Insuffisance cardiaque à FE préservée et phénotypage

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ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Liens d’intérêt

- Honoraires (conférences, boards)
  - Abbott
  - Alnylam
  - AstraZeneca
  - Boehringer Ingelheim
  - BMS
  - Novartis
  - Novo Nordisk
  - Pfizer

Quel est le problème ?

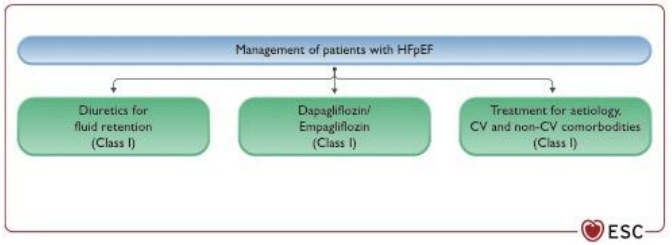
Type of HF		HF-rEF	HF- mrEF	HF-pEF
Criteria	1	Symptoms ± Signs	Symptoms ± Signs	Symptoms ± Signs
	2	**LVEF ≤ 40%**	**LVEF 41-49%**	**LVEF ≥ 50%**
	3	-	-	Objective evidence of LV diastolic dysfunction or raised LV filling pressures, including raised NP levels

Physiopathologie homogène

Polythérapie efficace pour tous

Physiopathologie hétérogène

Peu de traitement efficace pour tous



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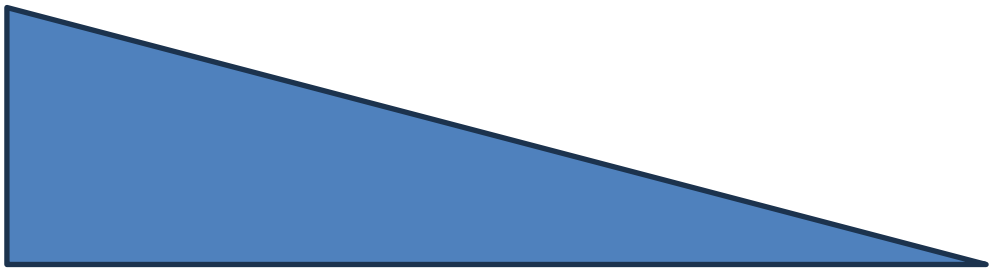
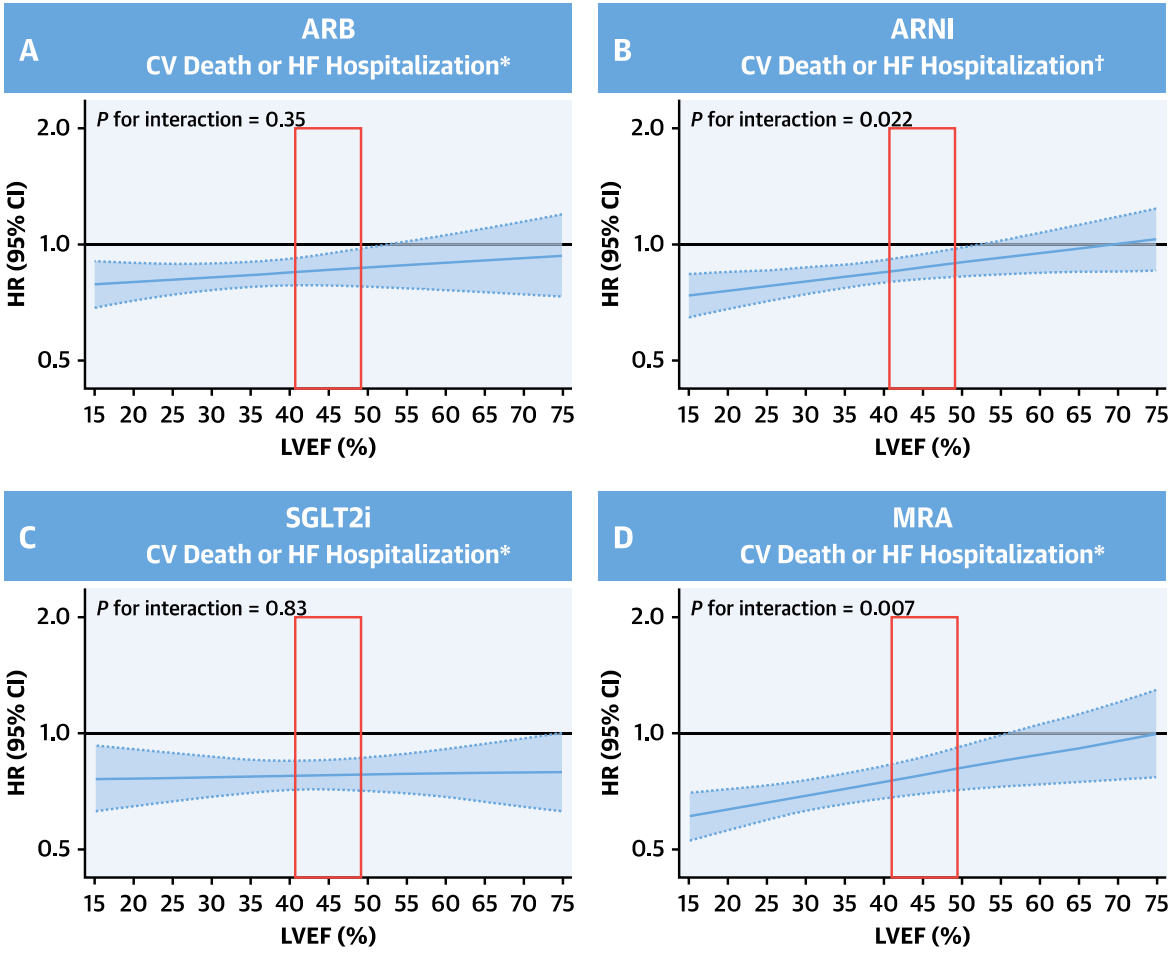
Efficacité des modulateurs neurohormonaux
(IEC, ARA2, BB, ARM, ARNi)

Activation neurohormonale



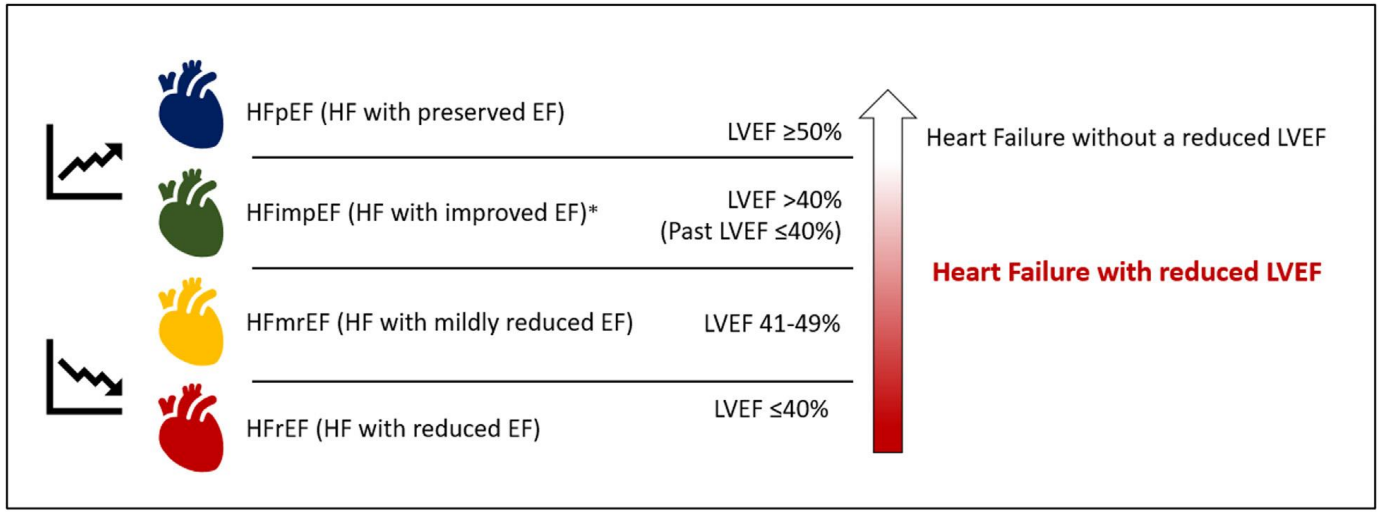
Faut-il reconsidérer le seuil de FEVG pour catégoriser l'IC ?

