InetCE

Volume 6	2002	Number 7

George E. MacKinnon III, Ph.D., R.Ph., FASHP
Founding Editor

Linda Swanson
Copy Editor

Internet Continuing Education (***InetCE***) provides free, continuing education to pharmacists and other health care providers 24 hours a day over the Internet at www.InetCE.com. These home study programs have assisted in keeping practitioners apprised of treatment-related topics in the changing health care environment since 1997.

InetCE grew out of a need for relevant, continuing education in health care, and to make it accessible to pharmacy practitioners in various practice settings. This format provides convenient instruction, on-line testing, evaluation, and certification. Continuing education examinations are graded automatically and, if successfully passed, the user can print the statement of credit.

ProCE, Inc. is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmaceutical education. Continuing education programs are developed in accordance with the ACPE's "Criteria for Quality and Interpretive Guidelines." *InetCE* is supported through an unrestricted educational grant provided by Pfizer Inc., U.S. Pharmaceuticals.

Management of Heart Failure: Part 2, Chronic

InetCE **221-146-04-062-H01**

Mohammad J. Tafreshi, Pharm.D.
Associate Professor of Pharmacy and Medicine
Cardiology Pharmacy Residency Director
College of Pharmacy – Glendale
Midwestern University
Glendale, Arizona

Kay S. Westfall, Pharm.D.
At the time of writing the manuscript, Dr. Westfall was a pharmacy student at Midwestern University College of Pharmacy – Glendale.

PLEASE NOTE: The content of the article was current at the time it was written. The exam for this article is not valid for CE credit after 10/01/2005.

LEARNING OBJECTIVES
After completing this continuing education program, the pharmacist should be able to:

1. Identify categories of heart failure (HF).
2. Identify the most current guidelines for treatment of chronic systolic HF.
3. Describe specific recommendations for treatment of patients with HF.
4. Describe possible future treatments for management of patients with chronic HF.

ABSTRACT: As a large percentage of our population will soon be reaching 65 years of age, heart failure (HF) is becoming the new epidemic of our time. Organizations and associations have coordinated their resources to produce guidelines and treatment options to better assist health care professionals.

HF has been classified into several different categories: right-sided versus left-sided, forward versus backward, systolic versus diastolic, high-output versus low-output, and acute versus chronic. This continuing education series is divided into 2 sections, Part 1 and Part 2. In Part 1, management of "acute" HF has already been addressed, and Part 2 is devoted to "chronic" HF.

Currently, there are 2 sets of classifications commonly used for categorizing patients with HF. These include New York Heart Association (NYHA) "classes" and American College of Cardiology, American Heart Association (ACC/AHA) "stages." The NYHA classification system uses "subjective" information to classify patients in a HF category. The new 2001 ACC/AHA guidelines for management of patients with chronic HF use more objective information to classify patients with HF.

The ultimate treatment goal is to decrease the development and progression of the disease and eliminate symptoms of HF. By achieving these goals, the patient should have a better quality of life and a longer life expectancy.

Since studies and trials have used the NYHA guidelines in their design and eligibility, NYHA and ACC/AHA guidelines should be used together. The ACC/AHA guidelines have constructed an organized system to make a recommendation for an ACC/AHA "staged" patient using NYHA class information. Additionally, the ACC/AHA guidelines have used a recommendation scale to rate each recommendation in each stage based on the level of evidence.

The medications in the guideline include diuretics, angiotensin converting enzyme (ACE) inhibitors, β-blockers, digoxin,

hydralazine-nitrate combination, angiotensin receptor blockers (ARBs), spironolactone, calcium channel blockers, antiarrhythmic agents, and intravenous (IV) inotropic agents.

This program is co-sponsored by ProCE, Inc. and Midwestern University College of Pharmacy Glendale. ProCE, Inc. is accredited by The Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmaceutical education. An on-screen statement of credit verifying participation in 0.2 CEUs (2.0 contact hours) will be displayed for printing to participants who successfully complete the examination. This activity has been assigned ACPE ID number 221-146-04-062-H01.

MANAGEMENT OF HEART FAILURE: PART 2, CHRONIC

Introduction

As a large percentage of our population will soon be reaching 65 years of age, heart failure (HF) is becoming the new epidemic of our time. Organizations and associations have coordinated their resources and references to produce guidelines and treatment options to better assist health care professionals.

