Treating heart failure in primary care
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Alosa Foundation
Treating heart failure in primary care

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Activity overview:
The primary goal of this educational program is to inform primary care physicians about the most recent evidence on treating heart failure (HF) in the outpatient setting.

In addition to providing this evidence report about HF epidemiology, burdens, and management options, the education program uses an innovative approach, academic detailing, one-on-one educational sessions with specially trained outreach educators (pharmacists, nurses, physicians) who present the educational material interactively. Reference cards for clinicians and education materials for family members are also provided.

Target Audience:
The educational program is designed for primary care physicians practicing internal medicine, primary care, family practice, and geriatrics, and other health care professionals who deliver primary care.

Learning Objectives:
Upon completion of this activity, participants will be able to:

• Identify risk factors for heart failure like hypertension, diabetes, and atrial fibrillation and treat them to prevent or delay the development of heart failure.
• In HF with reduced EF, titrate beta-blockers and either ACE inhibitors or ARBs to doses used in studies, or the highest dose tolerated by patients.
• Determine which patients who have symptomatic HF with reduced EF even when on ACE inhibitor or ARB are candidates for sacubitril/valsartan (Entresto) as a substitute for the ACE inhibitor or ARB.
• In patients presenting with HF with preserved EF, treat hypertension and manage comorbidities to control symptoms.
• After HF hospitalization, address possible medication non-adherence, review weight goals and reinforce salt or fluid restriction.
• Discuss goals of care and advance directives for patients with severe, end-stage HF.
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Setting the stage

Heart failure (HF) is a complex clinical syndrome resulting from a structural or functional impairment of ventricular filling or the ejection of blood.¹ Fundamentally, HF means the heart can’t pump enough blood to meet the body’s needs. HF can be classified in terms of the ejection fraction (EF), which is the amount of blood pumped out of the left ventricle with each cardiac cycle divided by the total amount of blood in the ventricle at the end of diastole. The point at which the EF is considered “preserved” or “reduced” is not absolute, although an EF of 55% or higher is often considered “normal.” Some clinical trials have defined “reduced” EF as ≤40% or ≤35%. Other trials have defined “preserved” EF as anywhere between >40% and >55%.¹

In this document the terms “heart failure with reduced ejection fraction” (HFrEF) and “heart failure with preserved ejection fraction” (HFpEF) will be used, with HFrEF defined as EF ≤40% and HFpEF defined as EF ≥50%.

Table 1: Heart failure classifications

<table>
<thead>
<tr>
<th>Classification</th>
<th>EF (%)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure with reduced ejection</td>
<td>≤40%</td>
<td>Also referred to as systolic HF.</td>
</tr>
<tr>
<td>fraction (HFrEF)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure with preserved ejection</td>
<td>≥50%</td>
<td>Also referred to as diastolic HF.</td>
</tr>
<tr>
<td>fraction (HFpEF)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HFpEF, borderline</td>
<td>41-49%</td>
<td>Characteristics, treatment patterns, and outcomes similar to patients with HFpEF.</td>
</tr>
<tr>
<td>HFpEF, improved</td>
<td>&gt;40%</td>
<td>Subset of patients with HFpEF who previously had HFrEF.</td>
</tr>
</tbody>
</table>

HFrEF and HFpEF can be difficult to distinguish by history, physical exam, and on many diagnostic tests (including EKG, chest x-ray, and laboratory testing). An echocardiogram is usually required to make a definitive distinction. Currently in the U.S. about half of HF cases are categorized as HFrEF and half as HFpEF. Morbidity and mortality rates for the two types are similar, with 1-year hospital admission rates of about 50% and 1-year mortality rates of approximately 22-29%.²

The pathophysiology of HF can affect both the left and right ventricles; chronic left ventricle (LV) dysfunction with high LV and pulmonary pressures will eventually lead to structural changes and right ventricular dysfunction. Isolated right ventricular (RV) HF is frequently associated with chronic lung disease (such as COPD, chronic pulmonary emboli, or pulmonary hypertension).

A commonly-used classification of HF symptom severity was developed by the New York Heart Association (Table 2). In this scheme, patients can move between classes. For example, during an HF exacerbation they may be in Class III but they may return to Class I or II after effective medical therapy.
Table 2: New York Heart Association HF classes

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No limitation on physical activity. Ordinary physical activity does not cause symptoms of HF.</td>
</tr>
<tr>
<td>II</td>
<td>Slight limitation of physical activity. Comfortable at rest, but ordinary activity causes symptoms of HF.</td>
</tr>
<tr>
<td>III</td>
<td>Marked limitation of physical activity. Comfortable at rest but less than ordinary activity causes symptoms of HF.</td>
</tr>
<tr>
<td>IV</td>
<td>Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.</td>
</tr>
</tbody>
</table>

The American College of Cardiology Foundation and American Heart Association (ACCF/AHA) have also developed a classification scheme that focuses on the progressive stages of HF, which are irreversible as patients move from one to the other (Table 3). As described later in this document, categorizing a patient’s HF class or stage can provide a helpful framework on which to base treatment and management decisions.

Table 3: Comparison of HF classification schemes

<table>
<thead>
<tr>
<th>ACCF/AHA Stages of HF</th>
<th>NYHA Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At high risk for HF but w/out structural heart disease or symptoms of HF</td>
</tr>
<tr>
<td>B</td>
<td>Structural heart disease but <strong>without signs or symptoms of HF</strong></td>
</tr>
<tr>
<td>C</td>
<td>Structural heart disease with <strong>prior or current symptoms of HF</strong></td>
</tr>
<tr>
<td>D</td>
<td><strong>Refractory HF</strong> requiring specialized interventions</td>
</tr>
</tbody>
</table>

HF is a major cause of morbidity and mortality, affecting 5.8 million people in the U.S., with that number expected to rise to 8 million by 2030.\textsuperscript{3,4} Approximately 825,000 new cases of HF are diagnosed each year, with prevalence rising steeply with age. Figure 1 shows representative prevalence rates by age and sex.\textsuperscript{3}
HF is associated with high mortality: about 20% of people with symptomatic HF die within a year of diagnosis and about half die within 5 years of diagnosis. Medical expenditures related to HF in the U.S. were about $31 billion in 2012, a figure expected to rise to $70 billion by 2030.

Although the morbidity and mortality associated with HF are high, the appropriate use of evidence-based treatments can prolong life and improve its quality. This module reviews evidence-based practices for the evaluation and management of HF in primary care settings.

**Risk factors and associated conditions**

Coronary heart disease is the largest risk factor for HF (with risk higher in men than in women), although diabetes and several other conditions also confer significant risk (Figure 2).
HF is also causally associated with a wide range of conditions, summarized in Table 4.

Table 4: Conditions associated with, or contributing causally to, HF

<table>
<thead>
<tr>
<th>Primary cardiovascular disease</th>
<th>Primary pulmonary disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Dilated cardiomyopathy/ familial</td>
<td>• Pulmonary hypertension</td>
</tr>
<tr>
<td>• Hypertrophic/ restrictive cardiomyopathy</td>
<td>• COPD</td>
</tr>
<tr>
<td>• Valvular dysfunction</td>
<td>• Obstructive sleep apnea</td>
</tr>
<tr>
<td>• Myocarditis/ pericarditis</td>
<td></td>
</tr>
<tr>
<td><strong>Toxin related</strong></td>
<td><strong>Infiltrative disease</strong></td>
</tr>
<tr>
<td>• Alcohol</td>
<td>• Amyloid</td>
</tr>
<tr>
<td>• Cocaine</td>
<td>• Cardiac sarcoid</td>
</tr>
<tr>
<td>• Chemotherapy (e.g. doxorubicin, trastuzumab)</td>
<td>• Glycogen storage diseases</td>
</tr>
<tr>
<td><strong>Endocrinopathies</strong></td>
<td></td>
</tr>
<tr>
<td>• Thyroid disease</td>
<td><strong>Other</strong></td>
</tr>
<tr>
<td>• Acromegaly/GH deficiency</td>
<td>• Lupus/ rheumatoid arthritis</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>• HIV</td>
</tr>
<tr>
<td>• Peripartum</td>
<td>• Peripartum</td>
</tr>
<tr>
<td>• Stress-induced</td>
<td></td>
</tr>
</tbody>
</table>

Evaluation

Patients with symptoms of new HF should be interviewed about past and present symptoms, when symptoms occur, and how/when the symptoms started. They should be queried about present and past use of alcohol, drugs, or chemotherapy agents, and all co-morbid conditions (e.g., ischemic heart disease, hypertension, obstructive sleep apnea, HIV, COPD).
Physical exam and history

Table 5: Components of a focused HF history

<table>
<thead>
<tr>
<th>Component</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Etiology of HF (cardiac and non-cardiac causes)</td>
<td></td>
</tr>
<tr>
<td>• Take a 3-generation history (dilated cardiomyopathy)</td>
<td></td>
</tr>
</tbody>
</table>
| • Symptoms | — Durations of symptoms  
— Triggers of dyspnea  
— Exercise capacity, fatigue, dyspnea  
— Palpitations, pre-syncope, implantable cardioverter defibrillator shocks  
— Presence of chest pain  
— Peripheral edema, ascites  
— Sleep problems (sleep apnea, orthopnea) |
| • Weight | — Gain: possible volume overload |
| • Medications that can exacerbate HF (e.g., NSAIDs) | |
| • Diet | — Sodium and fluid intake |
| • Recent or frequent hospitalizations | |

The following physical exam findings are common in patients with HF, although no single finding is particularly sensitive or specific:¹

• vital signs  
  — blood pressure (elevated or reduced)  
  — tachycardia  
  — weight gain  
• jugular venous pressure elevation  
• heart sounds  
  — extra heart sounds (S3, S4)  
  — murmurs suggest valvular heart disease  
• pulmonary status  
  — respiratory rate, rales, pleural effusion  
• hepatomegaly and/or ascites  
• peripheral edema

Lab tests during the initial workup of patients with HF may help determine etiology, rule out other conditions, or help guide management, and should include:⁹,¹⁰

• complete blood count  
• thyroid-stimulating hormone  
• urinalysis
Treating heart failure in primary care

- fasting glucose and lipid profile
- urinalysis
- liver function tests
- blood urea nitrogen and serum creatinine
- serum electrolytes (including magnesium and calcium)

Other lab testing should only be done if the history or exam suggests an unusual cause of HF (such as Cushing’s disease, HIV, or an infiltrative disease). Check cardiac enzymes (troponin I or T) if acute ischemia is suspected.

