Brigham and Women's Hospital
Founding Member, Mass General Brigham

TREATMENT OF HEART FAILURE IN 2026

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- Research focus: Cardio-Oncology

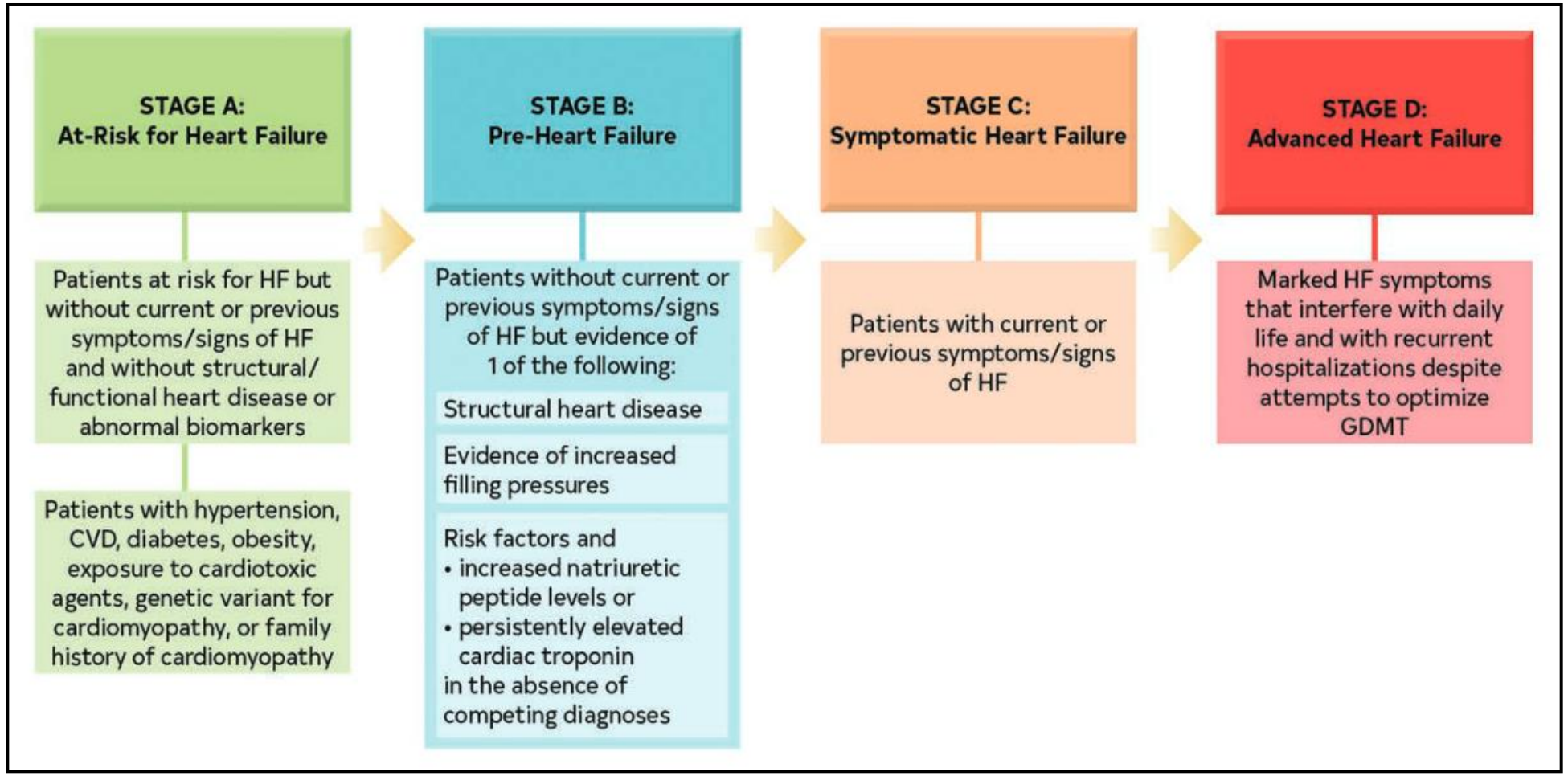
DISCLOSURES

- Research Support: Bristol Myers Squibb
- Consulting Fees: AstraZeneca, Takeda Oncology, and Teledoc
- Speaker Fees: Medical Learning Institute, Inc.

OBJECTIVES

- Focus on out-patient medical management of HF
- Foundational therapies
  - HFrEF: 4 pillars GDMT
  - HFpEF: from no GDMT → multiple disease modifying therapies
- Phenotype guided add-ons
- Novel HF therapies

Stages of Heart Failure



Heidenreich et al. Circulation 2022;145:e876-894.

Stage A HF: Primary Prevention of HF

- SBP < 130/80 mm Hg

- Age > 40, ≥ 1 CV RF
- BNP ≥ 50 pg/ml

- PREVENT- HF score

COR	LOE	Recommendations
1	A	1. In patients with hypertension, blood pressure should be controlled in accordance with GDMT for hypertension to prevent symptomatic HF.[46,111–118]
1	A	2. In patients with type 2 diabetes and either established cardiovascular disease or at high cardiovascular risk, SGLT2i should be used to prevent hospitalizations for HF.[119–121]
1	B-NR	3. In the general population, healthy lifestyle habits such as regular physical activity, maintaining normal weight, healthy dietary patterns, and avoiding smoking are helpful to reduce future risk of HF.[122–130]
2a	B-R	4. For patients at risk of developing HF, natriuretic peptide biomarker–based screening followed by team-based care, including a cardiovascular specialist optimizing GDMT, can be useful to prevent the development of LV dysfunction (systolic or diastolic) or new-onset HF.[131,132]
2a	B-NR	5. In the general population, validated multivariable risk scores can be useful to estimate subsequent risk of incident HF.[133–135]

Heidenreich et al. Circulation 2022;145:e876-894.
https://professional.heart.org/en/guidelines-and-statements/prevent-calculator

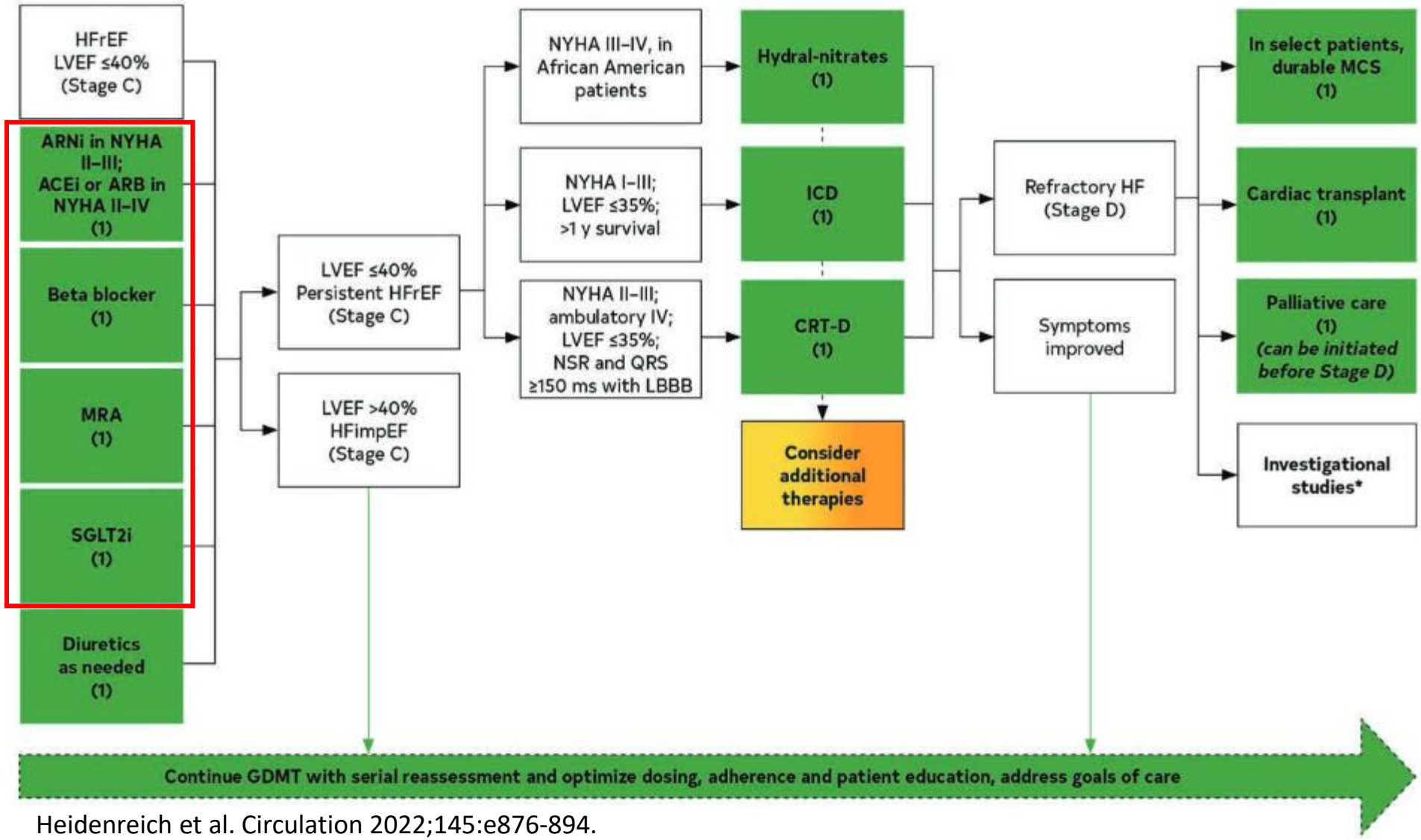
Stage B HF:
Preventing Symptomatic HF in Pre-HF

- ACEi + BB for LVEF ≤ 40%
- ARB for ACEi intolerant pts
- Statins for post-MI or ACS pts – *goal LDL < 55 mg/dL*
- ICD for NYHA Class I pts w/ LVEF ≤ 30%, 40 days after MI or 3 mths after revascularization
- *Non-dihydropyridine CCB and thiozolidinediones should be avoided in LVEF < 50%*

Heidenreich et al. Circulation 2022;145:e876-894.

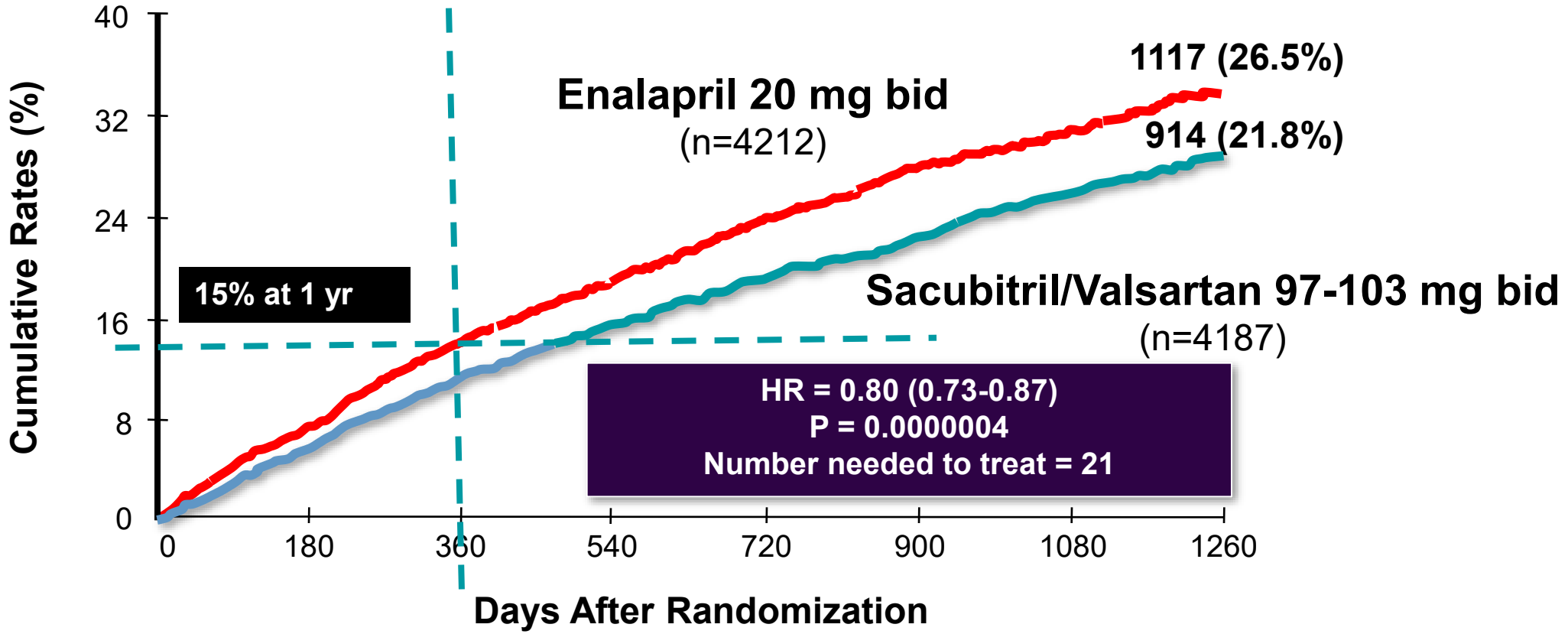
Stage C HF: Symptomatic HF

4 pillars of GDMT



Heidenreich et al. Circulation 2022;145:e876-894.

PARADIGM-HF: Primary Endpoint CV Death or HF Hospitalization



Major Side Effects: Hypotension, hyperkalemia, angioedema, renal dysfunction

McMurray JJ et al. N Engl J Med 2014;371:993-1004.

Guideline Update

2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

COR	LOE	Recommendations
I	B-R	ACEi OR ARB OR ARNI in conjunction with beta-blockers + MRA (where appropriate) is recommended for patients with chronic HFrEF to reduce morbidity and mortality.
I	B-R	In patients with chronic, symptomatic HFrEF NYHA class II or III who tolerate and ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality
III	B-R	ARNI should NOT be administered concomitantly with ACEi or within 36 hours of last ACEi dose
III	C=EO	ARNI should NOT be administered to patients with a history of angioedema

Yancy, et al. Circulation 2017;136:e137-161

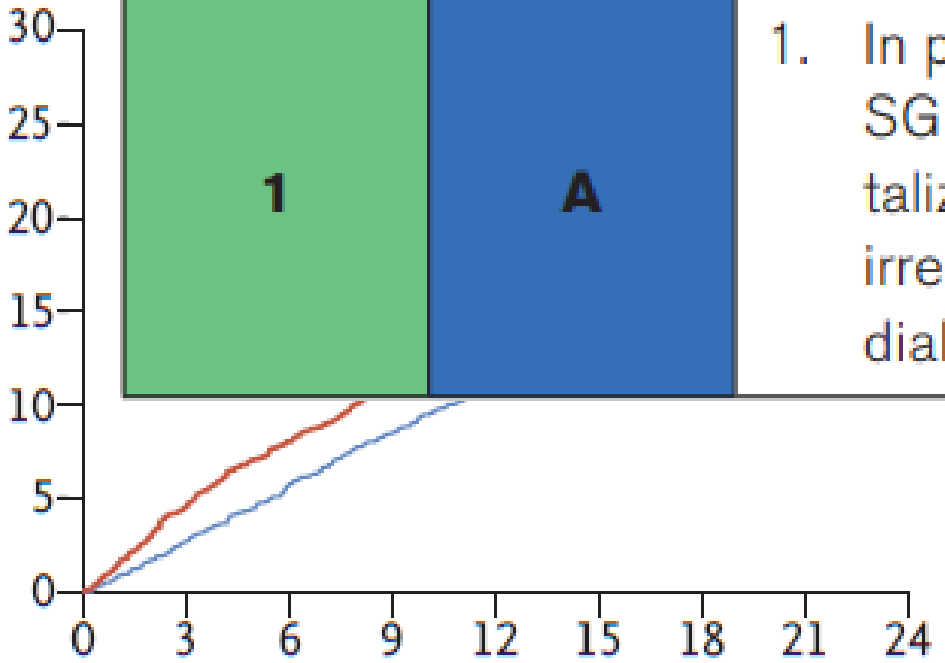
SGLT-2i for Symptomatic HFrEF

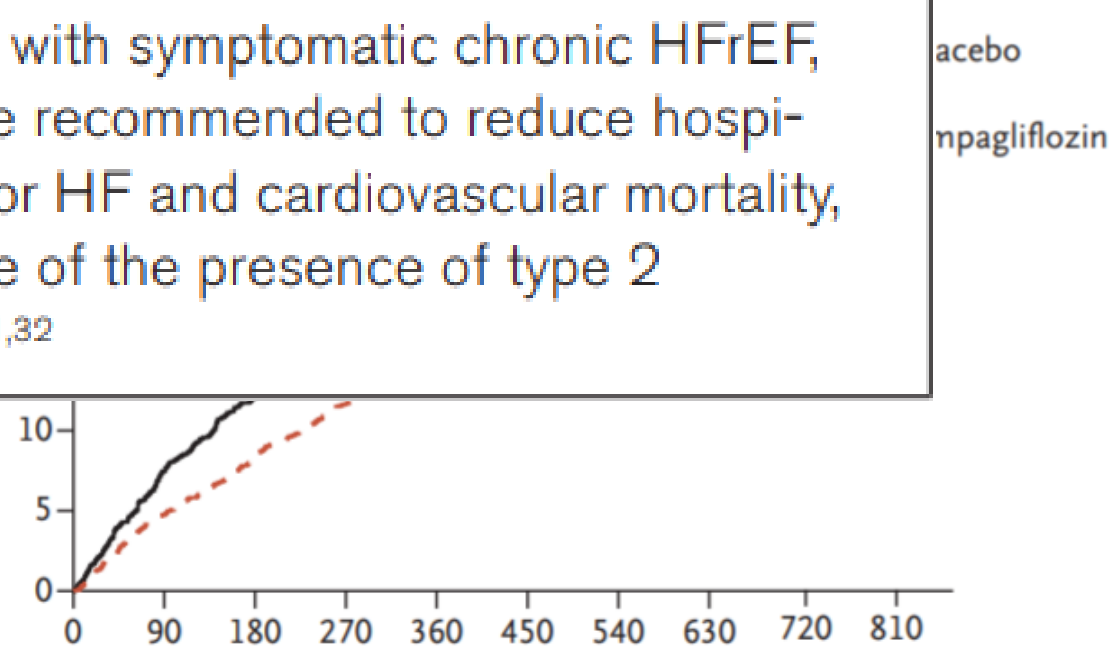
DAPA-HF:

