HFpEF: *Recognition and management in 2025 and beyond*

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Disclosures

None

Objectives

1. Understand the contemporary diagnostic algorithm for HFpEF
2. Discuss emerging data supporting GDMT (!) for HFpEF
3. Identify the patient with unexplained dyspnea who should be evaluated for exercise-HFpEF

Patient Vignette #1

- 71yoF with obesity (BMI 33), DM2 (A1c 8.1), HTN, CKD 2, pAF
- Now presenting to clinic with dyspnea and LE swelling.
- Recent negative stress test for above symptoms
- Current meds: losartan 50mg daily, metoprolol succinate 50mg daily, metformin 1000mg BID
- Vitals with BP of 138/87. Exam notable for JVD of 10cmH20 with + HJR, 1+ LE edema.
- NT-proBNP of 452. TTE demonstrated EF of 60%, mild LVH, LAE, dilated IVC.

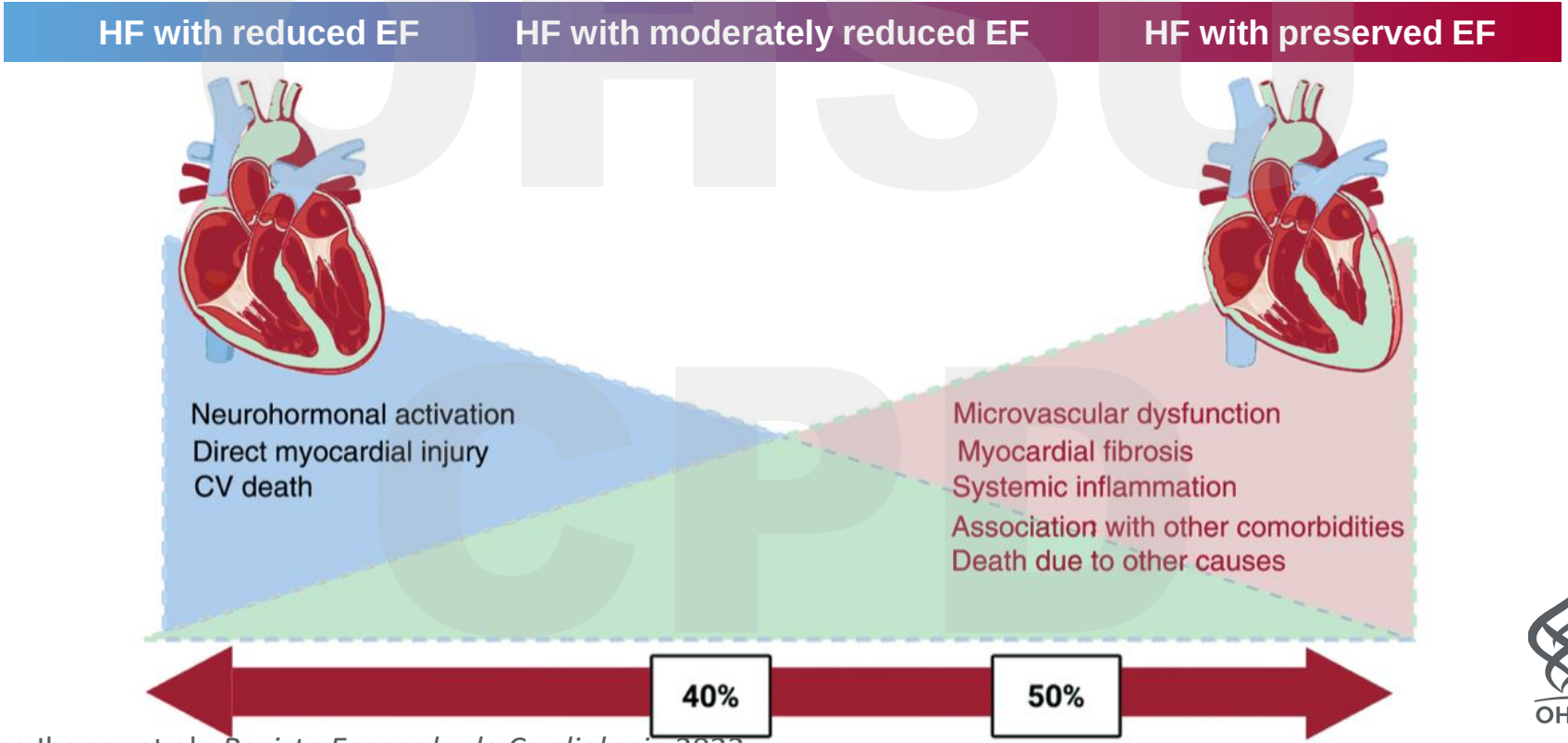
Patient vignette #2

- 61yo healthy F with hypertension, managed with HCTZ and amlodipine
- Has generally been quite active – biking, hiking, gardening
- Over the past 3-4 years, has felt significant shortness of breath with activity – particularly going up inclines, stairs, and gardening
- Exam: normal JVP, no murmurs, clear lungs, no LE edema. Vitals are normal. BMI is 26
- Workup: - TTE without any abnormalities.
  - NT-proBNP of 105
  - CT chest, PFTs normal
  - Negative stress test

Does each patient have HFpEF?

Next steps in management?

Pathology of HFrEF vs HFpEF: a cardiac vs a systemic disease



Riquena Ibanez et al. *Revista Espanola de Cardiologia* 2022

Universal definition of Heart Failure (2021)

Symptoms and/or signs of heart failure caused by a structural and/or functional cardiac abnormality and corroborated by either elevated natriuretic peptides OR objective evidence of pulmonary or systemic congestion at rest or with provocation.

Bozkurt et al. *J Cardiac Failure* 2021

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Above in the setting of an LVEF > 50% and not attributable to a specific cardiac etiology

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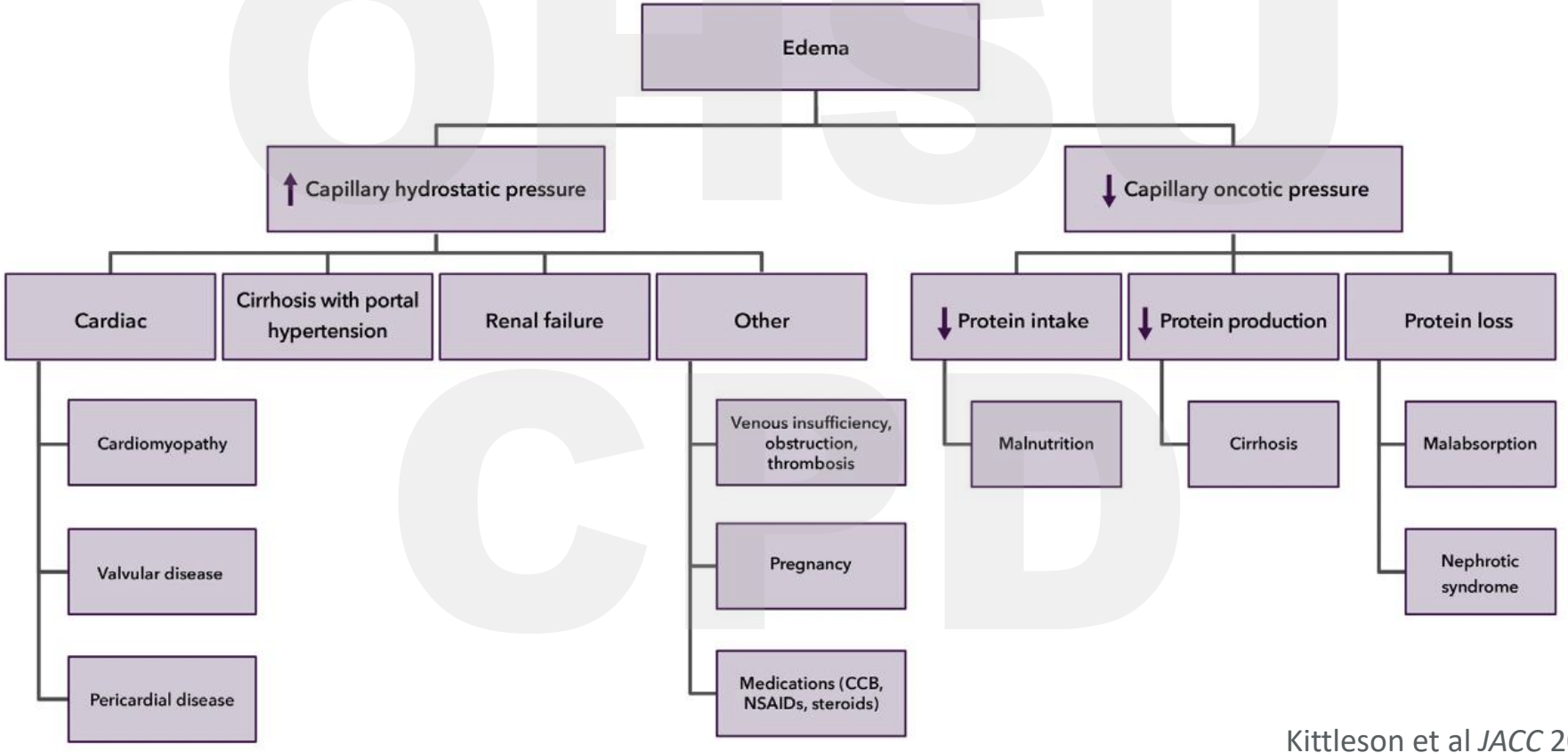
Bozkurt et al. *J Cardiac Failure* 2021

