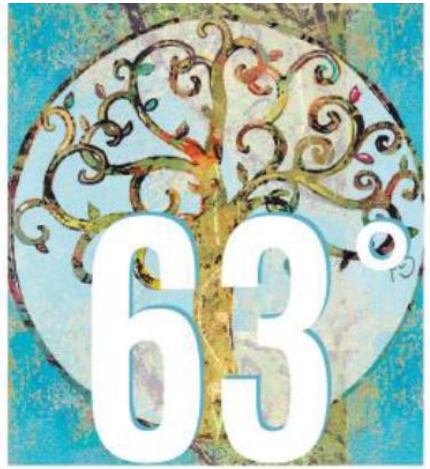

CONGRESSO NAZIONALE SIGG

GLI ANZIANI:
LE RADICI DA PRESERVARE

ROMA 28 novembre 01 dicembre 2018 Auditorium della Tecnica, Roma

LO SCOMPENSO CARDIACO A FUNZIONE SISTOLICA CONSERVATA: UN FENOTIPO NON SOLO GERIATRICO

Andrea Ungar, Md, PhD, FESC

Syncope Unit, Dept of Geriatrics and Intensive Care Medicine
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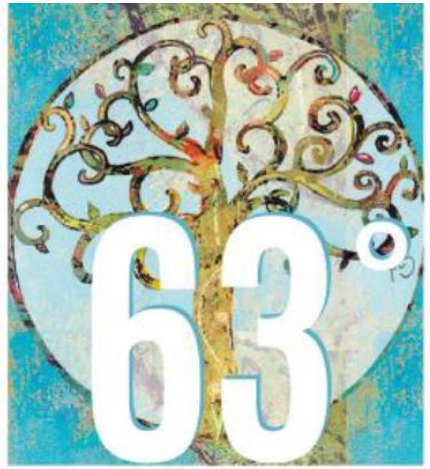

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GLI ANZIANI:
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ROMA 28 novembre 01 dicembre 2018 Auditorium della Tecnica, Roma

LO SCOMPENSO CARDIACO A FUNZIONE SISTOLICA CONSERVATA: [UN FENOTIPO NON SOLO GERIATRICO]

Andrea Ungar, Md, PhD, FESC

Syncope Unit, Dept of Geriatrics and Intensive Care Medicine
University of Florence

Lo scompenso cardiaco in Italia

180.584

Dimissioni ospedaliere

Fonte: Ministero della Salute. Dati SDO 2016.

Lo scompenso cardiaco in Italia

9.3

Giorni di degenza media

Fonte: Ministero della Salute. Dati SDO 2016.

Lo scompenso cardiaco in Italia

1.674.230

Giorni di degenza complessiva

Fonte: Ministero della Salute. Dati SDO 2016.

Lo scompenso cardiaco in Italia

317,57

Tasso di osp. (per 100.000 ab.)

1084,69

Tasso di osp. ≥ 65 aa (per 100.000 ab.)

Fonte: Ministero della Salute. Dati SDO 2016.


European Heart Journal Advance Access published May 20, 2016

European Heart Journal

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)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

Authors/Task Force Members: Piotr Ponikowski* (Chairperson) (Poland), Adriaan A. Voors* (Co-Chairperson) (The Netherlands), Stefan D. Anker (Germany), Héctor Bueno (Spain), John G. F. Cleland (UK), Andrew J. S. Coats (UK), Volkmar Falk (Germany), José Ramón González-Juanatey (Spain), Veli-Pekka Harjola (Finland), Ewa A. Jankowska (Poland), Mariell Jessup (USA), Cecilia Linde (Sweden), Petros Nihoyannopoulos (UK), John T. Parissis (Greece), Burkert Pieske (Germany), Jillian P. Riley (UK), Giuseppe M. C. Rosano (UK/Italy), Luis M. Ruilope (Spain), Frank Ruschitzka (Switzerland), Frans H. Rutten (The Netherlands), Peter van der Meer (The Netherlands)

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Definition of HF-ESC Guidelines

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).

BNP = B-type natriuretic peptide; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LAE = left atrial enlargement; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NT-proBNP = N-terminal pro-B type natriuretic peptide.

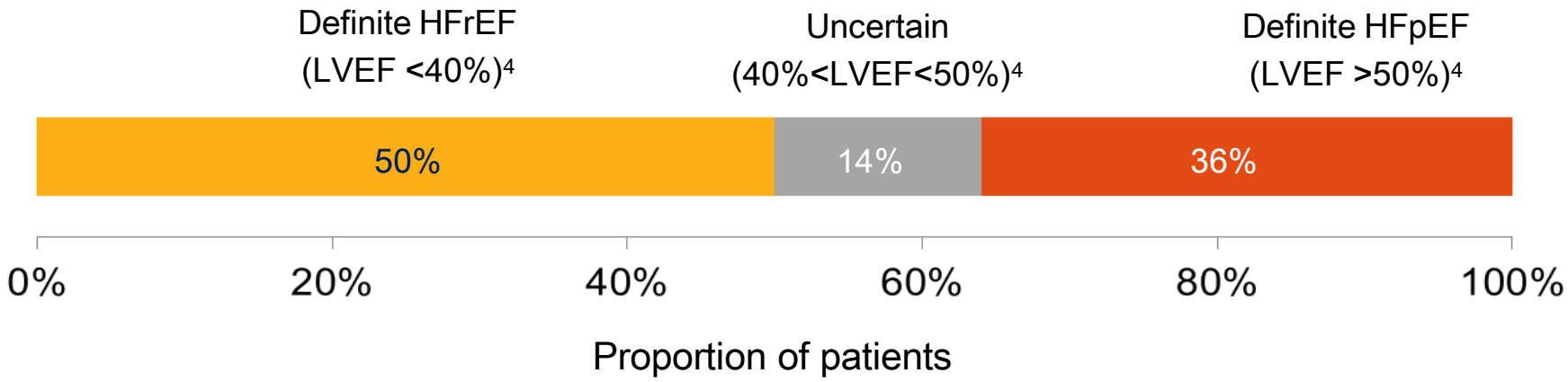
[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics.

[b]BNP>35 pg/ml and/or NT-proBNP>125 pg/mL

Ponikowski P et al. Eur Heart J 2016

The definition of HFpEF: is there a consensus

- There is no consensus concerning the cut-off for preserved LVEF[2]
- Approximately half of patients presenting with symptoms of HF have HFpEF[2]
- Patients with an LVEF in the range 40–50% represent **a gray zone** and may have primarily mild systolic dysfunction[3]

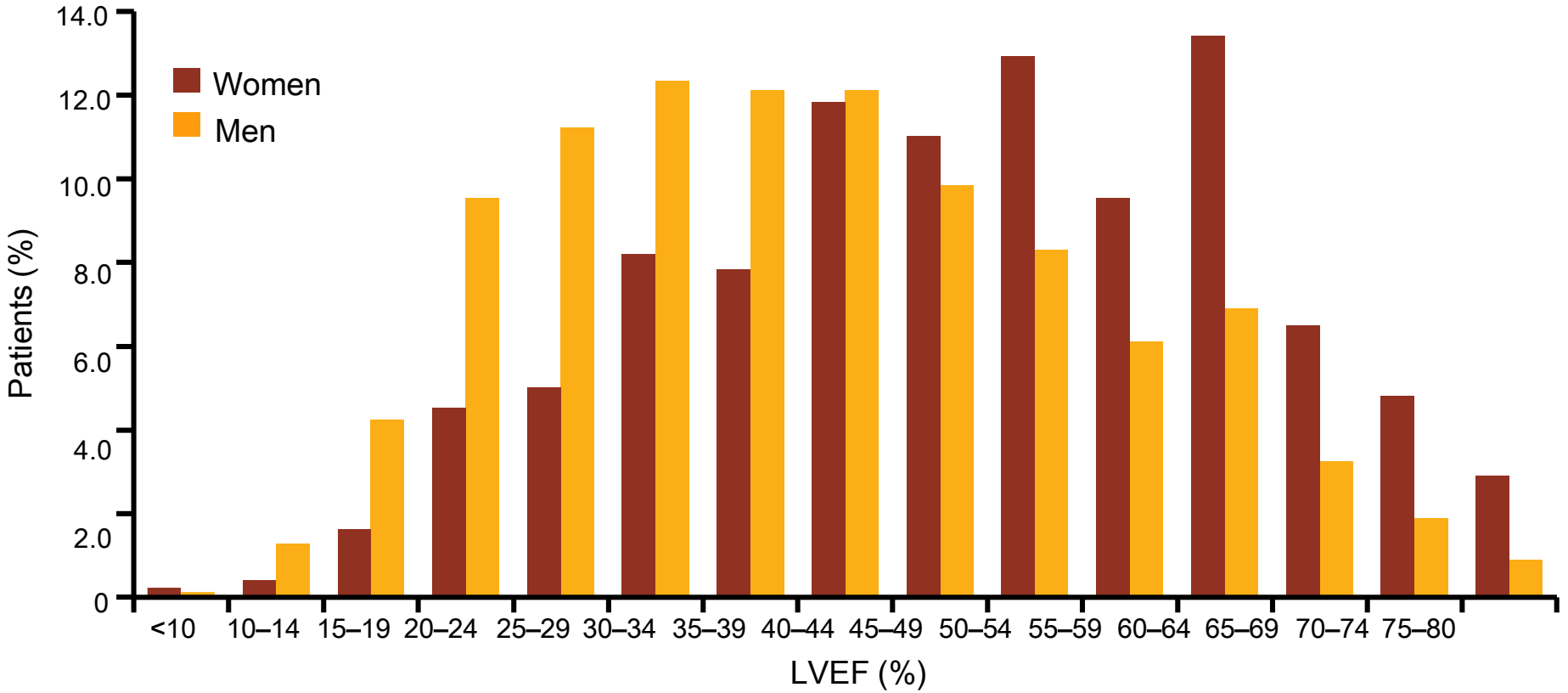


HF=heart failure; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction; LVEF=left ventricular ejection fraction

1. Hsich & Wilkoff. Clevelandclinic.org 2013. Available at: http://my.clevelandclinic.org/services/heart/disorders/heart-failure-what-is/ejectionfraction. Last accessed 9 Jan 2014; 2. Dickstein et al. Eur Heart J 2008;29:2388–442; 3. McMurray et al. Eur Heart J 2012;33,:1787–847; 4. Steinberg et al. Circulation 2012;126:65–75

Prevalence of HFpEF: effect of gender

- Distribution of LVEF amongst women (n=2,048) and men (n=3,249) enrolled in the EuroHeart Failure survey
  - 51% of men but only 28% of women had LVEF <40%



Cleland et al. Eur Heart J 2003;24:442–63

Epidemiology of heart failure with preserved ejection fraction

NATURE REVIEWS | CARDIOLOGY

VOLUME 14 | OCTOBER 2017 |

Shannon M. Dunlay[1,2], Véronique L. Roger[1,2] and Margaret M. Redfield[1]

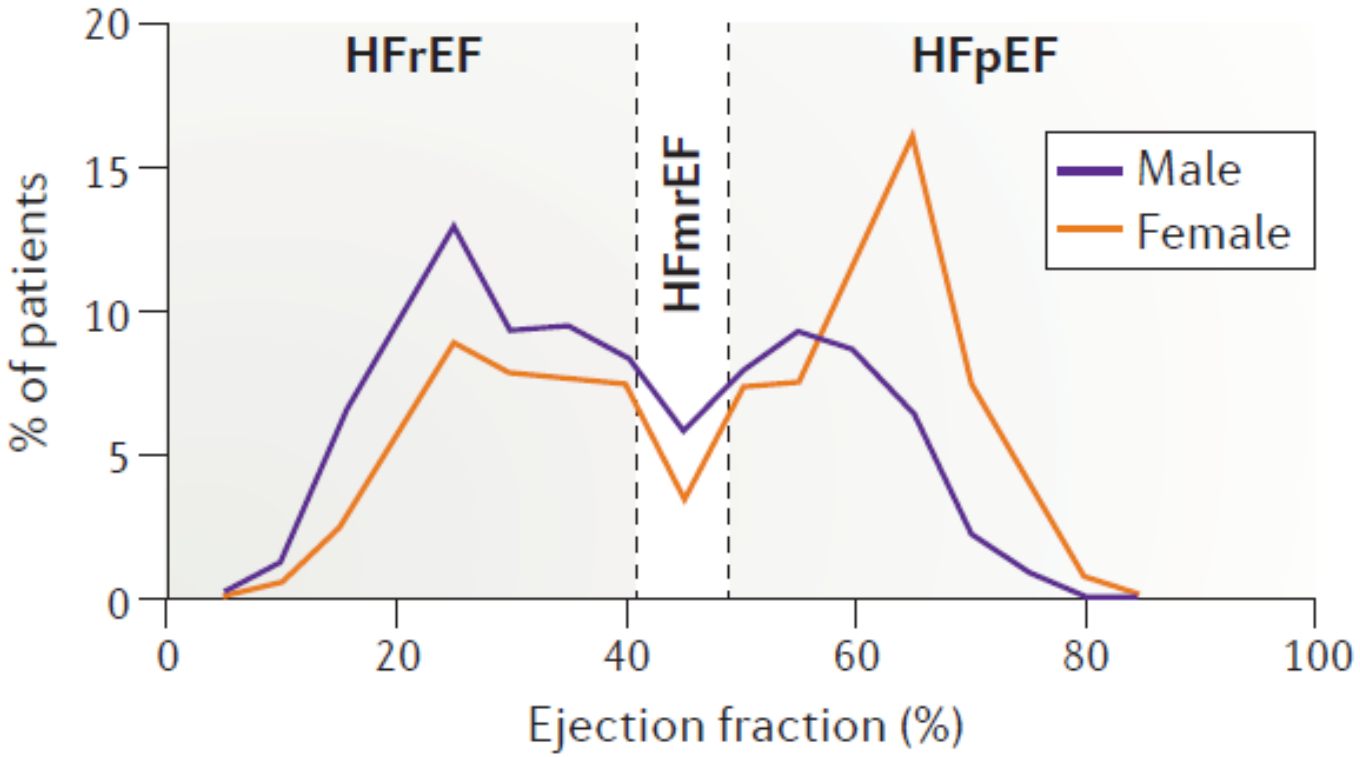


Figure 3 | **Distribution of left ventricular ejection fraction in incident heart failure.**

Epidemiology of heart failure with preserved ejection fraction

Shannon M. Dunlay[1,2], Véronique L. Roger[1,2] and Margaret M. Redfield[1]

NATURE REVIEWS | CARDIOLOGY

VOLUME 14 | OCTOBER 2017 |

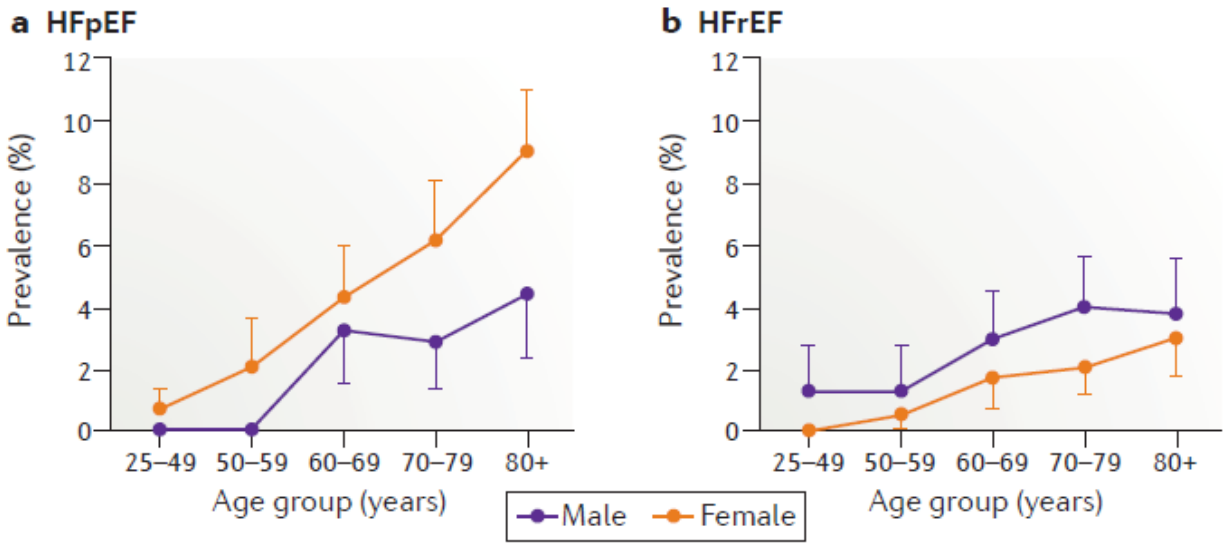


Figure 4 | **Prevalence of HFpEF and HFrEF by age and sex in a southwest European community-based cohort. a** | The prevalence of heart failure with preserved ejection

Box 1 | **Differential diagnosis of HFpEF**

Conditions that present with signs and symptoms of heart failure and a preserved ejection fraction (HFpEF), but are not included in the definition of HFpEF:

Uncorrected primary left-sided valvular heart disease*

- Aortic stenosis
- Aortic regurgitation
- Mitral stenosis
- Mitral regurgitation‡

Isolated right ventricular failure

- WHO groups 1,3,4, or 5 pulmonary hypertension§
- Genetic
  - Arrhythmogenic right ventricular dysplasia
- Congenital heart disease
- Isolated primary pulmonary or tricuspid valvular disease‡
- Right ventricular infarction

