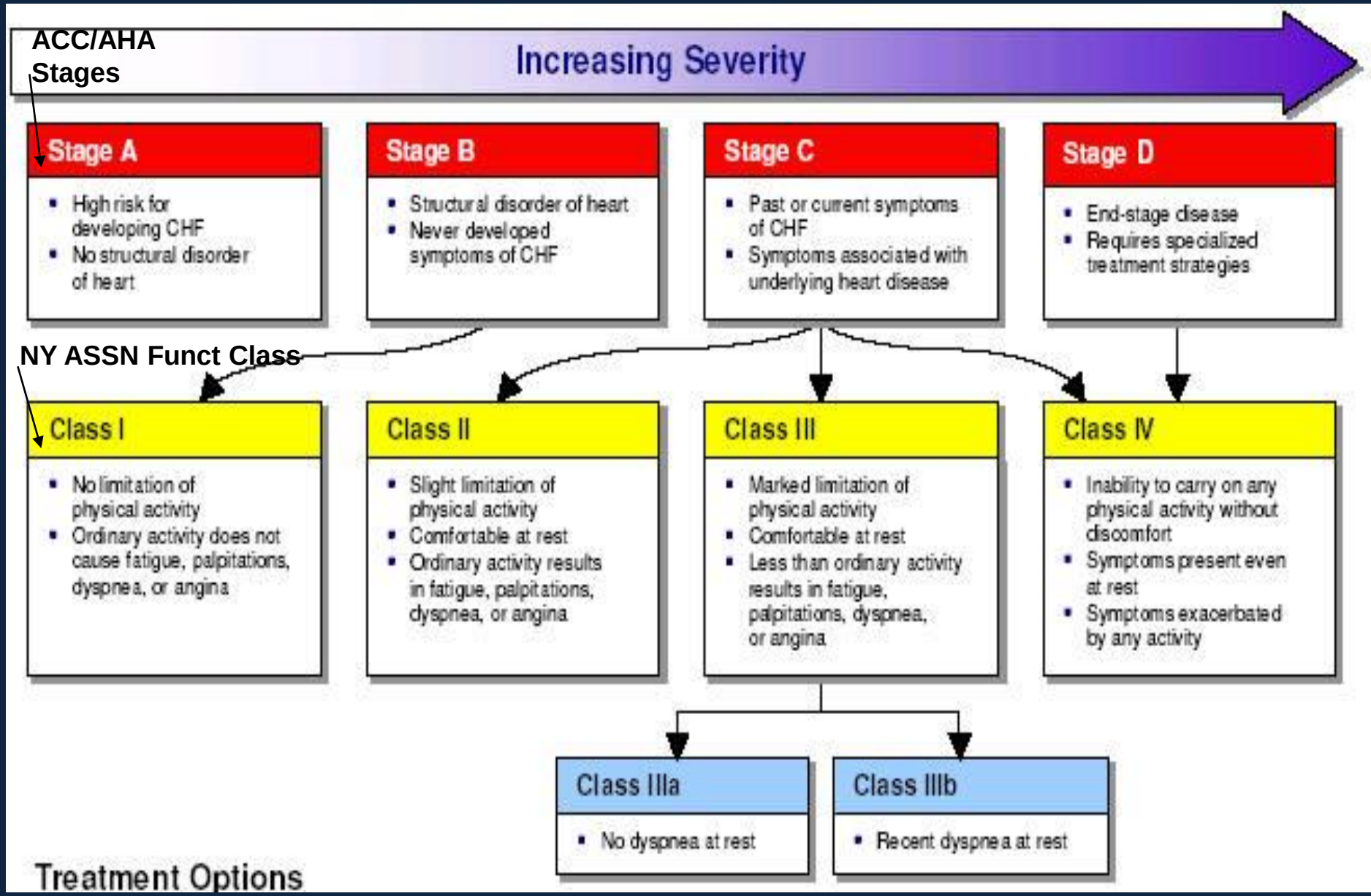
# Fenotipi nella Sindrome da Scompenso Cardiaco a funzione sistolica conservata (HFpEF)

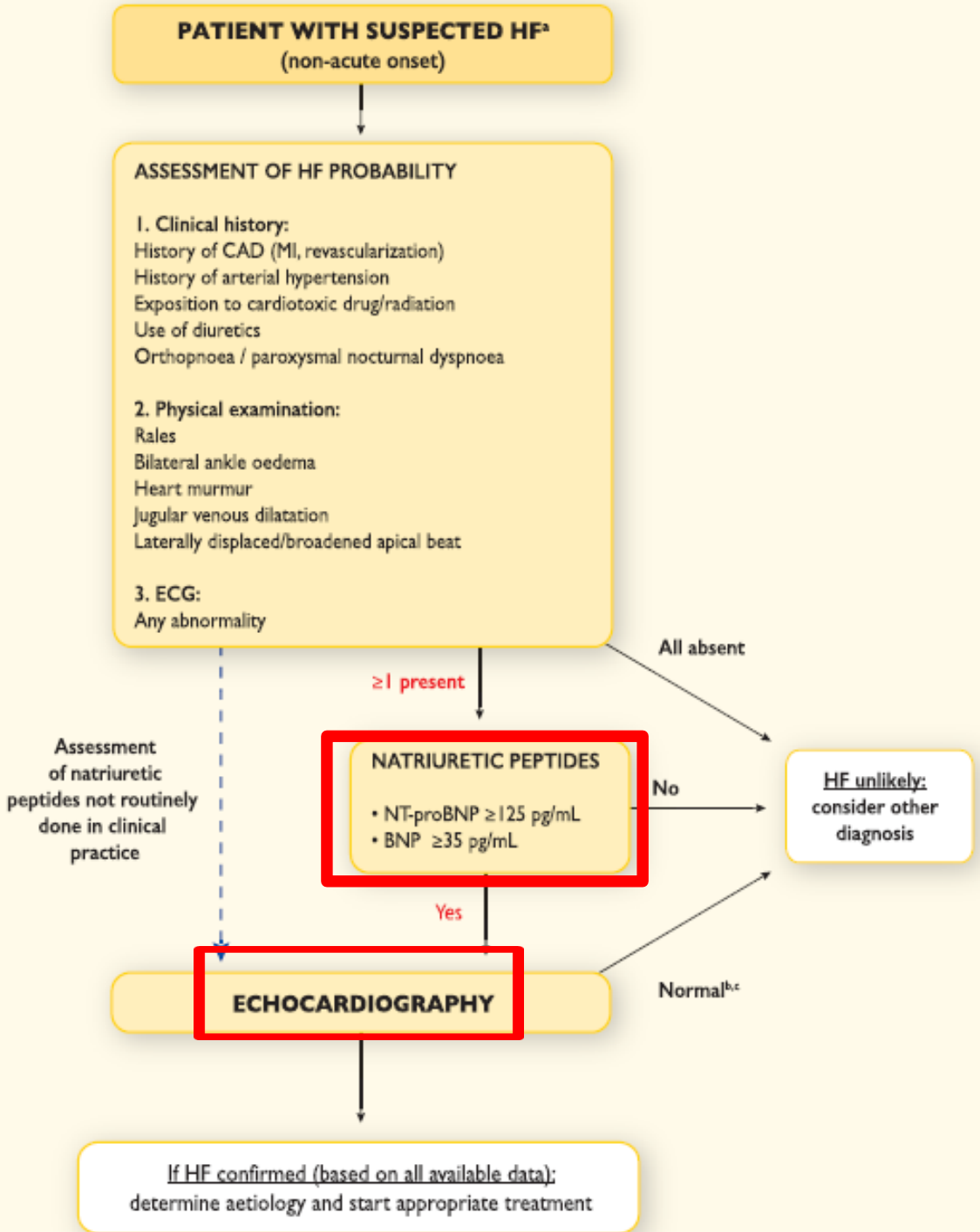
***Massimo Romano***

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

## 3.1 Definition of heart failure

HF is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.


ACC/AHA Stages
Increasing Severity
Stage A
High risk for developing CHF
No structural disorder of heart
Stage B
Structural disorder of heart
Never developed symptoms of CHF
Stage C
Past or current symptoms of CHF
Symptoms associated with underlying heart disease
Stage D
End-stage disease
Requires specialized treatment strategies
NY ASSN Funct Class
Class I
No limitation of physical activity
Ordinary activity does not cause fatigue, palpitations, dyspnea, or angina
Class II
Slight limitation of physical activity
Comfortable at rest
Ordinary activity results in fatigue, palpitations, dyspnea, or angina
Class III
Marked limitation of physical activity
Comfortable at rest
Less than ordinary activity results in fatigue, palpitations, dyspnea, or angina
Class IV
Inability to carry on any physical activity without discomfort
Symptoms present even at rest
Symptoms exacerbated by any activity
Class IIIa
No dyspnea at rest
Class IIIb
Recent dyspnea at rest
Treatment Options


PATIENT WITH SUSPECTED HF[a]
(non-acute onset)
ASSESSMENT OF HF PROBABILITY
1. Clinical history:
History of CAD (MI, revascularization)
History of arterial hypertension
Exposition to cardiotoxic drug/radiation
Use of diuretics
Orthopnoea / paroxysmal nocturnal dyspnoea
2. Physical examination:
Rales
Bilateral ankle oedema
Heart murmur
Jugular venous dilatation
Laterally displaced/broadened apical beat
3. ECG:
Any abnormality
All absent
≥1 present
Assessment of natriuretic peptides not routinely done in clinical practice
NATRIURETIC PEPTIDES
• NT-proBNP ≥125 pg/mL
• BNP ≥35 pg/mL
No
HF unlikely: consider other diagnosis
Yes
ECHOCARDIOGRAPHY
Normal[b,c]
If HF confirmed (based on all available data):
determine aetiology and start appropriate treatment

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

- The diagnosis of HFpEF is more challenging than the diagnosis of HFrEF.

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

- Patients with HFpEF generally do not have a dilated LV,  but instead often have an increase in LV wall thickness and/or increased left atrial (LA) size as a sign of increased filling pressures.

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

- Most have additional ‘evidence’ of impaired LV filling or suction capacity, also classified as diastolic dysfunction, which is generally accepted as the likely cause of HF in these patients (hence the term ‘diastolic HF’).

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

- However, most patients with HFrEF (previously referred to as ‘systolic HF’) also have diastolic dysfunction, and subtle abnormalities of systolic function have been shown in patients with HFpEF.

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

- Hence the preference for stating preserved or reduced LVEF over preserved or reduced ‘systolic function’.

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

European Heart Journal
doi:10.1093/eurheartj/ehw128

| 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];<br>2. At least one additional criterion:<br>a. relevant structural heart disease (LVH and/or LAE),<br>b. diastolic dysfunction (for details see Section 4.3.2). | 1. Elevated levels of natriuretic peptides[b];<br>2. At least one additional criterion:<br>a. relevant structural heart disease (LVH and/or LAE),<br>b. diastolic dysfunction (for details see Section 4.3.2). |

# Heart Failure With Preserved, Borderline, and Reduced Ejection Fraction

## 5-Year Outcomes

(J Am Coll Cardiol 2017;70:2476-86)

Years After Admission

HF*p*EF (EF ≥50%) HF*b*EF (EF 41-49%) HF*r*EF (EF ≤40%)

| Outcomes – 5-Year Event Rates (%) | | | | | |
|---|---|---|---|---|---|
| | Mortality | Readmission | CV Readmission | HF Readmission | Mortality/Readmission |
| HFrEF | 75.3 | 82.2 | 63.9 | 48.5 | 96.4 |
| HFbEF | 75.7 | 85.7 | 63.3 | 45.2 | 97.2 |
| HFpEF | 75.7 | 84.0 | 58.9 | 40.5 | 97.3 |

Shah, K.S. et al. J Am Coll Cardiol. 2017;70(20):2476-86.

