

# Balancing on 4 Pillars – Pharmacologic Approach to Heart Failure Management

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#### Updated Guidelines – May 2022

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#### **CLINICAL PRACTICE GUIDELINE: FULL TEXT**

## 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure



A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines



#### Evolution In The Approach to Heart Failure

#### **Traditional Paradigm**

- Heart Failure is a hemodynamic disorder
- Volume control is the cornerstone of therapy
- Patients "go into heart failure" but when symptoms improve they are "out of heart failure"
- Patients classified by NYHA class or functional capacity alone

#### **Challenging Tradition**

- NYHA class changes over time
- Heart failure is a cellular disease
- Despite symptomatic improvement neurohormonal, cytokine and cellular changes continue to occur and allow heart failure to progress
- Ejection Fraction (EF) does not correlate with functional capacity (NYHA class)



#### Shifting To a Chronic Disease Model – A Staging System

- The Heart Failure Staging system emphasizes:
  - 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 <u>changed the natural</u> <u>history of heart failure and are most effective when initiated early</u>



## Staging System

At Risk

Pre HF

	ACCF/AHA Stage (course of disease)*		NYHA Functional Classification (symptoms at that moment)**	
sk	A	At high risk for HF but without structural heart disease or symptoms of HF	None	
łF	В	Structural heart disease but without signs or symptoms of HF	I	No limitation of physical activity; ordinary physical activity does not cause HF symptoms
	С	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	Refractory HF requiring specialized interventions	IV	Unable to carry on any physical activity without HF symptoms, or symptoms at rest



#### **New Definitions**

- HF with reduced ejection fraction (HFrEF) includes people with LVEF ≤40%.
- HF with improved ejection fraction (HFimpEF) includes individuals with previous LVEF ≤40% and a follow-up measurement of LVEF >40%.
- HF with mildly reduced ejection fraction (HFmrEF) includes people with LVEF 41-49% and evidence of increased LV filling pressures.
- HF with preserved ejection fraction (HFpEF) includes individuals with LVEF ≥50% and evidence of increased LV filling pressures.



### HFrEF Update

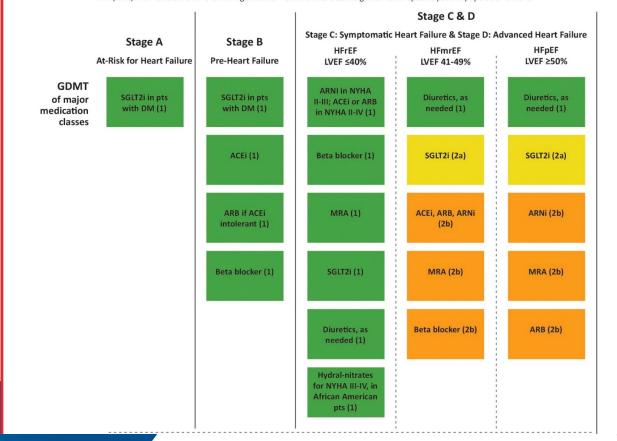
- 4 Classes of drugs now recommended for all patients with HFrEF (LVEF <40%)</li>
  - ARNI (Preferred) or ACE inhibitor or ARB
  - Beta Blocker (carvedilol, metoprolol succinate and bisoprolol)
  - Mineralocorticoid antagonist (spironolactone or eplerenone)
  - SGLT-2 inhibitor (empagliflozin or dapagliflozin) (with or without diabetes)
- Strategy start all 4 classes as quickly as possible then titrate doses
  - Consider adding all 4 classes as inpatient prior to discharge



#### CENTRAL ILLUSTRATION: 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

#### **Guideline Directed Medical Therapy Across Heart Failure Stages**

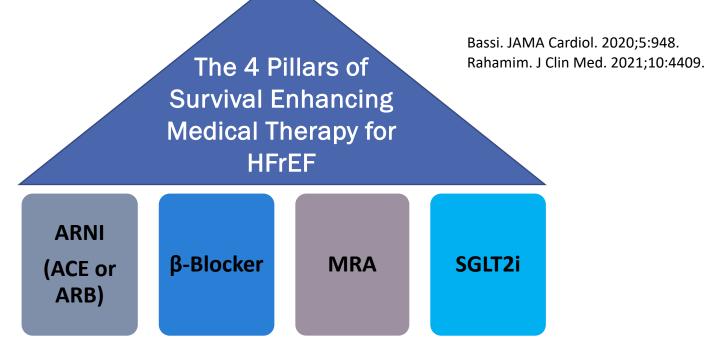
Use this tool to reference guideline directed medical therapy (GDMT) across the four ACC/AHA stages of Heart Failure (HF) as outlined in the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. See the guideline for specific patient population criteria.



