During the past 10 years, the philosophy of heart failure treatment has evolved from symptom control to a combined prevention and symptom-management strategy. Recent clinical trials have proved that early detection can delay progression. Treatment of asymptomatic left ventricular dysfunction is as important as treatment of symptomatic disease. The purpose of this review is to simplify recent guidelines for pharmacological management of chronic systolic heart failure for the primary care physician and the heart failure specialist. Early recognition and prevention therapies, combined with lifestyle modification, are essential in the treatment of heart failure. Therapy with angiotensin-converting enzyme inhibitors, β-blockers, and diuretics is now standard. Digoxin is added to improve clinical symptoms, especially in patients with atrial fibrillation. Aldosterone antagonists may be recommended in select patients with stable New York Heart Association class III or IV heart failure. If angiotensin-converting enzyme inhibitors are not tolerated, angiotensin receptor blockers, hydralazine hydrochloride, and isosorbide dinitrate are recommended. The data on antiarrhythmic and anticoagulation therapies are inconclusive.
DEFINITION

Heart failure is a complex clinical syndrome that may include fatigue and shortness of breath on exertion (and in advanced cases, at rest), orthopnea, paroxysmal nocturnal dyspnea, nocturia, mental status changes, anorexia, and abdominal pain. Patients have different symptoms based on clinical severity. The syndrome can result from any cardiac disorder that impairs the heart's ability to fill and/or relax or empty. Inability to fill and relax the left ventricle is diastolic dysfunction, defined as an elevated end-diastolic pressure in a normal-sized chamber, whereas difficulty emptying the left ventricle is systolic dysfunction, represented by a reduced ejection fraction. Ischemic (coronary artery disease [CAD]) and nonischemic conditions (hypertension, valvular disease, hypertension, thyroid disease, alcohol abuse, myocarditis, adult congenital heart disease, and cardiomyopathy) may cause systolic dysfunction. Coronary artery disease accounts for approximately two thirds of these cases, whereas "pure" diastolic dysfunction with preserved systolic function is seen in patients with left ventricular hypertrophy, hypertension, and CAD. The left ventricle's inability to relax efficiently may be transient, as in a patient with ischemia, or sustained, as in a patient with concentric myocardial hypertrophy or restrictive cardiomyopathy secondary to infiltrative disorders.

The severity of heart failure is defined symptomatically, and the most commonly used system is the New York Heart Association (NYHA) functional classification. Patients are grouped according to the degree of effort needed to elicit heart failure symptoms. Class I patients exhibit symptoms only at exertion levels similar to those achieved readily by healthy individuals, whereas class II patients have symptoms on ordinary exertion. Class III patients have symptoms on minimal exertion, and class IV patients have symptoms at rest. There are 2 major problems with the classification system, ie, a high degree of interobserver variability to assignment of class and an inability to detect small changes in clinical status. For now, this is the easiest method to group patients, despite limited ability to predict the degree of physiological systolic dysfunction.

Diagnostic examinations can help expedite appropriate treatment. The most valuable initial diagnostic examination is the 2-dimensional echocardiogram coupled with Doppler flow studies. It is easily accessible and inexpensive. Patients with ejection fractions of no greater than 0.40 are considered to have systolic dysfunction. The study assesses systolic and diastolic abnormalities involving the right and left sides of the heart, and it determines the presence of pericardial, endocardial, valvular, and vascular abnormalities. Patients with heart failure often have multiple cardiac abnormalities causing or contributing to their disease. Radionuclide ventriculography also reveals biventricular global and regional wall motion abnormalities. However, it does not permit assessment of other cardiac abnormalities. An assessment of ventricular function is recommended during the patient's initial presentation.

Repeated diagnostic testing is of debatable value. Without a corresponding clinical change in functional status, there is little value in slight changes in measured ejection fraction. Most believe that a repeated assessment of ejection fraction is warranted if there is a significant change in clinical status, or if the patient has had a recent event.

Heart failure specialists use exercise testing to better determine functional capacity. The measurement of peak oxygen consumption is a good measure of capacity, but it is not clear if exercise testing accurately measures daily physical stresses encountered by the patient. Exercise testing is highly dependent on the motivation of the patient and the physician.