# Fenotipi nella Sindrome da Scompenso Cardiaco a Frazione di Eiezione ≥50%  (HFpEF)

***Massimo Romano***

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

European Heart Journal
doi:10.1093/eurheartj/ehw128

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

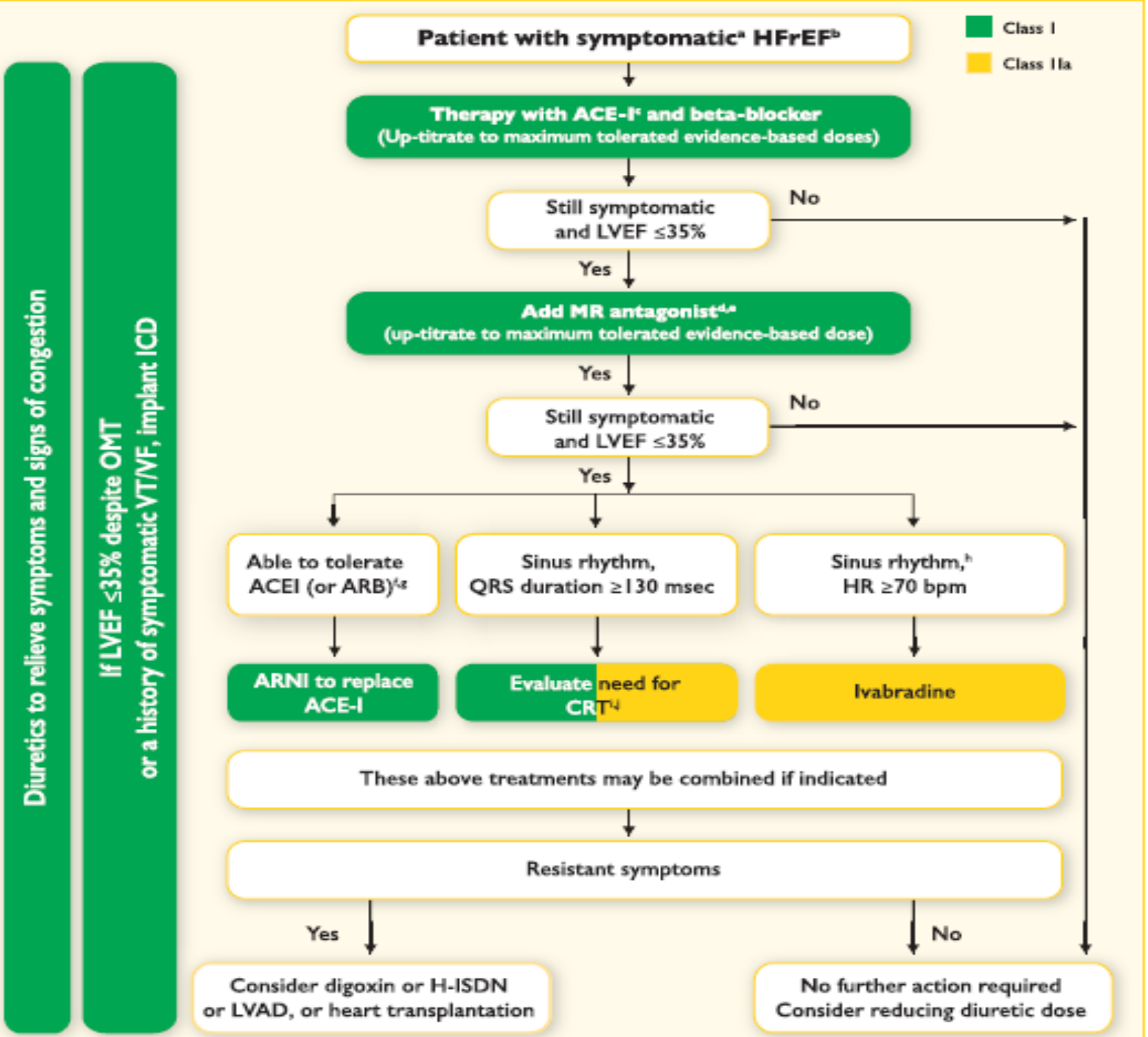
..... the rate of relaxation of the heart "is quite as important as the systolic contraction"...

If an old man's heart relaxes slowly, his capacity for physical exertion is thus limited.

Yendell Handerson, 1923

# Key structural alterations

- Left atrial volume index (LAVI) >34 mL/m2 or a left ventricular mass index (LVMI) ≥115 g/m2 for males and ≥95 g/m2 for females.
- E/e’ ≥13 and a mean e’ septal and lateral wall <9 cm/s.
- (indirect) echocardiographically derived measurements are longitudinal strain or tricuspid regurgitation velocity (TRV).


Class I
Class IIa
Patient with symptomatic[a] HFrEF[b]
Therapy with ACE-I[c] and beta-blocker
(Up-titrate to maximum tolerated evidence-based doses)
Still symptomatic and LVEF ≤35%
No
Yes
Add MR antagonist[d,e]
(up-titrate to maximum tolerated evidence-based dose)
Yes
Still symptomatic and LVEF ≤35%
No
Yes
Able to tolerate ACEI (or ARB)[f,g]
Sinus rhythm, QRS duration ≥130 msec
Sinus rhythm,[h] HR ≥70 bpm
ARNI to replace ACE-I
Evaluate need for CRT[i,j]
Ivabradine
These above treatments may be combined if indicated
Resistant symptoms
Yes
No
Consider digoxin or H-ISDN or LVAD, or heart transplantation
No further action required
Consider reducing diuretic dose
Diuretics to relieve symptoms and signs of congestion
If LVEF ≤35% despite OMT or a history of symptomatic VT/VF, implant ICD

## 9.1 Effect of treatment on symptoms in heart failure with preserved ejection fraction

Diuretics will usually improve congestion, if present, thereby improving symptoms and signs of HF. The evidence that diuretics improve symptoms is similar across the spectrum of LVEF.[178,179]

Evidence that beta-blockers and MRAs improve symptoms in these patients is lacking. There is inconsistent evidence for an improvement in symptoms in those treated with ARBs (only for candesartan was there an improvement in NYHA class)[309,310] and ACEIs.[311]

## 9.2 Effect of treatment on hospitalization for heart failure in heart failure with preserved ejection fraction

For patients in sinus rhythm, there is some evidence that nebivolol,[173,312,313] digoxin,[314] spironolactone[301] and candesartan[310] might reduce HF hospitalizations. For patients in AF, beta-blockers do not appear to be effective and digoxin has not been studied. The evidence in support of either ARBs[315] or ACEIs[311] is inconclusive.

## 9.3 Effect of treatment on mortality in heart failure with preserved ejection fraction

Trials of ACEIs, ARBs, beta-blockers and MRAs have all failed to reduce mortality in patients with HFpEF or HFmrEF. However, in older patients with HFrEF, HFpEF or HFmrEF, nebivolol reduced the combined endpoint of death or cardiovascular hospitalization,[173,312] with no significant interaction between treatment effect and baseline LVEF.[313]

## 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 |

# Heart Failure With Preserved Ejection Fraction

## In Perspective

DOI: 10.1161/CIRCRESAHA.119.313572

| Definition | Advantages | Disadvantages |
|---|---|---|
| Braunwald definition* | Fits the a priori definition of cardiac failure | Definitive measurements require invasive assessment with exercise |
| | Objective, relies upon measurable quantities | |
| Framingham criteria | Well-validated and widely accepted | Poorly sensitive |
| | High specificity | Requires multiple findings of right heart failure that are often restricted to patients with advanced HF |
| Hospitalization for HF | Unequivocal event of interest | Many HFpEF patients are never hospitalized |
| | Prognostic | May be confused with symptoms due to noncardiac causes |
| Natriuretic peptides | Widely available | Many patients with proven HFpEF have normal levels |
| | Easy to measure from blood samples | |
| | Prognostic | |
| ICD coding | Pragmatic definition of primary caregiver | Misdiagnosis or lack of diagnosis compromise sensitivity and specificity |
| Echocardiography | Widely available | Measurement variability may be high |
| | EF and diastolic function readily measurable | Normal EF does not mean normal function |
| | | Diastolic dysfunction common without HF |
| Consensus Guidelines | Based on expert opinion | Lack of validation against gold standard |
| | Generally incorporate components from the definitions above | Poor sensitivity |
| | | Often difficult to apply |

EF indicates ejection fraction; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; and ICD, implantable cardioverter defibrillator.

*Defined as An inability of the heart to pump blood to the body at a rate commensurate with its needs, or to do so only at the cost of high filling pressures.

**Phenotype-Specific Treatment of Heart Failure With Preserved Ejection Fraction**

A Multiorgan Roadmap

**Table. Unequal Structural, Functional, and Ultrastructural LV Characteristics in HFpEF and HFrEF**

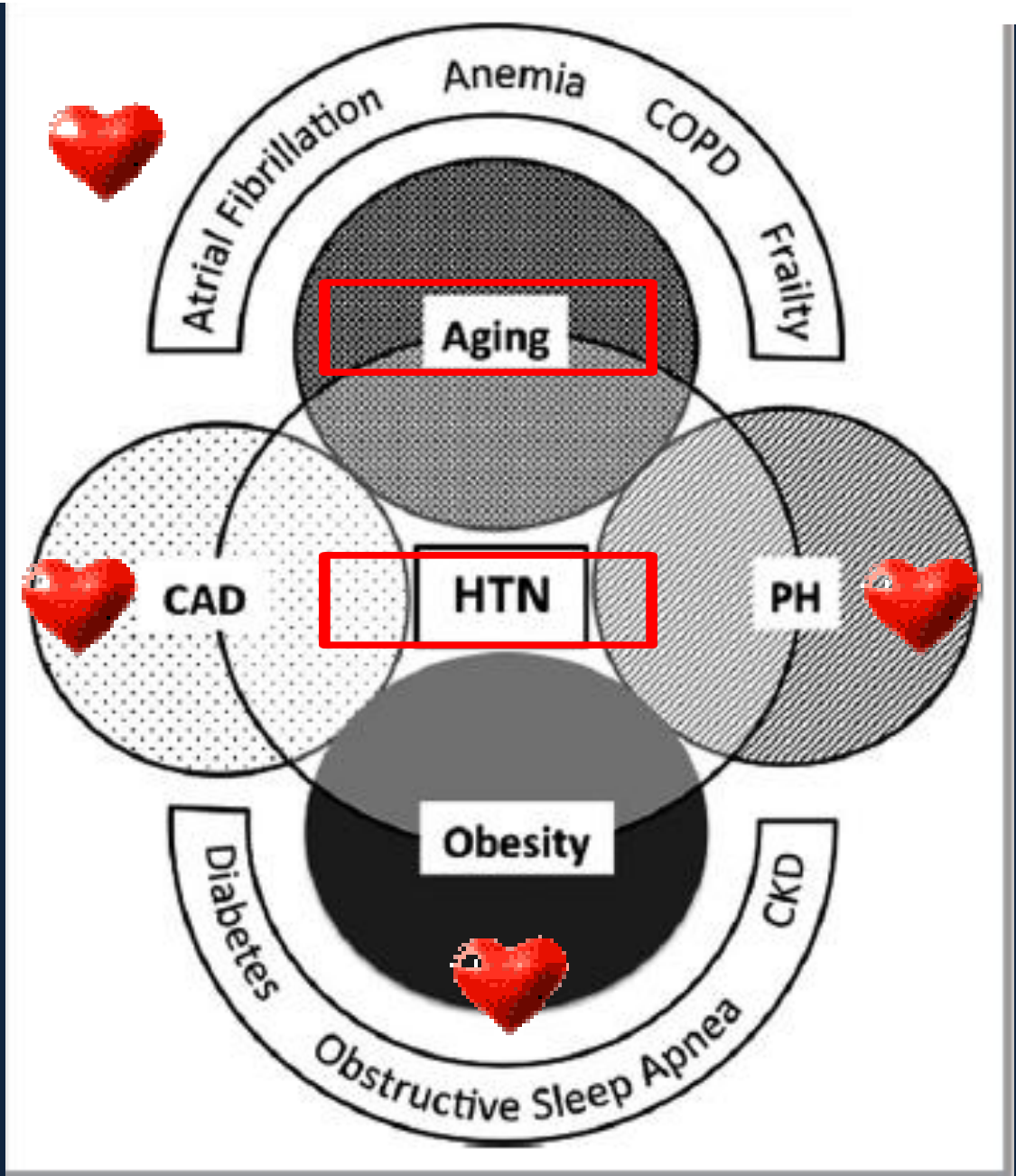
| | HFpEF | HFrEF |
|---|---|---|
| LV structure/function | | |
| End-diastolic volume | ↔ | ↑ |
| End-systolic volume | ↔ | ↑ |
| Wall thickness | ↑ | ↔ |
| Mass | ↑ | ↑ |
| Mass/volume ratio | ↑ | ↓ |
| Remodeling | Concentric | Eccentric |
| Ejection fraction | ↔ | ↓ |
| Stroke work | ↔ | ↓ |
| End-systolic elastance | ↔ | ↓ |
| End-diastolic stiffness | ↑ | ↓ |
| LV ultrastructure | | |
| Myocyte diameter | ↑ | ↔ |
| Myocyte length | ↔ | ↑ |
| Myocyte remodeling | Concentric | Eccentric |
| Fibrosis | Interstitial/reactive | Focal/ replacement |

HFpEF indicates heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and LV, left ventricular.

