Systolic and Diastolic Dysfunction: Four Upcoming Challenges

Promoting Early Detection

HFrEF: Beyond Neprilysin/Enalapril

HFmrEF: What Is It and How Does One Manage It ?

HFpEF: Etiopathogenetic Role and Impact of Comorbidities ?

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AMERICAN COLLEGE of CARDIOLOGY

Promoting Early Detection

2013 ACC/AHA Heart Failure Guidelines

TABLE 25G.1 ACC/AHA Guidelines for Treating Patients at High Risk of Developing Heart Failure (Stage A)

CLASS	INDICATION	LEVEL OF EVIDENCE
I	Hypertension and lipid disorders should be controlled in accordance with contemporary guidelines to lower the risk of HF.	A
I	In patients at increased risk, stage A, the optimal blood pressure in those with hypertension should be less than 130/80 mm Hg.	B-R
I	Other conditions that may lead to or contribute to HF, such as obesity, diabetes mellitus, tobacco use, and known cardiotoxic agents, should be controlled or avoided.	C
II	For patients at risk of developing HF, natriuretic peptide biomarker–based screening followed by team-based care, including a cardiovascular specialist optimizing GDMT, can be useful to prevent the development of left ventricular dysfunction (systolic or diastolic) or new-onset HF.	B-R

GDMT, Guideline-directed medical therapy; *HF*, heart failure.

Original Investigation

Natriuretic Peptide–Based Screening and Collaborative Care for Heart Failure

The STOP-HF Randomized Trial

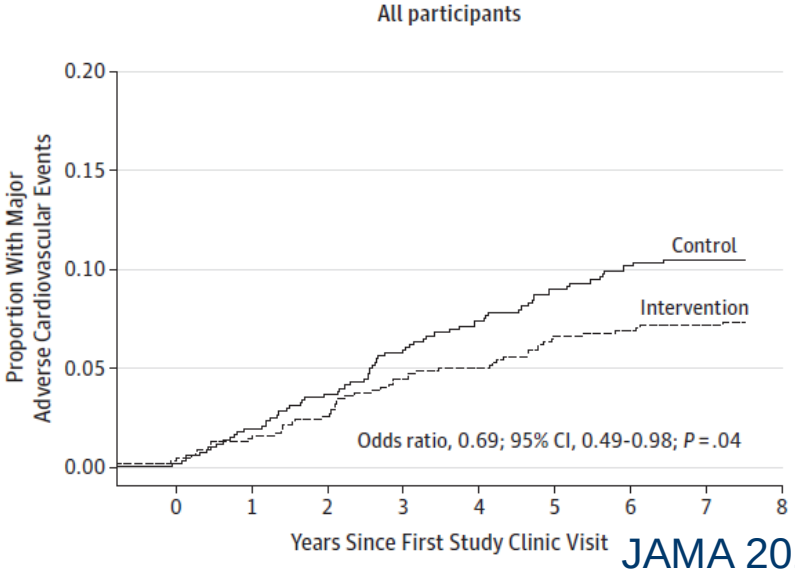
Mark Ledwidge, PhD; Joseph Gallagher, MB; Carmel Conlon, PhD; Elaine Tallon, PGDip; Eoin O'Connell, MLitt; Ian Dawkins, DPhil; Chris Watson, PhD; Rory O'Hanlon, MD; Margaret Bermingham, BSc(Pharm); Anil Patle, MBA; Mallikarjuna R. Badabhagni, RDCS; Gillian Murtagh, MD; Victor Voon, MB; Leslie Tilson, PhD; Michael Barry, MD; Laura McDonald; Brian Maurer, MD; Kenneth McDonald, MD

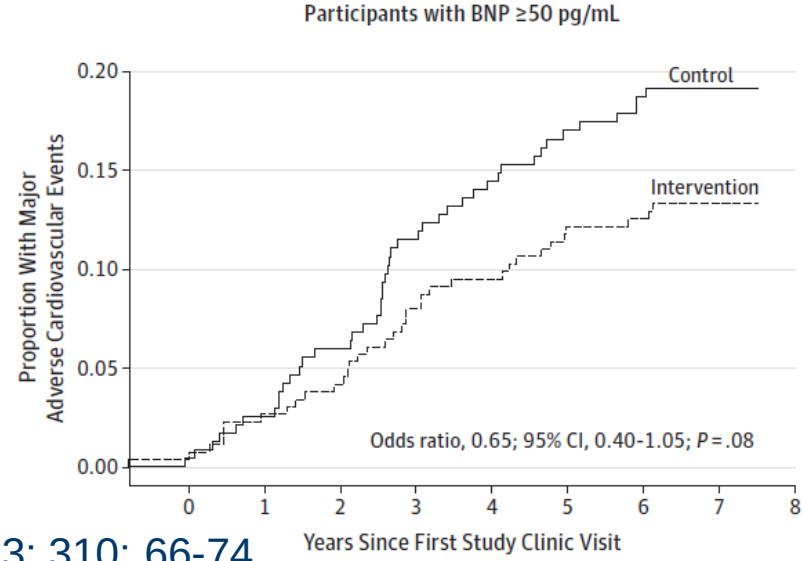
JAMA 2013; 310: 66-74

STOP-HF Primary end point

Participants with BNP ≥50 pg/mL	n=235	n=263				
Heart failure or LVD	44 (18.7)	25 (9.5)	0.44 (0.26-0.73)	.002	0.46 (0.27-0.79)	.005
Heart failure or LVSD	29 (12.3)	17 (6.5)	0.46 (0.24-0.90)	.03	0.48 (0.24-0.97)	.04
Asymptomatic LVSD	17 (7.2)	12 (4.6)	0.52 (0.24-1.14)	.11	0.51 (0.24-1.06)	.07
Asymptomatic LVDD	15 (6.4)	8 (3.0)	0.48 (0.21-1.07)	.08	0.58 (0.26-1.30)	.19
Asymptomatic LVD	32 (13.6)	20 (7.6)	0.47 (0.27-0.83)	.01	0.50 (0.28-0.90)	.02

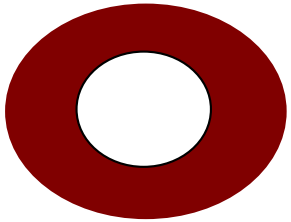
STOP-HF secondary end point (MACE arrhythmia, TIA, MI, PE, HF



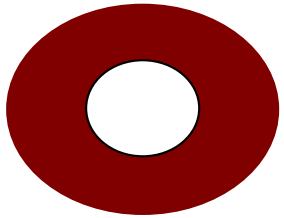


JAMA 2013; 310: 66-74

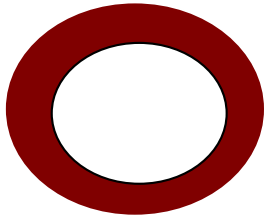
There are Three Types of Heart Failure That Can be Defined by LV Ejection Fraction



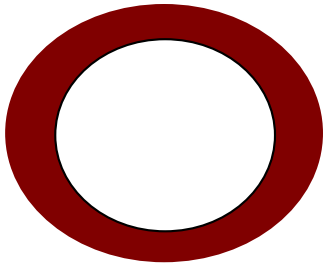
Normal Heart
LV EF ≥ 50%



Heart Failure with preserved LV EF ≥ 50% (HFpEF)



