Heart Failure Medication Management

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Dionne L. Knapp, PharmD, BCPS, CPP
Director of Pharmacy Education, EAHEC
Assistant Professor of Clinical Education, UNC ESOP
Clinical Assistant Professor of Family Medicine, ECU
Objectives

• Define heart failure and review classifications

• Summarize key drug therapy recommendations from the American College of Cardiology Foundation/American Heart Association guidelines

• Evaluate drug therapy options in the outpatient management of heart failure
Heart Failure Guidelines

• American College of Cardiology Foundation/American Heart Association (ACCF/AHA) (2013)
  – Available at www.acc.org and www.americanheart.org

• Heart Failure Society of America (2010)
  – Available at www.hfsa.org
Heart Failure
Definition

• Complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood

• Cardinal manifestations: dyspnea, fatigue, and fluid retention
# Definition of Heart Failure

<table>
<thead>
<tr>
<th>Classification</th>
<th>Ejection Fraction</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Heart Failure with Reduced Ejection Fraction (HFrEF)</td>
<td>≤40%</td>
<td>Also referred to as systolic HF. Randomized clinical trials have mainly enrolled patients with HFrEF and it is only in these patients that efficacious therapies have been demonstrated to date.</td>
</tr>
<tr>
<td>II. Heart Failure with Preserved Ejection Fraction (HFpEF)</td>
<td>≥50%</td>
<td>Also referred to as diastolic HF. Several different criteria have been used to further define HFpEF. The diagnosis of HFpEF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified.</td>
</tr>
<tr>
<td>a. HFpEF, Borderline</td>
<td>41% to 49%</td>
<td>These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patient with HFpEF.</td>
</tr>
<tr>
<td>b. HFpEF, Improved</td>
<td>&gt;40%</td>
<td>It has been recognized that a subset of patients with HFpEF previously had HFrEF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients.</td>
</tr>
</tbody>
</table>
Heart Failure Classifications

Important: Guides Place in Therapy for Medications
## Classification of Heart Failure

<table>
<thead>
<tr>
<th>ACCF/AHA Stages of HF</th>
<th>NYHA Functional Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>A At high risk for HF but without structural heart</td>
<td>None</td>
</tr>
<tr>
<td>disease or symptoms of HF.</td>
<td></td>
</tr>
<tr>
<td>B Structural heart disease but without signs or</td>
<td>I</td>
</tr>
<tr>
<td>symptoms of HF.</td>
<td>No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.</td>
</tr>
<tr>
<td>C Structural heart disease with prior or current</td>
<td>I</td>
</tr>
<tr>
<td>symptoms of HF.</td>
<td>No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.</td>
</tr>
<tr>
<td>II Slight limitation of physical activity.</td>
<td>Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.</td>
</tr>
<tr>
<td>III Marked limitation of physical activity.</td>
<td>Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.</td>
</tr>
<tr>
<td>IV Unable to carry on any physical activity</td>
<td>IV Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.</td>
</tr>
<tr>
<td>D Refractory HF requiring specialized interventions.</td>
<td></td>
</tr>
</tbody>
</table>
**Stages, Phenotypes and Treatment of HF**

**At Risk for Heart Failure**

**STAGE A**
At high risk for HF but without structural heart disease or symptoms of HF

- e.g., Patients with:
  - HTN
  - Atherosclerotic disease
  - DM
  - Obesity
  - Metabolic syndrome
  - Patients Using cardiotonics
  - With family history of cardiomyopathy

**THERAPY**
- Goals
  - Heart healthy lifestyle
  - Prevent vascular, coronary disease
  - Prevent LV structural abnormalities
- Drugs
  - ACEI or ARB in appropriate patients for vascular disease or DM
  - Statins as appropriate

**STAGE B**
Structural heart disease but without signs or symptoms of HF

- e.g., Patients with:
  - Previous MI
  - LV remodeling including LVH and low EF
  - Asymptomatic valvular disease

**THERAPY**
- Goals
  - Prevent HF symptoms
  - Prevent further cardiac remodeling
- Drugs
  - ACEI or ARB as appropriate
  - Beta blockers as appropriate
  - In selected patients
    - ICD
    - Revascularization or valvular surgery as appropriate

**STAGE C**
Structural heart disease with prior or current symptoms of HF

- e.g., Patients with:
  - Known structural heart disease and HF signs and symptoms

**THERAPY**
- Goals
  - Control symptoms
  - Improve HRQOL
  - Prevent hospitalization
  - Prevent mortality
- Drugs for routine use
  - Diuretics for fluid retention
  - ACEI or ARB
  - Beta blockers
  - Aldosterone antagonists
- Drugs for use in selected patients
  - Hydralazine/atosiban or inotropic agents
  - ACEI and ARB
  - Digoxin
  - In selected patients
    - CRT
    - ICD
    - Revascularization or valvular surgery as appropriate

**Heart Failure**

**STAGE D**
Refractory HF

- e.g., Patients with:
  - Marked HF symptoms at rest
  - Recurrent hospitalizations despite GDMT

