# Standard Operating Procedure

## Heart Failure with Reduced Ejection Fraction

Special Region (1)

Union Of Myanmar

Version (1)

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Approved by: Internal Medicine Unit

# 1. Purpose and Scope

This Standard Operating Procedure (SOP) provides evidence-based clinical guidance for the diagnosis, evaluation, and management of adult patients with Heart Failure with Reduced Ejection Fraction (HFrEF). The protocol is based on the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure and the 2024 ACC Expert Consensus Decision Pathway.

> **Target Population**
>
> Adult patients (18 years and older) with symptomatic chronic HFrEF, defined as left ventricular ejection fraction (LVEF) of 40% or less, in the ambulatory and hospital settings.

## Objectives

- Standardize the diagnostic evaluation and classification of HFrEF
- Ensure appropriate and timely initiation of Guideline-Directed Medical Therapy (GDMT)
- Provide a structured approach to medication titration and optimization
- Establish monitoring parameters and follow-up schedules
- Identify candidates for device therapy and advanced interventions
- Address special populations and health equity considerations

# 2. Definitions and Classifications

## 2.1 Diagnostic Criteria for HFrEF

Heart Failure with Reduced Ejection Fraction (HFrEF) is a clinical syndrome characterized by structural and/or functional cardiac abnormalities resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.

**Table: Classification of Heart Failure by LVEF**

| Category | LVEF Range | Description |
|---|---|---|
| HFrEF | <40% | Reduced ejection fraction; previously systolic HF |
| HFmrEF | 41-49% | Mildly reduced ejection fraction |
| HFpEF | >50% | Preserved ejection fraction |
| HFimpEF | >40% | Previously HFrEF with documented recovery to >40% |

> **Important Note**
>
> Patients with HFimpEF should continue GDMT even if asymptomatic, as discontinuation may lead to relapse of HF and LV dysfunction.

## 2.2 ACC/AHA Staging System

The ACC/AHA staging system emphasizes the progressive nature of heart failure and the importance of early intervention.

**Table: ACC/AHA Stages of Heart Failure**

| Stage | Description | Clinical Characteristics |
|---|---|---|
| Stage A - At Risk | Patients at risk but without symptoms, signs, or structural heart disease | Hypertension, CVD, diabetes, obesity, cardiotoxic exposure, family history |
| Stage B - Pre-HF | No symptoms but evidence of | Previous MI, LV remodeling, |

| Stage | Description | Clinical Characteristics |
|---|---|---|
| | structural disease or abnormal biomarkers | reduced LVEF, asymptomatic valvular disease |
| Stage C - Symptomatic HF | Current or previous symptoms/signs of HF | Dyspnea, fatigue, reduced exercise tolerance, fluid retention |
| Stage D - Advanced HF | Marked symptoms interfering with daily life despite optimal therapy | Recurrent hospitalizations, inotropic support, advanced therapies |

## 2.3 NYHA Functional Classification

The New York Heart Association (NYHA) functional classification is used to assess the severity of symptoms and exercise capacity.

**Table: NYHA Functional Classification**

| Class | Description |
|---|---|
| I | No limitation of physical activity. Ordinary activity does not cause symptoms. |
| II | Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity causes symptoms. |
| III | Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms. |
| IV | Unable to carry out any physical activity without symptoms. Symptoms may be present even at rest. |

# 3. Initial Patient Assessment

## 3.1 History and Physical Examination

A comprehensive clinical evaluation is essential for accurate diagnosis, risk stratification, and treatment planning. The assessment should include identification of etiology, precipitating factors, comorbidities, and social determinants of health.

Key components: Symptom assessment (dyspnea, orthopnea, PND, fatigue, edema); Functional status (exercise capacity, ADL limitations, recent hospitalizations); Etiology assessment (ischemic vs. non-ischemic, valvular, familial, toxin-induced); Precipitating factors (ACS, non-adherence, uncontrolled HTN, arrhythmias, infection, anemia); Comorbidities (CAD, HTN, diabetes, CKD, COPD, sleep apnea, obesity); Social determinants (education, income, insurance, health literacy, access to care).