Pericardial disease

- Tamponade
- Constrictive pericarditis

Specific cardiomyopathies

- Infiltrative (amyloidosis)‖
- Infectious/inflammatory
  - Sarcoidosis
  - Viral¶

Diagnosis of heart failure with preserved EF

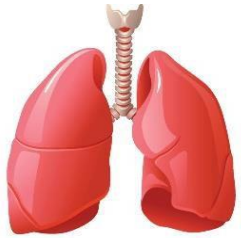
- The diagnosis of HFpEF remains challenging especially in the typical elderly patient with co-morbidities without signs of central fluid overload.
- LVEF is normal and signs and symptoms for HF are often non-specific.
- The diagnosis of HFpEF requires the following conditions to be fulfilled
  - The presence of symptoms and/or signs of HF
  - A ***preserved*** EF (defined as LVEF ¸50% or 40–49% for HFmrEF)
  - Elevated levels of NPs (BNP >35 pg/mL and/or NT-proBNP>125 pg/mL)
  - Evidence of other cardiac functional/structural alterations underlying HF (diastolic dysfunction, filling pressure)

Piotr Ponikowski et al. Eur Heart J 2016

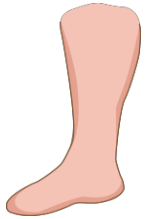
Symptoms and signs of HFpEF and HFrEF

Symptoms and signs of HFpEF/HFrEF[1–3]

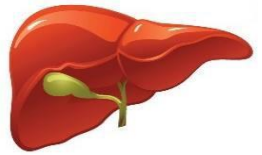
Third heart sound (gallop rhythm)*



Pulmonary congestion
- Rales
- Wheezing
- Chest pain
- Dyspnea
- Orthopnea



Edema

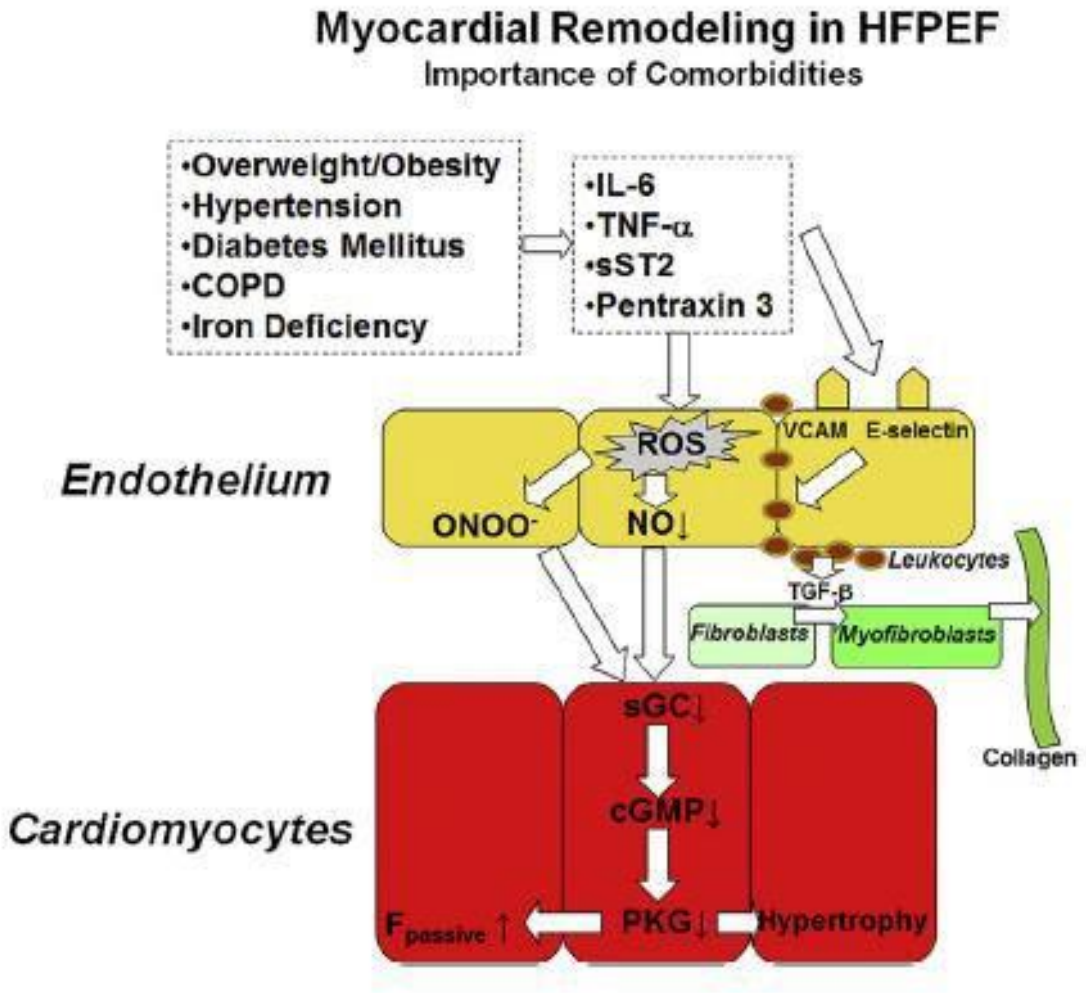


Hepatomegaly

*Assessed via auscultation with a stethoscope; may be confirmed by echocardiography
HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction

1. McMurray et al. Eur Heart J 2012;33,:1787–847; 2. Bhatia et al. N Engl J Med 2006;355:260–9; 3. Asher et al. Cardiac Physical Examination. In: Griffin et al, editors. The Cleveland Clinic Cardiology Board Review. 2nd ed, 2012;p10

Co-morbidities, inflammation and myocardial dysfunction in HEpEF



Paulus WJ et Al., JACC 2013;62(4):263–71

Epidemiology of heart failure with preserved ejection fraction

NATURE REVIEWS | CARDIOLOGY

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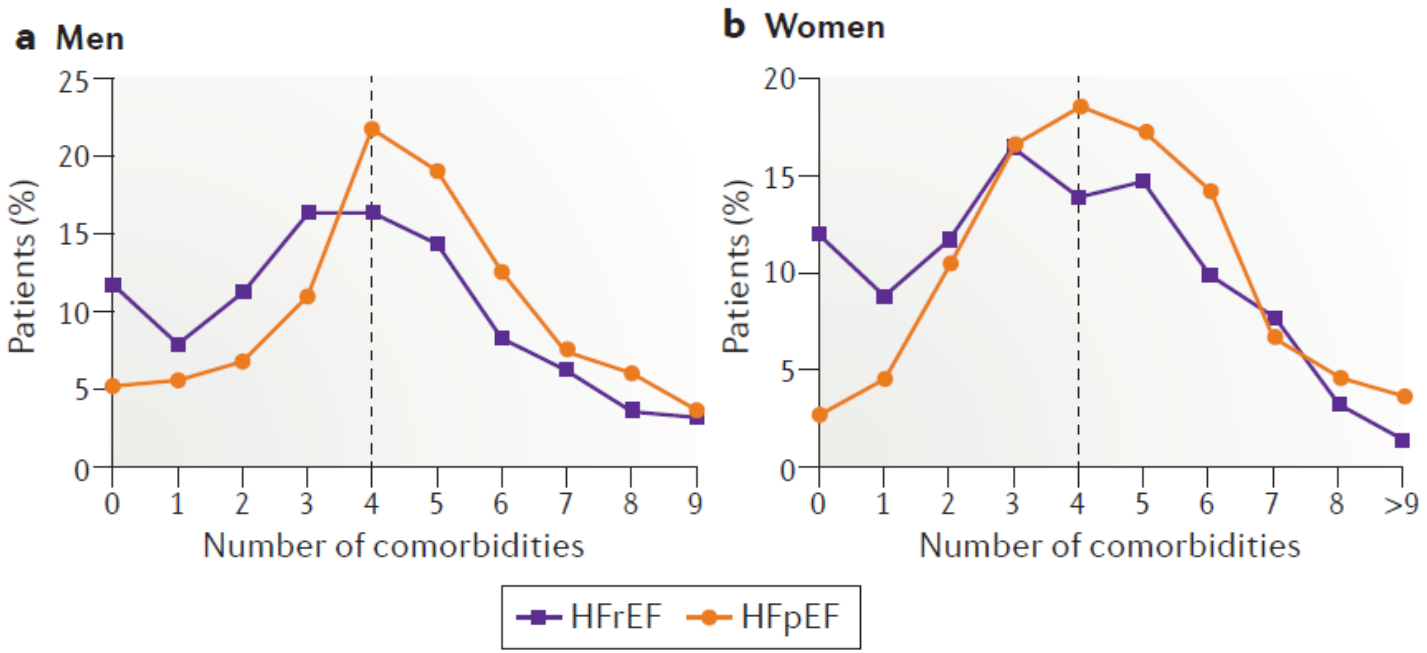
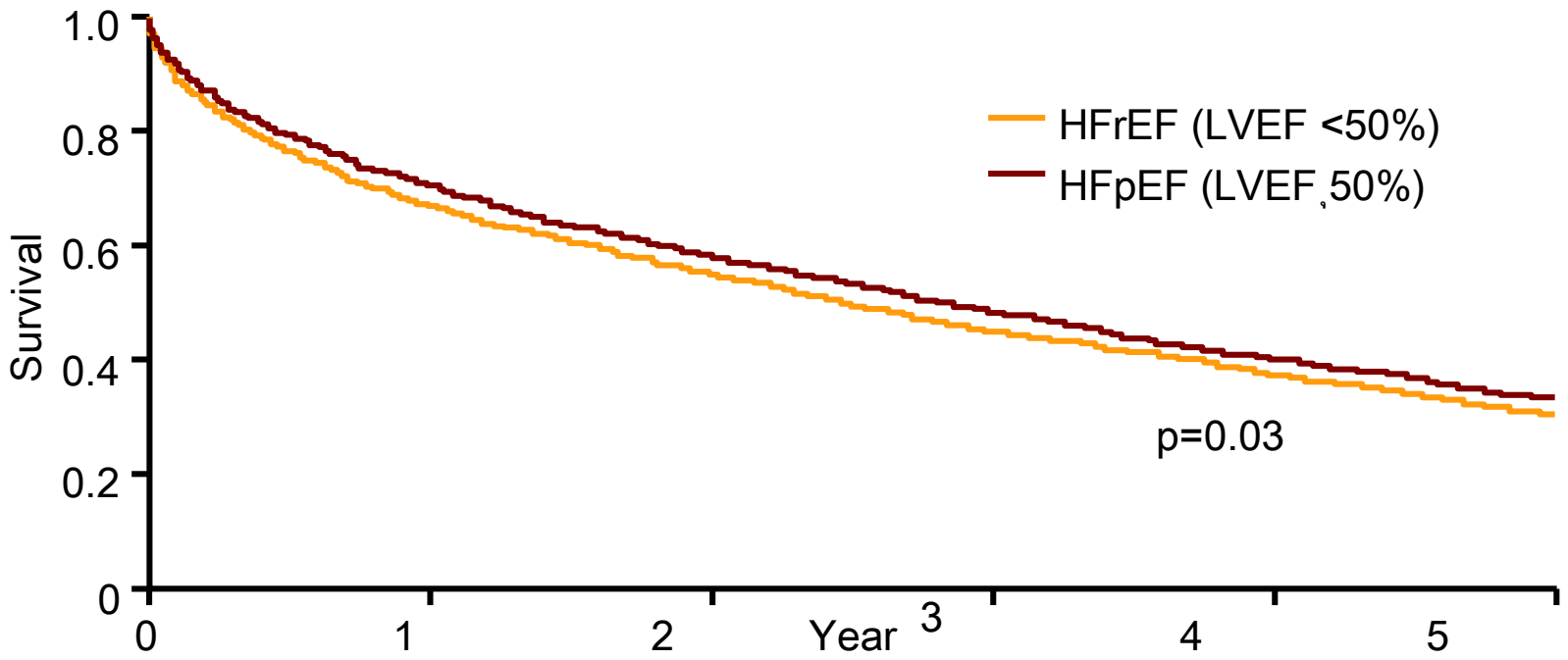


Figure 8 | **Multimorbidity in heart failure in the community.** The frequency distribution of number of comorbid conditions in **a** | men and **b** | women with heart failure with preserved ejection fraction (HFpEF) or heart failure with reduced ejection fraction (HFrEF). Patients with HFpEF more frequently had a higher number of comorbidities[54].

Mortality in patients with HFpEF and HFrEF

- Survival rate among patients with a discharge diagnosis of HF in the USA was slightly higher among patients with HFpEF than those with HFrEF between 1987–2001[1]
  - respective mortality rates were 29% and 32% at 1 year and 65% and 68% at 5 years [2,3]

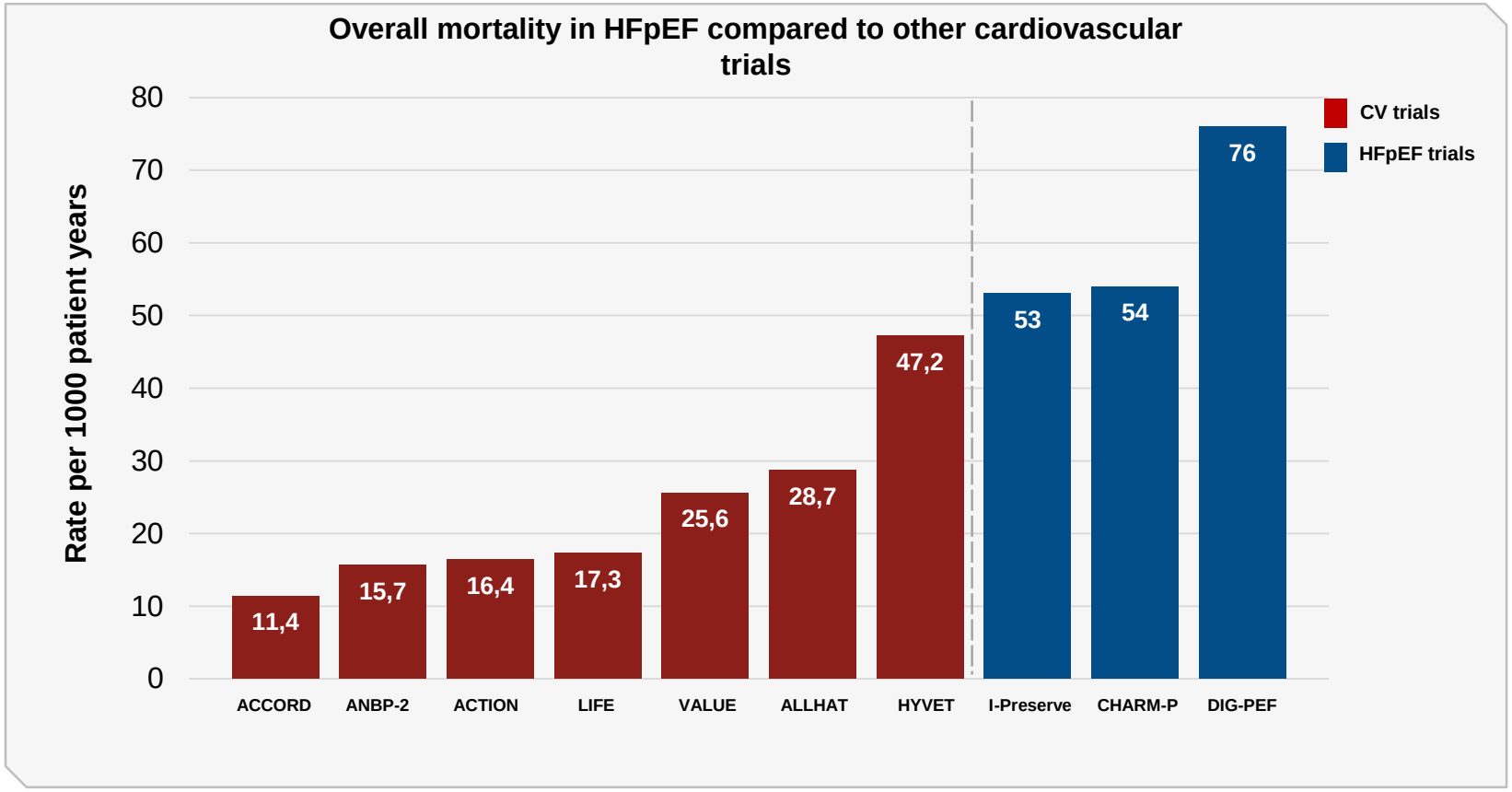


HF=heart failure; HFpEF=heart failure with preserved ejection fraction;
HFrEF=heart failure with reduced ejection fraction; LVEF=left ventricular ejection fraction

1. Owan et al. N Engl J Med 2006;355:251–9
2. Blanche et al. Swiss Med Wkly 2010;140:66–72
3. Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). Eur Heart J 2012;33:1750–7

