

Head Above Water

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

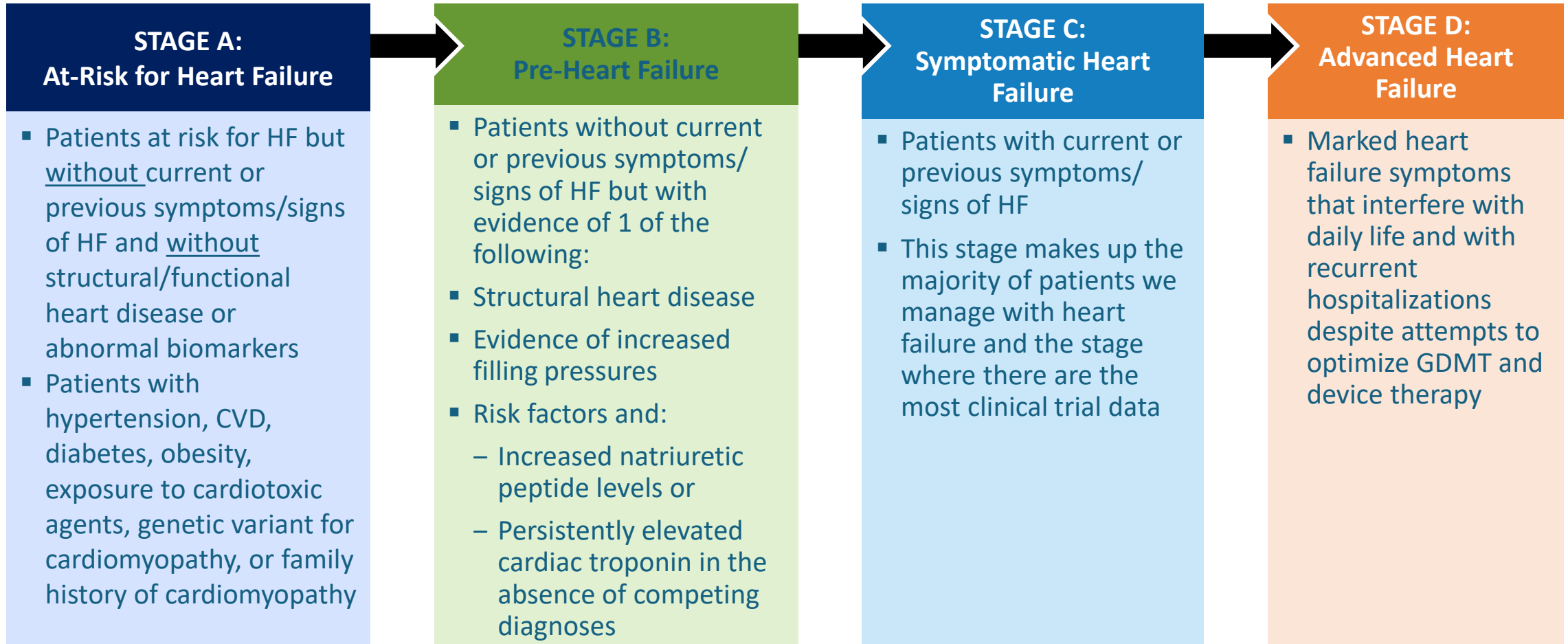
- Review the updated Heart Failure guidelines
- Discuss chronic management through lifestyle and the importance of pharmacologic treatment.

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

Stages of Heart Failure



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.

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

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- 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 NYHA 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

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

Managing Pre-HF: Treatment of Stage B HF

COR	LOE	Recommendations
1	A	1. In patients with LVEF \leq 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 \leq 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 \leq 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 \leq 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 \leq 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

Stage C Treatment Recommendations Across the Ejection Fraction Spectrum

Ejection Fraction Alphabet Soup

HF with reduced EF (HFrEF)

- HF with LVEF $\leq 40\%$

HF with mildly reduced EF (HFmrEF)

- HF with LVEF 41% to 49%

HF with preserved EF (HFpEF)

- HF with LVEF $\geq 50\%$

HF with improved EF (HFimpEF)

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

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

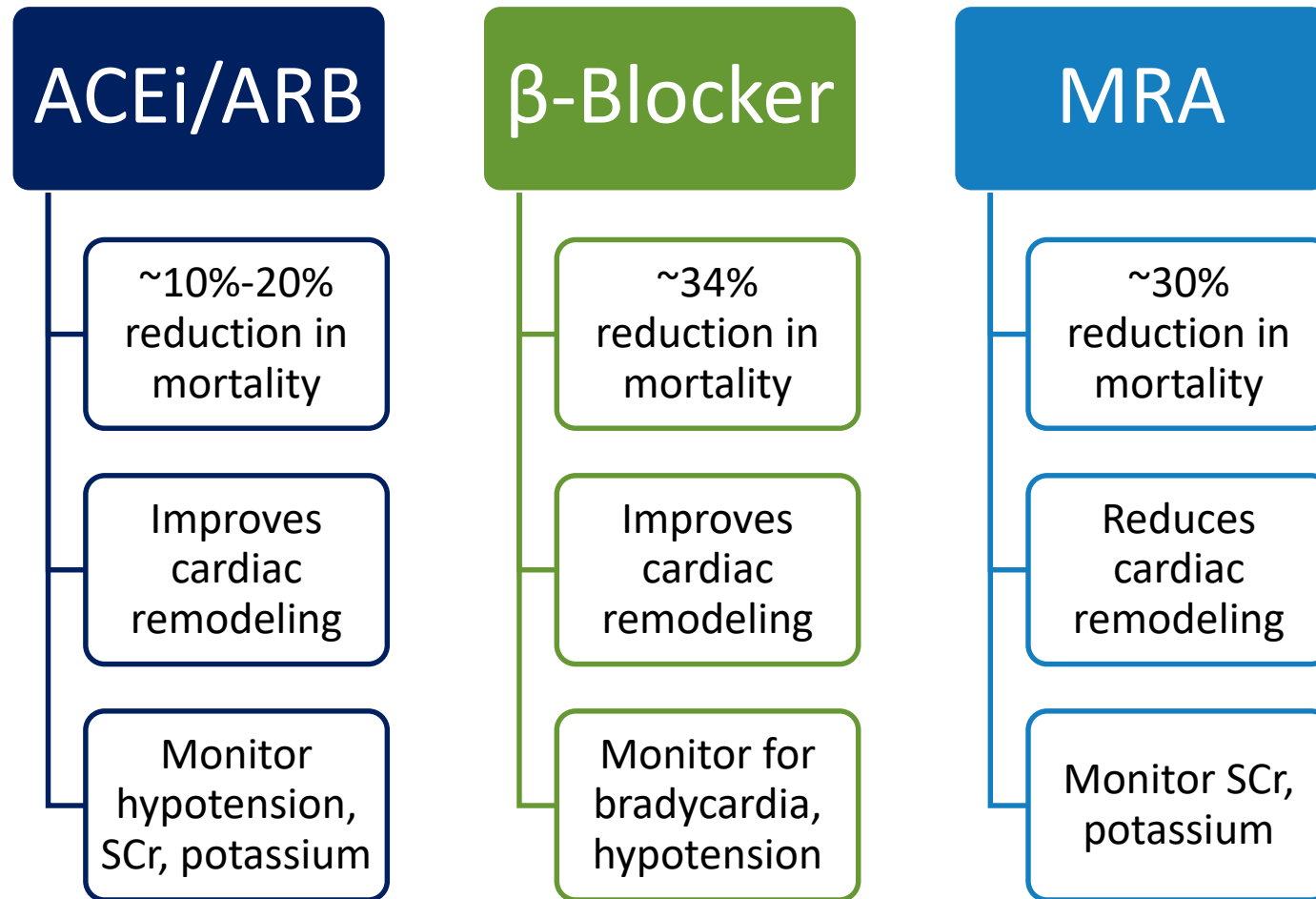
When starting medications for Indira's newly diagnosed HFrEF, Which of the following medications will provide Indira with mortality and CV hospitalization benefit?

