Heart Failure - Systolic Dysfunction

Patient population: Adult patients with left ventricular systolic dysfunction

Objectives: 1) To improve mortality and morbidity for patients with heart failure (HF).
2) To present a framework for treating patients with HF.

Key Points

Diagnosis.
- Ejection fraction (EF) evaluated to determine the etiology as systolic dysfunction rather than diastolic dysfunction or valvular heart disease [IA*].
- Serum BNP to help determine if dyspnea is due to HF [IC*].

Pharmacologic Therapy (See Table 1)
- For patients with systolic dysfunction (EF < 40%) who have no contraindications:
  - ACE (angiotensin-converting enzyme) inhibitors, ARB (angiotensin receptor blocker) or ARNI (angiotensin receptor blocker/neprilysin inhibitor) for all patients [IA*].
  - Beta blockers for all patients except those who are hemodynamically unstable, or those who have rest dyspnea with signs of congestion [IA*].
  - Aldosterone antagonist (low dose) for all patients with symptoms of heart failure or with a history of hospitalization for heart failure [IA*].
  - Isosorbide dinitrate-hydralazine combination for symptomatic HF patients who are African-American [IA*].
- Diuretics for symptomatic patients to maintain appropriate fluid balance [IC*].
- Digoxin only for patients who remain symptomatic despite diuretics, ACE inhibitors and beta blockers or for those in atrial fibrillation needing rate control [IA*].
- Sinus Node Modulator for patients who have been admitted to the hospital for HF within the last 12 months, have sinus rhythm with HR > 70 while on maximally tolerated or target dose of beta blocker [IIA*].

Device Therapy
- Implantable defibrillators considered for prophylaxis against sudden cardiac death in patients with EF ≤ 35% [IA*].
- Bi-ventricular pacemakers considered for patients requiring defibrillators who have symptomatic HF and QRS durations ≥ 120 msec [IA*].

Caution
- HF patients on multiple medications are at risk of potential drug interactions and side effects. For example, the risk of hyperkalemia is increased in patients with renal insufficiency treated with an aldosterone antagonist and an ACE inhibitor.

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These guidelines should not be construed as including all proper methods of care or excluding other acceptable methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific clinical procedure or treatment must be made by the physician in light of the circumstances presented by the patient.
**Figure 1. Identifying Systolic Heart Failure**

**B-type Natriuretic Peptide (BNP) Level**

- Likelihood that dyspnea is caused by HF as a function of BNP level.
- Measure ejection fraction. Is EF ≥ 40?
  - No
  - Yes

Systolic dysfunction is a possible or probable cause of symptoms. Classify by symptoms and treat.

- EF ≤ 35?
  - No
  - Yes

- Is life expectancy limited by non-cardiac disease?
  - No
  - Yes

- Does patient have CAD or symptomatic HF?
  - No
  - Yes

Refer to cardiology or electrophysiology to determine candidacy for implantable cardio-defibrillator and bi-ventricular pacemaker. *

The negative predictive value of a BNP<50 is 96%. The relative risk of heart failure for BNP > 250 is 7.0.

**Figure 2. Device Referral Algorithm**

1. Measure ejection fraction
2. Is EF ≤ 35?
   - No
   - Yes
3. Is life expectancy limited by non-cardiac disease?
   - No
   - Yes
4. Does patient have CAD or symptomatic HF?
   - No
   - Yes

* Device therapy, i.e. implantable cardio-defibrillator or Bi-ventricular pacemaker, can significantly improve mortality in appropriate patients. Determining appropriate clinical criteria can be complex and may require the assistance of a cardiologist or an electrophysiologist. The algorithm above gives guidance but is designed to be inclusive so that all eligible patients can at least be considered for a device. Refer to cardiology or to electrophysiology for further discrimination of device candidacy rather than just for device placement. Finally, the primary care physician should discuss device placement with patients before referral. Some patients may choose not to pursue this path because of prognosis, co-morbid conditions, or other personal values.
Table 1: Management of Heart Failure Due to Reduced Ejection Fraction

<table>
<thead>
<tr>
<th>NYHA Classification</th>
<th>ACC/AHA</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
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<tr>
<td>II – III</td>
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<tr>
<td>IV</td>
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</tbody>
</table>

**Symptoms**

<table>
<thead>
<tr>
<th>NYHA Classification</th>
<th>ACC/AHA</th>
<th>B</th>
<th>C</th>
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<td>II – III</td>
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<td>IV</td>
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</tbody>
</table>

**Pharmacologic Management**

<table>
<thead>
<tr>
<th>NYHA Classification</th>
<th>ACC/AHA</th>
<th>B</th>
<th>C</th>
<th>D</th>
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<tr>
<td>I</td>
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<td>II – III</td>
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<tr>
<td>IV</td>
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</table>

- **Either:**
  - ACE Inhibitor OR
  - ARB OR
  - Valsartan/sacubitril/ (ARNI)

**Beta Blocker**

- Yes

**Aldosterone antagonist**

- Yes

**Isosorbide dinitrate-hydralazine**

- Selected patients

**Diuretic**

- PRN congestion

**Digoxin**

- PRN

**Ivabradine**

- Selected patients

**Non-pharmacologic Management**

- Consider AICD/Bi-V pacemaker

- HF Disease Management

- Referral to Advanced Heart Failure Program

Shading: = Recommended, = Consider

- One trial has demonstrated superiority of valsartan/sacubitril/ (ARNI) over enalapril in symptomatic patients. Given the lack of real world experience, either option is reasonable. ARNI should not be used in conjunction with ACEI or ARB. Among those intolerant to ACEI due to cough, consider use of ARB. If intolerant due to renal disease, may substitute isosorbide dinitrate/hydralazine. If intolerant due to angioedema, may consider ARB (although there is some cross reactivity) or the combination of isosorbide dinitrate/hydralazine.

- No explicit evidence of benefit exists for beta blockers among asymptomatic patients, although many patients in this class will have other indications for beta blockers such as CAD.

- Beta blockers may be continued safely for patients with rest dyspnea except patients with signs of congestion or hemodynamic instability.

- The combination of isosorbide dinitrate/hydralazine benefited patients self-reported as black. This combination may be added for patients who remain symptomatic despite therapy with ACEIs and beta blockers and as tolerated without reducing the doses of ACEI or beta blocker to sub-target doses.

- Digoxin may provide symptomatic benefit. If no benefit is perceived, digoxin may be withdrawn; however, withdrawal may lead to clinical deterioration and should be done with caution.

- Indicated if in sinus with HR > 70 while on maximally tolerated dose beta blocker.

- Indication only for asymptomatic patients with ischemic cardiomyopathy

- Refer for shared medical decision-making regarding LVAD, transplant, or palliative care.
Table 2. Doses for Major Heart Failure Drugs

<table>
<thead>
<tr>
<th>Drug Class and Generic Name</th>
<th>Brand Name</th>
<th>Starting Dose</th>
<th>Target Dose or Common Dose</th>
<th>Target/Common Dose 30 Day Cost a</th>
<th>30 Day Cost a</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE – Inhibitor b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>Capoten</td>
<td>6.25 mg tid (1/2 tab c)</td>
<td>12.5 – 50 mg tid</td>
<td>$70-$130</td>
<td>$54-$107</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Vasotec</td>
<td>2.5 mg bid</td>
<td>10 mg bid</td>
<td>$9-$15</td>
<td>$51-$67</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>Monopril</td>
<td>5-10 mg daily</td>
<td>40 mg daily</td>
<td>$5-$8</td>
<td>$18</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Zestril, Prinivil</td>
<td>5 mg daily</td>
<td>10 – 20 mg daily</td>
<td>$4-$6</td>
<td>$46-$51</td>
</tr>
<tr>
<td>Perindopril</td>
<td>Aceon</td>
<td>2 mg daily</td>
<td>8-16 mg daily</td>
<td>$20-$40</td>
<td>$68-$192</td>
</tr>
<tr>
<td>Quinapril</td>
<td>Accupril</td>
<td>5 mg bid</td>
<td>10-20 mg bid</td>
<td>$8</td>
<td>$109</td>
</tr>
<tr>
<td>Ramipril</td>
<td>Altace</td>
<td>1.25 mg bid</td>
<td>5 mg bid</td>
<td>$6-$7</td>
<td>$141-$165</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>Mavik</td>
<td>1 mg daily</td>
<td>4 mg daily</td>
<td>$16</td>
<td>$68</td>
</tr>
<tr>
<td>Aldosterone Antagonist b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eplerenone</td>
<td>Inspra</td>
<td>25 mg daily</td>
<td>50 mg daily</td>
<td>$70-$83</td>
<td>$235</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Aldactone</td>
<td>12.5 mg daily</td>
<td>25 mg daily</td>
<td>$5</td>
<td>$28-$57</td>
</tr>
<tr>
<td>ARB b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>Atacand</td>
<td>4 mg daily</td>
<td>32 mg daily</td>
<td>$86-$107</td>
<td>$145</td>
</tr>
<tr>
<td>Valsartan</td>
<td>Diovan</td>
<td>40 mg bid</td>
<td>160 mg bid</td>
<td>$25-$30</td>
<td>$83-$114</td>
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<tr>
<td>Beta Blocker b</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Bisoprolol</td>
<td>Zebeta</td>
<td>1.25 mg daily (1/4 tab d)</td>
<td>10 mg daily</td>
<td>$7-$21</td>
<td>$42-$168</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>Coreg</td>
<td>3.125 mg bid</td>
<td>25 mg bid</td>
<td>$8</td>
<td>$45-$136</td>
</tr>
<tr>
<td>Metoprolol Succinate</td>
<td>Toprol XL</td>
<td>12.5 mg daily (1/2 tab)</td>
<td>200 mg daily</td>
<td>$8-$13</td>
<td>$20-$39</td>
</tr>
<tr>
<td>Neprilysin inhibitor/angiotensin receptor blocker</td>
<td>Sacubitril/valsartan</td>
<td>49/51 mg bid</td>
<td>97mg/103mg bid</td>
<td>n/a</td>
<td>$405</td>
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<tr>
<td>Sinus Node Modulator</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ivabradine</td>
<td>Corlanor</td>
<td>5 mg bid</td>
<td>7.5 mg bid</td>
<td>n/a</td>
<td>$405</td>
</tr>
</tbody>
</table>

Drugs Demonstrated to Decrease Mortality and/or Improve Symptoms b
### Table 2. Doses for Major Heart Failure Drugs, continued

<table>
<thead>
<tr>
<th>Drug Class and Generic Name</th>
<th>Brand Name</th>
<th>Starting Dose</th>
<th>Target Dose or Common Dose</th>
<th>Target/Common Dose 30 Day Cost a</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vasodilator b</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hydralazine</td>
<td>Hydralazine</td>
<td>37.5 mg tid</td>
<td>75 mg tid</td>
<td>$11-22</td>
</tr>
<tr>
<td>Isosorbide dinitrate-</td>
<td>BiDil (combination product)</td>
<td>20/37.5 mg tid</td>
<td>40/75 mg tid</td>
<td>n/a $95-190</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>Isordil</td>
<td>20 mg tid</td>
<td>40 mg tid</td>
<td>$60-90 $65-129</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs for Symptomatic Therapy b</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diuretics – Thiazide e</strong></td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
</tr>
<tr>
<td>Metolazone</td>
</tr>
<tr>
<td><strong>Diuretics – Loop e</strong></td>
</tr>
<tr>
<td>Bumetanide</td>
</tr>
<tr>
<td>Ethacrynic acid</td>
</tr>
<tr>
<td>Furosemide</td>
</tr>
<tr>
<td>Torsemide</td>
</tr>
<tr>
<td><strong>Inotrope b</strong></td>
</tr>
<tr>
<td>Digoxin</td>
</tr>
</tbody>
</table>

