Heart Failure in Ambulatory Care

What's New, What's Next?

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Disclosures

The planner(s) and speaker(s) have indicated that there are no relevant financial relationships with any ineligible companies to disclose.

Learning Objectives

At the end of this session, learners should be able to:

- Recognize the pathophysiology and classification of heart failure across the ejection fraction spectrum
- Identify strategies for implementation and titration of guideline-directed medication treatment (GDMT) for heart failure with reduced ejection fraction (HFrEF)
- Select a GDMT regimen for a patient with heart failure with preserved ejection fraction (HFpEF)
- Identify the updated literature surrounding HFpEF

Abbreviation Key

- ACE: angiotensin converting enzyme inhibitor
- ARB: angiotensin receptor blocker
- ARNi: angiotensin receptor / neprilysin inhibitor
- BB: beta blocker
- BP: blood pressure
- CCB: calcium channel blocker
- CV: cardiovascular
- DPP4i: Dipeptidyl peptidase-4 inhibitor
- EGFR: estimated Glomerular filtration rate
- GDMT: guideline directed medication therapy
- GLP1-RA: glucagon-like peptide 1-receptor agonist
- HCTZ: hydrochlorothiazide
- HF: heart failure
- HFH: heart failure hospitalizations
- 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 reduce ejection fraction
- HR: heart rate
- IV: intravenous
- KCCQ-TSS: Kansas City Questionnaire Total Symptom Score
- LVEF: left ventricular ejection fraction
- MDD: Max daily dose
- MRA: mineralocorticoid receptor antagonist
- NSAIDs: Non-steroidal anti-inflammatory drugs
- NYH: New York Heart Association
- O2: oxygen
- SCr: serum creatinine
- SGLT2i: sodium glucose transporter 2 inhibitor
- UTI: urinary tract infections

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Heart Failure with Reduced Ejection Fraction (HFrEF)

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HFrEF Outline

Heart failure background and pathophysiology

Pharmacotherapy overview

Therapy initiation strategies

Patient Cases

Heart Failure Overview

- Heart failure is a leading cause of hospitalization among older adults and is associated with high rates of readmission
- In 2022, heart failure accounted for 9.3% of all cardiovascular deaths in the United States (~87,000 patients)
- By 2030, total HF-related costs are projected to exceed $70 billion annually
- Hospitalizations and rehospitalizations account for 75–80% of direct HF-related healthcare costs

American Heart Association. 2025 Heart Disease and Stroke Statistics Update Fact Sheet https://www.heart.org/en/-/media/PHD-Files-2/Science-News/2/2025-Heart-and-Stroke-Stat-Update/2025-Statistics-At-A-Glance.pdf?sc_lang=en. Accessed July 8, 2025
Innovate Healthcare. Cardiovascular Business. Annual heart failure costs in the US could surpass $70B by 2030 January 25, 2022. Accessed July 8, 2025.

HFrEF

- Heart Failure with reduced Ejection Fraction (HFrEF)
- Characterized by a left ventricular ejection fraction (LVEF) of ≤40%
- Also known as **systolic HF** indicating impaired contractile function of the heart muscle

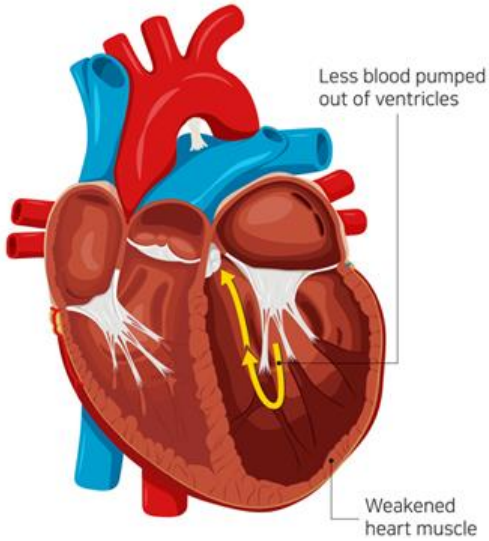

Figure 1. Systolic Dysfunction

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Understanding Congestive Heart Failure Symptoms – Dr Raghu. Accessed July 8,2025

HFrEF Pathophysiology

1. Hemodynamic changes
2. Neurohormonal activation
3. Structural remodeling

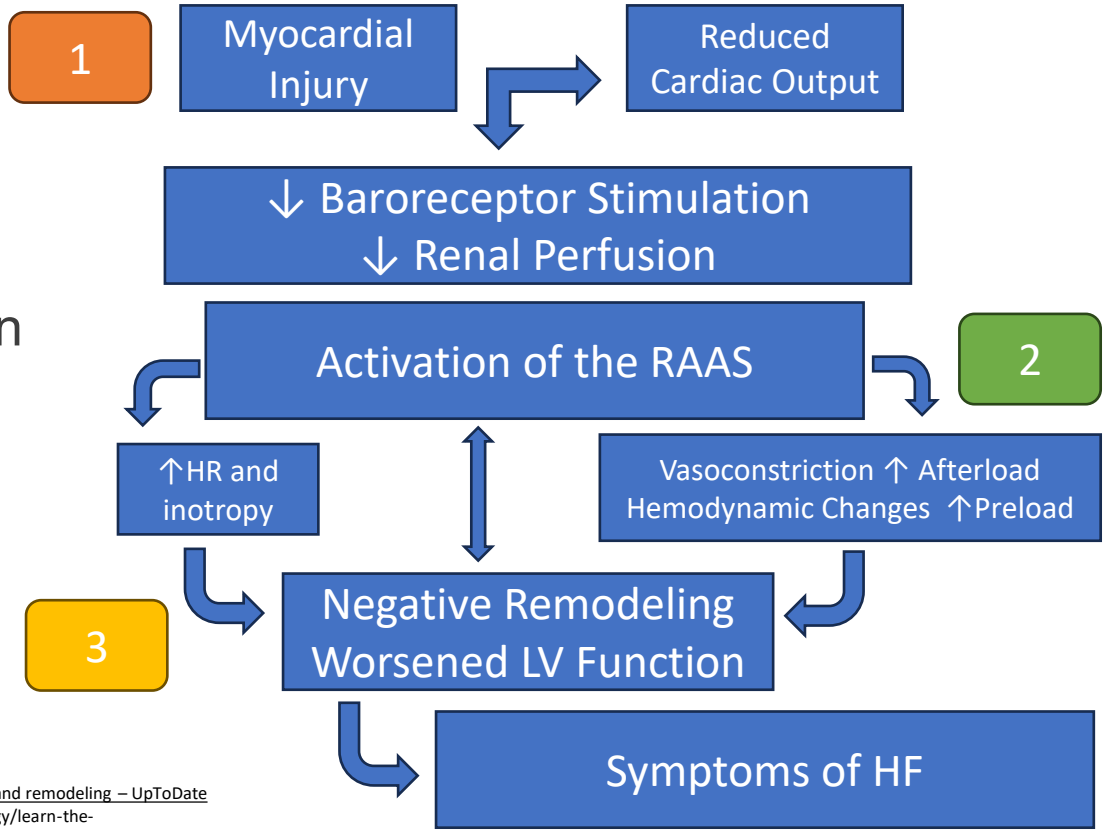

Figure. 2 HFrEF Pathophysiology Adapted from Healio

Pathophysiology of heart failure with reduced ejection fraction: Hemodynamic alterations and remodeling – UpToDate
Chronic Heart Failure – Healio.com. Access 23 July,2025. https://www.healio.com/cardiology/learn-the-heart/cardiology-review/topic-reviews/systolic-congestive-heart-failure

HF Symptoms

Figure 3. Pitting Edema

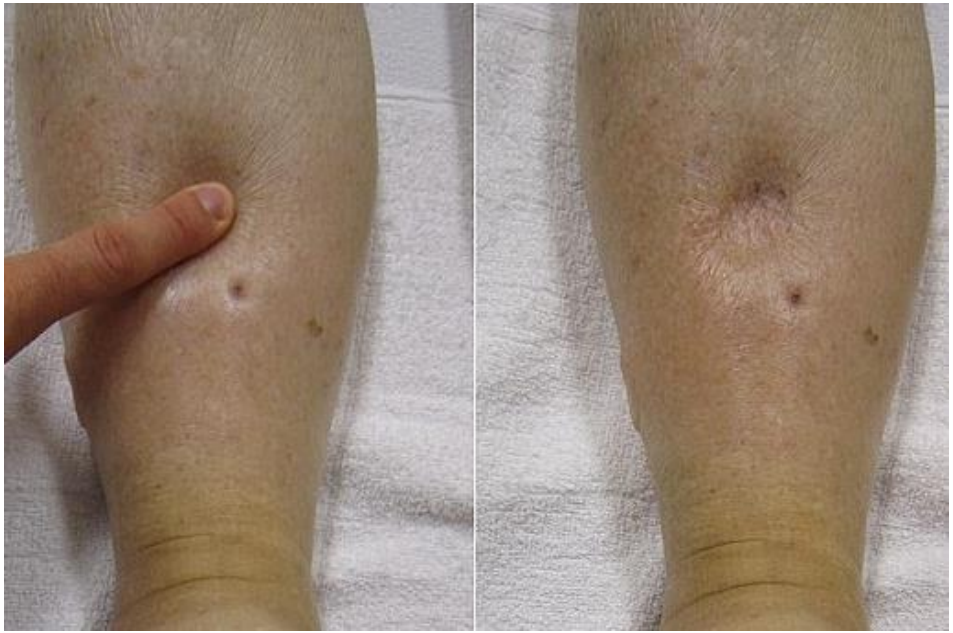

Image Courtesy of Dr. James Heilman – Creative Commons

Lack of O2

- Confusion
- Weight gain
- Fatigue
- Discolored or bluish skin
- Reduced exercise tolerance