ARA2, ARM, ARNi : efficaces jusque FE 50-55%

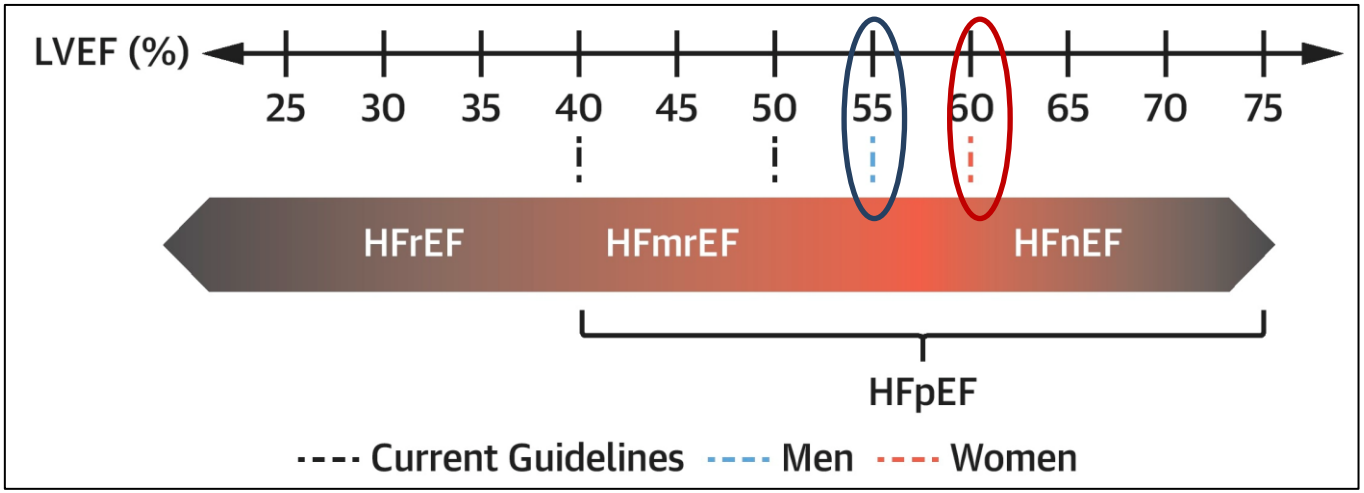


Dimond MG et al. JACC-HF 2024

Reconsidérer le seuil de FEVG pour catégoriser l'IC ?



Dimond MG et al. JACC-HF 2024



Lam C, Solomon SD. JACC 2021

Rechercher les causes génétiques (cardiomyopathies)

Keep them in mind !

Red flags

- Signes extracardiaques (canal carpien, dysautonomie …)
- Signes ECG (microvoltage, HVG …)
- Signes échocardiographiques

Démarche diagnostique exhaustive
(biologie et imagerie multimodale)

Amyloses AL et TTR	CMH sarcomériques	Fabry
Tafamidis Patisiran …	Inhibiteurs myosine Alcoolisation septale	Enzymothérapie de substitution ou molécule chaperon

IC-FEP et phenomapping (ou clustering)

Caractéristiques cliniques

Comorbidités

Données écho

Hémodynamique

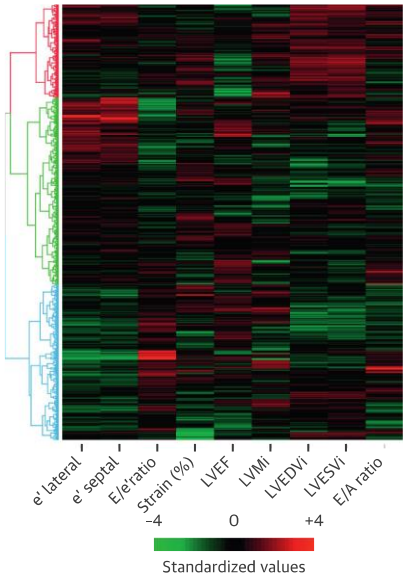
Biologie

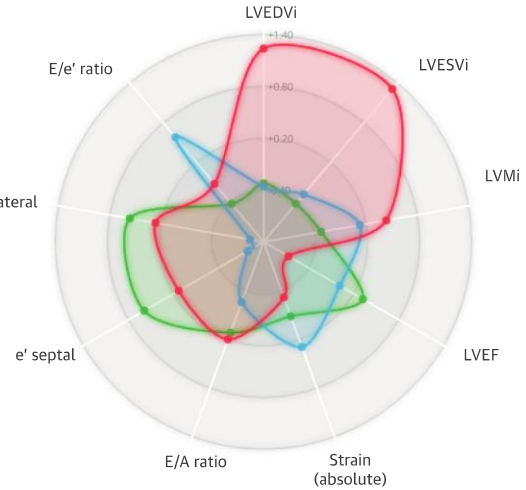
Biomarqueurs

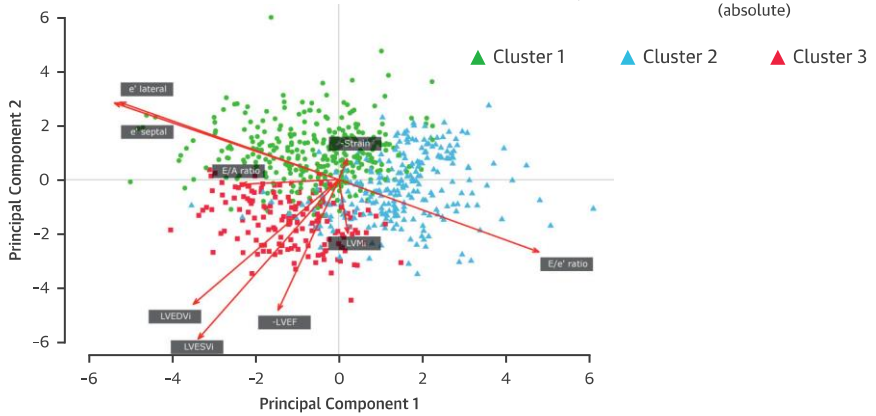
Techniques statistiques de clustering (IA)

