Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης
Α΄ Καρδιολογική Κλινική ΑΧΕΠΑ
Ιατρείο Πνευμονικής Υπέρτασης

Hot topics in pulmonary hypertension (group 2 and 3)

Καρδιακή ανεπάρκεια με διατηρημένο κλάσμα εξώθησης

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Conflicts of interest

Honoraria for lectures or Advisory boards

- Actelion Pharmaceuticals Ltd
- Bayer Healthcare
- Boehringer Ingelheim
- GlaxoSmithKline
- ELPEN
- GENESIS Pharma
- Lilly
- MSD
- Novartis
- Pfizer
- Servier
- United Therapeutics

HFpEF = a misunderstood disease in search of a therapy

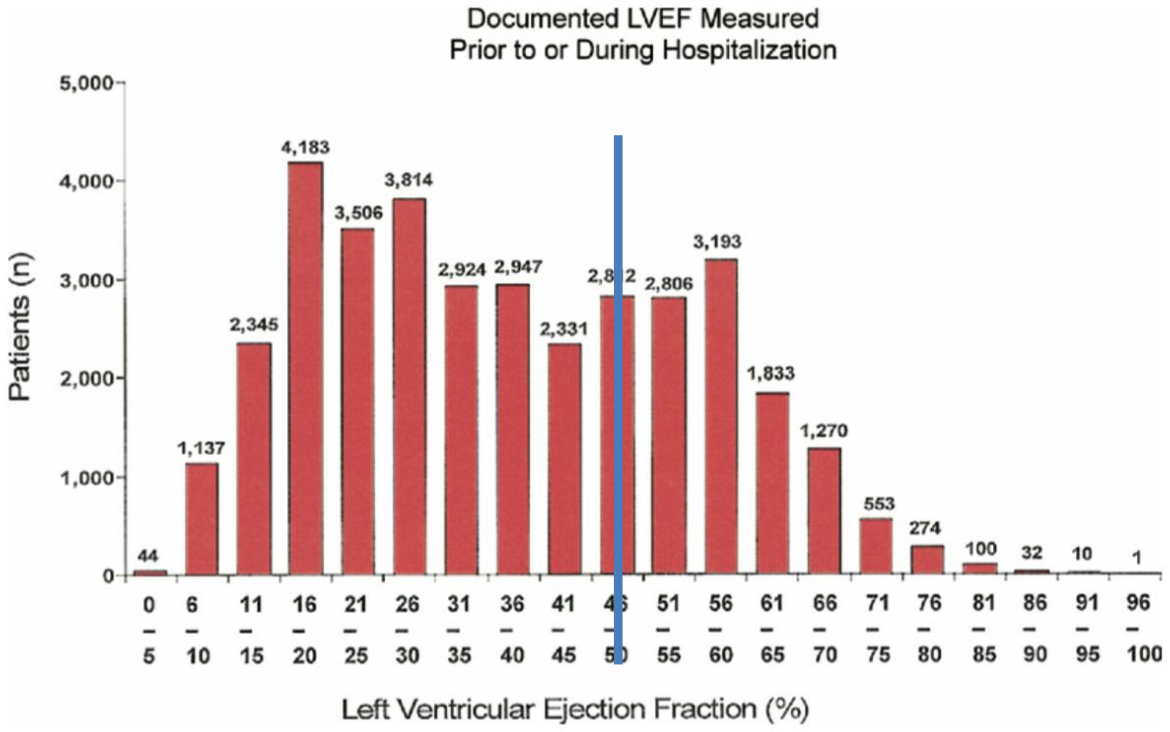
Heart Failure Definition

- The inability to provide adequate cardiac output to the body at rest or with exertion, or to do so only in the setting of elevated cardiac filling pressures
  - E. Braunwald modified by B. Borlaug and M. Redfield

- Clinically: A clinical syndrome characterized by breathlessness, fatigue and edema caused by an abnormality of the heart

Borlaug BA et al. Nat Rev Cardiol 2014

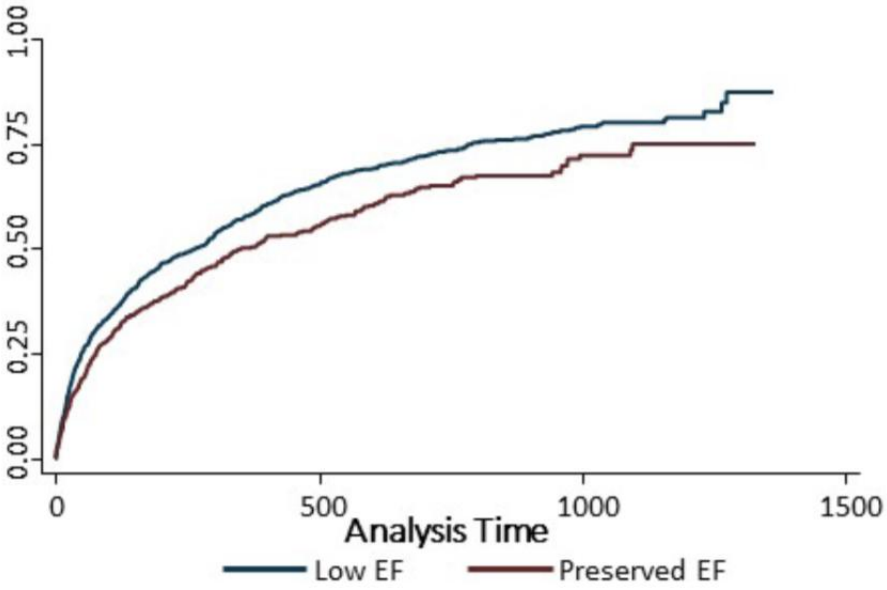
30 - 50% of all HF admissions



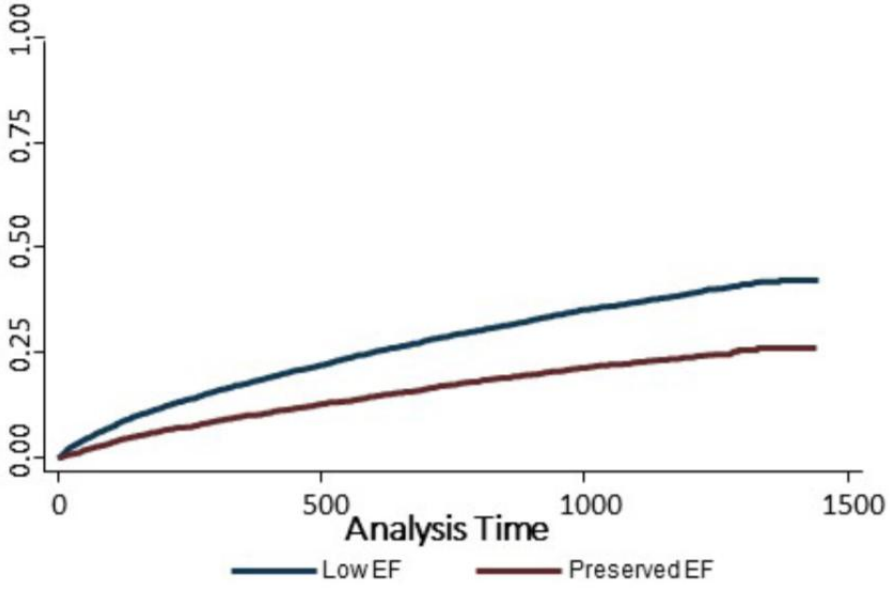
Fonarow GC et al. J Am Coll Cardiol 200

Patients Hospitalized With HF and HFpEF Have Similar Morbidity/Mortality as HFrEF

Time to Death/HF Hosp after a Hospitalization

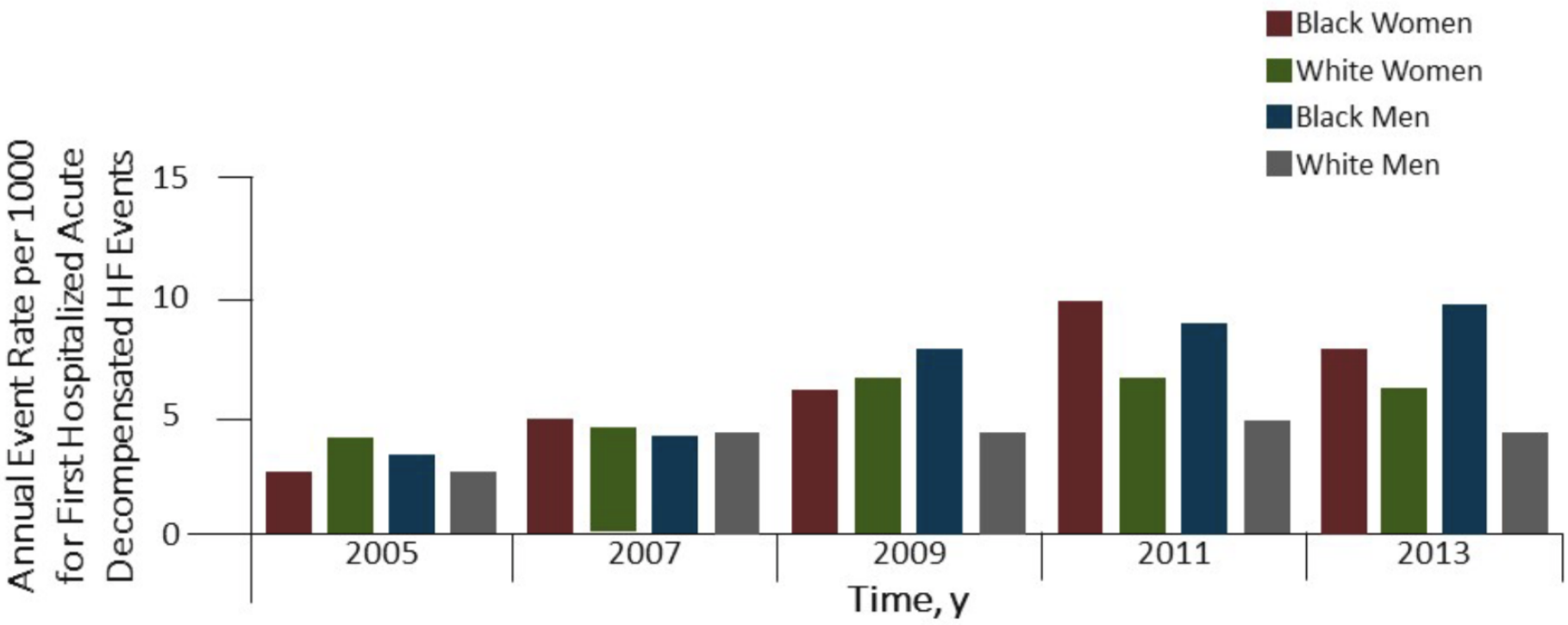


Time to Death/HF Hosp



Bello NA, et al. *Circ Heart Fail.* 2014;7:590-595.

HFpEF Is Increasing in Prevalence



Chang PP, et al. *Circulation*. 2018;138:12-24.

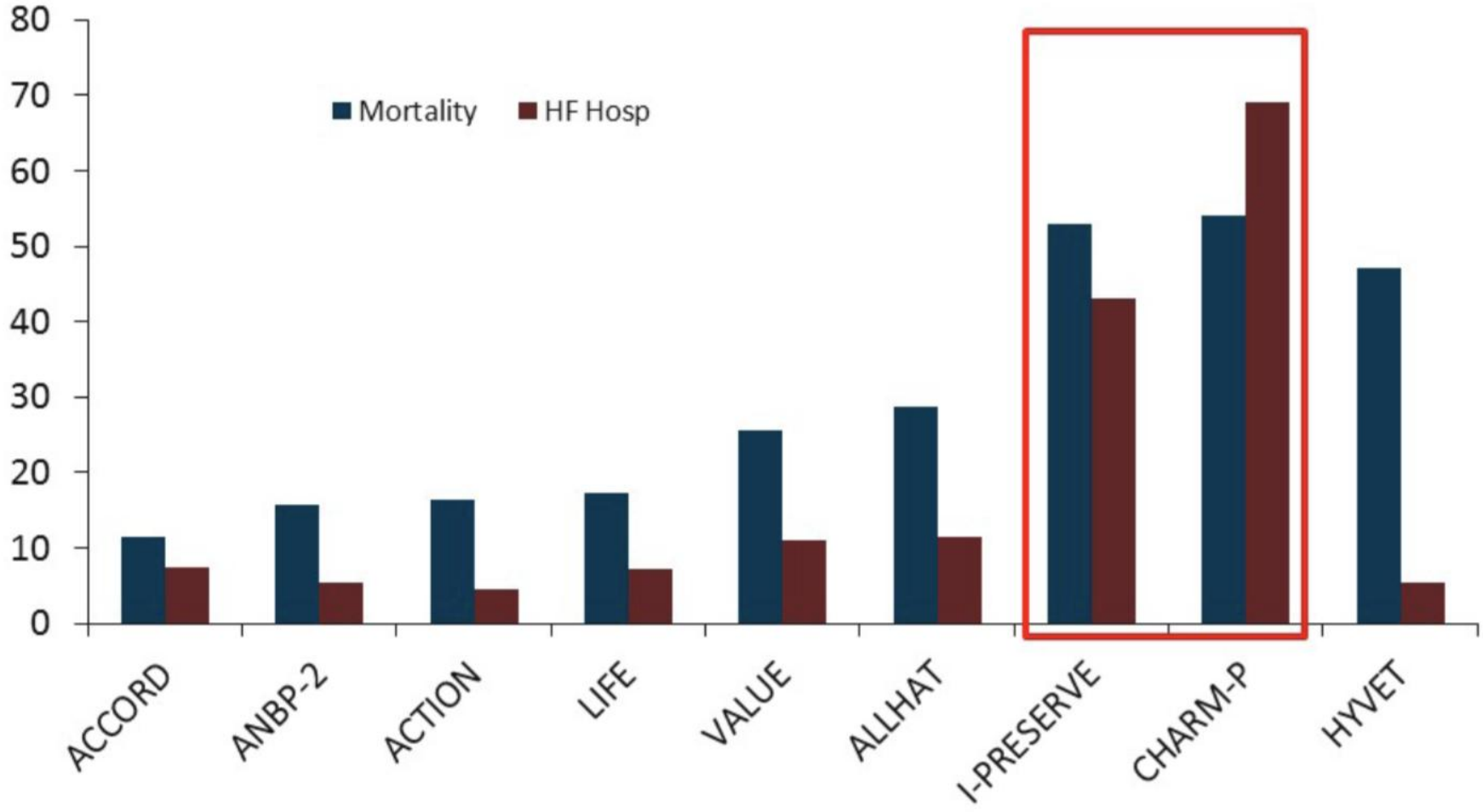
Presence of Comorbidities in HFpEF

	HFrEF	HFpEF	*P* value
Age (SD)	71.8 (12)	75.4 (11.5)	< .001
Hypertension, %	49.2	55.1	.005
Atrial Fibrillation, %	23.6	31.8	< .001
COPD, %	13.2	17.7	.002
Anemia, %	9.9	21.1	< .001

Please consult publication for full list of contributing factors

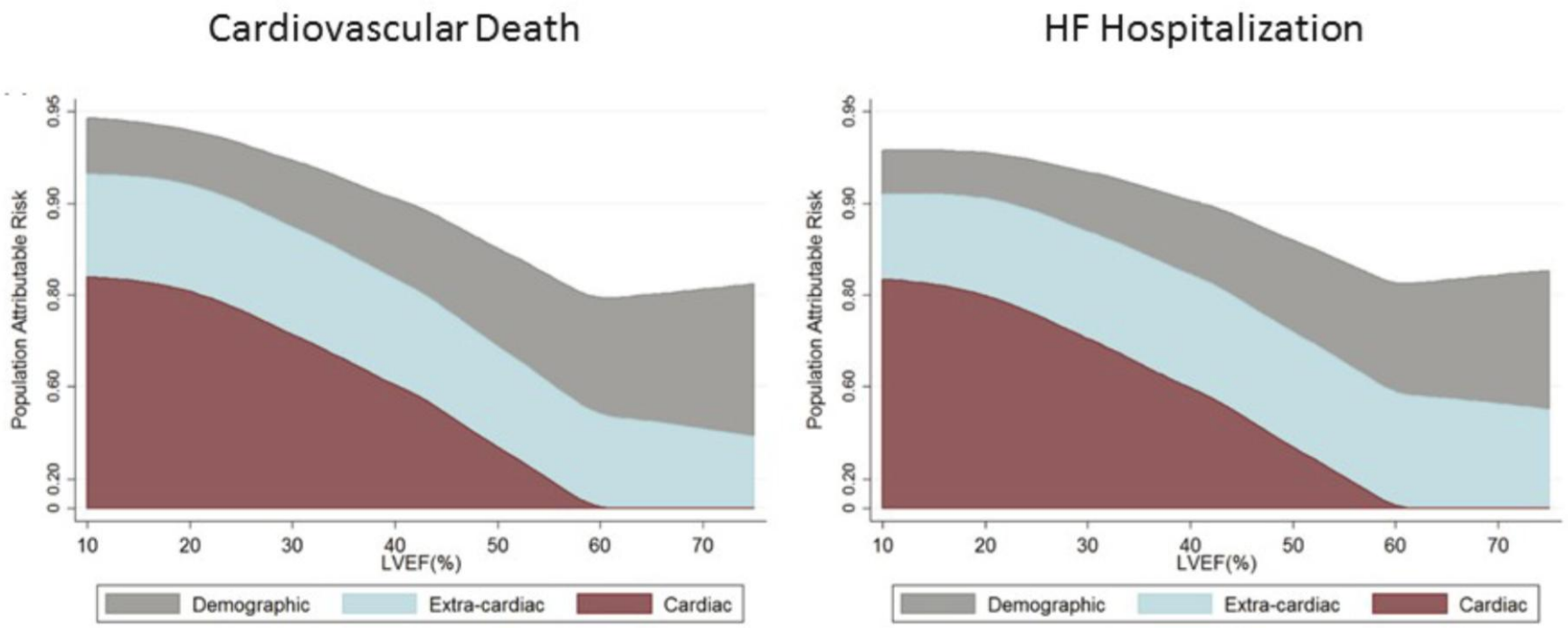
Bhatia RS, et al. *N Eng J Med*. 2006;355:260-269.

HF Hospitalization and Mortality Higher in HFpEF Than in Studies of Similar Comorbidity

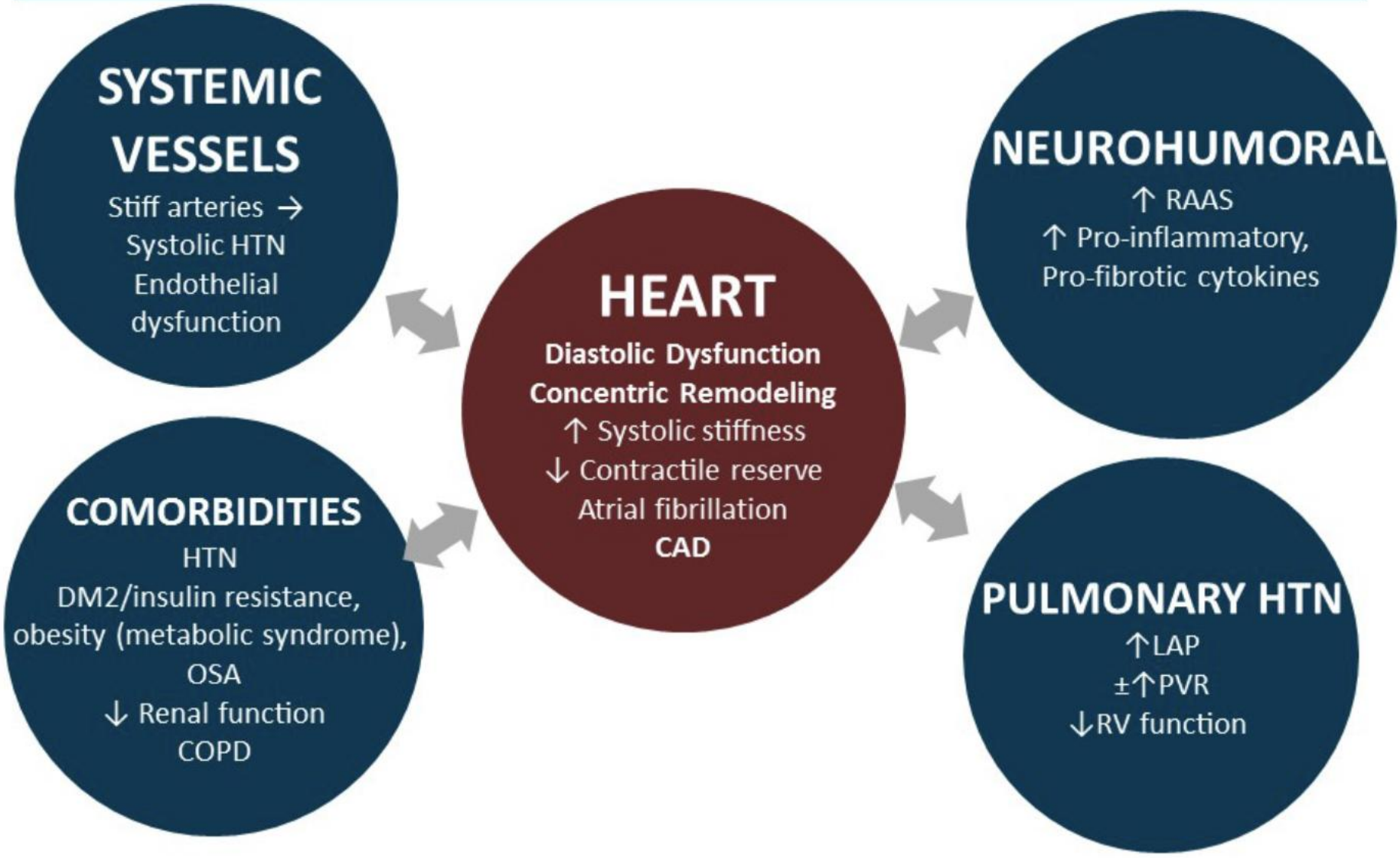


Campbell RT, et al. *Heart Fail Clin*. 2014;10:481-501.

