Treatment of Heart Failure With Normal Ejection Fraction

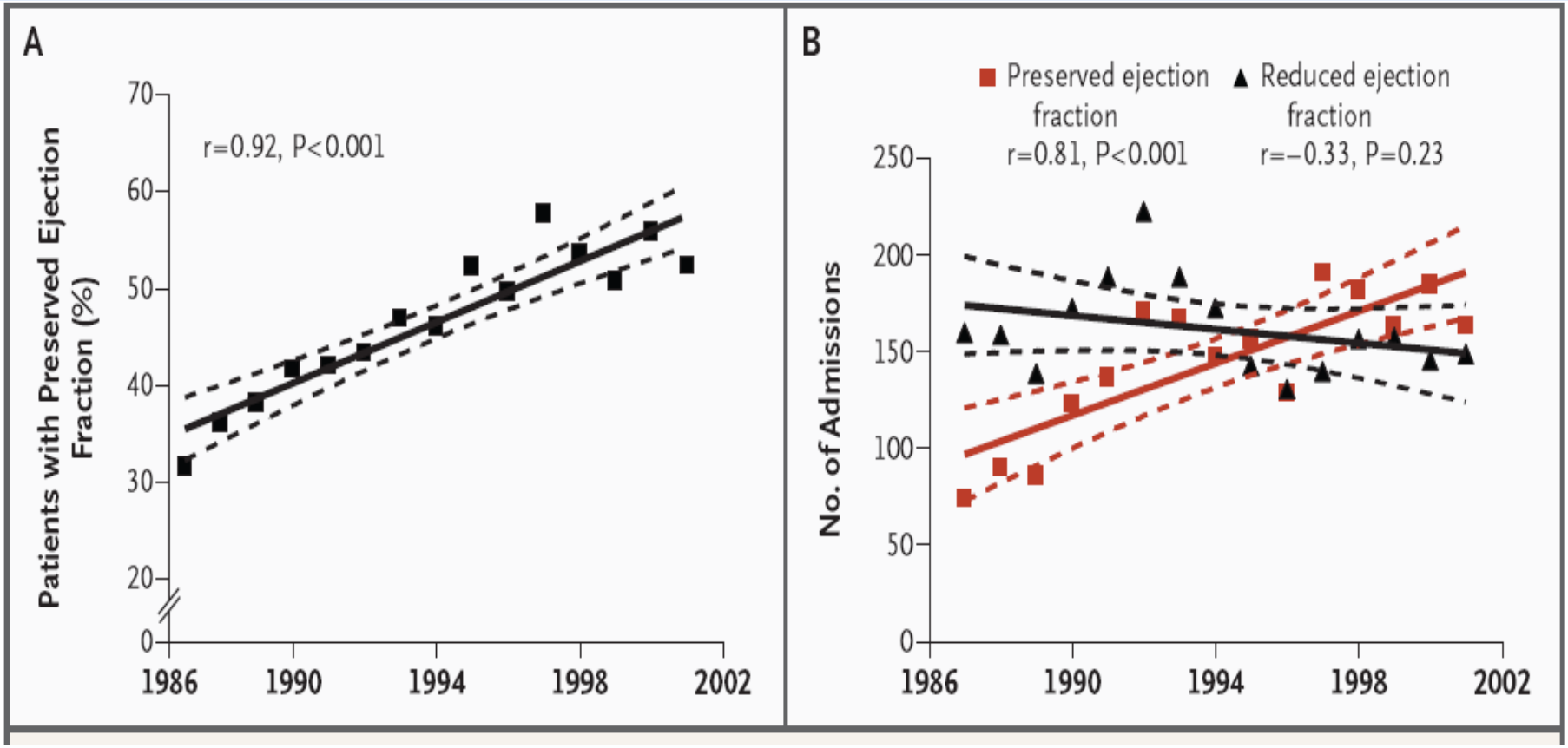
- An Inconvenient Truth! -

Regional Cardiovascular Center
Chungbuk National University Hospital

Kyung-Kuk Hwang

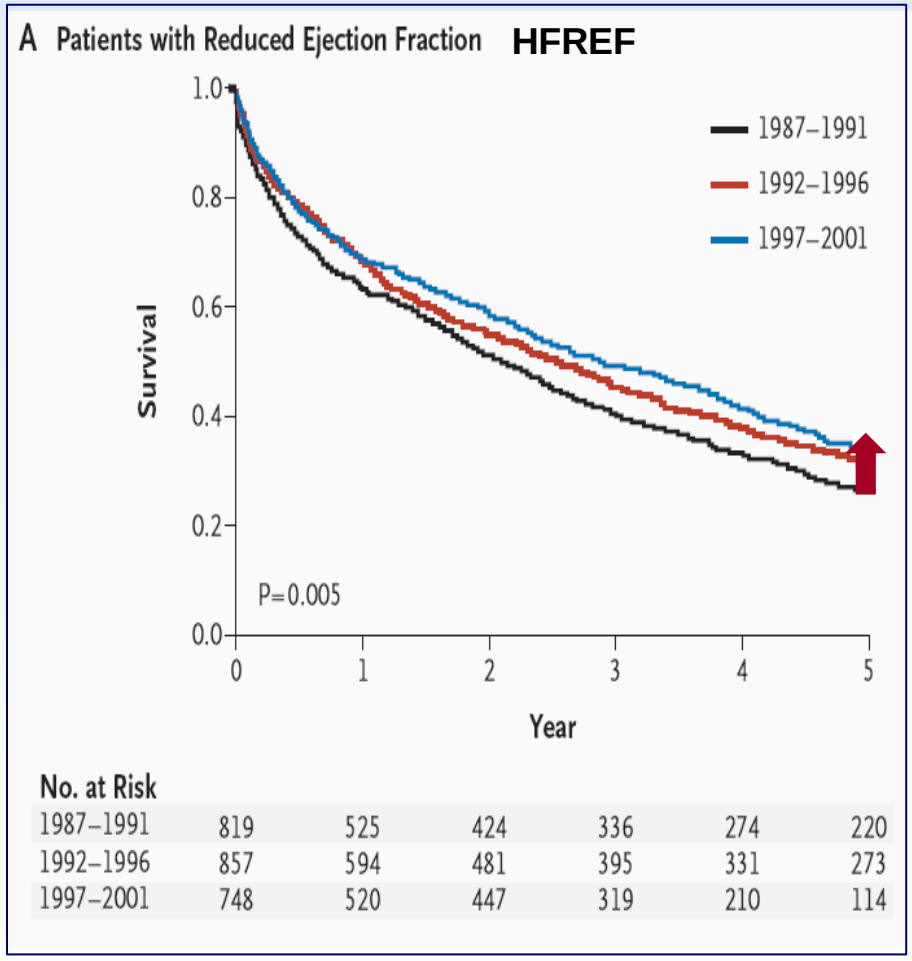
Prevalence HF with Preserved Ejection Fraction

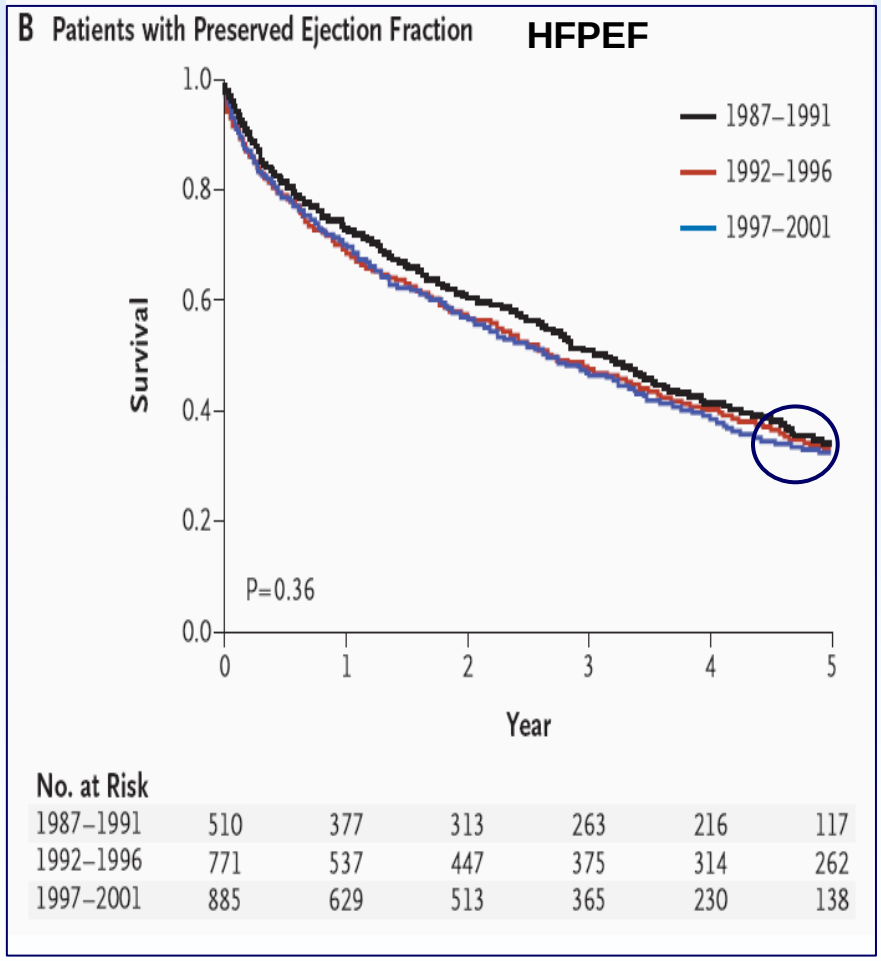
15-yr FU (1987-2001) in a single center study, N= 4596. EF ≥ 50%, N=2167 EF < 50%, N= 2429
More older, female, obese, HT, Af. Less CAD and VHD



