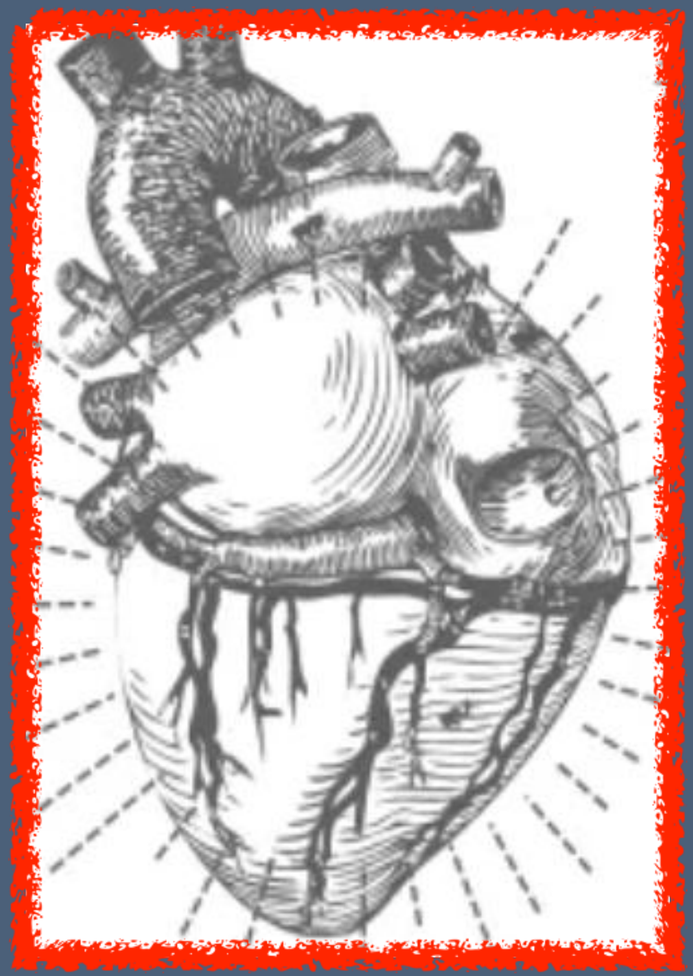
Heart Failure with Preserved Ejection Fraction (HFpEF) ❤️

Diagnostic Challenges and Evolving Management

Dr. Helen Dempster. November 5, 2025

Learning Objectives

- Define heart failure (HF) and HF with preserved ejection fraction (HFpEF)
- Recognize challenges in diagnosing HFpEF
- HFpEF is heterogeneous syndrome - review co-morbidities and drivers
- Review contemporary evidence based options for management



Heart Failure

….. is a clinical syndrome

- With symptoms and signs caused by a structural and/or functional cardiac abnormality
  - dyspnea, orthopnea, PND, fatigue, ankle swelling
  - elevated JVP, S3, hepatojugular reflux, crackles, edema
- **AND** corroborated by at least one of the following
  - Elevated BNP **and/or**
  - Objective evidence of cardiogenic, pulmonary or systemic congestion by diagnostic modalities (ie CXR, ECHO) or hemodynamic measurements (ie Cath) at rest or with provocation.

