



**ADVOCATE** HEALTH

# 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

# 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

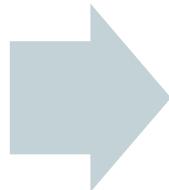
Defining mechanisms of benefit

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

# Ejection Fraction Cut-Offs

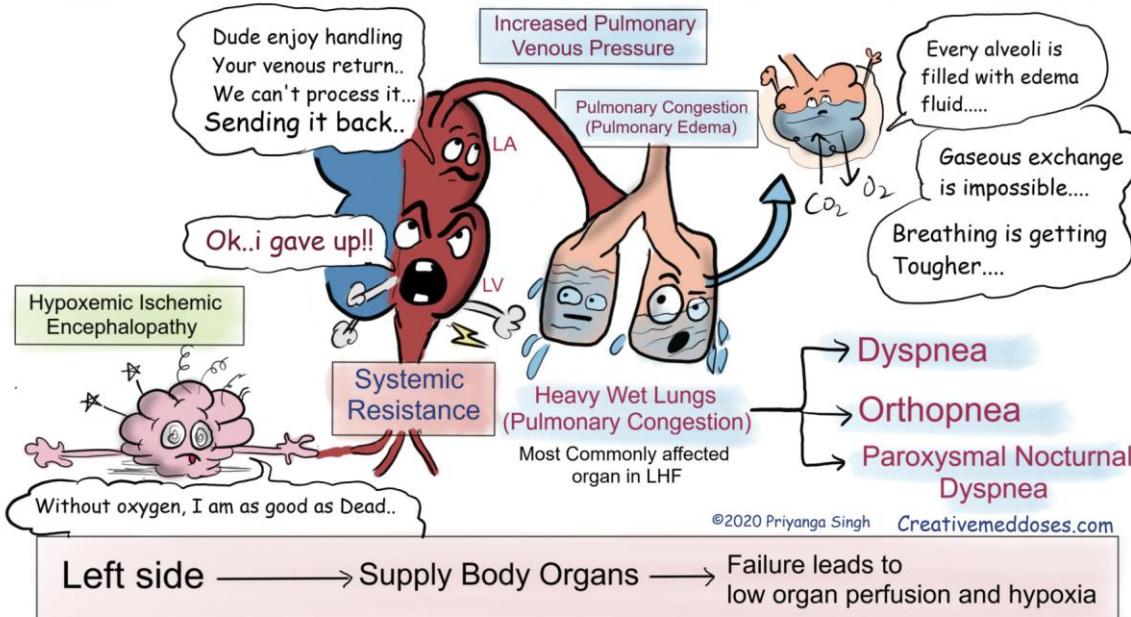
Type of HF	Ejection Fraction Cut-offs
Reduced	$\text{LVEF} \leq 40\%$
Improved (imp)	Initial $\text{LVEF} \leq 40\%$ and follow-up $\text{LVEF} > 40\%$
Mildly reduced (mr)	$\text{LVEF } 41 - 49\%$
Preserved	$\text{LVEF} \geq 50\%$



# Left vs Right Sided HF

## Left-sided Heart Failure

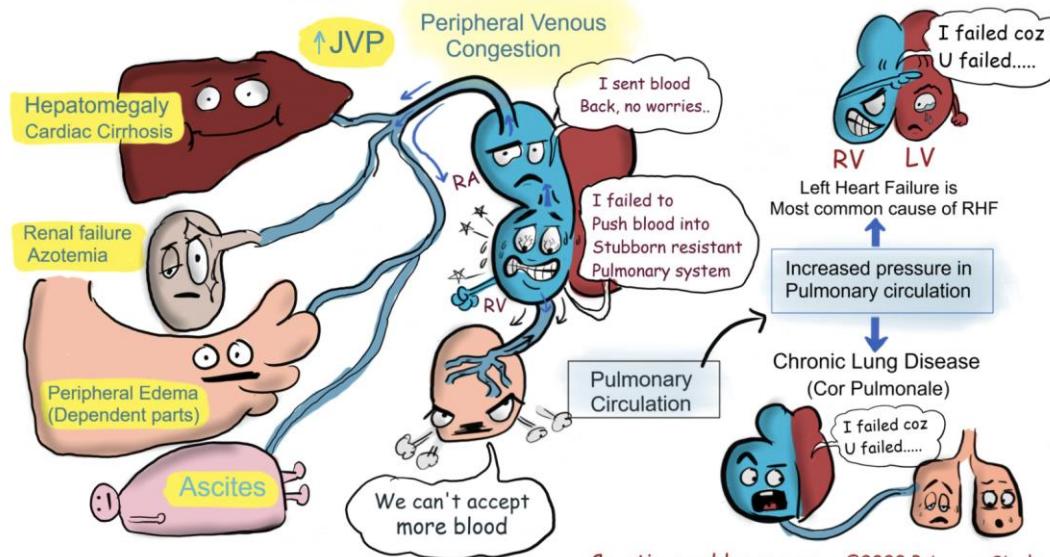
Left side → Venous Return from Lungs → Failure leads to Pulmonary Congestion & Pressure