Brain natriuretic peptide (BNP) testing

BNP is a natriuretic hormone released primarily from the heart. It is generated by myocytes in the presence of triggers such as myocardial "stretch" or other conditions. It can be measured in serum to help determine if symptoms, such as dyspnea, are due to HF (see Table 6). Two tests measure different sections of the same hormone: the BNP test and the N-terminal pro-BNP test.

Care should be taken in interpreting BNP test results, however, because the levels of natriuretic peptides may be elevated by a wide range of cardiac and non-cardiac conditions (e.g., valvular heart disease, atrial fibrillation, anemia, renal failure, bacterial sepsis). Higher BNP values are typically seen in older adults, women, and patients with atrial fibrillation.

Table 6: BNP and NT-proBNP diagnostic values

<table>
<thead>
<tr>
<th>BNP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100 pg/mL</td>
<td>Unlikely HF</td>
</tr>
<tr>
<td>100-400 pg/mL</td>
<td>Borderline</td>
</tr>
<tr>
<td>&gt;400 pg/mL</td>
<td>Suspect HF</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NT-proBNP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;300 pg/mL</td>
<td>Unlikely HF</td>
</tr>
<tr>
<td>&gt;450 pg/mL</td>
<td>Suspect HF in patients &lt;50 years</td>
</tr>
<tr>
<td>&gt;900 pg/mL</td>
<td>Suspect HF in patients 50-75 years</td>
</tr>
<tr>
<td>&gt;1800 pg/mL</td>
<td>Suspect HF in patients &gt;75 years</td>
</tr>
</tbody>
</table>

BNP testing may also help determine the prognosis of a HF patient. Elevated BNP levels are generally predictive of worse HF outcomes. In the Val-HeFT trial of 4300 patients with HFrEF, patients with the greatest percent decrease in BNP from baseline at 4 and 12 months had the lowest rates of morbidity and mortality, whereas patients with greatest percent increase in BNP had the highest morbidity and mortality.

BNP-guided therapy may improve mortality in HFrEF patients <74 years old but the evidence is mixed. In a meta-analysis of 8 randomized controlled trials that included 1,726 patients, mortality was reduced by 24% in the BNP-guided group compared to standard of care (RRR 0.76 CI 0.63 to 0.91; p=0.003), although no benefit was seen in patients >75 years. Patients in the BNP-guided group were more likely to achieve target doses of ACE inhibitors and beta-blockers, but given the heterogeneity of results, BNP-guided therapy is not broadly recommended.

6 | Treating heart failure in primary care
Non-invasive testing

An EKG and echocardiogram are both routinely performed in patients with new or worsening HF signs/symptoms. An EKG is valuable in determining the heart rate and rhythm (which may affect management), the presence of left ventricular hypertrophy, abnormal conduction, or Q waves suggesting prior myocardial infarction. An echocardiogram is valuable for assessing a number of structural cardiac elements that can affect patient management, including the LV EF, diastolic function or dysfunction, valvular function (stenosis or regurgitation), pericardial size/effusions, and inferior vena caval pressures. The chest X-ray can be valuable for ruling in or ruling out HF as the etiology of the patient’s symptoms (the typical findings in HF include interstitial edema and vascular congestion).

More sensitive cardiac imaging should be performed only in selected patients and most often in conjunction with a cardiologist. Cardiac MRI is a good diagnostic test for suspected myocardial pathology (such as infiltrative diseases) or pericardial pathology (such as malignant effusions). Cardiac CT (with or without CT angiogram) can detect cardiac vascular calcifications/stenosis, although the significance of these findings for management is not always clear and the testing carries the risks of radiation and contrast. A number of different types of cardiac nuclear perfusion scans can be performed if cardiac ischemia is suspected, the type of which will depend on locally available technology and cardiology preferences. These should be performed in patients whose HF etiology is not known after physical exam, laboratory testing, and EKG/echocardiography.

Invasive testing

Further invasive testing for patients with new or worsening HF should be dictated by the suspicion of the etiology of the HF. For patients with suspected or confirmed cardiac ischemia, cardiac catheterization may be pursued for diagnostic and/or therapeutic purposes. For patients with suspected myocarditis or myocardial infiltrative diseases, a myocardial biopsy may be appropriate.

Pulmonary disease work up

Patients with a history suggestive of obstructive sleep apnea (OSA) should be referred for a diagnostic sleep study, and for OSA management if sleep results are positive. Pulmonary function tests should be ordered on those with symptoms of COPD (chronic cough or sputum production, especially in smokers or those exposed to second hand smoke). A workup for chronic thromboembolic disease should be undertaken for those with suspected (or history of) venous thromboembolic disease.
Overview of HF management in primary care

The details of managing HF are driven by a patient’s HF stage, as outlined below. These are based on the ACCF/AHA staging system, which describes a patient’s progressive and irreversible pathophysiological changes over time. This system tries to help clinicians focus on how HF develops over time and, accordingly, begins with Stage A, in which patients do not actually have HF, but have an increased risk of HF, that can be reduced with treatment of their individual risk factors.

Figure 3: Management of patients by ACCF/AHA stage

<table>
<thead>
<tr>
<th>STAGE</th>
<th>MANAGEMENT STRATEGY</th>
</tr>
</thead>
</table>
| STAGE A: At risk for developing HF | • Urge lifestyle modification (e.g., diet, weight loss, exercise).  
• Treat comorbidities (e.g., hypertension, diabetes, hyperlipidemia, atrial fibrillation). |
| STAGE B: Asymptomatic with structural heart disease* | • Continue to treat comorbidities and recommend lifestyle modification.  
• Monitor for development of HF symptoms.  
Additional treatment for reduced EF patients only:  
• Initiate beta blockers and ACE inhibitors or ARBs.*  
• Use implantable cardioverter-defibrillators (ICDs) in post-MI patients. |
| STAGE C: Symptomatic Prior or current symptoms of HF | • Continue to treat comorbidities and recommend lifestyle modification.  
• Educate patients on self-care (e.g., salt restriction and HF symptoms).  
Additional treatment for reduced EF patients only:  
• Initiate beta blockers and an ACE inhibitor or ARB w/diuretics.  
Escalate pharmacologic treatment based on symptoms.  
• Utilize ICDs or cardiac resynchronization therapy (CRT). |
| STAGE D: Refractory or advanced HF | • Refer to cardiology for advanced therapies, such as left ventricular assist device (LVAD) or heart transplant, when indicated.  
• Discuss end-of-life treatment goals, as appropriate. |

Source: American College of Cardiology Foundation and American Heart Association

* Structural heart disease: left ventricular (LV) hypertrophy, LV dysfunction, prior myocardial infarction, or valvular disease

*ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker

Note that treating hypertension in Stage A patients, particularly in the elderly, can significantly lower the risk for HF, as illustrated in Figure 4.
In keeping with the recognition that HF develops over time, stage B (Figure 3 above) includes patients who have developed structural heart disease but are not yet symptomatic. Patients with Stage B HF (with either preserved or reduced ejection fraction) should be treated for hypertension, if needed, as well as with statins as appropriate. Patients with reduced EF should also be treated with an ACE inhibitor (ACEI) or an angiotensin receptor blocker (ARB); and a beta blocker. Non dihydropyridine calcium channel blockers (CCBs) should be avoided. Treatment of these patients can reduce or delay the development of HF symptoms. In patients with reduced EF and a prior myocardial infarction (MI), all of the above therapies should be used and an implantable cardioverter defibrillator (ICD) should be considered if the EF is less than 30% and the patients is more than 40 days post-MI.

Patients with symptomatic HF (Stages C & D) should be treated with evidence-based pharmacologic therapies, as appropriate. For those with reduced EF, devices such as ICDs and cardiac resynchronization therapy (CRT) may be appropriate.

**Non-pharmacological management**

**Dietary management**

Sodium restriction is routinely recommended in patients with symptomatic HF, although this is not based on clinical trials. Excess sodium commonly precipitates HF exacerbations and is a frequent cause of HF admissions. However, improvement in clinical outcomes with a reduced sodium diet has not been consistently demonstrated in studies. Recommendations for sodium intake for patients with symptomatic HF range from <2000 mg/day to <3000 mg/day. A lower sodium diet has been shown to reduce blood pressure and cardiovascular events in patients with hypertension, therefore, for patients who are at risk of HF or have asymptomatic HF, especially those with hypertension, a lower sodium diet is recommended.
ACCF/AHA HF Guidelines for sodium intake:

- HF stages A and B: <1500 mg/day
- HF stages C and D: <3000 mg/day

Some patients with HF will also need to restrict their fluid intake. Limiting fluid intake to around two liters per day is usually needed for most hospitalized patients, however fluid restriction is less commonly used in ambulatory patients who are not diuretic resistant or significantly hyponatremic.

**Treatment for sleep apnea**

Approximately 11% of patients with HF have obstructive sleep apnea and up to 40% have central sleep apnea. Apneic episodes can trigger the activation of sympathetic nervous system hormones that are detrimental to patients with HF, since they increase heart rate and blood pressure. Treatment of sleep apnea can improve cardiac function and symptoms. In a controlled trial, 258 patients with systolic HF (mean EF 25%) and sleep apnea were randomized to continuous positive airway pressure (CPAP) or no CPAP; the CPAP group had modest but significant increases in six minute walk tests (by about 20 meters) and ejection fraction (by about 2%), but there were no significant differences between the groups in HF hospitalizations or mortality.