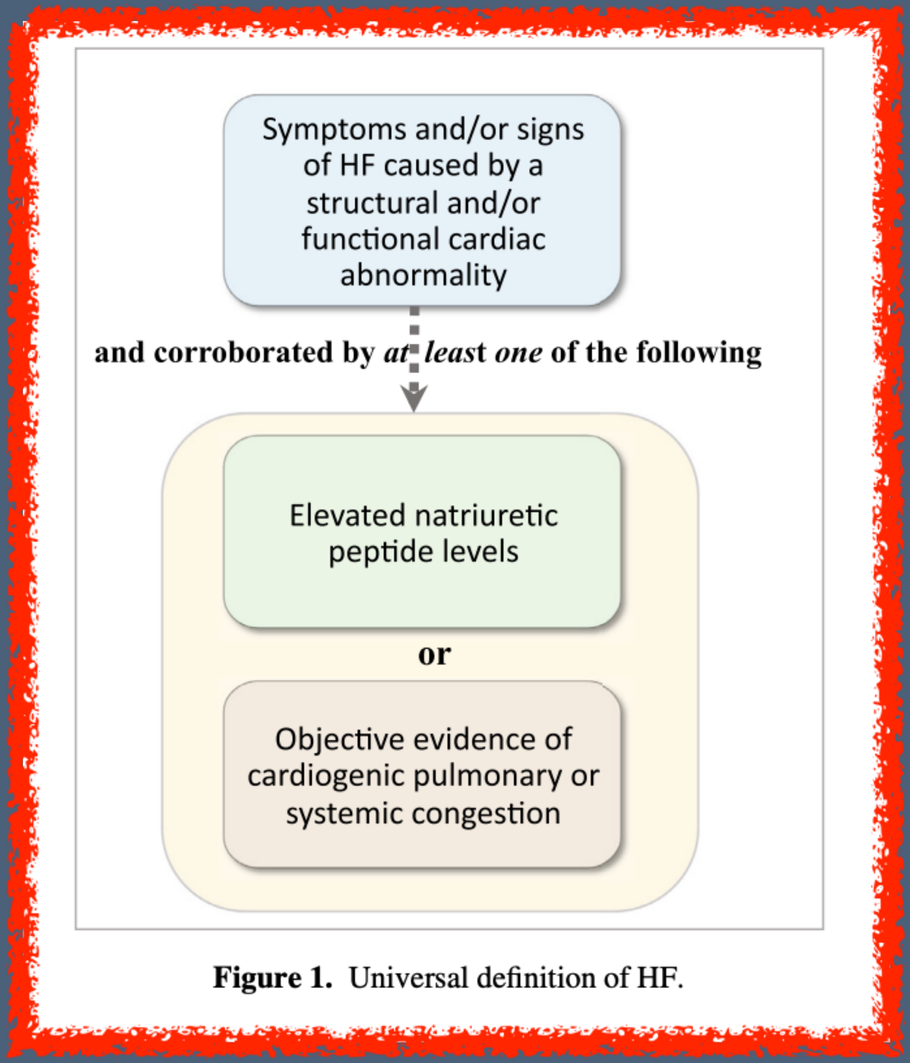
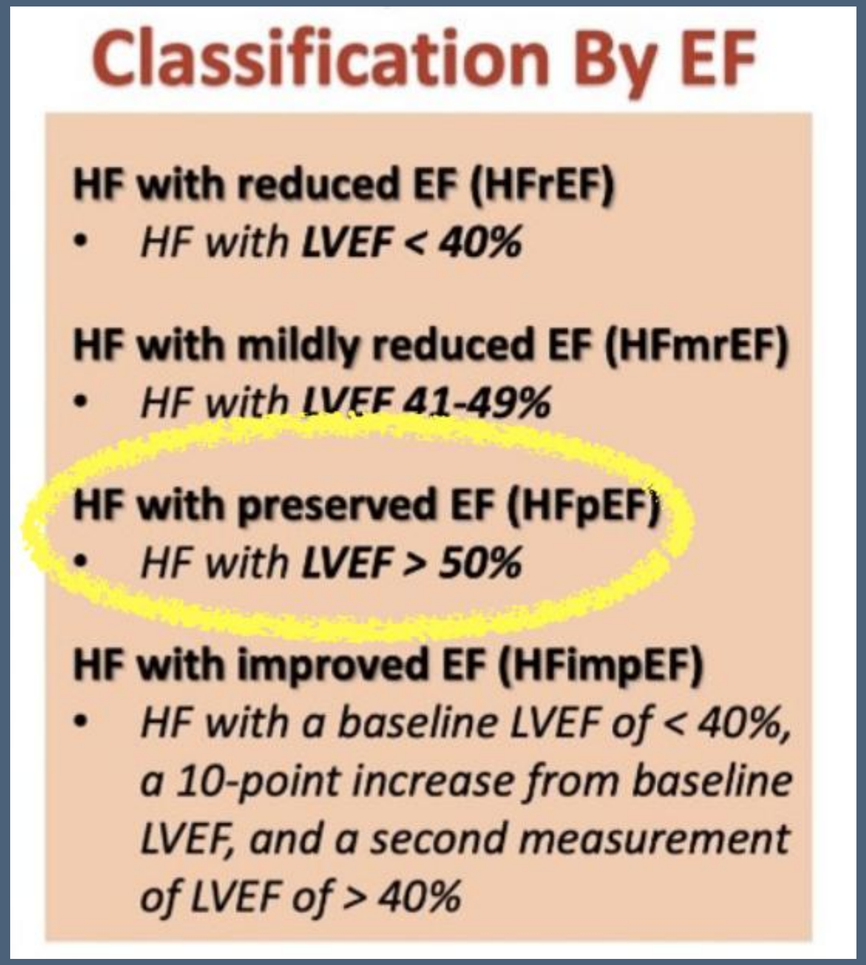


