Heart Failure Guideline Team

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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.

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 heart failure.

Key Points

Diagnosis

- Measure ejection fraction (EF) to determine if the etiology of the heart failure is systolic dysfunction (rather than diastolic dysfunction or valvular heart disease) *[IA*]*.
- Check serum B-type natriuretic peptide (BNP) to help determine if dyspnea is due to heart failure *[IC*]*.

Pharmacologic Therapy (See Table 1)

- For patients with systolic dysfunction (EF < 40%) who have no contraindications, consider:
  - Angiotensin receptor blocker–neprilysin inhibitor (ARNI) combination, angiotensin converting enzyme (ACE) inhibitor, or angiotensin receptor blocker (ARB) for all patients *[IA*]*.
  - Beta blockers for all patients except those who are hemodynamically unstable or 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 heart failure 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 heart failure within the last 12 months, have sinus rhythm with HR > 70 while on maximally tolerated or target dose of beta blocker *[IIA*]*.

Device Therapy

- Consider implantable cardioverter defibrillators (ICD) for prophylaxis against sudden cardiac death in patients with EF ≤ 35% *[IA*]*. See Figure 2.
- Consider biventricular pacemakers for patients requiring defibrillators who have symptomatic heart failure and QRS duration ≥ 120 msec *[IA*]*.

Caution

- Heart failure patients on multiple medications are at risk of potential drug interactions and adverse effects, such as hyperkalemia. Monitor potassium and estimated glomerular filtration rate (eGFR).

*** Strength of recommendation:**
I= generally should be performed; II = may be reasonable to perform; III = generally should not be performed.
Levels of evidence for the most significant recommendations
A = randomized controlled trials; B = controlled trials, no randomization; C = observational trials; D = opinion of expert panel

Clinical Background

Clinical Problem and Management Issues

Incidence

About 5.7 million Americans currently have heart failure, and an additional 400,000 develop heart failure annually. Each year 990,000 patients are admitted with heart failure as the primary diagnosis. Nearly 50% of patients die within five years of the onset of symptoms. The incidence increases with age, and heart failure is the most common cause of hospitalization in older adults. Since the American population is aging, the incidence of heart failure and associated morbidity and mortality will increase in the future.

Problems with Care

Our understanding of heart failure has changed dramatically over the past few decades. The most common cause of heart failure remains an ischemic insult. This insult initiates a cascade of events mediated by neurohormonal influences that adversely affect the heart.

Unlike some disease entities for which no therapies exist, in heart failure several pharmacologic and lifestyle interventions can improve mortality and quality of life. The many available treatments have resulted in confusion about who should be treated and how to initiate and titrate therapy for heart failure.

(continued on page 5)

Figure 1. Identifying Systolic Heart Failure

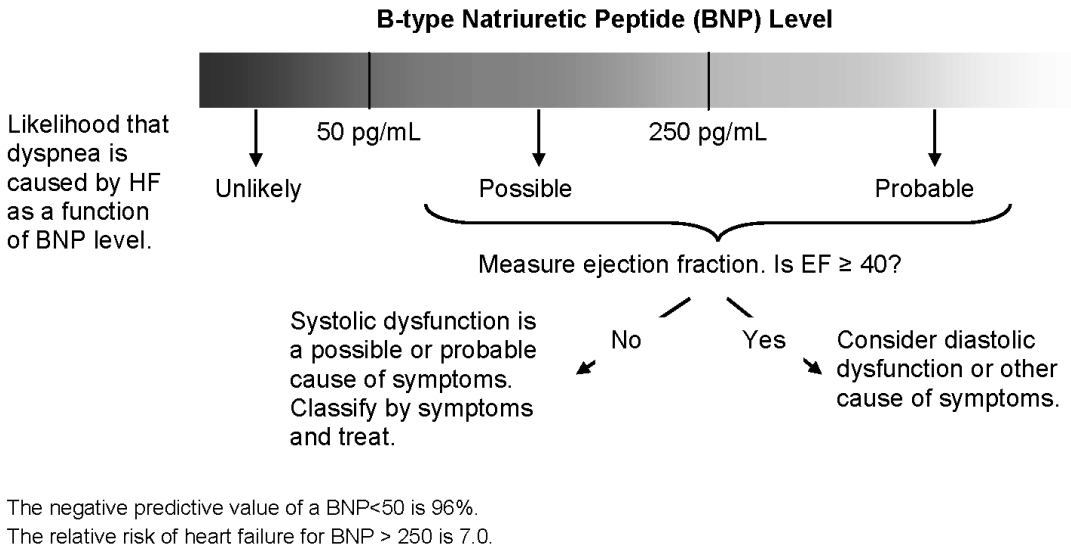
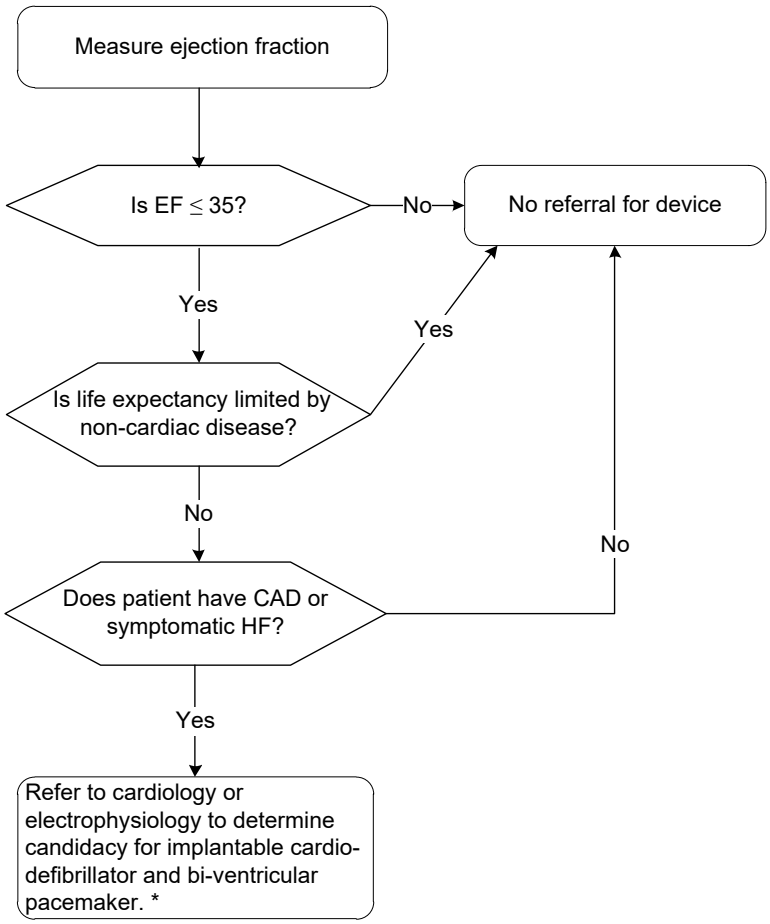


