Head Above Water

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Disclosures

- Relationship with Novartis Pharmaceuticals Corporation, Amgen, Amarin, Bayer, Pfizer, Lexicon Pharmaceuticals, and Idorsia that includes consulting or advising.
- Relationship with Janssen that includes research grant funding paid directly to the research department

Objectives

We will

- Review the updated Heart Failure guidelines
- Discuss chronic management through lifestyle and the importance of pharmacologic treatment.

Updated Heart Failure Nomenclature: At Risk and Pre-Heart Failure

Shifting to a Chronic Disease Model: A Staging System

- The heart failure staging system emphasizes that:
  - Heart failure (ventricular dysfunction) is a chronic disease
  - Even in the absence of symptoms, activation of neurohormones and negative remodeling of the ventricle can occur, leading to disease progression
  - Focusing on prevention of disease or disease progression has the biggest impact on both the patient and society
  - Specific risk factors can be identified and managed to prevent heart failure
  - Current medical and device therapies have changed the natural history of heart failure and are most effective when initiated early

Heidenreich. J Am Coll Cardiol. 2022;79:e263.

Stages of Heart Failure

STAGE A: At-Risk for Heart Failure

- Patients at risk for HF but without current or previous symptoms/signs of HF and without structural/functional heart disease or abnormal biomarkers
- Patients with hypertension, CVD, diabetes, obesity, exposure to cardiotoxic agents, genetic variant for cardiomyopathy, or family history of cardiomyopathy

STAGE B: Pre-Heart Failure

- Patients without current or previous symptoms/ signs of HF but with evidence of 1 of the following:
- Structural heart disease
- Evidence of increased filling pressures
- Risk factors and:
  - Increased natriuretic peptide levels or
  - Persistently elevated cardiac troponin in the absence of competing diagnoses

STAGE C: Symptomatic Heart Failure

- Patients with current or previous symptoms/ signs of HF
- This stage makes up the majority of patients we manage with heart failure and the stage where there are the most clinical trial data

STAGE D: Advanced Heart Failure

- Marked heart failure symptoms that interfere with daily life and with recurrent hospitalizations despite attempts to optimize GDMT and device therapy

Classification of HF: Stage and NYHA Class Overlay

ACC/AHA Stage (Course of Disease)*		NYHA Functional Classification (Symptom Status)†	
A (At Risk for HF)	At high risk for HF but without structural heart disease or symptoms of HF	**None**	
B (Pre-HF)	Structural heart disease, evidence of elevated LV pressures, or elevated natriuretic peptides or cardiac troponins (in patients with risk factors) but without signs or symptoms of HF	**I**	No limitation of physical activity Ordinary physical activity does not cause HF symptoms
C (Symptomatic HF)	Structural heart disease with prior or current symptoms of HF	**I**	No limitation of physical activity Ordinary physical activity does not cause HF symptoms
		II	Slight limitation of physical activity; comfortable at rest, but ordinary physical activity results in HF symptoms
		III	Marked limitation of physical activity; comfortable at rest, but less than ordinary activity causes HF symptoms
		IV	Unable to carry on any physical activity without HF symptoms, or symptoms at rest
D (Advanced HF)	Refractory HF requiring specialized interventions	**IV**	Unable to carry on any physical activity without HF symptoms, or symptoms at rest

*Patients should be treated to prevent progression and reduce morbidity and mortality.

†Patients should be treated to reduce symptoms or referred for advanced therapies or hospice.

Heidenreich. J Am Coll Cardiol. 2022;79:e263.

Case Study: Indira, a 72-Yr-Old Woman

History:

Reports intermittent lower extremity swelling for the past 3 mo

Has been experiencing increased SOB over the past 10 days; is now experiencing SOB at rest

Received an albuterol inhaler at a Minute Clinic for possible reactive airway disease

Past Medical History:

Hypertension

Hyperlipidemia

Migraines

Medications:

Lisinopril 10 mg daily

Atorvastatin 10 mg daily

Sumatriptan 50 mg as needed for migraine

Indira is found to have an EF of 35%. After diuresis, she is no longer experiencing symptoms of HF, even with physical activity. How would you classify her HF?

- AHA/ACC Stage B, NYHA Class I
- AHA/ACC Stage B, NYHA Class II
- AHA/ACC Stage C, NYHA Class I
- AHA/ACC Stage C, NYHA Class II

Indira is found to have an EF of 35%. After diuresis, she is no longer experiencing symptoms of HF, even with physical activity. How would you classify her HF?

- AHA/ACC Stage B, NYHA Class I
- AHA/ACC Stage B, NYHA Class II
- AHA/ACC Stage C, NYHA Class I
- AHA/ACC Stage C, NYHA Class II

RATIONALE

- EF of 35% with symptoms classifies patients as AHA/ACC Stage C
- Patients cannot change AHA/ACC stage
- Initial symptoms (HF symptoms at rest) classified this patient as NHYA Class IV; with symptom improvement (no symptoms with activity), this patient is now NYHA Class I
- Patients can move NYHA class

Stage A – At Risk Populations

1 in 5 Americans over 40 will develop HF in their lifetime

- Cardiovascular risk factors:
  - Age
  - Coronary artery disease
  - Hypertension
  - Hyperlipidemia
  - Diabetes
  - Peripheral vascular disease
  - Metabolic syndrome
  - Atrial fibrillation
- Non-cardiovascular risk factors:
  - Renal dysfunction
  - Anemia
  - Chronic obstructive pulmonary disease
  - Thyroid disease
  - Tobacco use
  - Toxic exposures
    - Chemotherapy
    - Drugs

American Heart Association - heart.org/en/health-topics/heart-failure/causes-and-risks-for-heart-failure/understand-your-risk-for-heart-failure. Pagell. Circulation. 2016;134:e32. Wan. J Am Coll Cardiol. 2014;63:407.

Managing Those at Risk: Treatment of Stage A HF

- **Goal**: prevent decline of heart function, development of symptoms
- Diagnose/treat hypertension and CV risk factors (eg, dyslipidemia) using current treatment guidelines (for hypertension target blood pressure <130/80 mm Hg)
- Other conditions/agents that may lead to or contribute to HF should be controlled or avoided (eg, obesity, diabetes, tobacco use, known cardiotoxic agents)
- More frequent screening for cardiac dysfunction or development of symptoms

Heidenreich. J Am Coll Cardiol. 2022;79:e263.

Managing Pre-HF: Treatment of Stage B HF

COR	LOE	Recommendations
1	A	1. In patients with LVEF ≤40%, ACE inhibitor should be used to prevent symptomatic HF and reduce mortality
1	A	2. In patients with a recent remote history of MI or ACS, statins should be used to prevent symptomatic HF and adverse cardiovascular events
1	B-R	3. In patients with a recent MI and LVEF ≤40% who are intolerant to ACE inhibitor, ARB should be used to prevent symptomatic HF and reduce mortality
1	B-R	4. In patients with a recent or remote history of MI or ACS and LVEF ≤40%, evidence-based β-blockers should be used to reduce mortality
1	B-R	5. In patients who are at least 40 days post-MI with LVEF ≤30% and NYHA class I symptoms while receiving GDMT and have reasonable expectation of meaningful survival for >1 yr, an ICD is recommended for primary prevention of sudden cardiac death to reduce total mortality
1	C-LD	6. In patients with LVEF ≤40%, β-blockers should be used to prevent symptomatic HF
3: Harm	B-R	7. In patients with LVEF <50%, thiazolidinediones should not be used because they increase the risk of HF, including hospitalizations
3: Harm	C-LD	8. In patients with LVEF <50%, nondihydropyridine calcium channel blockers with negative inotropic effects may be harmful

Heidenreich. J Am Coll Cardiol. 2022;79:e263.

Stage C Treatment Recommendations Across the Ejection Fraction Spectrum

Ejection Fraction Alphabet Soup

HF with reduced EF (HFrEF)

- HF with LVEF ≤40%

HF with mildly reduced EF (HFmrEF)

- HF with LVEF 41% to 49%

HF with preserved EF (HFpEF)

- HF with LVEF ≥50%

HF with improved EF (HFimpEF)

- HF with a baseline LVEF ≤40%, a ≥10-point increase from baseline LVEF, and a second measurement of LVEF >40%

Bozkurt. J Card Fail. 2021;27:P387.

