Pharmacologic Therapy for Patients with Chronic Heart Failure and Reduced Systolic Function: Review of Trials and Practical Considerations

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Heart failure (HF) is a complex clinical syndrome resulting from any structural or functional cardiac disorder impairing the ability of the ventricles to fill with or eject blood. The approach to pharmacologic treatment has become a combined preventive and symptomatic management strategy. Ideally, treatment should be initiated in patients at risk, preventing disease progression. In patients who have progressed to symptomatic left ventricular dysfunction, certain therapies have been demonstrated to improve survival, decrease hospitalizations, and reduce symptoms. The mainstay therapies are angiotensin-converting enzyme (ACE) inhibitors and β-blockers (bisoprolol, carvedilol, and metoprolol XL/CR), with diuretics to control fluid balance. In patients who cannot tolerate ACE inhibitors because of angioedema or severe cough, valsartan can be substituted. Valsartan should not be added in patients already taking an ACE inhibitor and a β-blocker. Spironolactone is recommended in patients who have New York Heart Association (NYHA) class III to IV symptoms despite maximal therapies with ACE inhibitors, β-blockers, diuretics, and digoxin. Low-dose digoxin, yielding a serum concentration <1 ng/mL can be added to improve symptoms and, possibly, mortality. The combination of hydralazine and isosorbide dinitrate might be useful in patients (especially in African Americans) who cannot tolerate ACE inhibitors or valsartan because of hypotension or renal dysfunction. Calcium antagonists, with the exception of amlodipine, oral or intravenous inotropes, and vasodilators, should be avoided in HF with reduced systolic function. Amiodarone should be used only if patients have a family history of sudden death, or a history of ventricular fibrillation or sustained ventricular tachycardia, and should be used in conjunction with an implantable defibrillator. Finally, anticoagulation is recommended only in patients who have concomitant atrial fibrillation or a previous history of cerebral or systemic emboli.

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Cardiovascular disease has been the number 1 cause of morbidity and mortality in the Western world for the past century. Whereas death rates from coronary artery disease and stroke decreased by nearly 50% over the past decade,[1] there has been a significant increase in the prevalence, morbidity, and mortality from chronic heart failure (HF).[2]

It is now estimated that almost 4.8 million people in the United States have HF, with approximately 550,000 new cases being diagnosed each year.[1] HF prevalence is increasing with age, ranging from <1% for patients <50 years of age to 5% for patients 50 to 70 years of age and 10% for all patients >70 years of age.[1] The mean age at diagnosis has increased from approximately 60 years in the 1950s to 80 years in the last decade.[3] Over the past 5 decades, the incidence of HF has decreased by 30% to 40% in women, but it has remained fairly constant in men.[3]

Despite advances in treatment and relative improvement in survival over the past decades,[3] HF mortality remains high, with nearly 300,000 patients dying of HF as the primary or contributory cause each year.[1,2] The 5-year survival rate for all patients with HF is around 50%, but patients with more advanced disease have a worse prognosis.[4]

The rate of hospitalizations because of HF has increased 250% in the past 2 decades to approximately 970,000 admissions in 1999.[5] The total number of hospitalizations exceeded 3 million when HF was listed as 1 of the first 3 discharge diagnoses. HF has become the number 1 volume diagnosis in the Medicare health system and the number 1 cause of readmission within 60 days of discharge.[5]

The estimated HF costs range from $21 to $50 billion dollars per year, 66% being spent in the hospital setting.[1,6] It is estimated that the cost of care of patients with HF is nearly 3 times greater than that for patients with cancer and twice as much as that spent for the care of patients with acute myocardial infarction.[6] The total loss of work productivity because of

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HF, beyond the direct healthcare cost, is estimated to be an additional $30 to $50 billion per year.[7]

EVOLVING CHARACTERISTICS OF CHRONIC HEART FAILURE

The 2001 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines define HF as "a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood and that it is characterized by specific symptoms (dyspnea and fatigue) and signs (fluid retention)."[8] These guidelines have taken an important step in acknowledging that the optimal treatment for HF starts with its prevention. Accordingly, it divides the syndrome in 4 stages: A, B, C, and D. Stage A includes the 50 to 60 million people in the United States who have coronary artery disease, hypertension, or diabetes mellitus and who, if untreated, are at risk of developing HF.[1,8,9] Stage B includes approximately 8 to 10 million patients with structural heart disease (either secondary to an acute myocardial infarction, hypertensive heart disease, or asymptomatic valvular disease) but who have not yet shown symptoms or signs of HF.[1,8,9] There are almost 5 million patients who have symptomatic HF responding to therapy; they are classified as stage C.[1,8,9] Finally, stage D includes the 50,000 to 200,000 patients with symptomatic end-stage HF refractory to the maximal available therapies.[8–10]

Today, patients with HF in the United States have many different characteristics compared with what was seen 30 to 40 years ago:

1. Coronary artery disease has replaced hypertension and valvular heart disease as the most common etiology for HF, accounting for nearly 70% of cases.[11] The prognosis in patients with severe left ventricular (LV) dysfunction and coronary artery disease is worse than the prognosis of HF in patients with normal coronary arteries.[12] Hypertension contributes significantly to the syndrome of HF in African Americans, perhaps up to 60% of the cases.[13,14]

2. There is an increased prevalence of patients with HF and preserved systolic function. In 3 well-controlled population-based studies in the United States, it was reported that 30% to 40% of HF cases occur in the setting of preserved systolic function.[15–17] Although diastolic dysfunction is, per se, a rare cause of HF, when combined with hypertension, diabetes, coronary artery disease, and/or atrial fibrillation, it results in a clinical syndrome of HF with preserved systolic function. Studies thus far show that these patients are more likely to be women, generally older, and have atrial fibrillation more often than those with LV systolic dysfunction.[18]

3. Systemic and pulmonary congestion is seen less frequently, even in patients with severe LV dysfunction. In the Studies of Left Ventricular Dysfunction (SOLVD), which enrolled patients with an ejection fraction (EF) $\leq$0.45, $<$35% of the patients had signs of systemic congestion.[19] This is probably the combined result of early recognition of LV dysfunction and the efficacy of available treatments that reduce or eliminate the signs and symptoms of congestion.[20]

4. Despite advances in the recognition and treatment of HF, mortality remains very high.[2,21] Most patients with HF die suddenly, presumably of ventricular arrhythmias, before they develop symptoms or after their symptoms have been controlled.[22] This is very different from what was seen decades ago, when most patients were dying with progressive circulatory failure.

PATHOPHYSIOLOGY OF CHRONIC HEART FAILURE WITH REDUCED SYSTOLIC FUNCTION

Our understanding of the pathophysiology of chronic HF with reduced systolic function is constantly evolving. Once considered a simple pump dysfunction, HF has come to be understood as a highly complex clinical syndrome in which coronary artery disease and its progression, neurohormonal activation, ventricular remodeling, as well as genetic factors play important roles.[23,24]

HF is initiated after an event damages the heart muscle or disrupts the ability of the myocardium to contract and/or relax. This event may have an abrupt onset (eg, an acute myocardial infarction) or an insidious onset (eg, hemodynamic pressure or volume overload from long-standing hypertension or valvular disease), or it may be hereditary (eg, dilated cardiomyopathy).[24,25] These events lead to subtle or overt ventricular dysfunction, resulting in decreased pumping capacity. Patients will often remain asymptomatic or minimally symptomatic after the initial pump dysfunction or will develop symptoms only after the dysfunction has been present for many years.[24]

Coronary artery disease: In the United States, coronary artery disease is the underlying etiology for HF in $>$70% of the cases.[11] Transient severe ischemic events may cause prolonged systolic dysfunction that persists, even after the ischemic event has resolved (stunning).[26] The sustained reduction in the coronary blood flow leads to a tissue perfusion that is sufficient to maintain viability but insufficient to maintain a normal contractility (hibernation).[27] However, hibernation cannot be maintained indefinitely, and eventually, myocardial necrosis ensues if coronary blood flow is not restored.[28] Ischemia and hibernation may lead to myocyte apoptosis,[28] which may result in progression of LV dysfunction.[23,29] Finally, episodes of reversible myocardial ischemia caused by coronary artery disease, when superimposed on a left ventricle with already depressed systolic function, may cause an exacerbation of HF.[11,30] Progression of coronary artery disease may also contribute to the progression of HF in a large number of patients.

The coronary endothelium plays an important role, not only in the control of coronary blood flow and patency, but also in the physiologic modulation of myocardial structure and function.[31] Endothelial dysfunction leads to impaired secretion of nitric oxide and prostacyclin, as well as increased release of endothelin

and angiotensin II, which will amplify the myocardial dysfunction.[31–33]

Neurohormonal and cytokine activation: Decreased cardiac performance characterized by a reduction in cardiac output and/or an increase in wall stress results in activation of neurohormonal systems, such as the adrenergic system, the renin–angiotensin–aldosterone system, and the hypothalamic–neurohypophyseal system, possibly related to baroreceptor abnormalities.[23,24] Continued activation of the adrenergic system increases ventricular afterload and, therefore, the hemodynamic burden placed on the failing ventricle. Its activation also leads to an increase in the heart rate and myocardial energy utilization. It may also cause hypertrophy, ischemia, tachyarrhythmias, and myocyte damage, perhaps through myocardial calcium overload or apoptosis.[29] Chronic β-adrenergic stimulation has been shown to induce expression of proinflammatory cytokines, such as tumor necrosis factor-α, interleukin-1, and interleukin-6.[34] Increased cytokine levels may result in the skeletal muscle myopathy characteristic of HF[35] and cause myocardial inflammation, cell proliferation, and apoptosis, thereby causing or intensifying HF.[36,37] Tumor necrosis factor-α also activates transcription factors and enzymes involved in signal transduction, and it induces a number of genes, including the fetal gene program.[38]

Activation of the renin–angiotensin–aldosterone system results in an increased level of angiotensin II, which increases ventricular afterload and causes myocyte hypertrophy, apoptosis, interstitial fibrosis, cardiac and vascular remodeling, and the secretion of aldosterone.[39] The latter also plays an important role in cardiac remodeling, fibroblast proliferation, and collagen deposition. These changes increase the passive stiffness of the ventricles and arterial bed, interfere with ventricular filling, and reduce arterial compliance.[39] Myocardial interstitial fibrosis and hypertrophy, along with myocyte slippage and interstitial growth, result in ventricular remodeling.[23]

There is increasing evidence of interplay between the adrenergic system and the renin–angiotensin–aldosterone system. Thus, in patients with HF, angiotensin-converting enzyme (ACE) inhibition has been found to reduce enhanced peripheral sympathetic nerve impulse traffic[40] and cardiac adrenergic drive.[41] The beneficial effects of ACE inhibitors appear to be especially prominent in patients with increased adrenergic activation.[42] Conversely, β-blockade reduces the secretion of renin, therefore reducing the levels of angiotensin and aldosterone.[43]

Arginine vasopressin is synthesized in the hypothalamus, and its release from the neurohypophysis is enhanced by osmolar stimuli as well as elevated concentrations of norepinephrine and angiotensin II. Increased release of arginine vasopressin in HF causes vasoconstriction (through binding to vasopressin$_1$ receptors), water retention, and dilutional hyponatremia (through binding to vasopressin$_2$ receptors).[23]

The vasodilator peptides, such as atrial natriuretic peptide and brain natriuretic peptide, are also overexpressed in chronic HF and exert a counterregulatory or beneficial effect. However, renal responsiveness to their action is impaired. This probably reflects changes in renal hemodynamics and a combination of receptor downregulation and increased cyclic guanosine monophosphate phosphodiesterase activity. The decreased responsiveness leads to enhanced local actions of angiotensin II and the sympathetic system in the kidney, resulting in salt retention and further deterioration of renal function and increased vasoconstriction.[44]

Remodeling: The development of myocardial hypertrophy initially represents an important adaptive mechanism to hemodynamic stress and is characterized by structural changes at the myocyte level that are translated into alterations in chamber size and geometry.[45] In addition to cardiac myocytes, the fibroblasts and the increased production of extracellular matrix participate in the remodeling process. Increased hemodynamic stress (either pressure or volume overload) appears to be sensed by myocytes, leading to changes in myocardial gene expression. Thus, hypertrophy is not just a quantitative increase in contractile proteins and other key elements that initiate and regulate contraction, but it is also associated with qualitative changes in gene expression that lead to an impairment of contractile function.[24]

The systemic vasoconstriction translates into increased afterload, which further reduces cardiac performance. In patients with HF, a marked increase in the LV diastolic pressure may be responsible for changes in the shape of the left ventricle from an ellipsoid to a more spherical configuration.[46,47] This change in ventricular geometry may result in papillary muscle rearrangement and secondary mitral insufficiency.[48,49]

In addition, the elevated LV end-diastolic pressure (wall stress) can cause subendocardial ischemia[49] that is perpetuated by tachycardia, which shortens the diastole and decreases the coronary filling time. This is reflected at a biochemical level by increased production of lactate, adenosine triphosphate, and creatine phosphate and at a histologic level through fibrosis.[49] All these changes may lower the threshold for malignant ventricular arrhythmias.[30]

Genetic factors: Several studies have shown that there might be a genetic predisposition to dilated cardiomyopathy. Specific loci have been found to be associated with early development of the disease,[50] and mutations in the amino acids of the actin domain have been associated with hereditary dilated cardiomyopathy.[51] Also, polymorphism in the β_2-adrenergic receptors (threonine-to-isoleucine switch at position 164) has been associated with a striking decrease in survival in patients who exhibit this mutation compared with those who have the wild type.[52]

Recently, it has been shown that a combination of receptor variants that results in increased synaptic norepinephrine release and enhanced receptor function in the myocyte would predispose persons to HF.[53]

Summary: It is clear now that patients with HF with reduced systolic function from ischemic and nonischemic causes have viable and noncontractile myocar-

dium. The amount of viability is probably greater in patients without severe symptoms. Because the response to therapies in terms of LV function is related to the amount of viable but noncontractile myocardium, it is possible that patients who will benefit the most from life-saving therapies are those who might have no or minimal symptoms, and they should be treated aggressively.

PHARMACOLOGIC MANAGEMENT OF SYMPTOMATIC CHRONIC HEART FAILURE WITH REDUCED SYSTOLIC FUNCTION

HF is not a single disease but rather a syndrome, a manifestation of different cardiovascular disorders, and not all patients should be treated in a similar manner. Treatment must be tailored according to the individual characteristics present in each patient. In the same patient, coronary artery disease, hypertension, diabetes, atrial fibrillation, an element of cardiomyopathy (caused by smoking or excess alcohol intake), and valvular heart disease may coexist and contribute in various amounts to the clinical picture of HF.

The management of HF is comprehensive and includes the following: (1) accurate diagnosis, assisted by measurement of brain natriuretic peptide[54] and by the use of echocardiography[8,55]; (2) identification and treatment of etiologic factors, such as ischemia or hypertension; (3) syndrome definition, for instance, HF with systolic dysfunction versus HF with preserved systolic function, right-sided versus left-sided HF, HF with congestion (wet) versus without congestion (dry), or high-output versus low-output state; (4) correction of precipitating causes, such as noncompliance with drugs, use of nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors, nasal decongestants, anemia, infections, pulmonary emboli, dietary indiscretion, inactivity, hyperthyroidism, etc; and (5) therapy, which has 4 major components: (a) interventions, such as exercise, vitamin supplementation, diet, and treatment for sleep apnea; (b) pharmacologic therapy; (c) electrical therapy (implantable cardioverter defibrillators, biventricular pacing); and (d) surgical therapy (coronary artery bypass grafting, LV-assisted device, ventricular reduction surgery, mitral valve repair, transplant).

Keeping in mind the complexity of HF management, the present review will focus only on the pharmacologic therapy for symptomatic patients with HF with systolic dysfunction responding to therapy (stage C). Other parts of this supplement will be addressing the treatment of patients in stages A, B, and D, as well as the other treatment options for patients in stage C.

