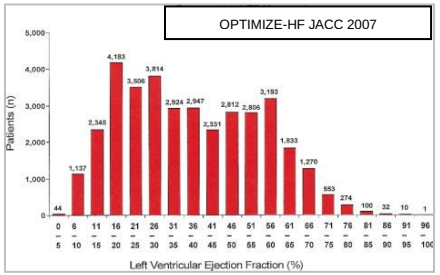
Heart Failure with Preserved Ejection Fraction

Introduction:

• Up to half (~ 50%) of all HF population (nejm 2006;355:251). 57% in THAI-ADHERE

• High mortality and morbidity - similar to HFrEF.

- A 1-yr mortality rate of 10-25% (eur J HF 2013;15:604).
- In RCTs, the average 1-yr mortality rate was 5-8%, which is lower than HFrEF (RR 0.7).
- A 6-mo repeat hospitalization ~ 50% in 6 months - similar to HFrEF



• Less talk about (comparing to HFrEF) due to trials in HFpEF have failed to showed survival benefit.

• The majority of deaths in HFPEF are CV deaths (60%), include SCD, HF death but compared with HFrEF, the non-CV deaths are more common.

Diagnosis

• The dx criteria is evolving but based on the same principle of other spectrums of HF syndrome, which are evidences of typical S&S and abnormal cardiac structure or function.

Evidence of typical S&S	- Breathlessness (exertional, PND), swelling, edema, fatigue - Elevated BNP may help[A].
Evidence of abn. structure or function [C]	- Relevant structure heart disease e.g. LVH, LAE and/or diastolic dysf[B] - LAVI > 34 ml/m2 - LVM ≥ 95 (female) - 115 (male) g/m2 - E/e' > 13; e' <9 cm/sec - Maybe abnormal only during exercise. Maybe normal if dehydrate - If uncertainty, RHC for ↑ LV filling pressure (LVEDP, PCWP, PA).
Evidence of pEF	Currently use ≥ 50%

[A] Required by ESC HF 2016 guideline. In chronic setting, unlikely if BNP < 35 or NT-BNP < 125 pg/ml (NPV > 95%)

[B] Diastolic HF (or HF with diastolic dysfunction) is not exactly the same as HFpEF.

[C] Some criteria e.g. Framingham, diastolic function is not needed or dx.

Pathophysiology

• Not fully understand (circ 2016;134:73)

• Pathogenesis: Fibrosis, systemic inflammation, oxidative stress, endothelial dysf, ↓NO bioavailability, ↑vol expansion, or normal aging. Key molecule = ↑CRP, ↑IL1RL1, ↑ROS, ↓ΔA-VO2, ↓sGC, ↓cGMP, ↓PKG

• From and/or leading to HTN, PH, obesity, DM, CKD, muscle dysf, endothelium dysf.

• LV Diastolic dysfunction may refer to

- Ventricular dysf: Impair relaxation/filling (upward shift of end diastolic P-V relationship), LA dysf, systolic dysf.
- Vascular dysf: Stiffening, impair vasodilator reserve, ventricular-arterial coupling

• Non-diastolic dysfunction mechanism: Chronotropic incompetence, PH, RV failure, hemodynamic load, ischemia

Cardiac patho in HFpEF

Cellular
↑ Myocyte diameter
↑ Fibril density
↑ Stiffen titin
↓ Ca handling
↑ Collagen

Ventricular
↑ Concentric LVH (↑ Mass)
↑ Wall thickness
↑ End diastolic stiffness
↔ LV size
↔ EF
↑ LVEDP

Systemic
↑ Neurohormonal activation

Selected RCT in HFpEF

Study	Interventions	EF cutoff	Sample	1° composite endpoint	HR p value
PEP CHF jacc 2006	perindopril f/u 26 mo	n/a n = 800	76 yo 55% female 79% HTN 30% CAD	All cause death/ HF hosp.	HR =0.92 (p=0.54)
CHARM-preserved eur H J 2006	candesartan f/u 36 mo	> 40 n = 3023	67 yo 40% female 23% HTN 57% CAD	CV death/ HF hosp.	HR =0.89 (p=0.12)
I-Preserved circ 2005	irbesartan f/u 50 mo	≥ 45 n = 4128	72 yo 60% female 64% HTN 25% CAD	All cause death/ CV hosp.	HR =0.95 (p=0.35)
TOPCAT nejm 2014	spironolactone 42 mo	≥ 45+ ↑BNP n = 3445	69 yo 52% female 91% HTN 59% CAD	CV death/ HF hosp./ SCA	HR =0.89 (p=0.14)

Other landmark study: DIG-PEF, SENIOR, J-DHF, RELAX-AHF, PARAMOUNT, PARAGON-HF

Phenotypic spectrum

• Classic case = Elderly woman with multiple CV and non CV diseases.

• Non-CV comorbidities are common e.g. DM, obesity, CKD, chronic lung dz, anemia (JACC 2014;64:2281).

• It is important to recognize the heterogeneity of the patho-phenotypic sprectrums that could direct treatments.

Treatment of HFpEF

• There are no medical treatments that consistently showed survival benefits in RCTs (JACC 2015; 65:1668).

• Guideline recommend treatment that target BP, HR, volume status and control comorbidities.

• Treatment may include

- Diuretics
- Spironolactone (see TOPCAT in table), ARNI?
- Statin?, inorganic nitrate/nitrite?, anticoagulation?

• Targeting comorbidities such as

- Revascularization (in CAD), pacing (in chronotropic incompetence), rate & rhythm control (in AF), PDE5i or sGC stimulator (in PH), caloric restriction, exercise training (in obesity)

Targeting HTN, PH AF, OSA.

• Make sure to look for a specific HFpEF that have unique etiology and treatment such as HCM, constrictive pericarditis, infiltrative cardiomyopathy e.g. amyloid, valvular heart e.g. AS, MS, MR, pure RV failure e.g. PE, ARVD, high output HF, PAH gr. I, ischemia.

• It is equally important or may be more important to improve QoL or ↓hosp rather than ↓death

Recommend reading

• HFpEF: A clinical dilemma. Eur Heart J 2014;35:1022–1032.

• Clinical Phenotypes in HFpEF. J Am Heart Assoc. 2016;5:e002477.