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

TREATMENT OF HEART FAILURE IN 2024

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- Clinical focus: Heart Failure and Cardio-Oncology
- Research focus: Cardio-Oncology

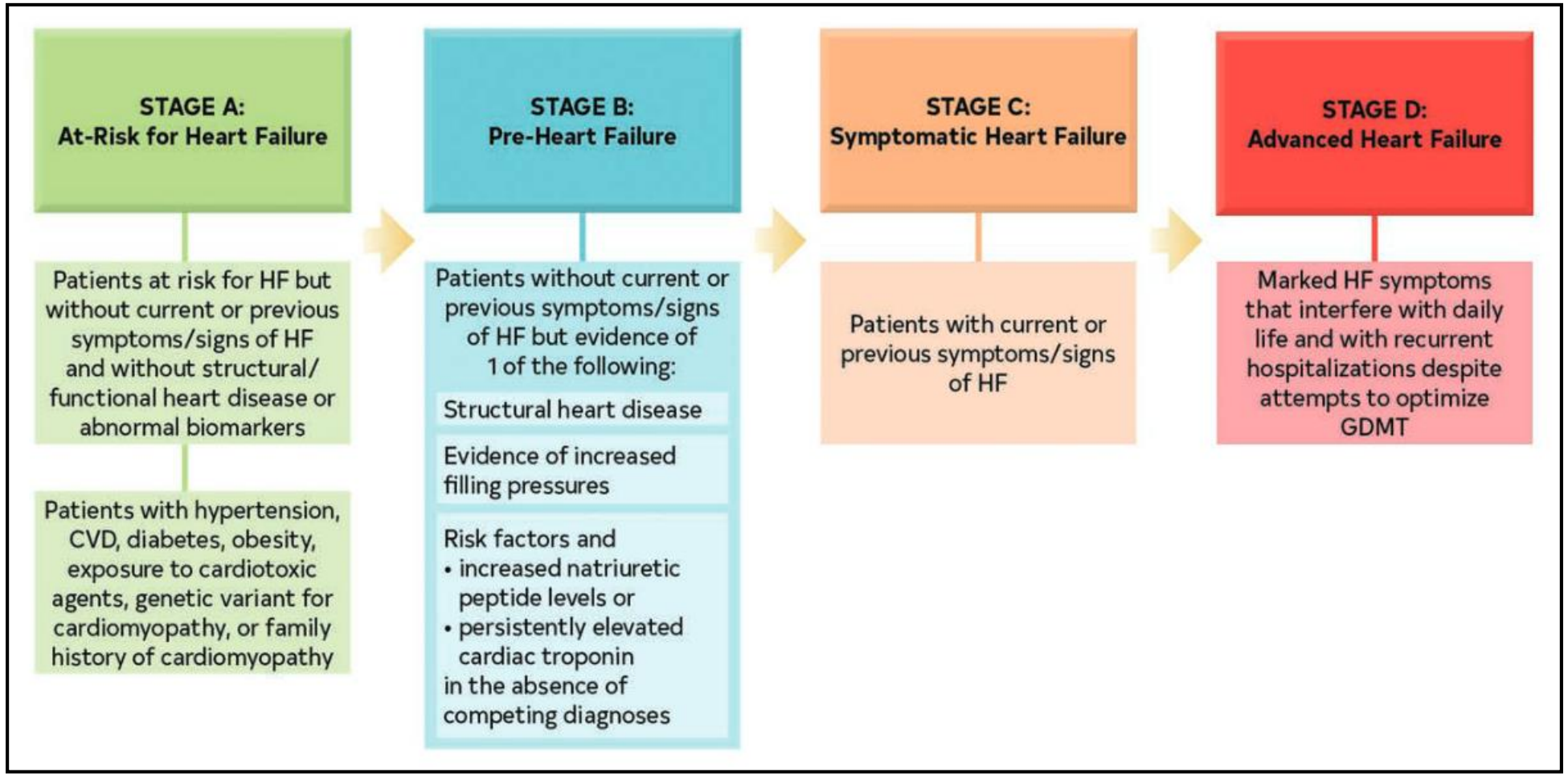
DISCLOSURES

- Research Support: Bristol Myers Squibb
- Consulting Fees: Altathera Pharmaceuticals, AstraZeneca, Regeneron Pharmaceuticals, and Takeda Oncology

OBJECTIVES

- Updates from the 2022 HF guidelines
- Novel therapies for HF w/ reduced ejection fraction (HFrEF)
- Novel therapies for HF w/ preserved ejection fraction (HFpEF)

Stages of Heart Failure



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

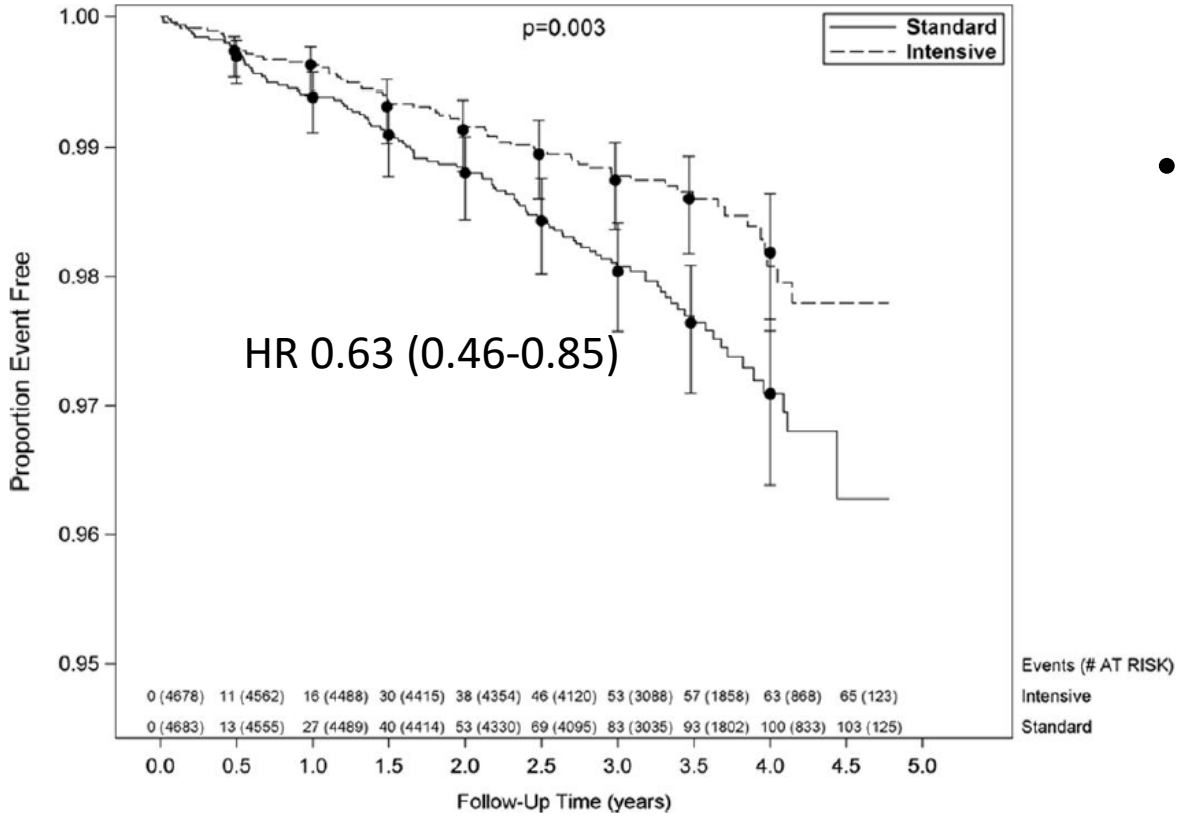
Stage A HF: Primary Prevention of HF

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.

SPRINT: Intensive BP Control Reduces Incident HF Hospitalizations

- N=9361 hi-CV risk pts w/ SBP 130-180
- RCT of intensive (< 120 mm Hg) vs. standard BP control (135-139 mm Hg)



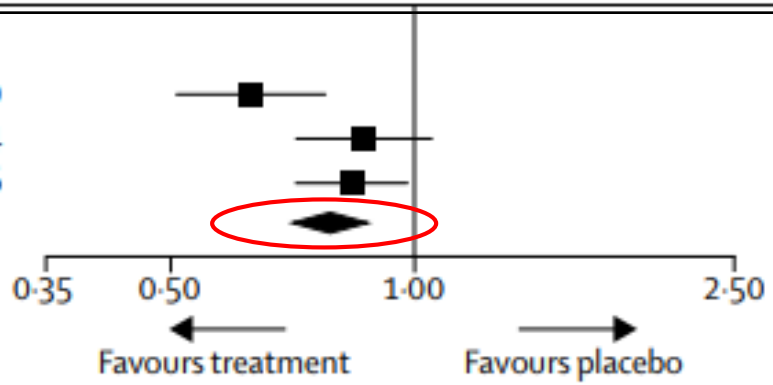
- **Target BP < 130/80**

Upadhya et al. Circ Heart Fail. 2017 Apr;10(4). pii: e003613

SGLT-2i Reduce HF Hospitalizations

- 34,322 pts w/ established CVD or at high-risk for CVD + Type II DM
  - Meta-analysis of 3 RCTs of SLGT-2i vs. placebo

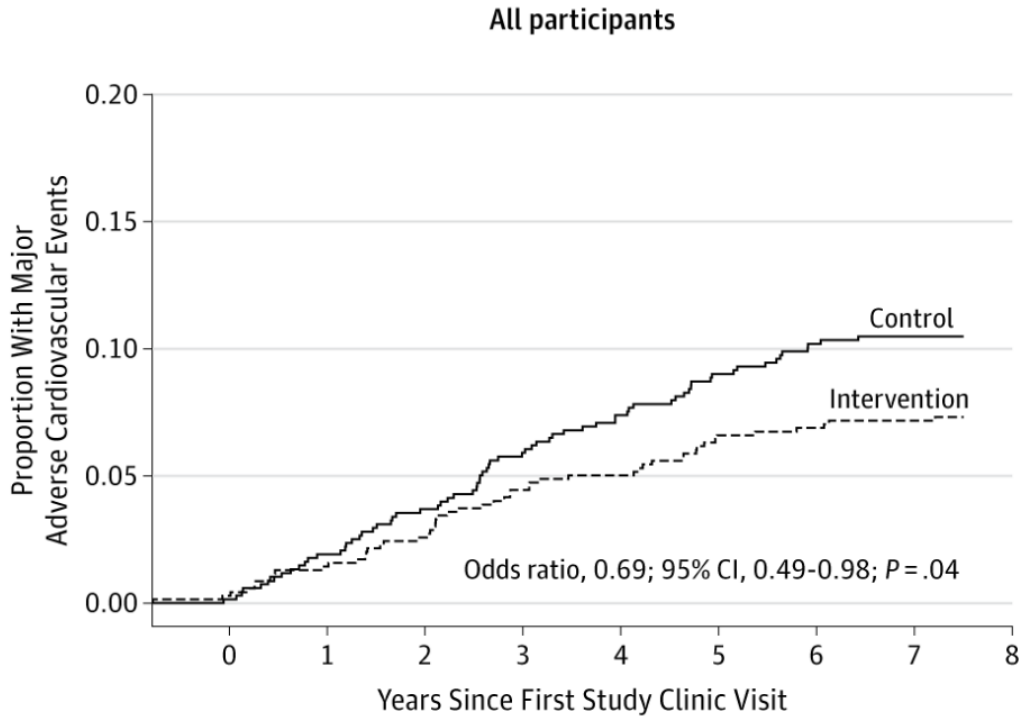
	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo			
Patients with no history of heart failure								
EMPA-REG OUTCOME	4225	2089	339	15·5	24·9	30·0		0·63 (0·51–0·78)
CANVAS Program	4992	3689	449	13·6	15·2	32·4		0·87 (0·72–1·06)
DECLARE-TIMI 58	7730	7706	599	8·9	10·5	37·6		0·84 (0·72–0·99)
Fixed effects model for no history of heart failure (p<0·0001)								**0·79 (0·71–0·88)**

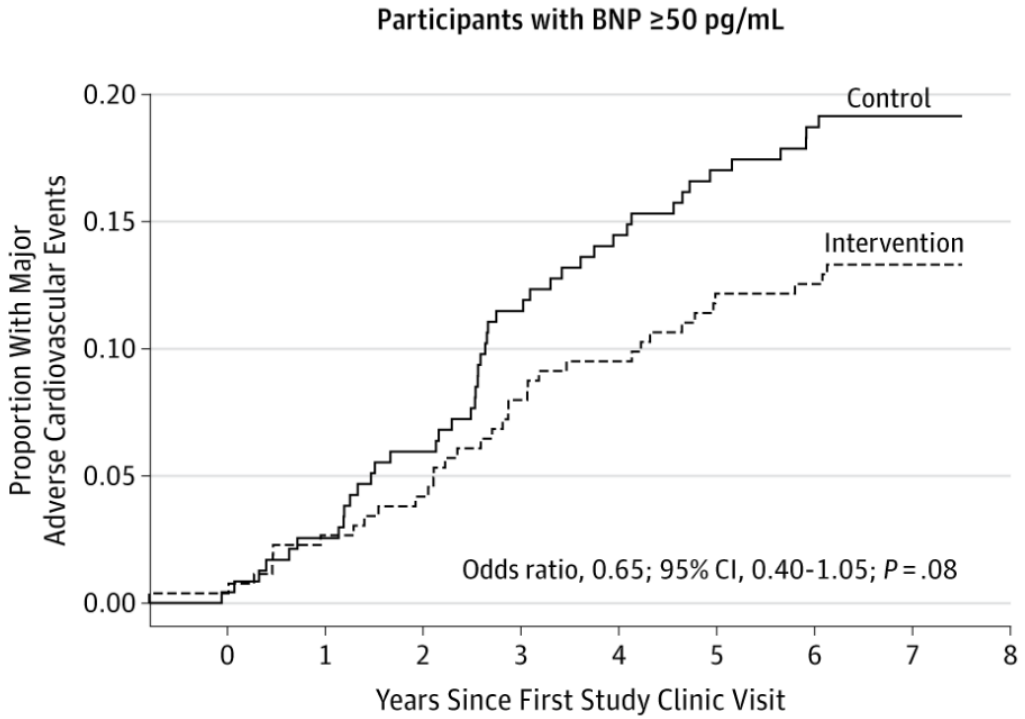


Zeniker et al. Lancet 2019;393:31-9.

