Heart Failure with Preserved Ejection Fraction Should We Target Comorbidities?

Christopher M. O´Connor, MD, FACC

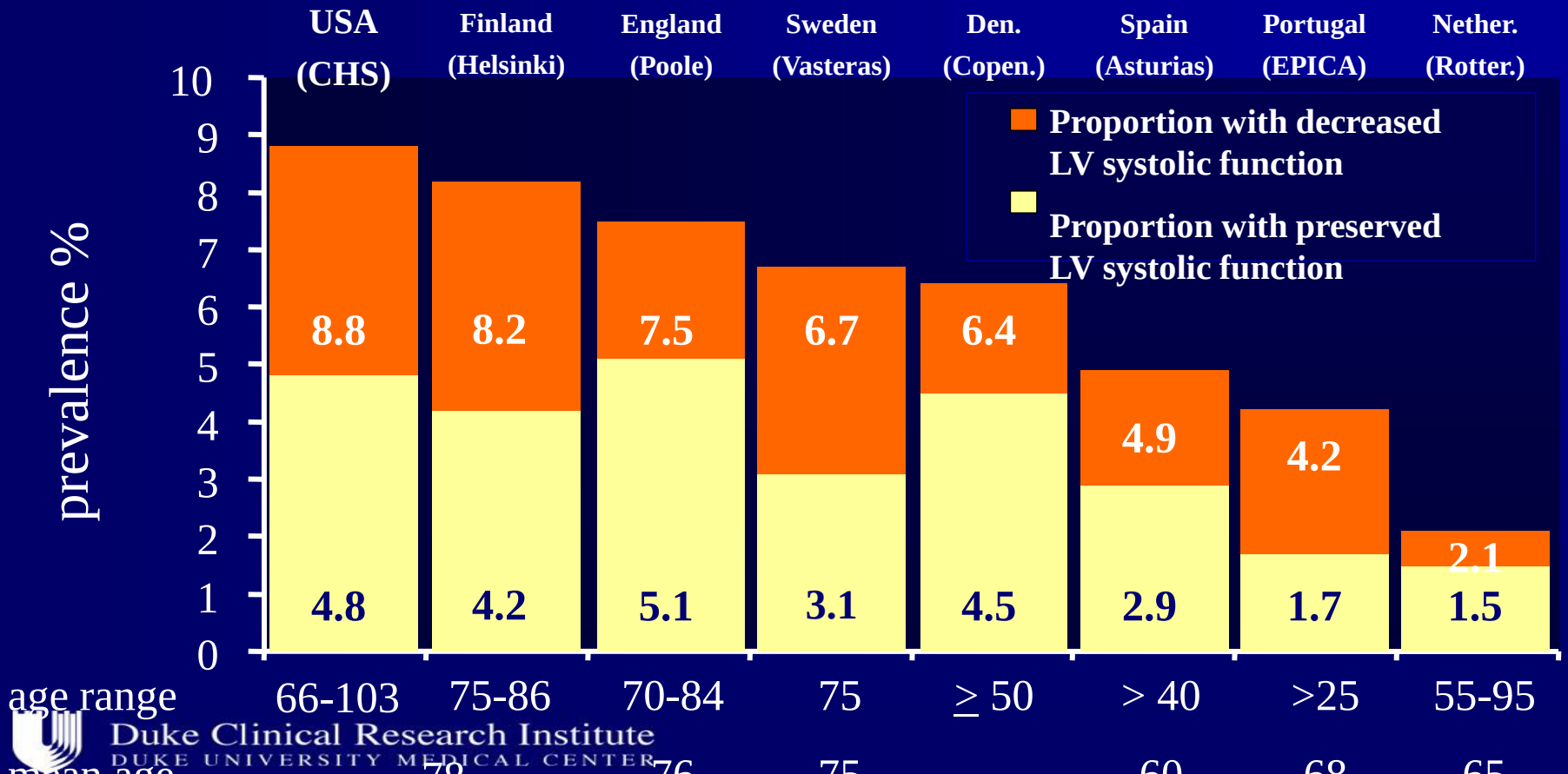
CEO and Executive Director, Inova Heart and Vascular Institute

Professor of Medicine(adj.) Duke University/DCRI

Editor in Chief, JACC: Heart Failure

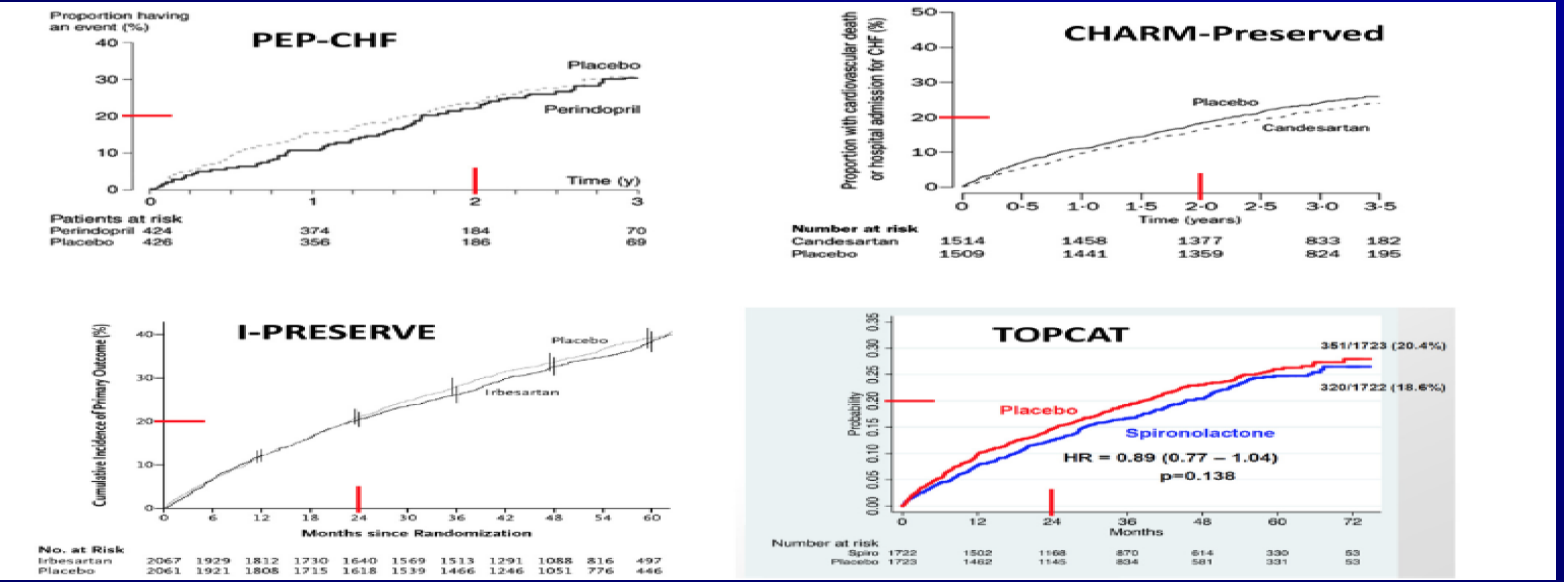
Duke Clinical Research Institute
DUKE UNIVERSITY MEDICAL CENTER