Fluid Build Up

- Lung congestion
- Shortness of breath
- Coughing and wheezing
- Loss of appetite
- Swelling of feet and abdomen

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Causes of HF

Most common causes:
Ischemic heart disease
Myocardial infarction
Hypertension
Valvular heart disease

- Familial or genetic cardiomyopathies
- Cardiotoxicity due to chemotherapy/other cardiotoxic medications
- Substance abuse (e.g., cocaine, alcohol, methamphetamines)
- Heart rhythm-related
- Amyloidosis
- Peripartum cardiomyopathy
- Myocarditis
- Autoimmune or rheumatologic causes
- Sarcoidosis
- Iron overload
- Endocrine or metabolic causes (e.g., diabetes, obesity, thyroid disorders)

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HF Classification by EF

Adapted from Table 4. Classification of HF by LVEF

Type of HF	Criteria
HFrEF (HF with reduced EF)	LVEF ≤ 40%
HFimpEF (HF with improved EF)	Previous LVEF ≤ 40% and follow up measurement of LVEF >40%
HFmrEF (HF with mildly reduced EF)	LVEF 41-49%
HFpEF (HF with preserved EF)	LVEF ≥ 50%

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New York Heart Association (NYHA) Classification

Table. Classification of NYHA

Class	Symptoms
I	No limitation of physical activity
II	Slight limitation of physical activity, comfortable at rest. Ordinary Physical activity results in fatigue, palpitations, SOB, chest pain
IIII	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitations, SOB, chest pain
IV	Symptoms of HF at rest. Any physical activity causes further discomfort

- Used to characterize symptoms and functional capacity of patients with **symptomatic (stage C) HF** or **advanced HF (stage D)**
- Subjective assessment that can change overtime
- Independent predictor of mortality
- Used to determine eligibility of patients for treatment strategies

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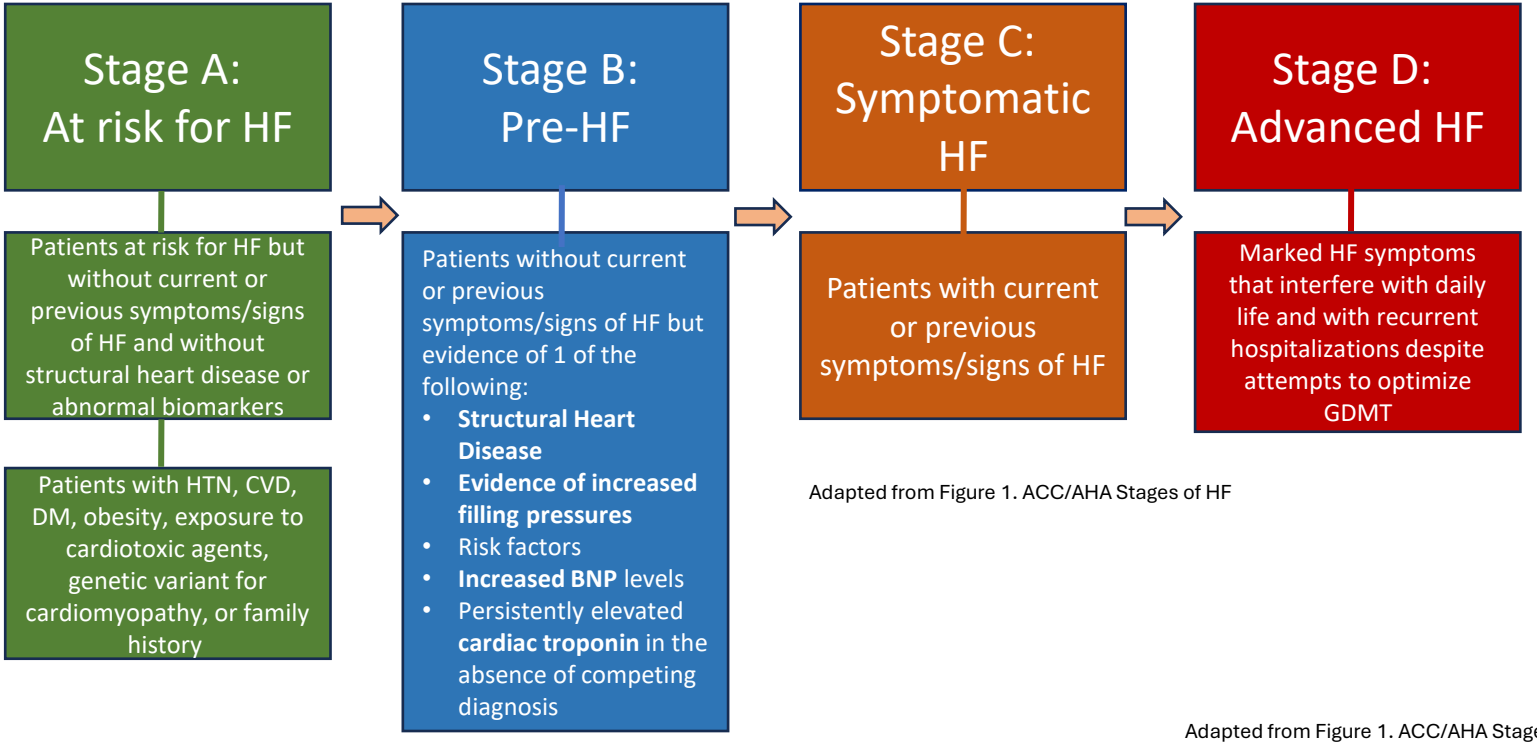
Figure 4. HF Stages



Adapted from Figure 1. ACC/AHA Stages of HF

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Stage C Heart Failure

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Nonpharmacologic Interventions

- Multidisciplinary approach
- Routine vaccinations against respiratory illness
- Education on HF to encourage engagement in self-care habits
- Avoiding excessive sodium (<2 g/day)
- Avoiding alcohol, smoking, and illicit substances
- Regular physical activity (if able to tolerate)

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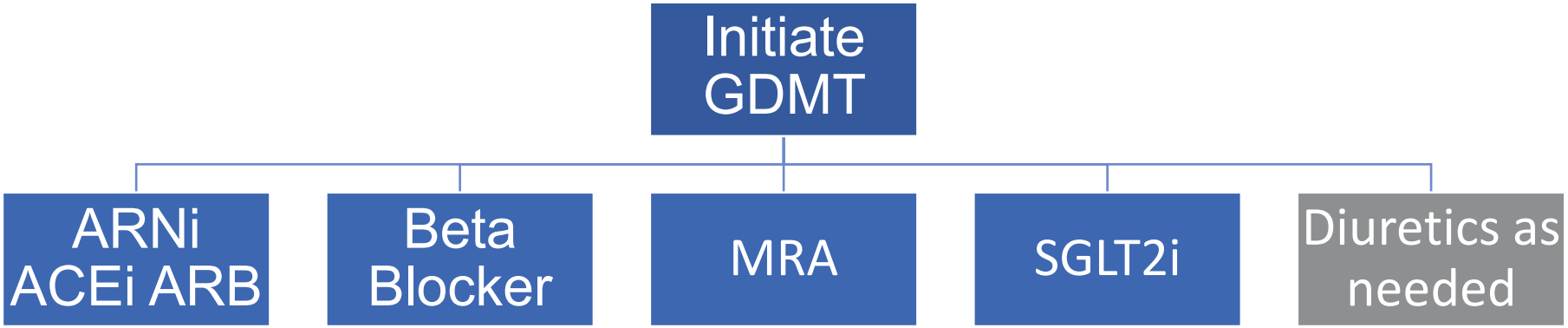
Pharmacotherapy

Guideline Directed Medication Therapy



The 4 “Pillars” of GDMT have demonstrated mortality benefit!

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Guideline Directed Medication Therapy

Initiate GDMT

- ARNi ACEi ARB
- Beta Blocker
- MRA
- SGLT2i
- Diuretics as needed

The 4 “Pillars” of GDMT have demonstrated mortality benefit!

