3rd Dubrovnik Cardiology Highlights

ESC Update Programme, Dubrovnik, 26.-29.9.2013

Heart Failure with Preserved Ejection Fraction- What is new?

Prof. Burkert Pieske

Department of Cardiology

Medical University Graz

&

Ludwig-Boltzmann-Institute

Translational HF Research

Medizinische Universität Graz

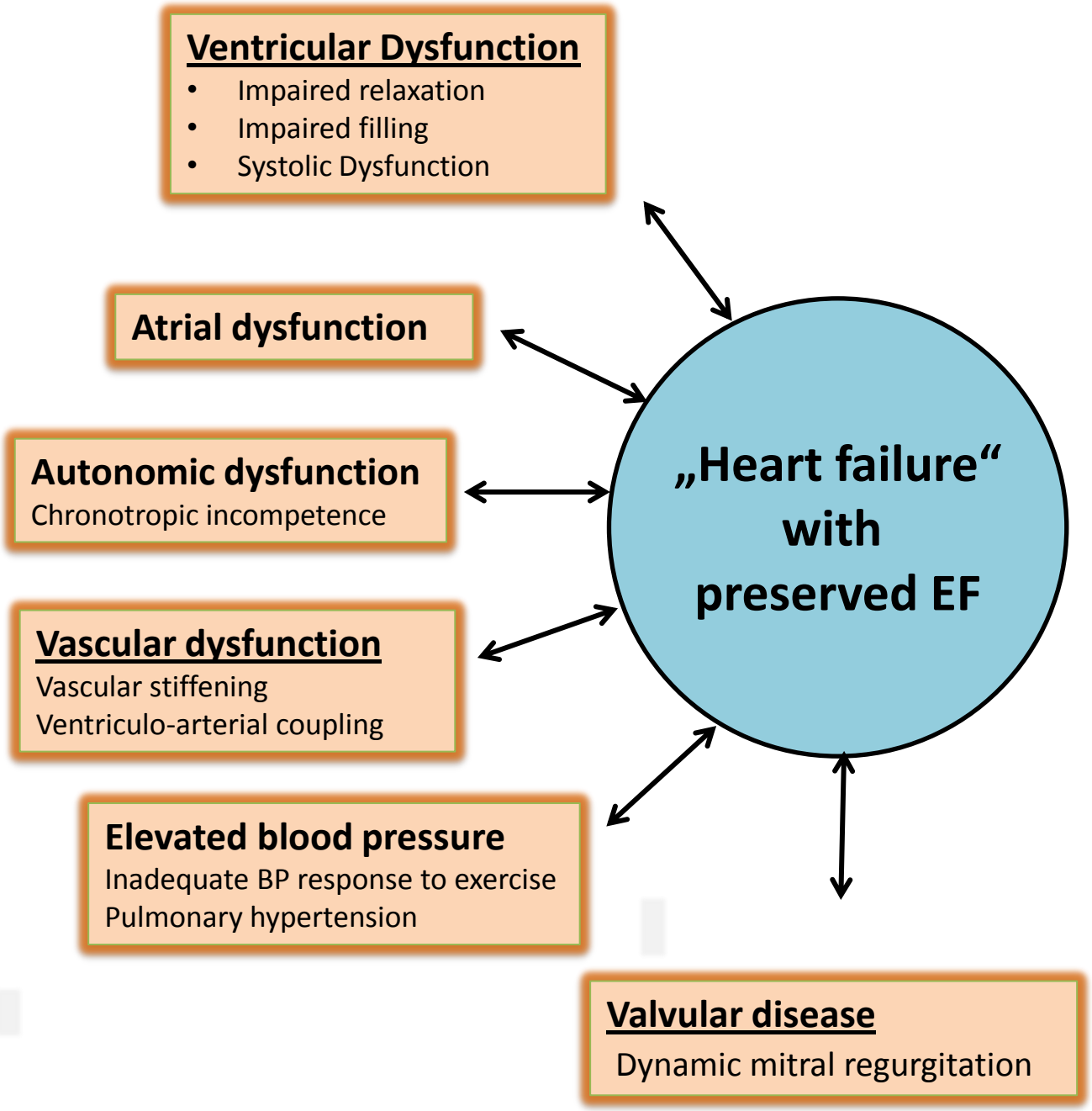
www.kardiologie-graz.at www.heart.lbg.ac.at

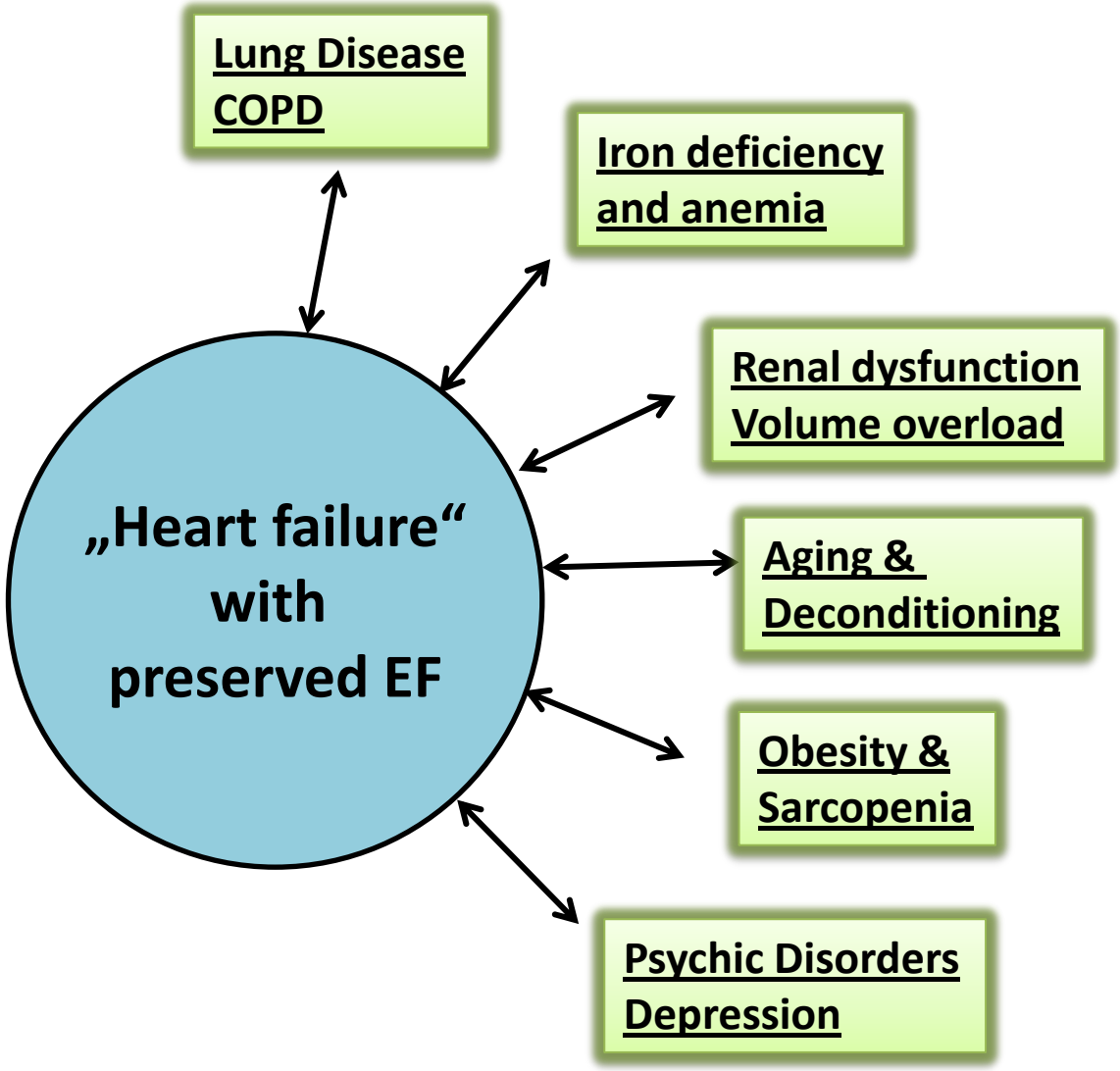
HFPEF, HFNEF, or Diastolic Heart Failure??

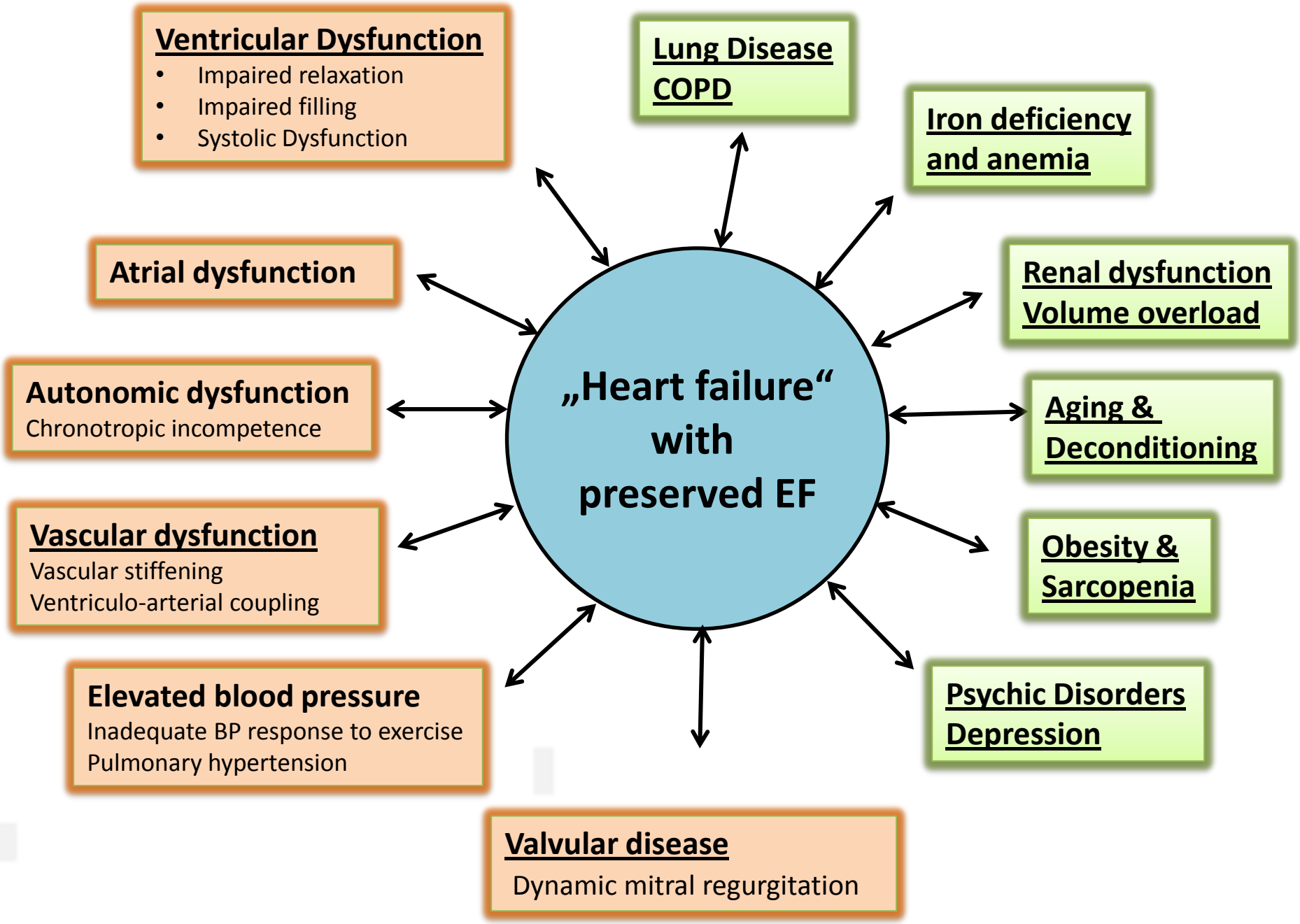
The Relationship Between Pressure and Volume

HFpEF – News 2013

- News I: Pathophysiology
- News II: Diagnosis?
- News III: Therapy?


Ventricular Dysfunction
• Impaired relaxation
• Impaired filling
• Systolic Dysfunction
Atrial dysfunction
Autonomic dysfunction
Chronotropic incompetence
Vascular dysfunction
Vascular stiffening
Ventriculo-arterial coupling
Elevated blood pressure
Inadequate BP response to exercise
Pulmonary hypertension
„Heart failure“ with preserved EF
Valvular disease
Dynamic mitral regurgitation


Lung Disease
COPD
Iron deficiency
and anemia
Renal dysfunction
Volume overload
„Heart failure“
with
preserved EF
Aging &
Deconditioning
Obesity &
Sarcopenia
Psychic Disorders
Depression