Clusters± mutuellement exclusifs

- Cluster 1
- Cluster 2
- Cluster3



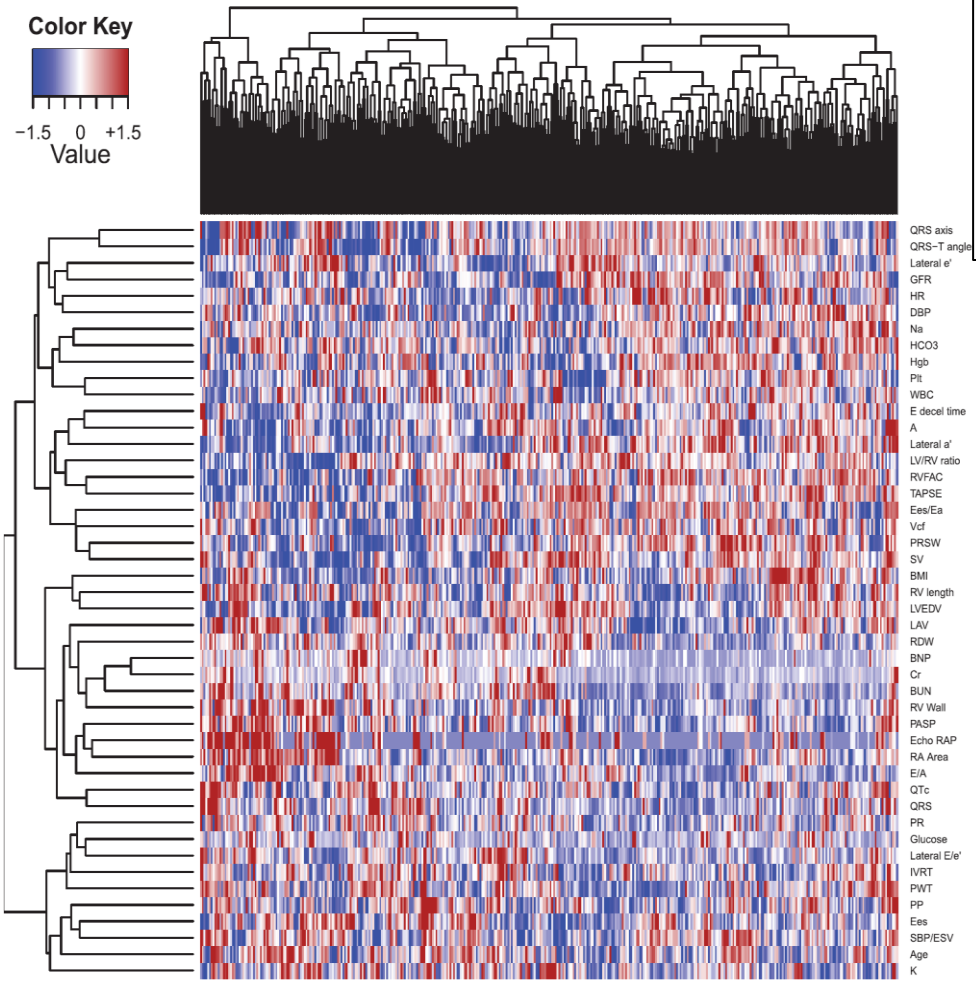




J Am Coll Cardiol 2017;70:1704–16

IC-FEP et phenomapping (ou clustering)

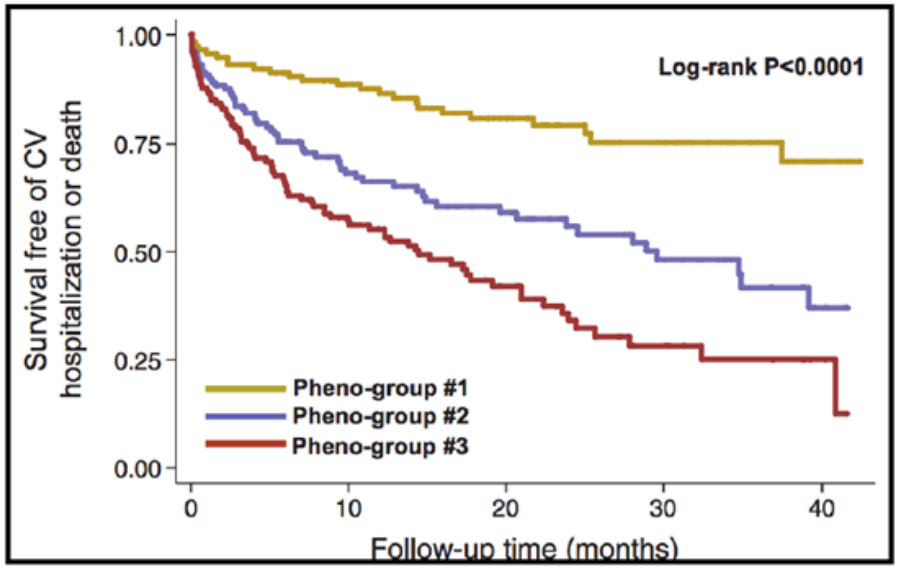
397 HFpEF patients,
67 variables
=> Hierarchical clustering analysis



1: younger, lower BNP, less LVH and DD

2: most DM, obesity, OSA, lowest e', highest PCWP

3: older, highest BNP, worst CKD, most electrical and echo changes, highest E/e', RV dysfunction



Shah et al. Circulation 2015; 131

IC-FEP et phenomapping

Clinical Phenogroups in Heart Failure With Preserved Ejection Fraction
Detailed Phenotypes, Prognosis, and Response to Spironolactone

P1

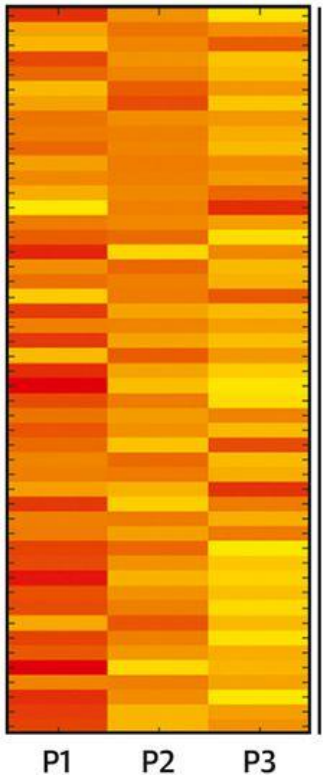
- Normal LV geometry
- Low arterial stiffness
- Low natriuretic peptides
- Markers of COPD (not genuine HFpEF?)
- Low event rate
- Preferentially enrolled in Russia/Georgia

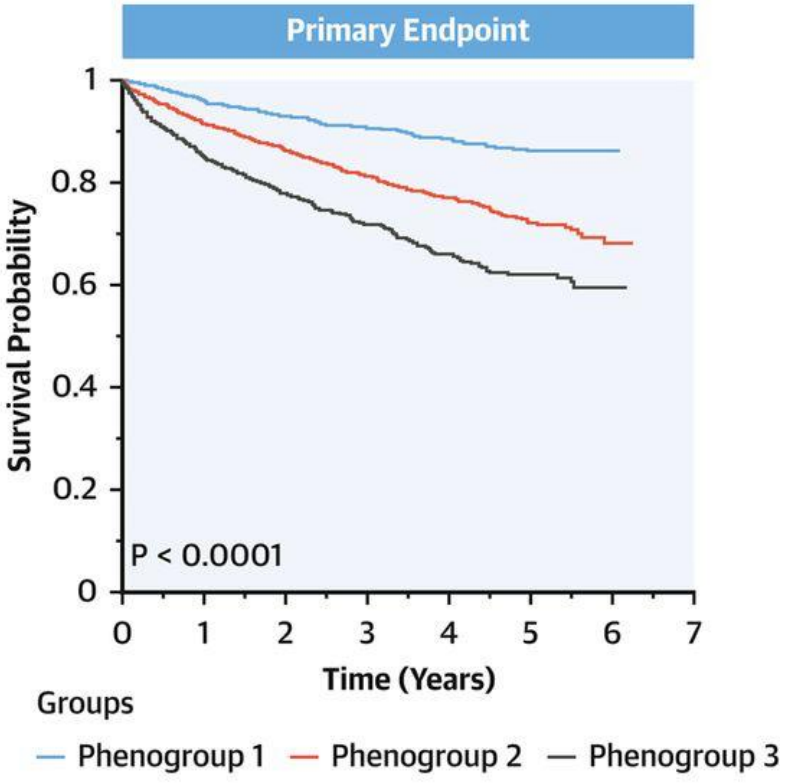
P2

- Concentric remodeling
- Very stiff arteries
- LA enlargement and AF
- High natriuretic peptides
- Innate immunity activation
- High risk of primary endpoint