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Renin-Angiotensin System Inhibition

PARADIGM-HF

Sacubitril-valsartan significantly reduced the composite endpoint of cardiovascular death or HF hospitalization by **20% relative to enalapril** (P<0.001)

- ACEi and ARB have demonstrated mortality benefit
- ARNi is recommended if tolerated to **further improve mortality benefit (PARADIGM-HF)**

Drug	Initial Dose	Target Dose
Sacubitril/ Valsartan	24/26mg-49/51mg BID	97/103mg BID
Lisinopril	2.5-5mg daily	20-40mg daily
Enalapril	2.5mg BID	10-20mg BID
Losartan	25-50mg daily	150mg daily
Valsartan	20-40mg BID	160mg BID

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
McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993-1004. doi:10.1056/NEJMoa1409077

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ACEi / ARB / ARNi Pearls

Treatment with ACEi or ARB provides **high economic value**

Intolerant to ACEi because of cough or angioedema = ARB is recommended to reduce morbidity and mortality

Do not administer an ARNi or ACEi if patient has any history of angioedema

36 hour washout required when switching ACEi to an ARNi to lower angioedema risk

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Beta Blockers

CIBIS-II	MERIT-HF	COPERNICUS
Trials stopped early given **significant reduction** in mortality		

- Shown to improve LVEF, lessen the symptoms of HF, and improve clinical status

Agent	Class/MOA	Initial Dose	Target Dose
Bisoprolol	B1 (cardio) selective	1.25mg daily*	10mg daily
Carvedilol IR	Nonselective with alpha 1 blocking activity	3.125mg BID	≤85kg: 25mg BID >85kg: 50mg BID
Carvedilol CR		10mg daily	80mg daily
Metoprolol succinate	B1 (cardio) selective	12.5-25mg daily	200mg daily

CIBIS-II Trial. Lancet. 1999;353(9146):9-13.
MERIT-HF Trial. Basic Res Cardiol. 2000;95 Suppl 1:I98-I103
COPERNICUS Trial. Circulation. 2002;106(17):2194-2199
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BB Pearls

Carvedilol preferred

- Cocaine use disorder
- More BP lowering effect needed

Metoprolol, bisoprolol preferred

- Uncontrolled Asthma, COPD patients or individuals with active wheezing

Do not initiate or increase while fluid overloaded

May initiate in mild fluid overload with concomitant diuretic adjustments

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MRA

RALES	EMPHASIS-HF
Trials stopped early for **reducing all-cause mortality via composite score**	

- Show improvements in all-cause mortality, HFH, and sudden cardiac death
- Recommended for patients with NYHA class II to IV symptoms
  - **If eGFR > 30 ml/min AND serum K < 5.0**

Agent	Initial Dose	Target Dose
Spironolactone	12.5-25mg daily	25-50mg in 1-2 daily doses
Eplerenone	25mg daily	50mg daily

RALES Trial. N Engl J med. 1999. 341. (10) 709-717.
EMPHASIS-HF Trial. N Engl J Med. 2011;364(1):11-21.
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MRA Pearls

May use eplerenone if gynecomastia

If using spiro 12.5 mg will need to use 25 mg tablets

- Pharmacies typically do not carry 12.5 mg, split tablets

May need to decrease or discontinue potassium supplementation upon starting

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SGLT2i

EMPEROR-Reduced	DAPA-HF
Demonstrated SGLT2 **significantly reduced the primary outcome composite of CV death or HFH**	

Agent	Dose
Dapagliflozin	10mg daily
Empagliflozin	10mg daily

In patients with symptomatic chronic HFrEF, SGLT2i are recommended to reduce hospitalization for HF and CV mortality, **irrespective of T2DM**

- Titration not needed - start at 10 mg

EMPERORROR-Reduced Trial. N Engl J med. 2020. 383: 1414-1424.
DAPA-HF Trial. N engl J Med. 2019. 381:1995-2008
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SGLT2i Pearls

- NOT recommended in patients with Type I Diabetes
- Caution in patients with uncontrolled Type II diabetes (A1c>10%) due to risk of GU infections
- Educate and monitor for GU infections, Fournier's gangrene, euglycemic DKA
- May consider lowering loop dose prior to initiation if patient susceptible to hypotension or hypovolemia
- Cost considerations

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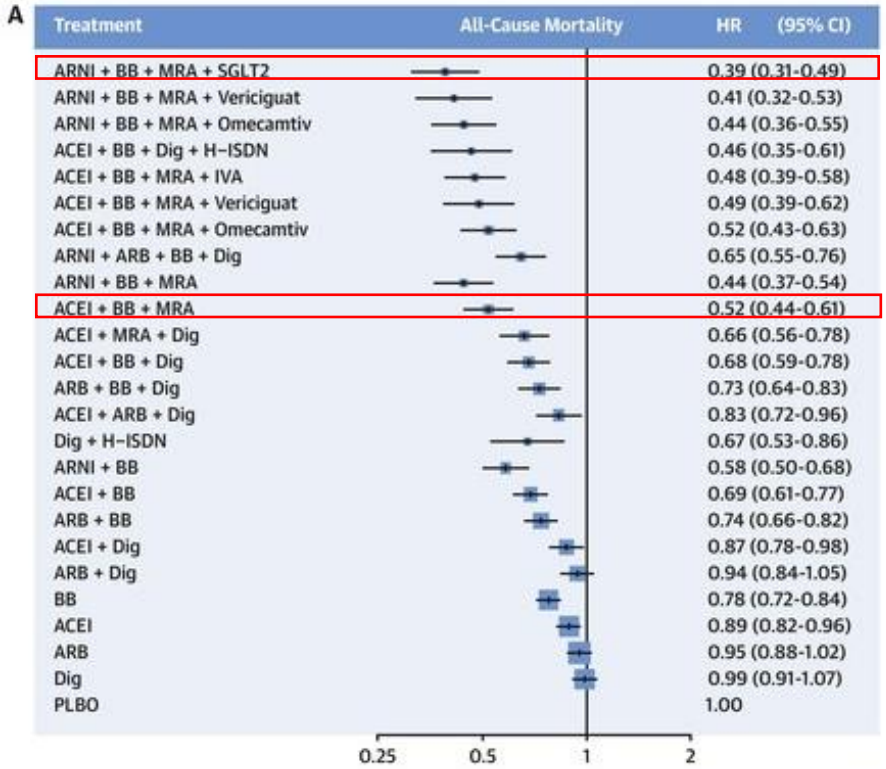
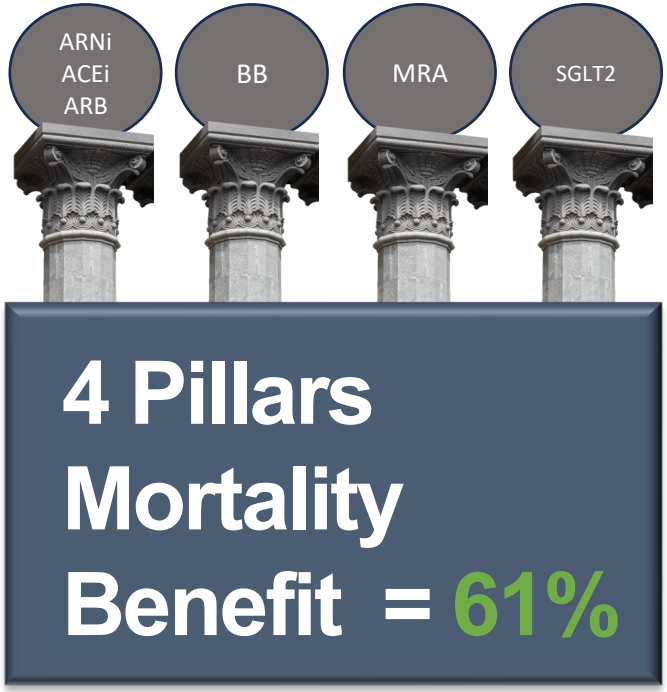
Figure. Relative Risk Reduction of Different Pharmacological Treatment Combinations for HF





Tromp, J et al. J Am Coll Cardiol HF. 2022;10(2):73-84.

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Diuresis Strategies

Treatment goal: eliminate clinical evidence of fluid retention, using the **lowest dose possible** to maintain euvolemia.

