Meeting-in-a-Box: Heart Failure GDMT

Participant Guide

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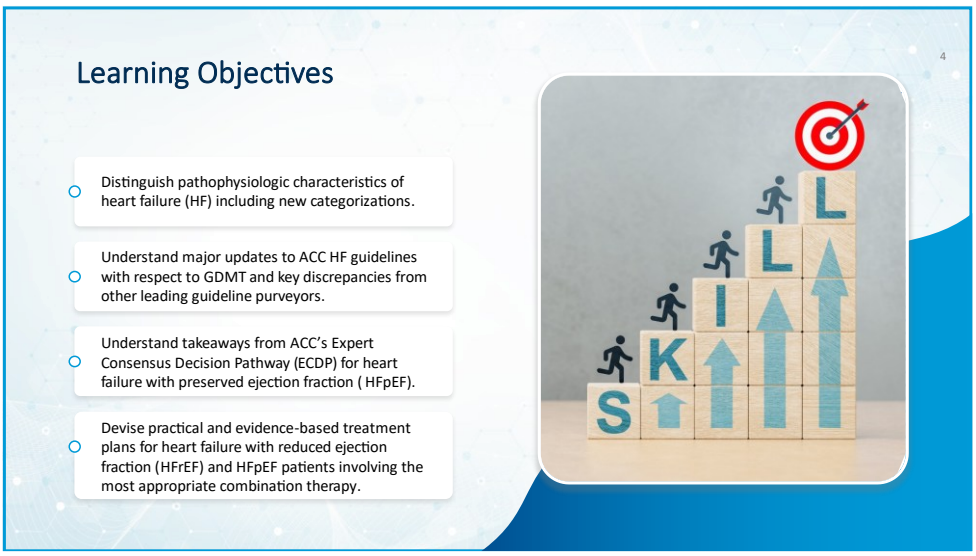
Learning Objectives

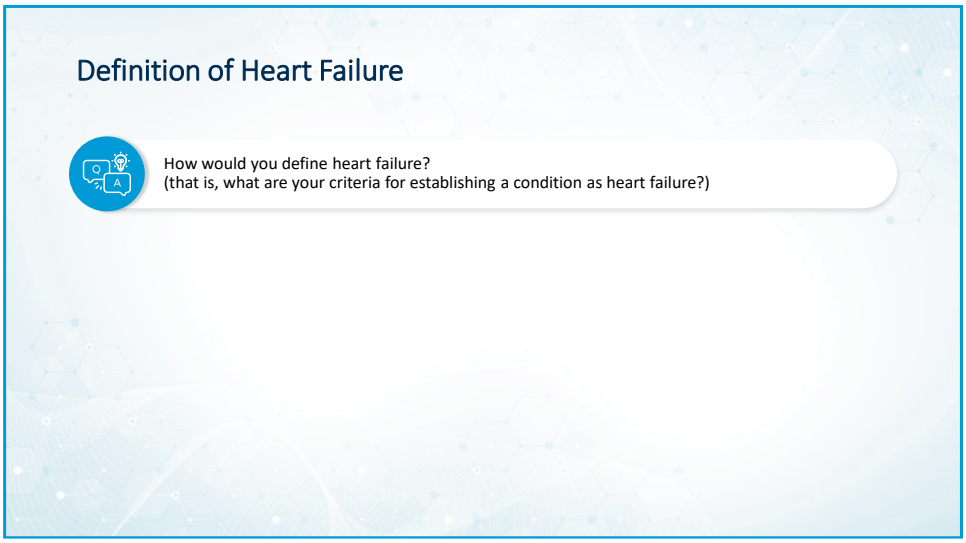


By the end of this module, you will be able to:

- Distinguish pathophysiologic characteristics of HF including new categorizations.
- Understand major updates to ACC HF guidelines with respect to guideline-directed medical therapy (GDMT) and key discrepancies from other leading guideline purveyors.
- Understand takeaways from ACC's Expert Consensus Decision Pathway (ECDP) for heart failure with preserved ejection fraction (HFpEF).
- Devise practical and evidence-based treatment plans for heart failure with reduced ejection fraction (HFrEF) and HFpEF patients involving the most appropriate combination therapy.

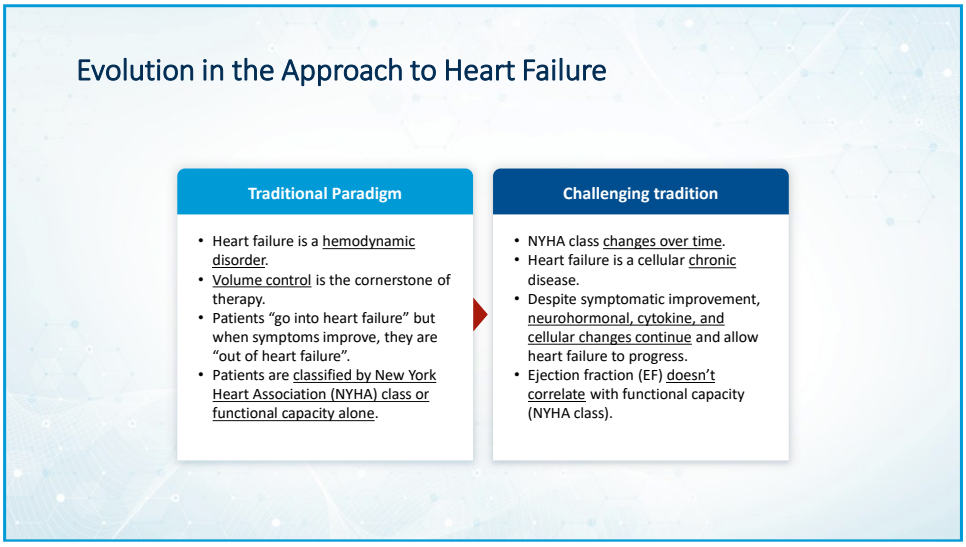
Section 1: Classification, Staging, and Diagnosis

Definition of Heart Failure



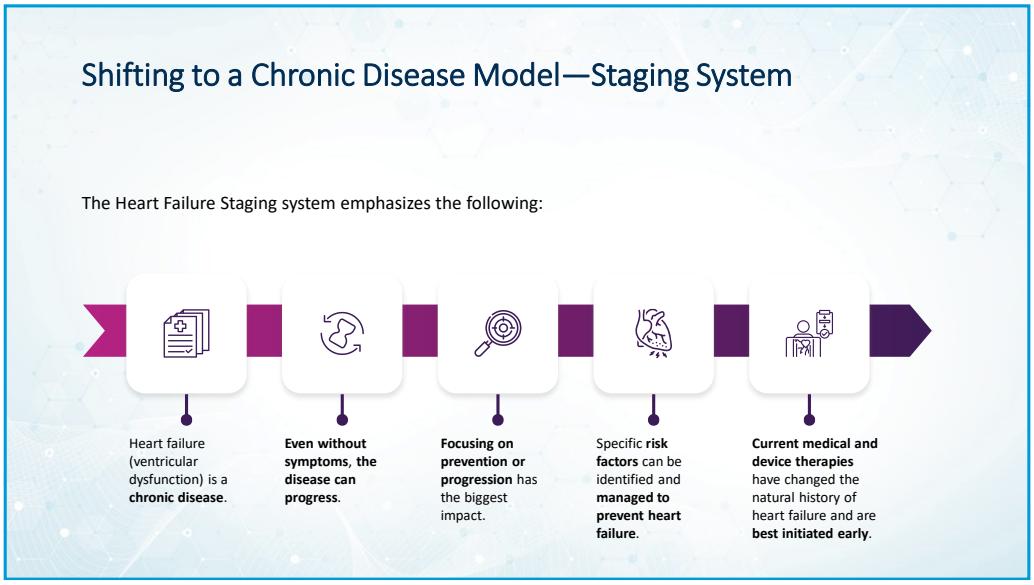
- Note your response in the space below and then discuss in the class.

Evolution in the Approach to Heart Failure



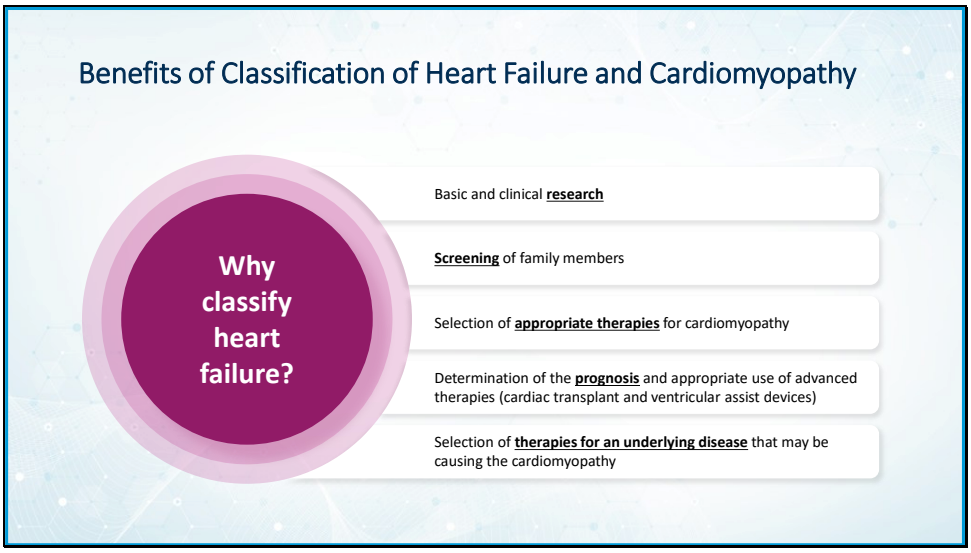
Notice the change in outlook toward heart failure. The universal definition is based on the new paradigm (Challenging tradition).

Shifting to a Chronic Disease Model—Staging System



- 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 (public health and cost).
- 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.

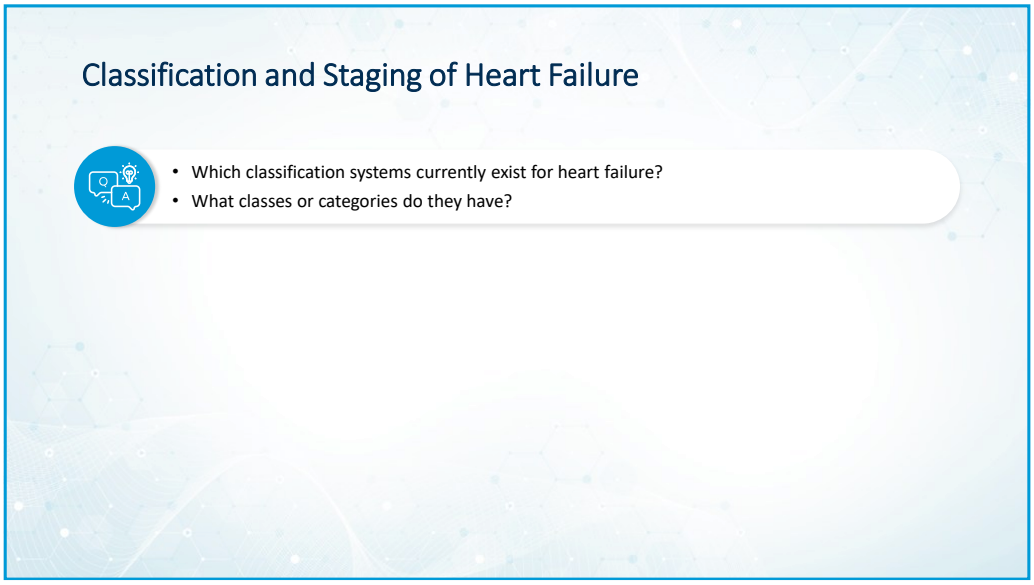
Benefits of Classification of Heart Failure and Cardiomyopathy



A classification and staging system is useful for heart failure and cardiomyopathy.

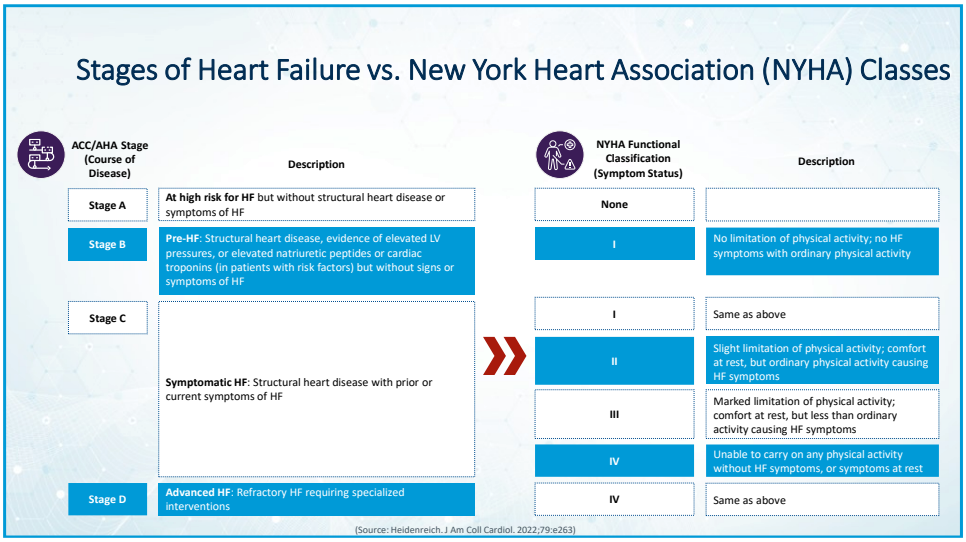
Notes:

Classification and Staging of Heart Failure



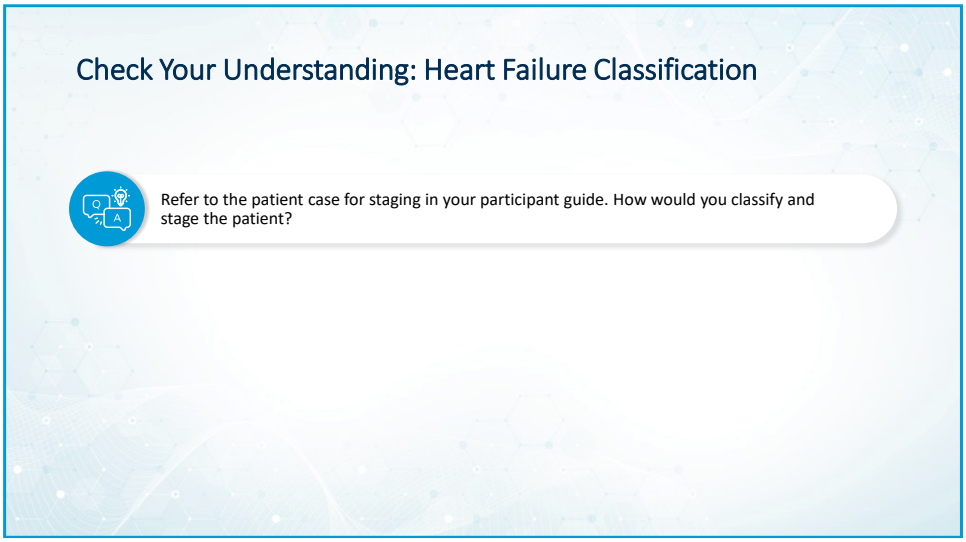
- Note your response in the space below and then discuss in the class.

Stages of Heart Failure vs. NYHA Classes



- Note that:
  - New York Heart Association (NYHA) classification represents the symptoms at the moment, whereas ACC/AHA Staging represents the course of disease and recommended therapies. It helps to identify therapies to prevent progression, reverse remodeling of the ventricle, reduce symptoms and reduce mortality, regardless of the current symptoms.
  - NYHA classification can change quickly.
  - Examples:
    - NYHA classification: 64-year-old man with left ventricular ejection fraction 35%; admitted to the hospital at NYHA Class IV; following diuresis and medication optimization discharged as NYHA Class II
    - ACC/AHA staging of patients: A 64-year-old man is ACC/AHA stage C, regardless of his current symptoms. He would benefit from at least the core four medication classes recommended for stage C.
  - Patients should be treated to prevent progression and reduce morbidity and mortality at each stage.
  - Once the patients' NYHA class is identified, they should be treated to reduce their symptoms or referred for advanced therapies or hospice.
- For more details of the updated heart failure staging system, refer to the article **Universal Definition and Classification of Heart Failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure** in the April 2021 issue of the Journal of Cardiac Failure (Volume 27, issue 4, pages 387-413).

Check Your Understanding: Heart Failure Classification



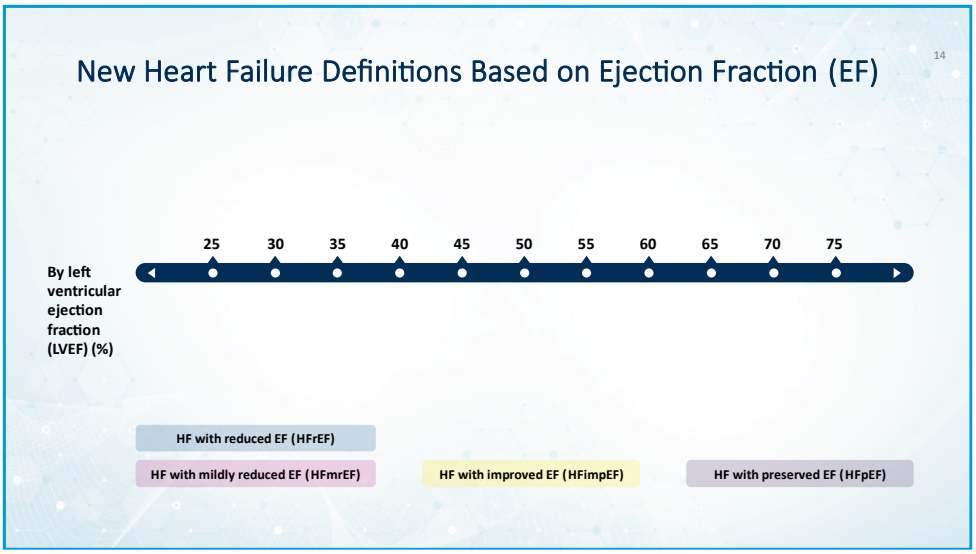
- Review the following patient case for staging and share your responses to the question on the slide. Use the blank space after the case to capture your response.

Case:
A 46-year-old man presents for a new patient visit. One year ago, he presented with shortness of breath and fatigue. An evaluation revealed a left ventricular ejection fraction of 35% with moderate mitral regurgitation. He was started on lisinopril 10 mg daily. A coronary angiogram revealed no evidence of coronary artery disease.

Today in the office, he reports that he has no shortness of breath and is able to work as a construction worker without limitation. On the weekend he plays football on a local team. His physical examination reveals blood pressure of 128/74 mmHg, heart rate 78 and regular, weight 74 kg. His cardiac examination reveals normal heart sounds with a soft blowing systolic murmur at the apex. He is warm and has no peripheral edema. His ECG reveals normal sinus rhythm with non-specific ST and T wave abnormalities.

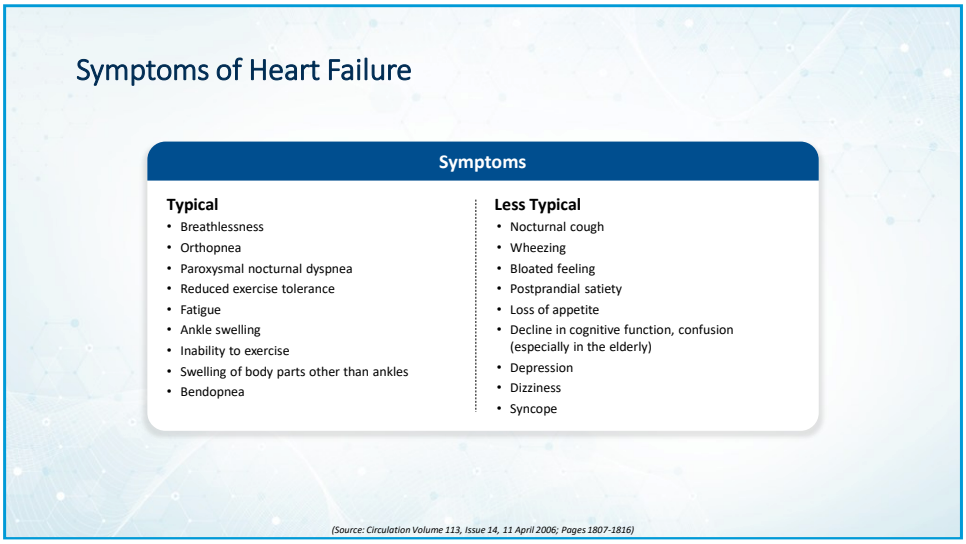
A repeat echocardiogram reveals a left ventricular ejection fraction of 40% with mild mitral regurgitation.

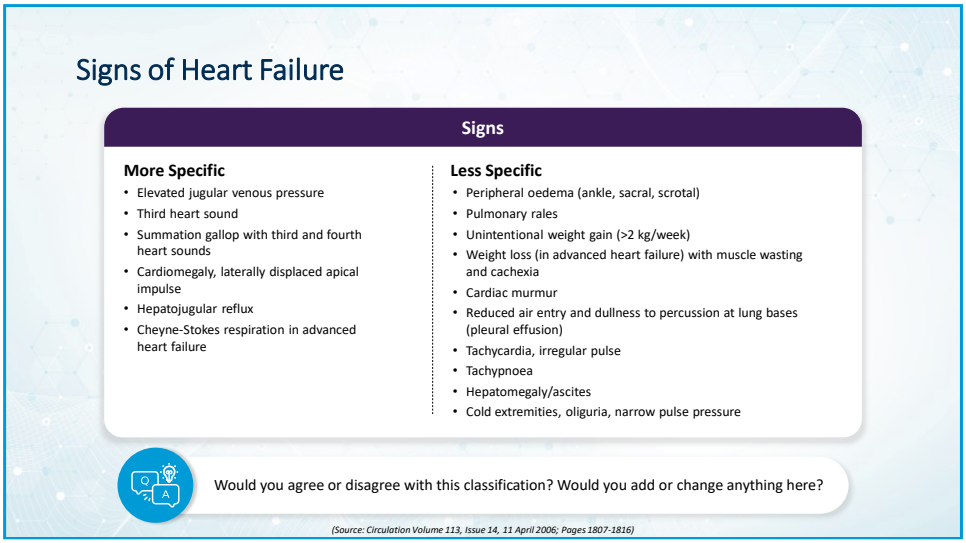
New Heart Failure Definitions Based on Ejection Fraction (EF)



- When we look at the heart failure classification, we also look at phenotypes according to the left ventricular ejection fraction (LVEF). Can you match the phenotypes on the slide with the corresponding LVEF% ranges?

