Heart Failure - Systolic Dysfunction

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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 treatment of patients with HF.

Key Points

Diagnosis.

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

Pharmacologic Therapy (See Table 1)

- For patients with systolic dysfunction (EF < 40%) who have no contraindications:
  - ACE (angiotensin-converting enzyme) inhibitors for all patients *[A*]*.
  - Beta blockers for all patients except those who are hemodynamically unstable, or those who have rest dyspnea with signs of congestion *[A*]*.
  - Aldosterone antagonist (low dose) for patients with rest dyspnea or with a history of rest dyspnea or for symptomatic patients who have suffered a recent myocardial infarction *[A*]*.
  - Isordil-hydralazine combination for symptomatic HF patients who are African-American *[A*]*.
  - ARBs (angiotensin receptor blockers) as a substitute for patients intolerant of ACE inhibitors *[A*]*.
  - Digoxin only for patients who remain symptomatic despite diuretics, ACE inhibitors and beta blockers or for those in atrial fibrillation *[A*]*.
  - Diuretics for symptomatic patients to maintain appropriate fluid balance *[C*]*.

Device Therapy

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

Other

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

* Levels of evidence reflect the best available literature in support of an intervention or test:
A=randomized controlled trials; B=controlled trials, no randomization; C=observational trials; D=opinion of expert panel.

Clinical Background

Clinical Problem and Current Dilemma

Incidence

Almost five million Americans currently have HF. An additional 400,000 develop HF annually. Each year, 875,000 patients are admitted with HF as the primary diagnosis. Overall, nearly 50% of patients die within five years of the onset of symptoms. The incidence of HF increases with age. HF is the most common cause of hospitalization in older adults. Since the American population is aging, the incidence of HF and its associated morbidity and mortality are expected to increase in the future.

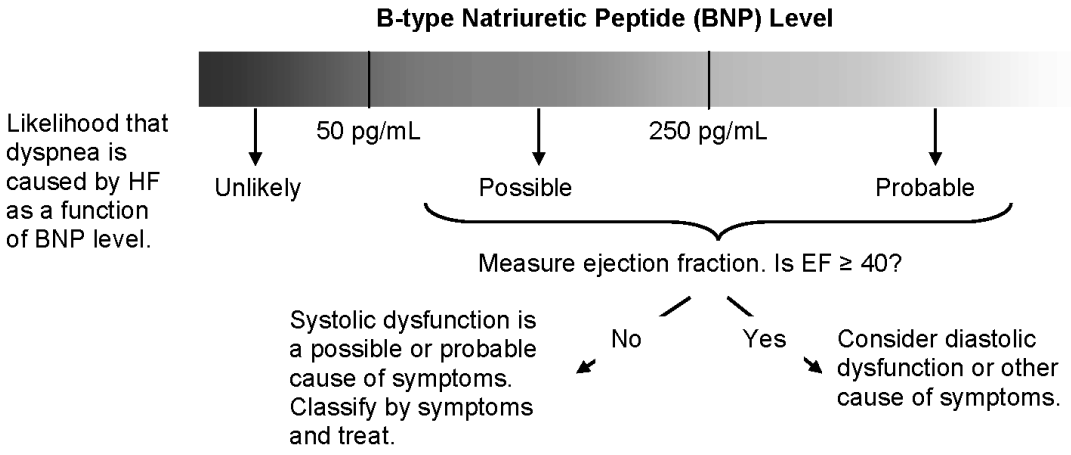
Problems with Care

Over the past decade, the understanding of HF has changed dramatically. The most common cause of HF 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 there are no therapies, in HF there are numerous pharmacologic and lifestyle interventions that can improve mortality. The fact that so many treatments are available has resulted in confusion among those who treat HF patients about how and in whom to initiate and titrate therapy.

(continued on page 5)

Figure 1. Identifying Systolic Heart Failure



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

Table 1. Treatment Classification for Heart Failure Patients with Left Ventricular Systolic Dysfunction

ACC/AHA Classification	**B (Asymptomatic)**	**C (Symptomatic)**		**D (Refractory)**
NYHA Classification	**I**	**II – III.a**	**III.b**	**IV**
Symptoms [1]	**Asymptomatic**	**Symptomatic without H/O Rest Dyspnea**	**Symptomatic with H/O Rest Dyspnea**	**Symptomatic with Rest Dyspnea**
ACE Inhibitor [2]	Yes	Yes	Yes	Yes
Beta Blocker	Yes [3]	Yes	Yes	Yes [4]
Aldosterone antagonist		Post MI [5]	Yes	Yes
Isordil-hydralazine		Selected patients [6]	Selected patients [6]	Selected patients [6]
Diuretic		PRN congestion	Yes	Yes
ARB		PRN [7]	PRN [8]	PRN [8]
Digoxin		PRN [7]	PRN [7]	PRN [7]

Note: Intensity of shading reflects strength of recommendation.

[1] ACE inhibitors, beta blockers, and spironolactone should not be removed if symptoms improve because these medications slow disease progression and decrease mortality.

[2] Although ACE inhibitors are listed first, there is evidence that either an ACE inhibitor or a beta blocker may be started first and then the other added. It is reasonable to titrate the dose of each agent in an alternating step-wise fashion to reach the target doses. For patients intolerant of ACE inhibitor, substitute an ARB.

[3] There is no explicit evidence of benefit for beta blockers among asymptomatic patients; although many patients in this class will have other indications for beta blockers such as CAD.