EPILOGUE

In the United States, 4.8 million persons have heart failure, with approximately 400,000 to 700,000 new cases each year. Heart failure affects approximately 1.5% to 2% of the population. At present, the prevalence in Americans older than 65 years is 6% to 10%, and this prevalence is expected to rise as the aged population grows and median life span increases. Heart failure is the leading cause of hospitalization, and in addition, as many as 20 million patients have an asymptomatic impairment of cardiac function, with symptoms likely to develop in the next 1 to 5 years. Despite the higher incidence of heart failure in men in every age group, the prevalence in women is approximately equal. Unfortunately, women only account for approximately 20% of patients in most clinical trials, which makes most of the treatment guidelines for women almost speculative.

Heart failure is a progressive, fatal disease. The number of deaths due to heart failure as a primary or secondary cause has increased 6-fold during the last 40 years despite new advances in treatment. The risk for death is 5% to 10% annually in patients with mild symptoms and increases to approximately 30% to 40% annually in patients with advanced disease. With the increasing prevalence, hospital expenditures have escalated. Annual direct expenditures, which include cost of medications, hospitalizations, nursing home admissions, and medical follow-up, are estimated at $20 billion to $40 billion. Thus, educating all physicians about treatment guidelines can have a significant public health impact.
PATHOPHYSIOLOGY

The philosophy of current treatment can best be understood by reviewing the evolution of heart failure models. From 1940 through 1960, heart failure was thought to result primarily from renal hypoperfusion. Standard treatment consisted of digoxin, diuretics, bed rest, and leg elevation, aimed at improving renal function and symptoms of dyspnea and edema. From the 1960s through the 1980s, physicians adopted the hemodynamic model, which suggested that increased ventricular wall stress is the principal cause of the heart failure syndrome. An initial injury is thought to initiate a deleterious feedback cycle by causing a change in left ventricular geometry of dilation and hypertrophy. This structural remodeling of the heart produced by cardiac dysfunction results in increased preload and afterload. In turn, the increased size causes increased wall stress, thus worsening cardiac performance. The change in geometry also increases mitral regurgitation, worsening ejection efficiency and further increasing wall stress. Treatment was aimed at vasodilation and improving ventricular contractility to improve cardiac output and to reduce the wall stress aggravated by elevated preload and afterload. However, clinical trials of inotropic agents did not produce long-term mortality benefits, contradicting predictions based on this model.

The change in focus to the endogenous factors that alter the long-term structure of the myocardium and vasculature has revolutionized heart failure treatment. Activation of neurohormonal systems plays an important role in cardiac remodeling (the alterations in ventricular architecture that occur during the development of heart failure). Many drug treatments now target the mediators of the neurohormonal systems activated in heart failure. Stimulation of the sympathetic and renin-angiotensin systems lead to elevated levels of norepinephrine, angiotensin II, aldosterone, and vasopressin. The net effects of these mediators are vasoconstriction, increased blood volume, increased heart rate, and increased contractility. Endogenous factors may not only increase hemodynamic stresses on the ventricle but also exert direct toxic effects on the heart. These effects may be mediated through various cell-signaling pathways that disturb normal myocyte activity, initiate apoptosis, and promote fibrosis. Other neurohormonal factor levels increased in patients are endothelin, epinephrine, growth hormone, cortisol, tumor necrosis factor, prostaglandins, substance P, adrenomedullin, and natriuretic peptides. Despite past controversy about the treatment of ischemic versus nonischemic heart failure, the present consensus is that they should be treated by the same guidelines. This seems logical because the present paradigm suggests they have similar pathophysiology (Figure 2).

Heart failure prevention and treatment now consists of a multidisciplinary approach, including lifestyle modification to prevent initial and recurrent injury and pharmacological intervention to prevent progression in asymptomatic and symptomatic patients. Coronary artery disease and hypertension are the 2 most common causes of heart failure. Two major trials have demonstrated that the prevention of both factors decreases the risk for development of heart failure. The treatment of hypertension in the Systolic Hypertension in the Elderly Program (SHEP) trial decreased the risk for development of heart failure by 81%. The treatment of hypercholesterolemia in the Scandinavian Simvastatin Survival Study (4S trial) with a hepatic hydroxymethyl glutaryl coenzyme A reductase inhibitor decreased the risk for development of heart failure by 20%. Modifying lifestyle factors that contribute to the pathophysiology of hypertension and CAD, such as smoking, obesity, excess alcohol intake, and diabetes, may also affect heart failure prevention. Identification and aggressive management of potential risk factors for cardiovascular disease remain important. However, large-scale clinical trial data have yet to demonstrate direct effects of adjustment of these factors on risk for development or acceleration of congestive heart failure (CHF).

