Heart Failure & Emerging Therapies

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CMEPRO

Objectives

Describe	Describe the pathophysiology and classifications for heart failure to guide appropriate assessment
List	List guideline-directed medical therapies and adjunct pharmacologic options to optimize treatment in patients with heart failure
Identify	Identify emerging therapies and incorporate new evidence into clinical decision making for heart failure treatment

Abbreviations

ACEI: angiotensin-converting enzyme inhibitor

AF: atrial fibrillation

ARB: angiotensin receptor blocker

ARNI: angiotensin receptor-neprilysin inhibitor

BNP: B-type natriuretic peptide

BP: blood pressure

cGMP: cyclic guanosine monophosphate

CV: cardiovascular

DOAC: direct oral anticoagulant

EF: ejection fraction

GDMT: guideline-directed medical therapy

HF: heart failure

HFimpEF: heart failure with improved ejection fraction

HFmrEF: heart failure with moderately reduced ejection fraction

HFpEF: heart failure with preserved ejection fraction

HFrEF: heart failure with reduced ejection fraction

HR: heart rate

LVEF: left ventricular ejection fraction

MRA: mineralocorticoid receptor antagonist

Non-DHP CCB: non-dihydropyridine calcium channel blockers

RAAS: renin-angiotensin-aldosterone system

RCT: randomized control trial

SGLT2: sodium-glucose co-transporter 2

Background

Epidemiology

~6.7 million Americans over 20 years of age have HF

↑ 8.5 million Americans by 2030

1 in 4 people will develop HF

Prevalence of HF with HFpEF is increasing

33% of Americans ar at-risk for Stage A HF

24-34% Americans have Stage B HF

Bozkurt B et al. *J Card Fail*. 2023 Oct;29(10):1412-1451.

Heart Failure Definitions

Definition: Structural or functional impairment of ventricular filling or ejection of blood

HF Subtype according to left ventricular ejection fraction (LVEF)	Criteria
HFrEF Heart failure with **reduced** ejection fraction	LVEF ≤ 40%
HFimpEF Heart failure with **improved** ejection fraction	Previous LVEF ≤40% and a follow-up measurement of LVEF >40%
HFmrEF Heart failure with **moderately reduced** ejection fraction	LVEF 41%-49%
HFpEF Heart failure with **preserved** ejection fraction	LVEF F ≥50%

Heidenreich PA et al. *Circulation*. 2022 May 3;145(18):e895-e1032.

ACC/AHA Stages

Stages	Definition
Stage A: At risk for heart failure	At risk for HF but without symptoms, structural heart disease, or cardiac biomarkers of stretch or injury
Stage B: Pre-heart failure	No symptoms or signs of HF and evidence of 1 of the following: • Structural heart disease • Evidence for increased filling pressures • Risk factors and increased levels of BNP or persistently elevated cardiac troponin
Stage C: Symptomatic heart failure	Structural heart disease with current or previous symptoms of HF
Stage D: Advanced heart failure	Marked HF symptoms that interfere with daily life and with recurrent hospitalizations despite attempts to optimize GDMT

