Same Symptoms, Different Stories

HFrEF and HFpEF Explained

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Disclosures

The planners and speaker have indicated that there are no relevant financial relationships with any ineligible companies to disclose.

Abbreviation Key

- **Afib =** atrial fibrillation
- **ACEi** = angiotensin-converting enzyme inhibitor
- **ADHF** = acute decompensated heart failure
- **ARB** = angiotensin receptor blocker
- **ARNi** = angiotensin receptor-neprilysin inhibitor
- **CVD** = cardiovascular disease
- **DM** = diabetes mellitus
- **EF** = ejection fraction
- **eGFR** = estimated Glomerular Filtration Rate
- **GDMT** = guideline-directed medical therapy
- **HFpEF** = heart failure with preserved ejection fraction
- **HFrEF** = heart failure with reduced ejection fraction
- **HTN** = hypertension
- **LVEF** = left ventricular ejection fraction
- **MRA** = mineralocorticoid receptor antagonist
- **NYHA** = New York Heart Association
- **QD** = once daily
- **SGLT2i** = Sodium-Glucose Transporter 2 inhibitor

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Learning Objectives

- Compare & contrast the differences in pathophysiology between HFrEF vs HFpEF
- Differentiate the current treatment options available for HFrEF and HFpEF
- Recall the mechanism of action of drugs used in HFrEF and HFpEF
- Outline new clinical trials for HFrEF and HFpEF

Outline

- Overview of heart failure
- Pathophysiology
- Treatment overview
- Defining mechanisms of benefit
- Literature review

What is Heart Failure?

Heart Failure

The heart cannot pump enough blood to meet the body's needs for blood and oxygen

Compensatory mechanisms

- Heart
- Blood vessels
- Kidney

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American Heart Association. What is heart failure?. 2025.

Ejection Fraction Cut-Offs

Type of HF	Ejection Fraction Cut-offs
Reduced	**LVEF ≤ 40%**
Improved (imp)	Initial LVEF ≤ 40% and follow-up LVEF > 40%
Mildly reduced (mr)	LVEF 41 – 49%
Preserved	**LVEF ≥ 50%**

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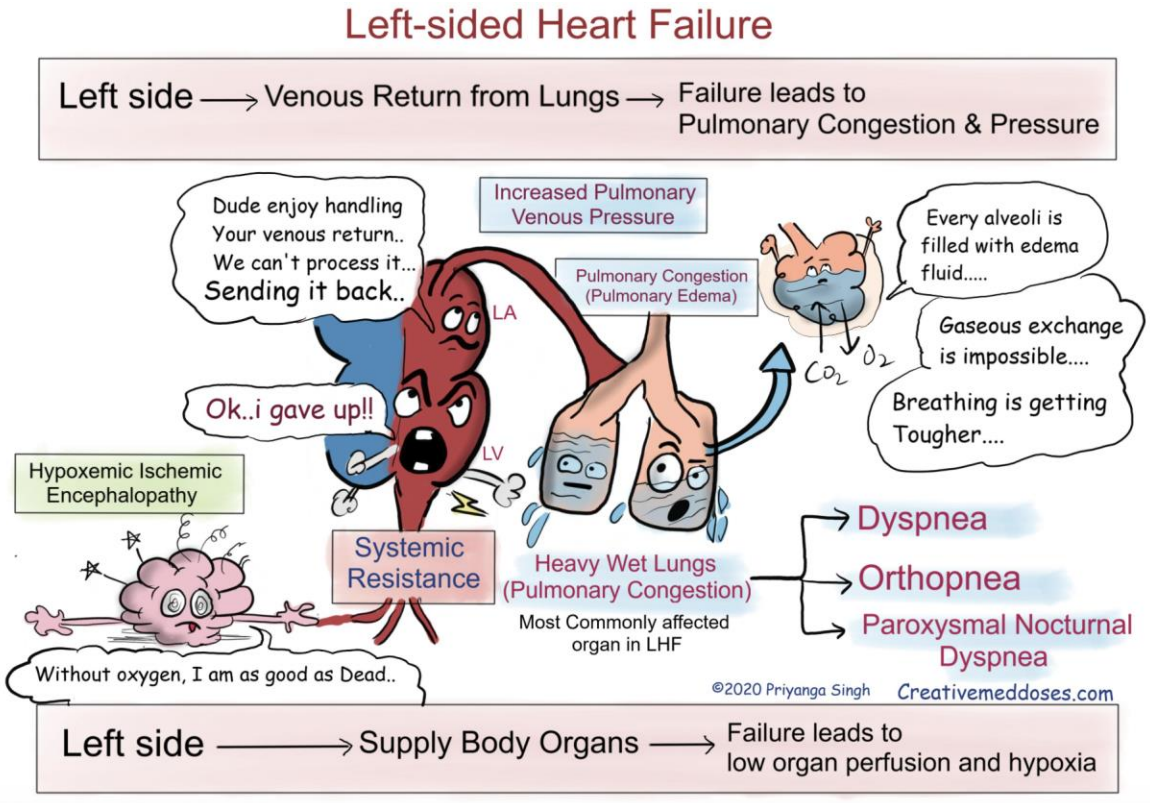
Heidenreich PA, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. *Circulation*. 2022

Left vs Right Sided HF



IQWiG. Heart failure: Learn More – Types of Heart Failure. InformedHealth.org [Internet]. 2023.
Singh P. Heart failure: Left Sided vs Right Sided. Creative Med Doses. 2020.

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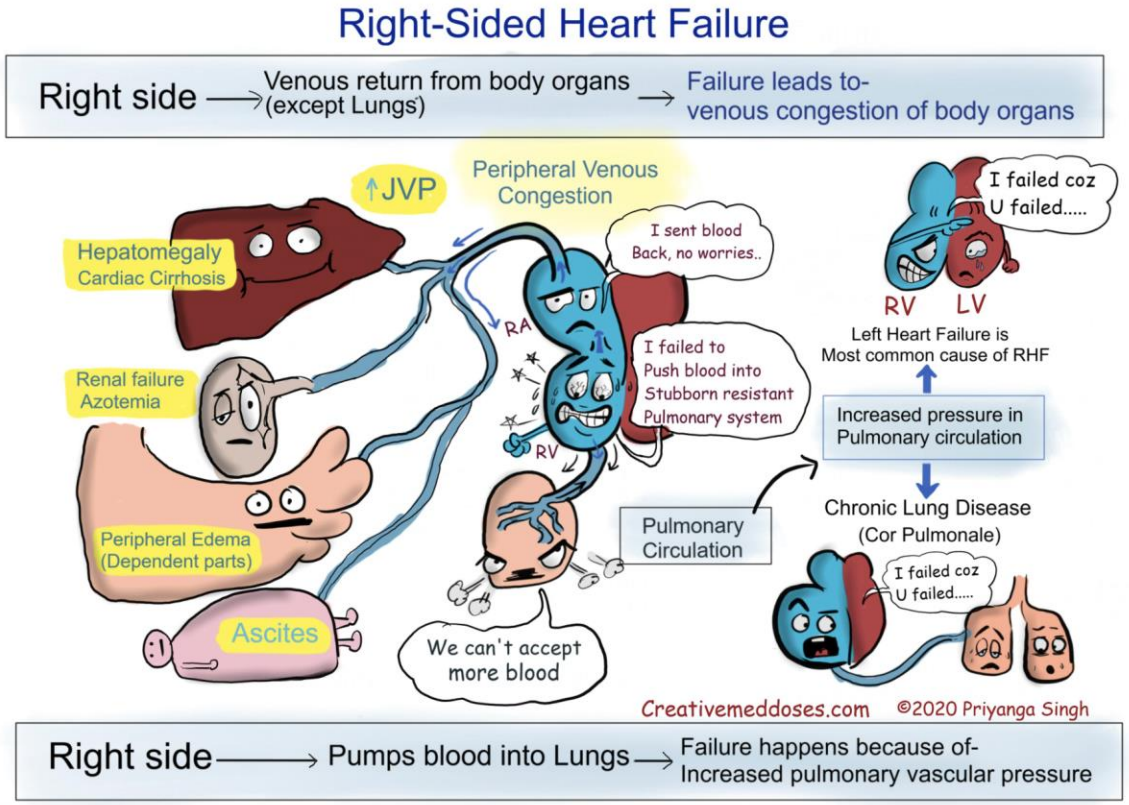
Left vs Right Sided HF Continued



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Singh P. Heart failure: Left Sided vs Right Sided. Creative Med Doses. 2020.

