HFpEF 2016 : Comorbidities and Outcomes

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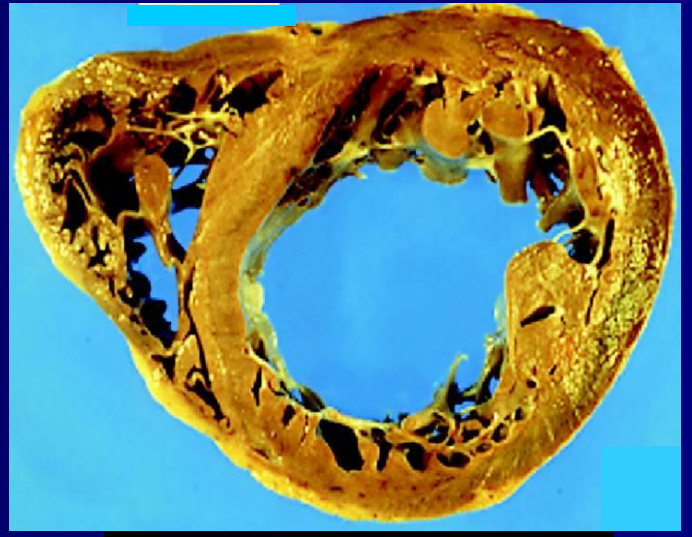
DISCLOSURES

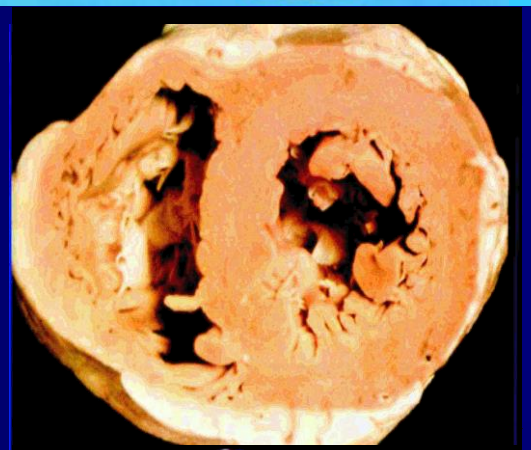
- Dr. O'Connor receives or has received research support and consulted for Bayer, Merck, Medtronic, Boston Scientific, ResMed, BMS, and NHLBI.

HFpEF

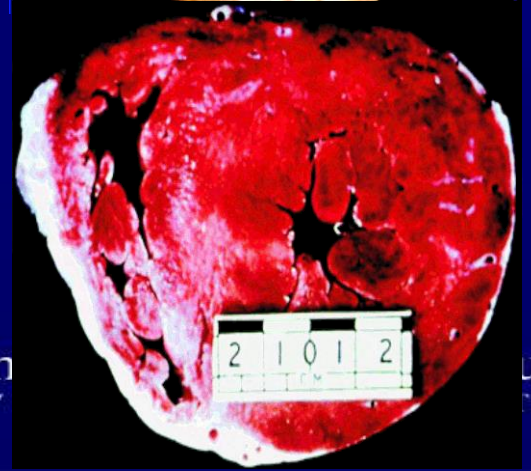
- Prevalent Disease
- High morbidity and cost to society
- No specific therapy beyond symptom reduction that is recommended or approved



Systolic Heart Failure



Normal



Diastolic Heart Failure

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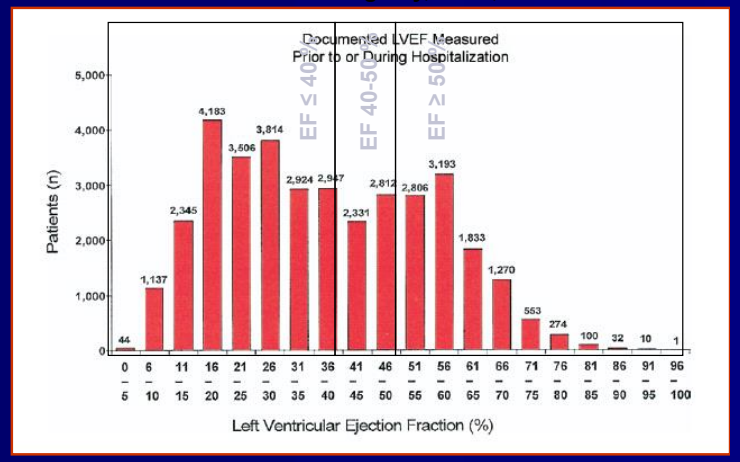
Aurigemma, Zile, Gaasch
Circulation 2005

Progress in HFpEF

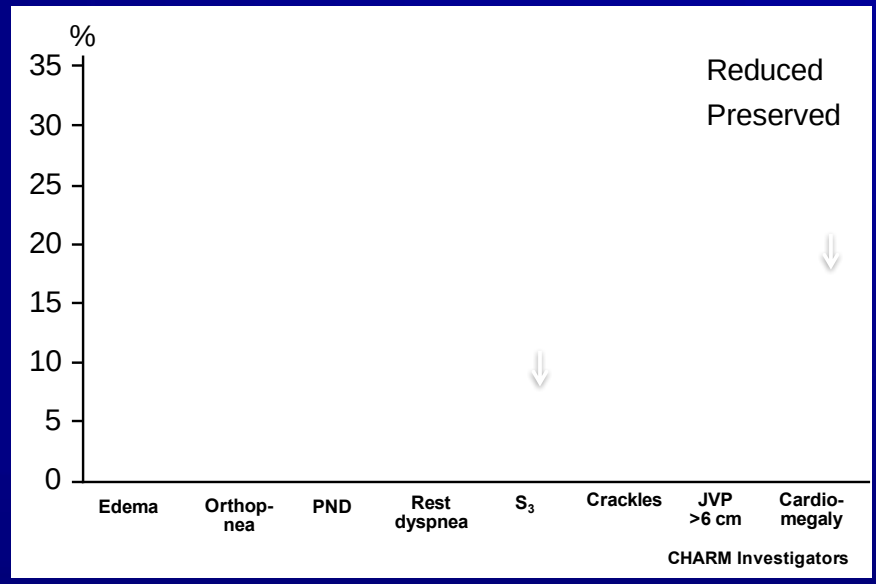
- Heterogeneity and pathophysiology
- Mid range LV ejection fraction (HFmrEF)
- Comorbidities
- Treatment

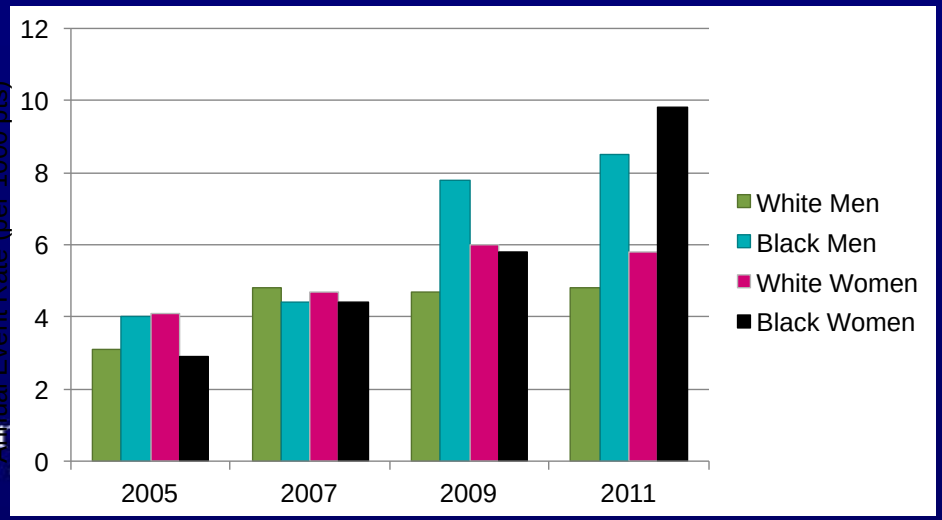
HFPEF: Half of Heart Failure, Similar Signs and Symptoms and Increasing in Prevalence

OPTIMIZE-HF Registry, N=41,267



Fonarow G et al. *JACC*. 2007; 50:768-777.





Why Prior HFpEF Trials have Not Been Successful

- Wrong Patients
- Comorbidities
- Wrong Endpoints
- No Disease
- Wrong Therapies

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Table 3.1 Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).

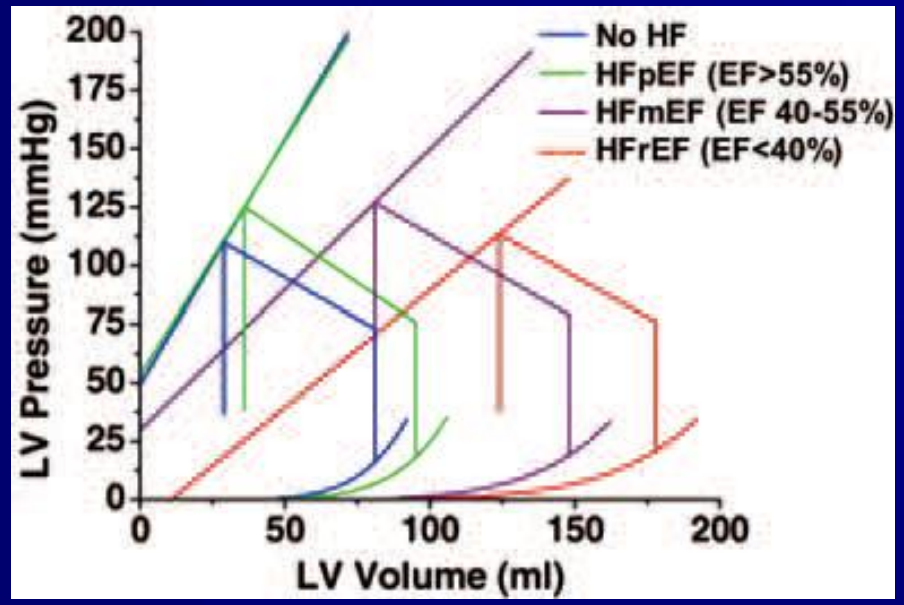
BNP = B-type natriuretic peptide; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LAE = left atrial enlargement; LVEF = left ventricular ejection fraction; LVH =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

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

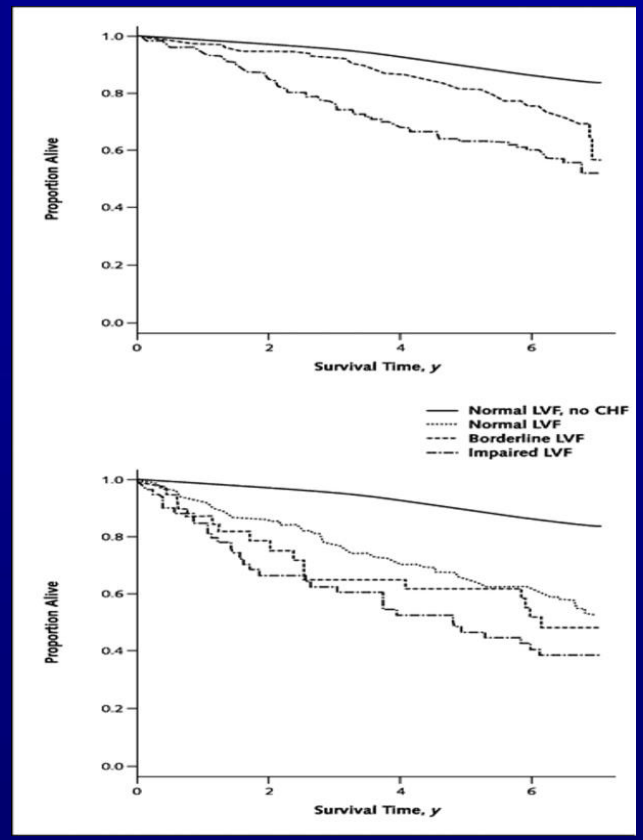
[b]BNP>35 pg/ml and/or NT-proBNP>125 pg/mL.

