HFpEF: Pathophysiology & Treatment

Barry A. Borlaug, MD
Mayo Clinic, Rochester, MN

borlaug.barry@mayo.edu

Disclosure

Financial Relationships

Research Support:

Aires Pharmaceuticals, Medtronic, GSK

Consulting/Advisory Board:

Amgen, Merck, AstraZeneca

Off-Label/Investigational Uses

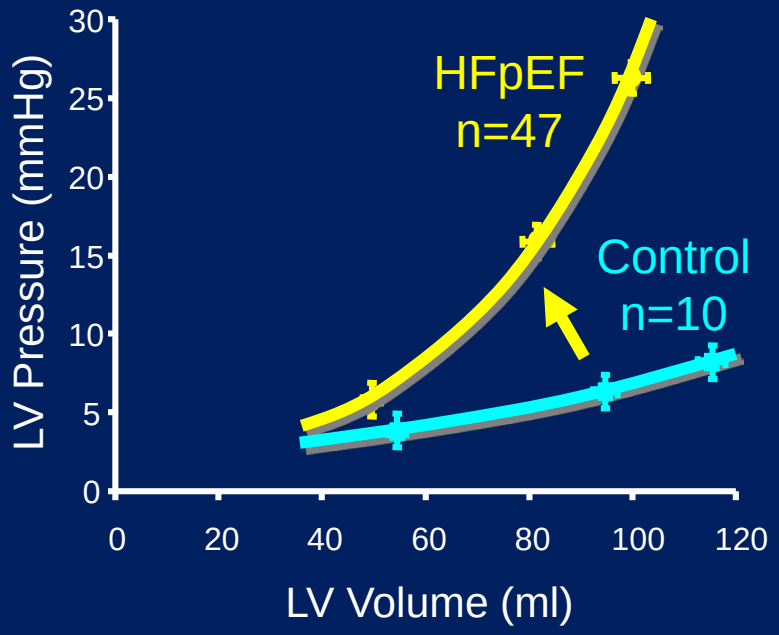
None

Outline

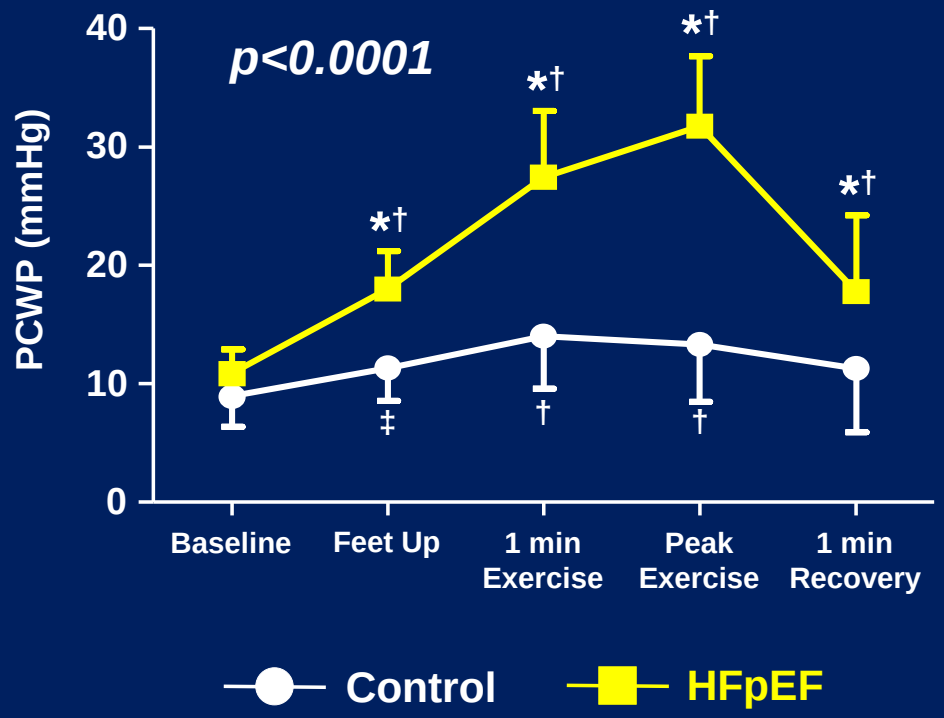
- Pathophysiology
- Treatment

Pathophysiology of HFpEF

LV Diastolic Dysfunction

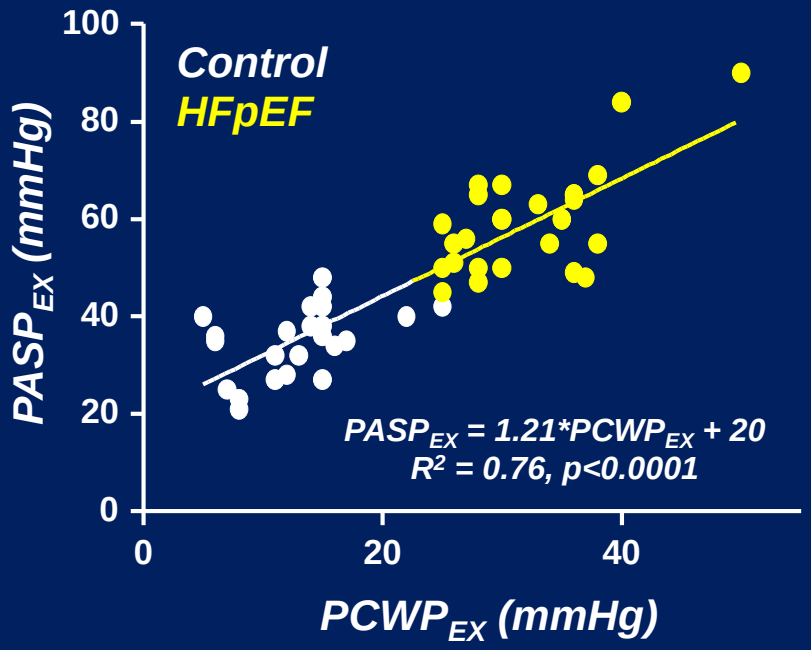


Zile *New Eng J Med* 2004

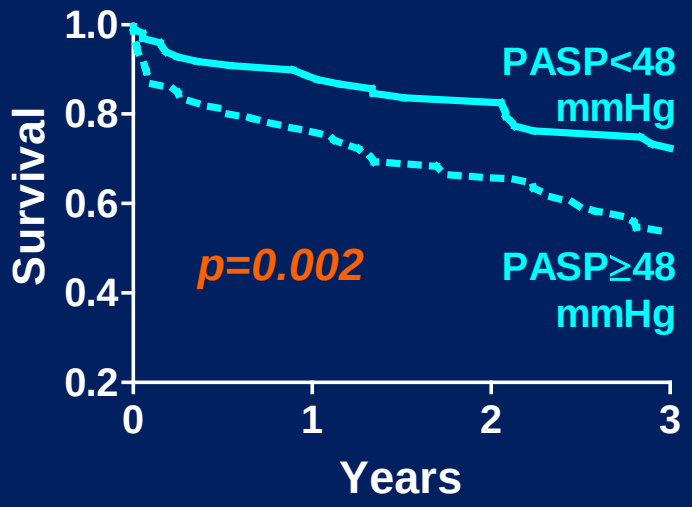


Borlaug *Circ Heart Fail* 2010

↑LVFP causes PH, linked to ↑mortality



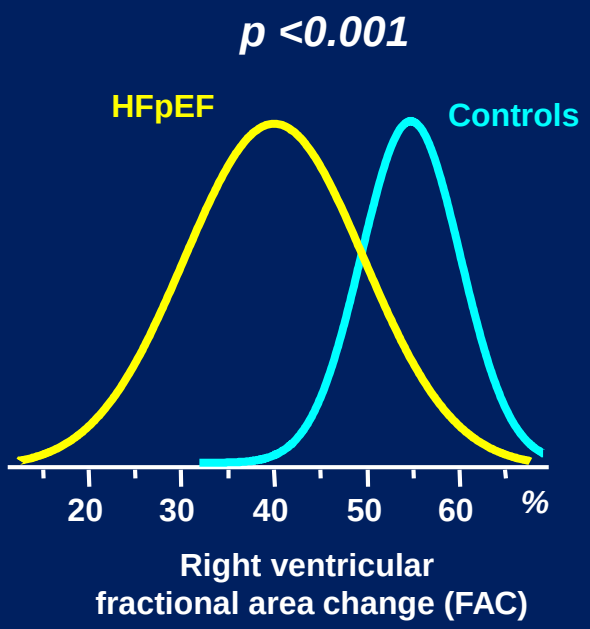
Borlaug *Circ Heart Fail* 2010

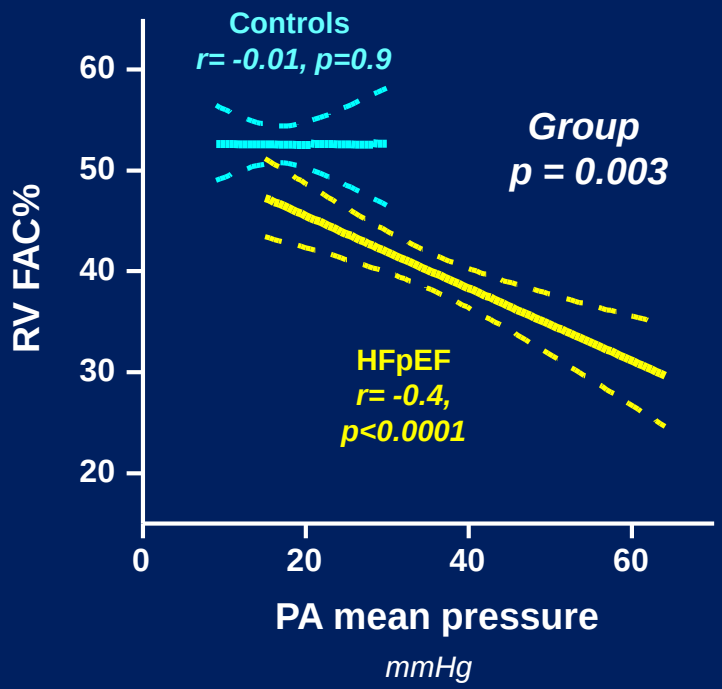


	Number remaining			
PASP<48 mmHg	98	86	80	44
PASP≥48 mmHg	105	78	67	38

Lam *J Am Coll Cardiol* 2009

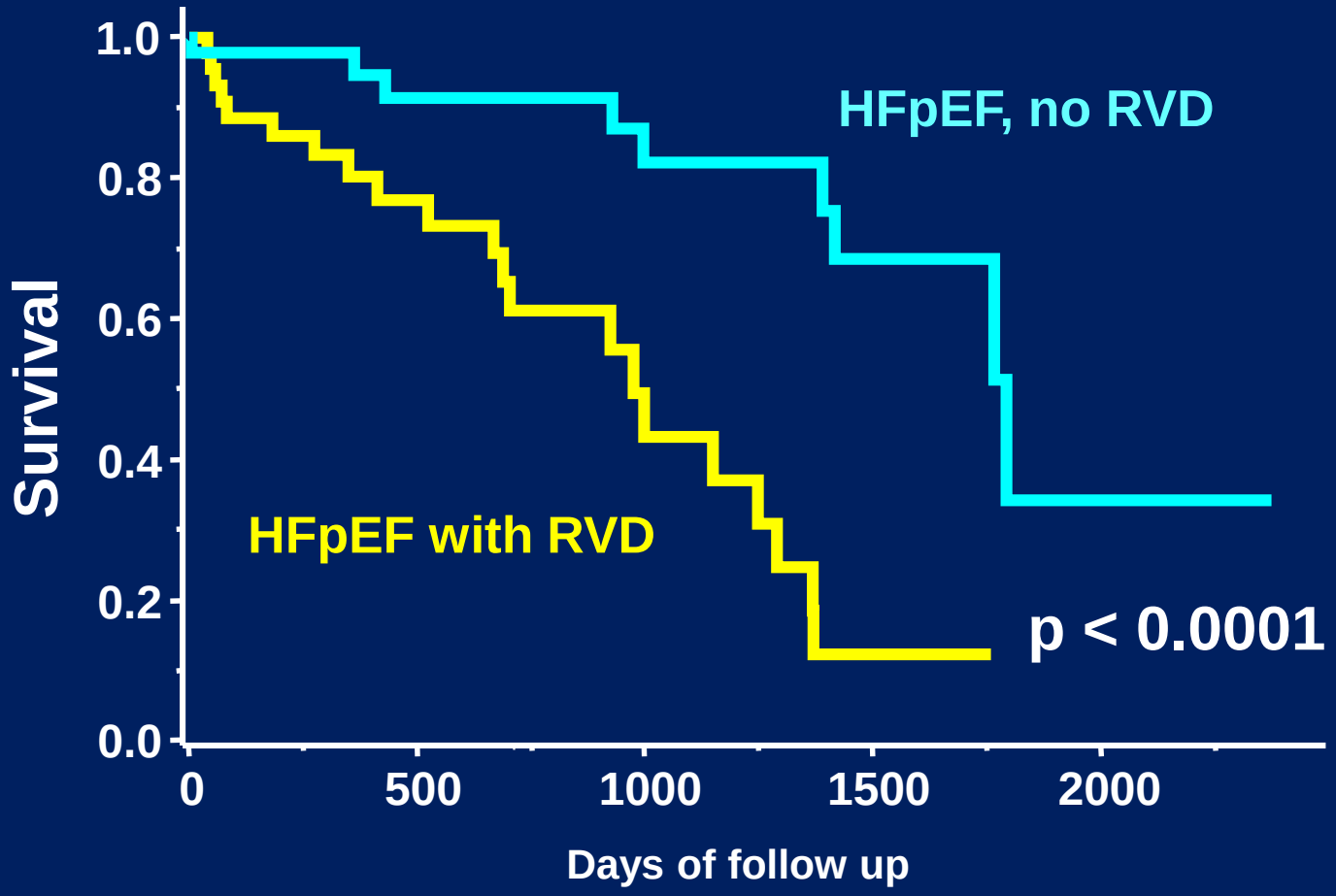
The RV: The first victim of PH





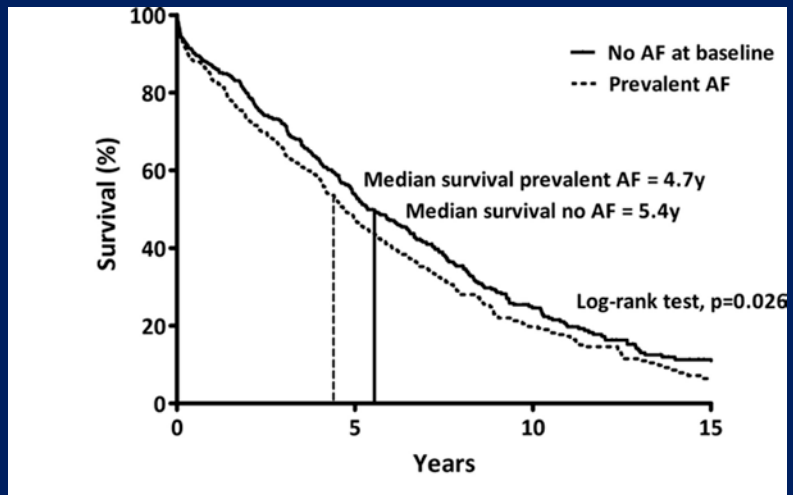
Melenovsky, Borlaug *Eur Heart J* 2014

RVD predicts ↑mortality in HFpEF, independent of PA pressures



Melenovsky, Borlaug *Eur Heart J* 2014

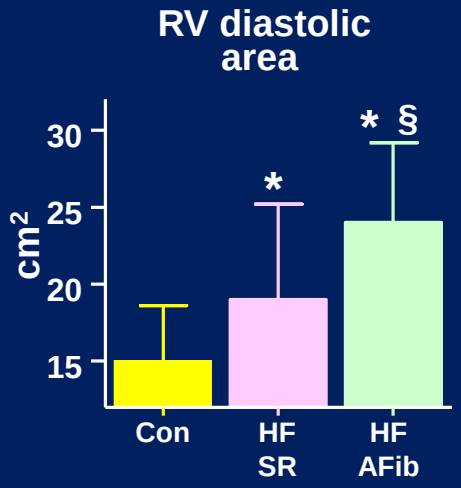
Afib in HFpEF

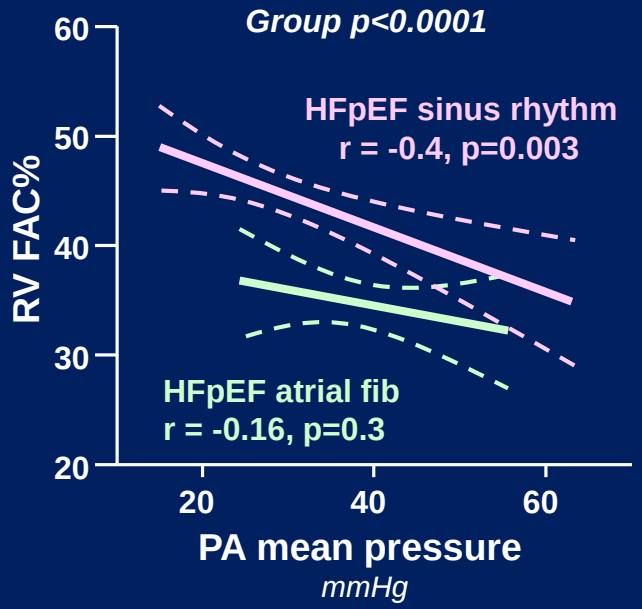


Model	Sample Size	Linear Regression Analysis (Peak Vo_2) Estimated Difference Between AF and SR, mL/kg per min	95% CI	*P* Value
