

# HEART FAILURE (including HFpEF)

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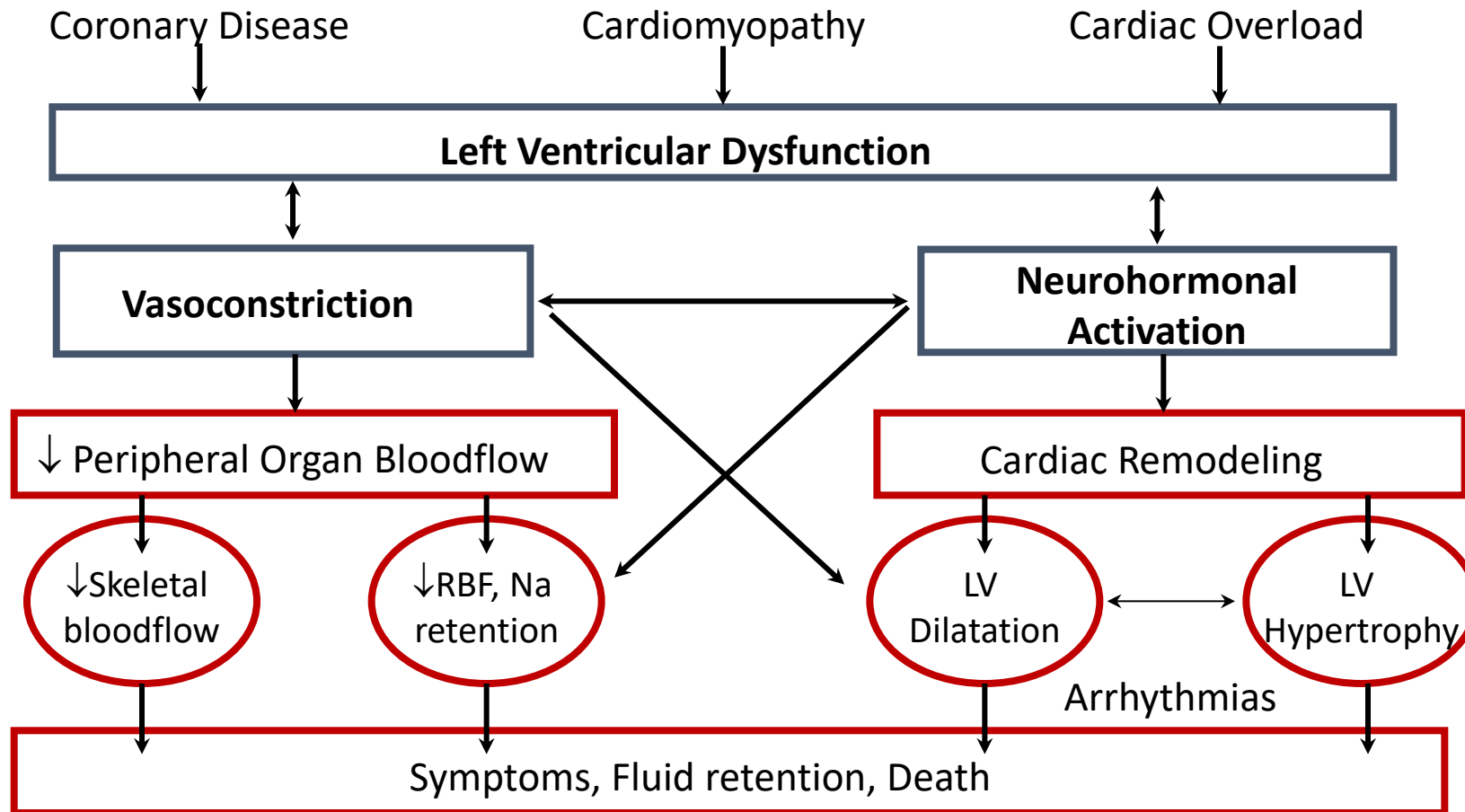
# Disclosures

- Consultant: AstraZeneca, Takeda Oncology
- Research support: Bristol Myers Squibb

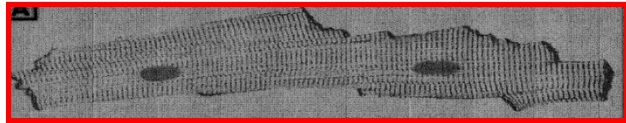
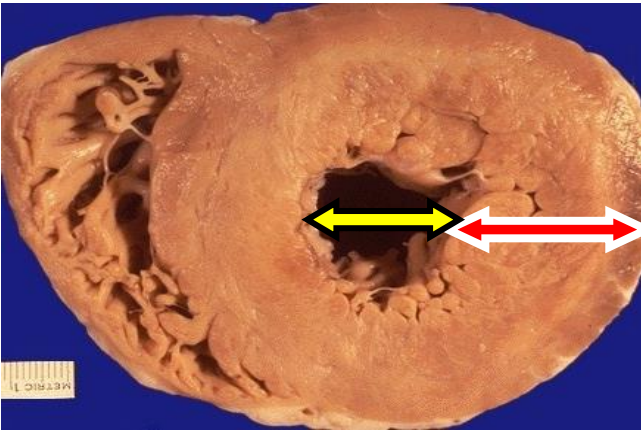
# Outline

- Outline the pathophysiology and epidemiology of heart failure
- Apply evidenced-based therapy to the population with heart failure and reduced EF (HFrEF)
- Discuss novel therapies for the management of heart failure with preserved EF (HFpEF)

# Pathophysiology of Heart Failure



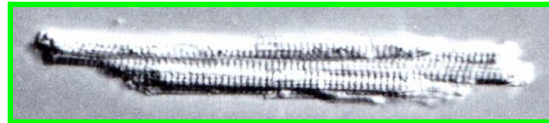
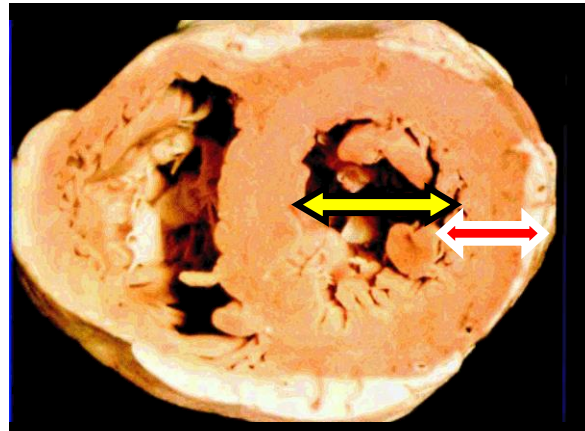
# Pathology of Heart Failure



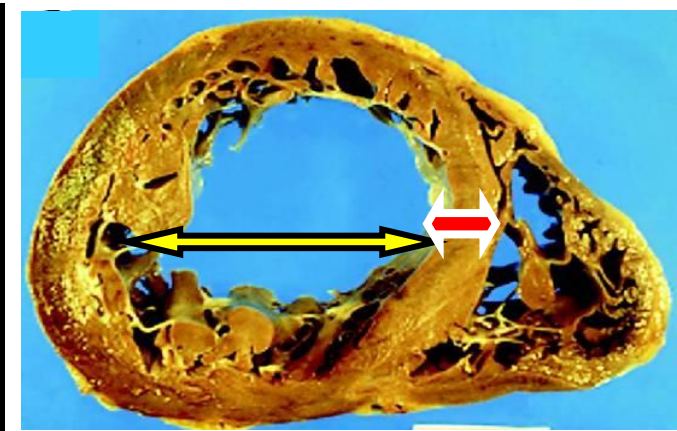
**HFpEF**

**Concentric Remodeling**

↑ Thickness  
↔ Volume  
↓ Volume / Mass



**normal**



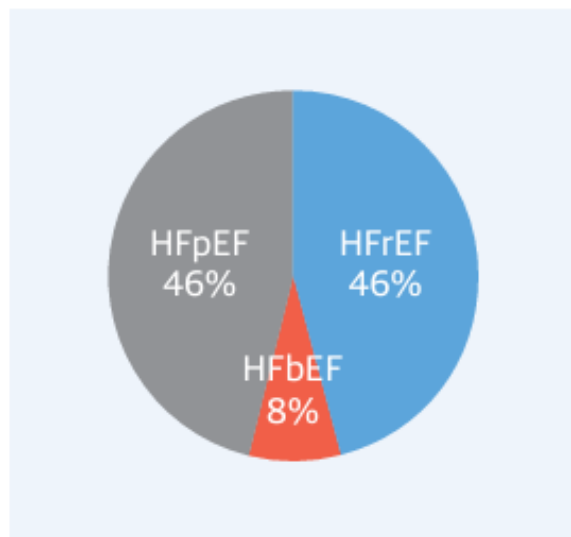
**HFrEF**

**Eccentric Remodeling**

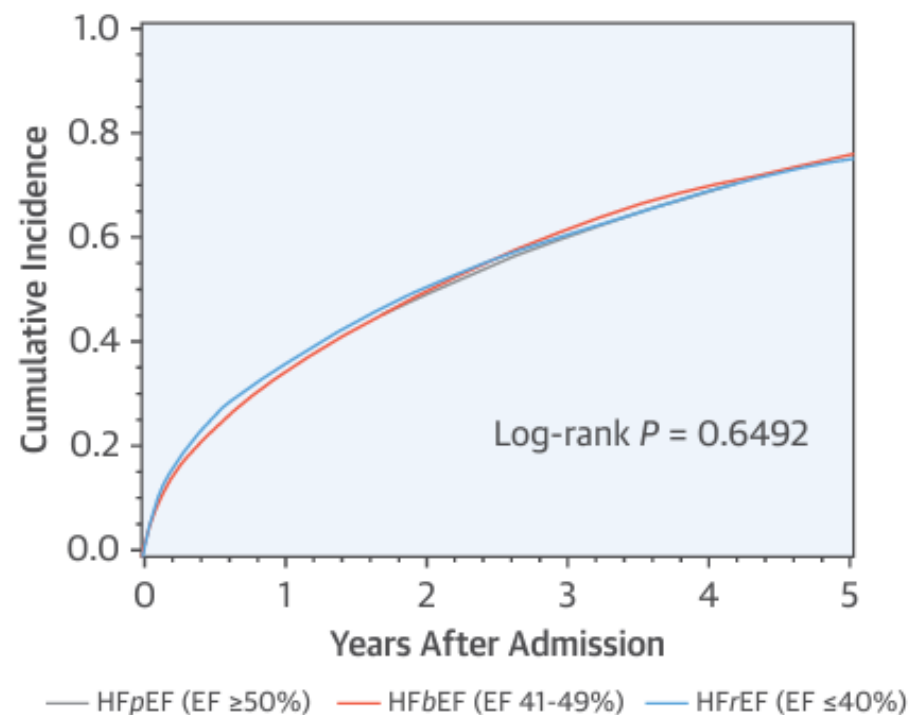
↔ Thickness  
↑ Volume  
↑ Volume / Mass

**CENTRAL ILLUSTRATION** 5-Year Outcomes in Patients Hospitalized With HF With Preserved, Borderline, and Reduced EF

Heart Failure



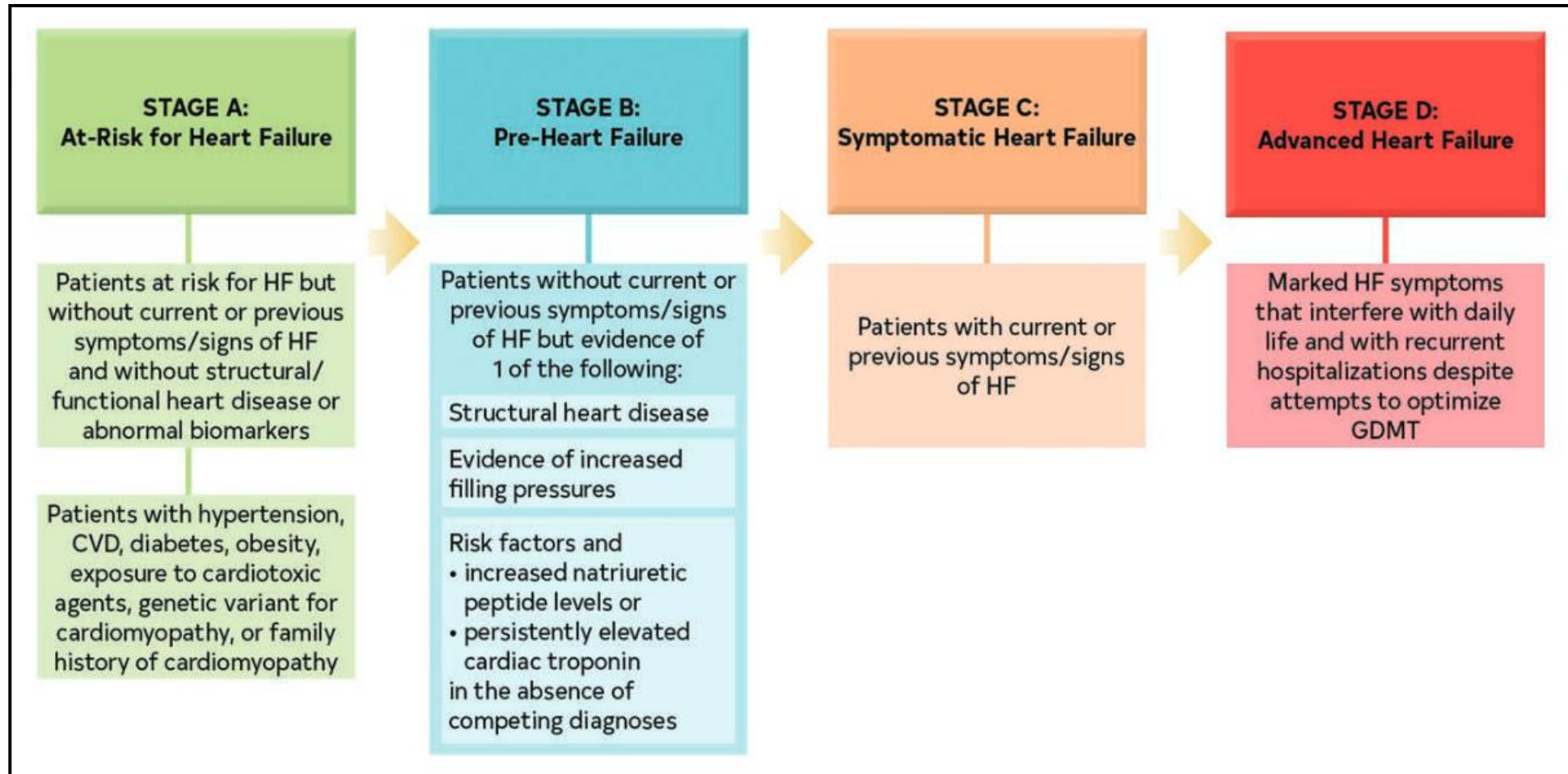
5-Year Mortality



Outcomes - 5-Year Event Rates (%)					
	Mortality	Readmission	CV Readmission	HF Readmission	Mortality/Readmission
HFrEF	75.3	82.2	63.9	48.5	96.4
HFbEF	75.7	85.7	63.3	45.2	97.2
HFpEF	75.7	84.0	58.9	40.5	97.3



# Stages of Heart Failure





## Stage A HF: Primary Prevention of HF

- BP Target < 130/80 mm Hg
  - *SPRINT trial: Intensive vs. usual BP control reduced HF hospitalizations*
- SGLT-2i in pts w/ DM + hiCVD risk
  - *EMPA-REG, CANVAS, DECLARE-TIMI 58: SGLT-2i reduce incident HF*
- BNP screening
  - *STOP-HF: BNP > 50 pg/ml to refer to CV specialist to reduce incident 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. <sup>46,111–118</sup>
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. <sup>119–121</sup>
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. <sup>122–130</sup>
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. <sup>131,132</sup>
2a	B-NR	5. In the general population, validated multivariable risk scores can be useful to estimate subsequent risk of incident HF. <sup>133–135</sup>

# Stage B HF:

## Preventing Symptomatic HF in Pre-HF

- Identify and treat any reversible causes of LV dysfunction
- ACEi + BB for LVEF  $\leq$  40%
- ARB for ACEi intolerant pts
- Aldosterone antagonist in post-MI LV dysfunction + DM
- ICD for NYHA Class I pts w/ LVEF  $\leq$  30%, 40 days after MI
- Non-dihydropyridine CCB and thiozolidinediones should be avoided in LVEF  $<$  50%