European heart Journal:published online: 20 May 2016

The middle child in heart failure: heart failure with mid-range ejection fraction (40–50%)

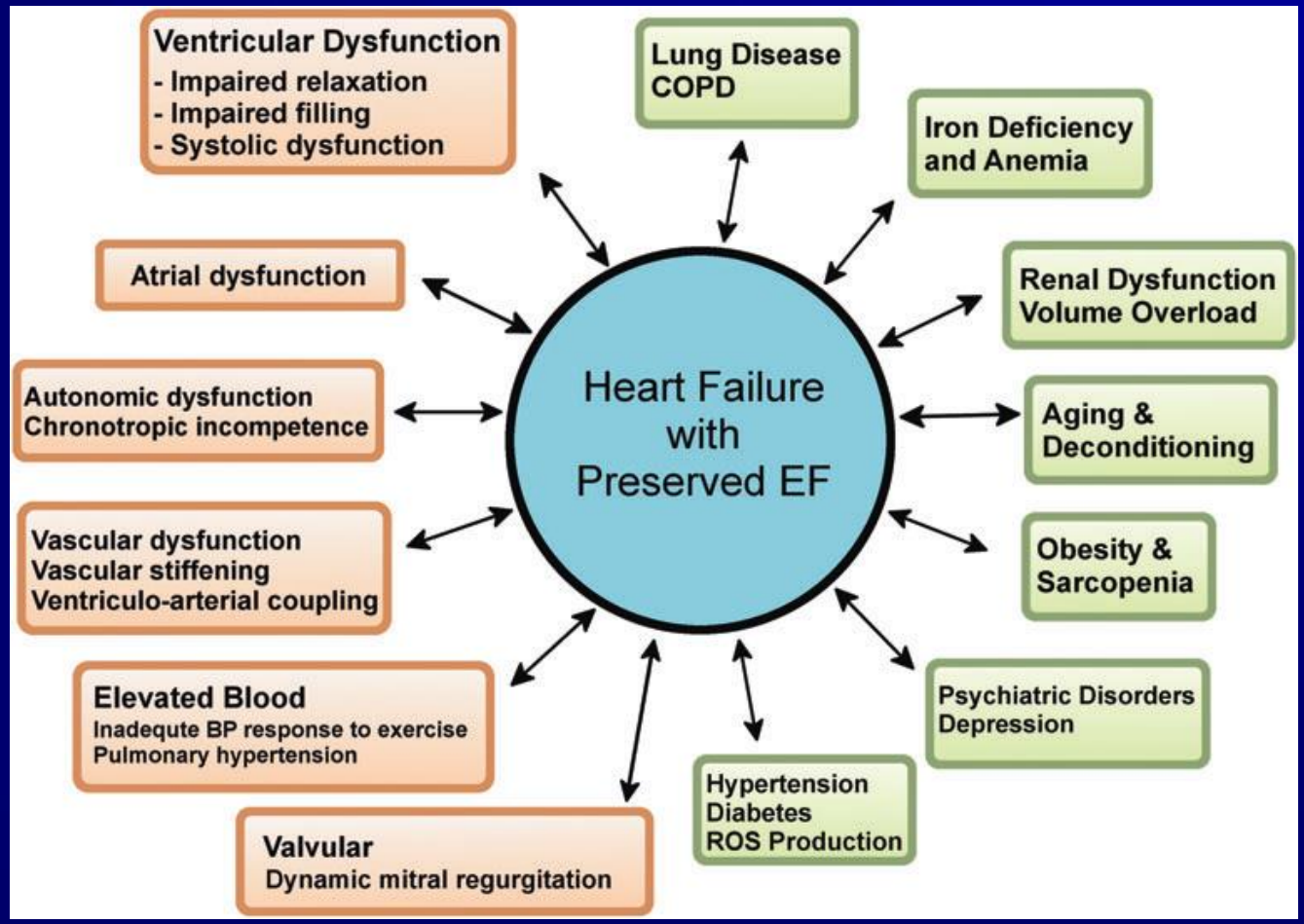


European Journal of Heart Failure (2014) **16**, 1049–1055



Annals of internal medicine 2002; 137:631-639

Heterogeneity of the heart failure with preserved ejection fraction syndrome.



European Heart Journal (2014) **35**, 1022–1032

*A **high degree of disease heterogeneity** exists*

The Heterogeneity of Heart Failure

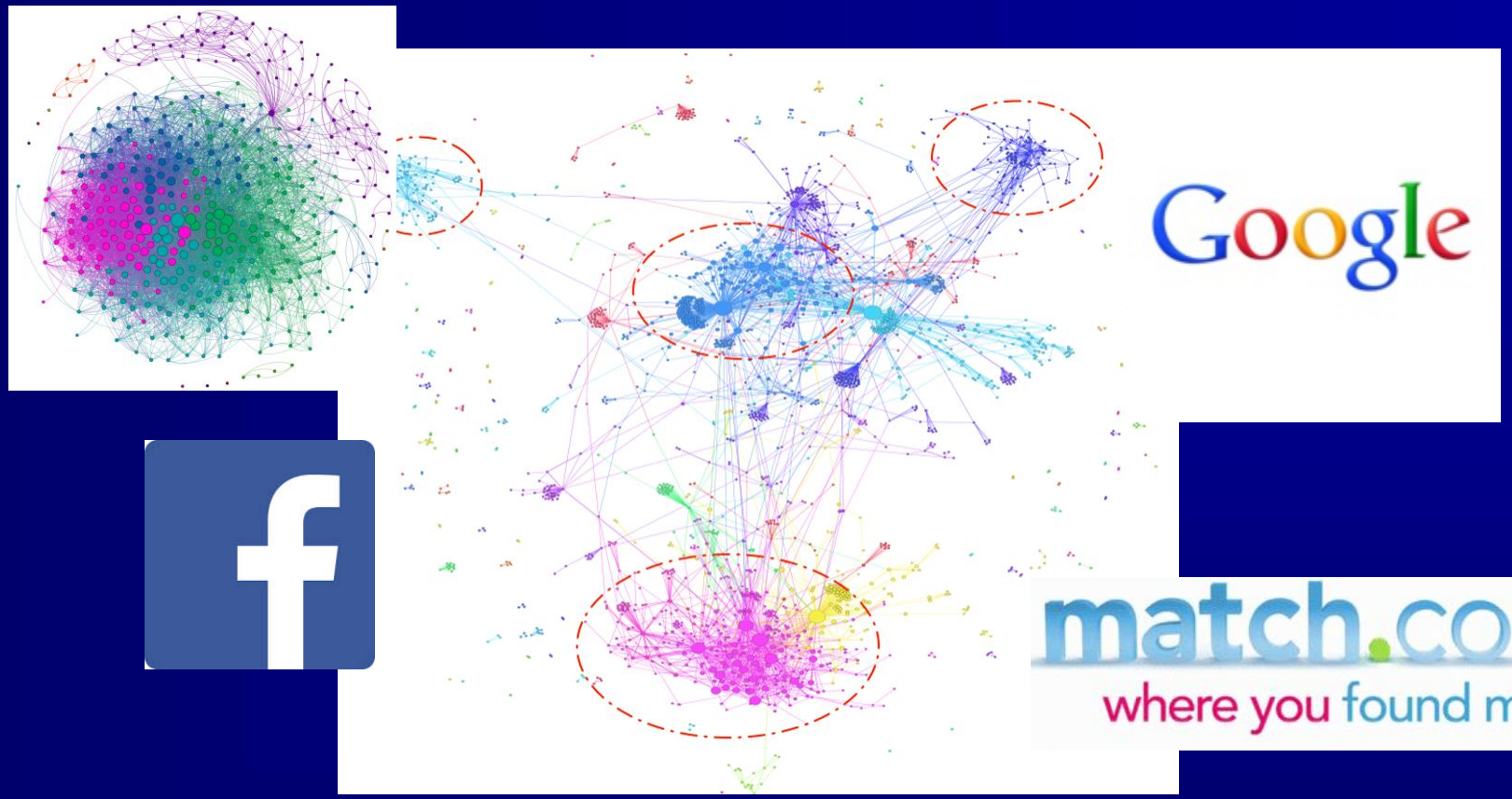
Will Enhanced Phenotyping Be Necessary for Future Clinical Trial Success?*

Gary S. Francis, MD, Rebecca Cogswell, MD, Thenappan Thenappan, MD

*more **accurate classification** of disease and*

*ultimately **enhance diagnosis** and **treatment***

Cluster Analysis



Cluster analysis is an unsupervised learning task of grouping a set of objects in such a way that objects in the same group are more similar to each other than to those in other groups

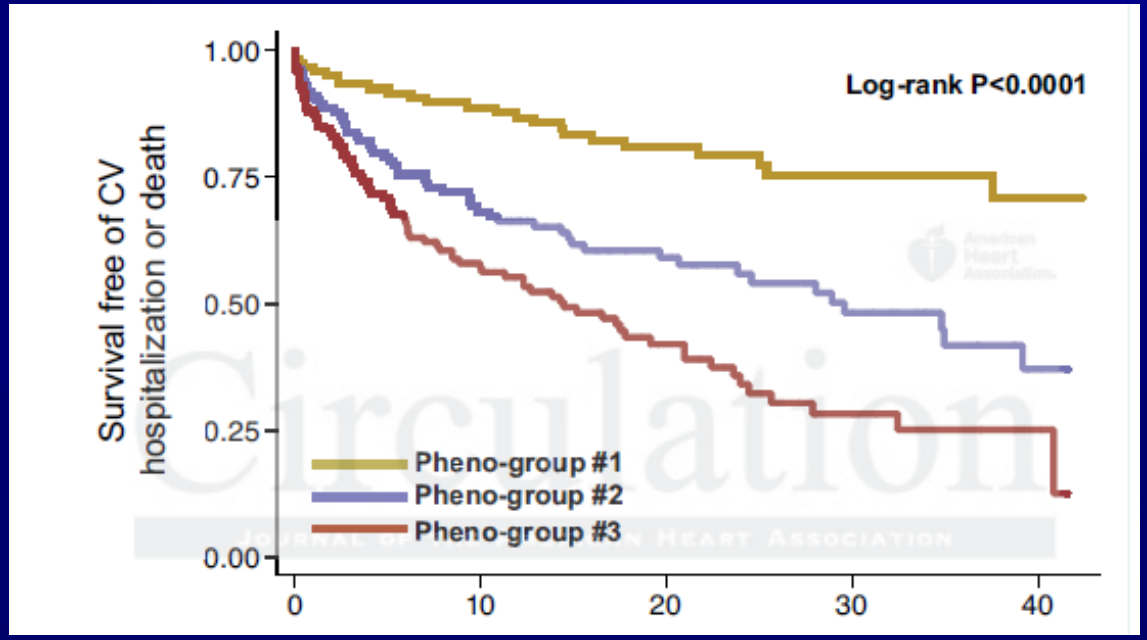
J Am Coll Cardiol. 2014;64:1765-74

Cluster Analysis of Heart Failure to Uncover Distinct Phenotypes?