Symptoms and Signs of Heart Failure

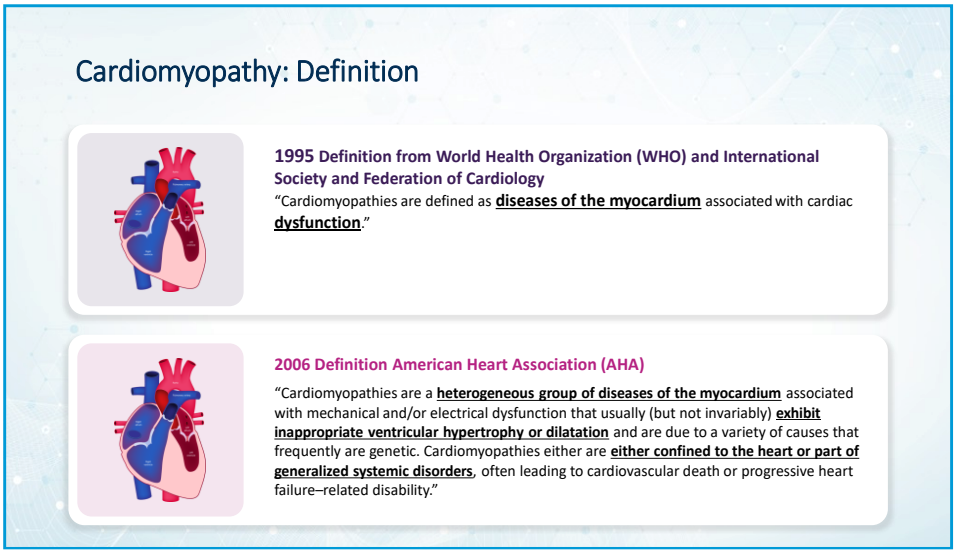




- The following symptoms and signs are most likely used in clinical trials, registries, risk scores, and are tested for sensitivity and specificity:
  - Paroxysmal nocturnal dyspnea
  - Orthopnea
  - Reduced exercise tolerance
  - Ankle swelling
  - Inability to exercise
  - Elevated jugular venous pressure
  - Third heart sound
  - Pulmonary rales

- The following signs/symptoms are often seen in cases of low perfusion and low cardiac output states:
  - Fatigue
  - Decline in cognitive function and confusion
  - Dizziness
  - Syncope
  - Cheyne-Stokes respiration
  - Cold extremities
- These symptoms may be common in the case of right heart failure or biventricular failure: Bloated feeling and postprandial satiety.
- Do you agree or disagree with this classification, based on your experience with patient cases. Do you have anything to add or update in this list?

Cardiomyopathy: Definition



- A related condition, cardiomyopathy, can lead to symptoms of heart failure.
- Its 1995 definition focused on clinical presentation (phenotype):
  - Dilated
  - Hypertrophic
  - Restrictive
  - Arrhythmogenic right ventricular cardiomyopathy
  - Unclassified
  - Specific – ischemic, valvular, hypertensive, metabolic, general system disease (lupus, sarcoid), muscular dystrophy and neuromuscular disorders
- In the 2006 definition of cardiomyopathy, the focus shifted to genetic and cellular causes—that is, pathology instead of clinical presentation. Cardiomyopathy is classified as one of two types: primary or secondary. Secondary cardiomyopathies are systemic diseases that impact the heart.

Primary Cardiomyopathy

Type	Examples
Genetic	Hypertrophic, arrhythmogenic right ventricular dysplasia, ion channel disorders, non-compaction, etc.
Mixed	Dilated and restrictive cardiomyopathies
Acquired	Inflammatory (myocarditis), stress induced, peripartum, tachycardia induced

(Source: Circulation Volume 113, Issue 14, 11 April 2006; Pages 1807-1816)

Secondary Cardiomyopathies

Type	Examples
Infiltrative	Amyloidosis
Toxic	Drugs, heavy metals, chemicals
Storage	Hemochromatosis
Endomyocardial	
Endocrine	Thyroid, pheochromocytoma, diabetes
Neuromuscular	Muscular dystrophy
Nutritional Deficiencies	Selenium, scurvy, beriberi, pellagra
Autoimmune	Systemic lupus erythematosus, scleroderma
Electrolyte imbalance	
Consequence of cancer therapy	Radiation, chemotherapy

(Source: Circulation Volume 113, Issue 14, 11 April 2006; Pages 1807-1816)

- Pathological processes that are a direct consequence of other cardiovascular abnormalities are not included in the 2006 classification:
  - Coronary disease
  - Valvular disease including rheumatic heart disease
  - Systemic hypertension
  - Congenital heart disease
- These are common and should be ruled out prior to considering primary or secondary cardiomyopathy.

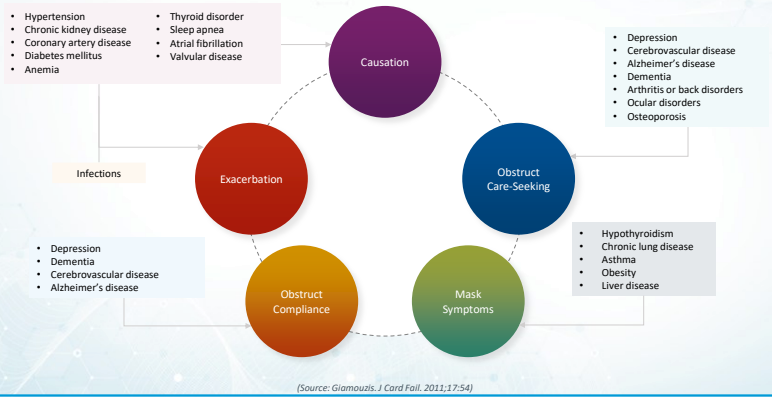
Comorbid Conditions and Heart Failure

Comorbid Conditions and Heart Failure

Comorbidity	Impact on outcomes or life quality
Myocardial Ischemia	Contribution to LV dysfunction
Atrial arrhythmias	Worsens symptoms, decreases cardiac performance
Anemia	Common; associated with worse outcome and increased symptoms
Sleep apnea	Common; associated with arrhythmias, pulmonary hypertension, biventricular dysfunction
Thyroid disorders	Either hypo- or hyperthyroidism can exacerbate heart failure
Depression	Common; worsens symptoms and complicates interpretation
Arthritis	Treatment with NSAIDs can exacerbate HF and renal dysfunction.
Diabetes	Associated with CAD and hyperlipidemia. Treatment with glitazones can complicate heart failure. Consider SGLT-2 inhibitors or GLP-1.
Hyperlipidemia	Associated with CAD
Erectile dysfunction	Common; associated with depression, non-compliance; worsens QOL
Diabetic cardiomyopathy	Structural myocardial abnormalities leading to both systolic and diastolic dysfunction and ultimately heart failure

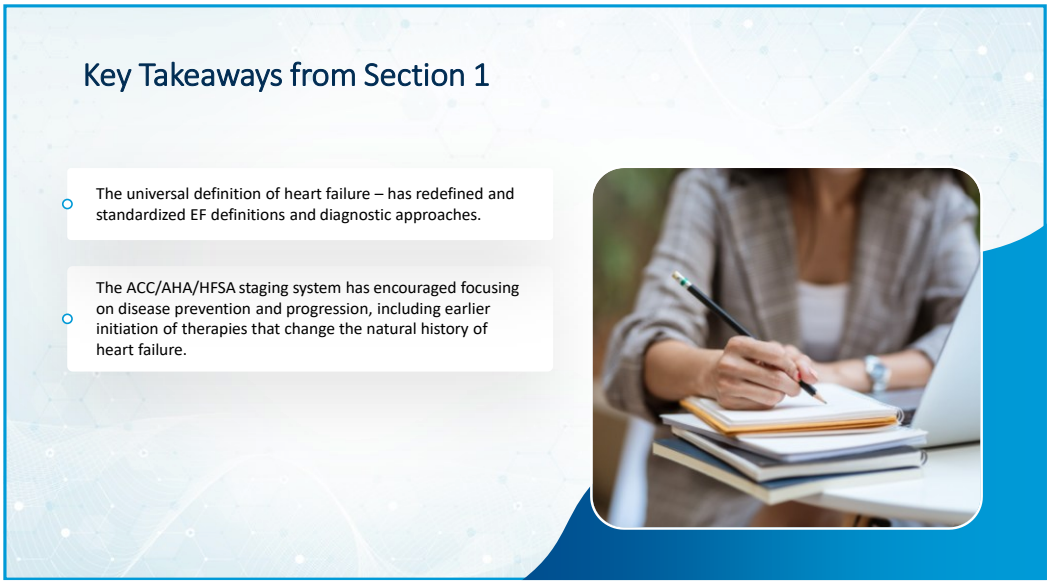
Comorbidities associated with heart failure may directly impact cardiomyopathy, if present. The comorbidities might also make management and compliance with medications more difficult.

Impact of Comorbidities for Patients with Heart Failure



(Source: Giamouzis. J Card Fail. 2011;17:54)

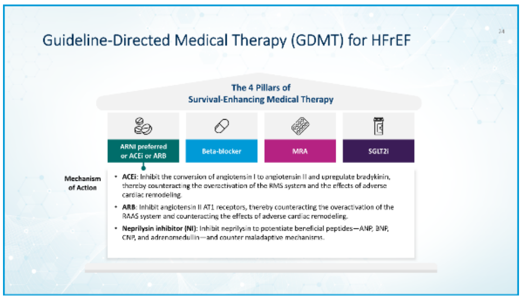
Key Takeaways from Section 1

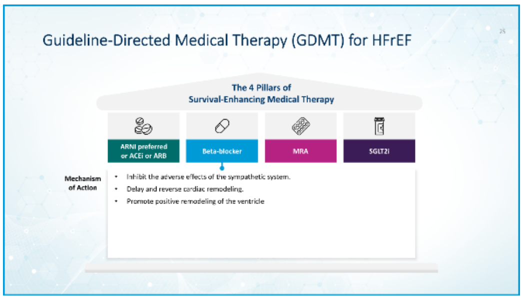


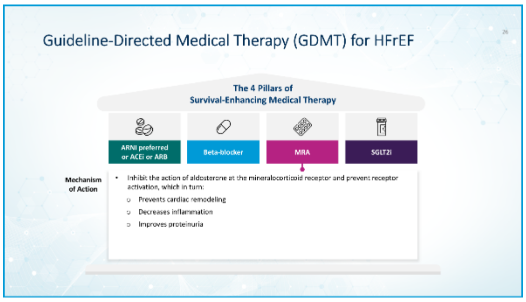
- Use the following space to capture your insights from section 1.

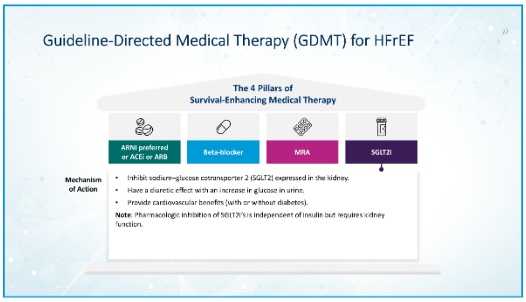
Section 2: Medical Management of HFrEF

Guideline-Directed Medical Therapy (GDMT) for HFrEF









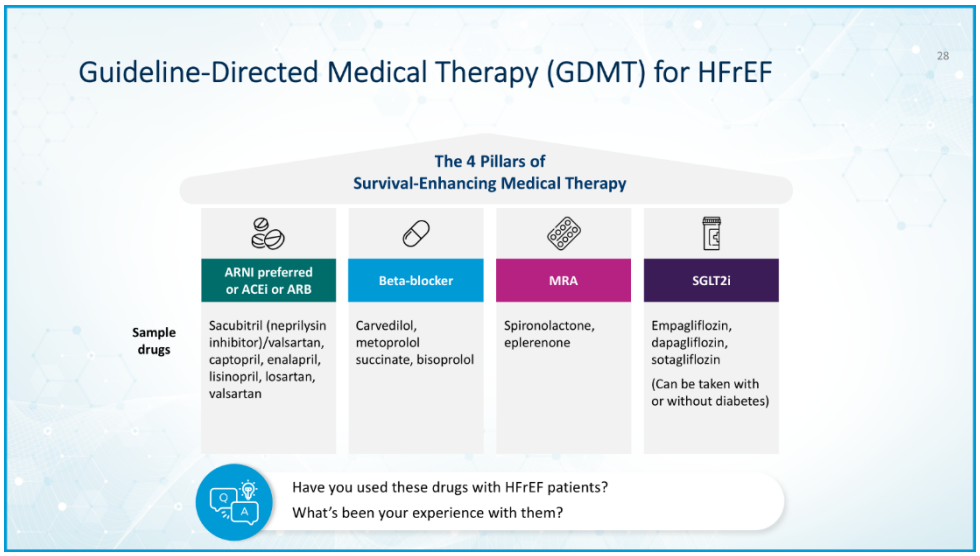
Four classes of drugs are now recommended for all patients with HFrEF (LVEF <40%): Angiotensin-converting-enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) + neprilysin inhibitor (NI) (ARNI), beta (β)-blocker, mineralocorticoid receptor antagonist (MRA), and SGLT2i.

Note:

- **ACE inhibitors**: This is the first class of drugs that have demonstrated reduction in morbidity and mortality in heart failure. They became the "gold standard" by which all subsequent drugs were compared and the "baseline therapy" to which all subsequent drugs were added.
- **ARB**: Their clinical effect was similar to ACE inhibitors.
- **ARNI**: The combination of an ARB, such as valsartan, and neprilysin inhibitor, sacubitril, was the first drug superior to an ACE inhibitor in a head-to-head clinical trial.
- **Beta (β)-blocker**: In the past, this drug was contraindicated in heart failure. It has a significant positive impact on morbidity and mortality and promotes positive remodeling of the ventricle. Select only evidence-based beta-blockers, such as metoprolol succinate, carvedilol, and bisoprolol.

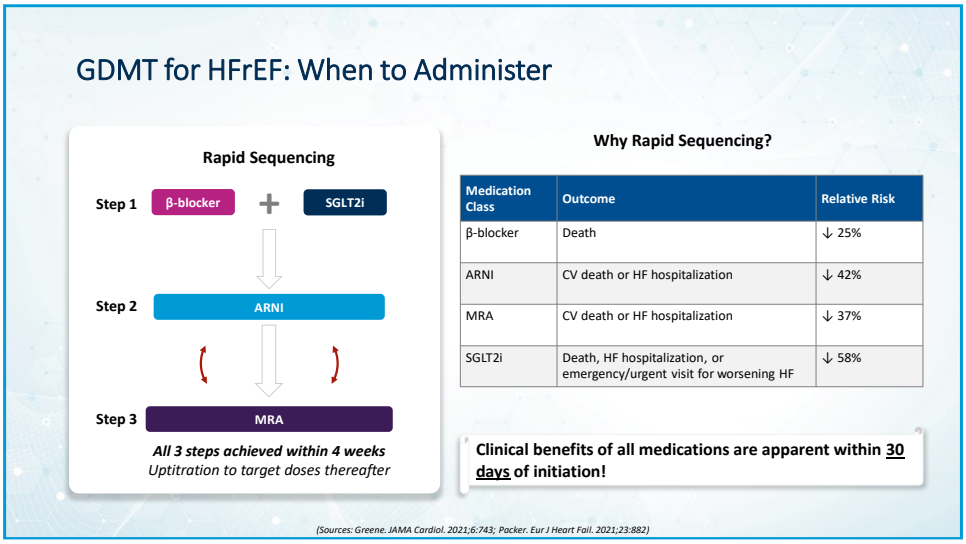
Loop diuretics are also commonly prescribed but they have had no role in changing the natural history of heart failure. A diuretic such as thiazide (metolazone) can be added, as needed, and titrated to signs and symptoms of fluid overload.

GDMT for HFrEF: Sample Drugs



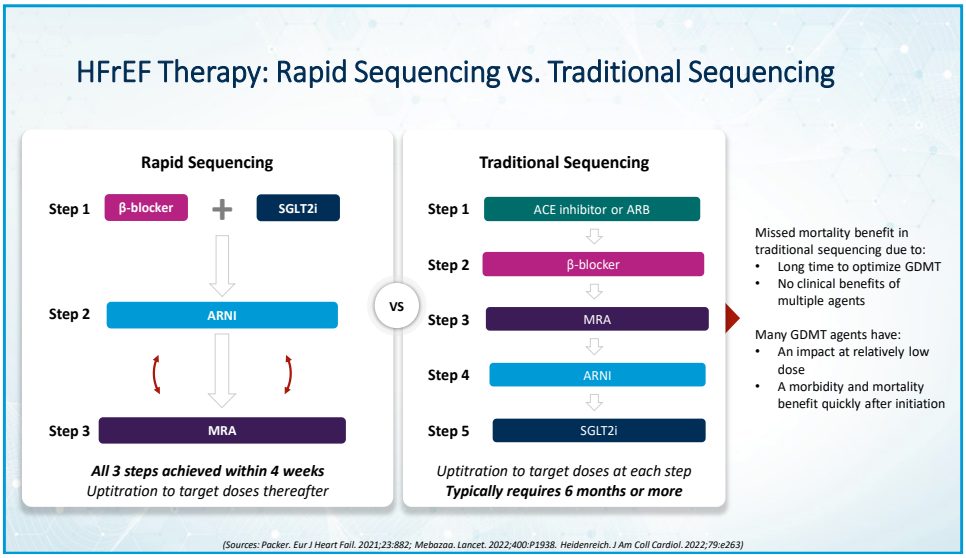
- This slide shows some samples of drugs belonging to each pillar of GDMT.
- Have you used these drugs with your patients? What's your experience with these drugs?

GDMT for HFrEF: When to Administer



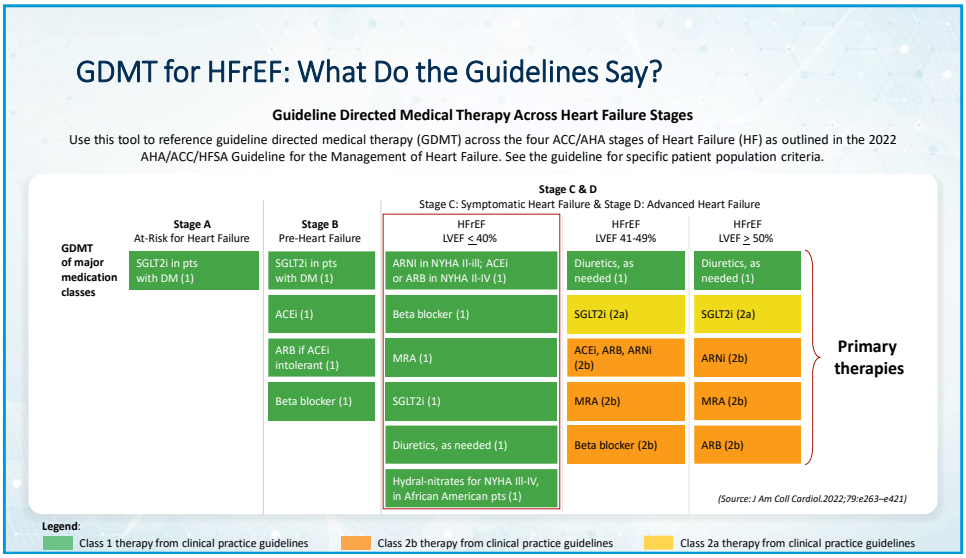
- Rapid sequencing is needed for all four classes of medication used in GDMT. Please refer to Appendix A of this guide for the findings of some clinical trials related to the outcomes, doses, and efficacy of these medicines.

HFrEF Therapy: Rapid Sequencing vs. Traditional Sequencing



- Rapid sequencing of the medicines is preferred over their traditional sequencing.
- Use the following space to note your observations and insights regarding sequencing the medicines.

GDMT for HFrEF: What Do the Guidelines Say?

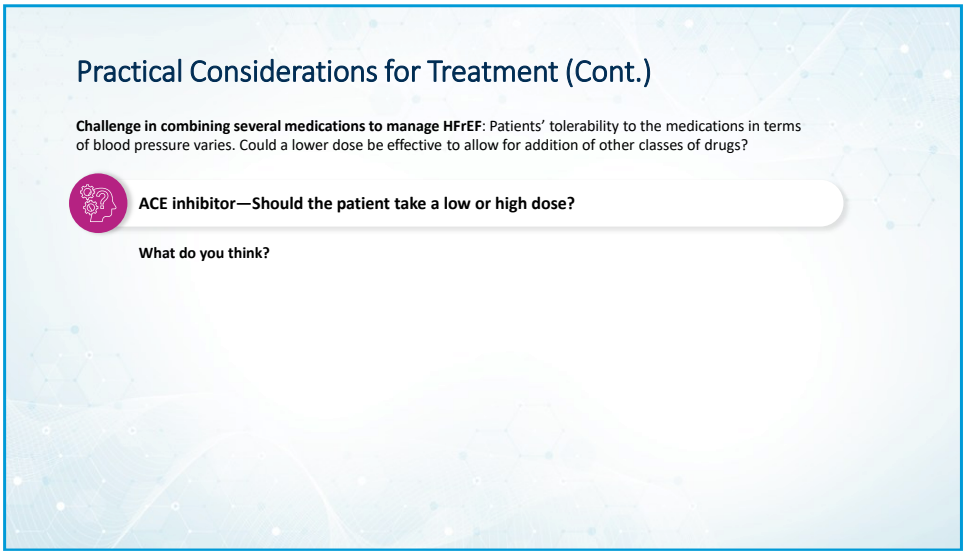


- The ACC/AHA guidelines also recommend the four classes of medications as primary therapies for HFrEF.
- Use the following space to note your insights from this guideline-recommended therapy.

Practical Considerations for Treatment

- Note your response to the question in the space below and then discuss in the class.

Practical Considerations for Treatment (Cont.)



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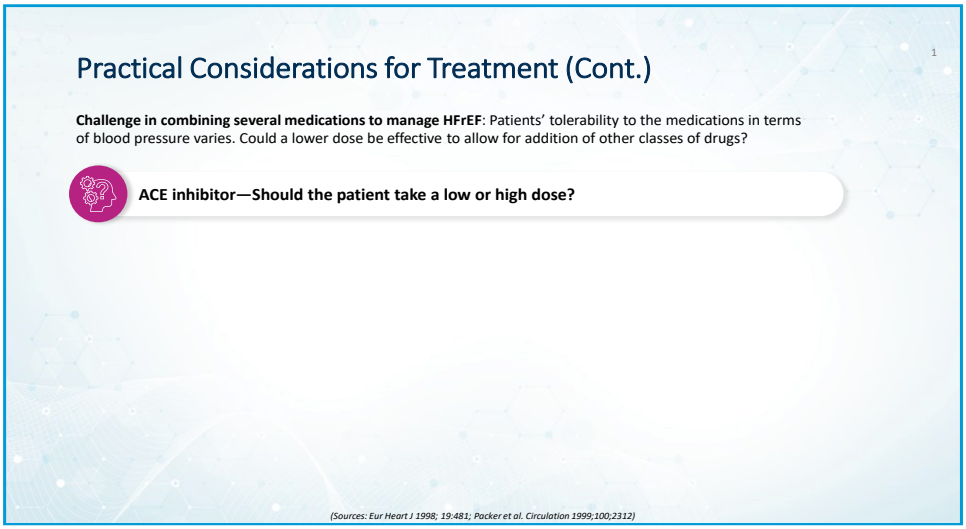
Practical Considerations for Treatment (Cont.)



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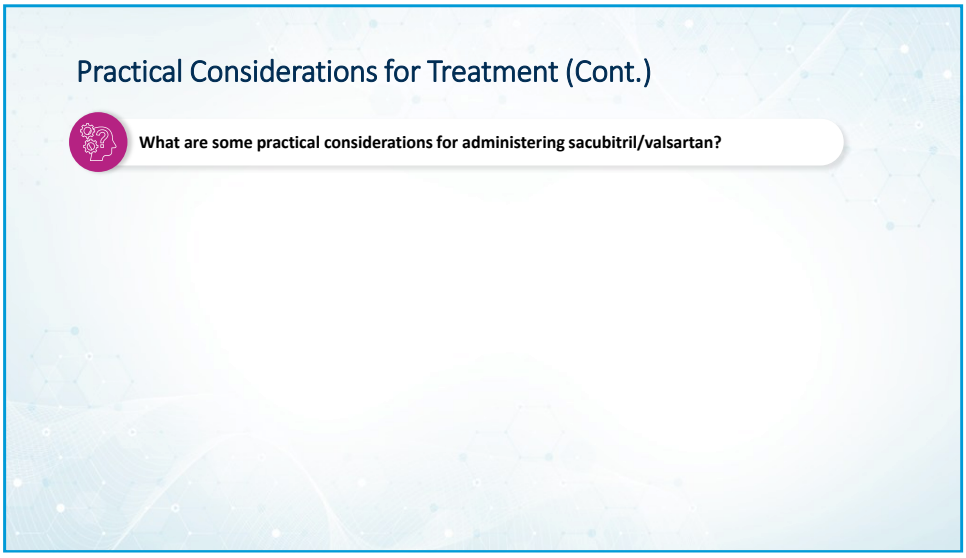
Practical Considerations for Treatment (Cont.)