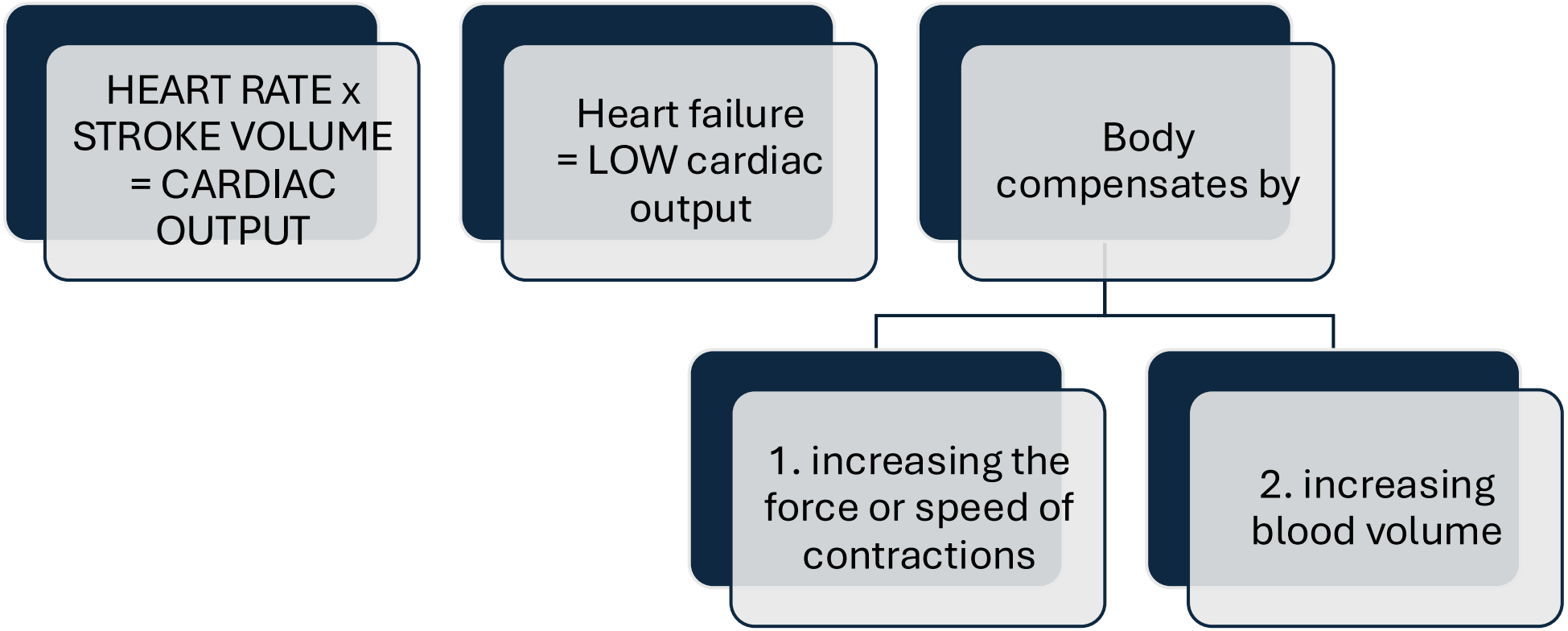
Heidenreich PA et al. *Circulation*. 2022 May 3;145(18):e895-e1032.

New York Heart Association (NYHA) Classes

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

Heidenreich PA et al. *Circulation*. 2022 May 3;145(18):e895-e1032.

Pathophysiology



Schwinger RHG. *Cardiovasc Diagn Ther*. 2021 Feb;11(1):263-276.

Learning Assessment #1: Pathophysiology & Classification

A 70-year-old woman presents with exertional dyspnea and lower extremity edema. Echocardiogram shows LVEF 55%, left ventricular hypertrophy, and elevated left atrial volume. BNP is mildly elevated. Which mechanism most directly explains her heart failure syndrome?

A. Impaired systolic contractility due to reduced myocardial calcium
B. Ventricular remodeling leading to reduced stroke volume
C. Increased ventricular stiffness resulting in impaired diastolic filling
D. Neurohormonal activation causing progressive myocyte apoptosis

Learning Assessment #1: Pathophysiology & Classification

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Foundational Guideline-Directed Medication Therapy (GDMT)

Four Pillars of GDMT

ARNI/ACEI/ARB

Evidence-based Beta-blockers

Mineralocorticoid antagonists (MRA)

SGLT2 inhibitors

All patients with stage C HFrEF should be on quadruple combination therapy; **Class 1 recommendation; LOE A**

Pillar I: ARNI/ACEI/ARB

ARNI (sacubitril/valsartan)

- 1st line RAAS modulating agent
- PARADIGIM-HF trial demonstrated proved reduction in mortality and hospitalization compared to ACEI
- Requires 36-hour washout after ACEI

ACE inhibitor

- Use when ARNI is not tolerated

ARB

- Use when ARNI and ACEI are not tolerated

COR	LOE	Recommendations
1	A	1. In patients with HFrEF and NYHA class II to III symptoms, the use of ARNi is recommended to reduce morbidity and mortality.[1–5]
1	A	2. In patients with previous or current symptoms of chronic HFrEF, the use of ACEi is beneficial to reduce morbidity and mortality when the use of ARNi is not feasible.[6–13]
1	A	3. In patients with previous or current symptoms of chronic HFrEF who are intolerant to ACEi because of cough or angioedema and when the use of ARNi is not feasible, the use of ARB is recommended to reduce morbidity and mortality.[14–18]

Heidenreich PA et al. *Circulation*. 2022 May 3;145(18):e895-e1032.