Figure 1. Universal definition of HF.

Classification of HF



Classification by Function

- **Class I** - no functional limitation
- **Class II** - slight limitation
  - comfortable at rest, ordinary activity causes symptoms
- **Class III** - marked limitation
  - comfortable at rest but less than ordinary activities causes symptoms
- **Class IV:** unable to carry out any physical activity without symptoms or symptoms at rest

Heart Failure with Preserved Ejection Fraction - HFpEF

1. **Signs and symptoms of heart failure**

   AND

2. **LVEF 50% or greater**

   AND

3. Objective evidence of cardiac structural or functional abnormalities

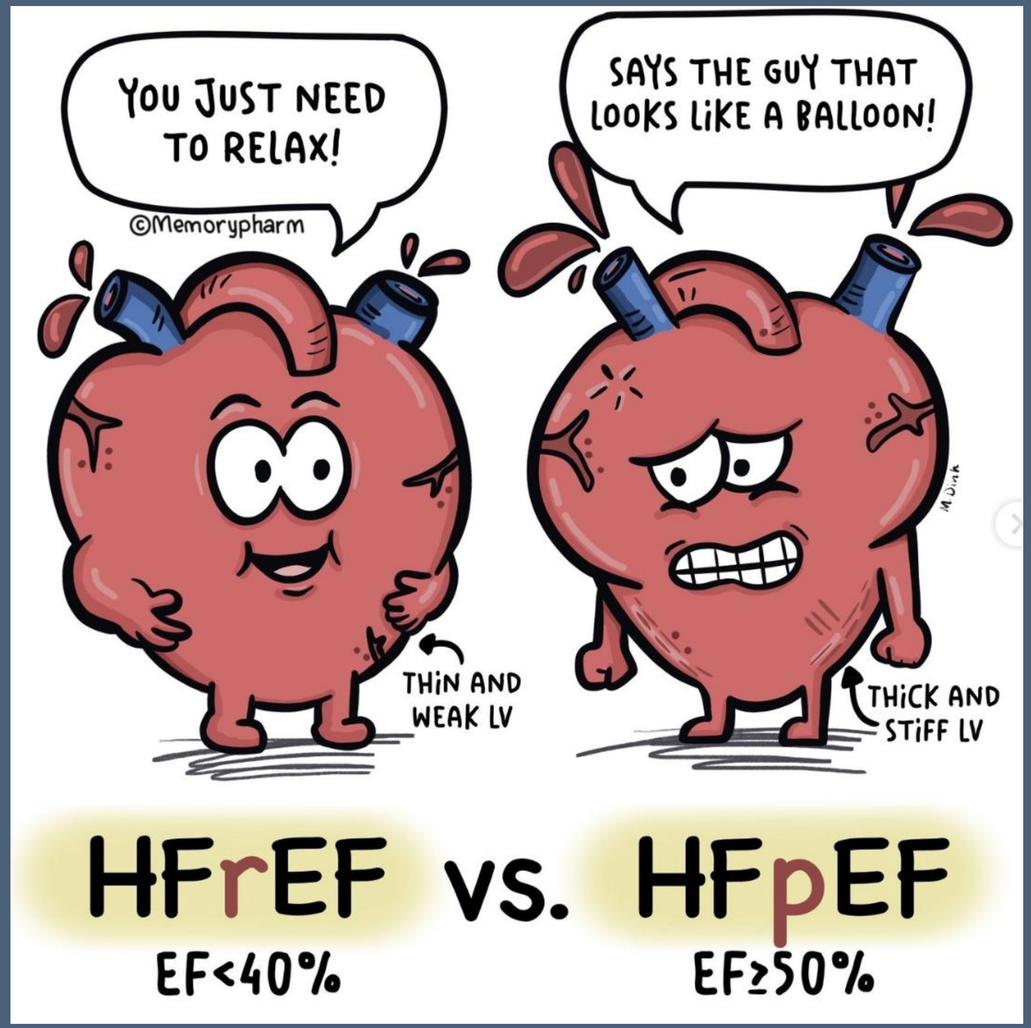
- LV diastolic dysfunction or raised LV filling pressures