Unadjusted	202	–1.2	–2.0 to –0.3	0.008
Adjusted for age/sex	202	–0.9	–1.7 to –0.1	0.03
Adjusted for age/sex/EF	199	–0.9	–1.8 to –0.1	0.03
Adjusted for age/sex/EF and exercise modality*	199	–1.0	–1.9 to –0.2	0.02

Zakeri *Circulation* 2013

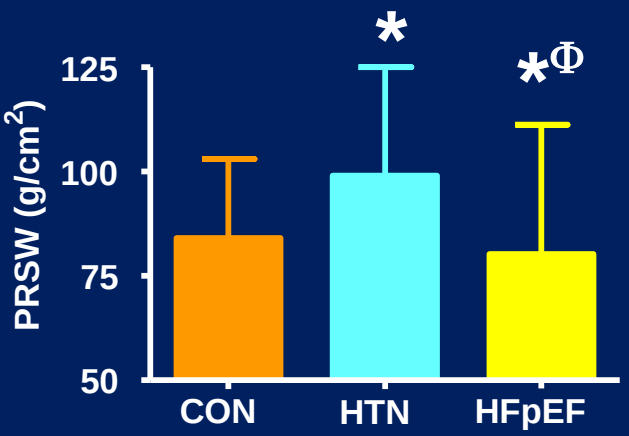
Zakeri *Circ Heart Fail* 2014

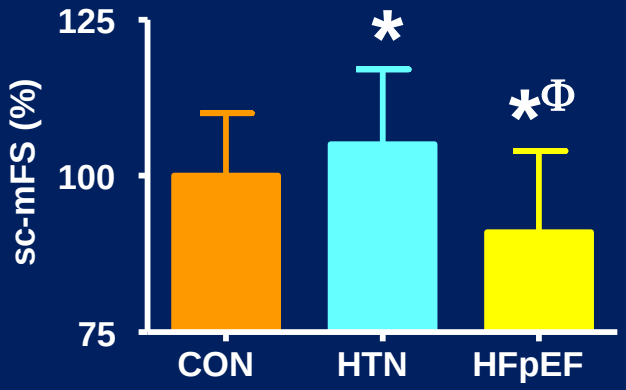


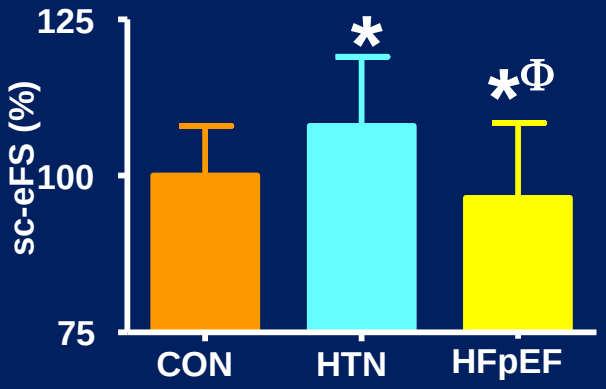


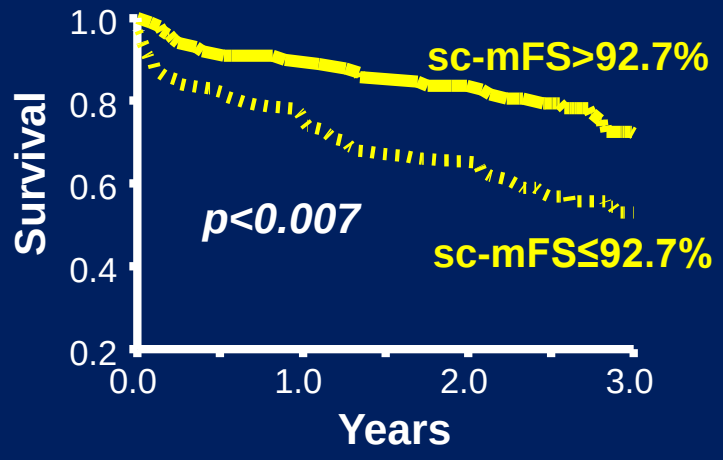
Melenovsky, Borlaug *Eur Heart J* 2014

LVEF is normal in HFpEF—but is contractility?









Borlaug *J Am Coll Cardiol* 2009

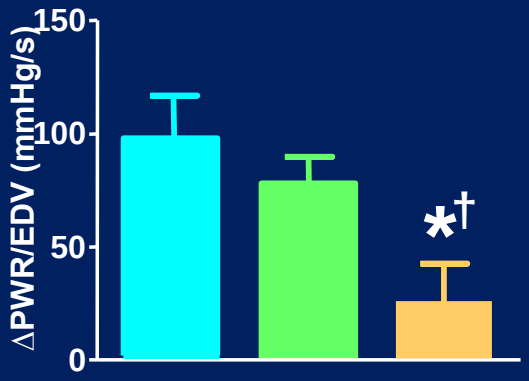
↓Contractile Reserve in HFpEF

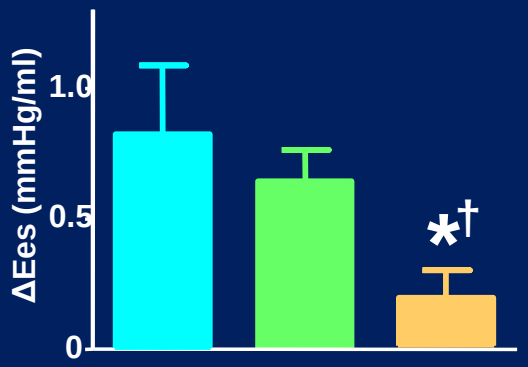
Control

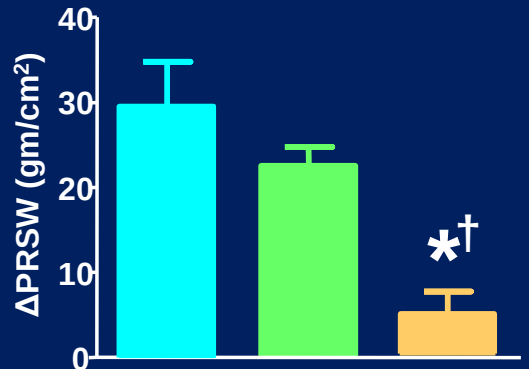
Hypertension

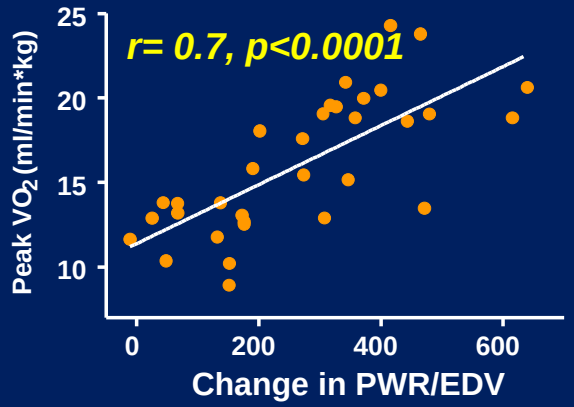
HFpEF

Borlaug *JACC* 2010





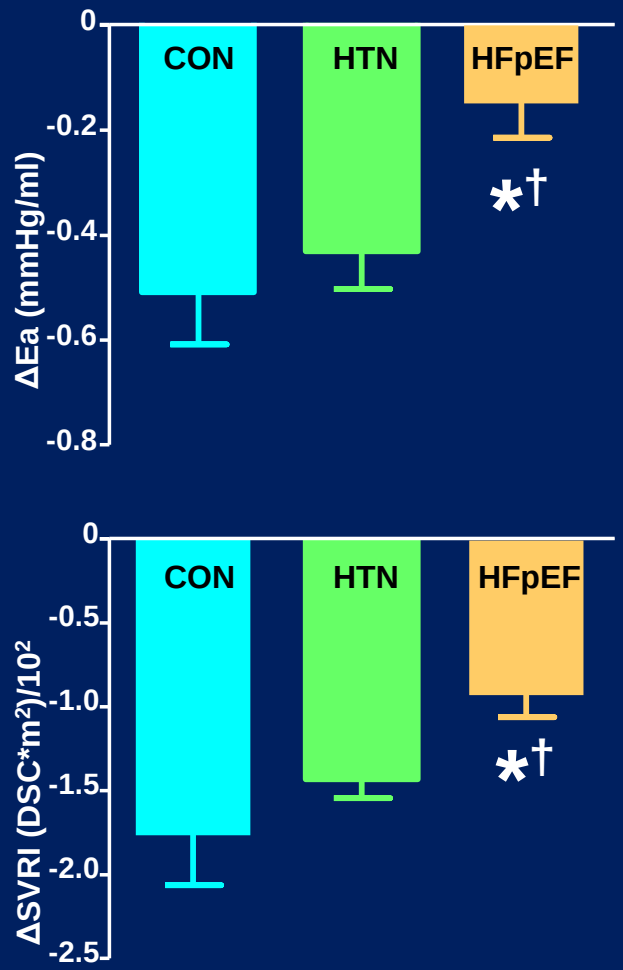




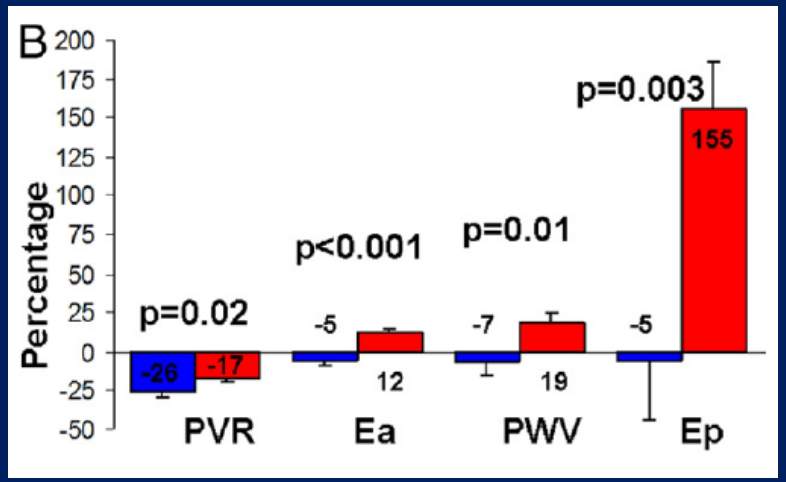
Others showing ↓Systolic reserve in HFpEF:

Liu Circulation 1993, Borlaug Circulation 2006, Ennezat JCF 2008, Tan JACC 2009, Phan JACC 2009, Lee EHJ 2010, Norman JCF 2011, Ohara iJACC 2012, Andersen Circ Heart Fail 2015

Abnormal Vasodilatation in HFpEF?

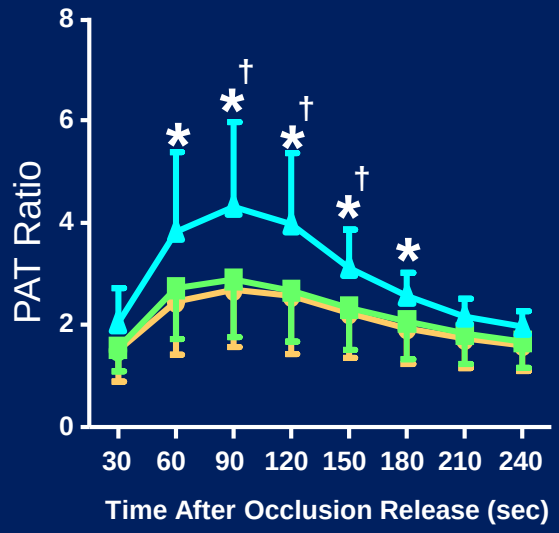


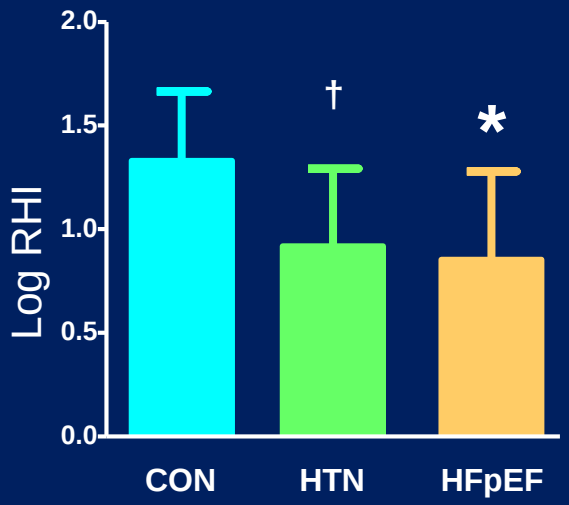
Borlaug *J Am Coll Cardiol* 2010

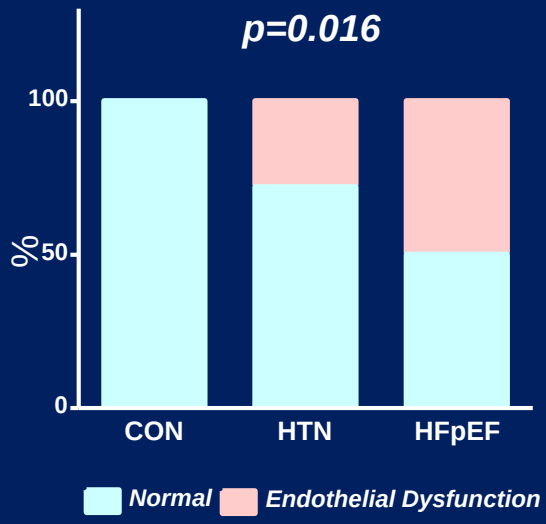


Tartiere-Kesri *J Am Coll Cardiol* 2012

Why the Abnormal Vasodilation?