HFpEF: More than comorbidities

Mortality in HFpEF trials was higher than other cardiovascular trials

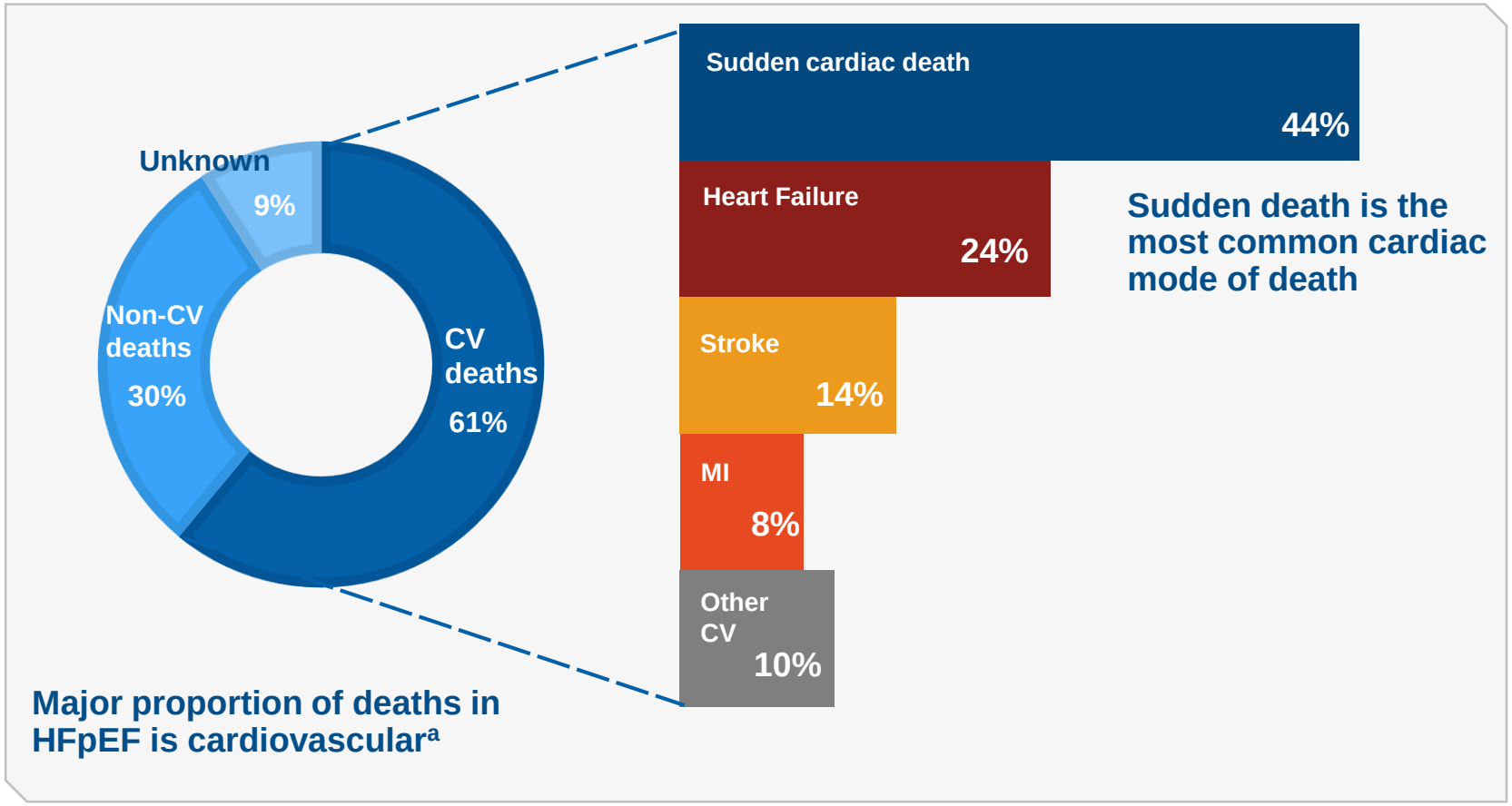


ACCORD [Action to Control Cardiovascular Risk in Diabetes], second Australian National Blood Pressure trial [ANBP-2], ACTION [A Coronary disease Trial Investigating Outcome with Nifedipine], Losartan Intervention for Endpoint reduction in hypertension [LIFE], VALUE [Valsartan Antihypertensive Long-term Use Evaluation], Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial [ALLHAT], and Hypertension in the Very Elderly Trial [HYVET]) and heart failure–preserved ejection fraction (HF-PEF) trials (DIG-PEF, CHARM-Preserved, and I-PRESERVE)

CV, cardiovascular; HFpEF, Heart failure with preserved ejection fraction

Campbell RT et al. J Am Coll Cardiol 2012;60:2349–56.

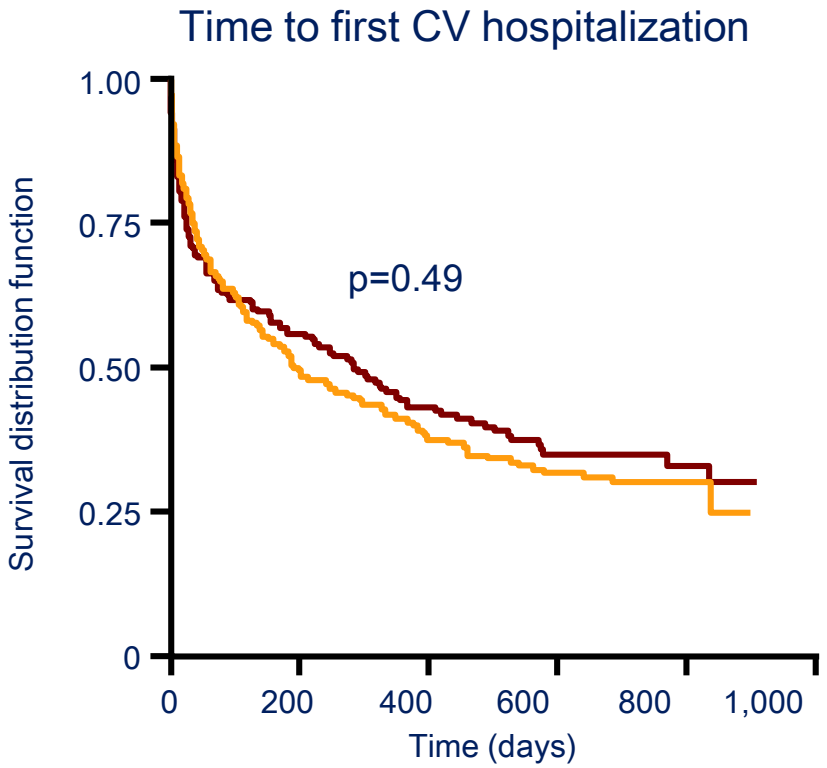
Specific Mode of Death: RCTs

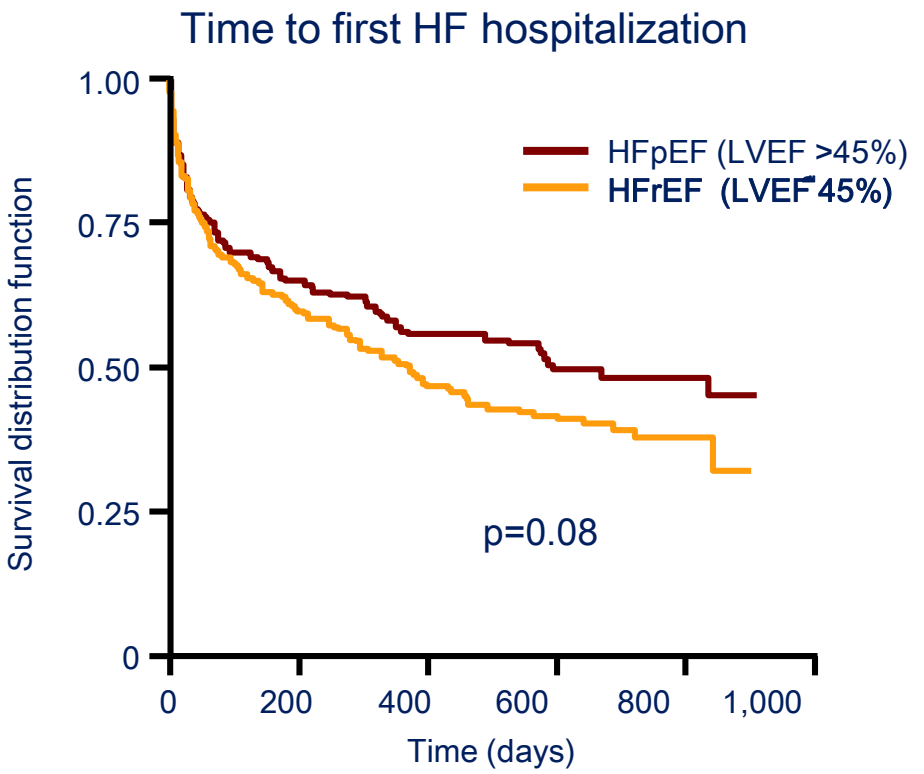


[a]Data from I-Preserve trial
CV, cardiovascular; HFpEF, heart failure with preserved ejection fraction; MI, myocardial infarction; RCT, randomized controlled trial
Chan MM and Lam CS. Eur J Heart Fail. 2013;15(6):604-13.

Rates of initial hospital admission are similar in patients with HFpEF and HFrEF

- In a retrospective study of 451 patients with HF in Sweden, time from diagnosis to first CV- or HF-related hospitalization was not significantly different between HFpEF and HFrEF



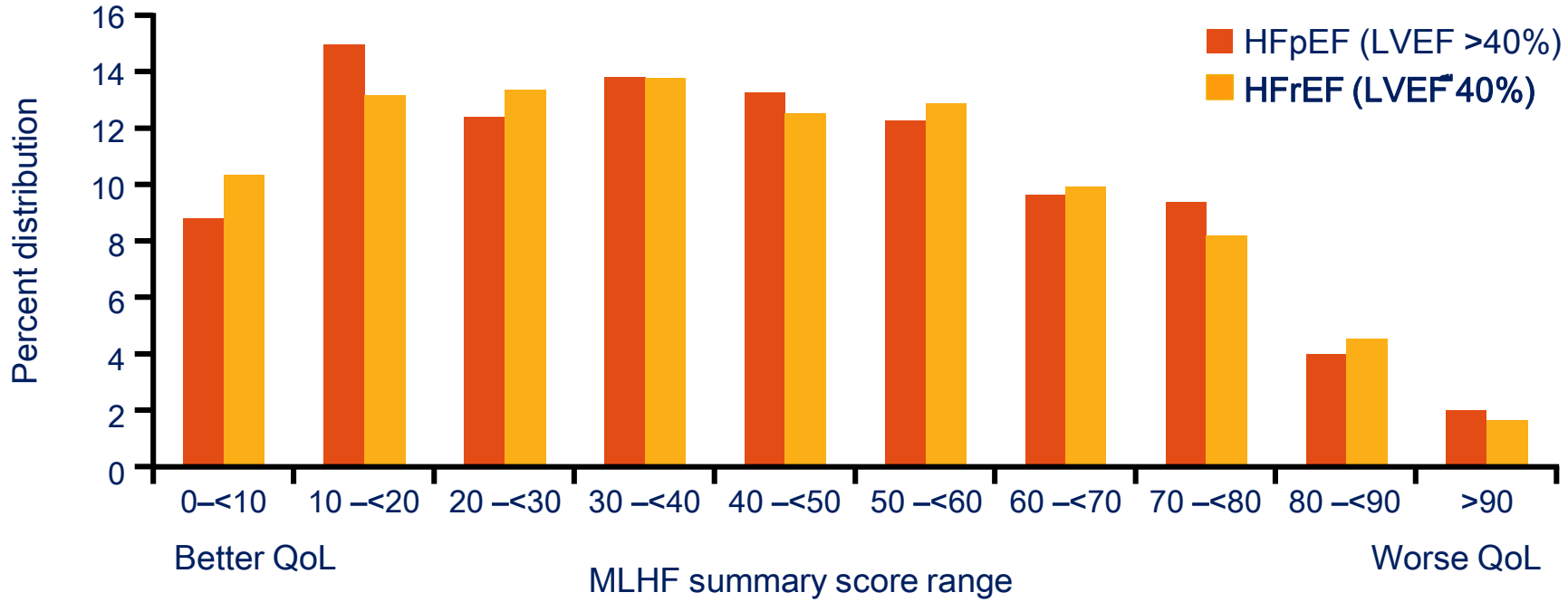


CV=cardiovascular; HF=heart failure; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction; LVEF=left ventricular ejection fraction

Wikstrom et al. ESC 2011 Gothenburg, Sweden, May 21–24, 2011

Health-related QoL in patients with HFrEF and HFpEF

Patients with HFpEF may have greatly reduced general and symptom-specific QoL[2]

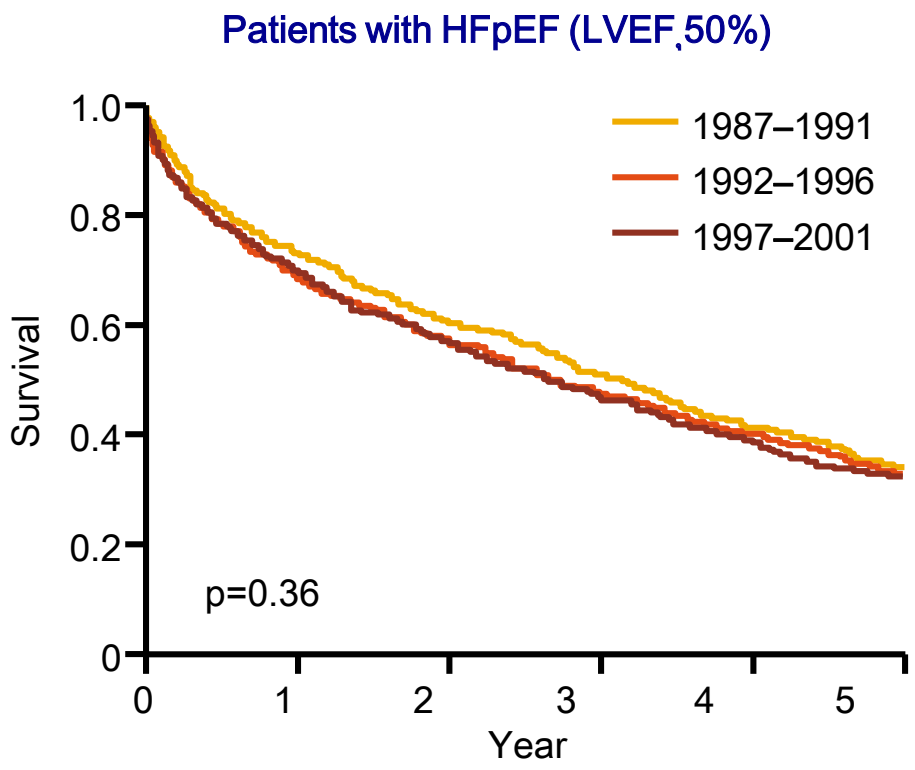


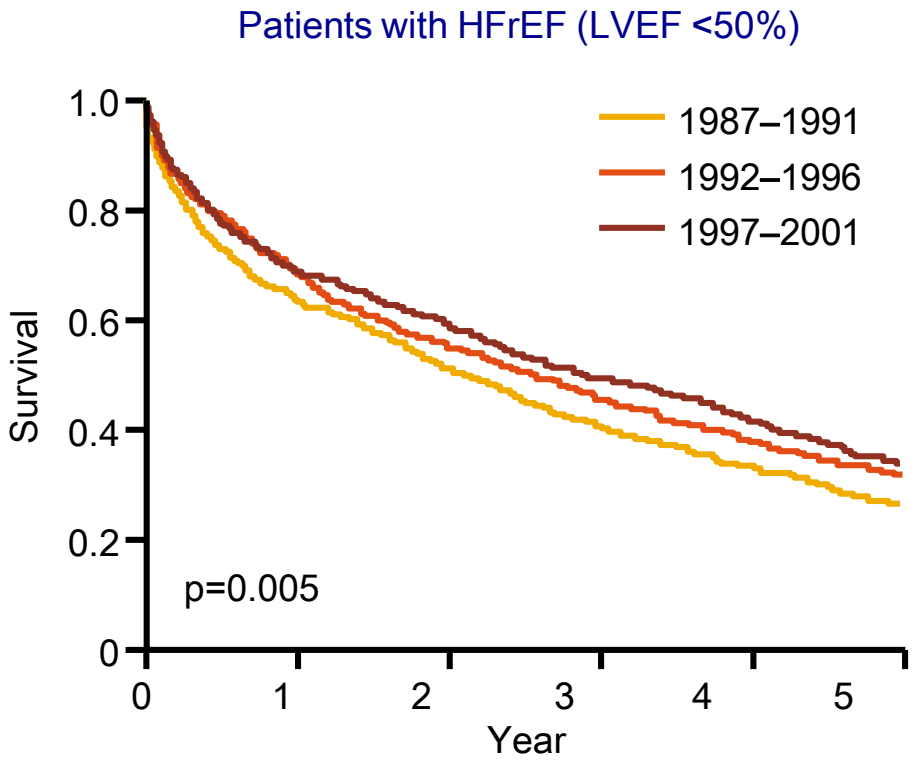
Distribution of the MLHF questionnaire responses in patients (n=2709) with HFpEF and HFrEF. Scores range from 0 to 105 with a low score reflecting a better health-related QoL. HF=heart failure; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction; LVEF=left ventricular ejection fraction; MLHF=Minnesota Living with Heart Failure; QoL=quality of life

1. Lewis et al. Eur J Heart Fail 2007;9:83–91
2. Kitzman et al. JAMA 2002;288:2144-50

Changes in survival rates over time in patients with HFrEF and HFpEF

- Survival rate among patients with a discharge diagnosis of HFpEF has not changed significantly over time





Owan et al. N Engl J Med 2006;355:251–9

Heart failure with preserved ejection fraction: from mechanisms to therapies

CLINICAL REVIEW
Novel therapeutic concepts

European Heart Journal (2018) **39**, 2780–2792

Carolyn S. P. Lam[1,2,3,4]*, Adriaan A. Voors[2], Rudolf A. de Boer[2], Scott D. Solomon[5,6], and Dirk J. van Veldhuisen[2]

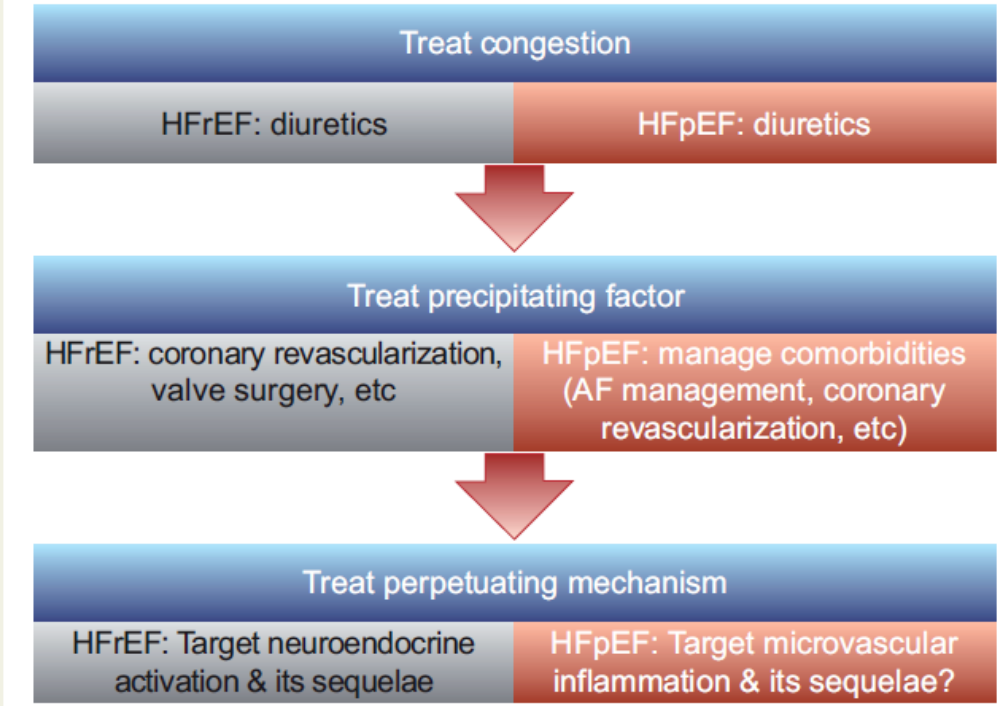


Figure 1 Principles of managing heart failure with preserved ejection fraction and heart failure with reduced ejection fraction. AF, atrial fibrillation.