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

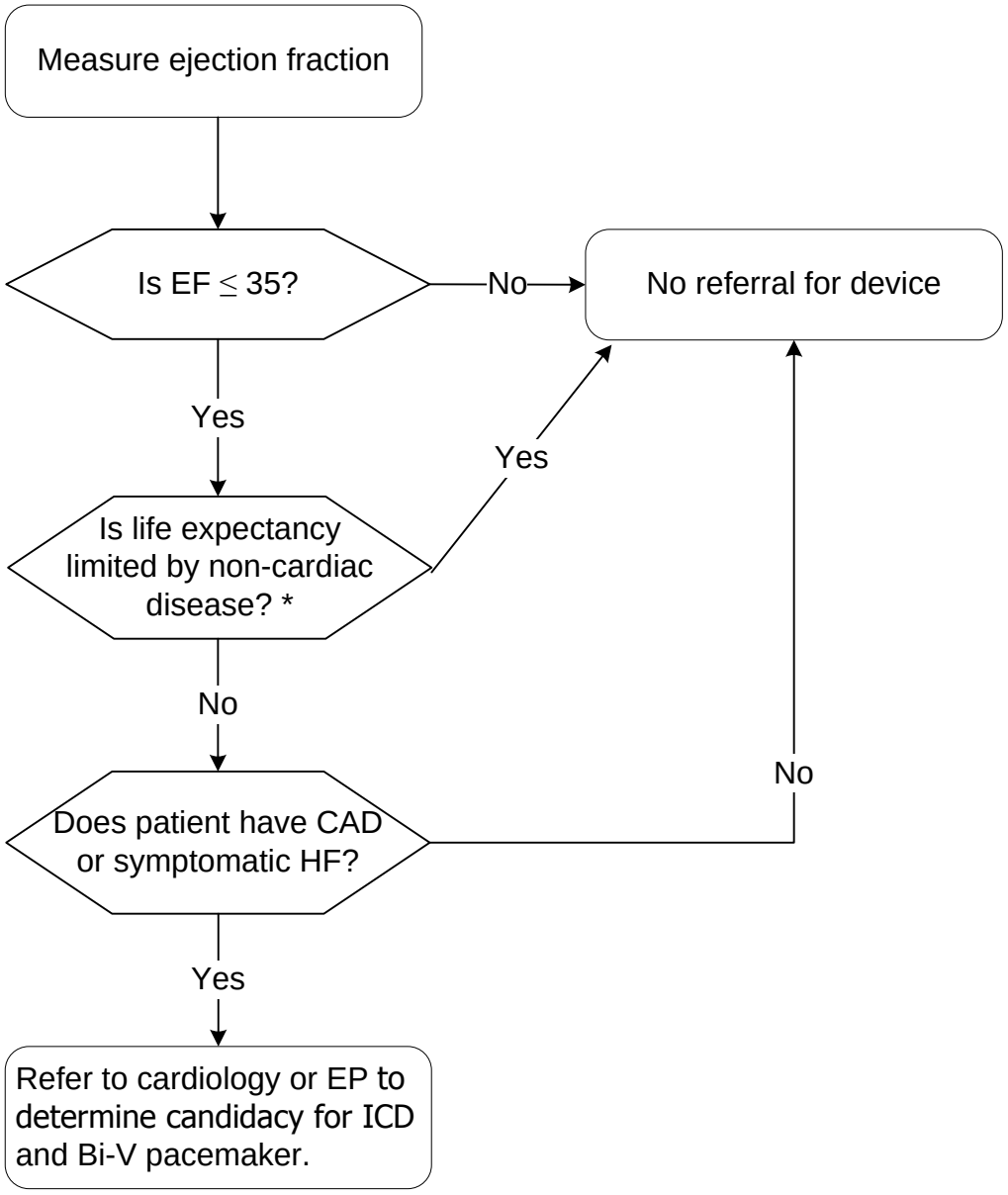
[5] An aldosterone antagonist may be appropriately initiated for symptomatic patients within 14 days of a MI.

[6] The benefit of the combination of isosorbide mononitrate-hydralazine was among patients self-reported as African-American. This combination may be added as tolerated by the blood pressure without reducing the doses of ACE-I or beta blocker to sub-target doses.

[7] These interventions may provide symptomatic benefit. If no benefit is perceived, the medications may be withdrawn. In the case of digoxin, however, withdrawal may lead to clinical deterioration and should be done with caution.

[8] When added to ACE inhibitors, ARB's may improve symptoms. There is little evidence to support the safety of ACE inhibitors/aldosterone antagonists/ARB's in the same patient. Since all agents can increase potassium levels, it may be prudent to avoid this combination or to use with great caution.

Figure 2. Device Referral Algorithm



EP – electrophysiology
ICD- implantable cardiodefibrillator
Bi-V- bi-ventricular pacemaker

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

Table 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 Improve Symptoms [b]					
ACE – Inhibitor [c]					
Captopril	Capoten	6.25 mg tid (1/2 tab[d])	12.5 – 50 mg tid	$6-12	$103-172
Lisinopril	Zestril, Prinivil	5 mg daily	10 – 20 mg daily	$9-10	$36-39
Enalapril	Vasotec	2.5 mg bid	10 mg bid	$10	$78
Trandolapril	Mavik	1 mg daily	4 mg daily	n/a	$36
Ramipril	Altace	1.25 mg bid	5 mg bid	n/a	$94
Aldosterone Antagonist [c]					
Spironolactone	Aldactone	12.5 mg daily	25 mg daily	$10	$22
Eplerenone	Inspra	25 mg daily	50 mg daily	n/a	$106
ARB [c]					
Candesartan	Atacand	4 mg daily	32 mg daily	n/a	$77
Valsartan	Diovan	40 mg bid	160 mg bid	n/a	$117
Beta Blocker [c]					
Bisoprolol	Zebeta	1.25 mg daily (1/4 tab[d])	10 mg daily	$30	$68
Metoprolol	Toprol XL	12.5 mg daily (1/2 tab)	200 mg daily	n/a	$63
Carvedilol	Coreg	3.125 mg bid	25 mg bid	n/a	$113
Vasodilator					
Isosorbide dinitrate-hydralazine	BiDil (combination product)	20/37.5 mg tid	40/75 mg tid	see below	$365
Isosorbide dinitrate	Isordil	20 mg tid	40 mg tid	$25	
Hydralazine	Hydralazine	37.5 mg tid	75 mg tid	$46	
Drugs for Symptomatic Therapy [e]					
Diuretics – Thiazide [f]					
Hydrochlorothiazide	HydroDiuril	25 mg daily	25 – 100 mg daily	$4-8	n/a
Metolazone	Zaroxolyn	2.5 mg daily	2.5 – 10 mg daily	$29-39	$43-97
Diuretics – Loop [f]					
Furosemide	Lasix	40 mg daily	40 – 400 mg daily-tid	$5-42	$10-242
Bumetanide	Bumex	1 mg daily	1 – 10 mg daily-tid	$9-136	$25-634
Ethacrynic acid	Edecrin	25 mg daily	25 – 200 mg daily-bid	n/a	$10-161
Torsemide	Demadex	20 mg daily	20 – 100 mg daily-bid	$22-140	$33-243
Inotrope [c]					
Digoxin	Lanoxin [g]	0.125 mg daily	0.125 – 0.375 mg daily	$7-9	$7-10

[a] Pricing information for brand products based on average wholesale price (AWP) – 10% found in the Amerisource Bergen 10/12/05 catalog. Pricing information for generic products is based on the Blue Cross Blue Shield Maximum Allowable Cost (MAC) price + $3 as posted on 7/28/06.
[b] Target doses in placebo controlled mortality trials.
[c] See interactions in Appendix A.
[d] Tablet is scored for ½ tablet only.
[e] Common doses.
[f] Diuretics have not been separately studied for target dose. Titrate as needed for symptom relief.
[g] Generic is available, but brand is usually dispensed.