Owan TE et al *N Eng J Med* 2006;355:251-9

Trends in Survival

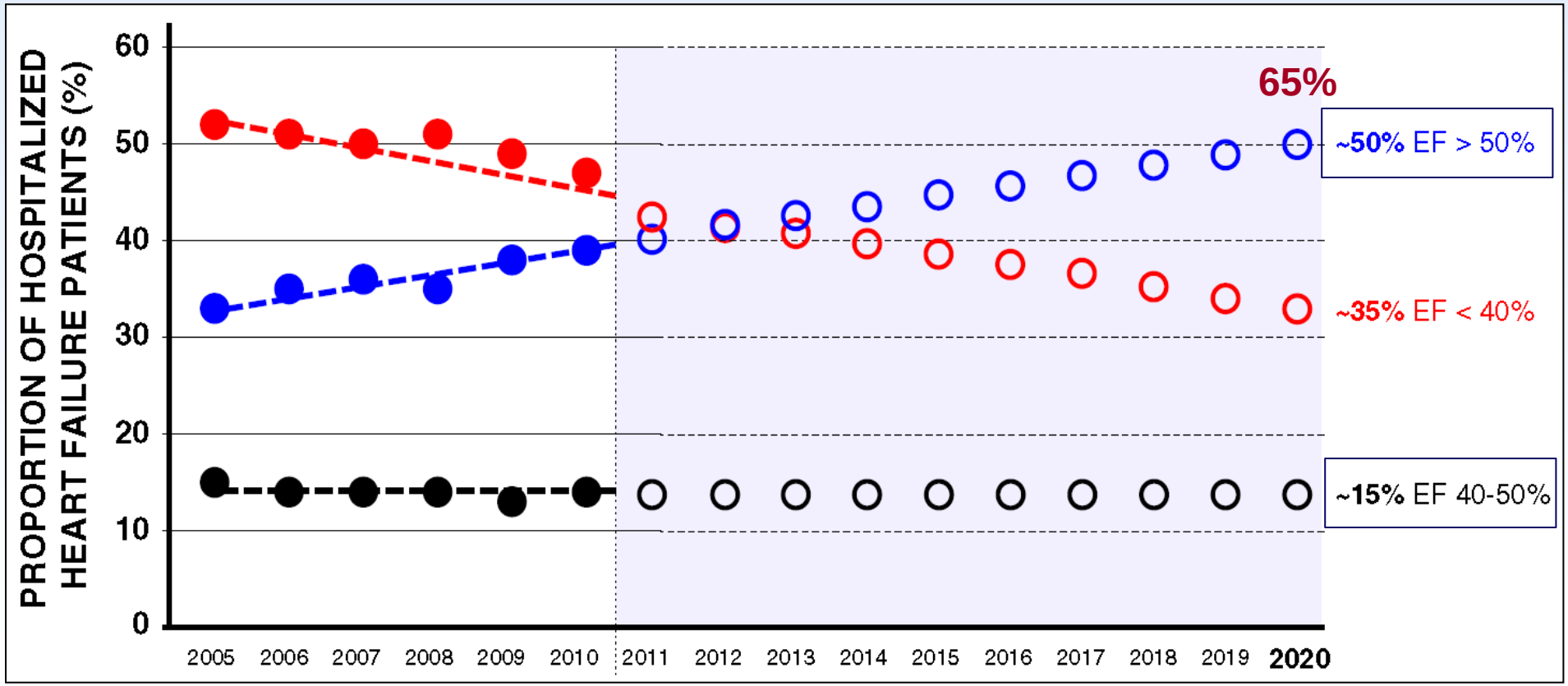




Theophilus E Owan et al *N Eng J Med* 2006;355:251-9

Changing Landscape of Heart Failure: in Hospitalized HF Pts

Get With the Guidelines-Heart Failure (GWTG-HF) Study , N=110,621, USA
using actual data on the proportion of hospitalization patients



Steinberg BA, Circulation 2012 126(1):65-75

Oktay A, Curr Heart Fail Rep 2013 10:401–10

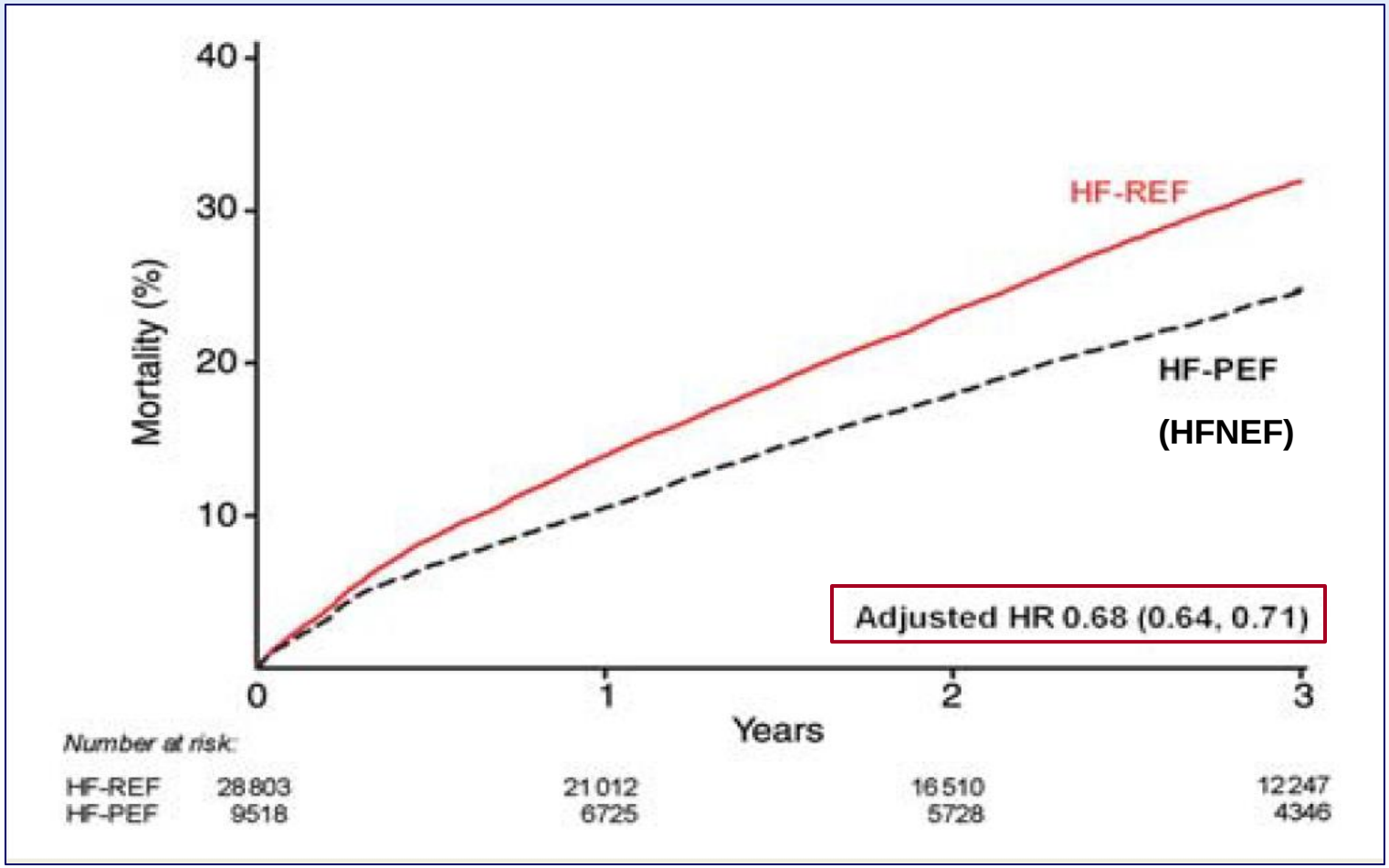
Outcomes of HFNEF Trials

Trial	N	Population	Protocol	Primary outcome	Event rate	Hazard ratio (p)	Follow-up
PEP-CHF 2006	850	HF and LVEF ≥ 45%	Perindopril 4 mg *vs* placebo	All-cause mortality and HF hospitalization	Primary outcome Placebo *vs* perindopril: 25.1% *vs* 23.6% All cause mortality: 13.3% *vs* 12.4% Annual mortality: 4.5% *vs* 4%	0.92 (0.5)	25 months
CHARM--Preserve 2003	3,023	HF and LVEF > 40%	Candesartan 32 mg *vs* placebo	CV death and HF hospitalization	Primary outcome Placebo *vs* candesartan: 24% *vs* 22% CV mortality: 11.3% *vs* 11.2% All-cause mortality: 16.1% *vs* 15.7%	0.89 (0.118)	36 months
Digoxin trial [19] 2006	988	HF and LVEF ≥ 45%	Digoxin 0.25 mg *vs* placebo	HF mortality and HF hospitalization	Primary outcome Placebo *vs* digoxin: 24% *vs* 21% All-cause mortality: 23.4% *vs* 23.4%	0.82 (0.136)	37 months
I-Preserve 2008	4,128	HF and LVEF ≥ 45%	Irbesartan 300 mg *vs* placebo	All-cause mortality and CV hospitalization	Primary outcome Placebo *vs* irbesartan: 21.1% *vs* 21.5% CV mortality: 14.6% *vs* 15% Annual mortality: 5.2% 25% sudden deaths	0.95 (0.35)	60 months

Sherazi S. Cradiolo J 2011 18:222-32

Meta-analysis Global Group in Chronic Heart Failure (MAGGIC)