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Signs and Symptoms of Heart Failure

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Framingham Heart Failure Diagnostic Criteria

Need 2 major or 1 major and 2 minor criteria

Major Criteria	Minor Criteria
Paroxysmal nocturnal dyspnea or orthopnea	Ankle edema
Neck-vein distension	Night cough
Rales	Dyspnea on exertion
Cardiomegaly	Hepatomegaly
Acute pulmonary edema	Pleural effusion
S3 gallop	Vital capacity decrease 1/3 from max
Increased venous pressure >16cm of water	Tachycardia
Circulation time ≥25 sec	**Major or minor criterion: weight loss ≥ 4.5kg in 5 days in response to treatment**
Hepatojugular reflux	

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McKee PA et. al. The natural history of congestive heart failure: the Framingham study. New England Journal of Medicine 1971

Symptoms

Abdominal pain	Anorexia Nausea	Bloating Constipation	Ascites	Dyspnea on exertion
Exercise intolerance	Paroxysmal nocturnal dyspnea	Orthopnea	Tachypnea	Cough
Fatigue Weakness	Nocturia	Confusion	Altered mental status	

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Heart Failure. Schwinghammer TL, et al. *DiPiro's Pharmacotherapy Handbook. 12e.* McGraw Hill; 2023

Physical Exam Findings

Pitting edema	Jugular venous distension	Hepatojugular reflex (HJR)	Hepatomegaly	Weight gain
Bibasilar rales	Pulmonary edema	S3 gallop	Pleural effusion	Decrease carotid upstrokes
Tachycardia	Pallor	Cyanosis of digits	Displaced point of maximal impulse	

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Heart Failure. Schwinghammer TL, et al. *DiPiro's Pharmacotherapy Handbook, 12e*. McGraw Hill; 2023.

Staging Heart Failure

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Stage A: At-Risk for Heart Failure

At risk for HF but without current or previous symptoms/signs of HF & without structural/functional heart disease or abnormal biomarkers

Patients with HTN, CVD, diabetes, obesity, exposure to cardiotoxic agents, genetic variant for cardiomyopathy, or family history of cardiomyopathy

ADVOCATE HEALTH

Heidenreich PA, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. *Circulation*. 2022

Stage B: Pre-Heart Failure

Patients without current or previous symptoms/signs of HF but evidence of 1 of the following:

Structural heart disease
Evidence of increased filing pressures
Risk factors and abnormal lab finding

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Heidenreich PA, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. *Circulation*. 2022

Stage C: Symptomatic Heart Failure

Evidence of structural heart disease

Patients with current or previous symptoms or signs of heart failure

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Heidenreich PA, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. *Circulation*. 2022

Stage D: Advanced Heart Failure

Marked HF symptoms that interfere with daily life

Recurrent hospitalizations

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Heidenreich PA, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. *Circulation*. 2022.

New York Heart Association Functional Classification

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Class	Symptoms
I	• No physical activity limitations
II	• Slight physical activity limitations • Comfortable at rest
III	• Marked physical activity limitations
IV	• Symptoms at rest • Any physical activity causes discomfort

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American Heart Association. Classes and Stages of Heart Failure. May 21, 2025.

Epidemiology

Incidence of Heart Failure

In 2017 estimate that 64.3 million people worldwide had HF

HF prevalence expected to increase 46% between 2012 and 2030

In the United States, more than 6 million people currently have HF

Incidence rate of HF is 20.9 per 1,000 person-years

GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, et al. a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018
Virani SS, et al. Heart disease and stroke statistics—2021 update. *Circulation* 2021
Lee MP, et al. Risk factors for heart failure with preserved or reduced ejection fraction among Medicare beneficiaries. *Clin Epidemiol.* 2020

Risk Factors

Males were more likely to develop HFrEF than HFpEF

Afib and pulmonary hypertension were more strongly associated with the risk of HFpEF

- Afib most influential comorbidity

Cardiomyopathy and myocardial infarction were more strongly associated with risk of HFrEF

- Cardiomyopathy most influential comorbidity

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Lee MP, et al. Risk factors for heart failure with preserved or reduced ejection fraction among Medicare beneficiaries. *Clin Epidemiol.* 2020

HFrEF vs HFpEF Pathophysiology

HFrEF – Initial Cardiac Insult

- Myocardial infarction
- Hypertension
- Idiopathic/genetic
- Valve abnormalities
- Viral illness
- Alcohol
- Drugs
- Tachycardia
- Connective tissue disease
- High output states

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Heart Failure. Schwinghammer TL, et al.*DiPiro's Pharmacotherapy Handbook, 12e*. McGraw Hill; 2023.

Compensatory Mechanisms

Myocardial dysfunction → Increased preload
Reduced systemic perfusion

↓

Activation of Renin-Angiotensin System (RAS)
and Sympathetic Nervous System (SNS)

↓

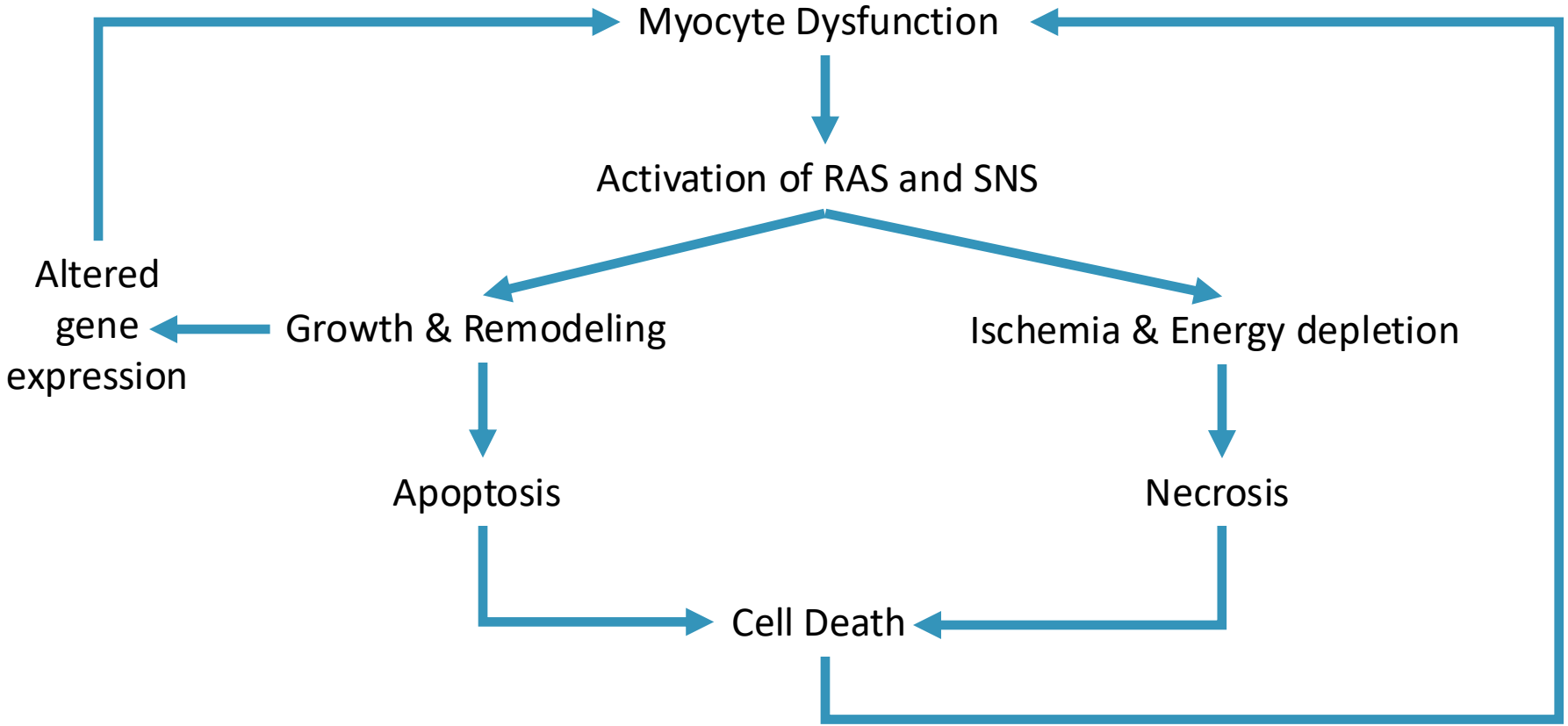
Kidney
- ↓ Renal blood flow
- ↑ Renin released
- ↑ Sodium resorption
- ↓ Response to natriuretic peptides