Pillar II: Beta Blockers

COR	LOE	Recommendation
1	A	1. In patients with HFrEF, with current or previous symptoms, use of 1 of the 3 beta blockers proven to reduce mortality (eg, bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalizations.[1–3]

Drug	Initial Daily Dose	Target Dose	Selectivity
Metoprolol succinate	12.5 – 25 mg once daily	200 mg daily	β1 > β2
Carvedilol	3.125 mg twice daily	25 – 50 mg twice daily	β1, β2, and α-1
Carvedilol CR	10 mg once daily	80 mg once daily	β1, β2, and α-1
Bisoprolol	1.25 mg once daily	10 once daily	β1 > β2

Heidenreich PA et al. *Circulation*. 2022 May 3;145(18):e895-e1032.

Pillar III: Mineralocorticoid Receptor Antagonists (MRA)

Drug	Initial Daily Dose	Target Dose	Consideration
Spironolactone	12.5 – 25 mg once daily	25 – 50 mg once daily	↓ Cost ↑ Side effects
Eplerenone	25 mg once daily	50 mg once daily	↑ Costs Highly selective for MRA = ↓ side effects ↑ drug interactions

COR	LOE	Recommendations
1	A	1. In patients with HFrEF and NYHA class II to IV symptoms, an MRA (spironolactone or eplerenone) is recommended to reduce morbidity and mortality, if eGFR is >30 mL/min/1.73 m^2 and serum potassium is <5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely monitored thereafter to minimize risk of hyperkalemia and renal insufficiency.[1–3]

Heidenreich PA et al. *Circulation*. 2022 May 3;145(18):e895-e1032.

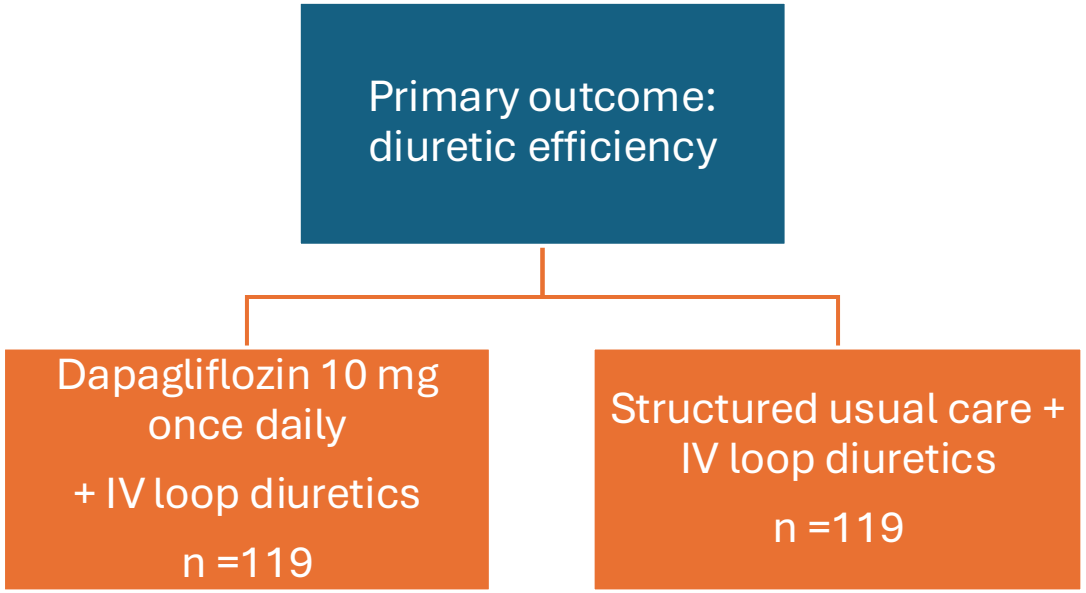
Pillar IV: Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors

COR	LOE	Recommendation
1	A	1. In patients with symptomatic chronic HFrEF, SGLT2i are recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes.[1,2]

Drug	Initial Dose	Target Dose
Empagliflozin	10 mg daily	10 mg daily
Dapagliflozin	10 mg daily	10 mg daily
Sotagliflozin	200 mg daily	400 mg daily

Heidenreich PA et al. *Circulation*. 2022 May 3;145(18):e895-e1032.

