Heart Failure with Preserved Ejection Fraction

Tim Jordan

Disclosures

No Relevant disclosures

Outline

1. **Define HFpEF**
2. **Diagnosis**
3. **Management**
4. **Other special entities – Amyloid and HCM**

Clinical scenario

71 y/o F with history of diabetes, atrial fibrillation, hypertension, obesity

- 6 months DOE worsening past 2 weeks
- 2-3 pillow orthopnea
- 2 weeks of LE swelling

Exam – BMI 34kg/m2, HR 70, BP 141/87, JVP 10 cm H20, lungs clear, heart RRR, 2+ edema bilaterally to shins

Echo shows increased wall thickness (septum 1.3cm), EF 57%, RVSP 43 mmHg, mild aortic stenosis

What is Heart Failure with Preserved Ejection Fraction (HFpEF)

- **The clinical syndrome of Heart Failure**
- **Ejection Fraction ≥50%**
- **Some objective evidence of resting or provokable elevated left ventricular filling pressures**
  - Elevated BNP, noninvasive and invasive hemodynamic measurements

Elevated RVSP

Symptoms	Signs
PND	Leg Edema
Orthopnea	Elevated JVP + HJR
DOE	Cardiomegaly
Fatigue	Pulmonary edema
Decrease exercise tolerance	

Prevalence and mortality of HFpEF

- **6.7 million Americans with HF, per person lifetime incidence ~24%**
- **> 50% have HFpEF → on the rise**
  - Older population, more diabetes, htn, obesity
  - The interplay of the cardiovascular-kidney-metabolic syndrome (CKM)
- **1 year mortality of 20-29% with frequent hospitalizations**
- **Large burden on health care and our patients**

Bozkurt et al. *J Card Fail* 2025;31:66-1164.

Highly prevalent but hard to diagnose?

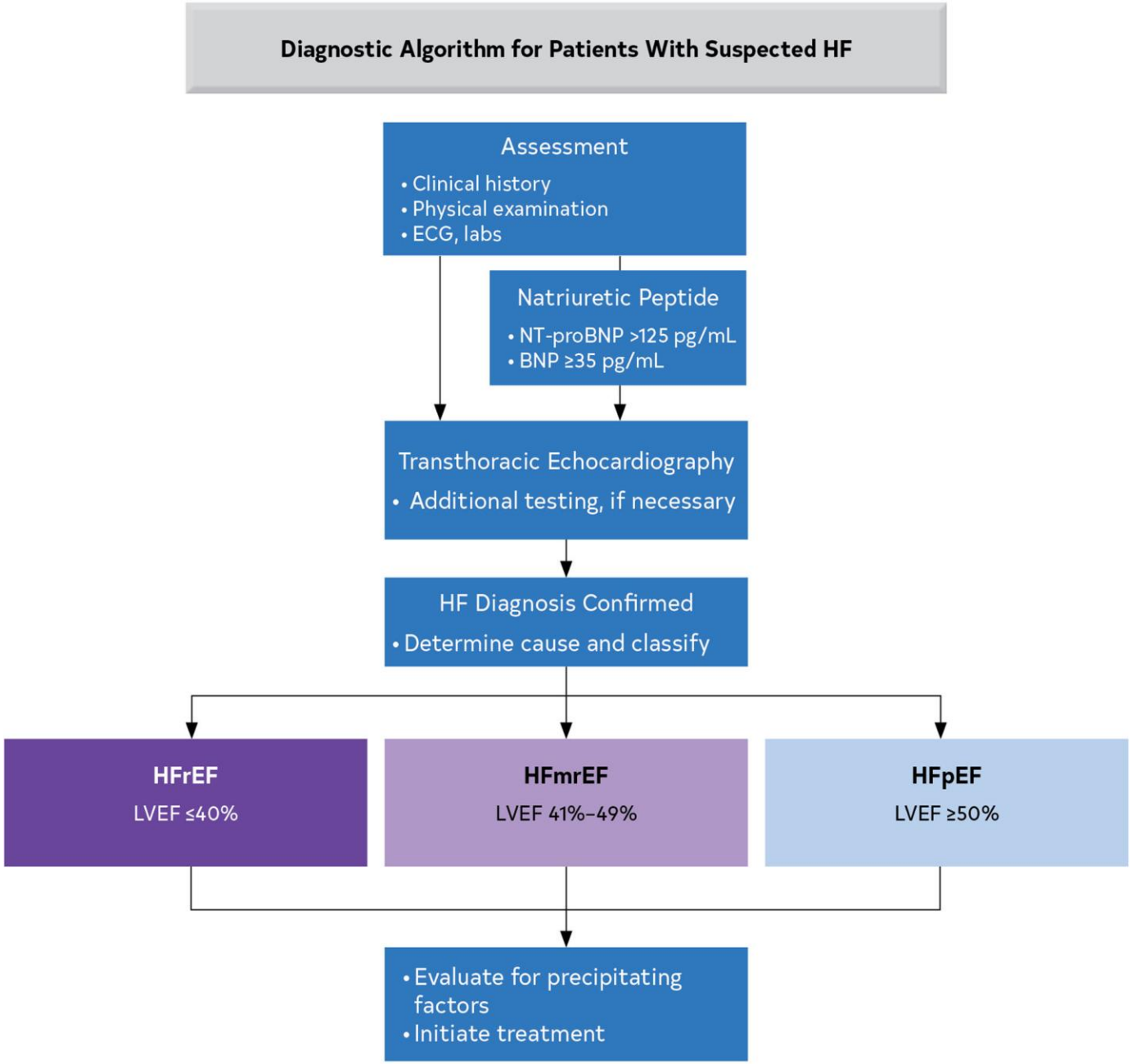
- **Many heterogenous conditions lead to clinical congestion and “heart failure”**

Rule out causes that have specific physiology and treatment.

HFpEF is dx of exclusion

Cardiac causes	Mimickers	Comorbidities
Hypertensive heart disease	Renal Failure	Hypertension
Valvular heart disease	Liver failure	DM2
Constrictive pericarditis	Obesity with edema	Atrial fibrillation
Restrictive CMY	Anemia	Obesity
Hypertrophic cardiomyopathy	Pulmonary Disease	Coronary artery disease
Amyloidosis	Chronic venous insufficiency	CKD
Sarcoidosis		Preeclampsia

Sentara


Diagnostic Algorithm for Patients With Suspected HF
Assessment
• Clinical history
• Physical examination
• ECG, labs
Natriuretic Peptide
• NT-proBNP >125 pg/mL
• BNP ≥35 pg/mL
Transthoracic Echocardiography
• Additional testing, if necessary
HF Diagnosis Confirmed
• Determine cause and classify
HFrEF
LVEF ≤40%
HFmrEF
LVEF 41%–49%
HFpEF
LVEF ≥50%
• Evaluate for precipitating factors
• Initiate treatment

B-Type Natriuretic Peptide (BNP)

NT proBNP > 125 pg/ml or BNP >35 pg/ml

Normal BNP does not exclude HFpEF

Elevated BNP does not confirm HFpEF

Echo findings

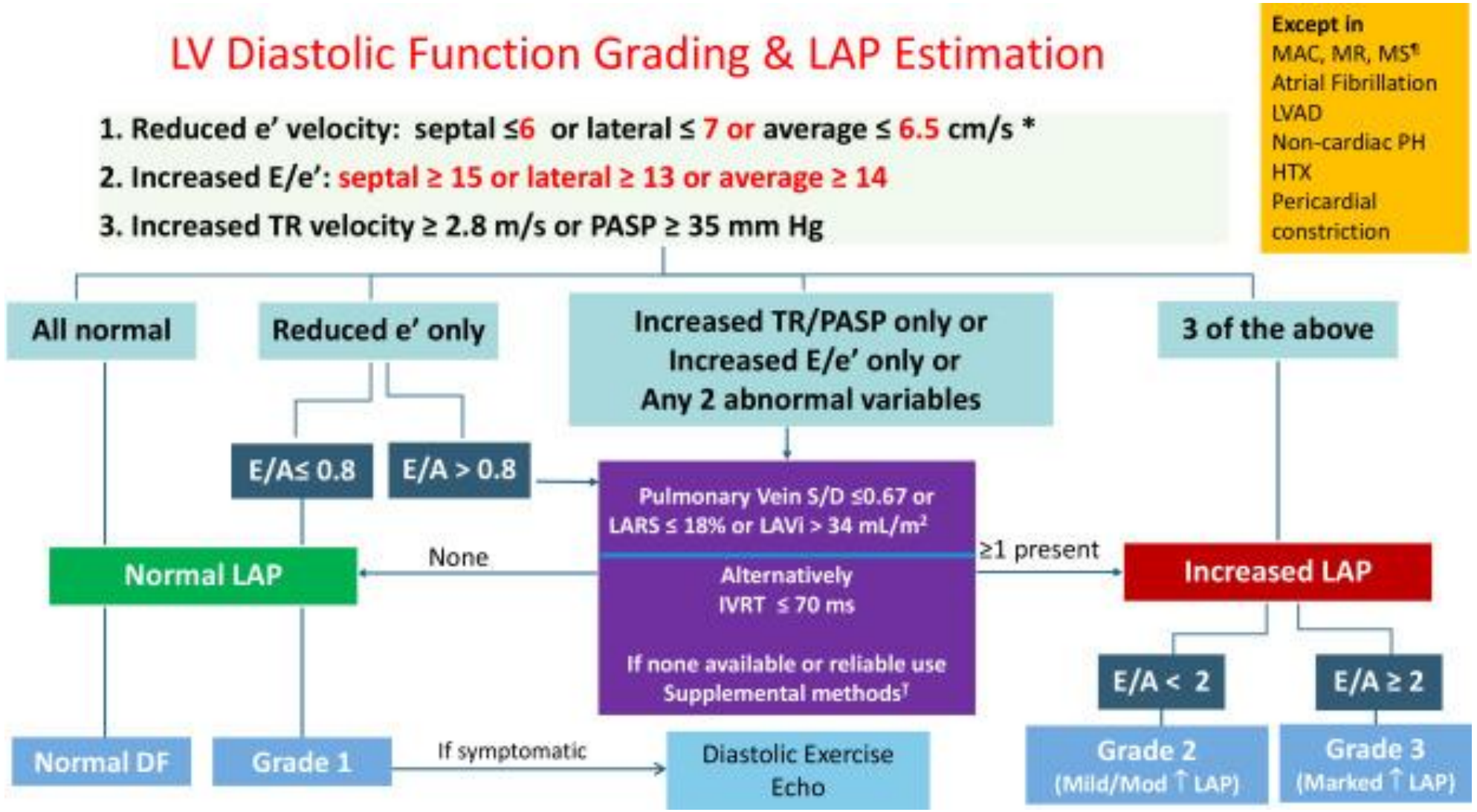
Diastolic dysfunction ≠ HFpEF

Diastolic dysfunction is an abnormality in relaxation and filling, separate from LVEF or symptoms

Echo findings alone cannot make or exclude dx of HFpEF

Echo findings
Increased LV wall thickness
Increased LA volume index > 34 ml/m2
Doppler tissue imaging: E/e', e' septal/lateral velocities
Mitral inflow velocities E/A
Increased TR velocity >2.8 m/s or PASP ≥ 35 mmHg
Pulmonary venous flow

2025 ASE Diastology Guidelines



H2FPEF SCORE

Prior to completion, confirm patient has exertional dyspnea and LVEF > 40%.