# Clinical Phenotypes in Heart Failure With Preserved Ejection Fraction

Rohan Samson, MD; Abhishek Jaiswal, MD; Pierre V. Ennezat, MD; Mark Cassidy, MD; Thierry H. Le Jemtel, MD

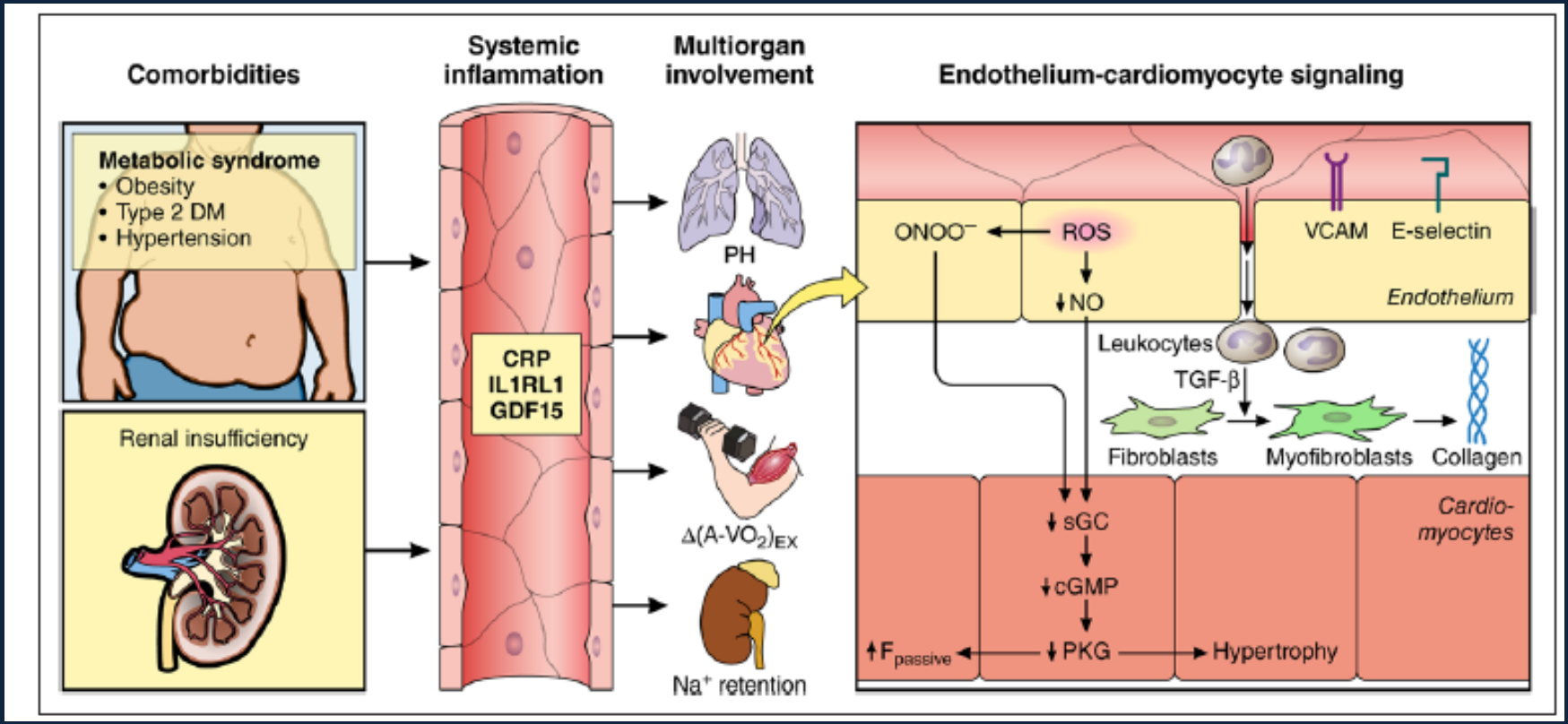
DOI: 10.1161/JAHA.115.002477



# Phenotype-Specific Treatment of Heart Failure With Preserved Ejection Fraction

## A Multiorgan Roadmap

*Circulation*. 2016;134:73-90.



# HFpEF patients

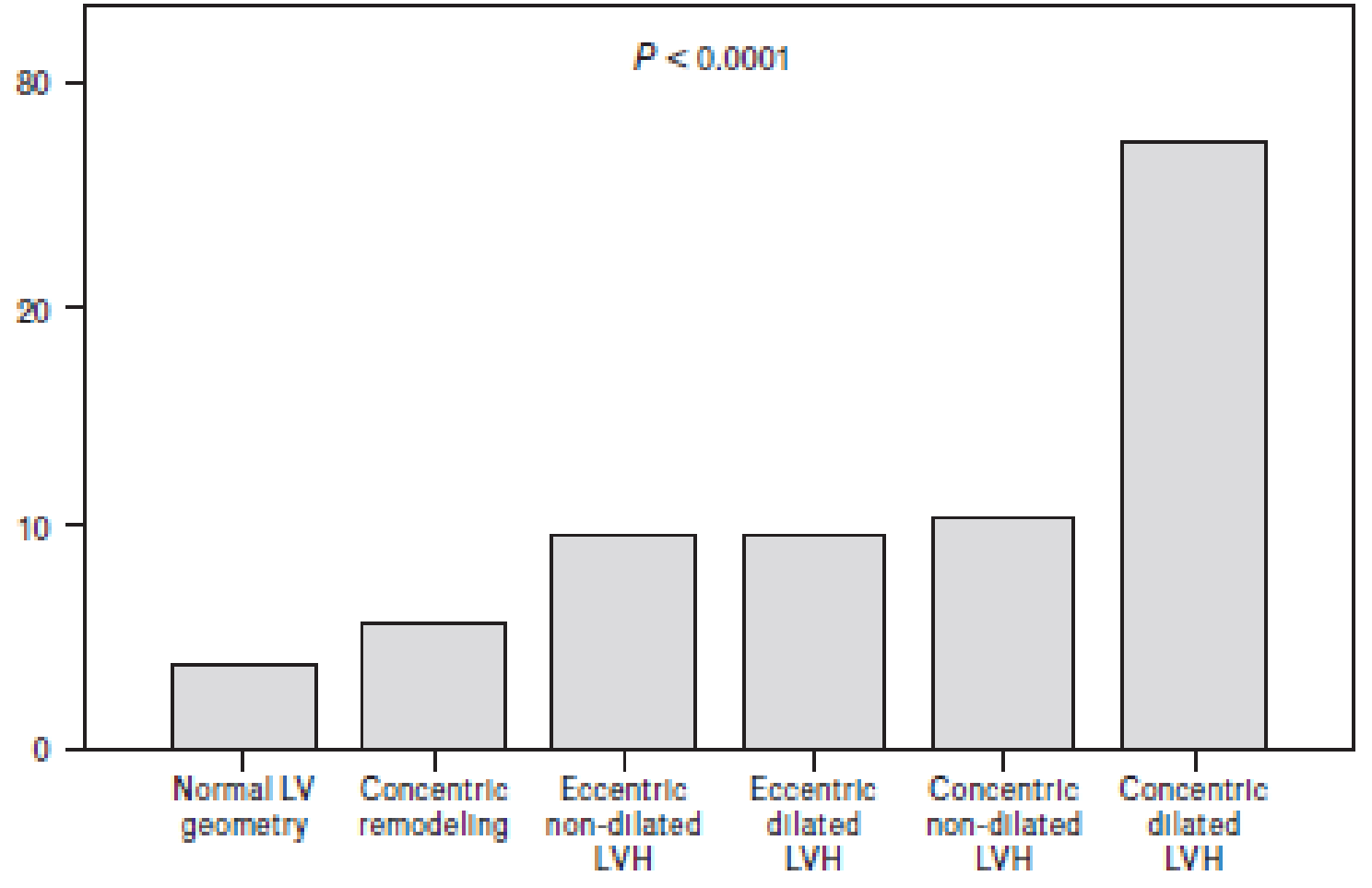
- advanced age and predominantly women
  multiple comorbidities such as
- **overweight/obesity (84%),**
- **arterial hypertension (60%–80%),**
- **type 2 diabetes mellitus (20%–45%),**
- renal insufficiency, and
- sleep apnea.

Cardiovascular risk in relation to a new classification of hypertensive left ventricular geometric abnormalities

Giovanni de Simone[a,b], Raffaele Izzo[a,b], Gerard P. Aurigemma[c], Marina De Marco[a,b], Francesco Rozza[d], Valentina Trimarco[a,e], Eugenio Stabile[a,f], Nicola De Luca[a,b], and Bruno Trimarco[a,f]

European Heart Journal (2013) **34**, 3419–3426

**DIABETES%**



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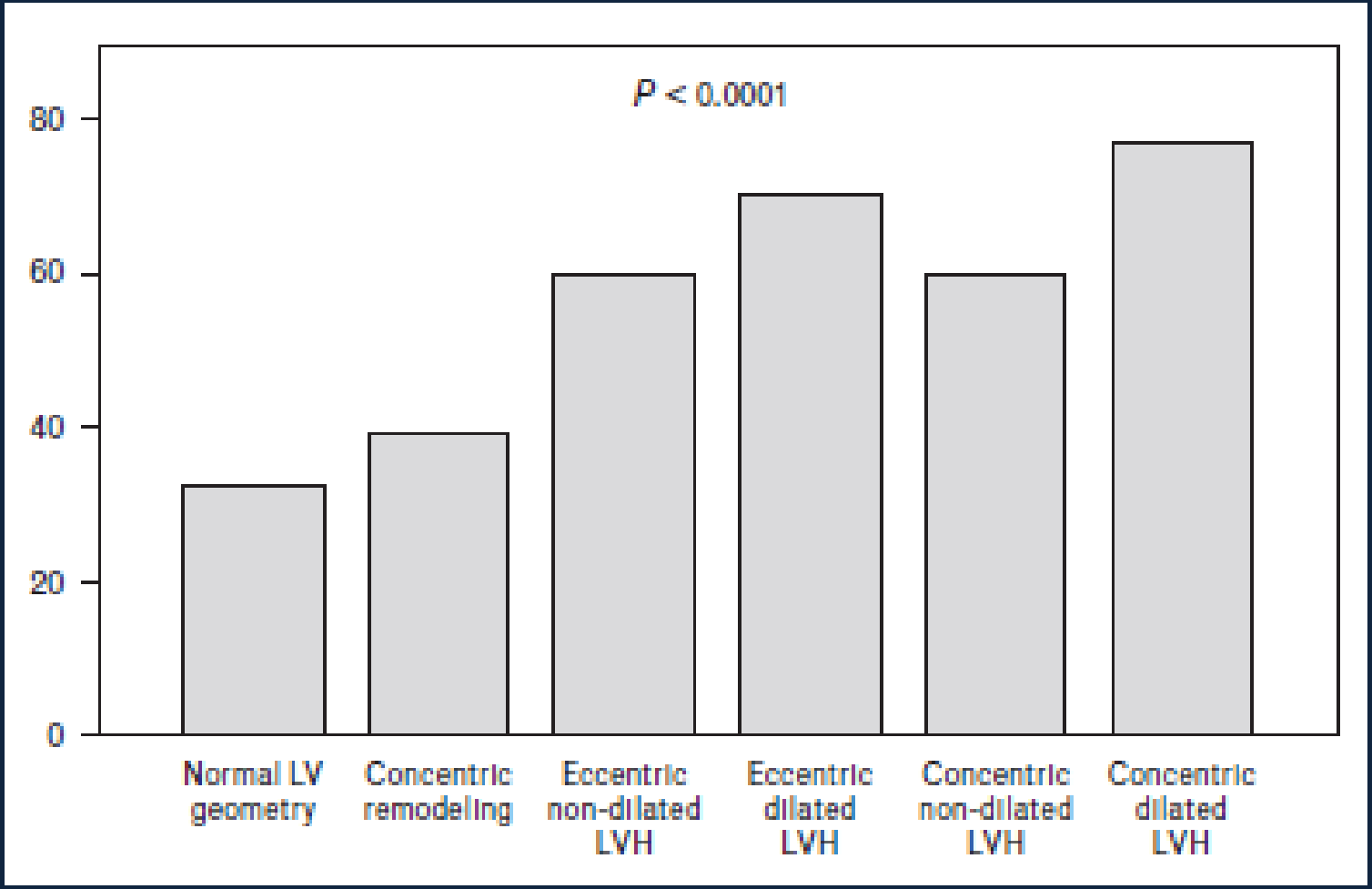
European Heart Journal (2013) **34**, 3419–3426

