Phenomapping for the diagnosis of HFpEF

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- Boehringer Ingelheim
- BMS
- Novartis
- Novo Nordisk
- Pfizer

What is the issue?

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

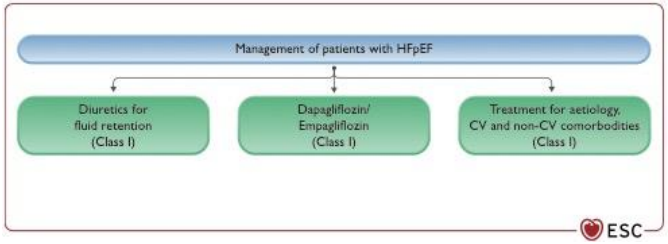
It could be useful to distinguish relevant HFpEF subgroups

(relatively) homogeneous pathophysiology

Strong evidence-based medicine for all of these patients

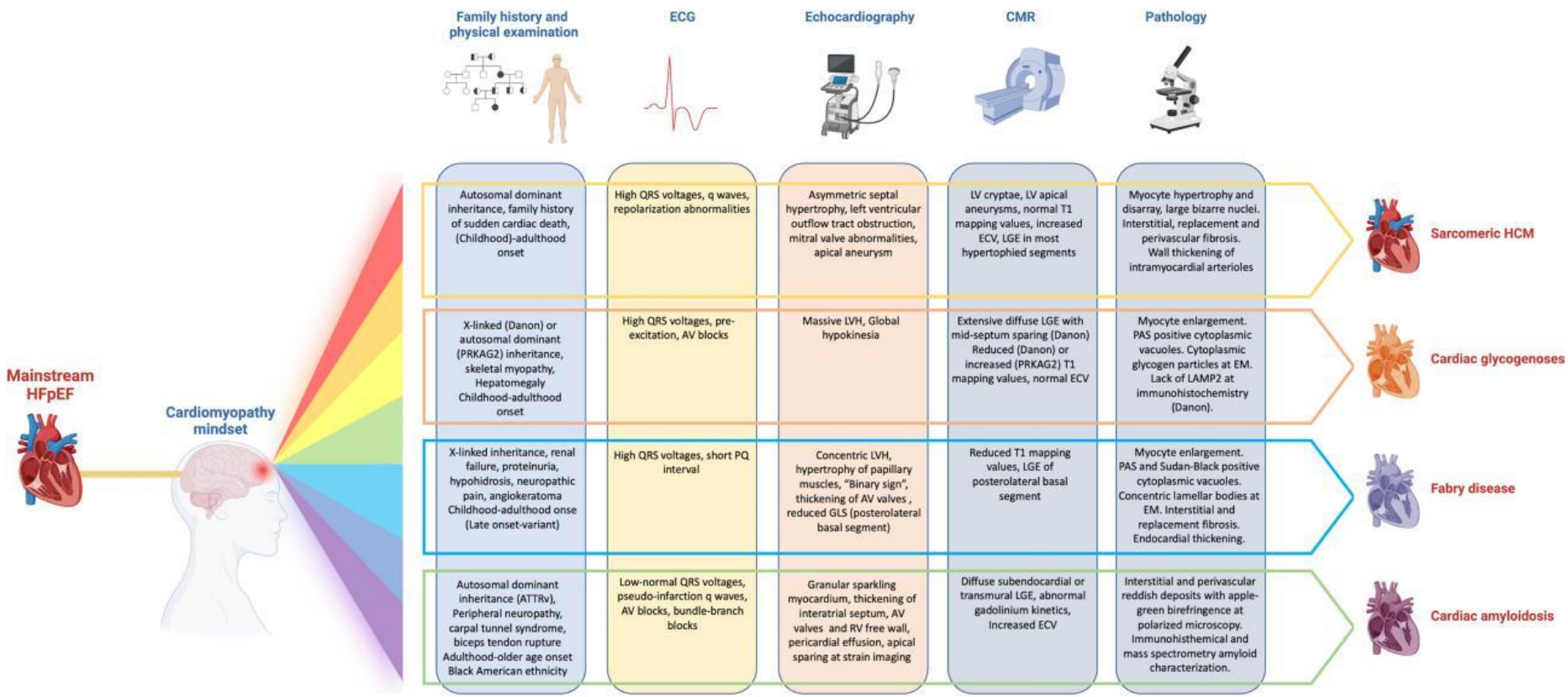
Herogeneous pathophysiology

Lack of evidence-based medicine



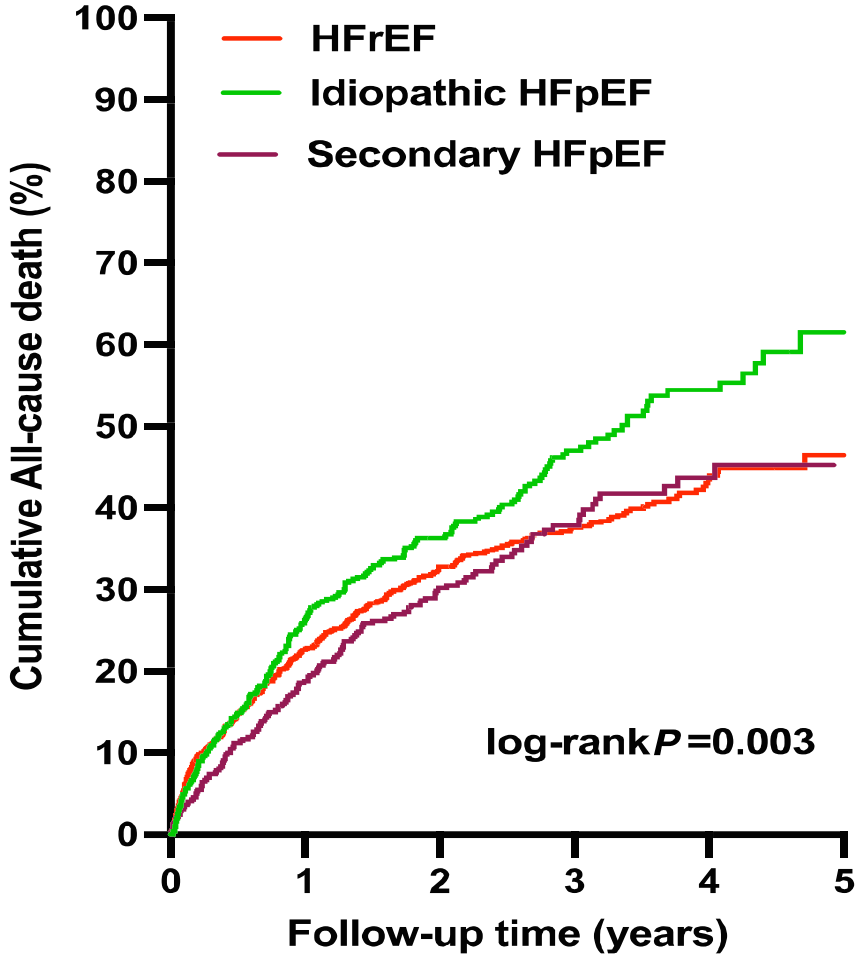
To look for cardiomyopathy/ secondary HFpEF

Keep in mind !