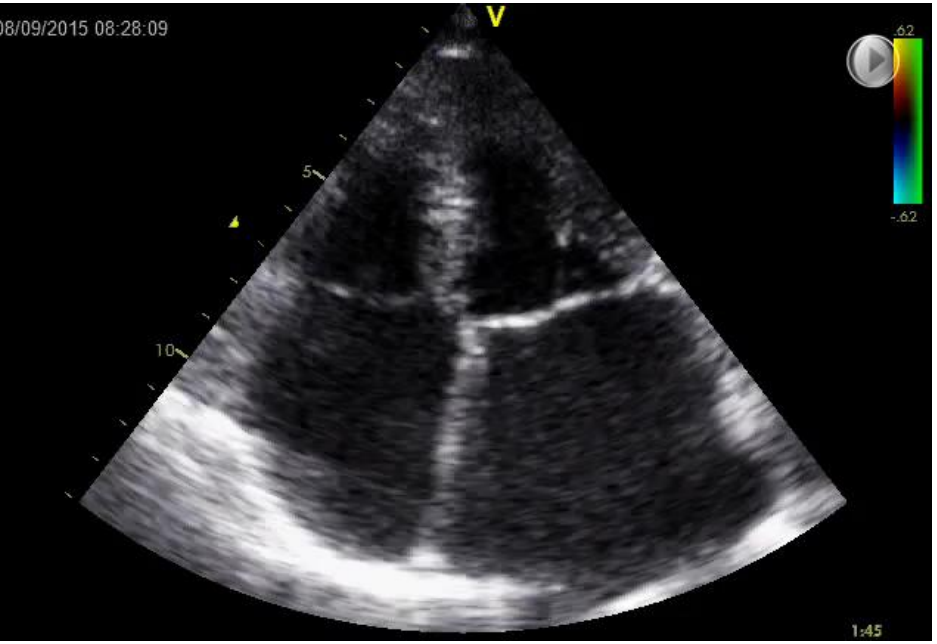
Attributable Risk in Patients With HF



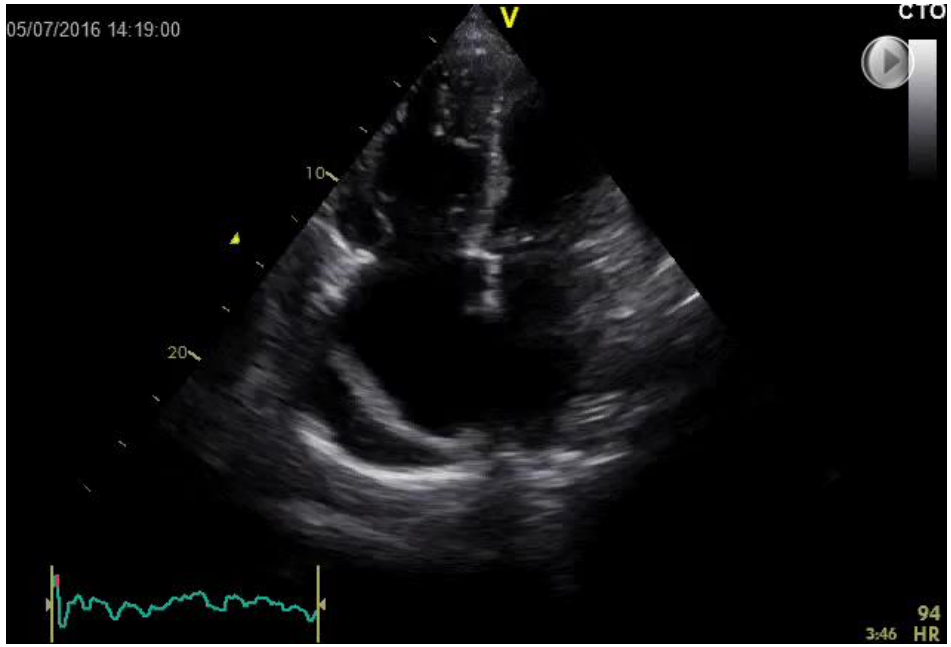
Pathophysiology of HFpEF



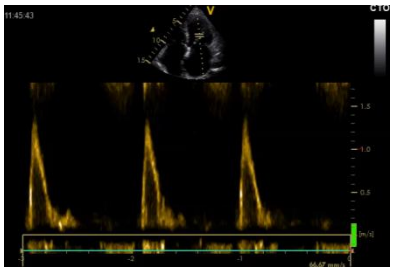
HFpEF: different phenotypes



74 year-old lady with chronic Afib
RVSP=38mmHg



62 year-old lady with chronic Afib
RVSP=78mmHg
Negative V/Q scan
Normal lung function

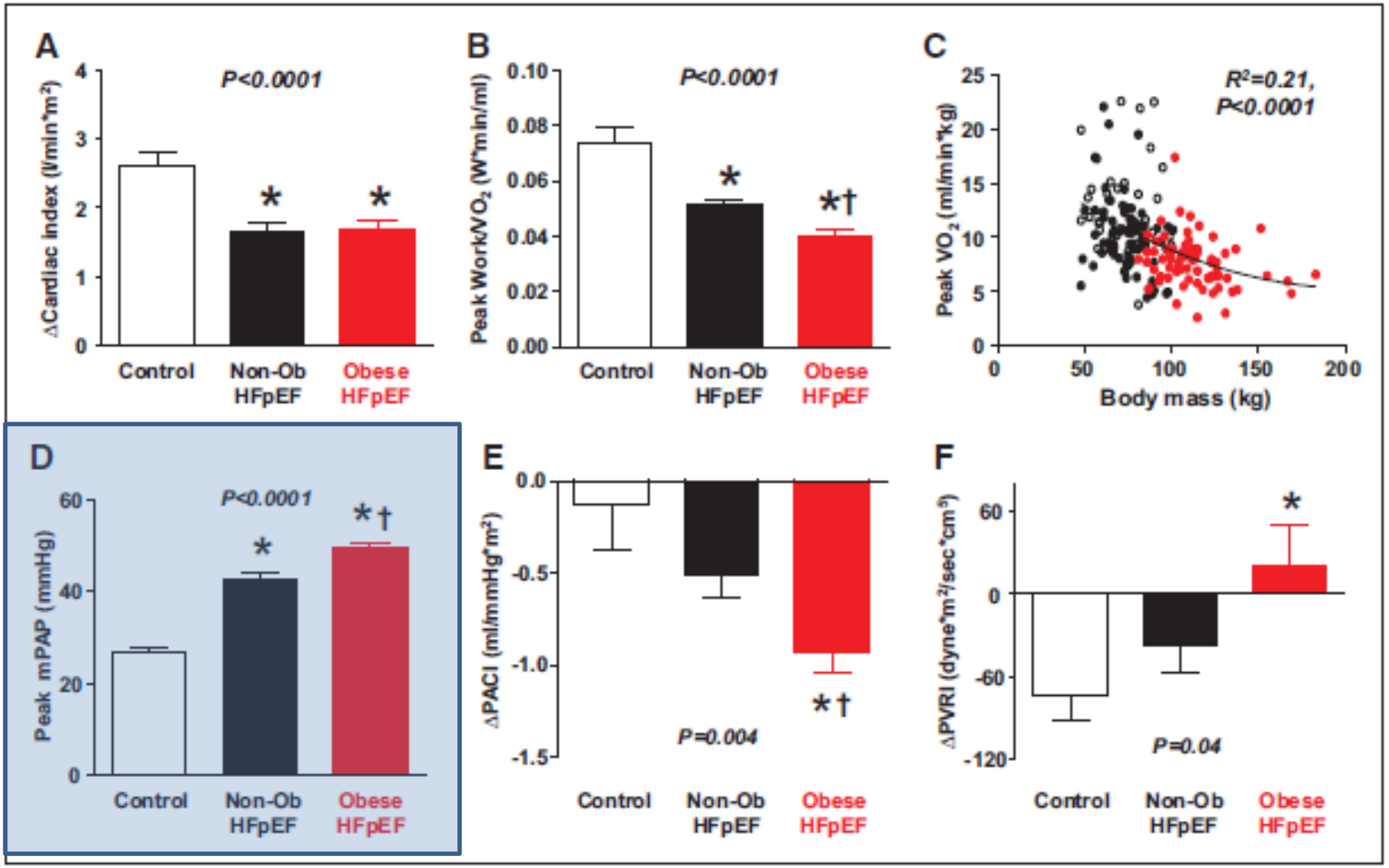


Phenotyping patients into pathophysiologically homogeneous groups may enable better targeting of treatment.

Evidence Supporting the Existence of a Distinct Obese Phenotype of Heart Failure With Preserved Ejection Fraction

Obokata M, et al. *Circulation. 2017.*

Exercise capacity and hemodynamic reserve is reduced in obese heart failure with preserved ejection fraction (HFpEF)



Diastolic dysfunction in HFpEF: Potential mechanisms

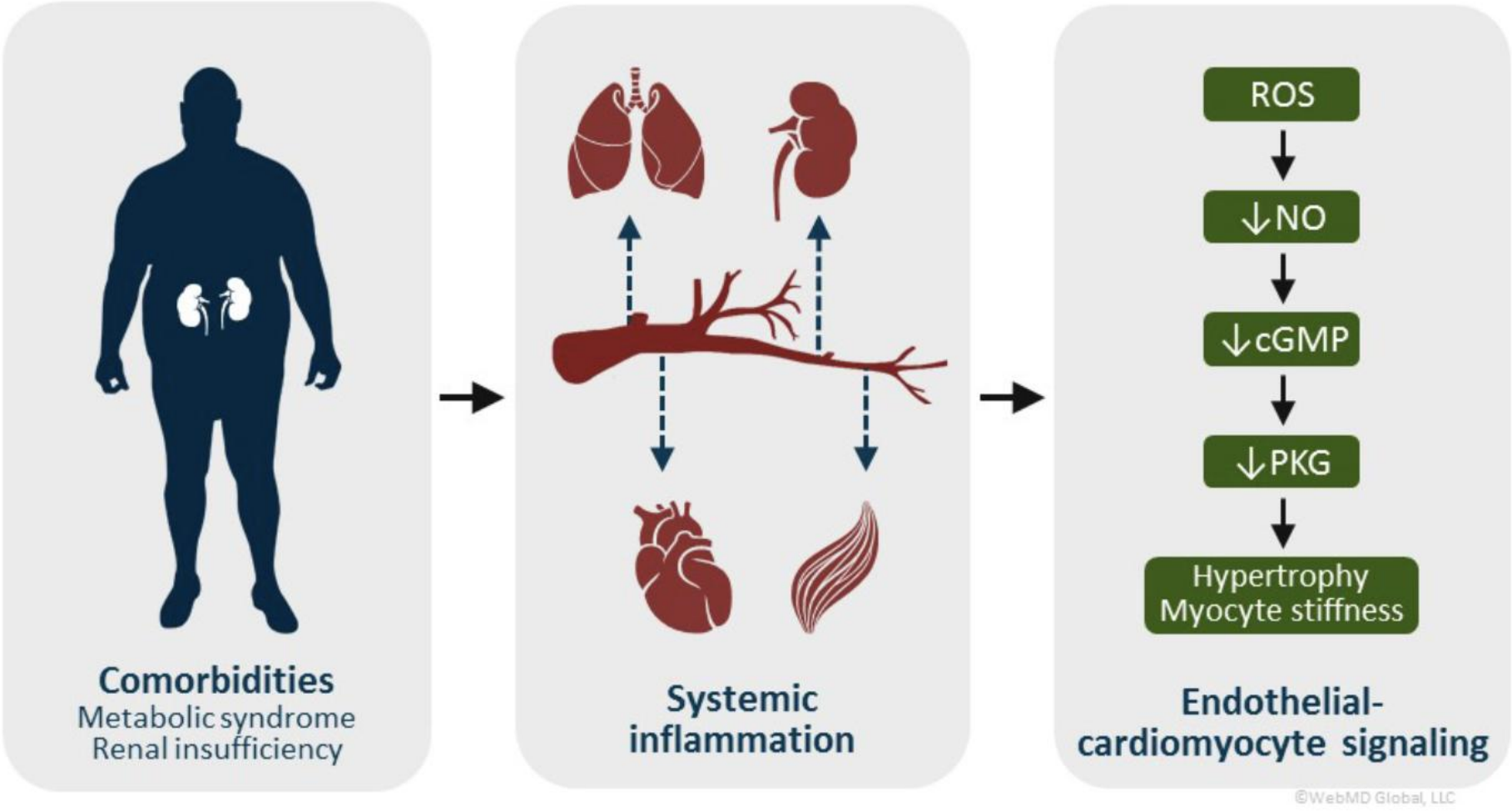
- Dysfunctional calcium handling
- Abnormalities in spring-like titin protein
- Myocardial fibrosis

Borlaug BA, et al. Eur Heart J. 2011

- Lower PKG and cGMP activity with increased oxidative stress

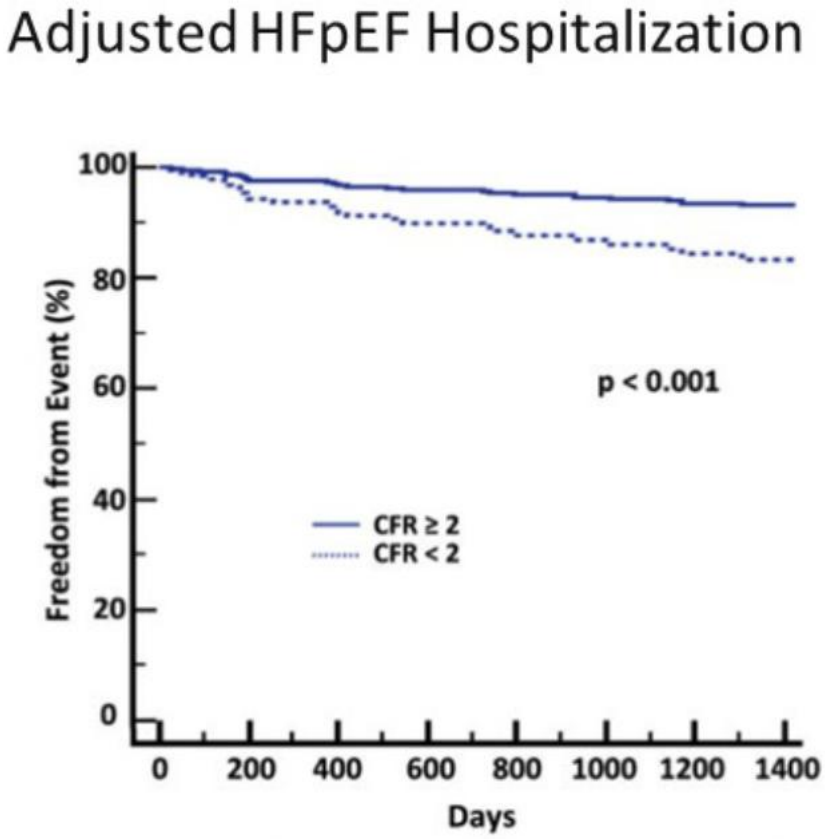
Greene SJ et al. JAHA 2013x

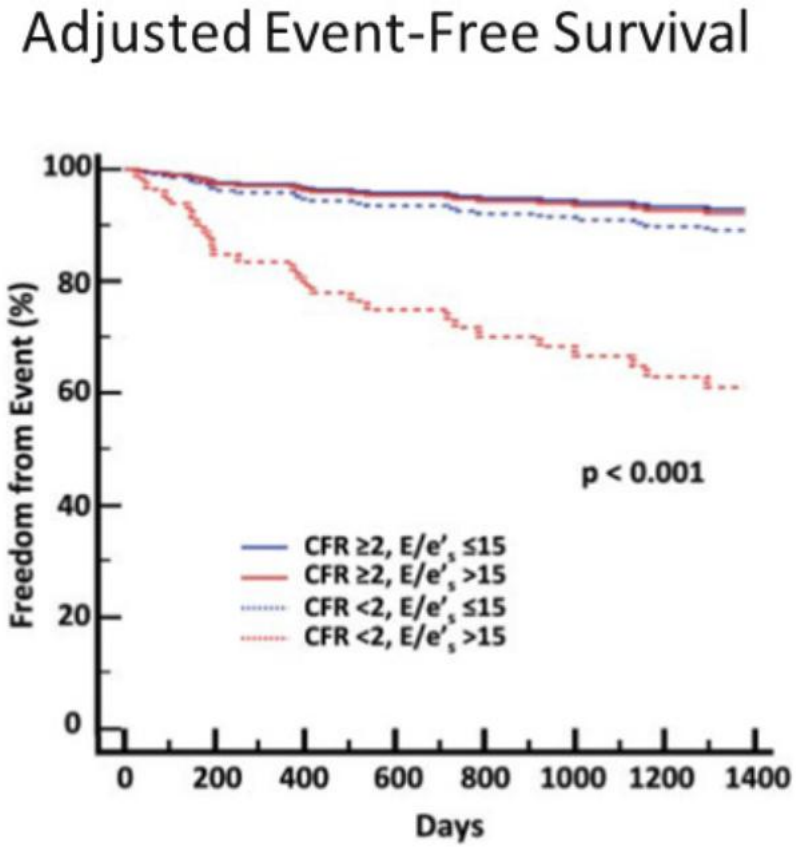
Potential role of inflammation in HFpEF



Shah S et al. Circulation 2016

Coronary microvascular dysfunction in HFpEF





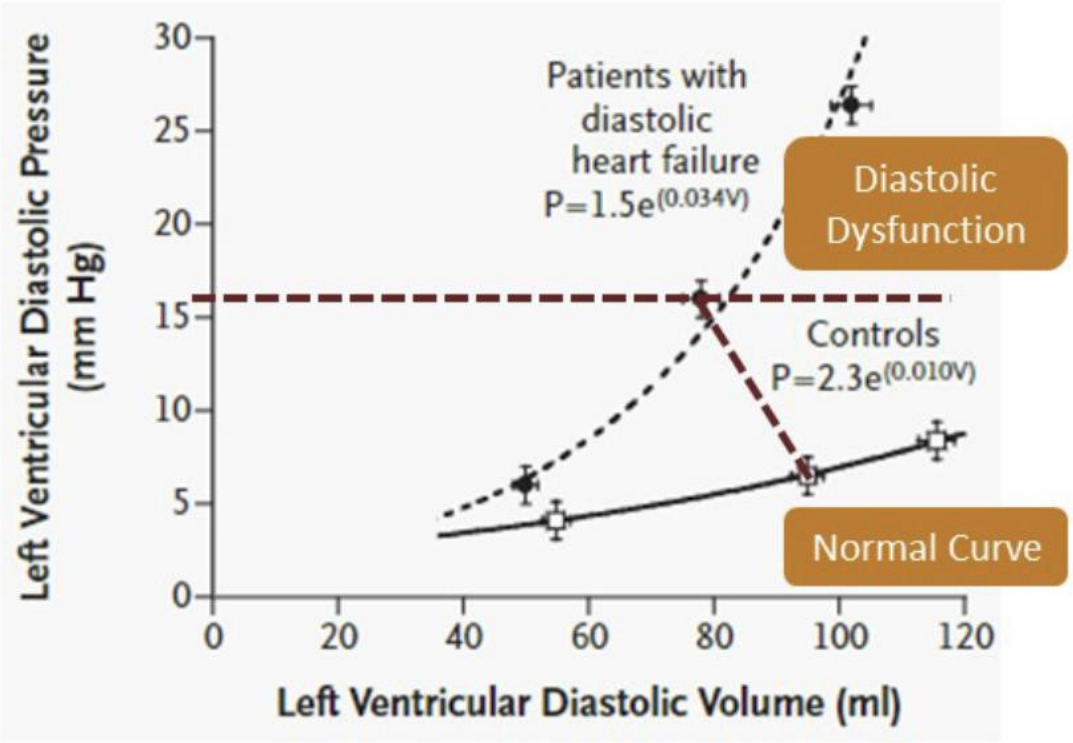
Taqueti VR et al. Eur Heart J 2018

Etiology of HFpEF

- The etiology of HFpEF is almost certainly heterogeneous

- We do not yet have enough understanding about the molecular mechanisms responsible fore all patients with HFpEF to offer “targeted” therapies

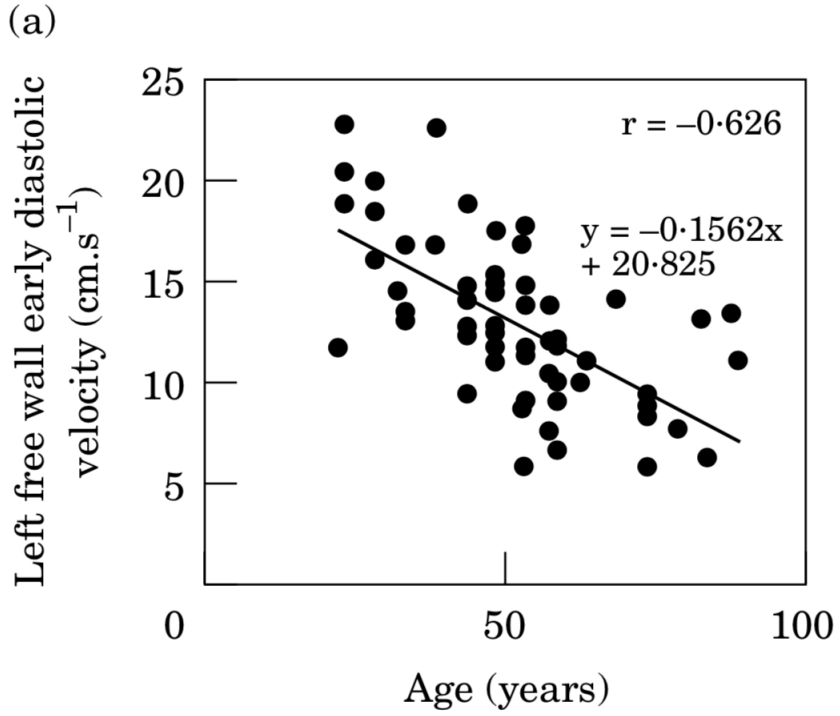
“Diastolic” Heart Failure



Zile MR, et al. *N Eng J Med*. 2004;350:1953-1959.

Age dependence of myocardial relaxation velocity in healthy hearts

- 60 healthy adults in Sweden aged 23-88
- Normal aging causes a decrease in early diastolic and a substantial increase in late diastolic myocardial lengthening velocities



Henein M et al. Eur Heart J 2002

High Prevalence of Diastolic Dysfunction Regardless of Clinical Status

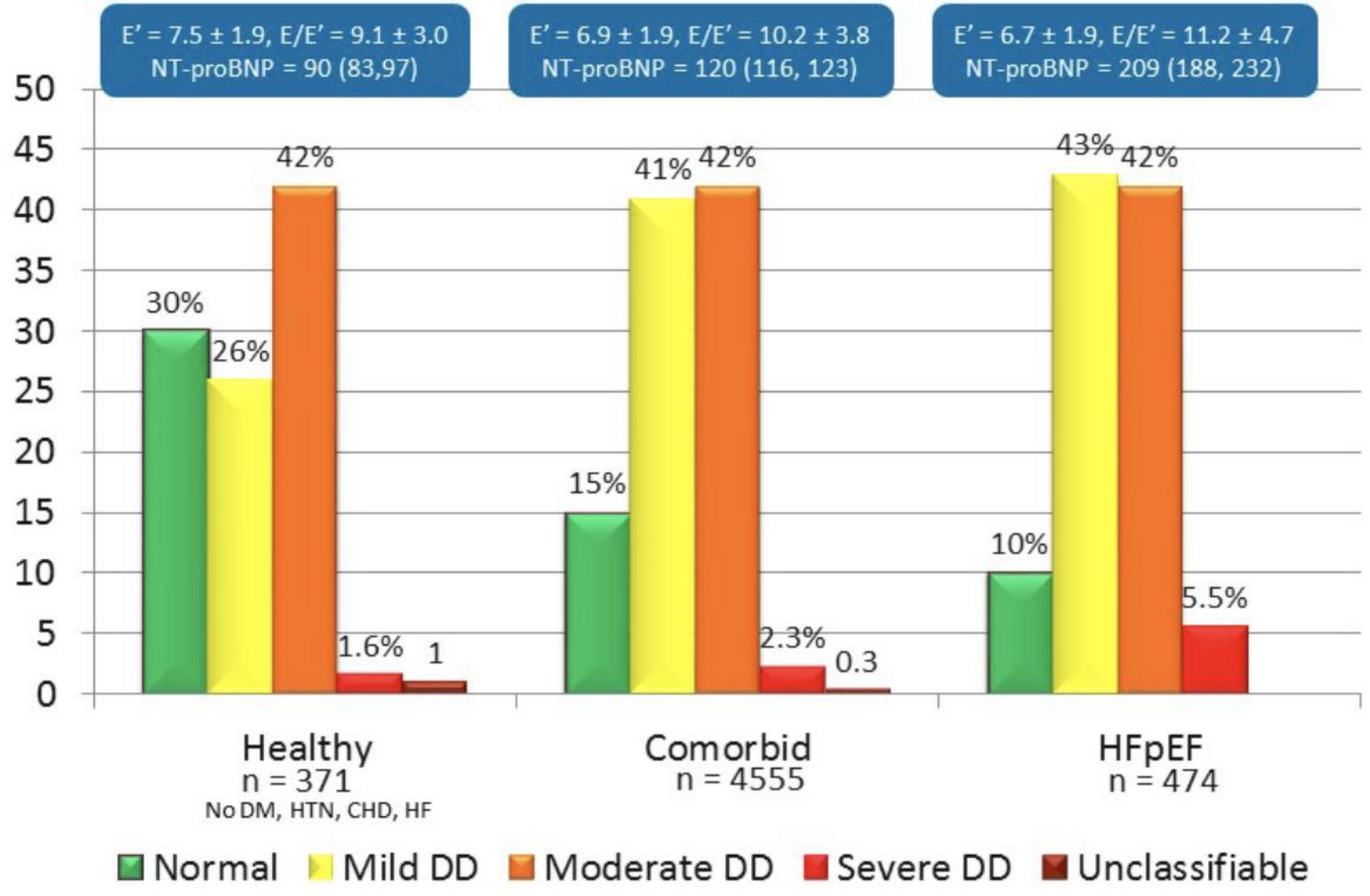
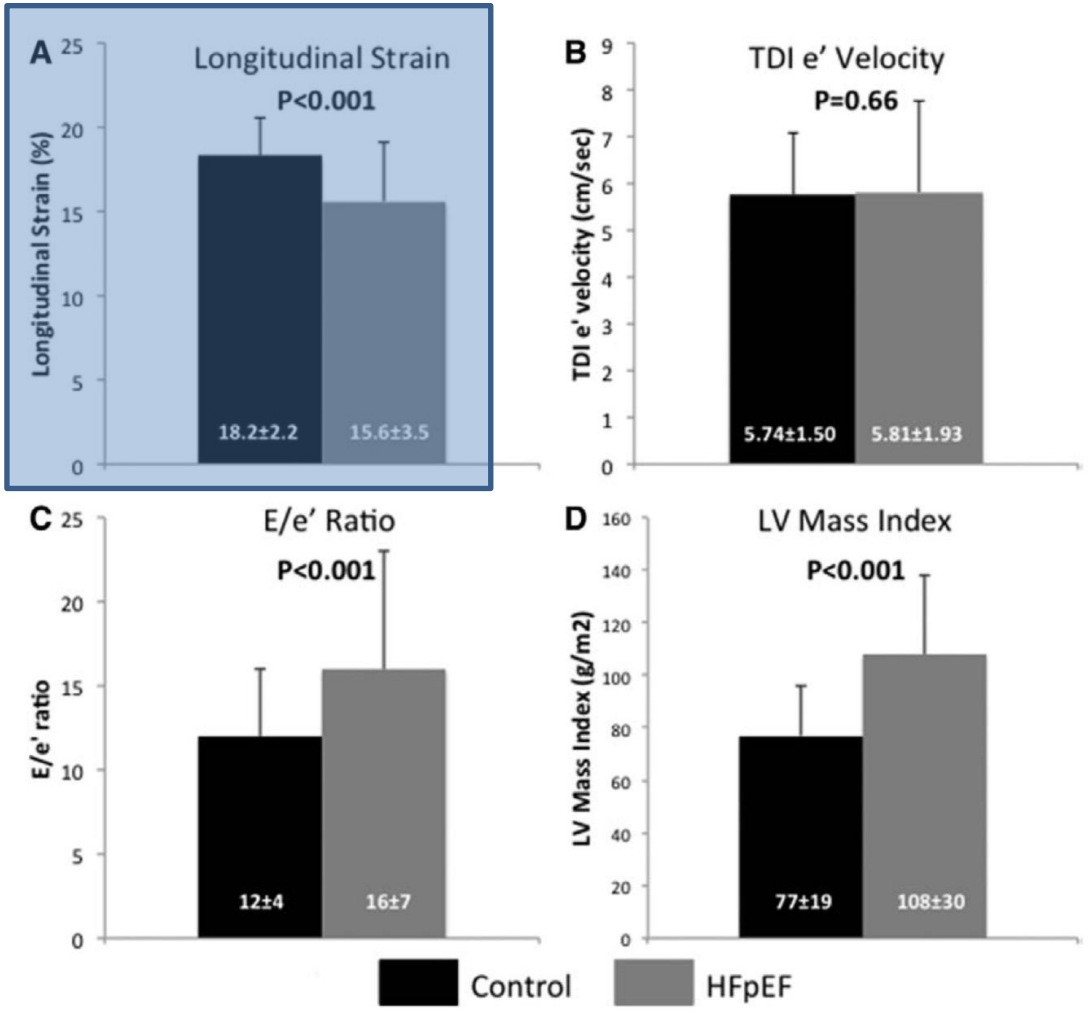


Image courtesy of Scott D. Solomon, MD; Shah A, et al. *Circulation.* 2017;135:426-439.