**Cardiac rehabilitation and exercise**

Cardiac rehabilitation that combines exercise, self-care education, and psychological support was shown to improve functioning and quality of life in elderly patients with HFrEF. The 6-month study of patients >60 years old with NYHA Class II or III HFrEF found significant improvements in a 6-minute walking test and a measure of quality of life. In addition, the patients undergoing cardiac rehabilitation had fewer hospitalizations and spent fewer days in the hospital. Despite this supportive evidence, cardiac rehabilitation remains underused. In light of the recent decision by the Centers for Medicare & Medicaid Services to include HFrEF as an eligible diagnosis, more effort should be made to use cardiac rehabilitation for appropriate patients.

Exercise training alone may improve the quality of life for patients with HF, but has not been shown to improve mortality. A large trial evaluated 2,331 stable outpatients with HFrEF (median EF 25%) who were randomized to 36 sessions (over three months) of supervised exercise training or usual care. After 30 months of follow up, the exercise group had improved HF symptoms and extended exercise duration. An 11% improvement in the combined endpoint of death or HF hospitalization was seen after controlling for important clinical conditions.

Exercise training has been less well studied in those with HFrEF, but does appear to be safe and modestly effective. A small randomized trial of older women with HFrEF found that a 12 week home-based exercise program improved their six minute walk test by about 300 feet, and significantly increased their quality of life, with no adverse events.
Weight monitoring
Patients with HF should weigh themselves daily on the same scale at the same time of day, ideally first thing in the morning, with instructions to phone their physician or to use extra diuretic if weight exceeds a given level. Daily weights can often be used in concert with a telemonitoring program, to adjust the regimen based on the weight.

Vaccines
Influenza (annually) and pneumococcal (when indicated) vaccines are important for all patients with HF.

Smoking and alcohol
Smoking cessation counseling and medical therapy should be offered to all patients with HF who are currently smoking. Medical therapy consists of nicotine replacement (in any form, e.g., patch, gum, inhaler) and either bupropion or varenicline. Bupropion is safe and effective in patients with heart disease. Based on current data, varenicline is likely safe in the post-myocardial infarction setting, but caution is still advised in patients at highest risk with active cardiovascular disease. All patients with HF should refrain from excessive alcohol intake (>1-2 drinks a day). Those with alcoholic cardiomyopathy should refrain completely.

Pharmacological management of HFrEF
While some pharmacologic therapies for HFrEF only reduce symptoms (e.g., diuretics), others can reduce hospitalizations and death (e.g., ACE inhibitors, ARBs, and beta blockers). Many of the effective pharmacologic therapies used in HF work by inhibiting some component of the sympathetic nervous system (e.g., beta blockers) or the renin-angiotensin-aldosterone system (e.g., ACE inhibitors or aldosterone antagonists). Other agents, such as diuretics, work by increasing sodium and water loss through the kidneys (i.e., natriuresis/diuresis). When used correctly, these agents can effectively reduce the morbidity and mortality associated with HF.

This section reviews pharmacological therapies with proven benefit for HFrEF patients:

- diuretics
- ACE Inhibitors
- ARBss
- beta blockers
- aldosterone antagonists
- digoxin

Since approximately 80% of HF patients are age 65 or older, clinicians must be mindful of the many ways that geriatric conditions can impact the use of medications and the potential complications arising from complex polypharmacy. Elderly patients are more likely to have contraindications to HF medications and are more susceptible to side effects. The general principles of geriatric prescribing apply: start low, go slow; titrate up as possible; increase the frequency of lab and vital sign monitoring.
Some therapies should be specifically avoided in patients with HF:

- calcium channel blockers (non-dihydropyridine)
- NSAIDs
- many anti-arrhythmics
- thiazolidinediones (glitazones)

**Diuretics**

The goal of using diuretics in patients with heart failure is to achieve euvolemia and reduce symptoms of congestion, such as shortness of breath or peripheral edema. A patient’s “dry weight” is generally the lowest measured weight of the patient, performed first thing in the morning, on a day when functional status is at its best: this should be the daily target weight. Patients should be encouraged to check their weight daily, and manage their diuretics based on this. This plan can be determined in advance (e.g., “If you gain more than 1 kg in weight in a day, take an extra dose of x mg of furosemide”). The plan may involve a telemedicine component, discussed further below. Diuretics should be combined with salt restriction, and in some cases fluid restriction, for maximal efficacy.¹⁰

**Figure 4: Diuretic types and site of effects on nephron**

Diuretics are primarily used to treat clinical signs and symptoms of volume overload. A meta-analysis of randomized placebo-controlled trials of diuretics (primarily loop or thiazide diuretics) found that these drugs reduce the risk of death in patients with HF, although sample sizes were small and confidence intervals wide.²⁷ Diuretics also improved exercise capacity, and reduced the risk of worsening HF (odds ratio 0.31; 95% CI 0.15 to 0.62; p=0.001).²⁷
**Loop diuretics**

Loop diuretics induce greater sodium excretion than any other diuretic type. Furosemide is most commonly used, based on its low cost and effectiveness in most patients. Torsemide and bumetanide have better and more predictable oral absorption than furosemide, and can be used in patients with poor oral absorption, such as that caused by right-sided heart failure and bowel edema. Dosing of loop diuretics generally needs to be higher with impaired renal function. Ethacrynic acid is a loop diuretic but not a sulfonamide, so it can be used in patients with sulfa allergy, although it is rarely used otherwise due to higher risk of ototoxicity. Starting dose of furosemide in treatment-naïve patients is 20-40 mg daily. Non-responders should be treated with increasing doses rather than increasing frequency of medication.

**Thiazides**

Thiazides cause less sodium excretion compared to loop diuretics but when used together the combination can cause potent diuresis. If patients continue to have hypervolemia despite adequate doses of loop diuretics, a thiazide can be added temporarily, or on an as-needed basis (based on weight or symptoms). Chronic daily use of thiazides combined with a loop diuretic is discouraged, given the risk of electrolyte depletion and volume depletion, and these patients should be very closely followed. Chlorthiazide or metolazone are the most commonly used in HF.

**Dosing**

**Table 7: Initial and maximum daily doses for common diuretics**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial daily dose</th>
<th>Maximum label total daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loop</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bumetanide (Bumex)</td>
<td>0.5-1 mg daily or BID</td>
<td>10 mg</td>
</tr>
<tr>
<td>Furosemide (Lasix)</td>
<td>20-40 mg daily or BID</td>
<td>600 mg</td>
</tr>
<tr>
<td>Torsemide (Demadex)</td>
<td>10-20 mg daily</td>
<td>200 mg</td>
</tr>
<tr>
<td><strong>Thiazide</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorothiazide (Diluril)</td>
<td>250-500 mg daily or BID</td>
<td>1000 mg</td>
</tr>
<tr>
<td>Hydrochlorothiazide (Microzide)</td>
<td>25 mg daily or BID</td>
<td>200 mg</td>
</tr>
<tr>
<td>Metolazone (Zaroxolyn)</td>
<td>2.5 mg daily</td>
<td>20 mg</td>
</tr>
</tbody>
</table>

**Safety**

All diuretics can cause electrolyte and metabolic disturbances (e.g., hypokalemia, hyperuricemia), which are generally dose-dependent.

**BOTTOM LINE:** Diuretics are primarily used to improve symptoms and volume status in patients with HF. Loop diuretics, such as furosemide, are first-line therapy; torsemide and bumetanide may have better oral absorption than furosemide, and ethacrynic acid can be used for sulfonamide allergic patients. This class can be combined with thiazides to enhance diuresis, but serum electrolytes should be followed closely. Patients should be monitored for adverse effects of diuretics, primarily electrolyte derangements and renal dysfunction.
**ACE inhibitors**

ACE inhibitors are first line therapy for all patients with HF; the most benefit occurs in those with symptomatic HFrEF. In the landmark CONSENSUS trial, patients with NYHA class IV HF randomized to enalapril (2.5 mg to 40 mg daily) had significantly lower 6-month mortality than those randomized to placebo (26% versus 44%; 40% relative reduction; p=0.002). A subsequent large randomized trial of patients with less symptomatic HF and EF <35% (SOLVD) found a significant 16% relative reduction in mortality and heart failure hospitalizations in those randomized to enalapril versus placebo (Figures 5-6). ACE inhibitors also significantly reduce mortality, HF hospitalizations, and incidence of HF symptoms in asymptomatic patients with reduced EF (<40%).

**Figure 5:** Percent mortality in patients with reduced EF (<35%) in enalapril versus placebo (SOLVD trial)
Figure 6: Reduction in morality and HF hospitalizations in asymptomatic patients with low EF (<40%) with enalapril versus placebo.

A meta-analysis of four ACEIs (captopril, enalapril, ramipril, and trandolapril) shows that the benefits of ACEIs are a class effect (Figure 7).
Sub-group analyses from the SOLVD and V-HeFT trials found that the survival benefit of ACE inhibitors was seen in white HF patients and not in black HF patients. Given that this effect has only been studied in subgroup analyses, the current guidelines recommend that ACE inhibitors be used as first line treatment for HFrEF in all patients, regardless of race.