Dapagliflozin – DICTATE-AHF



Background

Multi-center
Prospective
Randomized
Open-label

Objective:
Determine efficacy and safety of dapagliflozin in patients with ADHF

Key Results

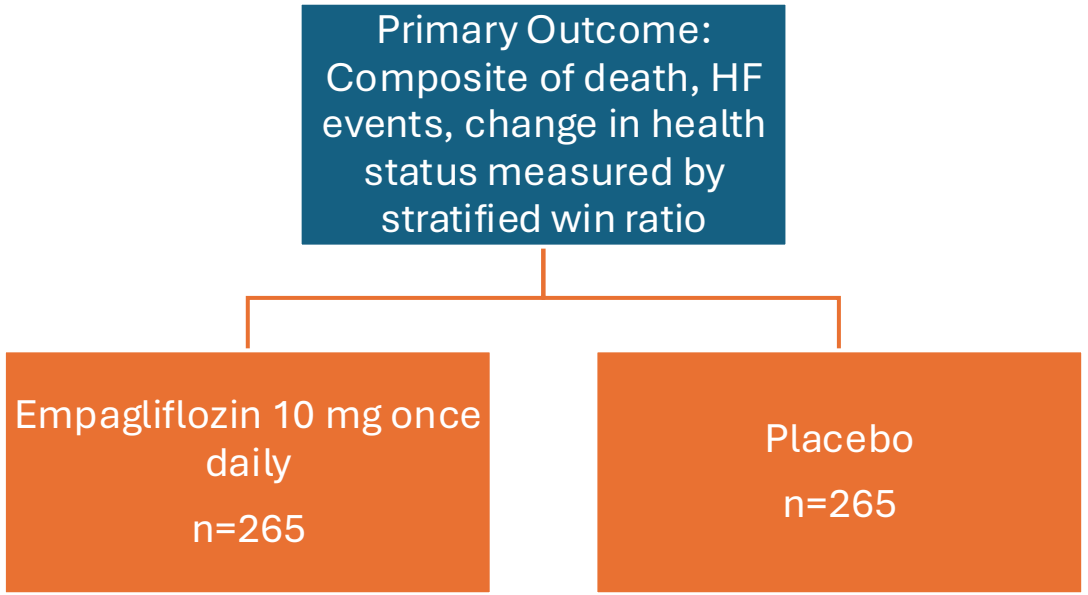
For diuretic efficiency, there was no difference between dapagliflozin and usual care (OR: 0.65; *P* = 0.06)

Associated with enhanced diuresis

No difference in safety outcomes

Cox ZL et al. *J Am Coll Cardiol*. 2024;83(14):1295-1306.

Empagliflozin - EMPULSE



Background

Randomized Double-blind Placebo-controlled

Objective:

Efficacy and safety of empagliflozin in patients with AHF

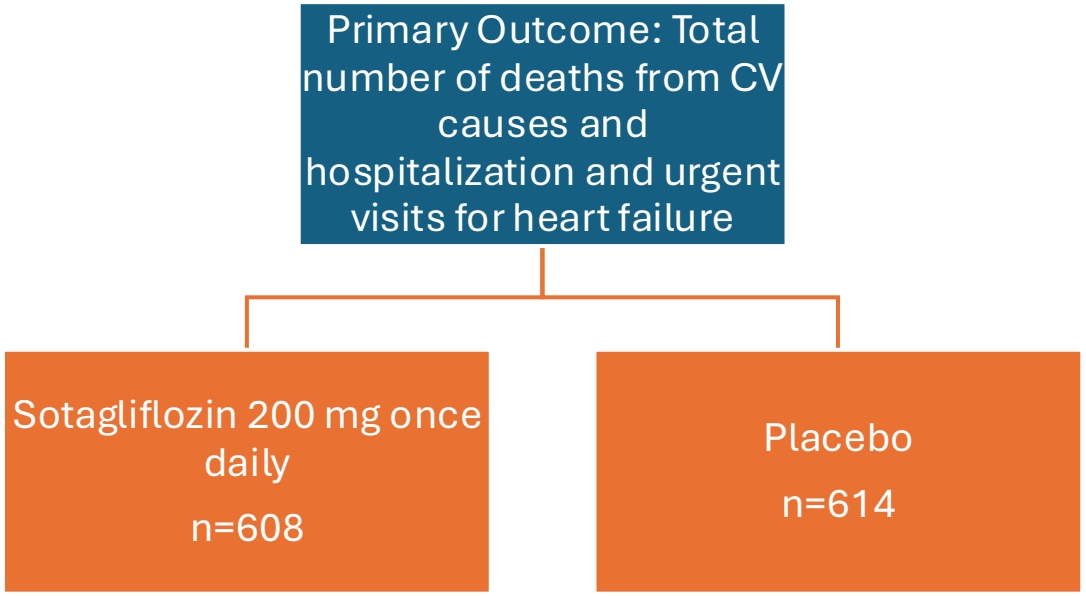
Key Results

Empagliflozin showed clinical benefit vs place in primary outcome (*P*=0.0054)