### Physical Examination Focus

- Vitals: Blood pressure (both arms), heart rate, orthostatic changes, weight, BMI, O2 saturation
- JVP: Assess volume status; elevated JVP is a sensitive indicator of elevated filling pressures
- Cardiac: S3 gallop, murmurs, displaced PMI, irregular rhythm
- Pulmonary: Crackles, pleural effusion, tachypnea
- Abdomen: Hepatomegaly, ascites, hepatojugular reflux
- Extremities: Peripheral edema (pitting), cool extremities (low output), cyanosis

## 3.2 Diagnostic Workup

**Table: Required Diagnostic Evaluation for HFrEF**

| Test/Procedure | Purpose | Class |
|---|---|---|
| Transthoracic Echocardiogram (TTE) | Confirm LVEF, assess chamber sizes, valves, diastolic function | Class I |
| 12-Lead ECG | Identify arrhythmia, ischemia, prior MI, conduction abnormalities | Class I |

| Test/Procedure | Purpose | Class |
|---|---|---|
| Chest X-Ray | Assess heart size, pulmonary congestion, pleural effusion | Class I |
| Cardiac MRI | Tissue characterization, scar assessment, infiltrative disease | Class I |
| Coronary Angiography / CCTA | Assess CAD as etiology (ischemic evaluation) | Class I |

## 3.3 Laboratory Evaluation

**Table: Initial Laboratory Workup**

| Test | Rationale |
|---|---|
| Natriuretic Peptides (BNP or NT-proBNP) | Diagnosis, prognosis, and serial monitoring of congestion |
| Complete Blood Count (CBC) | Anemia assessment, infection screening |
| Comprehensive Metabolic Panel | Kidney function (eGFR, creatinine), electrolytes (K+, Na+), liver function, glucose |
| Thyroid Function (TSH) | Hypo/hyperthyroidism as precipitating factor |
| Lipid Panel | Cardiovascular risk assessment |
| Iron Studies (Ferritin, TSAT) | Iron deficiency assessment (common comorbidity) |
| Troponin (hs-cTn) | Myocardial injury assessment |
| HbA1c (if diabetes risk) | Glycemic status |
| Urinalysis | Proteinuria, kidney disease assessment |

> **Key Diagnostic Thresholds**
>
> BNP: >400 pg/mL supports acute decompensated HF diagnosis. NT-proBNP: >900 pg/mL (age <50), >1,800 pg/mL (age 50-75). Iron Deficiency: Ferritin <100 ng/mL OR ferritin 100-299 ng/mL with TSAT <20%.

# 4. Guideline-Directed Medical Therapy (GDMT)

GDMT represents the cornerstone of HFrEF management. All patients with chronic symptomatic HFrEF (Stage C) should receive the 'four pillars' of therapy unless contraindicated. These therapies have demonstrated mortality benefit and reduction in HF hospitalizations.

## 4.1 The Four Pillars of HFrEF Therapy

- ARNI (Sacubitril/Valsartan) OR ACE-I/ARB if ARNI not feasible
- Evidence-Based Beta-Blocker (Carvedilol, Metoprolol succinate, or Bisoprolol)
- Mineralocorticoid Receptor Antagonist (Spironolactone or Eplerenone)
- SGLT2 Inhibitor (Dapagliflozin or Empagliflozin)

> **Clinical Evidence Summary**
>
> Each of the four pillars has demonstrated independent mortality benefit in randomized controlled trials. The combination of all four therapies is estimated to reduce all-cause mortality by up to 73% compared to no treatment. Simultaneous initiation and rapid up-titration is safe (STRONG-HF trial).

## 4.2 ARNI / ACE-I / ARB Therapy

Inhibition of the renin-angiotensin system is foundational to HFrEF management. Sacubitril/valsartan (ARNI) is preferred when feasible due to superior outcomes compared to enalapril in the PARADIGM-HF trial (HR 0.80 for CV death or HF hospitalization).

**Table: ACE-I / ARB / ARNI Dosing and Considerations**

| Agent | Starting Dose | Target Dose | Key Considerations |
|---|---|---|---|
| Sacubitril/Valsartan | 49/51 mg BID | 97/103 mg BID | Preferred; 36h washout from ACE-I; caution with SBP <100 |
| Enalapril | 2.5 mg BID | 10-20 mg BID | Well-established; cough and hyperkalemia |

| Agent | Starting Dose | Target Dose | Key Considerations |
|---|---|---|---|
| | | | limitations |
| Lisinopril | 2.5-5 mg daily | 20-40 mg daily | Once-daily dosing advantage |
| Candesartan | 4-8 mg daily | 32 mg daily | ARB alternative when ACE-I/ARNI not tolerated |
| Losartan | 25-50 mg daily | 150 mg daily | ARB option; less proven for mortality benefit |

> **Contraindications to ARNI**
>
> Within 36 hours of ACE inhibitor use; Any history of angioedema; Pregnancy (teratogenic); Severe hepatic impairment (Child-Pugh C); Concomitant aliskiren use in patients with diabetes.