P3

- Obesity/Diabetes
- Inflammation (TNF-α)
- Abnormal metabolism, liver and renal injury/dysfunction
- High renin
- Highest risk of primary endpoint
- Preferential response to spironolactone



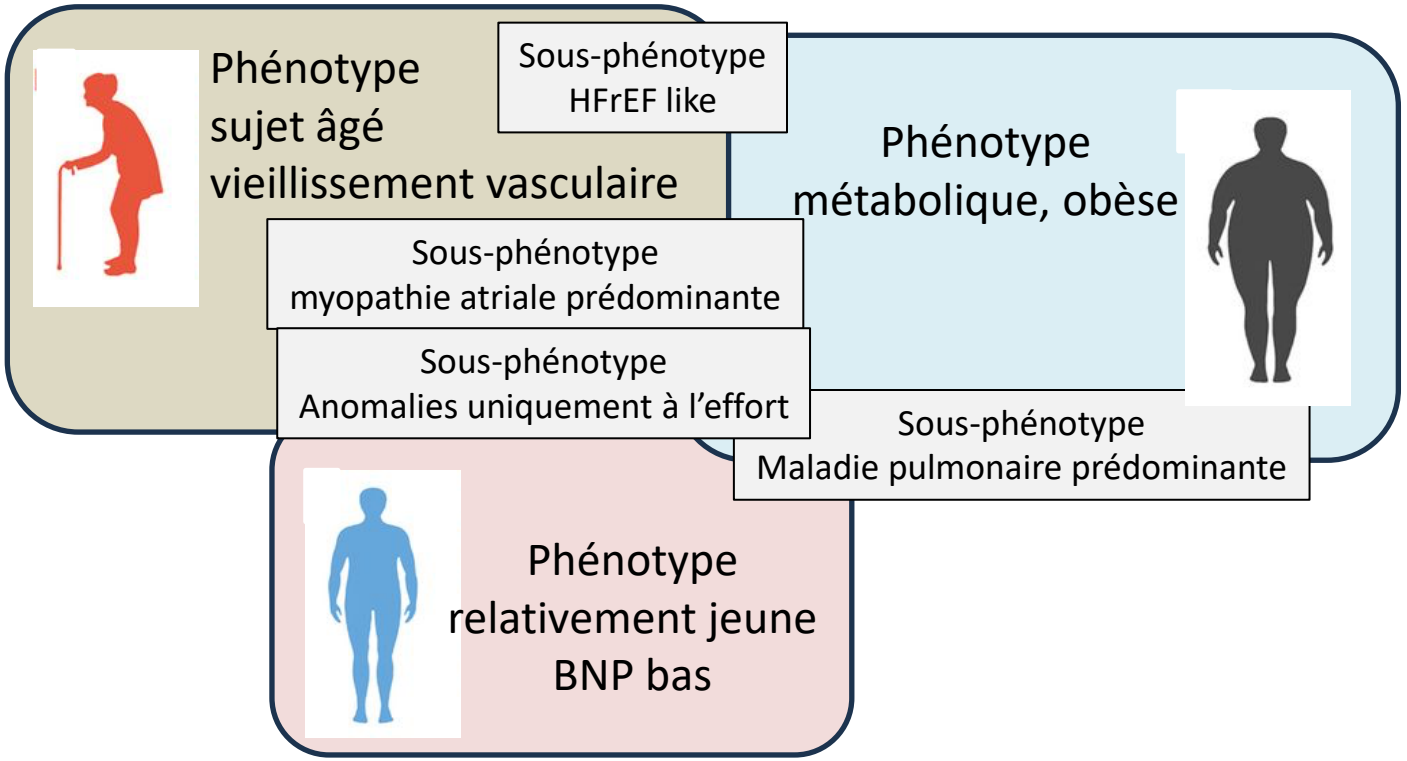


Cohen JB et al. JACC-HF 2020

Table 1 Summary of selected HFpEF phenomapping studies and data inputs

Study	Derivation		Validation		Data inputs								# of groups identified	Differential outcomes by group demonstrated
	Source	*n*	Source	*n*	Clinical	Basic Labs	Imaging	Select Biomarker	Large-scale 'Omics	ECG	Exercise data	Invasive Hemodynamics		
Shah *et al.*[1]	Single-centre/ clinical	397	External	107	✓	✓	✓	✓NP	-	✓	-	-[a]	3	✓
Kao *et al.*[10]	I-PRESERVE trial	4113	External	3203	✓	✓	-	-	-	-	-	-	6	✓
Przewlocka-Kosmala *et al.*[11]	Single-centre/ clinical	177[b]	n/a	n/a	-	-	✓	✓Galactin-3	-	-	✓	-	3	✓[c]
Cohen *et al.*[12]	TOPCAT trial	1765[d]	n/a	n/a	✓	-	-	-	-	-	-	-	3	✓
Segar *et al.*[13]	TOPCAT Americas	654	Int/ext	1113/ 198	✓	✓	✓	✓NP	-	✓	-	-	3	✓
Hedman *et al.*[14]	Multicentre registry	320	n/a	n/a	✓	✓	✓	✓NP	-	-	-	-	6	✓
Schrub *et al.*[15]	Multicentre registry	356	n/a	n/a	✓	✓	✓	-	-	-	-	-	3	-
Stienen *et al.*[16]	Multicentre registry	392	n/a	n/a	-	-	-	-	✓	-	-	-	2	✓
Harada *et al.*[17]	Single-centre/ clinical	350	Internal	133	✓	✓	✓	-	-	-	-	-	4	✓
Arevalo-Lorido *et al.*[18,e]	Multicentre registry	1934	n/a	n/a	✓	✓	-	-	-	-	-	-	7	✓
Sabbah *et al.*[19]	Multiple trials[f]	301	n/a	n/a	✓[g]	-	-	-	✓	-	-	-	3	✓
Uijl *et al.*[20]	Multicentre registry	6909	External	2153	✓	✓	-	-	-	-	-	-	5	✓
Gu *et al.*[21]	Single-centre/ clinical	970	External	290	✓	✓	✓	✓NP	-	-	-	-	3	✓
Casebeer *et al.*[22]	Clinical/claims	1515	n/a	n/a	✓	-	-	-	-	-	-	-	3	
Nouraei *et al.*[23]	Single-centre/ clinical	197	n/a	n/a	✓	✓	✓	-	-	-	-	-	6	✓
Wu *et al.*[24]	Multigenerational registry	125	n/a	n/a	-	-	-	-	✓	-	-	-	2	✓
Woolley *et al.*[25]	Multicentre registry	429	n/a	n/a	-	-	-	-	✓	-	-	-	4	✓
Hahn *et al.*[26]	Single-centre/ clinical	38	n/a	n/a	-	-	-	-	✓	-	-	-	3	✓
Jones *et al.*[27]	Single-centre/ clinical	21[h]	n/a	n/a	-	-	✓	-	-	-	-	✓	3	-
Fayol *et al.*[28]	Single-centre/ clinical	928	n/a	n/a	✓	✓	✓	✓NP	-	-	-	-	3	✓