#### Primary therapies

J Am Coll Cardiol.2022;79:e263-e421

#### 4 Pillars of GDMT for Heart Failure



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



## Angiotensin Receptor Blocker/Neprilysin Inhibitor

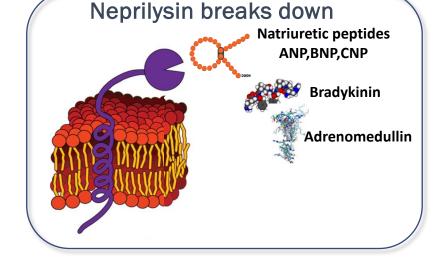


## Neprilysin Inhibition in Cardiovascular Disease

Sacubitril is a neprilysin inhibitor

Neprilysin Inhibition

> Potentiation of beneficial peptides ANP, BNP, CNP, adrenomedullin

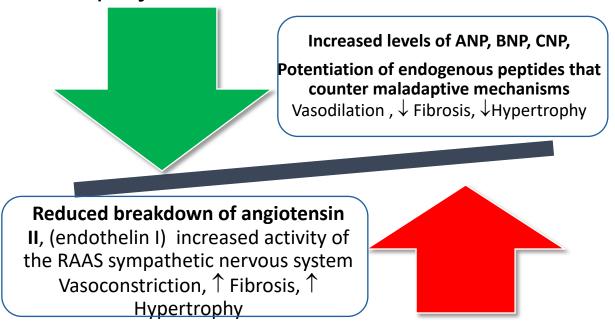


Counter maladaptive mechanisms

- Vasodilation
- ↓Fibrosis
- ↓ Hypertrophy



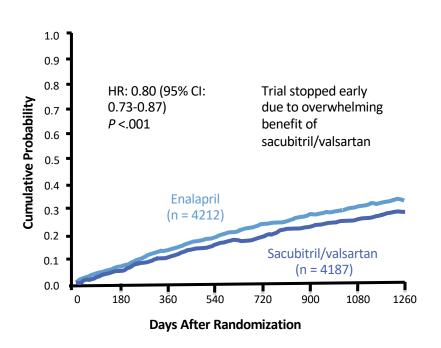
#### Balance of Neprilysin Inhibition



The antihypertensive effects may be offset by an increased activity of the RAAS and sympathetic nervous system and/or by downregulation of ANP receptors.



PARADIGM-HF — Reduction in CV Death or HF Hospitalization with sacubitril/valsartan



- 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)</li>
- Similar rates of angioedema, but:
  - Do not use with history of angioedema
  - Discontinue ACE inhibitor for ≥36 hours before starting
  - Can raise BNP levels but not NT-proBNP



### Sacubitril/Valsartan Safety Considerations

Warnings and Precautions	Contraindications	Common AEs
<ul> <li>Fetal toxicity: discontinue if pregnant</li> <li>Monitor for angioedema and hypotension</li> <li>Monitor renal function and potassium in susceptible patients</li> <li>Initiate ≥36 hours after last ACE inhibitor dose</li> </ul>	<ul> <li>Hypersensitivity to sacubitril or valsartan</li> <li>History of angioedema with ACE inhibitor or ARB</li> <li>Concurrent use with ACE inhibitors</li> <li>Concurrent use with aliskiren in patients with diabetes</li> </ul>	<ul> <li>Hypotension</li> <li>Hyperkalemia</li> <li>Cough</li> <li>Dizziness</li> <li>Renal failure</li> </ul>

Ponikowski. Eur Heart J. 2016;37:2129. Sacubitril/valsartan Pl. Yancy. Circulation. 2016;134:e282.



#### SGLT-2 Inhibitors

- Inhibitors of sodium–glucose cotransporter 2
- Lead to glucose increase in urine
- Diuretic effect
- Developed primarily for diabetes management



#### SGLT1 and SGLT2 Inhibitor



- **SGLT1** is the primary transporter for absorption of glucose and galactose in the GI tract
- Pharmacologic inhibition is independent of insulin and does not depend on kidney function
- Potential effects on atherosclerotic risks
- About 10% of glucose effect

**SGLT2** is expressed in the kidney, where it reabsorbs 90% of filtered glucose

Glomerulus

Cortex

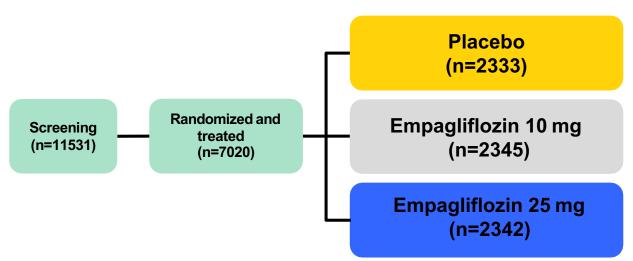
Collecting Duct

Distal convoluted tubule

Pharmacologic inhibition is independent of insulin but requires kidney function



## EMPA-REG OUTCOME – Design



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

Primary outcome -death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke Key secondary outcome primary outcome plus hospitalization for unstable angina Primary hypothesis was **noninferiority** for the primary outcome