Heart
- ↑ Myocyte necrosis/apoptosis
- ↑ LV remodeling
- ↑ Fibrosis
- ↑ Preload
- ↓ Beta-adrenergic responsiveness

Peripheral Vasculature
- ↑ Vasoconstriction
- ↑ Vascular stiffness

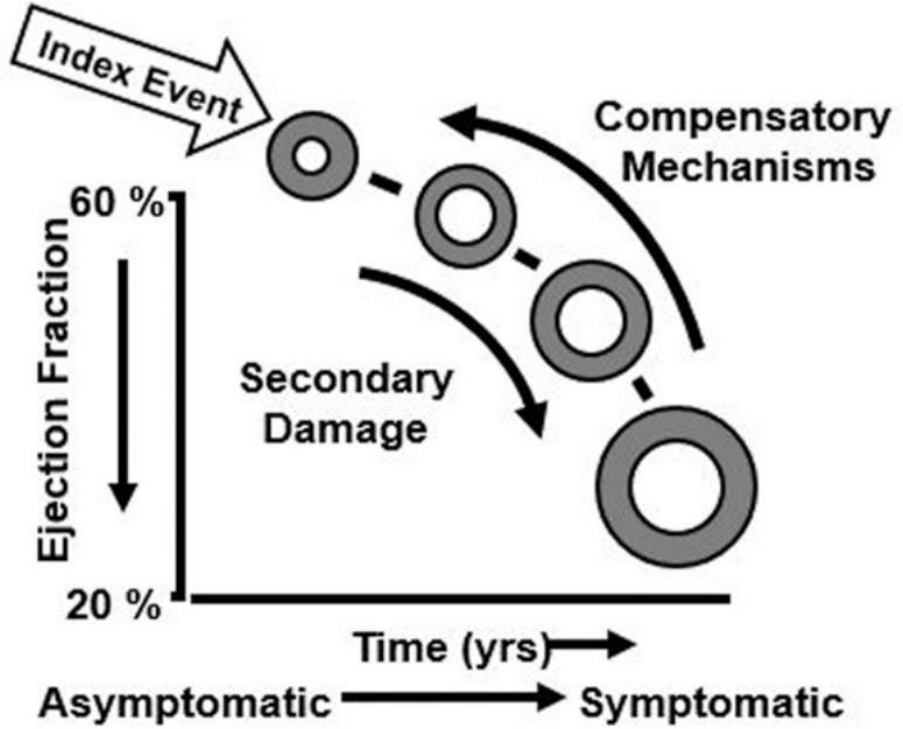
Mann DL, et al. Mechanisms and Models in Heart Failure: A Translational Approach. *Circ Res*. 2021
Eichhorn EJ, et al. Medical therapy can improve the biological properties of the chronically failing heart. *Circulation*. 1996
Mancini GB, et al. Pharmacologic Options for the Management of Systolic Heart Failure: Examining Underlying Mechanisms. *Can J Cardiol*. 2015

Myocyte Loss



Eichhorn EJ, et al. Medical therapy can improve the biological properties of the chronically failing heart. *Circulation*. 1996

Over Time



Mann DL, et al. Mechanisms and Models in Heart Failure: A Translational Approach. *Circ Res*. 2021
Narayan SI, et al. The Pathophysiology and New Advancements in the Pharmacologic and Exercise-Based Management of Heart Failure With Reduced Ejection Fraction. *Cureus*. 2023

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HFpEF Pathophysiology

Impaired myocardial relaxation +/- increased diastolic stiffness

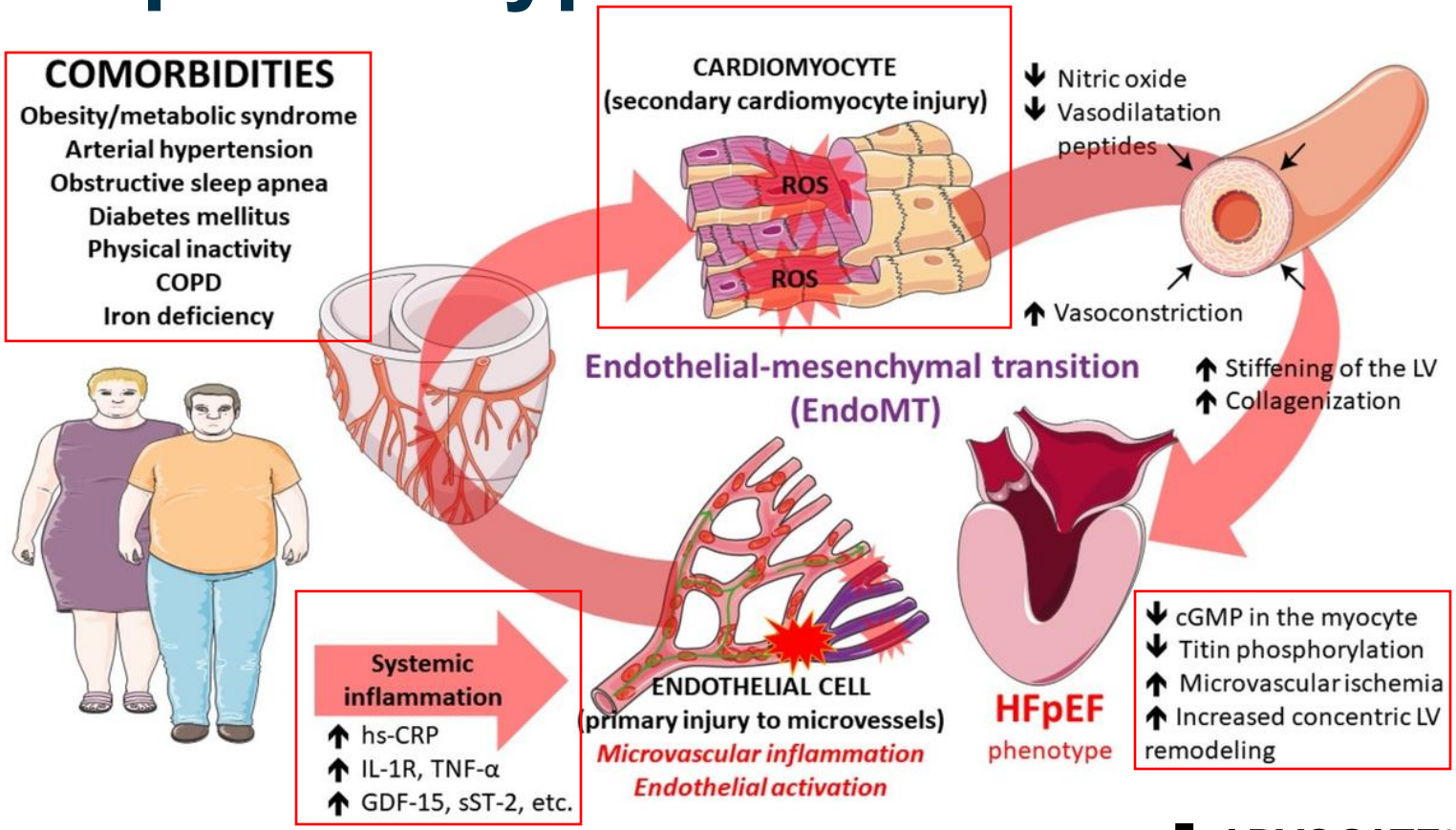
Ventricular chamber and ejection fraction are normal