IC-FEP et phenomapping
=> 3 phénotypes principaux



Clusters ou phénotypes agrégés
mais overlap
Sous phénotypes en sus

D'après Peters AE et al. Cardiovasc Res 2022; 118, 3403–3415

Etude PACIFIC : phénotypage approfondi

Etude APHP / MEDICEN

3 HFpEF (LVEF≥ 50%)
: 2 HFrEF (LVEF≤40%)
: 1 subject without HF

Informed consent

Prospective investigations

Deep phenotyping (1 day hospital stay)

Physical exam
Functional tests
Questionnaires

Cardiac MRI
Chest CT

TTE
Elastography

ECG

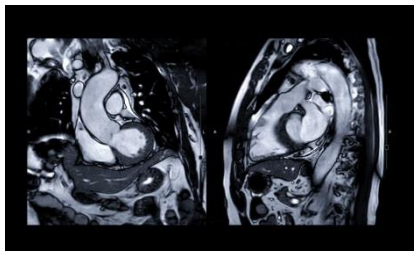
Biology
Arterial stiffness

+ cardiac dynamic monitoring (up to 14 days)

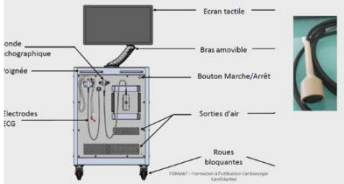
Data analysis

Develop novel diagnostic strategies for HFpEF

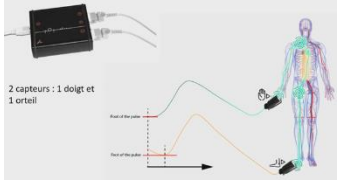
Stratify HFpEF into distinct subgroups



Mesure rigidité cardiaque



Mesure Rigidité artérielle



Hulot JS, … Logeart D. ACVD 2024, in press

IC-FEP et phénotypage : quelles conséquences thérapeutiques?

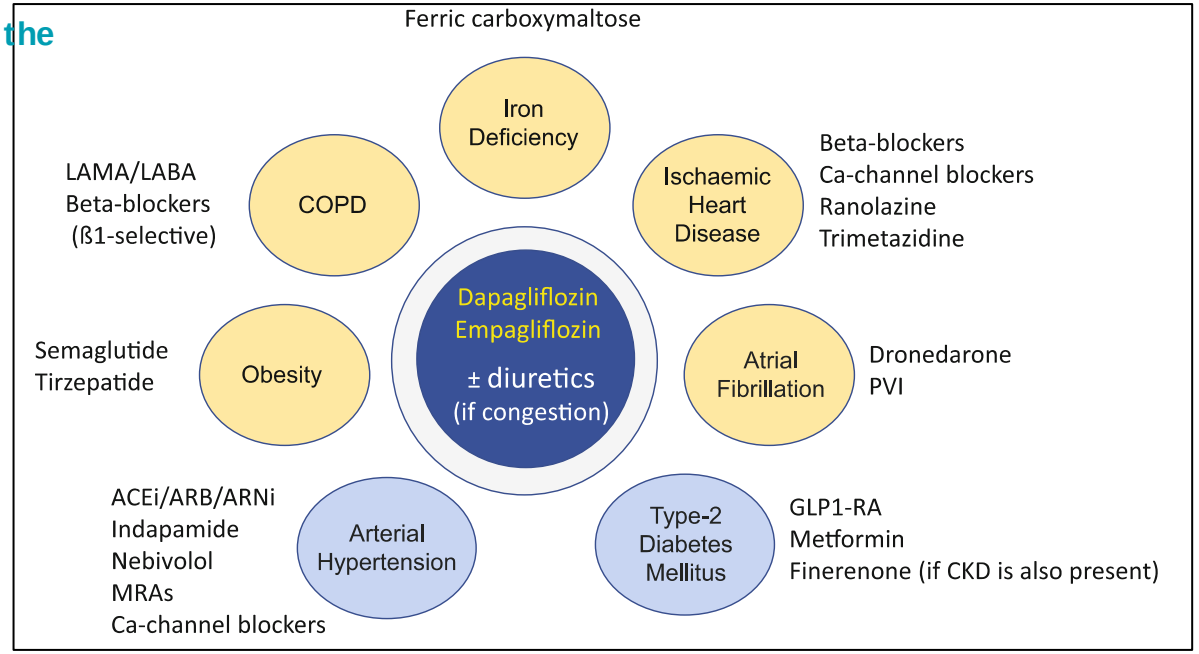
?

Phenotypage et conséquences thérapeutiques

Patient phenotype prof ling in heart failure with preserved ejection fraction to guide therapeutic decision making. A scientif c statement of the Heart Failure Association, the European Heart Rhythm Association of the European Society of Cardiology, and the European Society of Hypertension

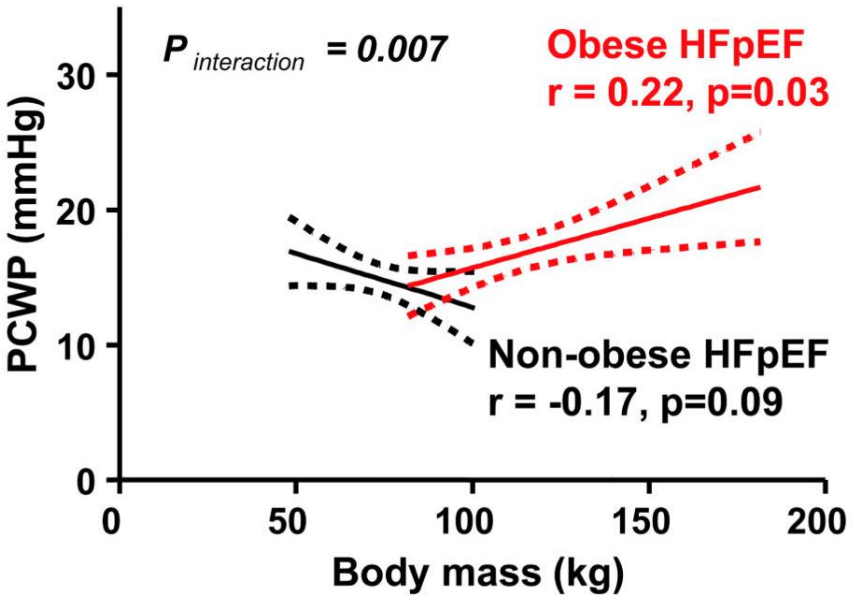
Table 1 List of primary and secondary heart failure with preserved ejection fraction phenotypes under consideration in this review