Heart failure with preserved ejection fraction: from mechanisms to therapies

Carolyn S. P. Lam[1,2,3,4]*, Adriaan A. Voors[2], Rudolf A. de Boer[2], Scott D. Solomon[5,6], and Dirk J. van Veldhuisen[2]

European Heart Journal (2018) **39**, 2780–2792

CLINICAL REVIEW

Novel therapeutic concepts

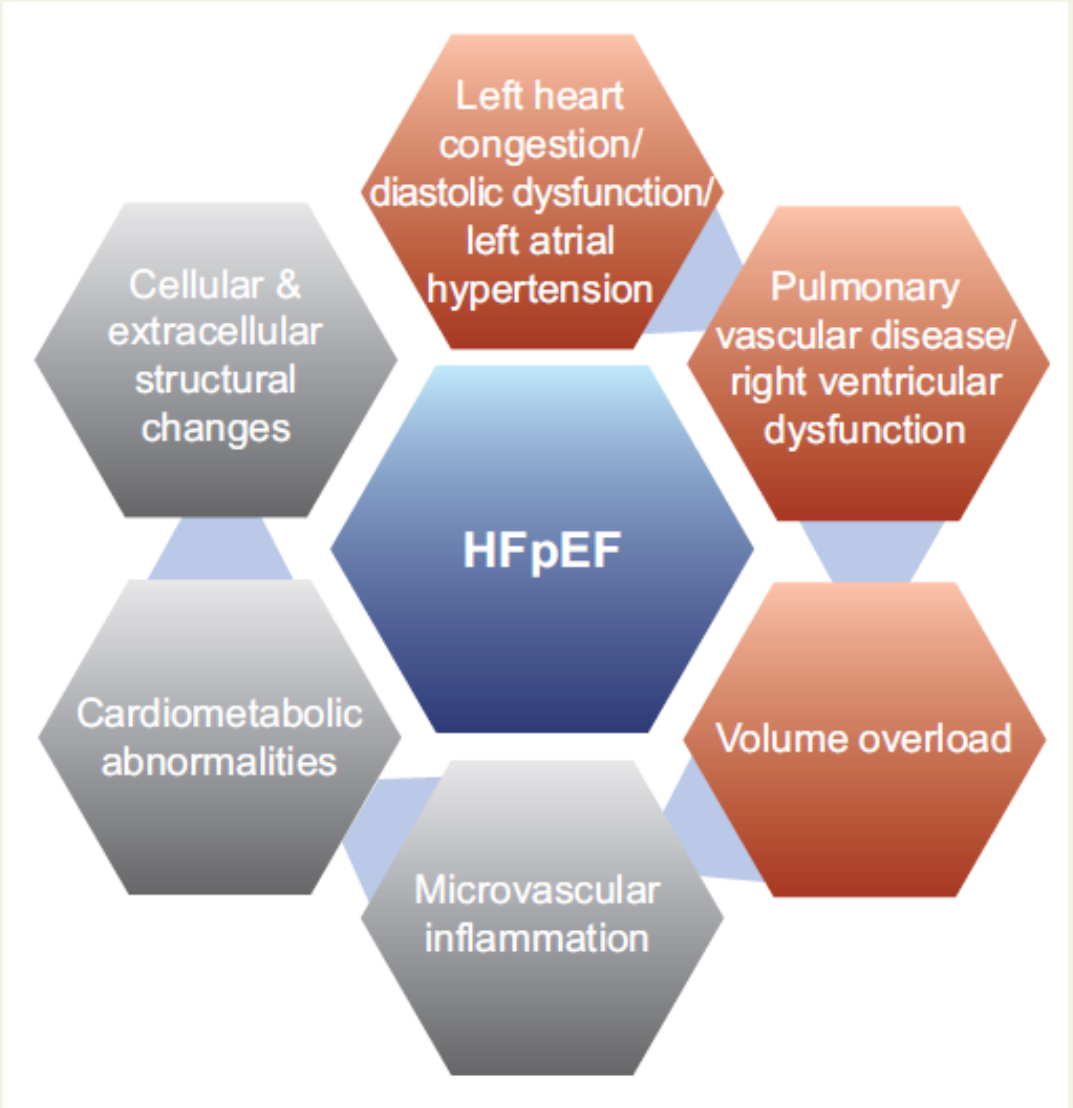
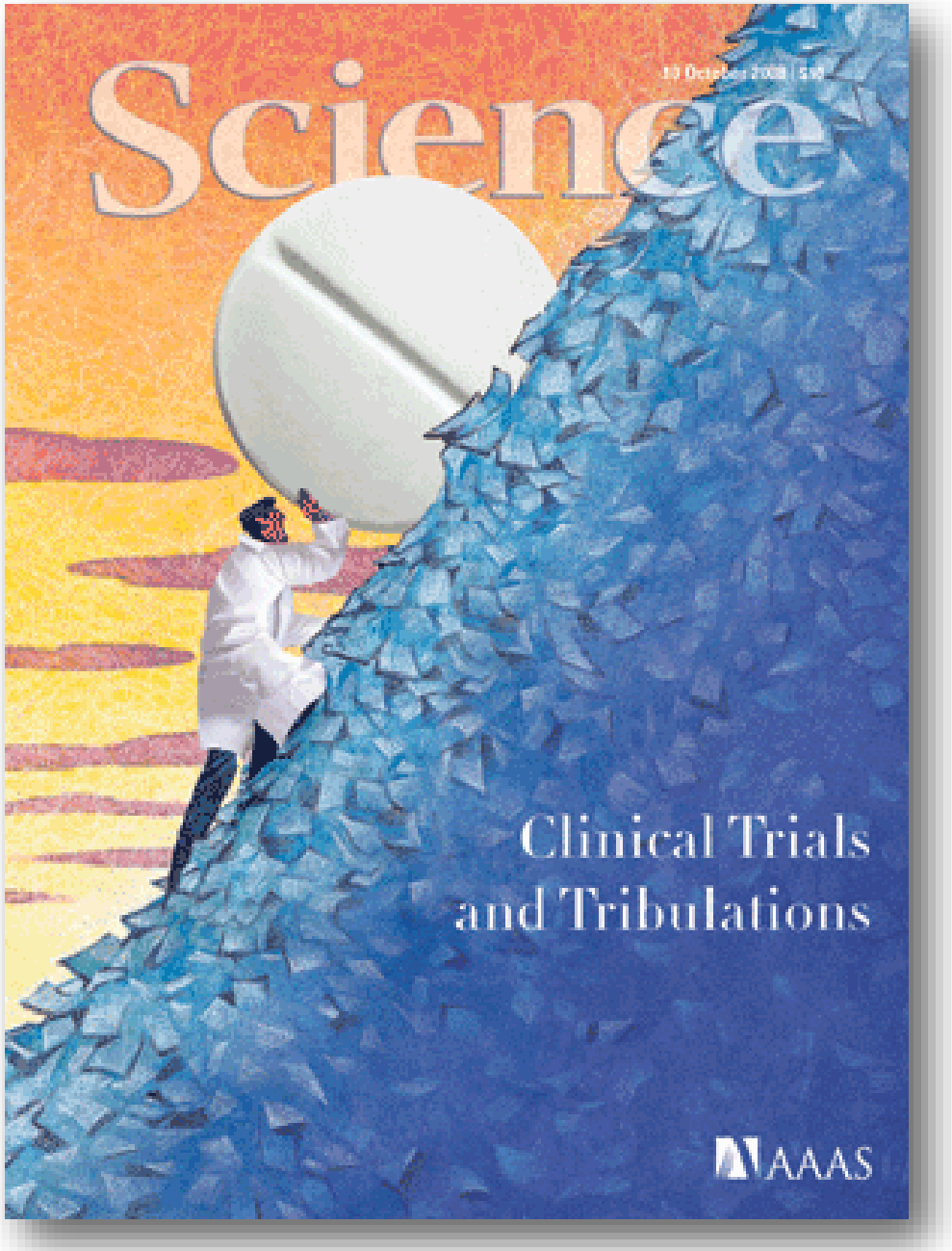


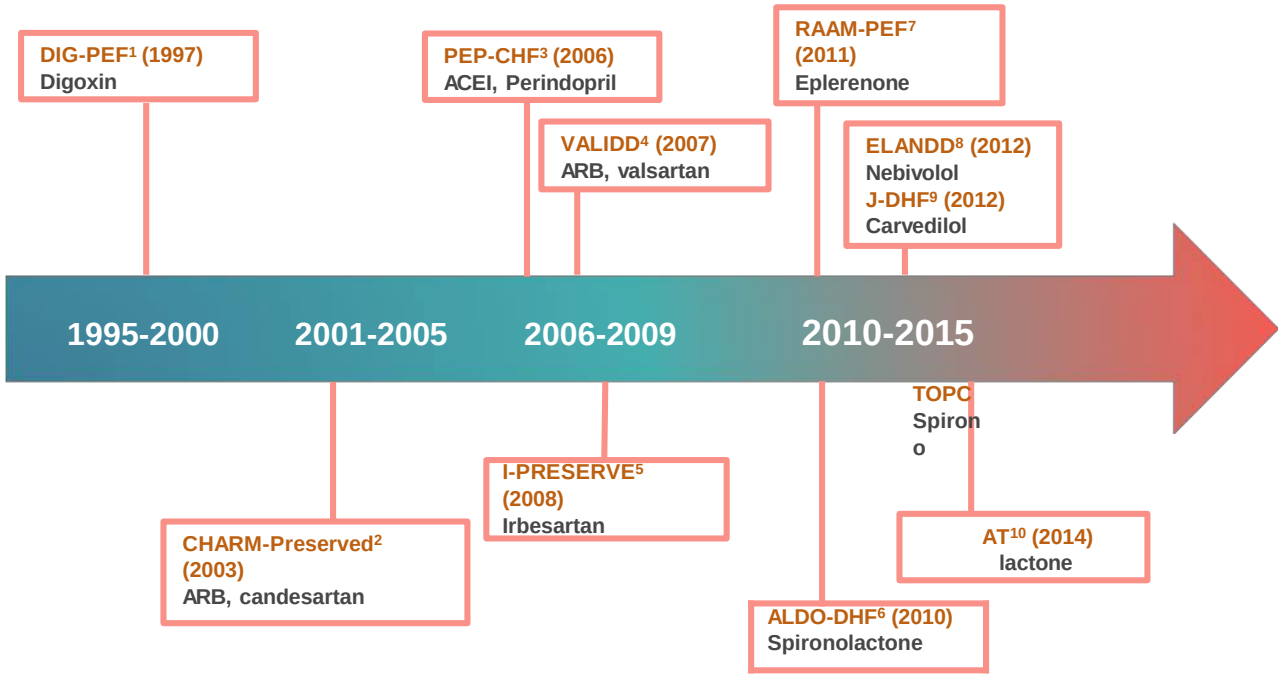
Figure 2 Mechanisms in heart failure with preserved ejection fraction. Six mechanisms are outlined in this review—three haemodynamic (orange) and three cellular/molecular (grey).



RCT?

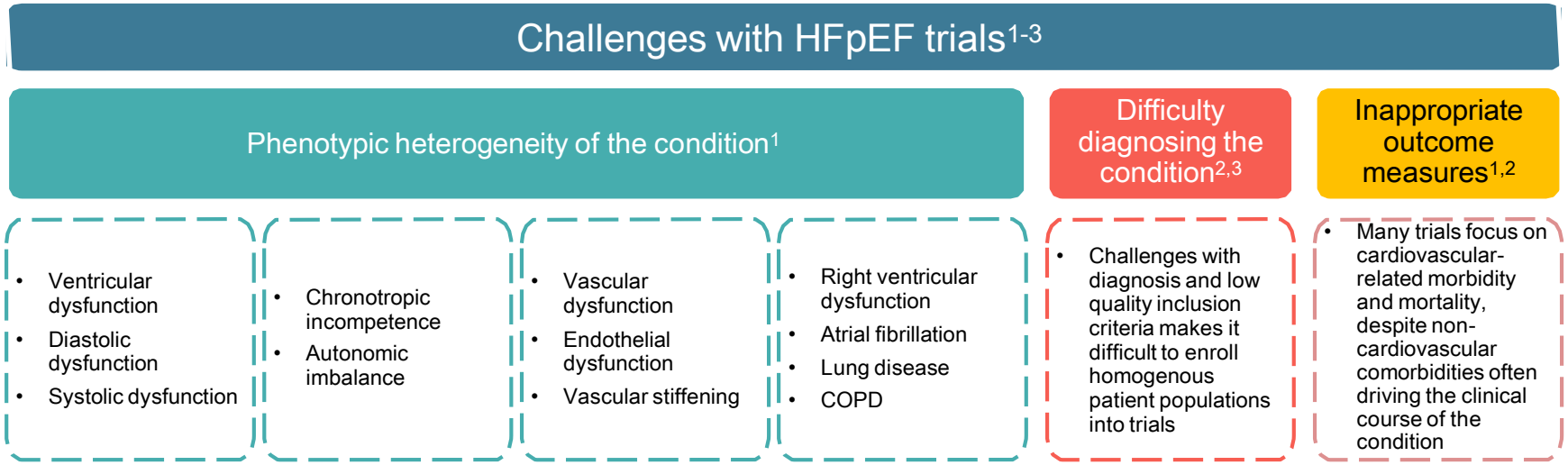
There is a need for therapeutic advances in patients with HFpEF

- While recent advances in the management of HFrEF have resulted in a significant extension of life expectancy,[1–5] this is not reflected in HFpEF
- No proven therapies exist for the treatment of HFpEF and little progress has been made towards identifying a suitable treatment in the last 30 years[6]



1. Digitalis Investigation Group. N Engl J Med 1997;336:525–33; 2. Yusuf et al. Lancet 2003;362:777–81; 3. Cleland et al. Eur Heart J 2006;27:2338–45;
4. Solomon et al. Lancet 2007;369:2079–87; 5. Massie et al. N Engl J Med 2008;359:2456–67; 5; 6. Edelmann et al. JAMA. 2013 Feb 27;309(8):781-91;
7. Deswal et al. J Card Fail 2011;17:634–42; 8. Conraads et al. Eur J Heart Fail 2012;14:219–25; 9. Yamamoto et al. Eur J Heart Fail 2013;15:110–18;
10. Pitt et al. N Engl J Med 2014;370:1383–9

There are many potential reasons why HFpEF Trials have produced inconsistent data and failed to meet their primary endpoints[1–3]



HFpEF, heart failure with preserved ejection fraction

1. Becher PM et al. World J Cardiol 2015;7(9):544–554; 2. Hempel C and Nielsen K. Cardiology today 2015. Available at: www.healio.com/cardiology;
3. Luo H et al. Int J Cardiol 2018;254;210–214

Recommendations for treatment in patients with HF with preserved EF% and HF with mid-range EF%

Recommendations	Class [a]	Level [b]	Ref [c]
it is recommended to screen patients with HFpEF or HFmrEF for both cardiovascular and non-cardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis.	I	C	
Diuretics are recommended in congested patients with HFpEF or HFmrEF in order to alleviate symptoms and signs.	I	B	178, 179

9.2 Effect of treatment on hospitalization for heart failure in heart failure with preserved ejection fraction

For patients in sinus rhythm, there is some evidence that nebivolol,[173,312,313] digoxin,[314] spironolactone[301] and candesartan[310] might reduce HF hospitalizations. For patients in AF, beta-blockers do not appear to be effective and digoxin has not been studied. The evidence in support of either ARBs[315] or ACEIs[311] is inconclusive.