Enter the points in the fields to the right for all conditions that apply to the patient.

H_2	Heavy	Body mass index > 30 kg/m²	+2	2
	Hypertensive	On > 2 anti-hypertensives	+1	0
F	Atrial Fibrillation	Paroxysmal or Persistent AF	+3	3
P	Pulmonary Hypertension	RVSP > 35 mmHg	+1	1
E	Elder	Age > 60 years	+1	1
F	Filling Pressure	E/e' > 9	+1	0
		Score (Sum of above numbers)		7

Consider sending high probability HFpEF patients for further evaluation	A score of	3	4	5	6+
	Indicates a HFpEF probability of	>50%	>70%	>80%	>90%

2-5 → more testing

When that is not enough → MUST PERTURB THE SYSTEM

- **1/3 of HFpEF patients have normal filling pressures at rest**
  - Stress testing → invasive or non invasive
  - Exercise echocardiography
  - Cardiopulmonary exercise testing (CPET)
  - Exercise right heart catheterization

Other testing

Cardiac MRI

infiltrative processes, constriction, previous infarcts or ischemic events

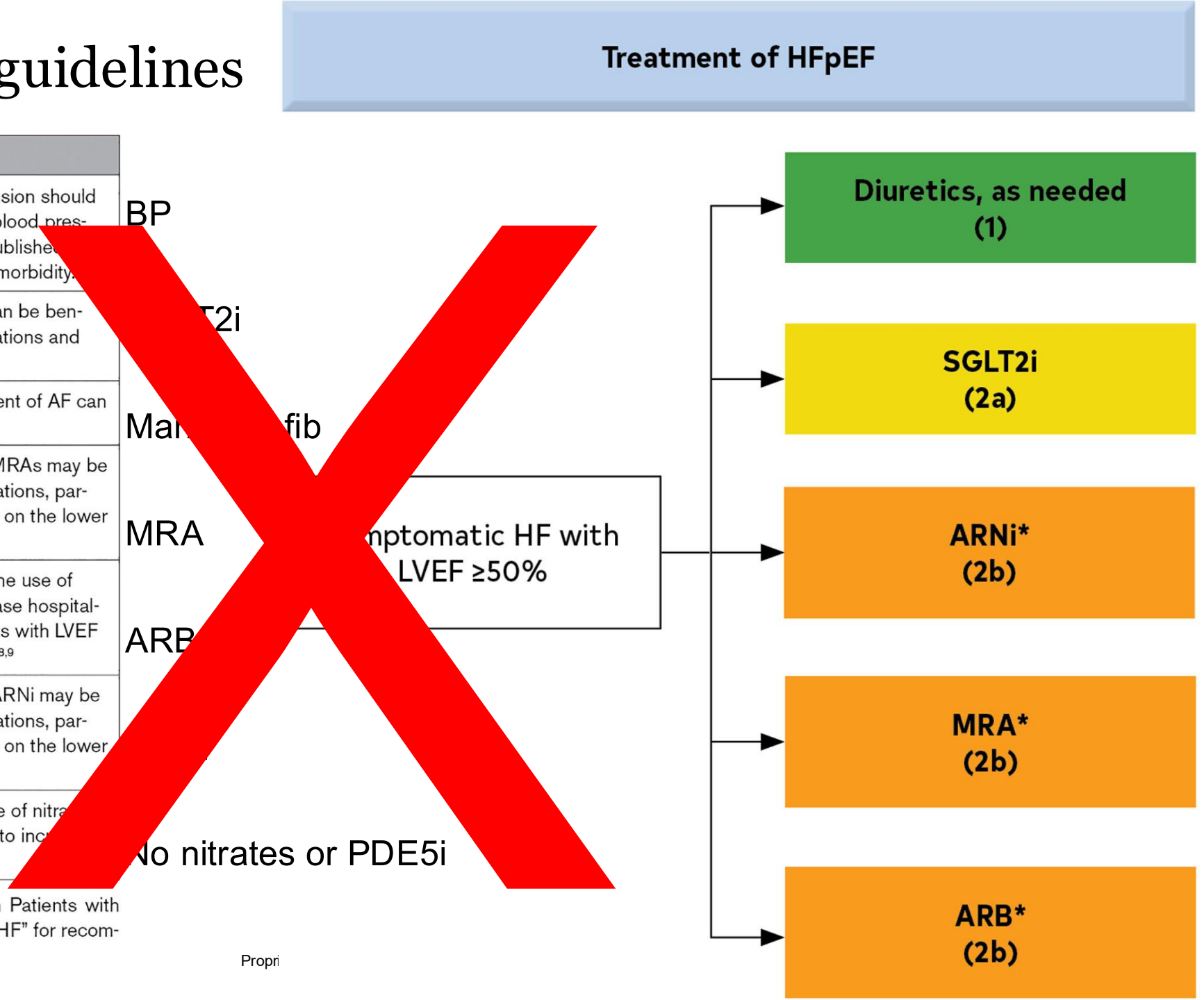
Genetic testing

Nuclear Scintigraphy Scan (PYP) if amyloid is suspected (more later)

Management – 2022 guidelines

COR	LOE	Recommendations
1	C-LD	1. Patients with HFpEF and hypertension should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity.
2a	B-R	2. In patients with HFpEF, SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality.[4]
2a	C-EO	3. In patients with HFpEF, management of AF can be useful to improve symptoms.
2b	B-R	4. In selected patients with HFpEF, MRAs may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[5–7]
2b	B-R	5. In selected patients with HFpEF, the use of ARB may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[8,9]
2b	B-R	6. In selected patients with HFpEF, ARNi may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[10,11]
3: No-Benefit	B-R	7. In patients with HFpEF, routine use of nitrates or phosphodiesterase-5 inhibitors to improve activity or QOL is ineffective.[12,13]

*See Section 7.2, "Diuretics and Decongestion Strategies in Patients with HF," and Section 10.2, "Management of Atrial Fibrillation (AF) in HF" for recommendations for use of diuretics and management of AF in HF.



HFpEF Pillars

SGLT2i

MRA both steroidal and non-steroidal (finerenone)

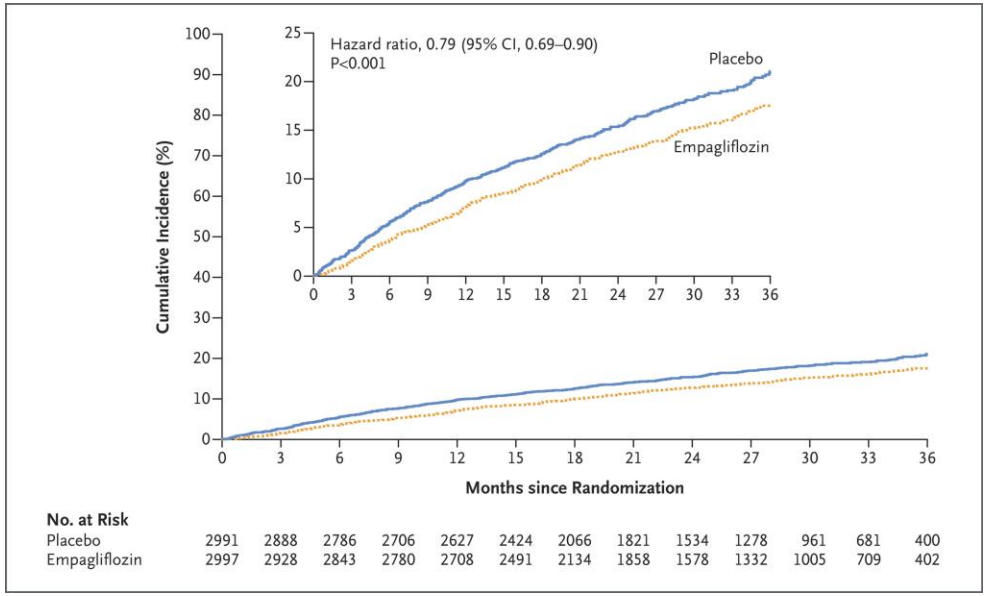
GLP1 RA

ARB and ARNI → in certain situations

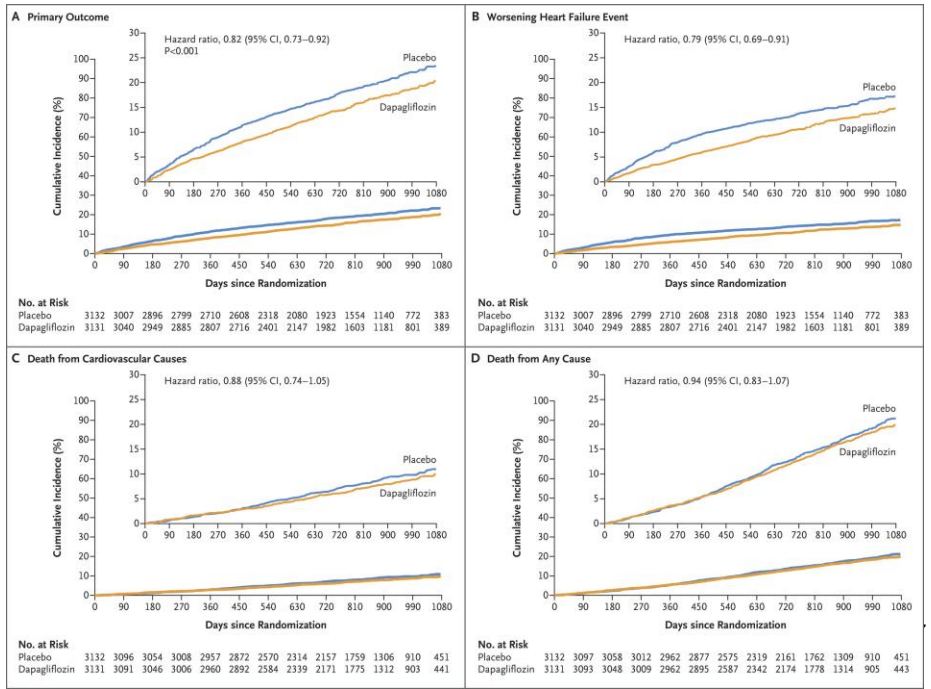
SGLT2i

- **Emperor-Preserved:** Empaglifozin (Jardiance) - 2021
- **Deliver:** Dapagliflozin (Farxiga) - 2022 (post guidelines)
- **Design:** RCT vs Placebo, NYHA II-IV, LVEF > 40%, elevated NT-proBNP (congested)
  - Emperor-Preserved: N = 5988
  - Deliver: N = 6263
- **Endpoints**: CV-death or HF hospitalization (plus urgent visits in DELIVER)
- **Results**:
  - Both drugs associated with ~20-21% reduction in endpoint;
  - benefit consistent across EF
  - Hospitalization primary driver
  - Meta-analysis of both studies showed CV-death benefit