Figure 2. Device Referral Algorithm



* Device therapy with an implantable cardioverter defibrillator or biventricular 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. The primary care physician should discuss device placement with patients before referral. Some patients may choose not to pursue this path because of prognosis, comorbid conditions, or personal values.

Table 1: Management of Heart Failure Due to Reduced Ejection Fraction

ACC/AHA	B	C		D
NYHA Classification	I	II – III		IV
Symptoms	Asymptomatic	Symptoms, Current or Prior		Recurrent or Ongoing Rest Dyspnea
		Never Hospitalized	History of Hospitalization	
Pharmacologic Management				
Either: ARNI OR ACE inhibitor OR ARB	ACE inhibitor	ARNI[a] or ACE inhibitor or ARB	ARNI[a] or ACE inhibitor or ARB	ARNI[a] or ACE inhibitor or ARB
Beta blocker	Yes[b]	Yes	Yes	Yes[c]
Aldosterone antagonist		Yes	Yes	Yes
Isosorbide dinitrate–hydralazine		Selected patients[d]	Selected patients[d]	Selected patients[d]
Diuretic		PRN congestion	PRN congestion	Yes
Digoxin		PRN[e]	PRN[e]	PRN[e]
Ivabradine			Selected patients[f]	Selected patients[f]
Nonpharmacologic management				
Consider AICD/Bi-V pacemaker	Selected patients[g]	Yes	Yes	Yes
Heart failure disease management			Yes	Yes
Referral to advanced heart failure program			Yes	Yes[h]

Darker Shading: = Recommended; Lighter shading: = Consider

[a] Two trials have demonstrated superiority of ARNI over enalapril in symptomatic patients. ARNI should not be used in conjunction with ACE inhibitor or ARB. Among those intolerant to ACE inhibitor due to cough, consider use of ARB. If intolerant due to chronic kidney 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.

[b] 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.

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

[d] The combination of isosorbide dinitrate–hydralazine benefited patients who self-reported as black. This combination may be added for patients who remain symptomatic despite therapy with ACE inhibitors and beta blockers and as tolerated without reducing the doses of ACE inhibitor or beta blocker to subtarget doses.

[e] 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.

[f] Indicated if in sinus rhythm with HR > 70 while on maximally tolerated dose of a beta blocker.

[g] Indication only for asymptomatic patients with ischemic cardiomyopathy

[h] Refer for shared medical decision-making regarding left ventricular assist device (LVAD), transplant, or palliative care

Table 2. Doses for Major Heart Failure Drugs

Drug Class and Generic Name	Brand Name	Starting Dose	Target Dose or Common Dose	Target/Common Dose 30 Day Cost [a] Generic	Brand
Drugs Demonstrated to Decrease Mortality and/or Improve Symptoms [b]					
ACE inhibitor [b]					
Captopril	Capoten	6.25 mg 3 times daily (1/2 tab [c])	12.5 – 50 mg 3 times daily	$34-109	$70-234
Enalapril	Vasotec	2.5 mg twice daily	10 mg twice daily	$14 all	$50-75
Fosinopril	Monopril	5-10 mg daily	40 mg daily	$6	$32
Lisinopril	Zestril, Prinivil	5 mg daily	10 – 20 mg daily	$3-5	$36
Perindopril	Aceon	2 mg daily	8-16 mg daily	$10-72	$31-151
Quinapril	Accupril	5 mg twice daily	10-20 mg twice daily	$13 all	$313
Ramipril	Altace	1.25 mg twice daily	5 mg twice daily	$10-18	$330-400
Trandolapril	Mavik	1 mg daily	4 mg daily	$10-15	$35
Aldosterone antagonist [b]					
Eplerenone	Inspra	25 mg daily	50 mg daily	$60-110	$369
Spironolactone	Aldactone	12.5 mg daily	25 mg daily	$4-6	$41-82
ARB [b]					
Candesartan	Atacand	4 mg daily	32 mg daily	$53-60	$180-294
Valsartan	Diovan	40 mg twice daily	160 mg twice daily	$27-32	$425-547
Beta blocker [b]					
Bisoprolol		1.25 mg daily (1/4 tab [d])	10 mg daily	$7-21	n/a
Carvedilol	Coreg	3.125 mg twice daily	25 mg twice daily	$6	$160 all
Metoprolol succinate	Toprol XL	12.5 mg daily (1/2 tab)	200 mg daily	$7-23	$22-102
ARNI					
Sacubitril–valsartan	Entresto	49 mg/51 mg twice daily	97 mg/103 mg twice daily	n/a	$550
Sinus node modulator					
Ivabradine	Corlanor	5 mg twice daily	7.5 mg twice daily	n/a	$475