HF is the most common diagnosis in people over 65 years of age. Patients with hypertension are 2 times more likely to develop HF, and patients who have had an acute myocardial infarction are 5 times more likely. There is a 25% greater HF occurrence in the black population than in the white population.[1-3] Today, there are almost 5 million Americans who live with chronic HF. This number represents men and women equally. With each passing year, the number is expected to rise owing to a longer HF life expectancy and an increase in the population of patients over 65 years old.[1-3]

This continuing education series is divided into 2 sections, Part 1 and Part 2. In Part 1, management of "acute" HF has been addressed, and Part 2 will be devoted to "chronic" systolic HF. Categories, causes, signs and symptoms, and prognosis of HF have been previously discussed in Part 1.[1-7]

Classifications

Currently, there are two sets of classifications commonly used for categorizing patients with HF. These include New York Heart Association (NYHA) "classes" and ACC/AHA "stages." The NYHA classification system uses "subjective" information to classify patients in a HF category. (Summarized in Table 1)

- Levels of exertion that produce symptoms in normal patients are classified as NYHA "class I."
- Symptoms experienced after ordinary exertion is "class II."
- "Class III" patients experience symptoms with less than ordinary exertion.
- "Class IV" patients have symptoms at rest.[9]

NYHA Classifications	Symptoms
Class I	Similar to non-HF patients
Class II	Upon ordinary exertion
Class III	With less than ordinary exertion
Class IV	At rest

Table 1

The new 2001 ACC/AHA guidelines for management of patients with chronic HF use more objective information to classify patients with HF. The following statements in quotes are directly from the published guidelines:

- Stage A includes "Patients at high risk of developing HF because of the presence of conditions that are strongly associated with the development of HF. Such patients have no identified structural or functional abnormalities of the pericardium, myocardium, or cardiac valves and have never shown signs or symptoms of HF." [10] Stage A patients are those who *only* have a high risk of developing chronic HF. These risks include systemic hypertension, coronary artery disease, diabetes mellitus, family history of cardiomyopathy, or personal history of alcohol abuse, cardiotoxic drugs, or rheumatic fever.

- Stage B includes "Patients who have developed structural heart disease that is strongly associated with the development of HF but who have never shown signs or symptoms of HF."[10] Stage B patients are classified based on the presence of structural heart disease *without* experiencing symptoms. Examples of structural heart disease include asymptomatic valve disease, prior myocardial infarction or left ventricular hypertrophy, fibrosis, dilatation, or hypocontractility.

- Stage C includes "Patients who have current or prior symptoms of HF associated with underlying structural heart disease." [10] Stage C patients experience symptoms of HF because of the presence of structural heart disease or may be currently asymptomatic but receiving treatment for past episodes. These symptoms can include shortness of breath and fatigue.

- Stage D includes "Patients with advanced structural heart disease and marked symptoms of HF at rest despite maximal medical therapy and who require specialized interventions." These patients require "mechanical circulatory support, continuous inotropic infusions, cardiac transplantation, or hospice care."[10] Stage D patients experience symptoms of HF at rest attributable to advanced structural heart disease.

The ultimate treatment goal is to decrease the development and progression of the disease and eliminate symptoms of HF. By achieving these goals, the patient should have a better quality of life and a longer life expectancy.

Since studies have used the NYHA guidelines in their design and eligibility, NYHA and ACC/AHA guidelines must be used together. The ACC/AHA guidelines have constructed an organized system to make a recommendation for an ACC/AHA "staged" patient using NYHA class information.

Additionally, the ACC/AHA guidelines have used a recommendation scale to rate each recommendation in each stage based on the level of evidence.

The Recommendation Sequence[10]

Class I	Conditions for which there is evidence and/or general agreement that a given procedure/therapy is useful and effective.
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of performing the procedure/therapy.
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III	Conditions for which there is evidence and/or general agreement that a procedure/therapy is not useful/effective, and in some cases may be harmful.

Levels of Evidence[10]

Level A	Data are derived from multiple randomized clinical trials.
Level B	Data are derived from a single randomized trial or non-randomized studies.
Level C	Recommendation is based on the consensus of opinion.

The medications in the guideline for chronic HF include diuretics, angiotensin converting enzyme (ACE) inhibitors, β-blockers, digoxin, hydralazine-nitrate combination, angiotensin receptor blockers (ARBs), spironolactone, calcium channel blockers, antiarrhythmic agents, and IV inotropic agents. After each section, the actual wording of the guidelines is also provided.

Diuretics

Diuretics are fast and effective at controlling fluid retention and reducing congestive symptoms. Some signs of effective diuresis may include reductions in jugular venous pressure, pulmonary congestion, peripheral edema, and body weight.[10] Despite a low-salt diet and restricted fluid intake, the ability of the body to control water weight gain may not be optimal in patients with HF. Since diuretics are associated with controlling signs and symptoms of HF and lack mortality reduction, long-term results of using diuretics as a single therapy is unknown. Therefore, diuretics should never be used alone in treatment of a HF patient. They should be combined with ACE inhibitors and β-blockers that have been proven to decrease mortality.[11]

Overdosing and underdosing a diuretic can change the pharmacodynamics of other medications used in chronic HF. Overdosing diuretics while using an ACE inhibitor or vasodilator combination can increase the effects, causing hypotension or renal insufficiency.[12] ARBs should also be suspected to induce the same effects under a high diuretic dose. Underdosing a diuretic can diminish ACE inhibitor effect, increase β-blocker effectiveness, and increase risk of bradycardia.[13] The dose of these drugs should be adjusted periodically according to the daily weight change occurring from fluid loss or fluid gain.[10]