CV Dea

EMPEROROR-REDUCED HF:

COR	LOE	Recommendation
1	A	1. In patients with symptomatic chronic HFrEF, SGLT2i are recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes.[31,32]



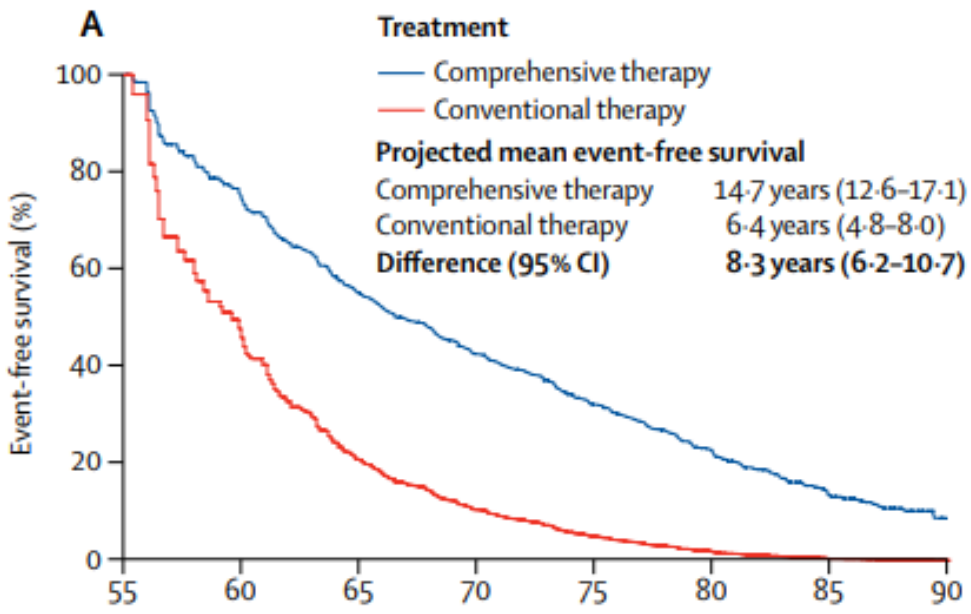


- Decrease progression of CKD

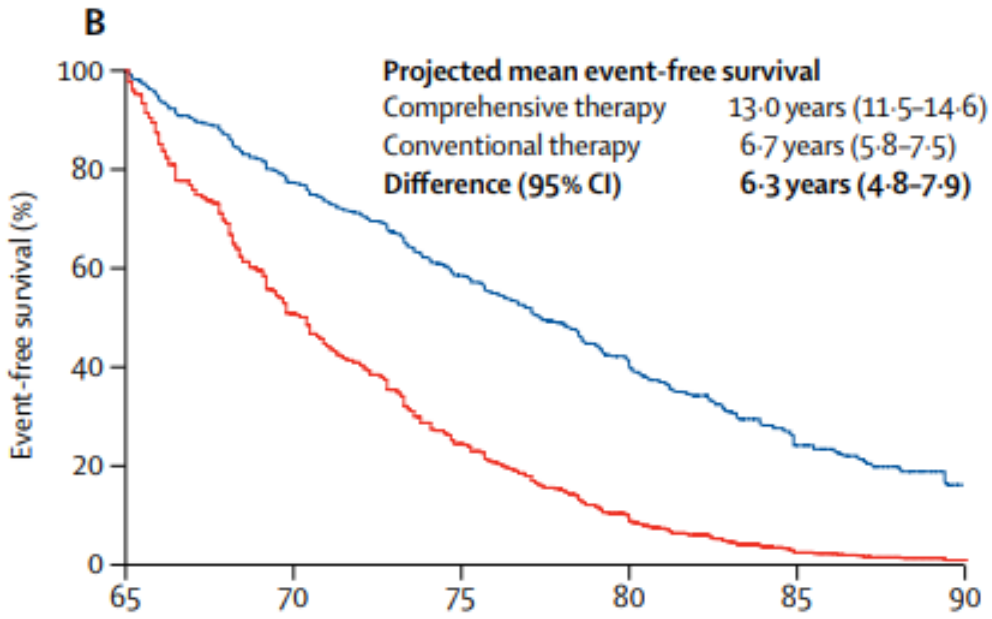
McMurray et al. NEJM 2019;381(21):1995; Packer et al. NEJM 2020;383(15):1413-24. .

Estimation of Lifetime Benefit of Comprehensive vs. Conventional HFrEF Therapy

Age ≥ 55 years



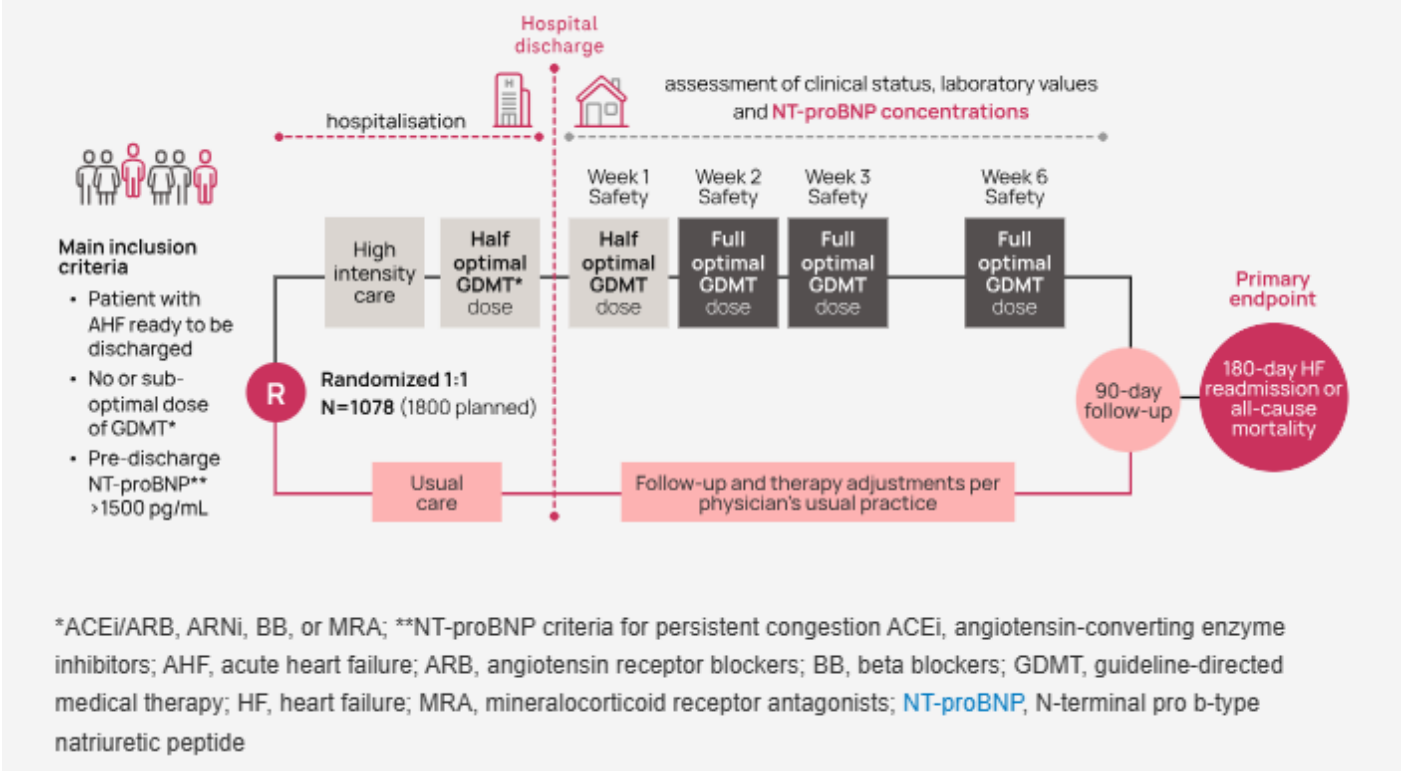
Age ≥ 65 years



Conventional: ACEi/ARB + beta-blocker
Comprehensive: ARNI + B-blocker + MRA + SGLT-2i

Vaduganathan et al. Lancet 2020;396:121-28.

STRONG-HF



*ACEi/ARB, ARNi, BB, or MRA; **NT-proBNP criteria for persistent congestion ACEi, angiotensin-converting enzyme inhibitors; AHF, acute heart failure; ARB, angiotensin receptor blockers; BB, beta blockers; GDMT, guideline-directed medical therapy; HF, heart failure; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro b-type natriuretic peptide

CV (cardiovascular) death	HF readmission	All-cause death
26% lower	44% lower	16% lower

Mebazaa et la. Lancet 2022;400:1938-52.

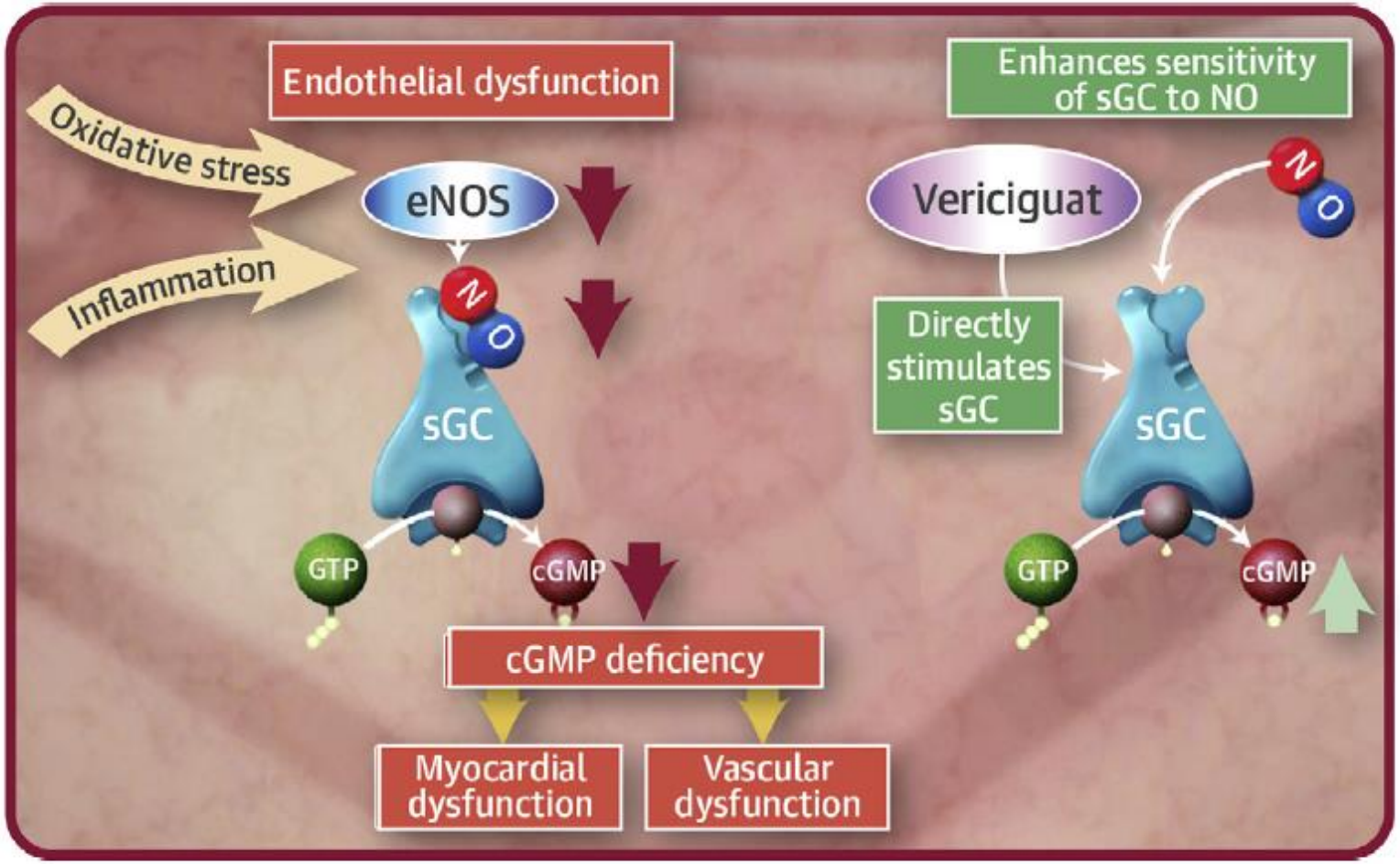
Question 1.

A 65 y.o. male w/ chronic HFrEF presents for a follow up visit after HF hospitalization. He reports dyspnea with 1 flight of stairs, 2 pillow orthopnea and mild lower extremity edema. His medications include sacubitril-valsartan 24-26 mg twice daily, spironolactone 25 mg daily, metoprolol succinate 25 mg daily and torsemide 80 mg daily. His exam reveals HR 85 bpm, BP 100/70 mm Hg, no JVD but mild HJR, clear lungs, RRR, systolic murmur c/w mitral regurgitation, and trace LE edema. Labs reveal Na 135 mEq/L, K 4.2 mEq/L, BUN 40 mg/dL, Cr 1.8 mg/dL, eGFR 41 ml/min/1.73m2, NT-proBNP 1500 pg/mL.

What is the next best step in his management?

A. Increase sacubitril-valsartan to 49-51 mg twice daily
B. Add empagliflozin 10 mg daily
C. Increase metoprolol succinate to 50 mg daily
D. Increases torsemide to 80 mg twice daily

Vericiguat: Mechanism of Action



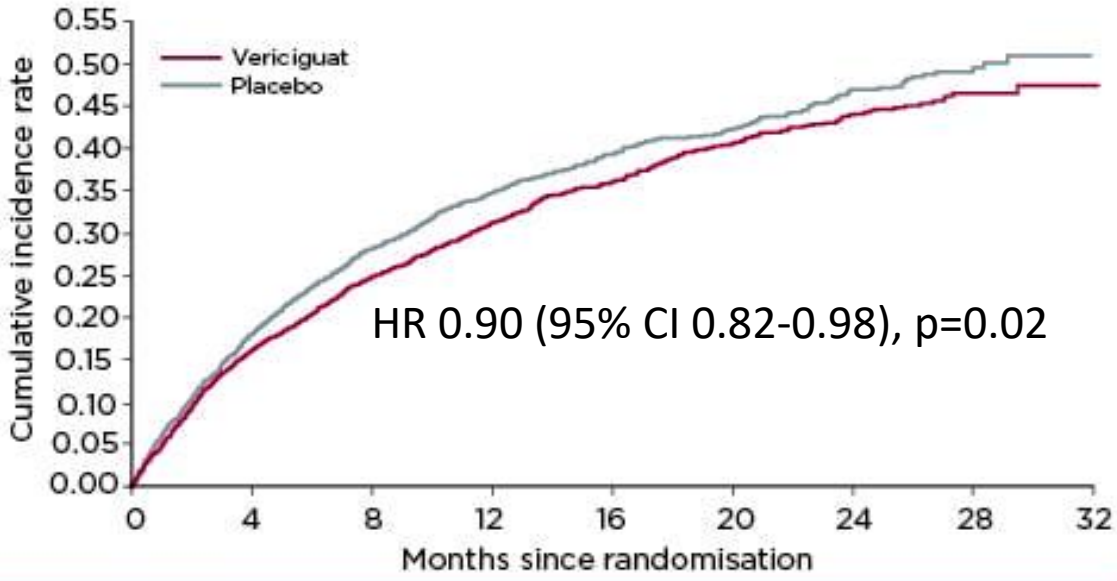
Armstrong, P.W. et al. J Am Coll Cardiol HF. 2018;6(2):96-104.

VICTORIA

- N=5,050 pts
- Symptomatic HFrEF
- LVEF ≤ 45%
- Elevated natriuretic peptides
- HF hospitalization w/in 6 mths or IV diuretics w/in 3 mths
- 60% on ACEi/ARB, BB and MRA

- Reduction in HF hosp but not CV death
- Side effects: anemia and hypotension

CV Death or HF Hospitalization



Number of subjects at risk									
Vericiguat	2,526	2,099	1,621	1,154	826	577	348	125	1
Placebo	2,524	2,053	1,555	1,097	772	559	324	110	0

Armstrong et al. NEJM 2020;382(20):1883-93.

