Key “phenotypes” of HFpEF

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-
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- I will **not** discuss off-label uses

Polling Question

According to evidence-based guidelines, which of the following is recommended therapy for HFpEF?

A) sacubitril/valsartan

B) SGTL2 inhibitor

C) exercise training & caloric restriction

D) mineralocorticoid therapy

E) exercise training

F) sildenafil

HFpEF Predisposition Phenotypes	HFpEF Clinical Presentation Phenotypes					
		Lung Congestion	+Chronotropic Incompetence	+Pulmonary Hypertension (CpcPH)	+Skeletal muscle weakness	+Atrial Fibrillation
	Overweight/obesity/ metabolic syndrome/ type 2 DM	• **Diuretics (loop diuretic in DM)** • **Caloric restriction** • Statins • Inorganic nitrite/nitrate • Sacubitril • Spironolactone	+Rate adaptive atrial pacing	+Pulmonary vasodilators (e.g. PDE5I)	**+Exercise training program**	+Cardioversion + Rate Control **+Anticoagulation**
	+Arterial hypertension	+ACEI/ARB	+ACEI/ARB +Rate adaptive atrial pacing	+ACEI/ARB +Pulmonary vasodilators (e.g. PDE5I)	+ACEI/ARB **+Exercise training program**	+ACEI/ARB +Cardioversion + Rate Control **+Anticoagulation**
	+Renal dysfunction	+Ultrafiltration if needed	+Ultrafiltration if needed +Rate adaptive atrial pacing	+Ultrafiltration if needed +Pulmonary vasodilators (e.g. PDE5I)	+Ultrafiltration if needed **+Exercise training program**	+Ultrafiltration if needed +Cardioversion + Rate Control **+Anticoagulation**
	+CAD	+ACEI +Revascularization	+ACEI +Revascularization +Rate adaptive atrial pacing	+ACEI +Revascularization +Pulmonary vasodilators (e.g. PDE5I)	+ACEI +Revascularization **+Exercise training program**	+ACEI +Revascularization +Cardioversion + Rate Control **+Anticoagulation**

Shah SJ et al. Phenotype-Specific Treatment of Heart Failure With Preserved Ejection Fraction: A Multiorgan Roadmap. Circulation. 2016 Jul 5;134(1):73-90.

HF*p*EF: “no evidence-based therapies”

NEWS | HEART FAILURE (/CHANNEL/HEART-FAILURE) | SEPTEMBER 11, 2019

PARAGON-HF Misses Endpoint in Preserved Heart Failure

Trial results presented at ESC Congress 2019 show greater treatment response in subgroups including women and those with ejection fraction below the median of 57 percent

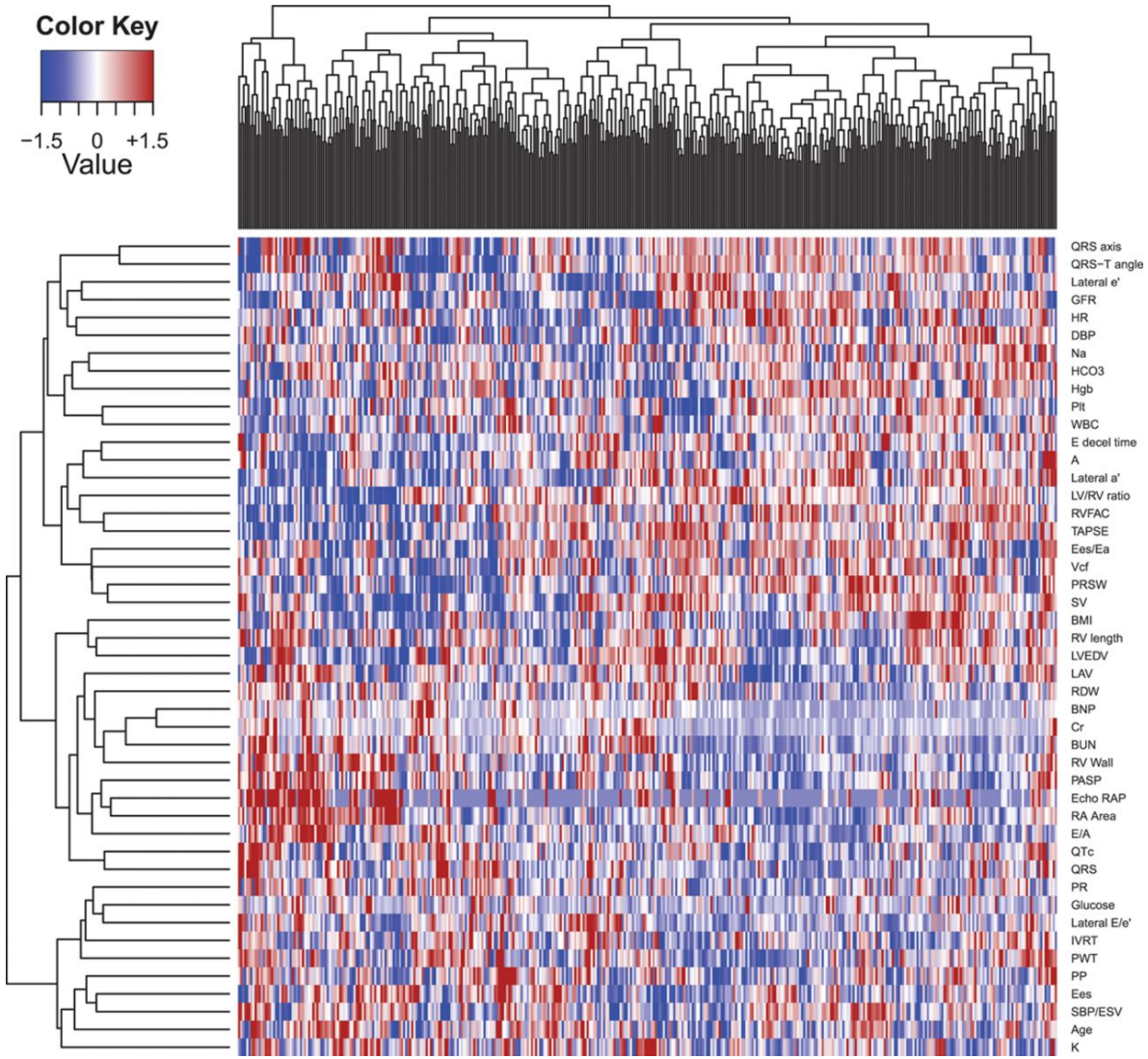
Clinical characteristics and risk factors from larger HF*p*EF trials

