Heart Failure Pharmacotherapy

Based on the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure, 2023 ACC ECDP on Management of HFpEF, 2024 ACC ECDP for Treatment of HFrEF, and 2024 ACC ECDP on Management of Patients Hospitalized with Heart Failure

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Heart Failure Categories

Stage

A — **At risk for HF**
- No HF signs/symptoms
- No structural/functional heart disease
- No abnormal biomarkers

B — **Pre-HF**
- No HF signs/symptoms
- **ONE** of the following:
  (1) Structural heart disease
  (2) ↑ filling pressures
  (3) Risk factors **PLUS** ↑ natriuretic peptides **OR** persistently ↑ cardiac troponin w/o competing diagnosis

C — **Symptomatic HF**
- Structural heart disease **AND**
- Current or previous HF symptoms

D — **Advanced HF**
- HF symptoms interfering with normal activity and/or recurrent HF hospitalizations (despite GDMT)

LVEF

HFrEF *(reduced EF)*	**LVEF ≤40%**
HFimpEF *(improved EF)*	**LVEF >40%** *(upon follow up after a previous measurement of LVEF ≤40%)*
HFmrEF *(mildly reduced EF)*	**LVEF 41-49%** *(w/ evidence of spontaneous/provokable ↑ LV filling pressures)*
HFpEF *(preserved EF)*	**LVEF ≥50%** *(w/ evidence of spontaneous/provokable ↑ LV filling pressures)*

NYHA Class

I	• No symptoms from ordinary daily activities
II	• No symptom at rest • Ordinary daily physical activities cause HF symptoms
III	• No symptom at rest • Activities lighter than ordinary daily physical activities cause HF symptoms
IV	• Symptoms at rest • Discomfort worsens with physical activities

Goals of Therapy

Stage A
- Primary prevention of heart failure

Stage B
- Prevention of clinical heart failure

Stage C
- Reduction of mortality
- Reduction of heart failure symptoms and hospitalization risk
- Elimination of potential barriers to self-care

Stage D
- Provision of inotropic support until mechanical circulatory support or cardiac transplantation is available
- Palliative symptom control and functional improvement (if not eligible for mechanical circulatory support or cardiac transplantation)

Pharmacotherapy Recommendations

Stage A
- Control BP in patients with hypertension
- SGLT2i in patients with T2DM **plus:**
  - Established CVD **or,**
  - High CV risk
- Manage existing comorbidities

Stage B
- ACEi and evidence-based BB in patients with LVEF ≤ 40%
  - If LVEF ≤ 40% **and recent MI**, use ARB if ACEi is not tolerated

Stage C (HFpEF)
- SGLT2i in **all patients** with HFpEF *(unless contraindicated)*
- May consider MRA and/or ARNi if LVEF < 55-60%
  - May consider regardless of LVEF for female patients
  - May consider ARB if unable to receive ARNi therapy
- PRN loop diuretic

Stage C (HFmrEF)
- PRN diuretics (**loop** preferred)
- SGLT2i may be beneficial
- May consider MRA, ACEi/ARB/ARNi, and evidence-based BB *particularly* if LVEF is closer to **HFrEF threshold**

Stage C (HFimpEF)
- Continue GDMT
  - Even if asymptomatic

Stage C (HFrEF)

All patients

★ **= 4 key drug classes of GDMT for HFrEF**

- **RAASi (ARNi/ACEi/ARB)** ★
  - Order of preference: ARNi > ACEi > ARB
  - ARNi: NYHA class II-III*
  - ACEi or ARB: NYHA class II-IV
  - **36-hour washout** required when switching between ACEi and ARNi (and vice versa)
- **Beta-blocker** (evidence-based) ★
  - Bisoprolol, carvedilol, metoprolol succinate
- **MRA** (e.g., eplerenone, spironolactone) ★
  - NYHA class II-IV
  - eGFR >30 mL/min/1.73m2
  - Serum potassium <5 mEq/L
- **SGLT inhibitor** ★
  - Dapagliflozin, empagliflozin, sotagliflozin
  - With or without T2DM
- **Diuretics** (as needed)
  - Loop diuretics preferred

**The 2022 guideline recommendation on using an ARNi is limited to patients with NYHA class II-III symptoms. However, the 2024 ECDP for treating HFrEF recommends the use of an ARNi to those who can tolerate it (including those with NYHA class IV symptoms).*