**Dose and type**

The goal dose of ACE inhibitor should be consistent with those used in clinical trials. In general, a low dose of an ACEI is better than no ACEI, but clinical trials demonstrated better outcomes with higher doses. The ATLAS trial, for example, compared low-dose (2.5–5 mg/day) to standard-dose (32.5–35 mg/day) lisinopril and found that the standard dose resulted in a non-significant 8% lower mortality, but a significant 24% reduction in hospitalization. There were higher rates of dizziness and hypotension in the standard-dose group, but similar rates of discontinuation between the groups. Given this, patients should be titrated to the highest tolerable dose (without adverse effects), being mindful that any dose is beneficial. No data support the superiority of any one ACE inhibitor over another.
Table 8: ACE-inhibitor dosing

<table>
<thead>
<tr>
<th>ACE-inhibitor</th>
<th>Initial dose</th>
<th>Maximum dose</th>
<th>Mean doses achieved in trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>6.25 mg TID</td>
<td>50 mg TID</td>
<td>123 mg/day</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 mg BID</td>
<td>10-20 mg BID</td>
<td>17 mg/day</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>5-10 mg daily</td>
<td>40 mg daily</td>
<td></td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5-5 mg daily</td>
<td>20-40 mg daily</td>
<td>35 mg/day</td>
</tr>
<tr>
<td>Perindopril</td>
<td>2 mg daily</td>
<td>8-16 mg daily</td>
<td></td>
</tr>
<tr>
<td>Quinapril</td>
<td>5 mg BID</td>
<td>20 mg BID</td>
<td></td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25-2.5 mg daily</td>
<td>10 mg daily</td>
<td></td>
</tr>
<tr>
<td>Trandolapril</td>
<td>1 mg daily</td>
<td>4 mg daily</td>
<td></td>
</tr>
</tbody>
</table>

Safety

Although most HF patients (85%-90%) can tolerate ACEIs, some side effects (e.g., dizziness, cough) are common, and other adverse events (e.g., elevated serum potassium or creatinine levels, angioedema) are possible. If cough is a serious side effect, consider switching to an ARB.

BOTTOM LINE: ACE inhibitors should be first-line therapy for most patients with HF. In patients with HFrEF, regardless of symptoms, ACE inhibitors reduce morbidity and mortality. Any dose and any type of ACE inhibitor is beneficial; higher doses may reduce hospitalizations, but are associated with higher risks of adverse events. Titrate to the maximally tolerated dose and only use lower doses if necessary. Cough is best addressed by switching to an ARB. Avoid abrupt withdrawal.

Angiotensin Receptor Blockers (ARBs)

Like ACE inhibitors, ARBs have been shown to reduce mortality and hospitalizations in patients with HFrEF, although this literature is smaller than that supporting ACE inhibitors. The CHARM Alternative trial studied patients with HFrEF who were intolerant of ACEIs. Those treated with candesartan had a 23% reduction in their risk for cardiovascular death or hospital admission for HF compared with those on placebo (Figure 9).
Combining an ARB with an ACEI was studied in the V-HeFT trial. Patients with HFrEF with mild-severe symptoms on optimal medical therapy (including an ACEI) were randomized to valsartan or placebo. The trial found that combination therapy (ARB and ACEI) compared to ACEI alone was associated with significant reductions in the combined outcome of morality, cardiac arrest, HF hospitalization, or IV inotrope/vasodilator for 4 hours. However combination therapy had an adverse effect on mortality among patients taking an ACEI, ARB, and beta blocker. In meta-analyses, combination therapy is associated with a 37% higher risk of medication discontinuation due to adverse events. Therefore combination therapy with an ACEI and ARB is not recommended.

A 2012 meta-analysis of 22 studies evaluated the effects of ARBs in 17,900 patients with EF ≤40% (mean 2.2 years). Compared to ACEIs, ARBs were associated with similar rates of mortality and hospitalizations. The difference in mortality and hospitalization rates between placebo and ARBs, did not reach statistical significance, however ARBs did have a trend towards improved rates. Furthermore, withdrawal due to adverse effects were 37% lower with ARBs compared to ACEIs (RR 0.63 [95% CI 0.52, 0.76]). Because large randomized, placebo-controlled trials, such as CHARM Alternative, demonstrated a positive clinical effect of ARBs in patients unable to tolerate ACEIs, ARBs are considered alternative first-line therapy to ACEIs in patients with HFrEF.
Dose and type

As with ACEIs, the goal of ARB dosing should be to titrate up to a maximally tolerated dose. Higher doses of ARBs have greater clinical impact but are associated with more adverse events, such as renal insufficiency or hyperkalemia. Thus patients undergoing dose titration must be monitored closely. Clinical benefit is still seen even if the maximally tolerated dose is lower than doses studied in clinical trials.\(^{38}\)

Table 9: Dosing for ARBs\(^{1}\)

<table>
<thead>
<tr>
<th></th>
<th>Initial dose</th>
<th>Maximum dose</th>
<th>Mean doses achieved in trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>4-8 mg daily</td>
<td>32 mg daily</td>
<td>24 mg/day</td>
</tr>
<tr>
<td>Losartan</td>
<td>25-50 mg daily</td>
<td>50-150 mg daily</td>
<td>129 mg/day</td>
</tr>
<tr>
<td>Valsartan</td>
<td>20-40 mg BID</td>
<td>160 mg BID</td>
<td>254 mg/day</td>
</tr>
</tbody>
</table>

Safety

Side effects of ARBs are similar to ACEIs except that ARBs pose a lower risk of cough and angioedema and a higher rate of hypotension. In the CHARM-overall trial, ARBs were significantly more likely than placebo to cause hypotension, as well as a significant increase in serum creatinine and potassium.\(^{39}\)

BOTTOM LINE: in patients with HFrEF, ARBs reduce morbidity and mortality. Guidelines recommend an ACEI as first line therapy for patients with current or prior symptoms, and ARBs in those who cannot tolerate an ACEI or who are already on an ARB for another indication. ACEIs and ARBs should not be routinely combined due to the increased risk of adverse effects.

Not all patients can tolerate ACEIs or ARBs: avoid in patients with severe renal artery stenosis, systolic BP <80 mmHg; serum creatinine >3 mg/dL; and serum potassium >5 mEq/L.

Beta blockers

Beta blockers can target various adrenergic receptors:

- \(\beta_1\)-receptor blockade: slows heart rate
- \(\beta_2\)-receptor blockade: causes smooth muscle contraction, including bronchospasm
- \(\alpha\)-receptor blockade: causes peripheral vasodilation

Bisoprolol and metoprolol are \(\beta_1\)-selective, while carvedilol has activity at \(\beta_1\), \(\beta_2\), and \(\alpha\) receptors. Beta blockers are routinely recommended in all patients with HFrEF who are already on an ACEI and still symptomatic. This is based on the randomized controlled trials summarized in Table 10.
Table 10: Efficacy of beta blockers in heart failure by trial and outcome

<table>
<thead>
<tr>
<th>Trial (drug)</th>
<th>Patient type studied and mean follow up</th>
<th>Primary outcome: All cause mortality (beta blocker versus placebo)</th>
<th>Secondary outcomes (beta blocker versus placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIBIS-II (bisoprolol)</td>
<td>EF&lt;35% NYHA class II-IV 15 months</td>
<td>12% vs 17% (p&lt;0.0001)</td>
<td>Sudden cardiac death 4% vs 6% (p=0.001)</td>
</tr>
<tr>
<td>MERIT-HF (metoprolol CR/XL)</td>
<td>EF&lt;40% NYHA class II-IV 12 months</td>
<td>7% vs 11% (p=0.006)</td>
<td>Sudden cardiac death 4% vs 7% (p=0.0002)</td>
</tr>
<tr>
<td>Carvedilol Prospective Randomized Cumulative Survival Study Group (carvedilol)</td>
<td>EF&lt;25% NYHA class III-IV 10 months</td>
<td>11% vs 17% (p=0.001)</td>
<td>Death or hospitalization 37% vs 45% (p&lt;0.001)</td>
</tr>
</tbody>
</table>

Dose and type

If a beta-blocker is started, it should be titrated to the highest tolerated dose. One randomized trial found a benefit of higher versus lower dosing of carvedilol on left ventricular function and mortality at 6 months in patients with HFrEF. Beta blockers differ in their pharmacological profiles and, therefore, a class effect cannot be assumed and only one of the three beta blockers that have been studied in heart failure is recommended.

Carvedilol was compared to short-acting metoprolol (metoprolol tartrate) in the COMET trial, which enrolled heart failure patients with HFrEF. Patients taking carvedilol had a 17% lower risk of death comparing to patients taking metoprolol tartrate (HR 0.83; 95% CI 0.74-0.93; p=0.0017). Therefore short-acting metoprolol tartrate is not recommended for the long-term treatment of patients with heart failure. One concern with this study was the lower dosing of metoprolol tartrate; some authors have speculated that improved results might have been seen with more frequent dosing.

Table 11: Mortality rates after treatment with carvedilol in HFrEF

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mortality (at 6 mo.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>16%</td>
</tr>
<tr>
<td>Low-medium dose carvedilol (6.25 mg-12.5 mg BID)</td>
<td>6-7%</td>
</tr>
<tr>
<td>High dose carvedilol (25 mg BID)</td>
<td>1%</td>
</tr>
</tbody>
</table>

Indirect evidence suggests that carvedilol (which has vasodilating effects) may be superior to non-vasodilating beta blockers (e.g., bisoprolol or metoprolol). A meta-analysis of 21 trials in almost 6,000 HF patients (with both reduced and preserved EF) found that overall mortality reduction was greater with carvedilol than the other beta blockers (54% versus 27%; p=0.007), particularly in patients without ischemic...
heart disease. Carvedilol lowers blood pressure more than the other agents, and may be the best agent in patients who also have hypertension.

Table 12: Beta blocker dosing

<table>
<thead>
<tr>
<th></th>
<th>Initial daily dose</th>
<th>Maximum dose</th>
<th>Mean dose achieved in trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg daily</td>
<td>10 mg daily</td>
<td>8.6 mg/day</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg BID</td>
<td>50 mg BID</td>
<td>37 mg/day</td>
</tr>
<tr>
<td>Carvedilol CR</td>
<td>10 mg daily</td>
<td>80 mg daily</td>
<td></td>
</tr>
<tr>
<td>Metoprolol XL</td>
<td>12.5-25 mg daily</td>
<td>200 mg daily</td>
<td>159 mg/day</td>
</tr>
</tbody>
</table>

Safety

In HF clinical trials, beta blockers were very well tolerated, with discontinuation rates lower than those for placebo.

