HFpEF Masterclasses
In centers of expertise

HFpEF Masterclasses
in centers of expertise

FRANCE

7th November 2024 - DAY 1

8th November 2024 - DAY 2

DEFINITIONS AND COMORBIDITIES IN HFpEF

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CHU ROUEN NORMANDIE

UNIVERSITÉ DE ROUEN NORMANDIE

Normandie Université

Instituts thématiques

Inserm
Institut national de la santé et de la recherche médicale

FHU REMOD-UHF

iRiB

Inserm U1096
Endothelium, Valvulopathy & Heart Failure

RHU STOP-RS

PulmoTension
Réseau Français de l'Hypertension Pulmonaire

GICC

SOCIÉTÉ FRANÇAISE DE CARDIOLOGIE
Groupe
Insuffisance Cardiaque
& Cardiomyopathies

Les jeunes de la FIC

FILIALE IMAGERIE CARDIOVASCULAIRE SFC

CONFLICTS OF INTEREST

Orateur : Charles Fauvel, Rouen

- ☑ Je déclare les liens d'intérêt potentiel suivants :
- Bourses de Recherche : Pfizer, Novartis
- Consultant : Actelion, Bayer
- Honoraires : Alnylam, AstraZeneca, Bayer, Boehringer Ingelheim, ZOLL, Bayer, MSD

DEFINITIONS OF HFpEF

Is it straightforward? … not as easy as it seems…

« The diagnosis of HFpEF remains challenging » (ESC 2021 HF guidelines)

What is « preserved » EF ?

Mc.Donagh et al, EHJ 2021

DEFINITIONS OF HFpEF

Is it straightforward? … not as easy as it seems…
« The diagnosis of HFpEF remains challenging » (ESC 2021 HF guidelines)

- **Before the 80-90's…**
  - Diagnosis of HF = « with the presence of a reduced LVEF » and major RCT included an upper LVEF exclusion criterion!
  - The « other type of HF » were described elsewhere

- **In the guidelines…**
  - ESC 2001 → « diastolic heart failure »
  - ACC/AHA 1995 → « diastolic dysfunction »

  - Very convenient but…
    - Diastolic dysfunction was more common in systolic HF than in the diastolic variety
    - Many with diastolic dysfunction were asymptomatic

  - ACC 2005/2009 update → « HF with normal LVEF » (no assumptions about underlying pathophysiology)

DEFINITIONS OF HFpEF

What is a preserved/normal LV ejection fraction ?

- **Guidelines → 50%** *T.McDonagh et al, EHJ 2022*
- **Echocardiograpy / sex differences → 52% male, 54% female**

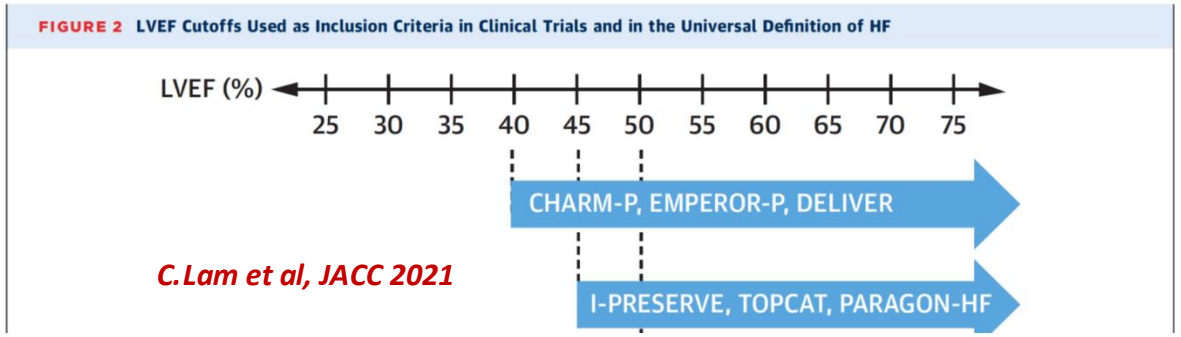
Table 4 Normal ranges and severity partition cutoff values for 2DE-derived LV EF

	Male			
	Normal range	Mildly abnormal	Moderately abnormal	Severely abnormal
LV EF (%)	52–72	41–51	30–40	<30
	Female			
	Normal range	Mildly abnormal	Moderately abnormal	Severely abnormal
	54–74	41–53	30–40	<30

NORMAL: 63±10%

R.Lang et al, EHJ CVI 2015

- **Clinical trials**



C.Lam et al, JACC 2021

Based on increased mortality risk and benefits of neurohormonal blockade benefit: 55-60%

DEFINITIONS OF HFpEF

HEMODYNAMIC ALTERATIONS IN HFPEF: not only diastolic dysfunction!

Circulation Research
Volume 124, Issue 11, 24 May 2019; Pages 1598-1617
https://doi.org/10.1161/CIRCRESAHA.119.313572

MEDICAL AND DEVICE-RELATED TREATMENT OF HEART FAILURE

Heart Failure With Preserved Ejection Fraction In Perspective

Marc A. Pfeffer, Amil M. Shah, and Barry A. Borlaug

LV stiffness → diastolic dysfunction

exercise.

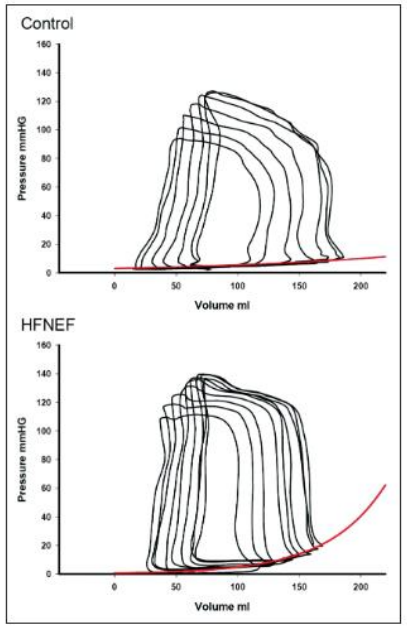


Figure 1. Representative PV loops during a preload reduction at sinus rhythm to obtain the end-diastolic PV relationship for a control subject and a patient with HFNEF. Red lines indicate the resulting end-diastolic PV relationship.

LV diastolic dysfunction and exercise symptoms

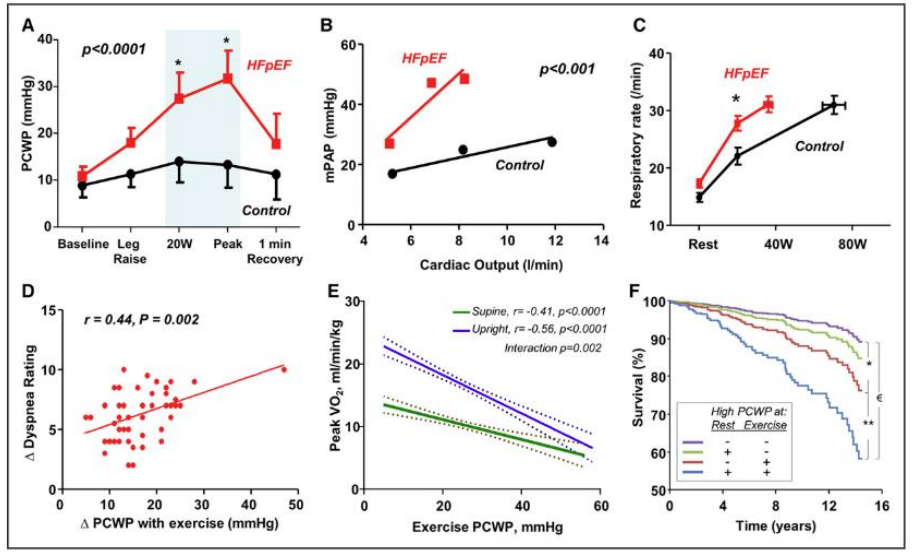


Figure 3. Relationship between exercise hemodynamics, symptoms, functional disability and outcomes in heart failure with preserved ejection fraction (HFpEF). A, As compared to controls

+/- LV systolic dysfunction

Coronary microvascular dysfunction

Extrinsic Restraint (pericardial strain, epicardial fat thickness..)

PH and RV dysfunction

LA dysfunction

DEFINITIONS OF HFpEF

ESC 2021 HF GUIDELINES

This guideline acknowledges the historical changes in nomenclature and the lack of consensus on the optimal LVEF cut-off to define the group of patients with HF without overtly reduced EF. The term 'pre-

Type of HF		HFpEF
CRITERIA	1	Symptoms ± Signs[a]
	2	LVEF ≥50%
	3	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

© ESC 2021

Parameter[a]	Threshold
LV mass index **Relative wall thickness**	≥**95** g/m^2 (Female), ≥**115** g/m^2 (Male) >**0.42**
LA volume index[a]	>**34** mL/m^2 (SR)
E/e' ratio at rest[a]	>**9**
NT-proBNP **BNP**	>**125** (SR) or >**365** (AF) pg/mL >**35** (SR) or >**105** (AF) pg/mL
PA systolic pressure **TR velocity at rest**[a]	>**35** mmHg >**2.8** m/s

*Of note, patients with a history of overtly reduced LVEF (≤40%), who later present with LVEF ≥50%, should be considered to have recovered HFrEF or 'HF with improved LVEF' (rather than HFpEF). Continued treatment for HFrEF is recommended in these patients.[271]