Trial name	Sample size, N	Drug	Age, y	Women, %	HTN, %	CAD, %	DM, %	Primary end-point	Overall result
RELAX [82]	216	Sildenafil	69	48	85	39	43	Peak VO_2	Neutral
TOPCAT [83, 8]	3445	Spironolactone	69	52	91	59	32	CV death, cardiac arrest, CHF hospitalization	Neutral
ALDO-DHF [84]	422	Spironolactone	67	52	92	40	17	Peak VO_2, Diastolic function	Neutral
I-PRESERVE [85, 90]	4133	Irbesartan	72	60	88	48	27	All-cause mortality, CV hospitalization	Neutral
CHARM-preserved [86]	3023	Candesartan	67	40	64	60	28	CV death, CHF hospitalization	Neutral
DIG-PEF [87]	988	Digoxin	67	41	60	56	29	CHF mortality, CHF hospitalization	Neutral
PEP-CHF [88]	850	Perindopril	75	55	79	27	21	All-cause mortality, CHF hospitalization	Neutral
SENIORS [89]	752	Nebivolol	76	50	78	77	24	All-cause mortality, CV hospitalization	Neutral

CAD coronary artery disease, *CHF* congestive heart failure, *CV* cardiovascular, *DM* diabetes mellitus, *HTN* hypertension

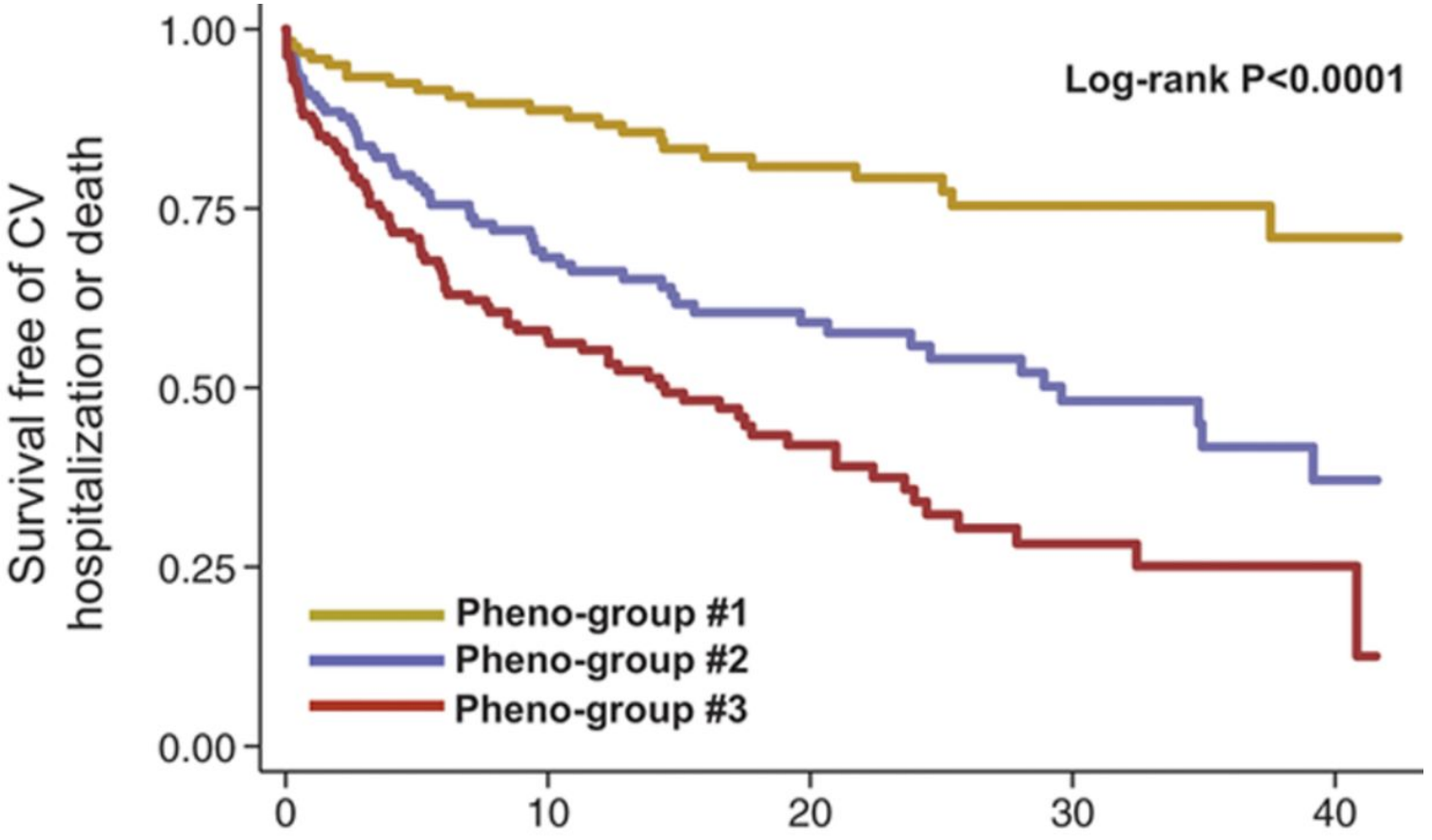
Andersen et al, Curr Cardiol Rep (2014) 16:501