Heart Failure with midrange LV EF ≥ 40 – 49 % (HFmrEF)

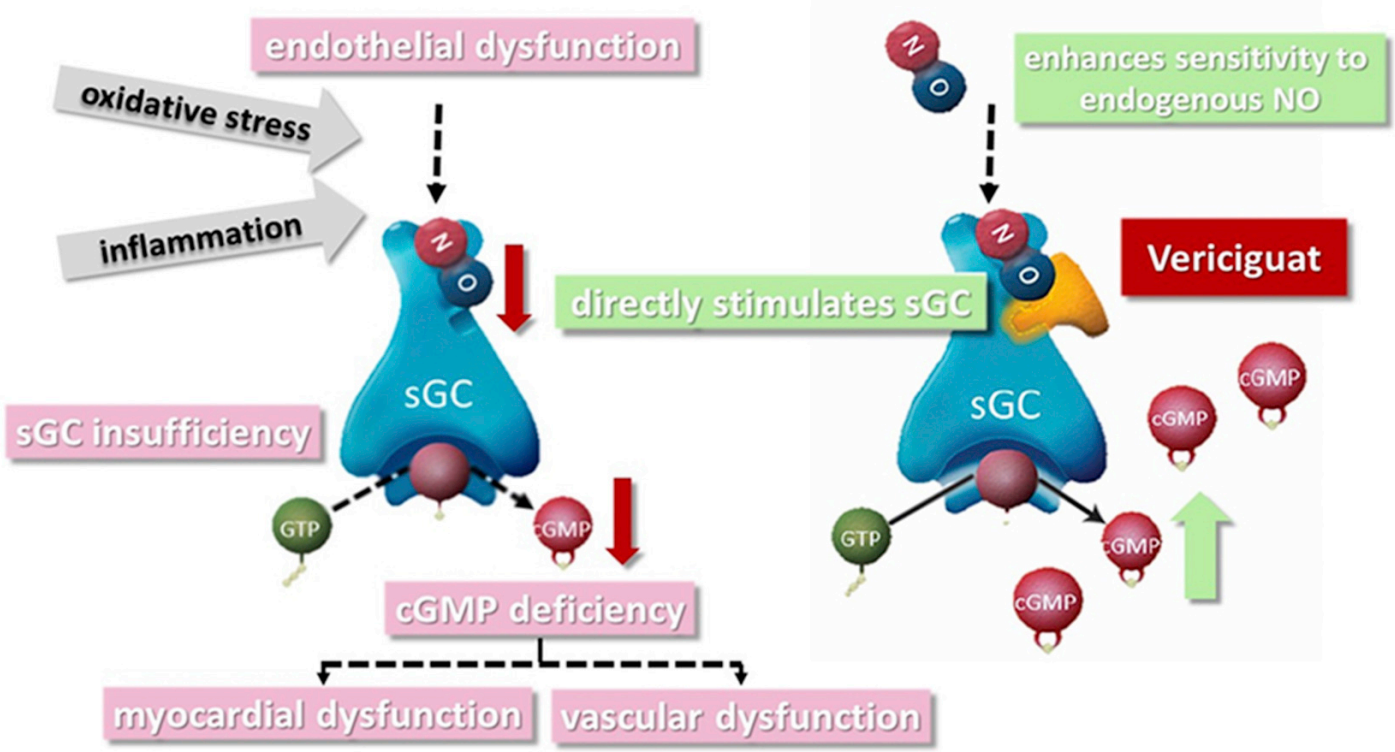


Heart Failure with reduced LV EF ≤ 35-40% (HFrEF)

HFrEF: Beyond Neprilysin/Enalapril

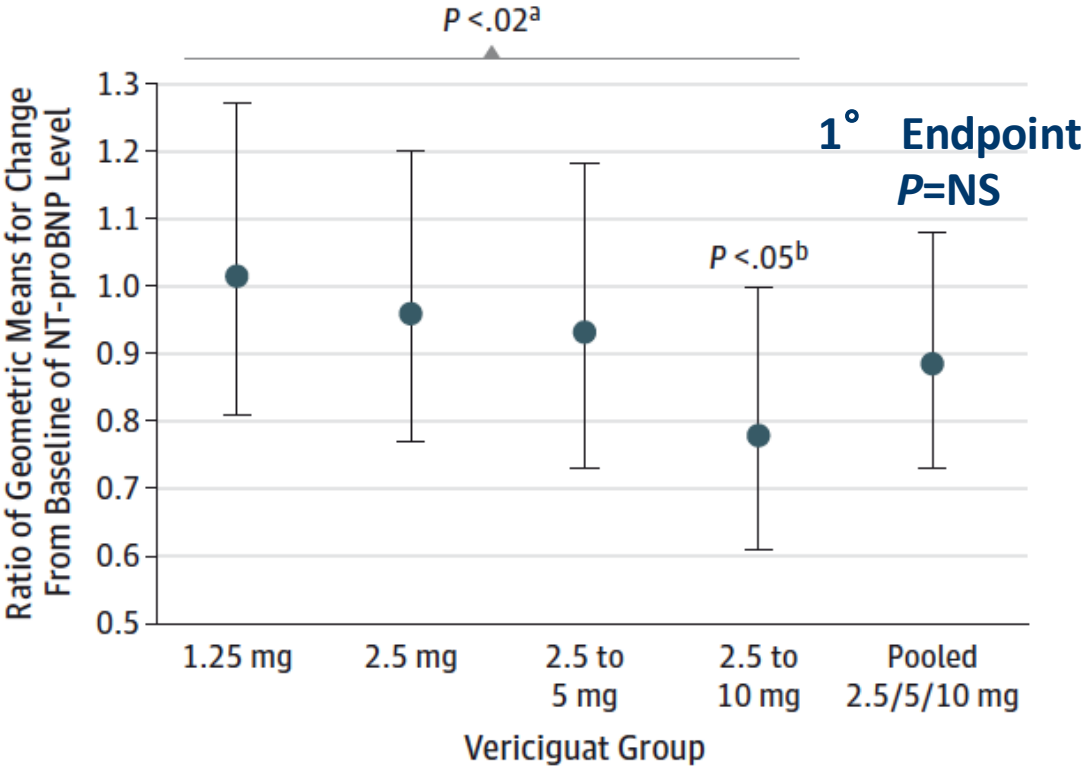
- Vericiguat
- Omecamtiv mecarbil
- BMS-986231 (HNO donor)
- Partial A1 receptor agonists
- Baroreceptor activation therapy (BAT)

Vericiguat:
Soluble Guanylate Cyclase (sGC) Stimulator



Armstrong et al. JACC:HF 2017 (online https://doi.org/10.1016/j.jchf.2017.08.013)