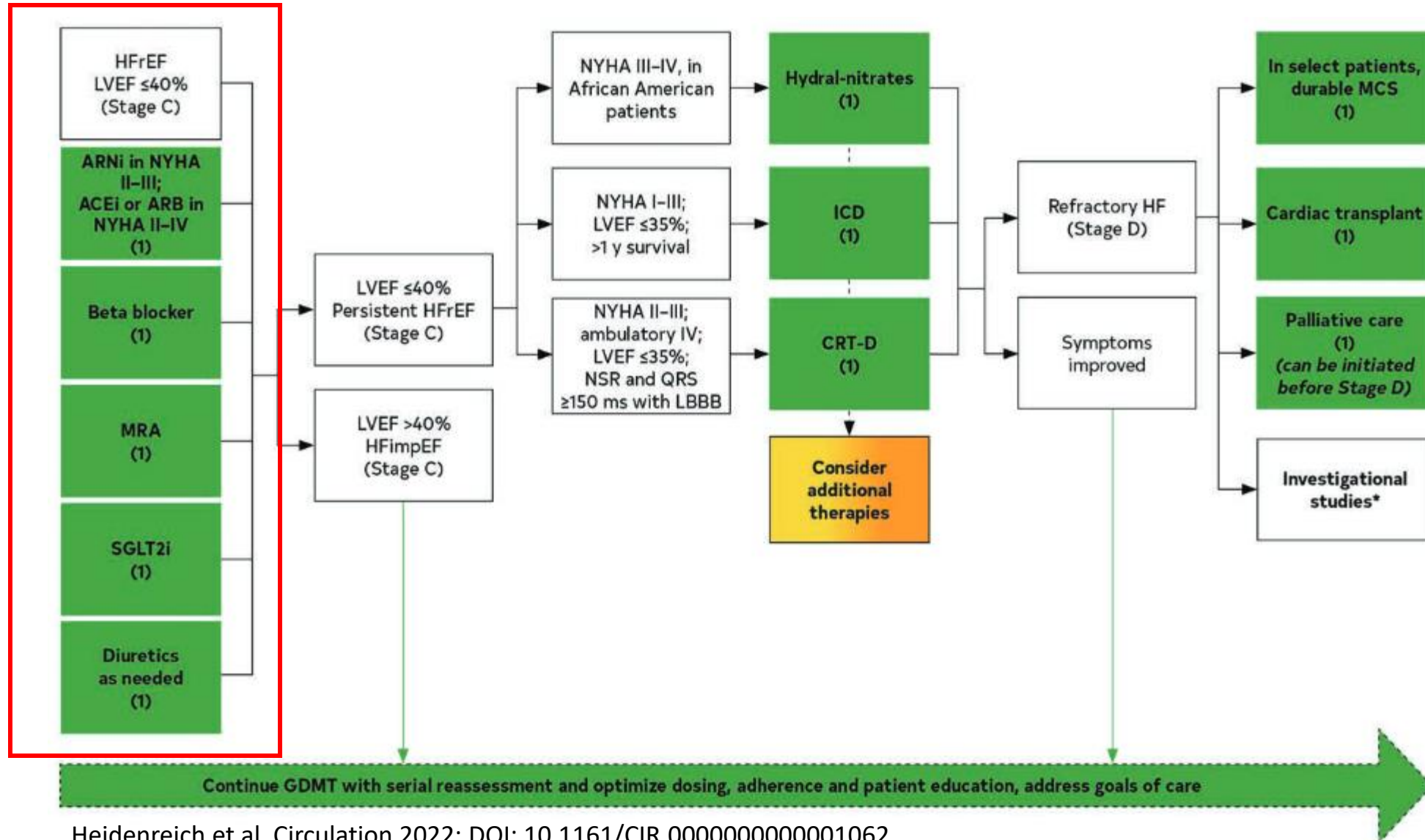
# Question 1

- A 39 y.o. AA man w/type II DM and hyperlipidemia presents with an acute anterior MI. He undergoes PTCA/DES to the LAD. Post-MI echo shows EF 30-35% w/ anterior akinesis. He has no symptoms of HF.
  - Which of the following medications would **NOT** be indicated for this patient?
- A) Lisinopril
  - B) Metoprolol succinate
  - C) Spironolactone
  - D) Furosemide
  - E) Empagliflozin

# Goals of Therapy for Symptomatic HF: Stage C HF

- Therapies to prevent dz progression and mortality
- Address precipitating factors
- Improve sxs and end-organ perfusion
- Reduce LOS and re-hospitalization
- *Institution of GDMT*
- *Manage related risks (sudden cardiac death)*
- *Identify and treat the causative/inciting factor*
- *Lower PCWP*
- *Increase CO*
- *Pt education*
- *Longitudinal dz management programs*

# Stage C HF: Symptomatic HF



# Trials of ACE Inhibitors in Heart Failure

	<u>Patients</u>	<u>NYHA Class</u>	<u>Placebo Mortality</u>	<u>Hazard ratio</u>
<b>V-HeFT II</b>	804	I-III	25% (Hyd/Iso)	0.72
<b>CONSENSUS I</b>	253	IV	44%	0.66
<b>SOLVD Tx</b>	2569	II-III	40%	0.84
<b>SOLVD Px</b>	4228	I	16%	0.91
<b>SAVE</b>	2231	Post MI EF<40%	25%	0.81
<b>ISIS-4</b>	58,050	24h post MI	7.7%	0.93

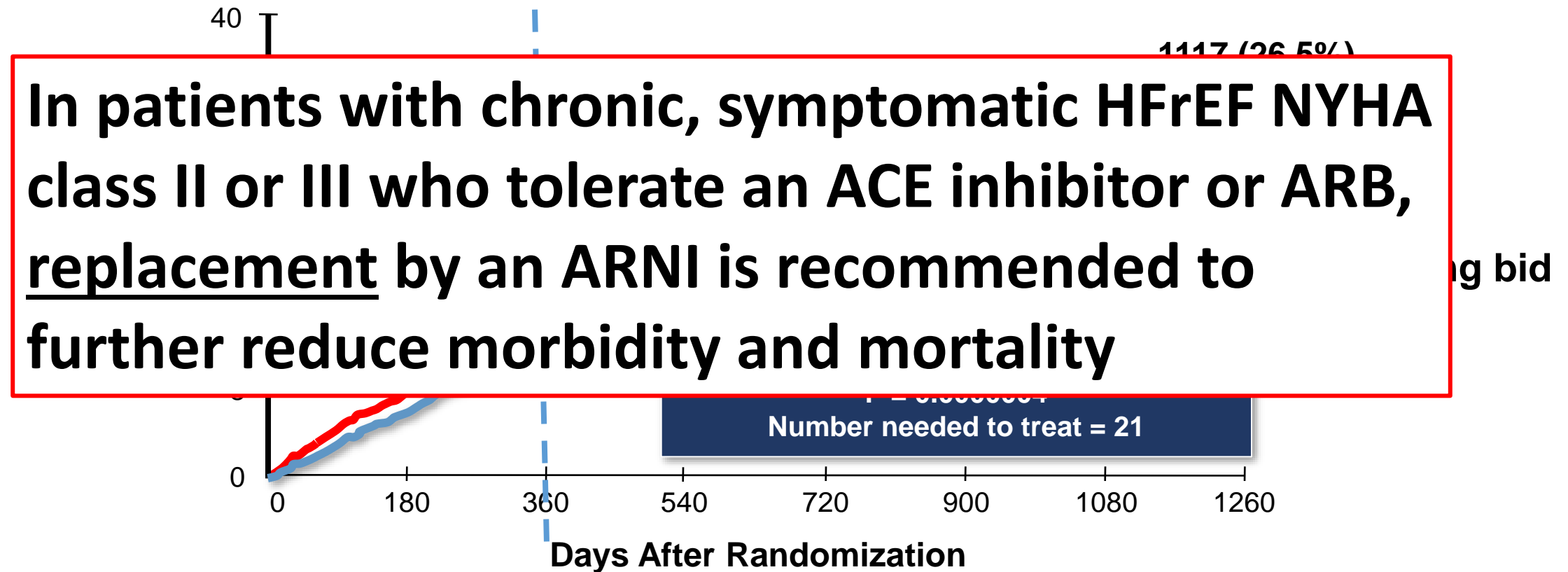
# ARB Trials in Heart Failure

	<u>ELITE I/II</u>	<u>OPTIMAAL</u>	<u>CHARM</u>	<u>VALIANT</u>	<u>ValHeFT</u>
<b><i>Patients (n)</i></b>	NYHA II-IV  722/3152	Acute MI/CHF  5477	NYHA II-IV  2548	Acute MI/CHF  14,808	NYHA II-IV  5010
<b><i>Study Design</i></b>	Losartan or Captopril	Losartan or Captopril	Candesartan and ACEI	Valsartan, Captopril, or both	Valsartan and ACEI
<b><i>β-blocker</i></b>	16% / 23%	79 %	55 %	70 %	35 %
<b><i>Mortality</i></b>	No difference	Captopril better	No difference	No differences	No difference
<b><i>HF Hosp</i></b>	No difference	Captopril better	Both better	Both better	Both better
<b><i>Other</i></b>	Losartan better tolerated	Losartan better tolerated	↓ Mort. w/ β-blker	↓ BP w/ both	↑ Mort. w/ β- blker



# 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.

# LIFE: Primary Endpoint NT-proBNP AUC

- N=335 pts, NYHA Class IV, EF  $\leq$  35%, BNP  $\geq$  250 or NT-proBNP  $\geq$  800 pg/ml, 3 mths of GDMT or intolerance, 1 sign of advanced HF (inotropes, EF  $\leq$  25%,  $\geq$  1 HF hospitalization, VO2 < 55% predicted, 6 min walk < 300 m)
- SBP < 90, eGFR < 20, K > 5.5

**ARNI is not recommended in NYHA Class IV HF**

End point	Enalapril (n=167)	Lisinopril (n=168)	ARNI (n=167)	P-value
Primary efficacy end point				
NT-proBNP AUC, median (IQR)	1.08 (0.75 to 1.60)	1.19 (0.91 to 1.64)	0.95 (0.84 to 1.08)	.45
No.	155	158	NA	NA
Secondary efficacy end points				
Days alive, out of hospital, and free from HF events, median (IQR) <sup>c</sup>	147.0 (9.0 to 164.0)	157.0 (53.5 to 164.0)	-11.2 (-26.4 to 4.0)	.15

Mann et al. JAMA Cardiol. 2022;7(1):17-25.

# β-Blocker Trials in Heart Failure

Trial	Target Dose (mg/d)	Mean Dose (mg/d))	Annual Mortality		RRR (%)
			Control	β-blocker	
Bisoprolol					
CIBIS I	5	3.8	11.0	8.7	NS
CIBIS II	10	7.5	13.2	8.8	34
Bucindolol					
BEST	100-200	76	17	15	NS
Metoprolol					
MDC	100-150	108	11.1	11.9	NS
MERIT-HF	200	159	11.0	7.2	34
Carvedilol					
US Carvedilol	12.5-100	45	14.4	5.9	65
COPERNICUS	50	37	18.5	11.4	38

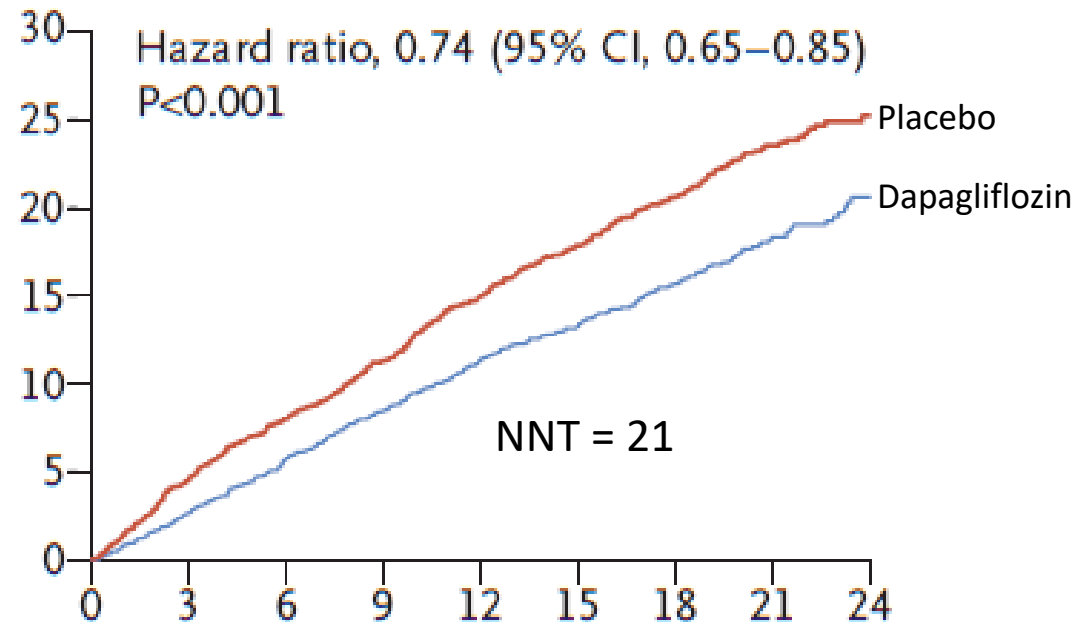
# Aldosterone Antagonists in HF

<b>Trial</b>	<b>N</b>	<b>LVEF</b>	<b>NYHA</b>	<b>End-pt</b>	<b>HR</b>
<b>RALES<sup>1</sup></b>	1663	≤ 35%	III-IV	All cause mortality	0.7, p<0.001
<b>EPHESUS<sup>2</sup></b>	6632	Post-MI EF < 40%	II or I w/ DM	All cause mortality	0.85, P=0.008
<b>EMPHASIS-HF<sup>3</sup></b>	2737	EF < 30% or EF 30-35% w/ QRS > 130	II	CV death or HF hosp.	0.63, p<0.0001

# SGLT-2i Improve Outcomes in HFrEF

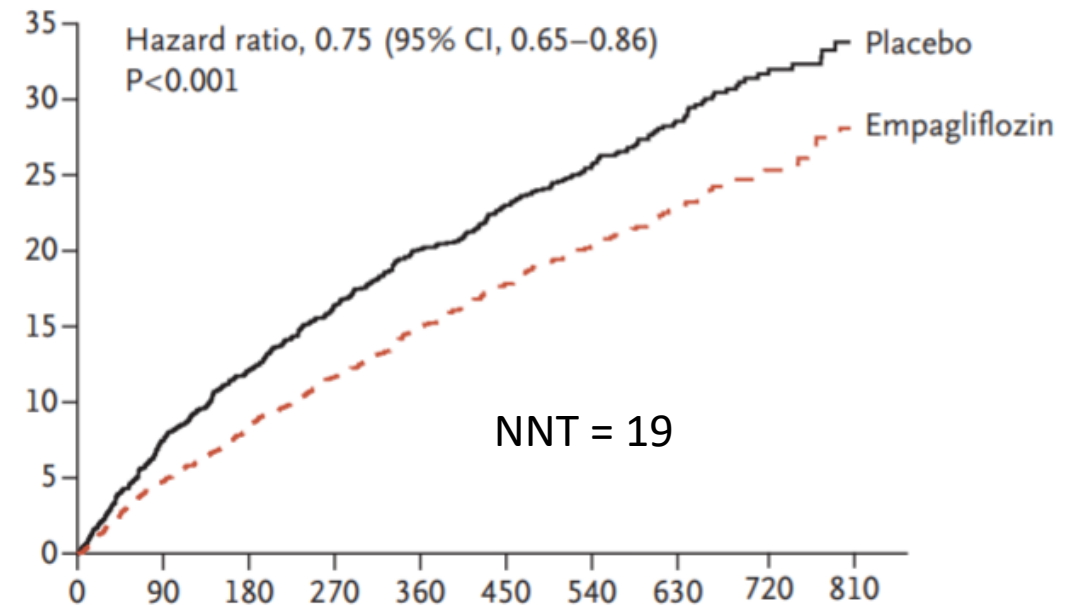
## DAPA-HF (N=4744)

1° Outcome: CV Death, Hospitalization/ED Visit for HF



## EMPEROR REDUCED-HF (N=3730)

1° Outcome: CV Death or HF Hospitalization

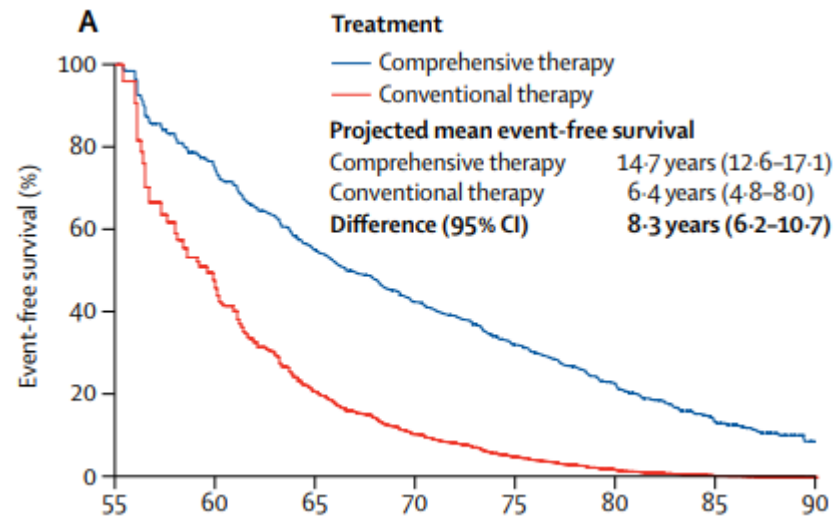


Side Effects: Hypovolemia, UTI (Fungal), Balanitis, DKA  
Empagliflozin showed lesser decline in eGFR over time

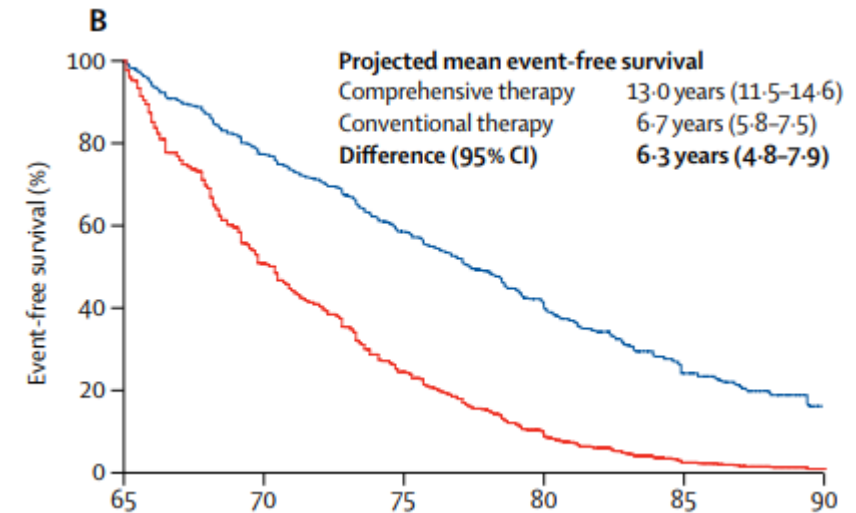
McMurray et al. NEJM 2019;381(21):1995;  
Packer et al. NEJM 2020;383(15):1413-24