Side effects of beta blockers include:
- Fluid retention and worsening HF (may improve with intensification of other therapies (e.g. diuretics)
- Fatigue, sexual dysfunction
- Bradycardia or heart block
- Hypotension (reduce diuretic therapy as appropriate; stagger dosing with ACEI)

Absolute contraindications for beta blockers include:
- Third degree heart block
- History of severe bronchospasm

Relative contraindications:
- Bradycardia <60 bpm
- Symptomatic hypotension
- Severe peripheral arterial disease

BOTTOM LINE: beta-blockers should be used in all patients with HFrEF who have current or prior HF symptoms. Dose of ACEI or ARB does not need to be maximized before starting a beta blocker. Guidelines recommend carvedilol CR (controlled release), metoprolol XL (extended release), or bisoprolol. Short-acting metoprolol is not recommended.

Dose should be titrated to the lowest tolerated heart rate. Continue with a beta blocker even if symptoms do not improve, unless intolerance or significant side effects are present. As with ACEIs and ARBS, try to avoid abrupt withdrawal.
Aldosterone-receptor antagonists

Two mineralocorticoid receptor antagonists are currently available in the United States: spironolactone and eplerenone. Although both medications block activity at the aldosterone receptor, eplerenone is more selective. While numerous clinical trials have evaluated the efficacy of each drug, no studies have directly compared spironolactone and eplerenone. Both have been shown to improve morbidity and mortality in patients with HFrEF, although both also increase the risk of hyperkalemia.

Table 13: Aldosterone antagonist study results

<table>
<thead>
<tr>
<th>Drug studied</th>
<th>RALES 46</th>
<th>EPHESUS 47</th>
<th>EMPHASIS-HF 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality, treatment vs. placebo</td>
<td>30% reduction (p&lt;0.001)</td>
<td>15% reduction (p=0.008)</td>
<td>22% reduction (p=0.01)</td>
</tr>
<tr>
<td>HF-related hospitalization, treatment vs. placebo</td>
<td>35% reduction (p&lt;0.001)</td>
<td>15% reduction (p=0.03)</td>
<td>39% reduction (p&lt;0.001)</td>
</tr>
</tbody>
</table>

Safety

The primary safety concern with aldosterone receptor antagonists is renal function decline and hyperkalemia. In the RALES trial, the median creatinine increase was 0.05 to 0.10 mg/dL and the median potassium increase was 0.30 mmol/L (at a mean study dose of 25 mg). In this trial, serious hyperkalemia occurred in 2% of the study group and 1% of the placebo group.

Similar results were found in the EMPHASIS-HF trial: potassium levels of >5.5 mmol/L were experienced by 7.2% of patients in the eplerenone group vs. 1.8% in the control group (p<0.001).

A population-based study of routine care found that after the publication of the RALES trial, as the rate of spironolactone use increased from 34 to 149 (per 1,000 HF patients), hospitalizations due to hyperkalemia also increased from 2 to 11 (per 1,000 patients) from 1994 to 2001.

Spironolactone can also cause endocrine side effects, which occurred in 10% of the treatment group (versus 3% of the placebo group). These included gynecomastia, breast pain, menstrual irregularities, impotence, and decreased libido. Discontinuation rates due to adverse events occurred in 8% of the treatment group and 5% of the placebo group.

The ACCF/AHA recommends against starting aldosterone antagonists in patients with:

- Creatinine >2.5 mg/dL (in men); >2.0 mg/dL (in women)
- Serum potassium >5.0 mEq/L

The ACCF/AHA recommends the following to reduce the risk of hyperkalemia and renal dysfunction associated with aldosterone antagonists:

- avoid NSAIDs
- reduce or discontinue all potassium supplements
- closely monitor potassium and creatinine levels (check in three days, then one week, then monthly for the first three months)
Table 14: Dosing recommendations for aldosterone antagonists

<table>
<thead>
<tr>
<th></th>
<th>Eplerenone</th>
<th>Spironolactone</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR* ≤50</td>
<td>30-49 mg daily</td>
<td>12.5-25 mg daily</td>
</tr>
<tr>
<td>Initial dose</td>
<td>25 mg daily</td>
<td>12.5 mg daily or</td>
</tr>
<tr>
<td></td>
<td>25 mg QOD</td>
<td>QOD</td>
</tr>
<tr>
<td>Maintenance</td>
<td>25 mg daily</td>
<td>25 mg daily or BID</td>
</tr>
<tr>
<td>dose</td>
<td>50 mg daily</td>
<td>12.5-25 mg daily</td>
</tr>
</tbody>
</table>

*eGFR = estimated glomerular filtration rate (mL/min/1.73m²)*

BOTTOM LINE: mineralocorticoid receptor antagonists can reduce mortality and morbidity in patients with HFrEF (<35%) and mild, moderate, or severe HF symptoms. Both can increase creatinine and potassium levels in a dose-dependent fashion and should not be used in those with creatinine >2.5 mg/dL (men) or >2.0 mg/dL (women).

Optimize ACEI/ARB and beta blocker doses before starting an aldosterone antagonist. Discontinue potassium supplements and avoid high-potassium foods. Monitor potassium and renal function at three days and again one week after initiation of therapy, then monthly for the first three months. Risk of hyperkalemia is increased with use of high dose ACEIs or combination of ACEI and ARB.

Hydralazine and Isosorbide Dinitrate

Hydralazine and isosorbide dinitrate lead to nitric oxidemediate vasodilatation. The V-HeFT II trial compared the combination of hydralazine and isosorbide dinitrate to enalapril in men with HFrEF and predominately mild to moderate HF symptoms. Two year mortality was lower in the with enalapril compared to the hydralazine/isosorbide dinitrate (18% versus 25%, p=0.016) although overall mortality did not reach statistical significance (p=0.08). Subgroup analysis demonstrated that the survival benefit of enalapril was experienced by white patients, whereas there was no difference between therapies in black patients. The A-HeFT trial subsequently randomized 1,050 black patients with HFrEF with moderate-severe heart failure symptoms to receive hydralazine and isosorbide dinitrate or placebo, in addition to evidence based therapies including beta blockers and ACE inhibitors or ARBs. This study demonstrated a 43% reduction in death from any cause with hydralazine and isosorbide dinitrate compared to placebo (HR 0.57; p=0.01). Despite this, combination therapy is not widely used in black patients. This may be due to the inconvenience of three times a day dosing. Additionally, combination therapy leads to higher rates of hypotension and dizziness compared to placebo.
Table 15: Outcomes of hydralazine + isosorbide versus placebo in black patients with symptomatic HF

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hydralazine + Isosorbide</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>6.2%</td>
<td>10.2%</td>
<td>0.02</td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>16%</td>
<td>24%</td>
<td>0.001</td>
</tr>
<tr>
<td>Change in quality of life at 6 months (lower better)</td>
<td>-5.6</td>
<td>-2.7</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**BOTTOM LINE:** Hydralazine combined with isosorbide dinirate reduces mortality and HF hospitalizations in black patients with reduced EF already on standard medical therapy, including beta blockers, ACEI or ARB, and an aldosterone receptor antagonist if tolerated. Combination therapy is also recommended for patients who cannot tolerate an ACEI or ARB.

**Digoxin**

Digoxin is the most widely-used formulation of digitalis, a compound that has been used for centuries to treat cardiac conditions because of its antiarrhythmic properties. Digoxin also increases cardiac contractility, which is the primary benefit of its use in HF. The only large randomized trial of digoxin enrolled patients with an EF <45% who were already on combinations of ACEIs and diuretics. After about three years of follow up, overall mortality and cardiac-specific mortality were no different between the groups, but significantly fewer patients in the digoxin group versus the placebo group were hospitalized for worsening heart failure (27% versus 35%; p<0.001). This reduction was most pronounced in the sub-group of patients with EF <35%, enlarged ventricular size, or moderate to severe symptoms. Current guidelines recommend the use of digoxin in patients with HFrEF, unless it is contraindicated, to decrease HF hospitalizations. Digoxin therapy is typically started at a dose of 0.125 to 0.25 mg daily.

**Safety**

In the digitalis trial, suspected digoxin toxicity (based on physician suspicion) occurred in 12% of the digoxin group and 8% of the placebo group (p<0.001), although only 2% of patients had digoxin levels exceeding 2 ng/mL, indicating that symptoms of toxicity are non-specific and difficult to attribute to increased drug levels. Digoxin toxicity occurs more commonly in patients with advanced age, low BMI, and renal insufficiency. Hypokalemia, hypomagnesemia, and hypothyroidism may induce toxicity at lower serum levels. Symptoms of digoxin toxicity include:

- cardiac arrhythmias (re-entrant rhythms and heart block)
- GI symptoms (anorexia, nausea, vomiting)
- neurologic symptoms (visual disturbances, confusion)

Observational studies have suggested that patients treated with digoxin for atrial fibrillation have higher mortality than those not treated with digoxin. Subsequent work, however, demonstrated that this increased risk is likely due to uncontrolled confounding, because patients treated with digoxin in observational studies tend to be sicker than those patients not treated with digoxin. Digoxin has not been shown to increase mortality in randomized controlled trials in patients with heart failure and can be used to reduce hospitalizations among symptomatic patients on optimal medical therapy, as long as levels are monitored.
Agents approved in 2015

In 2015, two new therapeutic agents were approved for use in patients with HFrEF: the SA node inhibitor ivabradine (Corlanor); and Entresto, which combines the neprilysin inhibitor sacubitril and the ARB valsartan.

