

VA



U.S. Department of Veterans Affairs

Veterans Health Administration
PBM Academic Detailing Service

A QUICK REFERENCE GUIDE (2019)

Managing Heart Failure in Primary Care

Improving Veteran Outcomes Through the
Use of Evidence-based Medicine

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Classification of Heart Failure (HF)¹

| Classification | Ejection Fraction (EF) (%) | Description |
|--|----------------------------|--|
| Heart Failure with Reduced Ejection Fraction (HFrEF) | ≤40 | Systolic HF; evidence that treatment with specific medication classes reduces mortality and hospitalizations |
| Heart Failure with Preserved Ejection Fraction (HFpEF), borderline | 41 to 49 | These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patients with HFpEF. |
| HFpEF, improved | >40, previously ≤40 | A subset of patients with HFpEF previously had HFrEF. Further research is needed to characterize these patients. |
| HFpEF | ≥50 | Diastolic HF; Management centers around treatment of blood pressure rather than use of specific medication classes. |

New York Heart Association (NYHA) Functional Classification of HF

NYHA Class I: No limitation of physical activity (ordinary physical activity does not cause HF symptoms)

NYHA Class II: Slight limitation of physical activity/symptoms with ordinary physical activity; no symptoms at rest

NYHA Class III: Marked limitations of physical activity/symptoms with less than ordinary physical activity; no symptoms at rest

NYHA Class IV: Unable to carry on physical activity without symptoms of HF; symptoms even at rest

Management of Heart Failure by Stage^{1,2}

| Stage | Description | NYHA Class | Management Strategy |
|-------|--|------------|--|
| A | At high risk for HF, but no structural disease or symptoms (e.g., HTN, diabetes, Afib) | None | Prevent by treating risk factors. |
| B | Structural heart disease, but no symptoms of HF | I | Continue to treat risk factors. Monitor for development of HF symptoms. Start ACEI, or ARB <u>and</u> BB if reduced EF \leq 40%. |
| C | Structural heart disease, with prior or current symptoms of HF | I–IV | Start and titrate ACEI, or ARB <u>and</u> BB; diuretics as needed. If needed, add other evidence-based pharmacotherapy to reduce symptoms and improve outcomes. |
| D | Refractory HF requiring specialized interventions | IV | Refer to specialist and establish patient specific goal for care. |

ACEI = angiotensin converting enzyme inhibitor; Afib = atrial fibrillation; ARB = angiotensin receptor blocker; BB = beta blocker; HTN = hypertension
 NYHA = New York Heart Association

Mortality-Reducing Medications and Patient Considerations for Heart Failure with Reduced Ejection Fraction (HFrEF)^{1,2}

| NYHA Class | Patient Considerations | GDMT Medication Options* |
|------------|---|--|
| I–IV | <ul style="list-style-type: none"> All patients unless contraindicated | ACEI, or ARB <u>and</u> BB |
| II–IV | <ul style="list-style-type: none"> EF \leq35% eGFR $>$30 mL/min/1.73 m² K⁺ $<$5.0 mEq/L SCr $<$2.5 (males) or $<$2.0 (females) | Aldosterone antagonist (e.g. spironolactone, eplerenone) |
| II–III | <ul style="list-style-type: none"> Symptomatic on ACEI, or ARB <u>and</u> BB No contraindication to ARB or sacubitril, or history of angioedema Discontinue ACEI or ARB before starting medication option | Angiotensin receptor blocker/ neprilysin inhibitor (sacubitril/ valsartan) |
| III–IV | <ul style="list-style-type: none"> African American patients Patients who cannot tolerate ACEI or ARB | Hydralazine/isosorbide dinitrate |

*Choices are not mutually exclusive, and no order is inferred. NYHA = New York Heart Association, GDMT = guideline-directed medical therapy, ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, BB = beta blocker, EF = ejection fraction, eGFR = estimated glomerular filtration rate, K⁺ = potassium, SCr = serum creatinine, SBP = systolic blood pressure