**OBESITY%**



# Lack of Reduction of Left Ventricular Mass in Treated Hypertension: The Strong Heart Study

Giovanni de Simone, MD; Richard B. Devereux, MD; Raffaele Izzo, MD, PhD; Daniela Girfoglio, MD; Elisa T. Lee, PhD; Barbara V. Howard, PhD; Mary J. Roman, MD

**Conclusions-—In a free-living population, higher BMI is associated with less reduction of hypertensive LVH; lack of reduction of LVM is independent of BP control and of types of antihypertensive treatment, but is associated with renal damage. (J Am Heart Assoc. 2013;2:e000144)**

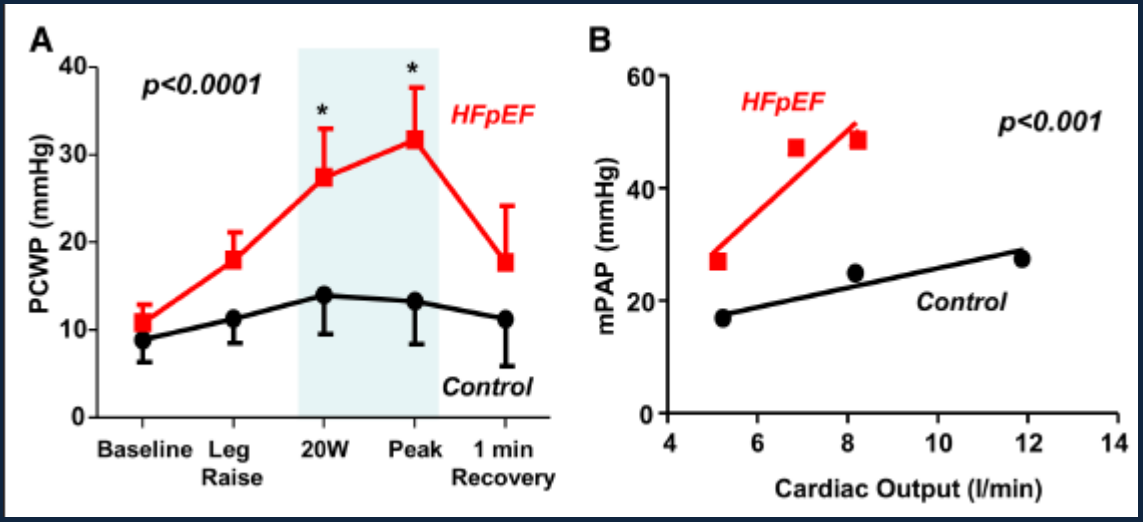
# Evidence Supporting the Existence of a Distinct Obese Phenotype of Heart Failure with Preserved Ejection Fraction

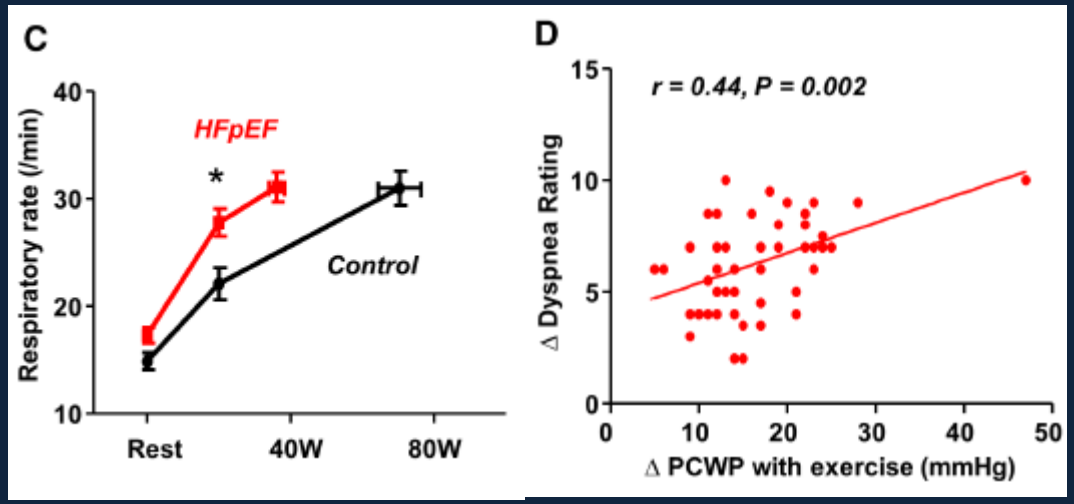
*Circulation*. 2017 July 04; 136(1): 6–19.

## Clinical Perspective

**What is New?**

- Obesity is common in heart failure with preserved ejection fraction (HFpEF) and has many cardiovascular effects, suggesting it may be a clinically relevant phenotype of HFpEF.
- Compared to non-obese HFpEF, obese HFpEF subjects display greater volume overload, more biventricular remodeling, greater right ventricular dysfunction, worse exercise capacity, more profound hemodynamic derangements, and impaired pulmonary vasodilation.
- Obese HFpEF subjects display other important contributors to high left filling pressures, including greater dependence on plasma volume expansion, increased pericardial restraint, and enhanced ventricular interaction, which is exaggerated as pulmonary pressure load increases.




# Heart Failure With Preserved Ejection Fraction
## In Perspective

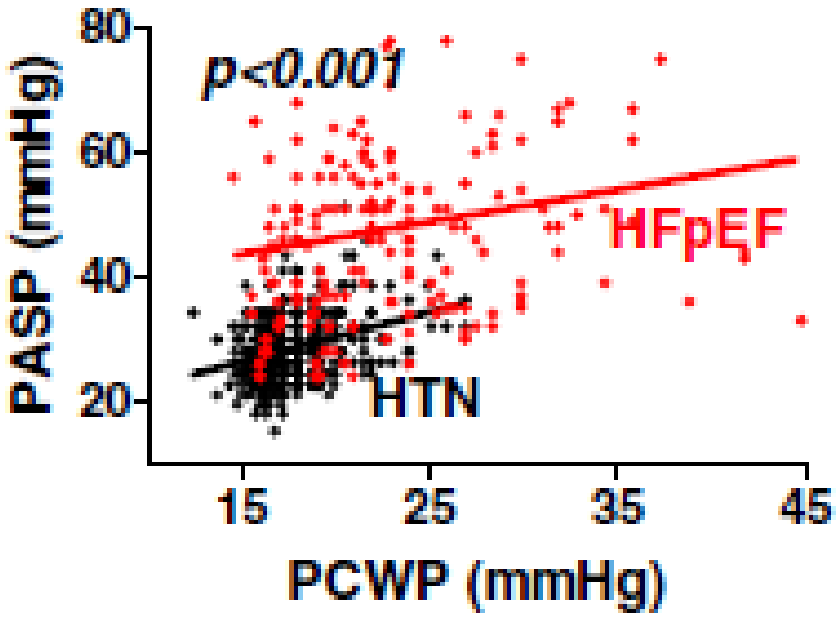
Marc A. Pfeffer, Amil M. Shah, Barry A. Borlaug

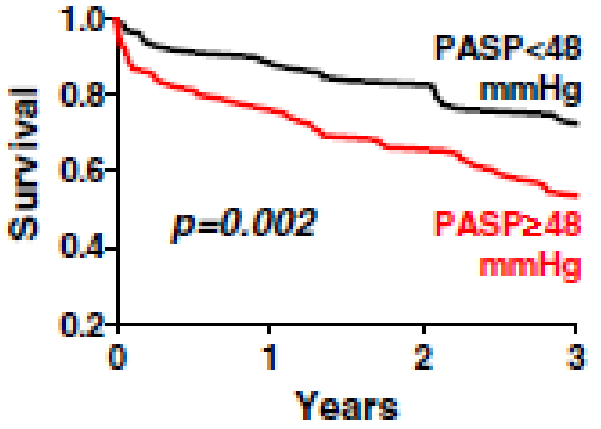
DOI: 10.1161/CIRCRESAHA.119.313572

## Pulmonary Hypertension in Heart Failure With Preserved Ejection Fraction

A Community-Based Study

(J Am Coll Cardiol 2009;53:1119–26)



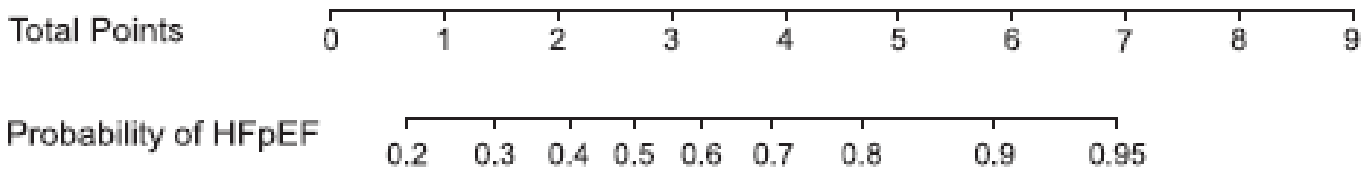




| Number remaining | | | | |
|---|---|---|---|---|
| PASP<48 mmHg | 98 | 86 | 80 | 44 |
| PASP≥48 mmHg | 105 | 78 | 67 | 38 |

# A Simple, Evidence-Based Approach to Help Guide Diagnosis of Heart Failure With Preserved Ejection Fraction

*Circulation*. 2018;138:861–870.

| | Clinical Variable | Values | Points |
|---|---|---|---|
| $H_2$ | **H**eavy | Body mass index > 30 kg/m$^2$ | 2 |
| | **H**ypertensive | 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 |
| $H_2$FPEF score | | | Sum (0-9) |



# HFpEF patients

- Biomarker profiles in HFpEF and HFrEF are consistent with the distinct origins of both HF phenotypes because they show lower markers of myocardial injury:

# HFpEF patients

(high-sensitivity troponin T) or of myocardial stress (Nterminal pro brain natriuretic peptide [N-terminal pro-BNP]) in HFpEF.

