Guideline for the Management of Heart Failure Caused by Systolic Dysfunction: Part II. Treatment

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Several large clinical trials conducted over the past decade have shown that pharmacologic interventions can dramatically reduce the morbidity and mortality associated with heart failure. These trials have modified and enhanced the therapeutic paradigm for heart failure and extended treatment goals beyond limiting congestive symptoms of volume overload. Part II of this two-part article presents treatment recommendations for patients with left ventricular systolic dysfunction. The authors recommend that, if tolerated and not contraindicated, the following agents be used in patients with left ventricular systolic dysfunction: an angiotensin-converting enzyme inhibitor in all patients; a beta blocker in all patients except those who have symptoms at rest; and spironolactone in patients who have symptoms at rest or who have had such symptoms within the past six months. Diuretics and digoxin should be reserved, as needed, for symptomatic management of heart failure. Other treatments or treatment programs may be necessary in individual patients. (Am Fam Physician 2001;64:1045-54.)

This article is one in a series developed in collaboration with the American Heart Association. Guest editor of the series is Sidney C. Smith, Jr., M.D., Chief Science Officer, American Heart Association, Dallas.

This is part II of a two-part article on heart failure. Part I, "Guideline Development, Etiology and Diagnosis," appeared in the September 1 issue (Am Fam Physician 2001;64:769-74).

Part I of this guideline detailed how the therapeutic paradigm of heart failure has changed over the past decade.[1] This new understanding of heart failure has led to new treatment approaches. The end point of treatment is no longer merely the limiting of congestive symptoms. Rather, the new standard for treatment also includes decreasing mortality.

Part II presents evidence-based treatment options that are practical for use by primary care physicians. The treatment guideline is based on the symptomatic classification scheme described in the first part of this article.[1] The methods for guideline development and the evidence weighting for the recommendations are also detailed in part I.[1]

Pharmacologic Therapy: Primary Drugs

In this guideline, drugs specifically indicated for use in patients with heart failure are referred to as "primary drugs." Use of these drugs according to the new classification scheme is presented in *Table 1*.[2] Dosing and cost information are provided in *Table 2*,[2] and "clinical pearls" are given in *Table 3*.[2] A comparison of the guideline's recommendations with those from other recent guidelines is presented in *Table 4*.[3-5] Common drug interactions are listed in *Table 5*.[2]

See editorial on page 934.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Angiotensin-converting enzyme (ACE) inhibitors are indicated in the treatment of all patients with systolic heart failure. A number of landmark randomized, controlled trials[6-8] have demonstrated the effectiveness of these drugs in reducing morbidity and mortality in asymptomatic and symptomatic patients. Unless absolutely contraindicated, ACE inhibitor therapy should be considered a priority (level of evidence: A—see *Table 1* in part I).

Because of perceived risks and contraindications, ACE inhibitors are often avoided in patients with heart failure. Renal dysfunction and cough should not be considered absolute contraindications to the use of these agents. When the systolic blood pressure is less than 100 mm Hg or the creatinine level is elevated, careful monitoring is warranted during the initiation of ACE inhibitor therapy.

The dosing of ACE inhibitors is controversial. Target dosages that reflect those used in mortality trials are provided in *Table 2*.[2] The table includes only agents that have been tested in mortality trials. The Assessment of Treatment with Lisinopril and Survival (ATLAS) Study[9] sought to explore whether higher dosages of ACE inhibitors would be

more effective. However, the ATLAS study compared high dosages to low dosages, and there was no comparison to the target dosages that had been shown to be effective in mortality trials.[10] At present, we cannot support the routine use of high dosages of ACE inhibitors as being more effective than the target dosages listed in *Table 2*[2] (level of evidence: D).

BETA BLOCKERS

Beta-blocker therapy is indicated in all patients with systolic heart failure except those with dyspnea at rest, those who are unable to tolerate beta blockers and those who are hemodynamically unstable (level of evidence: A). Randomized, controlled trials[11-13] have shown that treatment with carvedilol, metoprolol succinate (controlled release) or bisoprolol decreases mortality by at least 34 percent in patients with heart failure. These agents differ pharmacologically; however, they all have demonstrated benefit, and any of the three can be used. Comparative trials of various beta blockers are currently being conducted.

