Updates in Heart Failure Management with a Specific Focus on HFpEF & HFimpEF

A Presentation for HealthTrust Members
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Abbreviations

Abbreviation	Meaning/Phrase
ACEi	angiotensin-converting enzyme inhibitors
ARB	angiotensin (II) receptor blockers
ARNi	angiotensin receptor-neprilysin inhibitors
EF	ejection fraction
GDMT	guideline-directed medical therapy
HF	heart failure
HFimpEF	heart failure with improved ejection fraction
HFmrEF	heart failure with mildly reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
ISDN	isosorbide dinitrate
LVEF	left ventricular ejection fraction
MRA	mineralocorticoid receptor antagonists
SGLT2i	sodium-glucose cotransporter-2 inhibitors

Objectives

- Recall differences between heart failure (HF) subtypes: heart failure with preserved (HFpEF), heart failure with improved ejection fraction (HFimpEF), and heart failure with reduced ejection fraction (HFrEF)
- Identify the updated recommendations in the heart failure guidelines for HFpEF and HFimpEF management
- Recognize updated guideline recommendations for individualized treatment plans for patients with HFrEF, HFpEF or HFimpEF

Background

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Heart Failure Terminology

- HFrEF: heart failure with reduced ejection fraction
  - HF with LVEF ≤ 40%
- HFmrEF: heart failure with mildly reduced (mid range) ejection fraction
  - HF with LVEF 41-49%
- HFpEF: heart failure with preserved ejection fraction
  - HF with LVEF ≥ 50%
- HFimpEF: heart failure with improved ejection fraction
  - Previous LVEF ≤ 40% and a follow-up measurement of LVEF > 40%

Source: Heidenreich, PA, et al.Circulation. 2022;145:e895–e1032

Heart Failure Epidemiology

- 6.2 million Americans have heart failure
- 650,000 new cases annually
- Projected 46% increase by 2030
- Women are 2x more likely than men to develop HFpEF

Sources: Circulation 2006;114-1202-1213. N Engl J Med 2009;360:1418-28
AHA 2020 Heart Disease and Stroke Statistics. Circulation. 2020; 141(9):e139-e596
Roger VL.Circulation.2021; 128 (10) 1421-1434

Morbidity and Mortality

- Heart failure (HF) is the most common discharge diagnosis among patients > 65 years of age
- Mortality
  - The risk of sudden cardiac death is 6 to 9 times higher in patients with HF
  - Total deaths from HF increased from 275,000 in 2009 to 310,000 in 2014
- Growing health and economic burden for the U.S.
  - In 2017, there were 1.2 million HF hospitalizations among 924,000 patients with HF
  - Estimated that HF costs the U.S. healthcare system $31 billion annually
  - HF costs are projected to increase to $50 billion by 2030

Sources: Wang Out-of-Pocket Annual Health Expenditures and Financial Toxicity From Healthcare Costs in Patients With Heart Failure in the United States. Journal of the American Heart Association 2021
AHA 2025 Heart Disease and Stroke Statistics. Circulation. 2025; 141(9):e139-e596

Heart Failure Pathophysiology

- HF is a complex clinical syndrome caused by a structural and/or functional abnormality → signs and symptoms of reduced cardiac output
- Common insults causing cardiac dysfunction include:
  - Myocardial infarction (MI)
  - Valvular stenosis/regurgitation
  - Heart rhythm/conduction abnormalities
- Identification of pathophysiological mechanism leading to heart failure = crucial selecting appropriate therapeutic options

Sources Schwinger RHG. Pathophysiology of heart failure. *Cardiovasc Diagn Ther*. 2021;11(1):263-276.
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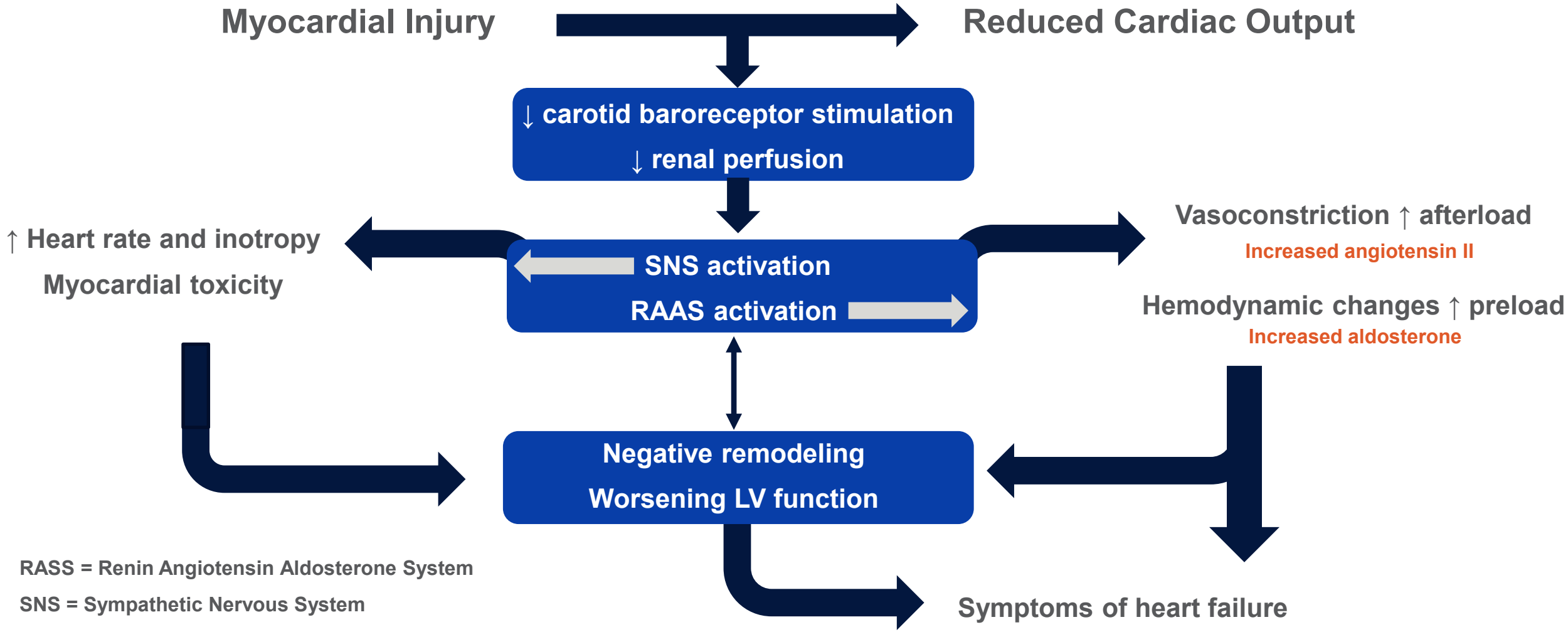
Heart Failure Pathophysiology