# Estimation of Lifetime Benefit of Comprehensive vs. Conventional HFrEF Therapy

Age  $\geq 55$  years



Age  $\geq 65$  years



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

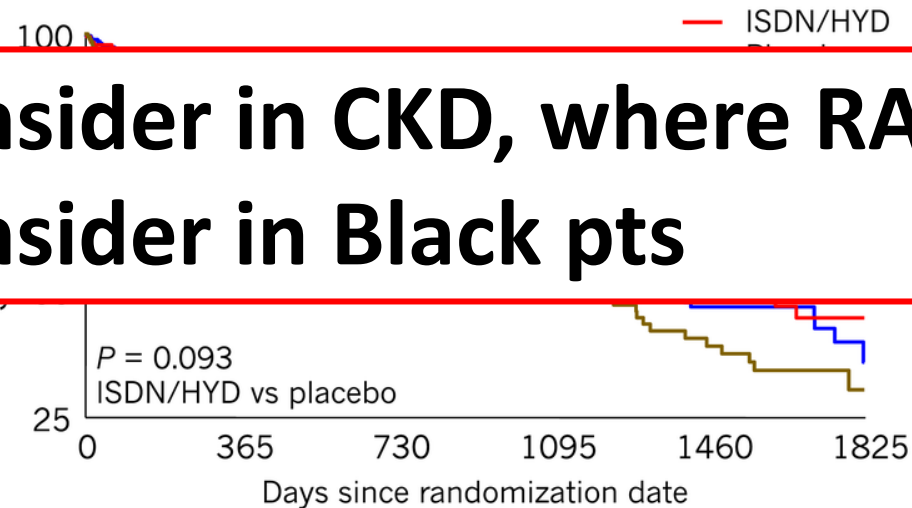
# Hydralazine/Isordil in HFrEF

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

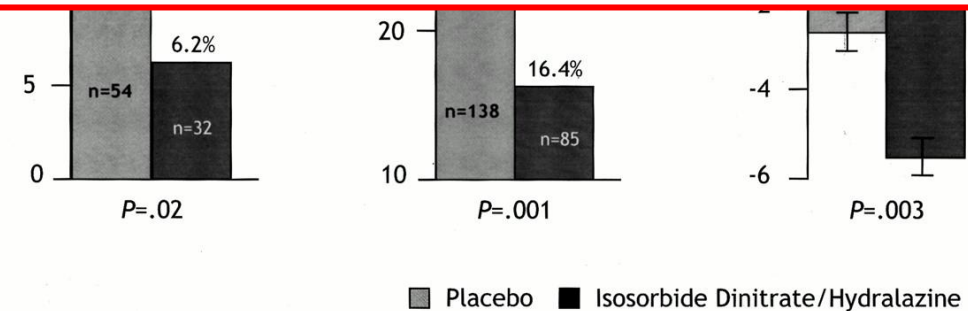
A-HEFT: Black pts, HFrEF, NYHA III-IV

A-HeFT: Components of Composite Score

- Consider in CKD, where RAASi and SGLT-2i contraindicated
- Consider in Black pts

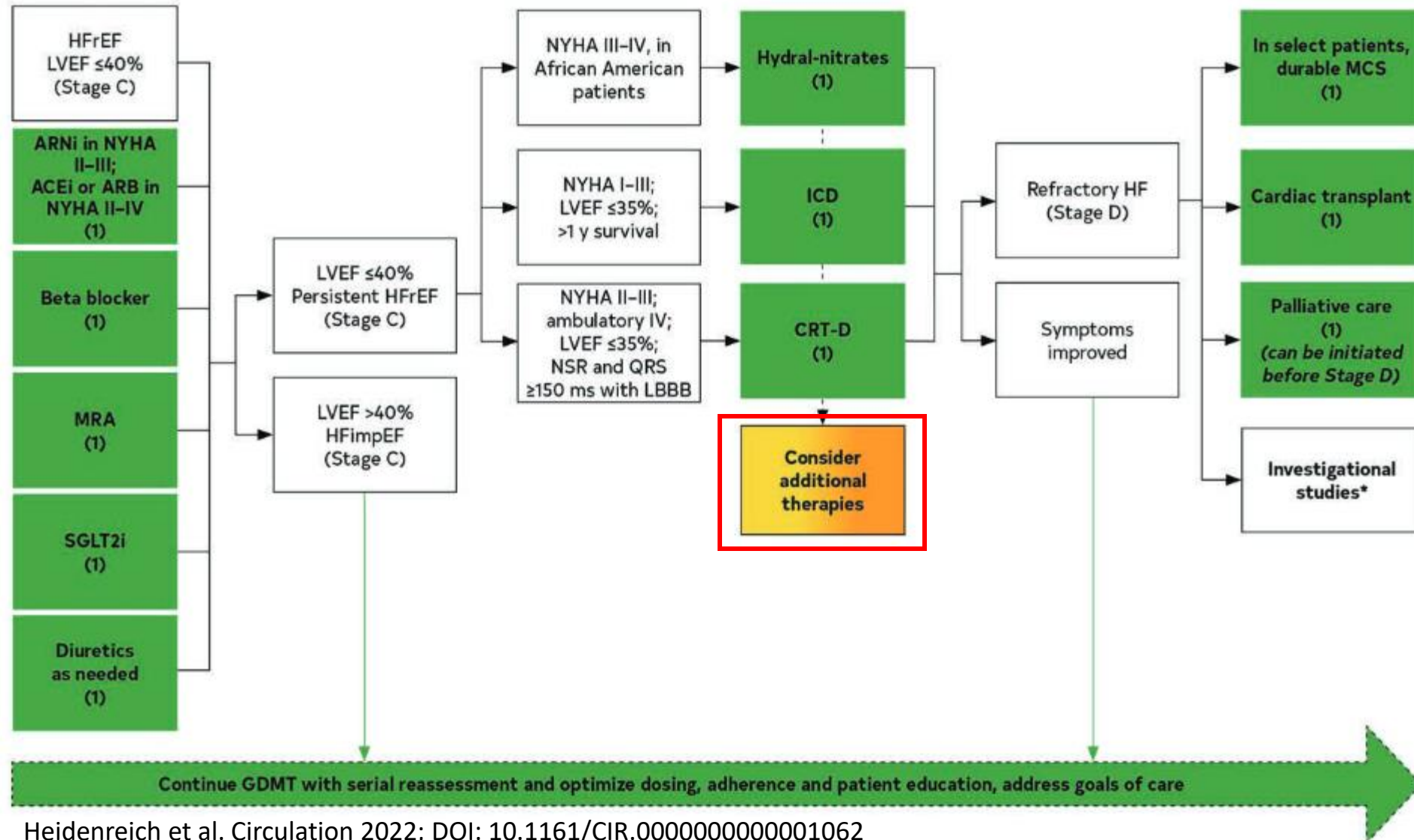


ISDN/HYD, n = 186	148	109	71	37	16
Placebo, n = 276	202	135	84	41	10
Prazosin, n = 183	135	94	58	27	7

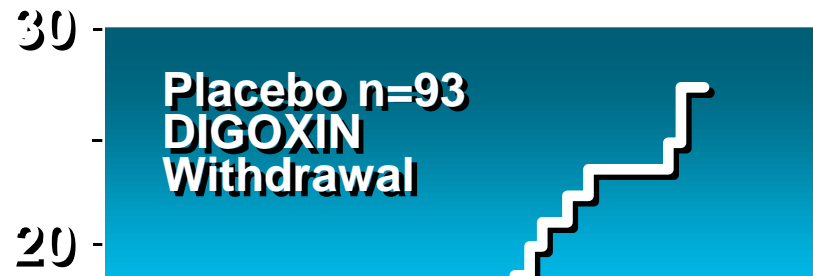




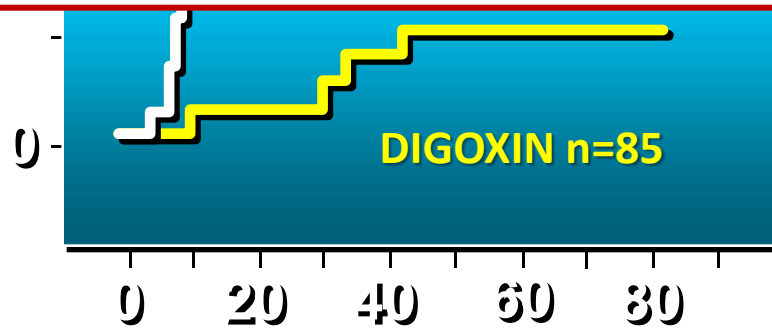
# Stage C HF: Symptomatic HF



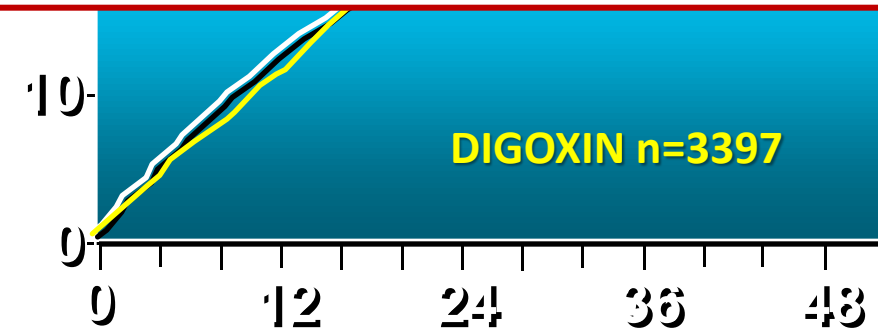
# Digoxin Reduces HF Hospitalization But Not Mortality



**No incremental benefit (and potential harm) at  
Levels > 1.0 ng/mL**

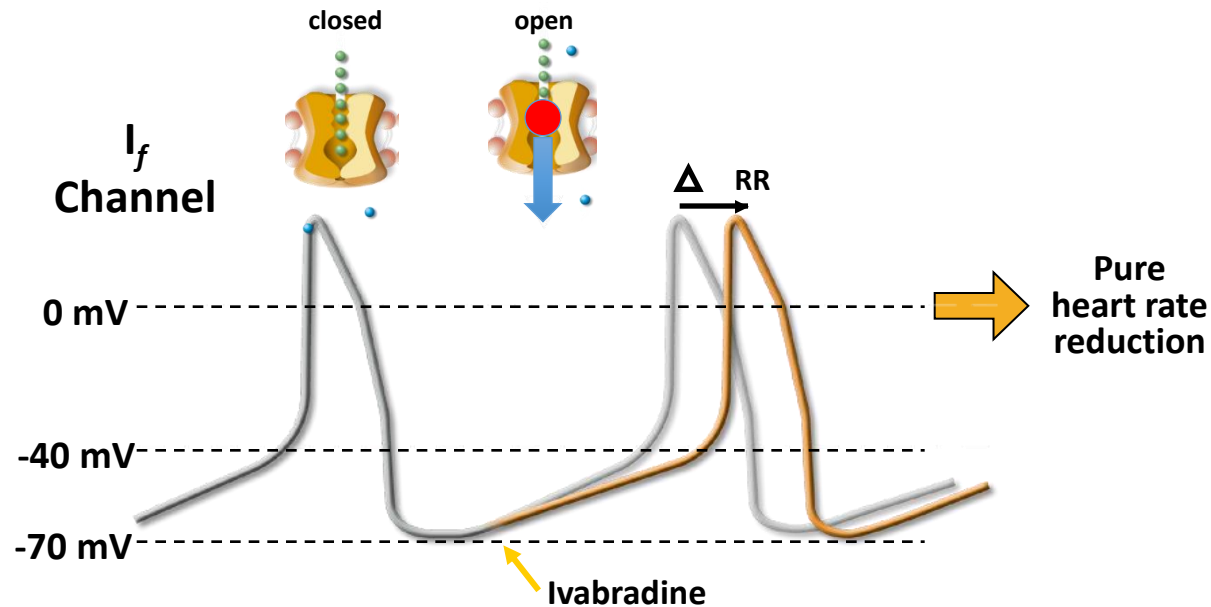


RADIANCE Trial  
NEJM 1993;329:1



DIG Trial  
NEJM 1997;336:525

# 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

# SHIFT: Ivabradine ( $I_f$ inhibitor in SA node)

- N=6,558

- EF < 25% NYHA II-IV

**Ivabradine may be beneficial to reduce HF hospitalization for patients with symptomatic HFrEF who are receiving GDMT, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of  $\geq 70$  bpm at rest.**

Side effects

- Symptomatic bradycardia: 5 vs 1%
- Phosphenes: 3 vs 1%



Months					
0	6	12	18	24	30
3264	2868	2489	2061	1089	439
3241	2928	2600	2173	1191	447

# IV Iron Repletion in HFrEF

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

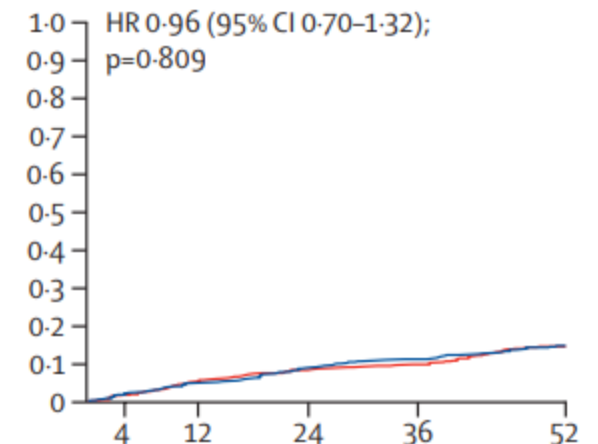
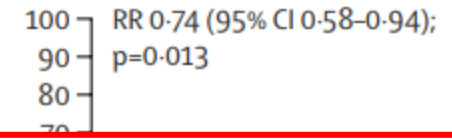
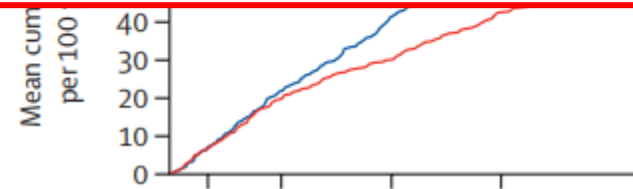
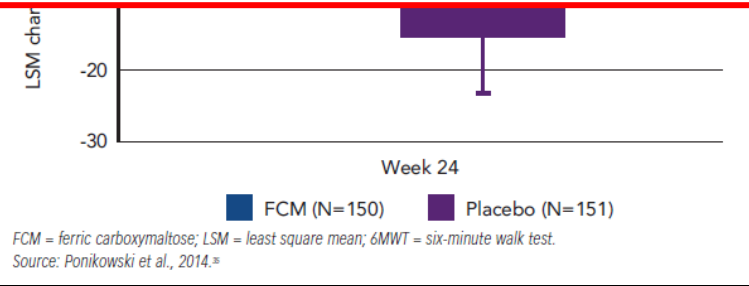
## CONFIRM-HF

## AFFIRM-AHF

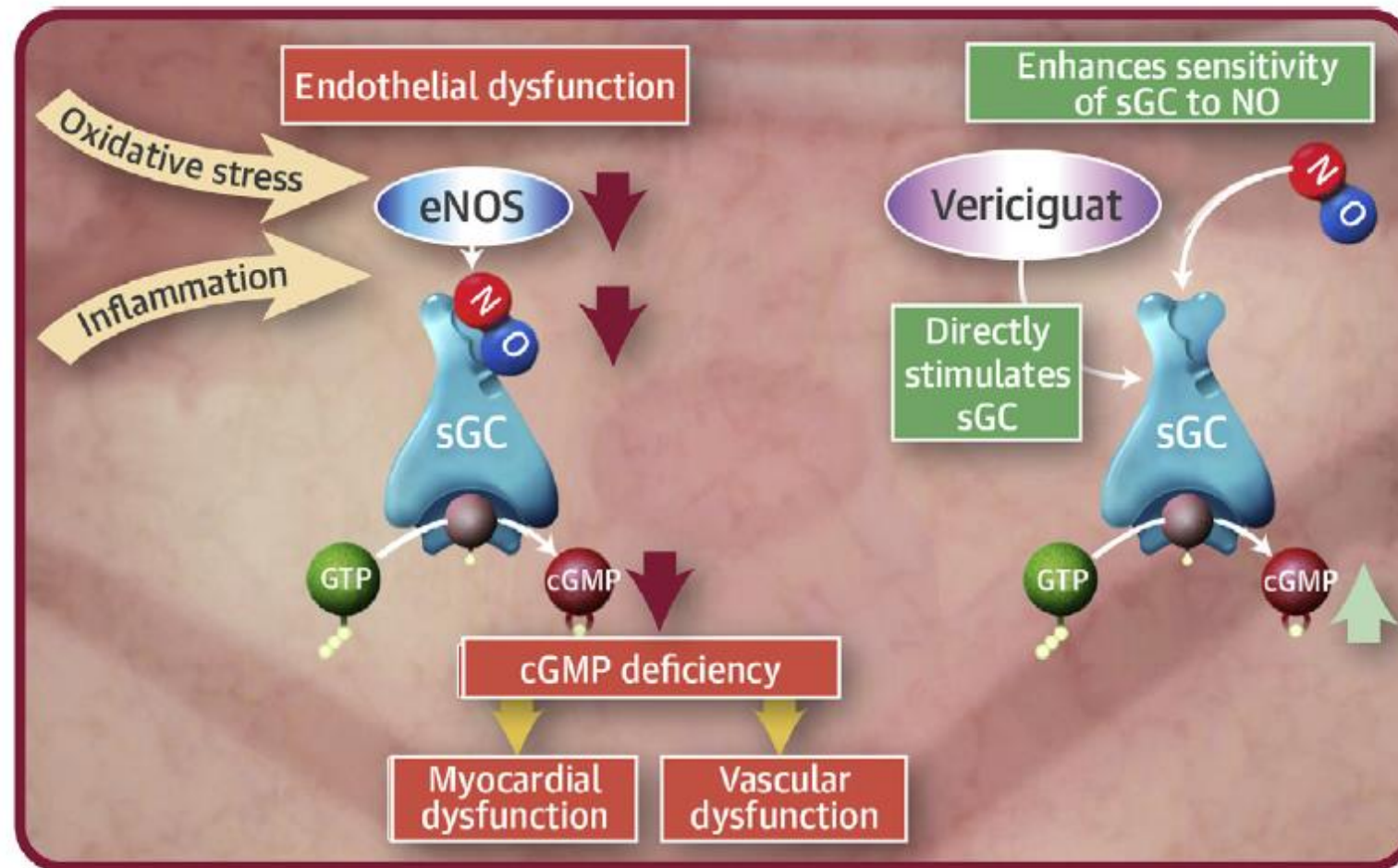
## C Total heart failure hospitalisations