THERAPIES THAT IMPROVE SURVIVAL

ACE inhibitors: BACKGROUND: ACE inhibitors act by blocking the conversion of angiotensin I into angiotensin II, breaking down the renin–angiotensin–aldosterone system that is activated in HF. This leads to a decrease in preload and afterload, with an improvement in the hemodynamic profile.[56] Aldosterone production also diminishes, and thus the sodium and water retention decreases.[56] Inhibition of angiotensin II leads to a decrease in cardiac remodeling, hypertrophy, apoptosis (either directly or by decreasing aldosterone production),[57] sympathetic activity,[40,41] and vasopressin levels.[23] ACE inhibitors may increase plasma concentrations of bradykinin, nitric oxide, and vasodilating prostaglandins.[58]

BENEFITS OF ACE INHIBITORS: *Clinical effects.* ACE inhibitors improve symptoms, New York Heart Association (NYHA) functional class, and exercise capacity in patients with HF, as shown in randomized, double-blind, placebo-controlled trials.[59–61] The Captopril Multicenter Research Group showed that captopril treatment improved the NYHA class in 61% of patients compared with only 24% of patients taking placebo over a 12-week period.[61] The improvement started as early as 2 weeks and was maintained over the course of the study. Treadmill exercise time was significantly and progressively improved throughout the 12 weeks of the study in 24% of captopril-treated patients, but in none of the placebo-treated patients.[61]

Hemodynamic effects. ACE inhibitors have a beneficial impact on hemodynamic effects in HF by decreasing the systemic vascular resistance, pulmonary capillary wedge pressure, right atrial pressure, and the LV end-diastolic and end-systolic dimensions, as observed by LeJemtel et al.[62] The hemodynamic effects were maintained during long-term treatment with enalapril, as shown by DiCarlo et al.[63] Long-term ACE inhibition significantly decreased LV dimensions and increased shortening fraction as determined by echocardiography.[64,65]

Effects on mortality and hospitalization. Indubitably, the most important benefit of therapy with ACE inhibitors is the dramatic increase in survival seen in patients with NYHA class II to IV and in all patients with LV systolic dysfunction after an acute myocardial infarction, even in those without symptoms or signs of HF. The first trial to show a survival benefit, the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) was conducted in patients with NYHA class IV who were randomized to receive enalapril or placebo.[66] At the end of the study (20 months), patients treated with enalapril had a significant 27% reduction in total mortality, the primary end point. It appeared that enalapril had no effect on sudden death but decreased mortality from progressive HF by 50%. After CONSENSUS, the SOLVD Treatment trial examined the effect of enalapril in patients with mild-to-moderate HF (NYHA class II to III).[67] Enalapril decreased the all-cause mortality by 16%, the mortality caused by progressive HF by 22%, and the combined point of death or hospitalizations for worsening HF by 26% compared with placebo. The decreased mortality was attributed to a decrease in the progression of HF because there was no effect on sudden death. The mortality benefit was lost after 5 years.[68] The SOLVD Prevention trial[69] enrolled patients with asymptomatic LV dysfunction and showed that, although there was no immediate mortality benefit, enalapril had a major effect in delaying the de-

velopment of HF (22.3 months vs 8.3 months in the enalapril and placebo groups, respectively), and in reducing the risk for first and multiple hospitalizations for HF by 36% and 44%, respectively.[69] A long-term follow-up study of the SOLVD trials, known as XSOLVD, showed that in the prevention arm, a significant mortality benefit was apparent at 5 years and was maintained at 12 years.[68] Retrospectively, there was also a significant reduction in the rate of myocardial infarction.[70]

Effect after myocardial infarction. Four major trials proved the favorable effects of prophylactic ACE inhibition after an acute myocardial infarction. After myocardial infarction, ACE inhibition attenuated ventricular dilation, reduced the incidence and hospitalization for HF, prevented recurrent ischemic events, and increased survival. The Survival and Ventricular Enlargement (SAVE) trial examined the effect of captopril in patients with an ejection fraction (EF) ≤ 0.40 but without overt HF or symptoms of myocardial ischemia. Captopril-treated patients had a 19% reduction in the all-cause mortality, a 22% reduction in the risk of hospitalization for HF, and a 25% reduction in the risk of recurrent myocardial infarction.[71] The Acute Infarction Ramipril Efficacy (AIRE) trial differed from SAVE in that the patients had overt signs of HF after an acute myocardial infarction, although NYHA class IV patients were excluded.[72] Patients treated with ramipril had a 27% reduction in mortality and a slightly lower rate of progression to severe HF. The Survival of Myocardial Infarction Long-Term Evaluation (SMILE) trial randomized 1,556 patients in Italy within 24 hours after an acute myocardial infarction to receive zofenopril or placebo for 6 weeks. A 34% reduction in mortality and incidence of severe HF was observed at 6 weeks, and a 29% reduction in mortality was observed after 1 year in the patients treated with the ACE inhibitor.[73] Finally, the Danish Trandolapril Cardiac Evaluation (TRACE) study evaluated the effect of trandolapril on patients with an LVEF ≤ 0.35 after myocardial infarction. Patients assigned to treatment with trandolapril had a 22% reduction in the risk of death from all causes and a 24% reduction in sudden death. The risk of progression to advanced HF was decreased by 29% with trandolapril, whereas the drug had no effect on the risk of recurrent myocardial infarction.[74]

ACE inhibitors significantly improve mortality in asymptomatic patients with LV dysfunction and symptomatic patients with NYHA class II to IV, improve symptoms and EF, decrease the readmission rate for HF, decrease the rate of reinfarction in patients with coronary artery disease, and have no effect on sudden death.

RECOMMENDATIONS ON THE USE OF ACE INHIBITORS: Based on data from published trials, ACC/AHA guidelines recommend ACE inhibitors as the first-line therapy for symptomatic HF with reduced systolic function and for asymptomatic LV dysfunction.[8] They should be used in conjunction with a diuretic to maintain the sodium balance and prevent the development of fluid overload. A β-blocker should be added in all patients without contraindications. Digoxin could also be part of the treatment regimen. ACE inhibitors should be started at low doses and gradually increased to the doses that have been shown to decrease mortality in clinical trials (Table 1). The doses used in clinical practice are often less than those demonstrated to be of benefit in clinical trials, mostly because of perceived adverse effects at higher doses.

To assess the difference between lower and higher doses of ACE inhibitors on mortality and hospitalizations for HF, the Assessment of Treatment with Lisinopril and Survival (ATLAS) trial randomized patients with HF, predominantly those with NYHA class III and with a LVEF <0.35, to receive lisinopril 32.5 to 35 mg/day versus 2.5 to 5 mg/day. During 46 months of follow-up time, all-cause mortality was not statistically different between groups, but high doses of lisinopril produced a significant 12% reduction in the combined end point of death or hospitalization for any reason compared with the low-dose regimen. In addition, high-dose lisinopril reduced HF hospitalizations by 25%.[75]

The Clinical Outcome with Enalapril in Symptomatic Chronic Heart Failure (NETWORK) trial compared different doses of enalapril and found no differences between high-dose and low-dose groups for any of the end points measured.[76]

The above studies suggest that the difference in efficacy between intermediate and high doses of an ACE inhibitor (if any) is likely to be very small. The ACC/AHA recommendations are that patients with HF should not generally be maintained on very low doses of an ACE inhibitor unless these are the only doses that can be tolerated.[8]

It has also been suggested that treatment with ACE inhibitors leads to different outcomes in whites compared with African Americans. In a recent retrospective analysis of the SOLVD trials, enalapril was associated with a 44% reduction in the risk for hospitalizations for HF among white patients ($p < 0.001$), but there was no significant reduction among African Americans ($p = 0.74$).[77] However, in another retrospective analysis of the same trial, treatment with enalapril was associated with a comparable reduction in the relative risk of development of symptomatic HF in African Americans (relative risk, 0.67; 95% confidence interval, 0.49 to 0.92; $p = 0.01$) and whites (relative risk, 0.61; 95% confidence interval, 0.53 to 0.70; $p = 0.001$).[78] Thus, all patients with HF, including African Americans, should receive ACE inhibitors as first-line treatment.

Once the drug has been titrated to the appropriate dose, patients can be maintained on long-term therapy with an ACE inhibitor with little difficulty. Renal function and serum potassium should be assessed within 1 to 2 weeks of initiating therapy and every 2 to 3 months thereafter.

The main adverse effects of the therapy are related to the angiotensin suppression (hypotension, increase in serum creatinine and potassium) and bradykinin potentiation (cough and angioedema). Usually, the initial hypotension responds to a decrease in the dose

TABLE 1 Target Doses of Angiotensin-Converting Enzyme Inhibitors for Heart Failure as Resulted from Clinical Trials

Agent	Starting Dosage	Target Dosage	Trial
Captopril	6.25 mg tid	25–50 mg tid	SAVE
Enalapril	5 mg bid	10 mg bid	SOLVD P/T
Fosinopril	10 mg qd	40 mg qd	FEST
Lisinopril	2.5 mg qd	40 mg qd	ATLAS
Ramipril	2.5 mg bid	5 mg bid	AIRE
Trandalopril	1 mg qd	4 mg qd	TRACE

AIRE = Acute Infarction Ramipril Efficacy; ATLAS = Assessment of Treatment with Lisinopril and Survival; FEST = Fosinopril Efficacy/Safety Trial; SAVE = Survival and Ventricular Enlargement trial; SOLVD P/T = Studies of Left Ventricular Dysfunction (Prevention/Treatment); TRACE = Trandalopril Cardiac Evaluation.

of diuretic agent, liberalization of salt intake, or initiation of a lower dose of ACE inhibitors. Patients generally will be able to tolerate ACE inhibitors in the long term. Treatment should be reassessed if levels of creatinine are ≥3.0 mg/dL or if serum potassium is ≥5.5 mEq/L.[8] Cough is a major reason for discontinuation of therapy, but ACE inhibitors should be discontinued only if cough is persistent and troublesome and should be replaced with angiotensin II receptor blockers. Patients should not be given ACE inhibitors if they are pregnant, have a history of angioedema or anuric renal failure during a previous exposure to this class, or if they are severely hypotensive and at risk of immediate cardiogenic shock.[8]

β-Adrenergic receptor blockers: BACKGROUND: Long-term activation of the sympathetic system is associated with an increase in ventricular volumes and pressures by causing peripheral vasoconstriction[79] and by impairing sodium excretion by the kidney.[80] Norepinephrine causes myocyte hypertrophy, changes gene expression and apoptosis, and induces myocardial ischemia.[81–83] Sympathetic activation is also correlated with increased arrhythmogenesis[84] and sudden death. β-Blockers act by inhibiting the adverse effects of the sympathetic nervous system activation in patients with HF.

BENEFITS OF β-BLOCKERS: *Clinical effects.* Several randomized, double-blind, placebo-controlled trials have shown that long-term use of β-blockers is associated with improved clinical status in patients with HF. Changes in exercise tolerance may not reflect the changes in clinical status because β-blockers blunt exercise-induced changes in heart rate and thus impair performance, even if they improve symptoms. In the Metoprolol in Dilated Cardiomyopathy (MDC) trial,[85] metoprolol increased exercise tolerance, enhanced quality of life, and improved NYHA class at 12 months, but not at 6 months. Treatment with metoprolol controlled-release/extended-release for 6 months did not improve symptoms or tolerance in the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) trial,[86] but when used for an average of 12 months in the Metoprolol Controlled-Release/Extended-Release Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF), it showed a significant improvement in clinical status and NYHA class.[87] Similar improvements in NYHA class were noted when bisoprolol was used for an average of 44 months in the first Cardiac Insufficiency Bisoprolol Study (CIBIS I) trial.[88]

The use of carvedilol in patients with NYHA class II to III was associated with an improvement in symptoms, NYHA class, and overall well-being, but not exercise tolerance.[89–92] Finally, in the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study evaluating patients with NYHA class IV, treatment with carvedilol for an average of 29 months was associated with an improvement in overall well-being.[93] Thus, it appears that clinical improvement with β-blocker therapy becomes evident after a longer period compared with ACE inhibitor treatment.

Effects on mortality and hospitalization. The effects of β-blockers on mortality were evaluated in several trials. The MERIT-HF trial, evaluating metoprolol controlled-release/extended-release, was conducted in almost 4,000 patients mostly (96.4%) with NYHA class II to III.[87] These patients had an EF <0.40 and were receiving ACE inhibitors, diuretics, and digoxin at the time of randomization. Overall, a 34% risk reduction in all-cause mortality was reported in the metoprolol group, with a 49% risk reduction in death caused by HF and 41% decrease in sudden death. The effects were more pronounced in 3.6% of patients who were in NYHA class IV.[94]

The addition of bisoprolol to standard therapy in the CIBIS trial was associated with a nonsignificant 20% reduction in the risk of death ($p = 0.22$) but with a significant 34% decrease in the risk of hospitalization for HF.[88] In the second CIBIS trial, which enrolled predominantly patients with NYHA class III, treatment with bisoprolol was associated with a 34% reduction in mortality, a 20% decrease in the risk of hospitalization for any reason, and a 32% reduction in the risk of hospitalization for HF.[95]

The US Carvedilol Heart Failure Study Group[96] evaluated the clinical effects of carvedilol in patients with HF in a series of 4 protocols. Although it was not a primary end point, overall mortality was significantly decreased by 65% in the carvedilol group when compared with placebo. The risk of cardiovascular-related hospitalization was also significantly decreased by 27%. Both the risk of death from progressive HF and the risk of sudden death were also decreased by carvedilol.[96] In the Australia and New Zealand carvedilol study, which enrolled patients with

NYHA class II to III, carvedilol decreased the risk of disease progression by 26% and reduced the risk of hospitalization for any reason by 23%. Although the trial was not powered to assess mortality, it reported a lower rate of mortality in patients with HF treated with carvedilol than in those who received placebo.[97] Finally, in the COPERNICUS trial, which enrolled patients with NYHA class IV and an EF <0.25, treatment with carvedilol was associated with a 35% reduction in the risk of death and a 24% decrease in the combined risk of death and hospitalization for any reason.[93]

The comparative efficacy of metoprolol and carvedilol is currently under investigation in the Carvedilol or Metoprolol European Trial (COMET),[98] with the results being expected later this year. Because this trial is not a direct comparison of carvedilol with metoprolol controlled-release/extended-release, the agent used in MERIT-HF, the usefulness of the study will be somewhat limited.

Bucindolol was the last of the β-blockers to be evaluated in a clinical trial.[99] The β-Blocker Evaluation of Survival Trial (BEST) produced equivocal results, showing a nonsignificant trend toward a decrease in all-cause mortality in the treatment group (33% vs 30% in the placebo and bucindolol group, respectively; $p = 0.1$). A possible explanation for the apparent difference between the results of this study and those of other β-blocker studies may be the unique pharmacologic properties of bucindolol, a nonselective β-blocking agent with strong β_2-adrenergic blocking and only weak α_1-blocking properties. Thus, bucindolol is uniquely sympatholytic among all β-blocking agents that have been evaluated in trials in patients with HF. Another trial, SR Moxonidine for Congestive Heart Failure (MOXCON), evaluating an agent with central sympatholytic properties, showed that moxonidine increased mortality by $>50\%$, despite decreasing the plasma norepinephrine levels by 23%.[100] Unlike receptor blockade, sympatholysis produces an irreversible loss of adrenergic support to the failing heart, which may be deleterious early in the course of therapy in patients with advanced HF because they are dependent on circulatory catecholamines.

An analysis of the US Carvedilol Heart Failure Study showed that race did not influence the response to carvedilol in patients with HF.[101] Long-term treatment with carvedilol improved cardiac function, lessened symptoms, and reduced the risk of death and hospitalization to a similar degree in both races. Furthermore, the favorable effect of carvedilol on clinical status, NYHA functional class, LVEF, the risk of the combined end point of death or hospitalization, and the progression of HF in African American patients was significant in its own.[101,102]

Effect after myocardial infarction. The effect of long-term β-blocker use in patients after myocardial infarction was tested in the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial. The trial enrolled patients after myocardial infarction with an LVEF <0.40 who were receiving ACE inhibitors for >48 hours. Carvedilol decreased all-cause mortality by 23% and the end point of all-cause mortality or nonfatal recurrent myocardial infarction by 29%.[103]

β-Blockers significantly improve mortality in symptomatic patients with NYHA class II to IV, improve symptoms and EF, and decrease sudden death, the rate of reinfarction in patients with coronary artery disease, and the readmission rate for HF.

RECOMMENDATIONS ON THE USE OF β-BLOCKERS: Based on the results from available studies, the ACC/AHA guidelines recommend that β-blockers should be routinely prescribed to all patients with asymptomatic LV dysfunction and stable HF caused by LV systolic dysfunction, unless they have a contraindication or have been shown to be intolerant to treatment with these drugs.[8,104] Patients should be clinically stable, receive ACE inhibitors (and possibly digoxin), and receive diuretics as needed to control the fluid retention associated with adrenergic blockade.[8,104] β-Blockers should be initiated at very low doses and increased gradually, typically at 2-week intervals, to achieve the target doses from published clinical trials (Table 2). A recent post-hoc analysis of the MERIT-HF trial showed that patients who did not achieve the target metoprolol controlled-release/extended-release dose (200 mg/day) had a similar 38% reduction in mortality as did patients who achieved the target dose.[105] These results support the idea of an individualized dose-titration regimen, which is guided by patient tolerability and the heart rate response.

The safety and feasibility of introducing β-blockers before hospital discharge has been proved in the Initiation Management Predischarge Process for Assessment of Carvedilol Therapy for Heart Failure (IMPACT-HF) trial. Significantly, more patients randomized to carvedilol predischarge were receiving a β-blocker at 60 days as compared with β-blocker initiation at physician discretion >2 weeks after discharge. In addition, significantly more patients randomized to carvedilol predischarge were receiving a higher dose at 60 days.[106] The adverse events were similar in both groups, and predischarge initiation of carvedilol was not associated with an increased risk of worsening HF, increased length of stay, or other serious adverse events.[106]

Only the β-blockers tested in clinical trials should be used because only they have been shown to have a mortality benefit. Some β-blockers have unique molecular structures that can contribute to their beneficial effect (eg, carvedilol is also an α-blocker, increases insulin sensitivity, and has antioxidant properties).[107,108] β-Blockers may differ in their intrinsic sympathomimetic or sympatholytic activity and lipophilicity. Because these pharmacologic differences might translate into therapeutic differences, a class effect cannot be assumed when treating HF.