STOP-HF Trial: BNP Screening and Cardiology Driven Risk Factor Modification Can Reduce Incident HF

- N=1374 pts, age > 40 yrs, ≥ 1 CV risk factor
- RCT: 1:1 usual care vs. BNP testing and referral to cardiology if BNP > 50 pg/ml
- Incident asymptomatic or symptomatic HF: OR 0.55 (95% CI 0.37-0.82), p=0.003





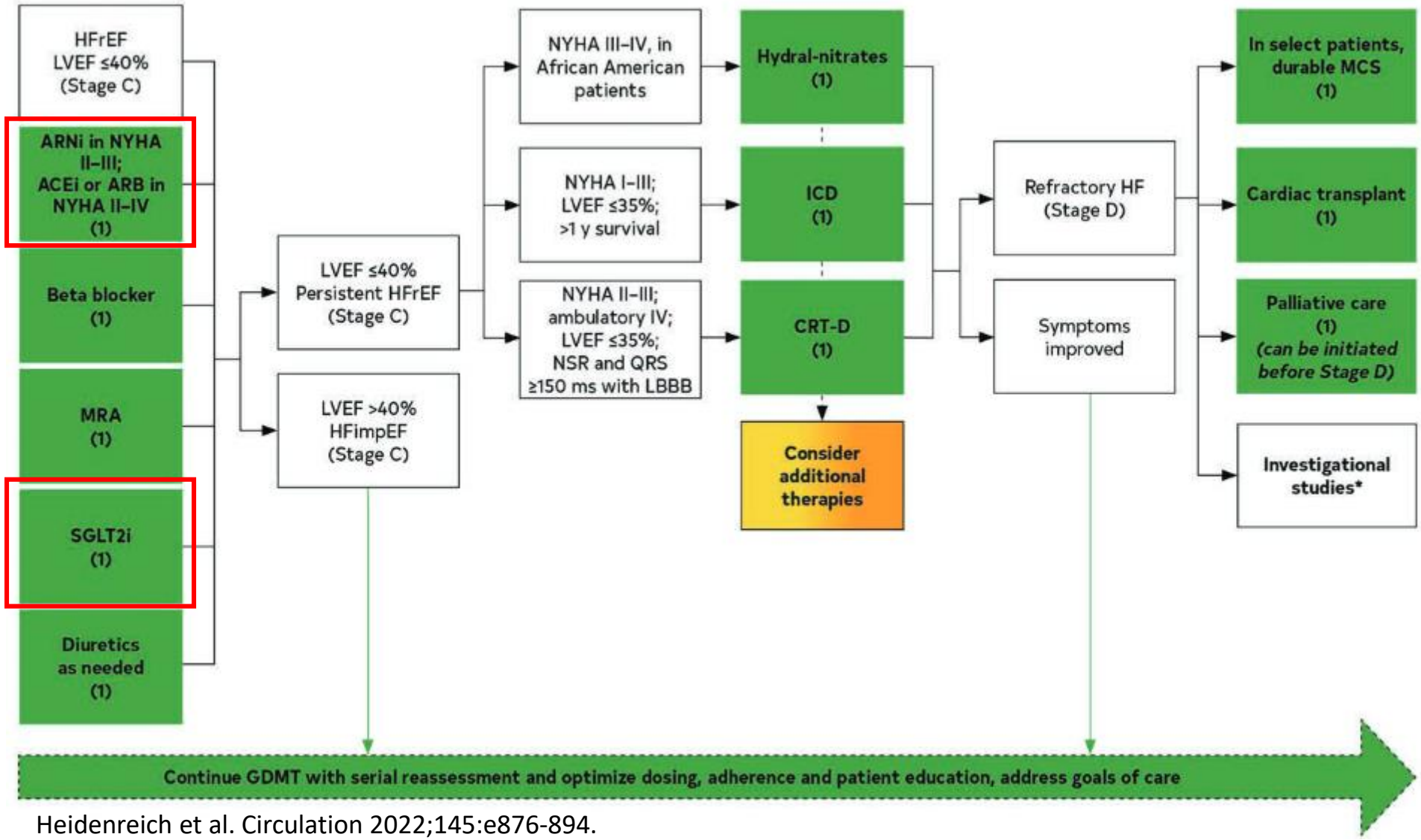
Ledwidge et al. JAMA 2013;310:66-74

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
- ICD for NYHA Class I pts w/ LVEF ≤ 30%, 40 days after MI
- *Non-dihydropyridine CCB and thiozolidinediones should be avoided in LVEF < 50%*

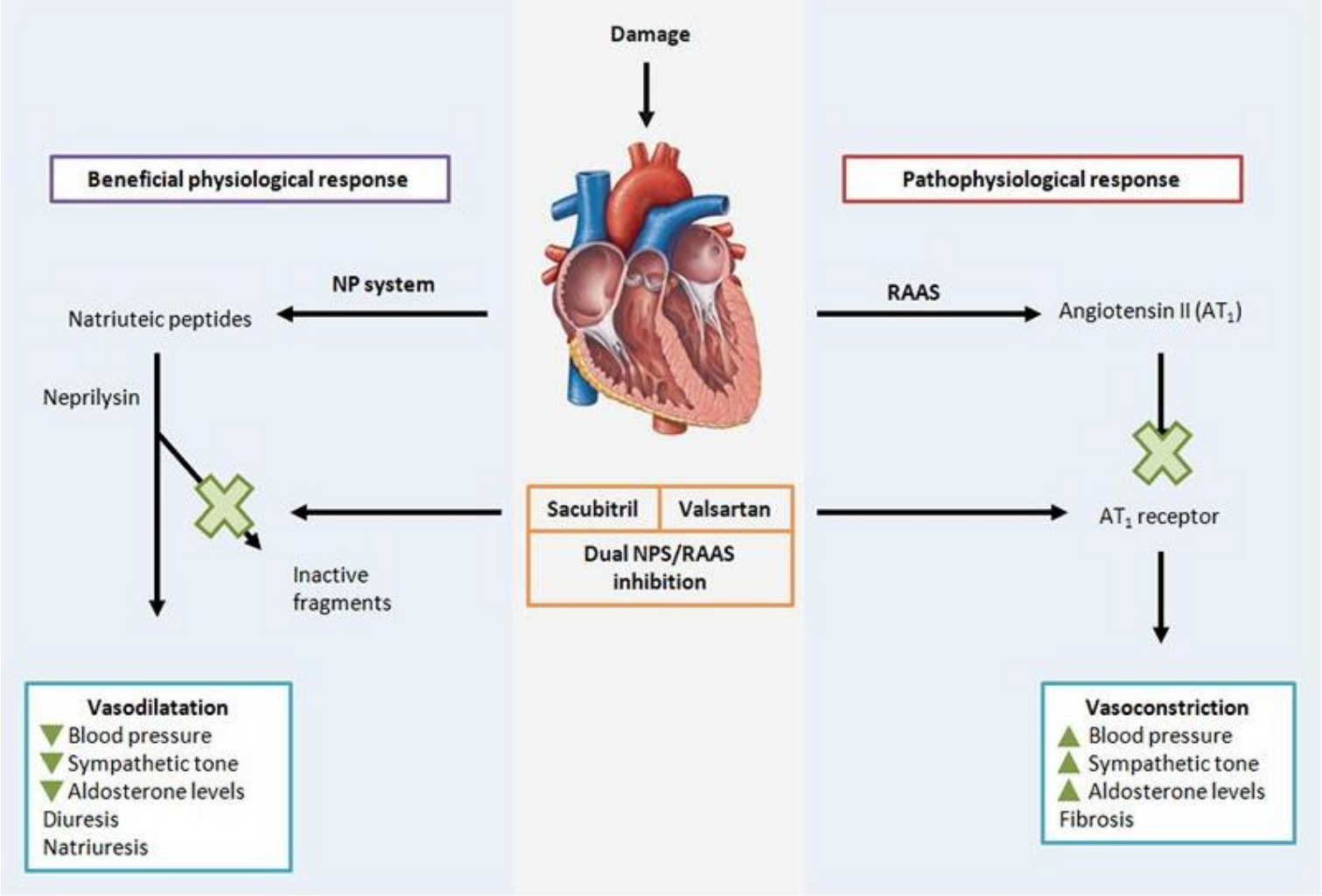
Heidenreich et al. Circulation 2022;145:e876-894.

Stage C HF: Symptomatic HF



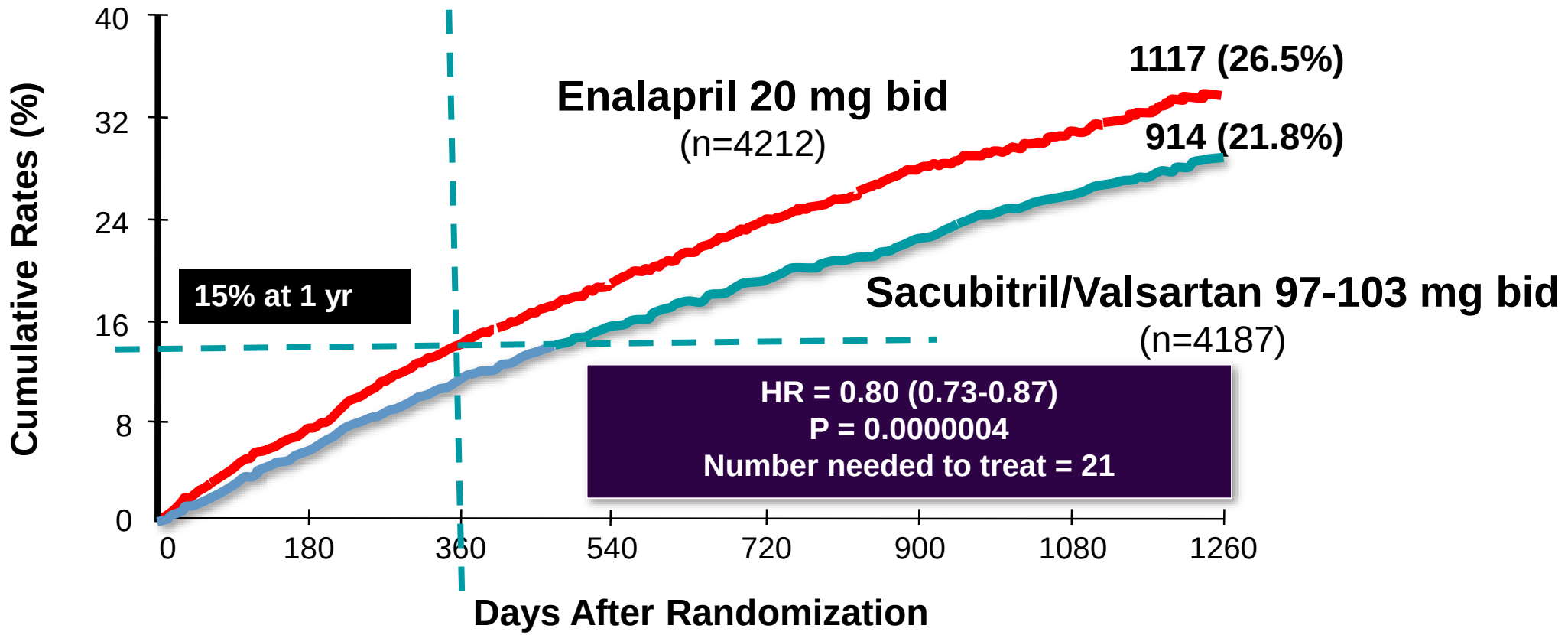
Heidenreich et al. Circulation 2022;145:e876-894.

Mechanism of ARNI



https://www.britishcardiovascularsociety.org/resources/editorials/articles/sacubitrilvalsartan-where-are-we-now

PARADIGM-HF: Primary Endpoint CV Death or HF Hospitalization

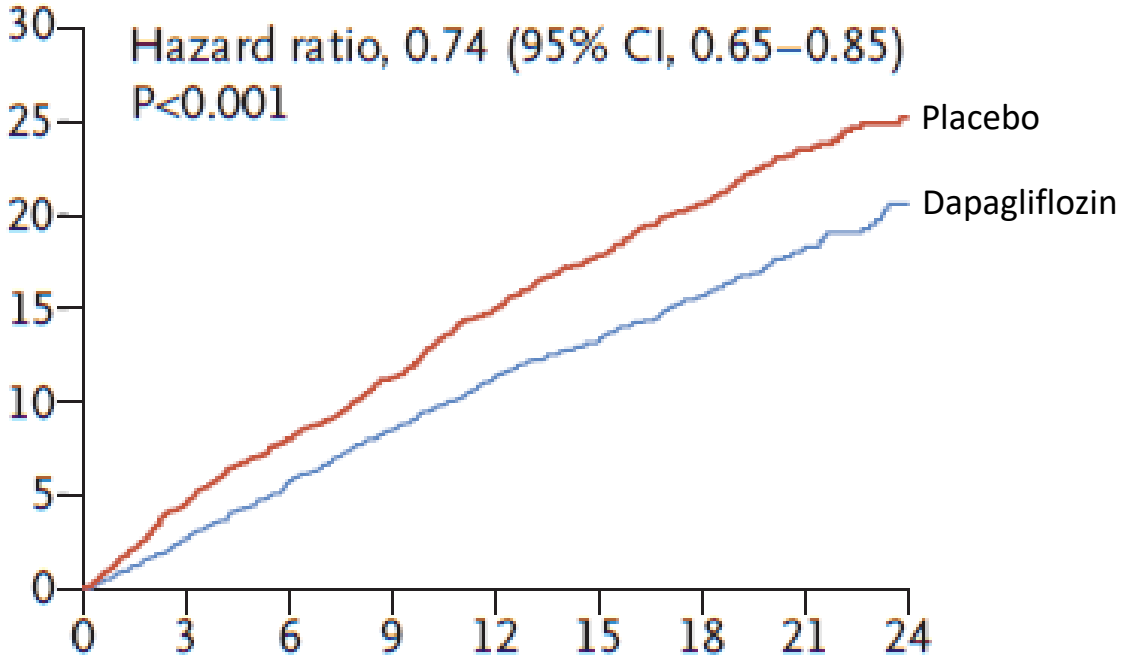


Major Side Effects: Hypotension, hyperkalemia, angioedema, renal dysfunction

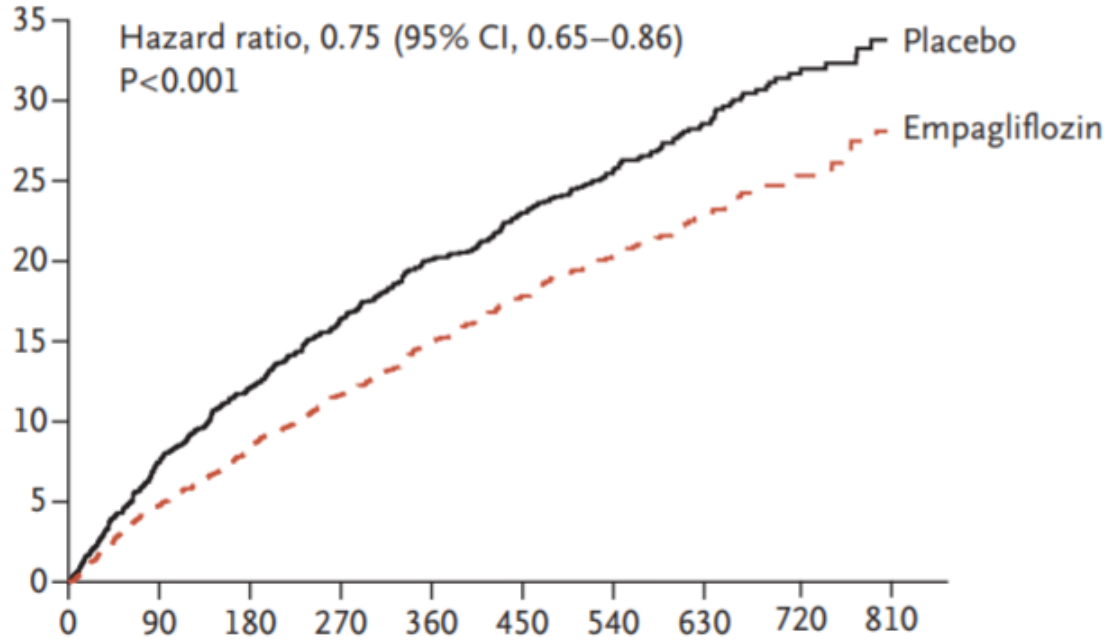
McMurray JJ et al. N Engl J Med 2014;371:993-1004.