Case Study (cont'd): Indira

- Indira's symptoms have resolved with diuresis, and she is now classified as AHA/ACC Stage C, NYHA Class I
- You have decided to start her on GDMT for her HFrEF (LVEF 35%)
  - Which medications do you want to initiate?

Which of the following medications will provide Indira mortality benefit for her HFrEF?

- Atorvastatin
- Furosemide
- Omega-3 fatty acids
- Sacubitril/valsartan

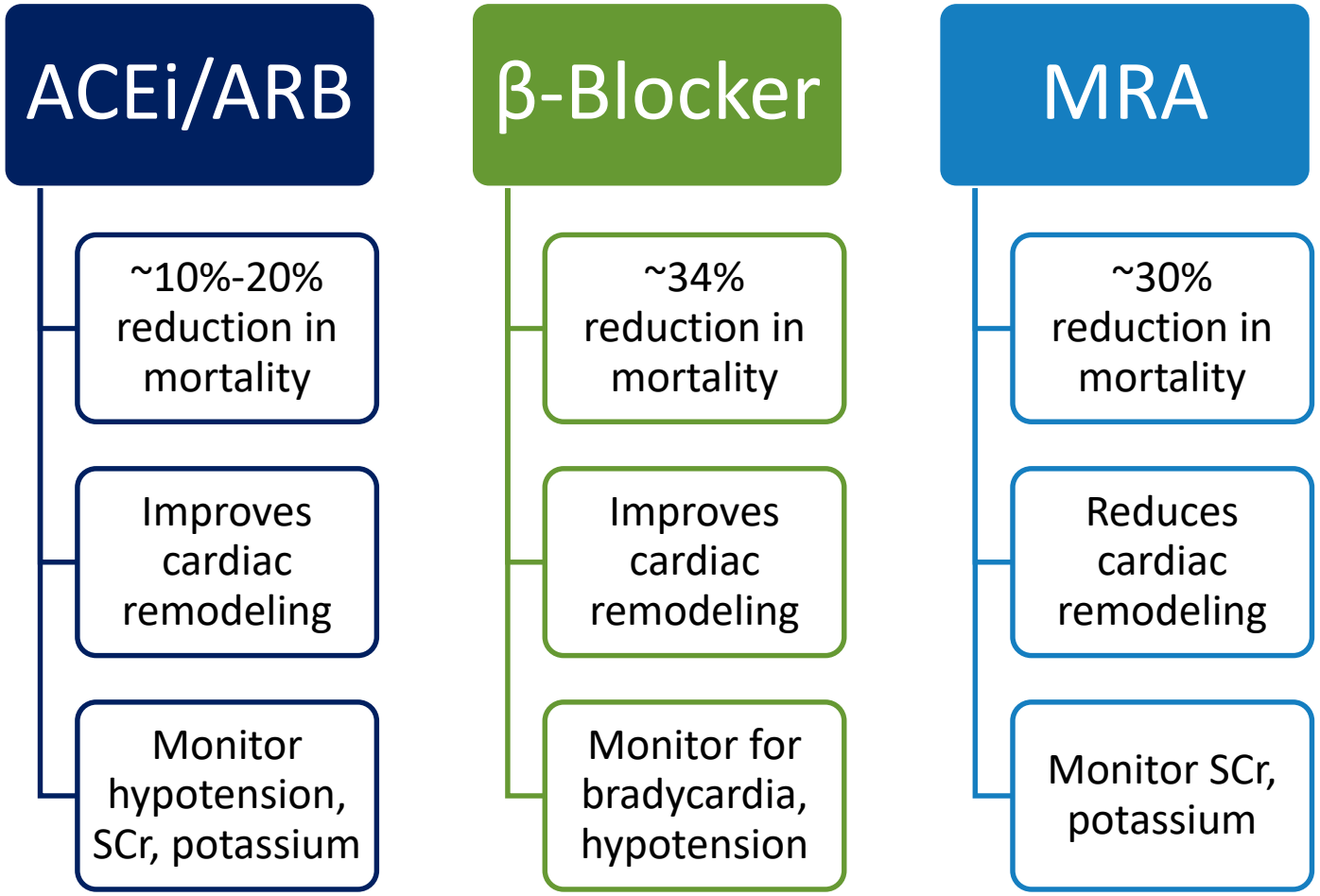
When starting medications for Indira's newly diagnosed HFrEF, Which of the following medications will provide Indira with mortality and CV hospitalization benefit?

- Atorvastatin
- Furosemide
- Omega-3 fatty acids
- Sacubitril/valsartan

RATIONALE

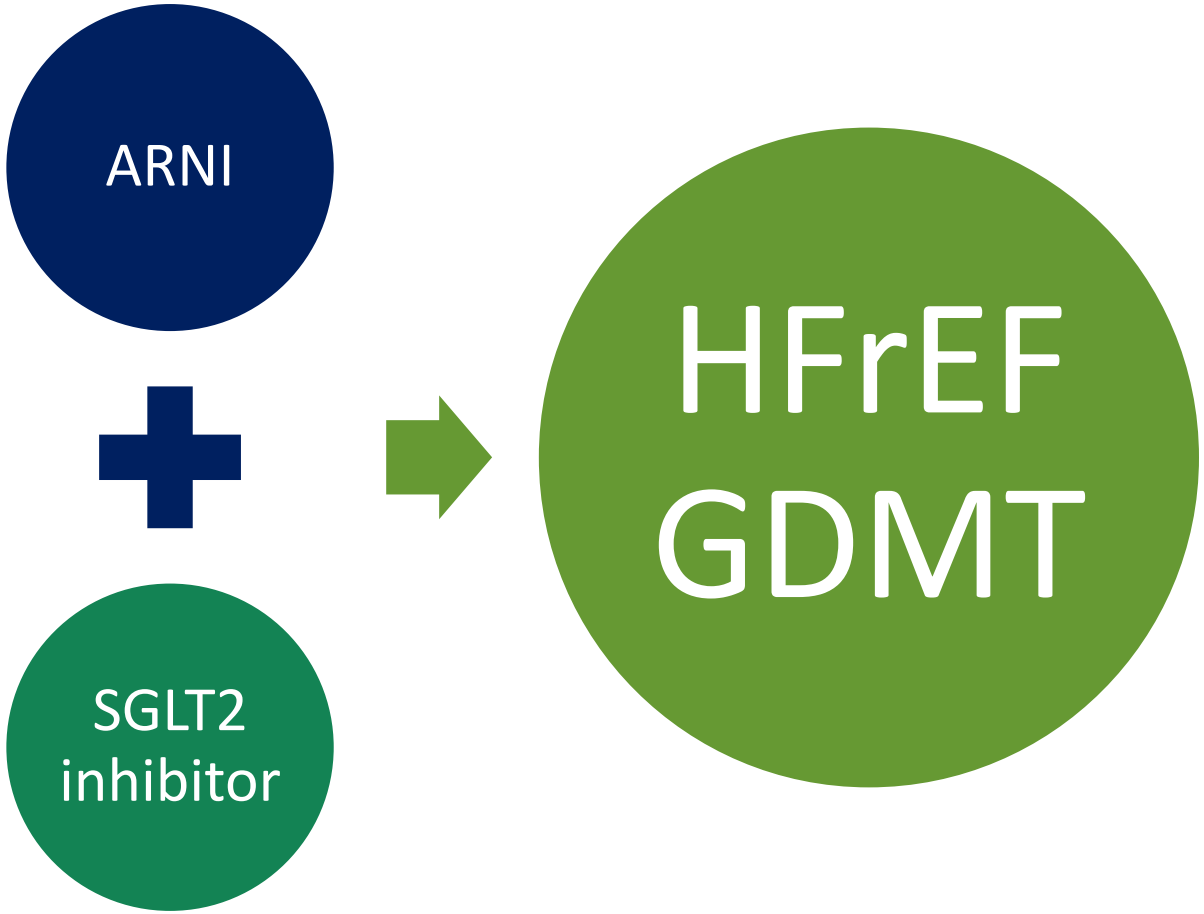
- The PARADIGM-HF trial demonstrated a reduction in CV death or HF hospitalization with use of sacubitril/valsartan in patients with HFrEF