Table 3. "Clinical Pearls" in the Pharmacologic Treatment of Heart Failure

Drug Category	"Clinical Pearls"
ACE Inhibitors/ARBs	• **Class effect**. ACE inhibitors appear to exhibit a class effect. All members of this class may be equally effective. • **Contraindications.** ACE inhibitors and ARBs may cause hyperkalemia in the presence of renal failure and should be avoided or used only with great caution among patients with Cr > 2.5, GFR < 30, or K > 5.0. Both classes of agents are contraindicated in patients with bilateral renal artery stenosis, unilateral renal artery stenosis with solitary kidney, pregnancy, and allergies. Angioedema can occur rarely with either class of agent.
Beta Blockers	• **Add when stable**. May be used in patients with heart failure due to systolic dysfunction who do not have contraindications noted above. They are to be added when patients are stable --- to arrest the progression of the disease; they are not to be added as rescue therapy for patients who are decompensating. • **Dosing**. Start at low dose and double the dose every 2 - 4 weeks as tolerated until target dose reached. Stop upward titration if patient intolerant of higher doses. (see Table 2 for dosing). • **Absolute contraindications.** Heart block, bradycardia, severe reversible airway disease. • **Relative Contraindications.** Rest dyspnea with signs of congestion, hemodynamic instability; Once these issues have resolved, beta blockers may be added to the chronic regimen.
Aldosterone antagonists	• **Hyperkalemia.** The risk of hyperkalemia may be significant. These risks can be minimized by avoiding use in patients with GFR < 30 or Cr > 2.5 and by insuring appropriate patient selection before initiating (see Table 1). Electrolytes must be monitored closely. Elevation of potassium to a level of 5.0 – 5.5 should prompt dose reduction or drug discontinuation.
Isordil-hydralazine	• **Dosing.** Thse 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 only per expert opinion. • **Contraindications.** Cannot be used concomitantly with phosphodiesterase inhibitors, e.g., sildenafil, tadalafil, and vardenafil.
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. • **Reduced need.** ACE inhibitors and beta blockers may reduce the need for diuretic therapy.
Combining Drugs	• **Starting other drugs.** The therapy described in Table 1 is the desired endpoint for patients in these classes. No data are available to indicate how best to introduce all of these medications. All of the major trials added beta blockers or spironolactone to background therapy of ACE inhibitors, diuretics, and sometimes digoxin. • **Electrolytes and renal function.** Many of the medications appropriate for HF (ACE/ARB/Aldosterone antagonists/Digoxin) can affect potassium or can be affected by potassium levels and renal function. Vigilant monitoring is required. • **Do not remove ACE inhibitors, beta blockers, spironolactone, or ARB's.** ACE inhibitors, beta blockers, spironolactone and ARB's should not be removed if symptoms improve because these medications slow disease progression and decrease mortality.
Referral	• **Consider referral for the following clinical situations:** - diagnostic procedures - revascularization procedures - worsening or refractory heart failure - ventricular arrhythmias - valvular heart disease - consideration for transplantation

Health care systems have targeted HF as a medical condition needing better disease-based management because of its prevalence and its management costs. Additionally, the vast information regarding new treatments available for HF patients has resulted in variation in the management of this condition across specialties and health systems and under use of medications that have been proven effective. Thus, treatment guidelines have evolved to improve the standardization of care using evidence-based approaches.

Rationale for Recommendations

Etiology/Natural History

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

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

Diagnosis

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

Although diastolic dysfunction is also a common cause of heart failure, no consensus exists regarding optimal techniques to quantitate the degree of dysfunction or to reliably make the diagnosis. 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 not infrequently mistakenly attributed to other causes including pneumonia, asthma, and peptic ulcer disease. Arrhythmias causing palpitations, dizziness, or aborted sudden death can be the initial manifestations of the disease.

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

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

The NYHA system was originally designed for use in research. As a practical clinical tool it has limitations. In 2001, the ACC/AHA proposed a new stratification scheme as noted below.

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

In the first iteration of this guideline, a classification that reflected the inclusion criteria was used to categorize patients into the major clinical trials. In this iteration of the guideline, this classification continued to be used to assist physicians in applying clinical data in practice. A correlation between the classification schemes is shown in Table 1.

Diagnostic studies. Several types of diagnostic studies may be performed.

Electrolytes. Monitoring of potassium and magnesium serum concentrations is essential in the majority of heart failure patients. Diuretics may significantly lower potassium and magnesium concentrations whereas aldosterone antagonists may increase these concentrations. ACE-inhibitors, ARB's, aldosterone antagonists, dietary factors (e.g. bananas and salt substitutes) may significantly increase potassium concentrations especially in the presence of renal impairment or when used in combination. A non-randomized population based study revealed increased hospitalization rates and mortality secondary to hyperkalemia among patients on aldosterone antagonists. These studies diverge from those of controlled clinical trials that demonstrated a favorable risk benefit ratio for aldosterone antagonists when administered to appropriate patients who are closely monitored. Nevertheless they emphasize the need for close monitoring of electrolytes. In general, 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. If required, potassium supplementation should be administered; usual dose range is 10 – 80 mEq/day with a potassium chloride preparation. Magnesium levels should be maintained around 2 mEq/L. The usual dose range for magnesium supplementation for asymptomatic patients with minor alterations in serum concentrations is likely to be 10 – 40 mEq/day.

Administering one to four tablets of products such as magnesium oxide or magnesium chloride may be sufficient for most patients. It should be noted that it is often easier to correct hypokalemia if hypomagnesmia is also corrected. Follow-up monitoring of serum electrolytes should be done when administering supplementations.

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). In this case fluid restriction and diuresis may correct the dilutional hyponatremia. In contrast, severe diuretic use and restriction of sodium can lead to total body sodium depletion likely requiring hospitalization for correction of hyponatremia. Monitoring of serum sodium should be included with monitoring of other electrolytes.

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.

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

Assessment of ejection fraction. The management of heart failure is based on the clinical presentation, the examination, and the determination of the EF.

Transthoracic echocardiography provides non-invasive diagnostic information readily and safely. It provides information on ventricular shape and function, wall thickness and valvular function – all helpful in the management of patients with heart failure. It is reliable, widely available, and inexpensive.

Radionuclide ventriculography or SPECT imaging may also be used to assess left ventricular and right ventricular ejection fraction. It does not allow assessment of valvular function or wall thickness.