Patients need not be receiving high doses of ACE inhibitors before being considered for a β-blocker. In patients receiving a low or intermediate dose of an ACE inhibitor, adding a β-blocker may improve symptoms and reduce the risk of death and hospital-

TABLE 2 Target Doses of β-Blockers for Heart Failure as Resulted from Clinical Trials

Agent	Starting Dosage	Target Dosage	Trial
Bisoprolol*	1.25 mg qd	10 mg qd	CIBIS II
Carvedilol	3.125 mg bid	25/50 mg bid	US Carvedilol Heart Failure Studies COPERNICUS
Metoprolol CR/XL	12.5/25 mg qd	200 mg qd	MERIT-HF

CIBIS II = Cardiac Insufficiency Bisoprolol Study II; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival trial; MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure.

*Not approved by the US Food and Drug Administration for treatment of heart failure in the United States; approved for heart failure treatment in several European countries.

TABLE 3 Comparative Effects of 2 Different Strategies in Patients Receiving Low-Dose Angiotensin-Converting Enzyme (ACE) Inhibitors

	Increasing ACE Inhibitor to Maximal Doses	Adding a β-Blocker to the ACE Inhibitor
Effect on symptoms	No change	Improved
Effect on risk of death	8% reduction	30%–40% reduction
Effect on risk of death and hospitalization	12% reduction	20%–40% reduction

Data from the ATLAS trial[38] were used to predict the effect of increasing the dose of the ACE inhibitor from low dose to maximal doses. Data from the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) and the US Carvedilol Study Group.[87,89–93] were used to predict effect of adding a β-blocker to the regimen of patients already taking low-to-intermediate doses of an ACE inhibitor.

Adapted from *Am J Med*.[109]

izations to a greater extent than increasing the dose of the ACE inhibitor to a maximally tolerated dose (Table 3).[109] High doses of an ACE inhibitor could also produce hypotensive effects that might impair the ability of some patients to tolerate β-blocker therapy.

Once the target dose has been achieved, patients can generally be maintained on long-term treatment with little difficulty. Abrupt withdrawal of β-blockers can lead to clinical deterioration and should be avoided, even in hospitalized patients who do not require inotropic support.[8,104]

Initially patients and physicians should be advised that β-blockers can worsen fluid retention and HF symptoms. This can be managed by increasing the diuretic dose to maintain patients at their dry weight. Treatment can also be associated with complaints of fatigue and weakness, which usually resolve in a few weeks.[8,104] Sometimes, it is necessary to decrease the dose of β-blocker or diuretic. Symptomatic bradycardia is also a serious adverse effect of β-blockers and requires a decrease in the dose or sometimes cardiac pacing to allow the use of this vital medication.[8,104] Finally, hypotension is a side effect seen, especially with nonselective blockers such as carvedilol. Usually, it is seen within the first 48 hours of initiation of therapy and subsides with repeated dosing without any change in the dose.[8,104] Administration of ACE inhibitors and diuretics at a different time of day than the β-blockers can minimize the hypotension and dizziness. Patients who exhibit a low systolic blood pressure should be evaluated for orthostatic changes. In the absence of orthostatic changes these patients probably can safely tolerate the addition of β-blockers to their ACE inhibitor and diuretic regimen.

Administration of β-blockers is contraindicated in patients with severe bronchospasm, systolic blood pressure <85 mm Hg, symptomatic bradycardia, or advanced heart block in the absence of a pacemaker.[8,104]

Aldosterone antagonists: BACKGROUND: Despite treatment with an ACE inhibitor or angiotensin II receptor blocker, patients with HF may demonstrate elevated aldosterone levels.[110,111] Mechanisms of "aldosterone escape" include alternative stimuli for aldosterone synthesis (such as adrenocorticotrophic hormone and endothelin), potassium-dependent aldosterone secretion, and reduced aldosterone clearance.[110] Aldosterone may have a number of detrimental effects in HF, such as causing potassium and magnesium wastage, baroreceptor dysfunction, and myocardial fibrosis; it can also decrease the neuronal uptake of norepinephrine, thereby enhancing the risk of cardiac arrhythmias.[42,112,113]

BENEFITS OF ALDOSTERONE ANTAGONISTS: *Clinical benefits and effects on mortality and hospitalization.* The effect of aldosterone-receptor blockade with spironolactone in patients with NYHA class III to IV who are treated with ACE inhibitors, diuretics, and digoxin was evaluated in the Randomized Aldactone Evaluation Study (RALES).[114] This trial showed a 30% reduction in all-cause mortality, a 31% reduction in cardiac deaths, and a 35% reduction for hospitalization for worsening HF. Patients also had a net improvement in symptoms and in NYHA class. Spi-

ronolactone appeared particularly beneficial in patients who were taking digoxin.[114] In the spironolactone group, 10% of men reported gynecomastia or breast pain. Serious hyperkalemia was uncommon in both the placebo and spironolactone groups, but it is seen much more frequently in clinical practice.

Effects after myocardial infarction. The effects of aldosterone antagonists in patients after myocardial infarction complicated by HF with reduced systolic function have been tested in the recently published Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS).[115] The trial randomized patients hospitalized with myocardial infarction, after a mean of 7 days, to eplerenone (a new selective aldosterone antagonist) or placebo in addition to standard medical therapy. Most patients received therapy with ACE inhibitors or angiotensin II receptor blockers (86%), β-blockers (75%), aspirin (88%), diuretics (60%), and statins (47%). The mean eplerenone dose achieved (43 mg daily) produced a significant 15% reduction in the all-cause mortality and a significant 13% reduction in the cardiovascular deaths or hospitalizations for cardiovascular causes.[115] Interestingly, the benefit was more pronounced in the group of patients who received both ACE inhibitors/angiotensin II receptor blockers and β-blockers, and was nonexistent in the patients who received neither class of drug. There was also a significant 21% reduction in the rate of sudden death from cardiac causes.[115] The only significant complication in the eplerenone group was the rate of serious hyperkalemia (5.5% vs 3.9% in the eplerenone and placebo group, respectively). [115]

RECOMMENDATIONS ON THE USE OF ALDOSTERONE ANTAGONISTS: Currently, the ACC/AHA guidelines recommend that spironolactone should be used in patients with recent or current NYHA class IV symptoms, despite use of ACE inhibitors, β-blockers, digoxin, and diuretics. Patients should have serum potassium levels <5 mEq/L and creatinine <2.5 mg/dL before therapy is initiated. Potassium should be monitored within 1 week of initiation and at least every 4 weeks for the first 3 months and every 3 months thereafter. Potassium should be monitored at any dose change in spironolactone or if there is a change in concomitant medications that affects potassium balance. The spironolactone dose (standard 25 mg/day) should be reduced if potassium levels are ≥ 5.4 mEq/L, and treatment should be discontinued if painful gynecomastia or serious hyperkalemia result.[8]

THERAPIES WITH POSSIBLE INCREASE IN SURVIVAL

Angiotensin II receptor blockers: BACKGROUND: These agents block the action of angiotensin II at the receptor level and conceivably could block the effects of angiotensin II produced, not only through the classical ACE pathway, but also by the chymase pathway. Available angiotensin II receptor blockers block only the angiotensin II type 1 receptors (associated with hypertrophy and remodeling) and enhance the activation of angiotensin II type 2 receptors, causing vasodilation.[116] Because some of the side effects of ACE inhibitors, such as angioedema and dry nonproductive cough, may be bradykinin related, an angiotensin II receptor blocker could provide the same beneficial effects as an ACE inhibitor, with fewer side effects.

BENEFITS OF ANGIOTENSIN II RECEPTOR BLOCKERS: *Effects on mortality and hospitalization.* The Evaluation of Losartan in the Elderly (ELITE) trial was conducted to determine whether losartan offers safety and efficacy advantages over ACE inhibition with captopril in the treatment of elderly patients with HF.[117] Although not the primary end point of the study, death and/or hospital admissions for HF were reduced by a nonsignificant 32% in the losartan group. This was attributed to a 46% reduction in all-cause mortality in patients receiving losartan, considered to be because of a reduction in sudden death. The HF hospitalization rate was identical in the 2 groups (5.7%).[117] The hypothesis that losartan might reduce mortality when compared with captopril was tested in a larger follow-up study. ELITE II showed no significant differences in all-cause mortality ($p = 0.16$), sudden death or resuscitated arrests ($p = 0.08$), or hospital admission rates ($p = 0.45$) between the 2 treatment groups.[118] Significantly fewer patients in the losartan group discontinued study treatment because of adverse effects, mainly angioedema and severe cough (9.7% vs 14.7%, $p < 0.001$). Losartan was not superior to captopril in improving survival in elderly patients with HF, but it was significantly better tolerated.[118]

The Valsartan Heart Failure Trial (Val-HeFT) investigators took a different approach, evaluating whether the administration of valsartan to patients with HF conventionally treated (ACE inhibitors, β-blockers, diuretics, and digoxin) would result in a clinical benefit.[119] The addition of valsartan did not improve mortality, but it did reduce the end point of mortality plus nonfatal morbid events, which were predominantly hospitalizations for HF, by 13.2%.[119] More patients in the valsartan group than in the placebo group had improvements in NYHA class (23.1% vs 20.7%) and fewer had worsening (10.1% vs 12.8%; $p < 0.001$). Similarly, dyspnea, fatigue, edema, and rales were more favorably affected by valsartan than by placebo ($p < 0.01$). Analyses of subgroups defined according to background therapy at baseline showed highly significant interactions. For instance, the small subgroup not receiving ACE inhibitors had a 33% reduction in mortality and a 54% reduction in the combined end point of mortality and morbidity with valsartan.[120] The larger subgroup of patients receiving both an ACE inhibitor and a β-blocker had a statistically significant 42% increase in mortality with valsartan ($p = 0.009$) and a trend toward an increase in the mortality and morbidity composite ($p = 0.10$).[119]

Effects after myocardial infarction. There are 2 major studies of angiotensin II receptor blockers in patients post–myocardial infarction that are deemed to clarify the potential clinical value of this mode of inhibiting the renin–angiotensin–aldosterone system. The Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL)[121]

was designed to prove that losartan would be superior or not inferior to captopril in decreasing all-cause mortality in patients with myocardial infarction complicated by systolic dysfunction. Patients were randomly assigned and titrated to a target dose of losartan (50 mg once daily) or captopril (50 mg 3 times daily) as tolerated. There was a trend toward decreased all-cause mortality in the captopril group compared with losartan ($p = 0.07$), and fewer captopril-treated patients had sudden death or a resuscitated cardiac arrest.[121] There was no difference between the 2 groups in fatal or nonfatal reinfarction or in the all-cause hospital admission rates. Losartan was significantly better tolerated than captopril, with fewer patients discontinuing study medication.[121] Critics of the study argue that the dose of losartan was too low because it was not different from that used in the ELITE trials, and a much higher dose (100 mg/day) might have shown a different effect.

The Valsartan in Acute Myocardial Infarction Trial (VALIANT)[122] is an even larger study that is simultaneously addressing whether valsartan can be considered superior to or as good as the proven captopril in high-risk patients with myocardial infarction. In addition, the trial is prospectively designed with equal statistical power to address whether the combination of valsartan and captopril is superior to captopril alone in reducing mortality in this patient population.

RECOMMENDATIONS ON THE USE OF ANGIOTENSIN II RECEPTOR BLOCKERS: The ACC/AHA guidelines recommend that angiotensin II receptor blockers should not be considered equivalent or superior to ACE inhibitors in the treatment of HF with reduced systolic function.[8] They should only be used if a patient has intolerance to ACE inhibitors secondary to intractable cough or angioedema. They are as likely as ACE inhibitors to cause hypotension, worsening renal function, and hyperkalemia.

Because OPTIMAAL showed no statistically significant mortality difference of losartan over captopril in total mortality, ACE inhibitors should remain the first-choice treatment in patients after complicated acute myocardial infarction.

Although the role of losartan and valsartan in patients intolerant of ACE inhibitors is not clearly defined, these drugs can be considered in such patients. When used, angiotensin II receptor blockers should probably be dosed twice daily because of their short half-life.[123]

Their role as an adjunct to ACE inhibitors remains to be defined, but angiotensin II receptor blockers should not be added in patients who are already taking ACE inhibitors and β-blockers.

Combination hydralazine-isosorbide: BACKGROUND: Long-acting nitrates, such as isosorbide dinitrate, are vasodilators and can also inhibit abnormal myocardial and vascular growth, therefore attenuating the remodeling process.[124,125] Hydralazine-isosorbide dinitrate, on the other hand, may interfere with the biochemical and molecular mechanisms responsible for the progression of HF as well as the development of nitrate tolerance.[126,127]

BENEFITS OF HYDRALAZINE-ISOSORBIDE: *Clinical benefits and effects on mortality and hospitalization.* Used alone or together, these agents decrease the preload and afterload, decrease mitral regurgitation, improve cardiac output, increase exercise capacity, modestly increase EF, and prolong survival in patients with HF.[128–131]

The effect of the hydralazine-isosorbide dinitrate combination on survival was evaluated in V-HeFT I.[130] In this trial, patients with NYHA class II to III who were taking digoxin and a diuretic agent were randomized to receive placebo, prazosin, or the combination of hydralazine-isosorbide dinitrate. Compared with placebo, the mortality-risk reduction in the group treated with hydralazine-isosorbide dinitrate was 36% by 3 years.[130] In contrast, the mortality in the prazosin group was similar with the placebo group. The LVEF increased significantly at 8 weeks and at 1 year in the group treated with hydralazine-isosorbide dinitrate, but not in the prazosin or placebo groups.[130] Given the survival benefit of ACE inhibitors in HF, V-HeFT II directly compared the combination of hydralazine-isosorbide dinitrate with enalapril in patients with predominantly NYHA class II to III.[131] Mortality at 2 years was significantly lower in the enalapril group than in the hydralazine-isosorbide dinitrate group (18% vs 25%, $p = 0.016$). In contrast, the combination of hydralazine-isosorbide dinitrate produced more favorable effects on the LVEF and exercise capacity determined by peak oxygen consumption.[131] In both trials, hydralazine-isosorbide dinitrate use produced frequent adverse reactions (primarily headache, gastrointestinal complaints, and fluid retention), and many patients could not continue treatment at target doses. Based on the above trials, the US Food and Drug Administration (FDA) did not find enough evidence to support the approval of the hydralazine-isosorbide dinitrate combination for the treatment of HF.[132]

Subgroup analysis of the V-HeFT trials showed a possible benefit of the hydralazine-isosorbide dinitrate combination in African Americans.[133] Therefore, this hypothesis is being tested in the African-American Heart Failure Trial (A-HeFT),[134] a study that includes African American patients with stable NYHA class III to IV on standard therapy. Patients must have prior HF-related events and an LVEF ≤ 0.35 or an LVEF < 0.45 with LV internal diastolic dimension > 2.9 cm/m^2. Randomization to the addition of placebo or a fixed combination of hydralazine-isosorbide dinitrate is stratified for β-blocker usage. All patients will be treated and observed until the last patient entered completes 6 months of follow-up time. The primary efficacy end point is a composite score, including quality of life, death, and hospitalization for HF.[134] Results are expected this year.