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a  Cost = For brand drugs, Average Wholesale Price minus 10%. AWP from Red Book Online 1/5/16. For generic drugs, Maximum Allowable Cost plus $3 from BCBS of Michigan MAC List, 1/1/16. Prices calculated for 30 day supply unless otherwise noted.

b Although other drugs are available in these classes, they have not been demonstrated to decrease mortality or improve symptoms in patients with heart failure.

c Common doses.

d Tablet is scored for ½ tablet only.

e Diuretics have not been separately studied for target dose. Titrate as needed for symptom relief.
<table>
<thead>
<tr>
<th>Drug Category</th>
<th>&quot;Clinical Pearls&quot;</th>
</tr>
</thead>
</table>
| ACE Inhibitors/ ARBs | **Class effect.** ACE inhibitors appear to exhibit a class effect. All members of this class may be equally effective.  
**Contraindications.** ACE inhibitors and ARBs may cause hyperkalemia in the presence of renal failure and should be avoided or used with great caution among patients with Cr > 2.5, GFR < 30, or K > 5.0. Both classes of agents are contraindicated in patients with bilateral renal artery stenosis, unilateral renal artery stenosis with solitary kidney, pregnancy, and allergies. Angioedema can occur rarely with either class of agent. |
| ARNI | **Contraindications.** ARNI should not be used concomitantly with ACEI or ARB. It may cause hypotension or, rarely, angioedema. All of the precautions appropriate for ARB apply to concerns for hyperkalemia and renal failure |
| Beta Blockers | **Add when stable.** May be used in patients with heart failure due to systolic dysfunction who do not have contraindications noted below. They are to be added when patients are stable to arrest the progression of the disease. They are not to be added as rescue therapy for patients who are decompensating.  
**Dosing.** Start at low dose and double the dose every 2 - 4 weeks as tolerated until target dose reached. Stop upward titration if patient intolerant of higher doses (see Table 3 for dosing).  
**Absolute contraindications.** Heart block, bradycardia, severe reversible airway disease.  
**Relative Contraindications.** Rest dyspnea with signs of congestion, hemodynamic instability. Once these issues have resolved, beta blockers may be added to the chronic regimen. |
| Aldosterone Antagonists | **Hyperkalemia.** The risk of hyperkalemia may be significant. These risks can be minimized by avoiding use in patients with GFR < 30 or Cr > 2.5 and by insuring appropriate patient selection before initiating (see Table 2). Electrolytes must be monitored closely as was done in clinical trials so that medication changes will be monitored at 5-7 days after dose change, and again in 30 days. Elevation of potassium > 5.0 should prompt dose reduction or drug discontinuation. |
| Isordil-hydralazine | **Dosing.** These medications are available as a fixed dose combination in branded form. Generic constituents should be just as effective. Clinical trials were performed using isosorbide dinitrate. Isosorbide mononitrate is dosed daily and is more convenient. Evidence of clinical equivalence of the mononitrate form is expert opinion.  
**Contraindications.** Cannot be used concomitantly with phosphodiesterase inhibitors, e.g., sildenafil, tadalafil, and vardenafil. |
| Ivabradine | **Initiation:** For patients with persistent symptoms and HR > 70 despite maximally tolerated or target dose beta blocker  
**Contraindication:** Atrial fibrillation |
| Diuretics | "**Background" therapy.** Though not specifically tested in clinical trials, diuretics should still be used as needed for volume overload. Diuretics were consistently part of background therapy in all published placebo controlled mortality trials of symptomatic patients in which ACE inhibitors, beta blockers, and aldosterone antagonists were tested. |
| Combining Drugs | **Starting other drugs.** The therapy described in Table 2 is the desired endpoint for patients with the indicated symptoms and history. No data are available to indicate how best to introduce all of these medications. All of the major trials added beta blockers or spironolactone to background therapy of ACE inhibitors, diuretics, and sometimes digoxin.  
**Electrolytes and renal function.** Many of the medications appropriate for HF (ACE, ARB, Aldosterone antagonists, Digoxin) can affect potassium or can be affected by potassium levels and renal function. Vigilant monitoring is required.  
**Do not remove ACE inhibitors, beta blockers, spironolactone, or ARB’s.** These drugs should not be removed if symptoms improve because these medications slow disease progression and decrease mortality. |
| Referral | **Consider referral for the following clinical situations:**  
- diagnostic procedures  
- revascularization procedures  
- worsening or refractory heart failure  
- ventricular arrhythmias  
- valvular heart disease  
- consideration for transplantation |
Health care systems have targeted HF as a medical condition needing better disease-based management because of its prevalence and its management costs. The vast information regarding new treatments available for HF patients has resulted in variation in the management of this condition across specialties and health systems and under use of medications that have been proven effective. Treatment guidelines use evidence based approaches to help standardize care.

**Rationale for Recommendations**

**Etiology/Natural History**

The most common cause of left ventricular systolic dysfunction is coronary artery disease producing ischemic cardiomyopathy. Non-ischemic cardiomyopathies may resolve within twelve months of the onset of symptoms in approximately 30% of cases.

Patients with both ischemic and non-ischemic disease may suffer frequent hospitalizations and are at increased risk of premature death. Dietary indiscretion in sodium intake and medication noncompliance are common reasons for heart failure decompensation. Progressive pump failure and malignant arrhythmias are the most common causes of death among HF patients.

**Diagnosis and Surveillance**

Heart failure with reduced ejection fraction (systolic dysfunction) is a commonly recognized cause of heart failure. Widely available techniques can quantitate the left ventricular ejection fraction and estimate the degree of systolic dysfunction.

As many as 50% of patients with heart failure have a preserved ejection fraction (HF-PEF). Historically, these patients were referred to as having diastolic dysfunction. Diastolic dysfunction may be identified on the basis of echocardiographic criteria, such as the ratio of early-to-late diastolic filling, short deceleration times, and isovolemic relaxation times. However, many patients with HF-PEF do not have echocardiographic evidence of diastolic dysfunction. Some patients may have concomitant systolic and diastolic heart failure. HF may be more simply conceived in terms of reduced (HF-REF) or preserved ejection fraction (HF-PEF), rather than in terms of systolic or diastolic dysfunction, respectively.

Other causes of heart failure are less common. Therefore, many clinical trials of heart failure have included only patients in whom heart failure could be confirmed with documented left ventricular systolic dysfunction.

**Presenting signs and symptoms.** Heart failure often presents initially either as dyspnea with exertion or with recumbency. Patients also commonly experience dependent edema, rapid fatigue, cough, and early satiety. These symptoms are sometimes mistakenly attributed to other causes including pneumonia, asthma, and peptic ulcer disease. Arrhythmias causing palpitations, dizziness, or aborted sudden death can be the initial manifestations of the disease.

**Classification.** Heart failure limits exercise capacity. In general, patients with more severe functional limitations have poorer survival. Some physicians use the four tier New York Heart Association (NYHA) classification of functional capacity to estimate prognosis in clinical practice and to selectively define study populations in clinical trials. The classification scheme is:

<table>
<thead>
<tr>
<th>NYHA Class</th>
<th>NYHA Symptom Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA Class I</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>NYHA Class II</td>
<td>Mildly symptomatic</td>
</tr>
<tr>
<td>NYHA Class III</td>
<td>Moderately symptomatic</td>
</tr>
<tr>
<td>NYHA Class IV</td>
<td>Symptoms at rest</td>
</tr>
</tbody>
</table>

The NYHA classification, originally designed as a research tool has been used to estimate prognosis in clinical practice and to selectively define study populations in clinical trials. In 2001, the ACC/AHA proposed a new stratification scheme:

<table>
<thead>
<tr>
<th>ACC/AHA Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At risk</td>
</tr>
<tr>
<td>B</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>C</td>
<td>Symptomatic</td>
</tr>
<tr>
<td>D</td>
<td>Refractory</td>
</tr>
</tbody>
</table>

In the prior iterations of this guideline, we have tried to provide a guide for therapeutic decisions according to inclusion criteria that were used to categorize patients into the major clinical trials. As new data has become available, we have modified those descriptions appropriately.

The relationship between the classification schemes is shown in Table 1.

**Diagnostic testing and evaluation.** Several methods are available to test and evaluate cardiac functioning.

**Ejection fraction.** Patients with a presumed diagnosis of HF should have assessment of systolic function as shown by ejection fraction. The assessment should be repeated when the clinical situation has changed and is not easily explainable through history or physical examination. Ejection fraction should be measured six months after surgical or percutaneous revascularization and managed based upon the post re-vascularization ejection fraction.

The management of HF is based on the clinical presentation, the examination, and the determination of the ejection fraction (EF). Echocardiography is commonly used, but other imaging modalities are also used including radionuclide ventriculography, contrast ventriculography, cardiac CT, gated SPECT, and MRI. Transthoracic
Echocardiography provides non-invasive diagnostic information readily and safely. It provides information on ventricular shape and function, wall thickness and valvular function— all helpful in the management of patients with HF. It is commonly used, widely available, and inexpensive.

While radionuclide ventriculography or gated SPECT imaging may also be used to assess left ventricular and right ventricular EF, it does not allow assessment of valvular function or wall thickness. Gated SPECT may have better inter-observer reliability than echocardiography in assessing ejection fraction. However, the cost and radiation exposure support echocardiography as an appropriate initial evaluation.

Functional testing. Exercise stress testing may have a role in the evaluation of some patients with heart failure. Exercise stress testing is useful in evaluating active and significant concomitant coronary artery disease and in assessing functional capacity.

Cardiopulmonary exercise testing can quantify a patient’s functional capacity. Testing may be indicated to document disability for insurance. Patients with poor ventilatory efficiency (VE/VCO2 slopes > 35) or very low peak oxygen consumptions (VO2 < 14) may be candidates for advanced heart failure interventions including ventricular assist devices and cardiac transplantation. Consider referring these patients to heart failure sub-specialists. When and exactly how to perform stress testing in this group is probably best decided with the aid of a cardiologist.

Cardiac catheterization. Coronary angiography and left heart cardiac catheterization is useful in the management of heart failure when the discovery of significant coronary artery disease or valvular heart disease would either impact medical treatment or provide the necessary information to proceed to surgery. See section on operative therapy for more detail.

Right heart catheterization may be useful in the development of a differential diagnosis and to guide therapy in patients for whom volume status is unclear.

The decision to proceed to cardiac catheterization should be made based on clinical presentation, patient features, non-invasive test results, and a substantial weighing of the risks and benefits. This decision should be individualized and is best made collaboratively with a cardiologist.

Electrocardiography. The majority of left ventricular systolic dysfunction is due to ischemic heart disease. Standard 12 lead electrocardiography (ECG) should be used to help determine whether ischemic heart disease is likely so that appropriate interventions for that condition can be initiated. A standard ECG can also identify some arrhythmias. For example, atrial fibrillation may not be apparent on physical examination especially in patients who are ventricularly paced, but can be recognized on the ECG. Similarly, other supraventricular arrhythmias, such as atrial flutter, may only be identified by the ECG. In addition, nodal or fascicular heart block can be recognized from the ECG as potential causes of dizziness or syncope.

Additionally, an ECG can be helpful to assess for dysynchrony between the right and left ventricles. A QRS duration greater than or equal to 120 msec is highly suggestive of dyssynchrony. Those with a QRS duration less than 120 msec may still have dysynchrony that can be detected on an echocardiogram. If dysynchrony is detected, patients may gain symptomatic and survival benefit from insertion of a bi-ventricular pacemaker (Bi-V).