Patients with a presumed diagnosis of heart failure should have echocardiography performed to assess systolic function. This should be repeated when the clinical situation has changed and is not easily explainable through history or physical examination.

Evaluation of coronary artery disease. Two common methods for evaluating coronary disease are exercise stress testing and cardiac catheterization.

Exercise stress testing may have a role in the evaluation of some patients with heart failure. The use of stress testing should be individualized. Blanket application to all patients is not indicated. Exercise stress testing is useful in evaluating active and significant concomitant coronary artery disease. When and exactly how to perform stress testing in this select group is probably best decided with the aid of a cardiologist.

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. Coronary artery bypass grafting in multi-vessel disease with depressed systolic function decreases mortality, and improves symptoms of angina significantly. The decision to proceed to cardiac catheterization should be made based on clinical presentation, patient features, non-invasive test results, and a substantial weighing of the risks and benefits. This decision should be individualized and is best made collaboratively with a cardiologist.

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 major survival advantage to patients with symptomatic or inducible ventricular arrhythmias and ischemic heart disease, with or without heart failure, who have implantable cardioverter-defibrillators (ICD). Studies have also demonstrated similar benefit for non-ischemic heart failure patients with ventricular arrhythmias. Ambulatory monitoring should be a part of the evaluation of any heart failure patient suspected of rhythm disturbances. If ventricular arrhythmias are present, the patient should be referred for further evaluation.

B-type natriuretic peptide (BNP) and its closely related N terminal fragment have recently been proven to have substantial usefulness in the diagnosis and prognosis of patients with heart failure. These biologically active proteins are present in cardiac myocytes, and are released in response to demands related to heart failure including stretching of myocytes. They are biologically active: augmenting urine volume and sodium excretion, inhibiting renin-angiotensin activation, and relaxing vascular smooth muscle. Their analogues 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 establish the diagnosis of heart failure in patients who present with dyspnea. BNP does not differentiate the cause of heart failure (diastolic dysfunction, systolic dysfunction, valvular heart disease, congenital heart disease, etc.) In acute care settings, high BNP levels correlate directly with the probability of heart failure and low BNP levels make heart failure unlikely. For example, a BNP of 50 pg/mL has a negative predictive value of 96%, whereas a BNP of 100 pg/mL has a positive predictive value of 79%, and a BNP of 150 pg/mL has a positive predictive value of 83. At a BNP of 250 pg/mL, the relative risk of heart failure is 7.0 (see Figure 1). BNP levels can be

increased by renal insufficiency and to lesser extremes by age and female gender. Obesity tends to lower BNP levels.

Elevated BNP levels in patients with an established diagnosis of heart failure are also powerful indicators of prognosis with relative risk of death increasing by 35% for each 100 pg/mL increase in BNP. Persistently elevated levels in patients being treated for heart failure indicates poorer prognosis. BNP level guided therapy of HF is still unproven.

Treatment

Non-pharmacologic treatment. Non-pharmacologic treatment options include exercise, dietary changes, and operative therapy.

Exercise. Many small and sometimes randomized clinical trials have examined the benefits of exercise training in heart failure. Different exercise formulas have been tested in both men and women. These studies have measured intermediate outcomes, such as ventilatory capacity, maximum oxygen consumption, skeletal muscle parameters, and neurohormonal levels, although a few have measured exercise capacity and quality of life. Exercise may be recommended based upon studies that have shown exercise to be safe under study conditions. However, no major randomized controlled trial is yet available with clinical outcomes such as medication reduction, decreased hospital days, or mortality.

Dietary changes. The guideline group is unaware of any controlled clinical trials of salt or fluid restriction in the treatment of heart failure. However, dietary sodium restriction may reduce the need for diuretics in patients with congestion. The most commonly recommended limit is 2000 mg of sodium daily. Restrictions in fluid intake to 2 L or less daily may be useful in patients with hyponatremia.

Operative therapy. Some causes of heart failure are potentially reversible. Patients with heart failure due to aortic stenosis should be considered for surgery, but the management of this condition is beyond the scope of this guideline. Similarly, patients with coronary artery disease should be considered for revascularization if indicated.

Automatic implantable cardiac defibrillators (ICD). Prophylactic implantation of ICD's has been demonstrated in large trials to decrease mortality in patients with HF who are receiving appropriate pharmacological therapy. In MADIT II patients with an EF of 30 percent or less who had a myocardial infarction (one month or more prior to study entry) experienced a hazard ratio for all cause mortality in the ICD group of 0.69 (P=0.016) relative to usual care. In DEFINITE patients with an EF less than 36 percent due to non-ischemic cardiomyopathy and non-sustained ventricular tachycardia or premature ventricular complexes, experienced a non-significant reduction in all cause mortality of 0.65 (P=0.08). The risk of mortality from arrhythmia was 0.20 (P=0.006). Most recently in SCD-HeFT, NYHA II – III patients with ischemic and non-ischemic EF of less than or equal to 35 percent experienced a risk of all cause mortality of 0.77 (P=0.007) with an ICD.

ICD placement should be considered in all HF patients who are symptomatic or who have CAD with an EF less than or equal to 35 percent. These patients should be referred to an electrophysiologist or cardiologist for evaluation. As part of the evaluation for ICD an ECG should be performed. This will define the QRS duration and assist in the decision whether the device should also provide Cardiac Resynchronization Therapy (CRT) (see Figure 2 and CRT section below).

There is evidence for other considerations when deciding whether to implant an ICD. ICD placement for primary prevention at the time of coronary artery bypass surgery (CABG) (CABG Patch 1997)), or acute myocardial infarction (DINAMIT) has not been shown to reduce death from all causes. Based on these data an ICD should not be implanted within one month following myocardial infarction or within three months following CABG.

In MADIT II and SCD HeFT survival benefit was only realized after one year, so consideration should be given as to whether the patient is expected to have a greater than one year life expectancy.

Resynchronization therapy. Bi-Ventricular (Bi-V) Pacing has been shown to decrease the composite of all cause death or hospitalization to 0.81 (P=0.014) in NYHA III/IV patients with an EF of 35 percent or less and a QRS interval of at least 120 msec (COMPANION 2004). The secondary endpoint of all cause mortality was reduced to 0.76 (P=0.059) and when an ICD was added to the Bi-V pacer the relative risk was 0.64 (P=0.003). Recently, in CARE-HF, patients with NYHA class III or IV heart failure with cardiac dyssynchrony, the combined endpoint of mortality or cardiovascular hospitalization was reduced 0.63 (P<0.001). Bi-V pacing also improved symptoms, and quality of life in CARE-HF.

