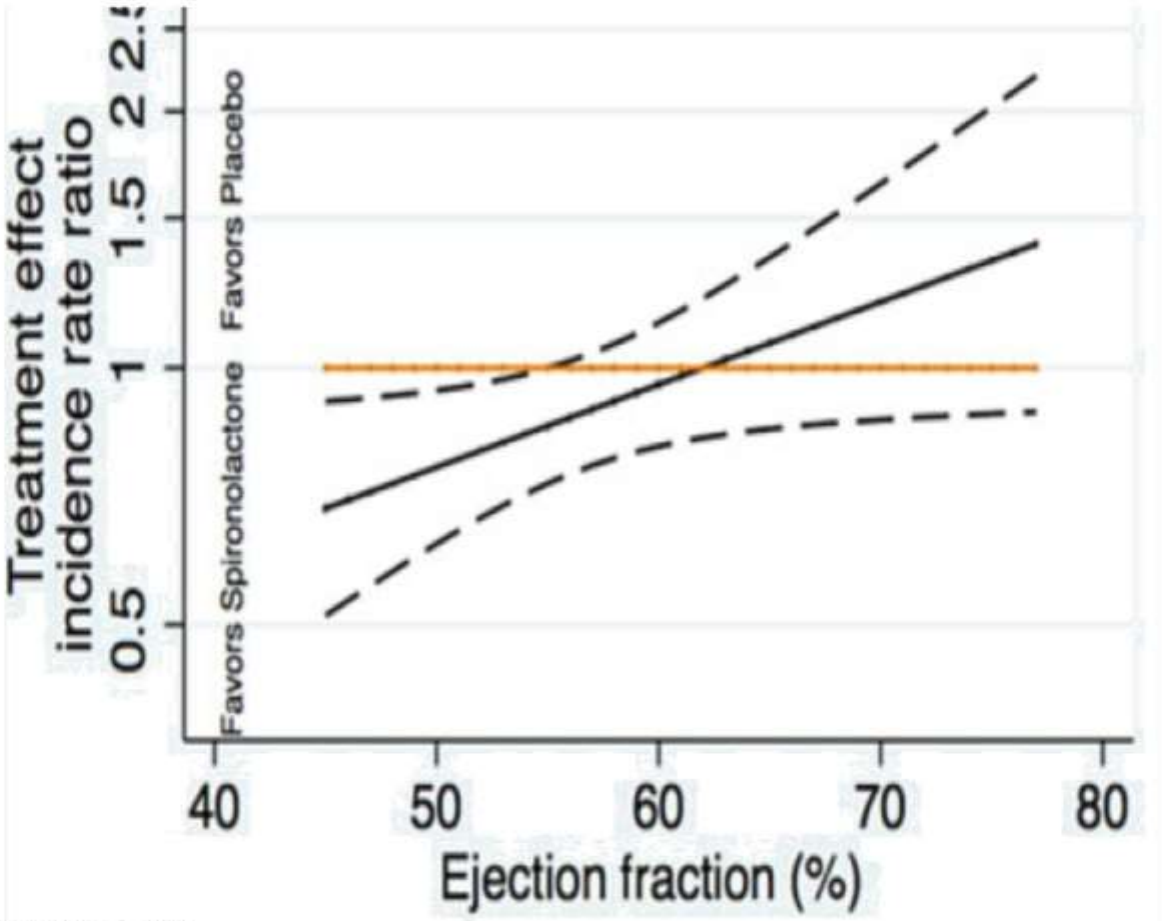


CV Death



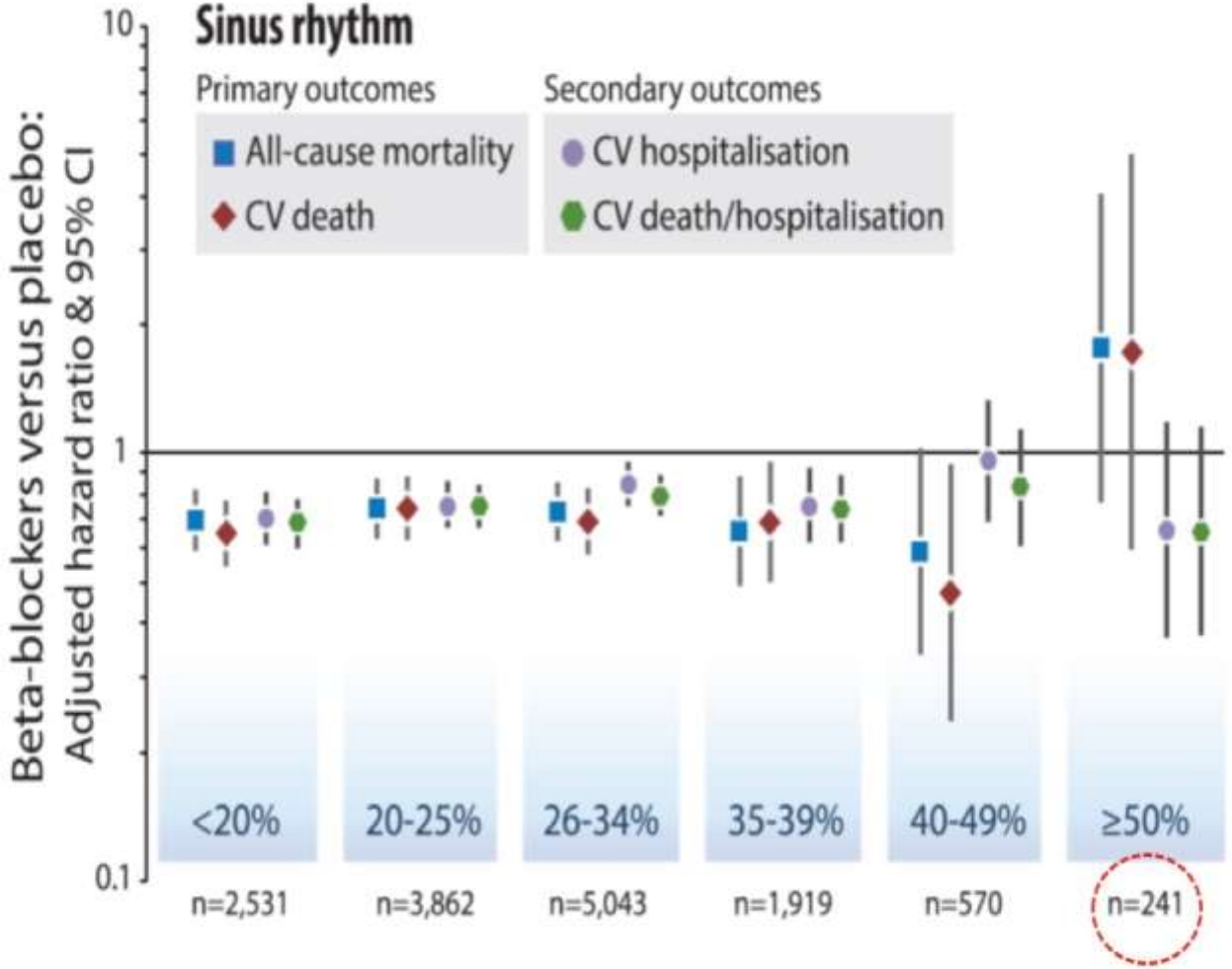
Lund et al *Eur J Heart Fail*, 2018;20:1230–1239.