# Left vs Right Sided HF Continued

## Right-Sided Heart Failure

Right side → Venous return from body organs (except Lungs) → Failure leads to-venous congestion of body organs



Right side → Pumps blood into Lungs → Failure happens because of-  
Increased pulmonary vascular pressure

# Signs and Symptoms of Heart Failure

# 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 $\geq$ 25 sec	**Major or minor criterion: weight loss $\geq$ 4.5kg in 5 days in response to treatment**
Hepatojugular reflux	

# 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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# 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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# Staging Heart Failure

# 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

# 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 filling pressures  
Risk factors and abnormal lab finding

# Stage C: Symptomatic Heart Failure



Evidence of structural heart disease



Patients with current or previous symptoms or signs of heart failure

# Stage D: Advanced Heart Failure



Marked HF symptoms that interfere with daily life



Recurrent hospitalizations

# New York Heart Association Functional Classification

Class	Symptoms
I	<ul style="list-style-type: none"><li>• No physical activity limitations</li></ul>
II	<ul style="list-style-type: none"><li>• Slight physical activity limitations</li><li>• Comfortable at rest</li></ul>
III	<ul style="list-style-type: none"><li>• Marked physical activity limitations</li></ul>
IV	<ul style="list-style-type: none"><li>• Symptoms at rest</li><li>• Any physical activity causes discomfort</li></ul>