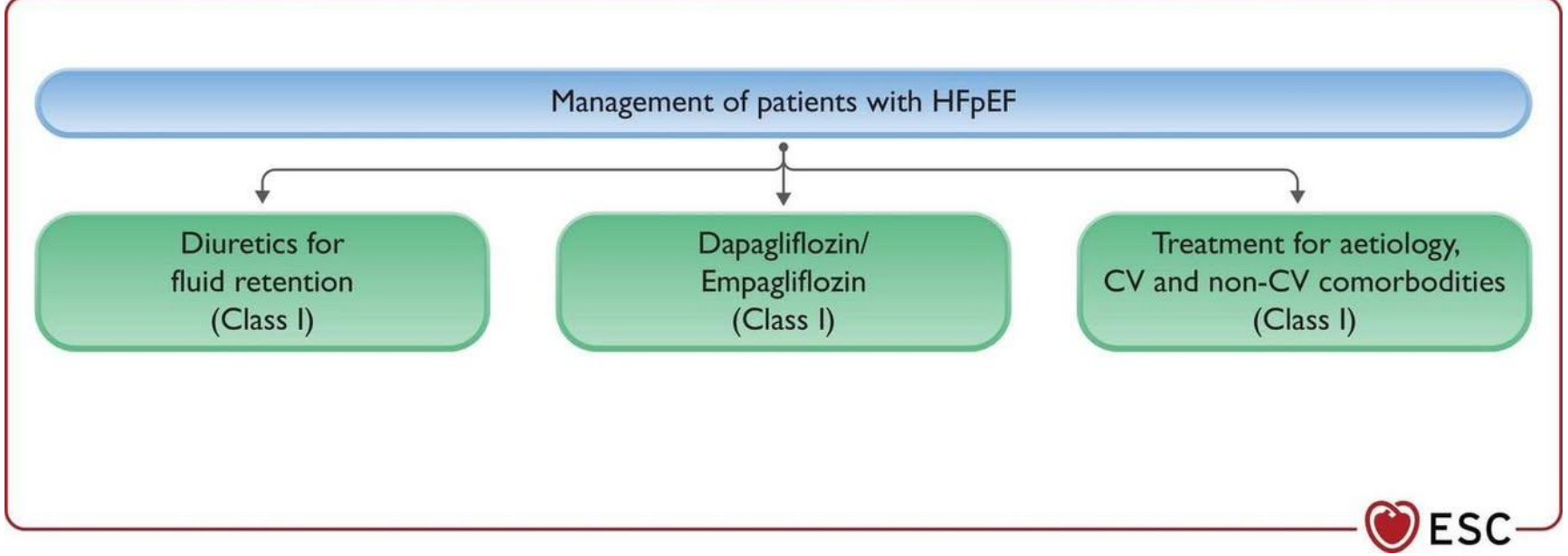
Emperor-Preserved

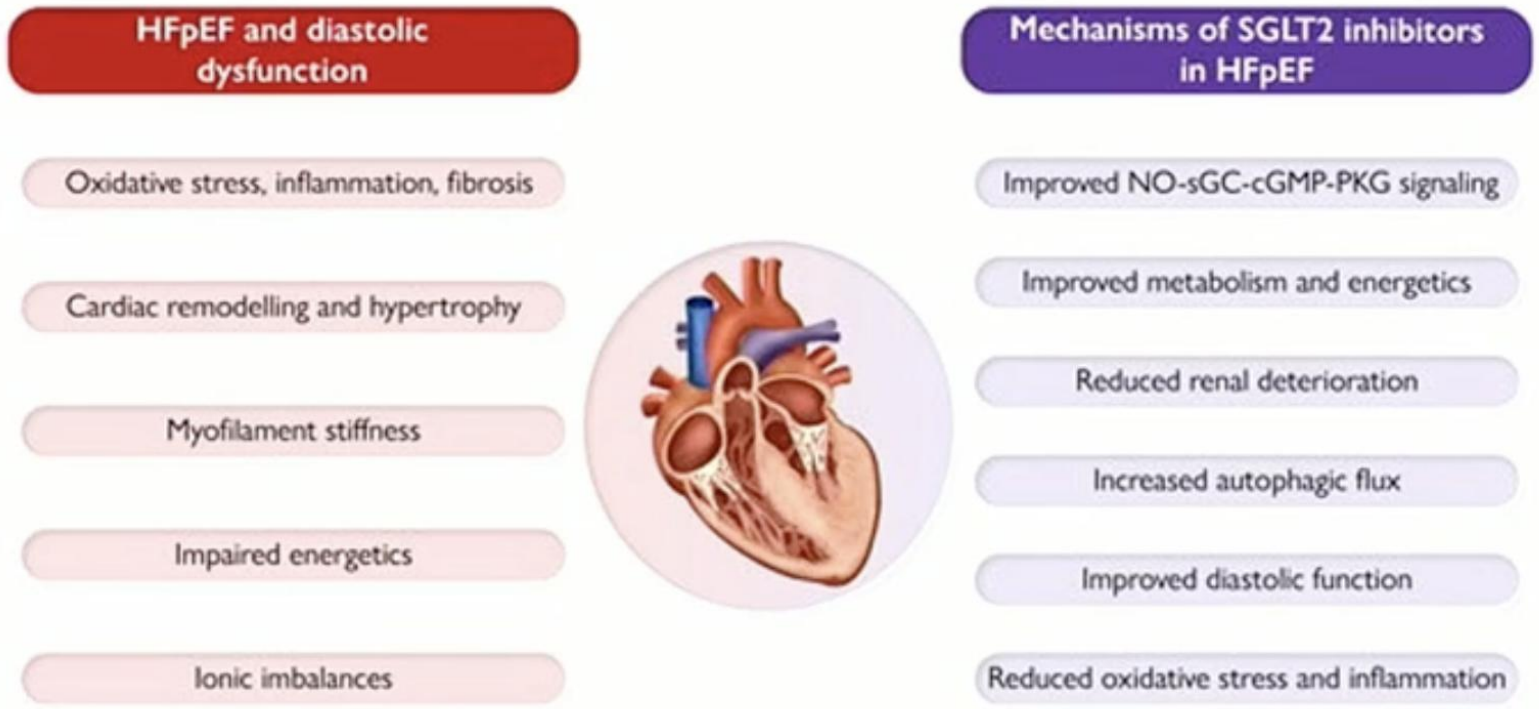


Deliver



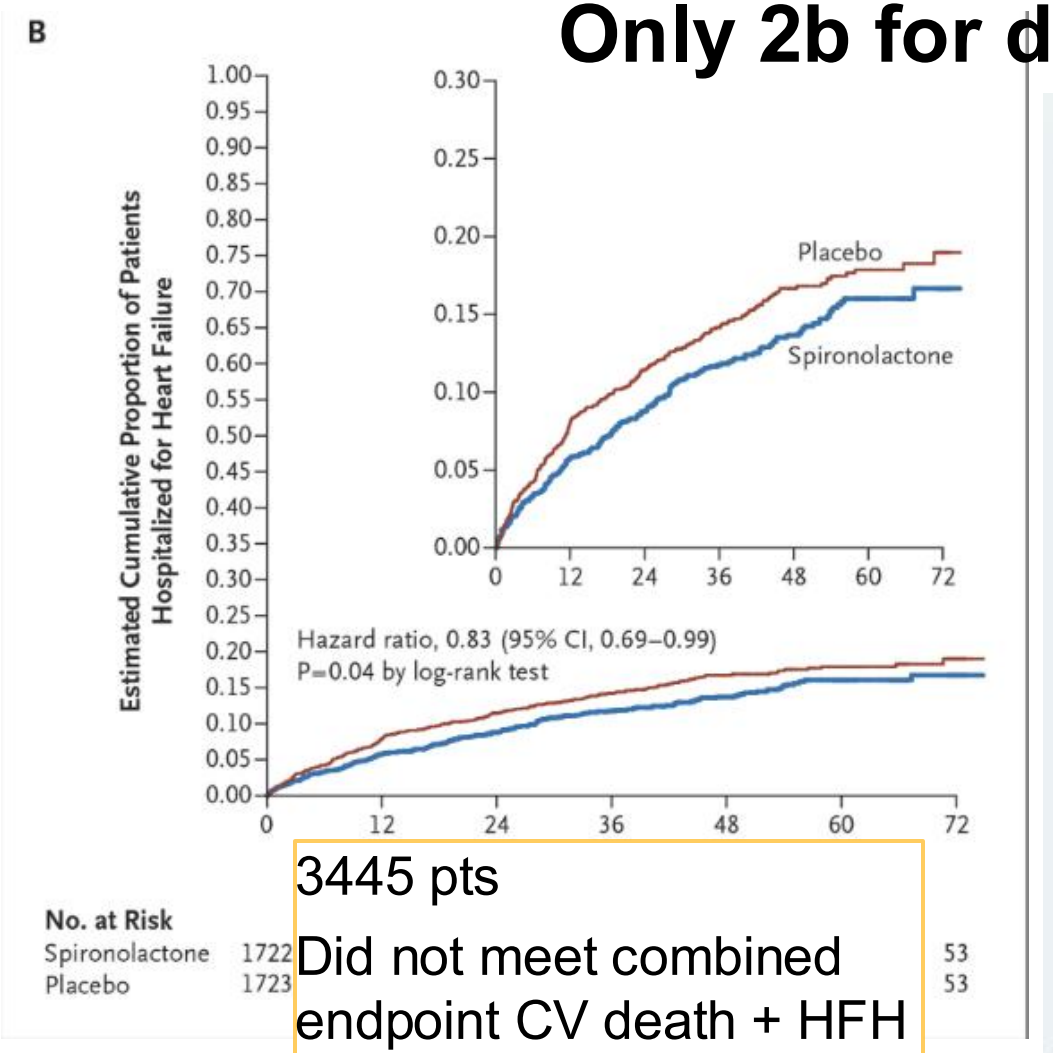
SGLT2i


Management of patients with HFpEF
Diuretics for fluid retention (Class I)
Dapagliflozin/ Empagliflozin (Class I)
Treatment for aetiology, CV and non-CV comorbodities (Class I)
ESC


HFpEF and diastolic dysfunction
Oxidative stress, inflammation, fibrosis
Cardiac remodelling and hypertrophy
Myofilament stiffness
Impaired energetics
Ionic imbalances
Mechanisms of SGLT2 inhibitors in HFpEF
Improved NO-sGC-cGMP-PKG signaling
Improved metabolism and energetics
Reduced renal deterioration
Increased autophagic flux
Improved diastolic function
Reduced oxidative stress and inflammation

MRA – spironolactone – TOPCAT – "Americas"