Drug	Initial Daily Dose	MDD	Duration of Action
Loop Diuretics			
Bumetanide	0.5–1.0 mg once or twice	10 mg	4–6 h
Torsemide	10-20 mg once	200 mg	12-16 h
Furosemide	20–40 mg once or twice	600 mg	6–8 h
Thiazide diuretics			
Metolazone	2.5 mg once	20 mg	12–24 h

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Additional Therapy

Hydralazine and Isosorbide

- Self-identified AA patients with NYHA class III-IV HFrEF who are on GDMT, hydralazine and isosorbide are recommended to improve symptoms and reduce morbidity and mortality
- Can be considered in patients who cannot tolerate ACEi /ARB/ARNi

Agent	Initial Dose	Target Dose
Isosorbide dinitrate plus hydralazine	20mg isosorbide plus 25mg hydralazine TID (fixed dose combination 20mg/37.5mg TID)	40mg isosorbide plus 100mg hydralazine TID (fixed dose combination 40mg/75mg TID)

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Other Treatments

Ivabradine: "funny current" inhibitor

- If resting HR remains > 70 BPM on max BB and GDMT and NYHA class II-III
- May be beneficial to reduce HFH and CV death
- No proven mortality benefit

Vericiguat: oral soluble guanylyl cyclase stimulator

- For frequent hospitalizations, SBP > 100mmHg and NYHA Class II-IV **without marked elevations to BNP**
- May be beneficial to reduce HFH and CV death
- No proven mortality benefit

Digoxin

- For HF targeting lower digoxin level of 0.8
- May beneficial to reduce HFH
- No proven mortality benefit

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Sequencing

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Sequencing

STRONG-HF (n=1,078)

Emphasized rapid titration of GDMT within 2 weeks post-discharge for acute HF

Each 10% increase in average dose was associated with a **11% reduction in all-cause death or HF readmission** (adjusted HR 0.89)

TITRATE-HF (n=4,288)

Ongoing long-term HF registry conducted in the Netherlands

44% of HFrEF patients were on **quadruple GDMT** (RAASi, BB, MRA, SGLT2i).

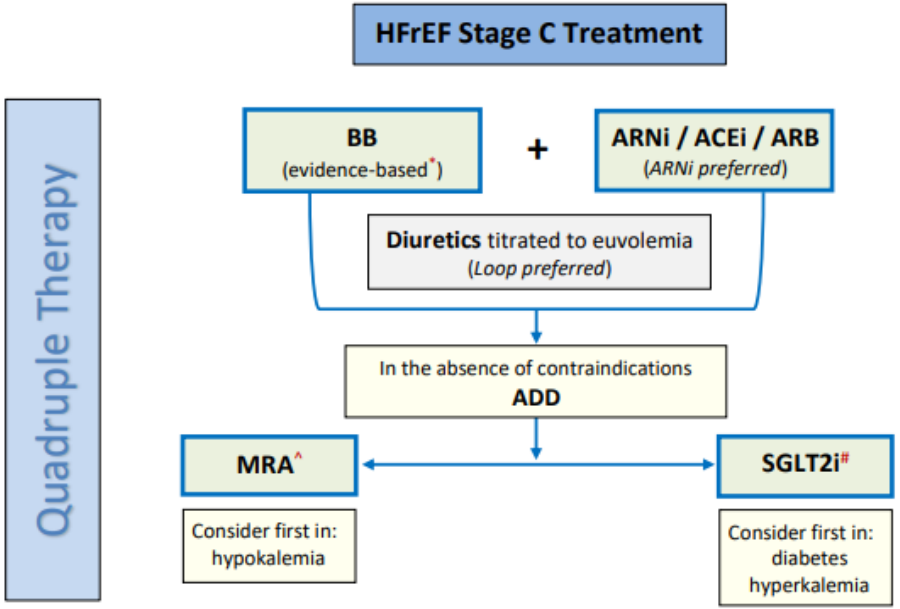
Only **1%** achieved **target doses for all four classes**

In each GDMT drug class, 19% to 36% of non-use in HFrEF patients was related to side-effects, intolerances, or contraindications.

Mebazaa A, et al. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF. *Lancet*. 2022;400(10367):1938-1952
Malgie J, et al. Contemporary guideline-directed medical therapy in de novo, chronic, and worsening heart failure patients: First data from the TITRATE-HF study. Eur J Heart Fail. 2024;26(7):1549-1560.

Sequencing

Figure. Standard Approach to Achieving Quadruple GDMT



* Evidence-based BB include carvedilol, metoprolol succinate, and bisoprolol
* eGFR ≥ 30 mL/min/1.73m^2 (or SCr ≤ 2.5 [male] / SCr ≤ 2.0 [female]) or K ≤ 5.0 mmol/L
# Refer to eGFR criteria for use

Original source AAH Ambulatory Heart Failure Management Clinical Practice Guidelines

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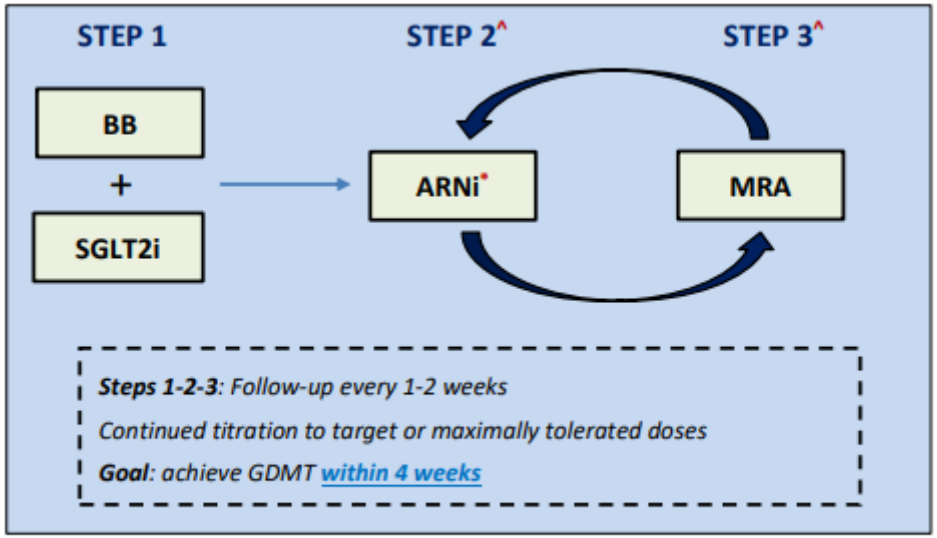
Alternative Sequencing

Figure. Alternative GDMT Initiation and Titration Algorithm



*Use ACEi/ARB if unable to start ARNi

^Sequencing of Steps 2 and 3 can be modified for clinical factors (BP, renal function, potassium)

Original source AAH Ambulatory Heart Failure Management Clinical Practice Guidelines

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Simultaneous Start

Simultaneous or Rapid Sequence Initiation of Quadruple GDMT					
Agent	Day 1	Day 7-14	Days 14-28	Day 21-42	After Day 42
ARNi*	Initiate at low dose	Continue current dose	**Titrate** dose as tolerated	**Titrate** dose as tolerated	Continue up titration of quadruple co mbination GDMT to maximally tole rated or target dose
BB	Initiate at low dose	**Titrate** dose as tolerated	**Titrate** dose as tolerated	**Titrate** dose as tolerated	
MRA	Initiate at low dose	Continue current dose	**Titrate** dose as tolerated	Continue current dose	
SGLT2i	Initiate	Continue current dose	Continue current dose	Continue current dose	

*Use ACEi/ARB if unable to start ARNi

Original source AAH Ambulatory Heart Failure Management Clinical Practice Guidelines

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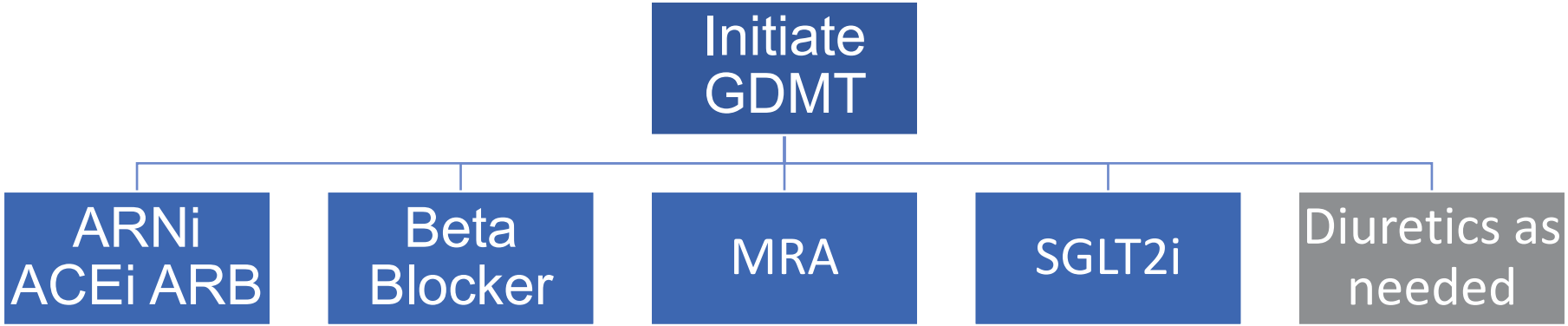
Lab Monitoring

Kidney function, potassium (K)