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

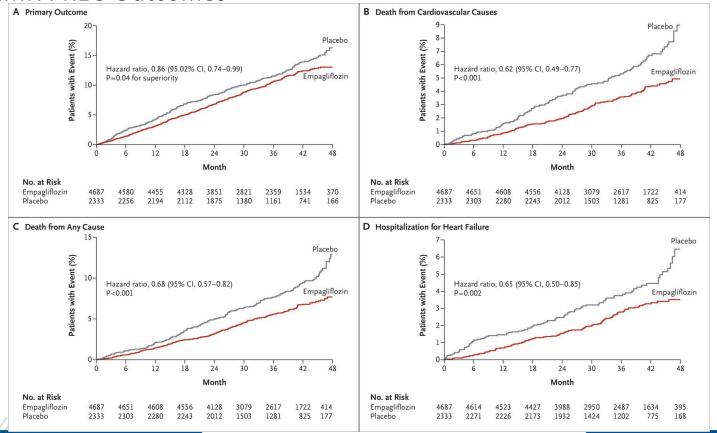


## EMPA-REG Outcomes – "Serendipity"

- The primary outcome occurred in a significantly lower percentage of patients in the empagliflozin group (490 of 4687 [10.5%]) than in the placebo group (282 of 2333 [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)</p>
- The key secondary outcome occurred in 599 of 4687 patients (12.8%) in the empagliflozin group and 333 of 2333 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).</li>



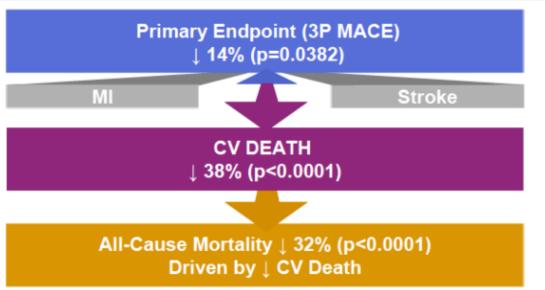
#### **EMPA-REG Outcomes**





## Serendipity

#### **EMPA-REG OUTCOME Trial: Key Results**



#### **Heart Failure**

- Hospitalization for Heart Failure or CV Death 

   34% (p<0.0001)</li>

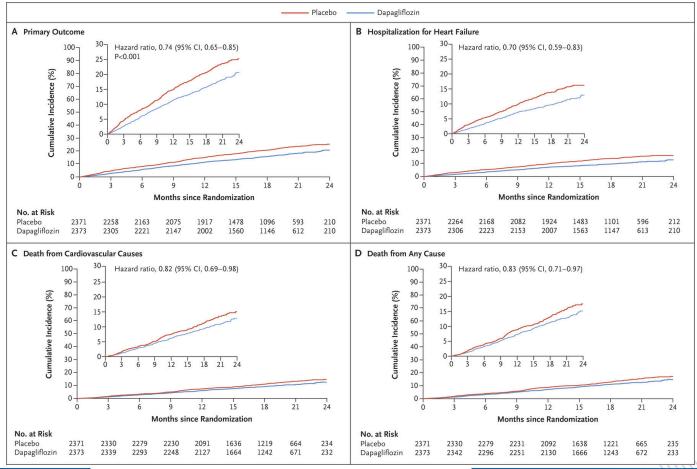


## Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction – DAPA-HF

- Randomized, placebo-controlled trial, evaluating the effects dapagliflozin in patients with heart failure and a reduced ejection fraction with or <u>without</u> 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



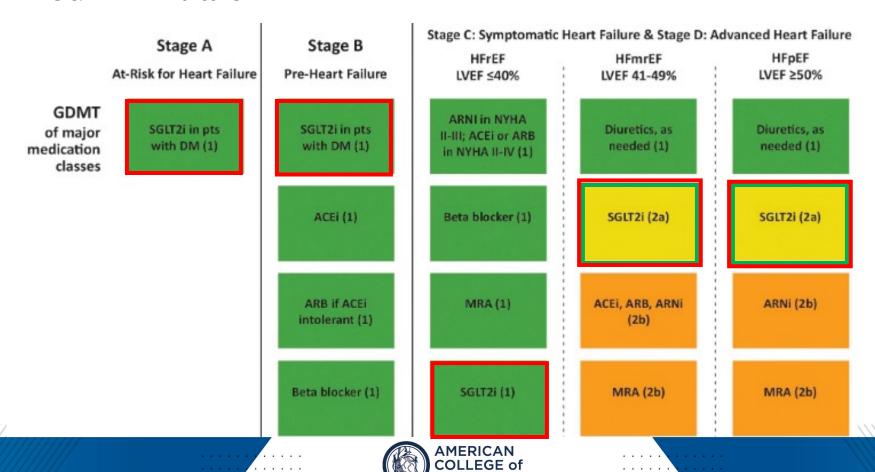
#### DAPA-HF



N Engl J Med 2019; 381:1995-2008



#### SGLT2 Inhibitors



CARDIOLOGY.