Mc.Donagh et al, EHJ 2021

DEFINITIONS OF HFpEF

Normal NTproBNP/BNP does not exclude HFpEF

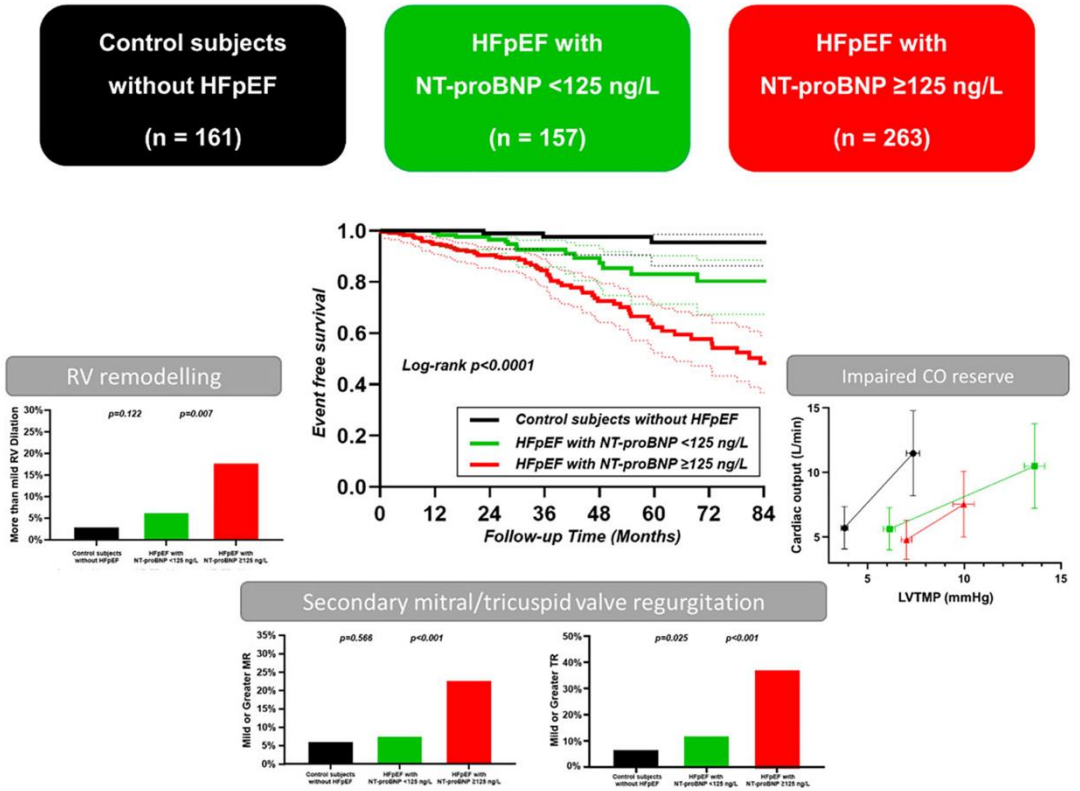
measures of cardiac dysfunction can improve the diagnostic specificity. The signs and symptoms of HF are frequently nonspecific and overlap with other clinical conditions. Elevated natriuretic peptide levels are supportive of the diagnosis, but normal levels do not exclude a diagnosis of HFmrEF or HFpEF. To improve the specificity of diagnosing HFmrEF and HFpEF,

DIFFERENT FROM THE 2016 ESC GUIDELINES

ESC European Society of Cardiology
European Heart Journal (2022) **43**, 1941–1951
https://doi.org/10.1093/eurheartj/ehab911
CLINICAL RESEARCH
Heart failure and cardiomyopathies

Heart failure with preserved ejection fraction in patients with normal natriuretic peptide levels is associated with increased morbidity and mortality

Frederik H. Verbrugge [1,2,3], Kazunori Omote[1], Yogesh N. V. Reddy[1], Hidemi Sorimachi[1], Masaru Obokata [1], and Barry A. Borlaug [1]*



Mc.Donagh et al, EHJ 2021

F.Verbrugge et al, EHJ 2022

DEFINITIONS OF HFpEF

ACC/AHA 2022 HF GUIDELINES

Table 4. Classification of HF by LVEF (Table view)

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 (eg, elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)
HFpEF (HF with preserved EF)	LVEF ≥50% Evidence of spontaneous or provokable increased LV filling pressures (eg, elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)

Same LVEF threshold
Symptoms and signs are not included

The diagnosis of HFpEF is often challenging. A clinical composite score to diagnose HFpEF, the H_2FPEF score,[5–7] integrates these predictive variables: obesity, atrial fibrillation (AF), age >60 years, treatment with ≥2 antihypertensive medications, echocardiographic E/e′ ratio >9, and echocardiographic PA systolic pressure >35 mm Hg. A weighted score based on these 6 variables was used to create the composite score ranging from 0 to 9. The odds of HFpEF doubled for each 1-unit score increase (odds ratio, 1.98; 95% CI: 1.74-2.30; P<0.0001), with a c-statistic of 0.841. Scores <2 and ≥6 reflect low and high likelihood, respectively, for HFpEF. A score between 2 and 5 may require further evaluation of hemodynamics with exercise echocardiogram or cardiac catheterization to confirm or negate a diagnosis of HFpEF. The use of this H_2FPEF score may help to facilitate discrimination of HFpEF from noncardiac causes of dyspnea and can assist in determination of the need for further diagnostic testing in the evaluation of patients with unexplained exertional dyspnea.[6,7]

PA.Heidenreich et al, Circ 2022

DEFINITIONS OF HFpEF

- Going further the definition → use of HFA-PEFF or H2FPEF score algorythm

No single echoparameter allows the diagnosis
Normal NTproBNP/BNP does not exclude HFpEF
Absence of LVH does not exclude HFpEF

Eur Heart J,2019;40;3297–3317,

No robust diagnostic validation
Too many end up proceeding to stress testing

	Clinical Variable	Values	Points
H_2	Heavy	Body mass index > 30 kg/m²	2
	Hypertensive	2 or more antihypertensive medicines	1
F	Atrial Fibrillation	Paroxysmal or Persistent	3
P	Pulmonary Hypertension	Doppler Echocardiographic estimated Pulmonary Artery Systolic Pressure > 35 mmHg	1
E	Elder	Age > 60 years	1
F	Filling Pressure	Doppler Echocardiographic E/e' > 9	1
	H_2FPEF score		Sum (0-9)

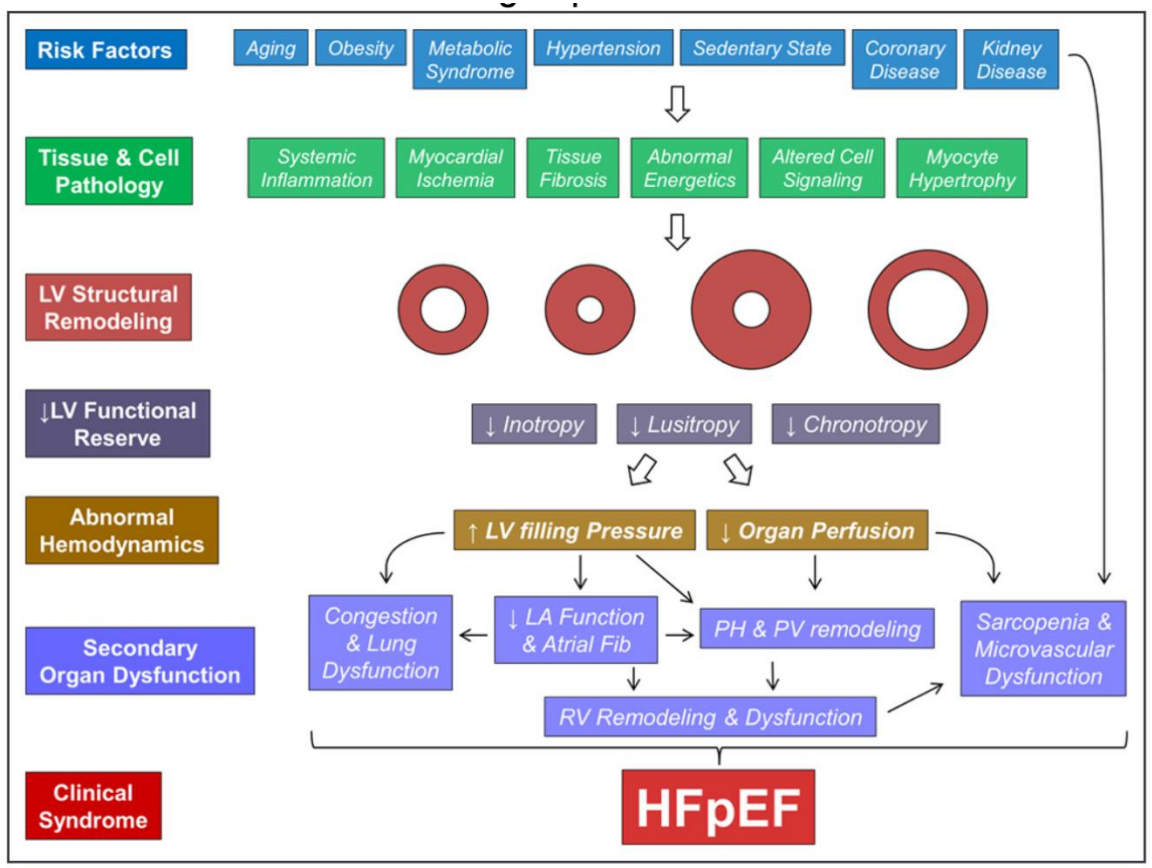
Total Points 0 1 2 3 4 5 6 7 8 9

Probability of HFpEF 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 0.95

Yogesh N.V. Reddy. Circulation. 138, Issue: 9, Pages: 861-870, DOI: (10.1161/CIRCULATIONAHA.118.034646)

COMORBIDITIES IN HFpEF

THE IMPORTANCE OF RISK FACTORS AND COMORBIDITIES IN HFPEF



RISK FACTORS AND COMORBIDITIES ARE DRIVING HFpEF PATHOPHYSIOLOGY

Figure 2. The Pathophysiologic Progression of heart failure with preserved ejection fraction (HFpEF). By cellular mechanisms that are as yet not completely understood, established risk factors