  AND

4. Exclusion of conditions that mimic HFpEF

- think about DDx dyspnea

- think about DDx edema



Indicators of Cardiac Abnormalities in HFpEF

The greater the number, the higher the likelihood of HFpEF

Indicators of Cardiac Abnormalities — The greater the number of abnormalities present, the higher the likelihood of HFpEF

Variable	At Rest	With Exercise
Left ventricular mass index	For women ≥95 g/m² For men ≥115 g/m²	— —
Relative wall thickness	>0.42	—
Left atrial volume index	Sinus rhythm >34 ml/m² Atrial fibrillation >40 ml/m²	— —
E:e′ at rest	>9	>15
NT-proBNP	Sinus rhythm ≥125 pg/ml Atrial fibrillation >365 pg/ml	— —
Pulmonary-artery systolic pressure estimated with echocardiography	>35 mm Hg	—
Tricuspid-regurgitation velocity at rest	>2.8 m/sec	>3.4 m/sec
Pulmonary capillary wedge pressure (PCWP)	≥15 mm Hg	≥25 mm Hg or PCWP:CO slope ≥2 mm Hg/liter/min
Left ventricle end diastolic pressure	≥16 mm Hg	—

Figure 1 (facing page). A Pragmatic Approach to the Diagnosis of Heart Failure with Preserved Ejection Fraction.
CO denotes cardiac output, E:e′ the ratio of E-wave velocity to e′ velocity (as assessed with echocardiography), and NT-proBNP N-terminal pro–B-type natriuretic peptide.

Evidence of

LV diastolic dysfunction

and/or

raised LV pressures

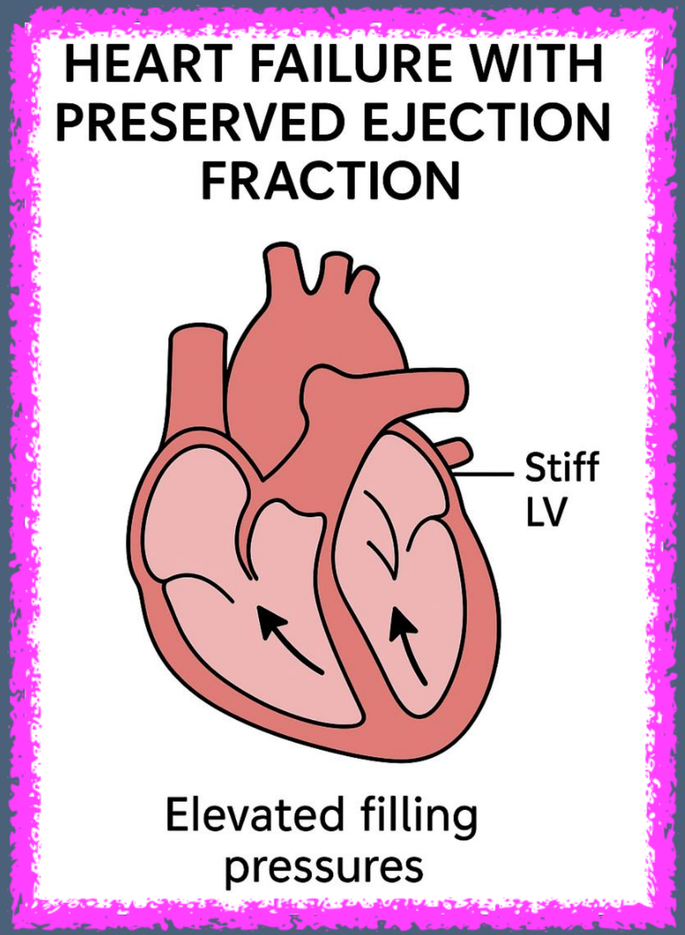
If dx still not clear..