Heterogenous disorder

Left ventricular hypertrophy most common structural abnormality associated with HFpEF

Heidenreich PA, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. *Circulation*. 2022
Heinzel FR, et al. Myocardial hypertrophy and its role in heart failure with preserved ejection fraction. *J Appl Physiol (1985)*. 2015
Kittleson MM, et al. 2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction. J Am Coll Cardiol. 2023.
D'Amario D, et al. Microvascular Dysfunction in Heart Failure With Preserved Ejection Fraction. *Front Physiol*. 2019
Davis BR, et al. Heart failure with preserved and reduced left ventricular ejection fraction in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. *Circulation*. 2008

Proposed Hypothesis



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D'Amario D, et al. Microvascular Dysfunction in Heart Failure With Preserved Ejection Fraction. *Front Physiol*. 2019

Assessment Question #1

Which of the following statement(s) is true regarding the pathophysiology of HFrEF and HFpEF?

A. In HFrEF, there is an increase in nitric oxide and brain natriuretic peptide

B. In HFrEF, there is activation of the RAAS and parasympathetic nervous system

C. In HFpEF, comorbidities such as diabetes and atrial fibrillation lead to a pro-inflammatory state

D. HFpEF is a homogenous disorder where patients will have the same morphology and functional presentation

HFrEF's Treatment Algorithm

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Stage A: At-Risk for Heart Failure

SGLT2i*

Optimize blood pressure

Optimize CVD management

*only in patients with diabetes

1 (Strong) | 2a (Moderate) | 2b (Weak)

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Heidenreich PA, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. *Circulation*. 2022

Stage B: Pre-Heart Failure

SGLT2i*

ACEi

ARB

*only in patients with diabetes

Beta Blocker

Optimize blood pressure

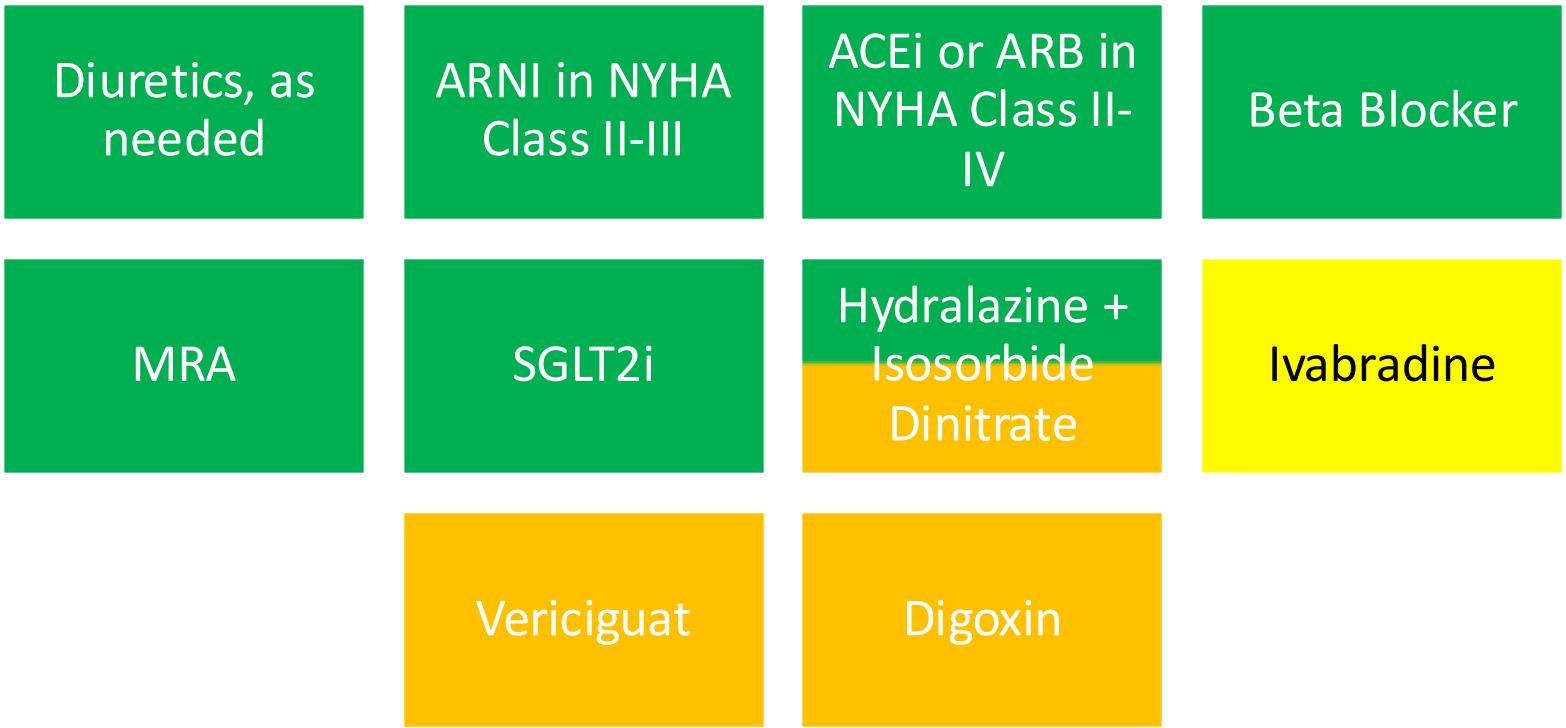
Optimize CVD management

1 (Strong) | 2a (Moderate) | 2b (Weak)

ADVOCATE HEALTH

Heidenreich PA, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. *Circulation*. 2022

Stage C and D: Symptomatic Heart Failure & Advanced Heart Failure



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Heidenreich PA, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. *Circulation*. 2022

HFpEF's Treatment Algorithm

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Standard of Care

Loop diuretic agents – fluid retention & NYHA Class II-IV

SGTL2i

MRA

ARNi

ARB

1 (Strong) | 2a (Moderate) | 2b (Weak)

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Kittleson MM, et al. 2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction. J Am Coll Cardiol. 2023.

Medication Dosing Review

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Class	Drug Name	Starting Dose	Target Dose
ACEi	Captopril	6.25-12.5 mg TID	25-50 mg TID
	Enalapril	1.25-2.5 mg BID	10 mg BID
	Lisinopril	2.5-5 mg QD	20-40 mg QD
	Ramipril	1.25-2.5 mg BID	5 mg BID
ARBs	Candesartan	4-8 mg QD	32 mg QD
	Losartan	25-50mg QD	150mg QD
	Valsartan	40 mg BID	160 mg BID
ARNI	Sacubitril/Valsartan	24/26 mg BID	97/103 mg BID

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Heart Failure. Schwinghammer TL, et al.*DiPiro's Pharmacotherapy Handbook, 12e*. McGraw Hill; 2023.

Class	Drug Name	Starting Dose	Target Dose
Beta Blockers	Carvedilol	3.125 mg BID	25 mg BID
	Bisoprolol	1.25 mg QD	10 mg QD
	Metoprolol CR/XL	12.5-25 mg QD	200 mg QD
MRAs	Spironolactone	12.5-25 mg QD	25-50 mg QD
	Eplerenone	25 mg QD	50 mg QD
SGLT2i	Empagliflozin	10 mg QD	25 mg if DM
	Dapagliflozin	5 mg QD	10 mg QD

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Heart Failure. Schwinghammer TL, et al.*DiPiro's Pharmacotherapy Handbook, 12e*. McGraw Hill; 2023.