In NYHA III/IV patients with an EF of 35 percent or less and a QRS interval of more than 120 msec consideration should be given to placement of a Bi-V pacing device. Such a patient should be referred to an electrophysiologist or cardiologist for evaluation. Whether the device should be implanted and whether it should also be capable of defibrillation is a complex consideration requiring the expertise of an electrophysiologist.

Major drugs. See Table 1 for use by treatment classification, Table 2 for dosing and cost, Table 3 for "clinical pearls", and the Appendix for common drug interactions.

Diuretics. Diuretics are used and often required to manage volume overload acutely and chronically. Since diuretics may produce potassium and magnesium wasting monitoring of these electrolytes is warranted.

Diuretics may enhance neurohormonal activation, however, diuretic effect on mortality is not known. Although no large controlled clinical studies of diuretics in the treatment of heart failure have been reported, the vast majority of patients with heart failure in trials of ACE inhibitors, beta blockers, spironolactone, and digoxin received diuretics as part of baseline therapy. Loop diuretics are the most potent individual agents, but are associated with acute and chronic distal tubular compensation (distal tubular hypertrophy). The dose of loop diuretic will vary greatly between patients and will be determined by individual response. Combining a loop diuretic with a thiazide diuretic increases diuretic potency by minimizing distal tubular compensation.

ACE Inhibitors. ACE inhibitors are indicated 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. Their use should be considered a priority of treatment, unless absolutely contraindicated.

ACE inhibitors are often avoided in patients with heart failure because of perceived risk and contraindications. It is very important that such patient factors as lower blood pressure, elevated serum creatinine, and cough not be considered absolute contraindications. When the systolic blood pressure is less than 100, or the creatinine is elevated, careful monitoring on initiating treatment is warranted.

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

For target doses of ACE inhibitors see Table 2.

Aldosterone Antagonists. Aldosterone antagonism is indicated in patients with systolic dysfunction and symptoms of heart failure including rest dyspnea or a history of rest dyspnea within the past six months. In addition, aldosterone antagonism is indicated in patients following recent myocardial infarction who develop systolic dysfunction with either manifest signs of heart failure or concomitant diabetes.

The two available agents, low dose spironolactone and eplerenone, differ in potency and side effects. Spironolactone is twice as potent as eplerenone as an aldosterone antagonist, but spironolactone also produces gynecomastia in 7% of men when administered at a dose of 25 mg daily, a side effect not seen with eplerenone. Low dose spironolactone (e.g., 12/5 -25 mg daily) is recommended for the treatment of systolic heart failure.

As aldosterone antagonists, both spironolactone and eplerenone are potassium sparing diuretics and can cause hyperkalemia especially when administered with angiotensin converting enzyme inhibitors or angiotensin receptor blockers. In presumably unselected populations, aldosterone antagonism has been associated with severe hyperkalemia and increased mortality. In the controlled clinical trials of aldosterone antagonists, severe hyperkalemia was rare, but patients with serum creatinines > 2.5 mg/dl were excluded and serum potassium levels were closely monitored with drug doses adjusted according to potassium levels. Even in these selected populations, patients with glomerular filtration rates < 50 ml/min developed hyperkalemia nearly twice as frequently as patients with glomerular filtration rates > 50 ml/min. Therefore, we do not recommend administration of aldosterone antagonists to patients with glomerular filtration rates < 50 ml/min.

Some experts believe that spironolactone may be beneficial in patients with mild heart failure and in those with diastolic disease. No large-scale clinical trials have yet addressed the safety or efficacy of this practice in these populations. If administration of aldosterone antagonism is extrapolated to patients without rest dyspnea, especially those not requiring loop diuretic therapy, we recommend close monitoring of serum potassium levels beginning within 1 week of drug therapy initiation.

Angiotensin receptor blockers. ARBs have been tested as agents for use in place of or in addition to ACE inhibitors. For the former application, there is ample evidence to support the use of ARB's for patients who cannot tolerate ACE inhibitors. The combination of isordil-hydralazine has also been used in this situation. There are no comparative trials of isordil-hydralazine and ARBs among ACE inhibitor intolerant patients. Evidence suggests equivalence of ARBs in comparison to ACE inhibitors. However, ACE inhibitors have the advantage of lower cost and more patient experience and are still the preferred first line agent for suppression of the renin-angiotensin system for most patients. ARBs may also safely be added to ACE inhibitors. This combination may be appropriate for patients who remain symptomatic despite therapy with diuretics, ACE inhibitors, and beta blockers to improve symptoms. Some of these patients who remain symptomatic may also be candidates for an aldosterone antagonist. As ACE inhibitors, ARBs and aldosterone antagonists may all increase potassium, they may represent a dangerous combination if used together.

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

Although the three known efficacious beta blockers differ pharmacologically, there has been no direct comparison between them. A comparative trial has demonstrated that carvedilol is superior to metoprolol tartrate in prolonging survival in patients with symptomatic heart failure when these agents are administered at doses of 25 mg BID versus 50 mg BID respectively. However, the dose and formulation of metoprolol in this study differed from the dose and formulation in the placebo-controlled trial in which metoprolol succinate was proven effective. It can then be argued that a high dose of metoprolol succinate might have yielded a different result. Thus, 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. The initial dosage level should be started (see Table 2), then doubled every two to four weeks until either unable to tolerate higher levels or the target dose is reached (see Table 2). Symptoms of increasing dyspnea, worsening heart failure, hypotension or symptoms of hypotension should prompt evaluation of the patient and may necessitate increasing diuretics or may require discontinuation or decrease of the beta blocker. Beta blockers should be added when patients are stable – to diminish the progression of the disease. They are not to be added as a rescue therapy for patients who are decompensating.

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

Recent trials in symptomatic patients have shown dramatic mortality benefits, making beta blockers a mainstay in heart failure treatment. Beta blockers have not been tested in patients with rest dyspnea and signs of congestion.

Digoxin. Digoxin is indicated in heart failure patients with atrial fibrillation. It may also be administered in symptomatic heart failure patients despite maximal individualized therapy with diuretics, ACE-inhibitors, and beta blockers to improve symptoms and to decrease hospitalization rates. The usual dose range for digoxin is 0.125 to 0.25 mg/day to be adjusted as needed based upon symptoms, other drugs, or renal impairment (see Table 2). In general, serum levels for treatment of symptomatic heart failure should be < 1 ng/ml when measured at least 6-8 hours after dosing. Levels for treatment of atrial fibrillation are often higher.

A post hoc analysis of the Digitalis Investigation Group study revealed a trend toward increased mortality among women taking digoxin. However digoxin levels were higher among women than men. A prospective trial to validate these results is unlikely. Use of digoxin in women may still be safe and effective with close monitoring of digoxin levels, especially for those with renal insufficiency. Also, studies have documented clinical deterioration among patients withdrawn from digoxin, though the number of patients in these trials was small. Discontinuing this drug should be done with caution.