SOCRATES-REDUCED: NT-proBNP



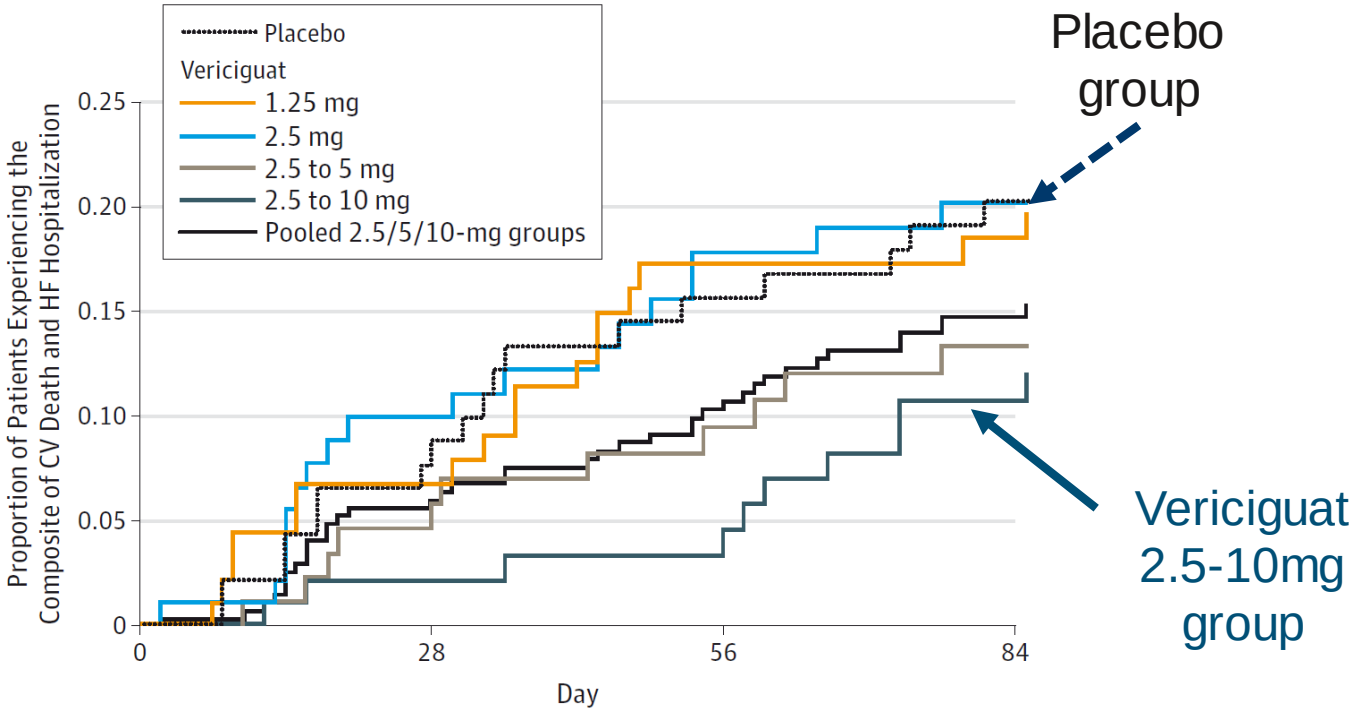
4

Pacebo (n = 92) or 1 of 4 daily target doses of oral vericiguat (1.25 mg [n = 91], 2.5 mg [n = 91], 5 mg [n = 91], 10 mg [n = 91]) for 12 weeks.

Gheorghiade M, et al. JAMA 2015;314:2251-2262.

SOCRATES-Reduced

CV death or HF hospitalization



Gheorghiade M, *et al. JAMA* 2015;314:2251-2262.

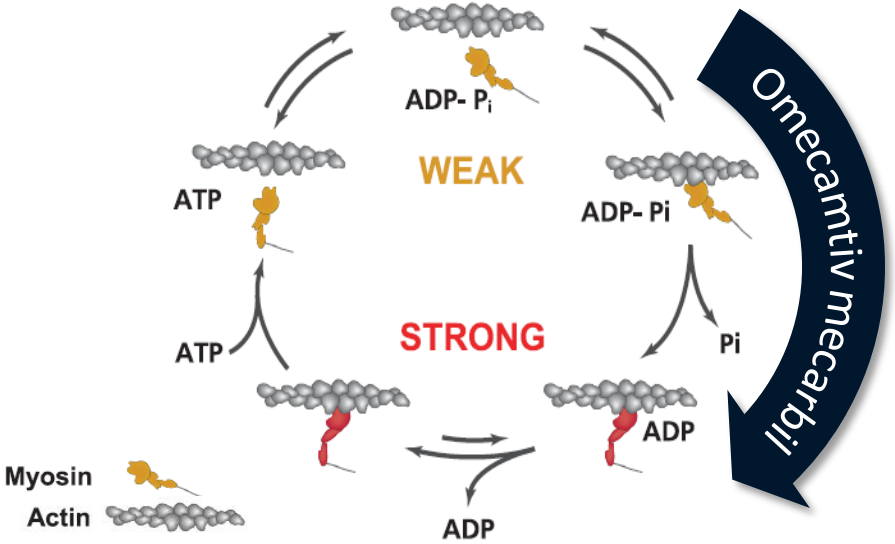
VerICiguaT Global Study in Subjects With Heart Failure With Reduced Ejection Fraction (VICTORIA)

- Target enrollment 4872 patients
- Vericiguat 2.5 mg uptitrated to 10 mg qd vs. Placebo
- Primary Outcome Measure: Time to Cardiovascular (CV) Death or Heart Failure Hospitalization
- Inclusion Criteria:
  - History of chronic HF (NYHA Class II-IV) on standard therapy before qualifying HF decompensation
  - Previous HF hospitalization within 6 months prior to randomization or intravenous (IV) diuretic treatment for HF (without hospitalization) within 3 months.
  - BNP levels: NSR-≥ 300 pg/mL; A Fib-≥ 500 pg/mL and NT-proBNP levels: NSR- ≥ 1000 pg/mL; A Fib- ≥ 1600 pg/mL within 30 days prior to randomization
  - LVEF<45% assessed within 12 months prior to randomization by any method

Clinicaltrials.gov NCT02861534

Omecamtiv Mecarbil (OM) is a Novel Selective Cardiac Myosin Activator

Mechanochemical Cycle of Myosin



Force production

OM increases the entry rate of myosin into the tightly-bound, force-producing state with actin

"More hands pulling on the rope"

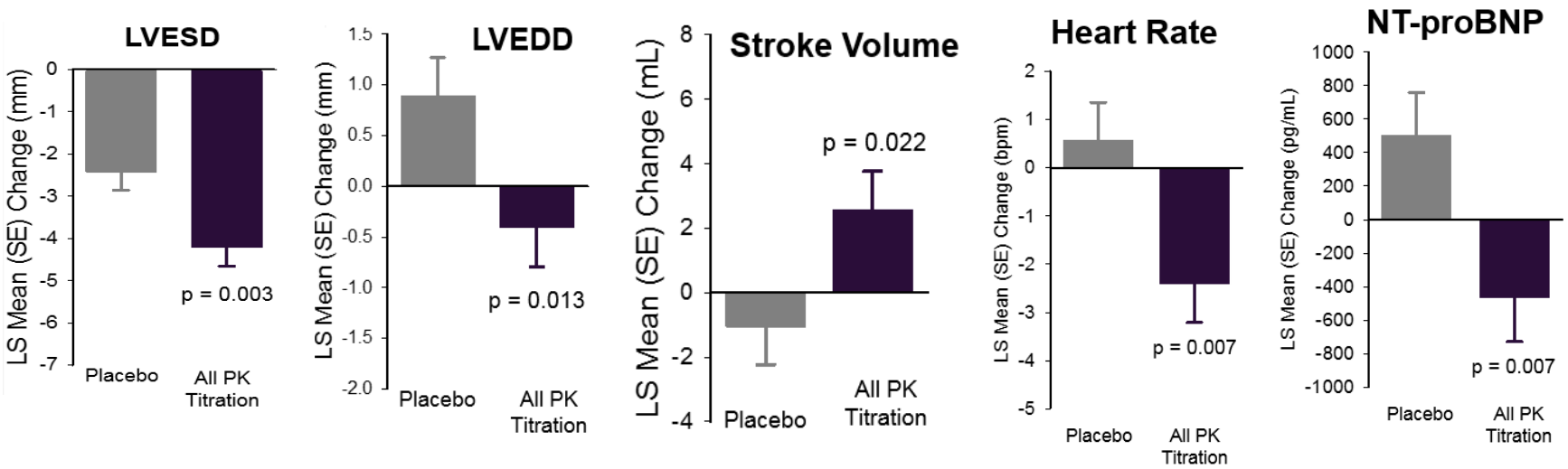
- Increases duration of systole
- Increases stroke volume
- No increase in myocyte calcium
- No change in dP/dt_{max}
- No increase in MVO_2