Prevalence of Heart Failure



Duke Clinical Research Institute
DUKE UNIVERSITY MEDICAL CENTER

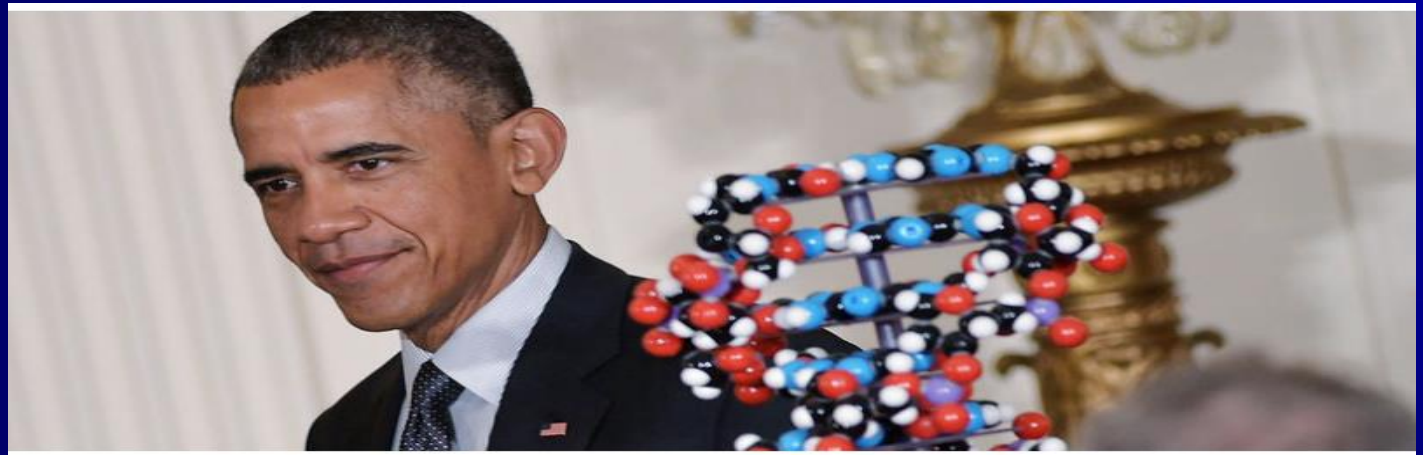
Why Have HFpEF Trials Failed?



Duke Clinical Research Institute
DUKE UNIVERSITY MEDICAL CENTER

Cleland JG, Pellicori P, Dierckx R. Heart Fail Clin. 2014

The New Era of Precision Science



US President Barack Obama walks past a 17-base pair DNA model as he arrives on stage to speak on investments in "precision medicine" on Jan. 30, 2015 in the East Room of the White House in Washington, DC. **Mandel Ngan/AFP/Getty**

Obama seeks $215 million for personalized medicine

PATHOPHYSIOLOGIC TARGETS

- Diastolic dysfunction
- Ventriculo-arterial disociation
- Pulmonary Hypertension
- Chronotropic Incompetance
- Systemic Hypertension
- Co-Morbidities

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Noncardiac Comorbidities in Heart Failure With Reduced Versus Preserved Ejection Fraction

Robert J. Mentz, MD,* Jacob P. Kelly, MD,* Thomas G. von Lueder, MD, PhD,† Adriaan A. Voors, MD,‡ Carolyn S.P. Lam, MBBS,§ Martin R. Cowie, MD, MSc,‖ Keld Kjeldsen, MD, DSc,¶ Ewa A. Jankowska, MD, PhD,# Dan Atar, MD, PhD,† Javed Butler, MD, MPH,** Mona Fiuzat, PharmD,* Faiez Zannad, MD,†† Bertram Pitt, MD,‡‡ Christopher M. O'Connor, MD*