TOPCAT: Primary Composite Endpoint



Solomon et al *Eur Heart J* 2016;37:455-462.

Effect of Beta-Blockers Across the LVEF Spectrum



Cleland JGF, et al. *Eur Heart J.* 2018;39:26-35. By permission of Oxford University Press.

Summary HFpEF as of Today

- HFpEF is a real HF syndrome
- Neurohormonal antagonists: trials neutral but may be effective in some patients
- Current recommendations: treat symptoms and comorbidities
- Future: Multiple phenotypes should be addressed:
  - HFmrEF: suitable for neurohormonal antagonists ?
  - HFpEF: suitable for strategies targeting comorbidities and inflammation ?

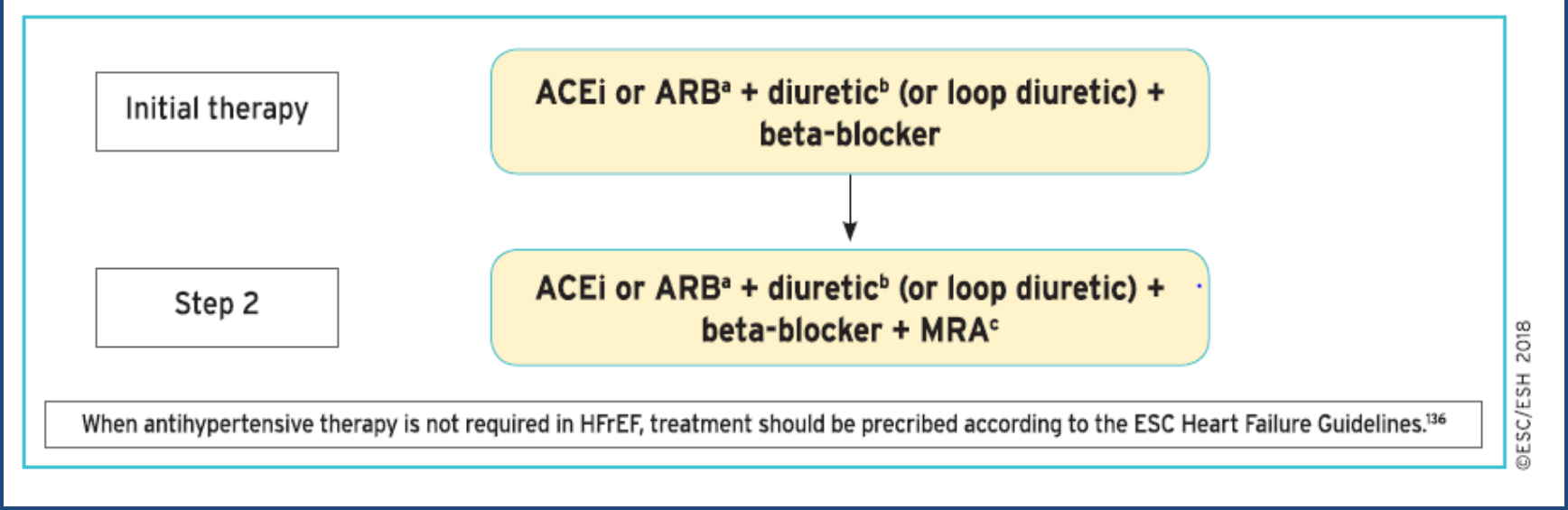
Conclusions

- Heart failure is a complex syndrome.
- Ventricular dysfunction follows a biological continuum and it is hard to dissect it in two categories according to ejection fraction.
- Recent studies and guidelines support the importance of a wide grey zone along EF distribution.
- Clinical evaluation beyond EF may support the use of more intensive therapies.
- Rebalance of neurohormonal dysfunction remains a therapeutic priority and ARNi may fulfill this objective in most patients with HF.

Thank you for Your Attention!

E: massimo.volpe@uniroma1.it

Drug treatment strategy for hypertension and hear failure with reduced ejection fraction, no specific indications for HFmrEF and HFpEF



2018 ESC/ESH Hypertension Guidelines