**THERAPY**
- Goals
  - Control symptoms
  - Improve HRQOL
  - Reduce hospital readmissions
  - Establish patient's end-of-life goals
- Options
  - Advanced care measures
  - Heart transplant
  - Chronic inotropes
  - Temporary or permanent MCS
  - Experimental surgery or drugs
  - Palliative care and hospice
  - ICD deactivation

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American Heart Association®
Guideline-Directed Medical Therapy (GDMT):
Represents optimal medical therapy as defined by ACCF/AHA guideline-recommend therapies (primarily Class I)
### Classification of Recommendations and Levels of Evidence

| LEVEL A | Multiple populations evaluated*  
Data derived from multiple randomized clinical trials or meta-analyses |
|---------|-------------------------------------------------------------------------|
| ■ Recommendation that procedure or treatment is useful/effective  
■ Sufficient evidence from multiple randomized trials or meta-analyses |
| LEVEL B | Limited populations evaluated*  
Data derived from a single randomized trial or nonrandomized studies |
| ■ Recommendation that procedure or treatment is useful/effective  
■ Evidence from single randomized trial or nonrandomized studies |
| LEVEL C | Very limited populations evaluated*  
Only consensus opinion of experts, case studies, or standard of care |
| ■ Recommendation that procedure or treatment is useful/effective  
■ Only expert opinion, case studies, or standard of care |

#### Suggested phrases for writing recommendations

- **LEVEL A**
  - Should be recommended
  - In scarcely
  - In selected/difficult/essential

- **LEVEL B**
  - May be recommended
  - In scarcely
  - In selected/difficult/essential
- **LEVEL C**
  - Not recommended
  - In scarcely
  - In selected/difficult/essential

#### Comparative effectiveness phrases

- Treatment A is
  - significantly
  - numerically
  - probably
  - not significantly
  - not numerically
  - probably not
  - not probably

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

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Recommendations for the Treatment of Stage A HF

• Hypertension and lipid disorders should be controlled in accordance with contemporary guidelines (COR I/LOE A)

• Other conditions that may lead to or contribute to HF, such as obesity, diabetes, tobacco use, and known cardiotoxic agents, should be controlled or avoided (COR I/LOE C)

• Use ACEI/ARB and statins in appropriate patients
# Recommendations for Treatment of Stage B HF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients with a history of MI and reduced EF, ACE inhibitors or ARBs should be used to prevent HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>In patients with MI and reduced EF, evidence-based beta blockers should be used to prevent HF</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>In patients with MI, statins should be used to prevent HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Blood pressure should be controlled to prevent symptomatic HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>ACE inhibitors should be used in all patients with a reduced EF to prevent HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Beta blockers should be used in all patients with a reduced EF to prevent HF</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>An ICD is reasonable in patients with asymptomatic ischemic cardiomyopathy who are at least 40 d post-MI, have an LVEF ≤30%, and on GDMT</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Nondihydropyridine calcium channel blockers may be harmful in patients with low LVEF</td>
<td>III: Harm</td>
<td>C</td>
</tr>
</tbody>
</table>
Recommendations for the Treatment of Stage C HFrEF
Pharmacologic Treatment for Stage C HFrEF

HFrEF Stage C
NYHA Class I – IV
Treatment:

Class I, LOE A
ACEI or ARB **AND**
Beta Blocker

For all volume overload,
NYHA class II-IV patients

Add

Class I, LOE C
Loop Diuretics

For persistently symptomatic
African Americans,
NYHA class III-IV

Add

Class I, LOE A
Hydral-Nitrates

For NYHA class II-IV patients,
Provided estimated creatinine
>30 mL/min and K+ <5.0 mEq/dL

Add

Class I, LOE A
Aldosterone Antagonist

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# Pharmacological Therapy for Management of Stage C HFrEF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diuretics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics are recommended in patients with HFrEF with fluid retention</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td><strong>ACE Inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors are recommended for all patients with HFrEF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td><strong>ARBs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARBs are recommended in patients with HFrEF who are ACE inhibitor intolerant</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>ARBs are reasonable as alternatives to ACE inhibitor as first line therapy in HFrEF</td>
<td>IIa</td>
<td>A</td>
</tr>
<tr>
<td>The addition of an ARB may be considered in persistently symptomatic patients with HFrEF on GDMT</td>
<td>IIb</td>
<td>A</td>
</tr>
<tr>
<td>Routine combined use of an ACE inhibitor, ARB, and aldosterone antagonist is potentially harmful</td>
<td>III: Harm</td>
<td>C</td>
</tr>
</tbody>
</table>
Pharmacological Therapy for Management of Stage C HFrEF (cont.)

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta Blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of 1 of the 3 beta blockers proven to reduce mortality is recommended for all stable patients</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td><strong>Aldosterone Antagonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldosterone receptor antagonists are recommended in patients with NYHA class II-IV HF who have LVEF ≤35%</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Aldosterone receptor antagonists are recommended in patients following an acute MI who have LVEF ≤40% with symptoms of HF or DM</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Inappropriate use of aldosterone receptor antagonists may be harmful</td>
<td>III:</td>
<td>Harm</td>
</tr>
<tr>
<td><strong>Hydralazine and Isosorbide Dinitrate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The combination of hydralazine and isosorbide dinitrate is recommended for African-Americans, with NYHA class III–IV HFrEF on GDMT</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>A combination of hydralazine and isosorbide dinitrate can be useful in patients with HFrEF who cannot be given ACE inhibitors or ARBs</td>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>
### Pharmacologic Therapy for Management of Stage C HFrEF (cont.)