# 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

# 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

# HFrEF vs HFpEF Pathophysiology

# HFrEF – Initial Cardiac Insult

Myocardial infarction

Hypertension

Idiopathic/genetic

Valve abnormalities

Viral illness

Alcohol

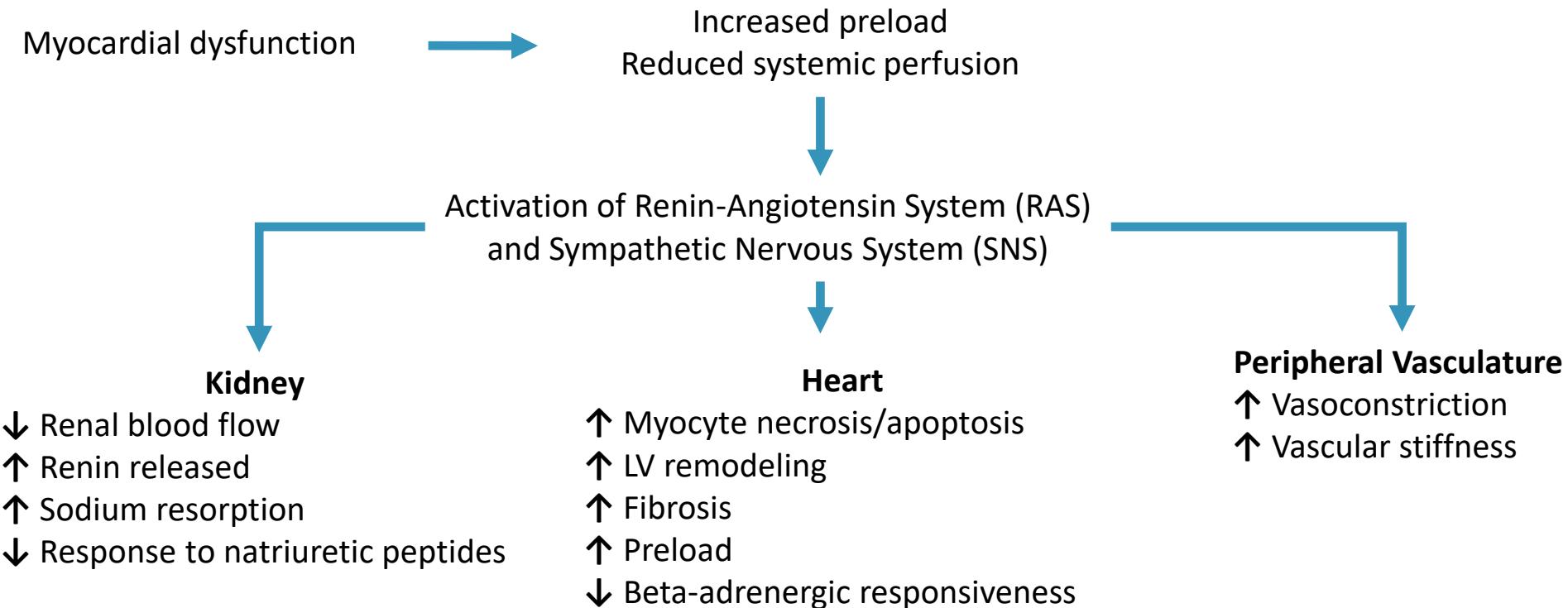
Drugs

Tachycardia

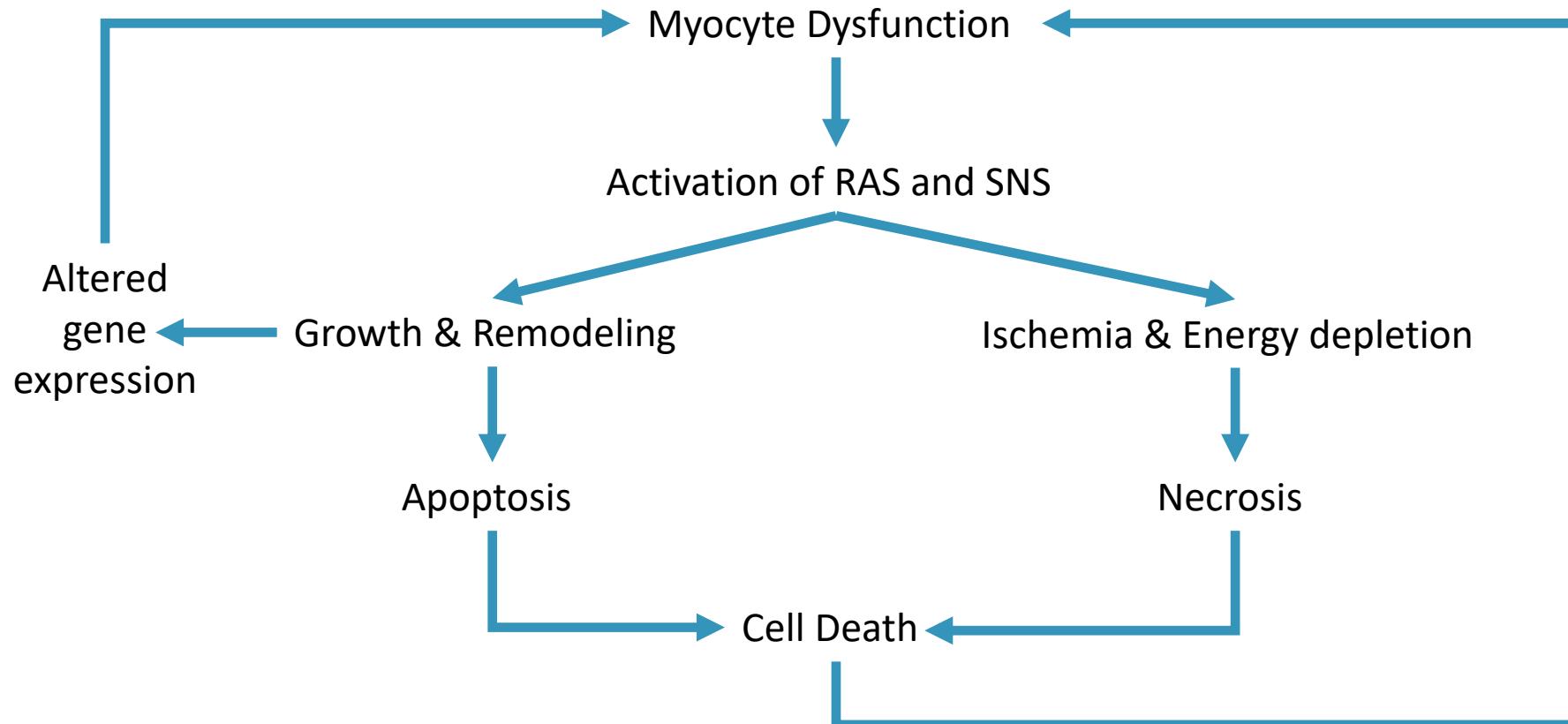
Connective tissue disease

High output states

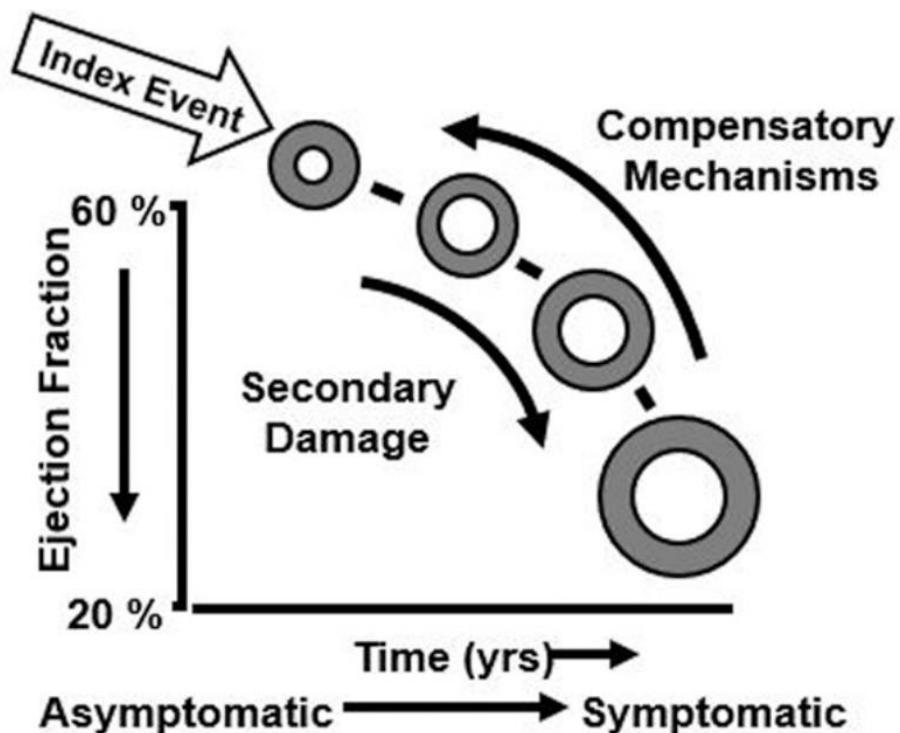
# Compensatory Mechanisms



# Myocyte Loss



# Over Time



# HFpEF Pathophysiology

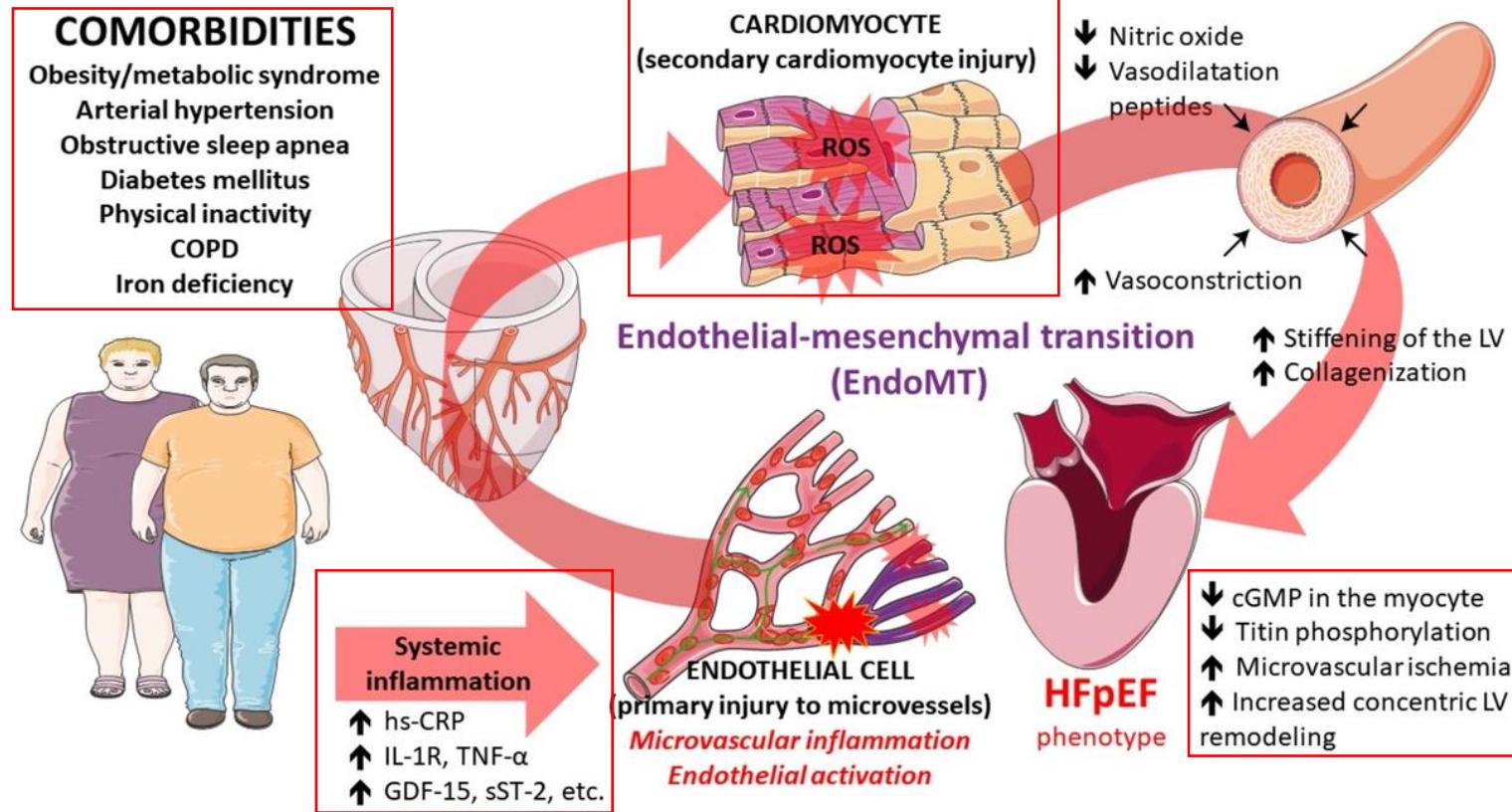
Impaired myocardial relaxation +/- increased diastolic stiffness

Ventricular chamber and ejection fraction are normal