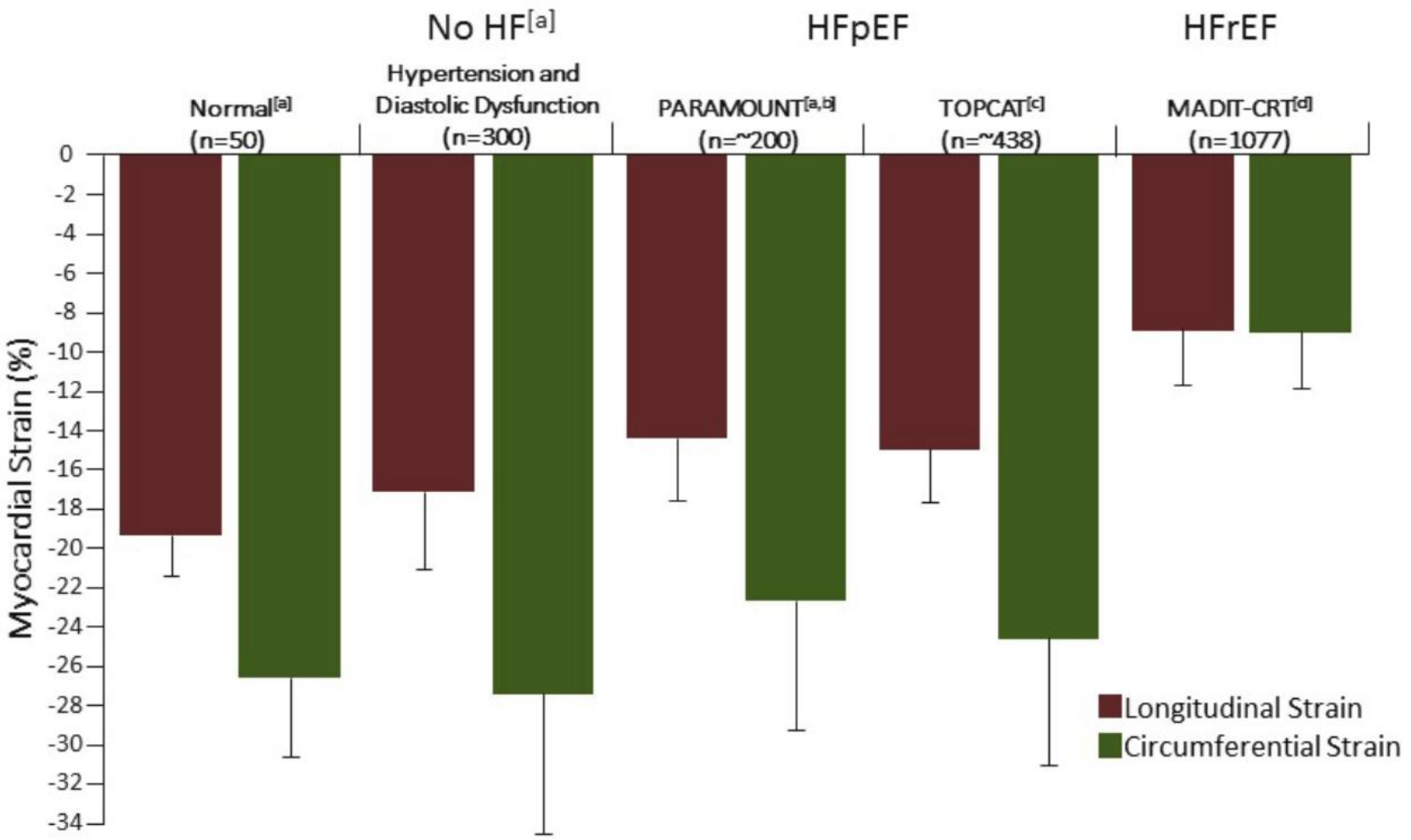
Systolic dysfunction in HFpEF

Longitudinal strain most likely represents systolic function of subendocardial myofiber bands



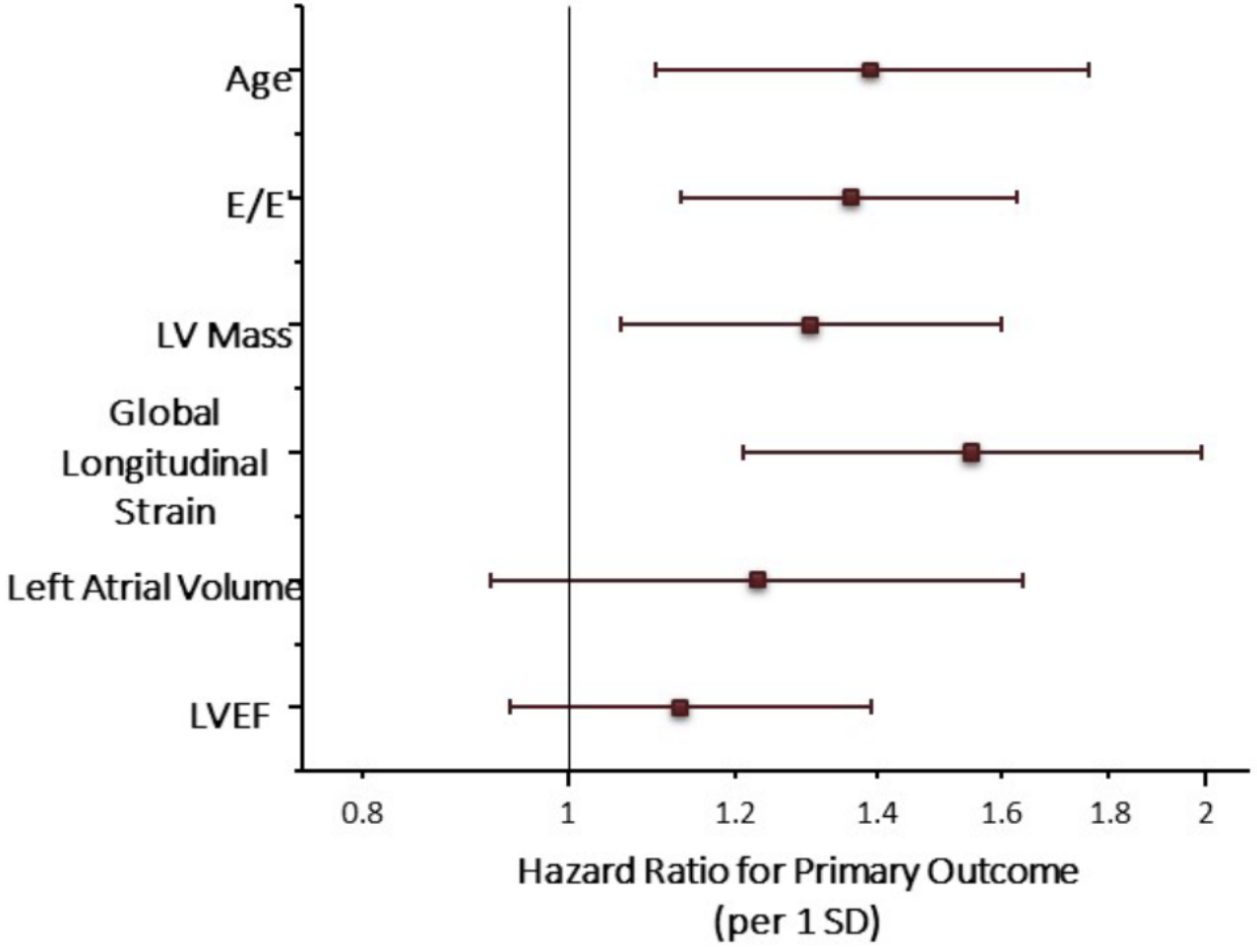
Shah A et al. Circulation 2015

Myocardial Strain in Healthy Hearts, HTN, HFpEF and HFrEF



a. Kraigher-Krainer E, et al. *J Am Coll Cardiol.* 2014;63:447-456; b. Solomon SD, et al. *Lancet*. 2012;380:1387-1395; c. Shah A, et al. *Circulation.* 2015;132:402-414; d. Knappe D, et al. *Circ HF.* 2011;4:433-440.

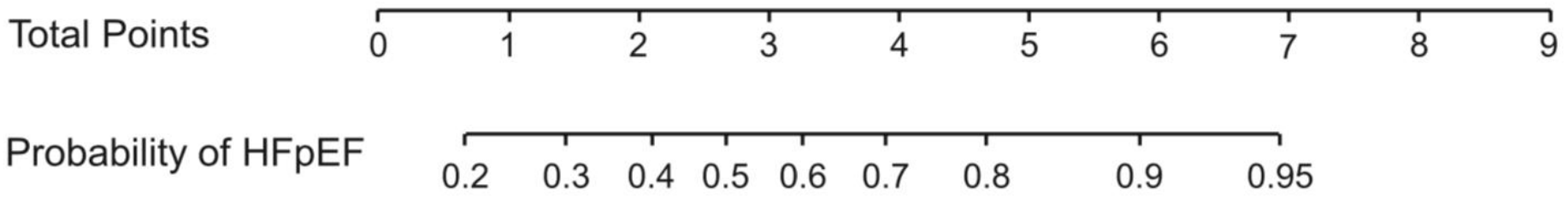
Prognostic Importance of Impaired Systolic Function in HFpEF and the Impact of Spironolactone



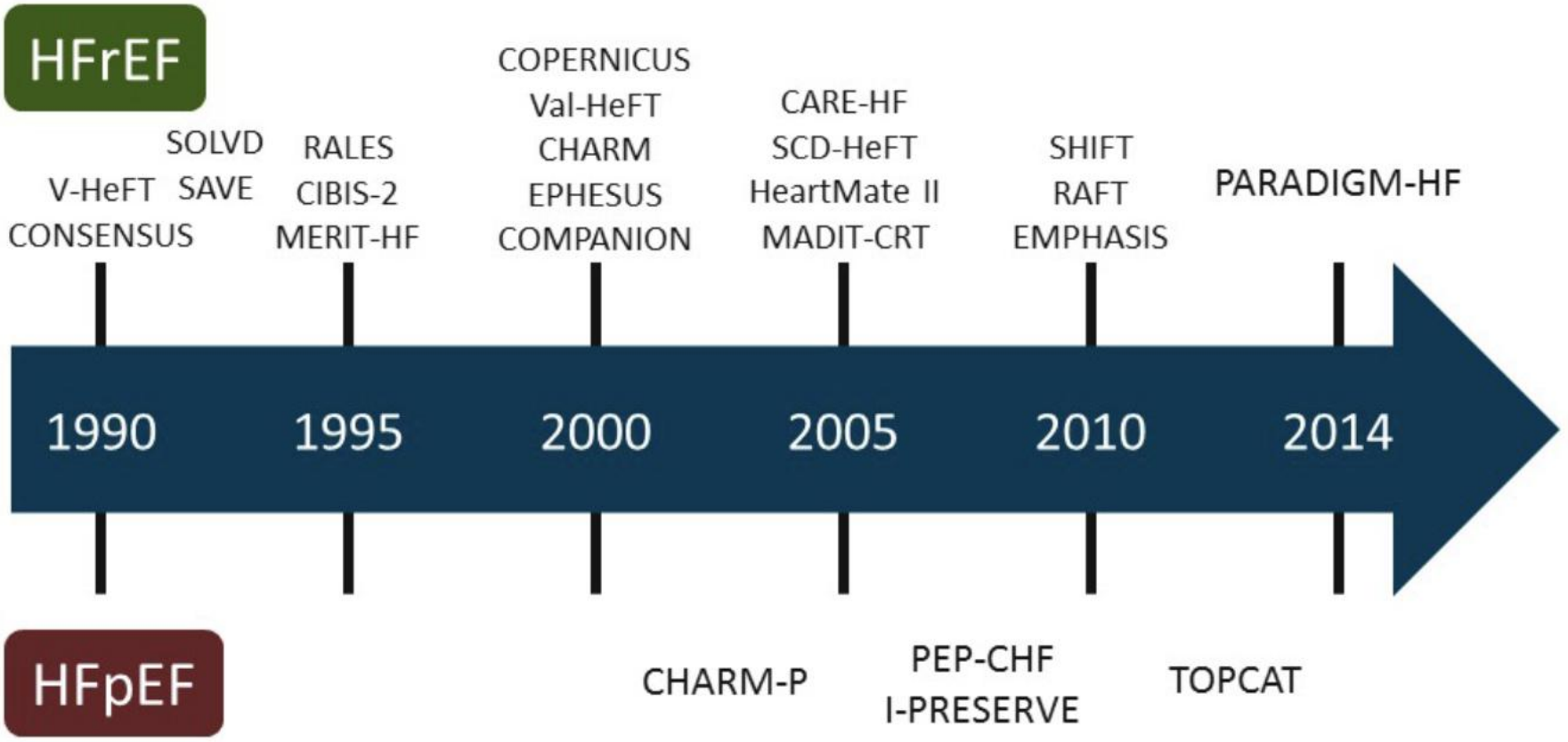
Univariate	Multivariate
P < .001	*P* = .005
P < .001	*P* = .017
P < .001	*P* = .025
P < .001	*P* = .001
P = .009	*P* = .083
P = .081	*P* = .70

Image courtesy of Scott D. Solomon, MD; Shah A, et al. *Circulation*. 2015;132:402-414.

	Clinical Variable	Values	Points
H_2	**H**eavy	Body mass index > 30 kg/m^2	2
	Hypertensive	2 or more antihypertensive medicines	1
F	Atrial **F**ibrillation	Paroxysmal or Persistent	3
P	**P**ulmonary Hypertension	Doppler Echocardiographic estimated Pulmonary Artery Systolic Pressure > 35 mmHg	1
E	**E**lder	Age > 60 years	1
F	**F**illing Pressure	Doppler Echocardiographic E/e' > 9	1
H_2FPEF score			Sum (0-9)



Landmark Heart Failure RCTs



ESC Guideline Recommendations: HFpEF

2012 ESC-Guidelines[a]

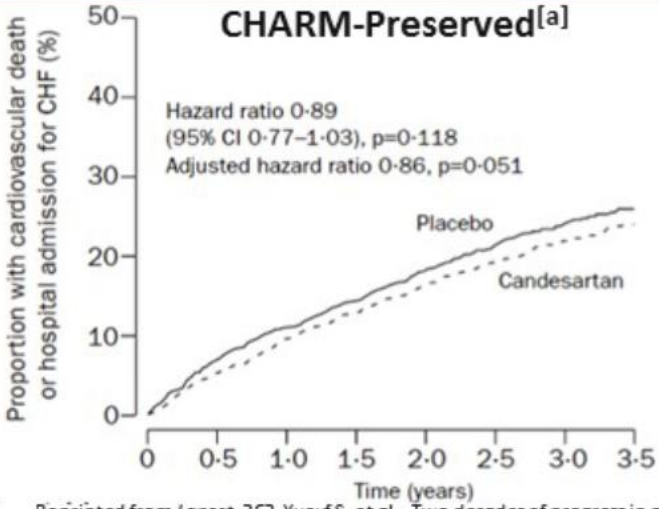
- No treatment has yet been shown, convincingly, to reduce morbidity and mortality in patients with HF-PEF

2016 ESC-Guidelines[b]

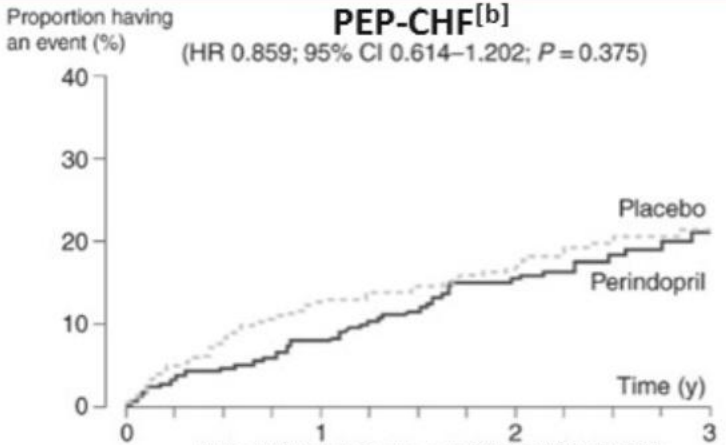
- No treatment has yet been shown, convincingly, to reduce morbidity and mortality in patients with HF-PEF

a. McMurray JJV, et al. *Eur Heart J*. 2012;33:1787-1847; b. Ponikoswki P, et al. *Eur Heart J*. 2016;18:891-975.

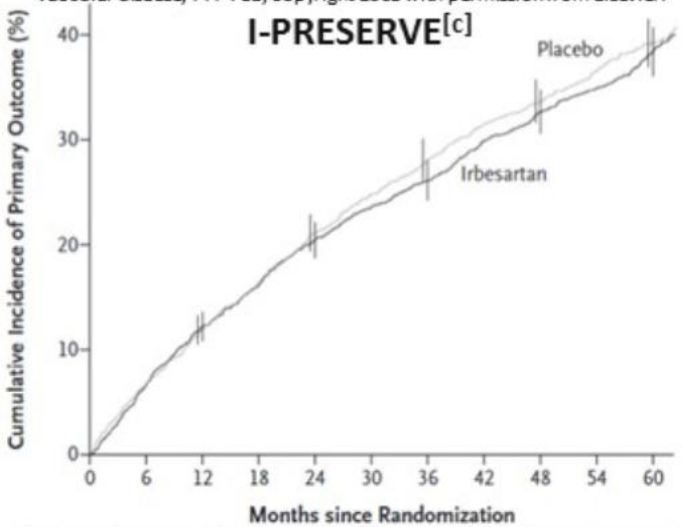
Outcomes Trials in HFpEF

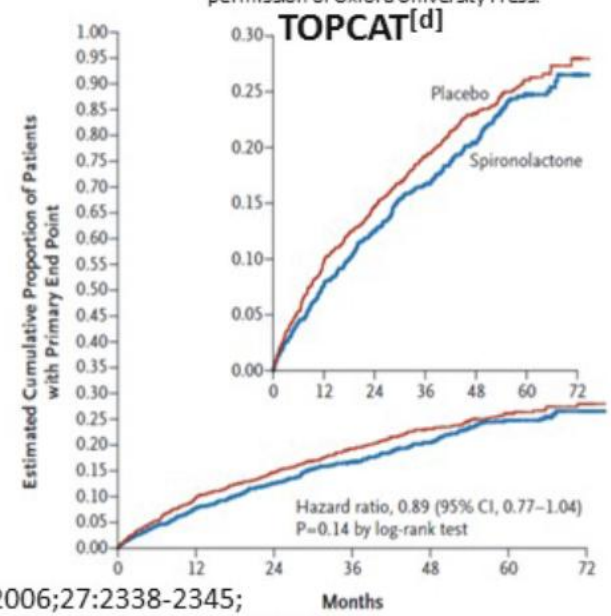


Reprinted from *Lancet*, 363, Yusuf S, et al., Two decades of progress in preventing vascular disease, 777-781, Copyright 2003 with permission from Elsevier.



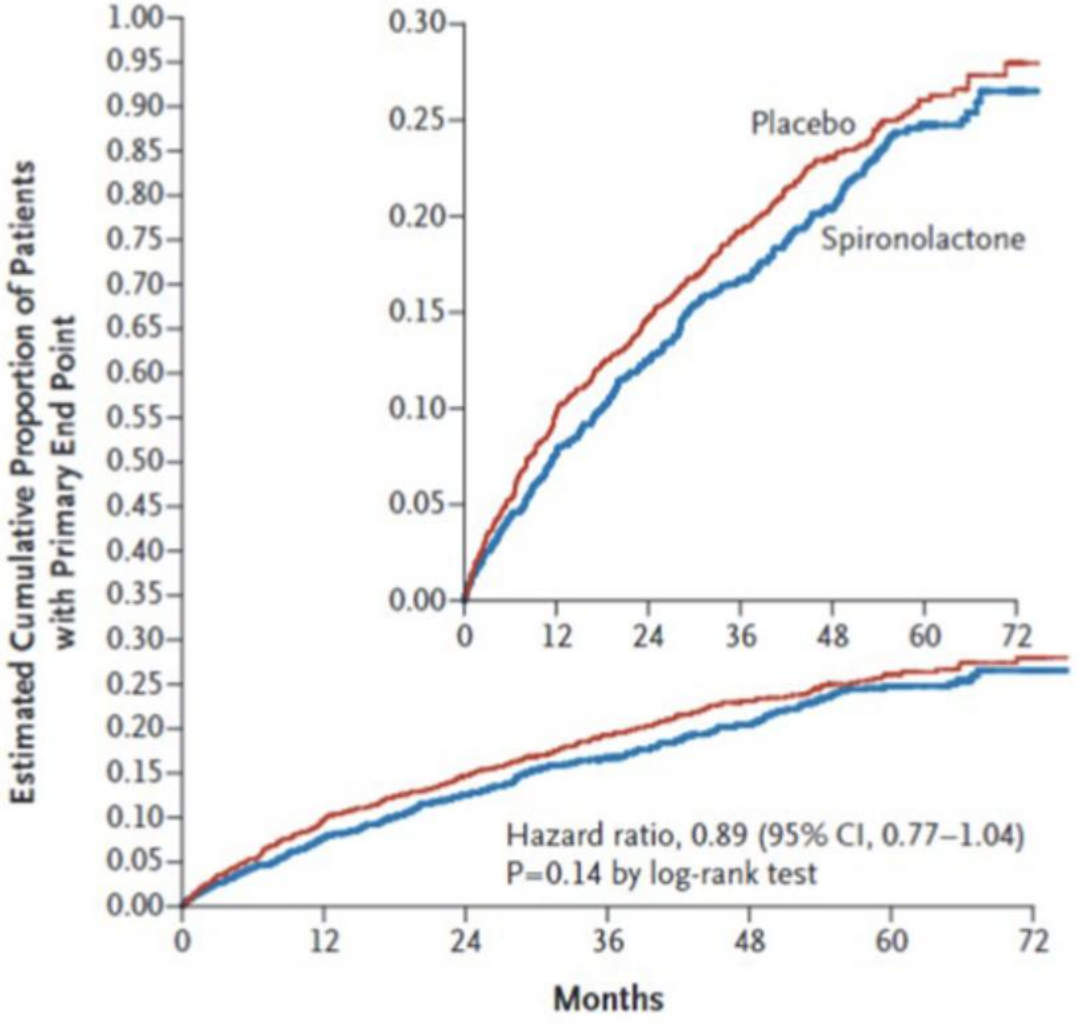
Cleland JGF, et al. *Eur Heart J.* 2006; 27:2338-2345. By permission of Oxford University Press.