## 4.3 Evidence-Based Beta-Blockers

Only three beta-blockers have demonstrated mortality benefit in HFrEF through randomized trials: carvedilol, metoprolol succinate (CR/XL), and bisoprolol. These agents should be preferred over other beta-blockers.

**Table: Evidence-Based Beta-Blocker Dosing**

| Agent | Starting Dose | Target Dose | Notes |
|---|---|---|---|
| Carvedilol | 3.125 mg BID | 25 mg BID | Non-selective with alpha-1 blockade |
| Metoprolol Succinate CR/XL | 12.5-25 mg daily | 200 mg daily | Once-daily; beta-1 selective |
| Bisoprolol | 1.25 mg daily | 10 mg daily | Beta-1 selective |

> **Beta-Blocker Initiation Timing**
>
> Beta-blockers should NOT be newly initiated in patients with acute decompensated HF. They

> are best tolerated when the patient is euvolemic. However, they should be continued during most hospitalizations unless low cardiac output, severe volume overload, or advanced AV block.

## 4.4 Mineralocorticoid Receptor Antagonists (MRAs)

MRAs (spironolactone and eplerenone) reduce mortality and morbidity in patients with HFrEF and NYHA class II-IV symptoms. They should be initiated in all eligible patients unless contraindicated.

**Table: MRA Dosing and Monitoring**

| Agent | Starting Dose | Maintenance | Monitoring |
|---|---|---|---|
| Spironolactone | 12.5-25 mg daily | 25-50 mg daily | K+, Cr at 1 week, 1 month, then q3 months |
| Eplerenone | 25 mg daily | 50 mg daily | Preferred if gynecomastia develops |

> **MRA Contraindications**
>
> Serum potassium >5.0 mEq/L at initiation; eGFR <30 mL/min/1.73 m2 (relative); Monitor K+ and Cr within 1 week of initiation, at 1 month, and every 3 months; Consider concomitant SGLT2 inhibitor use, which reduces hyperkalemia risk.

## 4.5 SGLT2 Inhibitors

SGLT2 inhibitors are now a foundational therapy for HFrEF, independent of diabetes status. DAPA-HF and EMPEROR-Reduced trials demonstrated significant reductions in CV death and HF hospitalization.

**Table: SGLT2 Inhibitor Dosing for HFrEF**

| Agent | Recommended Dose | Key Features |
|---|---|---|
| Dapagliflozin | 10 mg once daily | Fixed dose; well-tolerated at low BP |

| Agent | Recommended Dose | Key Features |
|---|---|---|
| Empagliflozin | 10 mg once daily | Fixed dose; may reduce eGFR initially |

> **SGLT2 Inhibitor Benefits**
>
> Mechanisms include osmotic diuresis, natriuresis, decreases in arterial pressure and stiffness, shift to ketone-based myocardial metabolism, reduction of preload and afterload, and favorable effects on autophagy and myocardial remodeling. These agents are uniquely well-tolerated in patients with lower blood pressures.

> **SGLT2 Inhibitor Precautions**
>
> Discontinue during acute illness, surgery, or before iodinated contrast procedures; Monitor for genitourinary infections; eGFR threshold: >=20-25 mL/min/1.73 m2; May cause euglycemic DKA (rare); counsel patients on sick-day rules.

## 4.6 Additional Therapies

### Diuretic Therapy

Loop diuretics (furosemide, torsemide, bumetanide) are essential for volume management but do not provide mortality benefit. Furosemide: 20-40 mg daily or BID (oral or IV). Torsemide: 10-20 mg daily (better bioavailability). Bumetanide: 0.5-1 mg daily or BID.

### Iron Supplementation

IV ferric carboxymaltose is recommended for patients with iron deficiency and HFrEF (Class 2a), improving symptoms, exercise capacity, and quality of life. Reassess iron studies periodically.