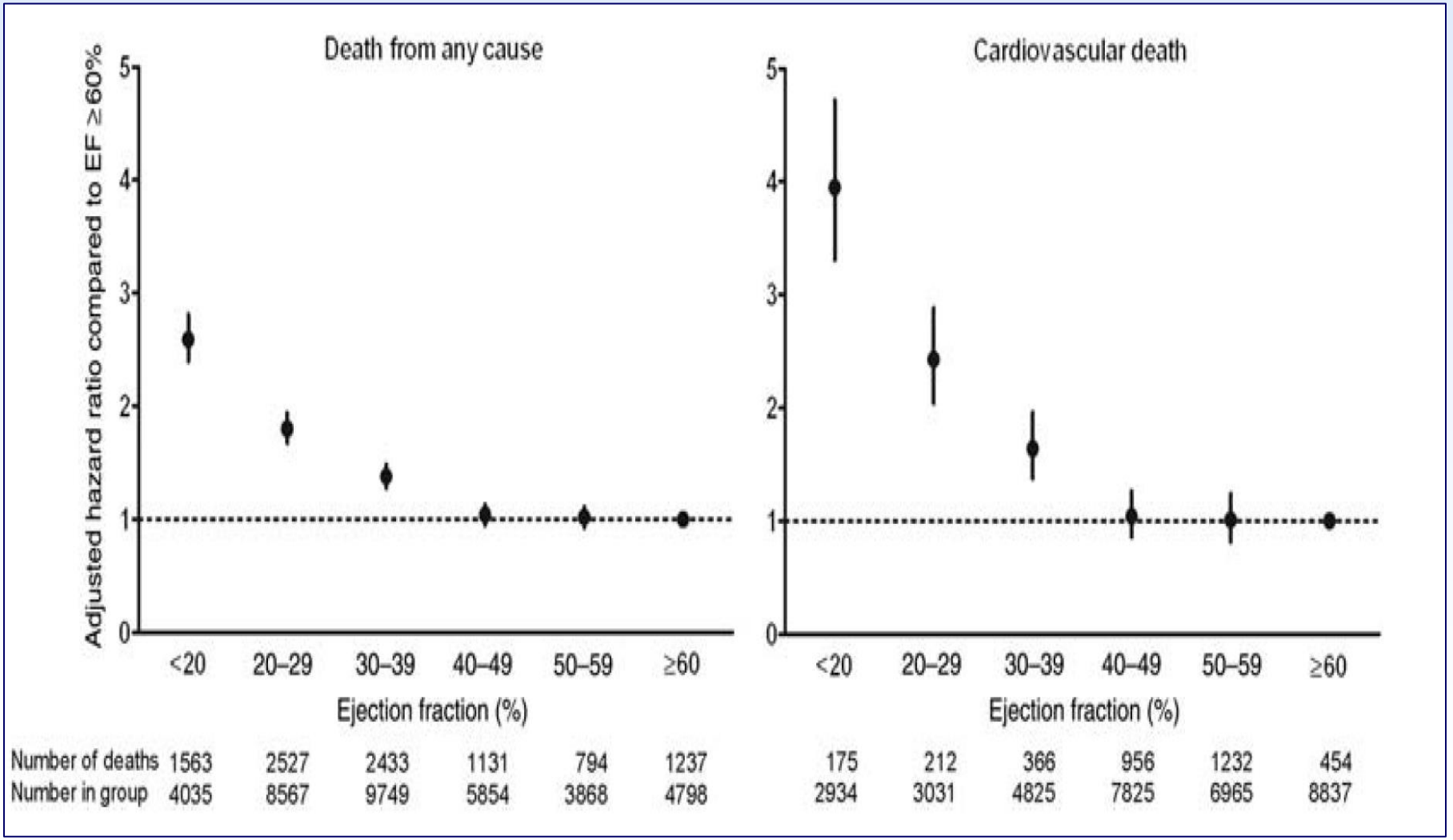
31 studies, N= 41,972. 10,347 with HFPEF(HFNEF) vs 31,625 with HFREF



Adjusted for age, gender, etiology of HF, hypertension, diabetes, atrial fibrillation.

Eur Heart J 2012 33:1750–57

Adjusted Hazards Ratios for All-cause Death, Cardiovascular Death



Eur Heart J 2012 33:1750–57

VIEWPOINT

Treatment of Heart Failure With Normal Ejection Fraction

An Inconvenient Truth!

Walter J. Paulus, MD, PhD, Joris J. M. van Ballegoij, BSc

Amsterdam, the Netherlands

Despite use of similar drugs, outcomes of recent heart failure (HF) trials were frequently neutral in heart failure with normal left ventricular ejection fraction (HFNEF) and positive in heart failure with reduced left ventricular ejection fraction (HFREF). The neutral outcomes of HFNEF trials were often attributed to deficient HFNEF patient recruitment with inclusion of many HFREF or noncardiac patients. Patient recruitment criteria of 21 HFNEF trials were therefore reviewed in reference to diagnostic guidelines for HFNEF. In the 4 published sets of guidelines, a definite diagnosis of HFNEF required the simultaneous and obligatory presence of signs and/or symptoms of HF and evidence of normal systolic left ventricular (LV) function and of diastolic LV dysfunction. In 3 of 4 sets of guidelines, normal systolic LV function comprised both a left ventricular ejection fraction (LVEF) >50% and an absence of LV dilation. Among the 21 HFNEF trials, LVEF cutoff values ranged from 35% to 50%, with only 8 trials adhering to an LVEF >50%. Furthermore, only 1 trial specified a normal LV end-diastolic dimension as an enrollment criterion and only 7 trials required evidence of diastolic LV dysfunction. Nonadherence to diagnostic guidelines induced excessive enrollment into HFNEF trials of HF patients with eccentric LV remodeling and ischemic heart disease compared with HF patients with concentric LV remodeling and arterial hypertension. Nonadherence to guidelines also led to underpowered HFNEF trials with a low incidence of outcome events such as death or HF hospitalizations. Future HFNEF trials should therefore adhere to diagnostic guidelines for HFNEF. (J Am Coll Cardiol 2010; 55:526–37)

Outcomes of Heart Failure (HF) Trials

- **Positive** in HF with reduced left ventricular ejection fraction (HFREF) trials
  vs
  Neutral in HF with normal left ventricular ejection fraction (HFNEF) trials

- In HFNEF trials targeting on

  ① clinical symptom, exercise capacity, diastolic dysfunction, quality of life
  : positive outcome

  ② mortality
  : no positive outcomes from all pharmacological drug
  (RAS antagonists, beta-blockers, calcium channel blockers, diuretics, digitalis, HMG CoA-reductase inhibitors, PDE-5 inhibitors)

Paulus WJ, JACC 2010 55:526-37

? Different Pathophysiology in HFNEF: vs HFREF

- Distinct patterns of structural remodeling

  Differential response to therapy

  - suggest that HFNEF and HFREF are 2 discrete entities with fundamentally different pathophysiologies

- (Unrevealed pathophysiological mechanism)
- Multiple comorbidities existence
- high non-cardiac deaths

? Neutral outcomes of HFNEF Trials

- ? Methodological flaws associated with inclusion criteria

- ? Specific pathophysiological features characterizing HFNEF

Paulus WJ, JACC 2010 55:526-37

? Methodological flaws of HFNEF Trials

- **HFNEF**
  - **diagnosis of exclusion**
  - **symptoms and signs of HF are nonspecific**

  some doubt about the nature of patients enrolled in clinical trials

Campbell RT, *JACC* 2012 60:2349-56

Paulus WJ, *JACC* 2010 55:526-37

? Methodological flaws of HFNEF Trials

- **Diagnostic Guideline for HFNEF**

	HFNEF Guidelines Year Published			
	ESC 1998	NHLBI 2000	LAHEY 2005	ESC 2007
HF signs and symptoms (other criteria)	Present	Present	Present	Present
Normal LV systolic function	LVEF >45% LVEDVI <102 ml/m^2	LVEF >50% within 72h HF episode	LVEF >50% LVEDVI <97 ml/m^2	LVEF >50% LVEDVI <97 ml/m^2
LV diastolic dysfunction	LVEDP >16 mm Hg PCW >12 mm Hg E/A <0.5 DT >280 ms IVRT >105 ms PVV >0.35 m/s Ard-Ad >20 ms	LVEDP >16 mm Hg PCW >12 mm Hg	LVEDP >16 mm Hg PCW >12 mm Hg E/A <0.5 DT >280 ms IVRT >105 ms LAE LVH	LVEDP >16 mm Hg PCW >12 mm Hg E/E′ >15 E/E′ >8 + NT-proBNP >220 pg/ml

Presence of HF signs and/or symptoms and normal LV systolic function and diastolic LV dysfunction

Paulus WJ, *JACC* 2010 55:526-37

Enrollment Criteria of Large HFNEF Outcome trials

	V-HeFTII Enalapril 2 years	DIG Digoxin 37 months	CHARM-P Candesartan 3 years	SENIORS Nebivolol 12 months	PEP-CHF Perindopril 2.1 years	I-PRESERVE Irbesartan 49.5 months
HF signs and symptoms (other criteria)	Present ($VO_2 \downarrow$)	Present	Present	Present	Present (3/9 criteria including prior MI)	Present
Normal LV systolic function	LVEF >35% CTR >0.55 LVEDDI >2.7 cm/m^2	LVEF >45%	LVEF >40%	LVEF >35%	LVEF >40% WMI >1.4	LVEF >45%
LV diastolic dysfunction	—	—	—	—	WT >13 mm IVRT >105 ms E/A <0.5 DT >280 ms LA diameter >25 mm/m^2	LAE LVH
Positive outcomes	Mortality −40%	Hospitalizations	Hospitalizations	Mortality+hospitalizations −14%	Hospitalizations and symptoms at 1 yr follow-up	—

Mismatch between guidelines and trials

Paulus WJ, *JACC* 2010 55:526-37

Recent Diagnostic Guideline for HFNEF

- **2013 ACC/AHA guideline**

  - clinical signs or symptoms of HF
    evidence of preserved or normal LVEF
    evidence of abnormal LV diastolic dysfunction (by EchoCG or cardiac cath.)