#### Adverse Effects of SGLT-2 Inhibitors

- Genital Fungal infections
- Serious genital infections Fournier's Gangrene
- Amputations seen with canagliflozin and ertugliflozin
- Euglycemic Ketoacidosis more common when fasting, acute changes in renal function or acute illness

 Developing guidelines to hold SGLT-2 inhibitors prior to surgical procedures or during acute hospitalizations

- Genital mycotic infections
- Fournier's gangrene
- Volume depletion
- Acute kidney injury
- Hypotension
- Increased LDL-cholesterol
- Increased hemoglobin and/or hematocrit
- Ketoacidosis
- Increased risk of lower limb amputations with canagliflozin and ertugliflozin; SGLT2 inhibitors should generally not be used in patients at risk for foot amputation
- Possible increased fracture risk
- Dapagliflozin is contraindicated for use in patients with active bladder cancer





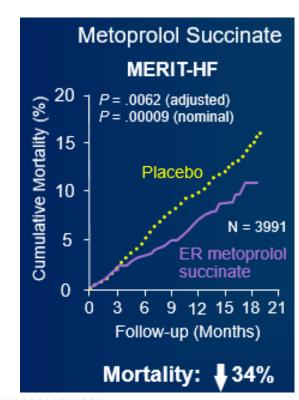
#### Beta Blockers

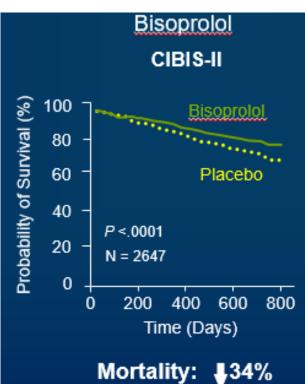
- Effect
  - Inhibit the adverse effects of sympathetic system
  - Delays and reverses remodeling
- Clinical use: Heart failure with reduced ejection fraction
  - Given to all patients with HFrEF in absence of fluid overload
- Adverse effects
  - Hypotension, bradycardia, worsening HF
- Select <u>only evidence based</u> beta blockers
  - Metoprolol succinate
  - Carvedilol
  - Bisoprolol

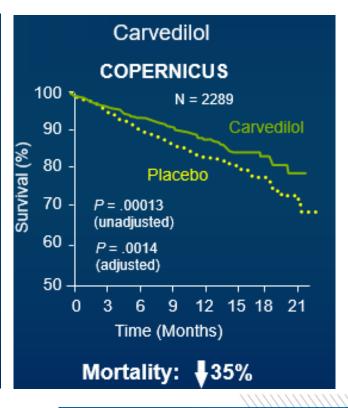
All have mortality data



#### Beta Blockers-Mortality Benefit HFrEF

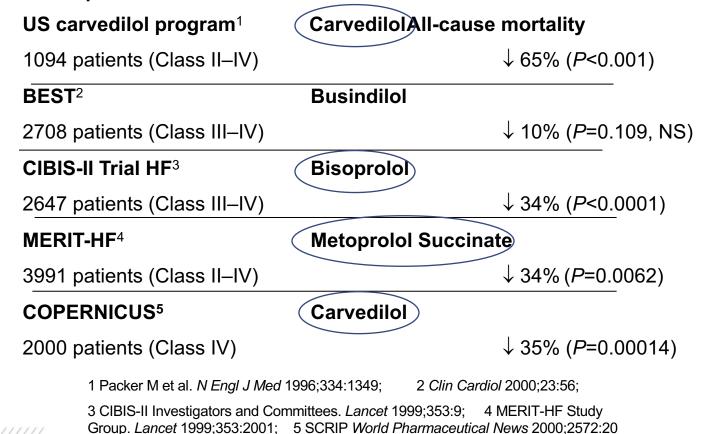








#### Effects of $\beta$ -Blockade on Mortality





## Aldosterone Antagonists: Spironolactone/Eplerenone

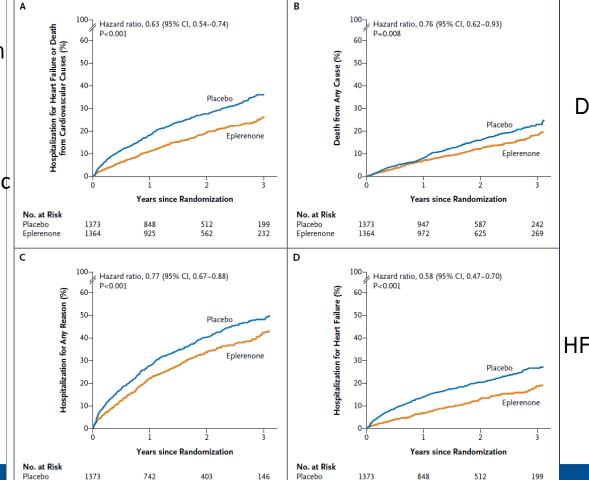
- Improved mortality for class IIIB or class IV patients RALES Trial
- Creatinine < 2.5 in men < 2.0 in women and Potassium < 5.0</li>
- More recent studies with eplerenone showed benefits in NYHA Class II to IV (Expanded indication)
- Contraindicated if on <u>both</u> ACE and ARB together due to risk of hyperkalemia
- Role of Fineronone to be defined but new data promising



HF Hospitalization or Death

Eplerenone in
Patients with Systolic
Heart Failure and
Mild Symptoms
(EMPHASIS-HF)

Hospitalization For Any Reason



Death Any Cause

HF Hospitalization

N Engl J Med 2011;364:11-21.