Figure 4: The CONFIRM-HF Study – Change in Six-minute

**In patients w/ NYHA Class II-III HF and iron deficiency, IV iron may be considered to improve functional capacity and quality of life**



# 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) <sup>†</sup>	P Value <sup>‡</sup>
	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 <sup>§</sup>	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 <sup>¶</sup>	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 <sup>§</sup>	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



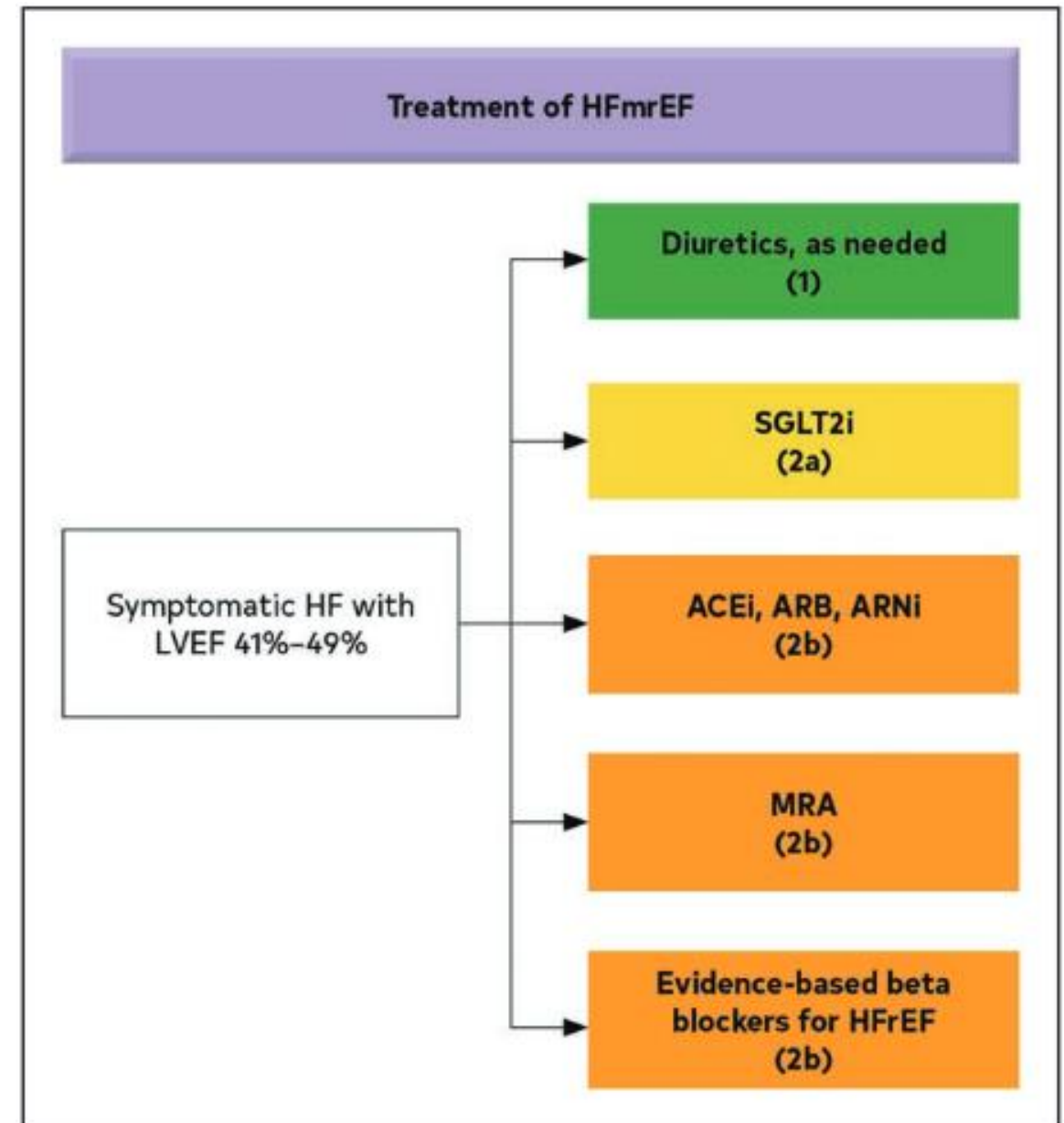
## Question 2

- Our AA pt w/ DMII and ischemic CMP (EF 30-35%) presents 2 years later w/ progressive shortness of breath and fatigue
- Medications include losartan 50 mg daily, metoprolol succinate 200 mg daily, aspirin 81 mg daily, and atorvastatin 80 mg daily, metformin 1000 mg twice daily, and empagliflozin 10 mg daily.
- His exam is notable for a HR 90 bpm, BP 110/60, JVP 14 cm of water, bibasilar crackles, irreg, irreg rhythm, NI S1, S2, and no edema.
- Labs with Na 137, K 4.8, BUN/Cr 25/1.4
- EKG with atrial fibrillation and VR 90 bpm. Old AMI.

## Question 2

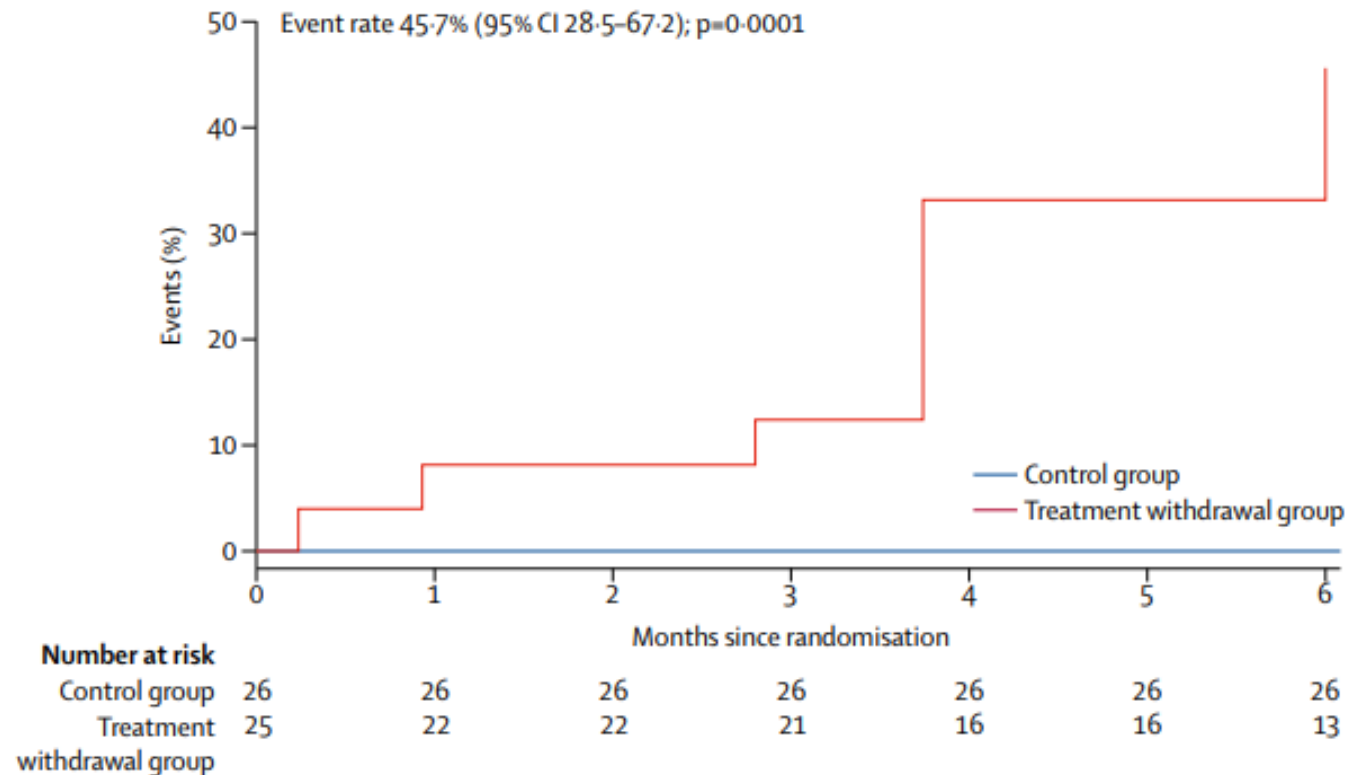
- In addition to diuresis, which of the following is the next best step in his management?
- A) Add ivabradine
  - B) Add digoxin
  - C) Add hydralazine and isosorbide
  - D) Stop losartan and start sacubitril/valsartan

# HF with Mid-Range LVEF



# Continue GDMT after LV Recovery: TRED-HF

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



# Cardiac Synchronization Therapy in HF

- In pts w/ EF < 35%, NSR, LBBB QRS > 120 msec, and on optimal medical therapy, CRT:
  - Promotes reverse remodeling (even in NYHA I)
  - Reduces HF hospitalizations (even in NYHA I)
  - Improves symptoms
  - Improves survival
- Predictors of benefit:
  - QRS duration  $\geq$  150 msec
- Can be considered in NYHA III-IV, non-LBBB, QRS > 150 msec
- Contraindicated in NYHA I-II, non-LBBB, QRS < 150 msec

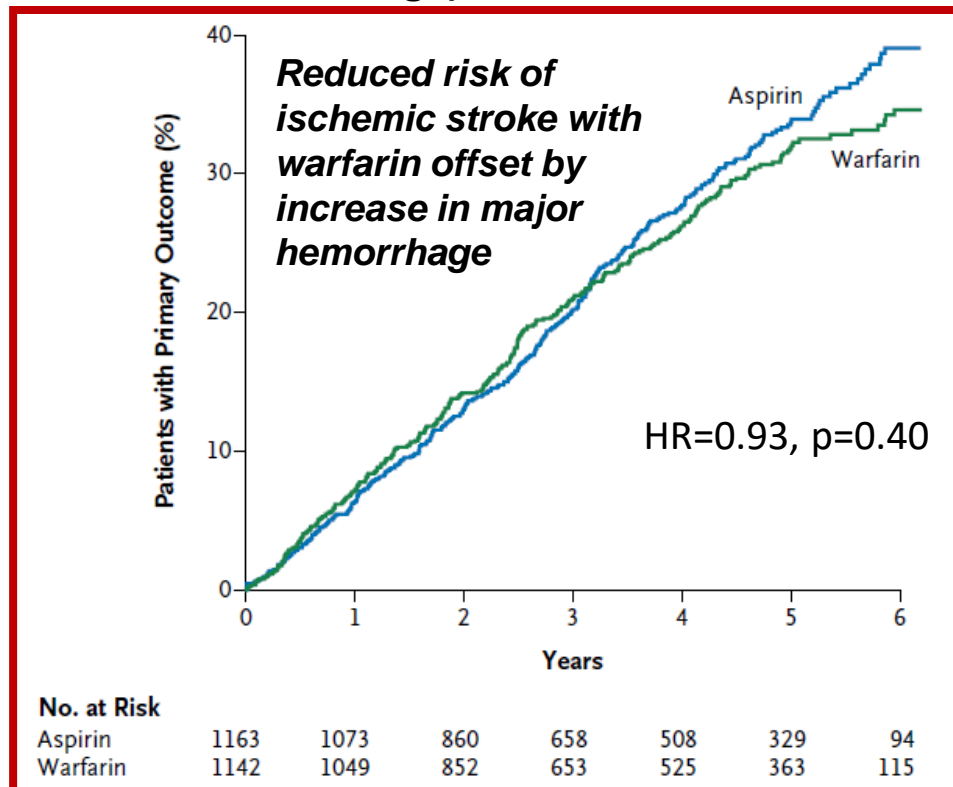
# Indications for ICD in Heart Failure

- Cardiac Arrest
- Sustained VT
- EF<40%, CAD, NSVT, inducible VT
- EF<30%, > 40d post-MI or 3mths post-revascularization, NYHA I-III
- EF<35%, Non-ischemic CMP, NYHA II-III
- *Contraindicated in NYHA IV, unless bridge to advanced therapies*

# Anticoagulation in Patients with HF and Sinus Rhythm

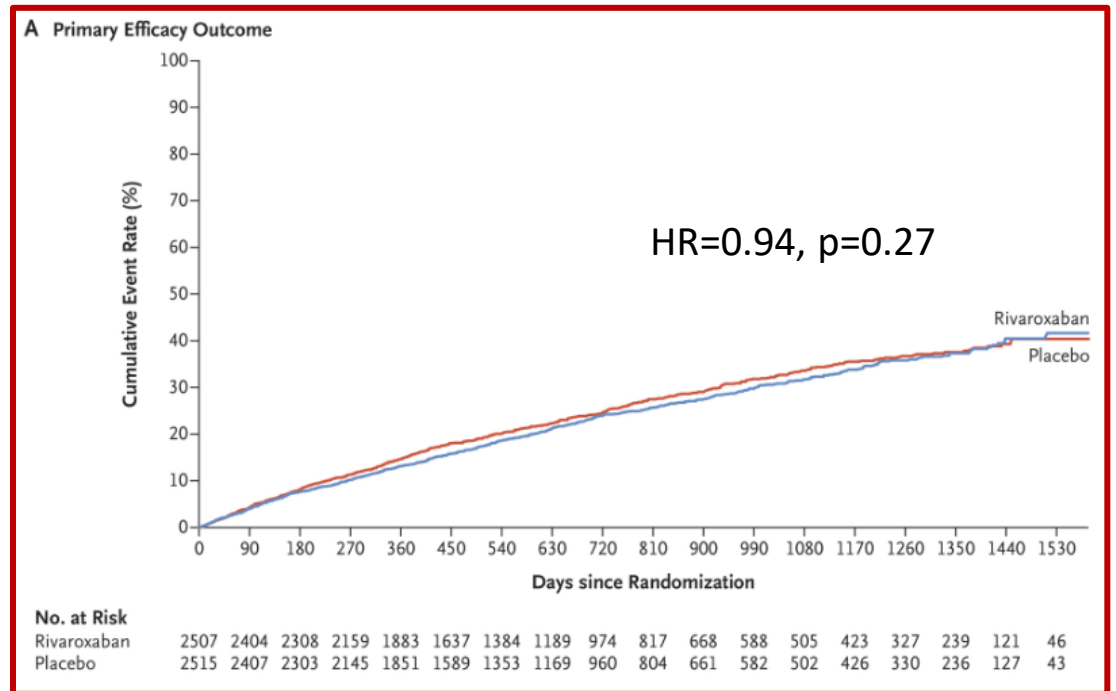
**WARCEF: ASA 325 mg vs. warfarin INR 2-3.5**

(N=2305; 1° Outcome: Death, ischemic stroke or intracerebral hemorrhage)



**COMMANDER: rivaroxaban 2.5 bid vs. placebo**

(N=5022; 1° Outcome: Death, MI or stroke)