European Heart Journal Advance Access published May 20, 2016

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Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

Ponikowski P et al. Eur Heart J 2016

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Ongoing HFpEF Clinical Trials (> 900 Participants)

Key words: "diastolic heart failure" or "HFpEF" or "heart failure with preserved ejection fraction". Accessed on: 8/15/2017

Study Name	n	Interventions	End	Primary Outcome Measures
Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction (PARAGON-HF)	4822	Drug: Sacubitril/valsartan Drug: Valsartan	2019	Cumulative number of primary composite events of cardiovascular (CV) death and total (first and recurrent) HF hospitalizations
A Randomized, Double-blind Controlled Study Comparing LCZ696 to Medical Therapy for Comorbidities in HFpEF Patients (PARALLAX)	2200	Drug: Sacubitril/valsartan Drug: Enalapril Drug: Valsartan Drug: Placebo	2019	Change from baseline in N-terminal pro-brain natriuretic peptide (NT-proBNP) after 12 weeks
Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure With Preserved Ejection Fraction (SPIRRIT)	3500	Drug: Spironolactone Other: Standard care	2021	Time to death from any cause
EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction (EMPEROR-Preserved)	4126	Drug: Empagliflozin Drug: Placebo	2020	Composite primary endpoint - Time to first event of adjudicated CV (Cardiovascular) death or adjudicated HHF (Hospitalisation for Heart Failure)
Teneligliptin on the Progressive Left Ventricular Diastolic Dysfunction With Type 2 Diabetes Mellitus Study (TOPLEVEL)	936	Drug: Teneligliptin	2019	Change of the ratio of peak velocity of early transmitral diastolic filling by echocardiography (E) to early diastolic mitral annular velocity by tissue Doppler echocardiography (E/e')

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)

Patients with symptomatic[a] HFrEF[b]

↓

Therapy with ACE-I[c] and beta-blocker
(up-titrate to maximum tolerated evidence-based doses)

↓

Still symptomatic and LVEF ≤35%

↓ Yes

Add MR antagonist[d,e]
(up-titrate to maximum tolerated evidence-based dose)

↓ Yes

Still symptomatic and LVEF ≤35%

No → (to Diuretics to relieve symptoms and signs of congestion)

↓ Yes

Able to tolerate ACEI (or ARB)[f,g]

↓

ARNI to replace ACE-I

Sinus rhythm[h], HR ≥70 beats/min

↓

Ivabradine

Diuretics to relieve symptoms and signs of congestion

If LVEF ≤35% despite OMT or a history of symptomatic VT/VF, implant ICD

Green indicates a **class I** recommendation;
Yellow indicates a **class IIa** recommendation.

Pharmacological treatments indicated in patients with symptomatic (NYHA Class II-IV) HFrEF

Recommendations	Class	Level
Sacubitril/valsartan is recommended as a **replacement for an ACEi** to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACEi, a beta-blocker and an MRA*	I	B

Patophysiology of HF: Neurohormonal activation theory

Cardiac structure/function abnormality

↓

Activation of compensatory mechanisms to maintain cardiac output and organ perfusion[1]

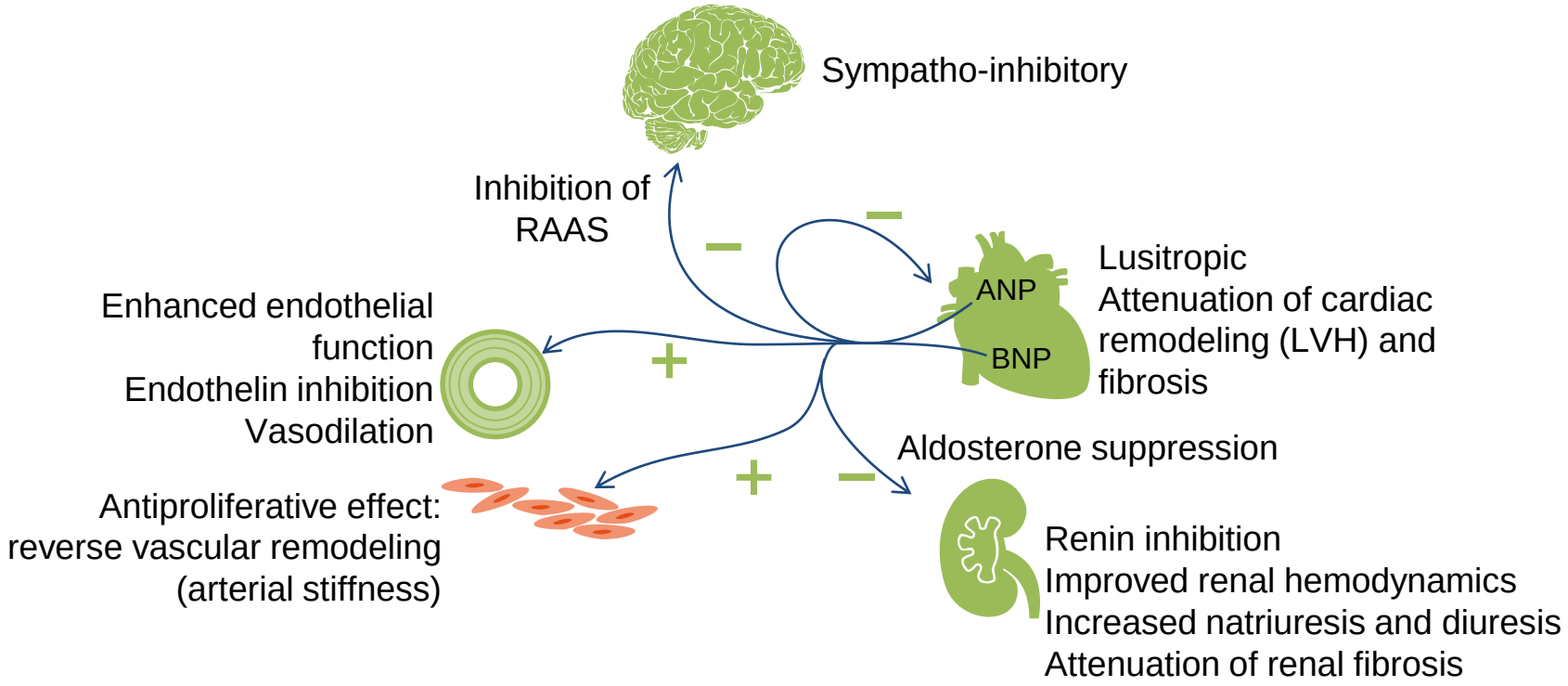
SNS	*RAAS*	*NP system*
Activated in response to reduced cardiac output[1]		Release of NPs in response to cardiac stress[2]
Short-term effects are beneficial in early HF[1]		Opposes the actions of the RAAS[2] and SNS[4,5]
Long-term activation exerts unfavourable effects[1,3]		

NP=natriuretic peptide; RAAS=renin angiotensin aldosterone system;SNS=sympathetic nervous system

1. Francis et al. Ann Intern Med 1984;101:370–7; 2. Clerico et al. Am J Physiol Heart Circ Physiol 2011;301:H12–H20;
3. Von Lueder et al. Circ Heart Fail 2013;6:594–605 4. Luchner & Schunkert. Cardiovasc Res 2004;63:443–9;
5. Thysgesen et al. Eur Heart J 2012;33:2001–6

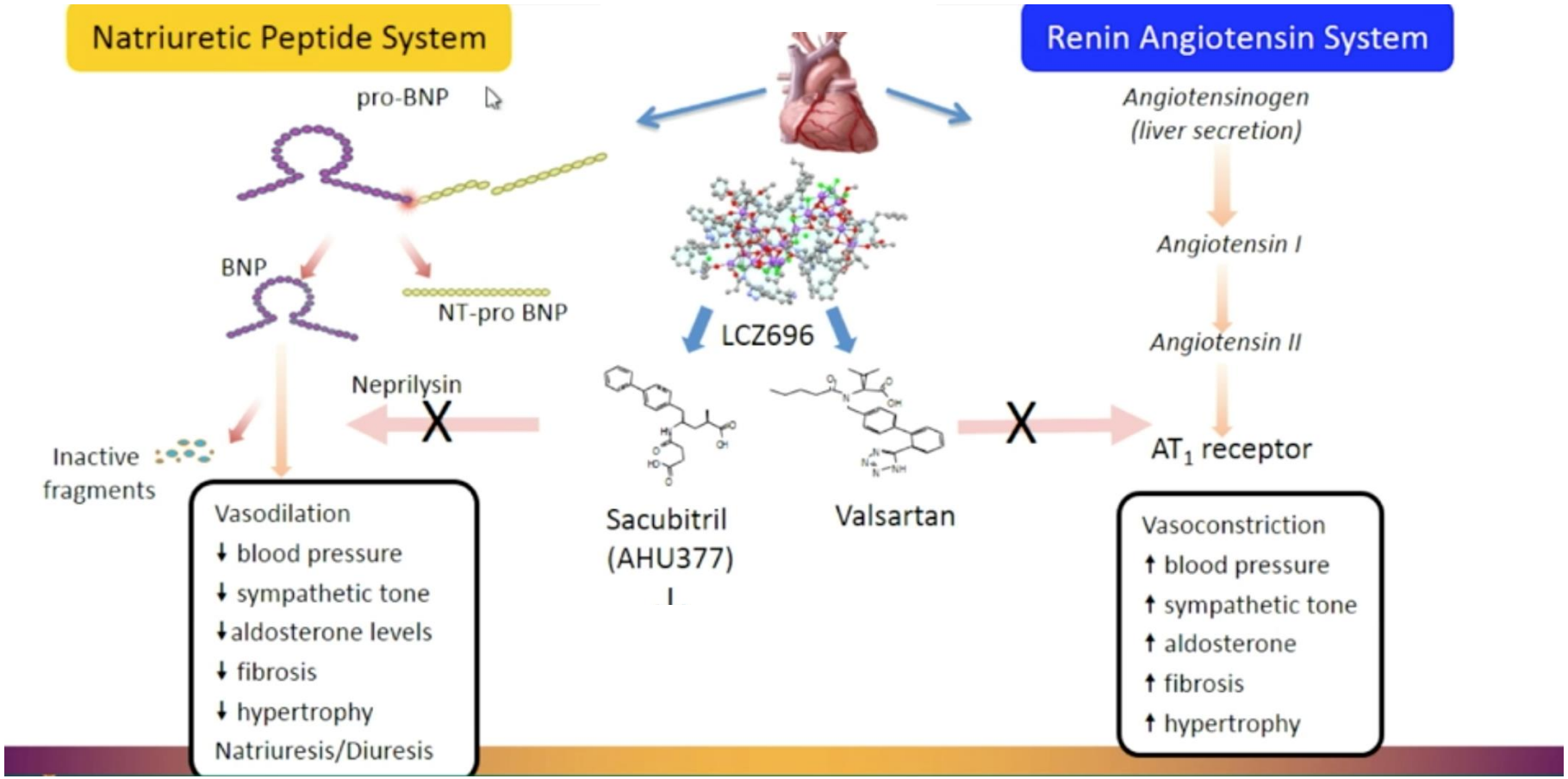
Natriuretic peptides have potential for protection of the heart, vessels and kidneys

NPs are released in response to cardiac wall stress and act in the brain, adrenal gland, kidney, vasculature and heart



ANP=atrial natriuretic peptide; BNP=brain natriuretic peptide; LVH=left ventricular hypertrophy; NPs=natriuretic peptides; RAAS=renin-angiotensin-aldosterone system

HFrEF: Sacubitril/Valsartan

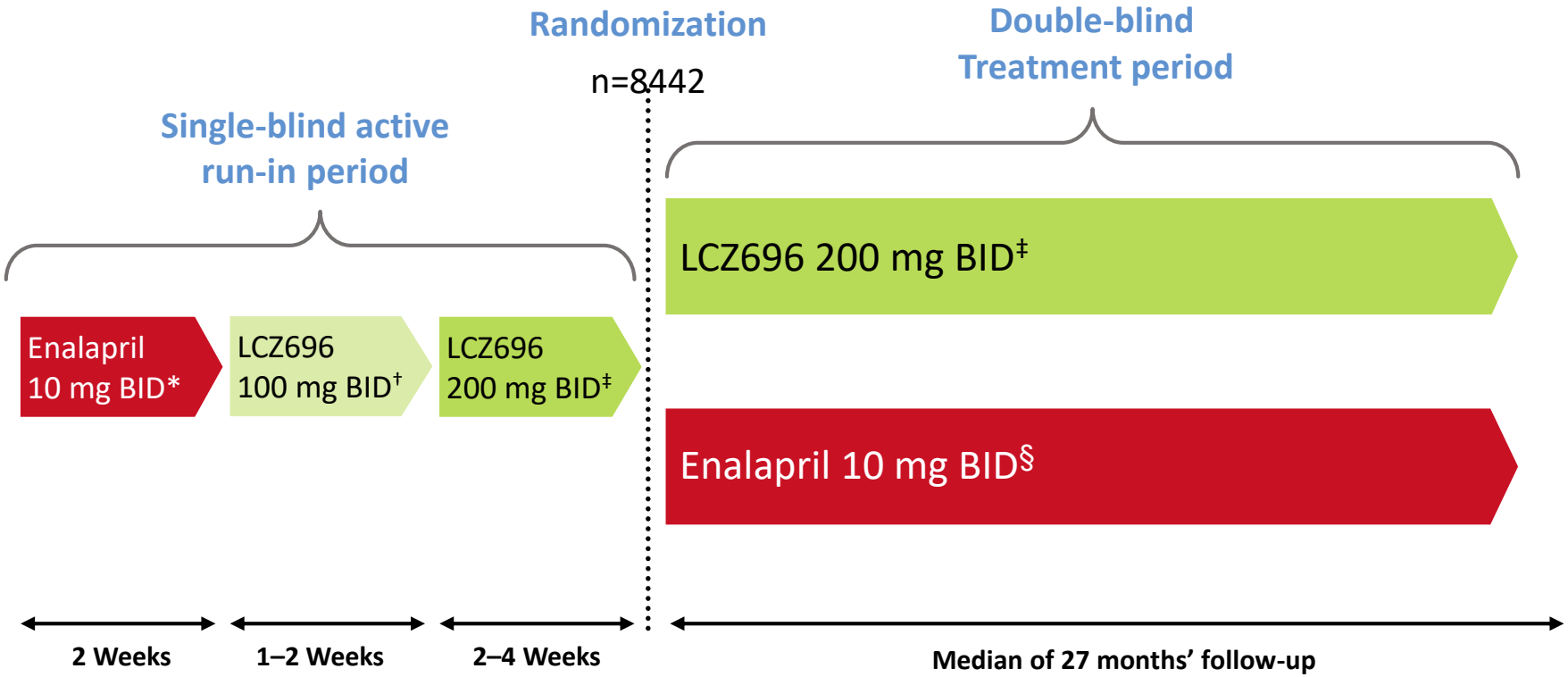


ORIGINAL ARTICLE

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

NYHA II, III, or IV
EF ≤ 40% (≤ 35%)
BNP ≥ 150 pg/ml
or
NT-proBNP ≥ 600 pg/ml



. N Engl J Med 2014

ORIGINAL ARTICLE

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

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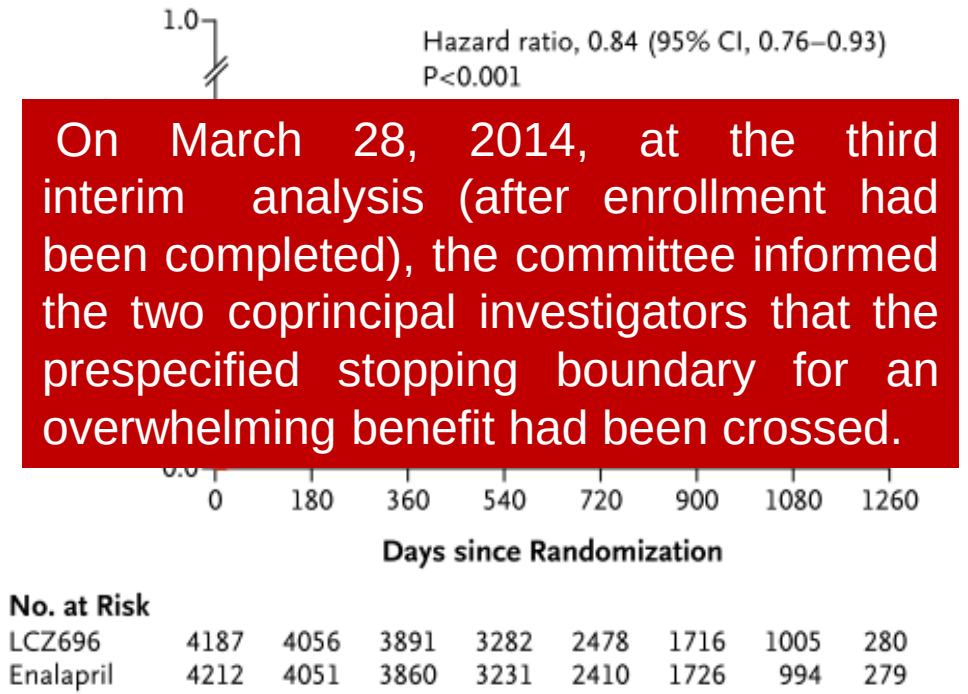
NYHA II, III, or IV
EF ≤ 40% (≤ 35%)
BNP ≥ 150 pg/ml
or
NT-proBNP ≥ 600 pg/ml

D Death from Any Cause



On March 28, 2014, at the third interim analysis (after enrollment had been completed), the committee informed the two coprincipal investigators that the prespecified stopping boundary for an overwhelming benefit had been crossed.