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Practical Considerations for Treatment (Cont.)

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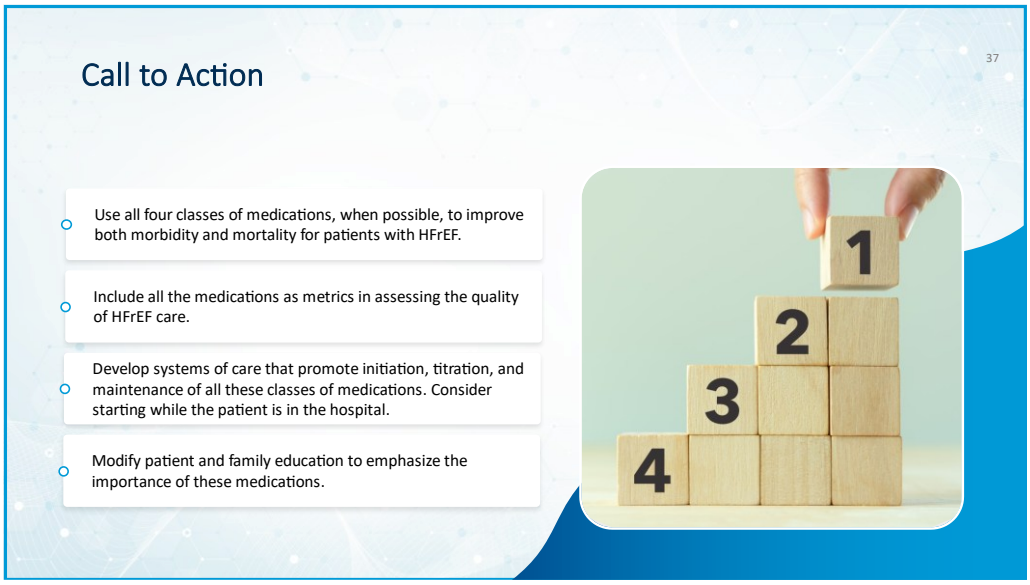
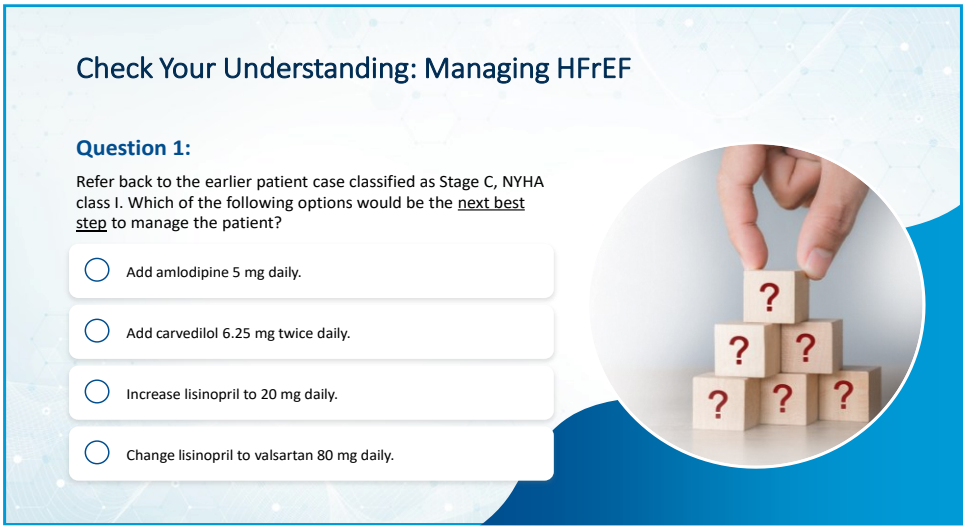
Call to Action



- Use the following space to note your insights from this section.

Check Your Understanding: Managing HFrEF



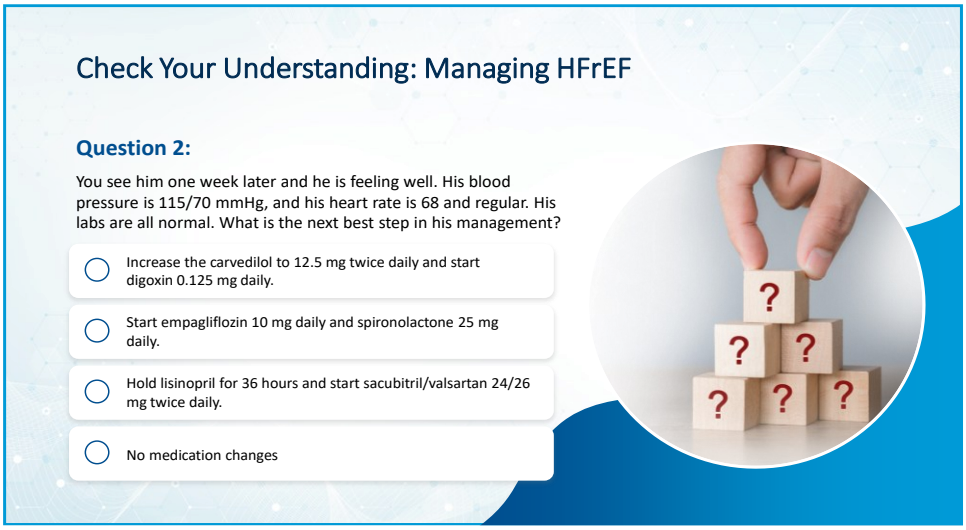
- Refer back to the following patient case again (classified as stage C, NYHA class I earlier). Then note and share your responses to the question on the slide.

  Case:
  A 46-year-old man presents for a new patient visit. One year ago, he presented with shortness of breath and fatigue. An evaluation revealed a left ventricular ejection fraction of 35% with moderate mitral regurgitation. He was started on lisinopril 10 mg daily. A coronary angiogram revealed no evidence of coronary artery disease.

  Today in the office, he reports that he has no shortness of breath and is able to work as a construction worker without limitation. On the weekend he plays football on a local team. His physical examination reveals blood pressure of 128/74 mmHg, heart rate 78 and regular, weight 74 kg. His cardiac examination reveals normal heart sounds with a soft blowing systolic murmur at the apex. He is warm and has no peripheral edema. His ECG reveals normal sinus rhythm with non-specific ST and T wave abnormalities.

  A repeat echocardiogram reveals a left ventricular ejection fraction of 40% with mild mitral regurgitation.

Check Your Understanding: Managing HFrEF



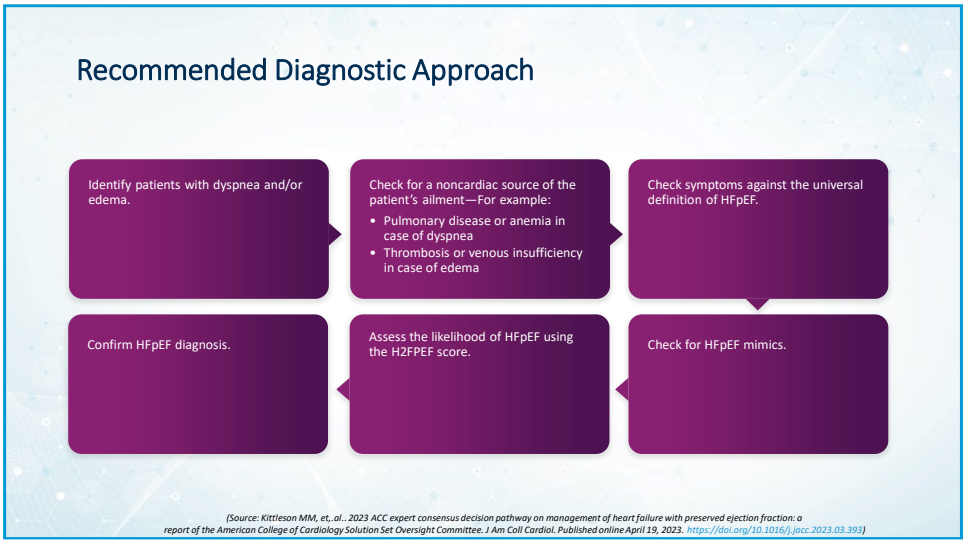
- Note and share your responses to the question on the slide.

Section 3: Medical Management of HFpEF

Diagnosis of HFpEF

- Note your response in the space below and then discuss in the class.

Recommended Diagnostic Approach



- This slide recommends a diagnostic approach for HFpEF. Refer to the following list of HFpEF mimics during diagnosis.

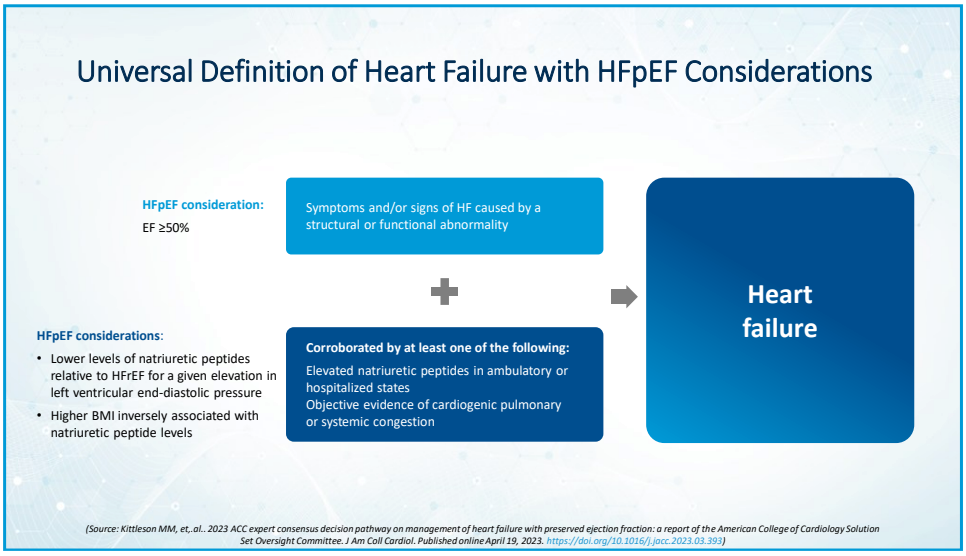
TABLE 1 Diagnostic Clues and Recommended Testing for HFpEF Mimics

HFpEF Mimic	Clinical Clues	Diagnostic Testing
Cardiac amyloidosis	Increased LV wall thickness Musculoskeletal issues (carpal tunnel syndrome, lumbar spinal stenosis) Neuropathy (sensory or autonomic)	Monoclonal protein screen (serum/urine immunofixation electrophoresis and serum free light chains) Technetium pyrophosphate scan (interpreted in the context of a negative monoclonal protein screen) Endomyocardial biopsy if monoclonal protein screen is positive
Hypertrophic cardiomyopathy	Unexplained LV hypertrophy LV outflow tract obstruction Family history	CMR if diagnosis is uncertain based on echocardiogram
Cardiac sarcoidosis	Extracardiac disease (pulmonary, ocular, dermatologic) High-degree atrioventricular block (especially if age <60 y) Ventricular arrhythmias	CMR FDG-PET scan Tissue biopsy (cardiac or extracardiac)
Hemochromatosis	Family history or history of frequent blood transfusions Diabetes Erectile dysfunction	Ferritin and transferrin *HFE* genetic testing CMR with T2* imaging
Fabry disease	Angiokeratomas Sensory neuropathy Proteinuria X-linked inheritance	Serum alpha-galactosidase level (in men) *GLA* genetic testing Biopsy of affected tissue
High-output HF	Echocardiogram with 4-chamber enlargement and/or increased LV outflow tract VTI	Investigate and treat underlying cause: anemia, arteriovenous malformations, cirrhosis, fistulas, thiamine deficiency
Myocarditis	Antecedent viral infection Elevated troponin in the absence of coronary artery disease Heart block and/or ventricular arrhythmias	CMR Endomyocardial biopsy
Pericardial disease	Prior cardiac surgery, chest radiation, or pericarditis Right-sided HF symptoms	CMR Right and left heart catheterization to demonstrate discordance in LV/RV pressure tracings during inspiration

CMR = cardiac magnetic resonance; FDG-PET = fluorodeoxyglucose-positron emission tomography; HF = heart failure; *HFE* = hereditary hemochromatosis gene; HFpEF = heart failure with preserved ejection fraction; LV = left ventricular; RV = right ventricular; VTI = velocity time integral.

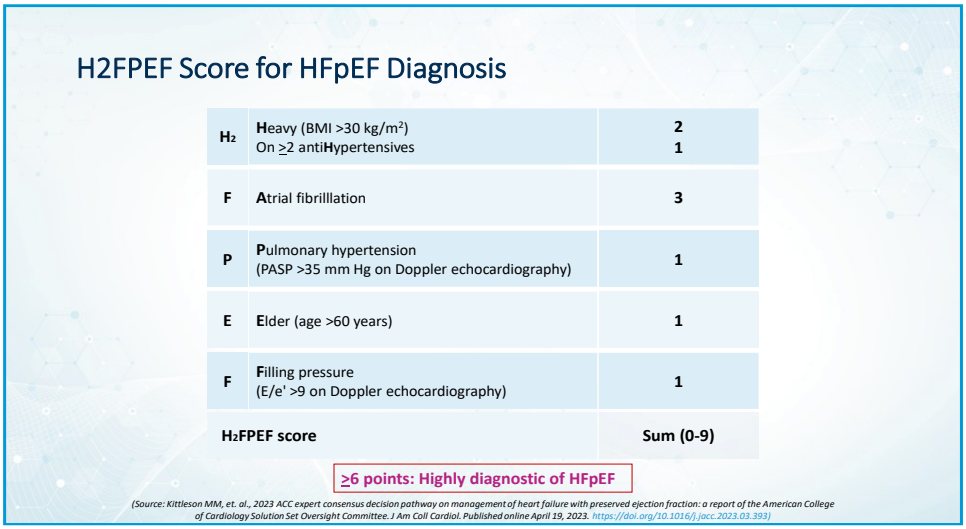
(Source: Kittleson MM, et,.al.. 2023 ACC expert consensus decision pathway on management of heart failure with preserved ejection fraction: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. Published online April 19, 2023. https://doi.org/10.1016/j.jacc.2023.03.393.)

Universal Definition of Heart Failure with HFpEF Considerations

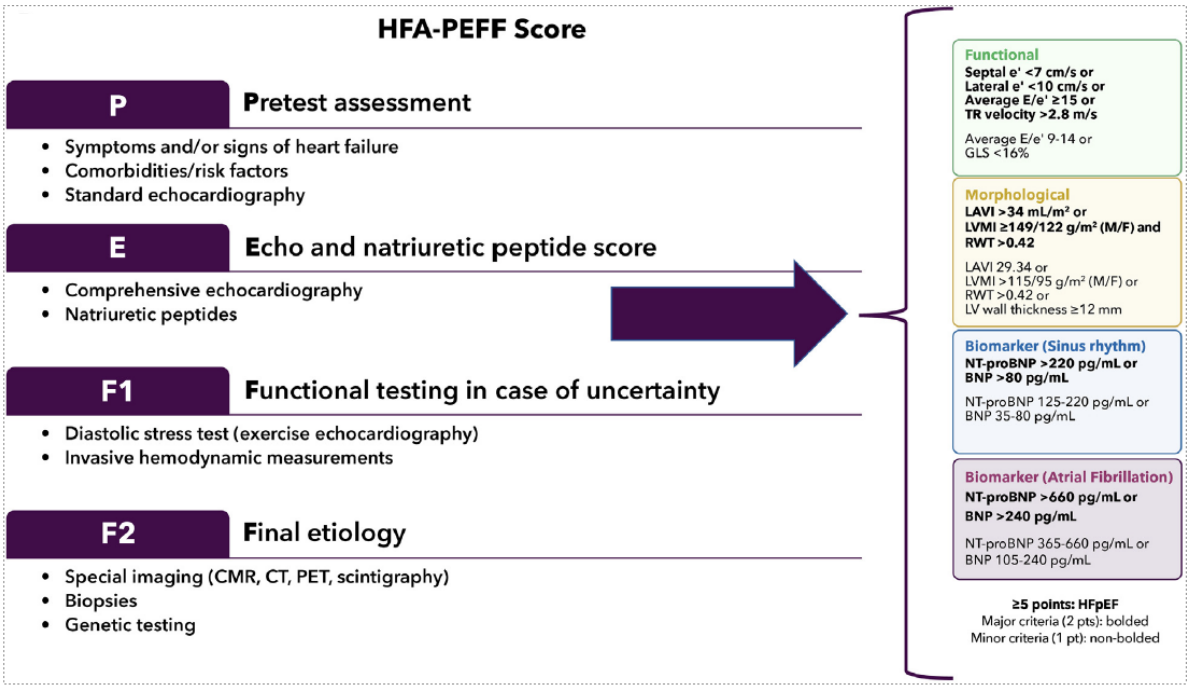


- Note your response in the space below and then discuss in the class.

H2FPEF Score for HFpEF Diagnosis

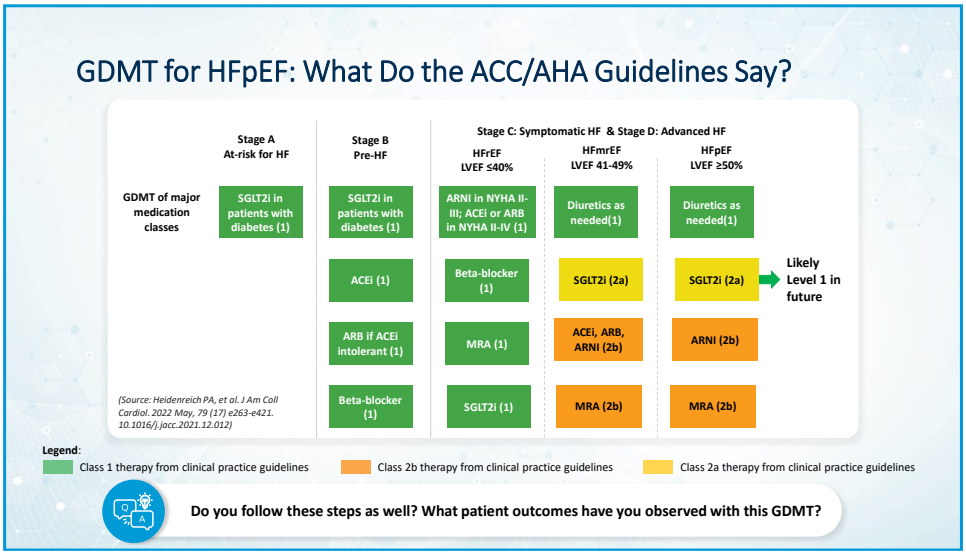


- In addition to the "universal definition" of heart failure that includes signs/symptoms in the setting of structural or function abnormality and elevated natriuretic peptides and/or evidence of congestion, several scores have been developed to enable clinicians to diagnose HFpEF. One of these is the H_2FPEF score.
- An alternate score for HFpEF diagnosis is HFAPEF, which is dependent on diagnostic test results.



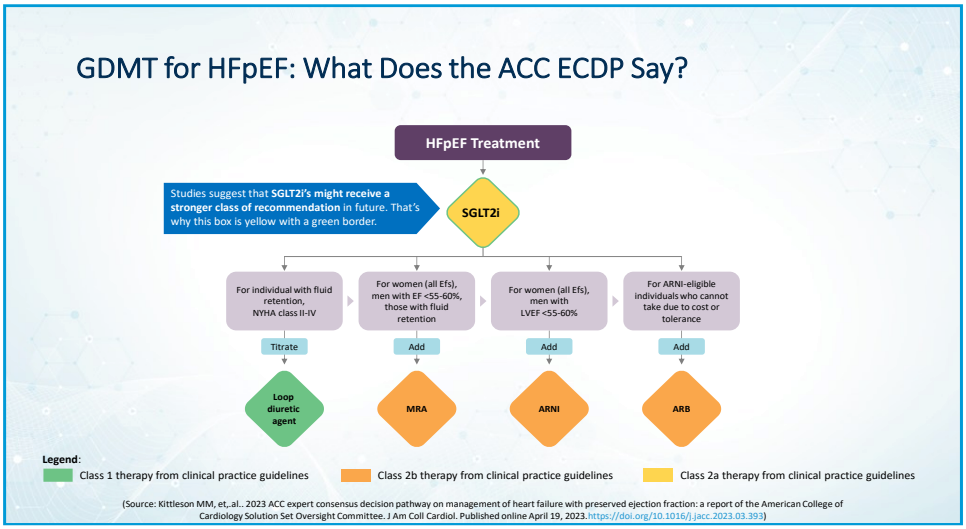
(Source: Kittleson MM, et. al., 2023 ACC expert consensus decision pathway on management of heart failure with preserved ejection fraction: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. Published online April 19, 2023. https://doi.org/10.1016/j.jacc.2023.03.393.)

GDMT for HFpEF: What Do the ACC/AHA Guidelines Say?



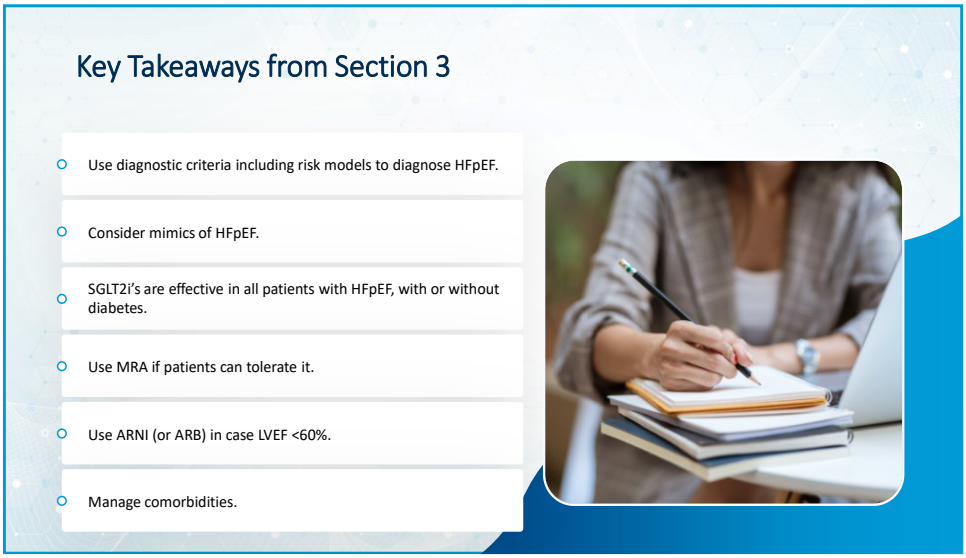
- This is the ACC/AHA-recommended GDMT for HFpEF. Are you aware of and following this GDMT for your HFpEF patients? If yes, what patient outcomes have you observed after this therapy?

GDMT for HFpEF: What Does the ACC Expert Consensus Decision Pathway (ECDP) Say?



- Contrast the earlier GDMT approach with the above ECDP-recommended treatment approach. Share your experience with this approach, if any.

Key Takeaways from Section 3



- Use the following space to note your learning from section 3.

Section 4: Time to Practice!