RASS = Renin Angiotensin Aldosterone System

SNS = Sympathetic Nervous System

Sources Schwinger RHG. Pathophysiology of heart failure. *Cardiovasc Diagn Ther*. 2021;11(1):263-276.
Heidenreich, PA, et al.Circulation. 2022;145:e895–e1032
Image adapted from : Steven Lome.LearnTheHeart

Pathophysiologic Differences in HFrEF vs HFpEF

- HFrEF (Systolic HF)
  - Structural alteration: eccentric left ventricular hypertrophy + dilated cardiomyopathy
    - Leading to volume overload
    - Volume overload is also mediated via neurohormonal activation (Renin-angiotensin-aldosterone system (RAAS))
- HFpEF (Diastolic HF)
  - Structural alteration: impaired ventricular relaxation/filling + ventricular stiffness
    - Pressure overload
    - Right sided congestion
    - Volume overload

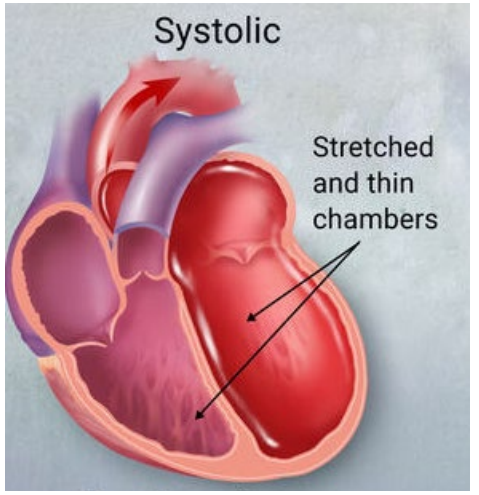
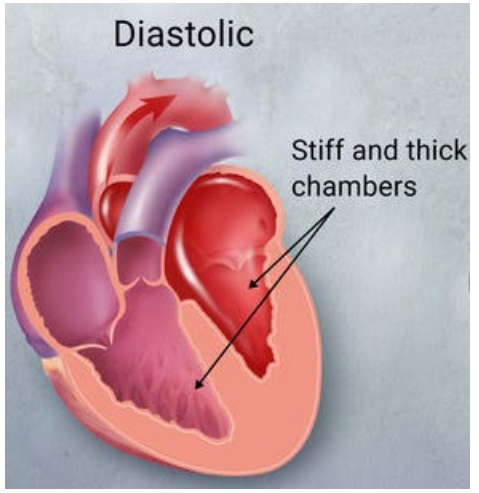


Image: Central Georgia Heart Center



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Pathophysiologic Differences in HFrEF vs HFpEF

- Differing heart failure subtypes
- Example:
  - Men with CAD + myocardial infarction:
    - Tend to have depressed LV function (HFrEF)
    - Higher risk of CV death
    - Usually respond favorably to RAAS inhibitors
  - Women with comorbidities associated with metabolic syndrome:
    - Typically, do not develop chamber dilation and LV function is maintained (HFpEF)
    - Lower risk of CV death
    - May not be as responsive to RAAS inhibitors