Only 2b for decreasing HFH

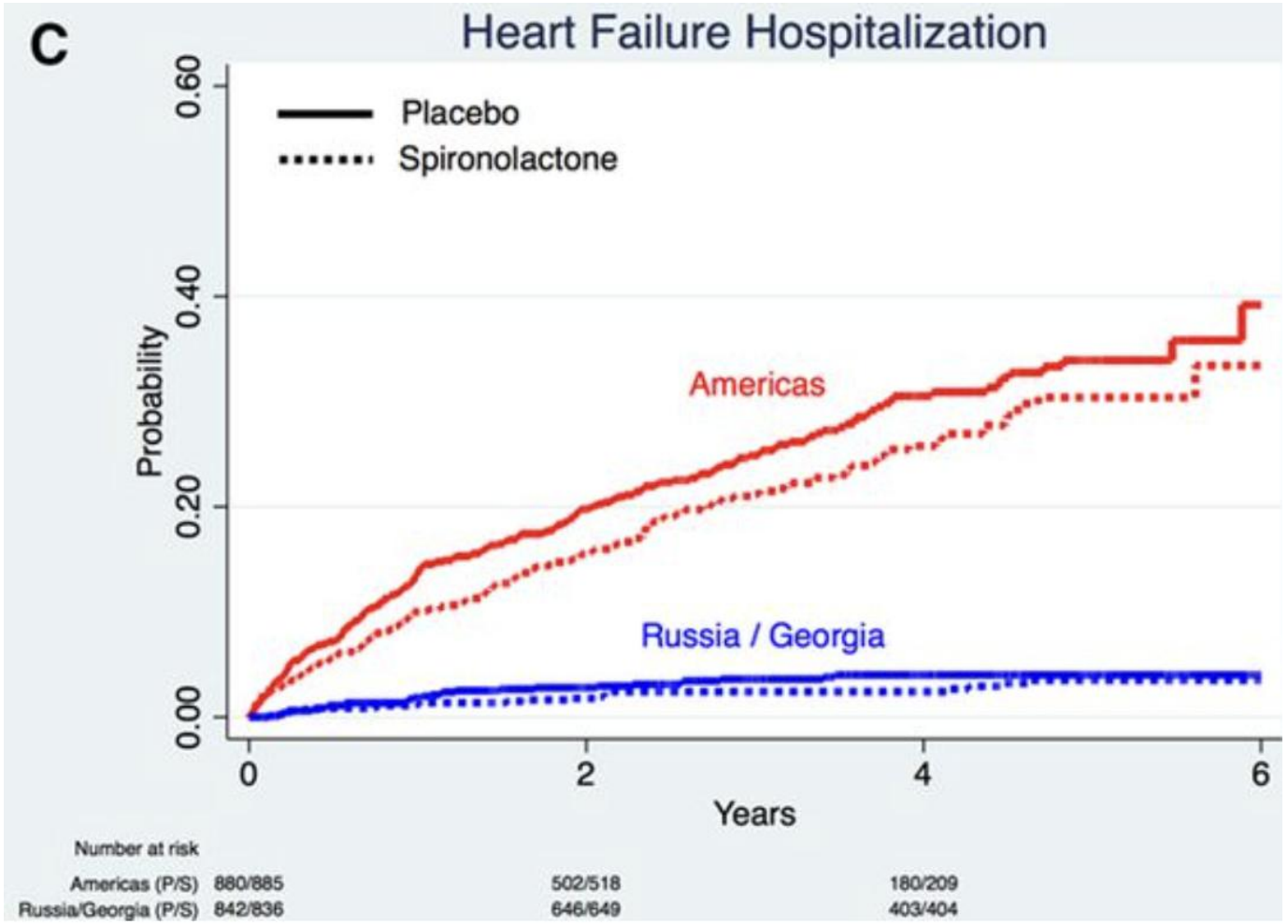


3445 pts

Did not meet combined endpoint CV death + HFH

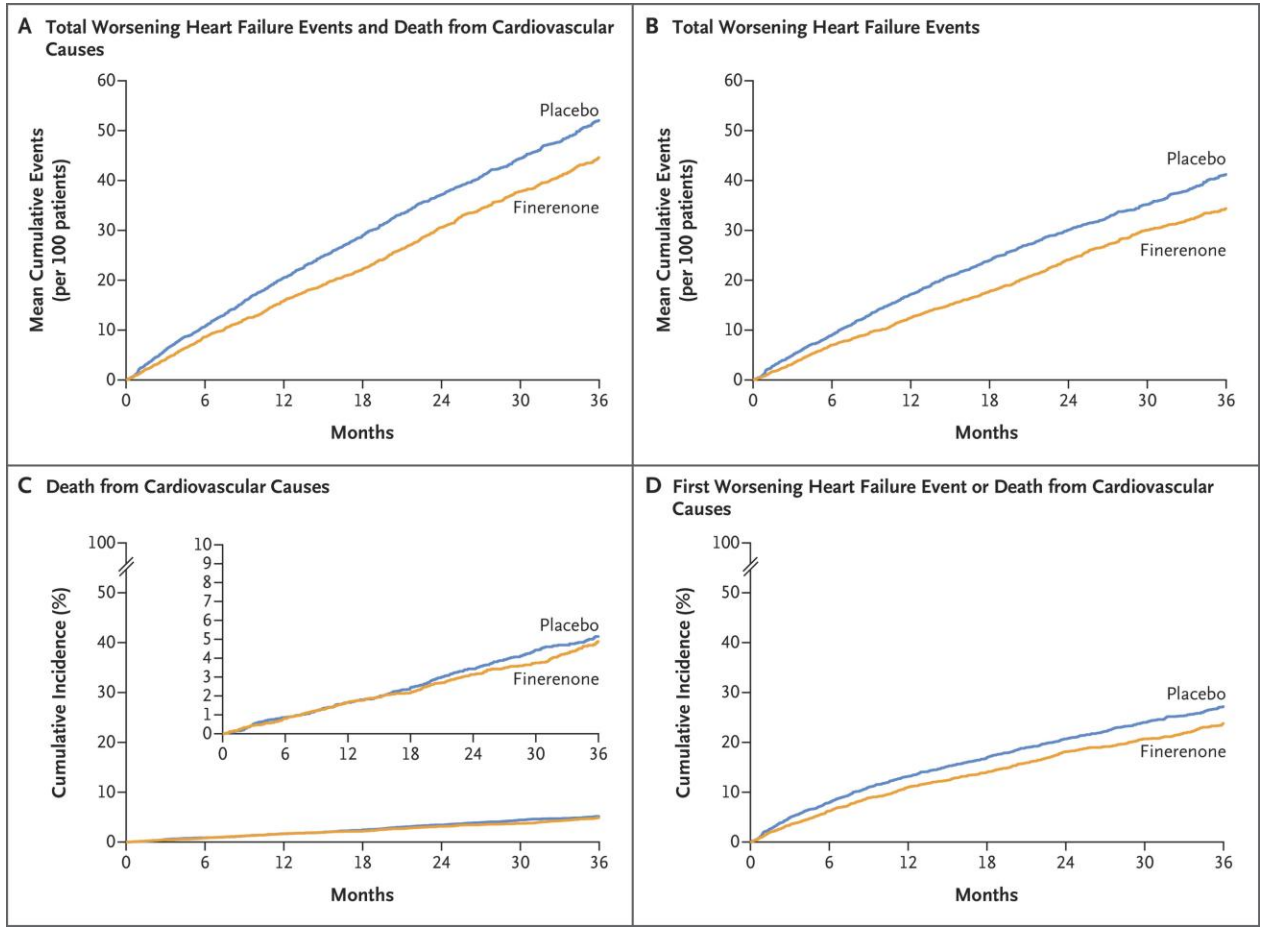
HF hosp 12% vs 14%

Rise in Cr and K



MRA – Finerenone → FINEARTS-HF Trial - 2024

- **N= 6016, LVEF ≥ 40%, Phase III**
- **Design:** Randomized, placebo-controlled, HFmrEF and HFpEF
- **Endpoint**: Combo CV death + HFH
- **Results**: 16% risk reduction in primary endpoint (RR = 0.84; P =0.007); 18% reduction in HF hospitalizations
- Benefit independent of SGLT2i



MRA - finerenone

FIGARO-DKD and FIDELIO-DKD showed benefit in patients with CKD and DM2 to reduced hospitalizations

ESC -→ 1a → second pillar next to SGLT2i especially in patients with CKD and DM2

Recommendations	Class[a]	Level[b]
In patients with T2DM and CKD,[c] SGLT2 inhibitors are recommended to reduce the risk of HF hospitalization or CV death.[35]	I	A
In patients with T2DM and CKD,[c] finerenone is recommended to reduce the risk of HF hospitalization.[10,11,34,40]	I	A

GLP1 RA → STEP-HFpEF Trial – Semaglutide - 2023

Trial: RCT in obese HFpEF pts w/wo DM2

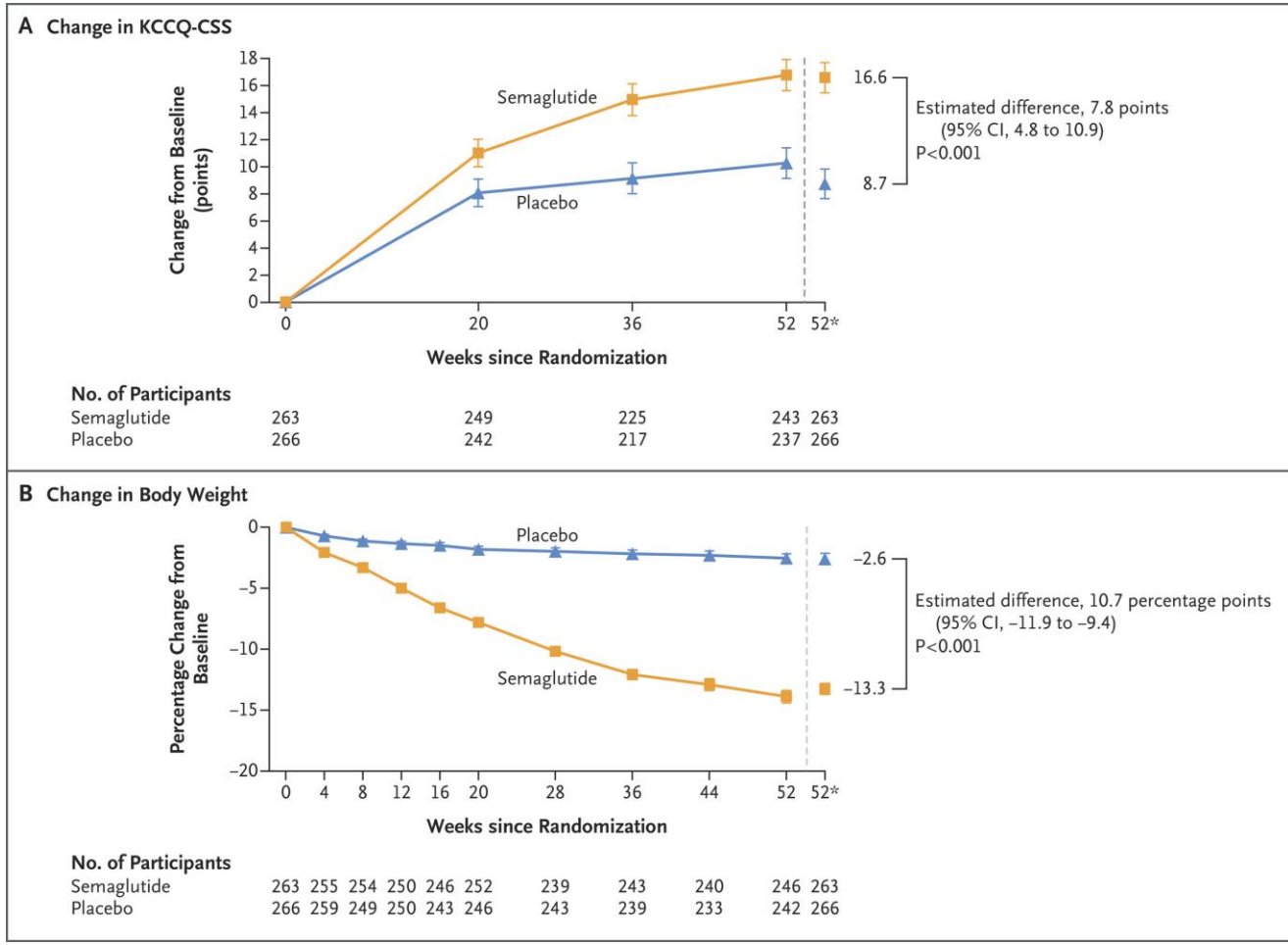
Design: 600 pts, semaglutide vs placebo, 52w