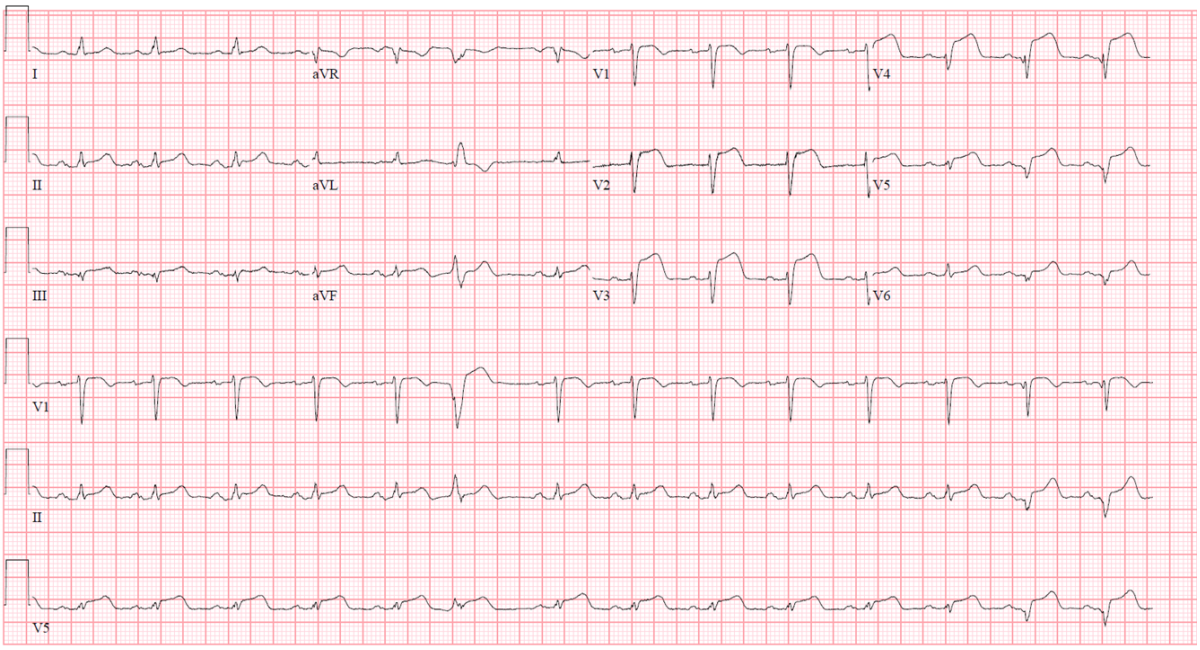
Patient Case 1: 64-Year-Old Man at the Emergency Department

Background: A 64-year-old man presents to the Emergency Department with sudden onset of chest pain, diaphoresis, nausea, and lightheadedness. He reports that he was attending his nephew's wedding, and the chest discomfort began while dancing but was not relieved with rest. Several family members who are physicians encouraged him to present for evaluation.

On arrival, he appears uncomfortable. His heart rate is 96 and regular, blood pressure 116/84, and oxygen saturation 94% on room air. He is 77 kg and 177 cm tall (body mass index (BMI) 24.6). On examination, he is diaphoretic with cool extremities. Cardiac examination shows a tachycardic regular rate and rhythm with S1 and S2 and a soft S4, II/VI systolic murmur at the apex, lungs with rales at the bases, abdomen flat, soft, and non-tender, and cool extremities with 1+ pulses in the groin and feet.

Past medical history: He has a past medical history of hypertension and was prescribed amlodipine 5 mg daily but reports that he does not take it daily but uses it only "when he feels he needs it". He had an elevated LDL two years ago but chose to manage it with diet.

His father died of a myocardial infarction at age 61 years, and his brother had bypass surgery at age 63 years. His ECG is as follows:



His blood test results are as follows:

Lab	Range	Value
Sodium	136-142 mEq/L	140
Potassium	3.5-5 mEq/L	4.0
BUN	8-23 mg/dL	27
Creatinine	0.6-1.2 mg/dL	1.6
WBC	4.5-11 X 10^3/mcL	5.4
Glucose	70-110 mg/dL	134
Hemoglobin	13.5 – 17.5 g/dL	13.9
Hematocrit	41-50%	39
Platelets	150-450 X 10^3/mcL	201
Troponin I High sensitivity	<0.4 ng/mL	1830
PT (INR)	10-13 sec	13 (1.1)
aPTT	25-40 sec	26

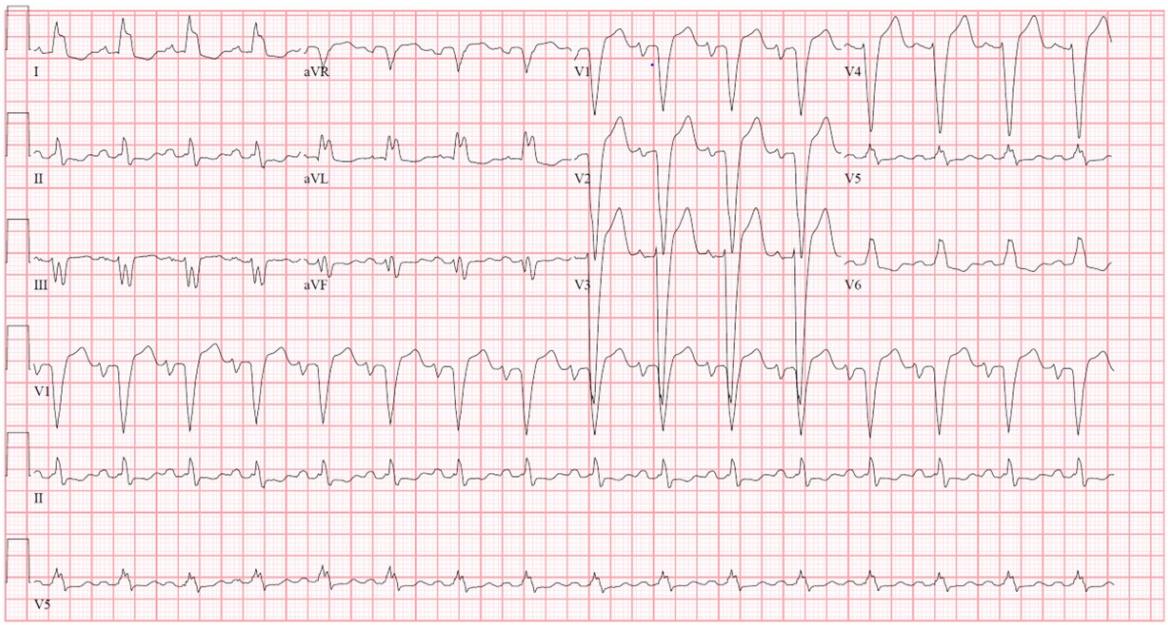
He received aspirin 325 mg chewed orally, prasugrel 60 mg orally X 1 dose, and heparin intravenously. He was then brought urgently to the catheterization laboratory.

His coronary angiogram reveals a 100% proximal left anterior descending artery lesion as well as a 50% mid-left circumflex lesion and a 60% mid-right coronary artery lesion.

He undergoes primary angioplasty of the left anterior descending artery with placement of a drug eluting stent. His catheterization laboratory course is complicated by an episode of sustained ventricular tachycardia requiring a single defibrillation shock. On arrival to the cardiac care unit (CCU), he is pain free but complains of shortness of breath.

A stat echocardiogram reveals an LVEF of 25% with mid to distal anterior and apical akinesis and moderate mitral regurgitation. He receives 40 mg IV furosemide and has 2.2 liters of urine output.

Telemetry reveals occasional PVCs, blood pressure 134/78, and heart rate 98 regular. His repeat ECG is as follows:



Labs Three Hours After Arrival in Cardiac Intensive Care Unit (CICU)

Lab	Range	Value
Sodium	136-142 mEq/L	138
Potassium	3.5-5 mEq/L	3.6
BUN	8-23 mg/dL	31
Creatinine	0.6-1.2 mg/dL	1.8
WBC	4.5-11 X 10^3/mcL	8.2
Glucose	70-110 mg/dL	149
Hemoglobin	13.5 – 17.5 g/dL	11.6
Hematocrit	41-50%	34
Platelets	150-450 X 10^3/mcL	179
Troponin I High sensitivity	<0.4 ng/mL	8,123
PT (INR)	10-13 sec	15.8 (16)
aPTT	25-40 sec	88

Question 1: In addition to aspirin 81 mg, prasugrel 10 mg daily, IV heparin, and metoprolol succinate 25 mg daily, what is the next best step in his management?

a) Lisinopril 5 mg daily
b) Amiodarone 400 mg three times daily
c) Enalaprilat 1.25 mg IV every 6 hours
d) Lidocaine 100 mg IV bolus then 1 mg/min IV
e) Amlodipine 5 mg daily

Note your response in the space below.

Follow-Up After 24 Hours

Over the next 24 hours, he reports feeling an improvement and is transferred out of the CICU to the telemetry unit.
His blood pressure is 127/72 mmHg, and his heart rate is 78 and regular.
His current medications include: lisinopril 5 mg daily, metoprolol succinate 25 mg daily, prasugrel 10 mg daily, aspirin 81 mg daily, and atorvastatin 80 m daily.
Repeat labs reveal BUN 26 mg/dL and creatinine 1.6 mg/dL.

Question 2: What is the next best step in the management of this patient?

a) Implant biventricular (BiV) pacemaker and implantable cardioverter-defibrillator (ICD).
b) Add spironolactone 25 mg daily and empagliflozin 10 mg daily.
c) Add diltiazem ER 120 mg daily.
d) Increase his dose of metoprolol succinate to 50 mg daily.

Note your response in the space below.

Follow-Up After Discharge

He is discharged home on day 4 on lisinopril 5 mg daily, metoprolol succinate 50 mg daily, spironolactone 25 mg daily, empagliflozin 10 mg daily, prasugrel 10 mg daily, aspirin 81 mg daily, and atorvastatin 80 mg daily. He is seen in the office one week after discharge. He reports that he has mild dyspnea on exertion with stairs but reports no chest pain, lightheadedness, or palpitations. He is feeling somewhat overwhelmed with his medications.

His blood pressure is 122/72 mmHg, and heart rate 72 and regular.

Question 3: What is the next best step in his management?

a) Discontinue lisinopril and after 36 hours start sacubitril/valsartan.
b) Add isosorbide mononitrate 30 mg once daily.
c) Increase empagliflozin to 25 mg daily.
d) Add hydralazine 10 mg every 8 hours and isosorbide dinitrate 10 mg every 8 hours.

Note your response in the space below.

Follow-Up Two Weeks Later

He is seen again in 2 weeks. He is tolerating his medications without side effects. He reports decreased dyspnea on exertion and has had no chest pain, lightheadedness, or syncope.

His medications: Sacubitril/valsartan 49/51 mg twice daily, metoprolol succinate 50 mg daily, spironolactone 25 mg daily, empagliflozin 10 mg daily, prasugrel 10 mg daily, aspirin 81 mg daily, and atorvastatin 80 mg daily

His vital signs: Blood pressure 98/72, heart rate 68 and regular

His repeat labs yield the following results:

Lab	Range	Value
Sodium	136-142 mEq/L	139
Potassium	3.5-5 mEq/L	4.4
BUN	8-23 mg/dL	24
Creatinine	0.6-1.2 mg/dL	1.4
WBC	4.5-11 X 10^3/mcL	6.1
Glucose	70-110 mg/dL	104
Hemoglobin	13.5 – 17.5 g/dL	13.1
Hematocrit	41-50%	39
Platelets	150-450 X 10^3/mcL	205
PT (INR)	10-13 sec	12 (1.1)
aPTT	25-40 sec	28

Question 4: What is the next best step in his management?

a) Add amlodipine 5 mg daily.
b) Add Omega-3 fatty acids daily.
c) Decrease sacubitril/valsartan to 24/26 mg (50 mg) twice daily.
d) No medication changes are required.

Note your response in the space below.

Follow-Up Three Months Later

The patient continues to do well and is enrolled in cardiac rehabilitation, which he tolerates without difficulty. His ECG is stable but he has occasional PVCs. He has mild dyspnea on exertion mostly with more than one flight of stairs. A repeat echocardiogram at three months reveals an LVEF of 40% with mild mitral regurgitation. His blood pressure at that visit is 98/70 mmHg with a heart rate of 64 beats/minute. His labs are stable from his last visit.

Question 5: What is the next best step in his management?

a) Place an ICD.
b) Place a biventricular pacemaker/ICD.
c) Continue current medications.
d) Reduce the dose of sacubitril/valsartan to 24/26 mg twice daily.

Note your response in the space below.

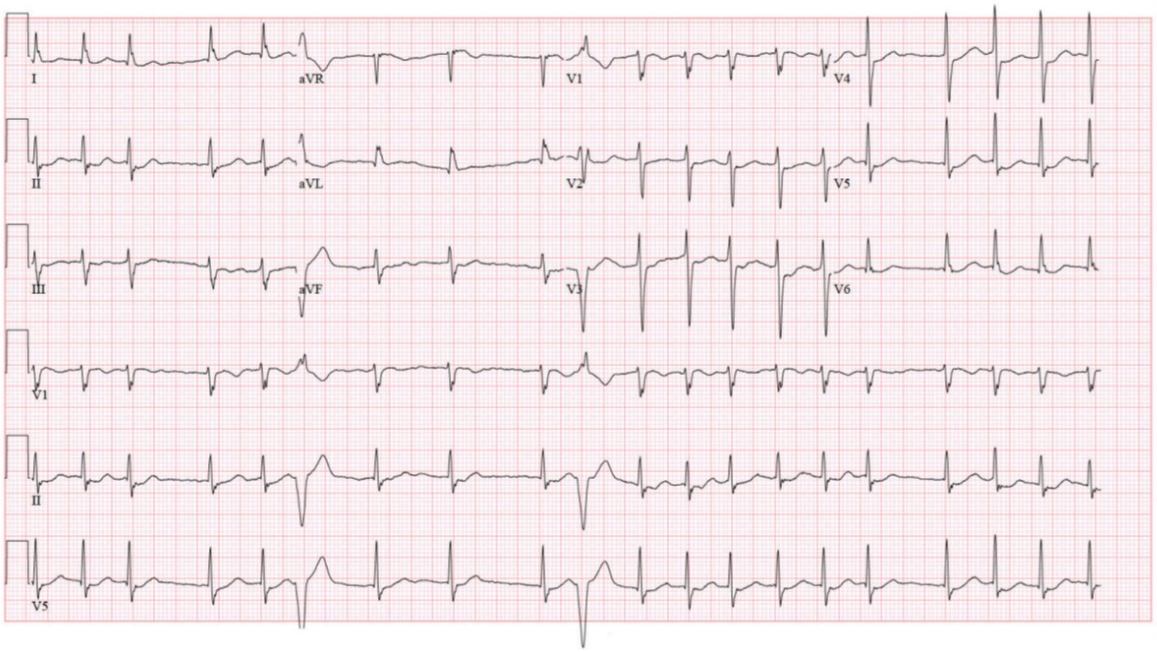
Patient Case 2: 46-Year-Old Woman at the Emergency Department

Background: A 46-year-old woman presents to the Emergency Department with about two days of increasing shortness of breath and palpitations. She was diagnosed with a non-ischemic cardiomyopathy about four years ago following a respiratory illness and has been managed with enalapril 10 mg twice daily, carvedilol 12.5 mg twice daily, and furosemide 40 mg daily.

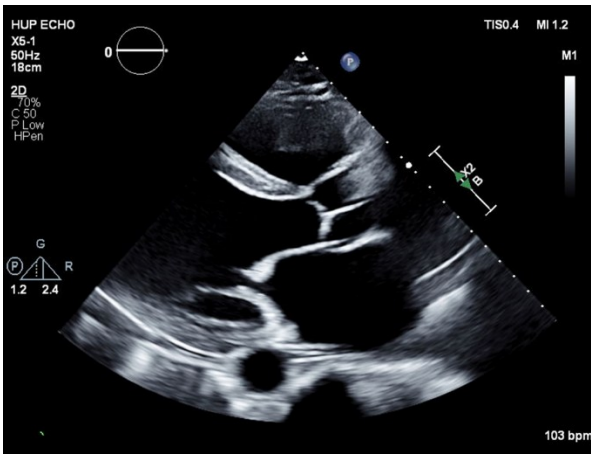
On arrival, she appears comfortable at rest but anxious. Her heart rate is 124 and irregular, blood pressure 131/84, and oxygen saturation 97% on room air. She is 64 kg and 160 cm tall (BMI 25). On examination, she is warm. Cardiac examination reveals a tachycardic irregular rate and rhythm with S1 and S2, II/VI systolic murmur at the apex, lungs clear, abdomen flat, soft, and non-tender, and cool extremities with 2+ pulses in the groin and feet. She has 1+ to 2+ peripheral edema.

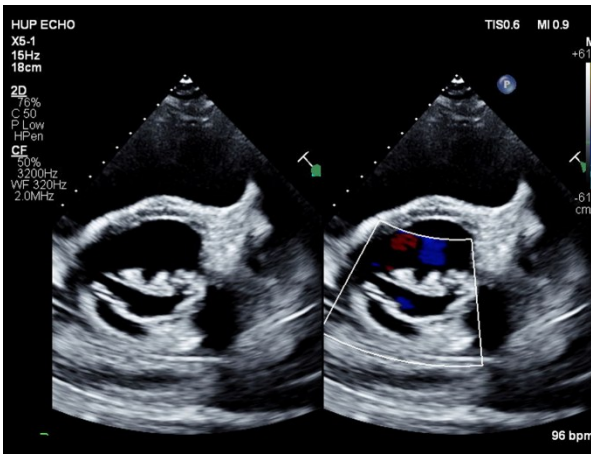
Past medical history: She has a history of a non-ischemic cardiomyopathy that was diagnosed four years ago when she presented with cough and fever and was diagnosed with a lobar pneumonia. Her LVEF was 40% with mild mitral regurgitation. A coronary angiogram was normal. Thyroid and iron studies were normal.

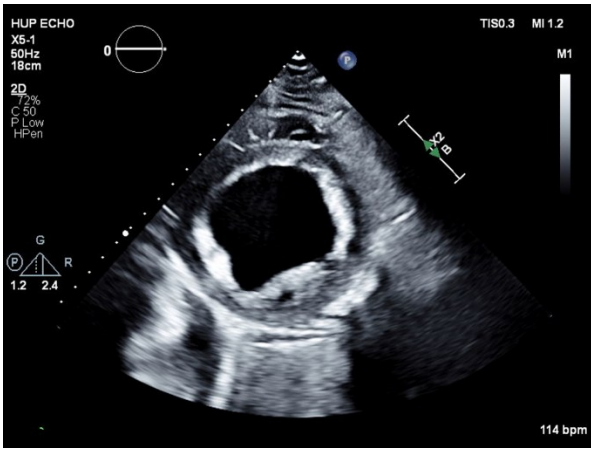
Her paternal uncle died of heart failure at 49 years and a cousin also had heart failure. Her paternal grandmother died “young” at the age of 36 years but the details are not known. She has two children aged 17 and 20 years, both of whom have no known medical conditions. Her ECG, labs, and ECHO tests are as follows:

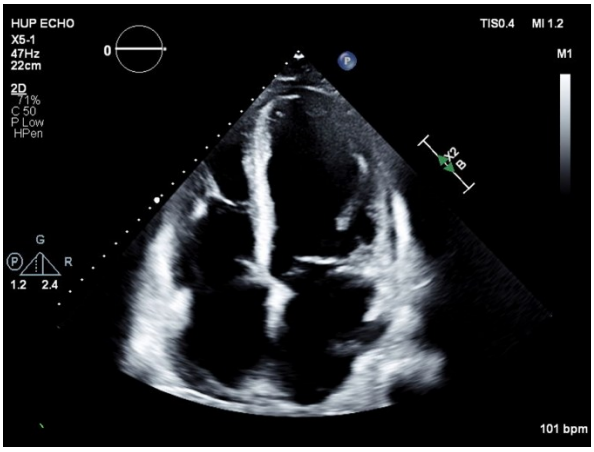


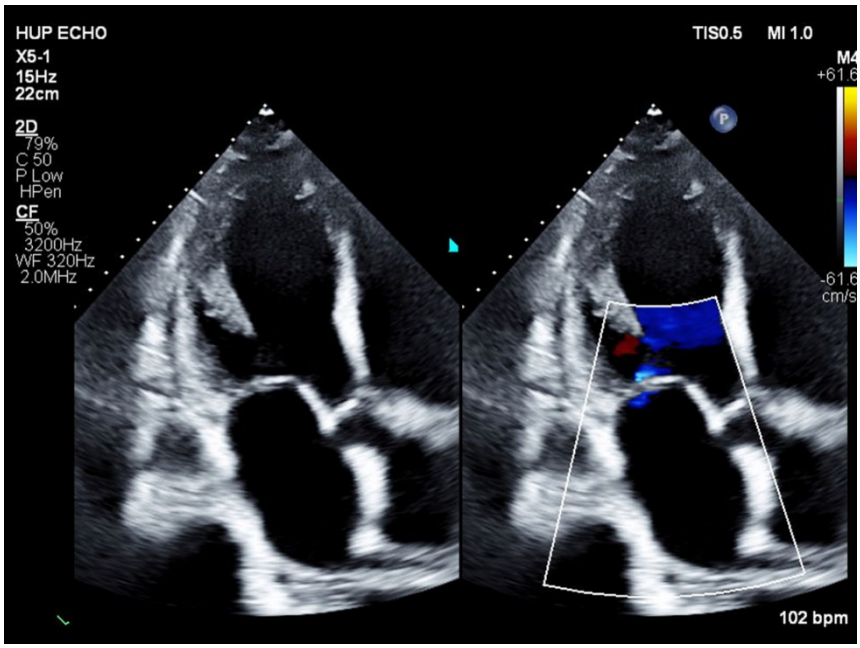
Lab	Range	Value
Sodium	136-142 mEq/L	141
Potassium	3.5-5 mEq/L	3.8
BUN	8-23 mg/dL	18
Creatinine	0.6-1.2 mg/dL	1.1
WBC	4.5-11 X 10^3/mcL	6.8
Glucose	70-110 mg/dL	98
Hemoglobin	13.5 – 17.5 g/dL	12.1
Hematocrit	41-50%	36
Platelets	150-450 X 10^3/mcL	168
Troponin I High sensitivity	<0.4 ng/mL	0.2
PT (INR)	10-13 sec	11 (1.0)
aPTT	25-40 sec	28
NT-Pro-BNP	<450 pg/mL	8562











The patient's echocardiogram revealed:

- Moderately dilated left ventricle with an LVEF of 10% with global hypokinesis
- Right ventricle top normal in size with moderate to severe decreased systolic function
- Severely dilated left atrium and moderately dilated right atrium
- Restricted mitral valve leaflet mobility with moderate mitral regurgitation
- Mild tricuspid regurgitation with a pulmonary artery systolic pressure of 30 mm Hg

She receives 40 mg IV furosemide and heparin IV. Over the next few hours, she produces only 500 cc of urine and notes ongoing dyspnea. She is started on amiodarone 400 mg every eight hours and receives 80 mg IV furosemide. She is admitted to the hospital and continues to have dyspnea with any activity. Her urine output over the next eight hours is 400 cc. Telemetry reveals atrial fibrillation with a ventricular response of 104 to 128 beats/minute and occasional PVCs. Her blood pressure is 101/65 mm Hg, heart rate 116 beats/minute and irregular, and pulse oximetry 98% on 2 liters oxygen via nasal cannula.