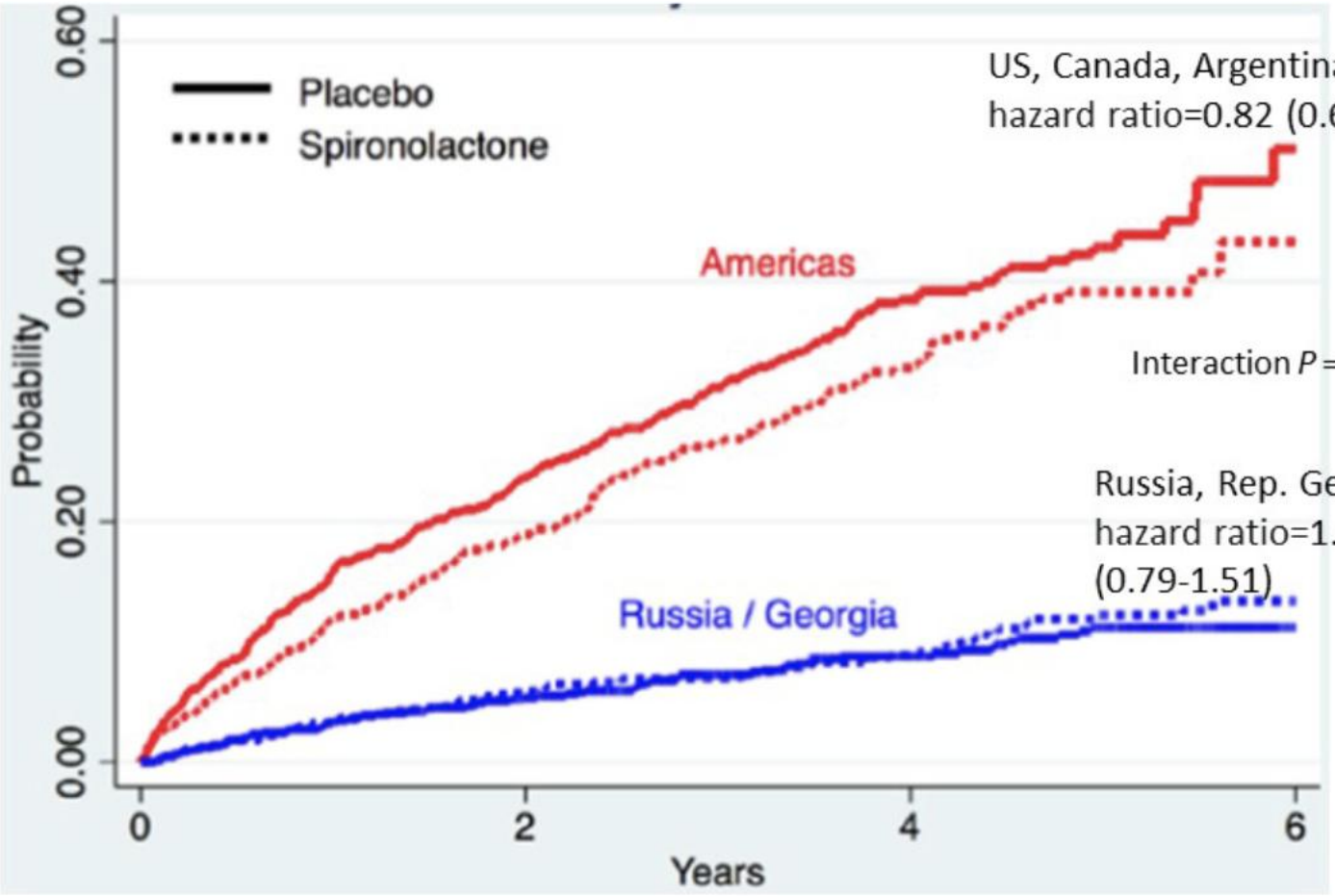
a. Yusuf S, et al. *Lancet*. 2003;363:777-781; b. Cleland JGF, et al. *Eur Heart J*. 2006;27:2338-2345;
c. Massie BM, et al. *N Eng J Med*. 2008;359:2456-2367; d. Pitt B, et al. *N Eng J Med*. 2014;370:1383-1392.

TOPCAT: Primary Outcome (CV Death, HF Hosp, or Resuscitated Cardiac Arrest)



Pitt B, et al. *N Eng J Med.* 2014;370:1383-1392.

TOPCAT: Results by Region



Pfeffer MA, et al. *Circulation*. 2015;131:34-42.

Quality of Life With Spironolactone

- Patients > 50 years of age with symptomatic HF and EF ≥ 45% who were enrolled in the TOPCAT study
- Patients enrolled also completed the KCCQ
- Adjusted mean changes in KCCQ for the spironolactone group were significantly better than those for the placebo group at the following visits:
  - 4 months (1.54 better; *P*=.002)
  - 12 months (1.35 better; *P*=.02)
  - 36 months (1.86 better; *P*=.02)

Lewis EF, et al. *Circ Heart Fail*. 2016;9:1-9.

What do we do in HFpEF in 2019?

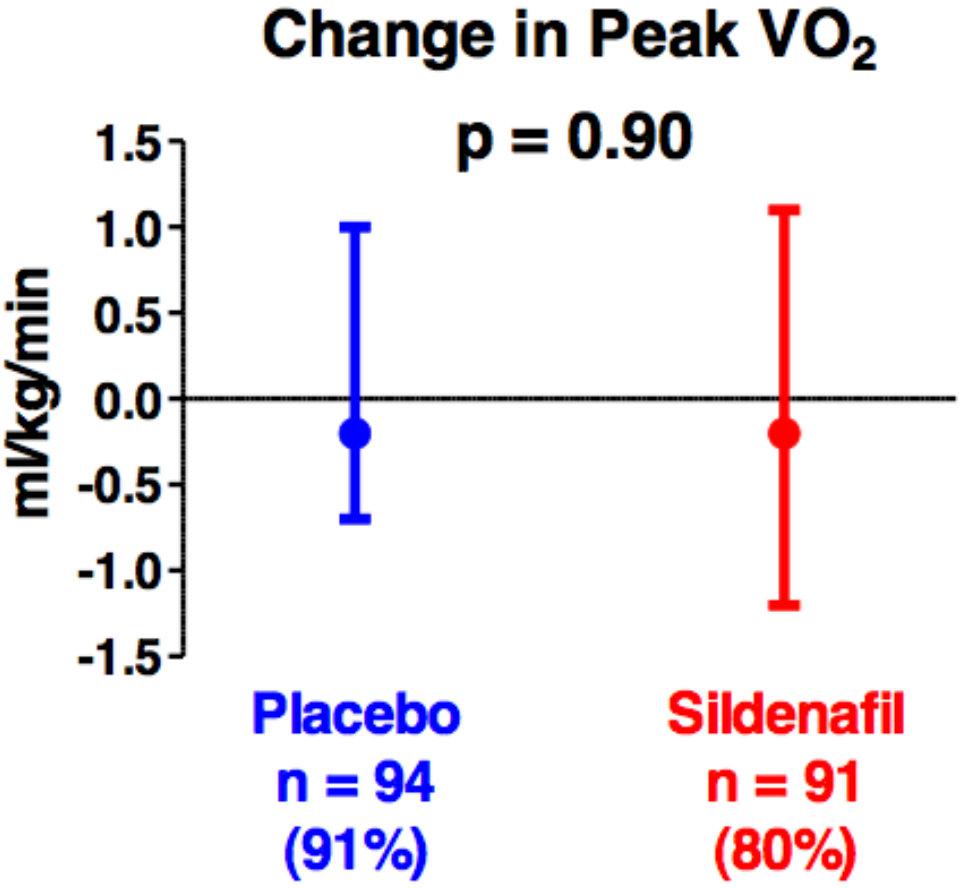
- Consider alternative diagnoses
- Prescribe diuretics to relieve congestion
- Treat hypertension
- Treat other comorbidities
- Rate or rhythm control of atrial fibrillation
- Treat ischemia
- Spironolactone?

Potential alternative diagnoses

- Amyloidosis and other cardiomyopaties
- Ischemic heart disease
- Lung disease
- Anemia, high output HF
- Hypertensive crisis

What Doesn't Work?

Results: Primary Endpoint



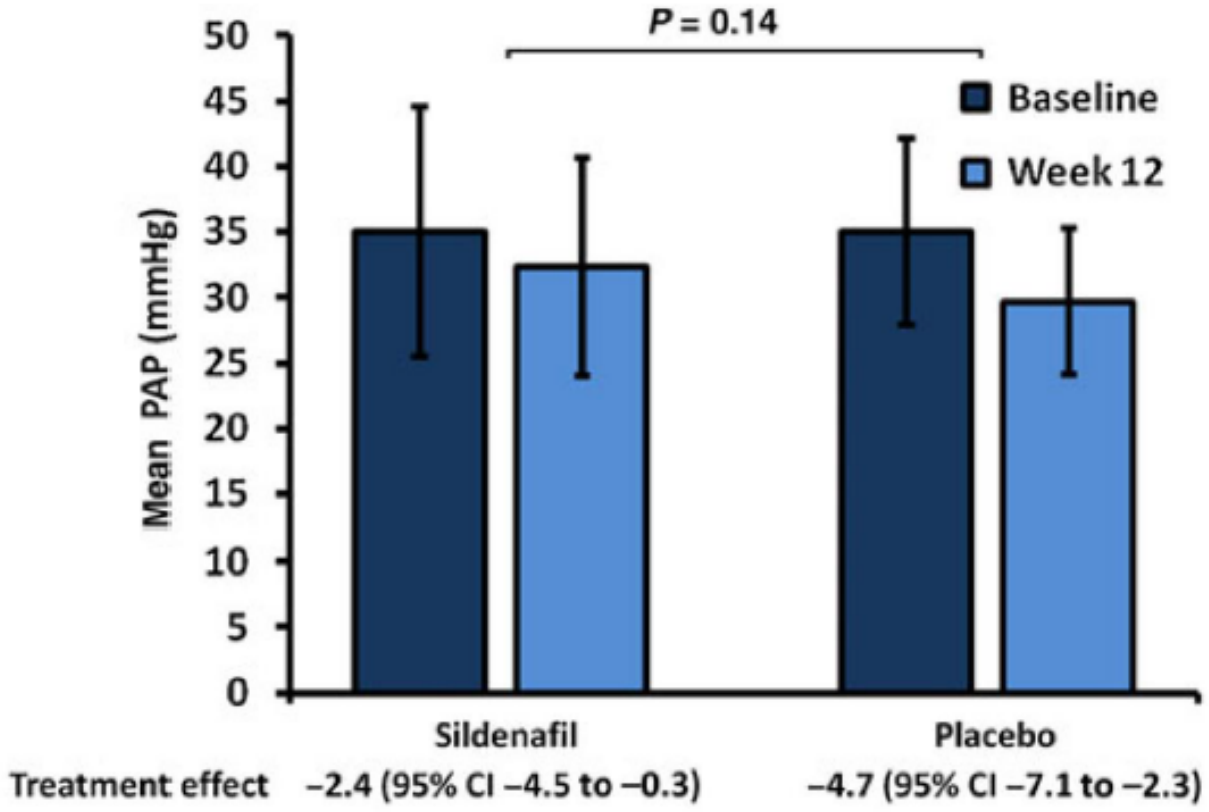
Sensitivity analyses for missing data

Multiple imputation: p = 0.98; LOCF: p = 0.98

Data are median and IQR

Sildenafil in Patients with HFpEF and Ipc-PH

A double-blind, randomized controlled Study (n=52)
(HFpEF, PH, mean PAPm 35 mHg, mean DPG 1 mmHg, mean PVR 2.4 WU)

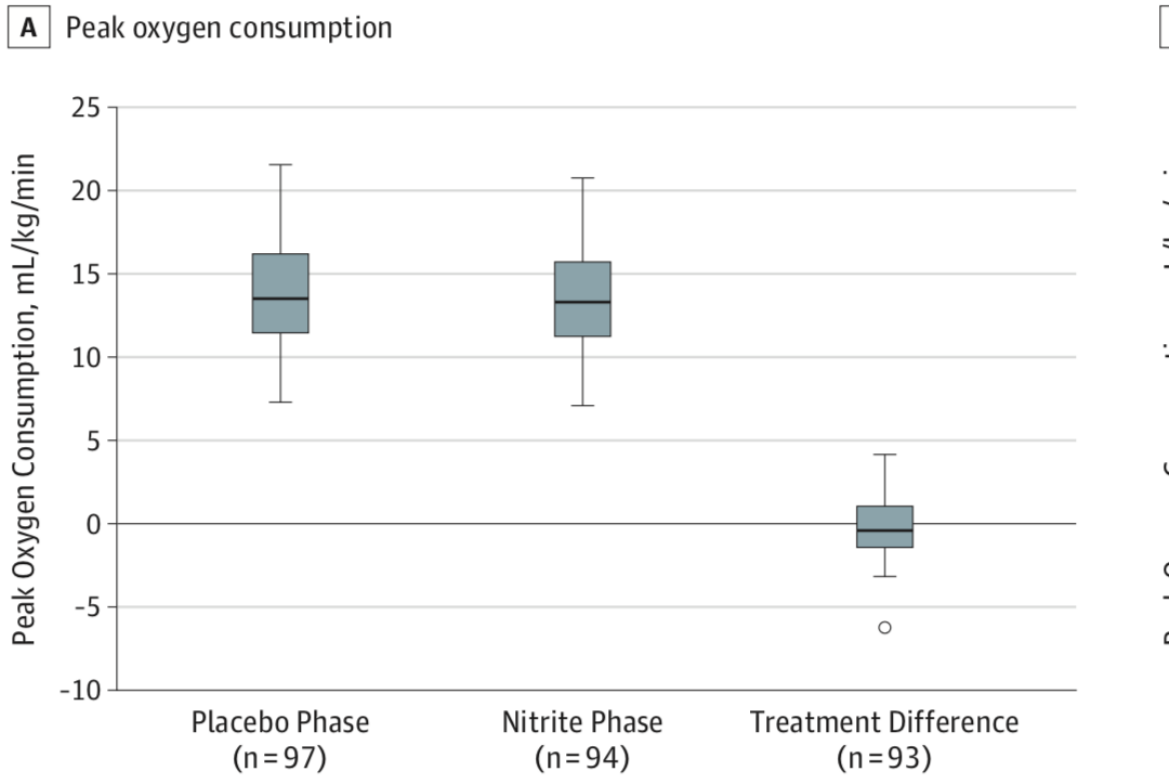


Hoendermis-ES et al., *Eur Heart J* 2015; 36: 2565-2573

JAMA | Original Investigation

Effect of Inorganic Nitrite vs Placebo on Exercise Capacity Among Patients With Heart Failure With Preserved Ejection Fraction

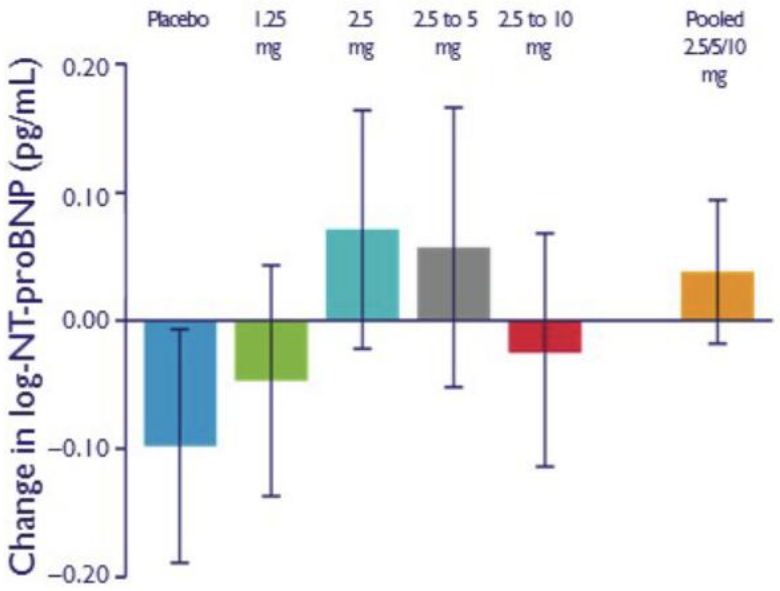
The INDIE-HFpEF Randomized Clinical Trial

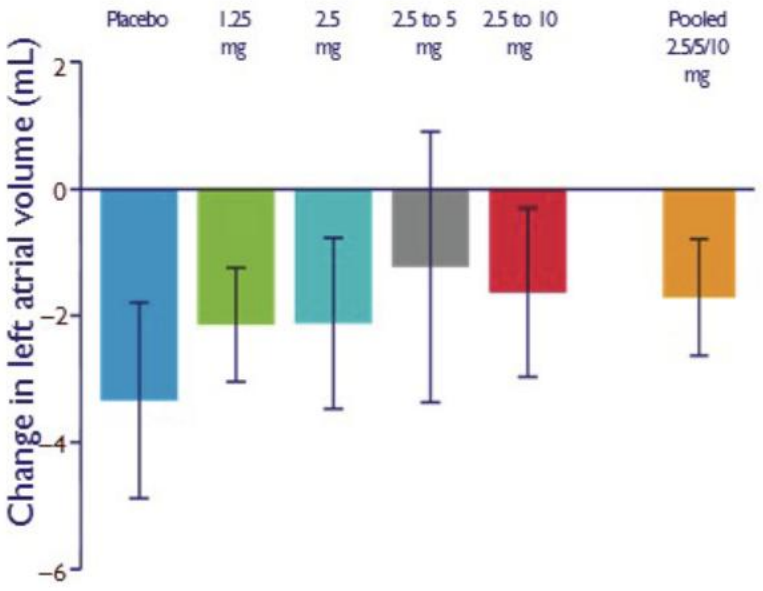


Borlaug BA et al. JAMA 2018

Vericiguat in HFpEF: SOCRATES-Preserved Primary Endpoint: log-NT-proBNP and LAV

No reduction in log-NT-proBNP or in LAV at Week 12 compared with placebo
Secondary QOL endpoints showed significant benefit at highest doses





Data are mean ± standard error for the per-protocol analysis sets

- There is no hint of cardiac benefit overall for vericiguat in HFpEF
- IT is unclear whether a hypothesis generating QOL benefit is due to other potential mechanisms or random

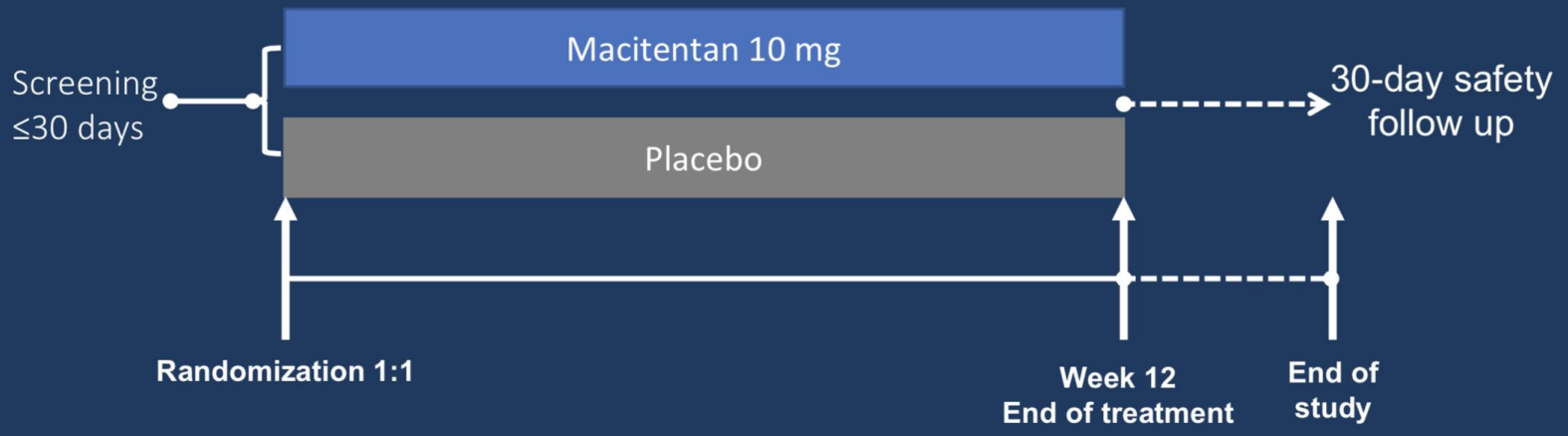
Image courtesy of Burkert Pieske, MD; Pieske B, et al. *Eur Heart J*. 2017;38:1119-1127.

EDIFY: No Improvement in Any of the Co-Primary Endpoints With Ivabradine

- 179 patients NYHA class II and III, in sinus rhythm, with HR of ≥ 70 bpm
- NT-proBNP of ≥ 220pg/mL (BNP ≥ 80 pg/mL) and LVEF of ≥45%
- Ivabradine (or placebo) was titrated to 7.5 mg twice daily
- Patients were followed for 8 months on the change and assessed for 3 co-primary endpoints: echo-Doppler E/e' ratio, distance on the 6-min walking test (6MWT), and plasma NT-proBNP concentration
- In patients with HFpEF, ivabradine did not improve outcomes

Komajda M, et al. *Eur J Heart Fail*. 2017;19:1495-1503.

- **MELODY-1 study objective**: To evaluate safety and tolerability of macitentan 10 mg in patients with CpcPH
- Only study so far with a strict HD inclusion criteria



Vachiéry JL, *et al. Eur Respir J* 2018; 51:1701886.

Main safety endpoint: Proportion of patients with significant fluid retention or NYHA FC worsening

	Macitentan	Placebo	Treatment effect % (95% CI*)	p-value
Subjects, *n*	31	32		
Significant fluid retention or worsening in NYHA FC from baseline⁺	7 (22.6)	4 (12.5)	10.08 (-15.07 to 33.26)	0.34
Significant fluid retention Increased body weight from baseline by ≥ 5% or ≥ 5 kg due to fluid overload Parenteral administration of diuretics	7 (22.6) 3 (9.7) 5 (16.1)	3 (9.4) 0 (0.0) 3 (9.4)	13.21 (-11.96 to 36.21)	0.18
Worsening in NYHA FC from baseline**	1 (3.2)	2 (6.3)		

Significant fluid retention **Macitentan: Days 10, 12, 28, 29, 57, 57, 65**

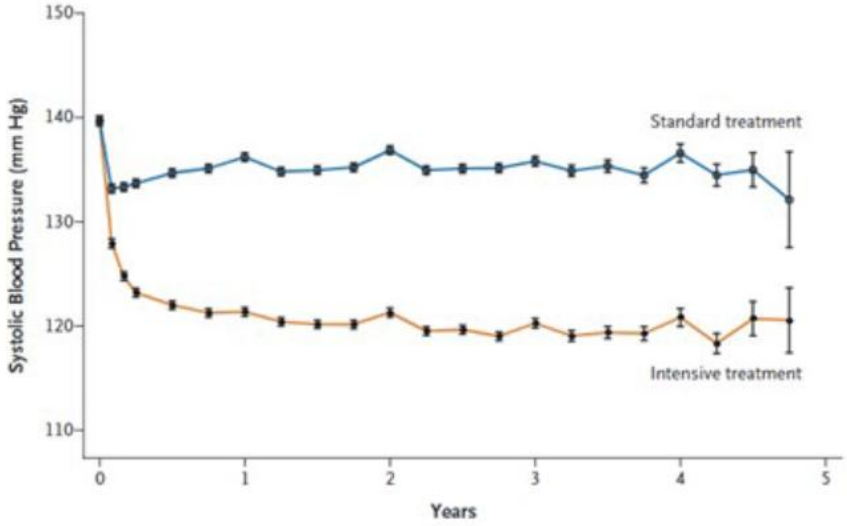
Placebo: Days 43, 50, 61

Data are *n* (%), unless otherwise stated. Safety analysis set
*Difference in proportions (%) of patients with at least 1 condition;
⁺Patients could meet both significant fluid retention and worsening in NYHA FC;
**NYHA FC worsened from III to IV in the macitentan patient and from II to III in both placebo patients.