Table 2 (continued). Doses for Major Heart Failure Drugs

Drug Class and Generic Name	Brand Name	Starting Dose	Target Dose or Common Dose	Target/Common Dose 30 Day Cost [a] Generic	Brand
Vasodilator [b]					
Hydralazine	Hydralazine	37.5 mg 3 times daily	75 mg 3 times daily	$17-31	n/a
Isosorbide dinitrate–hydralazine	BiDil (combination)	20/37.5 mg 3 times daily	40/75 mg 3 times daily	n/a	$330-660
Isosorbide dinitrate	Isordil	20 mg 3 times daily	40 mg 3 times daily	$56-108	$96-193
Drugs for Symptomatic Therapy [b]					
Diuretics – Thiazide [c]					
Hydrochlorothiazide	HydroDiuril	25 mg daily	25 – 100 mg daily	$4-7	$4-8
Metolazone	Zaroxolyn	2.5 mg daily	2.5 – 10 mg daily	$35-44	$88-100
Diuretics – Loop [c]					
Bumetanide	Bumex	1 mg daily	1 – 10 mg 1 – 3 times daily	$22-350	$75-534
Ethacrynic acid	Edecrin	25 mg daily	25 – 200 mg 1 – 2 times daily	$600	$1590
Furosemide	Lasix	40 mg daily	40 – 400 mg 1 – 3 times daily	$5-41	$36-862
Torsemide		20 mg daily	20 – 100 mg 1 – 2 times daily	$7-26	n/a
Inotrope [b]					
Digoxin	Lanoxin	0.125 mg daily	0.125 – 0.375 mg daily	$20-43	$400-1200

[a] Approximate Retail Cost - May vary from store to store. Cost = Average Wholesale Price minus 10%. AWP from Lexicomp Online 5/19. For generic drugs, Maximum Allowable Cost plus $3 from BCBS of Michigan MAC List, 5/19.

[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 3. "Clinical Pearls" in the Pharmacologic Treatment of Heart Failure with Reduced Ejection Fraction

Drug Category	"Clinical Pearls"
ACE inhibitors and ARBs	**Class effect**. All members of this class may be equally effective. **Contraindications.** ACE inhibitors and ARBs may cause hyperkalemia in the presence of chronic kidney disease and should be avoided or used only with great caution among patients with Cr > 2.5 mg/dL, eGFR < 30 mL/min, or K > 5.0 mEq/L. Both classes of agents are contraindicated in patients with bilateral renal artery stenosis, unilateral renal artery stenosis with solitary kidney, pregnancy, allergy to the drug, or a history of angioedema. Angioedema can occur with either class.
ARNI	**Contraindications.** Do not use ARNI concomitantly with an ACE inhibitor or ARB. ARNI may cause hypotension or angioedema. ARNI may cause hyperkalemia in the presence of chronic kidney disease and should be avoided or used only with great caution among patients with Cr > 2.5 mg/dL, eGFR < 30 mL/min, or K > 5.0 mEq/L. ARNI is contraindicated in patients with bilateral renal artery stenosis, unilateral renal artery stenosis with solitary kidney, pregnancy, allergy to ARB or ARNI, or a history of angioedema.
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 is reached. Stop upward titration if patient is 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 eGFR < 30 mL/min or Cr > 2.5 mg/dL and by insuring appropriate patient selection before initiating (see Table 2). Electrolytes must be monitored closely: 5-7 days after a dose change and again in 30 days. Elevation of potassium > 5.0 mEq/L should prompt dose reduction or drug discontinuation.
Isosorbide dinitrate – 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.** Nitrates cannot be used concomitantly with phosphodiesterase type 5 inhibitors (eg, avanafil, sildenafil, tadalafil, and vardenafil) due to the risk of profound hypotension.
Ivabradine	**Initiation:** Use for patients with persistent symptoms and HR > 70 despite maximally tolerated or target dose of a 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 kidney function.** Many of the medications appropriate for heart failure (ARNI, ACE inhibitors, ARBs, aldosterone antagonists, digoxin) can affect potassium or can be affected by potassium levels and kidney function. Closely monitor potassium levels and eGFR. **Do not remove ARNI, ACE inhibitors, beta blockers, spironolactone, or ARBs.** These drugs slow disease progression and decrease mortality, so do not stop them when symptoms improve.
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 heart failure as a medical condition needing better disease-based management because of its prevalence and its management costs. The vast amount of information regarding new treatments available for heart failure patients has resulted in variation in the management of this condition across specialties and health systems, as well as underuse of medications with proven effectiveness.

Rationale for Recommendations

Etiology and Natural History

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

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

Diagnosis and Surveillance

Heart failure with reduced ejection fraction (systolic dysfunction) is a commonly recognized cause of heart failure. Widely available techniques can measure 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 (HFpEF). 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 HFpEF do not have echocardiographic evidence of diastolic dysfunction. Some patients may have both systolic and diastolic heart failure. Heart failure may be more simply conceived in terms of reduced (HFrEF) or preserved ejection fraction (HFpEF), 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 heart failure.

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:

NYHA Class	Description
I	Asymptomatic
II	Mildly symptomatic
III	Moderately symptomatic
IV	Symptoms at rest

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 the following stratification scheme which closely, but not exactly, parallels the NYHA scheme. The relationship between the classification schemes is shown in Table 1.

ACC/AHA Class	Description
A	At risk
B	Asymptomatic
C	Symptomatic
D	Refractory

In the prior versions 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.

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

Ejection fraction. Patients with a presumed diagnosis of heart failure 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 revascularization ejection fraction.

