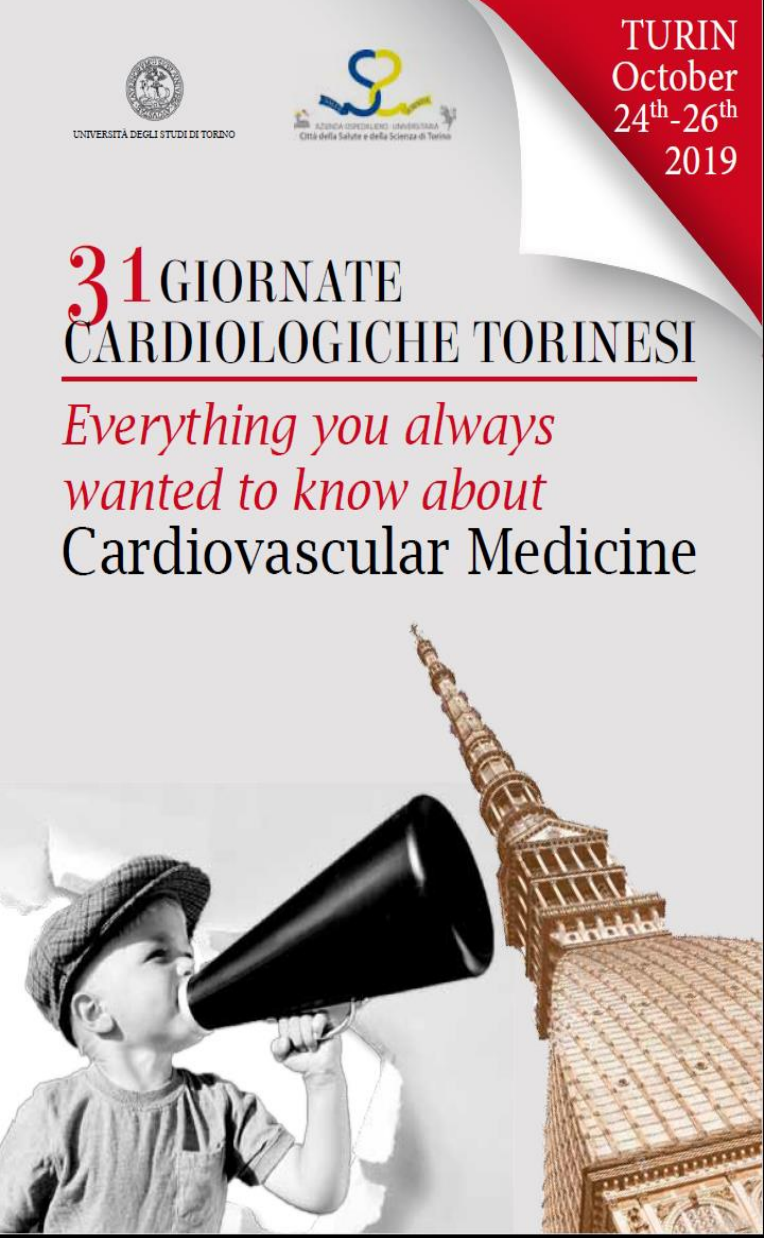



# Red flags for out-of-hospital heart failure diagnosis

**Prof Carlo Lombardi**
**Cattedra di Cardiologia Università e Spedali Civili di Brescia**

# La diagnosi di scompenso cardiaco nelle linee guida ESC

**Table 1 Diagnosis of heart failure**

| |
|---|
| The diagnosis of HF-REF requires three conditions to be satisfied: |
| 1. Symptoms typical of HF |
| 2. Signs typical of HF[a] |
| 3. Reduced LVEF |
| The diagnosis of HF-PEF requires four conditions to be satisfied: |
| 1. Symptoms typical of HF |
| 2. Signs typical of HF[a] |
| 3. Normal or only mildly reduced LVEF and LV not dilated |
| 4. Relevant structural heart disease (LV hypertrophy/LA enlargement) and/or diastolic dysfunction (see Section 4.1.2) |

Authors/Task Force Members et al. Eur Heart J 2012;33:1787-1847

# Terminology of heart failure based on ejection fraction

| 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). |

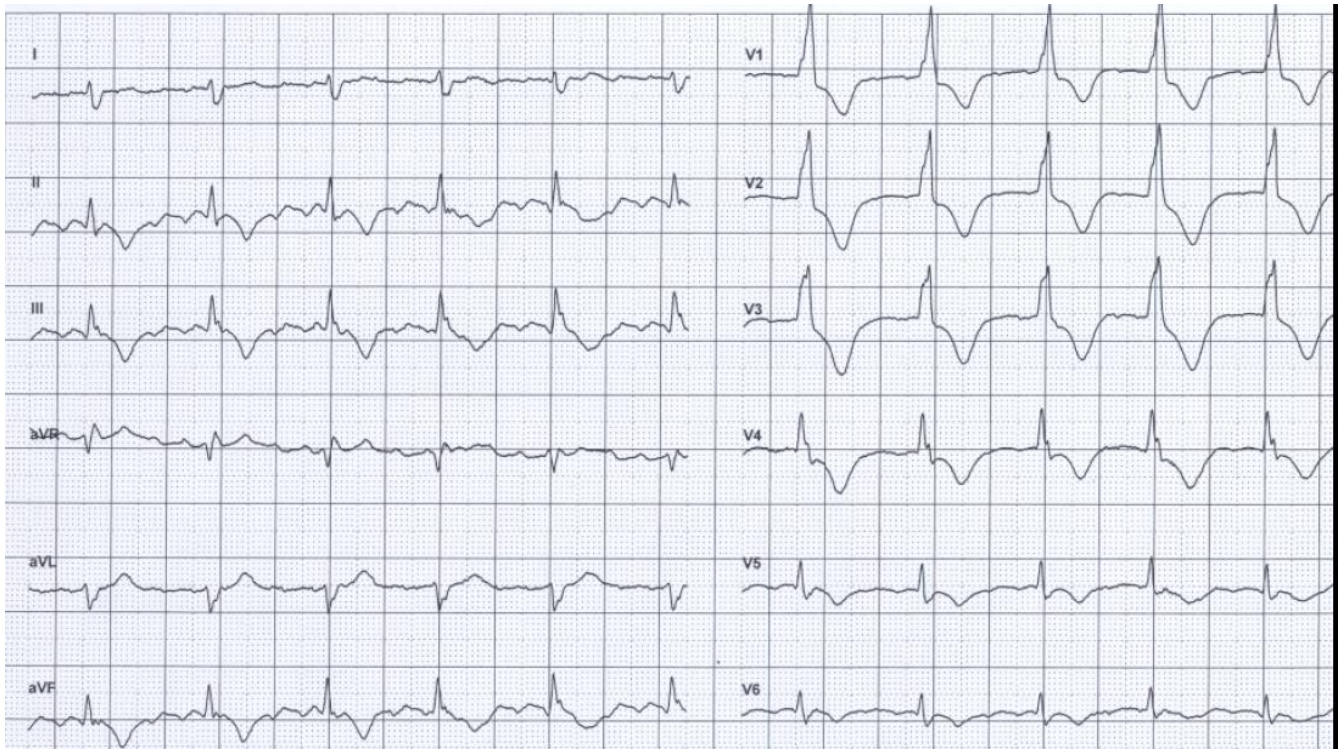
**ESC 2016:** "Signs and symptoms of HF are often non-specific and do not discriminate well between HF and other clinical conditions"