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

RATIONALE

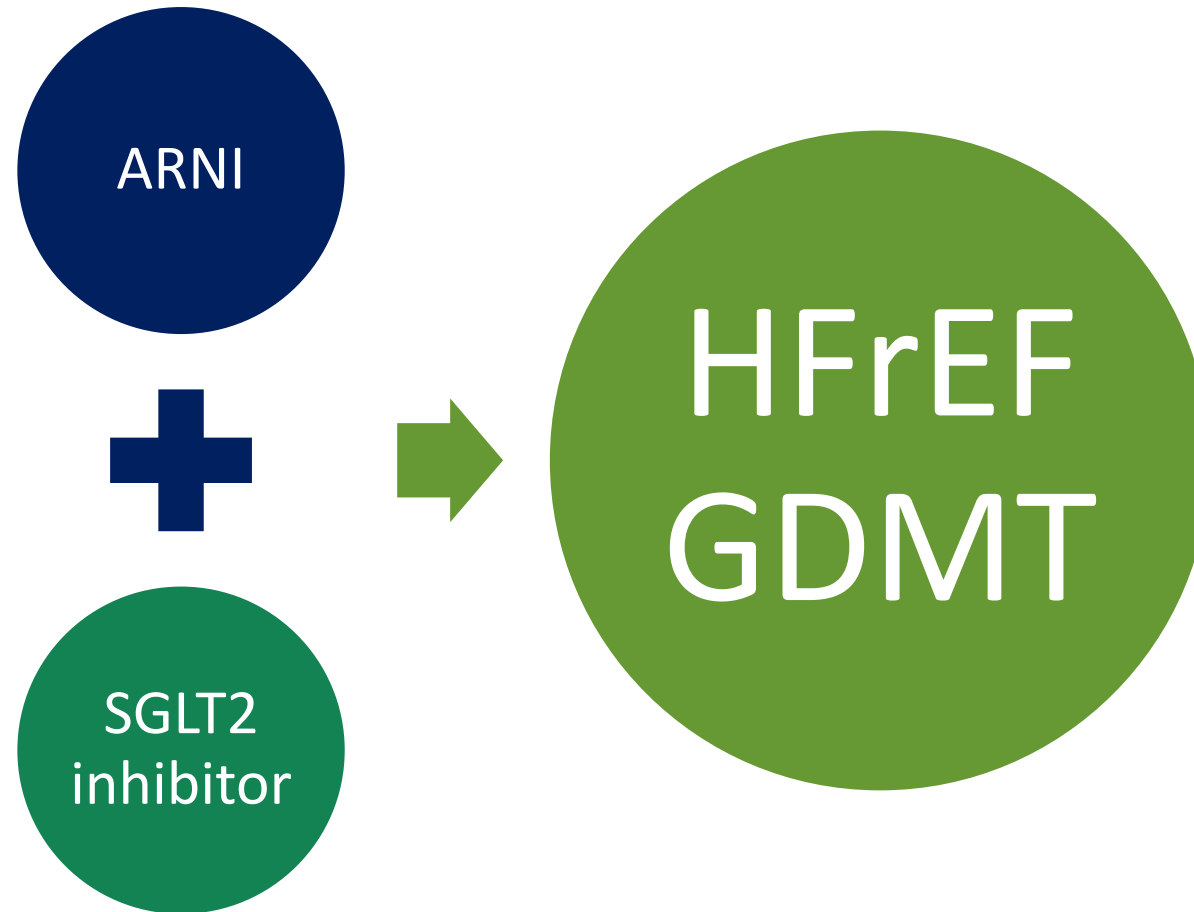
- The PARADIGM-HF trial demonstrated a reduction in CV death or HF hospitalization with use of sacubitril/valsartan in patients with HFrEF