. N Engl J Med 2014

Efficacy and safety of LCZ696 (sacubitril-valsartan) according to age: insights from PARADIGM-HF

	<55 years (*n* = 1624)	55–64 years (*n* = 2655)	65–74 years (*n* = 2557)	≥75 years (*n* = 1563)	*P* for trend
Age (years)	46.7 ± 6.7	59.94 ± 2.9	69.3 ± 2.9	79.1 ± 3.5	
Female, *N* (%)	321 (19.8%)	500 (18.8%)	584 (22.8%)	427 (27.3%)	<0.00

Nel confronto per fasce di età

Simile efficacia prognostica

Simile effetto sulla qualità della vita

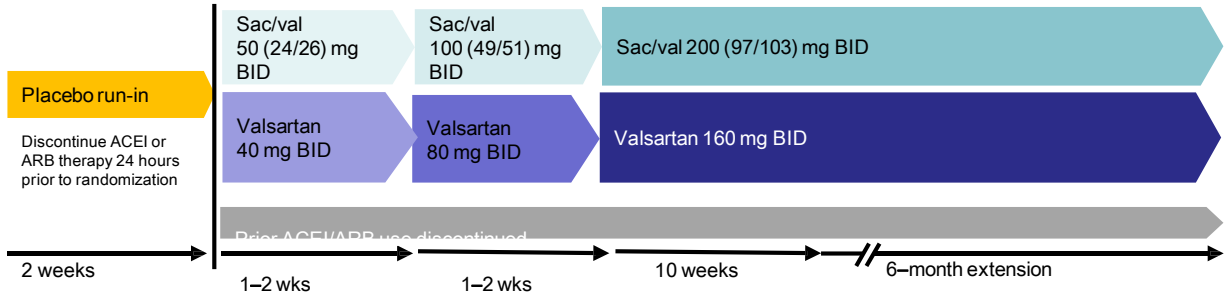
Simile profilo di safety

Jhund P et al. Eur Heart Journ 2015

	<55 years (*n* = 1624)		55–64 years (*n* = 2655)		65–74 years (*n* = 2557)		≥75 years (*n* = 1563)		*P*-value
	Enalapril	LCZ696	Enalapril	LCZ696	Enalapril	LCZ696	Enalapril	LCZ696	
Hypotension									
Symptomatic hypotension	60 (7.6)	96 (11.5)	111 (8.0)	158 (12.4)	124 (9.8)	195 (15.1)	93 (11.9)	139 (17.7)	0.95
Symptomatic hypotension with SBP <90 mmHg	12 (1.5)	24 (2.9)	12 (0.9)	33 (2.6)	21 (1.7)	32 (2.5)	14 (1.8)	23 (2.9)	0.77
Leading to discontinuation	3 (0.4)	5 (0.6)	7 (0.5)	5 (0.4)	9 (0.7)	12 (0.9)	10 (1.3)	14 (1.8)	0.94
Renal impairment, *N* (%)									
Serum creatinine ≥2.5 mg/dL	20 (2.6)	10 (1.2)	48 (3.5)	34 (2.7)	74 (5.9)	62 (4.8)	46 (5.9)	33 (4.2)	0.49
Serum creatinine ≥3.0 mg/dL	12 (1.5)	5 (0.6)	27 (2.0)	18 (1.4)	28 (2.2)	26 (2.0)	16 (2.1)	14 (1.8)	0.28
Leading to discontinuation	9 (1.1)	9 (1.1)	14 (1.0)	4 (0.3)	20 (1.6)	11 (0.9)	16 (2.1)	5 (0.6)	0.10
Hyperkalaemia, *N* (%)									
Serum potassium >5.5 mmol/L	89 (11.4)	97 (11.7)	254 (18.5)	220 (17.4)	232 (18.4)	218 (16.9)	152 (19.5)	139 (17.7)	0.70
Serum potassium >6.0 mmol/L	23 (2.9)	28 (3.4)	82 (6.0)	57 (4.5)	75 (6.0)	58 (4.5)	56 (7.2)	38 (4.8)	0.17
Leading to discontinuation	0 (0)	3 (0.4)	3 (0.2)	1 (0.1)	8 (0.6)	3 (0.2)	4 (0.4)	4 (0.5)	0.97
Cough, *N* (%)									
Any cough	137 (17.4)	106 (12.6)	198 (14.3)	130 (10.2)	167 (13.2)	161 (12.5)	99 (12.7)	77 (9.8)	0.58
Leading to discontinuation	4 (0.5)	0 (0)	14 (1.0)	4 (0.3)	7 (0.6)	3 (0.2)	5 (0.6)	1 (0.1)	0.73
Angioedema (adjudicated)									
No treatment/antihistamines only	2 (0.3%)	1 (0.1%)	1 (0.1%)	3 (0.2%)	1 (0.1%)	5 (0.4%)	1 (0.1%)	1 (0.1%)	0.20
Catecholamines/corticosteroids without hospitalization	1 (0.1%)	2 (0.2%)	2 (0.1%)	3 (0.2%)	0 (0.0%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	0.58
Hospitalized/no airway compromise	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.2%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.52
Airway compromise	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	–
Any adverse event leading to study-drug discontinuation, *N* (%)	16 (2.0%)	14 (1.7%)	35 (2.5%)	14 (1.1%)	43 (3.4%)	29 (2.2%)	35 (4.5%)	22 (2.8%)	0.85

PARAMOUNT-HF Study

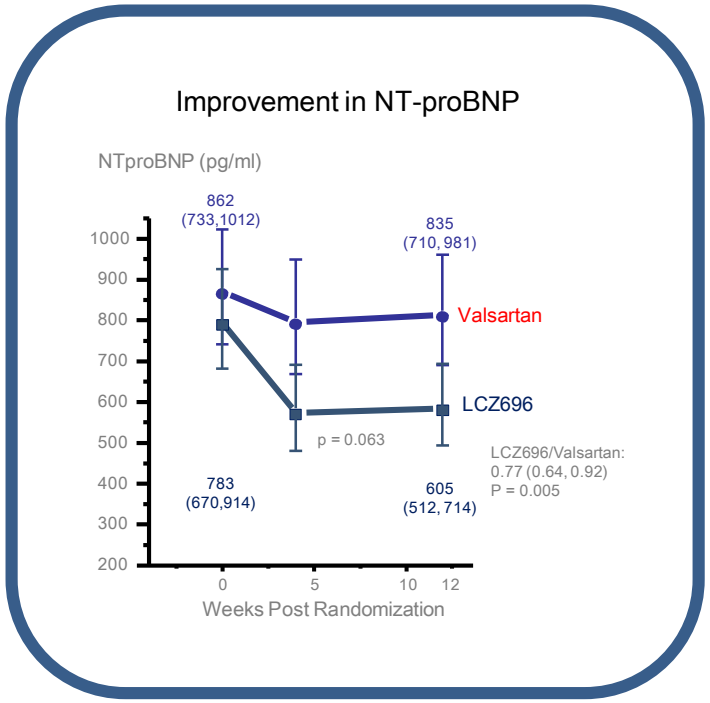
Study Design

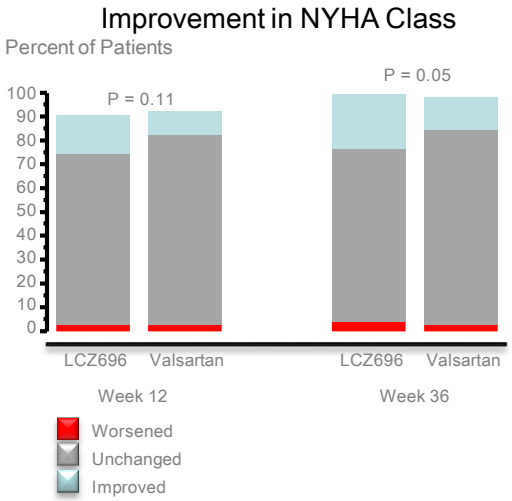


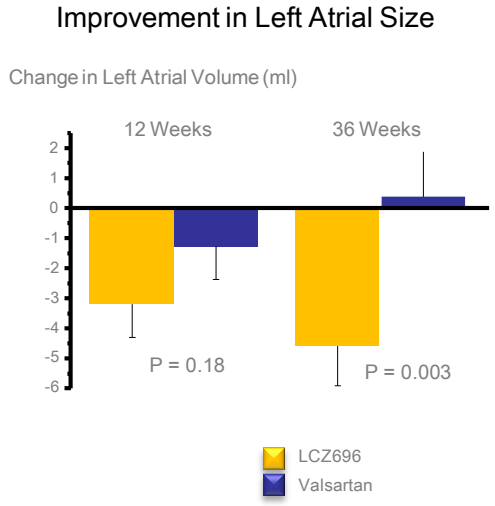
Design	• **12-week,** randomized, double-blind, active-controlled study evaluating sac/val 200 (97/103) mg BID compared with valsartan 160 mg BID followed by 6-month extension
Primary objective	• **NT-proBNP** reduction from baseline at 12 weeks (core study) with 6-month extension
Secondary objective	• **Echocardiographic** measures of diastolic function, left atrial size, LV size and function, PASP • HF **symptom**s, clinical composite assessment and **quality of life** (KCCQ) • Safety and tolerability
Population	• Approx. **290 patients** with CHF (NYHA class II-IV), LVEF ≥45%, and elevated NT-proBNP >400 pg/mL
Sample size	• Expected to screen 600 patients, randomize 290 (145 per arm), and complete 132 per arm • 80% power to detect a 25% reduction in NT-proBNP vs comparator

Solomon SD, et al. Lancet. 2012;380:1387–1395.

PARAMOUNT-HF Study
Sacubitril/Valsartan in HFpEF



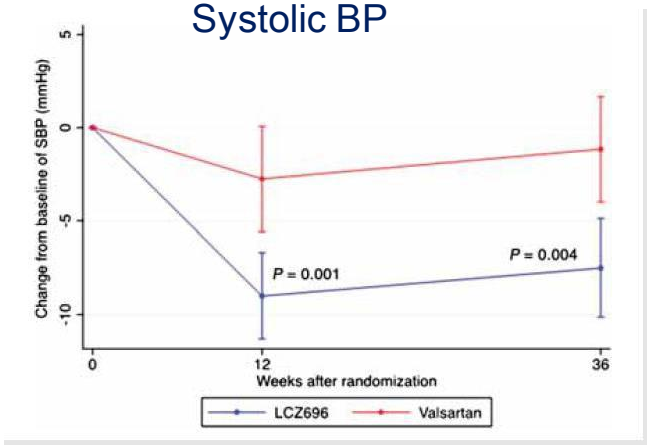




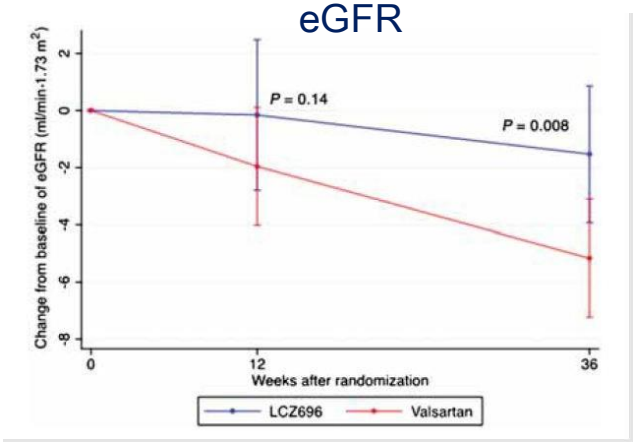
Solomon S et al. Lancet 2012

Renal effects of the angiotensin receptor neprilysin inhibitor LCZ696 in patients with heart failure and preserved ejection fraction in the PARAMOUNT Study