Phenomapping for Novel Classification of Heart Failure with Preserved Ejection Fraction

Running title: *Shah et al.; Phenomapping of HFpEF*

Sanjiv J. Shah, MD[1,2]; Daniel H. Katz, MD[1]; Senthil Selvaraj, MD, MA[1]; Michael A. Burke, MD[1]; Clyde W. Yancy, MD, MSc[1]; Mihai Gheorghiade, MD[1,3]; Robert O. Bonow, MD[1,3]; Chiang-Ching Huang, PhD[4]; Rahul C. Deo, MD, PhD[5]



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Circulation. 2014; Nov 14

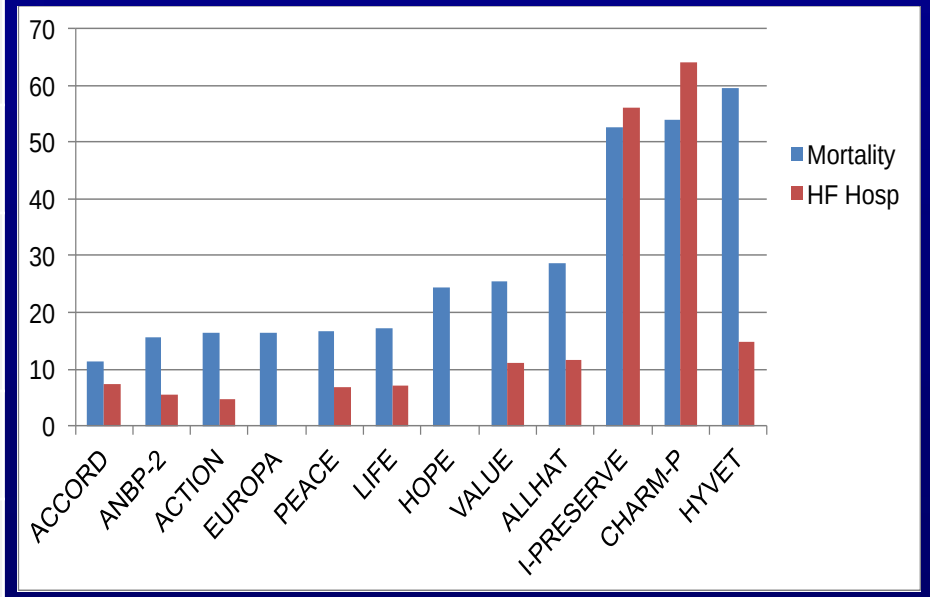
Implications of Co-Morbidities

- Increase heterogeneity
- Complicates management(Beta agonists;NSAID)
- Associated with worse outcomes
- Increase in non-cardiac outcomes

Mentz RJ and Felker GM. Heart Fail Clin 2013

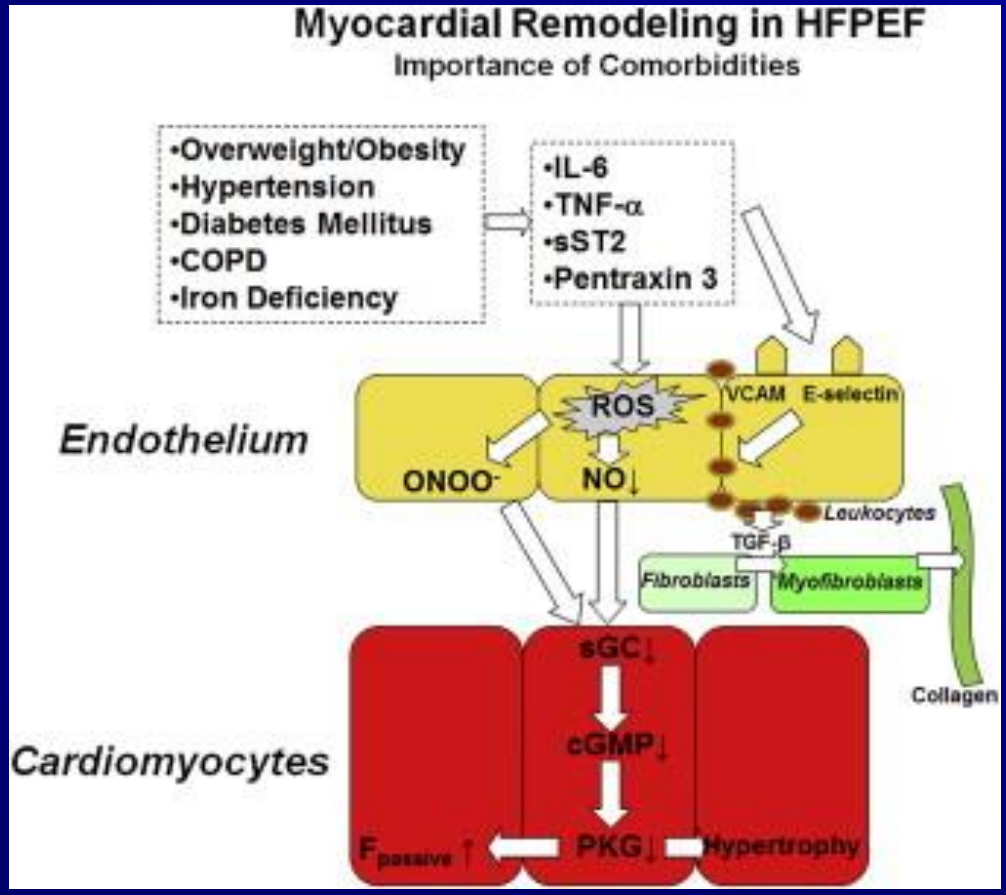
Real Disease or Just a Collection of Comorbidities?

	HFrEF	HFpEF	P-value
Age	71.8 ± 12	75.4 ± 11.5	< 0.001
Hypertension	49.2%	55.1%	0.005
Atrial Fibrillation	23.6%	31.8%	< 0.001
COPD	13.2%	17.7%	0.002
Anemia	9.9%	21.1%	< 0.001



Bhatia et al. NEJM 2006

Comorbidities drive myocardial dysfunction and remodeling in HF PEF



J Am Coll Cardiol 2013;62:263–71

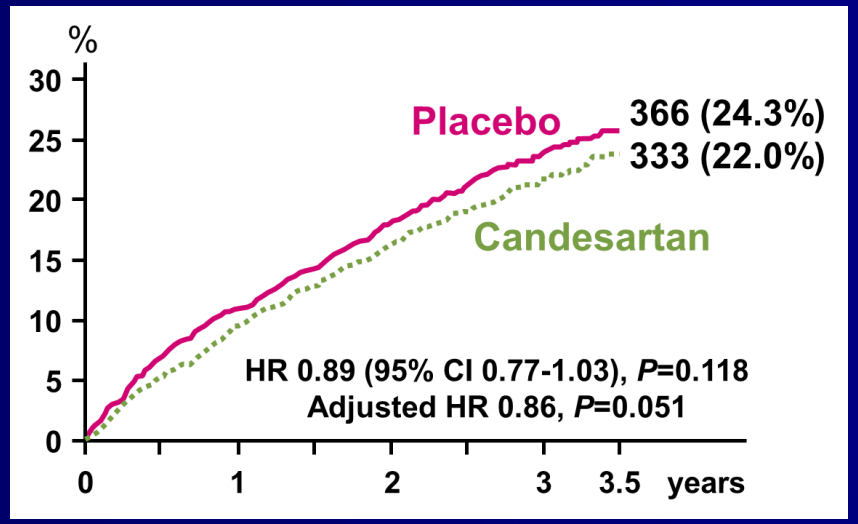
Bidirectional Impact

COMORBIDITY	BIDIRECTIONAL IMPACT ON DISEASE PROGRESSION	HEART FAILURE SPECIFICS
Chronic obstructive pulmonary disease	Inflammation; hypoxia; parenchymal changes; airflow limitation, leading to pulmonary congestion; abnormal left ventricular (LV) diastolic filling; inhaled beta-agonist cardiovascular effects Elevated LV end-diastolic pressure and beta-blocker use may compromise lung function	More prevalent in preserved ejection fraction (HFpEF), compared to reduced (HFrEF) Higher mortality risk in HFpEF
Anemia	Adverse LV remodeling; adverse cardiorenal effects; increased neurohormonal and inflammatory cytokines Inflammation; hemodilution; renal dysfunction; metabolic abnormalities exacerbate	More prevalent in HFpEF Similar increased risk for mortality in both groups
Diabetes	Diabetic cardiomyopathy; mitochondrial dysfunction; abnormal calcium homeostasis; oxidative stress; renin-angiotensin-aldosterone system (RAAS) activation; atherosclerosis; coronary artery disease Incident and worsening diabetes mellitus via sympathetic and RAAS activation	More prevalent in HFpEF Similar increased risk for mortality in both groups
Renal dysfunction	Sodium and fluid retention; anemia; inflammation; RAAS and sympathetic activation Cardiorenal syndrome through low cardiac output; accelerated atherosclerosis; inflammation; increased venous pressure	Similar prevalence in both groups Similar increased risk for mortality in both groups
Sleep-disordered breathing	Hypoxia; systemic inflammation; sympathetic activation; arrhythmias; hypertension (pulmonary and systemic); RV dysfunction; worsening congestion Rostral fluid movement may worsen pharyngeal obstruction; instability of ventilatory control system	Similar prevalence in both groups Unknown mortality differential associated with HFpEF vs. HFrEF
Obesity	Inflammation; reduced physical activity and deconditioning; hypertension; metabolic syndrome; diabetes mellitus Fatigue and dyspnea may limit activity; spectrum of metabolic disorders including nutritional deficiencies	More prevalent in HFpEF Obesity paradox; potential for a U-shaped association with mortality