Historical GDMT in HFrEF

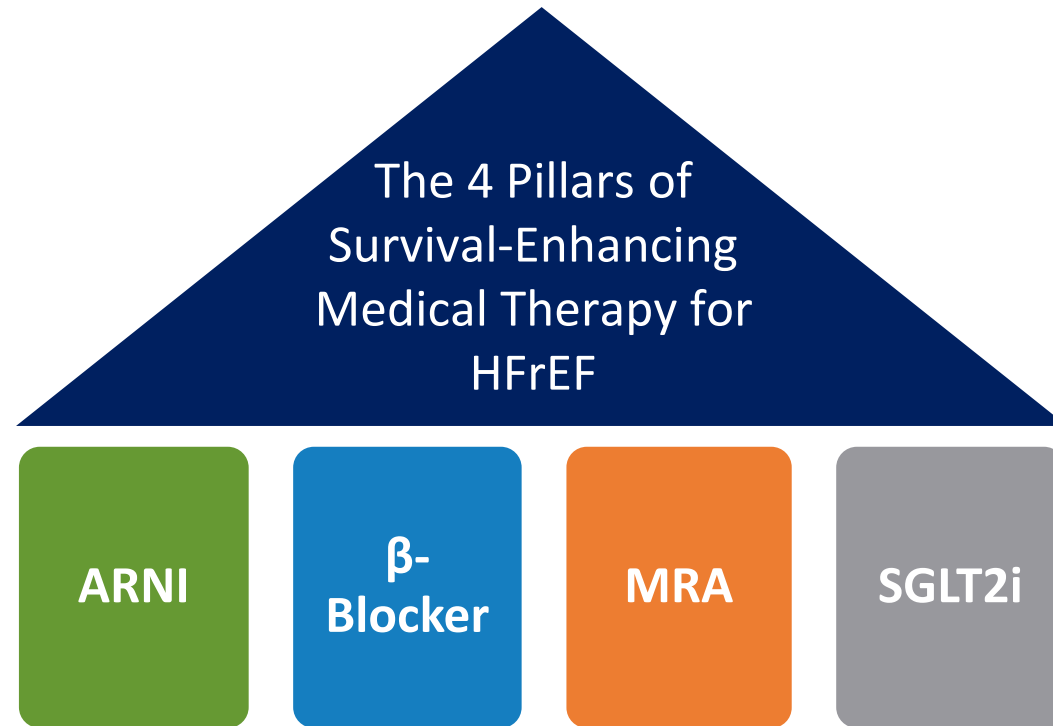


Packer. NEJM. 1999;100:2312. CIBIS-II Investigators and Committees. Lancet. 1999;353:9-13. MERIT-HF Study Group. Lancet. 1999;353:2001. Masarone. J Cardiovasc Dev Dis. 2021;8(9):101. Bhinder. Cardiol Rev .2020;28(3):107 Heidenreich. J Am Coll Cardiol. 2022;79:e263.