SGLT-2i for Symptomatic HFrEF

DAPA-HF:
CV Death, HF Hosp. or ED visit for HF



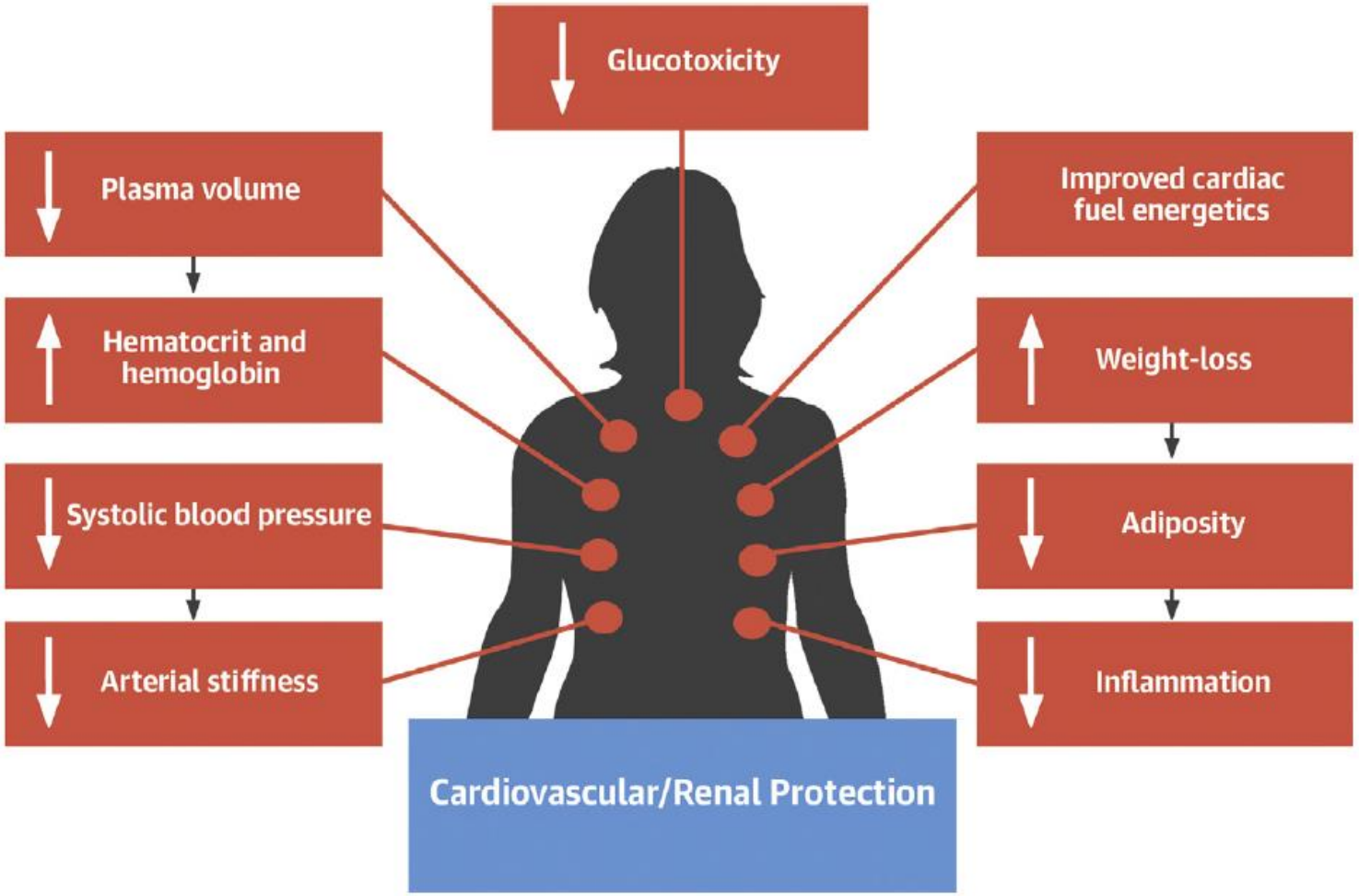
EMPEROROR-REDUCED HF:
CV Death or HF Hospitalization



Benefits are independent of DM

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

Potential Mechanisms for Cardiorenal Benefits of SGLT2i



Zelniker et al. JACC 2020;75(4):422

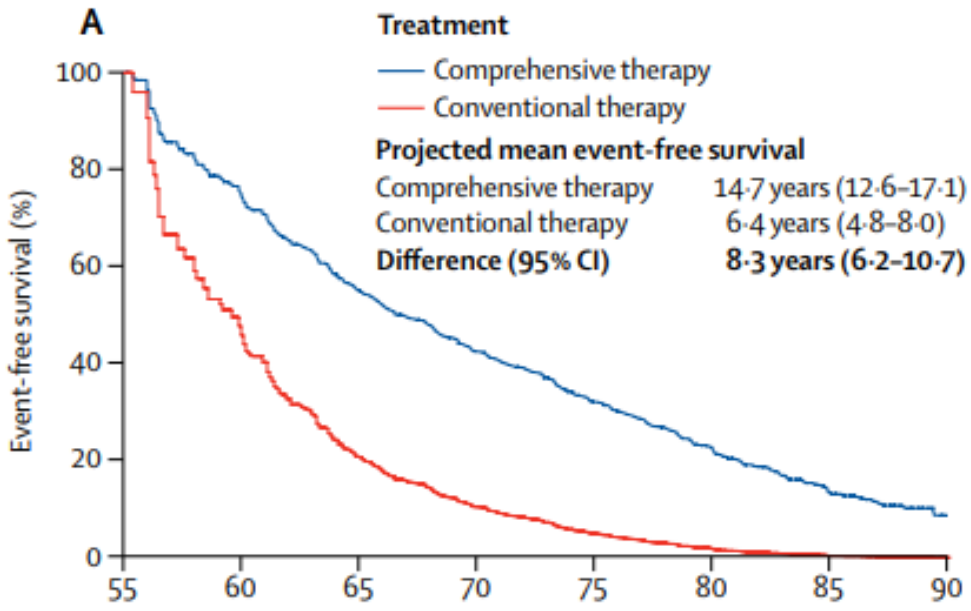
Guideline Update

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]

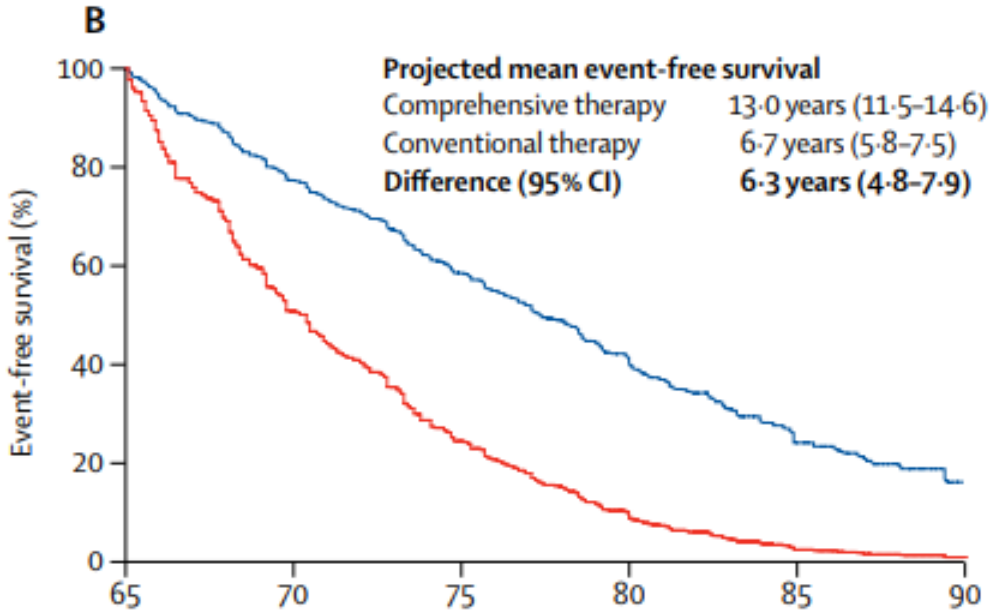
Heidenreich et al. Circulation 2022;145:e876-894.

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.

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 twice 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

TRANSFORM-HF: Torsemide vs. Furosemide

N=2859, HF hospitalization, LVEF < 40% or ↑ Natriuretic peptides

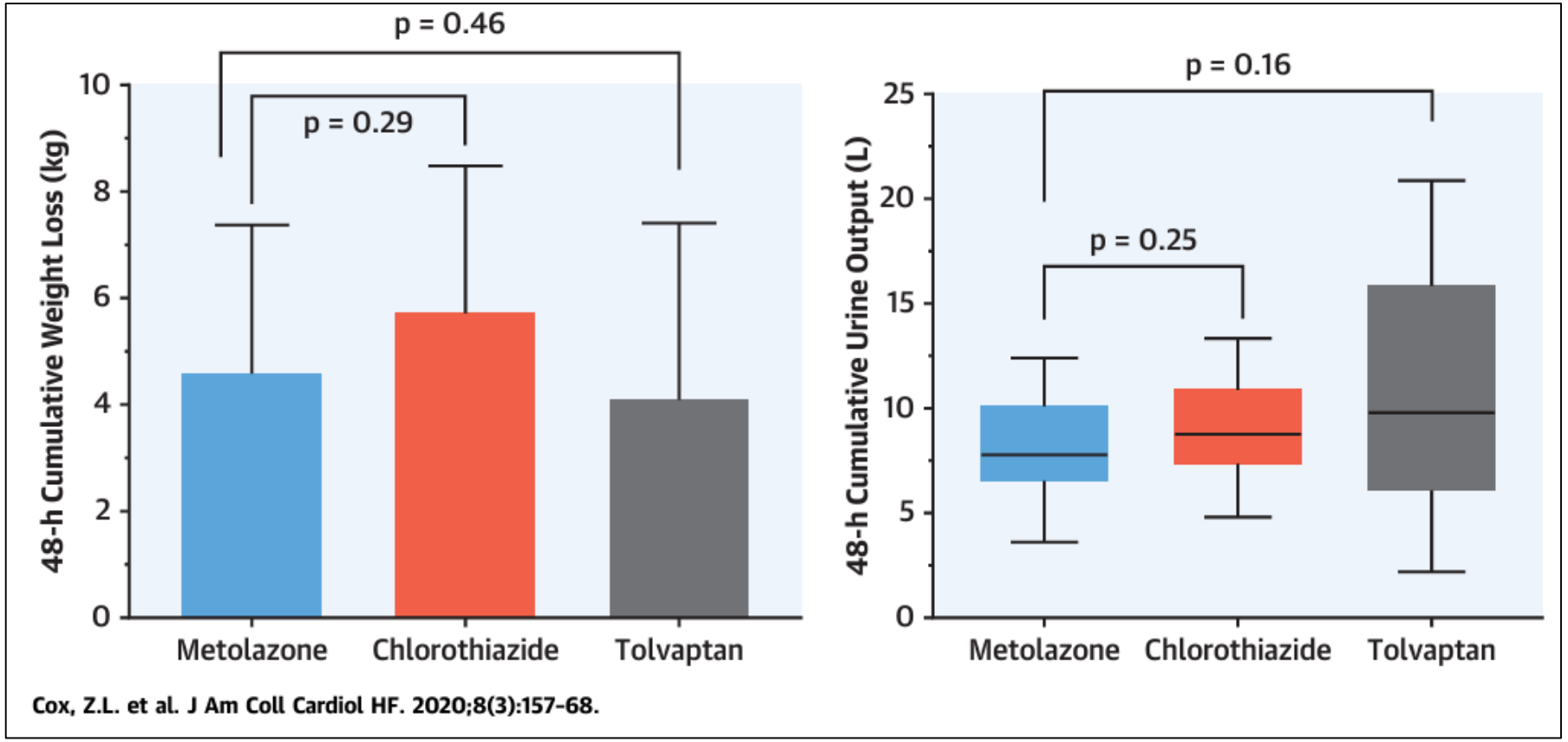
Variable	Torsemide (n = 1431) No. (%)	Torsemide (n = 1431) Events per 100 patient-years	Furosemide (n = 1428) No. (%)	Furosemide (n = 1428) Events per 100 patient-year	Risk reduction (95% CI)[a]	HR (95% CI)[b]	*P* value[b]
Primary outcome							
All-cause mortality	373 (26.1)	17.0	374 (26.2)	17.0	0.12 (−2.85 to 3.14)	1.02 (0.89 to 1.18)	.76
Secondary outcomes							
All-cause mortality or all-cause hospitalization (over 12 mo)	677 (47.3)	99.2	704 (49.3)	107.6	1.99 (−1.79 to 5.56)	0.92 (0.83 to 1.02)	
Total hospitalizations (over 12 mo)	940	106.3	987	111.9		RR, 0.94 (0.84 to 1.07)	
All-cause mortality or all-cause hospitalization (over 30 d)	149 (10.4)	147.2	157 (11.0)	157.5	0.58 (−1.80 to 2.75)	0.94 (0.75 to 1.18)	

Mentz et al. JAMA 2023;329 (3):214-223.

3-T Trial: Diuretic Strategies for ADHF with Diuretic Resistance

N=60, ADHF, < 2 L urine/12 hr despite IV Lasix ≥ 240 mg/day

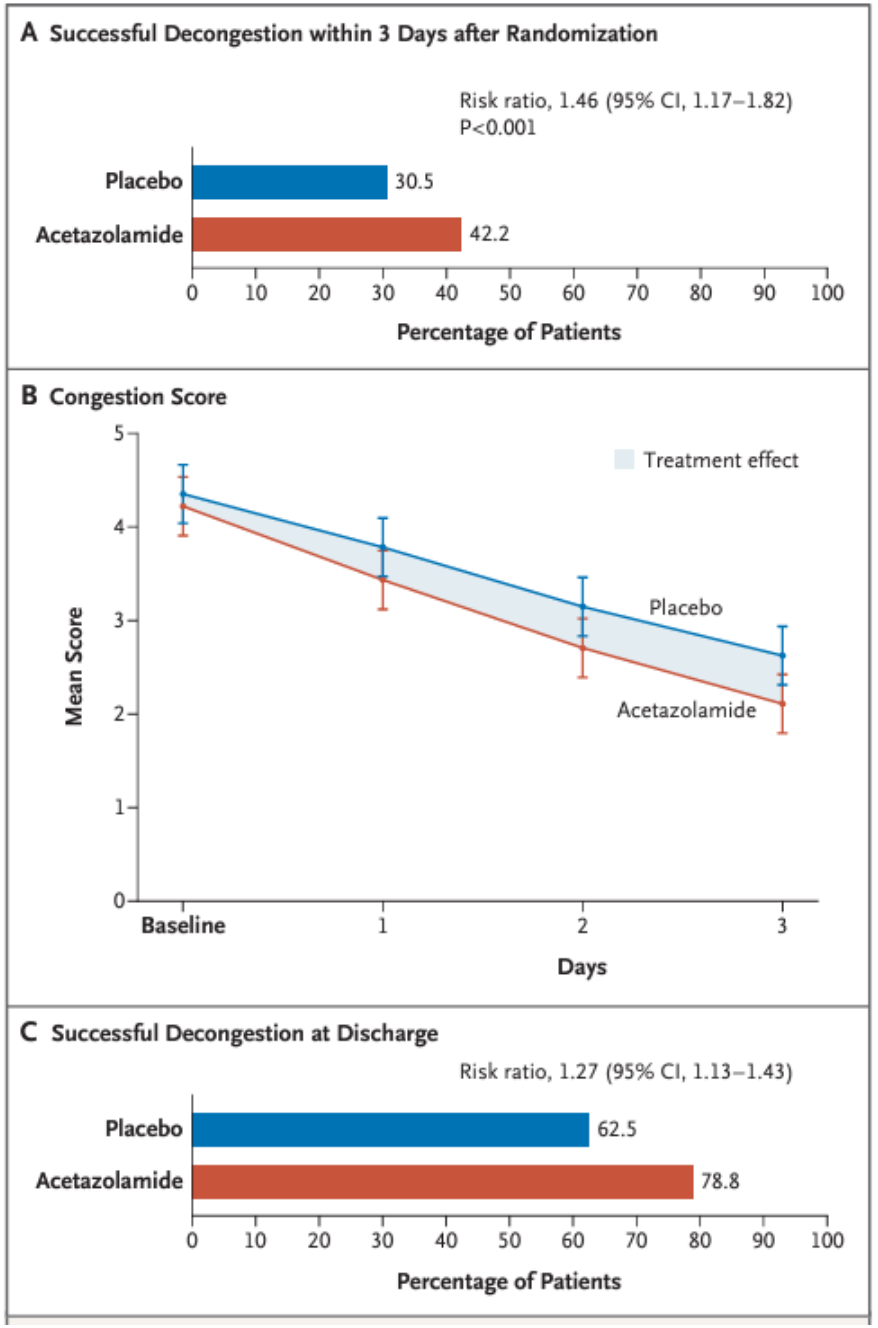
1:1:1 metolazone 5 mg po bid vs. chlorthalidone 500 mg IV bid vs. tolvaptan 30 mg po daily



Cox, Z.L. et al. J Am Coll Cardiol HF. 2020;8(3):157-68.