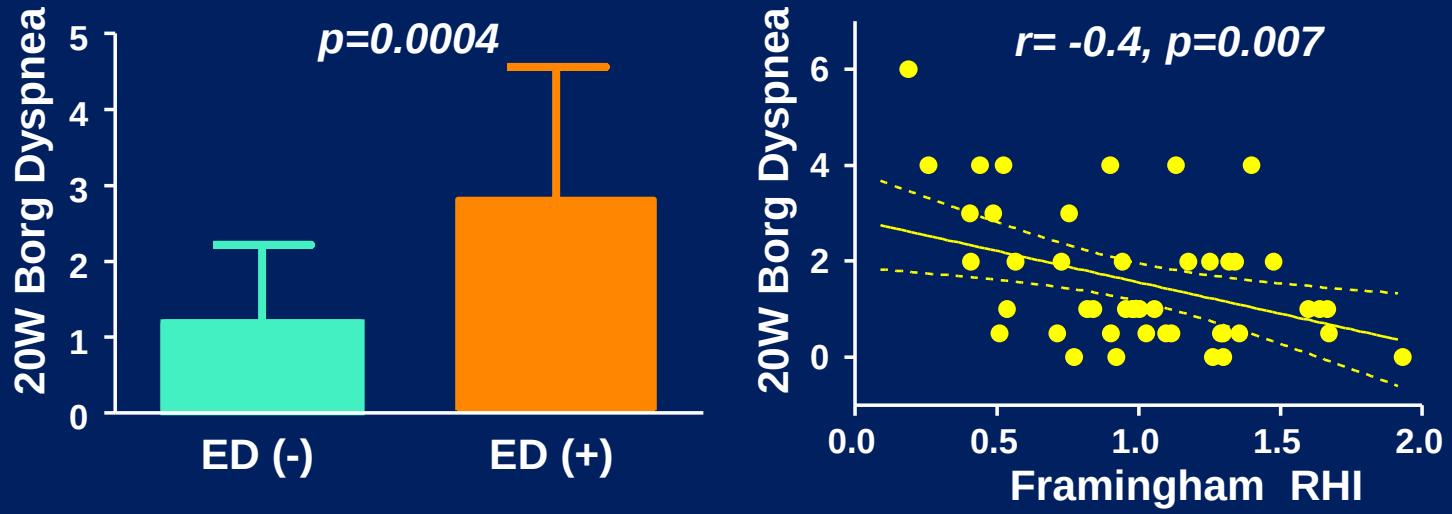






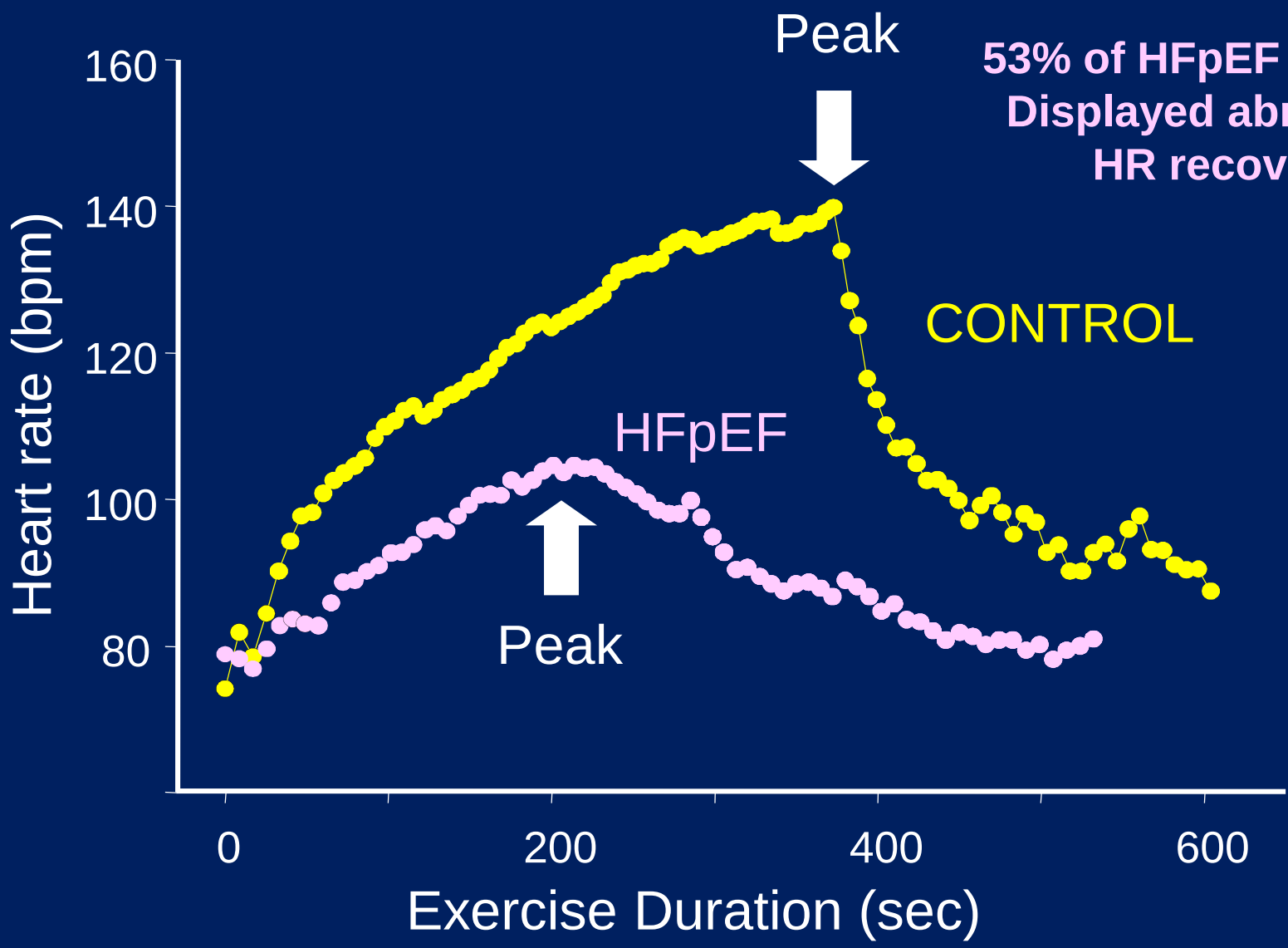
Borlaug *J Am Coll Cardiol* 2010

Endothelial Dysfunction associated with ↑DOE in HFpEF



Borlaug *J Am Coll Cardiol* 2010

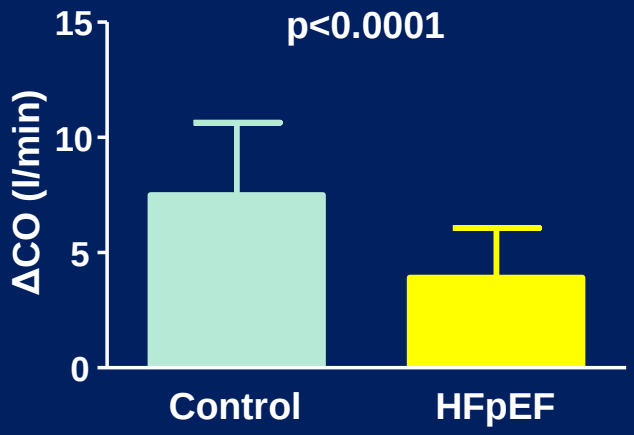
Chronotropic Incompetence in HFpEF

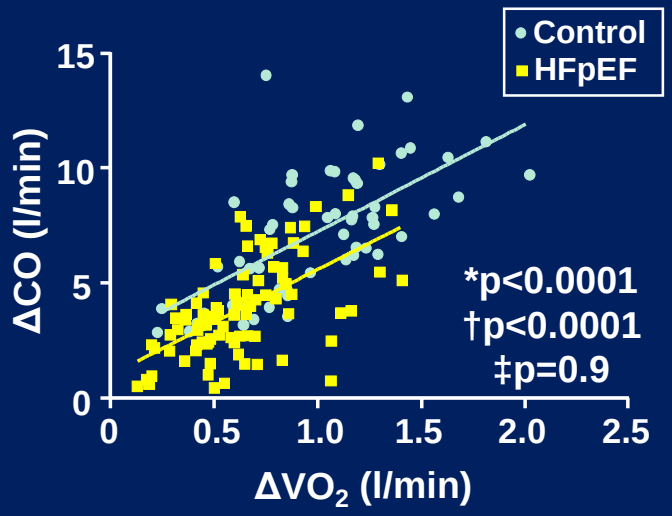


53% of HFpEF patients Displayed abnormal HR recovery

Borlaug *Circulation* 2006

Combined CV dysfunction: Limited CO reserve





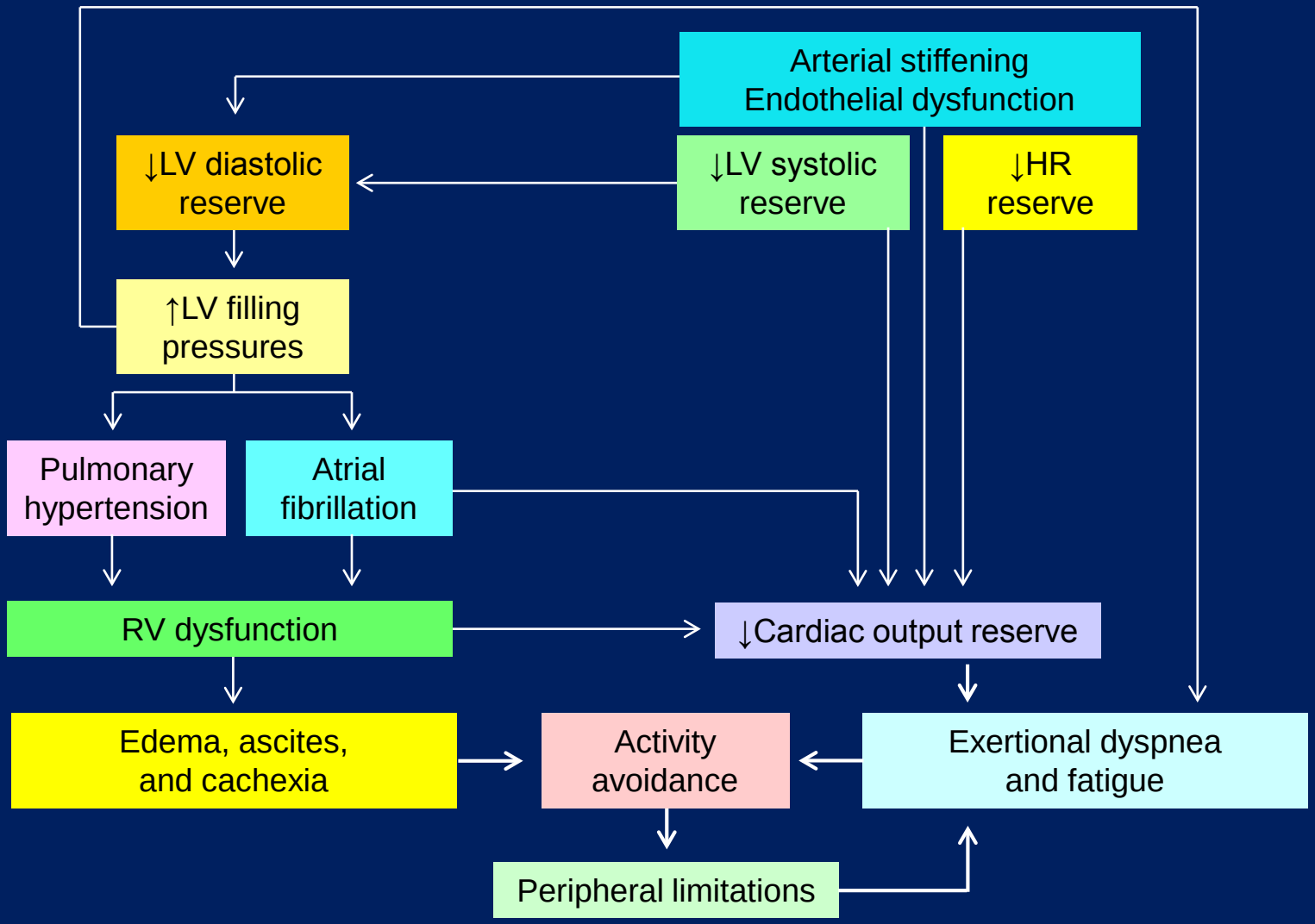
ΔCO/ΔVO2

+7.4±2.6
vs
+5.9±2.5

p=0.0005