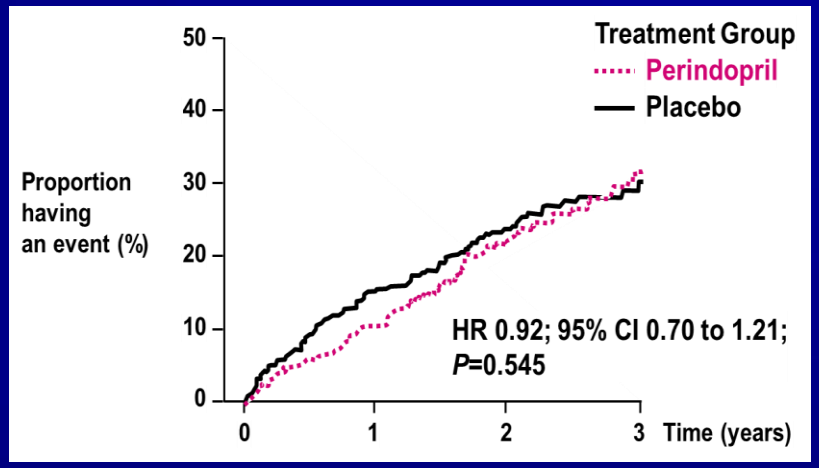
Mentz RJ, O'Connor CM et al. JACC 2014

Wrong Therapies?: Outcomes Trials in HFpEF

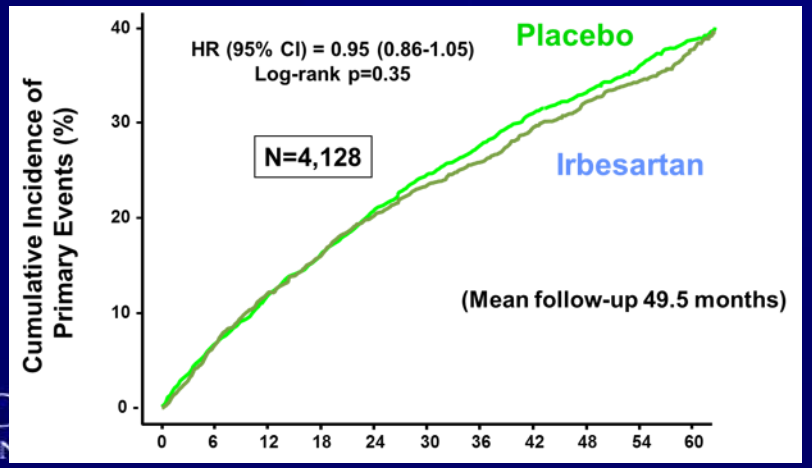
CHARM-Preserved



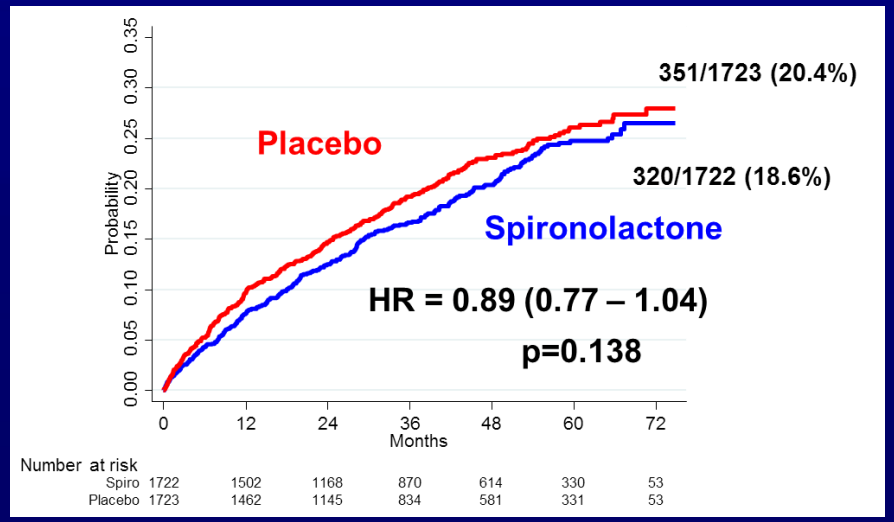
PEP-CHF



I-PRESERVE



TOPCAT



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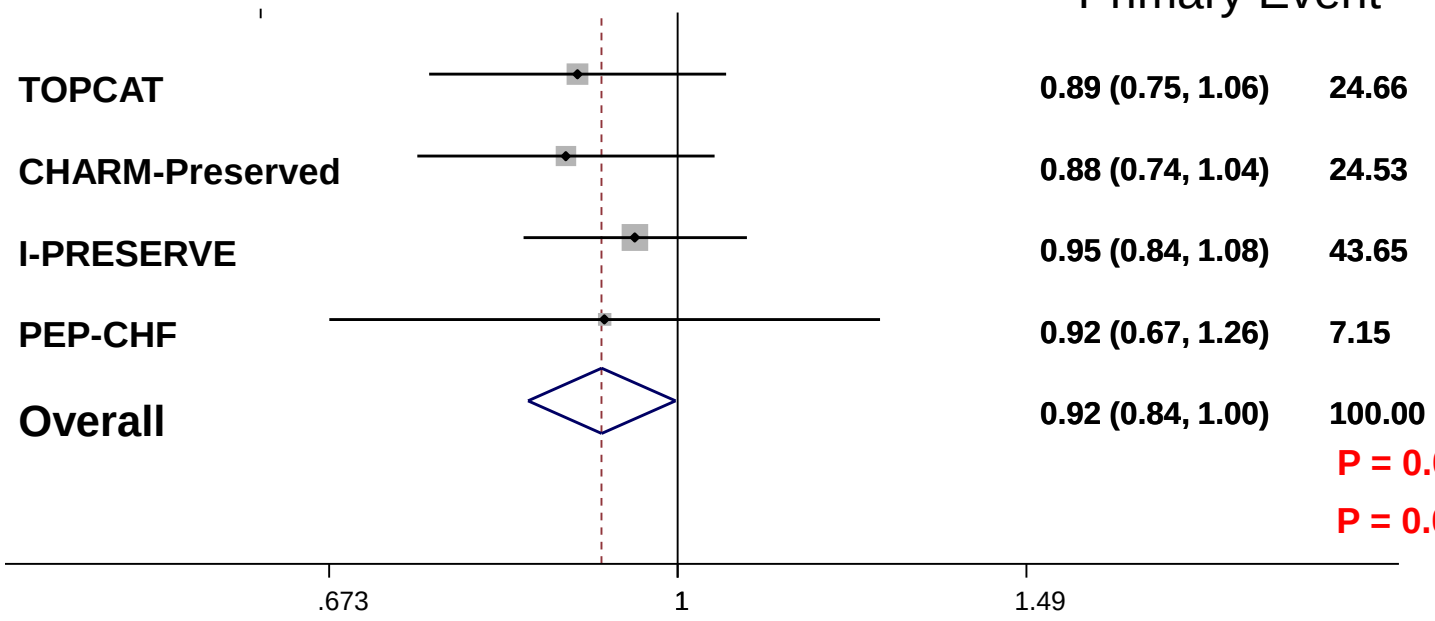
RAS Inhibitors in HFpEF