Echocardiogram will diagnose HFrEF. Diagnosing HFpEF is more challenging…

Step 1: Consider alternative diagnoses



Kittleson et al *JACC* 2023

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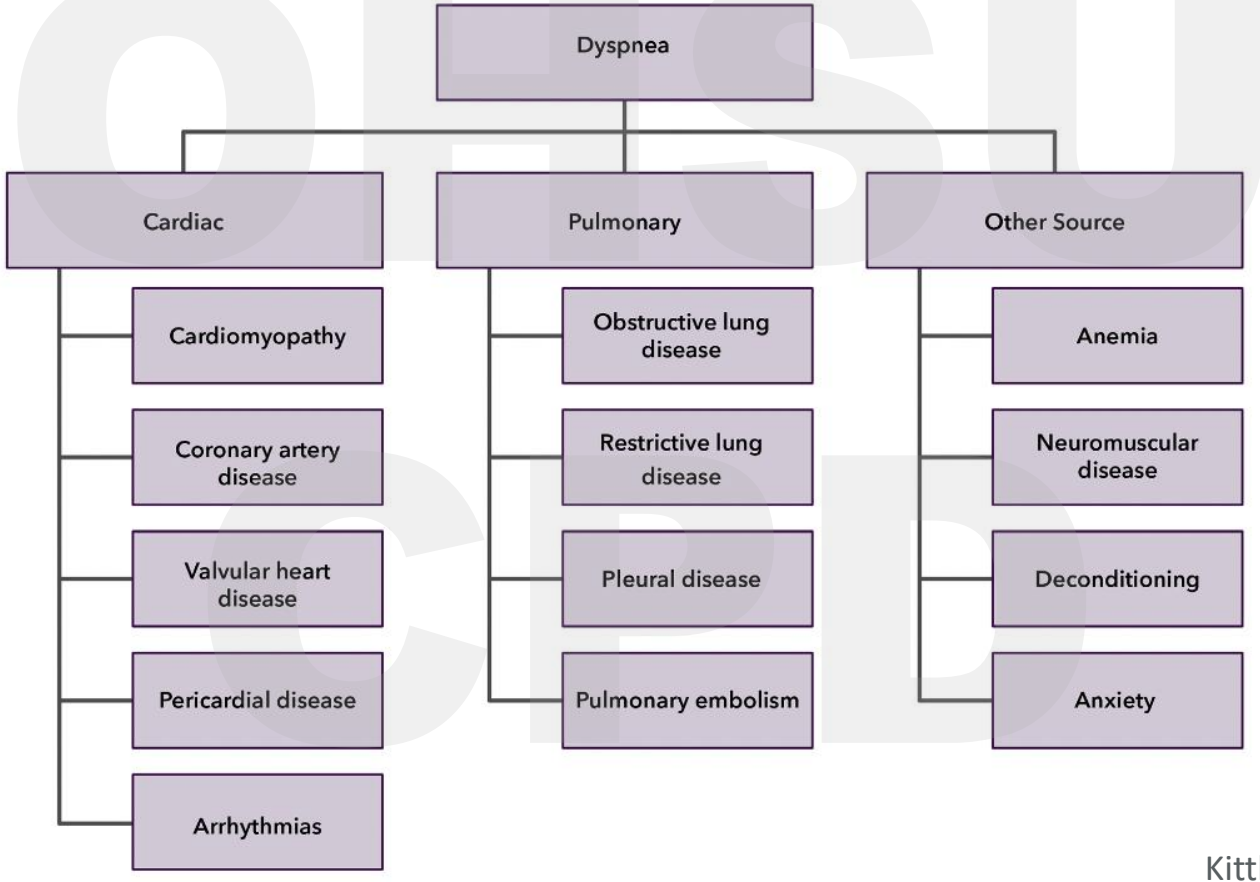

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Kittleson et al *JACC* 2023

Step 2: Universal HF diagnosis criteria

Signs and/or symptoms of heart failure

+

Elevated natriuretic peptide levels

Table 8. Natriuretic Peptide Levels Supporting Definition of HF

	Ambulatory	Hospitalized/ Decompensated
BNP, pg/mL	≥35	≥ 100
NT-proBNP, pg/mL	≥ 125	≥ 300

OR

Objective evidence of congestion

To start:
- Chest xray with pulmonary edema
- Dilated IVC on TTE

May include:
- Non-invasive echo stress test
- Right heart catheterization

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Bozkurt et al. *J Cardiac Failure* 2021

30% of individuals with HFpEF (proven by right heart catherization) do not have elevated biomarkers

Table 4. Clinical Predictors of normal B-type natriuretic peptide ≤100 pg/ml in patients with heart failure with preserved ejection fraction

Predictor	Univariate			Multivariate*		
	OR	95% CI	p Value	OR	95% CI	p Value
Age	0.73	0.54–0.99	0.042	0.95	0.67–1.35	0.77
Female gender	2.09	0.99–4.38	0.052	—	—	—
Chronic kidney disease	0.20	0.09–0.42	<0.001	0.22	0.10–0.49	<0.001
Atrial fibrillation	0.19	0.07–0.52	0.001	0.28	0.09–0.82	0.020
Coronary artery disease	2.02	0.96–4.26	0.063	—	—	—
Obesity	2.59	1.25–5.36	0.011	2.38	1.07–5.32	0.034

CI = confidence interval; OR = odds ratio.

Anjan et al *Am J Cardiology* 2012

Step 3:
H_2FPEF prediction score

Validated in an “unexplained dyspnea” population using right heart catheterization as gold standard diagnosis of HFpEF

Comorbidities feature heavily

Score range 1-9
1 = Unlikely
2-5 = Possible
6+ = Likely

H_2FPEF		
H_2	Heavy On > 2 antiHypertensives	2 1
F	Atrial Fibrillation	3
P	Pulmonary Hypertension PASP > 35mmHg on Doppler echocardiogram	1
E	Elder (age > 60)	1
F	Filling pressure (E/e'>9 on Doppler echocardiogram)	1

Kittleson et al *JACC* 2023
Reddy et al *Circulation* 2018

Putting it all together

Universal HF Criteria met (on first pass)?	+ Likelihood of HFpEF By H2FPEF Score	→ Outcome
✓	Likely	Diagnosis of HFpEF
✓	Unlikely / Intermediate	Rule out **cardiac** masqueraders
X	Likely	Treat empirically for HFpEF OR more testing
X	Intermediate	More testing (RHC or stress echo)
X	Unlikely	Not HFpEF

Consider cardiac masqueraders

- **Primary cardiomyopathy**
  - Amyloid
  - Hypertrophic CM
  - Sarcoid
  - Hemochromatosis
- **Pericardial Disease**
- **Valvular heart disease**
  - Aortic Stenosis
  - Aortic Regurgitation
  - Mitral Stenosis
  - Degenerative MV disease