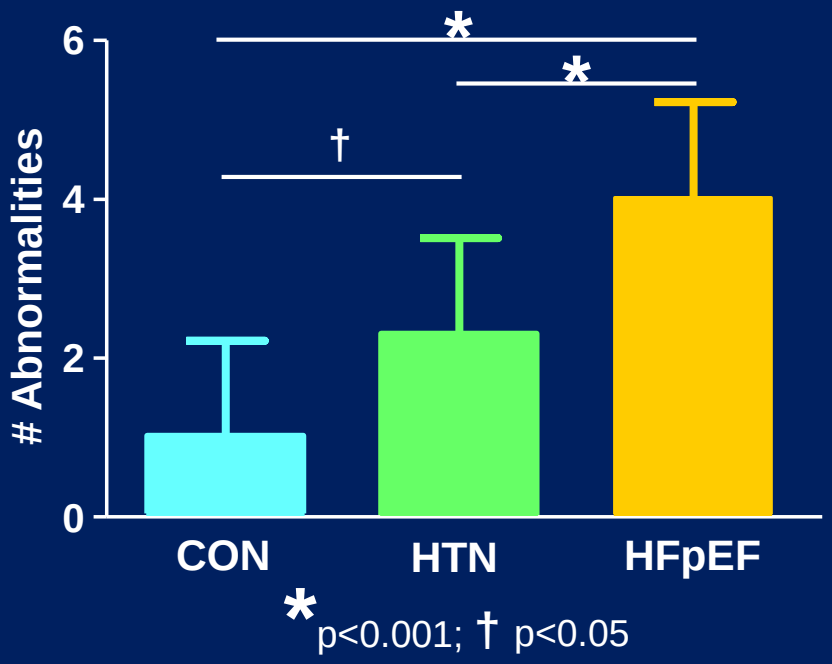
Abudiab *Eur J Heart Fail* 2013

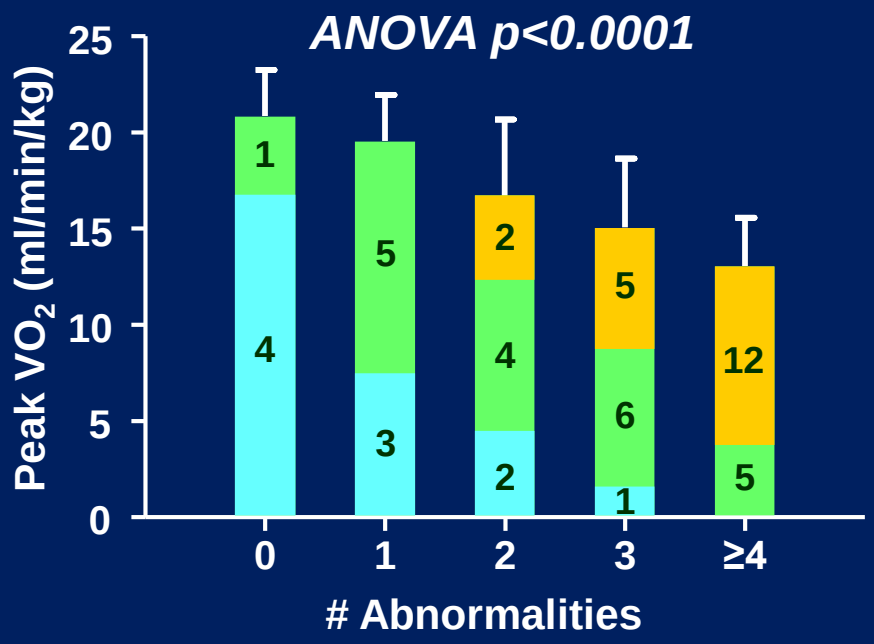
Pathophysiology of HFpEF



Borlaug *Nature Rev Cardiol* 2014

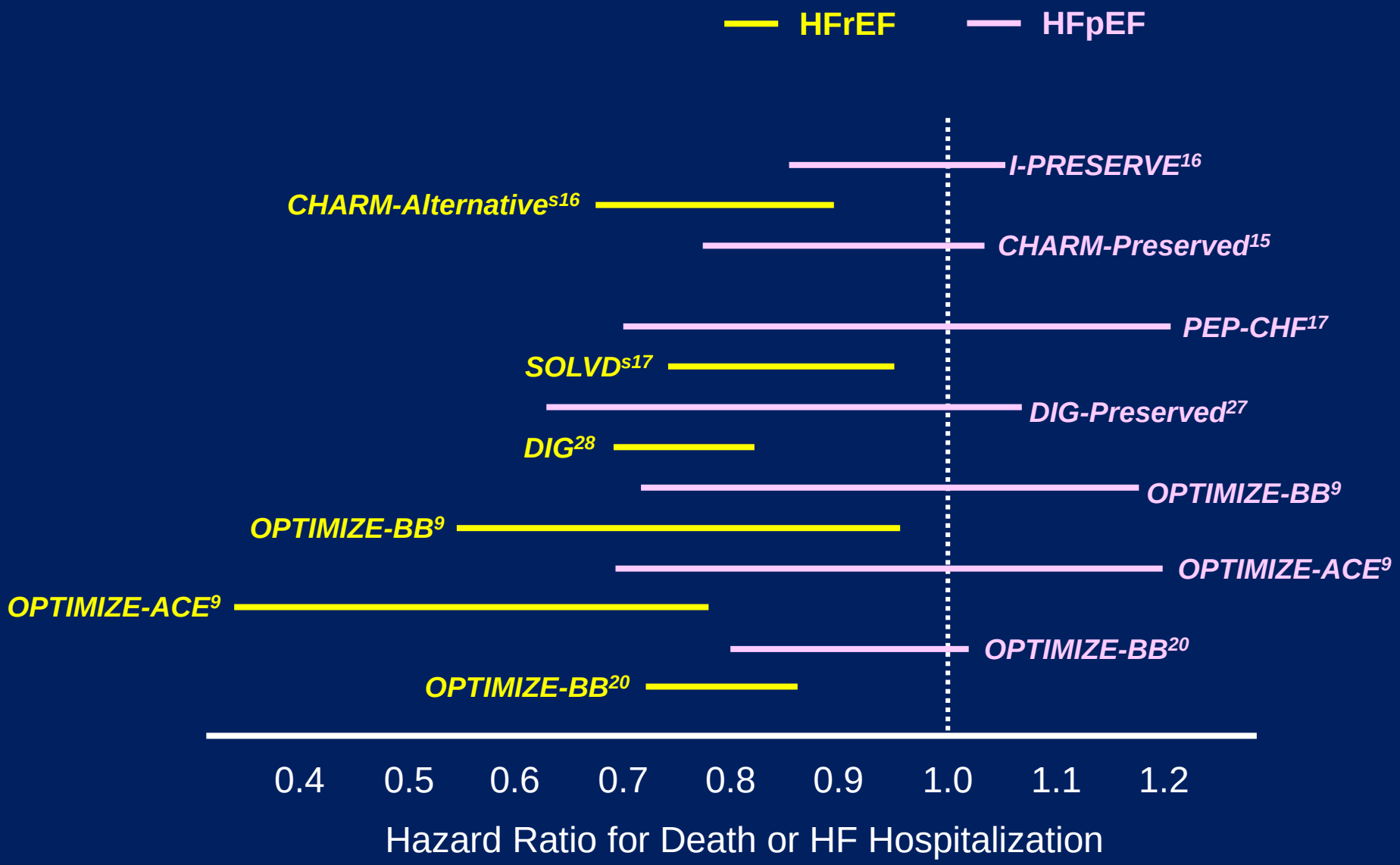
HFpEF ≠ Multiple diseases…
Multiple reserve limitations combine to cause HF





Borlaug *J Am Coll Cardiol* 2010

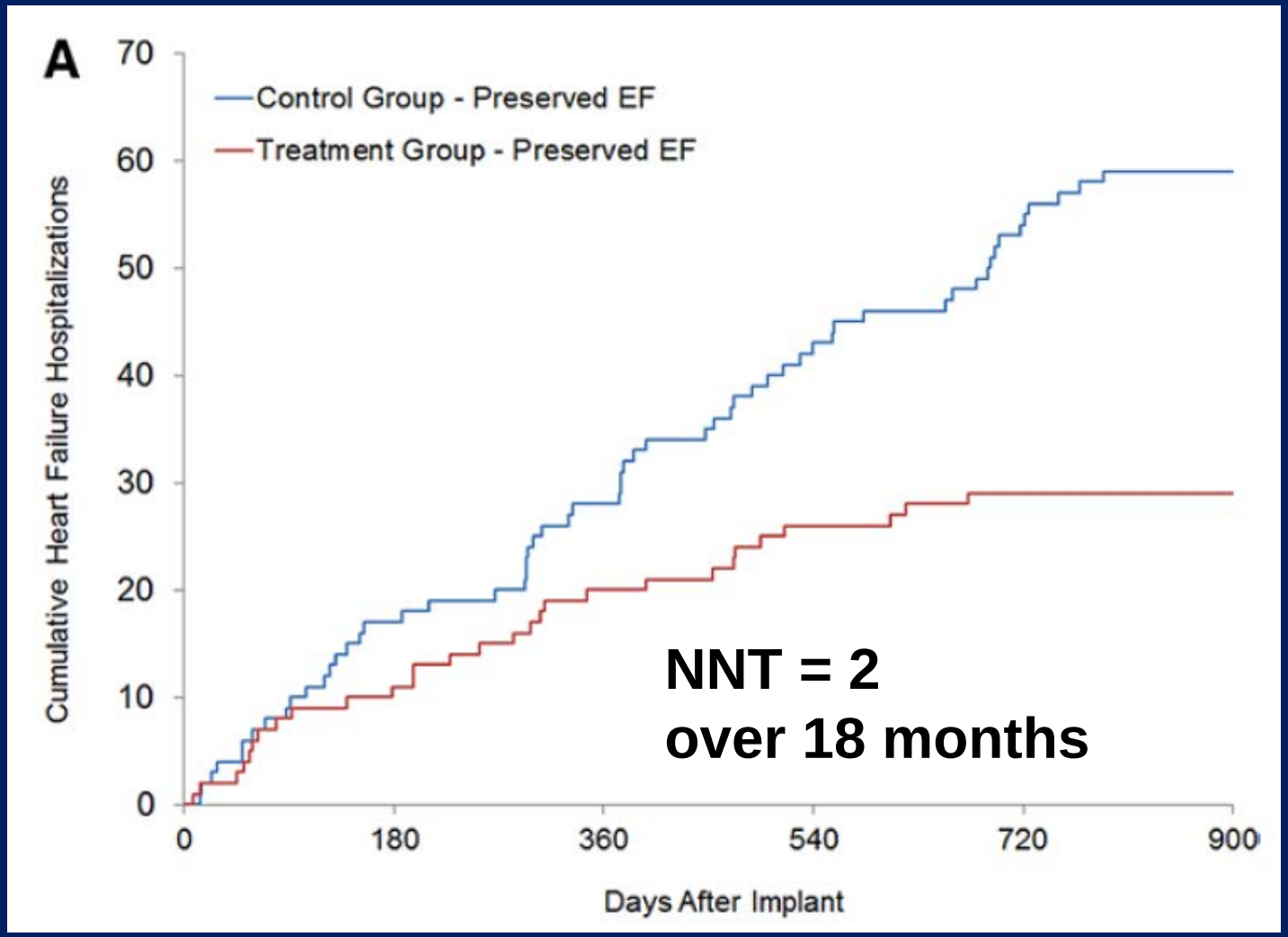
Treatment of HFpEF



Borlaug & Redfield *Circulation* 2011

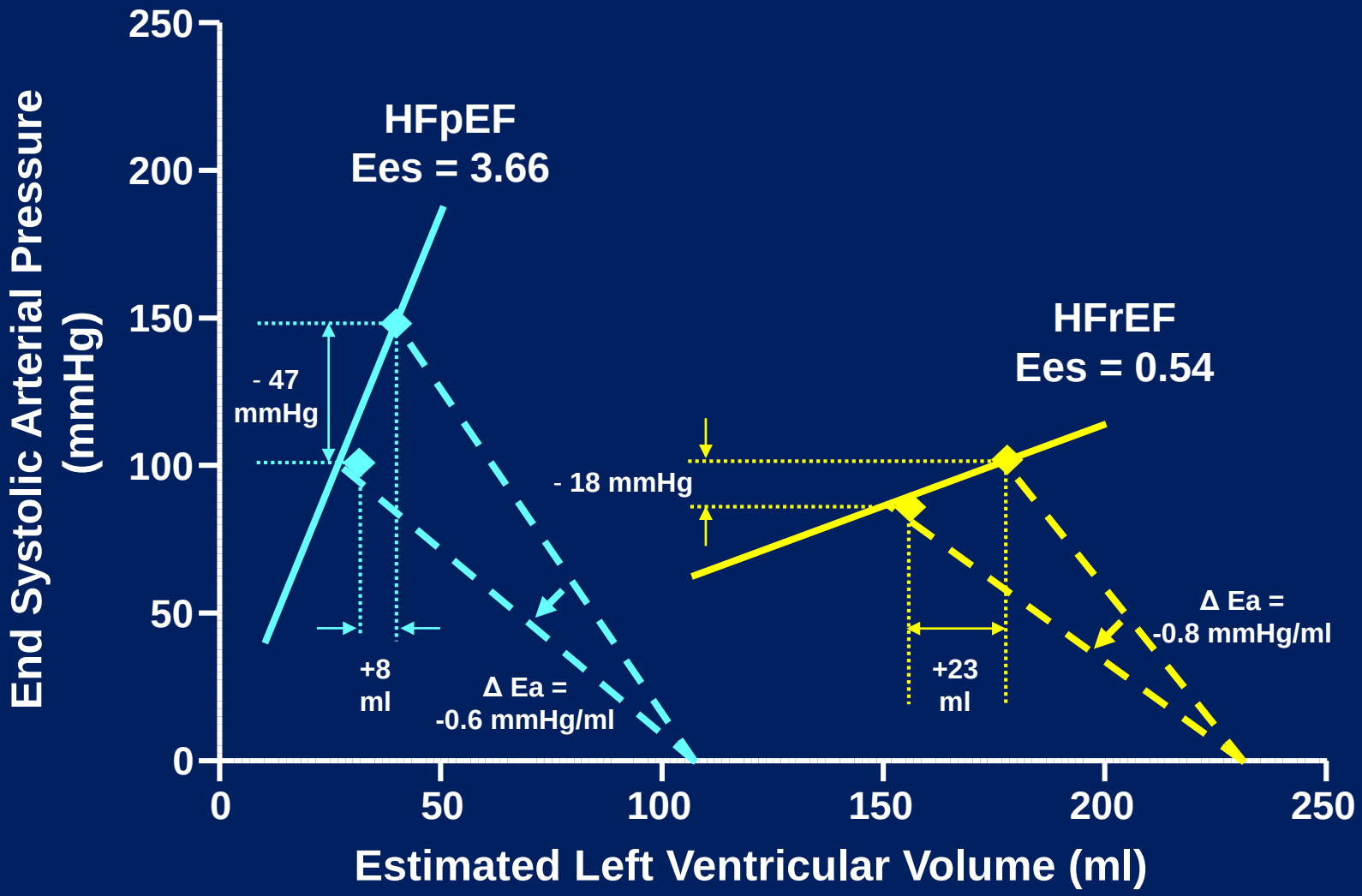
In the absence of convincing trial data, what should we do?