Digoxin has never been proven to have an impact on mortality -- only on symptoms and hospitalization rates. The collection of drugs that have a beneficial impact on mortality in heart failure is expanding. As an increasing number of medications can become a barrier to compliance, the role that digoxin will ultimately play in heart failure is unclear. Currently, the guideline group recommends considering digoxin in patients who remain symptomatic despite therapy with diuretics, ACE inhibitors, and beta blockers and in those who have atrial fibrillation. Digoxin may still be used among patients on spironolactone with the caveat that spironolactone may increase digoxin levels by decreasing renal excretion. This effect has not been reported with eplerenone

Direct acting vasodilators. 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 (Cohn, NEJM, 1991). In a post-hoc analysis of those trials the combination of isosorbide dinitrate and hydralazine was particularly effective in African American patients (Carson, J Card Fail, 1999). Improvement in mortality among African American patients using isosorbide dinitrite and hydralazine has since been demonstrated in a prospective trial in which these agents were added to usual background therapy (Taylor, NEJM, 2004). 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. Combined isosorbide dinitrate 40 mg with hydralazine 75 mg three times a day may be used as tolerated by blood pressure in symptomatic HF patients who are African American and may be used as a substitute for any HF patient who is intolerant of ACE inhibitors because of cough, angioedema, or renal failure. Headache may develop and can become less problematic with continued use

Minor drugs.

Calcium channel blockers. Calcium channel blockers (CCB's) have a limited role in the treatment of chronic heart failure. First generation agents (verapamil, diltiazem) were shown to have adverse outcomes in post-MI patients with systolic dysfunction. Subsequent studies in ischemic and nonischemic heart failure NYHA III/IV with other CCB's (e.g. amlodipine, felodipine) suggested their safety, but did not demonstrate their efficacy. A subgroup analysis of the original PRAISE randomized controlled trial using amlodipine found a 46% decrease in mortality in patients with non-ischemic heart failure. However, PRAISE 2 demonstrated no mortality benefit from amlodipine in nonischemic cardiomyopathy. Currently, no evidence supports the use of CCB's for treatment of heart failure,

however if CCB's are needed for management of hypertension amlodipine and felodipine appear to be safe.

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

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

Anti-arrhythmic drugs. While arrhythmias such as atrial fibrillation and non-sustained ventricular tachycardia are commonly encountered, there is no reproducible evidence that therapy with specific anti-arrhythmic drugs prior to developing arrhythmias is of significant benefit to patients with heart failure. Similarly, the primary treatment of patients with long QT interval and heart failure does not seem to affect important clinical endpoints in the absence of arrhythmia. We recommend the use of anti-arrhythmic drugs to treat arrhythmias that are discovered during the management of patients with heart failure, along with the careful use of implantable cardiac defibrillators discussed in this guideline.

The use of device therapy has supplanted the use of anti-arrhythmic drugs for primary treatment of ventricular arrhythmias. However, anti-arrhythmic therapy may be used in conjunction with device therapy in selected patients to suppress ventricular arrhythmias and minimize device firing.

For patients who have atrial fibrillation, rate control is of primary importance and may often be obtained with the use of beta blockers and digoxin which are also indicated in heart failure. Conversion to sinus rhythmn may be indicated in some patients. If this is to be attempted pharmacologically, amiodarone may be the agent of choice for patients with HF.

Lipid-lowering agents. The most common cause of heart failure secondary to systolic dysfunction is still ischemic damage. Retrospective cohort studies show statin drug therapy correlating with improved outcomes in patients with heart failure independent of cholesterol levels. We recommend management of cholesterol and the use of statin type drugs according to NCEP ATP III guideline for patients with heart failure

Other treatments.

Anti-thrombotics. This category of agents includes warfarin and aspirin.

Warfarin – Anticoagulation therapy is indicated in heart failure patients who are at risk for thromboembolism, which includes atrial fibrillation and history of previous embolization. Anticoagulation therapy has also been prescribed for patients with low EF or intracardiac thrombus. However, data supporting the use of anticoagulation are limited and controversial. The majority of studies did not correct for the presence of well established risk factors for thrombus formation and also neither the level of anticoagulation nor the initiation of anticoagulation was controlled. The appropriate dose of warfarin will be determined by the patient's INR and indication for anticoagulation therapy. Warfarin is indicated in patients with atrial fibrillation, demonstrated left ventricular thrombus, or history of embolic stroke with the likely source being dilated left ventricle.

Aspirin / clopidogrel – Many patients with heart failure due to ischemic cardiomyopathy are on aspirin. Though patients with heart failure who are already on aspirin may be maintained on aspirin, heart failure itself is not an indication to start aspirin. Controversial data suggests that ASA may interfere with ACE inhibitor effectiveness resulting in an increase in hospitalization rates for heart failure. It should be noted that patients with coronary artery disease or post myocardial infarction should be considered for low dose aspirin therapy (e.g. 81 mg/day). With the limited data available, it is reasonable to consider ASA therapy for heart failure patients with a recent coronary history. Heart failure patients with a remote coronary history may need to be considered more carefully for ASA therapy. Potential adverse affects of aspirin on gastric mucosa and on renal function should also be considered. In patients not able to tolerate aspirin therapy, clopidogrel therapy (75mg/day) may be considered. Limited data suggest similar benefits in heart failure patients regarding mortality, hospitalizations, and bleeding episodes as compared to ASA.

Influenza vaccination. Observational studies have demonstrated the general effectiveness of influenza vaccinations in older adults and those with chronic diseases. One large observational study demonstrated that influenza vaccination was associated with a significant reduction in both the rate (37% less) and cost (43% less) of hospitalization for heart failure.

Pneumococcal vaccination. 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. Pneumococcal vaccination is indicated for patients with heart failure.

Coenzyme Q10. Based on the limited data available, coenzyme Q10 cannot be recommended for the routine

treatment of heart failure or in patients administered HMG-CoA reductase (statin) therapy.

Coenzyme Q10 has been advertised by nutritional manufacturers and by some researchers as an effective treatment for heart failure. Although there are limited trials showing benefit with coenzyme Q10, there are no well-designed, large scale, placebo control trials evaluating this product. In fact, the best designed trials do not show benefit. It has been hypothesized that statin therapy may reduce Coenzyme Q10 levels and promote heart failure. However, current data do not support this hypothesis. Statin therapy for treatment of dysplipidemia without Coenzyme Q10 in cardiac patients actually show trends in reducing the incidence of heart failure and may be beneficial for the treatment of heart failure. At this time coadministration of Coenzyme Q10 with or without statin therapy is not recommended for prevention or to limit the progression of heart failure. Other considerations include: (1) dose to administer has not been established; (2) cost; adverse effects and drug interactions are not well defined but have included gastrointestinal complaints and elevated liver enzymes.