Benefits in HFrEF and HFpEF

Well tolerated

Sotaglifozin



Background

Multicenter
Randomized
Double-blind
Placebo-controlled

Objective:
Determine if sotagliflozin reduces CV death, hospitalization for HF, and urgent visits for HF

Key Results

33% relative risk reduction in the primary composite outcome

Significant reduction in HF hospitalizations and urgent HF visits

Increased risk of diarrhea and volume depletion

Titration of GDMT

Early Initiation of All Four Pillars

All 4 pillars can be started at once

STRONG-HF – multicenter, randomized, open-label trial

Included patients hospitalized with acute heart failure

- Usual care (n=536)
- High-intensity care (n=542)

Primary Endpoint

- 180-day all cause death and HF readmissions

Key Results

- Terminated early due to benefit
- Primary endpoint: 74 patients (15.2%) in high intensity group vs. 109 patients (23.3% in usual care) [p=0.0021]
- ***Start early and titrate rapidly!***

Monitoring parameters for GDMT

ARNI/ACEI/ARB	Beta-Blocker	MRA	SLGT2 inhibitor
•Blood pressure •Electrolytes •Kidney function Titrate every 1 to 2 weeks	•Heart rate •Blood pressure •Signs of congestion Titrate every 2 weeks	•Electrolytes •Kidney function Monitor 7 days after initiation or titration, monthly for 3 months, then every 3 months	•A1C hemoglobin

Maddox TM et al. *J Am Coll Cardiol*. 2024;83(15):1444-1488.

Diuretics & Congestion Management

Loop Diuretics

Use lowest effective dose to avoid hypotension and kidney impairment

Drug	Initial Daily Dose	Maximum Total Daily Dose	Duration of Action
Furosemide	20 – 40 mg once or twice	600 mg	6 – 8 hours
Torsemide	10 – 20 mg once	200 mg	12 – 16 hours
Bumetanide	0.5 – 1 mg once or twice	10 mg	4 – 6 hours

Oral equivalence: furosemide 40 mg = torsemide 20 mg = bumetanide 1 mg

Heidenreich PA et al. *Circulation*. 2022 May 3;145(18):e895-e1032.

Thiazide Diuretics

Drug	Initial Daily Dose	Maximum Total Daily Dose	Duration of Action
Chlorothiazide	250 – 500 mg once or twice	1000 mg	6 – 12 hours
Chlorthalidone	12.5 – 25 mg once	100 mg	24 – 72 hours
Hydrochlorothiazide	25 mg once or twice	200 mg	6 – 12 hours
Indapamide	2.5 mg once	5 mg	36 hours
Metolazone	2.5 mg once	20 mg	12 – 24 hours

1	B-NR	2. For patients with HF and congestive symptoms, addition of a thiazide (eg, metolazone) to treatment with a loop diuretic should be reserved for patients who do not respond to moderate- or high-dose loop diuretics to minimize electrolyte abnormalities.[6]

Heidenreich PA et al. *Circulation*. 2022 May 3;145(18):e895-e1032.

GDMT Adjuncts

- Ivabradine
- Hydralazine/Isosorbide dinitrate
- Vericiguat
- Digoxin

Ivabradine

- Mechanism of action
  - Selective If- channel inhibitor
  - Lowers heart rate without affecting blood pressure or contractility
- Adverse Effects
  - Bradycardia, hypertension, atrial fibrillation, visual disturbances
- SHIFT trial - randomized, double-blind, placebo-controlled
- Population
  - LVEF ≤35%, sinus rhythm, resting HR ≥70 bpm, on GDMT
- Primary outcome
  - Composite of CV death or HF hospitalization
- Key results
  - Addition of ivabradine vs placebo was 5% in mortality or hospitalization

COR	LOE	Recommendation
2a	B-R	1. For patients with symptomatic (NYHA class II to III) stable chronic HFrEF (LVEF ≤35%) who are receiving GDMT, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of ≥70 bpm at rest, ivabradine can be beneficial to reduce HF hospitalizations and cardiovascular death.[1,2]

Swedberg K et al. *Lancet*. 2010;376(9744):875-885. ;Heidenreich PA et al. *Circulation*. 2022 May 3;145(18):e895-e1032.