Historical GDMT in HFrEF



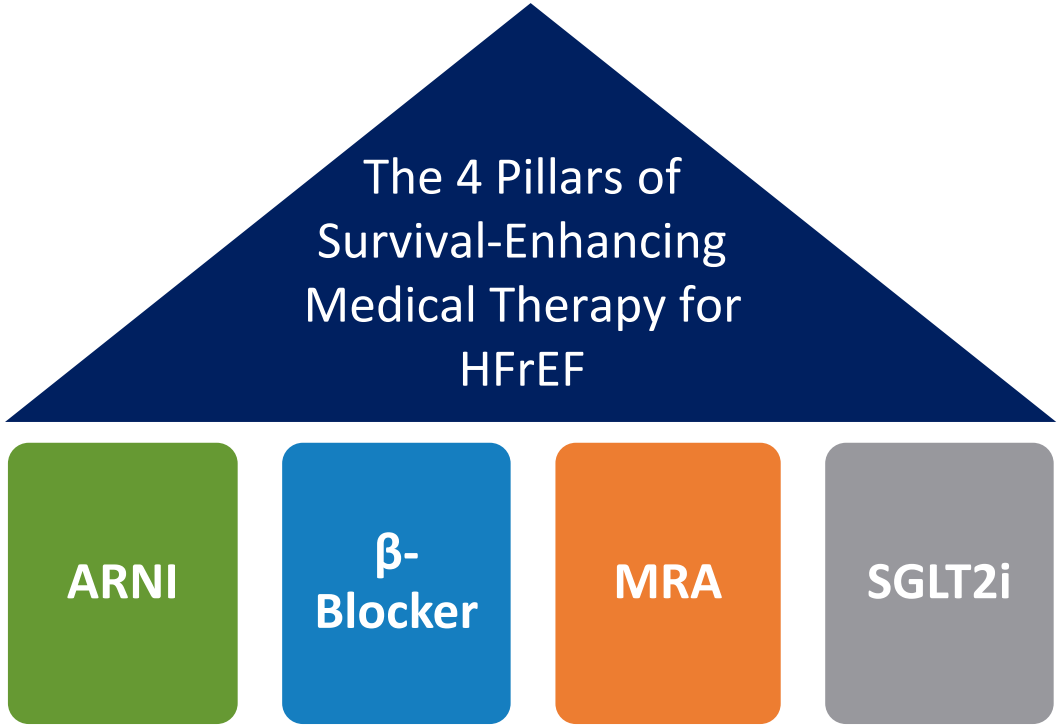
Packer. NEJM. 1999;100:2312. CIBIS-II Investigators and Committees. Lancet. 1999;353:9-13. MERIT-HF Study Group. Lancet. 1999;353:2001. Masarone. J Cardiovasc Dev Dis. 2021;8(9)101. Bhinder. Cardiol Rev .2020;28(3):107 Heidenreich. J Am Coll Cardiol. 2022;79:e263.

New Kids on the Block



1. Heidenreich. J Am Coll Cardiol. 2022;79:e263. 2. Kim. Sci Rep. 2021;11(1):22342

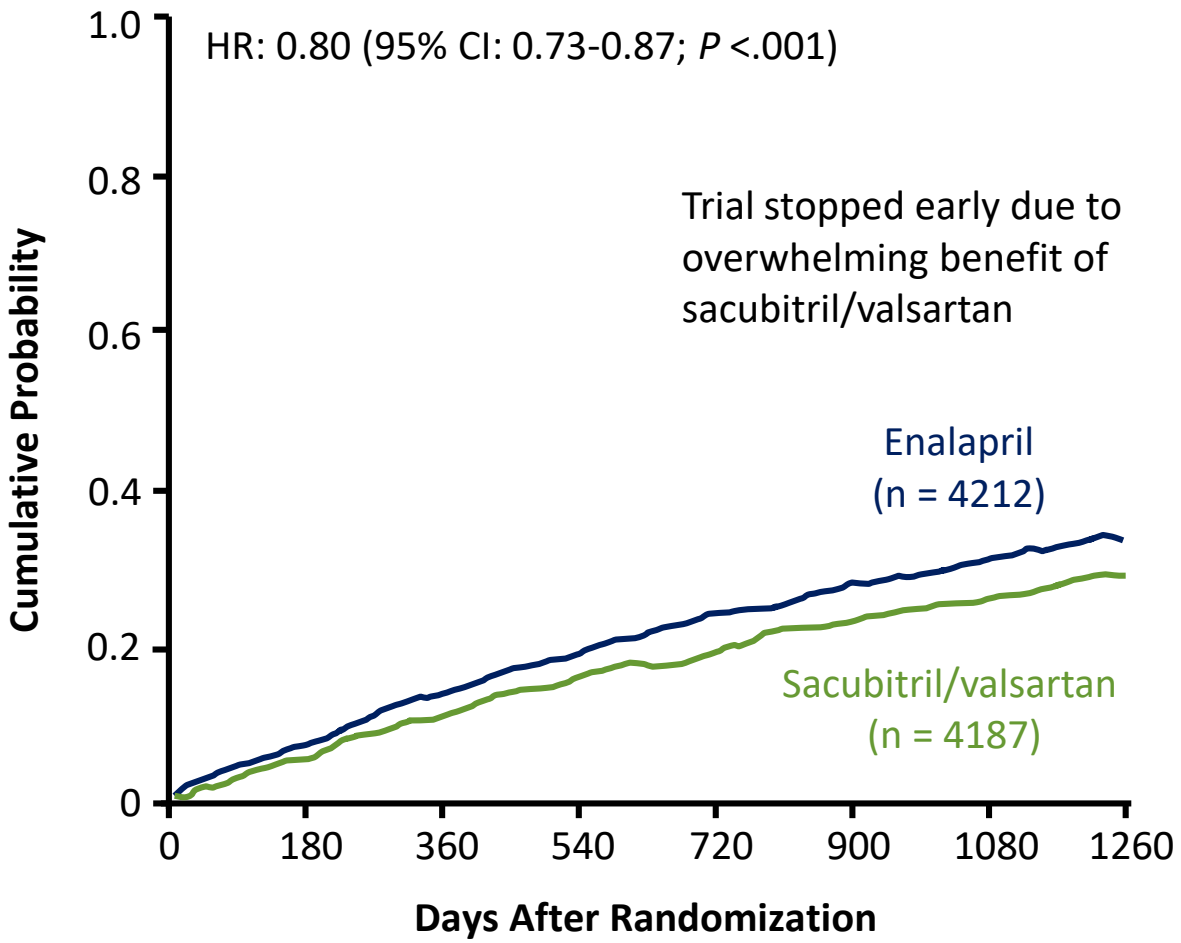
4 Pillars of GDMT for HFrEF



- Cumulative risk reduction in all-cause mortality if all 4 evidence-based medical therapies are used
  - Relative risk reduction 72.9%; absolute risk reduction: 25.5%; NNT = 3.9, over 24 mo

Bassi. JAMA Cardiol. 2020;5:948. Rahamim. J Clin Med. 2021;10:4409.