New Kids on the Block

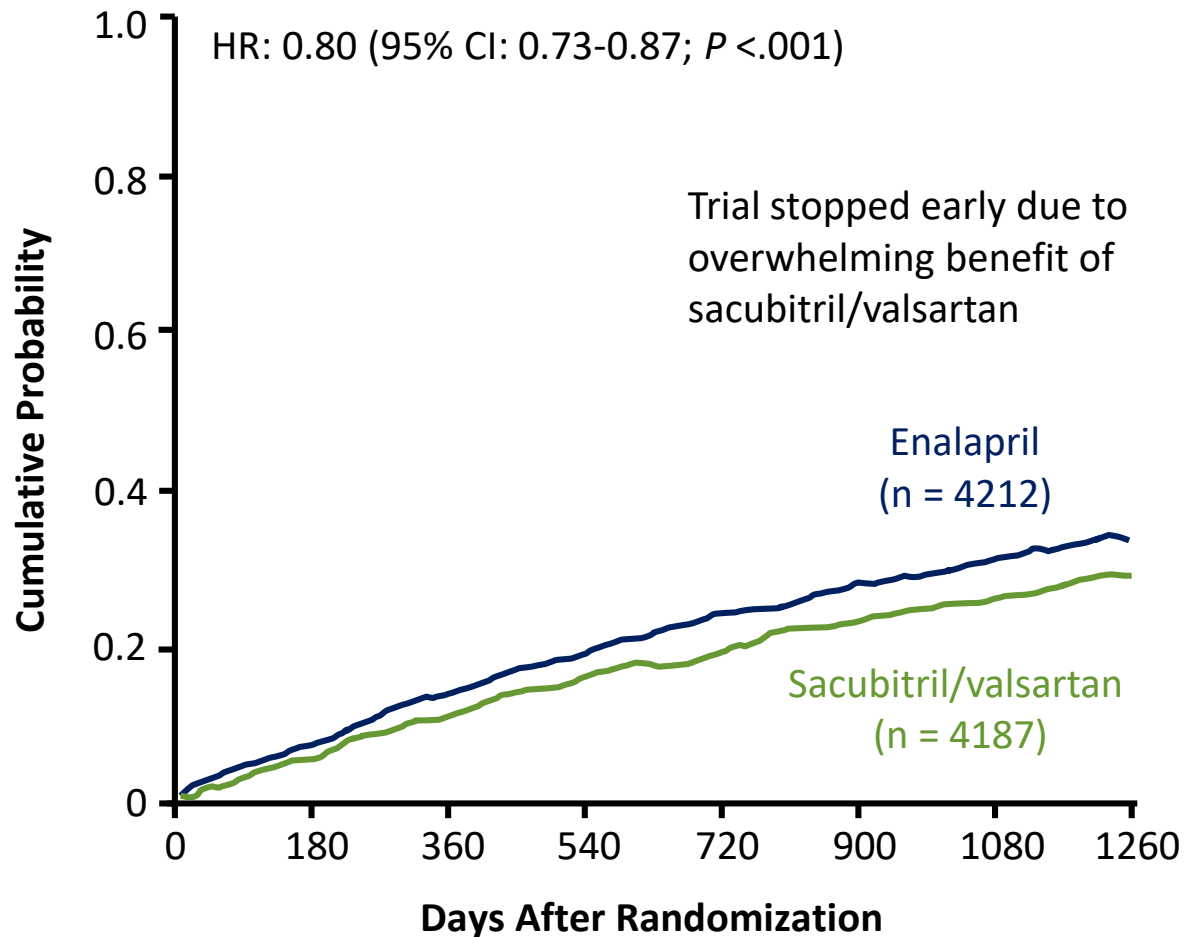


4 Pillars of GDMT for HFrEF



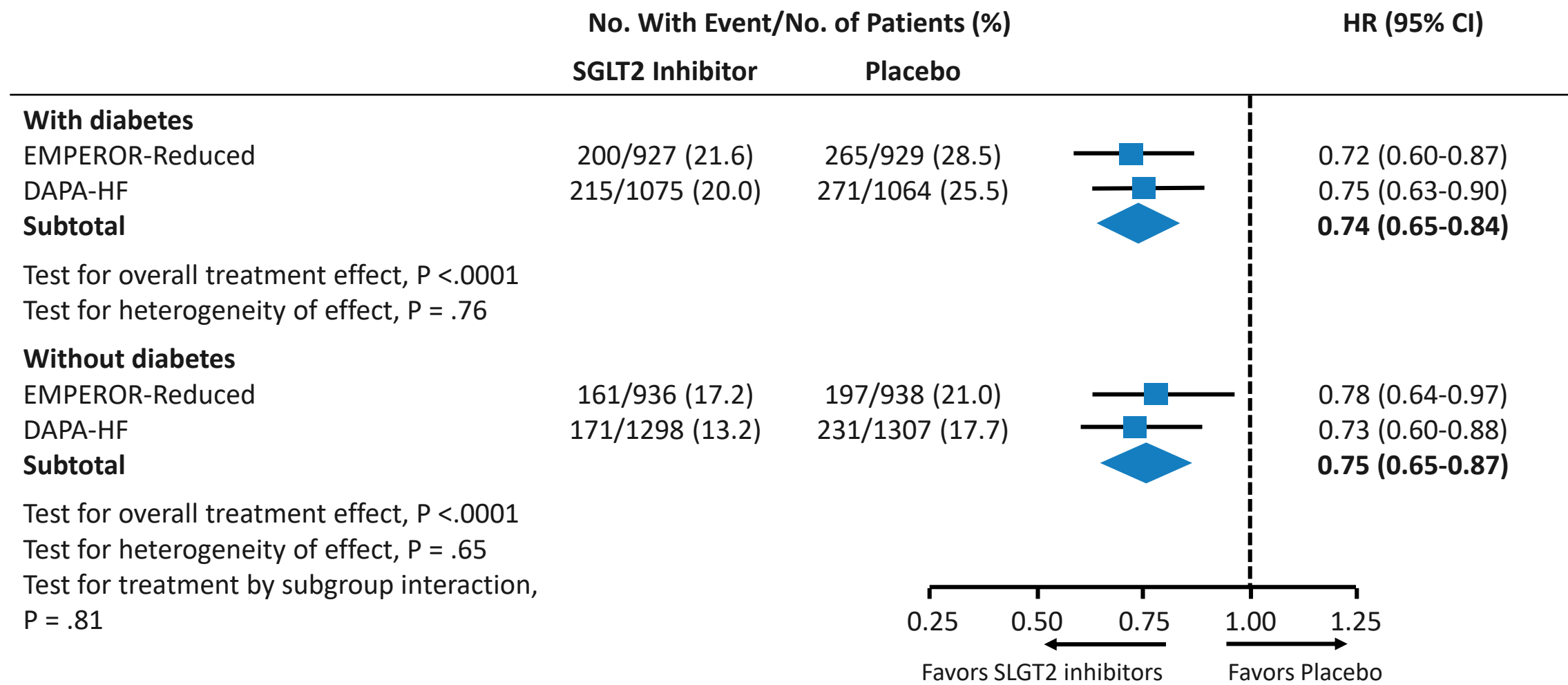
- Cumulative risk reduction in all-cause mortality if all 4 evidence-based medical therapies are used
 - Relative risk reduction 72.9%; absolute risk reduction: 25.5%; NNT = 3.9, over 24 mo

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

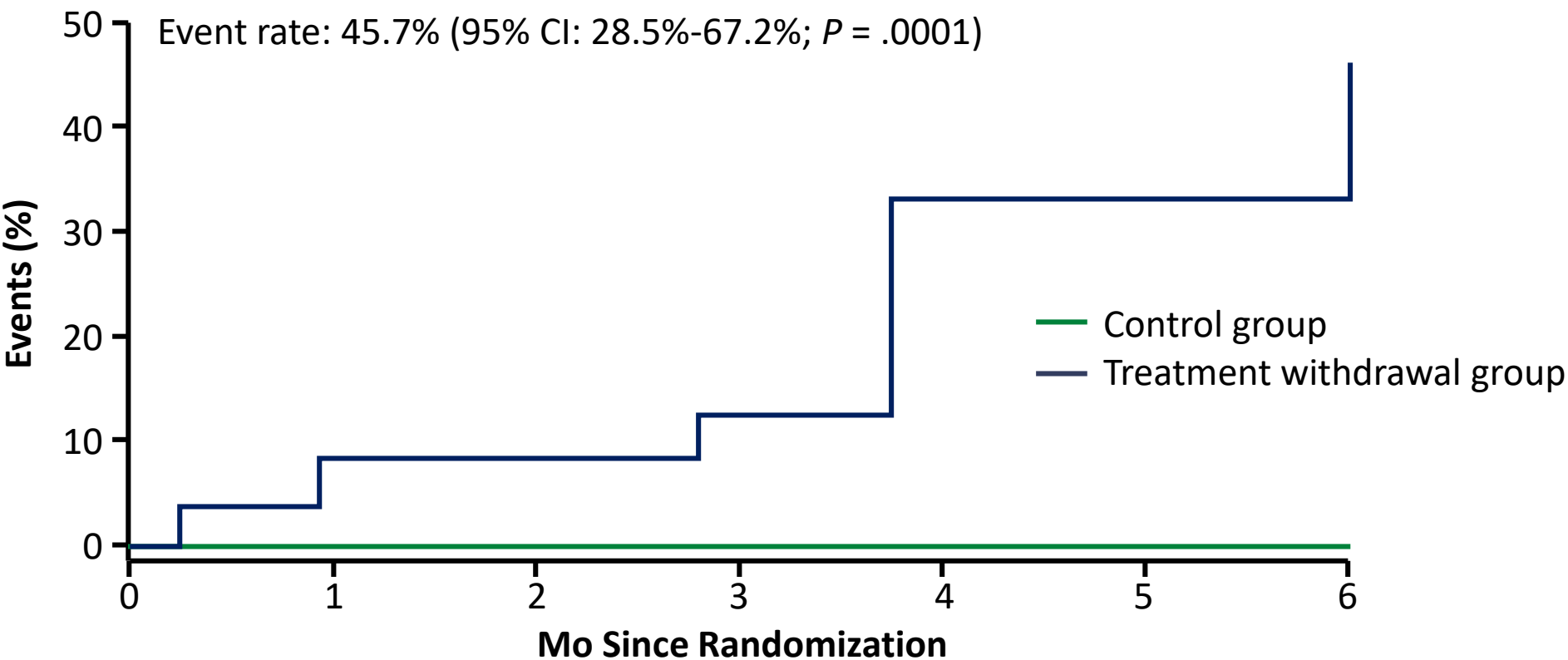
EMPEROR-Reduced and DAPA-HF: Reduction in HF Hospitalization or CV Death With SGLT2 Inhibitors in HFrEF



Therapies in HFimpEF (LVEF improved to $\geq 40\%$)