Phenotype heat map (phenomap) of HF*p*EF



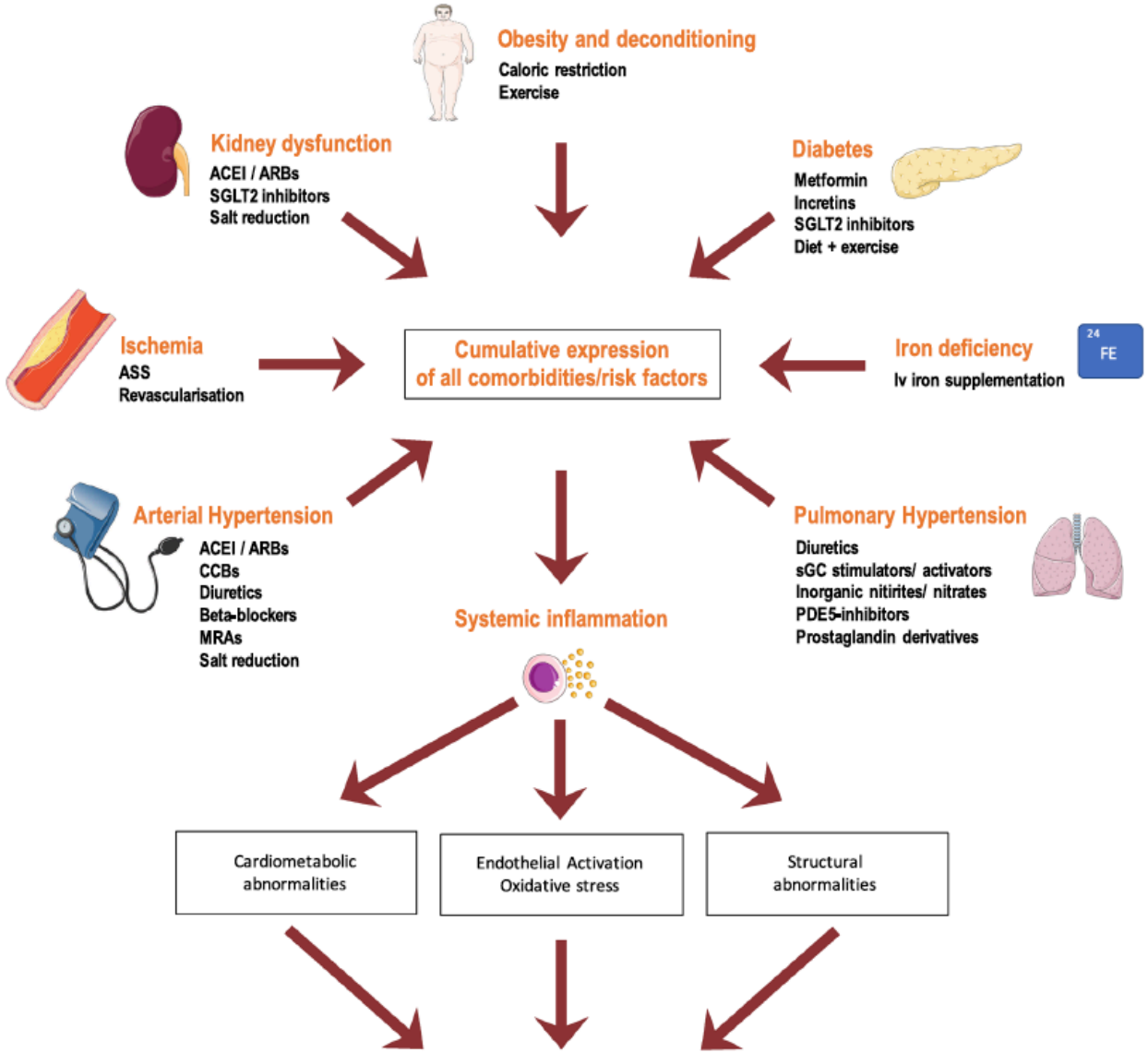
Shah S J et al. Circulation. 2015;131:269-279