Ivabradine

Ivabradine selectively inhibits an ion channel that controls the responsiveness of the sinoatrial (SA) node, and therefore directly reduces the heart rate. This agent was evaluated in the SHIFT trial, which randomized recently hospitalized patients with HFrEF on stable medical therapy with a resting heart rate >70 beats per minute to ivabradine or placebo. The majority of patients were on an ACEI/ARB and a beta-blocker, and more than half were taking an aldosterone receptor antagonist. After a median follow-up of almost 2 years, ivabradine significantly reduced the combined endpoint of CV death or HF hospitalization by 18% (95% CI 0.75-0.9; p< 0.0001). This effect was driven by a reduction in HF hospitalizations (HR 0.74; 95% CI 0.66-0.83; p<0.0001). Ivabradine did not significantly lower the risk of all-cause mortality or cardiovascular mortality and caused significantly more symptomatic bradycardia (5% vs. 1%; p<0.0001). Further analysis of the trial found the least benefit in those patients with higher beta blocker doses and lower baseline heart rates, indicating that this agent may only have a role in improving outcomes in patients who cannot tolerate, or cannot reduce their heart rate with, a beta blocker. Recommended dosing is 5 mg BID with an increase to 7.5 mg BID as tolerated.

Sacubitril/valsartan

Heart failure is a condition of overactivation of the neurohormonal system. Neprilysin is an endogenous chemical that breaks down beneficial endogenous vasoactive peptides, including natriuretic peptides. Sacubitril inhibits neprilysin and counteracts the neurohormonal overactivation that contributes to vasoconstriction, sodium retention, and maladaptive remodeling. It also promotes diuresis and natriuresis. Since inhibiting neprilysin may increase the production of angiotensin converting enzyme, however, the drug is combined with the ARB valsartan.

The combination of sacubitril and valsartan was studied in the PARADIGM-HF trial. In this RCT, 8399 patients with reduced EF (<35-40%), elevated BNP, and mild to severe HF symptoms on optimal medical therapy were randomized to sacubitril/valsartan 200 mg twice daily or enalapril 10 mg twice daily. Prior to randomization, patients underwent a 6-8 week run-in period where they sequentially received maximum dose enalapril and maximum dose sacubitril/valsartan. Patients tolerating both medications were randomized in the study; about 20% of patients did not tolerate both medications and were not included in the analysis. The majority of patients in the study were on a beta blocker and diuretic and about half were taking an aldosterone receptor antagonist.

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Compared to enalapril, sacubitril/valsartan reduced the combined end-point of CV death and HF hospitalization by 20% (HR 0.8; 95% CI 0.73-0.87; p < .001). Additionally, sacubitril/valsartan reduced the relative risk of all-cause mortality by 16% (p<0.001).

**Figure 10:** In PARADIGM-HF, sacubitril/valsartan improved patient outcomes more than enalapril alone.\(^{58}\)

The side effects of sacubitril/valsartan were similar to enalapril, although the incidence of symptomatic hypotension was higher with sacubitril/valsartan (14% vs. 9%) and angioedema, even though it only occurred in 0.5% of patients on sacubitril/valsartan, was about double the number of patients on enalapril.\(^{58}\)

We recommend that if patients with HFrEF are on optimal medical therapy, including ACEI/ARB, beta blocker, and aldosterone receptor antagonist, and continue to have HF symptoms, they should then switch from their ACEI or ARB to sacubitril/valsartan. If a patient is on an ACEI currently, it should be held for 36 hours prior to starting sacubitril/valsartan. Dosing is initially 100 mg BID, with an increase to 200 mg/day after 2-4 weeks as tolerated. Monitor renal function and potassium at the same frequency as for patients on an ACEI/ARB.

**BOTTOM LINE:** Guideline recommendations have not been released for either Ivabradine or sacubitril/valsartan in the United States. In patients with HFrEF on optimal medical therapy who are still symptomatic, sacubitril/valsartan can be used to reduce mortality and HF hospitalizations and should replace an ACEI or ARB. Ivabradine can also be used among patients with a HR >70 bpm but the main clinical benefit of this medication is reduction in HF hospitalizations. Both agents are relatively expensive, and cost should be considered in treatment decisions.
Summary of pharmacological treatments for HFrEF

All patients with HF, regardless of EF, should be treated for risk factors that can exacerbate their disease (e.g., hypertension, diabetes, and atrial fibrillation). Diuretics should be used for symptomatic patients and patients with clinical evidence of volume overload.

Patients with reduced EF should be started on an ACEI as first line therapy, then a beta blocker. If ACEI side effects develop, an ARB should be used instead. Titrate ACEIs or ARBs, and beta blockers to doses used in studies, or the highest dose tolerated by patients. Mortality and morbidity benefits for these agents are best at higher, study doses. A lower dose, however, is still more beneficial than not receiving treatment in patients who are unable to tolerate higher doses. For those who remain symptomatic, the next added agent should be an aldosterone receptor antagonist (spironolactone or eplerenone).

Patients who continue to have symptomatic HF on the above therapies may be candidates for sacubitril/valsartan (Entresto). Sacubitril/valsartan shows promise as a substitute therapy for ACEI or ARBs in HF with reduced EF, though it requires monitoring for hypotension.

The combination of hydralazine with isosorbide dinitrate should be considered for black patients, who have moderate to severe symptoms despite the therapies above or for white patients who cannot tolerate ACEI or ARB therapy. Digoxin and ivabradine can be used in appropriate patients who remain symptomatic despite other evidence-based medical therapies, to reduce the risk of hospitalization. See Appendix I.

Devices to treat HFrEF

Patients with HFrEF are at increased risk for ventricular tachyarrhythmias and sudden cardiac death (SCD). SCD, in fact, accounts for 30-50% of all HF-related cardiac deaths. Two types of treatments have been shown to reduce the risk of SCD in patients with HFrEF: implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy (CRT).

Implantable cardioverter defibrillators

ICDs act as both pacemakers and defibrillators. These devices (alone or in combination with cardiac resynchronization therapy) have been shown to improve symptoms and quality of life and reduce HF hospitalizations and mortality. ICDs can be used as both primary prevention (in patients without a history of SCD) and secondary prevention (in patients with a history of SCD).

ICDs reduce mortality among post-MI patients with reduced EF and patients with non-ischemic HF, as illustrated in Figure 11, which shows the results of a trial comparing conventional therapy, an ICD, or the antiarrhythmic agent amiodarone.
A meta-analysis of 3 large trials suggests that the benefits of ICDs may be attenuated in the elderly. The average age in ICD trials is 60-64, although almost half of new ICD implants are in patients older than 70.

The risks associated with ICD implantation are not trivial: about 30% of patients receiving an ICD experience at least one complication following implantation, and in 10% of these patients the complication is directly related to the procedure. The risks of complications are lower if the ICD is implanted by an experienced electrophysiologist.

Current guidelines recommend implantation of an ICD under the following conditions:

- Goal-directed medical therapy has been tried for ≥3-6 months
- ≥40 days after myocardial infarction
- Expected survival >1 year
- Patients with non-ischemic or ischemic HF with EF <35% and NYHA class II – III
- Patients with ischemic (post-MI) HF with EF <30% and NYHA class I

**BOTTOM LINE:** ICDs are indicated as primary prevention in patients with EF <35% on maximal medical therapy with mild-severe HF symptoms. ICDs are also indicated in asymptomatic post-MI patients with EF <30%. ICD complications occur in about 10% of patients, with risk lower if performed by an experienced electrophysiologist.
Cardiac resynchronization therapy

Delays of the intraventricular conduction system occur in about one-third of patients with HFrEF, identifiable by a QRS duration of >120 milliseconds on EKG. These patients usually have left bundle branch block (LBBB) or right bundle branch block (RBBB) on EKG. This conduction delay results in asynchronous contraction of the left and right ventricles, and resultant reduction of the cardiac output. Cardiac resynchronization therapy uses pacemaker leads placed in both ventricles to re-synchronize the contraction of both ventricles.

CRT has been shown to prolong survival, reduce hospitalizations, and improve symptoms in patients with HFrEF who have cardiac dyssynchrony. Patients with LBBB on EKG benefit more from CRT than patients with RBBB or non-LBBB on EKG. CRT can also improve LV systolic function and may reverse ventricular remodeling. Because effective CRT requires a high rate of ventricular pacing, the benefit for patients with AF is most evident in patients who have undergone atrioventricular nodal ablation or in patients with very good rate control. Many patients who qualify for CRT will also benefit from an ICD. Such combination devices are referred to as cardiac resynchronization therapy with defibrillator (CRT-D).

Table 16 summarizes the current guidelines for the use of CRT in patients with sinus rhythm, EF <35% and on guideline-directed medical therapy.

<table>
<thead>
<tr>
<th>Intraventricular conduction delay</th>
<th>QRS duration on ECG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>120-149 ms</td>
</tr>
<tr>
<td>LBBB</td>
<td>HF patients with NYHA class II-IV</td>
</tr>
<tr>
<td>Non-LBBB</td>
<td>HF patients with NYHA class III-IV</td>
</tr>
</tbody>
</table>

Patients with EF >35% and a narrow QRS may benefit from CRT if atrioventricular block is present and RV pacing is required more than 40% of the time. In such patients, biventricular pacing, compared to RV pacing alone, can reduce the risk of adverse cardiovascular events.
Figure 12: CRT survival improvement among patients with low ER and prolonged QRS

BOTTOM LINE: CRT reduces morbidity and mortality in HFrEF patients with cardiac dyssynchrony. Patients with LBBB on EKG with a QRS duration >120 msec and mild-severe HF symptoms derive the most benefit. Patients with non-LBBB on EKG with a QRS duration >150 msec derive more benefit than those with non-LBBB with QRS duration between 120-150 msec. Less symptomatic patients (class I-II) derive less benefit, but CRT is FDA approved for these patients.

