# Insuffisance Cardiaque à Fonction Préservée: Mythe ou Réalité?

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La Trahison des Images, René Magritte, 1929

JOURNEE DE FORMATION CONTINUE POSTUNIVERSITAIRE
ECU-UCL / ALFORMEC

# Plan

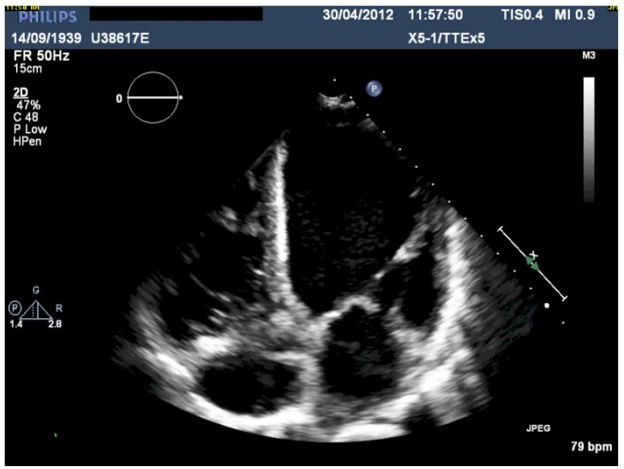
- Introduction
- Physiopathologie
- Mythes & Réalités
- Conclusion

# Introduction

# Définition de l'Insuffisance Cardiaque

L'insuffisance cardiaque (IC) est un syndrome clinique caractérisé par

- Un ensemble de symptômes et de signes typiques d'IC
- Des évidences objectives d'anomalies structurelles ou fonctionnelles du cœur au repos



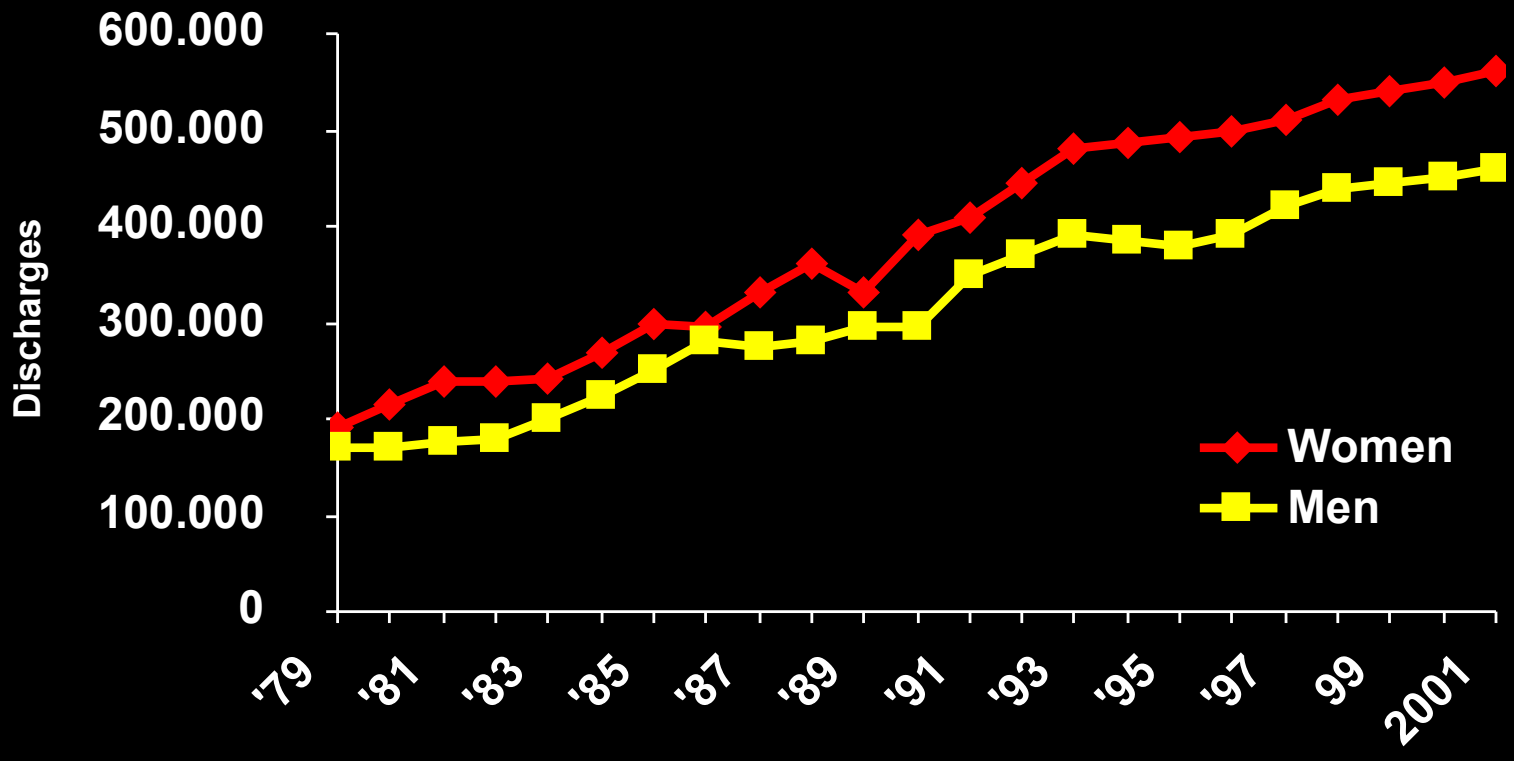
# Problème de Santé Publique Majeur!

| Prevalence Monde | Prévalence Belgique | Incidence Belgique | Hospitalisation USA | Coût USA |
|---|---|---|---|---|
| 26,000,000 | 200,000 | 15,000/an | 1,100,000 | $39 billion |

- La prévalence a doublé sur les 25 dernières années
- Patients fréquemment hospitalisés: >25% des patients sont réadmis dans les 30 jours, 65% la 1lère année
- Mortalité importante

[1] American Heart Association. 2014 Heart and Stroke Statistical Update. Dallas, Tex: American Heart Association; 2004.
[2] Hunt SA et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult. 2005.

# Augmentation des Hospitalisations



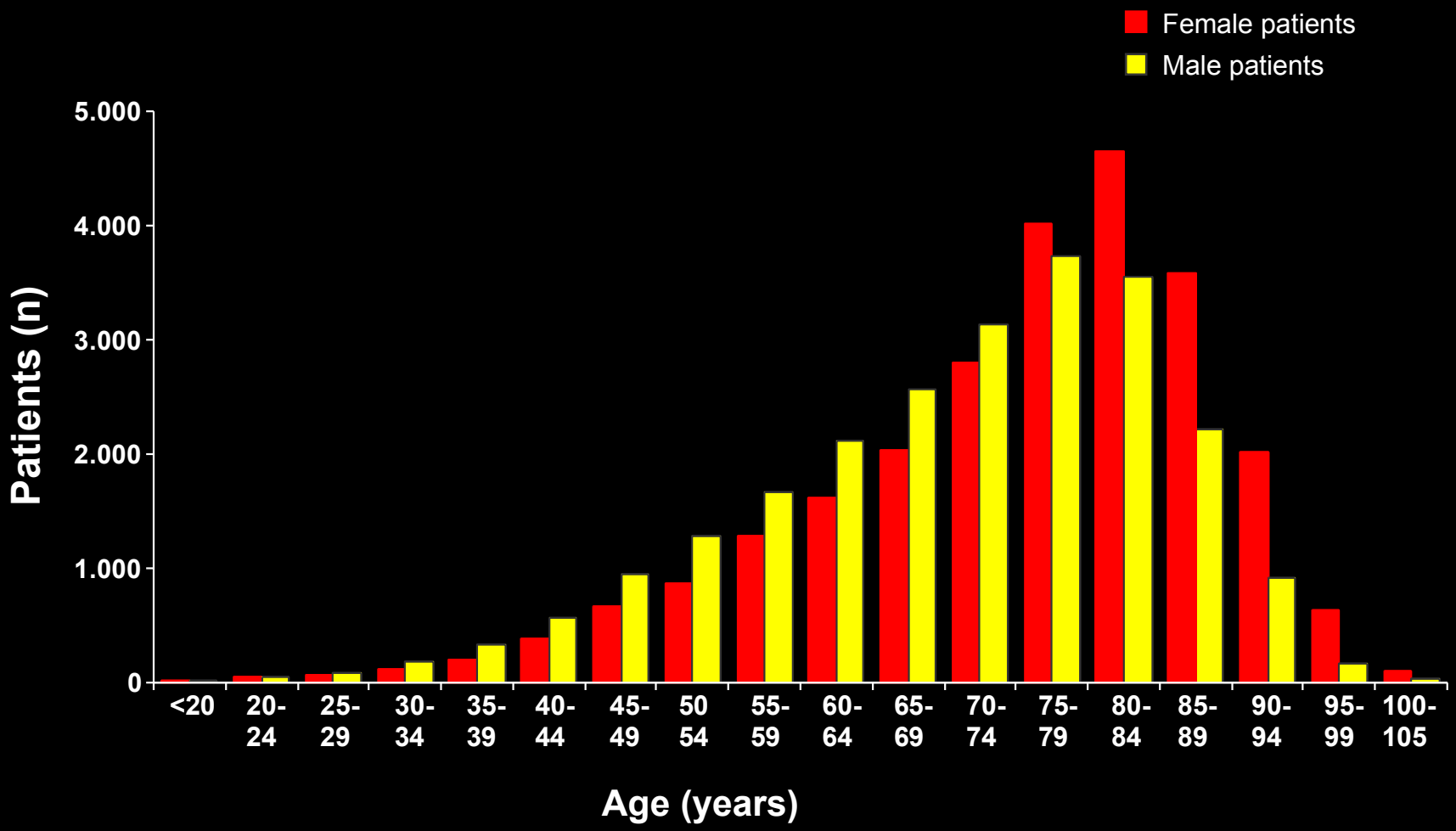

CDC/NCHS: Hospital discharges include patients both living and dead.

AHA, 1998 Heart and Stroke Statistical Update

NCHS, National Center for Health Statistics

AHA Heart and Stroke Statistical Update 2006

# Distribution des Patients Hospitalisés pour IC selon l'Age et le Sexe



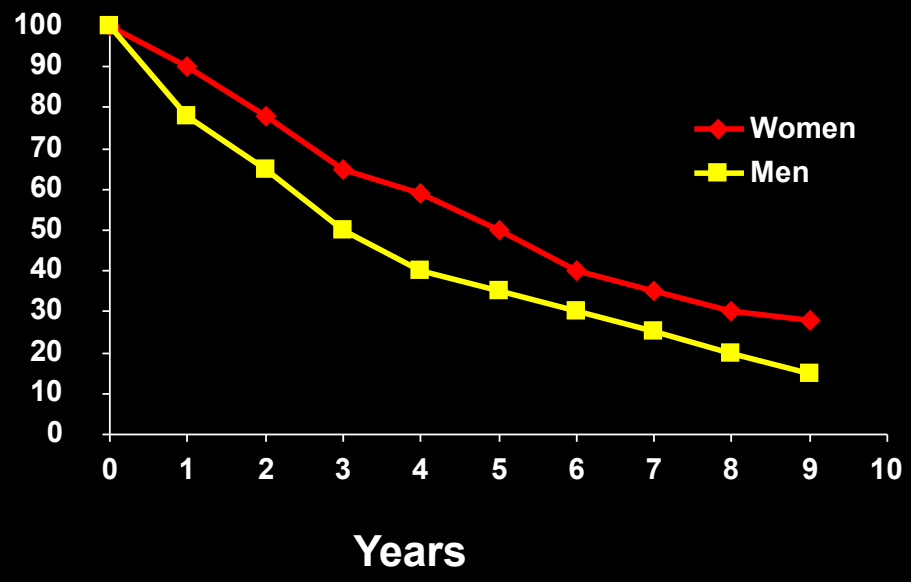

Fonarow G, et al. *J Am Coll Cardiol*. 2005;45:339A. Poster presented at ACC 2005. Fonarow G, et al. *J Am Coll Cardiol*. 2005;45:340A. Poster presented at ACC 2005.

# Pronostic

**Mortalité globale +/- 50% à 5 ans**

**Mortalité à 1 an de patients hospitalisés:**

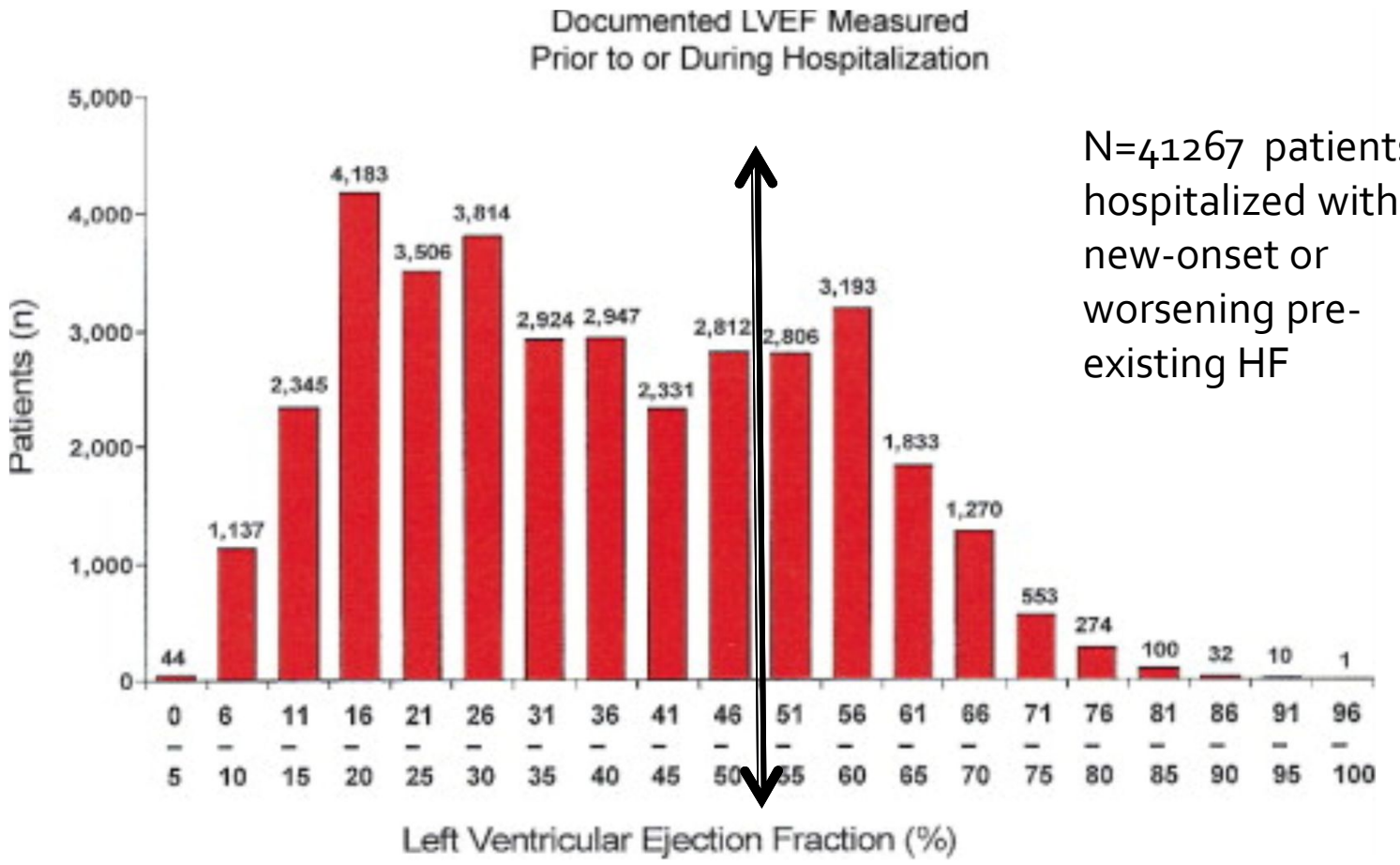
- **NYHA I à II: 10-20%**
- **NYHA III à IV: 40-60%**




Survival after the onset of congestive heart failure in Framingham Heart Study subjects

Ho Circulation 1993;88:107-115

# Tous les Patients Identiques?




N=41267 patients hospitalized with new-onset or worsening pre-existing HF

OPTIMIZE-HF, J Am Coll Cardiol. 2007; 50(8): 768-777

# Distribution Bimodale

**Community cohort of 1233 incident HF patients diagnosed from 1984 to 2009 in Olmsted County, Minnesota**

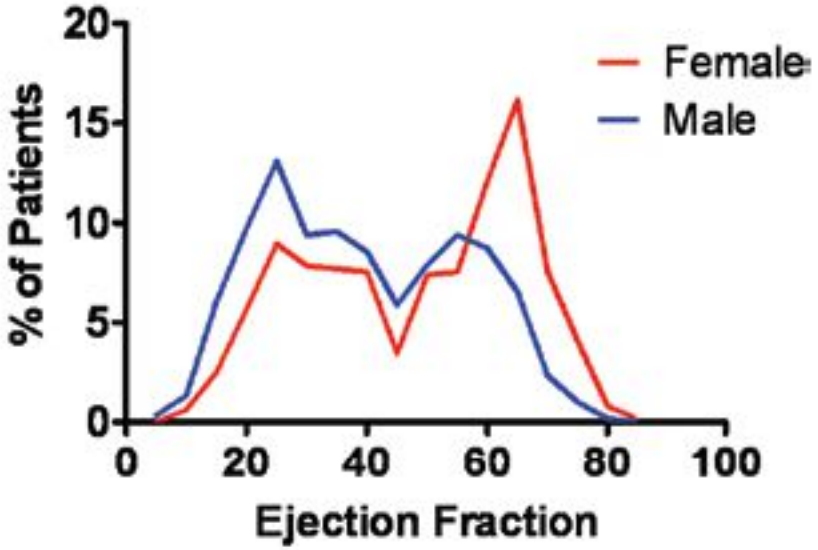
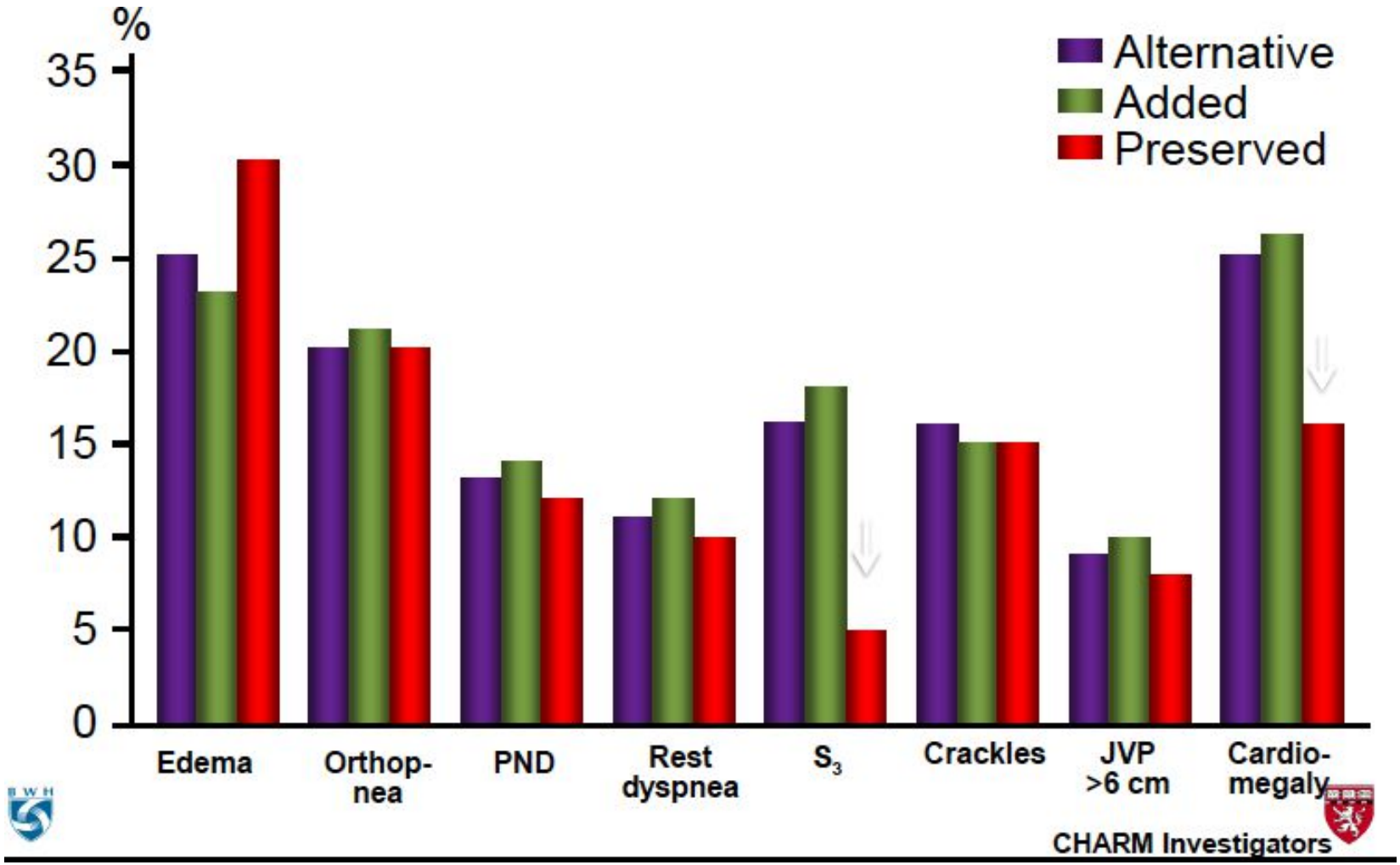



**Figure 1.** Distribution of ejection fraction (EF) at baseline. The distribution of EF (%) at incident heart failure (HF) diagnosis is shown for the 1233 HF patients.

Redfield, Circ Heart Fail. 2012;5:720-726

# Symptômes et signes (1)
# Identiques



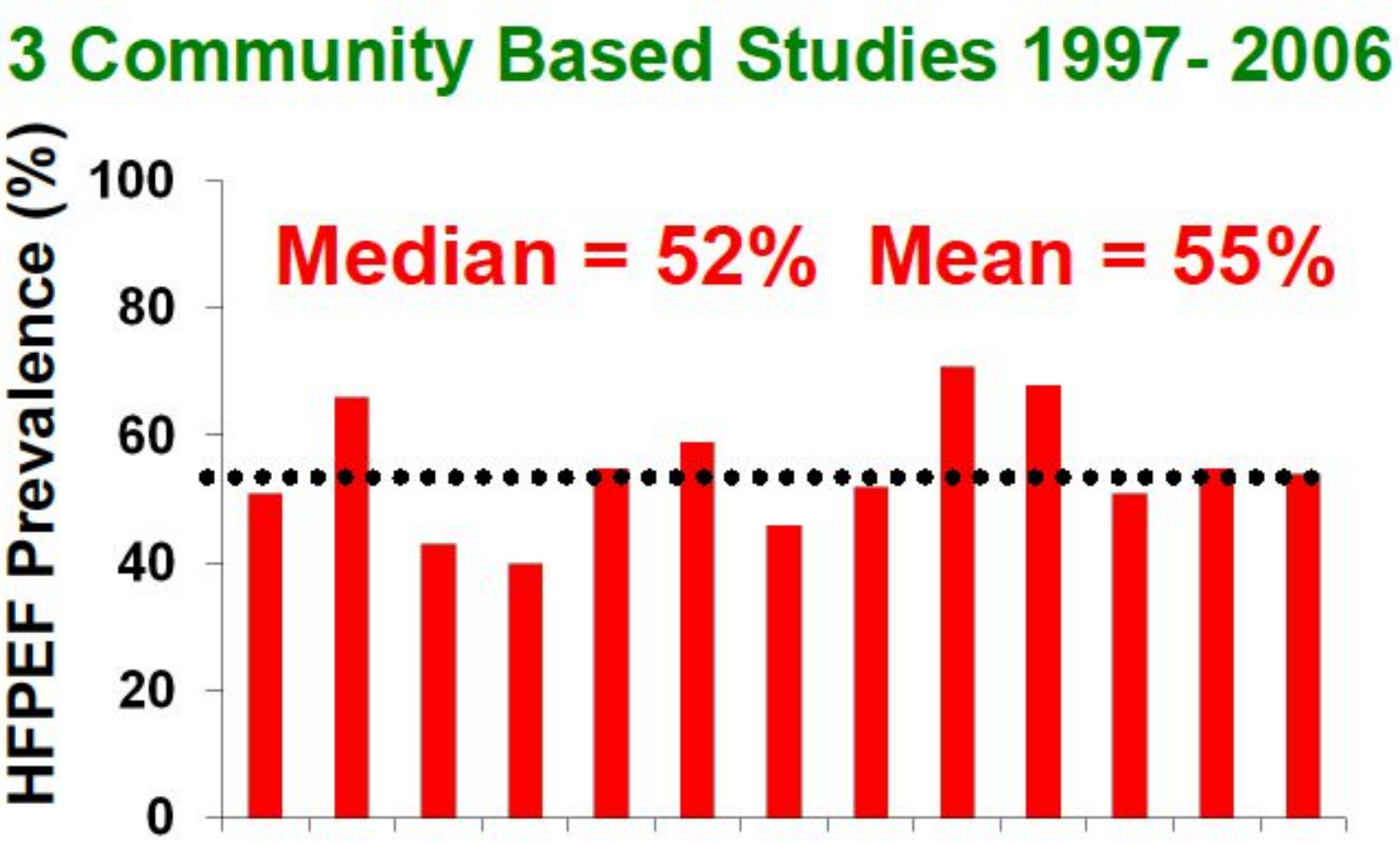
# Symptômes et signes (2)

| Characteristic | Patients With LVSD (n=20,118) | Patients With PSF (n=21,149) | *P* Value |
|---|---|---|---|
| **Dyspnea at rest (%)** | **44** | **44** | **.194** |
| **Dyspnea on exertion (%)** | **63** | **62** | **.206** |
| **Rales (%)** | **63** | **65** | **.001** |
| Jugular venous distension (%) | 33 | 26 | <.0001 |
| Mean SBP (mmHg) | 135 | 149 | <.0001 |
| Mean heart rate (bpm) | 89 | 85 | <.0001 |
| Mean BNP (pg/mL) | 1635 | 977 | <.0001 |
| Mean troponin I (ng/mL) | 1.60 | 0.74 | <.0001 |
| Mean serum creatinine (mg/dL) | 1.70 | 1.73 | <.0001 |
| Mean hemoglobin (g/dL) | 12.53 | 11.86 | <.0001 |

PSF = LVEF ≥40%.

Fonarow et al, OPTIMIZE-HF registry, JACC 2007

# Insuffisance Cardiaque avec FE Préservée: est-ce Fréquent?




*Hogg et al, JACC, 2004, Owan et al, Prog Cardiovas Dis, 2005 Owan et al, NEJM, 2006; Bursi F et al, JAMA, 2006*

# Prévalence -trends

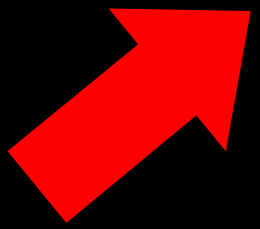

Di'ci 2020, 65% des patients hospitalisés pour insuffisance cardiaques auront une FE > 40%

Vieilissement de la population.

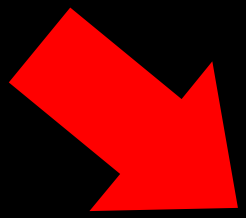
*Oktay, Rich, Shah. Curr Heart Fail Rep 2013*

# Physiopathologie

# Fonction Ventriculaire Gauche



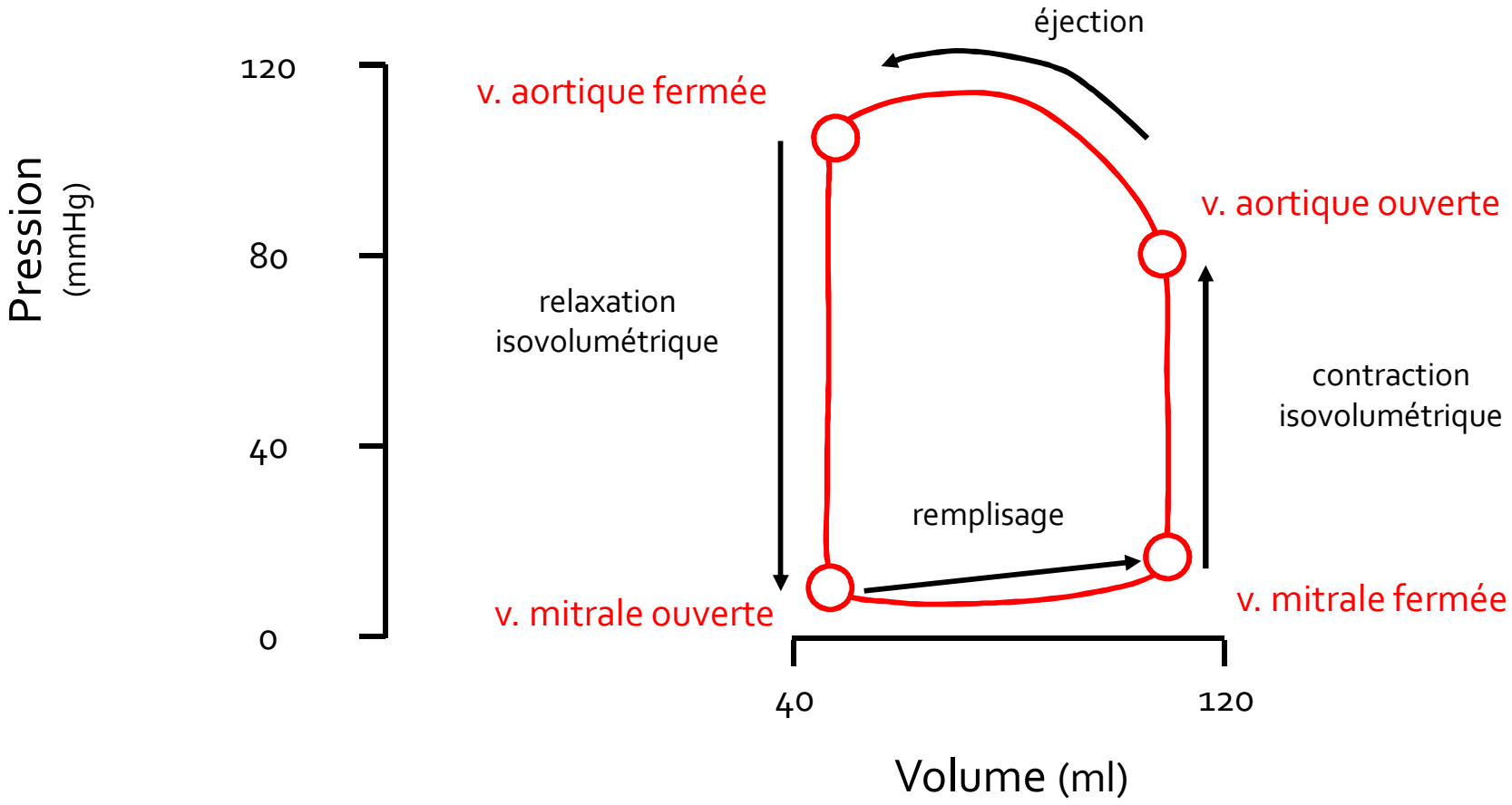
Systole



Diastole

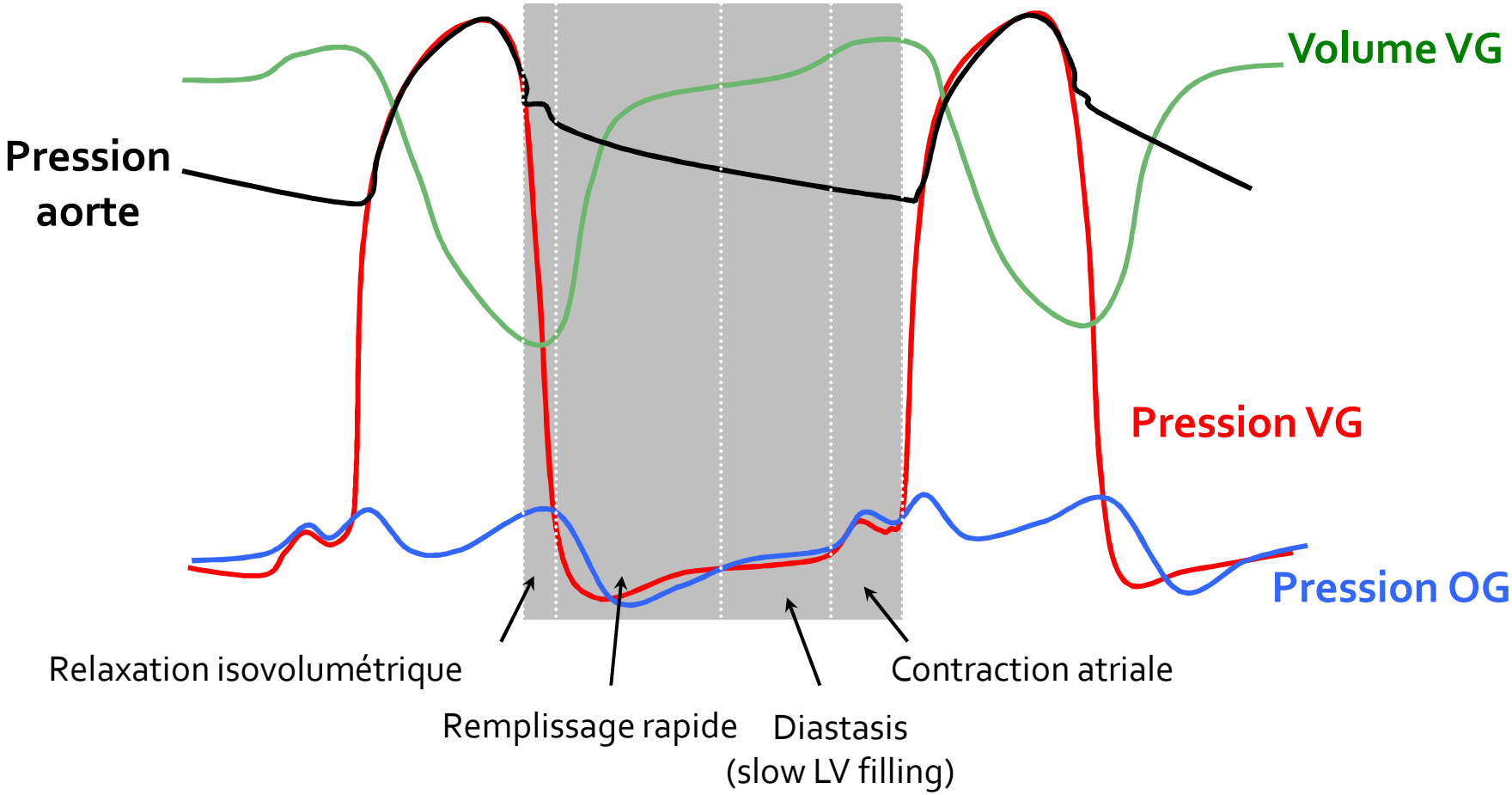
# Fonction Ventriculaire Gauche

## Boucle pression - volume et mouvements valvulaires



# Fonction Ventriculaire Gauche: Diastole

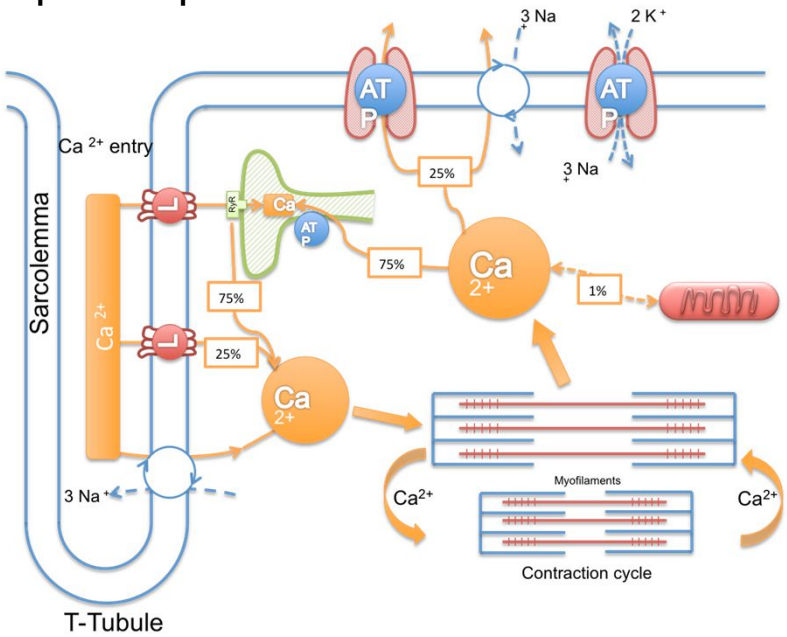
**Les différentes phases de la diastole**

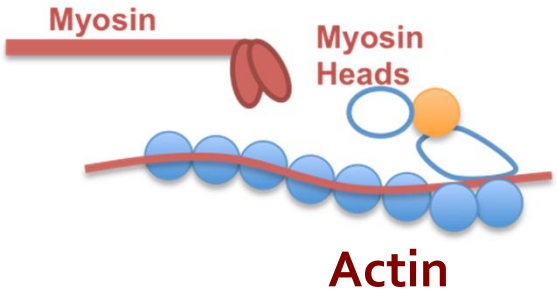


# Au niveau cellulaire:

DIASTOLE = l'ensemble des propriétés actives et passives du ventricule qui va lui permettre de se remplir à basse pression