HF progression is a common cause of diuretic resistance. Diuretic resistance can be overcome by changing to an IV formulation, adding another diuretic to the

regimen, or adding an inotropic agent (e.g., dopamine) to increase renal blood flow.[14-16]

Furosemide is the most commonly used diuretic for chronic HF owing to its high-ceiling effects. Many other diuretics, such as thiazides, metolazone, osmotic diuretics, spironolactone, triamterene, and amiloride can potentiate the effects of furosemide.[8] Metolazone is a thiazide-like diuretic that is commonly administered 30 minutes prior to furosemide during diuretic resistance because of its effectiveness in moderate renal failure (creatinine clearance <30 mL/min).[8,17] Other thiazides are less effective in patients with moderate renal failure, and should be used secondarily to metolazone.[2] The risk of electrolyte abnormalities markedly increases when diuretics are used in combination.[10] Therefore, patients need to be closely monitored when changing the dose or dosage form of diuretics or when adding another diuretic.[2]

ACC/AHA Guidelines

Stage C: (Class I)
Diuretics in patients who have evidence of fluid retention *(Level of Evidence: A)* [10]

Stage D:
All Measures listed as class I recommendations for patients in Stages A, B, C.
(Levels of Evidence: A, B, and C as appropriate) [10]

ACE Inhibitors

ACE inhibitors should be given to all left-sided systolic HF patients unless they are intolerant to ACE inhibitors or have an absolute contraindication to their use. Cough represents intolerance to ACE inhibitors. Because of the long-term benefits of ACE inhibitors, however, clinicians should encourage patients to continue taking these drugs if the cough is not severe.[10] Measures including addition of other medications have been tried successfully to manage cough associated with ACE inhibitors. "Although some have suggested that drugs in this class may differ in their ability to inhibit tissue ACE, no trial has shown that tissue ACE-inhibiting agents are superior to other ACE inhibitors in any clinical aspect of HF."[10] It is believed that ACE inhibitor effectiveness in chronic HF appears to be a class effect, but a selection preference should be given to the well-studied ACE inhibitors (e.g., captopril, enalapril, lisinopril, and ramipril).[10]

Several weeks to months may be required before patients taking ACE inhibitors experience any relief in symptoms. Even if symptoms do not improve, long-term treatment with an ACE inhibitor should be continued to reduce the risk of hospitalization or death.[10] Use of an ACE inhibitor decreases mortality regardless of symptoms and disease severity. The Studies of Left Ventricular Dysfunction Treatment (SOLVD) trial examined the effects of enalapril with conventional therapy compared with placebo and concluded that enalapril and combination therapy decreased mortality and hospitalization.[18] It was determined later that enalapril administered in addition to β-blockers improved mortality compared with either agent alone.[19] Current recommendations suggest that patients need not be taking high doses of ACE inhibitors

before being considered for treatment with a β-blocker because most patients enrolled in the β-blocker trials were not taking high doses of ACE inhibitors.[10] The synergistic effects between ACE inhibitors and β-blockers are considered to be more important than the dose. The Vasodilator Heart Failure Trial II (V-HeFT II) study compared the efficacy of enalapril with hydralazine plus isosorbide dinitrate combination. This study found that there was a significantly lower mortality with enalapril.[20]

ACC/AHA Guidelines

Stage A: (Class I)
ACE inhibition in patients with a history of atherosclerotic vascular disease, diabetes mellitus, or hypertension and associated cardiovascular risk factors
(Level of Evidence: B) [10]

Stage B: (Class I)
1. ACE inhibition in patients with a recent or remote history of myocardial infarction regardless of ejection fraction *(Level of Evidence: A)* [10]
2. ACE inhibition in patients with a reduced ejection fraction, whether or not they have experienced a myocardial infarction *(Level of Evidence: B)* [10]

Stage C: (Class I)
ACE inhibition in all patients, unless contraindicated *(Level of Evidence: A)* [10]

Stage D:
All Measures listed as class I recommendations for patients in Stages A, B, C
(Levels of Evidence: A, B, and C as appropriate) [10]

β-blockers

In the Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (MERIT-HF) study, metoprolol CR/XL significantly decreased hospitalization and mortality. [21] The U.S. Carvedilol HF study also proved that patients using carvedilol had a significantly lower risk of death compared with placebo.[22] The Cardiac Insufficiency Bisoprolol Study (CIBIS) II showed that bisoprolol treatment resulted in a significantly lower risk of death than placebo.[23]

With β-blocker therapy, it may take up to 2-3 months before patients notice any symptomatic relief.[10] Some contraindications for the use of β-blockers are symptomatic bradycardia or advanced heart block unless the patient has a pacemaker.[8] Although some patients with Class IV HF have been included in the published studies, the use of β-blockers in class I or IV NYHA patients is not currently recommended.[24]

β-blockers may decrease mortality in HF patients even without regression of symptoms. Selected β-blockers are more appropriate for treatment of chronic HF. Although metoprolol and bisoprolol have also been studied, currently, only carvedilol and extended-release metoprolol are FDA approved for treatment of HF.