RECOMMENDATIONS ON THE USE OF HYDRALAZINE-ISOSORBIDE USE: Based on the available data, the ACC/AHA guidelines do not recommend the hydralazine-isosorbide dinitrate combination for the treatment of

HF in patients who have no prior use of an ACE inhibitor.[8] Despite the lack of data with the vasodilator combination in patients who are intolerant of ACE inhibitors, the combined use of hydralazine-isosorbide dinitrate may be considered as a therapeutic option in such patients, particularly in African Americans or in those who cannot take an ACE inhibitor because of hypotension or renal insufficiency. However, compliance with this combination has generally been poor because of the large number of tablets required and the high incidence of adverse reactions. There is no controlled experience with the addition of hydralazine-isosorbide dinitrate to therapy with an ACE inhibitor or a β-blocker. Therefore, this combination should not be used in this setting.[8]

SYMPTOMATIC THERAPIES

Digoxin: BACKGROUND: Digoxin exerts its effects by inhibition of sodium-potassium adenosine triphosphatase (Na^+K^+ ATPase). In the myocardium this results in an increase in myocardial contraction.[135,136] Inhibition of Na^+K^+ ATPase in the vagal afferent fibers sensitizes the cardiac baroreceptors, reducing the sympathetic outflow from the central nervous system.[137,138] By inhibiting Na^+K^+ ATPase in the kidney, digoxin reduces the renal tubular reabsorption of sodium, resulting in the suppression of renin secretion from the kidneys.[137] These observations have led to the hypothesis that digoxin acts in HF primarily by attenuating the activation of neurohormonal systems and not as a positive inotropic drug.[137,138]

BENEFITS OF DIGOXIN: *Clinical effects.* The beneficial effects of digoxin in HF include reduced symptoms, improvement in NYHA class, increased exercise time, modestly increased LVEF, enhanced cardiac output, and decreased HF hospitalizations.[138,139] When digoxin is withdrawn from the medical therapy, these benefits are lost, as shown in the Randomized Assessment of Digoxin and Inhibitors of Angiotensin-Converting Enzyme (RADIANCE) and the Prospective Randomized Study of Ventricular Function and the Efficacy of Digoxin (PROVED) trials.[140,141] Their design was similar except that the RADIANCE trial included ACE inhibitors and diuretics as background therapy, whereas in the PROVED study, patients received diuretics only. Digoxin withdrawal has been associated with an increased hospitalization rate, decreased exercise time and EF, and an increased heart rate, body weight, and cardiothoracic ratio on chest x-ray.[140,141]

Effects on mortality and hospitalization. The Digitalis Investigation Group (DIG) trial tested the effects of digoxin on survival in patients with HF in normal sinus rhythm.[142] The trial enrolled 7,788 patients, of whom 87% had systolic dysfunction. They were randomized to a mean dose of 0.25 mg of digoxin or placebo, with a background therapy of ACE inhibitors and diuretic agents. Before enrollment, >50% of the patients in this trial were not receiving digoxin. For both groups, the all-cause mortality was 35% and the cardiovascular mortality was 30%.[142] There was a trend toward a decrease in mortality caused by HF in the digoxin group, but this was offset by an increase in death for other causes that included deaths presumed to result from arrhythmias. Thus, digoxin was shown to have a bidirectional effect on mortality. To date, it is the only positive inotropic agent with a neutral effect on mortality (Table 4). The DIG trial showed that digoxin reduced the risk of hospitalizations as well as the risk for hospitalizations because of worsening HF ($p < 0.001$),[142] confirming the results of the PROVED and RADIANCE trials. Digoxin decreased the need for medical co-intervention for worsening HF, and the benefits were more marked in patients with NYHA class IV, greater cardiothoracic ratio on chest x-ray, or a lower LVEF.[142]

Subgroup analysis from the DIG trial showed a relation between serum digoxin concentration and mortality. In this empirical observation, the risk of death increased significantly if the digoxin level exceeded 1 ng/mL.[143] A post-hoc analysis of the DIG trial showed that the serum digoxin concentration of 0.5 to 0.8 ng/mL is associated with a decrease in all-cause mortality in men. This relation was maintained even after multivariable adjustment: hazard ratio, 0.8 (95% CI, 0.68 to 0.94).[144] A similar analysis for women could not be done because the serum digoxin concentration was not available in most women. A recent post-hoc subgroup analysis of the patients enrolled in the DIG trial showed that women who were randomly assigned to digoxin had a higher rate of death than women who were randomly assigned to placebo (33.1% vs 28.9%).[145] In the multivariable analysis, digoxin was associated with a significantly higher risk of death among women, but it had no significant effect among men. However, because serum digoxin concentrations were measured in <33% of patients at 1 month, the trial had insufficient statistical power to test whether the interaction between sex and digoxin therapy was independent of sex-based differences in serum digoxin concentration.[145] Therefore, it is probably not advisable to stop the digoxin in women, but rather a smaller dose should be given that would result in a serum digoxin concentration <1.0 ng/mL.[145,146]

Recent retrospective cohort analysis of the combined PROVED and RADIANCE databases indicates that patients with a low serum digoxin concentration (0.5 to 0.9 ng/mL) were no more likely to have worsening symptoms of HF on maintenance digoxin than those with moderate (0.9 to 1.2 ng/mL) or high (>1.2 ng/mL) serum digoxin concentrations. All serum digoxin concentration groups were significantly less likely to deteriorate during follow-up study compared with patients withdrawn from digoxin.[147]

RECOMMENDATIONS ON THE USE OF DIGOXIN: According to ACC/AHA guidelines, digoxin should be used to improve symptoms in patients treated with diuretics, ACE inhibitors, and β-blockers. Digoxin could be used to reduce symptoms in patients who have been started on, but have not yet responded symptomatically to, treatment with an ACE inhibitor or a β-blocker, or it could be used in patients who remain symptomatic despite therapy with the neuro-

TABLE 4 Effect of the Study Drug on the Occurrence of Death or Hospitalization Due to Worsening Heart Failure

Variable	No. of Patients with ≥1 Event (% Randomized)		Absolute Difference, % (95% CI)†	Risk Ratio (95% CI)‡
	Digoxin*	Placebo*		
Ejection fraction				
0.25–0.45	613/2,270 (27.0)	735/2,273 (32.3)	−5.3 (−8.0 to −2.7)	0.80 (0.72 to 0.89)
<0.25	428/1,127 (38.0)	556/1,130 (49.2)	−11.2 (−15.3 to −7.2)	0.68 (0.60 to 0.77)
Previous use of digoxin				
Yes	550/1,498 (36.7)	688/1,519 (45.3)	−8.6 (−12.1 to −5.1)	0.74 (0.66 to 0.83)
No	491/1,899 (25.9)	603/1,884 (32.0)	−6.2 (−9.0 to −3.3)	0.77 (0.68 to 0.86)
Cause of heart failure				
Ischemic	731/2,405 (30.4)	873/2,398 (36.4)	−6.0 (−8.7 to −3.3)	0.79 (0.72 to 0.88)
Nonischemic	306/983 (31.1)	413/996 (41.5)	−10.3 (−14.5 to −6.1)	0.67 (0.58 to 0.77)
Cardiothoracic ratio				
≤0.55	600/2,220 (27.0)	724/2,233 (32.4)	−5.4 (−8.1 to −2.7)	0.79 (0.71 to 0.88)
>0.55	441/1,176 (37.5)	567/1,170 (48.5)	−11.0 (−14.9 to −7.0)	0.69 (0.61 to 0.78)
NYHA class				
I or II	601/2,275 (26.4)	739/2,296 (32.2)	−5.8 (−8.4 to −3.1)	0.78 (0.70 to 0.87)
III or IV	438/1,118 (39.2)	552/1,105 (50.0)	−10.8 (−14.9 to −6.7)	0.70 (0.61 to 0.79)
Overall study population	1,041/3,397 (30.6)	1,291/3,403 (37.9)	−7.3 (−9.5 to −5.0)	0.75 (0.69 to 0.82)

CI = confidence interval; NYHA = New York Heart Association.

*Numbers of patients shown for the subgroups do not all add up to the total number in the group because of missing data for some patients.

†Absolute differences were calculated by subtracting the percentage of patients with ≥1 event in the placebo group from the corresponding percentage of patients in the digoxin group (before values were rounded). The p values for the interaction of the variables shown with the study assignments were as follows: ejection fraction, p = 0.02; previous digoxin use, p = 0.54; cause of heart failure, p = 0.11; cardiothoracic ratio, p = 0.02; and NYHA class, p = 0.02.

‡Risk ratios and CIs were estimated from the Cox proportional-hazards model that used the date of the first event. The p values for the interaction of the variables shown with the study assignments were as follows: ejection fraction, p = 0.05; previous digoxin use, p = 0.60; cause of heart failure, p = 0.06; cardiothoracic ratio, p = 0.10; and NYHA class, p = 0.15.

Adapted from *N Engl J Med*.[142]

hormonal antagonists. In patients not taking ACE inhibitors or β-blockers, treatment with digoxin should not be stopped, but appropriate therapy with the neurohormonal antagonists should be instituted.[8] If a patient has atrial fibrillation with a rapid ventricular rate, the β-blocker dose should be increased rather than increasing the dose of digoxin, because higher serum digoxin concentrations are associated with increased adverse effects. The digoxin dose should be low (0.125 mg/day) because this dose was shown to control symptoms and was safe.[8] The drug should be used cautiously in patients who are taking other medications that can depress atrioventricular conduction and should not be used in patients with significant sinus or atrioventricular blocks, unless they have a pacemaker. The major side effects include cardiac arrhythmias (eg, ectopic and reentrant cardiac rhythms and heart block), gastrointestinal symptoms (eg, anorexia, nausea, and vomiting), and neurologic complaints (eg, visual disturbances, disorientation, and confusion). Digitalis toxicity is commonly associated with serum digoxin levels >2 ng/mL, but they may occur with lower digoxin levels, especially if hypokalemia, hypomagnesemia, or hypothyroidism are present.[8]

Diuretics: BACKGROUND: Diuretics inhibit the sodium and water reabsorption at specific sites in the renal tubules. Loop diuretics act on the loop of Henle, and their inhibition of sodium chloride transport exceeds the rate-limited sodium chloride reabsorption in the more distal nephron, thereby producing a maximal diuretic effect equivalent to 20% to 25% of the filtered sodium load. Currently available loop diuretics include furosemide, bumetanide, torsemide, and ethacrynic acid. Because of their potency, they are generally effective in patients with advanced renal insufficiency (glomerular filtration rates <25 mL/min).[148] Distal tubular diuretics, with the exception of metolazone, are generally 6 to 8 times less potent than the loop diuretics and are thus reserved for patients with mild fluid retention. They are ineffective as the glomerular filtration rates decrease to levels <25 to 30 mL/min. Traditionally, they are classified into potassium-wasting (thiazides, chlorthalidone, and metolazone) and potassium-sparing diuretics (triamterene, amiloride, and spironolactone). Potassium-wasting diuretics decrease sodium reabsorption in the cortical segment of the ascending limb of the loop of Henle and the distal convoluted tubule, and they are associated with an increase in urinary potassium excretion. Potassium-sparing diuretics are not potent enough when used alone, but they may be used to avoid the potassium-wasting effects of diuretics that act at more proximal nephron sites.[148]

The plasma half-life of a diuretic determines its frequency of administration. Thiazides and distal tubule diuretics have longer half-lives that allow them to be given once daily or even every other day (eg, metolazone). The plasma half-life of loop diuretics ranges from 1 to 4 hours. Once a dose of a loop diuretic has been administered, its effect dissipates before the next dose is given. During this time, the nephron avidly reabsorbs sodium, resulting in rebound sodium retention that nullifies the prior natriuresis.[148]

BENEFITS OF DIURETICS: *Clinical effects.* Several trials have demonstrated the ability of diuretics to decrease signs of fluid retention in patients with

TABLE 5 Diuretics Used in the Management of Heart Failure

Agent	Starting Dosage	Total Maximal Daily Dosage	Primary Site of Action
Bumetanide	0.5–1 mg qid/bid	10 mg	Loop of Henle
Ethacrynic acid	25 mg qid/bid	50–200 mg	
Furosemide	20–40 mg qid/bid	500 mg	
Torsemide	10–20 mg qid/bid	200 mg	
Chlorothiazide	500 mg qid/bid	500–1,500 mg	Distal tubule (potassium wasting)
Hydrochlorothiazide	25 mg qid/bid	25–100 mg	
Metolazone	2.5–5 mg qid	2.5–20 mg	
Amiloride	5 mg qid	5–20 mg	Distal tubule (potassium sparing)
Spironolactone*	25 mg qid/bid	25–200 mg	
Triamterene	50 mg qid/bid	100–300 mg	

*For use as aldosterone receptor blocker, see text.

HF.[149,150] In these short-term studies, diuretic use has led to a reduction in jugular venous pressures, pulmonary congestion, peripheral edema, and body weight, all observed within days. Diuretics have been shown to improve cardiac function, symptoms, and exercise tolerance in patients with HF.[151] Unfortunately, diuretics activate the neurohormonal vasoconstrictor systems that have been implicated in the progression of the disease, increasing plasma renin activity and concentrations of angiotensin II, aldosterone, and norepinephrine.[152] Long-term diuretic use also decreases circulating concentrations of the vasodilating natriuretic peptides.[152] This imbalance may partially explain the development of progressive diuretic resistance that is commonly seen in advanced HF.

Effects on mortality and hospitalization. There have been no long-term studies of diuretic therapy in HF, and, thus, their effects on morbidity and mortality are not known. A retrospective analysis of the SOLVD trials showed that non–potassium-sparing diuretic use is associated with an increased risk of arrhythmic death (relative risk, 1.33; 95% confidence interval, 1.05 to 1.69; $p = 0.02$).[153] Use of a potassium-sparing diuretic alone or in combination with other diuretics was not associated with increased risk of arrhythmic death (relative risk, 0.9; 95% confidence interval, 0.61 to 1.31; $p = 0.6$).[153] The recently presented Torasemide in Congestive Heart Failure (TORIC) study compared the efficacy of torsemide and furosemide in HF.[154] Although not designed as a mortality study, TORIC showed fewer deaths in the torsemide-treated patients (2.2% vs 4.5% in the torsemide and furosemide group, respectively).[154] The study also showed fewer hypokalemic episodes in the torsemide patients and similar NYHA class improvement in both groups. Another recent published trial suggested that the use of torsemide is associated with fewer HF rehospitalizations and fewer hospital days for HF admission than with the use of furosemide.[155] Although the above trials enrolled a relatively small number of patients, had an open-label design, and the percentage of patients receiving ACE inhibitors and β-blockers was small, these observations deserve further investigation. Thus, it is prudent to use the lowest dose of diuretic that helps control congestion and perhaps use torsemide, which has a more predictable bioavailability and may be safer than furosemide.

RECOMMENDATIONS ON THE USE OF DIURETICS: Diuretics improve symptoms within hours or days, whereas the clinical effects of ACE inhibitors or β-blockers may take weeks or months to become apparent. ACC/AHA guidelines recommend that diuretics be prescribed to all patients who have evidence of fluid retention and that they should be combined with an ACE inhibitor and a β-blocker (and usually digoxin).[8] Therapy is initiated with low doses, and the dose is increased until urine output increases and weight decreases, generally by 0.5 to 1.0 kg/day. The treatment goal is to eliminate physical signs of fluid retention. Once fluid retention has resolved, treatment with the diuretic should be maintained to prevent the recurrence of volume overload. Patients are commonly prescribed a fixed dose of diuretic (Table 5), but the dose should be adjusted periodically, allowing the patient to make changes in dose if his or her weight increases or decreases beyond a specified range.[8] Diuretics should be dosed based on their half-life. Loop diuretics, with a shorter half-life, should be dosed twice daily to prevent rebound sodium retention. Thiazides can be given once daily, and metolazone, which has a longer half-life, can be safely given every other day.[148]

Appropriate dosing of diuretics is crucial for the success of other drugs used in treating HF. Using too low a dose causes fluid retention, which can diminish the response to ACE inhibitors and increase the risk of treatment with β-blockers.[8] Use of inappropriately high doses of diuretics leads to volume contraction, an increased risk of hypotension, and renal insufficiency with ACE inhibitors.[8]

Patients may become unresponsive, even to high doses of diuretics, if their diet contains large amounts of sodium, if they are taking nonsteroidal anti-inflammatory drugs or cyclooxygenase 2 inhibitors, or if they have a significant impairment of renal function.[8] Diuretic resistance can generally be overcome by the intravenous administration of diuretics (including the use of continuous infusions), the use of ≥ 2 diuretics in combination (eg, furosemide and metolazone), or

the use of diuretics together with drugs that increase renal blood flow (eg, positive inotropic agents).[8]

Volume and electrolyte depletion are the most common complications of chronic diuretic therapy. Volume depletion may result in hypotension and/or diminished renal perfusion, leading to the development of prerenal azotemia or acute intrinsic renal failure that may resolve by decreasing the diuretic dose. Hypokalemia and hypomagnesemia may increase the risk of life-threatening ventricular arrhythmias in patients with HF and may contribute to the incidence of sudden death, particularly during treatment with digoxin. Usually, combining ACE inhibitors and, if appropriate, spironolactone, will minimize potassium loss. Magnesium and/or potassium supplements can be given as needed. If hypotension or azotemia is observed, the rapidity of diuresis could be reduced, but diuresis should be maintained until fluid retention is eliminated. Diuretics may also cause metabolic alkalosis, carbohydrate intolerance, hyperuricemia, hypersensitivity reactions, and acute pancreatitis.[8]

THERAPIES THAT ARE NOT BENEFICIAL

Calcium antagonists: Although all calcium antagonists have anti-ischemic properties and cause systemic vasodilation, they have not demonstrated sustained improvement in patients with HF. In fact, worsening symptoms and increased mortality have been reported, possibly because of their negative inotropic effect and reflex neurohormonal activation. The first-generation calcium antagonists, such as diltiazem and nifedipine, were found to exacerbate HF and/or increase mortality in patients after myocardial infarction with pulmonary congestion or an EF <0.40.[156,157] The newer calcium antagonists, amlodipine and felodipine, appear to have less negative inotropic effects and do not have the deleterious effects seen with earlier drugs in this class.

The long-term effect of amlodipine on morbidity and mortality in patients with advanced HF was examined in the Prospective Randomized Amlodipine Survival Evaluation (PRAISE I) trial.[158] Although amlodipine produced a 9% reduction in the combined risk of fatal and nonfatal events and decreased the risk of all-cause mortality by 16%, these reductions were not statistically significant.[158] Amlodipine had no significant effect on mortality in the subset of patients with coronary artery disease. However, in the patients with nonischemic cardiomyopathy, mortality was significantly decreased by 46%, and the combined risk of fatal and nonfatal events was significantly decreased by 31% with amlodipine.[158] Amlodipine had no effect on the frequency of worsening HF associated with hospitalizations or the rate of myocardial infarction, but the amlodipine group had a higher incidence of pulmonary and leg edema, as well as renal failure. To further test the hypothesis that amlodipine benefits patients with nonischemic primary cardiomyopathy, the investigators conducted the PRAISE II trial. The preliminary results did not show any difference in the outcomes between the amlodipine and placebo groups.[159]

V-HeFT III attempted to determine the effect of extended-release felodipine on exercise capacity and HF symptoms after 12 weeks of therapy in male patients being treated with ACE inhibitors and diuretics, but it failed to show any benefit.[160] Overall mortality and the need for hospitalization in patients assigned to receive felodipine did not differ from that in the placebo control group.[160]

Based on available data, calcium antagonists are not recommended for the treatment of HF. Diltiazem, verapamil, and nifedipine should be avoided in patients with HF with reduced systolic function. The vasculoselective agents, such as amlodipine, may be considered for the management of hypertension in patients with LV systolic dysfunction who are also receiving standard HF therapy.