NSAIDS / COX II inhibitors. No reported prospective controlled trials have evaluated the safety or efficacy of NSAIDs or COX - II inhibitors in patients with heart failure. However, many heart failure patients are on these medications for other indications. NSAIDs can have interactions with several other medications frequently used in heart failure such as ACE inhibitors and warfarin. NSAIDS may also have deleterious affects on renal function. Observational trials have demonstrated an increase in admissions for HF patients using NSAIDs or COX-II inhibitors. Use of NSAIDs or COX-II inhibitors is discouraged for patients with heart failure.

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.

Complimentary and alternative medicine / treatments (CAM's). A number of non-traditional treatments may be helpful to patients with congestive heart failure, especially in terms of symptom control and improved quality of life. Cohort studies show that patients with higher spirituality indices have higher quality of life scores. Slow breathing techniques and tai chi have improved oxygen utilization, BNP levels, quality of life, and symptoms. The preparation Crataegus has been studied and found to be effective in a small trial comparing it to ACE inhibitor and diuretic therapy. Few of these studies are of size and scope to warrant major changes in the management of heart failure.

Systems aiding treatment.

Disease-based management. For patients with severe heart failure or recurrent hospitalizations, a heart failure program consisting of close telephone follow-up by physician supervised specialty nurses may reduce or prevent recurrent hospitalizations. In a randomized study of patients with high use of heart failure medications disease management led to fewer hospitalizations for heart failure although the benefit was less significant at 9 months than at 3 months. In a larger study including arms with both nurse telephone support and home tele-monitoring both lead to decreased mortality compared to usual care and this persisted at 8 months of follow-up. Additionally in three meta analyses disease management reduced hospital admission rates. Many other less rigorous studies have suggested that specialized heart failure clinics decrease hospitalizations through careful outpatient follow-up directed towards risk factors for hospitalization. Most of these have involved patients with severe heart failure and a history of recurrent heart failure admissions. Once a patient has been admitted to the hospital for heart failure they are at high risk for re-hospitalization and should be considered for disease-based management.

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

Summary of treatment strategy. Patients with heart failure secondary to systolic dysfunction gain symptomatic and/or survival benefit from at least five classes of medications in combination with dietary sodium restriction. Identification of a patient's symptomatic class can aid in the addition of step-wise therapy and help to reduce unnecessary poly-pharmacy.

Special Circumstances and Populations

Comorbidities

Renal Insufficiency. Acute and chronic renal insufficiency is common in patients with heart failure especially in patients with more severe symptoms. Over 75% of patients hospitalized for heart failure have moderate or severe renal insufficiency defined by a glomerular filtration rate < 60 ml/min. Renal insufficiency may be a consequence of renal hypoperfusion from either an inadequate or maldistributed cardiac output. Renal insufficiency may also represent intrinsic kidney disease or pharmacologic or other extrinsic toxicity. Regardless of the etiology, renal insufficiency 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.

Renal insufficiency can complicate and frustrate treatment for patients with heart failure. Renal insufficiency alters the pharmacokinetics of concomitant therapy with aldosterone antagonists and digoxin and can increase the risk of toxicity from these agents. Renal insufficiency can impair the response to angiotensin converting enzyme inhibitors and diuretics. Furthermore, diuretics, which are frequently necessary to diminish congestive symptoms, can concomitantly decrease glomerular filtration rates and contribute to additional diuretic resistance. A small study demonstrated that a selective adenosine antagonist could blunt the effect of loop diuretics on glomerular filtration rates but no large controlled trials have been performed and these agents are not available. Low volume ultrafiltration has gained FDA approval as an outpatient office procedure, but no large clinical trials are available to guide the role of this intervention. In end-stage renal disease, dialysis or renal transplantation can improve left ventricular ejection fraction.

To avoid renal insufficiency we recommend avoidance of all non-steroidal anti-inflammatory drugs in patients with heart failure. We also recommend that aldosterone antagonists should either be avoided or very closely monitored in patients with glomerular filtration rates < 50 ml/min. Digoxin doses should be lowered in patients with renal insufficiency.

Anemia. Anemia is common in patients with left ventricular systolic dysfunction, especially in patients with severe heart failure symptoms. The anemia of heart failure is independently associated with a poor prognosis and increased mortality. This anemia is often associated with blunted erythropoietin production and defective iron supply, and a small trial has demonstrated that treatment with subcutaneous erythropoietin and intravenous iron appears to improve symptoms, LVEF, and renal function. Large, randomized, controlled trials of erythropoietin and iron are being planned but have not yet been performed. There are no controlled clinical trials of transfusion in patients with heart failure, but transfusion in other, critically ill, anemic patients adversely affects outcomes. Therefore, we do not recommend treating anemic heart failure patients with either transfusions or erythropoietin and iron pending the results of trials to evaluate the benefits and potential risks (including thrombosis) of therapy.

Diabetes. Approximately one third of patients with heart failure have concomitant diabetes. Since heart failure is associated with insulin resistance, it contributes to diabetes and relative hyperglycemia. In addition, treatment for heart failure with cardioselective beta blockers (ie metoprolol and bisoprolol) as opposed to non-selective beta blockers (ie carvedilol) can also independently increase insulin resistance.

Thiazolidinediones, used in the treatment of diabetes, can complicate the treatment of heart failure. A recent trial has demonstrated that pioglitazone can significantly reduce heart attacks, strokes, and death in diabetics. However, thiazolidinediones are associated with fluid retention and edema especially in patients also receiving insulin. Therefore, thiazolidinediones should be administered with caution in patients with heart failure especially in patients whose fluid balance is tenuous.

Sleep Apnea. Sleep disoriented breathing reportedly occurs in over half of patients with heart failure approximately equally divided between obstructive sleep apnea and central sleep apnea. Obstructive apnea occurs more commonly in patients with the metabolic syndrome and is associated with hypertension and progressive left ventricular dysfunction. One small study demonstrated that continuous positive airway pressure can reduce blood pressure and improved left ventricular dysfunction in these patients. However, in heart failure patients with central sleep apnea the effects of positive airway pressure are ambiguous. The largest reported study demonstrated that continuous positive airway pressure decreased the degree of disordered breathing and marginally improved exercise capacity but did not alter mortality or the need for heart transplantation. 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.