- 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***

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

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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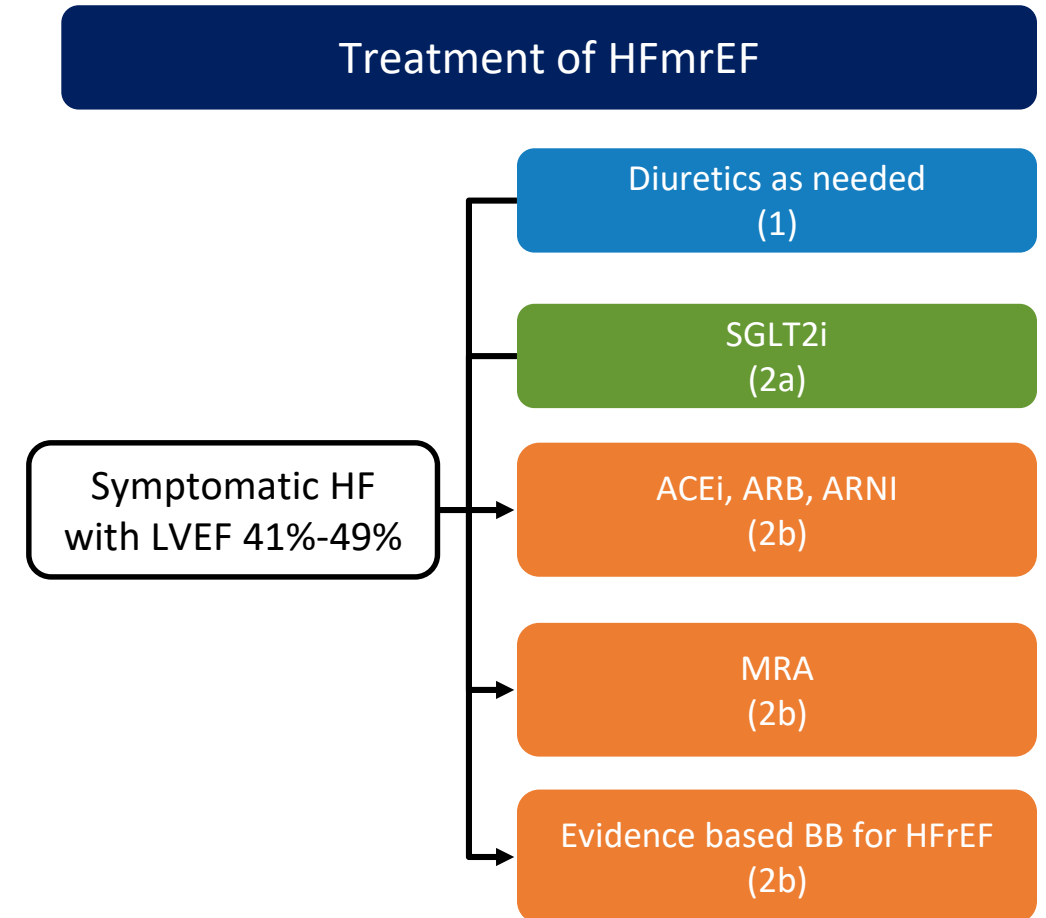
- A. Increase the patient's SGLT2 inhibitor to twice daily
- B. Decrease the patient's β -blocker dose
- C. Discontinue therapy as the patient has achieved their goal
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RATIONALE

- This patient presented with HFrEF (defined as a LVEF $\leq 40\%$)
- 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

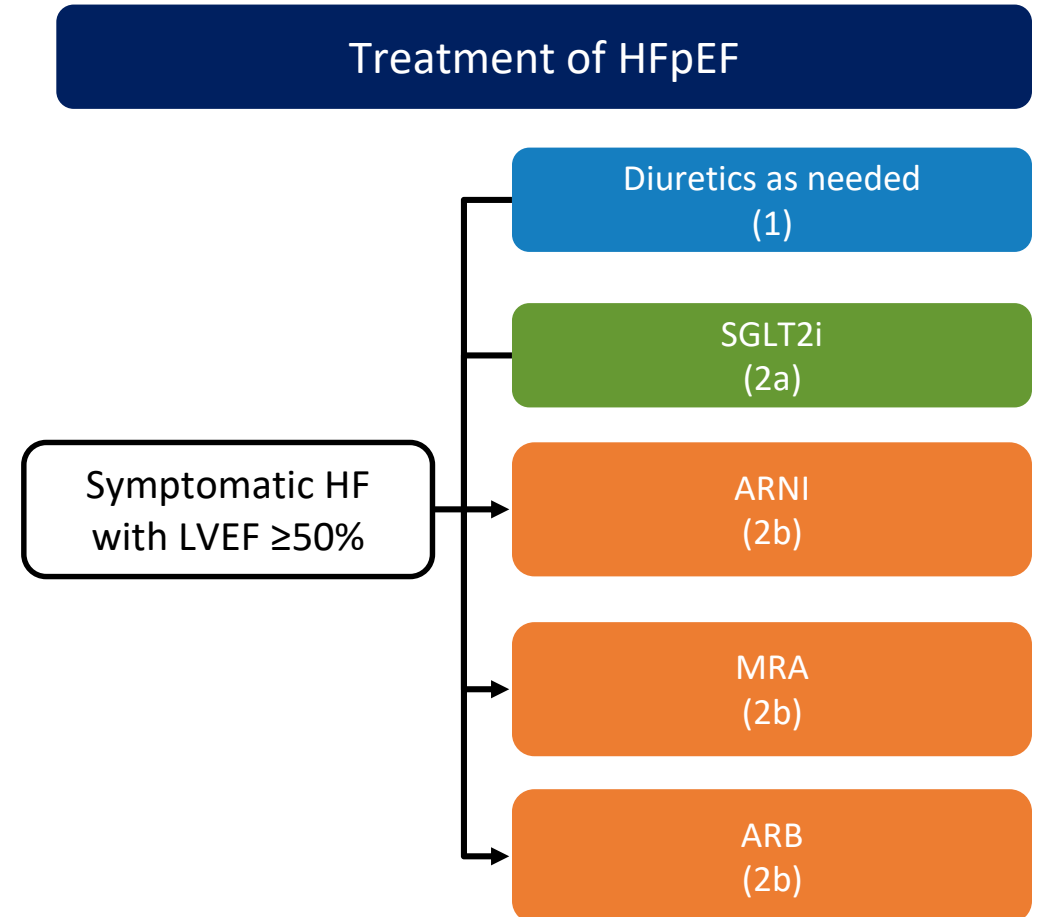
Therapies in HFmrEF (LVEF 41%-49%)

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



Therapies in HFpEF (EF $\geq 50\%$)