H2FPEF score >= 6 points highly suggestive

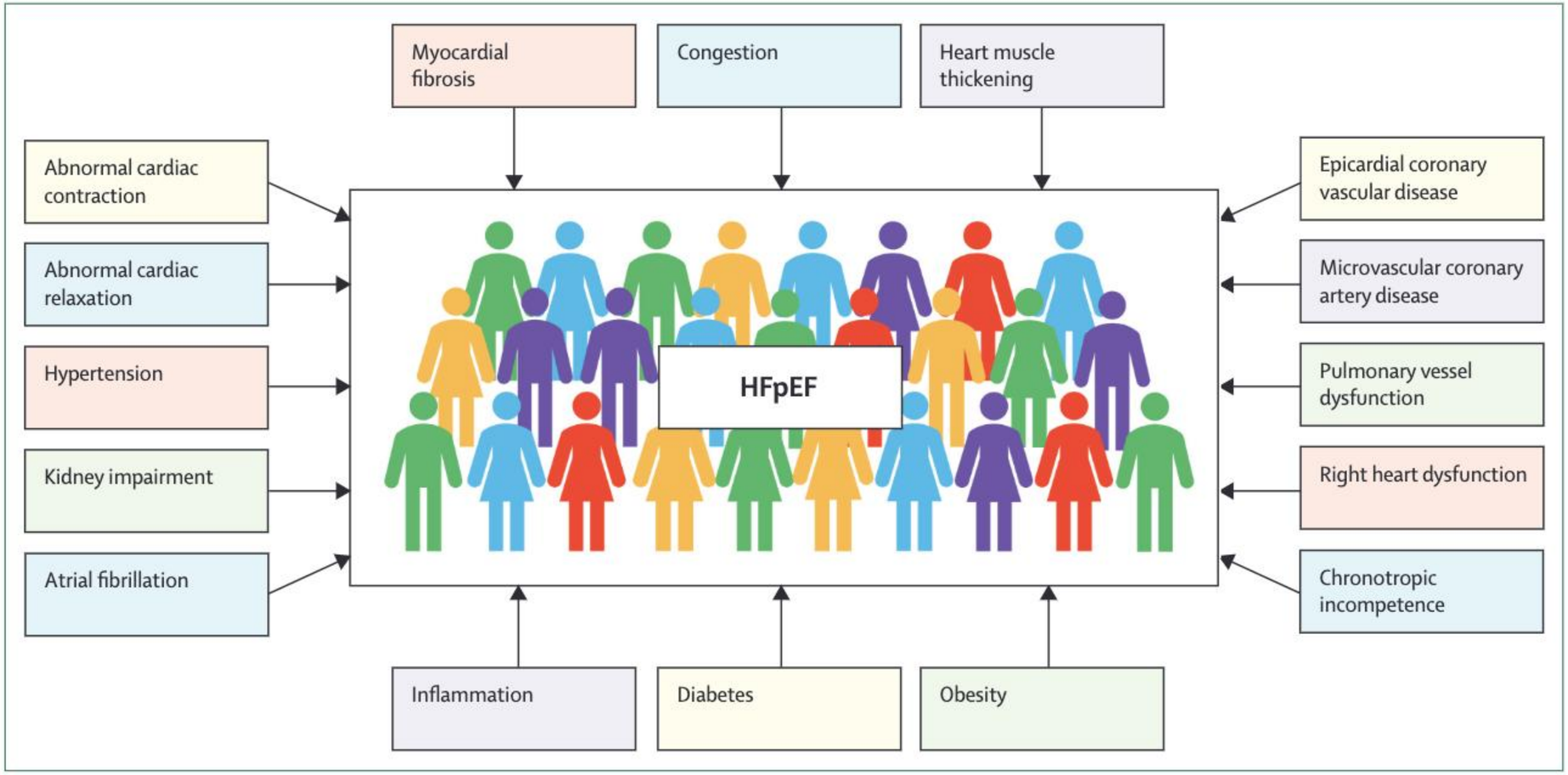
- **H**eavy: BMI>30 kg/M2 **(+2)**
- **H**ypertensive: 2 or more antihypertensives **(+1)**
- Atrial **F**ibrillation **(+3)**
- **P**ulmonary Hypertension: on ECHO **(+1)**
- **E**lder: >60 years **(+1)**
- **F**illing pressure: doppler E/é > 9 **(+1)**