M.Pfeffer et al, Circulation Research 2019

COMORBIDITIES IN HFpEF

THE IMPORTANCE OF RISK FACTORS AND COMORBIDITIES IN HFPEF

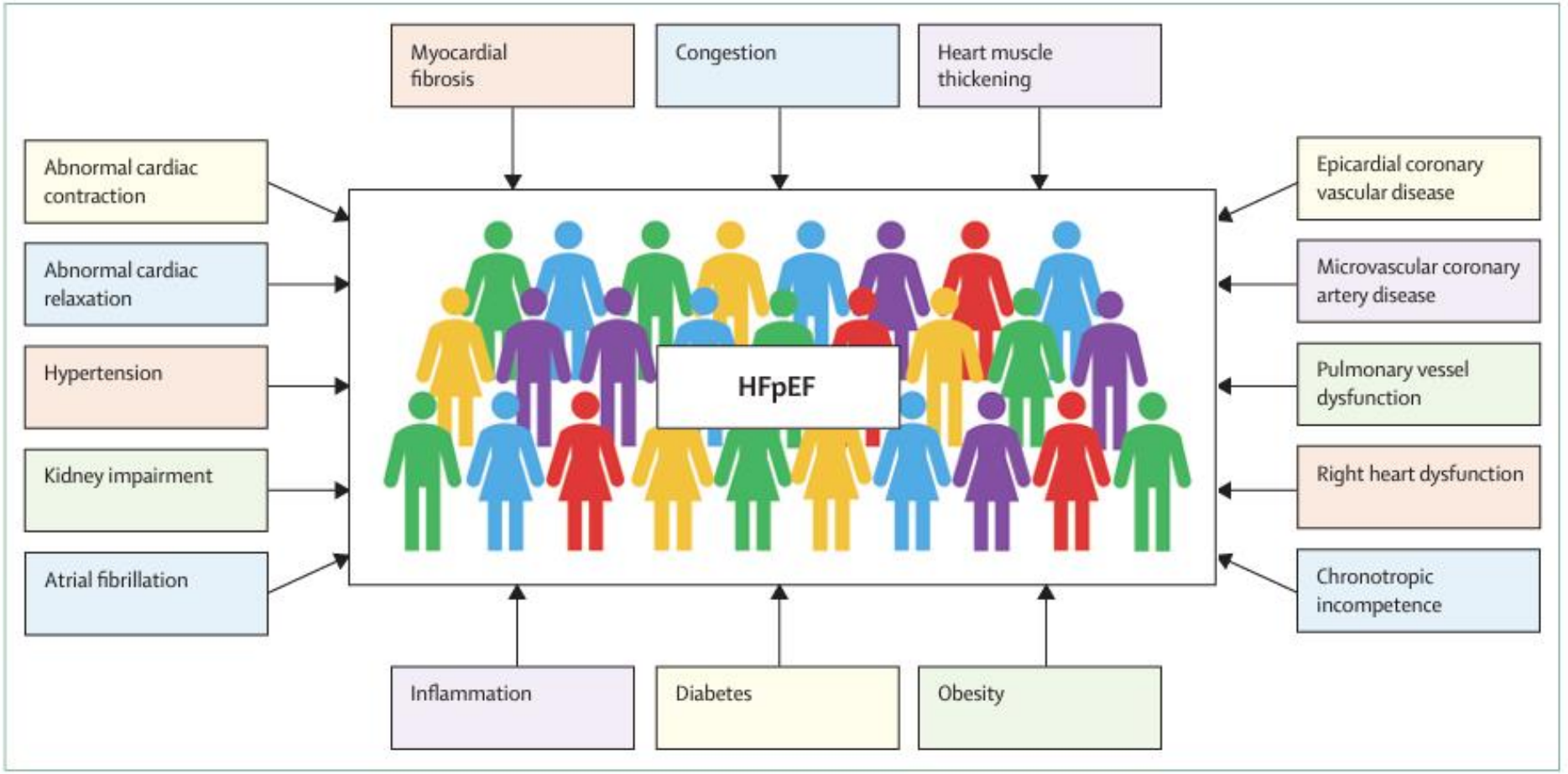


Figure 1: **Interacting causes, contributors, or drivers of HFpEF reflecting the complex and heterogeneous underlying pathophysiology**
HFpEF=heart failure with preserved ejection fraction.

P.Campbell et al, Lancet 2024

COMORBIDITIES IN HFpEF

THE IMPORTANCE OF RISK FACTORS AND COMORBIDITIES IN HFpEF

Differences in clinical presentation and co-morbidities between HF categories

	HFrEF	HFmrEF	HFpEF
Phenotype			
Age	↑	↑↑	↑↑↑
Women	↓↓	↓	↑
Ischaemic heart disease	↑↑↑	↑↑↑	↑
Atrial fibrillation	↑	↑↑	↑↑↑
Hypertension	↑	↑↑	↑↑↑
Chronic kidney disease	↑↑	↑↑	↑↑↑
Natriuretic peptide levels	↑↑↑	↑	↑
Prognosis			
Cardiovascular risk	↑↑↑	↑	↑
Non-cardiovascular risk	↑	↑	↑↑
Treatment			
RAS inhibitors, β-Blockers, MRA, ARNI, SGLT2i — Relative effect	+++	+++ (Ongoing trials on MRA and SGLT2i)	±
RAS inhibitors, β-Blockers, MRA, ARNI, SGLT2i — Absolute effect	+++	+ (Ongoing trials on MRA and SGLT2i)	±
ICD, CRT	+++	±	±

HFrEF characteristics | HFpEF characteristics | Intermediate characteristics

Savarese GL et al Eur J Heart Fail 2023

COMORBIDITIES IN HFpEF

THE IMPORTANCE OF RISK FACTORS AND COMORBIDITIES IN HFpEF

Patient characteristics in patients with LVEF >40% in recent clinical trials

NYHA II : 75-82%
Hypertension : 9/10 cases
Diabetes : ½ cases
COPD 1/10 case
AF ½ case
Stroke 1/10

TABLE 4 Comparison of Baseline Characteristics in Various Trials in Heart Failure With LVEF >40%

	DELIVER (n = 6,263)	EMPEROR-Preserved (n = 5,988)	PARAGON-HF (n = 4,822)	TOPCAT-Americas (n = 1,767)	I-PRESERVE (n = 4,128)	CHARM-Preserved (n = 3,023)
Age, y	72 ± 10	72 ± 9	73 ± 8	72 (64 to 79)	72 ± 7	67 ± 11
Women, %	44	45	52	50	60	40
NYHA functional class, %						
II	75	82	77	59	22	61
III	25	18	27	35	77	38
IV	0.3	0.3	0.6	1	3	2
Hypertension, %	89	90	96	90	89	64
Type 2 diabetes, %	45	49	43	45	27	28
COPD, %	11	13	14			
Smoker, %	8	7	7	7		14
History of MI, %	26	29	22	20	23.5	44
History of AFF, %	56	52	52	42	29	29
AFF at screening, %	42	35	32	34	29	29
Stroke, %	9 (stroke/TIA)	10	10	9	10	9
Prior HF hospitalization, %						
Within 6 mo						
Within 12 mo	26	23	48			
Any prior hospitalization	40			59	23	68
Subacute	10					
LVEF, mean %	54	54	58	58	60	54
eGFR, mean mL/min/1.73 m^2	61	61	62	61	73	72
NT-proBNP, median, pg/mL	1,011	974	885	900	339	–
ACEi, %	33	40	40	50	26	19
ARB, %	34	39	45	31	–	–
ARNI, %	4	2	–	–	–	–
MRA, %	39	37	24	–	15	12

Values are mean ± SD or n.
COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; TIA = transient ischemic attack; other abbreviations as in Table 1.

Solomon S et al. JACC HF 2022

COMORBIDITIES IN HFpEF

THE IMPORTANCE OF RISK FACTORS AND COMORBIDITIES IN HFPEF

Circulation
Volume 131, Issue 3, 20 January 2015; Pages 269-279
https://doi.org/10.1161/CIRCULATIONAHA.114.010637

HEART FAILURE

Phenomapping for Novel Classification of Heart Failure With Preserved Ejection Fraction

Editorial see p 232

Sanjiv J. Shah, MD, Daniel H. Katz, MD, Senthil Selvaraj, MD, MA, Michael A. Burke, MD, Clyde W. Yancy, MD, MSc, Mihai Gheorghiade, MD, Robert O. Bonow, MD, Chiang-Ching Huang, PhD, and Rahul C. Deo, MD, PhD

Pheno-group 1	Pheno-group 2	Pheno-group 3
• *N=128*	• *N=120*	• *N=149*
• Younger	• Obese	• Older
• Moderate diastolic dysfunction	• Diabetic	• Chronic kidney disease
• Normal BNP	• Obstructive sleep apnea	• Pulmonary hypertension
	• Worst LV relaxation	• RV dysfunction

DIFFERENT RISK PROFIL DEPENDING ON COMORBIDITIES

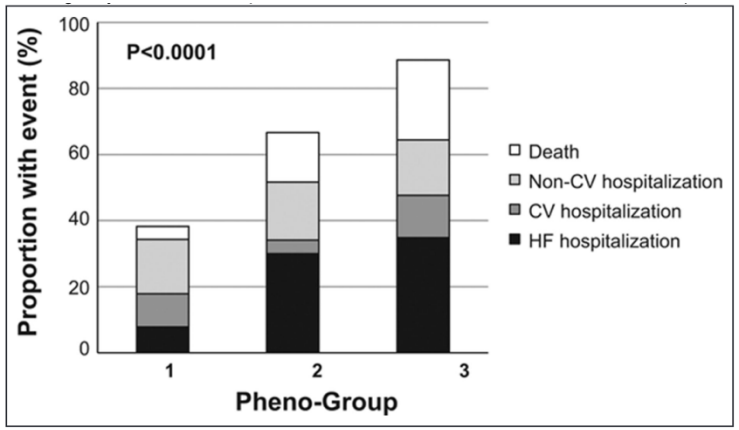


Figure 3. Outcomes by heart failure with preserved ejection fraction phenogroup. Stacked bar graph of outcomes shows the step-wise increase in adverse events from phenogroup 1 to phenogroup 3.

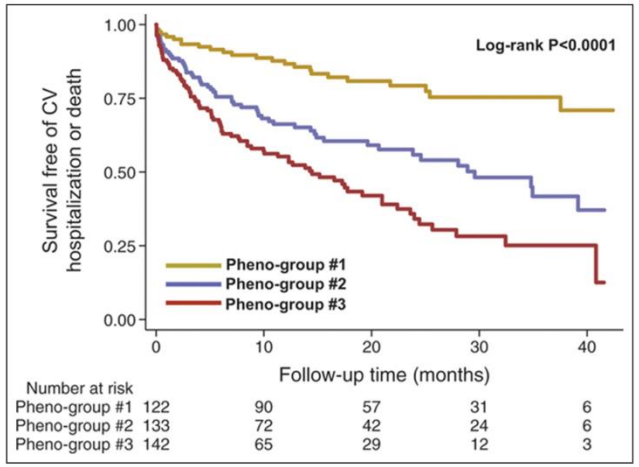


Figure 4. Survival free of cardiovascular (CV) hospitalization or death stratified by phenogroup. Kaplan–Meier curves for the combined outcome of heart failure hospitalization, cardiovascular hospitalization, or death stratified by phenogroup.