Ambulatory rhythm monitors. A major cause of death in heart failure is sudden death presumably due to arrhythmias. Over the past few years, several convincing studies have demonstrated a significant survival advantage to patients with symptomatic or inducible ventricular arrhythmias and ischemic heart disease, with or without heart failure, who have implantable cardioverter-defibrillators (ICD). Studies have also demonstrated similar benefit for non-ischemic heart failure patients with ventricular arrhythmias. Ambulatory monitoring should be a part of the evaluation of any heart failure patient suspected of rhythm disturbances. If ventricular arrhythmias are present, the patient should be referred for further evaluation.

B-type natriuretic peptide (BNP). BNP and its closely related N terminal fragment have recently been proven to have substantial usefulness in the diagnosis and prognosis of patients with heart failure. These biologically active proteins are present in cardiac myocytes, and are released in response to demands related to heart failure including stretching of myocytes. They are biologically active: augmenting urine volume and sodium excretion, inhibiting renin-angiotensin activation, and relaxing vascular smooth muscle. Their analogs may have useful clinical applications in the future. These hormone biomarkers are measurable in concentrations of picograms per milliliter, and commercially available assays, including point of care methodology, are now widely available.

BNP can be used to help establish the diagnosis of heart failure in patients who present with dyspnea. BNP does not differentiate the cause of heart failure (heart failure with preserved ejection fraction, heart failure with reduced ejection fraction, systolic dysfunction, valvular heart disease, congenital heart disease, etc.) In acute care settings, high BNP levels correlate directly with the probability of heart failure and low BNP levels make heart failure unlikely. For example, a BNP of 50 pg/mL has a negative predictive value (the ability of a negative test to indicate no disease) of 96%, whereas a BNP of 100 pg/mL has a positive predictive value of 79%, and a BNP of 150 pg/mL has a positive predictive value of 83%. At a BNP of 250 pg/mL, the relative risk of heart failure is 7.0 (see Figure 1). BNP levels can be increased by renal
insufficiency and to lesser extremes by age and female gender. Obesity tends to lower BNP levels and obese patients may have low or normal BNP levels even in the setting of elevated filling pressures.

Elevated BNP levels in patients with an established diagnosis of heart failure are also powerful indicators of prognosis. Persistently elevated levels in patients being treated for heart failure indicates poorer prognosis. Trials of BNP or N-terminal pro BNP (NT proBNP) guided outpatient management have shown mixed results. The largest study did not show a significant improvement in clinical endpoints when NT pro BNP guided managements was compared with symptoms guided management. However, a modest benefit occurred in a planned subgroup analysis of patient younger than 75. The utility of BNP measurements in the emergency setting to guide decisions about admission or therapy has also been studied with mixed results.

**Electrolytes.** Problems with electrolyte balance can easily occur in patients with HF.

**Potassium and magnesium.** Monitoring of potassium and magnesium serum concentrations is essential in the majority of heart failure patients. Diuretics may significantly lower potassium and magnesium concentrations whereas ACE-inhibitors, ARB’s, aldosterone antagonists, dietary factors (e.g. bananas and salt substitutes) may significantly increase potassium concentrations, especially in the presence of renal impairment or when used in combination. In general, based on clinical perspective, potassium levels should be maintained between 4.0 – 5.0 mEq/L. Circadian variation may lower potassium levels by up to 0.5 mEq/L during the early morning hours in a given patient. Artifically elevated potassium levels may occur due to hemolysis of the sample and due to hand clinching during phlebotomy.

If required, potassium supplementation should be administered; usual dose range is 10 – 80 mEq/day with a potassium chloride preparation. Other salt forms include potassium phosphate and potassium bicarbonate. Microencapsulated formulations may have better patient appeal and GI tolerance.

Magnesium levels should be maintained between 1.5 – 2.4 mEq/L. The usual dose range for magnesium supplementation for asymptomatic patients with minor alterations in serum concentrations is one to four tablets of a product such as magnesium oxide 400 mg (242 elemental magnesium content). Magnesium chloride is better absorbed than magnesium oxide but is only available over the counter and may not be available in consistent doses. Also, there is no data to guide converting between the different magnesium salts. Diarrhea can be a dose limiting side effect. Hypokalemia is often easier to correct if hypomagnesemia is also corrected. When administering supplemenations serum electrolytes should be monitored. In addition, serum electrolytes should be monitored with any change in diuretic dosing, change in renal function, or addition of drugs that may either promote hyper- or hypokalemia warrant monitoring of electrolyte concentrations.

**Sodium.** Patients with heart failure may have low serum sodium levels. Often these low levels are the result of extracellular fluid excess leading to a dilutional hyponatremia (excess total body sodium and larger excess of total body water). Fluid restriction and diuresis may correct the dilutional hyponatremia. In contrast, diuretic use in patients with free access to fluid can lead to total body sodium depletion. Monitoring of serum sodium should be included with monitoring of other electrolytes.

**Lifestyle Management**

Lifestyle management includes patient education, exercise, and dietary changes.

**Patient education.** Patient education on several topics at the time of discharge is a Joint Commission (JC) core measure. Many heterogenous studies have examined the role and the effectiveness of patient education in heart failure. The modalities studied include: videos, face to face counseling by nurses or nutritionists, telephone counseling, mailings, and web based counseling. The settings include the time of discharge, during a clinical visit, and in the patient’s home. Most interventions were successful in increased patient knowledge about heart failure and measures to control heart failure. However, more comprehensive programs, often involving nurses or case managers who made repeated contacts with patients, were successful at actually improving clinical outcomes.

Patient education should address the following.

**Serious condition.** Heart failure is a serious condition that results from the heart’s inability to pump a sufficient amount of blood.

**Symptoms to watch for.** Tell your doctor at once if you have these or other symptoms of heart failure:

- **Weight gain** of more than 3 pounds in 1 week, or progressive weight gain over weeks or months
- **Shortness of breath**
- **Swollen ankles or feet or generalized swelling of limbs, face, and neck**
- **Fatigue**
- **Irregular heart rhythm** (palpitations or feeling of thumping in chest)
- **Dizziness or fainting**
- **Loss of appetite**
- **Persistent cough**

**Lifestyle.** Maintain your health and monitor changes in your health:

- **Weigh yourself** daily, at the same time of day, if possible and keep a weight log.
- **Restrict sodium** in your diet
- **Avoid excessive eating and drinking**.

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Medications. Develop and follow a schedule for taking your medications regularly. As you may be on multiple medications, there is the potential for side effects and interactions. Talk to your doctor before adding any new or over the counter medications or herbal supplements.

Doctor’s appointments. Keep all appointments with your doctor.

The UMHS Patient Education Clearinghouse links to several materials that address the topics discussed above. To access a current list of materials go to http://www.med.umich.edu/careguides and type “Heart Failure” in the keyword search box.

Exercise. Many clinical trials (some randomized) have examined the benefits of a variety of exercise training formulas in both men and women with heart failure. The majority of trials have included patients with NYHA class II/III heart failure. These studies have measured clinical outcomes such as admission rates and mortality and intermediate outcomes, such as ventilatory capacity, maximum oxygen consumption, skeletal muscle parameters, neurohormonal levels, exercise capacity and quality of life.

Overall study results found that exercise has:

• No significant impact on short-term or long-term all-cause mortality or overall hospital admission rates. A Cochrane review of available studies reached this conclusion.
• Improvement in health related quality of life and a 28% reduction in heart failure related hospital admissions.

In the HF-ACTION trial, exercise appeared to be safe with participants engaging in exercise times per week followed by prescribed home-based training at the same intensity 5 times per week.

Dietary changes. No large prospective clinical trials of salt or fluid restriction exist for the treatment of heart failure.

Common clinical practice is to recommend limiting sodium intake to 2000 mg daily and fluid intake to 2 L or less daily, especially in patients with hyponatremia. One prospective study suggested that fluid restriction might be more important than sodium restriction.

Surgery and Resynchronization

Operative therapy. No clear consensus exists regarding which patients to refer for coronary artery bypass grafting (CABG). Decisions to pursue revascularization should be individualized. A shared medical decision should involve the patient, the surgeon, and the primary care physician.

Ischemic heart failure is potentially reversible; however indications for CABG have been unclear. The Surgical Treatment for Ischemic Heart Failure Trial randomized 1,212 patients with an EF less than or equal to 35% either to medical therapy or to medical therapy plus CABG. In an intention to treat analysis, the groups did not differ significantly in terms of the primary endpoint of all cause mortality; though a non-significant trend favored CABG. Owing to a significant crossover between groups, an as-treated analysis provided a different result, revealing a statistically significant 30% reduction in all cause mortality for patients undergoing CABG. The death rate for CABG was initially higher, then subsequently lower, resulting in no difference over the entire two-year surveillance period. Assessment of myocardial viability did not distinguish patients with a differential benefit for CABG versus medical therapy.

Patients with heart failure due to aortic stenosis should be considered for surgical or percutaneous valvular replacement, but the management of this condition is beyond the scope of this guideline.

Automatic implantable cardiac defibrillators (ICD). ICD placement should be considered in all HF patients who are symptomatic or have a history of ischemic cardiomyopathy and with an EF ≤ 35%. Patients should have an estimated life expectancy > 1 year. These patients should be referred to an electrophysiologist or cardiologist for evaluation.

Part of the evaluation for ICD should be an ECG. This will define the QRS duration and help determine whether the device should also provide Cardiac Resynchronization Therapy (CRT; see below) to improve symptoms.

Prophylactic implantation of ICD’s has been demonstrated in large trials to decrease mortality in patients with HF who are receiving appropriate pharmacological therapy. In patients with systolic heart failure, placement of an ICD lowered all cause mortality (relative risk of approximately 0.70 across the MADIT II, DEFINITE, and SCD-HeFT trials). The relative risk of mortality from arrhythmia was 0.20 (DEFINITE trial).

Considerations regarding implantation an ICD include:

• An ICD should not be implanted within one month following myocardial infarction or within three months following CABG (data from CABG Patch (1997) and DINAMIT (2004)).
• Survival benefit is only realized after one year (MADIT II and SCD HeFT trials), so the patient’s life expectancy should be greater than a year.
• Women meeting criteria for ICD placement should be referred to an electrophysiologist or cardiologist no differently than men. However, some question exists regarding whether women benefit from ICD and whether they have more device implantation complications (SCD-HeFT, INTRINSIC RV, Meta analyses x 2). In the past fewer ICD’s have been placed in women so data are limited.
CRT with biventricular (Bi-V) pacing has been shown to decrease the composite of all-cause death or hospitalization by 19% in HF patients with NYHA III or IV symptoms, an LVEF ≤ 35%, and a QRS interval ≥ 120 msec. All-cause mortality alone was reduced by 24%. When an ICD was added to the Bi-V pacer, all-cause mortality was reduced by 36%. Also, when biventricular pacing alone was restricted to HF patients with NYHA class III or IV symptoms, an LVEF ≤ 35%, and either a QRS interval ≥ 150 msec or a QRS interval ≥ 120 msec with echocardiographic evidence of cardiac dyssynchrony, the combined endpoint of mortality or cardiovascular hospitalization was reduced by 37%. Biventricular pacing also improved symptoms, and quality of life. Benefit occurred primarily in patients with left bundle branch block.

Bi-V pacing may also benefit less symptomatic HF patients (NYHA I – II) with an LVEF ≤ 40% and a QRS interval ≥ 120 msec. In two clinical trials in this group of patients, time to first hospitalization or death was significantly delayed by 56% and 62%. Again, benefit occurred primarily in HF patients with left bundle branch block.