PARADIGM-HF: Reduction in CV Death or HF Hospitalization With Sacubitril/Valsartan in HFrEF

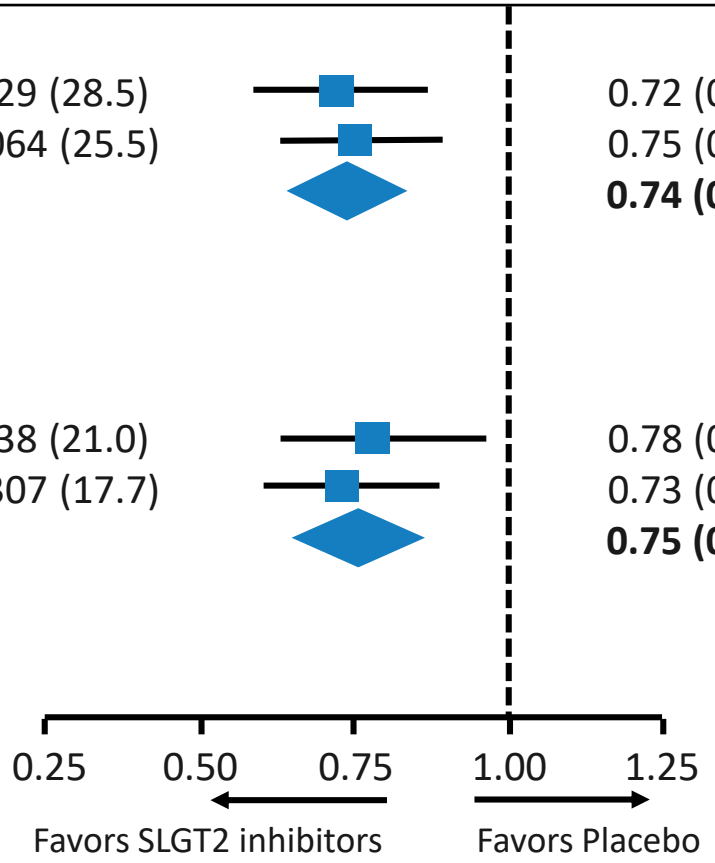


- ~20% reduction in sudden death, CV death, and HF hospitalizations when compared with ACE inhibitor
- Lower rates of discontinuation with sacubitril/valsartan due to AEs (*P* = .03) **or renal impairment (*P* = .002)**
- More symptomatic hypotension with sacubitril/valsartan

McMurray. NEJM. 2014;371:993..

EMPEROR-Reduced and DAPA-HF: Reduction in HF Hospitalization or CV Death With SGLT2 Inhibitors in HFrEF

	No. With Event/No. of Patients (%)		HR (95% CI)
	SGLT2 Inhibitor	Placebo	
With diabetes			
EMPEROR-Reduced	200/927 (21.6)	265/929 (28.5)	0.72 (0.60-0.87)
DAPA-HF	215/1075 (20.0)	271/1064 (25.5)	0.75 (0.63-0.90)
Subtotal			**0.74 (0.65-0.84)**
Test for overall treatment effect, P <.0001			
Test for heterogeneity of effect, P = .76			
Without diabetes			
EMPEROR-Reduced	161/936 (17.2)	197/938 (21.0)	0.78 (0.64-0.97)
DAPA-HF	171/1298 (13.2)	231/1307 (17.7)	0.73 (0.60-0.88)
Subtotal			**0.75 (0.65-0.87)**
Test for overall treatment effect, P <.0001			
Test for heterogeneity of effect, P = .65			
Test for treatment by subgroup interaction, P = .81			



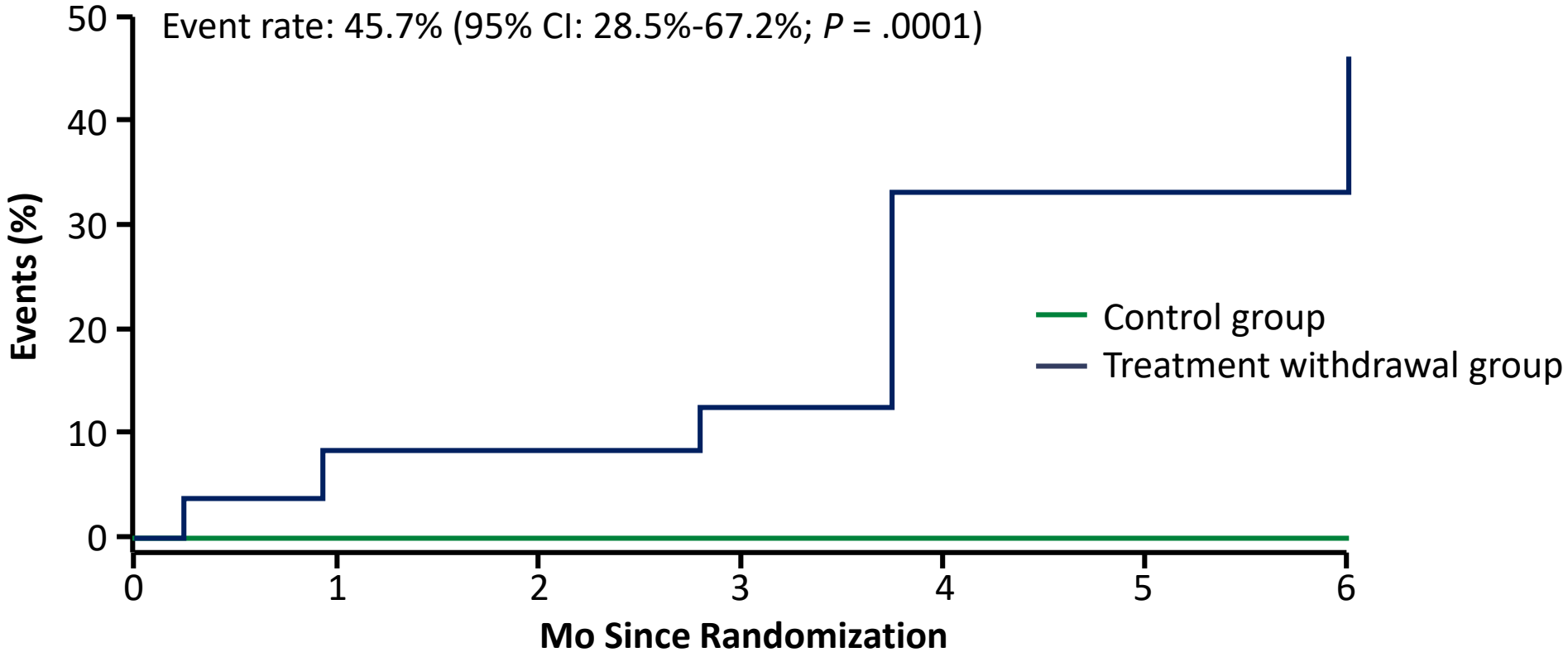
Zannad. Lancet. 2020;396:819.

Therapies in HFimpEF (LVEF improved to ≥40%)

- TRED-HF trial randomized patients with recovered LVEF to withdrawing medications vs continuing medications
  - Improved LVEF is used to refer to those patients with previous HFrEF (LVEF <40%), who now have an LVEF >50%
  - Primary endpoint: A relapse of dilated cardiomyopathy within 6mo
  - Trial was stopped due to worsening LVEF and symptomatic HF in the withdrawal group
  - Validated the laboratory observation that even in the setting of a recovered LVEF, there are cellular and extracellular changes in the myocardium
- ***These patients should continue their HFrEF treatment***

Halliday. Lancet. 2019;393:61.

TRED-HF Trial



Patients at Risk, n							
Control group	26	26	26	26	26	26	26
Treatment Withdrawal withdrawal group	25	22	22	21	16	16	13

The Lancet **2019 39361-73DOI: (10.1016/S0140-6736(18)32484-X)**

According to the TRED-HF trial, what should be done when a patient's LVEF improves from 35% to 50% while on GDMT?