SJ.Shah et al, Circulation 2015

COMORBIDITIES IN HFpEF

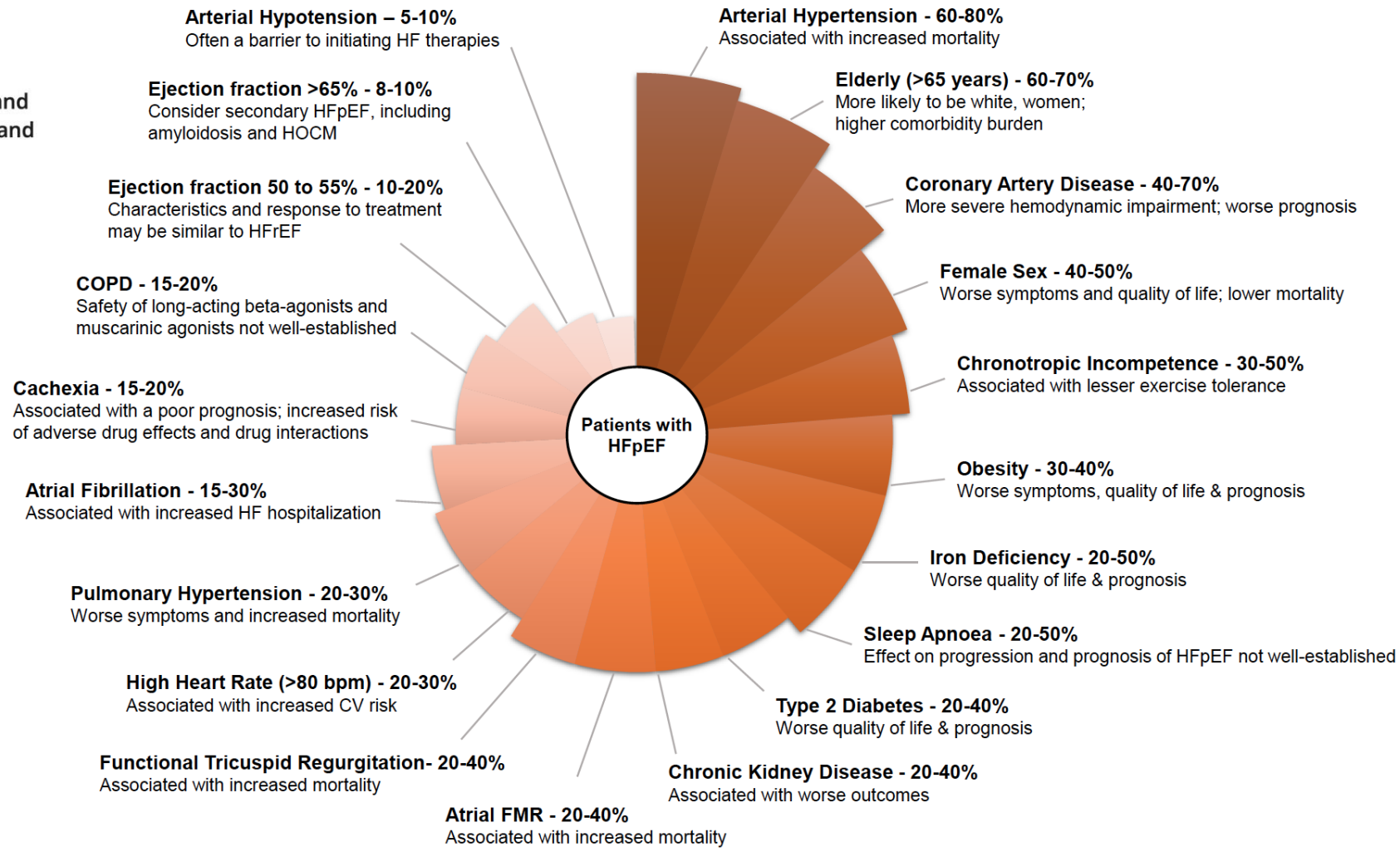
European Journal of Heart Failure

Position Paper | Free Access

Patient Phenotype Profiling in Heart Failure with Preserved Ejection Fraction to Guide Therapeutic Decision Making A Scientific Statement of the Heart Failure Association (HFA) and the European Heart Rhythm Association (EHRA) of the ESC, and the European Society of Hypertension (ESH)

Stefan D. Anker MD, PhD, Muhammad Shariq Usman MD, Markus S. Anker MD, Javed Butler MD, MPH, MBA, Michael Böhm MD, William T Abraham MD ... See all authors

First published: 19 May 2023 | https://doi.org/10.1002/ejhf.2894



Anker SD et al. EJHF 2023

COMORBIDITIES IN HFpEF

HYPERTENSION

European Journal of Heart Failure (2017) 19, 1574–1585
doi:10.1002/ejhf.813

RESEARCH ARTICLE

Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry

Ovidiu Chioncel*

Table 1 Baseline characteristics in chronic heart failure patients stratified by ejection fraction

	All ($n = 9134$)	EF <40% ($n = 5460$)	EF 40–50% ($n = 2212$)	EF >50% ($n = 1462$)	P-value
Geographic distribution, *n* (%)					
Eastern	1607 (17.6)	1014 (18.6)	384 (17.4)	209 (14.3)	
Northern	665 (7.3)	444 (8.1)	151 (6.8)	70 (4.8)	
Southern	5174 (56.6)	2995 (54.8)	1226 (55.4)	953 (65.2)	
Western	721 (7.9)	492 (9.0)	148 (6.7)	81 (5.5)	
North Africa	559 (6.1)	227 (4.2)	255 (11.5)	77 (5.3)	
Middle East	408 (4.5)	288 (5.3)	48 (2.2)	72 (4.9)	
Age, years, mean ± SD	64.8 ± 13.3	64.0 ± 12.6	64.2 ± 14.2	68.6 ± 13.7	<0.001
Age ≥75 years, %	25.7	21.9	26.4	38.9	<0.001
Female gender, %	28.2	21.6	31.5	47.9	<0.001
BMI, kg/m^2, mean ± SD	28.1 ± 5.1	27.8 ± 4.9	28.6 ± 5.4	28.4 ± 5.4	<0.001
SBP, mmHg, mean ± SD	124.3 ± 20.8	121.6 ± 20.0	126.5 ± 21.1	130.98 ± 21.4	<0.001
SBP ≤110 mmHg, %	30.3	34.4	27.0	19.9	<0.001
Heart rate, b.p.m., mean ± SD	72.9 ± 15.4	72.9 ± 15.1	73.2 ± 15.9	72.5 ± 15.5	0.344
Heart rate ≥70 b.p.m., %	55.7	56.4	55.6	53.5	0.108
NYHA class III/IV, %	26.0	30.6	18.4	20.3	<0.001
Pulmonary congestion, %	74.4	74.5	71.7	77.5	0.031
Peripheral congestion, %	28.4	29.4	26.0	29.0	0.002
Peripheral hypoperfusion, %	3.2	3.9	2.7	1.8	<0.001
HF history with previous hospitalization, %	47.4	47.1	48.1	47.4	0.774
HF diagnosis >12 months, %	61.8	58.9	67.4	64.7	<0.001
Primary aetiology, %					
Ischaemic heart disease	42.9	48.6	41.8	23.7	<0.001
Hypertension	7.9	4.5	9.6	18.1	<0.001
Hypertension treatment	58.5	55.6	60.1	67.0	<0.001
Idiopathic dilated cardiomyopathy	29.5	35.1	27.6	11.6	<0.001
	8.2	4.4	10.0	19.5	<0.001

85%

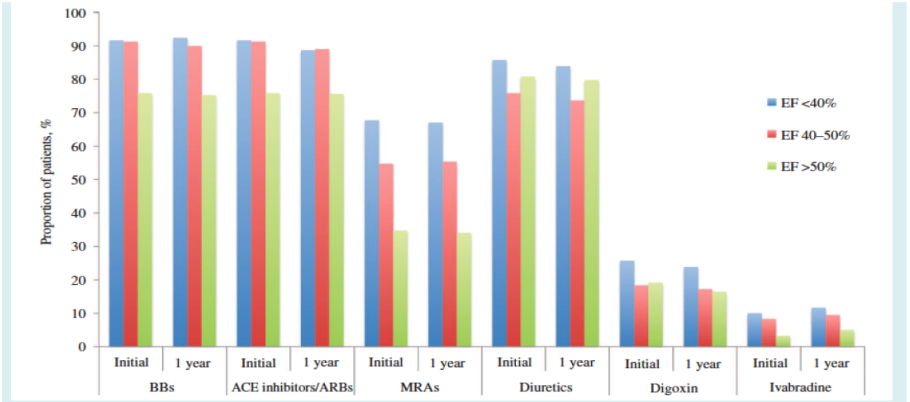


Figure 2 Pharmacological treatments administered in 9134 heart failure patients at entry and at 1 year of follow-up according to ejection fraction (EF) category. ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; BB, beta-blockers; MRAs, mineralocorticoid receptor antagonists.