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Digoxin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin can be beneficial in patients with HFrEF</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td><strong>Anticoagulation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with chronic HF with permanent/persistent/paroxysmal AF and an</td>
<td></td>
<td></td>
</tr>
<tr>
<td>additional risk factor for cardioembolic stroke should receive chronic</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>anticoagulant therapy*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The selection of an anticoagulant agent should be individualized</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Chronic anticoagulation is reasonable for patients with chronic HF who have</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>permanent/persistent/paroxysmal AF but without an additional risk factor for</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cardioembolic stroke*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulation is not recommended in patients with chronic HFrEF without</td>
<td>III: No Benefit</td>
<td>B</td>
</tr>
<tr>
<td>AF, prior thromboembolic event, or a cardioembolic source</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Statins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins are not beneficial as adjunctive therapy when prescribed solely for HF</td>
<td>III: No Benefit</td>
<td>A</td>
</tr>
<tr>
<td><strong>Omega-3 Fatty Acids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omega-3 PUFA supplementation is reasonable to use as adjunctive therapy in</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>HFrEF or HFpEF patients</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Pharmacological Therapy for Management of Stage C HFrEF (cont.)

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Other Drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutritional supplements as treatment for HF are not recommended in HFrEF</td>
<td>III: No Benefit B</td>
<td></td>
</tr>
<tr>
<td>Hormonal therapies other than to replete deficiencies are not recommended in HFrEF</td>
<td>III: No Benefit C</td>
<td></td>
</tr>
<tr>
<td>Drugs known to adversely affect the clinical status of patients with HFrEF are potentially harmful and should be avoided or withdrawn</td>
<td>III: Harm B</td>
<td></td>
</tr>
<tr>
<td>Long-term use of an infusion of a positive inotropic drug is not recommended and may be harmful except as palliation</td>
<td>III: Harm C</td>
<td></td>
</tr>
<tr>
<td><strong>Calcium Channel Blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium channel blocking drugs are not recommended as routine in HFrEF</td>
<td>III: No Benefit A</td>
<td></td>
</tr>
</tbody>
</table>
Recommendations for the Treatment of Stage C HFpEF
## Treatment of HFpEF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic and diastolic blood pressure should be controlled according to published clinical practice guidelines</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Diuretics should be used for relief of symptoms due to volume overload</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Coronary revascularization for patients with CAD in whom angina or demonstrable myocardial ischemia is present despite GDMT</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Management of AF according to published clinical practice guidelines for HFpEF to improve symptomatic HF</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Use of beta-blocking agents, ACE inhibitors, and ARBs for hypertension in HFpEF</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>ARBs might be considered to decrease hospitalizations in HFpEF</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Nutritional supplementation is not recommended in HFpEF</td>
<td>III: No Benefit</td>
<td>C</td>
</tr>
</tbody>
</table>
Pharmacotherapy Options for HFrEF
## Heart Failure Management

<table>
<thead>
<tr>
<th>HF Severity</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage B</strong></td>
<td><strong>ACE Inhibitor or ARB</strong>&lt;br&gt;<strong>Beta-blocker</strong></td>
</tr>
<tr>
<td><strong>Class I</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Stage C</strong></td>
<td><strong>ACE Inhibitor or/and ARB</strong>&lt;br&gt;<strong>Beta-blocker</strong>&lt;br&gt;<strong>Diuretic</strong>&lt;br&gt;<strong>Aldosterone antagonist</strong>&lt;br&gt;<strong>Hydralazine/isosorbide dinitrate</strong>&lt;br&gt;<strong>Digoxin</strong>&lt;br&gt;<strong>CRT; ICD</strong></td>
</tr>
<tr>
<td><strong>Class I-IV</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Stage D</strong></td>
<td><strong>All Stage C medications</strong>&lt;br&gt;<strong>Inotropic agents; vasodilators</strong>&lt;br&gt;<strong>Experimental drugs/surgery</strong>&lt;br&gt;<strong>ICD deactivation</strong>&lt;br&gt;<strong>Transplant</strong>&lt;br&gt;<strong>Mechanical circulatory support</strong>&lt;br&gt;<strong>Pallative care and hospice</strong></td>
</tr>
<tr>
<td><strong>Class IV</strong></td>
<td></td>
</tr>
</tbody>
</table>
Diuretics

• Goal of treatment is to eliminate clinical evidence of fluid retention

• No long-term studies for morbidity and mortality
  – Use in patients to improve symptoms
  – Use in combination with GDMT

ACCF/AHA 2013
HFSA 2010
Diuretics

• Diuretic of choice: loop

• Available agents:
  – Furosemide 40 mg = bumetanide 1 mg = torsemide 20 mg = ethacrynic acid 50 mg
  – Furosemide most commonly used
  – Bumetanide and torsemide have increased oral bioavailability
## Loop Diuretics