Assessment Question #2

OG is a 65-year-old male with normal renal function and a PMH of diabetes, CHF with a LVEF 39%, and atrial fibrillation who presents to the clinic with increased lower extremity edema and increased shortness of breath with normal daily activities. The patient is currently on metoprolol succinate 50mg once daily, metformin 1,000mg BID, and empagliflozin 25mg once daily.

Which of the following agents could be recommended to add to this patient based on the 2022 AHA guidelines? Select all that apply.

A. Valsartan/sacubitril
B. Furosemide
C. Carvedilol
D. Spironolactone

Defining Mechanisms of Benefit

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HFrEF – SGLT2i

- Stimulation of natriuresis and osmotic diuresis
- Decreases tubuloglomerular feedback
- Inhibition of cardiac fibrosis
- Decreases central nervous system sympathetic nervous activity
- Shifts to ketone based myocardial metabolism

ADVOCATE HEALTH

Mann DL, et al. Mechanisms and Models in Heart Failure: A Translational Approach. *Circ Res*. 2021

HFrEF – Beta Blocker

- Blocks adrenergic receptors
- Heart rate reduction
- Reduce myocardial oxygen consumption
- Strongly modulate LV remodeling

ADVOCATE HEALTH

Mann DL, et al. Mechanisms and Models in Heart Failure: A Translational Approach. *Circ Res*. 2021

HFrEF – MRAs

- Inhibit effects of aldosterone
- Decrease preload and vascular congestion
- Improve endothelial function
- Block effects of norepinephrine from sympathetic nerve terminals

ADVOCATE HEALTH

Mann DL, et al. Mechanisms and Models in Heart Failure: A Translational Approach. *Circ Res*. 2021
Ferreira JP, et al. Mineralocorticoid Receptor Antagonists in Heart Failure: An Update. *Circ Heart Fail*. 2024

HFrEF – ACEi/ARB

ACEi – angiotensin converting enzyme inhibitor

- Inhibits conversion of angiotensin I to angiotensin II

ARB – angiotensin receptor blocker

- Block angiotensin I receptor

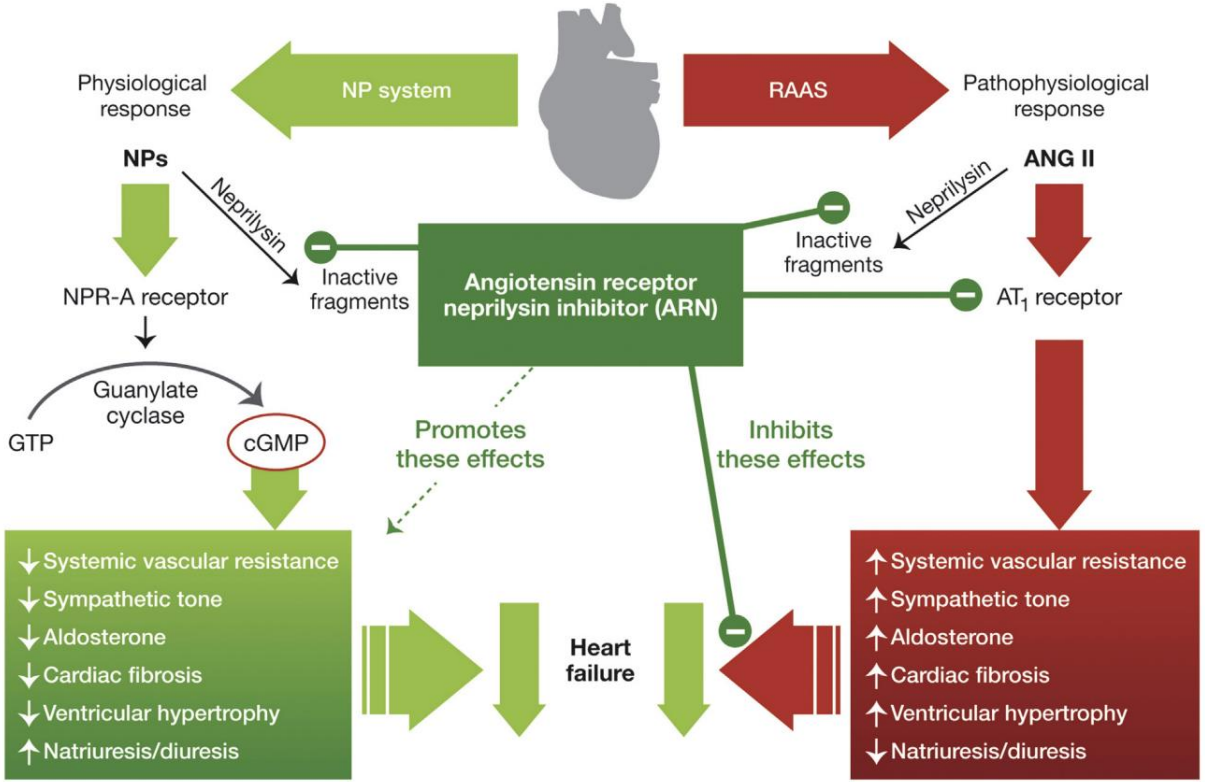
Both agents:

- Decrease preload and vascular congestion
- Stop vasoconstriction
- Attenuate cardiac remodeling

ADVOCATE HEALTH

Mann DL, et al. Mechanisms and Models in Heart Failure: A Translational Approach. *Circ Res.* 2021

HFrEF - ARNi



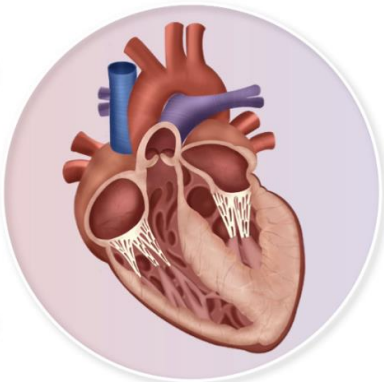
ADVOCATE HEALTH

Mann DL, et al. Mechanisms and Models in Heart Failure: A Translational Approach. *Circ Res.* 2021

HFpEF – SGLT2i

HFpEF and diastolic dysfunction

- Oxidative stress, inflammation, fibrosis
- Cardiac remodelling and hypertrophy
- Myofilament stiffness
- Impaired energetics
- Ionic imbalances



Mechanisms of SGLT2 inhibitors in HFpEF

- Improved NO-sGC-cGMP-PKG signaling
- Improved metabolism and energetics
- Reduced renal deterioration
- Increased autophagic flux
- Improved diastolic function
- Reduced oxidative stress and inflammation

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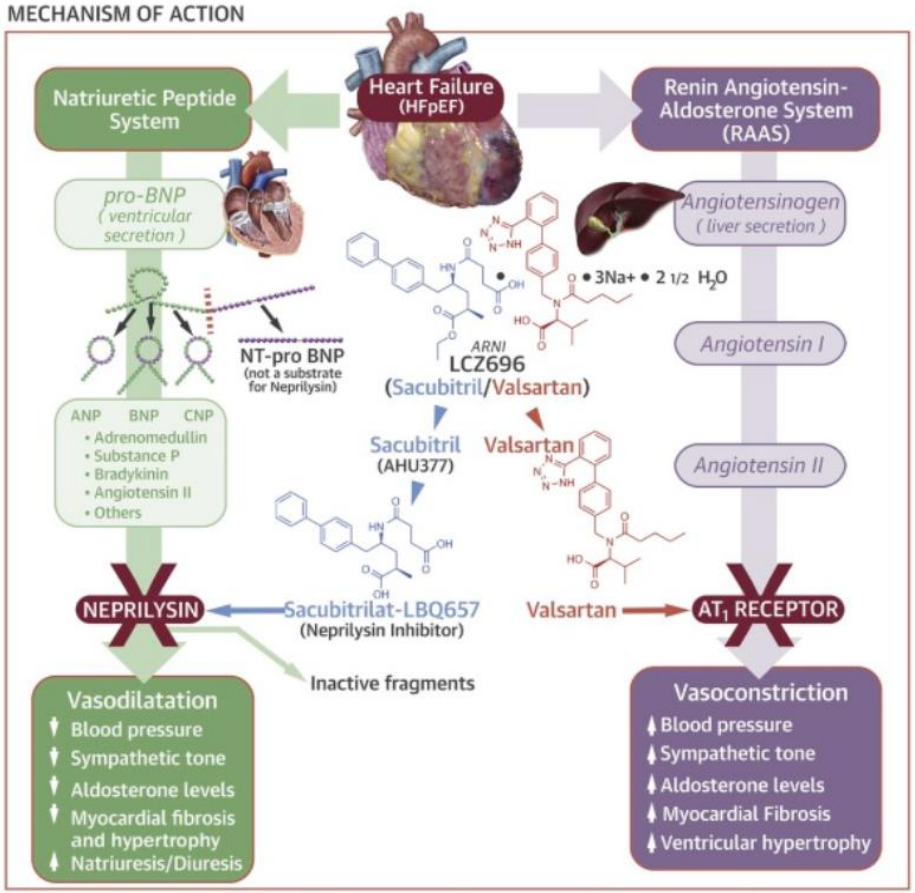
Pandey AK, et al. Mechanisms of benefits of sodium-glucose cotransporter 2 inhibitors in heart failure with preserved ejection fraction. *Eur Heart J*. 2023