Malik FI, *et al. Science* 2011; 331:1439-43.

Shen YT, *et al. Circ Heart Fail* 2010;3:522-7.

Planelles-Herrero VJ, *et al. Nat Commun* 2017;8:190.

Effects of Omecamtiv Mecarbil on Secondary Endpoints at 20 Weeks



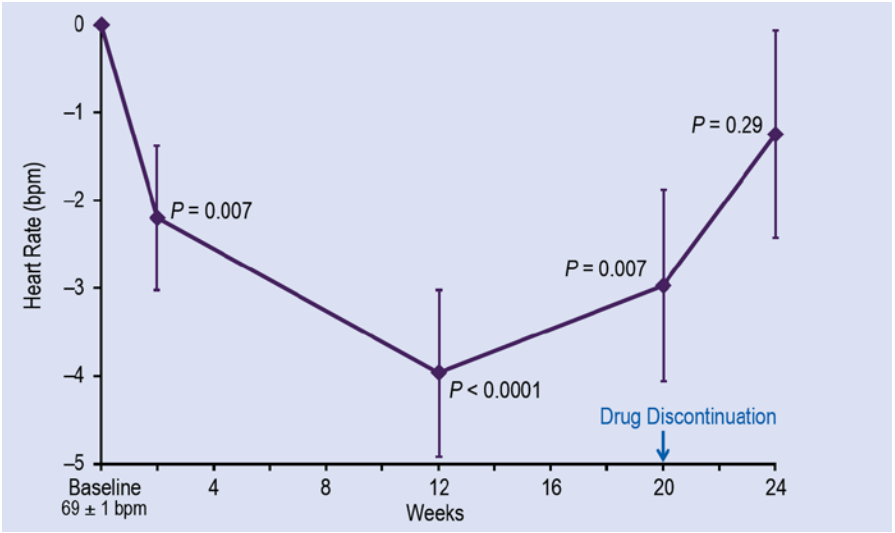
Placebo, n= 149;
All PK-Titration, n= 146

Teerlink JR, *et al. Lancet* 2016; 388: 2895-903.

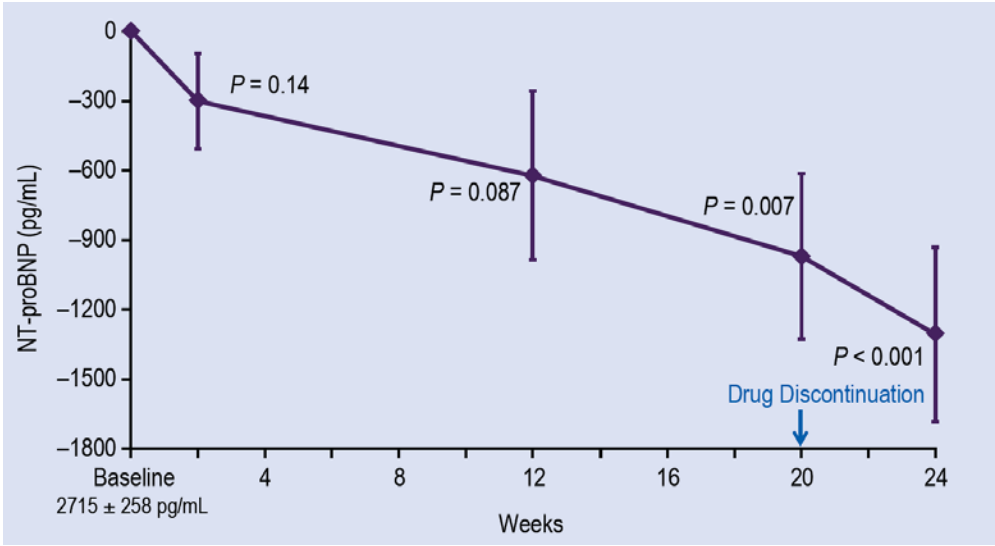
COSMIC-HF

Effect of Omecamtiv Mecarbil through Time

Change from Baseline in Heart Rate (bpm)



Change from Baseline in NT-proBNP (pg/mL)



Teerlink JR, *et al*. *HFSA 2016*.

GALACTIC-HF

- Chronic HF pts on standard of care therapy, LVEF ≤35%, NYHA II-IV, HF hospitalization within 12 months, elevated natriuretic peptides
- 1° endpoint: CV death & HF Events
- ~8,000 patient, event-driven trial, powered for CV death

clinicaltrials.gov NCT02929329

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HFmrEF: What Is It and How Does One Manage It ?

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ESC Guidelines: Definition of HFmrEF

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.

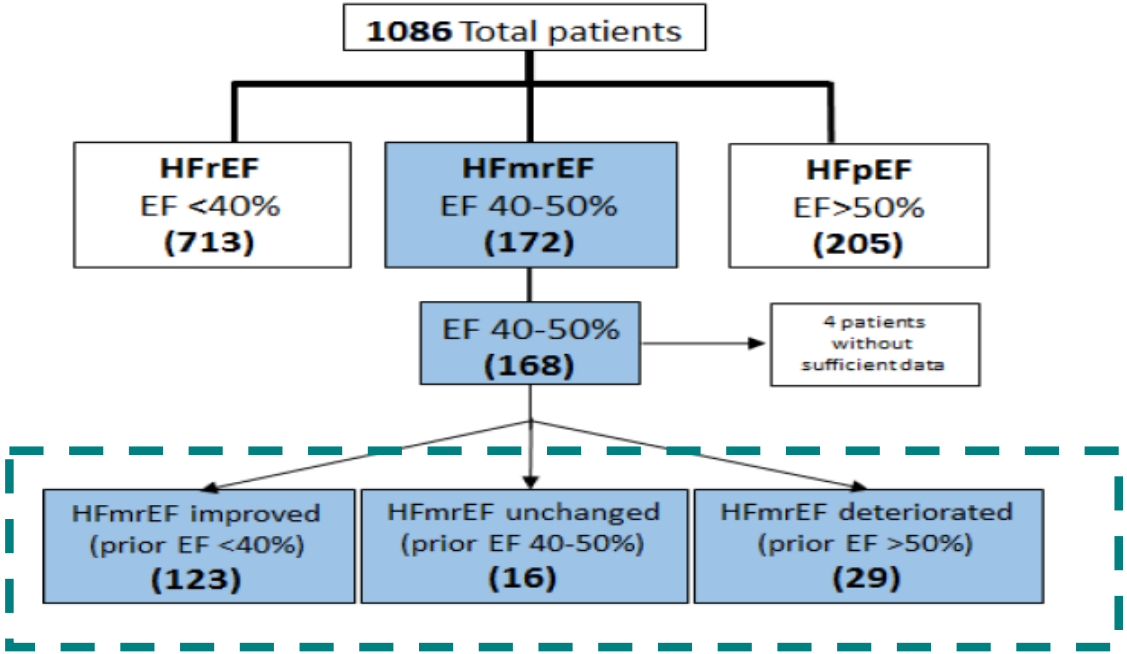
[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics.