BMP prior to initiation and 1- 2 weeks after initiation or titration

May cause increase in SCr but continue unless > 30% from baseline

Guideline Directed Medication Therapy



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Treatments to Avoid

Medication Class	Examples	Mechanism
NSAIDs (Nonsteroidal Anti-inflammatory Drugs)	Ibuprofen, Naproxen, Indomethacin, meloxicam, nabumetone, celecoxib	Sodium and water retention causes ↑ preload and afterload
Thiazolidinediones	Pioglitazone, Rosiglitazone	Fluid retention via PPAR-γ activation
DPP-4 inhibitors	Saxagliptin, alogliptin	Increased hospitalization risk
Non-DHP Calcium Channel Blockers	Verapamil, Diltiazem	Negative inotropy causes ↓ cardiac output
Class I Antiarrhythmics	Flecainide, Propafenone	Negative inotropy and proarrhythmic risk
Class III Antiarrhythmics	Dronedarone	Increased mortality in HF patients
Corticosteroids	Prednisone, Dexamethasone	Sodium and water retention
Androgenic/Estrogenic Hormone	Testosterone, Estrogen	Fluid retention
Chemotherapy Agents	Anthracyclines (Doxorubicin), Trastuzumab	Direct cardiotoxicity
Sympathomimetics	Decongestants (Pseudoephedrine)	↑ HR and BP causes ↑ cardiac workload

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HFimpEF (<40% → 40%+)

- Trials demonstrate continuation of GDMT despite LVEF recovery
- **Indefinite therapy**

HFmrEF (41-49%)

- Trials demonstrate GDMT benefit

Summary

4 Pillars of GDMT = 61% reduction in all cause mortality

Treatment is individualized to patients based on:

- Vital signs
- Tolerance
- Electrolytes
- Functional Status
- Renal Function
- Comorbidities
- Monitoring capabilities
- Affordability / access

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Assessment Question #1

Patient: JT a 68-year-old white male

Past Medical History:
- HFrEF diagnosed 2 years ago (most recent LVEF 30% 11/10/25)
- NYHA Class III symptoms
- Hypertension, Type 2 Diabetes Mellitus (A1c 10%)

Objective:
BP: 120/74 mmHg, HR: 62 bpm
K+: 4.5 mmol/L, SCr: 1.1 mg/dL, eGFR = 62 ml/min, NT-proBNP: 28 mg/dl

- Current medications:
  - **Lisinopril 10 mg daily**
  - **Metoprolol succinate 100 mg daily**
  - **Furosemide 40 mg daily**
  - **Metformin XR 500 mg twice daily**

Assessment Question #1

Which of the following is the MOST appropriate next step in optimizing GDMT for this patient?

A. Increase Furosemide 80 mg once daily
B. Switch Lisinopril to Sacubitril/Valsartan immediately
C. Add Spironolactone 25 mg once daily
D. Add Ivabradine 2.5 mg twice daily

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Assessment Question #2

Patient: LR 72-year-old African American female

Past medical history:
- HFrEF (LVEF 35%) diagnosed 6 months ago
- NYHA Class II symptoms
- HTN, CKD Stage 4

Objective
BP: 118/76 mmHg, HR: 68 bpm, eGFR: 25 mL/min/1.73m^2, A1c = 5.8%

- Current medications:
  - **Carvedilol 6.125 mg twice daily**
  - **Losartan 100 mg daily**
  - **Empagliflozin 10 mg daily**
  - **Furosemide 20 mg daily**

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Assessment Question #2

Which of the following best describes the role of SGLT2 inhibitors in this patient's heart failure management?

A. Empagliflozin should be discontinued due to her renal function
B. SGLT2i are only indicated for glycemic control in diabetic patients
C. Empagliflozin provides CV benefit in HFrEF regardless of diabetes
D. SGLT2 inhibitors are contraindicated in NYHA Class II heart failure

Heart Failure with Preserved Ejection Fraction (HFpEF)

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HFpEF Outline

Background

GDMT Recommendations

Updated or Emerging Literature

Definition of HFpEF

Clinical syndrome:

EF > 50%

Signs/symptoms of HF

Plus one of the following:

- Objective evidence of cardiogenic pulmonary or systemic congestion
- Elevated natriuretic peptides

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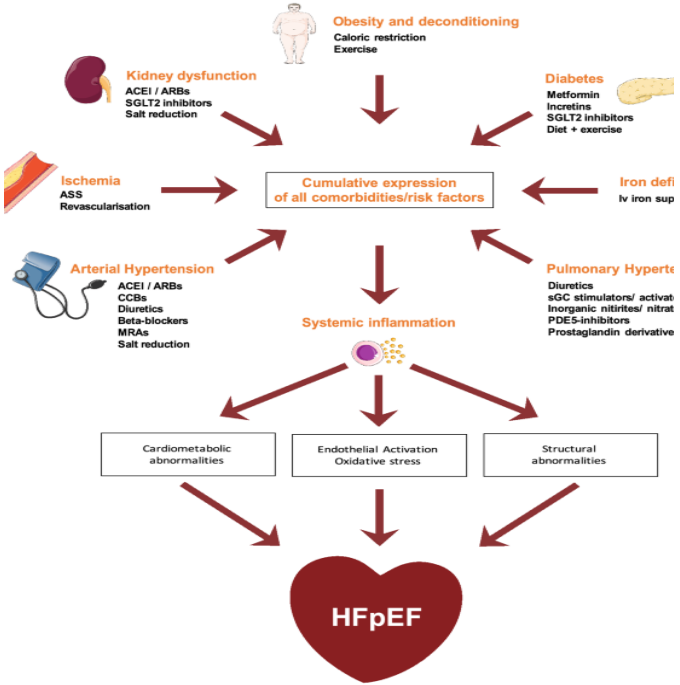
Pathophysiology

Multifactorial syndrome:

- Caused by multiple pathological mechanisms
- Cardiac aging and cardiometabolic disorders
- Higher prevalence of comorbidities



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Wintrich J, Kindermann I, Ukena C, et al. Therapeutic approaches in heart failure with preserved ejection fraction: past, present, and future. *Clin Res Cardiol.* 2020;109(9):1079-1098.

Epidemiology of HFpEF

- HFpEF affects ~ 3 million people within the United States
- Represents ~ 50% of all heart failure hospitalizations
- Mortality associated with HFpEF ranges
  - 15% at 1 year
  - 75% at 5 to 10 years after hospitalization
- Mortality often driven by non-cardiac comorbidities (e.g. HTN,DM, renal failure)

American College of Cardiology. *Focus on Heart Failure | HFpEF: Where We Stand in 2025.* ACC.org. Published June 1, 2025.
Cannata A, McDonagh TA. Heart failure with preserved ejection fraction. *N Engl J Med.* 2025;392:173-184.
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ADVOCATE HEALTH

Risk Factors

Demographics
- Older age
- Female sex

Cardiac
- Atrial fibrillation
- Valvular heart disease

Cardiometabolic
- HTN
- T2DM

Pulmonary & Renal
- OSA
- CKD

Other
- High sodium diet
- Chronic systemic inflammation

ADVOCATE HEALTH

American College of Cardiology. (2025, June 1). *Focus on Heart Failure | HFpEF: Where We Stand in 2025.*

Diagnosis of HFpEF

Physical examination	• Dyspnea, JVD, Edema
Differential diagnosis	• Non-cardiac & cardiac mimics • Pulmonary testing
Laboratory	• BNP > 35 pg/mL • NT-proBNP > 125 pg/mL
Imaging	• Echocardiogram
Scoring systems	• H2FPEF • HFA-PEFF

ADVOCATE HEALTH

2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction: A Report of the American College

Limitations in Diagnosis

- **Lack of single diagnostic test for definitive diagnosis**
- **Factors Affecting Natriuretic Peptide Interpretation**
  - **Falsely Elevated Levels**
    - Renal Impairment
    - Atrial Fibrillation
  - **Falsely Reduced Levels**
    - Obesity

ADVOCATE HEALTH

Screening

In adults who are at increased risk for the development of asymptomatic cardiac structure or functional abnormalities consider:

- Screening adults with diabetes by measuring a BNP or NT-proBNP
- In asymptomatic individuals with diabetes and abnormal BNP or NT-proBNP an echocardiogram is recommended

American Diabetes Association Professional Practice Committee for Diabetes*; 10. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes—2026. *Diabetes Care* 1 January 2026; 49 (Supplement_1): S216–S245.