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

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

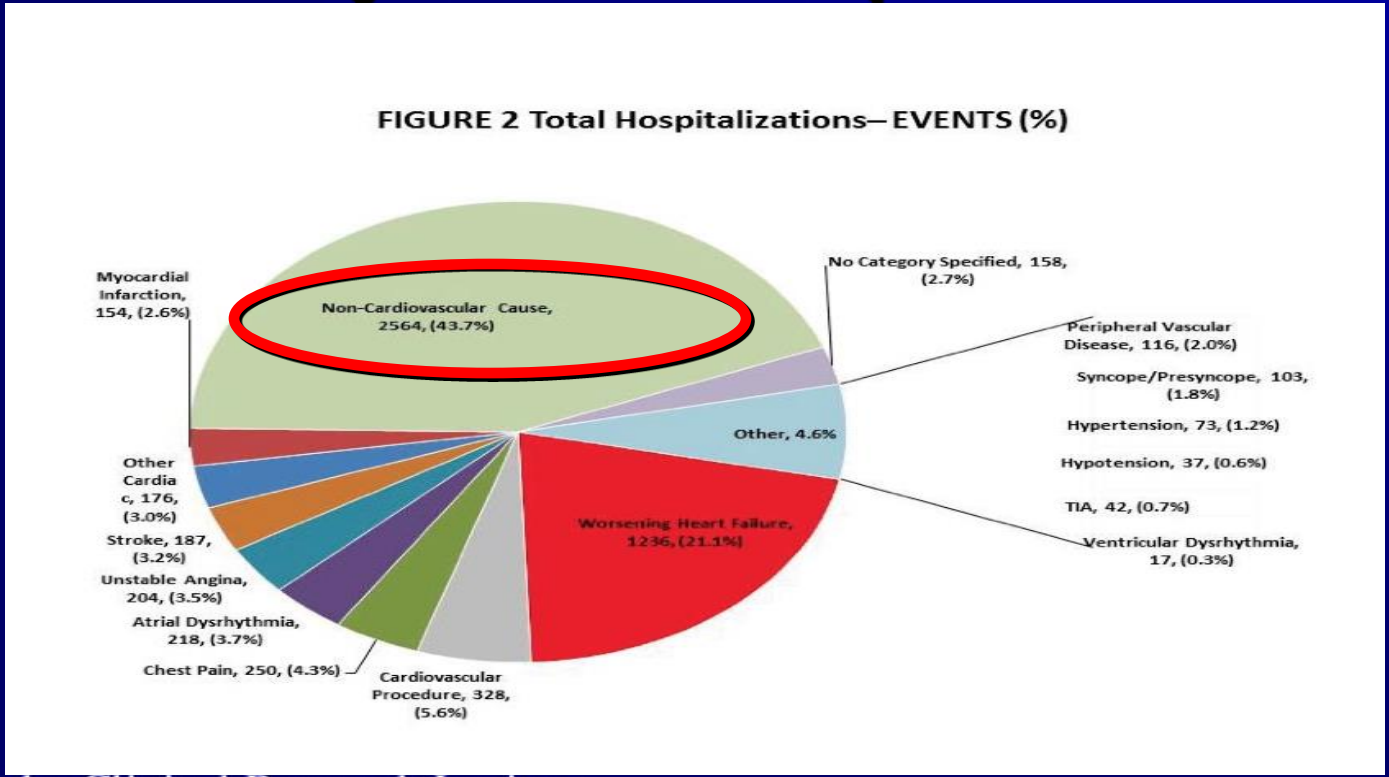
Mentz RJ, O'Connor CM et al. JACC 2014

HFpEF vs. HFrEF

	ADHERE Registry(2)		GWTG Registry(8)	
	Reduced	Preserved	EF<40%	EF≥50%
Age (y)	70 ± 14	74 ± 13	70 (58-80)	78 (67-85)
Female	40%	62%	36%	63%
African American	22%	17%	25%	16%
Medical History				
COPD or asthma	27%	31%	27%	33%
CRI	26%	26%	48%	52%
Anemia	-	-	14%	22%
Diabetes mellitus	40%	45%	22% oral/ 18% insulin	24% oral/ 22% insulin

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

Total Hospitalizations I-Preserve: Many Comorbid Hospitalizations



Carson,JACC-HF 2015

Mode of Death HFpEF I-Preserve

Table 4. Mortality Rate for Each Mode of Death

	Total	Placebo	Irbesartan	*P*
All cause	52.4	52.3	52.6	0.98
Cardiovascular	31.7	31.8	31.5	0.91
Sudden death	13.8	14.2	13.3	0.64
Heart failure	7.4	6.6	8.3	0.21
MI	2.7	2.8	2.6	0.83
Stroke	4.5	4.8	4.3	0.59
Cardiovascular procedure	0.8	0.2	1.3	0.03
Other cardiac death	0.6	0.7	0.5	0.51
Other vascular death	1.9	2.5	1.3	0.08
Noncardiovascular	16	16.1	15.8	0.86
Unknown	4.8	4.4	5.2	0.51

Mortality rate is expressed as rate per 1000 patient-years.

- 60% cardiovascular death
- 40% non-cardiovascular death or unknown
- 40 per cent Non-CV= Cancer
- HF low rate for mode of death
- May require a doubling of sample size for mortality component
- Similar Issue with HFH

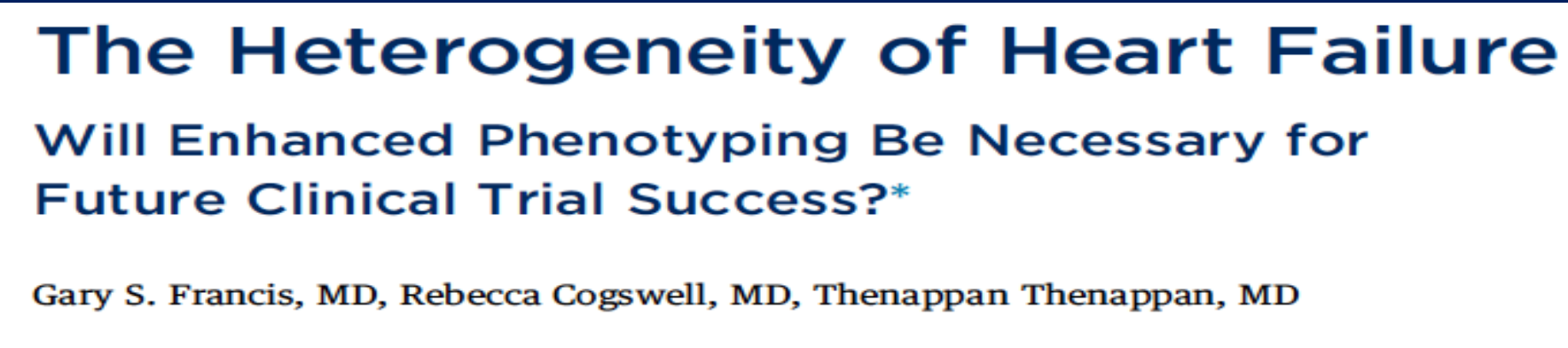
Zile,Circ HF 2010

Implications of Comorbidities

- 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

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



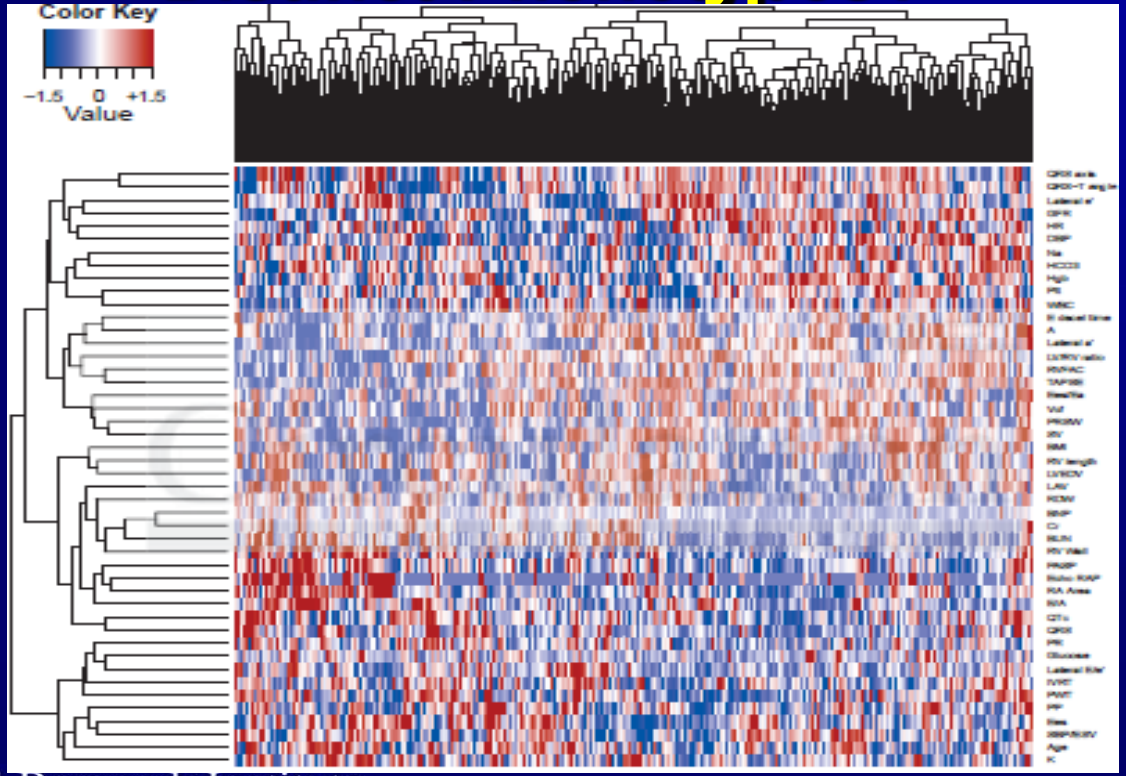
The Heterogeneity of Heart Failure

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

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

*and **molecular measures** may provide a more **accurate classification** of disease and ultimately **enhance diagnosis** and **treatment***