Heterogenous disorder

Left ventricular hypertrophy most common structural abnormality associated with HFpEF

# Proposed Hypothesis



# 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

# 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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# 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)



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

Diuretics, as needed

ARNI in NYHA Class II-III

ACEi or ARB in NYHA Class II-IV

Beta Blocker

MRA

SGLT2i

Hydralazine + Isosorbide Dinitrate

Ivabradine

Vericiguat

Digoxin

1 (Strong)

2a (Moderate)

2b (Weak)

# HFpEF's Treatment Algorithm

# Standard of Care

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

SGTL2i

MRA

ARNi

ARB

1 (Strong)

2a (Moderate)

2b (Weak)



# Medication Dosing Review

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



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

# Assessment Question #2

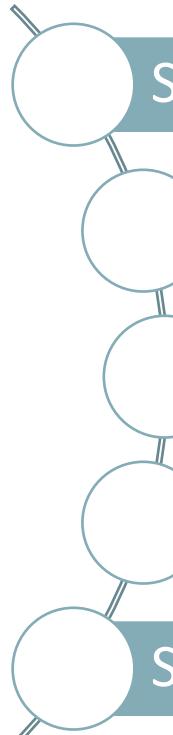
OG is a 65-year-old male with normal renal function and a PMH of diabetes, CHF with a LVEF 39%, and atrial fibrillation who presents to the clinic with increased lower extremity edema and increased shortness of breath with normal daily activities. The patient is currently on metoprolol succinate 50mg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