Survival from cardiovascular hospitalization or death stratified by phenogroup

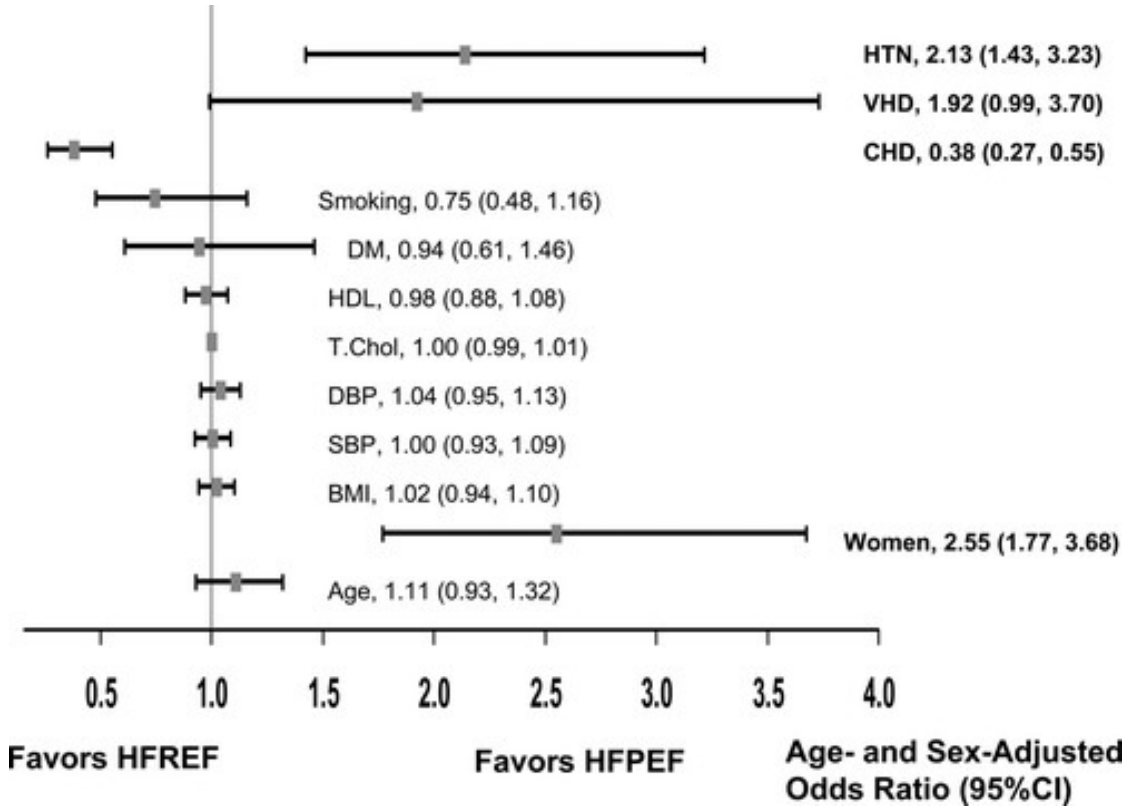


Number at risk					
Pheno-group #1	122	90	57	31	6
Pheno-group #2	133	72	42	24	6
Pheno-group #3	142	65	29	12	3

Shah S J et al. Circulation. 2015;131:269-279


Obesity and deconditioning
Caloric restriction
Exercise
Kidney dysfunction
ACEI / ARBs
SGLT2 inhibitors
Salt reduction
Diabetes
Metformin
Incretins
SGLT2 inhibitors
Diet + exercise
Ischemia
ASS
Revascularisation
Cumulative expression of all comorbidities/risk factors
Iron deficiency
Iv iron supplementation
24
FE
Arterial Hypertension
ACEI / ARBs
CCBs
Diuretics
Beta-blockers
MRAs
Salt reduction
Pulmonary Hypertension
Diuretics
sGC stimulators/ activators
Inorganic nitirites/ nitrates
PDE5-inhibitors
Prostaglandin derivatives
Systemic inflammation
Cardiometabolic abnormalities
Endothelial Activation Oxidative stress
Structural abnormalities
HFpEF