Vachiéry JL, *et al. Eur Respir J* 2018; 51:1701886.

What Might Work?

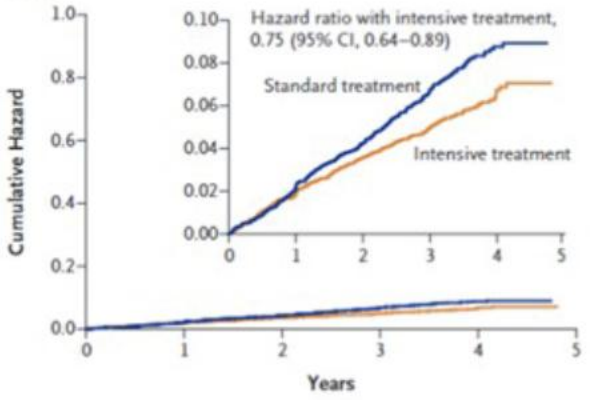
SPRINT: BP Lowering Reduces Adverse Outcomes
HF Hospitalization Reduced 38%



No. with Data										
Standard treatment	4683	4345	4222	4092	3997	3904	3115	1974	1000	274
Intensive treatment	4678	4375	4231	4091	4029	3920	3204	2035	1048	286

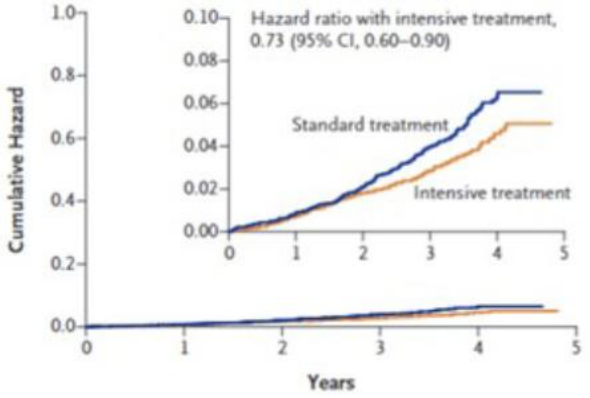
Mean No. of Medications										
Standard treatment	1.9	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.9
Intensive treatment	2.3	2.7	2.8	2.8	2.8	2.8	2.8	2.8	2.8	3.0

Primary Outcome



No. at Risk					
Standard treatment	4683	4437	4228	2829	721
Intensive treatment	4678	4436	4256	2900	779

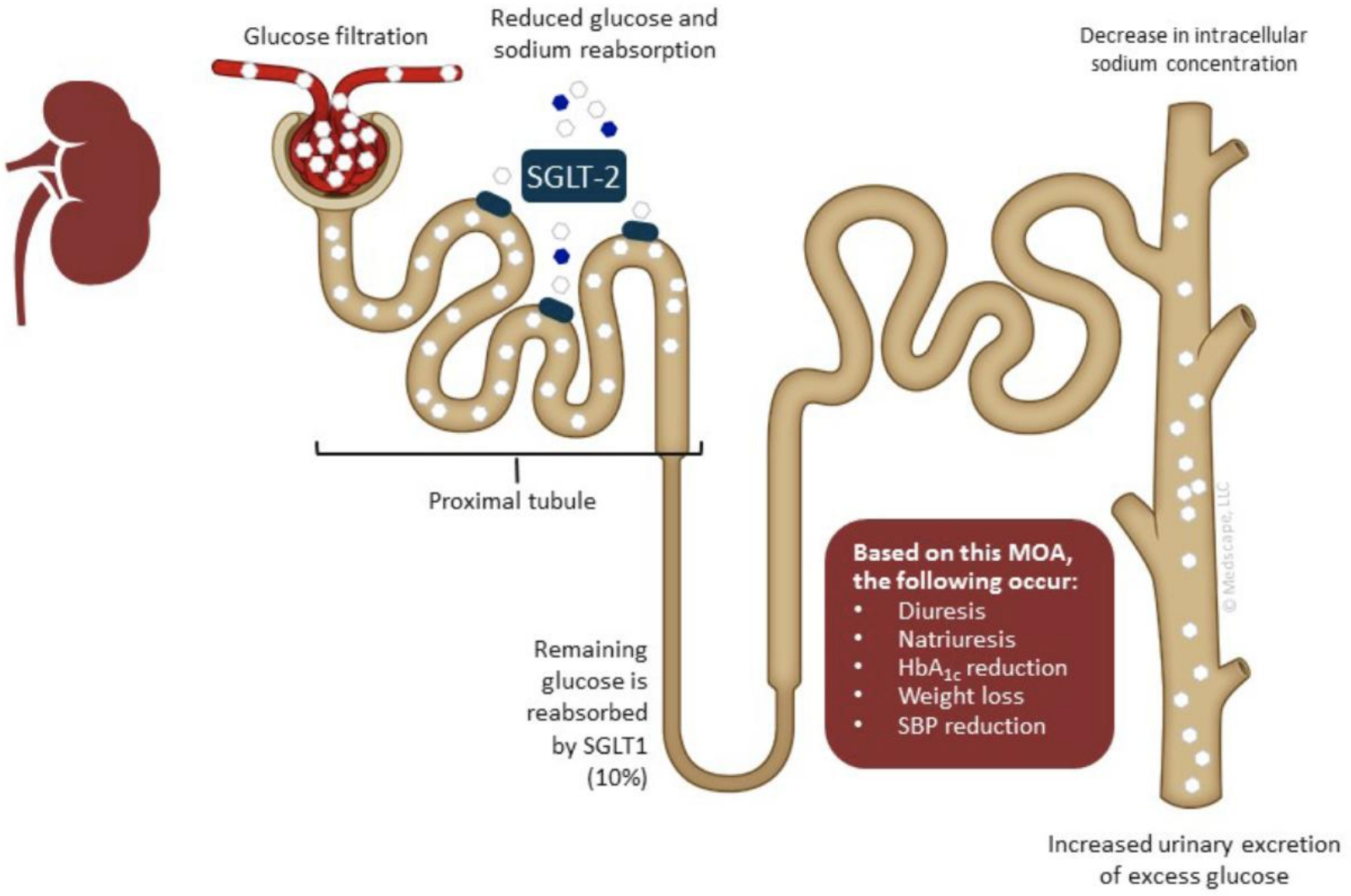
Death from Any Cause



No. at Risk					
Standard treatment	4683	4528	4383	2998	789
Intensive treatment	4678	4516	4390	3016	807

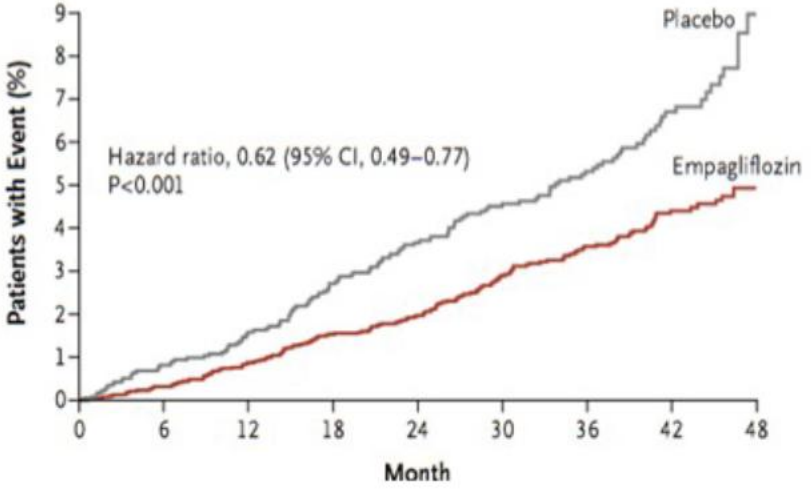
SPRINT Investigators. *N Engl J Med*. 2015;373:2103-2116.

SGLT-2 Inhibitors Block SGLT-2 and Reduce Glucose and Na+ Reabsorption 1,2,3

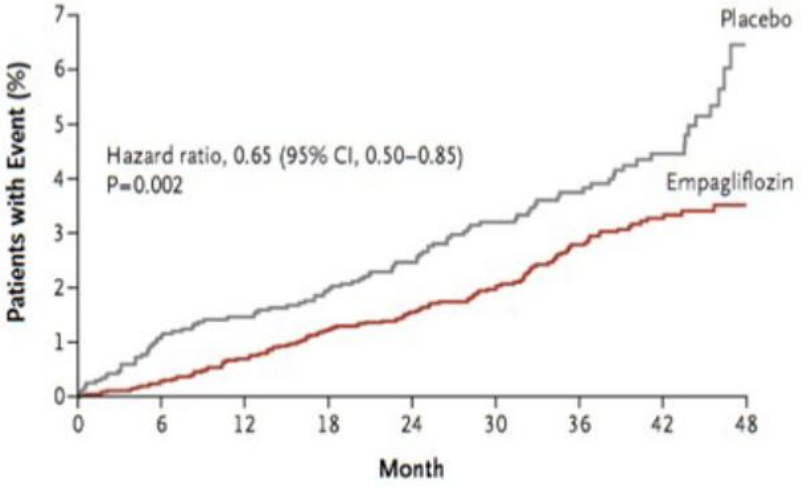


CV Death and Hospitalization for HF in EMPA-REG

Death from Cardiovascular Causes



Hospitalization for Heart Failure



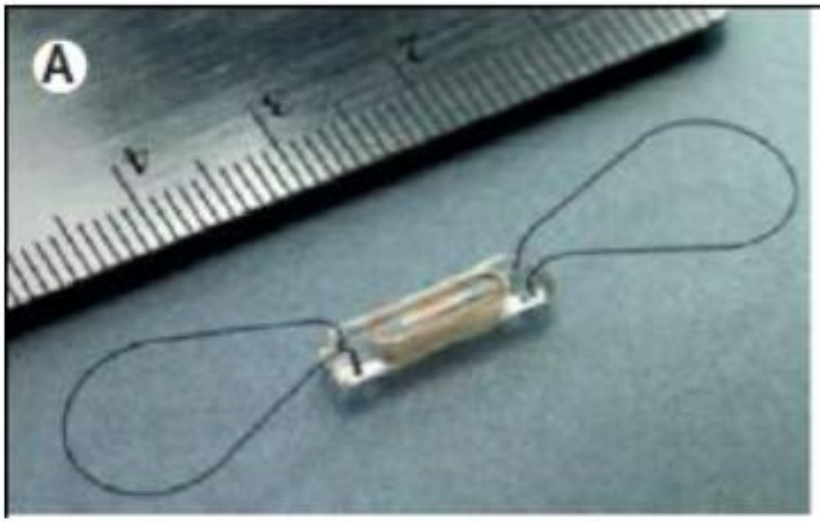
Zinman B, et al. *N Engl J Med.* 2015;373:2117-2128.

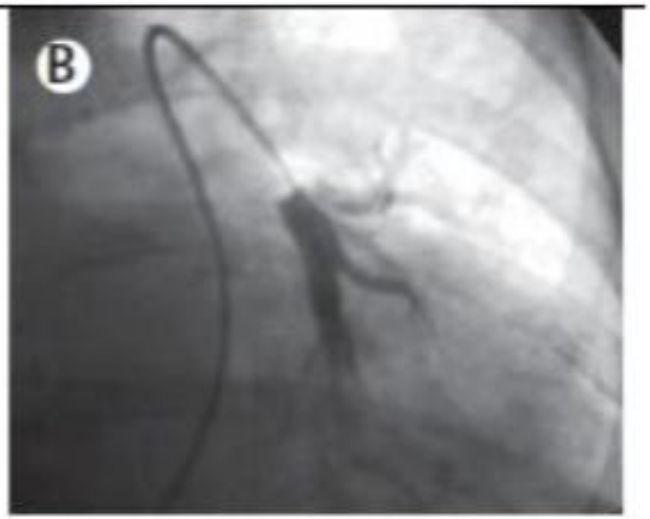
Two HFpEF Outcomes Trials With SGLT-2 Inhibitors

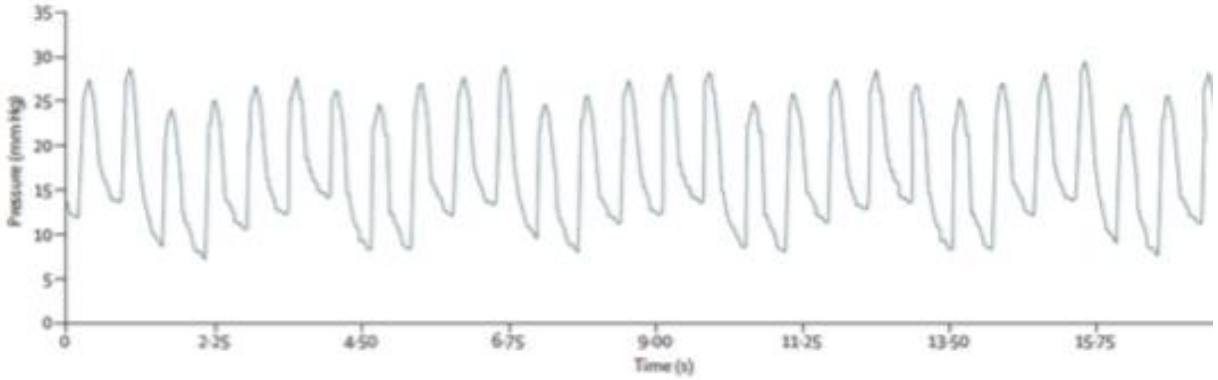
- EMPEROR Preserved[a]
  - Phase 3; randomized, double-blind, placebo-controlled trial
  - Exploring efficacy and safety of once-daily empagliflozin 10 mg compared with placebo in patients with chronic HFpEF
  - Inclusion criteria include:
    - NT-proBNP levels > 300 pg/mL for patients without AF; > 900 pg/mL for patients with AF
  - Composite endpoint – time to first adjudicated CV death or HHF
- DELIVER Study[b]
  - Phase 3; randomized, double-blind, placebo-controlled trial
  - Evaluating the effects of dapagliflozin on reducing CV death or worsening HF in patients with HFpEF

a. ClinicalTrials.gov. NCT03057951; b. ClinicalTrials.gov. NCT03619213.

Wireless pulmonary artery haemodynamic monitoring in CHF: a randomised controlled trial



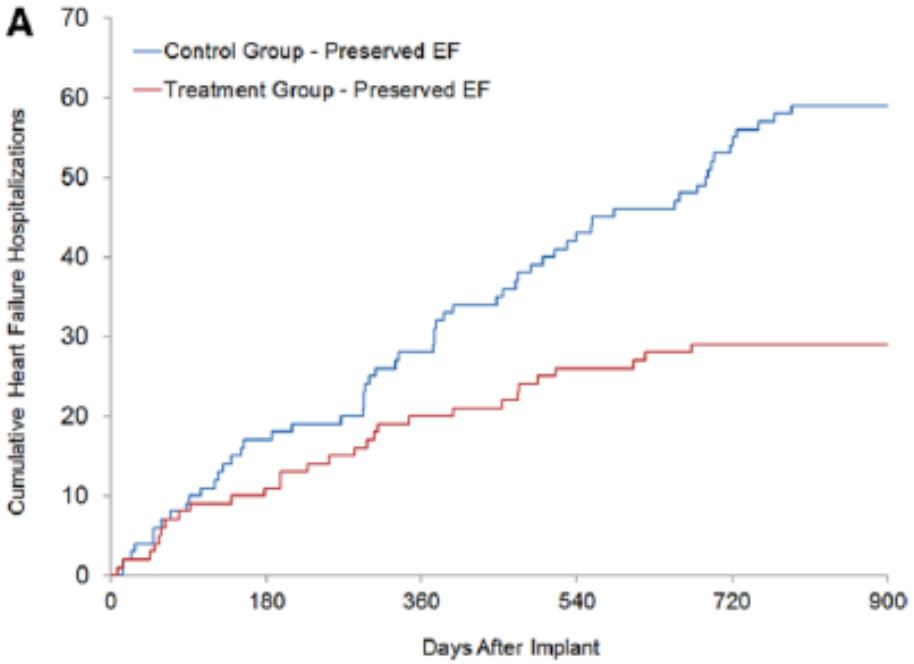


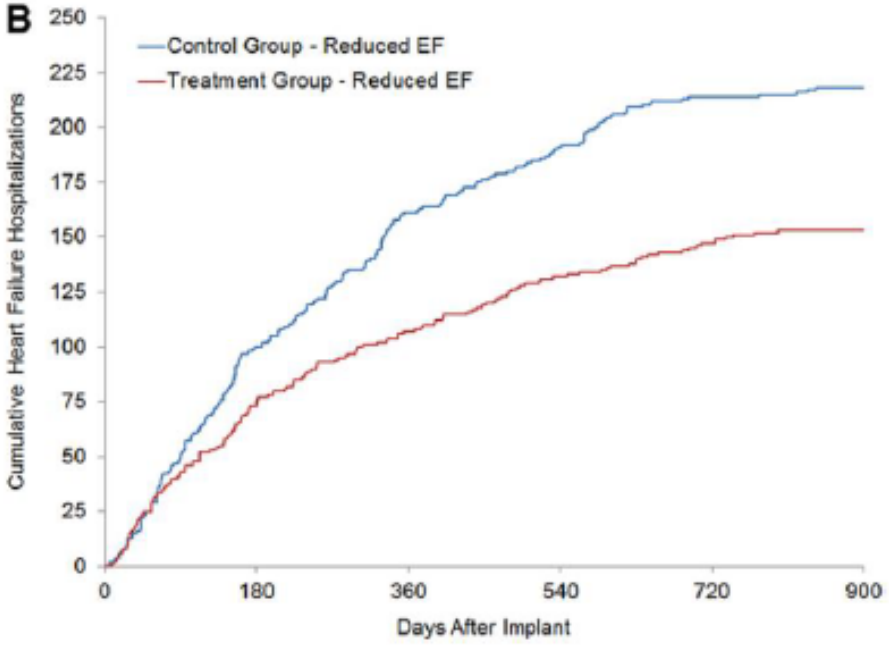


Abraham, Lancet 2011

Reduction in HF hospitalisations with CardioMEMS

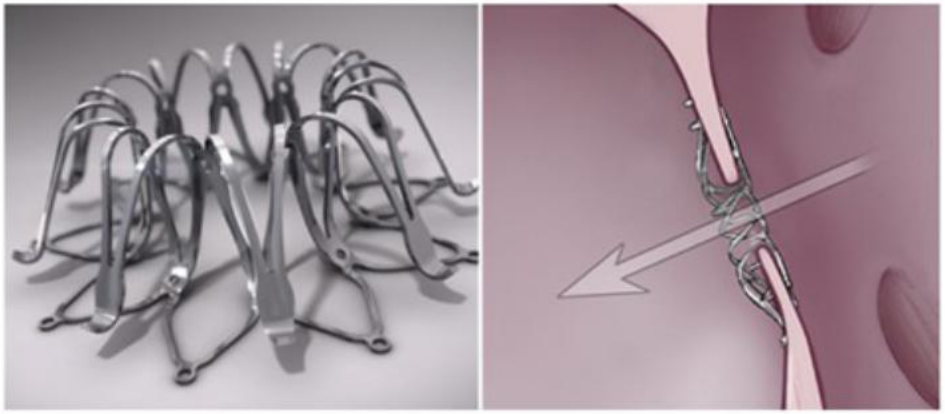
- CardioMEMS Heart Sensor
- Hemodynamically guided HF management vs. standard of care
- HFpEF patients: Hospitalizations 50% lower after 17.6 months
- Response to elevated PAP: more diuretics and vasodilator therapies

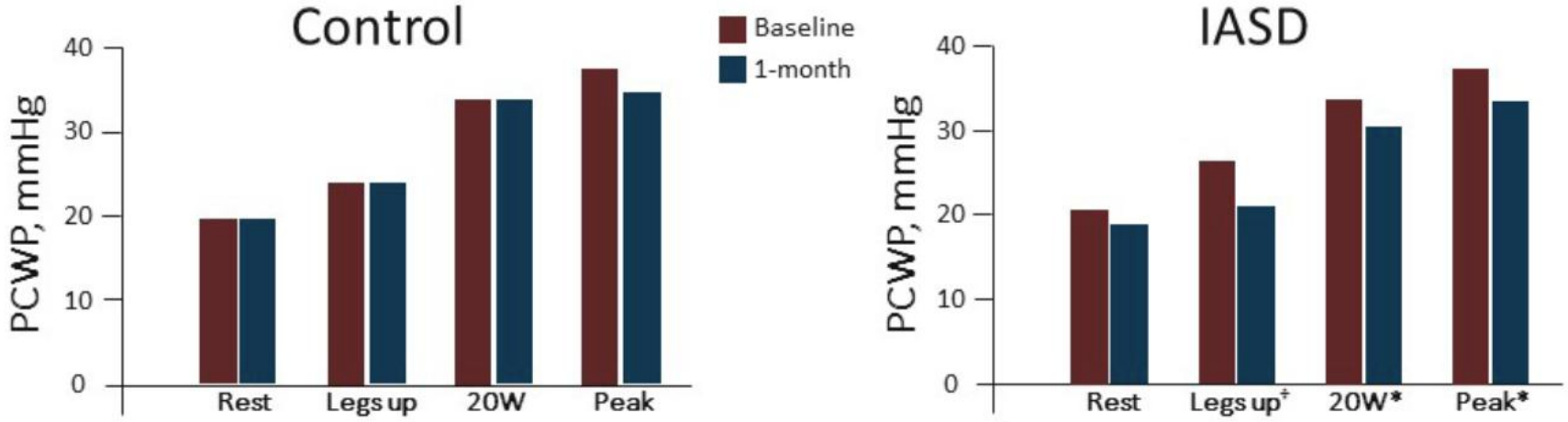




Adamson PB et al. *Circ Heart Fail* 2014; 7: 935-944

Interatrial Shunt Device



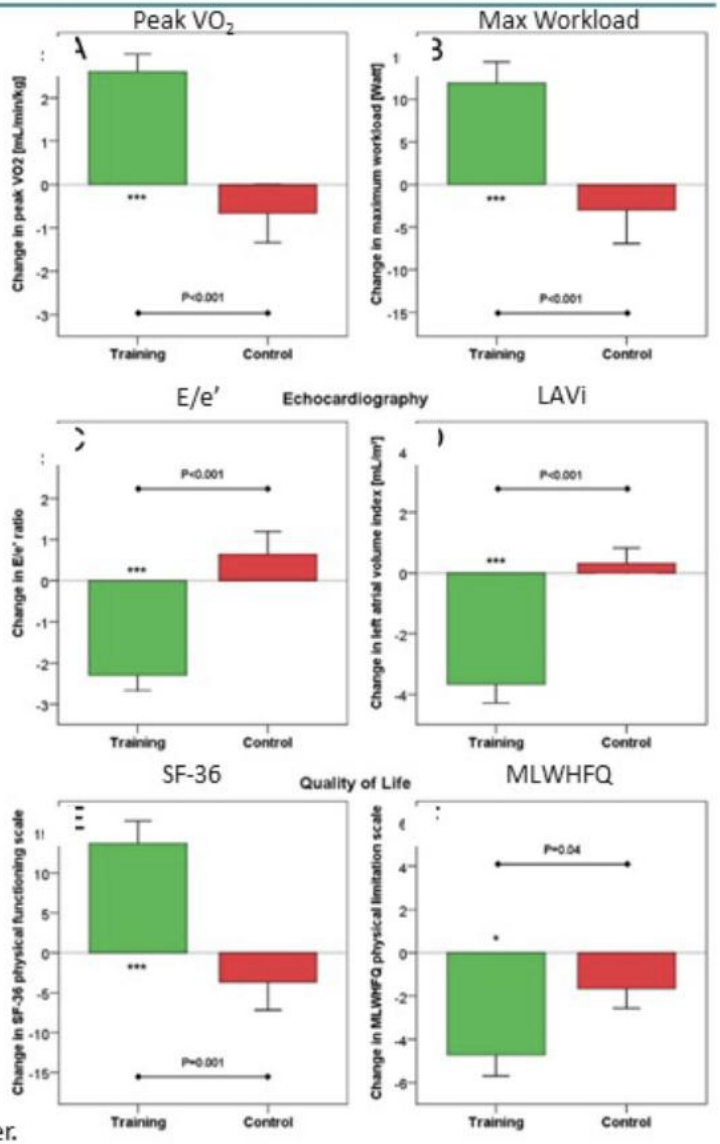


*$P < .05$. †$P < .01$.