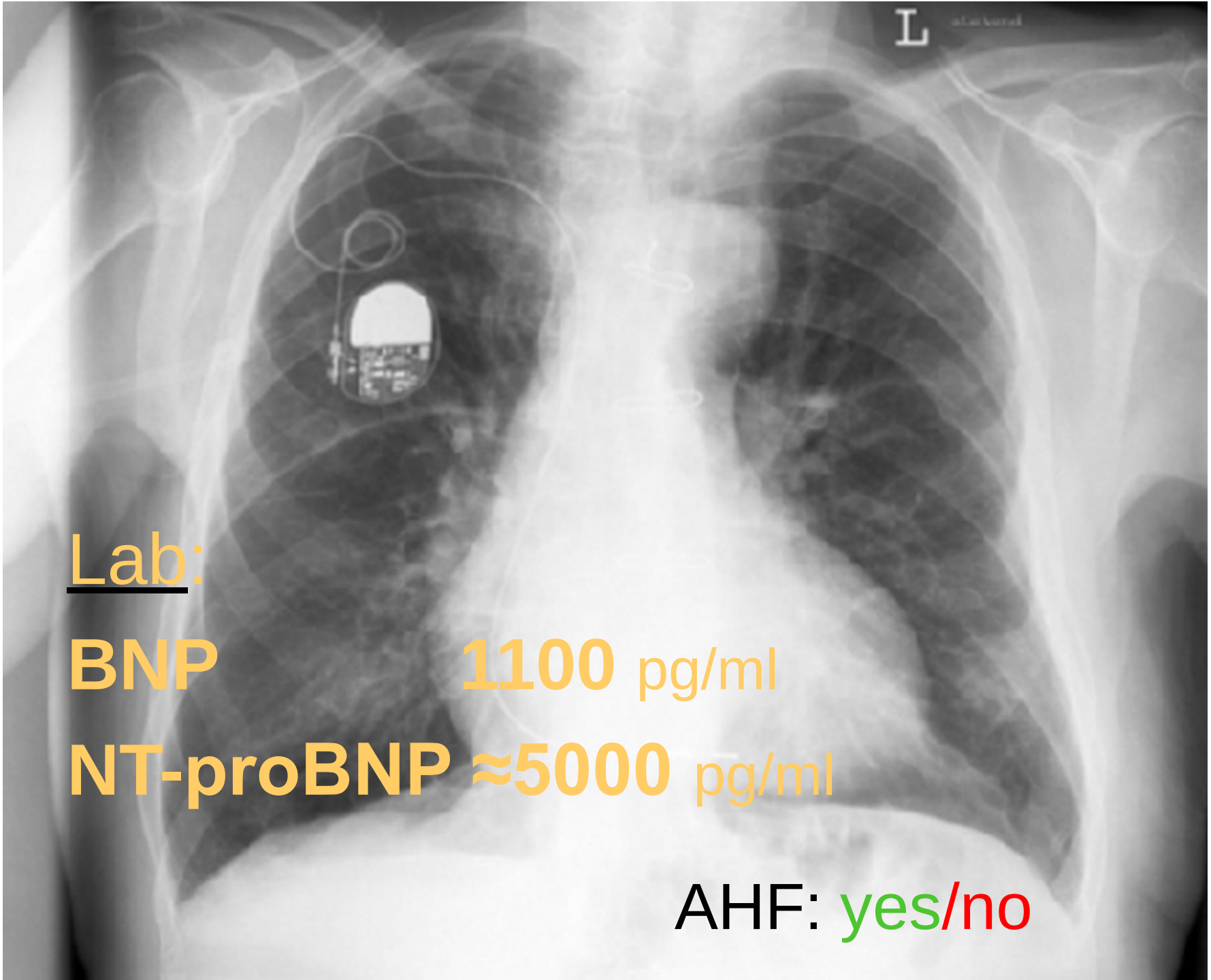
Ponikowski, Voors et al. Eur J Heart Fail 20 MAY 2016 DOI: 10.1002/ejhf.592

# Clinical Case

- **Hystory**: 68y male, CAD, CABG, persistent Afib, VVIR-PM, EF 35%, COPD
- **Acute dyspnea, since 24h**+ coughing, sputum⇧
- Previously: Exertional dyspnea, never at rest
- **Vitals**: RR 26, Temp 38,5°, Puls 60, BP 120/80, **Oxy 94%**
- **Physical:**
  - Tachypnea, no rales, wheezing
  - Neck veins +/-, mild ankle, edema
  - no 3

# ECG




Lab:
BNP 1100 pg/ml
NT-proBNP ≈5000 pg/ml
AHF: yes/no

# Take home messages

**Fever and a systemic infection** are not only common causes of “exacerbated COPD“, but also the most common triggers of AHF

In patients with heart disease an **obstructive auscultation** (wheezing) is equally likely due to pulmonary congestion („cardiac asthma“) vs COPD

**BNP or NT-proBNP** play an important role in the diagnostic evaluation patients with dyspnea whenever HF is included in the differential diagnosis.

| Recommendations | Class [a] | Level [b] |
|---|---|---|
| Upon presentation a measurement of plasma natriuretic peptide level (BNP, NT-proBNP or MR-proANP) is recommended in all patients with acute dyspnoea and suspected AHF to help in the differentiation of AHF from non-cardiac causes of acute dyspnoea. | I | A |

Ponikowski P, et al. Eur Heart J 2016

# NT-pro BNP and BNP

| | Cutoff-points (pg/mL | | | | | |
|---|---|---|---|---|---|---|
| | **NT-proBNP** | | | **BNP** | | |
| | Age <50 | Age 50-75 | Age >75 | Age <50 | Age 50-75 | Age >75 |
| **Acute setting, patient with acute dyspnea** (4, 11) | | | | | | |
| HF unlikely | <300 | | | <100 | | |
| HF possible | 300–450 | 300–900 | 300–1800 | 100–400 | | |
| HF likely | >450 | >900 | >1800 | >400 | | |
| **Non-acute setting, patient with mild symptoms** (2) | | | | | | |
| HF unlikely | <125 | | | <35 | | |
| HF likely | >600 | | | >150 | | |

Mueller C, et al. Eur J Heart Fail 2019

# Terminology of heart failure based on ejection fraction

| Type of HF | | HFrEF | HFmrEF | HFpEF |
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# Heart Failure With a Mid-Range Ejection Fraction