# 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

# HFrEF – Beta Blocker



Blocks adrenergic receptors

Heart rate reduction

Reduce myocardial oxygen consumption

Strongly modulate LV remodeling

# HFrEF – MRAs



Inhibit effects of aldosterone

Decrease preload and vascular congestion

Improve endothelial function

Block effects of norepinephrine from sympathetic nerve terminals

# HFrEF – ACEi/ARB

ACEi – angiotensin converting enzyme inhibitor

- Inhibits conversion of angiotensin I to angiotensin II

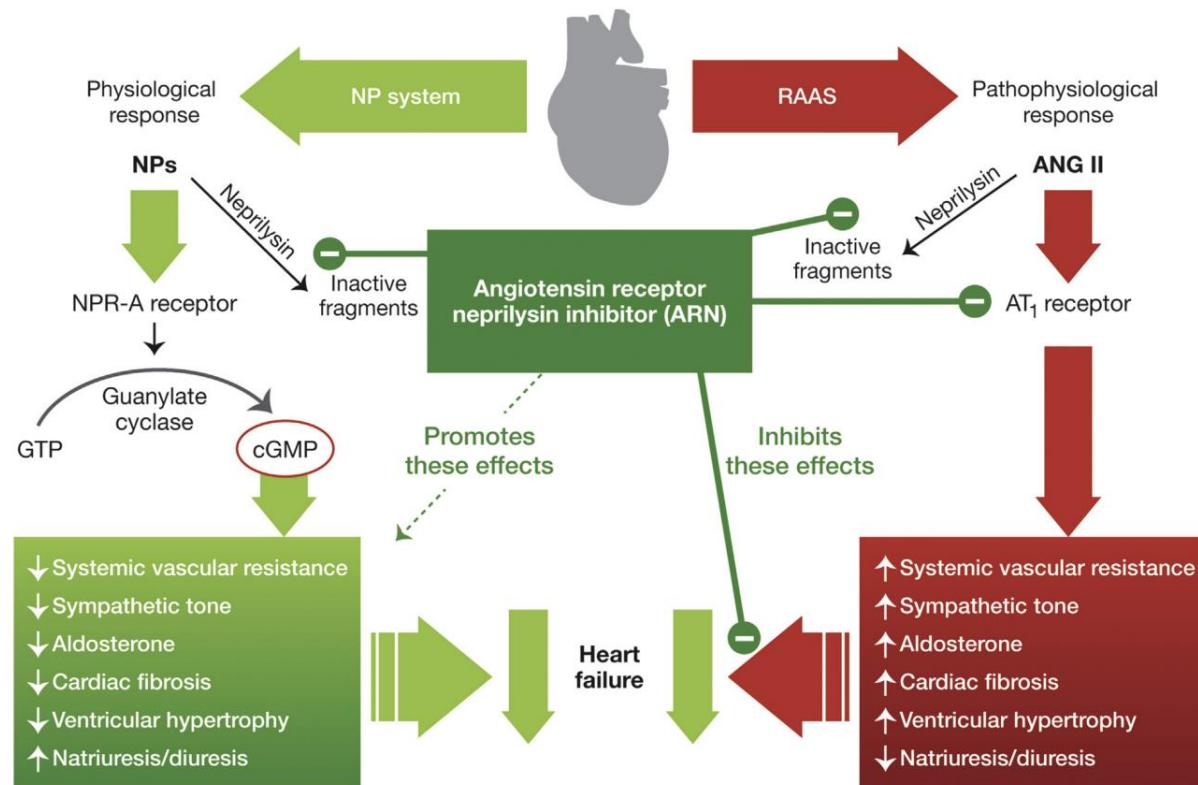
ARB – angiotensin receptor blocker

- Block angiotensin I receptor

Both agents:

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

# HFrEF - ARNi



# HFpEF – SGLT2i

## HFpEF and diastolic dysfunction

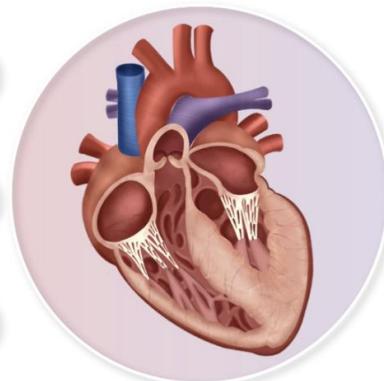
Oxidative stress, inflammation, fibrosis