Although beta blockers must be administered cautiously to patients with heart failure, primary care physicians can prescribe them safely *(Table 3)*.[2] The initial dosage should be doubled every two to four weeks until the patient is unable to tolerate higher levels or the target dosage is reached *(Table 2)*.[2] Patients who develop hypotension, symptoms of hypotension, increasing dyspnea or worsening heart failure should be evaluated. It may be necessary to increase the diuretic dosage, decrease the beta-blocker dosage or discontinue the beta blocker.

Beta blockers should only be added when patients are clinically stable. The purpose of beta-blocker therapy is to slow the progression of the disease. Beta blockers are not to be added as rescue drugs in patients who are decompensating.

Most patients with known asymptomatic left ventricular dysfunction have also had a myocardial infarction. The benefits of beta blockers in such patients have been well described, and these agents should be administered[14] (level of evidence: A). Many other patients in this group may have hypertension or other indications for beta-blocker therapy. No comparable data are available on asymptomatic patients with idiopathic heart failure. We recommend at least consideration of beta-blocker therapy in asymptomatic patients (level of evidence: D).

Some uncertainty still exists about the safety and efficacy of beta blockers in patients with dyspnea at rest. Two large trials—the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial[15] and the Beta

TABLE 1
Treatment Classification of Patients with Heart Failure Caused by Left Ventricular Systolic Dysfunction

Symptoms	*Pharmacology*
Asymptomatic*	ACE inhibitor Beta blocker
Symptomatic†	ACE inhibitor Beta blocker Diuretic If symptoms persist: digoxin (Lanoxin)
Symptomatic with recent history of dyspnea at rest‡	Diuretic ACE inhibitor Spironolactone (Aldactone) Beta blocker Digoxin
Symptomatic with dyspnea at rest§	Diuretic ACE inhibitor Spironolactone Digoxin

ACE = angiotensin-converting enzyme.

**—Patients with asymptomatic left ventricular systolic dysfunction may be identified in a number of contexts, including postmyocardial infarction, hypertension and, in some patients, nonischemic dilated cardiomyopathy.*

†—Patients without physical signs of congestion respond to ACE inhibitors and beta blockers. Diuretics are primarily for the treatment of edema and congestion.

‡—Patients who improve symptomatically should continue taking all five medications, with diuretic dosing modified according to the magnitude of congestion.

§—Patients who are symptomatic with dyspnea at rest should not be started on beta-blocker therapy. However, patients who develop dyspnea at rest during beta-blocker therapy may respond to increased diuretic therapy without requiring beta-blocker withdrawal.

Adapted with permission from Heart failure—systolic dysfunction. Retrieved May 22, 2001, from: http://cme.med.umich.edu/pdf/guideline/heart.pdf.

Blocker Evaluation Survival Trial (BEST)[16]—were designed to address this issue.

The data safety monitoring board stopped the COPERNICUS trial early because of significant improvements in mortality.[15] Over-

Unless absolutely contraindicated, treatment with an angiotensin-converting enzyme (ACE) inhibitor should be considered a priority in all patients with systolic heart failure.

TABLE 2
Dosages of Primary Drugs Used in the Treatment of Heart Failure

Drug	*Starting dosage*	*Target dosage or common dosage*	*Cost for brand name (generic)**
Decrease mortality and improve symptoms†			
ACE inhibitors‡			
Captopril (Capoten)	6.25 mg three times daily (one-half tablet§)	12.5 to 50 mg three times daily	$ 82 (52 to 58)
Enalapril (Vasotec)	2.5 mg twice daily	10 mg twice daily	68 (46 to 48)
Lisinopril (Zestril)	5 mg daily	10 to 20 mg daily	29
Ramipril (Altace)	1.25 mg twice daily	5 mg twice daily	60
Trandolapril (Mavik)	1 mg daily	4 mg daily	22
Aldosterone antagonist‡			
Spironolactone (Aldactone)	25 mg daily	25 mg daily	14 (12 to 13)
Beta blockers‡			
Bisoprolol (Zebeta)	1.25 mg daily (one-fourth tablet§)	10 mg daily	36
Carvedilol (Coreg)	3.125 mg twice daily	25 to 50 mg twice daily	95
Metoprolol tartrate (Lopressor)	12.5 mg twice daily (one-fourth tablet§)	50 to 75 mg twice daily	42 (26 to 31)
Metoprolol succinate (Toprol-XL)	12.5 mg daily (one-half tablet§)	200 mg daily	52
Treat symptoms‖			
Thiazide diuretics¶			
Hydrochlorothiazide (Esidrex)	25 mg daily	25 to 100 mg daily	5 (1 to 3)
Metolazone (Zaroxolyn)	2.5 mg daily	2.5 to 10 mg daily	20
Loop diuretics¶			
Bumetanide (Bumex)	1 mg daily	1 to 10 mg once to three times daily	14 (12 to 13)
Ethacrynic acid (Edecrin)	25 mg daily	25 to 200 mg once or twice daily	10
Furosemide (Lasix)	40 mg daily	40 to 400 mg once to three times daily	8 (4 to 5)
Torsemide (Demadex)	20 mg daily	20 to 200 mg once or twice daily	23
Inotrope‡			
Digoxin (Lanoxin#)	0.125 mg daily	0.125 to 0.375 mg daily	6 (3 to 5)