A. Increase the patient's SGLT2 inhibitor to twice daily
B. Decrease the patient's β-blocker dose
C. Discontinue therapy as the patient has achieved their goal
D. Nothing; continue current therapy

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B. Decrease the patient's β-blocker dose

C. Discontinue therapy as the patient has achieved their goal

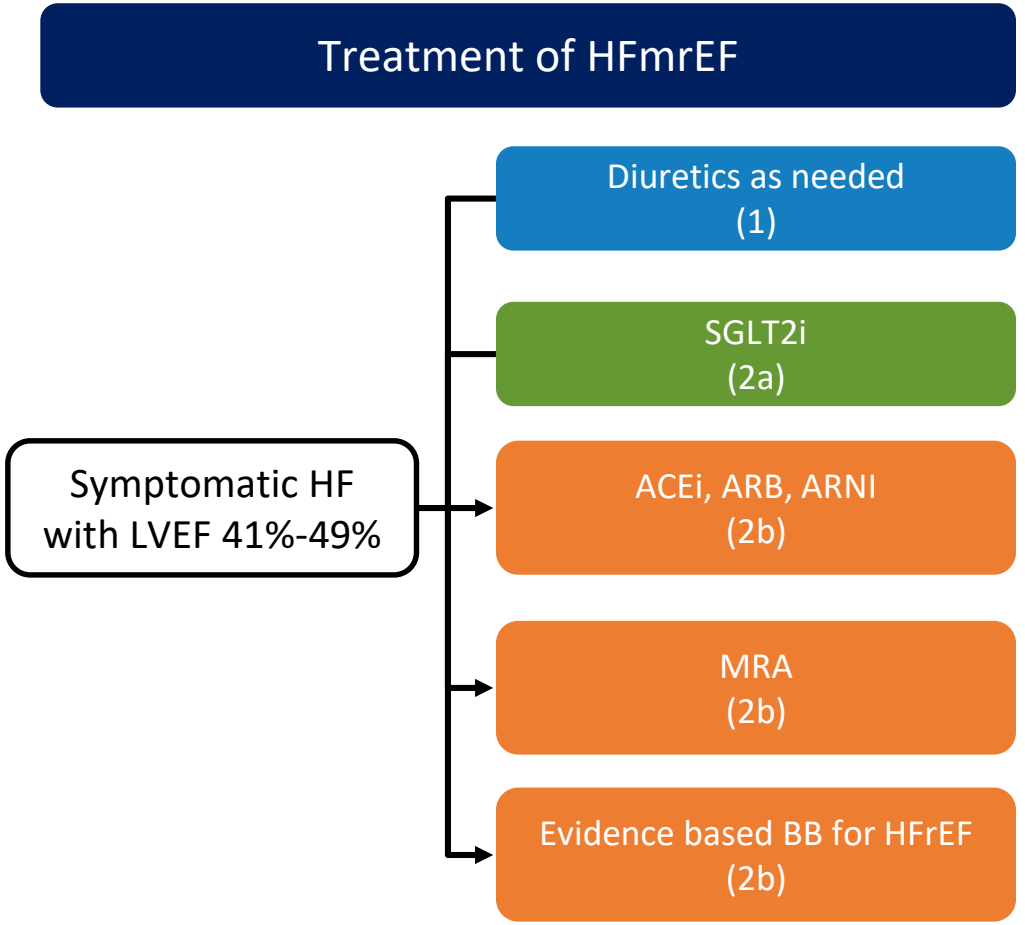
D. Nothing; continue current therapy

RATIONALE

- This patient presented with HFrEF (defined as a LVEF ≤40%)
- With medication therapy, their EF improves to 50%, categorizing them as HFimpEF
- Based on the TRED-HF trial, patients with HFimpEF should continue all GDMT

Therapies in HFmrEF (LVEF 41%-49%)

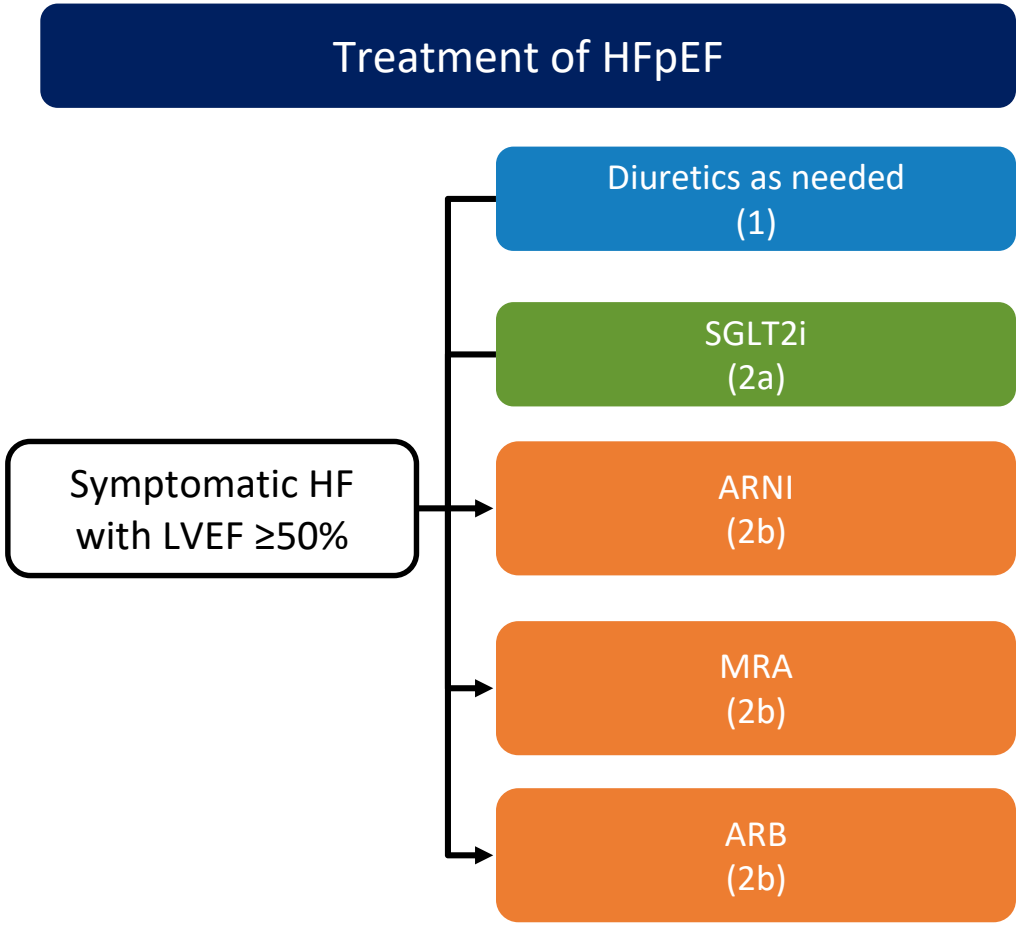
- May be reasonable to treat these patients as HFrEF
  - Particularly in lower range HFmrEF



Heidenreich. J Am Coll Cardiol. 2022;79:e263.

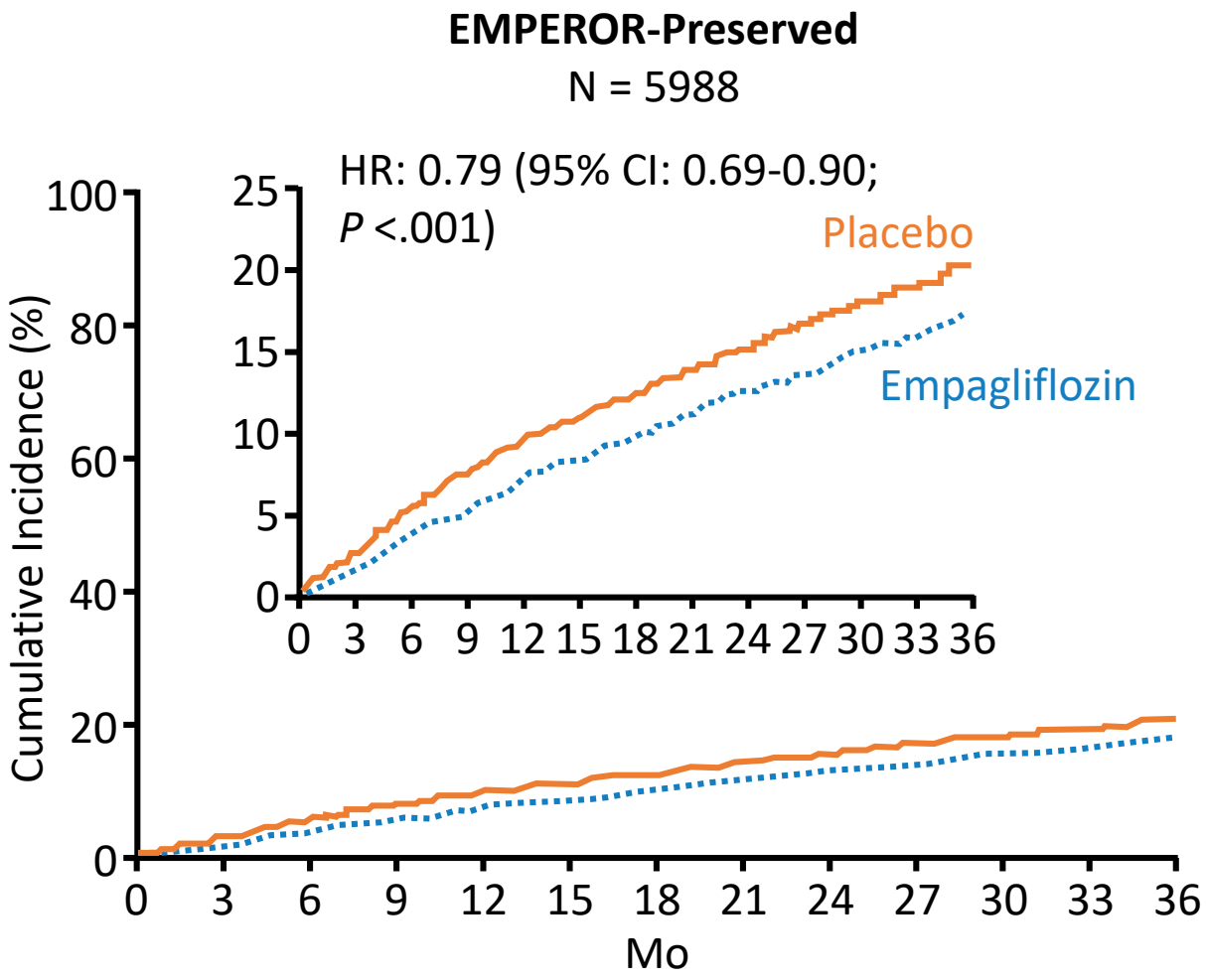
Therapies in HFpEF (EF ≥50%)