Her next set of lab results are as follows:

Lab	Range	Value
Sodium	136-142 mEq/L	137
Potassium	3.5-5 mEq/L	3.6
BUN	8-23 mg/dL	29
Creatinine	0.6-1.2 mg/dL	1.6
WBC	4.5-11 X 10^3/mcL	8.1
Glucose	70-110 mg/dL	99
Hemoglobin	13.5 – 17.5 g/dL	12.3
Hematocrit	41-50%	37
Platelets	150-450 X 10^3/mcL	154
Troponin I High sensitivity	<0.4 ng/mL	0.2
PT (INR)	10-13 sec	12 (1.0)
aPTT	25-40 sec	70
NT-Pro-BNP	<450 pg/mL	10522
TSH	0.5-5 milliunits/L	3.8

Question 1: What is the next best step in her management

a) Discontinue enalapril and start sacubitril/valsartan 49/51 (100 mg) twice daily.
b) Increase carvedilol to 25 mg twice daily.
c) Discontinue carvedilol and start metoprolol succinate 100 mg daily.
d) Perform transesophageal echocardiogram and, if appropriate, electrical cardioversion.

Note your response in the space below.

Further Investigations

She undergoes an emergent transesophageal echocardiogram that reveals no evidence of left atrial thrombus. She then undergoes a successful electrical cardioversion that restores normal sinus rhythm.

Over the next four hours, she produces one liter of urine and reports improved dyspnea. Her blood pressure is 116/84 and heart rate 78 beats/minute and regular. Her oxygen saturation is 97% on room air. Now her lab results are as follows:

Lab	Range	Value
Sodium	136-142 mEq/L	137
Potassium	3.5-5 mEq/L	3.2
BUN	8-23 mg/dL	24
Creatinine	0.6-1.2 mg/dL	1.4
WBC	4.5-11 X 10^3/mcL	7.8
Glucose	70-110 mg/dL	92
Hemoglobin	13.5 – 17.5 g/dL	11.9
Hematocrit	41-50%	34
Platelets	150-450 X 10^3/mcL	161
Troponin I High sensitivity	<0.4 ng/mL	0.4
PT (INR)	10-13 sec	13 (1.1)
aPTT	25-40 sec	75
NT-Pro-BNP	<450 pg/mL	9854

Question 2: In addition to continuing the heparin, amiodarone and carvedilol, what is the next best step in her management?

a) Add spironolactone 25 mg daily
b) Increase enalapril to 20 mg twice daily
c) Start furosemide infusion at 1 mg/min after an 80 mg IV bolus
d) Start lidocaine infusion at 1 mg/min following 150 mg bolus

Note your response in the space below.

Next 48 Hours

Over the next 48 hours, she continues to improve and produces 3.8 liters of urine. She notes markedly improved symptoms and denies any lightheadedness or palpitations when ambulating. Telemetry reveals normal sinus rhythm with rare premature ventricular contractions.

Her blood pressure is 110/70 mm Hg and heart rate 74 beats/minute and regular.

Her medications: Enalapril 10 mg twice daily, carvedilol 12.5 mg twice daily, spironolactone 25 mg daily, amiodarone 400 mg, IV heparin, and furosemide 40 mg daily

Her revised lab results:

Lab	Range	Value
Sodium	136-142 mEq/L	140
Potassium	3.5-5 mEq/L	3.6
BUN	8-23 mg/dL	18
Creatinine	0.6-1.2 mg/dL	1.0
WBC	4.5-11 X 10^3/mcL	6.2
Glucose	70-110 mg/dL	89
Hemoglobin	13.5 – 17.5 g/dL	12.2
Hematocrit	41-50%	36
Platelets	150-450 X 10^3/mcL	189
Troponin I High sensitivity	<0.4 ng/mL	0.2
PT (INR)	10-13 sec	12 (1.0)
aPTT	25-40 sec	71
NT-Pro-BNP	<450 pg/mL	1020

Question 3: What is the next best step in her management?

a) Change carvedilol to metoprolol succinate 100 mg daily.
b) Stop enalapril and 36 hours later start sacubitril/valsartan 49/51 (100 mg) twice daily.
c) Start empagliflozin 10 mg daily.
d) Start digoxin 0.125 mg daily.

Note your response in the space below.

Post-Discharge Follow-Up

She is discharged home on enalapril 10 mg twice daily, carvedilol 12.5 mg twice daily, spironolactone 25 mg daily, amiodarone 200 mg daily, apixaban 5 mg twice daily, and furosemide 40 mg daily.
She returns to the office one week after discharge. She reports no palpitations and only mild dyspnea on exertion with stairs and inclines.
An ECG reveals normal sinus rhythm. Her blood pressure is 118/74 mm Hg and heart rate 72 beats/minute and regular.

Question 4: What is the next best step in her management?

a) Stop enalapril and 36 hours later start sacubitril/valsartan 49/51 (100 mg) twice daily.
b) Refer for atrial fibrillation ablation.
c) Discontinue apixaban.
d) Stop enalapril and start amlodipine 5 mg daily.

Note your response in the space below.

Subsequent Developments

She returns to the clinic 3 months later and repeat echocardiogram reveals an LVEF of 35%. She reports feeling well with the exception of intermittent orthostatic hypotension. On examination, her neck veins are flat and she has no peripheral edema but she is warm with normal pulses.

Her labs are stable with the exception of a BUN of 28 mg/dL and creatinine of 1.5 mg/dL. Her NT-ProBNP is 208 pg/mL.

The furosemide is discontinued, and she is reminded to monitor her weights and symptoms closely. Over the next two years, she reports only mild dyspnea on exertion and has no recurrence in atrial fibrillation or volume overload.

Her medications include sacubitril/valsartan 49/51 mg (100 mg) twice daily, carvedilol 25 mg twice daily, spironolactone 25 mg daily, and empagliflozin 10 mg daily.

Three months after her last visit, she is seen in the setting of lightheadedness and fatigue. She is found to have a blood pressure of 92/73 mm Hg with a creatinine of 1.9 mg/dL and a BUN of 31 mg/dL. On examination, she has peripheral edema and elevated jugular venous pressure.

The dose of sacubtril/valsartan is reduced to 24/26 mg (50 mg) twice daily, and furosemide 40 mg was added back to her regimen.

She is seen two weeks later with worsening symptoms and ongoing hypotension. Her blood pressure is 94/74 mm Hg and heart rate 84 beats/minute and regular.

Her ECG reveals a normal sinus rhythm with non-specific ST and T-wave abnormalities and is unchanged.

A repeat echocardiogram reveals an LVEF of 25% with moderate mitral regurgitation. Her lab results turn out as follows:

Lab	Range	Value
Sodium	136-142 mEq/L	132
Potassium	3.5-5 mEq/L	5.1
BUN	8-23 mg/dL	41
Creatinine	0.6-1.2 mg/dL	2.1
WBC	4.5-11 X 10^3/mcL	9.0
Glucose	70-110 mg/dL	98
Hemoglobin	13.5 – 17.5 g/dL	11.8
Hematocrit	41-50%	34
Platelets	150-450 X 10^3/mcL	168
Troponin I High sensitivity	<0.4 ng/mL	0.4
PT (INR)	10-13 sec	12 (1.0)
aPTT	25-40 sec	27
NT-ProBNP	<450 pg/mL	6349

Question 5: What is the next best step in her management?

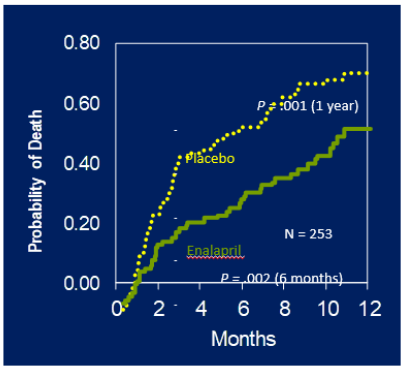
a) Stop sacubitril/valsartan and start hydralazine 25 mg three times daily and isosorbide dinitrate 10 mg three times daily.
b) Refer for mitral valve transcatheter edge to edge repair.
c) Refer to an advanced heart failure center.
d) Stop carvedilol and start metoprolol succinate 50 mg daily.

Note your response in the space below.

Appendix A: Clinical Studies Related to Heart Failure Therapy

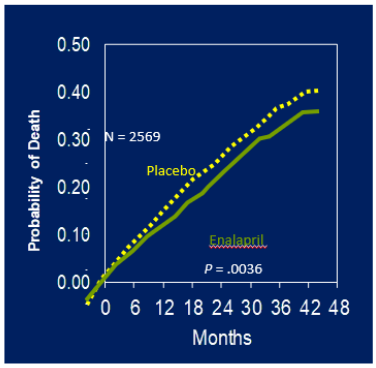
ACE Inhibitors–Mortality Benefit HFrEF

CONSENSUS



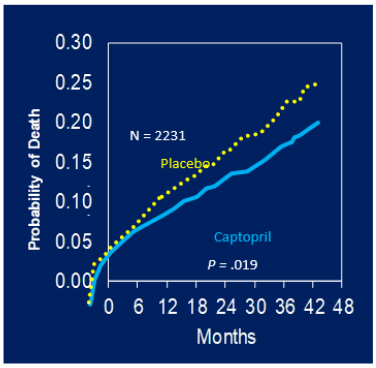
Mortality: ↓ 31%

SOLVD



Mortality: ↓ 16%

SAVE



Mortality: ↓ 19%

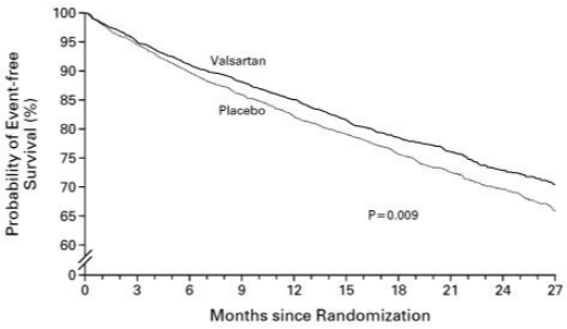
(Sources: CONSENSUS Trial Study Group. N Engl J Med. 1987;316:1429-1435; Pfeffer MA, et al. N Engl J Med 1992;327:669-677; SOLVD Investigators, et al. N Engl J Med. 1991;325:293-302)

ACE Inhibitor Dosing

Mechanism of Action	Drug	Initial Daily Dose(s)	Max Dose(s)	Mean RCT Dose
Inhibit the conversion of angiotensin I to angiotensin II and upregulate bradykinin, thereby counteracting the overactivation of the RMS system and the effects of adverse cardiac remodeling.	Captopril	6.25mg TID	50mg TID	122.7mg QD
	Enalapril	2.5mg BID	10–20mg BID	16.6mg QD
	Fosinopril	5–10mg QD	40mg QD	NA
	Lisinopril	2.5–5mg QD	20–40mg QD	32.5–35.0mg QD
	Perindopril	2mg QD	8–16mg QD	NA
	Quinapril	5mg BID	20mg BID	NA
	Ramipril	1.25–2.5mg QD	10mg QD	NA
	Trandolapril	1mg QD	4mg QD	NA

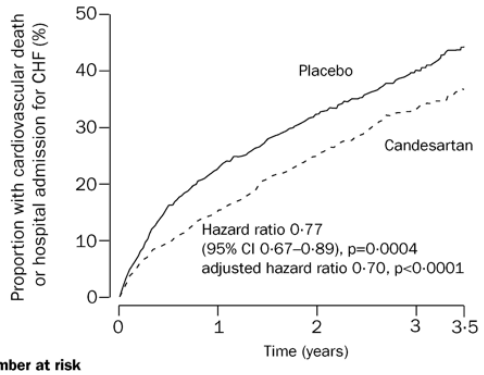
ARB

ValHeft



Probability of Freedom from the Combined End Point (Death from Any Cause, Cardiac Arrest with Resuscitation, Hospitalization for Worsening Heart Failure, or Therapy with Intravenous Inotropes or Vasodilators).

CHARM-Alternative



Number at risk

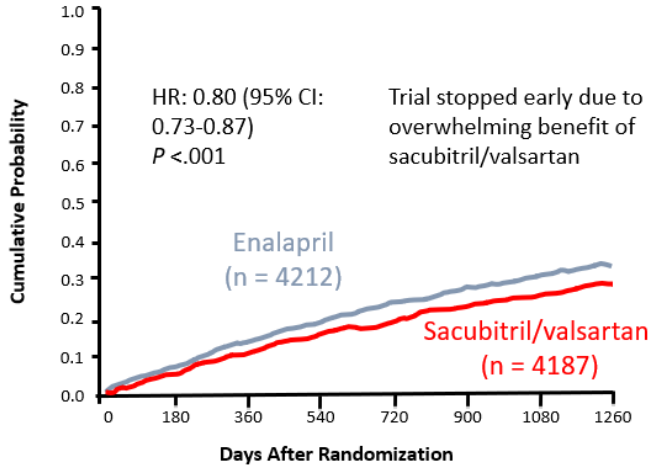
Candesartan	1013	929	831	434	122
Placebo	1015	887	798	427	126

(Sources: N Engl J Med 2001; 345:1667-1675; Lancet, Volume 362, Issue 9386, 6 September 2003, Pages 772-776)

ARB Dosing

Mechanism of Action	Drug	Initial Daily Dose(s)	Max Dose(s)	Mean RCT Dose
Inhibits angiotensin II AT1 receptors, thereby counteracting the overactivation of the RAAS system and the effects of adverse cardiac remodeling	Candesartan	4–8mg QD	32mg QD	24mg QD
	Losartan	25–50mg QD	50–150mg QD	129mg QD
	Valsartan	20–40mg BID	160mg BID	254mg QD

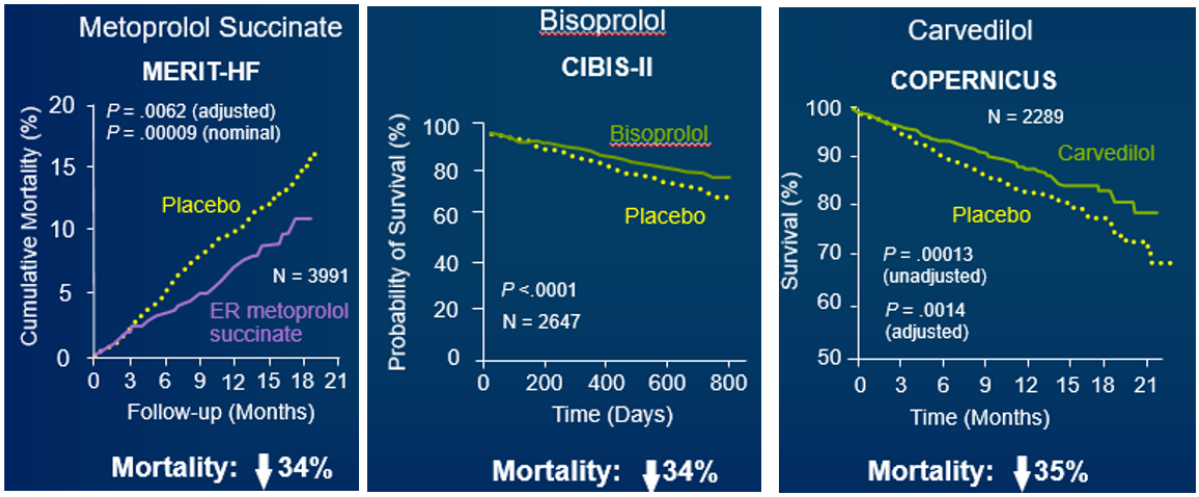
PARADIGM-HF–Reduction in CV Death or HF Hospitalization with Sacubitril/Valsartan



(Source: McMurray. N Engl J Med. 2014;371:993. Yancy. Circulation. 2016;134:e282)

- Lower rates of discontinuation with sacubitril/valsartan due to AEs (P = .03) or renal impairment (P = .002)
- More symptomatic hypotension with sacubitril/valsartan (P <.001)
- Similar rates of angioedema, but:
  - Do not use with a history of angioedema.
  - Discontinue an ACE inhibitor for ≥36 hours before starting.
- Possibility of raised BNP levels but not NT-proBNP levels

Beta-Blockers–Mortality Benefit in HFrEF



(Sources: CIBIS-II Investigators and Committees. *Lancet*. 1999;353:9-13; MERIT-HF Study Group; *Lancet.* 1999;353:2001-2007; Packer M, et al. *N Engl J Med*. 2001;344:1651-1658)

Effects of β-Blockade on Mortality

US carvedilol program[1] 1094 patients (Class II–IV)	**Carvedilol**	**All-cause mortality** ↓ 65% (*P*<0.001)
BEST[2] 2708 patients (Class III–IV)	**Busindilol**	↓ 10% (*P*=0.109, NS)
CIBIS-II Trial HF[3] 2647 patients (Class III–IV)	**Bisoprolol**	↓ 34% (*P*<0.0001)
MERIT-HF[4] 3991 patients (Class II–IV)	**Metoprolol Succinate**	↓ 34% (*P*=0.0062)
COPERNICUS[5] 2000 patients (Class IV)	**Carvedilol**	↓ 35% (*P*=0.00014)

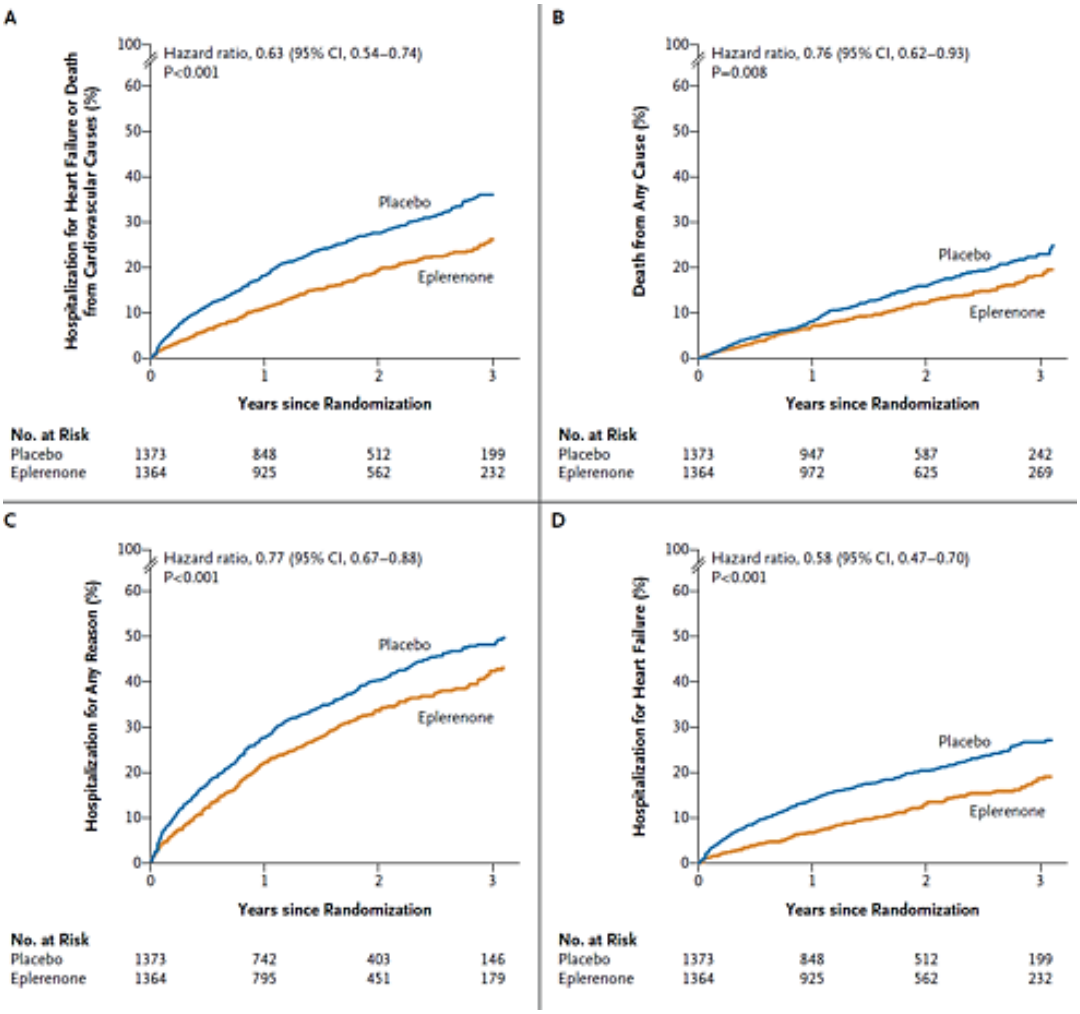
Once considered taboo in the treatment of heart failure, β-blockers have recently demonstrated significant reductions in mortality and improved survival in clinical trials involving >12,000 patients with NYHA functional class II–IV[1-5].

1. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med.* 1996;334:1349-1355.
2. Progress in clinical trials. *Clin Cardiol.* 2000;23:56-58.
3. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet.* 1999;353:9-13.
4. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet.* 1999;353:2001-2007.
5. Beta-blockers under-used in heart failure. *SCRIP World Pharmaceutical News.* 2000;2572:20.

MRA: Spironolactone/Eplerenone

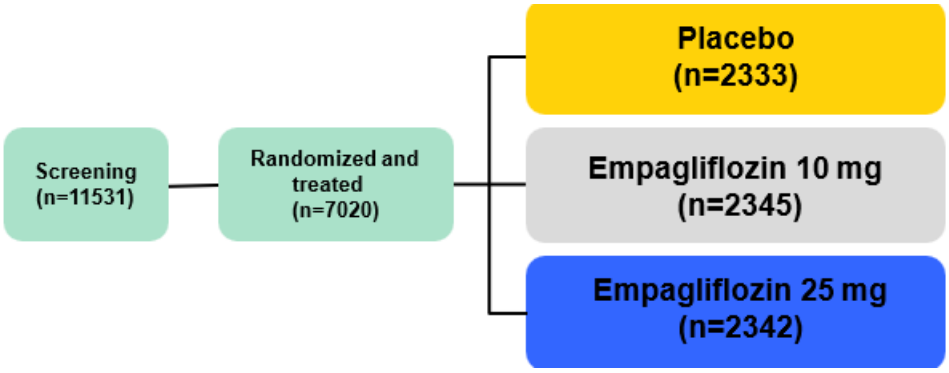
Benefits:

- Improved mortality for class IIIB or class IV patients (Reference: RALES trial)
- Creatinine <2.5 in men, <2.0 in women, potassium <5.0
- More recent studies with eplerenone showed benefits in NYHA class II to IV. It is contraindicated if the patient is on both ACE and ARB due to the risk of hyperkalemia.