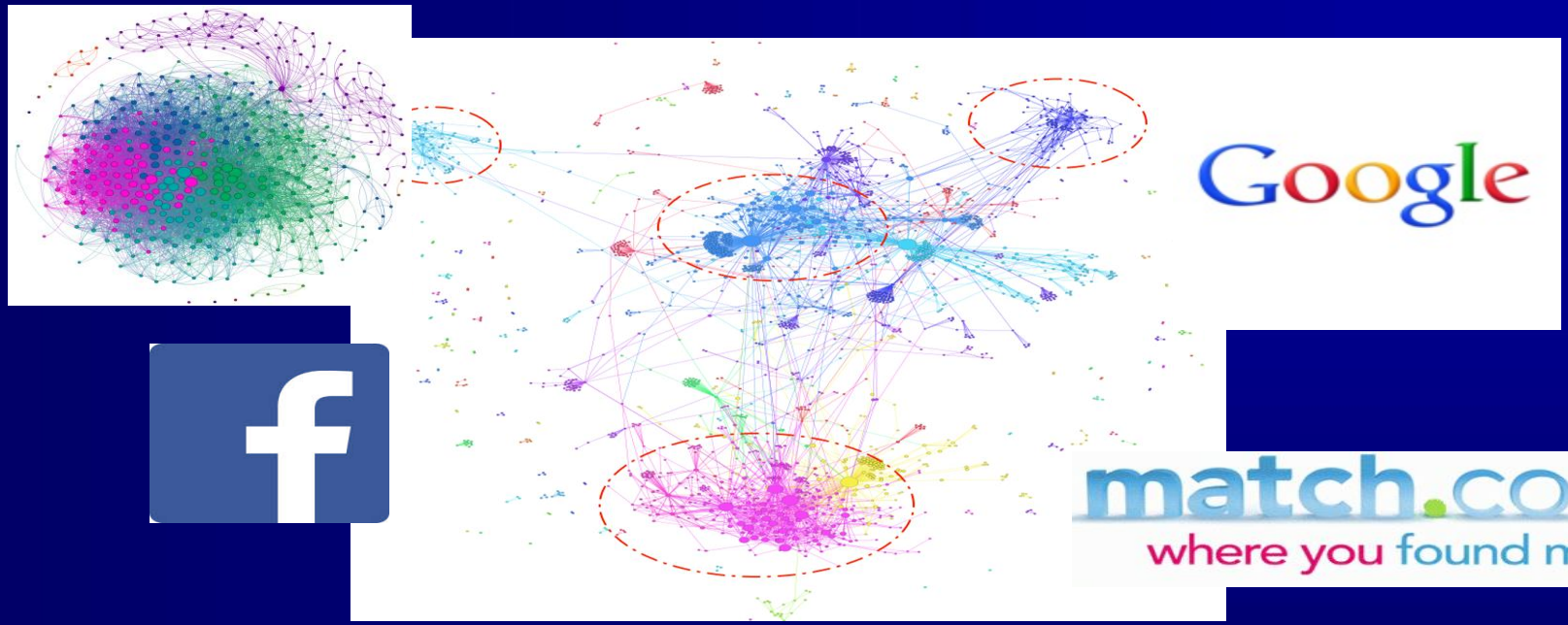
Cluster Analysis of Heart Failure to Uncover Distinct Phenotypes?



Duke Clinical Research Institute
DUKE UNIVERSITY MEDICAL CENTER

Circulation. 2014; Nov 14

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

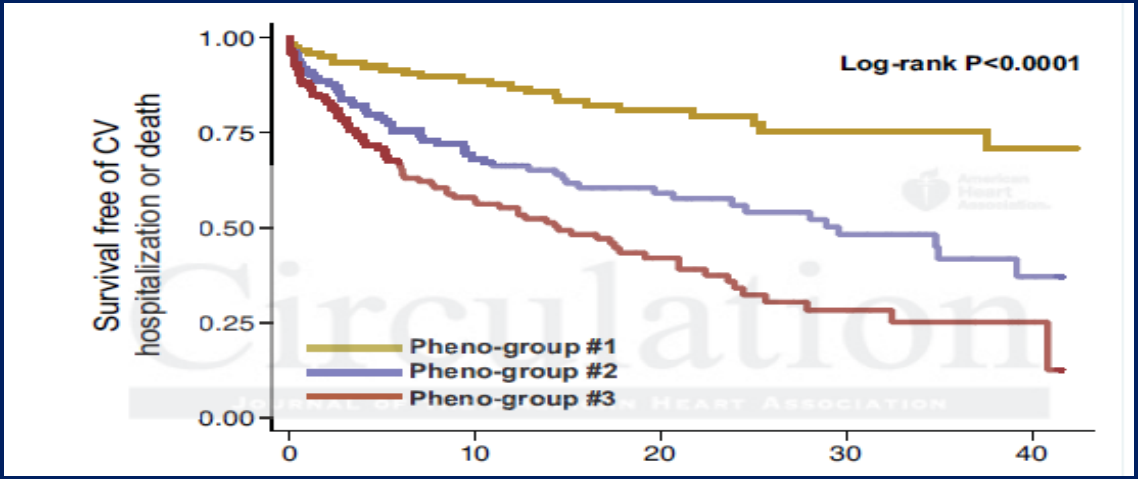
J Am Coll Cardiol. 2014;64:1765-74

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]