## A Disorder That a Psychiatrist Would Love

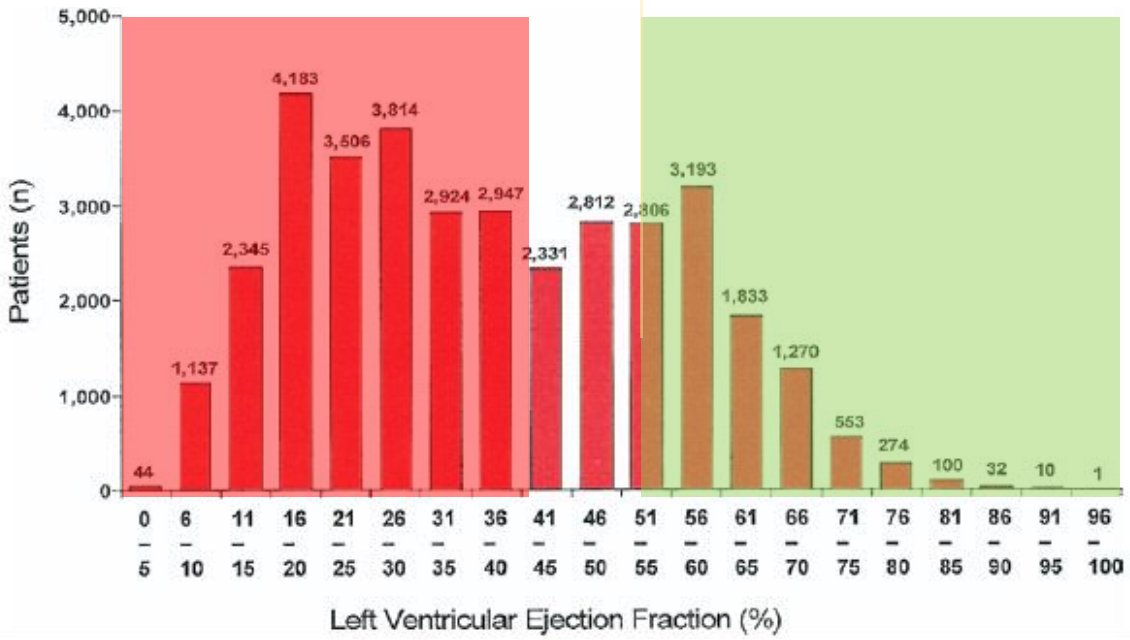
Milton Packer, MD

“This is not a clinical disorder with distinguishable features; it is the artifact of the arbitrary compartmentalization of the numerical values of a very poor biomarker.”

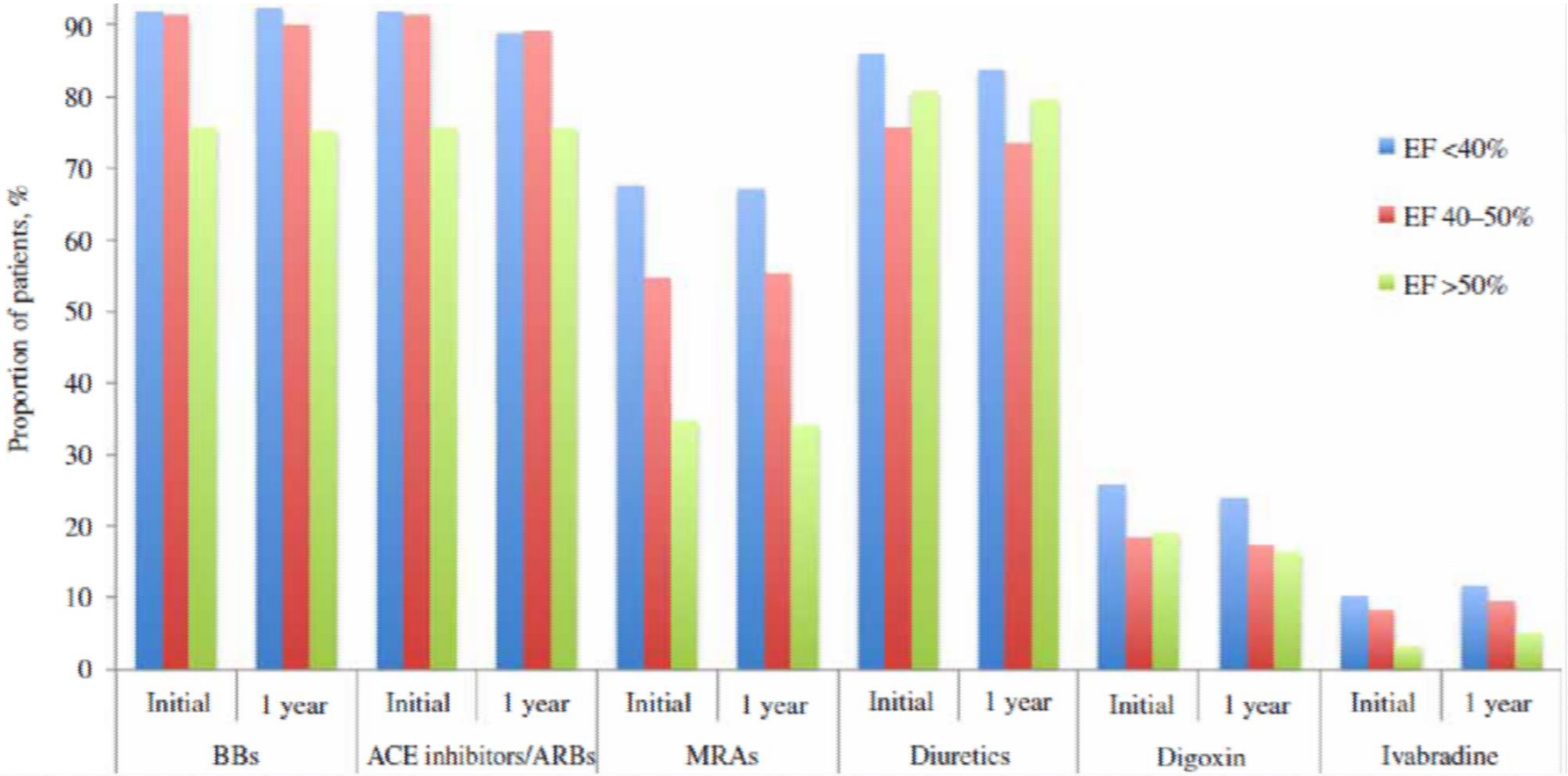
# The Ejection Fraction "Spectrum" of Heart Failure

- Fino al 1985 si parlava solo di "heart failure" – la FE non era parte della diagnosi
- La FE è diventata importante per identificare i pazienti che nei trials clinici avevano avuto un benefico da terapie «innovative»
- "Preserved" è stato associato a tutto ciò che non era "Reduced"
- Diastolic Heart  Failure" –no "evidenced-based" therapy LVEF > 40%
- Ma qualcosa è successo nel 2016 → HFpEF è stato diviso in una nuova categoaria che rappresenta 8%-20%