# HFpEF patients

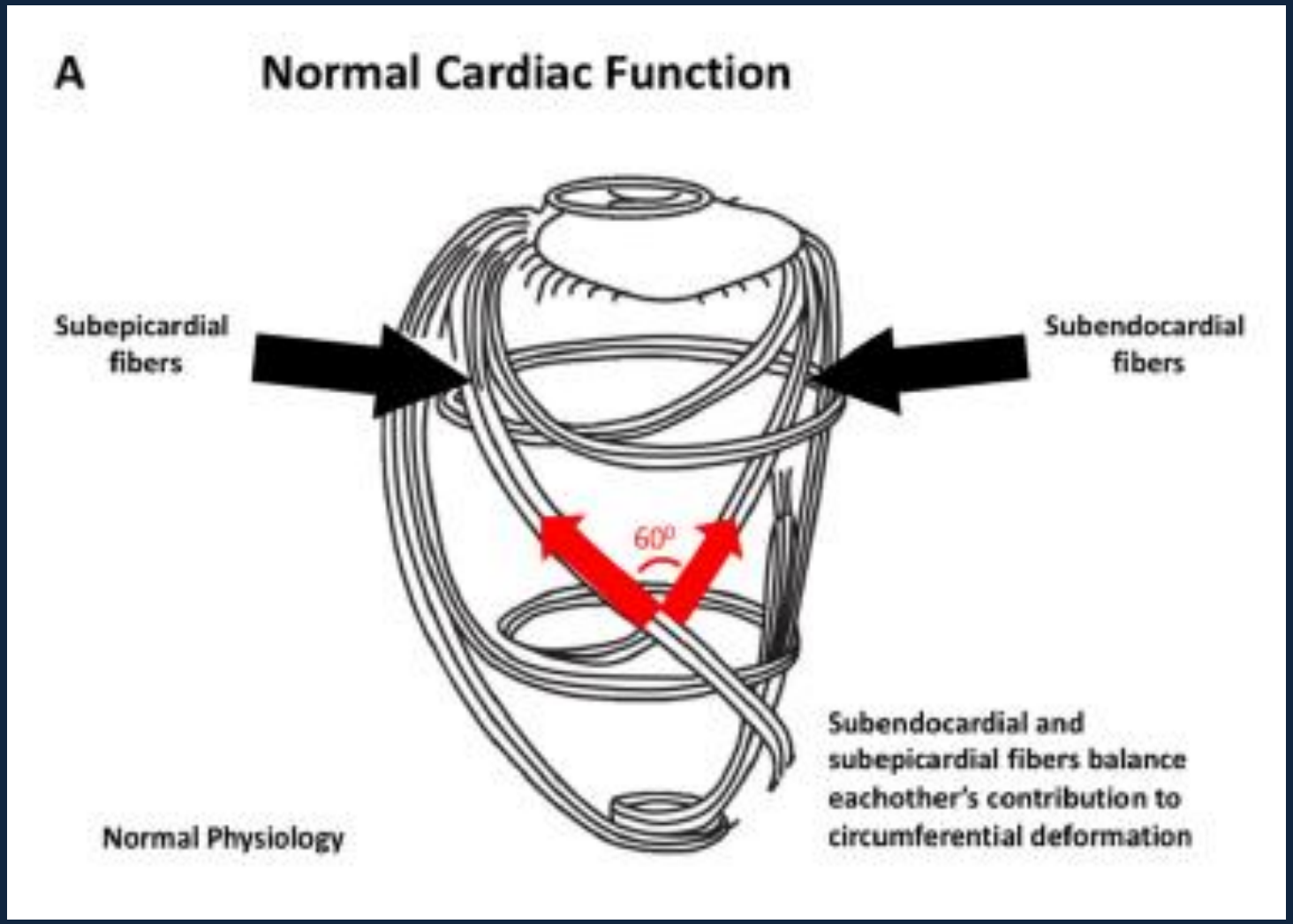
- Lower N-terminal pro-BNP is explained by concentric LV remodeling/hypertrophy in HFpEF in contrast to eccentric LV remodeling/hypertrophy in HFrEF;

# HFpEF patients

•and by visceral distribution of adipose tissue in the mostly overweight or obese HFpEF patients, which is associated with
•decreased production and
•increased clearance of natriuretic peptides (NPs).

•NTpro BNP ≥ 125 pg/mL
•BNP ≥ 35 pg/mL

# Echo and heart failure: when do people need an echo, and when do they need natriuretic peptides?



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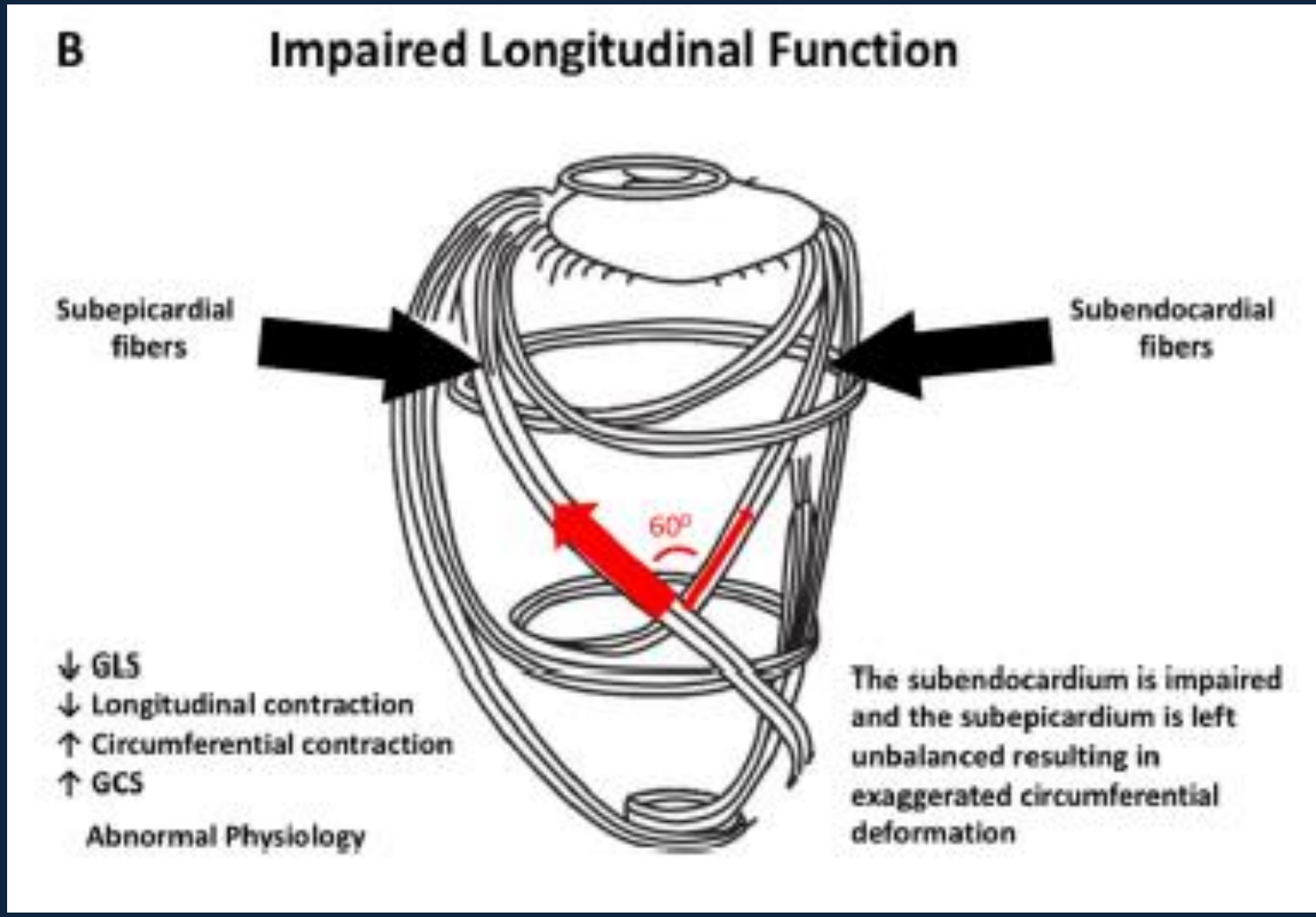
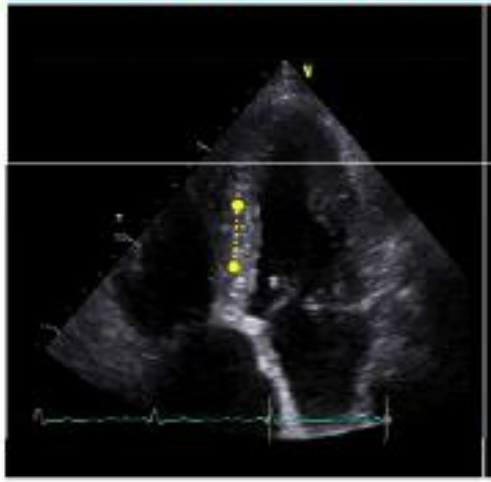
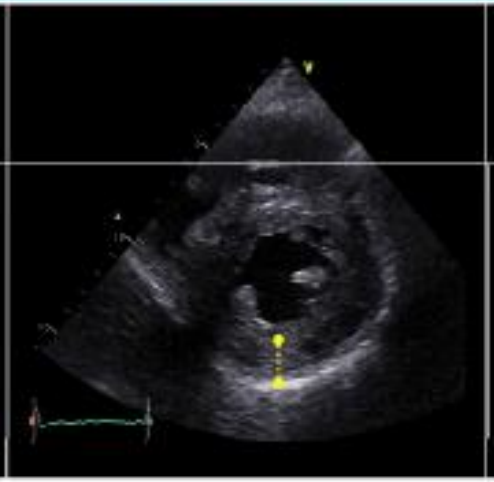
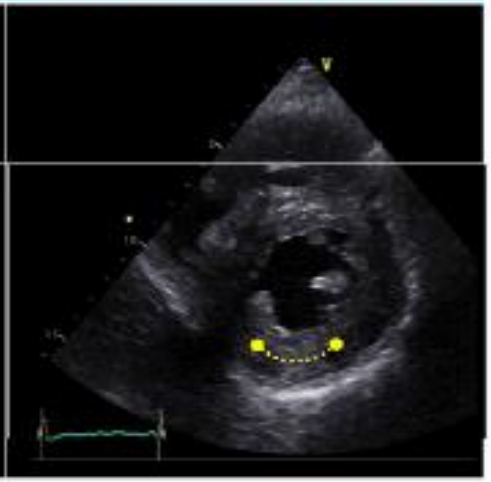
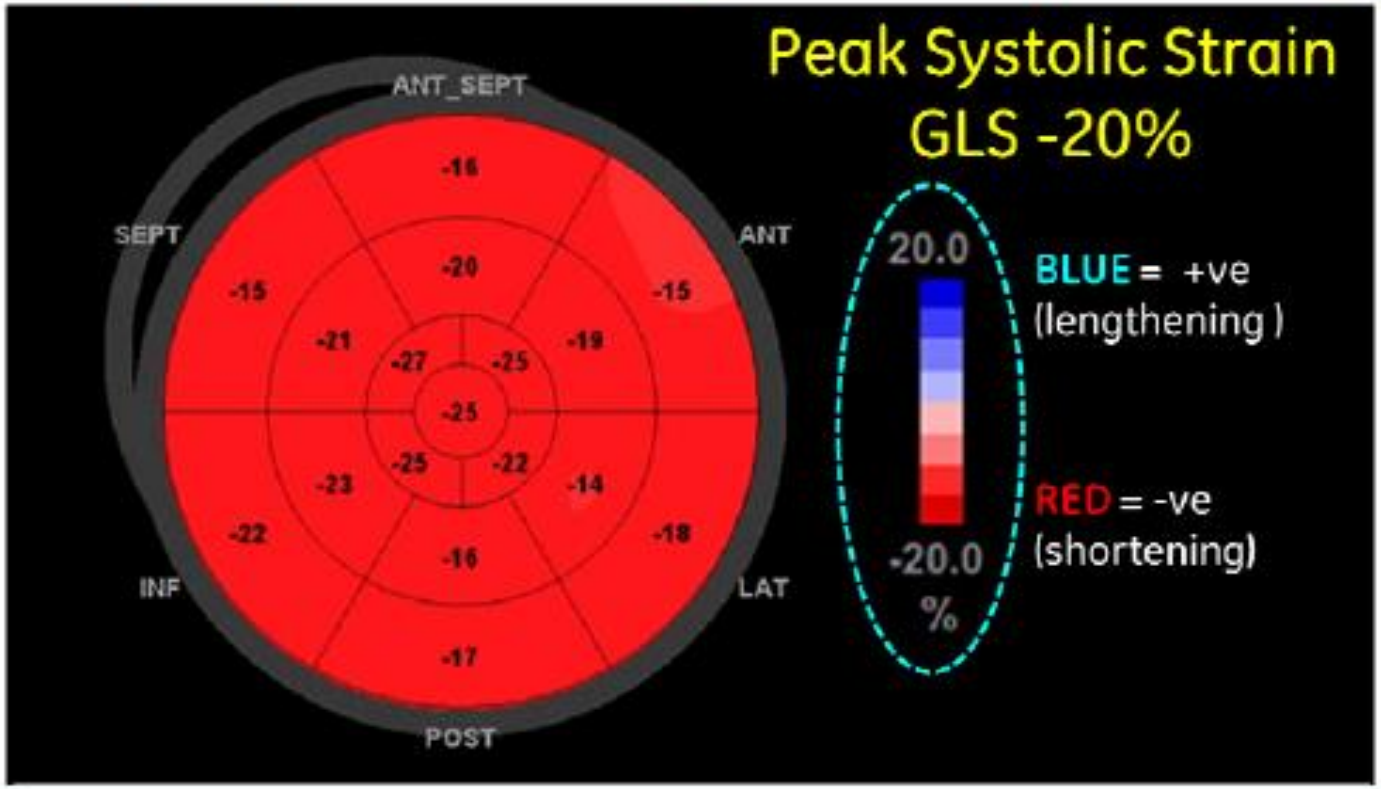