HFpEF – MRAs

- Reduce excessive fibrosis
- Decrease proinflammatory pathways
- Prevention of cardiac remodeling
- Decrease blood pressure

Ferreira JP, et al. Mineralocorticoid Receptor Antagonists in Heart Failure: An Update. *Circ Heart Fail*. 2024

HFpEF – ARBs and ARNi



Solomon SD, et al. Angiotensin Receptor Neprilysin Inhibition in Heart Failure With Preserved Ejection Fraction: Rationale and Design of the PARAGON-HF Trial. *JACC Heart Fail*. 2017

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Assessment Question #3

Of the statements below, please select the true statements.

I. SGLT2i have no beneficial mechanism of action in HFrEF nor HFpEF

II. MRAs can decrease cardiac remodeling via reduction in fibrosis in HFrEF & HFpEF

III. ACEi/ARB/ARNi are all able to decrease preload, prevent vasoconstriction, and attenuate cardiac remodeling

IV. Beta blockers bind to cholinergic receptors which enhances cardiac myocyte function

A. I only

B. II and III

C. I and IV

D. II, III, and IV

Medication Use Challenges

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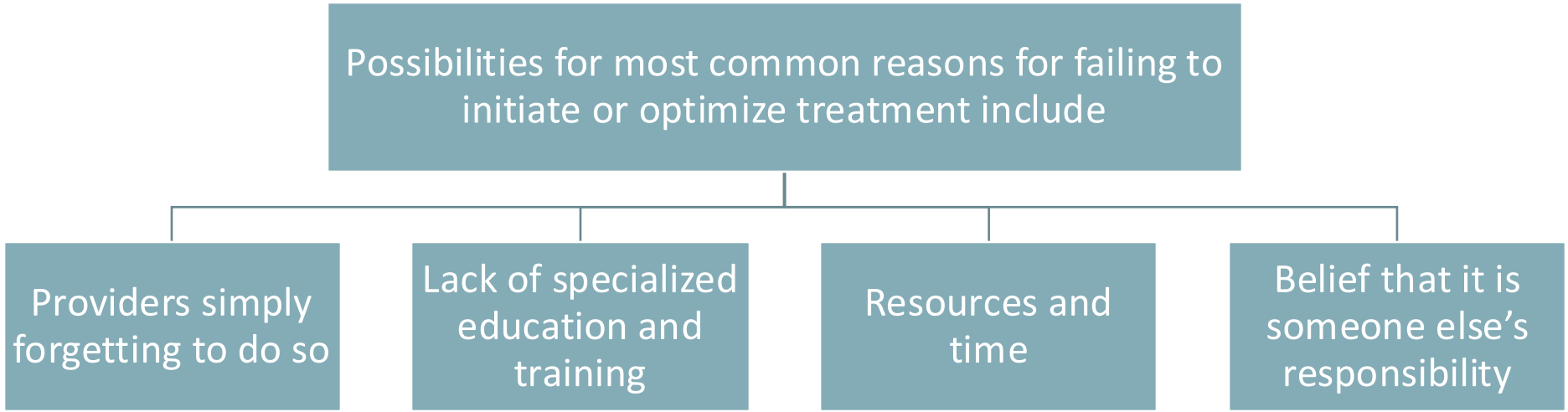
Cracks in the System



Pierce JB, et al. Quality care and outcomes among patients hospitalized for heart failure in rural vs urban US hospitals. *JAMA Cardiol.* 2023
Ouwerkerk Wet al. Determinants and clinical outcome of uptitration of ACE-inhibitors and beta-blockers in patients with heart failure. *Eur Heart J*. 2017
Jarjour M, et al. Care Gaps in Adherence to Heart Failure Guidelines: Clinical Inertia or Physiological Limitations?. *JACC Heart Fail*. 2020
Al-Tamimi MA, et al. Factors Associated With Hospital Readmission of Heart Failure Patients. *Front Pharmacol*. 2021

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Clinical Pharmacists Role

2018 study completed at Advocate Trinity Hospital examined hospitalizations before and after implementation of a clinical pharmacist

- Found a 50% decrease in heart failure hospitalizations in patients regularly scheduled with a clinical pharmacist within the first 10 months
- 2% of high-risk patients had 30-day readmission for HF when regularly seen by clinical pharmacists

ADVOCATE HEALTH

Schumacher C, et al. The Effect of Clinical Pharmacists on Readmission Rates of Heart Failure Patients in the Accountable Care Environment. *J Manag Care Spec Pharm*. 2018

Clinical Pharmacists Role Continued

Inpatient and outpatient clinical pharmacists have varying types of contributions, however, there are some aspects that are consistently performed in both settings

- Medication reconciliation
- Patient education
- Providing pharmacotherapeutic recommendation and monitoring
- Improving medication adherence
- Access to medications and transitions of care

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Cheng JW. Current perspectives on the role of the pharmacist in heart failure management. *Integr Pharm Res Pract*. 2018

HFrEF Literature Review

- QUAD Score
- DIGIT-HF

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QUAD Score

Retrospective, observational study

Primary Outcome

- Composite of 1st unplanned hospitalization for HF (HHF) or all-cause morality at 1 year