"Marginal" Effect



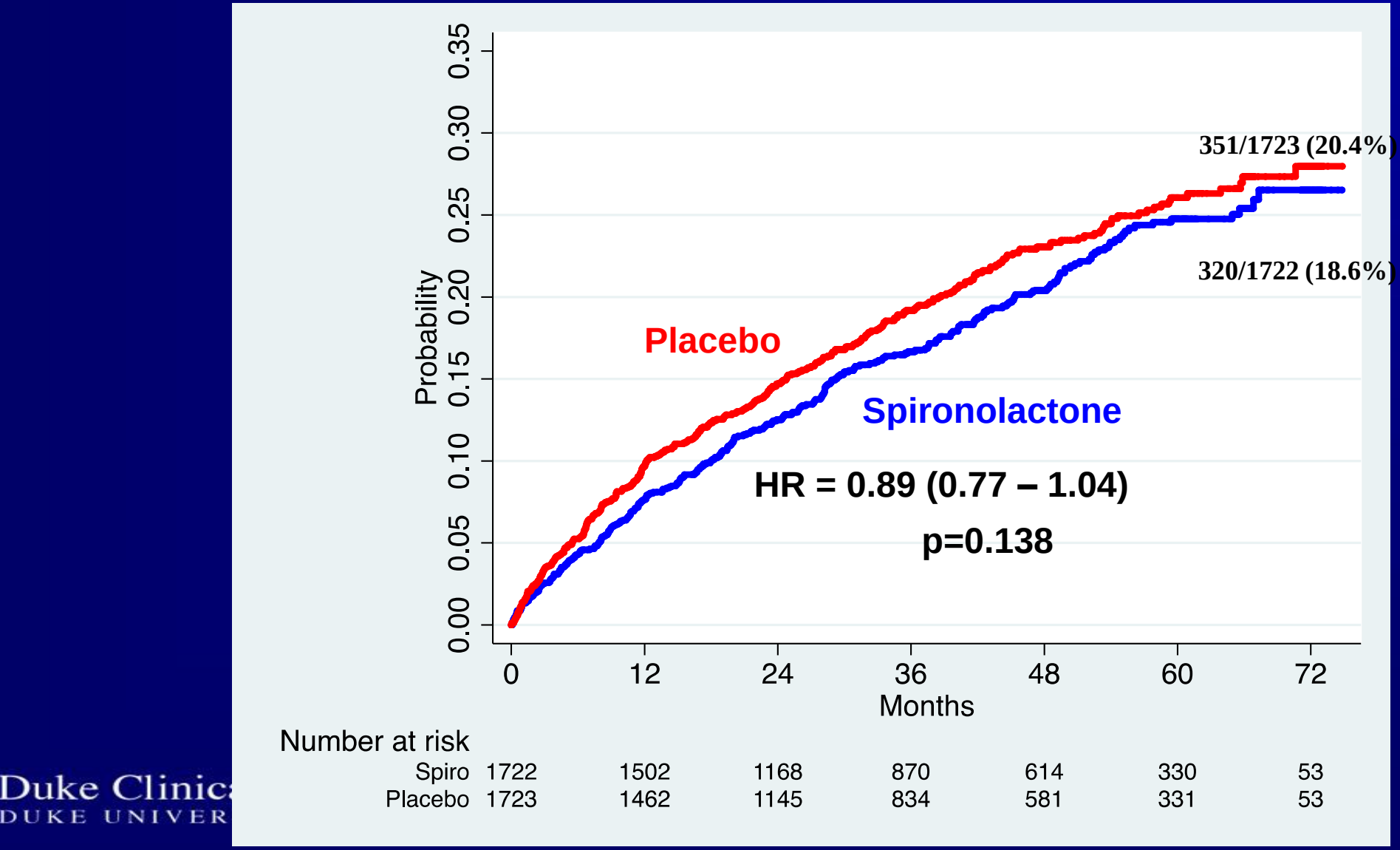
P = 0.043 Primary Event

P = 0.053 CV Death or HHF

2016 ESC Guidelines

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

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



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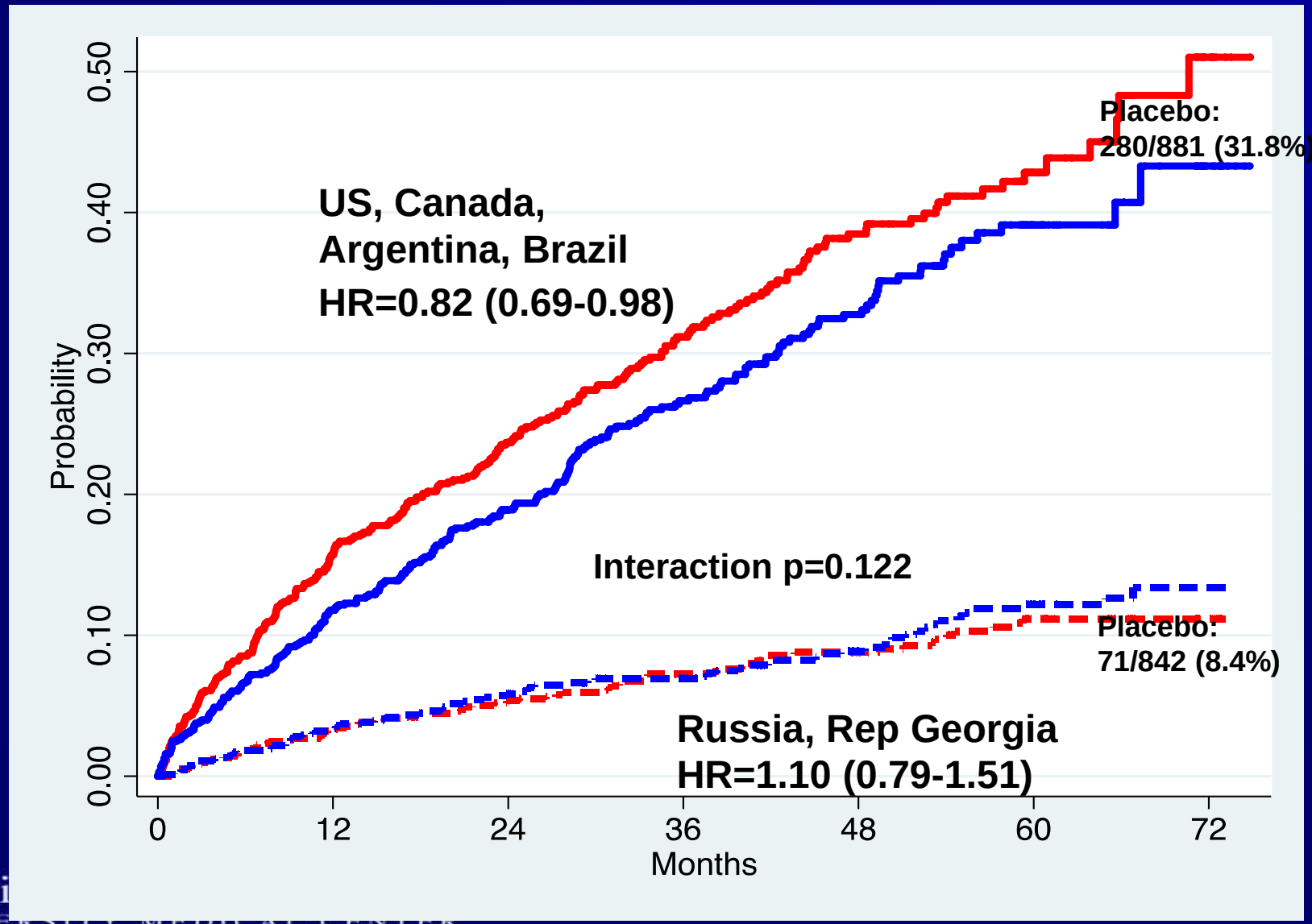
Wrong Patients?: TOPCAT: Results by Region



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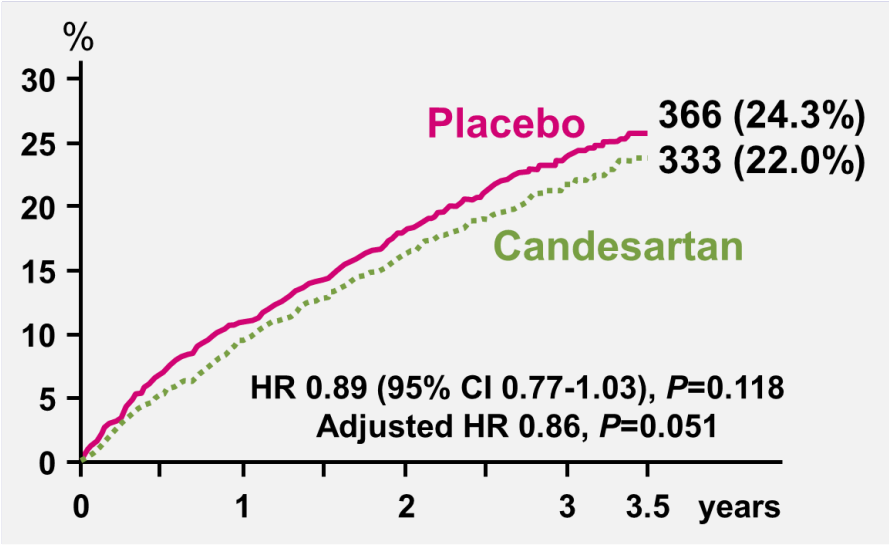
Pfeffer MA et al. Circulation. 2015 Jan 6;131(1):34-42

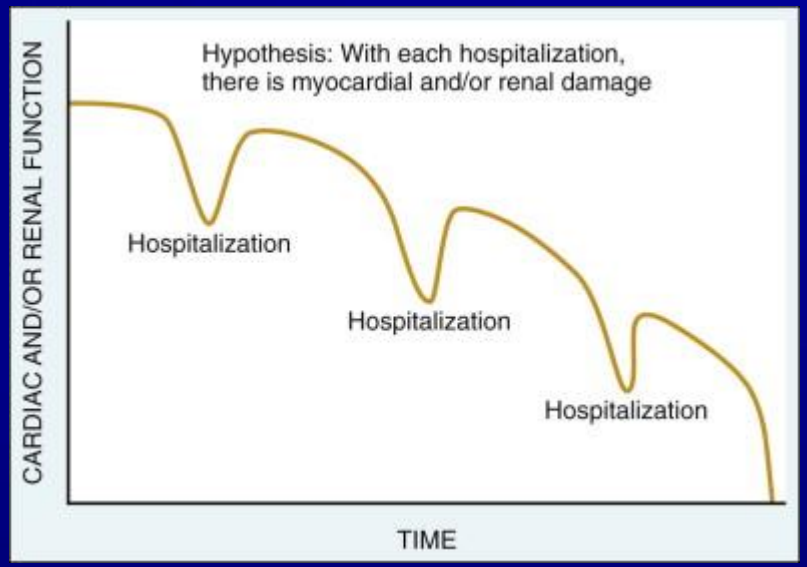
TOPCAT: WHY

- Many patients in Russian and Georgia did not have a rise in potassium with spironolactone (Pfeffer et al. Circulation 2015)
- Canrenone, a spironolactone metabolite, not elevated in many patients in Russia and Georgia (O'Meara et al. HFSA 2016)
- These data suggest that these patients were likely NOT taking study drug!

Wrong Endpoints?

Time to first event analysis may not capture the full burden of disease and "throws out" many informative endpoints after the first





- Perhaps utilizing recurrent non-fatal events can improve our power, reduce sample size, and better capture the burden of disease

Analysing recurrent hospitalizations in heart failure: a review of statistical methodology, with application to CHARM-Preserved

Jennifer K. Rogers[1]*, Stuart J. Pocock[1], John J.V. McMurray[2], Christopher B. Granger[3], Eric L. Michelson[4], Jan Östergren[5], Marc A. Pfeffer[6], Scott D. Solomon[6], Karl Swedberg[7,8], and Salim Yusuf[9]

HF Hospitalisations	Candesartan (N=1513)	Placebo (N=1508)
≥ 1 Admission	229	278
≥ 2 Admissions	94	114
All Admissions	390	547
Unused Admissions	126	269

Rate Ratios for Composite of Recurrent Heart Failure Hospitalisations and Cardiovascular Death			
	HR	95% CI	P-value
Poisson	0.78	(0.69,0.87)	<0.001
Negative Binomial	0.75	(0.62,0.91)	0.003
Andersen-Gill (robust SE)	0.78	(0.65,0.93)	0.006
Joint Frailty Model			
Rate ratio	0.69	(0.55,0.85)	<0.001

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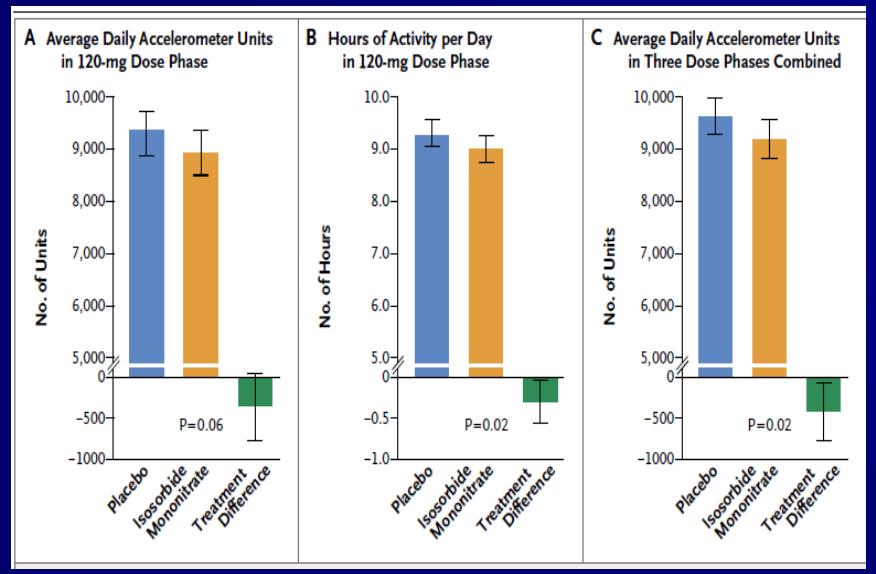
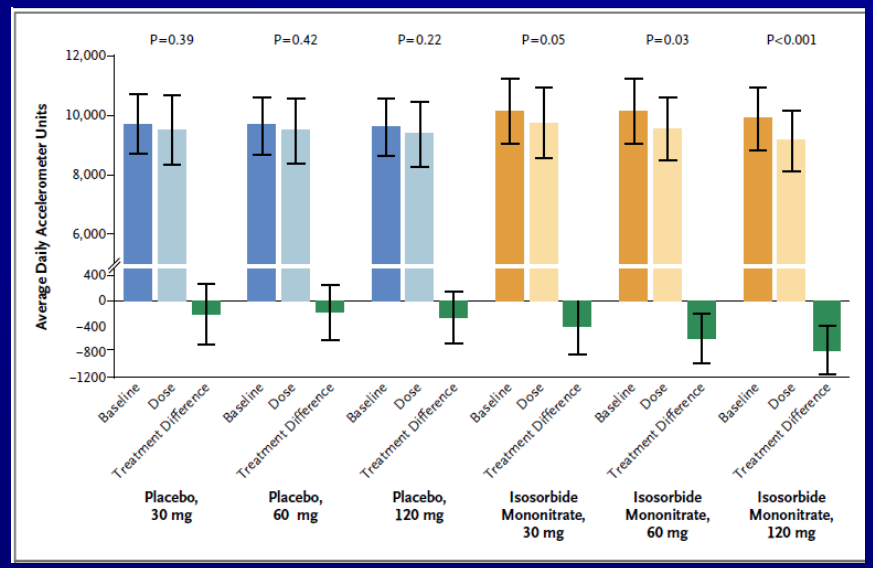
Rogers et al. Eur J Heart Fail 2014