GUIDELINES FOR DRUG THERAPY

Pharmacological intervention continues to be the mainstay of management of CHF, and abundant clinical trial data describe the specific effects of various agents. Although sometimes puzzling and contradictory, the extensive clinical trial database for heart failure has provided clinicians with important information, and this serves as the basis for guidelines proposed by various expert committees.

Diuretics

Clinical trials have demonstrated fast improvement in sodium excretion, symptoms of fluid overload, exercise tolerance, and improvement of...
cardiac function with diuretics. Most long-term trials include patients receiving diuretics, but there are no long-term studies of diuretics in heart failure (we refer here to thiazides and loop diuretics and reserve discussion of spironolactone for a separate category). Therefore, there is no proven mortality benefit. Patients should not be prescribed diuretics as monotherapy, should start diuretic therapy for symptoms of fluid reten-
tion, and should continue using these agents after improvement of symp-
toms.

The practitioner should carefully titrate these medications to avoid excessive volume depletion but allow for some decreased renal function. Undertitration of primary diuretics can diminish the patient’s response to angiotensin-converting enzyme (ACE) inhibitors (resulting from a state of relative volume overload) and increase the frequency of adverse effects of treatment with \( \beta \)-blockers. Although ACE inhibitors and digoxin have weak diuretic properties, only primary diuretics can control fluid overload adequately. Loop diuretics should be used as first-line agents, with thia-
zides added for refractory fluid overload. Diuretic treatment should be combined with a low-salt diet, a \( \beta \)-blocker, and an ACE inhibitor.

The practitioner should begin with oral furosemide, 20 to 40 mg once daily. Dose titration goals are maintenance of adequate renal perfusion, avoidance of symptomatic hypotension, and achievement of stable weight. Hydrochlorothia-
zide, 25 mg, can be added with refractory fluid overload to escalating furosemide doses. With doses of oral furosemide of 120 mg twice daily, 2.5 to 5.0 mg of metolazone can be added 30 minutes before each dose for improved diuresis. Adding metolazone should be approached with caution because of the potential for severe hypokalemia and hy-
pomagnesemia. The practitioner may switch furosemide to bu-
methamide, 2 to 4 mg/d, with 2.5 mg of metolazone added as needed.

**ACE Inhibitors**

Angiotensin-converting enzyme inhibitors have beneficial effects in the treatment and prevention of heart failure. Six ACE inhibitors are approved by the Food and Drug Ad-
ministration for the management of heart failure, ie, captopril, enalapril maleate, lisinopril, quinapril hydro-
chloride, trandolapril, and fosinopril sodium. Ramipril is approved for the treatment of heart failure after a myocardial infarction. The first study to demonstrate a clinical ben-
efit in symptoms was the Captopril Multicenter Study in 1983. Many double-blind placebo-controlled tri-
als with different ACE inhibitors supported these findings. However, 4 major trials of intermediate to long-
term duration established the morbidity and mortality benefit of ACE inhibitors.

**Captopril-Digoxin Multicenter Trial.** The trial studied patients with mild to moderate heart failure, (NYHA class II, 81%) of ischemic and nonischemic origins who were already receiving diuretics and were randomized to additional treat-
ment with placebo, digoxin (up to 0.375 mg/d), or captopril (up to 150 mg/d). Captopril decreased emergency care or hospitalization for worsening heart failure compared with placebo.

**Studies of Left Ventricular Dysfunction Treatment Trial.** The Stud-
ies of Left Ventricular Dysfunction (SOLVD) Treatment trial also studied patients with mild to moderate heart failure (NYHA classes II and III) with ischemic and nonisch-
emic origins. Patients were randomized to receive placebo or enalapril maleate (up to 20 mg/d) in addition to conventional therapy. The combination of enalapril and con-
ventional therapy decreased all-cause mortality and the risk for death or hospitalization for heart fail-
ure compared with that for placebo.

**Vasodilator Heart Failure Trial II.** Patients with NYHA classes II and III heart failure were randomized to enalapril maleate (up to 20 mg/d) or a combination of hydralazine (300 mg/d) plus isosorbide dinitrate (160 mg/d), with both regimens added to con-
ventional therapy. At 2 years, enalapril reduced the risk for death 28% more than the combination va-
sodilator therapy.