# Question 3

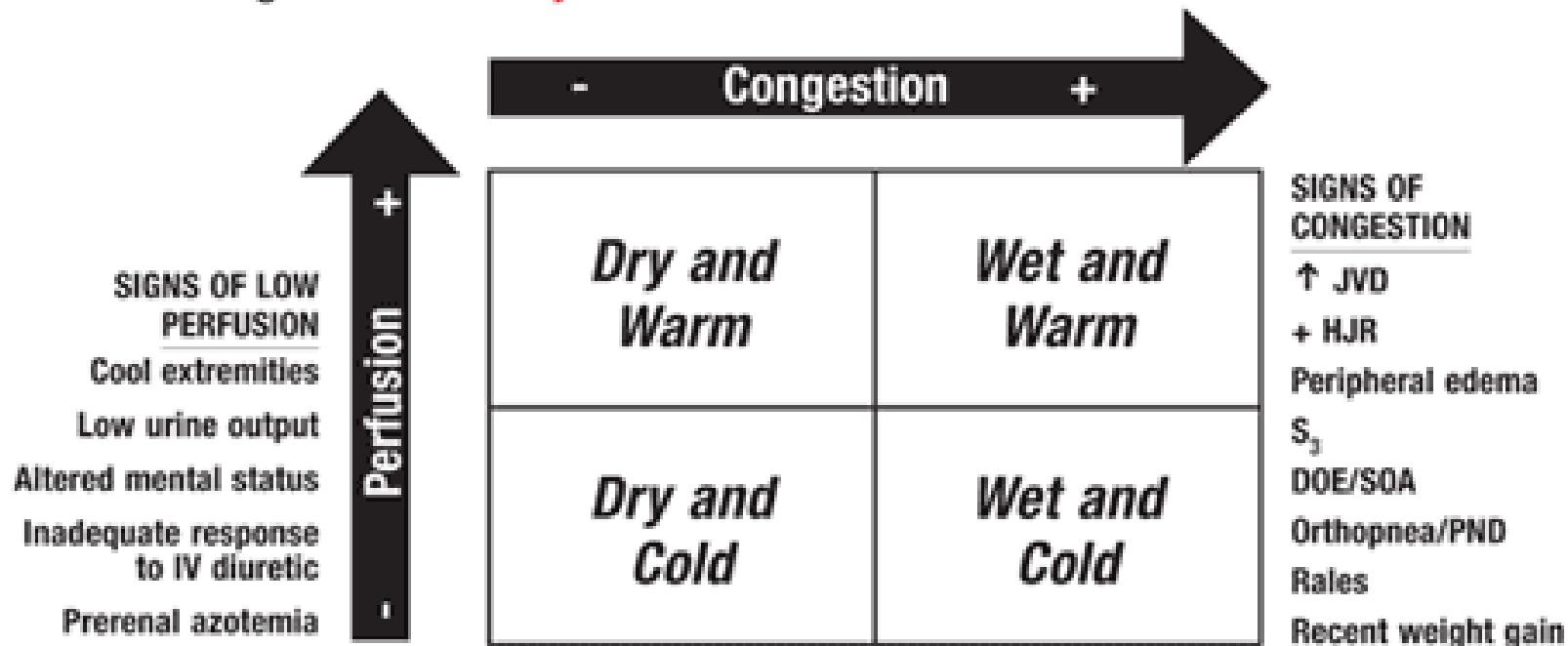
- Our pt does well for a few years and then presents with a 1-week history of profound weakness and severe dyspnea with minimal exertion.
- Exam shows HR 110 bpm, BP 85/70 mmHg, RR 22, Sats 90% RA
- JVP to angle of jaw, bilateral crackles, Tachy, regular, + MR, 2+ edema, extremities are lukewarm to the touch
- Labs: Na 132, K 4.8, BUN/Cr 45/2.1, ALT 300, AST 282, NT-proBNP 4,500
- Nasopharyngeal swab: + Influenza A
- Echo shows a decline in his EF to 15%, severe MR, mild-moderate TR

## Question 3

- In addition to IV diuretics and oxygen, which of the following would you do next in this patient?
  - A) IV dobutamine
  - B) IV milrinone
  - C) PA line to help decide if he needs inotropic support
  - D) Intra-aortic balloon pump

# Symptomatic HF is a Clinical Diagnosis

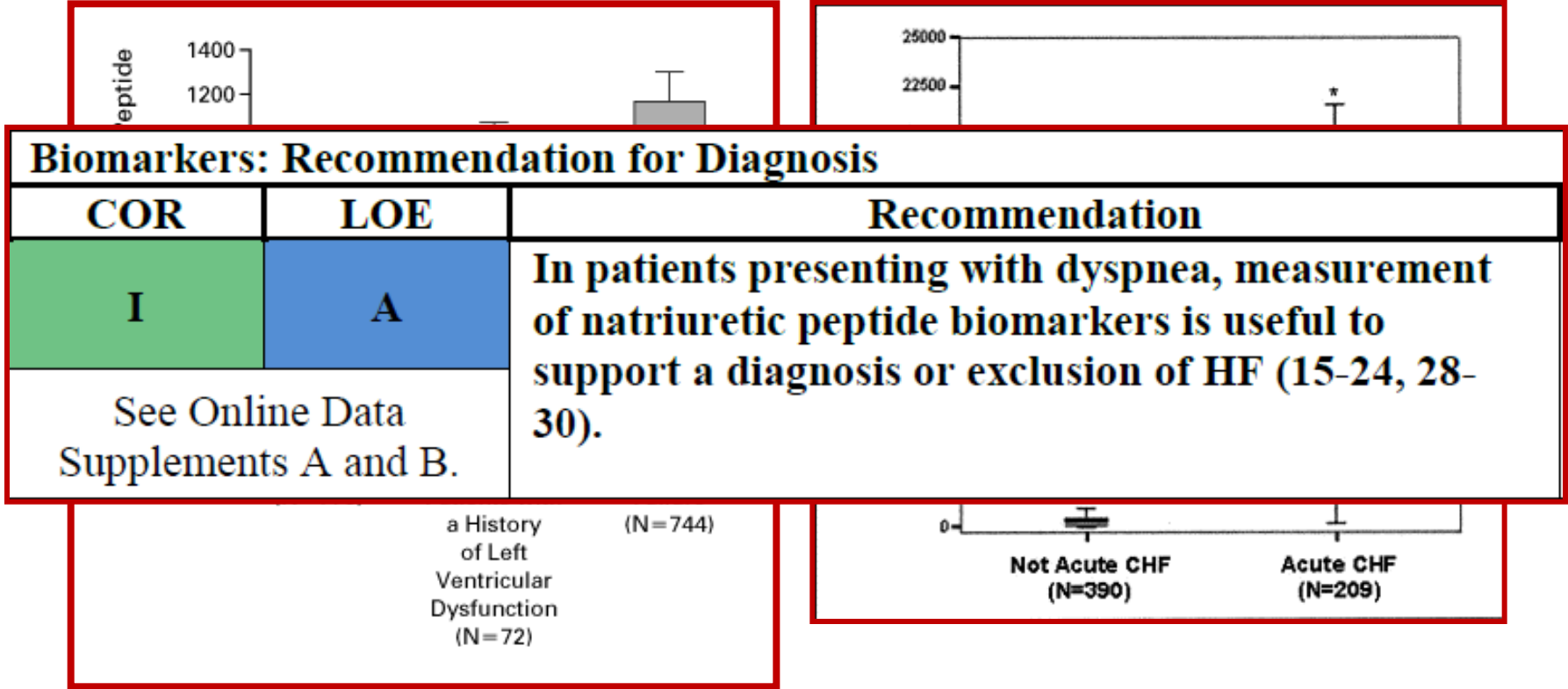
Figure 1. Hemodynamic/Clinical State in Acute Heart Failure



↑: increased; +: positive; -: negative; DOE: dyspnea on exertion; HJR: hepatojugular reflux; JVD: jugular venous distention; PND: paroxysmal nocturnal dyspnea; S<sub>3</sub>: ventricular filling murmur; SOA: shortness of air.

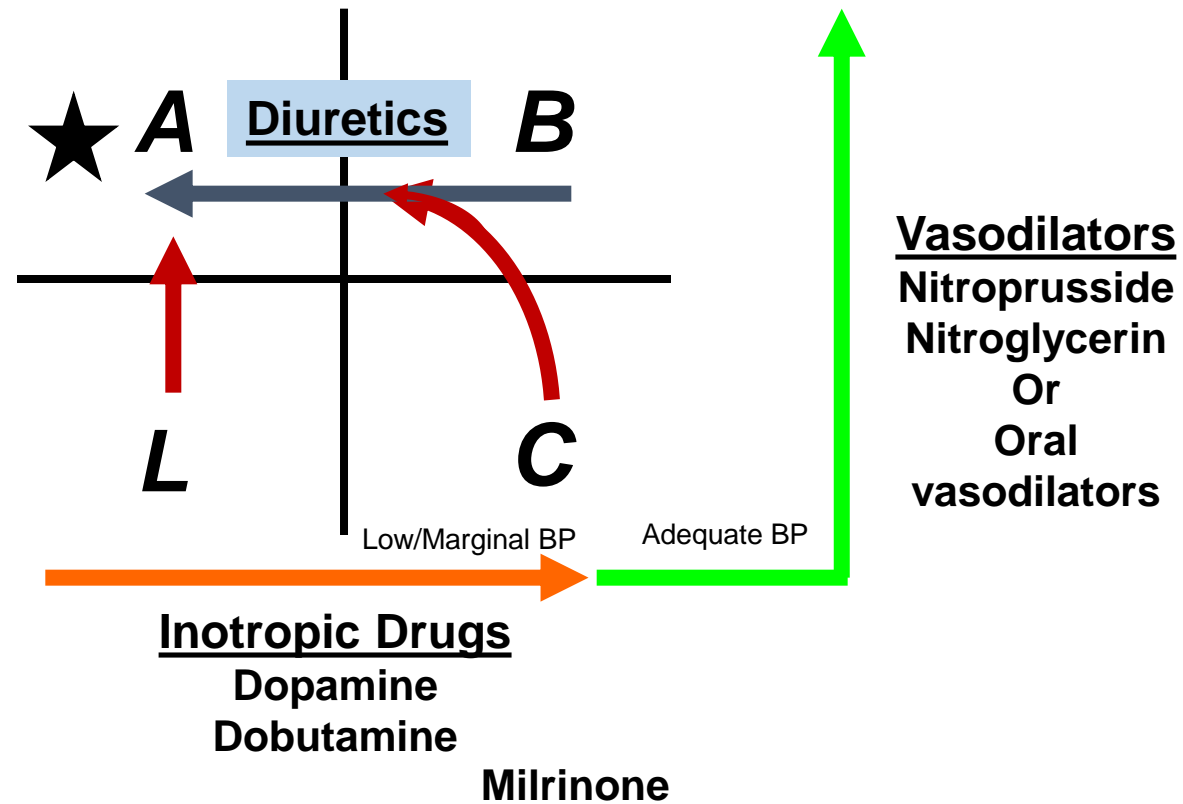
Source: References 10, 11.

# BNP to Assist Diagnosis of HF



Maisel AS, et al. NEJM 2002;347:161  
Januzzi J et al. Am Heart J 2005;149:744.

# Treatment of Decompensated HF



# Diuretic Trials in Heart Failure

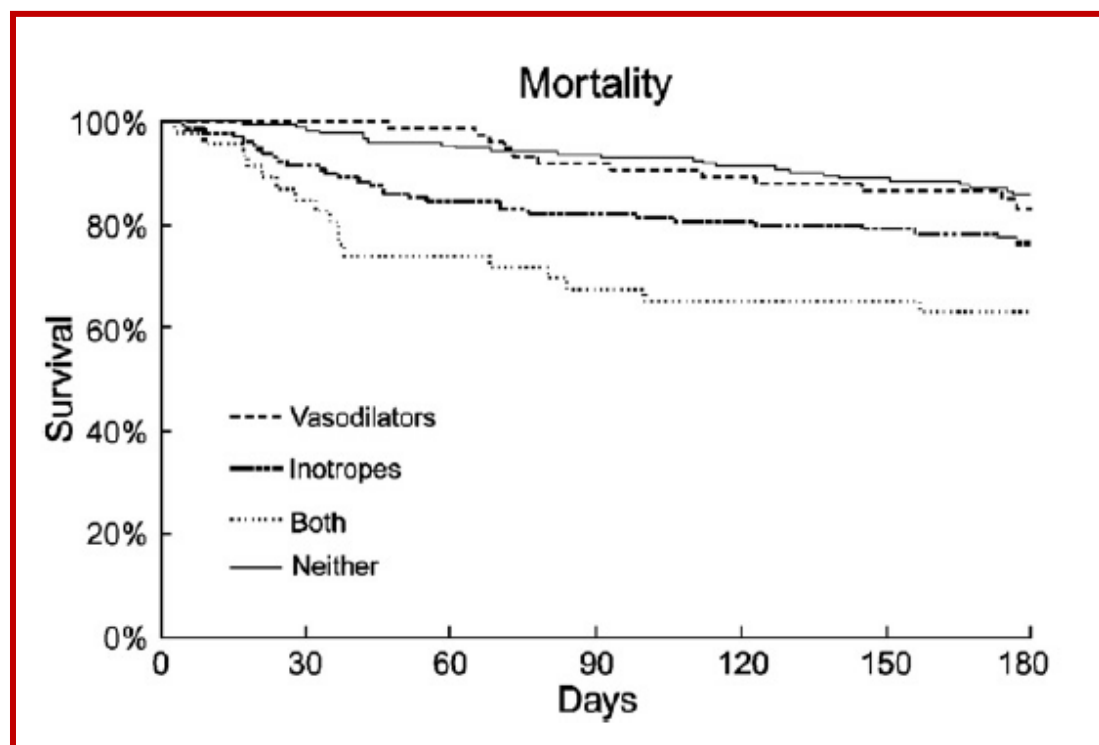
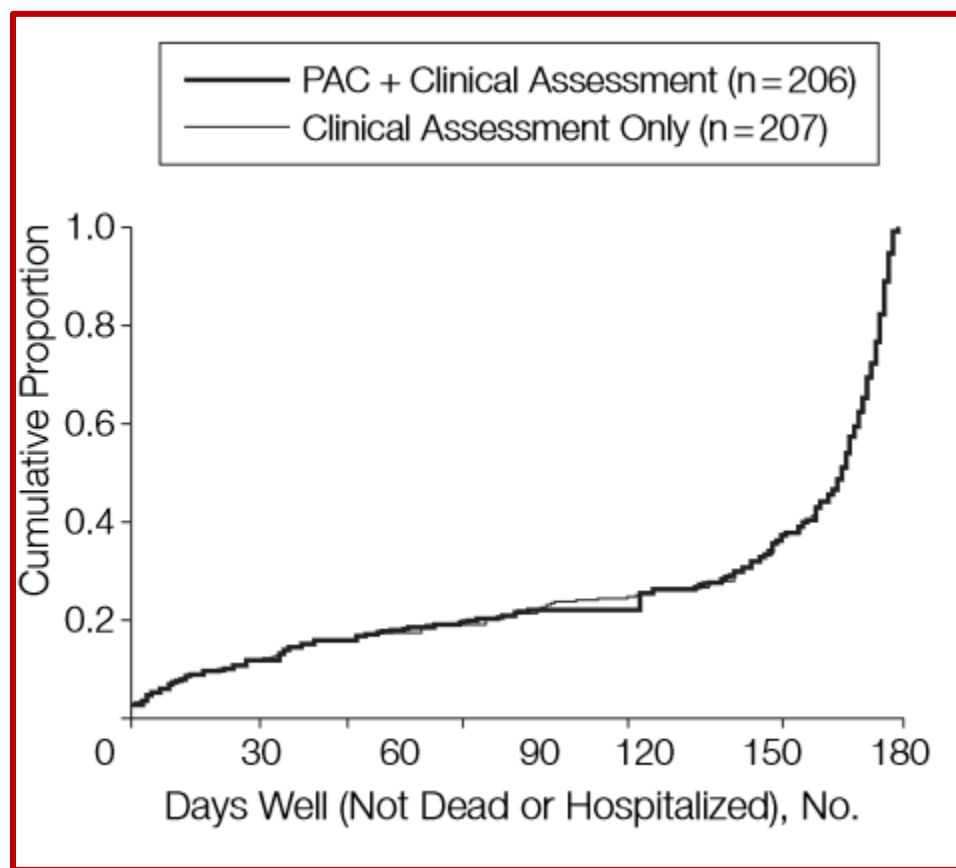
Trial	N	Inclusion	Agents	Outcomes
DOSE	308	-HFrEF and HFpEF -ADHF w/in 24 hours of admission	High dose vs. low dose furosemide	- ↓ dyspnea, ↑ wt loss, and ↑ WRF @ 72 hours - No change in death, re-hospitalization or ED visits @ 60 days
			Furosemide bolus IV twice daily vs. continuous infusion	- No difference in dyspnea, wt loss or WRF - No change in death, re-hospitalization or ED visits @ 60 days
TRANSFORM -HF	2859	-recent HF hospitalization -EF < 40% and ↑ NPs	1:1 Torsemide vs furosemide	-No difference in all-cause mortality or HF hospitalizations @ f/u 17.4 mths

# Trials for Diuretic Resistance in Heart Failure

Trial	N	Inclusion	Agents	Outcomes
3-T	60	-HFrEF and HFpEF -ADHF -< 2 L urine in 12 hrs despite ≥ IV furosemide 240 mg/d	1:1:1 Metolazone 5 mg bid vs. chlorthalidone 500 mg IV bid vs. tolvaptan 30 mg qd	- No change in wt loss or urine output @ 48 hours
ADVOR	519	-HFrEF and HFpEF -ADHF + Elevated NPs -IV furosemide ≤ 80 mg/day - No SGLT-2i	1:1 Acetazolamide 500 mg daily vs. placebo	- ↑decongestion @ 72 hours - No difference in death or HF rehospitalization @ 3 months
CLOTOTIC	230	-HFrEF and HFpEF -w/in 24 hours of admission w/ ADHF	1:1 5 days of HCTZ vs placebo	- No difference in HF rehospitalization of all-cause mortality @ 90 days - Increased hypokalemia and WRF w/ HCTZ
DAPA-RESIST	60	-HFrEF and HFpEF -ADHF -< 1 kg weight loss in 24 hours despite IV furosemide ≥ 160 mg/day	1:1 Dapagliflozin 10 mg daily vs. metolazone 5-10 mg/day	- No difference in weight change @ 96 hours - Less increase in BUN/Cr and less hypokalemia and hyponatremia but not statistically significant

# Inotropes Increase Mortality in ADHF: ESCAPE

433 pts w/ ADHF, EF < 30%, SBP ≤ 125 mm Hg, 1 sign + symptom of HF, HF hosp. w/in previous yr



Binanay et al. 2005;294(13):1625-1633;  
Elkayam et al. Am Heart J 2007;153:98-104.