ADVOR: Diuretics ± Acetozolamide for ADHF

- N=519 pts
- ADHF
- HFpEF + HFrEF
- NT-proBNP > 1000 pg/ml *or* BNP > 250 pg/ml
- IV Lasix ≤ 80 mg/day
- *No SGLT-2i*



Mullens et al. N Engl J Med 2022;387:1185-95.

CLOROTIC Trial: Diuretics ± HCTZ for ADHF

Study population

Randomized, double-blind, placebo-controlled clinical trial

History of chronic heart failure

Treatment with oral furosemide (80-240 mg/day)

Admission for acute decompensation

230 patients were randomized to 5 days of oral treatment with hydrochlorothiazide or placebo

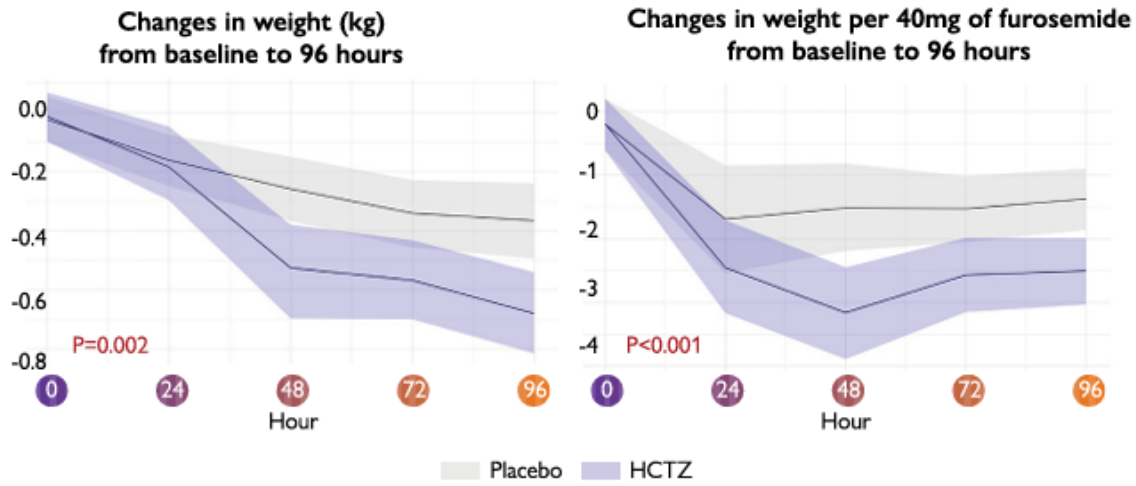
83 years-old

48% women

Comorbidities

HF-PEF 65%

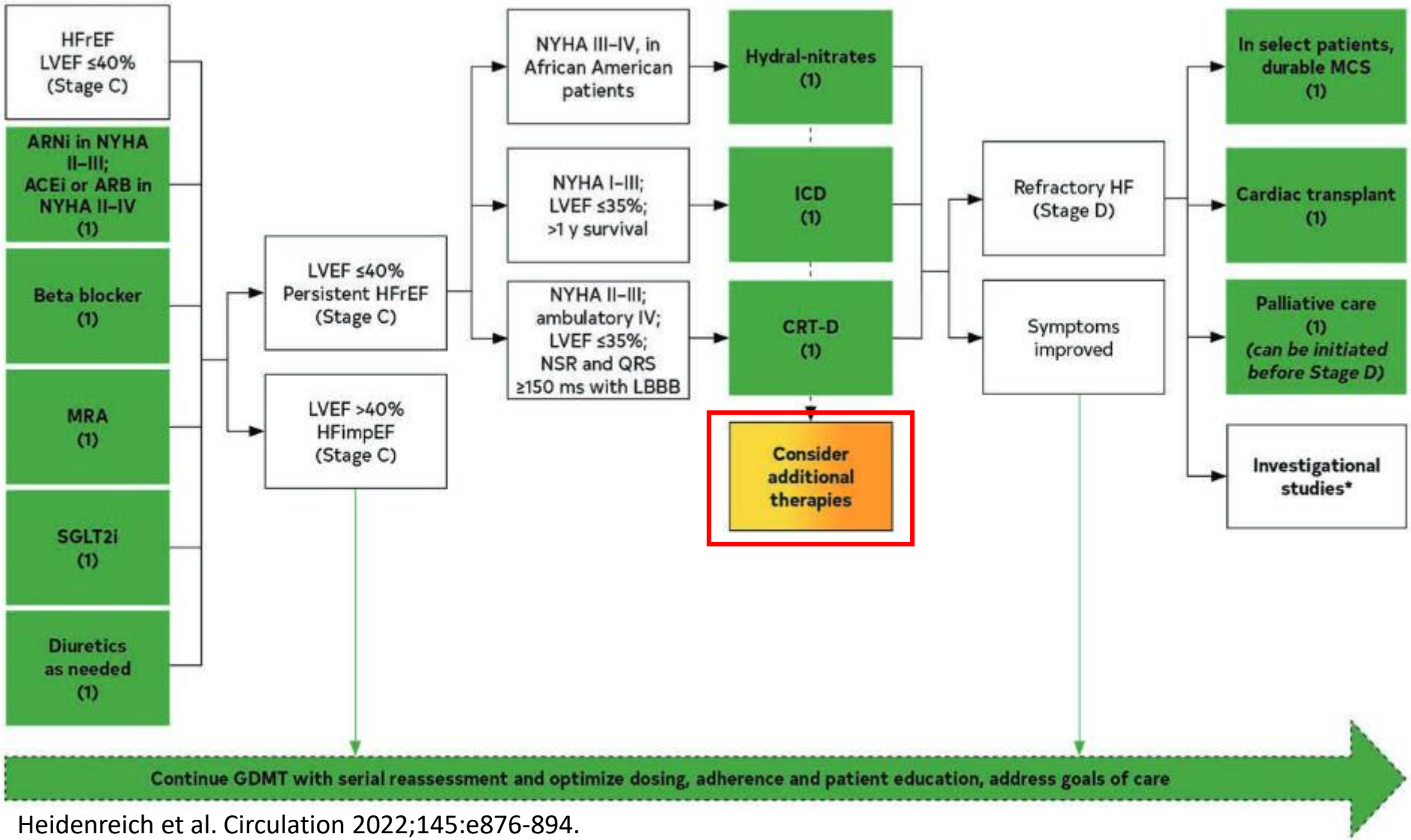
Efficacy



Safety	Placebo	HCTZ	p-value
All-cause mortality at 90 days	19 (16.4%)	23 (20.2%)	0.566
All-cause rehospitalizations at 90 days	40 (34.5%)	43 (37.7%)	0.709
Impaired renal function (serum creatinine and eGFR)	20 (17.2%)	53 (46.5%)	<0.001
Hyponatraemia (Na+ ≤ 130 mmol/L) - (Na+ ≤ 125 mmol/L)	6 (5.2%)–2 (1.7%)	10 (8.8%)–3 (2.6%)	0.416–0.682
Hypokalaemia (K+ ≤ 3.0 mmol/L) - (K+ ≤ 2.5 mmol/L)	18 (16.1%)–0 (0.0%)	43 (40.6%)–2 (1.8%)	<0.001–0.245
Serious adverse events	27 (23.3%)	26 (22.8%)	0.93

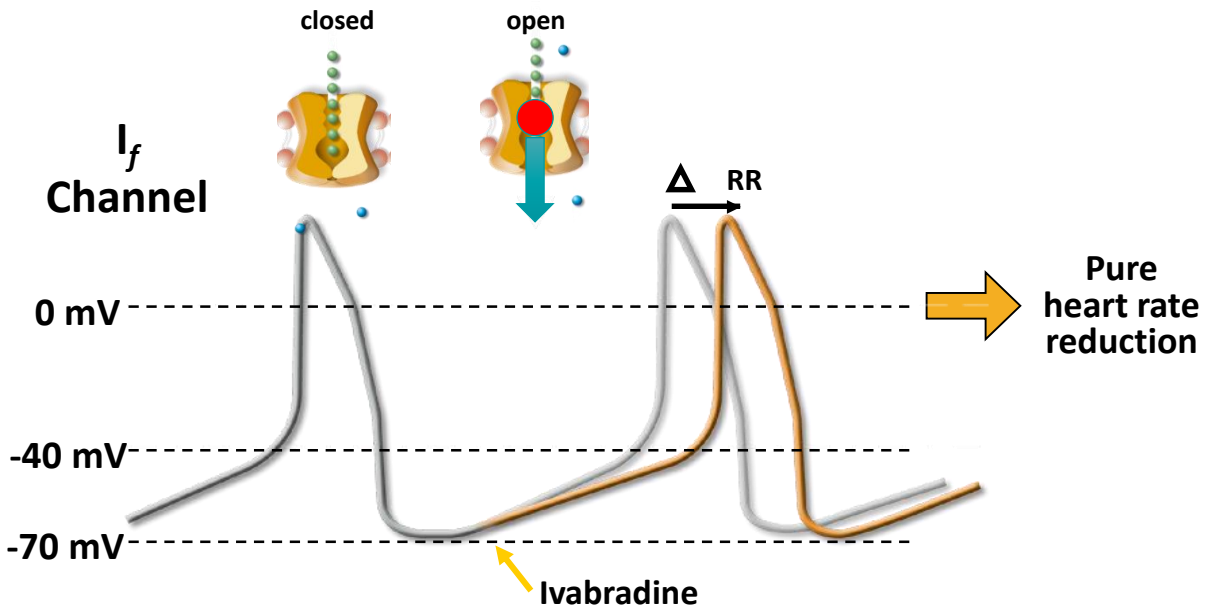
Trullas et al. Eur Heart J 2023;44:411-21.

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

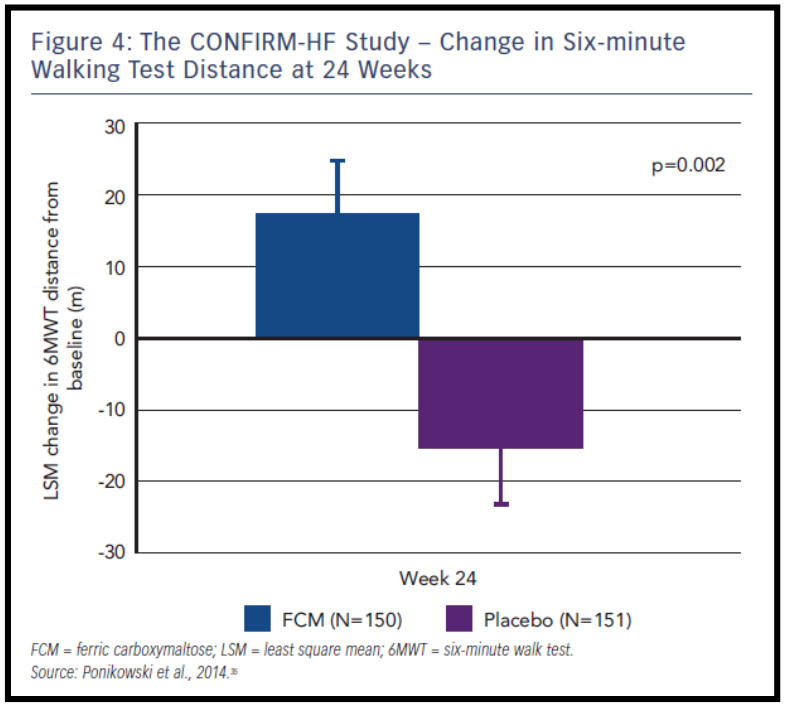
COR	LOR	
IIa Moderate	**B-R**	**Ivabradine may be beneficial to reduce HF hospitalization for patients with symptomatic stable chronic HFrEF who are receiving GDMT, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of ≥ 70 bpm at rest.**

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

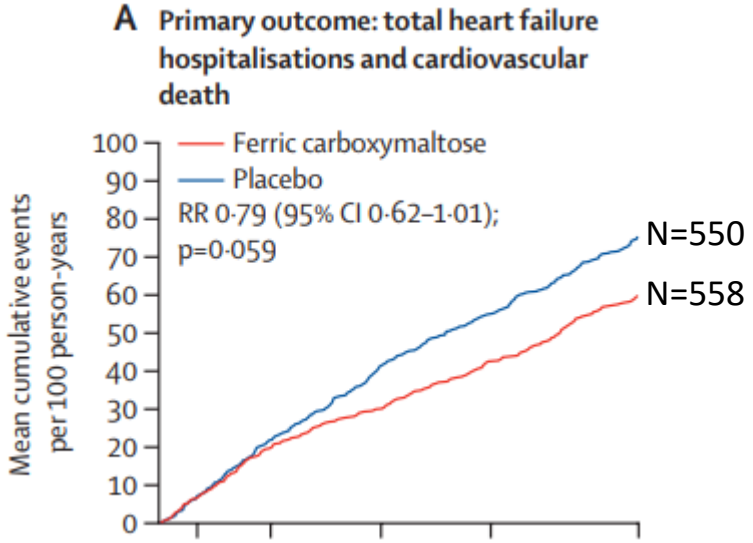
Treatment of Iron Deficiency in HFrEF

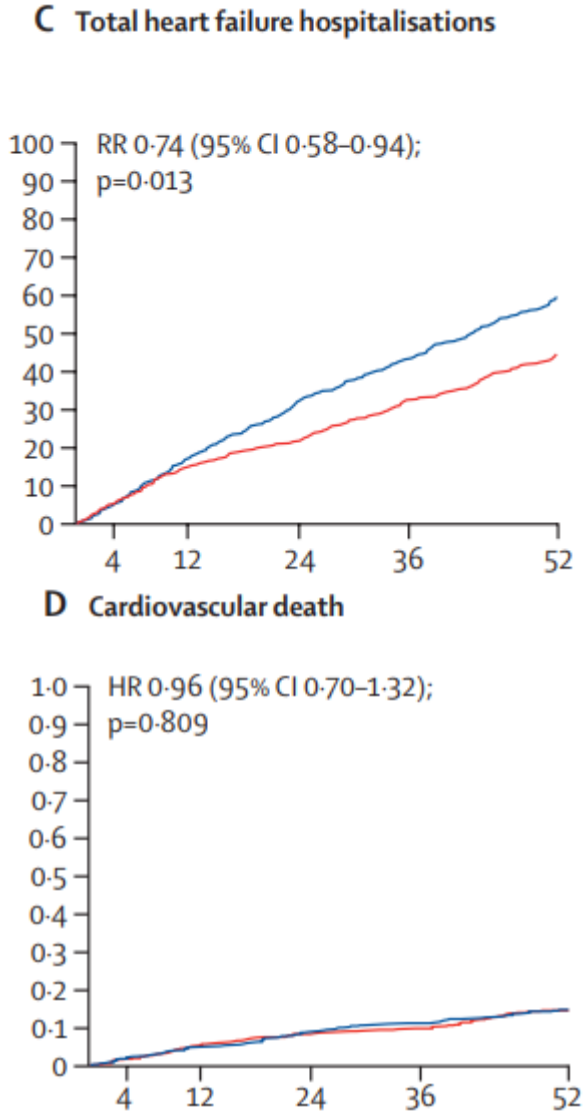
- NYHA II-IV HFrEF, ferritin < 100 ng/ml *OR* ferritin 100-300 ng/ml + transferrin saturation < 20%