Ventricular Dysfunction
• Impaired relaxation
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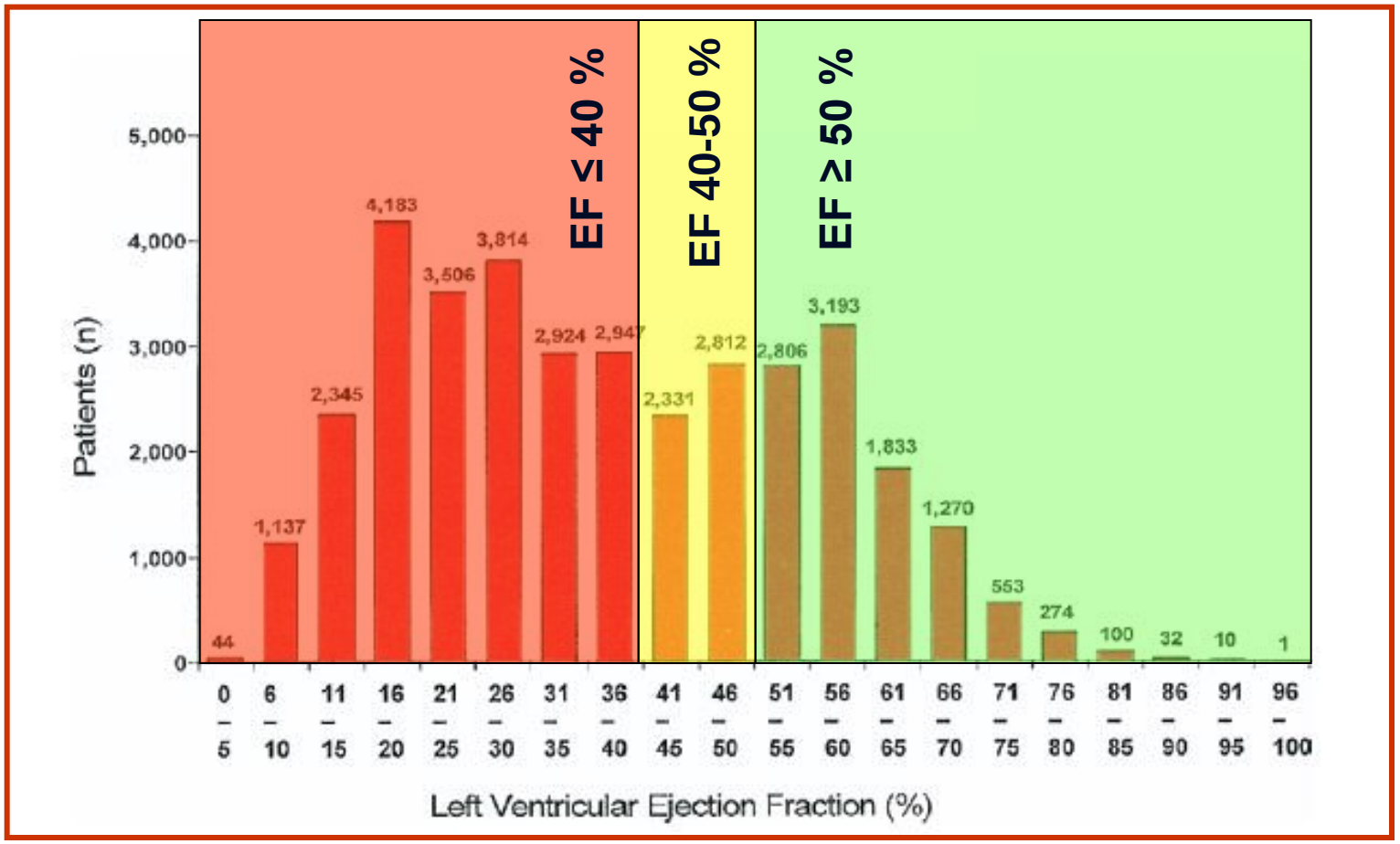
Psychic Disorders Depression
Valvular disease
Dynamic mitral regurgitation

HFpEF – News 2013

- News I: Pathophysiology
- News II: Diagnosis?
- News III: Therapy?

Mega-Trial Approach: HF + “preserved EF”



I-Preserve Echo Substudy

Prevalence and Significance of Alterations in Cardiac Structure and Function in Patients With Heart Failure and a Preserved Ejection Fraction

Michael R. Zile, MD; John S. Gottdiener, MD; Scott J. Hetzel, MS; John J. McMurray, MD; Michel Komajda, MD; Robert McKelvie, MD; Catalin F. Baicu, PhD; Barry M. Massie, MD; Peter E. Carson, MD; for the I-PRESERVE Investigators

Background—The purpose of this study was to examine the prevalence of abnormalities in cardiac structure and function present in patients with heart failure and a preserved ejection fraction (HFPEF) and to determine whether these alterations in structure and function were associated with cardiovascular morbidity and mortality.

Methods and Results—The Irbesartan in HFPEF trial (I-PRESERVE) enrolled 4128 patients; echocardiographic determination of left ventricular (LV) volume, mass, left atrial (LA) size, systolic function, and diastolic function were made at baseline in 745 patients. The primary end point was death or protocol-specific cardiovascular hospitalization. A secondary end point was the composite of heart failure death or heart failure hospitalization. Associations between baseline structure and function and patient outcomes were examined using univariate and multivariable Cox proportional hazard analyses. In this substudy, LV hypertrophy or concentric remodeling was present in 59%, LA enlargement was present in 66%, and diastolic dysfunction was present in 69% of the patients. Multivariable analyses controlling for 7 clinical variables (including log N-terminal pro-B–type natriuretic peptide indicated that increased LV mass, mass/volume ratio, and LA size were independently associated with an increased risk of both primary and heart failure events (all $P<0.05$).

Conclusions—Left ventricular hypertrophy or concentric remodeling, LA enlargement, and diastolic dysfunction were present in the majority of patients with HFPEF. Left ventricular mass and LA size were independently associated with an increased risk of morbidity and mortality. The presence of structural remodeling and diastolic dysfunction may be useful additions to diagnostic criteria and provide important prognostic insights in patients with HFPEF.

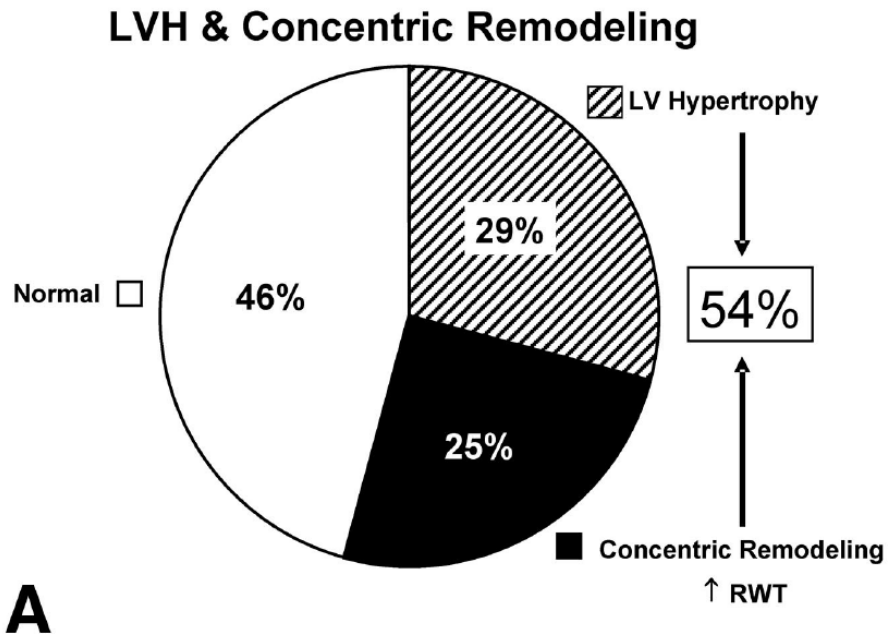
Clinical Trial Registration Information—http://www.clinicaltrials.gov. Unique identifier: NCT00095238.

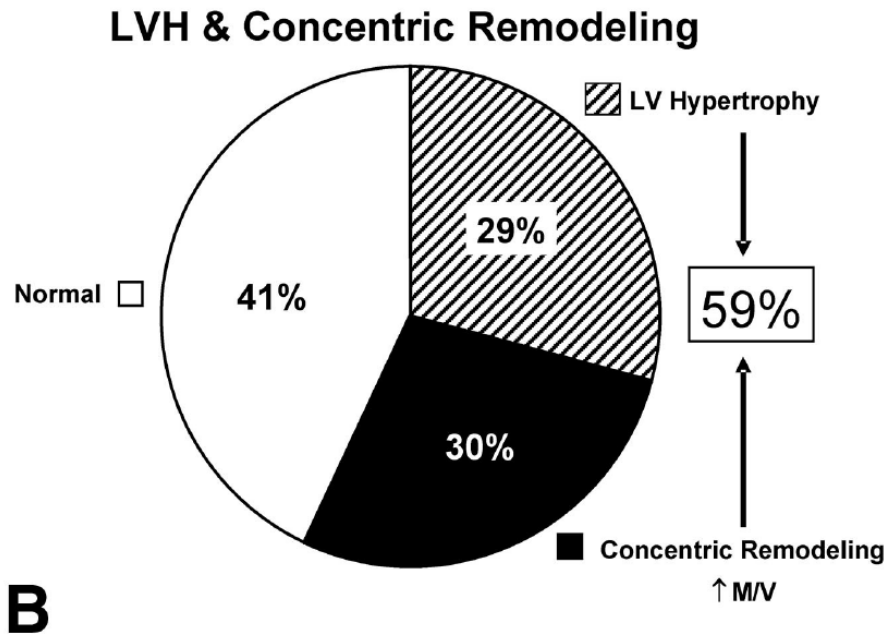
(*Circulation*. 2011;124:00-00.)

Key Words: heart failure ■ echocardiography ■ ventricular ejection fraction

Structural LV Remodeling

Almost 50%: no structural LV Remodeling!





Zile et al.; Circulation 2011; 124

HFA/ESC Recommendations

How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology

Walter J. Paulus[1]*, Carsten Tschöpe[2], John E. Sanderson[3], Cesare Rusconi[4], Frank A. Flachskampf[5], Frank E. Rademakers[6], Paolo Marino[7], Otto A. Smiseth[8], Gilles De Keulenaer[9], Adelino F. Leite-Moreira[10], Attila Borbély[11], István Édes[11], Martin Louis Handoko[1], Stephane Heymans[12], Natalia Pezzali[4], Burkert Pieske[13], Kenneth Dickstein[14], Alan G. Fraser[15], and Dirk L. Brutsaert[9]

[1]*Laboratory of Physiology, VU University Medical Center, Van der Boechorststraat, 7, 1081 BT, Amsterdam, The Netherlands;* [2]*Charité Universitätskliniken, Campus Benjamin Franklin, Berlin, Germany;* [3]*Keele University, Stoke-on-Trent, UK;* [4]*S.Orsola Hospital, Brescia, Italy;* [5]*University of Erlangen, Germany;* [6]*University of Leuven, Belgium;* [7]*Universita degli Studi del Piemonte Orientale, Novara, Italy;* [8]*Rikshospitalet, Oslo, Norway;* [9]*Middelheim Ziekenhuis, Antwerp, Belgium;* [10]*University of Porto, Portugal;* [11]*Institute of Cardiology UDMHSC, Debrecen, Hungary;* [12]*University Hospital Maastricht, The Netherlands;* [13]*Georg-August-Universität, Göttingen, Germany;* [14]*Stavanger University Hospital, Norway; and* [15]*University of Wales College of Medicine, Cardiff, UK*

Received 28 November 2006; accepted 23 February 2007; online publish-ahead-of-print 11 April 2007

See page 2421 for the editorial comment on this article (doi:10.1093/eurheartj/ehm412)

Paulus W et al., Eur Heart J 2007; 2539-2550

HFA/ESC Recommendations: Diagnosis

1. Signs and/or Symptoms of Heart Failure

2. Preserved global systolic LV Function (EF>50%)

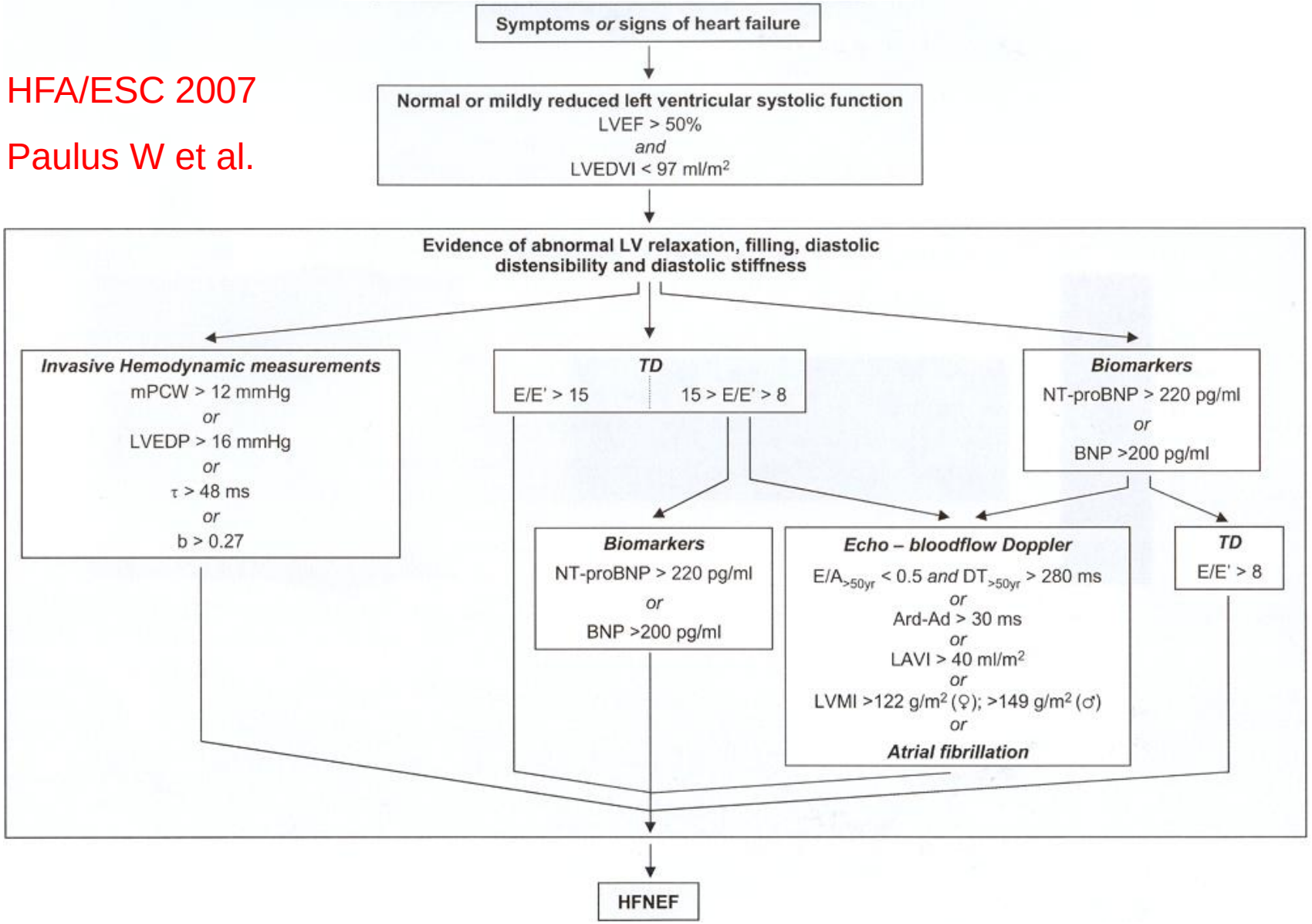
3. Indices of abnormal LV relaxation, filling, compliance or stiffness