**Pharmaceutical Therapy**

**Major drugs.** See Table 1 for drug use by patient classification, Table 2 for dosing and cost, Table 3 for “clinical pearls”, and the Appendix for common drug interactions.

**Diuretics.** Diuretics are used and often required to manage volume overload acutely and chronically. The dose of loop diuretic will vary greatly between patients and will be determined by individual response. Since diuretics may produce potassium and magnesium wasting, monitoring of these electrolytes is warranted.

Diuretic effect on mortality is not known. Although no large controlled clinical studies of diuretics in the treatment of heart failure have been reported, the vast majority of patients with heart failure received diuretics as part of baseline therapy in trials of ACE inhibitors, beta blockers, spironolactone, and digoxin.

All loop diuretics have similar efficacy when administered in appropriate doses. The most commonly used loop diuretic is furosemide. However, others may be preferred in specific situations.

- As patients begin to decompensate, torsemide can be considered as an alternative to furosemide in patients who are frequently hospitalized for fluid accumulation. Torsemide’s rate of absorption is not significantly altered when patients become decompensated unlike furosemide. Changes in drug absorption may be one of the factors that lead to frequent hospitalizations with individual patients.

- Ethacrynic acid is an option for patients with allergies to furosemide, bumetanide and torsemide due to lack of sulfur moieties.

Combining a loop diuretic with a thiazide diuretic increases diuretic effect by minimizing distal tubular compensation. Loop diuretics are most often used because of their diuretic potency, but can be associated with acute and chronic distal tubular compensation (distal tubular hypertrophy) resulting in decreased urine output. While adding a thiazide diuretic minimizes distal tubal compensation, the increase in diuretic response will likely result in an increase in the loss of potassium and magnesium. Additional monitoring of serum electrolytes may be needed.

The effect of a thiazide diuretic to increase diuretic responsiveness appears to be a class effect. Hydrochlorothiazide (usual dose range 25-100 mg once or twice daily) and metolazone (usual dose range 2.5 mg – 10 mg once daily) are common thiazide diuretics used in combination with loop diuretics. The long duration of action of metolazone may make it more effective than hydrochlorothiazide in some patients.

No data support the sequential timing of loop and thiazide diuretics. Specifically, no data support the concept of administering the thiazide diuretic 30 minutes before a loop diuretic.

In patients with chronic kidney disease, higher doses of a thiazide diuretic may be needed. However, at higher dose levels patients may see a robust response to combination therapy leading to potential adverse effects associated with excessive diuresis. Aggressive or excessive diuresis can lead to electrolyte depletion, decreased blood pressure, and worsening renal function, which may require additional monitoring of the patient. Therefore, a loop and thiazide diuretic are often utilized together, periodically, over a short time frame to increase diuresis, rather than utilizing them in combination for long term.

**Renin Angiotensin Aldosterone System (RAAS) antagonist choices.** Previously RAAS antagonism was achieved through ACE or ARB in all patients and an aldosterone antagonist in appropriate patients. The PARADIGM HF study (NEJM 2014) changed the paradigm by demonstrating superiority of a new class of drug – angiotensin receptor/neprilysin inhibitor or ARNI – as compared to enalapril. All patients with heart failure and reduced ejection fraction still need RAAS inhibition, but the choice of agent (ACE, ARB, or ARNI) is now more complicated (see Table 1).

ACE Inhibitors. ACE inhibitors are beneficial in the treatment of all patients with systolic heart failure. A number of landmark randomized controlled trials have demonstrated their effectiveness in impacting morbidity and mortality in both asymptomatic and symptomatic patients. Ace inhibitors have long been considered a cornerstone of therapy for all patients, unless absolutely contraindicated. The PARADIGM HF study showed superiority of ARNI over enalapril (see ARNI section, below); however, the study patients received enalapril first to insure tolerance. Given the lack of real world experience with ARNI therapy,
either ACE or ARNI may be reasonable at this time. Dual therapy with both ACE and ARNI is contraindicated. See Table 2 for target dosing information.

ACE inhibitors are often avoided in patients with heart failure because of perceived risk and contraindications. Patient factors such as lower blood pressure, elevated serum creatinine, and cough should not be considered absolute contraindications. When initiating treatment careful monitoring is warranted if the systolic blood pressure is < 100 mmHg or the creatinine is elevated.

Some patients will not tolerate ACE inhibitors. In this setting either an ARB or isordil-hydralazine may be used to substitute. If ACE inhibitors are contraindicated due to renal failure, then isordil-hydralazine is preferred.

**Angiotensin receptor blockers.** ARBs have been tested alone as agents for use in place of or in addition to ACE inhibitors and more recently in combination with a neprilysin inhibitor against an ACE inhibitor (see ARNI section for details). As a substitute for ACE inhibitors, ample evidence supports the use of ARB's for patients who cannot tolerate ACE inhibitors. Evidence suggests equivalence of ARBs in comparison to ACE inhibitors. However, ACE inhibitors have the advantage of lower cost and more patient experience and are still the preferred first line agent for suppression of the renin-angiotensin system for most patients. (The combination of isordil-hydralazine has also been used in patients who cannot tolerate ACE inhibitors. No trials compare isordil-hydralazine and ARBs among ACE inhibitor intolerant patients.)

Adding ARBs to ACE inhibitors is not recommended. ARBs have been added safely to ACE inhibitors to reduce persistent symptoms in clinical trials of heart failure patients. However, adverse events with this combination among non-heart failure patients have raised reservations about using these drugs in combination.

ACE inhibitors, ARBs, and aldosterone antagonists may all increase potassium. They may represent a dangerous combination if used together.

**Angiotensin II Receptor Blocker Neprilysin Inhibitor (ARNI).** ARNI therapy is superior to ACE in symptomatic patients with HFrEF. Neural endopeptidase (neprilysin) is an enzyme that is widely expressed and has many functions, but modifications of neprilysin function have not resulted in a clinically useful agent until now. In the PARADIGM HF trial a neprilysin inhibitor in combination with an ARB (valsartan) was tested against enalapril 10 mg BID among 8,842 patients with symptomatic HFrEF. The study was planned for 34 months, but was stopped at 27 months due to superiority of the study drug in the primary endpoint – a composite of death from cardiovascular causes or a first hospitalization from HF (HR 0.80, p = sig; NNT 22). The cost of ARNI therapy is significant with an estimated cost per Quality Adjusted Life Year of $51,000.

The benefit of ARNI therapy over enalapril is quite impressive and gives credence to consideration of ARNI therapy as the new standard. However, application has been slow: this is a new class of drug that has been tested only in one trial, unopposed neprilysin therapy had untoward side effects in trials, and post marketing data are not yet available. ARNI has the same contraindications as ACE/ARB and is not to be used in combination with ACE.

**Beta blockers.** Beta blockade is indicated in heart failure patients with systolic dysfunction except those who are dyspneic at rest with signs of congestion, are hemodynamically unstable, or are intolerant of beta blockers (see algorithm). Recent trials in symptomatic patients have shown dramatic mortality benefits, making beta blockers a mainstay in heart failure treatment. Beta blockers have not been demonstrated to show benefit in patients with rest dyspnea and signs of congestion.

Most patients with known asymptomatic left ventricular dysfunction are also post MI. The benefit of beta blockers in these patients has been well described and beta blockers should be given. No comparable data exist for asymptomatic patients with idiopathic heart failure.

Beta blockers cannot be presumed to have a class effect on heart failure. Three beta blockers – carvedilol, metoprolol succinate, and bisoprolol at target doses of 25 mg BID, 200 mg daily, and 10 mg daily respectively – have been shown in randomized controlled trials to produce similar, profound, and statistically significant decreases in mortality in patients with heart failure. However, at least one other beta blocker has failed to reduce mortality in a placebo-controlled trial. Only the three beta blockers, carvedilol, metoprolol succinate, and bisoprolol, titrated to the target doses in the placebo-controlled trials should be used.

No evidence clearly demonstrates the overall superiority of one of the three known efficacious beta blockers. The three do differ pharmacologically. However, only one flawed trial has directly compared two of them. Carvedilol is superior to metoprolol tartrate in prolonging survival in patients with symptomatic heart failure when these agents are administered at doses of 25 mg BID versus 50 mg BID respectively. However, the dose and formulation of metoprolol in this study differed from the dose and formulation in the placebo-controlled trial in which metoprolol succinate was proven effective. A high dose of metoprolol succinate might have yielded a different result. Whether the comparative trial demonstrates the superiority of carvedilol or the critical importance of dose and drug formulation in treating patients with heart failure cannot be resolved. No further comparative trials of beta blockers are underway.

Beta blockers should be administered to heart failure patients with some caution, but clearly they can be
administered safely by primary care physicians. Beta blockers should be added when patients are stable – to diminish the progression of the disease. They are not to be added as a rescue therapy for patients who are decompensating. The initial dosage level should be started (see Table 2), then doubled every two to four weeks until either unable to tolerate higher levels or the target dose is reached (see Table 2). Symptoms of increasing dyspnea, worsening heart failure, hypotension or symptoms of hypotension should prompt evaluation of the patient and may necessitate increasing diuretics or may require discontinuation or decrease of the beta blocker.

**Aldosterone Antagonists.** Aldosterone antagonism is indicated in all patients with systolic dysfunction and symptomatic heart failure and in patients following a recent myocardial infarction who develop systolic dysfunction with either manifest signs of heart failure or concomitant diabetes. Aldosterone antagonists significantly reduce both mortality and hospitalizations for heart failure.

Administer aldosterone antagonists to patients with symptomatic heart failure and serum creatinine < 2.5 mg/dl or a glomerular filtration rate > 30 ml/min per 1.73 M² of body surface area and without baseline hyperkalemia (> 5 mEq/L). After initiating an aldosterone antagonist, serum potassium levels should be closely monitored, especially in patients with mild symptoms.

The two available agents, low dose spironolactone and eplerenone, differ in potency and in other effects including the anti-androgenic effects of spironolactone. Spironolactone is twice as potent as eplerenone as an aldosterone antagonist, but spironolactone also produces gynecomastia in 7% of men when administered at a dose of 25 mg daily, a side effect not seen with eplerenone. The agents were tested in different populations, spironolactone in patients with severe heart failure and eplerenone in patients with mild heart failure and in patients post-myocardial infarction.

As aldosterone antagonists, both spironolactone and eplerenone are potassium sparing diuretics and can cause hyperkalemia, especially when administered concomitantly with angiotensin converting enzyme inhibitors or angiotensin receptor blockers. In the clinical trial of aldosterone antagonism in patients with severe heart failure, severe hyperkalemia was rare (2%). However, severe hyperkalemia was more common in the clinical trials of patients post-myocardial infarction (5.5%) and in patients with less severe heart failure (8%). In these clinical trial populations, selection criteria excluded patients with baseline renal dysfunction or baseline hyperkalemia. In presumably less selected populations, aldosterone antagonism has been associated with more frequent severe hyperkalemia and increased mortality.

Direct acting vasodilators. Combined isosorbide dinitrate 40 mg with hydralazine 75 mg three times a day may be used as tolerated by blood pressure in symptomatic HF patients who are African American and may be used as a substitute for any HF patient who is intolerant of ACE inhibitors or ARB’s. This combination may also be used as tolerated by blood pressure in HF patients who are persistently symptomatic on ACE inhibitors, ARB’s, and/or beta blockers. Headache may develop but will often improve with continued use.