Back to patient #1

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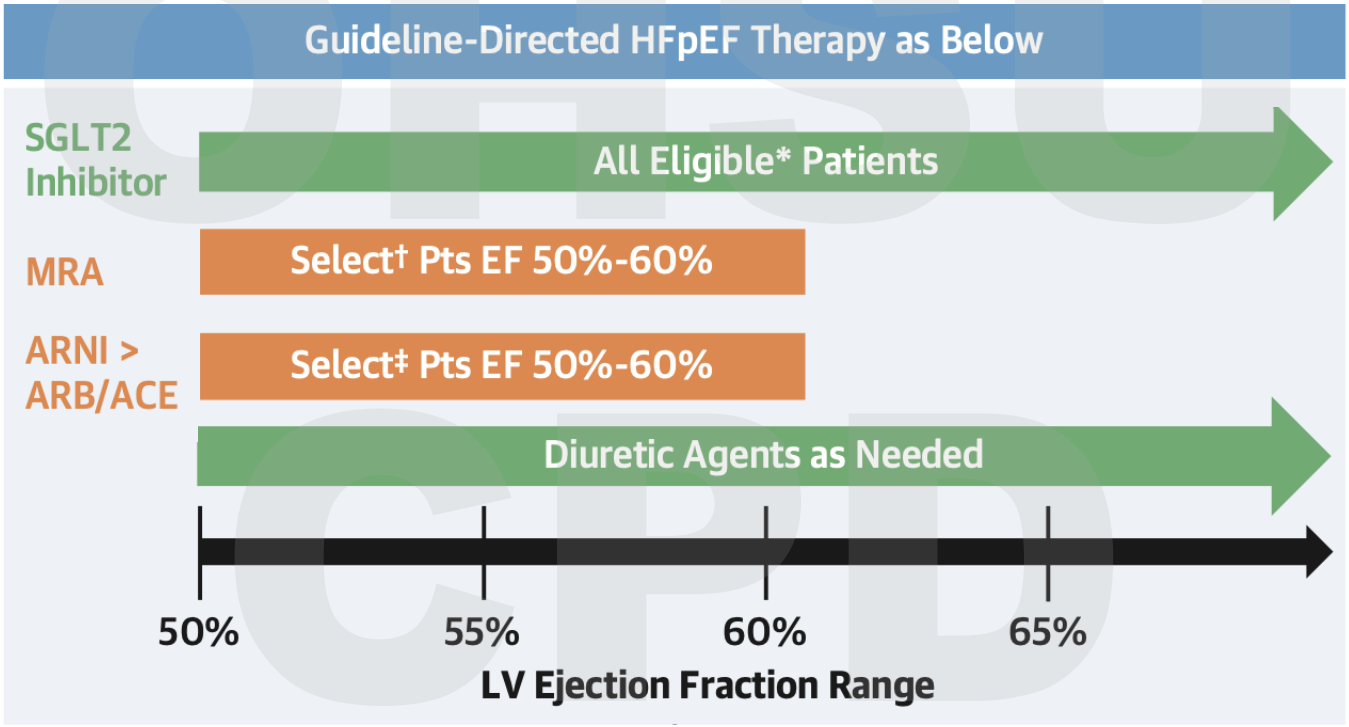
Does this patient have HFpEF? YES

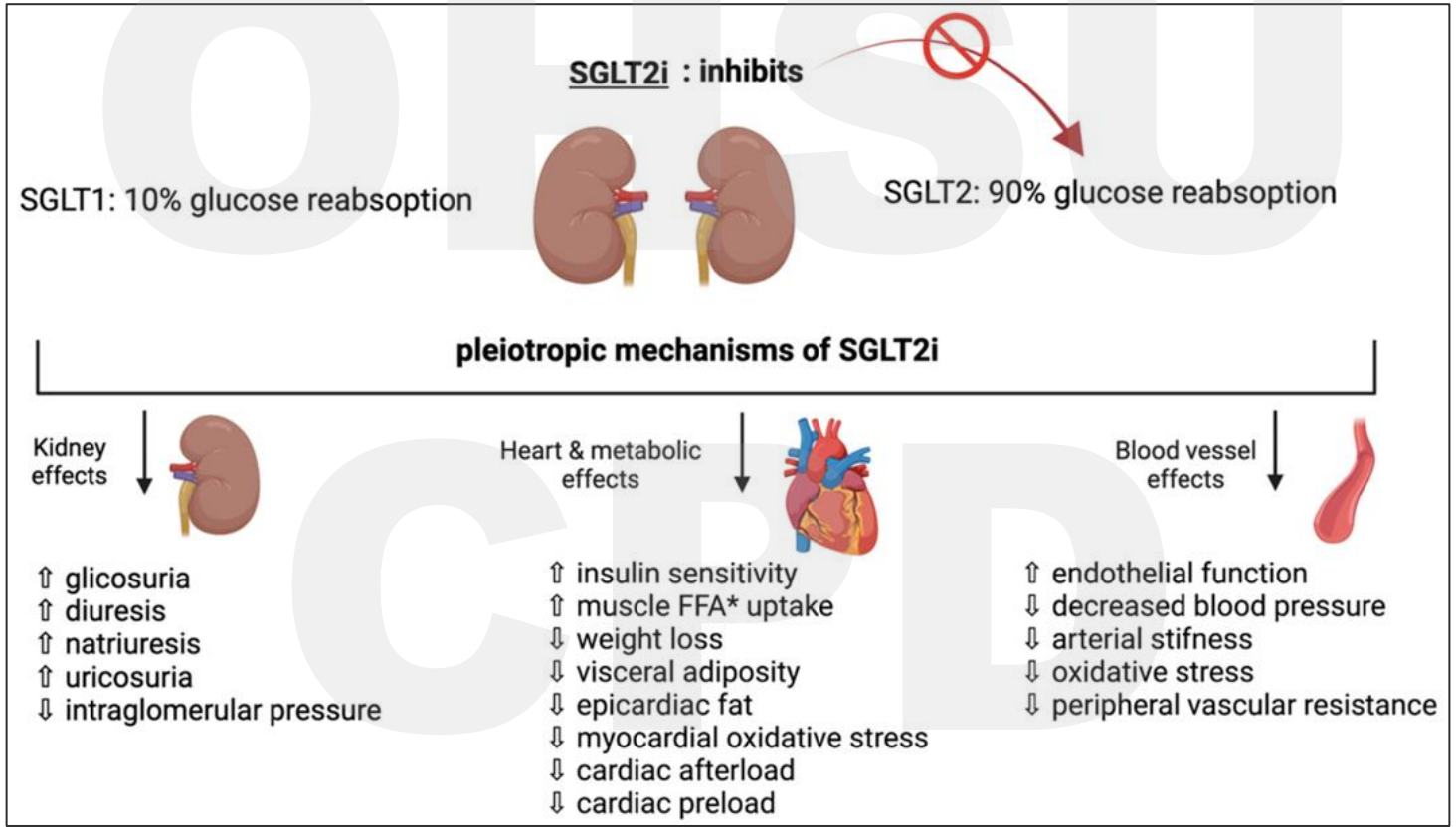
Next steps in management?

Step 1: Decongest

Step 2: GDMT (but the evidence is rapidly evolving!)