Feldman T, et al. *Circulation*. 2018;137:364-375.

Potential Benefit of Exercise Training on Peak VO_2 on E/e' and QOL

- N=64 (56% female)
- Age 65 ± 7 years
- 2:1 randomization
- Supervised endurance/resistance training + usual care vs usual care alone
- Endpoints:
  - Primary: Change in peak VO_2 after 3 months
  - Secondary: Effect on cardiac structure, diastolic function, QOL



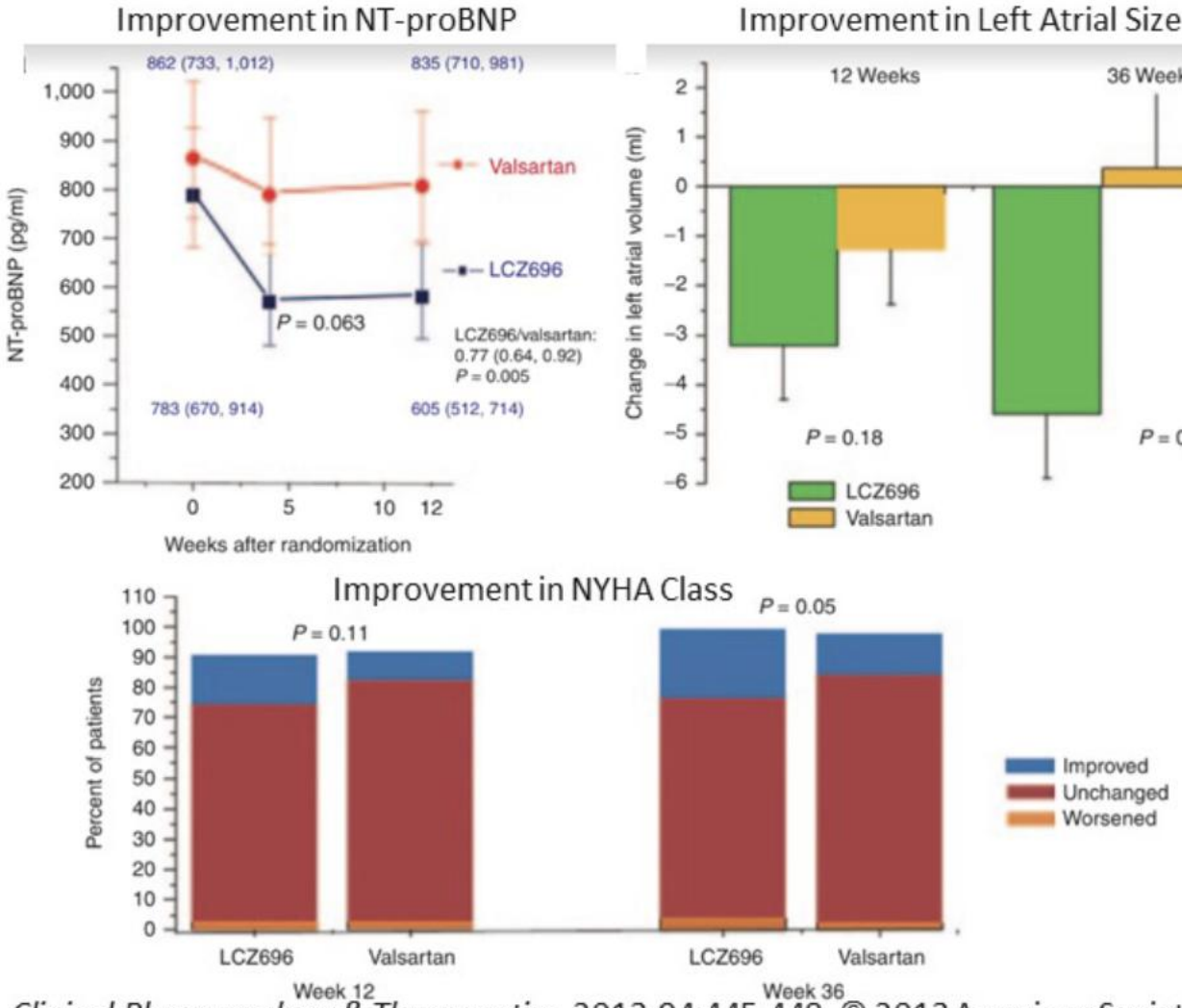
Reprinted from *JACC*, 58(17), Edelmann, et al., TExercise Training Improves Exercise Capacity and Diastolic Function in Patients With Heart Failure With Preserved Ejection Fraction: Results of the Ex-DHF (Exercise training in Diastolic Heart Failure) Pilot Study, 1780-91, Copyright 2012, with permission from Elsevier.

Exercise and Diet Improve Peak VO_2 and KCCQ in HFpEF

- 100 older (67 ± 5 years) obese women (n=81) and men (n=19) with chronic stable HFpEF were enrolled
- 26 participants were randomized to exercise alone; 24 to diet alone; 25 to diet + exercise; and 25 to control
- Intervention consisted of 20 weeks of diet and/or exercise
- Exercise capacity measured as peak VO_2 was the primary outcome; HF-specific QOL was measured by the KCCQ
- Results:
  - By main effects analysis, peak VO_2 was significantly increased by both interventions
  - Diet, but not exercise significantly increased the QOL score

Kitzman DW, et al. *JAMA.* 2016;315:36-46.

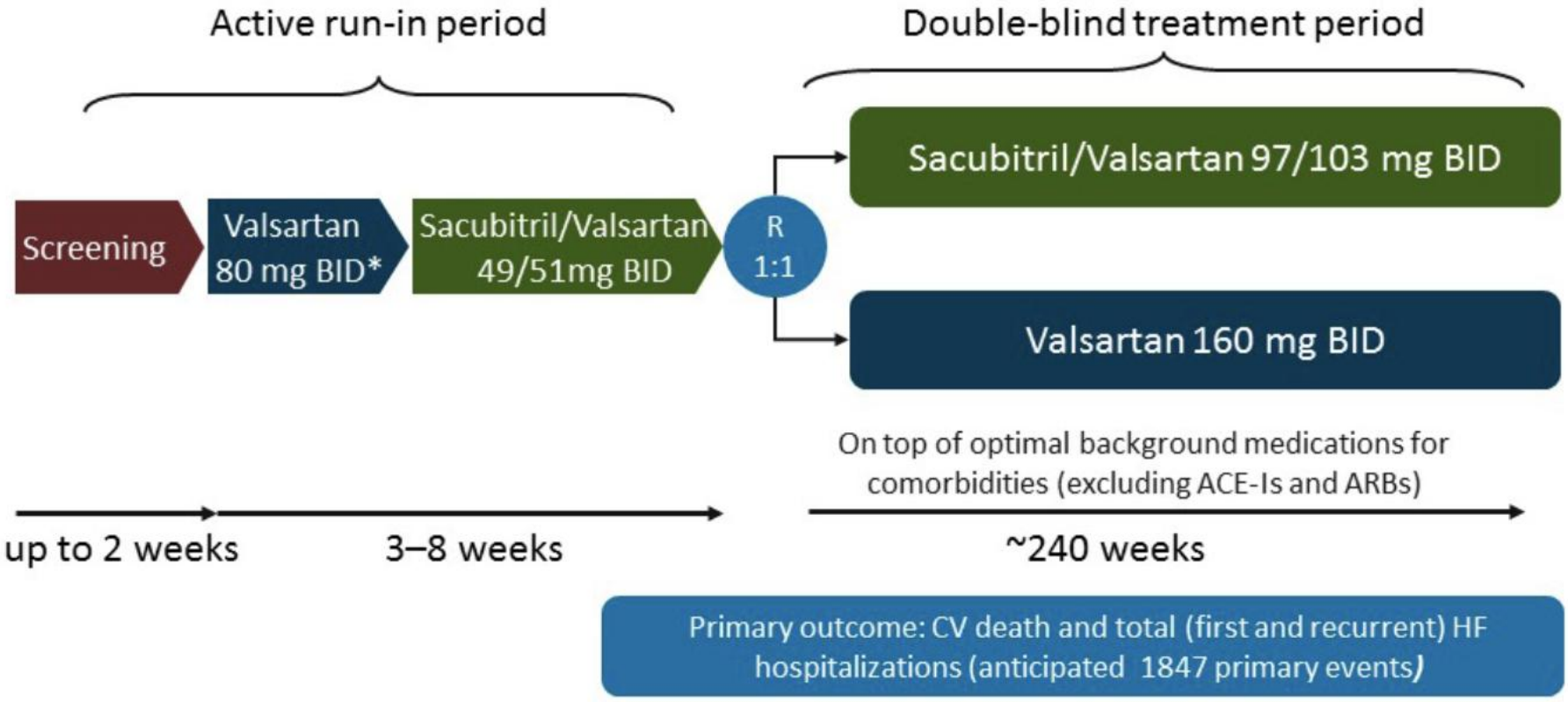
PARAMOUNT: Significant Improvement in Several Domains With Sacubitril/Valsartan



Vardeny, et al. *Clinical Pharmacology & Therapeutics*. 2013;94:445-448. © 2013 American Society for Clinical Pharmacology and Therapeutics.

PARAGON HF

Target patient population: ~4800 patients with symptomatic HF (NYHA class II–IV) and LVEF ≥45%



*Consult publication for study details

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

Acknowledgements

AHEPA University Hospital

Pulmonary Hypertension and Congenital Heart Disease Unit

Thank you

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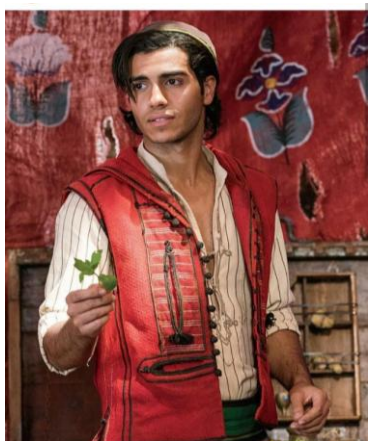
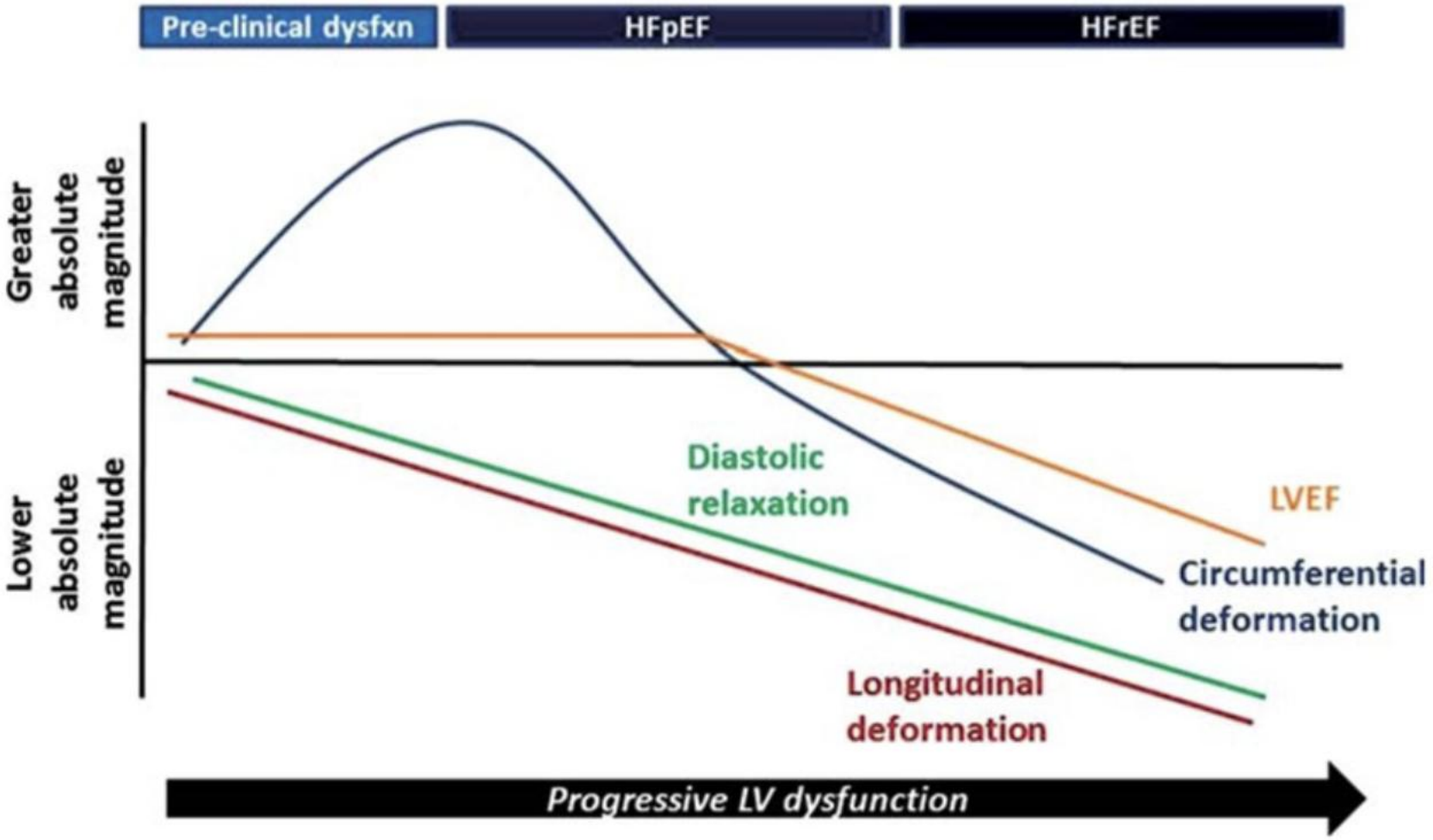


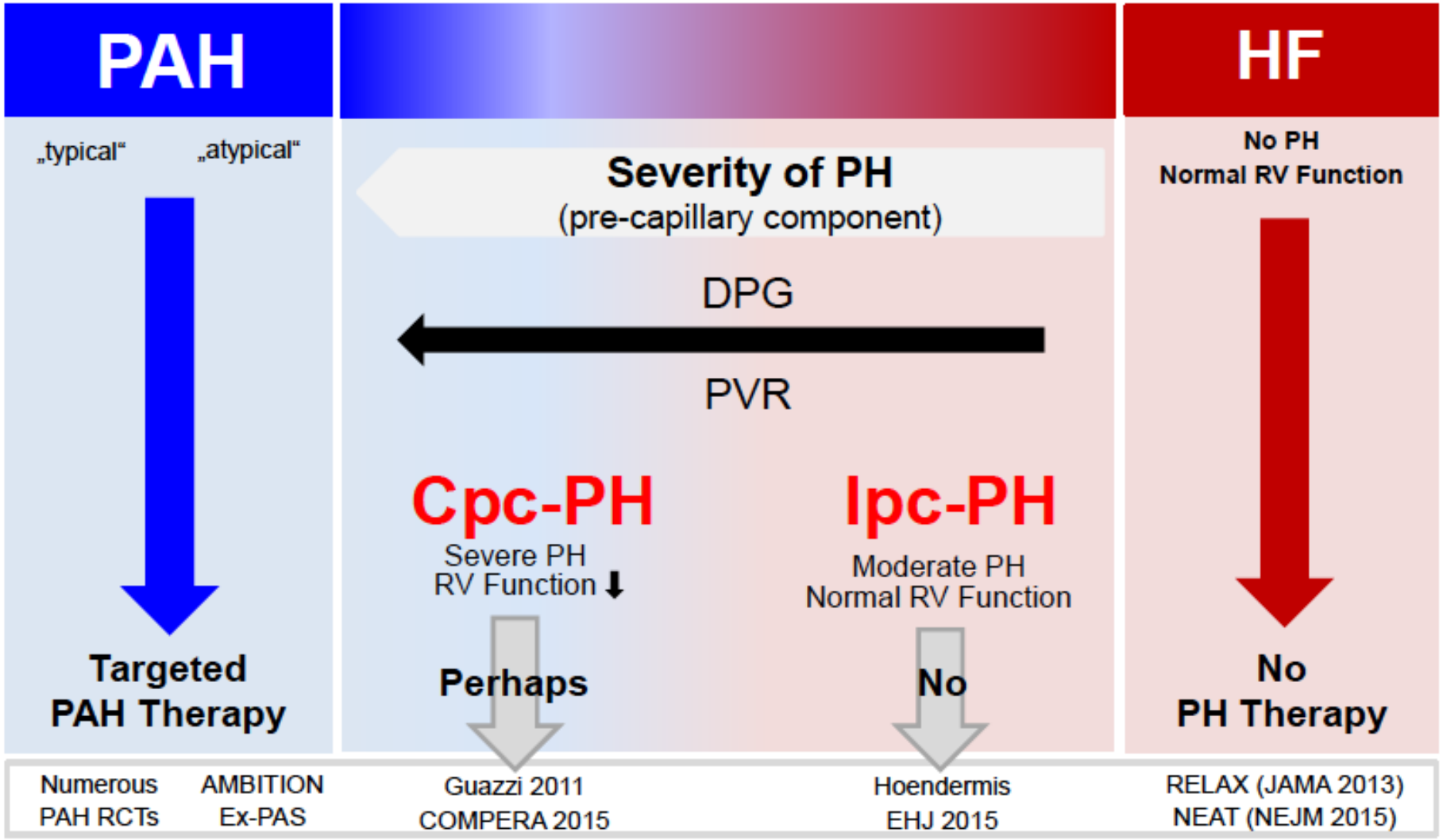
Thank you

Progressive Abnormalities in LV Diastolic and Systolic Function Underlying Heart Failure Across the LVEF Spectrum



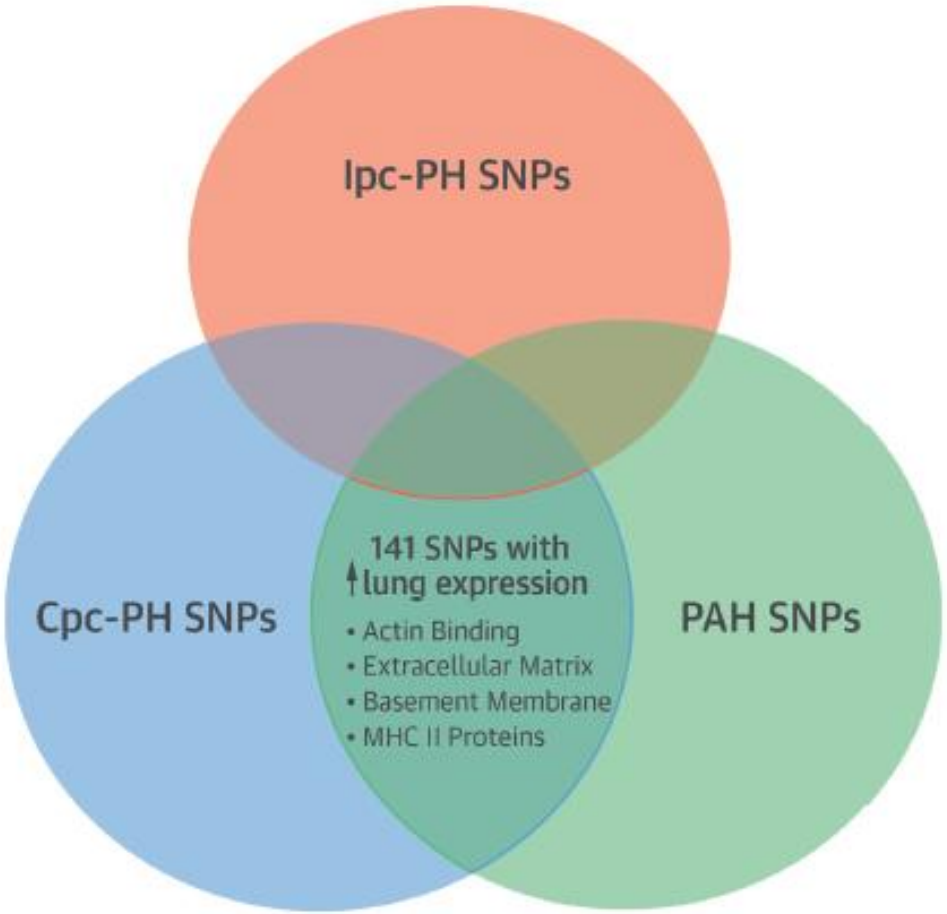
Shah A, et al. *Eur Heart J*. 2012;33:1716-7. By permission of Oxford University Press.