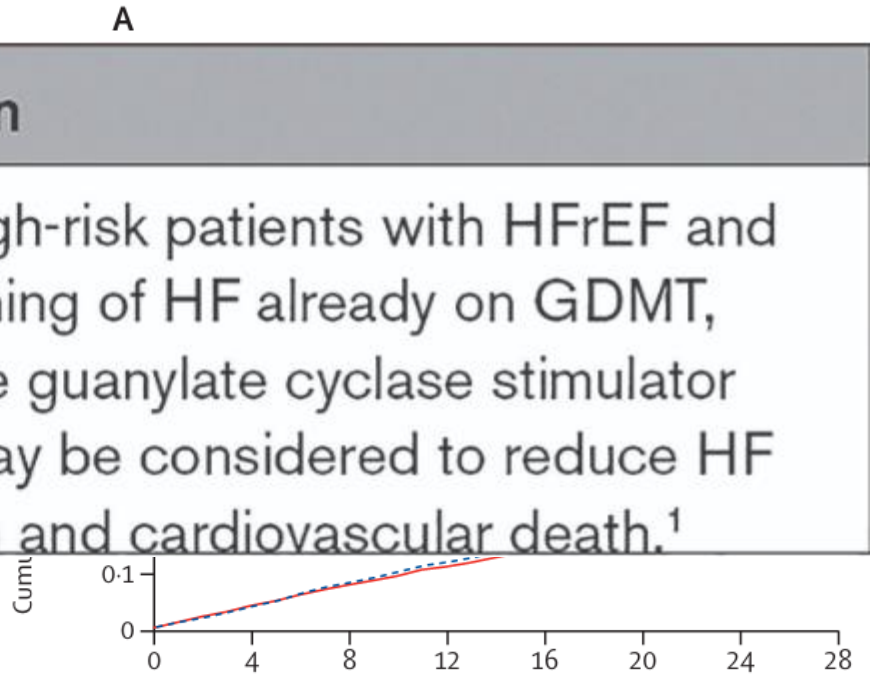
VICTOR

- N=6,105 pts
- Stable symptomatic HFrEF
- LV
- E
  p
- N
  w
- ~

COR	LOE	Recommendation
2b	B-R	1. In selected high-risk patients with HFrEF and recent worsening of HF already on GDMT, an oral soluble guanylate cyclase stimulator (vericiguat) may be considered to reduce HF hospitalization and cardiovascular death.[1]

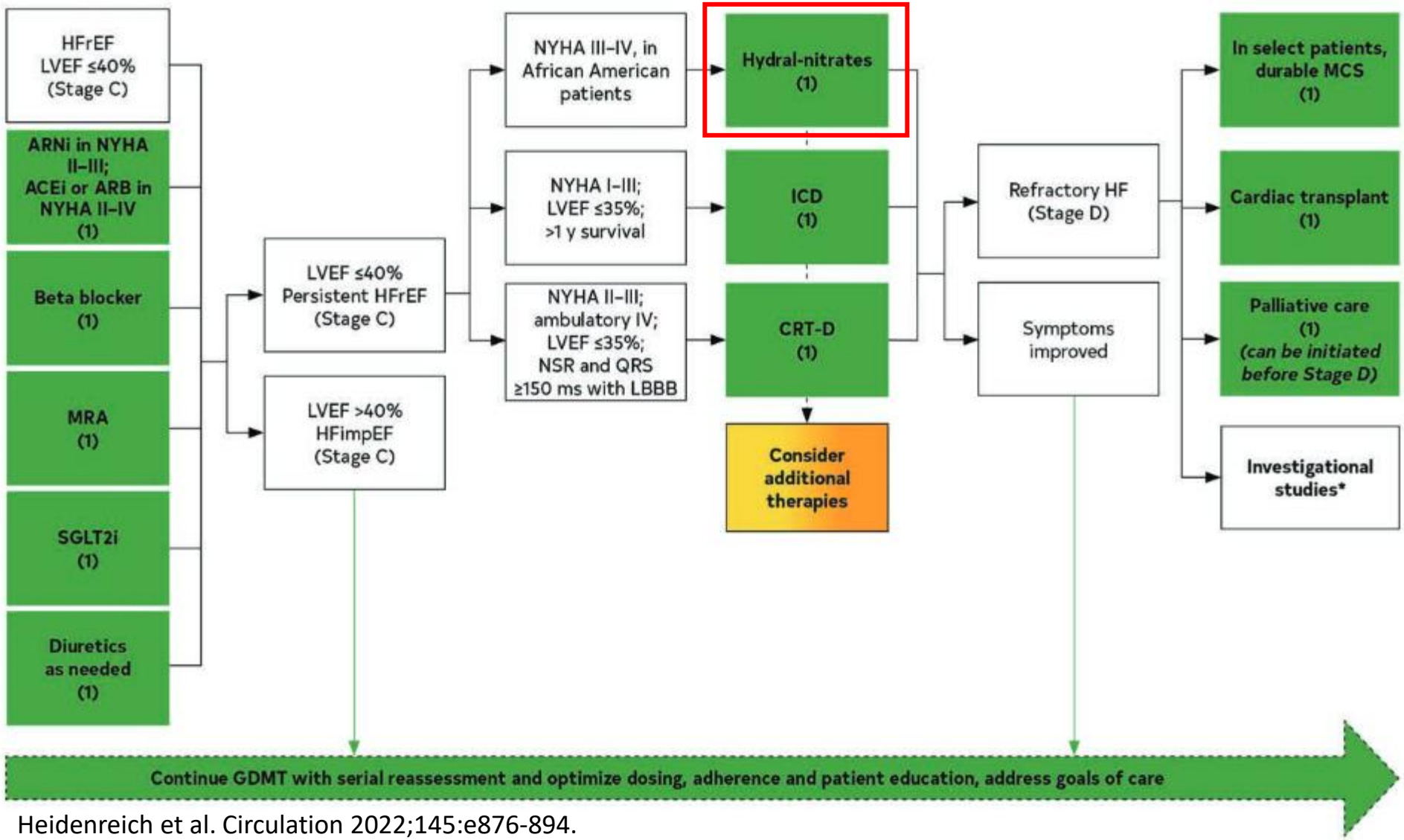
- Reduced CV and all-cause death but did not reduce HF hosp.
- Pooled analyses suggest small benefit in both HF hosp and mortality, particularly for NT-proBNP < 6000 pg/ml

CV Death or HF Hospitalization



Butler et al. Lancet 2025; 406: 1341–50

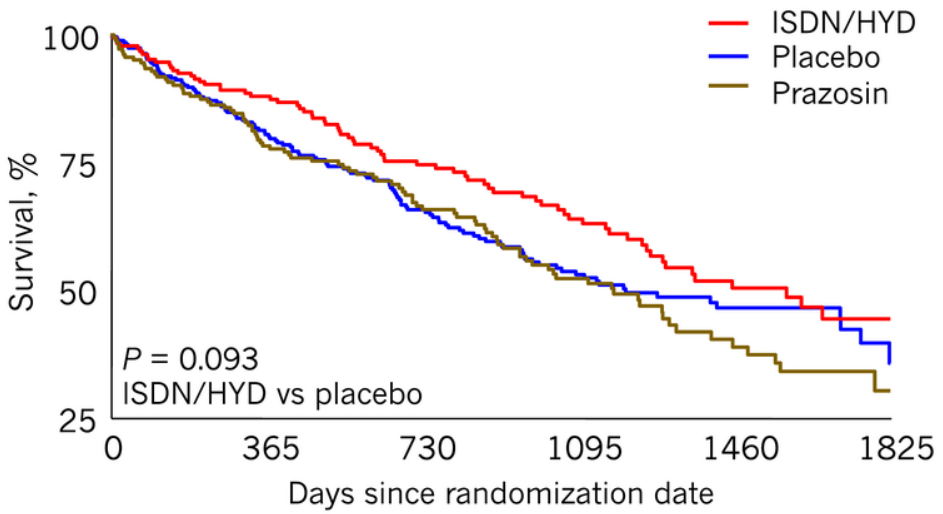
Stage C HF: Symptomatic HF



Heidenreich et al. Circulation 2022;145:e876-894.

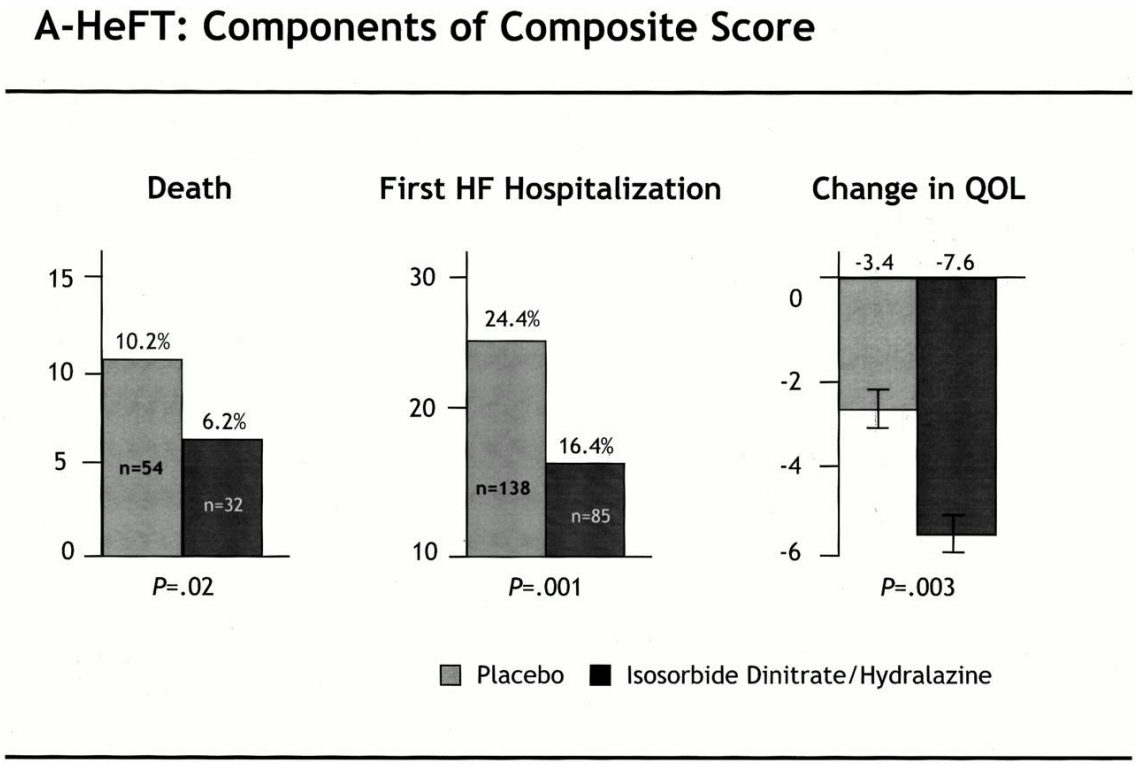
Hydralazine/Isordil in HFrEF

V-HEFT 1: EF < 45%, NYHA II-IV HF



ISDN/HYD, n =	186	148	109	71	37	16
Placebo, n =	276	202	135	84	41	10
Prazosin, n =	183	135	94	58	27	7

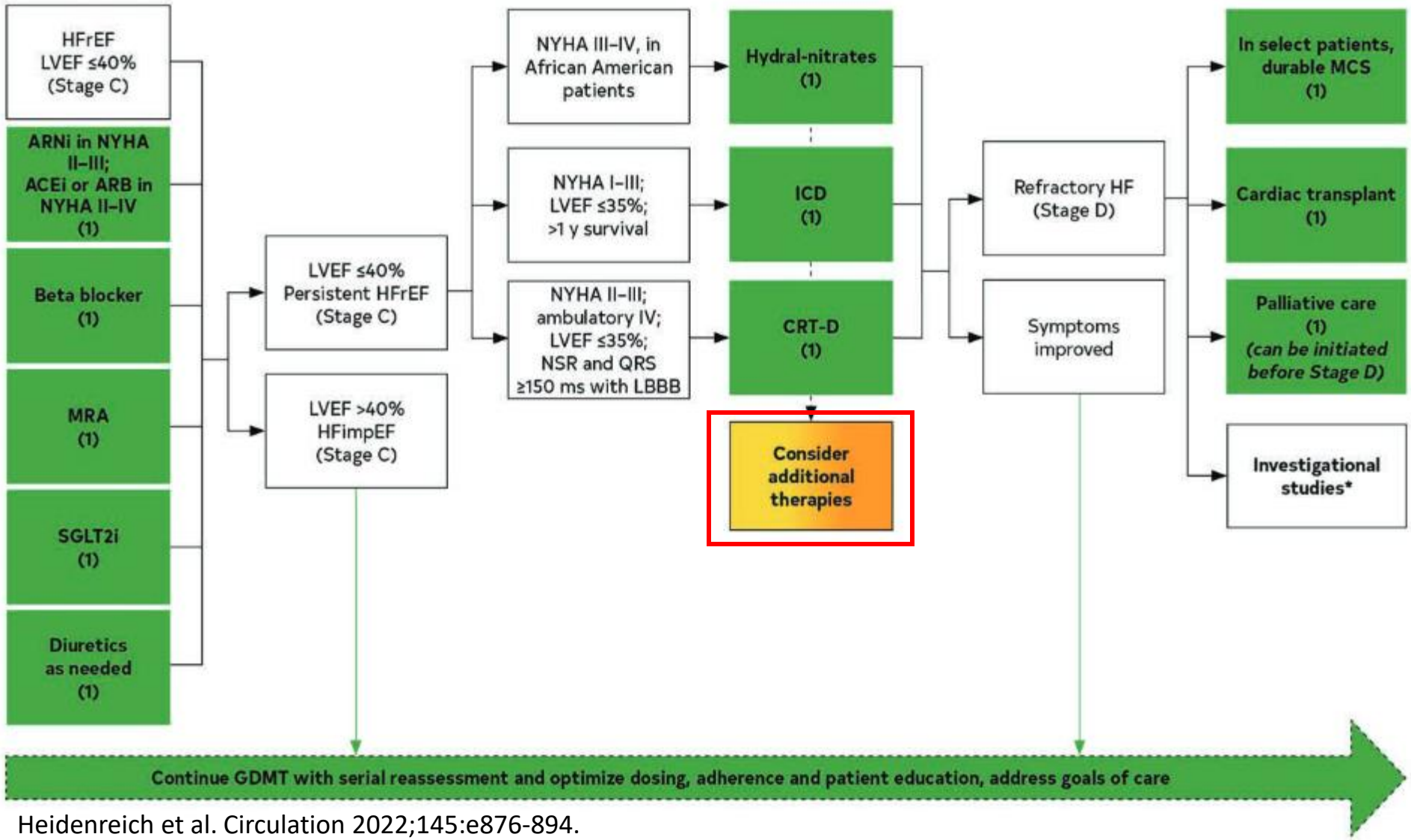
A-HEFT: Black pts, HFrEF, NYHA III-IV



- Consider in CKD, where RAASi and SGLT-2i contraindicated
- Consider as add-on Rx in Black pts

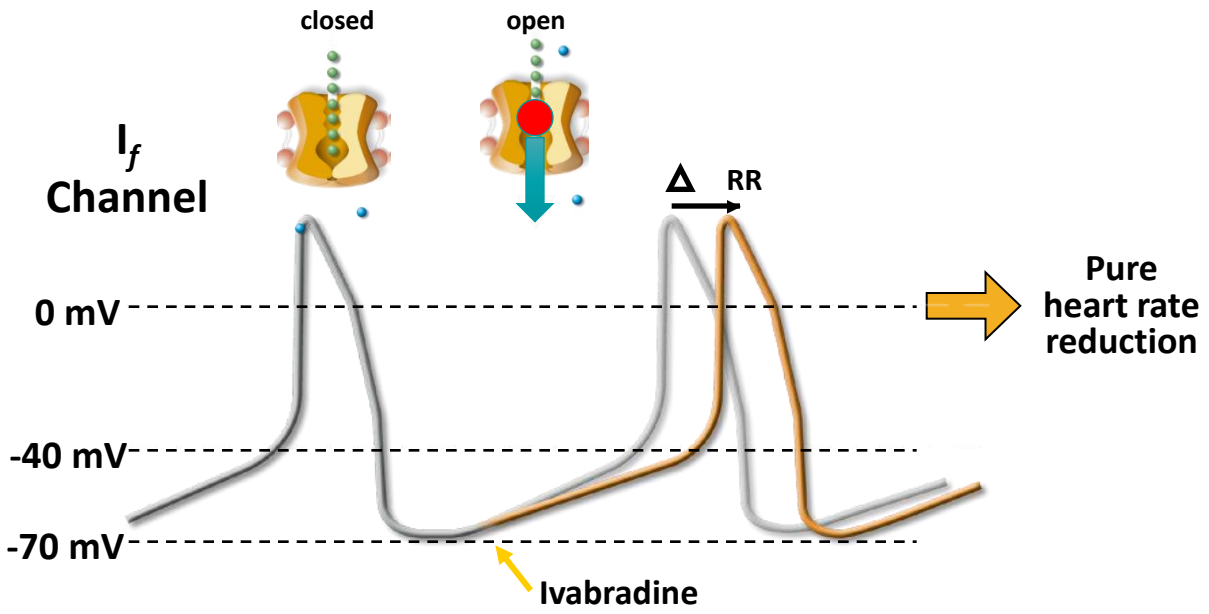
Cohn et al. NEJM 1986;314:1547; Taylor etal NEJM 2004;351:2049.

Stage C HF: Symptomatic HF



Heidenreich et al. Circulation 2022;145:e876-894.

Ivabradine: A selective I_f Inhibitor



I_f inhibition reduces the diastolic depolarization slope, thereby lowering heart rate
No effect on myocardial contractility or relaxation
Use-dependent block = low risk of bradycardia

Thollon et al. Br J Pharmacol. 1994;112:37-42.