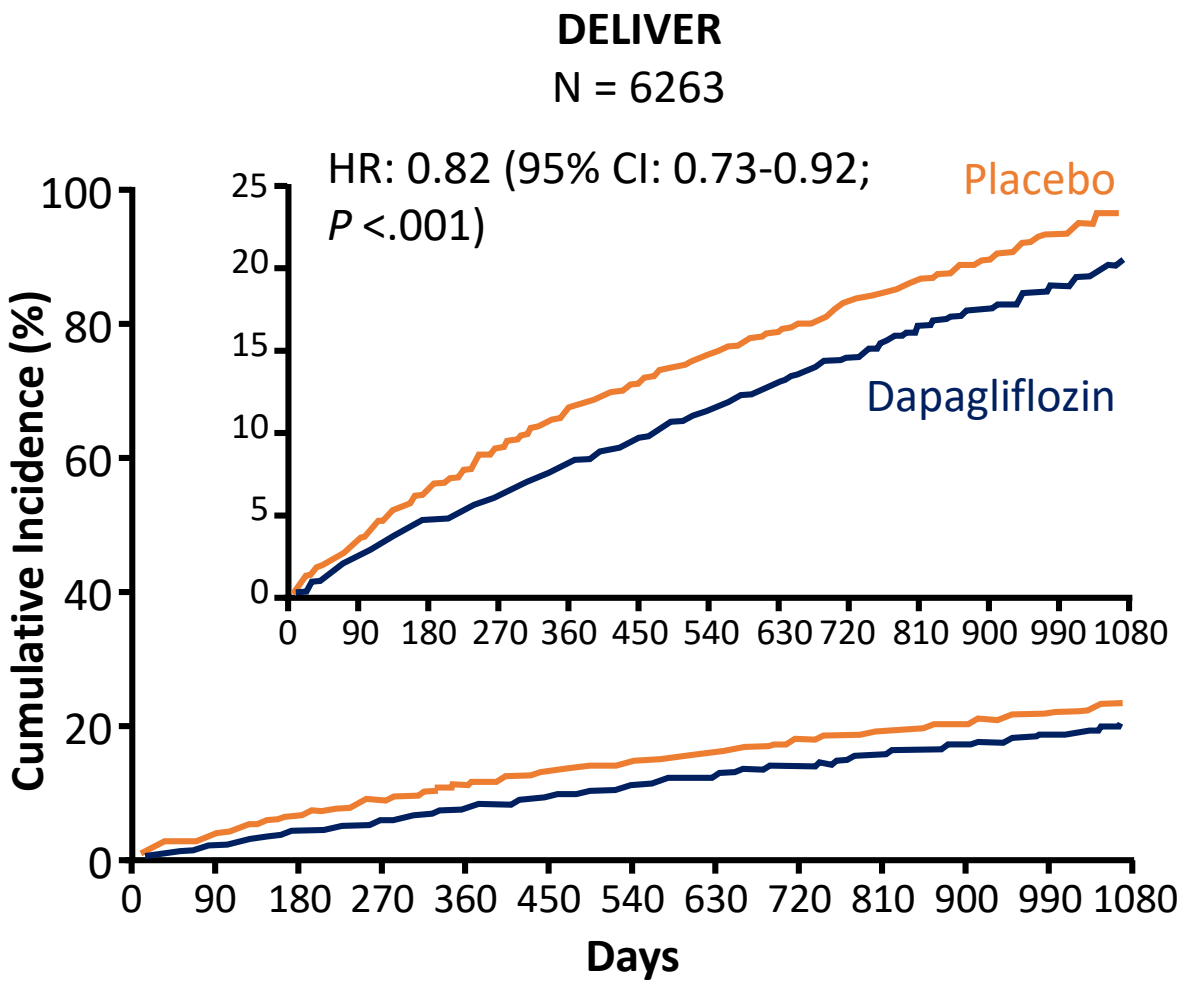
- Treat underlying contributing comorbidities
  - Iron deficiency anemia
  - Atrial fibrillation
  - Hypertension
  - Ischemic disease, etc
- Exercise program and cardiac rehab



Heidenreich. J Am Coll Cardiol. 2022;79:e263.