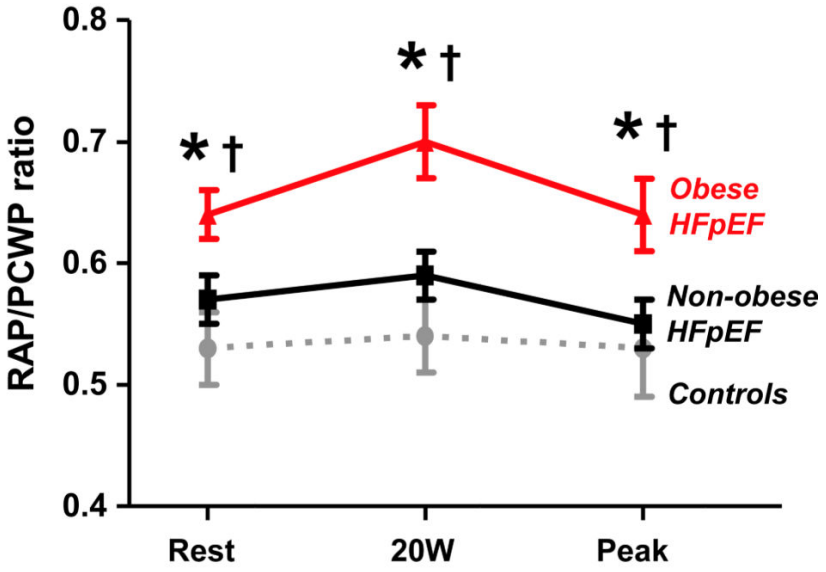
Primary HFpEF
Age
Sex
Type 2 diabetes mellitus
Obesity
Sleep apnoea
Arterial hypertension
Arterial hypotension
Pulmonary hypertension
Chronic obstructive pulmonary disease
Iron deficiency
Coronary artery disease
Atrial fibrillation
High heart rate
Chronotropic incompetence
Atrial functional mitral regurgitation
Functional tricuspid regurgitation
Cachexia and sarcopenia
Very high ejection fraction (>65%/>70%)
LVEF between 50% and 55%
HFpEF in patients with cancer
Secondary HFpEF
Restrictive cardiomyopathies
Hypertrophic cardiomyopathy
Constrictive pericarditis
Valvular heart disease



European Journal of Heart Failure (2023) **25**, 936–955

IC-FEP et obésité

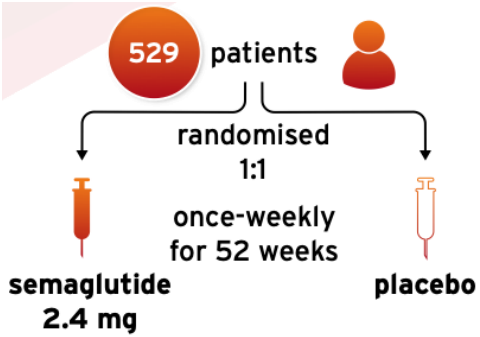


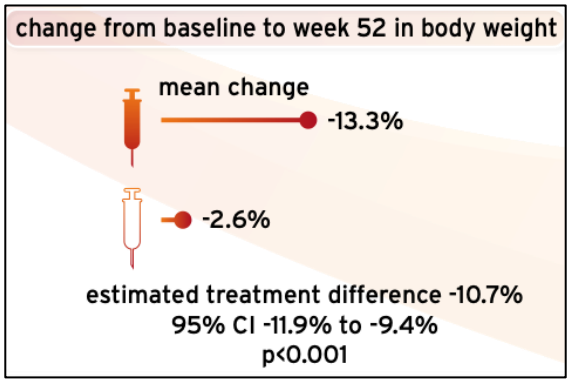


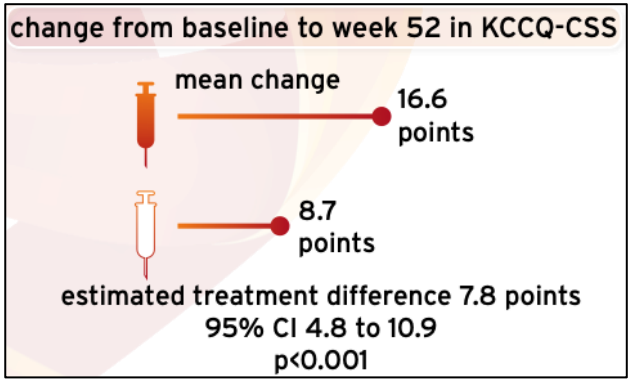
Circulation. 2017; 136(1): 6–19.

STEP-HFpEF trial

Semaglutide (GLP1a)