<table>
<thead>
<tr>
<th>Loop Diuretic</th>
<th>Initial Daily Dose(s)</th>
<th>Max Daily Dose</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bumetanide</td>
<td>0.5 – 1.0 mg qd/bid</td>
<td>10 mg</td>
<td>4-6 hours</td>
</tr>
<tr>
<td>Furosemide</td>
<td>20 – 40 mg qd/bid</td>
<td>600 mg</td>
<td>6-8 hours</td>
</tr>
<tr>
<td>Torsemide</td>
<td>10 – 20 mg qd</td>
<td>200 mg</td>
<td>12-16 hours</td>
</tr>
</tbody>
</table>

All available in generic  
Cost per month <$20 per [www.goodrx.com](http://www.goodrx.com) (9/14)
Diuretics

• Dosing
  – PRN based on weight
  – Initiate starting dose, then double dose until desired diuresis
  – Appropriate use is a key element in the success of other drugs used in treating HF

• Watch for electrolyte imbalances, volume depletion, hypotension, and renal insufficiency
Diuretics

• Patients may become refractory
  – Due to increased dietary sodium intake, administration of NSAIDS, gut wall edema (↓ furosemide absorption up to 50%), significant impairment of renal function or perfusion, etc.

• Resistance can be overcome by:
  – IV administration
  – Combination of loop and thiazide diuretic
    • Metolazone (2.5-10 mg qd) is the thiazide of choice
Neurohormonal activation

Angiotensinogen

Angiotensin I

Angiotensin II

Aldosterone secretion

Sodium and water reabsorption

Vasoconstriction

Aldosterone blocker

ACE-I

ARB

SNS

β-blockers

Adapted from Critical Care Nurse, Macklin M, April 2001
ACE Inhibitors

• Use in all ACCF/AHA Stages and NYHA Classes of HF, unless contraindicated

• Decreases cardiovascular morbidity, mortality, and recurrence of MI (in pts with or without LV dysfunction)
ACE Inhibitors

- Benefit considered class effect
  - Consider cost/convenience in choosing agent

- Use target doses, if possible
  - Recommend using highest tolerable dose during concomitant up titration of beta-blockers

- Use with caution if low SBP (<80 mm Hg), increased serum creatinine (>3 mg/dL), bilateral RAS, or elevated K+ levels (>5 mEq/L)

ACCF/AHA 2013
HFSA 2010
<table>
<thead>
<tr>
<th>ACE Inhibitor</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril (Capoten®)</td>
<td>50 mg TID</td>
</tr>
<tr>
<td>Enalapril (Vasotec®)</td>
<td>10 mg BID</td>
</tr>
<tr>
<td>Lisinopril (Prinivil®, Zestril®)</td>
<td>20 mg QD</td>
</tr>
<tr>
<td>Quinapril (Accupril®)</td>
<td>20 BIDψ</td>
</tr>
<tr>
<td>Ramipril (Altace®)</td>
<td>10 mg QDψ</td>
</tr>
<tr>
<td>Trandolapril (Mavik®)</td>
<td>4 mg QDψ</td>
</tr>
<tr>
<td>Fosinopril (Monopril®)</td>
<td>40 mg QDψ</td>
</tr>
<tr>
<td>Perindopril (Aceon®)</td>
<td>8 mg QDψ</td>
</tr>
</tbody>
</table>

All available in generic
Cost per month <$20 per [www.goodrx.com](http://www.goodrx.com) (9/14)
Ψ No study data on dose

ACCF/AHA 2013
HFSA 2010
ACE Inhibitors

• Adverse effects
  – Hypotension, renal insufficiency, hyperkalemia, cough (up to 20%), angioedema (0.1-0.5%)

• Monitor serum creatinine and potassium at baseline, 1-2 weeks after initiation, and after dosage changes
Alternatives to ACE Inhibitors

• Use one of the following medications if a patient is intolerant to an ACE inhibitor:
  – Angiotension receptor blocker (ARB)
  – Hydralazine + isosorbide dinitrate combination

• ACE inhibitors remain preferred over both options due to morbidity and mortality data
Angiotensin Receptor Blockers

- Morbidity and mortality data available
- Alternative when intolerant to an ACE inhibitor, primarily due to cough
- May consider use in patients that experienced angioedema while on an ACE inhibitor
  - Use caution - evaluate underlying risk and recognize angioedema has been reported with ARBs
**Angiotensin Receptor Blockers**

- Alternative as first-line therapy, especially if already taking an ARB for another indication

- Consider combination with ACE inhibitor and a beta blocker in patients that are persistently symptomatic in whom an aldosterone antagonist is not indicated or tolerated

- Triple combination (ACE inhibitor + ARB + aldosterone antagonist) is **not** recommended due to high risk of hyperkalemia