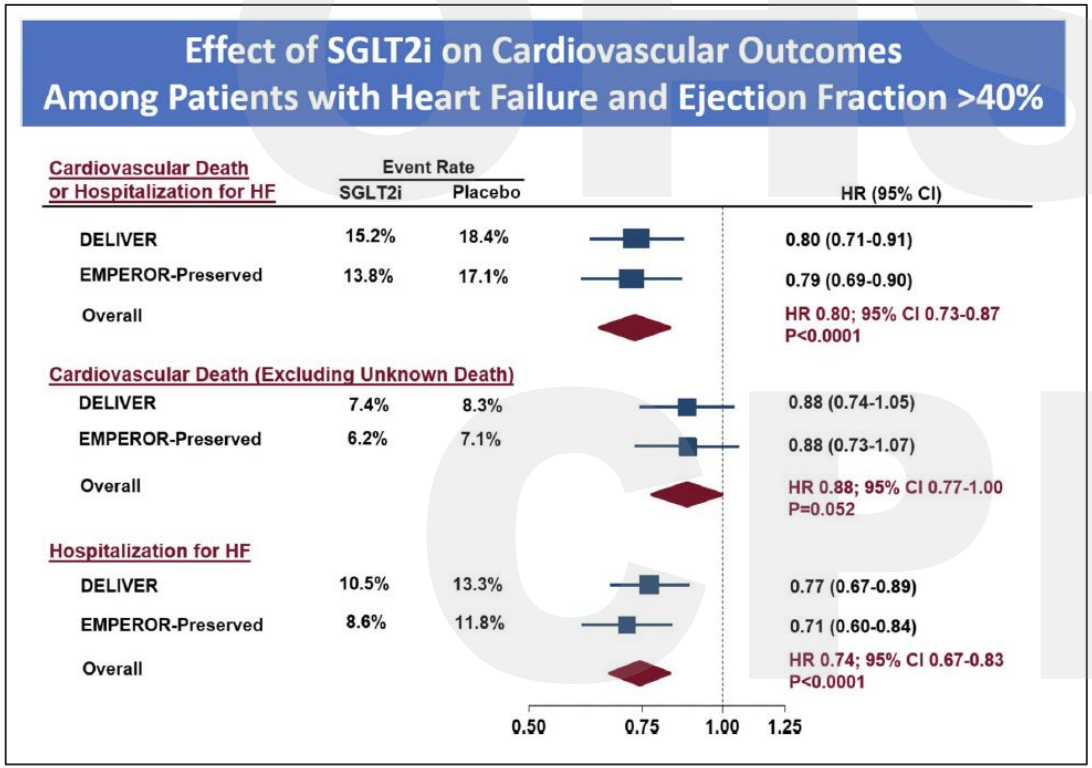


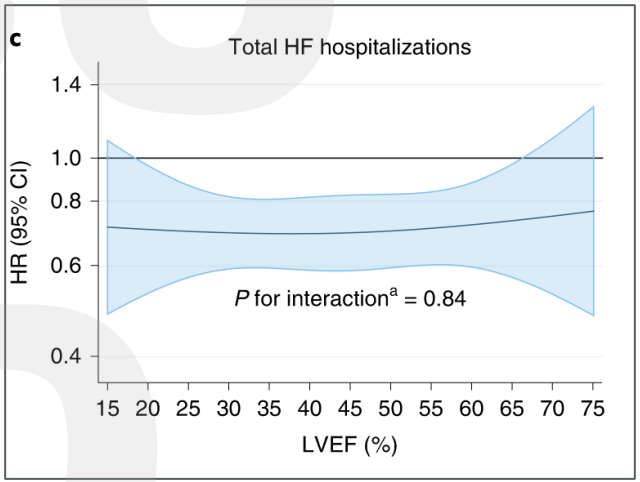
SGLT2i's target the cardio-metabolic-renal axis



Muscoli et al *Pharmaceutics* 2022

Meta-analysis of SGLT2i HFpEF trials (EF > 40%) demonstrates positive effect, mainly reduction in HF hospitalizations

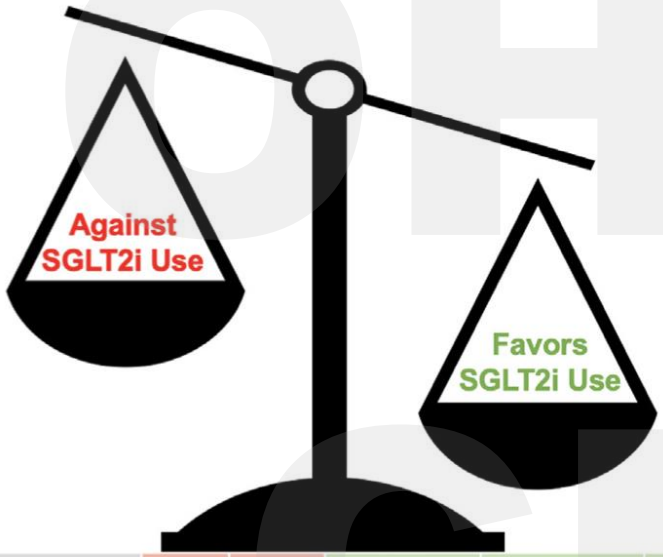




Greene et al. *American Journal of Cardiovascular Drugs* 2024

Jhund et al. *Nature Med* 2022

For *most* patients, benefit of SGLT2i outweighs risk of infection



	MGI	UTI	HF admission	CV mortality	Total Mortality
Absolute Risk Reduction (%)	-0.3	-0.2	5.6	1.1	1.3
NNT-H/NNT-B	356	557	18	93	76

Risk highest in first 3-6 months

Do not initiate if:
- Current UTI/MGI
- ADPKD

Specialist input:
- Recurrent UTIs/MGIs
- MDRO

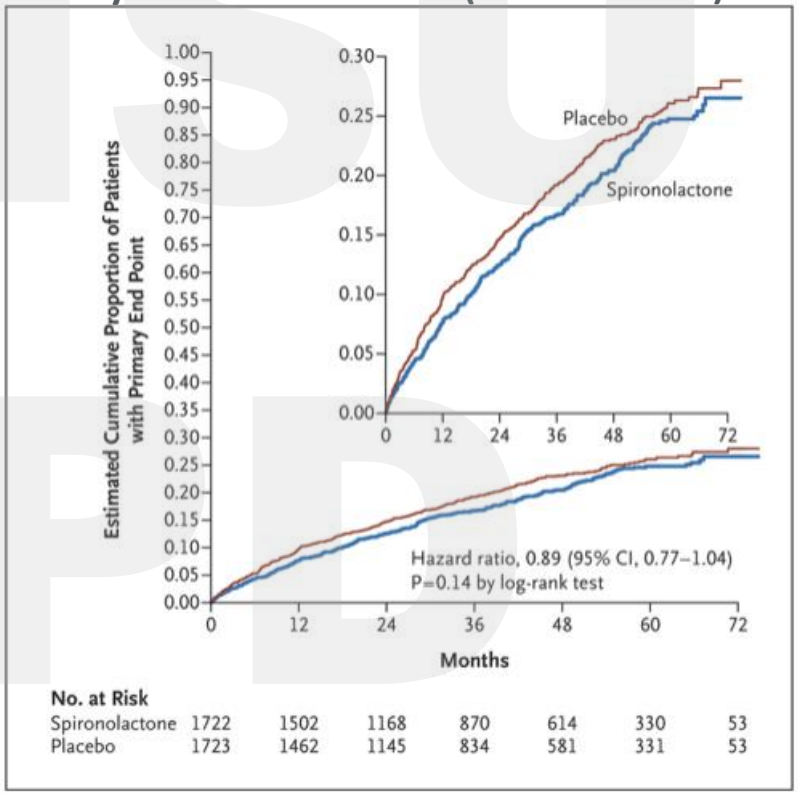
Treat through:
- Uncomplicated UTI/MGI

Duvalyan et al. *J Cardiac Failure* 2024

The controversial TOPCAT trial (2015)

- Multinational, randomized trial
- Spironolactone vs placebo in EF > 40%
- Primary outcome: CV death and HF hospitalization
- HR 0.89 (CI 0.77 – 1.04)
- Concern for regional variation in outcomes, baseline event rate, and “side effect” profile

Primary outcome: HR 0.89 (CI 0.77 – 1.04)