# Direction of Motion

| Direction | Longitudinal | Radial | Circumferential |
|---|---|---|---|
| |  |  |  |
| Systole | Shortening = -ve | Thickening = +ve | Shortening = -ve |
| (Diastole) | (Lengthening = +ve) | (Thinning = -ve) | (Lengthening = +ve) |

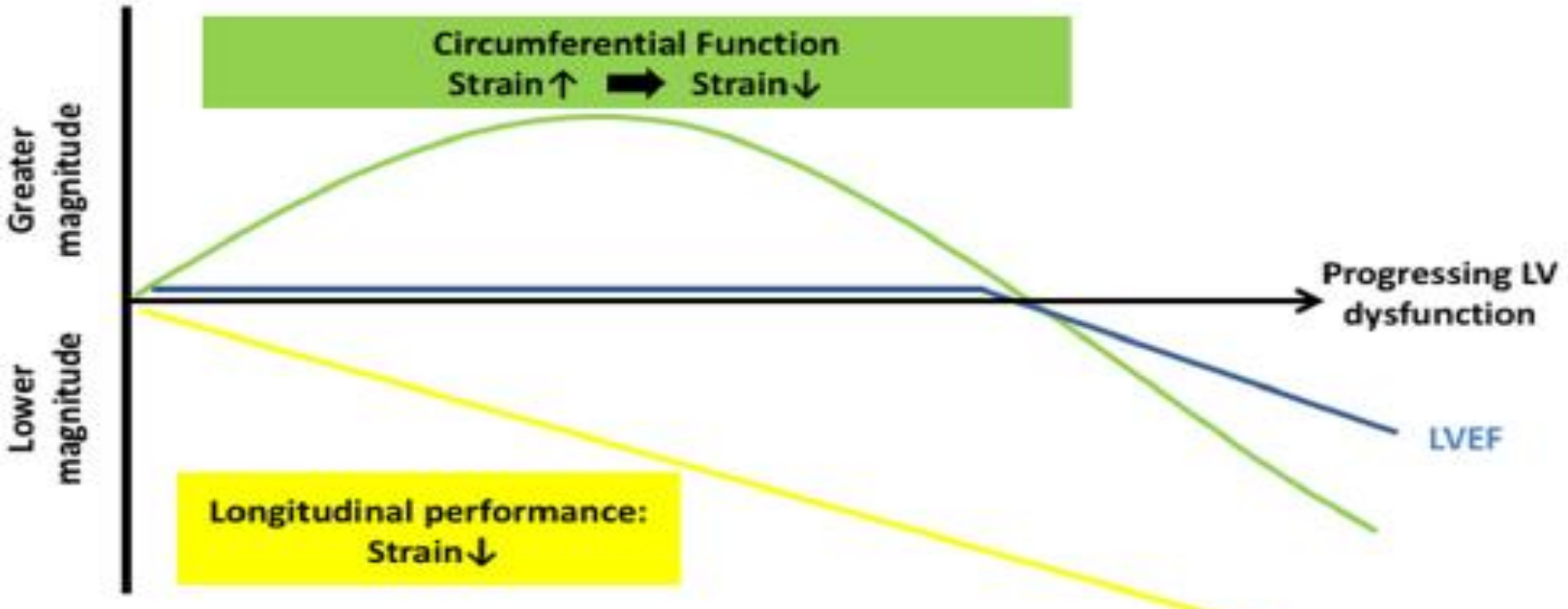
# Display of GLS (Bull's Eye Plot)



STAGE A HF → STAGE C HF → STAGE D HF

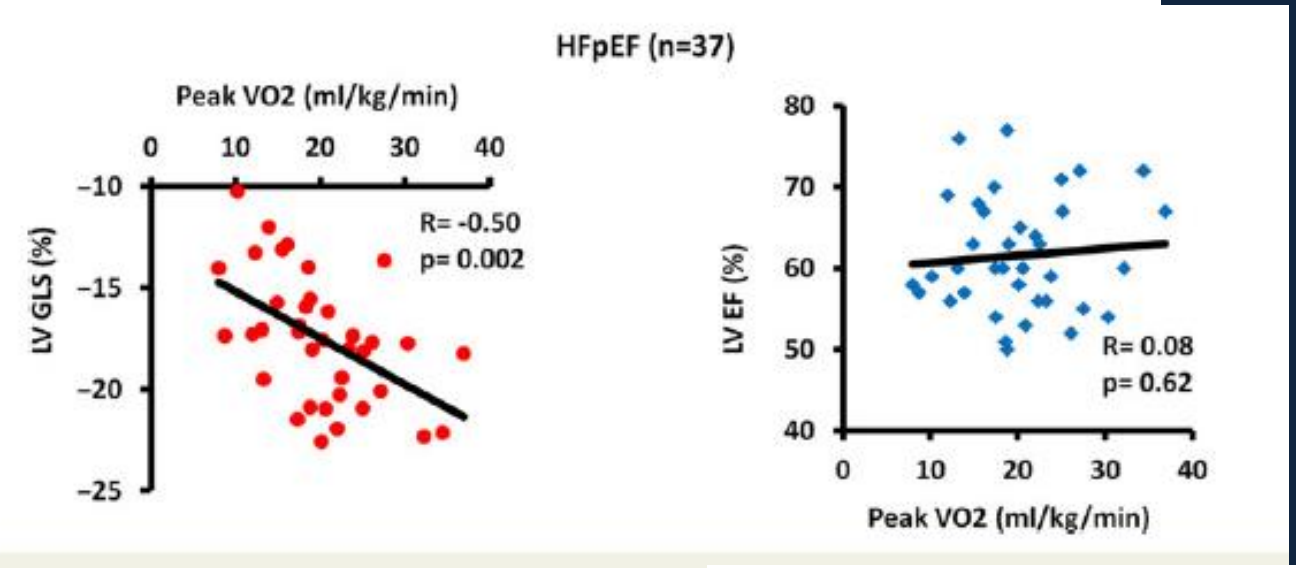
| LV function and parameter | Subclinical Dysfunction | HFpEF | HFrEF |
|---|---|---|---|
| LVEF | Normal | Normal | ↓↓ |
| Longitudinal Function GLS | ↓ | ↓↓ | ↓↓↓ |
| Circumferential Function GCS | Normal | ↑ | ↓↓ |

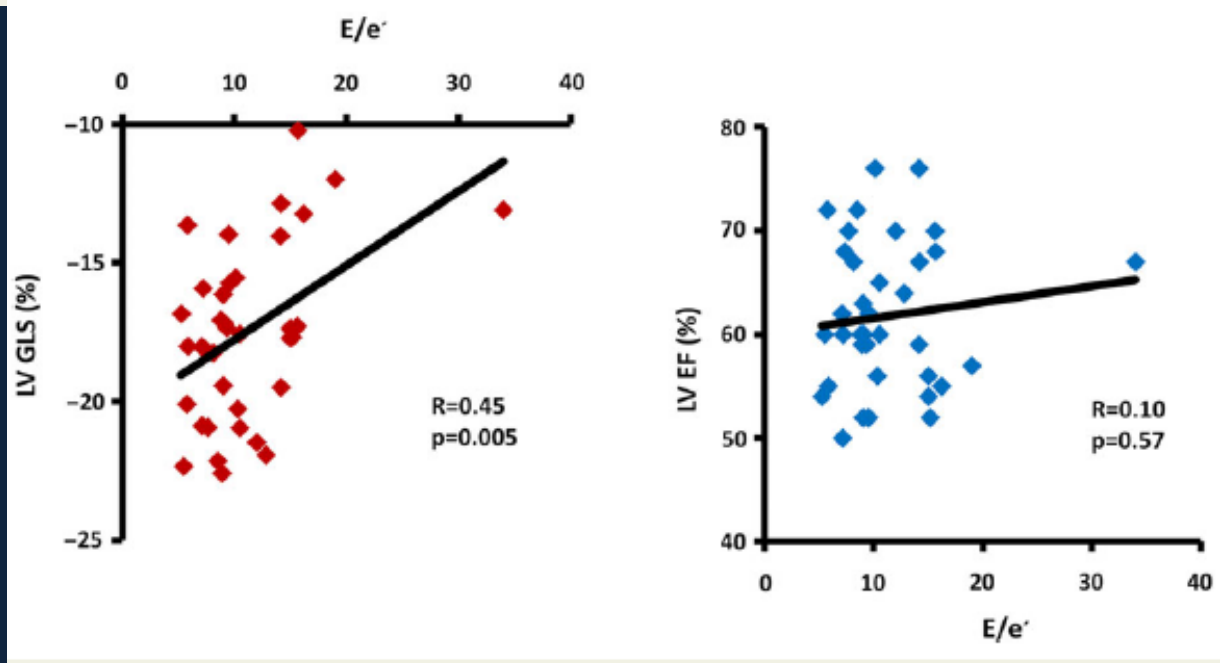
*Initiators and Accelerators:* Increasing age, Hypertension, Diabetes, Ischemic disease, Obesity, Renal insufficiency, Valvular disease



# Left ventricular global longitudinal strain is associated with exercise capacity in failing hearts with preserved and reduced ejection fraction

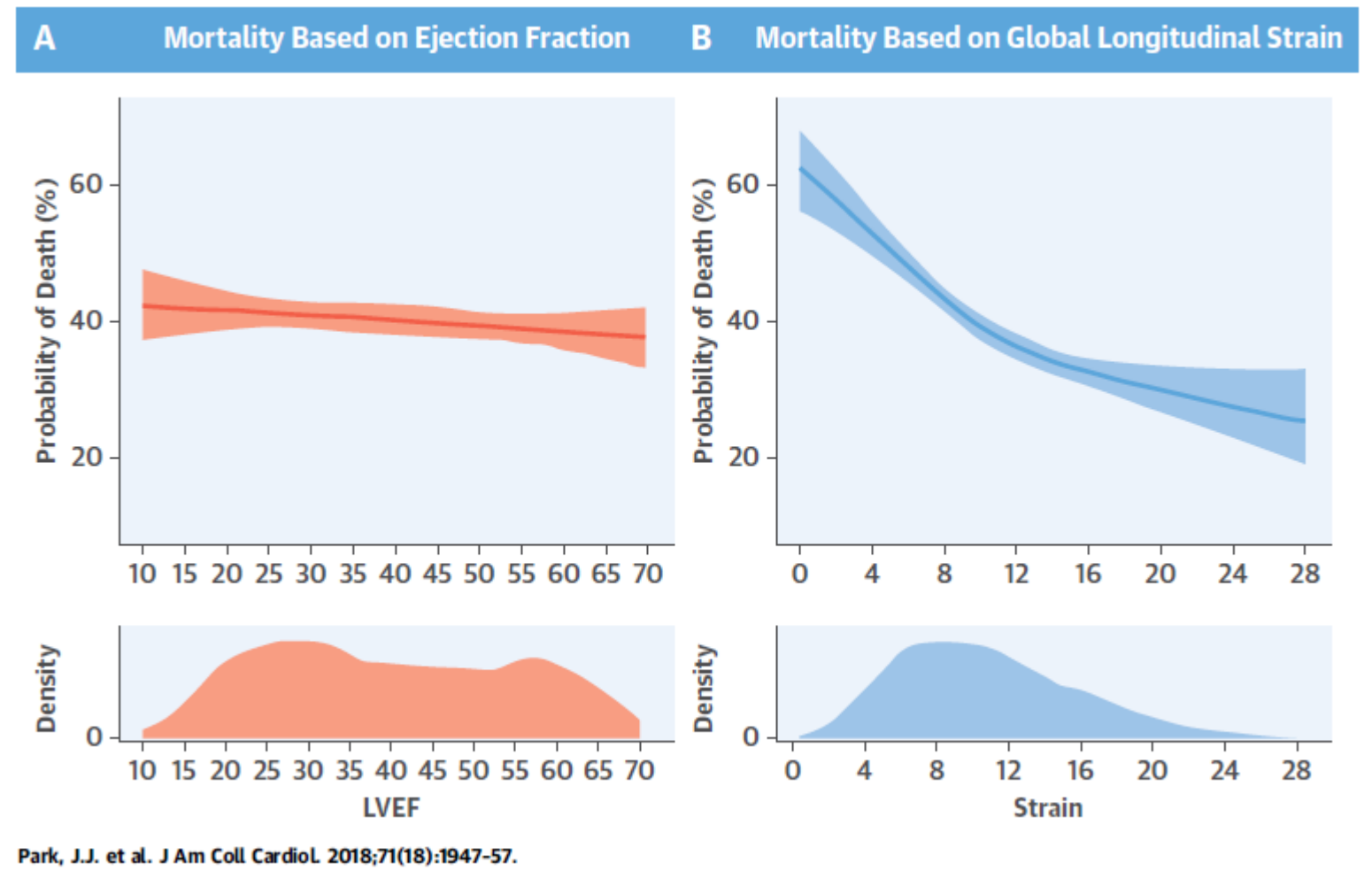
European Heart Journal – Cardiovascular Imaging (2015) **16**, 217–224