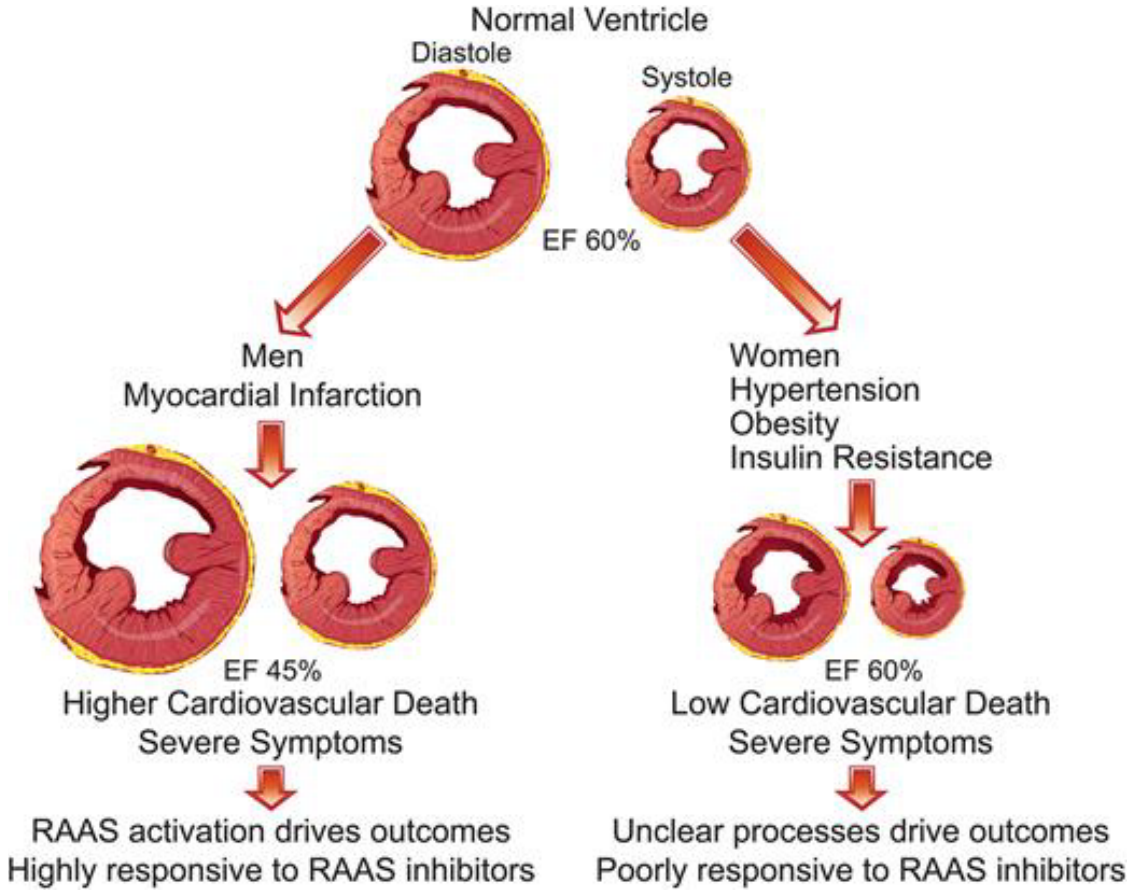

Image: Eur. Heart J. (2015), Fig 1; 10.1093/eurheartj/ehv561

Sources: Schwinger RHG. Pathophysiology of heart failure. *Cardiovasc Diagn Ther.* 2021;11(1):263-276.
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Signs and Symptoms of Heart Failure

- The different types of HF are indistinguishable by signs and symptoms alone

Volume Overload

- Peripheral edema
- Jugular venous distension
- Pulmonary edema
- Hepatomegaly

Reduced Cardiac Output

- Weakness
- Fatigue
- Cool, clammy skin
- Decreased urine output

Source: Heidenreich, PA, et al.Circulation. 2022;145:e895–e1032

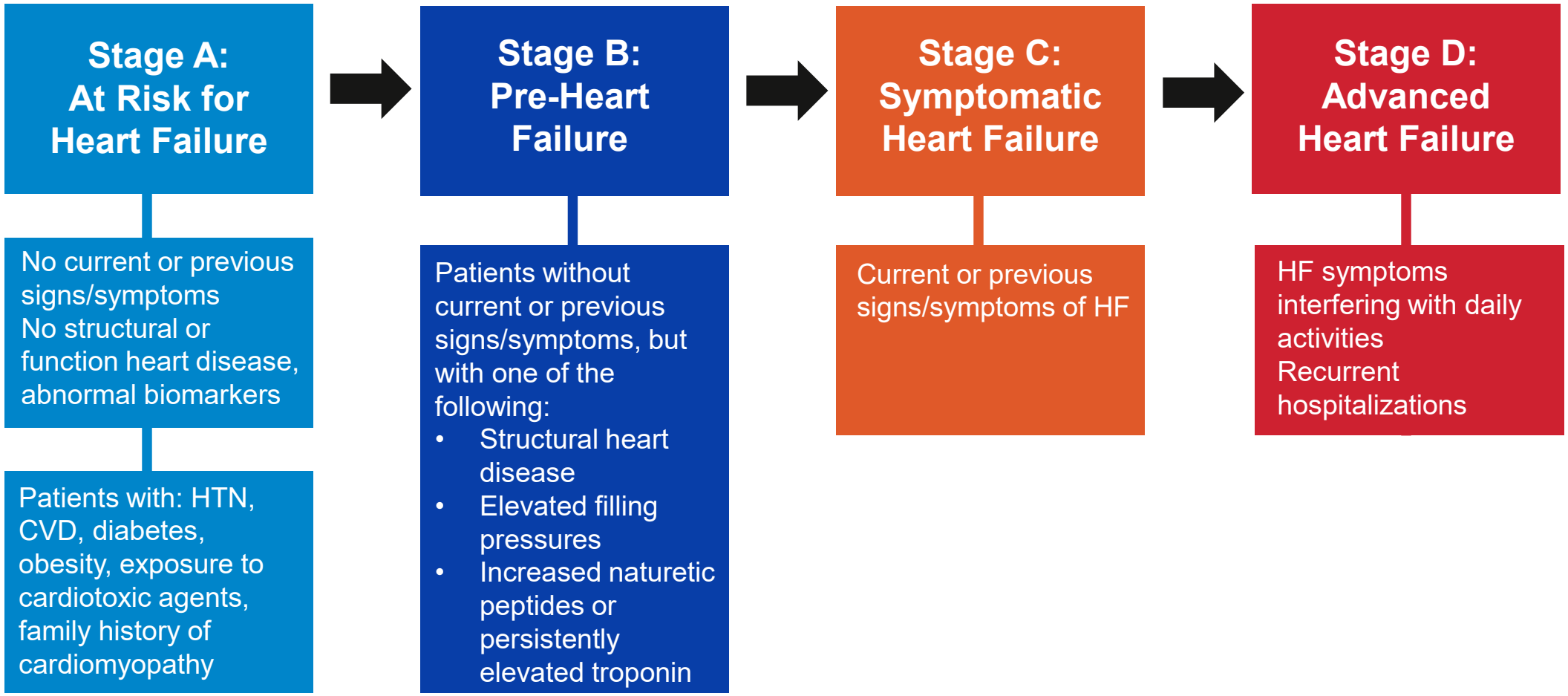
Assessing Progression of Heart Failure

- There are **4 stages** of heart failure—A, B, C, and D
  - Allows health care professionals to monitor disease status
  - Helps measure a patient's overall heart function
  - Patients with symptomatic (stage C) or advanced HF (stage D) are further categorized by the severity of symptoms