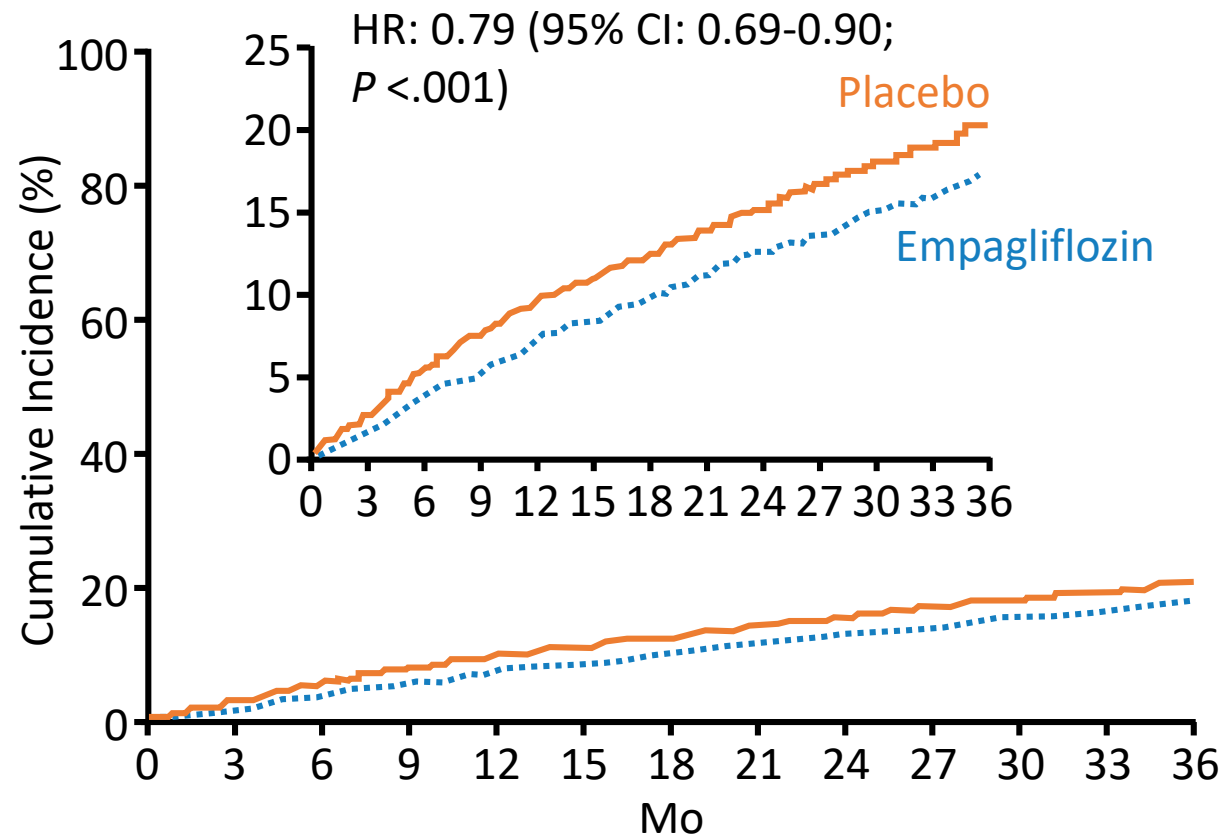
- Treat underlying contributing comorbidities
 - Iron deficiency anemia
 - Atrial fibrillation
 - Hypertension
 - Ischemic disease, etc
- Exercise program and cardiac rehab