# Global Longitudinal Strain to Predict Mortality in Patients With Acute Heart Failure

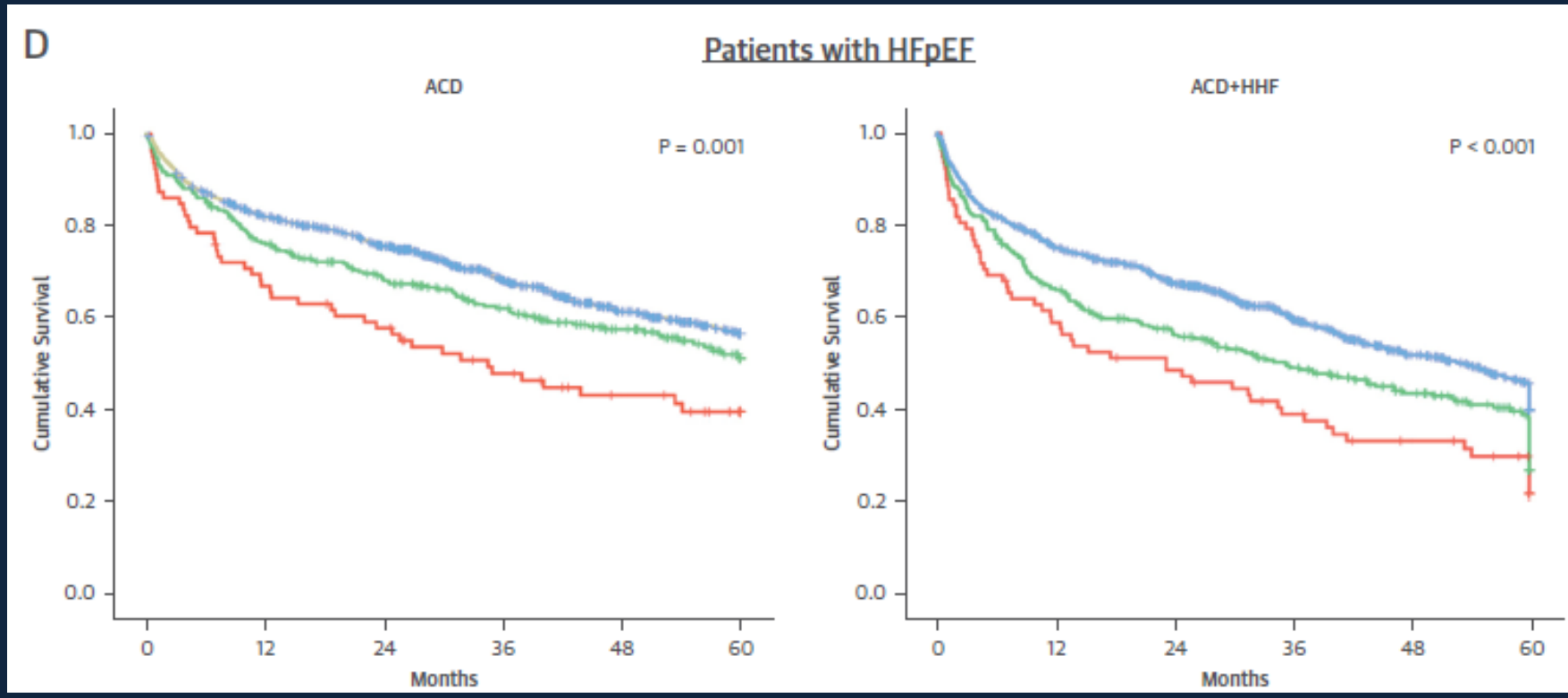
(J Am Coll Cardiol 2018;71:1947–57)




Park, J.J. et al. J Am Coll Cardiol. 2018;71(18):1947-57.

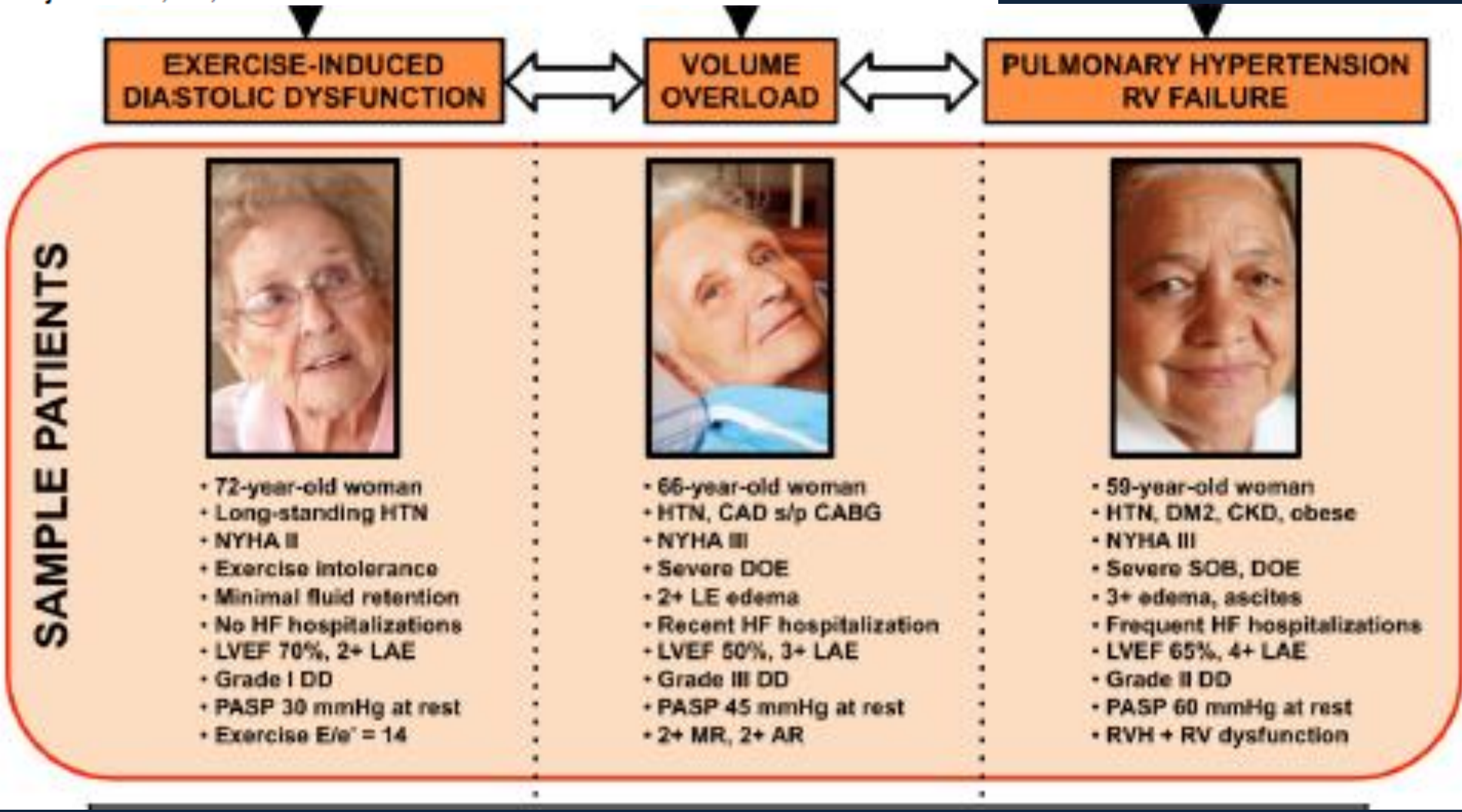
# Global Longitudinal Strain to Predict Mortality in Patients With Acute Heart Failure

(J Am Coll Cardiol 2018;71:1947–57)



# Matchmaking for the Optimization of Heart Failure with Preserved Ejection Fraction Clinical Trials: No Laughing Matter

Sanjiv J. Shah, MD, FACC




*J Am Coll Cardiol.* 2013 October 8; 62(15):

# HFpEF:
# 3 different clinical profiles

## 1) Exercise-induced diastolic dysfunction

ambulatory patients with NYHA class II-III symptoms, impaired LV relaxation (grade I), ~ normal BNP levels

Shah SJ et al. .JACC2013 doi 10.16/j.jacc2013.07.010

# HFpEF:
# 3 different clinical profiles

## 2) Chronic volume overload

patients with NYHA class II-IV with history of hypertension and of HF hospitalisation, elevated BNP, and/or left atrial enlargement

Shah SJ et al. .JACC2013 doi 10.16/j.jacc2013.07.010

# HFpEF:
# 3 different clinical profiles

## 3) Right HF/ pulmonar hypertension

patients with NYHA class III-IV symptoms with evidence of pulmonary vascular disease and/or right ventricular dysfunction

Shah SJ et al. .JACC2013 doi 10.16/j.jacc2013.07.010

# HF-PEF subtypes/clusters

| A | B | C | D | E | F |
|---|---|---|---|---|---|
| 100% men | 96% women | Men or women | 100% women | 100% men | mostly women (77.5%) |
| 65 years | 65 years | 70 years | 73 years | 75 years | 82 years |
| Low rates of Afib, renal disease, valvular disease | low rates of AF, renal dysfunction, and valvular disease | Obesity, DM, CAD, anemia | average rates of DM, hyperlipidemia, obesity, renal insufficiency | lower BMI, +AF +CAD. | lower BMI +AF, valvular disease, renal dysfunction, and anemia. |

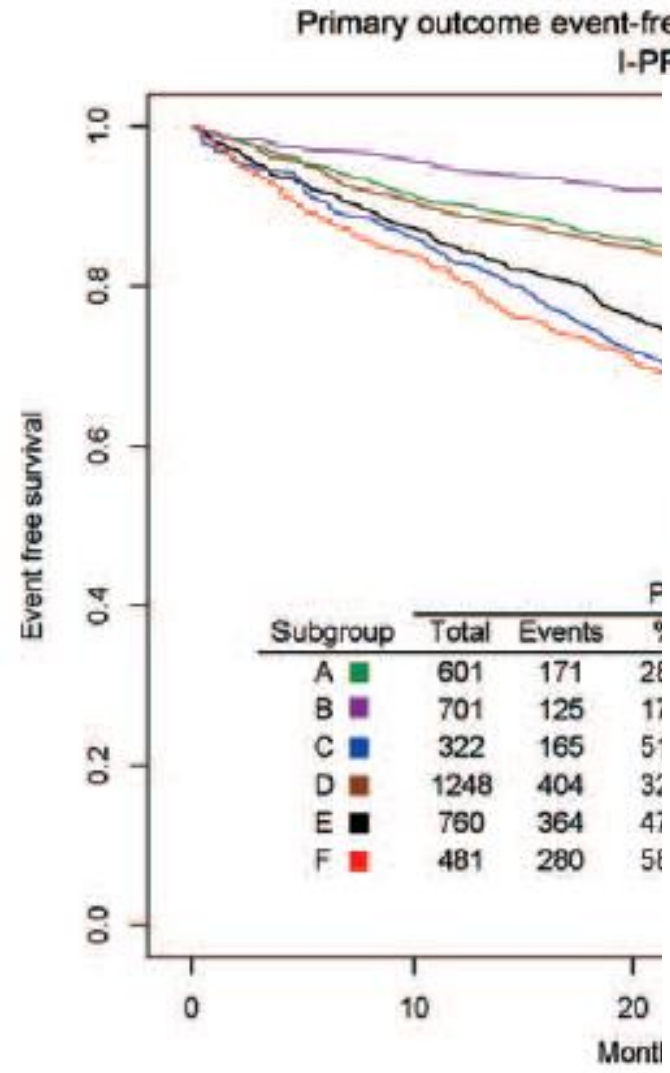
**No difference in symptoms, SBP, BNP across groups**