SHIFT Trial: Effect of Ivabradine on Outcomes

Endpoints	HR	95% CI	p value
Primary composite endpoint (CV death or hospitalization for worsening HF)	0.82	[0.75,0.90]	p<0.0001
All-cause mortality	0.90	[0.80,1.02]	p=0.092
Death from HF	0.74	[0.58,0.94]	p=0.014
All-cause hospital admission	0.89	[0.82,0.96]	p=0.003
Any CV hospital admission	0.85	[0.78,0.92]	p=0.0002
CV death/hospitalization for HF or non-fatal MI	0.82	[0.74,0.89]	p<0.0001

Swedberg K, et al. Lancet. 2010;376(9744):875-885

Guideline Update

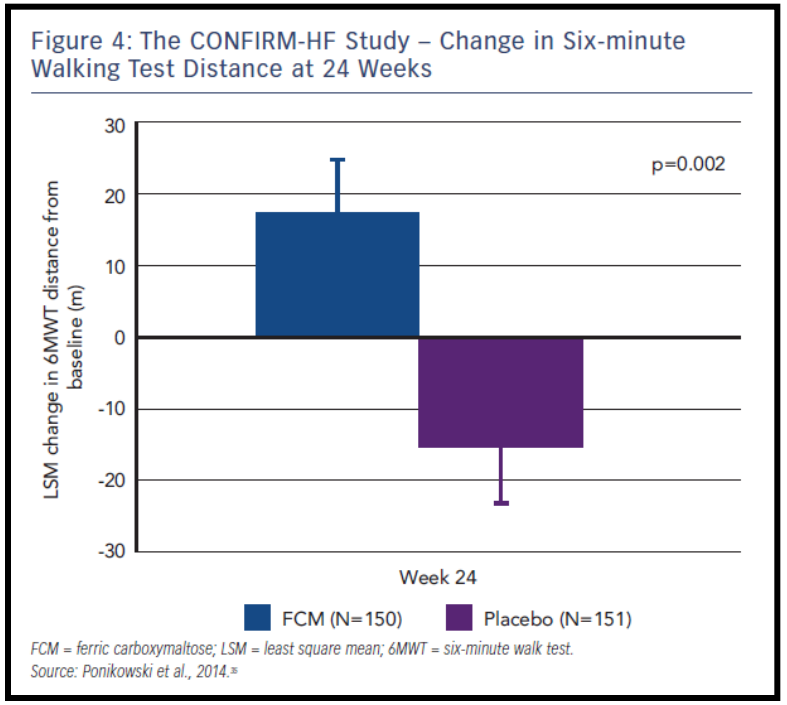
COR	LOR	
IIa Moderate	**B-R**	**Ivabradine may be beneficial to reduce HF hospitalization for patients with symptomatic stable chronic HFrEF who are receiving GDMT, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of ≥ 70 bpm at rest.**

Yancy, et al. Circulation 2017;136:e137-161

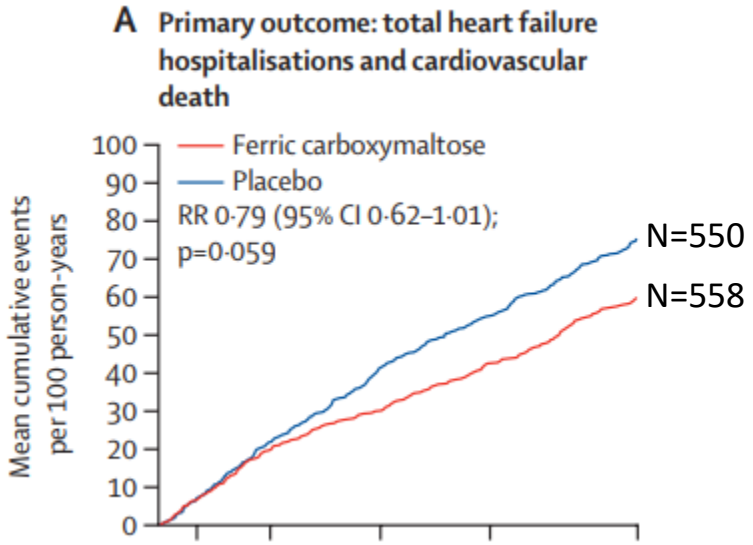
Treatment of Iron Deficiency in HFrEF

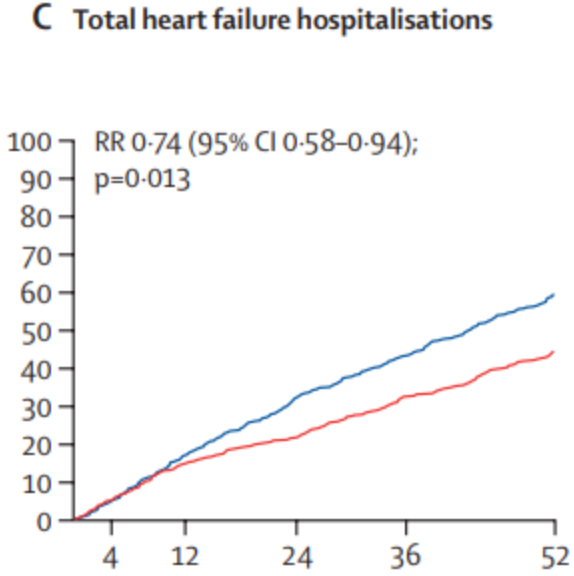
- NYHA II-IV HFrEF, ferritin < 100 ng/ml *OR* ferritin 100-300 ng/ml + transferrin saturation < 20%

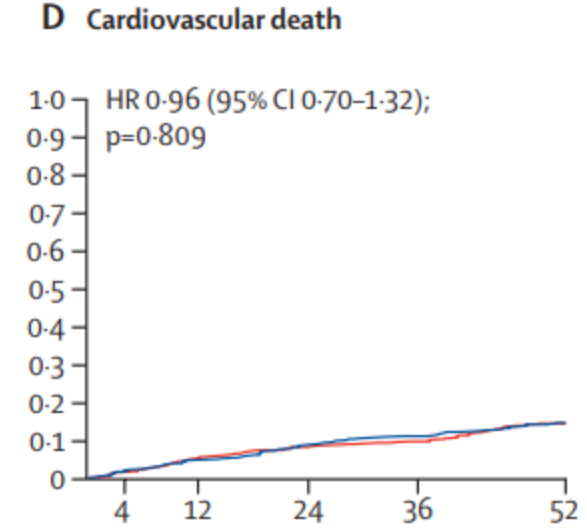
CONFIRM-HF



AFFIRM-AHF







Ponikowski et al. Eur Heart J 2015;36(11):657; Ponikowski et al. Lancet 2020;396(10266):1895.

Guideline Update

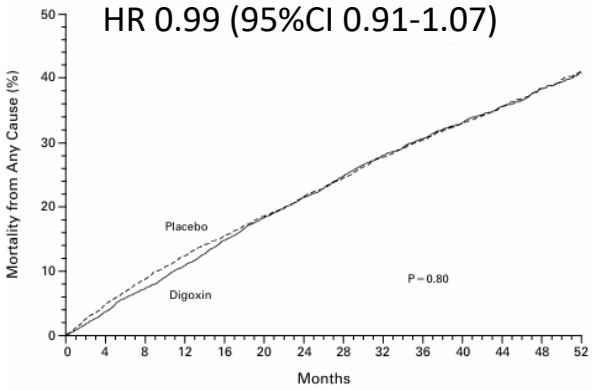
Recommendations for Anemia		
COR	**LOE**	**Recommendations**
IIb	**B-R**	**In patients with NYHA class II and III HF and iron deficiency (ferritin <100 ng/mL or 100 to 300 ng/mL if transferrin saturation is <20%), intravenous iron replacement might be reasonable to improve functional status and QoL(173, 174).**
See Online Data Supplement D.		
III: No Benefit	**B-R**	**In patients with HF and anemia, erythropoietin-stimulating agents should not be used to improve morbidity and mortality (176).**
See Online Data Supplement D.		

Yancy, et al. Circulation 2017;136:e137-161

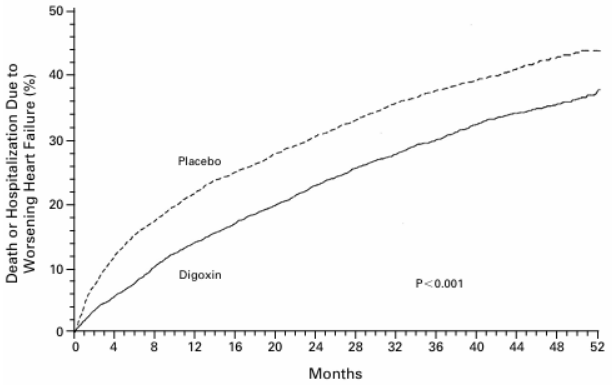
Digitalis

DIG: Digoxin vs placebo

All-Cause Mortality:
HR 0.99 (95%CI 0.91-1.07)

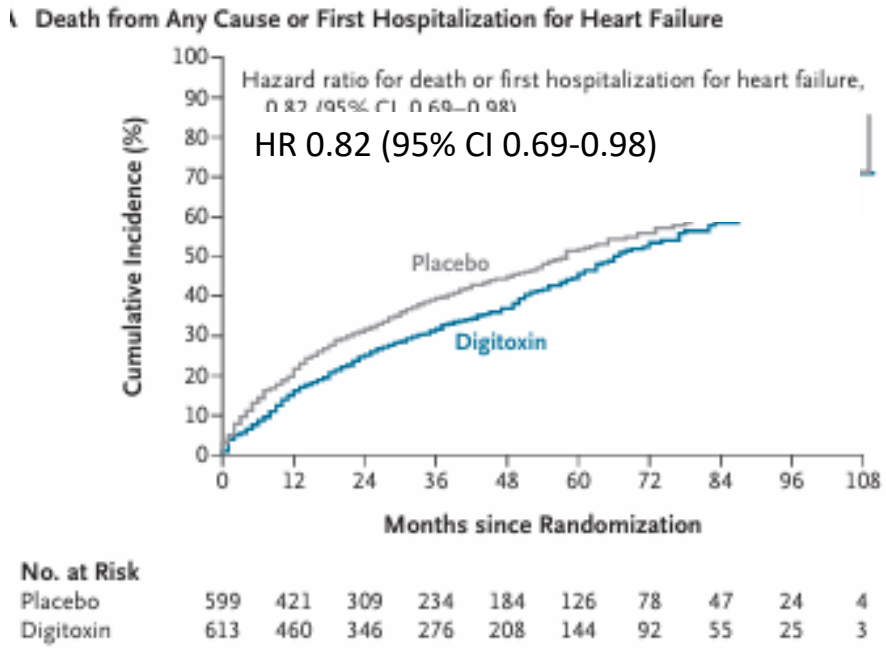


Death or Hosp due to Worsening HF
HR 0.75 (95%CI 0.69-0.82)



Gorlin et al. NEJM 1997;336:525-533.

DIGIT-HF: Digitoxin vs placebo



Bavendiek et al. NEJM 2025;393:1155-65.

Digitalis

- Digoxin: renal clearance, shorter half-life, widely used
- Digitoxin: hepatic clearance, very long half-life, not available in US
- Two trials conducted in different eras of background GDMT
- *Should be used at low doses (target level 0.5-0.8ng/mL)*

COR	LOE	Recommendation
2b	B-R	1. In patients with symptomatic HFrEF despite GDMT (or who are unable to tolerate GDMT), digoxin might be considered to decrease hospitalizations for HF.[1,2]

Heidenreich et al. Circulation 2022; 145 (18):e895-e1032

Question 2.

A 70 y.o. female with a history of HTN, hyperlipidemia, type II DM, CAD, paroxysmal afib and ischemic cardiomyopathy (EF 30%) presents with NYHA Class III symptoms of HF. After optimizing her volume status, she remains dyspneic while walking around the house. Her vital signs are notable for HR 80 bpm, BP 118/80 mm Hg. Her exam shows JVP 11 cm of water, mild bibasilar crackles, irregularly, irregular rhythm, + MR, + TR, and chronic 1+ bilateral edema. Her laboratory values are notable for Na 136 mEq/L, K 4.8 mEq/L, BUN 50 mg/dL, creatinine 2.4 mg/dL, eGFR 18 ml/min/1.73m2, NT-proBNP 2500 pg/mL. Her medications include apixaban 5 mg twice daily, atorvastatin 80 mg daily, carvedilol 6.25 mg twice daily, hydralazine 100 mg three times daily, isosorbide mononitrate 60 mg daily, insulin, torsemide 160 mg twice daily and multivitamin.

What is the next best step to improve her symptoms?

A. Add empagliflozin 10 mg daily
B. Add ivabradine 5 mg twice daily
C. Add vericiguat 10 mg daily
D. Add Entresto 24-26 mg twice daily

Who To Refer for Advanced Heart Failure Evaluation (C2D population)?

- Persistent NYHA III/IV symptoms despite maximal medical therapy
- Escalating diuretic requirements (furosemide > 160 mg/d ± thiazides)
- ≥ 2 HF hospitalizations in past yr or HF hospitalization requiring ICU care
- Repeated ICD shocks for ventricular arrhythmias
- Intolerance of previously tolerated GDMT due to hypotension or worsening Cr
- RV failure, progressive kidney and liver failure
- Progressive hyponatremia
- Cardiac cachexia
- Objective limitation in exercise capacity
  - 6 min walk < 300 m or peak VO2 < 12-14 ml/kg/min or < 50% predicted
- Need for IV inotropes during admission or at home

Dunlay et al. JAMA Cardiol. 2025;10(4):391-398.

Take Home Messages

For HFrEF:

- Try to get all pts on 4 drug GDMT

- Start early, broad, and then titrate to target doses

- Consider add-on therapy
  - Hydralazine/isordil in Black pts or unable to take RAAS blockade
  - Ivabradine if SR and high HR despite max beta-blockade
  - Vericiguat in high-risk but not end-stage pts, eGFR 15-30
  - ?Dig if BP limits other HF meds
  - IV iron if iron deficient

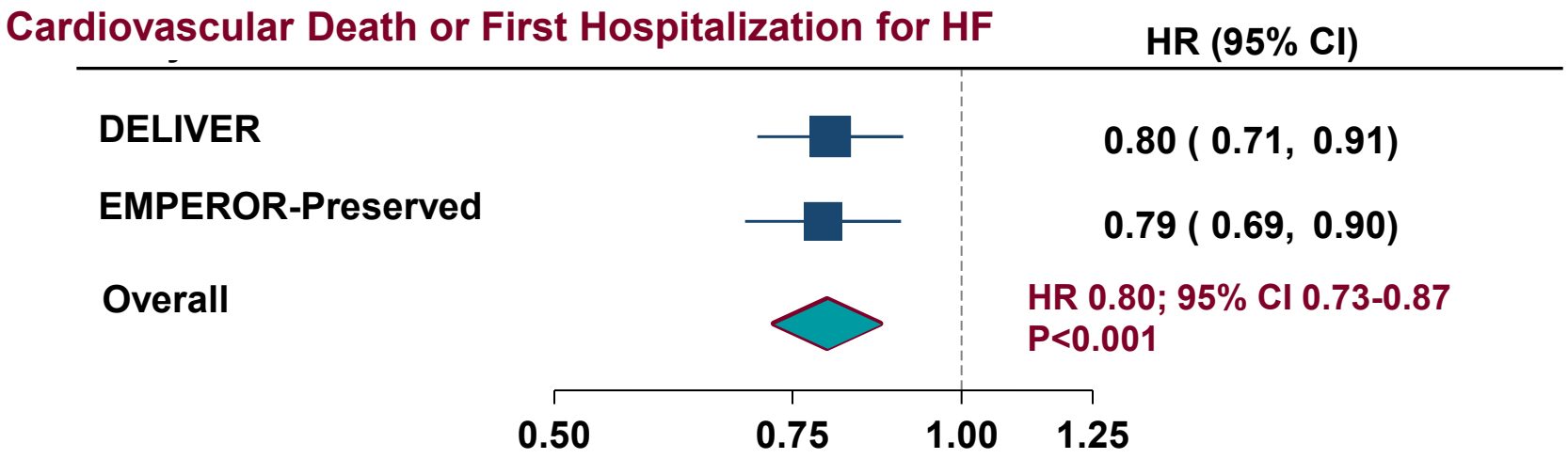
- Device therapies in appropriate pts

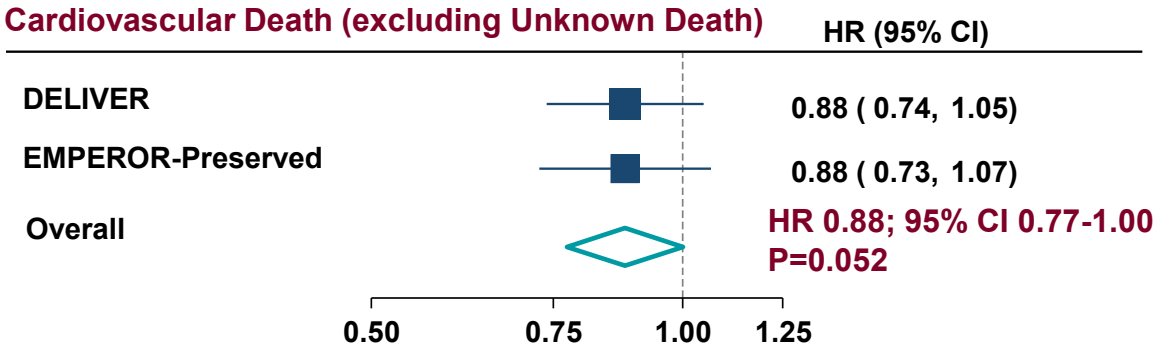
Guideline Update for HFpEF

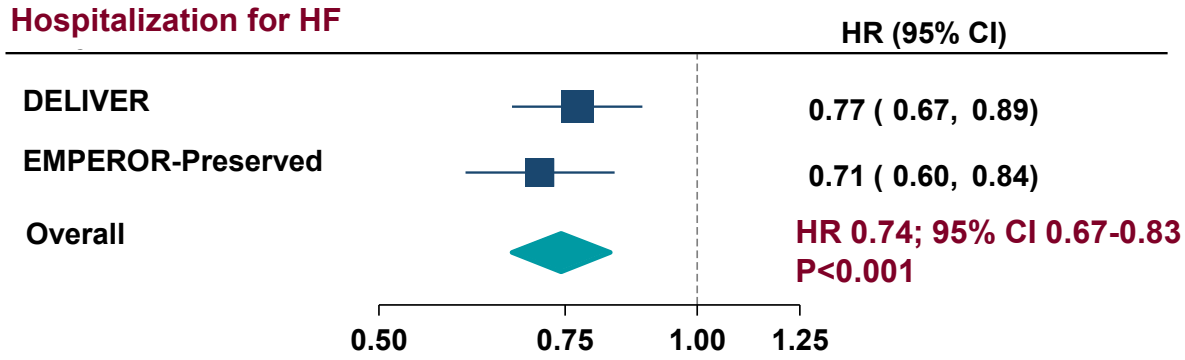
COR	LOE	Recommendations
1	C-LD	1. Patients with HFpEF and hypertension should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity.[44–46]
2a	C-EO	2. In patients with HFpEF, management of AF can be useful to improve symptoms.
2a	B-R	1. In patients with HFpEF, SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality.[33]
2b	B-R	2. In selected patients with HFpEF, MRAs may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[38,42,43]
2b	B-R	3. In selected patients with HFpEF, ARNi may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[35,40]
3: No Benefit	B-R	4. In patients with HFpEF, routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or quality of life is ineffective.[49,50]

Heidenreich et al. Circulation 2022;145:e876-894

DELIVER and EMPEROR-Preserved Meta-Analysis:



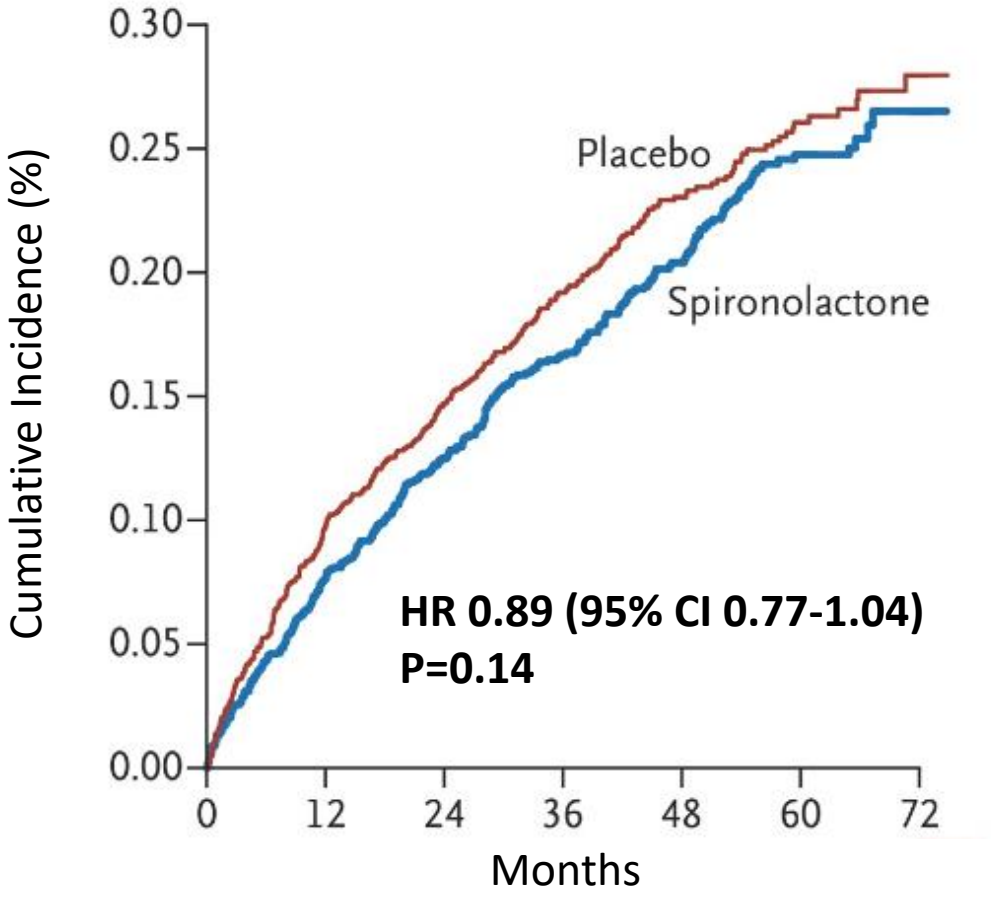


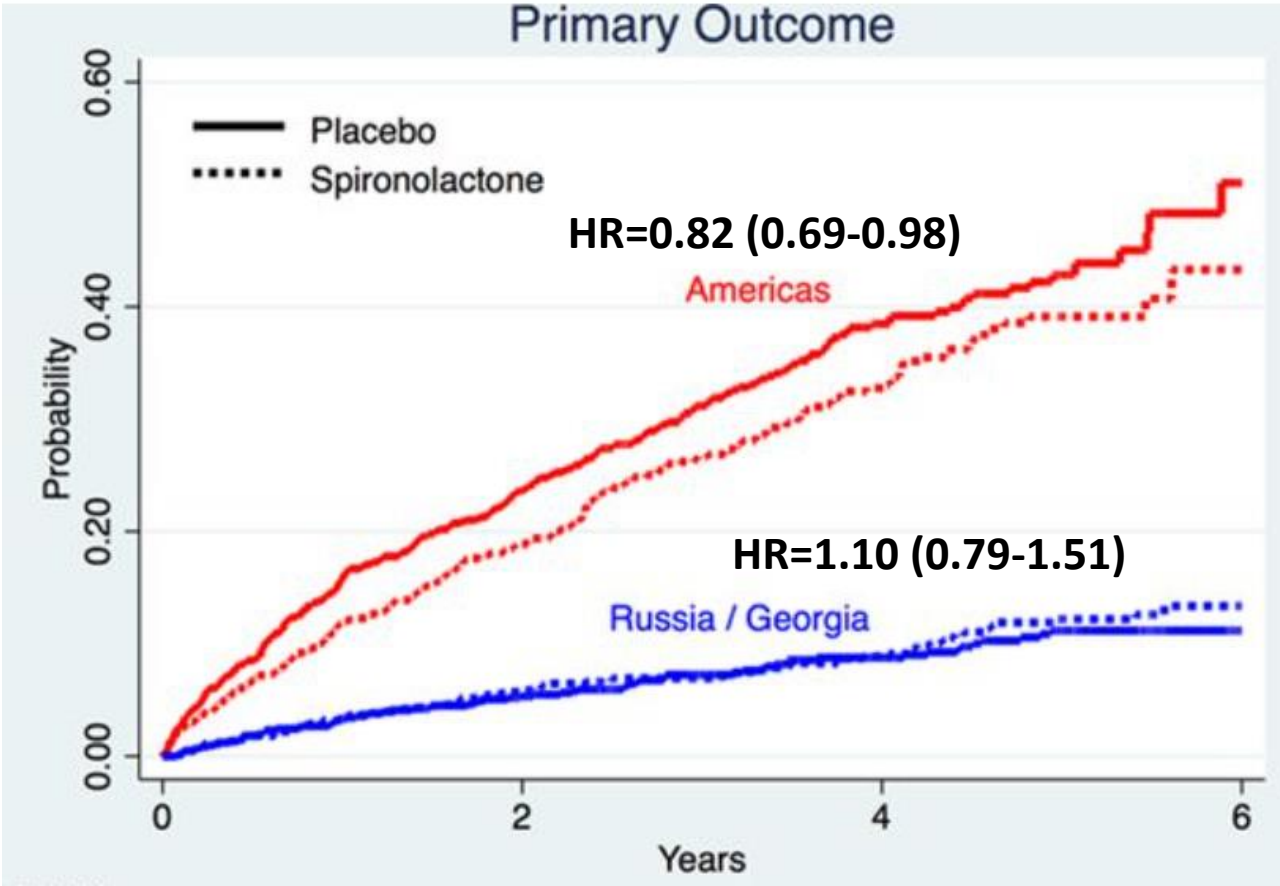


Vaduganathan M, et al. Lancet 2022

$P_{heterogeneity}$ >0.10 for all endpoints

TOPCAT: Spironolactone in HFpEF
1° Endpt: CV mortality, Aborted CV death, or HF Hosp.



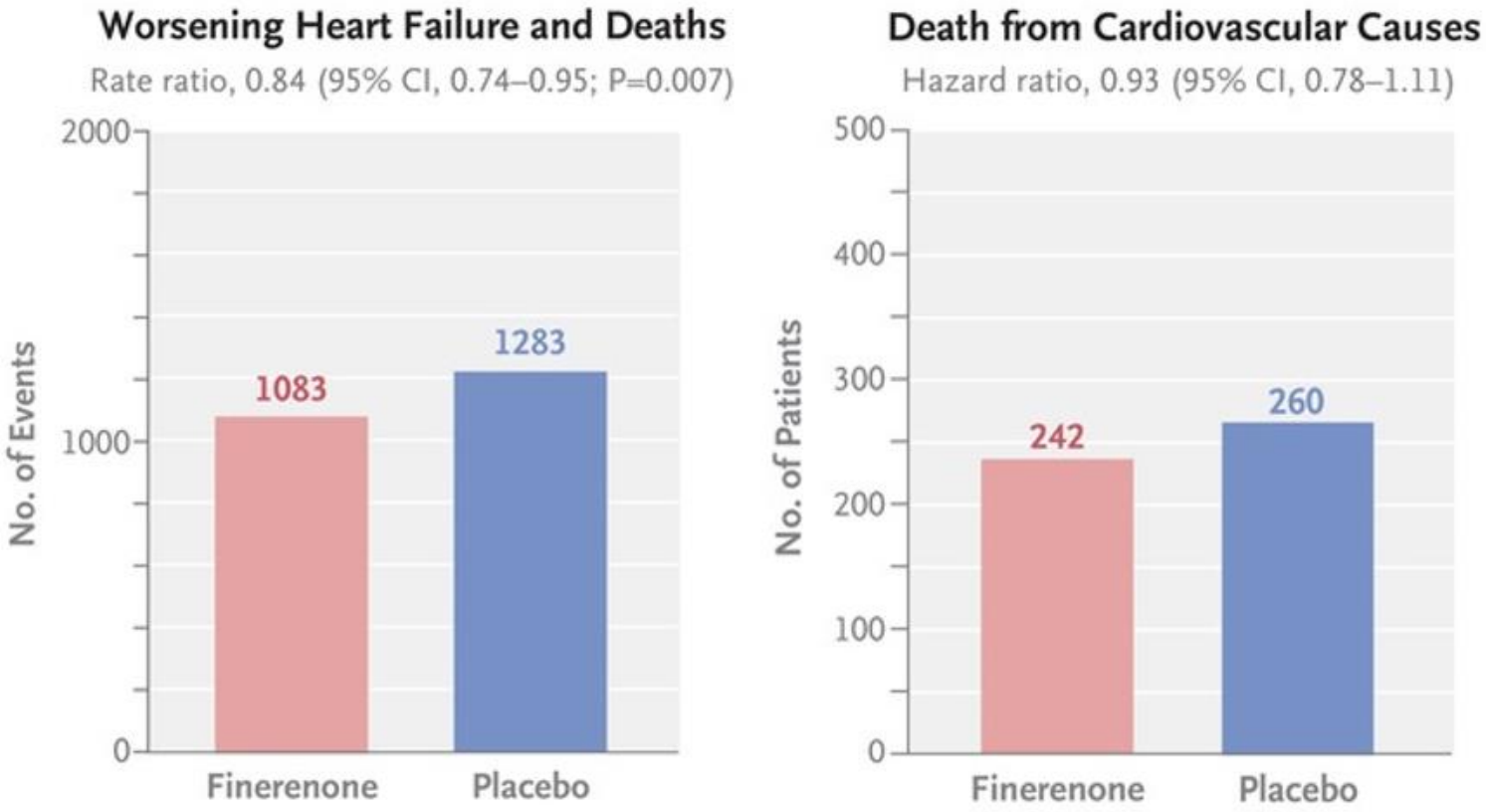


Pitt et al. NEJM 2014; 370:1383-1392; Pfeffer et al. Circulation 2015;131:34-42.

FINEARTS: Finerenone in HFpEF
1° Endpt: CV death and worsening HF events

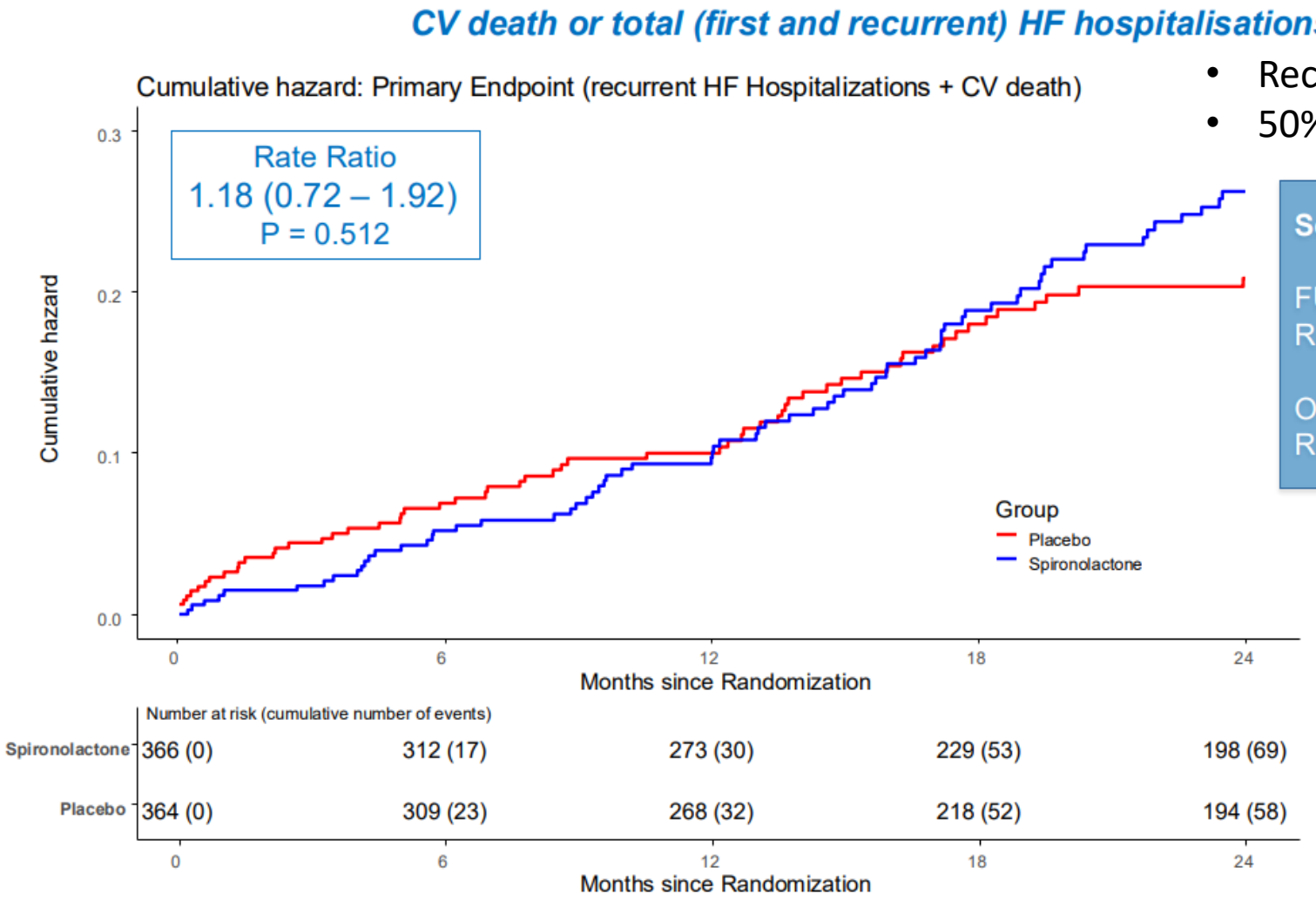
- N=6001 pts
- Age ≥ 40 yrs, LVEF≥ 40%, structural heart dz, NYHA II-IV HF, ↑NPs
- RCT: 1:1 Finerenone 20 or 40 mg daily vs. placebo
- Median f/u: 32 mths

- ↑ hyperkalemia



Solomon et al. NEJM 2024;391:1475-85.

SPIRIT-HF: Spironolactone in HFmrEF and HFpEF



- Recruited < 50% pts due to COVID
- 50% stopped drug by 21 mths

Sensitivity Analyses:

FU restricted to 12 months:
RR 0.93 (0.49 – 1.78), p=0.83

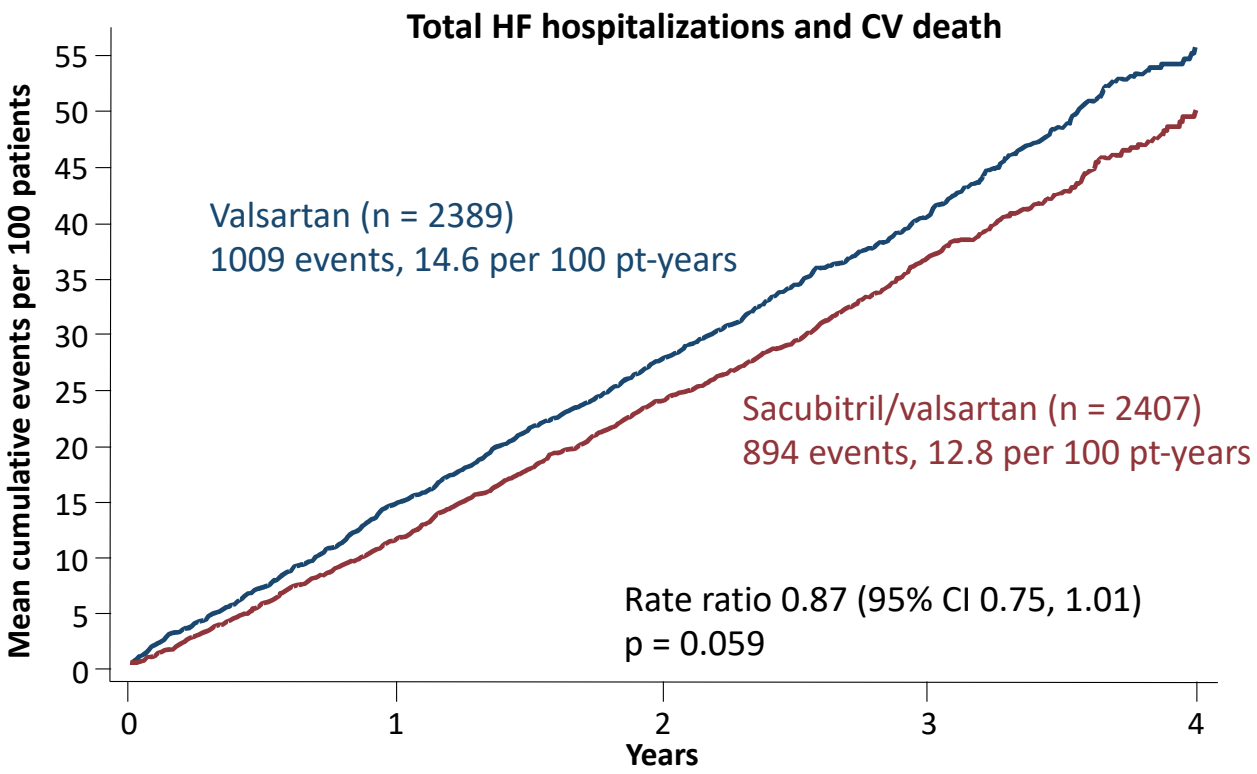
On treatment analysis
RR 0.94 (0.49 – 1.79), p=0.84