# Who to Refer for Advanced Therapies?

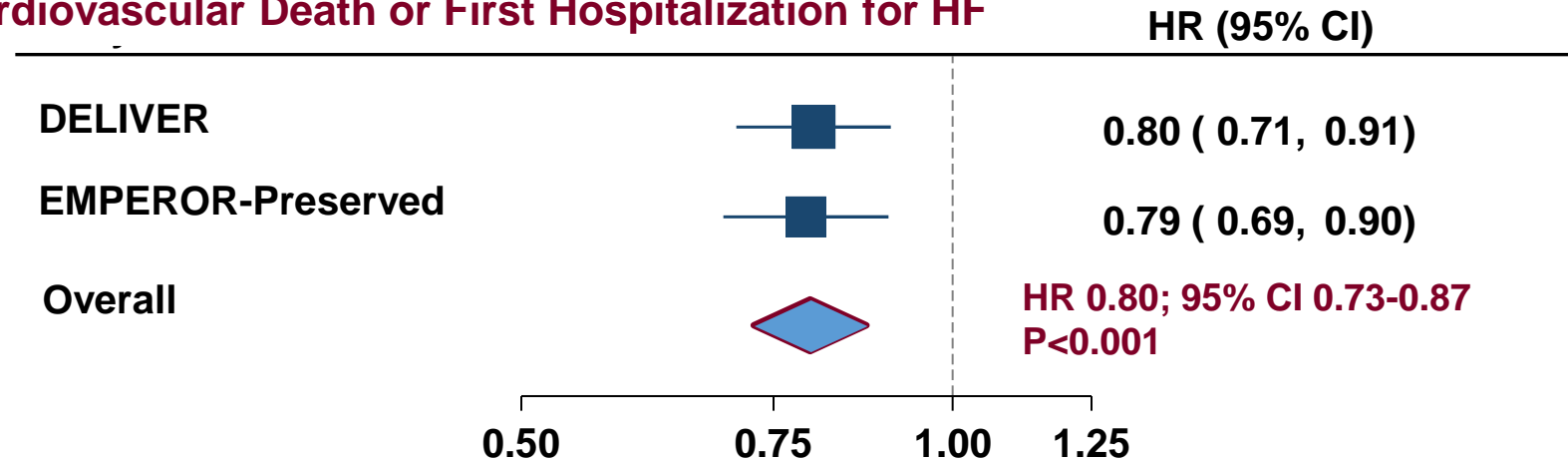
- Escalating diuretic dose requirements
- Progressive renal dysfunction
- Increasing frequency of HF hospitalization
- Increasing burden of ventricular arrhythmias
- Intolerance of standard medical therapy
- Refractory HF symptoms
- Need for inotropic support
- > 5% non-fluid related weight loss (cachexia)
- Peak oxygen consumption  $\leq 10$  ml/kg/min w/ RER >1

# Guideline Update for HFpEF

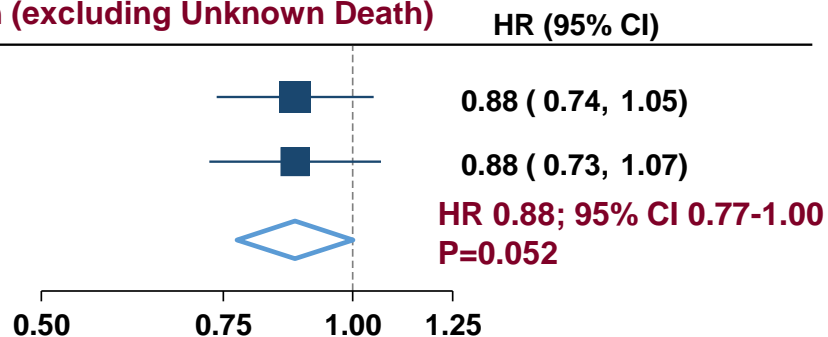
COR	LOE	Recommendations
<b>1</b>	<b>C-LD</b>	1. Patients with HFpEF and hypertension should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity. <sup>44-46</sup>
<b>2a</b>	<b>C-EO</b>	2. In patients with HFpEF, management of AF can be useful to improve symptoms.
<b>2a</b>	<b>B-R</b>	1. In patients with HFpEF, SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. <sup>33</sup>
<b>2b</b>	<b>B-R</b>	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. <sup>38,42,43</sup>
<b>2b</b>	<b>B-R</b>	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. <sup>35,40</sup>
<b>3: No Benefit</b>	<b>B-R</b>	4. In patients with HFpEF, routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or quality of life is ineffective. <sup>49,50</sup>

# DELIVER and EMPEROR-Preserved Meta-Analysis:

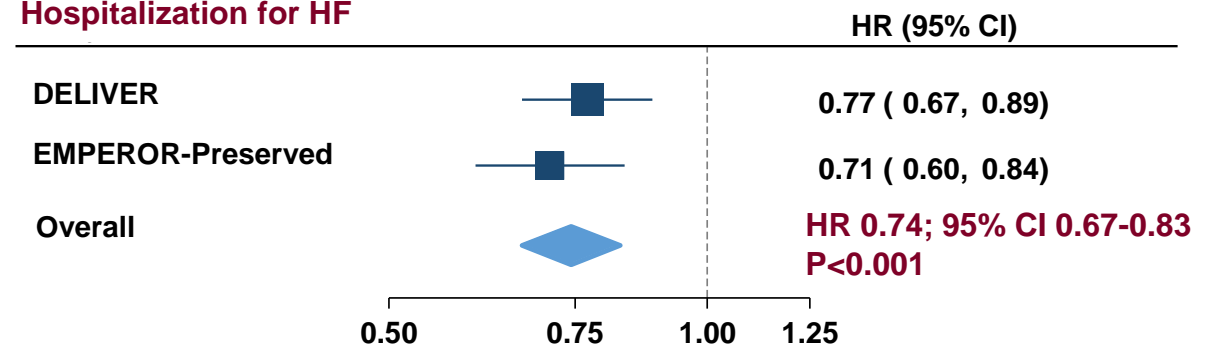
## Cardiovascular Death or First Hospitalization for HF



## Cardiovascular Death (excluding Unknown Death)

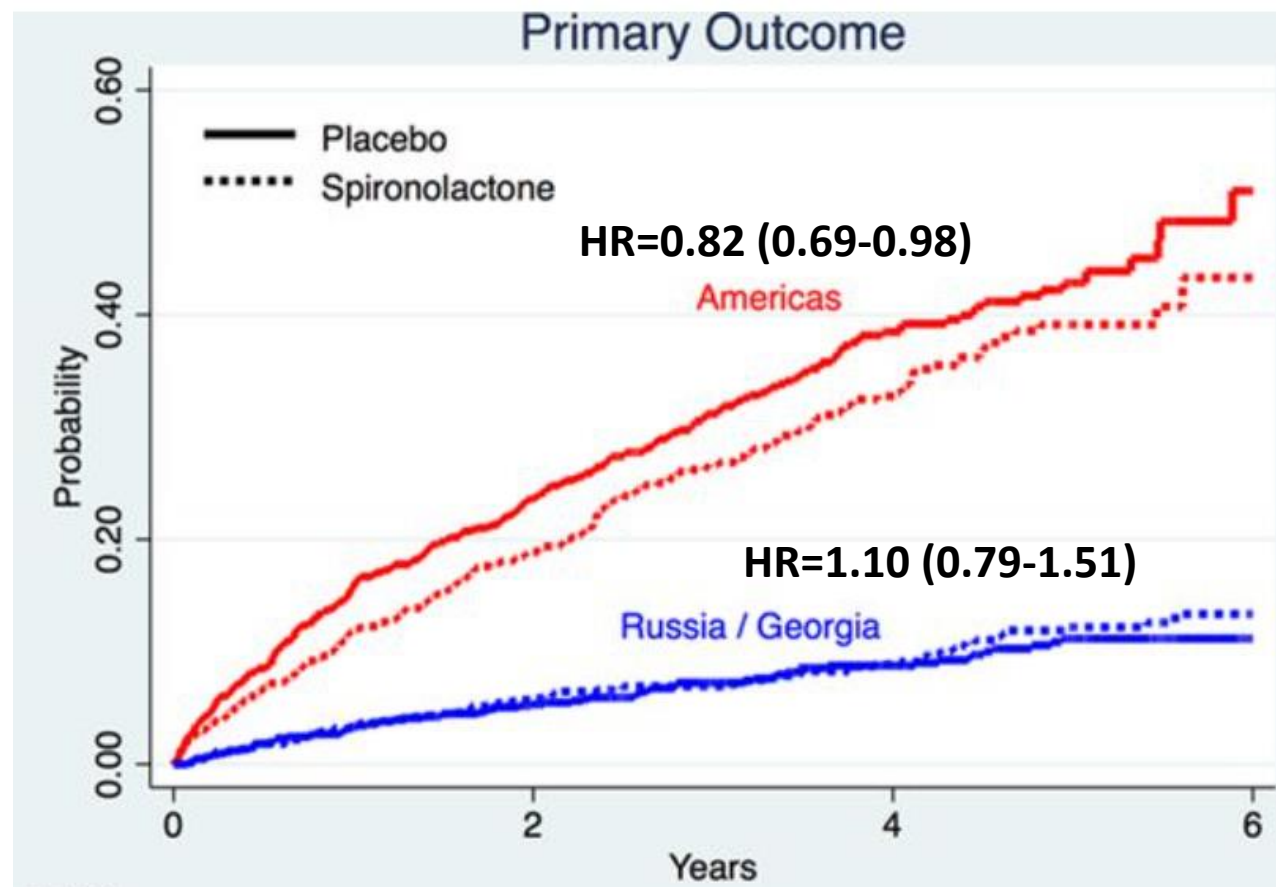
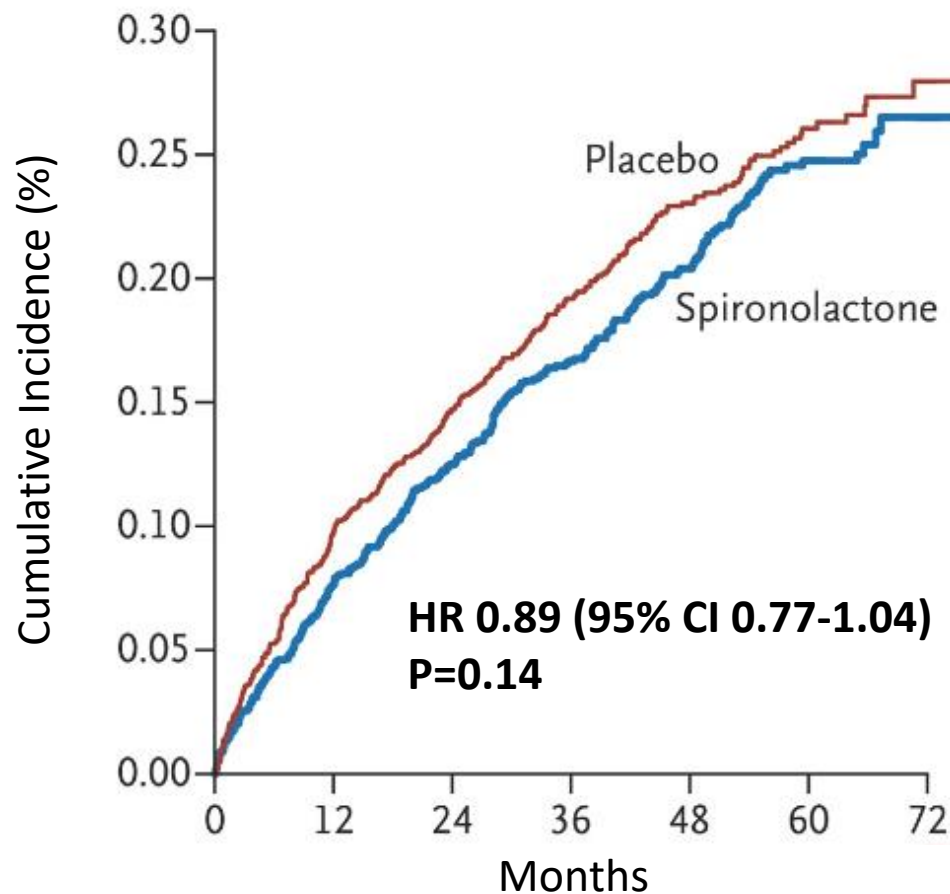


## Hospitalization for HF



# TOPCAT: Spironolactone in HFpEF

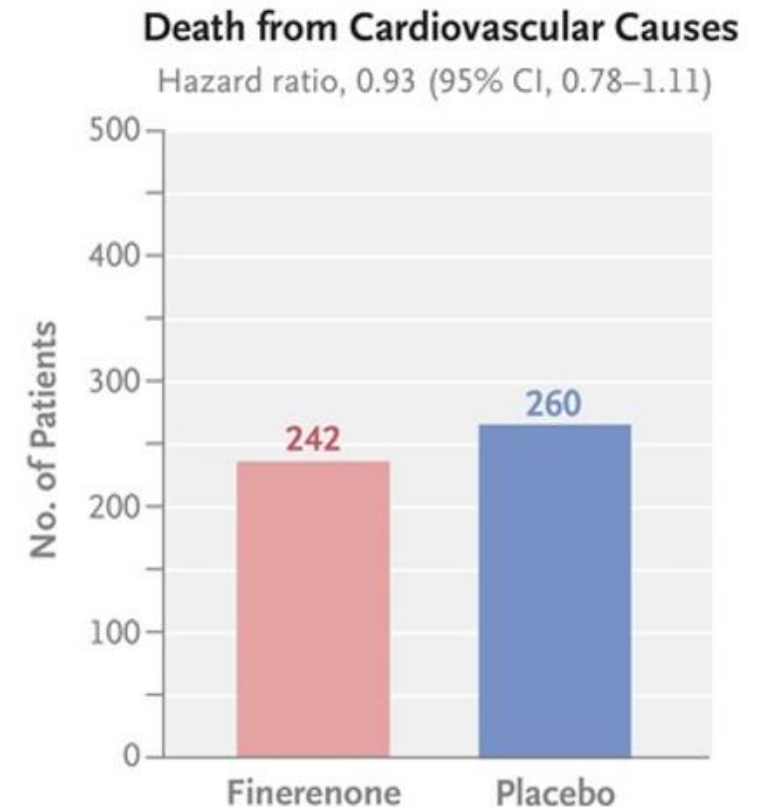
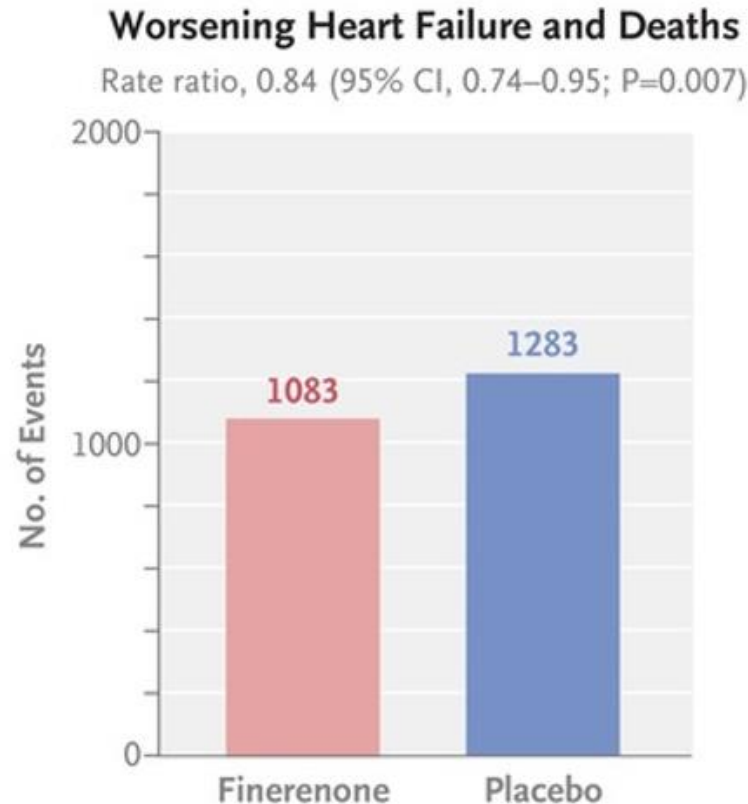
## 1° Endpt: Cv Mortality, Aborted CV Death or HF Hosp.