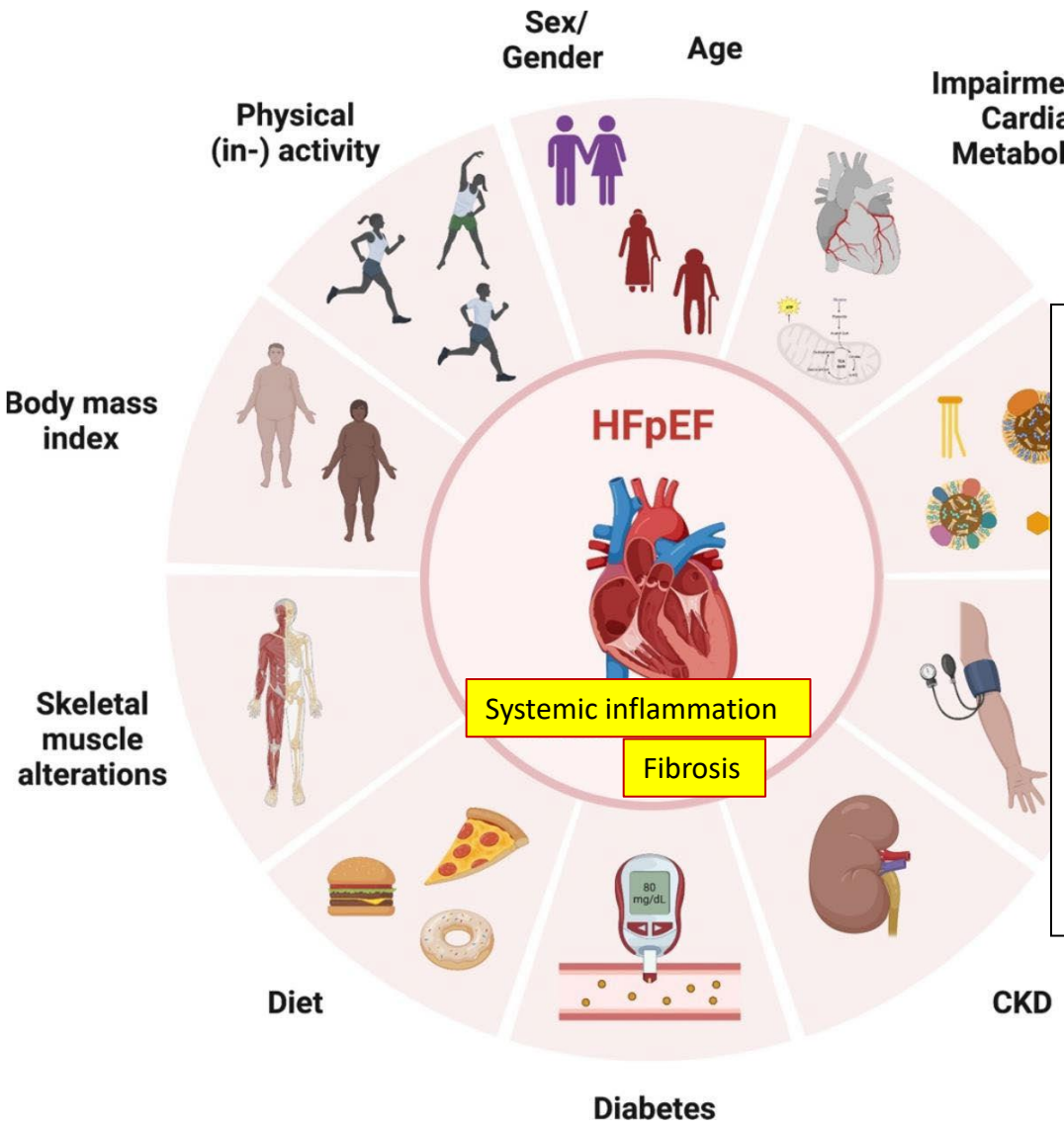


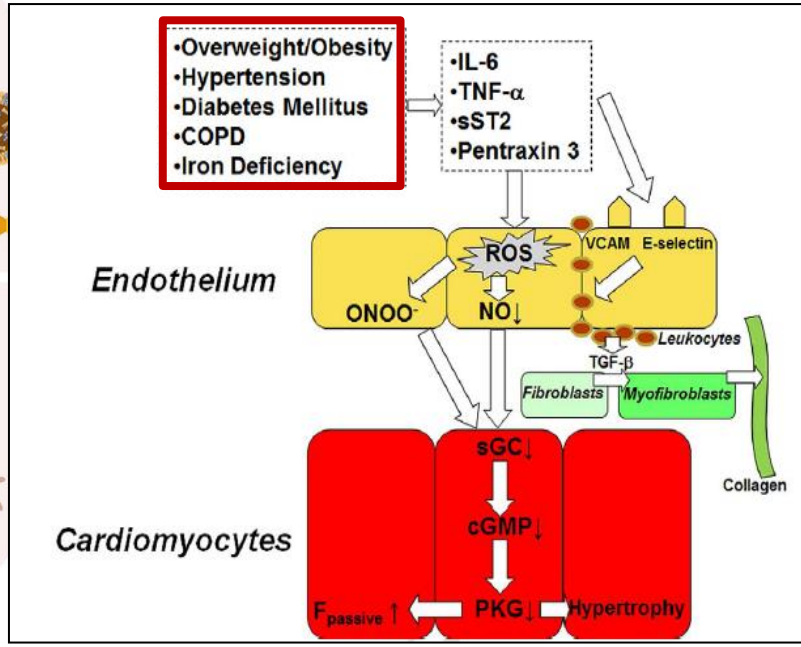




N Engl J Med 2023; 389:1069-1084

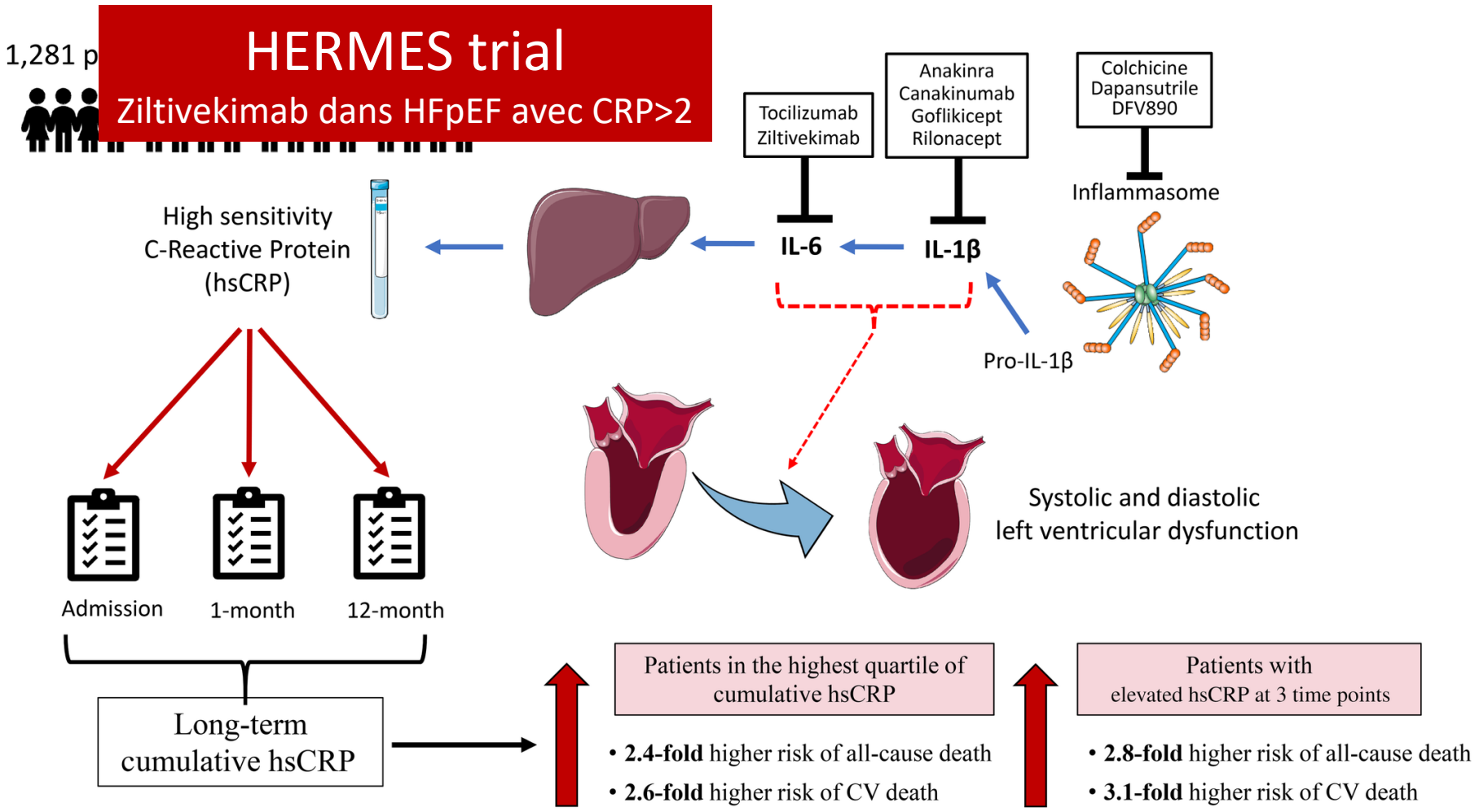
IC-FEP et inflammation





Paulus W et al. JACC 2013

IC-FEP et CRP élevée



JAHA 2023;12:e031786

CONCLUSION

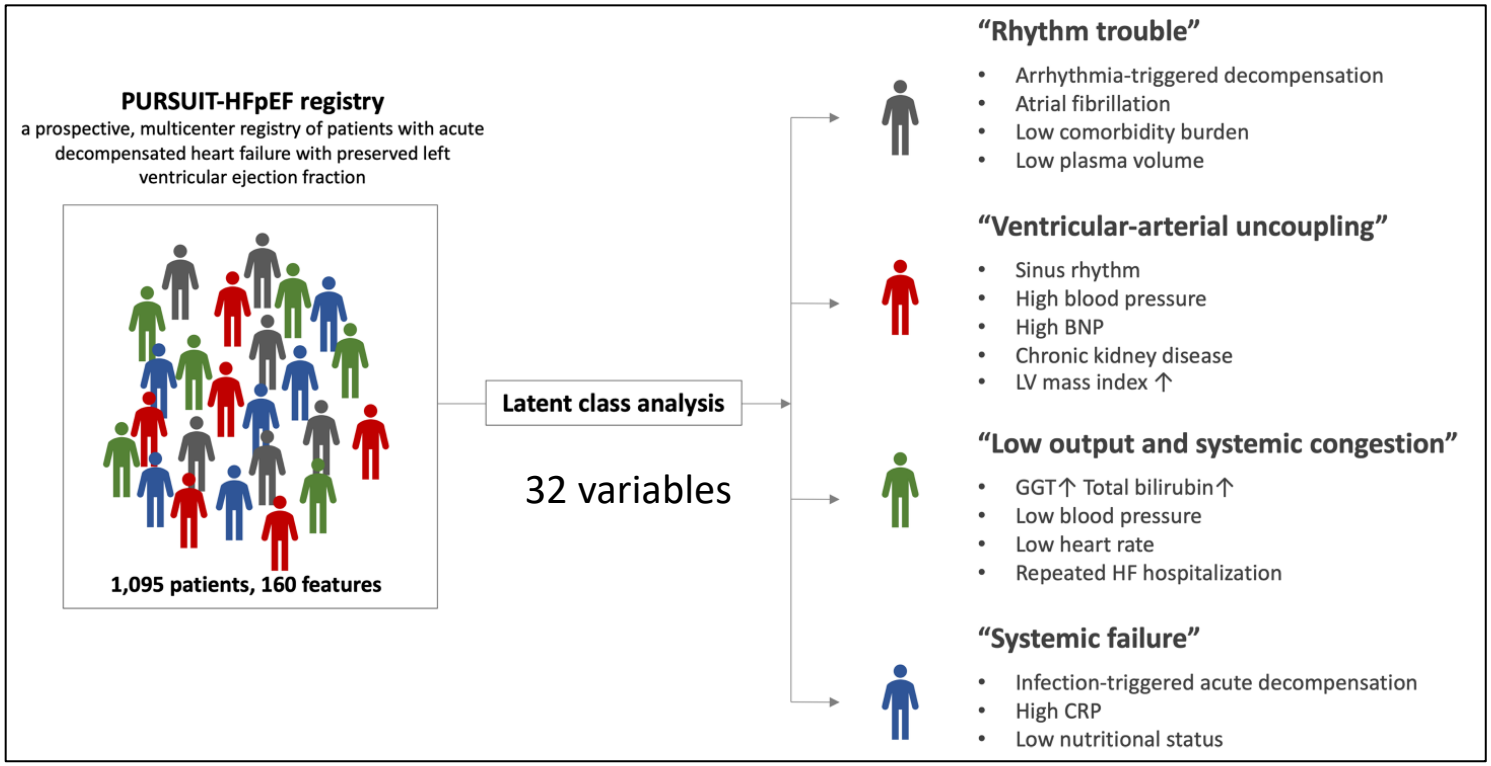
- ❑ IC à FE préservée : définition et physiopathologie complexe et multiple
  => peu de traitements applicables à tous

- ❑ Phenotypage = outil statistique pour individualiser des (nouveaux?) phénotypes ou clusters pertinents

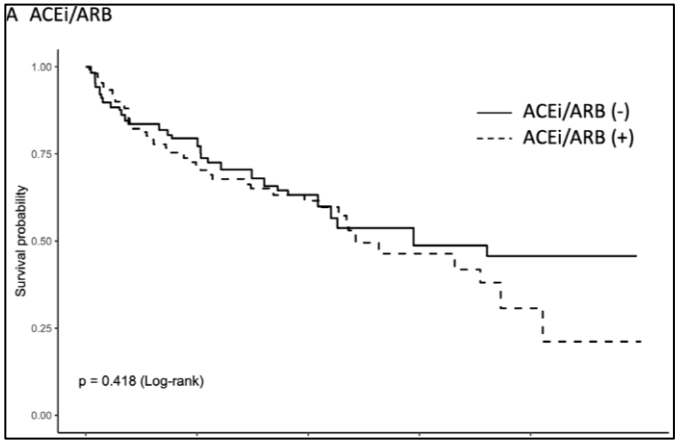