Hypertension and HFpEF

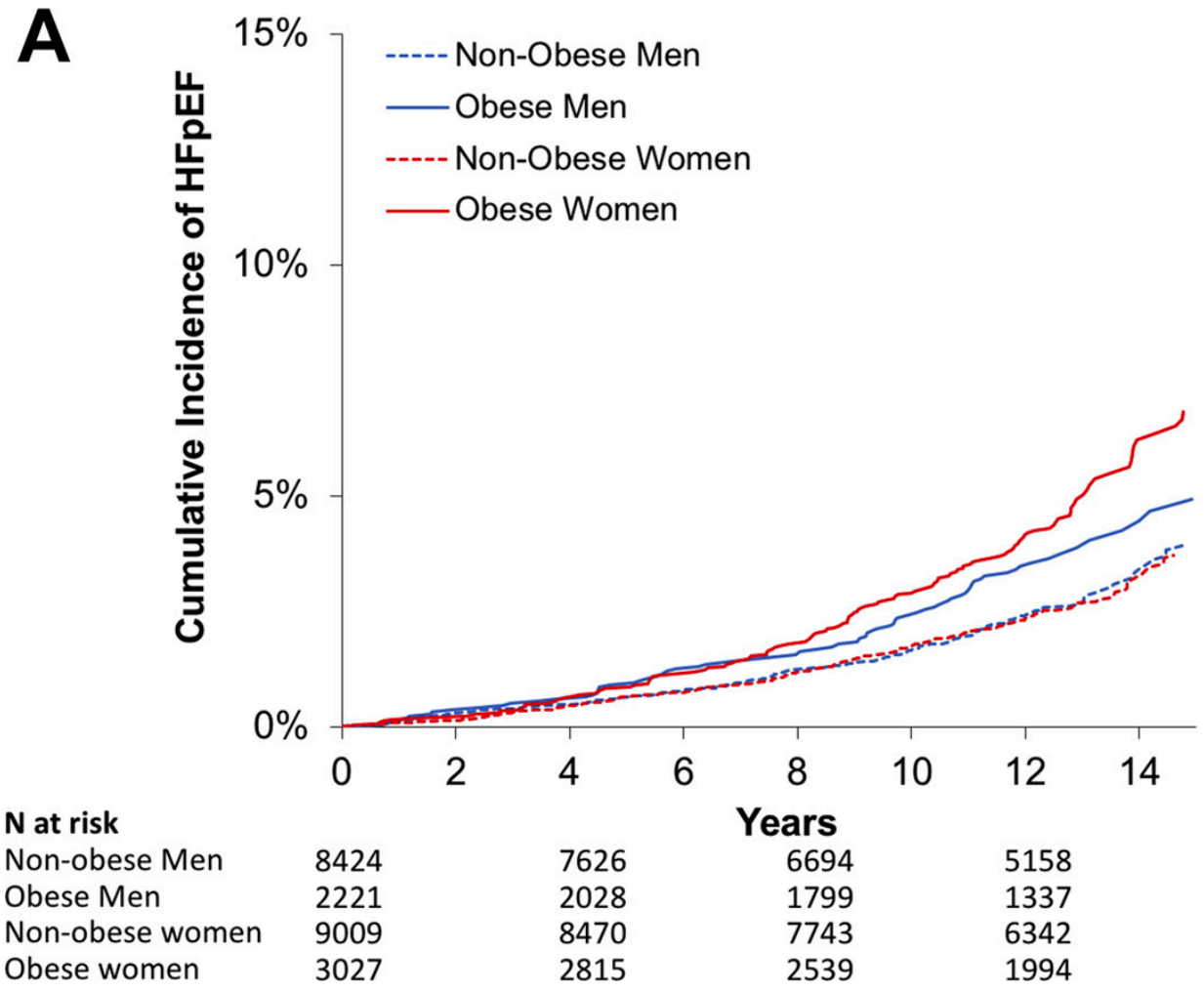


Lee et al., Circulation. Relation of Disease Pathogenesis and Risk Factors to Heart Failure With Preserved or Reduced Ejection Fraction, Volume: 119, Issue: 24, Pages: 3070-3077

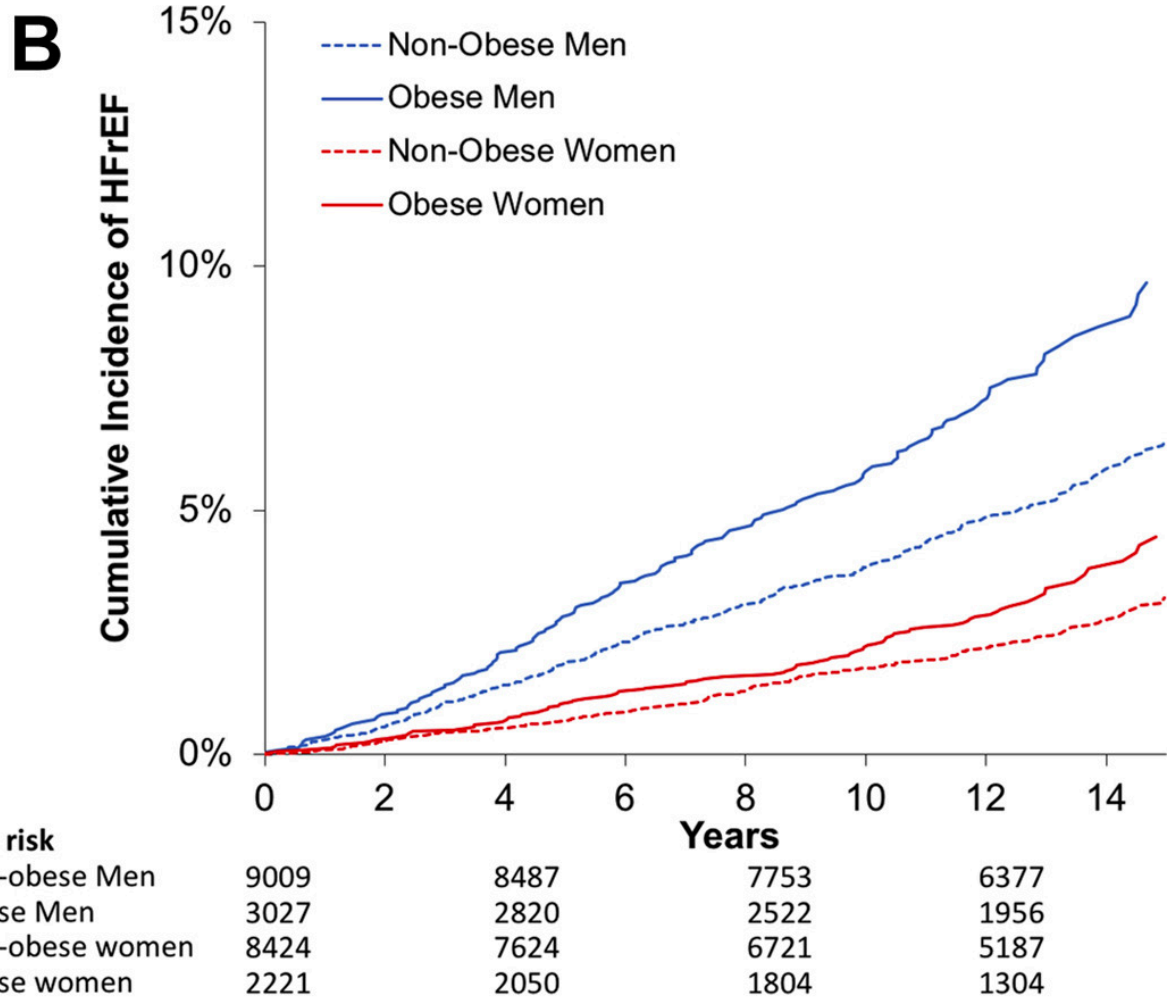
Hypertension and HFpEF

- Symptomatic control
- Long-standing hypertension is a predisposing factor for HFpEF,→ excellent blood pressure control is needed in these patients to achieve a blood pressure ≤130/80 mm Hg,
- Some observational analyses have cautioned against excessively lowering the systolic blood pressure to levels <120 mm Hg
- **β-blockers studies** in HFpEF patients have been less encouraging. In a patient-level meta-analysis of 11 randomized trials with 14 262 patients with HF in sinus rhythm, β-blocker reduced the risk of all-cause and cardiovascular mortality over a median 1.3-year follow-up in those with mid-range EF (ie, 40%–49%), but not in those with EF ≥50%
- β-blockers, ACE inhibitors, ARBs, and ARNIs is limited, and have no role in HFpEF without an alternative indication (e.g., hypertension, chronic kidney disease, etc).