Specific patients

- **Hydralazine + isosorbide dinitrate**
  - African American patients on GDMT
  - NYHA class III-IV; persistently symptomatic
- **Ivabradine**
  - NYHA class II-III and LVEF **≤35%**
  - On GDMT including **max tolerated BB**
  - In sinus rhythm with resting HR ≥70 BPM
- **Vericiguat**
  - NYHA class II-IV and LVEF **<45%**
  - Recent HF worsening
  - ↑ BNP or NT-proBNP
- **Digoxin**
  - If symptomatic despite GDMT **or**
  - Unable to tolerate GDMT
- **Potassium binders**
  - e.g., **Patiromer**, **sodium zirconium cyclosilicate**
  - Patients with hyperkalemia (K+ ≥5.5 mEq/L) while on RAASi
- **Omega-3 PUFA** (may consider as an adjunct)
  - NYHA class II-IV

Selected Medications That May Cause or Exacerbate HF

COX inhibitors (e.g., NSAIDs)	• ↑ H2O retention, ↑ vascular resistance, ↓ response to diuretics • **Immediate** onset, **major** induction/precipitation of HF
Thiazolidinediones	• Potential blockage of calcium channel • **Intermediate** onset, **major** induction/precipitation of HF
Saxagliptin, Alogliptin	• Mechanism is unclear • **Immediate or delayed** onset, **major** induction/precipitation of HF
Flecainide, Disopyramide	• Proarrhythmic, negative inotropic effects • **Immediate to intermediate** onset, **major** induction/precipitation of HF
Sotalol	• Proarrhythmic effects, beta blockade • **Immediate to intermediate** onset, **major** induction/precipitation of HF
Dronedarone	• Negative inotropic effects • **Immediate to intermediate** onset, **major** induction/precipitation of HF
Doxazosin	• Beta-1 stimulation, ↑ renin and aldosterone • **Intermediate to delayed** onset, **moderate** induction/precipitation of HF
Diltiazem, Verapamil	• Negative inotropic effects • **Immediate to intermediate** onset, **major** induction/precipitation of HF
Nifedipine	• Negative inotropic effects • **Immediate to intermediate** onset, **moderate** induction/precipitation of HF

Recreated from Table 13 from the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

Patients Hospitalized With HF

- Initiate/continue/optimize GDMT as clinically appropriate when possible, along with monitoring and follow-up
  - Especially the **4 key classes**: **RAASi, BB, MRA, SGLTi**
- An **SGLT inhibitor** may be initiated or continued **regardless of LVEF at any time** during hospitalization once patient is hemodynamically stable with eGFR ≥20 mL/min/m2
- Start **IV loop diuretic** as soon as appropriate for decongestion & symptom reduction
  - If inadequate response, increase dose or add another diuretic (thiazide-type, carbonic anhydrase inhibitor, MRA)
- If BP is normal/high, consider adding **IV nitroglycerin** or **nitroprusside** to help manage shortness of breath
- If presenting with **cardiogenic shock**, start an **IV inotropic agent** to maintain adequate systemic perfusion

Abbreviations

ACEi angiotensin-converting enzyme inhibitor
ARB angiotensin (II) receptor blocker
ARNi angiotensin receptor-neprilysin inhibitor
BB beta-blocker
BNP B-type natriuretic peptide
BP blood pressure
CVD cardiovascular disease
eGFR estimated glomerular filtration rate
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
LV left ventricular
LVEF left ventricular ejection fraction
MI myocardial infarction
MRA mineralocorticoid receptor antagonist
NT-proBNP N-terminal prohormone of B-type natriuretic peptide
NYHA New York Heart Association
PRN as needed
PUFA polyunsaturated fatty acid
RAASi renin-angiotensin-aldosterone system inhibitor
SGLT(2)i sodium-glucose cotransporter (2) inhibitor
T2DM type 2 diabetes mellitus

References:
[1] Classes of Heart Failure. American Heart Association. May 31, 2017. https://www.heart.org/en/health-topics/heart-failure/what-is-heart-failure/classes-of-heart-failure **[2]** Heidenreich PA, Bozkurt B, Aguilar D, et al. 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. Circulation. 2022;145(18):e895-e1032. doi:10.1161/CIR.0000000000001063 **[3]** Kittleson M, Panjrath G, et al. 2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction. J Am Coll Cardiol. 2023. doi:10.1016/j.jacc.2023.03.393 **[4]** Maddox TM, Januzzi JL Jr, Allen LA, et al. 2024 ACC Expert Consensus Decision Pathway for Treatment of Heart Failure With Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2024;83(15):1444-1488. doi:10.1016/j.jacc.2023.12.024 **[5]** Writing Committee, Hollenberg SM, Stevenson LW, et al. 2024 ACC Expert Consensus Decision Pathway on Clinical Assessment, Management, and Trajectory of Patients Hospitalized With Heart Failure Focused Update: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. Published online August 2, 2024. doi:10.1016/j.jacc.2024.06.002

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