- The New York Heart Association (NYHA) Functional Classification
  - Four classes (I, II, III, and IV) based on limitations of physical activity
  - Patients with **stage 3 or greater** HF are assigned a baseline score
  - After baseline is established, additional NYHA scores can be assigned to gauge treatment efficacy

Source: Heidenreich, PA, et al.Circulation. 2022;145:e895–e1032

Stages of Heart Failure



Source Heidenreich, PA, et al.Circulation. 2022;145:e895–e1032

Classes of Heart Failure

Reminder: patients are only assigned a classification if their heart failure is stage C or greater

NYHA Functional Classification	
Class	**Symptoms**
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or shortness of breath.
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, shortness of breath or chest pain.
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, shortness of breath or chest pain.
IV	Symptoms of heart failure at rest. Any physical activity causes further discomfort.

Source Heidenreich, PA, et al.Circulation. 2022;145:e895–e1032

General Goals of Therapy

- By using Guideline-Directed Medical Therapy (GDMT) to achieve these goals, the healthcare team and patients work to:
  - Enhance overall patient well-being
  - Reduce admission burden on the healthcare system
  - Reduce patient burden of healthcare-related costs associated with hospitalizations

Source: Heidenreich, PA, et al.Circulation. 2022;145:e895–e1032

Assessment Question #1

- Which of the following left ventricular ejection fraction (LVEF) corresponds to HFrEF?

  A. LVEF = 55%

  B. LVEF = 50%

  C. LVEF = 45%

  D. LVEF = 35%

Assessment Question #1: Correct Response

- Which of the following left ventricular ejection fraction (LVEF) corresponds to HFrEF?

  A. LVEF = 55%

  B. LVEF = 50%

  C. LVEF = 45%

  D. LVEF = 35%

HFrEF Overview

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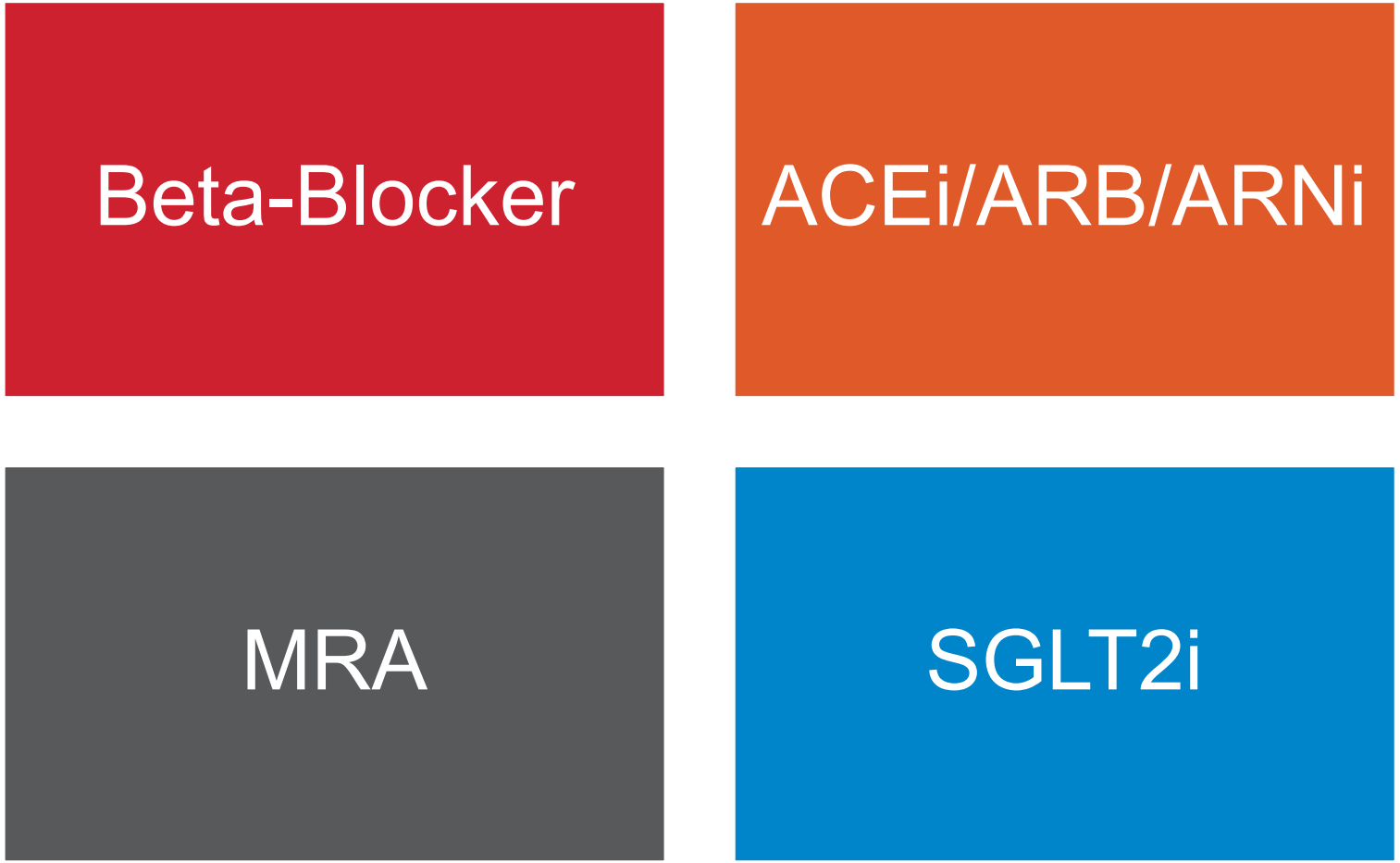
Landmark Trials in HFrEF Therapy