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

Ponikowski et al Eur Heart J. 2016; 18:1-85

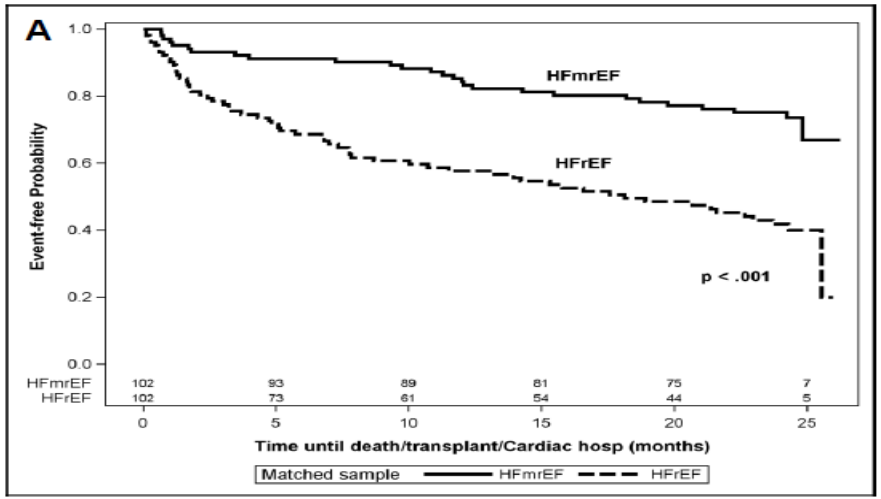
Natural History of Functional Responders with a Mid-Range LVEF (HFmrEF)

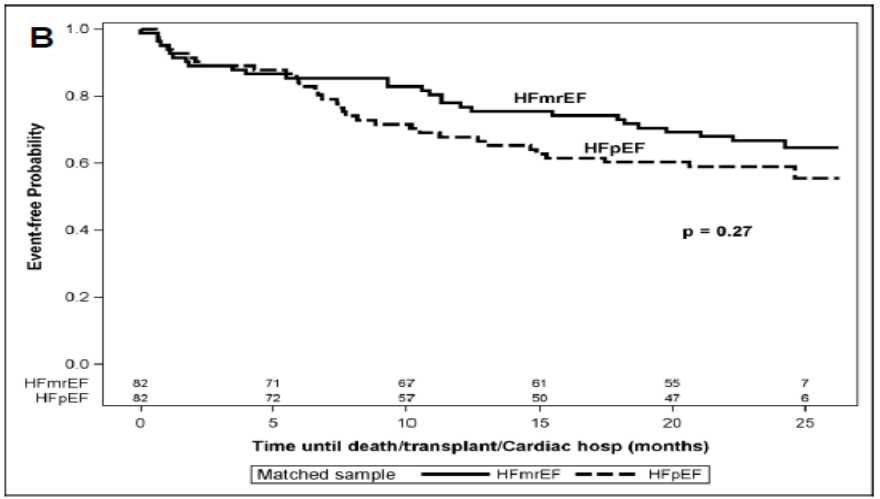
Wash U-HF registry



Rastogi et al; Eur J Heart Fail, in press DOI: 10.1002/ejhf.879

Natural History of Functional Responders with a Mid-Range LVEF (HFmrEF)





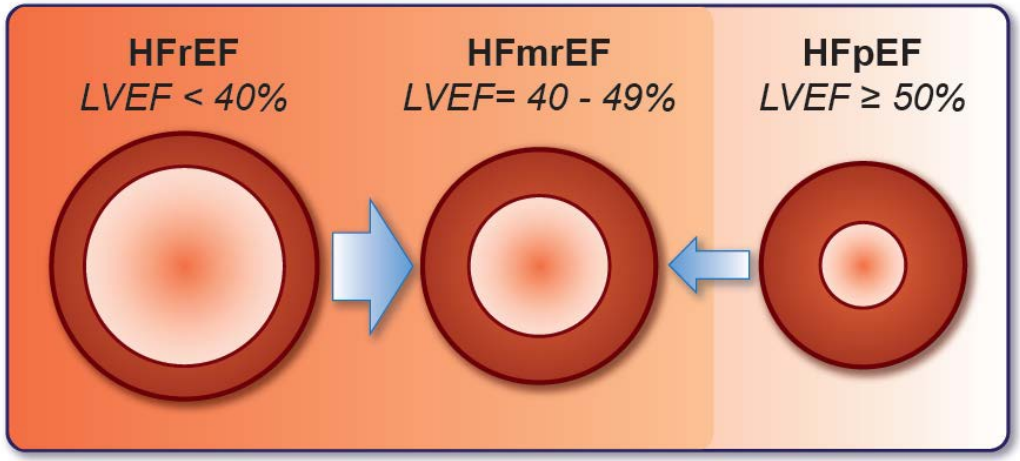
Rastogi et al; Eur J Heart Fail, in press DOI: 10.1002/ejhf.879

How Does One Manage HFmrEF ?

Recommendations for treatment of patients with heart failure with preserved ejection fraction and heart failure with mid-range ejection fraction