Medications that Reduce Hospitalizations without Mortality Benefit and Patient Considerations for Heart Failure with Reduced Ejection Fraction (HFrEF)^{1,2}

| NYHA Class | Patient Considerations | GDMT Medication Options* |
|------------|---|---|
| II–IV | <ul style="list-style-type: none"> Evidence of fluid overload | Diuretic (e.g. furosemide, torsemide, bumetanide) |
| II–IV | <ul style="list-style-type: none"> Symptomatic heart failure Use with caution in patients with renal dysfunction Target trough level 0.5–0.9 ng/ml | Digoxin |
| II–III | <ul style="list-style-type: none"> Symptomatic heart failure Ejection fraction <35% HR ≥70 BPM on maximally tolerated dose BB or patient unable to tolerate BB or has contraindications to BB | Ivabradine |

*Choices are not mutually exclusive, and no order is inferred. NYHA = New York Heart Association, GDMT = guideline-directed medical therapy, HR = heart rate, BPM = beats per minute, BB = beta blocker

Commonly Used Heart Failure Medications^{1,3}

| ACE Inhibitors (ACEI) | | | | | Effect in Patients with HFrEF | |
|-----------------------|--------------------------|-------------------------|-----------------------|---|-------------------------------|-----------|
| Medication | Starting Daily Dose (mg) | Target Daily Dose (mg)* | Comments | Monitor | Mortality | Morbidity |
| Enalapril | 2.5 BID | 10–20 BID | Use ACEI prior to ARB | Serum K+ and renal function at baseline and within one to two weeks of initiation | ↓ | ↓ |
| Fosinopril | 5–10 | 40 | | | | |
| Lisinopril | 2.5–5 | 20–40 | | | | |
| Ramipril | 1.25–2.5 | 10 | | | | |

*Use highest tolerated dose while maintaining adequate blood pressure. ACE = angiotensin converting enzyme, ARB = angiotensin receptor blocker, HFrEF = heart failure with reduced ejection fraction, K+ =potassium, BID = twice daily. Please see VA National Formulary for current list of formulary medications (<https://www.pbm.va.gov/PBM/NationalFormulary.asp>)

continued from page 6 (Commonly Used Heart Failure Medications)

| ARBs | | | | | Effect in Patients with HFrEF | |
|-------------|--------------------------|-------------------------|-----------------------|---|-------------------------------|-----------|
| Medication | Starting Daily Dose (mg) | Target Daily Dose (mg)* | Comments | Monitor | Mortality | Morbidity |
| Losartan | 25–50 | 150 | Use ACEI prior to ARB | Serum K+ and renal function at baseline and within one to two weeks of initiation | ↓ | ↓ |
| Valsartan | 40 BID | 160 BID | | | | |
| Candesartan | 4–8 | 32 | | | | |

*Use highest tolerated dose while maintaining adequate blood pressure. Please see VA National Formulary for current list of formulary medications (<https://www.pbm.va.gov/PBM/NationalFormulary.asp>) ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, HFrEF = heart failure with reduced ejection fraction, K+ =potassium, BID = twice daily.

continued from page 7 (Commonly Used Heart Failure Medications)

| Beta Blockers | | | | | Effect in Patients with HFrEF | |
|----------------------|--------------------------|---|---|---------|-------------------------------|-----------|
| Medication | Starting Daily Dose (mg) | Target Daily Dose (mg)* | Comments | Monitor | Mortality | Morbidity |
| Carvedilol IR | 3.125 BID | Patient weight <187 lbs: 25 BID; ≥187 lbs: 50 BID | Avoid in heart block, bradycardia, severe reversible airway | HR/BP | ↓ | ↓ |
| Metoprolol succinate | 12.5–25 | 200 | | | | |
| Bisoprolol | 1.25 | 10 | | | | |

Please see VA National Formulary for current list of formulary medications (<https://www.pbm.va.gov/PBM/NationalFormulary.asp>)