Treatment Goals

- Reduce symptoms and physical limitations
- Prevent heart failure hospitalizations
- Decrease cardiovascular morbidity and mortality
- Management of other comorbidities
  - HTN
  - Diabetes
  - Atrial fibrillation
  - Obesity
  - CKD

Kittleson MM, Panjrath GS, Amancherla K, et al. *2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction*. J Am Coll Cardiol. 2023;Epub April 19

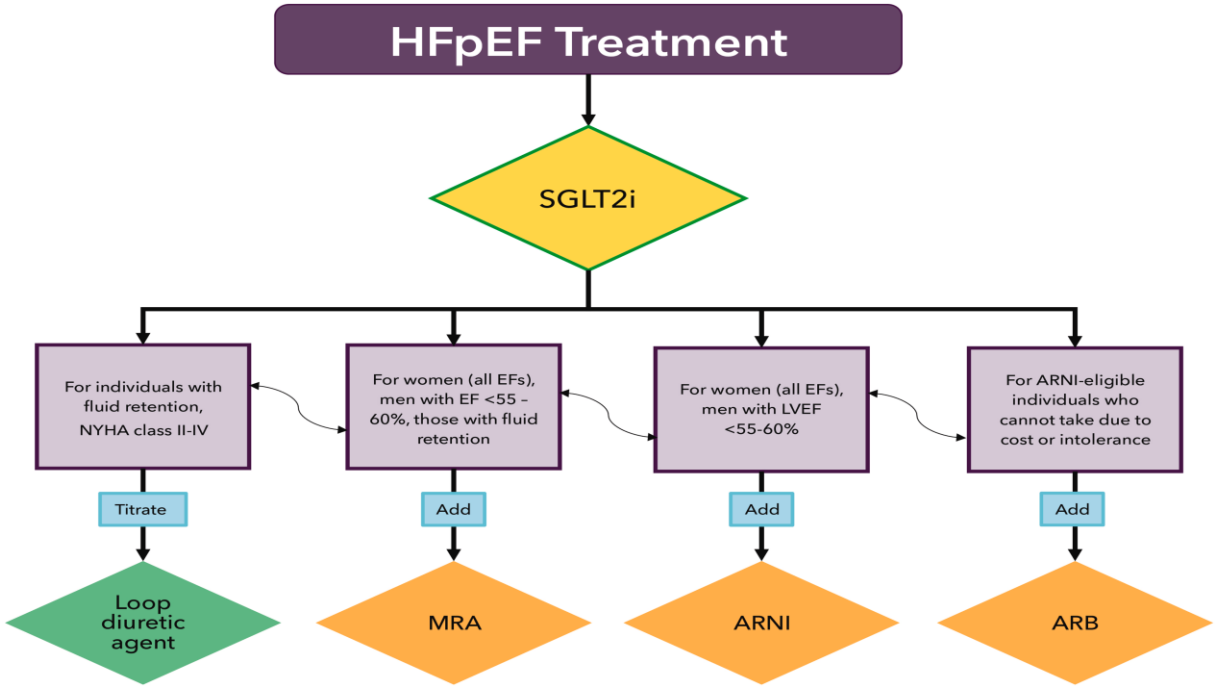
HFpEF Outline

Background

GDMT Recommendations

Updated or Emerging Literature

Current GDMT Recommendations



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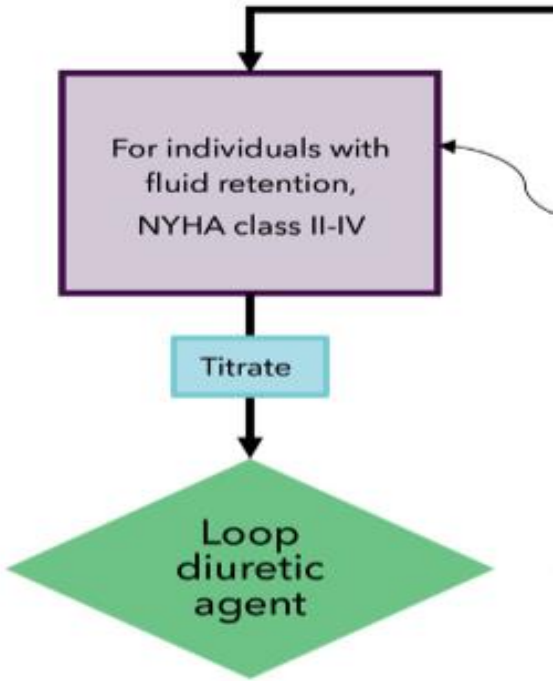
2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction: A Report of the American College

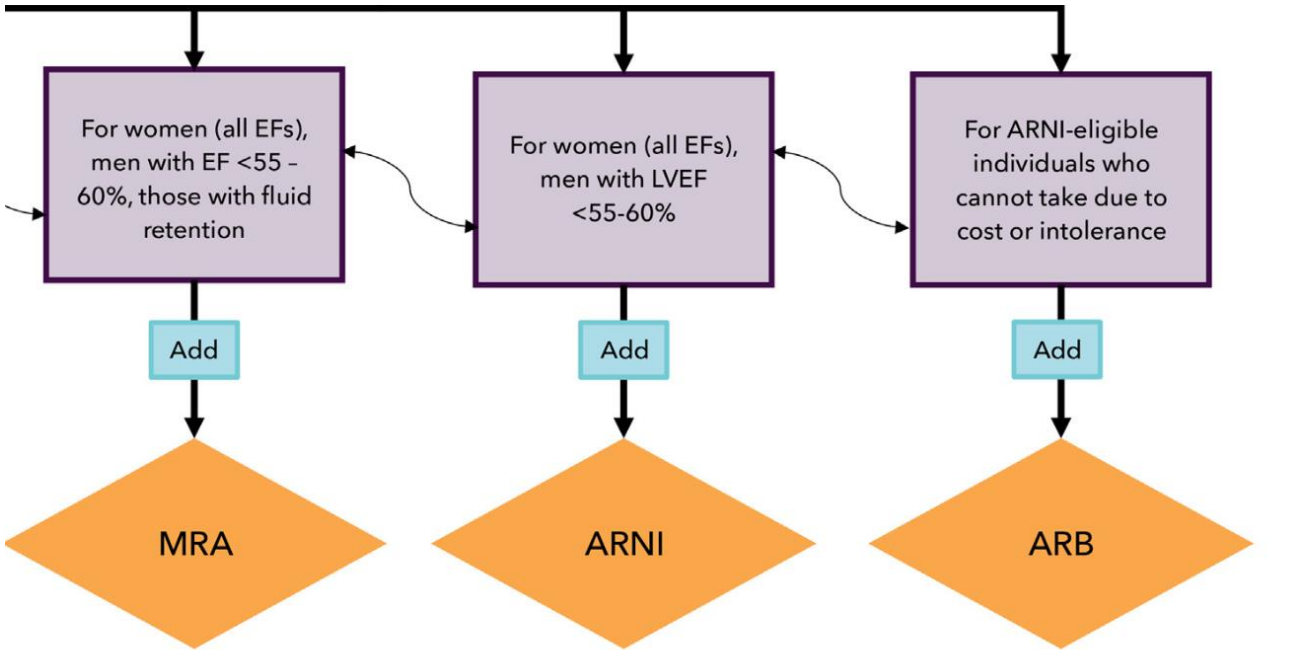
Current GDMT Recommendations



ADVOCATE HEALTH

2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction: A Report of the American College

Current GDMT Recommendations



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2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction: A Report of the American College

Current GDMT Recommendations

Drug class	Starting dose	Target dose
SGLT2i - **Dapagliflozin** - **Empagliflozin**	10 mg daily	10 mg daily
ARNIs **- Sacubitril/valsartan**	24/26 mg twice daily	97/103 mg twice daily
ARBs - **Candesartan**	4-8 mg daily	32 mg daily
MRA **- Spironolactone**	25 mg daily	50 mg daily

ADVOCATE HEALTH

2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction: A Report of the American College

SGLT2i

Trial	Primary outcome	Results	Rec
DELIVER Dapagliflozin EF > 40%	Composite: • Worsening heart failure • Cardiovascular death	Primary outcome: • Dapagliflozin group: 512 of 3131 (16.4%) patients • Placebo group: 610 of 3132 (19.5%) patients Hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.92; P<0.001.	2a
EMPEROR-PRESERVED Empagliflozin EF > 40%	Composite: • Cardiovascular death • Hospitalization for heart failure	Primary outcome: • Empagliflozin group: 415 of 2997 patients (13.8%) • Placebo group: 511 of 2991 patients (17.1%) Hazard ratio, 0.79; 95% confidence interval [CI], 0.69 to 0.90; P<0.001.	

Solomon SD, McMurray JJV, Claggett B, et al. *Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction*. N Engl J Med. 2022;387(12):1089-1098.
Anker SD, Butler J, Filippatos G, et al. *Empagliflozin in Heart Failure with a Preserved Ejection Fraction*. N Engl J Med. 2021;385(16):1451-1461.

ARNIs

Trial	Primary outcome	Results	Rec
PARAGON-HF Sacubitril/valsartan EF > 45%	Composite: • Total HF hospitalizations • Cardiovascular death	Primary outcome: • Sacubitril/valsartan group: 894 events • Valsartan group: 1009 events Hazard ratio, 0.87; 95% CI: 0.75-1.01	2b

ADVOCATE HEALTH

Solomon SD, McMurray JJV, Anand IS, et al. *Angiotensin–neprilysin inhibition in heart failure with preserved ejection fraction.* **N Engl J Med.** 2019;381(17):1609-1620

ARBs

Trial	Primary outcome	Results	Rec
CHARM-PRESERVED Candesartan EF > 40%	Composite: • Hospitalization • CV death	Primary outcome: • Candesartan: 333 events • Placebo: 366 events Adjusted HR: 0.86; 95% CI: 0.74-1.00	2b

Pfeffer MA, Swedberg K, Granger CB, et al. *Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme.* **Lancet.** 2003;362(9386):759-766

MRAs

Trial	Primary outcome	Results	Rec
TOPCAT Spironolactone EF > 45%	Composite: • Death from CV causes • Aborted cardiac arrest • Hospitalization for HF	Primary outcome: • Spironolactone group: 320 events • Placebo group: 351 events Hazard ratio 0.89; 95% CI 0.77–1.04.	2b

ADVOCATE HEALTH

Pitt B, Pfeffer MA, Assmann SF, et al; TOPCAT Investigators. Spironolactone for Heart Failure with Preserved Ejection Fraction. N Engl J Med. 2014; 370(15):1383–1392.