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

HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

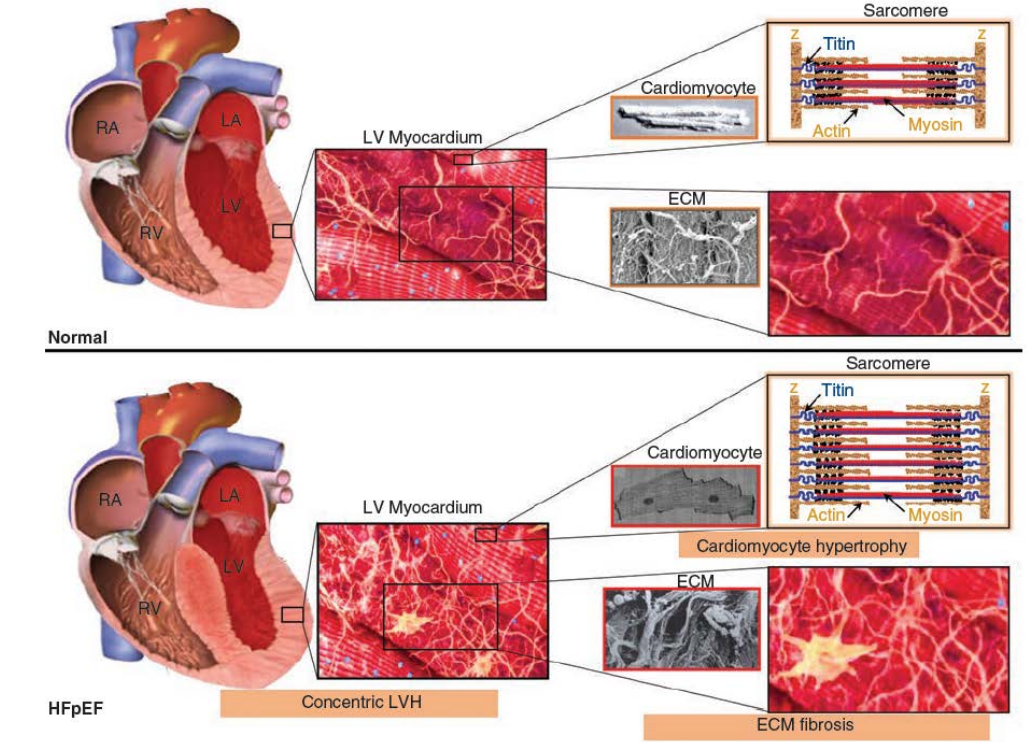


To determine the correct therapy, one needs to know the trajectory of the LV EF?

Ponikowski et al Eur Heart J. 2016; 18:1-85

HFpEF: Etiopathogenetic Role and Impact of Comorbidities

Pathophysiology of HFpEF



Hemodynamics of HFpEF

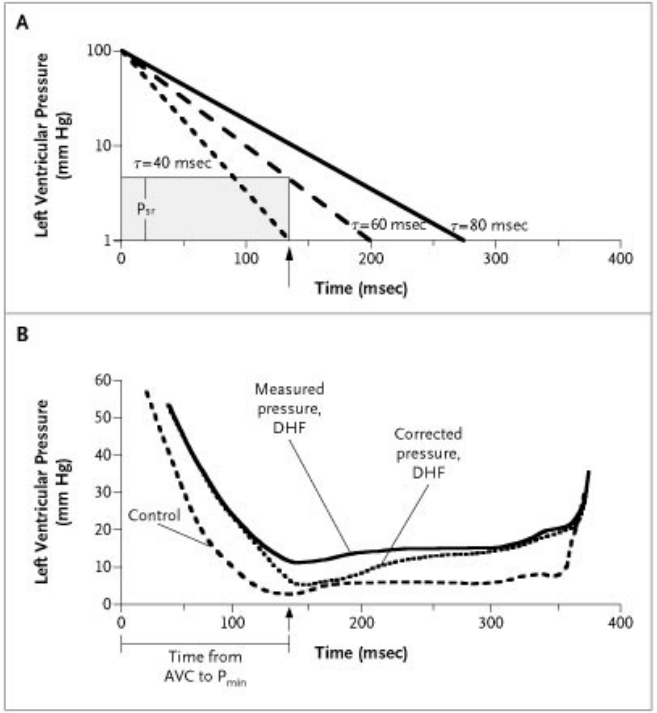
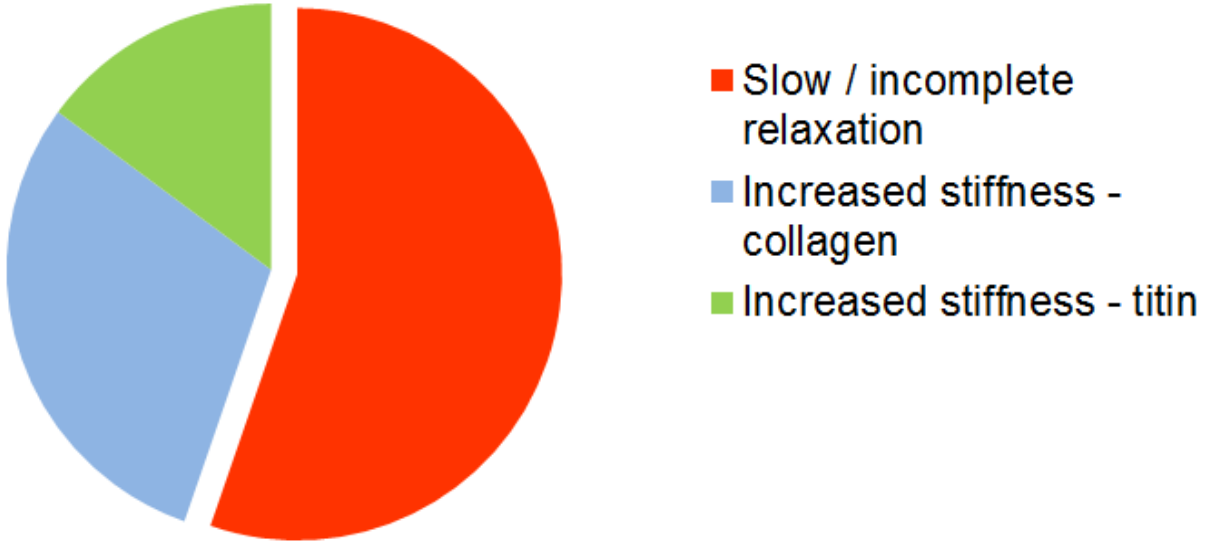


Table 1. Left Ventricular Pressure, Volume, Relaxation, and Passive Stiffness.*

Variable	Patients with Diastolic Heart Failure (N=47)	Controls (N=10)	P Value
Body-surface area (m^2)	2.2±0.25	2.1±0.18	0.31
Heart rate (beats/min)	71±11	73±13	0.81
Volume at P_{min} (ml)	51±13	55±7	0.31
Volume at P_{preA} (ml)	75±15	88±8	0.03
End-diastolic volume (ml)	103±22	115±9	0.01
P_{min} (mm Hg)	12±6	4±1	<0.001
P_{preA} (mm Hg)	16±5	6±2	<0.001
End-diastolic pressure (mm Hg)	25±6	8±2	<0.001
τ (msec)	59±14	35±10	0.01
P_{sr} (mm Hg)	7±5	0	<0.001
Corrected minimal diastolic pressure (mm Hg)	5±2	4±1	0.10
Measured stiffness			
Curve-fitting constant	6.5±4.3	2.3±0.8	0.003
Stiffness constant	0.02±0.01	0.01±0.01	0.01
Corrected stiffness			
Curve-fitting constant	1.5±1.1	2.3±0.8	0.03
Stiffness constant	0.03±0.01	0.01±0.01	<0.001

Zile et al. N Engl J Med 2004;350:1953-1959.