Oral inotropic agents: For many years, HF was considered a defect in cardiac contractility, and positive inotropes have long been considered an attractive pharmacologic target. Although inotropic agents may improve hemodynamics and relieve symptoms in the short term, long-term therapy has failed to produce significant clinical benefits, and, in most instances, it has shown increased mortality in patients with HF. Only digoxin, which has weak inotropic properties, has been shown to have a neutral effect on mortality.[142] Nonglycoside inotropic agents include the following: (1) β-adrenergic drugs (ie, xamoterol), (2) phosphodiesterase inhibitors (ie, amrinone, enoximone, milrinone), (3) dopaminergic agents (ie, ibopamine), and (4) mixed or unknown activity (ie, pimobendan, vesnarinone, flosequinan).

The Xamoterol in Severe Heart Failure Study examined the effect of xamoterol, a β_1-adrenergic selective partial agonist, on survival in patients with NYHA class III to IV.[161] Patients treated with xamoterol had significantly higher rates of all-cause mortality, mortality from progressive HF, and sudden death than those assigned to the placebo group. The excess number of deaths with xamoterol led to early termination of this study.[161]

Phosphodiesterase inhibitors combine positive inotropic activity with vasodilation. They increase cardiac output, decrease LV filling pressures, and lower both vascular resistance and venous tone. The Enoximone Multicenter Trial (EMT) investigated enoximone combined with digoxin and diuretics in patients with NYHA class II to III.[162] Although not a survival trial, EMT showed that enoximone was associated with a higher total mortality and mortality from progressive HF compared with placebo. Enoximone had no effect on HF symptoms or exercise capacity.[162]

The larger Prospective Randomized Milrinone Survival Evaluation (PROMISE) trial assessed the effect of milrinone and conventional therapy on mortality in a population of patients with NYHA class III to IV.[163] Patients treated with milrinone showed a 28% increase in all-cause mortality and a 34% increase in cardiovascular deaths over placebo. Adverse effects of milrinone were apparent in all patient subgroups and were

most pronounced in patients with NYHA class IV, who had a 53% increase in mortality. Treatment with milrinone was also associated with an increased frequency of hospitalization and more frequent study withdrawal because of drug side effects.[163]

Ibopamine interacts with the cardiac β-receptors, producing a weak inotropic response, and with the dopaminergic receptors in peripheral vessels, resulting in decreased peripheral vascular resistance and enhanced renal blood flow in the kidney. Although it appears to improve the neurohormonal profile[164] and is as effective as captopril and diuretics in reducing symptoms of HF,[165] the second Prospective Randomized Study of Ibopamine on Mortality and Efficacy (PRIME II) trial showed a significantly higher death rate in the ibopamine-treated patients than with placebo.[166]

The Pimobendan in Congestive Heart Failure (PICO) trial evaluated the effect of pimobendan, a positive inotropic agent with a dual mechanism of action involving both calcium sensitization and phosphodiesterase inhibition properties, on exercise capacity in patients with NYHA class II to III.[167] Addition of pimobendan to standard therapy with a diuretic agent and an ACE inhibitor resulted in a significant increase in exercise capacity after 24 weeks of treatment compared with placebo. No significant effect on oxygen consumption or quality of life was noted, but overall mortality during the treatment and follow-up period was 1.8 times greater in patients treated with pimobendan than in those receiving placebo.[167]

Vesnarinone is a phosphodiesterase inhibitor and a potassium antagonist. Its effect on mortality in patients with symptomatic HF was evaluated in 2 trials. The smaller Vesnarinone Study Group (VeSG) trial showed that patients who received vesnarinone 60 mg/day, digoxin, and ACE inhibitors had a 62% decrease in all-cause mortality and a 50% reduction in morbidity and mortality combined.[168] In contrast to the favorable effect on mortality seen with 60 mg/day of vesnarinone, a doubling of the dose to 120 mg/day increased mortality. Therefore, this arm of the study was discontinued.[168] Subsequently, the larger Vesnarinone Trial (VEST) examined mortality in 3,600 patients observed for 9 months. A 26% increase in all-cause mortality occurred with the 60-mg/day dose of vesnarinone.[169] A statistically nonsignificant 14% increase in all-cause mortality was observed in patients receiving 30 mg/day of vesnarinone. Because of the mortality findings, VEST was prematurely discontinued.[169] Based on these trials that indicated increased mortality, oral inotropic agents are contraindicated in the management of HF.

Only a few small trials evaluated the intermittent or continuous long-term use of intravenous inotropes in the management of HF. The disappointing results suggested little efficacy and an increase in mortality.[170–172] Recently published trials showed that even short-term use of intravenous inotropes for management of HF exacerbations is associated with increased mortality in the long run and does not result in any significant symptomatic improvement over placebo.[173,174] Given the lack of convincing evidence of clinical benefit and the abundant evidence of increased mortality, the ACC/AHA guidelines recommend that intravenous inotropes should not be used intermittently or continuously in the treatment of patients with HF and should be considered only as palliative therapy for end-stage disease.[8]

Systemic vasodilators: HF is characterized by decreased cardiac performance, which leads to neurohormonal activation, resulting in increased systemic vascular resistance that causes further decrease in cardiac performance. Improvement in hemodynamics with vasodilators was thought to prevent progression of HF and improve survival. The effect of several direct vasodilators on mortality in patients with HF was evaluated in clinical trials and produced disappointing results.

Flosequinan is a direct vasodilator with dose-dependent positive inotropic and chronotropic effects. The Prospective Randomized Flosequinan Longevity Evaluation (PROFILE) trial evaluated the efficacy of flosequinan in patients with NYHA class III to IV. The study was terminated prematurely because of a 41% increase in the risk of death in patients treated with flosequinan.[175] Flosequinan may increase levels of circulating neurohormones[176] and heart rate, and the activation of the neurohormonal system may contribute to the progression of HF. Initially approved by the FDA for therapy of HF, flosequinan was withdrawn based on the results of PROFILE.

Epoprostenol causes direct vasodilation of the pulmonary and systemic arteries, resulting in a reduction in afterload, as well as increased cardiac output and stroke volume. An initial pilot study in 33 patients with advanced HF reported significant improvement in the 6-minute walk test and a trend toward improved survival in patients receiving continuous intravenous infusion of epoprostenol.[177] The Flolan International Randomized Survival Trial (FIRST) showed that intravenous epoprostenol combined with standard therapy was associated with a higher overall mortality compared with standard therapy alone.[178] This observation led to the premature discontinuation of the trial. Because of the negative effects of these drugs on survival, they should not be used in the treatment of HF.

Antiarrhythmic agents: Ventricular ectopic activity is common in patients with HF. Sudden cardiac death, frequently resulting from ventricular arrhythmias, accounts for 40% to 50% of the mortality in these patients.[179,180] Empirical antiarrhythmic therapy for patients with HF has no proven benefit and has been associated with a higher incidence of proarrhythmic complications in patients with LV systolic dysfunction.[181] After the increased mortality seen in the Cardiac Arrhythmia Suppression Trial (CAST) and in CAST II, class I antiarrhythmics are contraindicated in the treatment of patients with HF.[182,183]

Amiodarone is an antiarrhythmic agent with low proarrhythmic potential and a favorable hemodynamic profile. Several studies evaluated the effect of amiodarone on mortality in patients with HF. In the Grupo

de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA), amiodarone 300 mg/day, combined with standard therapy in patients with NYHA class II to IV, was associated with a 28% reduction in the risk of death and a 31% reduction in the combined risk of death or hospitalization for worsening HF in patients with advanced disease.[184] There was trend toward a reduction in the risk of death because of progressive HF and the risk of sudden death.[184]

The Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure (HF-STAT) involved patients with mild HF and asymptomatic ventricular arrhythmias, manifested as >10 premature ventricular contractions per hour.[185] No significant differences in overall mortality, sudden death, or death from overt HF were detected between the amiodarone and placebo treatment groups for the study population as a whole or for the subgroup of patients with coronary artery disease. However, a trend toward a reduction in overall mortality was noted among amiodarone-treated patients with nonischemic cardiomyopathy. Amiodarone suppressed ventricular arrhythmias and improved the LVEF.[185]

The European Myocardial Infarct Amiodarone Trial (EMIAT) assessed the effect of amiodarone versus placebo in patients after myocardial infarction with an EF <0.40. Amiodarone had no significant effect on total mortality in these patients. Sudden death, however, was decreased by 35% with amiodarone. A favorable interaction was apparent between the concomitant use of β-blockers and cardiac mortality, independent of LV function.[186]

Because of the conflicting evidence and its known toxicity, the prophylactic use of amiodarone to prevent sudden cardiac death in patients with HF is not recommended in the current ACC/AHA guidelines.[8] It should be used in combination with a β-blocker and an implantable cardioverter defibrillator in patients with a history of sudden death, ventricular fibrillation, or sustained ventricular tachycardia.[8] Patients on amiodarone therapy should be monitored for the occurrence of thyroid, ocular, pulmonary, or hepatic abnormalities. Thyroid and liver function tests, as well as chest x-ray, should be assessed at baseline and every 6 months during therapy. Pulmonary function tests should be obtained at baseline and repeated only if findings on follow-up chest x-ray are abnormal. Patients taking amiodarone, digoxin, and warfarin should be carefully monitored for drug interactions.[8]

The Survival with Oral *d*-sotalol (SWORD) trial examined the effect of treatment with *d*-sotalol in patients with a previous myocardial infarction and LV dysfunction. The study was terminated prematurely because of a statistically significant 65% increase in the risk of death in the *d*-sotalol group. The higher mortality was attributable to an excess of presumed arrhythmic deaths, which were increased by 77%.[187] Consequently, sotalol is contraindicated in patients with HF.

ANTICOAGULATION AND ANTIPLATELET AGENTS

Theoretically, patients with HF have an increased risk of thromboembolic events because of stasis of blood in the cardiac chambers[188] and increased activity of procoagulant factors.[189] However, in large studies, the risk of thromboembolism in clinically stable patients has been only 1% to 3% per year, even in those with a very low EF and echocardiographic evidence of intracardiac thrombi.[190,191] Because the benefit–risk ratio is low, anticoagulation is not justified in these patients. Currently, there are no published controlled trials of warfarin or other antithrombotic agents in patients with HF, but in several retrospective analyses, the risk of thromboembolic events in patients taking warfarin was not lower than in patients not treated with antithrombotic drugs.[190] Currently, the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) study is evaluating the role of aspirin, clopidogrel, and warfarin in patients with HF. In the absence of definitive trials, it is not clear how anticoagulants should be prescribed in patients with HF. According to the ACC/AHA guidelines, anticoagulation with warfarin is most justified in patients with HF who have had a previous embolic event or who have paroxysmal or chronic atrial fibrillation,[8,192] and it probably should not be prescribed in patients who are in normal sinus rhythm, even with a low EF.[8]

INVESTIGATIONAL THERAPIES

Vasopeptidase inhibitors: HF is characterized not only by enhanced activation of endogenous vasoconstrictor neurohormonal systems, such as the renin–angiotensin–aldosterone system or endothelin, but also by the diminished responses to endogenous vasodilator systems, such as natriuretic peptides.[193] Recently, there has been interest in the development of vasopeptidase inhibitors that block not only the ACE, which leads to decreased levels of angiotensin II, but also the neutral endopeptidase, which leads to enhanced activity of endogenous vasodilators.[193] In the Inhibition of Metalloproteinase BMS-186716, Omipatrilat, in a Randomized Exercise and Symptom Study (IMPRESS), patients with NYHA class II to IV were randomized to receive either omapatrilat or lisinopril. Exercise treadmill test performance improved similarly in both groups.[194] Omapatrilat-treated patients with NYHA class III to IV had a greater functional improvement than those treated with lisinopril, and there was a trend in favor of omapatrilat on the combined end point of death or admission for worsening HF ($p = 0.052$).[194] However, the much larger Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) produced disappointing results. When compared with enalapril, omapatrilat did not reduce significantly the rate of death and HF hospitalizations (the primary end point) or all-cause mortality. Treatment with omapatrilat was associated with more hypotensive episodes than ena-

lapril.[195] Thus, at present, this drug class has no role in HF management.

Cytokine antagonists: Patients with HF have elevated levels of tumor necrosis factor that correlate with the severity of symptoms.[196] Tumor necrosis factor has been associated with LV dysfunction, cardiomyopathy, and pulmonary edema.[197–199] It was proposed that etanercept, an antagonist of tumor necrosis factor, might be effective in the treatment of HF. Based on pilot data of survival benefit with tumor necrosis factor antagonism,[200] the Randomized Etanercept North American Strategy to Study Antagonism of Cytokines (RENAISSANCE) and the Research into Etanercept Antagonism in Ventricular Dysfunction (RECOVER) trials enrolled patients with NYHA class II to IV who were treated with placebo or various doses of etanercept. The Randomized Etanercept World-Wide Evaluation (RENEWAL) results pooled all patients from both trials for a combined primary end point of all-cause mortality and HF hospitalization. However, in 2001 when interim analysis indicated that therapy would not demonstrate benefit, the studies were stopped by their steering committees. Analysis of hazard ratios for death/worsening HF showed that in the RECOVER study, patients receiving the higher dose appeared to show slightly better results than those receiving the lower dose.[201] In the RENAISSANCE study, the hazard ratio was increased in both of the etanercept treatment groups. There was a trend toward an increased risk of death in the etanercept group for both studies combined (odds ratio, 1.10). There was also an indication of worse outcome in patients with nonischemic HF and in those aged <65 years. It was concluded that although the RENEWAL study did not conclusively demonstrate harm, the risk ratio for worsening HF was increased in the RENAISSANCE study, and it was suggested that etanercept be used with caution in patients with rheumatoid arthritis with concomitant HF.[201]

Infliximab is a monoclonal antibody that binds to tumor necrosis factor, thereby inhibiting its action. The Effects of Anti-Tumor Necrosis Factor-α Therapy Against Chronic Heart Failure (ATTACH) trial was designed as a pilot trial to assess the efficacy and safety of infliximab in HF.[202] Patients with NYHA class III to IV on standard therapy were randomized to 2 doses of infliximab (low and high) and placebo. There were strong trends toward an increase in the percentage of patients with worsening clinical status, largely because of an increase in deaths or hospitalization for HF at week 28 in the infliximab groups. It was concluded that infliximab did not improve outcomes in HF and that it was associated with an increased incidence of worsening of HF, which continued after therapy was stopped. In view of these findings, the investigators concluded that infliximab should be avoided in patients with HF.[202]

Endothelin antagonists: Endothelins are a family of peptides that mediate vascular tone. Endothelin-1 is a potent vasoconstrictor that can adversely affect the structure and function of the heart and peripheral blood vessels.[203] Circulating levels of endothelin-1 are elevated in patients with HF,[204] and they correlate with symptomatic and hemodynamic severity.[205] There are 2 types of endothelin-1 antagonists under evaluation: those that block the receptors for endothelin-1 and those that inhibit the endothelin-converting enzyme. So far, clinical studies have evaluated endothelin receptor blockers only. The Enrasentan Cooperative Randomized Evaluation (ENCOR) trial randomized 419 patients with NYHA class II to III to several arms: enrasentan (a combined endothelin A/B receptor antagonist) at 3 doses, high-dose enalapril, and placebo. All patients received standard therapy that included digoxin, diuretics, β-blockers, vasodilators, and "standard doses" of ACE inhibitors.[206] There was no dose response seen in the enrasentan group. There was no statistically significant difference when all groups treated with enrasentan were compared with placebo. However, there was a trend toward favoring placebo ($p = 0.0644$). There was also a trend toward higher mortality and a higher incidence of adverse effects in the enrasentan group.[206]

The Research on Endothelin Antagonism in Chronic Heart Failure (REACH 1) trial studied bosentan (a combined endothelin A/B receptor antagonist) in patients with NYHA class III to IV. The study had to be terminated early because of elevated hepatic transaminases, which were reversible on drug cessation. Of the patients who completed the study, there was a 41% reduction in all-cause hospitalization.[207] The Endothelin Antagonists Cooperative Randomized Evaluation (ENABLE) trial consisted of 2 parallel identical studies, ENABLE-1 in the United States and ENABLE-2 in Europe, Israel, and Australia.[208] It compared bosentan (at much lower doses than used in REACH 1) with placebo. There was no statistical difference in the rate of cardiac death or HF hospitalization or in all-cause mortality with bosentan over placebo.[208] There was a significant increase in both body fluid retention and elevated liver function enzymes in those randomized to treatment with bosentan. Thus, endothelin antagonists with the doses and agents studied to date offer no benefit and can cause potential harm if used in patients with chronic HF.

The fourth Randomized Intravenous Tezosentan (RITZ 4) trial is a recently completed trial evaluating the effects of tezosentan, a dual endothelin A/B receptor antagonist, in patients with acute HF in the setting of an acute coronary syndrome.[209] The results are expected later this year.