HFrEF HFpEF HFmrEF



# Management of HFmrEF patients: Real world experience
## Data from ESC HF Registry on 9134 HF patients




Chioncel O et al. Eur J Heart Fail 2017 ;19:1574-85

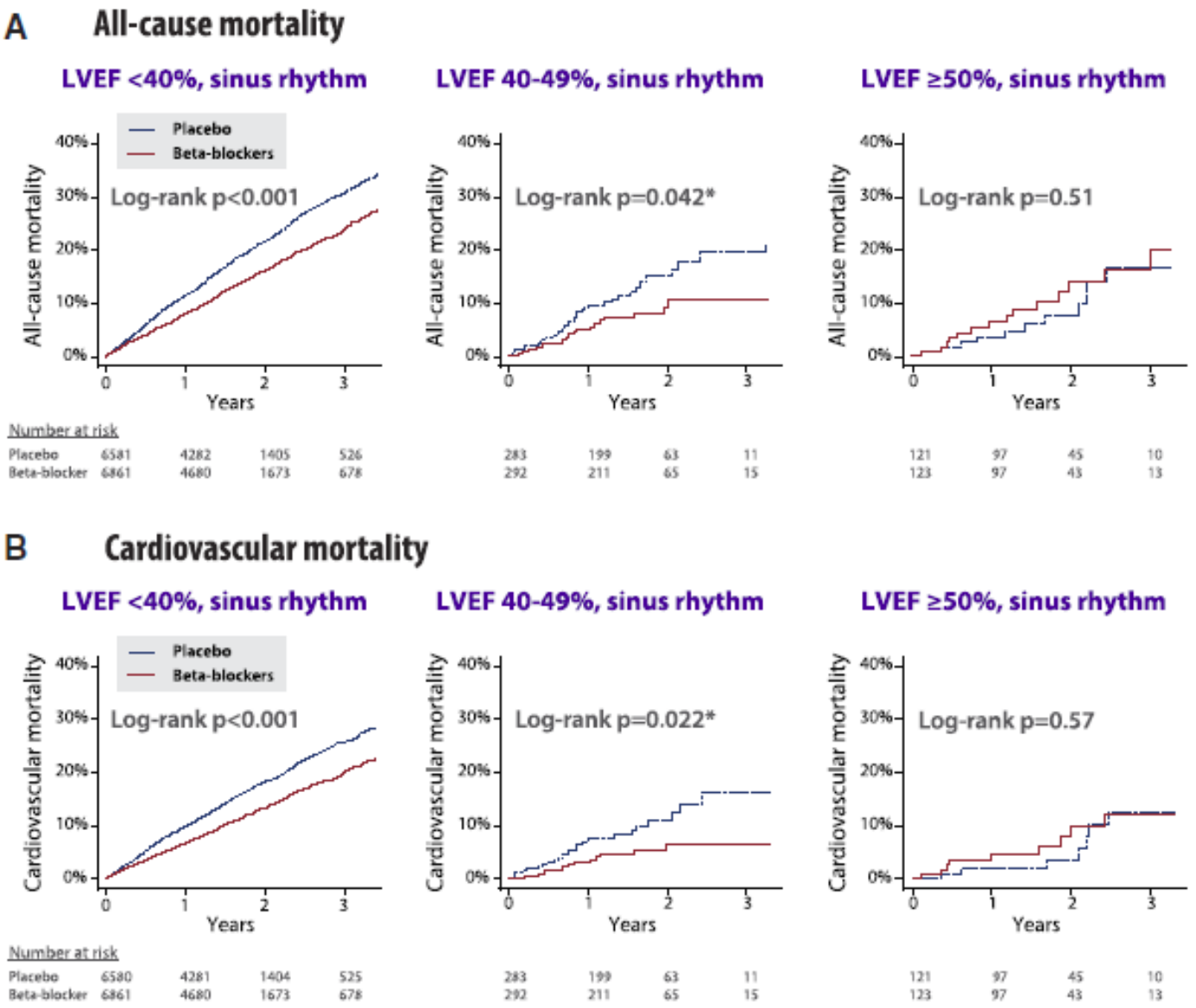
# HFmrEF is similar to HFrEF

**Table 1** Baseline characteristics according to ejection fraction category

| Variable | EF < 40% HFrEF (*n* = 4323, 57%) | EF 40–49% HFmrEF (*n* = 1322, 17%) | EF ≥ 50% HFpEF (*n* = 1953, 26%) | P-value for trend* |
|---|---|---|---|---|
| Candesartan | 2155 (49.8%) | 667 (50.5%) | 980 (50.2%) | 0.77 |
| Clinical | | | | |
| Age, years | 65 ± 11 | 65 ± 11 | 67 ± 11 | 0.001 |
| Female gender | 1116 (25.8%) | 395 (29.9%) | 888 (45.5%) | <0.001 |
| Race | | | | 0.035 |
| European | 3865 (89.4%) | 1237 (93.6%) | 1767 (90.5%) | |
| Black | 194 (4.5%) | 43 (3.3%) | 89 (4.6%) | |
| Other | 264 (6.1%) | 42 (3.2%) | 97 (5.0%) | |
| NYHA class | | | | <0.001 |
| II | 1460 (33.8%) | 763 (57.7%) | 1193 (61.1%) | |
| III | 2713 (62.8%) | 550 (41.6%) | 721 (36.9%) | |
| IV | 150 (3.5%) | 9 (0.7%) | 39 (2.0%) | |
| EF, % | 30 (23–35) | 44 (41–46) | 58 (53–63) | <0.001 |
| BMI, kg/m$^2$ | 27.1 (24.1–30.3) | 27.8 (25.0–31.2) | 28.6 (25.4–32.6) | <0.001 |
| SBP, mmHg | 126 (112–140) | 130 (120–145) | 140 (124–150) | <0.001 |
| DBP, mmHg | 76 (70–80) | 80 (70–85) | 80 (70–85) | <0.001 |
| Physical exam oedema | 968 (22.4%) | 306 (23.2%) | 579 (29.6%) | <0.001 |
| Creatinine, mg/dL | 1.21 ± 0.85 | 1.16 ± 0.43 | 1.11 ± 0.41 | 0.001 |
| HF cause | | | | |
| Ischaemic | 2810 (65.0%) | 885 (66.9%) | 985 (50.4%) | <0.001 |
| Idiopathic | 1017 (23.5%) | 173 (13.1%) | 137 (7.0%) | <0.001 |
| Hypertensive | 275 (6.4%) | 168 (12.7%) | 538 (27.5%) | <0.001 |
| Medical history | | | | |
| Previous HF | 3189 (73.8%) | 926 (70.0%) | 1310 (67.1%) | <0.001 |
| MI | 2520 (58.3%) | 761 (57.6%) | 722 (37.0%) | <0.001 |
| Angina pectoris | 2388 (55.2%) | 813 (61.5%) | 1150 (58.9%) | 0.001 |
| CABG | 1075 (24.9%) | 336 (25.4%) | 380 (19.5%) | <0.001 |
| PCI | 659 (15.2%) | 241 (18.2%) | 328 (16.8%) | 0.06 |
| Stroke | 376 (8.7%) | 123 (9.3%) | 164 (8.4%) | 0.8 |
| DM | 1236 (28.6%) | 378 (28.6%) | 549 (28.1%) | 0.71 |
| Hypertension | 2100 (48.6%) | 743 (56.2%) | 1342 (68.7%) | <0.001 |
| AF | 1132 (26.2%) | 339 (25.6%) | 612 (31.3%) | <0.001 |