(Source: N Engl J Med 2011;364:11-21)

EMPA-REG OUTCOME – Trial Design



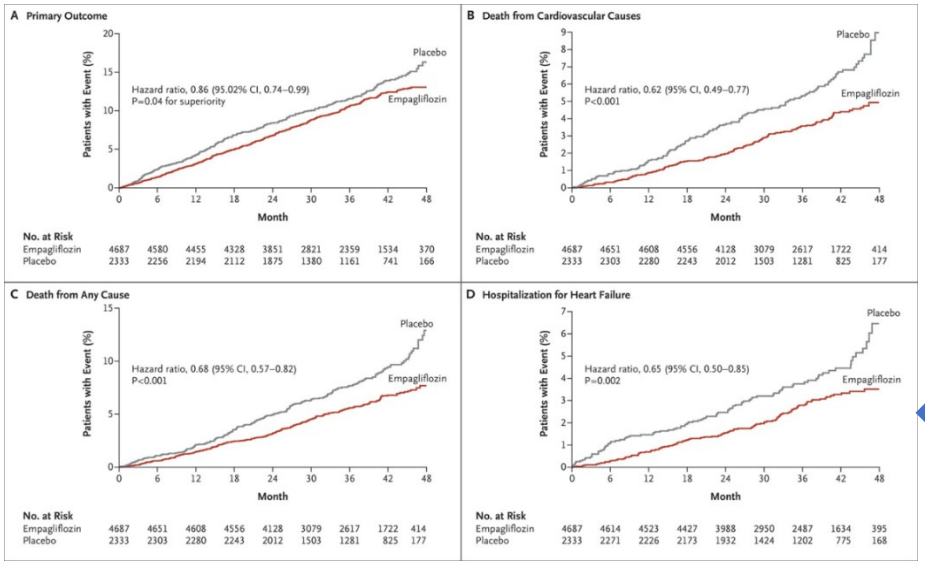
(Source: Zinman B et al. N Engl J Med 2015 [Epub ahead of print])

Key inclusion criteria:

- Adults with type 2 diabetes and established CVD
- BMI ≤45 kg/m2; HbA1c 7-10%; eGFR ≥30 mL/min/1.73m2 (MDRD)
- 10.2% of patients enrolled with pre-existing heart failure

Outcomes:

- **Primary outcome**: Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The primary outcome occurred in a significantly lower percentage of patients in the empagliflozin group (490 of 4,687 [10.5%]) than in the placebo group (282 of 2,333 [12.1%]) (hazard ratio in the empagliflozin group, 0.86; 95.02% confidence interval [CI], 0.74 to 0.99; P<0.001 for **noninferiority** and P=0.04 for **superiority**)
- **Key secondary outcome**: Primary outcome plus hospitalization for unstable angina. The key secondary outcome occurred in 599 of 4,687 patients (12.8%) in the empagliflozin group and 333 of 2,333 patients (14.3%) in the placebo group (hazard ratio, 0.89; 95% CI, 0.78 to 1.01; P<0.001 for **noninferiority** and P=0.08 for superiority).
- **Primary hypothesis**: Noninferiority for the primary outcome



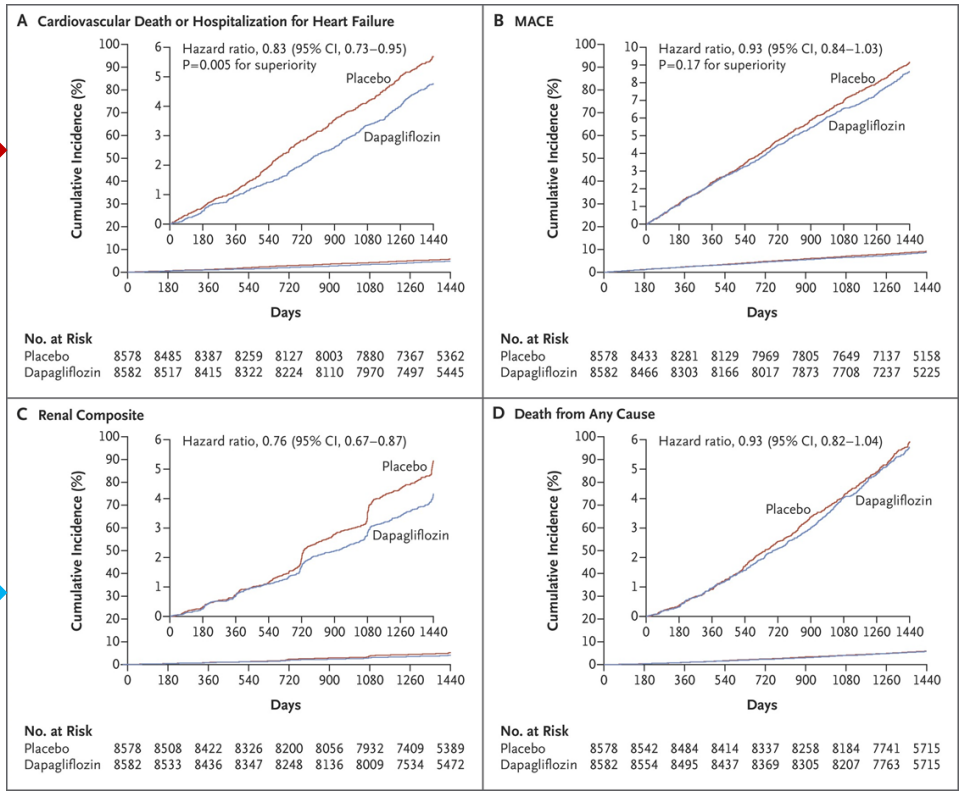
(Source: N Engl J Med. 2015 Nov 26;373(22):2117-28)

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes (DECLARE–TIMI 58)

This was a randomized trial of patients with type 2 diabetes, treatment with dapagliflozin, which did not result in a higher or lower rate of cardiovascular death, myocardial infarction, or stroke than a placebo. But it resulted in a lower rate of hospitalization for heart failure.

Cardiovascular

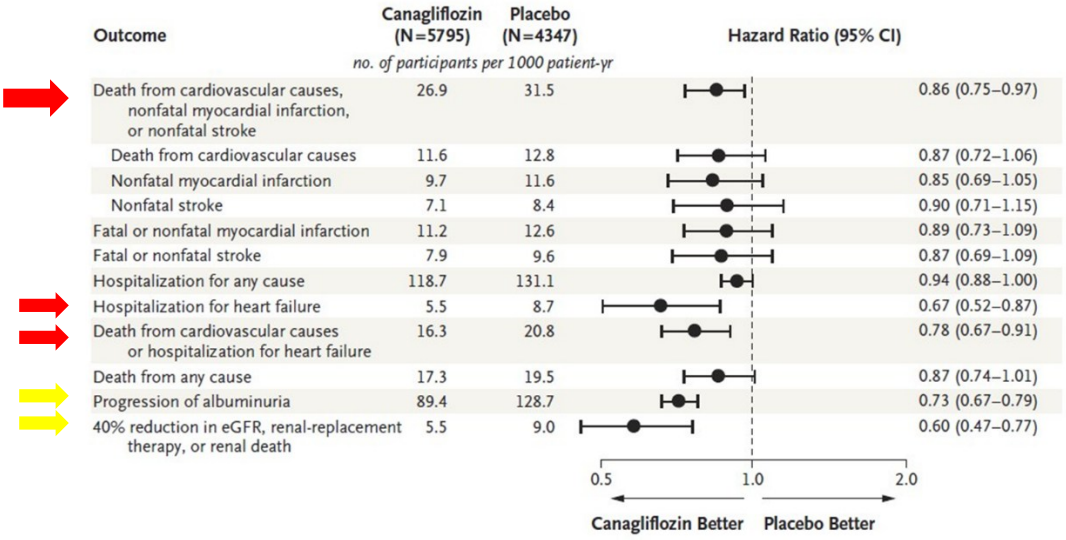
Renal



(Source: Wiviott SD et al. N Engl J Med 2019;380:347-357)

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes (CANVAS)

- Patients with type 2 diabetes at risk for cardiovascular disease received the SGLT2i canagliflozin or a placebo and were followed for 188 weeks.
- Canagliflozin reduced the risk of cardiovascular events.

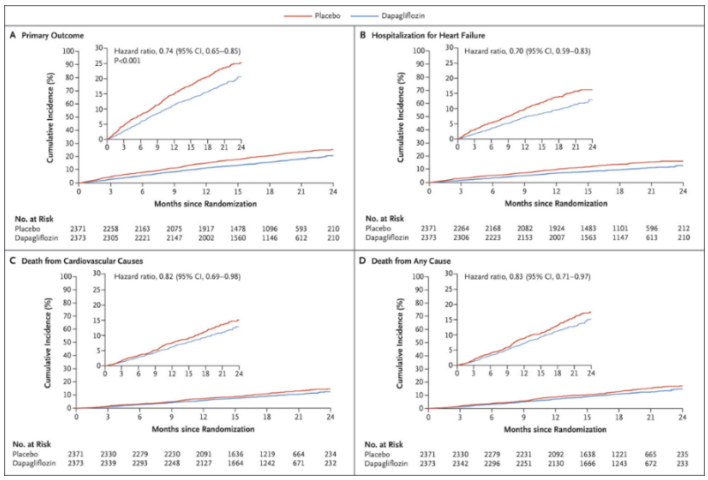


Outcome	Canagliflozin (N=5795)	Placebo (N=4347)	Hazard Ratio (95% CI)
	no. of participants per 1000 patient-yr		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	26.9	31.5	0.86 (0.75–0.97)
Death from cardiovascular causes	11.6	12.8	0.87 (0.72–1.06)
Nonfatal myocardial infarction	9.7	11.6	0.85 (0.69–1.05)
Nonfatal stroke	7.1	8.4	0.90 (0.71–1.15)
Fatal or nonfatal myocardial infarction	11.2	12.6	0.89 (0.73–1.09)
Fatal or nonfatal stroke	7.9	9.6	0.87 (0.69–1.09)
Hospitalization for any cause	118.7	131.1	0.94 (0.88–1.00)
Hospitalization for heart failure	5.5	8.7	0.67 (0.52–0.87)
Death from cardiovascular causes or hospitalization for heart failure	16.3	20.8	0.78 (0.67–0.91)
Death from any cause	17.3	19.5	0.87 (0.74–1.01)
Progression of albuminuria	89.4	128.7	0.73 (0.67–0.79)
40% reduction in eGFR, renal-replacement therapy, or renal death	5.5	9.0	0.60 (0.47–0.77)

(Source: Neal B, Perkovic V, Mahaffey KW, et. al. 2017, N Engl J Med, Vol. 377, pp. 644-57)

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction (DAPA-HF)

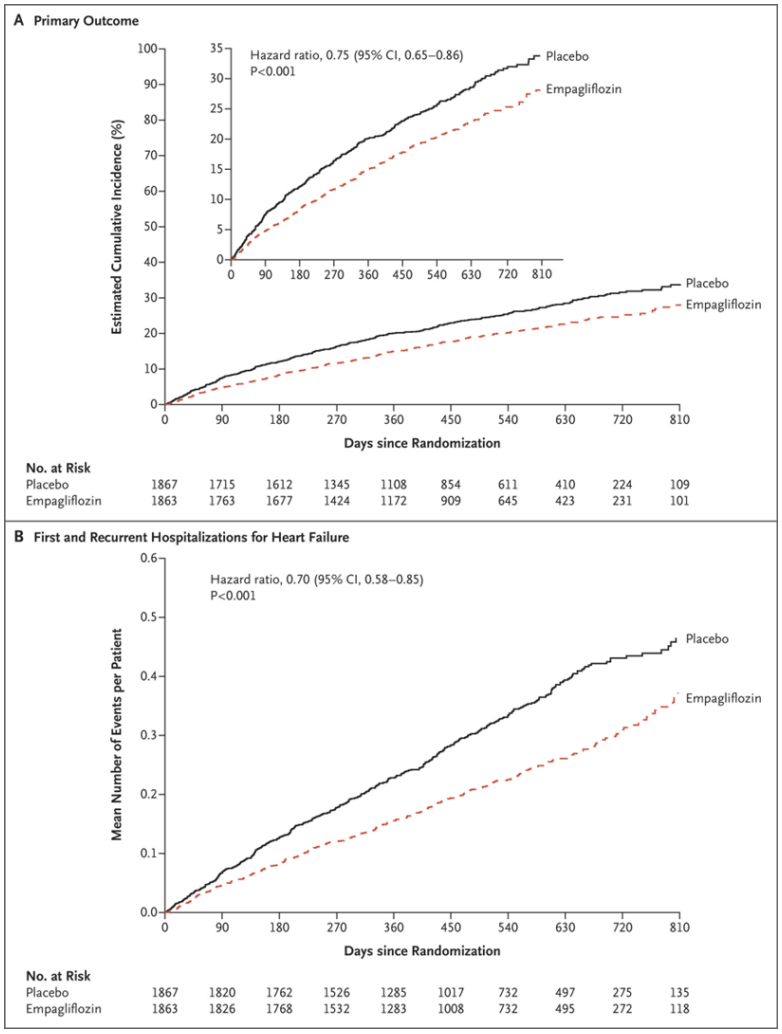
- Randomized, placebo-controlled trial evaluating the effects dapagliflozin in patients with HFrEF with or without type 2 diabetes
- The risk of worsening heart failure or cardiovascular death was lower among those who received dapagliflozin, regardless of the presence or absence of diabetes.



(Source: McMurray JJV et al. N Engl J Med 2019;381:1995-2008)

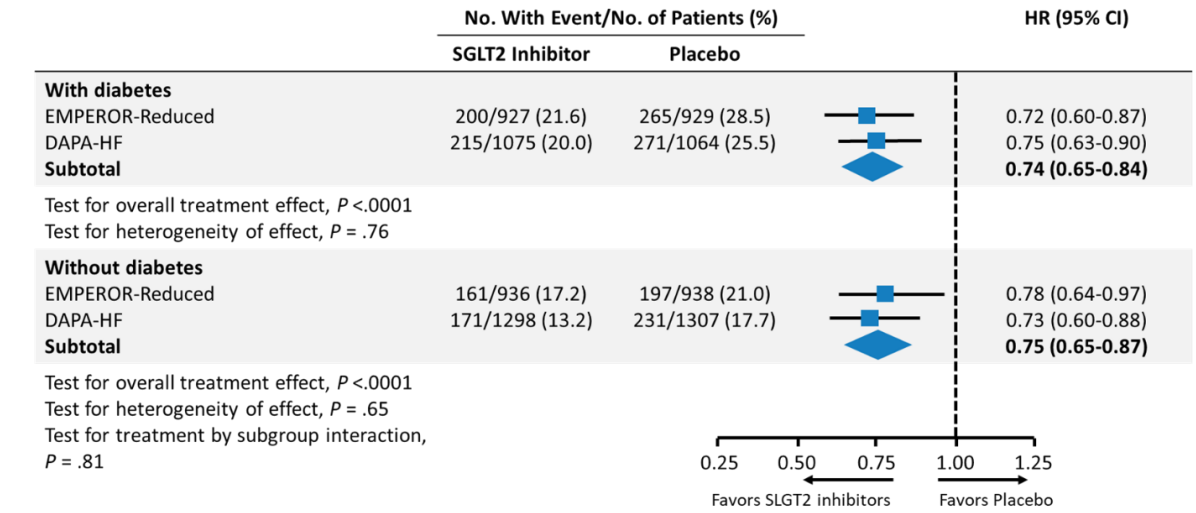
EMPEROR-REDUCED Trial

- Double-blind trial—randomly assigned 3,730 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive empagliflozin (10 mg once daily) or a placebo in addition to recommended therapy.
- The primary outcome was a composite of cardiovascular death or hospitalization for worsening heart failure.
- Those in the empagliflozin group had a lower risk of cardiovascular death or hospitalization for heart failure than those in the placebo group, regardless of the presence or absence of diabetes.



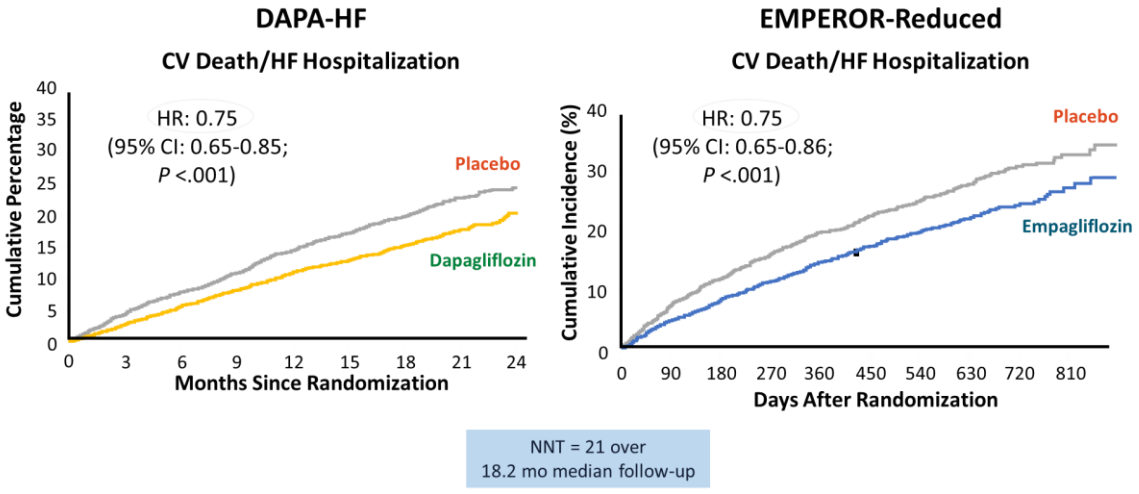
(Source: N Engl J Med 2020; 383:1413-1424)

EMPEROR-Reduced and DAPA-HF: Reduction in HF Hospitalization or Cardiovascular Death With SGLT2i in HFrEF With or Without Diabetes



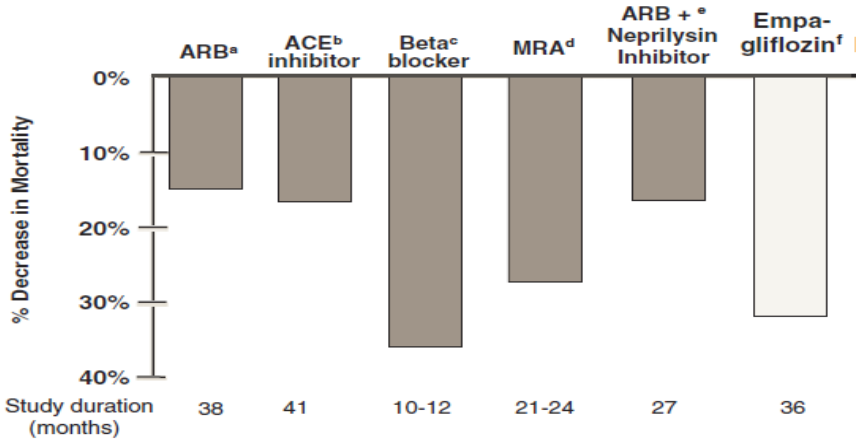
Zannad. Lancet. 2020;396:819.

Similar Results for both Agents (Dapagliflozin and Empagliflozin)



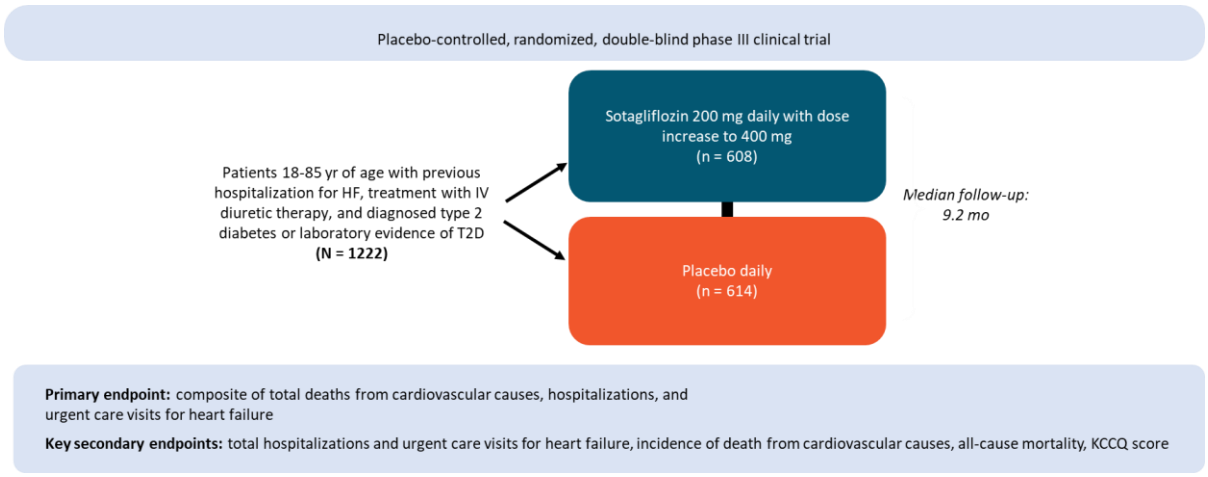
(Source: McMurray. NEJM. 2019;381:1995. Packer. NEJM. 2020;383:1413)

Comparison of Mortality Reduction in HF Trials with EMPA-REG Trial in Patients with Diabetes



(Source: **European Journal of Heart Failure (2017) 19, 43–53)**

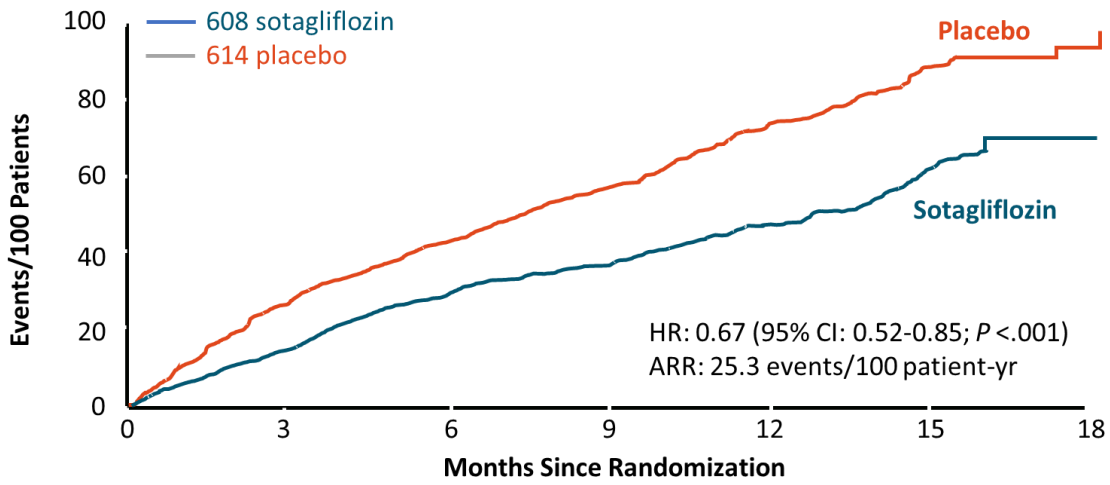
SOLOIST-WHF: Efficacy of Sotaglifozin in Heart Failure with Diabetes



Sotagliflozin is a non-selective SGLT-1 and SGLT-2 inhibitor. **Both renal and GI receptors are inhibited**.