Finally, some “evidence” that Diuretics Work…



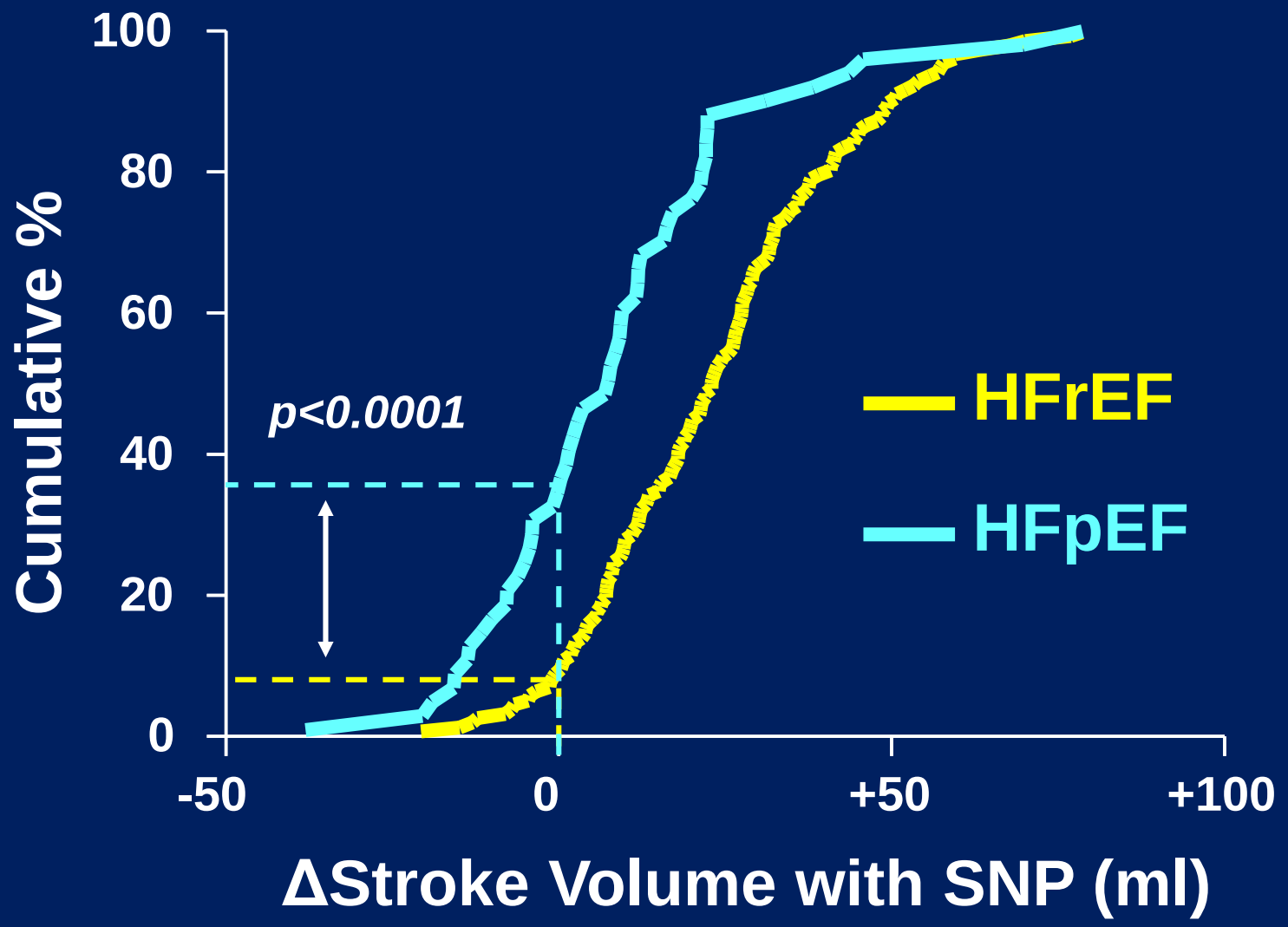
Adamson *Circ Heart Fail* 2014

Need to be careful with vasodilators…



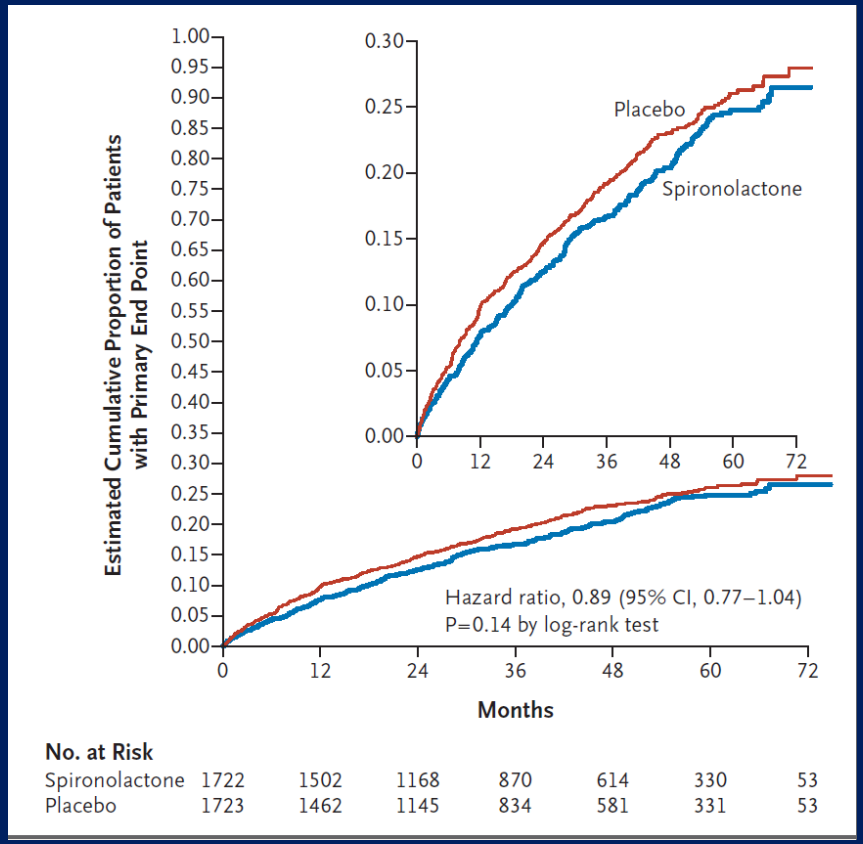
Schwartzenberg…Borlaug *J Am Coll Cardiol* 2012

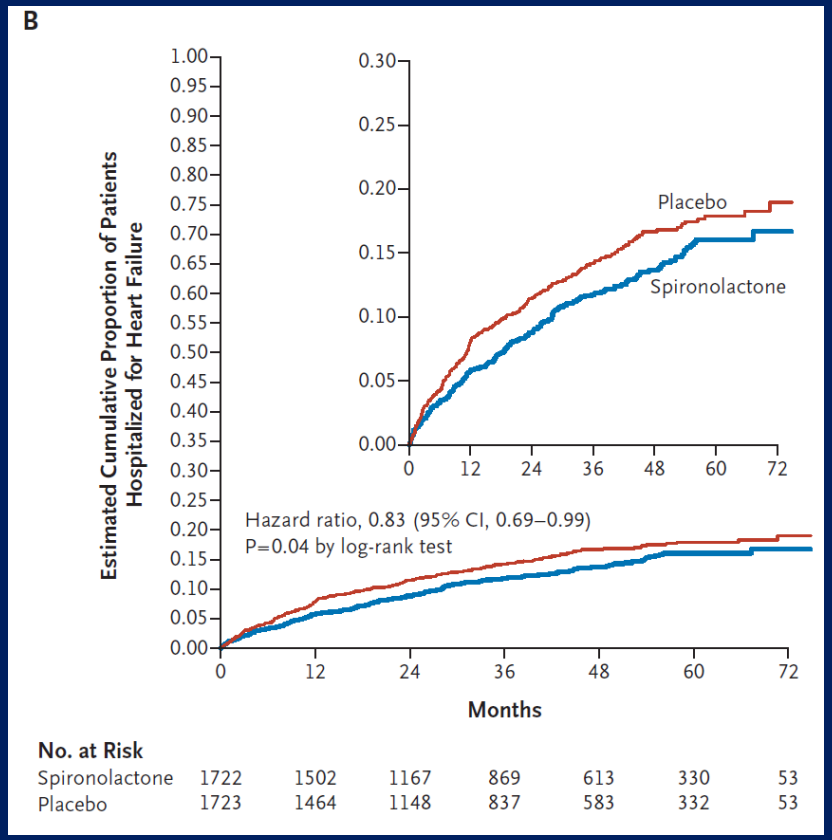
Stiffer LV: Greater Vulnerability to Preload ↓



Schwartzenberg...Borlaug *J Am Coll Cardiol* 2012

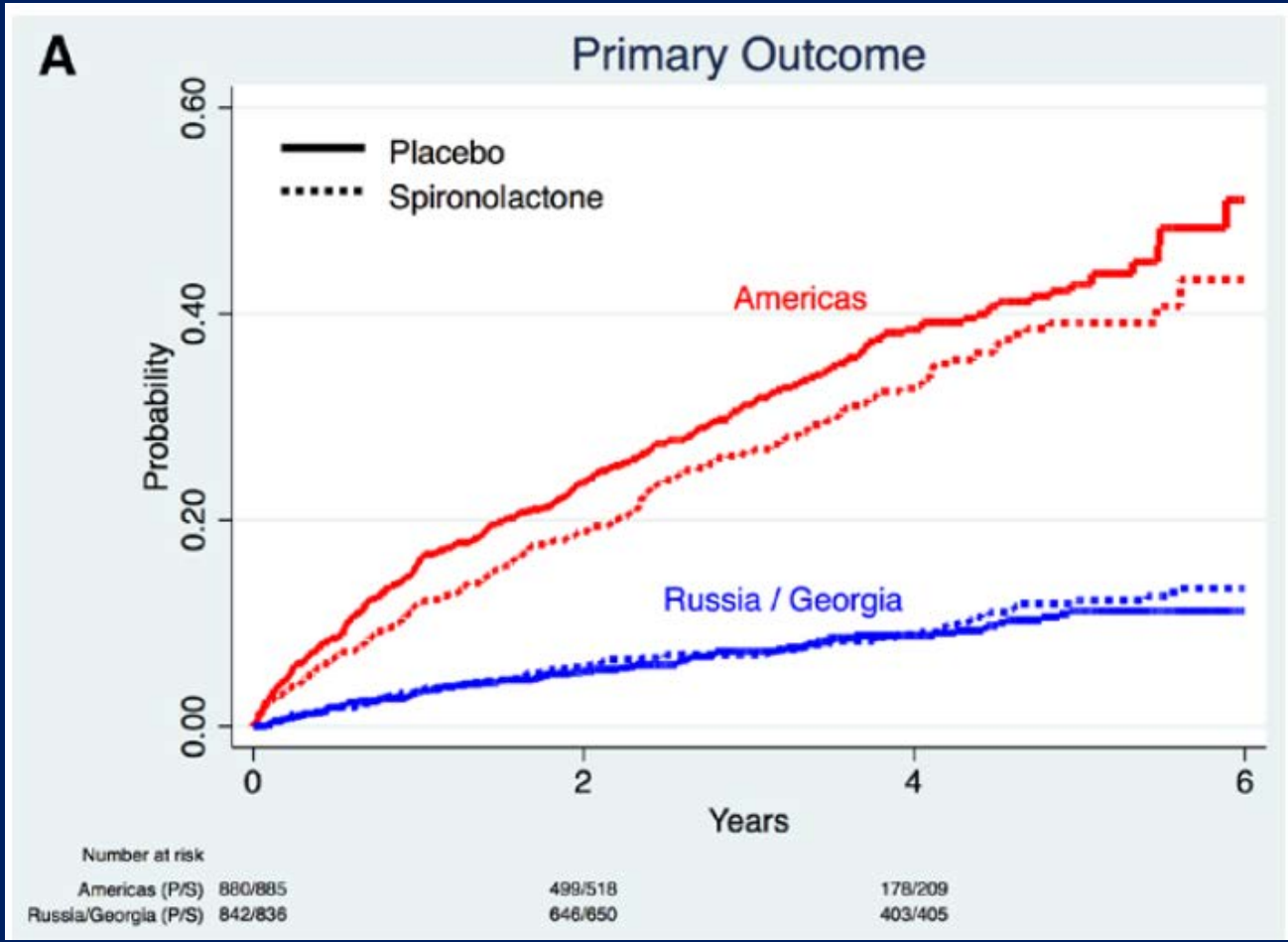
How about Aldosterone antagonists?





Pitt, Pfeffer et al. *New Engl J Med* 2014

Did all these patients really have HFpEF?



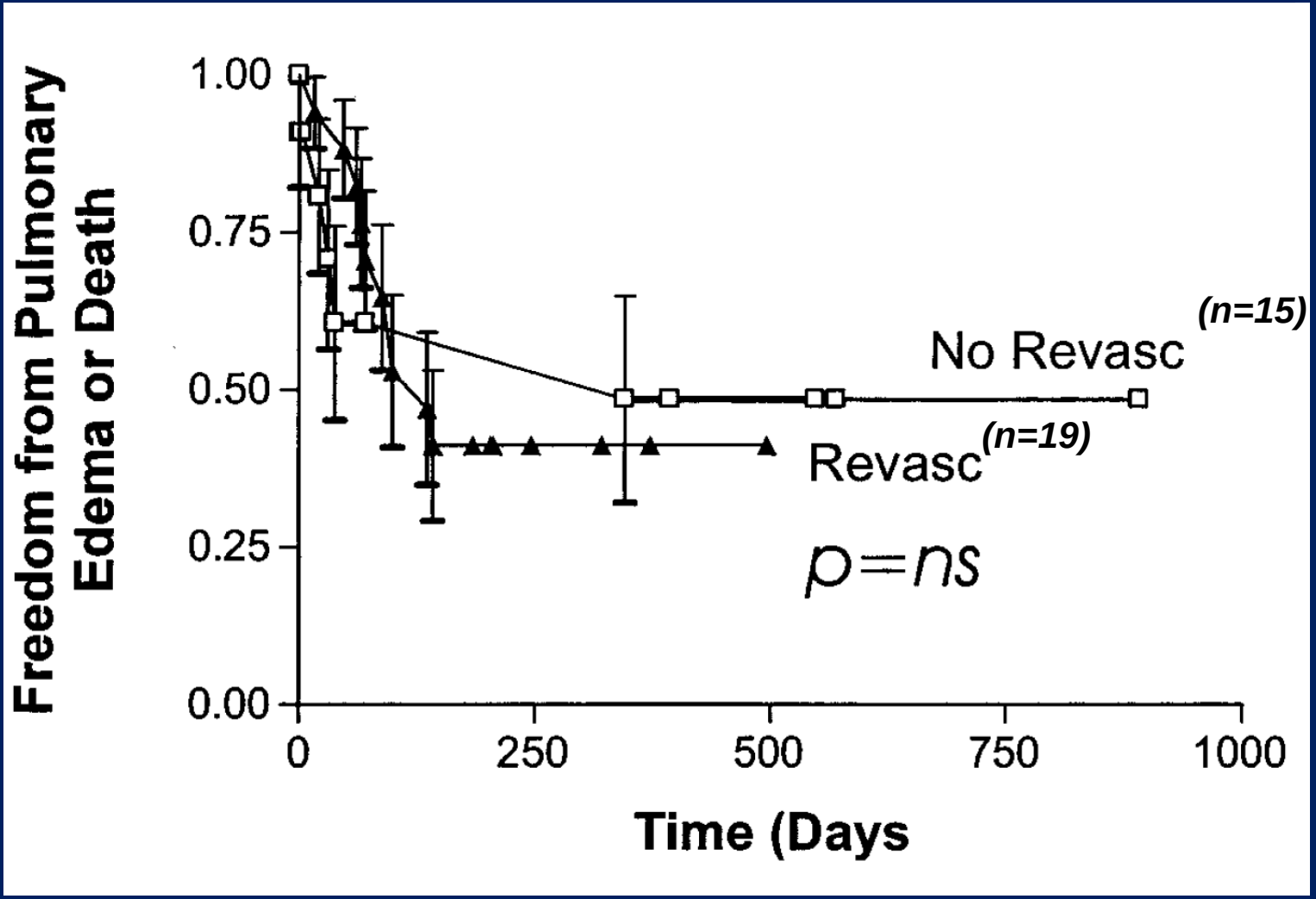
Pfeffer *Circulation* 2014

Therapeutic Advances in HFpEF over 25 years

	1990	2013
↓ BP	X	X
Diuretics	X	X
Rx Ischemia	X	X
Consider BB/ACE/Ca	X	X
↓ HR in AFib	X	X
Consider CDV in AFib	X	X

Chatterjee K: Western Journal of Medicine: 1990
ACC/AHA HF Guidelines, Circulation, 2013

What do we know about Ischemia in HFpEF?



Kramer *Am Heart J* 2000

Implications of Coronary Artery Disease in Heart Failure With Preserved Ejection Fraction

Seok-Jae Hwang, MD, PhD,*† Vojtech Melenovsky, MD, PhD,*‡ Barry A. Borlaug, MD*

Rochester, Minnesota; Jinju, Republic of Korea; and Prague, Czech Republic

Objectives This study investigated the characteristics, evaluation, prognostic impact, and treatment of coronary artery disease (CAD) in patients with heart failure and preserved ejection fraction (HFpEF).