CONFIRM-HF



AFFIRM-AHF





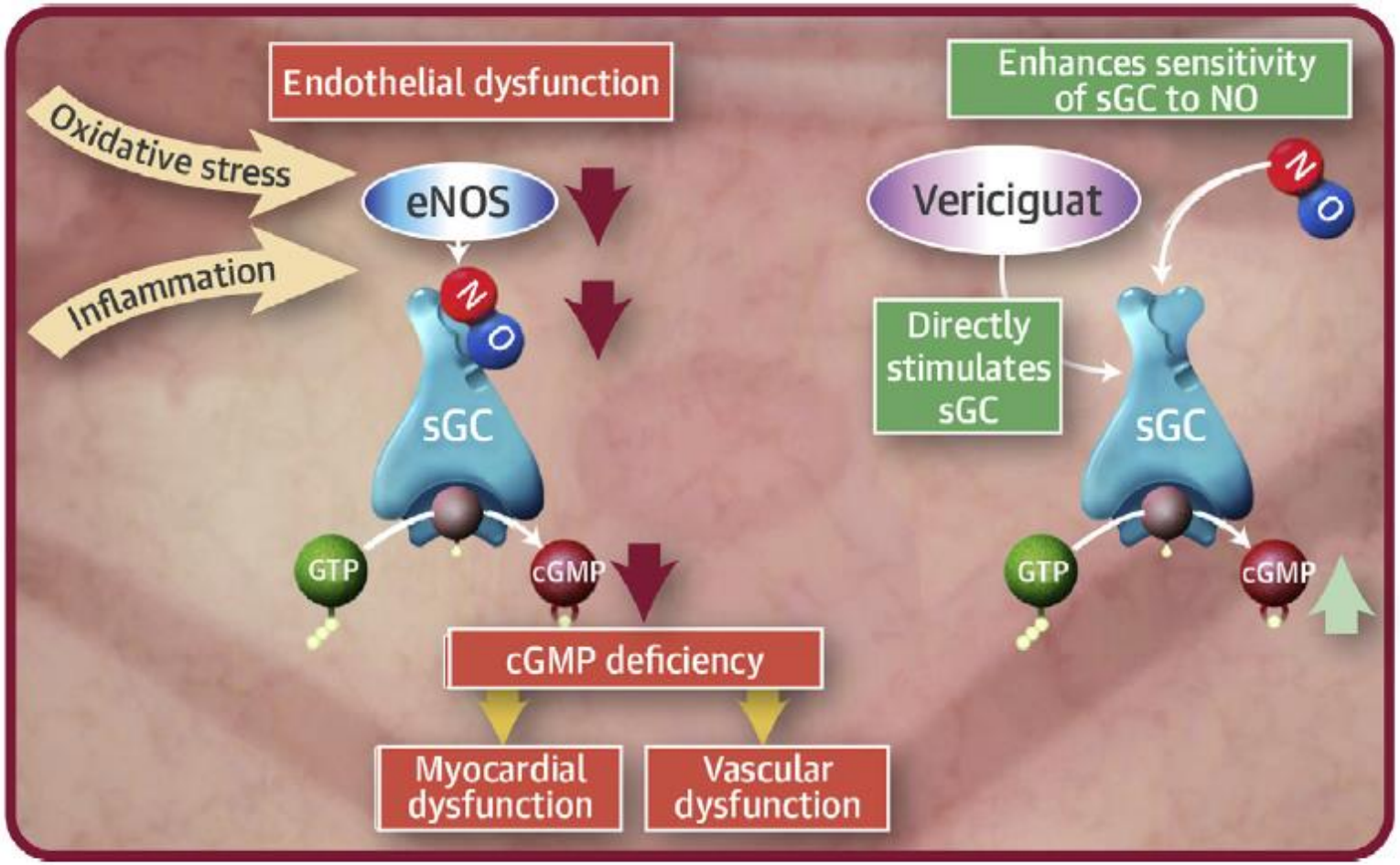
Ponikowski et al. Eur Heart J 2015;36(11):657; Ponikowski et al. Lancet 2020;396(10266):1895.

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

Vericiguat: Mechanism of Action



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

VICTORIA: Individual Endpoints

Outcome	Vericiguat (N=2526)		Placebo (N=2524)		Hazard Ratio (95% CI)†	P Value‡
	no. (%)	*events/100 patient-yr*	*no. (%)*	*events/100 patient-yr*		
Primary composite outcome and components						
Death from cardiovascular causes or first hospitalization for heart failure	897 (35.5)	33.6	972 (38.5)	37.8	0.90 (0.82–0.98)	0.02
Death from cardiovascular causes§	206 (8.2)		225 (8.9)			
Hospitalization for heart failure	691 (27.4)		747 (29.6)			
Secondary outcomes						
Death from cardiovascular causes	414 (16.4)	12.9	441 (17.5)	13.9	0.93 (0.81–1.06)	
Hospitalization for heart failure	691 (27.4)	25.9	747 (29.6)	29.1	0.90 (0.81–1.00)	
Total hospitalizations for heart failure¶	1223	38.3	1336	42.4	0.91 (0.84–0.99)	0.02
Secondary composite outcome and components						
Death from any cause or first hospitalization for heart failure	957 (37.9)	35.9	1032 (40.9)	40.1	0.90 (0.83–0.98)	0.02
Death from any cause§	266 (10.5)		285 (11.3)			
Hospitalization for heart failure	691 (27.4)		747 (29.6)			
Death from any cause	512 (20.3)	16.0	534 (21.2)	16.9	0.95 (0.84–1.07)	0.38

Armstrong et al. N Engl J Med 2020;382(20):1883-93

Comparison of New Therapies for HFrEF

	PARADIGM-HF	DAPA-HF	VICTORIA
Study Drug	Sacubitril-Valsartan vs. Enalapril	Dapagliflozin vs. Placebo	Vericiguat vs. Placebo
Median F/U, mths	27	18	11
LVEF, %	29	31	29
NYHA III-IV, %	25	33	41
eGFR, ml/min/1.73m^2	68	66	61
NT-proBNP, pg/mL	1615	1437	2821
1-yr Event rate in Controls	13.2	15.6	37.8
HR: CV death/HF hosp.	0.80 (0.73-0.89)	0.74 (0.65-0.850	0.90 (0.82-0.98)
HR: CV Death	0.80 (0.71-0.89)	0.82 (0.69-0.98)	0.93 (0.81-1.06)
HR: HF Hospitalization	0.79 (0.71-0.89)	0.70 (0.59-0.83)	0.90 (0.81-1.0)

Butler et al. 2020. doi:10.1161/CirculationAHA.120.047086

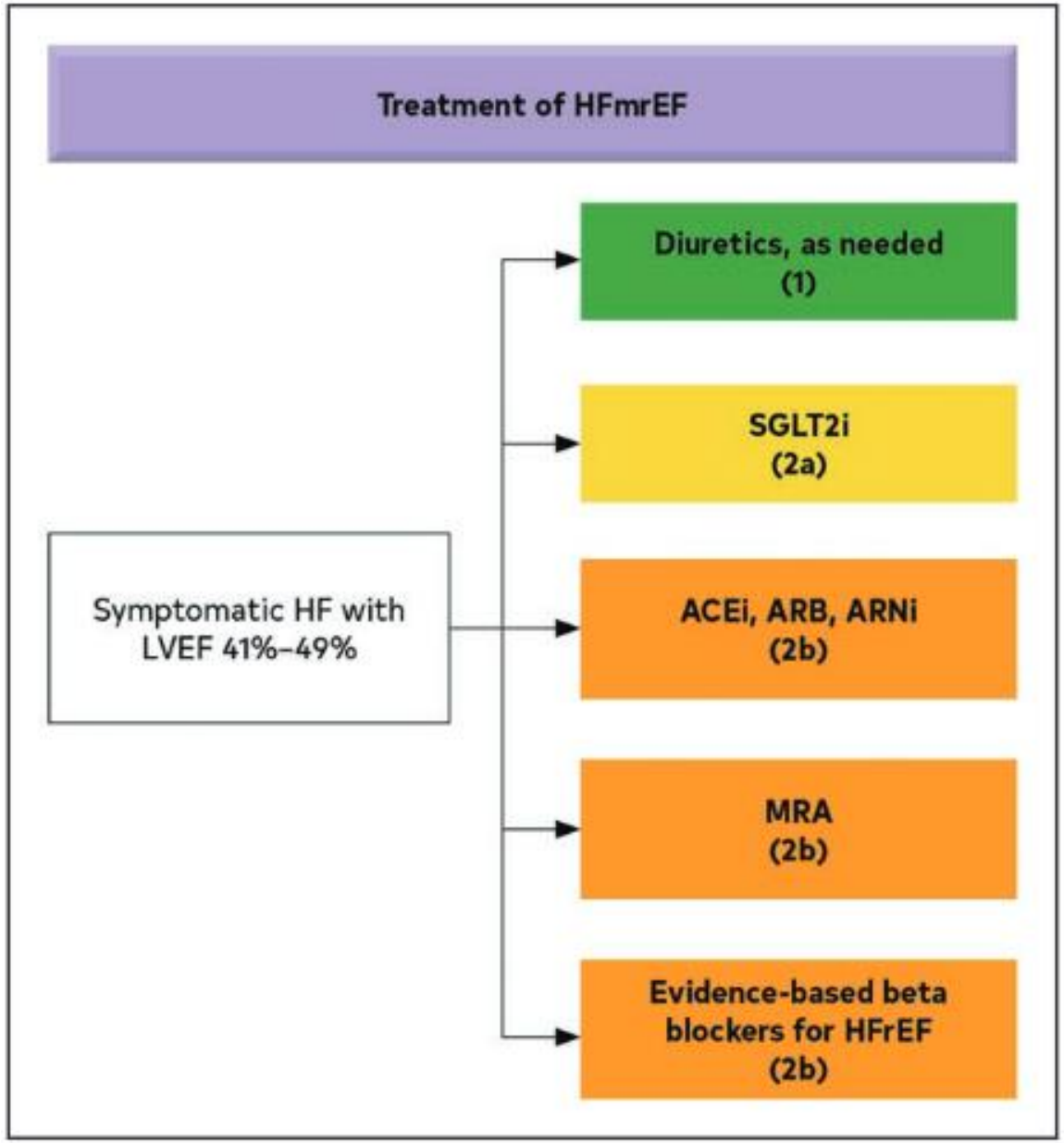
Question 2.

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 20 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

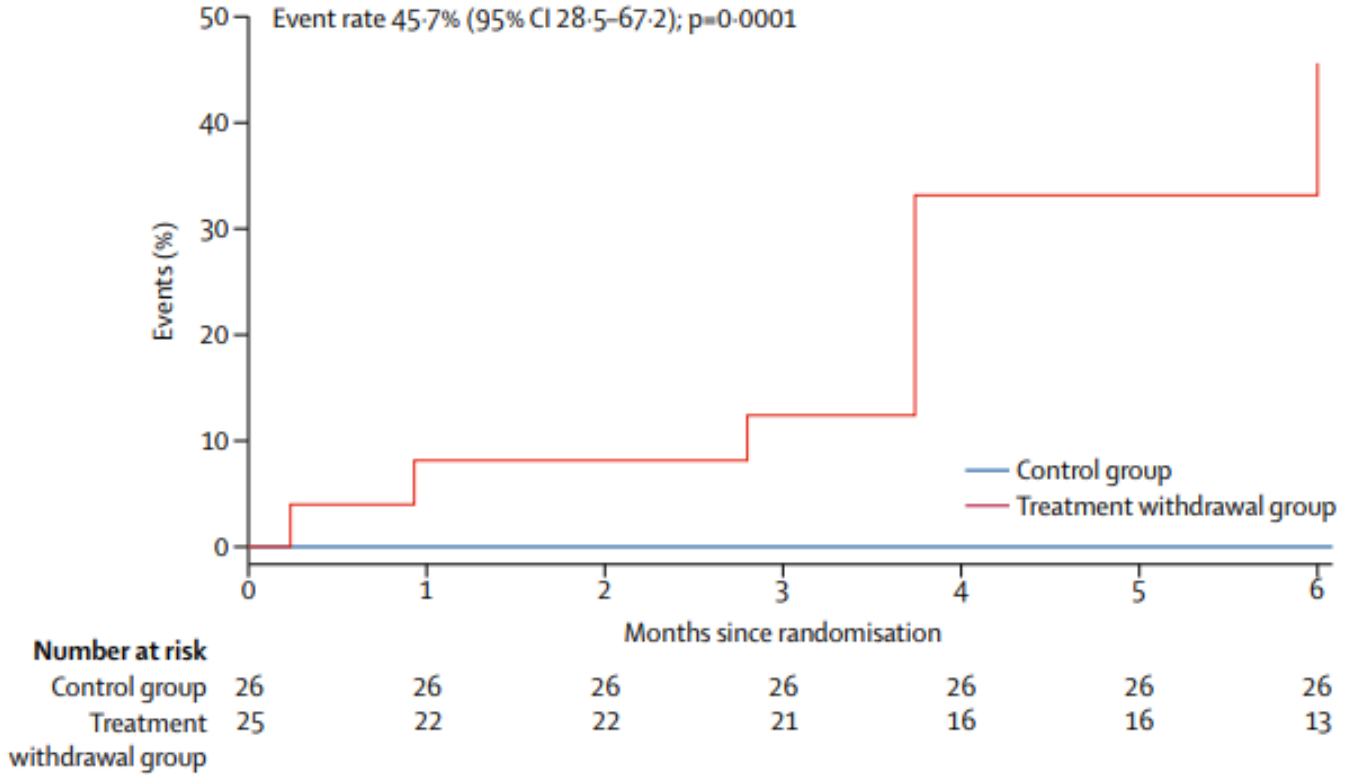
HF with Mid-Range LVEF (41-49%)



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



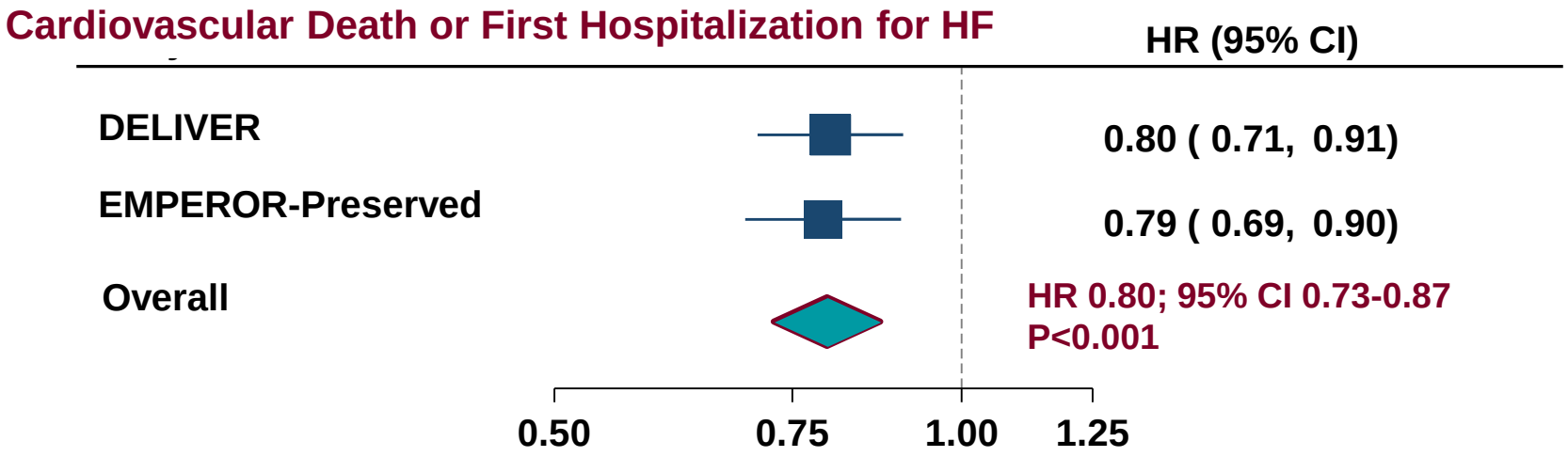
Halliday et al. Lancet 2019;393:61-73.