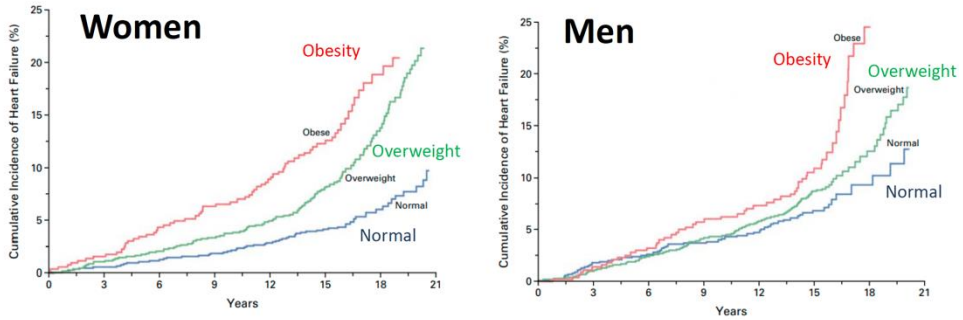
History of HTN:

- Emperor Preserved: 90.5%
- Deliver: 90.1%

Anker SD et al. EJHF 2023

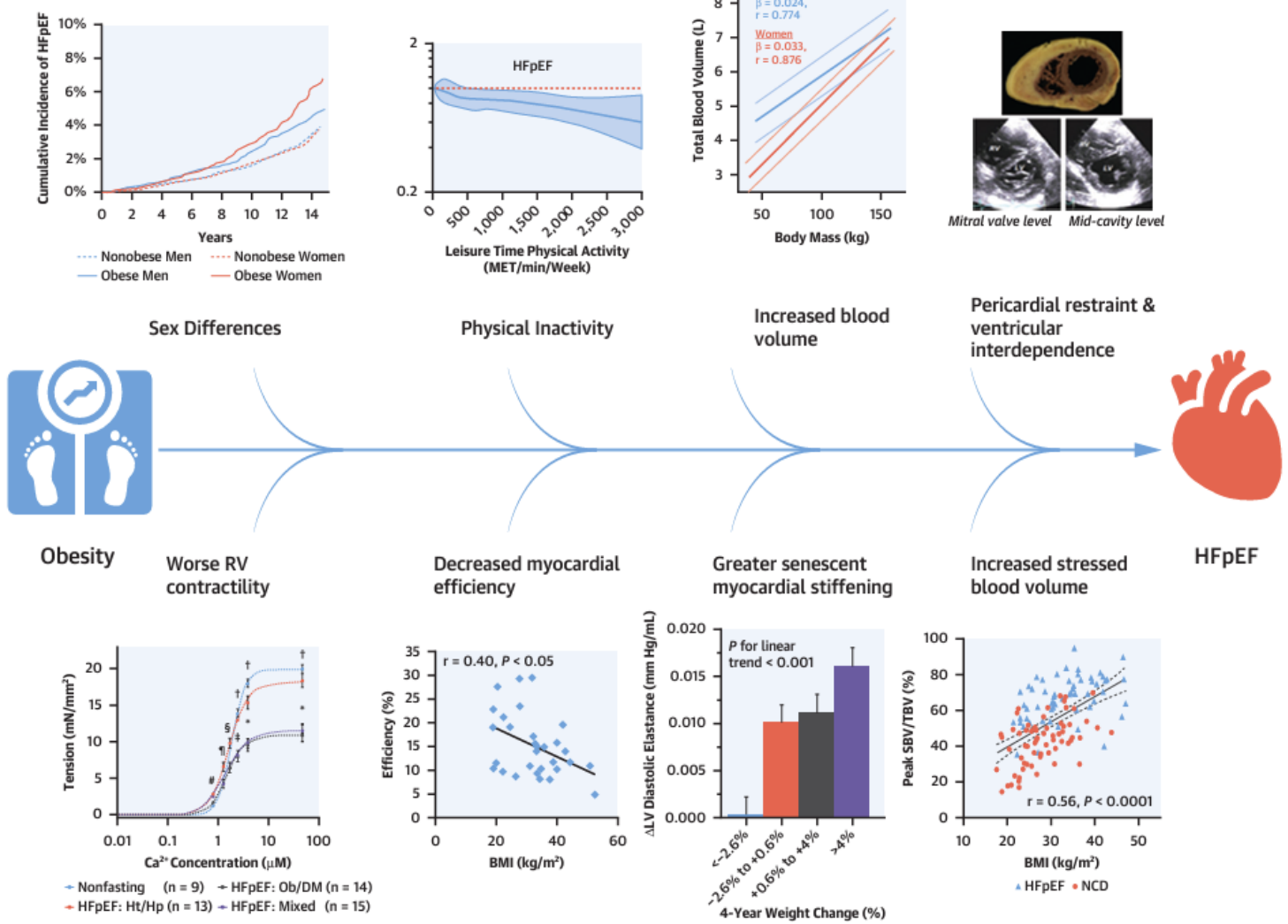
COMORBIDITIES IN HFpEF

OBESITY



Kenchaiah et al. N Engl J Med 2002; 347:305-313

FIGURE 2 Pathophysiology of Obesity-Related HFpEF



COMORBIDITIES IN HFpEF

OBESITY

As a potential target…

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 21, 2023 VOL. 389 NO. 12

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

M.N. Kosiborod, S.Z. Abildstrøm, B.A. Borlaug, J. Butler, S. Rasmussen, M. Davies, G.K. Hovingh, D.W. Kitzman, M.L. Lindegaard, D.V. Møller, S.J. Shah, M.B. Treppendahl, S. Verma, W. Abhayaratna, F.Z. Ahmed, V. Chopra, J. Ezekowitz, M. Fu, H. Ito, M. Lelonek, V. Melenovsky, B. Merkely, J. Núñez, E. Perna, M. Schou, M. Senni, K. Sharma, P. Van der Meer, D. von Lewinski, D. Wolf, and M.C Petrie, for the STEP-HFpEF Trial Committees and Investigators*

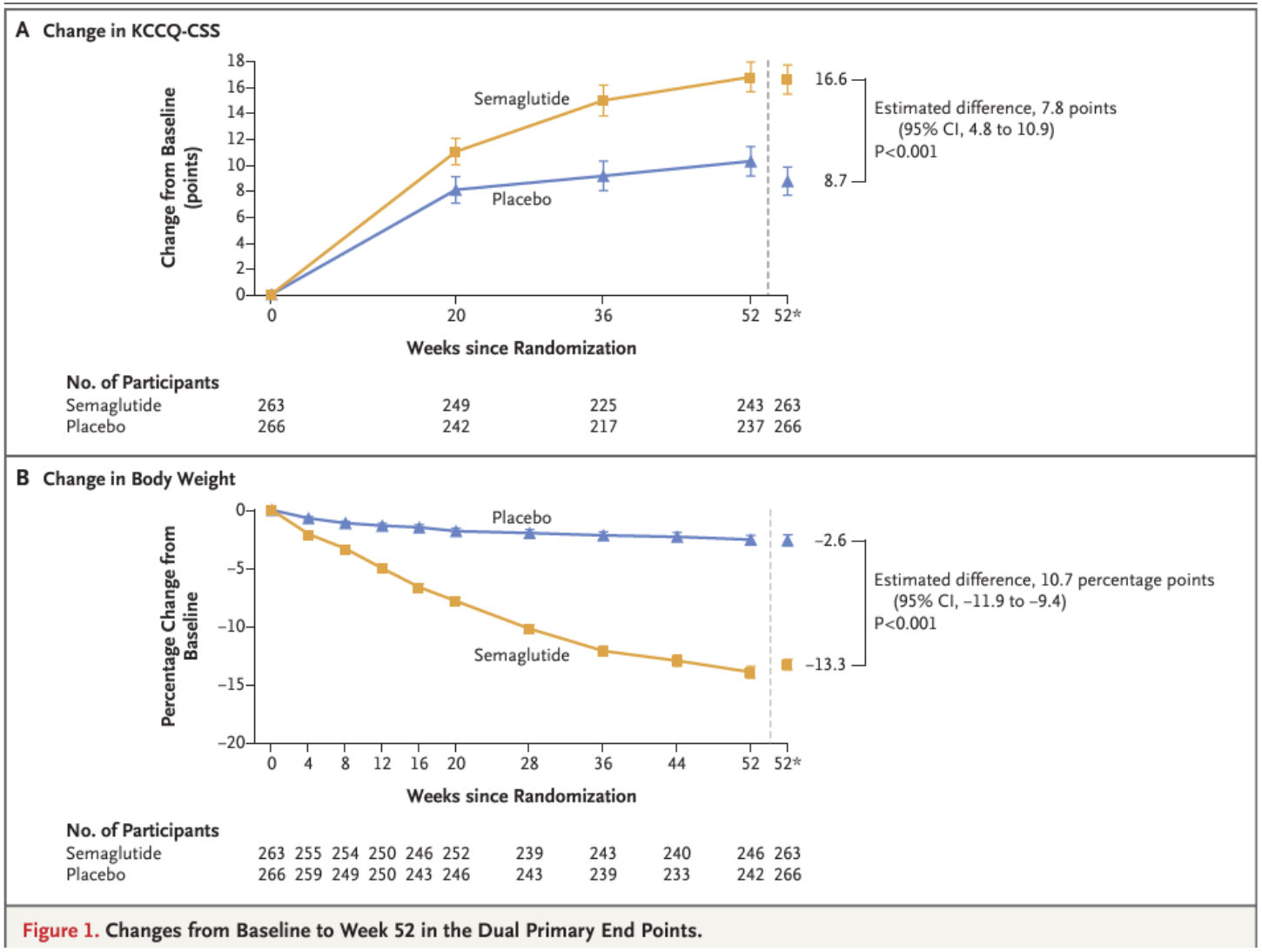


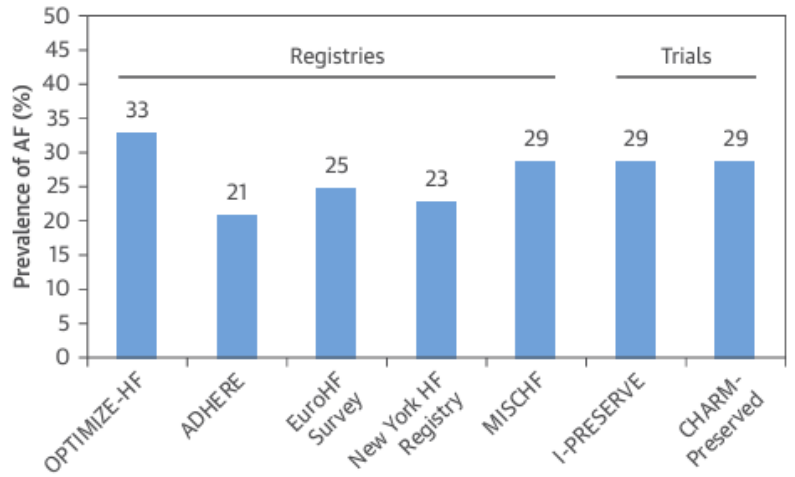
Figure 1. Changes from Baseline to Week 52 in the Dual Primary End Points.