Drug Class	Trial *Bolded if mortality benefit	Mortality Benefit
ACEi	**CONSENSUS (1987)**; **SOLVD (1991)**	Yes
ARB	**Val-HEFT (2001)**; **CHARM-Alternative (2003)**; HEAAL (2009)	Yes
ARNi	**PARADIGM-HF (2014)**; PIONEER-HF (2019)	Yes
SGLT2i	**DAPA-HF (2019)**; EMPEROR-Reduced (2020)	Yes
Beta-Blocker	**CIBIS-11 (1999)**; **MERIT-HF (1999)**; **COPERNICUS (2002)**; COMET (2003)	Yes
MRA	**RALES (1999)**; **EMPHASIS-HF (2011)**	Yes
ISDN/Hydralazine	**A-HEFT (2004)**	Yes
Ivabradine	**SHIFT (2010)**	Yes
Vericiguat	**VICTORIA (2020)**	Yes
Loop Diuretics	N/A	No
Digoxin	DIG (1997)	No

Source: Gajjela et al. *Cureus*. 2021

GDMT in HFrEF: The “Four Pillars”



Source: Heidenreich, PA, et al.Circulation. 2022;145:e895–e1032

HFrEF Treatment: Beta-Blockers

carvedilol
(Coreg)

metoprolol succinate
(Toprol XL)

bisoprolol

Dosing	Carvedilol: 3.125 mg BID; target 25 mg BID (≤85kg) or 50 mg BID (>85kg) Metoprolol: 12.5-25 mg daily; target 200 mg daily Bisoprolol: 1.25 mg daily; target 10 mg daily
Adverse Effects	Bradycardia, shortness of breath, weight gain, edema, fatigue
Pearls	• Start at low dose and titrate every 2 weeks as tolerated • May initially worsen HF (negative inotrope) • Avoid in patients with acute decompensated HF

HFrEF Treatment: ARNi

sacubitril/valsartan (Entresto)

Dosing	24/26 mg BID; target 97/103 BID • Initiate at 24/26 if on low-dose* ACEi/ARB or no previous ACEi/ARB use • Initiate at 49/51 mg BID if on moderate to high-dose** ACEi/ARB
Adverse Effects	Angioedema, hypotension, hyperkalemia, AKI/renal dysfunction, dizziness
Pearls	• Preferred over ACEi/ARB • Requires 36-hr washout period when switching from an ACEi • No washout period required when switching from an ARB • Contraindicated in pregnancy (fetal toxicity)

***low dose ACEi/ARB:≤10 mg enalapril or equivalent OR ≤ 160 mg valsartan or equivalent**
****moderate to high dose ACEi/ARB:>10 mg enalapril or equivalent OR > 160 mg valsartan or equivalent**

HFrEF Treatment: ACEi

lisinopril (Zestril)

enalapril (Vasotec)

benazepril (Lotensin)

ramipril (Altace)

Dosing	Varies based on agent; titrate to max target dose
Adverse Effects	Dry cough, angioedema, hypotension, AKI/renal dysfunction, hyperkalemia
Pearls	• May initially increase serum creatinine by up to ~30% • Contraindicated in pregnancy (fetal toxicity)

HFrEF Treatment: ARB

losartan (Cozaar)

valsartan (Diovan)

olmesartan (Benicar)

candesartan (Atacand)

Dosing	Varies based on agent; titrate to max target dose
Adverse Effects	Angioedema, hypotension, AKI/renal dysfunction, hyperkalemia
Pearls	• May initially increase serum creatinine by up to~30% • Contraindicated in pregnancy (fetal toxicity)

HFrEF Treatment: MRA

spironolactone
(Aldactone)

eplerenone
(Inspra)

Dosing	Spironolactone: 12.5-25 mg once daily; target 50 mg/day Eplerenone: 25 mg once daily; target 50 mg/day
Adverse Effects	Hyperkalemia, gynecomastia, hirsutism (less with eplerenone)

Pearls	• Renal dosing recommendations differ based on indication
	  • Spironolactone is not recommended in eGFR < 30
	  • eGFR 30-50: 12.5 mg daily or every other day; max 25 mg/day
	  • Eplerenone is contraindicated in eGFR ≤ 30
	  • eGFR 31-49: 25 mg daily or every other day; max 25 mg/day
	• Do not initiate if K ≥ 5.0; other HF agents may also increase K

HFrEF Treatment: SGLT2i

empagliflozin
(Jardiance)

dapagliflozin
(Farxiga)

Dosing	Empagliflozin: 10 mg once daily Dapagliflozin: 10 mg once daily
Adverse Effects	Genitourinary infections, euglycemic diabetic ketoacidosis (DKA), hypotension, hypovolemia, acute kidney injury (AKI)

Pearls	• Renal dosing recommendations differ based on indication
	  • Empagliflozin benefit shown in eGFR ≥ 20
	  • Dapagliflozin should not be initiated in eGFR < 25 for HF but can be continued if already taking
	  • Avoid use in hemodialysis or CRRT
	• Also indicated for use in type 2 diabetes and chronic kidney disease (CKD)