PAH vs. PH in Heart Failure: Spectrum of Phenotypes and Therapeutic Consequences



Cpc-PH: Combined post- and pre-capillary PH
Ipc-PH: Isolated post-capillary PH

Genetic similarities



Assad et al. J Am Coll Cardiol 2016

Management of pulmonary hypertension in left heart disease

Recommendations	Class[a]	Level[b]
Optimization of the treatment of the underlying condition is recommended before considering assessment of PH-LHD (i.e. treating structural heart disease).	I	C
It is recommended to identify other causes of PH (i.e. COPD, SAS, PE, CTEPH) and to treat them when appropriate before considering assessment of PH-LHD.	I	C
It is recommended to perform invasive assessment of PH in patients on optimized volume status.	I	C
Patients with PH-LHD and a severe pre-capillary component as indicated by a high DPG and/or high PVR should be referred to an expert PH center for a complete diagnostic work-up and an individual treatment decision.	IIa	C
The importance and role of vasoreactivity testing is not established in PH-LHD, except in patients who are candidates for heart transplantation and/or LV assist device implantation.	III	C
The use of PAH approved therapies is not recommended in PH-LHD.	III	C

Eur Heart J, 2015 doi: 10.1093/eurheartj/ehv317
Eur Respir J, 2015 doi: 10.1183/ 13993003.01032-2015

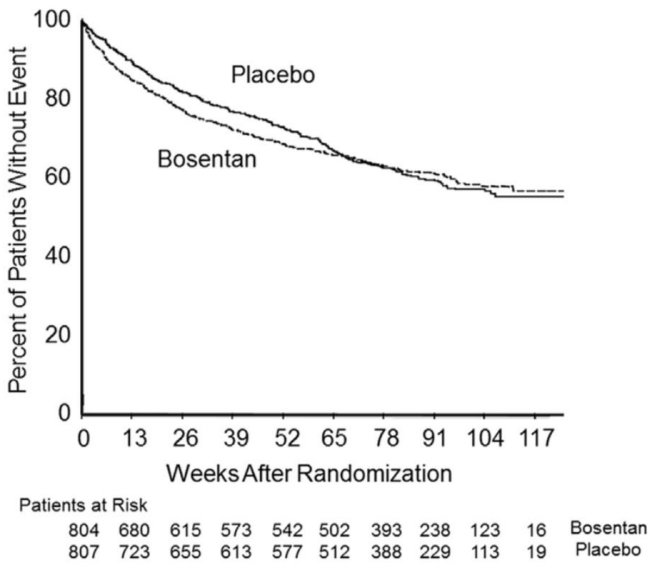
Long-Term Effect of Endothelin Receptor Antagonism With Bosentan on the Morbidity and Mortality of Patients With Severe Chronic Heart Failure

Primary Results of the ENABLE Trials

TABLE 1 Baseline Demographic and Clinical Characteristics

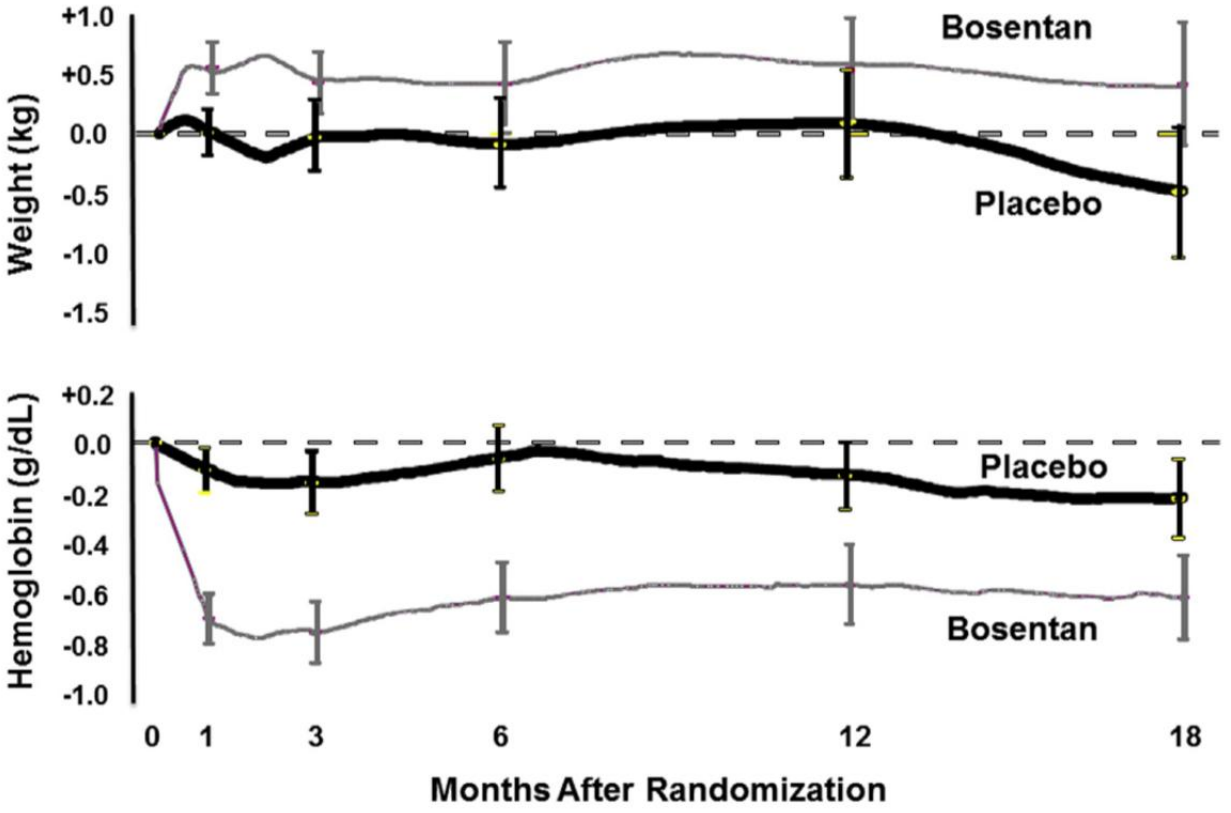
	Placebo (n = 807)	Bosentan (n = 804)
Age, yrs	66.9 ± 11.0	67.5 ± 11.0
Men/women	602/205	595/209
Race, black	47 (5.8)	53 (6.6)
Left ventricular ejection fraction	25.2 ± 6.3	24.8 ± 6.5
Etiology of heart failure, ischemic	575 (70.9)	542 (67.4)
Hospitalization for heart failure within 12 months	333 (41.3)	324 (40.7)
NYHA functional class IIIb/IV	734/73	730/74
History of coronary artery surgery	256 (31.7)	293 (36.4)
History of diabetes	265 (32.8)	271 (33.7)
Use of loop diuretics	769 (95.3)	767 (95.4)
Use of ACE inhibitor or angiotensin receptor blocker	773 (95.8)	772 (96.0)
Use of beta-blocker	404 (50.1)	417 (51.9)
Use of digitalis glycosides	460 (57.0)	468 (58.2)
Use of spironolactone	199 (24.7)	222 (27.6)
Use of nitrates	387 (44.2)	358 (44.5)
Use of hydralazine	17 (2.1)	16 (2.0)
Use of aspirin	410 (50.8)	391 (48.6)
Use of implantable cardioverter-defibrillator	45 (5.6)	66 (8.2)
Systolic blood pressure, mm Hg	119.8 ± 17.5	121.2 ± 18.5
Heart rate, beats/min	74.1 ± 11.6	74.3 ± 11.8
Serum creatinine, mg/dl	1.3 ± 0.4	1.3 ± 0.4

FIGURE 1 Freedom From All-Cause Mortality or Hospitalization for Heart Failure (Coprimary Endpoint)

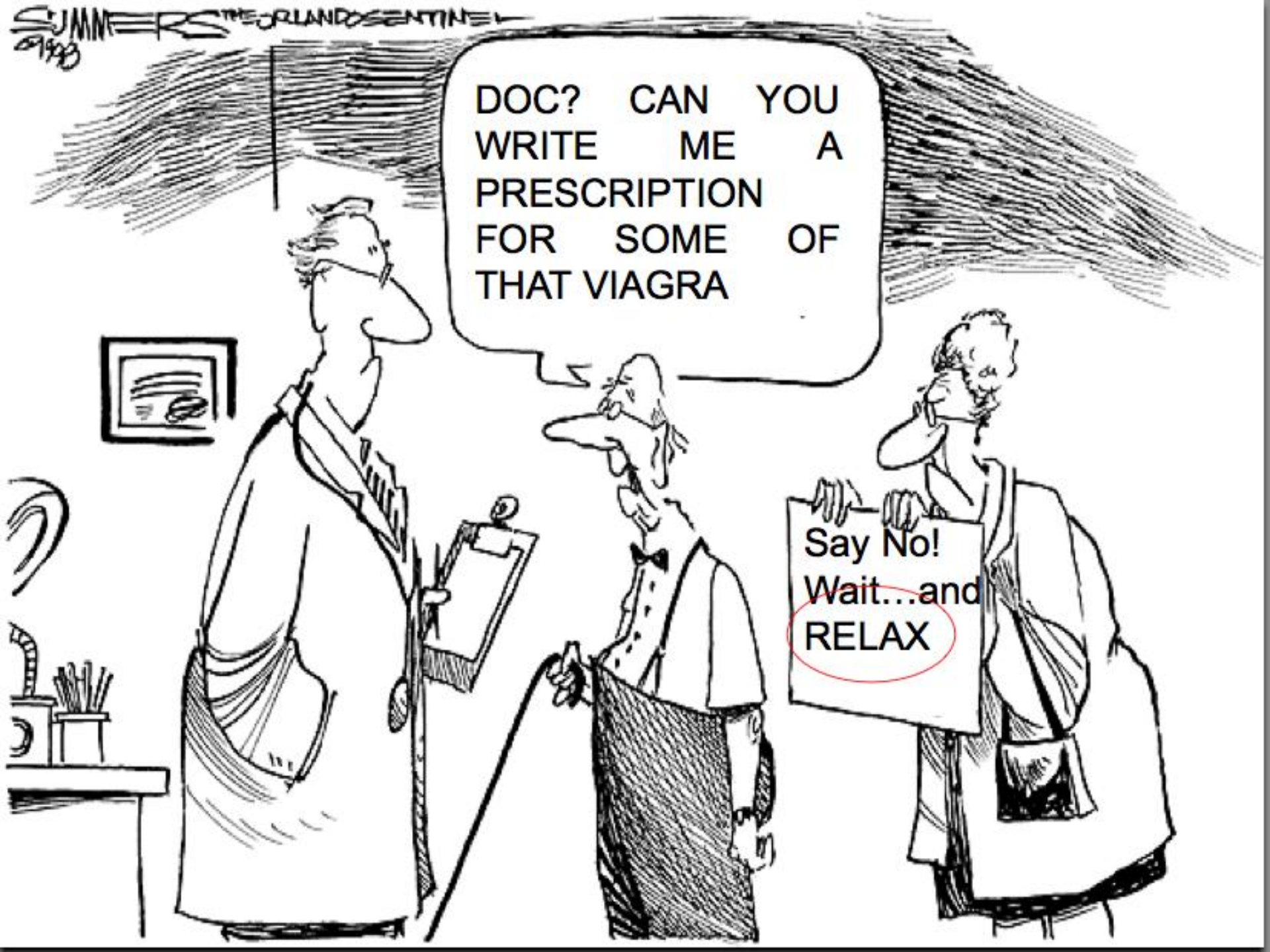


Packer M et al. JACC Heart Fail 2017

FIGURE 4 Changes in Body Weight and Hemoglobin in the Placebo and Bosentan Groups During Double-Blind Therapy



Packer M et al. JACC Heart Fail 2017


SUMMERS THE ORLANDO SENTINEL
DOC? CAN YOU WRITE ME A PRESCRIPTION FOR SOME OF THAT VIAGRA
Say No!
Wait…and
RELAX

HEART FAILURE NETWORK

Effect of Phosphodiesterase-5 Inhibition on Exercise Capacity and Clinical Status in Heart Failure with Preserved Ejection Fraction (RELAX):

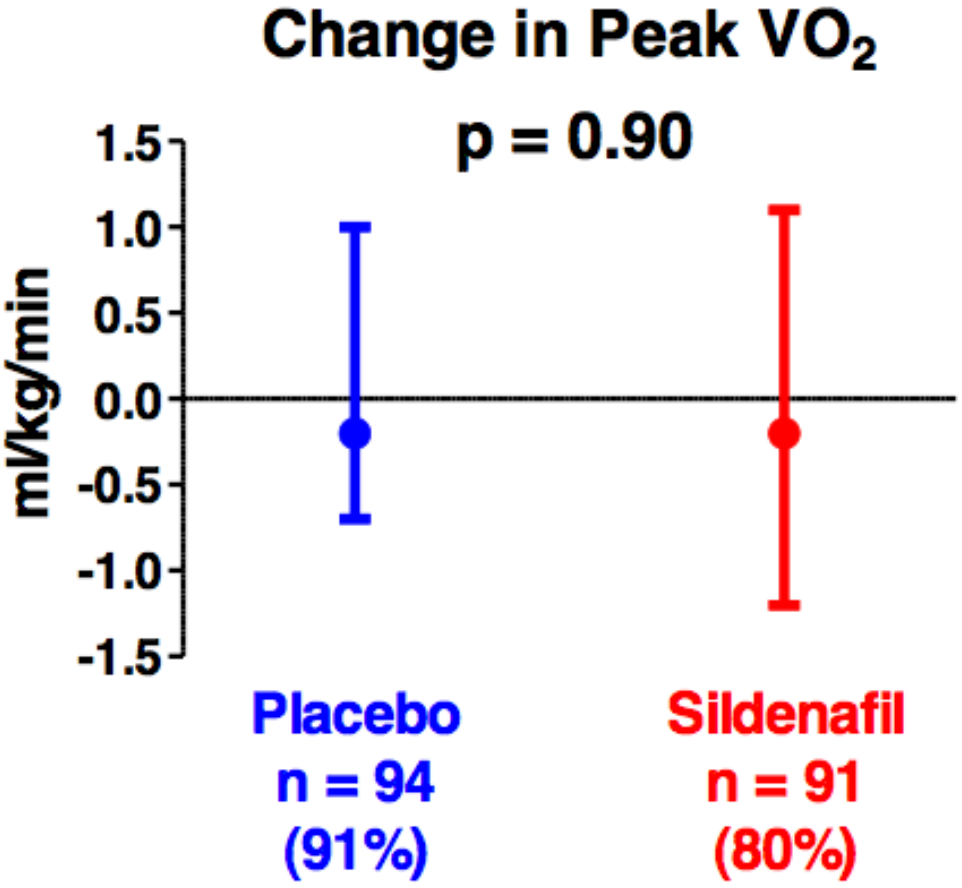
A Randomized Clinical Trial

Margaret M Redfield, MD
on behalf of the
NHLBI Heart Failure Clinical Research Network

U.S. Department of Health and Human Services
National Institutes of Health

National Heart Lung and Blood Institute
People Science Health

Results: Primary Endpoint



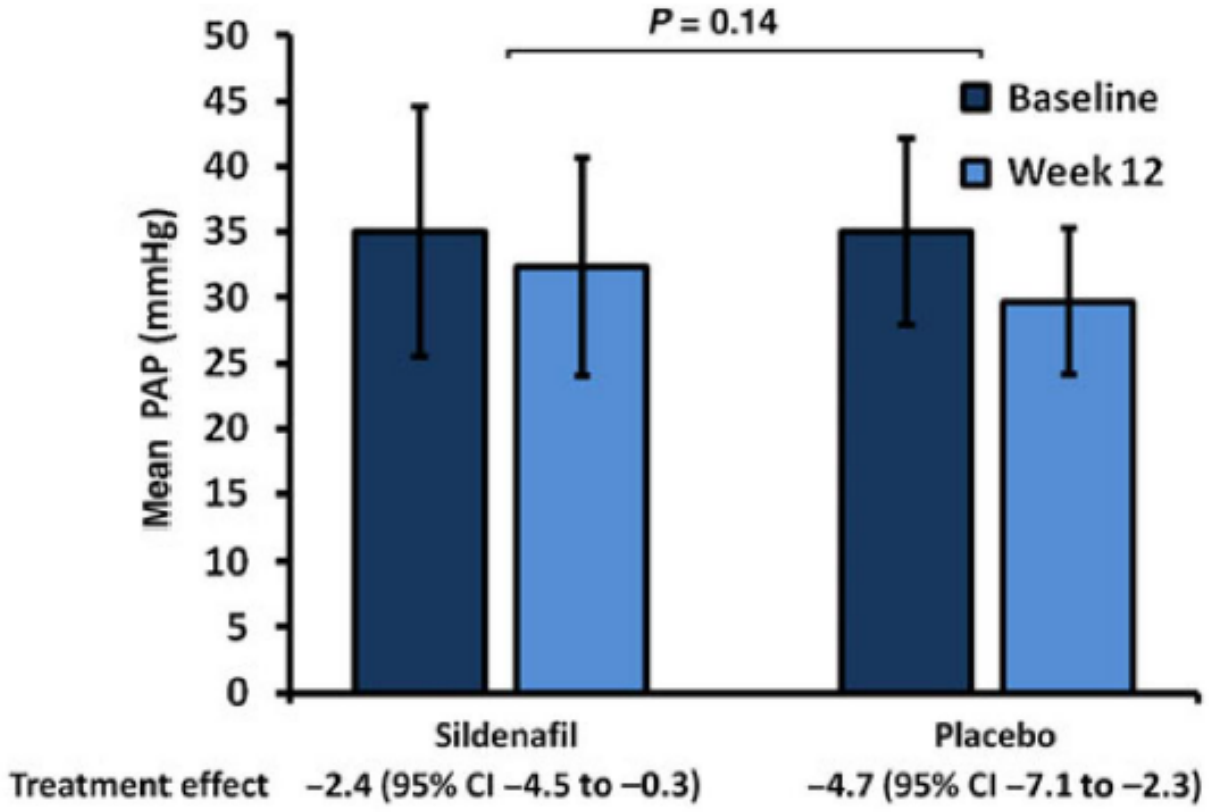
Sensitivity analyses for missing data

Multiple imputation: p = 0.98; LOCF: p = 0.98

Data are median and IQR

Sildenafil in Patients with HFpEF and Ipc-PH

A double-blind, randomized controlled Study (n=52)
(HFpEF, PH, mean PAPm 35 mHg, mean DPG 1 mmHg, mean PVR 2.4 WU)



Hoendermis-ES et al., *Eur Heart J* 2015; 36: 2565-2573

Management of pulmonary hypertension in left heart disease

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Eur Heart J, 2015 doi: 10.1093/eurheartj/ehv317
Eur Respir J, 2015 doi: 10.1183/ 13993003.01032-2015

- Males/females aged ≥18 years
- Chronic heart failure fulfilling the following criteria
  - Relevant structural heart disease and/or diastolic dysfunction
  - Ejection fraction ≥30% measured by echocardiography
  - NYHA functional class II or III
- 6MWD ≥150 m

- PH in WHO group 2 with the following RHC criteria
  - mPAP ≥25 mmHg at rest
  - PVR ≥ 3WU at rest
  - DPG ≥7 mmHg
  - PAWP 15–25 mmHg
- Optimal treatment of left heart failure with stable dose of oral diuretics

Vachiéry JL, *et al. Eur Respir J* 2018; 51:1701886.

Macitentan in pulmonary hypertension due to left ventricular dysfunction

	Macitentan	Placebo	Total
Subjects n	31	32	63
NYHA functional class n (%)			
II	5 (16.1)	10 (31.3)	15 (23.8)
III	26 (83.9)	22 (68.8)	48 (76.2)
Median (IQR) 6MWD m	300 (216–435)	305 (207–380)	300 (215–410)
Median (IQR) NT-proBNP pg·mL^{-1}	1458 (830–2700)	1756 (992–3503)	1515 (959–2921)
Median (IQR) pulse rate# beats·min^{-1}	80.0 (71.0–84.0)	74.5 (62.0–82.0)	77.0 (67.0–84.0)
Median (IQR) blood pressure¶ mmHg			
Systolic blood pressure	129.0 (120.0–138.0)	133.0 (119.0–147.5)	130.0 (120.0–140.0)
Diastolic blood pressure	77.0 (70.0–87.0)	72.0 (69.0–80.0)	75.0 (70.0–83.0)
Median (IQR) haemodynamic parameters			
PVR dyn·s·cm^{-5}	450.0 (296.0–590.0)	483.5 (362.0–738.5)	462.0 (341.0–695.0)
mPAP mmHg	44.0 (40.0–54.0)	48.5 (38.5–53.5)	47.0 (40.0–54.0)
mRAP mmHg	13.0 (10.0–17.0)	12.5 (10.0–16.5)	13.0 (10.0–17.0)
PAWP mmHg	20.0 (18.0–21.0)	20.0 (16.0–23.0)	20.0 (17.0–22.0)
TPR dyn·s·cm^{-5}	762.0 (571.0–1143.0)	882.5 (664.5–1191.0	813.0 (591.0–1158.0)
Cardiac index L·min^{-1}·m^{-2}	2.40 (2.10–3.00)	2.20 (1.90–2.60)	2.35 (1.90–2.70)
Cardiac output L·min^{-1}	4.90 (3.70–5.80)	4.15 (3.80–5.05)	4.60 (3.70–5.60)
TPG mmHg	27.0 (21.0–33.0)	27.5 (21.5–33.5)	27.0 (21.0–33.0)
DPG mmHg	10.0 (8.0–15.0)	10.0 (8.0–13.5)	10.0 (8.0–14.0)
Mixed venous oxygen saturation %	72.0 (61.0–73.0)	61.0 (49.0–65.0)	64.5 (59.0–72.0)

Vachiéry JL et al. Eur Respir J. 2018

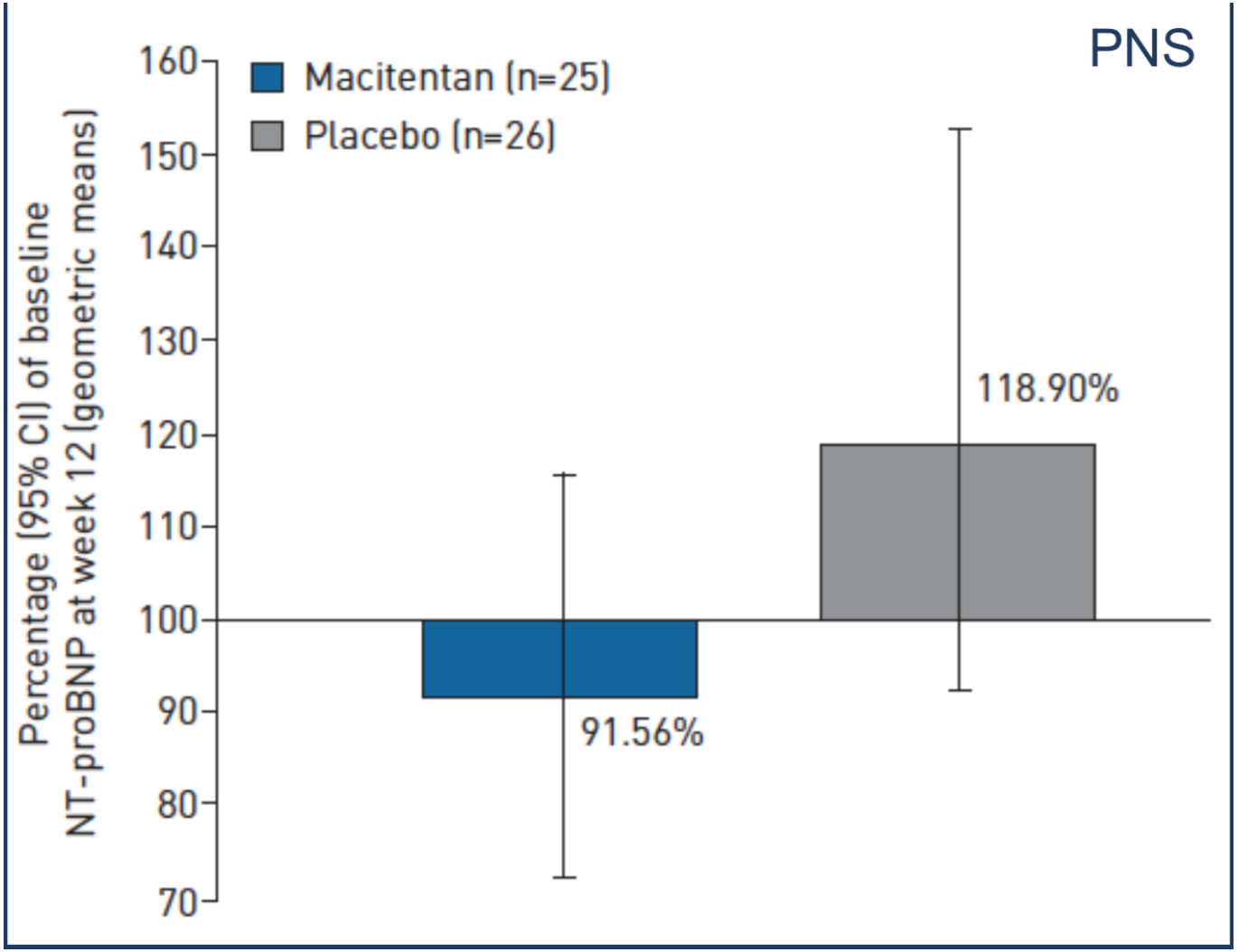
Exploratory hemodynamics analysis

TABLE 4 Treatment effect for haemodynamic parameters at week 12

	Mean absolute change from baseline (95% CI)
PVR dyn·s·cm^{-5}	0.93 (0.64–1.36)[#,¶]
mPAP mmHg	0.3 (–4.3–4.9)
mRAP mmHg	0.7 (–2.2–3.6)
PAWP mmHg	–0.3 (–4.2–3.7)
TPR dyn·s·cm^{-5}	–162.2 (–318.0–6.5)
Cardiac index L·min^{-1}·m^{-2}	0.4 (0.1–0.7)
Cardiac output L·min^{-1}	0.8 (0.3–1.4)
TPG mmHg	0.7 (–3.7–5.1)
DPG mmHg	–0.4 (–4.5–3.6)
Mixed venous oxygen saturation %	–0.4 (–4.6–3.8)

Vachiery JL et al. Eur Respir J 2018; 51: 1701886 [https://doi.org/10.1183/13993003.01886-2017[

Exploratory biomarker analysis



Short-term RCTs have failed to show evidence of PAH-specific therapy in PH-LHD

Study	Study Drug	N	Duration	Population	Primary endpoint	Result
Guazzi [1]	Sildenafil	44	12 mo	HFpEF	HD, RV performance	Improvement in PVR and exercise
LEPHT [2]	Riociguat	201	16 W	HF rEF	Change in mPAP at rest from baseline to week 16	No significant effect on mPAP compared with pbo
Hoendermis[3]	Sildenafil	52	12 W	HF pEF	Change in mPAP from baseline to week 12	No reduction in mPAP or improvement in other parameters
SIOVAC [4]	Sildenafil	231	24 W	VHD	Composite of all-cause mortality or hospital admission for HF, worsening of WHO FC, or of GA score	Associated with unfavourable clinical outcomes compared with placebo
MELODY-1[5]	Macitentan	48	12 W	HF LVEF > 30%	Proportion of subjects with significant fluid retention or worsening in FC	Main endpoint more frequently met on macitentan (+10%)