**Cooperative North Scandinavian Enalapril Survival Study.** Patients with NYHA class IV ischemic and nonischemic heart failure were randomized to enalapril maleate (up to 40 mg/d) or placebo added to con-
ventional therapy. The study demonstrated a 27% reduction in all-
cause mortality at 6 months. Patients improved functional class and re-
duced their requirement for other heart failure medications.

Despite copious aggregate evidence of their benefits, ACE inhibi-
tors have been underprescribed in the United States and abroad. Angiotensin-converting enzyme inhibi-
tors are also given in lower doses by practitioners than in clinical tri-
als protocols. A few recent studies have addressed the issue of ACE inhibitor dose effects. The Assess-
ment of Treatment with Lisinopril and Survival (ATLAS) Study evalu-
ated the difference between high-
(32.5-35.0 mg/d) and low-dose (2.5-
5.0 mg/d) lisinopril in patients with NYHA classes II through IV heart failure. The study demonstrated no improvement in mortality, but a de-
creased hospitalization rate for all causes and heart failure in the high-
dose group.

The Network Study evaluated different doses of enala-
pril maleate (2.5, 5.0, or 10.0 mg twice daily) and demonstrated no difference between high- and low-dose groups for any end point measure. Finally, the ongoing Accu-
pril Congestive Heart Failure Investigation and Economic Var-
able Evaluation (ACHEVE) trial is presently evaluating different doses of quinapril hydrochloride (5-20 mg twice daily) and mortality. Although underdosing of ACE inhibi-
tors has been a prominent concern for many heart failure specialists, avail-
able data have yet to verify subthera-
pue effects of treatment regimens involving lower doses than those de-
scribed in the original trials.

Angiotensin-converting en-
yme inhibitors are recommended preventive treatment in patients who have experienced a recent or re-
move ischemic or nonischemic event resulting in systolic dysfunction. Four major trials supporting this
statement are the Survival and Ventricular Enlargement Trial (SAVE; up to 150 mg/d),68 the Acute Infarction Ramipril Efficacy Trial (AIRE; 2.5 or 5.0 mg twice daily),69,70 the Trandolapril Cardiac Evaluation Study (TRACE; up to 4 mg/d),71 and the previously described SOLVD Trial (evaluating the group of asymptomatic and symptomatic patients).72 Post hoc analysis of ACE inhibitor plus β-blocker therapy in the SOLVD database73 showed that the combination of β-blocker and enalapril was associated with a greater reduction in mortality than the use of either agent alone.

Treatment with ACE inhibitors should begin with lower doses, and, if tolerated, titrated to maximum. Recommended target doses are 150 mg/d for captopril, 20 mg/d for enalapril maleate, 40 mg/d for lisinopril, 10 mg/d for ramipril, 40 mg/d for quinapril hydrochloride, and 4 mg/d for trandolapril. Renal function and serum potassium levels should be assessed within 1 to 2 weeks of initiation and every 2 to 3 months thereafter. Tests may need to be repeated more frequently in patients with preexisting hypertension, diabetes, azotemia, or hypokalemia or in patients receiving potassium supplementation.68 Controversy exists among heart failure specialists on whether there is significant literature documenting the attenuation of ACE inhibitor benefit with the use of aspirin therapy.5 Most physicians believe that the evidence is not strong, and thus use both agents.

Titration of ACE inhibitor therapy combined with diuretics needs careful clinical and diagnostic monitoring. Serum creatinine level is expected to increase but may remain stable, whereas potassium level, depending on the patient and diuretic dose, may increase, decrease, or remain unchanged. There is no consensus on the potassium level that should be tolerated. A level below 3.8 mmol/L or higher than 5.8 mmol/L is a concern, and potassium supplement therapy should be reduced or added to achieve safe levels. The goal is to achieve adequate renal perfusion, to avoid symptomatic hypotension, and to insure the absence of congestion.