HFrEF Treatment Summary

The Four Pillars

Beta-Blocker

ARNi/ACEi/ARB

MRA

SGLT2i

- Most benefit shown with **all four** medication classes used - initiate patient on all if able
- Unique side effects and monitoring for each class

Source: Heidenreich, PA, et al.Circulation. 2022;145:e895–e1032

Implementing Heart Failure Therapies

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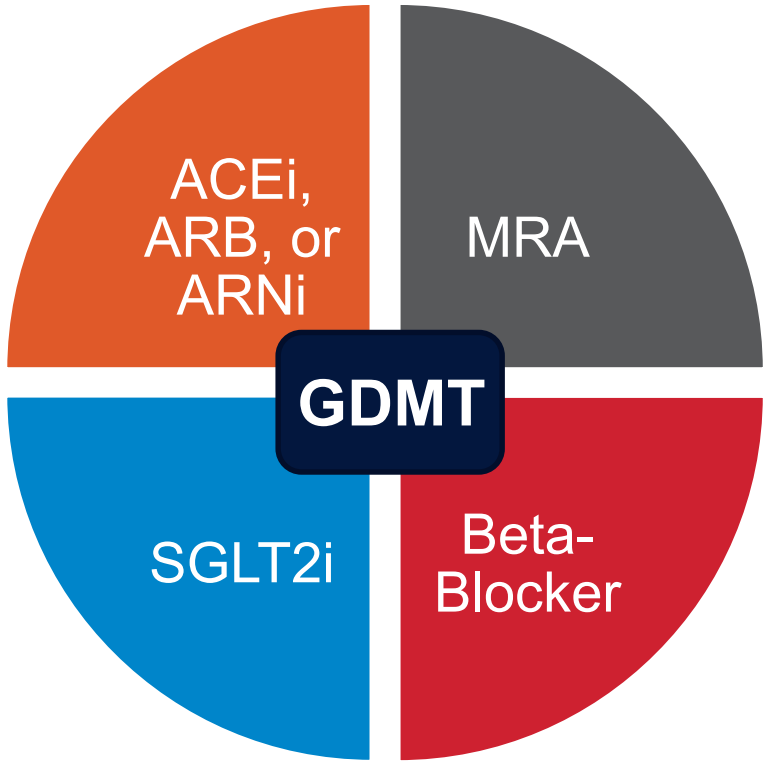
GDMT Therapy Initiation and Optimization

- Generally, prioritize initiation of **all 4** core GDMT classes before dose titration of a single agent
  - Titrate to goal doses
  - Titrating every 1 to 2 weeks as tolerated
- During Hospitalization
  - Pre-existing GDMT should be continued unless contraindicated
  - If not already, initiate GDMT once clinically stable
  - GDMT should be reinitiated as soon as possible if discontinuation is necessary



Heidenreich, PA, et al.Circulation. 2022;145:e895–e1032

Summary of Safety Considerations

Beta-Blocker	ACE, ARB, ARNi	MRA	SGLT2i
• Bradycardia • Bradyarrhythmias • Reflex tachycardia with acute withdrawal	• Renal impairment • Hypotension • Hyperkalemia • Angioedema	• Renal impairment • Hyperkalemia • Gynecomastia (spironolactone)	• Renal impairment • Hypotension • Genital mycotic infections • Euglycemic ketoacidosis

- Expect a bump in SCr when initiating or uptitrating an ACE, ARB, or ARNi
- GDMT initiation/optimization should **NOT** be delayed unless change in SCr > 30% above baseline

Source Heidenreich, PA, et al.Circulation. 2022;145:e895–e1032

HFimpEF Treatment

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What is HFimpEF?

- Among patients with HFrEF,10-60% experience improvement of LVEF
  - Can occur spontaneously
  - Result due to treatment with GDMT
- HFimpEF: heart failure with improved ejection fraction
  - Previous LVEF ≤ 40% and a follow-up measurement of LVEF > 40%
- Associated with improved prognosis, but risk of relapse still remains
- Think “remission” rather than full recovery

Sources: Heidenreich, PA, et al.Circulation. 2022;145:e895–e1032
Kodur, et al. J Am Coll Cardiol HF. 2025 Apr, 13 (4) 537–553

HFimpEF Treatment

- Patients previously on GMDT since they fell into the HFrEF category prior to improvement
- **Continue GDMT**, even if asymptomatic
  - Improvement in EF ≠ cure
    - Reflects remission that requires GDMT to be maintained
    - Patients likely to relapse after withdrawal of GDMT
    - Reverse remodeling regression can cause worsening symptoms

Source Heidenreich, PA, et al.Circulation. 2022;145:e895–e1032

Continuing GDMT in HFimpEF

Trial Name	**TRED-HF (2018)**
Patient Characteristics	Patients with previous HF, now asymptomatic, and improved LVEF improved from < 40% to ≤ 50%
Primary Intervention	Patients randomized to supervised withdrawal of GDMT or to GDMT continuation
Results	In the first 6 months, 44% of patients in the withdrawal group had relapse vs. 0% in the continuation group (p = 0.0001)
Study Conclusion	Withdrawal of GDMT among patients with recovered LVEF results in relapse of HF Treatment should continue indefinitely

Source: Hallida et al. *Lancet*. 2018

HFimpEF Bottom Line

- **Continue GDMT**
- There is continuing clinical debate on if all patients need to continue full-dose GDMT to prevent relapse
  - Clinical benefit vs medication burden and financial cost
- Questions for future research:
  - Can patients safely de-escalate some or all of GDMT?
  - Are there certain patient populations with HFimpEF that need to continue full-dose GDMT indefinitely?