  - excluding other potential non-cardiac causes of symptoms suggestive of HF.

- **2012 ESC guideline**

  - symptoms typical of HF
    signs typical of HF
    normal or only mildly reduced LVEF and LV not dilated
    relevant structural heart dis.(LV hypertrophy/LA enlargement) and/or diastolic dysfunction

Definitions of HF*r*EF and HF*p*EF

Classification	EF (%)	Description
I. Heart failure with reduced ejection fraction (HF*r*EF)	≤40	Also referred to as systolic HF. Randomized clinical trials have mainly enrolled patients with HF*r*EF, and it is only in these patients that efficacious therapies have been demonstrated to date.
II. Heart failure with preserved ejection fraction (HF*p*EF)	≥50	Also referred to as diastolic HF. Several different criteria have been used to further define HF*p*EF. The diagnosis of HF*p*EF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified.
a. HF*p*EF, borderline	41 to 49	These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patients with HF*p*EF.
b. HF*p*EF, improved	>40	It has been recognized that a subset of patients with HF*p*EF previously had HF*r*EF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients.

2013 ACC/AHA guideline

- ? Specific pathophysiological features characterizing HFNEF

Paulus WJ, JACC 2010 55:526-37

HFNEF: Heterogeneous Dis. with Multifactorial Pathophysiology

- **LV diastolic dysfunction**

  - abnormal LV active relaxation and increased LV passive stiffness

  - abnormal LV active relaxation
  : related to ischemia of cardiomyocytes
  or abnormality in myocardial energy metabolism

  - increased diastolic LV stiffness
  : ↑ LVEDP, ↓ stroke volume → limit cardiac output

  : excessive collagen type I deposition → stiff and noncompliant extracellular matrix
  titin phosphorylation deficit → ↑ stiffness

HFNEF: Heterogeneous Dis. with Multifactorial Pathophysiology

Several studies from both animals and humans

- Autonomic dysfunction
- Reduced vasodilator reserves
- Impaired heart rate recovery
- Chronotropic incompetence
- Diastolic and systolic dyssynchrony
- Abnormal ventricular vascular coupling**.**
- Renin-angiotensin-aldosterone system and sympathetic nervous system were upregulated in HFPEF

Diversity of underlying mechanisms/ comorbidities

Complex clinical syndrome
Associated with multiple pathophysiological alterations

This makes treating HFNEF a clinical challenge

Novel Paradigm for HFNEF

" Systemic proinflammatory state induced by comorbidities"
is the cause of myocardial structural and functional alterations

Comorbidities such as overweight, obesity, diabetes, chronic obstructive pulmonary disease, hypertension