Endpoints: KCCQ-CSS change, wt change

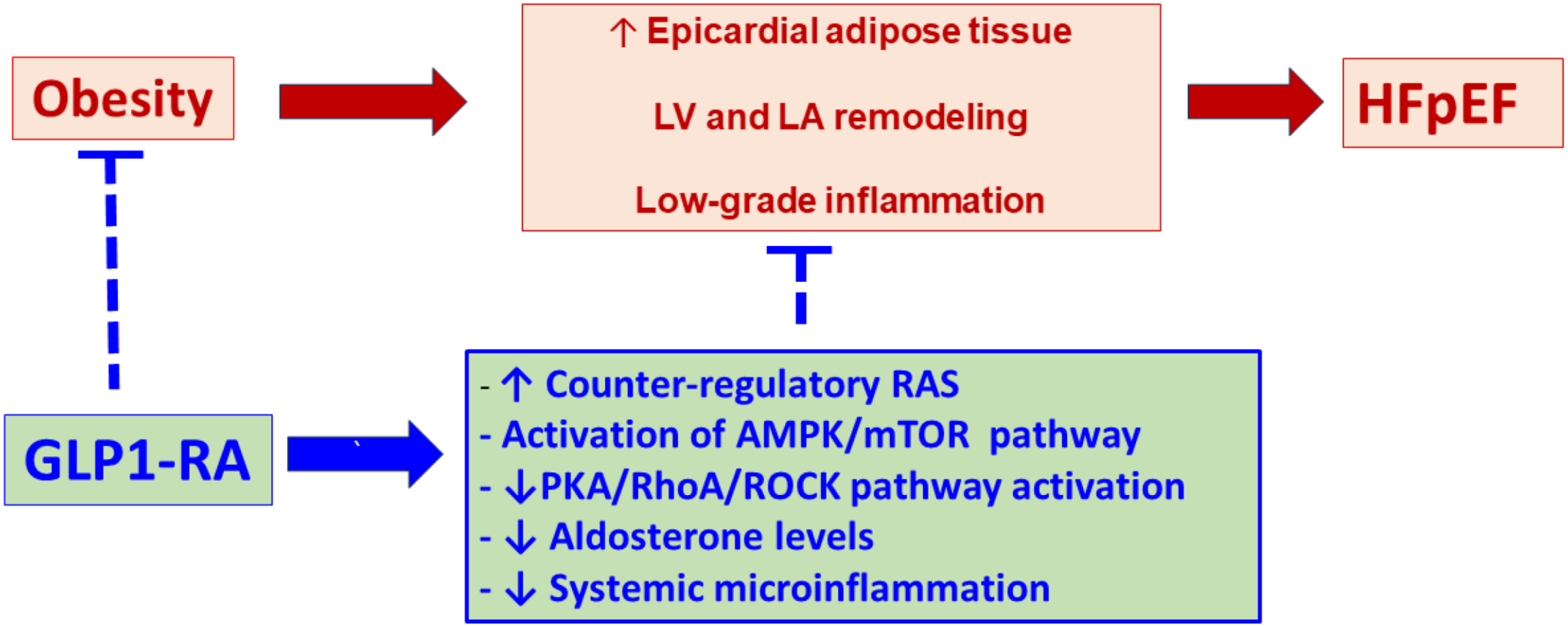
6MWD, CRP, hierarchal composite

Results:

- **Improvement of KCCQ-CSS (7.3 pts p< 0.001)**
- **Weight -9.8% vs 3.4%**
- **6MWD + 14m**
- **CRP -33%**