Group 3
Older
Male
Comorbidities
Renal Dz
BNP elevation

EUROPEAN SOCIETY OF CARDIOLOGY®

European Journal of Heart Failure (2015) **17**, 925–935
doi:10.1002/ejhf.327

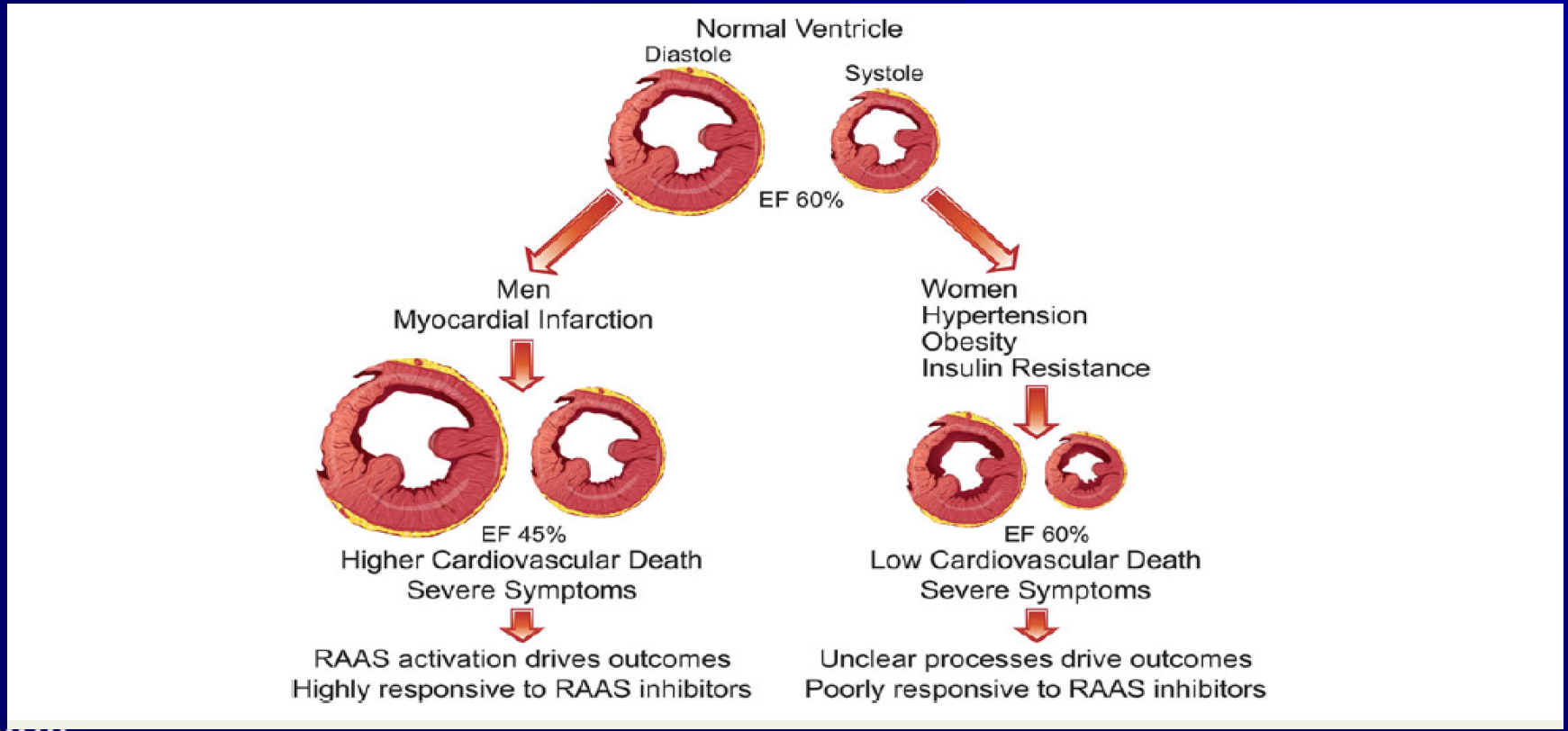
Characterization of subgroups of heart failure patients with preserved ejection fraction with possible implications for prognosis and treatment response

David P. Kao[1]*, James D. Lewsey[2], Inder S. Anand[3], Barry M. Massie[4], Michael R. Zile[5], Peter E. Carson[6], Robert S. McKelvie[7], Michel Komajda[8], John JV McMurray[2], and JoAnn Lindenfeld[1]

Two High Risk Groups

- Obesity
- Diabetes
- Hyperlipidemia
- Anemia
- Renal Insufficiency
- Older
- Female
- Low BMI
- Afib
- Valvular Heart Dz

Simplified Phenotype Analysis : HFpEF



Borlaug EHJ 2015

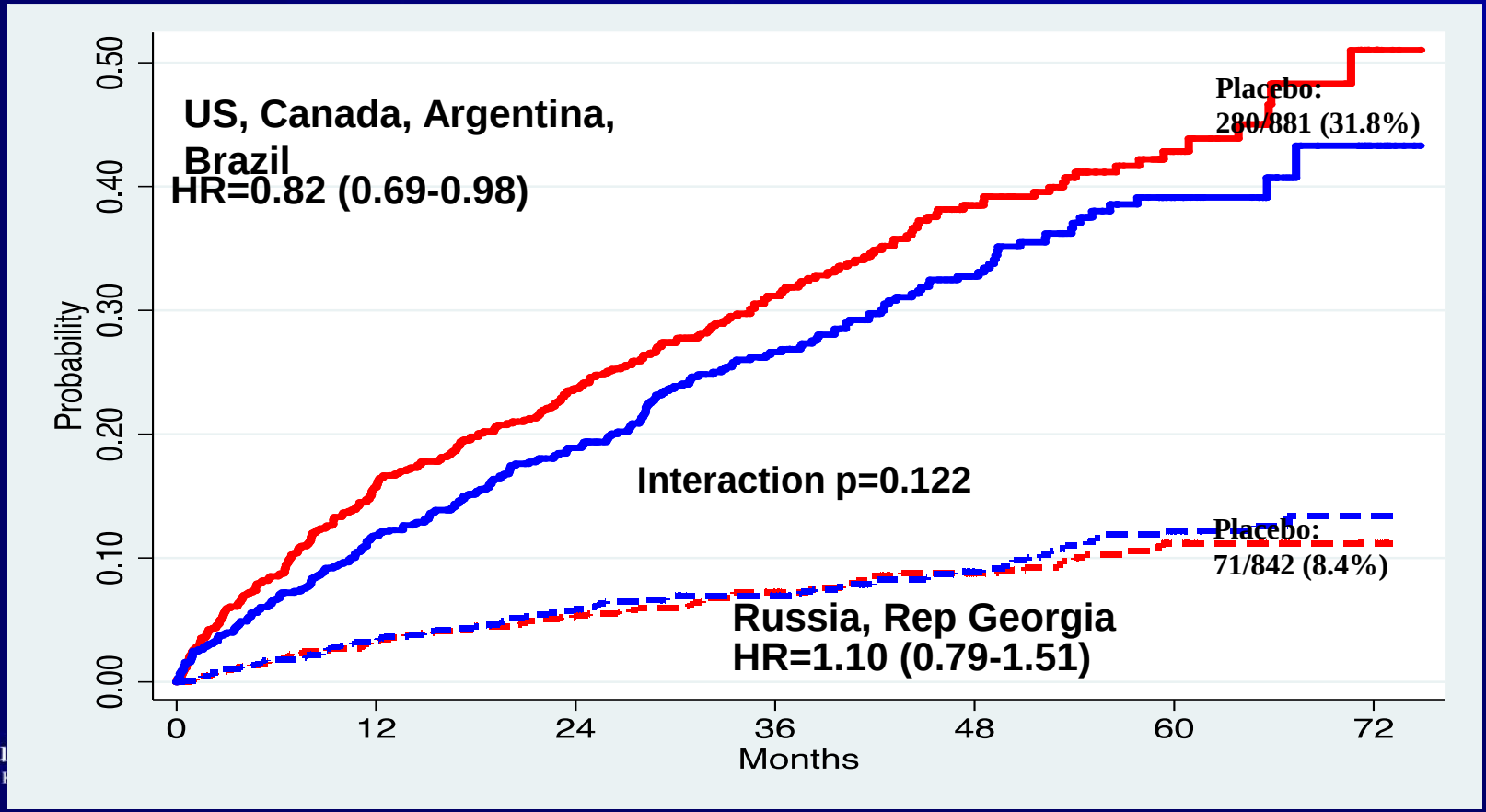
The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Lessons from the TOPCAT Trial

John J.V. McMurray, M.D., and Christopher O'Connor, M.D.