Pharmacological management of HFpEF

As with patients with reduced EF, treatment goals for those with preserved EF are to improve symptoms, reduce volume overload, lower hypertension, and reduce comorbid conditions (e.g., atrial fibrillation and ischemic heart disease). Hypertension should be treated as recommended by current clinical guidelines, including treatment with diuretics, ACEIs or ARBs, or calcium channel blockers.

Clinicians should be aware that excessive treatment poses risks in patients with symptomatic HFpEF because patients with a small, stiff left ventricle may be very sensitive to medications that reduce LV filling. Treatment with even standard dose diuretics or dihydropyridine calcium channel blockers may reduce preload and cause hypotension. Patients on these medications should be monitored for dizziness, syncope, and orthostatic hypotension.

Medications that can improve survival in patients with reduced EF have generally not been effective in improving survival in patients with preserved EF. The ACEI perindopril may reduce hospitalizations in patients with HFpEF, but the evidence is limited. The PEP-HF trial randomized >800 patients with HFpEF...
to ACE inhibitor or placebo, and did not find any difference in the primary outcome (death or HF hospitalization), or most of the secondary outcomes. Similarly, two RCTs of ARBs in HFpEF found no difference in the primary outcomes (composite of CV death, and HF hospitalization).

Evidence for clinical benefits of ARBs for those with preserved EF is equally weak. The CHARM-preserved trial found a marginal benefit for candesartan in patients with normal EF, and a meta-analysis that combined the CHARM-preserved trial with the I-PRESERVE trial did not find a benefit of ARBs for mortality or HF hospitalizations in patients with normal EF.

In the 2014 TOPCAT study spironolactone was found to modestly lower the rate of hospitalization in patients with HFpEF (12% vs. 14.2%) but patients on spironolactone had double the rate of hyperkalemia (18.7% vs. 9.1%).

The findings from studies of beta-blockers in patients with HFpEF have been modestly positive. The largest trial enrolled elderly patients recently hospitalized for HF (SENIORS trial) and randomized them to the beta blocker nebivolol or placebo. The analysis found beneficial effects of nebivolol on all outcomes that were similar between the preserved and reduced EF groups; outcomes included mortality, CV hospitalizations, HF hospitalizations, all-cause hospitalizations and sudden cardiac death (SCD). Ongoing clinical trials will further investigate the role of beta blockers in patients with HFpEF. Current guidelines do not recommend beta blocker use in these patients unless needed for another indication.

The only large randomized trial of digoxin in patients with HFpEF did not find any benefit on mortality or CV hospitalization.

**Patient education and disease management**

Patients should be educated about their disease, symptoms, medications, diet, and weight management. Education should be tailored to the patient’s literacy level, cultural context, resources, and social support levels. The patient should be asked to demonstrate understanding of the concepts listed above, by reiterating the elements in their own words. Difficulty in affording medications, getting transportation to pick up medications, and any other barriers should be addressed. Support for dietary and weight management from family and friends should be assessed.

Many outpatient and hospital systems have instituted telemonitoring systems to remotely monitor and manage HF patients for physical signs (such as weight, vital signs, or urine output), symptoms (such as edema or shortness of breath), laboratory values (such as creatinine or BNP), and medication/dietary compliance (by self-report or by use of more sophisticated devices). The potential benefit of telemedicine programs is the early detection and management of disease deterioration. It is generally accomplished by the transmission of information to a provider, who uses standard guidelines and operating procedures to direct the patient on how best to proceed. Regular telephone contact with the patient can prevent HF exacerbations and hospital admissions. A systematic review of 56 articles found numerous outcome improvements in telemonitoring in randomized trials (Table 17)
Table 17: Efficacy of telemonitoring technologies in HF^{76}

<table>
<thead>
<tr>
<th>Type of telemonitoring modality</th>
<th>Outcomes improved in randomized trials</th>
</tr>
</thead>
</table>
| Device-based: Participants enter data into a device, which is transmitted to a monitoring station | Decreased mortality  
Decreased hospitalizations  
Decreased anxiety / depression scores  
Increased self-efficacy scores  
Increased exercise adherence  
Increased QOL |
| Telephone touch-pad-based: Participants enter data into a telephone, which is transmitted to a monitoring station | Decreased hospitalizations  
Decreased time to target beta blocker |
| Video consultation-based: Participants were monitored by video conferences by nurses | No improvements |
| Website-based: Participants enter data into a website, which was monitored by healthcare professionals | Decreased hospital days |
| Combinations | Decreased ED visits and charges  
Decreased readmission rates  
Decreased hospital days  
Decreased mortality  
Decreased cardiac claims (e.g. cost) |

Managing common comorbid conditions

Patients with HF often have many co-morbid conditions that can affect the management of their heart disease. According to Medicare claims data, about 40% of patients with HF have 5 or more co-morbid conditions.^{77} Many older patients with HF are already taking multiple medications for their cardiac disease; the mean number of medications in all Medicare patients recently discharged is 7, with a mean of 10 daily doses.^{77} Therefore, careful attention must be paid to managing other co-morbid conditions without inducing unnecessary polypharmacy. This section will briefly discuss the most commonly associated co-morbid conditions, and how they impact the management of HF.

Hyperlipidemia

Two large randomized trials (GISSI-HF trial and the CORONA trial) in patients with symptomatic systolic HF found no benefit in any of the outcomes in patients randomized to rosuvastatin versus placebo.^{78,79} There are no randomized trials of statin therapy in patients with HFpEF. Therefore statin therapy should not be initiated in HF patients for the purpose of improving outcomes, in the absence of other indications for statin therapy (e.g., ischemic heart disease).
Hypertension
Concomitant hypertension can worsen the symptoms of HF; blood pressure should be controlled at least to goal levels based on JNC-8 standards (BP <140/90 for most patients, and <130/80 in those with renal dysfunction). Some recommend lower targets (<130/80) for all patients with HF and recent studies suggest benefit for even lower targets. Many medications used to treat HF are effective anti-hypertensives, including ACEIs, ARBs, beta blockers, and diuretics.

Atrial fibrillation
The most common arrhythmia in patients with HF is atrial fibrillation, which occurs in 30% to 40% of HF patients admitted to the hospital. Atrial fibrillation can exacerbate HF symptoms by reducing the “atrial kick”, or amount of blood that fills the ventricle during diastole, and therefore the cardiac output. Although rhythm control has historically been recommended for patients with heart failure, the AF-CHF trial of patients with AF and HFrEF found no significant difference between rate and rhythm control for a range of clinical outcomes, including death from CV causes, death from any cause, stroke, worsening heart failure, and a composite of several of these outcomes.

Renal dysfunction
About 40% of HF patients also have chronic renal dysfunction, defined as creatinine clearance <60 ml/min. This is likely a consequence of low cardiac output and decreased renal perfusion with intrarenal vasoconstriction. About a third of patients admitted with HF have elevated serum creatinine (e.g., >0.3 mg/dL over baseline), which is associated with higher morbidity and mortality compared to patients without such elevation.

Many of the medications used to treat HF need to be adjusted for renal dysfunction. ACEIs and ARBs both cause a transient reduction in creatinine clearance rates, although both are beneficial in patients with renal dysfunction -- especially when associated with proteinuria. The aldosterone antagonists should be used with caution in patients with renal dysfunction, with close monitoring of renal function and electrolytes (primarily potassium), and are contraindicated with creatinine clearance <10 ml/min. Doses of loop diuretics generally must be increased as the creatinine clearance is decreased. The use of digoxin should be limited in those with renal dysfunction, and the dose should be appropriately decreased based on the creatinine clearance. Digoxin dosing calculators can help determine appropriate daily dosing. Beta blocker doses generally do not have to be adjusted for creatinine clearance, although atenolol, which is renally cleared, should be avoided.

BOTTOM LINE: comorbid conditions are common in patients with HF, complicating its management. Medications to be avoided include NSAIDS, non-dihydropyridine calcium channel blockers, and glitazones, all of which can worsen HF.
Advanced Heart Failure

Advanced HF (also called “end stage” or “refractory” HF) is characterized by:

- Marked symptoms of dyspnea or fatigue at rest with minimal exertion despite optimal medical therapy (e.g., persistent dyspnea while dressing or bathing, inability to walk one block due to dyspnea or fatigue)
- Intolerance to ACEIs or beta blockers
- Escalating diuretic doses (lasix doses >160 mg/day)
- Signs or symptoms of end-organ hypoperfusion (e.g., hypotension, progressive renal dysfunction, mental status changes)
- Frequent visits to the ER or hospital admissions with volume overload and/or decompensation
- Worsening renal function
- Worsening serum sodium (<133 mEq/L)

In patients presenting with symptoms suggesting of advanced HF, assess for other potential causes that can exacerbate HF or mimic HF symptoms, such as ischemic heart disease, concomitant pulmonary disease, sleep disordered breathing, and thyroid disorders.

The goals in treating advanced HF are to control symptoms, improve quality of life, reduce hospital admissions and to identify the patient’s end-of-life goals (advanced care directives should be discussed with all patients). In addition to the HF management strategies appropriate for earlier stages of HF, the following treatment options or management approaches should be considered for patients with advanced HF:

- Chronic inotropes
- Mechanical circulatory support (MCS) device (e.g., left ventricular assist devices)
- Heart transplant
- Experimental therapies
- Palliative care and hospice

Consider referral to cardiology to manage the following conditions that may be contributing to ongoing symptoms or clinical decline:

- Atrial fibrillation with difficult rate control
- Coronary artery disease
- Aortic stenosis
- Mitral regurgitation

**Inotropic support**

Inotropes (e.g., dobutamine and milronone) are medications that increase cardiac contractility. Other positive inotropic agents increase the concentration of intracellular cyclic AMP, either by promoting its synthesis (beta-adrenergic agonists) or by retarding its degradation (phosphodiesterase inhibitors). The use of cyclic AMP—enhancing agents has been viewed as a particularly rational approach to the treatment of advanced heart failure, since the production of cyclic AMP is deficient in failing human hearts. Long-term use of infused inotropic drugs is potentially harmful for patients with HFrEF, the exception being patients with advanced HF who cannot be stabilized with standard medical treatment.1
Mechanical circulatory support

The most common type of mechanical circulatory support (MCS) for patients with advanced HF are ventricular assist devices (VADs), which are mechanical pumps that bypass the ventricle. VADs can support the left ventricle (LVAD) the right ventricle (RVAD) or both (BiVAD) and can be used short- or long-term, either with percutaneous placement or as implants.