**—Estimated cost to the pharmacist, rounded to the nearest dollar, for 30 days of treatment using the lowest target or common dosage, based on average wholesale prices in Red book. Montvale, N.J.: Medical Economics Data, 2001. Cost to the patient will be higher, depending on prescription filling fee.*
†—Target dosages as used in placebo-controlled mortality trials.
‡—See drug interactions in Table 5.
§—Tablet is scored for one-half tablet only.
‖—Common dosages are given.
¶—Diuretics have not been separately studied for target dosages. Titrate as needed for relief of symptoms.
#—Generic drug is available, but brand name drug is usually dispensed.

Adapted with permission from Heart failure—systolic dysfunction. Retrieved May 22, 2001, from: http://cme.med.umich.edu/pdf/guideline/heart.pdf.

TABLE 3
'Clinical Pearls' in the Pharmacologic Treatment of Heart Failure

Drug category	*Clinical pearls*
ACE Inhibitors	ACE inhibitors appear to exhibit a class effect. All members of this class may be equally effective.
	The ideal dosage of ACE inhibitors is controversial.*
Beta blockers	Beta blockers should not be given to patients with absolute contraindications to their use, such as heart block or bradycardia.
	Beta blockers should not be used in patients who have dyspnea at rest or who are hemodynamically unstable, or as initial therapy in patients who are hospitalized for heart failure. Once these issues have resolved, beta blockers may be added to the chronic treatment regimen. Beta blockers may be added when patients are stable. They may be used in patients with heart failure caused by systolic dysfunction who do not have contraindications to their use.
	Beta blockers are to be added to arrest the progression of the disease; they are not to be added as rescue therapy for patients who are decompensating.
	Beta blockers should be initiated in a low dosage; the dosage should then be doubled every 2 to 4 weeks as tolerated until the target dosage is reached (see Table 2).
	No clinical differences have been demonstrated among beta blockers that have a proven mortality benefit in the treatment of heart failure.
Diuretics	Diuretics are included as background therapy. Although diuretics have not been specifically tested in clinical trials, they should still be used as needed for the treatment of volume overload. Diuretics have consistently been part of background therapy in all published placebo-controlled mortality trials of ACE inhibitors, beta blockers and spironolactone (Aldactone) in the treatment of symptomatic patients.
	ACE inhibitors and beta blockers may reduce the need for diuretic therapy.
Combining drugs	Many patients with heart failure may benefit from both beta blockers and ACE inhibitors. Which to start first, or which to use if the patient's blood pressure will not tolerate both, is controversial.†
	The drug therapies listed in Table 1 are the desired end points for patients in the symptomatic classes. No data are available to indicate how best to introduce all of these medications. In all major trials, a beta blocker or spironolactone was added to background therapy of ACE inhibitors, diuretics and, sometimes, digoxin (Lanoxin).
	ACE inhibitors, beta blockers and spironolactone should not be stopped if symptoms improve, because these medications slow disease progression and decrease mortality.
Referral	Consider referral in the following clinical situations: Diagnostic procedure Revascularization procedure Worsening or refractory heart failure Ventricular arrhythmia Valvular heart disease Consideration of transplantation

ACE = angiotensin-converting enzyme.