ACCF/AHA 2013
HFSA 2010
# Angiotensin Receptor Blockers

- Use recommended ARBs at target doses

<table>
<thead>
<tr>
<th>ARB</th>
<th>Target Dose</th>
<th>Cost/month*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan (Atacand®)</td>
<td>32 mg qd</td>
<td>$50-110</td>
</tr>
<tr>
<td>Valsartan (Diovan®)</td>
<td>160 mg bid</td>
<td>$110-230</td>
</tr>
<tr>
<td>Losartan (Cozaar®)</td>
<td>150 mg qd</td>
<td>$8-35</td>
</tr>
</tbody>
</table>

All available in generic

*www.goodrx.com (9/14)
Angiotensin Receptor Blockers

• Same precautions as ACE inhibitors

• Adverse effects
  – Hypotension, renal insufficiency, hyperkalemia, angioedema (lower incidence than with ACEIs)

• Monitor serum creatinine and potassium at baseline, 1-2 weeks after initiation, and after dosage changes

ACCF/AHA 2013
HFSA 2010
Beta-Blockers

• Use in ACCF/AHA Stages B – D and all NYHA Classes of HF, unless contraindicated

• Decreases cardiovascular morbidity, mortality, and recurrence of MI

• Recommended even if pt has concomitant DM, asthma/COPD, or PVD

ACCF/AHA 2013
HFSA 2010
Beta-Blockers

- Use caution in pts with diabetes with recurrent hypoglycemia, reactive airway disease, or resting limb ischemia
  - Do not use in asthma patients with active bronchospasm

- Use considerable caution in pts with marked bradycardia (<55 beats/min) or marked hypotension (SBP < 80 mmHg)
Beta-Blockers

• Not considered a class effect - use agents studied
  – Carvedilol, metoprolol succinate, bisoprolol
    • Similar efficacy in trials
    • Most data in Class II-III
  – Consider carvedilol over other agents in pts with EF <25% or those needing additional BP lowering
Beta-Blockers

• Dosing
  – Start low and go slow
  – Titrate at 2-week intervals (adjust as necessary)
  – Use target doses, if possible

• Adverse effects
  – Bradycardia, hypotension, fatigue, fluid retention
  – Patients usually feel worse for a while

ACCF/AHA 2013
HFSA 2010
<table>
<thead>
<tr>
<th>Beta-Blocker</th>
<th>Target Dose</th>
<th>Cost/month*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol (Zebeta®)</td>
<td>10 mg qd</td>
<td>$20-25</td>
</tr>
<tr>
<td>Carvedilol (Coreg®)</td>
<td>25 mg bid (&lt;85 kg)</td>
<td>&lt;$15</td>
</tr>
<tr>
<td>(Coreg CR®)</td>
<td>50 mg bid (&gt;85 kg)</td>
<td>$180-200</td>
</tr>
<tr>
<td></td>
<td>80 mg qd</td>
<td></td>
</tr>
<tr>
<td>Metoprolol succinate</td>
<td>200 mg qd</td>
<td>$15-25</td>
</tr>
<tr>
<td>(Toprol XL®)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*www.goodrx.com (9/14)

All available in generic, except Coreg CR

ACCF/AHA 2013
HFSA 2010
Which Beta Blocker is Best?

• Guidelines do not recommend one agent over another
• No head-to-head mortality comparisons
• Comparative data has suggested superiority of carvedilol; however, studies had flaws
• Recent cohort study comparing carvedilol and metoprolol succinate found no significant difference in all cause mortality

*JAMA Intern Med. Published online August 31, 2014. doi:10.1001/jamainternmed.2014.3258*
Beta-Blockers During Decompensation of HF

• Can be used in pts with recent decompensation after optimization of fluid status and d/c of IV diuretics, vasodilators, and inotropic support

• Avoid abrupt discontinuation. Continue therapy in most pts during an exacerbation, if possible.
  – May require temporary reduction in dose or discontinuation. Reinstate or gradually increase before hospital discharge.

ACCF/AHA 2013
HFSA 2010
Aldosterone Antagonists

- Decreases morbidity and mortality

- Recommended in patients with NYHA Class II – IV HF and who have LVEF ≤35%, unless contraindicated
  - Pts with NYHA Class II HF should have a h/o prior CV hospitalization or elevated plasma natriuretic peptide levels
  - Recommended following an acute MI in patients who have LVEF ≤40% who develop HF symptoms or who have a history of diabetes, unless contraindicated

ACCF/AHA 2013
HFSA 2010
Aldosterone Antagonists

- Consider adding to patients who are already on ACE inhibitors (or ARBs) and beta blockers
- Limited data to support or refute that available agents (spironolactone and eplerenone) are interchangeable
Aldosterone Antagonists

• **Eplerenone** (Inspra®)
  - Selective mineralocorticoid antagonist
  - HF post MI, HTN, mild to moderate HF (NYHA class II)
  - Target: 50 mg qd
  - Drug interactions (3A4)
  - No gynecomastia
  - Expensive: generic $50-90/month*

• **Spironolactone** (Aldactone®)
  - Nonselective mineralocorticoid antagonist
  - Moderate to severe HF (NYHA class III-IV)
  - Target: 25 mg qd
  - Gynecomastia
  - Inexpensive: generic <$10/month*