GLP1 RA → help symptoms, reduce plasma volume, weight loss, ? Decrease CV events



GIP/GLP1-RA → Tirzepatide (mounjaro) → SUMMIT

2024

N = 731

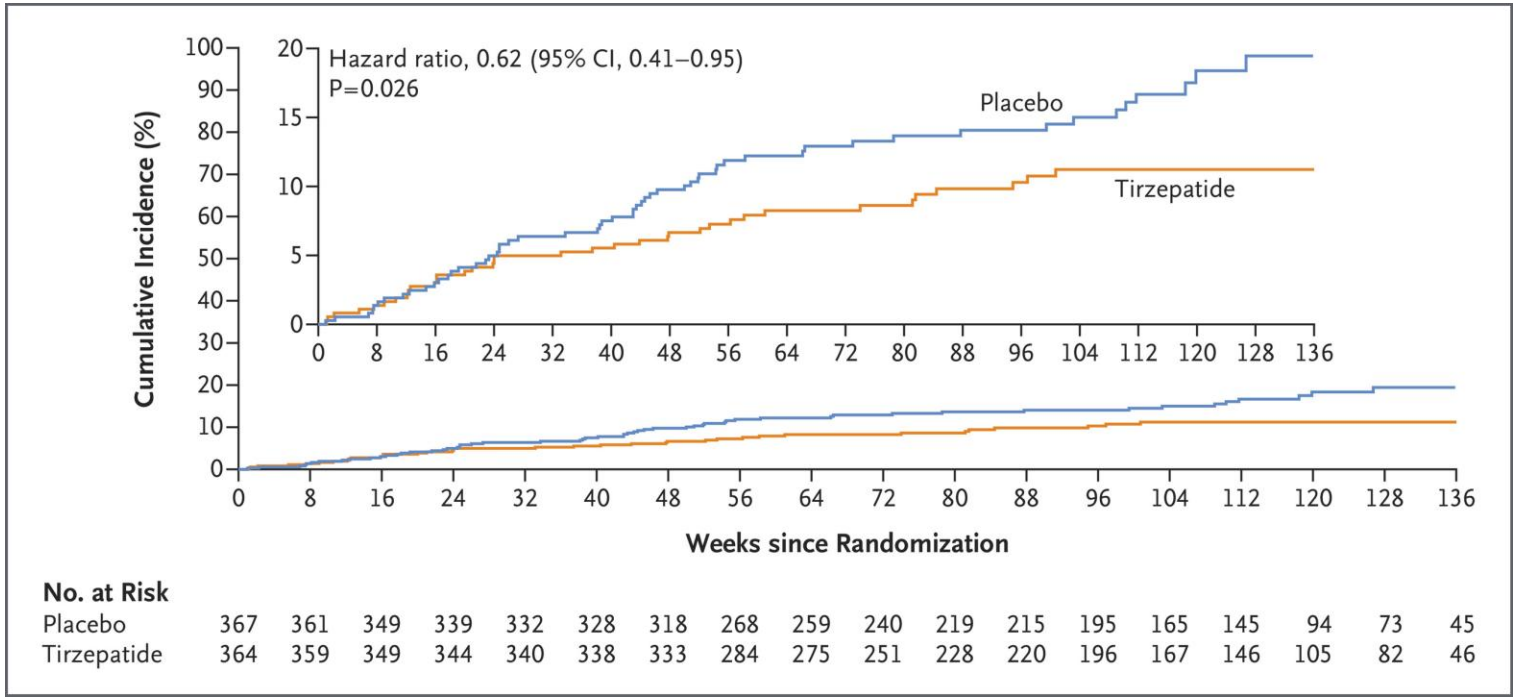
RCT tirzepatide vs placebo

HFpEF and BMI ≥ 30; 52 wks

Tirzepatide 5, 10 and 15 mg /wk vs placebo

Composite of adjudicated death from CV

Causes or worsening HF event



Results

38% risk reduction in time to first occurrence of HF outcomes

KCCQ-CSS 24.8 points vs 15.0 points

Body weight reduction 15.7% vs 2.2%

However, HF events number low → 29 HF events vs 52 despite n

We will see what FDA says…

ARNI/ARB – Sacubitril/Valsartan and Candesartan

Paragon HF

N = 4822

EF ≥ 45%

Sacubitril/Valsartan

Composite CV dea

HFH 690 vs 797 (p

valsartan group aw

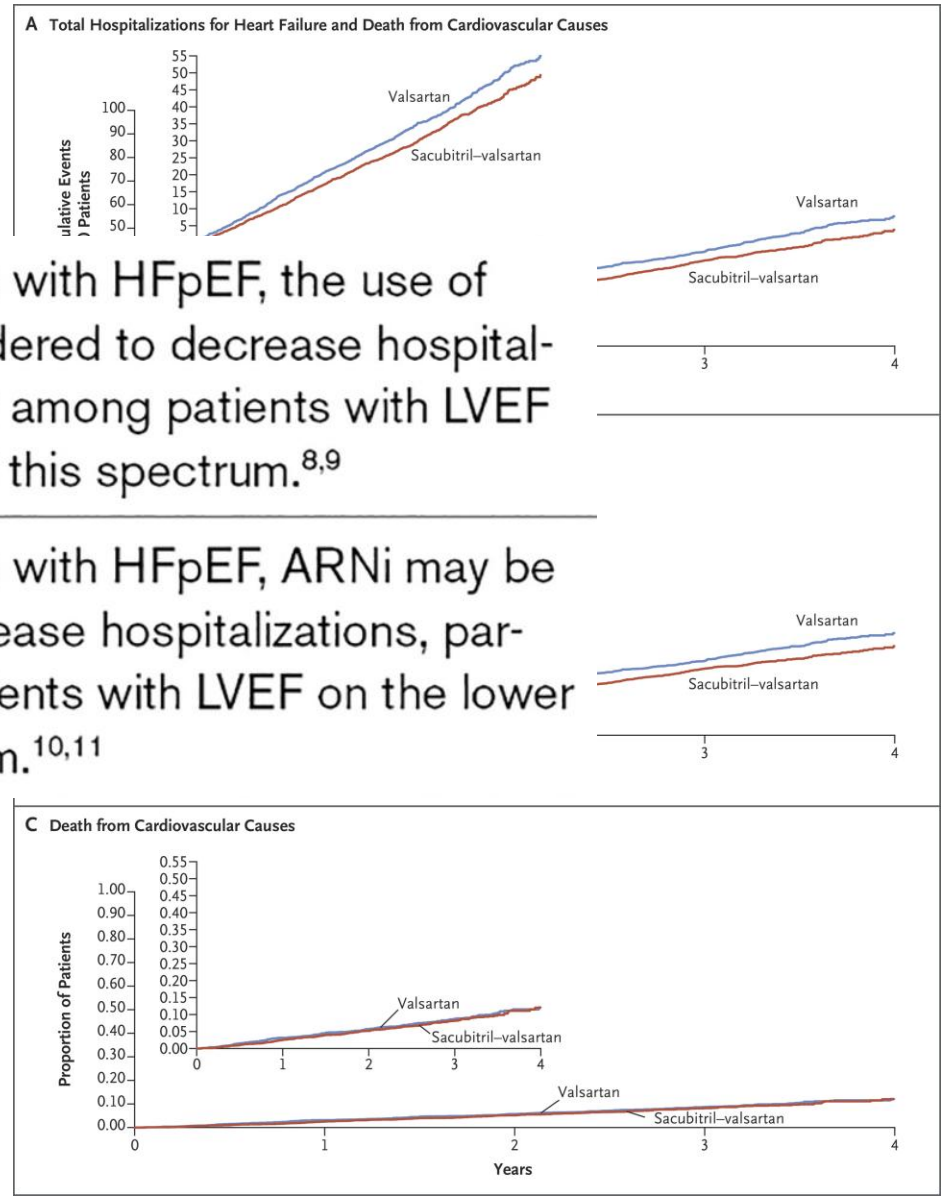
Subgroup – women

end of spectrum

2b	B-R
2b	B-R

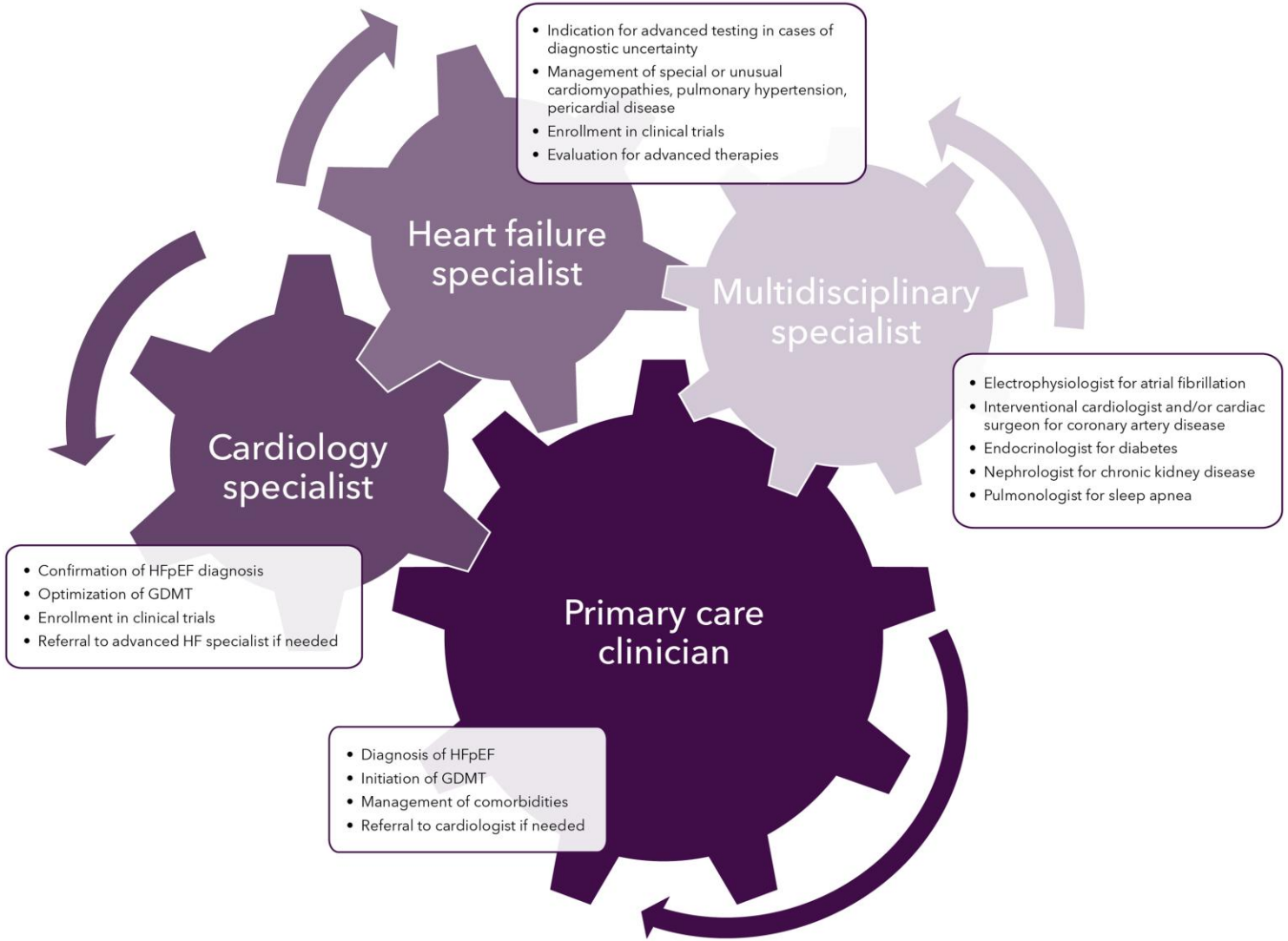
5. In selected patients with HFpEF, the use of ARB may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[8,9]

6. In selected patients with HFpEF, ARNi may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[10,11]



Charm Trial – candesartan in EF ≥40%, decreased HFH, similar in that on lower end of EF spectrum