**Courrant électrique de dépolarisation= TRIGGER**



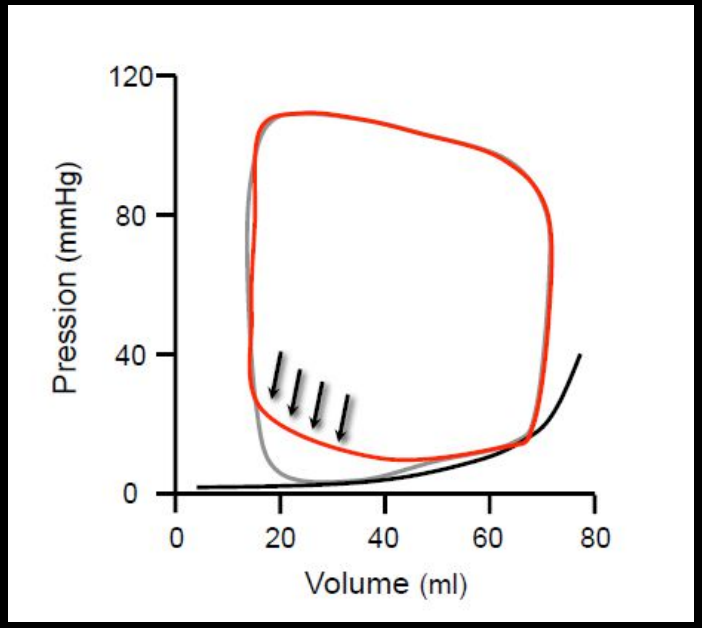




propriétés actives → **relaxation ventriculaire: consommation énergie**

propriétés passives → **distensibilité ventriculaire**

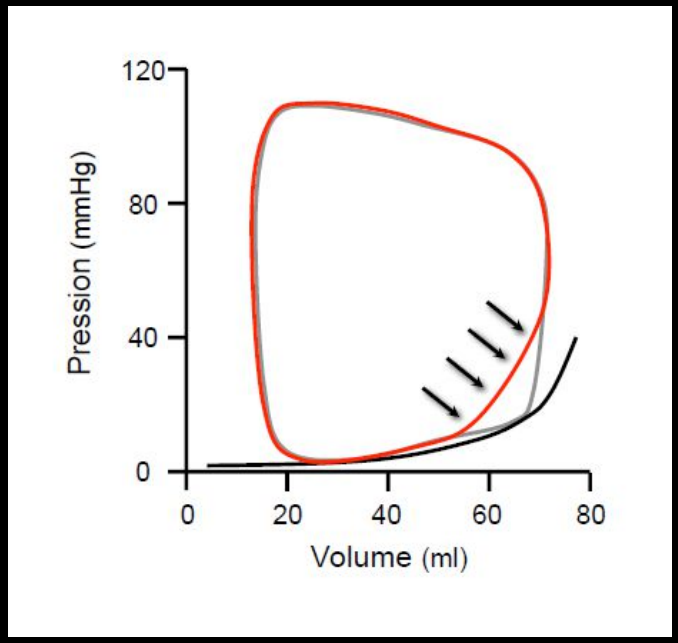
# Mécanismes de la Dysfonction Diastolique

## ANOMALIES de la RELAXATION du VG (phase active)




Ischémie, Δ charge
Anomalie uptake Ca++

## ANOMALIES de la DISTENSIBILITE du VG




HVG, fibrose sévère, maladie infiltrative (amyloidose)
Anomalies péricarde, compression

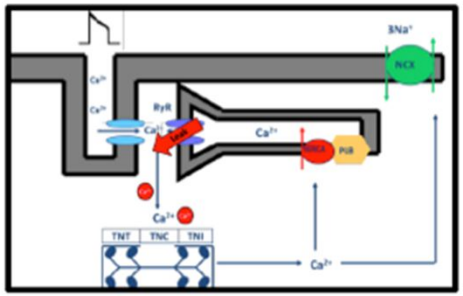
# Mécanismes Potentiels

CARDIOMYOCYTES

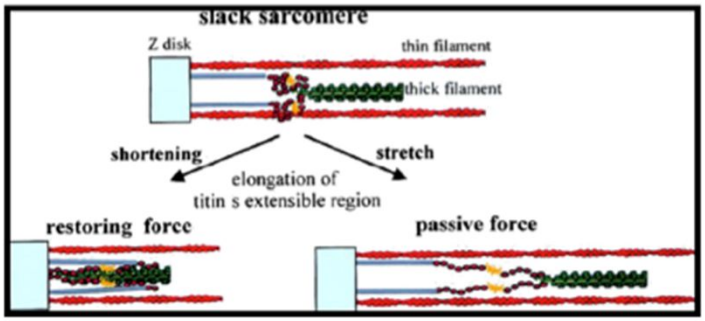
CALCIUM

CYTOSQUELETTE (microtubule, desmine, titine)

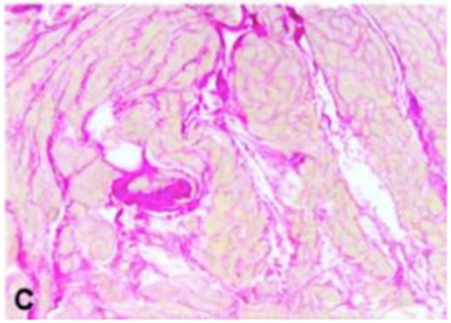
Dysfunctional Calcium handling




Abnormalities in spring-like Titin protein

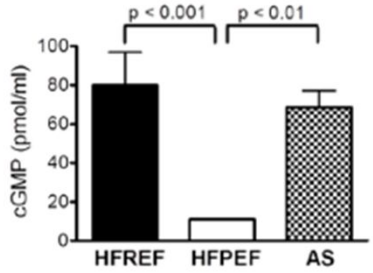



Increased extracellular fibrosis, reduced ventricular compliance & shift in the PV relationship




MATRICE EXTRACELLULAIRE

Myocardial cGMP in HFPEF

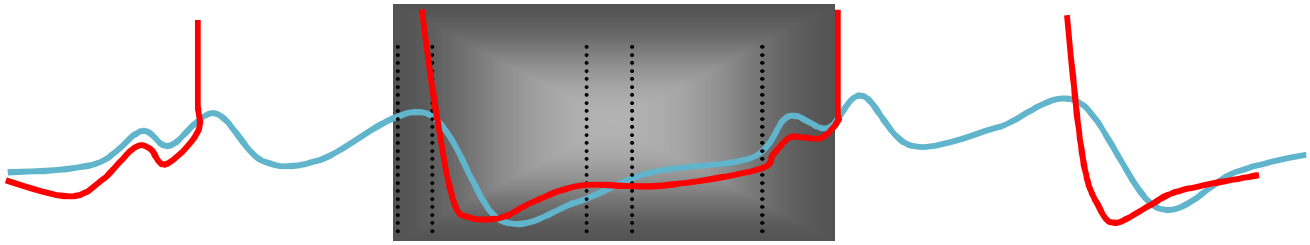



Van Heerebeek L,...Paulus WJ. AHA 2011
AOS 503.02

cGMP

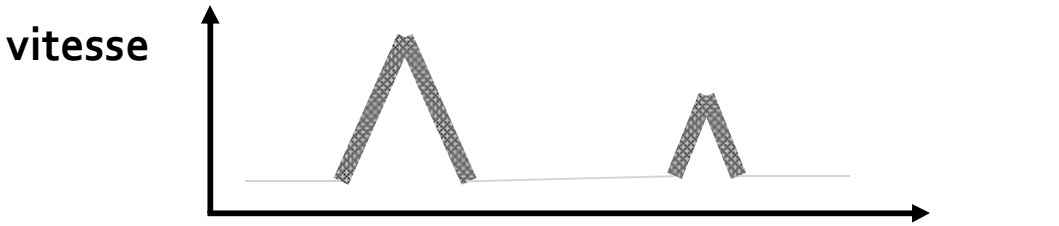
# Fonction Ventriculaire Gauche: Diastole


**Remplissage ventriculaire**



remplissage rapide

contraction atriale



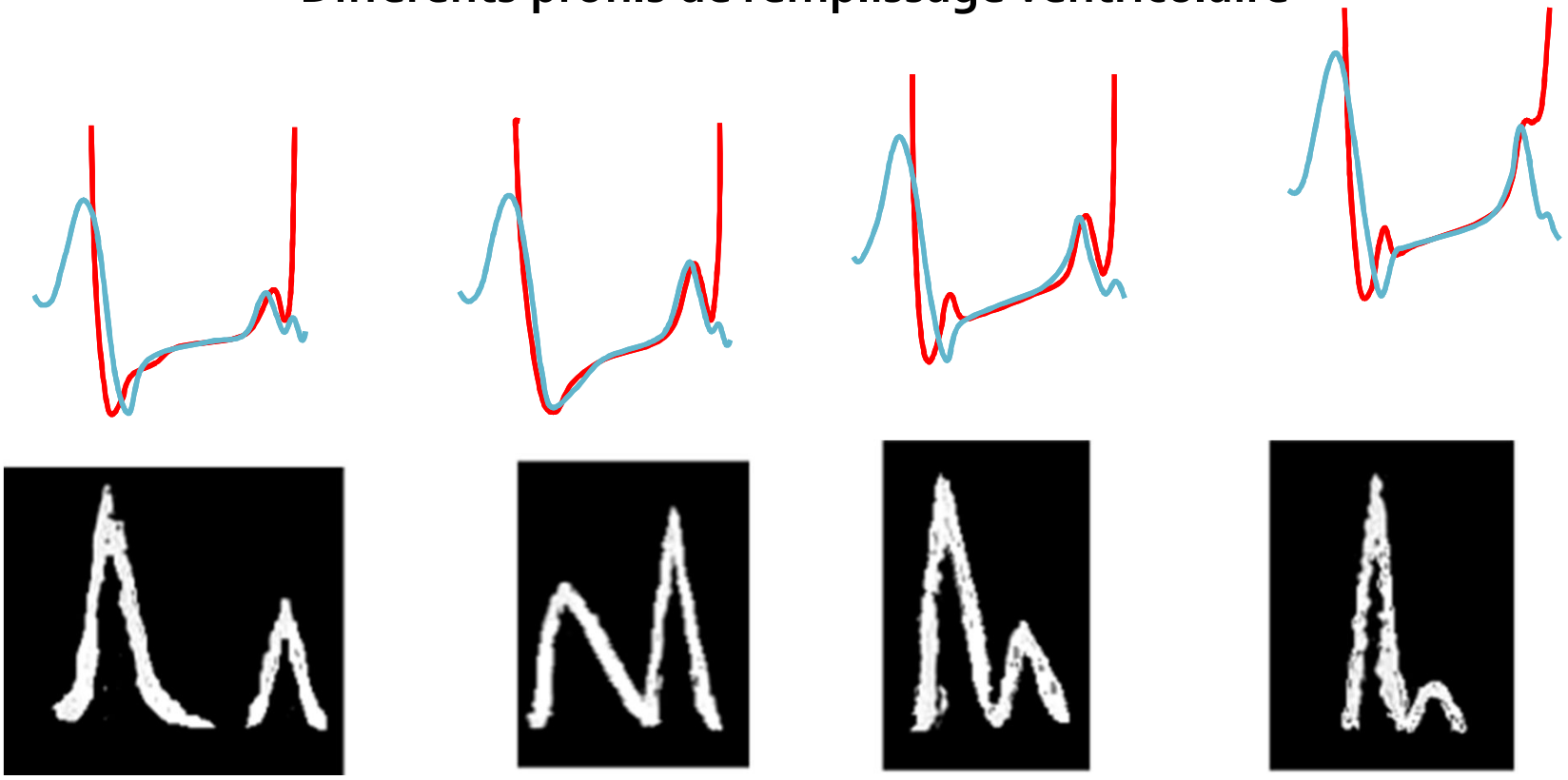

Onde E

Onde A

# Fonction ventriculaire gauche

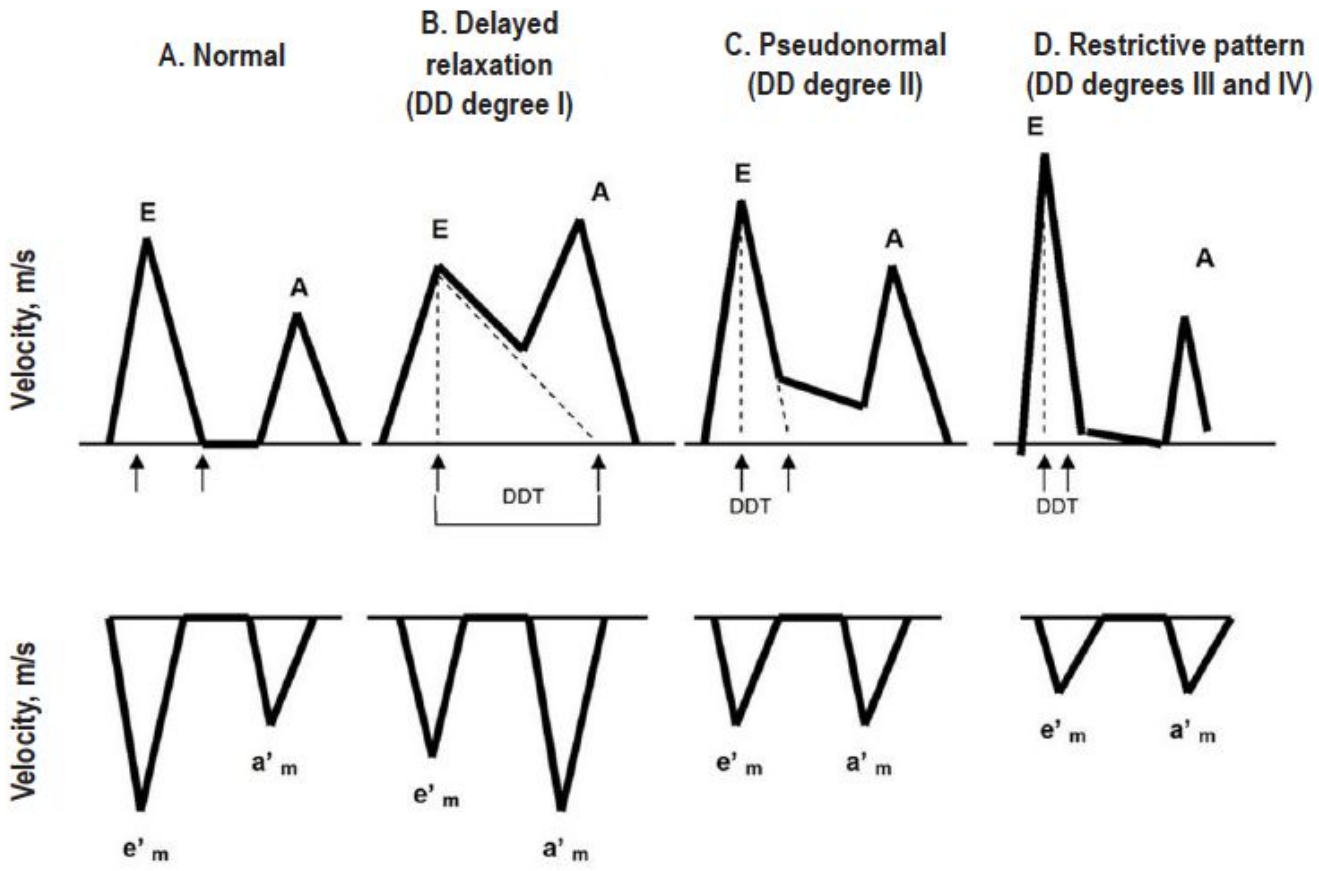
## La fonction diastolique

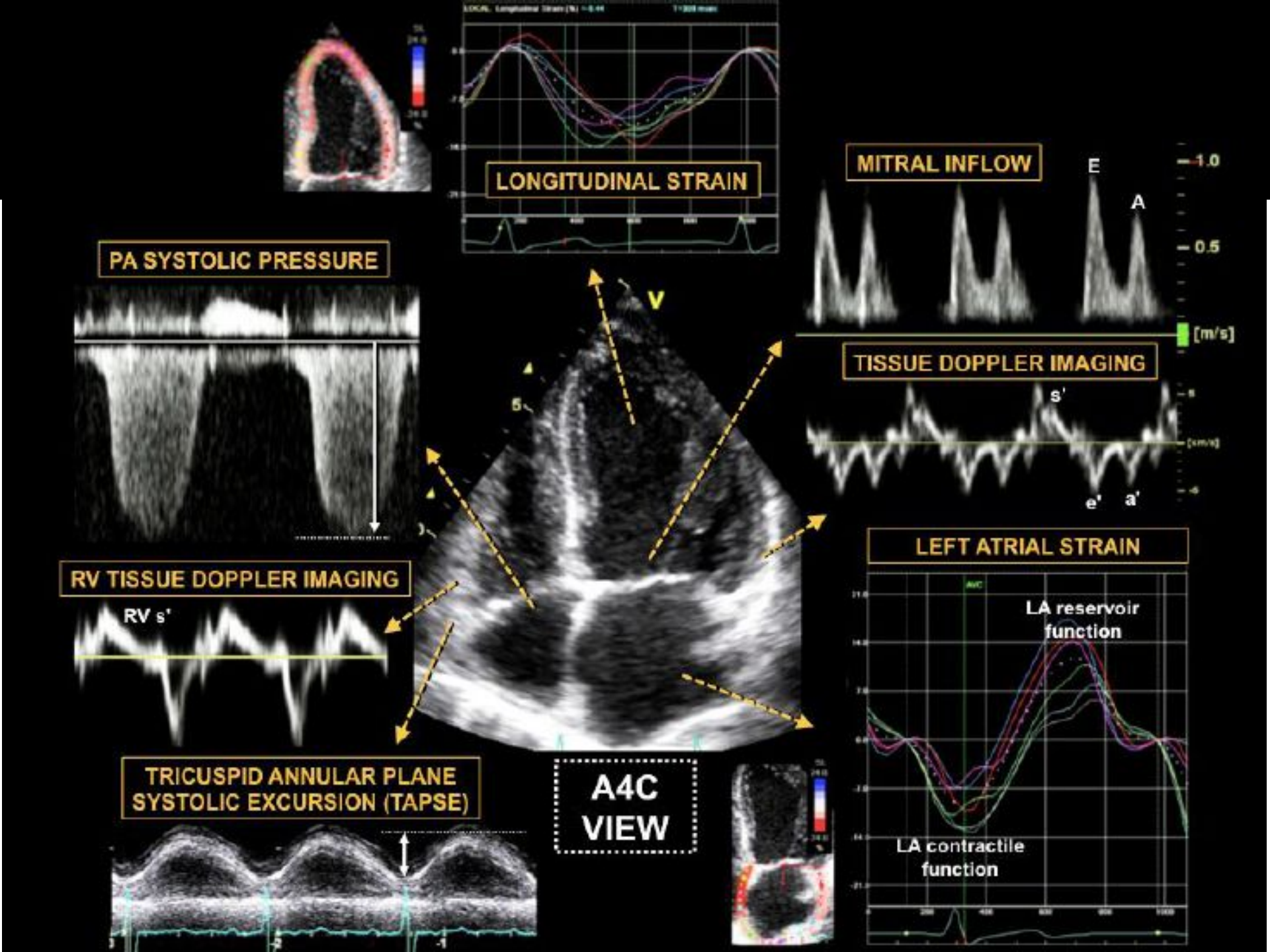
**Différents profils de remplissage ventriculaire**



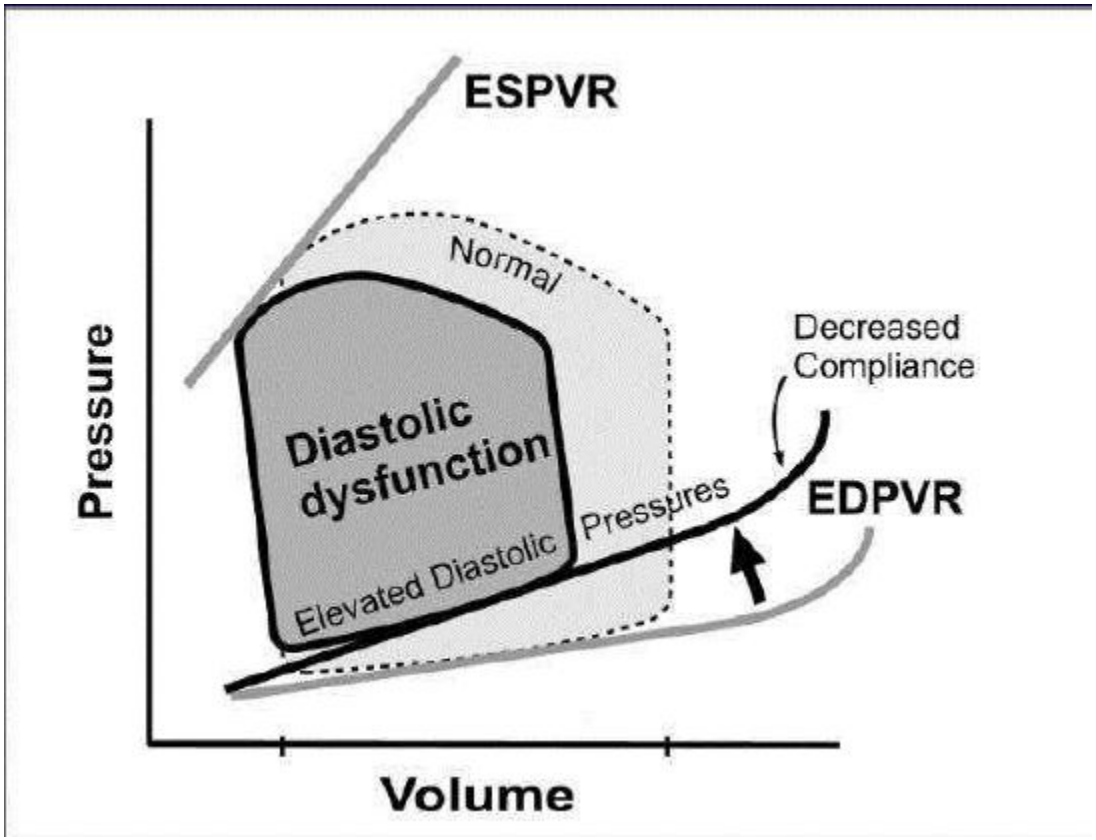
normal ⟷ relaxation anle $P_{OG}$ nle ⟷ relaxation anle $P_{OG}$ ↗ ⟷ relaxation anle $P_{OG}$ ↗↗

# Standard Doppler




LONGITUDINAL STRAIN
MITRAL INFLOW
E
A
1.0
0.5
[m/s]
PA SYSTOLIC PRESSURE
V
TISSUE DOPPLER IMAGING
s'
e'
a'
LEFT ATRIAL STRAIN
RV TISSUE DOPPLER IMAGING
RV s'
LA reservoir function
LA contractile function
TRICUSPID ANNULAR PLANE SYSTOLIC EXCURSION (TAPSE)
A4C VIEW

# GOLD Standard




MESURES INVASIVES

# Mythes et Misconceptions

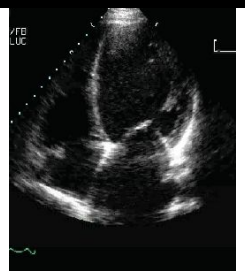
# Mythe n°1

Le diagnostique de l'IC à fonction préservée est difficile

1. **Symptômes et/ou signes d'insuffisance cardiaque**

- Dyspnée, orthopnée, dyspnée paroxystique nocturne, fatigue, intolérance à l'effort
- Jugulaires, RHJ, oedèmes, ascite, crépitants

# INSUFFISANCE CARDIAQUE A FONCTION REDUITE



# INSUFFISANCE CARDIAQUE A FONCTION PRESERVEE

**1. Symptômes et/ou signes d'insuffisance cardiaque**

- Dyspnée, orthopnée, dyspnée paroxystique nocturne,

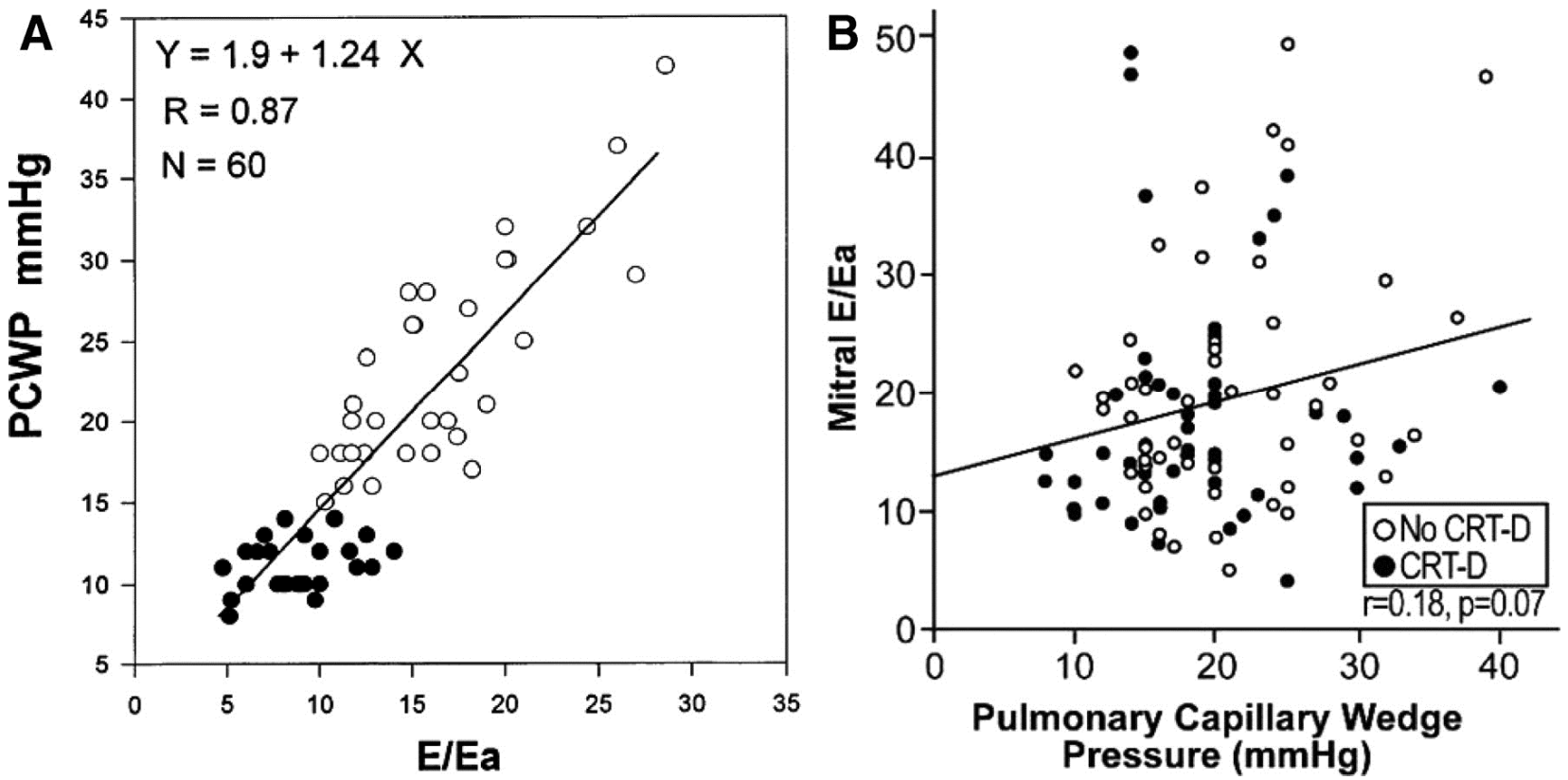
- Elévation du BNP ou NT-proBNP
- Anomalies E/A, E/e'
- Pression capillaire >15mmHg ou pression télédiastolique VG >15mmHG

# Insuffisance Cardiaque à Fonction Préservée

- Dysfonction diastolique (DD) à l'échocardiographie
  - Pas requise pour le diagnostique
  - Souvent non interprétée ou mal interprétée
  - Grade 2 (modérée) ou grade 3 (sévère)= outil utile, mais pas indispensable
  - Patients peuvent avoir de l'IC à fonction préservée avec DD discrète

- Si doute:  cathétérisme cardiaque – mesures invasives

# Relations entre E/Ea et Pression Capillaire

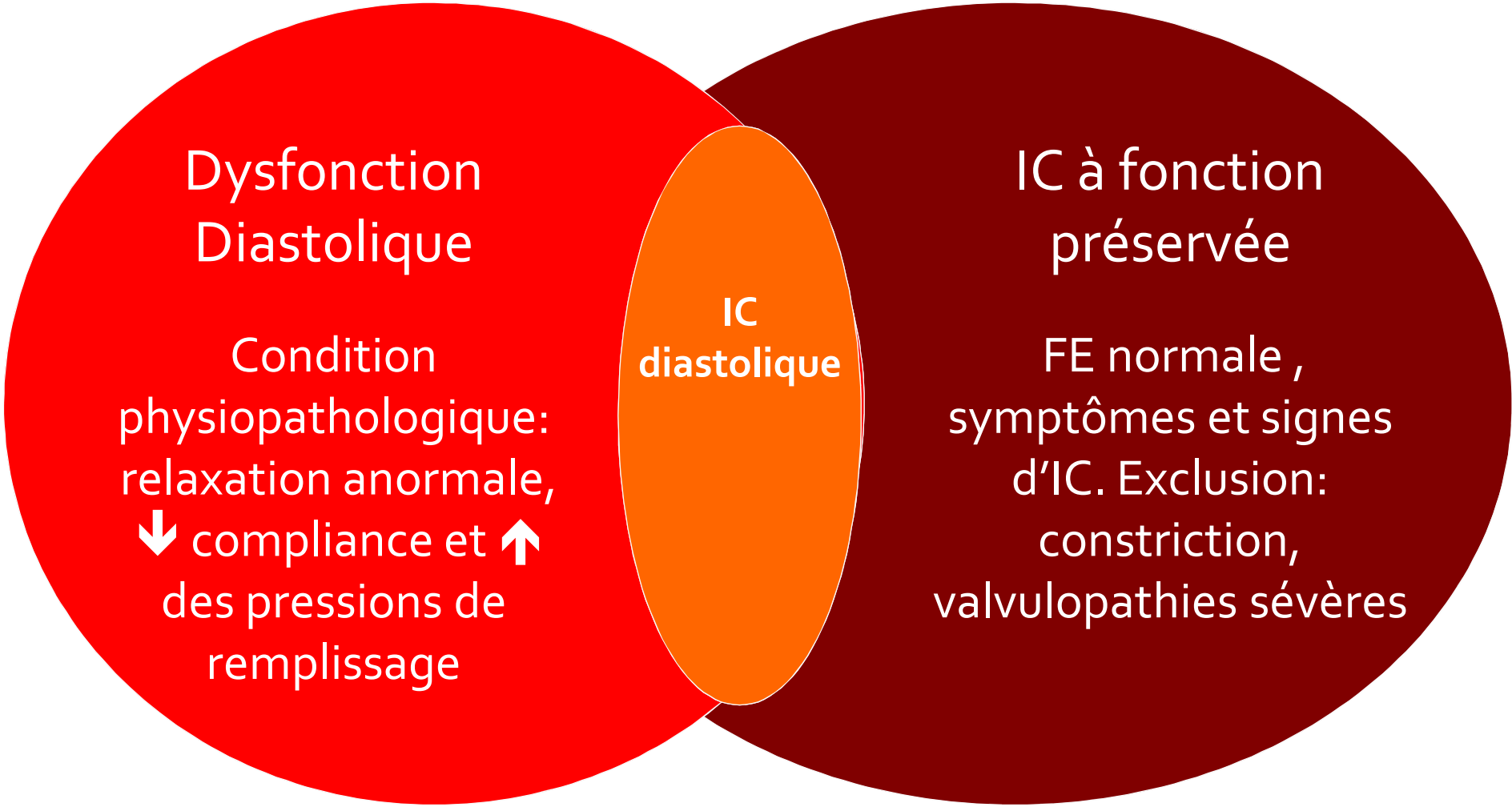



Solomon S D , Stevenson L W Circulation 2009;119:13-15

# Mythe n°2

Dysfonction diastolique = insuffisance cardiaque diastolique = insuffisance cardiaque à fonction préservée

# Dysfonction Diastolique vs. IC Diastolique vs. IC à Fonction Préservée



# Dysfonction Diastolique vs. IC Diastolique vs. IC à Fonction Préservée

Insuffisance cardiaque diastolique pure = un syndrome rare

# Dysfonction Diastolique est EXTREMEMENT Prévalente

2042 résidents du Olmsted County, Minnesota, âgés ≥45 ans, inclus de Juin 1997 à Septembre 2000.

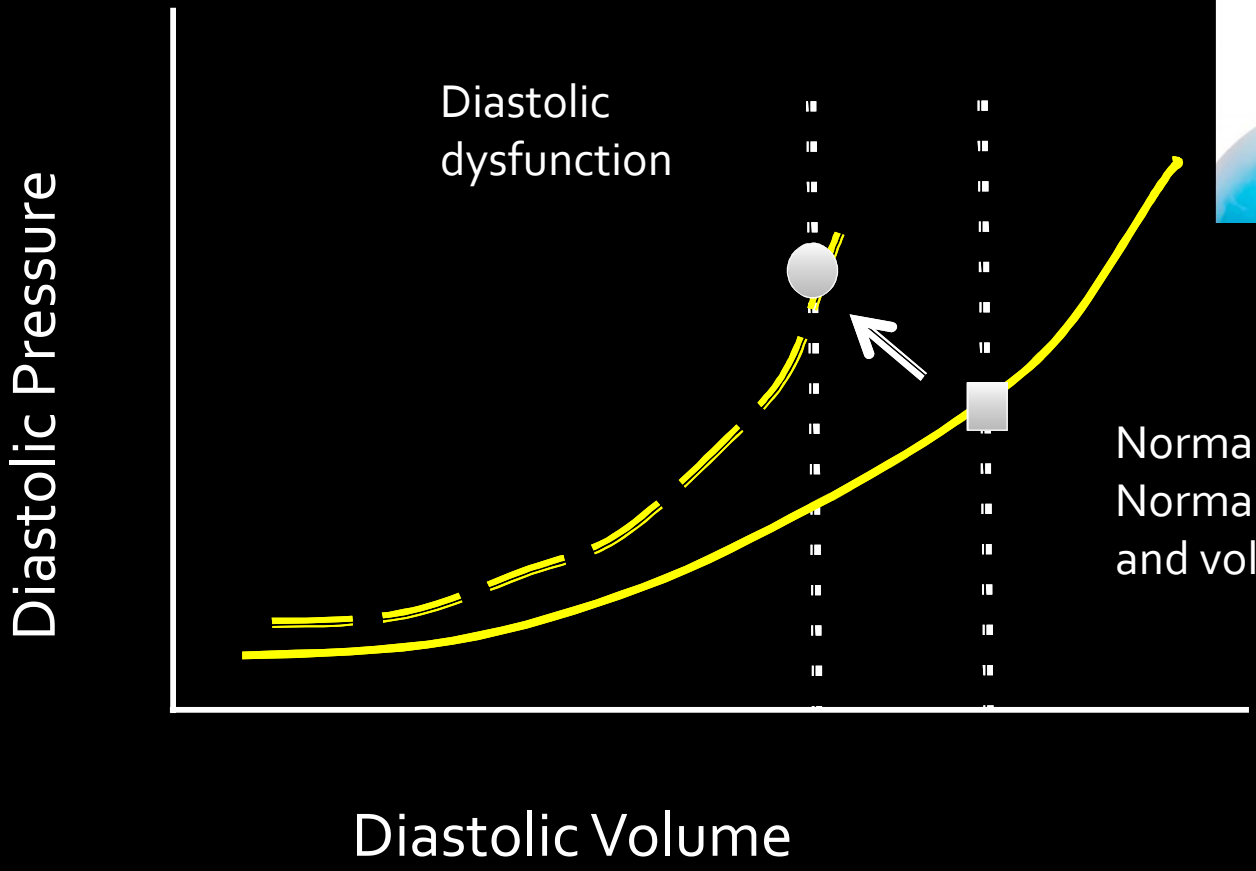
**Table 1.** Prevalence of Systolic and Diastolic Dysfunction According to Age and Sex*

| Variables | No. (%) of Patients Affected | | | | |
|---|---|---|---|---|---|
| | Age Group, y | | | | |
| | 45-54 | 55-64 | 65-74 | ≥75 | Overall |
| | Diastolic Dysfunction | | | | |
| Mild | | | | | |
| All | 27 (4.8) | 72 (13.2) | 149 (34.2) | 123 (52.8) | 371 (20.8) |
| Men | 20 (7.2) | 43 (16.0) | 76 (37.2) | 49 (57.0) | 188 (22.5) |
| Women | 7 (2.4) | 29 (10.4) | 73 (31.6) | 74 (50.3) | 183 (19.4) |
| Moderate | | | | | |
| All | 8 (1.4) | | | | |
| Men | 5 (1.8) | | | | |
| Women | 3 (1.0) | | | | |
| Severe | | | | | |
| All | 0 (0) | | | | |
| Men | 0 (0) | | | | |
| Women | 0 (0) | | | | |

25% de la population générale a un certain degré de dysfonction diastolique.
Pq certains deviennent symptomatiques?