4. BNP or NTproBNP

Diagnosis: Diastolic Heart Failure

HFA/ESC 2007

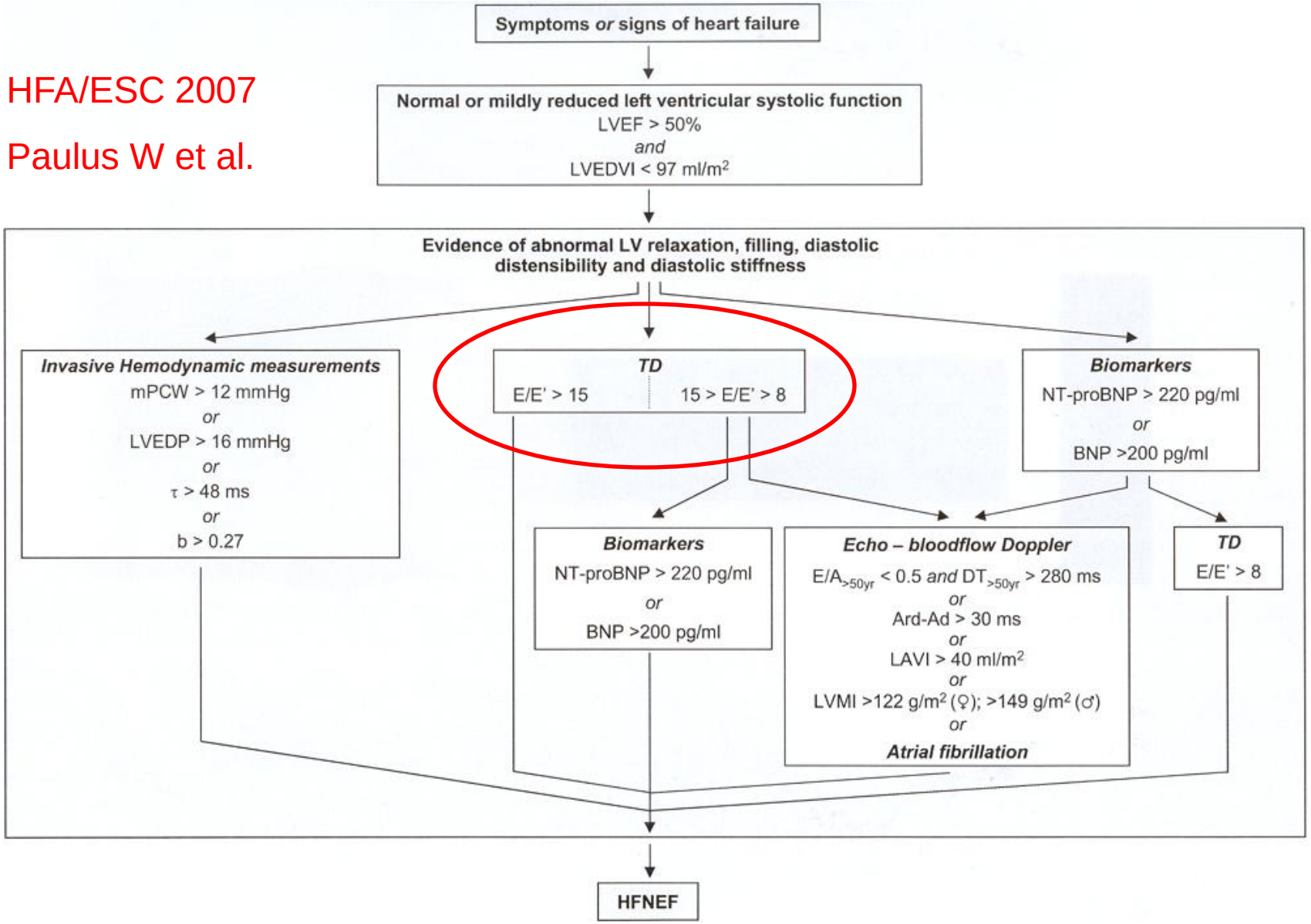
Paulus W et al.



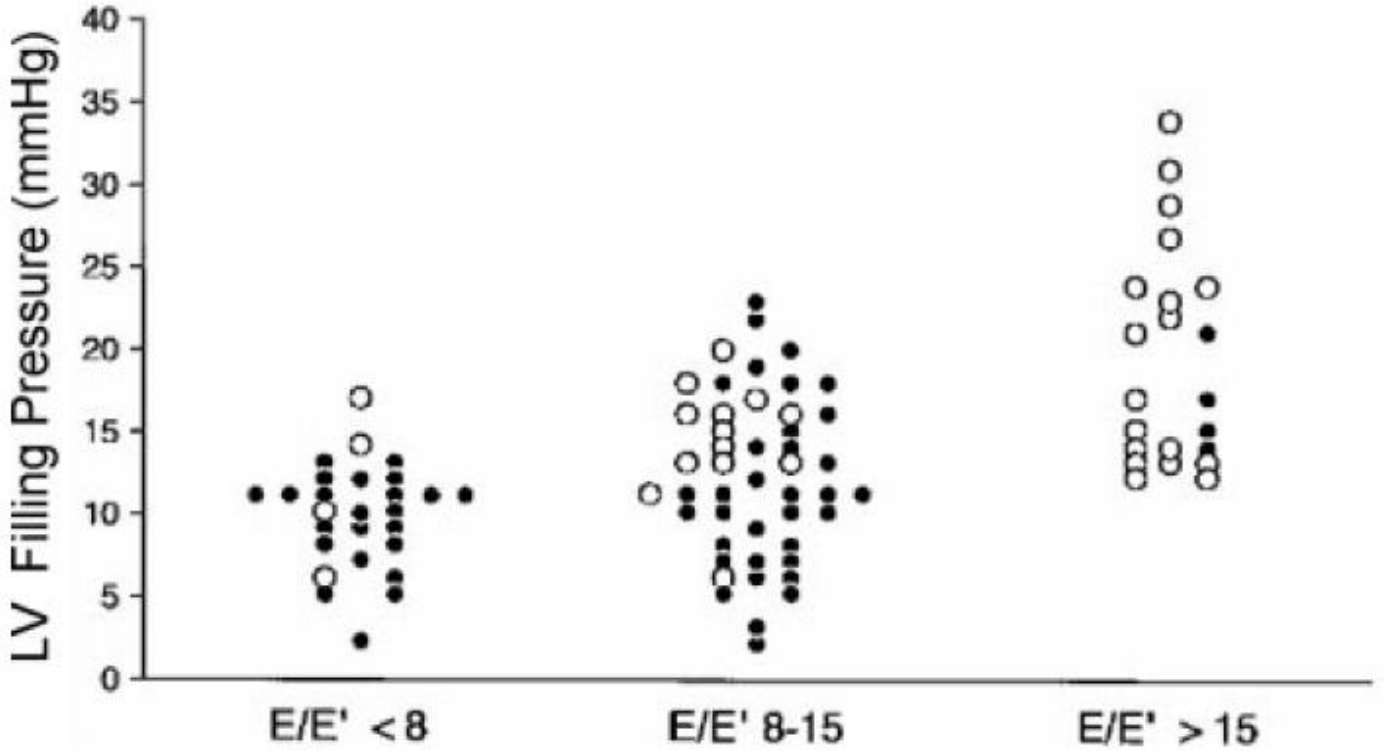
Diagnosis: Diastolic Heart Failure

HFA/ESC 2007

Paulus W et al.



E/é and LVEDP



Little et al.; Circulation 2009; 120: 802-809

Diagnosis: Diastolic Heart Failure

Change in Paradigms 2013:

- New Echo Techniques & Parameters
  (e.g., strain, torsion)
- Echo Stress test („Diastolic Stress Test“)!
- New Biomarkers: Subgroups, Response to Therapy (e.g., Galectin-3, ST2)

HFpEF – News 2013

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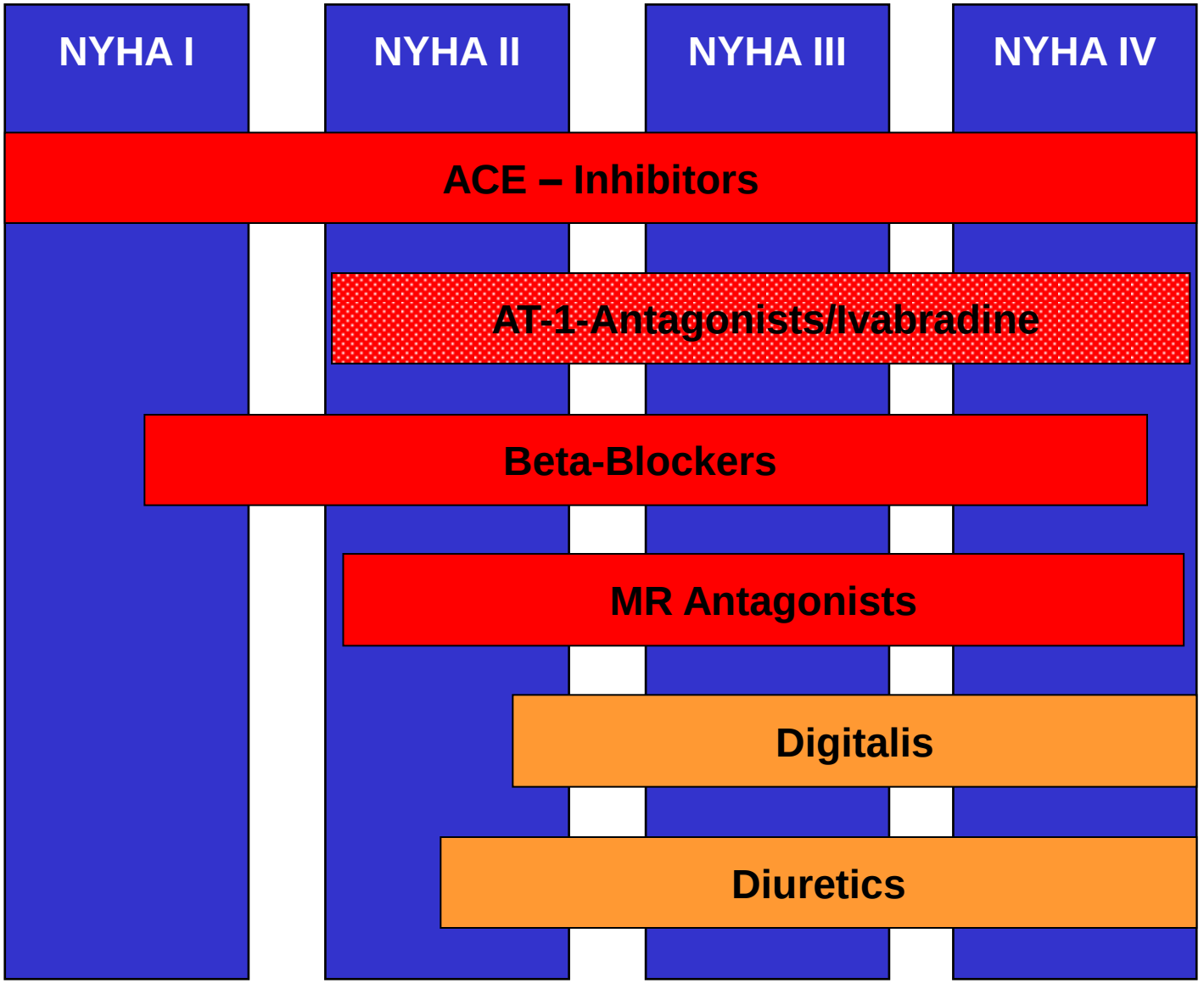
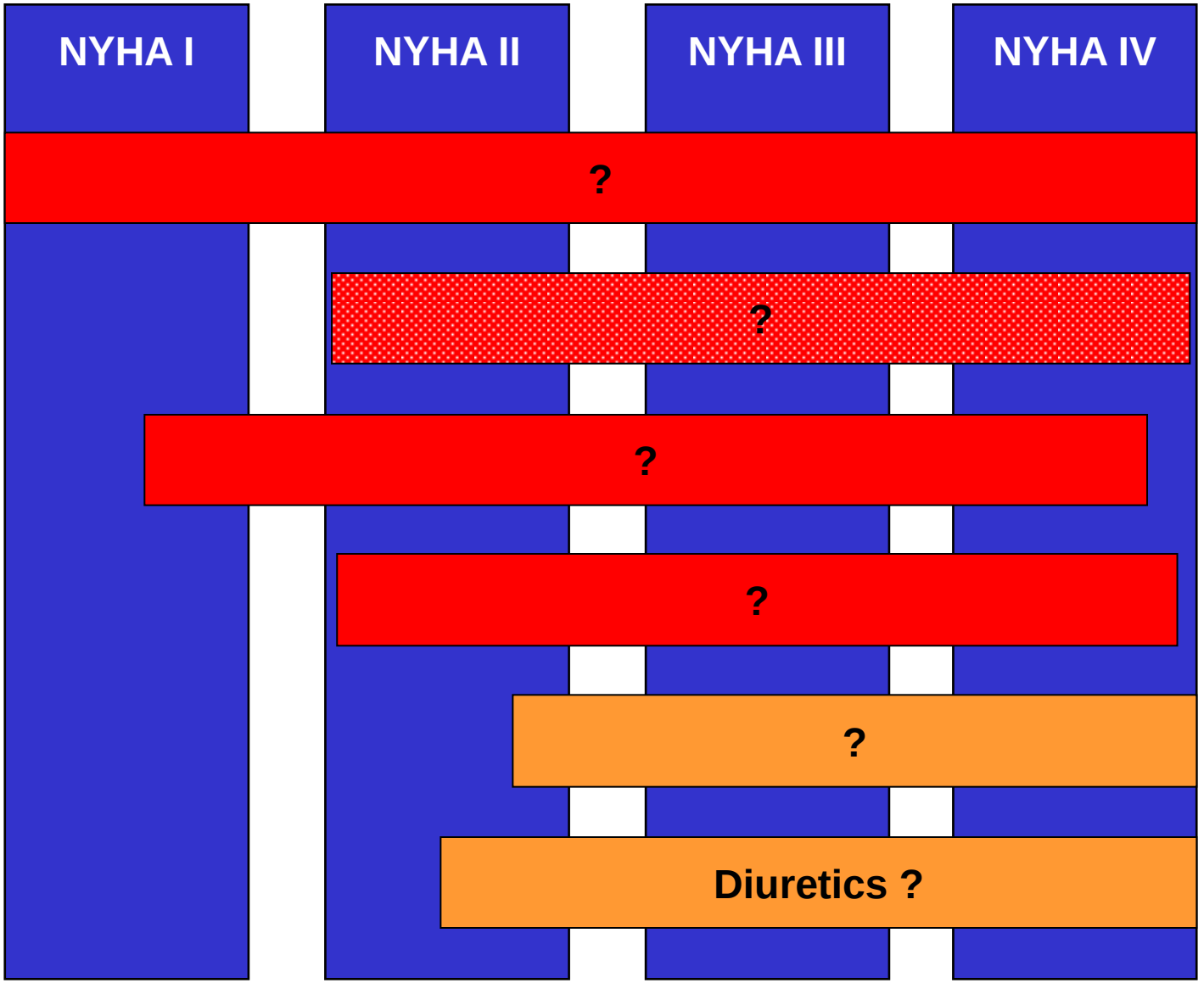
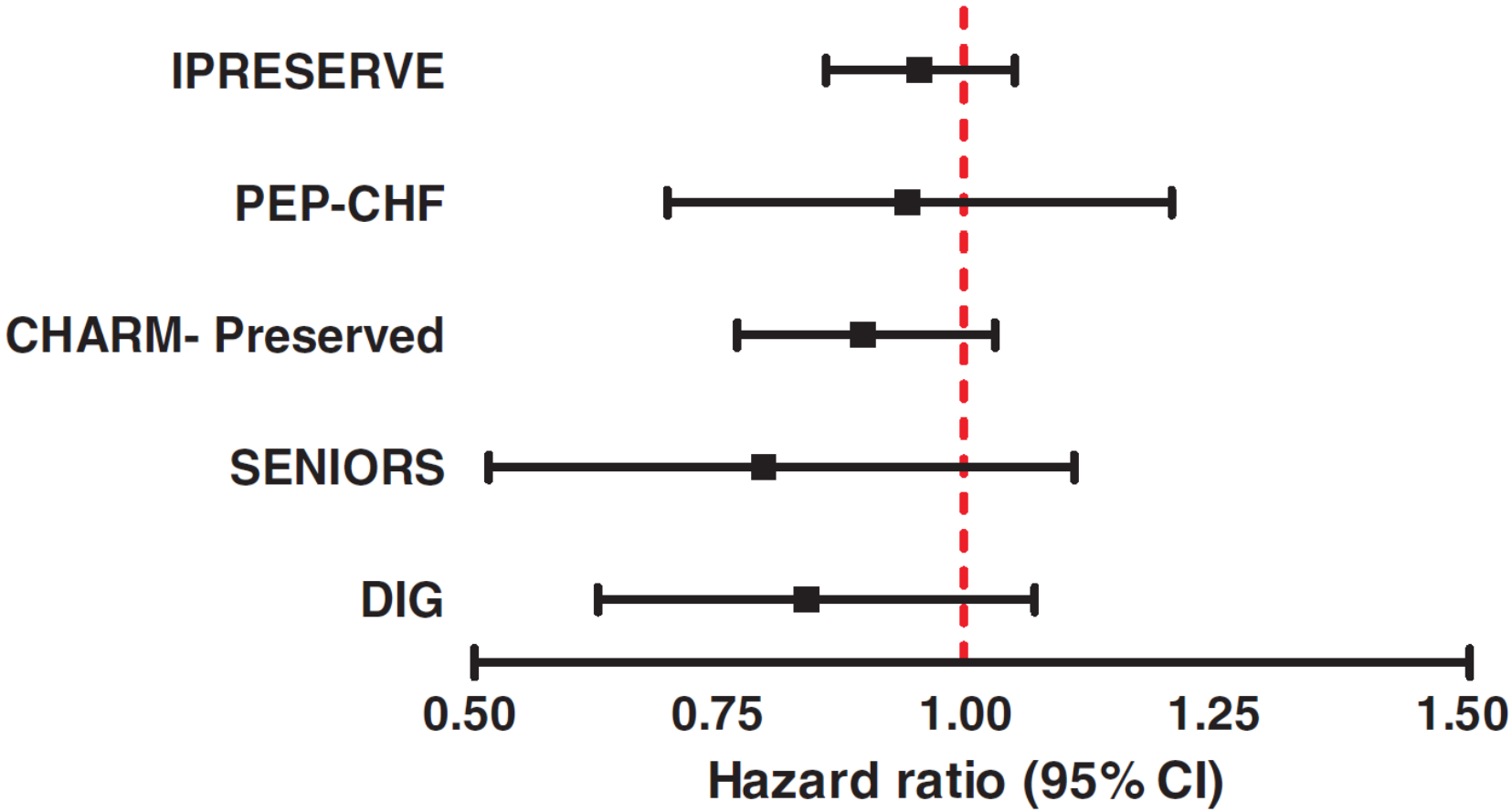
Systolic Heart Failure: Therapy 2013