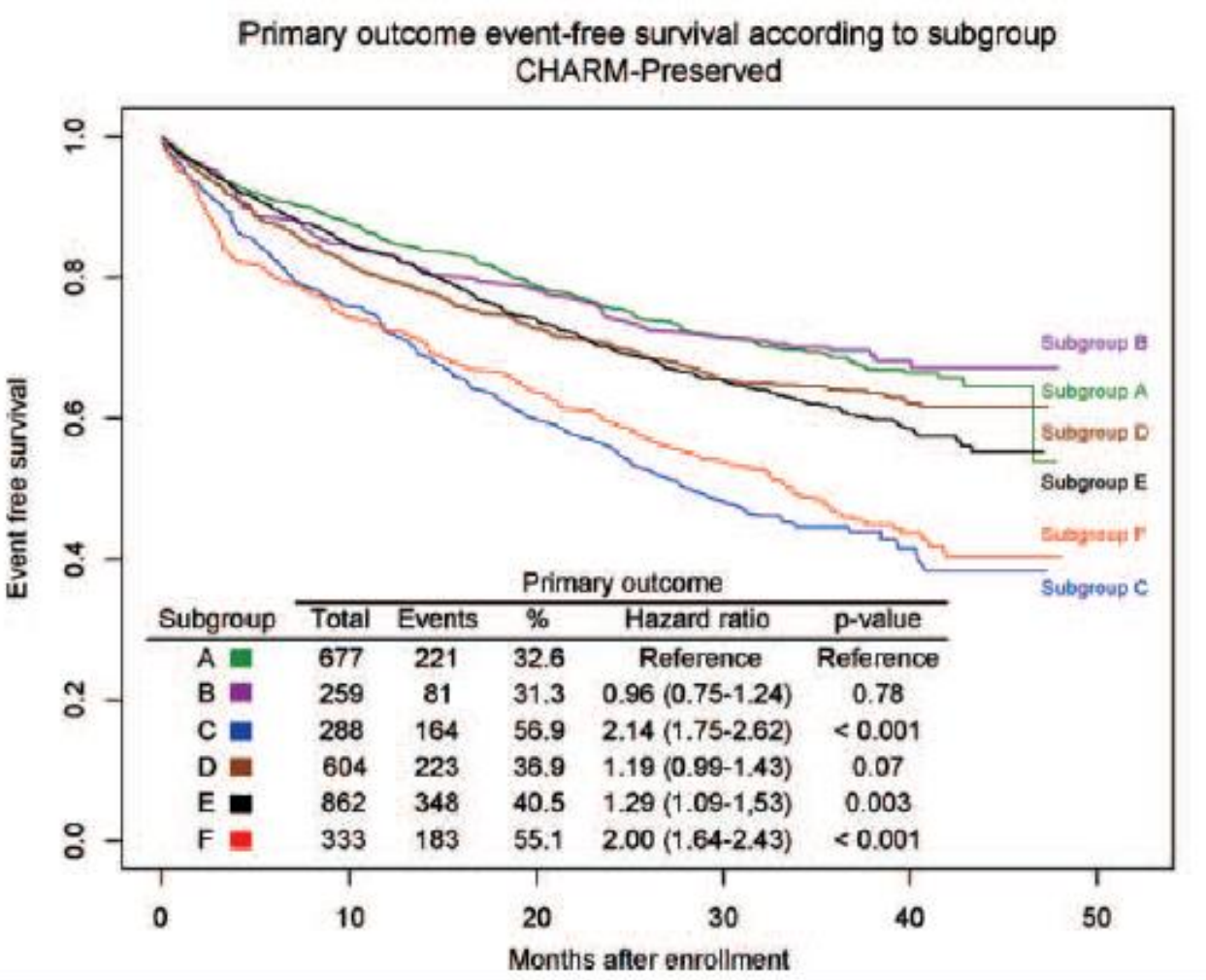
I-PRESERVE, CHARM-P data

Kao, EJHF 2015

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

European Journal of Heart Failure (2015) 17, 925–935



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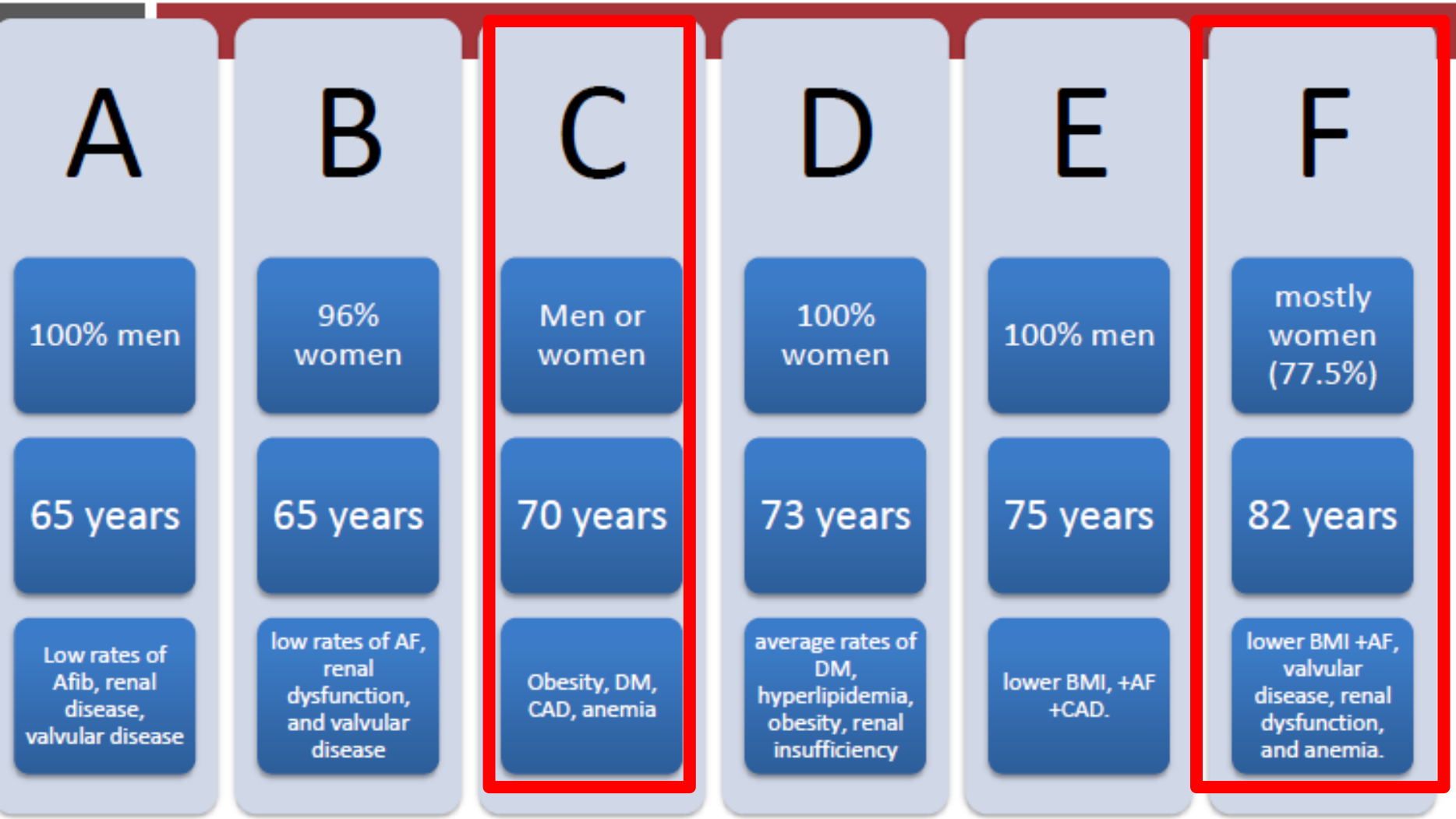


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The two subgroups with the **worst event-free survival** in both studies were characterized by a high prevalence of

- obesity, hyperlipidaemia, diabetes mellitus, anaemia, and renal insufficiency (Subgroup C) and by
- female predominance, advanced age, lower body mass index, and high rates of atrial fibrillation, valvular disease, renal insufficiency, and anaemia (Subgroup F).

# Phenotypic Treatment Strategy

- **Lung Congestion/Metabolic Risk Phenotype**
- **Arterial Hypertension**
- **Renal Dysfunction**
- **Coronary Artery Disease**
- **Chronotropic Incompetence**
- **Pulmonary Hypertension**
- **Skeletal Muscle Weakness**
- **Atrial Fibrillation**

# Lung Congestion/Metabolic Risk Phenotype

- *Diuretics*
- *Caloric Restriction*
- *Statins*
- *Inorganic Nitrite/Nitrate*
- *Sacubitril and Other PKG-Stimulating Drugs*
- *Spironolactone and E-Matrix Modification*

| 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)**<br>• **Caloric restriction**<br>• Statins<br>• Inorganic nitrite/nitrate<br>• Sacubitril<br>• Spironolactone | +Rate adaptive atrial pacing | +Pulmonary vasodilators (e.g. PDE5I) | **+Exercise training program** | +Cardioversion + Rate Control<br>**+Anticoagulation** |
| | +Arterial hypertension | +ACEI/ARB | +ACEI/ARB<br>+Rate adaptive atrial pacing | +ACEI/ARB<br>+Pulmonary vasodilators (e.g. PDE5I) | +ACEI/ARB<br>**+Exercise training program** | +ACEI/ARB<br>+Cardioversion + Rate Control<br>**+Anticoagulation** |
| | +Renal dysfunction | +Ultrafiltration if needed | +Ultrafiltration if needed<br>+Rate adaptive atrial pacing | +Ultrafiltration if needed<br>+Pulmonary vasodilators (e.g. PDE5I) | +Ultrafiltration if needed<br>**+Exercise training program** | +Ultrafiltration if needed<br>+Cardioversion + Rate Control<br>**+Anticoagulation** |
| | +CAD | +ACEI<br>+Revascularization | +ACEI<br>+Revascularization<br>+Rate adaptive atrial pacing | +ACEI<br>+Revascularization<br>+Pulmonary vasodilators (e.g. PDE5I) | +ACEI<br>+Revascularization<br>**+Exercise training program** | +ACEI<br>+Revascularization<br>+Cardioversion + Rate Control<br>**+Anticoagulation** |

The NEW ENGLAND JOURNAL of MEDICINE

# Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction

- Sacubitril–valsartan did not result in a significantly lower rate of total hospitalizations for heart failure and death from cardiovascular causes among patients with heart failure and an ejection fraction of 45% or higher;
- Among 12 prespecified subgroups, there was suggestion of heterogeneity with possible benefit with sacubitril–valsartan in patients with lower ejection fraction and in women.

for the PARAGON-HF Investigators and Committees

DOI: 10.1056/NEJMoa1908655

*Mentre si preparava la cicuta, Socrate stava provando un'aria sul flauto. Gli fu chiesto: a cosa ti servirà visto che devi morire ? Rispose: a imparare l'aria sul flauto prima di morire.*

Platone. Apologia di Socrate