- ❑ Utilité clinique : reste largement à démontrer, overlap des phénotypes, beaucoup de variables importantes actuellement non prises en compte

- ❑ Perspectives
  - Raffinement du phénotypage avec plus de variables
  - Essais cliniques basés sur certains phénotypes
  - Extension d'indications de traitements déjà validés ailleurs

IC-FEP et clustering



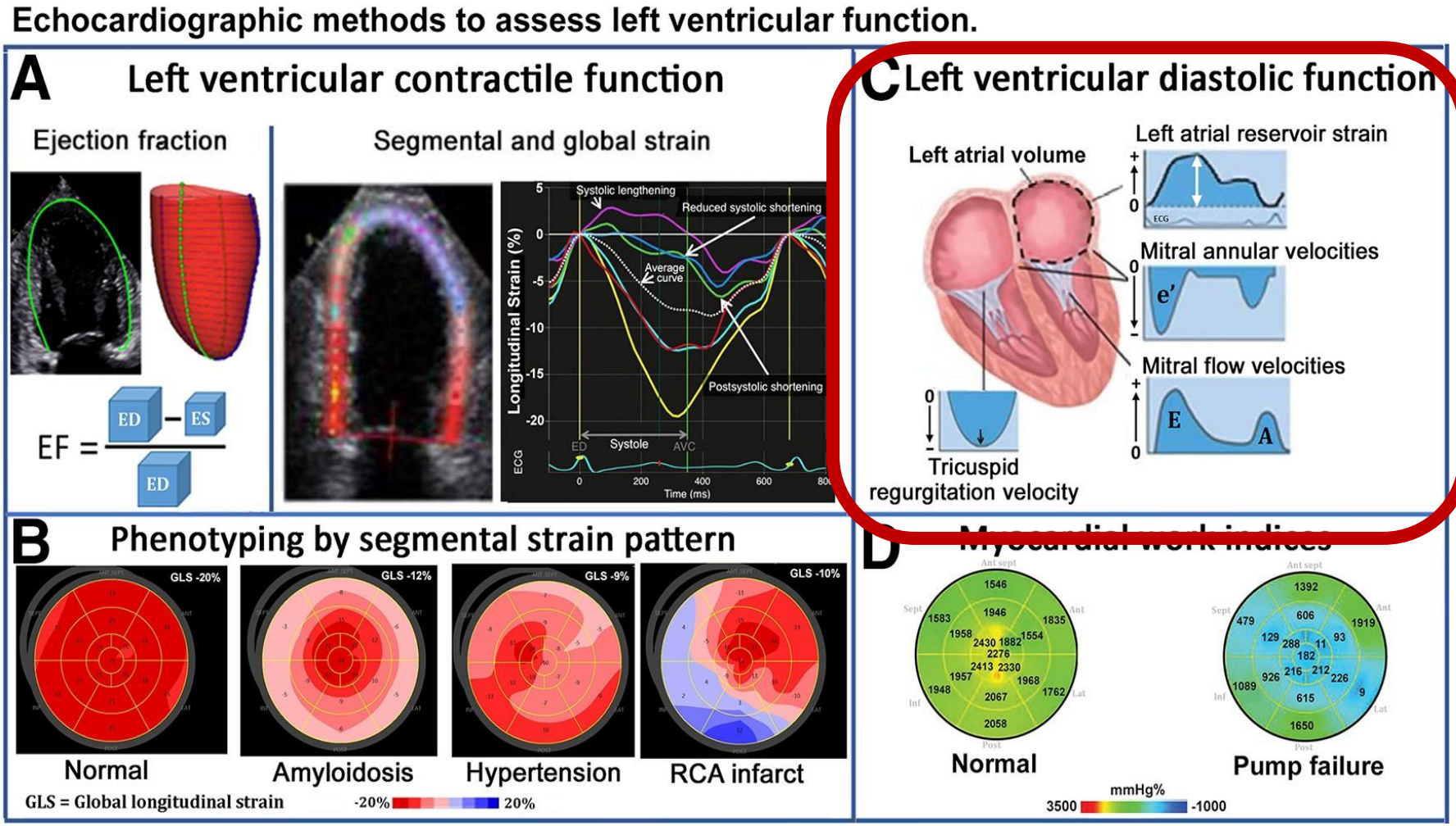
Heart. 2022 ;108(19):1553-1561



Efficacité des ARM dans le phénotype 2

Sotomi Y, *et al*. *Heart* 2023;109:1231–1240.

Les critères écho



Eur Heart J Cardiovasc Imaging. 2023, 24: 1329–1342