→ Proinflammatory state

→ Coronary microvascular endothelial inflammation

→ ↓ NO bioavailability, cGMP contents, protein kinase G activity

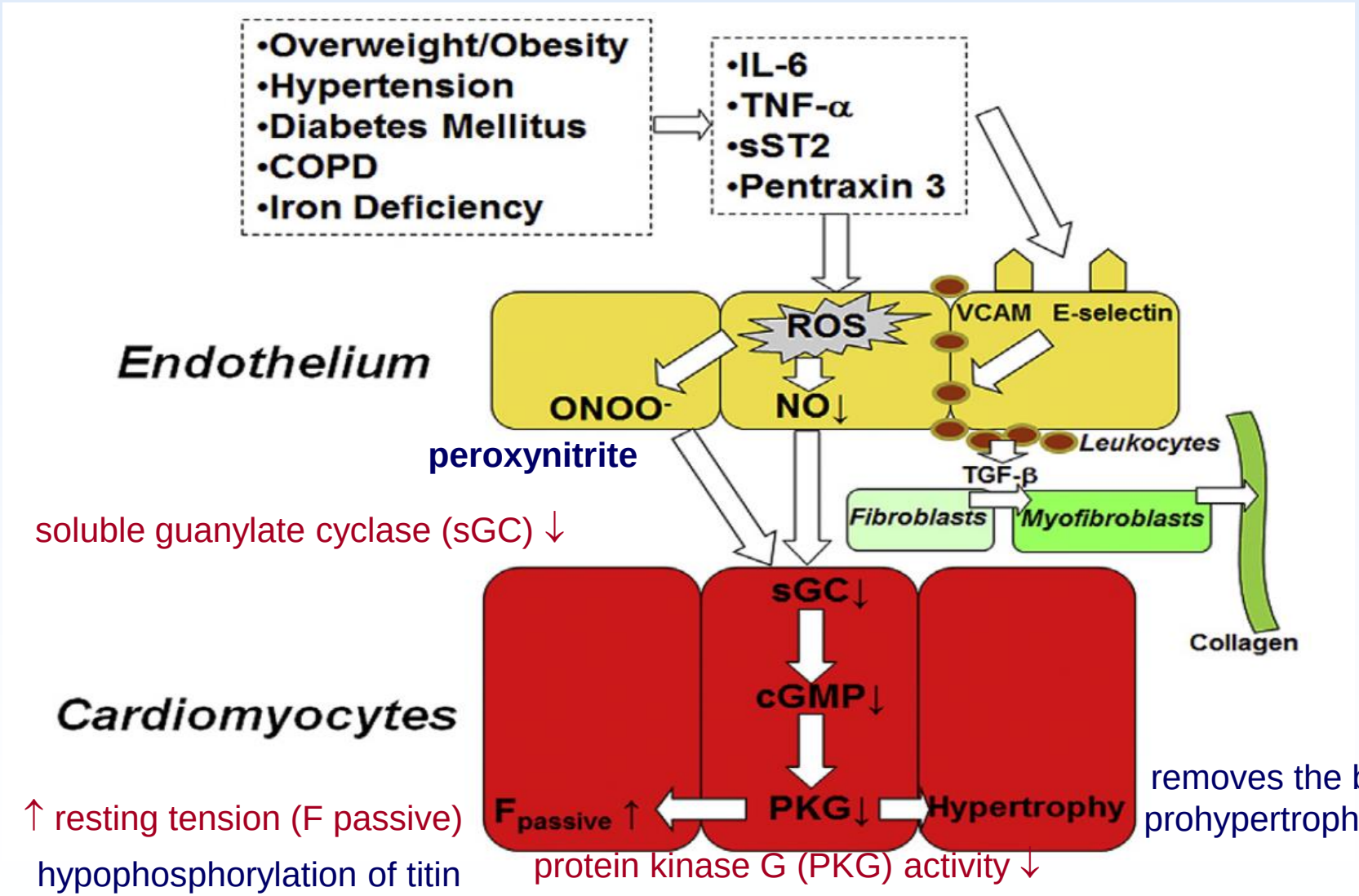
→ ↑ resting tension

→ High diastolic left ventricular stiffness

→ HF sequence

Paulus WJ, JACC 2013 62:263-71

Comorbidities Drive Myocardial Dysfunction And Remodeling in HFNEF

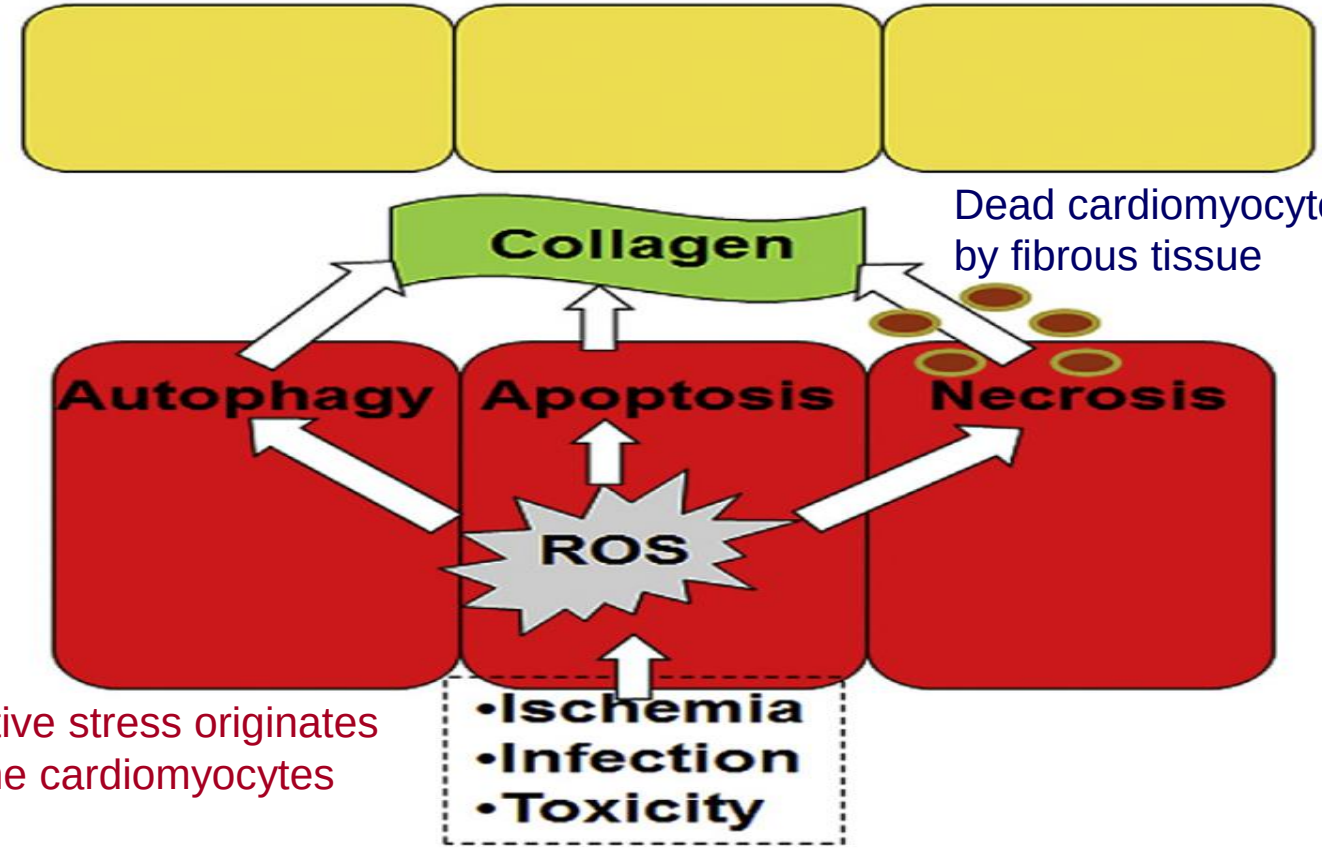


Paulus WJ, JACC 2013 62:263-71

Myocardial Remodeling in HFREF

LV remodeling: driven by progressive loss of cardiomyocytes

Dead cardiomyocytes are replaced by fibrous tissue



Dead cardiomyocytes are replaced by fibrous tissue

Oxidative stress originates in the cardiomyocytes

Paulus WJ, JACC 2013 62:263-71

New HFNEF paradigm: Diagnostic/ Therapeutic Implications

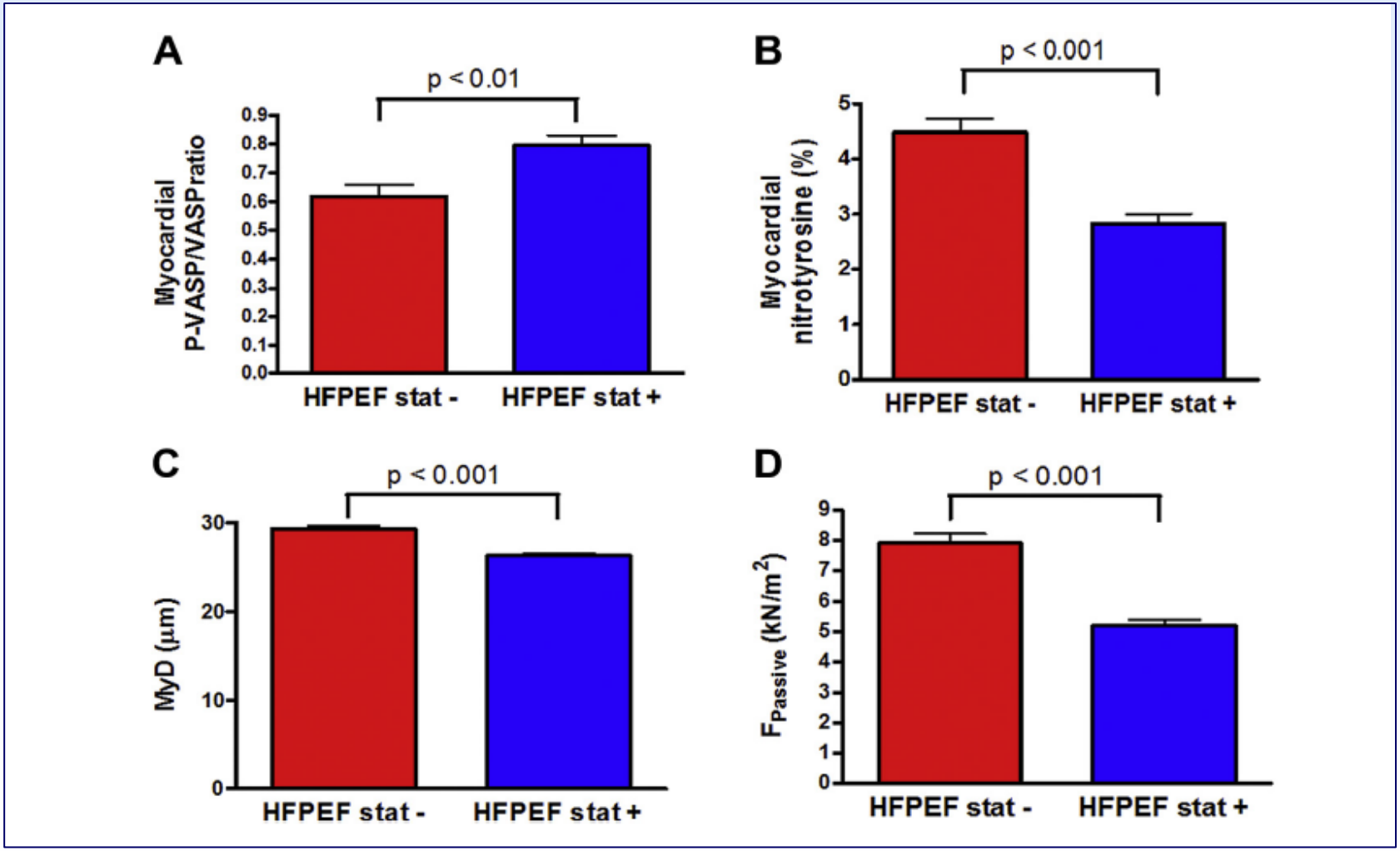
- **Diagnostic implication :** useful to HFNEF diagnosis

  - anthropometric measures
    comorbidities
    vascular hyperemic responses
    plasma markers of oxidative stress or inflammation

- **Therapeutic implication:** interfering HFNEF-specific myocardial signaling
  - restoring strategies for
    ① myocardial NO bioavailability, cGMP contents, PKG activity,
    ② endothelial function
    through NO donor, PDE-5 inhibitor, anti-oxidative substances (ie.statin)

Paulus WJ, JACC 2013 62:263-71

Diagnostic and Therapeutic Implications



Paulus WJ, JACC 2013 62:263-71

Specific Therapeutic Agents - Theoretical Benefits

- ***ACE inhibitors***
  - Angiotensin Ⅱ contributes to
    LV myocardial hypertrophy and fibrosis, impairs LV relaxation, and increases the stiffness of the left ventricle

  - **PEP-CHF** : no significant difference in the primary endpoint
    but, significant reduction in hospitalization for HF

Cleland JG, *Eur Heart J,* 2006

- ***ARB***
  - **CHARM-Preserved**
    : reduced hospitalization

Yusuf S, *Lancet,* 2003

  - **Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction trial**

Massie BM, *N Engl J Med* 2008;

Renin-Angiotensin System (RAS) Antagonists in HFNEF

- The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)-Preserved trial
  : moderate reduction in HF hospitalization,
  30% reduction in the risk of death at 1 year (P< 0.001)
  9% reduction (P > 0.055) over the full-duration follow up of 38 months

- The Perindopril for Elderly People with Chronic Heart Failure (PEP-CHF) study
  : improved symptoms and exercise capacity and HF hospitalization
  no reduction in long-term morbidity and mortality.

- The Irbesartan in heart failure with preserved systolic function (I-Preserve) trial
  : no reduction in primary composite outcome of death or cardiovascular hospitalization.

- N= 53,878 from 18 RCTs and 12 observational studies
  : 18.6-month FU, all-cause mortality was unimproved
  tendencies toward marginal benefits in primary outcomes

Statin

- Statins, as anti-inflammatory agents : first-line therapy in CAD and hyperlipidemia

- CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) trial
  : neutral regarding the efficacy of statins in patients with HFREF.

- Fukuta et al: significant relative risk reduction in mortality in HFPEF (LVEF > 50%) pts with statin for 21months.

- 270 patients with HFPEF, follow-up for 5 years
  - improved survival compared to patients without statin therapy (HR= 0.65; 95%CI: 0.45-0.95, *P* = 0.029).
  - survival benefit was maintained after adjusting for differences in baseline characteristics, comorbidities, and other medications

- Some small observational studies
  : seems to be associated with improved survival benefit in pts with HFPEF

Phosphodiesterase-5 Inhibition (PDE-5 Inhibition)

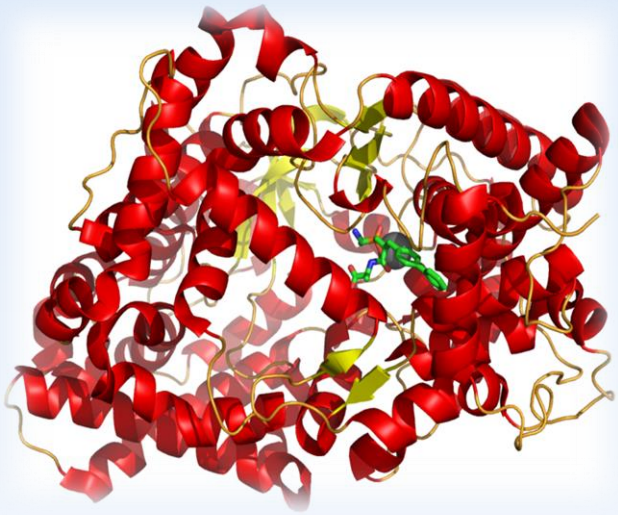
- RELAX trial
  : PDE-5 inhibition in improvement of clinical status, exercise capacity in diastolic HF
  N=216, HFNEF (LVEF > 50%), reduced exercise capacity and increased NTBNP
  or elevated invasively measured LV filling pressures

  Sildenafil group (n=113) or placebo (n=103)
  primary endpoint : peak oxygen consumption after 24 weeks of therapy
  secondary end points: change in 6-minutewalk distance, clinical status assessment.

  : failed to achieve improvement in exercise capacity in patients with HFNEF

  : efficacy of PDE-5 inhibition on survival benefit - needs to be evaluated in large RCTs.