COMORBIDITIES IN HFpEF

AF

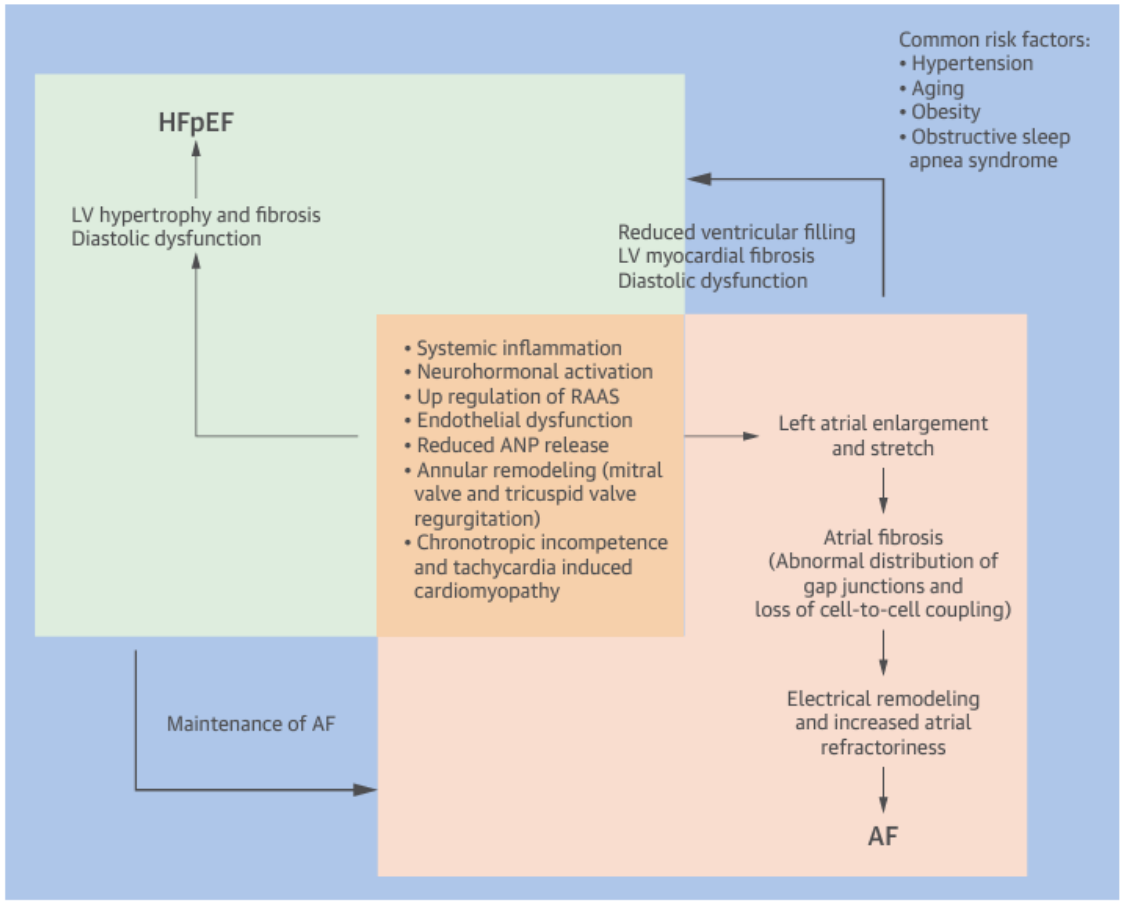
Both prevalent and incident AF are associated with increased mortality in HFpEF (HR: 1.30 and 2.45, respectively, compared with patients with no AF)

FIGURE 2 Prevalence of AF in HFpEF



The prevalence of AF in HFpEF varies in 7 large heart failure trials. I-PRESERVE = Irbesartan in Heart Failure With Preserved Ejection Fraction study; ADHERE registry = Acute Decompensated Heart Failure National Registry; CHARM-Preserved study = Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity study; EuroHF Survey = Euro Heart Failure Survey; MISCHF study = Management to Improve Survival in Congestive Heart Failure study; OPTIMIZE-AF study = Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure study; other abbreviations as in Figure 1.

FIGURE 3 Pathophysiology and Shared Mechanisms in HFpEF and AF



Common mechanisms involved in HFpEF, AF, and the combination of these conditions. ANP = atrial natriuretic peptide; LV = left ventricular; RAAS = renin-angiotensin-aldosterone system; other abbreviations as in Figure 1.

Kotecha et al, JACC 2016

COMORBIDITIES IN HFpEF

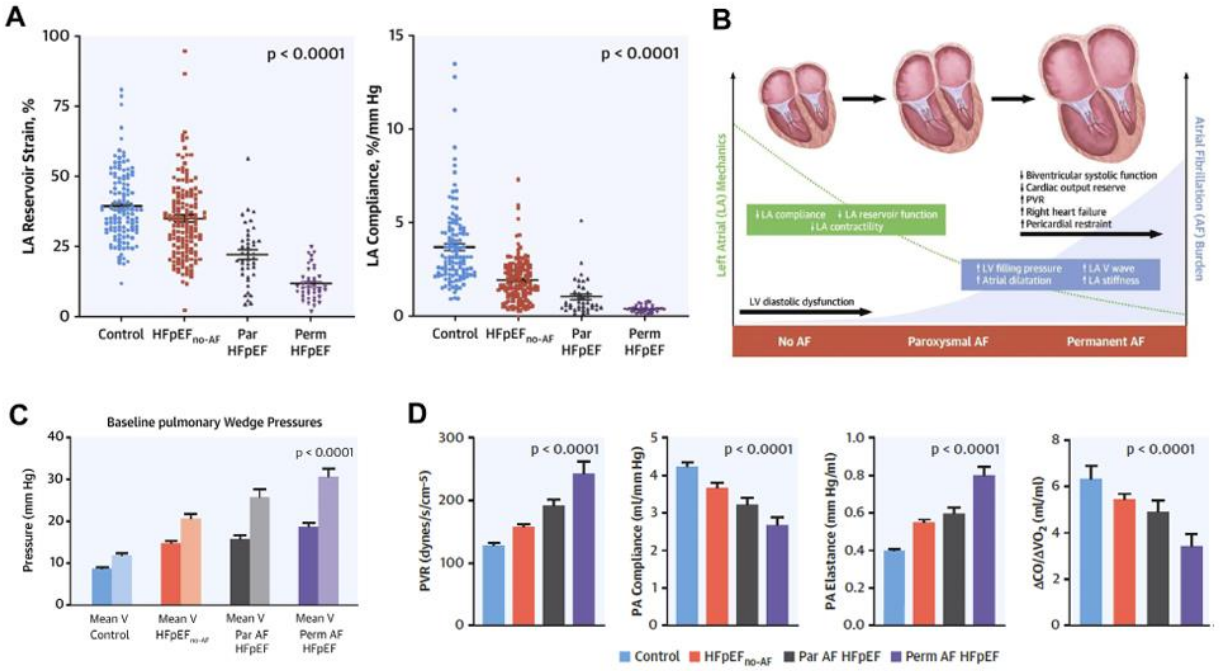
AF

REVIEW TOPIC OF THE MONTH

Screening for Unrecognized HFpEF in Atrial Fibrillation and for Unrecognized Atrial Fibrillation in HFpEF

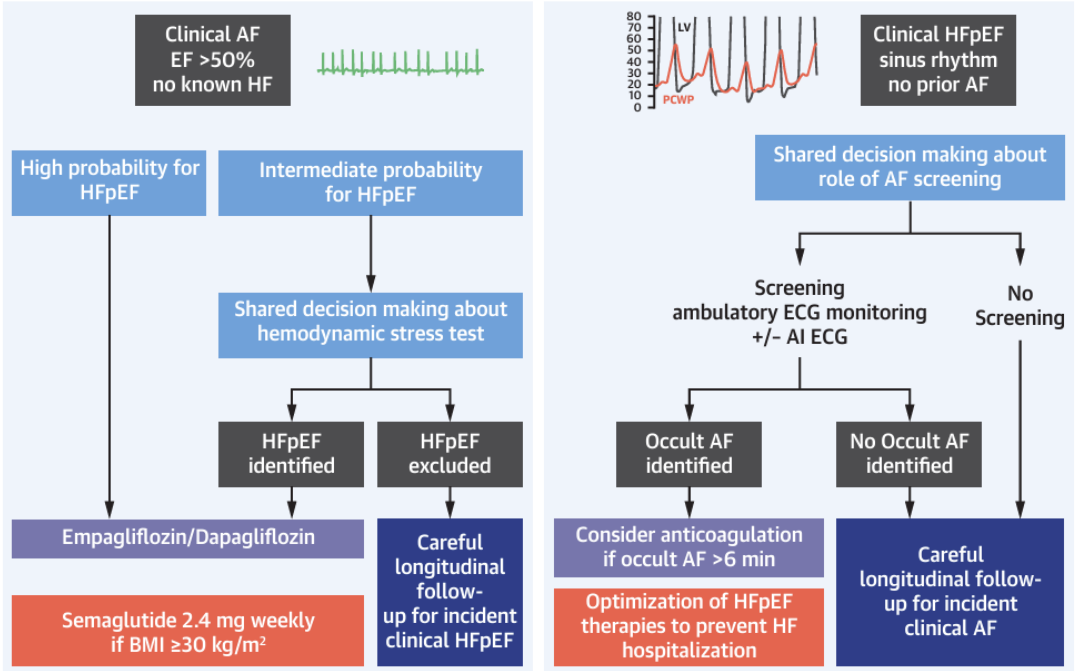
Yogesh N.V. Reddy, MD, MSc,[a] Peter Noseworthy, MD,[a] Barry A. Borlaug, MD,[b,*] Nancy M. Albert, PhD[b,*]

FIGURE 2 Worsening HFpEF Hemodynamics With Progressive AF Burden



With progressive AF burden, there is progressive worsening of left atrial (LA) function (A), global cardiac remodeling (B), and hemodynamics (C, D). Modified with permission from Reddy et al.[1] CO = carbon monoxide; LV = left ventricular; PA = pulmonary artery; Par = paroxysmal; Perm = permanent; PVR = pulmonary vascular resistance; VO_2 = oxygen consumption; other abbreviations as in Figure 1.

CENTRAL ILLUSTRATION Screening Approach for HFpEF and AF



Reddy YNV, et al. J Am Coll Cardiol HF. 2024;12(6):990-998.

Summary of approach to (left panel) patients with clinical atrial fibrillation (AF) at risk for occult heart failure with preserved ejection fraction (HFpEF) and (right panel) patients with clinical HFpEF at risk for occult AF. AI = artificial intelligence; BMI = body mass index (measured in kg/m^2); ECG = electrocardiogram; EF = ejection fraction; HF = heart failure; LV = left ventricular; PCWP = pulmonary capillary wedge pressure.