*www.goodrx.com (9/14)
Aldosterone Antagonists

• Adverse effects
  – Renal insufficiency, hyperkalemia

• Adjust initial regimen to every-other-day dosing if CrCl 30-49 mL/min

• Potassium supplements should be discontinued or dose reduced

• Stop during an episode of diarrhea or dehydration or while loop therapy is interrupted
Aldosterone Antagonists

• **Not recommended when:**
  – SCr >2 (females) or >2.5 (males) mg/dL  **OR**
  – CrCl <30 mL/min
  – K⁺ >5 mEq/L

• **Monitor serum creatinine and potassium**
  – ACCF/AHA: baseline, 3 days, 1 week, monthly x 3 months, every 3 months
  – HFSA: baseline, 1 week, 1 month, every 3 months
Hydralazine and Isosorbide Dinitrate

• Morbidity and mortality data available

• Recommended in African Americans with NYHA Class III-IV HF receiving optimal therapy with an ACE inhibitor and beta blocker, unless contraindicated

• Benefit in non-African Americans is unknown
  – HFSA states that you may consider use in non-African Americans who remain symptomatic despite optimal therapy
Hydralazine and Isosorbide Dinitrate

• Alternative to ACE inhibitors and ARBs
  – Due to drug intolerance, hypotension, hyperkalemia, or renal insufficiency
  – ACE inhibitors have demonstrated greater benefits in comparative trial
Hydralazine and Isosorbide Dinitrate

- Dosing
  - Generic (~$100/month*)
    - Hydralazine 75 mg qid + isosorbide dinitrate 40 mg qid
  - BiDil® (~$400/month*)
    - Hydralazine 37.5mg / isosorbide dinitrate 20mg
    - Target dose: 2 tabs tid

- Adverse effects: HA, hypotension, dizziness, and GI complaints

*www.goodrx.com (9/14)
Digoxin

• Decreases symptoms and hospitalizations; No effect on mortality

• Consider as add–on therapy to standard therapy (GDMT) to improve symptoms

• May also be added to initial regimen in pts with severe symptoms, who have not yet responded to GDMT

ACCF/AHA 2013
HFSA 2010
Digoxin

- **Dosing**
  - 0.125 mg - 0.25 mg QD (generic $10-35/month*)
  - Adjust dose with renal dysfunction

- **Monitoring**
  - Digoxin levels as needed; target <1 ng/mL
    - 0.5-0.9 ng/mL per ACCF/AHA
    - 0.7-0.9 ng/mL per HFSA
  - Serum creatinine and potassium

- **Use caution in the elderly**

- **Watch for drug interactions**

*www.goodrx.com (9/14)*
Digoxin

- Adverse effects
  - Arrhythmias, nausea, vomiting, anorexia, visual halos, photophobia, fatigue, weakness, dizziness, HA, confusion
- Overt toxicity associated with levels >2 ng/mL
- Hypokalemia, hypomagnesemia, and hypothyroidism may increase risk of toxicity at lower digoxin levels
Calcium Channel Blockers

• Not recommended as routine treatment for patients with HFrEF and should generally be avoided

• May consider amlodipine in the management of HTN or IHD in pts with HF because it is well tolerated and had neutral effects on morbidity and mortality in trials
  – If use, monitor for peripheral edema

ACCF/AHA 2013
HFSA 2010
Future Medication Options

• Ivabradine
  – FDA fast track designation for chronic heart failure
  – Inhibits the I_f (pacemaker) current in the sinoatrial node to decrease heart rate
  – SHIFT trial demonstrated a reduction in CV death or hospitalization for worsening heart failure

• Valsartan/sacubitril
  – ARB + neprilysin inhibitor
  – PARADIGM-HF trial demonstrated superiority over enalapril to reduce risk of death and hospitalization

Pharmacotherapy Options for HFpEF
Heart Failure with Preserved Ejection Fraction

• Very limited outcome studies available

• No randomized, controlled trials have shown a delay in disease progression or reduction in mortality

• Treatment goals focus on reducing symptoms, managing associated disease(s), reducing risk factors, and modifying underlying pathophysiology
Goals of Therapy

- Reduce the congestive state
- Maintain atrial contraction and prevent tachycardia
- Slow HR to allow for adequate filling of left ventricle
- Treat and prevent myocardial ischemia
- Control hypertension
- Promote regression of hypertrophy and prevent myocardial fibrosis

ACCF/AHA Recommendations

• Control blood pressure according to guidelines
• Use diuretics to relieve symptoms of volume overload
• Coronary revascularization in appropriate pts
• Manage atrial fibrillation according to guidelines
• Use beta-blockers, ACE inhibitors, and ARBs for hypertension
• Use of ARBs may be considered to decrease hospitalizations
• Routine use of nutritional supplements not recommended
HFpEF Treatment Options
Per HFSA

- Diuretics
- ACE Inhibitors or ARBs
- Beta-Blockers (non-ISA)
- Calcium Channel Blockers
  - Diltiazem
  - Verapamil
Diuretics

• For all patients with HFpEF and fluid overload
  – Begin with thiazide or loop diuretic
  – Loop preferred in severe volume overload or if inadequate response to thiazide
  – Avoid excessive diuresis, which may lead to orthostatic changes in blood pressure and worsening renal function