**—The authors of this article support the target dosages of ACE inhibitors used in placebo-controlled mortality trials (see Table 2); however, some experts advocate the use of even higher dosages.*

†*—The authors of this article believe that ACE inhibitors should be started first, but that beta blockers should be added unless contraindicated.*

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all, carvedilol reduced mortality by 35 percent over placebo. However, these data have not yet been published, and some controversy exists concerning the exclusion criteria used in patient selection. Patients who had overt volume overload and patients who recently required intravenous inotropic agents were among those who were excluded from the COPERNICUS trial.

BEST was stopped early without demonstration of a significant mortality benefit.[16] The results of this study also remain unpublished, and information is available only from early data releases. The BEST study investigated the beta blocker bucindolol, and some researchers believe that the results of the trial may be specific to this drug. Racial differences were also discovered in BEST, and it is unclear whether the high number of black patients, whose outcomes were the worst in the trial, may have affected the overall outcome. Also, it is possible that the negative result came from the inclusion of a relatively high number of patients with dyspnea at rest.

Pending complete review of the data, we cannot recommend the use of beta blockers in all patients with dyspnea at rest (level of evidence: D). There may be instances in which, with appropriate surveillance, beta blockers may be used safely in these patients.

Beta blockers should not be given if their use is absolutely contraindicated because of conditions such as bradycardia, heart block or severe bronchospastic disease. Diabetes and mild asthma should not be considered absolute contraindications to the use of these drugs. Patients with these comorbid conditions should be given a trial of beta blockers.

SPIRONOLACTONE

Spironolactone is a potassium-sparing diuretic and an aldosterone antagonist. The Randomized Aldactone Survival Study (RALES)[5] recently demonstrated that aldosterone antagonism with spironolactone lowers mortality and hospitalization rates in patients with systolic dysfunction who have

TABLE 4
Comparison of Guidelines for the Management of Systolic Dysfunction*

Drug class	*University of Michigan*	*CONSENSUS–HF*[3]	*Heart Failure Society of America*[4]
ACE inhibitors	All patients with systolic dysfunction	All patients with systolic dysfunction	All patients with systolic dysfunction
Beta blockers†	All patients except those with dyspnea at rest	All patients in NYHA class II or III Await additional data on NYHA class IV No comment made on NYHA class I	All patients in NYHA class II and III Insufficient evidence to recommend for patients in NYHA class IV Considered for patients in NYHA class I
Spironolactone (Aldactone)	Patients with dyspnea at rest or recent history of dyspnea at rest	"Consideration in patients with recent or current class IV symptoms"[3(p27A)]‡	"Considered for patients receiving standard therapy who have severe heart failure (recent or recurrent class IV)"[4(p374)]
Diuretics	All symptomatic patients, dosed as necessary to control symptoms	All symptomatic patients, dosed as necessary to control symptoms	All symptomatic patients, dosed as necessary to control symptoms
Digoxin (Lanoxin)	As needed in patients with persistent symptoms or recurrent hospitalizations; used, as indicated, in conjunction with ACE inhibitors, beta blockers, diuretics and aldosterone antagonists	"To improve the clinical status of patients with heart failure in conjunction with diuretics, an ACE inhibitor, and a beta blocker"[3(p23A)]	"Considered for patients who have symptoms of heart failure and NYHA class IV…while receiving standard therapy"[4(p366-8)]

ACE = angiotensin-converting enzyme; NYHA = New York Heart Association.

**—All recommendations for drug administration are for those circumstances in which the drugs are tolerated and not contraindicated.*
†—The guidelines agree on the administration of beta blockers to all patients with symptoms, except those who are having symptoms at rest. In addition, the guidelines agree that beta blockers should not be given to patients having symptoms at rest, pending the completion of ongoing trials. The University of Michigan guideline recommends giving beta blockers to asymptomatic patients, because most of these patients also have another indication for beta blockers (e.g., recent myocardial infarction or hypertension). CONSENSUS-HF does not address this group, and the Heart Failure Society of America suggests that beta blockers be "considered" in this group. No trials have been completed to specifically address the safety or efficacy of beta blockers in patients with asymptomatic left ventricular systolic dysfunction.
‡—The results of the Randomized Aldactone Evaluation Study (RALES)[5] had not been published when the recommendations were made.