European Heart Journal (2023) 44, 656–667
https://doi.org/10.1093/eurheartj/ehac764

Aetiological classification and prognosis in patients with heart failure with preserved ejection fraction



ESC Heart Failure 2022; 9: 519–530

Let's move on to new ways of classifying HF patients

VIEWPOINT

Heart Failure

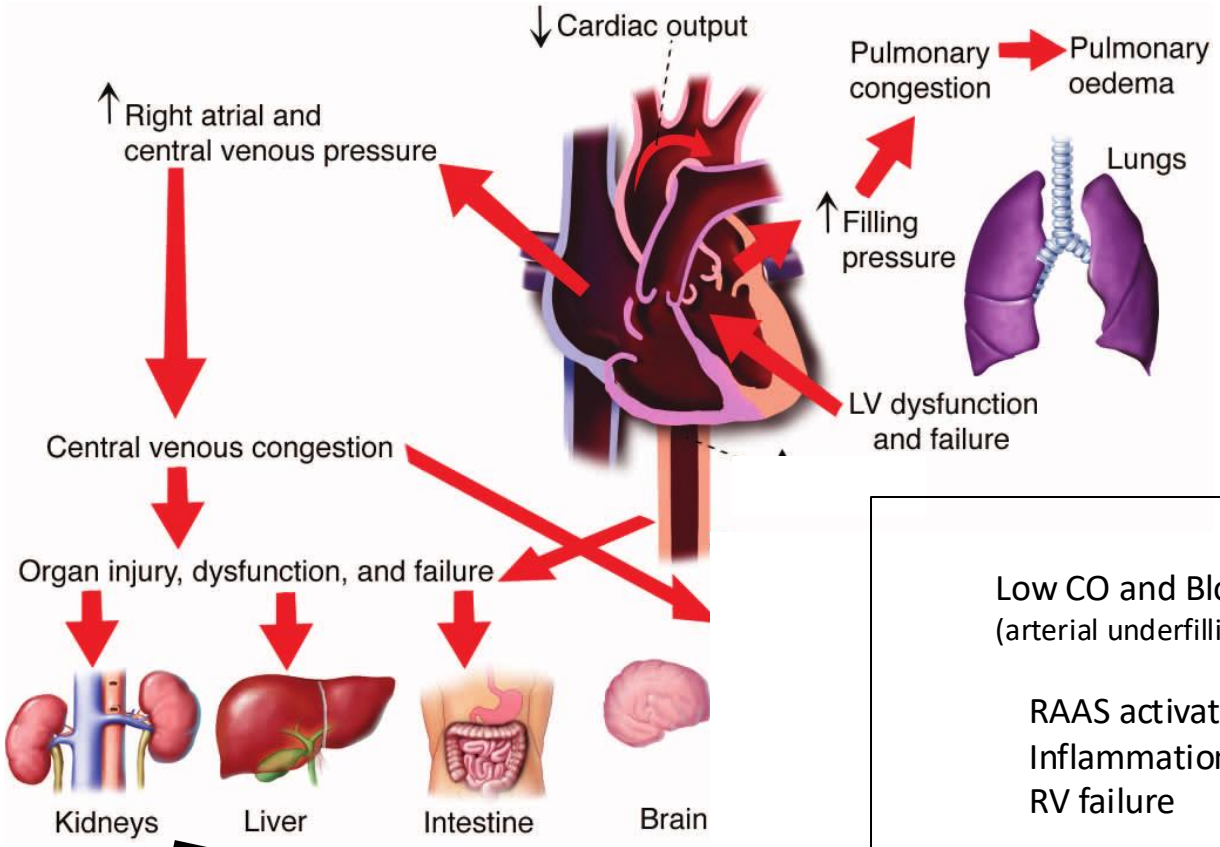
TNM-Like Classification

Francesco Fedele, MD, Paolo Severino, MD, Simone Calcagno, MD, Massimo Mancone, MD, PHD
Rome, Italy

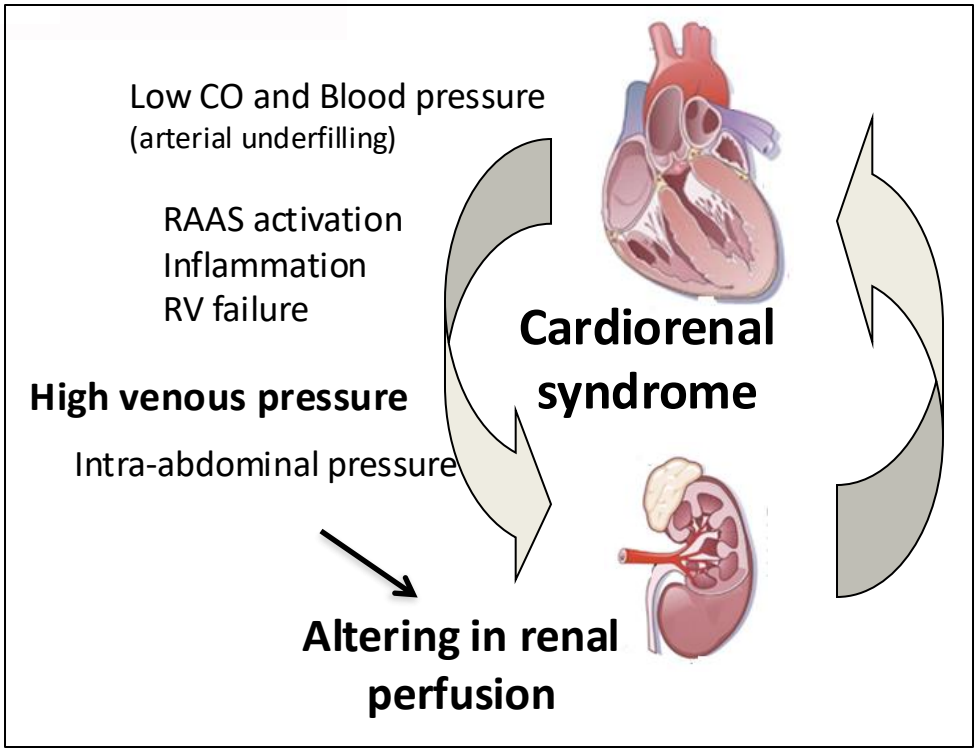
Heart	Lung	Malfunction of Other Organs
H-1: impaired systolic or diastolic function of LV without structural damage	**L-0:** no lung involvement **L-1:** Hemodynamic congestion **L-2:** Clinical congestion **L-3:** Cardiac lung*	**M-0:** no malfunction of other organs **M-1:** single organ damage due to HF **M-2:** double organ damage due to HF **M-3:** multiple organ damage
H-2: LV with systolic or diastolic dysfunction and structural damage (hypertrophy, previous myocardial infarction)		
H-3: systolic and diastolic dysfunction (and/or EF< 35%) with left ventricular remodeling	**Parameters of pulmonary damage:** -Precapillary pulmonary hypertension (mPAP > 25mmHg ; PAWP < 15mmHg) -Post-capillary pulmonary hypertension (mPAP > 25mmHg; PAWP > 15mmHg) -Pleural effusion -Pulmonary edema	**Other Organs:** - Kidney - Liver - Central nervous system
H-4: biventricular systolic and diastolic dysfunction		