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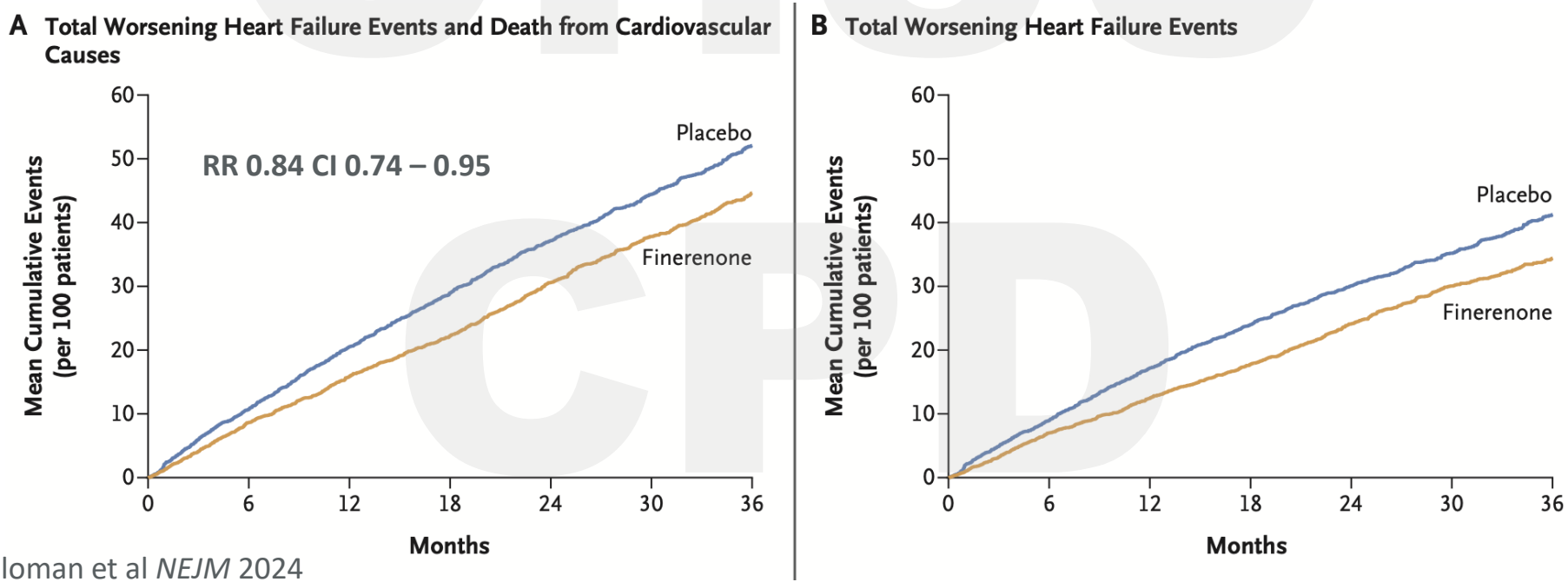
MRAs revisited in 2024: Finerenone in HFpEF

- Non-steroidal MRA
- Mineralocorticoid receptor controls inflammatory and fibrotic responses to injury
- Finerenone interacts with MR on the kidney AND the heart, unlike the steroidal MRAs
- Finerenone demonstrated to have renal protective effects in diabetics with proteinuria

Finerenone in HFmrEF or HFpEF (FINEARTS-HF) 2024

LVEF > 40%, NYHA Class II – IV symptoms
Structural disease and elevated NT-proBNP
Randomized 1:1 to Finerenone vs Placebo

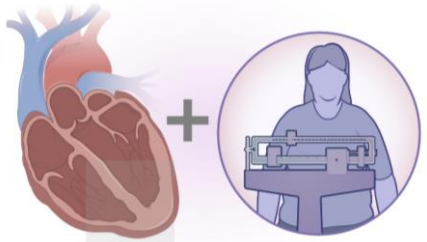


Soloman et al *NEJM* 2024

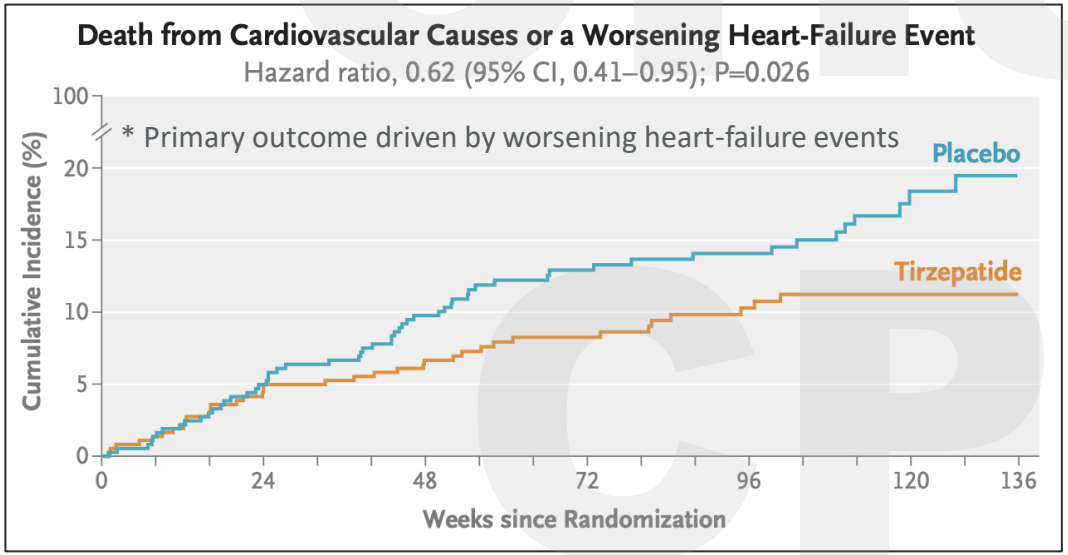
A few MRA take away points (for now)

- FINEARTS suggests a class effect for MRAs.
- Main impact is a reduction in heart failure hospitalizations (unlike HFrEF which is a mortality benefit)
- Rate of hyperkalemia was high (double rate of placebo) but severe hyperkalemia (> 6) absolute rate was low (2-3%)
- Finerenone may have a pathophysiologic benefit in HFpEF over spironolactone
- Diabetic and CKD status may also play a role

More recently… a focus on targeting obesity in HFpEF



SUMMIT HF: Tirzepatide for patients with HFpEF and obesity (2024)



- GLP-1 and GIP agonist
- BMI > 30, EF > 50% AND HF hospitalization within 12 months or eGFR < 70 mL/min/1.73m^2
- Powered for clinical primary outcome
- 50% with HF hospitalizations, 19% on SGLT2i
- 13.9% change in body weight (treatment arm)

Packer et al. *NEJM* 2024

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High intolerance rate

Weight loss vs. targeted effect?

Not FDA approved for HFpEF indication = challenging to get insurance to cover

Patient #1 Next steps?

- Start a loop diuretic
- Start SGLT2i and monitor kidney function
- Consider starting an MRA if hypertensive or ongoing congestion
- Start GLP-1 agonist if affordable, encourage weight loss strategies
- Assess for and treat comorbidities

Circling back to Patient #2

- 61yo active F with progressive dyspnea on exertion
- Only medical comorbidity is HTN
- Workup including stress test, pulmonary workup all negative
- Normal echo and biomarkers
- H2

Does this patient have HFpEF?

Next steps in management?

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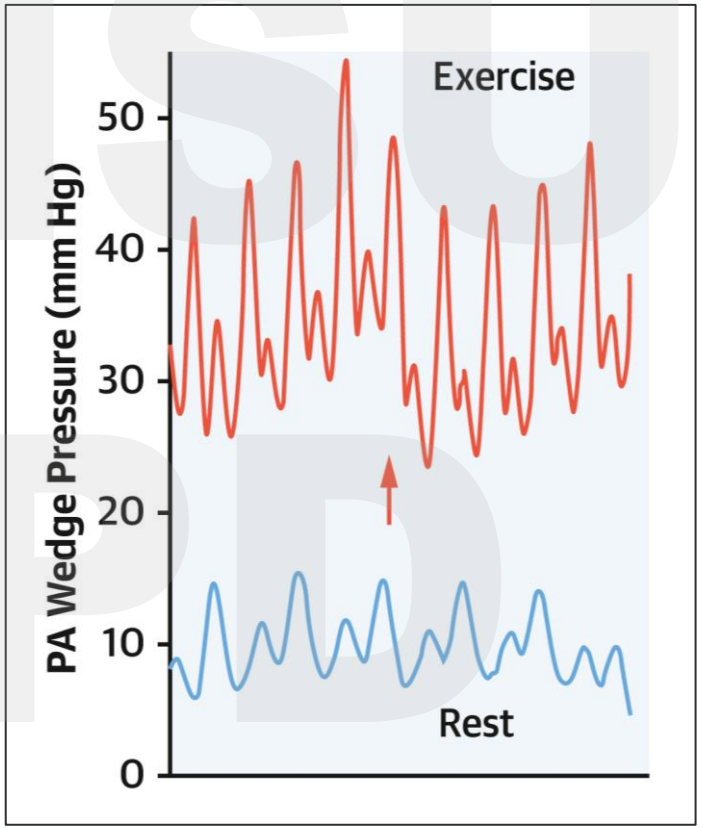
Bozkurt et al. *J Cardiac Failure* 2021