**Eplerenone** 

1364

795

451

Figure 1. Cumulative Kaplan—Meier Estimates of Rates of the Primary Outcome and Other Outcomes, According to Study Group.

Eplerenone

1364

925

562

232

179

## Heart Failure with Improved Ejection Fraction

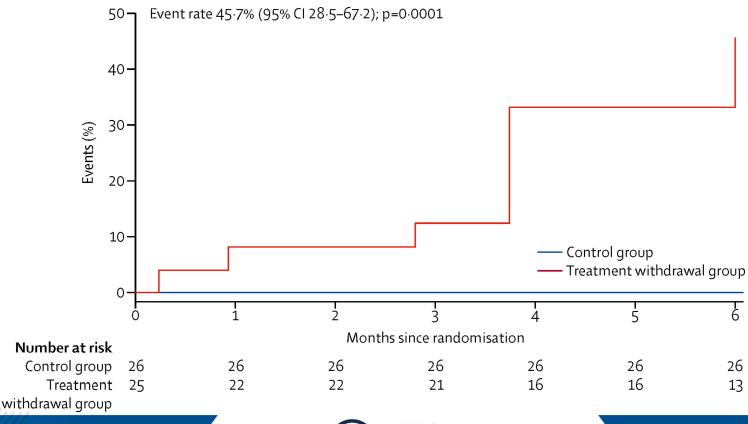
Improved LVEF is used to refer to those patients with previous HFrEF who now have an LVEF >40%

<u>These patients should continue their HFrEF treatment</u>
(At least ACE/ARB/ARNI and Beta Blocker)

TRED-HF Trial randomized patients with recovered LVEF to withdrawing medications versus continuing medications



#### **TRED-HF Trial**



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



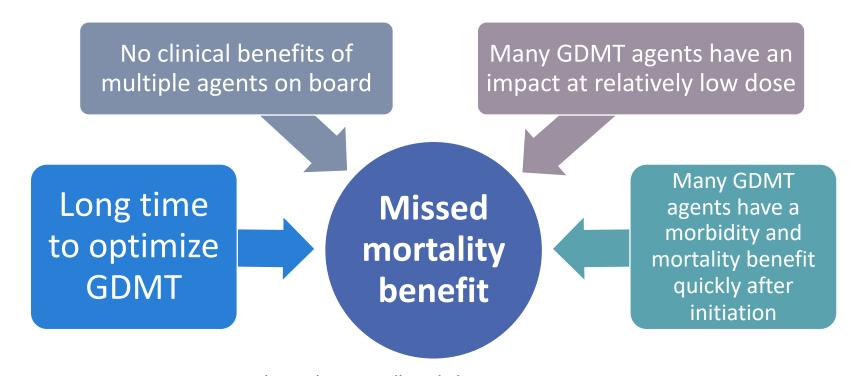
## Traditionally - Sequential Approach

- Typically started with a vasodilator to "unload" ventricle
- Titrated to maximally tolerated dose (more recently "low to moderate" dose)
- Beta blocker added
- Starting at low dose and titrating upward
- Additional medications added "if needed" for symptoms, blood pressure or heart rate control

Yancy. J Am Coll Cardiol. 2013:15;62(16):e147-239.



## Consequences of Traditional Sequencing



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



## Is it safe to start all 4 classes quickly?

#### Strong HF Trial

 Multinational, multicenter, open-label, randomized, parallelgroup study designed to assess the safety and efficacy of up-titration of guideline-recommended heart failure medical therapy, including β blockers, angiotensin converting enzyme (ACE) inhibitors (or angiotensin receptor blockers [ARBs] if the patient was intolerant to ACE inhibitors) or angiotensin receptor-neprilysin (ARN) inhibitors, and mineralocorticoid receptor antagonists, on morbidity and mortality when initiated and up-titrated early after hospitalization for acute heart failure

Mebazaa. Lancet. 2022;400:P1938.