Neutral Endopeptidase (NEP)



- Also known as
  neprilysin,
  membrane metallo-endopeptidase (MME),
  cluster of differentiation 10 (CD10),
  common acute lymphoblastic leukemia antigen (CALLA)
- Enzyme encoded by the MME gene (human)

- NEP: zinc-dependent, membrane bound endopeptidase
  - hydrolyses peptides on the amino side of hydrophobic residues
- Expression: widely expressed in mammals
  - kidney, lung, endothelial cells, vascular smooth muscle cells, cardiac myocytes, fibroblasts, neutrophils, adipocytes, testes, brain

Neutral Endopeptidase (NEP)

- Critical for the processing and catabolism

  ① vasoactive peptides and peptides involved in diuresis, natriuresis

  : natriuretic peptides (NPs), angiotensin I, bradykinin, endothelin-1

  ② other substrates

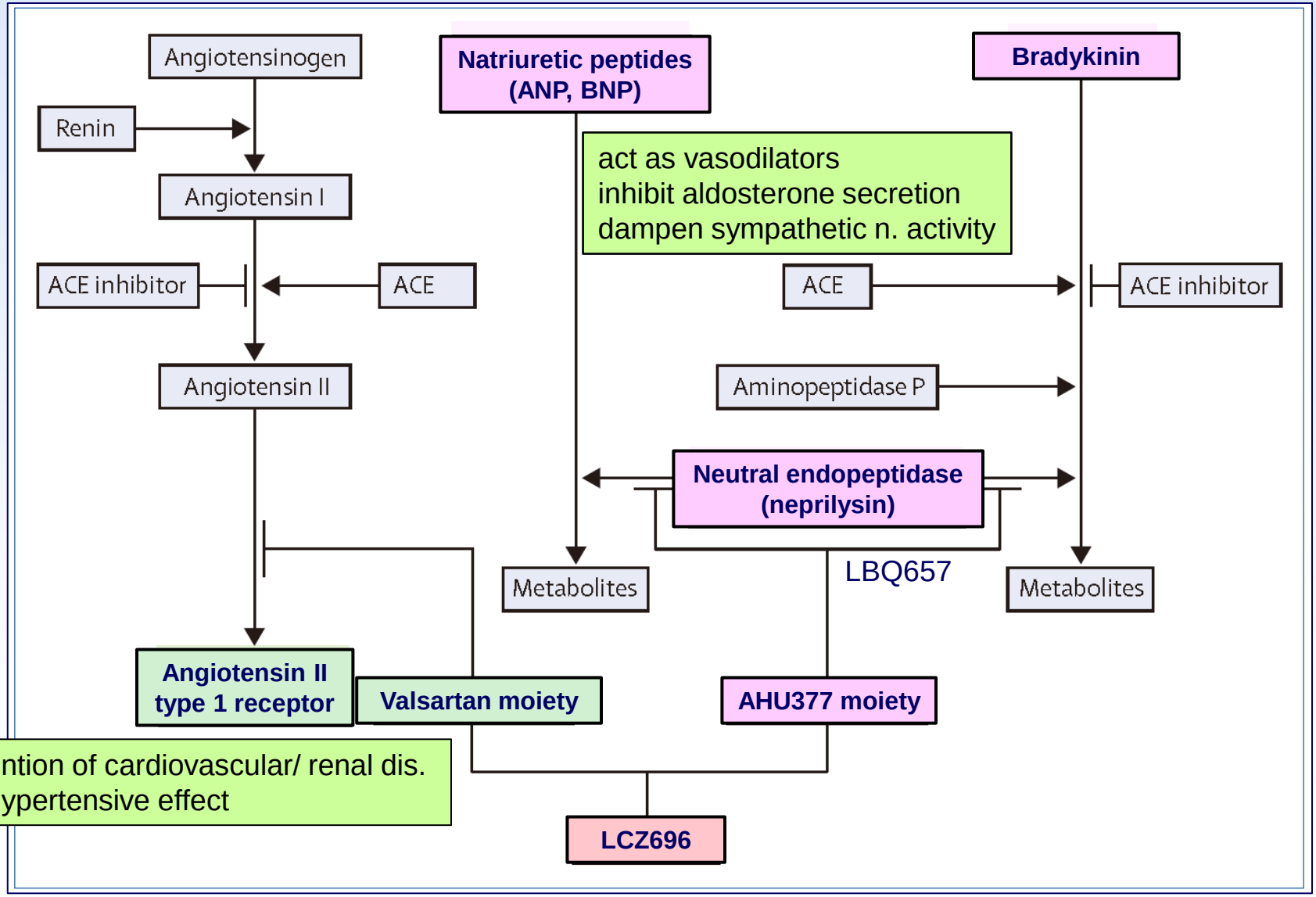
  opioid peptides
  substance P
  peptides involved in regulation of inflammation
  amyloid β-protein
  gastrin

Dual inhibition of NEP and ARB: LCZ696

- Novel class of drug: ARB and neutral endopeptidase (NEP) inhibition (ARNi).

- LCZ696 (sucabitril valsartan sodium hydrate)
  - 1:1 ratio blockade of AT1R (valsartan moiety) and NEP inh (AHU377 prodrug moiety)
    AHU377 prodrug : LBQ657 active moiety

Mechanism of LCZ696 on RAS and natriuretic peptides



Waeber B, Lancet 2010 375: 1228-9

Dual inhibition of NEP and ARB: LCZ696 in HF

- Ongoing trial: LCZ696 in chronic HF and in chronic HF with preserved EF

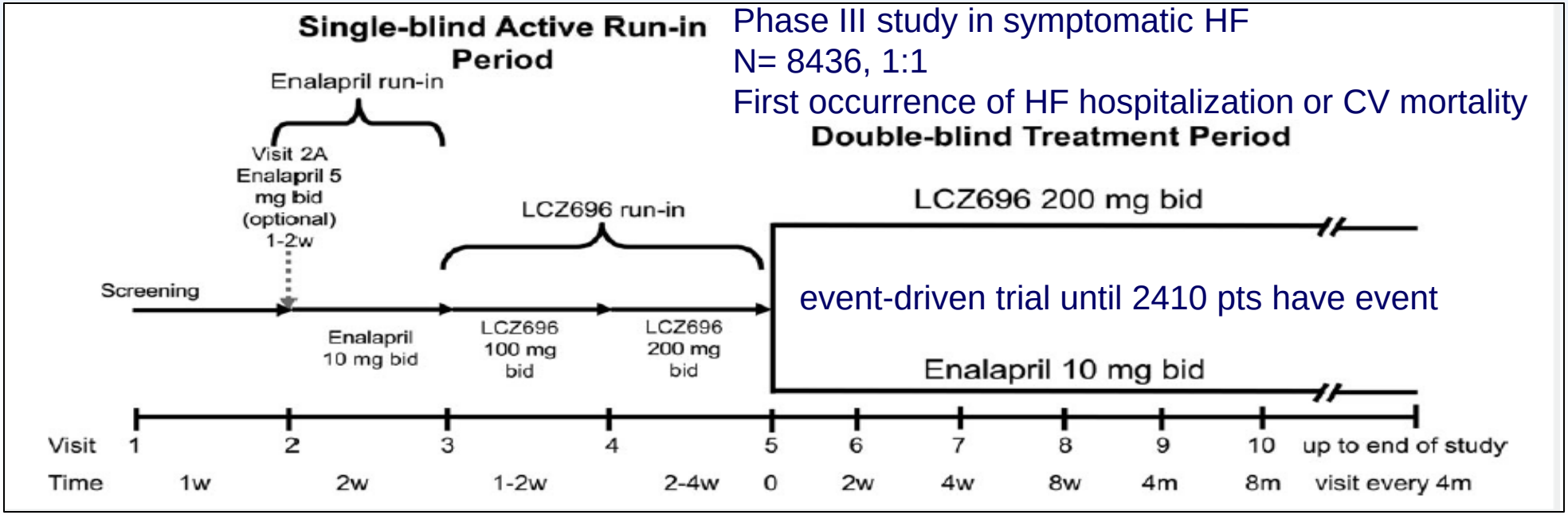
- PARADIGM-HF trial
  - Phase III study in symptomatic HF
    LCZ696 vs enalapril : first occurrence of HF hospitalization or CV mortality

- Paramount HF trial
  - Phase II, HF with preserved EF
  - NYHA class II–III HF, LV EF 45% or higher, NT-proBNP greater than 400 pg/mL
  - LCZ696 vs valsartan: actions on neurohormones and on EchoCG findings

STUDY DESIGN PAPER

Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF)

John J. V. McMurray[1]*, Milton Packer[2], Akshay S. Desai[3], Jim Gong[4], Martin P. Lefkowitz[4], Adel R. Rizkala[4], Jean Rouleau[5], Victor C. Shi[4], Scott D. Solomon[3], Karl Swedberg[6], and Michael R. Zile[7], on behalf of the PARADIGM-HF Committees and Investigators†



Phase III study in symptomatic HF
N= 8436, 1:1
First occurrence of HF hospitalization or CV mortality

McMurray J, *Eur J Heart Fail* 2013, 15: 1066-73

PARAMOUNT: RCT, Phase 2 trial

- Phase 2, randomised, parallel-group, double-blind multicenter trial
- Patients with NYHA class II–III HF, LV EF 45% or higher, NT-proBNP greater than 400 pg/mL.
- Randomly assigned (1:1) by central interactive voice response system
  LCZ696 titrated to 200 mg twice daily
  or valsartan titrated to 160 mg twice daily, and treated for 36 weeks.
- Primary endpoint was change in NTproBNP, a marker of left ventricular wall stress, from baseline to 12 weeks;

Angiotensin receptor neprilysin inhibitor LCZ696 in HFpEF

The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial

*Scott D Solomon, Michael Zile, Burkert Pieske, Adriaan Voors, Amil Shah, Elisabeth Kraigher-Krainer, Victor Shi, Toni Bransford, Madoka Takeuchi, Jianjian Gong, Martin Lefkowitz, Milton Packer, John J V McMurray, for the Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) Investigators**

Summary

Background Heart failure with preserved ejection fraction is associated with substantial morbidity and mortality, but effective treatments are lacking. We assessed the efficacy and safety of LCZ696, a first-in-class angiotensin receptor neprilysin inhibitor (ARNI), in patients with this disorder.