Impaired Relaxation vs. Increased Stiffness in HFpEF



Phenomapping for Novel Classification of Heart Failure With Preserved Ejection Fraction

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

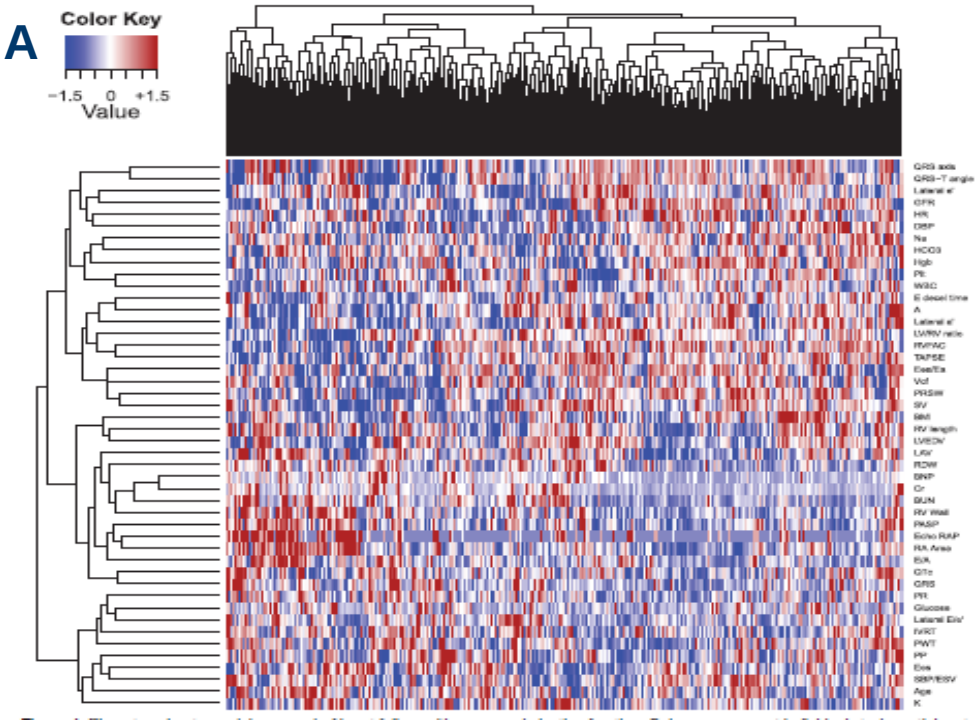
Background—Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous clinical syndrome in need of improved phenotypic classification. We sought to evaluate whether unbiased clustering analysis using dense phenotypic data (phenomapping) could identify phenotypically distinct HFpEF categories.

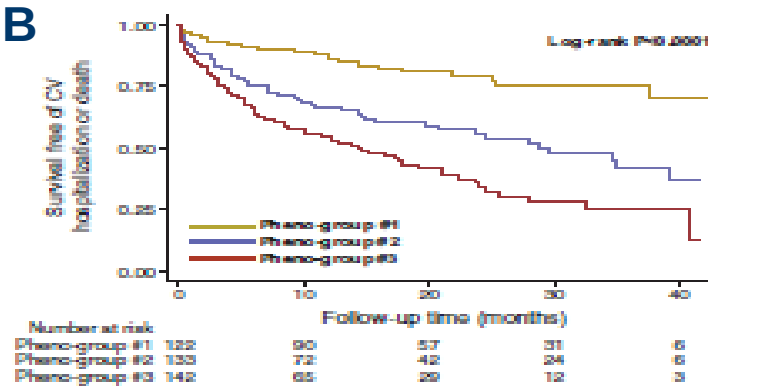
Methods and Results—We prospectively studied 397 patients with HFpEF and performed detailed clinical, laboratory, ECG, and echocardiographic phenotyping of the study participants. We used several statistical learning algorithms, including unbiased hierarchical cluster analysis of phenotypic data (67 continuous variables) and penalized model-based clustering, to define and characterize mutually exclusive groups making up a novel classification of HFpEF. All phenomapping analyses were performed by investigators blinded to clinical outcomes, and Cox regression was used to demonstrate the clinical validity of phenomapping. The mean age was 65±12 years; 62% were female; 39% were black; and comorbidities were common. Although all patients met published criteria for the diagnosis of HFpEF, phenomapping analysis classified study participants into 3 distinct groups that differed markedly in clinical characteristics, cardiac structure/function, invasive hemodynamics, and outcomes (eg, phenogroup 3 had an increased risk of HF hospitalization [hazard ratio, 4.2; 95% confidence interval, 2.0–9.1] even after adjustment for traditional risk factors [$P<0.001$]). The HFpEF phenogroup classification, including its ability to stratify risk, was successfully replicated in a prospective validation cohort (n=107).

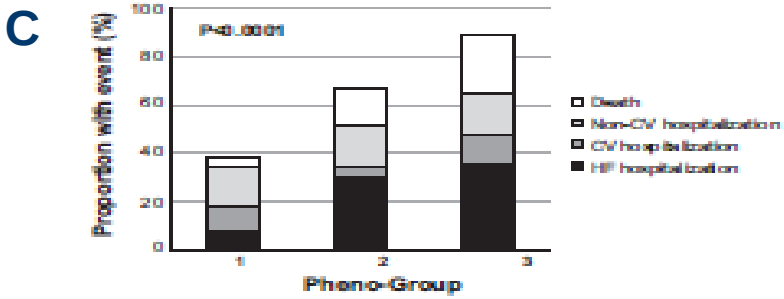
Conclusions—Phenomapping results in a novel classification of HFpEF. Statistical learning algorithms applied to dense phenotypic data may allow improved classification of heterogeneous clinical syndromes, with the ultimate goal of defining therapeutically homogeneous patient subclasses. (***Circulation***. **2015;131:269-279. DOI: 10.1161/CIRCULATIONAHA.114.010637.)**

Key Words: cluster analysis ■ echocardiography ■ heart failure, diastolic ■ patient outcome assessment