Reddy et al, JACC HF 2024

COMORBIDITIES IN HFpEF

CKD

INTRODUCTION

There is a high prevalence of chronic kidney disease (CKD) in patients with heart failure with preserved ejection fraction (HFpEF), ranging from 40% to 60%, with these estimates dependent in part on evolution of the clinical definitions of HFpEF.[1-3] The presence of CKD, as defined by an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, is associated with an increased risk of adverse clinical outcomes, including death, cardiovascular events, and heart failure hospitalizations, and poses additional challenges in caring for patients with HFpEF, including appropriate diagnosis and selection of therapies. Although there have

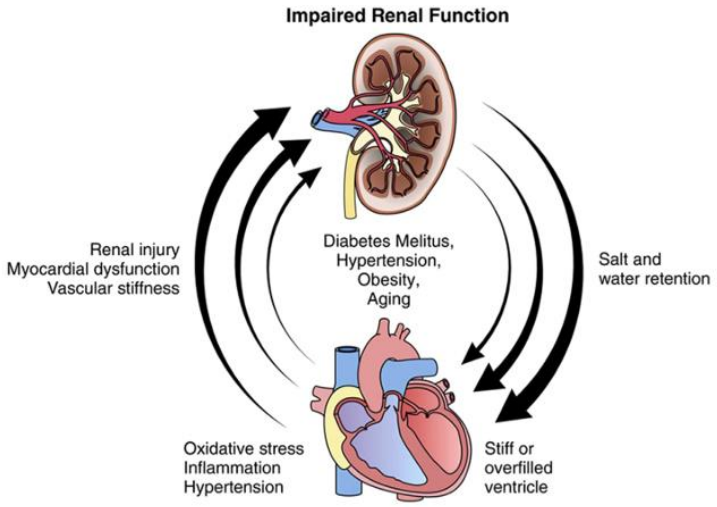


Figure 1. HFpEF as a vicious cycle of volume overload maintained by renal dysfunction.

Table 2. Examples of Trials in HFpEF With Cardiovascular and Kidney Inclusion/Exclusion Criteria and Outcomes

Class of Drug	Trial	N	Years	Intervention	Median Follow-up Duration	EF Threshold	Kidney Exclusion Criterion	Primary Trial End Point	Chronic Kidney Slope Estimation
ARNI	PARAGON-HF[6]	4,822	2014- 2016	Sacubitril-valsartan versus valsartan	34 months	≥45%	eGFR <30 mL/min/1.73 m^2	Lower risk of composite end point of HF hospitalization and CV death with sacubitril-valsartan versus valsartan (risk ratio, 0.87, 95% CI, 0.75-1.01)	Sacubitril-valsartan: −2.0 mL/min/1.73 m^2 per year (95% CI, −2.2 to −1.9) Valsartan: −2.7 mL/min/1.73 m^2 per year (95% CI, −2.8 to −2.5)[3]
SGLT2 inhibitor	EMPEROR-Preserved[31]	5,988	2017- 2020	Empagliflozin versus placebo	26 months	>40%	eGFR <20 mL/min/1.73 m^2	Lower hazard of composite end point of CV death or HF hospitalization (HR, 0.79, 95% CI, 0.69-0.90)	Empagliflozin: −1.25 ± 0.11 mL/min/1.73 m^2 per year Placebo: −2.62 ± 0.11 mL/min/1.73 m^2 per year[69]
SGLT2 inhibitor	DELIVER[30]	6,263	2018- 2020	Dapagliflozin versus placebo	28 months	>40%	eGFR <25 mL/min/1.73 m^2	Lower hazard of composite end point of unplanned HF hospitalization or urgent visit for HF or CV death (HR, 0.82, 95% CI, 0.73-0.92)	Dapagliflozin: 0 mL/min/1.73 m^2 per year (95% CI, −0.2 to 0.3) Placebo: −1.4 mL/min/1.73 m^2 per year (95% CI, −1.7 to −1.1)[32]

Abbreviations: ARNI, angiotensin receptor-neprilysin inhibitor; CI, confidence interval; CV, cardiovascular; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; SGLT2, sodium-glucose cotransporter 2.

ML.Tuttle, Seminar in Nephrology, 2024

COMORBIDITIES IN HFpEF

CKD

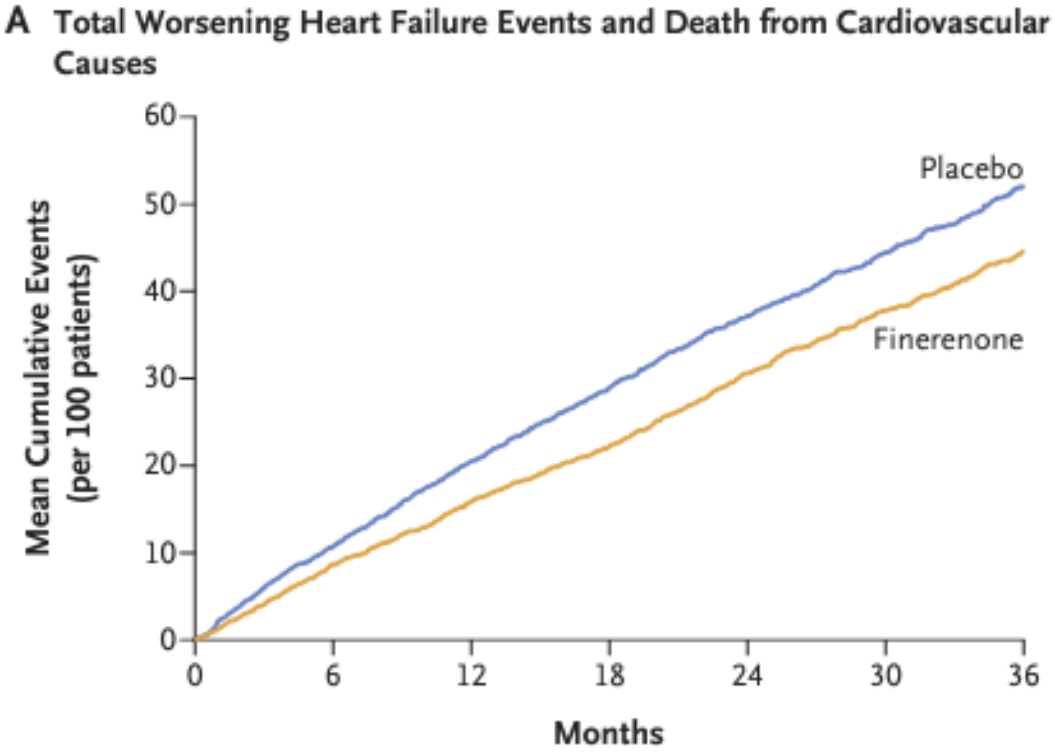
Finerenone to halt kidney dysfunction?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 24, 2024 VOL. 391 NO. 16

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*

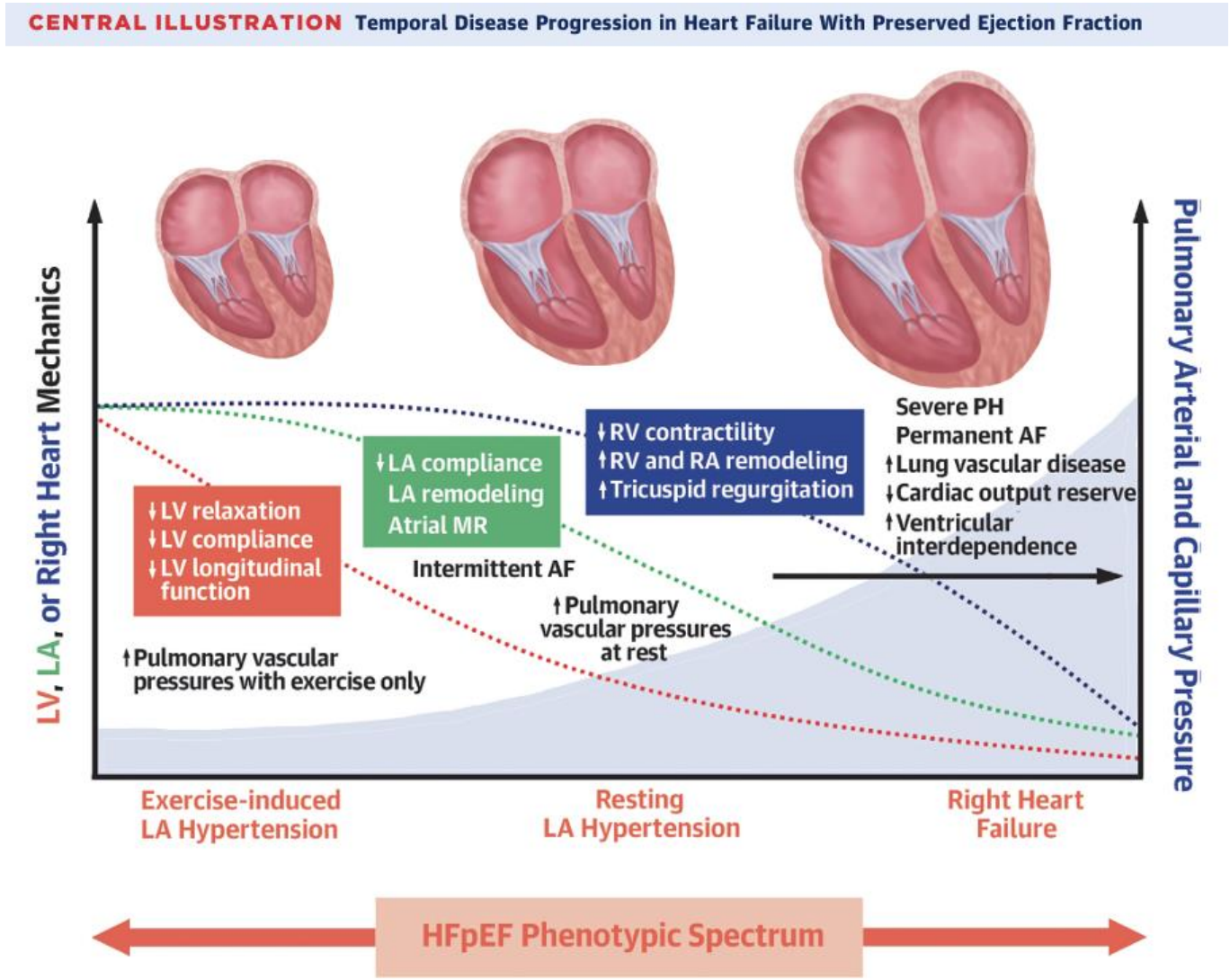


Kidney composite outcome§			
No. of patients (%)	75 (2.5)	55 (1.8)	—
Hazard ratio (95% CI)	—	—	1.33 (0.94–1.89)

COMORBIDITIES IN HFpEF

PULMONARY HYPERTENSION

FROM A LEFT TO A RIGHT PHENOTYPE



Borlaug BA, et al. J Am Coll Cardiol. 2023;81(18):1810-1834.