The management of heart failure is based on clinical presentation, physical examination, and 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 noninvasive diagnostic information readily and safely. It provides information on

ventricular shape and function, wall thickness and valvular function, all of which are helpful in the management of patients with heart failure. 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 interobserver reliability than echocardiography in assessing ejection fraction. However, the cost and radiation exposure of these modalities 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 quantitate a patient's functional capacity. Testing may be indicated to document disability for insurance. Patients with poor ventilatory efficiency (V_E/V_{CO2} slopes > 35) or very low peak oxygen consumptions (V_{O2} < 14) may be candidates for advanced heart failure interventions including ventricular assist devices and cardiac transplantation. Consider referring these patients to heart failure subspecialists. 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, noninvasive 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.

The ECG can be helpful to assess for dyssynchrony between the right and left ventricles. A QRS duration ≥ 120 msec is highly suggestive of dyssynchrony. Those with a QRS duration < 120 msec may still have dyssnchrony that can be detected on an echocardiogram. If dysynchrony is detected, patients may gain symptomatic and survival benefit from insertion of a biventricular pacer (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 nonischemic 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 substantial usefulness in the diagnosis and prognosis of patients with heart failure. These 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. However, BNP does not differentiate the cause of heart failure (eg, heart failure with preserved ejection fraction, heart failure with reduced ejection fraction, 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 (see Figure 1). 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. BNP levels can be increased by chronic kidney disease 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 BNP levels in patients being treated for heart failure indicates a poorer prognosis. Trials of outpatient management guided by BNP or N-terminal proBNP (NT proBNP) have shown mixed results. The largest study did not show a significant improvement in clinical endpoints when NT proBNP guided management was compared with symptom-guided management. However, a modest benefit occurred in a planned subgroup analysis of patients younger than 75 years. 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 heart failure.

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. ACE inhibitors, ARBs, aldosterone antagonists, and dietary factors (eg, bananas and salt substitutes) may significantly increase potassium concentrations, especially in patients with chronic kidney disease or when these interventions are 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. Artifactually elevated potassium levels can occur due to hemolysis of the sample and due to hand clenching during phlebotomy.

If required, potassium supplementation should be administered; the 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 gastrointestinal 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 adverse effect. Hypokalemia is often easier to correct if hypomagnesemia is also corrected. When administering supplementation, serum electrolytes should be monitored. Serum electrolytes should also be monitored with any change in diuretic dosing, change in renal function, or addition of drugs that can promote hyperkalemia or hypokalemia.

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 increasing patient knowledge about heart failure and measures to control heart failure. However, comprehensive programs, often involving nurses or case managers who made repeated contacts with patients, were more 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

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:

- Improves health related quality of life and reduces heart failure related hospital admissions by 28%.
- Has no significant impact on short- or long-term all-cause mortality or overall hospital admission rates. A Cochrane review of available studies reached this conclusion.

In the HF-ACTION trial, exercise appeared to be safe, with participants engaging in exercise 3 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 ≤ 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, although a nonsignificant 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 heart failure patients who are symptomatic or have a history of ischemic cardiomyopathy and with an EF ≤ 35%. See Figure 2. 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 (see below) to improve symptoms.

Prophylactic placement of ICDs has been demonstrated in large trials to decrease mortality in patients with heart failure who are receiving appropriate pharmacological therapy. In patients with systolic heart failure, use 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 placement of 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.
- To date, fewer ICDs have been placed in women, so data are limited. 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).

Cardiac resynchronization therapy with biventricular (Bi-V) pacing has been shown to decrease the composite of all-cause death or hospitalization by 19% in heart failure 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 heart failure 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 heart failure 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 heart failure 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 Appendices A, B, and C for common drug interactions.

Diuretics. Diuretics are used to manage volume overload acutely and chronically. Loop diuretics are most often used because of their diuretic potency, but they can be associated with acute and chronic distal tubular compensation (distal tubular hypertrophy) resulting in decreased urine output. The dose of loop diuretic varies greatly between patients, so dosing is determined by individual response. Since diuretics cause potassium and magnesium wasting, monitoring of these electrolytes is warranted.

The effect of diuretics 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. The rate of absorption for torsemide 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 lacks sulfur moieties and is a diuretic option for patients who have allergies to furosemide, bumetanide, and torsemide.

Combining a loop diuretic with a thiazide diuretic increases the diuretic effect by minimizing distal tubular compensation. However, the increase in diuretic response will likely result in increased 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 doses 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 Antagonist Choices. All patients with heart failure and reduced ejection fraction need inhibition of the renin angiotensin aldosterone system. Three options exist: ARNI, ACE inhibitor, or ARB. For most patients, ARNI should be the preferred choice (see Table 1).

Angiotensin Receptor Blocker–Neprilysin Inhibitor (ARNI). 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 recently. In the PARADIGM HF trial a neprilysin inhibitor (sacubitril) in combination with an ARB (valsartan) was tested against enalapril 10 mg twice daily 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 ARNI study drug in the primary endpoint – a composite of death from cardiovascular causes or a first hospitalization from heart failure (HR 0.80, p = sig; NNT 22). In the PIONEER-HF study, ARNI therapy was compared to enalapril in acute decompensated heart failure. In this randomized controlled trial of 881 patients, those receiving ARNI therapy had a greater reduction in NT-proBNP. The study was not powered to detect clinical outcomes. ARNI has the same contraindications as ACE inhibitors and ARBs, and is not to be used in combination with ACE inhibitor. The cost of ARNI therapy is significant, with an estimated cost per Quality Adjusted Life Year of $51,000. Lack of insurance coverage or patient preference may exclude ARNI as an option. ACE inhibitors or ARBs are still valid options in these situations.