Diastolic Heart Failure: Therapy 2013



Large Trials in HFPEF – no clear benefit



Redfield M, Circ Heart Fail 2012;5;653-659

Emerging Therapies

1. Pharmacological management

   Ivabradine

   PDE-5 Inhibition

   Guanylate cyclase stimulation

   Neprilysin Inhibition

   MR antagonists

2. Interventions and Devices

   Renal Denervation

   Interatrial Shunting, Vagus/Baroreceptor stimulation..

3. Physical acitvity and Exercise

Ivabradine – I_f channel inhibition

Heart rate reduction by I_f-inhibition improves vascular stiffness and left ventricular systolic and diastolic function in a mouse model of heart failure with preserved ejection fraction

Jan-Christian Reil[1]*, Mathias Hohl[1], Gert-Hinrich Reil[2], Henk L. Granzier[3], Mario T. Kratz[1], Andrey Kazakov[1], Peter Fries[4], Andreas Müller[4], Matthias Lenski[1], Florian Custodis[1], Stefan Gräber[5], Gerd Fröhlig[1], Paul Steendijk[6], Hans-Ruprecht Neuberger[1†], and Michael Böhm[1†]

Genetic mouse model of HFPEF (db/db)

Invasive hemodynamics with Ivabradine

Ivabradine improved diastolic function

Reil et al, Eur Heart J, 2012:1-11

Study CL2-16257-101

Effects of ivabradine *versus* placebo on cardiac function, exercise capacity, and neuroendocrine activation, in patients with Chronic Heart Failure and Preserved left ventricular Ejection Fraction

An 8-month, randomised double-blind, placebo controlled, international, multicentre study

Phase II

Ivabradine phase II study in HFPEF

Primary objective

Ivabradine vs placebo on diastolic function, exercise capacity and neuroendocrine activation over an 8-month treatment period in patients with chronic HF-PEF

Primary endpoint

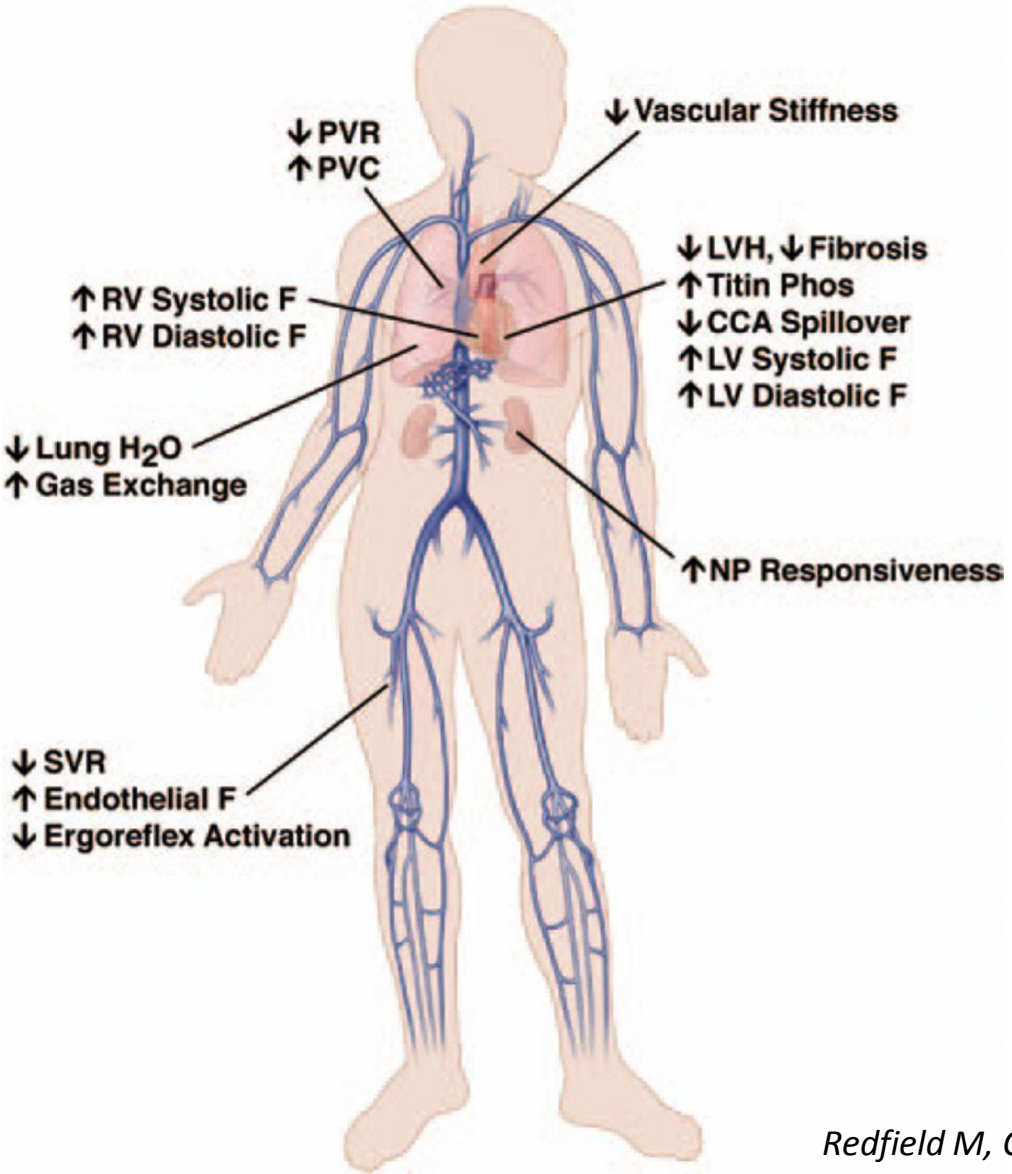
Co-primary endpoint based on echocardiography (E/e'), neuroendocrine activation (NT-proBNP) and six-minute walk test evaluated at 8 months

Secondary objectives

-To evaluate the effects of ivabradine compared to placebo on cardiac function and structural parameters, quality of life (KCCQ) , NYHA classification and other biomarkers
-To evaluate the safety and tolerance profile of ivabradine compared to placebo

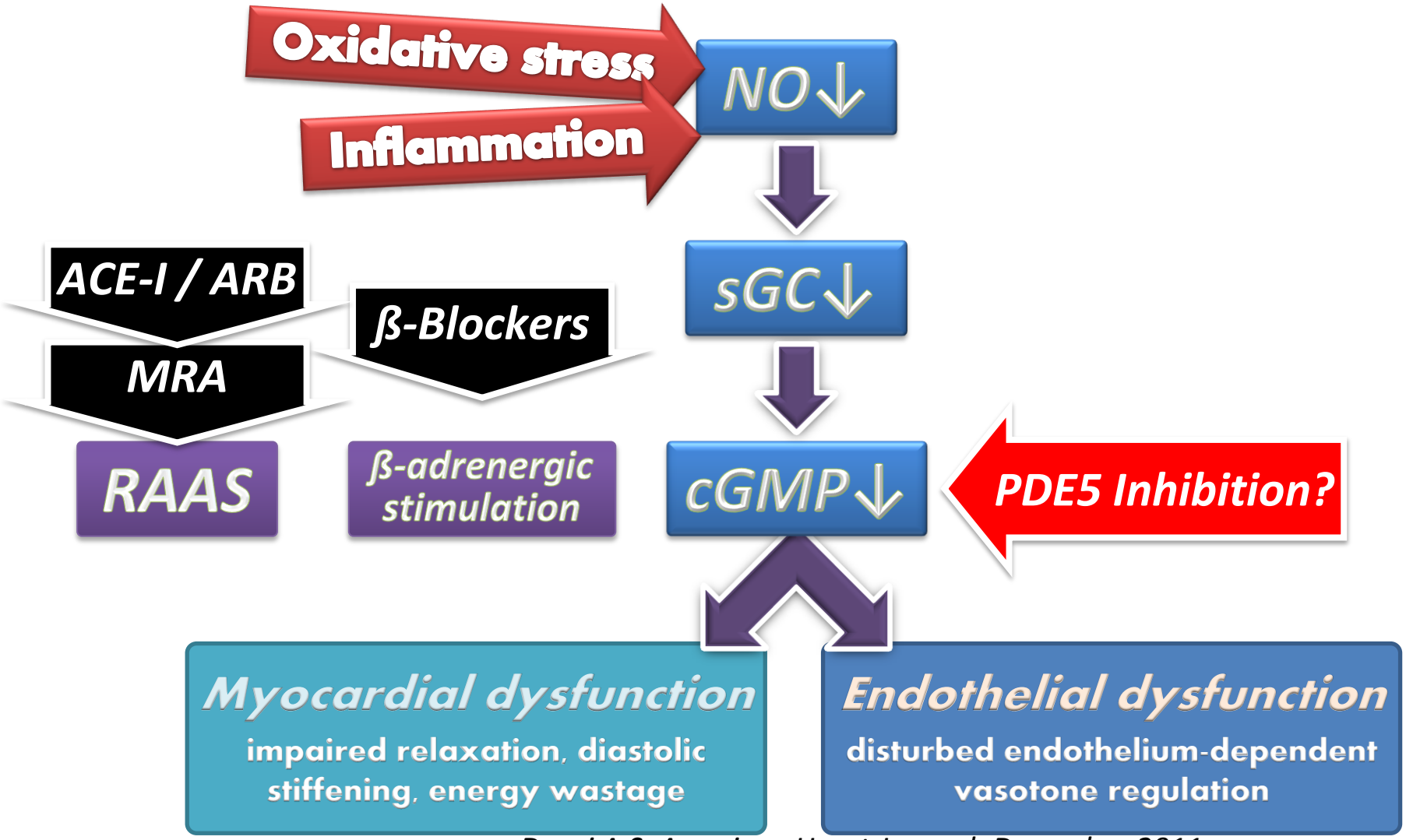
Start: May 2013 !

Increasing cyclic GMP in HFPEF ?