ACC/AHA Guidelines

Stage B: (Class I)
1. Beta-blockade in patients with a recent myocardial infarction regardless of ejection fraction *(Level of Evidence: A)* [10]
2. Beta-blockade in patients with a reduced ejection fraction, whether or not they have experienced a myocardial infarction *(Level of Evidence: B)* [10]

Stage C: (Class I)
Beta-adrenergic blockade in all stable patients, unless contraindicated. Patients should have no or minimal evidence of fluid retention and should not have required treatment recently with an intravenous positive inotropic agent. *(Level of Evidence:* A) [10]

Stage D
All Measures listed as class I recommendations for patients in Stages A, B, C
(Levels of Evidence: A, B and C as appropriate) [10]

Digoxin

Digoxin may be used in the management of symptomatic HF patients who have an ejection fraction of <30% or for the control of atrial fibrillation and flutter.[25] The Digitalis Investigation Group (DIG) study concluded that digoxin does not improve mortality but may decrease the risk of hospitalization.[26] This study also showed class III and IV patients may gain the greatest benefit from digoxin.[26]

Discontinuation of digoxin has shown to decrease exercise endurance, ejection fraction, and functional status of patients with HF.[27]

There may be little relationship between serum digoxin concentration and the drug's therapeutic effects when it is used for management of HF patients; therefore, digoxin should be dosed based on patients' symptom.[10,28]

ACC/AHA Guidelines

Stage B: (Class III)
Treatment with digoxin in patients with left ventricular dysfunction, who are in sinus rhythm *(Level of Evidence: C)* [10]

Stage C: (Class I)
Digitalis for the treatment of symptoms of HF, unless contraindicated
(Level of Evidence: A) [10]

Stage D
All Measures listed as class I recommendations for patients in Stages A, B, C.
(Levels of Evidence: A, B, and C as appropriate) [10]

Hydralazine-Isosorbide dinitrate

Hydralazine-isosorbide dinitrate combination decreases mortality, but may have less benefit compared with ACE inhibitors.[20] Experience with these drugs in the management of HF patients is considerably less than that with ACE inhibitors.[10] Clinicians may use this combination after an ACE inhibitor has previously been used and had to be discontinued, owing to a contra-indication or intolerance.[10]

ACC/AHA Guidelines

Stage B: (Class IIb)
Long-term treatment with systemic vasodilators in patients with severe aortic regurgitation *(Level of Evidence: B)* [10]

Stage C: (Class IIa)
A combination of hydralazine and a nitrate in patients who are being treated with digitalis, diuretics, and a β-blocker and who cannot be given an ACE inhibitor because of hypotension or renal insufficiency *(Level of Evidence: B)* [10]

Stage C: (Class IIb)
Addition of a nitrate (alone or in combination with hydralazine) to an ACE inhibitor in patients who are also being given digitalis, diuretics, and a β-blocker
(Level of Evidence: B) [10]

Angiotensin Receptor Blockers (ARBs)

There is no evidence supporting the use of ARBs over ACE inhibitors.[29] In the Evaluation of Losartan In the Elderly (ELITE II) trial, there were fewer patients on ARBs that discontinued treatment because of side effects, such as cough compared with ACEIs.[30] ARBs are as likely as ACE inhibitors to produce hypotension, worsening renal function, and hyperkalemia.[10] It is not recommended to use an ARB before using an ACE inhibitor. If the patient develops an intractable cough or angioedema, it would be appropriate to use an ARB instead of an ACE inhibitor.

It is not recommended to add an ARB to the combination therapy of a β-blocker and ACE inhibitor.

ACC/AHA Guidelines

Stage C: (Class IIa)
Angiotensin receptor blockade in patients who are being treated with digitalis, diuretics, and a β-blocker and who cannot be given an ACE inhibitor because of cough or angioedema
(Level of Evidence: A) [10]

Stage C: (Class IIb)
Addition of an angiotensin receptor blocker to an ACE inhibitor *(Level of Evidence: B)* [10]

Stage C: (Class III)
1. Use of an angiotensin receptor blocker instead of an ACE inhibitor in patients with HF who have not been given or who can tolerate an ACE inhibitor *(Level of Evidence: B)* [10]
2. Use of an angiotensin receptor blocker before a β-blocker in patients with HF who are taking an ACE inhibitor *(Level of Evidence: A)* [10]

Spironolactone

The Randomized ALdactone Evaluation Study (RALES) evaluated NYHA class IV patients and concluded that spironolactone reduced the risk of mortality of patients with severe HF.[31] This study also recognized a significant reduction in hospitalization for decompensating HF, which is attributable to reduction of vascular and myocardial fibrosis. When spironolactone was used together with ACE inhibitors, risks of sudden death and progressive HF were reduced. Thus, the addition of low doses of spironolactone should be considered in patients with recent or current symptoms at rest despite the use of standard treatments.[10] Spironolactone is an appropriate medication for NYHA class IV patients with severe HF.[31]