Information from the text of this article, and from Consensus recommendations for the management of chronic heart failure. On behalf of the membership of the Advisory Council to Improve Outcomes Nationwide in Heart Failure. Am J Cardiol 1999;83(2A):1A-38A, and Heart Failure Society of America (HFSA) practice guidelines. HFSA guidelines for management of patients with heart failure caused by left ventricular systolic dysfunction—pharmacologic approaches. J Card Fail 1999;5:357-82.

dyspnea at rest or a history of dyspnea at rest within the past six months. Significant hyperkalemia was rare (incidence: 0.5 percent), even though patients were also receiving ACE inhibitors. Asymptomatic gynecomastia was also relatively uncommon (7 percent) when the drug was given in an average dosage of 25 mg daily. Patients with heart failure, dyspnea at rest (current or recent) and no significant renal impairment (serum creatinine level of less than 2.5 mg per dL [221 mmol per L]), should be treated with spironolactone in a dosage of 25 mg daily (level of evidence: A).

To minimize the possibility of hyperkalemia, primary care physicians should be cognizant of the risk factors for this disorder, which include decreased renal function, potassium supplementation and the use of ACE inhibitors or adrenergic receptor blockers. As a diuretic, spironolactone may also affect fluid balance, which should be monitored.

Some experts believe that spironolactone also may be beneficial in patients with less severe heart failure and in those with diastolic disease. However, no large-scale clinical trials have addressed the safety or efficacy of spironolactone therapy in these patients.

DIURETICS

Although no large, controlled clinical studies have been conducted on the use of diuretics in the treatment of heart failure, these drugs have been given to most patients as part of baseline therapy in trials of ACE inhibitors,

TABLE 5
Common Drug Interactions

Drug or drug class	*Interacting drugs*	*Effect*
ACE inhibitors	Antacids	Decreased drug absorption
	Lithium	Increased lithium levels
	NSAID	May decrease renal function
	Spironolactone (Aldactone)	With co-administration, may result in elevated potassium levels, especially in the elderly and in patients with renal dysfunction
Amiodarone (Cordarone)	Beta blockers	Decreased heart rate and atrioventricular node conduction
	Calcium channel blockers (e.g., diltiazem [Cardizem] and verapamil [Calan])	Decreased heart rate and atrioventricular node conduction
	Digoxin (Lanoxin)	Increased digoxin concentration, decreased heart rate and atrioventricular node conduction
	Quinidine	Increased quinidine concentration
	Phenytoin (Dilantin)	Increased phenytoin concentration, decreased amiodarone concentration
	Procainamide (Pronestyl)	Increased procainamide concentration
	Theophylline	Increased theophylline concentration
	Warfarin (Coumadin)	Increased INR
Beta blockers	Amiodarone, diltiazem, verapamil, propafenone (Rythmol), sotalol (Betapace)	Decreased heart rate and atrioventricular node conduction
Digoxin	Amiodarone	Increased digoxin concentration, decreased heart rate and atrioventricular node conduction
	Antacids	Decreased digoxin absorption (space administration of drugs at least 2 hours apart)
	Beta blockers	Carvedilol (Coreg) may increase digoxin concentration; decreased heart rate and atrioventricular node conduction
	Cholestyramine (Questran), colestipol (Colestid)	Decreased digoxin absorption
	Diltiazem, verapamil	Increased digoxin concentration, decreased heart rate and atrioventricular node conduction
	Omeprazole (Prilosec)	Increased digoxin concentration
	Propafenone	Increased digoxin concentration, decreased heart rate and atrioventricular node conduction
	Quinidine	Increased digoxin concentration
	Rifampin (Rifadin)	Decreased digoxin concentration
	Sotalol	Decreased heart rate and atrioventricular node conduction
	Spironolactone	Increased digoxin concentration; interferes with some digoxin assays, yielding falsely elevated digoxin concentrations
Warfarin	Amiodarone, antibiotics (including trimethoprim-sulfamethoxazole [Bactrim, Septra] and erythromycin), antidepressants, beta blockers, cimetidine (Tagamet), fluconazole (Diflucan), itraconazole (Sporanox), ketoconazole (Nizoral), lovastatin (Mevacor), omeprazole, oral diabetic agents, phenytoin, propafenone, quinidine, quinine, simvastatin (Zocor)	Increased INR
	NSAIDs, aspirin, ticlopidine (Ticlid), clopidogrel (Plavix)	Increased risk of bleeding because of effect on platelet function
	Phenobarbital, rifampin, cholestyramine, carbamazepine (Tegretol), phenytoin, spironolactone, sucralfate (Carafate)	Decreased INR

ACE = angiotensin-converting enzyme; NSAIDs = nonsteroidal anti-inflammatory drugs; INR = International Normalized Ratio.