Vasopressin$_2$ receptor antagonists: Arginine vasopressin is a nonpeptide hormone with cardiovascular and renal effects mediated through 2 receptor subtypes: the vasopressin$_{1A}$ receptor, found on vascular smooth muscle cells and in the myocardium, and the vasopressin$_2$ receptors, found in the distal tubule of the kidney.[210,211] Stimulation of the vasopressin$_{1A}$ receptor results in vasoconstriction in the peripheral and coronary circulations and has other effects, such as increasing the myocardial intracellular calcium levels and myocyte hypertrophy.[210–212] The vasopressin$_2$ receptor mediates renal water retention and is predom-

TABLE 6 Effects of Drugs in Heart Failure (HF) with Reduced Systolic Function

Agent	Symptoms	Worsening/Hospitalization for HF	Mortality
ACE inhibitors	Improve	Decrease	Decrease in asymptomatic and NYHA class II to IV patients
β-Blockers (bisoprolol, carvedilol, and metoprolol CR/XL)	Improve	Decrease	Decrease in NYHA class II to IV patients
ARB (valsartan)	Improve	Decrease	May decrease in ACE inhibitor–intolerant patients May increase in patients taking both ACE inhibitors and β-blockers
Aldosterone receptor antagonists (spironolactone)	Improve	Decrease	Decrease in NYHA class III to IV patients
Hy-ISDN	No effect	No effect	May decrease, especially in African Americans
Digoxin	Improve	Decrease	Neutral or may increase when SDC >1 ng/mL or may decrease when SDC is 0.5 to 0.8 ng/mL
Loop diuretics	Improve	Decrease	May Increase
Calcium antagonists (amlodipine)	May worsen	No effect	No effect
Inotropic agents (oral and IV)*	May improve	No effect	Increase
Systemic vasodilators†	May improve	No effect	Increase

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; EF = ejection fraction; IV = intravenous; NYHA = New York Heart Association; SDC = serum digoxin concentration.

*Other than digoxin.

†Epoprostenol and flosequinan.

inantly responsible for the antidiuretic effect of this hormone.[210,211] In HF and LV dysfunction, arginine vasopressin release is stimulated by baroreceptors sensing changes in intra-arterial plasma volume and neurohormones, such as angiotensin II.[212]

A recent study evaluating the hemodynamic effects of an intravenous combined vasopressin$_{1A}$ and vasopressin$_2$ receptor antagonist in patients with advanced HF showed that short-term antagonism of arginine vasopressin receptors with conivaptan produced favorable hemodynamic and renal effects.[213] Decreases in pulmonary capillary wedge pressure and right atrial pressure were accompanied by substantial increases in urine output, without affecting systemic blood pressure, heart rate, or serum electrolytes.[213]

A recently presented study assessed the effects of 3 different doses of tolvaptan, an oral vasopressin$_2$ receptor antagonist, administered for 25 days in patients with HF and NYHA class II to III with signs of congestion. Patients were on stable doses of furosemide. Treatment with tolvaptan was associated with a significant increase in urine output and decrease in body weight compared with placebo, which was evident at 24 hours and was maintained for the duration of the study.[214] Marked reduction in leg edema was observed in the tolvaptan group compared with placebo.[214] Tolvaptan normalized serum sodium in patients with baseline hyponatremia and did not increase the serum sodium above normal values in patients with normal levels at baseline.[215] Treatment with tolvaptan was not associated with changes in blood pressure or in serum potassium.[214,215]

The short-term and long-term effects of tolvaptan in patients admitted for worsening HF were tested in the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV-CHF) trial. The trial enrolled patients in NYHA class III to IV with signs of congestion who were randomized to 3 different doses of tolvaptan or placebo that were continued for 7 weeks after discharge.[216] The primary end points of the study are change in body weight within 24 hours after the first in-hospital dose and clinical worsening of HF within 60 days. The results are expected this year.[216]

CONCLUSION

HF is a progressive syndrome, and the pharmacologic treatment has become a combined symptomatic–preventive management strategy. Ideally, treatment should be started for patients at risk and when structural damage is not yet done. However, if patients progress to symptomatic LV dysfunction, certain therapies have shown a benefit in improving symptoms and mortality (Table 6). The mainstays of therapy are ACE inhibitors and β-blockers (bisoprolol, carvedilol, and metoprolol CR/XL) with diuretics to control fluid retention. If patients manifest hypotension because of the medications, it is better to use lower doses of ACE inhibitors and β-blockers combined than the maximum dose of either agent alone and/or to space the administration of these drugs throughout the day. If patients are intolerant to ACE inhibitors because of intractable cough or angioedema, valsartan can be substituted. Aldosterone antagonists are recommended in patients with stable NYHA class III to IV who are symptomatic despite standard therapy and who have a serum creatinine level of <2.5 mg/dL and a potassium level of <5.0 mEq/L. Low-dose digoxin yielding a serum digoxin concentration <1 ng/mL could be added to

improve symptoms. The combination hydralazine-isosorbide dinitrate could be used if ACE inhibitors or valsartan are not tolerated, especially in African Americans. Amiodarone is recommended together with a β-blocker and an implantable cardioverter defibrillator in patients with a history of sudden death, ventricular fibrillation, or sustained ventricular tachycardia. Anticoagulation is recommended only in patients who have had a previous embolic event or who have paroxysmal or chronic atrial fibrillation. Finally, calcium antagonists should be avoided in patients with HF and reduced systolic function.

1. American Heart Association. *2002 Heart and Stroke Statistical Update*. Dallas, TX: American Heart Association, 2002.
2. Miller LW, Missov ED. Epidemiology of heart failure. *Cardiol Clin* 2001;19: 547–555.
3. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, Murabito JM, Vasan RS. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med* 2002;347:1397–1402.
4. Zannad F, Briancon S, Juilliere Y. Incidence, clinical and etiologic features, and outcomes of advanced chronic heart failure: the EPICAL Study. *J Am Coll Cardiol* 1999;33:734–742.
5. Haldeman GA, Croft JB, Giles WH, Rashidee A. Hospitalization of patients with heart failure: National Hospital Discharge Survey, 1985 to 1995. *Am Heart J* 1999;137:352–360.
6. O'Connell JB, Bristow MR. Economic impact of heart failure in the United States: time for a different approach. *J Heart Lung Transplant* 1994;13:S107–S112.
7. Malek M. Health economics of heart failure. *Heart* 1999;82:IV11–IV13.
8. Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldman AM, Francis GS, Ganiats TG, Goldstein S, Gregoratos G, Jessup ML, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. 2001. Available at: http://www.acc.org. Accessed February 22, 2003.
9. Gheorghiade M, Gattis WA, O'Connor CM. Treatment gaps in the pharmacological management of heart failure. *Rev Cardiovasc Med* 2002;3:S11–S19.
10. Felker GM, O'Connor CM. Inotropic therapy for heart failure: an evidence-based approach. *Am Heart J* 2001;142:393–401.
11. Gheorghiade M, Bonow RO. Chronic heart failure in the United States: a manifestation of coronary artery disease. *Circulation* 1999;97:282–289.
12. Bart BA, Shaw LK, McCants CB, Fortin DF, Lee KL, Califf RM, O'Connor CM. Clinical determinants of mortality in patients with angiographically proven ischemic and non-ischemic cardiomyopathy. *J Am Coll Cardiol* 1997;30:1002–1008.
13. Mathew J, Davidson S, Narra L, Hafeez T, Garg R. Etiology and characteristics of heart failure in blacks. *Am J Cardiol* 1996;78:1447–1450.
14. Yancy CW. Heart failure in African Americans: a cardiovascular enigma. *J Card Fail* 2000;6:183–186.
15. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction. *J Am Coll Cardiol* 1999;33:1948–1955.
16. Senni M, Tribouilloy CM, Rodeheffer RJ, Jacobsen SJ, Evans JM, Bailey KR, Redfield MM. Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. *Circulation* 1998;98:2282–2289.
17. Kitzman DW, Gardin JM, Gottdiener JS, Arnold A, Boineau R, Aurigemma G, Marino EK, Lyles M, Cushman M, Enright PL, for the Cardiovascular Health Study Research Group. Importance of heart failure with preserved systolic function in patients ≥65 years of age: Cardiovascular Health Study. *Am J Cardiol* 2001;87:413–419.
18. Choudhury L, Gheorghiade M, Bonow RO. Coronary artery disease in patients with heart failure and preserved systolic function. *Am J Cardiol* 2002; 89:719–722.
19. Bourassa MG, Gurne O, Bangdiwala SI, Ghali JK, Young JB, Rousseau M, Johnstone DE, Yusuf S, for the Studies of Left Ventricular Dysfunction (SOLVD) Investigators. Natural history and patterns of current practice in heart failure. *J Am Coll Cardiol* 1993;22(suppl A):14A–19A.
20. Gheorghiade M, Cody RJ, Francis GS, McKenna WJ, Young JB, Bonow RO. Current medical therapy for advanced heart failure. *Am Heart J* 1998;135:S231–S248.
21. Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation* 1993;88:107–115.
22. Stevenson WG, Stevenson LW, Middlekauff HR, Saxon LA. Sudden death prevention in patients with advanced ventricular dysfunction. *Circulation* 1993; 88:2953–2961.
23. Braunwald E, Bristow MR. Congestive heart failure: fifty years of progress. *Circulation* 2002;102:IV14–IV23.
24. Mann D. Mechanisms and models in heart failure: a combinatorial approach. *Circulation* 1999;100:999–1008.
25. Francis GS. Pathophysiology of chronic heart failure. *Am J Med* 2001;110: 37S–46S.
26. Ambrosio G, Betocchi S, Pace L, Losi MA, Perrone-Filardi P, Soricelli A, Piscione F, Taube J, Squame F, Salvatore M, Weiss JL, Chiariello M. Prolonged impairment of regional contractile function after resolution of exercise induced angina: evidence of myocardial stunning in patients with coronary artery disease. *Circulation* 1996;94:2455–2464.
27. Bonow RO. The hibernating myocardium: implications for management of congestive heart failure. *Am J Cardiol* 1995;75(suppl):17A–25A.
28. Elsasser A, Schlepper M, Klovekorn WP, Cai W, Zimmermann R, Muller KD, Strasser R, Kostin S, Gagel C, Munkel B, Schaper W, Schaper J. Hibernating myocardium: an incomplete adaptation to ischemia. *Circulation* 1995;92:2920–2931.
29. Sabbah HN. Apoptotic cell death in heart failure. *Cardiovasc Res* 2000;45: 704–712.
30. Taneja T, Gheorghiade M, Bonow RO. Heart failure in the new millennium: emerging concepts in its pathophysiology. *Advances in Rehabilitation* 2000;10: 61–76.
31. Paulus WJ, Vantrimpont PJ, Shah AM. Paracrine coronary endothelial control of left ventricular function in humans. *Circulation* 1995;92:2119–2126.
32. Colucci WS. Myocardial endothelin: does it play a role in myocardial failure? *Circulation* 1996;93:1069–1072.
33. Deedwania P. Endothelin, the bad actor in the play: a marker or mediator of cardiovascular disease. *J Am Coll Cardiol* 1999;33:939–942.
34. Murray DR, Prabhu SD, Chandrasekar B. Chronic β-adrenergic stimulation induces myocardial proinflammatory cytokine expression. *Circulation* 2000;101: 2338–2341.
35. Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. *N Engl J Med* 1990;223:236–241.
36. Torre-Amione G, Kapadia S, Lee J, Durand JB, Bies RD, Young JB, Mann DL. Tumor necrosis factor-α and tumor necrosis factor receptors in the failing human heart. *Circulation* 1996;93:704–711.
37. Bozkurt B, Kribbs SB, Clubb FJ, Michael LH, Didenko VV, Hornsby PJ, Seta Y, Oral H, Spinale FG, Mann DL. Pathophysiologically relevant concentrations of tumor necrosis factor-α promote progressive left ventricular dysfunction and remodeling in rats. *Circulation* 1998;97:1382–1391.
38. Bazzoni F, Beutler B. The tumor necrosis factor ligand and receptor families. *N Engl J Med* 1996;334:1717–1725.
39. Weber KT. Extracellular matrix remodeling in heart failure. *Circulation* 1997;96:4065–4082.
40. Grassi G, Cattaneo BM, Seravalle G, Lanfranchi A, Pozzi M, Morganti A, Carugo S, Mancia G. Effects of chronic ACE inhibition on sympathetic nerve traffic and baroreflex control of circulation in heart failure. *Circulation* 1997;96: 1173–1179.
41. Gilbert EM, Sandoval A, Larrabee P, Renlund DG, O'Connell JB, Bristow MR. Lisinopril lowers cardiac adrenergic drive and increases β-receptor density in the failing human heart. *Circulation* 1993;88:472–480.
42. MacFadyen RJ, Barr CS, Struthers AD. Aldosterone blockade reduces vascular collagen turnover, improves heart rate variability, and reduces early morning rise in heart failure patients. *Cardiovasc Res* 1997;35:30–34.
43. Francis GS. The relationship of the sympathetic nervous system and the renin-angiotensin system in congestive heart failure. *Am Heart J* 1989;118:642–648.
44. Rahman SN, Kim GE, Mathew AS, Goldberg CA, Allgren R, Schrier RW, Conger JD. Effects of atrial natriuretic peptide in clinical acute heart failure. *Kidney Int* 1994;45:1731–1738.
45. Gerdes AM, Kellerman SE, Moore JA, Muffly KE, Clark LC, Reaves PY, Malec KB, McKeown PP, Schocken DD. Structural remodeling of cardiac myocytes from patients with chronic ischemic heart disease. *Circulation* 1992; 86:426–430.
46. Kono T, Sabbah HN, Stein PD, Brymer JF, Khaja F. Left ventricular shape as a determinant of functional mitral regurgitation in patients with severe heart failure secondary to either coronary artery disease or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1991;68:355–359.
47. Nass O, Rosman H, Al-Khaled N, Shimoyama H, Alam M, Sabbah HN, Goldstein S. Relation of left ventricular chamber shape in patients with low (≤40%) ejection fraction to severity of functional mitral regurgitation. *Am J Cardiol* 1995;76:402–404.
48. Edwards NC, Sinusas AJ, Bergin JD, Watson DD, Ruiz M, Beller GA. Influence of subendocardial ischemia on transmural myocardial function. *Am J Physiol* 1992;262:H568–H576.
49. Unverferth DV, Magorien RD, Lewis RP, Leier CV. The role of subendocardial ischemia in perpetuating myocardial failure in patients with nonischemic congestive cardiomyopathy. *Am Heart J* 1983;105:176–179.
50. Leiden JM. The genetics of dilated cardiomyopathy: emerging clues to the puzzle. *N Engl J Med* 1997;337:1080–1081.
51. Olson TM, Michels VV, Thibodeau SN, Tai YS, Keating MT. Actin mutations in dilated cardiomyopathy: a heritable form of heart failure. *Science* 1998; 280:750–752.
52. Liggett SB, Wagoner LE, Craft LL, Hornung RW, Hoit BD, McIntosh TC,