Redfield, JAMA 2003

# La Dysfonction Diastolique est Présente MAIS seule Responsable?




Zile et al, NEJM, 350 (19): 1953

# Intolérance à l'effort? Inadaption du Débit Cardiaque?

**Table 1 Baseline characteristics**

| | Control ($n = 73$) | HFpEF ($n = 109$) | *P*-value |
|---|---|---|---|
| Clinical characteristics | | | |
| Age (years) | 59 ± 14 | 67 ± 11 | <0.0001 |
| Female (%) | 75 | 72 | 0.6 |
| Body mass index (kg/m$^2$) | 29.1 ± 5.5 | 33.2 ± 7.0 | <0.0001 |
| Body surface area (m$^2$) | 1.95 ± 0.26 | 2.08 ± 0.29 | 0.002 |
| Hypertension (%) | 64 | 82 | 0.009 |
| Diabetes (%) | 16 | 33 | 0.01 |
| Beta-blockers (%) | 33 | 61 | 0.0003 |
| Diuretics (%) | 18 | 69 | <0.0001 |
| Haemoglobin (g/dL) | 13.1 ± 1.7 | 12.4 ± 1.5 | 0.006 |
| Estimated GFR (mL/min/1.73 m$^2$) | 67 ± 20 | 55 ± 18 | 0.0001 |
| BNP (pg/mL) | 36 (15, 71) | 112 (49, 207) | <0.0001 |

Eur J Heart Fail. 2013 Jul;15(7):776-85

# Hémodynamique de Repos

| | Control ($n = 73$) | HFpEF ($n = 109$) | *P*-value |
|---|---|---|---|
| LV morphology and function | | | |
| LV end-diastolic volume (mL) | 117 ± 25 | 115 ± 33 | 0.6 |
| LV end-systolic volume (mL) | 41 ± 14 | 38 ± 15 | 0.3 |
| LV mass (g/height$^{2.7}$) | 45 ± 15 | 51 ± 18 | 0.015 |
| Left atrial volume (mL) | 59 ± 15 | 93 ± 29 | <0.0001 |
| Left atrial volume index (mL/m$^2$) | 30 ± 7 | 45 ± 13 | <0.0001 |
| LVEF (%) | 63 ± 8 | 65 ± 7 | 0.09 |
| E/A ratio | 1.0 ± 0.3 | 1.3 ± 0.8 | 0.006 |
| E′ (cm/s) | 7 ± 4 | 7 ± 3 | 0.9 |
| E/E′ ratio | 11 ± 5 | 14 ± 8 | 0.004 |
| Resting haemodynamics | | | |
| Heart rate (b.p.m.) | 71 ± 11 | 69 ± 10 | 0.4 |
| Systolic blood pressure (mmHg) | 138 ± 21 | 141 ± 24 | 0.5 |
| Mean blood pressure (mmHg) | 98 ± 15 | 95 ± 15 | 0.2 |
| Pulse pressure (mmHg) | 60 ± 14 | 70 ± 21 | 0.0009 |
| Systemic $O_2$ content (mL/dL)[a] | 16.4 ± 1.6 | 15.6 ± 2.1 | 0.11 |
| PA $O_2$ content (mL/dL)[a] | 12.6 ± 1.5 | 11.3 ± 1.7 | 0.001 |
| Right atrial pressure (mmHg)[a] | 4 ± 2 | 9 ± 4 | <0.0001 |
| PA systolic pressure (mmHg)[a] | 26 ± 6 | 39 ± 11 | <0.0001 |
| Mean PA pressure (mmHg)[a] | 16 ± 4 | 25 ± 7 | <0.0001 |
| PCWP (mmHg)[a] | 9 ± 3 | 16 ± 6 | <0.0001 |
| Cardiac output (L/min) | 5.4 ± 1.4 | 5.4 ± 1.7 | 0.9 |
| Cardiac index (L/min/m$^2$) | 2.8 ± 0.7 | 2.6 ± 0.8 | 0.2 |
| PVR (mmHg/L/min)[a] | 1.2 ± 0.7 | 2.0 ± 1.3 | 0.008 |
| Ea (mmHg/mL) | 1.7 ± 0.4 | 1.8 ± 0.6 | 0.4 |

Eur J Heart Fail. 2013 Jul;15(7):776-85

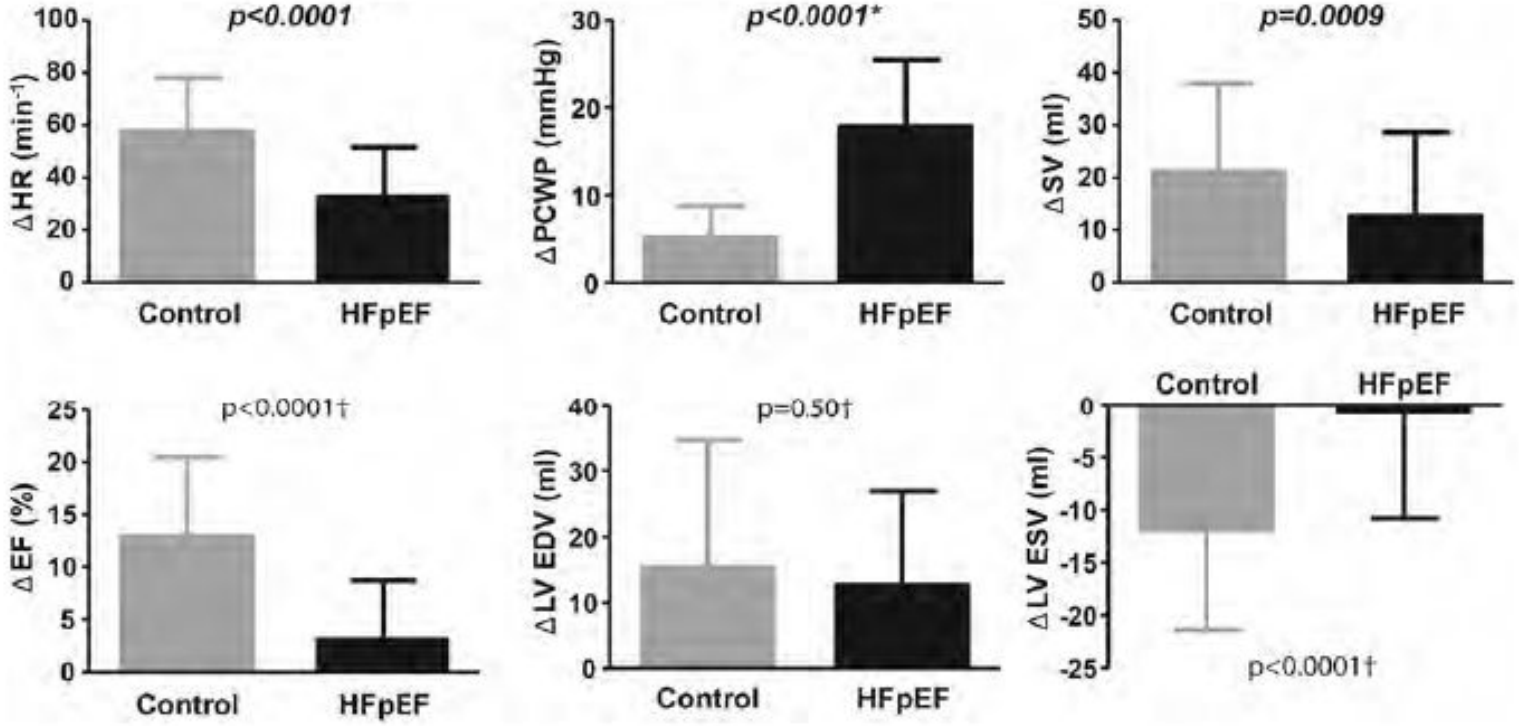
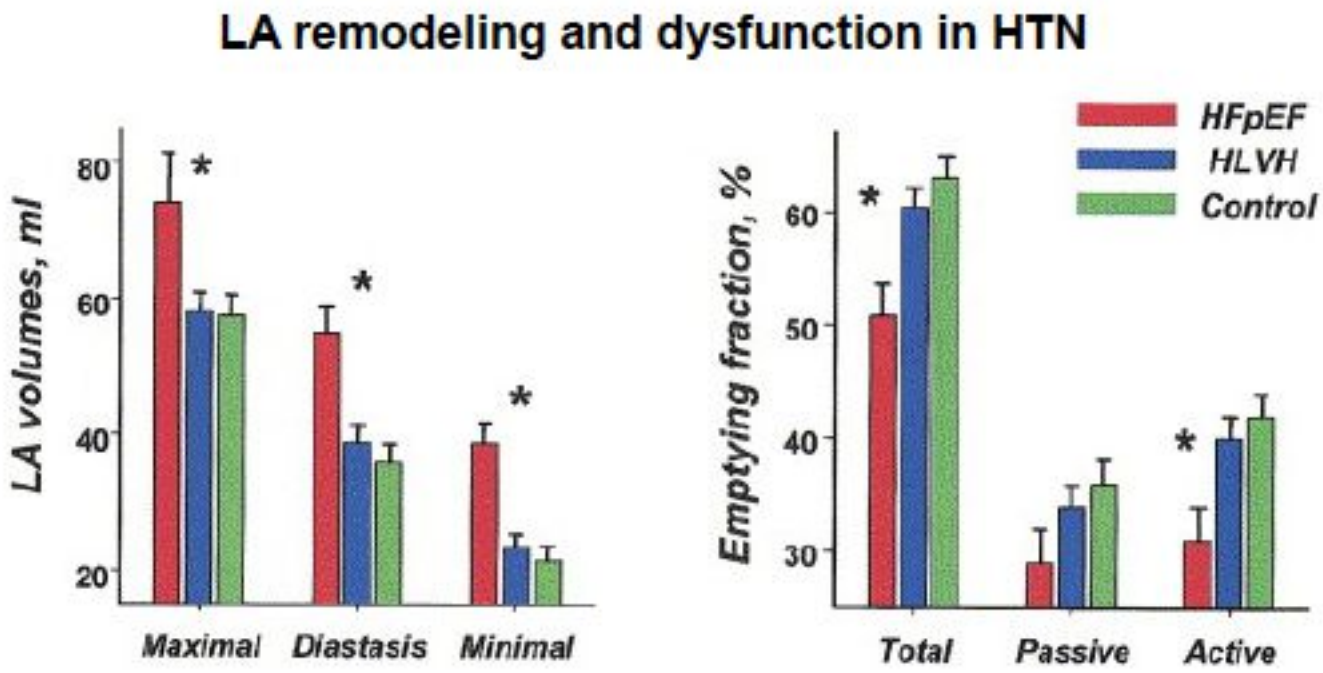


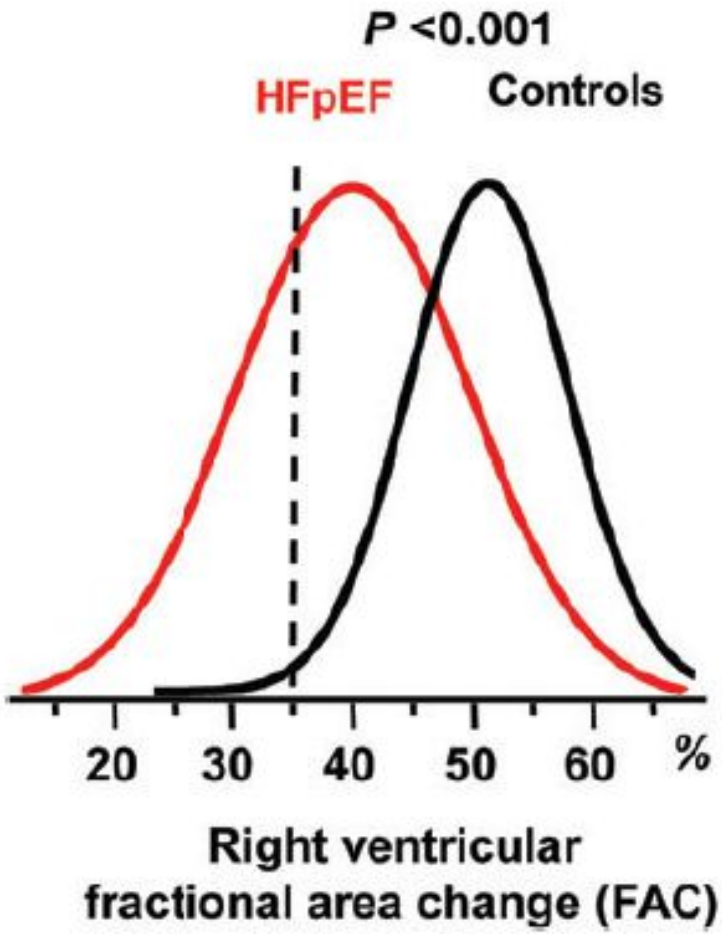

**Figure 1** Haemodynamic changes with exercise in heart failure with preserved ejection fraction (HFpEF; black) compared with controls (grey). *Data available only for cohort 1 ($n = 71$ HFpEF and 25 controls); †Data available only for cohorts 2 and 3 ($n = 38$ HFpEF and 48 controls). EDV, end-diastolic volume; HR, heart rate; SV, stroke volume.

# Oreillette gauche




Melenovsky JACC 2007

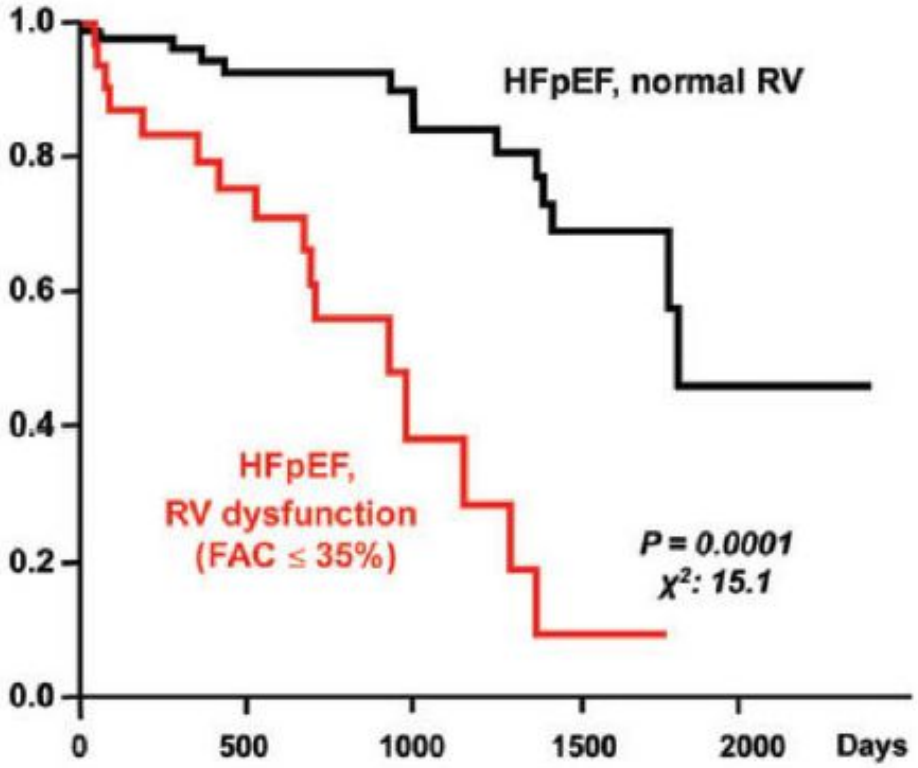
# Dysfonction Ventriculaire Droite




Dysfonction VD (RV FAC < 35%) présente chez 33% des patients avec IC fonction préservée

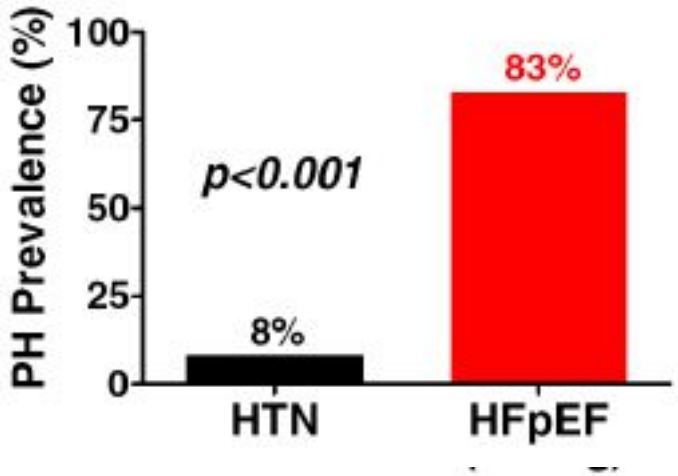
Melenovsky et al Eur Heart J 2014

# Dysfonction VD et Pronostique




Melenovsky et al Eur Heart J 2014

# Hypertension Pulmonaire est Fréquente dans IC Fonction Préservée



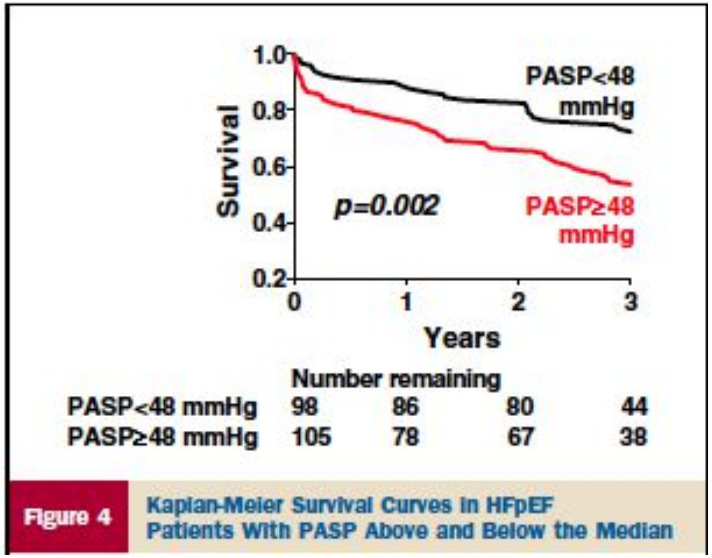




Figure 4 Kaplan-Meier Survival Curves in HFpEF Patients With PASP Above and Below the Median

**Pulmonary hypertension (PH) is highly prevalent in HFpEF**

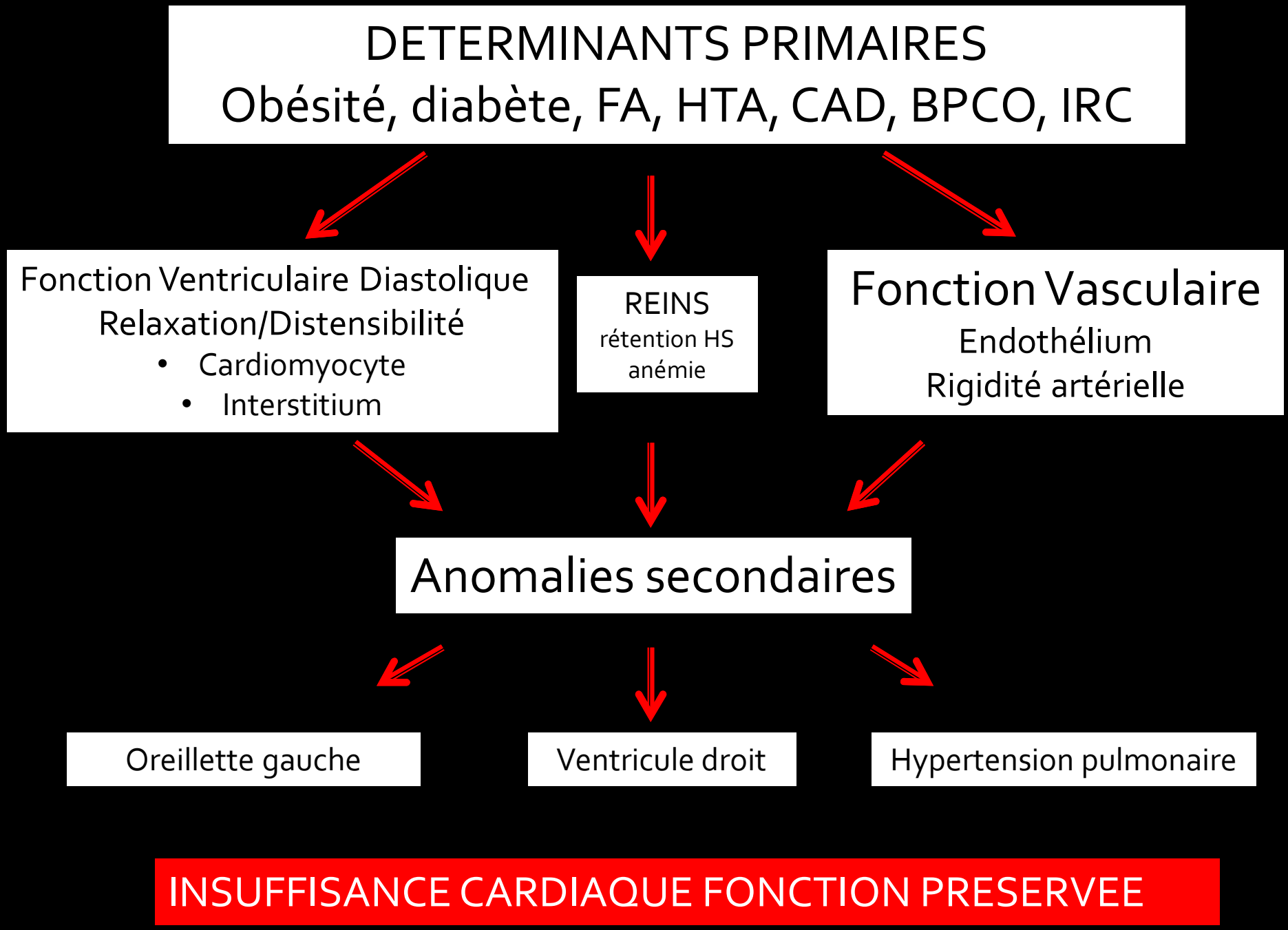
Marqueur de sévérité et chronicité

Lam JACC 2009

DYSFONCTION DIASTOLIQUE

≠

SEUL FACTEUR PRECIPITANT


DETERMINANTS PRIMAIRES
Obésité, diabète, FA, HTA, CAD, BPCO, IRC
Fonction Ventriculaire Diastolique
Relaxation/Distensibilité
• Cardiomyocyte
• Interstitium
REINS
rétention HS
anémie
Fonction Vasculaire
Endothélium
Rigidité artérielle
Anomalies secondaires
Oreillette gauche
Ventricule droit
Hypertension pulmonaire
INSUFFISANCE CARDIAQUE FONCTION PRESERVEE

# Femme, hypertendue, obèse, avec des chevilles gonflées?

EST-CE VRAIMENT AUSSI SIMPLE?

# Nombreuses Comorbidités

| Characteristic | LVSD (n=20,118) | 40%≤ EF ≤50% (n=7,321) | EF >50% (n=10,072) | *P* Value* |
|---|---|---|---|---|
| **Age, mean (years)** | **70.4** | **74.3** | **75.6** | **<.0001** |
| **Male (%)** | **62** | **48** | **32** | **<.0001** |
| African American (%) | 21 | 15 | 15 | .880 |
| Atrial arrhythmia (%) | 28 | 33 | 32 | .179 |
| **Ischemic etiology (%)** | **54** | **49** | **32** | **<.0001** |
| Insulin-treated diabetes (%) | 15 | 18 | 16 | .013 |
| Non–insulin-treated diabetes (%) | 24 | 26 | 25 | .418 |
| **Hypertension (%)** | **66** | **74** | **77** | **<.0001** |
| **Mean LVEF %** | **24.3** | **45** | **61** | **<.0001** |

**P* value (40%≤ EF ≤50% vs EF >50%).
PSF = preserved systolic function.

Fonarow et al, OPTIMIZE-HF registry, JACC 2007

# Nombreuses Comorbidités

| Characteristic | SOLVD | TOPCAT | I-PRESERVE | PEP-CHF | *SENIOR* |
|---|---|---|---|---|---|
| **N** | 2569 | 3445 | 4133 | 850 | 752 |
| **Age, mean (years)** | 61 | 69 | 72 | 75 | 76 |
| **Female (%)** | 20 | 52 | 60 | 55 | 50 |
| **Hypertension (%)** | 41 | 91 | 88 | 79 | 78 |
| **CAD** | 71 | 47 | 48 | 27 | 77 |
| **Diabetes (%)** | 25 | 32 | 27 | 21 | 24 |
| **Atrial arrhythmia (%)** | 9 | 35 | 29 | 20 | 36 |
| **CKD (%)** | -- | 38 | 31 | -- | -- |
| **Mean LVEF %** | 25 | 57 | 59 | 55 | 49 |
| **BMI (kg/m2)** | 26 | 31 | 30 | 28 | -- |

# En résumé,

- Age: DHF > SHF
- Femmes: DHF > SHF
- Hypertension: DHF > SHF
- Obésité: DHF ≥ SHF
- Diabète: DHF = SHF
- Maladie coronaire: DHF < SHF

*Lam et al, Eur J Heart Fail 2011*

# Mythe n° 3

Un BNP normal exclus l'IC à fonction préservée

# BNP comme outil diagnostic

- Données limitées dans IC à fonction préservée
- BNP <100pg/mL, NT-proBNP <120: valeurs seuils supposées avec bonne valeur prédictive négative
- Obésité: très fréquente et associée à une ↘ BNP

# BNP normal dans IC fonction préservée?

- Etude prospective
- 159 patients avec IC fonction préservée. Critères Framingham pour IC
- Tous les patients ont eu un cathétérisme cardiaque droit et une mesure de BNP
- PCPW >15mmHg ou LVEDP>15mmHg chez tous les patients

Anjan V, Shah SJ et al, Am J Cardiol 2012

46/159 (29%) ont un BNP<100pg/mL

- Plus jeunes
- Plus obèses
- PCWP élevée dans les 2 groupes (25mmHg vs. 27mmHg)
- Meilleur pronostique (HR 0.25 pour décès/hospitalisation)

BNP <100pg/mL dans un tiers cas
Association avec forme moins sévère d'IC fonction préservée
MAIS toujours symptomatique (PCWP +/- 25mmHg)

Anjan V, Shah SJ et al, Am J Cardiol 2012

# Mythe n° 4

## L'IC à fonction préservée est une maladie à visage unique

# Cancer vs. IC Fonction Préservée Visage Unique?

**CANCER**
**APPROCHE OPTIMALE**

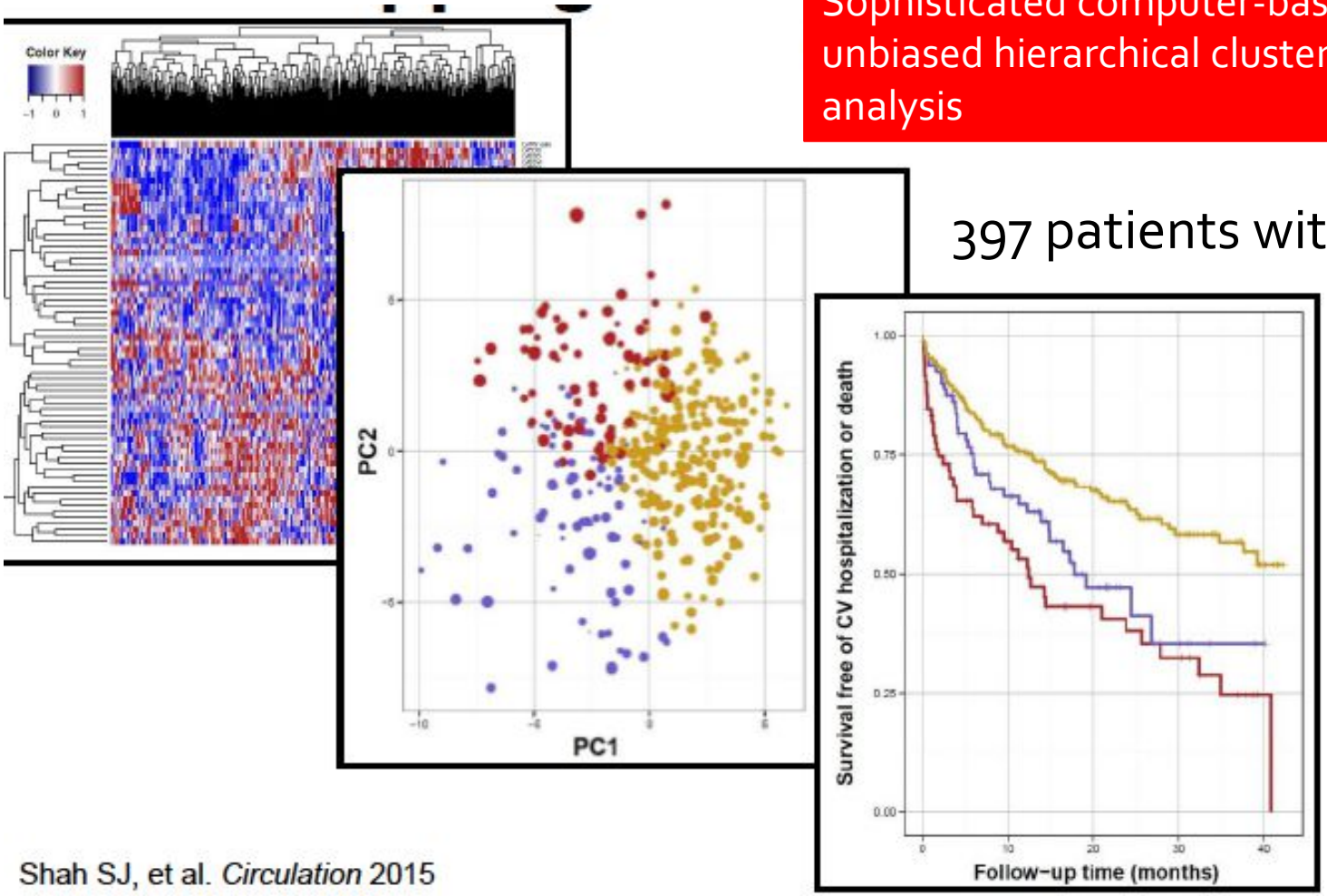
- Biopsie tissulaire
- Imagerie
- Analyse phénotypique
  - Taille de la tumeur, extension
  - Histologie
- Expression génétique

TRAITEMENT CIBLE

# Phénomapping

Sophisticated computer-based unbiased hierarchical cluster analysis

397 patients with HFpEF




Shah SJ, et al. *Circulation* 2015

67 variables possibles (n=46 analyse finale)

397 patients IC fonction préservée

Cohorte de validation (n=107)

| Phenotypic Domain | Phenotypes |
|---|---|
| Demographics | Age* |
| Physical characteristics | Body mass index,* heart rate,* systolic blood pressure, diastolic blood pressure,* pulse pressure* |
| Laboratory | Sodium,* potassium,* bicarbonate,* blood urea nitrogen,* creatinine,* estimated GFR,* fasting glucose,* white blood cell count,* hemoglobin,* red cell distribution width,* platelet count,* B-type natriuretic peptide* |
| ECG | PR interval,* QRS duration,* QTc interval,* QRS axis,* T-wave axis, QRS-T angle* |
| Echocardiography | |
| Left heart structure | LV end-diastolic volume,* LV end-systolic volume, LV end-diastolic dimension, LV end-systolic dimension, septal wall thickness, posterior wall thickness,* LV mass, left atrial volume* |
| LV systolic function | LV ejection fraction, tissue Doppler s′ velocity (septal and lateral), velocity of circumferential fiber shortening* |
| LV diastolic function | Mitral inflow characteristics (E velocity, A velocity,* E/A ratio,* E deceleration time,* IVRT*), tissue Doppler characteristics (septal e′ and lateral e′* velocities; septal a′ and lateral a′* velocities; septal E/e′ and lateral E/e′* ratios) |
| Right heart structure | RV basal diameter, RV maximal diameter, RV length,* RV wall thickness,* RV end-diastolic area, RV end-systolic area, RV/LV maximal diameter ratio,* right atrial area* |
| RV function | RV fractional area change,* tricuspid annular plane systolic excursion* |
| Hemodynamics | Stroke volume,* cardiac output, PA systolic pressure,* RA pressure* |
| Pressure-volume analysis | Effective arterial elastance, end-systolic elastance,* systolic blood pressure/end-systolic volume ratio,* end-diastolic elastance, ventricular-arterial coupling,* preload recruitable stroke work,* pulse pressure/ stroke volume ratio |

**Elévation de la pression OG à l'effort**

- 70 ans, NYHA II
- HTA de longue date
- Intolérance à l'effort
- Peu de congestion
- Pas d'hospitalisation IC
- FE 70%,? OG+
- DD grade I
- PAPs 30mmHg

**Surcharge volémique**

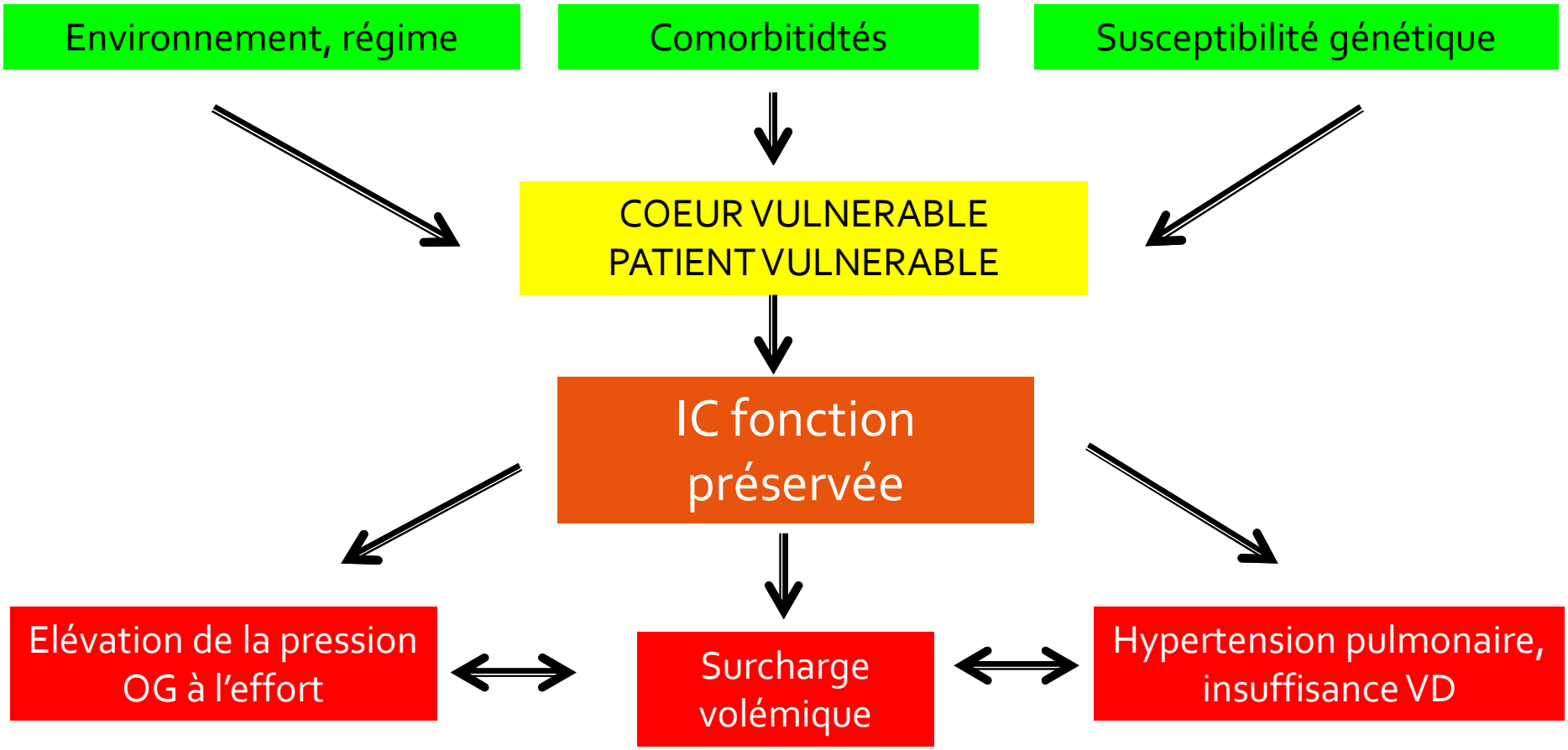
- 76 ans, NYHA III
- HTA, atcds PAC
- Intolérance à l'effort
- OMI ++
- Hospitalisation récente IC
- FE 50%? OG++
- DD grade III
- PAPs 45mmHg
- IM 2+, Iao 2+

**Hypertension pulmonaire, insuffisance VD**

- 79 ans, NYHA III
- HTA, diabète, IRC
- Dyspnée sévère
- OMI +++, ascite
- Plusieurs hospitalisations
- FE 65%, OG+++
- DD grade II
- PAPs 60mmHg
- Dysfonction VD, HVD

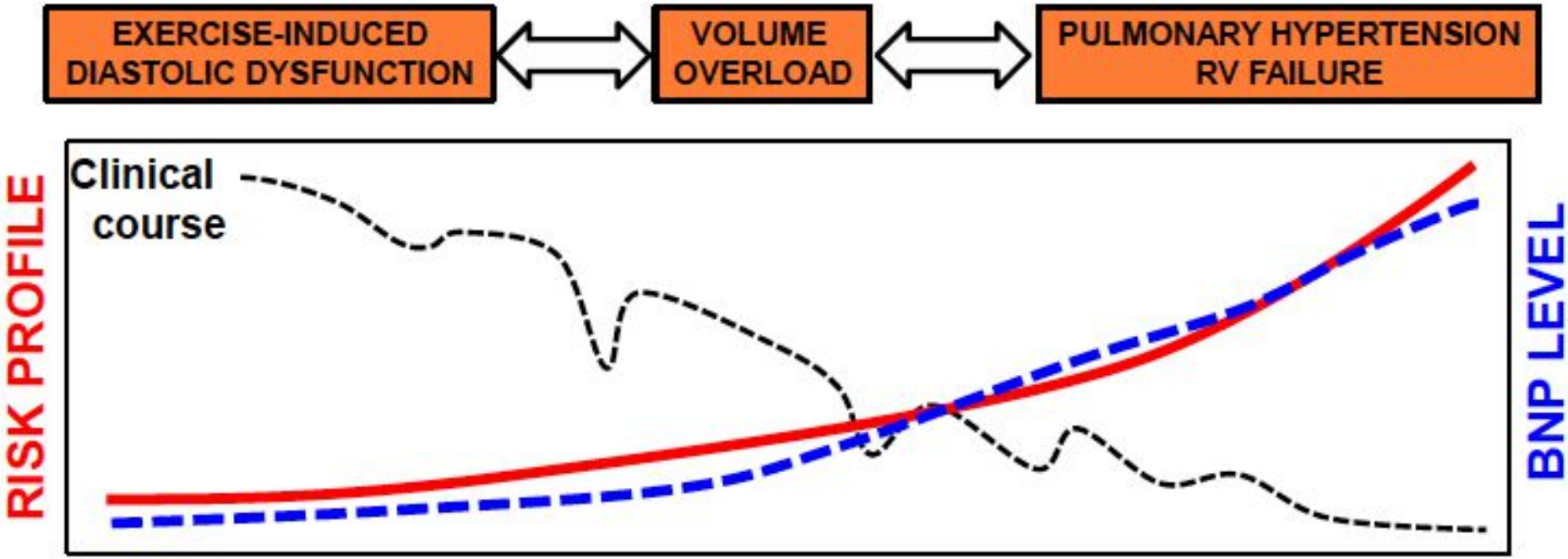
Shah SJ, JACC 2013;62(15):1339-42.