β-Adrenergic Receptor Blockers

Blockade of β-adrenergic receptors, previously contraindicated as a heart failure treatment, is now a pivotal treatment modality. Early studies of β-blocker treatment demonstrated clinically beneficial effects but failed to prove a reduction in mortality.74-77 Patients with minimal or mild symptoms failed to improve NYHA class,78,79 but decreased their likelihood of clinical exacerbations.79 Selective β1-receptor inhibitors (metoprolol succinate and bisoprolol fumarate) and an agent with both β1- and β2-receptor inhibition (carvedilol) have improved symptoms and ejection fraction80 in patients with moderate to severe symptoms.3,8 The controversy and fear that β-blockers may increase mortality previously discouraged many physicians from prescribing these agents. Recent data, however, have lessened these fears.34,80-82

The Cardiac Insufficiency Bisoprolol Study. Two thousand six hundred forty-seven patients with moderate to severe heart failure (mostly NYHA class III) were randomized to placebo or bisoprolol fumarate, 20 mg, with conventional therapy and followed up for up to 28 months. Treatment demonstrated a 34% reduction in mortality, a 20% reduction in risk for any hospitalization, and a 32% decrease in heart failure hospitalization.83

The Metoprolol CR/XL Randomized Intervention Trial in Heart Failure. Three thousand nine hundred ninety-one patients in Europe and the United States were randomized to placebo or metoprolol.81,82 Doses were titrated to 100 to 200 mg/d as tolerated by each patient. The mean age of patients was 64 years, and more than 95% were in NYHA classes II to III. At 1 year, there was a 34% reduction in mortality resulting in an early termination of the study. The study demonstrated a 38% decrease in cardiovascular mortality, a 41% decrease in sudden death, a 49% decrease in death due to progressive heart failure, and a 35% reduction in the number of patients hospitalized for heart failure.84-87

The US Carvedilol Heart Failure Trials Program. Four separate multicenter trials involving 1094 patients examined patients with mild, moderate, and severe heart failure of ischemic and nonischemic origins. The trials were the Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise (PRECISE; up to 25 mg twice daily; if weight >85 kg, then up to 50 mg twice daily),88 the Multicenter Oral Carvedilol Heart Failure Assessment Study (MOCHA; 6.25, 12.5, or 25.0 mg twice daily),89 a study of the safety and efficacy of carvedilol in severe heart failure (up to 50 mg twice daily),90 and a study evaluating carvedilol’s ability to alter the clinical progression of heart failure in patients with mild symptoms (up to 100 mg/d).78 A prospective analysis of the combined data from all 4 studies evaluated mortality or hospitalization during 6 months, or 12 months in the group with mild heart failure.90 The study demonstrated a 65% decrease in death and resulted in early termination. There was a lower risk for worsening heart failure in the patients with severe heart failure, but the number of deaths and hospitalizations was too small for analysis.

Retrospective Analysis of SOLVD Data. As mentioned, the SOLVD Trial demonstrated reduced mortality with combination therapy of ACE inhibitors and β-blockers.73 Of the patients in the NYHA class II prevention arm, 24% received a β-blocker, compared with only 8% in the class II to III treatment arm. Each agent individually in both groups demonstrated a mortality benefit.

Recently, the Beta-Blocker Survival Trial (BEST),74 a trial of bucindolol hydrochloride (a nonselective β-blocker) to evaluate mortality in patients with NYHA classes III and IV, was terminated early because of increased mortality.95 This raises some questions about the use of nonselective β-blockers in more advanced disease. The Carvedilol Prospective Randomized Cumulative Survival Trial (COPERNICUS) sought to answer the question of safety and improved mortality in NYHA class IV patients.68 The trial was recently stopped because of a
highly significant mortality benefit in the carvedilol group.8,93 At present, the Carvedilol or Metoprolol European Study (COMET) is evaluating the use of carvedilol and metoprolol for a 4-year period.8

All patients with stable NYHA class II or III heart failure due to left ventricular systolic dysfunction are recommended to receive β-blockers; β-blockers are also recommended in diabetic patients.94 Therapy with β-blockers should not be started during an acute worsening of clinical status or evidence of fluid overload. During acute episodes for patients already taking β-blockers, the dose should be decreased, or stopped if the patient is in severe failure.8 If the patient experiences mild to moderate symptoms, the dose may be halved or continued with temporary lowering of the ACE inhibitor dose and increasing doses of diuretics. Often, the early fluid retention induced by β-blockade lessens with continued therapy. If the patient experiences symptomatic hypotension, the doses of β-blocker and ACE inhibitors should be separated by at least 1 to 2 hours.

