Treatment of Congestive Heart Failure

Guidelines for the Primary Care Physician and the Heart Failure Specialist

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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.

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During the past 10 years, the philosophy of heart failure treatment has evolved from symptom control to a combined prevention and symptom-management strategy. Within cardiology, heart failure specialists have been trained to tackle this now enormous field. Our continually improving understanding of the pathophysiology of heart failure has accelerated the development of new treatments. However, no single measurement accurately reflects the effectiveness of therapy. Exhaustive guidelines that attempt to simplify treatment, written by various authoritative bodies, make for intimidating reading.

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. Because heart failure specialists are usually referred symptomatic patients, their patients usually enter the heart failure treatment triangle after the prevention stage (Figure 1). Most patients with asymptomatic left ventricular dysfunction and early stages of heart failure will be seen by a general practitioner. The general practitioner will need to identify these patients and begin preventive therapy. Improved prevention and early intervention should be promoted.

Therefore, despite the inherent complexities of heart failure therapy, it is important for all physicians to know current management strategies to prevent end-stage disease.

The treatment of heart failure encompasses pharmacological therapy and includes surgical approaches such as revascularization of coronary arteries, mitral valve repair, aortic valve replacement, ventriculotomy, cardiomyoplasty, and left ventricular assist devices with heart transplant. 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.
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.1,7 Ischemic (coronary artery disease [CAD]) and nonischemic conditions (hypertension, valvar disease, hypertension, thyroid disease, alcohol abuse, myocarditis, adult congenital heart disease, and cardiomyopathy) may cause systolic dysfunction.1,7 A coronary artery disease accounts for approximately two thirds of these cases8,10,11 whereas “pure” diastolic dysfunction with preserved systolic function is seen in patients with left ventricular hypertrophy, hypertension, and CAD.1 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.7,12

The severity of heart failure is defined symptomatically, and the most commonly used system is the New York Heart Association (NYHA) functional classification.13 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.13 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.8 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.8

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.8

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.15 Exercise testing is highly dependent on the motivation of the patient and the physician.15

EPIDEMIOLOGY

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.20 Despite the higher incidence of heart failure in men in every age group, the prevalence in women is approximately equal.21 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.23 With the increasing prevalence, hospital expenditures have escalated.20 Annual direct expenditures, which include cost of medications, hospitalizations, nursing home admissions, and medical follow-up, are estimated at $20 billion to $40 billion.8,19 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 treat 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 vs nonischemic heart failure, the present consensus is that they should be treated by the same guidelines. This seems logical because the present paradigm suggests that they have similar pathophysiology.

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
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 Administration for the management of heart failure, ie, captopril, enalapril maleate, lisinopril, quinapril hydrochloride,trandolapril, and fosinopril sodium. Ramipril is approved for the treatment of heart failure after a myocardial infarction. The first study to demonstrate a clinical benefit in symptoms was the Captopril Multicenter Study in 1983. Many double-blind placebo-controlled trials 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 treatment 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 Studies of Left Ventricular Dysfunction (SOLVD) Treatment trial also studied patients with mild to moderate heart failure (NYHA classes II and III) with ischemic and nonischemic 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 conventional therapy decreased all-cause mortality and the risk for death or hospitalization for heart failure 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 conventional therapy. At 2 years, enalapril reduced the risk for death 28% more than the combination vasodilator therapy.60

**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 conventional therapy.61 The study demonstrated a 27% reduction in all-cause mortality at 6 months. Patients improved functional class and reduced their requirement for other heart failure medications.

Despite copious aggregate evidence of their benefits, ACE inhibitors have been underprescribed in the United States and abroad.6,21,62,64 Angiotensin-converting enzyme inhibitors are also given in lower doses by practitioners than in clinical trials.5 A few recent studies have addressed the issue of ACE inhibitor dose effects. The Assessment of Treatment with Lisinopril and Survival (ATLAS) Study evaluated 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.9 The study demonstrated no improvement in mortality, but a decreased hospitalization rate for all causes and heart failure in the high-dose group.9,60 The Network Study evaluated different doses of enalapril 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 measured. Finally, the ongoing Acu- pril Congestive Heart Failure Investigation and Economic Variable Evaluation (ACHIEVE) trial is presently evaluating different doses of quinapril hydrochloride (5-20 mg twice daily) and mortality.67,68 Although underdosering of ACE inhibitors has been a prominent concern for many heart failure specialists, available data have yet to verify subtherapeutic effects of treatment regimens involving lower doses than those described in the original trials.

Angiotensin-converting enzyme inhibitors are recommended preventive treatment in patients who have experienced a recent or remote ischemic or nonischemic event resulting in systolic dysfunction.8
The combination of enalapril with the use of aspirin therapy.8 Attenuation of ACE inhibitor benefits 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.78 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. Tables 3-8. The controversy and fear that β-blockers may increase mortality previously encouraged many physicians from prescribing these agents. Recent data, however, have lessened these fears.38,80-82

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

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.78 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.38 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.38,80-82

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 (PRECEDE; 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),91 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.92 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.93 The trial was recently stopped because of a
highly significant mortality benefit in the carvedilol group. At present, the Carvedilol or Metoprolol European Study (COMET) is evaluating the use of carvedilol and metoprolol for a 4-year period.