SPIRIT-HF
DZHK TRIAL 08

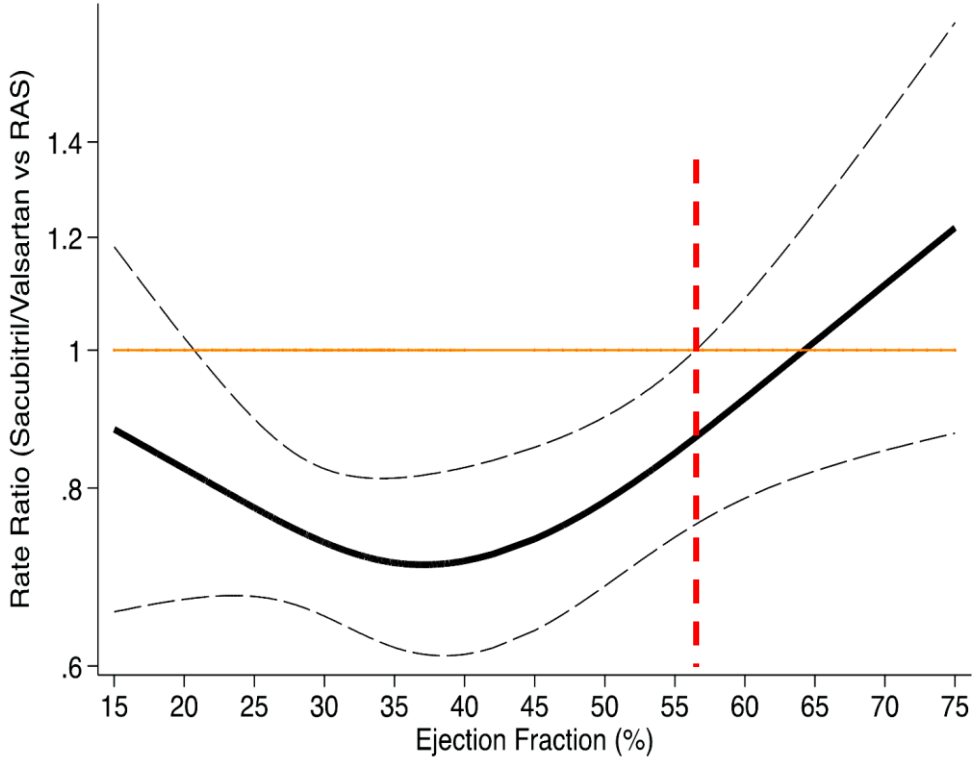
Edelman et al. ACC 2026

ARNI in HF with HFmrEF or HFpEF

PARAGON-HF Primary Results



PARADIGM-HF/PARAGON-HF Pooled

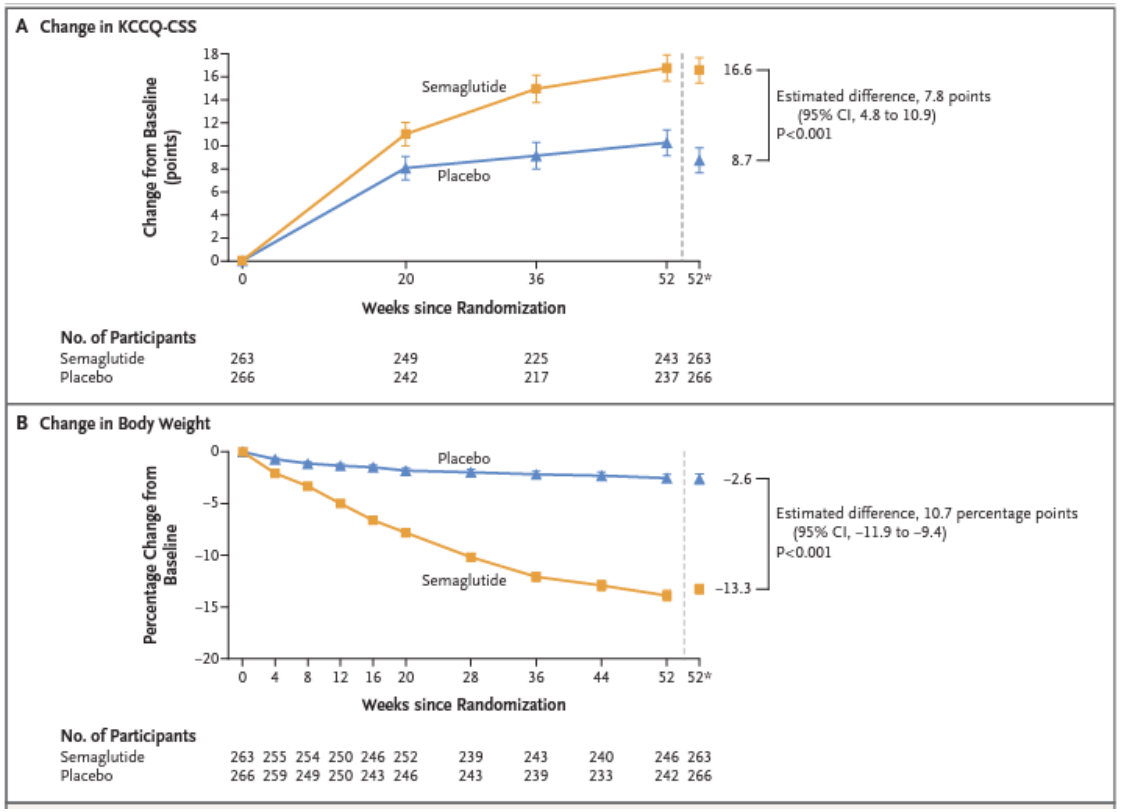


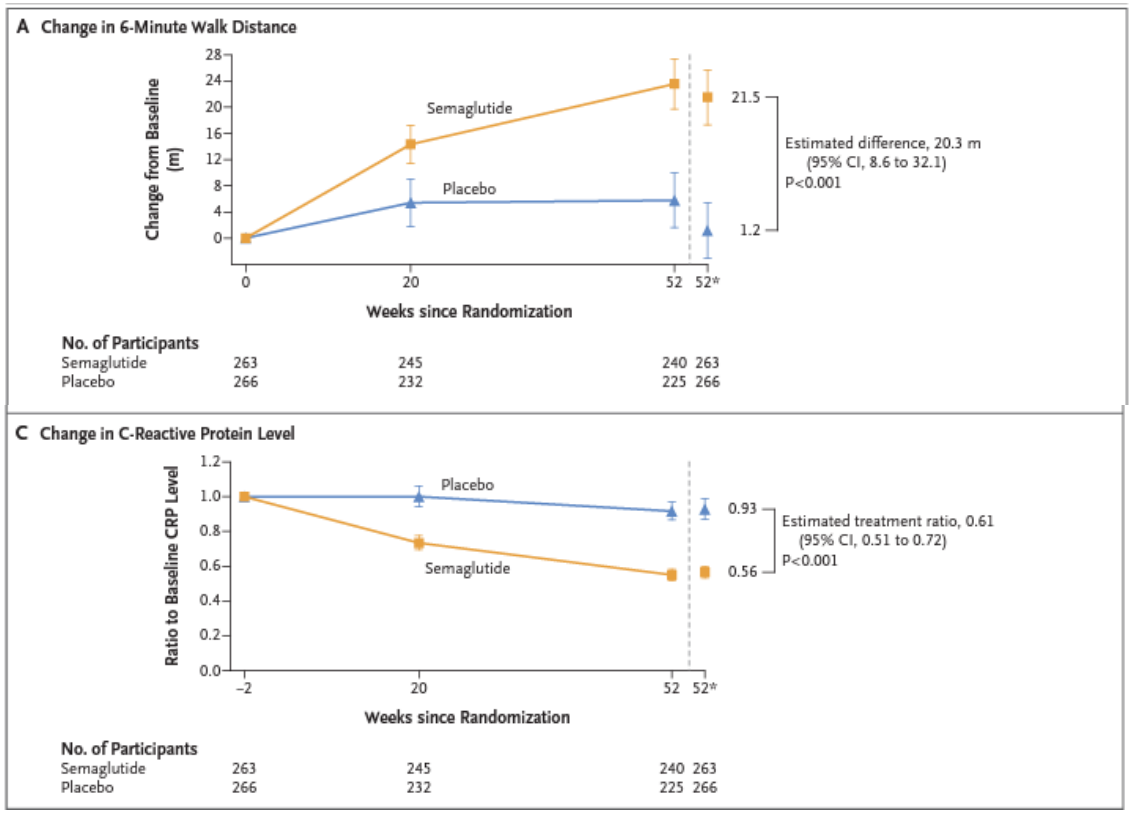
Feb 2021 US FDA approval for sacubitril/valsartan in expanded population, emphasizing benefits in EF 'below normal' w/ decreasing benefit as EF increases

Solomon SD, et al. N Engl J Med 2019; Solomon SD, Circulation 2020

GLP-1 agonists in HFpEF: STEP-HFpEF

N=529 pts, symptomatic HFpEF (EF ≥ 45%), BMI ≥ 30
RTC: Semaglutide 2.4 mg weekly vs. placebo X 52 weeks

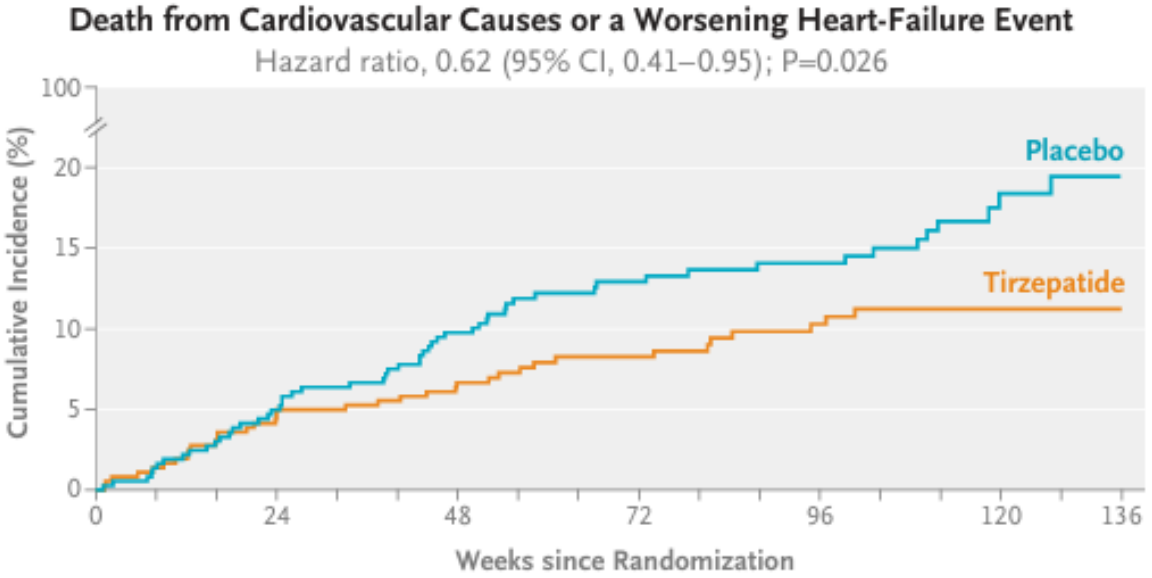




Kosiborod et al. N Engl J Med 2023;389:1069-84.

SUMMIT: GLP-1 and GIP Agonist in HFpEF

- N=732 pts
- Age ≥ 40 yrs, BMI ≥ 30, NYHA II-IV HF, LVEF ≥ 50%, ↑ NPs, LAE or ↑PCWP @ rest or exercise, ≥ 30 HF hosp. w/in 1 yr or eGFR < 70.
- RCT: 1:1 tirzepatide up to 15 mg SC weekly vs. placebo x 52 weeks
- Median f/u = 104 weeks



- Discontinuation due to GI side effects:
  - 6.3% vs 1.4%

- Wt loss: 13.9% vs 2.2%
- Change in KCCQ: 19.5 vs 12.7
- Change in 6 min walk distance: 26 vs 10.1 m
- Change in CRP: 38.8% vs 5.9%

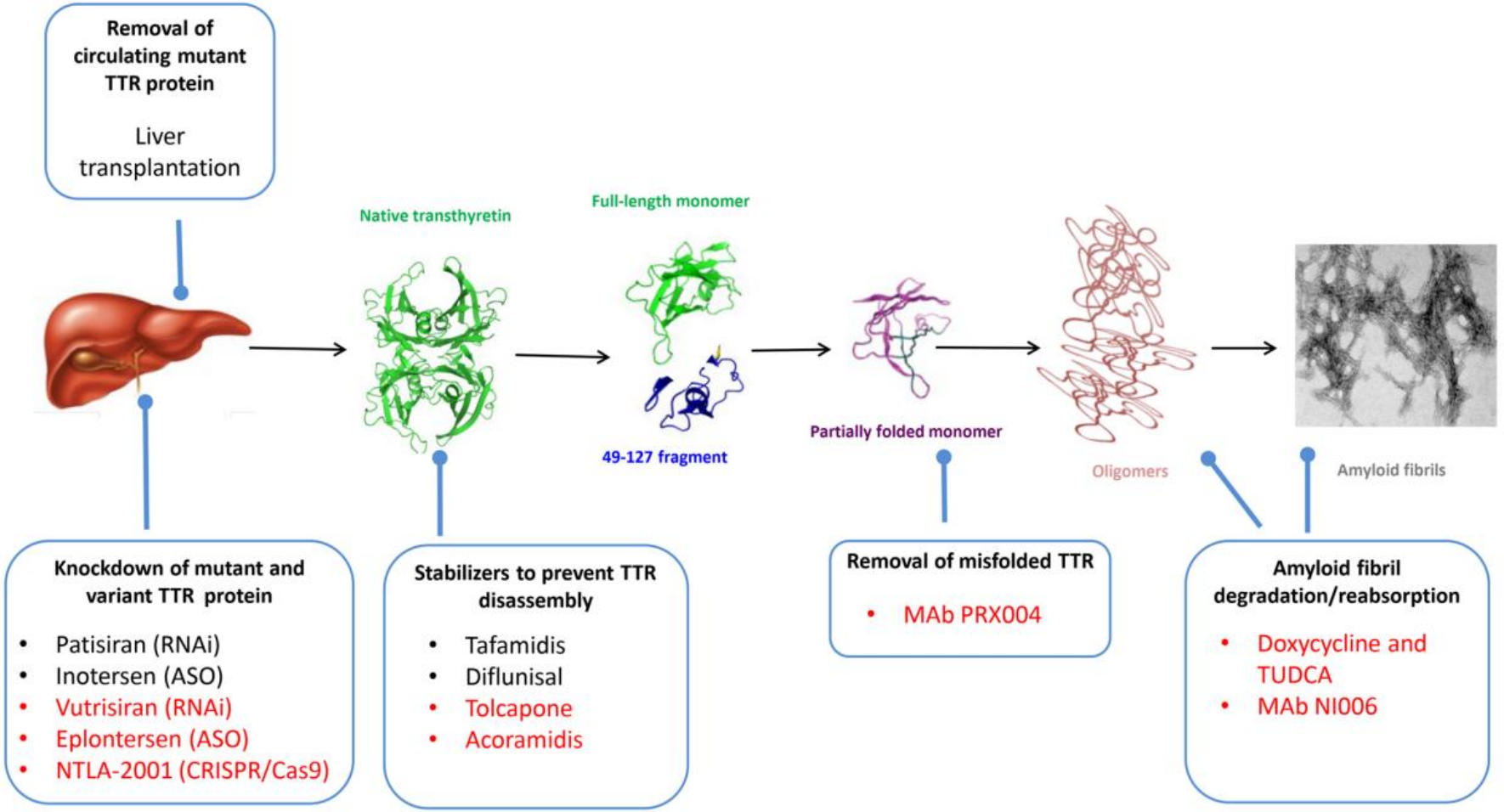
Packer et al. NEJM 2025;392:427-32.

Question 3.

Which of the following therapies has not been shown to reduce HF hospitalizations in HFpEF?

A. Empagliflozin
B. Sacubitril-Valsartan
C. Finerenone
D. Semiglutide
E. Tirzepatide
F. B and D

Therapies for ATTR Amyloidosis



Obici et al. Neurotherapeutics 2021;18:2286-2302.

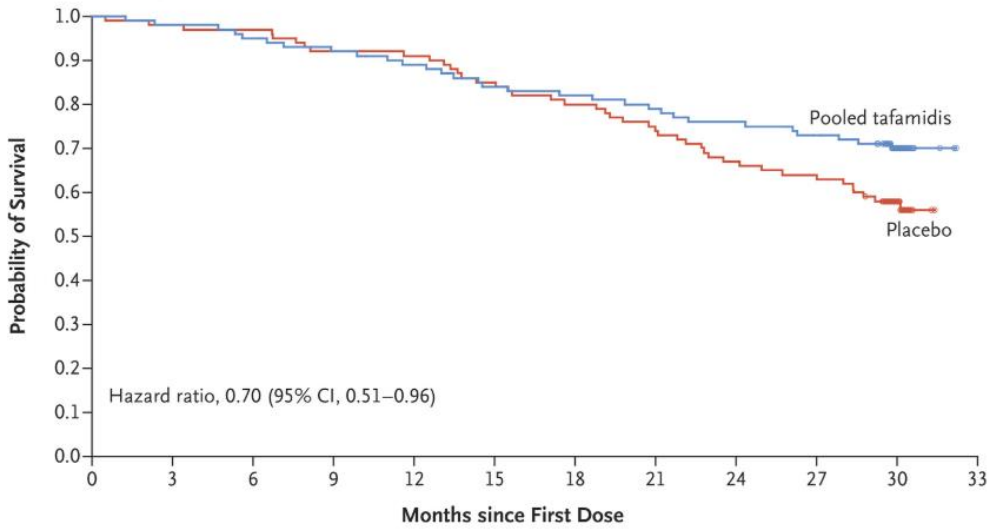
Stabilizers for TTR Cardiac Amyloid

- N=441, ATTR amyloid (wt or mutant), NYHA I-III
- RCT: 2:1:2 tafamadis 80 mg vs 20 mg qd vs placebo

A Primary Analysis, with Finkelstein–Schoenfeld Method

	No. of Patients	P Value from Finkelstein–Schoenfeld Method	Win Ratio (95% CI)	Patients Alive at Mo 30 *no. (%)*	Average Cardiovascular-Related Hospitalizations during 30 Mo among Those Alive at Mo 30 *per patient per yr*
Pooled Tafamidis	264	<0.001	1.70 (1.26–2.29)	186 (70.5)	0.30
Placebo	177			101 (57.1)	0.46

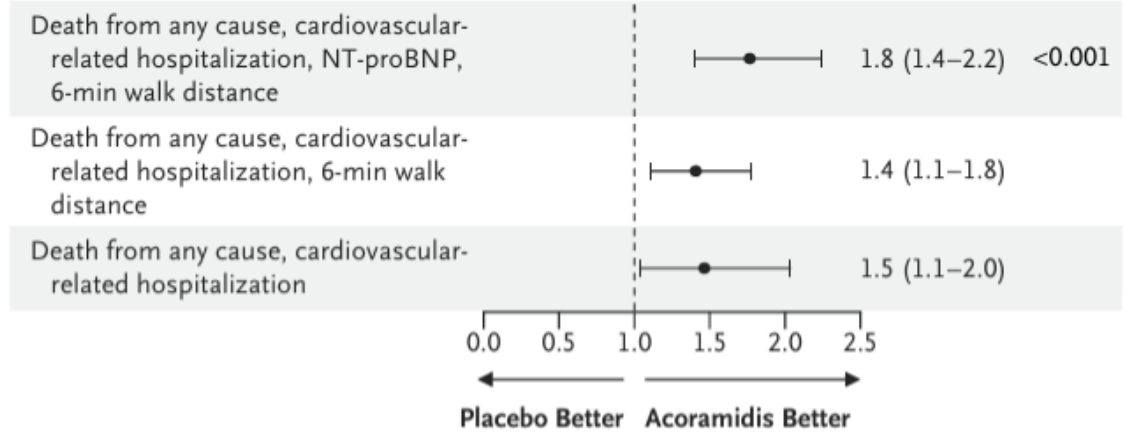
B Analysis of All-Cause Mortality



Maurer et al. NEJM 2018;379(11):1007-16

- N=632, ATTR amyloid (wt or mutant), NYHA I-III
- RTC: 2:1 acoramidis 800 mg bid vs placebo

Primary Efficacy Analysis and Prespecified Secondary Analyses



Gillmore et al. NEJM 2024;390:132-42.