Importance of multidisciplinary care



Spidey senses come out

Younger than 60 y/o

Don’t have typical comorbidities

Progressive symptoms

Relatively low QRS voltage

Family history

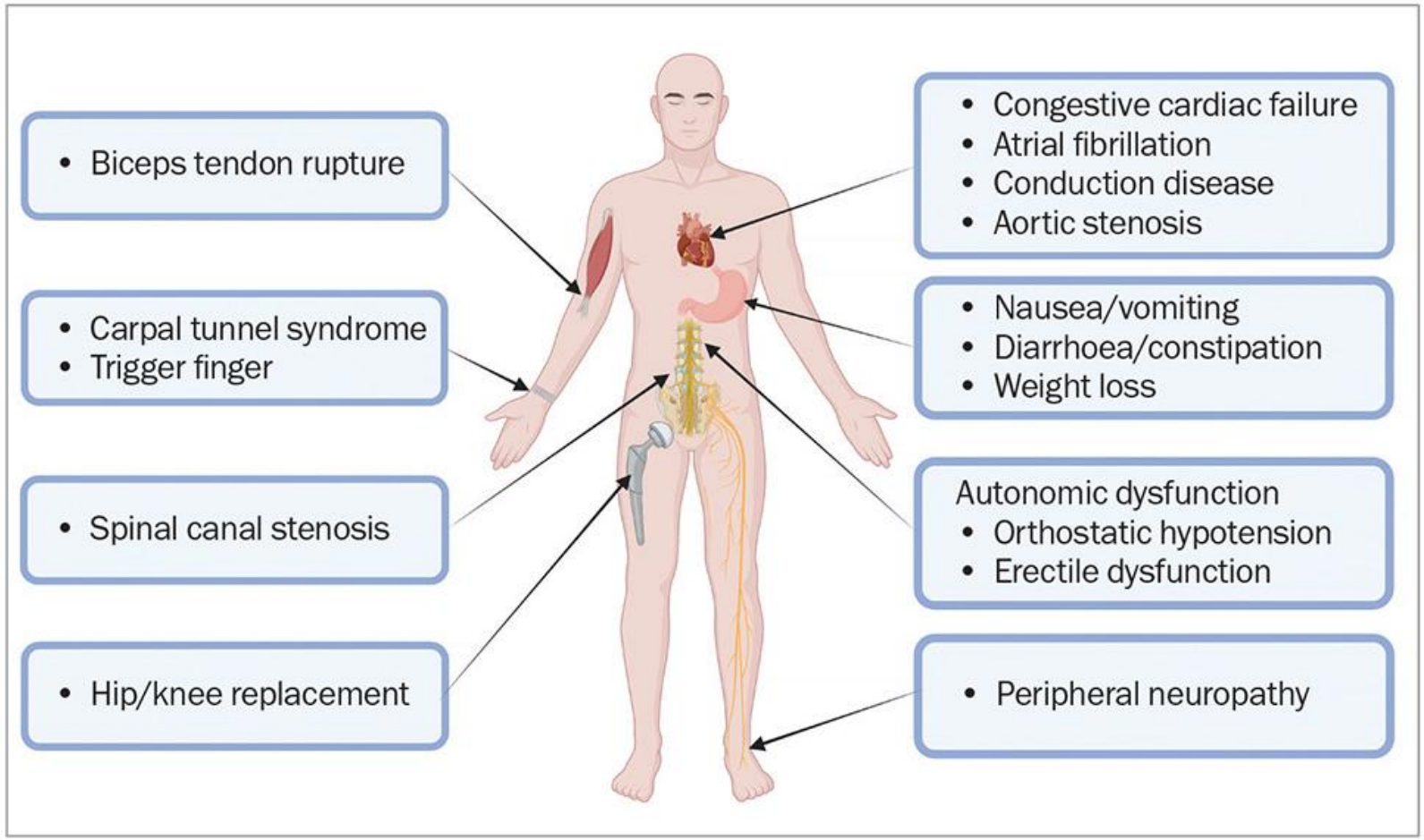
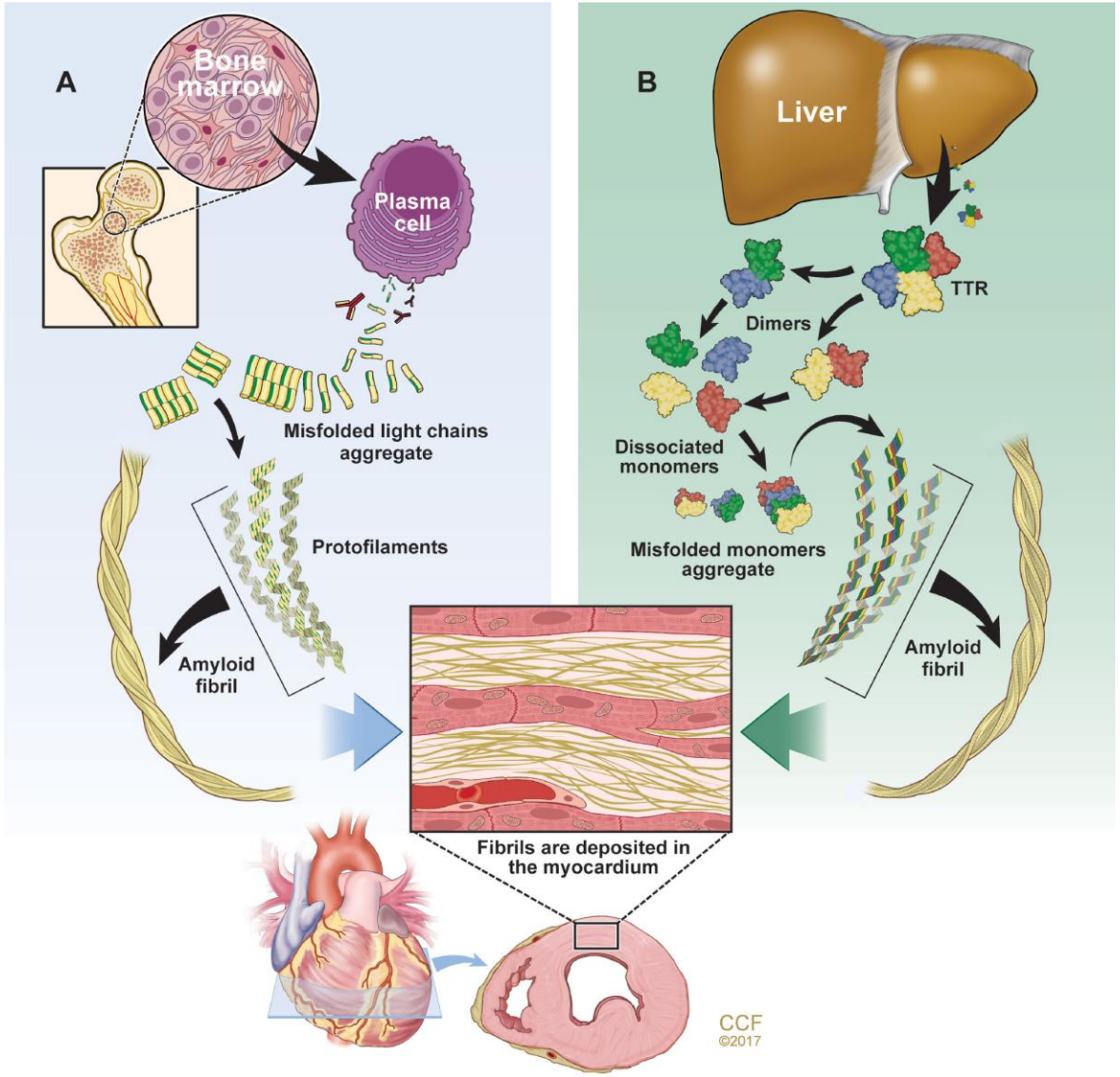
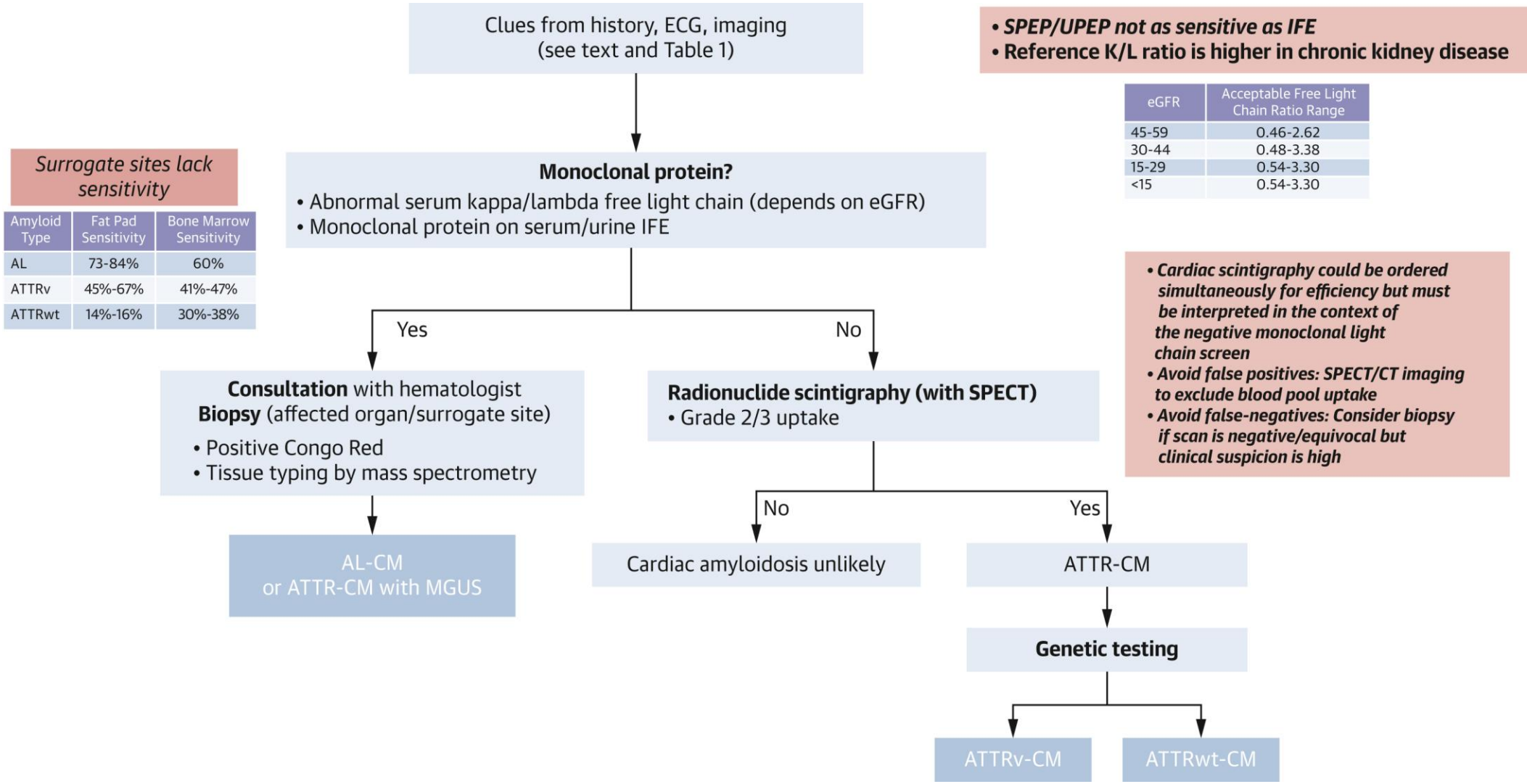


Figure 1. Common organ manifestations of transthyretin amyloidosis.
Created with Biorender.com.

Amyloid - Cardiac Amyloid – AL and ATTR



Amyloid – diagnostic algorithm



Surrogate sites lack sensitivity

Amyloid Type	Fat Pad Sensitivity	Bone Marrow Sensitivity
AL	73-84%	60%
ATTRv	45%-67%	41%-47%
ATTRwt	14%-16%	30%-38%

- ***SPEP/UPEP not as sensitive as IFE***
- **Reference K/L ratio is higher in chronic kidney disease**

eGFR	Acceptable Free Light Chain Ratio Range
45-59	0.46-2.62
30-44	0.48-3.38
15-29	0.54-3.30
<15	0.54-3.30

- ***Cardiac scintigraphy could be ordered simultaneously for efficiency but must be interpreted in the context of the negative monoclonal light chain screen***
- ***Avoid false positives: SPECT/CT imaging to exclude blood pool uptake***
- ***Avoid false-negatives: Consider biopsy if scan is negative/equivocal but clinical suspicion is high***