Hydralazine/Isosorbide Dinitrate

- Mechanism of action
  - Hydralazine: arterial vasodilator
  - Isosorbide dinitrate: venous vasodilator
- Adverse Effects
  - Headache, chest pain, dizziness, weakness
- A-HeFT trial: randomized, double-blind, placebo-controlled
- Population
  - Self-identified black patients with symptomatic HFrEF
- Primary Outcome
  - Composite score including all-cause mortality, HF hospitalization, quality of life
- Key Results
  - 43% reduction in all-cause mortality
  - 33% reduction in first HF hospitalization

COR	LOE	Recommendations
1	A	1. For patients self-identified as African American with NYHA class III-IV HFrEF who are receiving optimal medical therapy, the combination of hydralazine and isosorbide dinitrate is recommended to improve symptoms and reduce morbidity and mortality.[1,2]
2b	C-LD	3. In patients with current or previous symptomatic HFrEF who cannot be given first-line agents, such as ARNi, ACEi, or ARB, because of drug intolerance or renal insufficiency, a combination of hydralazine and isosorbide dinitrate might be considered to reduce morbidity and mortality.[4,5]

Franciosa JA et al. *J Card Fail*. 2002;8(3):128-135.; Heidenreich PA et al. *Circulation*. 2022 May 3;145(18):e895-e1032.

Vericiguat

- Mechanism of action
  - Soluble guanylate cyclase (sGC) stimulator
  - Enhances nitric oxide signaling → ↑cGMP
- Adverse effects
  - Hypotension, anemia
- VICTORIA Trial – randomized, double-blind, placebo-controlled
- Population
  - Symptomatic HFrEF (EF <45%)
  - Recent worsening HF event
- Primary outcome
  - Composite of CV death or HF hospitalization
- Key results
  - 10% relative risk reduction in primary outcome
  - Greatest benefit in high-risk patients with recent decompensation

COR	LOE	Recommendation
2b	B-R	1. In selected high-risk patients with HFrEF and recent worsening of HF already on GDMT, an oral soluble guanylate cyclase stimulator (vericiguat) may be considered to reduce HF hospitalization and cardiovascular death.[1]

Armstrong PW et al. *N Engl J Med*. 2020;382(20):1883-1893.; Heidenreich PA et al. *Circulation*. 2022 May 3;145(18):e895-e1032.

Digoxin

- Mechanism of action
  - Inhibits Na^+/K^+-ATPase pump → ↑ intracellular Ca^{++}
  - Increases contractility
- Adverse Effects
  - Narrow therapeutic index
  - Target serum level: 0.5 – 0.9 ng/mL at least 6-8 hours after last dose
  - Toxicity risk increases with renal dysfunction, older adults, drug interactions

COR	LOE	Recommendation
2b	B-R	1. In patients with symptomatic HFrEF despite GDMT (or who are unable to tolerate GDMT), digoxin might be considered to decrease hospitalizations for HF.[1,2]

Heidenreich PA et al. *Circulation*. 2022 May 3;145(18):e895-e1032.

Learning Assessment #2: GDMT & Adjunctive Therapy

A 68-year-old man with chronic HFrEF (LVEF 30%), NYHA Class II symptoms, and a history of hypertension presents for follow-up.

Current medications include:

- Lisinopril 20 mg daily
- Metoprolol succinate 100 mg daily
- Furosemide 40 mg daily
- Empagliflozin 10 mg daily

Average vital signs over the past week & labs:

- BP: 122/74 mmHg
- HR: 68 bpm
- K^+: 4.4 mEq/L
- eGFR: 58 mL/min/1.73m^2

Which medication optimization is most appropriate to reduce morbidity & mortality?

A. Increase furosemide to 80 mg daily
B. Add spironolactone 50 mg daily
C. Add Ivabradine 5 mg twice daily
D. Switch lisinopril to sacubitril/valsartan 24/26 mg twice daily

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Comorbidity Management

Iron Deficiency Anemia

- Definition
  - ferritin level <100 µ/L or 100 to 300 µ/L and transferrin saturation is <20%
- Associated with reduced exercise capacity and worse QOL
- Key Trials
  - FAIR-HF trial
  - AFFIRM-AHF
- IV iron preferred
  - Ferric carboxymaltose
- Oral iron often ineffective due to poor absorption

COR	LOE	Recommendations
Management of Anemia or Iron Deficiency		
2a	B-R	1. In patients with HFrEF and iron deficiency with or without anemia, intravenous iron replacement is reasonable to improve functional status and QOL.[1–4]

Heidenreich PA et al. *Circulation*. 2022 May 3;145(18):e895-e1032.