The difficulties in treating NYHA classes III and IV patients may best be managed by a heart failure specialist. For long-term therapy, titration to the highest dose tolerated is recommended for best results.8 It is still unknown which agent is the most effective or whether patients with NYHA class I heart failure may benefit from treatment.

Aldosterone Antagonists

The guidelines published this year in the American Journal of Cardiology acknowledged that aldosterone antagonists merit consideration in heart failure treatment but could not recommend their use. However, with the publication of the Randomized Aldactone Evaluation Study (RALES),95 most heart failure specialists are recommending spironolactone in a select group of patients. The patients studied in the trial had stable NYHA class III or IV heart failure, an ejection fraction of less than 0.35, a serum creatinine level of less than 221 μmol/L (2.5 mg/dL), and a potassium level of less than 5.0 mmol/L.8 Patients were treated with an ACE inhibitor and a loop diuretic but were not allowed potassium-sparing diuretics. Vasodilators and digitalis were allowed. The double-blind trial randomized 1663 patients to placebo or 25 mg of spironolactone. The trial terminated early because of the significant mortality benefit seen in the spironolactone group. Patients had a 30% reduction in the risk for death and a 31% risk reduction in the risk for death due to cardiac causes.95

Digoxin

Clinical trials of digoxin have shown a benefit in symptomatic relief, quality of life, functional capacity, and exercise tolerance in patients with mild to moderate heart failure.8,58,75,96 The withdrawal of digoxin therapy has resulted in significant clinical deterioration.97 The only trial that has evaluated long-term therapy, the Digitalis Investigation Group (DIG) Trial, demonstrated a decreased risk for all-cause and heart failure hospitalization, but failed to demonstrate a mortality benefit.98 Digoxin is recommended for the control of ventricular response in patients with atrial fibrillation. Digoxin can be added to therapy consisting of ACE inhibitors, diuretics, and β-blockers in patients with a normal sinus rhythm to improve clinical symptoms and to reduce the number of heart failure hospitalizations in NYHA classes II to IV patients. Digoxin levels should not be checked routinely, except to exclude toxic effects of digitalis (Figure 3).8

NONRECOMMENDED DRUGS

Other drug classes have been studied and have produced small significant morbidity and/or mortality benefit. However, the benefits are not enough to recommend these therapies for all patients. Other agents show much promise and are theoretically effective but have been inadequately studied in human trials to date.

Angiotensin Receptor Blockers

Long-term studies of angiotensin receptor blockers have demonstrated similar hemodynamic and neurohormonal effects as ACE inhibitors, but have not demonstrated consistent effects on symptoms or exercise tolerance.8 Angiotensin receptor blockers appear to be safe in heart failure patients. The Evaluation of Losartan in the Elderly (ELITE) Study compared captopril or losartan potassium with conventional therapy in 722 patients aged at least 65 years.89 There was no difference in renal function, hospitalizations for heart failure, or the combined risk of morbidity and mortality between captopril and losartan groups. A single-blinded study demonstrated consistent hemodynamic improvements at 28 days in NYHA classes II, III, and IV patients given valsartan in addition to their long-term ACE inhibitor therapy.68,100 Also, the Randomized Angiotensin Receptor Antagonist–Angiotensin-Converting Enzyme Inhibitor Study (RAAS) is evaluating the safety and tolerability of combination therapy (losartan and enalapril) vs standard- or high-dose enalapril.101 In the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD), patients with mild to moderate symptoms (NYHA classes II-IV) were randomized to candesartan, enalapril, or both with conventional therapy. There was no significant difference in exercise tolerance or cardiac events among groups.102 It is unclear if the receptor blockers will have a similar mortal-
ity benefit in heart failure patients. A trial of more than 3000 patients, Evaluation of Losartan in the Elderly II (ELITE II), compared losartan and captopril and reported no difference in mortality.\textsuperscript{103} Two large multicenter trials,Valsartan Heart Failure Trial (Val-HeFT) and Can-desartan in Heart Failure Assessment in Reduction of Mortality and Morbidity (CHARM), are currently evaluating this issue.\textsuperscript{104} Angiotensin receptor blockers are only recommended if ACE inhibitors are not tolerated because of angioedema or cough. Current evidence does not support combined ACE inhibitor and angiotensin receptor blocker therapy.