Promising Therapies

NEAT-HFpEF:Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction (LVEF>50%)

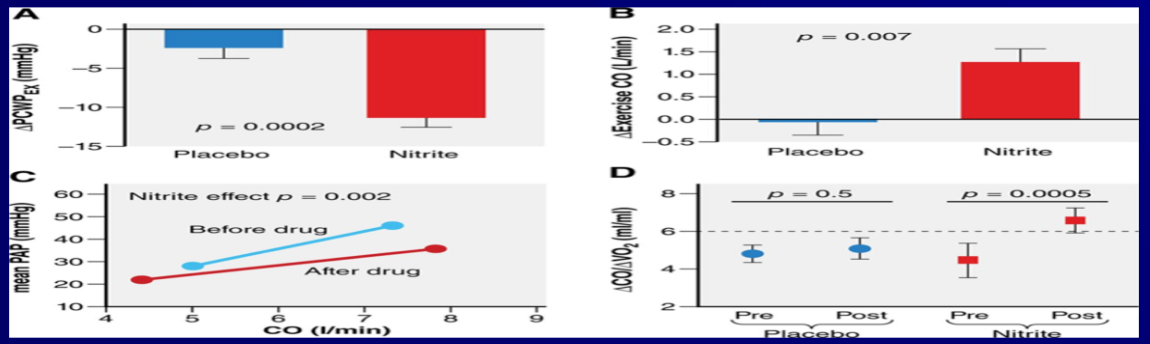




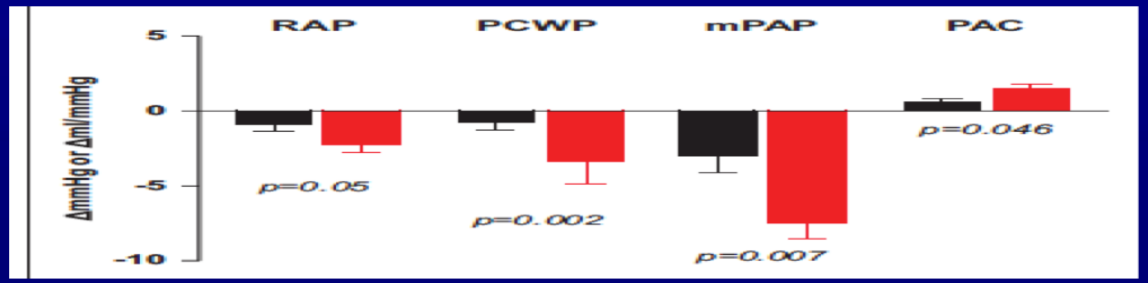
NEJM 2016: 373:2314-24

Nitrites in HFpEF

acute infusion of inorganic nitrite on exercise hemodynamics



Inhaled sodium nitrite hemodynamics



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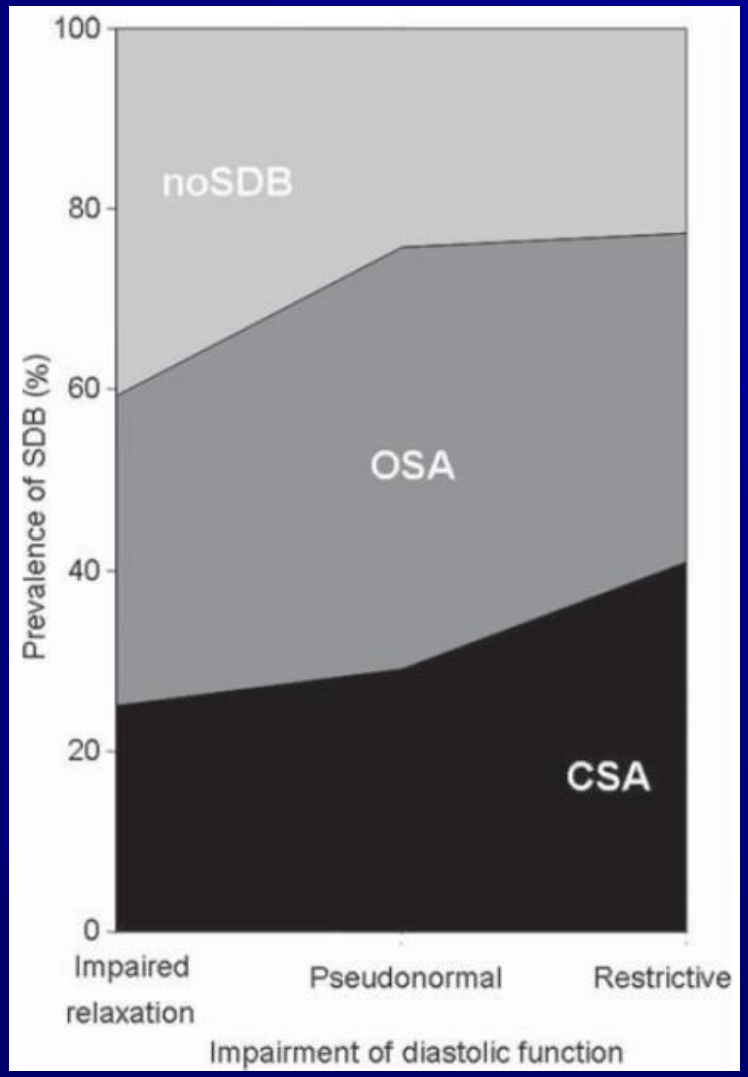
Circulation. 2016;134:73-90

❖ Circ Res 2016;119:880-886

SDB prevalence in HFpEF



Bitter et al., Eur J Heart Fail 2009

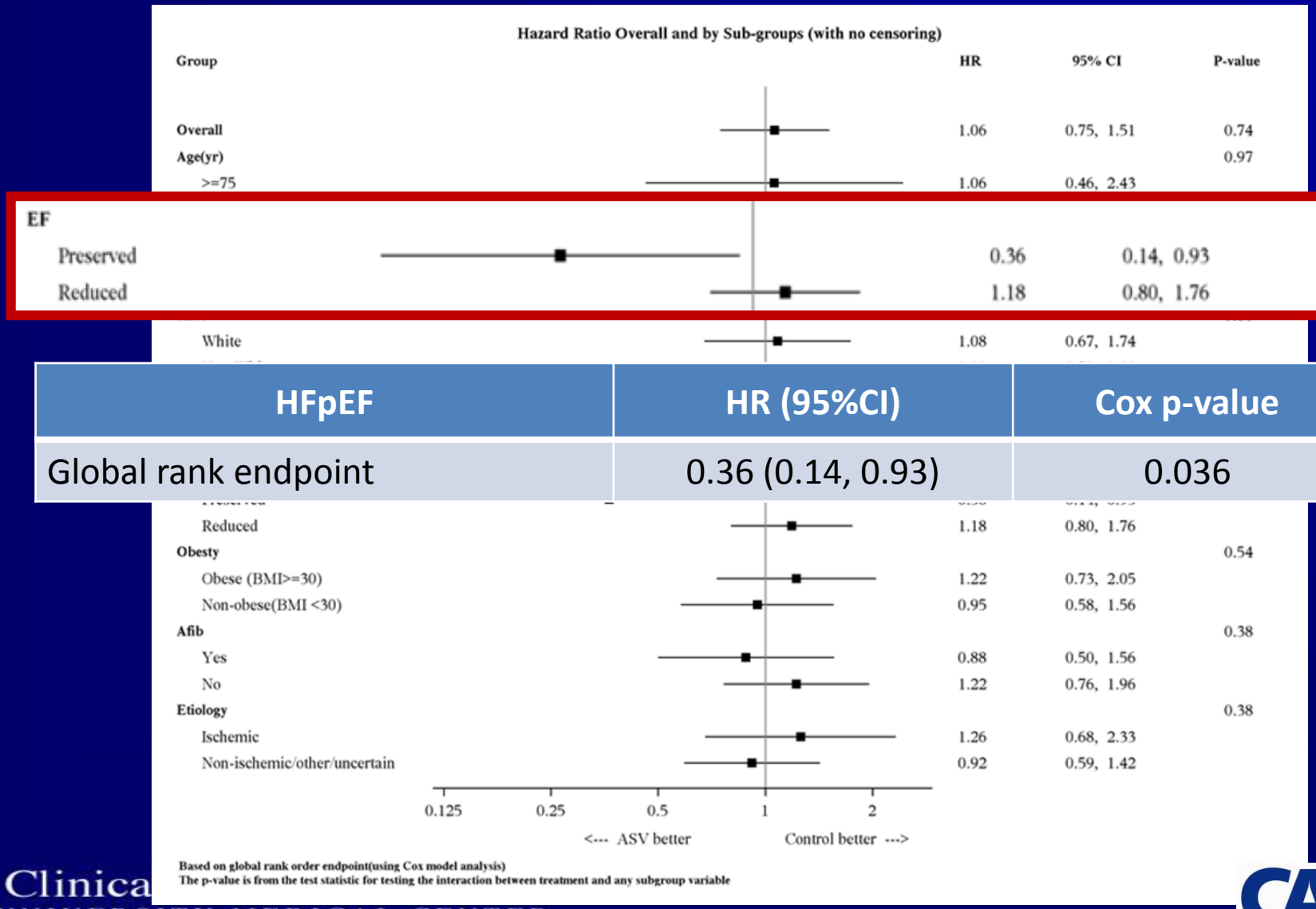
CAT-HF Study Objectives

- **Evaluate the effect of minute ventilation-targeted adaptive servo-ventilation (ASV) in acute decompensated heart failure (HF) patients on outcomes at 6 months.**

- **Primary Outcome**
  - Global Rank Endpoint: Rank order response based on survival free from CV hospitalization and improvement in functional capacity measured by 6MWD

- **Key Secondary Outcomes**
  - CV and all-cause death
  - SDB parameters
  - Change in 6MWD

CAT-HF Prespecified Analysis: Primary Endpoint



HFpEF	HR (95%CI)	Cox p-value
Global rank endpoint	0.36 (0.14, 0.93)	0.036

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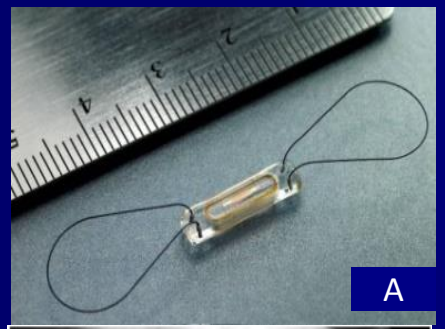
CAT-HF
Cardiovascular Improvements with MV ASV Therapy in Heart Failure