Atrial Fibrillation (AF)

- AF may worsen HF, but HF may also increase risk of AF
- Choice of therapy should consider EF, blood pressure, renal function and other comorbidities
- Stroke prevention
  - Anticoagulation based on CHA_2DS_2-VASc
  - DOACs preferred over warfarin
- Rate control
  - Beta-blockers, non-DHP CCB
  - Digoxin
- Rhythm control
  - Amiodarone or dofetilide
  - Catheter ablation if symptoms are caused by AF

COR	LOE	Recommendations
1	A	1. Patients with chronic HF with permanent-persistent-paroxysmal AF and a CHA_2DS_2-VASc score of ≥2 (for men) and ≥3 (for women) should receive chronic anticoagulant therapy.[1–5]
1	A	2. For patients with chronic HF with permanent-persistent-paroxysmal AF, DOAC is recommended over warfarin in eligible patients.[2–10]

Heidenreich PA et al. *Circulation*. 2022 May 3;145(18):e895-e1032.

Therapies in the Pipeline

Omecamtive Mecarbil

- Mechanism of action
  - Selective cardiac myosin activator
  - Improves cardiac contractility without increasing intracellular Ca^{++}
- GALACTIC-HF – randomized, double-blind, placebo-controlled
- Population
  - Symptomatic HFrEF (EF $\leq$35%)
  - High-risk patients
- Primary outcome
  - Composite of CV death or first HF event
- Key results
  - Modest but significant reduction in primary outcome
  - Greatest benefit observed in patients with LOW EF (<28%)

Teerlink JR et al. *Eur J Heart Fail*. 2020;22(11):2160-2171.

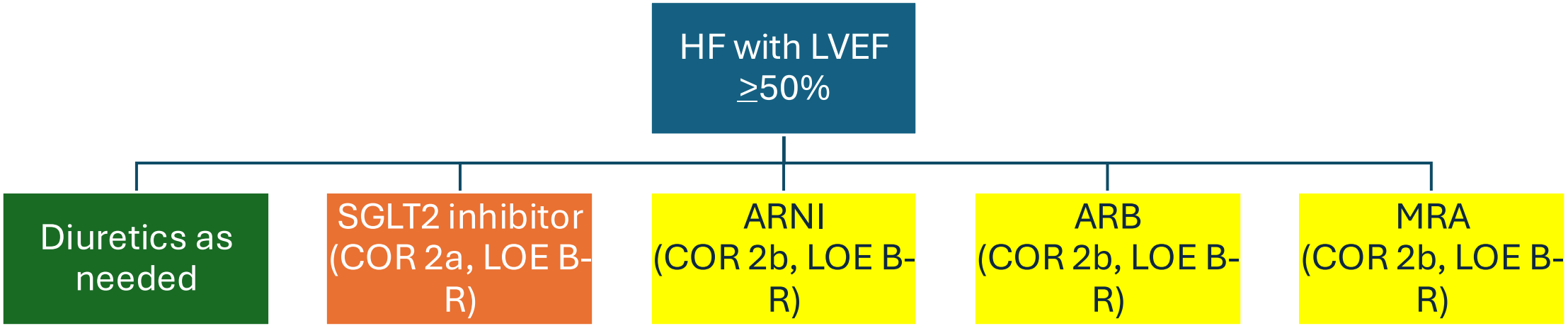
Ziltivekimab

- Mechanism of action
  - Monoclonal antibody targeting interleukin-6 (IL-6)
  - Reduces inflammation implicated in atherosclerosis, cardiac remodeling
- HERMES-HF Trial – Phase 2, randomized, placebo-controlled
- Population: primarily HFpEF and elevated CRP
- Primary outcome: reduction in inflammatory biomarkers
- Trial is ongoing

Petrie M et al. *Journal of Cardiac Failure*. 2024;30(1):126-126.

Beyond HFrEF Treatment

HFpEF



Heidenreich PA et al. *Circulation*. 2022 May 3;145(18):e895-e1032.