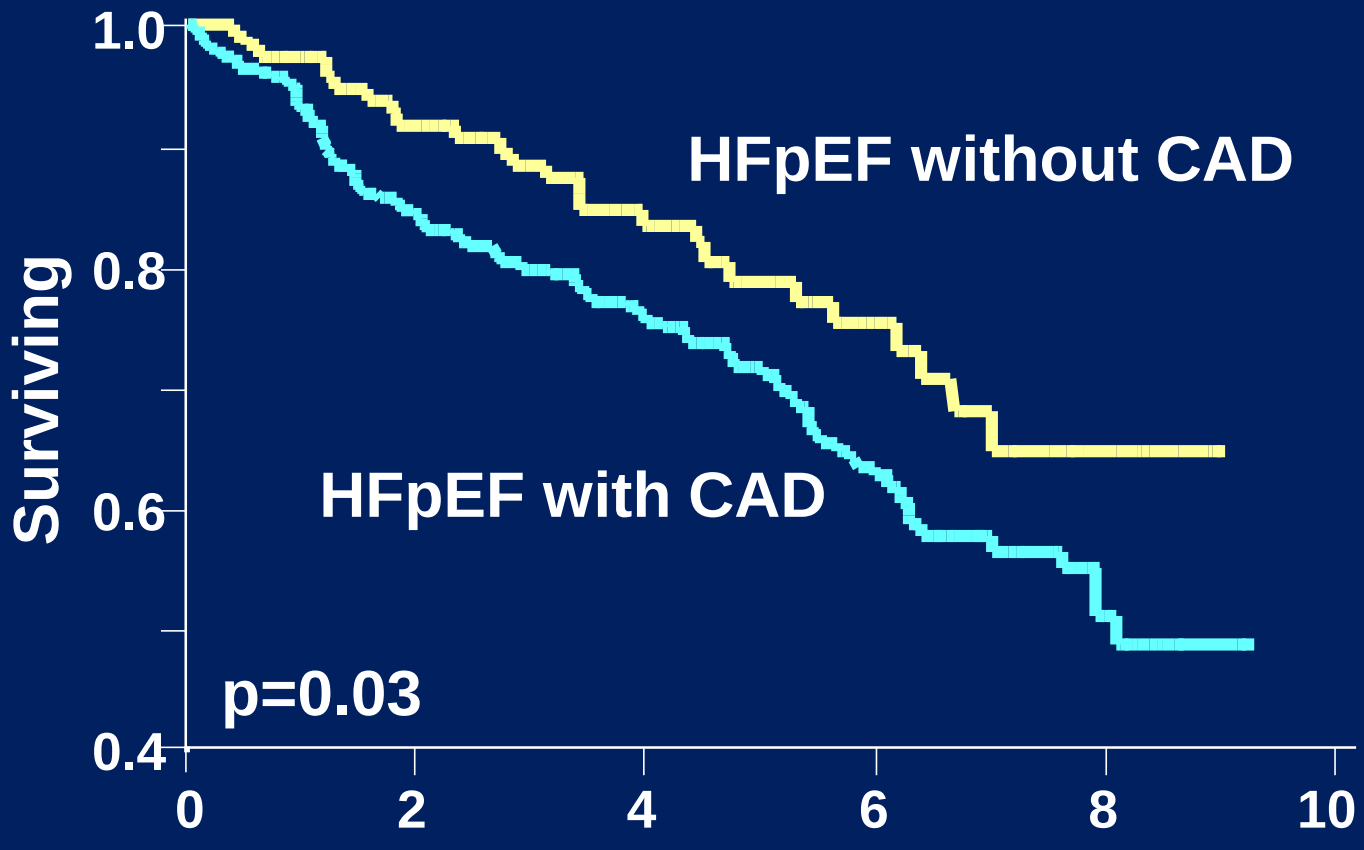
Background CAD is common in patients with HFpEF, but it remains unclear how CAD should be categorized, evaluated for, and treated in HFpEF.

Methods Clinical, hemodynamic, echocardiographic, treatment, and outcome characteristics were examined in consecutive patients with previous HFpEF hospitalizations who underwent coronary angiography.

Results Of the 376 HFpEF patients examined, 255 (68%) had angiographically-proven CAD. Compared with HFpEF patients without CAD, patients with CAD were more likely to be men, to have CAD risk factors, and to be treated with anti-ischemic medications. However, symptoms of angina and heart failure were similar in patients with and without CAD, as were measures of cardiovascular structure, function, and hemodynamics. Compared with patients without CAD, HFpEF patients with CAD displayed greater deterioration in ejection fraction and increased mortality, independent of other predictors (hazard ratio: 1.71, 95% confidence interval: 1.03 to 2.98; $p = 0.04$). Complete revascularization was associated with less deterioration in ejection fraction and lower mortality compared with patients who were not completely revascularized, independent of other predictors (hazard ratio: 0.56, 95% confidence interval: 0.33 to 0.93; $p = 0.03$).

Conclusions CAD is common in patients with HFpEF and is associated with increased mortality and greater deterioration in ventricular function. Revascularization may be associated with preservation of cardiac function and improved outcomes in patients with CAD. Given the paucity of effective treatments for HFpEF, prospective trials are urgently needed to determine the optimal evaluation and management of CAD in HFpEF. (J Am Coll Cardiol 2014;63:2817–27)

Impact of CAD on Outcome in HFpEF

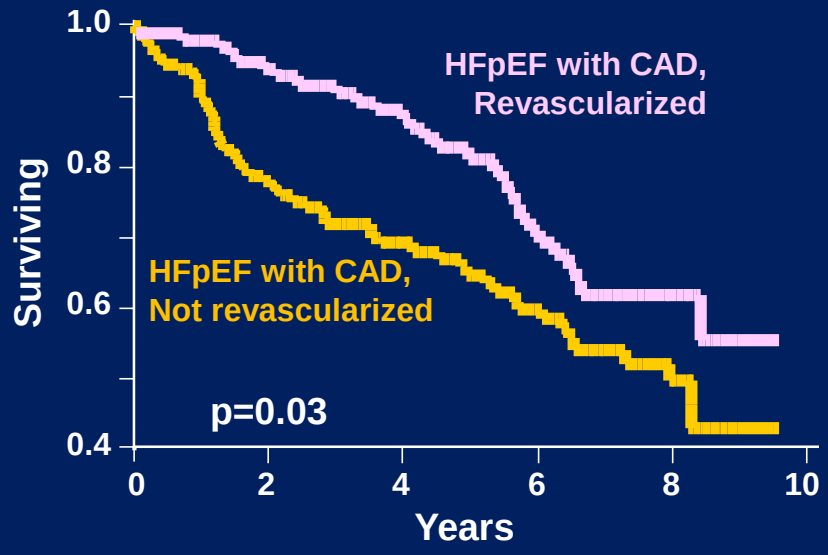


Number remaining

CAD (-)	121	90	60	34	14
CAD (+)	255	193	129	83	23

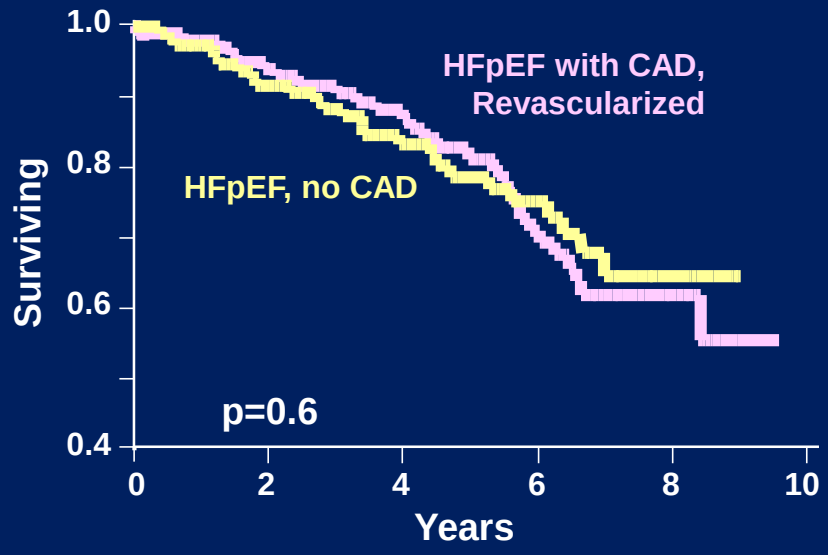
Hwang *J Am Coll Cardiol* 2014

Does Revascularization improve survival?



Number remaining

Revasc (+)	101	85	63	37	11
Revasc (-)	154	108	68	47	13

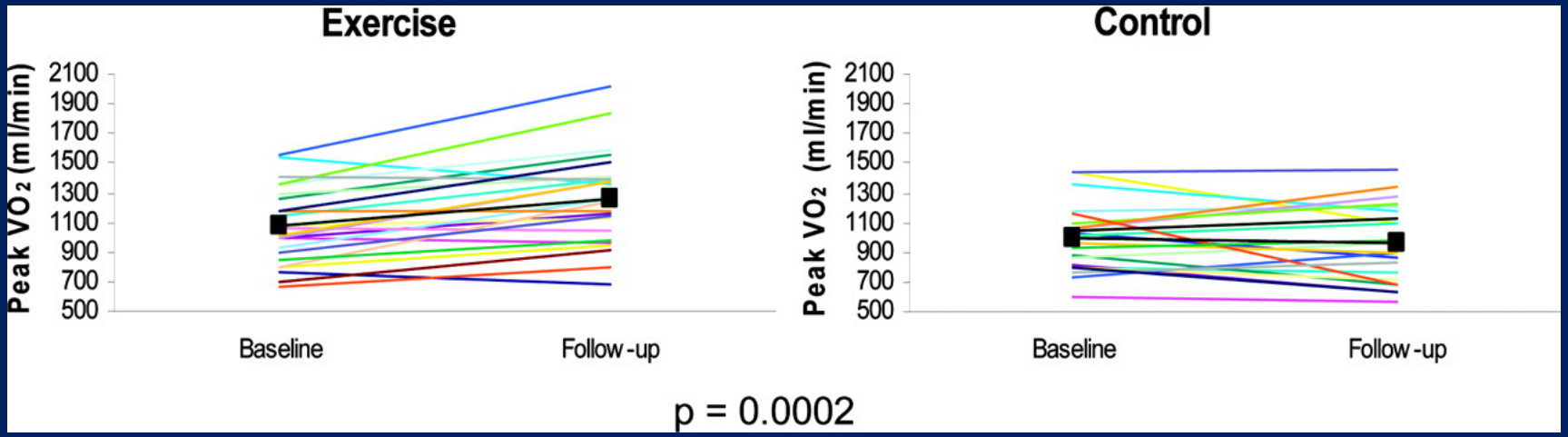


Number remaining

Revasc (+)	101	85	63	37	11
CAD (-)	121	90	60	34	14

Hwang *J Am Coll Cardiol* 2014

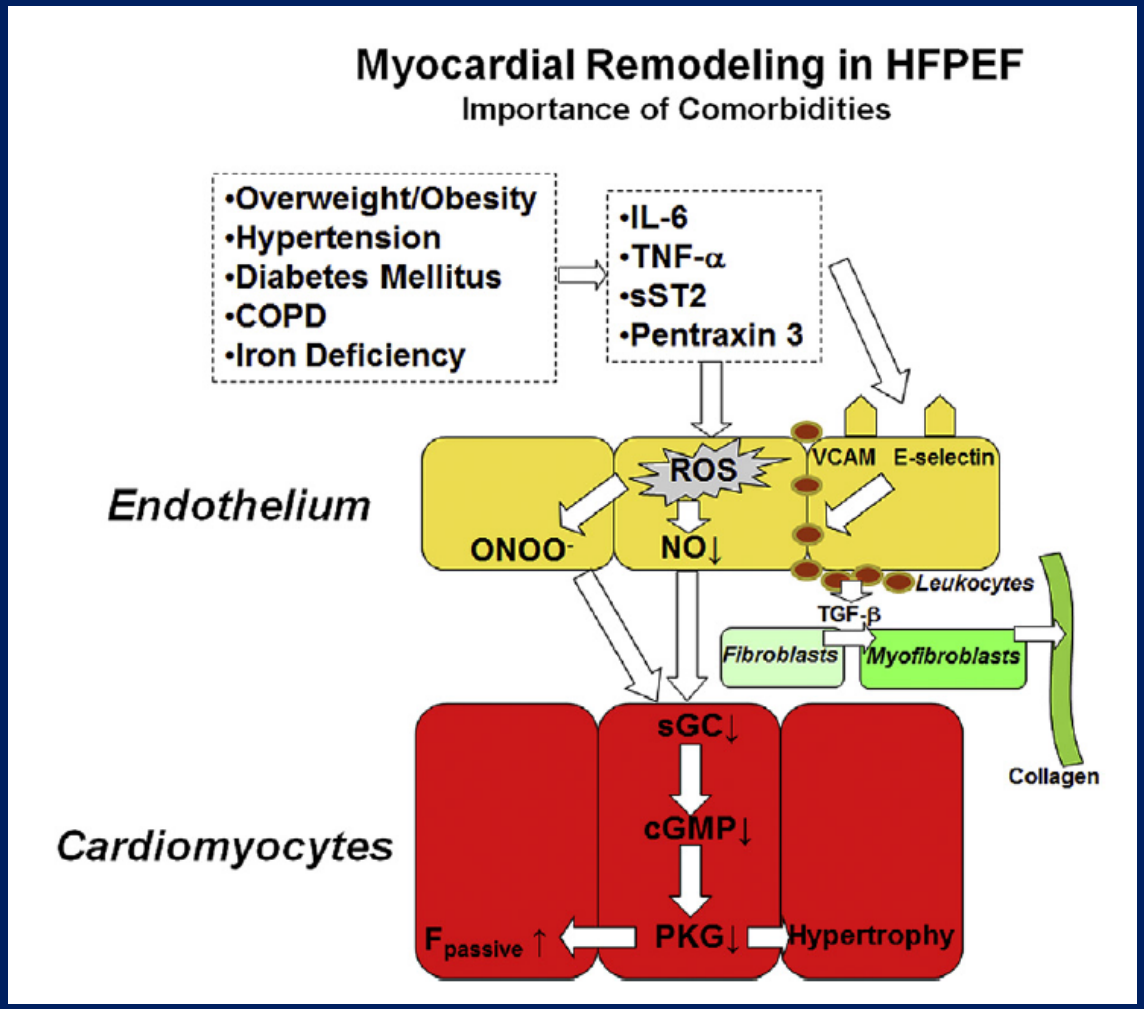
Exercise training works (but isn't paid for!)



Kitzman *Circ Heart Fail* 2010

What is on the horizon?

NO-cGMP-PKG candidate target



Paulus & Tschope J Am Coll Cardiol 2013

ORIGINAL CONTRIBUTION

ONLINE FIRST

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

A Randomized Clinical Trial

Margaret M. Redfield, MD
Horng H. Chen, MD
Barry A. Borlaug, MD
Marc J. Semigran, MD
Michael M. Givertz, MD
Elizabeth O. Ofili, MD
Christopher M. O'Connor, MD
G. Michael Felker, MD
Steven R. Goldsmith, MD
Bradley A. Bart, MD
Steven E. McNulty, MS
Jenny C. Ibarra, MSN
Grace Lin, MD
Jae K. Oh, MD
Manesh R. Patel, MD
Raymond J. Kim, MD
Russell P. Tracy, PhD
Eric J. Velazquez, MD
Kevin J. Anstrom, PhD
Adrian F. Hernandez, MD
Alice M. Mascette, MD
Eugene Braunwald, MD
for the RELAX Trial

Importance Studies in experimental and human heart failure suggest that phosphodiesterase-5 inhibitors may enhance cardiovascular function and thus exercise capacity in heart failure with preserved ejection fraction (HFPEF).

Objective To determine the effect of the phosphodiesterase-5 inhibitor sildenafil compared with placebo on exercise capacity and clinical status in HFPEF.

dicates better status; expected value with no treatment effect, 95) based on time to death, time to cardiovascular or cardiorenal hospitalization, and change in quality of life for participants without cardiovascular or cardiorenal hospitalization at 24 weeks.

Results Median age was 69 years, and 48% of patients were women. At baseline, median peak oxygen consumption (11.7 mL/kg/min) and 6-minute walk distance (308 m) were reduced. The median E/e' (16), left atrial volume index (44 mL/m^2), and pulmonary artery systolic pressure (41 mm Hg) were consistent with chronically elevated left ventricular filling pressures. At 24 weeks, median (IQR) changes in peak oxygen consumption (mL/kg/min) in patients who received placebo (−0.20 [IQR, −0.70 to 1.00]) or sildenafil (−0.20 [IQR, −1.70 to 1.11]) were not significantly different (P=.90) in analyses in which patients with missing week-24 data were excluded, and in sensitivity analysis based on intention to treat with multiple imputation for missing values (mean between-group difference, 0.01 mL/kg/min, [95% CI, −0.60 to 0.61]). The mean clinical status rank score was not significantly different at 24 weeks between placebo (95.8) and sildenafil (94.2) (P=.85). Changes in 6-minute walk distance at 24 weeks in patients who received placebo (15.0 m [IQR, −26.0 to 45.0]) or sildenafil (5.0 m [IQR, −37.0 to 55.0]; P=.92) were also not significantly different. Adverse events occurred in 78 placebo patients (76%) and 90 sildenafil patients (80%). Serious adverse events occurred in 16 placebo patients (16%) and 25 sildenafil patients (22%).