Epidemiology

- Three key epidemiological features of HFpEF are:
  1. **Increasing prevalence with AGE**
  2. **FEMALE SEX - gender specific RF's**
  3. **CO-MORBIDITIES - obesity, diabetes, HTN**
     - either contribute to myocardial stiffness (eg metabolic, inflammatory)
     - Or exacerbate the functional abnormality (afib, valve disease)
- ~ 50% of heart failure patients, on the rise
- Similar mortality to HFrEF, hospitalization rate and QOL



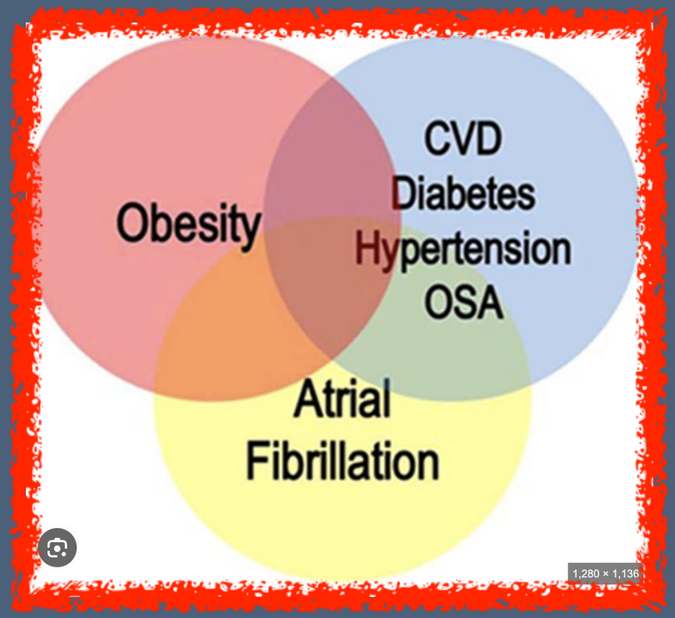
Not just “diastolic dysfunction” but a systemic syndrome…. inflammation is proposed as a central mechanism in pathogenesis

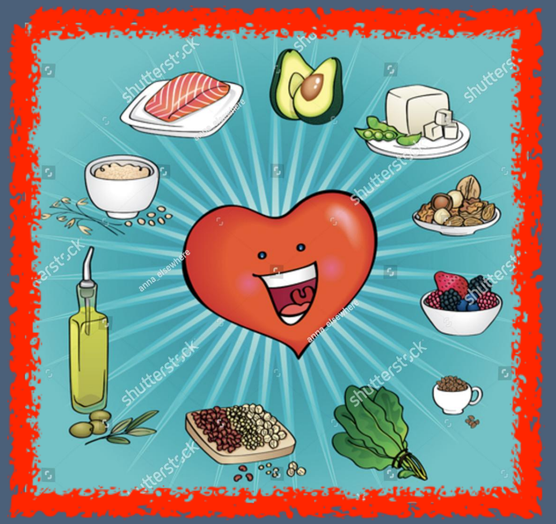


Management of HFpEF ❤️

Management

- **1. Manage co-morbidities**
  - HTN, DM, obesity, AF, sleep apnea
- **2. Non pharm management**
  - exercise, weight loss, healthy diet
- **3. Pharm management**
  - Anything other than diuretics?…….