Exploratory (post-hoc):Placebo vs. Spiro by Region



LVEF Matters in HFpEF : Less Than 50 Spiro Most Benefit

Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction

Scott D. Solomon, Brian Claggett, Eldrin F. Lewis, Akshay Desai, Inder Anand, Nancy K. Sweitzer, Eileen O'Meara, Sanjiv J. Shah, Sonja McKinlay, Jerome L. Fleg, George Sopko, Bertram Pitt, Marc A. Pfeffer **on behalf of for the TOPCAT Investigators**

DOI: http://dx.doi.org/10.1093/eurheartj/ehv464 ehv464 First published online: 15 September 2015

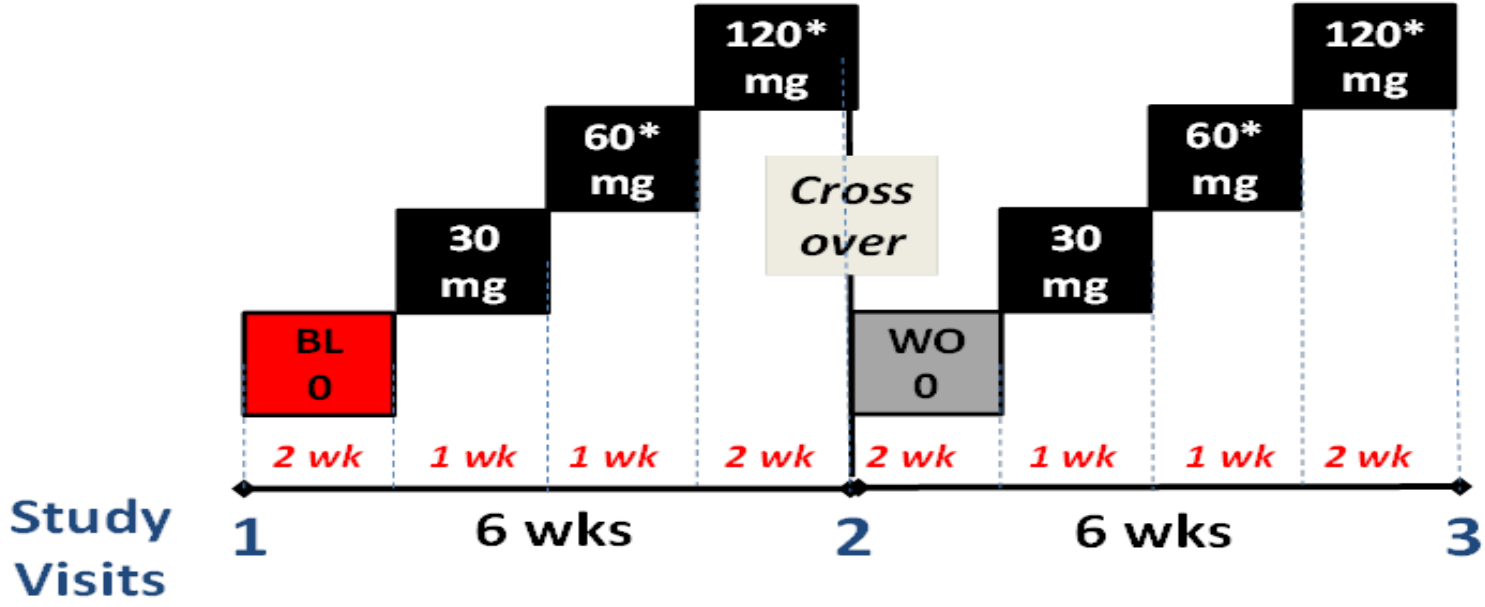
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction

Margaret M. Redfield, M.D., Kevin J. Anstrom, Ph.D., James A. Levine, M.D., Gabe A. Koepp, M.H.A., Barry A. Borlaug, M.D., Horng H. Chen, M.D., Martin M. LeWinter, M.D., Susan M. Joseph, M.D., Sanjiv J. Shah, M.D., Marc J. Semigran, M.D., G. Michael Felker, M.D., Robert T. Cole, M.D., Gordon R. Reeves, M.D., Ryan J. Tedford, M.D., W.H. Wilson Tang, M.D., Steven E. McNulty, M.S., Eric J. Velazquez, M.D., Monica R. Shah, M.D., and Eugene Braunwald, M.D., for the NHLBI Heart Failure Clinical Research Network