# 3 Types de Présentation



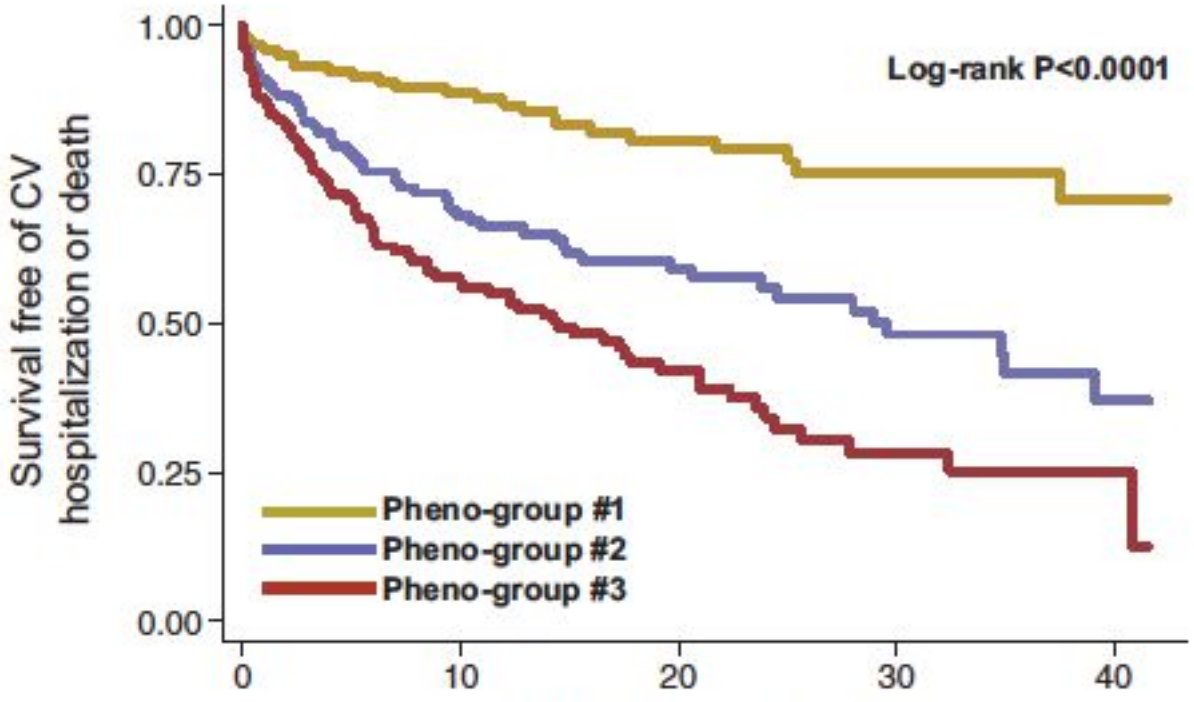

Shah SJ, JACC 2013;62(15):1339-42 et Circulation. 2015;131:269-279

# Interactions




Shah SJ. *JACC* 2013

# Pronostique selon Phénotype




| Number at risk | | | | | |
|---|---|---|---|---|---|
| Pheno-group #1 | 122 | 90 | 57 | 31 | 6 |
| Pheno-group #2 | 133 | 72 | 42 | 24 | 6 |
| Pheno-group #3 | 142 | 65 | 29 | 12 | 3 |

# Catégories Cliniques de l'IC Fonction Préservée

1. "Garden-variety" (HTN, diabète, obésité)
2. Cardiopathie ischémique
3. Insuffisance cardiaque droite
4. Tableau dominé par FA
5. "Pathologies hypertrophiques"
6. Haut débit
7. Maladie valvulaire (plusieurs lésions 2+)
8. Causes rares (zèbre)

# Mythe n° 5

Ceci n'est pas de l'insuffisance cardiaque

# Nombreuses comorbidités

Table 1. Characteristics of Patients.*

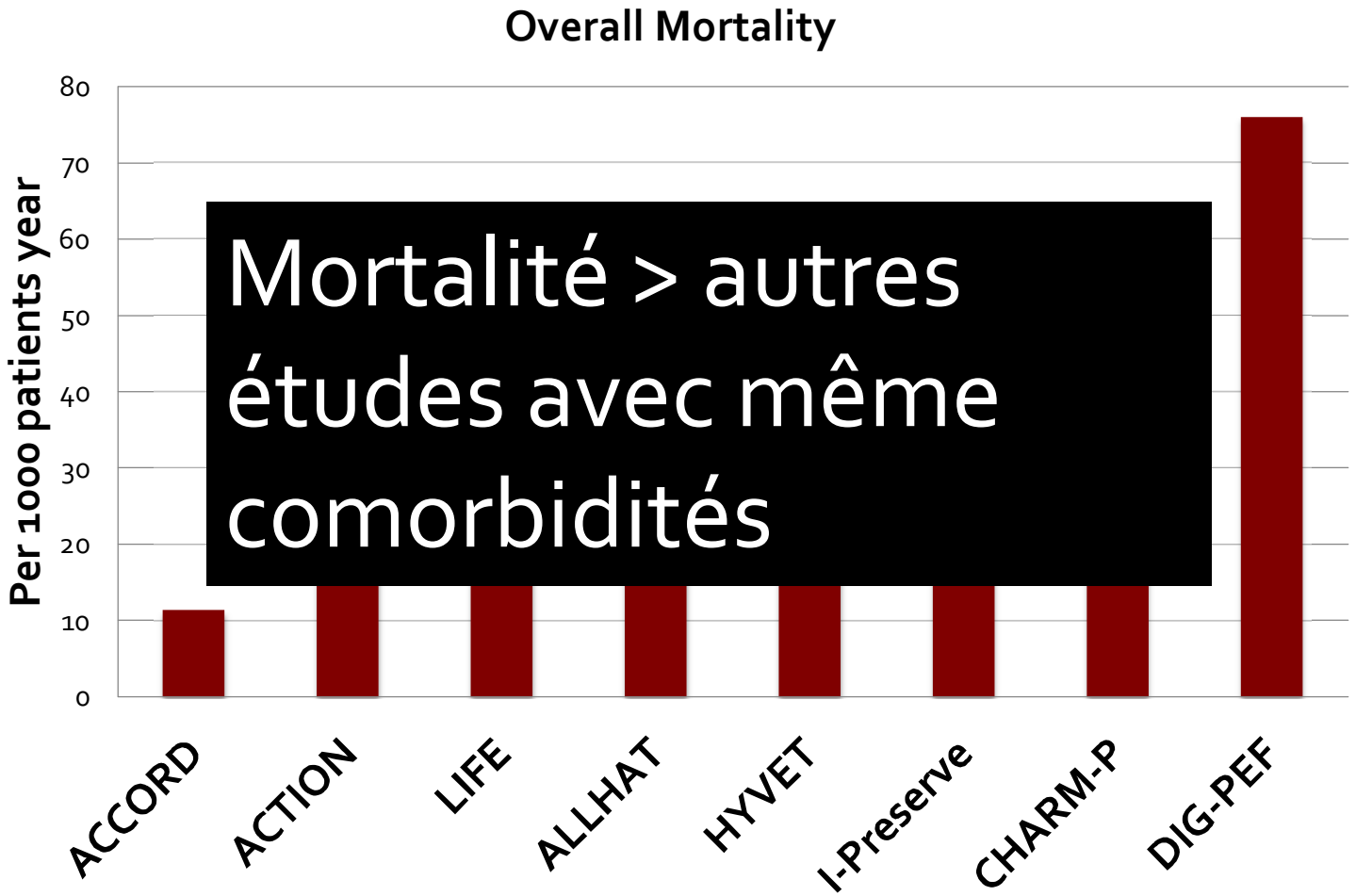
| Characteristic | Reduced Ejection Fraction (<40%) (N=1570) | Preserved Ejection Fraction (>50%) (N=880) | P Value |
|---|---|---|---|
| Mean LVEF — % | 25.9 | 62.4 | <0.001 |
| Age — yr | 71.8 ± 12 | 75.4 ± 11.51 | <0.001 |
| Male sex — no. (%) | 983 (62.6) | 302 (34.3) | <0.001 |

| | 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 |

| | | | |
|---|---|---|---|
| Peptic ulcer disease — no. (%) | 94 (6.0) | 74 (8.4) | 0.02 |
| Hepatitis or cirrhosis — no. (%) | 20 (1.3) | 16 (1.8) | 0.28 |
| Dementia — no. (%) | 76 (4.8) | 49 (5.6) | 0.43 |
| Hemoglobin <10 g/dl — no. (%) | 155 (9.9) | 186 (21.1) | <0.001 |
| Mean systolic blood pressure — mm Hg | 146 | 156 | <0.001 |
| Mean respiratory rate — breaths/min | 26 | 26 | 0.17 |
| Serum sodium <136 mmol/liter — no. (%) | 362 (23.1) | 209 (23.8) | 0.70 |
| Serum creatinine >150 mmol/liter — no. (%) | 296 (18.9) | 195 (22.2) | 0.95 |

Bhatia et al, NEJM 2006

# Comorbidités… oui, mais




Campbell R, JACC 2012, 60: 2349-56

# Est-ce bien de l'IC?

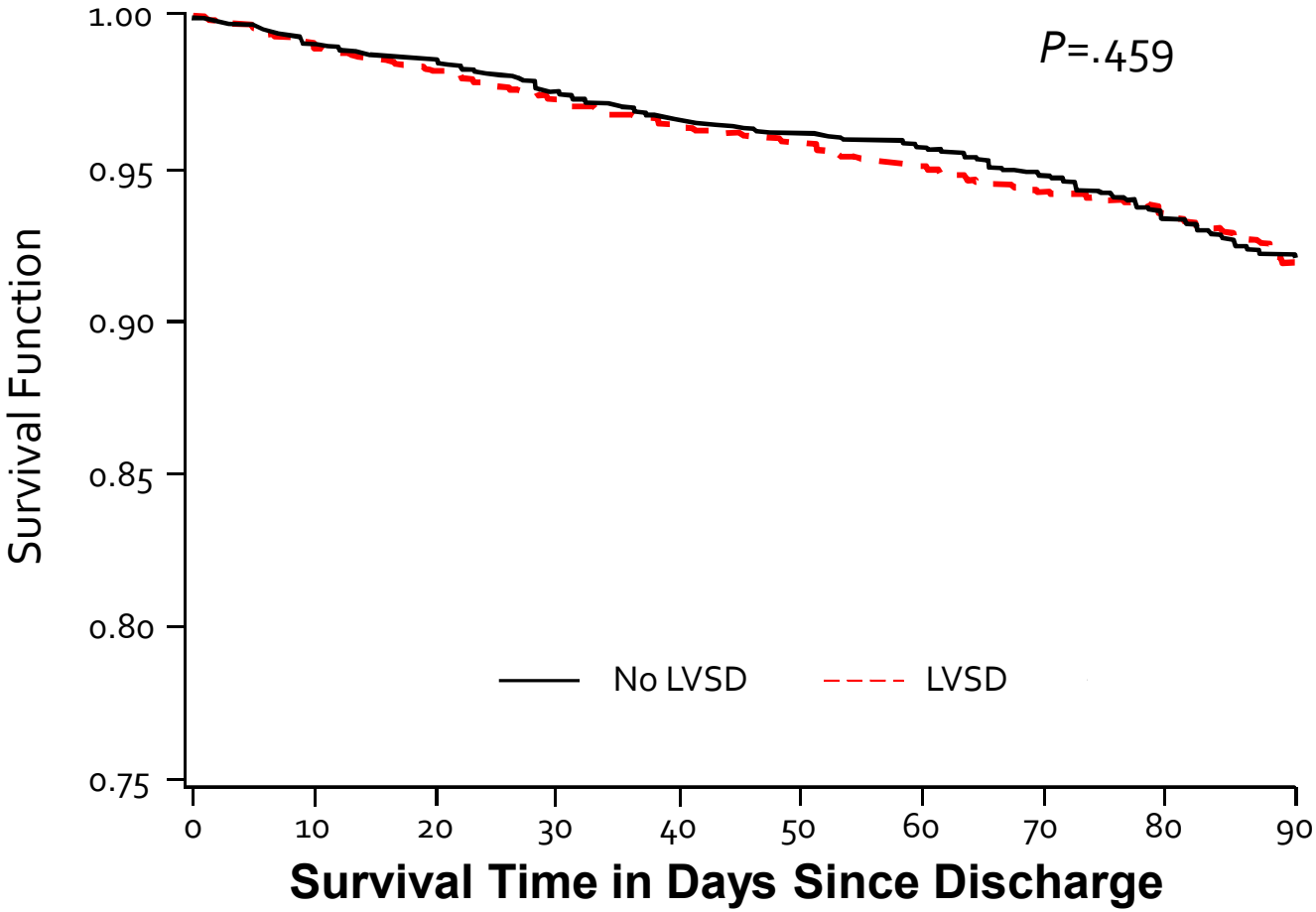
59 patients IC fonction préservée vs. 60 patients avec fonction réduite et 28 contrôles matchés pour l'âge

| | DHF | SHF | CON |
|---|---|---|---|
| Peak VO2 | 14.2±0.5* | 13.1±0.5* | 19.9±0.7 |
| AT | 9.1±0.3* | 8.7±0.3* | 11.5±0.4 |
| Norepinephrine | 306±64* | 287±62* | 169±80 |
| MLHFQ | 24.8±4.4 | 43.8±3.9 | - |

*P<0.05 vs CON; †P<0.05 vs DHF

Kitzman et al, JAMA 2002

# Survie à 60-90 jours

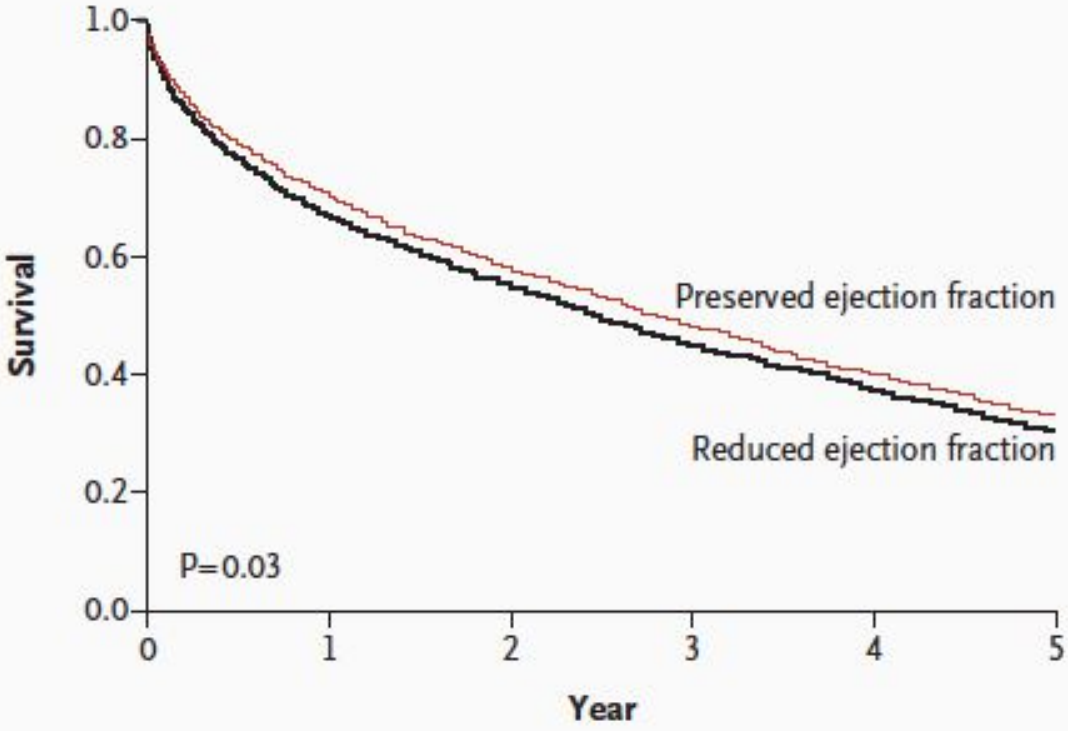



| | | | | |
|---|---|---|---|---|
| **LVSD** | **2,294** | **2,188** | **1,994** | **469** |
| **No LVSD** | **2,604** | **2,471** | **2,195** | **441** |

**P* value (40%≤ EF ≤50% vs EF >50%).

Fonarow et al, OPTIMIZE-HF registry, JACC 2007

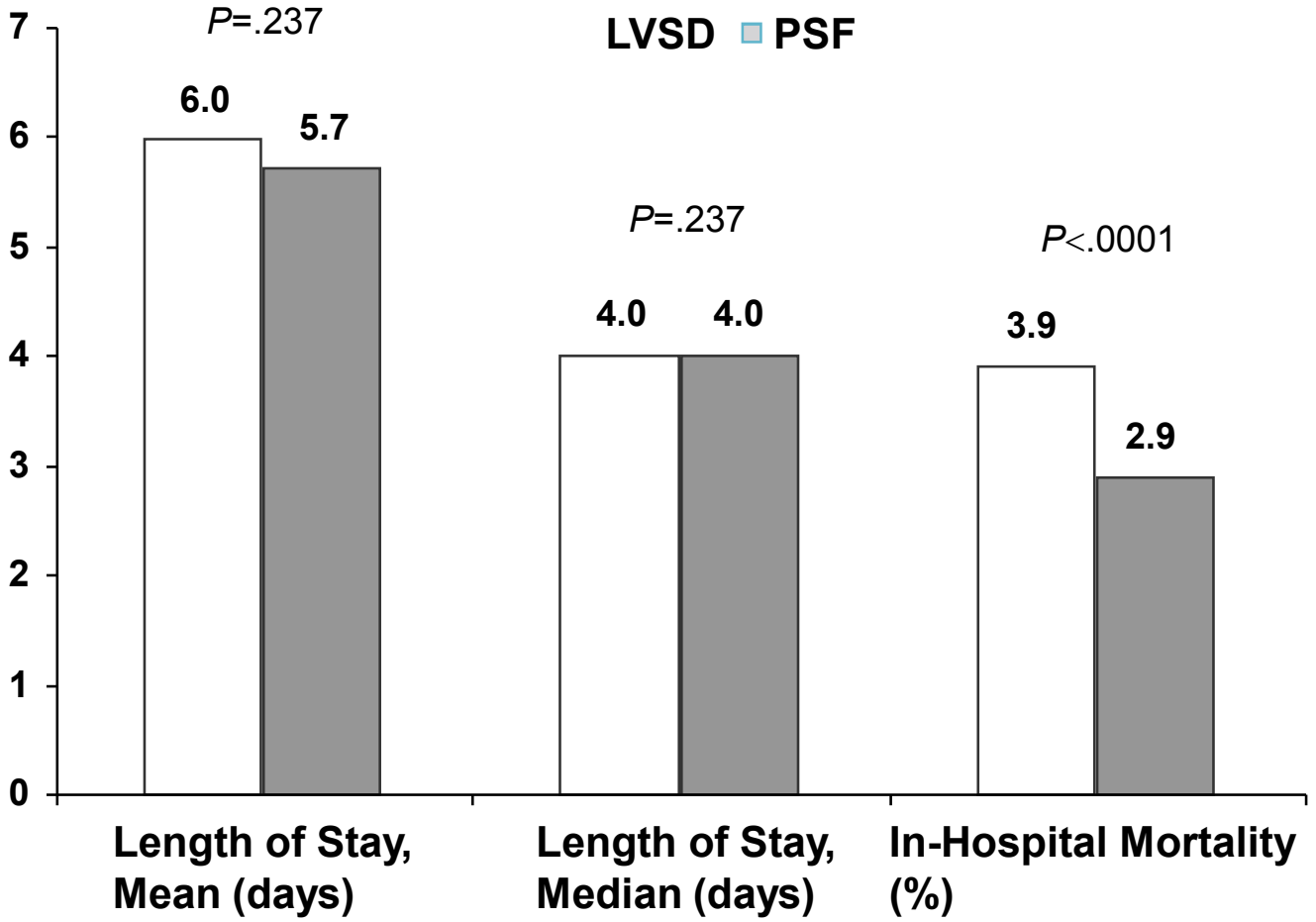
# Survie à Long Terme




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Reduced ejection fraction | 2424 | 1637 | 1350 | 1049 | 813 | 604 |
| Preserved ejection fraction | 2166 | 1539 | 1270 | 1001 | 758 | 574 |

OwanT et al. N EnglJ Med 2006;355:251-

# Séjour hospitalier




PSF = LVEF ≥40%.

Fonarow et al, OPTIMIZE-HF registry, JACC 2007

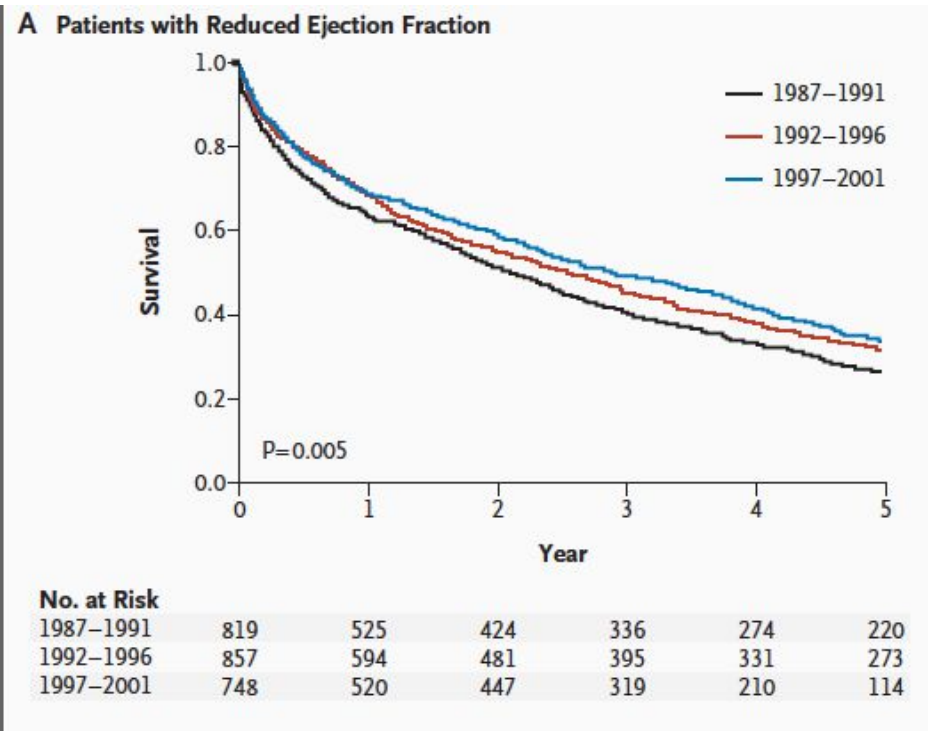
# Pas de différence de pronostic!

| Outcome | LVSD (n=20,118) | 40%≤ EF ≤50% (n=7,321) | EF >50% (n=10,072) | *P* Value* |
|---|---|---|---|---|
| In-hospital mortality: all patients | 3.9 | 3.0 | 2.9 | .647 |
| Follow-Up Cohort | | | | |
| Post-discharge mortality | 9.8 | 9.2 | 9.3 | .887 |
| Rehospitalization | 29.9 | 29.0 | 30.9 | .366 |
| Post-discharge mortality/ rehospitalization | 36.1 | 35.1 | 36.8 | .436 |

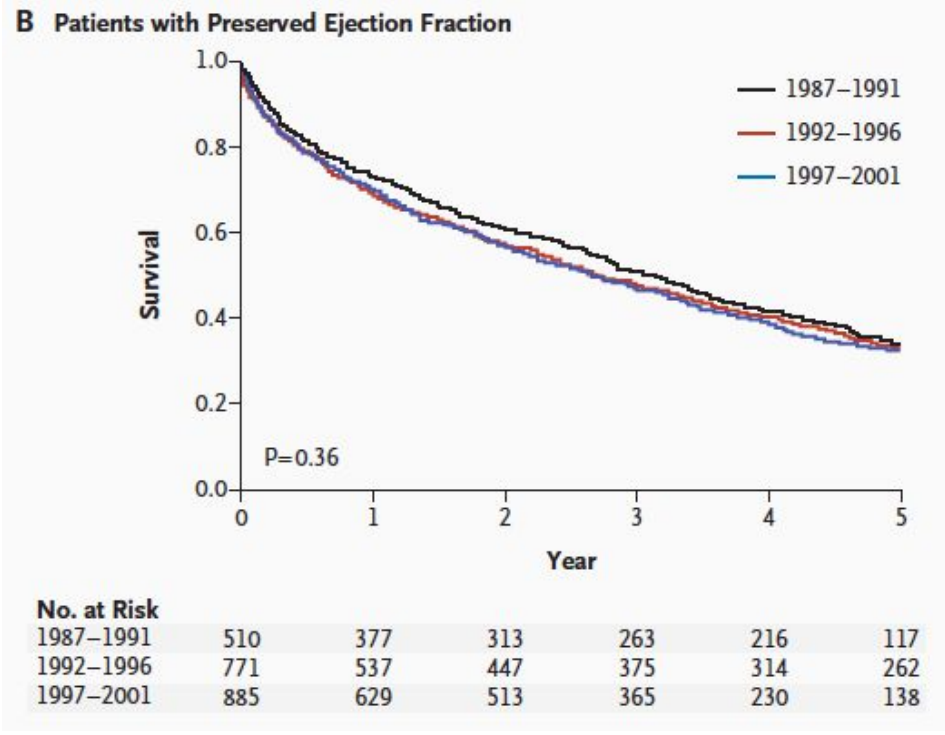
**P* value (40%≤ EF ≤50% vs EF >50%).

Fonarow et al, OPTIMIZE-HF registry, JACC 2007

# Et aucune amélioration




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| 1987–1991 | 819 | 525 | 424 | 336 | 274 | 220 |
| 1992–1996 | 857 | 594 | 481 | 395 | 331 | 273 |
| 1997–2001 | 748 | 520 | 447 | 319 | 210 | 114 |




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| 1987–1991 | 510 | 377 | 313 | 263 | 216 | 117 |
| 1992–1996 | 771 | 537 | 447 | 375 | 314 | 262 |
| 1997–2001 | 885 | 629 | 513 | 365 | 230 | 138 |

Owan TE, et al. *N Engl J Med*. 2006;355:251-259.

# Mythe n° 6

## Pas de Traitement

European Heart Journal Advance Access published May 20, 2016


European Heart Journal
doi:10.1093/eurheartj/ehw128

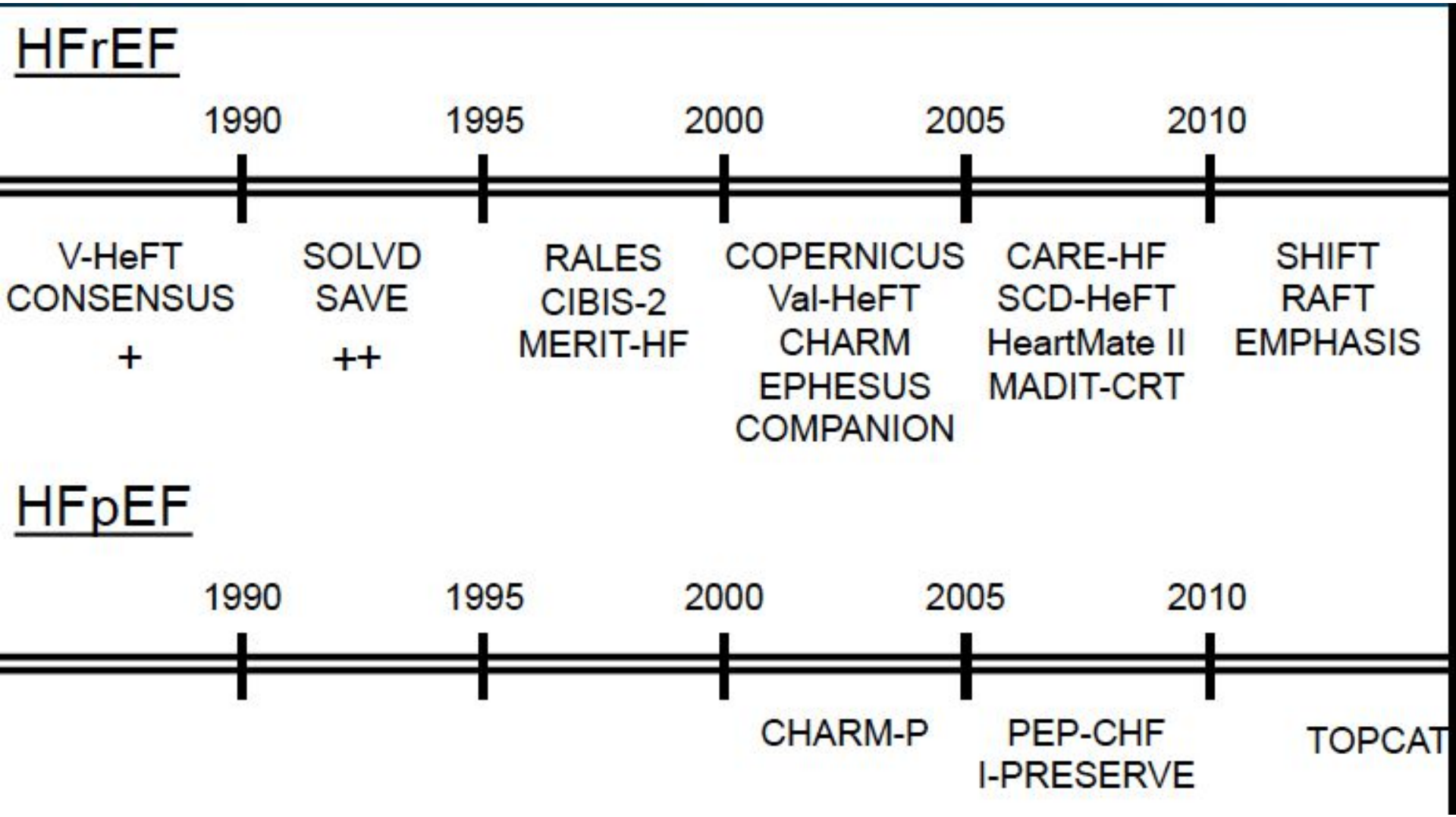
ESC GUIDELINES

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

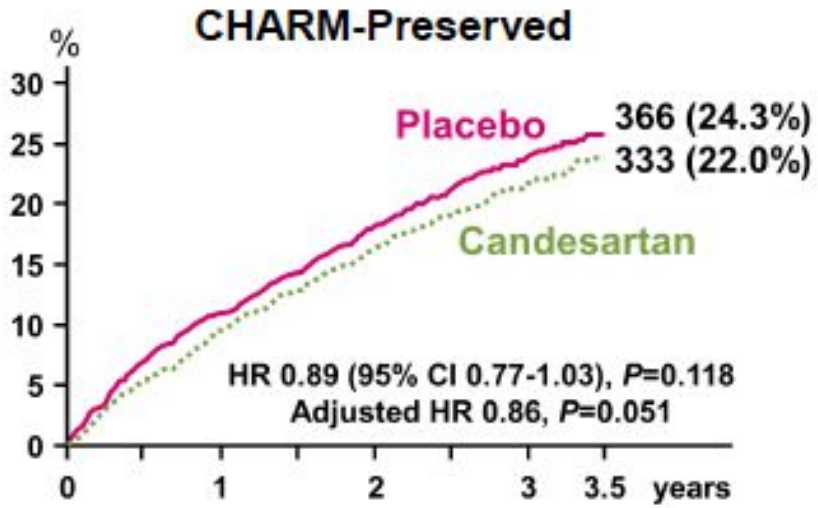
## 8. Pharmacological treatment of heart failure with 'preserved' ejection fraction (diastolic heart failure)

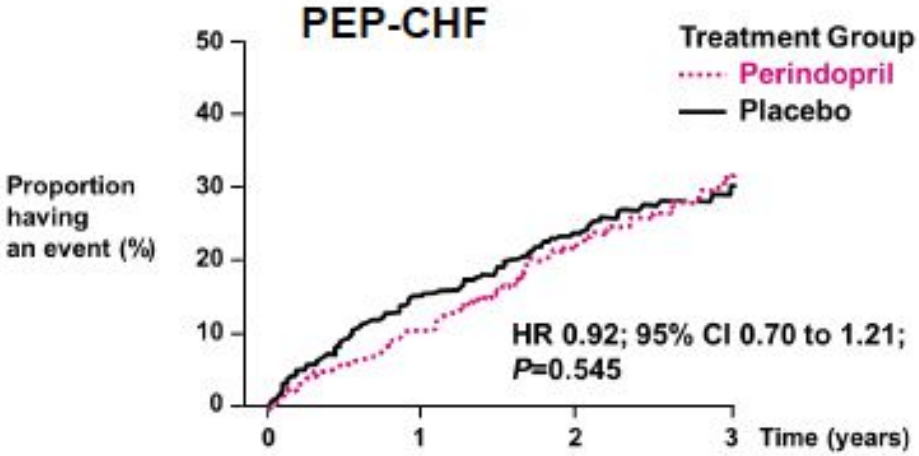
No treatment has yet been shown, convincingly, to reduce morbidity or mortality in patients with HFpEF or HFmrEF. However, since these patients are often elderly and highly symptomatic, and often have a poor quality of life,[307] an important aim of therapy may be to alleviate symptoms and improve well-being.[308]