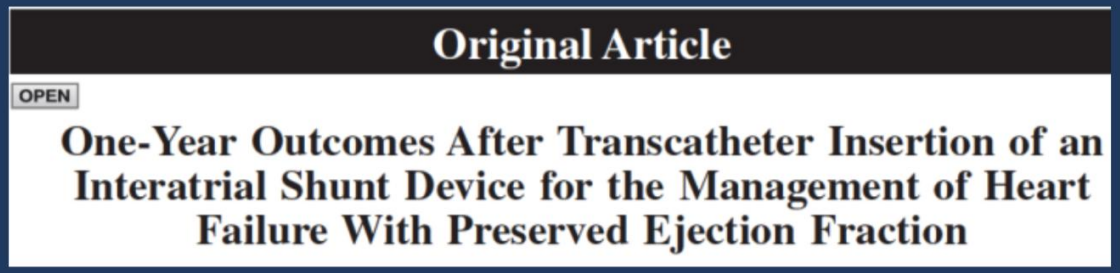
1. Guazzi et al. Circulation 2011. Bonderman et al. Circulation 2013; 128: 502-511. 2. Bonderman D et al. Chest. 2014;146(5):1274-85. 3. Hoendermis E, et al. Eur Heart J 2015; 36:2565-73. 4. Bermejo J et al. Eur Heart J 2017; 38. doi:10.1093/eurheartj/ehx700. 5.Vachiery JL et al. Eur Respir J 2018; 51: 1702589

Planned/ongoing studies for the treatment of PH due to HFpEF

Study	Study Drug	N	Duration	Population	Primary outcome
SERENADE NCT03153111	Macitentan	300	52 W	• LVEF ≥ 40% and ESC defined HFpEF • HF hospitalization < 12 months and/or PAWP or LVEDP > 15 mmHg within 6 m • Elevated NT-proBNP • PVD or RVD	• % change from baseline in NT-proBNP @W24
SOPRANO NCT02554903	Macitentan	78	12 W	• LVAD within 45 days • PH (RHC) PAWP ≤ 18 mmHg + PVR > 3 WU	• PVR ratio of Week 12 to Baseline
NCT03037580	Oral treprostinil	310	24 W	• HFpEF with RHC 90 days of randomizatio • 6MWD > 200 meters	• Change in 6MWD from Baseline to Week 24
DYNAMIC NCT02744339	Oral riociguat 1.5 mg tid	114	26 W	• HFpEF • mPAP ≥ 25 mmHg + PAWP > 15 mmHg	• Change in CO
PASSION *	Oral tadalafil	320	NA	• HF pEF • PH with PAWP > 15 mmHg AND mPAP ≥ 25 mmHg AND PVR > 3 WU	• Time to 1st event (HF hospitalization or death, independently adjudicated)

* Courtesy of Stephan Rosenkranz and Marius Hoeper

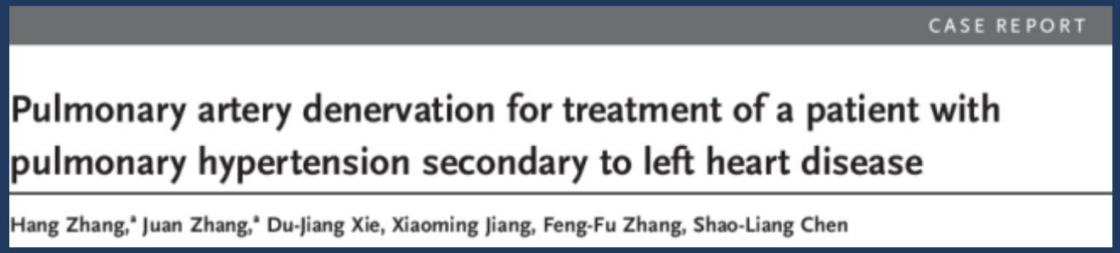
Mechanical intervention to improve HFpEF and/or PH-LHD


Original Article

OPEN

One-Year Outcomes After Transcatheter Insertion of an Interatrial Shunt Device for the Management of Heart Failure With Preserved Ejection Fraction

- Hasenfuss G et al. Lancet. 2016;387:1298–1304
- Kaye DM et al. Circ Heart Fail. 2016;9:e003662.


CASE REPORT

Pulmonary artery denervation for treatment of a patient with pulmonary hypertension secondary to left heart disease

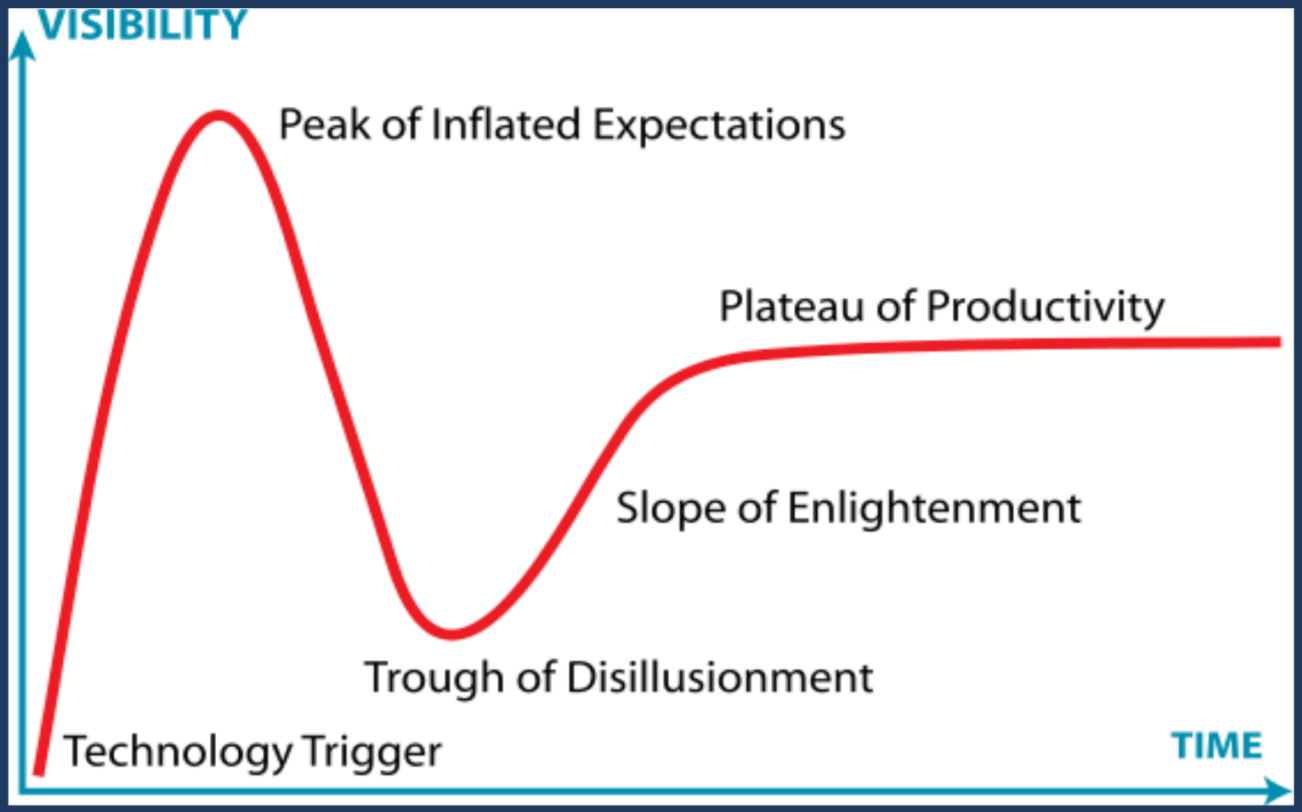
Hang Zhang,* Juan Zhang,* Du-Jiang Xie, Xiaoming Jiang, Feng-Fu Zhang, Shao-Liang Chen

- Chen SL et al. Circ Cardiovasc Interv 2015;8:e002837 8
- Zang H et al. Pulm Circ 2016;6:240-243

Management of pulmonary hypertension in left heart disease

Recommendations	Class[a]	Level[b]
Optimization of the treatment of the underlying condition is recommended before considering assessment of PH-LHD (i.e. treating structural heart disease).	I	C
It is recommended to identify other causes of PH (i.e. COPD, SAS, PE, CTEPH) and to treat them when appropriate before considering assessment of PH-LHD.	I	C
It is recommended to perform invasive assessment of PH in patients on optimized volume status.	I	C
Patients with PH-LHD and a severe pre-capillary component as indicated by a high DPG and/or high PVR should be referred to an expert PH center for a complete diagnostic work-up and an individual treatment decision.	IIa	C
The importance and role of vasoreactivity testing is not established in PH-LHD, except in patients who are candidates for heart transplantation and/or LV assist device implantation.	III	C
The use of PAH approved therapies is not recommended in PH-LHD.	III	C

Eur Heart J, 2015 doi: 10.1093/eurheartj/ehv317
Eur Respir J, 2015 doi: 10.1183/ 13993003.01032-2015



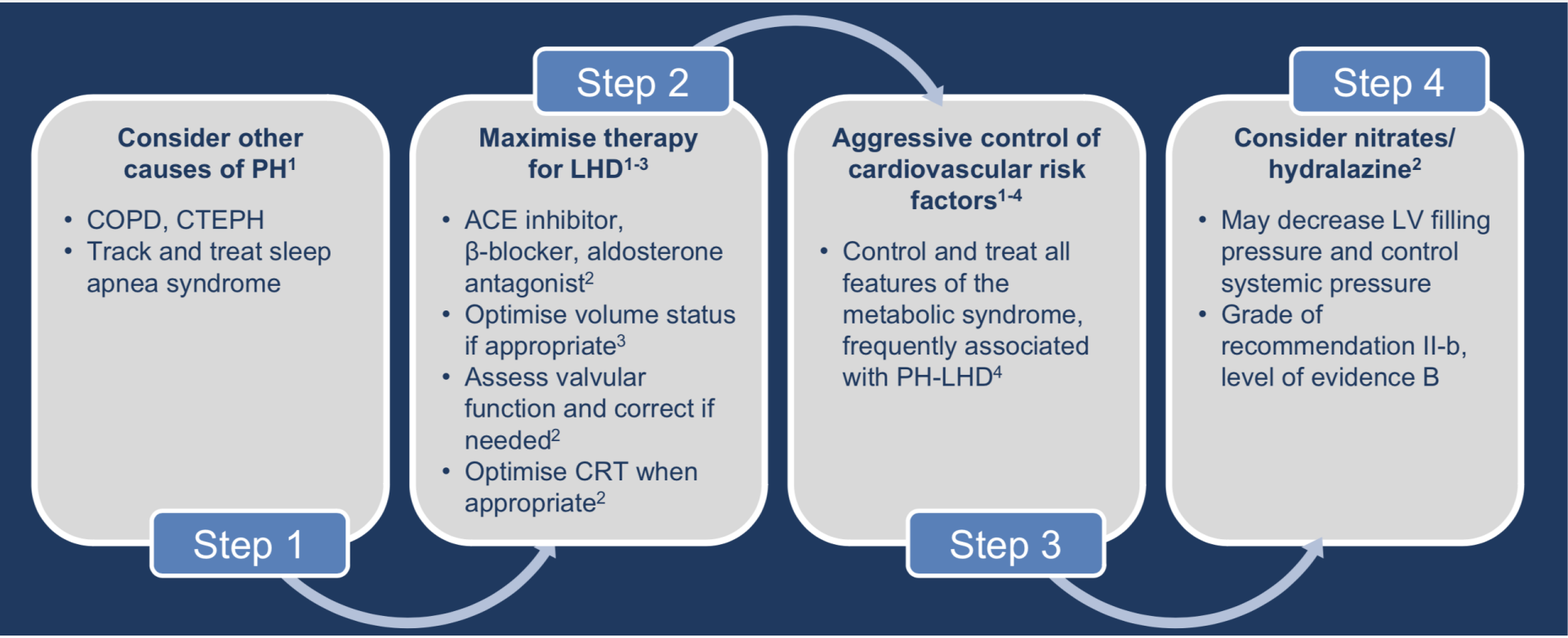
https://www.gartner.com/en/research/methodologies/gartner-hype-cycle

Take home messages

- If pursued, future trials should be limited to PH due to HFpEF with CpcPH. The agent of choice should ideally be a HFpEF disease-modifying drug.

- A proof-of-concept study should be performed first, with safety and tolerability, haemodynamic and/or CPET efficacy end-points.

Management of PH-LHD patients: focus on the left heart and comorbidities



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

- No standard care for patients with HFpEF
- No study met the primary endpoint
- PH is a complication of the disease with no established therapy

Pulmonary Hypertension Phenotypes: „Typical“ and „atypical“ IPAH versus CpcPH-HFpEF

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Pre-Capillary, Combined, and Post-Capillary Pulmonary Hypertension

A Pathophysiological Continuum

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Opitz et al., COMPERA Investigators, *J Am Coll Cardiol* 2016; 68: 368-378

Pre-Capillary, Combined, and Post-Capillary Pulmonary Hypertension

A Pathophysiological Continuum

TABLE 1 Baseline Characteristics

	All Patients (N = 786)	Typical IPAH (n = 421)	Atypical IPAH (n = 139)	Typical vs. Atypical IPAH p Value	PH-HFpEF (n = 226)	Typical IPAH vs. PH-HFpEF p Value	Atypical IPAH vs. PH-HFpEF p Value
Age, yrs	66.6 ± 15.0	61.5 ± 17.3	71.3 ± 9.2	<0.001	73.2 ± 8.3	<0.001	0.434
Female	467 (59.4)	250 (59.4)	77 (55.4%)	1.000	140 (61.9)	1.000	0.686
BMI, kg/m^2	28.1 (24.5-32.6)	26.0 (23.3-29.8)	32.2 (28.3-36.0)	<0.001	29.6 (25.7-34.0)	<0.001	0.002
WHO-FC				0.089		<0.001	0.315
I/II	91 (11.8)	71 (17.4)	12 (8.8)		8 (3.6)		
III	540 (70.3)	275 (67.6)	96 (70.6)		169 (75.1)		
IV	137 (17.8)	61 (15.0)	28 (20.6)		48 (21.3)		
6MWD, m	289.5 ± 121.8	319.0 ± 123.5	250.5 ± 104.2	<0.001	260.0 ± 115.0	<0.001	0.787
RAP, mm Hg	9.8 ± 5.4	8.5 ± 5.2	8.9 ± 4.8	0.615	12.9 ± 4.8	<0.001	<0.001
PAPm, mm Hg	46.0 ± 11.9	46.9 ± 13.3	43.9 ± 10.7	0.025	45.7 ± 9.4	0.437	0.326
PAWP, mm Hg	12.5 ± 6.0	9.3 ± 3.4	10.0 ± 3.6	0.186	19.9 ± 4.4	<0.001	<0.001
TPG, mm Hg	33.5 ± 13.1	37.6 ± 13.6	33.9 ± 11.1	0.006	25.8 ± 9.1	<0.001	<0.001
Cardiac index, l/min/m^2	2.2 ± 0.8	2.3 ± 0.8	2.2 ± 0.8	0.629	2.2 ± 0.7	0.653	0.988
PVR, Wood Units	9.6 ± 6.7	10.8 ± 6.0	9.8 ± 10.6	0.309	7.0 ± 3.4	<0.001	<0.001
SvO_2, %	62.2 ± 9.0	62.1 ± 9.9	62.7 ± 9.0	0.804	62.1 ± 6.9	0.999	0.863
BNP, pg/ml	269 (127-541)	287 (119-543)	200 (115-469)	1.000	310 (186-638)	0.963	0.312
NT-proBNP, pg/ml	1,738 (621-3,891)	1,435 (541-3,888)	1,683 (478-2,815)	1.000	2,196 (1,125-4,285)	0.021	0.066
Arterial hypertension	66.5	43.2	98.6	<0.001	91.9	<0.001	0.021
CAD	32.0	15.7	59.7	<0.001	46.4	<0.001	0.049
Diabetes mellitus	30.6	10.7	74.8	<0.001	41.2	<0.001	<0.001
AF	28.9	10.7	42.4	<0.001	54.4	<0.001	0.187
BMI >30 kg/m^2	37.6	23.5	65.2	<0.001	47.1	<0.001	0.002

TABLE 2 Targeted PH Therapies

	All Patients	Typical IPAH	Atypical IPAH	Typical vs. Atypical IPAH p Value	PH-HFpEF	Typical IPAH vs. PH-HFpEF p Value	Atypical IPAH vs. PH-HFpEF p Value
PH treatment initiated within first 3 months							
n	786	421	139		226		
ERA	22.6	31.4	22.3	0.157	6.6	<0.001	<0.001
PDE5i	82.4	76.7	81.3	0.870	93.8	<0.001	0.001
PCA	1.7	2.6	0.7	0.931	0.4	0.197	1.000
2 or more PH drugs	11.7	17.8	7.9	0.013	2.7	<0.001	0.112
Anticoagulation	63.0	56.3	69.8	0.016	71.2	0.001	1.000
PH treatment at 1 year							
n	396	207	81		108		
ERA	36.4	48.3	35.8	0.195	13.9	<0.001	0.002
PDE5i	80.6	83.6	75.3	0.391	78.7	0.857	1.000
PCA	4.5	5.8	4.9	1.000	1.9	0.452	1.000
2 or more PH drugs	30.6	44.4	25.9	0.014	7.4	<0.001	0.003
Anticoagulation	67.5	62.8	71.6	0.513	73.4	0.184	1.000

Opitz et al. J Am Coll Cardiol 2016

TABLE 3 Discontinuations of PH Therapies

	All Patients (N = 786)	Typical IPAH (n = 421)	Atypical IPAH (n = 139)	Typical vs. Atypical IPAH p Value	PH-HFpEF (n = 226)	Typical IPAH vs. PH-HFpEF p Value	Atypical IPAH vs. PH-HFpEF p Value
PDE5i ever	696 (88.5)	359 (85.3)	120 (86.3)	1.000	217 (96.0)	<0.001	0.003
Patients with follow-up	618	306	106		206		
PDE5i discontinuations	79 (12.8)	27 (8.8)	14 (13.2)	0.578	38 (18.4)	0.005	0.795
Side effects	23 (3.7)	8 (2.6)	4 (3.8)	1.000	11 (5.3)	0.454	1.000
Efficacy failure	33 (5.3)	9 (2.9)	3 (2.8)	1.000	21 (10.2)	0.003	0.071
Other*	25 (4.0)	11 (3.6)	7 (6.6)	0.801	7 (3.4)	1.000	0.745
ERA ever	322 (41.0)	225 (53.4)	61 (43.9)	0.188	36 (15.9)	<0.001	<0.001
Patients with follow-up	281	190	56		35		
ERA discontinuations	56 (19.9)	28 (14.7)	13 (23.2)	0. 462	15 (42.9)	0.001	0.188
Side effects	36 (12.8)	18 (9.5)	10 (17.9)	0.286	8 (22.9)	0.117	1.000
Efficacy failure	9 (3.2)	4 (2.1)	1 (1.8)	1.000	4 (11.4)	0.066	0.210
Other†	11 (3.9)	6 (3.2)	2 (3.6)	1.000	3 (8.6)	0.447	1.000

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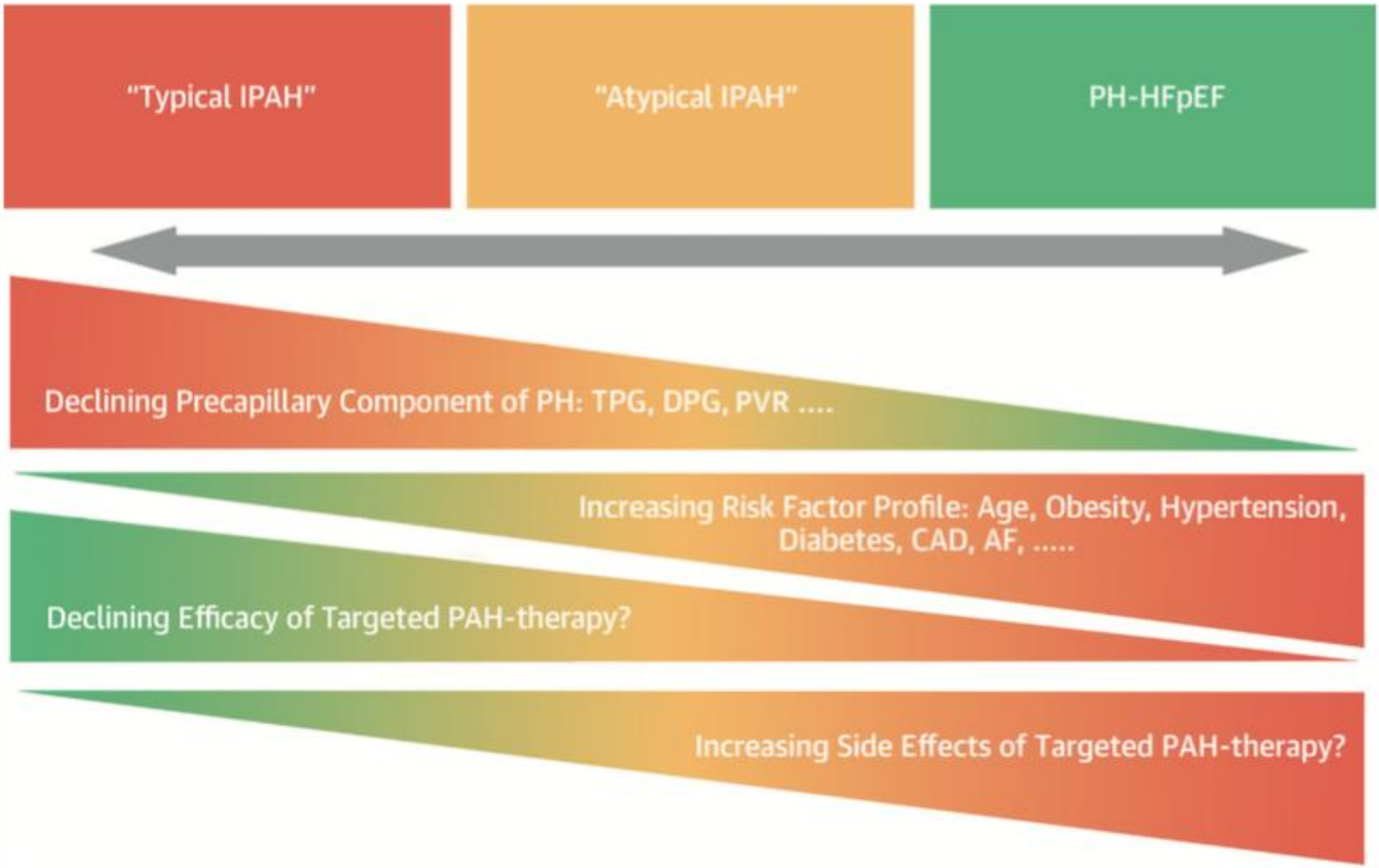
TABLE 4 Response to Targeted PH Therapy

	Typical IPAH	Atypical IPAH	Typical vs. Atypical IPAH p Value	PH-HFpEF	Typical IPAH vs. PH-HFpEF p Value	Atypical IPAH vs. PH-HFpEF p Value
6MWD, m						
Baseline	320 (234 to 417)	250 (175 to 332)	<0.001	270 (165 to 345)	<0.001	1.000
12 months	414 (324 to 460)	310 (240 to 379)	<0.001	330 (194 to 380)	<0.001	1.000
Change from baseline in 6MWD, m						
Mean ± SD	52 ± 101	58 ± 84	1.000	33 ± 82	0.453	0.904
Median (IQR)	50 (1 to 00)	60 (10 to 75)		29 (−10 to 74)		
WHO-FC I/II						
Baseline	17.4	8.8	0.056	3.6	<0.001	0.164
12 months	39.5	26.2	0.208	23.0	0.026	1.000
Improvement of WHO-FC	34.5	36.9	1.000	36.8	1.000	1.000
Change from baseline in NT-proBNP/BNP, %	−42.6 (−77.1 to 17.4)	−35.9 (−69.9 to 13.8)	1.000	−13.7 (−40.6 to 32.2)	0.031	0.248

Opitz et al. J Am Coll Cardiol 2016

CENTRAL ILLUSTRATION Pulmonary Hypertension in Typical PAH, Atypical PAH, and HFpEF



Opitz, C.F. et al. J Am Coll Cardiol. 2016;68(4):368–78.

Recent Trials in Heart Failure and PH