Redfield M, Circulation. 2012;5;653-659

Insufficient soluble Guanylate Cyclase (sGC): an unmet mechanism in HFPEF



Desai A S, American Heart Journal, December 2011

RELAX

Ludwig Boltzmann Institute
Translational Heart Failure Research

Effect of Phosphodiesterase-5 Inhibition on Exercise Capacity and Clinical Status in Heart Failure With Preserved Ejection Fraction

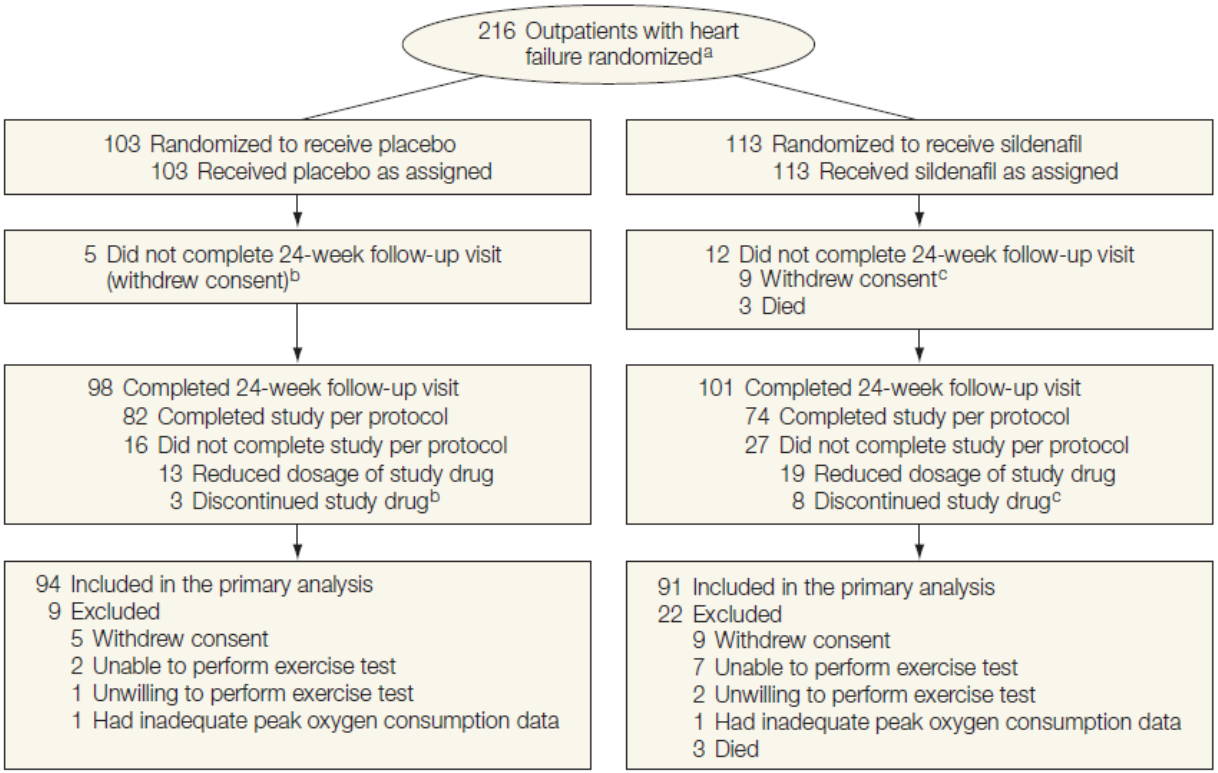
A Randomized Clinical Trial

216 patients

Randomized, double blind, placebo-controlled
Sildenafil 3x20mg (12w), 3x60mg 12w)

EF>50%
Elevated NTproBNP

PEP: peak VO2



Redfield M, JAMA, 2013;309(12)

RELAX

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Translational Heart Failure Research

Outcomes after 24 weeks:

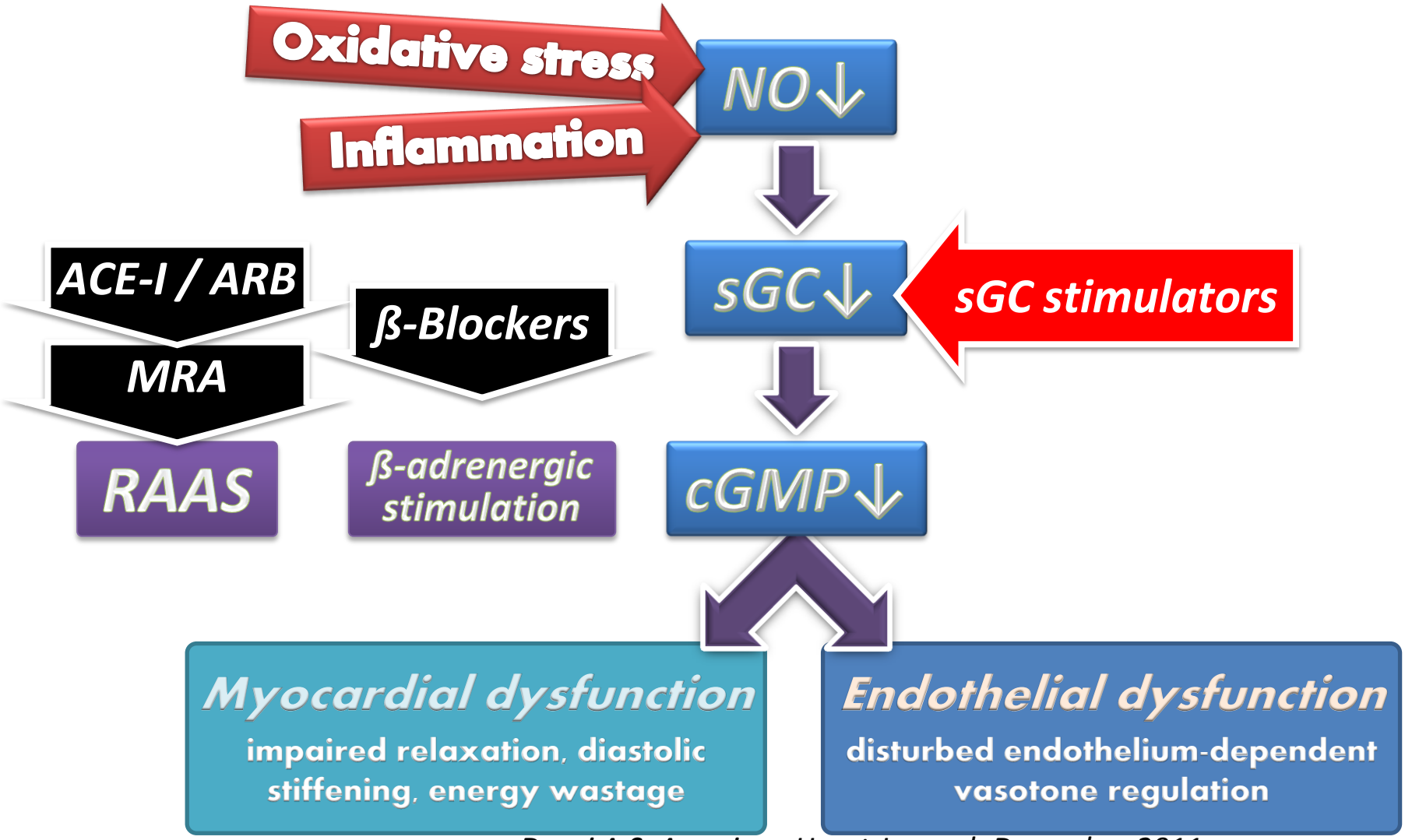
Table 3. Primary, Secondary, and Safety End Points

	Placebo		Sildenafil		
	No. of Patients	Variable	No. of Patients	Variable	*P* Value
Primary end point					
Change in peak oxygen consumption at 24 wk, median (IQR), mL/kg/min	94	−0.20 (−0.70 to 1.00)	91	−0.2 (−1.70 to 1.11)	.90
Secondary end points					
Clinical rank score, mean[a]	94	95.8	95	94.2	.85
Change in 6-minute walk distance at 24 wk, median (IQR), m	95	15.0 (−26.0 to 45.0)	90	5.0 (−37.0 to 55.0)	.92
Change in peak oxygen consumption at 12 wk, median (IQR), mL/kg/min	96	0.03 (−1.10 to 0.67)	97	0.01 (−1.35 to 1.25)	.98
Change in 6-minute walk distance at 12 wk, median (IQR), m	96	18.0 (−14.5 to 48.0)	99	10.0 (−25.0 to 36.0)	.13
Components of clinical rank score at 24 wk					
Death, No. (%)[b]	103	0	113	3 (3)	.25
Hospitalization for cardiovascular or renal cause, No. (%)	103	13 (13)	113	15 (13)	.89
Change in MLHFQ, median (IQR)	91	−8 (−21 to 5)	91	−8 (−19 to 0)	.44
Safety end points, No. (%)					
Adverse events	103	78 (76)	113	90 (80)	.49
Serious adverse events	103	16 (16)	113	25 (22)	.22

Abbreviations: IQR, interquartile range; MLHFQ, Minnesota Living with Heart Failure Questionnaire.
[a] A mean value of 95 in each group is expected under the null hypothesis of no treatment effect.
[b] Site investigator identified causes of death were sudden death (n=1), progressive cardiorenal failure (n=1), and noncardiovascular (n=1).

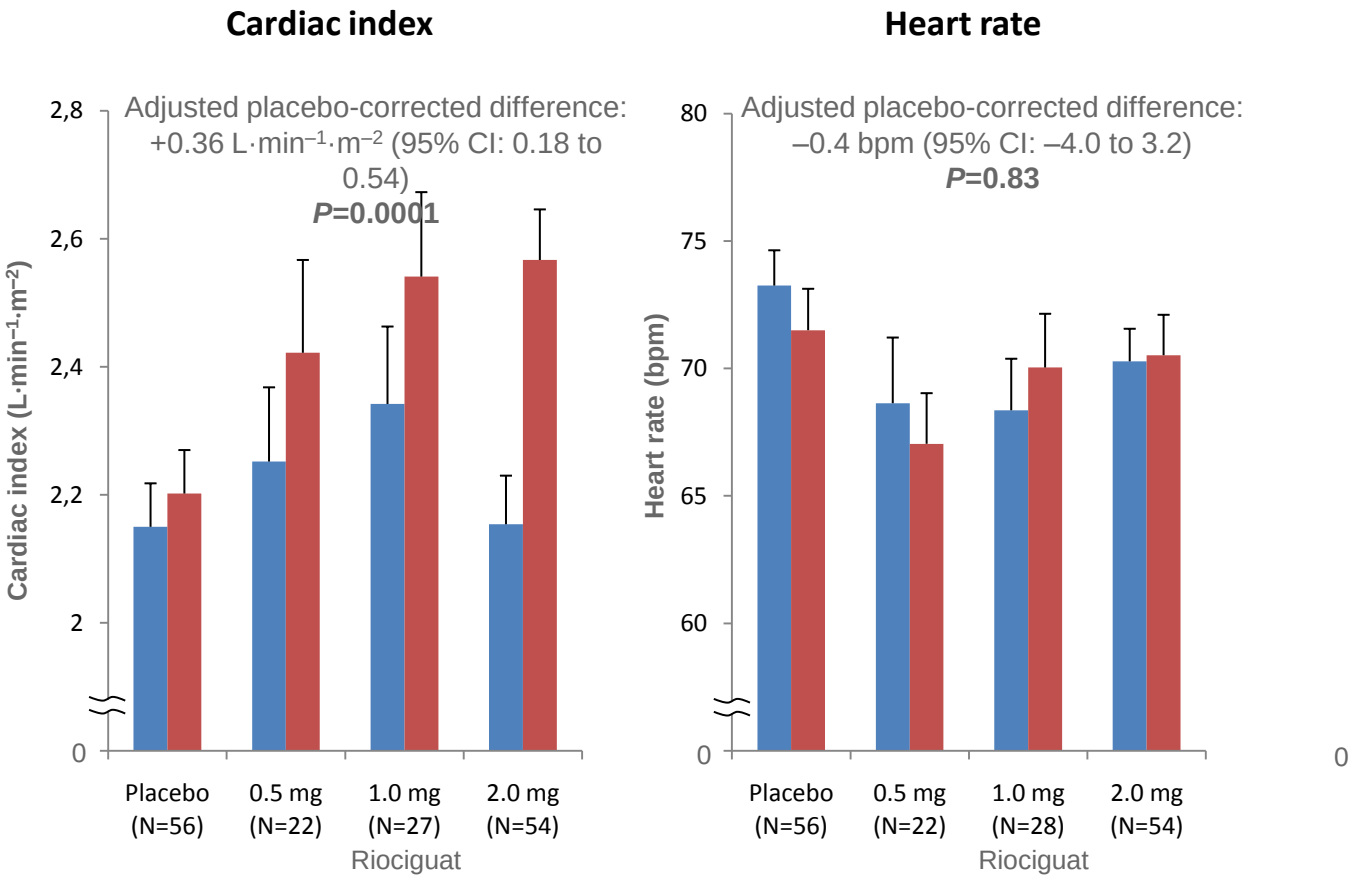
Redfield M, JAMA, 2013;309(12)

Insufficient soluble Guanylate Cyclase (sGC): an unmet mechanism in HFPEF



Desai A S, American Heart Journal, December 2011

Changes from baseline in cardiac index, heart rate, and MAP at 16 weeks



SOCRATES Study Program: parallel phase IIb studies with once daily oral sGC stimulator (coming Fall 2013)

	SOCRATES-REDUCED	***SOCRATES-PRESERVED***
Indication	HF with reduced EF (HFrEF)	HF with preserved EF (HFpEF)
LVEF	<45%	≥45%
Medical need	High event rates after hospitalization for HF despite standard treatment	No specific standard therapy approved
Evidence	Well tolerated cardiac index increase at 16 weeks Riociguat added to standard therapy in systolic HF and sec. PH (LEPHT)	• cGMP deficiency: causal role in HFPEF • Myocardial and vascular targets
Design	Parallel conduct of two dose finding ph IIb studies, each with 5 parallel arms (2 low doses and 2 with uptitration to higher doses) in patients stabilized after hospitalization for worsening chronic HF	