SGLT2i for all who can tolerate

- Empaglifozin 10 mg po daily (EMPEROR - preserved) [8]
- Dapagliflozin 10 mg po daily (DELIVER)[9]
- 20% reduction in composite endpoint of HF hospitalization and CV death (driven by former) regardless of diabetes status
- Also improved QOL, functional status, exercise capacity
- No clear independent mortality benefit
- Based on these finding, now a foundational therapy for HFpEF regardless of diabetes status : Class I ESC, Class 2a AHA*

Diuretics for fluid retention

Reduce congestion, symptoms and risk of hospitalization (class I)

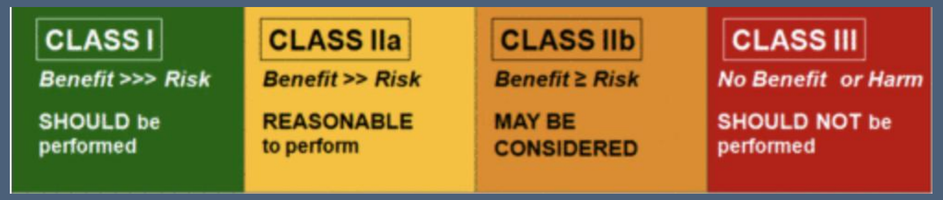
Loop diuretics(furosemide)

+/- thiazide (if HTN)

+/- MRA

"A necessary evil?"
Use lowest possible dose and consider stopping when euvolemic

What else for HFpEF ?



- modest benefit in reduced hospitalizations in subgroups …..class IIb
  - Spironolactone: class II b (TOPCAT)[10]
  - Sacubitral valsartan: class II b for women with HFpEF and men EF<55-60% (PARAGON-HF)[12]
  - Candesartan: class IIb for ARNI eligible who cannot take (CHARM-preserved)[13]
- **Practical point:**
  - choose if you have another compelling indication (HTN, additional diuresis)
  - Monitor renal function and K
- **New kid on the block that looks promising for HFpEF and HFmrEF…**
  - finerenone (non steroidal MRA) 20 or 40 mg daily had a significantly lower rate of composite of total worsening HF events + death from CV causes compared to placebo [11*] driven by decrease in HF events (18% less)
- Associated with better pt-reported health status, increased risk of hyperkalemia

- **SEMAGLUTIDE:** multiple recent RCT's: HFpEF + obesity, +/- diabetes [15, 17, 18, 19]
  - Semaglutide 2.4 mg sc q weekly vs placebo over ~ one year
  - Improved symptoms, QOL, exercise capacity, reduced body weight
  - Reduced HF events (RRR 41%, ARR 1.9%), no sig effect on CV death
- **TIRZEPATIDE:** one trial, RCT, earlier this year: HFpEF + obesity [16]
  - Tirzepatide 15mg sc weekly vs placebo over 2 years
  - Improved symptoms, QOL, exercise capacity and body weight
  - reduced risk of composite primary endpoint of CV death or worsening HF by 38% vs placebo - driven by HF event reduction, no sig difference in all cause mortality

Research

JAMA | Original Investigation

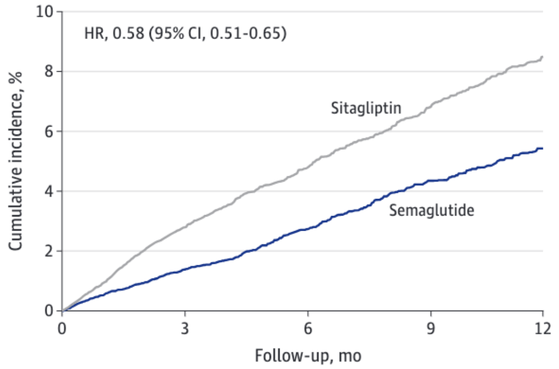
Semaglutide and Tirzepatide in Patients With Heart Failure With Preserved Ejection Fraction

Nils Krüger, MD; Sebastian Schneeweiss, MD, ScD; Kenshiro Fuse, MD, MPH; Sofiya Matseyko; Sushama Kattinakere Sreedhara, MBBS; Georg Hahn, PhD; Heribert Schunkert, MD; Shirley V. Wang, PhD

- Recent study (JAMA October 15, 2025) [17] in pts with obesity, diabetes and HFpEF
  - Pts initiating semaglutide or tirzepatide had a 42% lower risk of hospitalization for HF or all cause mortality vs sitagliptin - also driven by HF hospitalization
  - In head to head comparison, tirzepatide not better than semaglutide
- **Bottom Line:** these agents reduce HF hospitalization and functional status, no independent mortality benefit
- Promising… need more trials, useful in HFpEF if not obese?