J Am Coll Cardiol 2014;63:1959–60

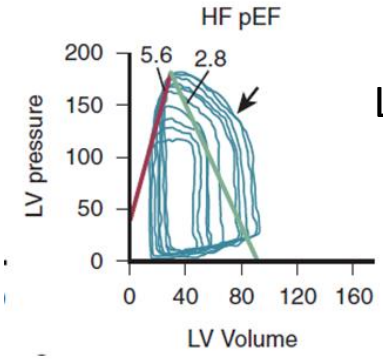
HF and dysfunction of other organs



Cardiorenal syndrome
(> 20% of AHF patients)
⇒ worsens prognosis
⇒ altered diuretic response



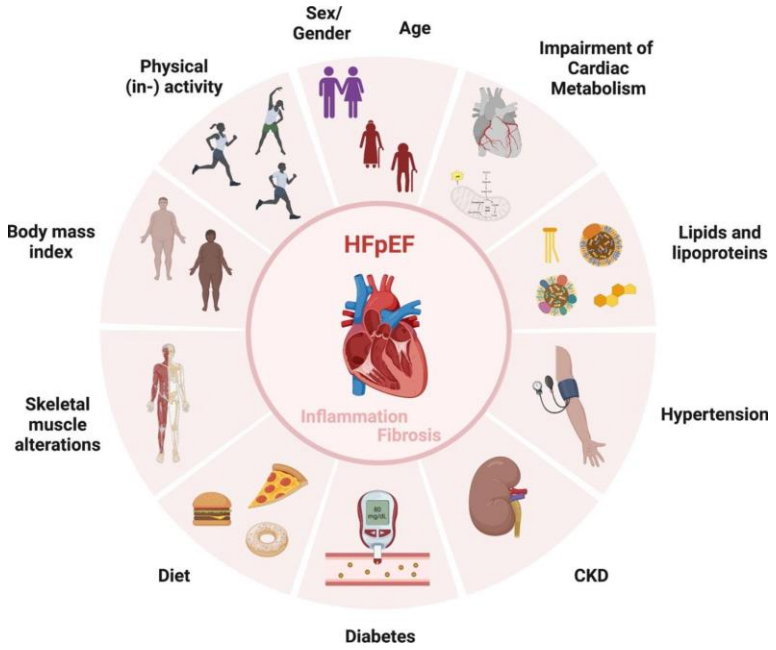
HFpEF: numerous and complex mechanisms => patient profiling taking into account this complexity



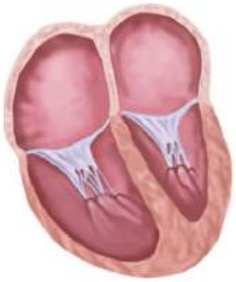
LV and vascular stiffness

Endothelial dysfunction

Comorbidities



Atrial myopathy



Pulmonary Hypertension
RV dysfunction

Chronotropic incompetence

Dysfunction of other organs

HFpEF and phenomapping (clustering)