Secondary Outcomes

- Components of primary outcome
- Time taken to final therapy titration

Useability of QUAD Score

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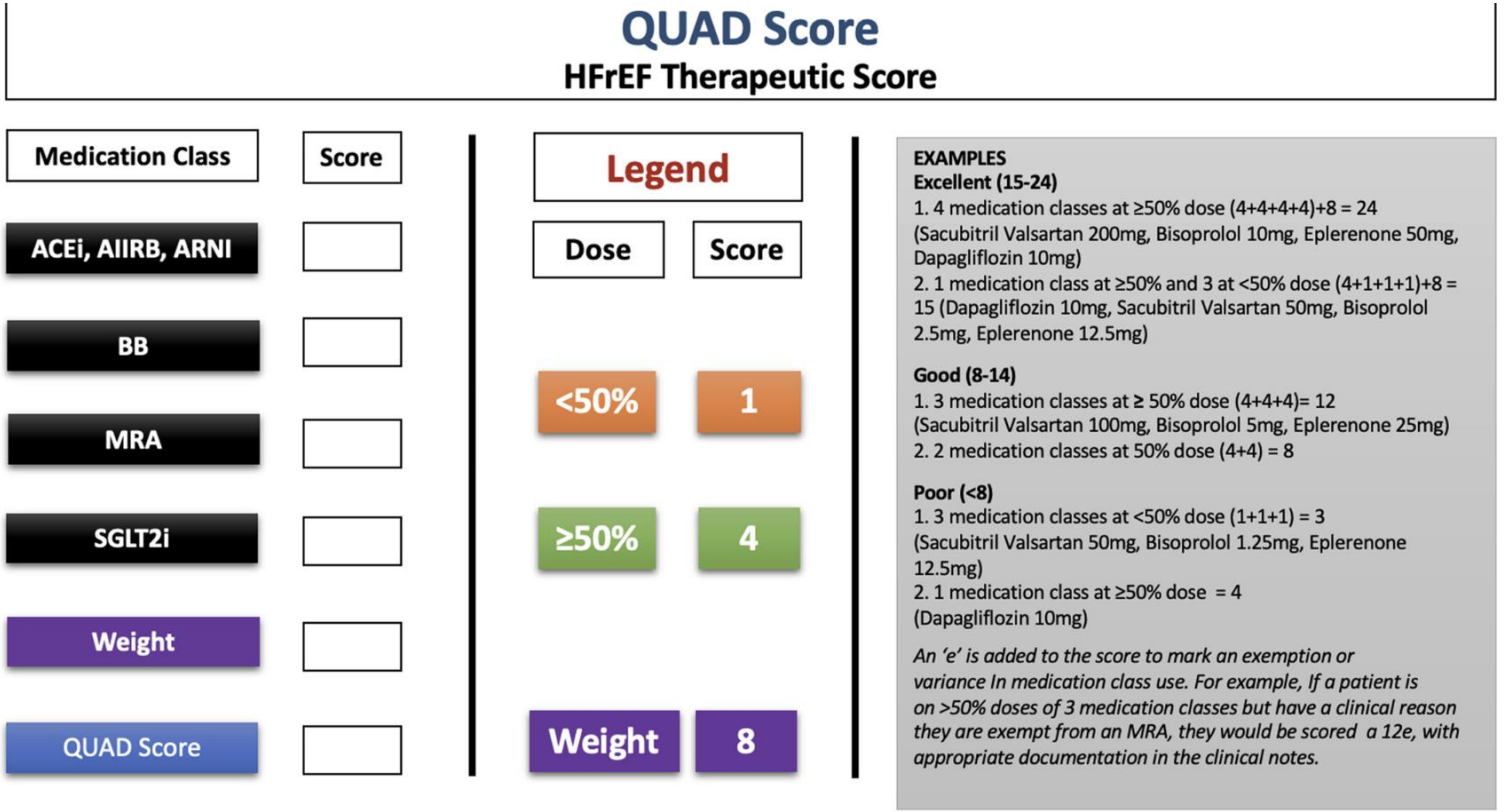
Savage HO, et al. A novel treatment score (QUAD score) to promote treatment optimization in heart failure with a reduced ejection fraction. *ESC Heart Fail*. 2025.

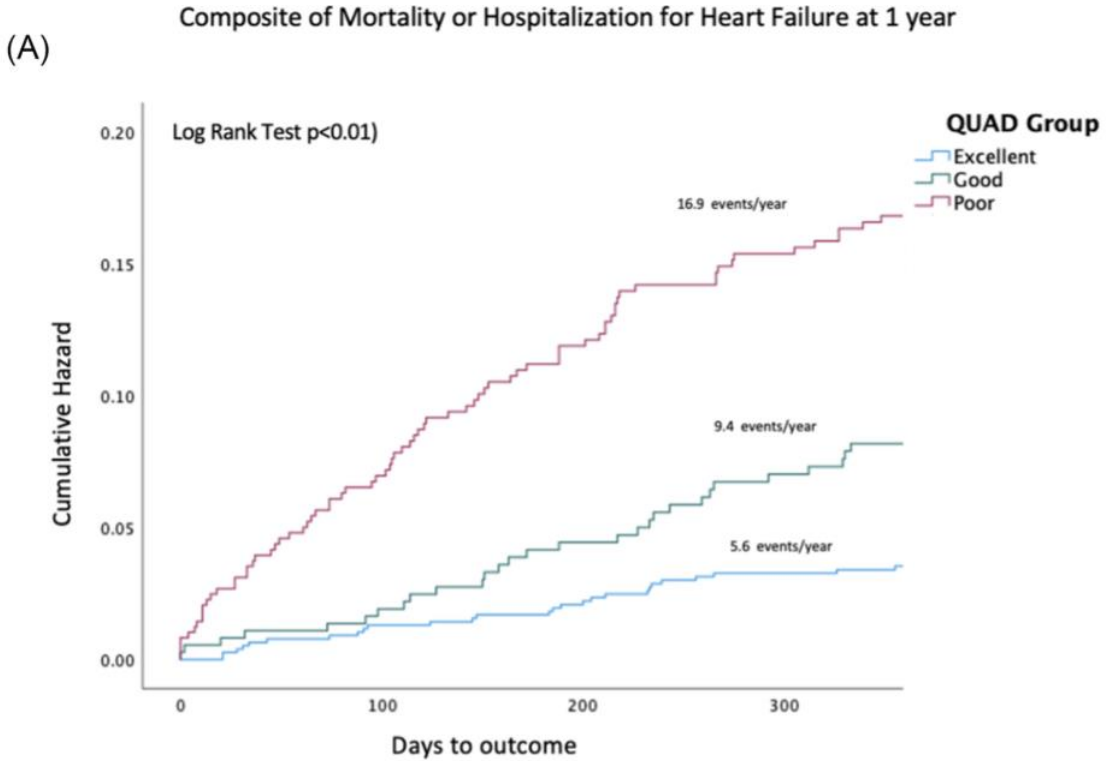
QUAD Score



ADVOCATE HEALTH

Savage HO, et al. A novel treatment score (QUAD score) to promote treatment optimization in heart failure with a reduced ejection fraction. *ESC Heart Fail*. 2025.

Results



ADVOCATE HEALTH

Savage HO, et al. A novel treatment score (QUAD score) to promote treatment optimization in heart failure with a reduced ejection fraction. *ESC Heart Fail*. 2025.

Results

Primary Outcome Components			Time taken to final optimization
QUAD Score	**HHF**	**Mortality**	**Median (IQR) days**
Excellent	3.2%	2.4%	174 (99– 290)
Good	3.9%	6.5%	133 (80 – 232)
Poor	7.7%	13.1%	108 (57 – 193)

ADVOCATE HEALTH

Savage HO, et al. A novel treatment score (QUAD score) to promote treatment optimization in heart failure with a reduced ejection fraction. *ESC Heart Fail*. 2025.

Conclusion

Simple tool

↓

Incentivize and audit GDMT

↓

Excellent scores associated with better outcome

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Savage HO, et al. A novel treatment score (QUAD score) to promote treatment optimization in heart failure with a reduced ejection fraction. *ESC Heart Fail*. 2025.

DIGIT-HF

Evaluate efficacy and safety of digitoxin at lower concentrations

Digitoxin starting dose = 0.07mg QD

- Decreased to 0.05 mg QD or increased to 0.1 mg QD

Noninferiority defined by hazard ratio of no more than 1.303

Lower participants than anticipated participated in the trial

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Bavendiek U, et al. Digitoxin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 2025

Outcomes

Primary

- Composite of death from any cause or hospital admission for worsening heart failure

Secondary

- Death from any cause
- Composite of death from any cause and any hospitalization due to HF
- Death from HF
- Composite of death from cardiovascular causes or first hospitalization for HF

Safety

- Digitoxin concentrations, adverse events

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Bavendiek U, et al. Digitoxin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 2025

Results

Primary outcome and components	Digitoxin N = 613	Placebo N = 599	Hazard/Rate Ratio (95% CI)
Death from any cause or first hospitalization for HF	242 (39.5%)	264 (44.1%)	0.82 (0.69 to 0.98)
Death from any cause	167 (27.2%)	177 (29.5%)	0.86 (0.69 to 1.07)
First hospitalization for HF	172 (28.1%)	182 (30.4%)	0.85 (0.69 to 1.05)

Key secondary outcome	Digitoxin N = 613	Placebo N = 599	Hazard/Rate Ratio (95% CI)
Death from any cause and hospitalization for HF	537 25.1 events/100 pt yr	531 26.6 events/100 pt yr	0.85 (0.67 to 1.09)