# FINEARTS: Finerenone in HFpEF

## 1° Endpt: CV death and Worsening HF events

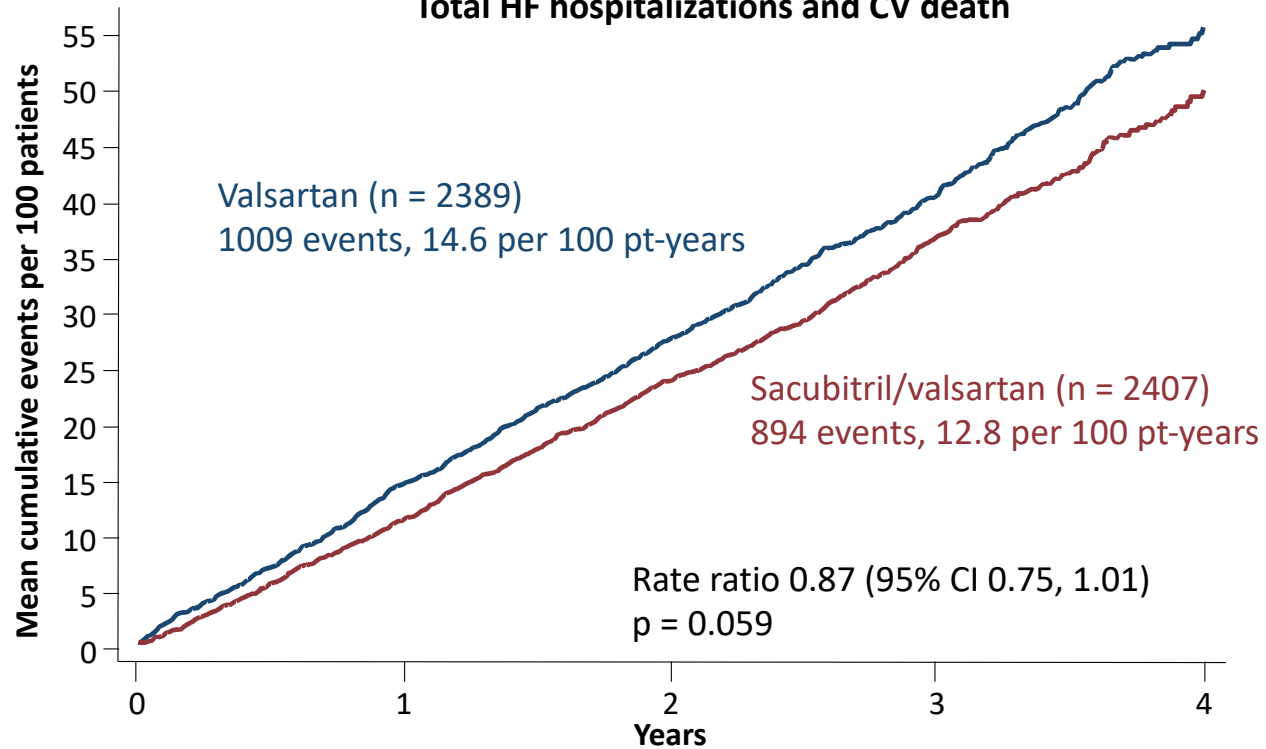
- N=6001 pts
- Age  $\geq$  40 yrs, LVEF  $\geq$  40%,  
structural heart dz, NYHA II-IV HF,  $\uparrow$ NPs
- RCT: 1:1 Finerenone 20 or 40 mg daily vs. placebo
- Median f/u: 32 mths
- $\uparrow$  hyperkalemia



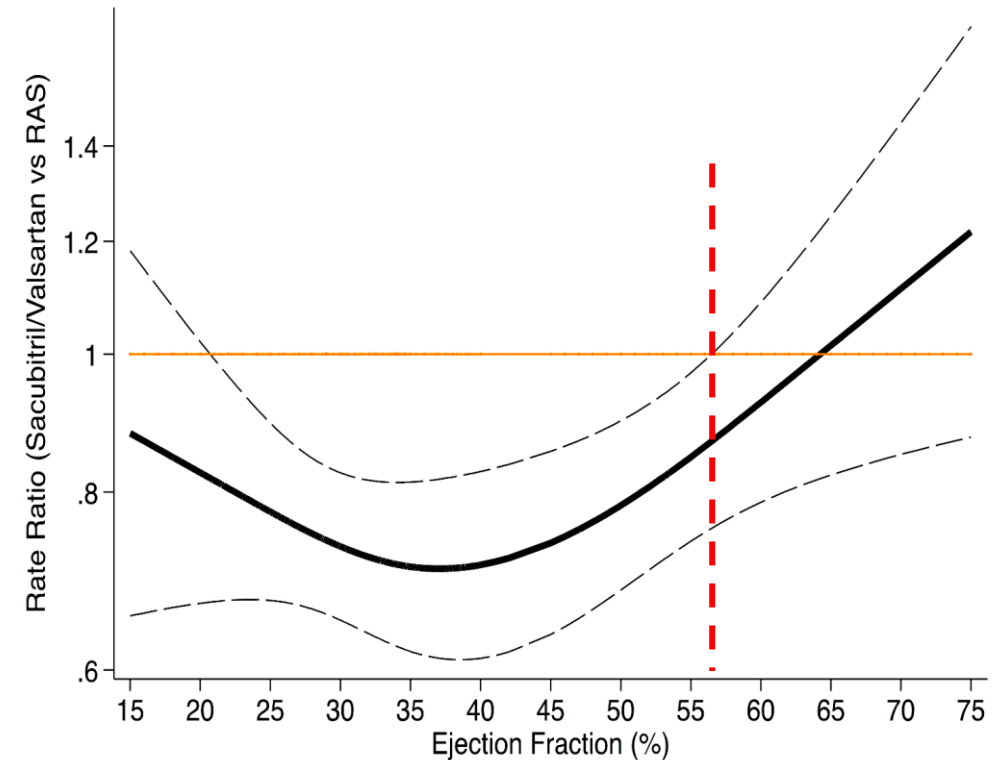
# ARNI in HF with HFmrEF or HFpEF

## PARAGON-HF Primary Results

Total HF hospitalizations and CV death



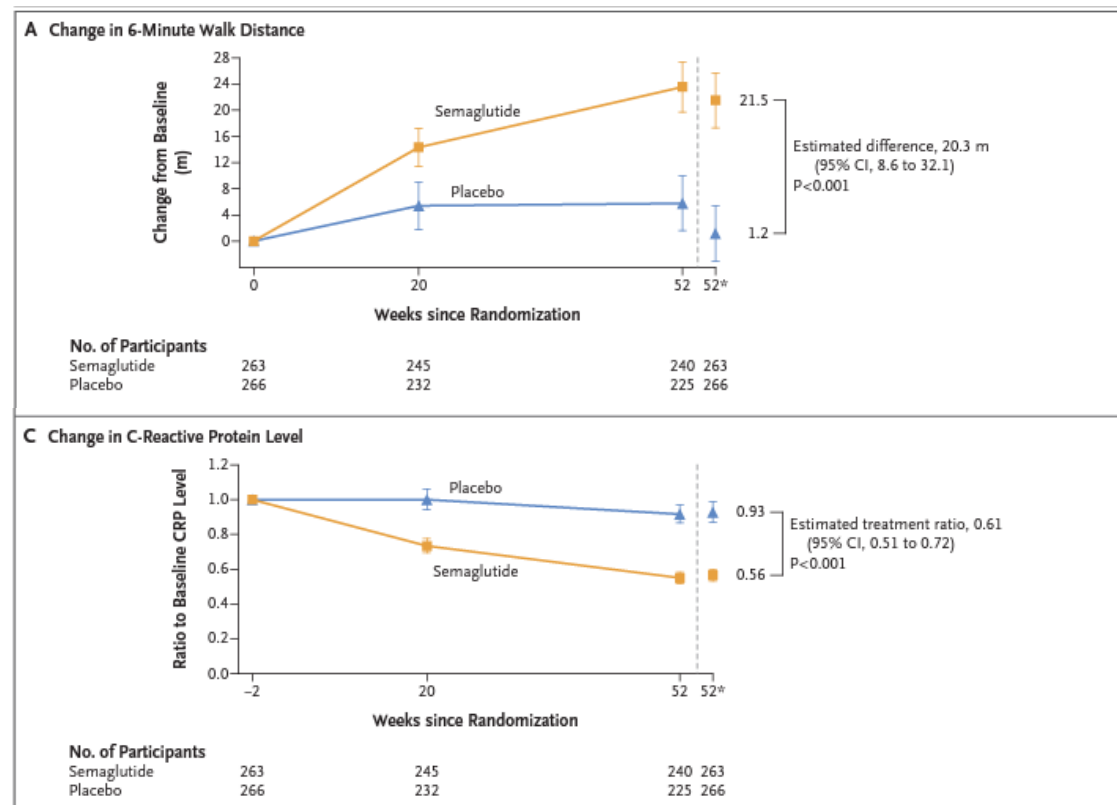
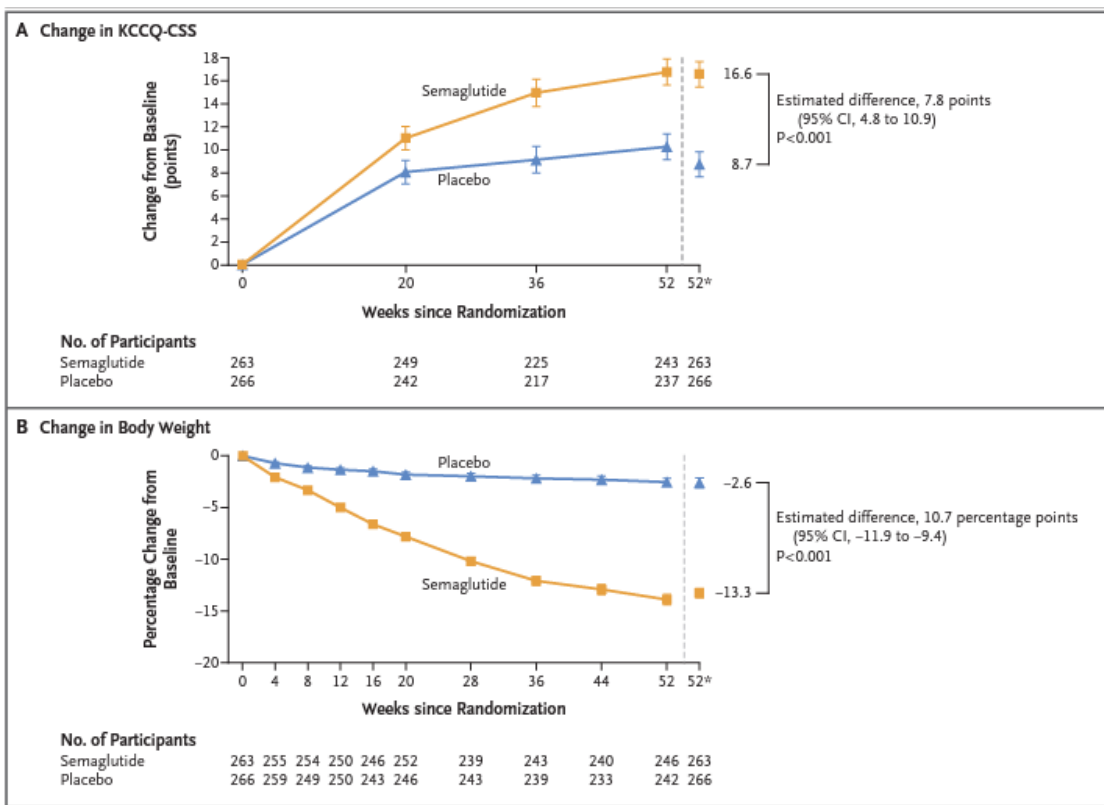
## PARADIGM-HF/PARAGON-HF Pooled



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

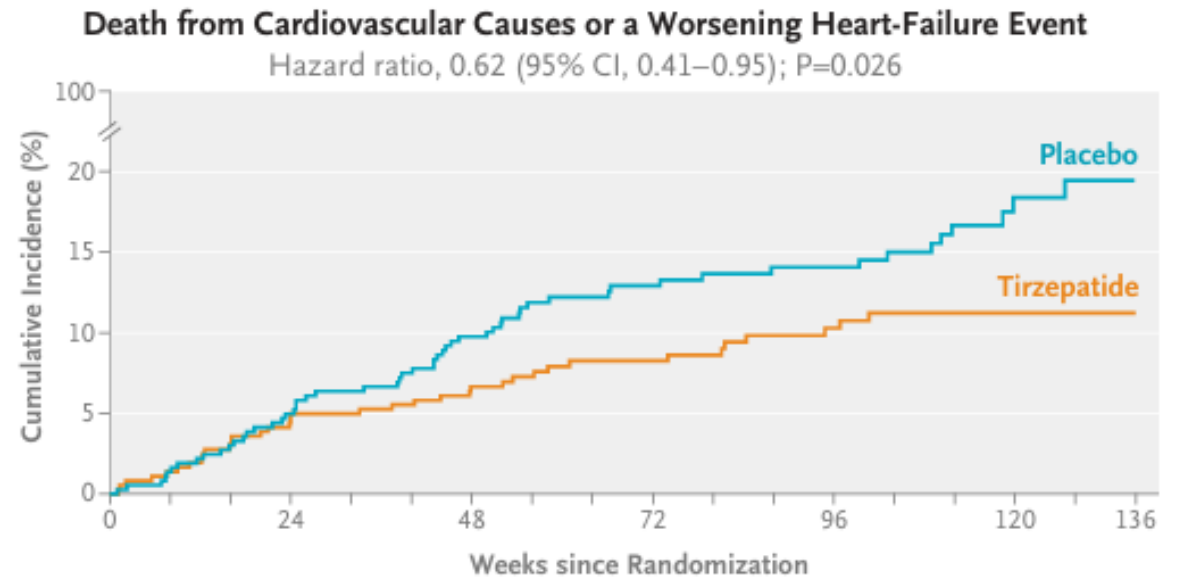
# GLP-1 agonists in HFpEF: STEP-HFpEF

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



# SUMMIT: GLP-1 and GIP Agonist in HFpEF

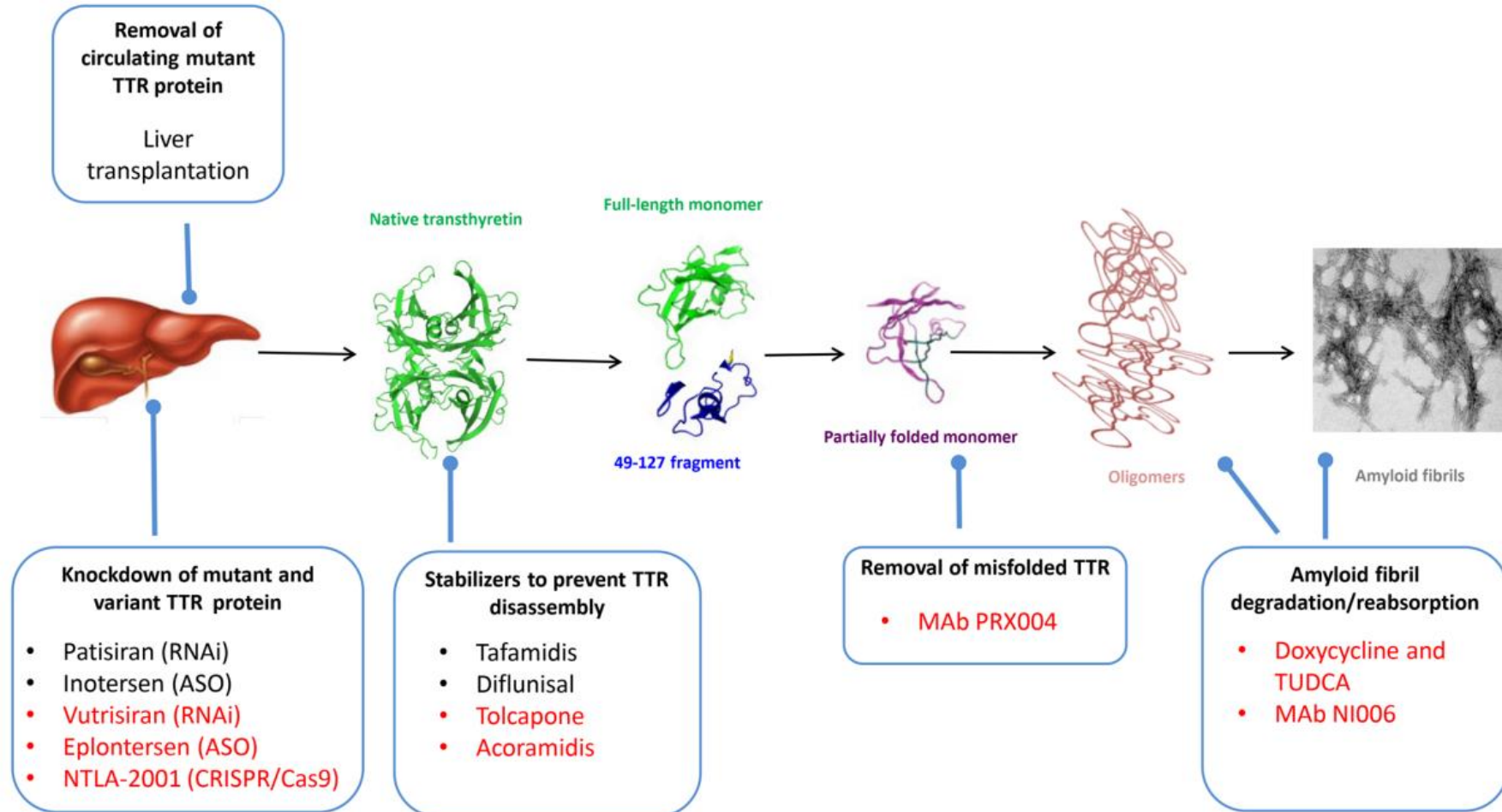
- N=732 pts
- Age  $\geq 40$  yrs, BMI  $\geq 30$ , NYHA II-IV HF, LVEF  $\geq 50\%$ ,  $\uparrow$  NPs, LAE or  $\uparrow$  PCWP @ rest or exercise,  $\geq 30$  HF hosp. w/in 1 yr or eGFR  $< 70$ .
- RCT: 1:1 tirzepatide up to 15 mg SC weekly vs. placebo x 52 weeks
- Median f/u = 104 weeks
- Discontinuation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