## The Intervention — High Intensity

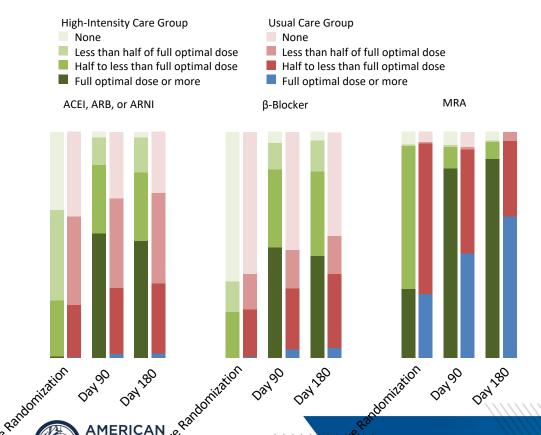
- Algorithm combining optimization of oral heart failure therapies and frequent visits, including circulating NTproBNP measures, to assess congestion.
  - First dose adjustment occurred just after randomization (within 2 days before anticipated hospital discharge), when patients were prescribed medical therapy with β blockers, renin-angiotensin blockers (ie, ACE inhibitors [or ARBs if intolerant to ACE inhibitors] or ARN inhibitors), and mineralocorticoid receptor antagonists adjusted to at least half the optimal doses
  - Patients were assessed by the study team at 1, 2, 3, and 6 weeks after randomization

Mebazaa, Lancet. 2022;400:P1938.



## STRONG-HF: Target GDMT Doses in High-Intensity vs Usual Care

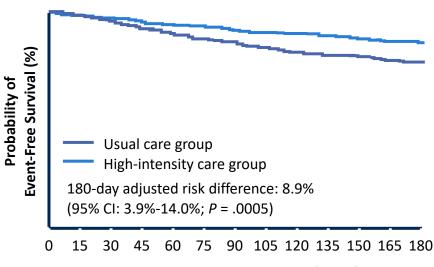
- More patients in high-intensity group received target GDMT dosages at 90 days
  - ARNI/ACEI/ARB:55% vs 2%
  - β-blocker: 49% vs4%
  - MRA: 84% vs 46%



# STRONG-HF: All-Cause Mortality

- More patients in high-intensity group felt better and lived longer
  - NYHA class I/II at 90 days: 83% vs 67%
  - Primary endpoint of reduction in death/HFH at 180 days: 15% vs 23%
  - Driven by HFH: 9.5% vs 17%

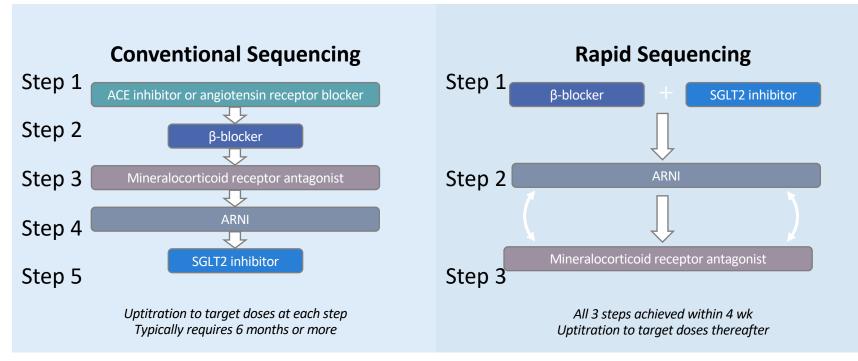
Terminated early because of larger than expected difference in groups; withholding intensive treatment strategy would be **unethical** 



**Time Since Randomization (Days)** 



## The Need for Speed



Packer. Eur J Heart Fail. 2021;23:882



## Why Is Rapid Initiation Important?

<b>Medication Class</b>	Outcome	Relative Risk
β-Blocker	Death	<b>↓</b> 25%
ARNI	CV death or HF hospitalization	<b>↓</b> 42%
MRA	CV death or HF hospitalization	<b>↓</b> 37%
SGLT2i	Death, HF hospitalization, or emergency/urgent visit for worsening HF	↓ 58%

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

Greene. JAMA Cardiol. 2021;6:743.



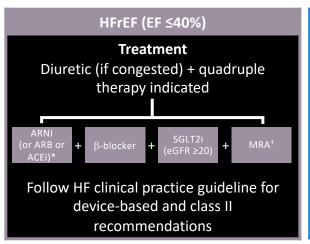
## Management of Heart Failure Summary

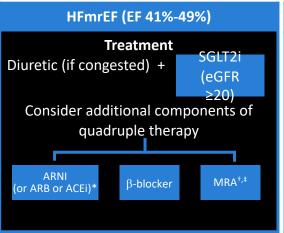
#### **Manage Comorbid Disease**

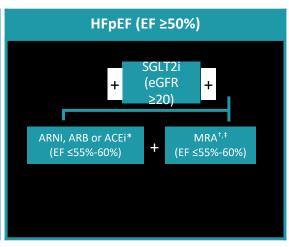
Lifestyle therapy

BP, lipid, and glucose control

ASCVD interventions as indicated







<sup>\*</sup>ARNI preferred over ARB or ACEi. †Spironolactone or eplerenone. Avoid eplerenone if eGFR ≤30 mL/min/1.73m<sup>2</sup>, †If T2D + CKD with UACR ≥30 mg/g, use finerenone.