(Source: Solomon. NEJM. 2022;387:1089)

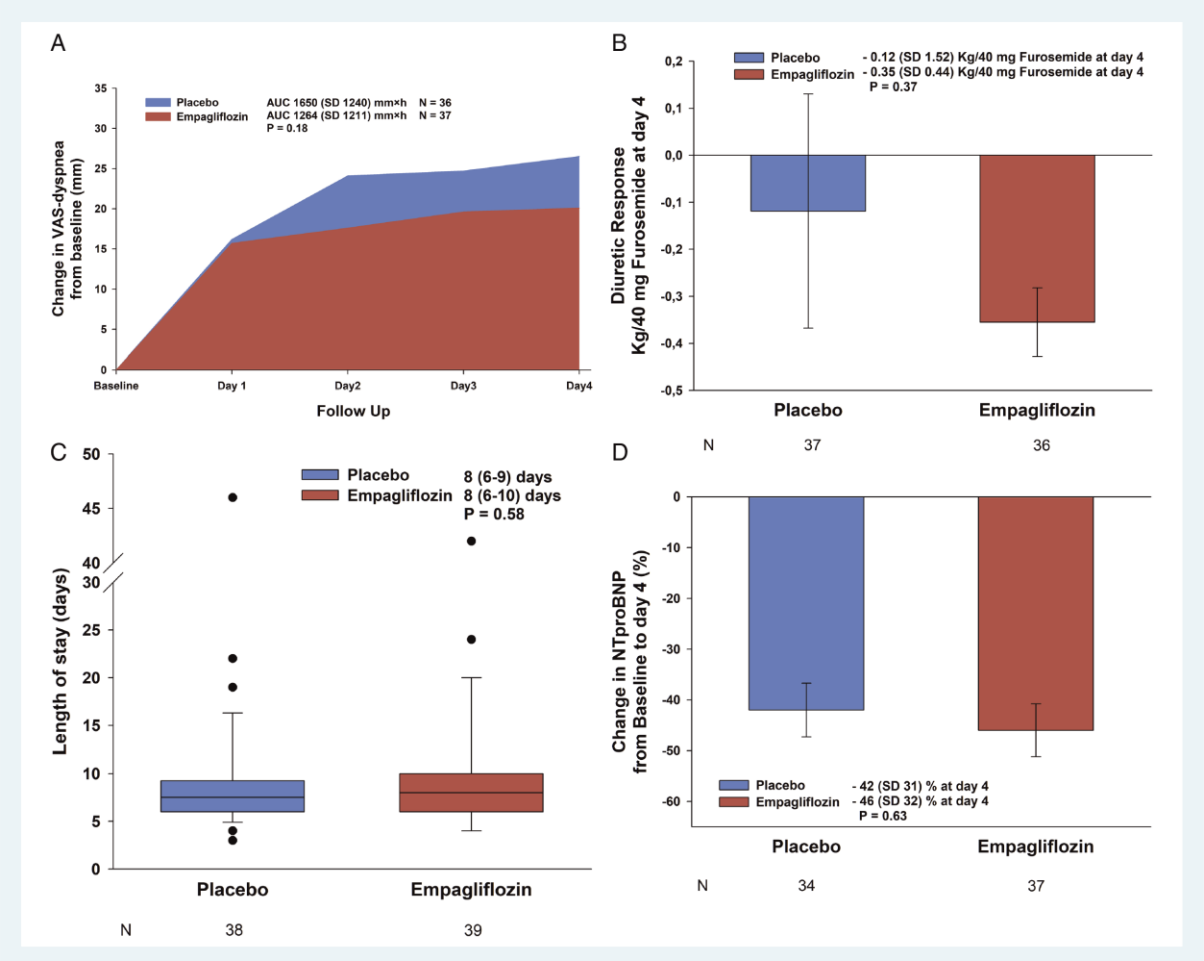
Total Deaths from Cardiovascular Causes, Hospitalizations, and Urgent Care Visits for Heart Failure

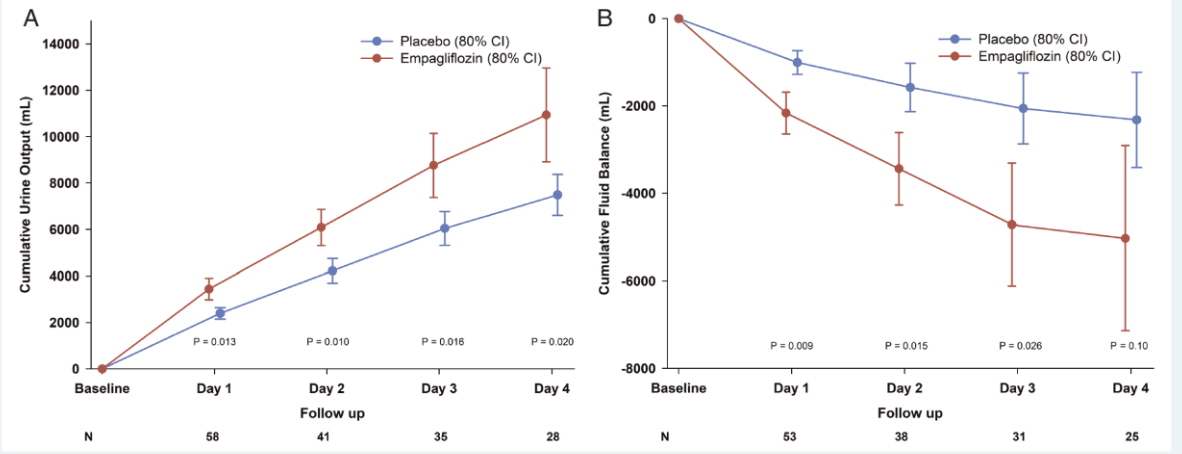


(Source: Bhatt. NEJM. 2021;384:117)

EMPA-RESPONSE-AFH Trial

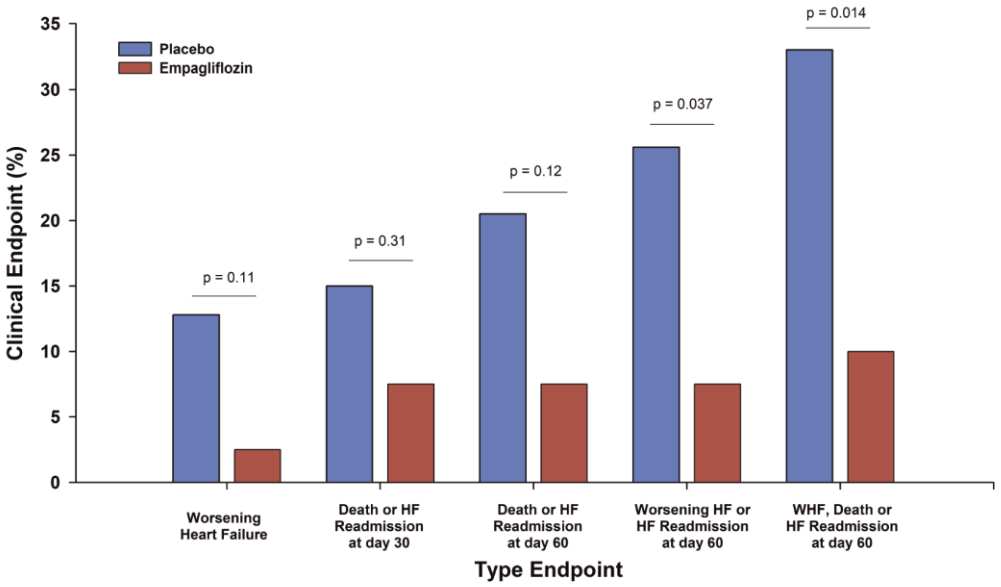
- Randomized, placebo-controlled, double-blind, parallel group, multicenter pilot study
- Randomized 80 acute heart failure patients with and without diabetes to either empagliflozin 10 mg/day or placebo for 30 days
- Primary outcomes: Change in visual analogue scale (VAS) dyspnea score, diuretic response (weight change per 40 mg furosemide), change in NT-proBNP, and length of hospital stay
- Secondary outcomes: Safety and clinical endpoints





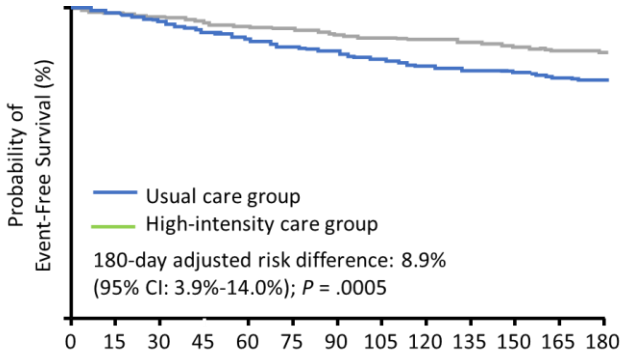
(Source: Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF). Eur J Heart Fail. 2020 Apr;22(4):713-722. doi: 10.1002/ejhf.1713. Epub 2020 Jan 7. PMID: 31912605)

Empagliflozin vs. Placebo in Acute Heart Failure



(Source: Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF). Eur J Heart Fail. 2020 Apr;22(4):713-722. doi: 10.1002/ejhf.1713. Epub 2020 Jan 7. PMID: 31912605)

STRONG-HF: All-Cause Mortality

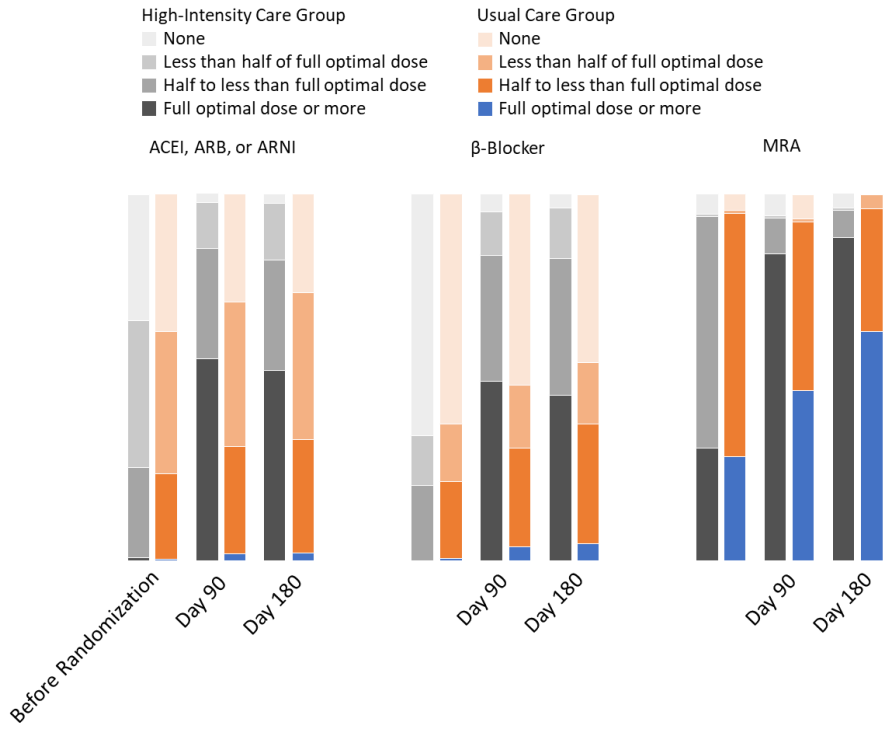


More patients in the high-intensity group felt better and lived longer.

- NYHA class I/II at 90 days: 83% vs. 67%
- Primary endpoint of reduction in death/heart failure hospitalization at 180 days: 15% vs. 23%
- Driven by heart failure hospitalization: 9.5% vs. 17%

The trial was terminated early due to a larger than expected difference in groups; withholding an intensive treatment strategy would be unethical.

Target GDMT Doses in High-Intensity vs. Usual Care



More patients in the high-intensity group received target GDMT doses at 90 days.

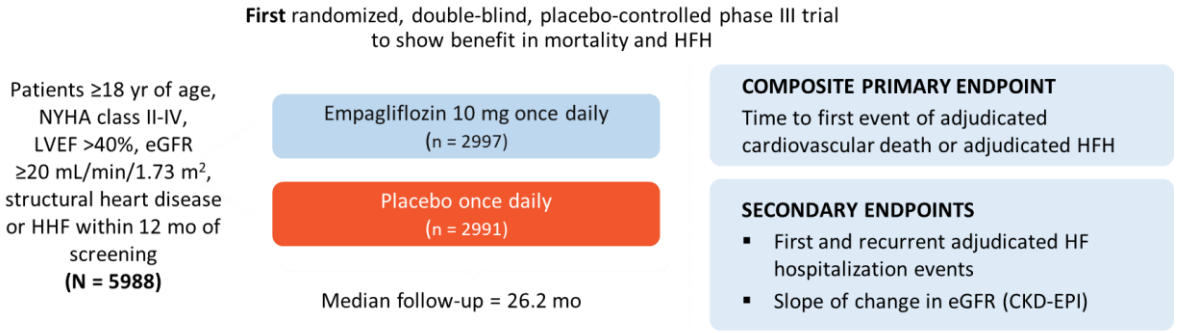
- ARNI/ACEI/ARB: 55% vs. 2%
- β-blocker: 49% vs. 4%
- MRA: 84% vs. 46%

(Source: Mebazaa. Lancet. 2022;400:P1938)

Extension of SGLT-2 Inhibitors

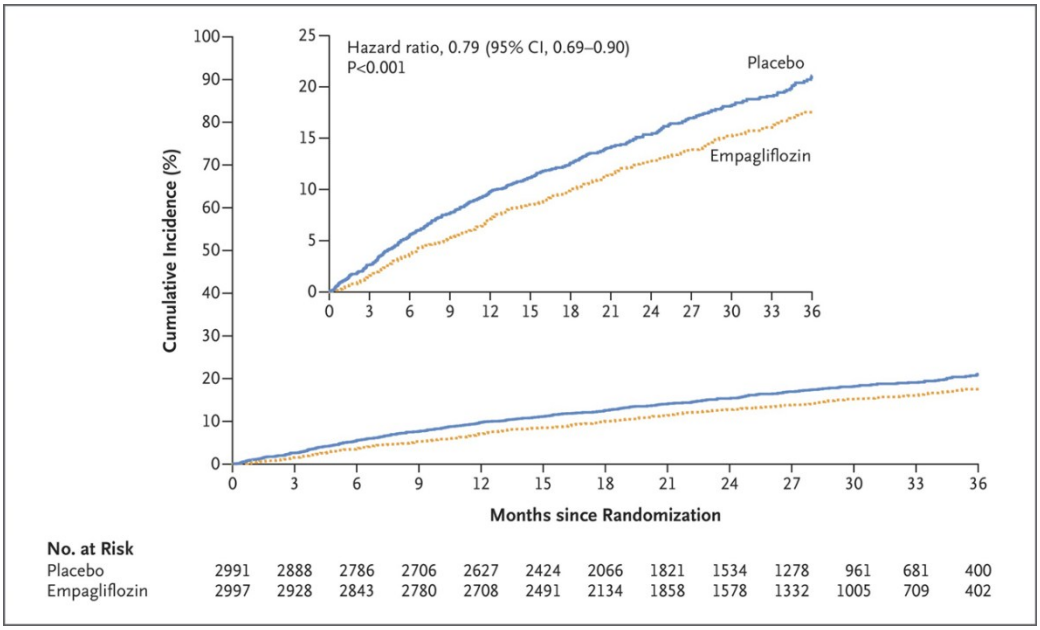
- TOP CAT trial
  - Benefit seen with spironolactone for patients with HFpEF
  - Controversial trial: Benefit seen in North America and Western Europe but not Georgia/Eastern Europe
- EMPEROR PRESERVED trial
  - First randomized clinical trial to show benefits in mortality and hospitalization
  - Major change in the management of HFpEF
- DELIVER-HF trial
  - Second randomized trial to show benefits in mortality and hospitalization

EMPEROR-Preserved: Empagliflozin for Treatment of HFpEF in Addition to SoC, Regardless of Patients' Diabetes Mellitus Status



(Source: Anker. NEJM. 2021;385:1451)

EMPEROR Preserved: Primary Outcome, a Composite of Cardiovascular Death or Hospitalization for Heart Failure



(Source: Anker SD et al. N Engl J Med 2021;385:1451-1461)

PRESERVED-HF: Dapagliflozin in HFpEF (Pilot)

Placebo-controlled, randomized, multicenter phase IV clinical trial

Patients ≥19 yr of age, NYHA class II-IV and EF ≥45%, NT-proBNP ≥225 pg/mL or BNP ≥75 pg/mL; patients with atrial fibrillation must have BNP ≥100 pg/mL or NT-proBNP ≥375 pg/mL
(N = 324)

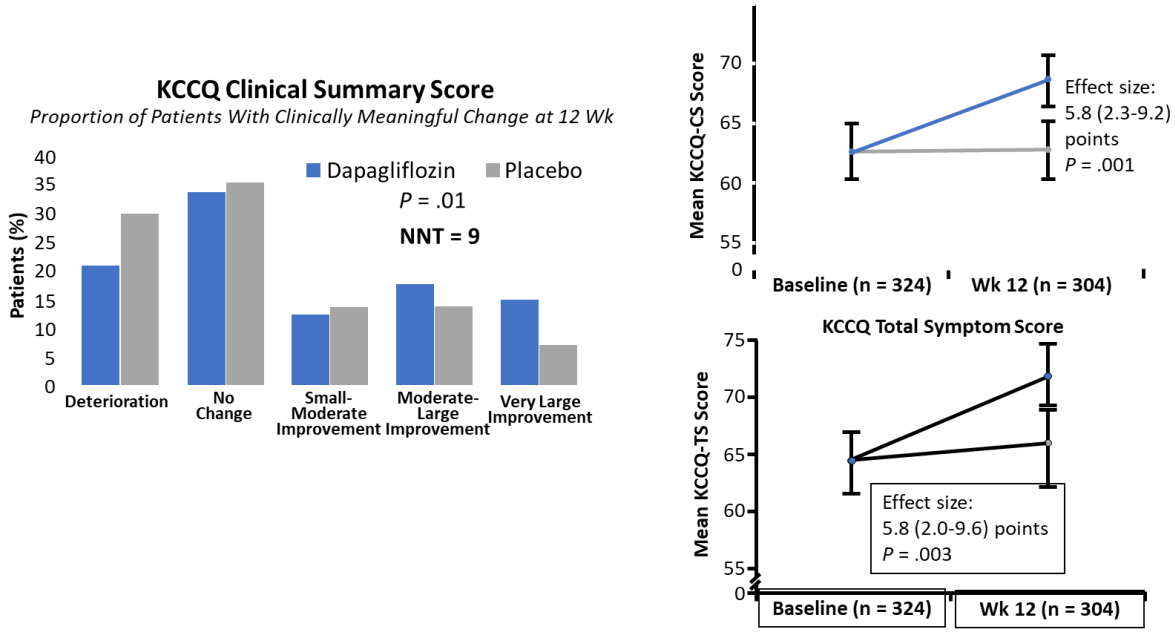
Dapagliflozin 10 mg daily for 12 wk (n = 162)

Placebo 10 mg daily for 12 wk (n = 162)

Primary endpoint: total symptom score of KCCQ

Key secondary endpoints: 6-min walk test, KCCQ Overall Summary Score, clinically relevant changes in KCCQ-CS and -OS, change from baseline in weight, natriuretic peptides, glycated hemoglobin, and systolic blood pressure

Dapagliflozin improved the KCCQ Clinical Summary Score.



(Source: Nassif. Nat Med. 2021;27:1954)

DELIVER: Dapagliflozin for Patients with HFpEF

Placebo-controlled, randomized, double-blind, international, multicenter phase III clinical trial

Patients ≥40 yr of age, stabilized HF, LVEF ≥40%, evidence of SHD, elevated natriuretic peptide level; patients with prior LVEF ≤40% were eligible if LVEF ≥40% at enrollment **(N = 6263)**

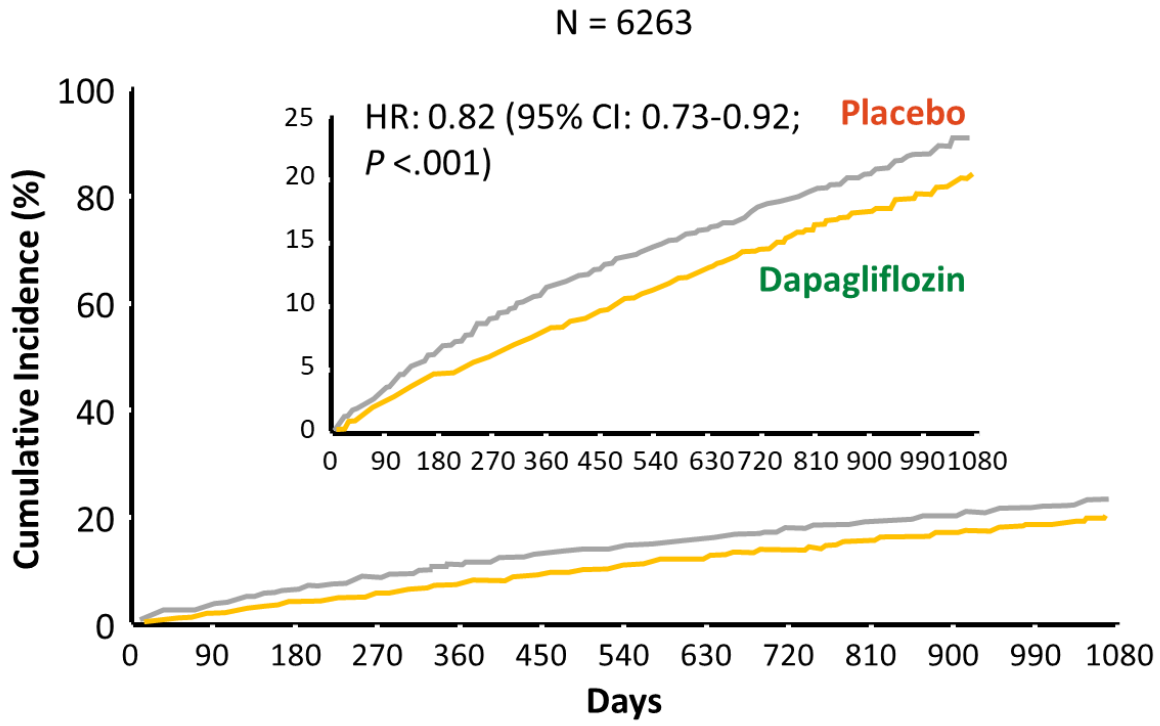
Dapagliflozin 10 mg daily + usual therapy (n = 3131)

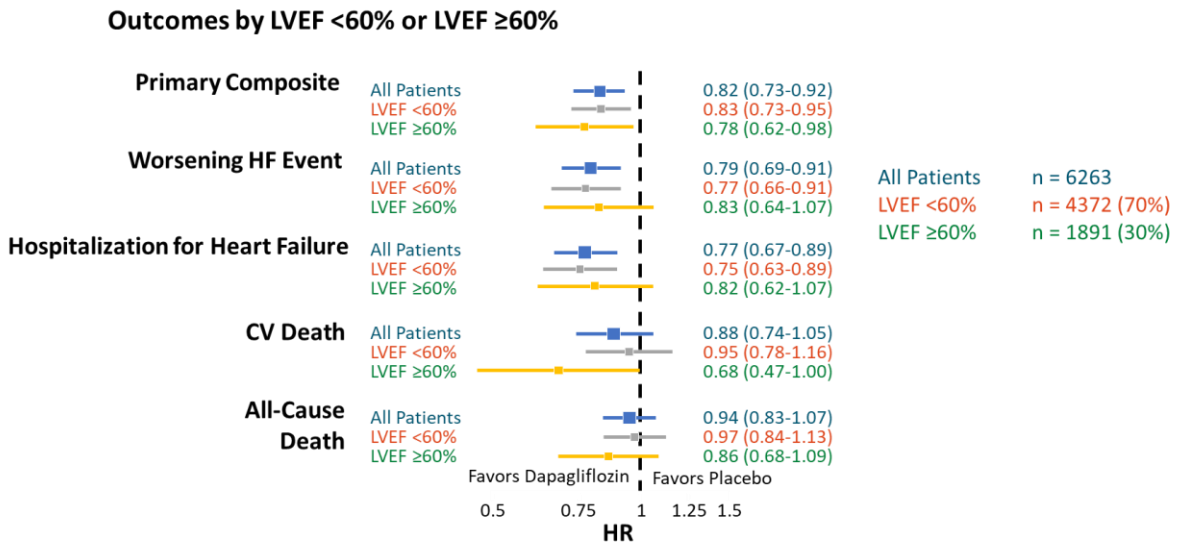
Placebo 10 mg daily + usual therapy (n = 3132)

Median follow-up: 2.3 yr

Primary endpoint: composite of worsening HF (hospitalization or urgent visit) or cardiovascular death