Helios-B: Vutrisiran (RNAi) for ATTR Amyloidosis

RCT: 1:1 Vutrisiran 25 mg q 12 weeks vs placebo x 36 mths

654 adults

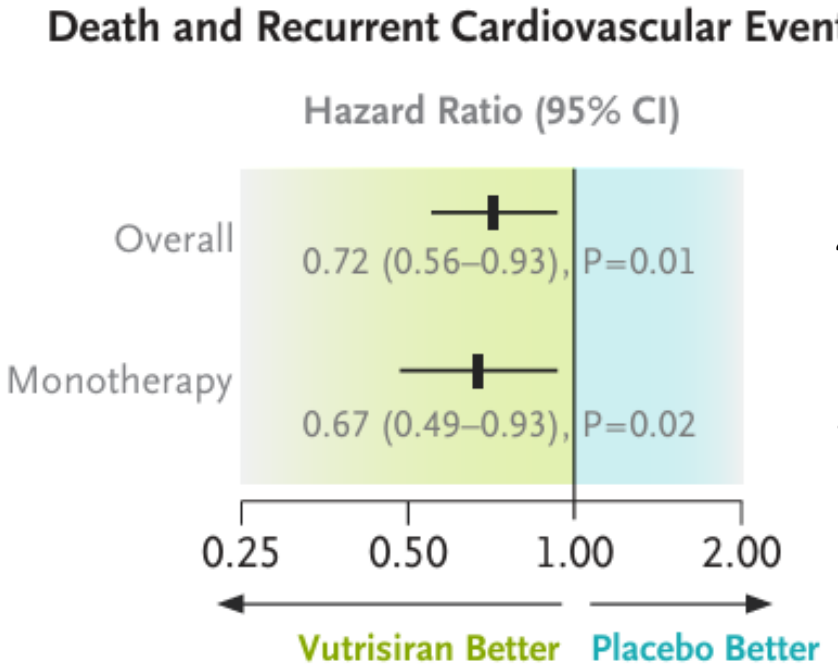
Median age, 77 years

Men: 93%; Women: 7%

Presence of TTR amyloid deposits in a tissue-biopsy specimen or fulfillment of scintigraphy-based diagnostic criteria for ATTR amyloidosis with cardiomyopathy

Cardiac involvement as assessed with transtho-racic echocardiography

Clinical history of heart failure



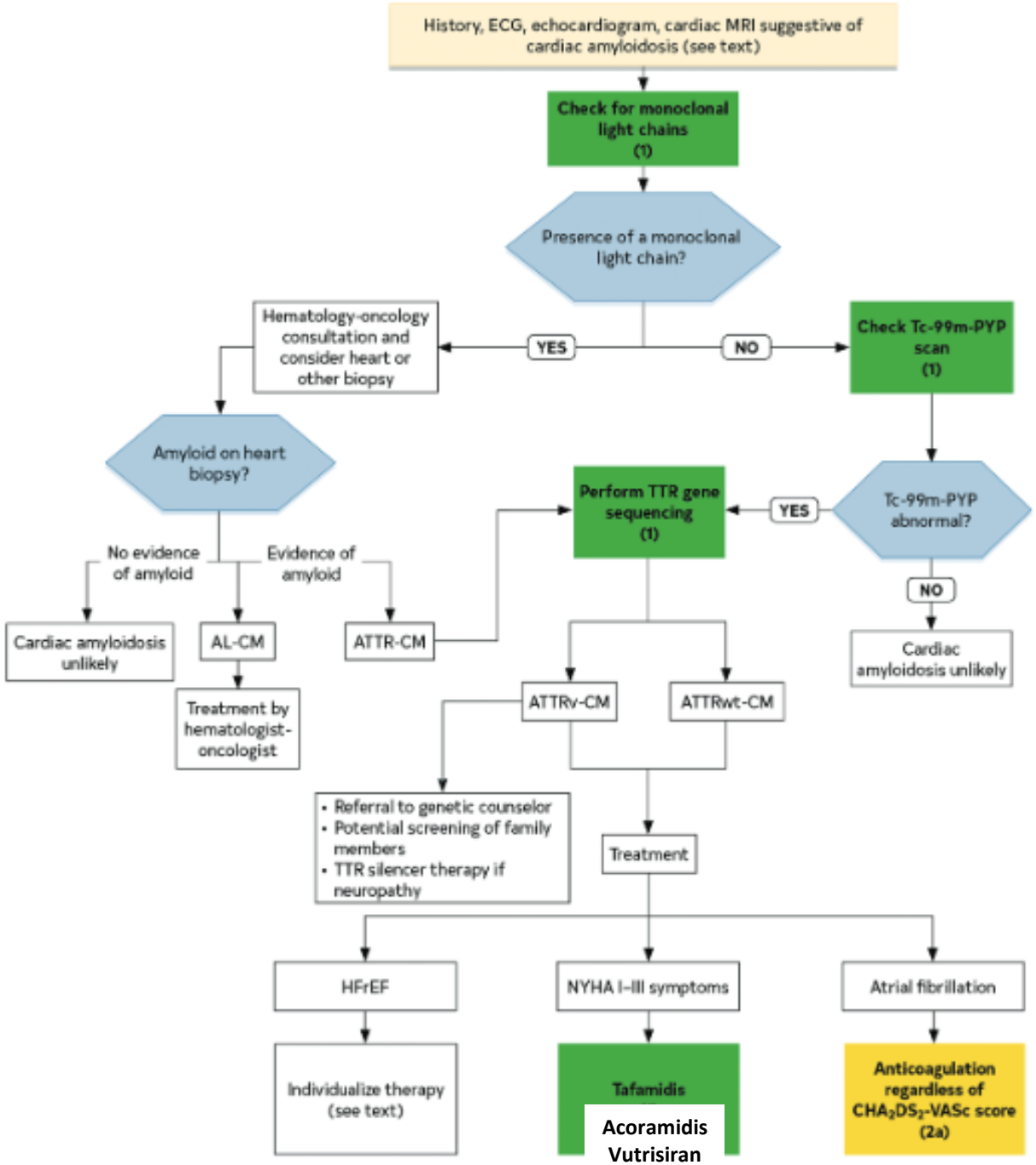
40% on tafamadis @ baseline

20% started tafamadis during trial

Fontana et al. NEJM 2025;392:33-44.

Diagnostic and Management Algorithm for Cardiac Amyloidosis

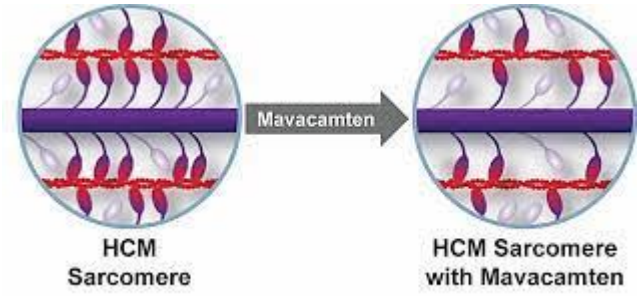
- Biceps tendon rupture
- Bilateral carpal tunnel syndrome
- Lumbar spinal stenosis
- Peripheral neuropathy
- LVH on echo
- Biatrial enlargement
- Low QRS voltage on ECG despite LVH



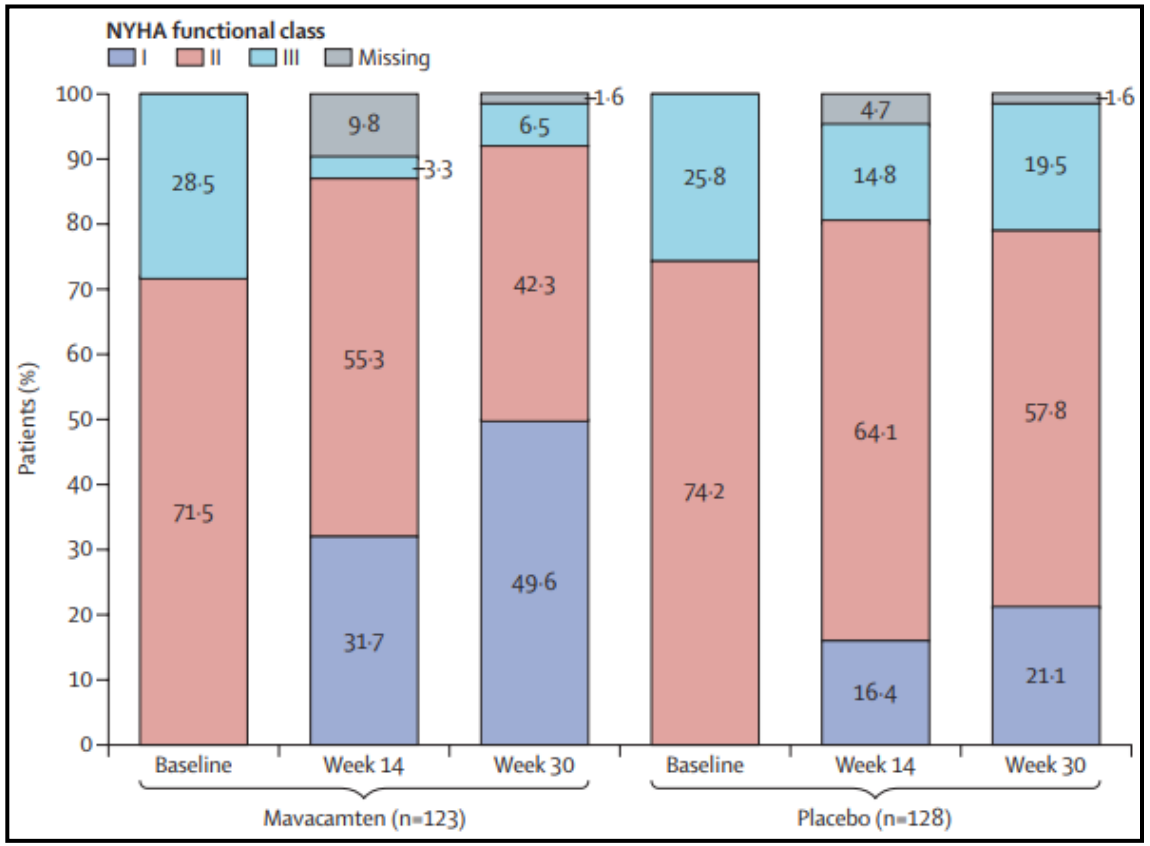
Heidenreich et al. Circulation 2022; 145;e876-894.

EXPLORER-HF: Mavacamten for Hypertrophic Obstructive Cardiomyopathy

Inhibitor of cardiac myosin: reduces # of cross-bridges between actin and myosin



- N=251 pts, HCM, LVOT gradient > 50 mmHg, NYHA II-III
- **1° Endpoint**: ≥ 1.5 ml/kg/min ↑ in peak VO2 + ≥ 1 NYHA Class ↓ in sxs *OR* ≥ 3 ml/kg/min ↑ in peak VO2 w/ stable sxs
- **37% vs. 17%, p=0.0005**



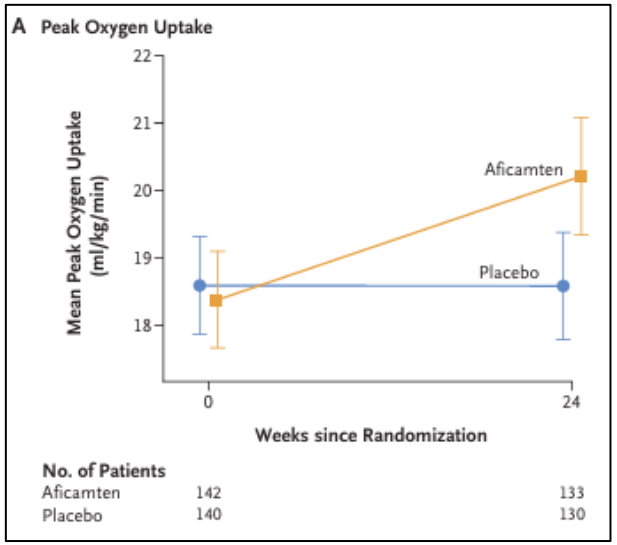
Olivotto et al. Lancet 2020;396:759-69.

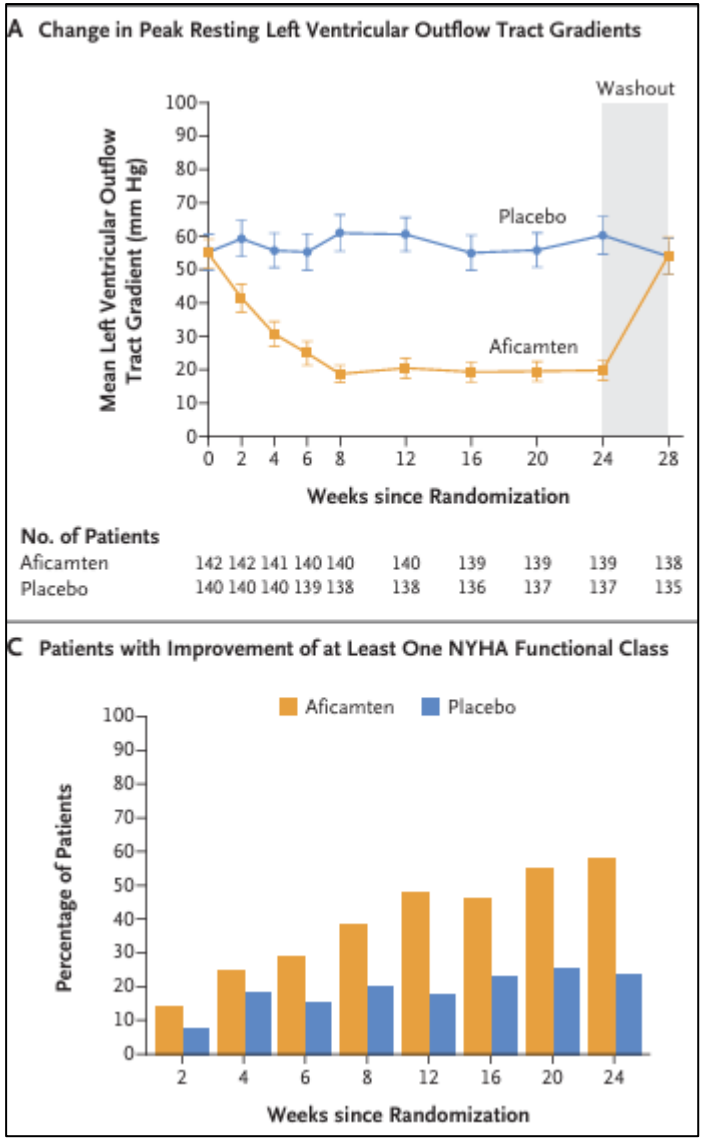
SEQUOIA-HCM: Aficamten for Obstructive HCM

- N=282 pts
- EF ≥ 60%,
- LVOT gradient ≥ 30 mm Hg @ rest or ≥ 50 mm Hg w/ Valsalva
- NYHA II-III HF

- RCT: 1:1 aficamten 20-50 mg daily vs placebo

- 1° Endpt: change in peak VO2

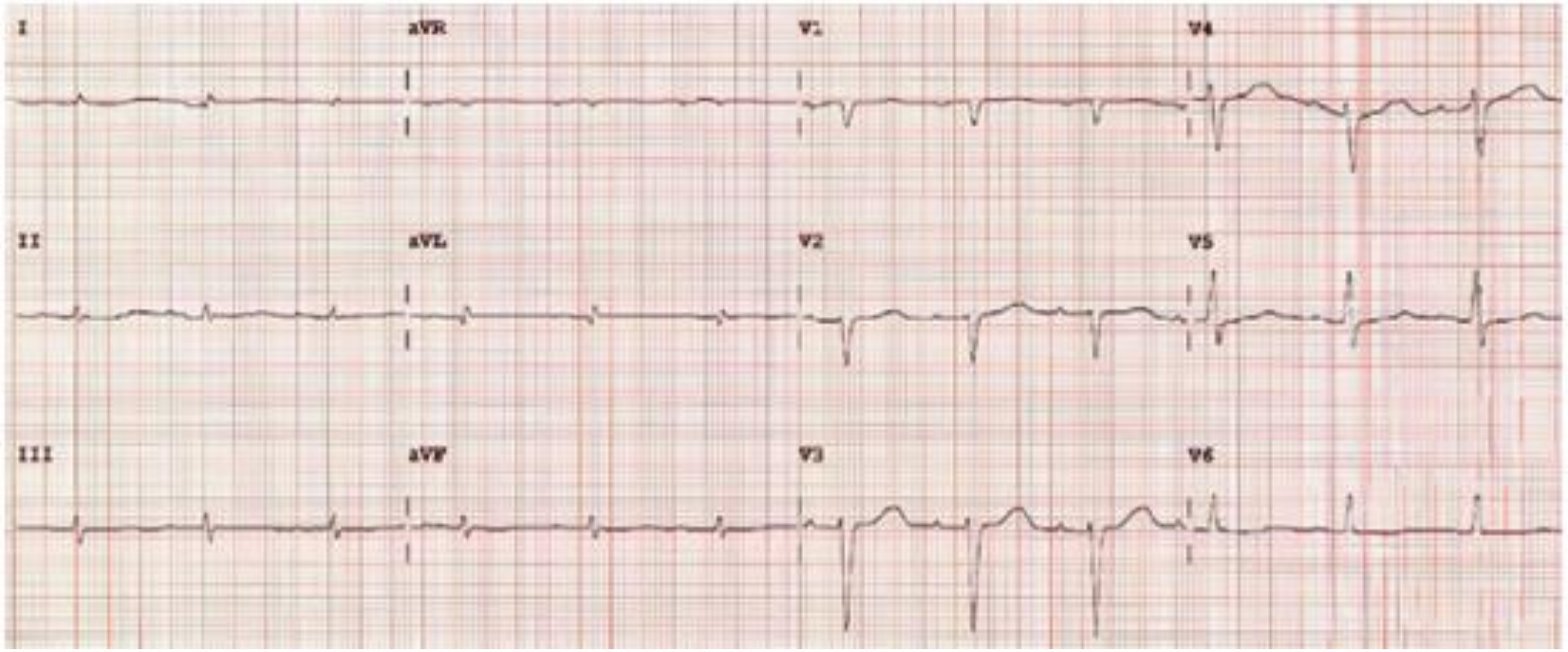




Maron et al. NEJM 2024;390:1849-61.