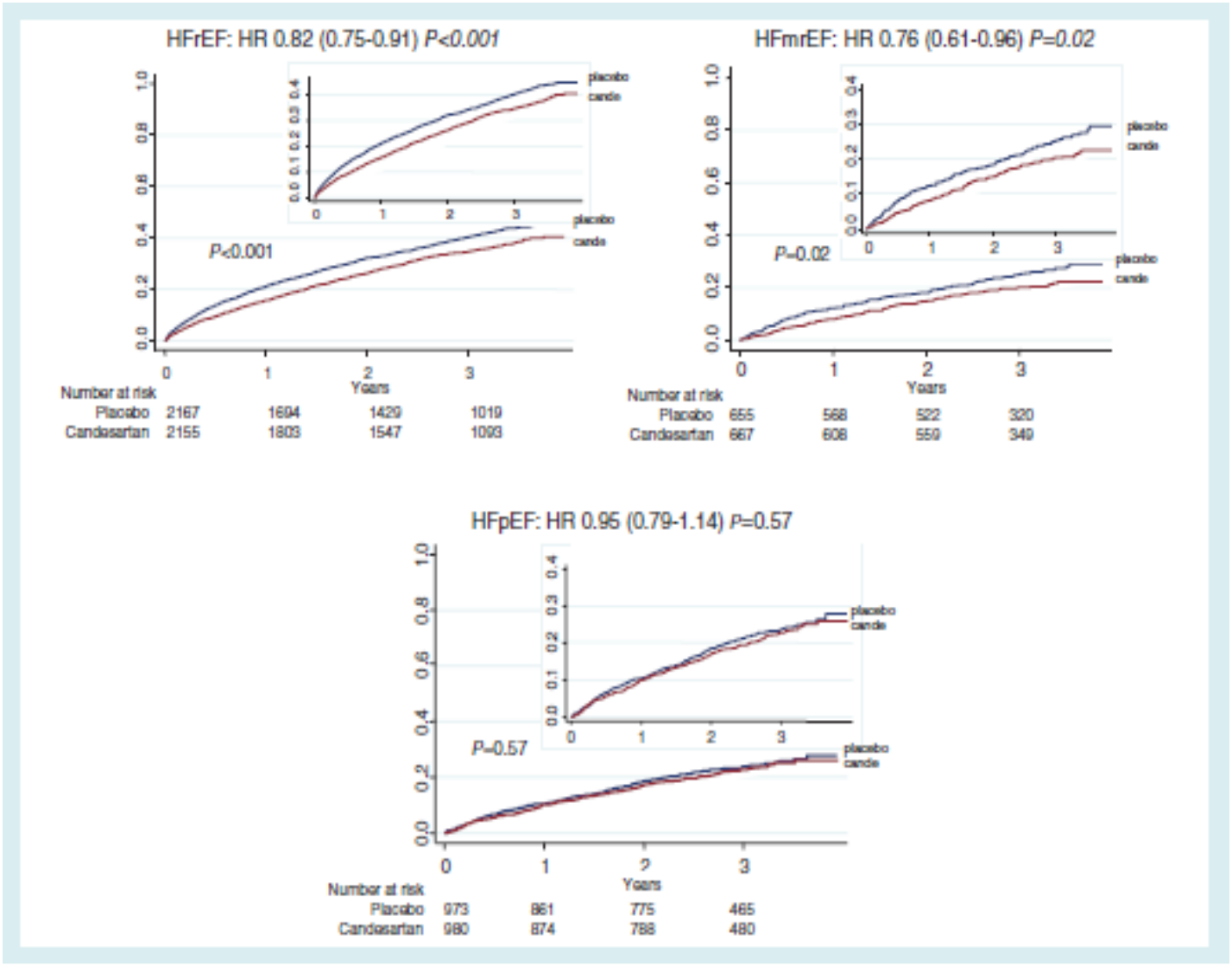
Lund… Solomon, EJHF 2018

# Beta-blockers improve LVEF and prognosis for pts with HF



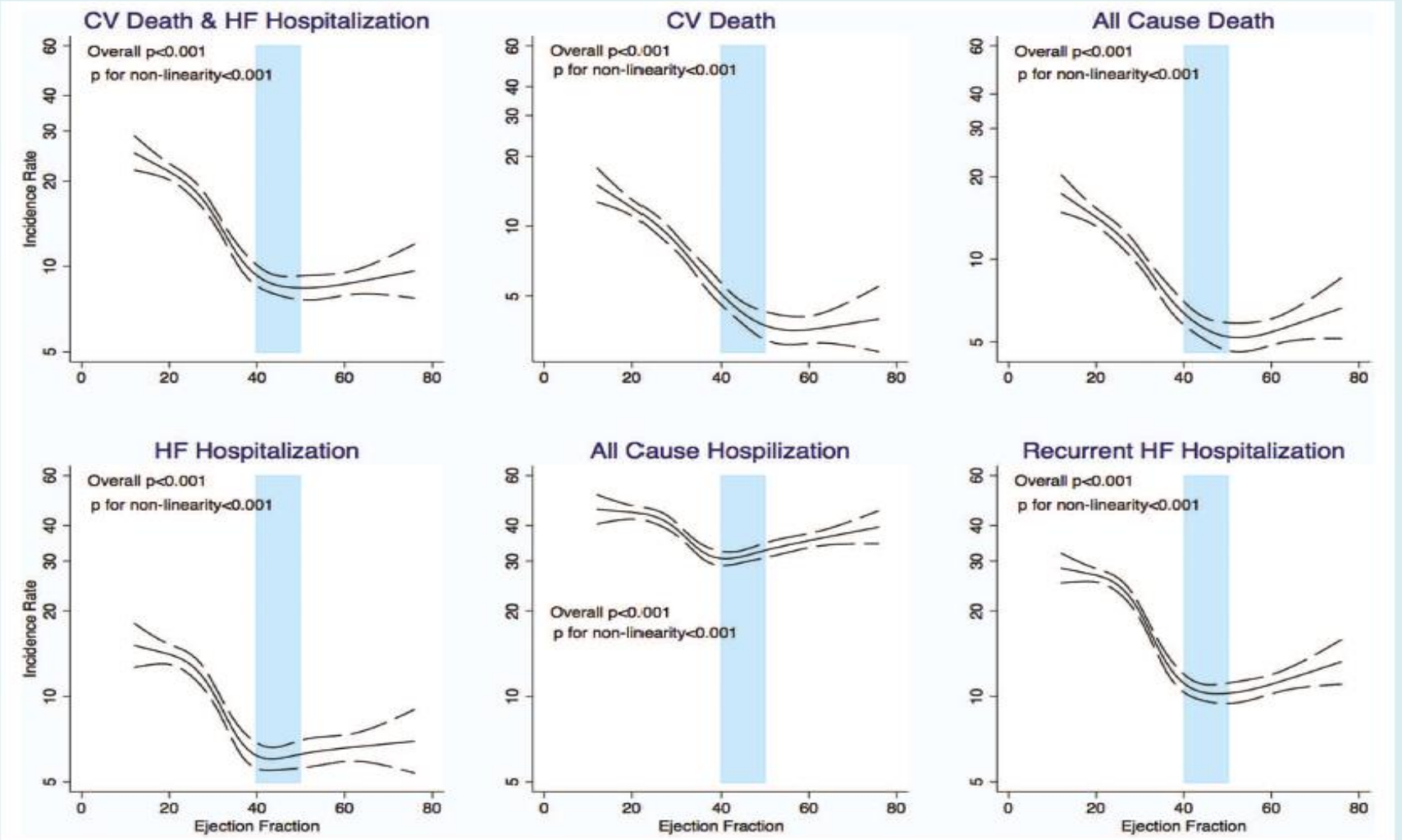

Cleland , et al European Heart Journal (2018) 39, 26–35

# Heart failure with mid-range ejection fraction in CHARM




Lund… Solomon, EJHF 2018

# Association between ejection fraction as a continuous variable and outcomes




Lund… Solomon, EJHF 2018

# HFmrEF è una sindrome diversa da HFpEF ma simile HFrEF

HFmrEF è una categoria distinta : SI

- Se utilizziamo la FE per «categorizzare» i pazienti

E’ simile a HFrEF: SI

- Caratteristiche cliniche simili
- Prognosi simile ma non uguale (leggermente migliore)
- Efficacia del trattamento con farmaci HFrEF

# Tutta colpa della FE?

- Parametro conosciuto da tutti i medici
- E’ accettata per definire la diagnosi di SC ed anche la prognosi
- Determina più di ogni altra cosa le decisioni terapiche
- Continua ad essere utilizzata nei trials