Right heart catheterization with exercise

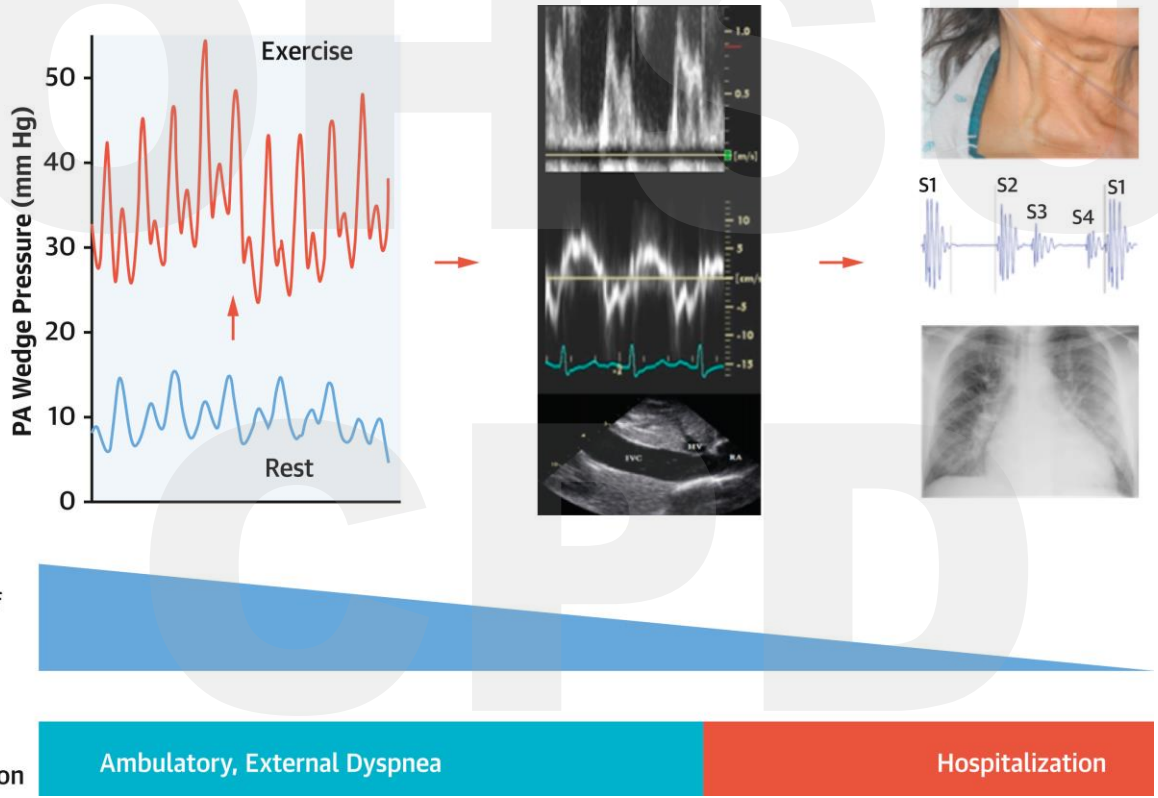
Gold standard for diagnosis of HFpEF

Hemodynamic HFpEF:
rPAWP > 15mmHg
ePAWP > 25mmHg



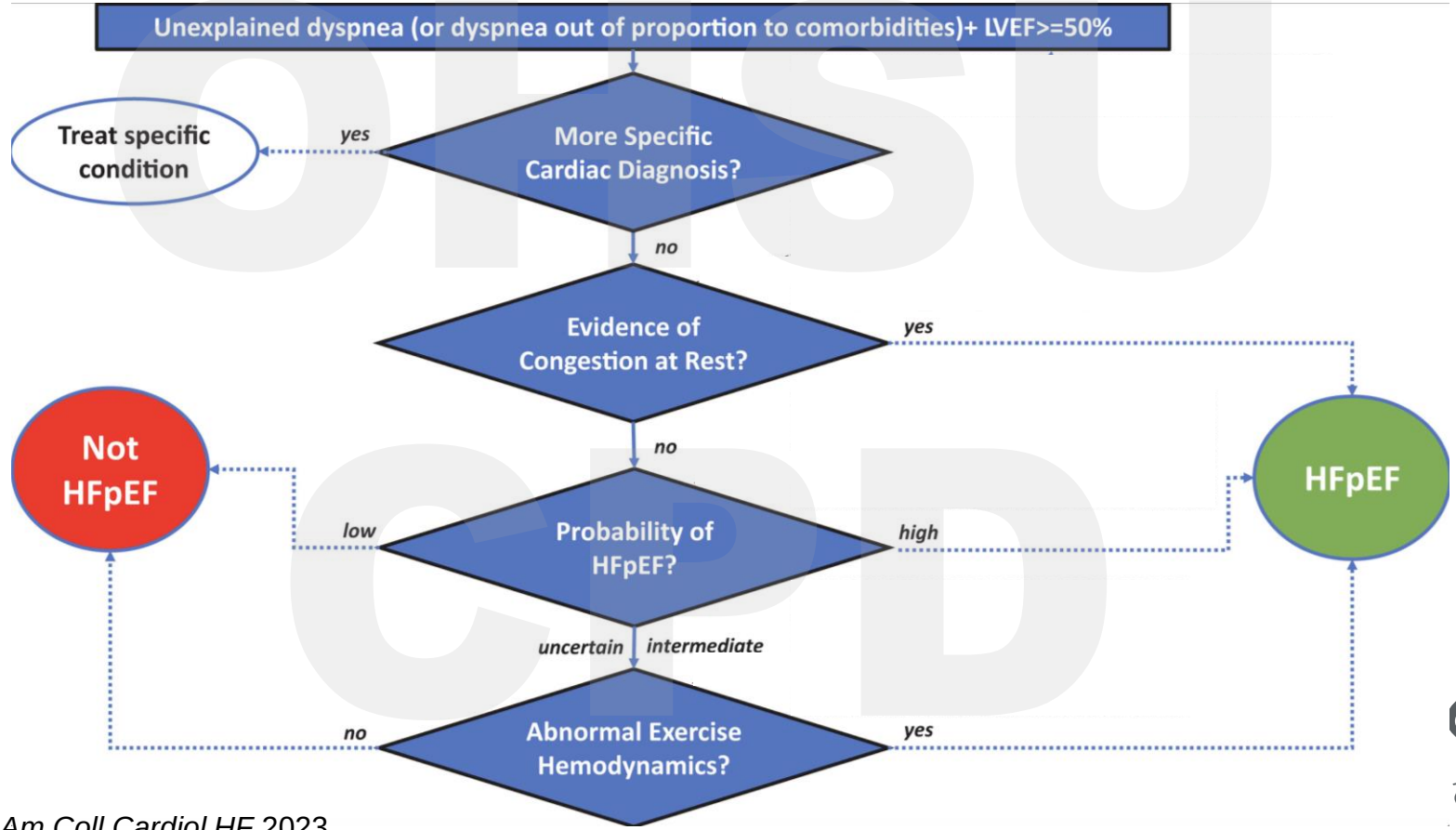
Borlaug et al. *J Am Coll Cardiol HF* 2023