# 5. GDMT Initiation and Titration Protocol

## 5.1 Starting and Target Doses

**Table: Summary of GDMT Starting and Target Doses**

| Drug Class | Agent | Starting Dose | Target Dose |
|---|---|---|---|
| ARNI | Sacubitril/Valsartan | 49/51 mg BID | 97/103 mg BID |
| ACE-I | Lisinopril | 2.5-5 mg daily | 20-40 mg daily |
| Beta-Blocker | Carvedilol | 3.125 mg BID | 25 mg BID |
| Beta-Blocker | Metoprolol succinate | 12.5-25 mg daily | 200 mg daily |
| MRA | Spironolactone | 12.5-25 mg daily | 25-50 mg daily |
| MRA | Eplerenone | 25 mg daily | 50 mg daily |
| SGLT2-i | Dapagliflozin | 10 mg daily | 10 mg daily (fixed) |
| SGLT2-i | Empagliflozin | 10 mg daily | 10 mg daily (fixed) |
| Sinus node inhibitor | Ivabradine | 5 mg BID | 7.5 mg BID |
| sGC stimulator | Vericiguat | 2.5 mg daily | 10 mg daily |

## 5.2 Titration Algorithm

Step 1 - Diagnosis and Assessment: Confirm HFrEF (LVEF <40%), assess NYHA class, evaluate volume status, identify contraindications, obtain baseline labs.

Step 2 - Initiate ARNI: Start sacubitril/valsartan if no contraindications. If switching from ACE-I, ensure 36-hour washout. Monitor BP, K+, Cr within 1-2 weeks.

Step 3 - Initiate Beta-Blocker: Start carvedilol, metoprolol succinate, or bisoprolol when patient is euvolemic. Do NOT initiate during acute decompensation.

Step 4 - Initiate MRA: Add spironolactone or eplerenone. Check K+ and Cr within 1 week, then at 1 month.

Step 5 - Initiate SGLT2 Inhibitor: Add dapagliflozin or empagliflozin 10 mg daily. No titration required.

Step 6 - Rapid Titration: Double doses every 2-4 weeks as tolerated. Goal: target doses within 3 months.

Step 7 - Add Ivabradine if resting HR >70 bpm on maximally tolerated beta-blocker, in sinus rhythm, NYHA II-III.

Step 8 - Consider Vericiguat for high-risk patients with recent worsening (Class 2b indication).

Step 9 - Reassess LVEF 3-6 months after target/maximally tolerated GDMT to evaluate need for ICD/CRT.

> **Simultaneous vs. Sequential Initiation**
>
> Simultaneous initiation of multiple GDMT agents is encouraged where possible. The STRONG-HF trial demonstrated that rapid up-titration with close follow-up is safe and reduces 180-day death or HF readmission compared with usual care.

## 5.3 Monitoring Parameters

**Table: Monitoring Schedule During GDMT Titration**

| Parameter | Frequency | Action Thresholds |
|---|---|---|
| Blood Pressure | Each visit | Hold/dose reduce if SBP <85 mmHg or symptomatic hypotension |
| Heart Rate | Each visit | Target resting HR 50-70 bpm; hold if HR <50 bpm |
| Serum Potassium | 1 week post-MRA, then monthly, then q3 months | Hold MRA if K+ >5.5 mEq/L; reinitiate when K+ <5.0 |
| Serum Creatinine / eGFR | 1-2 weeks post-initiation, then per clinical status | Acceptable rise <30% from baseline or Cr <3.0 mg/dL |
| BNP / NT-proBNP | Baseline, then serial | >50% reduction indicates favorable response |
| Weight | Daily at home; each clinic visit | >2-3 lb gain in 1 day or >5 lb in 1 week warrants evaluation |

# 6. Device Therapy and Advanced Interventions

### Advanced Therapy Referral (Stage D)

Timely referral to an advanced heart failure center is recommended when any of the following are present (I Need Help mnemonic):

- I - IV inotropes required
- N - NYHA class IIIB or IV with persistent symptoms
- E - Elevated natriuretic peptides (persistently elevated)
- E - Ejection fraction <25%
- D - Defibrillator shocks (recurrent appropriate ICD therapies)
- H - Hospitalizations (1+ HF hospitalization in 12 months)
- E - Edema despite escalating diuretics (refractory congestion)
- L - Low systolic blood pressure (<90 mmHg)
- P - Prognostic medication intolerance (cannot tolerate GDMT)

# 7. Special Populations

### Older Adults and Frail Patients

- Start at lower doses and titrate more cautiously
- Monitor closely for hypotension, falls, and renal function
- Consider polypharmacy and drug interactions
- Frailty assessment should guide intensity of therapy