Walsh RA. The Ile164 β_2-adrenergic receptor polymorphism adversely affects the outcome of congestive heart failure. *J Clin Invest* 1998;102:1534–1539.
53. Small KM, Wagoner LE, Levin AM, Kardia SLR, Liggett SB. Synergistic polymorphisms of β_1- and α_{2C}-adrenergic receptors and the risk of congestive heart failure. *N Engl J Med* 2002;347:1135–1142.
54. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu AHB, et al, for the Breathing Not Properly Multinational Study Investigators. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002;347:161–167.
55. Cheitlin MD, Alpert JS, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davidson TW, Davis JL, Douglas PS, Gillam LD, et al. ACC/AHA guidelines for the clinical application of echocardiography: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Clinical Application of Echocardiography). *J Am Coll Cardiol* 1997;29:862–879.
56. Bristow MR, Port JD, Kelly RA. Inhibitors of the renin-angiotensin-aldosterone system. In: Braunwald E, Libby P, Zipes DD, Zipes DP, eds. *Heart Disease: A Textbook of Cardiovascular Medicine.* Philadelphia: WB Saunders, 2001:582–583.
57. Bastien NR, Juneau AV, Ouellette J, Lambert C. Chronic AT1 receptor blockade and angiotensin-converting enzyme inhibition in (HF 146) cardiomyopathic hamsters: effects on cardiac hypertrophy and survival. *Cardiovasc Res* 1999;43:77–85.
58. Brown NJ, Ryder D, Gainer JV, Morrow JD, Nadeau J. Differential effects of angiotensin-converting enzyme inhibitors on the vasodepressor and prostacyclin responses to bradykinin. *J Pharmacol Exp Ther* 1996;279:703–712.
59. Sharpe DN, Murphy J, Coxon R, Hannan SF. Enalapril in patients with chronic heart failure: a placebo-controlled, randomized, double-blind study. *Circulation* 1984;70:271–278.
60. The Captopril-Digoxin Multicenter Research Group. Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. *JAMA* 1988;259:539–544.
61. The Captopril Multicenter Research Group. A placebo-controlled trial of captopril in refractory chronic congestive heart failure. *J Am Coll Cardiol* 1983;2:755–763.
62. LeJemtel TH, Keung E, Frishman WH, Ribner HS. Hemodynamic effects of captopril in patients with severe heart failure. *Am J Cardiol* 1982;49:1484–1488.
63. DiCarlo L, Chatterjee K, Parmley WW, Swedberg K, Atherton B, Curran D, Cucci M. Enalapril: a new angiotensin-converting enzyme inhibitor in chronic heart failure: acute and chronic hemodynamic evaluations. *J Am Coll Cardiol* 1983;2:865–871.
64. Awan NA, Amsterdam EA, Hermanovich J, Bommer WJ, Needham KE, Mason DT. Long-term hemodynamic and clinical efficacy of captopril therapy in ambulatory management of chronic congestive heart failure. *Am Heart J* 1982; 103:474–479.
65. Konstam MA, Rousseau MF, Kronenberg MW, Udelson JE, Melin J, Stewart D, Dolan N, Edens TR, Ahn S, Kinan D, for the SOLVD Investigators. Effects of the angiotensin-converting enzyme inhibitor enalapril on the long-term progression of left ventricular dilation in patients with asymptomatic systolic dysfunction. *Circulation* 1993;88:2277–2283.
66. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study. *N Engl J Med* 1987;316:1429–1435.
67. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293–302.
68. Jong P, Yusuf S, for the XSOLVD Investigators. Extended follow-up of the Studies of Left Ventricular Dysfunction (SOLVD) prevention and treatment trials. Presented at the European Society of Cardiology Meeting; August 31-September 4, 2002; Berlin, Germany.
69. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992;327:685–691.
70. Yusuf S, Pepine CJ, Garces C, Pouler H, Salem D, Kostis J, Benedict C, Rousseau M, Bourassa M, Pitt B. Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions. *Lancet* 1992;340:1173–1178.
71. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, on behalf of the SAVE Investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial. *N Engl J Med* 1992;327:669–677.
72. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993;342:821–828.
73. Ambrosioni E, Borghi C, Magnani B. The effect of the angiotensin-converting enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction: the Survival of Myocardial Infarction Long-Term Evaluation (SMILE) Study Investigators. *N Engl J Med* 1995;332:80–85.
74. Kober L, Torp-Pedersen C, Carlsen JE, Bagger H, Eliasen P, Lyngborg K, Videbaek J, Cole DS, Auclert L, Pauly NC, for the Trandolapril Cardiac Evaluation (TRACE) Study Group. A clinical trial of the angiotensin-converting enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1995;333:1670–1676.
75. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, Ryden L, Thygesen K, Uretsky BF, on behalf of the ATLAS Study Group. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. *Circulation* 1999;100:2312–2318.
76. NETWORK Investigators. Clinical outcome with enalapril in symptomatic chronic heart failure: a dose comparison. *Eur Heart J* 1998;19:481–489.
77. Exner DV, Dries DL, Domanski MJ, Cohn JN. Lesser response to angiotensin-converting enzyme inhibitor therapy in black as compared with white patients with left ventricular dysfunction. *N Engl J Med* 2001;344:1351–1357.
78. Dries DL, Strong MH, Cooper RS, Drazner MH. Efficacy of angiotensin-converting enzyme inhibition in reducing progression from asymptomatic left ventricular dysfunction to symptomatic heart failure in black and white patients. *J Am Coll Cardiol* 2002;40:311–317.
79. Smith KM, Macmillan JB, McGrath JC. Investigation of α_1-adrenergic receptor subtypes mediating vasoconstriction in rabbit cutaneous resistance arteries. *Br J Pharmacol* 1997;122:825–832.
80. Elhawary AM, Pang CC. α_{1B}-Adrenergic receptors mediate renal tubular sodium and water reabsorption in the rat. *Br J Pharmacol* 1994;111:819–824.
81. Hasenfuss G, Holubarsch C, Blanchard EM, Mulieri LA, Alpert NR, Just H. Influence of isoproterenol on myocardial energetics: experimental and clinical investigations. *Basic Res Cardiol* 1989;84:S147–S155.
82. Knowlton KU, Michel MC, Itani M, Shubeita HE, Ishihara K, Brown JH, Chien KR. The α_{1A}-adrenergic receptor subtype mediates biochemical, molecular, and morphologic features of cultured myocardial cell hypertrophy. *J Biol Chem* 1993;268:15374–15380.
83. Communal C, Singh K, Pimentel DR, Colucci WS. Norepinephrine stimulates apoptosis in adult rat ventricular myocytes by activation of the β-adrenergic pathway. *Circulation* 1998;98:1329–1334.
84. Kaumann AJ, Sanders L. Both β_1- and β_2-adrenoceptors mediate catecholamine evoked arrhythmias in isolated human right atrium. *Naunyn Schmiedebergs Arch Pharmacol* 1993;348:536–540.
85. Waagstein F, Bristow MR, Swedberg K, Camerini F, Fowler MB, Silver MA, Gilbert EM, Johnson MR, Goss FG, Hjalmarson A. Beneficial effect of metoprolol in idiopathic dilated cardiomyopathy. *Lancet* 1993;342:1441–1446.
86. The RESOLVD Investigators. Effects of metoprolol CR in patients with ischemic and dilated cardiomyopathy: the randomized evaluation of strategies for left ventricular dysfunction pilot study. *Circulation* 2000;101:378–384.
87. Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, Wikstrand J, El Allaf D, Vitovec J, Aldershvile J, et al, for the MERIT-HF Study Group. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). *JAMA* 2000;283:1295–1302.
88. CIBIS Investigators and Committees. A randomized trial of β-blockade in heart failure: the Cardiac Insufficiency Bisoprolol Study (CIBIS). *Circulation* 1994;90:1765–1773.
89. Colucci WS, Packer M, Bristow MR, Gilbert EM, Cohn JN, Fowler MB, Krueger SK, Hershberger R, Uretsky BF, Bowers JA, et al, for the US Carvedilol Heart Failure Study Group. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. *Circulation* 1996;94:2800–2806.
90. Packer M, Colucci WS, Sackner-Bernstein JD, Liang CS, Goldscher DA, Freeman I, Kukin ML, Kinhal V, Udelson JE, Klapholz M, et al. Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure: the PRECISE Trial: Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise. *Circulation* 1996;94:2793–2799.
91. Bristow MR, Gilbert EM, Abraham WT, Adams KF, Fowler MB, Hershberger RE, Kubo SH, Narahara KA, Ingersoll H, Krueger S, Young S, Shusterman N, for the MOCHA Investigators. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. *Circulation* 1996;94:2807–2816.
92. Cohn JN, Fowler MB, Bristow MR, Colucci WS, Gilbert EM, Kinhal V, Krueger SK, LeJemtel T, Narahara KA, Packer M, et al. Safety and efficacy of carvedilol in severe heart failure. *J Card Fail* 1997;3:173–179.
93. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Roecker EB, Schultz MK, DeMets DL, for the Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;344: 1651–1658.
94. Goldstein S, Fagerberg B, Hjalmarson A, Kjekshus J, Waagstein F, Wedel H, Wikstrand J, for the MERIT-HF Study Group. Metoprolol controlled/extended release in patients with severe heart failure: analysis of the experience in the MERIT-HF study. *J Am Coll Cardiol* 2001;38:932–938.
95. CIBIS II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS II): a randomised trial. *Lancet* 1999;353:9–13.
96. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med* 1996;334:1349–1355.
97. Australia-New Zealand Heart Failure Research Collaborative Group. Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. *Lancet* 1997;349:375–380.
98. Poole-Wilson PA, Cleland JG, Di Lenarda A, Hanrath P, Komajda M, Metra M, Remme WJ, Swedberg K, Torp-Pedersen C. Rationale and design of the carvedilol or metoprolol European trial in patients with chronic heart failure: COMET. *Eur J Heart Fail* 2002;4:321–329.

99. The Beta-Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med* 2001;344:1659–1667.
100. Coats AJS. Heart failure 99: the MOXCON story. *Int J Cardiol* 1999;71: 109–111.
101. Yancy CW, Fowler MB, Colucci WS, Gilbert EM, Bristow MR, Cohn JN, Lukas MA, Young ST, Packer M, for the US Carvedilol Heart Failure Study Group. Race and the response to adrenergic blockade with carvedilol in patients with chronic heart failure. *N Engl J Med* 2001;344:1358–1365.
102. Moore JD, Mason DA, Green SA, Hsu J, Liggett SB. Racial differences in the frequencies of cardiac β_1-adrenergic receptor polymorphisms: analysis of c145AG and c1165GC. *Hum Mutat* 1999;14:271–275.
103. The CAPRICORN Investigators. Effect of carvedilol on outcome after myocardial infarction in patients with left ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 2001;357:1385–1390.
104. Gheorghiade M, Colluci WS, Swedberg K. β-Blockers in chronic heart failure. *Circulation*. In press.
105. Wikstrand J, Hjalmarson A, Waagstein F, Fagerberg B, Goldstein S, Kjekshus J, Wedel H. Dose of metoprolol CR/XL and clinical outcomes in patients with heart failure: analysis of the experience in metoprolol CR/XL randomized intervention trial in chronic heart failure (MERIT-HF). *J Am Coll Cardiol* 2002;40:491–498.
106. Gheorghiade M, Gattis WA, Lukas MA, O'Connor CM. Rationale and design of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy for Heart Failure (IMPACT-HF) study. *Am Heart J* 2003; 145(suppl):S60–S61.
107. Metra M, Giubbini R, Nodari S, Boldi E, Modena MG, Dei Cas L. Differential effects of β-blockers in patients with heart failure: a prospective, randomized, double-blind comparison of the long-term effects of metoprolol versus carvedilol. *Circulation* 2000;102:546–551.
108. Jacob S, Rett K, Wicklmayr M, Agrawal B, Augustin HJ, Dietze GJ. Differential effect of chronic treatment with two β-blocking agents on insulin sensitivity: the carvedilol-metoprolol study. *J Hypertens* 1996;14:489–494.
109. Packer M. Current role of β-adrenergic blockers in the management of chronic heart failure. *Am J Med* 2001;110:81S–94S.
110. Struthers AD. Why does spironolactone improve mortality over and above an ACE inhibitor in chronic heart failure? *Br J Clin Pharmacol* 1999;47:479–482.
111. Jorde UP, Vittorio T, Katz SD, Colombo PC, Latif F, LeJemtel TH. Elevated plasma aldosterone levels despite complete inhibition of the vascular angiotensin-converting enzyme in chronic heart failure. *Circulation* 2002;106:1055–1057.
112. Struthers AD. Aldosterone escape during angiotensin-converting enzyme inhibitor therapy in chronic heart failure. *J Card Fail* 1996;2:47–54.
113. Zannad F, Alla F, Dousset B, Perez A, Pitt B. Limitation of excessive extracellular matrix turnover may contribute to survival benefit of spironolactone therapy in patients with congestive heart failure. *Circulation* 2000;102:2700–2706.
114. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J, for the Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;341:709–717.
115. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, and Gatlin M, for the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;348:1309–1321.
116. Burnier M. Angiotensin II type 1 receptor blockers. *Circulation* 2001;103: 904–912.
117. Pitt B, Segal R, Martinez FA, Meurers G, Cowley AJ, Thomas I, Deedwania PC, Ney DE, Snavely DB, Chang PI. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet* 1997;349:747–752.
118. Pitt S, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm JA, Konstam MA, Riegger G, Klinger GH, Neaton J, Sharma D, Thiyagarajan B. Randomised trial of losartan versus captopril on mortality in patients with symptomatic heart failure: the losartan heart failure survival study, ELITE II. *Lancet* 2000;355:1582–1587.
119. Cohn JN, Tognoni G, for the Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;345:1667–1675.
120. Maggioni AP, Anand I, Gottlieb SO, Latini R, Tognoni G, Cohn JN, and the Val-HeFT Investigators. Effects of valsartan on morbidity and mortality in patients with heart failure not receiving angiotensin-converting enzyme inhibitors. *J Am Coll Cardiol* 2002;8:1414–1421.
121. Dickstein K, Kjekshus J, and the OPTIMAAL Steering Committee for the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. *Lancet* 2002;360:752–760.
122. Pfeffer M, McMurray J, Leizorovicz A, Maggioni A, Rouleau J, Van De Werf F, Henis M, Neuhart E, Gallo P, Edwards S, et al. Valsartan in acute myocardial infarction trial (VALIANT): rationale and design. *Am Heart J* 2000; 140:727–734.
123. Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, et al, for the LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002;359:995–1003.
124. Calderone A, Thaik CM, Takahashi N, Chang DLF, Colucci WS. Nitric oxide, atrial natriuretic peptide, and cyclic GMP inhibit the growth-promoting effects of norepinephrine in cardiac myocytes and fibroblasts. *J Clin Invest* 1998;101:812–818.
125. Jugdutt BI, Khan MI. Effect of prolonged nitrate therapy on left ventricular remodeling after canine acute myocardial infarction. *Circulation* 1994;89:2297–2307.
126. Keith M, Geranmayegan A, Sole MJ, Kurian R, Robinson A, Omran AS, Jeejeebhoy KN. Increased oxidative stress in patients with congestive heart failure. *J Am Coll Cardiol* 1998;31:1352–1356.
127. Bauer JA, Fung HL. Concurrent hydralazine administration prevents nitroglycerin-induced hemodynamic tolerance in experimental heart failure. *Circulation* 1991;84:35–39.
128. Leier CV, Huss P, Magorien RD, Unverfderth DV. Improved exercise capacity and differing arterial and venous tolerance during chronic isosorbide dinitrate therapy for congestive heart failure. *Circulation* 1983;67:817–822.
129. Elkayam U, Roth A, Kumar A, Kulick D, McIntosh N, McKay CR, Rahimtoola SH. Hemodynamic and volumetric effects of venodilation with nitroglycerin in chronic mitral regurgitation. *Am J Cardiol* 1987;60:1106–1111.
130. Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, Dunkman WB, Jacobs W, Francis GS, Flohr KH, for the Veterans Administration Cooperative Study Group. Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration Cooperative Study. *N Engl J Med* 1986;314:1547–1552.
131. Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, Smith R, Dunkman WB, Loeb H, Wong M. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991;325:303–310.
132. Roden RL. Cardiovascular news: cardiovascular and renal advisory panel of the United States Food and Drug Administration considers four drugs. *Circulation* 1997;95:2335–2337.
133. Carson P, Ziesche S, Johnson G, Cohn JN. Racial differences in response to therapy for heart failure: analysis of the vasodilator-heart failure trials. *J Card Fail* 1999;5:178–187.
134. Franciosa JA, Taylor AL, Cohn JN, Yancy CW, Ziesche S, Olukotun A, Ofili E, Ferdinand K, Loscalzo J, Worcel M, for the A-HeFT Investigators. African-American Heart Failure Trial (A-HeFT): rationale, design, and methodology. *J Card Fail* 2002;8:128–135.
135. Akera T, Baskin SI, Tobin T, Brody TM. Ouabain: temporal relationship between the inotropic effect and the in vitro binding to, and dissociation from, Na^+K^+ activated ATPase. *Naunyn Schmiedebergs Arch Pharmacol* 1973;277: 151–162.
136. Gheorghiade M, Ferguson D. Digoxin: a neurohormonal modulator in heart failure? *Circulation* 1991;84:2181–2186.
137. Kjeldsen K, Norgaard A, Gheorghiade M. Myocardial Na^+K^+ ATPase: the molecular basis for the hemodynamic effect of digoxin therapy in congestive heart failure. *Cardiovasc Res* 2002;55:710–713.
138. Eichhorn E, Gheorghiade M. Digoxin. *Prog Cardiovasc Dis* 2002;44:251–266.
139. Tauke J, Goldstein S, Gheorghiade M. Digoxin for chronic heart failure: a review of the randomized controlled trials with special attention to the PROVED and RADIANCE trials. *Prog Cardiovasc Dis* 1994;37:49–58.
140. Packer M, Gheorghiade M, Young JB, Costantini PJ, Adams KF, Cody RJ, Smith LK, Van Voorhees L, Gourley LA, Jolly MK, for the RADIANCE Study Group. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting enzyme inhibitors. *N Engl J Med* 1993;329:1–7.
141. Uretsky BF, Young JB, Shahidi FE, Yellen LG, Harrison MC, Jolly MK, on behalf of the PROVED Investigative Group. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED Trial. *J Am Coll Cardiol* 1993;22:955–962.
142. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997;336:525–533.
143. Gheorghiade M, Pitt B. Digitalis Investigation Group (DIG) trial: a stimulus for further research. *Am Heart J* 1997;134:3–12.
144. Rathore SS, Curtis JP, Wang Y, Bristow MR, Krumholz HM. Association of serum digoxin concentration and outcomes in patients with heart failure. *JAMA* 2003;289:871–878.
145. Rathore SS, Wang Y, Krumholz HM. Sex-based differences in the effect of digoxin for the treatment of heart failure. *N Engl J Med* 2002;347:1403–1411.
146. Eichhorn E, Gheorghiade M. Digoxin: new perspective on an old drug. *N Engl J Med* 2002;347:1394–1395.
147. Adams KF Jr, Gheorghiade M, Uretsky BF, Patterson JH, Schwartz TA, Young JB. Clinical benefits of low serum digoxin concentrations in heart failure. *J Am Coll Cardiol* 2002;39:946–953.
148. Brater DC. Pharmacology of diuretics. *Am J Med Sci* 2000;319:38–50.
149. Wilson JR, Reichek N, Dunkman WB, Goldberg S. Effect of diuresis on the performance of the failing left ventricle in man. *Am J Med* 1981;70:234–239.
150. Bayliss J, Norell M, Canepa-Anson R, Sutton G, Poole-Wilson P. Untreated heart failure: clinical and neuroendocrine effects of introducing diuretics. *Br Heart J* 1987;57:17–22.
151. Patterson JH, Adams KF Jr, Applefeld MM, Corder CN, Masse BR. Oral torsemide in patients with chronic congestive heart failure: effects on body