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. 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. 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. It is still unknown 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), 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 2.1 mg/dL (2.5 mmol/L), and a potassium level of less than 5.0 mmol/L. 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.

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. The withdrawal of digoxin therapy has resulted in significant clinical deterioration. 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. 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 digoxin.

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. 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. 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. 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. 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.

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.102 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.8 Angiotensin receptor blockers are only recom-
mended if ACE inhibitors are not tol-
erated 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 hydra-
lazine hydrochloride and isosorbide decreases mortality in heart failure patients.104 However, in a direct com-
parison with enalapril, enalapril had a larger mortality benefit.60 Most physicians first substitute an angio-
tensin receptor blocker if an ACE in-
hibitor is not tolerated. Therefore, this regimen should only be consid-
ered if ACE inhibitors are not toler-
ated and/or the patient has renal insufficiency.

Calcium Antagonists
No clinical trials have proven a mor-
tality benefit with calcium antago-
nists. Some have demonstrated no apparent harm, and that they may be used if a calcium antagonist is in-
dicated. Amlodipine besylate with standard therapy in the Prospec-
tive Randomized Amlodipine Sur-
vival Evaluation (PRAISE) demon-
strated no clear benefit on mortality or major cardiovascular hospitaliza-
tions.105 Although amlodipine did not affect the combined risk for death and major cardiovascular hospital-
ization, it appeared to lower the risk for death in a retrospective sub-
group analysis of patients with a nonischemic cardiomyopathy. Al-
though PRAISE-2 hoped to con-
firm this trend,106 the attempt failed.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.108 Thus, although these calcium channel blockers do not have any additional benefits for heart failure patients, they appar-
ently do not place the patient at in-
creased risk for mortality.

Inotropic Drugs and Vasodilators
Despite the emergence of new ino-
tropic agents, the results do not seem promising. The recent Vesna-
rnone Trial demonstrated an in-
crease in mortality among patients with severe heart failure.11,109 The use of intermittent infusion of inotro-
pic agents has no proven mortality benefit,110,111 and long-term treat-
ment increases mortality.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 ad-
anced-stage heart failure.110 If pa-
tients 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 nitroglyc-
erin (arterial and venous vasodilator). Both agents can have adverse ef-
facts. Tolerance develops quickly to nitroglycerin, and sodium nitro-
prusside administration is associa-
ted with accumulation of toxic me-
tabolites. These drugs are not useful in the routine management of con-
gestive heart failure.

Antiarrhythmic Agents
Antiarrhythmic agents are recom-
mended if the atrial or ventricular ar-
rrhythmia causes a clinical deterio-
ration. Amiodarone reduced the risk for death and hospitalization for heart failure in heart failure pa-
tients in the Grupo de Estudio de la Sobrevie de la Insuficiencia Cardiaca en Argentina (GESICA).113 However, in the Congestive Heart Failure Survival Trial of Antiarrhyth-
ic Therapy (CHF STAT),114 amio-
darone did not improve all-cause mortal-
ty in patients with asymp-
tomatic arrhythmia. Treatment was associated with an improved ejec-
tion fraction. Amiodarone thus ap-
ppears relatively safe and is pre-
ferred in the treatment of atrial arrhythmias in heart failure pa-
tients.

Other agents have been studied for treatment of atrial arrhyth-
mas, but are not recommended. Un-
fortunately, D-sotalol hydrochloride increases risk for death.115 There has not been a large-scale trial with D,L-
sotalol. Dofetilide, a promising new drug, increases conversion to nor-
mal sinus rhythm, maintains sinus rhythm, and reduces the risk for hos-
pitalization in heart failure patients with atrial fibrillation.116 It does not alter all-cause mortality.116

Atrial fibrillation is the most com-
mon nonfatal arrhythmia experi-
enced by the CHF patient. Amio-
darone is recommended for pa-
tients who require lowering of the heart rate despite use of digoxin and β-blockers. Amiodarone has num-
erous adverse effects, most com-
monly thyroid dysfunction, pulmo-
nary fibrosis, gastrointestinal tract upset, corneal deposits, and prolongation of the QT interval, occasion-
ally leading to ventricular arrhyth-
mas. Amiodarone therapy typically is started orally at 200 to 400 mg/d. The practitioner must reduce the di-
goxin dose (to avoid elevation of di-
goxin level with concurrent amio-
darone administration) and β-blocker dose (to avoid excessive bradycardia). Patients with signifi-
cant lung disease present a thera-
peutic challenge, as amiodarone and β-blockers may be contraind-
cated. This problem is assessed on a case-by-case basis. Finally, dofe-
tilide represents an intriguing alter-
native, the use of which awaits fur-
ther study.

Treatment of ventricular ar-
rrhythmias in patients with end-
stage heart failure is debatable. Tre-
mament with amiodarone at a dose of 200 to 400 mg/d (sometimes with a loading dose) is useful in selected pa-
tients. It is unclear if implantable car-
dioverter-defibrillators have a mor-
tality benefit in heart failure patients. The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) is cur-
rently addressing this issue.8

Anticoagulation
Anticoagulation in patients with-
out atrial fibrillation and with di-
minished left ventricular function re-
 mains 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 asynergy, 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).

### 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 2.21 µmol/L (2.5 mg/dL), and a potassium level of less than 5.0 mEq/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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