Direct acting vasodilators were among the first medications shown to improve survival in heart failure. Subsequently, randomized controlled trials demonstrated that ACE inhibitors were superior, particularly in class I and II heart failure. In a post-hoc analysis of those trials the combination of isosorbide dinitrate and hydralazine was particularly effective in African American patients. Improvement in mortality among African American patients using fixed dose isosorbide dinitrate and hydralazine has since been demonstrated in a prospective trial in which these agents were added to usual background therapy. Patients in this trial self-identified as African-American, but a substudy of that trial identified a genetic polymorphism more common among African Americans as the trait most likely to predict responsiveness to this drug combination.

**Digoxin.** Consider using digoxin in patients who remain symptomatic despite therapy with diuretics, ACE inhibitors, and beta blockers and in those who have atrial fibrillation. Digoxin may still be used among patients on spironolactone with the caveat that spironolactone may increase digoxin levels by decreasing renal excretion. This effect has not been reported with eplerenone. As an increasing number of medications can become a barrier to compliance, digoxin is more often used as a tertiary drug.

Digoxin can improve symptoms and reduce hospitalization rates in heart failure patients who remain symptomatic despite maximal individualized therapy with diuretics, ACE-inhibitors, and beta blockers. Digoxin has no effect on overall mortality. Since digoxin has not been shown to improve mortality, other therapies that do affect mortality are recommended before digoxin.

The usual dose range for digoxin is 0.125 to 0.25 mg/day to be adjusted as needed based upon symptoms, other drugs, or renal impairment (see Table 2). Retrospective analysis of the only large heart failure trial for digoxin suggests that serum levels for treatment of symptomatic heart failure should be < 1 ng/ml when measured at least 6-8 hours after dosing. Digoxin may also be used to help control ventricular response rate in patients with heart failure and atrial fibrillation. Levels needed to control ventricular response rate may need to be above 1 ng/ml.

**Sinus Node Modulator.** Ivabradine may be indicated for patients admitted to the hospital within the last 12 months for decompensated HFrEF, who remain symptomatic, have sinus rhythm with rate > 70 and who are on at least 50% of the target dose of beta blocker.
Ivabradine, as a sinus node modulator, is the sole agent in a new class of drug. In the SHIFT trial (Lancet 2010) ivabradine was tested against placebo in 6,558 patients over the course of 22.9 months. The ivabradine group had an 18% lower rate of reaching the primary endpoint of cardiovascular death or hospitalization for decompensated HF (NNT 26). Most of the benefit was in reduced hospitalizations and all of the benefit was among those with HR > 70. SHIFT recruited patients who had been admitted to the hospital for HF within the past 12 months. A prior trial (BEAUTIFUL) that tested ivabradine across all classes of HF was not positive. Ivabradine should only be used for patients in sinus rhythm. As the mortality benefit of beta blockers has been clearly demonstrated, every effort should be made first to titrate the beta blocker to target dose before initiating ivabradine.

**Minor drugs.** Other frequently relevant drugs include calcium channel blockers, inotropes, anti-arrhythmic drugs, and lipid-lowering agents.

**Calcium channel blockers.** Currently, no evidence supports the use of CCBs for treatment of systolic heart failure (HF). However, if CCB’s are needed for management of hypertension, second generation agents appear to be safe. First generation agents (verapamil, diltiazem) were shown to have adverse outcomes in post-MI patients with systolic dysfunction. Subsequent studies in ischemic and nonischemic HF NYHA III/IV with other CCB’s (e.g. amlodipine, felodipine) suggested their safety, but did not demonstrate their efficacy. A subgroup analysis of the first randomized controlled trial using amlodipine found a 46% decrease in mortality in patients with non-ischemic HF. However, a subsequent trial demonstrated no mortality benefit from amlodipine in nonischemic cardiomyopathy.

**Inotropes.** Intravenous inotropic therapy with sympathomimetics (dobutamine or dopamine) or phosphodiesterase inhibitors (milrinone) may have a role in the treatment of patients hospitalized for acutely decompensated heart failure who do not respond adequately or in a timely manner to diuretic therapy. Inotropic agents may increase cardiac output and decrease systemic and pulmonary vascular resistance. Although these therapies may improve symptoms and decrease hospitalizations, they are associated with increased mortality.

Intermittent bolus or continuous home infusion therapy of either dobutamine or milrinone is not recommended for routine management of heart failure. Continuous intravenous inotropic therapy may have a role in palliation of patients with end stage heart failure or as a bridge to transplantation. Home therapy should only be considered in end-stage heart failure patients with full acknowledgment that this therapy may increase their mortality and should only be directed by a heart failure specialist.

**Anti-arrhythmic drugs.** While arrhythmias such as atrial fibrillation and non-sustained ventricular tachycardia are commonly encountered, no reproducible evidence indicates that patients with heart failure will significantly benefit either from specific anti-arrhythmic drugs prior to developing arrhythmias or from the treatment of the arrhythmia.

The use of device therapy has supplanted the use of anti-arrhythmic drugs for primary treatment of ventricular arrhythmias. However, anti-arrhythmic therapy may be used in conjunction with device therapy in selected patients to suppress ventricular arrhythmias and minimize device firing. Antiarrhythmic drugs that have potent negative inotropic effects such as flecainide should be avoided in heart failure patients with or without device therapy. Antiarrhythmic pharmacotherapy does not directly improve a patient’s heart failure functional status or mortality.

**Lipid-lowering agents.** The most common cause of heart failure secondary to systolic dysfunction is still ischemic damage. However, no broad indication exists for statin therapy in all patients with symptomatic systolic heart failure. Two large randomized trials assessed the effect of rosuvastatin in patients with symptomatic systolic heart failure. One trial enrolled all patients with heart failure while the other trial was limited to only those patients with heart failure due to ischemia. Neither trial showed a significant benefit in either survival or cardiac events. The ischemic trial did show a slight decrease in cardiac hospitalizations. No safety concerns occurred for statin therapy in these high risk patients. The decision to use or not to use a statin should be individualized based on the patient’s other medical problems and after discussion between the patient and the physician.

Supplementation with fish oils may be beneficial in patients with heart failure. Several cohort studies suggest that increased fish consumption is associated with a lower risk of developing heart failure. One large randomized study of n-3 polyunsaturated fatty acids (PUFA) supplementation in patients with symptomatic heart failure showed a small but significant reduction in death and hospitalization.

**Other drugs.** Questions sometimes arise regarding the use of anti-thrombotics, NSAIDS, and narcotics.

**Anticoagulation.** Warfarin therapy is not routinely indicated for the treatment of heart failure. Anticoagulation therapy is indicated in heart failure patients who are at risk for thromboembolism, including atrial fibrillation, history of previous embolization, and placement of mechanical valves. Anticoagulation therapy has also been prescribed for patients with low EF or demonstrated left ventricular thrombus. However, data supporting the use of anticoagulation for these conditions, especially low EF, are limited and controversial.

The appropriate dose of warfarin is determined by the patient’s INR and indication for anticoagulation therapy. Patients on warfarin therapy should be carefully monitored for bleeding and interactions with prescription drugs, nonprescription drugs, natural products, and food.
Antiplatelet. Heart failure is not an indication for aspirin therapy. However, heart failure is not a contraindication for aspirin therapy in patients with coronary artery disease. Controversial data suggest that aspirin may interfere with ACE inhibitor efficacy; however, the clinical relevance is not clear. Aspirin therapy has also been associated with an increase in hospitalization rates for heart failure (compared to anticoagulant therapy), although this is controversial. However, patients with coronary artery disease or post myocardial infarction should be considered for low dose aspirin therapy (e.g. 81 mg/day). With the limited data available, it is reasonable to consider aspirin therapy for heart failure patients with a coronary history. Potential adverse effects of aspirin on gastric mucosa and on renal function should also be considered. In patients not able to tolerate aspirin therapy, clopidogrel therapy (75mg/day) may be considered. Limited data suggest similar benefits in heart failure patients regarding mortality, hospitalizations, and bleeding episodes as compared to aspirin.

Antithrombotics. Heart failure patients with non-valvular atrial fibrillation may be considered for alternative therapies other than warfarin. Newer agents e.g. dabigatran (a direct thrombin inhibitor) and rivaroxaban and apixaban (direct factor Xa inhibitors) appear to be more efficacious (preventing stroke and systemic embolism), safer (causing less major and intracerebral hemorrhage), and more convenient (obviating the need for monitoring anticoagulation) than warfarin. These newer agents will likely replace warfarin in many patients in the future. However, regardless of the antithrombotic, the risk of bleeding appears to increase with age, renal dysfunction, and through a variety of drug interactions. In general, the primary indication for antithrombotics in left ventricular systolic dysfunction is to prevent thromboembolic events associated with atrial fibrillation. (Also see section on atrial fibrillation.)

NSAIDS / COX II inhibitors. NSAIDs and COX-II inhibitors should be avoided in heart failure patients if possible. No reported prospective controlled trials have evaluated the safety or efficacy of NSAIDs or COX - II inhibitors in patients with heart failure. However, many heart failure patients are on these medications for other indications. NSAIDs can have interactions with several other medications frequently used in heart failure such as ACE inhibitors and warfarín. Observational trials have demonstrated an increase in admissions for HF patients using NSAIDs or COX-II inhibitors. Long term NSAID treatment increases the risk of GI bleeding and renal insufficiency.

Narcotics. No reported controlled trials have evaluated the efficacy of narcotics in patients with heart failure. Narcotics may be used safely, if prescribed appropriately for other indications in patients who have heart failure. Narcotics have historically been used for acute symptomatic treatment of patients with end-stage heart failure. Ample anecdotal experience supports this indication for narcotics in end-stage heart failure.

Vaccination

Influenza vaccination. Influenza vaccination is now recommended by the Centers for Disease Control for all individuals age 6 months and older. Observational studies have demonstrated the general effectiveness of influenza vaccinations in older adults and those with chronic diseases.

In an observational study during two influenza seasons and including >140,000 individuals ≥ 65 years in each season, influenza vaccination was associated with a 19 percent reduction in risk of hospitalization for cardiac disease. More specifically, during the two seasons there were 0.81 and 0.73 relative risks of hospitalization for heart failure, 0.52 and 0.50 relative risks for death from all causes among individuals who received vaccination.

Pneumococcal vaccination. Pneumococcal vaccination is indicated for patients with heart failure. The incidence and the mortality of pneumococcal disease are highest in older adults and in those with comorbidities. Studies have demonstrated that pneumococcal vaccination provides clinical protection in these patients (A single dose of PPV-24 prior to age 64, followed by a second dose at least 5 years apart at or after age 65).

Complimentary and Alternative Medicine (CAM)

A number of non-traditional treatments may be helpful to patients with congestive heart failure, especially in terms of symptom control and improved quality of life. Cohort studies show that patients with higher scores on a measure of spirituality have higher quality of life scores. Slow breathing techniques and tai chi have improved oxygen utilization, BNP levels, quality of life, and symptoms. However, in general, these studies are not of sufficient size and scope to warrant major changes in the management of heart failure.

Hawthorn. The data do not support the routine use of hawthorn in treating heart failure. Hawthorn (crataegus) has been studied in a moderate-sized placebo controlled trial of HF patients and was shown to be safe, but did not impact mortality. In one small-sized study it may have improved exercise capacity at high doses.

Mind-body exercises (Tai Chi and yoga). Incorporation of mind-body exercises as part of a therapeutic lifestyle choice can be a consideration for heart failure patients.

Mind-body exercises represent an alternative exercise program that includes a meditative component. Small studies in stable heart failure patients have shown that Tai Chi can improve quality of life, mood, and exercise self-efficacy. Tai Chi may also improve sleep stability. Yoga has been shown to improve exercise tolerance and a trend toward improvement in quality of life. The number of
studies performed and the number of HF patients studied regarding mind-body exercises have been small. However, limited data does suggest some benefit in stable heart failure patients.