Adapted with permission from Heart failure—systolic dysfunction. Retrieved May 22, 2001, from: http://cme.med.umich.edu/pdf/guideline/heart.pdf.

beta blockers, spironolactone (Aldactone) and digoxin (Lanoxin).

Loop diuretics are the most potent agents in the diuretic class, but they are associated with acute and chronic distal tubular compensation. Combining a loop diuretic with a thiazide diuretic increases diuretic potency by minimizing distal tubular compensation. Both loop and thiazide diuretics produce urinary potassium and magnesium wasting.

Diuretics should be used as needed to treat volume overload. Diuretic therapy may be needed acutely and chronically (level of evidence: D).

DIGOXIN

Digoxin is indicated in the treatment of patients with heart failure who also have atrial fibrillation (level of evidence: A). It is also indicated to improve symptoms and decrease hospitalization rates in patients with symptomatic heart failure (level of evidence: A). The appropriate dosage is 0.25 mg daily; the dosage can be adjusted as needed, based on symptoms, other drugs or renal impairment *(Table 2)*.[2]

Digoxin has been shown to have an impact on symptoms and hospitalization rates, but not on mortality.[17] The number of drugs that have a beneficial impact on mortality in heart failure is expanding. Because taking an increasing number of medications can become a barrier to compliance, the role that digoxin will ultimately play in the treatment of heart failure is unclear.

Currently, we recommend the use of digoxin in patients who are symptomatic despite treatment with diuretics, ACE inhibitors and beta blockers. We also recommend digoxin therapy for patients with dyspnea at rest or a recent history of dyspnea at rest.

Pharmacologic Therapy: Secondary Drugs

Drugs occasionally used in patients with heart failure but not specifically recommended for use in this setting are referred to as "secondary drugs" in this guideline.

DIRECT-ACTING VASODILATORS

In combination, the direct-acting vasodilators isosorbide dinitrate (Isordil) and hydralazine (Apresoline) were the first medications shown to improve survival in heart failure.[18] Subsequently, randomized, controlled trials demonstrated that ACE inhibitors were superior to these agents.[7] Guidelines from the Agency for Health Care Policy and Research[19] indicate that direct-acting vasodilators can be considered a potential alternative if ACE inhibitors are poorly tolerated in patients with heart failure (level of evidence: A). A retrospective analysis[20] of these clinical trials suggests that blacks may gain greater benefit from isosorbide dinitrate and hydralazine than nonblacks.

CALCIUM CHANNEL BLOCKERS

Calcium channels blockers have no direct role in the treatment of heart failure resulting from systolic dysfunction. The first-generation agents diltiazem and nifedipine were shown to have adverse outcomes in patients with systolic dysfunction who had had a myocardial infarction[21,22] (level of evidence: A). Subsequent studies[23,24] using the dihydropyridine calcium channel blockers (i.e., amlodipine and felodipine) in patients with New York Heart Association (NYHA) III/IV symptoms suggested that the drugs were safe but did not demonstrate their efficacy (level of evidence: A).

A subgroup analysis[23] of a randomized, controlled trial involving amlodipine suggested a mortality benefit in patients with nonischemic heart failure. However, a larger subsequent study[25] found no benefit in administering amlodipine to patients with nonischemic cardiomyopathy. Currently, no evidence supports the use of calcium channel blockers in patients with heart failure (level of evidence: A).

INOTROPES

Intravenous inotropic therapy with the sympathomimetics (dobutamine [Dobutrex]

or dopamine [Intropin]) or the phosphodiesterase inhibitors (milrinone [Primacor] or amrinone [Inocor]) is reserved for use in patients hospitalized for acutely decompensated heart failure who do not respond adequately or in a timely manner to diuretic therapy, although mortality data are lacking.[26] Inotropic agents may increase cardiac output and decrease systemic and pulmonary vascular resistance. Intermittent bolus treatment or continuous home infusion therapy with dobutamine or milrinone is not currently indicated for the routine management of heart failure (level of evidence: C).