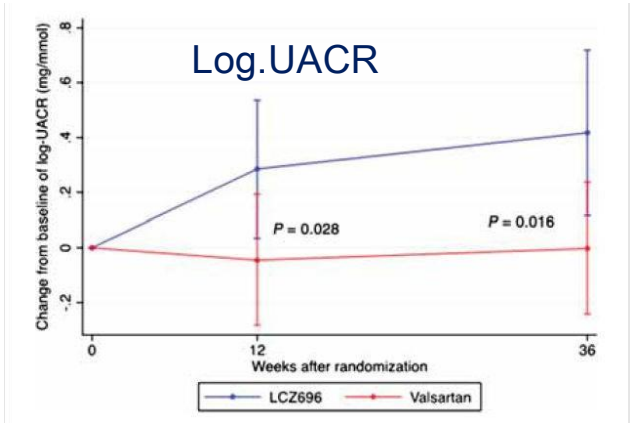
Systolic BP



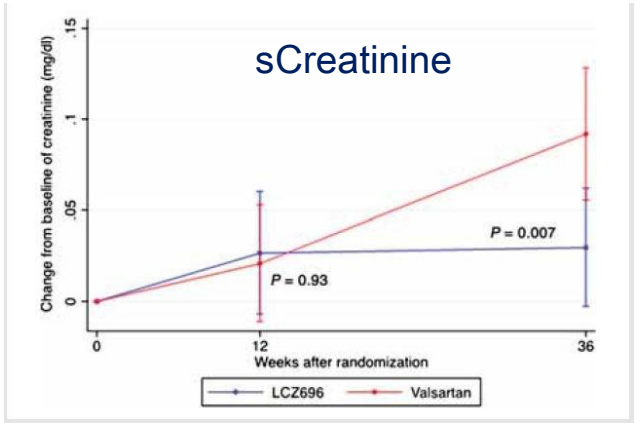
eGFR



Log.UACR

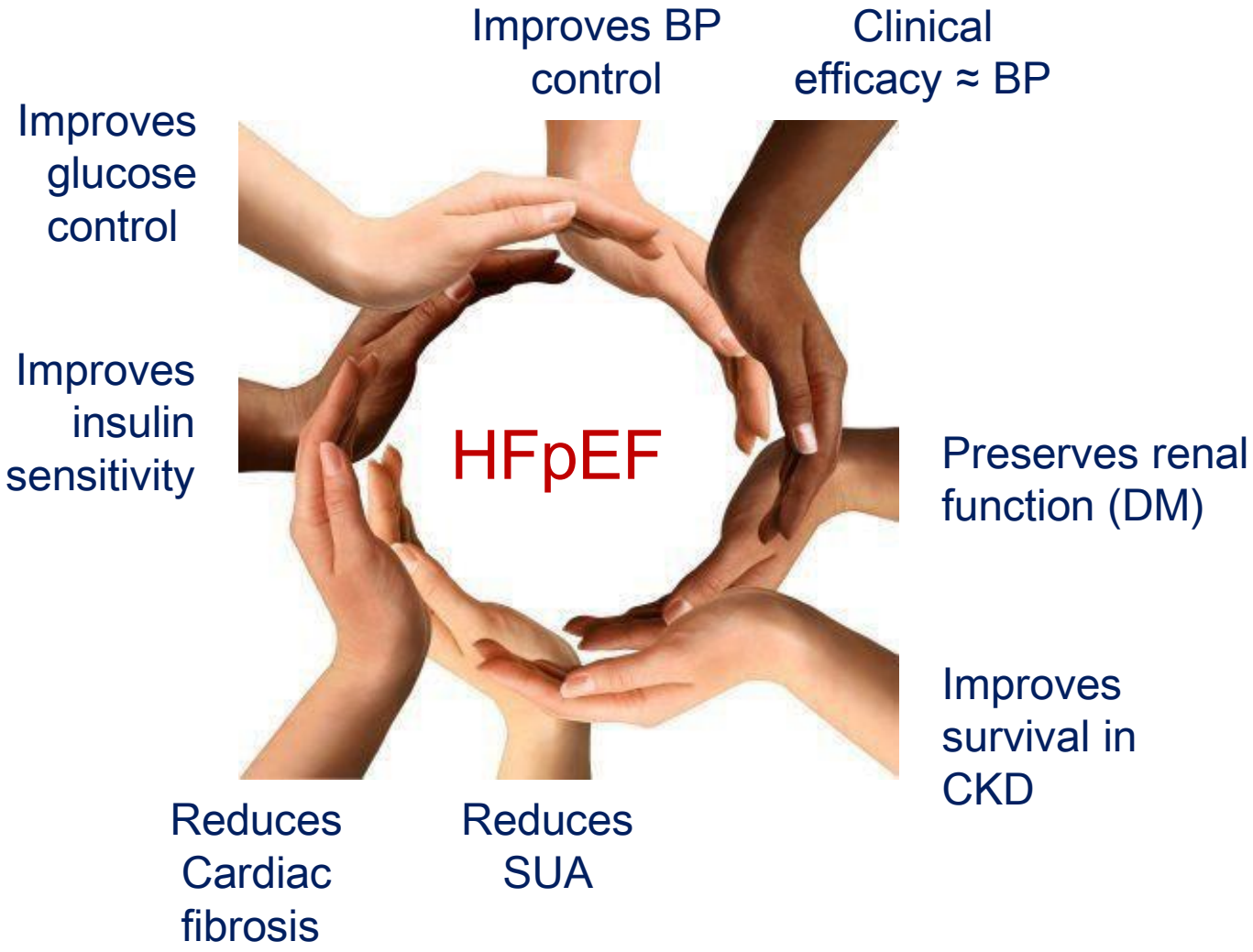


sCreatinine

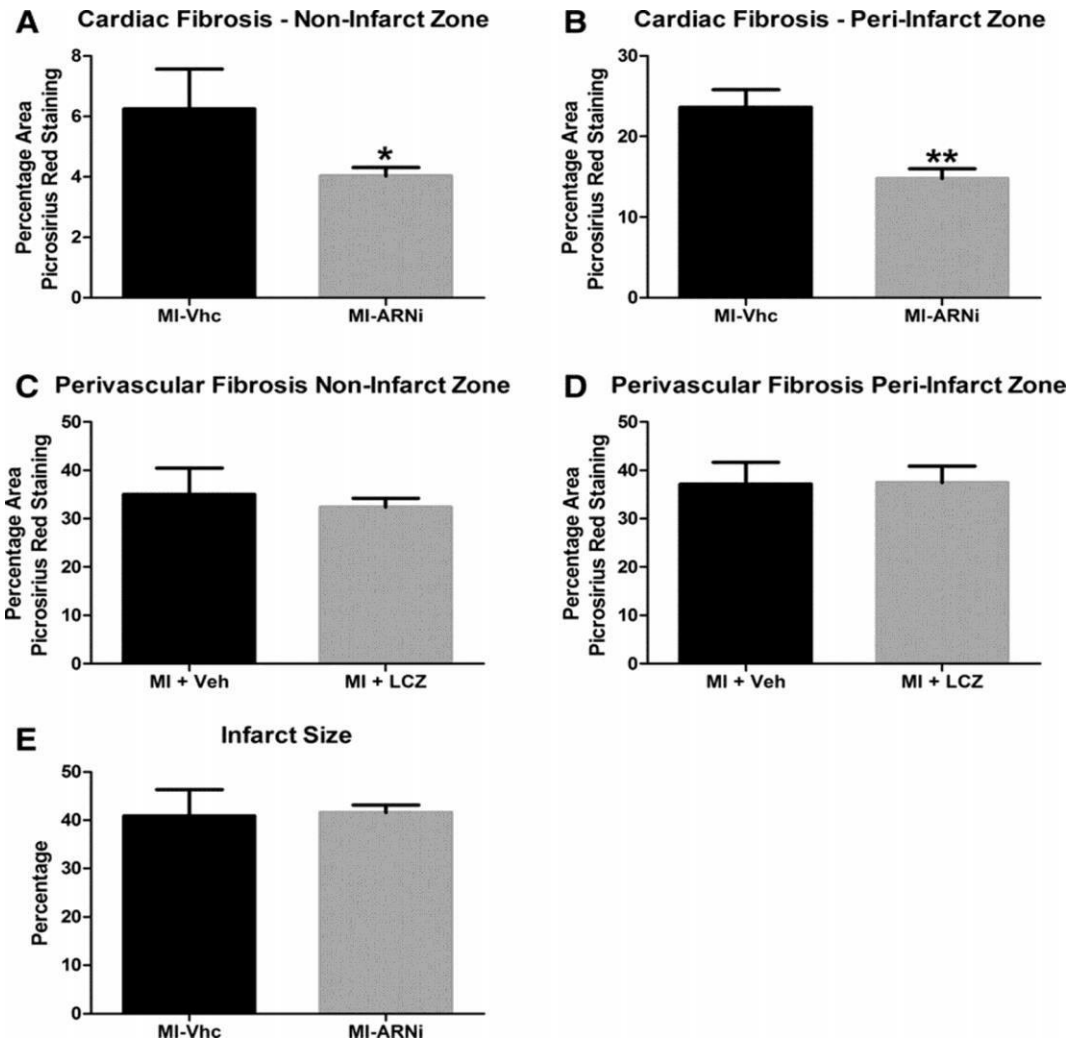


Voors AA et al, Eur J Heart Fail, 2015

Potential benefits of Sacubitril/Valsartan in HFpEF

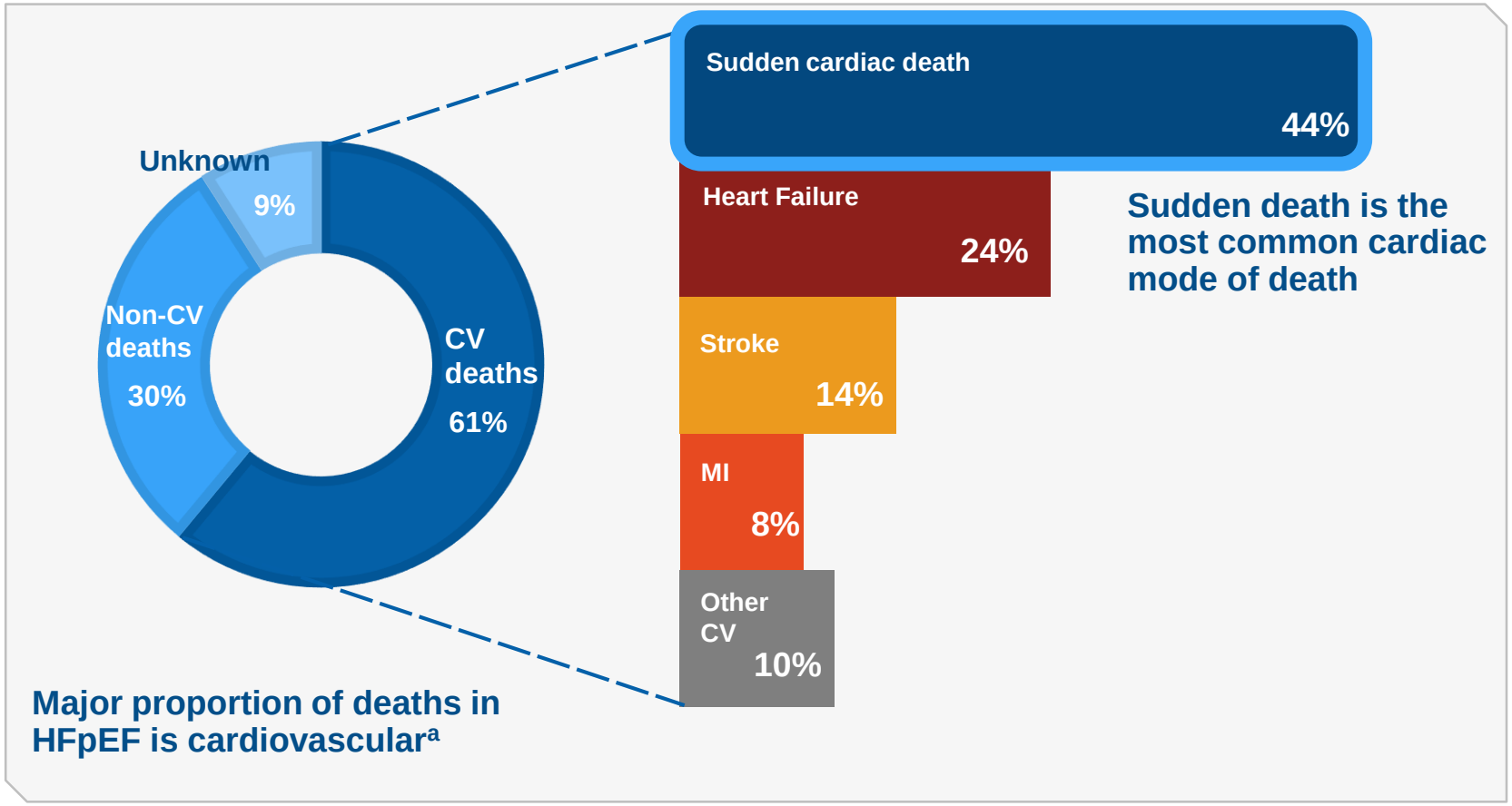


Effects of chronic administration of LCZ696 on cardiac fibrosis after myocardial infarction (MI).



Thomas G. von Lueder et al. Circ Heart Fail. 2015;8:71-78

Specific Mode of Death: RCTs



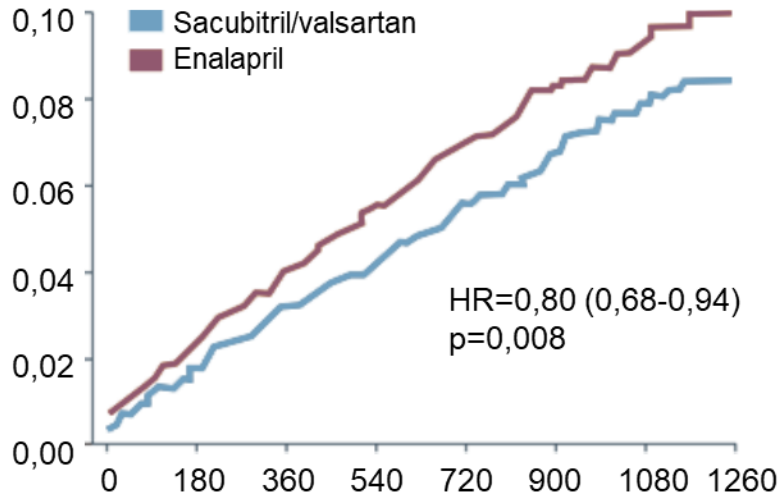
[a]Data from I-Preserve trial
CV, cardiovascular; HFpEF, heart failure with preserved ejection fraction; MI, myocardial infarction; RCT, randomized controlled trial
Chan MM and Lam CS. Eur J Heart Fail. 2013;15(6):604-13.

Sacubritil/valsartan riduce la morte improvvisa

Il trattamento con Sacubitril/valsartan ha significativamente ridotto il rischio di morte improvvisa rispetto a enalapril, HR: 0,80 (IC al 95%; 0,68–0,94, p=0,008).[1]

La proporzione relativa di morti improvvise, rispetto alle morti per WHF, è proporzionale alla gravità dell'HF secondo la classe funzionale NYHA, che per questo studio erano le classi II–III e che è stata osservata anche in altre sperimentazioni cliniche in pazienti con caratteristiche simili.[1]

Curva di sopravvivenza di Kaplan–Meier per il tempo alla morte improvvisa per trattamento[1]



N° pazienti a rischio				
Sacubitril/valsartan	4,212	3,860	2,410	994
Enalapril	4,187	3,891	2,478	1,005

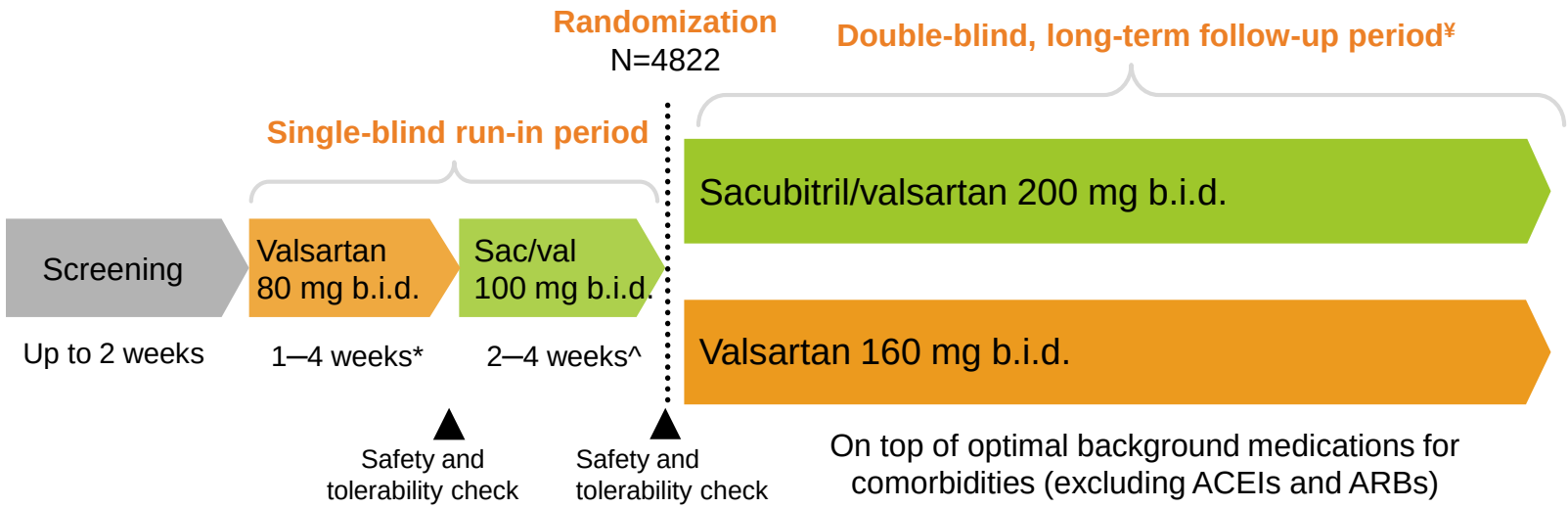
Deasy et al. Eur Heart J 2015;36:1990–1997.

PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HFpEF): Study Design and Baseline Characteristics

- Solomon et al., JACC: Heart Fail. 2017 Jul;5(7):471-482
- Solomon et al., Circ Heart Fail. 2018.
- DOI: 10.1161/CIRCHEARTFAILURE.118.004962

Study design

- A randomized, double-blind, parallel group, active-controlled, event driven trial



**Eligible patients were exposed to valsartan 80 mg b.i.d. for 1–2 weeks. Patients on low pre-study ACEI/ARB doses or those with tolerability concerns were first started on valsartan 40 mg b.i.d. 1–2 weeks and then up-titrated to valsartan 80 mg b.i.d. for 1–2 weeks*

^Patients tolerating valsartan 80 mg b.i.d. for 1–2 weeks were switched to sacubitril/valsartan 100 mg b.i.d for 2–4 weeks

¥Follow-up visits occurred at 4, 16, 32, and 48 weeks and every 12 weeks thereafter. All patients were followed until target number of primary composite (CV deaths and total HF hospitalizations) occur or 26 months after randomization of the last patient elapse, whichever occurs last

- ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; b.i.d, twice daily; CV, cardiovascular; HF, heart failure; sac/val, sacubitril/valsartan

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

Key eligibility criteria

Key inclusion criteria:

- Age ≥50 years; LVEF ≥45%
- Symptoms of HF requiring treatment with diuretic(s) for ≥30 days prior to screening
- Current symptomatic HF (NYHA class II–IV)
- Structural heart disease within the 6 months prior to screening (LAE and/or LVH)
- Patients with at least 1 of the following:
  - HF hospitalization within 9 months prior to screening and NT-proBNP >200 pg/mL for patients without AF or >600 pg/mL for patients with AF*

    OR
  - NT-proBNP >300 pg/mL for patients without AF or >900 pg/mL for patients with AF*

Key exclusion criteria:

- History of LVEF <40%
- MI, CABG or any event within the 6 months prior to screening that could have reduced the LVEF (unless LVEF confirmed as ≥45%)
- Current acute decompensated HF requiring therapy
- Requirement for treatment with two or more of the following: ACEI, ARB or renin inhibitor
- SBP <110 mmHg OR SBP ≥180 mmHg at screening^
- Serum potassium >5.2 mmol/L at screening, or >5.4 mmol/L at the end of each run-in period
- eGFR <30 mL/min/1.73m^2 at screening, OR at the end of each run-in period eGFR <25 mL/min/1.73m^2 or eGFR reduction of >35% compared to that at screening

**Patients with AF at screening were limited to approximately 33% of the study sample; ^If SBP >150 mmHg and <180 mmHg, the patient should be receiving ≥3 antihypertensive drugs*

- ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AF, atrial fibrillation; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; HF, heart failure; LAE, left atrial enlargement; LVH, left ventricular hypertrophy; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association;SBP, systolic blood pressure

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

Objectives (1/2)

Primary objective

- To evaluate the efficacy of sacubitril/valsartan compared with valsartan in reducing the rate of the composite endpoint of CV death and total (first and recurrent) HF hospitalizations

Secondary objectives

- To compare the effects of sacubitril/valsartan vs. valsartan on:
  - improvement in the KCCQ clinical summary score for HF symptoms and physical limitations at 8 months
  - improvement in NYHA functional classification at 8 months
  - delay in the time to the first occurrence of a composite renal endpoint*
  - delay in the time to all-cause mortality

**Defined as renal death or progression to end-stage renal disease or ≥50% decline in eGFR relative to baseline*

- CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association

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

Patient disposition

11302 patients screened at 788 centers in 43 countries

▼

5754 entered valsartan run-in phase

▼

5210 entered sacubitril/valsartan run-in phase

▼

4822 patients randomized to receive sacubitril/valsartan or valsartan

Common reasons for **screen failure** were:
- Insufficient NT-proBNP: 61%
- Elevated potassium: 10%
- eGFR below inclusion cut-off: 6%
- Diagnoses other than HFpEF: 6%
- Elevated LFTs: 4%

Common reasons for **run-in failures** were:
- Predefined safety AEs*: 65%
- Subject decision: 15%
- Protocol deviation: 12%
- Non-compliance: 5%
- Death: 2%

**Includes hypotension, hyperkalemia, and renal dysfunction*

AE, adverse events; eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; LFTs, liver function tests; NT-proBNP, N-terminal pro-B-type natriuretic peptide

Solomon, SD et al., *Circ Heart Fail.* 2018;11:e004962.
DOI: 10.1161/CIRCHEARTFAILURE.118.004962