Phenomapping of HFpEF

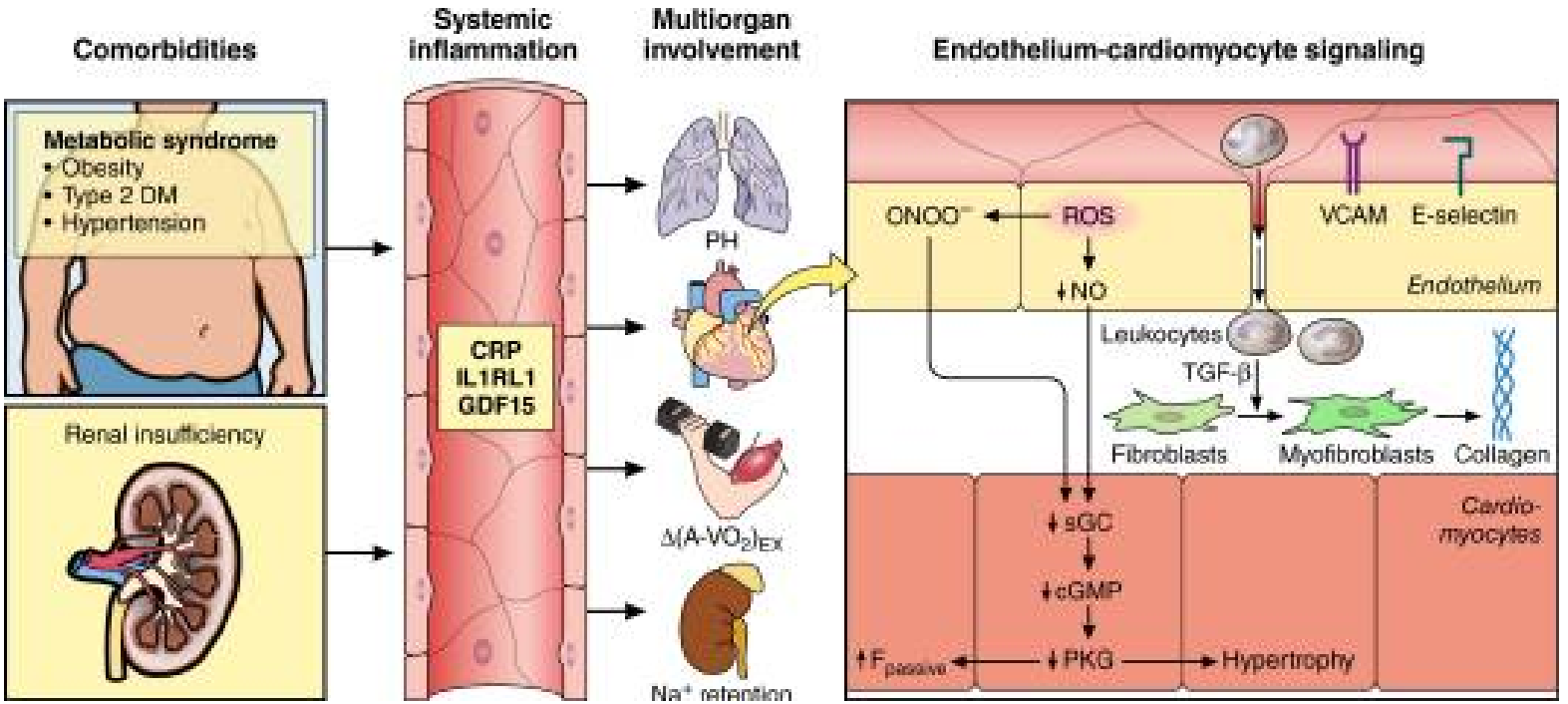






Shah et al Circ 2015; 131: 269-279

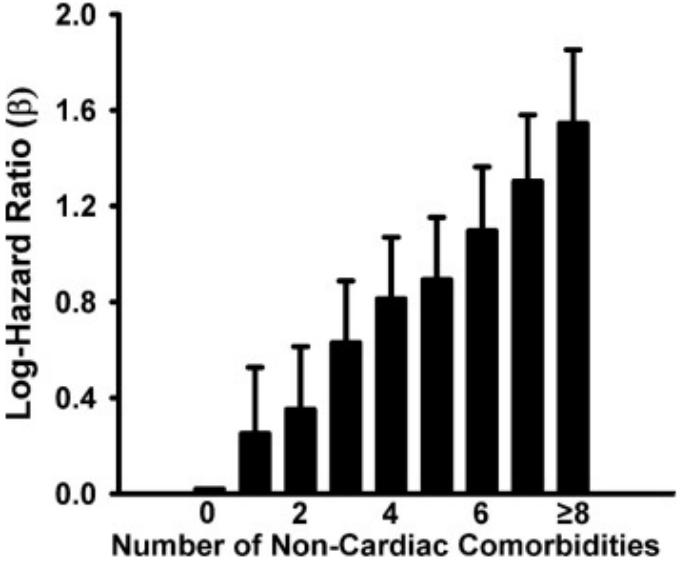
Systemic and Myocardial Signaling in HFpEF

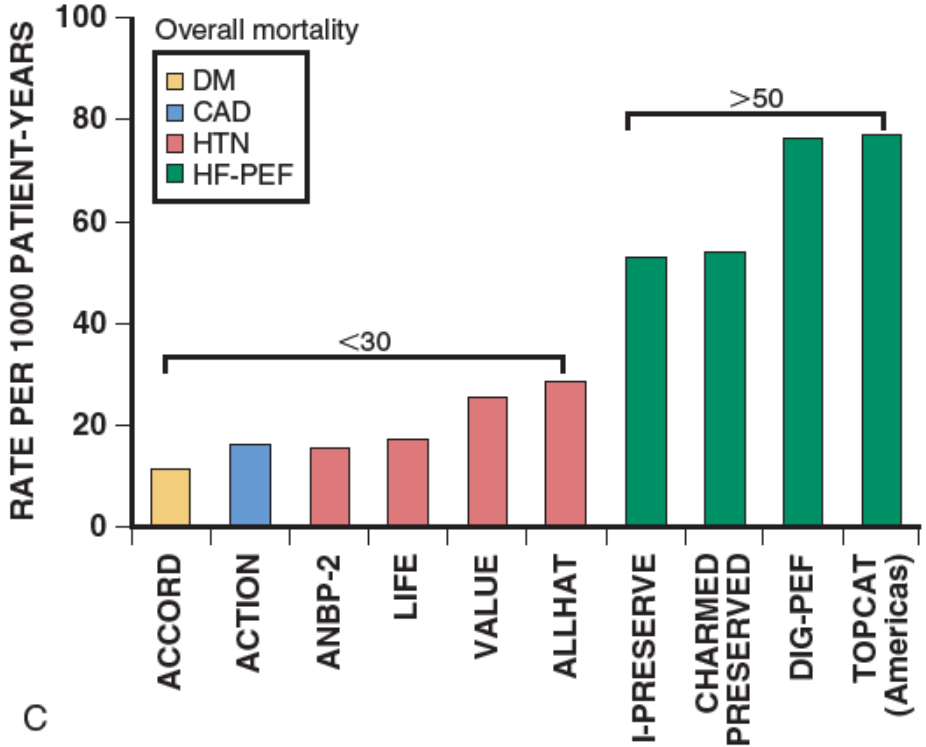


Shah et al. Circ 2017;134:73-90.

Effect of Co-Morbidities in HFpEF

All cause hospitalization





C

Treatment by Co-Morbidities in HFpEF

HFpEF Predisposition Phenotypes	HFpEF Clinical Presentation Phenotypes				
	Lung Congestion	+Chronotropic Incompetence	+Pulmonary Hypertension (CpcPH)	+Skeletal muscle weakness	+Atrial Fibrillation
Overweight/obesity/ metabolic syndrome/ type 2 DM	• **Diuretics (loop diuretic in DM)** • **Caloric restriction** • Statins • Inorganic nitrite/nitrate • Sacubitril • Spironolactone	+Rate adaptive atrial pacing	+Pulmonary vasodilators (e.g. PDE5I)	**+Exercise training program**	+Cardioversion +Rate Control **+Anticoagulation**
+Arterial hypertension	+ACEI/ARB	+ACEI/ARB +Rate adaptive atrial pacing	+ACEI/ARB +Pulmonary vasodilators (e.g. PDE5I)	+ACEI/ARB **+Exercise training program**	+ACEI/ARB +Cardioversion +Rate Control **+Anticoagulation**
+Renal dysfunction	+Ultrafiltration if needed	+Ultrafiltration if needed +Rate adaptive atrial pacing	+Ultrafiltration if needed +Pulmonary vasodilators (e.g. PDE5I)	+Ultrafiltration if needed **+Exercise training program**	+Ultrafiltration if needed +Cardioversion +Rate Control **+Anticoagulation**
+CAD	+ACEI +Revascularization	+ACEI +Revascularization +Rate adaptive atrial pacing	+ACEI +Revascularization +Pulmonary vasodilators (e.g. PDE5I)	+ACEI +Revascularization **+Exercise training program**	+ACEI +Revascularization +Cardioversion +Rate Control **+Anticoagulation**

Shah et al. Circ 2017;134:73-90.

Who knew HFpEF was so complicated ?

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