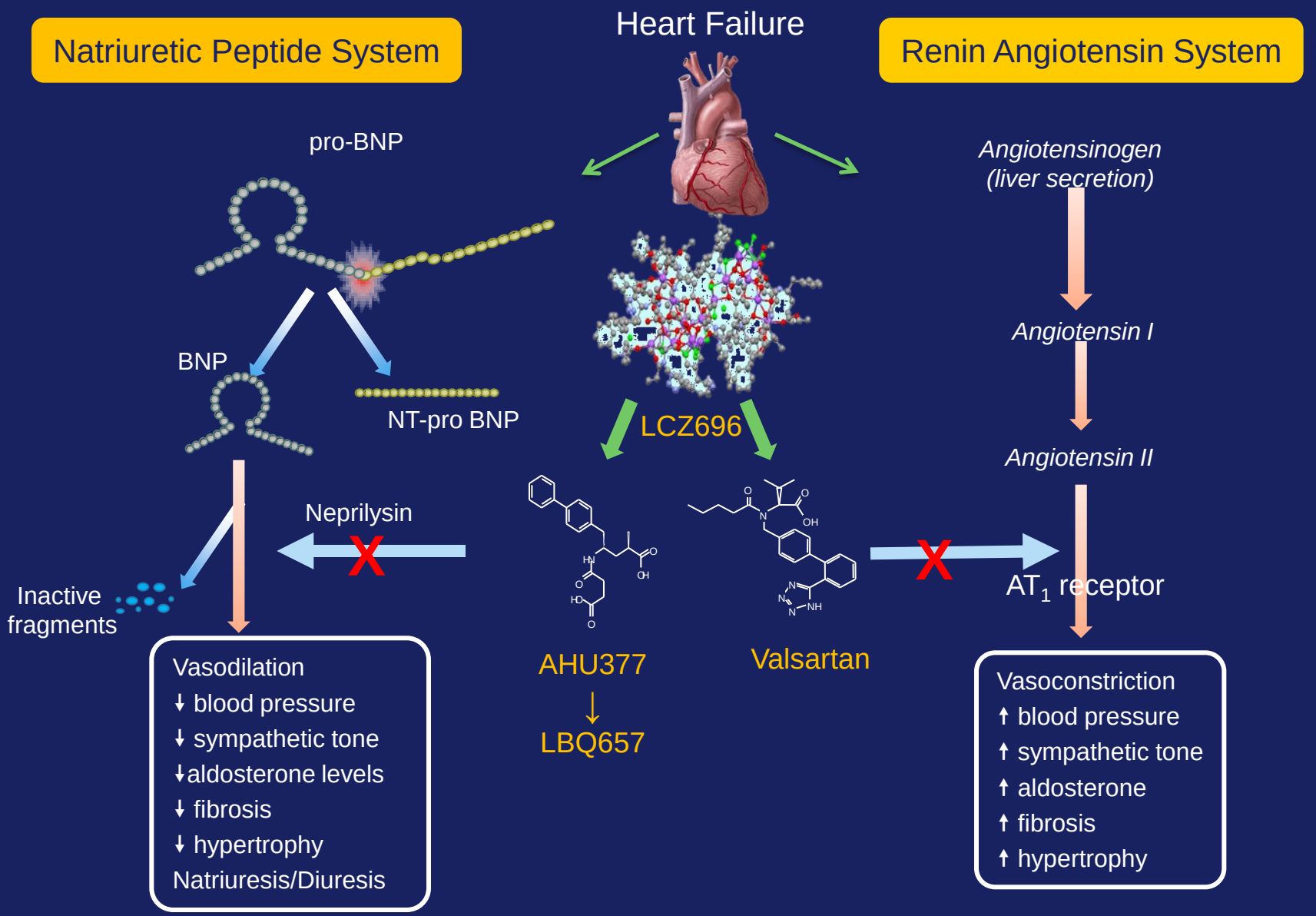
Neprilysin Inhibition – The PARAMOUNT Trial

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

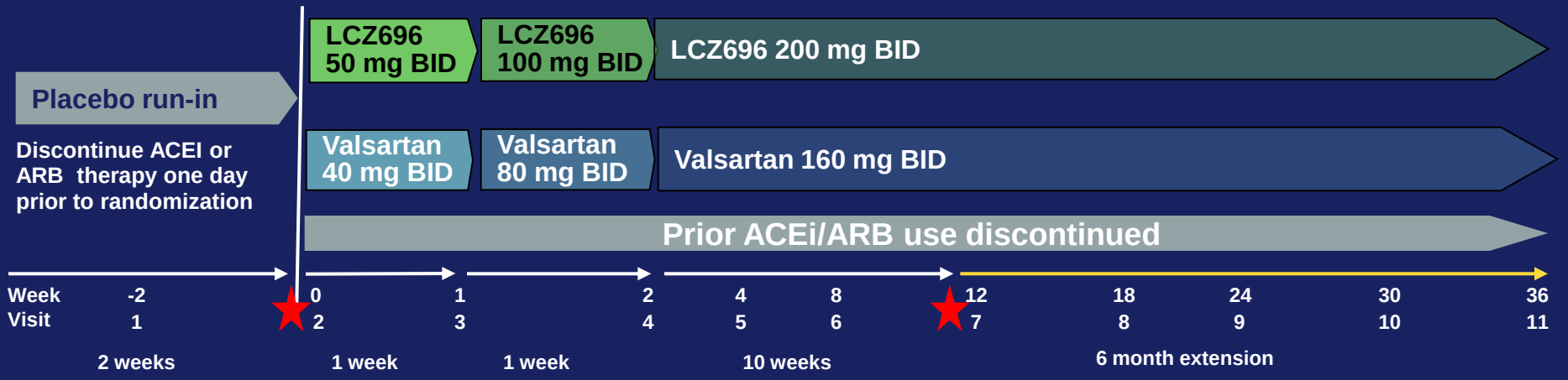
*Scott D Solomon, Michael Zile, Burkert Pieske, Adriaan Voors, Amil Shah, Elisabeth Kraigher-Krainer, Victor Shi, Toni Bransford, Madoka Takeuchi, Jianjian Gong, Martin Lefkowitz, Milton Packer, John J V McMurray, for the Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved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

Solomon S D, Lancet 2012;380:1387-95

LCZ696 – A First-in-Class Angiotensin Receptor Neprilysin Inhibitor



PARAMOUNT: Study Design

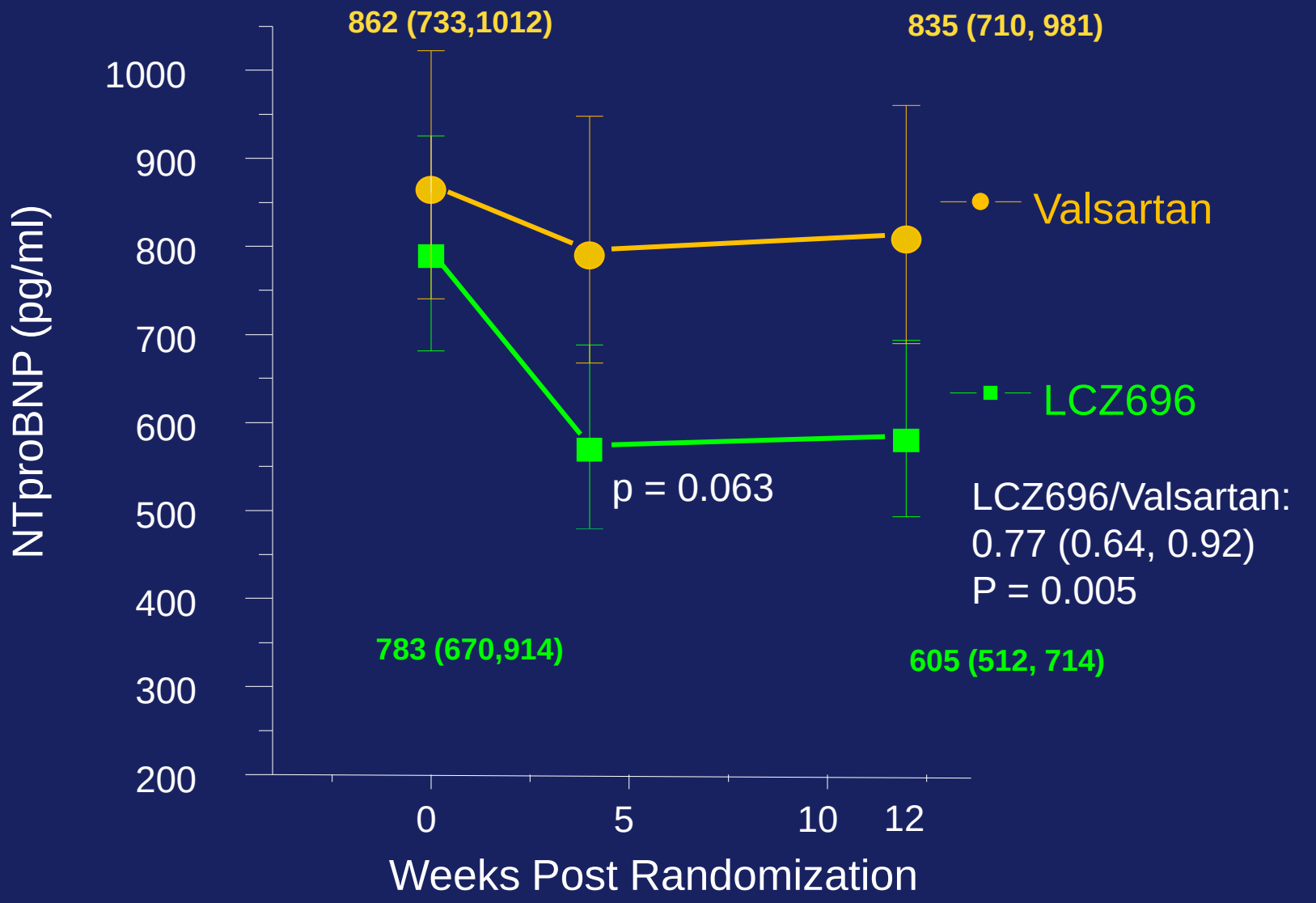


Primary objective	NT pro-BNP reduction from baseline at 12 weeks
Secondary objectives	▪ Echocardiographic measures of diastolic function, left atrial size, LV size and function, PASP ▪ HF symptoms, Clinical composite assessment and Quality of life (KCCQ) ▪ Safety and tolerability

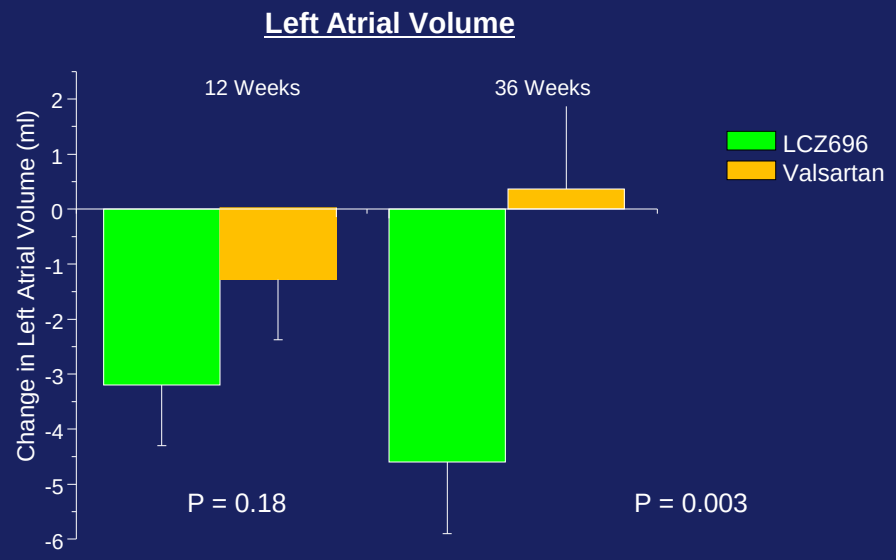
★ Baseline randomization visit and visit at end of 12 weeks of core study

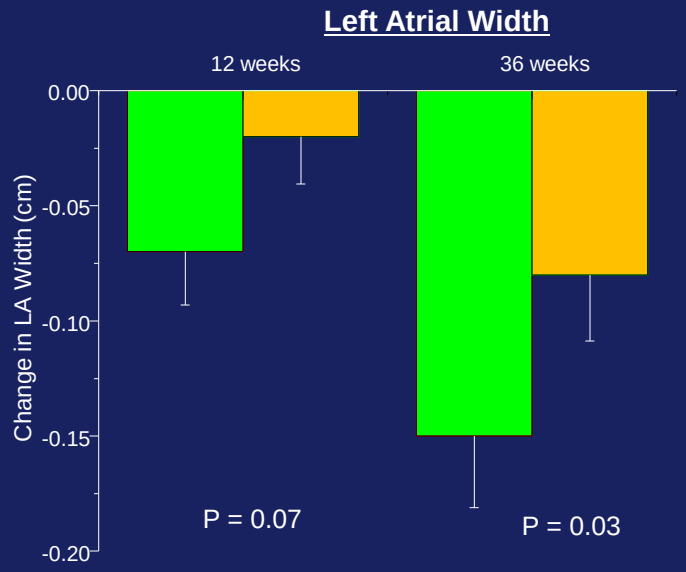
Clinicaltrials.gov NCT00887588

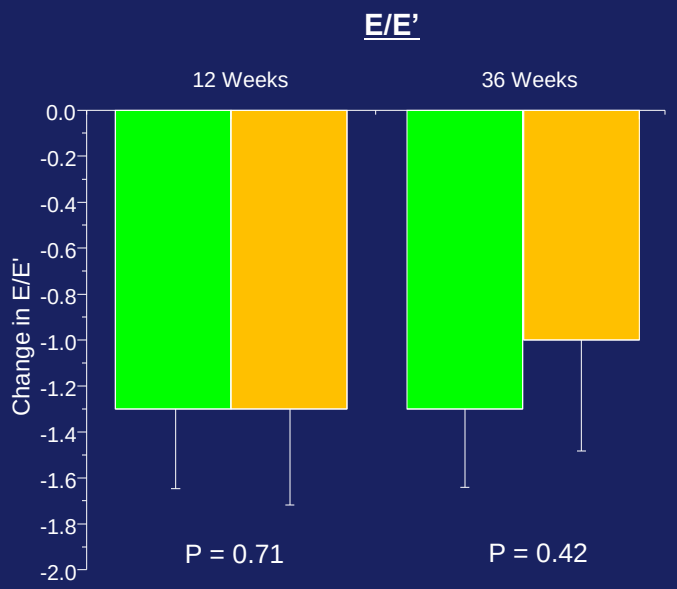
Primary Endpoint: NT-proBNP at 12 Weeks

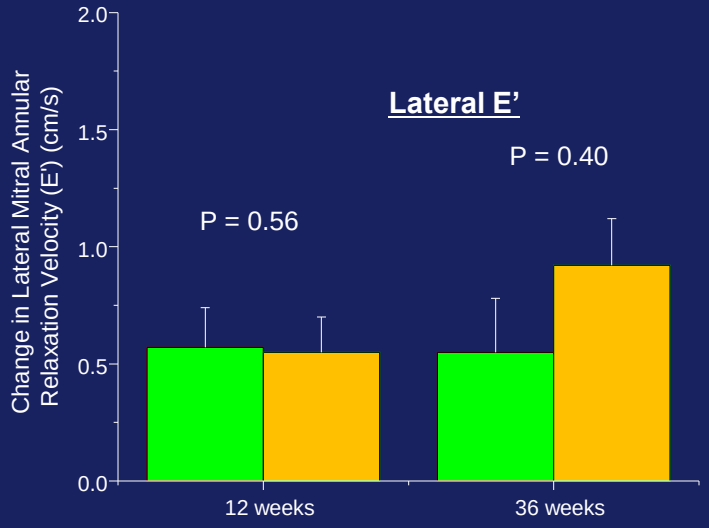


Changes in Key Echocardiographic Measures









No Significant Changes in LV volumes, Ejection Fraction, or LV mass at 12 or 36 weeks

MR Receptor Antagonism – Aldo-DHF

Effect of Spironolactone on Diastolic Function and Exercise Capacity in Patients With Heart Failure With Preserved Ejection Fraction

The Aldo-DHF Randomized Controlled Trial

Frank Edelmann, MD
Rolf Wachter, MD
Albrecht G. Schmidt, MD
Elisabeth Kraigher-Krainer, MD
Caterina Colantonio, MD
Wolfram Kamke, MD
André Duvinage, MD
Raoul Stahrenberg, MD
Kathleen Durstewitz, MD
Markus Löffler, MD
Hans-Dirk Düngen, MD
Carsten Tschöpe, MD
Christoph Herrmann-Lingen, MD
Martin Halle, MD
Gerd Hasenfuss, MD
Götz Gelbrich, PhD
Burkert Pieske, MD
for the Aldo-DHF Investigators

Importance Diastolic heart failure (ie, heart failure with preserved ejection fraction) is a common condition without established therapy, and aldosterone stimulation may contribute to its progression.