### Chronic Kidney Disease

- ARNI/ACE-I/ARB and MRAs may worsen renal function initially; acceptable if <30% rise
- SGLT2 inhibitors may reduce eGFR initially but provide long-term kidney protection
- Torsemide may be preferred over furosemide in advanced CKD

### Diabetes Mellitus

- SGLT2 inhibitors provide dual cardiorenal benefit
- Adjust insulin/sulfonylurea to minimize hypoglycemia risk when initiating SGLT2-i

> **Pregnancy**
>
> ACE inhibitors, ARBs, and ARNIs are CONTRAINDICATED in pregnancy. Women of childbearing potential should be counseled and use reliable contraception. Hydralazine and nitrates are preferred for afterload reduction during pregnancy.

# 8. Hospitalized Patients

Hospitalization for acute decompensated HF represents a critical inflection point requiring careful assessment, decongestion, and optimization of GDMT prior to discharge.

Step 1 - Initial Assessment: Evaluate severity of congestion, assess perfusion (warm/cold, wet/dry profile), identify precipitating factors.

Step 2 - Diuretic Therapy: Initiate IV loop diuretics (furosemide 2-2.5x home oral dose). Goal: adequate urine output, clinical decongestion.

Step 3 - Continue GDMT: Continue oral beta-blocker unless low cardiac output, severe volume overload, or advanced AV block.

Step 4 - Initiate/Add GDMT: Begin ARNI, SGLT2-i, and MRA prior to discharge if not contraindicated. Do NOT newly initiate beta-blocker during decompensation.

Step 5 - VTE Prophylaxis: Recommended in all hospitalized patients unless contraindicated.

Step 6 - Discharge Planning: Schedule early follow-up (within 7 days), provide medication education, ensure loop diuretic with plan for self-titration.

### Common Precipitating Factors

- Acute coronary syndrome
- Non-adherence to medications or diet (sodium restriction)
- Uncontrolled hypertension
- Atrial fibrillation and other arrhythmias
- Anemia, infection, thyroid dysfunction
- Medications with negative inotropy or sodium retention

> **Post-Discharge Mortality Risk**
>
> The post-discharge period carries the highest risk for mortality and rehospitalization. Early follow-up within 7 days and rapid GDMT optimization significantly improves outcomes. Structured disease management programs with embedded medication titration plans are recommended.

# 9. Follow-Up and Monitoring

Longitudinal care with serial reassessment is essential for optimizing outcomes in HFrEF. The goals are to maintain clinical stability, optimize GDMT to target or maximally tolerated doses, and identify disease progression.

**Table: Recommended Follow-Up Schedule**

| Timeframe | Activities |
|---|---|
| Post-discharge | 7-day follow-up (phone or in-person); medication reconciliation; assess symptoms and weight trend |
| Months 1-3 | Every 2-4 weeks during GDMT titration; labs (K+, Cr) with each titration or at least monthly |
| Months 3-6 | Monthly visits; repeat echocardiogram at 3-6 months after achieving target/maximum GDMT |
| Long-term (stable) | Every 3-6 months; routine labs q3-6 months; annual BNP/NT-proBNP; periodic iron studies |

## Key Components of Each Follow-Up Visit

- Symptom review: NYHA class, exercise tolerance, orthopnea, edema
- Vitals: Weight, BP, HR (assess orthostatic changes)
- Medication review: Adherence, side effects, current doses, up-titration candidacy
- Laboratory monitoring: Per protocol based on current GDMT
- Patient education reinforcement: Sodium restriction, fluid management, sick-day rules
- Advance care planning: Goals of care discussion, especially with disease progression

> **Red Flags Requiring Urgent Evaluation**
>
> Resting dyspnea or dyspnea at minimal exertion; Weight gain >5 lb in 1 week or >2-3 lb in 1 day; Worsening peripheral edema or new abdominal distension; Syncope or presyncope; Chest pain; ICD firing; Sustained palpitations or irregular heartbeat.

## Lifestyle and Self-Management Counseling

- Dietary sodium restriction: Generally <2-3 g/day sodium; consider fluid restriction if hyponatremic
- Daily weights: Same time, same scale; call provider for rapid weight gain
- Physical activity: Cardiac rehabilitation referral (Class I); regular aerobic exercise as tolerated
- Smoking cessation: Absolute requirement
- Vaccinations: Annual influenza, pneumococcal, COVID-19 boosters

# 10. References

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