HFSA 2010
ACE Inhibitors and ARBs

• Consider an ACE inhibitor or ARB in the absence of other indications

• ACE inhibitors should be considered in all patients who have:
  – Symptomatic atherosclerotic disease OR
  – Diabetes and one additional risk factor

• In patients who meet the above criteria but are intolerant to ACE inhibitors, ARBs should be considered

HFSA 2010
Beta-Blockers

• Recommended in patients who have HFpEF and:
  – Prior MI
  – Hypertension
  – Atrial fibrillation (requiring rate control)

HFSA 2010
Calcium Channel Blockers

• Consider in patients with HFpEF and:
  – Atrial fibrillation (requiring rate control) and intolerance to beta-blockers
    • Options: diltiazem and verapamil
  – Symptom limiting angina
  – Hypertension

HFSA 2010
Chronic Heart Failure
Conclusions

• Heart failure is associated with significant morbidity and mortality
• Follow guideline recommendations regarding drug therapy, which are supported by evidence
• ACE inhibitors (ARBs) and beta-blockers should be used in all patients, if possible
• Close follow-up and adherence to therapy is important
Questions?
Additional Charts for Reference
Strategies for Achieving Optimal GDMT
(ACCF/AHA 2013)

1. Uptitrate in small increments to the recommended target dose or the highest tolerated dose for those medications listed in Table 15 with an appreciation that some patients cannot tolerate the full recommended doses of all medications, particularly patients with low baseline heart rate or blood pressure or with a tendency to postural symptoms.

2. Certain patients (eg, the elderly, patients with chronic kidney disease) may require more frequent visits and laboratory monitoring during dose titration and more gradual dose changes. However, such vulnerable patients may accrue considerable benefits from GDMT. Inability to tolerate optimal doses of GDMT may change after disease-modifying interventions such as CRT.

3. Monitor vital signs closely before and during uptitration, including postural changes in blood pressure or heart rate, particularly in patients with orthostatic symptoms, bradycardia, and/or “low” systolic blood pressure (eg, 80 to 100 mm Hg).
Strategies for Achieving Optimal GDMT
(ACCF/AHA 2013)

4. Alternate adjustments of different medication classes (especially ACE inhibitors/ARBs and beta blockers) listed in Table 15. Patients with elevated or normal blood pressure and heart rate may tolerate faster incremental increases in dosages.

5. Monitor renal function and electrolytes for rising creatinine and hyperkalemia, recognizing that an initial rise in creatinine may be expected and does not necessarily require discontinuation of therapy; discuss tolerable levels of creatinine above baseline with a nephrologist if necessary.

6. Patients may complain of symptoms of fatigue and weakness with dosage increases; in the absence of instability in vital signs, reassure them that these symptoms are often transient and usually resolve within a few days of changes in therapy.
Strategies for Achieving Optimal GDMT
(ACCF/AHA 2013)

7. Discourage sudden spontaneous discontinuation of GDMT medications by the patient and/or other clinicians without discussion with managing clinicians.

8. Carefully review doses of other medications for HF symptom control (eg, diuretics, nitrates) during uptitration.

9. Consider temporary adjustments in dosages of GDMT during acute episodes of noncardiac illnesses (eg, respiratory infections, risk of dehydration, etc).