TOPCAT

- Hard to interpret because results looked very different depending on geographic location
- Patients from Russia and Georgia had very low event rates and many had no detectable drug levels, raising concerns for non-adherence
- In contrast, patients from the Americas had higher event rates and clear drug exposure, and this group did show a significant benefit

Table 4. Summary of Trial Outcomes by Treatment Arm and Region

	Americas (n=1767)			Russia/Georgia (n=1678)				
	No. (%) With Event [Incidence Rate per 100 patient-y]			No. (%) With Event [Incidence Rate per 100 patient-y]				
Outcome	Spironolactone (n=886)	Placebo (n=881)	HR (95% CI) *P* Value	Spironolactone (N=836)	Placebo (N=842)	HR (95% CI) *P* Value	*P*, Regional Difference*	*P*, Treatment-by-Region Interaction
Primary outcome	242 (27.3) [10.4]	280 (31.8) [12.6]	0.82 (0.69–0.98) 0.026	78 (9.3) [2.5]	71 (8.4) [2.3]	1.10 (0.79–1.51) 0.58	<0.001	0.12

Pitt B, Pfeffer MA, Assmann SF, et al; TOPCAT Investigators. Spironolactone for Heart Failure with Preserved Ejection Fraction. N Engl J Med. 2014; 370(15):1383–1392.
Pfeffer MA, Claggett B, Assmann SF, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. Circulation. 2015;131(1):34-42. doi:10.1161/circulationaha.114.013255

Assessment Question #3

JD is a 67-year-old female with a past medical history of obesity, HLD, T2DM and HTN. She presents to clinic with increased SOB and mild lower extremity edema. Initial labs show BP of 142/87 mmHg, NT-proBNP of 2,895, GFR of 72 mL/min, A1c 8.4%, potassium WNL, and EF of 67%. HFpEF is diagnosed.

Her current medications include: losartan 25 mg daily, atorvastatin 20mg daily and metformin 1000 mg twice daily. Which of the following would be the most appropriate therapeutic change for HFpEF management?

A. Start pioglitazone 15 mg once daily
B. Start empagliflozin 10 mg once daily
C. Stop losartan and change to lisinopril 20 mg once daily
D. Start metoprolol succinate 25 mg once daily

HFpEF Outline

Background

GDMT Recommendations

Updated or Emerging Literature

Non-steroidal Mineralocorticoid Receptor Antagonist

ADVOCATE HEALTH

Finerenone vs Spironolactone

	Spironolactone *	Finerenone
Mechanism of action	Competitive antagonist of mineralocorticoid receptor; preferentially acts in kidney **Steroidal**	Selective, high-affinity antagonist of mineralocorticoid receptor; balanced heart/kidney distribution **Non-steroidal**
Hormonal adverse effects	Gynecomastia Menstrual irregularity Impotence	None
Class effects	Hyperkalemia Hypotension Renal dysfunction Electrolyte imbalances	

* FDA approved for the management of HTN

Lexicomp. Finerenone: Drug Information. Lexicomp Online. Wolters Kluwer Health, Inc.
Lexicomp. Spironolactone: Drug Information. Lexicomp Online. Wolters Kluwer Health, Inc.

ADVOCATE HEALTH

Finerenone – Renal Dosing

Renal adjustments	Initial Dose
eGFR > 60 mL/min	20 mg once daily Target dose of 40 mg once daily
eGFR > 25 < 60 mL/min	10 mg once daily Target dose of 20 mg once daily
eGFR < 25 mL/min	Use not recommended
Maintenance dose is determined by serum potassium & eGFR measured 4 weeks after initiation of therapy or after a dose adjustment Continue to monitor serum potassium and eGFR periodically during therapy and adjust dose as needed.	

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Lexicomp. Finerenone: Drug Information. Lexicomp Online. Wolters Kluwer Health, Inc.

Finerenone – Potassium Dosing

Current serum potassium	Current finerenone dose		
	10 mg once daily	20 mg once daily	40 mg once daily
<5 mEq/L	Increase to 20 mg once daily.	Maintain 20 mg once daily if eGFR <60 mL/minute/1.73 m^2 at initiation. Otherwise increase the dose to 40 mg once daily.	Maintain 40 mg once daily.
≥5 to <5.5 mEq/L	Continue 10 mg once daily.	Continue 20 mg once daily.	Continue 40 mg once daily
≥5.5 to <6 mEq/L	Interrupt therapy. Restart at 10 mg once daily when serum potassium <5.5 mEq/L.	Decrease to 10 mg once daily.	Decrease to 20 mg once daily.
≥6 mEq/L	Interrupt therapy. Restart at 10 mg once daily when serum potassium <5.5 mEq/L.		

ADVOCATE HEALTH

Lexicomp. Finerenone: Drug Information. Lexicomp Online. Wolters Kluwer Health, Inc.

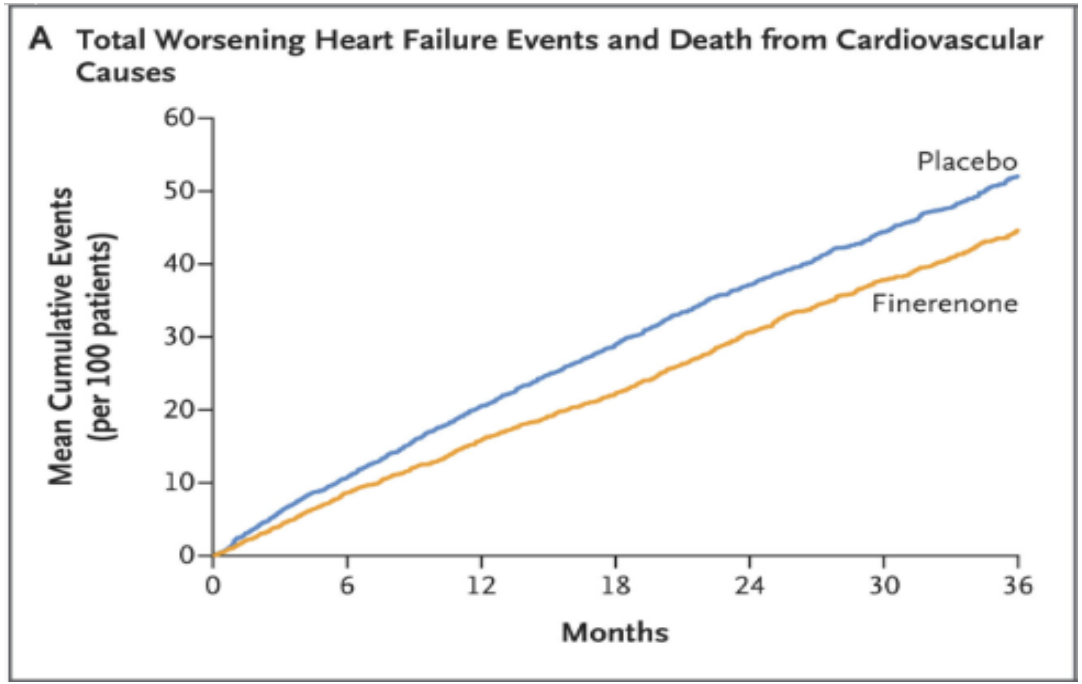
Finerenone in Heart Failure with mildly reduced or preserved ejection fraction (FINEARTS-HF)

Trial design	International, double-blind trial that occurred across 37 countries and 654 sites
Objective	Compared finerenone against placebo in HFmrEF & HFpEF patients
Inclusion criteria	• Age > 40 years old • Symptomatic heart failure • LVEF > 40% • Evidence of structural heart disease • Elevated levels of natriuretic peptides
Primary outcome	Composite • Total worsening HF events (First or recurrent unplanned hospitalizations or urgent care visit) • Heart failure deaths from cardiovascular causes
Methods	Participants were randomized 1:1 to finerenone (20 mg or 40 mg daily, titrated based on kidney function) or matching placebo in addition to their other therapies N=6001

ADVOCATE HEALTH

Filippatos G, Butler J, Lam CSP, et al. Finerenone in heart failure and mildly reduced or preserved ejection fraction. *N Engl J Med.* 2023;389(9):803-814.