# Terminology of heart failure based on ejection fraction

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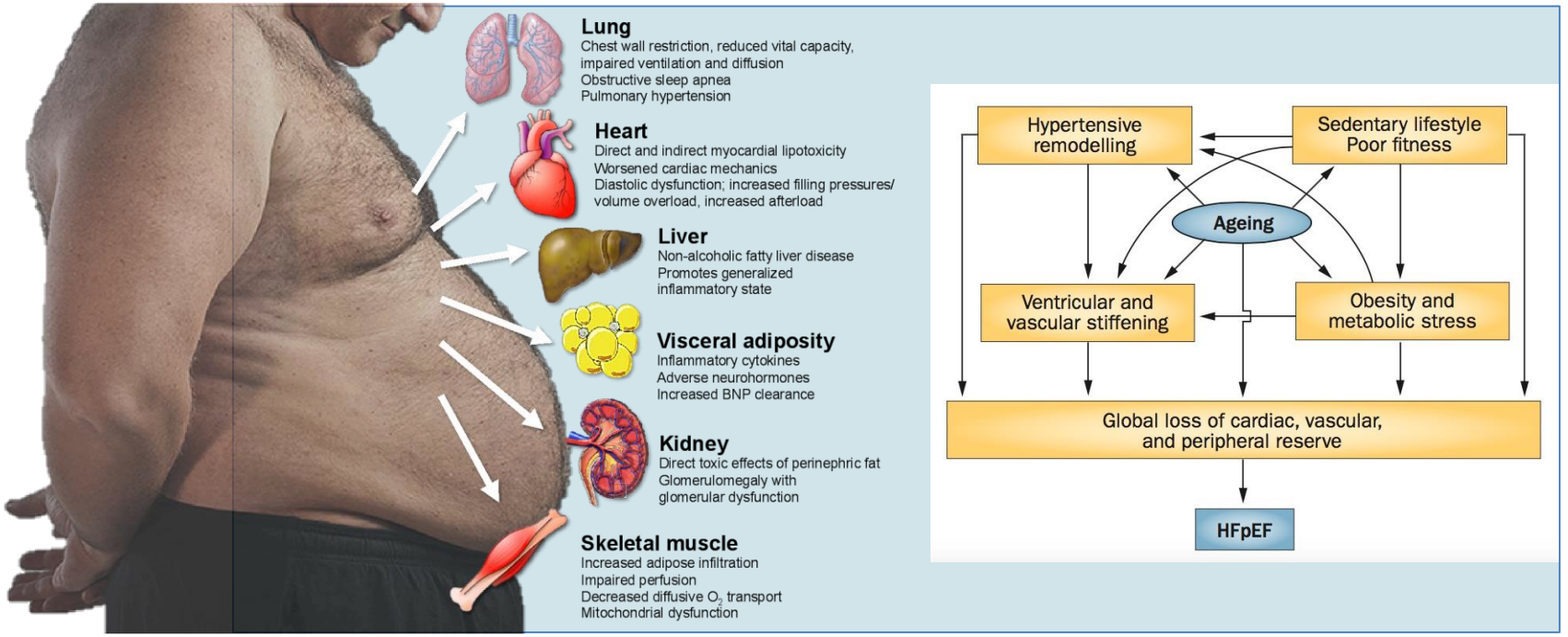
**ESC 2016:** "Signs and symptoms of HF are often non-specific and do not discriminate well between HF and other clinical conditions"

Ponikowski, Voors et al. Eur J Heart Fail 20 MAY 2016 DOI: 10.1002/ejhf.592

# Defining “HFpEF” in 2019

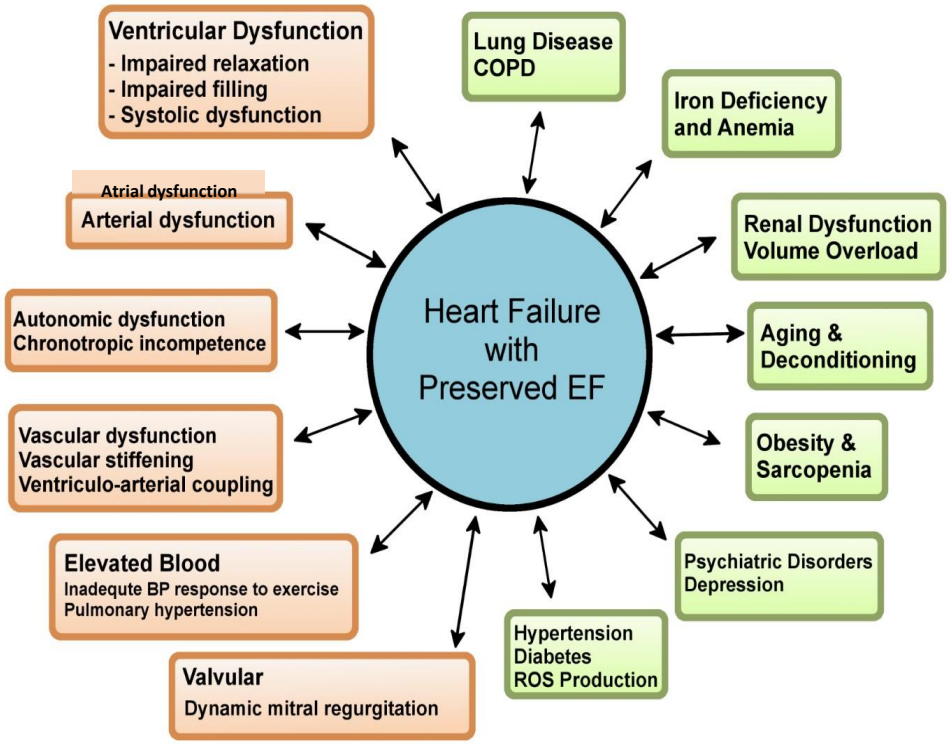



*Kitzman D, Shah SJ. JACC 2016; Borlaug B. Nat Rev Cardiol*

# ESC 2016: Who Are These Patients?

**Typical demographics and comorbidities associated with HFpEF**

| |
|---|
| Advanced age |
| Arterial hypertension |
| Atrial fibrillation |
| Female gender |
| Kidney dysfunction |
| Metabolic syndrome |
| Obesity |
| Physical deconditioning |
| Pulmonary disease (e.g. COPD) |
| Pulmonary hypertension |
| Sleep apnoea |




Ponikowski P, et al. Eur Heart J 2016; 37:2129–200. Supplementary Appendix;
Senni M,..Pieske B, Eur Heart J 2014; 35:2797–811.