ACC/AHA Guidelines

Stage C: (Class IIa)

Spironolactone in patients with recent or current Class IV symptoms, preserved renal function, and a normal potassium concentration *(Level of Evidence: B)* [10]

Calcium Channel Blockers

Calcium channel blockers lack studies supporting their effectiveness in chronic HF. Two long-term studies have shown amlodipine and felodipine to be safe; however, they are not indicated for treatment of HF. Amlodipine or felodipine may be used for HF patients if there are indications for their use (indications other than HF). The Prospective Randomized Amlodipine Survival Evaluation (PRAISE) study examined amlodipine besylate and standard therapy and concluded that it had no clear benefit pertaining to mortality or hospitalization.[32] The Vasodilator Heart Failure Trial (V-HeFT) III trial also showed no benefits with mortality or hospitalization using felodipine.[33]

ACC/AHA Guidelines

Stage C: (Class III)
Use of a calcium channel blocking drug as a treatment for HF *(Level of Evidence: B)* [10]

Antiarrhythmic Agents

An increase in arrhythmic activity is common in HF. The strain of fluid or pressure overload with the addition of ectopic foci may increase the chance of decompensation. Antiarrhythmic agents, therefore, may have a role in chronic HF management to decrease HF progression and severity. Class III antiarrhythmic agents (i.e., amiodarone and dofetilide) have been studied for their potential usefulness in HF patients. The Grupo de Estudio de la

Sobrevidea en la Insuficiencia Cardiaca en Argentina (GESICA) study showed no improvement in mortality but a definite decrease in hospitalizations owing to complex ventricular arrhythmias.[34] The appropriateness of its use, however, should be weighed against its long-term side effects and quality of life. The Danish Investigations of Arrhythmia and Mortality On Dofetilide (Diamond) trial studied dofetilide and showed a reduction in hospitalization, but no effect on mortality.[35]

Positive Inotropic Agents

The usefulness of positive inotropic agents in management of HF lies in short-term symptomatic relief and as a bridge to heart transplantation. Use of the beta-adrenergic agonist, dobutamine, may increase the risk of focal ectopic development and sudden death.[36-37] The phosphodiesterase inhibitor milrinone has the capability of vasodilation and inotropic action. These agents, along with others used in management of acute HF, had been previously discussed in Part 1.

ACC/AHA Guidelines

Stage C: (Class III)
Long-term intermittent use of an infusion of a positive inotropic drug *(Level of Evidence: C)* [10]

Stage D: (Class III)
Routine intermittent infusions of positive inotropic agents *(Level of Evidence: B)* [10]

Possible Future Treatments for Management of Chronic HF

Vasopeptidase Inhibitors

The neutral endopeptidase is an enzymatic pathway for the degradation of A-type natriuretic peptide, B-type natriuretic peptide, C-type natriuretic peptide, bradykinin, and adrenomedullin. The results of inhibiting this pathway may include vasodilation, decreased peripheral vascular resistance, blood pressure, and angiotensin II. Currently, omapatrilat, fasidotrilat, and sampatrilat are being evaluated in this class. This class appears promising for the future of HF treatment.[38]

Cytokine Antagonists

Tumor necrosis factors decrease endothelium-dependent vasodilation and increase systemic vascular resistance. The anti-tumor necrosis factor (cytokine antagonist) etanercept may improve systemic vasodilation in advanced chronic HF. It may also have some anti-inflammatory properties by decreasing the vasoreactivity of the endothelial cells. [39]

Endothelin Antagonists

Endothelin antagonists (bosentan, tezosentan) inhibit endothelin-mediated vasoconstriction. In a study, 61 patients in NYHA class III or IV HF showed no change in heart rate, a dose-dependent increase in CI, reduced PCWP, and reduced pulmonary and systemic vascular resistance. Tezosentan's vasodilatory response has stimulated further interest in the management of acute HF with this agent. [40]

Conclusion

HF is a clinical syndrome that has many levels of complexity. The new ACC/AHA guidelines are a welcomed addition to the NYHA guidelines. This different approach will help recognize the risks for developing HF and will bring attention to the asymptomatic or silent HF patients. By understanding and adhering to the published guidelines, hopefully, patients with HF may have a longer life expectancy and a better quality of life. Specialized HF clinics have been proven, numerous times, to be ideal for the long-term management of HF patients.

The following is derived directly from the published guidelines.

ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult

A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure)

Recommendations for Patients at High Risk of Developing HF (Stage A)

Class I

1. Control of systolic and diastolic hypertension in accordance with recommended guidelines *(Level of Evidence: A)*
2. Treatment of lipid disorders, in accordance with recommended guidelines *(Level of Evidence: B)*
3. Avoidance of patient behaviors that may increase the risk of HF (e.g., smoking, alcohol consumption, and illicit drug use) *(Level of Evidence: C)*
4. ACE inhibition in patients with a history of atherosclerotic vascular disease, diabetes mellitus, or hypertension and associated cardiovascular risk factors *(Level of Evidence: B)*
5. Control of ventricular rate in patients with supraventricular tachyarrhythmias *(Level of Evidence: B)*
6. Treatment of thyroid disorders *(Level of Evidence:* C)
7. Periodic evaluation for signs and symptoms of HF *(Level of Evidence: C)*

Class IIa

1. Noninvasive evaluation of left ventricular function in patients with a strong family history of cardiomyopathy or in those receiving cardiotoxic interventions *(Level of Evidence: C)*

Class III

1. Exercise to prevent the development of HF (Level of Evidence: C)
2. Reduction of dietary salt beyond that which is prudent for healthy individuals in patients without hypertension or fluid retention (Level of Evidence: C)
3. Routine testing to detect left ventricular dysfunction in patients without signs or symptoms of HF or evidence of structural heart disease *(Level of Evidence: C)*
4. Routine use of nutritional supplements to prevent the development of structural heart disease *(Level of Evidence:* C).

Recommendations for Patients With Asymptomatic Left Ventricular Systolic Dysfunction (Stage B)

Class I

1. ACE inhibition in patients with a recent or remote history of myocardial infarction regardless of ejection fraction *(Level of Evidence: A)*
2. ACE inhibition in patients with a reduced ejection fraction, whether or not they have experienced a myocardial infarction *(Level of Evidence: B)*
3. Beta-blockade in patients with a recent myocardial infarction regardless of ejection fraction *(Level of Evidence: A)*
4. Beta-blockade in patients with a reduced ejection fraction, whether or not they have experienced a myocardial infarction *(Level of Evidence: B)*
5. Valve replacement or repair for patients with hemodynamically significant valvular stenosis or regurgitation *(Level of Evidence: B)*
6. Regular evaluation for signs and symptoms of HF *(Level of Evidence:* C)
7. Measures listed as Class I recommendations for patients in Stage A *(Levels of Evidence: A, B, and C, as appropriate*).

Class IIb

1. Long-term treatment with systemic vasodilators in patients with severe aortic regurgitation *(Level of Evidence: B)*

Class III

1. Treatment with digoxin in patients with left ventricular dysfunction, who are in sinus rhythm *(Level of Evidence: C)*
2. Reduction of dietary salt beyond that which is prudent for healthy individuals in patients without hypertension or fluid retention *(Level of Evidence: C)*
3. Exercise to prevent the development of HF *(Level of Evidence: C)*
4. Routine use of nutritional supplements to treat structural heart disease or prevent the development of symptoms of HF *(Level of Evidence: C)*

Recommendations for Treatment of Symptomatic Left Ventricular Systolic Dysfunction (Stage C)

Class I

1. Diuretics in patients who have evidence of fluid retention *(Level of Evidence: A)*
2. ACE inhibition in all patients, unless contraindicated (see text). *(Level of Evidence: A)*
3. Beta-adrenergic blockade in all stable patients, unless contraindicated (see text) Patients should have no or minimal evidence of fluid retention and should not have required treatment recently with an intravenous positive inotropic agent *(Level of Evidence:* A)
4. Digitalis for the treatment of symptoms of HF, unless contraindicated [see text] *(Level of Evidence: A)*
5. Withdrawal of drugs known to adversely affect the clinical status of patients (e.g., nonsteroidal anti-

inflammatory drugs, most antiarrhythmic drugs, and most calcium channel blocking drugs; see text) *(Level of Evidence: B)*

6. Measures listed as Class I recommendations for patients in stages A and B
   (Levels of Evidence: A, B, and C, as appropriate).

Class IIa

1. Spironolactone in patients with recent or current Class IV symptoms, preserved renal function and a normal potassium concentration *(Level of Evidence: B)*
2. Exercise training as an adjunctive approach to improve clinical status in ambulatory patients *(Level of Evidence: A)*
3. Angiotensin receptor blockade in patients who are being treated with digitalis, diuretics, and a β-blocker and who cannot be given an ACE inhibitor because of cough or angioedema *(Level of Evidence: A)*
4. A combination of hydralazine and a nitrate in patients who are being treated with digitalis, diuretics, and a β-blocker and who cannot be given an ACE inhibitor because of hypotension or renal insufficiency *(Level of Evidence: B)*

Class IIb

1. Addition of an angiotensin receptor blocker to an ACE inhibitor. *(Level of Evidence: B)*
2. Addition of a nitrate (alone or in combination with hydralazine) to an ACE inhibitor in patients who are also being given digitalis, diuretics, and a β-blocker. *(Level of Evidence: B)*