The benefit of ARNI therapy over enalapril appears to be substantial and gives credence to consideration of ARNI therapy as the new standard. However, application has been slow for several reasons: this is a new class of drug that has been tested only in a few trials, unopposed neprilysin therapy caused adverse effects in trials, and post marketing data are not yet available.

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; however, the study patients received enalapril first to insure tolerance. Given the lack of real world experience with ARNI therapy, either ACE inhibitor or ARNI may be reasonable at this time. Dual therapy with both ACE inhibitor 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 mm Hg, or the creatinine is elevated.

Some patients will not tolerate ACE inhibitors. In this setting ARNI, ARB, or isosorbide dinitrate–hydralazine may be used to substitute. If ARNI, ACE inhibitors, and ARBs are all contraindicated, then isosorbide dinitrate–hydralazine is preferred.

Angiotensin receptor blockers. Ample evidence supports the use of ARBs for patients who cannot tolerate ACE inhibitors. Evidence suggests the benefit of ARBs is equivalent to ACE inhibitors. However, ACE inhibitors have the advantage of lower cost and more patient experience so they are still preferred over ARBs for suppression of the renin-angiotensin system for most patients. (Isosorbide dinitrate–hydralazine therapy has also been used in patients who cannot tolerate ACE inhibitors. No trials have compared isosorbide dinitrate–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.

ARNI, ACE inhibitors, ARBs, and aldosterone antagonists all can increase potassium; they pose a risk of hyperkalemia if used in combination.

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 Table 1). Trials of beta blockers in symptomatic heart failure 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 myocardial infarction. 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 twice daily, 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 twice daily versus 50 mg twice daily 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 higher 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, in order 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, then doubled every two to four weeks until the patient is 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 eGFR > 30 mL/min per 1.73 m^2 of body surface area and without baseline hyperkalemia (K > 5.0 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 antiandrogenic 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, an effect not seen with eplerenone.

Both spironolactone and eplerenone are potassium-sparing diuretics and can cause hyperkalemia, especially when administered concomitantly with ARNI, ACE inhibitors or ARBs. 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 patients who were 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 heart failure patients who are African American, and may be used as a substitute for any heart failure patient who is intolerant of ACE inhibitors or ARBs. This combination may also be used as tolerated by blood pressure in heart failure patients who are persistently symptomatic on ACE inhibitors, ARBs, 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 dinitrite 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, as well as 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 dysfunction (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, a sinus node modulator, 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 this drug class. 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 heart failure (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 heart failure within the past 12 months. A prior trial (BEAUTIFUL) that tested ivabradine across all classes of heart failure 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 for heart failure include calcium channel blockers, inotropes, antiarrhythmic drugs, and lipid-lowering agents.

Calcium channel blockers (CCBs). Currently, no evidence supports the use of CCBs for treatment of systolic heart failure. However, if CCBs are needed for management of hypertension, the second generation agents appear to be safe.

First generation agents (verapamil, diltiazem) were shown to have adverse outcomes in post myocardial infarction patients with systolic dysfunction. Subsequent studies in ischemic and nonischemic NYHA III/IV heart failure of other CCBs (eg, 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 nonischemic heart failure. However, a subsequent trial demonstrated no mortality benefit from amlodipine in nonischemic cardiomyopathy.

Inotropes. Intravenous inotropic therapy with sympathomimetics (dobutamine or dopamine) or phosphodiesterase type 3 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.

Antiarrhythmic drugs. While arrhythmias such as atrial fibrillation and nonsustained ventricular tachycardia are commonly encountered, no reproducible evidence indicates that patients with heart failure will significantly benefit either from specific antiarrhythmic drugs prior to developing arrhythmias or from the treatment of the arrhythmia.

The use of device therapy has supplanted the use of antiarrhythmic drugs for primary treatment of ventricular arrhythmias. However, antiarrhythmic 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 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 omega-3 polyunsaturated fatty acids 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 anticoagulants, nonsteroidal antiinflammatory drugs (NSAIDs), and narcotics in patients with heart failure.

Anticoagulation 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 those with 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.

Warfarin. 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 foods.

Direct oral anticoagulants (DOACs). Heart failure patients with nonvalvular atrial fibrillation may be considered for alternative therapies other than warfarin. Direct oral anticoagulants (DOACs) such as dabigatran (a direct thrombin inhibitor) and apixaban, edoxaban, and rivaroxaban (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 medications will likely replace warfarin in many patients in the future. However, regardless of the antithrombotic medication used, the risk of bleeding appears to increase with age, renal dysfunction, and through a variety of drug interactions. In general, the primary indication for anticoagulation in left ventricular systolic dysfunction is to prevent thromboembolic events associated with atrial fibrillation. (Also see section on atrial fibrillation.)

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 who have coronary artery disease or have had a myocardial infarction should be considered for low dose aspirin therapy (81 mg/day). The 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 (75 mg/day) may be considered. Limited data for clopidogrel as compared to aspirin suggest similar benefits in heart failure patients regarding mortality, hospitalizations, and bleeding episodes.

NSAIDs. NSAIDs, including COX-2 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-2 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 warfarin. Observational trials have demonstrated an increase in admissions for heart failure patients using NSAIDs or COX-2 inhibitors. Long term NSAID treatment also increases the risk of gastrointestinal bleeding and renal dysfunction.

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.

Impact of withdrawal of therapy. Patients who have heart failure with reduced ejection fraction (HFrEF) may experience improved heart function following treatment for heart failure. Coincident with improved function, they may experience an improvement in heart failure symptoms. Based on a recent pilot study, these patients should remain on heart failure therapy.