Handelsman. J Diabetes Complications. 2022;36:108101.



#### Call To Action

- Using all 4 classes of medications, when possible, can improve both morbidity and mortality for patients with HFrEF
- Include all 4 classes of medications as metrics in assessing the quality of HFrEF care
- Develop systems of care that promote initiation, titration and maintenance of all 4 classes of medications
  - Consider starting while in hospital for initiation
- Modify patient and family education to emphasize the importance of all 4 classes of medications



#### Barriers To Optimal Care for Heart Failure Patients

**Personal Factors** 

- Lack of self-care knowledge
- HF-related negative emotions
- Difficulty of changing habits

**Disease Burden** 

- Progressive physical decline
- Comorbid
  Conditions
- > Financial Strain

**Inefficient Support System** 

- Inadequate social support
- Healthcare providers inattention to self-care
- ➤ Limited access to healthcare providers

J Caring Sci. 2020 Oct 20;10(4):196-204.



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



- Comorbid conditions are common in patients with HF
  - 85% of patients have
    ≥2 additional chronic conditions
  - 42% of patients have
    ≥5 additional comorbidities





**Sleep Apnea** 

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



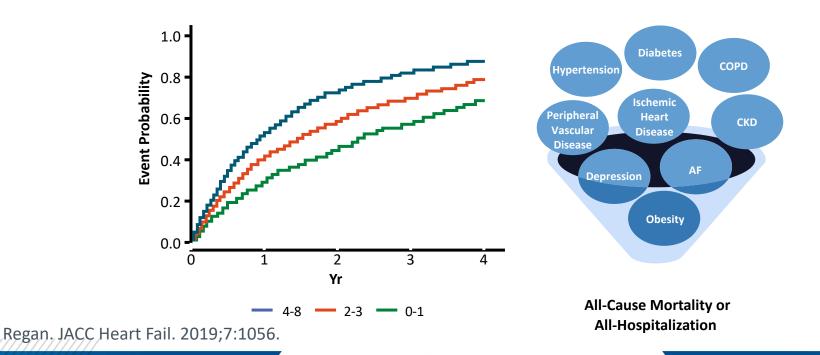
# Consequences of Comorbidities

- 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



#### Comorbidities Drive Mortality and Hospital Admissions

Impact of Cumulative Number of Comorbidities on All-Cause Mortality or All-Hospitalization



**AMERICAN** 

### **Common Comorbidities**

#### Hypertension

- Lifestyle modifications
- Medication therapy

#### Anemia

- Erythrocyte-stimulating agents
  - No clinical benefit
- IV iron
  - Improved outcomes

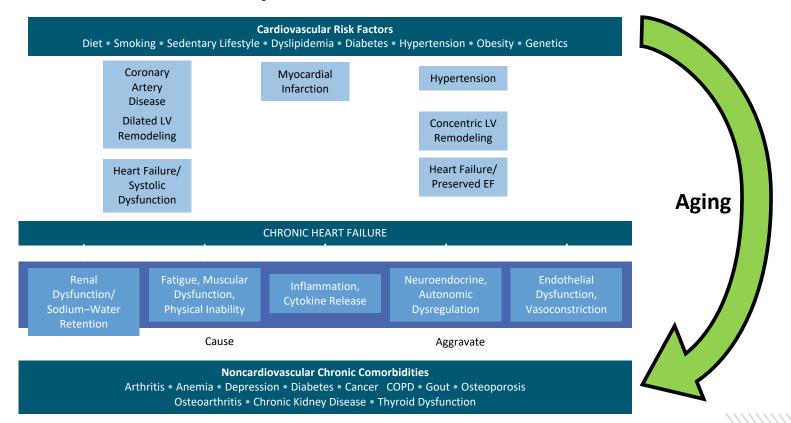
# Sleep-Disordered Breathing

- Screening and treatment of OSA
- Avoid ASV in patients with HFrEF with central sleep apnea

Screever. Clin Res Cardiol. 2023;112:123.



## Comorbidities May Exacerbate Heart Failure





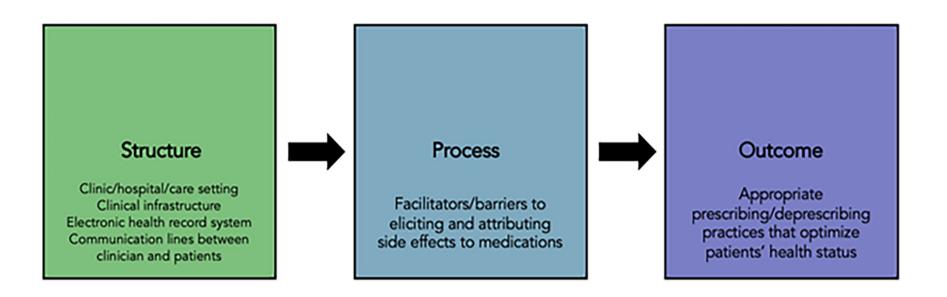
Medications

#### Patient Factors

- Pill burden
- Side-effects
- Intended effects
  - Diuresis/Incontinence limiting travel
- Social roles
  - Caregiver for others
  - Burden
- Competing lifestyle advice
- Cost