Source: Kodur, et al. J Am Coll Cardiol HF. 2025 Apr, 13 (4) 537–553

Assessment Question #2:

- Which of the following aligns with updated guideline recommendations for the management of a patient with HFimpEF?

A. Continue all GDMT except for SGLT2i

B. Continue all GDMT despite improved EF

C. Down titrate all GDMT since EF has improved

D. Discontinue all GDMT since the patient no longer has HFrEF

Assessment Question #2: Correct Response

- Which of the following aligns with updated guideline recommendations for the management of a patient with HFimpEF?

A. Continue all GDMT except for SGLT2i

B. Continue all GDMT despite improved EF

C. Down titrate all GDMT since EF has improved

D. Discontinue all GDMT since the patient no longer has HFrEF

HFpEF Treatment

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Landmark Trials in HFpEF Therapy

Drug Class	Trial *Bolded if mortality benefit	Mortality Benefit	Reduction in HF Hospitalization
ACEi	PEP-CHF (2006)	No	Yes
ARB	CHARM-Preserved (2003) I-PRESERVE (2008)	No No	Yes No
ARNi	PARAGON-HF (2019)	No	No
SGLT2i	**EMPEROR-Preserved (2021)** **DELIVER (2022)**	Yes Yes	Yes Yes
MRA	TOPCAT (2014)	No	Yes

Sources: Maryniak et al. *Cardiol J*. 2022
Gajjela et al. *Cureus*. 2021

Landmark Trials in HFpEF Therapy

Trial Name	**TOPCAT (2014)**	PARAGON-HF (2019)	EMPEROR-Preserved (2021)	DELIVER (2022)
Patient Characteristics	EF ≥ 45% and symptomatic HF	EF ≥ 45%, NYHA class II-IV HF, elevated natriuretic peptides, and structural heart disease	EF > 40% and NYHA class II-IV HF	EF > 40% and HF
Primary Intervention	Spironolactone 15-45 mg daily vs. placebo	Sacubitril 97mg/valsartan 103 mg BID vs. valsartan 160 mg BID	Empagliflozin 10 mg once daily vs. placebo	Dapagliflozin 10 mg once daily vs. placebo
Primary Outcome	Composite of death from CV causes, aborted cardiac arrest, or HF hospitalization	Composite of total hospitalizations for HF and death from CV causes	Composite of CV death or HF hospitalization	Composite of worsening HF or CV death
Study Conclusion	**Spironolactone did not reduce risk of the primary composite outcome but lowered risk of HF hospitalizations**	Sacubitril/valsartan did not lower risk of CV death or HF hospitalizations -May have benefit in women with EF 45-57%	Empagliflozin reduced the combined risk of CV death or HF hospitalization	Dapagliflozin reduced the combined risk of worsening HF or CV death among patients with HFpEF or HFmrEF

CV: cardiovascular

Source: Maryniak et al. *Cardiol J*. 2022

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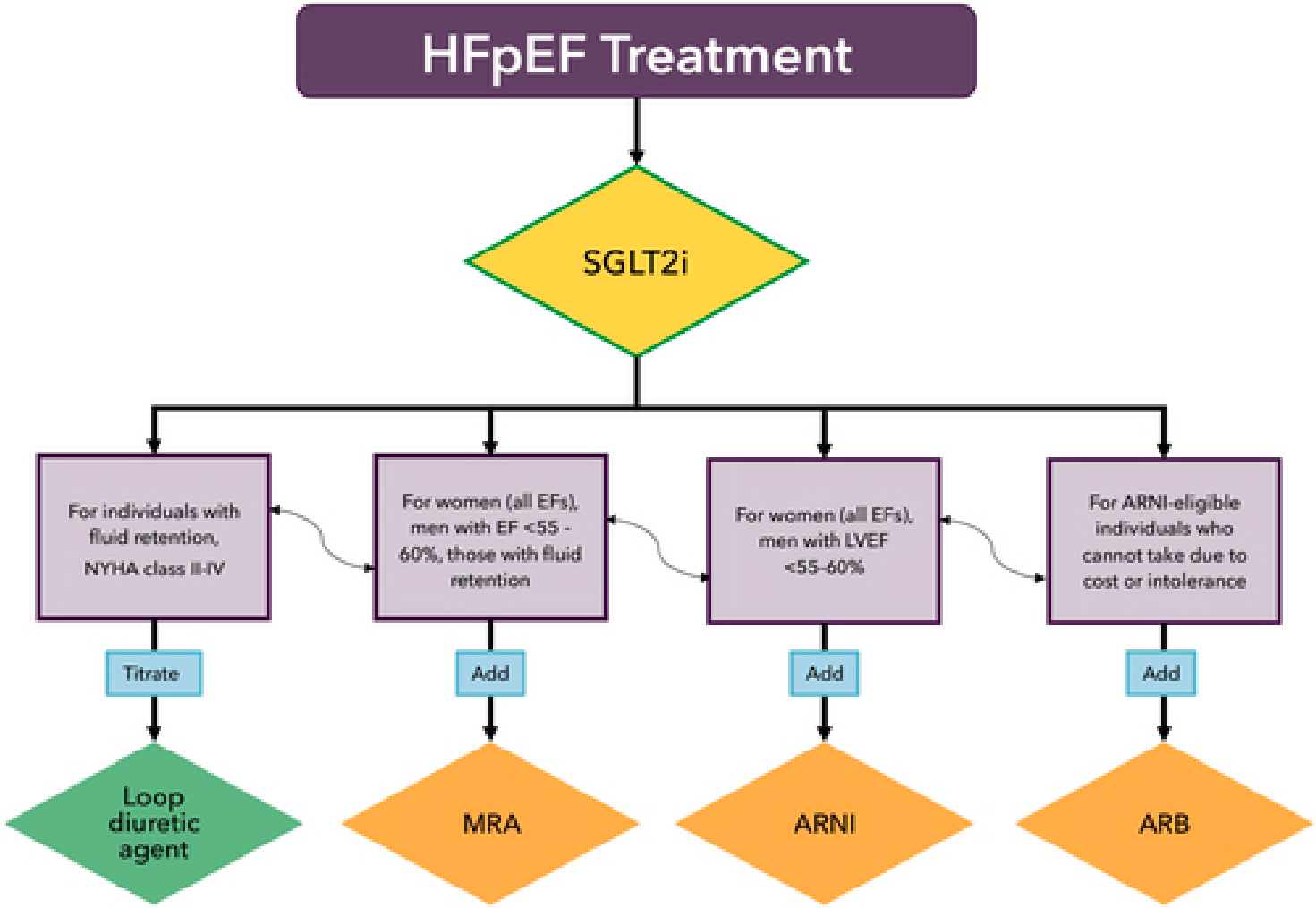
Source: Maryniak et al. *Cardiol J*. 2022