Finerenone in Heart Failure with mildly reduced or preserved ejection fraction (FINEARTS-HF)



ADVOCATE HEALTH

Filippatos G, Butler J, Lam CSP, et al. Finerenone in heart failure and mildly reduced or preserved ejection fraction. *N Engl J Med.* 2023;389(9):803-814.

Finerenone in Heart Failure with mildly reduced or preserved ejection fraction (FINEARTS-HF)

Results	**Primary outcome:** • Finerenone: 624 events • Placebo: 1283 events • Rate ratio: 0.84; 95% CI, 0.74-0.95; P=0.007.	**Total worsening heart failure events:** • Finerenone: 842 events • Placebo: 1024 events • Rate ratio: 0.82; 95% CI 0.71–0.94; P=0.006. **Cardiovascular death:** • Finerenone: 242 death • Placebo: 260 deaths • Hazard ratio: 0.93, 95% CI 0.78–1.11.
Conclusion	In patients with heart failure and mildly reduced or preserved ejection fraction, finerenone resulted in a significantly lower rate of a composite of total worsening heart failure events and death from cardiovascular causes than placebo	

ADVOCATE HEALTH

Filippatos G, Butler J, Lam CSP, et al. Finerenone in heart failure and mildly reduced or preserved ejection fraction. *N Engl J Med.* 2023;389(9):803-814.

Differences	TOPCAT (Spironolactone)	FINEARTS-HF (Finerenone)
Participants:	LVEF > 45% Adults > 50	LVEF > 40% Adults > 40
Average EF	The mean baseline ejection fraction: • 58%	The mean baseline ejection fraction: • 53%
Primary outcomes:	Composite: • Cardiovascular death • HF hospitalization • Aborted cardiac arrest	Composite: • Total worsening HF events (First or recurrent unplanned hospitalizations or urgent care visit) • Heart failure deaths from cardiovascular causes

Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med.* 2014;370(15):1383-1392
Filippatos G, Butler J, Lam CSP, et al. Finerenone in heart failure and mildly reduced or preserved ejection fraction. *N Engl J Med.* 2023;389(9):803-814.

Assessment Question #4

Which of the following factors complicates a direct comparison of the results of the TOPCAT vs FINEARTS-HF trial:

A. TOPCAT had a stricter primary endpoint

B. TOPCAT enrolled patients with a higher average EF and in both trials the therapeutic benefit decreased as EF increased.

C. TOPCAT had significant regional variability, with much better results in the Americas where the protocol was appropriately followed.

D. All of the above

GLP-1 Receptor Agonists

- **Semaglutide**
- **Tirzepatide**

ADVOCATEHEALTH

Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity (SUMMIT)

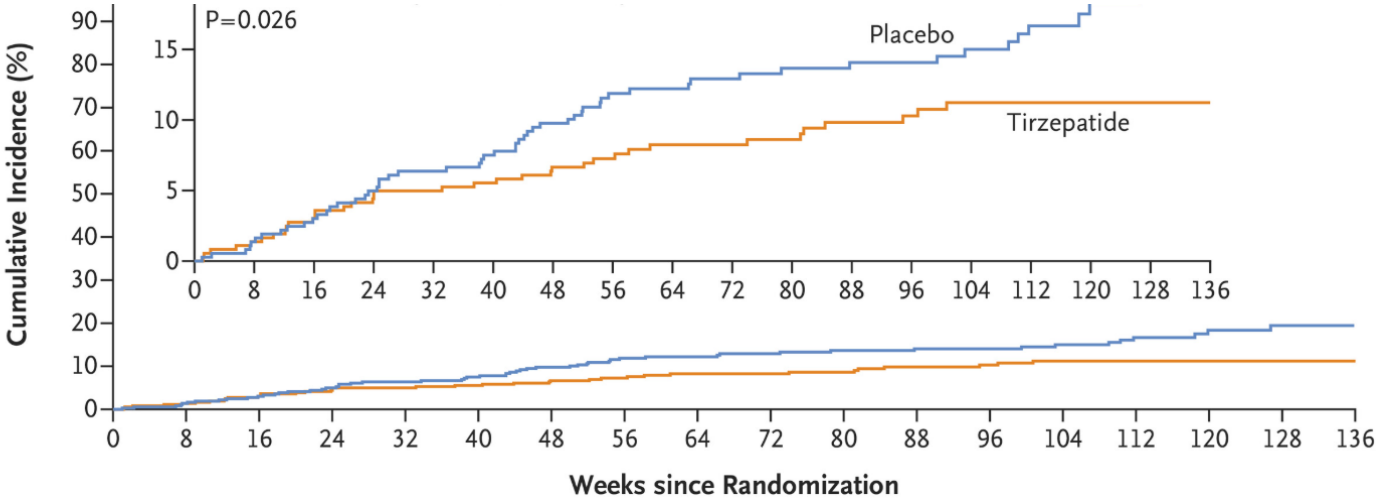
Trial design	International, randomized, double-blind placebo-controlled trial
Objective	Compared tirzepatide titrated up to a dose of 15 mg weekly against placebo in patients with preserved ejection fraction
Inclusion criteria	• Age > 40 years old • LVEF > 50% • BMI > 30 kg/m2 • Functional and symptomatic requirements
Primary outcomes	Composite: • Adjudicated death from CV causes • Worsening HF events The change in baseline to 52 weeks in KCCQ-CSS
Methods	Patients with an EF of at least 50% and a BMI of at least 30 were assigned 1:1 to receive tirzepatide (up to 15 mg subcutaneously once per week) or placebo for at least 52 weeks. N= 731

ADVOCATE HEALTH

Packer M, Zile MR, Kramer CM, et al; SUMMIT Trial Study Group. Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity. *N Engl J Med*. 2024

Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity (SUMMIT)

Composite of death from CV causes or a worsening HF event



No. at Risk																		
Placebo	367	361	349	339	332	328	318	268	259	240	219	215	195	165	145	94	73	45
Tirzepatide	364	359	349	344	340	338	333	284	275	251	228	220	196	167	146	105	82	46

ADVOCATE HEALTH

Packer M, Zile MR, Kramer CM, et al; SUMMIT Trial Study Group. Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity. *N Engl J Med*. 2024

Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity (SUMMIT)

Results	**Primary outcome:** • Tirzepatide: 36 patients • Placebo: 56 patients • Hazard ratio: 0.62; 95% CI: 0.41-0.95; P=0.026 **Worsening heart failure events:** • Tirzepatide: 29 events • Placebo: 52 events • Hazard ratio: 0.54; 95% CI: 0.34–0.85 **Cardiovascular death:** • Tirzepatide: 8 events • Placebo: 5 events • Hazard ratio: 1.58; 95% CI: 0.52–4.83	**Second primary outcome:** Quality of life (KCCQ-CSS change at 52 weeks): • Tirzepatide: +19.5 points • Placebo: +12.7 points • Difference: +6.9; 95% CI: 3.3–10.6, p<0.001
Conclusion	In patients with heart failure with preserved ejection fraction and obesity tirzepatide led to a lower risk of a composite of death from cardiovascular causes or worsening heart failure than placebo and improved health status.	

ADVOCATE HEALTH

Packer M, Zile MR, Kramer CM, et al; SUMMIT Trial Study Group. Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity. *N Engl J Med*. 2024

GLP1-RA – Titration Schedules

Tirzepatide (Zepbound ®)	
Week	Dose
Week 1 – Week 4	2.5 mg once weekly
Week 5 – Week 8	5 mg once weekly
Week 9 – Week 12	7.5 mg once weekly
Week 13 – Week 16	10 mg once weekly
Week 16 – Week 20	12.5 mg once weekly
Week 20 – Week 24	15 mg once weekly

ADVOCATE HEALTH

Tirzepatide: Drug Information. *Lexicomp Online*, Wolters Kluwer Health, Inc.

GLP1-RA – Titration Schedules

Semaglutide (Wegovy ®)	
Week	Dose
Week 1 – Week 4	0.25 mg once weekly
Week 5 – Week 8	0.5 mg once weekly
Week 9 – Week 12	1 mg once weekly
Week 13 – Week 16	1.7 mg once weekly
Week 17 and on	2.4 mg once weekly

Semaglutide (Ozempic ®)	
Week	Dose
Week 1 – Week 4	0.25 mg once weekly
Week 5 – Week 8	0.5 mg once weekly
Week 9 – Week 12	1 mg once weekly
Week 13 – Week 16	2 mg once weekly

ADVOCATE HEALTH

Semaglutide: Drug Information. *Lexicomp Online*, Wolters Kluwer Health, Inc.

Place in Therapy

Finerenone in HFpEF

- Patients who have experienced hormonal adverse effects with spironolactone
- Individuals with concerns related to orthostasis
- Patients for whom cost is not a significant factor

GLP-1 Receptor Agonists in HFpEF

- Improve symptoms and enhance physical function in patients with HFpEF
- Optimize glycemic management for individuals with type 2 diabetes & promote weight loss
- HFpEF and not HFrEF
- Overall decrease in multiple risk factors

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Questions?

02/24/2025

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