LVADs can be used either as a bridge to heart transplant or as a destination therapy to improve survival and enhance quality of life. When used as a destination therapy they have been shown to improve the survival of patients with end-stage HF. Early types of LVAD devices improved survival by 48% compared to medical therapy alone. New LVADs using a continuous flow have demonstrated even greater improvement in survival with actuarial survival of 80% at one year and 70% at two years.

Figure 13: Survival rates comparing medical therapy with three types of LVADs.

Note that, in general, patients getting LVADs live longer, but have higher rates of complications such as bleeding, stroke, and sepsis.

Cardiac transplant

Cardiac transplant is a last resort for patients with HF and refractory symptoms. About 2000 heart transplants are performed annually in the U.S., with an average 5-year survival rate of >70%. Patients must be carefully screened for their ability to endure the surgery, and to emotionally and logistically comply with all post-transplant medications and other therapies. Given the scarcity of heart donors, many patients need a MCS placement while waiting for a donor heart.
Common contraindications to transplant include:

- short life expectancy despite a transplant
- comorbidities such as fixed pulmonary hypertension or renal failure
- advanced age

**Indications for hospitalization**

Several factors increase the need for hospitalization in HF, although individual differences in patients’ functional status, home and caregiver situation, and resources will help shape the decision to admit or treat at home.

**Table 18: Relative indications for hospital admission for HF**

<table>
<thead>
<tr>
<th>HF symptoms with end-organ decompensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>hypoxia (saturations &lt;90%)</td>
</tr>
<tr>
<td>altered mental status</td>
</tr>
<tr>
<td>worsening renal function</td>
</tr>
<tr>
<td>acute coronary syndrome</td>
</tr>
</tbody>
</table>

| Worsened dyspnea, especially dyspnea at rest |
| Hypotension                                 |
| New or hemodynamically significant arrhythmia (such as atrial fibrillation) |
| Major electrolyte abnormality              |
| Significant weight gain (usually >5 kg above baseline) or worsening edema |
| Repeated ICD firings                        |

Transitions of care are important and can help limit hospital readmission. HF patients who receive comprehensive discharge planning compared to usual care have:

- 25% lower risk of hospital readmission
- trend towards lower mortality
- improved HF-related quality of life scores
- lower medical costs

Comprehensive planning may include:

- medication review and counseling by pharmacist
- dietary counseling
- information about sodium and fluid restriction
- post-discharge home visit and/or telephone calls
**End of life care**

A recent analysis of Medicare beneficiaries found that 80% of those with HF were hospitalized within the last 6 months of life, with a significant increase in ICU days and overall costs during the last six months of life. However, the same analysis found the use of hospice increased from 19% of patients (before the last six months of life) to 40% of patients (within the last 6 months of life). End of life care should be discussed with all patients/families who have class IV symptoms despite maximal medical therapy. This discussion should involve:

- symptomatic therapy for dyspnea (including oxygen therapy).
- symptomatic therapy for anxiety or depression (if present).
- information on how to prepare a medical power of attorney, living will, and “do not resuscitate” orders.
- discussion of the potential futility of invasive management at the end of life (eg ICUs, ventilators, cardiac resuscitation).
- discussion of the potential benefits of hospice care (at home or in a facility).
- discussion of inactivating an ICD (if present).

Initiation of discussions about patient wishes for end of life care can also be helpful for patients at less advanced stages of HF, allowing them time to consider their preferences and discuss their decisions with family members and/or a health care proxy.
### Costs

<table>
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<th>Costs</th>
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<td>metoprol succinate (generic) 150mg</td>
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<table>
<thead>
<tr>
<th>ACE inhibitors</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
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<td>$4</td>
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<tr>
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<tr>
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<td>captopril (generic) 50mg</td>
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<table>
<thead>
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<th>ARBs</th>
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<td>candesartan (Atacand) 8mg</td>
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<td>spironolactone (generic) 75mg</td>
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<td>eplerenone (generic) 50mg</td>
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<tr>
<td>eplerenone (Inspra) 50mg</td>
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<table>
<thead>
<tr>
<th>Diuretics</th>
<th>Costs</th>
</tr>
</thead>
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<td>metolazone (Zaroxolyn) 5mg</td>
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</tr>
<tr>
<td>hydrochlorothiazide (generic) 25mg</td>
<td>$4</td>
</tr>
<tr>
<td>bumetanide (generic) 1mg</td>
<td>$27</td>
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<tr>
<td>torsemide (generic) 10mg</td>
<td>$21</td>
</tr>
<tr>
<td>torsemide (Demadex) 10mg</td>
<td>$66</td>
</tr>
<tr>
<td>furosemide (generic) 40mg</td>
<td>$4</td>
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<tr>
<td>furosemide (Lasix) 40mg</td>
<td>$29</td>
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<table>
<thead>
<tr>
<th>Other drugs</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>digoxin (generic) 0.25mg</td>
<td>$34</td>
</tr>
<tr>
<td>digoxin (Lanoxin) 0.25mg</td>
<td>$224</td>
</tr>
<tr>
<td>hydralazine+Isosorbide dinitrate (Bidil) 112.5/60mg</td>
<td>$200</td>
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<tr>
<td>hydralazine (generic) 112.5mg</td>
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<tr>
<td>isosorbide dinitrate (generic) 60mg</td>
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<tr>
<td>ivabradine (Corlanor) 10mg</td>
<td>$363</td>
</tr>
<tr>
<td>sacubitril/valsartan (Entresto) 97mg/103mg</td>
<td>$392</td>
</tr>
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Prices from goodrx.com, November 2015. Listed doses are based on Defined Daily Doses by the World Health Organization, and should not be used for dosing in all patients.
Putting it all together

All patients with HF should be treated for risk factors that can exacerbate their disease (e.g., hypertension, diabetes, and atrial fibrillation), and prescribed a diuretic to reduce volume overload.

Non-pharmacologic therapy for all HF patients should consist of sodium and fluid restriction, commensurate with the degree of symptoms and edema. Patients should avoid smoking and alcohol, and be educated on vaccines, and exercise. Co-morbid conditions are common and should be carefully addressed to avoid polypharmacy and drug interactions. Acute exacerbations should be managed with diuretics, with more aggressive interventions reserved for unstable patients. Patient education is an important component of HF care, and should include planning for end of life care in class IV patients.

After HF hospitalization, address non-adherence concerns, review weight goals and salt or fluid restriction, and refer for cardiac rehabilitation.

HFrEF patients

Patients with reduced EF should be started on an ACE inhibitor as first line therapy, then a beta blocker. For those who remain symptomatic, next line agents should be either an ARB (as an alternative to an ACE, not in addition to an ACD) or aldosterone antagonist (spironolactone for those with Class III-IV symptoms, or eplerenone for those with Class II-IV symptoms). Titrate ACE inhibitors, ARBs, and beta blockers to doses used in studies, or the highest dose tolerated by patients. Mortality and morbidity benefits for these agents are best at higher, study doses. However, a lower dose is still more beneficial than not receiving treatment in patients who are unable to tolerate higher doses.

Patients who have symptomatic HF on an ACE inhibitor or ARB may be candidates for sacubitril/valsartan. Sacubitril/valsartan shows promise as a substitute therapy for ACE inhibitors or ARBs in HFrEF, though it requires monitoring for hypotension, worsening renal function and increases in serum potassium.

Aldosterone antagonists are generally preferable to combining an ACE and ARB, based on a lack of mortality benefit for this combination, and the increased risk of adverse effects (e.g. renal insufficiency, hypotension, and hyperkalemia). The combination of hydralazine with isosorbide dinitrate should be considered for black patients, who do not response as well to ACE or ARB therapy, as well as white patients who require additional therapy for symptom management. Digoxin is usually reserved for patients who remain symptomatic despite all of the above medical therapies, to reduce the risk of hospitalization. Invasive therapies, including ICDs, CRT, MCS, and transplantation, should be considered depending on the patient’s ejection fraction and QRS duration.

HFpEF patients

For those with HFpEF, guidelines recommend the following medications to reduce volume overload and hypertension, generally in this order:

- diuretics (thiazide or loop)
- ACEI or ARB (especially with prior MI, CAD, or diabetes)
- beta blocker (especially with prior MI, CAD, angina or atrial fibrillation)
Appendix I

Algorithm for pharmacologic treatment of HFrEF

INITIAL THERAPY

ACE inhibitor (or ARB) + loop diuretic for volume control

beta blocker*

Optimize ACE inhibitor / ARB and beta blocker doses

aldosterone antagonist
If GFR > 30 and K+ < 5

African Americans with moderate to severe symptoms

hydralazine / isosorbide dinitrate

Stop ACEI or ARB and start sacubitril / valsartan

Add digoxin and /or ivabradine
Use ivabradine for patients with HR > 70 on maximally tolerated beta blockers

Refer to cardiology for consideration of advanced therapies

* Trials enrolled patients with symptoms, but current guidelines recommend the use of beta blockers in most HF patients.
References


Landmark NIH study shows intensive blood pressure management may save lives [press release]. September 11, 2015.


About this publication

These are general recommendations only; specific clinical decisions should be made by the treating physician based on an individual patient’s clinical condition.

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