New paradigm: data driven statistical analysis

Clinical characteristics

Imaging

Comorbidities

Hemodynamics

Biology

Biomarkers

Statistical clustering techniques

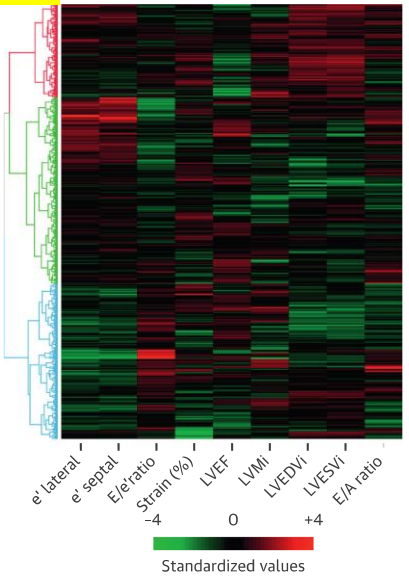
Unsupervised statistical learning

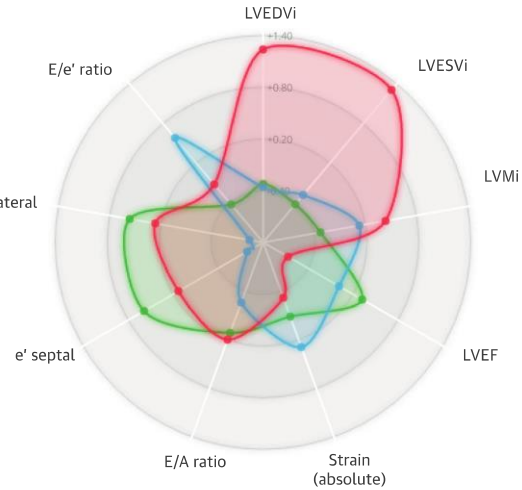
Clusters ± mutually exclusive

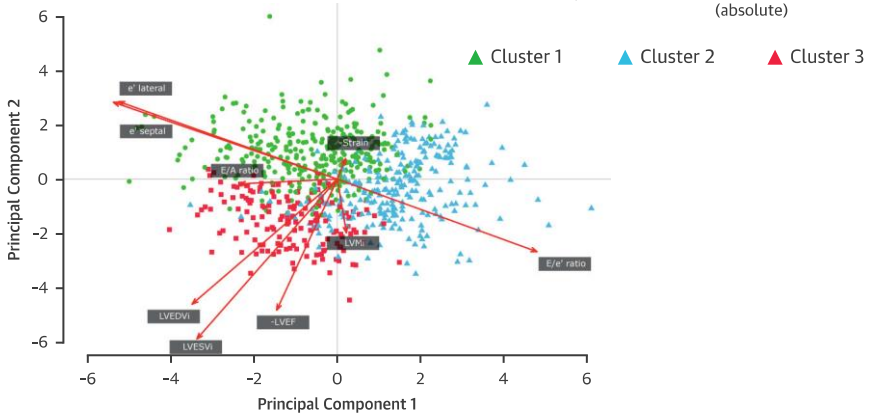
Cluster 1

Cluster 2

Cluster3



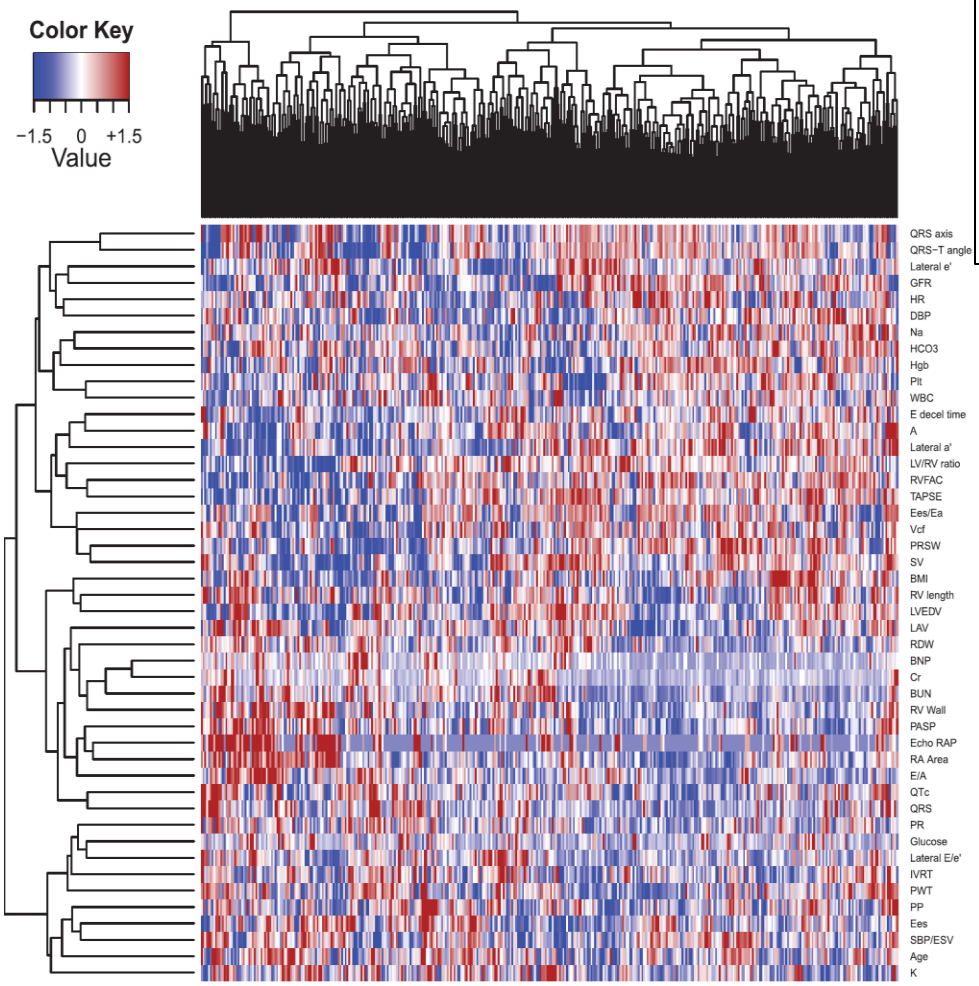




J Am Coll Cardiol 2017;70:1704–16

HFpEF and phenomapping (or clustering)

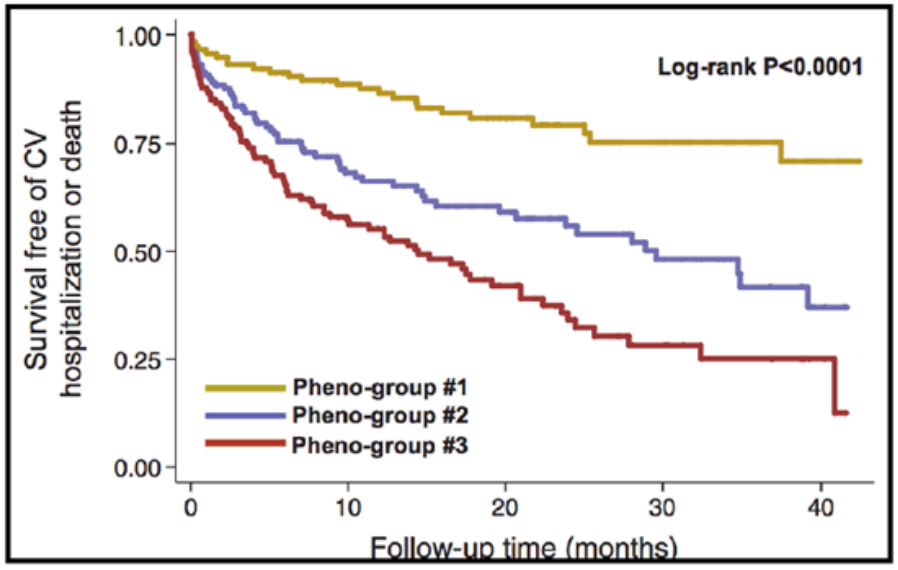
397 HFpEF patients,
67 variables
=> Hierarchical clustering analysis