Objective To assess the efficacy and safety of long-term aldosterone receptor blockade in heart failure with preserved ejection fraction. The primary objective was to determine whether spironolactone is superior to placebo in improving diastolic function and maximal exercise capacity in patients with heart failure with preserved ejection fraction.

Design and Setting The Aldo-DHF trial, a multicenter, prospective, randomized, double-blind, placebo-controlled trial conducted between March 2007 and April 2012 at 10 sites in Germany and Austria that included 422 ambulatory patients (mean age, 67 [SD, 8] years; 52% female) with chronic New York Heart Association class II or III heart failure, preserved left ventricular ejection fraction of 50% or greater, and evidence of diastolic dysfunction.

Intervention Patients were randomly assigned to receive 25 mg of spironolactone once daily (n=213) or matching placebo (n=209) with 12 months of follow-up.

Main Outcome Measures The equally ranked co–primary end points were changes in diastolic function (E/e') on echocardiography and maximal exercise capacity (peak Vo_2) on cardiopulmonary exercise testing, both measured at 12 months.

Results Diastolic function (E/e') decreased from 12.7 (SD, 3.6) to 12.1 (SD, 3.7) with spironolactone and increased from 12.8 (SD, 4.4) to 13.6 (SD, 4.3) with placebo (adjusted mean difference, −1.5; 95% CI, −2.0 to −0.9; $P<.001$). Peak Vo_2 did not significantly change with spironolactone vs placebo (from 16.3 [SD, 3.6] mL/min/kg to 16.8 [SD, 4.6] mL/min/kg and from 16.4 [SD, 3.5] mL/min/kg to 16.9 [SD, 4.4] mL/min/kg, respectively; adjusted mean difference, +0.1 mL/min/kg; 95% CI, −0.6 to +0.8 mL/min/kg; $P=.81$). Spironolactone induced reverse remodeling (left ventricular mass index declined; difference, −6 g/m²; 95% CI, −10 to−1 g/m²; $P=.009$) and improved neuroendocrine activation (N-terminal pro–brain-type natriuretic peptide geometric mean ratio, 0.86; 95% CI, 0.75-0.99; $P=.03$) but did not improve heart failure symptoms or quality of life and slightly reduced 6-minute walking distance (–15 m; 95% CI, –27 to –2 m; $P=.03$). Spironolactone also modestly increased serum potassium levels (+0.2 mmol/L; 95% CI, +0.1 to +0.3; $P<.001$) and decreased estimated glomerular filtration rate (−5 mL/min/1.73 m²; 95% CI, −8 to −3 mL/min/1.73 m²; $P<.001$) without affecting hospitalizations.

Conclusions and Relevance In this randomized controlled trial, long-term aldosterone receptor blockade improved left ventricular diastolic function but did not affect maximal exercise capacity, patient symptoms, or quality of life in patients with heart failure with preserved ejection fraction. Whether the improved left ventricular function observed in the Aldo-DHF trial is of clinical significance requires further investigation in larger populations.

Trial Registration clinicaltrials.gov Identifier: ISRCTN94726526; Eudra-CT No: 2006-002605-31

JAMA. 2013;309(8):781-791 www.jama.com

HEART FAILURE (HF) WITH preserved ejection fraction (EF) accounts for more than 50% of the total HF population.[1] Community-based cohort studies have shown that mortality rates are similar in HF with preserved EF compared with HF with reduced EF,[1] but data from large clinical trials point toward a better outcome in HF with preserved EF. This may indicate that comorbidities that are typically excluded in trials may contribute to the poor prognosis in HF with preserved EF.[1-6] Left ventricular diastolic dysfunction and adverse cardiac remodeling are considered major

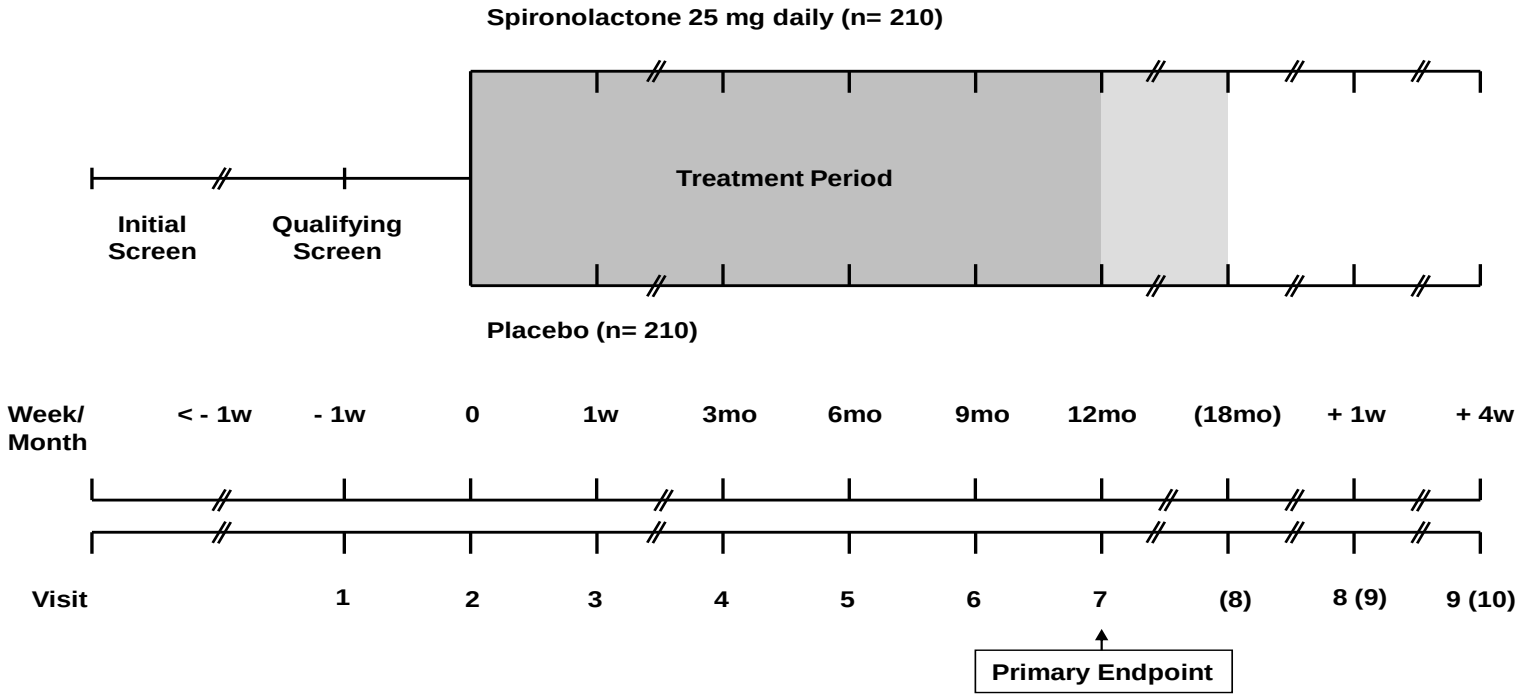
For editorial comment see p 825.

Author Affiliations are listed at the end of this article.
A complete list of the Aldo-DHF Investigators appears in the eAppendix.
Corresponding Author: Burkert Pieske, MD, Department of Cardiology, Medical University Graz, Auenbruggerplatz 15, A-8010 Graz, Austria (burkert.pieske@medunigraz.at).

Edelmann F,.. Pieske B. JAMA 2013; February 27, 2013-Vol 309, No.8

Aldo-DHF Study Design

Multicenter, randomised, placebo-controlled double-blind, two-armed parallel-group study

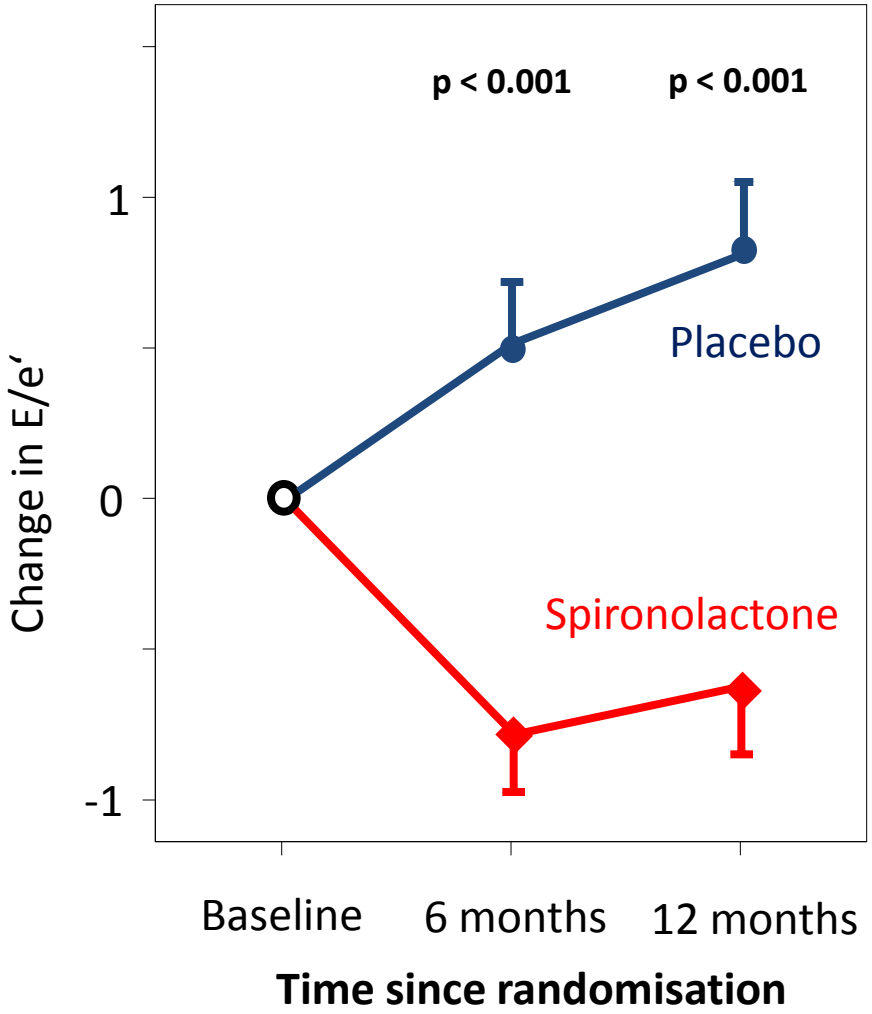


Equally ranked co-primary endpoints: Change in diastolic function (E/é) and maximal exercise capacity (peak VO_2) after 12 months for spironolactone compared to placebo.

Secondary endpoints: Changes in other echocardiographic measures of cardiac function and structure; Changes in other measures of exercise capacity; Neuroendocrine activation; HF symptoms; Quality of life; Safety and tolerability of study medication.

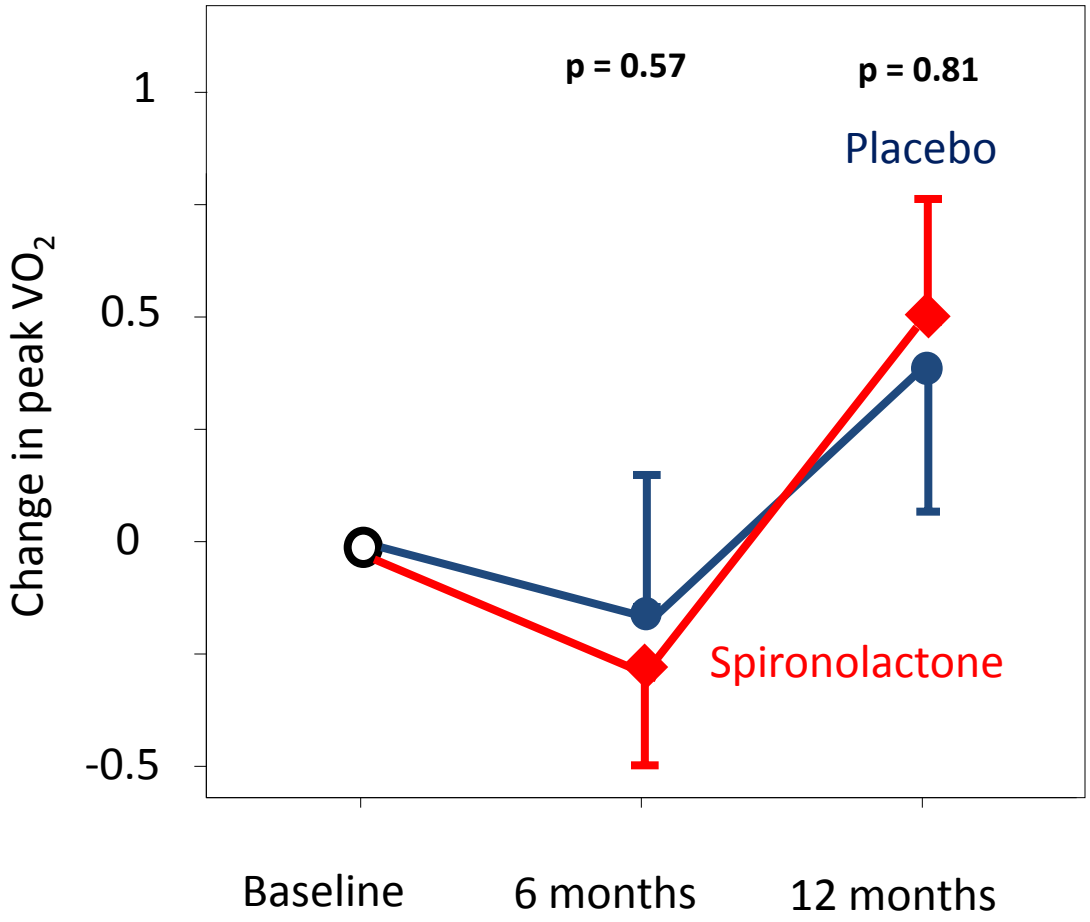
Primary endpoint - E/é

Spironolactone: 12.7±3.6 to 12.1±3.7
Placebo: 12.8±4.4 to 13.6±4.3
(**P<0.001** for difference between groups)