**Chocolate.** The benefit of chocolate for the treatment of heart failure is not known. Routine use of chocolate cannot be recommended for the treatment of heart failure. Chocolate can lead to obesity and changes in lipid profiles. However, natural products that are rich in flavanols, such as chocolate, are thought to provide cardiovascular benefit. In a prospective observational trial, intake of chocolate at a rate ≥ 2 servings per week decreased the rate of incident heart failure or heart failure death among a group of 30,000 Swedish women without a history of coronary artery disease. Intake at higher doses worsened outcomes. If patients want to incorporate chocolate as part of their therapeutic lifestyle choice, the amount consumed should be limited (chocolate is high in calories and fat) and the type of chocolate should probably have high concentration of cocoa solids.

**Coenzyme Q10.** Based on the limited data available, coenzyme Q10 cannot be recommended for the routine treatment of heart failure or in patients administered HMG-CoA reductase (statin) therapy.

Coenzyme Q10 has been advertised by nutritional manufacturers and by some researchers as an effective treatment for heart failure. Although limited trials have shown benefit with coenzyme Q10, no large, placebo controlled trials have been performed, and the best designed trials do not show benefit. Other considerations that limit recommendation of coenzyme Q10 include: (1) dose to administer has not been established; (2) cost; (3) adverse effects are not well defined but have included gastrointestinal complaints and elevated liver enzymes; (4) drug interactions are not well defined, but may include interaction with warfarin.

**Vitamin D.** Given the association between low vitamin D levels and cardiovascular outcomes, vitamin D supplementation may be considered for heart failure patients with low vitamin D levels (or any patient with or at risk for insufficient vitamin D levels). The prevalence of vitamin D insufficiency (<30 ng/mL) ranges from 30-70% of the population or higher. Risk factors for vitamin insufficiency include: inadequate sunlight exposure (including use of sunscreen, living in northern latitudes); advanced age; dark skin tone; obesity; certain religious beliefs (e.g., covering of exposed skin areas).

Patients need sufficient levels of vitamin D to maintain bone health (i.e., prevention of rickets in children). Vitamin D receptors are located throughout the body, including the heart, and vitamin D plays an important in the cardiovascular system. A number of association studies link low vitamin D levels to increased total mortality, cardiovascular mortality, myocardial infarction, and to heart failure. However, the role of vitamin D supplementation to treat or prevent cardiovascular disease, including heart failure, has not yet been established.

**Alcohol.** Several factors associated with the effect of alcohol on heart failure are unknown. Given the potential risk of chronic alcohol consumption (including addiction, inappropriate risk taking, and disease progression) routine consumption of alcohol is not recommended.

If patients want to include light to moderate alcohol consumption as a lifestyle choice, risks of heavy consumption should be re-enforced, including increasing cardiovascular risk (J- or U-shape association). Epidemiologic studies (no prospective studies) demonstrate a protective effect of light to moderate alcohol intake against cardiovascular disease. Among patients with EF <35%, light to moderate alcohol consumption (an average of 0-2 drinks/day) was associated with an overall mortality rate of 0.75 (p < 0.001). This benefit was realized primarily among those with ischemic cardiomyopathy.

**Systems Aiding Treatment**

Hospitalization for HF is a powerful marker for subsequent re-hospitalization and mortality. Patients with severe HF, repeated hospitalizations for HF, and possibly upon first hospitalization for HF, should be enrolled in a HF disease management program.

**HF disease management program.** HF disease management programs substantially reduce mortality and HF hospitalizations. A 2004 meta-analysis of 29 trials including 5,039 patients, the vast majority of whom were enrolled post-hospitalization for HF, estimated that HF disease management reduced mortality and hospitalizations by 25% and 26% respectively. HF disease management programs should be multidisciplinary and should at least include intense patient support by HF trained nurses, HF patient education, and facilitated access to physicians trained in HF.

**Telemanagement.** The role of telemanagement in HF is controversial. Different kinds of telemanagement have been tested as additions to HF disease management programs or as alternatives for patients who cannot gain access to a HF disease management program. Formats include structured telephone support and semi-automated telemonitoring. Multiple trials of telemanagement yielded variable outcomes across heterogeneous interventions and populations. A Cochrane meta-analysis of 5,613 patients included in trials through 2008 found that telemonitoring reduced all-cause mortality by 34% and that both telemonitoring and structured telephone support reduced HF hospitalizations by 21% and 23% respectively. However, a 2010 telemonitoring trial of 1,652 patients in which daily data were transmitted to physicians rather than nurses showed no benefit.

**Surveillance and follow-up.** No trials guide the frequency of follow-up and surveillance. This decision should be
made as a clinical judgment based upon the status of the patients. Patients with worse symptoms, those recently hospitalized, and those for whom the medical regimens are changing may need more frequent surveillance.

**Special Circumstances and Populations**

Several contextual factors are relevant to preventing and providing care for heart failure. Hypertension is a risk factor for heart failure that can be prospectively addressed. Patients with heart failure often have one or more comorbid conditions that modify usual care. In addition to systolic dysfunction, heart failure may result from diastolic dysfunction or valvular heart disease. Older patients vary widely in physical and mental functioning and in circumstances. Palliative care and end of life considerations are important for patients with severe heart failure. Each of these topics is addressed briefly below.

**Hypertension Control**

Epidemiologic data have identified hypertension as a risk factor for heart failure through two potential mechanisms.
- Hypertension may lead to left ventricular hypertrophy and subsequent diastolic dysfunction.
- Hypertension is a recognized risk factor for coronary artery disease, which is the most common etiology of left ventricular systolic dysfunction.

See “UMHS Clinical Guideline: Essential Hypertension” for additional information on diagnosis and treatment of hypertension.

**Comorbidities**

Kidney disease. Acute kidney injury and chronic kidney disease (CKD) are common in patients with heart failure, especially in patients with more severe symptoms. Over 75% of patients hospitalized for heart failure have stage III, IV, or V CKD defined by a glomerular filtration rate < 60 ml/min. CKD may be a consequence of renal hypoperfusion from either an inadequate or maldistributed cardiac output. CKD may also represent intrinsic kidney disease or pharmacologic or other extrinsic toxicity. Regardless of the etiology, CKD is associated with an increased risk of mortality and morbidity in patients with heart failure, especially in the presence of hypotension. For patients hospitalized with heart failure, the combination of serum urea nitrogen > 43 mg/dl, serum creatinine > 2.75 mg/dl, and hypotension (defined by a systolic blood pressure < 115 mm Hg) is associated with a 25% in-hospital mortality rate.

CKD can complicate and frustrate treatment for patients with heart failure. CKD alters the pharmacokinetics of concomitant therapy with aldosterone antagonists and digoxin and can increase the risk of toxicity from these agents. CKD can impair the response to angiotensin converting enzyme inhibitors and diuretics. Furthermore, diuretics, which are frequently necessary to control congestive symptoms, can concomitantly decrease glomerular filtration rates and contribute to additional diuretic resistance. Low volume ultrafiltration has been recommended as an outpatient office procedure, but no large clinical trials are available to guide the role of this intervention. In end-stage renal disease, dialysis or renal transplantation can sometimes improve left ventricular ejection fraction.

To avoid renal insufficiency, avoid all non-steroidal anti-inflammatory drugs in patients with heart failure. Aldosterone antagonists should either be avoided or very closely monitored in patients with glomerular filtration rates < 30 ml/min. Digoxin doses should be lowered in patients with renal insufficiency.

Further information about modifying the use of drugs in patients with CKD is contained in the UMHS clinical guideline “Management of Chronic Kidney Disease.”

Anemia. Anemia is common in patients with left ventricular systolic dysfunction, especially in patients with severe heart failure symptoms. The anemia of heart failure is independently associated with a poor prognosis and increased mortality. This anemia is often associated with blunted erythropoietin production and defective iron supply, and a small trial has demonstrated that treatment with subcutaneous erythropoietin and intravenous iron appears to improve symptoms, LVEF, and renal function. Randomized controlled trials of intravenous iron in patients with heart failure and iron deficiency improved quality of life and functional capacity, but show no improvement in mortality. One trial of darbepoetin in anemic patients with heart failure showed a non-significant trend towards reduced mortality and morbidity. A recent meta-analysis showed similar trends. No controlled clinical trials have studied transfusion in patients with heart failure, but transfusion in other, critically ill, anemic patients can adversely affect outcomes.

Atrial fibrillation. Atrial fibrillation is common among patients with heart failure and is associated with a poor prognosis and an increased risk of hospitalization for heart failure. Rapid ventricular rate responses to atrial fibrillation may worsen left ventricular dysfunction, worsen heart failure symptoms, and, in some cases, constitute the primary etiology of the left ventricular dysfunction. Atrial fibrillation also increases the risk of thromboembolic events, especially stroke.

Strategies by cardiology subspecialists to convert and maintain sinus rhythm in patients with atrial fibrillation and left ventricular systolic dysfunction are frequently unsuccessful, whether by using anti-arrhythmic medications (e.g. amiodarone, dofetilide, etc) or by performing electrophysiologic interventions (including atrial fibrillation ablation). Thus, ventricular rate control and anticoagulation are critical. Although strict rate control (< 80 bpm at rest
and < 110 bpm with exercise) yielded equivalent outcomes to rhythm control, recent data in patients with normal systolic function suggest that lenient resting rate control (< 110 bpm at rest) may provide equivalent or even superior benefit. It is not known if these observations about lenient rate control can be extended to patients with left ventricular systolic dysfunction. Beta blockers are more effective than digoxin in blocking exercise-induced increases in ventricular rate, although the combination of these agents may be especially efficacious. Calcium channel blockers (particularly nondihydropyridines diltiazem and verapamil) can induce worsening heart failure and should be avoided as ventricular rate controlling agents in patients with left ventricular systolic dysfunction.

The primary indication for antithrombotics in left ventricular systolic dysfunction is to prevent thromboembolic events associated with atrial fibrillation. Warfarin anticoagulation (INR 2 – 3) decreases that thromboembolic risk in patients with atrial fibrillation and CHADS2 scores ≥ 2. See the earlier section on antithrombotics for information about them and their use in patients with heart failure.

Depression. Depression may occur in over 20% of patients with heart failure. Depression has been independently associated with poor outcomes including increased risk of mortality and morbidity. Patients with heart failure should be evaluated for depression and routine evaluation can be considered. The most effective treatment for depression in patients with heart failure is not known. A recent small short-term randomized placebo controlled trial demonstrated that SSRI therapy (sertraline) was safe in heart failure patients, but no more effective than placebo. Nurse-facilitated support for these patients may have contributed to placebo effect. Non-pharmacological therapy can be considered in treating depression in heart failure patients. Tricyclic antidepressants should probably be considered last line and use with extreme caution in heart failure patients, in part due to their effect on QT interval prolongation and association with increase cardiovascular events.

Diabetes. Approximately one-third of patients with heart failure have comitant diabetes. Heart failure patients with diabetes have poorer outcomes than patients without diabetes. Heart failure is associated with insulin resistance and may contribute to diabetes and relative hyperglycemia. In addition, treatment for heart failure with beta blocker therapy can independently increase insulin resistance and affect glucose control. The non-selective beta blocker carvedilol may have less effect on these factors compared to the non-selective beta blockers metoprolol and bisoprolol. However, beta blockers are recommended and should be administered to patients with heart failure and diabetes. Secondary analyses from large prospective trials have shown benefit of using beta blocker therapy in patients with heart failure and diabetes.