SGLT2 Inhibitors and HFpEF

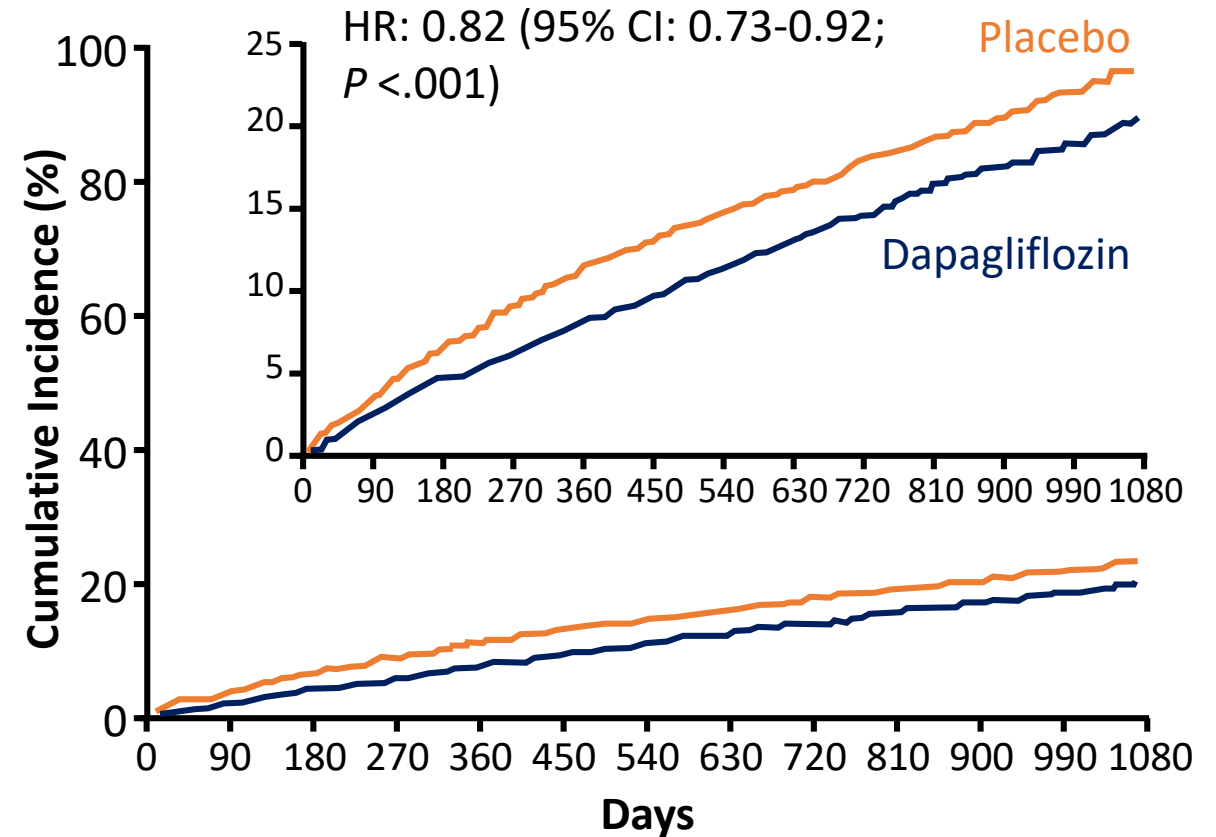
EMPEROR-Preserved

N = 5988



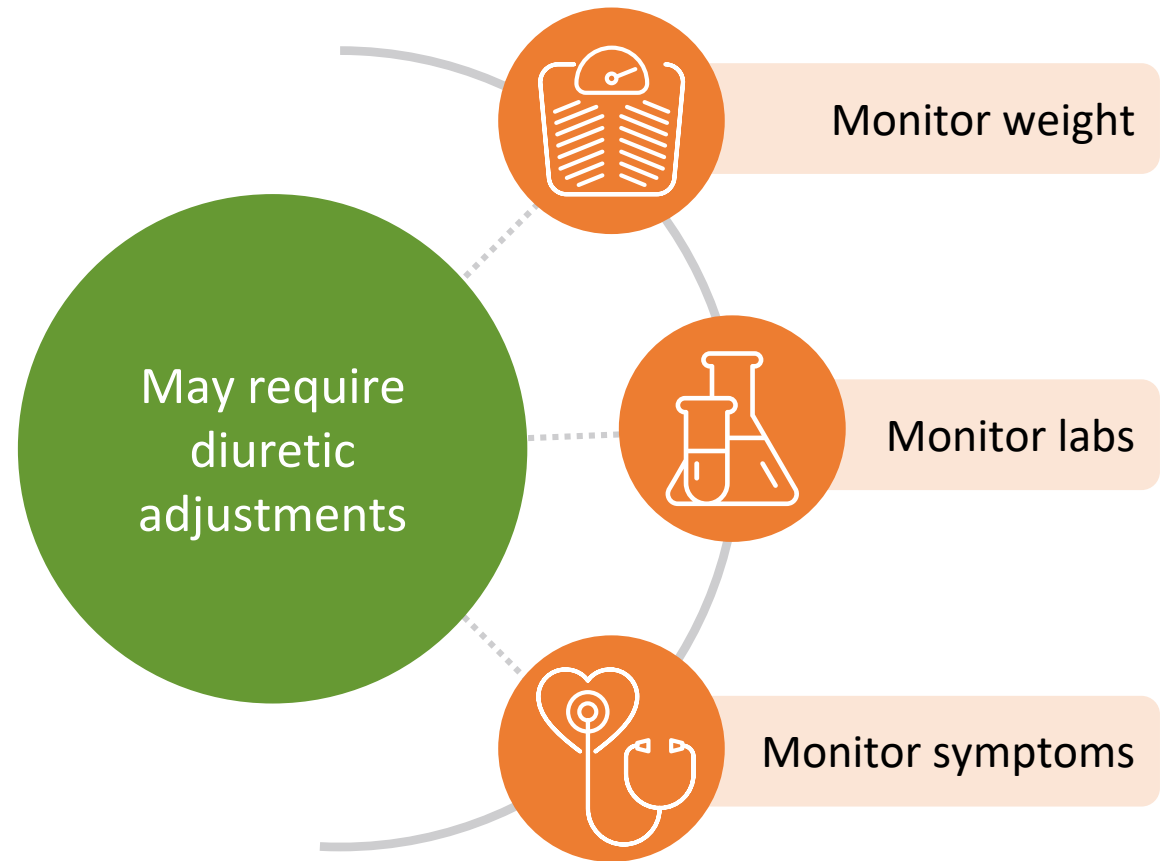
DELIVER

N = 6263



Use of SGLT2 Inhibitors: MAWDS

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



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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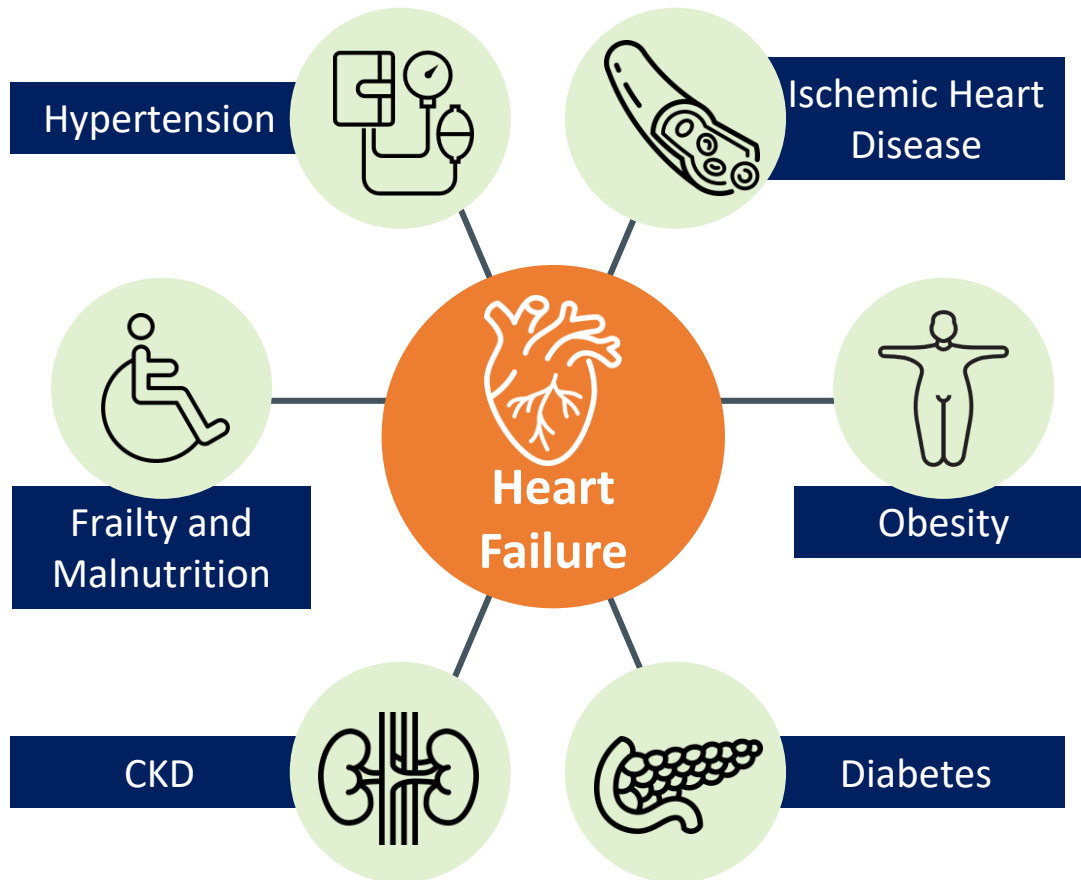
RATIONALE