The study was an open-label, randomized trial of phased withdrawal of pharmacological treatment, and addressed what would happen if a patient with recovered dilated cardiomyopathy and absence of symptoms were to withdraw heart failure treatment. The primary endpoint was relapse of cardiomyopathy within 6 months as defined by one of the following: reduction in LVEF > 10% and to < 50%, an increase of LVEDV >10% to higher than the normal range, a two-fold rise in baseline NT-pro-BNP to > 400 ng/L, or clinical evidence of heart failure.

A total of 51 patients were enrolled. Among the 25 patients undergoing phased withdrawal of treatment, 11 met the primary endpoint of relapse within 6 months compared to none undergoing continued treatment. Event rate 45.7% (95% CI 28.5 – 67.2; p=.0001). In the end 25 (50%) of the patients successfully completed 6 months of followup without reinitiation of treatment. After 6 months, 25 (96%) of the 26 patients initially assigned to continued treatment underwent phased withdrawal of treatment, where 9 patients met criteria for relapse during the following 6 months. Combining these populations, 40% of the patients experienced relapse of their heart failure, and in total 50% were able to be withdrawn successfully. None of the patients enrolled had ischemic cardiomyopathy. The patients in the treatment withdrawal group had a longer duration of diagnosis of dilated cardiomyopathy, were more likely to be in atrial fibrillation, and were more likely to have had an unplanned heart failure admission.

Vaccination

Influenza vaccination. Influenza vaccination is recommended by the Centers for Disease Control and Prevention 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.

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.

Complementary and Alternative Medicine (CAM)

A number of CAM 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 heart failure patients and was shown to be safe, but did not impact mortality. In one small 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 life style 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 with a trend toward improvement in quality of life. The number of studies performed and the number of heart failure 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 life style choice, the amount consumed should be limited (because chocolate is high in calories and fat) and the type of chocolate should probably have high concentration of cocoa solids.

Coenzyme Q_{10}. Based on the limited data available, coenzyme Q_{10} cannot be recommended for the routine treatment of heart failure or in patients administered HMG-CoA reductase (statin) therapy.

Coenzyme Q_{10} 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 Q_{10}, no large, placebo-controlled trials have been performed, and the best designed trials do not show benefit. Other considerations that limit recommendation of coenzyme Q_{10} 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 patients with low vitamin D levels or at risk for low 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 (eg, covering of exposed skin areas).

Patients need sufficient levels of vitamin D to maintain bone health (ie, prevention of rickets in children). Vitamin D receptors are located throughout the body, including the heart, and vitamin D plays an important role 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 (but no prospective studies) appear to 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 heart failure is a powerful marker for subsequent rehospitalization and mortality. Patients with severe heart failure and repeated hospitalizations for heart failure should be enrolled in a heart failure disease management program. There may also be a benefit to enrolling patients upon their first hospitalization for heart failure.

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

Telemanagement. The role of telemanagement in heart failure is controversial. Different kinds of telemanagement have been tested as additions to heart failure disease management programs or as alternatives for patients who cannot gain access to a heart failure disease management program. Formats include structured telephone support and semiautomated 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 heart failure 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 followup. No trials guide the frequency of followup and surveillance for heart failure. This decision should be made as a clinical judgment based upon the status of the patient. 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 the 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 as an eGFR < 60 mL/min for 3 months or more. 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 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 ACE inhibitors, ARBs, ARNI, and diuretics. Furthermore, diuretics, which are frequently necessary to control congestive symptoms, can concomitantly decrease glomerular filtration rates and contribute to additional diuretic resistance. In end-stage renal disease, dialysis or renal transplantation can sometimes improve left ventricular ejection fraction.

To help prevent renal dysfunction, avoid all nonsteroidal anti-inflammatory drugs in patients with heart failure. Aldosterone antagonists should either be avoided or very closely monitored in patients with eGFR < 30 mL/min. Digoxin doses should be lowered in patients with chronic kidney disease.

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. Iron deficiency anemia is common among patients with symptomatic heart failure and left ventricular systolic dysfunction. In some studies, the anemia of heart failure has been independently associated with a poor prognosis and increased mortality. Multiple factors may contribute to this anemia including: iron deficiency, hemodilution from volume overload, renal dysfunction, circulating cytokines, and an ACE inhibitor-induced increase in a tetrapeptide that inhibits erythropoiesis.

Iron deficiency, defined by the absence of stainable bone marrow iron, has been reported in 40-73% of patients with heart failure and is better detected by low transferrin saturations (< 20%) than by low ferritin levels. No controlled clinical trials have examined transfusion in patients with heart failure, but transfusion in other critically ill anemic patients can adversely affect outcomes. Administration of darbopoetin has been associated with higher rates of thromboembolism and no clinical benefit in this population of patients. Randomized controlled trials of intravenous iron in patients with heart failure and iron deficiency improved quality of life and functional capacity, but showed no improvement in mortality. Ironically, the clinical benefit from intravenous iron was not correlated with a rise in hemoglobin level. A recent, small trial of oral iron did not demonstrate clinical benefit.

To treat iron deficiency anemia in patients with symptomatic heart failure and left ventricular systolic dysfunction:

- Assess anemic patients for low transferrin saturations.
- Consider administering intravenous iron in patients with transferrin saturations < 20%, ferritin levels < 100 ng/mL, and who are not volume overloaded.
- Do not administer erythropoietin stimulating agents or oral iron.

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 constitutes 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 antiarrhythmic medications (eg, amiodarone, dofetilide) or by performing electrophysiologic interventions (including atrial fibrillation ablation). Therefore, 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 an 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 the nondihydropyridines diltiazem and verapamil) can induce worsening heart failure; they 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 mortality and morbidity. Patients with heart failure should be evaluated for depression. 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. Nonpharmacological therapy can be considered in treating depression in heart failure patients. Tricyclic antidepressants should be avoided or used with extreme caution in heart failure patients, in part due to their effect on QT interval prolongation and association with increased cardiovascular events.