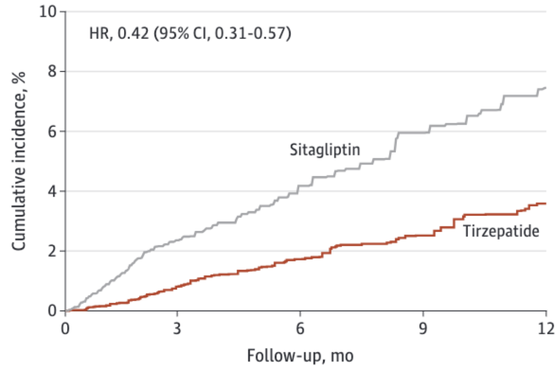
Figure 2. Propensity Score–Adjusted Cumulative Incidence for the Primary Composite End Point of Heart Failure Hospitalization or All-Cause Mortality in Patients Initiating Semaglutide vs Sitagliptin, Tirzepatide vs Sitagliptin, or Tirzepatide vs Semaglutide

A Semaglutide vs sitagliptin



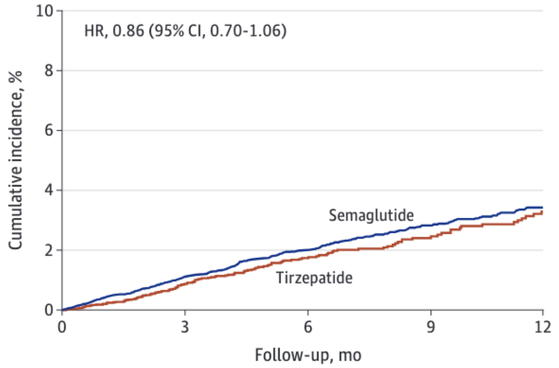
No. at risk					
Semaglutide	7640	5257	2865	1873	1284
Death	0	27	45	60	70
HHF	0	73	107	129	138
Sitagliptin	7640	5497	3234	2087	1352
Death	0	57	92	112	126
HHF	0	139	194	229	249

B Tirzepatide vs sitagliptin



No. at risk					
Tirzepatide	1647	1092	635	403	265
Death	0	6	9	11	12
HHF	0	8	12	14	16
Sitagliptin	1647	1116	588	328	198
Death	0	12	21	23	25
HHF	0	25	31	37	39

C Tirzepatide vs semaglutide



No. at risk					
Tirzepatide	5746	3851	2261	1402	874
Death	0	16	28	33	37
HHF	0	25	41	48	54
Semaglutide	5746	3938	1965	1064	649
Death	0	16	28	35	36
HHF	0	38	54	60	63

JAMA October 14, 2025. Vol 334, no 14. [17]

Some practical management approaches for HFpEF and co-morbidities

- Regular exercise and healthy diet for all; HFpEF tend to be more salt sensitive
- Diuresis (loop diuretics) if volume overloaded
- **To reduce HF events/hospitalizations, improved functional status and QOL, consider:**
  - **SGLT2i for all**
  - **semaglutide or tirzepatide with obesity (BMI>=30)**
- **HTN:** consider spironolactone, ARB
- **Diabetes**: likely already on SGLT2i, may be on GLP-1 RA
- **CKD:** likely already on SGLT2i, probably ARB
- Watch for/screen for **sleep apnea**

Summary

- HFpEF at least 50% of all HF cases , mortality+morbidity = HFrEF
- Challenging to diagnose: dyspnea +/- edema + EF >50% is not necessarily HFpEF : need to think of DDX
- co-morbidities like diabetes, obesity, HTN are drivers of the disease, gender-specific RF for women
- manage co-morbidities, diuretics as needed
- GDMT: No clear independent mortality benefit alone with any agent but:
  - SGLT2i reduce HF events/hospitalizations (diabetes or not) and improve QOL, function
  - Semaglutide, tirzepatide (BMI>=30) reduce HF events/hospitalizations and improve QOL, function
  - Studies ongoing for GLP-1 RA’s, GIP-GLP RA’s, eplerenone… stay tuned

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