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

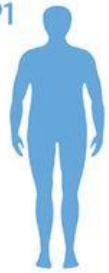


Shah et al. Circulation 2015; 131

HFpEF and phenomapping

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

P1



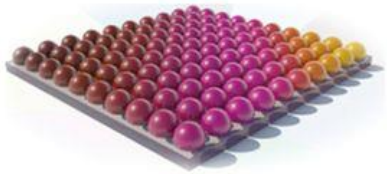
- Normal LV geometry
- Low arterial stiffness
- Low natriuretic peptides
- Markers of COPD (not genuine HFpEF?)
- Low event rate
- Preferentially enrolled in Russia/Georgia

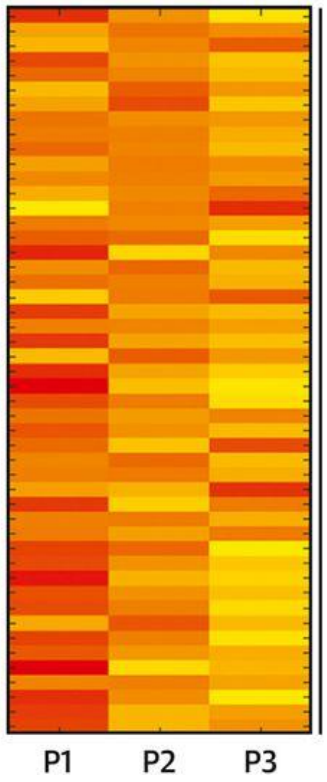
P2

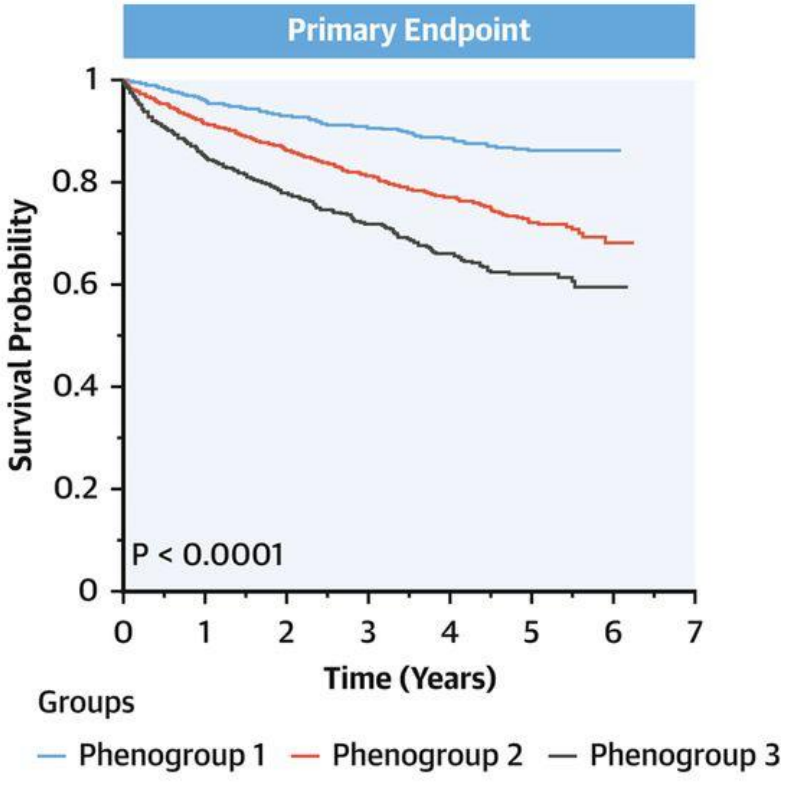
- Concentric remodeling
- Very stiff arteries
- LA enlargement and AF
- High natriuretic peptides
- Innate immunity activation
- High risk of primary endpoint