- 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

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

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

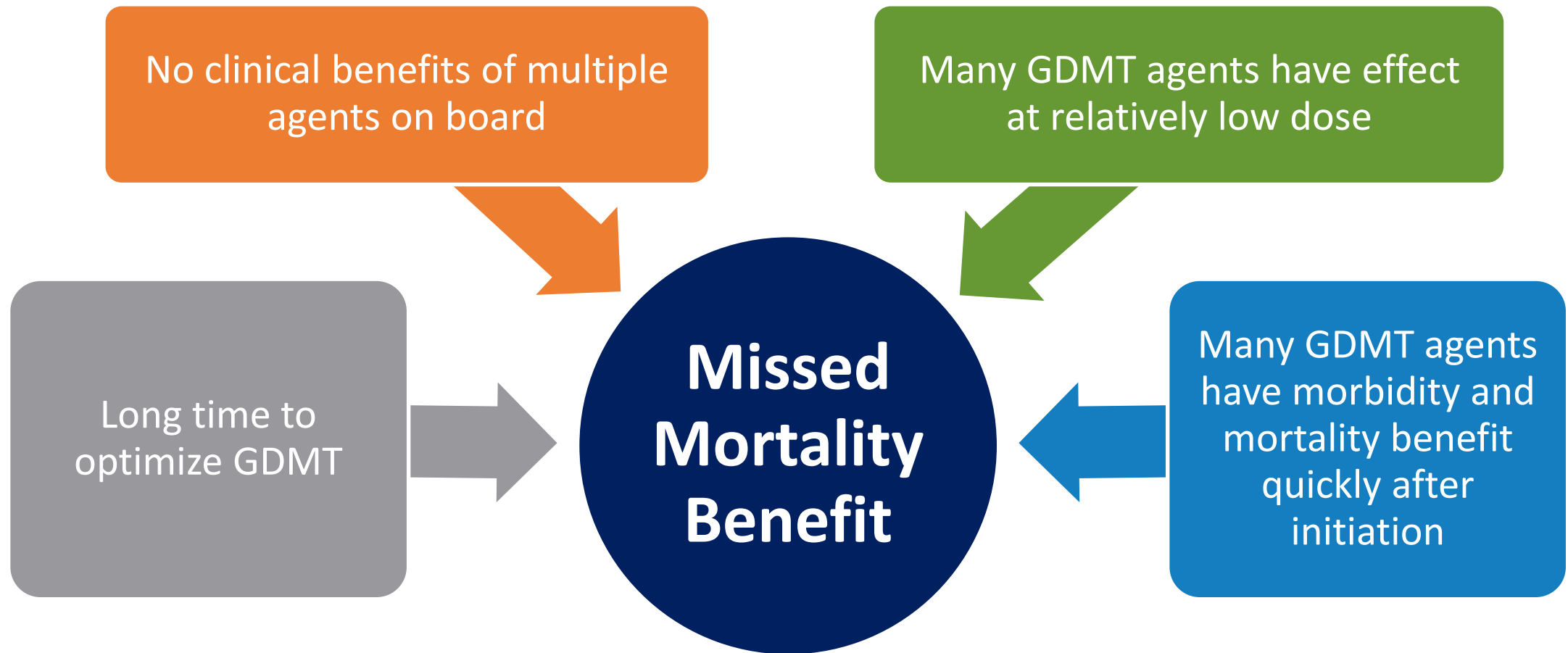
Example: Renal Failure

May limit our ability to utilize RAAS agents, MRAs, and SGLT2 inhibitors

May make volume management more challenging

Initiation and Titration of GDMT in HFrEF

Traditional Sequencing Consequences



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%

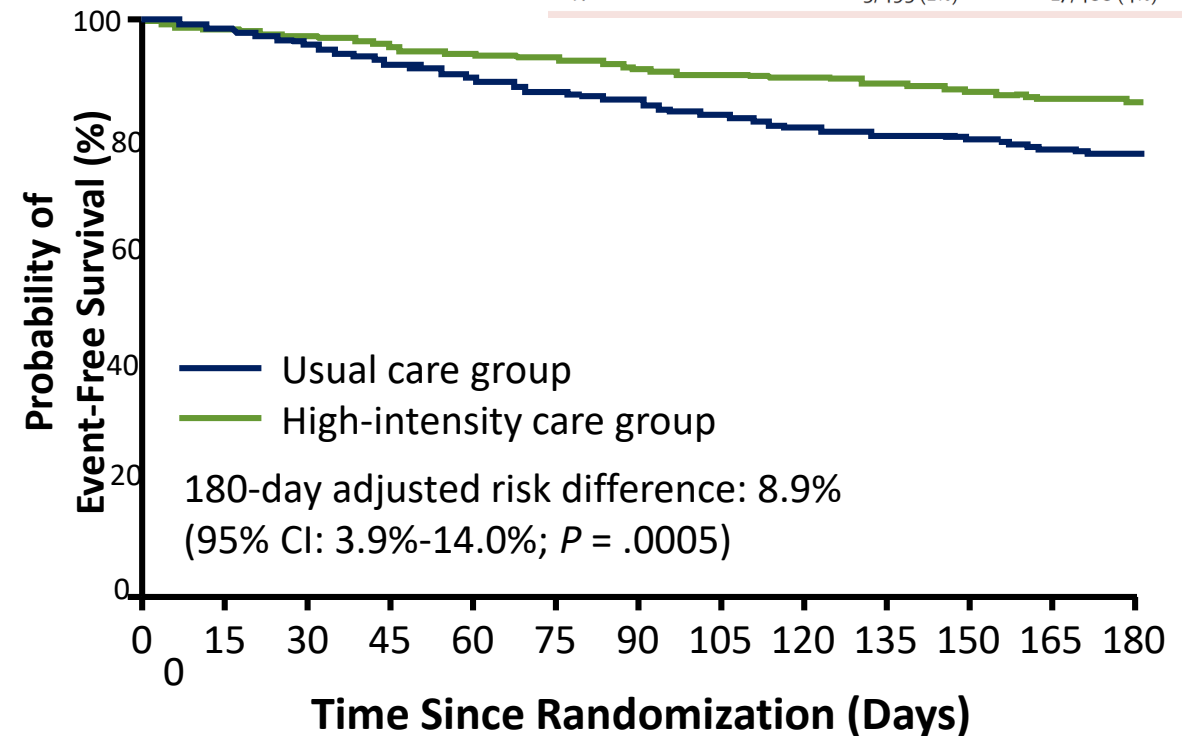
Clinical benefits of all medications are apparent within 30 days of initiation

STRONG-HF: All-Cause Mortality

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%)

- 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



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

Q & A