ANTICOAGULANTS

Anticoagulation therapy is indicated in patients with heart failure who are at risk for thromboembolism. Included in this group are patients with atrial fibrillation, demonstrated left ventricular thrombus or a history of embolic stroke with the likely source being a dilated left ventricle[27,28] (level of evidence: A).

Anticoagulation therapy has also been prescribed for patients with a low ejection fraction or an intracardiac thrombus (level of evidence: C). However, data supporting the use of anticoagulant drugs for this indication are limited and controversial. The majority of studies did not correct for the presence of well-established risk factors for thrombus formation and did not control for the level of anticoagulation or the initiation of anticoagulation. If anticoagulation is needed, the appropriate dose of warfarin (Coumadin) is determined by the patient's International Normalized Ratio (INR). The target INR will depend on the clinical condition necessitating therapy.

ANGIOTENSIN RECEPTOR BLOCKERS

Angiotensin receptor blockers are safe[29] but have never been shown to be more effective[30] than ACE inhibitors in mortality trials of patients with heart failure. In a recently completed study,[31] no improvement in all-cause mortality occurred when angiotensin receptor blockers were added to background therapy consisting of ACE inhibitors and, sometimes, beta blockers. Furthermore, a subgroup analysis[31] showed a 10 percent increase in the composite end point of mortality plus morbidity among patients receiving valsartan whose baseline therapy included a beta blocker.

We recommend the use of angiotensin receptor blockers only in patients who are intolerant of ACE inhibitors. Even in this setting, we recommend that these agents be used with caution in patients who are also taking beta blockers (level of evidence: A).

ANTIARRHYTHMIC DRUGS AND DEVICES

Evidence is inconsistent regarding the benefit of antiarrhythmic therapy in patients with heart failure.[32,33] At this time, it does not appear that substantial benefit is derived from the application of antiarrhythmic therapy in patients who have heart failure and an asymptomatic rhythm disturbance. There are benefits from use of implantable cardioverter defibrillators in selected patients. This issue is discussed in part I of this article.[1]

Arrhythmias such as atrial fibrillation, ventricular tachycardia and bradyarrhythmias are common in patients with heart failure. Therefore, individualized management is recommended (level of evidence: D).

Some frequently used antiarrhythmics, including calcium channel blockers, beta blockers and digoxin, are addressed in other sections of this article. Amiodarone (Cordarone), a common antiarrhythmic, has a number of drug interactions that should be noted (*Table 5*).[2]

ASPIRIN

Aspirin is used in many patients with heart failure caused by ischemic cardiomyopathy. Although patients with heart failure who are already taking aspirin may be maintained on the drug, heart failure itself is not an indication to start aspirin therapy (level of evidence: D). Potential adverse affects of aspirin on gastric mucosa and on renal function should be

considered. Patients with heart failure caused by coronary artery disease should be maintained on aspirin (level of evidence: A).

There are theoretic concerns about aspirin negating some of the beneficial impact of ACE inhibitors. However, no clinical data have demonstrated a harmful effect from combining these agents.

Nonpharmacologic Treatment

EXERCISE

Many small and sometimes randomized clinical trials have examined the benefits of exercise training in patients with heart failure.[34] Different exercise formulas have been tested in men and women. The clinical trials have measured intermediate outcomes such as ventilatory capacity, maximum oxygen consumption, skeletal muscle parameters and neurohormonal levels; a few have measured exercise capacity and quality of life.

Exercise may be recommended based on clinical trials that have shown exercise to be safe under study conditions (level of evidence: D). As yet, however, no major randomized, controlled trial has demonstrated an improvement in clinical outcomes such as medication reduction, decreased hospital days or mortality.

DIETARY CHANGES

We are 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 (level of evidence: D). The most commonly recommended limit is 2,000 mg of sodium daily. Restricting fluid intake to 2 L or less daily may be useful in patients with hyponatremia.

SURGERY

Some causes of heart failure are potentially reversible. Surgery should be considered in patients with heart failure resulting from aortic stenosis, but the management of this condition is beyond the scope of this article. Similarly, revascularization, if indicated, should be considered in patients with coronary artery disease (level of evidence: D).

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