ADVOCATE HEALTH

Bavendiek U, et al. Digitoxin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 2025

Safety Outcomes

Mean serum concentration at

- 6 weeks: 17 ± 5.9 ng/mL
- 12 months: 13.5 ± 5.1 ng/mL

Serious adverse event

- Occurred in 4.7% in digitoxin group and 2.8% in the placebo group

Discontinuation

- Occurred in 9.1% in digitoxin group and 10.2% in the placebo group

ADVOCATE HEALTH

Bavendiek U, et al. Digitoxin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 2025

Conclusion

Patients with HFrEF on GDMT benefited from digitoxin

Lower combined risk of death from any cause or hospital admission for worsening heart failure than placebo

ADVOCATE HEALTH

Bavendiek U, et al. Digitoxin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 2025

HFpEF Literature Review

- FINEARTS-HF
- STEP-HFpEF and STEP-HFpEF DM
- SUMMIT

FINEARTS-HF

Assess efficacy of finerenone in patients with HFmrEF or HFpEF

Randomized, placebo-controlled, event-driven Phase 3 trial

- Starting dose: finerenone 10mg or 20mg
- Dose adjusted based on eGFR
- Titration occurred after 4 weeks

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Solomon SD, et al. Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N Engl J Med*. 2024

Outcomes

Primary

- Composite of total worsening HF events and death from cardiovascular causes

Secondary

- Total worsening HF events
- Death from cardiovascular causes
- Changes in the Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Improvement in NYHA Functional Class
- Kidney composite outcomes
- Composite of sustained decrease in eGFR ≥ 50%, decline in eGFR <15, or initiation of long-term dialysis or kidney transplant
- Death from any cause

ADVOCATE HEALTH

Solomon SD, et al. Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N Engl J Med*. 2024

Results

Primary Outcome	Finerenone N = 3003	Placebo N = 2998	Rate Ratio (95% CI) P value
Total worsening HF event and death from CV causes - # of events (%)	1083 (36.06%)	1283 (42.8%)	0.84 (0.74 – 0.95) P = 0.007
Total worsening HF events - # of events (%)	842 (28.04%)	1024 (34.16%)	0.82 (0.71 – 0.94) P = 0.006
Death from CV causes - # of pts (%)	242 (8.1%)	260 (8.7%)	Hazard ratio 0.93 (0.78 – 1.11)

Secondary outcomes	Finerenone	Placebo	Difference (95% CI) P value
Change from baseline in KCCQ	8.0 ± 0.3	6.4 ± 0.3	1.6 (0.8 – 2.3) P < 0.001

ADVOCATE HEALTH

Solomon SD, et al. Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N Engl J Med*. 2024

Conclusion

Significant reduction in rates of composite worsening HF events and death from CV causes

Significant reduction rates of worsening HF events alone

No difference in rate of death from CV causes alone

ADVOCATE HEALTH

Solomon SD, et al. Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N Engl J Med*. 2024

STEP-HFpEF and STEP-HFpEF DM

	STEP-HFpEF	STEP-HFpEF DM
Objective	Evaluate if semaglutide can lead to reductions in symptoms, physical limitations, and weight loss compared to placebo	Evaluate the efficacy and safety of semaglutide in patients with obesity, HFpEF, and DM
Design	Randomized, double-blind placebo-controlled trial	
Dose	Starting dose: semaglutide 0.25mg SC once weekly Max dose: semaglutide 2.4mg SC once weekly	

Kosiborod MN, et al. Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. *N Engl J Med*. 2023
Kosiborod MN, et al. Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes. *N Engl J Med*. 2024

Outcomes

	STEP-HFpEF	STEP-HFpEF DM
Primary	Change in KCCQ Percent change in body weight	
Secondary	Change in 6-minute walk distance Hierarchical composite reported as win ratio Change in C-reactive protein level	

Kosiborod MN, et al. Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. *N Engl J Med*. 2023
Kosiborod MN, et al. Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes. *N Engl J Med*. 2024

Results

	STEP-HFpEF			STEP-HFpEF DM		
Outcome	**Semaglutide** N = 263	**Placebo** N = 266	**Estimated Difference or Ratio** (95% CI) **P-value**	**Semaglutide** N = 310	**Placebo** N = 306	**Estimated Difference or Ratio (95% CI) P-value**
Change in KCCQ -points	16.6	8.7	7.8 (4.8 – 10.9) P < 0.001	13.7	6.4	7.3 (4.1 – 10.4) P < 0.001
Percent change in body weight	-13.3	-2.6	-10.7 (-11.9 to -9.4) P < 0.001	-9.8	-3.4	-6.4 (-7.6 to -5.2) P < 0.001
Change in 6-minute walk distance – m	21.5	1.2	20.3 (8.6 – 32.1) P < 0.001	12.7	-1.6	14.3 (3.7 – 24.9) P = 0.008

Kosiborod MN, et al. Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. *N Engl J Med*. 2023
Kosiborod MN, et al. Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes. *N Engl J Med*. 2024

Conclusions

STEP-HFpEF	STEP-HFpEF DM
Semaglutide had a larger reductions in symptoms, physical limitations, improved exercise function, and had greater weight loss than placebo	Semaglutide had a larger reduction in HF symptoms, physical limitations, and had greater weight loss than placebo.

Kosiborod MN, et al. Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. *N Engl J Med*. 2023
Kosiborod MN, et al. Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes. *N Engl J Med*. 2024

SUMMIT

Evaluate tirzepatide for patients with HFpEF and obesity

Double-blind, randomized, placebo-controlled Phase 3 trial

- Starting dose of tirzepatide: 2.5mg SC once weekly
- Max dose of tirzepatide: 15mg SC once weekly
- Titration occurred every 4 weeks

ADVOCATE HEALTH

Packer M, et al. Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity. *N Engl J Med*. 2025

Outcomes

Primary

- Composite of adjudicated death from cardiovascular causes or worsening HF events
- Change from baseline to 52 weeks in KCCQ total symptom score

Secondary outcomes

- Change at 52 weeks in 6-minute walk distance
- Percent change at 52 weeks in body weight
- Percent change at 52 weeks in high-sensitivity C-reactive protein level

ADVOCATE HEALTH

Packer M, et al. Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity. *N Engl J Med*. 2025

Results

Primary Outcomes	Tirzepatide N = 364	Placebo N = 367	Hazard Ratio or Difference (95% CI); P – value
Composite adjudicated death from CV causes or worsening HF event -no. (%)	36 (9.9%)	56 (15.3%)	0.62 (0.41 – 0.95) P = 0.026
Adjudicated death from CV causes -no. (%)	8 (2.2%)	5 (1.4%)	1.58 (0.52 – 4.83)
Adjudicated worsening HF events -no. (%)	29 (8%)	52 (14.2%)	0.54 (0.34 – 0.85)
Change at 52 weeks in KCCQ	19.5 ± 1.2	12.7 ± 1.3	6.9 (3.3 – 10.6) P < 0.001

ADVOCATE HEALTH

Packer M, et al. Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity. *N Engl J Med*. 2025

Conclusion

Significant reduction in rates of composite death from CV causes or worsening HF events

Significant reduction in worsening HF events alone

No difference in rate of death from CV causes alone

ADVOCATE HEALTH

Packer M, et al. Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity. *N Engl J Med*. 2025

Assessment Question #4

Which of the following statements are NOT true? Select all that apply.

A. There was no significant difference between finerenone and placebo in the composite primary endpoint
B. There was a significant difference between finerenone and placebo in the composite primary endpoint
C. There was no significant difference between finerenone and placebo for worsening HF events alone
D. There was no significant difference between finerenone and placebo for death from CV causes alone

Take Away Points

- HF is a diverse disease state with many different treatment algorithms available
- Emphasis should be placed on counseling patients and medication reconciliations
- Emerging roles for pharmacists to handle drug titration
- New literature is still coming out regarding HF
- New and promising therapeutic options are emerging

Resources

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Resources

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Resources

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Questions?

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