Diabetes. Approximately one-third of patients with heart failure have concomitant diabetes. Though the optimal strategy to treat diabetes in patients with heart failure is not known (due in part to lack of randomized control trials), several new classes of drugs for diabetes have shown benefit and may now be preferred in heart failure patients.

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 nonselective beta blocker carvedilol may have less effect on these factors compared to the nonselective 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.

Metformin should be considered first line therapy in stable compensated heart failure patients, even with decreased renal function. Previous meta-analyses have shown that metformin is associated with a reduction in mortality and cardiovascular mortality and may reduce heart failure hospitalizations. A historical concern with metformin had been the potential for patients to develop lactic acidosis, including in patients with reduced kidney function and patients with heart failure. Recently, the FDA has revised its warning regarding renal function and the use of metformin and has moved from a creatinine to eGFR definition of CKD. Specifically, metformin is contraindicated in patients with an eGFR below 30 mL/min per 1.73 m^2 of body surface area. This less-stringent definition increases the number of patients who can benefit from the use of metformin. Insulin is required in patients with type 1 diabetes and those with poorly-controlled type 2 diabetes mellitus. Insulin therapy is associated with sodium retention and may require adjustment of the patient's diuretic dose.

In regard to combination therapy, recent data suggest that empagliflozin, a sodium-glucose cotransporter-2 inhibitor (SGLT2), should be considered for initial add-on therapy. Empagliflozin was studied in approximately 7,000 patients with type 2 diabetes mellitus with the primary outcome of cardiovascular death, nonfatal MI, and nonfatal stroke. The results demonstrated a significant 14% reduction in the primary endpoint ($p = 0.04$). Secondary analysis demonstrated a 35% reduction in heart failure admissions ($p = 0.002$) in the empagliflozin group (2.7% vs 4.1% in the placebo group). The results of this study led to empagliflozin's current indication for lowering A1c levels and reducing the risk of cardiovascular death in patients with type 2 diabetes mellitus and established cardiovascular disease. Another SGLT2 inhibitor, dapagliflozin, has also demonstrated reduced hospitalizations for heart failure. The study included 17,160 patients with type 2 diabetes mellitus; hospitalizations for heart failure were significantly lower in the treatment arm compared to placebo (2.5% vs 3.3% with HR 0.73, 95% CI 0.61-0.88). Currently, dapagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control. Of particular note with the use of SGLT2 inhibitors is that patients may experience an osmotic diuresis and a lowering of blood pressure. Adjustment of a patient's diuretic dose or therapies that lower blood pressure may be needed. SGLT2 inhibitors are also associated with an

increased risk of urinary tract infections and Fournier gangrene. One agent in this class, canagliflozin, carries a black box warning for increased amputation risk. Given the recent data, SGLT2 inhibitors may be considered in the future not only for diabetes treatment but also to improve cardiovascular outcomes.

Liraglutide may be another consideration for add-on therapy since a reduction in cardiovascular events was observed in patients with established cardiovascular disease. However, there appears to be no benefit in reducing heart failure hospitalizations.

Diabetes therapies associated with worsening heart failure should be avoided, including thiazolidinediones (eg, pioglitazone, rosiglitazone). Until further data is available, dipeptidyl peptidase-4 inhibitors (eg, alogliptin, linagliptin, saxagliptin, sitagliptin) should also be avoided in patients with heart failure.

Erectile dysfunction (ED). The occurrence of erectile dysfunction in patients with heart failure 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 (eg, avanafil, sildenafil, tadalafil, vardenafil). Small studies suggest that PDE-5 inhibitors are effective in treating ED in heart failure patients and appear to be safe. However, the use of PDE-5 inhibitors is contraindicated in patients taking nitrates due to the 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 sleep apnea occurs more commonly in patients with the metabolic syndrome and is associated with hypertension, progressive left ventricular dysfunction, and a higher risk of death.

One small study demonstrated that continuous positive airway pressure can reduce blood pressure and improve left ventricular dysfunction in heart failure patients with obstructive sleep apnea. 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 – HFpEF)

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 (ie, HFpEF).

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

Most patients with heart failure are over age 65, and in general, the majority of the items in this guideline apply to older adults with heart failure. 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 comorbid 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 comorbidities exist. Less symptomatic patients have a much better prognosis.

We recommend discussing goals of care and advance directives with patients and family in the context of heart failure management. Additionally, consultation with a hospice and palliative medicine physician can 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. 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 cardiodefibrillator, LVAD; revascularization; diuretics; angiotensin converting enzyme (ACE) inhibitors; angiotensin receptor antagonist/blocker; aldosterone antagonists; digoxin; beta blockers; vasodilators (eg, nitrates, hydralazine); calcium channel blockers; inotropic agents; antiarrhythmics; lipid lowering drugs; fish oil, anticoagulants, antithrombotics and antiplatelet agents; influenza vaccination; pneumovax immunization; coenzyme Q_{10}; NSAIDs; narcotics; vitamin D; other complementary and alternative medicine: nutritional supplements, herbal remedies (eg, hawthorn), chocolate, alcohol, tai chi; disease based management; telemanagement (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; as well as 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 randomized controlled trials 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 as 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:

- 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

Blue Care Network

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 (eg, 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, BCBSM, BCN).

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 (ACO, BCBSM, BCN).

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 (ACO, BCBSM, BCN).

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

Warfarin therapy for heart failure 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 (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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1999: William E. Chavey, MD, Family Medicine; Caroline S. Blaum, MD, Geriatric Medicine; Barry E. Bleske, PharmD, Pharmacy; R. Van Harrison, PhD, Medical Education; Sean K. Kesterson, MD, General Medicine; John M. Nicklas, MD, Cardiology. Consultants: Robert J. Cody, MD, Cardiology; Bertram Pitt, MD, Cardiology.