The optimal strategy to treat diabetes in patients with heart failure is not known, due in part to lack of randomized control trials. Metformin has been shown to improve outcomes in patients with diabetes. While metformin use in patients with poor renal function has been historically discouraged due to the perceived risk of developing lactic acidosis metformin can be used safely in patients with mild impairment in kidney function and in some patients with moderate impairment in kidney function. Retrospective reviews and recent observational study have suggested that metformin is safe in heart failure patients and may be associated with lower mortality rates.

Thiazolidinediones, which are used in the treatment of diabetes, can complicate the treatment of heart failure. One trial demonstrated that pioglitazone can significantly reduce heart attacks, strokes, and death in diabetics. However, thiazolidinediones are associated with fluid retention and edema, especially in patients also receiving insulin, which can lead to hospitalization for fluid management. In addition, concerns exist for rosiglitazone and for increased cardiovascular risk and increased risk of bladder cancer with pioglitazone. Therefore, thiazolidinediones should be administered with caution in patients with heart failure, especially in patients whose fluid balance is tenuous.

Outcomes with the other treatment strategies for diabetes (insulin, sulfonylureas, incretine modulators) in patients with heart failure are not known.

Erectile dysfunction. The occurrence of erectile dysfunction (ED) in patients with HF is common. More than 60% of heart failure patients are estimated to report some degree of ED. ED in heart failure patients may result from a number of causes. ED may also contribute or lead to depression. One of the approaches to treating ED is the use of phosphodiesterase type 5 (PDE-5) inhibitors (e.g. sildenafil). Small studies suggest that the use of PDE-5 inhibitors are effective in treating ED in heart failure patients and appear to be safe. The use of PDE-5 inhibitors is contraindicated in patients taking nitrates due to profound hypotension that may develop.

Sleep apnea. Sleep disoriented breathing reportedly occurs in over half of patients with heart failure approximately equally divided between obstructive sleep apnea and central sleep apnea. Obstructive apnea occurs more commonly in patients with the metabolic syndrome and is associated with hypertension, progressive left ventricular dysfunction and higher risk of death.

One small study demonstrated that continuous positive airway pressure can reduce blood pressure and improve left ventricular dysfunction in these patients. However, in heart failure patients with central sleep apnea the effects of positive airway pressure are ambiguous. The largest reported study demonstrated that continuous positive airway pressure decreased the degree of disordered breathing and marginally improved exercise capacity, but did not alter mortality or the need for heart transplantation.
However, a subgroup analysis showed that those who had the largest reduction in apneic events had improved left ventricular function and survival.

We recommend positive airway pressure for patients with heart failure with significant obstructive sleep apnea. We also recommend trials of positive airway pressure for severely symptomatic heart failure patients with central sleep apnea to determine if the intervention improves exercise tolerance.

**Diastolic Dysfunction (Heart Failure with Preserved Ejection Fraction – HF-PEF)**

Diastolic dysfunction is a term reflecting increasing filling pressures due to increased stiffness or thickness of the ventricular wall. Diastolic dysfunction can result in heart failure with a normal EF.

No clear consensus exists on diagnostic criteria for diastolic dysfunction and no clear evidence exists in clinical trials to guide therapy. The recommendations in this guideline are designed to be applied to patients with left ventricular systolic dysfunction. The treatment of diastolic dysfunction is evolving. A detailed recommendation is beyond the scope of this guideline.

**Valvular Heart Disease**

The recommendations in this guideline refer to the treatment of heart failure due to cardiomyopathy. Heart failure due to primary valvular heart disease is quite different and requires different treatment. For example, agents that cause afterload reduction can improve left ventricular systolic dysfunction but can cause hemodynamic deterioration in patients with aortic stenosis.

A detailed recommendation for the treatment of heart failure due to valvular heart disease is beyond the scope of this guideline. However, patients with heart failure due to valvular disease – such as aortic stenosis – should be referred to cardiology.

**Older Adults with Systolic Heart Failure**

In general, the majority of the items in this guideline apply to older adults with heart failure, and most patients with heart failure are over age 65. The prevalence of heart failure increases with age. It is 2% in those 40-59, over 5% in those 60-69, and over 10% in those 70 or older. Most randomized controlled trials have included older adults, but not those older than 80. However, patients should not be denied known beneficial therapy on the basis of age. No trials have ever addressed issues in nursing home residents.

The heterogeneity of older adults means that all management must be individualized, especially in the oldest age groups. Older adults must be carefully monitored for adverse effects of recommended medications and interactions with other medications they may be taking for co-morbid conditions. Issues affecting ability to comply with therapy must be evaluated, including cognitive and affective disorders, ability to pay for medications, and need for caregiver assistance due to disabilities.

**Palliative Care and End of Life Considerations**

The diagnosis of heart failure brings a prognosis that is limited, although difficult to predict for an individual. Patients with severe heart failure and symptoms at rest are at substantial risk of dying within one year, particularly if co-morbidities exist. Less symptomatic patients have a much better prognosis.

We recommend discussing advance directives with patients and family in the context of heart failure management. Additionally, consultation with a hospice and palliative medicine physician might enhance symptom assessment and control in some patients. No definitive, evidence-based criteria exist for when to add palliative care to the multidisciplinary team caring for the patient with heart failure. However, when it is added a recent review of palliative care in advanced heart failure support recommends that it include:

- good patient-professional and inter-professional communication
- coordination of care
- awareness of the broader needs of patients and their families beyond those specifically linked to the heart failure state.

Symptom assessment and control is one of the foundations of palliative care. In heart failure the control of symptoms is also a focus of other key providers (primary care and cardiology) in addition to their focus on disease modification. One tool familiar to the palliative care provider is the Memorial Symptom Assessment Scale (MSAS). When used to measure symptoms in 103 heart failure patients it was able to identify distressful symptoms related to impairment in quality of life as measured by the Multidimensional Index of Life Quality.

**Strategy for Literature Search**

The literature search for this project started with the results of literature searches performed in 1998 and 2005 for earlier versions of this guideline. A new search was conducted prospectively using the major keywords of: congestive heart failure, guidelines, controlled trials, cohort studies, published 4/1/05 to 3/1/11, adults, English language on Medline. Terms used for specific topic searches within the major key words included: electrolytes; functional or stress testing; catheterization; electrogram; left ventricular ejection fraction measurement; echocardiography, sestamibi, radionuclide ventriculogram; natriuretic peptides (A-,B-[BNP], and c-type), troponin, biomarkers; education; dietary restriction; salt substitutes; exercise; devices: ICD, biventricular pacing, AICD, implantable cardiofibrillator, LVAD; revascularization;
diuretics; angiotensin converting enzyme (ACE) inhibitors; angiotensin receptor antagonist/blocker; aldosterone antagonists; digoxin; beta blockers; vasodilators (e.g., nitrates, hydralazine); calcium channel blockers; inotropic agents; anti-arrhythmics; lipid lowering drugs; fish oil, anti-coagulants, anti-thrombotics and antiplatelet agents; influenza vaccination; pneumovax immunization; coenzyme Q10; NSAIDS; narcotics; vitamin D; other complementary and alternative medicine: nutritional supplements, herbal remedies (e.g., hawthorn), chocolate, alcohol, tai chi; disease based management; telemangement (diuretics & weight); comorbid conditions: renal insufficiency, atrial fibrillation, anemia, sleep apnea, diabetes, depression, erectile dysfunction, dementia, arthritis, sinus node inhibition (beta blockers), hypernatremia (vasopressin antagonists); gender differences; racial differences and pharmacotherapy; end of life considerations, palliative care; any other reference identified by the major keywords and not included in results of specific topic searches. Specific search strategies are available upon request.

The search was conducted in components each keyed to a specific causal link in a formal problem structure (available upon request). The search was supplemented with very recent clinical trials known to expert members of the panel. Negative trials were specifically sought. The search was a single cycle. Conclusions were based on prospective randomized controlled trials if available, to the exclusion of other data; if RCTs were not available, observational studies were admitted to consideration. If no such data were available for a given link in the problem formulation, expert opinion was used to estimate effect size.

**Related National Guidelines**

This guideline generally conforms to:

ACC/AHA focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults (2009)

European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure (2012)

Heart Failure Society of America: evaluation of patients for ventricular dysfunction and heart failure (2010)

**Measures of Clinical Performance**

National programs that have clinical performance measures for care of heart failure include the following.

Centers for Medicare & Medicaid Services:

- Physician Quality Reporting Measures for Group Practice Reporting Option (GPRO)
- Clinical Quality Measures for financial incentives for Meaningful Use of certified Electronic Health Record technology (MU)

• Quality measures for Accountable Care Organizations (ACO)

National Committee for Quality Assurance: Healthcare Effectiveness Data and Information Set (HEDIS)

Regional programs that have clinical performance measures of heart failure include the following.

Blue Cross Blue Shield of Michigan: Physician Group Incentive Program clinical performance measures (PGIP)

These program’s clinical performance measures for heart failure are summarized below. When programs have measures, the measures are generally similar, although specific details vary (e.g., population inclusions and exclusions).

**Measurement of left ventricular function (LVEF).** The percentage of patients aged 18 years and older with a diagnosis of heart failure who have quantitative or qualitative results of LVEF assessment recorded (ACO). Also, the percentage of patients hospitalized with a principal diagnosis of HF with LVEF testing during the current year (ACO).

**Patient education.** The percentage of patients aged 18 years and older with a diagnosis of heart failure provided with patient education on disease management and health behavior changes during one or more visits within 12 months (ACO).

**Weight management.** For patients aged 18 years and older with a diagnosis of heart failure, the percentage of patient visits with weight management recorded (ACO).

**ACE inhibitor or ARB therapy for patients with a reduced LVEF.** The percentage of patients aged 18 years and older with a diagnosis of heart failure and reduced LVEF prescribed ACE inhibitor or ARB therapy (GPRO, MU, ACO, PGIP).

**Beta-blocker therapy for reduced LVEF.** Percentage of patients aged 18 years and older with a diagnosis of heart failure who and LVEF < 40% prescribed beta-blocker therapy (GPRO, MU, ACO)

**LDL screening.** The percentage of patients between 18 and 75 years of age with heart failure with an LDL measured within 12 months (PGIP).

**Warfarin therapy for HF patients with atrial fibrillation.** Percentage of all patients aged 18 and older with a diagnosis of heart failure and paroxysmal or chronic atrial fibrillation prescribed warfarin therapy (GPRO, MU, ACO).

**Hospital admissions.** For the population aged 18 years and older in the Metropolitan Area or county, the rate of discharges per 100,000 population with a principal diagnosis of HF (ACO).
Disclosures

The University of Michigan Health System endorses the Guidelines of the Association of American Medical Colleges and the Standards of the Accreditation Council for Continuing Medical Education that the individuals who present educational activities disclose significant relationships with commercial companies whose products or services are discussed. Disclosure of a relationship is not intended to suggest bias in the information presented, but is made to provide readers with information that might be of potential importance to their evaluation of the information.

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Review and Endorsement

Drafts of this guideline were reviewed in clinical conferences and by distribution for comment within departments and divisions of the University of Michigan Medical School to which the content is most relevant: Cardiology, Family Medicine, General Medicine, and Geriatric Medicine. The final version was endorsed by the Clinical Practice Committee of the University of Michigan Faculty Group Practice and the Executive Committee for Clinical Affairs of the University of Michigan Hospitals and Health Centers.

Annotated References

National/International Guidelines


ACE inhibitors


Angiotensin receptor blockers


Angiotensin receptor blockers are effective when used in place of ACE inhibitors and may be effective when added to ACE inhibitors among selected patients.