# HFpEF challenges

- Rising prevalence
- High morbidity & mortality
- Multiple pathophysiologic contributors
- Few available therapies
- *Need new solutions: Diagnostic and therapeutic*

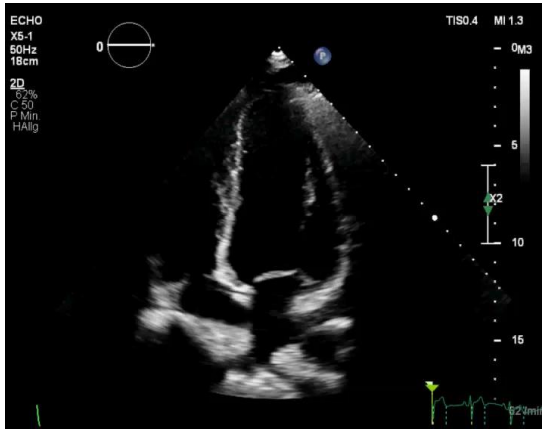
# ESC 2016 Key Diagnostic HFpEF Criteria

| | |
|---|---|
| **“Preserved” EF:** | ≥50% |
| **Structural alterations:** | LAVI >34 ml/m$^2$ or LVMI ≥115 (males)/ ≥95 (females) mg/m$^2$ |
| **Functional alterations:** | E/é ≥13<br>é (mean septal and lateral) <9 cm/s |
| **NT-proBNP:** | >125 pg/ml or (SR; increase with AF!) |
| **BNP:** | >35 pg/ml |

Ponikowski P, et al. Eur Heart J 2016; 37:2129–200.

# Echocardiography in Heart Failure

## Normal Heart

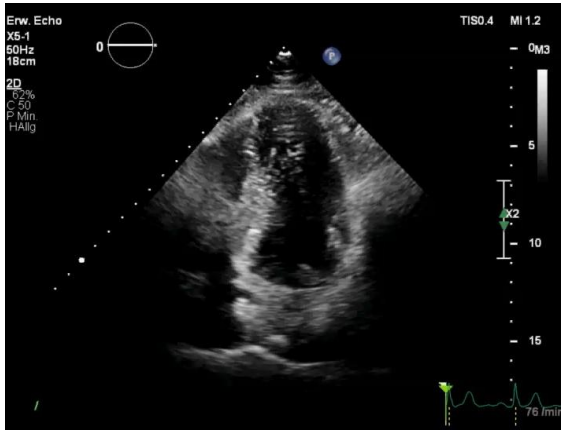



- Normal pump function
- Normal LV size
- Normal atria

## HF with reduced EF


- Reduced pump function
- Dilated LV
- Enlarged atria

## Patient with suspected HFpEF



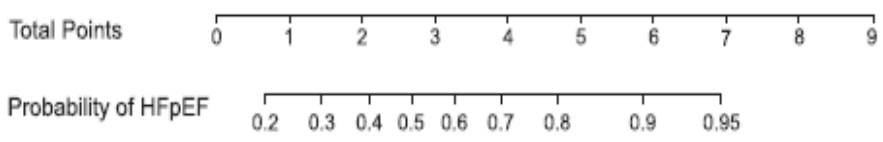

- Normal pump function
- Normal LV size
- LVH, Enlarged atria

# HFpEF diagnosis: A score approach

**Table 3. Multivariable Predictors of HFpEF**

| | OR (95% CI) | β Estimate | *P* Value |
|---|---|---|---|
| Multivariable model (AICc, 393.72; AUC, 0.854; *P*<0.0001) | | | |
| Atrial fibrillation | 4.59 (1.84–13.22) | 1.52 | 0.0007 |
| Body mass index >30 kg/m² | 2.90 (1.68–5.09) | 1.07 | 0.0001 |
| Age >60 y | 2.12 (1.12–3.82) | 0.75 | 0.01 |
| Treatment with ≥2 antihypertensives | 1.78 (1.04–3.02) | 0.58 | 0.03 |
| E/e' ratio >9 | 1.87 (1.07–3.26) | 0.63 | 0.03 |
| Pulmonary artery systolic pressure >35 mm Hg | 1.74 (0.92–3.35) | 0.55 | 0.09 |
| Diabetes mellitus or prediabetes | 1.67 (0.97–2.87) | 0.51 | 0.06 |
| LA volume index >30 mL/m² | 1.59 (0.88–2.88) | 0.47 | 0.1 |
| Chronic kidney disease stage 3 or greater | 1.46 (0.66–3.30) | 0.37 | 0.4 |
| NT-proBNP >275 pg/mL | 1.26 (0.66–2.41) | 0.23 | 0.5 |
| $H_2$FPEF score (AICc, 393.36; AUC, 0.841; *P*<0.0001) | | | |
| Body mass index >30 kg/m² | 3.10 (1.85–5.18) | 1.13 (Score 2) | <0.0001 |
| Atrial fibrillation | 5.78 (2.28–14.62) | 1.75 (Score 3) | <0.0001 |
| Age >60 y | 2.83 (1.65–4.84) | 1.04 (Score 1) | 0.0001 |
| Treatment with ≥2 antihypertensives | 1.99 (1.18–3.33) | 0.69 (Score 1) | 0.01 |
| E/e' >9 | 2.15 (1.27–3.67) | 0.77 (Score 1) | 0.005 |
| Pulmonary artery systolic pressure >35 mm Hg | 2.05 (1.11–3.78) | 0.72 (Score 1) | 0.02 |

| | Clinical Variable | Values | Points |
|---|---|---|---|
| $H_2$ | Heavy | Body mass index > 30 kg/m² | 2 |
| | Hypertensive | 2 or more antihypertensive medicines | 1 |
| F | Atrial Fibrillation | Paroxysmal or Persistent | 3 |
| P | Pulmonary Hypertension | Doppler Echocardiographic estimated Pulmonary Artery Systolic Pressure > 35 mmHg | 1 |
| E | Elder | Age > 60 years | 1 |
| F | Filling Pressure | Doppler Echocardiographic E/e' > 9 | 1 |
| $H_2$FPEF score | | | Sum (0-9) |