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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.

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Atrial fibrillation

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RACE II randomized controlled trial in patients with atrial fibrillation demonstrating that lenient rate control (< 110 bpm) was at least equivalent to stricter rate control in avoiding subsequent clinical events. However, because only 10% 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

McAlister FA, Stewart S, Ferrua S, et al. Multidisciplinary strategies for the management of heart failure patients at high risk for readmission. J Am Coll Cardiol 2004 Aug 18;44:810-9.

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

Inglis SC, Clark RA, Mcalister FA et al. Structured telephone support or telemonitoring programmes for patients with chronic heart failure. Cochrane Database Syst Rev 2010;36:2301-9.

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.

Chaudhry SI, Mattera JA, Curtis JP, et al. Telemonitoring in patients with heart failure. NEJM 2010 Dec 9;363:2301-9.

Randomized controlled trial demonstrating no benefit from telemonitoring in patients recently hospitalized for heart failure.

Appendix A. Common Drug Interactions

Drug Class	Interacts with	Effect
ACE inhibitor	Antacids	↓ drug absorption
	Lithium	↑ lithium levels
	NSAID	May decrease renal function
	Aldosterone antagonists or ARBs	Coadministration may result in elevated potassium level, especially in the elderly and patients with renal dysfunction
ARB	Lithium	↑ lithium levels
	NSAID	May decrease renal function
	Aldosterone antagonists or ACE inhibitors	Coadministration may result in elevated potassium level, especially in the elderly and patients with renal dysfunction
Amiodarone	Beta blockers	↓ HR, AV node conduction
	Calcium channel blockers (diltiazem, verapamil)	↓ HR, AV node conduction
	Digoxin	↑ digoxin concentration; ↓ HR, AV node conduction
	Quinidine	↑ quinidine concentration
	Phenytoin	↑ phenytoin concentration; ↓ Amiodarone concentration
	Procainamide	↑ procainamide concentration
	Theophylline	↑ theophylline concentration
	Warfarin	↑ in INR
	Atorvastatin, simvastatin, lovastatin	↑ in statin concentrations
Beta blocker	Amiodarone, diltiazem, verapamil, propafenone, sotalol	↓ HR, AV node conduction
Digoxin	Amiodarone	↑ digoxin concentration; HR, AV node conduction
	Antacids	↓ oral digoxin absorption, space drugs at least 2 hours apart
	Beta blockers	Carvedilol may ↑ digoxin concentration; ↓HR, AV node conduction
	Cholestyramine, colestipol	↓ digoxin absorption
	Diltiazem, verapamil	↑ digoxin concentration; ↓ HR, AV node conduction
	Omeprazole	↑ digoxin concentration
	Propafenone	↑ digoxin concentration; ↓ HR, AV node conduction
	Quinidine	↑ digoxin concentration
	Rifampin	↓ digoxin concentration
	Sotalol	↓ HR, AV node conduction
	Spironolactone	↑ digoxin concentration; interferes with some digoxin assays yielding falsely elevated digoxin concentration
	Atorvastatin, simvastatin, lovastatin	↑ digoxin concentration
Warfarin	Amiodarone, antibiotics (including trimethoprim-sulfamethoxazole and erythromycin), antidepressants, beta blockers, cimetidine, fluconazole, itraconazole, ketoconazole, lovastatin, omeprazole, oral diabetic medications, phenytoin, propafenone, quinidine, quinine, rosuvastatin, simvastatin	↑ INR
	NSAID, aspirin, ticlopidine, clopidogrel	↑ risk of bleeding due to effect on platelet function
	Phenobarbital, rifampin, cholestyramine, carbamazepine, phenytoin, spironolactone, sucralfate	↓ INR

Appendix B. Potential and Documented Interactions of Herbs with Warfarin

(from Am J Health-Syst Pharm—Vol 57 Jul 1, 2000)

Potential Increase in Risk of Bleeding				
Angelica root	Celery	Horse chestnut	Quassia	
Arnica flower	Chamomile	Licorice root	Red clover	
Anise	Clove	Lovage root	Rue	
Asafoetida	Fenugreek	Meadowsweet	Sweet clover	
Bogbean	Feverfew	Onion	Turmeric	
Borage seed oil	Garlic	Parsley	Willow bark	
Bromelain	Ginger	Passionflower herb		
Capsicum	Ginko	Poplar		
Documented Reports of Possible Increase in Warfarin Effects				
Danshen	Devils Claw	Dong quai	Papain	Vitamin E
Documented Reports of Possible Decrease in Warfarin Effects				
Coenzyme Q10	Ginseng	Green tea [a]		

[a] Excessive amounts are necessary for this interaction to occur.

Appendix C. Potential Effects of Herbal Treatments and Vitamins in Heart Failure

May have some degree of diuretic action			
Aconite	Buchu	Dandelion	Juniper
Alisma plantago	Conch grass	Horsetail rush	Licorice
Bearberry			
May increase heart failure or promote arrhythmia formation			
Belladonna	Oleander	Vitamin E	Yohimbine
Ma Huang (ephedra)			
May cause potassium loss			
Herbal laxatives			

May interact with heart failure drugs

St. John's Wort:
- Decrease digoxin concentrations
- Decrease atorvastatin, simvastatin, and lovastatin concentrations
- Decrease diltiazem and verapamil concentrations

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

Black Cohosh
- Increase metoprolol and carvedilol effects

Dong quai, feverfew, garlic, ginger, ginkgo, and kava
- Increase effects of antiplatelet drugs