Overt congestion is actually just the tip of the HFpEF iceberg



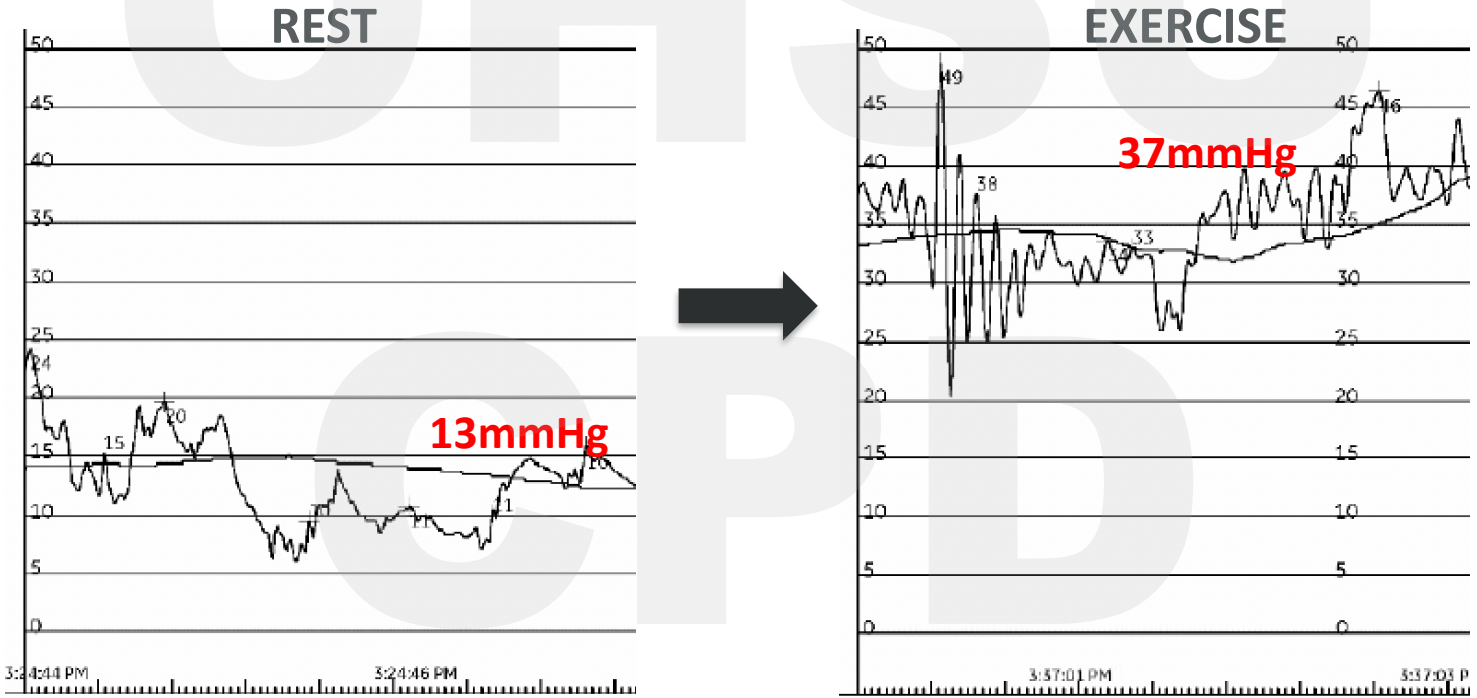
Borlaug et al. *J Am Coll Cardiol HF* 2023

Algorithm to identify patients with HFpEF



Desai et al. *J Am Coll Cardiol HF* 2023

Patient #2 undergoes an exercise RHC



From patients…

“I was told nothing was wrong with me and it was in my head”

“I was told to lose weight”

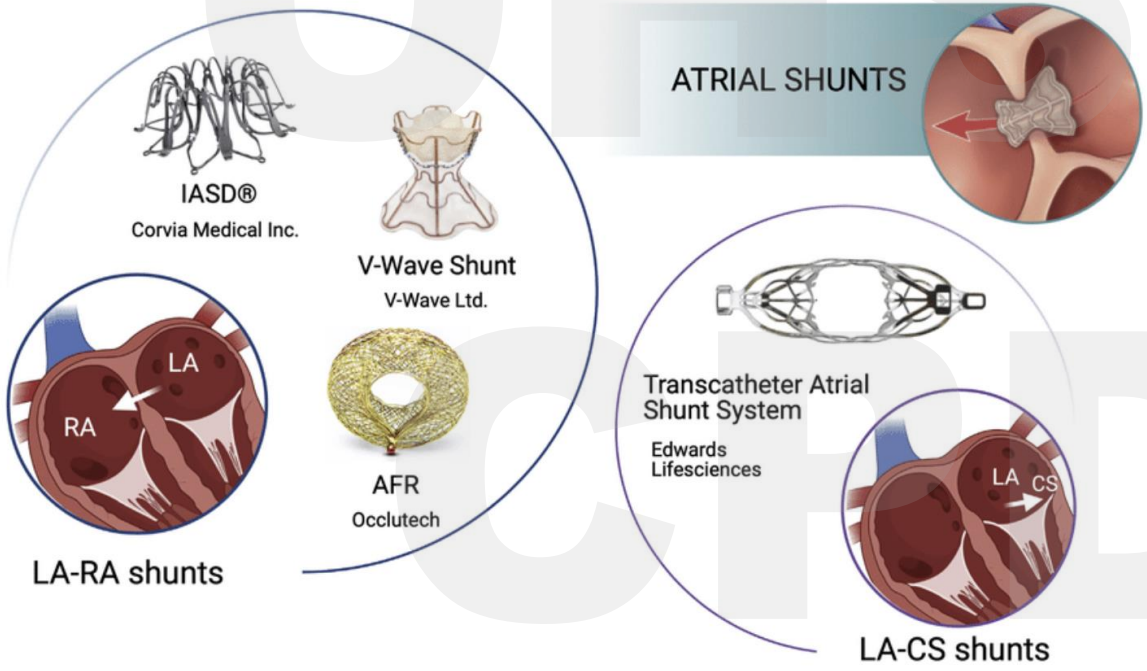
“It took me three years and multiple doctors to get this diagnosis!”

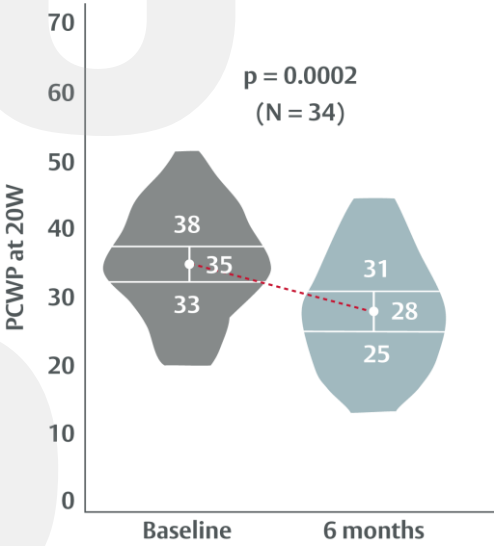
Patient #2 undergoes an exercise RHC

This patient would not have been included in any of the aforementioned HFpEF trials

- EMPEROR-Preserved: LVEF > 40%, NYHA Class II-IV, NT-proBNP > 300 pg/mL
- DELIVER-HF: LVEF > 40%, structural heart disease (LVH or LAE), NT-proBNP > 300 pg/mL
- TOPCAT: LVEF > 45%, HF hospitalization within 12 months or NT-proBNP > 360 pg/mL
- FINEARTS-HF: LVEF > 40%, structural heart disease (LVH or LAE), NT-proBNP > 300 pg/mL
- SUMMIT-HF: LVEF > 50%, BMI > 30, HF hospitalization or eGFR < 70 mL/min/1.73m^2

Interatrial shunting to reduce left atrial pressure (LAP) during exercise is an experimental device therapy





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Initial results have been (very) conflicting but trials are ongoing