Conclusion and Relevance Among patients with HFPEF, phosphodiesterase-5 inhibition with administration of sildenafil for 24 weeks, compared with placebo, did not result in significant improvement in exercise capacity or clinical status.

Trial Registration clinicaltrials.gov Identifier: NCT00763867

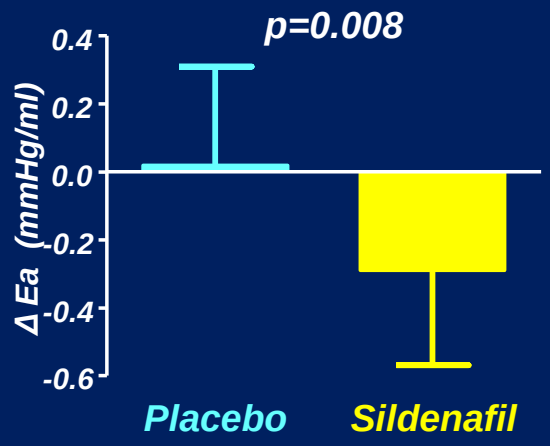
JAMA. 2013;309(12):doi:10.1001/jama.2013.2024 www.jama.com

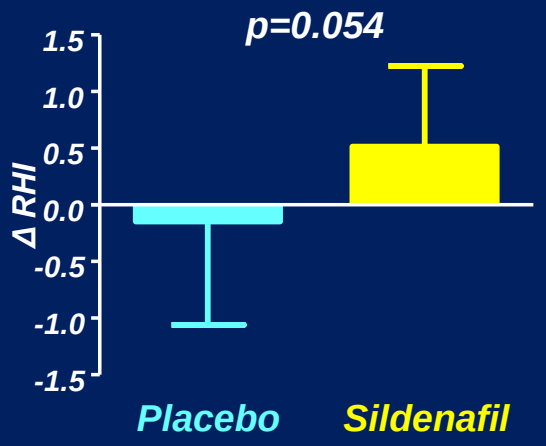
Author Affiliations are listed at the end of this article.
Corresponding Author: Margaret M. Redfield, MD, Division of Cardiovascular Diseases, Mayo Clinic, 200 First St SW, Guggenheim 9, Rochester, MN 55905 (redfield.margaret@mayo.edu).

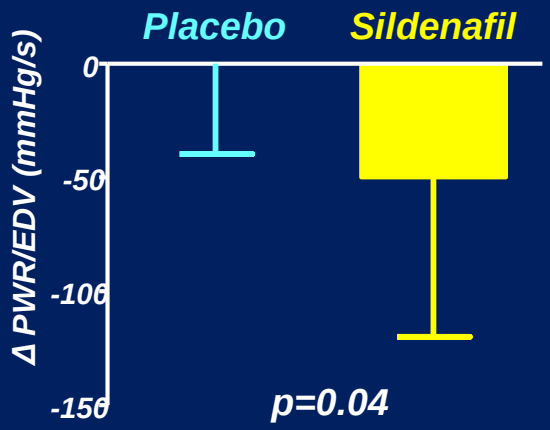
Conclusion and Relevance Among patients with HFPEF, phosphodiesterase-5 inhibition with administration of sildenafil for 24 weeks, compared with placebo, did not result in significant improvement in exercise capacity or clinical status.

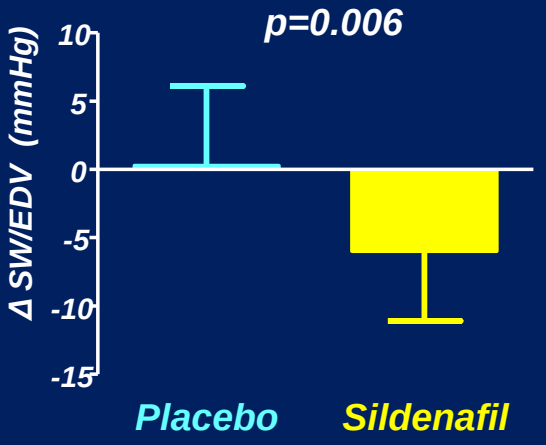
Redfield JAMA 2013

Why didn't PDE5i work in HFpEF?



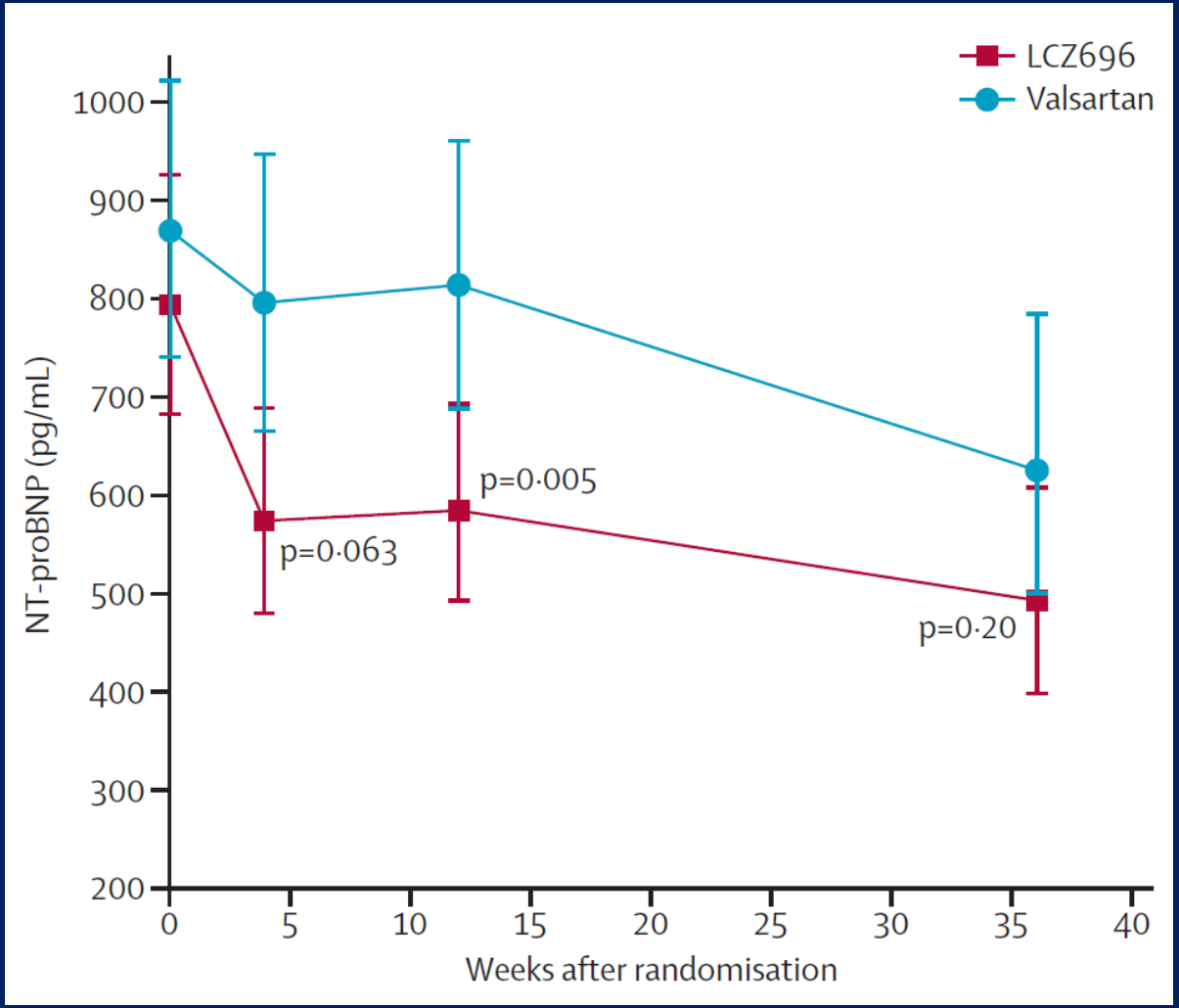






Borlaug *Circ Heart Fail* 2015

Targeting cGMP via ↑NP



Solomon Lancet 2012

Targeting cGMP w organic nitrates

Advances in Clinical Trials

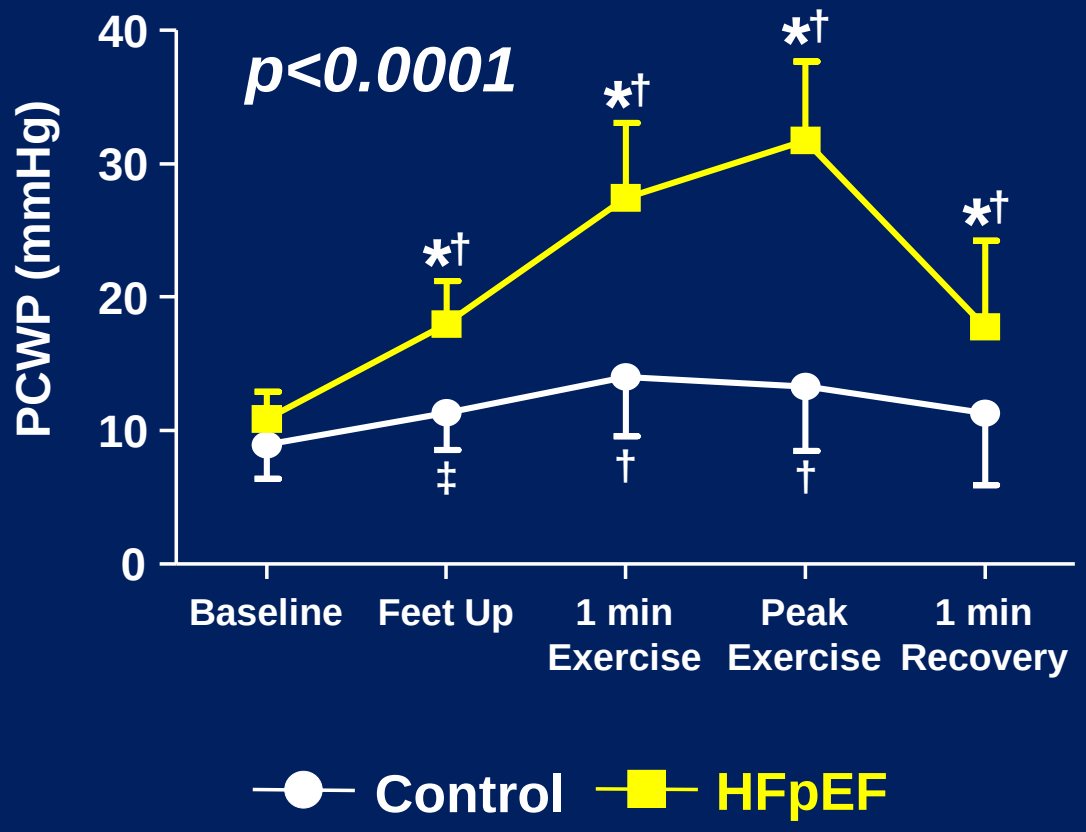
Nitrate's Effect on Activity Tolerance in Heart Failure With Preserved Ejection Fraction Trial

Rationale and Design

Rosita Zakeri, MBChB, PhD; James A. Levine, MD, PhD; Gabriel A. Koepp; Barry A. Borlaug, MD; Julio A. Chirinos, MD, PhD; Martin LeWinter, MD; Peter VanBuren, MD; Victor G. Dávila-Román, MD; Lisa de las Fuentes, MD; Prateeti Khazanie, MD, MPH; Adrian Hernandez, MD; Kevin Anstrom, PhD; Margaret M. Redfield, MD