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

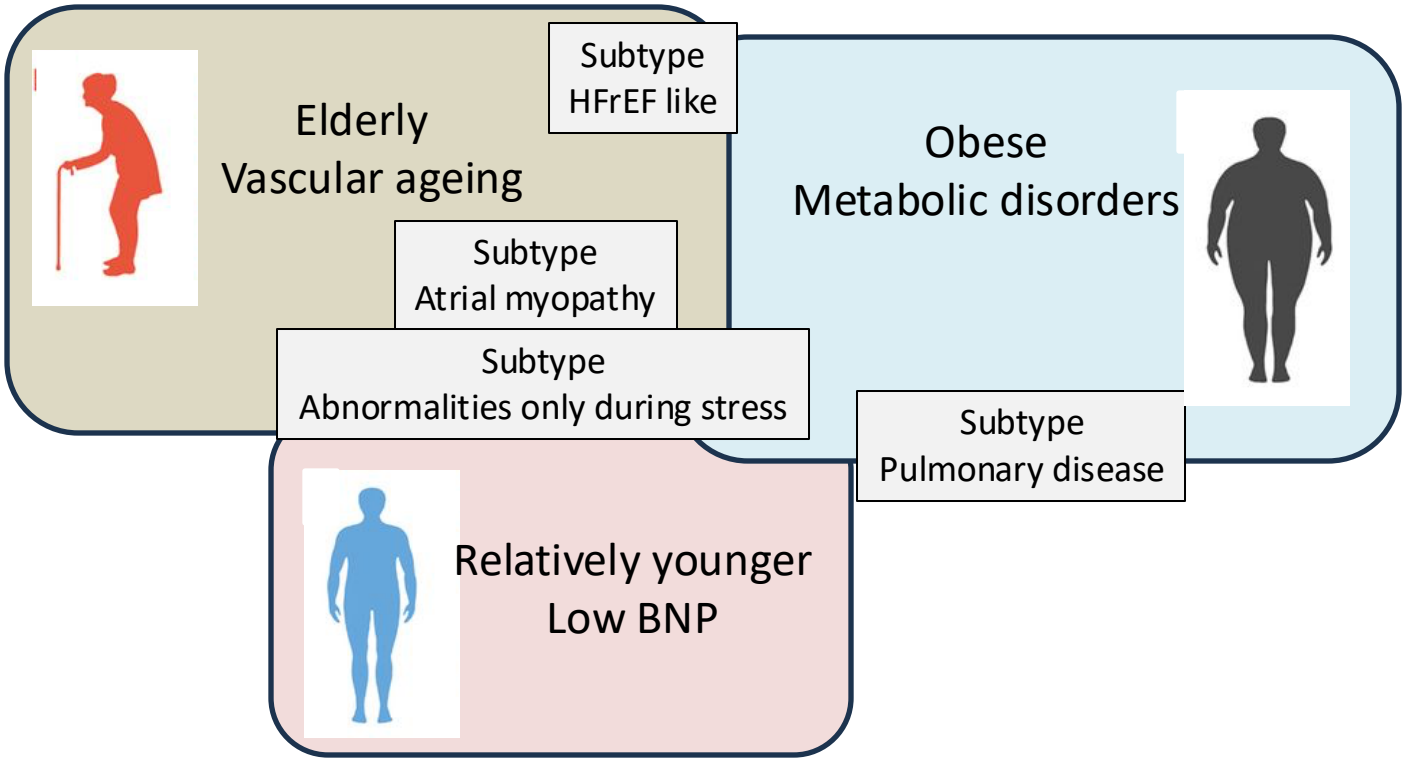
HFpEF and phenomapping

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	✓

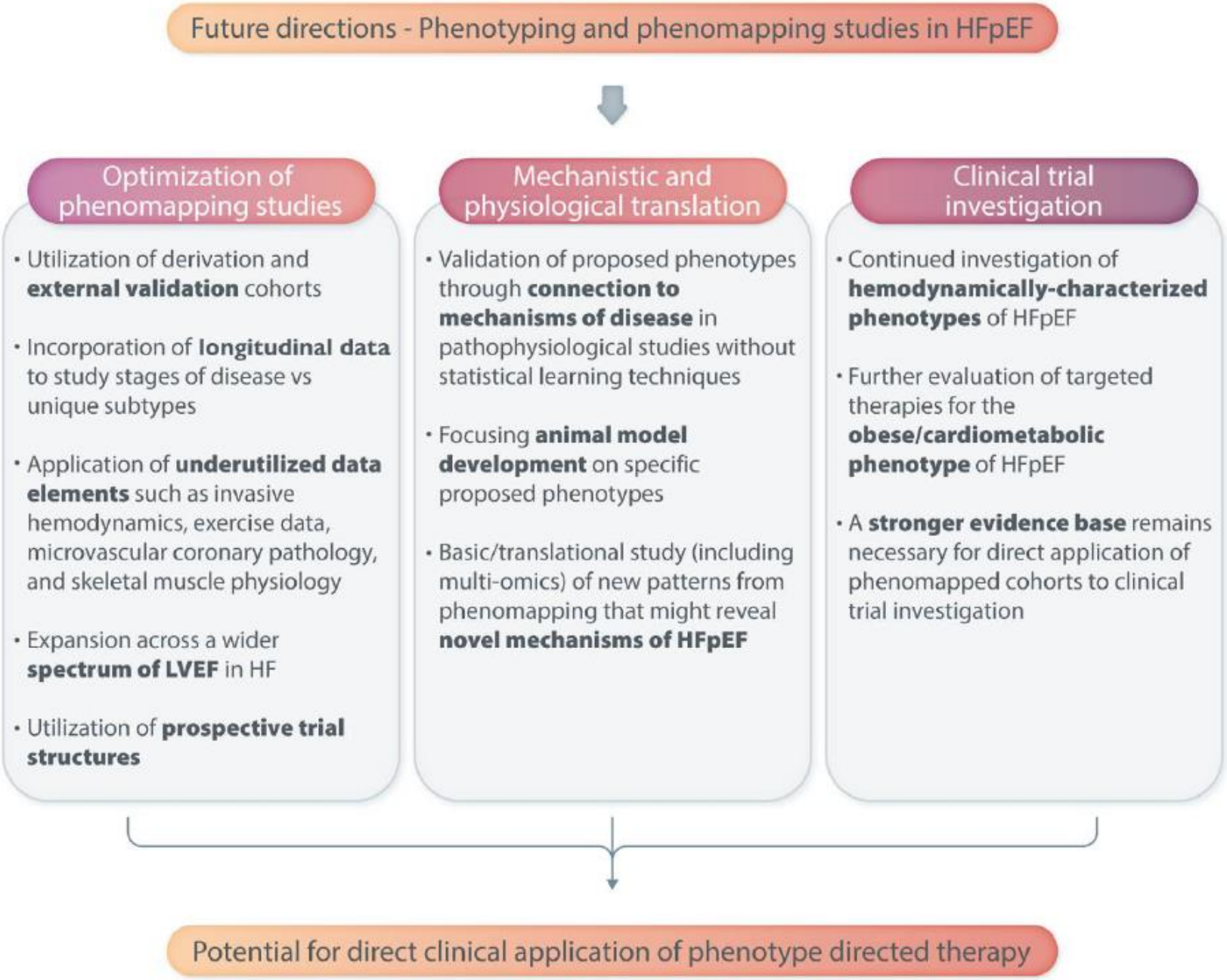
Cardiovascular Research (2023) 118, 3403–3415