Baseline characteristics of randomized and run-in failure

Randomized patients

- Age: 73 ± 8 years
- Females: 52%
- NYHA class II/III: 72%/27%
- LVEF: 58 ± 8%
- Medical history
  - Prior HF hospitalization: 48%
    - Of these, 79.2% within 9 months
  - AF/atrial flutter based on ECG at screening: 32%
  - Diabetes: 43%
  - CKD: 47%
- Medical therapies at baseline
  - ACEI or ARB: 85%
  - β-blockers: 80%
  - MRA: 27%
- MAGGIC risk score: 20 (IQR 16-24) More details

Run-in failure patients vs. randomized patients

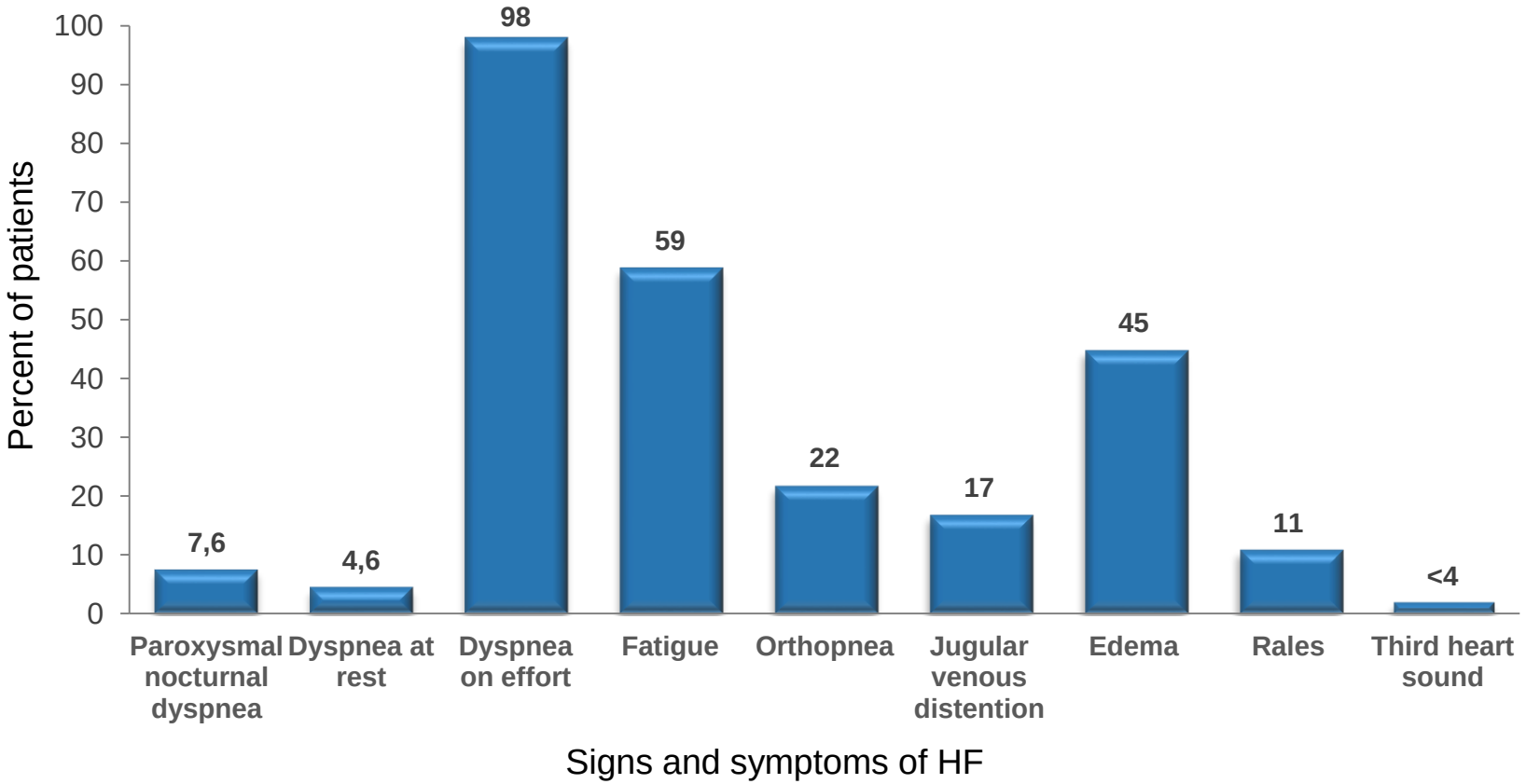
- Slightly older
- Slight ↑ NYHA class III and ↓ NYHA class II
- ↑ hospitalized for HF
- ↑ NT-proBNP
- ↓ eGFR
- ↓ SBP
- ↓ use of ACEI, ARB, and β-blockers

More details

- ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; AF, atrial fibrillation; CKD, chronic kidney disease; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HF, heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor blocker; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure

Solomon, SD et al., *Circ Heart Fail.* 2018;11:e004962.
DOI: 10.1161/CIRCHEARTFAILURE.118.004962

HF signs and symptoms at baseline in randomized patients



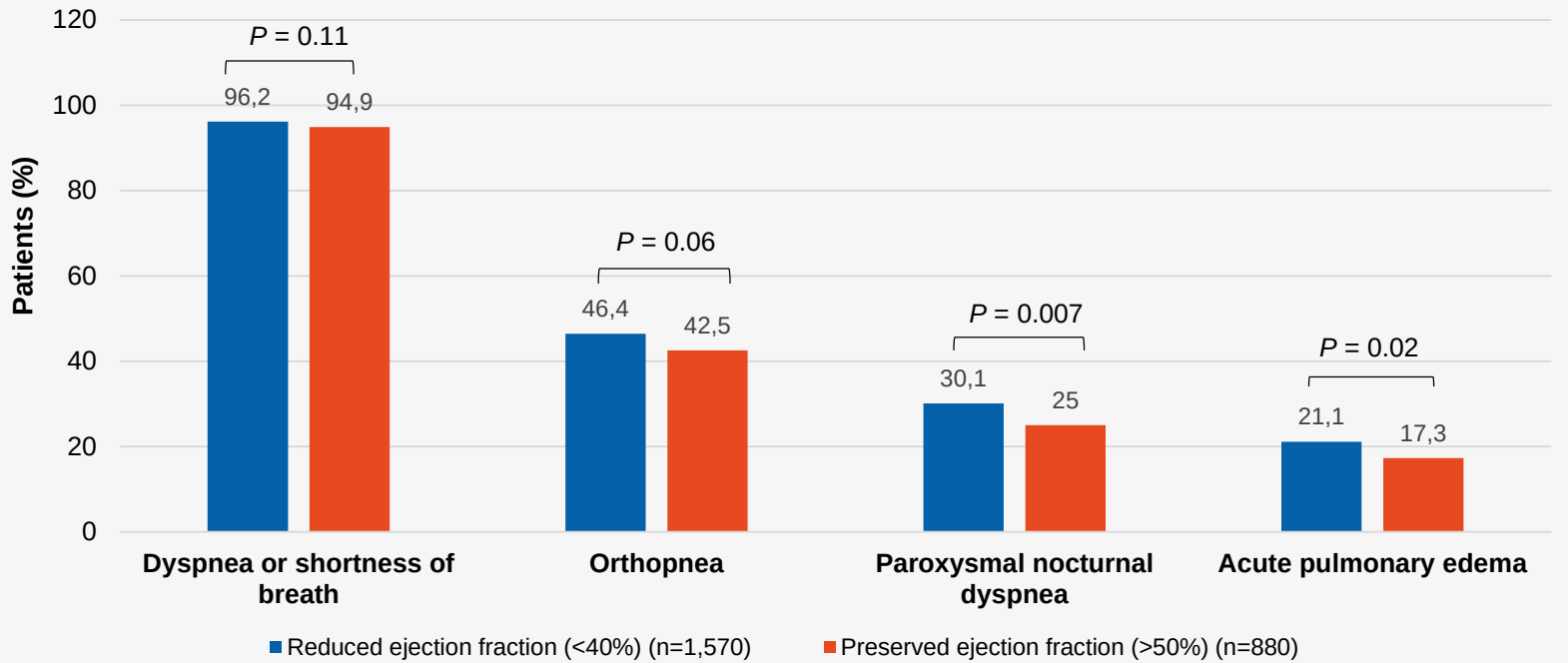
- HF, heart failure

Solomon, SD et al., *Circ Heart Fail.* 2018;11:e004962.
DOI: 10.1161/CIRCHEARTFAILURE.118.004962

Symptoms in HFpEF

Presenting symptoms in patients with HFpEF are largely similar to those in patients with HFrEF

The main differences are that patients with HFpEF have lower rates of acute pulmonary edema and paroxysmal nocturnal dyspnea



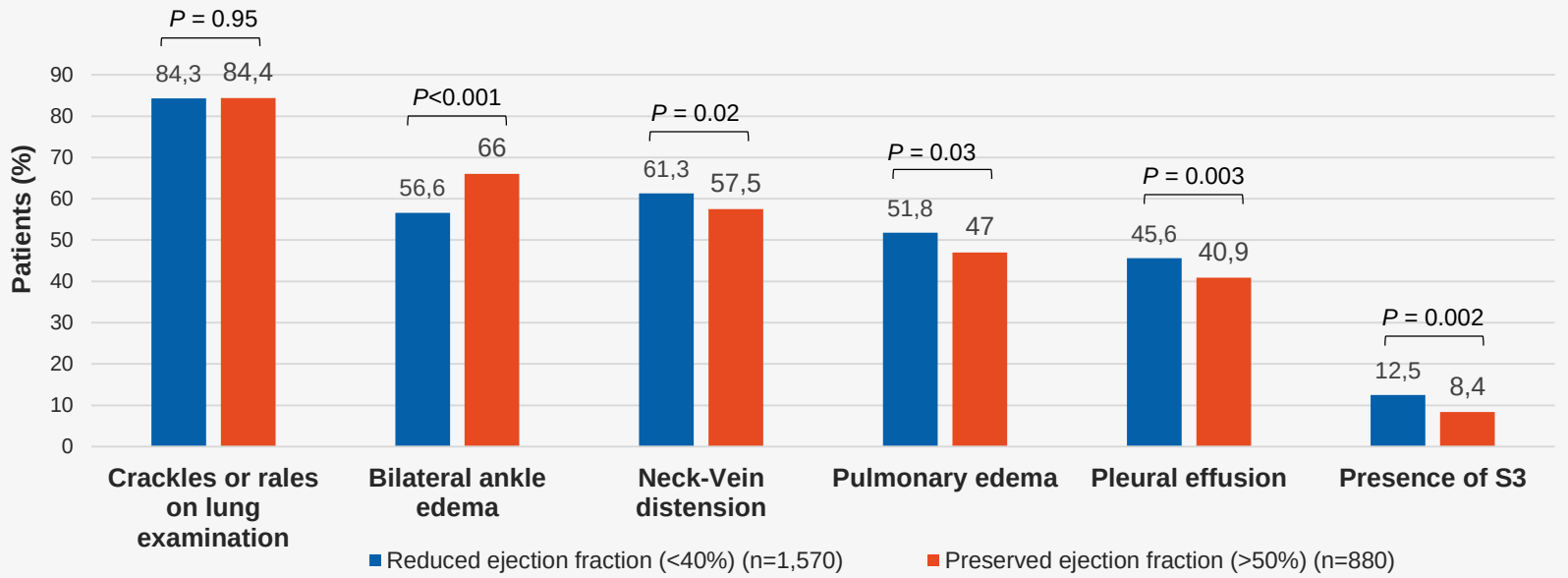
HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; S3, third heart sound; S4, fourth heart sound.

Bhatia RS, et al. N Engl J Med. 2006;355(3):260–269.

Signs in HFpEF

Presenting signs in patients with HFpEF are largely similar to those in patients with HFrEF

The main differences are that patients with HF*p*EF have lower rate of S3 heart sounds and chest radiographic signs and a higher rate of bilateral ankle edema



HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; S3, third heart sound; S4, fourth heart sound.

Bhatia RS, et al. N Engl J Med. 2006;355(3):260–269.

Evolution of a Geriatric Syndrome: Pathophysiology and Treatment of Heart Failure with Preserved Ejection Fraction

J Am Geriatr Soc 65:2431–2440

Bharathi Upadhya, MD, Barbara Pisani, MD, and Dalane W. Kitzman, MD

NEW PARADIGM FOR THE PATHOPHYSIOLOGY OF HFpEF

The involvement of this broad array of abnormalities in

… and its nearly exclusive existence in older persons has led to recognition of HFpEF as a true geriatric syndrome…..

comorbidities, systemic, multiorgan involvement, and its nearly exclusive existence in older persons has led to recognition of HFpEF as a true geriatric syndrome. It has

… a new paradigm of HFpEF, whereby aging along with multiple comorbidities in HFpEF may initiate or aggravate chronic systemic inflammation …..

als with HFpEF through a signaling cascade, which may begin with coronary microvascular endothelial dysfunction (Figure 2).[8,75] This reduces myocardial nitric oxide bioavailability and leads to low protein kinase G (PKG) activity in cardiomyocytes, which become stiff and hypertrophied.[8] These alterations also promote microvascular rarefaction and dysfunction in cardiac[24] and skeletal muscle.[57,76]

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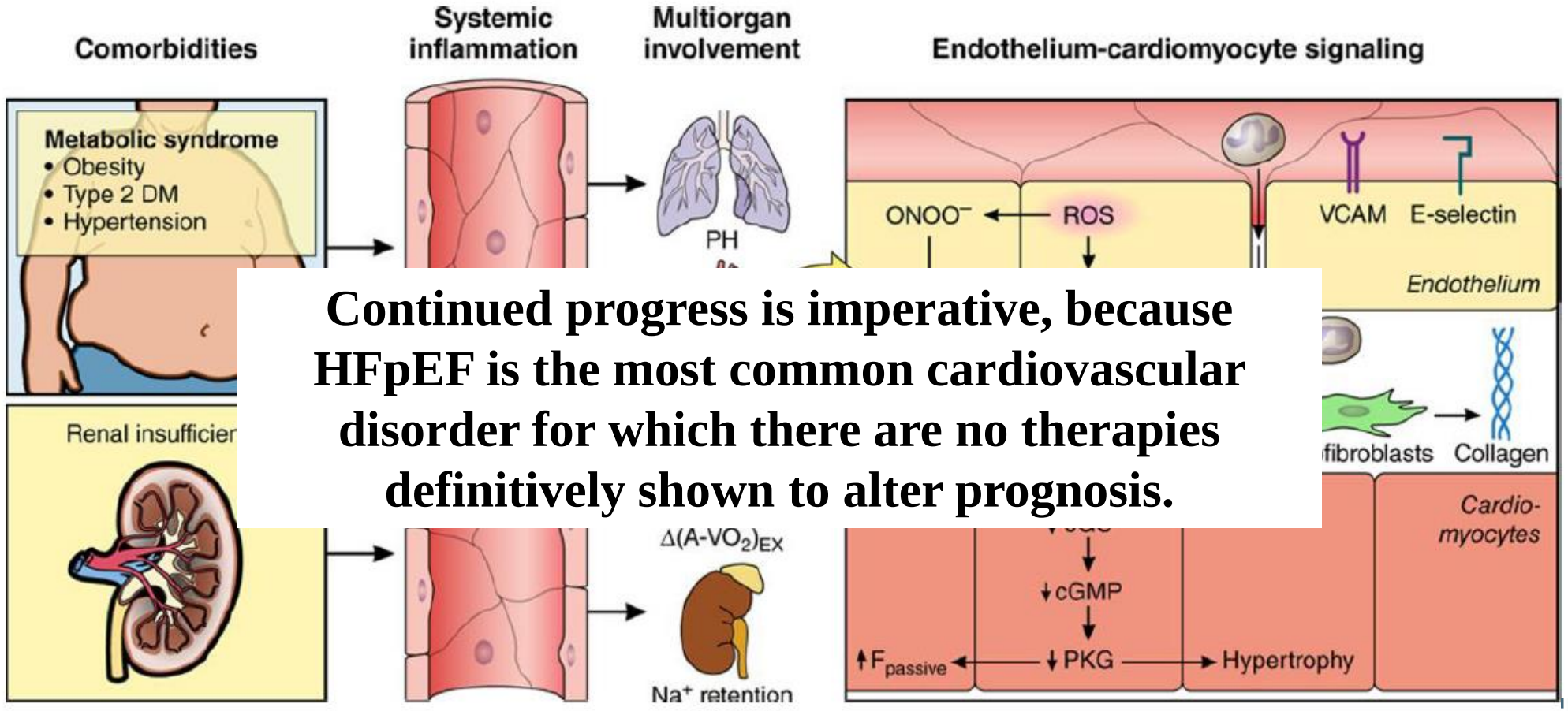
Systemic and myocardial signaling in heart failure with preserved ejection fraction (HFpEF).



Continued progress is imperative, because HFpEF is the most common cardiovascular disorder for which there are no therapies definitively shown to alter prognosis.

In Conclusione

- Lo scompenso cardiaco a funzione conservata ha una elevata prevalenza, probabilmente presenta aspetti fisiopatologici diversi e in buona parte sconosciuti.
- Al momento la mortalità è elevata (soprattutto cardiovascolare ed in particolare improvvisa). Non esistono evidenze di trattamento efficaci in termini di morbilità e mortalità.
- Il Sacubitril/Valsartan è una vera e propria speranza per il futuro di questi pazienti…….

Lo scopriremo il prossimo anno!!!!!

Grazie per la vostra attenzione