Implantable Hemodynamic Monitoring System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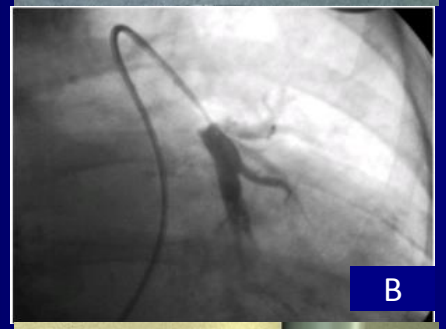
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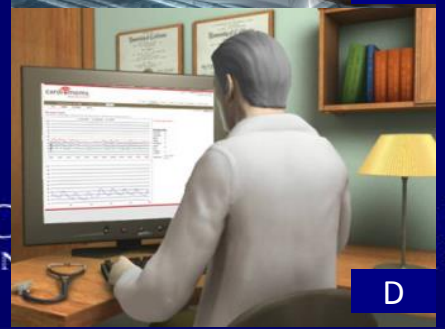
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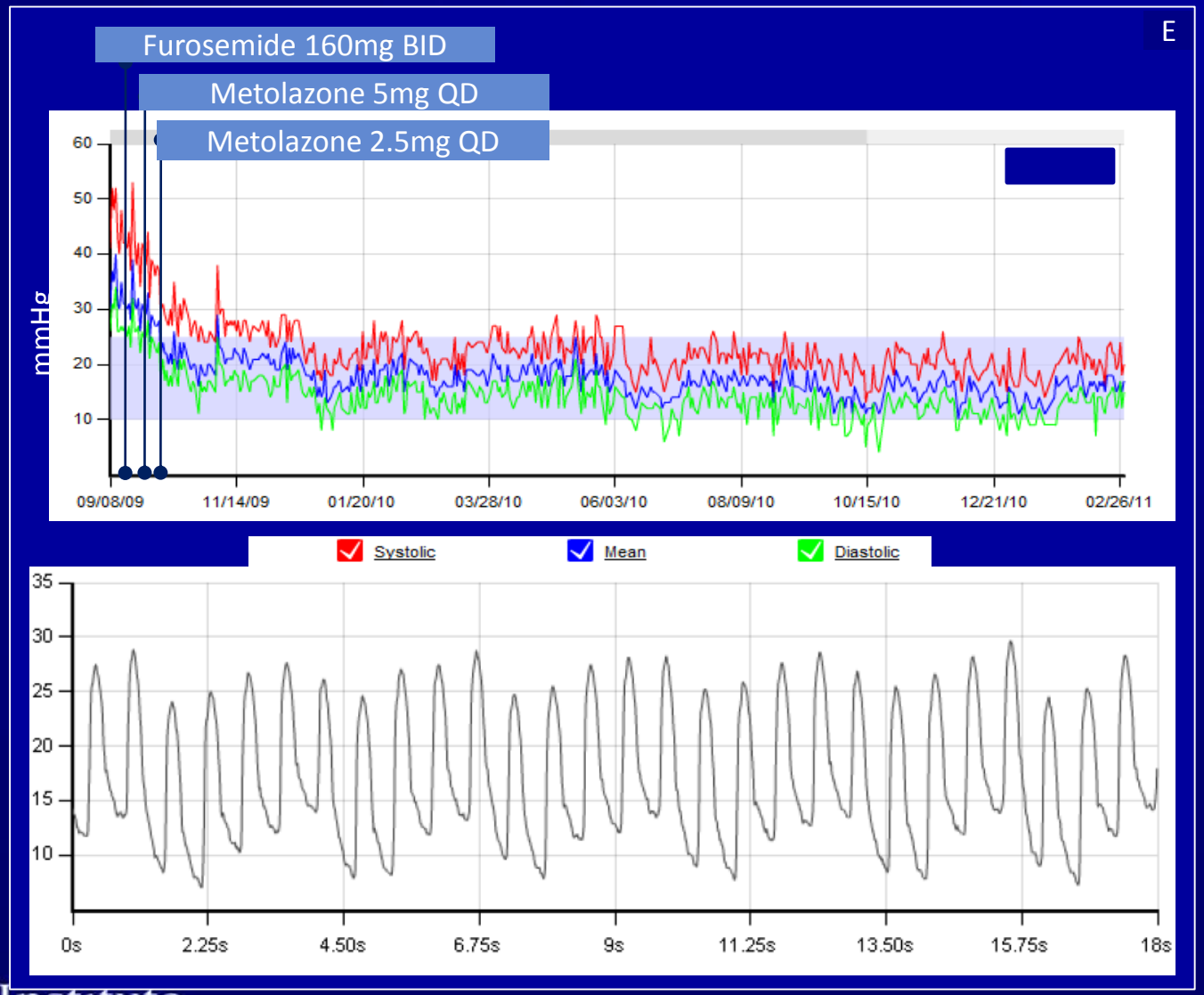

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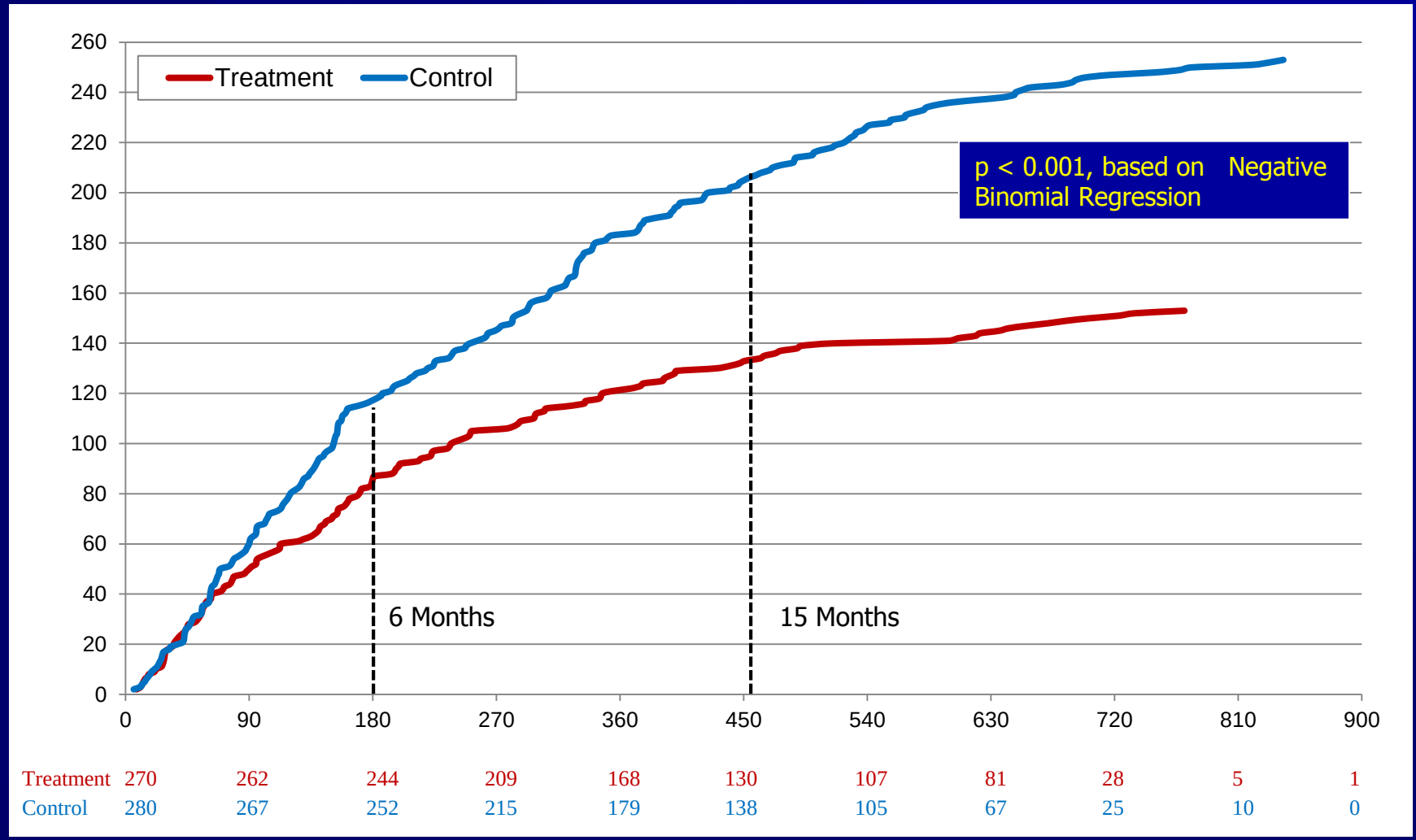
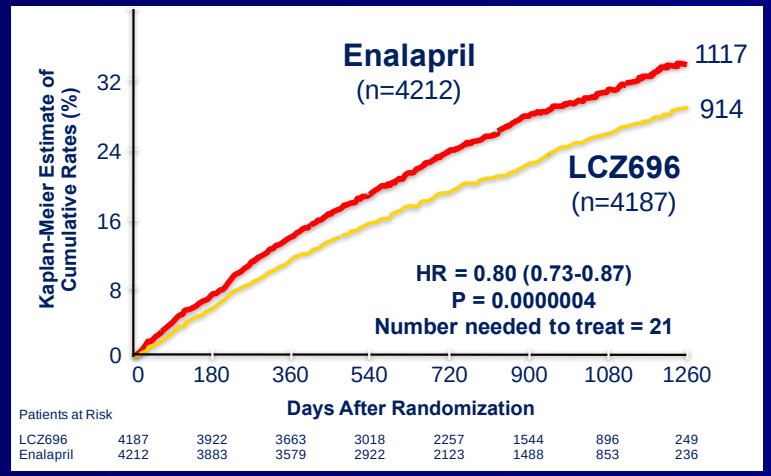
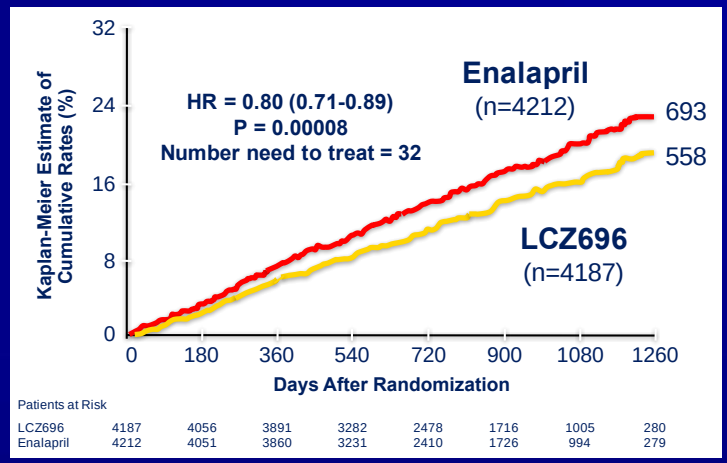
Cumulative HF Hospitalizations Over Entire Randomized Follow-Up Period