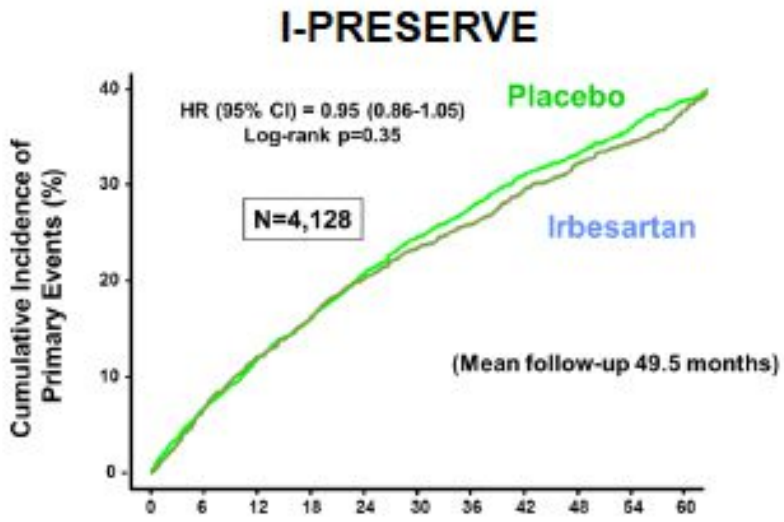
# Etudes randomisées

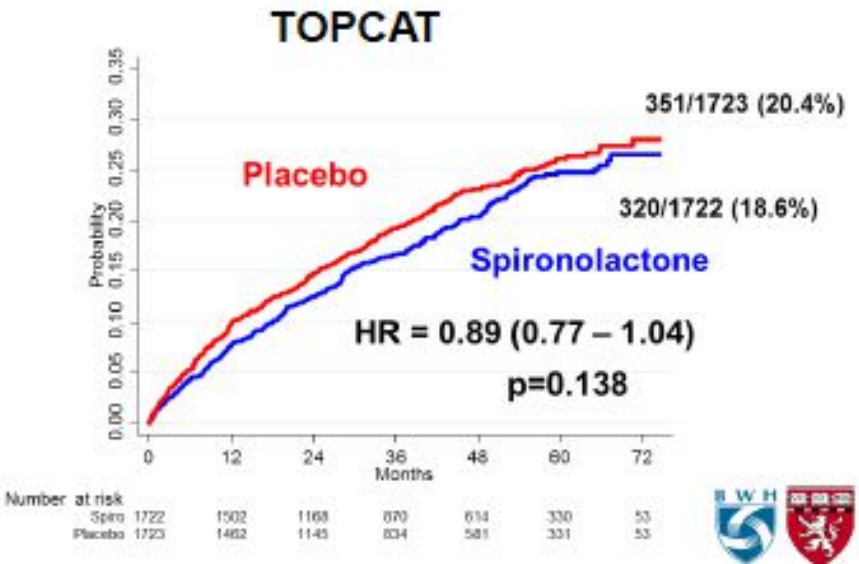


# Aucun bénéfice…



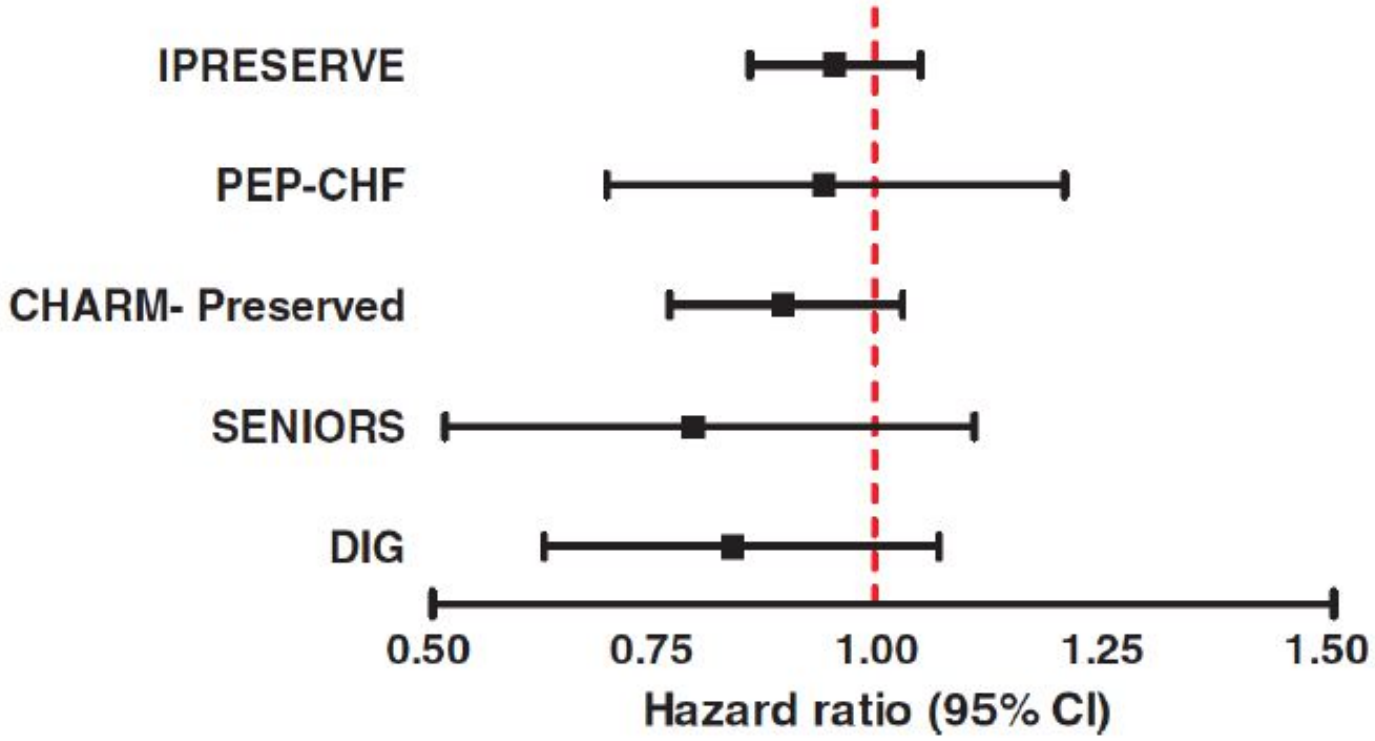



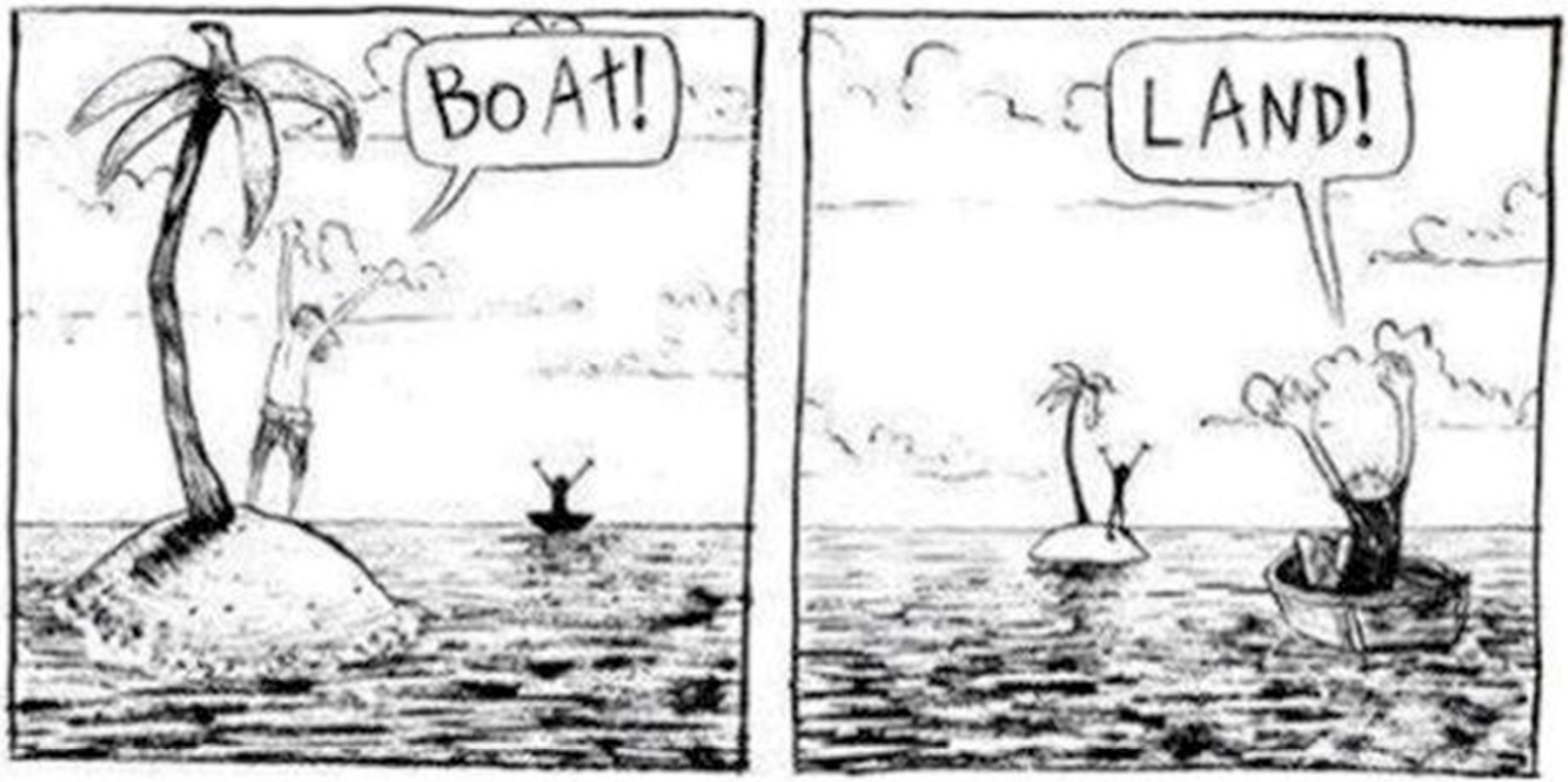



| Trial | Intervention | Primary Results |
|---|---|---|
| DIG-PEF | Digoxin | Negative |
| CHARM-Preserved | Candesartan | Negative |
| PEP-CHF | Perindopril | Negative |
| I-PRESERVE | Irbesartan | Negative |
| RELAX-HFpEF | Sildenafil | Negative |
| TOPCAT | Spironolactone | Negative |

# MAIS




Redfield Circ Heart Fail 2012




Perspective...

# DIGOXINE-Dig-HF

**TABLE 1.** BASE-LINE CHARACTERISTICS OF THE STUDY PATIENTS ACCORDING TO TREATMENT GROUP.*

| CHARACTERISTIC | DIGOXIN (N=3397) | PLACEBO (N=3403) |
|---|---|---|
| Age (yr) — mean ±SD | 63.4±11.0 | 63.5±10.8 |
| Ejection fraction — mean ±SD | 28.6±8.9 | 28.4±8.9 |
| Median duration of CHF — mo | 17 | 16 |
| | % of patients | |
| Female sex | 22.2 | 22.5 |
| Nonwhite race | 14.4 | 14.8 |
| Age >70 yr | 26.7 | 27.4 |
| Method of assessing ejection fraction | | |
| Radionuclide ventriculography | 65.0 | 64.2 |
| Two-dimensional echocardiography | 29.5 | 30.0 |
| Contrast angiography | 5.5 | 5.8 |
| Cardiothoracic ratio >0.55 | 34.6 | 34.4 |
| NYHA class | | |
| I | 13.7 | 13.0 |
| II | 53.3 | 54.5 |
| III | 30.7 | 30.5 |
| IV | 2.2 | 1.9 |
| Primary cause of CHF | | |
| Ischemic | 70.8 | 70.4 |
| Nonischemic | 29.0 | 29.3 |
| Idiopathic | 15.5 | 14.1 |
| Hypertensive | 8.0 | 9.2 |
| Other‡ | 5.4 | 6.0 |
| Concomitant medications | | |
| Diuretics | 81.2 | 82.2 |
| ACE inhibitors | 94.1 | 94.8 |
| Nitrates | 42.1 | 43.1 |
| Other vasodilators§ | 0.9 | 1.5 |
| Daily dose of study medication prescribed | | |
| 0.125 mg | 17.5 | 17.4 |
| 0.250 mg | 70.6 | 70.0 |
| 0.375 mg | 10.3 | 11.3 |
| 0.500 mg | 1.1 | 0.9 |

**450 patients par groupe FE>45%**

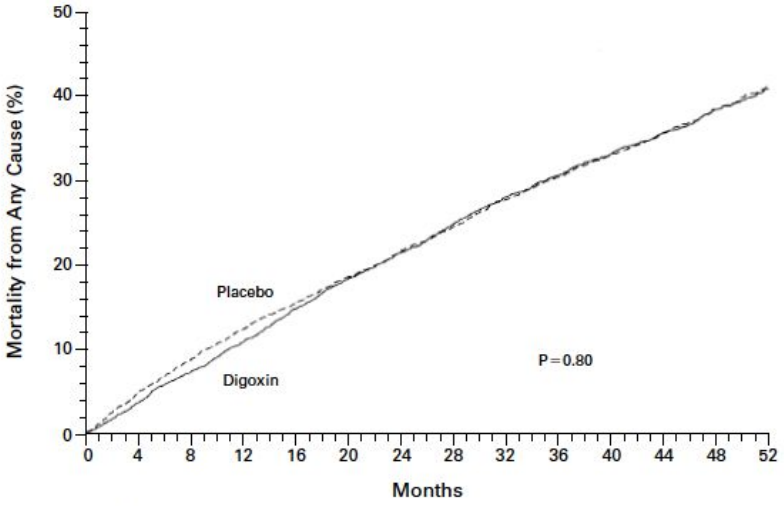
The New England Journal of Medicine



VOLUME 336 FEBRUARY 20, 1997 NUMBER 8

THE EFFECT OF DIGOXIN ON MORTALITY AND MORBIDITY IN PATIENTS WITH HEART FAILURE

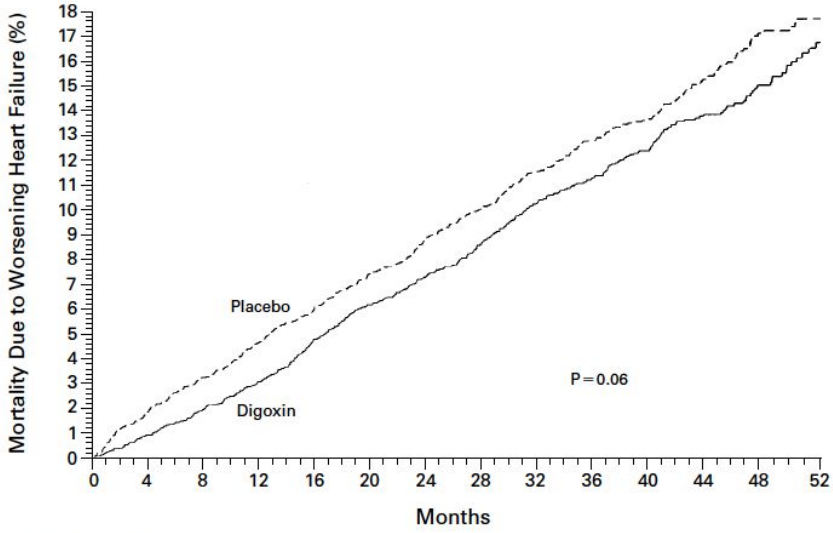
# DIGOXINE




No. of Patients at Risk

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 3403 | 3239 | 3105 | 2976 | 2868 | 2758 | 2652 | 2551 | 2205 | 1881 | 1506 | 1168 | 734 | 339 |
| Digoxin | 3397 | 3269 | 3144 | 3019 | 2882 | 2759 | 2644 | 2531 | 2184 | 1840 | 1475 | 1156 | 737 | 335 |

**Figure 1.** Mortality in the Digoxin and Placebo Groups.
The number of patients at risk at each four-month interval is shown below the figure.




No. of Patients at Risk

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
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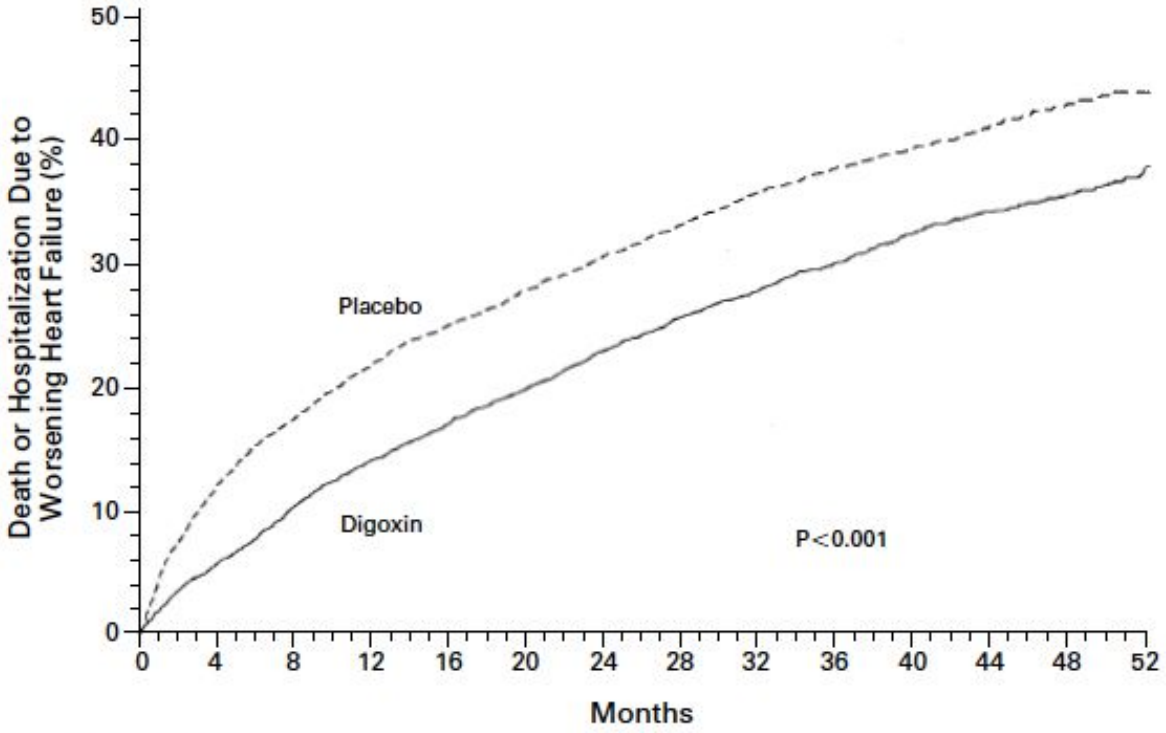
| Digoxin | 3397 | 3269 | 3144 | 3019 | 2882 | 2759 | 2644 | 2531 | 2184 | 1840 | 1475 | 1156 | 737 | 335 |

**Figure 2.** Mortality Due to Worsening Heart Failure in the Digoxin and Placebo Groups.
The number of patients at risk at each four-month interval is shown below the figure.

# DIGOXINE




No. of Patients at Risk

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 3403 | 2915 | 2674 | 2473 | 2328 | 2197 | 2071 | 1954 | 1659 | 1397 | 1111 | 859 | 546 | 250 |
| Digoxin | 3397 | 3120 | 2888 | 2696 | 2544 | 2392 | 2241 | 2115 | 1825 | 1521 | 1188 | 916 | 578 | 255 |

**Figure 3.** Incidence of Death or Hospitalization Due to Worsening Heart Failure in the Digoxin and Placebo Groups.

The number of patients at risk at each four-month interval is shown below the figure.

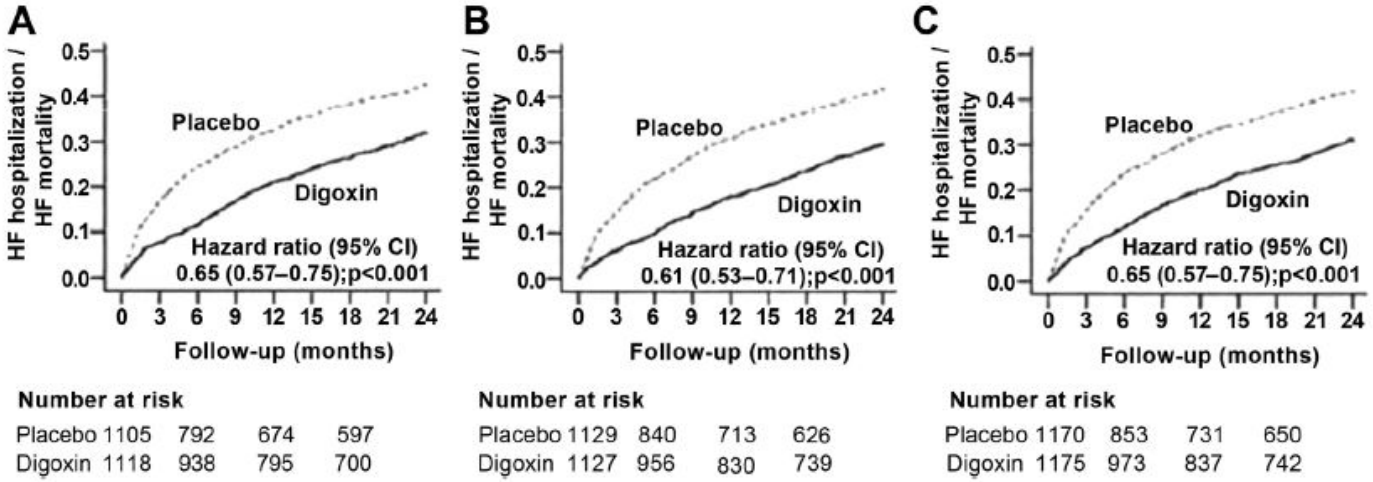



**Figure 5** Kaplan-Meier Plots for Hospitalization or Death Due to HF by Treatment Groups in High-Risk Patients, Including NYHA Functional Class III or IV, LVEF <25%, and Cardiothoracic Ratio >55% in the DIG Trial

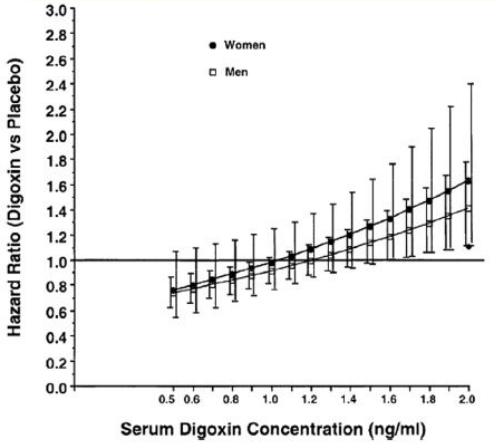



**Figure 4** Point Estimate and 95% Confidence Intervals of Hazard of Death From Any Cause for Men and Women by SDC

SDC = serum digoxin concentration. Reprinted, with permission, from Adams

DOSAGE SANGUIN: 0,6-1ng/mL
Prudence si IR

FA

| | | |
|---|---|---|
| For patients in NYHA Class I–III, digoxin, should be considered when ventricular rate remains high[d] despite beta-blockers or when beta-blockers are not tolerated or contra-indicated. | IIa | B |

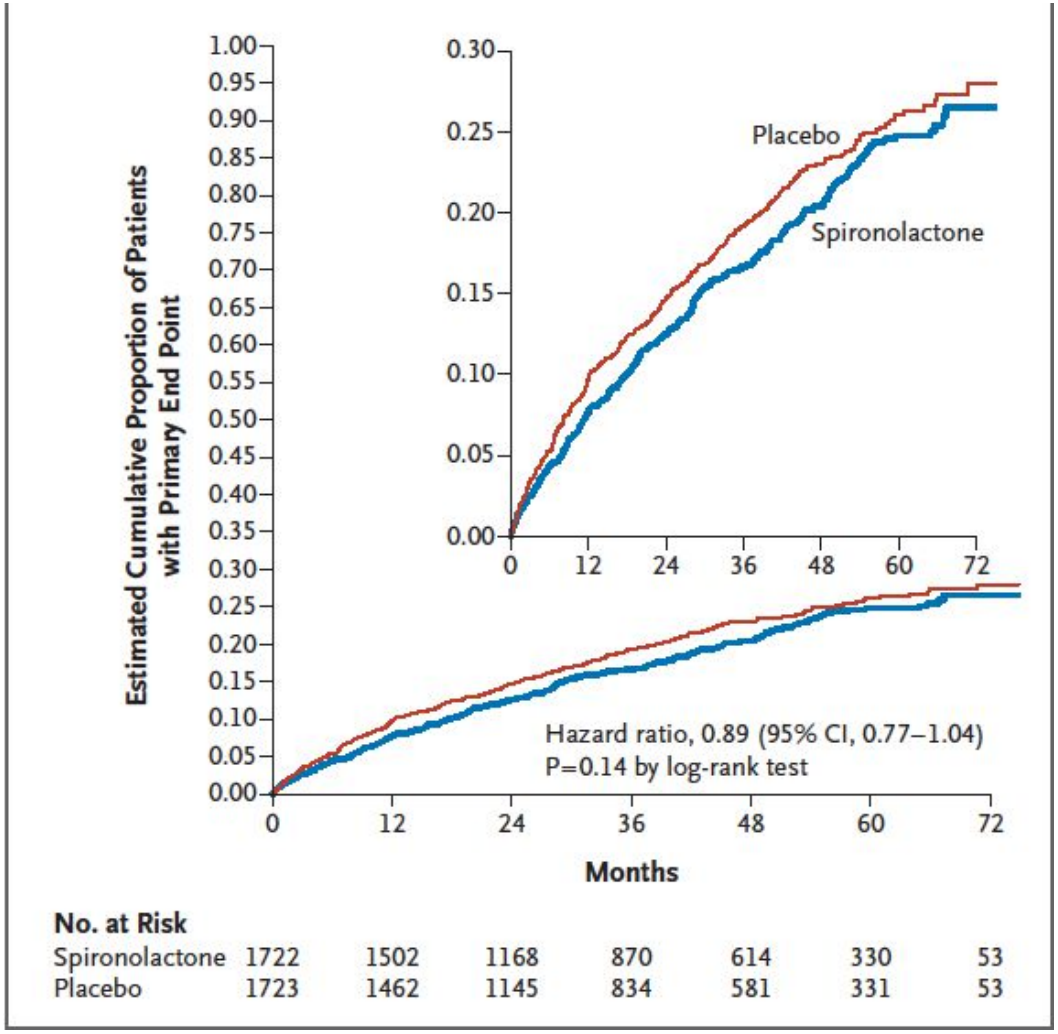
| Digoxin | | |
|---|---|---|
| Digoxin may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE-I (or ARB), a beta-blocker and an MRA, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations). | IIb | B |

# Etude TOPCAT

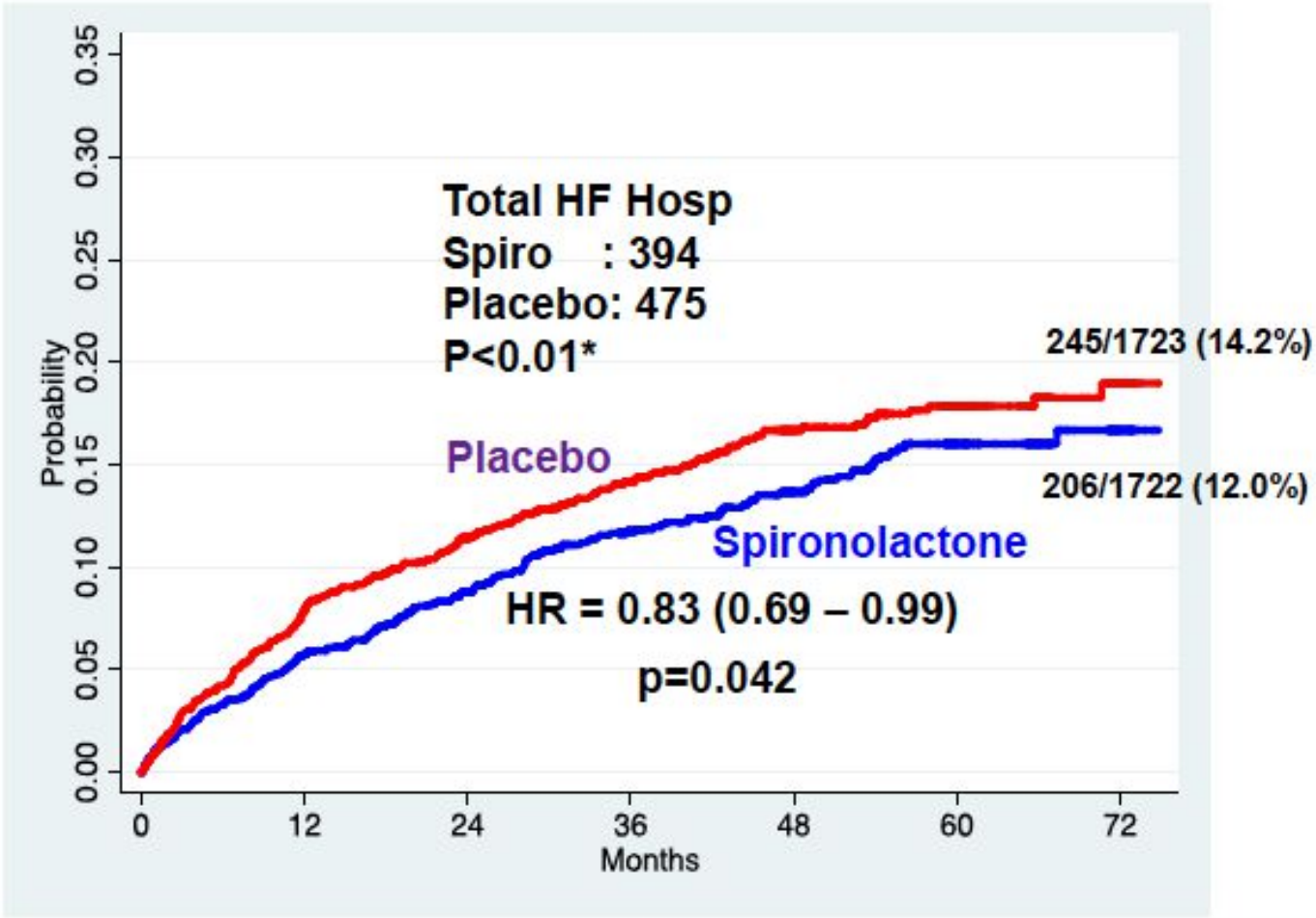
**Table 1. Selected Baseline Characteristics of the Study Patients.***

| Characteristic | Spironolactone (N=1722) | Placebo (N=1723) |
|---|---|---|
| Age — yr | | |
| Median | 68.7 | 68.7 |
| Interquartile range | 61.0–76.4 | 60.7–75.5 |
| Age ≥75 yr — no. (%) | 495 (28.7) | 453 (26.3) |
| Female sex — no. (%) | 888 (51.6) | 887 (51.5) |
| White race — no. (%)† | 1525 (88.6) | 1537 (89.2) |
| Left ventricular ejection fraction — % | | |
| Median | 56 | 56 |
| Interquartile range | 51–61 | 51–62 |
| NYHA functional classification — no. (%) | | |
| I | 56 (3.3) | 53 (3.1) |
| II | 1090 (63.3) | 1104 (64.1) |
| III | 568 (33.0) | 553 (32.1) |
| IV | 7 (0.4) | 8 (0.5) |
| Missing data | 1 (<0.1) | 5 (0.3) |
| Eligibility stratum | | |
| Hospitalization in previous year with management of heart failure as major component — no. (%) | 1232 (71.5) | 1232 (71.5) |
| Elevated natriuretic peptides in previous 60 days — no. (%)‡ | 490 (28.5) | 491 (28.5) |
| BNP — pg/ml | | |
| Median | 236 | 235 |
| Interquartile range | 149–414 | 141–410 |
| NT-proBNP — pg/ml | | |
| Median§ | 887 | 1017 |
| Interquartile range | 537–1634 | 627–2258 |

# Etude TOPCAT

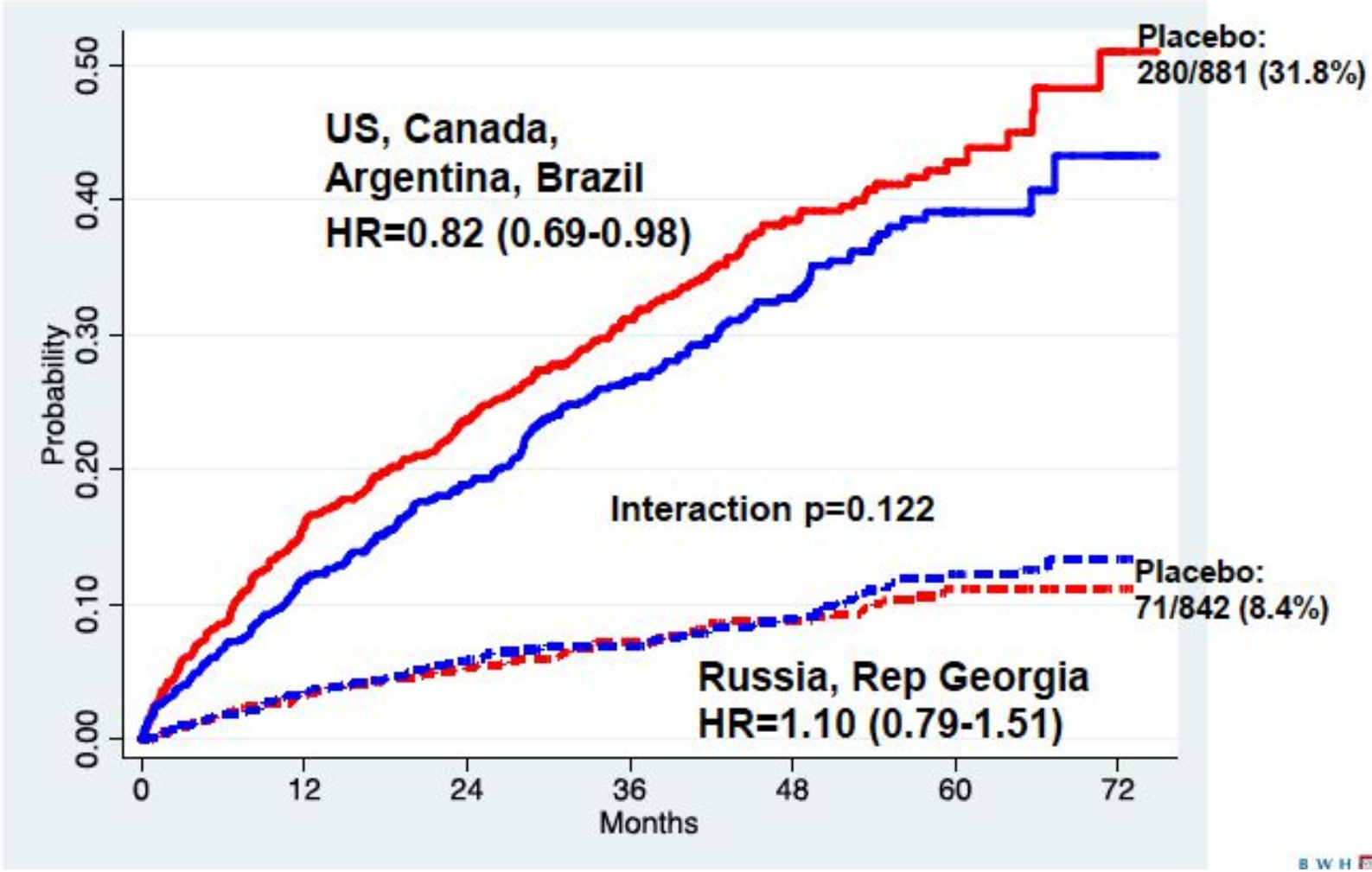


# TOPCAT: réduction des hospitalisations pour IC




*poisson regression

# Biais à l'inclusion



# TOPCAT: sous-groupe

| Enrolled by: | Spiro | Placebo | Hazard Ratio (95% CI) P-value |
|---|---|---|---|
| **Natriuretic peptide** | **78/490** (15.9%) | **116/491** (23.6%) | **0.65** (0.49-0.87) **0.003** |
| **Heart Failure Hosp** | **242/1232** (19.6%) | **235/1232** (19.1%) | **1.01** (0.84-1.21) **0.923** |

***P=0.013 for interaction**

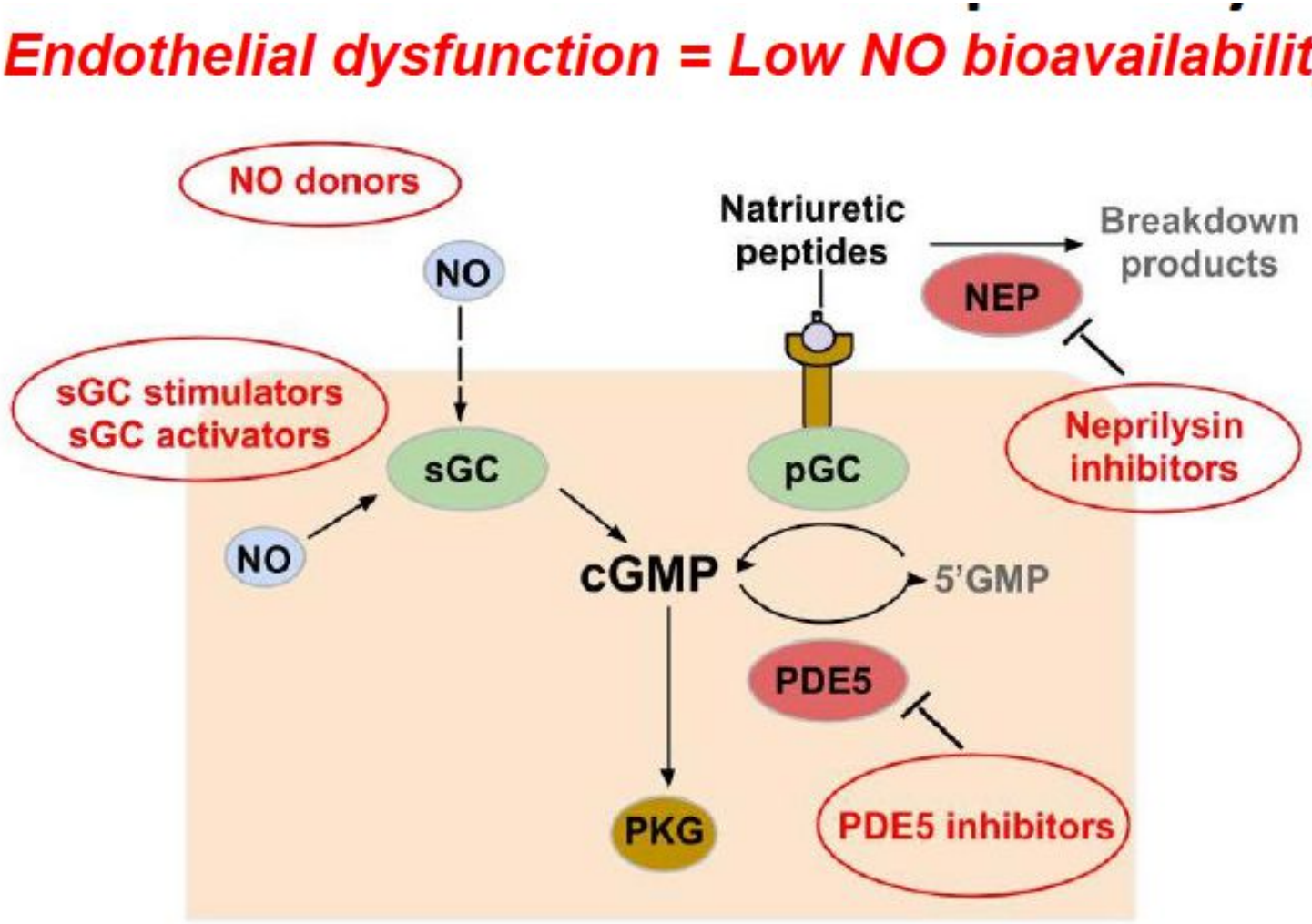
Bénéfice chez les patients inclus avec peptides natriurétiques élevés

# Inhibiteur des Phosphodiestérases-5

- RCT Sildénafil (50mg 3x/jour) vs. placebo
- 44 patients avec IC fonction préservée et PAPs>40mmHg
- A 6 et 12 mois,  Sildénafil montre:
  - Réduction PAPm, pression OD et résistances pulmonaires
  - Amélioration fonction VD
  - Amélioration QOL

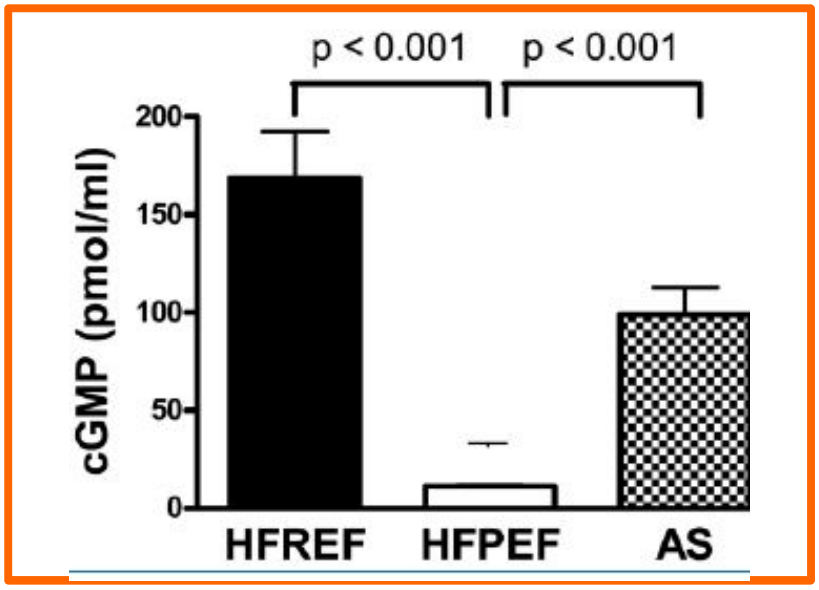
Guazzi et al, Circulation 2011

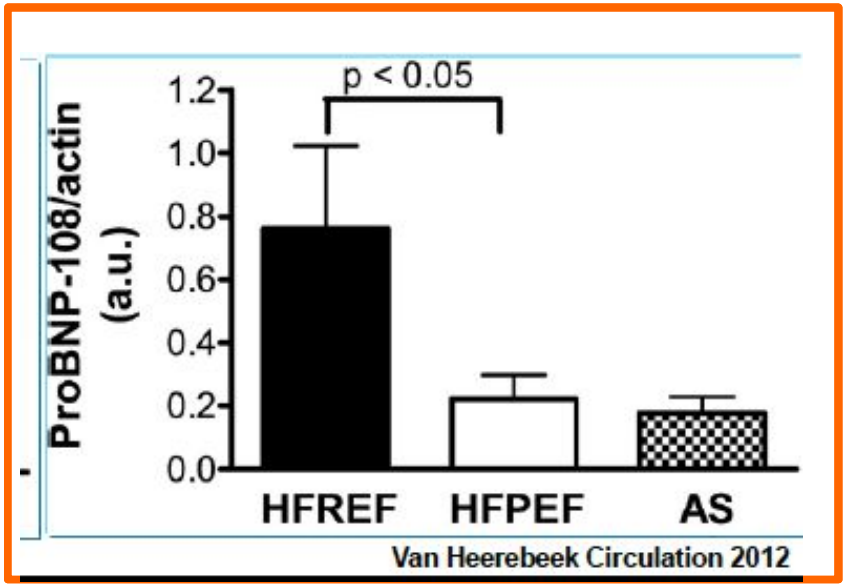
# Rôle du NO et du cGMP?