Methods PARAMOUNT was a phase 2, randomised, parallel-group, double-blind multicentre trial in patients with New York Heart Association (NYHA) class II–III heart failure, left ventricular ejection fraction 45% or higher, and NT-proBNP greater than 400 pg/mL. Participants were randomly assigned (1:1) by central interactive voice response system to LCZ696 titrated to 200 mg twice daily or valsartan titrated to 160 mg twice daily, and treated for 36 weeks. Investigators and participants were masked to treatment assignment. The primary endpoint was change in NT-proBNP, a marker of left ventricular wall stress, from baseline to 12 weeks; analysis included all patients randomly assigned to treatment groups who had a baseline and at least one postbaseline assessment. This trial is registered at Clinicaltrials.gov, number NCT00887588.

Findings 149 patients were randomly assigned to LCZ696 and 152 to valsartan; 134 in the LCZ696 group and 132 in the valsartan group were included in analysis of the primary endpoint. NT-proBNP was significantly reduced at 12 weeks in the LCZ696 group compared with the valsartan group (LCZ696: baseline, 783 pg/mL [95% CI 670–914], 12 weeks, 605 pg/mL [512–714]; valsartan: baseline, 862 pg/mL [733–1012], 12 weeks, 835 [710–981]; ratio LCZ696/valsartan, 0·77, 95% CI 0·64–0·92, p=0·005). LCZ696 was well tolerated with adverse effects similar to those of valsartan; 22 patients (15%) on LCZ696 and 30 (20%) on valsartan had one or more serious adverse event.

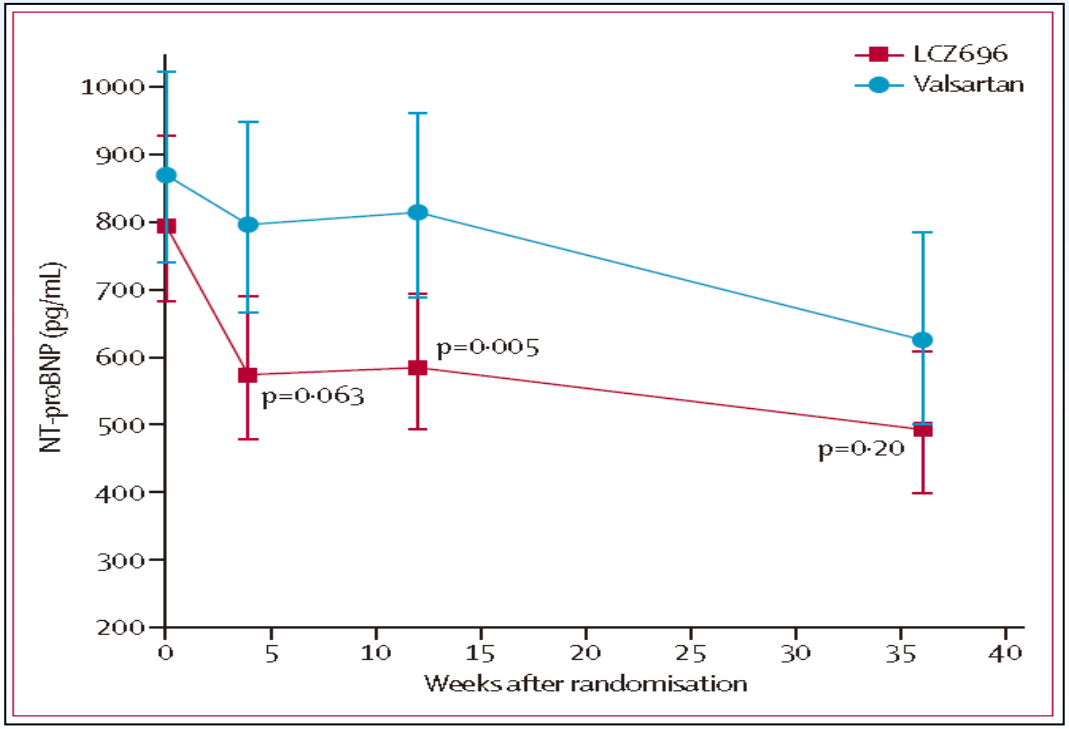
Interpretation In patients with heart failure with preserved ejection fraction, LCZ696 reduced NT-proBNP to a greater extent than did valsartan at 12 weeks and was well tolerated. Whether these effects would translate into improved outcomes needs to be tested prospectively.

Solomon SD, Lancet 2012 380: 1387–95

NT-proBNP at baseline, 12 weeks, and 36 weeks

	NT-proBNP (pg/mL) at 12 weeks			NT-proBNP (pg/mL) at 36 weeks		
	n	Baseline	12 weeks	n	Baseline	36 weeks
LCZ696	134	783 (670–914)	605 (512–714)	115	763 (646–901)	496 (401–613)
Valsartan	132	862 (733–1012)	835 (710–981)	116	822 (688–983)	607 (484–760)
Ratio of change (LCZ696/valsartan)	..	..	0·77 (95% CI 0·64–0·92), p=0·005	..	..	0·85 (95% CI 0·65–1·09), p=0·20

Data for NT-proBNP are geometric mean (95% CI).



Solomon SD, Lancet 2012380: 1387–95

Changes in EchoCG parameters at 12 and 36 weeks

	12 weeks							36 weeks						
	LCZ696			Valsartan			p value	LCZ696			Valsartan			p value
	n	Baseline	Δ from baseline	n	Baseline	Δ from baseline		n	Baseline	Δ from baseline	n	Baseline	Δ from baseline	
Ejection fraction	114	58·2% (7·6)	1·06% (5·0)	118	58·0% (8·0)	1·04% (4·9)	0·85	94	58·3% (7·7)	2·7% (6·5)	111	58·1% (8·0)	3·07% (5·9)	0·69
Lateral mitral annular relaxation velocity (e′; cm/s)	97	7·7 (2·7)	0·57 (1·7)	106	7·2 (2·9)	0·55 (1·5)	0·56	84	7·6 (2·7)	0·55 (2·3)	96	7·3 (2·8)	0·92 (2·0)	0·40
Mitral inflow velocity to mitral annular relaxation velocity ratio (E/e′)	96	12·6 (8·4)	−1·3 (3·4)	106	13·0 (7·3)	−1·3 (4·3)	0·71	83	12·3 (5·5)	−1·3 (3·1)	95	12·7 (6·2)	−1·0 (4·7)	0·42
Early to late mitral inflow velocity ratio (E/A)	72	1·1 (0·56)	−0·09 (0·36)	78	1·1 (0·66)	−0·08 (0·67)	0·90	60	1·1 (0·51)	−0·05 (0·39)	68	1·1 (0·65)	−0·03 (0·61)	0·43
Left atrial width (cm)	116	3·7 (0·42)	−0·07 (0·25)	114	3·7 (0·53)	−0·02 (0·22)	0·07	99	3·7 (0·43)	−0·15 (0·31)	108	3·7 (0·53)	−0·08 (0·30)	0·03
Left atrial volume (mL)	113	67·0 (23·2)	−3·2 (12·2)	119	68·1 (28·1)	−1·3 (12·5)	0·18	96	65·3 (22·5)	−4·6 (13·7)	112	68·3 (29·3)	0·37 (15·9)	0·003
Left atrial volume index (mL/m²)	110	35·9 (12·5)	−0·98 (7·6)	118	36·5 (14·4)	−0·41 (6·8)	0·45	90	35·0 (11·7)	−2·6 (7·3)	106	36·8 (14·8)	0·31 (9·3)	0·007
Left ventricular end-diastolic volume (mL)	114	110·3 (26·4)	−2·90 (10·5)	118	113·1 (31·3)	−3·27 (12·3)	0·99	94	111·8 (26·3)	−10·4 (14·4)	111	114·3 (31·5)	−12·7 (17·3)	0·39
Left ventricular end-systolic volume (mL)	114	46·5 (15·7)	−3·3 (6·5)	118	48·5 (20·9)	−2·7 (8·9)	0·97	95	46·9 (15·8)	−6·9 (9·1)	111	48·8 (20·6)	−8·70 (11·0)	0·31
Left ventricular mass index (kg/m²)	112	77·4 (20·7)	−1·2 (13·0)	112	78·8 (21·5)	−4·2 (11·8)	0·10	91	76·6 (19·8)	−2·8 (14·0)	100	79·5 (22·7)	−1·9 (19·2)	0·35
Relative wall thickness	116	0·38% (0·09)	−0·002% (0·045)	114	0·37% (0·07)	0·001% (0·033)	0·76	98	0·37% (0·07)	0·01% (0·06)	107	0·37% (0·07)	0·01% (0·06)	0·96
Tricuspid regurgitant velocity (m/s)	45	2·5 (0·36)	0·008 (0·25)	42	2·5 (0·33)	0·09 (0·33)	0·19	35	2·6 (0·44)	−0·01 (0·24)	42	2·52 (0·34)	0·06 (0·35)	0·38

Data are mean (SD). Baseline data are presented for follow-up values.