**Hydralazine and Isosorbide**

The combination therapy of hydralazine hydrochloride and isosorbide decreases mortality in heart failure patients.\textsuperscript{104} However, in a direct comparison with enalapril, enalapril had a larger mortality benefit.\textsuperscript{60} Most physicians first substitute an angiotensin receptor blocker if an ACE inhibitor is not tolerated. Therefore, this regimen should only be considered if ACE inhibitors are not tolerated and/or the patient has renal insufficiency.

**Calcium Antagonists**

No clinical trials have proven a mortality benefit with calcium antagonists. Some have demonstrated no apparent harm, and that they may be used if a calcium antagonist is indicated. Amlodipine besylate with standard therapy in the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) demonstrated no clear benefit on mortality or major cardiovascular hospitalizations.\textsuperscript{105} Although amlodipine did not affect the combined risk for death and major cardiovascular hospitalization, it appeared to lower the risk for death in a retrospective subgroup analysis of patients with a nonischemic cardiomyopathy. Although PRAISE-2 hoped to confirm this trend,\textsuperscript{106} the attempt failed.\textsuperscript{107} In the third Vasodilator Heart Failure Trial (V-HeFT III), felodipine with standard therapy had no effect on exercise tolerance or all-cause mortality.\textsuperscript{108} Thus, although these calcium channel blockers do not have any additional benefits for heart failure patients, they apparently do not place the patient at increased risk for mortality.

**Inotropic Drugs and Vasodilators**

Despite the emergence of new inotropic agents, the results do not seem promising. The recent Vesnarinone Trial demonstrated an increase in mortality among patients with severe heart failure.\textsuperscript{11,109} The use of intermittent infusion of inotropic agents has no proven mortality benefit,\textsuperscript{110,111} and long-term treatment increases mortality.\textsuperscript{11,100,112} Continuous infusion is often used as a bridge to cardiac transplantation and may have some improvement on the quality of life in patients with advanced-stage heart failure.\textsuperscript{112} If patients require continuous inotropic agents, they should be referred to a heart failure specialist.

Additional therapies include the use of intravenous vasodilators such as sodium nitroprusside (pure arterial vasodilator) and nitroglycerin (arterial and venous vasodilator). Both agents can have adverse effects. Tolerance develops quickly to nitroglycerin, and sodium nitroprusside administration is associated with accumulation of toxic metabolites. These drugs are not useful in the routine management of congestive heart failure.

**Antiarrhythmic Agents**

Antiarrhythmic agents are recommended if the atrial or ventricular arrhythmia causes a clinical deterioration. Amiodarone reduced the risk for death and hospitalization for heart failure in heart failure patients in the Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA).\textsuperscript{113} However, in the Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF STAT),\textsuperscript{114} amiodarone did not improve all-cause mortality in patients with asymptomatic arrhythmia. Treatment was associated with an improved ejection fraction. Amiodarone thus appears relatively safe and is preferred in the treatment of atrial arrhythmias in heart failure patients.

Other agents have been studied for treatment of atrial arrhythmias, but are not recommended. Unfortunately, D-sotalol hydrochloride increases risk for death.\textsuperscript{115} There has not been a large-scale trial with D,L-sotalol. Dofetilide, a promising new drug, increases conversion to normal sinus rhythm, maintains sinus rhythm, and reduces the risk for hospitalization in heart failure patients with atrial fibrillation.\textsuperscript{116} It does not alter all-cause mortality.\textsuperscript{116}

Atrial fibrillation is the most common nonfatal arrhythmia experienced by the CHF patient. Amiodarone is recommended for patients who require lowering of the heart rate despite use of digoxin and \(\beta\)-blockers. Amiodarone has numerous adverse effects, most commonly thyroid dysfunction, pulmonary fibrosis, gastrointestinal tract upset, corneal deposits, and prolongation of the QT interval, occasionally leading to ventricular arrhythmias. Amiodarone therapy typically is started orally at 200 to 400 mg/d. The practitioner must reduce the digoxin dose (to avoid elevation of digoxin level with concurrent amiodarone administration) and \(\beta\)-blocker dose (to avoid excessive bradycardia). Patients with significant lung disease present a therapeutic challenge, as amiodarone and \(\beta\)-blockers may be contraindicated. This problem is assessed on a case-by-case basis. Finally, dofetilide represents an intriguing alternative, the use of which awaits further study.