Class III

1. Long-term intermittent use of an infusion of a positive inotropic drug *(Level of Evidence: C)*
2. Use of an angiotensin receptor blocker instead of an ACE inhibitor in patients with HF who have not been given or who can tolerate an ACE inhibitor. *(Level of Evidence: B)*
3. Use of an angiotensin receptor blocker before a β-blocker in patients with HF who are taking an ACE inhibitor *(Level of Evidence: A)*
4. Use of a calcium channel blocking drug as a treatment for HF. *(Level of Evidence: B)*
5. Routine use of nutritional supplements (coenzyme Q10, carnitine, taurine, and antioxidants) or hormonal therapies (growth hormone or thyroid hormone) for the treatment of HF *(Level of Evidence: C)*

Recommendations for Patients With Refractory End-Stage HF (Stage D)

Class I

1. Meticulous identification and control of fluid retention *(Level of Evidence: B)*
2. Referral for cardiac transplantation in eligible patients *(Level of Evidence: B)*
3. Referral to an HF program with expertise in the management of refractory HF *(Level of Evidence: A)*
4. Measures listed as class I recommendations for patients in Stages A, B, and C *(Levels of Evidence: A, B, and C, as appropriate*)

Class IIb

1. Pulmonary artery catheter placement to guide therapy in patients with persistently severe symptoms *(Level of Evidence: C)*
2. Mitral valve repair or replacement for severe secondary mitral regurgitation *(Level of Evidence: C)*
3. Continuous intravenous infusion of a positive inotropic agent for palliation of symptoms *(Level of Evidence: C)*

Class III

1. Partial left ventriculectomy *(Level of Evidence: C)*
2. Routine intermittent infusions of positive inotropic agent*s* *(Level of Evidence: B)*

References

1. Advisory Council to Improve Outcomes Nationwide in Heart Failure (ACTION HF). *Am J Cardiol.* 1999;83:1A-38A.
2. Brunwald, Fauci, Kasper, et al. Harrison's Principles of Internal Medicine 15th ed. McGraw-Hill Companies, Inc. 2001.
3. National Heart, Lung, and Blood Institute. Congestive Heart Failure Data Fact Sheet, Congestive Heart Failure in the United States: A New Epidemic. Available at: http://www.nhlbi.nih.gov/health/public/heart/other/CHF.htm. Accessed January 25, 2002
4. Bonaduce D, Petretta M, Marciano F, et al. Independent and incremental prognostic value of heart rate variability in patients with chronic heart failure. *Am Heart J*. 1999;138(2 Pt I):273-84.
5. Metra M, Faggiano P, D'Aloia A, et al. Use of cardiopulmonary exercise testing with hemodynamic monitoring in the prognostic assessment of ambulatory patients with chronic heart failure. *J Am Coll Cardiol*. 1999;33(4):943-50.
6. Isnard R, Pousset F, Trochu J, et al. Prognostic value of neurohormonal activation and cardiopulmonary exercise testing in patients with chronic heart failure. *Am J Cardiol*. 2000;86(4):417-21.
7. Cicoira M, Davos C, Florea V, et al. Chronic heart failure in the very elderly: Clinical status, survival and prognostic factors in 188 patients more than 70 years old. *Am Heart J*. 2001;142:1-8.
8. Maisel A. B-Type Natriuretic Peptide in the Diagnosis and Management of Congestive Heart Failure. *Cardiology Clinics*. 2001;19(4).
9. Criteria Committee NYHA, Inc. Diseases of the Heart and Blood Vessels: Nomenclature and Criteria for Diagnosis. Boston, Mass: Little Brown & Co; 1964:114
10. American College of Cardiology and the American Heart Association Task Force. ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult. Available at: http://www.acc.org/clinical/guidelines/failure/hf_index.htm. Accessed January 18, 2002.
11. Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. The Captopril-Digoxin Multicenter Research Group. *JAMA*. 1988;259:539-44.
12. Cody RJ, Covit AB, Schaer GL, Laragh JF, Sealey JE, Feldschuc J. Sodium and water balance in chronic congestive heart failure. *J Clin Invest.* 1986;77:1441-52.
13. Sackner-Bertsein J, Krum H, Goldsmith RL, et al. Should worsening heart failure early after initiation of beta-blocker therapy for chronic heart failure preclude