HFrEF = heart failure with reduced ejection fraction, BID = twice daily, lbs = pounds, IR = immediate release, HR = heart rate, BP = blood pressure

| Aldosterone Antagonists | | | | | Effect in Patients with HFrEF | |
|-------------------------|--|---|---|--|-------------------------------|-----------|
| Medication | Starting Daily Dose (mg) | Target Daily Dose (mg) | Comments | Monitor | Mortality | Morbidity |
| Spirolactone* | 12.5–25 CrCl <50: 12.5 daily or every other day | 25 daily or BID CrCl <50: 12.5–50 daily | Avoid starting if: creatinine >2.5 (male) or >2.0 (female) eGFR ≤30; or K+ ≥5 mEq/L If K+ increase ≤6 mEq/L or worsening renal function, hold until K+ <5. Consider restart at lower dose 72 hours after resolution. | Check K+ and renal function after two to three days <u>and</u> after seven days; monthly for three months then every three months. | ↓ | ↓ |
| Eplerenone* | 25 CrCl <50: 25 mg every other day | 50 CrCl <50: 25 daily | | | | |

*For those at high risk of hyperkalemia or who have marginal renal function (eGFR 30–49 mL/min/1.73 m²), an initial regimen of every-other-day dosing is advised. Please see VA National Formulary for current list of formulary medications (<https://www.pbm.va.gov/PBM/NationalFormulary.asp>)

HFrEF = heart failure with reduced ejection fraction, eGFR = estimated glomerular filtration rate, K+ potassium, CrCl = Creatinine clearance mL/min, BID = twice daily

| Diuretics | | | | | Effect in Patients with HFrEF | |
|-------------|--------------------------------------|-------------------------|---|---|-------------------------------|---|
| Medication | Starting Daily Dose (mg) | Maximal Daily Dose (mg) | Comments | Monitor | Mortality | Morbidity |
| Furosemide | 20–40 daily or BID | 600 | Furosemide 40mg ≈ Torsemide 20mg ≈ Bumetanide 1mg IV to PO: Furosemide 20:40 Bumetanide 1:1 Torsemide 1:1 | Serum K+, Mg, renal function, volume status | No Reduction |  |
| Bumetanide | 0.5–1 daily or BID | 10 | | | | |
| Torsemide | 10–20 daily | 200 | | | | |
| Metolazone* | 2.5–10 daily or once daily with loop | 20 | | | | |

*Can be used for sequential nephron blockade when given once with a loop diuretic. Please see VA National Formulary for current list of formulary medications (<https://www.pbm.va.gov/PBM/NationalFormulary.asp>)

HFrEF = heart failure with reduced ejection fraction, K+ potassium, BID = twice daily, Mg = magnesium, IV = intravenous, PO = by mouth

| Vasodilators | | | | | Effect in Patients with HFrEF who are African American or not treated with an ACEI or ARB | |
|--|--------------------------|----------------------------------|---|---------|---|-----------|
| Medication | Starting Daily Dose (mg) | Target Daily Dose (mg) | Comments | Monitor | Mortality | Morbidity |
| Hydralazine | 25 TID | 75 TID (225 total daily dose) | | BP | ↓ | ↓ |
| Isosorbide dinitrate | 20 TID | 40 TID (120 total daily dose) | DO NOT use with PDE inhibitors. Common side effects including flushing, hypotension, and headache can be minimized by utilizing a slow titration schedule. | BP | | |
| Hydralazine 37.5mg/ Isosorbide 20mg | 1 tablet TID | 2 tablets TID | | BP | | |

Please see VA National Formulary for current list of formulary medications (<https://www.pbm.va.gov/PBM/NationalFormulary.asp>)