Study Design: *Randomized, double-blind, placebo-controlled crossover study*

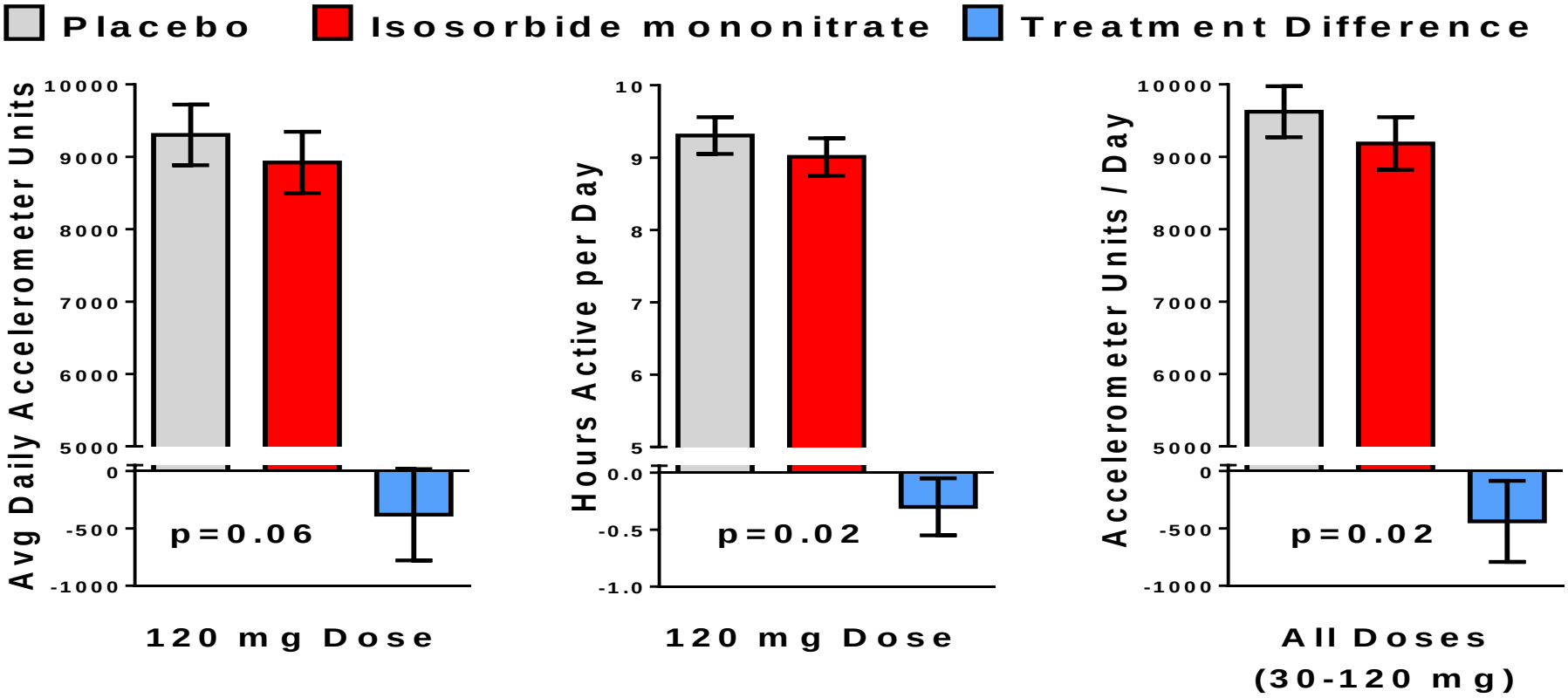


** Or maximally tolerated dose*

NEAT Primary End-point

- Average daily accelerometer units (AAU) during the 120 mg (or maximally tolerated) dose
  - *Two hip-worn, tri-axial, high sensitivity accelerometers*
  - *Worn 24 hours per day (except bathing)*
  - *Throughout the entire study*

Primary and Secondary Endpoints



Journal of the American College of Cardiology

Volume 66, Issue 15, 13 October 2015, Pages 1672–1682

Original Investigation

Sodium Nitrite Improves Exercise Hemodynamics and Ventricular Performance in Heart Failure With Preserved Ejection Fraction

Barry A. Borlaug, MD, Katlyn E. Koepp, BS, Vojtech Melenovsky, MD, PhD

Duke Clinical Research Institute
DUKE UNIVERSITY MEDICAL CENTER

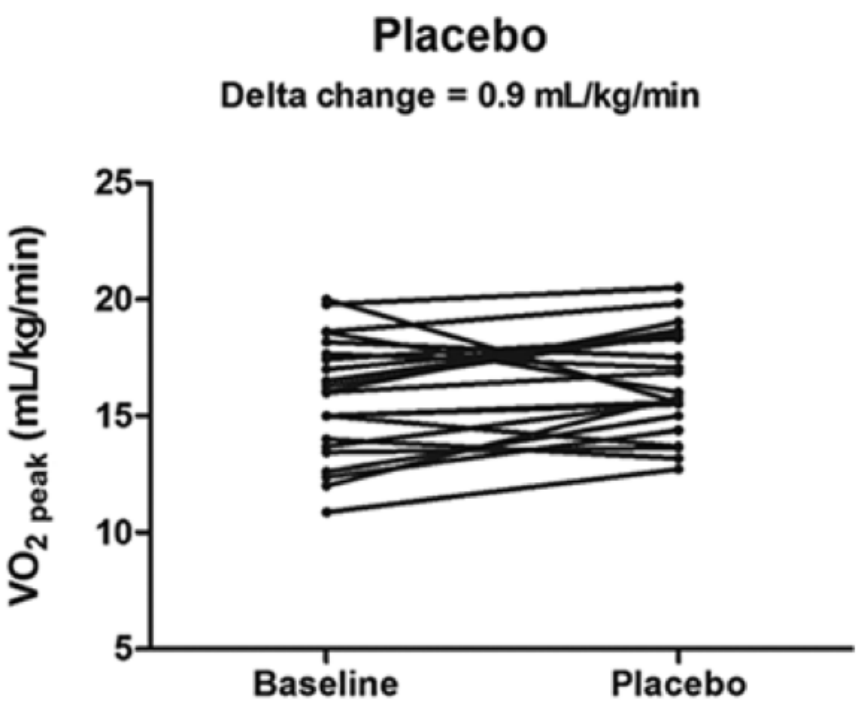
Heart Failure

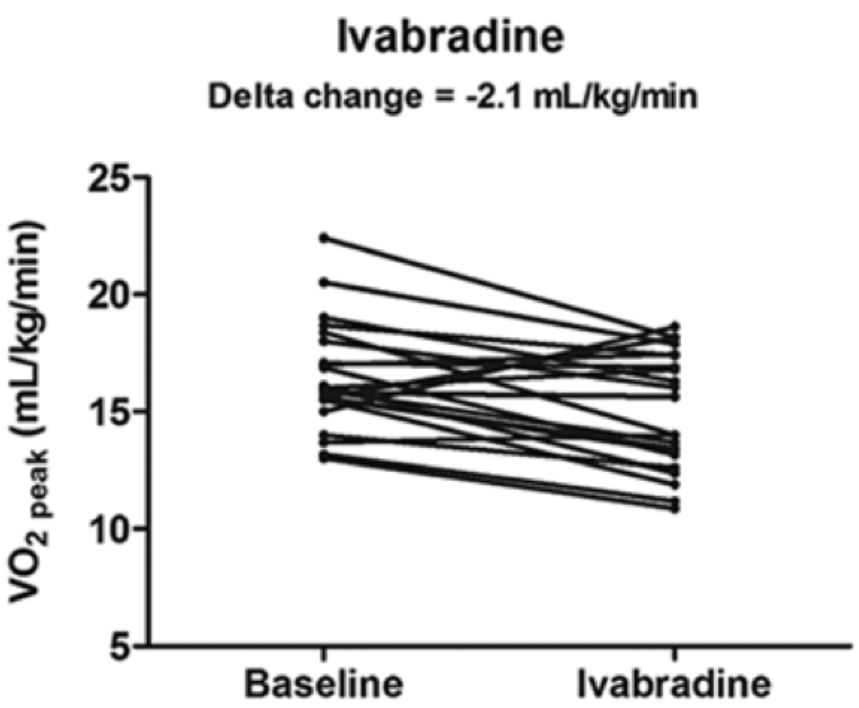
OPEN

Effect of Selective Heart Rate Slowing in Heart Failure With Preserved Ejection Fraction