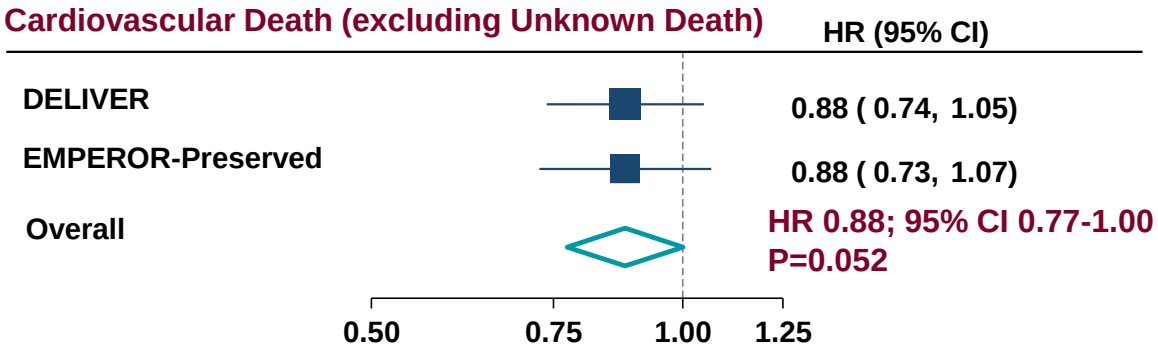
Guideline Update for HFpEF

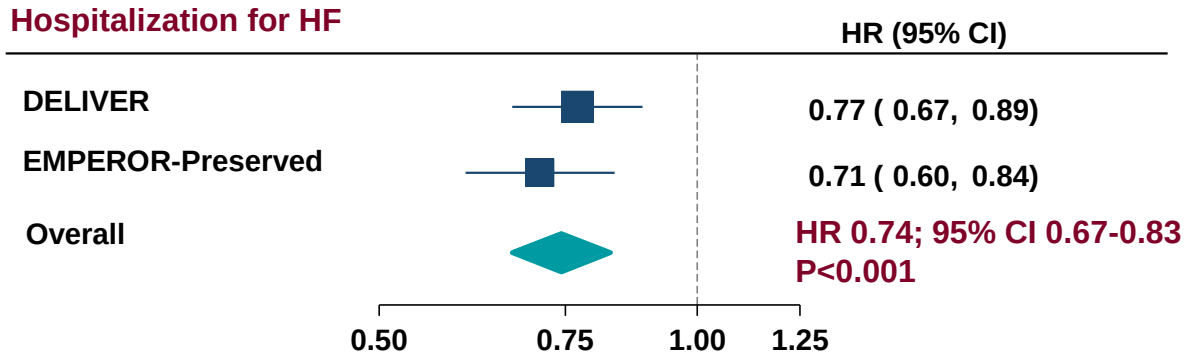
COR	LOE	Recommendations
1	C-LD	1. Patients with HFpEF and hypertension should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity.[44–46]
2a	C-EO	2. In patients with HFpEF, management of AF can be useful to improve symptoms.
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:



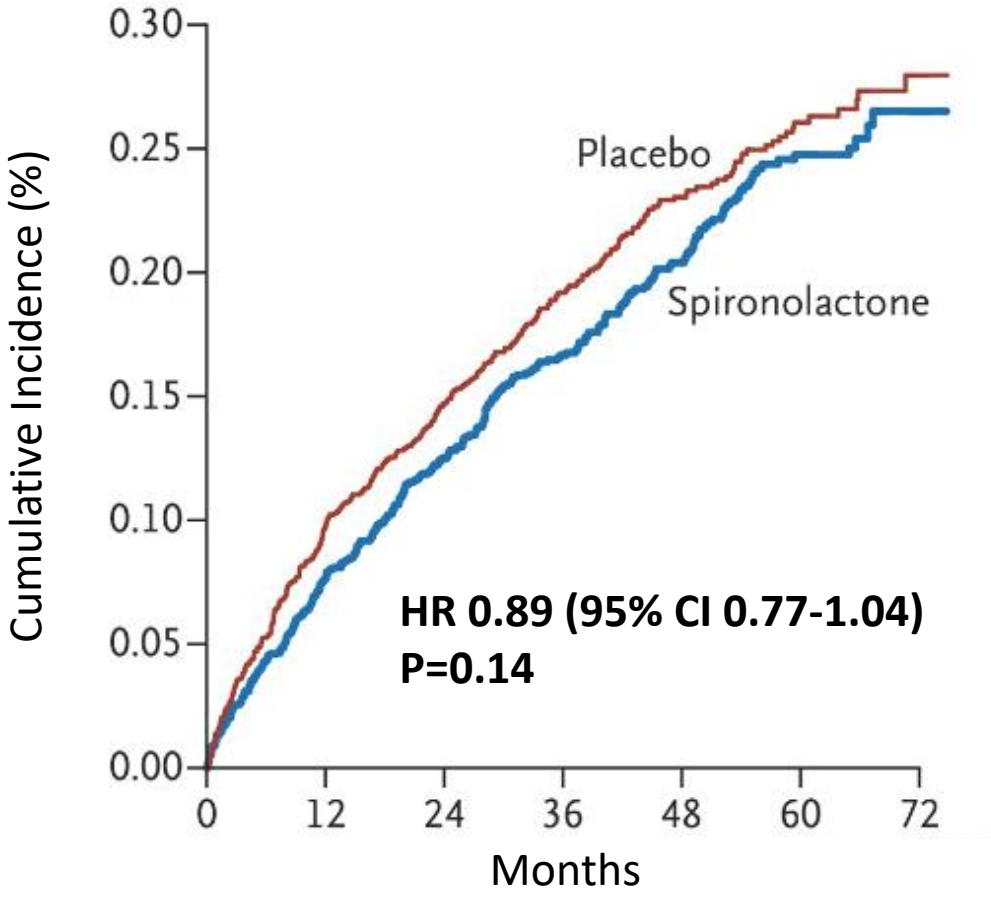


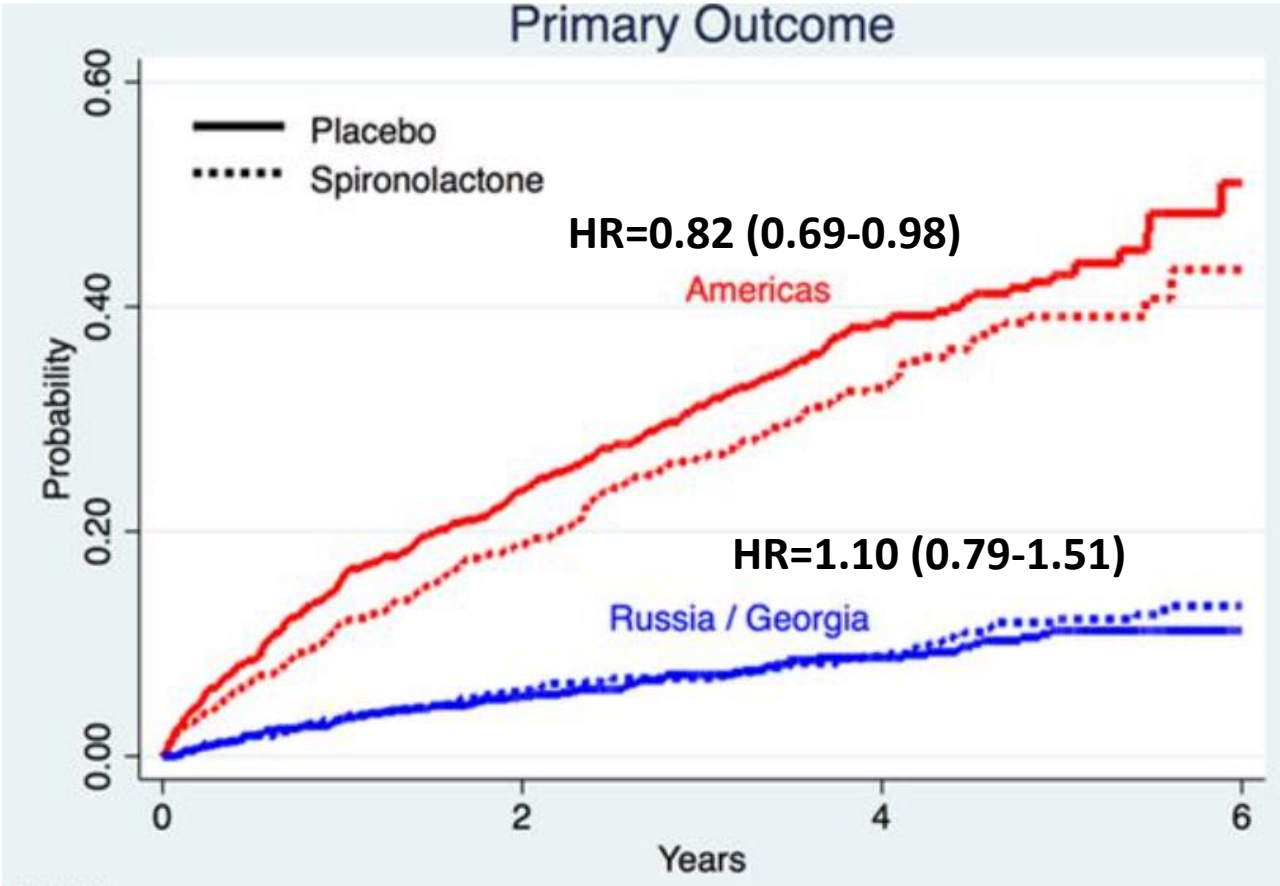


Vaduganathan M, et al. Lancet 2022

$P_{heterogeneity}$ >0.10 for all endpoints

TOPCAT: Spironolactone in HFpEF

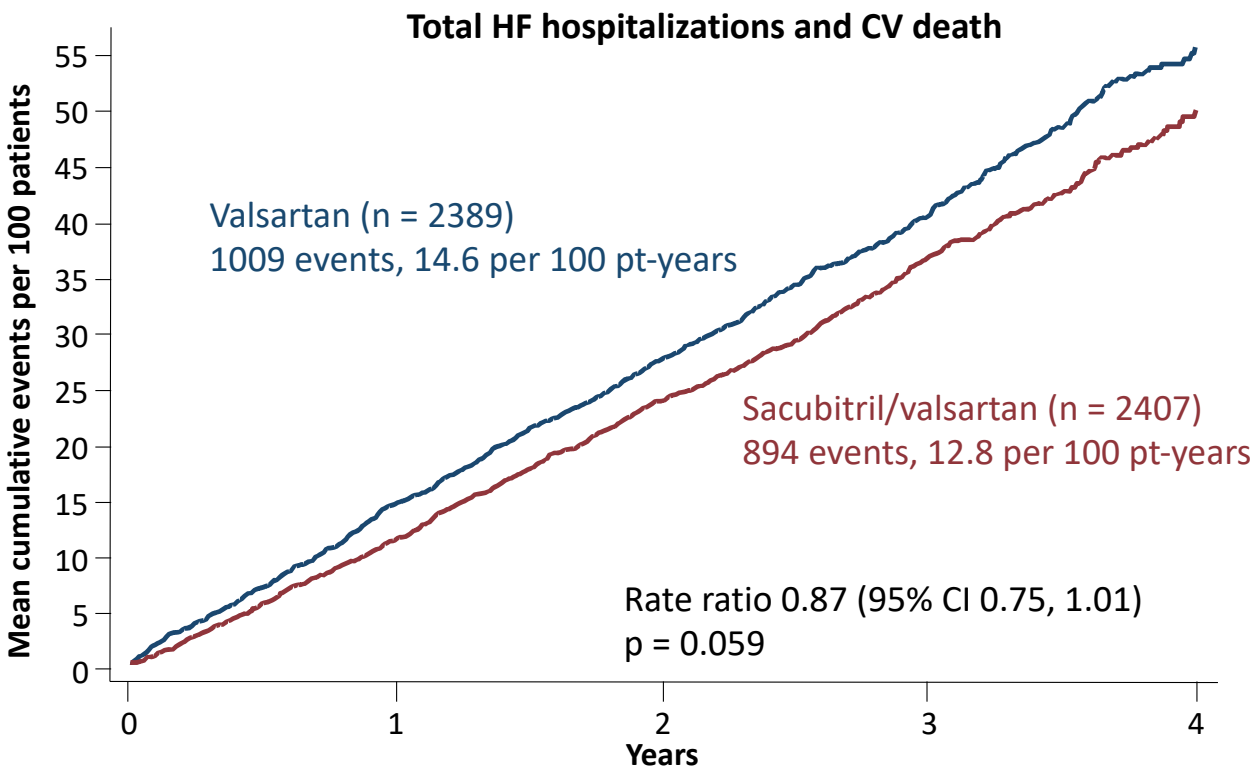




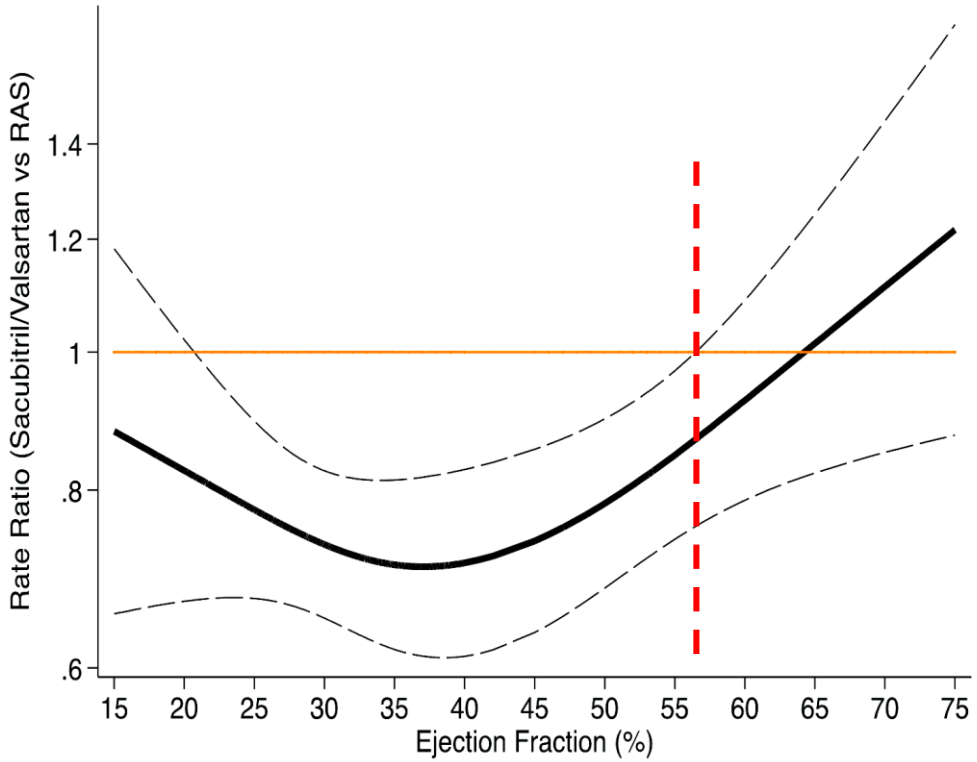
Pitt et al. NEJM 2014; 370:1383-1392; Pfeffer et al. Circulation 2015;131:34-42.