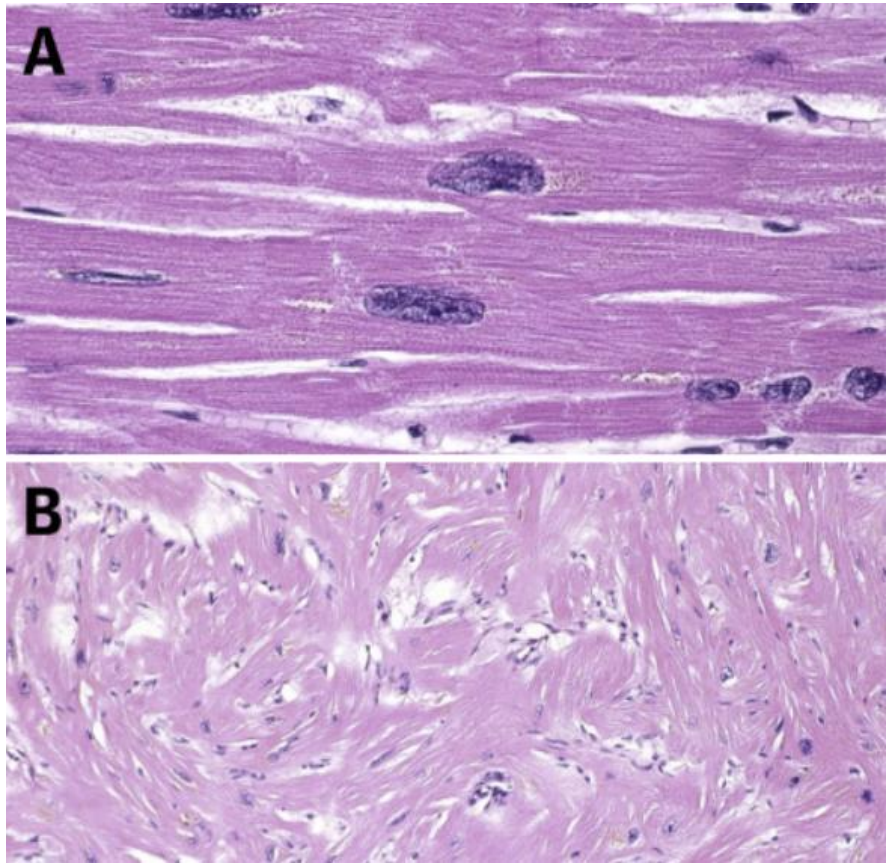
Amyloid – therapy

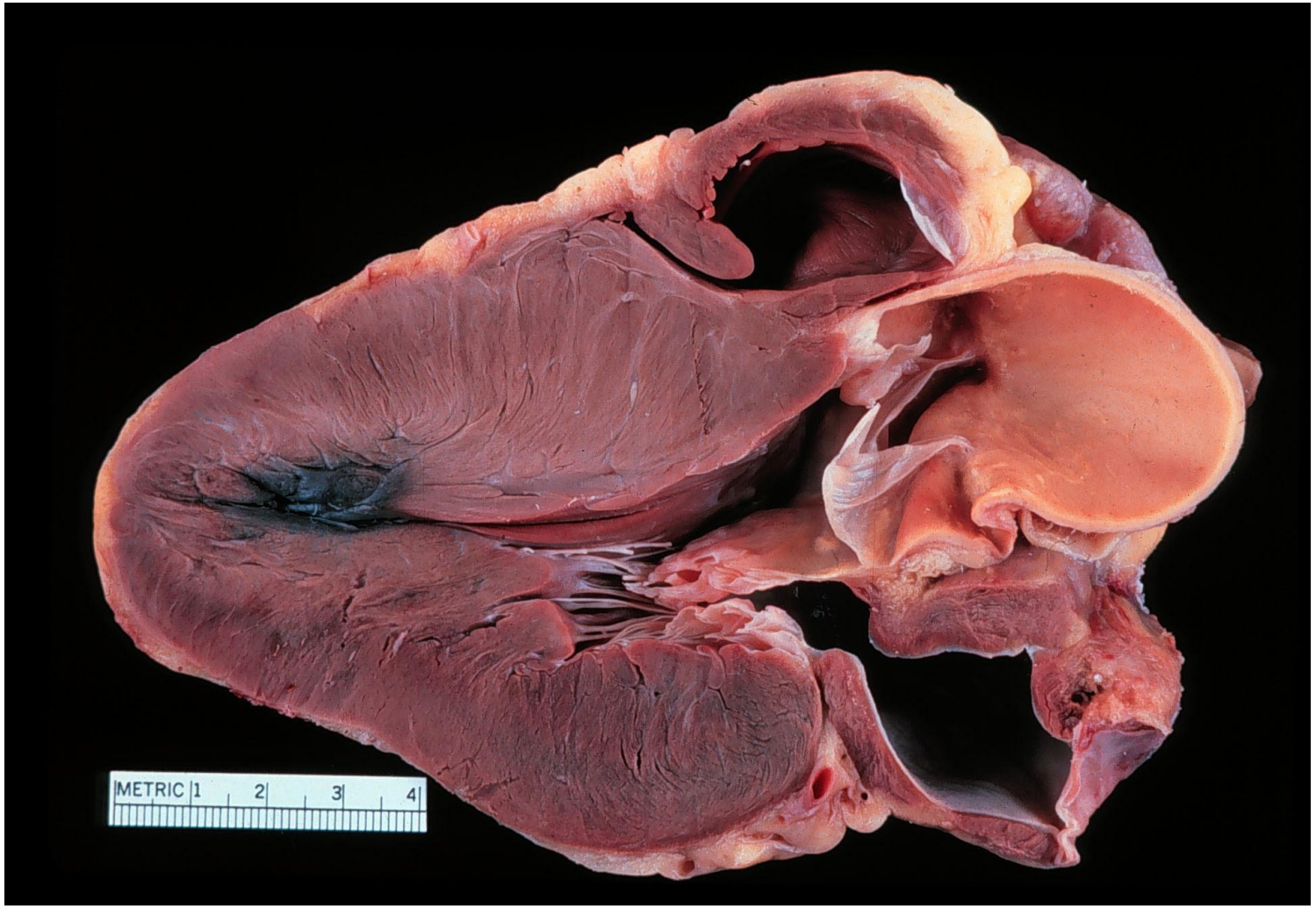
	Tafamidis	Acoramidis	Vutrisiran
Mechanism of action	Transthyretin stabilizer at T4 binding site	Transthyretin stabilizer hydrogen bonds at T4 binding site (mimicking the stabilizing transthyretin p.Thr139Met variant)	siRNA *TTR* gene silencer
Trial	ATTR-ACT[10]	ATTRibute-CM[11]	HELIOS-B[12]
Years conducted (published)	2013-2018 (2018)	2019-2023 (2024)	2019-2024 (2025)
Study type	Randomized, double-blind, placebo-controlled phase 3	Randomized, double-blind, placebo-controlled phase 3	Randomized, double-blind, placebo-controlled phase 3
Primary outcome	Death, CV hospitalizations win ratio: 1.7 (95% CI, 1.3-2.3)	Death, CV hospitalizations, NT-proBNP change, 6MWT change win ratio 1.8 (95% CI, 1.4-2.2)	Death, recurrent CV events: HR: 0.72 (95% CI: 0.56-0.93)
Side effects¶	Similar to placebo	Diarrhea (12%) Abdominal pain (5%)	Pain in extremity (15%) Arthralgia (11%) Dyspnea (7%) Vitamin A decreased (7%) Injection site reaction (4%)
Vitamin A supplementation	Not required	Not required	Supplement containing the locally RDA of vitamin A

Amyloid - Therapy

- **Unknowns**
  - What should initial therapy be?
  - Does combination therapy work?
  - Superiority of agents
  - How to monitor response?
  - Prevention of disease?
- **Next steps**
  - CRISPR-Cas9 → in vivo gene editing → permanent shut off
  - Depleter trials → monoclonal antibodies (NI006)

HCM – Hypertrophic Cardiomyopathy





Unexplained thickness > 1.5cm

AD pattern 60-70%

1/200 to 1/500 people globally

HCM – Hypertrophic Cardiomyopathy

- **Beta blockers and/or CCB reduce diastolic filling time and negative inotrope (HR 60-70 goal)**
- **Often intolerant of afterload reducing meds (SBP goal 120-135, avoid dehydration)**
- **Atrial and ventricular arrhythmias common → assess SCD risk**
- **Disease modifying therapies → myosin inhibitor therapy, myectomy, alcohol septal ablation**
  - HOCM > HCM
- **Needs familial screening**

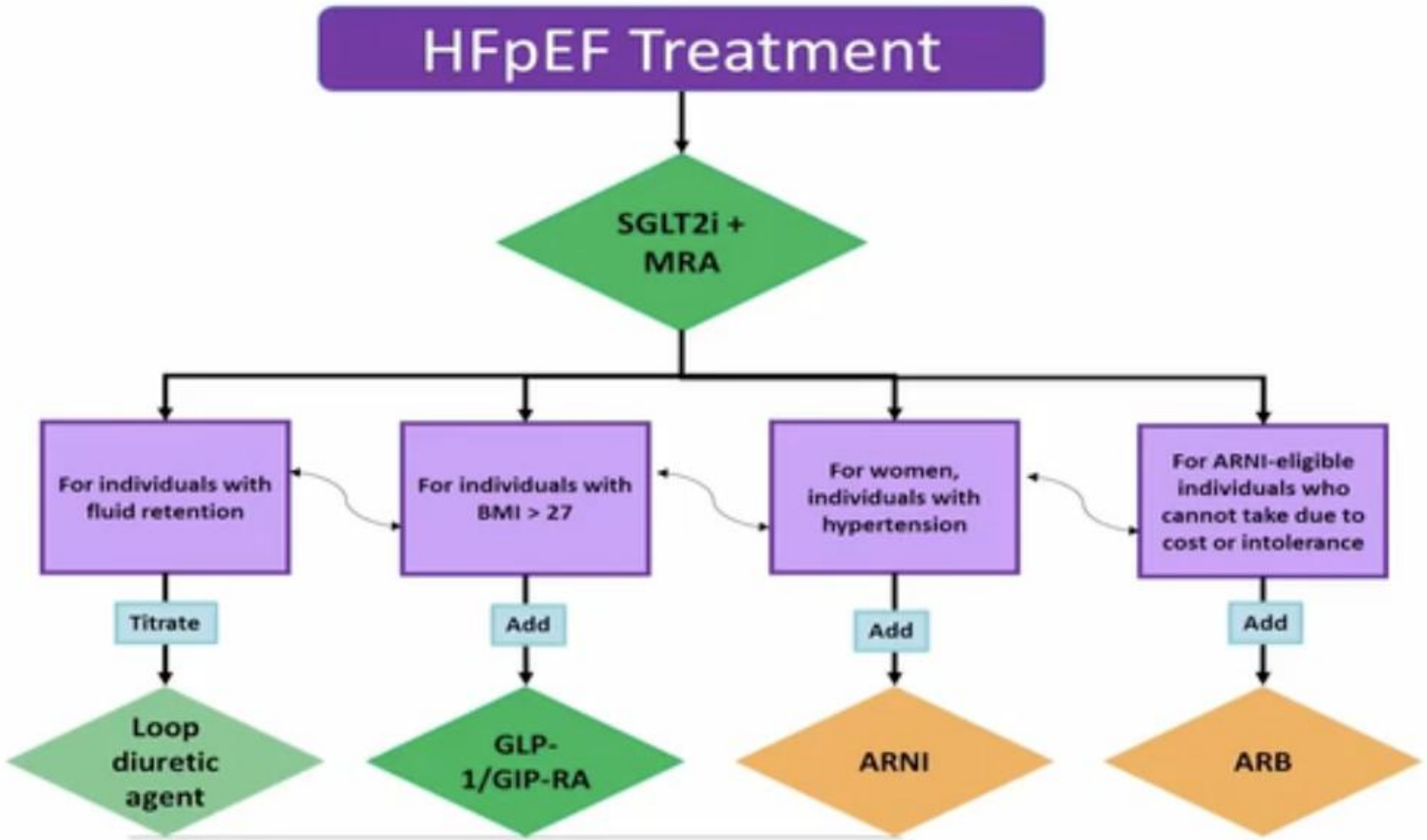
Familial screening --> genetics may change

- Proband gene + and family (-) → no further testing (unless genetics reclassified later)
- Proband gene + --> family gene + → intervals below
- Proband gene (-) → intervals below

Age of First-Degree Relative	Initiation of Screening	Repeat ECG, Echo
Pediatric		
Children and adolescents from genotype-positive families, and families with early onset disease	At the time HCM is diagnosed in another family member	Every 1-2 y
All other children and adolescents	At any time after HCM is diagnosed in a family member but no later than puberty	Every 2-3 y
Adults	At the time HCM is diagnosed in another family member	Every 3-5 y

Ommen et al. Circulation 2024

HFpEF by the Guidelines



Heidenreich P et al. 2022 ACC/AHA/HFSA Heart Failure Guideline.

Adapted from Kittleson et al. J Am Coll Cardiol. 2023 May, 81 (18) 1835–1878

Summary points and hot takes

HFpEF is now the more prevalent form of HF

HFpEF is a clinical diagnosis → HF, EF ≥ 50%, resting or provokable increased LV filling pressures

Must perturb the system to rule in or out

We now have GDMT for HFpEF!

- SGLT2i, MRA, GLP1 RA (BMI >27), +/- ARNI/ARB

Evaluate for other cardiomyopathies – HCM, Amyloid etc

(we have disease modifying therapies for these too!)

Questions

Works cited

1. Bozkurt B, Ahmad T, Alexander K, et al. HF STATS 2024: heart failure epidemiology and outcomes statistics an updated 2024 Report from the Heart Failure Society of America. *J Card Fail* 2025;31:66-1164.
2. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol* 2017;14:591-602.
3. Borlaug BA, Sharma K, Shah SJ, Ho JE. Heart failure with preserved ejection fraction: JACC Scientific Statement. *J Am Coll Cardiol* 2023;81:1810-34.
4. Larson KF, Malik A, Brozovich FV. Aging and heart failure with preserved ejection fraction. *Compr Physiol* 2022;12:3813-22.
5. Owan TE, Hodge DO, Herges RM, et al. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006;355:251-9.
6. Oktay AA, Rich JD, Shah SJ. The emerging epidemic of heart failure with preserved ejection fraction. *Curr Heart Fail Rep* 2013;10:401-10.
7. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: Executive Summary. *Circulation* 2022;145:e876-e94.
8. https://www.nejm.org/doi/full/10.1056/NEJMoa2107038 – emperor-preserved
9. https://www.nejm.org/doi/full/10.1056/NEJMoa2206286 - deliver
10. https://www.nejm.org/doi/full/10.1056/NEJMoa1313731 – TOPCAT
11. FINEARTS-HF https://www.nejm.org/doi/full/10.1056/NEJMoa2407107