Komajda and Lam Eur Heart J 2014

# Rôle du NO – voie cGMP

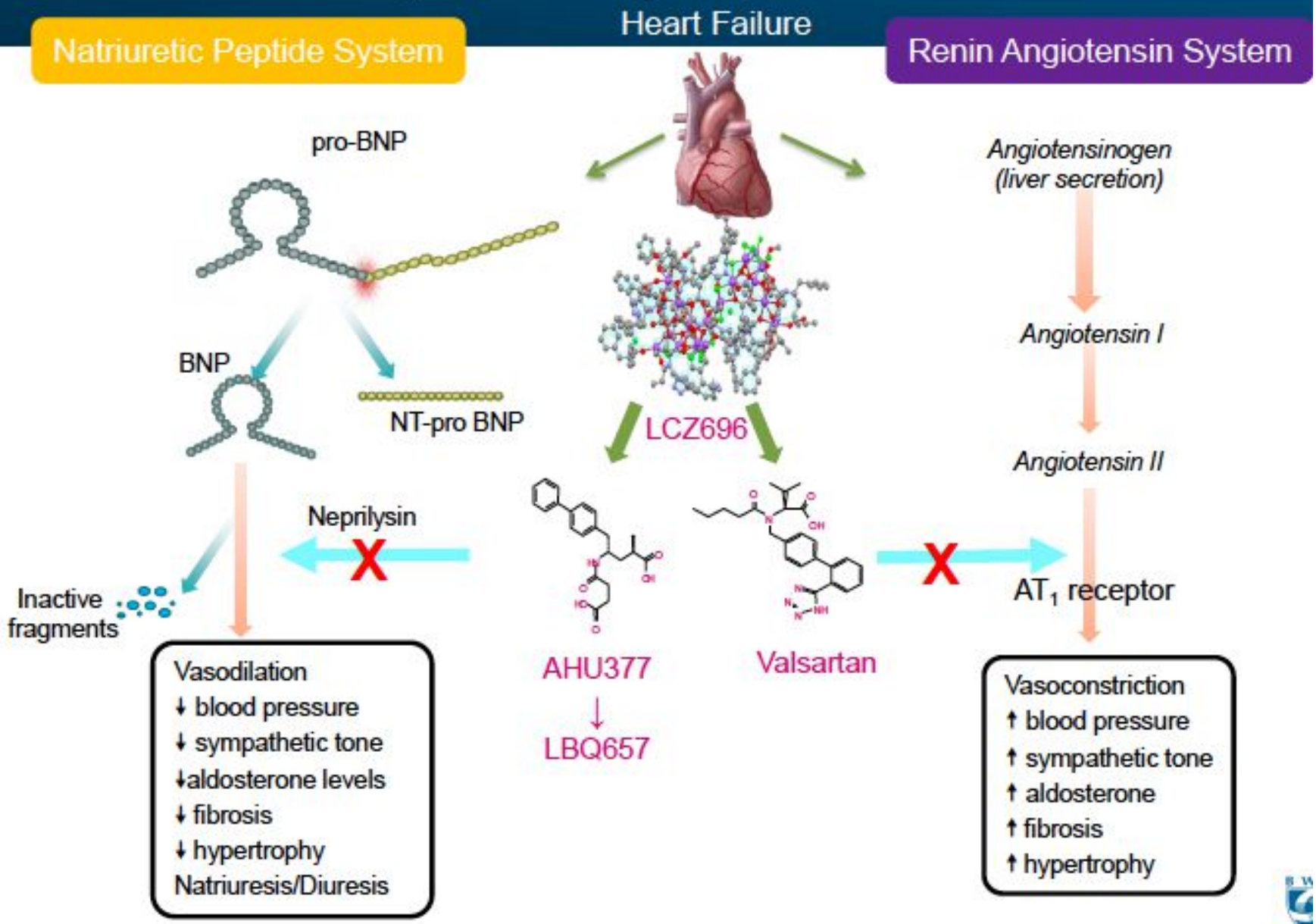


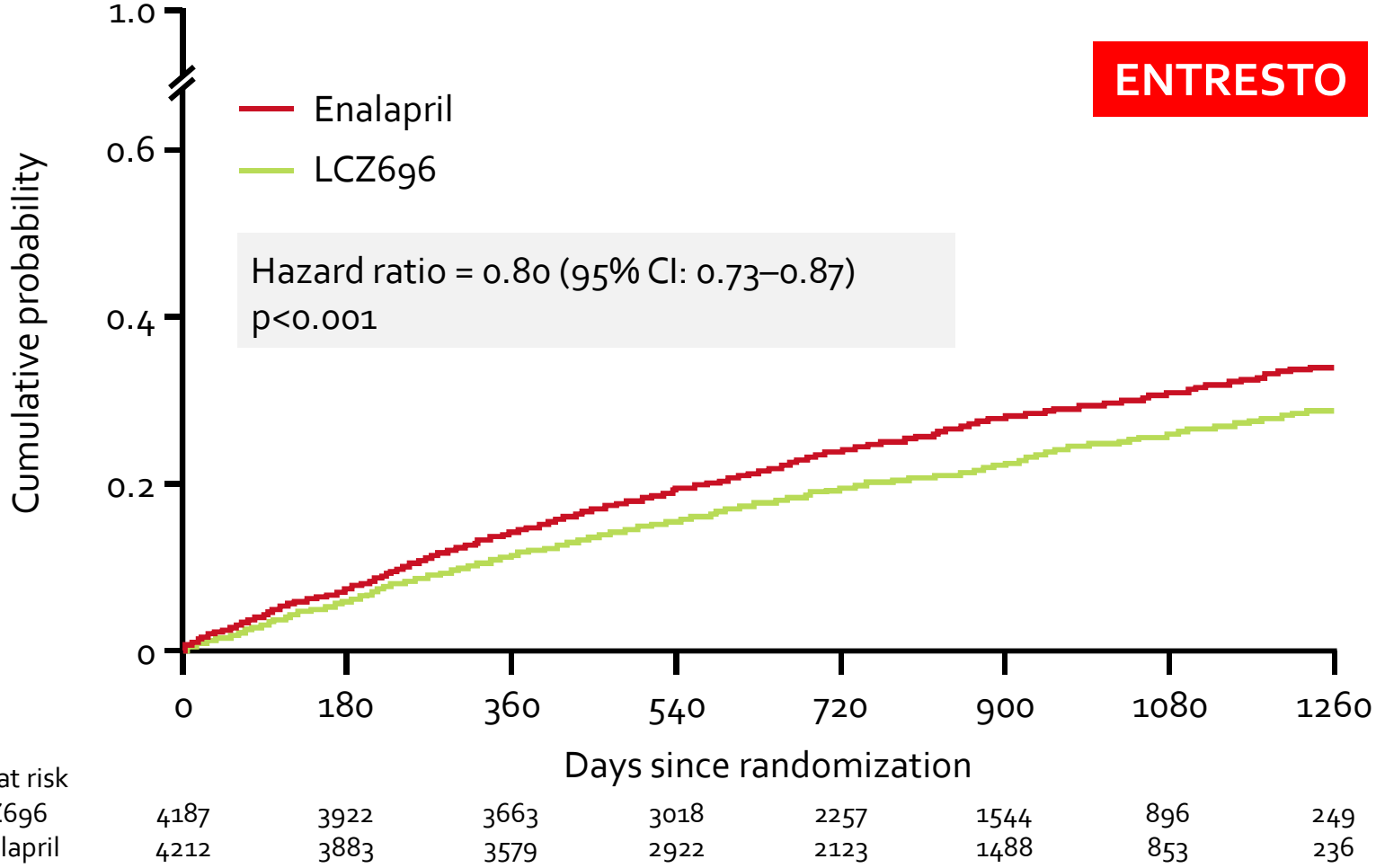
# *So*luble Guanylate *C*yclase stimulato*r* He*a*r*t* Failur*e* *S*tudies:
# The SOCRATES Program

| | SOCRATES-REDUCED | SOCRATES-PRESERVED |
|---|---|---|
| Design | 2 randomized parallel-group, placebo-controlled, double-blind, dose finding phase IIb studies of 4 dose regimens of the oral sGC stimulator BAY1021189 over 12 weeks | |
| Inclusion Criteria | Worsening chronic heart failure requiring hospitalization (or IV diuretic treatment for HF without hospitalization) with initiation of study treatment after clinical stabilization | |
| | LVEF <45% | LVEF ≥45% |
| Primary Outcome Measure | NT-proBNP at 12 weeks | NT-proBNP / left atrial volume at 12 weeks (split $\alpha$: each $p<0.025$) |
| Enrollment | 410 patients in 5 arms | 470 patients in 5 arms |
| Study Start Date | Oct 2013 | |
| CT.gov Identifier | NCT01951625 | NCT01951638 |

# LCZ696 – A First-in-Class Angiotensin Receptor Neprilysin Inhibitor



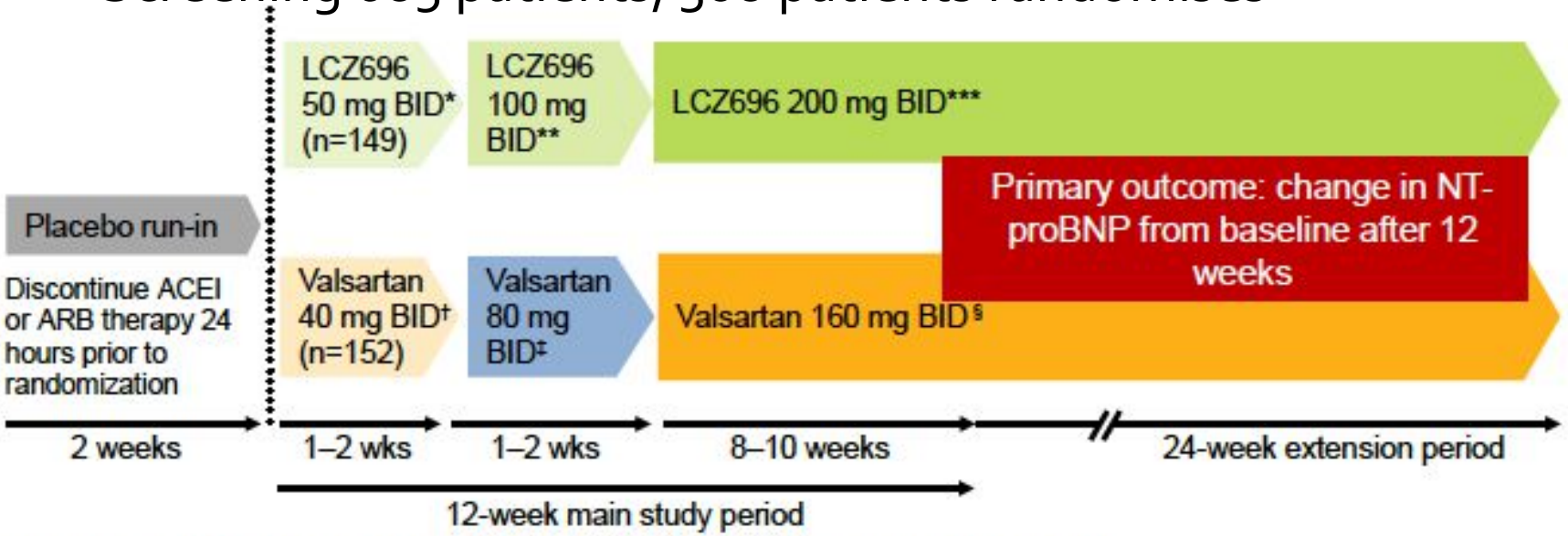
# PARADIGM: Death from CV Causes or First Hospitalization for HF




PARADIGM-HF, N Engl J Med 2014;371:993-1004

# PARAMOUNT: LCZ696 vs. Valsartan dans IC fonction préservée

- Etude phase II, multicentrique, randomisée, double aveugle,
- LCZ696 200mg 2x/j vs. Valsartan 160mg 2x/j
- FE >45%
- Screening 685 patients, 308 patients randomisés




*100 mg TDD; **200 mg TDD; ***400 mg TDD; †80 mg TDD; ‡160 mg TDD; §320 mg TDD

Solomon et al. Lancet 2012;380:1387–95

# PARAMOUNT:diminution significative du NT-proBNP à 12 semaines

- Reduction in NT-proBNP from baseline to Week 12 was significantly greater with LCZ696 compared with valsartan (p=0.005)

| NT-proBNP (geometric mean) | LCZ696 (n=134) | Valsartan (n=132) | LCZ696 vs valsartan |
|---|---|---|---|
| Baseline, pg/mL (95% CI) | 783 (670, 914) | 862 (733, 1,012) | 0.77* (0.64, 0.92) p=0.005 |
| Week 12, pg/mL (95% CI) | 605 (512, 714) | 835 (710, 981) | |

*0.77=ratio of the change from baseline treatment effect between LCZ696 and valsartan. LCZ696 reduced NT-proBNP 23% more than valsartan with a p value of 0.005.

Solomon et al. Lancet 2012;380:1387–95

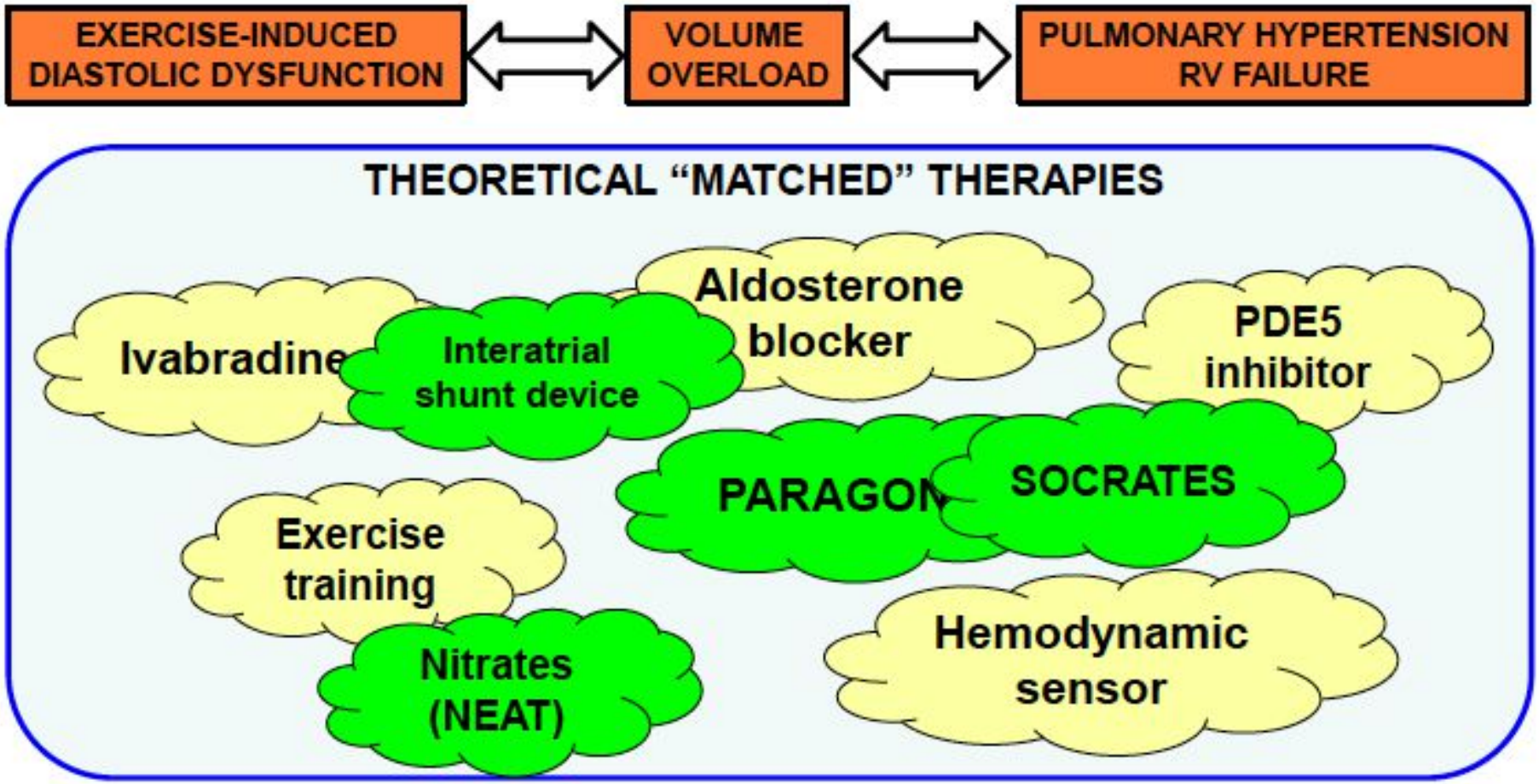

# PARAGON-HF: Prospective comparison of ARni with Arb Global Outcomes in heart failure with preserved ejectioN fraction

A randomized, double blind, trial to evaluate the long-term efficacy and safety profile of the angiotensin receptor neprilysin inhibitor (ARNI), LCZ696, compared with valsartan, in patients with heart failure with preserved ejection fraction (HFpEF)

Solomon et al. Poster presentation at ESC-HF Congress, 25 May 2013;
Novartis data on file: GMA&HEOR_LCZ696B_PARAGON-HF study_XXXX_001_2.0

# Algorithme de Traitement

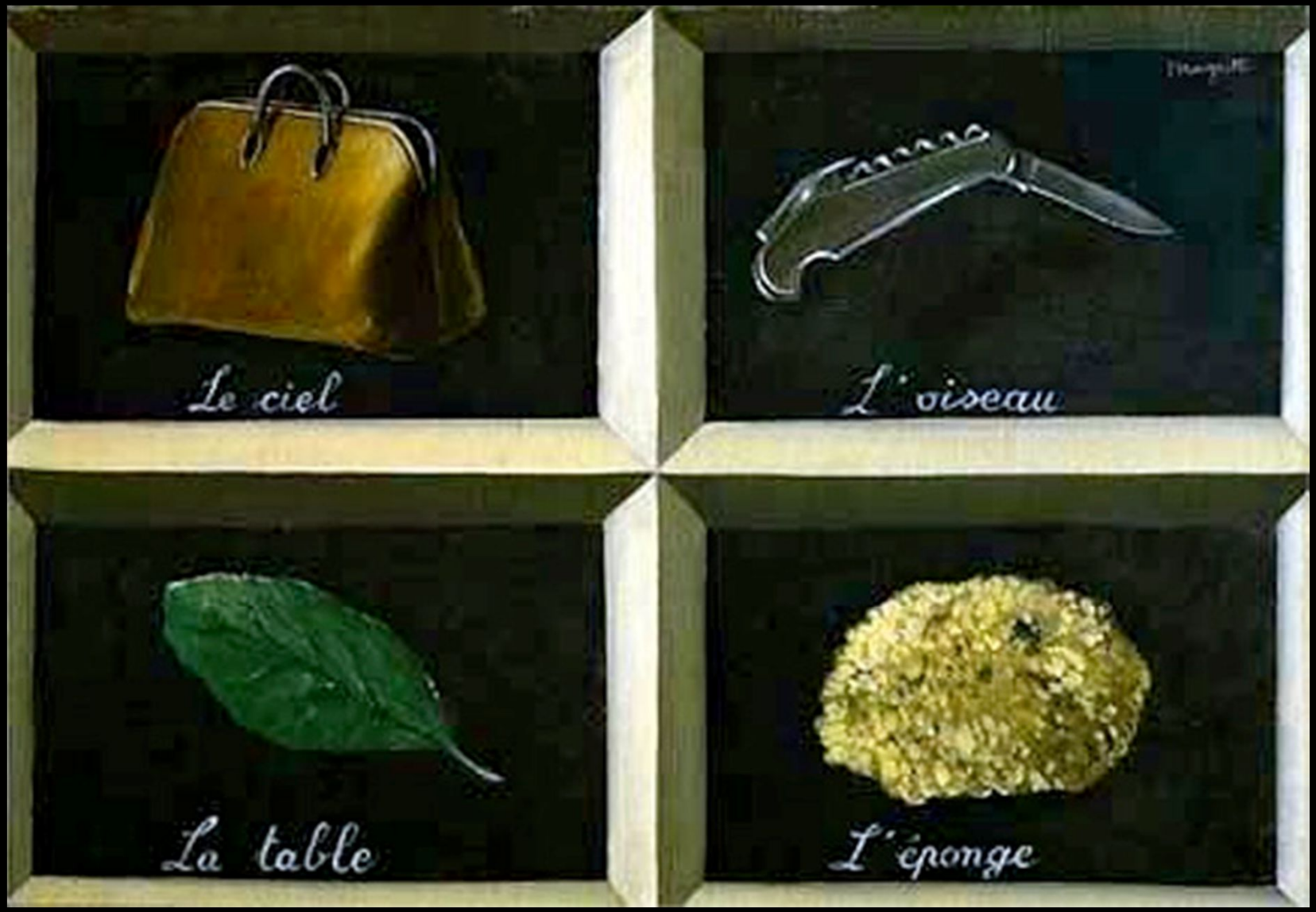
- Poser un diagnostique précis
  - IC fonction préservée est fréquente
  - Ne pas oublier les zèbres (amyloidose, …)
  - Cathérisme cardiaque gauche/droit si doute
- Traiter les causes sous-jacentes
- Traiter l'HTA, la surcharge de volume
- Traiter agressivement les comorbidités
- Education, maladie chronique




Shah SJ. *JACC* 2013

# Conclusion

- Problème de santé publique majeur
- IC à fonction préservée ne doit pas être sous-estimée
- Plus qu'un simple amalgame de comorbidités
- Le **diagnostique reste CLINIQUE**
- **Attention aux zèbres**
- Nouvelles études en cours




La Clef des Songes, René Magritte, 1927

European Heart Journal Advance Access published May 20, 2016

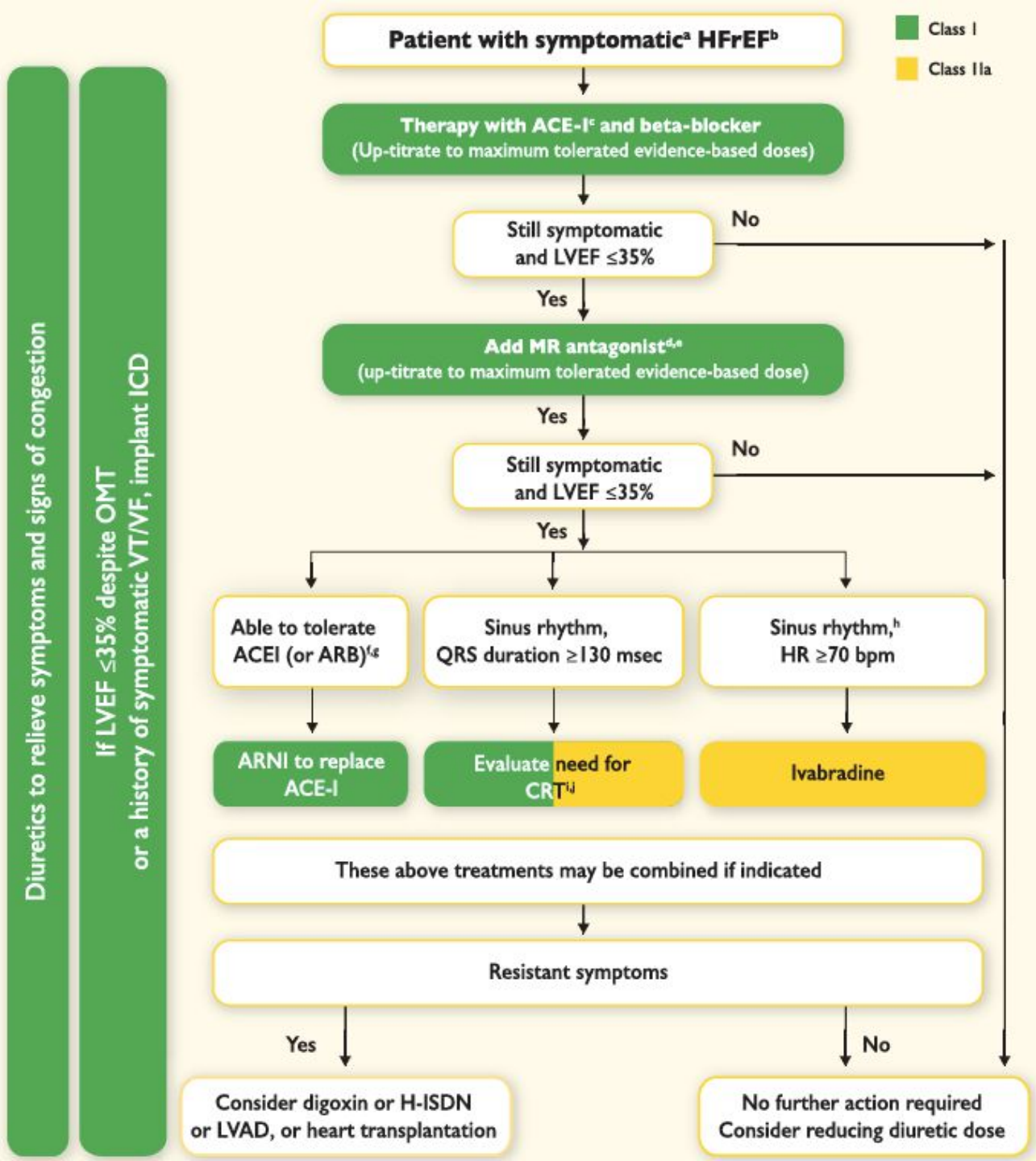

European Heart Journal
doi:10.1093/eurheartj/ehw128

ESC GUIDELINES

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

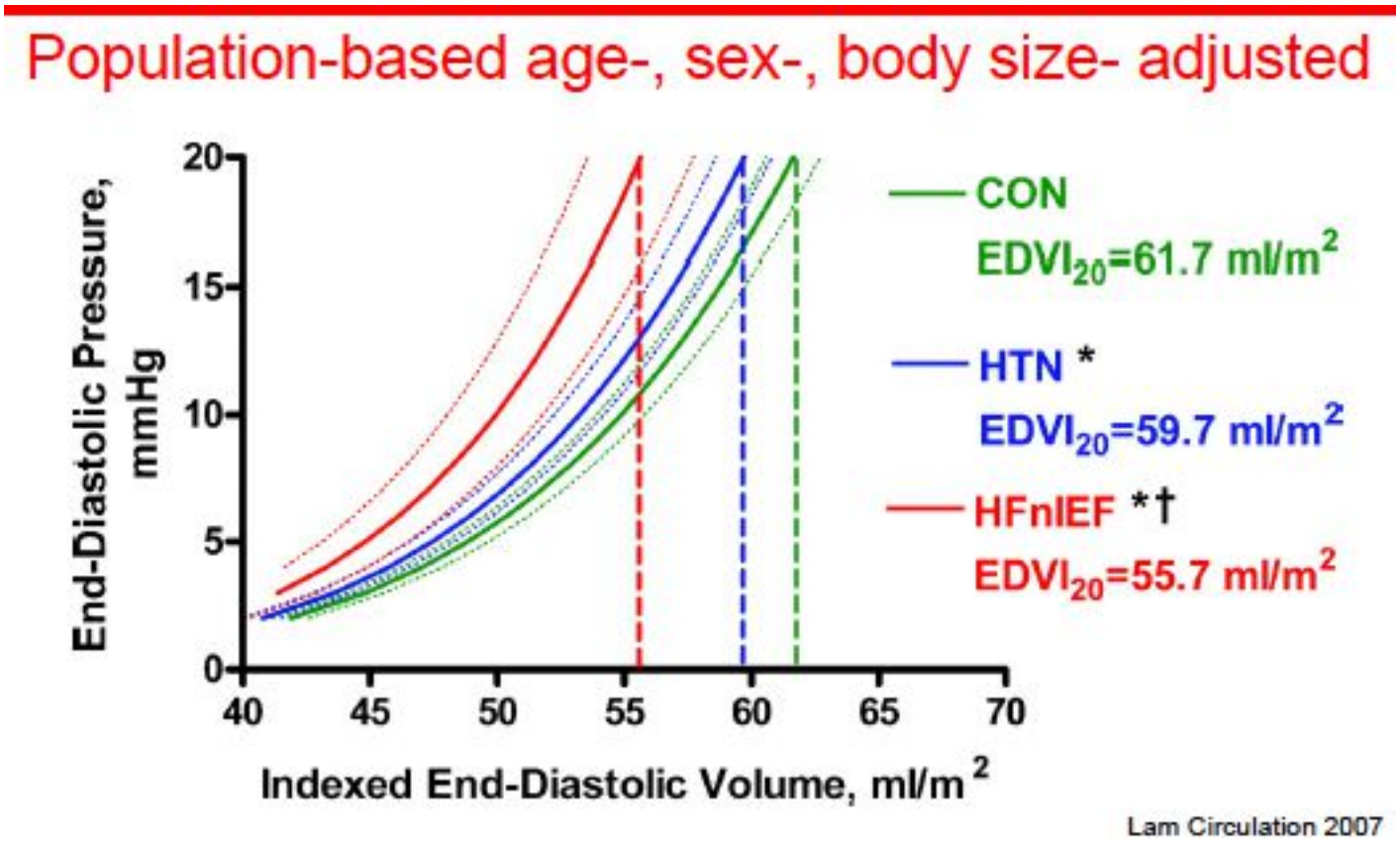
# Nouvelle classification

| HFrEF | HFmEF | HFpEF |
|---|---|---|
| Symptômes ±signes | Symptômes ±signes | Symptômes ±signes |
| LVEF<40% | LVEF 40-49% | LVEF≥50% |
| - | Augmentation des NP<br><br>et<br><br>Au moins un critère:<br>- HVG et/ou dilatation OG<br>- Dyfonction diastolique | Augmentation des NP<br><br>et<br><br>Au moins un critère:<br>- HVG et/ou dilatation OG<br>- Dyfonction diastolique |


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

# Dysfonction Diastolique bien présente et joue un rôle

**Résidents du Olmsted County (Minn) sans maladie cardiovasculaire (n=617), avec HTA mais pas d'IC (n =719), ou avec IC fonction préservée (n=244)**



# Hémodynamique à l'Effort

**Table 2 Exercise responses**

| | Control ($n = 73$) | HFpEF ($n = 109$) | *P*-value |
|---|---|---|---|
| Exercise performance | | | |
| Peak workload (W) | 80 ± 30 | 40 ± 20 | <0.0001 |
| Resting $VO_2$ (mL/min) | 261 ± 65 | 249 ± 78 | 0.3 |
| Resting $VO_2$ (mL/kg/min) | 3.26 ± 0.63 | 2.72 ± 0.68 | <0.0001 |
| Exercise $VO_2$ (mL/min) | 1269 ± 395 | 899 ± 312 | <0.0001 |
| Exercise $VO_2$ (mL/kg/min) | 15.7 ± 4.2 | 9.8 ± 3.0 | <0.0001 |
| $\Delta VO_2$ (mL/min) | +1008 ± 354 | +651 ± 272 | <0.0001 |
| $\Delta VO_2$ (mL/kg/min) | +12.5 ± 3.9 | +7.1 ± 2.8 | <0.0001 |
| Exercise systemic $O_2$ content (mL/dL)[a] | 17.0 ± 1.6 | 16.2 ± 2.1 | 0.11 |
| Exercise PA $O_2$ content (mL/dL)[a] | 8.4 ± 1.9 | 6.9 ± 2.1 | 0.003 |
| Resting $AVO_2$diff (mL/dL) | 5.1 ± 1.8 | 4.8 ± 1.3 | 0.2 |
| Exercise $AVO_2$diff (mL/dL) | 10.1 ± 2.8 | 9.9 ± 3.2 | 0.7 |
| $\Delta AVO_2$diff (mL/dL) | +5.0 ± 1.8 | +5.2 ± 2.5 | 0.6 |
| Peak exercise haemodynamics | | | |
| Heart rate (b.p.m.) | 128 ± 23 | 101 ± 20 | <0.0001 |
| Systolic BP (mmHg) | 183 ± 34 | 166 ± 34 | 0.001 |
| Mean BP (mmHg) | 122 ± 22 | 112 ± 22 | 0.005 |
| PA systolic pressure (mmHg)[a] | 41 ± 9 | 68 ± 13 | <0.0001 |
| Mean PA pressure (mmHg)[a] | 26 ± 6 | 46 ± 9 | <0.0001 |
| PCWP (mmHg)[a] | 14 ± 4 | 33 ± 8 | <0.0001 |
| Cardiac output (L/min) | 12.5 ± 2.8 | 9.2 ± 2.8 | <0.0001 |
| Cardiac index (L/min/$m^2$) | 6.4 ± 1.3 | 4.4 ± 1.2 | <0.0001 |
| PVR (mmHg/L/min)[a] | 1.0 ± 0.4 | 1.5 ± 1.1 | <0.05 |
| Ea (mmHg/mL) | 1.7 ± 0.5 | 1.8 ± 0.7 | 0.8 |