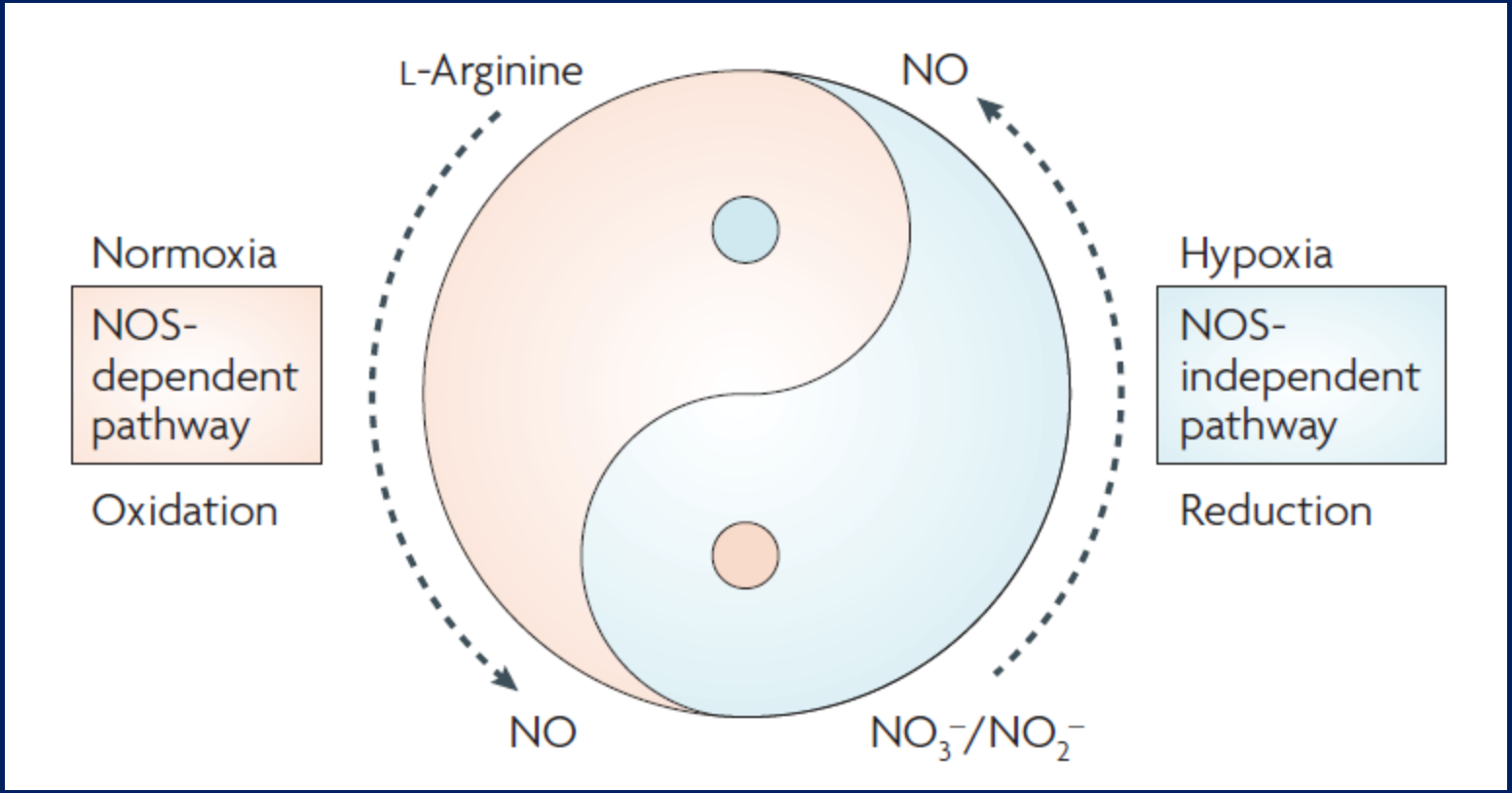
Zakeri *Circ Heart Fail* 2015

Clinical Dilemma:
The ephemeral nature of ↑PCWP in HFpEF



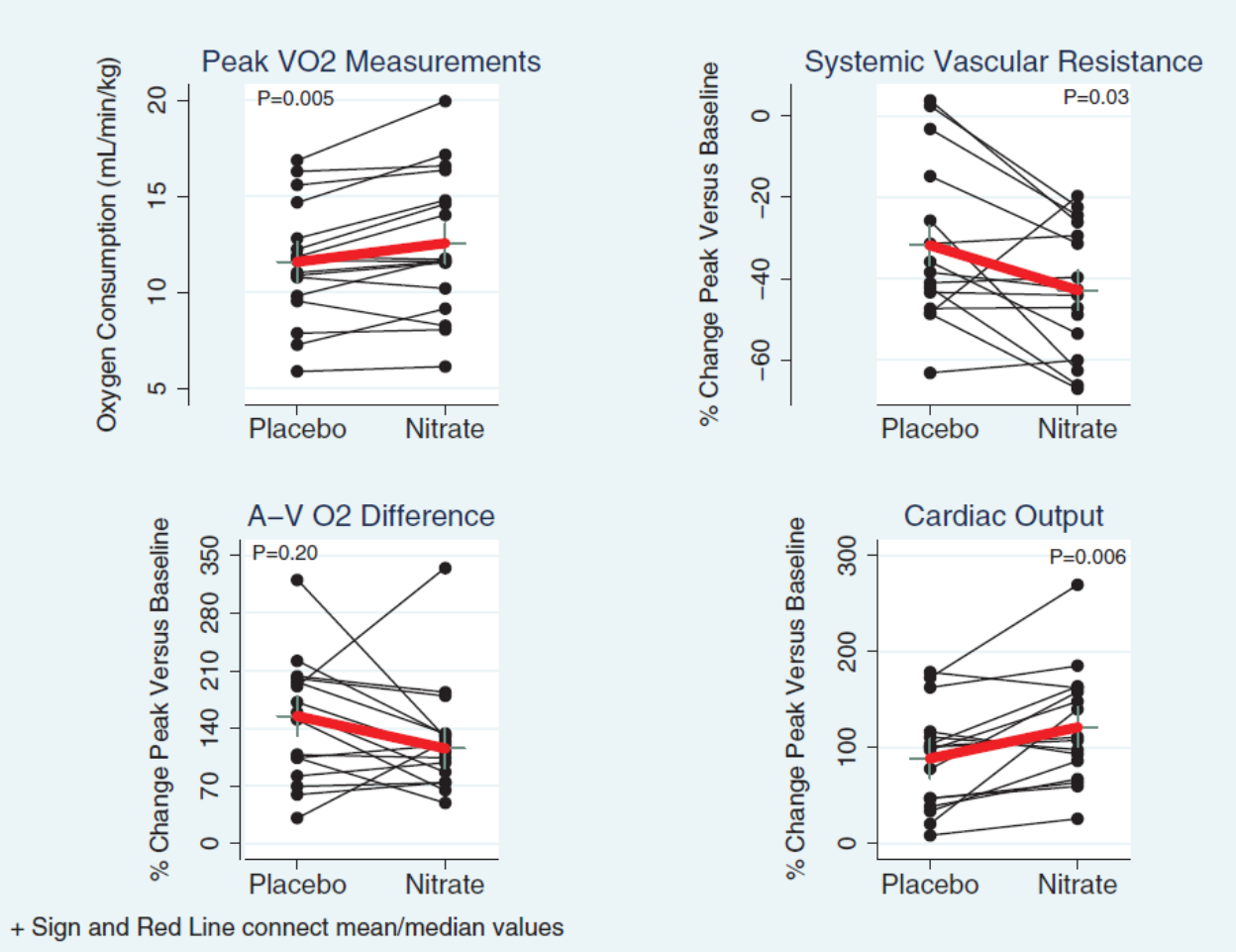
Borlaug *Circ Heart Fail* 2010

Nitrite: An Alternative source of NO/cGMP



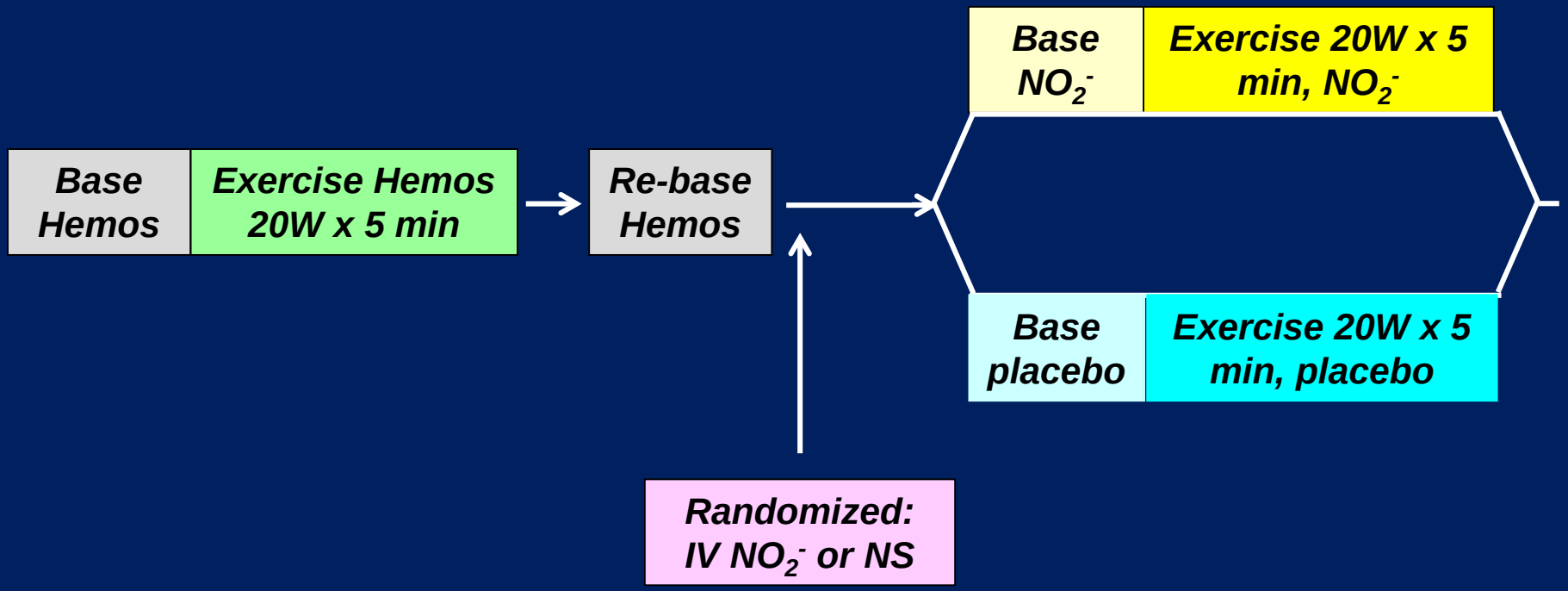
Lundberg *Nature Rev Cardiol* 2008

Beetroot Juice in HFpEF ↑Aerobic Capacity



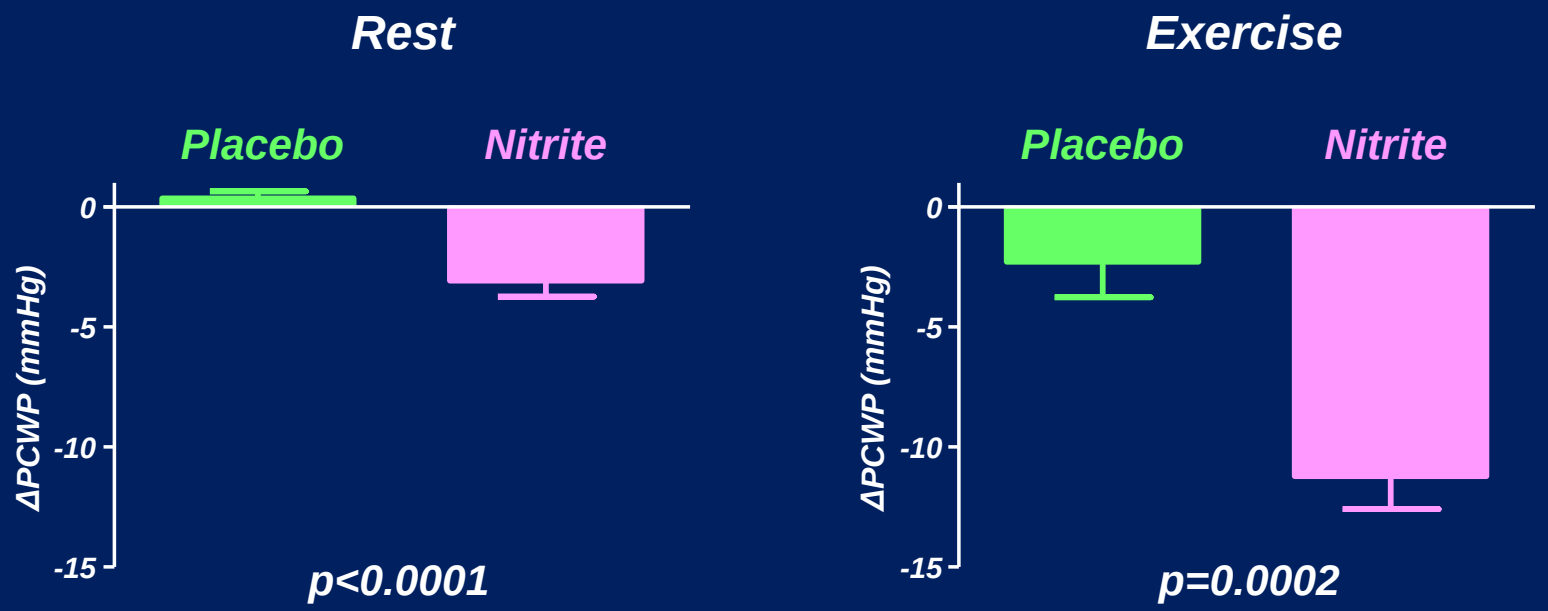
Zamani et al. *Circulation* 2015

NO_2^- effects on Exercise Hemos & Cardiac Reserve

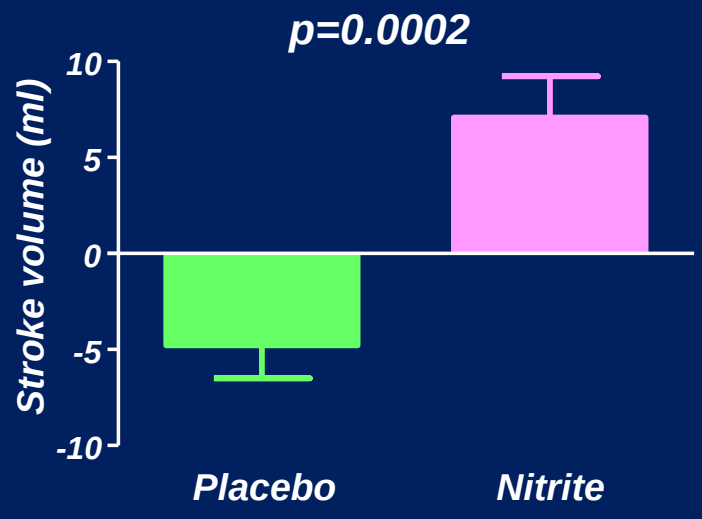


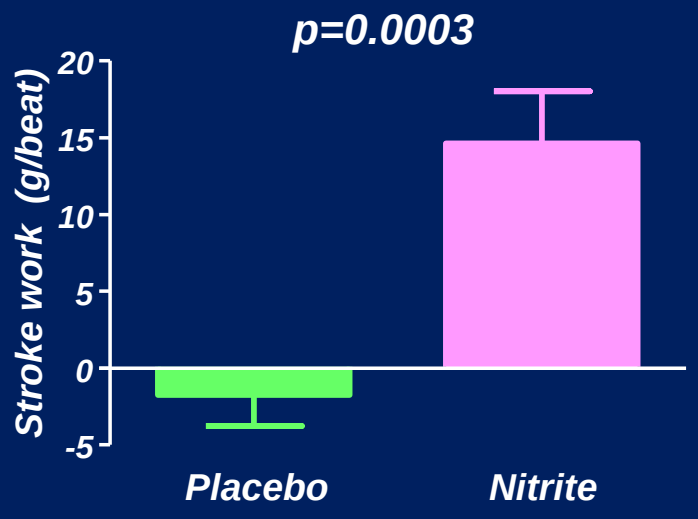
Borlaug, Koepp et al. *J Am Coll Cardiol* 2015

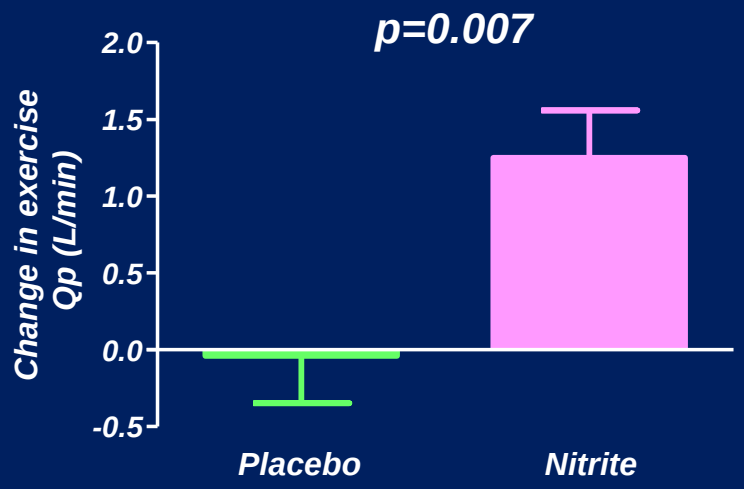
Change in PCWP after study drug

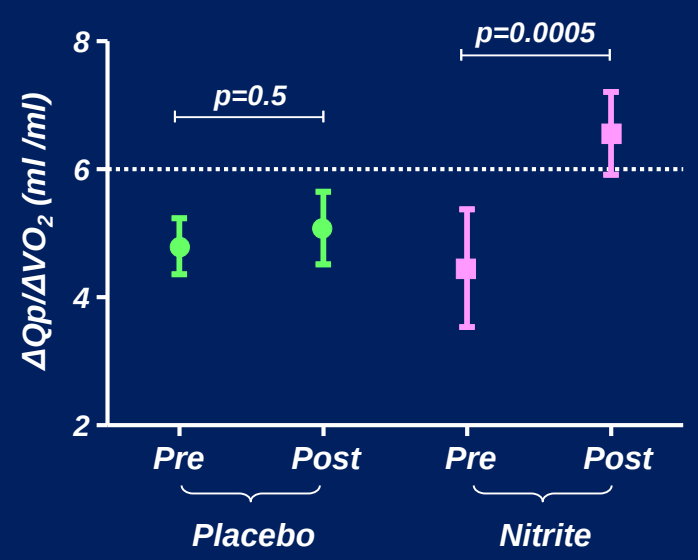


Borlaug, Koepp et al. *J Am Coll Cardiol* 2015









Borlaug, Koepp et al. *J Am Coll Cardiol* 2015

Summary

- **Pathophysiology is complex**
  - **EF is preserved—but systolic function is not**
  - **Much more than diastolic dysfunction: LVSD, RVD, vascular, autonomic, peripheral**
  - **Heterogeneity but also combined reserve dysfunction**
- **Treatment**
  - **Nothing proven yet**
  - **Exciting new studies coming soon**

Thanks!