Obesity-Targeted Therapies

Summit (tirzepatide)

- **Design**: Phase 3, randomized, placebo-controlled
- **Population**: adults with HFpEF & obesity
- **Primary outcome**: composite of CV death or worsening HF
- **Key results**: 38% reduction in risk of primary outcome (HR 0.62) vs placebo

STEP-HFpEF (semaglutide)

- **Design**: Randomized, placebo-controlled
- **Population**: symptomatic HFpEF with obesity
- **Primary outcome**: HF symptom burden and weight
- **Key results**: 7.8-point difference in questionaries related to symptom burden (P<0.001) and -10.7% difference with semaglutide vs placebo (P<0.001).

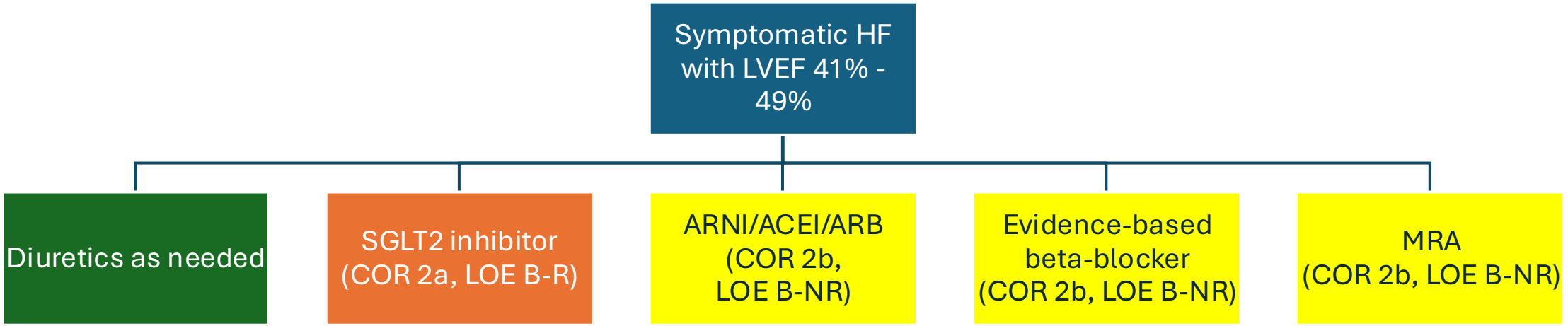
Packer M et al. *N Engl J Med*. 2025;392(5):427-437; Davies MJ et al. *Lancet Diabetes Endocrinol*. 2025;13(3):196-209.

Finerenone

- Mechanism of action
  - Nonsteroidal MRA
  - Anti-inflammatory and anti-fibrotic → improves cardiac and renal remodeling
- Key trial & Results
  - FINEARTS Trial
  - Included patients with symptomatic HF with LVEF ≥40%
  - 16% relative risk reduction in CV death or total HF events
- Clinical role
  - Consider in HFpEF or HFmrEF
  - Not a replacement for steroidal MRAs in HFrEF
- Monitoring
  - K^+ and renal function

Solomon SD et al. *N Engl J Med*. 2024;391(16):1475-1485.

HFmrEF: Treatment Options



- No prospective RCT for HFmrEF
- Treat similarly to HFrEF with preferential use of SGLT2 inhibitor

Heidenreich PA et al. *Circulation*. 2022 May 3;145(18):e895-e1032.

HFimpEF

- **Continue** GDMT event if ejection fraction improves
- GDMT required to maintain improvements in cardiac function

Recommendation for HF With Improved Ejection Fraction
Referenced studies that support the recommendation are summarized in the Online Data Supplements.

COR	LOE	Recommendation
1	B-R	1. In patients with HFimpEF after treatment, GDMT should be continued to prevent relapse of HF and LV dysfunction, even in patients who may become asymptomatic.[1]

Heidenreich PA et al. *Circulation*. 2022 May 3;145(18):e895-e1032.

Learning Assessment #3: Emerging Therapies

Which emerging therapy has demonstrated the greatest benefit in patients with very low ejection fraction (<20%)?

A. Omecamtive mecarbil
B. Ziltivemkimab
C. Finerenone
D. Ferric carboxymaltose

Learning Assessment #3: Emerging Therapies

Which emerging therapy has demonstrated the greatest benefit in patients with very low ejection fraction (<20%)?

A. **Omecamtive mecarbil**
B. Ziltivemkimab
C. Finerenone
D. Ferric carboxymaltose

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