Older Adults with Systolic Heart Failure

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

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

Hypertension

Epidemiologic data have identified hypertension as a risk factor for heart failure through two potential mechanisms. (1) Hypertension may lead to left ventricular hypertrophy and subsequent diastolic dysfunction. (2) Hypertension is a recognized risk factor for coronary artery disease, which is the most common etiology of left ventricular systolic dysfunction. Treating hypertension may prevent the development of clinical heart failure. (For diagnosis and

treatment recommendations, see "UMHS Clinical Guideline: Essential Hypertension".)

In the SHEP trial (Systolic Hypertension in the Elderly Program), 4736 patients with systolic hypertension were treated with chlorthalidone versus placebo. The treatment group had a relative risk of fatal or nonfatal heart failure of 0.51 ($p<0.001$). The study did not distinguish between diastolic or systolic dysfunction as the etiology of failure. Meta-analyses have corroborated this finding.

See the UMHS Clinical Care Guideline on Essential Hypertension for additional information on diagnosis and treatment of hypertension.

Diastolic Dysfunction

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. There is a lack of consensus on the diagnostic criteria for diastolic dysfunction and also a lack of evidence from clinical trails 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.

Advance Directives

The diagnosis of heart failure almost always raises concern by the patient and family regarding prognosis, options for treatment, risks of testing, and need for surgery. These concerns are valid. Patients with severe heart failure and symptoms at rest are at substantial risk of dying within one year, particularly if co-morbidities exist. Less symptomatic patients have a much better prognosis.

We recommend discussing advance directives with patients and family in the context of heart failure management. Advance directives include durable power of attorney for health care and a "living will". In advanced heart failure with no effective treatment options, palliative care and hospice care may be considered.

Information the Patient Needs to Know

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.
- 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.

Exercise. Continue to be active except as limited by symptoms.

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

Strategy for Literature Search

The literature search for this project started with the results of the literature search performed in 1998 for an earlier version of this guideline. Then a search was conducted prospectively using the major keywords of: *congestive heart failure*, *guidelines*, *controlled trials*, *published 1/1/98 to 3/31/05*, *adults*, *English language* on Medline. Terms used for specific topic searches within the major key words included: BNP and B-type natriuretric peptide; left ventricular ejection fraction measurement: echocardiography, sestamibi, radionuclide ventriculogram; aldosterone antagonists; beta blockers; angiotensin converting enzyme (ACE) inhibitora; angiotensin receptor antagonist/blocker, diuretics; digoxin; lipid lowering drugs; devices: ICE, biventricular pacing, AICD, implantable cardiodefibrillator; vasodilators (e.g., nitrates, hydralazine); calcium channel blockers, anti-coagulants; anti-arrhythmics; influenza vaccination; pneumovax immunization; inotropic agents; narcotics; electrolytes; NSAIDS; coenzyme Q10; disease based management; exercise; dietary restrictions;

salt substitutes; functional testing, stress testing; catheterization; electrocardiogram; revascularization; telemanagement (diuretics & weight); gender differences; racial differences and pharmacotherapy; comorbid conditions: anemia, diabetes, depression, erectile dysfunction, sleep apnea, dementia, arthritis; complementary and alternative medicine: nutritional supplements, herbal remedies (e.g., hawthorn); any other reference identified by the major keywords and not included in results of specific topic searches. Specific search strategy 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 clinical trials if available, to the exclusion of other data; if RCTs were not available, observational studies were admitted to consideration. If no such data were available for a given link in the problem formulation, expert opinion was used to estimate effect size.

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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Direct acting vasodilators

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

A-HeFT demonstrated the benefit of adding isordil-hydralazine to African-American patients who remained symptomatic despite background therapy.

Angiotensin receptor blockers

Pfeffer MA, et. al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet. 2003 Sep 6;362(9386):759-66.

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

Device therapy

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Bardy and colleagues demonstrated the benefit of implantable defibrillators among patients with NYHA class II or III CHF and LVEF of 35 percent or less.

Appendix A. Common Drug Interactions

Drug Class	Interacts with	Effect
ACE Inhibitors	Antacids	↓ drug absorption
	Lithium	↑ lithium levels
	NSAID	May decrease renal function
	Aldosterone Antagonists/ARBS	Coadministration may result in elevated potassium level especially in the elderly and patients with renal dysfunction
ARBS	Lithium	↑ lithium levels
	NSAID	May decrease renal function
	Aldosterone Antagonists/ACE-Inhibitors	Coadministration may result in elevated potassium level especially in the elderly and patients with renal dysfunction
Amiodarone	B-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 Blockers	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 2hrs apart
	B-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 Bactrim and Erythromycin), Antidepressants, Beta-Blockers, Cimetidine, Fluconazole, Itraconazole, Ketoconazole, Lovastatin, Omeprazole, Oral Diabetic Agents, Phenytoin, Propafenone, Quinidine, Quinine, Rosuvastatin, Simvastatin	↑ INR
	NSAID, ASA, Ticlopioine, 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 Arnica flower Anise Asafoetida Bogbean Borage seed oil Bromelain Capsicum	Celery Chamomile Clove Fenugreek Feverfew Garlic Ginger Ginko	Horse chestnut Licorice root Lovage root Meadowsweet Onion Parsley Passionflower herb Poplar	Quassia Red clover Rue Sweet clover Turmeric Willow bark	
Documented Reports of Possible Increase in Warfarin's Effects				
Danshen	Devils Claw	Dong quai	Papain	Vitamin E
Documented Reports of Possible Decrease in Warfarin's Effects				
Coenzyme Q10	Ginseng	Green tea [a]		

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

Appendix C. CAM and CHF Interactions

May have some degree of diuretic action			
Aconite Alisma plantago Bearberry	Buchu Conch grass	Dandelion Horsetail rush	Juniper Licorice
May increase heart failure or promote arrhythmia formation			
Belladonna MaHuang	Oleander	Vitamin E	Yohimbine
Herbal laxatives can cause potassium loss			
Potential herb and CHF drug interactions			

St. John's Wort:

- Decrease digoxin concentrations
- Decrease atorvastatin, simvastatin, and lovastatin concentrations
- Decrease diltiazem and verapamil concentrations
- Decrease effect of warfarin

Goldenseal:

- Increase metoprolol and carvediolol effects
- Increase atorvastatin, simvastatin, and lovastatin concentrations
- Increase diltiazem and verapmil concentrations

Black Cohosh

- Increase metoprolol and carvedilol effects

Anti-platelet drugs (increase effects)

- Dong quai, feverfew, garlic, ginger, ginkgo, kava