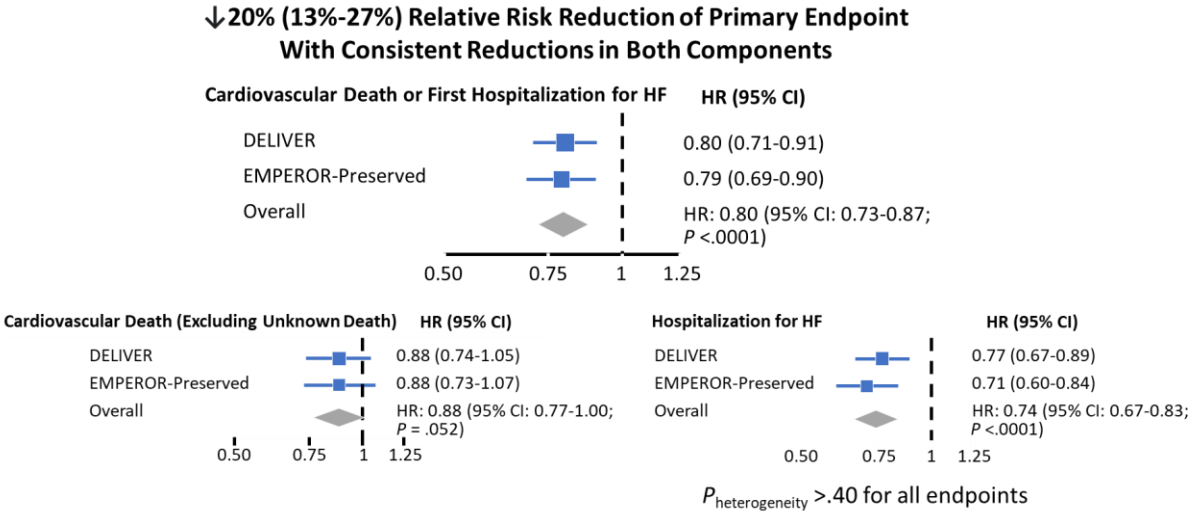
Key secondary endpoints: total number of worsening HF events and cardiovascular death, change in total symptom score on KCCQ, all-cause mortality





(Source: Solomon. NEJM. 2022;387:1089)

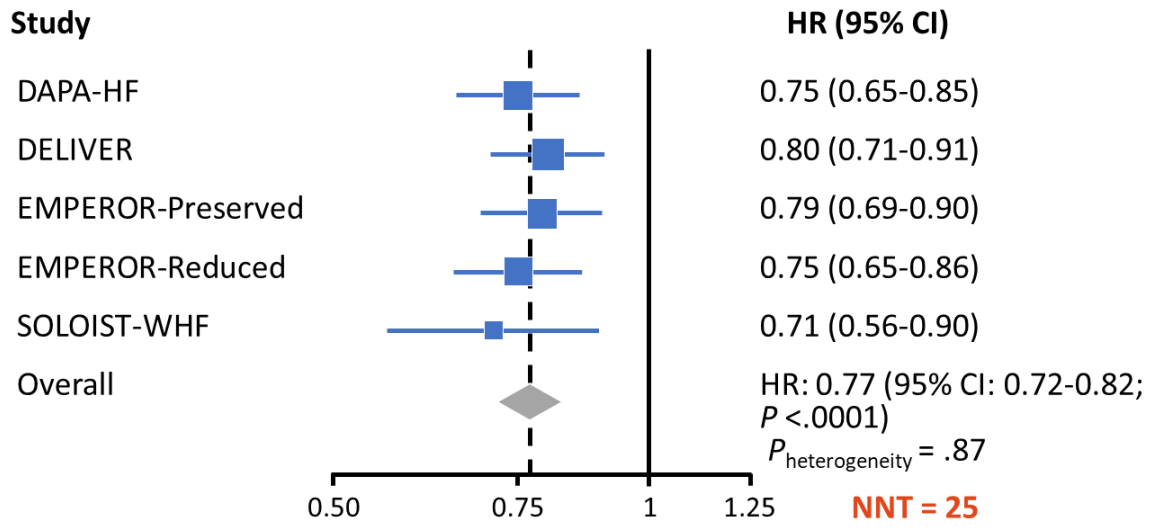
DELIVER and EMPEROR-Preserved Meta-Analysis



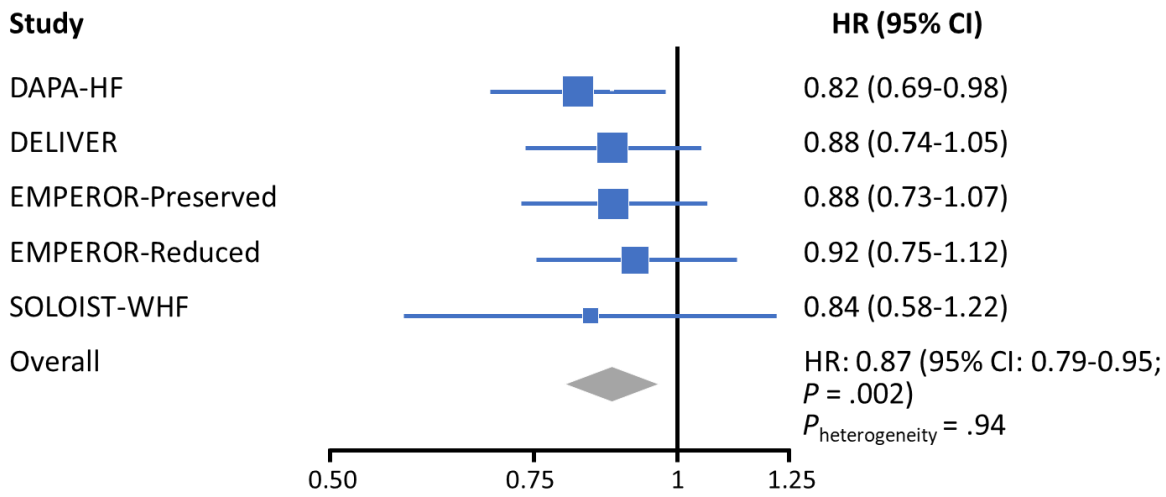
(Source: Kotit. Glob Cardiol Sci Pract. 2023;2023:e202314)

Meta-Analysis of Five Large Placebo-Controlled Trials

↓23% (18%-28%) Relative Risk Reduction of Primary Endpoint (CV Death or HF Hospitalization)



↓13% (5%-21%) Relative Risk Reduction of CV Death



(Source: Kotit. Glob Cardiol Sci Pract. 2023;2023:e202314)

HFpEF Trials

- Over the past 20 years, very few therapies have been shown to be effective for the treatment of HFpEF.
  - Negative trials: Perindopril, irbesartan, beta-blockers, nitrates, digoxin, ivabradine, sildenafil, and serelaxin

Appendix B: Reference Case of a 23-Year-Old Woman with Mild Hypertension and Peripheral Edema

Background: A 23-year-old woman presented to the Emergency Department with two months of shortness of breath and abdominal pain. She is two months post-partum and had delivered a healthy baby girl. Her pregnancy was complicated by mild hypertension and peripheral edema.

Past medical history: One month post-partum, she presented with abdominal discomfort and increased liver function tests. She underwent a cholecystectomy. She tolerated the cholecystectomy and was discharged home.

In the days and weeks following the surgery, the symptoms of abdominal bloating and dyspnea on exertion persisted. She then developed worsening ankle edema and was struggling to keep up with the care of her daughter. For these symptoms, she presented to the Emergency Department. Her home medications were prenatal vitamin and hydrochlorothiazide 25 mg daily. She is nursing.

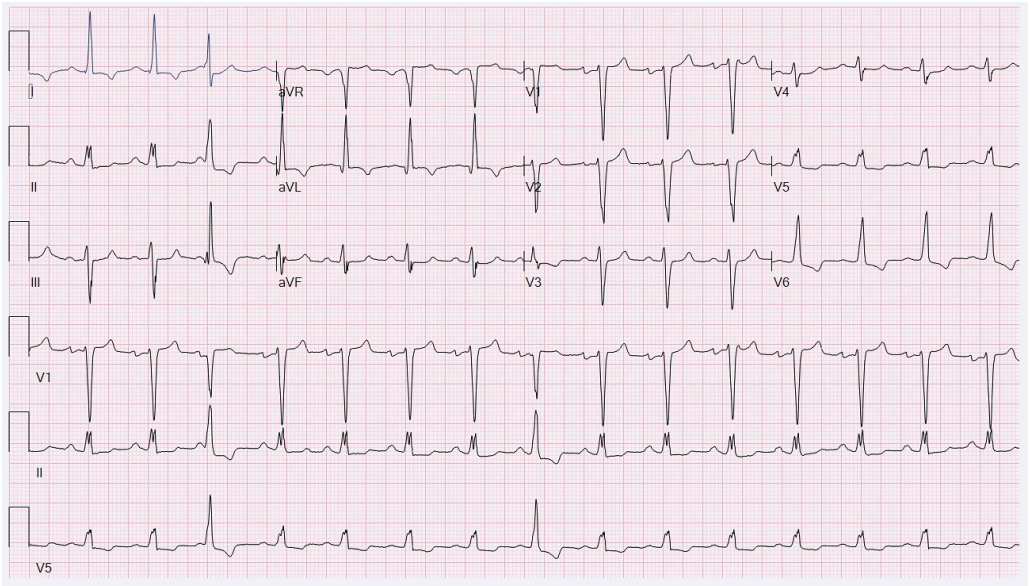
At the Emergency Department, she appeared mildly uncomfortable.

Her vital signs were as follows:

- Temperature: 36.4°C
- Blood pressure: 132/82 mm Hg
- Heart rate: 110 beats/minute
- Respiratory rate: 16 - 98% on room air

Her JVP was elevated with small v-waves, RRR tachycardic with normal S1 and S2 with a blowing systolic murmur at the apex, lungs with rales at both bases, mildly distended abdomen with liver edge about 1 cm below the costal margin, and 1+ pitting edema to the mid-shins bilaterally.

Her ECG is as follows:

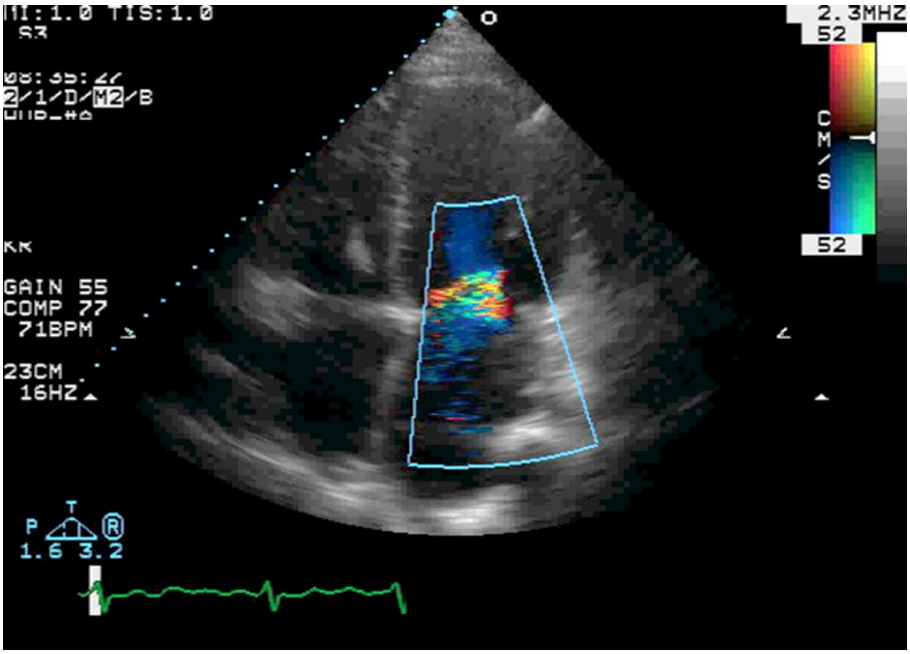


Her lab findings are provided below:

Lab	Range	Value
Sodium	136-142 mEq/L	137
Potassium	3.5-5 mEq/L	3.8
BUN	8-23 mg/dL	19
Creatinine	0.6-1.2 mg/dL	0.9
WBC	4.5-11 X 10^3/mcL	4.8
Glucose	70-110 mg/dL	97
Hemoglobin	13.5 – 17.5 g/dL	10.9
Hematocrit	41-50%	31
Platelets	150-450 X 10^3/mcL	227
Troponin I high sensitivity	<0.4 ng/mL	0.8
PT (INR)	10-13 sec	11 (1.0)
NT-ProBNP	<450 pg/mL	2084

A transthoracic echocardiogram revealed the following:

- Dilated left ventricle with an LVEF of 15%
- Moderate to severe mitral regurgitation due to annular dilation
- Mildly decreased right ventricular function
- Small left ventricular thrombus



Question 1: Which of the following is the next best step in her management?

A. Start spironolactone 25 mg daily.
B. Start amiodarone 400 mg daily.
C. Refer for ICD implantation.
D. Start lidocaine infusion.

Note your observations in the space below.

The correct answer here should be option A. The goal in HFrEF is to GDMT as soon as possible. Given normal renal function and a mildly decreased serum potassium in the setting of a reasonable blood pressure, initiation of spironolactone is the next best step. PVCs and non-sustained ventricular tachycardia are common in the setting of cardiomyopathy especially during episodes of acute heart failure. Amiodarone is contraindicated in breastfeeding and would not be indicated regardless of sustained arrhythmias. Lidocaine is also not indicated in this setting. Although she may ultimately benefit from ICD placement, her LVEF may improve with GDMT, obviating the need for the ICD.

She continues to diurese, and her labs remain stable with electrolytes in range. Her symptoms are much improved with on-going IV diuresis daily.
Current vital signs: Blood pressure 118/79 mm Hg, heart rate 86 and regular

Question 2: Which of the following is the next best step in her management?

A. Add atenolol 25 mg once daily.
B. Add dapagliflozin 10 mg daily.
C. Add carvedilol 3.125 mg twice daily.
D. Add empagliflozin 10 mg daily.

Note your observations in the space below.

The correct answer here should be option C. As her volume overload is resolving, beta blockade can safely be added to her regimen. This is one of the four core classes of GDMT for HFrEF. Only three beta-blockers are recommended in the guidelines as evidenced-based, including metoprolol succinate, carvedilol, and bisoprolol. Starting low-dose carvedilol, which is considered safe in breastfeeding, is the correct answer and may help to suppress PVCs and reduce the risk of arrhythmias. Both empagliflozin and dapagliflozin are not felt to be safe in breastfeeding at this time but may in the future as more data become available. Atenolol is not one of the evidence-based beta-blockers.

Follow-Up After Two Days

Over the next two days, the dose of carvedilol is increased to 12.5 mg twice daily and the IV furosemide is transitioned to oral furosemide 20 mg daily. Warfarin is initiated, and the heparin discontinued when her INR is 2.0 or greater.

She reports feeling much improved and is ambulating in the corridor without dyspnea or lightheadedness. She continues to nurse and pump milk for her daughter. She reports no known history of cardiomyopathy or sudden cardiac death in family members.

Her blood pressure is 104/68 mm Hg, heart rate 62 and regular, and telemetry reveals occasional PVCs. A cardiac MRI reveals a structurally normal heart with an LVEF of 30% and mild to moderate mitral regurgitation. A small mobile thrombus is seen near the LV apex. There is no significant late gadolinium enhancement.

Question 3: Which of the following should be performed prior to her discharge?

A. Repeat echocardiogram.
B. BiV pacemaker placement.
C. Heart failure education and early post-discharge follow-up appointment.
D. Repeat thyroid stimulating hormone level.

Note your observations in the space below.

The correct answer here should be option C. The current heart failure guidelines and subsequent consensus documents recommend heart failure education for all heart failure patients and their families. This education should include information about the pathophysiology of heart failure, lifestyle changes including diet and exercise, medication education, self-monitoring including daily weights and symptom assessment and when to contact the provider. In addition, a follow-up appointment within seven days of discharge is also recommended. There is no indication to repeat an echocardiogram at this time because it will not change her management. In addition, there is no indication for BiV pacemaker placement at this time because she has not been on GDMT. Thyroid dysfunction is common in the post-partum period but her thyroid-stimulating hormone (TSH) was in range early in the admission and a repeat TSH would not change management at this time.
She is discharged home and is seen in the clinic one week later.

Follow-Up One Week Later
The patient reports dyspnea with more than one flight of stairs but is otherwise asymptomatic. She reports no lightheadedness, palpitations, or syncope. An ECG reveals normal sinus rhythm with an incomplete left bundle branch block pattern.
Her blood pressure is 105/70 mm Hg and her heart rate 66 and regular. Her medications include valsartan 40 mg twice daily, carvedilol 12.5 mg twice daily, spironolactone 25 mg daily, warfarin 5 mg daily, and prenatal vitamin daily.

Her labs are as follows:

Lab	Range	Value
Sodium	136-142 mEq/L	140
Potassium	3.5-5 mEq/L	4.4
BUN	8-23 mg/dL	16
Creatinine	0.6-1.2 mg/dL	0.9
WBC	4.5-11 X 10^3/mcL	5.4
Glucose	70-110 mg/dL	90
Hemoglobin	13.5 – 17.5 g/dL	11.1
Hematocrit	41-50%	33
Platelets	150-450 X 10^3/mcL	265
INR	1.0	2.1
NT-ProBNP	<450 pg/mL	550

Given the clinical presentation and evaluation, she is given the diagnosis of peri-partum cardiomyopathy. She is counseled on the importance of contraception, and an IUD is placed.

Follow-Up Few Months Later
She is seen three months later. A repeat echocardiogram reveals an improved LVEF of 40 to 45%. There is no evidence of LV thrombus seen with an echo contrast agent. She remains with minimal symptoms but is concerned about remaining on the medications long term. She is planning on continuing to nurse her daughter for a total of one year.

Over the next nine months, she remains stable with the exception of orthostatic lightheadedness and the furosemide is discontinued with stable weights and symptoms. The warfarin is discontinued after a 6-month course.

At one year following her presentation, she informs you that she has weaned her daughter and continues to have no exercise limitation, lightheadedness. or palpitations. Her blood pressure is 100/70 mm Hg and heart rate is 62 and regular. A repeat echocardiogram reveals an LVEF of 40% with mild mitral regurgitation. No thrombus is seen in the left ventricle. Her labs are unchanged.

Question 4: Which of the following should be the next step in her management?

A. Start empagliflozin 10 mg once daily.
B. Increase carvedilol to 25 mg twice daily.
C. Stop spironolactone.
D. Restart furosemide 20 mg daily.

Note your observations in the space below.

The correct answer here should be option A. Given on-going left ventricular dysfunction and the fact that she is no longer nursing, the goal is to initiate and maintain all four classes of GDMT. As such, empagliflozin, an SGLT2i, should be added to her regimen. This would take priority over increasing other classes of medications. Given her heart rate and blood pressure, there may not be much benefit in increasing her carvedilol. With the emphasis on comprehensive GDMT and in the absence of side-effects or lab abnormalities, the spironolactone should be continued. She has no evidence of volume overload. Therefore, standing furosemide should not be restarted.

Follow-Up in Subsequent Years

Over the next five years, she does well without changes to her medical regimen—with the exception of stopping the prenatal vitamin when she stopped breastfeeding. She then presents to the Emergency Department with several weeks of fatigue, lightheadedness, and dyspnea on exertion. She had not been weighing herself regularly but then noted a 10-pound weight gain with edema in both her feet and ankles. She had taken two doses of furosemide 20 mg orally, which she had at home, but noted only a modest increase in urine output.

Her blood pressure is 88/70 mm Hg and her heart rate is 70 and regular.

A repeat echocardiogram reveals an LVEF of 25% with moderate to severe mitral regurgitation.

Additional family history is obtained that three months ago, her 19-year-old first cousin died suddenly while playing basketball. Her father was diagnosed with a non-ischemic cardiomyopathy about one year ago. In addition, her paternal aunt has been admitted with heart failure several times over the past five years.

Her labs are as follows:

Lab	Range	Value
Sodium	136-142 mEq/L	132
Potassium	3.5-5 mEq/L	4.9
BUN	8-23 mg/dL	34
Creatinine	0.6-1.2 mg/dL	1.8
WBC	4.5-11 X 10^3/mcL	5.4
Glucose	70-110 mg/dL	105
Hemoglobin	13.5 – 17.5 g/dL	12.1
Hematocrit	41-50%	36
Platelets	150-450 X 10^3/mcL	295
INR	1.0	1.2
NT-ProBNP	<450 pg/mL	8800
Beta HCG		Negative

The dose of valsartan is reduced to 40 mg daily, and the dose of spironolactone is reduced to 12.5 mg daily. She is diuresed with IV furosemide over several days, and her weight is reduced by about nine pounds. She is improved but continues with significant dyspnea on exertion with ongoing orthostatic lightheadedness. Her dose of carvedilol is reduced to 6.25 mg daily with some improvement in the lightheadedness. A repeat cardiac MRI reveals an LVEF of 20 to 25% with moderate to severe mitral regurgitation in the setting of a dilated left ventricle, moderate right ventricular dysfunction, and extensive late gadolinium enhancement. She has no LV thrombus. Her BUN and creatinine improve to 29 mg/dL and 1.2 mg/dL, respectively.

Question 5: Which of the following should be the next step in her management?

A. Refer to an advanced heart failure program.
B. Start prednisone 40 mg daily.
C. Discontinue valsartan and start sacubitril/valsartan 49/51 (100) mg twice daily.
D. Start milrinone 0.125 mcg/kg/min.

Note your observations in the space below.

The correct answer here should be option A. This patient is developing worsening heart failure symptoms and left ventricular dysfunction despite appropriate GDMT. There is no evidence of non-adherence or other precipitating factors for the acute heart failure. Inability to tolerate previously tolerated doses of GDMT due to hypotension or worsening renal function is a sign of worsening heart failure that warrants referral to an advanced heart failure program for multidisciplinary management and consideration for heart transplant or ventricular assist device. There is no evidence of an inflammatory cardiomyopathy, and her blood pressure will likely not tolerate transition from a reduced dose of valsartan to mid-dose sacubitril/valsartan. Although there is concern for a low cardiac output state, the improvement in renal function and volume status with diuretics is reassuring. Therefore, empiric milrinone without a right heart catheterization is not indicated at this time.

She stabilizes and is discharged home on reduced medication doses and furosemide 40 mg twice daily with follow-up in the advanced heart failure program. She is also referred for an ICD, given her depressed ejection fraction and extensive late gadolinium enhancement on the cardiac MRI.

Question 6: Which of the following would be indicated at this time?

A. Endomyocardial biopsy.
B. Viral IGM and IGG titers.
C. Serum protein electropheresis.
D. Genetic testing.

Note your observations in the space below.

The correct answer here should be option D. This patient has worsening heart failure despite appropriate GDMT. Since her initial presentation more than five years ago, additional family history has come to light including a history of non-ischemic cardiomyopathy in her father's family as well as an unexplained sudden cardiac death. This suggests the possibility of a genetic cardiomyopathy. As such, genetic testing with a referral to a genetic counselor is the next best step to determine if a specific pathogenic gene is present. This may provide prognosis and risk assessment for her but also allow appropriate screening and intervention in other family members if a gene is identified. Given no evidence of acute inflammation or amyloid on the cardiac MRI, an endomyocardial biopsy, viral antibody titers, and a serum protein electrophoresis are very unlikely to yield any helpful information.
For some women, a pregnancy can unmask a previously asymptomatic cardiomyopathy that could be genetic. These are often classified as peripartum cardiomyopathies but the left ventricular function may not normalize with medical therapy post-partum and the cardiomyopathy may progress over time. In these clinical settings, genetic testing can be helpful to identify a root cause, risk stratify, and enable appropriate screening of potentially at-risk family members.

Note your response in the space below.

One Year Later

- Empagliflozin 10 mg is added to sacubitril/valsartan, carvedilol, and spironolactone for the patient. She reports mild symptoms.

Question for reflection: What advice would you give her for a subsequent pregnancy?

Note your response in the space below.

Three Years Later

The patient's follow-up three years later reveals worsening shortness of breath. Her furosemide is increased to 40 mg twice daily. Her repeat echocardiogram shows LVEF 20% and moderate mitral regurgitation. Additional family history indicates:

- Father with cardiomyopathy
- First cousin sudden cardiac death age 19 years
- Paternal aunt with heart failure and ventricular tachycardia

Questions for reflection:

- What testing would you order?
- What's your diagnosis?

Note your response in the space below.