HFpEF and phenomapping
=> 3 aggregate overlapping phenotypes across studies



Clustered phenotypes
but overlap
=> sub-phenotypes en sus

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

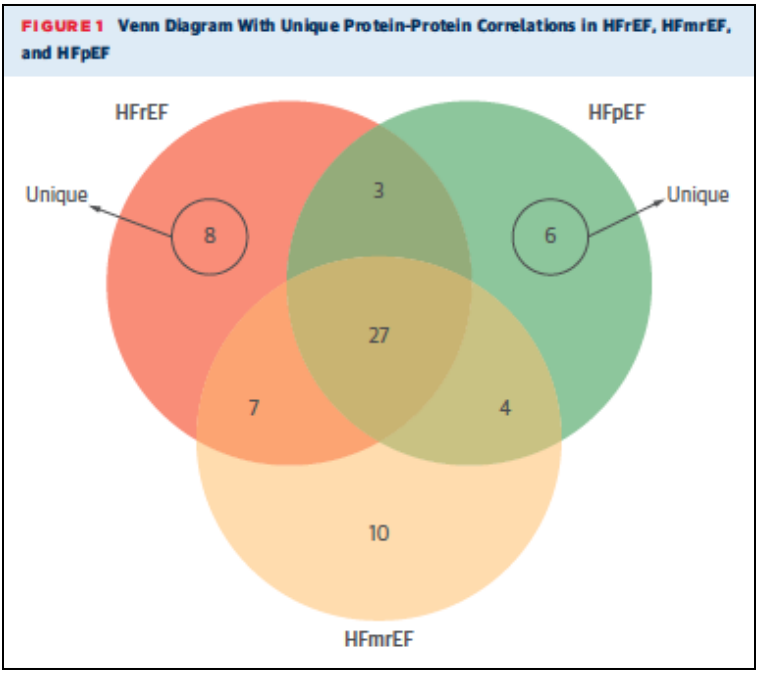


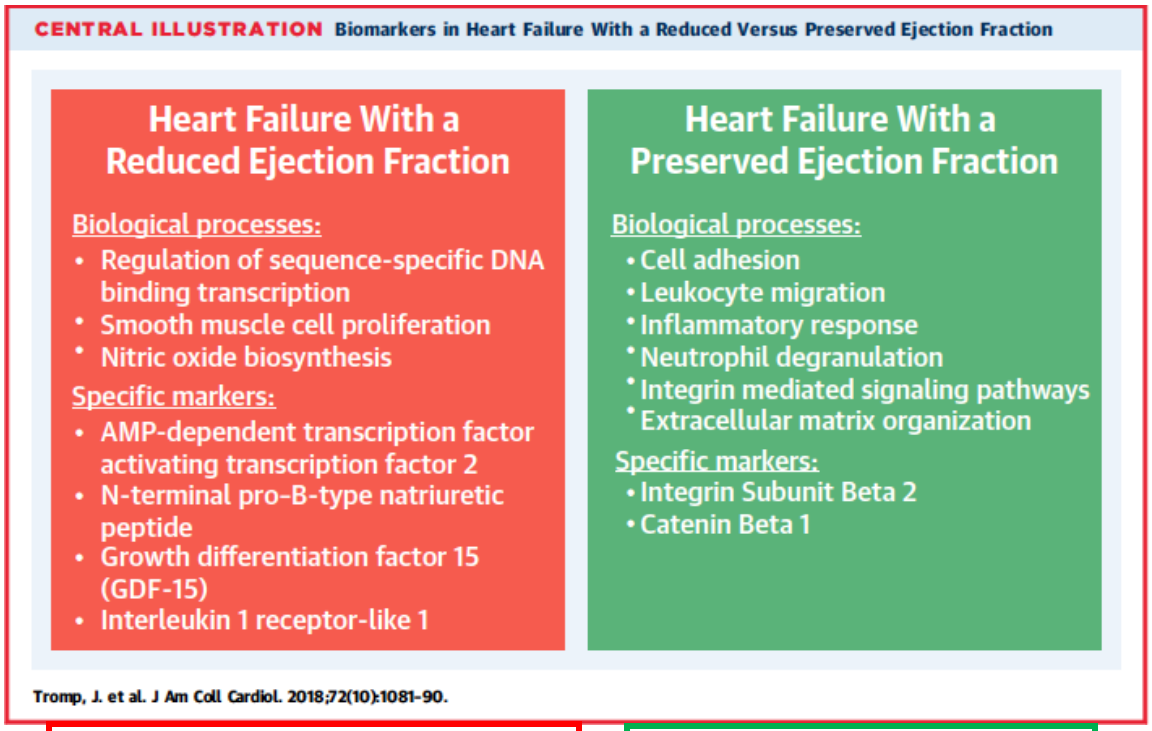
Peters AE et al. Cardiovasc Res 2022; 118, 3403–3415

HF and phenomapping using omics

BIOSTAT-CHF (BIOlogy Study to TAilored Treatment in Chronic Heart Failure)

Identifying biological pathways by using biomarkers





Olink Proseek Multiplex CVD III96X96 kit (Olink Proteomics)

HF-rEF
- cellular growth
- cardiac stress response
- métabolism

HF-pEF
- inflammation
- EC matrix

Tromp J et al. J Am Coll Cardiol 2018;72

PACIFIC: data driven research project aiming at redefining and profiling HFpEF

Etude prospective (APHP / MEDICEN grant)

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

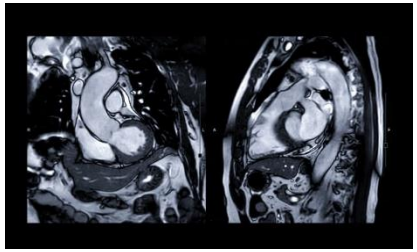
Biology
Arterial stiffness

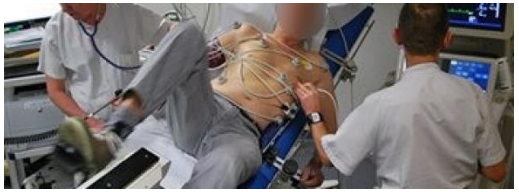
+ cardiac dynamic monitoring (up to 14 days)

Data analysis

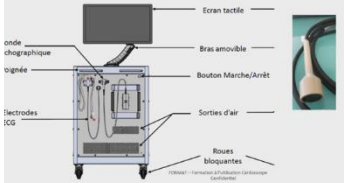
Develop novel diagnostic strategies for HFpEF

Stratify HFpEF into distinct subgroups

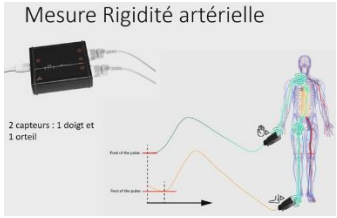




Mesure rigidité cardiaque



Mesure Rigidité artérielle



Linking to
national health datahub
(SNDS)

Hulot JS et al. ArchCarVascDis 2024

IC-FEP et phénotypage : quelles conséquences thérapeutiques?

HFpEF, phenomapping and therapeutic consequences

Clinical Phenogroups in HFpEF: Detailed Phenotypes, Prognosis, and Response to Spironolactone

P1

- Normal LV geometry
- Low arterial stiffness
- Low natriuretic peptides
- Markers of COPD (not genuine HFpEF?)
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P2