weight, edema, and electrolyte excretion: Torsemide Investigators Group. *Pharmacotherapy* 1994;14:514–521.
152. Hensen J, Abraham WT, Durr J, Schrier RW. Aldosterone in congestive heart failure patients: analysis of determinants and role in sodium retention. *Am J Nephrol* 1991;11:441–446.
153. Cooper HA, Dries DL, Davis CE, Shen YL, Domanski MJ. Diuretics and risk of arrhythmic death in patients with left ventricular dysfunction. *Circulation* 1999;100:1311–1315.
154. Cosin J, Diez J, on behalf of the TORIC Investigators. Torsemide in chronic heart failure: results of the TORIC study. *Eur J Heart Fail* 2002;4:507–513.
155. Murray MD, Deer MM, Ferguson JA, Dexter PR, Bennett SJ, Perkins SM, Smith FE, Lane KA, Adams LD, Tierney WM, Brater DC. Open-label randomized trial of torsemide compared with furosemide therapy for patients with heart failure. *Am J Med* 2001;111:513–520.
156. Elkayam U, Amin J, Mehra A, Vasquez J, Weber L, Rahimtoola SH. A prospective, randomized, double-blind, crossover study to compare the efficacy and safety of chronic nifedipine therapy with that of isosorbide dinitrate and their combination in the treatment of chronic congestive heart failure. *Circulation* 1990;82:1954–1961.
157. Goldstein RE, Boccuzzi SJ, Cruess D, Nattel S. Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction: the Adverse Experience Committee, Multicenter Diltiazem Postinfarction Research Group. *Circulation* 1991;83:52–60.
158. Packer M, O'Connor CM, Ghali JK, Pressler ML, Carson PE, Belkin RN, Miller AB, Neuberg GW, Frid D, Wertheimer JH, Cropp AB, DeMets DL, for the Prospective Randomized Amlodipine Survival Evaluation Study Group. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. *N Engl J Med* 1996;335:1107–1114.
159. Packer M, on behalf of PRAISE II Investigators. Preliminary results of the Second Prospective Randomized Amlodipine Survival Evaluation. Presented at the 49th Annual Scientific Session of the American College of Cardiology, March 12-16, 2000; Anaheim, California.
160. Cohn JN, Ziesche S, Smith R, Anand I, Dunkman WB, Loeb H, Cintron G, Boden W, Baruch L, Rochin P, Loss L, for the Vasodilator-Heart Failure Trial Study Group. Effect of the calcium antagonist felodipine as supplementary vasodilator therapy in patients with chronic heart failure treated with enalapril: V-HeFT III. *Circulation* 1997;96:856–863.
161. The Xamoterol in Severe Heart Failure Study Group. Xamoterol in severe heart failure. *Lancet* 1990;336:1–6.
162. Uretsky BF, Jessup M, Konstam MA, Dec GW, Leier CV, Benotti J, Murali S, Herrmann HC, Sandberg JA. Multicenter trial of oral enoximone in patients with moderate to moderately severe congestive heart failure: lack of benefit compared with placebo. Enoximone Multicenter Trial Group. *Circulation* 1990; 82:774–780.
163. Packer M, Carver JR, Rodeheffer RJ, Ivanhoe RJ, Di Bianco R, Zeldis SM, Hendrix GH, Bommer WJ, Elkayam U, Kukin ML, for the PROMISE Study Research Group. Effect of oral milrinone on mortality in severe chronic heart failure. *N Engl J Med* 1991;325:1468–1475.
164. Van Veldhuisen DJ, Man In't Veld AJ, Dunselman PHJM, Lok DJA, Dohmen HJM, Poortermans JC, Withagen AJAM, Pasteuning WH, Brouwer J, Lie KI, on behalf of the DIMT Study Group. Double-blind placebo-controlled study of ibopamine and digoxin in patients with mild to moderate heart failure: results of the Dutch Ibopamine Multicenter Trial (DIMT). *J Am Coll Cardiol* 1993;22:1564–1573.
165. Dohmen HJ, Dunselman PH, Poole-Wilson PA. Comparison of captopril and ibopamine in mild to moderate heart failure. *Heart* 1997;78:285–290.
166. Hampton JR, van Veldhuisen DJ, Kleber FX, Cowley AJ, Ardia A, Block P, Cortina A, Cserhalmi L, Follath F, Jensen G, et al, for the Second Prospective Randomised Study of Ibopamine on Mortality and Efficacy (PRIME II) Investigators. Randomised study of effect of ibopamine on survival in patients with advanced heart failure. *Lancet* 1997;349:971–977.
167. The Pimobendan in Congestive Heart Failure (PICO) Investigators. Effect of pimobendan on exercise capacity in patients with heart failure: main results from the Pimobendan in Congestive Heart Failure (PICO) trial. *Heart* 1996;76: 223–231.
168. Feldman AM, Bristow MR, Parmley WW, Carson PE, Pepine CJ, Gilbert EM, Strobeck JE, Hendrix GH, Powers ER, Bain RP, White BG, for the Vesnarinone Study Group. Effects of vesnarinone on morbidity and mortality in patients with heart failure. *N Engl J Med* 1993;329:149–155.
169. Cohn JN, Goldstein SO, Greenberg BH, Lorell BH, Bourge RC, Jaski BE, Gottlieb SO, McGrew F 3rd, DeMets DL, White BG. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure: Vesnarinone Trial Investigators. *N Engl J Med* 1998;339:1810–1816.
170. Dies F, Krell MJ, Whitlow P. Intermittent dobutamine in ambulatory outpatients with chronic heart failure [abstract]. *Circulation* 1986;74:II-38.
171. Oliva F, Latini R, Politi A, Staszewsky L, Maggioni AP, Nicolis E, Mauri F. Intermittent 6-month low-dose dobutamine infusion in severe heart failure: DICE Multicenter Trial. *Am Heart J* 1999;138:247–253.
172. Elis A, Bental T, Kimchi O, Ravid M, Lishner M. Intermittent dobutamine treatment in patients with chronic refractory congestive heart failure: a randomized, double-blind, placebo-controlled study. *Clin Pharmacol Ther* 1998;63:682–685.
173. Silver MA, Horton DP, Ghali JK, Elkayam U. Effect of nesiritide versus dobutamine on short-term outcomes in the treatment of patients with decompensated heart failure. *J Am Coll Cardiol* 2002;39:798–803.
174. Cuffe SM, Califf RM, Adams KF, Benza R, Bourge R, Colluci WS, Massie BM, O'Connor CM, Pina I, Quigg R, Silver MA, Gheorghiade M. Short-term intravenous milrinone for acute exacerbation of chronic heart failure. *JAMA* 2002;287:1541–1547.
175. Packer M, Rouleau J, Swedberg K, Pitt B, Fisher L, Klepper M, and the PROFILE Investigators and Coordinators. Effect of flosequinan on survival in chronic heart failure: preliminary results of the PROFILE study [abstract]. *Circulation* 1993;88:I-501.
176. Packer M, Narahara KA, Elkayam U, Sullivan JM, Pearle DL, Massie BM, Creager MA. Double-blind, placebo-controlled study of the efficacy of flosequinan in patients with chronic heart failure: Principal Investigators of the REFLECT Study. *J Am Coll Cardiol* 1993;22:65–72.
177. Sueta CA, Gheorghiade M, Adams KF, Bourge RC, Murali S, Uretsky BF, Pritzker MR, McGoon MD, Butman SM, Grossman SH, et al, for the Epoprostenol Multicenter Research Group. Safety and efficacy of epoprostenol in patients with severe congestive heart failure. *Am J Cardiol* 1995;75(suppl):34A–43A.
178. Califf RM, Adams KF, McKenna WJ, Gheorghiade M, Uretsky BF, McNulty SE, Darius H, Schulman K, Zannad F, Handberg-Thurmond E, et al. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: the Flolan International Randomized Survival Trial (FIRST). *Am Heart J* 1997;134:44–54.
179. Francis GS. Development of arrhythmias in the patient with congestive heart failure: pathophysiology, prevalence, and prognosis. *Am J Cardiol* 1986;57:3–7.
180. Chakko CS, Gheorghiade M. Ventricular arrhythmias in severe heart failure: incidence, significance, and effectiveness of antiarrhythmic therapy. *Am Heart J* 1985;109:497–504.
181. Podrid PJ, Lampert S, Graboys TB, Blatt CM, Lown B. Aggravation of arrhythmia by antiarrhythmic drugs: incidence and predictors. *Am J Cardiol* 1987;59:38–44.
182. Echt DS, Liebson PR, Mitchell B, Peters RW, Obias-Manno D, Barker AH, Arensberg D, Baker A, Friedman L, Greene HL, Huther ML, Richardson DW, and the CAST Investigators. Mortality and morbidity in patients receiving encainide, flecainide, or placebo: the Cardiac Arrhythmia Suppression Trial. *N Engl J Med* 1991;324:781–788.
183. The Cardiac Arrhythmia Suppression Trial II Investigators. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. *N Engl J Med* 1992;327:227–233.
184. Doval HC, Nul DR, Grancelli HO, Perrone S, Bortman GR, Curiel R, for Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina. Randomised trial of low-dose amiodarone in severe congestive heart failure. *Lancet* 1994;344:493–498.
185. Singh SN, Fletcher RD, Fisher SG, Singh BN, Lewis HD, Deedwania PC, Massie BM, Colling C, Lazzeri D, for the Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. *N Engl J Med* 1995;333: 77–82.
186. Julian DG, Camm AJ, Frangin G, Janse MJ, Munoz A, Schwartz PJ, Simon P, for the European Myocardial Infarct Amiodarone Trial Investigators. Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT. *Lancet* 1997;349:667–674.
187. Waldo AL, Camm AJ, De Ruyter H, Friedman PL, Mac Neil DJ, Pauls JF, Pitt B, Pratt CM, Schwartz PJ, Veltri EP, for the SWORD Investigators. Effect of *d*-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. *Lancet* 1996;348:7–12.
188. Fuster V, Gersh BJ, Giuliani ER, Tajik AJ, Brandenburg RO, Frye RL. The natural history of idiopathic dilated cardiomyopathy. *Am J Cardiol* 1981;47:525–531.
189. Jafri SM. Hypercoagulability in heart failure. *Semin Thromb Hemost* 1997; 23:543–545.
190. Dunkman WB, Johnson GR, Carson PE, Bhat G, Farrell L, Cohn JN, for the V-HeFT VA Cooperative Studies Group. Incidence of thromboembolic events in congestive heart failure. *Circulation* 1993;87:VI94–VI101.
191. Cioffi G, Pozzoli M, Forni G, Franchini M, Opasich C, Cobelli F, Tavazzi L. Systemic thromboembolism in chronic heart failure: a prospective study in 406 patients. *Eur Heart J* 1996;17:1381–1389.
192. Shivkumar K, Jafri SM, Gheorghiade M. Antithrombotic therapy in atrial fibrillation: a review of randomized trials with special reference to the Stroke Prevention in Atrial Fibrillation II (SPAF II) trial. *Prog Cardiovasc Dis* 1996; 38:337–342.
193. Rademaker MT, Charles CJ, Espiner EA, Nicholls MG, Richards AM, Kosoglou T. Combined neutral endopeptidase and angiotensin-converting enzyme inhibition in heart failure: role of natriuretic peptides and angiotensin II. *J Cardiovasc Pharmacol* 1998;31:116–125.
194. Rouleau JL, Pfeffer MA, Stewart DJ, Isaac D, Sestier F, Kerut EK, Porter CB, Proulx G, Qian C, Block AJ. Comparison of vasopeptidase inhibitor, omapatrilat, and lisinopril on exercise tolerance and morbidity in patients with heart failure: IMPRESS randomised trial. *Lancet* 2000;356:615–620.
195. Packer M, Califf RM, Konstam MA, Krum H, McMurray JJ, Rouleau JL, Swedberg K. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). *Circulation* 2002;106:920–926.
196. Torre-Amione G, Kapadia S, Benedict C, Oral H, Young JB, Mann DL. Proinflammatory cytokine levels in patients with depressed left ventricular ejec-

tion fraction: a report from the Studies of Left Ventricular Dysfunction (SOLVD). *J Am Coll Cardiol* 1996;27:1201–1206.
197. Franco F, Thomas GD, Giroir B, Bryant D, Bullock MC, Chwialkowski MC, Victor RG, Peshock RM. Magnetic resonance imaging and invasive evaluation of development of heart failure in transgenic mice with myocardial expression of tumor necrosis factor-α. *Circulation* 1999;99:448–454.
198. Yue P, Massie BM, Simpson PC, Long CS. Cytokine expression increases in nonmyocytes from rats with postinfarction heart failure. *Am J Physiol* 1998; 275:H250–H258.
199. Herrera-Garza E, Stetson S, Cubillos-Garzon A, Vooletich M, Farmer JA, Torre-Amione G. Tumor necrosis factor-α: a mediator of disease progression in the failing human heart. *Chest* 1999;115:1170–1174.
200. Bozkurt B, Torre-Amione G, Warren MS, Whitmore J, Soran OZ, Feldman AM, Mann DL. Results of targeted anti-tumor necrosis factor therapy with etanercept (ENBREL) in patients with advanced heart failure. *Circulation* 2001; 103:1044–1047.
201. Mann D, for the RENEWAL Investigators. Effects of etanercept on the morbidity and mortality in patients with chronic heart failure: results of the Randomized Etanercept World-Wide Evaluation (RENEWAL) Study. Presented at the Heart Failure Update Meeting; June 8-11, 2002; Oslo, Norway.
202. Packer M, for the ATTACH Investigators. Effects of anti-TNF-α therapy against chronic heart failure. Presented at the Heart Failure Update Meeting, June 8-11, 2002; Oslo, Norway.
203. Kelly JJ, Whitworth JA. Endothelin-1 as a mediator in cardiovascular disease. *Clin Exp Pharmacol Physiol* 1999;26:158–161.
204. McMurray JJ, Ray SG, Abdullah I, Dargie HJ, Morton JJ. Plasma endothelin in chronic heart failure. *Circulation* 1992;85:1374–1379.
205. Pousset F, Isnard R, Lechat P, Kalotka H, Carayon A, Maistret G, Escolano S, Thomas D, Komajda M. Prognostic value of plasma endothelin-1 in patients with chronic heart failure. *Eur Heart J* 1997;18:254–258.
206. Abraham WT, for the ENCOR Investigators. Effects of enrasentan, a non-selective endothelin receptor antagonist, in class II-III heart failure: results of the ENCOR Trial. Presented at the 50th Annual Scientific Session of the American College of Cardiology, March 18-21, 2001; Orlando, Florida.
207. Packer M, Caspi A, Charlon V, Cohen-Solal A, Kiowski W, Kostuk W, Krum H, Levine B, Massie B, McMurray J, Swedberg K. Multicenter, double-blind, placebo-controlled study of long-term endothelin blockade with bosentan in chronic heart failure: results of the REACH-1 trial [abstract]. *Circulation* 1998;98:I-3.
208. Packer M, for the ENABLE Investigators. Effects of endothelin receptor antagonist bosentan on the morbidity and mortality in patients with chronic heart failure: results of the ENABLE 1 and 2 programs. Presented at the 51st Annual Scientific Session of the American College of Cardiology; March 17-20, 2002; Atlanta, Georgia.
209. O'Connor CM, Gattis WA, Adams KF, Shah MR, Kobrin I, Frey A, Gheorghiade M. Tezosentan in patients with acute heart failure and acute coronary syndromes: design of the Randomized Intravenous Tezosentan Study (RITZ-4). *Am Heart J* 2002;144:583–588.
210. Goldsmith SR. Vasopressin: a therapeutic target in congestive heart failure? *J Card Fail* 1999;5:347–356.
211. Walker BR, Childs ME, Adams EM. Direct cardiac effects of vasopressin: role of V1- and V1-vasopressinergic receptors. *Am J Physiol* 1988;255:H261–H265.
212. Schrier RW, Berl T, Anderson RJ. Osmotic and nonosmotic control of vasopressin release. *Am J Physiol* 1979;236:F321–F332.
213. Udelson JE, Smith WB, Hendrix GH, Painchaud CA, Ghazzi M, Thomas I, Ghali JK, Selaru P, Chanoine F, Pressler ML, Konstam MA. Acute hemodynamic effects of conivaptan, a dual V1A and V2 vasopressin receptor antagonist, in patients with advanced heart failure. *Circulation* 2001;104:2417–2423.
214. Gheorghiade M, Niazi I, Ouyang J, Czerwlec F, Kambayashi JI, Orlandi C. Chronic effects of vasopressin receptor blockade with tolvaptan in congestive heart failure: a randomized, double-blind trial [abstract]. *Circulation* 2000;102: II-592.
215. Gheorghiade M, Konstam MA, Udelson JE, Ouyang J, Orlandi C. Vasopressin receptor blockade with tolvaptan in chronic heart failure: differential effects in normonatremic and hyponatremic patients [abstract]. *Circulation* 2000; 102:II-438.
216. Gheorghiade M, Gattis WA, Barbagelata A, Adams K, Orlandi C, O'Connor CM, for the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF) Investigators. Rationale and study design for a multicenter, randomized, double-blind, placebo-controlled study of the effects of tolvaptan on the acute and chronic outcomes of patients hospitalized with worsening congestive heart failure. *Am Heart J* 2003;145:S51–S54.