Nikhil Pal, MBBS, MRCP; Nadiya Sivaswamy, MD; Masliza Mahmod, DPhil, MRCP; Arash Yavari, DPhil, MRCP; Amelia Rudd, HND; Satnam Singh, MBBS, MRCP; Dana K. Dawson, DM, DPhil; Jane M. Francis, DCR(R); Jeremy S. Dwight, MD, FRCP; Hugh Watkins, MD, PhD, FRCP, FMedSci; Stefan Neubauer, MD, FRCP, FACC, FMedSci; Michael Frenneaux, PhD, FRCP, FMedSci*; Houman Ashrafian, MA, DPhil, MRCP*

Duke Clinical Research Institute
DUKE UNIVERSITY MEDICAL CENTER


Placebo
Delta change = 0.9 mL/kg/min
$VO_{2\ peak}$ (mL/kg/min)
25
20
15
10
5
Baseline
Placebo


Ivabradine
Delta change = -2.1 mL/kg/min
$VO_{2\ peak}$ (mL/kg/min)
25
20
15
10
5
Baseline
Ivabradine

SPRINT

Examine effect of more intensive high blood pressure treatment than is currently recommended

Randomized Controlled Trial
Target Systolic BP

Intensive Treatment	*Standard Treatment*
Goal SBP < 120 mm Hg	*Goal SBP < 140 mm Hg*

SPRINT design details available at:

- *ClinicalTrials.gov (NCT01206062)*
- *Ambrosius WT et al. Clin. Trials. 2014;11:532-546.*

Duke Clinical Research Institute
DUKE UNIVERSITY MEDICAL CENTER

SPRINT
Systolic Blood Pressure Intervention Trial

SPRINT Primary Outcome

	Intensive		Standard			
	No. of Events	Rate, %/year	No. of Events	Rate, %/year	HR (95% CI)	P value
Primary Outcome	243	1.65	319	2.19	0.75 (0.64, 0.89)	<0.001
All MI	97	0.65	116	0.78	0.83 (0.64, 1.09)	0.19
Non-MI ACS	40	0.27	40	0.27	1.00 (0.64, 1.55)	0.99
All Stroke	62	0.41	70	0.47	0.89 (0.63, 1.25)	0.50
All HF	62	0.41	100	0.67	0.62 (0.45, 0.84)	0.002
CVD Death	37	0.25	65	0.43	0.57 (0.38,	0.005

Hope for HFpEF

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

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

LCZ696: Favorable on the most likely Surrogate

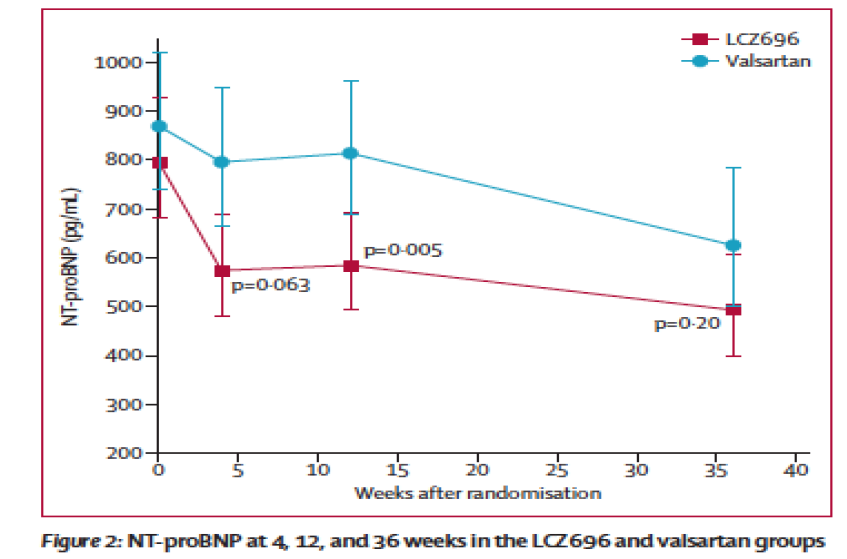


Figure 2: NT-proBNP at 4, 12, and 36 weeks in the LCZ696 and valsartan groups

- Reduced NT-proBNP
- Reduced LA size
- Improved NYHA Class
- PARAGON OUTCOME Trial

Solomon,Lancet,2012

EUROPEAN SOCIETY OF CARDIOLOGY®

European Journal of Heart Failure (2014) **16**, 671–677
doi:10.1002/ejhf.76

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

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

JACC: Heart Failure

Published by Elsevier Inc.

Vol. 2, No. 2, 2014
ISSN 2213-1779/$36.00
http://dx.doi.org/10.1016/j.jchf.2013.10.006

MINI FOCUS ISSUE: HEART FAILURE WITH PRESERVED EJECTION FRACTION State-of-the-Art Papers

CME

Developing Therapies for Heart Failure With Preserved Ejection Fraction

Current State and Future Directions

Javed Butler, MD, MPH,[1] Gregg C. Fonarow, MD,[2] Michael R. Zile, MD,[3] Carolyn S. Lam, MD,[4] Lothar Roessig, MD,[5] Erik B. Schelbert, MD, MS,[6] Sanjiv J. Shah, MD,[7] Ali Ahmed, MD,[8] Robert O. Bonow, MD,[7] John G. F. Cleland, MD,[9] Robert J. Cody, MD, MBA,[10] Ovidiu Chioncel, MD, PHD,[11] Sean P. Collins, MD,[12] Preston Dunnmon, MD,[13] Gerasimos Filippatos, MD,[14] Martin P. Lefkowitz, MD,[15] Catherine N. Marti, MD,[1] John J. McMurray, MD,[16] Frank Misselwitz, MD,[5] Savina Nodari, MD,[17] Christopher O'Connor, MD,[18] Marc A. Pfeffer, MD,[19] Burkert Pieske, MD,[20] Bertram Pitt, MD,[21] Giuseppe Rosano, MD,[22] Hani N. Sabbah, PHD,[23] Michele Senni, MD,[24] Scott D. Solomon, MD,[19] Norman Stockbridge, MD, PHD,[13] John R. Teerlink, MD,[25] Vasiliki V. Georgiopoulou, MD,[1] Mihai Gheorghiade, MD[7]

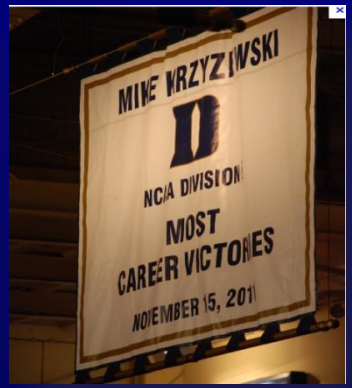
Duke Clinical Research Institute
DUKE UNIVERSITY MEDICAL CENTER

Like Duke BB This Year : There Is Hope

One Facility More Important

One Group More Visible

One Tradition More Talked About



One Area Where the Expectations Are Higher