10. Educate patients, family members, and other clinicians about the expected benefits of achieving GDMT, including an understanding of the potential benefits of myocardial reverse remodeling, increased survival, and improved functional status and HRQOL.
## Drugs Commonly Used for HFrEF (Stage C HF)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Daily Dose(s)</th>
<th>Maximum Doses(s)</th>
<th>Mean Doses Achieved in Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>6.25 mg 3 times</td>
<td>50 mg 3 times</td>
<td>122.7 mg/d (421)</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 mg twice</td>
<td>10 to 20 mg twice</td>
<td>16.6 mg/d (412)</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>5 to 10 mg once</td>
<td>40 mg once</td>
<td>-----------</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5 to 5 mg once</td>
<td>20 to 40 mg once</td>
<td>32.5 to 35.0 mg/d (444)</td>
</tr>
<tr>
<td>Perindopril</td>
<td>2 mg once</td>
<td>8 to 16 mg once</td>
<td>-----------</td>
</tr>
<tr>
<td>Quinapril</td>
<td>5 mg twice</td>
<td>20 mg twice</td>
<td>-----------</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25 to 2.5 mg once</td>
<td>10 mg once</td>
<td>-----------</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>1 mg once</td>
<td>4 mg once</td>
<td>-----------</td>
</tr>
<tr>
<td><strong>ARBs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>4 to 8 mg once</td>
<td>32 mg once</td>
<td>24 mg/d (419)</td>
</tr>
<tr>
<td>Losartan</td>
<td>25 to 50 mg once</td>
<td>50 to 150 mg once</td>
<td>129 mg/d (420)</td>
</tr>
<tr>
<td>Valsartan</td>
<td>20 to 40 mg twice</td>
<td>160 mg twice</td>
<td>254 mg/d (109)</td>
</tr>
<tr>
<td><strong>Aldosterone Antagonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>12.5 to 25 mg once</td>
<td>25 mg once or twice</td>
<td>26 mg/d (424)</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>25 mg once</td>
<td>50 mg once</td>
<td>42.6 mg/d (445)</td>
</tr>
</tbody>
</table>
### Drugs Commonly Used for HFrEF (Stage C HF) (cont.)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Daily Dose(s)</th>
<th>Maximum Doses(s)</th>
<th>Mean Doses Achieved in Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta Blockers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg once</td>
<td>10 mg once</td>
<td>8.6 mg/d (118)</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg twice</td>
<td>50 mg twice</td>
<td>37 mg/d (446)</td>
</tr>
<tr>
<td>Carvedilol CR</td>
<td>10 mg once</td>
<td>80 mg once</td>
<td>------</td>
</tr>
<tr>
<td>Metoprolol succinate extended release</td>
<td>12.5 to 25 mg once</td>
<td>200 mg once</td>
<td>159 mg/d (447)</td>
</tr>
<tr>
<td>(metoprolol CR/XL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hydralazine &amp; Isosorbide Dinitrate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixed dose combination (423)</td>
<td>37.5 mg hydralazine/20 mg isosorbide dinitrate 3 times daily</td>
<td>75 mg hydralazine/40 mg isosorbide dinitrate 3 times daily</td>
<td>~175 mg hydralazine/90 mg isosorbide dinitrate daily</td>
</tr>
<tr>
<td>Hydralazine and isosorbide dinitrate (448)</td>
<td>Hydralazine: 25 to 50 mg, 3 or 4 times daily and isosorbide dinitrate: 20 to 30 mg 3 or 4 times daily</td>
<td>Hydralazine: 300 mg daily in divided doses and isosorbide dinitrate 120 mg daily in divided doses</td>
<td>------</td>
</tr>
</tbody>
</table>
### Review of the Evidence

<table>
<thead>
<tr>
<th>Drug or Drug Class</th>
<th>NNT</th>
<th>Outcome Prevented</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE Inhibitors</td>
<td>6</td>
<td>One death over 1 year; NYHA Class III-IV</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>One death over 1 year; NYHA Class I-II</td>
</tr>
<tr>
<td>Beta-Blockers</td>
<td>23</td>
<td>One death over 1 year</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>One hospitalization over 1 year</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>9</td>
<td>One death over 2 years; NYHA Class III - IV</td>
</tr>
<tr>
<td>Hydralazine + isosorbide dinitrate</td>
<td>14</td>
<td>One death over 1 year</td>
</tr>
<tr>
<td>Digoxin</td>
<td>9</td>
<td>ED visits or hospitalizations</td>
</tr>
</tbody>
</table>

*Am Fam Physician* 2001;64:1393-8
## Review of the Evidence

<table>
<thead>
<tr>
<th>Drug or Drug Class</th>
<th>NNT</th>
<th>Outcome Prevented</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan (ACEI intolerant)</td>
<td>14</td>
<td>One CV death or hospital admission over ~3 years</td>
</tr>
<tr>
<td>(ACEI + ARB)</td>
<td>23</td>
<td>One CV death or hospital admission over ~3 years</td>
</tr>
<tr>
<td>Valsartan (ACEI + ARB)</td>
<td>23</td>
<td>One hospitalization over 23 months</td>
</tr>
<tr>
<td>Hydralazine/isosorbide dinitrate (BiDil®)</td>
<td>25</td>
<td>One death from any cause over 18 months</td>
</tr>
<tr>
<td>- In African Americans</td>
<td>12</td>
<td>One hospitalization over 18 months</td>
</tr>
</tbody>
</table>
## Review of the Evidence

<table>
<thead>
<tr>
<th>Drug or Drug Class</th>
<th>NNT</th>
<th>Outcome Prevented</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eplerenone - Post MI</td>
<td>44</td>
<td>One death from any cause over 16 months</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>One CV death or hospitalization over 16 months</td>
</tr>
<tr>
<td>Eplerenone - NYHA Class II</td>
<td>13</td>
<td>One death from CV causes or hospitalization for heart failure over 21 months</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>One death from any cause over 21 months</td>
</tr>
</tbody>
</table>
## HFP EF Clinical Trials

<table>
<thead>
<tr>
<th>Trial (Therapy)</th>
<th>n</th>
<th>EF (%)</th>
<th>Outcome/Benefit</th>
</tr>
</thead>
</table>
| PEP-CHF (perindopril)    | 852 | ~40    | • No change in composite endpoint  
                             |     |        | • Reduced hospitalization for HF                                                 |
| CHARM-Preserved (candesartan) | 3023 | >40    | • No change in composite endpoint  
                             |     |        | • Reduced hospitalization for HF                                                 |
| I-PRESERVE (irbesartan)  | 4128| >45    | • No change in composite endpoint                                                 |
| SENIORS trial (nebivolol) | 2128| >35    | • Reduced all-cause mortality or CV hospitalization                               |
| DIG trial (digoxin)      | 988 | >45    | • No change in primary or secondary end points                                   |

Adapted from PSAP-VII Chronic Heart Failure, 2011