Obesity and HFpEF



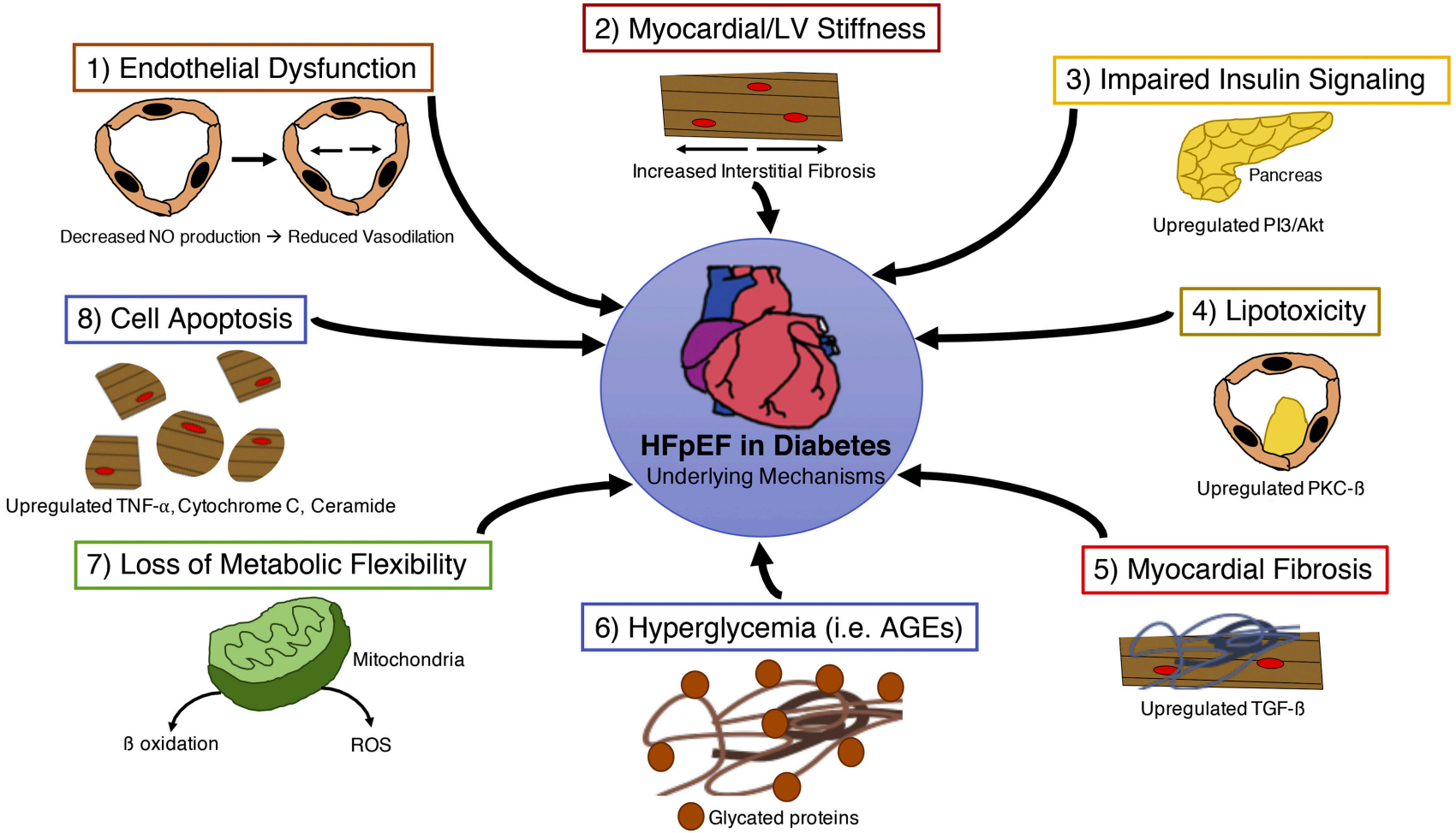
N at risk				
Non-obese Men	8424	7626	6694	5158
Obese Men	2221	2028	1799	1337
Non-obese women	9009	8470	7743	6342
Obese women	3027	2815	2539	1994



N at risk				
Non-obese Men	9009	8487	7753	6377
Obese Men	3027	2820	2522	1956
Non-obese women	8424	7624	6721	5187
Obese women	2221	2050	1804	1304