HFrEF = heart failure with reduced ejection fraction, TID = three times daily. BP = blood pressure, PDE = phosphodiesterase

| Neprilysin inhibitor/ARB | | | | | Effect in Patients with HFrEF | |
|---|---------------------------------------|--|--|---|-------------------------------|-----------|
| Medication | Starting Daily Dose (mg) | Target Daily Dose (mg) | Comments | Monitor | Mortality | Morbidity |
| Sacubitril/valsartan*† ‡ (not on ACEI or ARB or on low doses or CrCl <30 ml/min) | Sacubitril 24/ valsartan 26 BID | Sacubitril 97/valsartan 103 BID | If switching from ACEI, allow a 36-hour washout period before initiating sacubitril/valsartan. | Serum K+ and renal function at baseline and within one to two weeks of initiation | ↓ | ↓ |
| Sacubitril/valsartan*† (switching from ACEI or ARB at standard doses) | Sacubitril 49/ valsartan 51 BID | Sacubitril 97/ valsartan 103 BID | | | | |

*Unless specified, use highest tolerated dose while maintaining adequate BP. †Initiation preferred by cardiology, ‡These patients were not studied in PARADIGM-HF. Please see VA National Formulary for current list of formulary medications (<https://www.pbm.va.gov/PBM/NationalFormulary.asp>)
ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, HFrEF = heart failure with reduced ejection fraction, BID = twice daily, K+ = potassium

| Digoxin and Ivabradine | | | | | Effect in Patients with HFrEF | |
|------------------------|--|--|---|------------------------------|-------------------------------|-----------|
| Medication | Starting Daily Dose (mg) | Target Daily Dose (mg) | Comments | Monitor | Mortality | Morbidity |
| Digoxin | 0.125 (requires renal dose adjustment) | | Use lower dose in older patients. | Target trough: 0.5–0.9 ng/mL | No Reduction | ↓ |
| Ivabradine*† | 2.5–5 BID | 7.5 mg BID (dependent on HR; see comments) | Adjust dose after two weeks based on resting HR. HR >60: increase dose by 2.5mg (given twice daily) up to max dose of 7.5 mg. HR 50–60: maintain dose. HR <50 or symptoms of bradycardia: decrease dose by 2.5 mg (given twice daily.) | Heart rate | No Reduction | ↓ |

*Unless specified, use highest tolerated dose while maintaining adequate HR. Please see VA National Formulary for current list of formulary medications (<https://www.pbm.va.gov/PBM/NationalFormulary.asp>), †Initiation preferred by cardiology; CrCl = Creatinine clearance mL/min, HFrEF = heart failure with reduced ejection fraction, BID = twice daily, HR = heart rate

Relative Contraindicated Medications in HFrEF^{5,12}

| Medication | Issue |
|--|--|
| Intermittent claudication agents | <ul style="list-style-type: none">• Medications with the same pharmacologic effects have caused decreased survival in patients with Class III-IV HF.• Cilostazol is contraindicated in patients with heart failure of any severity. |
| Non-dihydropyridine calcium channel blockers (e.g., verapamil and diltiazem) | <ul style="list-style-type: none">• Negative inotropic effects |
| Thiazolidinediones (e.g., rosiglitazone, pioglitazone) | <ul style="list-style-type: none">• Increase fluid retention and blood pressure• May cause or exacerbate heart failure |
| Some anti-arrhythmics (e.g., flecainide and propafenone) | <ul style="list-style-type: none">• Increase risk of hospitalization for HF exacerbation• Increase risk of mortality |
| Systemic nonsteroidal anti-inflammatory drugs (NSAID) | <ul style="list-style-type: none">• May cause sodium and water retention, peripheral vasoconstriction, worsen heart failure, and decrease renal function. |

Medications to be Used with Caution in HFrEF^{5,12}

| Medication | Issue |
|---|--|
| Corticosteroids | <ul style="list-style-type: none">• Increased fluid and sodium retention and blood pressure• High dose may cause arrhythmias. |
| Dipeptidyl peptidase-4 (DPP-4) inhibitors | <ul style="list-style-type: none">• Increased risk of developing HF in patients with pre-existing heart and/or kidney disease |
| Miscellaneous | <ul style="list-style-type: none">• Clozapine may cause cardiomyopathy and myocarditis.• Tricyclic antidepressants may prolong QT interval, contribute to hypotension.• Medications that increase fluid retention (e.g. gabapentin) and contribute to peripheral edema |