Primary endpoint - peak VO_2

Spironolactone: 16.3±3.6 to 16.8±4.6mL/min/kg
Placebo: 16.4±3.5 to 16.9±4.4mL/min/kg
(**P=0.67** for difference between groups)



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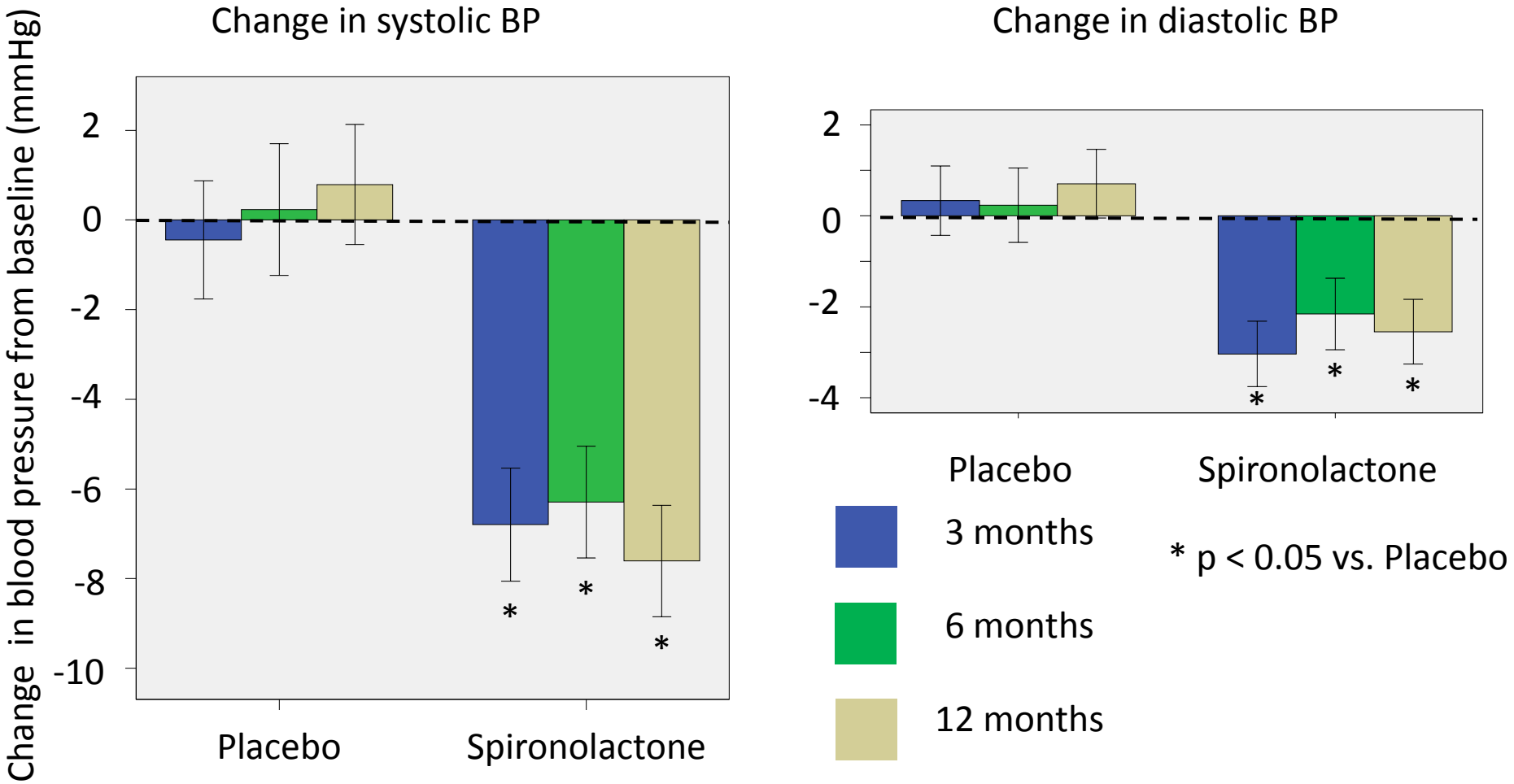
Blood Pressure (BP)



Results for functional and structural reverse remodelling remained significant after adjusting for blood pressure effects

TOPCAT: Trial Design

Desai A S, American Heart Journal, 2011

- **AGE ≥ 50 YRS**
- **EF ≥ 45% WITHIN 6 MONTHS**
- **HEART FAILURE SYMPTOMS AND SIGNS**
- **CONTROLLED SYSTOLIC BP (< 140 mm Hg)***
- **SERUM K^+ ≤ 5.0 MMOL/L**

PLUS ONE OF THE FOLLOWING:

- **HF HOSPITALIZATION WITHIN 12 MONTHS**
- **BNP ≥ 100 PG/ML**
- **N-TERMINAL PRO-BNP ≥ 360 PG/ML**

N=3500

RANDOMIZE

PLACEBO 15 MG	**SPIRONOLACTONE 15 MG**

Week 0

DOSE TITRATION (TARGET 30 MG)
**** Optional Titration to 45 mg at 4 mos***

Week 4

COMPOSITE PRIMARY ENDPOINT
CV death, Aborted cardiac arrest, Hospitalization for management of HF

~ 3.25 yrs

Emerging Therapies

1. Pharmacological management

   Ivabradine

   PDE-5 Inhibition

   Guanylate cyclase stimulation

   Neprilysin Inhibition

   MR antagonists

2. Interventions and Devices

   Renal Denervation

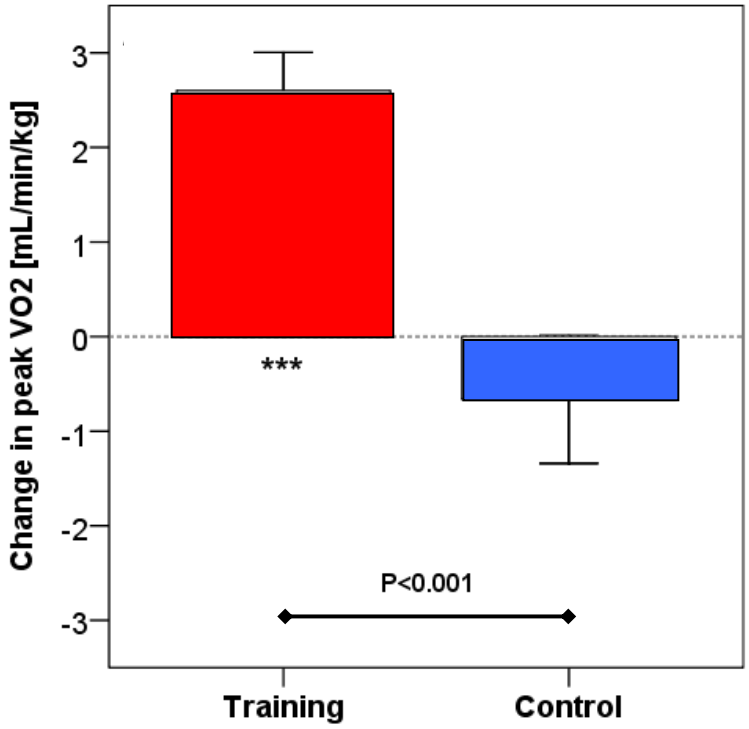
   Interatrial Shunting

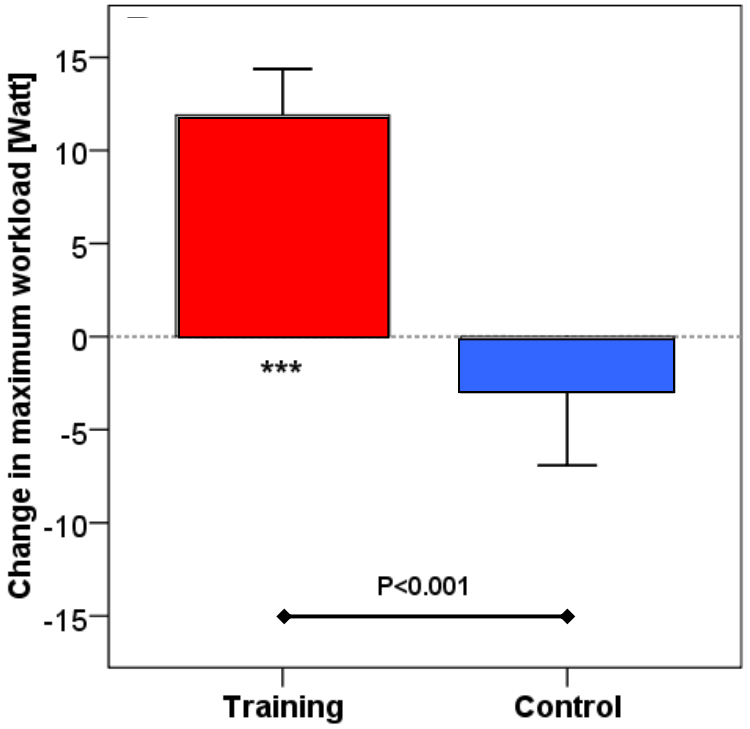
3. Physical acitvity and Exercise

Results: Exercise Capacity

Primary Endpoint: peak VO2

Maximum Workload

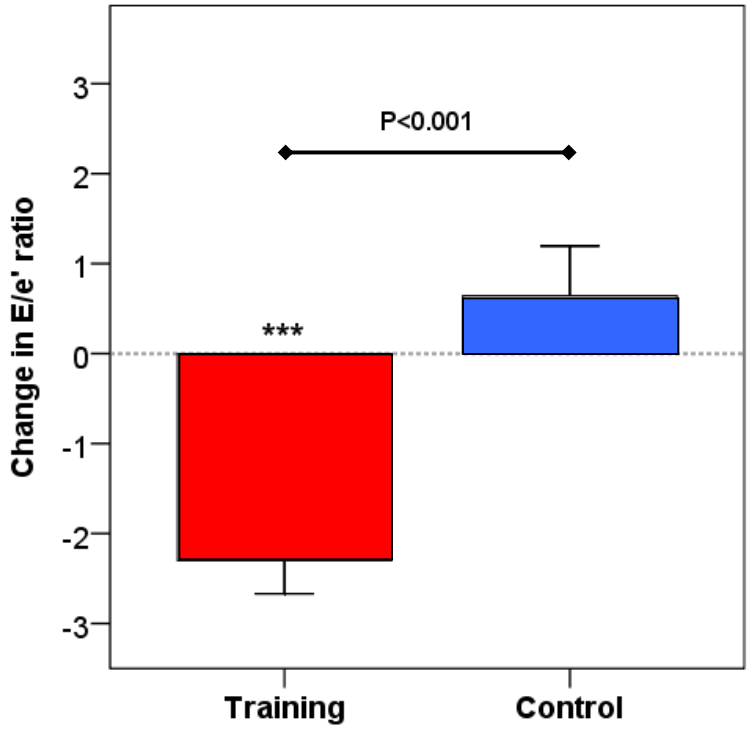




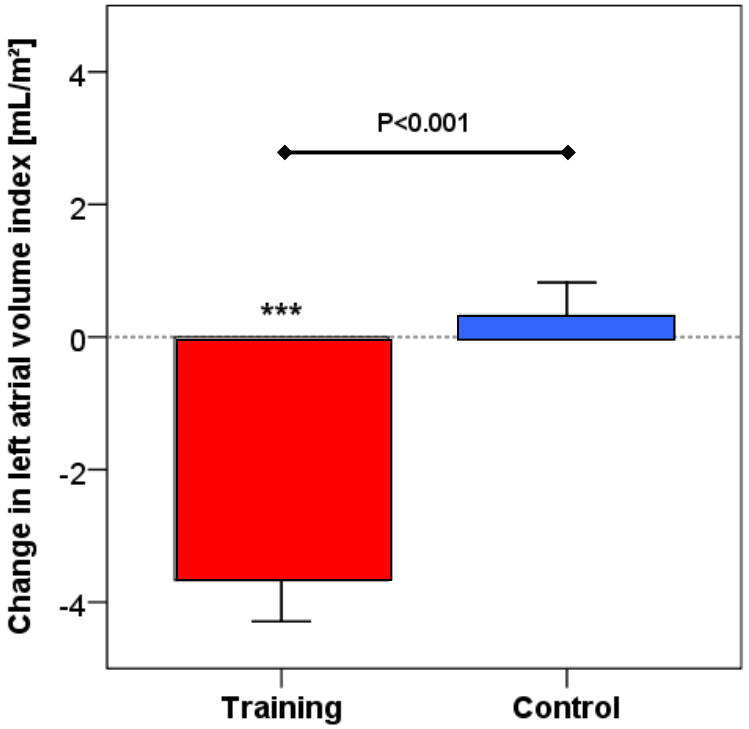
Edelmann F & Pieske B, JACC 2011;

Diastolic Function & LA remodeling

Change in E/é Ratio



Change in LA Volume Index



Summary I

1. 50% of HF patients have HFPEF

1. Pathophysiology/Etiology is complex and multifactorial, comorbidities can contribute

2. Diagnosis?: EF>50% + objective evidence of diastolic dysfunction. Biomarkers? Stress test?

1. General management: Loop diuretics, risk factor control

Summary II

1. No established targeted therapy for HFPEF

2. New pharmacological approaches under investigation:

    Ivabradine (Phase II: Start 2013)
    Soluble Guanlyte cyclase stimulation (Phase II: Start 2013)
    Neprilysin inhibition (Phase III: Start 2013)
    MR Antagonists (Phase III: Ongoing)

3. New devices and interventions

4. Physical acivity and exercise training (Phase II: Ongoing)