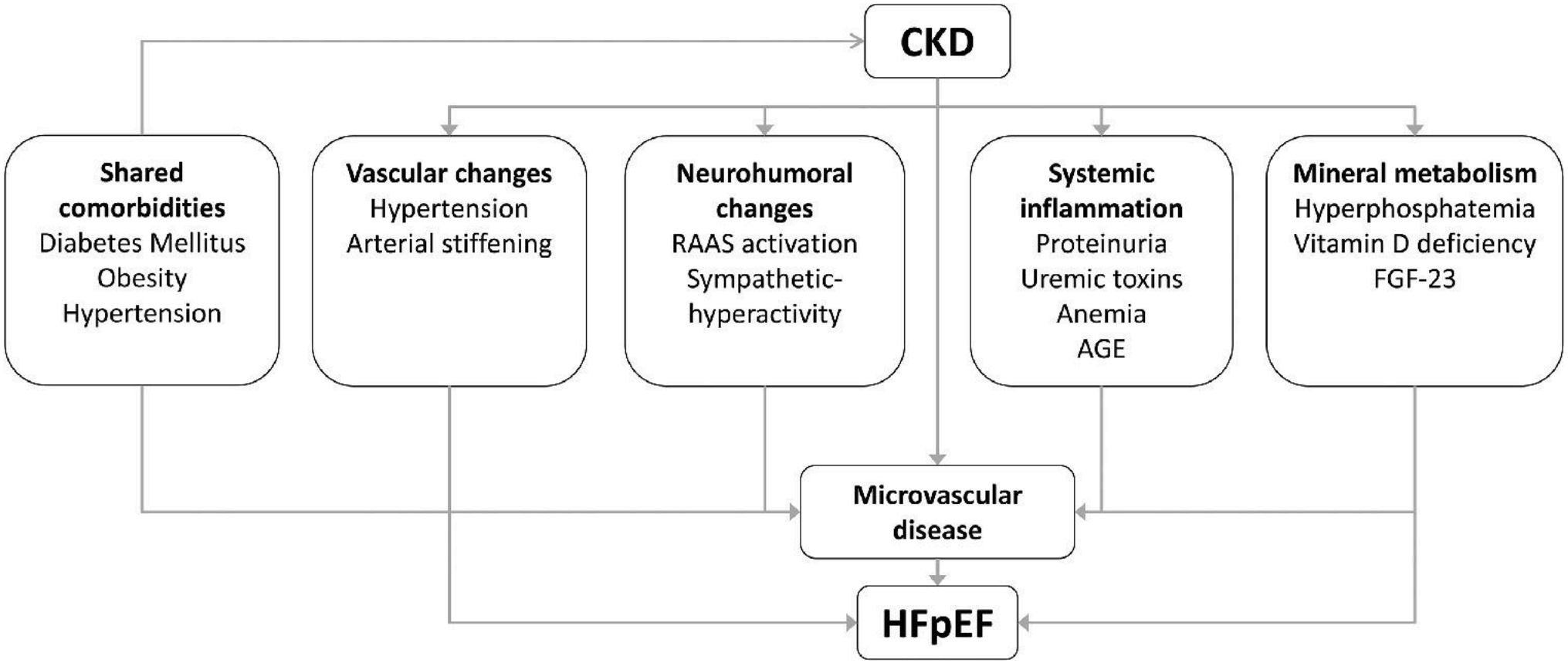
Savji N et al. The Association of Obesity and Cardiometabolic Traits With Incident HFpEF and HFrEF. JACC Heart Fail. 2018 Aug;6(8):701-709.

Diabetes and HFpEF



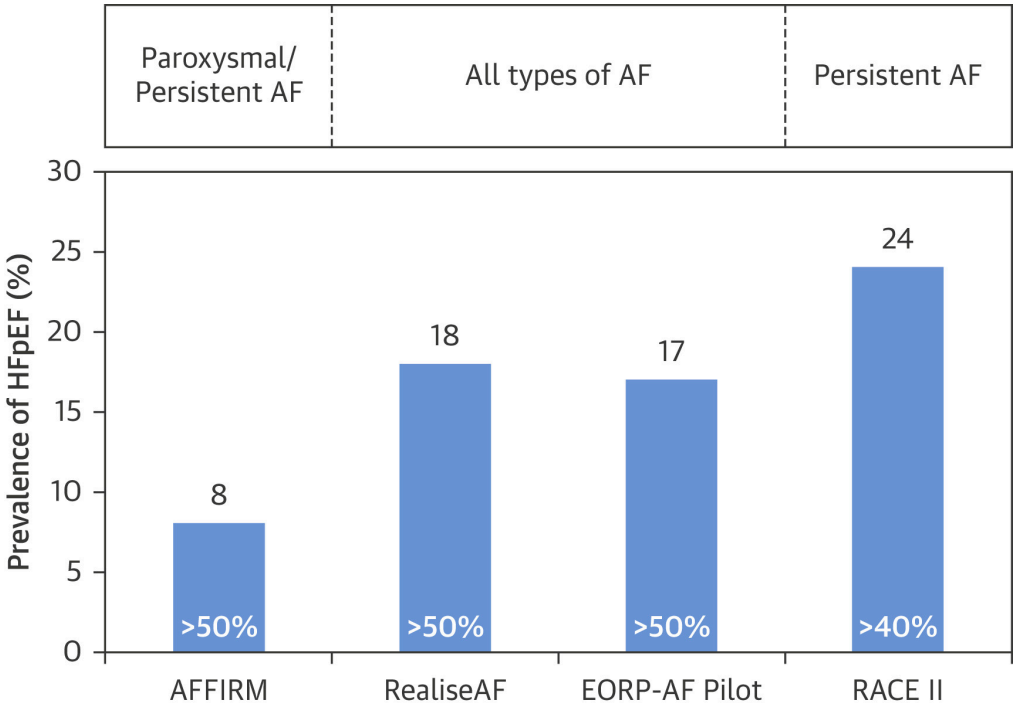
Meagher P et al. Heart Failure With Preserved Ejection Fraction in Diabetes: Mechanisms and Management. Can J Cardiol. 2018 May;34(5):632-643.