Treatment of ventricular arrhythmias in patients with end-stage heart failure is debateable. Treatment with amiodarone at a dose of 200 to 400 mg/d (sometimes with a loading dose) is useful in selected patients. It is unclear if implantable cardioverter-defibrillators have a mortality benefit in heart failure patients. The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) is currently addressing this issue.\textsuperscript{8}

**Anticoagulation**

Anticoagulation in patients without atrial fibrillation and with diminished left ventricular function re-
Clinical Trials Evaluating Anticoagulation in Congestive Heart Failure*

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Name of Trial</th>
<th>NYHA Class</th>
<th>Drugs Compared</th>
<th>LVEF for Study Entry</th>
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<td>Aspirin, clopidogrel, warfarin</td>
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<td>WARCEF</td>
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<tr>
<td>WASH</td>
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<td>II, III, IV</td>
<td>Warfarin, aspirin, no antiplatelet therapy</td>
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*NYHA indicates New York Heart Association; LVEF, left ventricular ejection fraction.

maintains controversial. There has been no double-blind placebo-controlled trial in heart failure patients. Patients with dilated cardiomyopathy are predisposed to thromboembolism because of increased stasis in dilated chambers, regional wall motion abnormalities causing asynchrony, poor contractility, and atrial fibrillation. In 1981, Fuster et al. retrospectively observed an 18% frequency of thromboembolism with an incidence of 3.5 per 100 patient-years in patients with nonischemic dilated cardiomyopathy.

Verification of this low incidence has been observed in recent heart failure trials. Warfarin sodium reduced all-cause mortality and the risk for death or hospitalization for heart failure in a recent SOLVD cohort study. It is hoped that the Warfarin Aspirin Study in Heart Failure (WASH Trial), the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) Trial, and the Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) Trial will answer some of this uncertainty. The WASH Trial is a randomized, open, parallel study comparing warfarin, aspirin, and no antithrombotic therapy in NYHA classes II to IV patients. The WATCH Trial will compare aspirin, clopidogrel, and warfarin in NYHA classes II to IV patients with an ejection fraction of no greater than 0.30, and the WARCEF Trial will compare warfarin and aspirin in NYHA classes I to III patients with an ejection fraction of no greater than 0.30. The combined data from the WATCH and WARCEF trials will have sufficient power to determine if warfarin reduces stroke risk in patients with an ejection fraction of no greater than 0.30 (Table and Figure 4).

**POSTHOSPITALIZATION DISCHARGE GUIDELINES**

The inpatient stay for the heart failure patient is only a small part of his or her overall long-term treatment. Patients and caregivers need education about salt and fluid restriction and the importance of checking weight daily. Depending on their motivation and ability to comply, selected patients may be taught to use diuretics on a personalized sliding scale. Patients should be counseled to call the practitioner for a net weight gain of 0.5 to 1.5 kg or clinical signs such as peripheral edema, change in number of pillows needed to sleep, or decreasing exercise tolerance. Hospital admissions may be avoided by early intervention by the practitioner.

**CONCLUSIONS**

The pharmacological treatment of heart failure has become a combined symptomatic-preventive management strategy. Although the plethora of data on heart failure management can be overwhelming, it “is not as complicated as it looks.” Therapy with ACE inhibitors, β-blockers, and diuretics is now standard. Digoxin is added to improve clinical symptoms, especially in patients with atrial fibrillation. Aldosterone antagonists may be recommended in patients with stable NYHA class III or IV heart failure, an ejection fraction less than 0.35, a serum creatinine level of less than 221 µmol/L (2.5 mg/dL), and a potassium level of less than 5.0 mmol/L. Hydralazine and isosorbide are recommended if ACE inhibitors are not tolerated. Angiotensin receptor blockers are only recommended if ACE inhibitors are not tolerated (cough or angioedema). Specialists in heart failure are unsure if a small amount of ACE inhibitor and β-blocker is better than the maximum dose of either agent alone. Antiarrhythmic agents are recommended if the atrial or ventricular arrhythmia causes a clinical deterioration, and anticoagulation is still a controversial issue.

Early recognition and prevention therapies, combined with life-
style modification, are essential. The literature is extensive, but the treatment is logical. Apply the guidelines to every patient as an individual, adjusting the treatment regimen as indicated by a patient’s condition and what the growing medical evidence base deems appropriate.

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Corresponding author and reprints: David A. Baran, MD, Box 1030, The Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029.

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