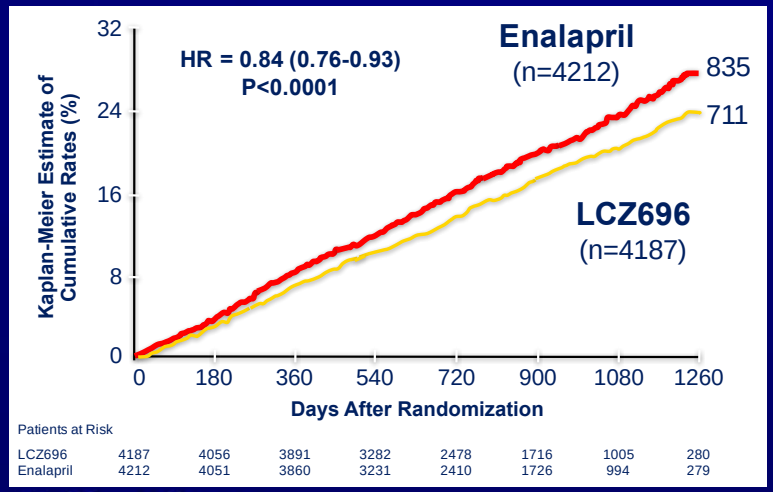


PARADIGM-HF Primary Results

Significant Reduction in Primary Endpoints, CV Death and All-Cause Mortality

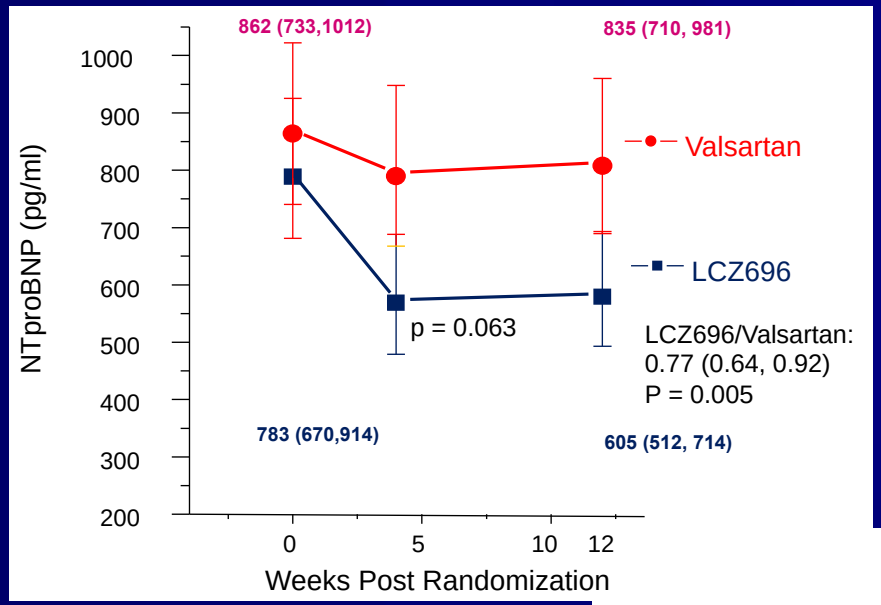




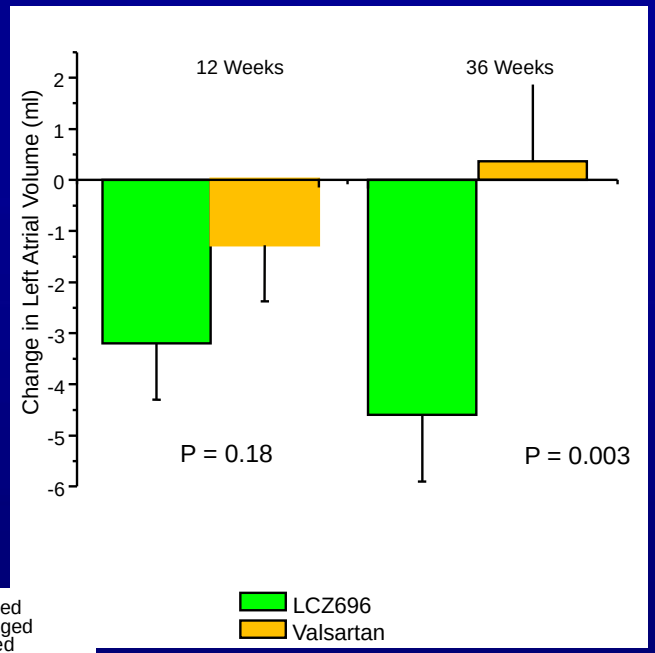


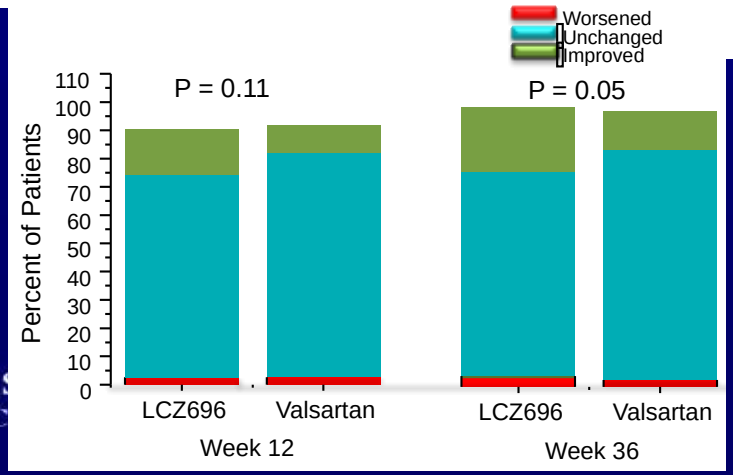
PARAMOUNT: Significant Improvement in Several Domains

Improvement in NT-proBNP



Improvement in Left Atrial Size

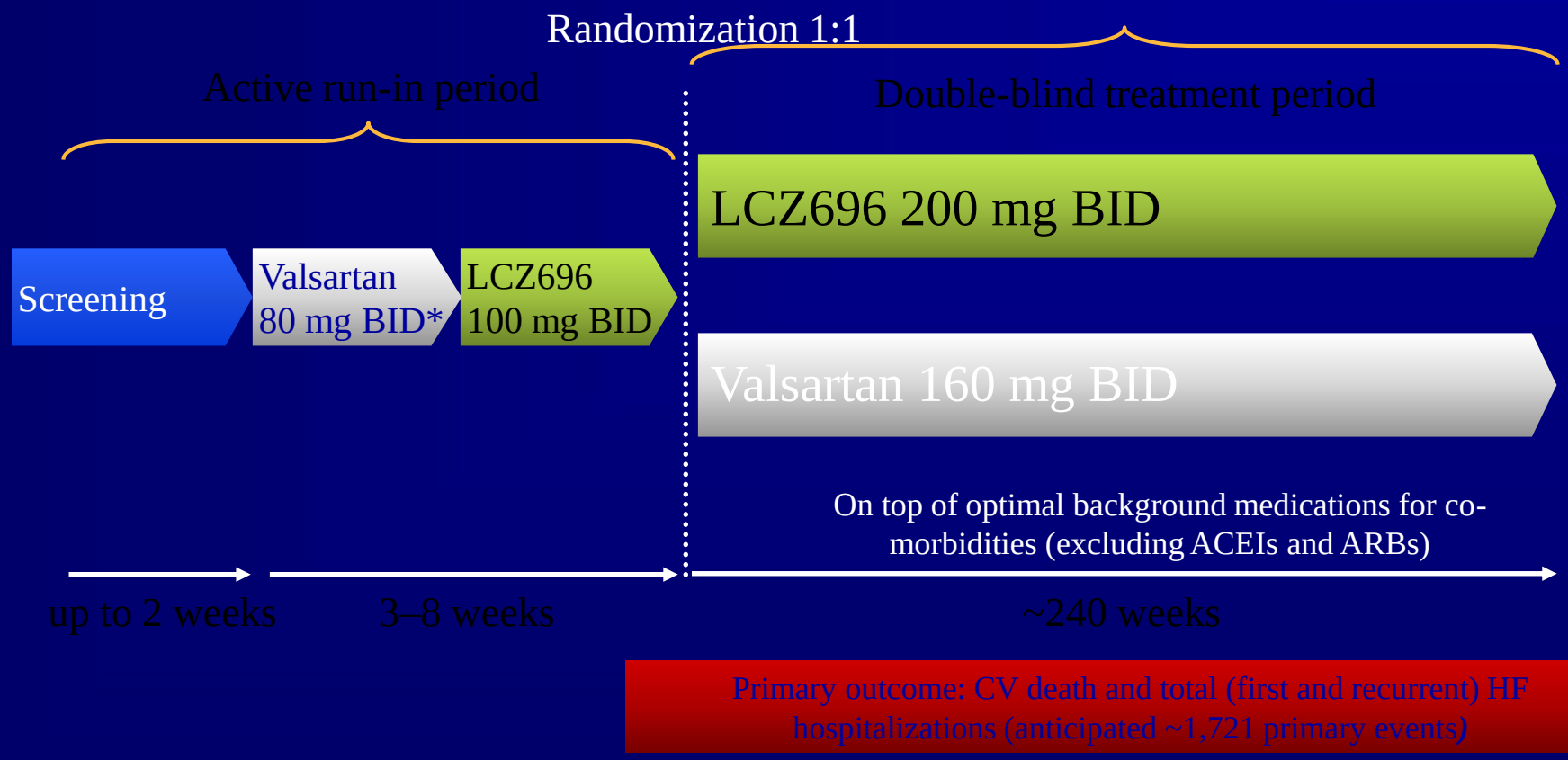




Solomon et al. Lancet 2012

PARAGON-HF: study design

Target patient population: ~4,600 patients with symptomatic HF (NYHA Class II–IV) and LVEF ≥45%, Structural Heart Disease, and Natriuretic Peptide Elevation



PARAGON-HF
Current Status

- 11,024 patients screened
- 4309 patients currently randomized
- 223 patients in screening (success rate 54%) and 396 patients in run-in (success rate ~84%)
- All screening activities will cease prior to holidays 2016!
- LPLV expected in March 2019, FIR July 2019

INfluenza Vaccine to Effectively Stop CardioThoracic Events and Decompensated Heart Failure in Patients with CVD (INVESTED)

Post-MI or HF Hospitalization

N = 9300 total patients
up to 3 yrs exposure

~16,000 pt-years total exposure

RANDOMIZED 1:1 DOUBLE BLIND ANNUAL VACCINE STRATEGY

All other CV Rx per treating MD

High Dose Trivalent Influenza Vaccine

Standard Dose Quadrivalent Influenza Vaccine

Duration
3 Influenza Seasons
+ Vanguard Season

Followed up to 4 times a year with annual re-vaccination to assigned strategy

Primary EP
Death or Cardiopulmonary Hospitalization

The O'Connor Formula

- Confirm Diagnosis(NT proBNP,Echo HFH)
- Identify and Treat Comorbidities
- Volume Management
- Spiro
- Cardio-MEMs for recurrent HFH
- Enroll in Clinical Trials(Paragon, Invested)

The Year in Review : HFpEF

- Heterogeneity and pathophysiology – concepts may link to personalized medicine
- Mid range LV ejection fraction (HFmEF)- possible benefit from systolic heart failure therapies
- Comorbidities – can confuse the correct diagnosis but also likely promote the development and progression of HFpEF
- Treatment Challenging

How Will President-Elect Trump Influence HF Care

- Health Care Systems will have reduced margins for uncompensated care, innovation, and expensive therapies
- Move to Bundle Care Initiatives will slow
- The threshold for evidence generation at the FDA will be less

Predictive Medicine : A New Treatment or Another Championship?