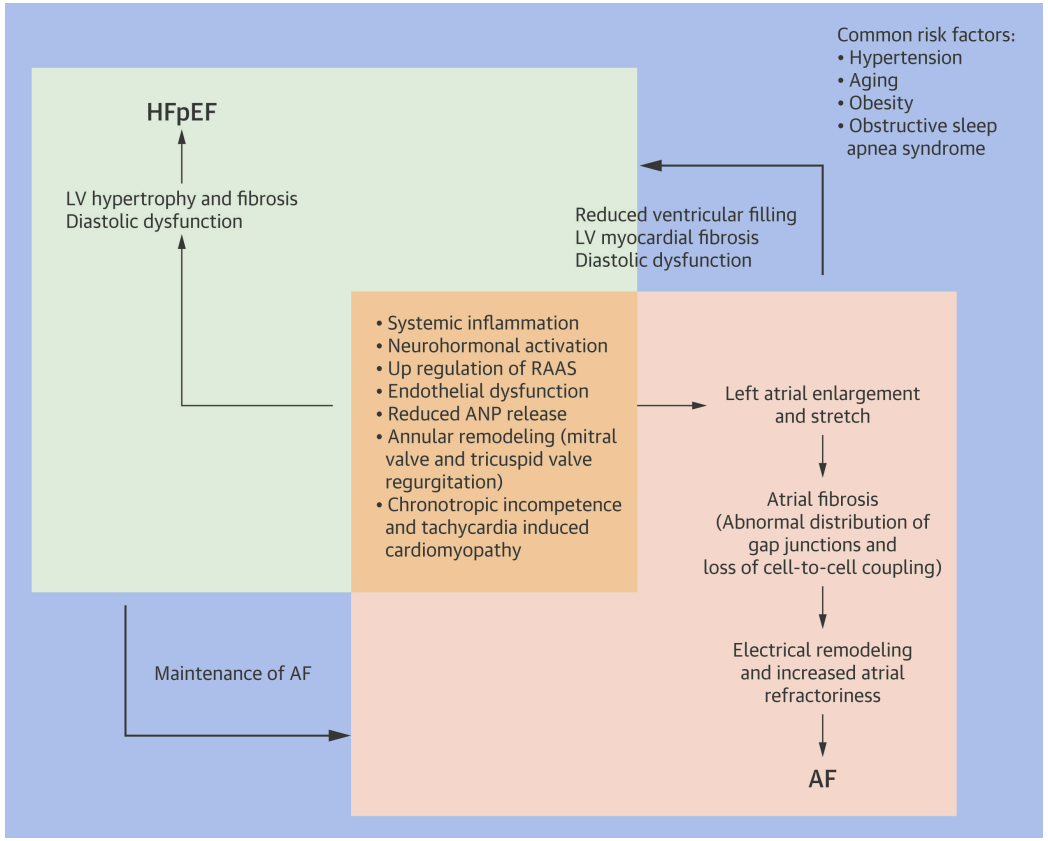
Chronic kidney disease and HFpEF



Frvan de Wouw J et al. Chronic Kidney Disease as a Risk Factor for Heart Failure With Preserved Ejection Fraction: A Focus on Microcirculatory Factors and Therapeutic Targets. Front Physiol. 2019 Sep 4;10:1108.

Atrial fibrillation and HFpEF





Kotecha D et al, Heart Failure With Preserved Ejection Fraction and Atrial Fibrillation: Vicious Twins. J Am Coll Cardiol. 2016 Nov 15;68(20):2217-2228.

Other phenotypes:

- IHD / CAD associated HFpEF
- Pulmonary HTN HFpEF

Physical Activity to Prevent and Treat HF

- Increased cardiorespiratory fitness is strongly associated with decreased incident HF and has benefit in ***both*** HFrEF and HFpEF.
- Exercise training has functional benefits in HFpEF and HFrEF but only survival benefits in HFrEF
- In HFrEF, the HF-ACTION (Efficacy and Safety of Exercise Training in Patients With Chronic Heart Failure) trial was a prospective RCT of ET in 2,231 HFrEF patients with NYHA functional class II to IV symptoms. Patients were randomized to usual care plus aerobic ET, consisting of 36 supervised sessions followed by home-based training, or usual care alone. Exercise did not significantly affect all-cause mortality or all-cause hospitalization; however, there was a reduction in mortality seen after adjustment for covariates. Men and women undergoing ET had equal improvement of peak VO_2 at 3 months.

Exercise and HFpEF

- In HFpEF, ET has been proven to be efficacious for improving peak VO2 .
- Centers for Medicare & Medicaid Services coverage for cardiac rehabilitation in HFpEF has been limited.
- Recently, a small study suggested that HFpEF patients had greater peak VO2 improvement in response to 16-week supervised moderate-intensity endurance training compared with those with HFrEF.

JAMA. 2016;315(1):36-46. doi:10.1001/jama.2015.17346

Research

Original Investigation

Effect of Caloric Restriction or Aerobic Exercise Training on Peak Oxygen Consumption and Quality of Life in Obese Older Patients With Heart Failure With Preserved Ejection Fraction

A Randomized Clinical Trial

Dalane W. Kitzman, MD; Peter Brubaker, PhD; Timothy Morgan, PhD; Mark Haykowsky, PhD; Gregory Hundley, MD; William E. Kraus, MD; Joel Eggebeen, MS; Barbara J. Nicklas, PhD

Therapy for HFpEF in 2020 (regardless of phenotype)

- HFpEF is a multifactorial condition with coronary microvascular dysfunction secondary to systemic inflammation, obesity, inactivity, and plasma volume expansion.
- Similar to HFrEF management, **comorbidities and risk factors such as blood pressure and weight control are key**

Intervention	Trial Name	Clinical Trial Registration Number	Primary Outcome
Primary Outcome	OPTIMIZE-HFPEF	NCT02425371	Clinical score status
Empagliflozin (SLGT-2 inhibitor)	EMPEROR-Preserved	NCT03057951	Composite of cardiac mortality or HF hospitalizations
Dapagliflozin (SLGT-2 inhibitor)	PRESERVED-HF	NCT03030235	Natriuretic peptide levels
Spironolactone	SPIRRIT	NCT02901184	All-cause mortality
Neprilysin inhibitors	PARALLAX	NCT03066804	Quality of life

Thank you for your attention