SGLT2 Inhibitors and HFpEF

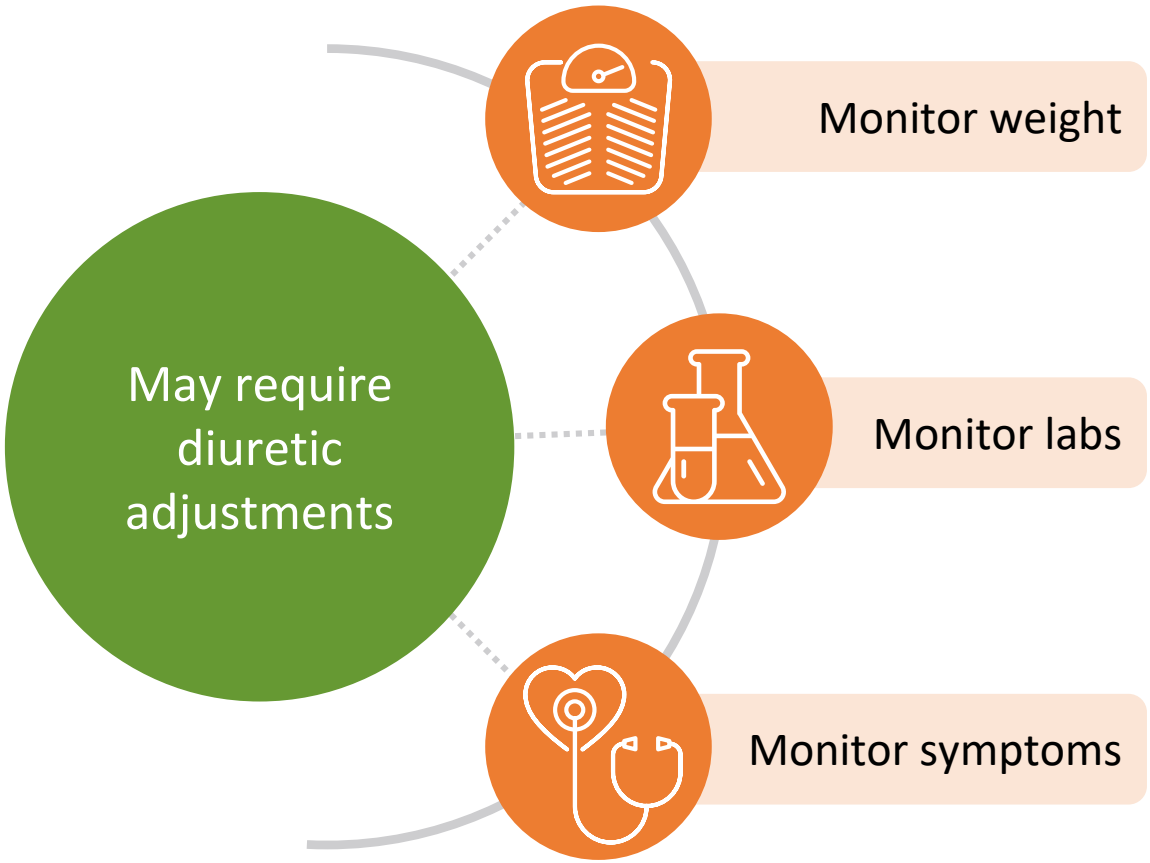




1. Anker. NEJM. 2021;385:1451. 2. Solomon. NEJM. 2022;387:1089.

Use of SGLT2 Inhibitors: MAWDS

SGLT2 inhibitors are indicated for patients with both HFrEF and HFpEF *with and without* diabetes to improve cardiovascular outcomes



McMurray. NEJM. 2019;381:1995. Mordi. Circulation. 2020;142:1713. Anker. NEJM. 2021;385:1451

A patient with an LVEF of 55% and HFpEF takes furosemide at home. Which of the following would be the most appropriate agent to add to the patient's regimen?

A. Empagliflozin
B. Isosorbide/hydralazine
C. Losartan
D. Sacubitril/valsartan

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RATIONALE

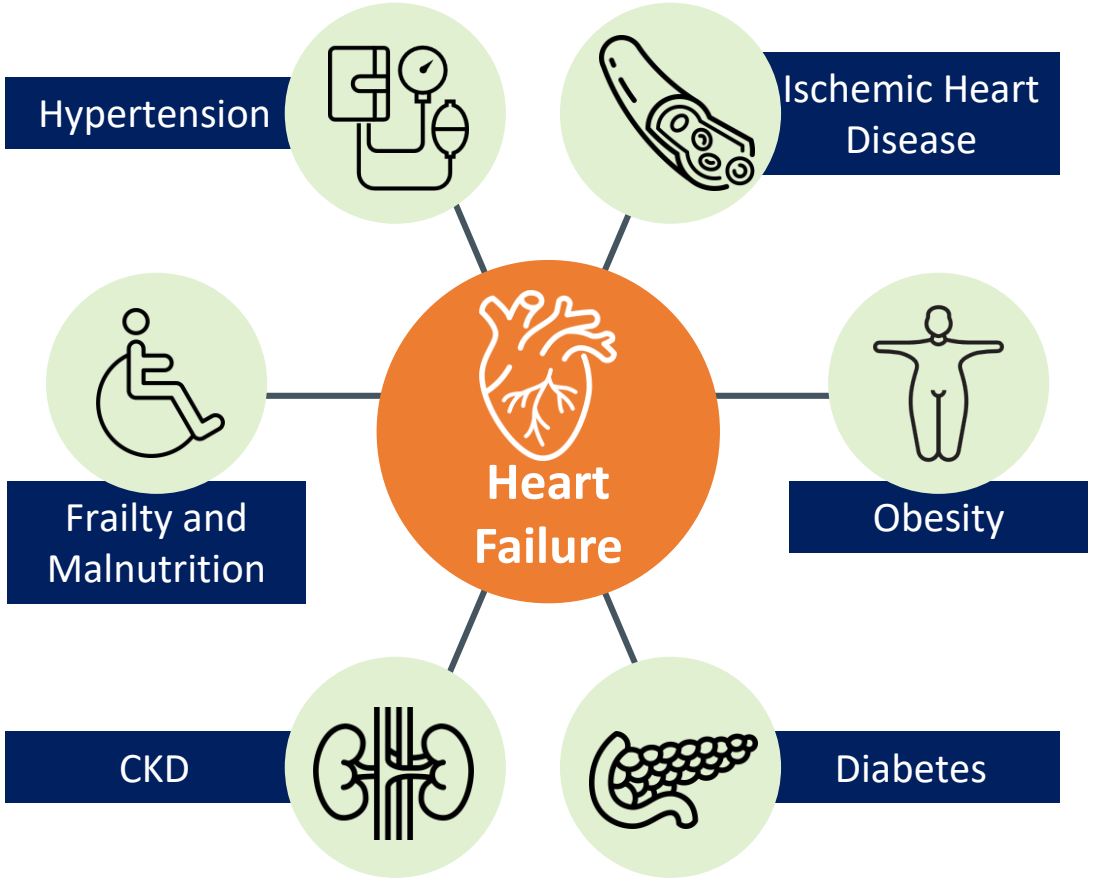
- Empagliflozin, an SGLT2 inhibitor, demonstrated decreased CV death and HF hospitalizations in HFpEF (EMPEROR-Preserved)
- SGLT2 inhibitors are a 2a recommendation where losartan and sacubitril/valsartan are 2b recommendations

Adverse Effects of SGLT2 Inhibitors

- Genital fungal infections
- Serious genital infections → Fournier gangrene
- Possible increased risk of amputations seen with canagliflozin and ertugliflozin
  - Possible increased fracture risk with canagliflozin
- Dapagliflozin
  - Contraindicated for use in patients with active bladder cancer
- Volume depletion
- Acute kidney injury
- Hypotension
- Euglycemic ketoacidosis
  - More common when NPO, with acute changes in renal function, or with acute illness
  - Developing guidelines to hold SGLT2 inhibitors before surgical procedures or acute hospitalizations

Canagliflozin PI. Dapagliflozin PI. Das. J Am Coll Cardiol. 2020;76:1117. Ertugliflozin PI. Kaze. Cardiovasc Diabetol. 2022;21:47.

Initiating Pharmacotherapy—It's Complicated: The Impact of Comorbidities



- Comorbid conditions are common in patients with HF
  - 86% of patients have ≥2 additional chronic conditions
  - 42% of patients have ≥5 additional comorbidities

Chamberlain. Am J Med. 2015;128:38. Palazzuoli. Heart Fail Rev. 2022;27:767.
Wong. Am J Med. 2011;124:136.

Consequences of Comorbidities

- May limit use of GDMT
  - Renal dysfunction
  - Autonomic dysfunction in diabetes
- Adds complexity and cost to medical regimens
- Complicates lifestyle recommendations
  - Diabetic/low-sodium/low-fat/fluid-restricted diets
- Affect frailty
- Compound risk of additional cardiovascular events