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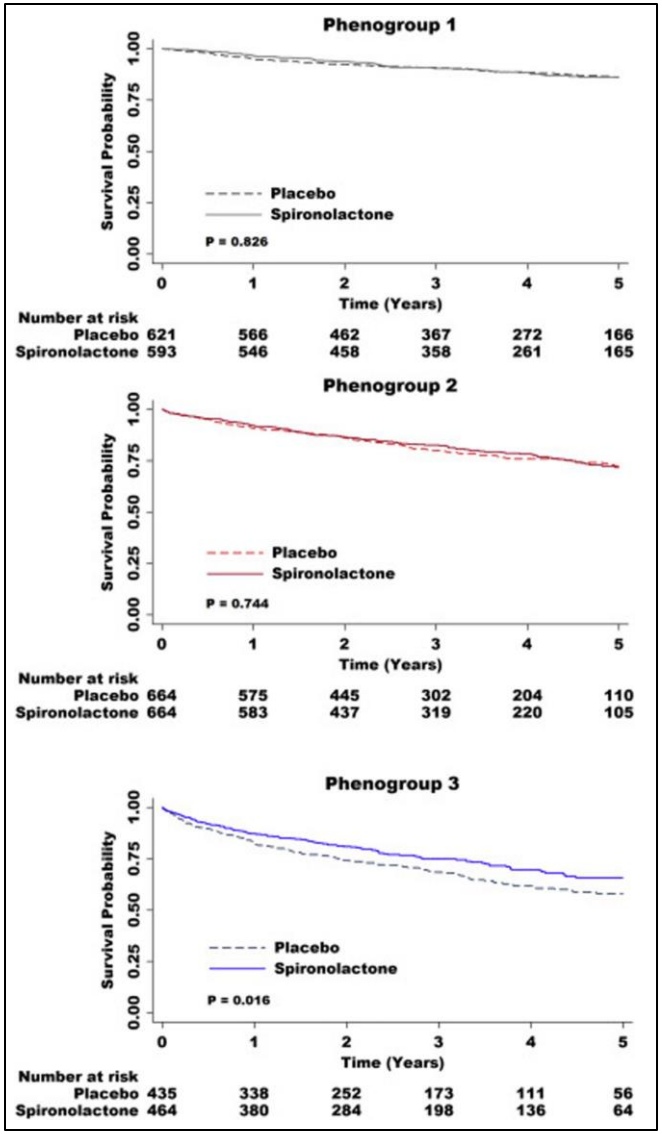
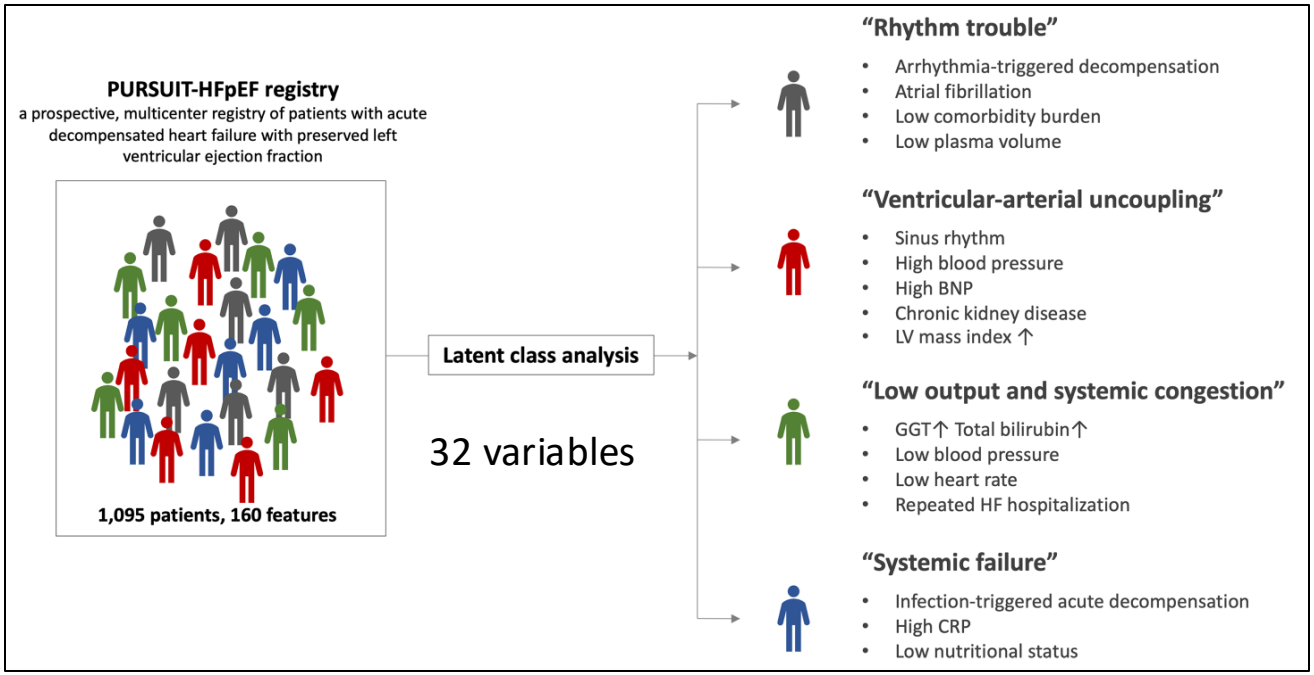
Cohen JB et al. JACC-HF 2020



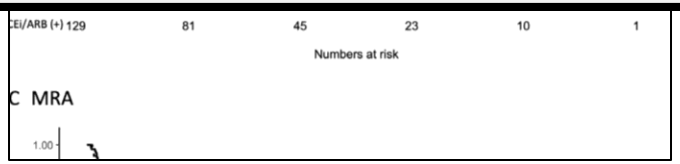
HFpEF, clustering and therapeutic impact



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

Table 2 Clinical impact of medications in each phenotype

	Phenotype 1		Phenotype 2		Phenotype 3		Phenotype 4	
	wHR (95% CI)	P value	wHR (95% CI)	P value	wHR (95% CI)	P value	wHR (95% CI)	P value
ACEi/ARB	1.03 (0.71 to 1.51)	0.860	1.24 (0.73 to 2.09)	0.425	0.66 (0.48 to 0.92)	0.014	0.86 (0.59 to 1.25)	0.432
Beta blockers	1.13 (0.81 to 1.58)	0.482	1.45 (0.83 to 2.52)	0.193	0.82 (0.58 to 1.17)	0.279	1.33 (0.89 to 1.99)	0.161
MRA	1.07 (0.75 to 1.53)	0.720	0.40 (0.21 to 0.75)	0.005	1.06 (0.76 to 1.49)	0.737	1.04 (0.70 to 1.54)	0.847
Statins	1.04 (0.48 to 2.26)	0.915	1.26 (0.74 to 2.15)	0.388	0.43 (0.21 to 0.88)	0.020	0.69 (0.27 to 1.79)	0.447



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

CONCLUSION

- Traditional strategies for understanding pathophysiology and testing interventions in HFpEF as a single disease phenotype have proven challenging with modest efficacy results

- Phenomapping is a powerful statistical tool to identify (maybe) relevant phenotypes or clusters

- Clinical usefulness of such phenomapping: not validated so far…

- Issues: overlap of phenotypes and subtypes, many important variables currently not taken into account …

- Perspectives
  - Refinement with more (relevant) variables (hemodynamics?, omics?)
  - Clinical trials based on certain phenotypes (ex: REDUCE-LAP2, STEP-HF…)
  - Extension of indications for treatments already validated elsewhere