Eur J Heart Fail. 2013 Jul;15(7):776-85

# Anomalies de la Fonction Systolique:
## MESURE DE LA DEFORMATION MYOCARDIQUE

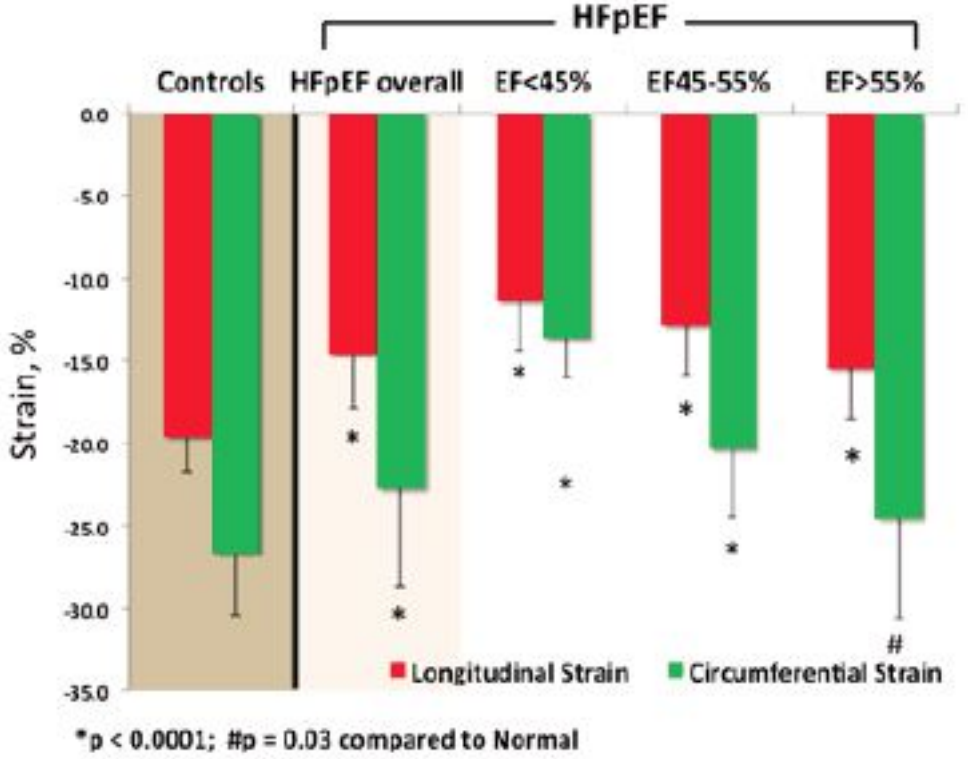
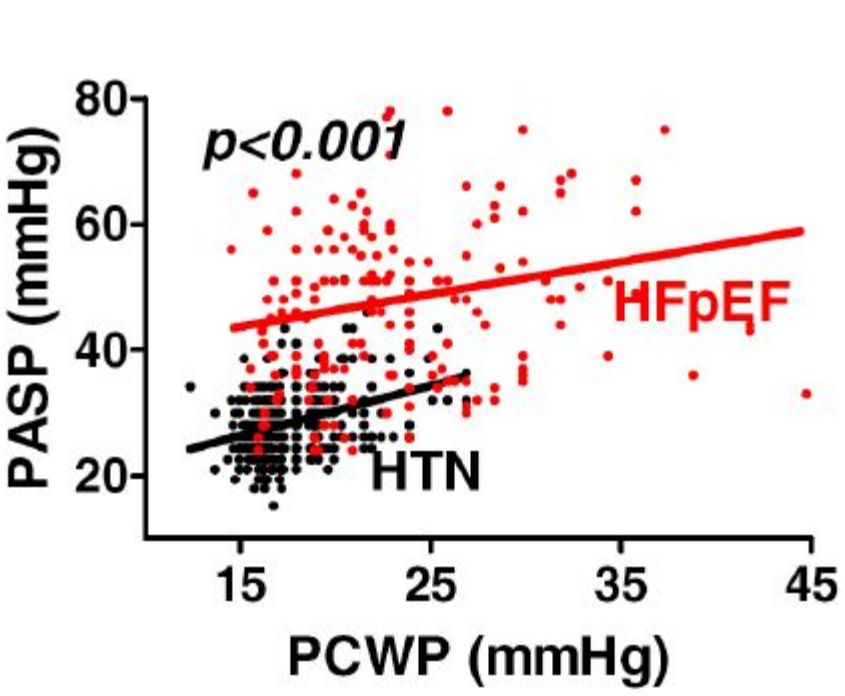
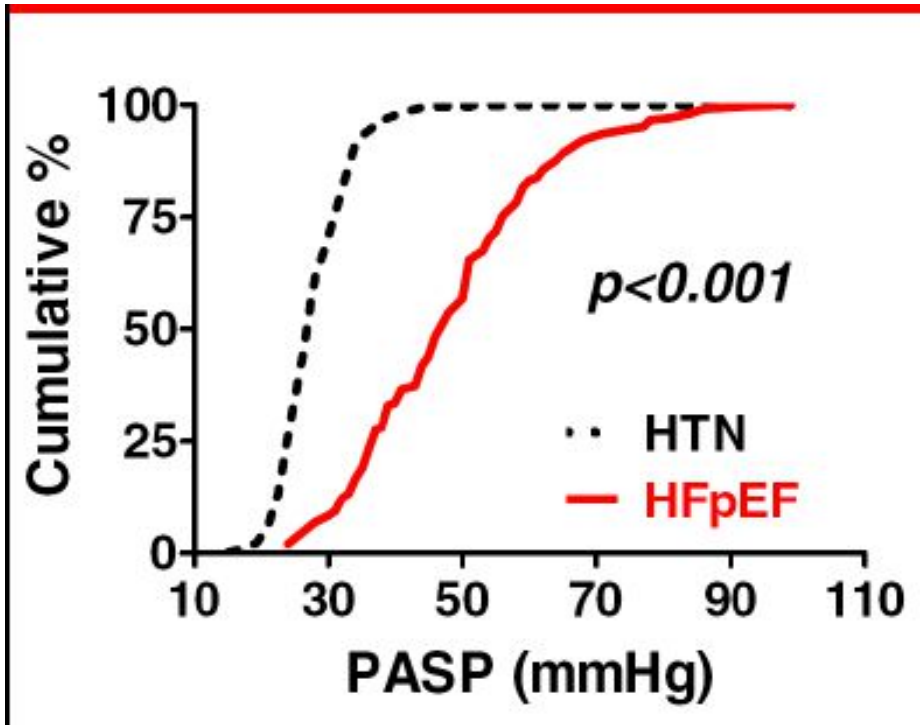



Figure 1: Strain in Controls (n=50) compared to HFpEF overall (n=232) and in 3 LVEF categories

In this contemporary clinical trial, in addition to diastolic dysfunction, HFpEF was characterized by impaired systolic deformation which was associated with higher NT-pro BNP

# Hypertension Pulmonaire

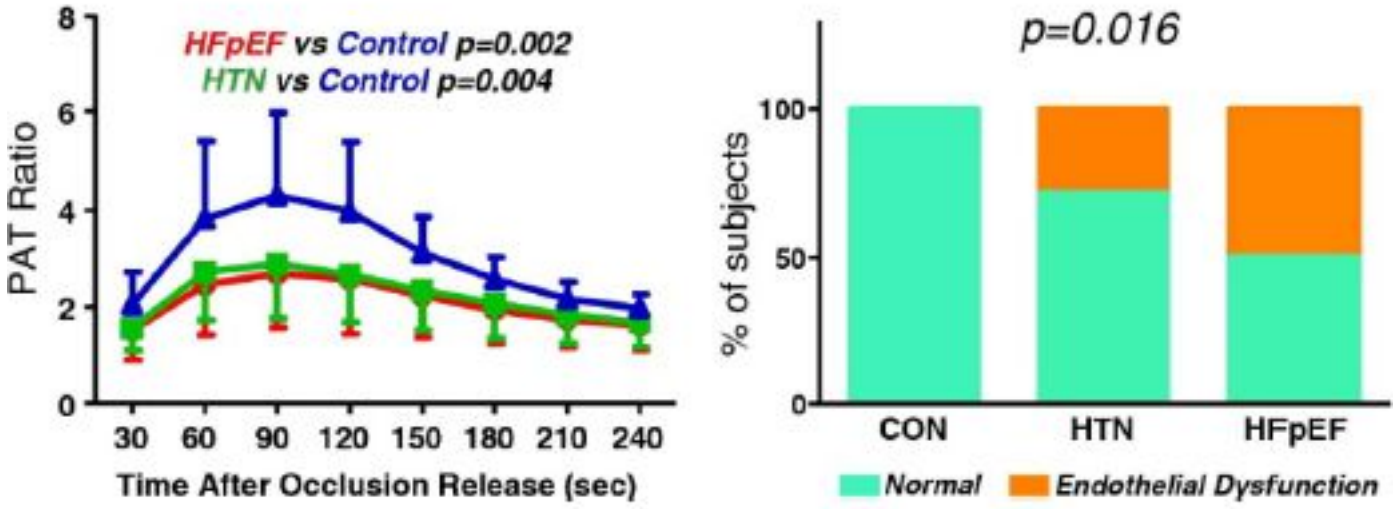



PHT may be a critical component of HFpEF

Lam CS, JACC 2009

# Dysfonction Endothéliale




**Prevalence of endothelial dysfunction:**
**0% in controls, 28% in HTN, 42% in HFPEF**

Borlaug JACC 2010

PAT=peripherial arterial tonometry

**Table 2. Autopsy Characteristics**

| | Control | HFpEF | *P* Value |
|---|---|---|---|
| n | 104 | 124 | |
| Body mass index, kg/m$^2$ | 25.6 (21.2–30.4) | 28.0 (23.7–34.5) | 0.006 |
| Body surface area, m$^2$ | 1.8 (1.6–2.0) | 1.9 (1.7–2.1) | 0.003 |
| Heart weight at autopsy, g | 335 (280–380) | 538 (440–659) | <0.0001 |
| Heart weight at autopsy/ BSA, g/m$^2$ | 190 (171–207) | 275 (233–344) | <0.0001 |
| Heart weight at autopsy/ height, g/m | 203 (173–233) | 323 (266–389) | <0.0001 |
| Percent expected heart weight, % | 112 (101–132) | 169 (144–202) | <0.0001 |
| Gross pathology | | | |
| Left ventricular hypertrophy | 15% | 74% | <0.0001 |
| Right ventricular hypertrophy | 9% | 50% | <0.0001 |
| Left ventricular dilation | 2% | 37% | <0.0001 |
| Right ventricular dilation | 13% | 48% | <0.0001 |
| Atrial dilation | 7% | 52% | <0.0001 |
| Infarct (old) | 2% | 42% | <0.0001 |
| Infarct (acute) | 1% | 11% | 0.002 |
| Fibrosis | 1% | 25% | <0.0001 |
| Microscopic pathology | | | |
| Hypertrophy | 15% | 31% | 0.007 |
| Infarct | 0% | 20% | <0.0001 |
| Fibrosis | 43% | 58% | 0.04 |
| Coronary artery stenosis total score | 6 (4–8) | 12 (8–14) | <0.0001 |
| Quantitative histology | | | |
| MVD, microvessels/mm$^2$ | 1316 (1148–1467) | 961 (800–1370) | <0.0001 |
| % Area fibrosis | 7.1 (5.1–9.0) | 9.6 (6.8–13.5) | <0.0001 |

# Hemodynamic responses to vasodilator therapy in patients with HFpEF versus HFrEF

**Table 1** Baseline Characteristics

| | HFrEF (n = 174) | HFpEF (n = 83) | p Value |
|---|---|---|---|
| Age, yrs | 56 ± 12 | 69 ± 9 | <0.0001 |
| Female | 25 | 71 | <0.0001 |
| Body mass index, kg/m$^2$ | 29.5 ± 5.8 | 33.2 ± 8.3 | <0.0001 |
| Body surface area, m$^2$ | 2.07 ± 0.25 | 2.05 ± 0.30 | 0.60 |
| Comorbidities | | | |
| Hypertension | 48 | 66 | 0.02 |
| Diabetes mellitus | 44 | 45 | 0.90 |
| Coronary disease | 69 | 61 | 0.40 |
| COPD | 17 | 18 | 0.90 |
| Medications | | | |
| Beta-blockers | 90 | 78 | 0.002 |
| ACEI or ARB | 88 | 76 | 0.02 |
| Diuretics | 95 | 89 | 0.10 |
| Aldosterone antagonists | 48 | 16 | <0.0001 |
| Digoxin | 58 | 20 | <0.0001 |
| Calcium antagonists | 8 | 41 | <0.0001 |

J Am Coll Cardiol 2012;59:442–51

# Hemodynamic responses to vasodilator therapy in patients with HFpEF versus HFrEF

| | | | |
|---|---|---|---|
| Laboratory values | | | |
| Sodium, mmol/l | 139 (137–141) | 141 (138–142) | <0.0001 |
| Hemoglobin, g/dl | 13.0 ± 1.9 | 12.1 ± 1.7 | 0.001 |
| GFR, ml/min/1.73 $m^2$ | 65 (45–80) | 57 (47–69) | 0.10 |
| NT-proBNP, pg/ml | 3,913 (2,177–8,160) | 1,360 (781–3,716) | 0.002 |
| BNP, pg/ml | 751 (352–1,520) | 371 (206–597) | 0.0001 |
| Cardiomegaly on chest film | 73 | 56 | 0.01 |
| Echocardiography | | | |
| LV septum, mm | 10 (9–11) | 10 (10–12) | <0.0001 |
| LV diastolic dimension, mm | 68 ± 11 | 48 ± 5 | <0.0001 |
| LV end-diastolic volume, ml | 246 ± 90 | 108 ± 28 | <0.0001 |
| LV mass, g | 311 ± 105 | 198 ± 56 | <0.0001 |
| LV mass/end-diastolic volume | 1.32 ± 0.38 | 1.91 ± 0.57 | <0.0001 |
| Left atrial volume, ml/$m^2$ | 58 ± 19 | 49 ± 22 | <0.0001 |
| LV ejection fraction, % | 22 ± 9 | 63 ± 6 | <0.0001 |
| Grade 3 or 4 mitral regurgitation, % | 27 | 0 | <0.0001 |
| Severe tricuspid regurgitation, % | 19 | 15 | 0.50 |
| E/A ratio | 2.5 (1.7–3.3) | 1.3 (1.1–2.1) | <0.0001 |
| Tissue Doppler E', cm/s | 4.0 (3.0–5.0) | 6.0 (4.0–7.0) | <0.0001 |
| E/e' ratio | 22 (17–32) | 18 (14–27) | 0.007 |
| Deceleration time, ms | 139 ± 34 | 179 ± 39 | <0.0001 |
| RV dysfunction,* % | 54 | 18 | <0.0001 |

J Am Coll Cardiol 2012;59:442–51

**Table 2** Baseline Hemodynamics

| | HFrEF (n = 174) | HFpEF (n = 83) | p Value |
|---|---|---|---|
| Peripheral hemodynamics | | | |
| Heart rate, beats/min | 70 (62–81) | 70 (60–76) | 0.20 |
| Systolic BP, mm Hg | 113 (100–127) | 166 (144–180) | <0.0001 |
| Mean BP, mm Hg | 80 (74–92) | 104 (93–118) | <0.0001 |
| Systemic arterial saturation, % | 93 (90–96) | 94 (90–96) | 0.80 |
| Central hemodynamics | | | |
| Right atrial pressure, mm Hg | 14 ± 6 | 14 ± 6 | 0.80 |
| Mean PA pressure, mm Hg | 40 ± 9 | 41 ± 10 | 0.50 |
| PA systolic pressure, mm Hg | 59 ± 14 | 64 ± 18 | 0.02 |
| PCWP, mm Hg | 25 ± 6 | 22 ± 6 | 0.30 |
| LV end-diastolic pressure, mm Hg | 26 ± 6 | 22 ± 6 | 0.008 |
| Flow and resistance data | | | |
| Cardiac output, l/min | 4.0 (3.4–4.8) | 4.7 (4.1–6.0) | <0.0001 |
| SV, ml | 58 (44–71) | 73 (56–85) | <0.0001 |
| Pulmonary artery saturation, % | 55 (50–62) | 61 (57–67) | <0.0001 |
| PVR, Woods units | 3.3 (2.4–4.6) | 3.3 (2.0–5.0) | 0.80 |
| Arterial-ventricular coupling | | | |
| Ees, mm Hg/ml | 0.54 (0.40–0.85) | 3.7 (3.0–4.7) | <0.0001 |
| Ea, mm Hg/ml | 1.7 (1.5–2.4) | 2.0 (1.6–2.8) | 0.03 |
| Coupling ratio, Ea/Ees | 3.3 (2.1–4.8) | 0.58 (0.40–0.72) | <0.0001 |

**Table 3. Clinical and Laboratory Characteristics Stratified by Phenogroup**

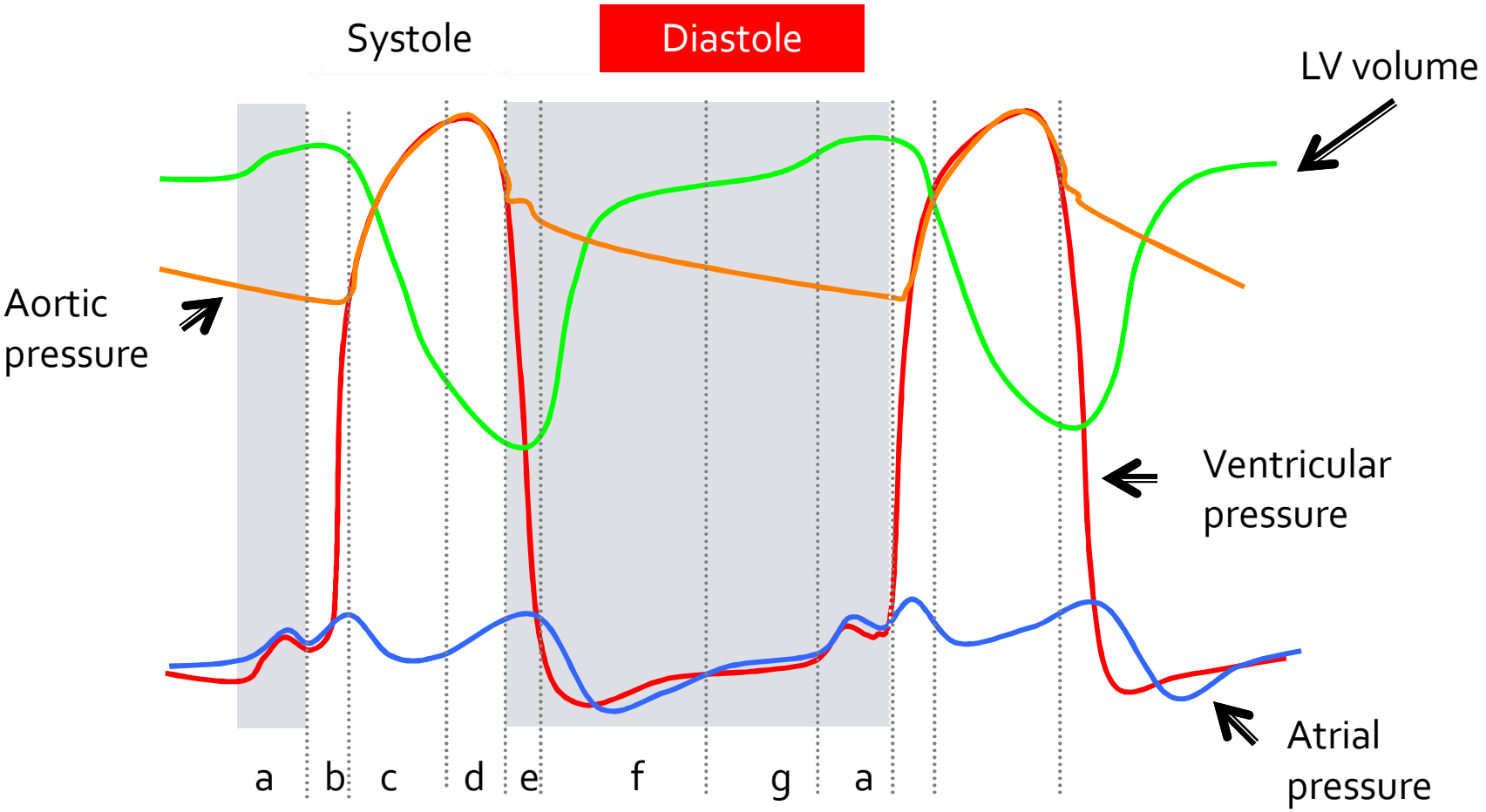
| Clinical Characteristic | Group 1 (n=128) | Group 2 (n=120) | Group 3 (n=149) | *P* Value |
|---|---|---|---|---|
| Age, y | 60.7±13.6 | 65.7±11.3 | 67.3±13.1 | <0.001 |
| Female, n (%) | 86 (67) | 81 (68) | 82 (55) | 0.049 |
| Race, n (%) | | | | 0.32 |
| White | 72 (56) | 58 (48) | 77 (52) | |
| Black | 42 (33) | 54 (45) | 56 (37) | |
| Other | 14 (11) | 8 (7) | 16 (11) | |
| NYHA functional class, n (%) | | | | 0.17 |
| I | 25 (20) | 11 (9) | 13 (9) | |
| II | 61 (48) | 40 (33) | 56 (38) | |
| III | 38 (30) | 64 (53) | 78 (52) | |
| IV | 3 (2) | 5 (4) | 2 (1) | |
| Comorbidities, n (%) | | | | |
| Coronary artery disease | 54 (42) | 58 (48) | 75 (50) | 0.38 |
| Hypertension | 84 (66) | 108 (90) | 112 (75) | <0.001 |
| Hyperlipidemia | 65 (51) | 75 (62) | 73 (49) | 0.06 |
| Diabetes mellitus | 12 (9) | 63 (52) | 50 (34) | <0.001 |
| Obesity | 65 (51) | 84 (70) | 55 (37) | <0.001 |
| Chronic kidney disease | 8 (6) | 41 (34) | 79 (53) | <0.001 |
| Atrial fibrillation | 17 (13) | 26 (22) | 64 (43) | <0.001 |
| Chronic obstructive pulmonary disease | 43 (34) | 46 (38) | 56 (38) | 0.70 |
| Obstructive sleep apnea | 35 (27) | 60 (50) | 46 (31) | <0.001 |

| | | | | |
|---|---|---|---|---|
| Vital signs and laboratory data | | | | |
| Heart rate, bpm | 77.2±14.5 | 74.7±14.9 | 71.6±12.6 | 0.004 |
| Systolic blood pressure, mm Hg | 122.4±16.6 | 129.2±19.0 | 123.0±22.7 | 0.011 |
| Diastolic blood pressure, mm Hg | 73.3±10.2 | 70.1±10.2 | 67.3±13.6 | <0.001 |
| Pulse pressure, mm Hg | 49.1±12.4 | 59.2±16.9 | 55.7±19.6 | <0.001 |
| Body mass index, $kg/m^2$ | 31.2±7.3 | 37.0±10.7 | 28.9±7.4 | <0.001 |
| Serum sodium, mEq/L | 139.0±3.0 | 138.4±2.6 | 137.9±2.9 | 0.01 |
| Blood urea nitrogen, mg/dL | 13.7±4.5 | 24.4±11.8 | 33.6±19.9 | <0.001 |
| Serum creatinine, mg/dL | 0.9±0.2 | 1.3±0.4 | 2.3±2.2 | <0.001 |
| Estimated GFR, $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ | 79.5±21.2 | 53.8±17.6 | 43.9±27.3 | <0.001 |
| Fasting glucose, mg/dL | 98.4±15.6 | 153.2±85.2 | 111.5±29.2 | <0.001 |
| Hemoglobin, g/dL | 12.5±1.7 | 11.8±1.8 | 11.4±1.9 | <0.001 |
| B-type natriuretic peptide, pg/mL | 72 (26–161) | 188 (83–300) | 607 (329–1138) | <0.001 |
| Medications, n (%) | | | | |
| ACE inhibitor or ARB | 61 (48) | 84 (70) | 72 (48) | <0.001 |
| β-Blocker | 67 (52) | 89 (74) | 112 (75) | <0.001 |
| Calcium channel blocker | 31 (24) | 45 (38) | 44 (30) | 0.073 |
| Nitrate | 5 (4) | 19 (16) | 33 (22) | <0.001 |
| Loop diuretic | 40 (31) | 82 (68) | 109 (73) | <0.001 |
| Thiazide diuretic | 31 (24) | 35 (29) | 26 (17) | 0.073 |
| Statin | 48 (38) | 72 (60) | 73 (49) | 0.002 |
| Aspirin | 48 (38) | 62 (52) | 75 (50) | 0.042 |
| Heart failure duration, mo | 0.8 (0.4–4.3) | 0.9 (0.4–16.3) | 0.9 (0.4–11.7) | 0.21 |
| MAGGIC risk score | 15.6±6.7 | 19.8±5.8 | 22.8±7.5 | <0.001 |

**Table 4. ECG, Echocardiographic, and Invasive Hemodynamic Characteristics Stratified Phenogroup**

| Parameter | Group 1 (n=128) | Group 2 (n=120) | Group 3 (n=149) | *P* Value |
|---|---|---|---|---|
| ECG | | | | |
| PR interval, ms | 166.6±29.6 | 174.2±29.8 | 183.3±53.5 | 0.007 |
| QRS duration, ms | 93.8±21.0 | 91.3±13.6 | 112.7±33.3 | <0.001 |
| QTc interval, ms | 450.6±35.2 | 449.8±34.0 | 464.6±48.9 | 0.005 |
| QRS axis, degrees | 10.7±39.0 | 20.4±38.4 | −4.2±60.7 | <0.001 |
| QRS-T angle, degrees | 42.6±41.7 | 53.4±44.0 | 86.6±54.0 | <0.001 |
| Echocardiography | | | | |
| LV end-diastolic volume, mL | 81.2±23.4 | 84.2±24.0 | 84.6±32.3 | 0.56 |
| LV end-systolic volume, mL | 31.6±12.1 | 33.1±12.1 | 35.4±19.2 | 0.12 |
| Relative wall thickness | 0.47±0.11 | 0.49±0.09 | 0.56±0.20 | <0.001 |
| LV mass index, g/m$^2$ | 89.1±22.6 | 96.4±26.3 | 122.0±47.3 | <0.001 |
| Left atrial volume index, mL/m$^2$ | 29.1±11.1 | 31.5±10.6 | 40.9±16.7 | <0.001 |
| LV ejection fraction, % | 61.8±5.6 | 61.2±6.5 | 60.0±7.1 | 0.05 |
| Stroke volume, mL | 84.8±22.9 | 88.6±32.0 | 80.7±31.3 | 0.09 |
| Cardiac output, L-min$^{-1}$-m$^{-2}$ | 6.5±2.0 | 6.6±2.5 | 5.8±2.6 | 0.006 |
| Pulmonary artery systolic pressure, mm Hg | 35.3±9.7 | 43.5±14.6 | 51.2±16.3 | <0.001 |
| Right atrial pressure, mm Hg | 6.0±2.7 | 6.9±3.5 | 9.8±4.7 | <0.001 |
| E velocity, cm/s | 93.2±28.6 | 103.2±34.5 | 118.2±40.9 | <0.001 |
| A velocity, cm/s | 82.8±22.5 | 93.1±26.3 | 81.6±38.7 | 0.01 |
| E/A ratio | 1.2±0.5 | 1.1±0.4 | 1.7±1.0 | <0.001 |
| Tissue Doppler e' velocity, cm/s | 9.3±3.2 | 7.5±2.1 | 7.9±3.4 | <0.001 |
| E/e' ratio | 11.2±3.7 | 15.2±6.4 | 18.6±10.6 | <0.001 |
| Diastolic dysfunction grade, n (%) | | | | <0.001 |
| Normal diastolic function | 21 (16) | 9 (8) | 2 (1) | |
| Grade I (mild) diastolic dysfunction | 15 (12) | 16 (13) | 12 (8) | |
| Grade II (moderate) diastolic dysfunction | 60 (47) | 56 (47) | 43 (29) | |
| Grade III (severe) diastolic dysfunction | 23 (18) | 31 (26) | 83 (56) | |
| Indeterminate diastolic function | 9 (7) | 8 (7) | 9 (6) | |
| RV basal diameter, cm | 3.6±0.6 | 3.8±0.5 | 4.2±0.8 | <0.001 |
| RV end-diastolic area index, cm/m$^2$ | 12.4±2.1 | 12.7±2.4 | 16.2±4.7 | <0.001 |
| RV end-systolic area index, cm/m$^2$ | 6.7±1.5 | 7.2±1.5 | 9.9±3.4 | <0.001 |
| RV wall thickness, cm | 0.46±0.03 | 0.50±0.07 | 0.56±0.11 | <0.001 |
| RV fractional area change | 0.46±0.06 | 0.43±0.05 | 0.40±0.08 | <0.001 |
| TAPSE, cm | 2.2±0.6 | 2.1±0.6 | 1.7±0.6 | <0.001 |
| Invasive hemodynamics (n=216) | | | | |
| Right atrial pressure, mm Hg | 10.5±4.6 | 15.3±6.5 | 14.6±6.8 | <0.001 |
| Pulmonary artery systolic pressure, mm Hg | 42.4±12.0 | 55.9±15.4 | 56.7±19.7 | <0.001 |
| Pulmonary artery diastolic pressure, mm Hg | 21.7±6.3 | 28.2±7.7 | 26.5±9.1 | <0.001 |
| Mean pulmonary artery pressure, mm Hg | 28.8±7.7 | 35.9±9.9 | 36.6±11.7 | <0.001 |
| Pulmonary capillary wedge pressure, mm Hg | 19.9±6.3 | 24.6±8.3 | 23.7±9.7 | 0.002 |
| Pulmonary vascular resistance, Wood units | 1.2±2.5 | 2.8±4.6 | 2.3±3.7 | 0.043 |
| Cardiac output, L/min | 6.1±2.1 | 6.5±2.1 | 5.8±2.3 | 0.15 |

# Le Cycle Cardiaque: 7 Phases




(a) atrial systole, (b) isovolumetric contraction, (c) rapid ejection, (d) reduced ejection, (e) isovolumetric relaxation, (f) rapid filling and (g) slow LV filling (diastasis)

# Déterminants de la Fonction Diastolique

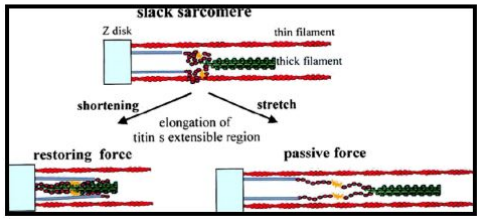
**Facteurs extrinsèques au ventricule**

- propriétés péricardiques
- interaction ventriculaire
- compression extrinsèque

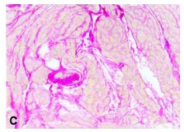
**Facteurs intrinsèques au ventricule**

- **Cardiomyocyte**
  - **Concentration Ca++, réticulum sarcoplasmique,**
  - **Myofilaments: troponine C Ca++ binding,…**
  - **Energétique: ratio ADP/ATP**
  - **Cytosquelette: microtubule, desmin, actine, titine**

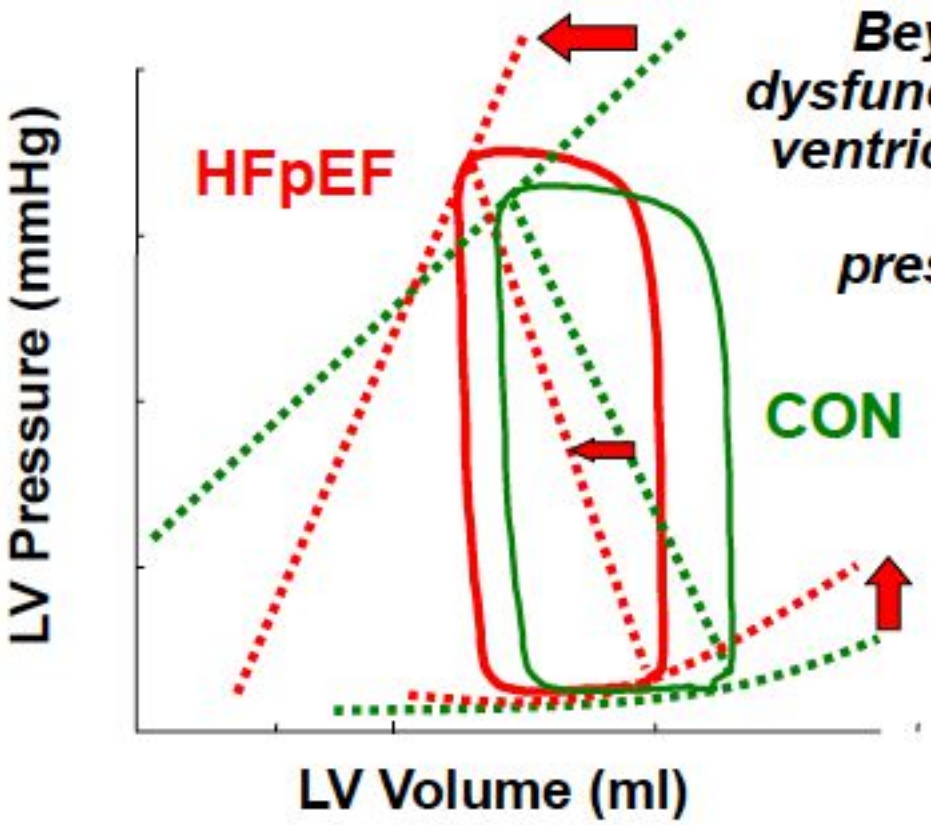
Abnormalities in spring-like Titin protein




- **Matrice extracellulaire: anomalie collagène, fibrose,…**



# Altération Boucle Pression-Volume

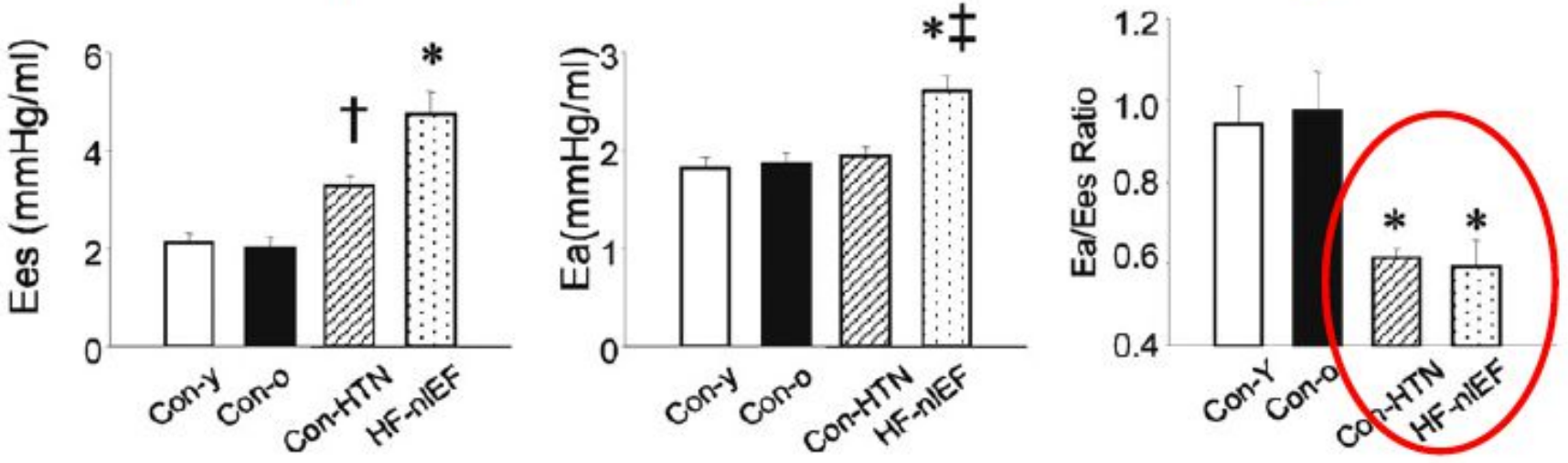



***Beyond diastolic dysfunction, systolic ventricular-vascular stiffening are present in HFpEF***

Lam Circulation 2007

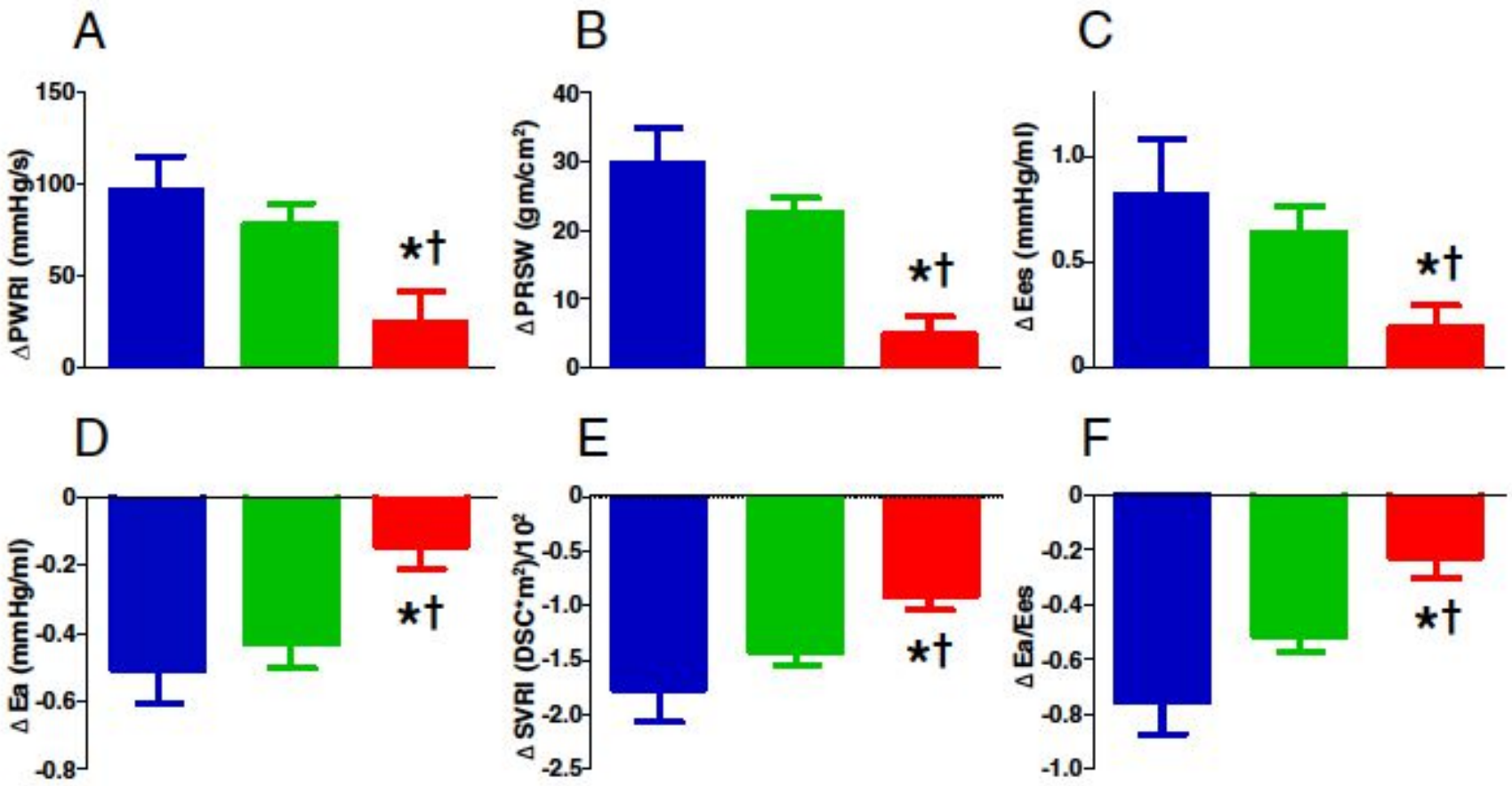
# Coupling Artério-Ventriculaire

Matching between vascular and LV systems (Ea/Ees coupling ratio) is important for net cardiac performance and cardiac energetics