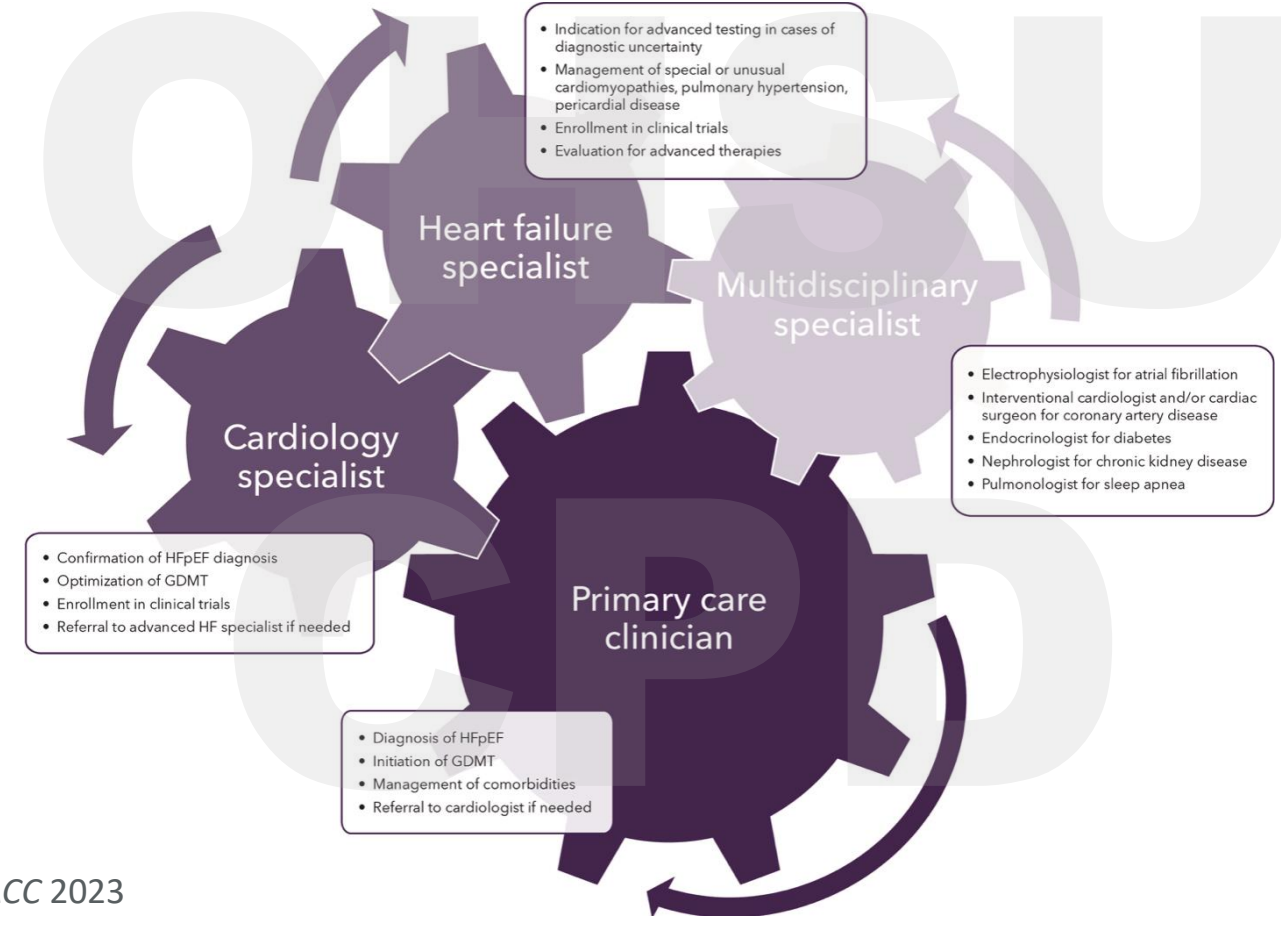
ALT-FLOW (LA-Coronary Sinus) – Positive

REDUCE LAP-HF II (LA-RA) – Neutral (Positive subpopulation)

RELIEVE HF (LA-RA) - Negative

Urey et al. *European J of Heart Failure* 2024
Stone et al. *Circulation* 2024
Gustaffson et al. JA*CC HF* 2024

Multidisciplinary care is essential!



Kittleson et al *JACC* 2023

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Take home points

- HFpEF is a complex, systemic illness along the cardio-metabolic-renal axis. HFpEF GDMT targets are beginning to include inflammation and obesity.
- Strongest evidence to date is for SGLT2 inhibitors. MRAs and GLP1 agonists are emerging treatment pathways.
- Maintain a high suspicion for exercise-HFpEF in patients with unexplained dyspnea, even in the face of normal echo / biomarkers – this is an under-diagnosed yet highly symptomatic population.
- Treatment options to improve QOL in exercise-HFpEF are desperately needed. Keep an eye on clinical/device trials.

Thank you for being here!

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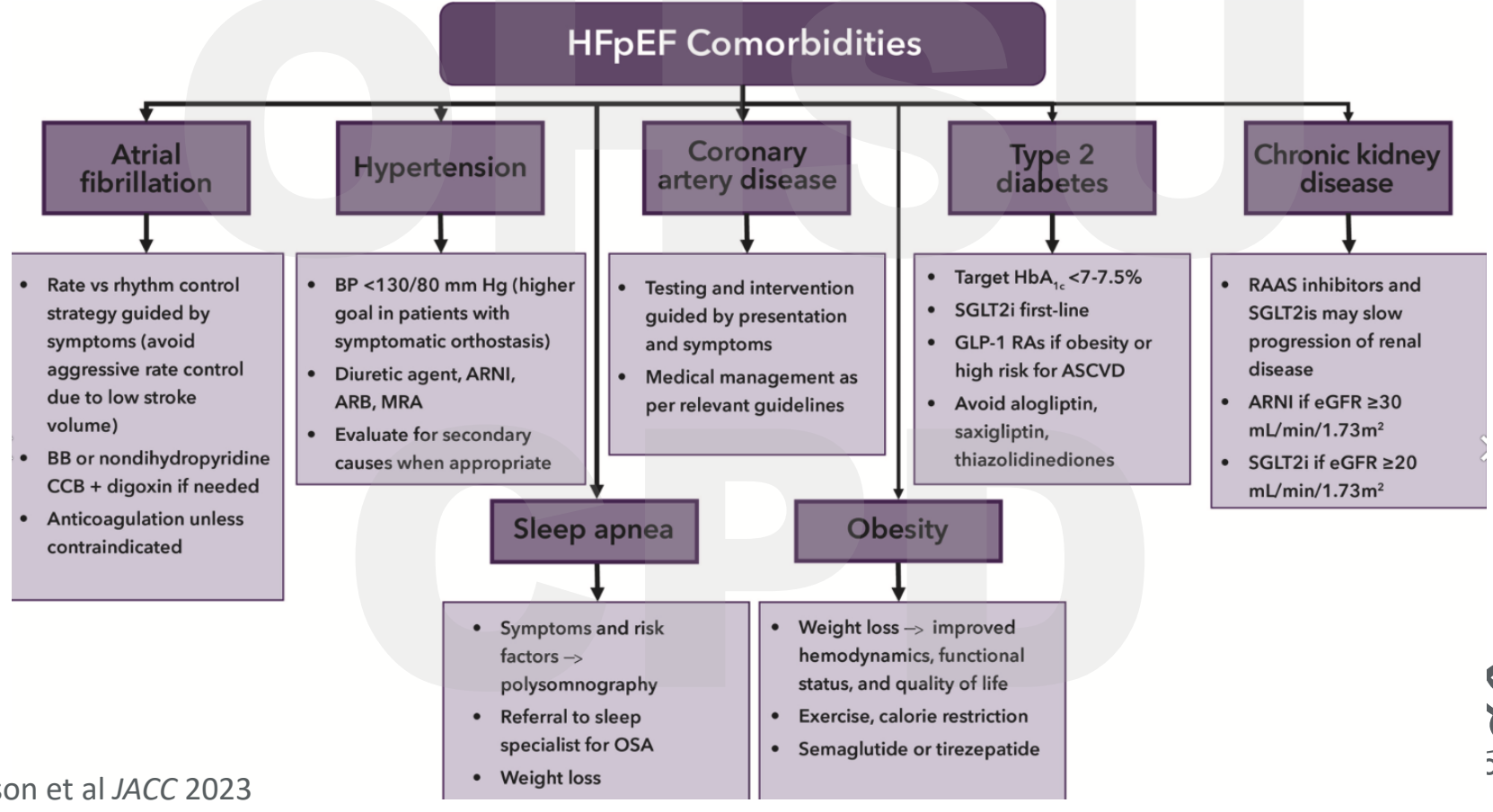
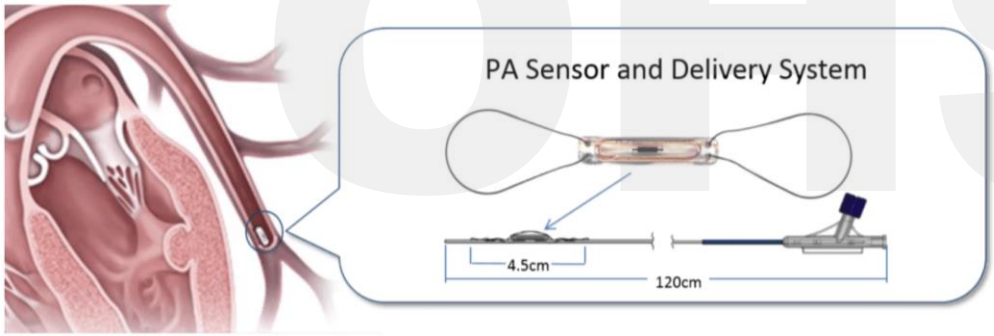
Step 3: Management of comorbidities



Kittleson et al *JACC* 2023

Implantable Pulmonary Artery (PA) sensor monitoring for outpatient fluid management



Prevent HF hospitalizations in patients with HFpEF

Consider if:

- Frequent hospitalizations
- Challenging exam
- AKIs with diuresis
- Reliable patient

https://www.azheartarrhythmia.com/contents/ep-procedures/cardiomems-implantation