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

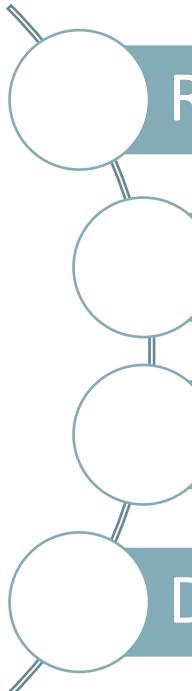
Reduced renal deterioration

Increased autophagic flux

Improved diastolic function

Reduced oxidative stress and inflammation

# HFpEF – MRAs



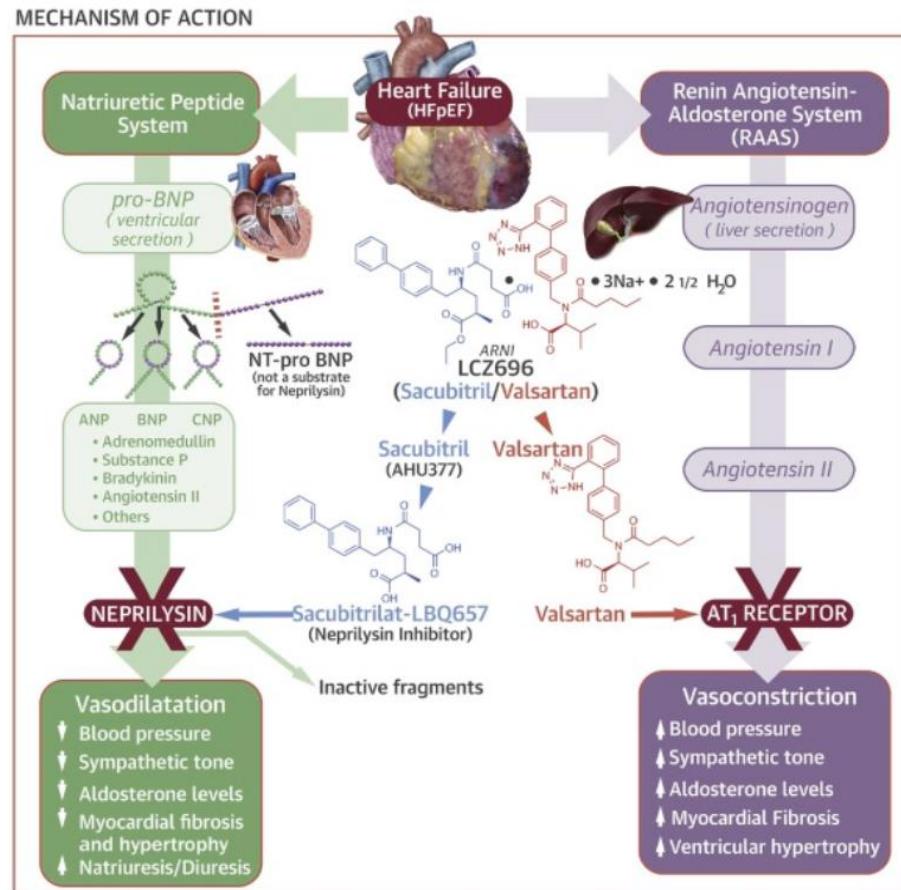
Reduce excessive fibrosis

Decrease proinflammatory pathways

Prevention of cardiac remodeling

Decrease blood pressure

# HFpEF – ARBs and ARNi



# 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

# Cracks in the System

Possibilities for most common reasons for failing to initiate or optimize treatment include

Providers simply forgetting to do so

Lack of specialized education and training

Resources and time

Belief that it is someone else's responsibility

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

# 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

# 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



# HFrEF Literature Review

- QUAD Score
- DIGIT-HF

# QUAD Score

Retrospective, observational study

## Primary Outcome

- Composite of 1<sup>st</sup> unplanned hospitalization for HF (HHF) or all-cause mortality at 1 year

## Secondary Outcomes

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

## Usability of QUAD Score

# QUAD Score

## QUAD Score HFrEF Therapeutic Score

Medication Class	Score
ACEi, AIIRB, ARNI	<input type="text"/>
BB	<input type="text"/>
MRA	<input type="text"/>
SGLT2i	<input type="text"/>
Weight	<input type="text"/>
QUAD Score	<input type="text"/>

Legend	
Dose	Score
<50%	1
≥50%	4
Weight	8

### EXAMPLES

#### Excellent (15-24)

- 4 medication classes at ≥50% dose  $(4+4+4+4)+8 = 24$   
(Sacubitril Valsartan 200mg, Bisoprolol 10mg, Eplerenone 50mg, Dapagliflozin 10mg)
- 1 medication class at ≥50% and 3 at <50% dose  $(4+1+1+1)+8 = 15$   
(Dapagliflozin 10mg, Sacubitril Valsartan 50mg, Bisoprolol 2.5mg, Eplerenone 12.5mg)