Heart Failure Medications in Chronic Kidney Disease (CKD)^{13,14}

CKD Stage 3 (eGFR $\geq 30 \leq 59$ mL/min/1.73m²)

- ACEI or ARB recommended.
- Beta blocker recommended.
- Aldosterone antagonist (AA) recommended if HF symptoms persistent despite ACEI (or ARB) and beta blocker.
- Do not use AA if K⁺ >5, or SCr >2.5 for males or SCr >2.0 for females.
- Angiotensin receptor-neprilysin inhibitor (ARNI) recommended as an alternative to an ACEI or ARB.
- Ivabradine recommended as indicated.
- Digoxin recommended as indicated (renal dose adjustment required).

CKD Stage 4 and 5 (eGFR <30 mL/min/1.73m²)

- ACEI or ARB might be considered with careful monitoring of renal function and electrolytes.
- ACEI or ARB are safe to use in patients on dialysis.
- Beta blocker recommended.
- Avoid aldosterone antagonist.
- ARNI may be considered, but has not been studied in this population.
- Ivabradine may be considered.
- Digoxin recommended as indicated (renal dose adjustment required).

Medication Considerations for Treatment of Heart Failure with Preserved Ejection Fraction (HFpEF)^{1,2}

| Treatment options | Recommendations | Medication Considerations |
|-------------------------------|--|---|
| Blood Pressure Control | <ul style="list-style-type: none"> Hypertension should be controlled to prevent morbidity* Patients with Stage C HFpEF and persistent hypertension, after management of volume overload, should be prescribed GDMT and titrated to achieve SBP <130 mm Hg, if safely achievable¹ | <ul style="list-style-type: none"> It is reasonable to treat hypertension with <ul style="list-style-type: none"> ACEI ARB Beta-blockers Note: no class of antihypertensive is contraindicated on the basis of HFpEF When selecting medication consider other co-morbidities and the potential benefits |
| Angiotensin Receptor Blockers | <ul style="list-style-type: none"> Might help reduce hospitalizations¹⁵ | <ul style="list-style-type: none"> Might consider use in HFpEF Prescribe cautiously May provide additional benefits: <ul style="list-style-type: none"> Hypertension Albuminuria |

*In accordance to clinical practice guidelines. GDMT = guideline directed medical therapy, SBP = systolic blood pressure, ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, eGFR = estimated glomerular filtration rate

| Treatment options | Recommendations | Medication Considerations |
|-------------------------|--|---|
| Aldosterone Antagonists | <ul style="list-style-type: none">• Might help reduce heart failure related hospitalization¹⁶• Subgroup analysis of the North American population suggests benefit in the composite of death, aborted cardiac death, and heart failure hospitalizations¹⁶ | <ul style="list-style-type: none">• Reasonable in HFpEF<ul style="list-style-type: none">o Age 50 or oldero HF hospitalization within the last year or elevated BNPo Creatinine <2.5 mg/dL,o potassium <5.0 mEq/Lo eGFR >30ml/min/1.73m² and stable |
| Fluid Management | <ul style="list-style-type: none">• Diuretics should be used for relief of symptoms due to volume overload in patients with HFpEF | <ul style="list-style-type: none">• Loop diuretics are preferred in symptomatic patients• No or minimal edema consider thiazide for hypertension management |

*In accordance to clinical practice guidelines. GDMT = guideline directed medical therapy, SBP = systolic blood pressure, ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, eGFR = estimated glomerular filtration rate

Other Considerations:

- Nutritional supplements have no benefit
- The routine use of nitrates or PD5 inhibitors are not recommended for symptomatic relief of Heart Failure, but may be safely used if otherwise indicated

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