HFpEF Treatment Nuances

- SGLT2i – mortality benefit AND reduced risk of HF hospitalizations
- MRA – no mortality benefit but reduced risk of HF hospitalizations
  - Women with any EF
  - Men with EF <55-60%
- ARNi (PARAGON-HF)
  - Women with any EF
  - Men with EF <55-60%
- Beta-Blockers not studied in HFpEF

Summary: Treatment of Symptomatic HFpEF



Source Heidenreich, PA, et al.Circulation. 2022;145:e895–e1032

Assessment Question #3

- A 67-year-old female patient with a history of hypertension and HFpEF presents with fluid retention and dyspnea. Her EF is 55% and she is currently on an angiotensin receptor blocker (ARB) and a beta-blocker. Which is the most appropriate addition to her regimen based on updated guidelines?

A. Beta-Blockers

B. Loop Diuretics

C. MRA

D. SGLT2i

Assessment Question #3: Correct Response

- A 67-year-old female patient with a history of hypertension and HFpEF presents with fluid retention and dyspnea. Her EF is 55% and she is currently on an angiotensin receptor blocker (ARB) and a beta-blocker. Which is the most appropriate addition to her regimen based on updated guidelines?

A. Beta-Blockers

B. Loop Diuretics

C. MRA

D. SGLT2i

Additional Drugs in HF

Loop Diuretics

- Utilized to manage volume overload

Digoxin

- May help alleviate symptomatic HF despite GDMT

Ivabridine

- May help reduce heart rate in symptomatic chronic HFrEF patients despite GDMT with maximum tolerated dose of a beta-blocker

Vericiguat

- May reduce HF and cardiovascular death in HFrEF patients already optimized on GDMT with worsening HF

Source Heidenreich, PA, et al.Circulation. 2022;145:e895–e1032

Potentially Harmful Drugs in HF

- Nondihydropyridine CCBs (verapamil, diltiazem)
- Thiazolidinediones (“-glitazone”)
- DPP-4 inhibitors (“-gliptin)[1]
- Class IC antiarrhythmics (flecanide, propafenone, etc.)[2]
- NSAIDs[3]
- Cilostazol

1: Increase the risk of HF hospitalizations in patients with T2DM and high CV risk
2: May increase risk of mortality in HFrEF
3: Worsen HF symptoms in HFrEF

Source Heidenreich, PA, et al.Circulation. 2022;145:e895–e1032

On the Horizon

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Finerenone (Kerendia)

FINEARTS-HF (2024)

- Patients with HF and EF ≥ 40% with a primary composite outcome of total worsening HF events and death from CV causes
- Finerenone reduced combined risk of worsening HF events and death from CV causes in patients with HFpEF or HFmrEF

- MRA
- **Mortality benefit shown**
  - Different from previous studies of MRA in HFpEF
- Ongoing studies:
  - REDEFINE-HF
  - FINALITY-HF
  - CONFIRMATION-HF
- Not yet FDA-approved for use in HF

Source: Solomon et al. *N Engl J Med*. 2024

GLP-1 Agonists

FIGHT (2016)	STEP-HFpEF (2023)	SUMMIT (2025)
• Liraglutide (up to 1.8 mg/day) in HFrEF • No reduction in frequency of death or hospitalization	• Semaglutide (2.4 mg once weekly) in HFpEF and obesity • Led to greater reduction in symptoms and physical limitations, greater improvement in exercise function, and greater weight loss	• Tirzepatide (up to 15 mg once weekly) in HFpEF and obesity • Led to lower risk of composite death from CV causes or worsening HF

- Ongoing studies in various CV-related conditions
- May provide benefit in patients with HF and other comorbidities

Sources: Packer et al. *N Engl J Med*. 2025
Kosiborod et al. *N Engl J Med*. 2023
Margulies et al. *JAMA*. 2016

GLP-1 Agonists

liraglutide (Victoza)

semaglutide (Ozempic)

tirzepatide (Mounjaro)

dulaglutide (Trulicity)

Dosing	Varies based on agent; titrate every 4 weeks based on tolerance
Adverse Effects	GI symptoms (nausea, vomiting, diarrhea, dyspepsia), AKI, pancreatitis, hypoglycemia
Pearls	• Indicated in type 2 diabetes and weight loss management (only Ozempic and Zepbound approved for weight management) • Must discontinue 2 weeks prior to anesthesia/surgery (aspiration risk) • Subcutaneous injection daily or weekly (administration instructions and safety)

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Thank you!!

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