## Monitoring for Side Effects



## **Overcoming Patient Barriers**

- Provide patient and care-giver education that accounts for health literacy and culture
- Include the "data" around the impact of core medical therapy
  - "Less likely to come into the hospital"
  - "Fewer symptoms"
  - "Survive longer"
- Empower patients to "control their disease"
- Using tools like daily weights or symptom assessments to allow for early detection of exacerbation of heart failure
- Leverage multidisciplinary teams that are diverse encourage patients and care-givers to "connect" with the team members to whom they can develop longer term relationships
- Encourage shared decision making



#### **Cost Considerations**

- Some of the core medications can have significant cost
  - SGLT-2 inhibitors, ARNI(?)
  - Non-core medications NOAC for anticoagulation, inhalers for COPD
- When asking about adherence be sure to inquire about the financial burdens of medical therapy
- Identify sources of financial assistance
  - Co-pay cards
  - Pharmaceutical assistance programs
  - Grants
  - Local resources
- May need to consider alternatives
  - ACE or ARB for ARNI

Challenging and time consuming

Can be delegated to other team members
if available



# Multidisciplinary Teams

#### General HF multidisciplinary care

Advanced HF physician

Primary care physician

Nurse practitioner/physician assistant

Pharmacist (either cardiology or general medicine trained)

**Psychologist** 

HF specialty nurse

Transitions of care nurse

Dietician

Physical therapist

Social worker

Patient navigator

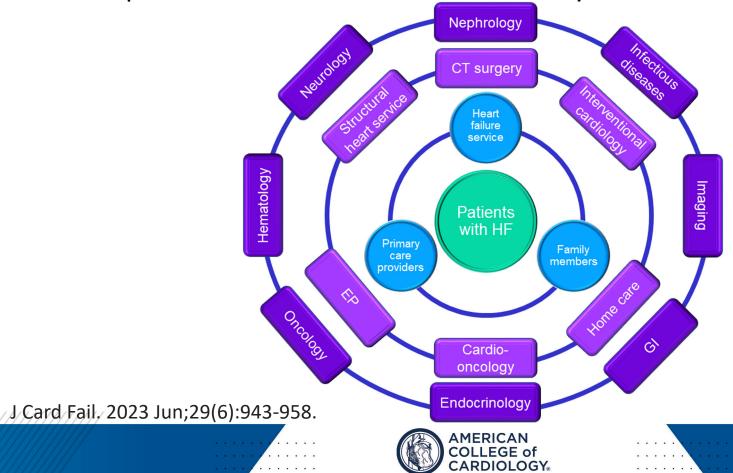
Palliative care provider

Home care

J Card Fail. 2023 Jun;29(6):943-958.



### Comprehensive Heart Failure System of Care



## Pulling It All Together

- **➤** Leverage EHR Tools
- Develop checklists,
   flowsheets, or pathways
   that best serve the clinic
   & population
- ➤ Measure performance to identify opportunities

- Develop a system to assess patients with heart failure at every visit
- Review GDMT and consider re-challenging if appropriate
- Reinforce education
- Ask about adherence
- Ask about side-effects
- Ask about any barriers cost, logistics, shifting caregiver roles
- Engage the larger team whenever feasible
- Encourage questions and concerns
- Engage in shared decision making
- Discuss goals and advanced care planning early in the course and re-evaluate especially following acute events
- Consider involving a heart failure multi-disciplinary team



## **EHR Tools**

#### Make it easy to the "right" thing

*	Heart Failure "Tab" - Inpatient	Consolidates all the HF related data into a single place in the chart – meds, I/O, weights, LVEF, Labs
-\-	Heart Failure "Checklist"- Inpatient	Drive care by supporting initiation of GDMT with point of care guidance, standard orders and a dashboard
U	Templated HF visit notes- Outpatient	Capture data elements – NYHA class, weight, vital signs and medications  Tools to assess side-effects and adherence
613	HF Flowsheet – Outpatient	Capture LVEF, NYHA class, weights, meds, labs longitudinally
	1 click referral to pharmacist, palliative	care, sleep medicine, EP



#### Conclusions

- Heart failure is a complex chronic disease that often is complicated by multiple comorbidities
- Rapid initiation of the 4 core heart failure therapies leads to the best outcomes
- Developing systems of care to manage heart failure facilitates the care of heart failure patients throughout the course of the disease
- Multidisciplinary teams improve heart failure outcomes and encourage patient self-management
- Measuring performance metrics enables identification of opportunities for improvement





# Please evaluate this session using the QR Code