Angiotensin II Receptor Blocker Neprilysin Inhibitor (ARNI)


The PARADIGM HF study demonstrated superiority of ARNI compared to enalapril. However, this is a new class of drug, tested only in one trial, unopposed nepriylisin therapy had untoward side effects in trials, post-marketing data are not yet available, and the cost is significant.

**Beta-Blockers**


Randomized controlled trial demonstrating the effectiveness of bisoprolol in treating systolic dysfunction.


Randomized controlled trial demonstrating the effectiveness of carvedilol in treating systolic dysfunction.


Randomized controlled trial demonstrating the benefits of sustained release metoprolol among patients with heart failure due to systolic dysfunction.


Randomized controlled trial demonstrated the superiority of carvedilol over short acting metoprolol.

**Aldosterone antagonists**


Randomized controlled trial demonstrating that spironolactone reduced mortality and hospitalizations in patients with systolic dysfunction and severe heart failure symptoms.


Randomized controlled trial demonstrating that the second generation aldosterone antagonist, eplerenone, reduced mortality and heart failure hospitalizations in patients 14 days post MI with systolic dysfunction or diabetes.


Randomized controlled trial demonstrating that eplerenone reduced mortality and heart failure hospitalizations among patients with systolic dysfunction and mild heart failure symptoms.

**Direct acting vasodilators**

Taylor et. al., Combination of Isosorbide Dinitrate and Hydralazine in Blacks with heart Failure. NEJM 2004;351:2049-57.

A-HeFT randomized controlled trial demonstrating the benefit of adding isordil-hydralazine to African-American patients who remained symptomatic despite background therapy with ACE inhibitors and beta blockers.

**Digoxin**


Randomized controlled trial demonstrating the effectiveness of digoxin in treating systolic dysfunction.

**Sinus node modulator - ivabradine**


In the SHIFT trial of patients admitted to the hospital within the past 12 months, ivabradine reduced hospitalizations, with all of the benefit among those with HR ≥ 70.

**Device therapy**


MUST randomized controlled trial demonstrating that only defibrillators reduced mortality in patients with CAD and systolic dysfunction in an EP guided treatment strategy.

MADIT-II randomized controlled trial demonstrating that defibrillators reduced mortality in patients with CAD with systolic dysfunction and EF ≤ 30%.


SCD-HeFT randomized controlled trial demonstrating the benefit of implantable defibrillators versus placebo or amiodarone among patients with NYHA class II or III CHF and LVEF of 35 percent or less.


COMPANION randomized controlled trial demonstrating that resynchronization with bi-ventricular pacing independently reduced mortality and heart failure hospitalizations in patient with heart failure and systolic dysfunction and that the benefit added to the mortality benefit from ICD’s.

Exercise


HF-ACTION randomized controlled trial demonstrating that exercise training produced nonsignificant reductions in mortality and hospitalizations in patients with heart failure during 30 months of followup.

Anemia


BNP


Patient Education


Fish oil


Randomized controlled trial demonstrating that the fish oil, n-3 PUFA, yielded a small reduction in mortality and heart failure hospitalizations in patients with heart failure.

Statins


Randomized control trials demonstrating that rosuvastatin did not reduce mortality in patients with heart failure.

Atrial fibrillation


RACE II randomized controlled trial in patients with atrial fibrillation demonstrating that lenient rate control (< 110 bpm) was at least equivalent to more strict rate control in avoiding subsequent clinical events. However, because only10% of the patients had been previously hospitalized for heart failure, the results may not be applicable to patients with heart failure.

The Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of
rate control and rhythm control in patients with atrial fibrillation. NEJM 2002 Dec 5;347:1825-33.

AFFIRM randomized controlled trial demonstrating that rhythm control was not superior to rate control in patients with atrial fibrillation. However, 23% of the patients had a history of heart failure, and among those patients rhythm control trended superior.

**Disease-based management**


A meta-analysis of 29 trials demonstrating that heart failure disease management reduced mortality and heart failure hospitalizations.


A Cochrane meta-analysis demonstrating that telemonitoring reduced mortality and that telemonitoring and structured telephone support reduced mortality and heart failure hospitalizations in patients with heart failure.


Randomized controlled trial demonstrating no benefit from telemonitoring in patients recently hospitalized for heart failure.
## Appendix A. Common Drug Interactions

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Interacts with</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE Inhibitors</strong></td>
<td>Antacids</td>
<td>↓ drug absorption</td>
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<tr>
<td></td>
<td>Lithium</td>
<td>↑ lithium levels</td>
</tr>
<tr>
<td></td>
<td>NSAID</td>
<td>May decrease renal function</td>
</tr>
<tr>
<td></td>
<td>Aldosterone Antagonists/ARBS</td>
<td>Coadministration may result in elevated potassium level especially in the elderly and patients with renal dysfunction</td>
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<td><strong>ARBS</strong></td>
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<td>Coadministration may result in elevated potassium level especially in the elderly and patients with renal dysfunction</td>
</tr>
<tr>
<td><strong>Amiodarone</strong></td>
<td>B-Blockers</td>
<td>↓ HR, AV node conduction</td>
</tr>
<tr>
<td></td>
<td>Calcium Channel Blockers (diltiazem, verapamil)</td>
<td>↓ HR, AV node conduction</td>
</tr>
<tr>
<td></td>
<td>Digoxin</td>
<td>↑ Digoxin concentration; ↓ HR, AV node conduction</td>
</tr>
<tr>
<td></td>
<td>Quinidine</td>
<td>↑ Quinidine concentration</td>
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<tr>
<td></td>
<td>Phenytoin</td>
<td>↑ Phenytoin concentration; ↓ Amiodarone concentration</td>
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<tr>
<td></td>
<td>Procainamide</td>
<td>↑ Procainamide concentration</td>
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<td></td>
<td>Theophylline</td>
<td>↑ Theophylline concentration</td>
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<tr>
<td></td>
<td>Warfarin</td>
<td>↑ in INR</td>
</tr>
<tr>
<td></td>
<td>Atorvastatin, Simvastatin, Lovastatin</td>
<td>↑ in statin concentrations</td>
</tr>
<tr>
<td><strong>Beta Blockers</strong></td>
<td>Amiodarone, diltiazem, verapamil, propafenone, sotalol</td>
<td>↓ HR, AV node conduction</td>
</tr>
<tr>
<td><strong>Digoxin</strong></td>
<td>Amiodarone</td>
<td>↑ Digoxin concentration; HR, AV node conduction</td>
</tr>
<tr>
<td></td>
<td>Antacids</td>
<td>↓ oral Digoxin absorption, space drugs at least 2hrs apart</td>
</tr>
<tr>
<td></td>
<td>B-Blockers</td>
<td>Carvedilol may ↑ Digoxin concentration; ↓HR, AV node conduction</td>
</tr>
<tr>
<td></td>
<td>Cholestyramine, Colestipol</td>
<td>↓ Digoxin absorption</td>
</tr>
<tr>
<td></td>
<td>Diltiazem, Verapamil</td>
<td>↑ Digoxin concentration; ↓ HR, AV node conduction</td>
</tr>
<tr>
<td></td>
<td>Omeprazole</td>
<td>↑ Digoxin concentration</td>
</tr>
<tr>
<td></td>
<td>Propafenone</td>
<td>↑ Digoxin concentration; ↓ HR, AV node conduction</td>
</tr>
<tr>
<td></td>
<td>Quinidine</td>
<td>↑ Digoxin concentration</td>
</tr>
<tr>
<td></td>
<td>Rifampin</td>
<td>↓ Digoxin concentration</td>
</tr>
<tr>
<td></td>
<td>Sotalol</td>
<td>↓ HR, AV node conduction</td>
</tr>
<tr>
<td></td>
<td>Spironolactone</td>
<td>↑ Digoxin concentration; interferes with some digoxin assays yielding falsely elevated Digoxin concentration</td>
</tr>
<tr>
<td></td>
<td>Atorvastatin, Simvastatin, Lovastatin</td>
<td>↑ Digoxin concentration</td>
</tr>
<tr>
<td><strong>Warfarin</strong></td>
<td>Amiodarone, Antibiotics (including Bactrim and Erythromycin),</td>
<td>↑ INR</td>
</tr>
<tr>
<td></td>
<td>Antidepressants, Beta-Blockers,</td>
<td>↑ risk of bleeding due to effect on platelet function</td>
</tr>
<tr>
<td></td>
<td>Cimetidine, Fluconazole, Itraconazole, Ketoconazole,</td>
<td>↓ INR</td>
</tr>
<tr>
<td></td>
<td>Lovastatin, Omeprazole, Oral Diabetic Agents, Phenytoin,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Propafenone, Quinidine, Quinine, Quinine, Rosuvastatin, Simvastatin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NSAID, ASA, Ticlopiine, Clopidogrel</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phenobarbital, Rifampin, Cholestyramine, Carbamazepine, Phenytoin,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spironolactone, Sucralfate</td>
<td></td>
</tr>
</tbody>
</table>
Appendix B. Potential and Documented Interactions of Herbs with Warfarin  
(from Am J Health-Syst Pharm—Vol 57 Jul 1, 2000)

<table>
<thead>
<tr>
<th>Potential Increase in Risk of Bleeding</th>
<th>Horse chestnut</th>
<th>Quassia</th>
<th>Red clover</th>
<th>Race</th>
<th>Sweet clover</th>
<th>Turmeric</th>
<th>Willow bark</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angelica root</td>
<td>Celery</td>
<td>Licorice root</td>
<td>Lovage root</td>
<td>Meadowsweet</td>
<td>Onion</td>
<td>Parsley</td>
<td>Passionflower herb</td>
</tr>
<tr>
<td>Arnica flower</td>
<td>Chamomile</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anise</td>
<td>Clove</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Asafoetida</td>
<td>Fenugreek</td>
<td></td>
<td></td>
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<tr>
<td>Bogbean</td>
<td>Feverfew</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Borage seed oil</td>
<td>Garlic</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Bromelain</td>
<td>Ginger</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Capsicum</td>
<td>Ginko</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Documented Reports of Possible Increase in Warfarin’s Effects

<table>
<thead>
<tr>
<th>Danshen</th>
<th>Devils Claw</th>
<th>Dong quai</th>
<th>Papain</th>
<th>Vitamin E</th>
</tr>
</thead>
</table>

Documented Reports of Possible Decrease in Warfarin’s Effects

<table>
<thead>
<tr>
<th>Coenzyme Q10</th>
<th>Ginseng</th>
<th>Green tea a</th>
</tr>
</thead>
</table>

a Excessive amounts are necessary for this interaction to occur.

Appendix C. CAM and CHF Interactions

<table>
<thead>
<tr>
<th>May have some degree of diuretic action</th>
<th>Buchu</th>
<th>Conch grass</th>
<th>Dandelion</th>
<th>Horsetail rush</th>
<th>Juniper</th>
<th>Licorice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aconite</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alisma plantago</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Bearberry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>May increase heart failure or promote arrhythmia formation</th>
<th>Oleander</th>
<th>Vitamin E</th>
<th>Yohimbine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belladonna</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MaHuang</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Herbal laxatives can cause potassium loss

Potential herb and CHF drug interactions

St. John’s Wort:
- Decrease digoxin concentrations
- Decrease atorvastatin, simvastatin, and lovastatin concentrations
- Decrease diltiazem and verapamil concentrations
- Decrease effect of warfarin

Goldenseal:
- Increase metoprolol and carvedilol effects
- Increase atorvastatin, simvastatin, and lovastatin concentrations
- Increase diltiazem and verapamil concentrations

Black Cohosh
- Increase metoprolol and carvedilol effects

Anti-platelet drugs (increase effects)
- Dong quai, feverfew, garlic, ginger, ginkgo, kava