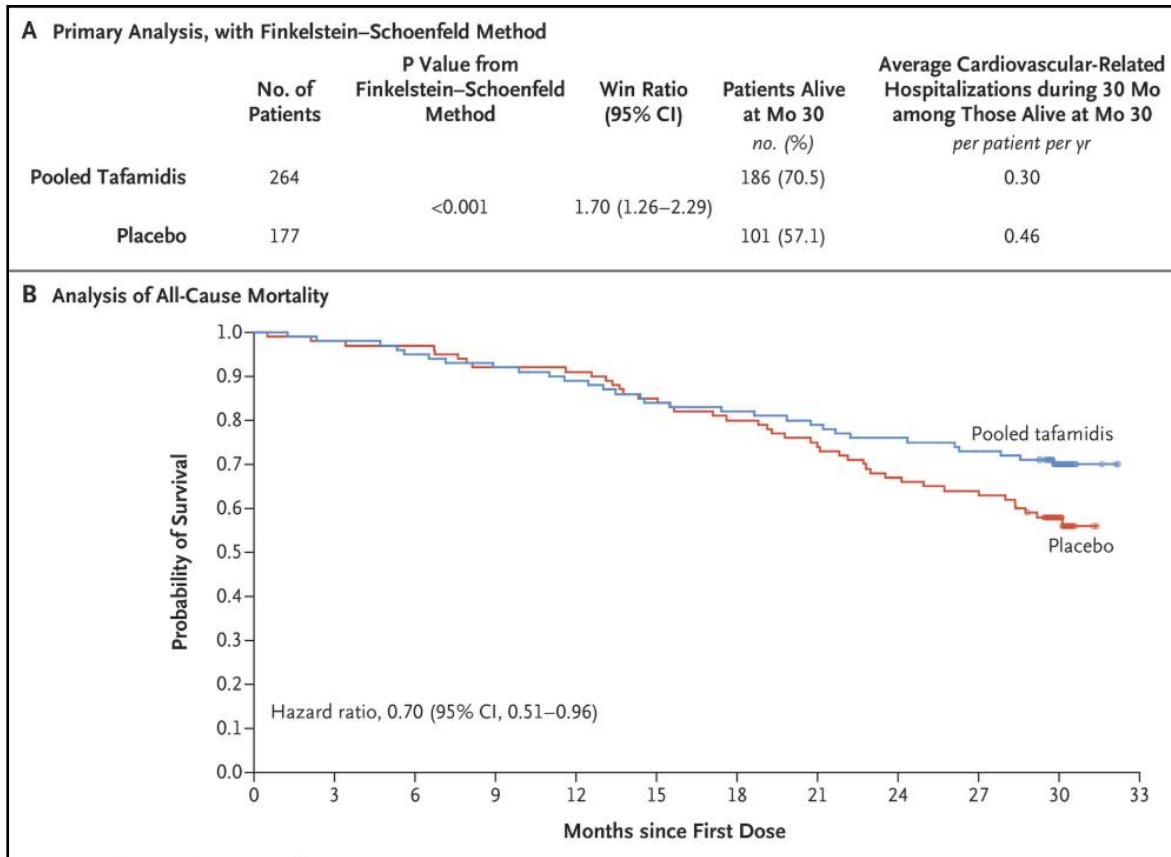
# Therapies for ATTR Amyloidosis



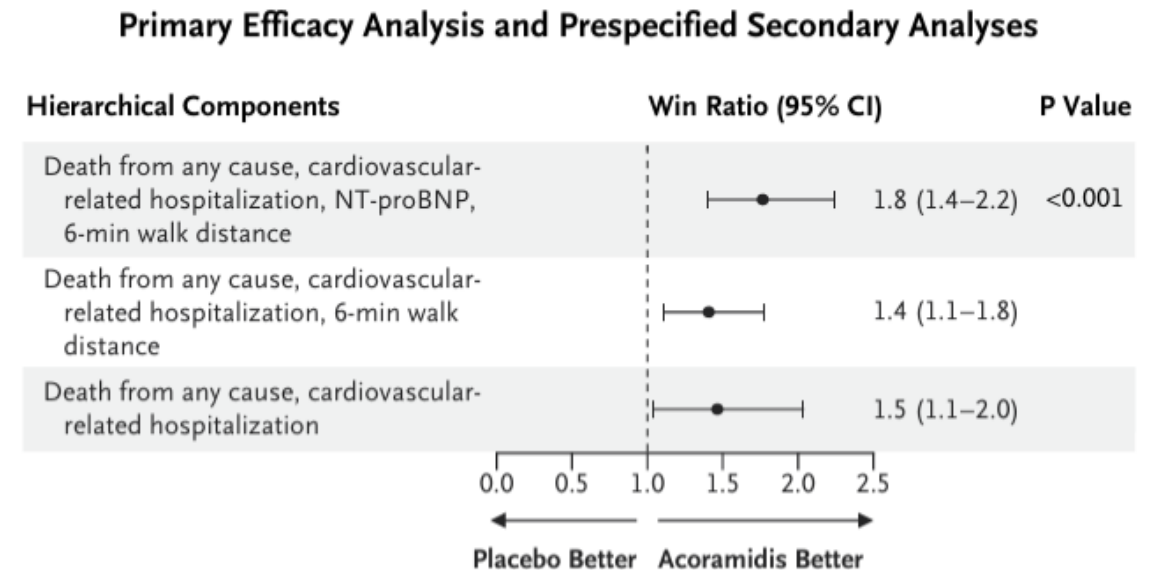
# Stabilizers for TTR Cardiac Amyloid

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

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



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



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

# Helios-B: Vutrisiran (RNAi) for ATTR Amyloidosis

654 adults

Median age, 77 years

Men: 93%; Women: 7%

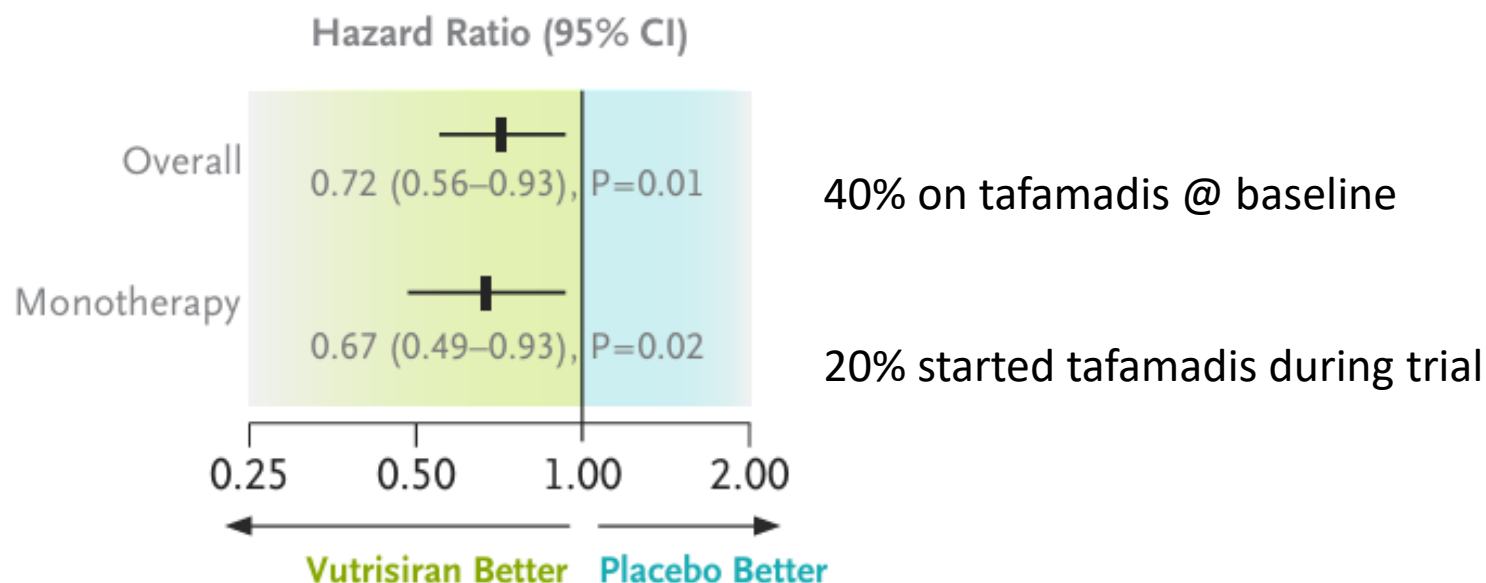
Presence of TTR amyloid deposits in a tissue-biopsy specimen or fulfillment of scintigraphy-based diagnostic criteria for ATTR amyloidosis with cardiomyopathy

Cardiac involvement as assessed with transthoracic echocardiography

Clinical history of heart failure

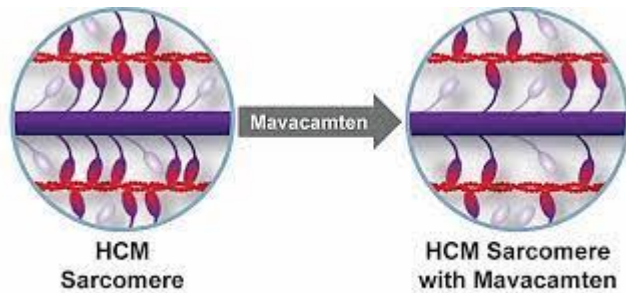
RCT: 1:1 Vutrisiran 25 mg q 12 weeks vs placebo x 36 mths

## Death and Recurrent Cardiovascular Events

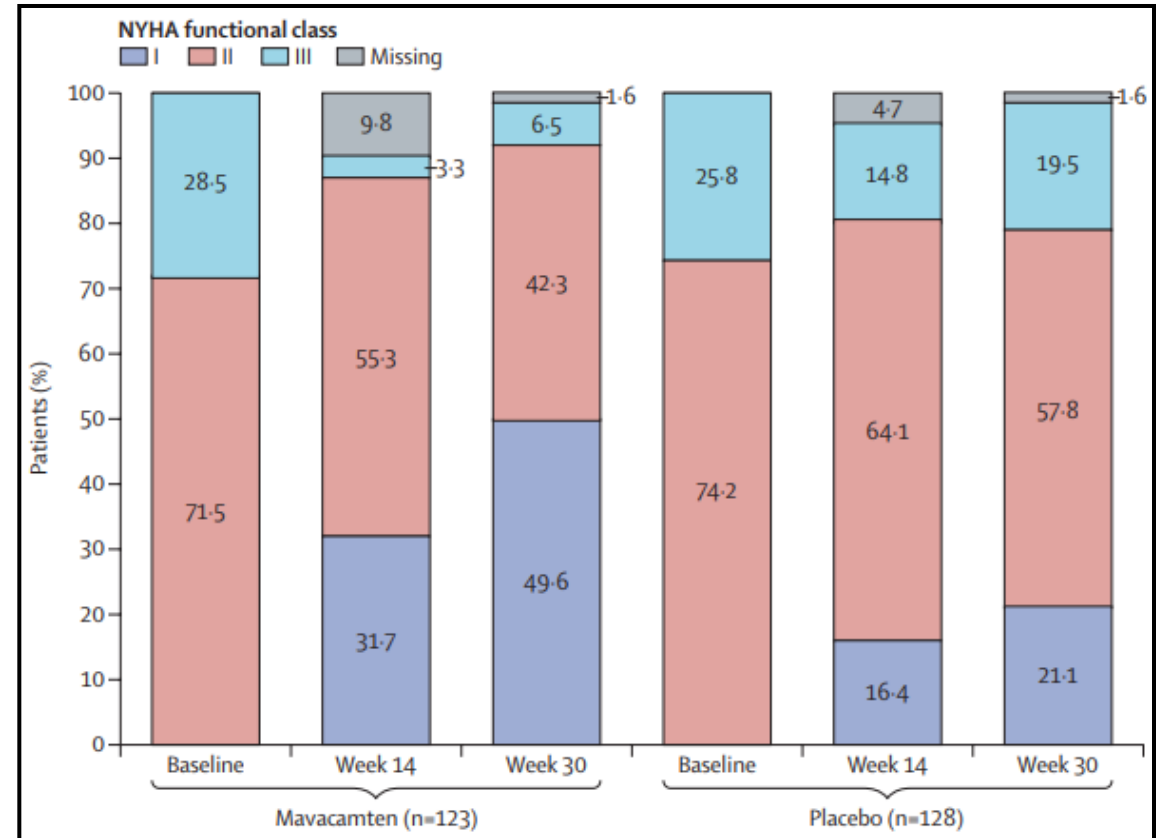


# EXPLORER-HF: Mavacamten for Hypertrophic Obstructive Cardiomyopathy

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

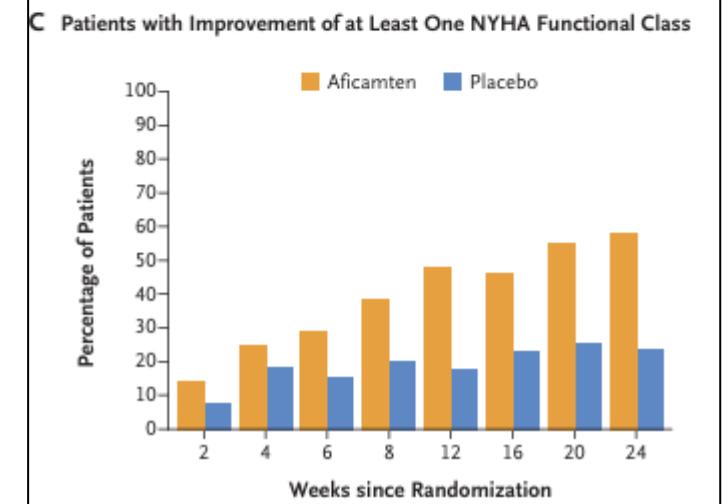
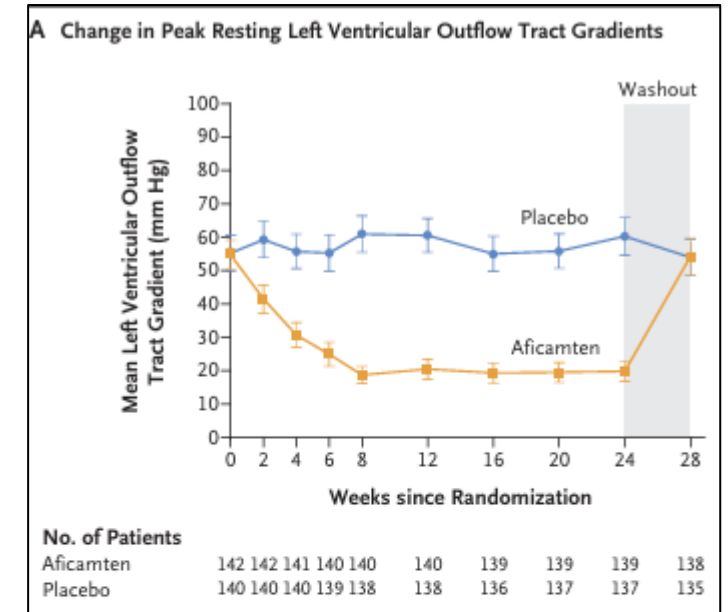
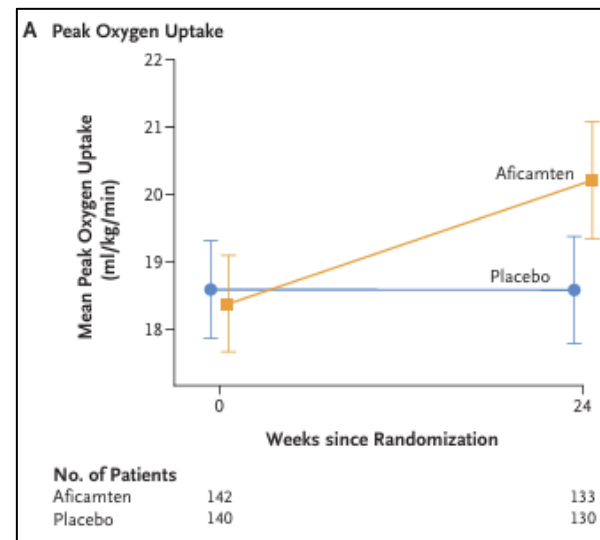


- N=251 pts, HCM, LVOT gradient > 50 mmHg, NYHA II-III
- **1° Endpoint:**  $\geq 1.5$  ml/kg/min  $\uparrow$  in peak VO<sub>2</sub> +  $\geq 1$  NYHA Class  $\downarrow$  in sx OR  $\geq 3$  ml/kg/min  $\uparrow$  in peak VO<sub>2</sub> w/ stable sx: **37% vs. 17%, p=0.0005**



# SEQUOIA-HCM: Aficamten for Obstructive HCM

- N=282 pts
- EF  $\geq$  60%,
- LVOT gradient  $\geq$  30 mm Hg @ rest or  $\geq$  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



# Congestive Heart Failure: Summary

- Heart failure is a clinical diagnosis
- BNP can be helpful when diagnosis is uncertain, but should not replace clinical assessment
- ACEi and beta-blockers are cornerstones of HF therapy and should be titrated to target doses if tolerated
- ARBs should be used in ACEi intolerant patients (cough, angioedema)
- Substitution w/ ARNI should be considered in pts on ACEi or ARB to reduce HF mortality and hospitalization
- Beta blockers should not be started in acutely decompensated patients

# Congestive Heart Failure: Summary

- Aldosterone antagonists are increasingly the favored 'second-line' after ACEi/ARB/ARNI and beta-blocker
- SGLT-2i reduce HF hospitalizations and mortality, regardless of DM
- Hydralazine/Isosorbide is an alternative for the ACEi/ARB intolerant and may be added for those still symptomatic on ACEi/Beta-blocker/aldosterone antagonist
- Digoxin and ivabradine can be considered to reduce HF hospitalization
- IV iron repletion can be considered to improve functional capacity
- Device Therapy (ICD +/- CRT) is appropriate for many HF patients with LVEF  $\leq 35\%$
- For HFpEF, SGLT2i reduce HF hospitalizations (can consider ARB or MRA)
- For HFpEF with obesity, GLP-1 agonists promote weight loss and improve symptoms

# References

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3. Solomon SD et al. Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N Engl J Med*. 2024 Oct 24;391(16):1475-1485.
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7. Gillmore JD et al. Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy. *N Engl J Med*. 2024 Jan 11;390(2):132-142.
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9. 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.
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