Kawaguchi Circulation 2003

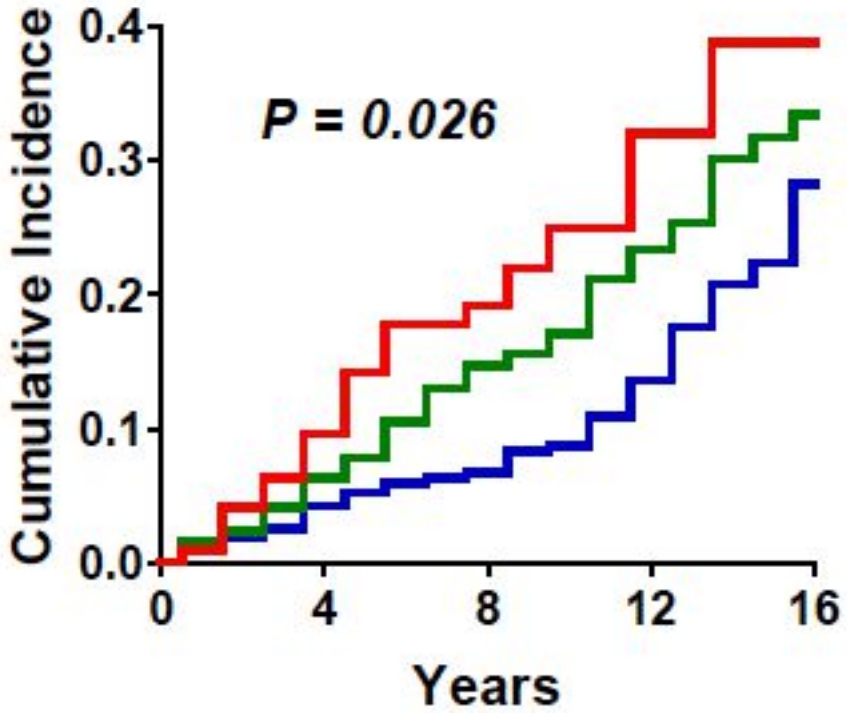
# Réserve à l'Effort




Borlaug et al, JACC 2010

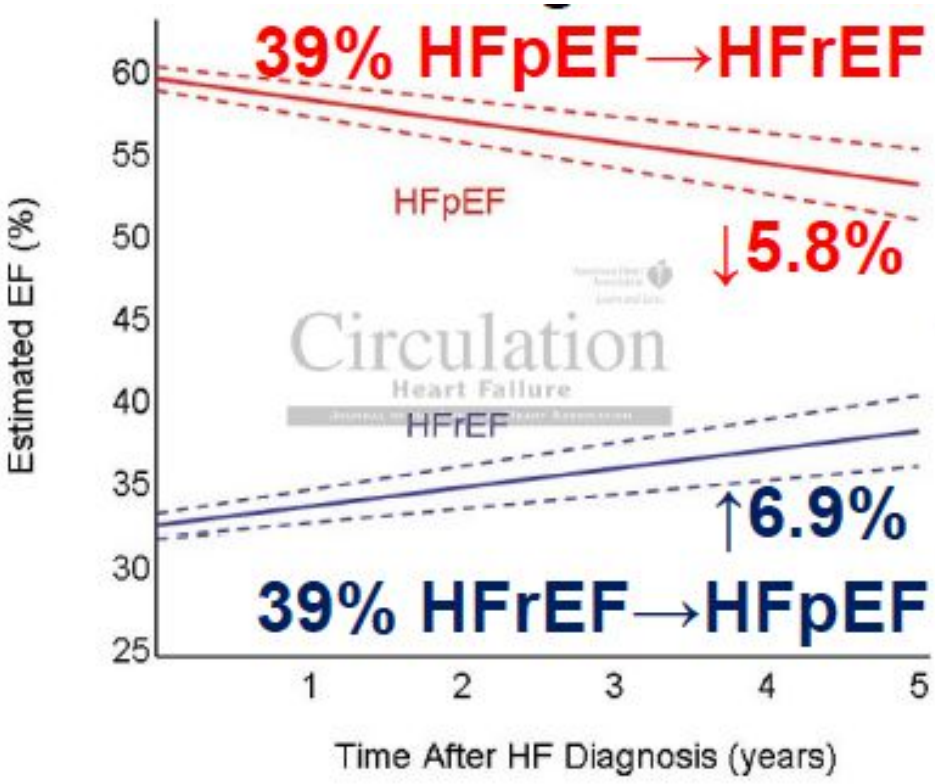
# Comorbidités et Incidence

**Framingham Heart Study (N=1038) followed for 11y**




| Factor | Cutoff |
|---|---|
| Creatinine | > 92.8 µmol/l |
| **FEV1:FVC** | **< 91 % predicted** |
| Hb | < 13 g/dl |

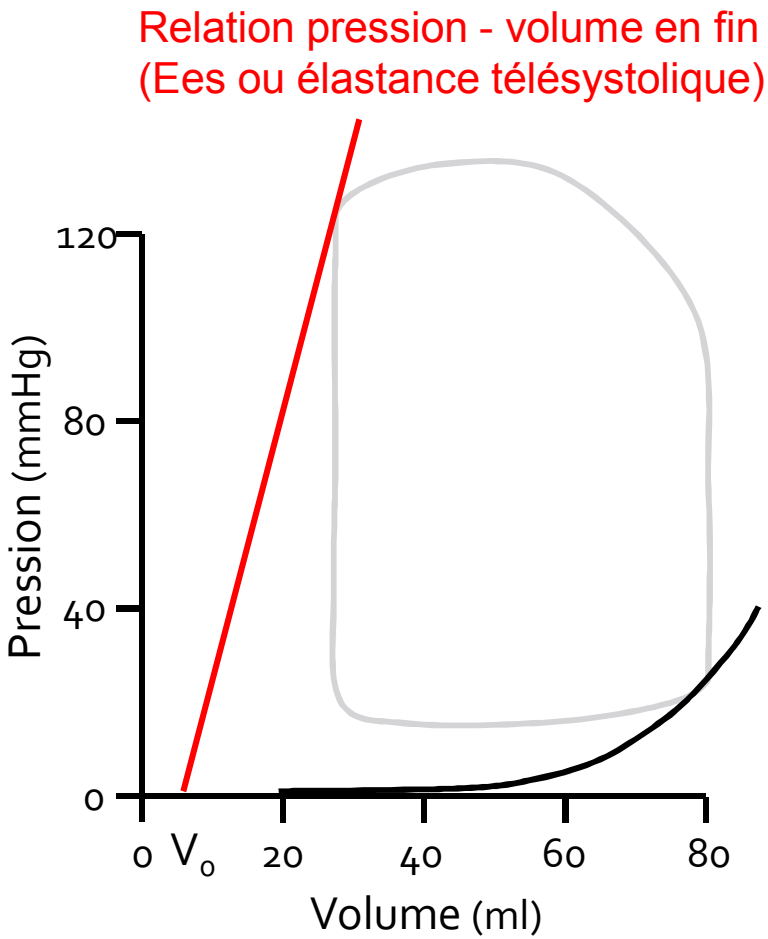
Lam Circulation 2011




- In HFpEF: greater ↓EF in older patients and **those with CAD**
- In HFrEF: Greater ↑EF in women, younger patients, **those without CAD**, and those treated

Dunlay, Circ Heart Failure 2012

# Relation pression - volume en fin de systole (Ees)

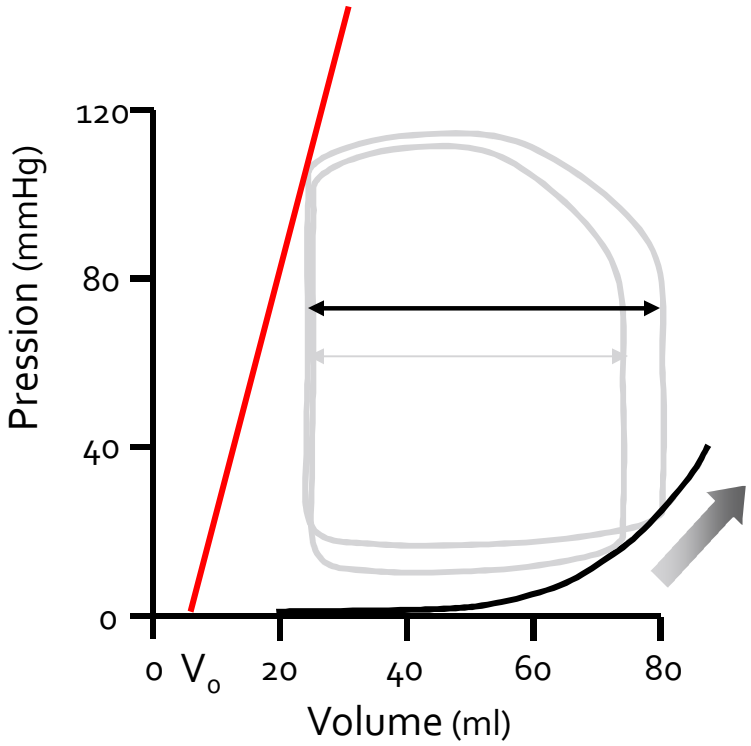



$$P_{TS} = E_{es} (VTS - V_0)$$

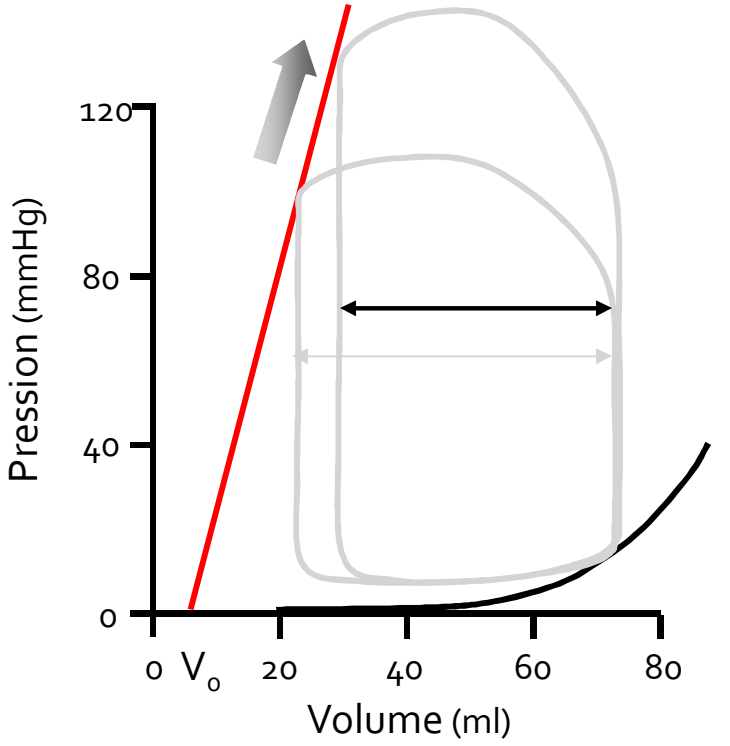
$$E_{es} = \frac{P_{TS}}{(VTS - V_0)}$$

# Influence de la précharge et de la postcharge sur la boucle pression volume

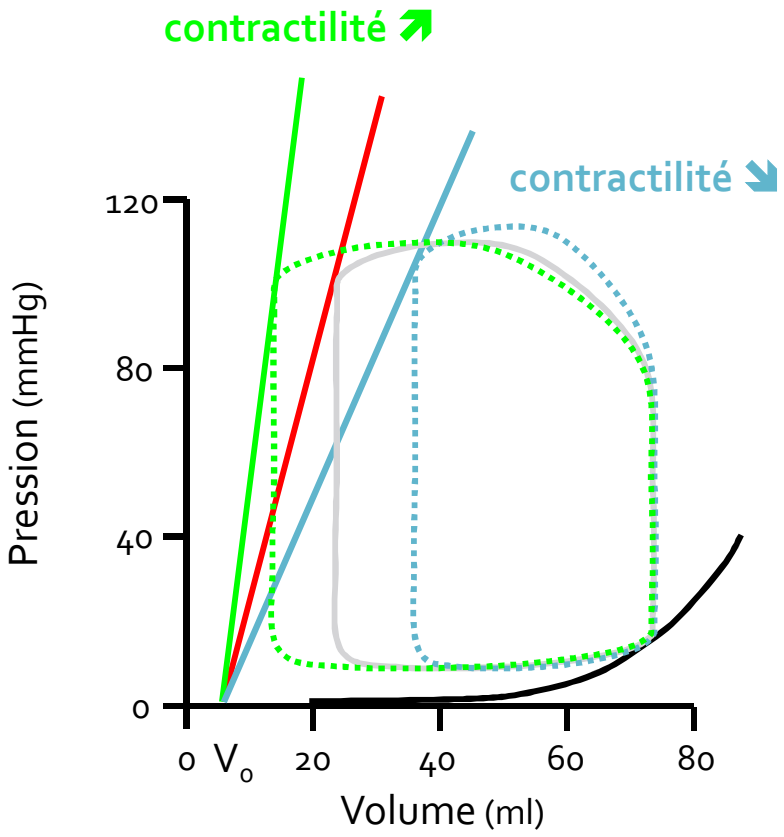
précharge ↗ ⇨ volume télédiastolique ↗
⇨ volume éjecté ↗




postcharge ↗ ⇨ volume télésystolique ↗
⇨ volume éjecté ↘



# Influence de la contractilité sur la boucle pression volume



# Ultrastructure

| | HFpEF | HFrEF |
|---|---|---|
| Cardiomyocyte diameter | ↑ | ↓ |
| Myofibrillar density | ↑ | ↓ |
| Passive cardiomyocyte resting tension | ↑↑ | ↑ |
| Cardiomyocyte calcium sensitivity | ↑↑ | ↑ |
| Abnormal phosphorylation of sarcomeric proteins | ↑↑ | ↑ |
| Titin isoform N2BA/N2B ratio | ↓ | ↑ |
| Myocardial protein kinase G activity | ↓ | ↑ |
| Myocardial oxidative stress | ↑ | ↔ |
| Myocardial cyclic guanosine monophosphate concentration | ↓ | ↑ |
| Myocardial pro-B-type natriuretic peptide-108 expression | ↔/↑ | ↑↑ |
| Mysial collagen volume fraction | ↑ | ↓ |
| Perivascular collagen volume fraction | ↑ | ↑↑ |
| Scar-related collagen volume fraction | ↑ | ↑↑ |
| Endomyocardial MMP-1:TIMP-1 ratio | ↔ | ↑↑ |
| Myocardial advanced glycation end products in diabetic HF | ↑ | ↑↑ |

Komajda and Lam EHJ 2014

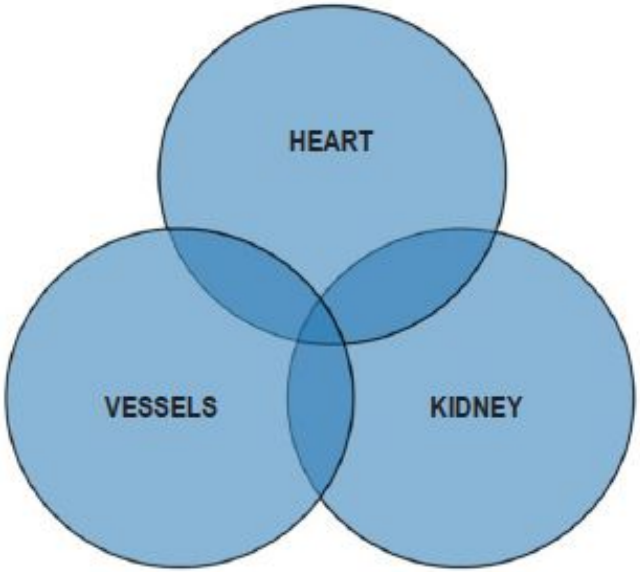
Increased ventricular stiffness

Delayed ventricular relaxation

Ventricular hypertrophy

Chronotropic incompetence

Loss of cardiac reserve




Increased central aorta stiffness

Abnormal Ventricular-arterial coupling

Limited vasodilator reserve

Hypertensive response to exercise

Endothelial dysfunction

Renin-angiotensin activation

Sodium and water retention

Anemia

# Fonction ventriculaire gauche

## La fonction diastolique

### La relaxation ventriculaire

➡ Inactivation et dissipation de l'interaction actine - myosine

réuptake de Calcium par le réticulum sarcoplasmique

➡ Forces de rappel élastique

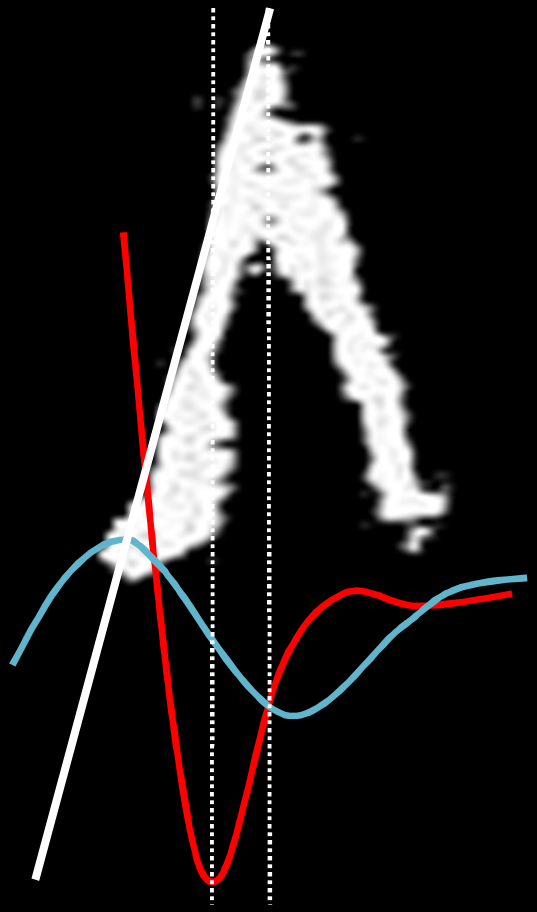
volume télésystolique < volume à l'équilibre

⇨ forces de rappel ↗ si volume télésystolique ↘
(fonction de la contractilité)
⇨ forces de rappel entraînent une succion ventriculaire

# Fonction ventriculaire gauche

## La fonction diastolique

### Remplissage rapide

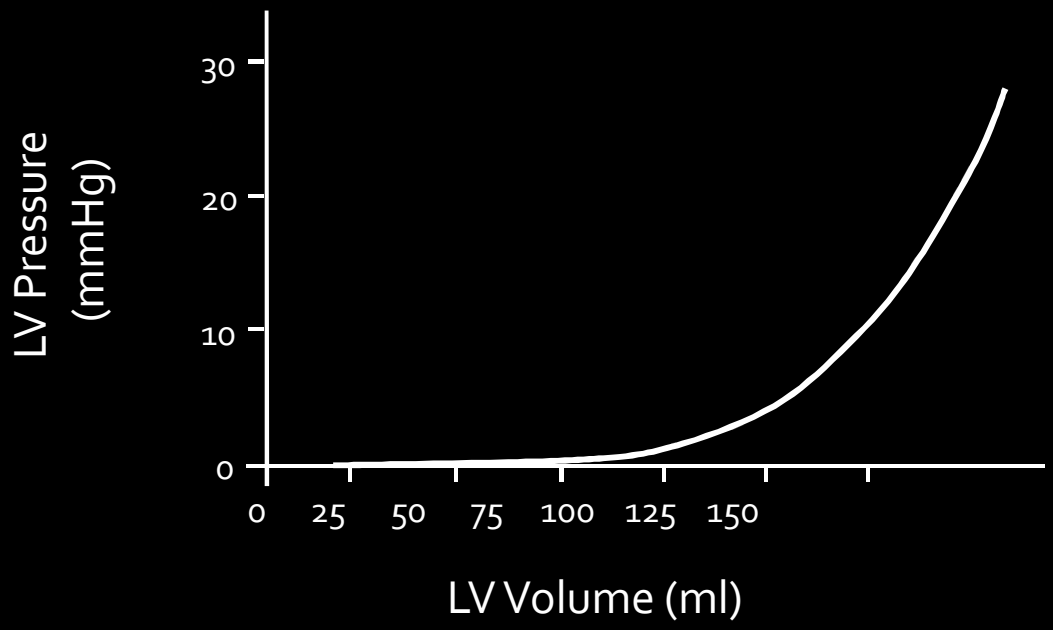


- ⇨ poursuite de la relaxation ventriculaire
- ⇨ chute de la presion ventriculaire sous la pression auriculaire: ouverture de la valvule mitrale
- ⇨ poursuite de la dépressurisation ventriculaire **: succion ventriculaire**

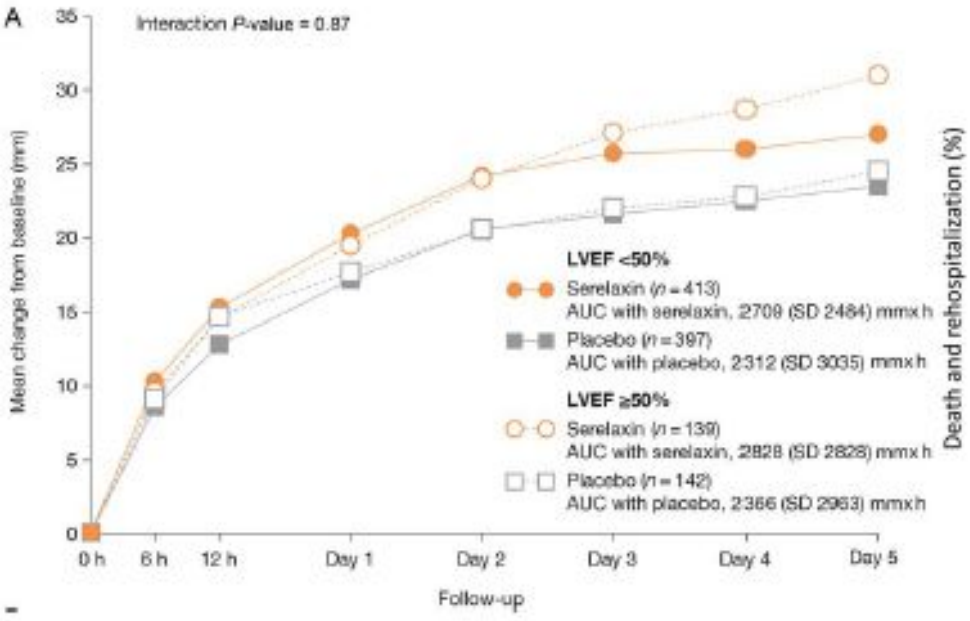
# Fonction ventriculaire gauche

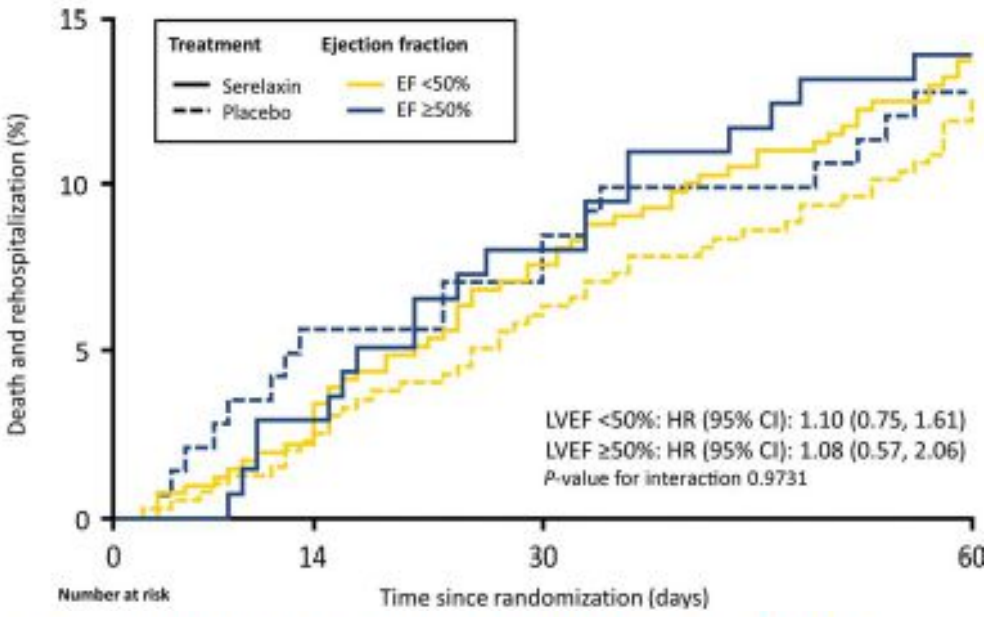
## La fonction diastolique

**Relation pression - volume à l'état passif**
**Distensibilité ventriculaire**



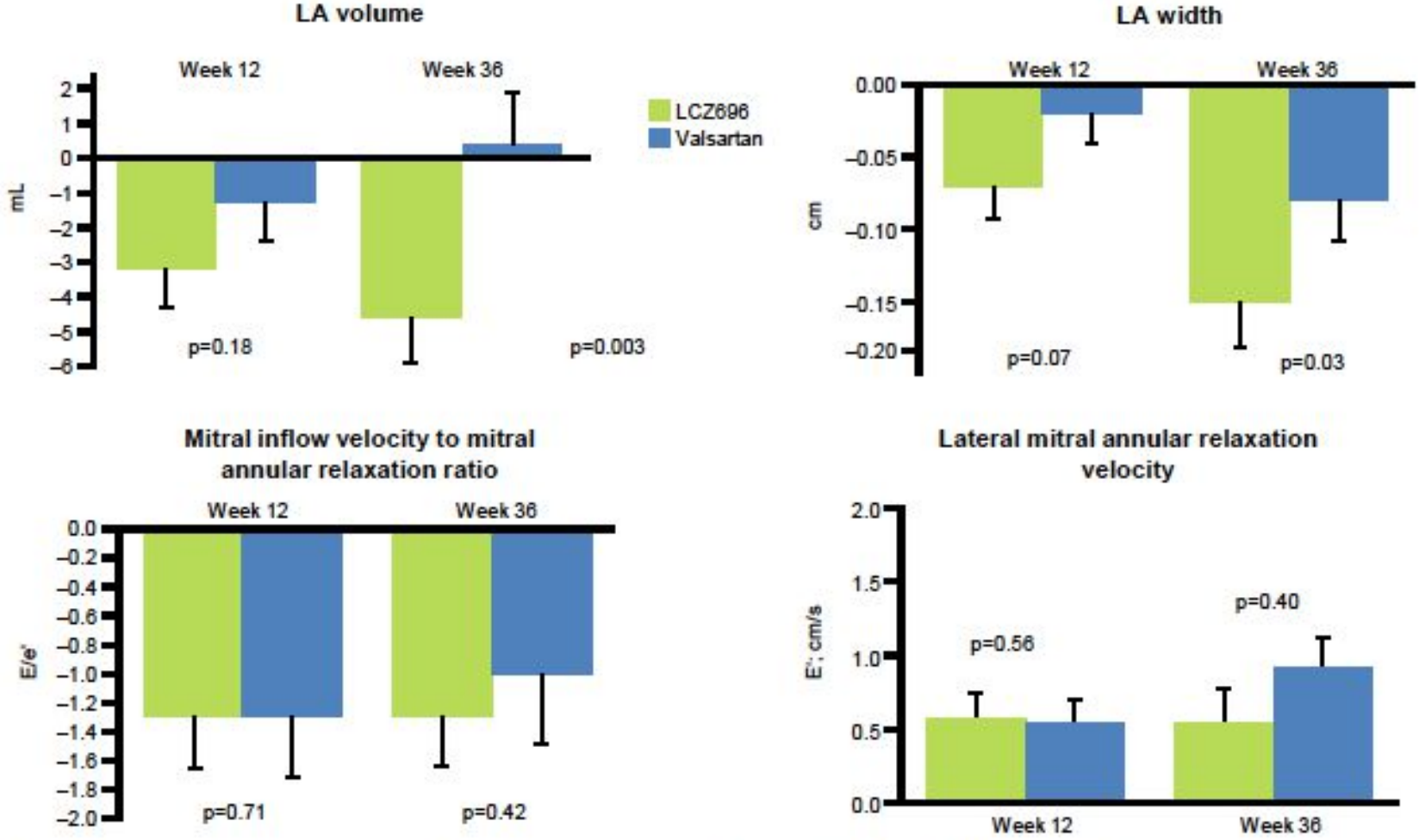
# Sérélaxine




In AHF patients with HFpEF compared with those with HFrEF, serelaxin was well tolerated and effective in relieving dyspnoea and had a similar effect on short- and long-term outcome, including survival improvement.

Filippatos G et al. Eur Heart J 2014;35:1041-1050



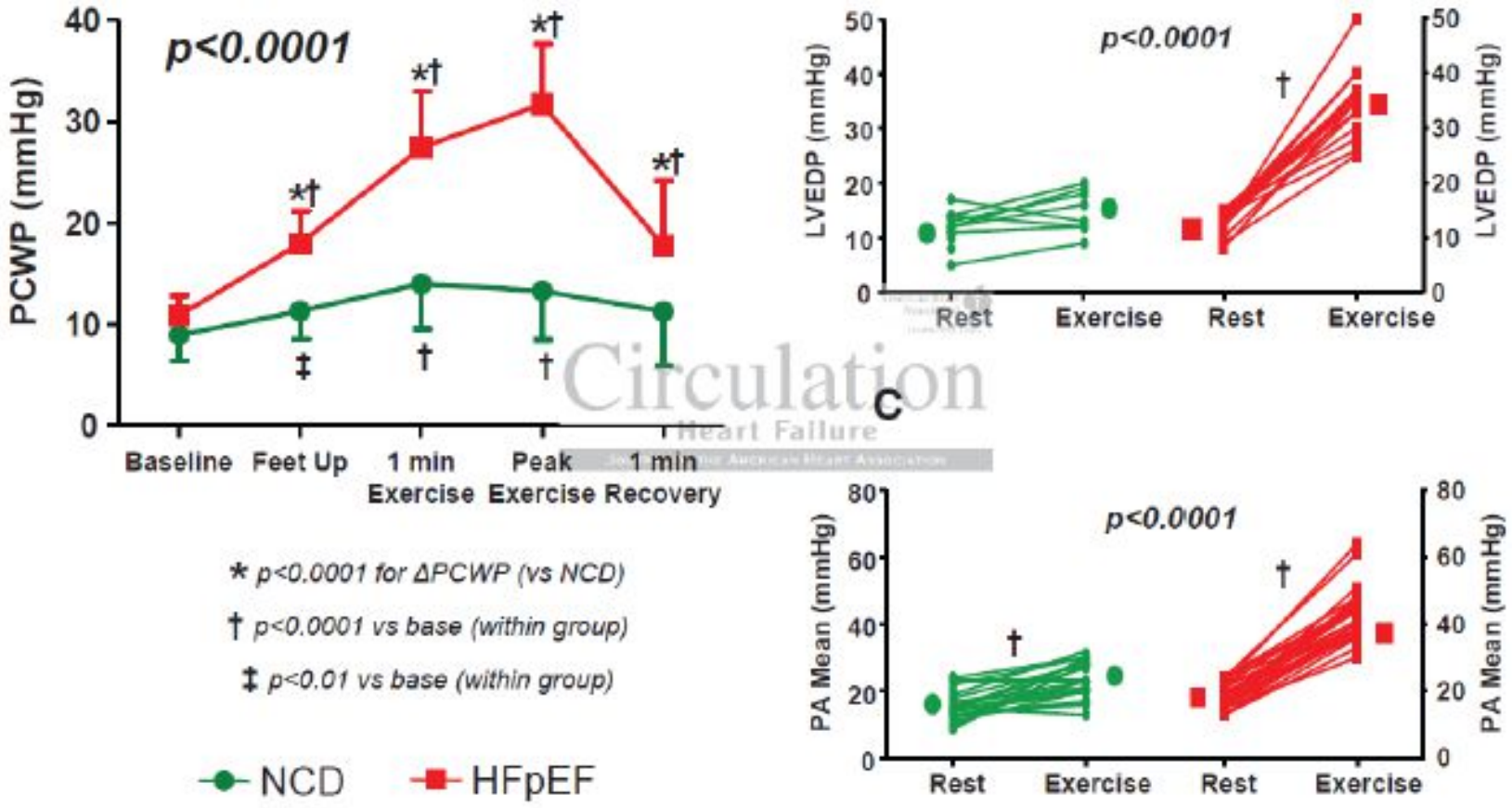

No significant changes were observed in LV volumes, ejection fraction, or LV mass at Weeks 12 or 36

LA=left atrial

Solomon et al. Lancet 2012;380:1387–95

# Hémodynamique à l'effort

Dyspnée effort, FE >50%, pas maladie coronaire, BNP normal
hémodynamique de repos normale,




Borlaug et al, Circ HF 2010

# IMPACT PRONOSTIQUE

**Table 5. Association of RV Function, PASP, and TR With Adverse Outcomes in HFpEF**

| | All-Cause Mortality | | CV Mortality | | First HF Hospitalization | | All HF Hospitalizations | |
|---|---|---|---|---|---|---|---|---|
| | HR (CI) | *P* Value | HR (CI) | *P* Value | HR (CI) | *P* Value | HR (CI) | *P* Value |
| Univariate analysis | | | | | | | | |
| PASP (per SD) | 1.53 (1.37–1.69) | <0.0001 | 1.67 (1.40–1.96) | <0.0001 | 1.47 (1.25–1.71) | <0.0001 | 1.48 (1.26–1.74) | <0.0001 |
| TAPSE (per SD) | 0.82 (0.73–091) | 0.0003 | 0.73 (0.60–0.87) | 0.0005 | 0.72 (0.61–0.85) | <0.0001 | 0.71 (0.60–0.86) | 0.002 |
| Semiquantitative RVD (any) | 1.68 (1.32–2.12) | <0.0001 | 2.12 (1.45–3.05) | 0.0002 | 2.42 (1.73–3.35) | <0.0001 | 2.59 (1.81–3.70) | <0.0001 |
| TR | | <0.0001 | | <0.0001 | | 0.003 | | 0.001 |
| Mild–moderate | 1.41 (1.07–1.87) | 0.01 | 1.41 (0.88–2.32) | 0.16 | 1.43 (0.95–2.2) | 0.08 | 1.34 (0.84–2.12) | 0.22 |
| Moderate–severe | 2.45 (1.83–3.30) | <0.0001 | 2.77 (1.70–4.62) | <0.0001 | 2.14 (1.38–3.38) | 0.0007 | 2.31 (1.43–3.73) | 0.0006 |
| Multivariable analysis | | | | | | | | |
| Model 1: PASP, TAPSE, and comorbidities* | | | | | | | | |
| PASP (per SD) | 1.50 (1.33–1.68) | <0.0001 | 1.57 (1.29–1.90) | <0.0001 | 1.44 (1.21–1.71) | <0.0001 | 1.50 (1.27–1.76) | <0.0001 |
| TAPSE (per SD) | 0.99 (0.79–1.01) | 0.08 | 0.77 (0.64–0.94) | 0.01 | 0.82 (0.68–0.99) | 0.03 | 0.83 (0.70–0.98) | 0.03 |
| Model 2: PASP, semiquantitative assessment of RV function, and comorbidities* | | | | | | | | |
| PASP (per SD) | 1.42 (1.26–1.60) | <0.0001 | 1.48 (1.21–1.78) | 0.0001 | 1.27 (1.06–1.51) | 0.01 | 1.30 (1.08–1.57) | 0.005 |
| RVD (any) | 1.35 (1.03–1.77) | 0.03 | 1.85 (1.20–2.80) | 0.006 | 1.99 (1.35–2.90) | 0.0006 | 1.81 (1.18–2.78) | 0.007 |

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# Rôle du NO et du cGMP?