ARNI in HF with HFmrEF or HFpEF

PARAGON-HF Primary Results



PARADIGM-HF/PARAGON-HF Pooled

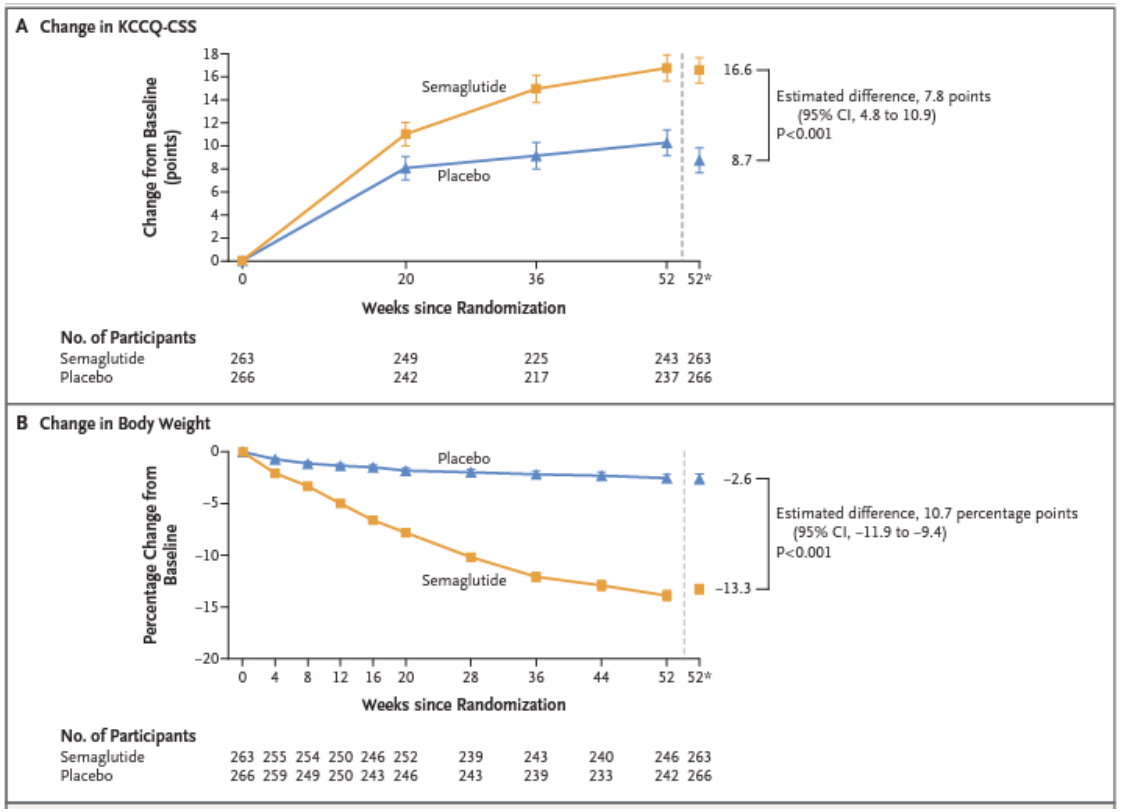


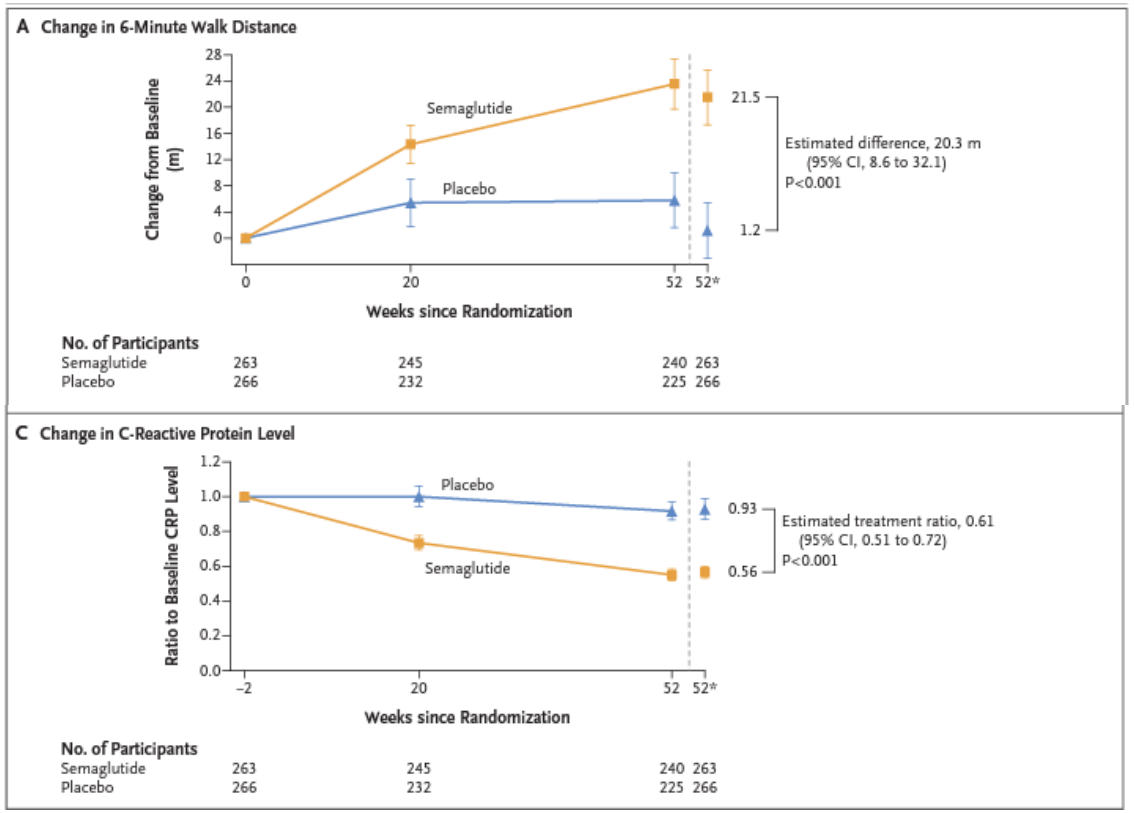
Feb 2021 US FDA approval for sacubitril/valsartan in expanded population, emphasizing benefits in EF 'below normal'

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

GLP-1 agonists in HFpEF

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



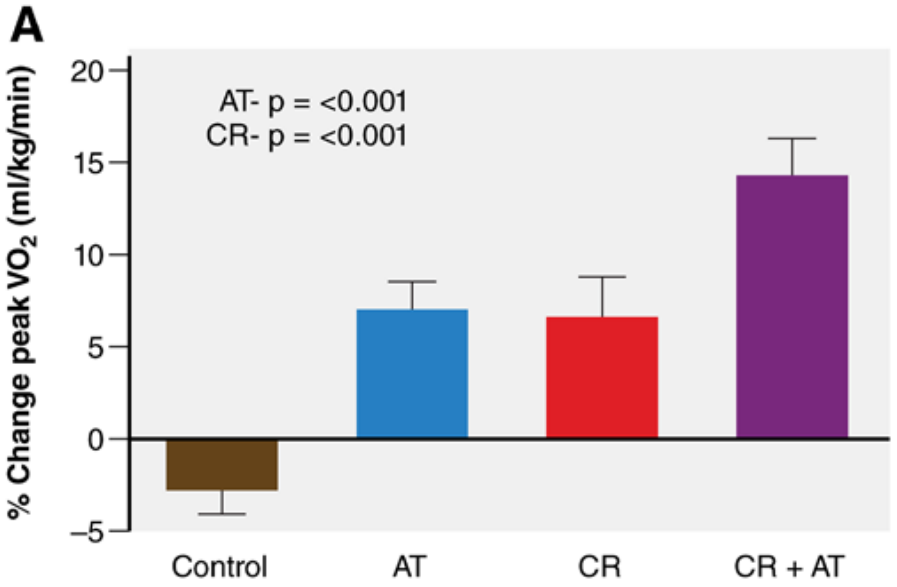


Kosiborod et al. N Engl J Med 2023;389:1069-84.

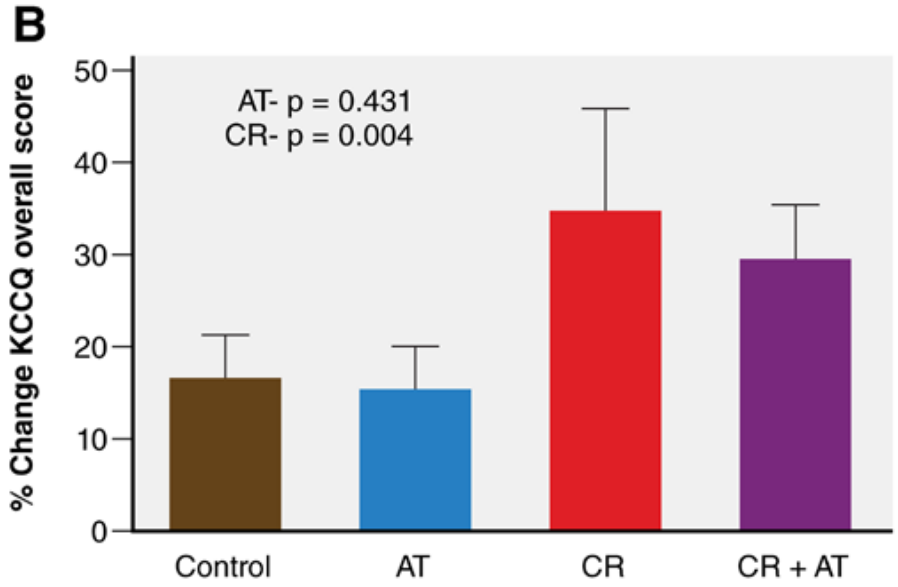
Diet and Exercise in HFpEF

N=100 pts, mean age 67, mean BMI 39.3
RTC: 2 x 2 design; 20 wks of diet, exercise, both or neither

Exercise Capacity



Quality of Life



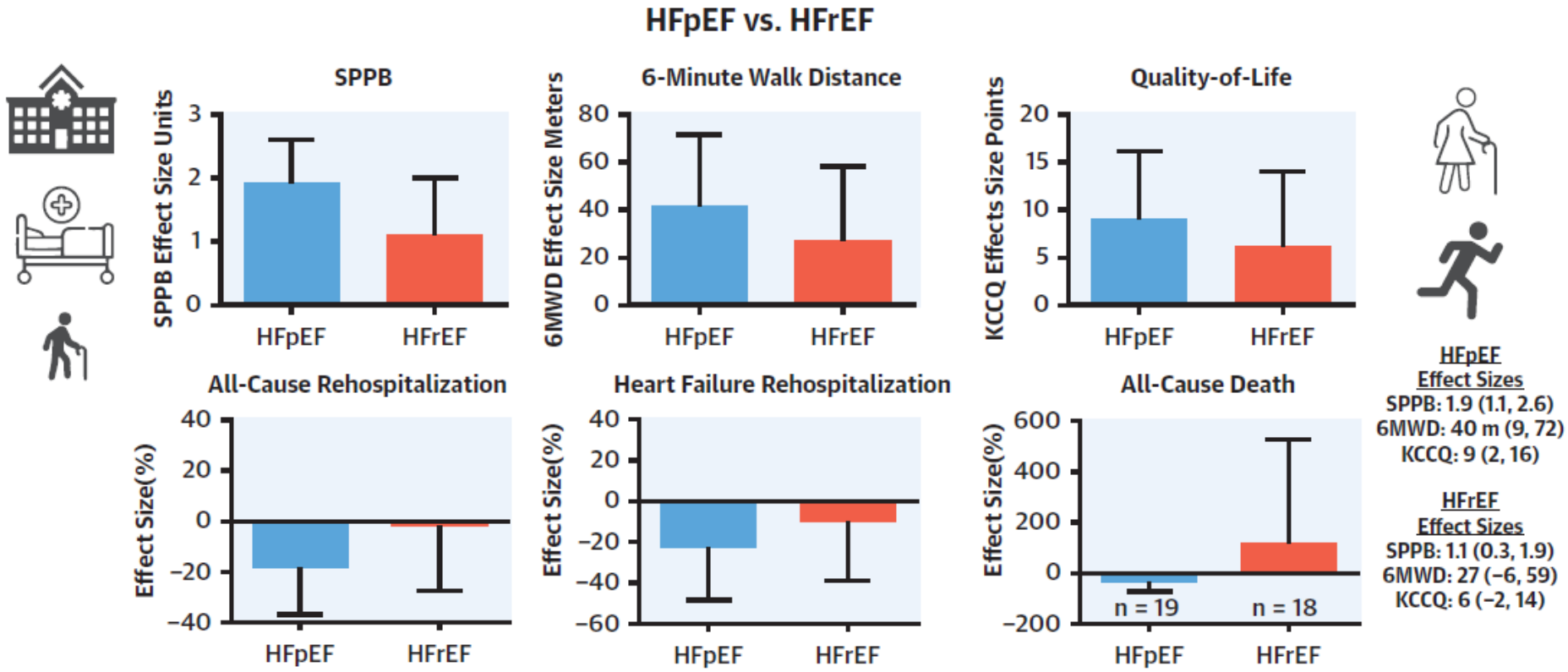
AT = aerobic exercise training, CR = caloric restriction

- Improvements in weight, CRP, LV mass

Kitzman et al. JAMA 2016; 315(1):36-46

REHAB-HF Trial: HFpEF Outcomes

N=360 pts, age > 60, recent admission for HF
RCT: 12 wks of structured physical therapy

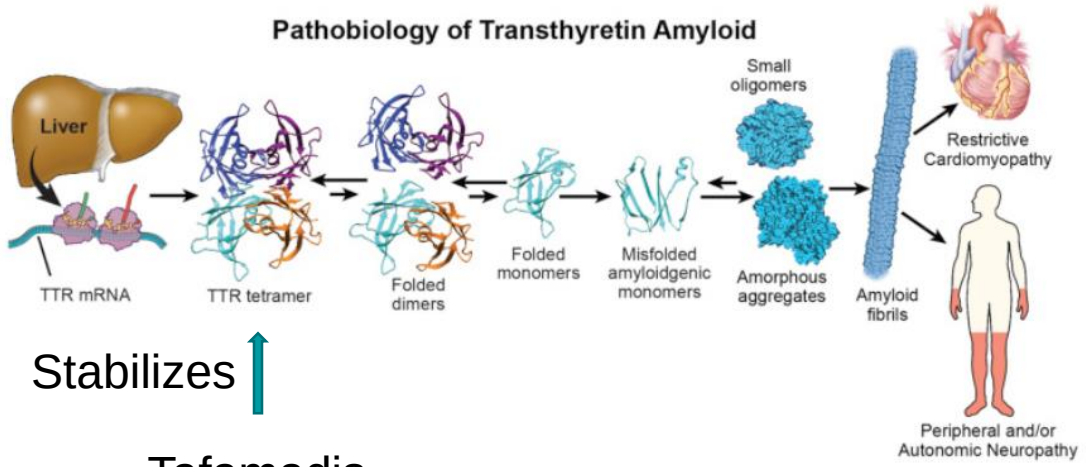


Compared to patients with HFrEF, those with HFpEF may derive greater benefit from the intervention.