long-term treatment [abstract]? *Circulation*. 1995:92:I-395.
14. Dormans RP, van Meyel JJ, Gerlag PG, Tan Y, Russel FG, Smits P. Diuretic efficacy of high dose furosemide in severe heart failure: bolus injection versus continuous infusion. *J Am Coll Cardiol*. 1996;28:376-82
15. Epstein M, Lepp BA, Hoffman DS, Levinson R. Potentiation of furosemide by metolazone in refractory edema. *Curr Ther Res*. 1977;21:656-67.
16. Oster JR, Epstein M, Smoller S. Combined therapy with thiazide-type and loop diuretic agents for resistant sodium retention. *Ann Intern Med*. 1983;99:405-6.
17. Gromberg-Maitland M, Baran DA, Fuster V. Treatment of Congestive Heart Failure; Guidelines for the Primary Care Physician and the Heart Failure Specialist. *Arch Intern Med*. 2001;161:342-52.
18. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fraction and congestive hart failure. *N Engl J Med*. 1991;325:293-302.
19. Exner D, Dries DL, Waclawiw MA, Shelton B, Domanski MJ. Beta-adrenergic blocking agent use and mortality in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a post hoc analysis of the Studies of Left Ventricular Dysfunction. *J Am Coll Cardiol*. 1999;33:916-23.
20. Cohn J, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med*. 1991;325:303-10.
21. The International Steering Committee. Rationale, design, and organization of the Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (MERIT-HF). *Am J Cardiol*. 1997;80:54J-58J.
22. Packer M, Bristow MR, Cohn JN, et al. For the US Carvedilol Heart Failure Study Group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med*. 1996;334:1349-55.
23. CIBIS II Steering Committee. Design of the Cardiac Insufficiency Bisoprolol Study (CIBIS II). *Fundam Clin Pharmacol*. 1997;11:138-142.
24. Smith AJ, Wehner JS, Manley HJ, et al. Current role of B-adrenergic blockers in the treatment of chronic congestive heart failure. *Am J Health-Syst Pharm*.2001;58:140-5.
25. Erdmann E. The management of heart failure – an overview. *Basic Res Cardiol*. 2000; 95;Suppl. 1, I/3-I/7.
26. The Digitalis Investigation Group. The Effect of Digoxin on Mortality and Morbidity in Patients with Heart Failure. *N Engl J Med*. 1997;336:525-33.
27. Packer M, Gheorghiade M, Young JB, et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting enzyme inhibitors. *N Engl J Med*. 1993;329:1-7.
28. Tafreshi MJ, Burke TG, Hobbs RA, et al. Management of Patients with High Serum Digoxin Concentrations with Oral Activated Charcoal. *Clinical Research and Regulatory Affairs*. 1999;16(3):127-37.
29. McKelvie RS, Yusuf S, Pericak D, et al. Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. The RESOLVD Pilot Study Investigators. *Circulation*. 1999;100:1056-64.
30. Pitt B, Poole-Wilson PA Segal R, et al. Effect of losartan compared with captopril on mortality in

patients with symptomatic heart failure: randomised trial the Losartan Heart Failure Survival Study ELITE II. *Lancet.*2000;355(9215):1582-7
31. Pitt B, Zannad F, Remme WJ, et al. For the Randomized Aldactone Evaluation Study Investigators (RALES). The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999;341:709-17.
32. Packer M, O'Conner CM, Ghali JK, et al. For the Prospective Randomized Amlodipine Survival Evaluation Study Group. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. *N Engl J Med*. 1996;335:1107-14.
33. Cohn J, Ziesche S, Smith R, et al. For the Vasodilator Heart Failure Trial (V-HeFT) Study Group. Effect of calcium antagonist felodipine as supplementary vasodilator therapy in patients with chronic heart failure treated with enalapril: V-HeFT III. *Circulation*. 1997;96:856-63.
34. Dovel HC, Nul DR, Grancelli HO, Perrone SV, Bortman GR, Curiel R. for Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA). Randomized trial of low-dose amiodarone in severe congestive heart failure. *Lancet*. 1994;344:493-8.
35. Pedersen OD, Bagger H, Keller N, et al. Efficacy of Dofetilide in the Treatment of Atrial Fibrillation-Flutter in Patients With Reduced Left Ventricular Function: A Danish Investigations of Arrhythmia and Mortality ON Dofetilide (DIAMOND) Substudy. *Circulation*. 2001;104(3):292-296.
36. O'Connor CM, Gattis WA, Swedberg K. Managing the Patient with Advanced Heart Failure; Current and novel pharmacologic approaches in advanced heart failure. *Am Heart J*. 1998;135:S249-S263.
37. Mehra MR, Ventura HO, Kapoor C, Stapleton DD, Zimmerman D, Smart FW. Safety and clinical utility of long-term intravenous milrinone in advanced heart failure. *Am J Cardiol*. 1997;80:61-4.
38. Corti R, Burnett JC, Rouleau JL, et al. Vasopeptidase Inhibitors: A New Therapeutic Concept In Cardiovascular Disease? *Circulation*. 2001;104(15):1856-62.
39. Fichtlscherer S, Rossig L, Breuer S, et al. Tumor Necrosis Factor Antagonism With Etanercept Improves Systemic Endothelial Vasoreactivity in Patients With Advanced Heart Failure. *Circulation*. 2001;104(25):3023-3025.
40. Torre-Amione G, Young JB, Durand JB, et al. Hemodynamic Effects of Tezosentan, an Intravenous Dual Endothelin Receptor Antagonist, in Patients With Class III to IV Congestive Heart Failure. *Circulation*. 2001;103(7):973-80.