Table 3: **Changes in echocardiographic measures at 12 weeks and 36 weeks**

Independence of the blood pressure lowering effect and efficacy of the angiotensin receptor neprilysin inhibitor, LCZ696, in patients with heart failure with preserved ejection fraction: an analysis of the PARAMOUNT trial

Pardeep S. Jhund[1,2], Brian Claggett[1], Milton Packer[3], Michael R Zile [4], Adriaan A. Voors[5], Burkert Pieske[6], Martin Lefkowitz[7], Victor Shi[7], Toni Bransford[7], John J. V. McMurray[2], and Scott D Solomon[1]*

[1]Cardiovascular Division, Brigham and Women's Hospital, Boston, MA, USA; [2]BHF Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK; [3]Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas, TX, USA; [4]Ralph H. Johnson Veterans Affairs Medical Center and Medical University of South Carolina, Charleston, SC, USA; [5]Department of Cardiology, University Medical Centre, Groningen, University of Groningen, Groningen, the Netherlands; [6]Department of Cardiology, Medical University Graz, Graz, Austria; and [7]Novartis Pharmaceuticals, East Hanover, NJ, USA

Received 23 October 2013; revised 3 January 2014; accepted 17 January 2014

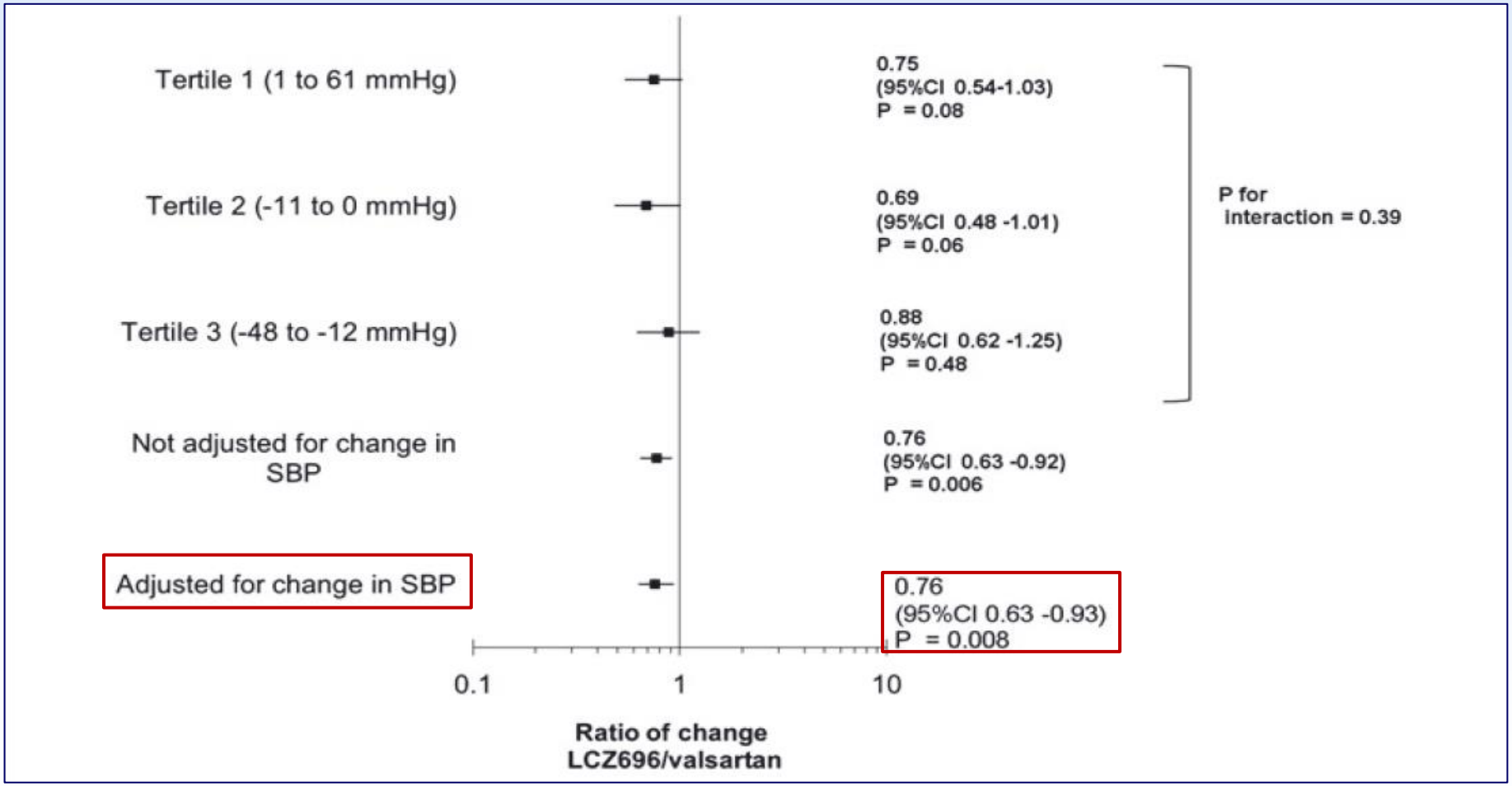
Aims The first in class angiotensin receptor neprilysin inhibitor, LCZ696 has been shown to reduce levels of *N*-terminal pro-brain natriuretic peptide (NT-proBNP), reduce left atrial size and improve New York Heart Association (NYHA) class in patients with heart failure with preserved ejection fraction (HFpEF). We examined whether the effects of LCZ696 were independent of systolic blood pressure (SBP) lowering.

Methods and results In the Prospective comparison of ARNi (angiotensin receptor neprilysin inhibitor) with ARB (angiotensin receptor blocker) on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) trial 301 patients were randomly assigned to LCZ696 or valsartan. We examined the relationship between SBP lowering and LCZ696 on NT-proBNP level, left atrial size, NYHA class and estimated glomerular filtration rate (eGFR). By 12 weeks blood pressure was reduced by 9 mmHg (SD 15)/5 mmHg (SD 11) in patients receiving LCZ696 in comparison with 3 mmHg (SD 17)/2 mmHg (SD 12) in those receiving valsartan. The change in NT-proBNP was poorly correlated with change in SBP (LCZ696, $r = 0.17$, $P = 0.06$; valsartan, $r = 0.05$, $P = 0.58$) After adjustment for change in SBP, the ratio of change in NT-proBNP at 12 weeks for LCZ696 vs. valsartan was 0.76 (95% CI 0.63–0.93, $P = 0.008$), and similar to the ratio not adjusting for SBP (0.76, 95% CI 0.63–0.92, $P = 0.006$); P for interaction was 0.38). Similarly, reduction in left atrial volume index at 36 weeks, improvement in NYHA class and eGFR were all independent of the change in SBP.

Conclusion In patients with HFpEF, the effect of the angiotensin receptor neprilysin inhibitor LCZ696 on NT-proBNP, left atrial volume, functional class, and eGFR was independent of reduction in SBP.

Keywords Blood pressure • Heart failure • Neprilysin inhibitor • NT-proBNP • Preserved ejection fraction

Ratio of Change in NT-proBNP at 12 weeks : LCZ696 vs Valsartan



Jhund PS, Eur Heart Fail 2014

Change in LA diameter, LA volume and eGFR at 36 Weeks

	Tertile 1, $n = 89$ (−50 to −12 mmHg) Change (95%CI)	Tertile 2, $n = 83$ (−11 to −2 mmHg) Change (95%CI)	Tertile 3, $n = 78$ (3–62 mmHg) Change (95%CI)	Overall	
				P LCZ696 vs. valsartan (adjusted for change in SBP at 36 weeks)	*P* for interaction
Left atrial diameter					
LCZ696	−0.15(−0.25 to −0.06)	−0.12(−0.23 to −0.01)	−0.19(−0.32 to −0.05)	0.03	0.91
Valsartan	−0.04(−0.14 to −0.06)	−0.07(−0.16 to −0.02)	−0.11(−0.22 to −0.01)		
Left atrial indexed volume					
LCZ696	−2.65 (−4.71 to −0.59)	−1.77 (−4.87 to −1.34)	−3.74 (−7.18 to −0.29)	0.01	0.61
Valsartan	−0.28(−3.54 to −2.98)	0.22 (−2.69 to −3.14)	0.80(−2.53 to 4.13)		
eGFR					
LCZ696	−3.83(−6.99 to −0.67)	−1.28(−6.26 to −3.70)	1.86(−3.02 to −6.74)	0.002	0.69
Valsartan	−9.09(−12.78 to −5.41)	−3.03(−7.16 to −1.11)	−4.28(−7.34 to −1.23)		

Jhund PS, Eur Heart Fail 2014

Summary (I)

- Neutral outcomes in HFNEF
  - from methodological flaws associated with inclusion criteria
  - from specific pathophysiological features characterizing HFNEF

- Newly proposed paradigm for HFNEF development
  - systemic proinflammatory state induced by comorbidities
    : the cause of myocardial structural and functional alterations

  Comorbidities such as overweight, obesity, DM, COPD, HT
  $\rightarrow$ proinflammatory state $\rightarrow$ coronary microvascular endothelial inflammation
  $\rightarrow \downarrow$ NO bioavailability, cGMP contents, protein kinase G activity
  $\rightarrow \uparrow$ resting tension $\rightarrow$ high diastolic left ventricular stiffness $\rightarrow$ HF

Summary (II)

- This paradigm suggests important therapeutic implications for interfering HFNEF-specific myocardial signaling.

  Restoring strategies for

  myocardial NO bioavailability, cGMP contents and PKG activity,

  endothelial function

  through NO donor, PDE-5 inhibitor, anti-oxidative substances.

- More specialized, phenotype-specific HFNEF approach is needed
  - more sensitive (bio)marker of systolic and diastolic function
  - more specific pathophysiological features characterizing HFNEF

Summary (III)

- “HFNEF is a heterogeneous disorder with multifactorial pathophysiology”
- Still our understanding of HFNEF pathophysiology is limited
- Optimal treatment - largely undefined
- Although treatment options remain unclear concerning mortality,

  most of patients have significant comorbidities strongly associated with mortality.

Conclusion

- Comorbidities should be treated under the guidance of evidence-based medicine
- HFNEF patients are often older
  - improvements of clinical symptom, exercise capacity and QoL may be more important than mortality only
- Recent HFNEF trials
  - positive in clinical symptom, exercise capacity and QoL improvements.
- Further ongoing studies (especially, matched to guideline) are necessary
  - to increase understanding of pathophysiology
    to develop new therapeutic strategies in HFNEF patients