Mentz RJ, JACC:Heart Fail 2021

Tafamadis for TTR Cardiac Amyloid

N=441, ATTR amyloid (wt or mutant), NYHA I-III



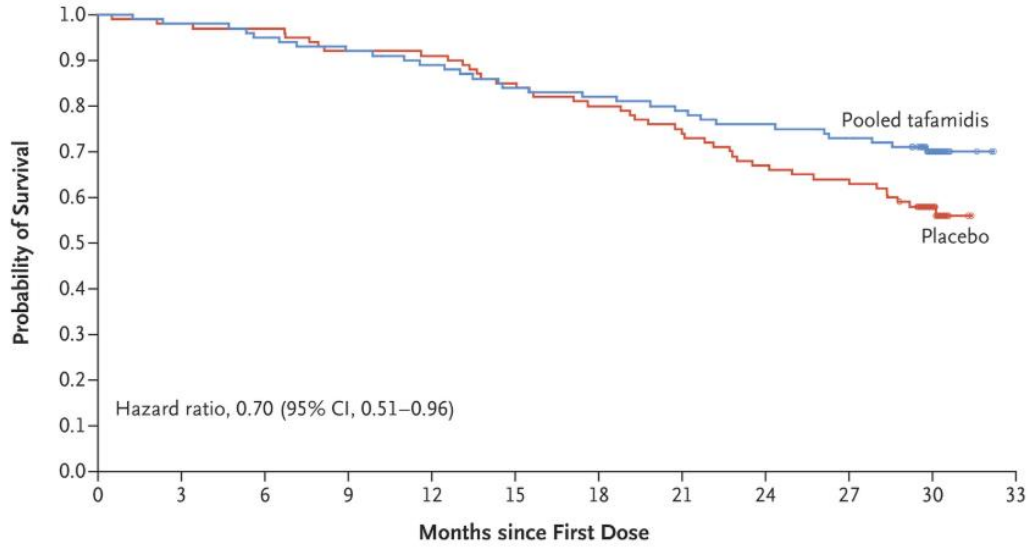
Stabilizes

Tafamadis

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			186 (70.5)	0.30
		<0.001	1.70 (1.26–2.29)		
Placebo	177			101 (57.1)	0.46

B Analysis of All-Cause Mortality



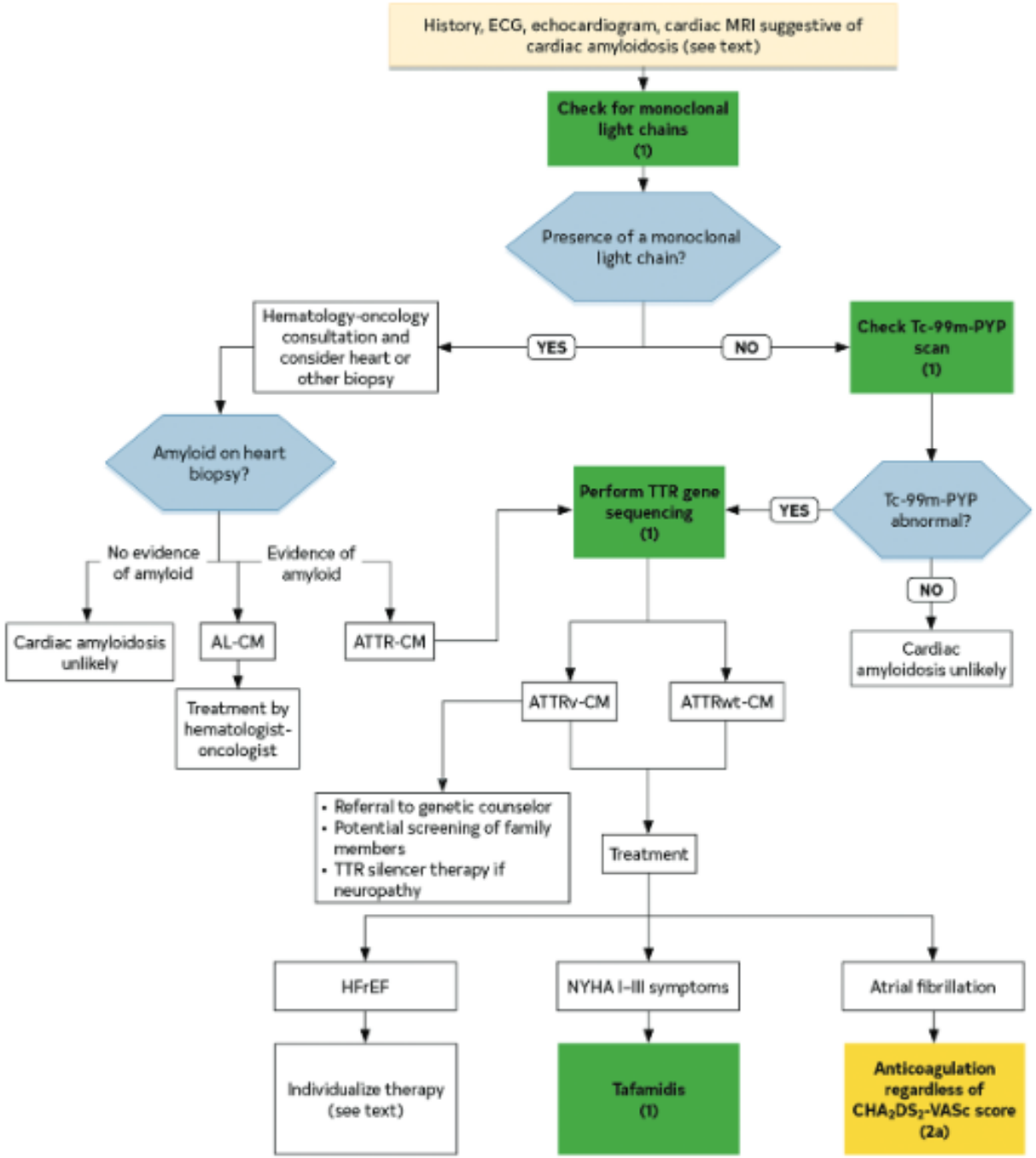
No. at Risk (cumulative no. of events)

Pooled tafamidis	264 (0)	259 (5)	252 (12)	244 (20)	235 (29)	222 (42)	216 (48)	209 (55)	200 (64)	193 (71)	99 (78)	0 (78)
Placebo	177 (0)	173 (4)	171 (6)	163 (14)	161 (16)	150 (27)	141 (36)	131 (46)	118 (59)	113 (64)	51 (75)	0 (76)

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

Diagnostic and Management Algorithm for Cardiac Amyloidosis

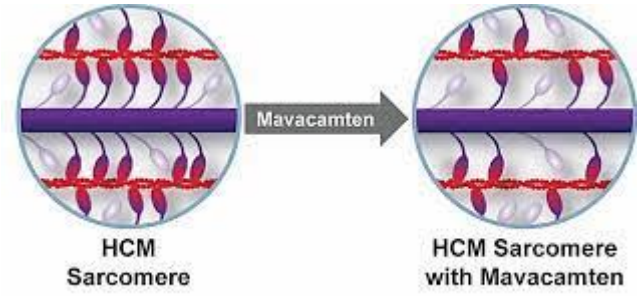
- Biceps tendon rupture
- Bilateral carpal tunnel syndrome
- Lumbar spinal stenosis
- Peripheral neuropathy
- LVH on echo
- Biatrial enlargement
- Low QRS voltage on ECG despite LVH



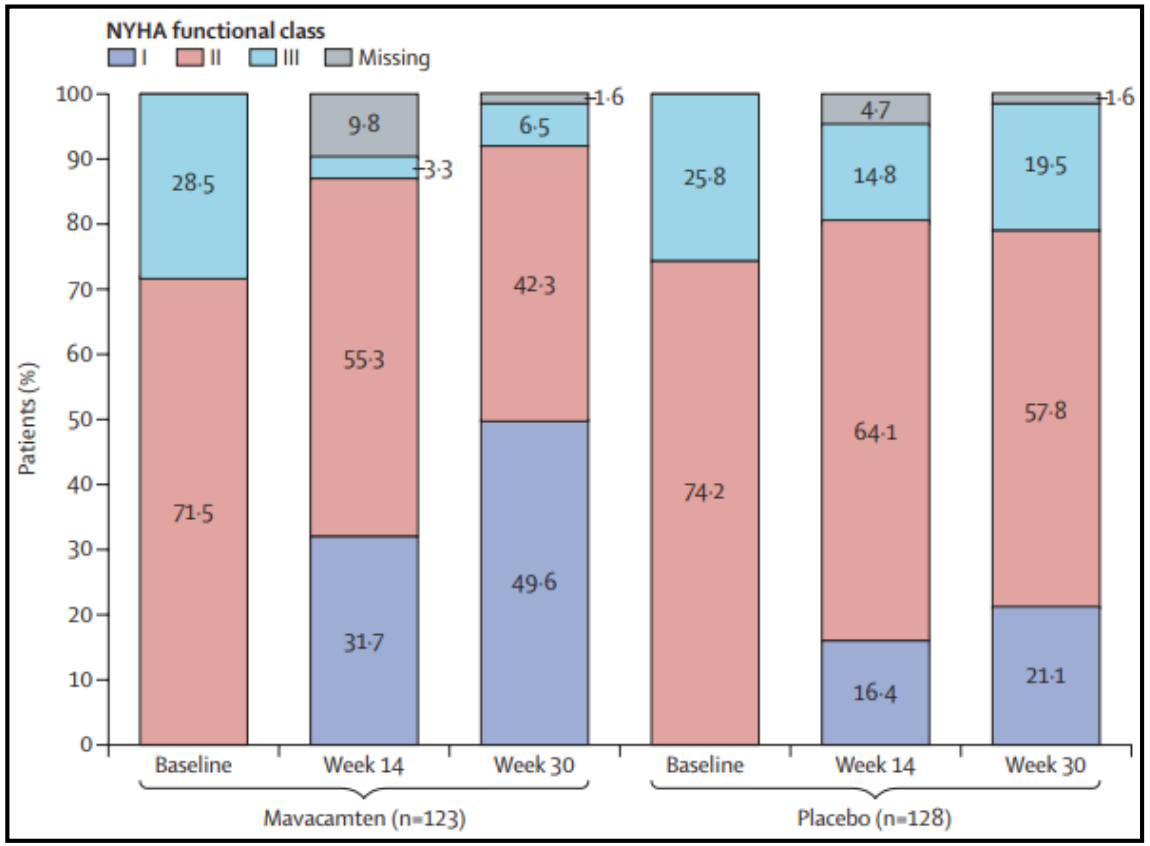
Heidenreich et al. Circulation 2022; 145;e876-894.

EXPLORER-HF: Mavacamten for Hypertrophic Obstructive Cardiomyopathy

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



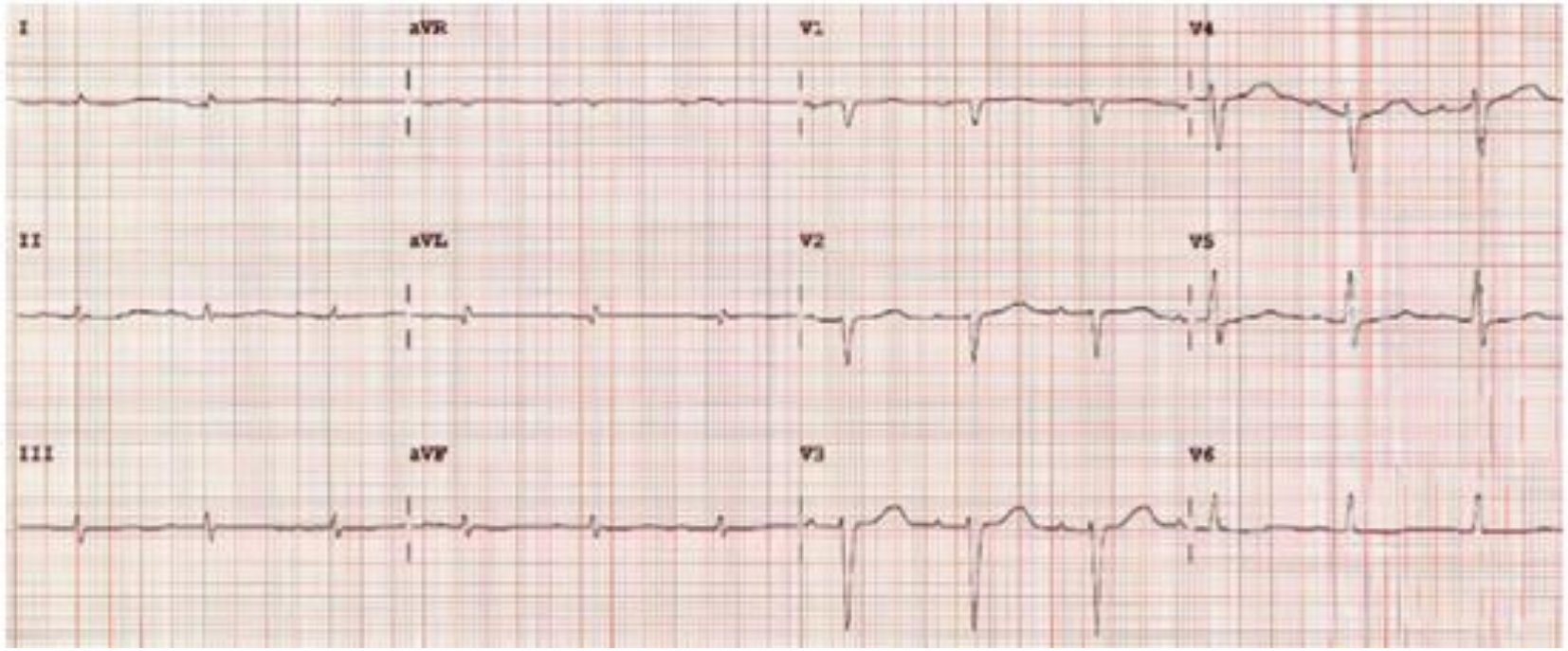
- N=251 pts, HCM, LVOT gradient > 50 mmHg, NYHA II-III
- **1° Endpoint**: ≥ 1.5 ml/kg/min ↑ in peak VO2 + ≥ 1 NYHA Class ↓ in sxs *OR* ≥ 3 ml/kg/min ↑ in peak VO2 w/ stable sxs
- **37% vs. 17%, p=0.0005**



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

Question 3.

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 3 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

Take Home Messages

For Stage A HF:

- ✓Target BP < 130/80 mm Hg
- ✓For diabetics w/ CV risk, consider SGLT2 inhibitors to reduce risk of incident HF
- ✓Consider BNP for risk stratification and aggressive RF management in pts with CV risk factors

For Stage C HF w/ reduced EF:

- ✓Use ARNi over ACEi/ARB to reduce morbidity/mortality in NYHA II-III pts
- ✓Use SGLT2i to reduce mortality and HF hospitalizations, even in patients w/o DM
- ✓Maximize GDMT as tolerated to improve sxs and mortality
- ✓Add ivabradine to reduce HF hospitalizations if SR w/ HR ≥ 70 bpm, despite max beta-blockade
- ✓Consider IV iron if iron deficient to reduce symptoms and HF hospitalizations
- ✓Consider vericiguat to reduce HF hospitalizations, esp. in sicker pts with eGFR 15-30

Take Home Messages

For HF w/ preserved EF

- ✓Consider SGLT-2i to reduce HF hospitalizations
- ✓Consider ARNI/MRAs to reduce HF hospitalizations in pts with EF < 55%
- ✓Promote diet, exercise, and weight loss to improve outcomes
- ✓Remember HFpEF is a heterogeneous syndrome and consider specific therapies for certain diagnoses
- ✓Look for clues of TTR amyloidosis and consider tafamadis to reduce mortality and HF hospitalizations if present
- ✓Consider mavacamten in symptomatic patients with hypertrophic obstructive cardiomyopathy to improve exercise capacity and symptoms

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2. Mann et al. Sacubitril/Valsartan in Advanced Heart Failure With Reduced Ejection Fraction: Rationale and Design of the LIFE Trial. JAMA Cardiol. 2022;7(1):17-25.
3. Armstrong et al. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med 2020;382(20):1883-93.
4. Solomon et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med 2022;387(12):1089-1098.
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6. Solomon et al. Sacubitril/Valsartan Across the Spectrum of Ejection Fraction in Heart Failure. Circulation 2020;141(5):352-361.
7. Maurer et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2018 Sep 13;379(11):1007-1016.
8. Olivoto et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2020;396:759-69.

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 m2. 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. Furthermore, she has adequate BP room to tolerate additional vasodilation.

Answer 3.

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.