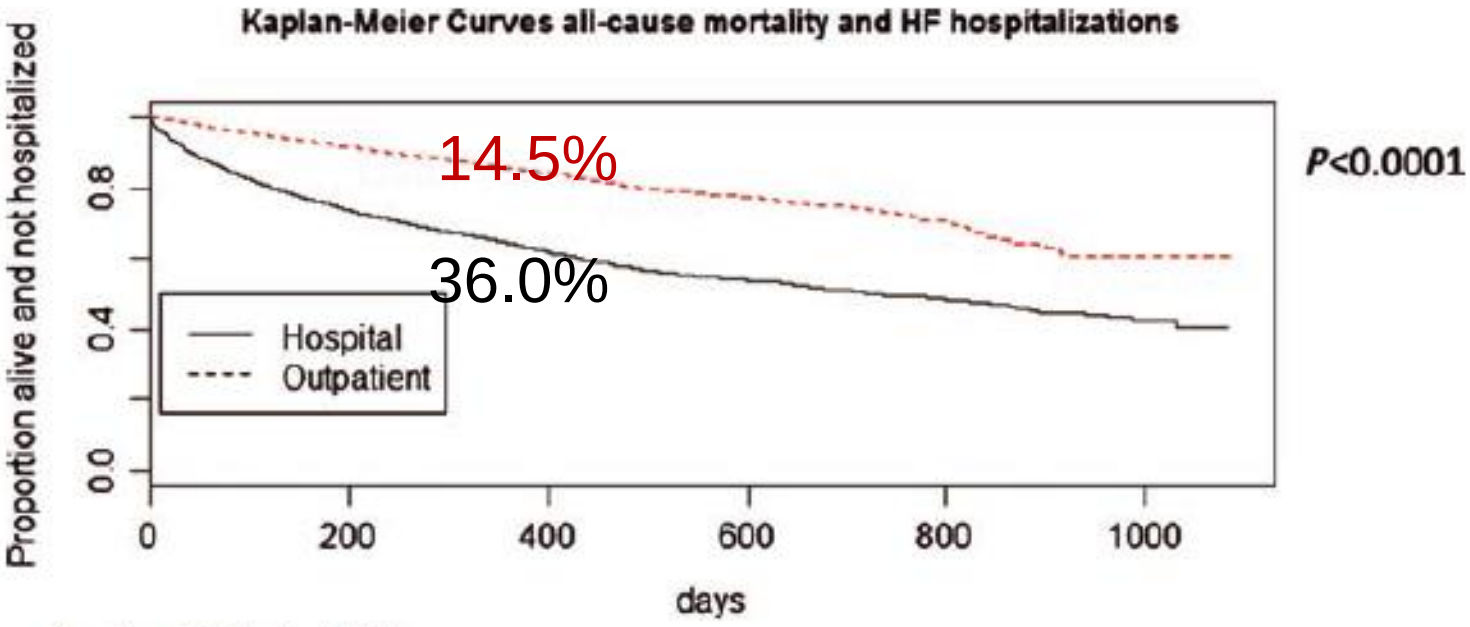

*Reddy Y et al., Circulation 2018;138:861-870*

# Objective demonstration of structural and/or functional alterations as the underlying cause for the clinical presentation

| Alterations | Cut-off values |
|---|---|
| Structural | |
| Left atrial volume index | > 34 mL/$m^2$ |
| Left ventricular mass index | > 115 g/$m^2$ males<br>> 95 g/$m^2$ females |
| Functional | |
| E/e’ | ≥ 13 |
| Mean e’ septal and lateral wall | < 9 cm/s |

Ponikowski, Voors et al. Eur J Heart Fail 20 MAY 2016 DOI: 10.1002/ejhf.592

# All-cause mortality and HF-hospitalizations in the European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT)



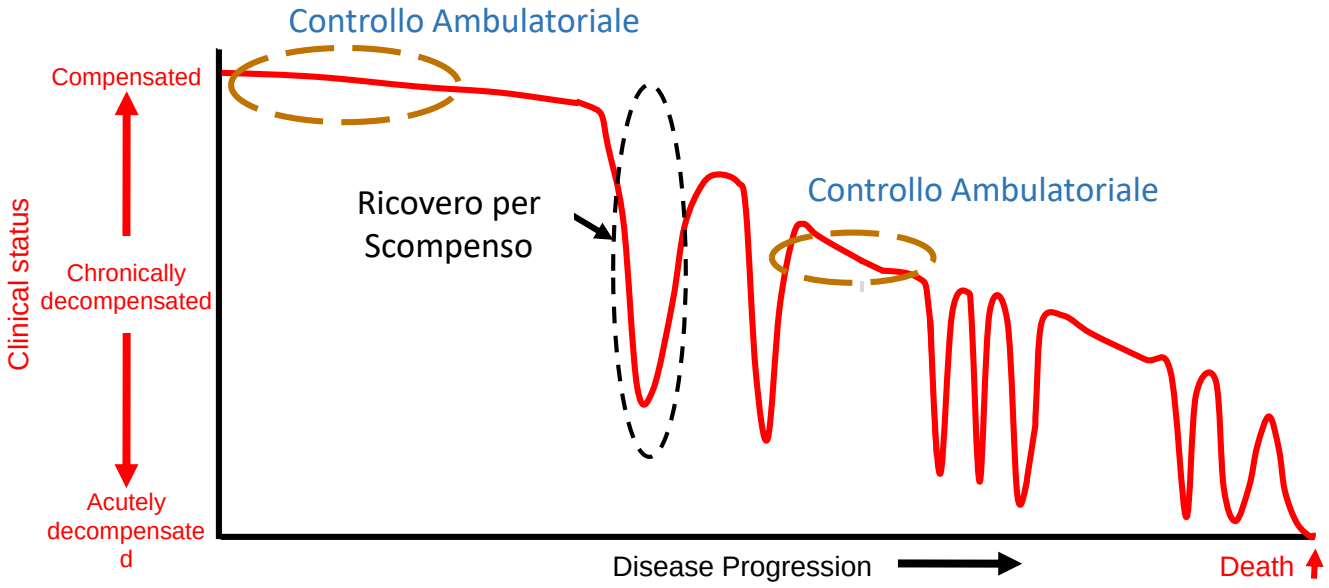

Number of Patients at Risk:

| | | | | | | |
|---|---|---|---|---|---|---|
| Hospital | 4958 | 3369 | 1457 | 708 | 336 | 52 |
| Outpatient | 7378 | 6513 | 2221 | 684 | 242 | 67 |

Crespo-Leiro et al. Eur J Heart Fail 2016; 18:613-62

# HF è una sindrome progressiva, caratterizzata da diverse situazioni cliniche:

**- apparente stabilità sintomatologica (visita di controllo ambulatoriale)**




Adapted from Gheorghiade et al. 2005[2]

HF, heart failure



1. Ahmed et al. Am Heart J 2006;151:444–50; 2. Gheorghiade et al. Am J Cardiol 2005;96:11G–17G; 3. Gheorghiade, Pang. J Am Coll Cardiol 2009;53:557–73; 4. Holland et al. J Card Fail 2010;16:150–6; 5. Muntwyler et al. Eur Heart J 2002;23:1861–6; 6. McCullough et al. J Am Coll Cardiol 2002;39:60–9; 7. McMurray JJ. et al. Eur Heart J. 2012;33(14):1787–1847