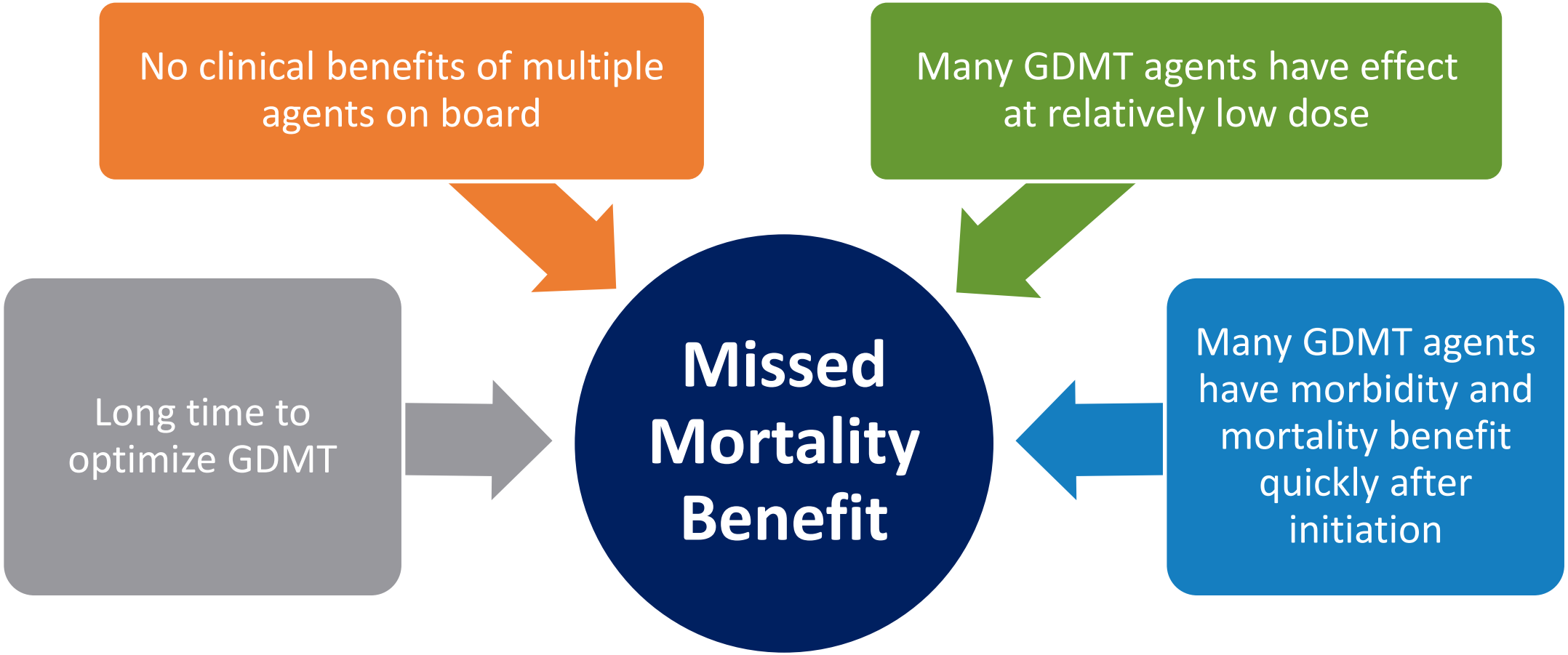
Example: Renal Failure

- May limit our ability to utilize RAAS agents, MRAs, and SGLT2 inhibitors
- May make volume management more challenging

Szlagor. Int J Mol Sci. 2023;24(3):2988. Chamberlain. Am J Med. 2015;128:38. Bozkurt. Circulation. 2016;134:e535
Salmon. Card Fail Rev. 2022;8:e07.

Initiation and Titration of GDMT in HFrEF

Traditional Sequencing Consequences



Heidenreich. J Am Coll Cardiol. 2022;79:e263. Mebazaa. Lancet. 2022;400:P1938.

Why Is Rapid Initiation Important?

Medication Class	Outcome	Relative Risk
β-blocker	Death	↓ 25%
ARNI	CV death or HF hospitalization	↓ 42%
MRA	CV death or HF hospitalization	↓ 37%
SGLT2 inhibitor	Death, HF hospitalization, or emergency/urgent visit for worsening HF	↓ 58%

Clinical benefits of all medications are apparent within 30 days of initiation

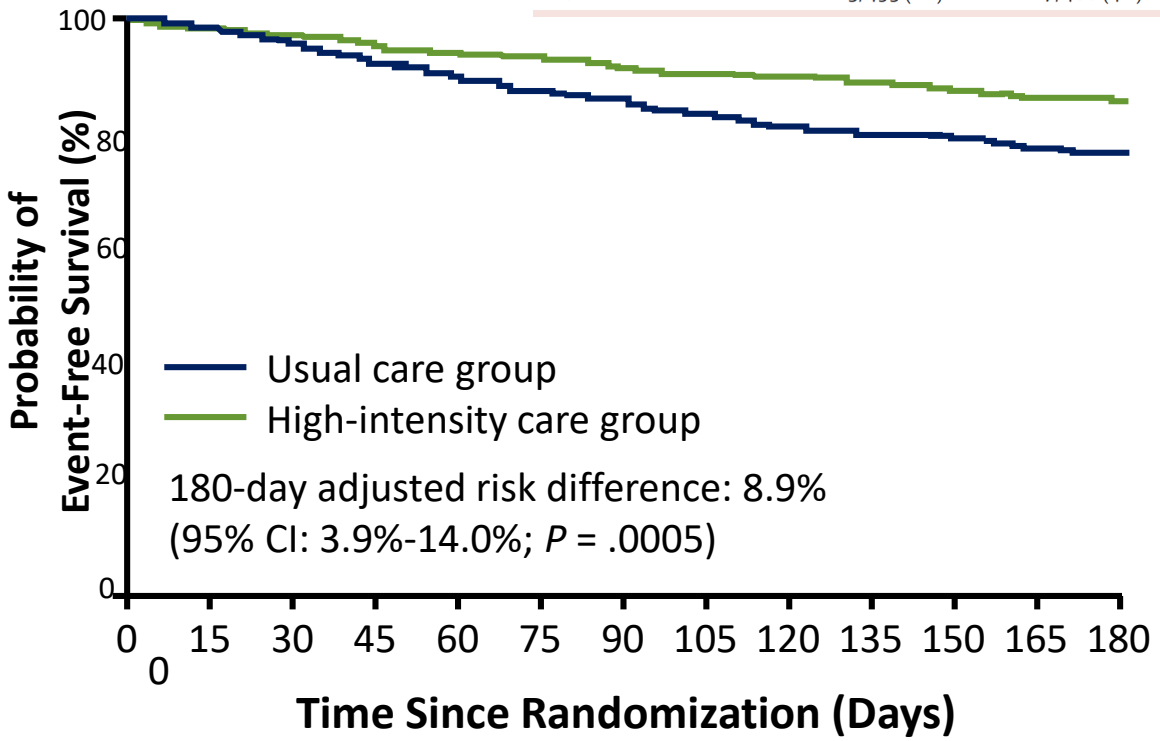
Greene. JAMA Cardiol. 2021;6:743.

STRONG-HF: All-Cause Mortality

- More patients in high-intensity group felt better and lived longer
  - NYHA class I/II at 90 days: 83% vs 75%
  - Primary endpoint of reduction in death/HFH at 180 days: 14% vs 23%
  - Driven by HFH: 9.5% vs 17%

Terminated early because of larger than expected difference in groups; withholding intensive treatment strategy would be unethical

NYHA class	High-intensity care group (n=542)	Usual care group (n=536)
Baseline	..	..
I	34/542 (6%)	28/534 (5%)
II	315/542 (58%)	326/534 (61%)
III	188/542 (35%)	177/534 (33%)
IV	5/542 (1%)	3/534 (1%)
Day 90	..	..
I	116/495 (23%)	76/488 (16%)
II	297/495 (60%)	288/488 (59%)
III	77/495 (16%)	107/488 (22%)
IV	5/495 (1%)	17/488 (4%)



Mebazaa. Lancet. 2022;400:P1938.

A 67-yr-old patient with no PMH is admitted for
newly diagnosed HFrEF. Which of the following GDMT strategies will provide the greatest mortality benefit?

A. Ensuring PCP follow-up within 1 wk of discharge to initiate GDMT
B. Ensuring adequate supply of diuretics at discharge to manage volume
C. Initiating an ARNI and titrating to maximum effect prior to discharge
D. Initiating all 4 GDMT agents at maximally tolerated doses

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RATIONALE

- Patients receive the greatest mortality benefit from GDMT when initiating all agents in a rapid sequencing fashion
- The STRONG-HF trial demonstrated patients receiving high-intensity care lived longer and experienced fewer hospitalizations than those who received lower-intensity care

SUMMARY

- Identify patients “at-risk” for Heart Failure (HF)
- Staging (A-D) and symptoms (NYHA I-IV) assessment will inform acute and chronic management of HF
- Guideline-directed medical therapy (GDMT) pillars for ALL heart failure (HFrEF, HFmrEF, and HFpEF) include: SGLT-inhibitors, ACEi/ARB/ARNI, and MRA (soon to include nsMRA)
- Only HFrEF includes β-blockers as a 4th pillar of GDMT
- Evidence demonstrates benefit with ongoing GDMT regardless of “EF recovery”
- Early and rapid initiation of **ALL** GDMT (in-hospital) demonstrates reduced mortality and rehospitalization.

Q & A