#### Good (8-14)

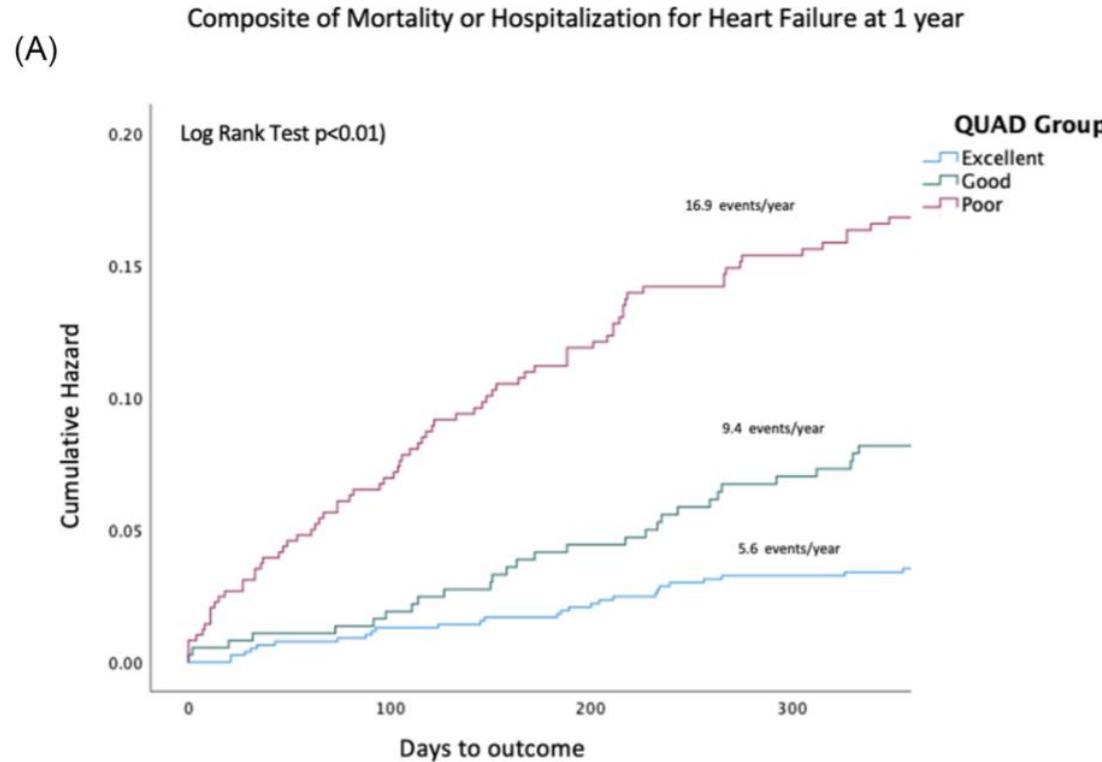
- 3 medication classes at ≥ 50% dose  $(4+4+4)= 12$   
(Sacubitril Valsartan 100mg, Bisoprolol 5mg, Eplerenone 25mg)
- 2 medication classes at 50% dose  $(4+4) = 8$

#### Poor (<8)

- 3 medication classes at <50% dose  $(1+1+1) = 3$   
(Sacubitril Valsartan 50mg, Bisoprolol 1.25mg, Eplerenone 12.5mg)
- 1 medication class at ≥50% dose = 4  
(Dapagliflozin 10mg)

An 'e' is added to the score to mark an exemption or variance in medication class use. For example, If a patient is on >50% doses of 3 medication classes but have a clinical reason they are exempt from an MRA, they would be scored a 12e, with appropriate documentation in the clinical notes.

# Results



# 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)

# Conclusion

Simple tool



Incentivize and audit GDMT



Excellent scores associated with better outcome

# 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

# 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

# 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)



# Safety Outcomes

## Mean serum concentration at

- 6 weeks:  $17 \pm 5.9 \text{ ng/mL}$
- 12 months:  $13.5 \pm 5.1 \text{ ng/mL}$

## 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

# 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

# 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

# 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  $\geq 50\%$ , decline in eGFR  $<15$ , or initiation of long-term dialysis or kidney transplant
- Death from any cause

# 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



# 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

# 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	

# 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	

# 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

# 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.

# 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

# 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

# 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	$19.5 \pm 1.2$	$12.7 \pm 1.3$	6.9 (3.3 – 10.6) P < 0.001



# 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

# 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

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, Abate D, Abate KH. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;392:1789–858.
2. Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke statistics—2021 update. *Circulation* 2021;143:e254–743.
3. Lee MP, Glynn RJ, Schneeweiss S, et al. Risk factors for heart failure with preserved or reduced ejection fraction among Medicare beneficiaries: application of competing risks analysis and gradient boosted model. *Clin Epidemiol* 2020;12:607–16.
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# Questions?

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