Question 4.

A 55 y.o. Black man presents with progressive shortness of breath and fatigue for the past 3 months. On review of systems, he reports numbness and tingling in both his feet > hands and pain in his feet that has limited his walking. He denies any CV risk factors and states that his father died of heart failure at the age of 60 years. His exam is unremarkable except for mild JVD. His labs are also within normal limits except for an elevated NT-proBNP of 1280 pg/mL. His echo shows LVEF of 50-55% and concentric LVH with a wall thickness of 13 mm. His EKG is shown below:



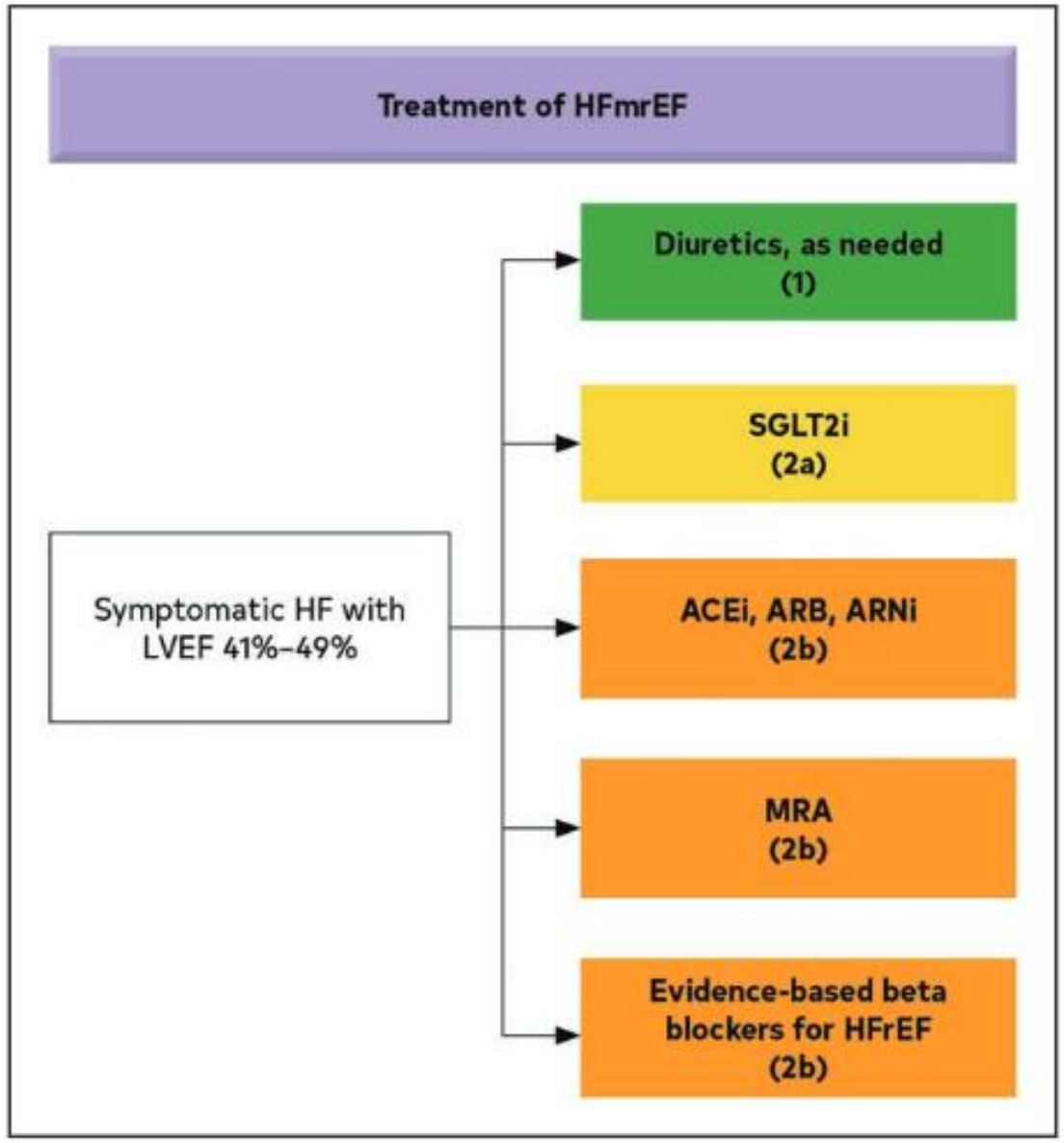
Question 4 contd.

What is the next best diagnostic test?

A. Serum and urine protein electrophoresis
B. Right and left heart catheterization
C. Genetic testing for non-ischemic cardiomyopathy
D. Technetium 99-m pyrophosphate scan

HF with Mid-Range LVEF (41-49%)

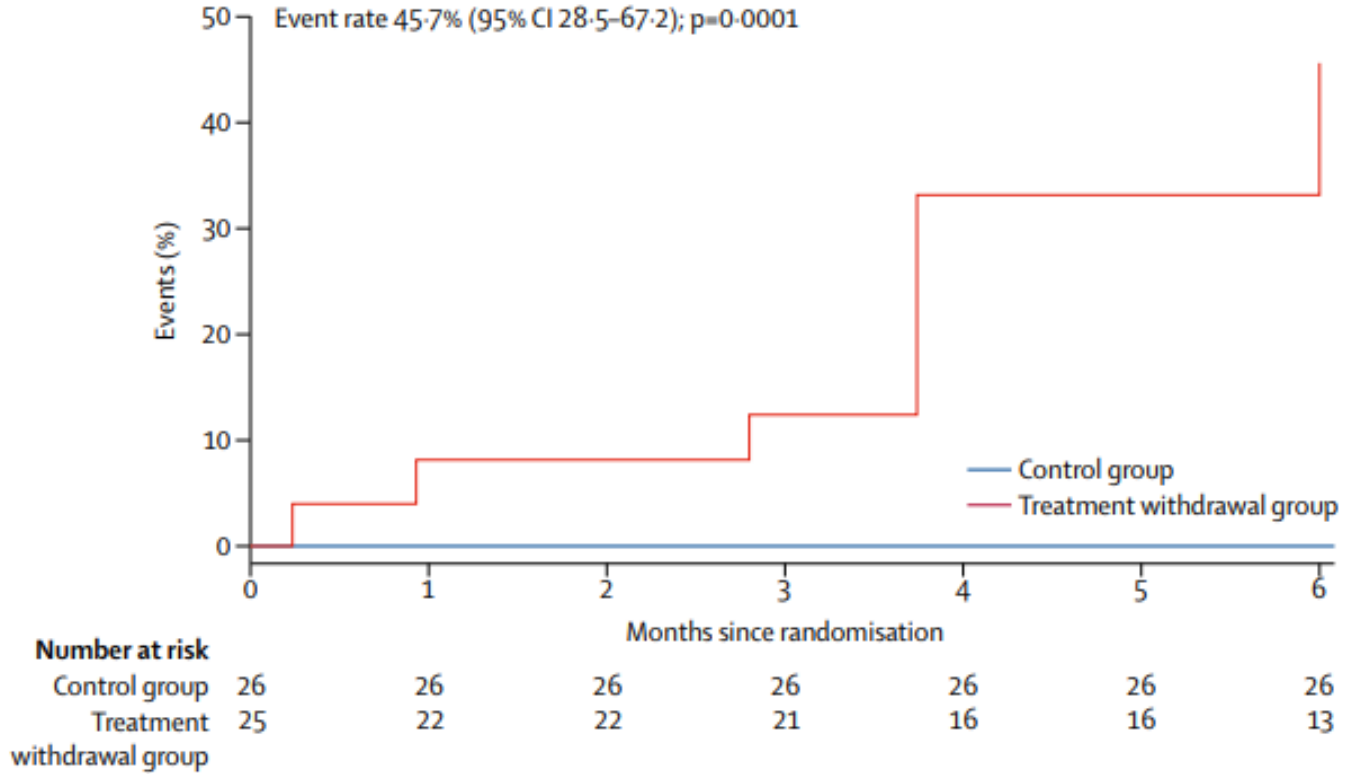
- EMPEROR-Preserved and DELIVER
  - LVEF ≥ 40%
- PARAGON-HF
  - LVEF ≥ 45%
- FINE-ARTS
  - LVEF ≥ 40%



Heidenreich et al. Circulation 2022;145:e876-894

Rationale for Continued GDMT after LV Recovery: TRED-HF

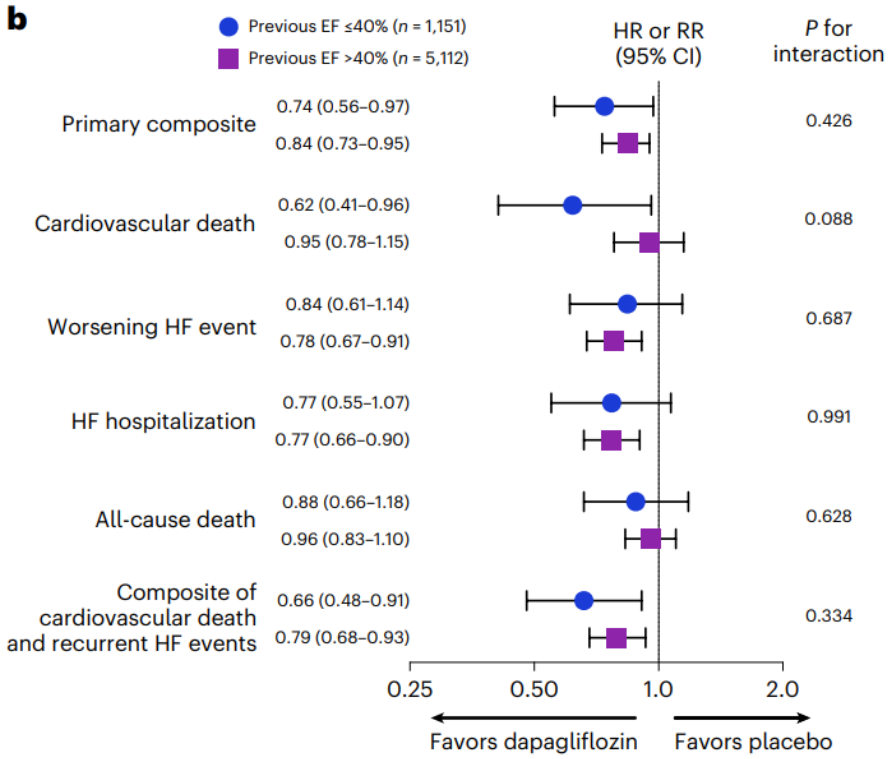
- 51 pts w/ prior HFrEF on GDMT who had recovered: EF > 50%, nl LVEDVi, no sxs, BNP < 250
  - Open label study of GDMT withdrawal
- End-pt: recurrent LVEF < 50%, ↑ LVEDVi, BNP > 400, HF sxs



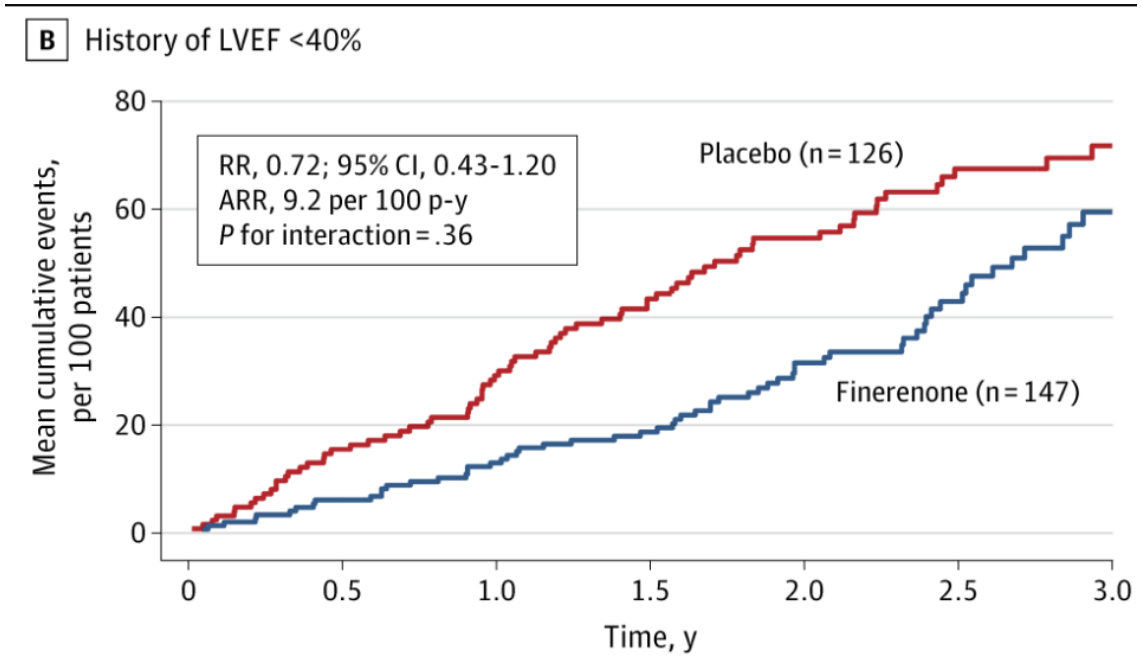
Halliday et al. Lancet 2019;393:61-73.

HF with Improved EF
LVEF ≤ 40% improved by ≥10% to EF >40%

Post-hoc analysis of DELIVER



Post-hoc analysis of FINE-ARTS



Vardeny et al. Nature Med. 2022;28:2504-11; Pabon et al. JAMA Cardiol. 2025;10(7):740-5.

What's Coming Next?

- Myosin activators
  - Omecamtiv mecarbil, Danicamtiv
- Anti-inflammatory therapies
  - Anakinra (IL-1 antagonist)
  - Ziltivekimab (IL-6 inhibitor)
- Gene/ RNA based therapies
  - Augmentation of cardiac contractility – SERCA2a, Adenylyl cyclase type 6
  - siRNA and anti-sense oligonucleotides for ATTR cardiomyopathy
  - Gene editing with CRISPR
- Sotatercept: fusion protein targeting activin/TGF-β (anti-remodeling in pulmonary vasculature)
  - CADENCE trial: improved hemodynamics and 6-min walk in Grp 2 PH with HFpEF

Take Home Messages

For HFmrEF and HFpEF:

- SGLT-2i: reduce morbidity (and mortality)

- MRA:
  - Fineranone: new option to reduce HF hospitalizations
  - Spironolactone: probably helpful but data unclear

- ARNI: reduces HF hospitalizations in patients with below normal EF, w/ decreasing benefit as EF increases

- HFpEF is a cardiometabolic disease: GLP-1 agonists are emerging therapies

HFimpEF: residual risk remains and continue GDMT indefinitely

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12. Fontana M et al. Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy. N Engl J Med. 2025 Jan 2;392(1):33-44.
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14. Maron MS et al. Aficamten for Symptomatic Obstructive Hypertrophic Cardiomyopathy. N Engl J Med. 2024 May 30;390(20):1849-1861.

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Answer 1.

Correct Answer: B

All patients with HFrEF should be on a 4-drug regimen to reduce the risk of HF hospitalization and death. These include ARNI/ACEi/ARB + b-blocker + MRA + SGLT-2i. This patient is already on the first 3 drugs, albeit at low doses. The guidelines recommend that you add a SGLT-2i before trying to maximize the doses of the other drugs. While you could give more torsemide, he is very mildly volume overloaded and the increase may result in worsening renal dysfunction. SGLT-2i also has a mild diuretic effect and therefore this may result in some diuresis while preserving renal function in the long run.

Answer 2.

Correct Answer: C

This patient is in NYHA Class III HF despite being on a good medical regimen. She cannot tolerate RAAS inhibition due to her renal function. She is therefore on hydralazine and isordil per the guidelines. She cannot take SGLT-2i since they are currently contraindicated in patients with eGFR < 25 ml/min/1.73 m^2. She cannot take ivabradine since she is in afib. Therefore, the only viable choice for her would be to add vericiguat which is safe to use in patients with eGFR 15-30 ml/min/1.73 m^2. Furthermore, she has adequate BP room to tolerate additional vasodilation.

Answer 3.

Correct Answer: E

SGLT-2i, finerenone, and tirzepatide have all been shown to reduce HF hospitalizations in RCTs of patients with HFpEF.
Trials of candesartan, sacubitril-valsartan, and spironolactone suggested a trend towards improvement but did not significantly reduce HF hospitalizations in patients with HFpEF.
STEP-HFpEF evaluated changes in quality of life, 6 min walk distance and biomarkers but did not evaluate hard-endpoints such as HF hospitalizations or mortality in patients with HFpEF. Therefore, it is not known whether semiglutide reduces HF hospitalizations in patients with HFpEF.

Answer 4.

Correct answer: A

This patient's history (HF sxs and peripheral neuropathy) and test findings (LVH with decreased voltage on EKG) are concerning for cardiac amyloidosis. His race and family history raise the concern for mutant ATTR amyloidosis. V122I is a common pathogenic TTR mutation that is found in 3-4% of individuals of African ancestry in the US and is associated with cardiomyopathy and heart failure. The algorithm suggested by the guidelines recommends checking serum light chains as the first step in patients with a suspicion for cardiac amyloidosis. If this is negative, one would proceed with a technetium 99-m pyrophosphate scan which if positive can be diagnostic of ATTR amyloidosis.