COMORBIDITIES IN HFpEF

PULMONARY HYPERTENSION

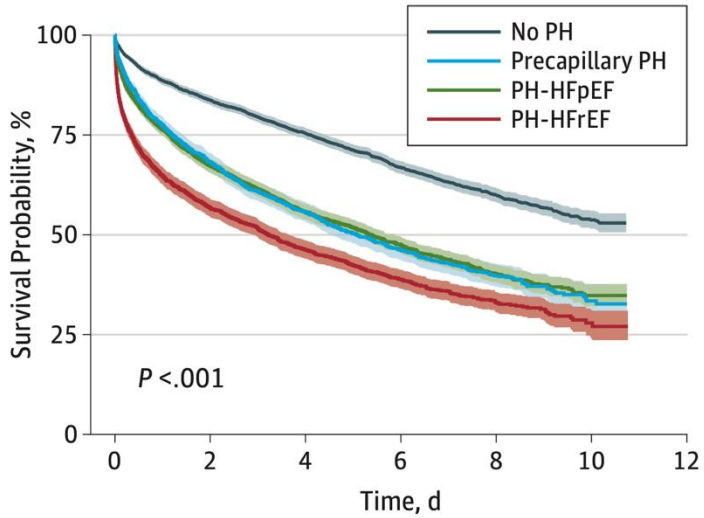
JAMA Cardiology | Original Investigation

Association Between Hemodynamic Markers of Pulmonary Hypertension and Outcomes in Heart Failure With Preserved Ejection Fraction

Rebecca R. Vanderpool, PhD; Melissa Saul, MS; Mehdi Nouraie, MD, PhD; Mark T. Gladwin, MD; Marc A. Simon, MD, MS

About 50% of patients with HFpEF have PH (36% to 83% according to registries) – Guazzi et al, JACC 2020

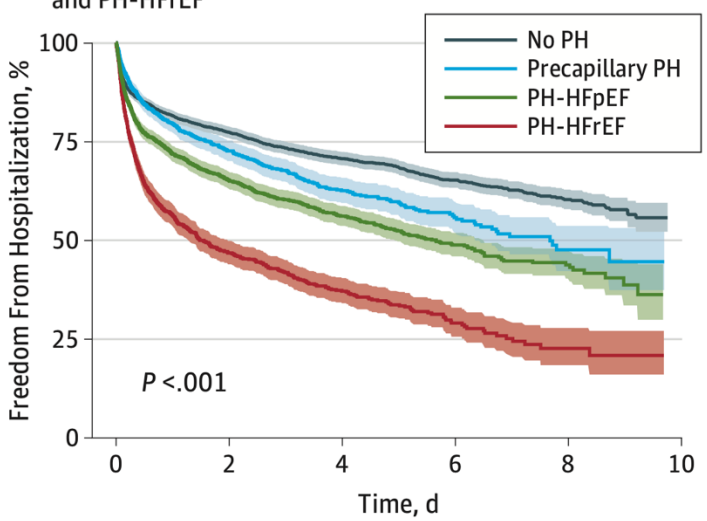
C Survival in precapillary PH, PH-HFpEF, and PH-HFrEF



No. at risk

No PH	3792	3176	2569	1608	908	252
Precapillary PH	1595	1088	768	416	194	56
PH-HFpEF	2577	1735	1226	740	356	79
PH-HFrEF	1813	1028	727	424	176	32

D Freedom from cardiac hospitalizations in precapillary PH, PH-HFpEF, and PH-HFrEF



No. at risk

No PH	3807	2007	1225	637	253	
Precapillary PH	1600	650	314	128	32	
PH-HFpEF	2587	939	460	213	68	
PH-HFrEF	1819	390	184	70	14	

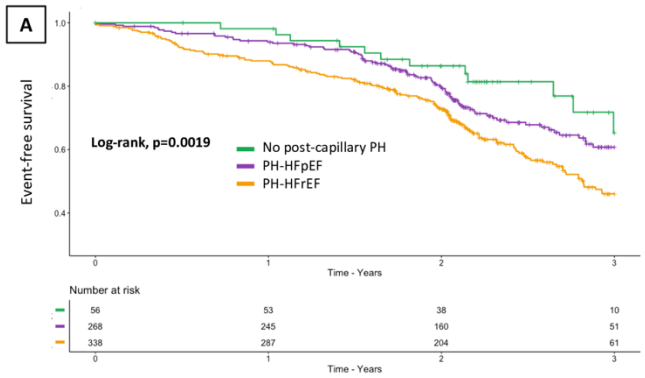
COMORBIDITIES IN HFpEF

PULMONARY HYPERTENSION

ESC European Society of Cardiology
European Heart Journal (2024) 00, 1–15
https://doi.org/10.1093/eurheartj/ehae467
CLINICAL RESEARCH
Heart failure and cardiomyopathies

Post-capillary pulmonary hypertension in heart failure: impact of current definition in the PH-HF multicentre study

Charles Fauvel [1,2,3], Thibaud Damy [4], Emmanuelle Berthelot[5,6], Fabrice Bauer[2,3,7], Jean-Christophe Eicher[8], Pascal de Groote[9,10], Jean-Noël Trochu [11], François Picard[12], Sébastien Renard[13], Hélène Bouvaist[14], Damien Logeart[15], François Roubille[16], Olivier Sitbon[5,17,18], and Nicolas Lamblin [9,10,19]*



Higher level of mPAP and PVR in HFpEF compared with HFrEF

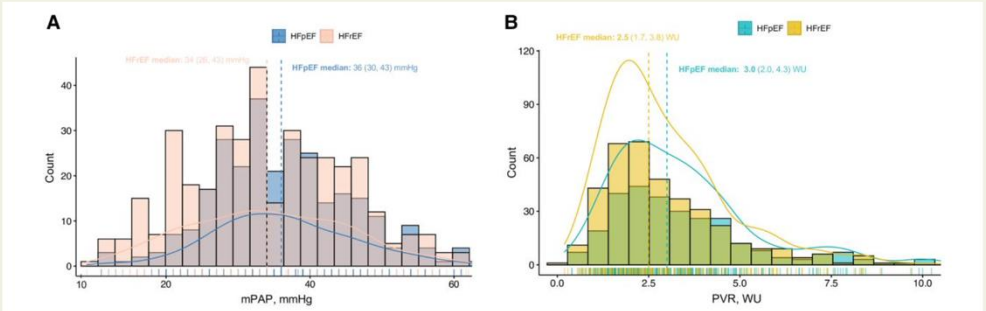
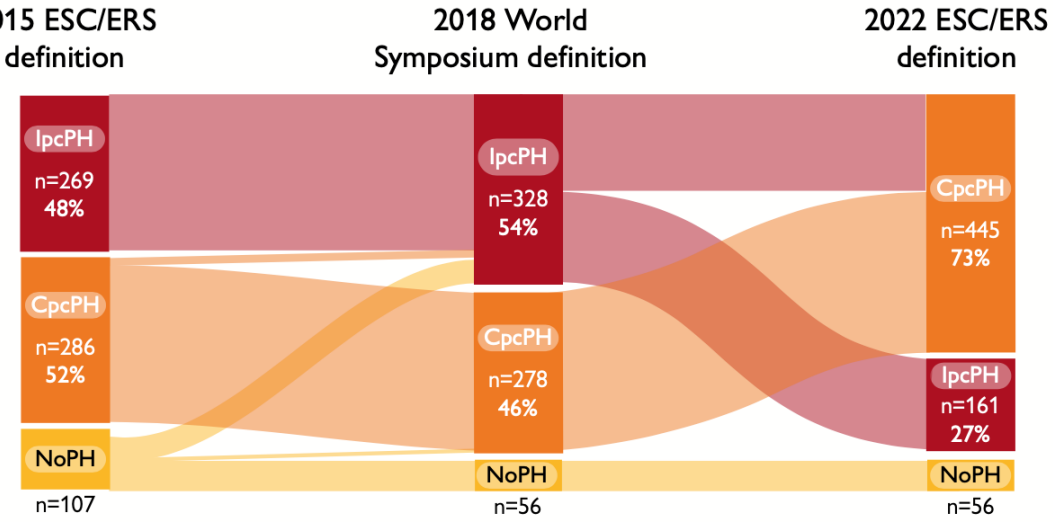


Figure 1 Histogram and density curves for mean pulmonary artery pressure and pulmonary vascular resistance ($n = 662$). This plot shows the relative homogeneous distribution of mean pulmonary artery pressure (*A*) and pulmonary vascular resistance (*B*) among the patients included in this study and stratified by the type of heart failure. The curved line is a density curve (i.e. proportion of values in each range), while the histogram shows the counts of values in each range. The dashed lines intercept the median value of mean pulmonary artery pressure (*A*) and pulmonary vascular resistance (*B*) for each of the subgroup. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; PVR, pulmonary vascular resistance; mPAP, mean pulmonary artery pressure

Proportion of PH-HFpEF and CpcPH-HFpEF patients will increase because of definition change

Impact of changes in definitions:

moderate pcPH increase but huge CpcPH increase



By ↓mPAP from 25 to 20 mmHg

+10%

Increase in the prevalence of pcPH

By ↓PVR from 3 to 2 WU

+60%

Increase in the prevalence of CpcPH

TAKE HOME MESSAGES

- Define HFpEF remains challenging since it remains an heterogeneous population
  - LVEF threshold: 50%
  - What is « preserved » ? Use « HFnEF » term ?

- HFpEF is ''not only diastolic dysfunction''

- Normal NTproBNP/BNP does not exclude HFpEF

- Comorbidities …
  - Are highly prevalent in HFpEF population
  - Are part of HFpEF syndrome definition
  - Should be considered since it may exist potential specific treatment

HFpEF Masterclasses
in centers of expertise

FRANCE

7th November 2024 - DAY 1
8th November 2024 - DAY 2

THANK YOU FOR YOUR ATTENTION!

Dr Charles FAUVEL, MD, PhD student
Rouen University Hospital, Cardiology Department